

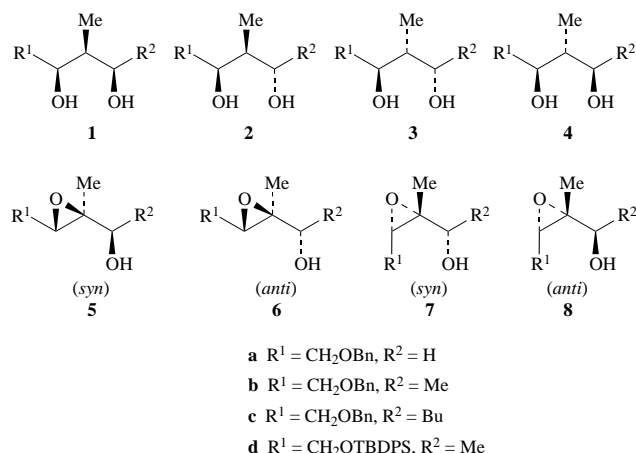
Anti-Markovnikov opening of trisubstituted epoxy alcohols: application in the synthesis of 2-methyl-1,3-diols †

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2-Methyl-1,3-diols are synthesized by regioselectively opening trisubstituted epoxides, prepared from 2-methylbut-2-en-1-ols at the more substituted carbon using Cp_2TiCl -cyclohexa-1,4-diene.

The stereotriads **1–4**, the four possible diastereomers of the 2-methyl-1,3-diol framework, appear ubiquitously in various propionate-derived polyketide natural products.¹ Herein we report a method for the synthesis of stereotriads **1–3** which involves opening of trisubstituted epoxy alcohols **5–8**, prepared easily from the corresponding 2-methylbut-2-en-1-ols.



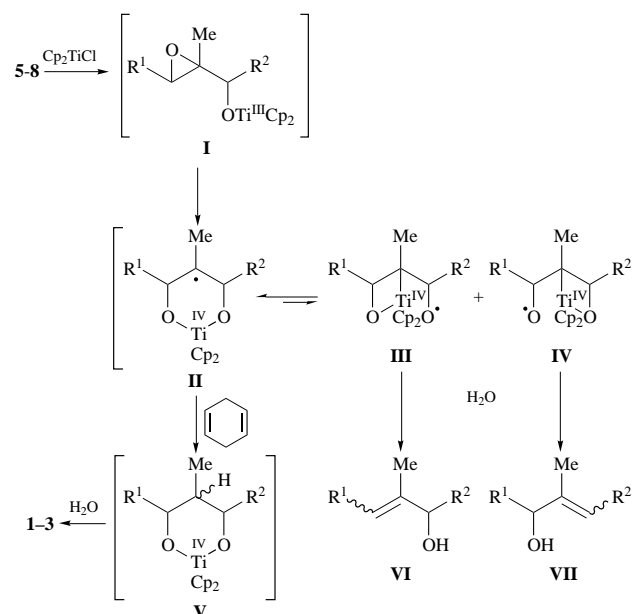
All our attempts to open epoxides, **5–8** with various hydride reagents² resulted in the attack only at the less substituted centre leading to the formation of mainly the 1,2-diol. Even Red-Al which is known to give exclusively 1,3-diols from disubstituted epoxy alcohols³ failed to deliver us the desired 2-methyl-1,3-diols. There are only two reports⁴ on the selective formation of 2-methyl-1,3-diols from the epoxides of 4-alkyl-substituted 2-methylbut-2-en-1-ols using Red-Al. This reagent is also reported to have led to the exclusive formation of 1,2-diol from a similar trisubstituted epoxy alcohol, but with no alkyl substituent at the 4-position.⁵ In our hands, reactions with Red-Al were extremely slow and the small amounts of products formed contained either only traces of 1,3-diols or none at all.

RajanBabu *et al.*⁶ reported the selective formation of the less substituted alcohol in the opening of trisubstituted epoxides with paramagnetic Cp_2TiCl in the presence of cyclohexa-1,4-diene which acts as a donor of hydrogen atoms. The greater stability of tertiary radicals over secondary ones was believed to be the reason behind the selective formation of less-substituted alcohols in their radical-mechanism based epoxide opening process. The same titanocene reagent in the absence of any hydrogen source gave allylic alcohols from disubstituted epoxy alcohols as reported by Yadav *et al.*⁷

The failure encountered by us to obtain 2-methyl-1,3-diols by ring opening of trisubstituted epoxy alcohols **5–8** with hydride

reagents prompted us to use instead Cp_2TiCl -cyclohexa-1,4-diene to get the targeted products. The results of our studies are summarised in Table 1. In all the substrates ‡ studied only 1,3-diols were formed and there was no trace of any 1,2-isomer in any of these cases. In order to minimize the elimination and obtain maximum yield of the desired 1,3-diol, the reactions were started at $-15^\circ C$ and allowed slowly to warm to room temperature. Further reduction in temperature slowed down the reactions considerably. When the reactions were worked up after 30–60 min, small amounts of eliminated products, **VI** and **VII** (Scheme 1), were obtained as side products along with the desired 1,3-diols. Which of the two (**VI** and **VII**) would form preferentially depended on the stabilities of the olefins and also the reaction conditions. When a different hydrogen source such as triethylsilane was used, unsuccessfully, to obtain 1,3-diols, both the olefins were formed in equal amounts. Also each olefin formed was a mixture of two geometric isomers.

When the reactions were allowed to proceed for longer, after about 4–6 h the only spot shown by TLC was that of the 1,3-diol. Possibly the initially formed $-OTi^{III}Cp_2$ species **I** (Scheme 1) underwent an intramolecular electron-transfer process to give the six-membered Ti^{IV} -intermediate **II** which remained in



Scheme 1 Mechanism of the opening of epoxy alcohols with Cp_2TiCl -cyclohexa-1,4-diene

‡ The epoxy alcohols were prepared from the corresponding 2-methylbut-2-en-1-ols using either MCPBA or the Sharpless method. In reactions with MCPBA both *syn*- and *anti*-products were formed and were separated by standard silica gel column chromatography. The enantiomeric purities of the substrates prepared by the Sharpless method were not determined. But all the epoxy alcohols used were diastereomerically pure as determined by 1H NMR spectroscopy.

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Table 1 Regioselective opening of epoxy alcohols with Cp₂TiCl-cyclohexa-1,4-diene

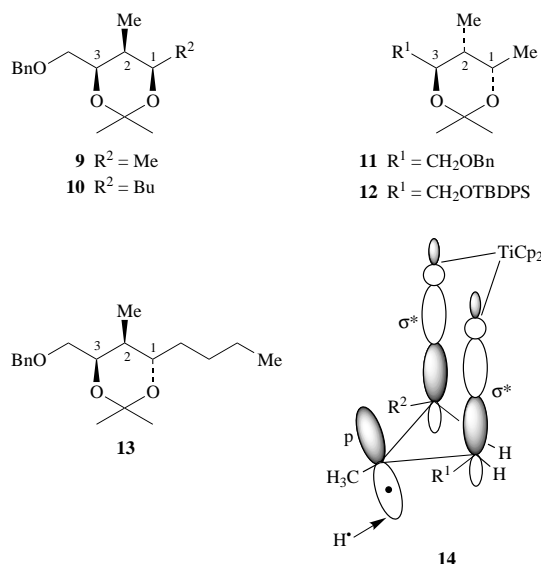
Entry	Epoxy alcohol	t/h	Products (ratio) ^a	Yield ^b (%)
1	5a	4	3a + 2a (4.4:1)	83
2	5b	6	1b + 4b (5:1)	84
3	6b	6	3b + 2b (3.5:1)	85
4	5c	5	1c	82
5	6c	4	2c	88
6	7b	6	3b + 2b (3.5:1)	84
7	7d	4	3d + 2d (4:1)	85
8	8b	6	1b + 4b (5:1)	86

^a Ratios determined by ¹H NMR spectroscopy. ^b Yields refer to isolated yields.

equilibrium with two possible four-membered intermediates, **III** and **IV**, which bear a more reactive oxygen free radical. The equilibrium lay largely towards **II**, which has the more stable carbon radical which on hydrogen abstraction from cyclohexa-1,4-diene slowly gave the thermodynamically controlled product, the desired 1,3-diols. Even if the oxygen free radicals of **III** and **IV** abstracted hydrogen during the reaction, the presence of an excess of titanocene reagent regenerated the radical driving the equilibrium more towards **II** and leading to the formation of 1,3-diol exclusively.

This explains why premature termination of the reaction gave the kinetically controlled elimination products as well as the desired 1,3-diols. The assumption that the reaction goes *via* the six-membered Ti^{IV}-intermediate **II** is also supported by the observed facial selectivity in the hydrogen abstraction process giving rise to diastereoselective product formation. Unlike the classical S_N2-type hydride opening of epoxides where exclusive diastereoselectivity is observed, the present radical-mediated reaction was feared to lead to the epimerization of the radical-bearing centre. However, surprisingly, excellent diastereoselection was observed during the hydrogen abstraction. This is attributed to the cyclic intermediate **II**, where stereochemistries at C1 and C3 and sizes of R¹ and R² are probably the deciding factors for the observed facial selectivity.

In entries 4 and 5, diastereoselections were exclusive as no minor isomer was detected by ¹H NMR spectroscopy. Both epoxy alcohols **5b** and **8b** gave the same diol **1b** as the major product. Similarly **3b** was the major product obtained from both **6b** and **7b**. The stereochemistries of **3a** and **2a** were confirmed by comparing their ¹H NMR spectra with those of authentic samples, prepared by dimethylcopper lithium-opening of *trans*- and *cis*-4-benzyloxy-2,3-epoxybutan-1-ol, respectively. The mixture of diastereomers obtained from **5b** (and **8b**) was converted to the acetonides. The major acetonide



9 from diol **1b** (entries 2 and 8) showed both $J_{1,2}$ and $J_{2,3} = 2.3$ Hz confirming it to be the *syn,syn*-isomer with equatorial C2-H. The acetonide **10** prepared from diol **1c** (entry 4) also showed the same coupling constants. Of the two methyls of the acetonide function, the axial methyl showed an NOE with both C1-H and C3-H suggesting a perfect chair conformation. This was further supported by ¹³C NMR spectroscopy of **10** which showed the methyls of the acetonide at 19.7 and 30.1 ppm and the ketal carbon at 98.85 ppm.⁸ The major acetonide **11** from the isomeric mixture of diols in entries 3 and 6 had $J_{1,2} = 4.8$ Hz. Although $J_{2,3}$ could not be determined because of overlapping signals, the $J_{1,2}$ of the minor acetonide was 6.2 Hz which led us to conclude that the major product was 1,2-*syn*. In the ¹³C NMR spectrum of **11**, the chemical shifts for the *gem*-dimethyls were 23.9 and 25.1 ppm and that for the ketal carbon was 100.5 ppm proving it to be 1,3-*anti*.⁸ In a similar way the 1,2-*syn* and 2,3-*anti* relationships in **3d** (entry 7) were determined by preparing its acetonide **12** which had $J_{1,2} = 5.3$ Hz and $J_{2,3} = 8.1$ Hz. The coupling constants suggest a twist-boat conformation for **12**.⁹ The acetonide **13** prepared from diol **2c** had $J_{1,2} = 7$ Hz and $J_{2,3} = 4.7$ Hz which confirmed its assigned stereochemistry.

The exact mechanism to explain the observed trend in the diastereoselection during the hydrogen abstraction step is presently being worked out. It is believed that the conformation of the six-membered intermediate **II** plays an important role in the process. Probably, in the chair-type conformation, **14**, the approach of the hydrogen atom is antiperiplanar to the α-C–O bond which, having the lowest σ* orbital energy, occupies, in the reactive conformer, a position eclipsing the singly occupied p-orbital at the radical centre¹⁰ enabling maximum overlap lowering the energy of the p-orbital and, consequently, minimizing the free energy of activation for the reaction. What happens in the twist-boat conformation of **II** is not yet fully understood. Here, probably, the sizes of R¹ and R² also decide the stereochemical outcome of the reaction. It appears that when R¹ is bigger than R², the product is **3**, whereas with bigger R², the formation of **2** is preferred. The clear picture will emerge only after the correct conformations of six-membered Ti^{IV}-intermediates (**II**) are known. It can be stated at this point that this method cannot be used to synthesize the stereotriad **4**.

The Cp₂TiCl used in our reactions was generated *in situ* from Cp₂TiCl₂, freshly fused anhydrous ZnCl₂ and dry activated Zn powder.^{6,7} An excess of reagents was used since otherwise with molar equivalents of reagents rapid decolorisation took place leaving the reaction incomplete.

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§ In a typical experiment, freshly fused anhydrous ZnCl₂ (5 mol equiv.) was added at room temperature under a nitrogen atmosphere to a mixture of Cp₂TiCl₂ (5 mol equiv.) and dry activated Zn powder (10 equiv.) in freshly dried THF (2 ml per mmol of titanocene reagent). The mixture was stirred at room temperature for 1 h and the colour gradually changed from red to dark green. It was then cooled to –15 °C and a solution of epoxy alcohol and cyclohexa-1,4-diene (5 mol equiv.) in dry THF (2 ml per mmol of epoxy alcohol) was added slowly with a syringe. The reaction mixture was allowed to warm to room temperature during 2 h and stirring continued for an additional 2–4 h, by which time the only spot in TLC was that of the 1,3-diol. It was then worked up by adding 1 M HCl and extracted with EtOAc. The EtOAc extracts were combined, washed with brine, dried over anhydrous Na₂SO₄ and concentrated. Purification by silica gel column chromatography gave the desired 1,3-diols.

Data for **3b**: syrupy liquid, $R_f = 0.5$ (silica, EtOAc–light petroleum, 1:1); δ_H (200 MHz, CDCl₃, J /Hz) 7.3 (m, 5 H, aromatic), 4.54 (s, 2 H, PhCH₂O), 3.98 (m, 1 H, Cl-H), 3.8 (dt, J 8.2, 3.6, 1 H, C3-H), 3.54 (dd, J 8.2, 3.6, 1 H, C4-H), 3.43 (t, J 8.2, 1 H, C4-H'), 2.8 (br s, 2 H, OH), 1.68 (m, 1 H, C2-H), 1.15 (d, J 6.3, 3 H, Cl-CH₃), 0.87 (d, J 6.7, 3 H, C2-CH₃); m/z (CI) 223 (M – H⁺), Calc. for C₁₃H₂₀O₃: M , 224.

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