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A Novel Route to *trans*-Epoxidation of Terpinen-4-ol

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Summary. Pure (*1S,2R,4S*)-1,2-epoxy-*p*-menthan-4-ol and (*1R,2S,4R*)-1,2-epoxy-*p*-menthan-4-ol (*trans*-epoxides of (*4S*)-terpinen-4-ol and (*4R*)-terpinen-4-ol) were prepared and certain reactions of these compounds with nucleophilic reagents were studied. It was shown that the *Fürst-Plattner* rule regarding the *trans*-diaxial opening of cyclohexene epoxides predicts the predominant products in all cases studied.

Keywords. Terpinen-4-ol; *trans*-Epoxidation; Tosylation; Acetylation.

Introduction

Oxiranes (epoxides) are compounds which are widely distributed in nature and are of industrial, mechanistic, and biochemical interest. The ease of preparation of epoxides and their facile ring opening have made them important intermediates in organic chemistry for the past several decades. Presently the main objective in organic synthesis is to develop reactions which are enantio-, diastereo-, regio-, and chemoselective.

The epoxidation of an unsaturated substrate may be achieved by treatment with different peroxycarboxylic acids. Oxidation of terpinen-4-ol with buffered peracetic acid [1] gave the two epoxides, *cis:trans* = 7:3, which were separated by g.l.c. and oxidation with peroxylauric acid in chloroform gave the two epoxides in the ratio 3:2 [1, 2].

We developed a new regio- and stereoselective method for the preparation of (*1S,2R,4S*)-1,2-epoxy-*p*-menthan-4-ol (**3a**) and (*1R,2S,4R*)-1,2-epoxy-*p*-menthan-4-ol (**3b**) which consists of a two step process: a regioselective tosylation followed by nucleophilic substitution, which leads to *trans*-epoxides. The structures of the obtained *trans*-epoxides were determined by spectroscopical analysis and chemical reactions.

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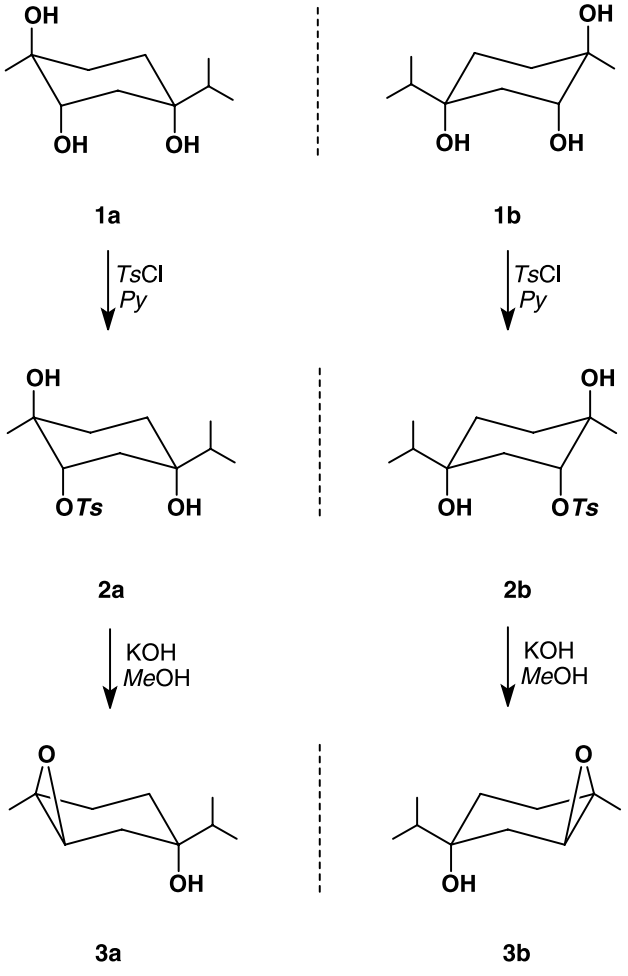
Results and Discussions

The starting materials (*1S,2S,4S*)-*p*-menthane-1,2,4-triol (**1a**) and (*1R,2R,4R*)-*p*-menthane-1,2,4-triol (**1b**) were obtained by *trans*-dihydroxylation of (*4S*)- and (*4R*)-terpinen-4-ol, using H_2O_2 in presence of V_2O_5 [3].

The tosylation of alcohols is a very common reaction, which is often used to facilitate subsequent nucleophilic substitution. A number of alcohols have been converted to the corresponding arenesulfonates by using lengthy the conventional tosylation procedures, in which the tosylates have been prepared in pyridine [4].

The first step of our reaction required the preparation of the 2-tosyl derivative (**2a**). We used two different approaches in order to optimize yields and simplify reaction workup (Scheme 1).

First, the tosylation reaction was performed in the usual way using pyridine as the base. However, it was observed that the formation of the pyridinium salts in this kind of reaction resulted in a concomitant loss of the desired tosylate. Also, according to the conventional tosylation, when the tosylate prepared is an oil (like in our



Scheme 1

case) a thorough elimination of the pyridine from the final product requires either repeated neutralization with aqueous hydrochloric acid or purification by column chromatography.

Many of the tosylations reported in literature [5] were carried out by using chloroform as the solvent and in order to eliminate the disadvantages mentioned above, we performed the tosylation reaction under these conditions. This procedure avoids formation of unwanted pyridinium salts inherent to reactions where higher relative quantities of pyridine are employed.

It has to be mentioned that freshly purified tosyl chloride [6] should be used for best results, because upon prolonged standing the material develops impurities of *p*-toluenesulfonic acid and HCl. This method is advantageous over the conventional tosylation in pyridine, regarding the work-up procedure, the yield, and the purity of the product.

The highest yields of pure tosylate based on starting alcohol were obtained using a 1:2:3 ratio of alcohol/tosyl chloride/pyridine in chloroform. Our results are summarized in Table 1.

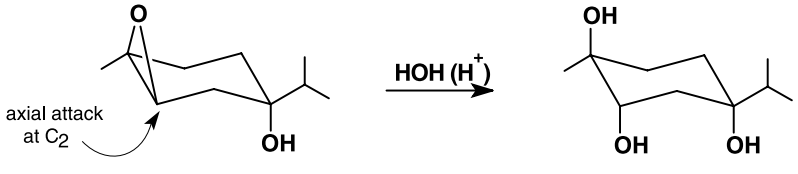
The second step of the method requires the treatment of the obtained 2-tosyl derivative with a methanolic solution of potassium hydroxide in order to prepare (*1S,2R,4S*)-1,2-epoxy-*p*-menthan-4-ol (**3a**). This process is stereoselective and takes place by an SN_2 intramolecular substitution in quantitative yield.

In order to derive the structure of **3a**, chemical reactions, which involve oxirane opening were performed. Opening of cyclohexene oxides generally proceeds in such fashion that the *trans*-diaxial rather than the *trans*-diequatorial product is obtained (*Fürst-Plattner* rule [7, 8]).

In the case of the *cis*-epoxide of terpinen-4-ol [9], axial attack at the higher substituted C_1 by water (SN_2) upon the protonated epoxide leads to **1a** where the two hydroxyl groups have *trans*-diaxial orientation. The same compound was obtained when the *trans*-epoxide of terpinen-4-ol reacted with water (Scheme 2).

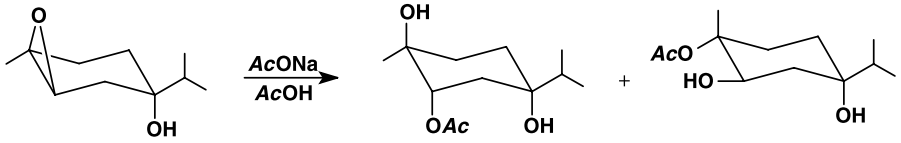
Table 1. Tosylation of **1a** in chloroform

Entry	Alcohol/mmol	*p-Ts*Cl/mmol	Pyridine/mmol	Yield/%
1	10	10	10	58
2	10	10	20	62
3	10	20	30	70
4	10	20	60	65



3a **1a**

Scheme 2



3a 4a 5a

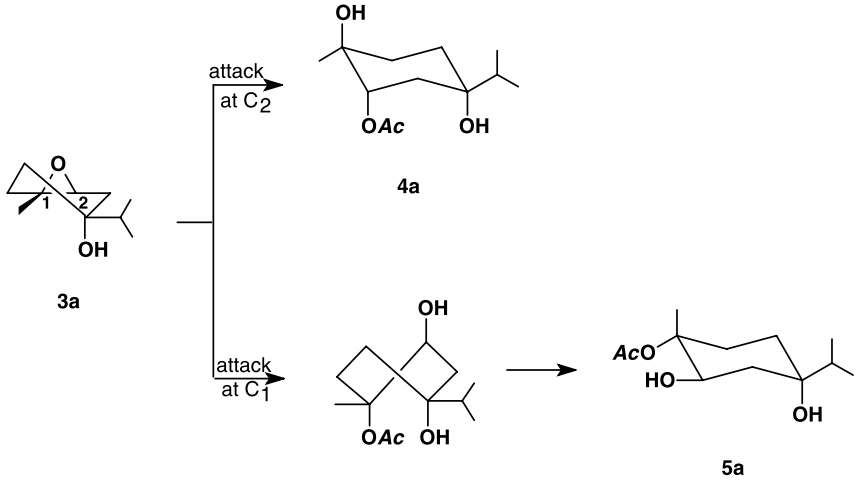
Scheme 3

For a better explanation of the different behavior of the two epoxides, the reaction of the *trans*-epoxide in a sodium acetate buffered solution of acetic acid was investigated.

Three major effects must be considered when a reaction involves cyclohexene epoxides ring opening: conformational effects, the primary steric effect (the incoming reagent in the attack of an epoxide normally attacks the least substituted carbon of the oxirane linkage unless there are remarkable polar or conjugative effects), and conformational preference of the resulting products.

In the case of nucleophilic attack, the primary steric effect is observed for the *cis*-isomer, for which diaxial opening involves attack at the tertiary carbon. For the *trans*-isomer we cannot rationalize the formation of **5a** on the basis of any steric effect, the formation of this secondary product can be explained by the existence of a partial positive charge on the tertiary carbon atom, the reaction approaching an SN_1 mechanism.

The action of acetic acid–sodium acetate solution upon **3a** (Scheme 4) at the less substituted C(2) center leads to diaxially disubstituted chair conformation of **4a** (major product) and an attack at more substituted C(1) center gives rise to the diaxially disubstituted twist conformation of the cyclohexane ring which must then invert to the diequatorially disubstituted chair form of **5a** with *trans*-diequatorial orientation of the acetoxy and hydroxyl groups (minor product). In the same manner, **3b** gave the other enantiomer **4b** as major product.



Scheme 4

In summary, it is apparent that in reactions of nucleophilic reagents on *cis*- and *trans*-epoxides of terpinen-4-ol, the *Fürst-Plattner* rule of diaxial opening correctly predicts the predominant products.

Experimental

(1S,2S,4S)-2-Tosyl-p-menthane-1,4-diol (**2a**, $C_{17}H_{28}SO_5$)

(*1S,2S,4S*)-*p*-Menthane-1,2,4-triol (**1a**, 1.88 g, 10 mmol) was dissolved in 10 cm^3 of $CHCl_3$ at room temperature. Pyridine (2.41 cm^3, 30 mmol) was then added, followed by 3.81 g of *p*-toluenesulfonyl chloride (20 mmol) in small portions with constant stirring. The reaction was completed after 24 h. Ether (40 cm^3) and 10 cm^3 of H_2O were added and the organic layer was washed successively with 2 *N* HCl, 5% $NaHCO_3$ solution, and H_2O and then dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude tosylate was chromatographed (ethylacetate:toluene = 5:1) on a silica gel column to yield 2.39 g of an oil (70%); $[\alpha]_D = +32^\circ\ cm^3\ g^{-1}\ dm^{-1}$ ($c = 1.0$ in *Et*OH). (1R,2R,4R)-2-Tosyl-*p*-menthane-1,4-diol (**2b**), $[\alpha]_D = -28.9^\circ\ cm^3\ g^{-1}\ dm^{-1}$ ($c = 1.0$ in *Et*OH) was obtained in pure form from (*1R,2R,4R*)-*p*-menthane-1,2,4-triol (**1b**). ^{1}H NMR (*DMSO*-d_6, 500 MHz): $\delta = 7.7$ (1H, d, C_{arom}), 7.55 (1H, d, C_{arom}), 7.35 (1H, d, C_{arom}), 7.1 (1H, d, C_{arom}), 4.75 (1H, s, C_4OH), 3.75 (1H, s, C_1OH), 2.0 (1H, dd, H_{3eq}), 1.8 (1H, dd, H_{6eq}), 1.6 (1H, dd, H_{5eq}), 1.40 (1H, hept., H_8), 1.35 (1H, dd, H_{3ax}), 1.24 (1H, dd, H_{6ax}), 1.20 (1H, dd, H_{5ax}), 1.3 (3H, s, CH_3), 1.2 (3H, s, CH_3), 0.9 (6H, d, $2CH_3$) ppm; ^{13}C NMR (*DMSO*-d_6, 125 MHz): $\delta = 144.2$ (C_{14}), 138.0 (C_{11}), 128.5 (C_{13}), 125.0 (C_{12}), 75.5 (C_2), 71.3 (C_1), 69.4 (C_4), 36 (C_3), 34.0 (C_8), 32.5 (C_5), 30.8 (C_6), 21.3 (C_{15}), 21.0 (C_7), 17.1 (C_9 and C_{10}) ppm; MS: m/z (%) = 127 (47), 109 (49), 83 (50), 71 (49), 57 (95), 55 (61), 43 (100).

Synthesis of (1S,2R,4S)-1,2-Epoxy-p-menthan-4-ol (**3a**)

To a solution of potassium hydroxide (20 mmol) in 10 cm^3 of methanol 3.42 g of (*1S,2S,4S*)-2-tosyl-*p*-menthane-1,4-diol (**2a**) (10 mmol) were added and the reaction mixture was stirred at room temperature for 24 h. After this time, the solution was poured into water and extracted with ether. The extracts were washed with water and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the product was chromatographed (ethylacetate:toluene = 5:1) on a silica gel column to yield 1.56 g of an oil (92%); $[\alpha]_D = +3.5^\circ\ cm^3\ g^{-1}\ dm^{-1}$ ($c = 0.2$ in *Et*OH) (Ref. [2] $[\alpha]_D = +3.2^\circ\ cm^3\ g^{-1}\ dm^{-1}$ ($c = 0.2$ in *Et*OH)). (*1R,2S,4R*)-1,2-Epoxy-*p*-menthan-4-ol (**3b**), $[\alpha]_D = -3.4^\circ\ cm^3\ g^{-1}\ dm^{-1}$ ($c = 1.0$ in *Et*OH) was obtained in a similar way from (*1R,2R,4R*)-2-tosyl-*p*-menthane-1,4-diol (**2b**). ^{1}H-NMR (*DMSO*-d_6, 500 MHz): $\delta = 4.0$ (1H, s, C_4OH), 2.8 (1H, t, H_2), 1.92 (1H, dd, H_{3eq}), 1.8 (1H, dd, H_{6eq}), 1.65 (1H, dd, H_{5eq}), 1.40 (1H, hept., H_8), 1.35 (1H, dd, H_{3ax}), 1.24 (1H, dd, H_{6ax}), 1.20 (1H, dd, H_{5ax}), 1.1 (1H, s, CH_3), 0.9 (6H, d, $2CH_3$) ppm; ^{13}C-NMR (*DMSO*-d_6, 125 MHz): $\delta = 70.0$ (C_4), 59.0 (C_2), 57.0 (C_1), 34.5 (C_3), 32.8 (C_8), 29.5 (C_5), 26.3 (C_6), 23 (C_7), 16.2 (C_9), 16.1 (C_{10}) ppm; MS: m/z (%) = 170 (4), 109 (32), 71 (28), 55 (39), 43 (100).

Synthesis of (1S,2S,4S)-2-Acetoxy-p-menthan-1,4-diol (**4a**)

(*1S,2R,4S*)-1,2-Epoxy-*p*-menthan-4-ol (0.5 g, 3 mmol) was added to a solution of 1.5 g of sodium acetate in 10 cm^3 of glacial acetic acid and stirred at room temperature for 48 h. After this period, the solution was diluted with 300 cm^3 of H_2O, neutralized with sodium bicarbonate, and extracted with chloroform and dried over anhydrous sodium sulfate. The chloroform was evaporated and the crude product was chromatographed. Ethylacetate eluted (*1S,2S,4S*)-2-acetoxy-*p*-menthan-1,4-diol as an oil which gave 0.58 g of needles from ether (82%); mp 115°C; $[\alpha]_D = +27.2^\circ\ cm^3\ g^{-1}\ dm^{-1}$ ($c = 1.1$ in *Et*OH) (Ref. [10] $[\alpha]_D = +27.8^\circ\ cm^3\ g^{-1}\ dm^{-1}$; $c = 1.15$ in *Et*OH). Further elution gave (*1S,2R,4S*)-*p*-menthane-1-acetoxy-2,4-diol (**5a**) as an oil which gave crystals from ether. (*1R,2R,4R*)-*p*-Menthane-2-

acetoxy-1,4-diol (**4b**), $[\alpha]_D = -25.8^\circ\ cm^3\ g^{-1}\ dm^{-1}$ ($c = 1.0$ in *Et*OH) was obtained in the same way from (*1R,2S,4R*)-1,2-epoxy-*p*-menthan-4-ol. ^{1}H-NMR (*DMSO*-d_6, 500 MHz): $\delta = 4.65$ (1H, s, C_4OH), 3.7 (1H, s, C_1OH), 3.4 (1H, dd, H_2), 1.98 (3H, s, $COCH_3$), 1.90 (1H, dd, H_{3eq}), 1.8 (1H, dd, H_{6eq}), 1.65 (1H, dd, H_{5eq}), 1.40 (1H, hept., H_8), 1.30 (1H, dd, H_{3ax}), 1.24 (1H, dd, H_{6ax}), 1.20 (1H, dd, H_{5ax}), 1.1 (3H, s, CH_3), 0.83 (6H, d, $2CH_3$) ppm; ^{13}C-NMR (*DMSO*-d_6, 125 MHz): $\delta = 169.5$ (C_{11}), 75.0 (C_2), 71.1 (C_1), 69.2 (C_4), 35.8 (C_3), 34.0 (C_8), 32.5 (C_5), 30.7 (C_6), 23.8 (C_{12}), 21.2 (7), 17.0 (C_9 and C_{10}) ppm; MS: m/z (%) = 127 (75), 109 (82), 99 (34), 81 (46), 71 (59), 55 (37), 43 (100).

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