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Stereoselective *trans*-dihydroxylation of terpinen-4-ol: synthesis of some stereoisomers of *p*-menthane-1,2,4-triol

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Abstract—A high level of *trans*-stereoselectivity in the dihydroxylation of the homoallylic alcohol, terpinen-4-ol **1** (R = H) has been achieved. Thus, the enantiomeric triols **2a** and **2b** were separately synthesized in high yield and with high stereoselectivity by *trans*-dihydroxylation of the enantiomeric (4*S*)-terpinen-4-ol **1a** (R = H), and (4*R*)-terpinen-4-ol **1b** (R = H), respectively, using hydrogen peroxide as oxidant and V_2O_5 as catalyst. In the same way, the enantiomeric triols **3a** and **3b** were obtained from the enantiomeric (4*S*)-terpinen-4-yl tosylate **1a** (R = tosyl) and (4*R*)-terpinen-4-yl tosylate **1b** (R = tosyl), respectively.

The *trans*-dihydroxylation of an alkene may be achieved by its treatment with a suitable peroxycarboxylic acid, the reaction proceeding by initial *cis* addition to give an epoxide (oxirane), which undergoes acid-catalyzed ring scission in an *anti* manner through attack by the corresponding carboxylic acid, normally present in the reaction medium, to give a mixture of monoesters. Hydrolysis of the ester mixture then affords in most cases a mixture of diastereomeric 1,2-diols[1–3] with stereochemistry resulting from overall *trans*-addition to the alkene. Hydrogen peroxide can also oxidize alkenes to diols *trans*-dihydroxylation with the advantage that the free diols are obtained directly. Certain oxides, such as WO_3,[4,5] SeO_2[6] and V_2O_5[7] react with H_2O_2 to give unstable inorganic peroxy acids as the reactive species and catalyze the oxidation. The *trans*-stereochemistry of the addition suggests that the intermediates are epoxides, which readily undergo ring-opening under acidic conditions. In our research we investigated the stereoselectivity of the *trans*-dihydroxylation (via epoxidation) of the homoallylic alcohol, terpinen-4-ol and some its derivatives using H_2O_2 as oxidant and catalytic amounts of V_2O_5. We have found that vanadium is a very efficient catalyst in this reaction. V_2O_5 was reacted with H_2O_2 at 30°C for 20 min to give a red solution of the active epoxidizing agent peroxyvanadic acid.[8] This epoxidizing agent was then added to the reaction mixture. The reaction of terpinen-4-ol with H_2O_2/V^{5+} gave the triol in better yield and selectivity than with other transition-metal catalysts (e.g. Mo, W). Both of these methods were far better than the outcome when a peracid system was used (see Table 1). It is well known that the rate of epoxidation of allylic alcohols with hydroperoxides in the presence

Table 1. *trans*-Dihydroxylation of **1a** with different oxidants and catalysts[a]

Oxidant	Catalyst	Products[b] ratio **2a**:**3a**	% Yield	% d.e.	Method Ref.
CH_3COOH/H_2O_2		72:28	32	44	12b,c
$HCOOH/H_2O_2$		76:24	30	52	12b
CH_3CN/H_2O_2		80:20	52	60	
H_2O_2	$(NH_4)_5H_4[PMo_6V_6O_{40})$	75:25	25	50	
H_2O_2	Na_2WO_4	90:10	81	80	
H_2O_2	V_2O_5	97:3	87	94	

[a] All stoichiometric reactions were carried out in acetone at a concentration of 1.34 M in each reagent and 0.007 M of catalyst; temp. 55°C, time 3 h.

[b] Analyzed by GC–MS.

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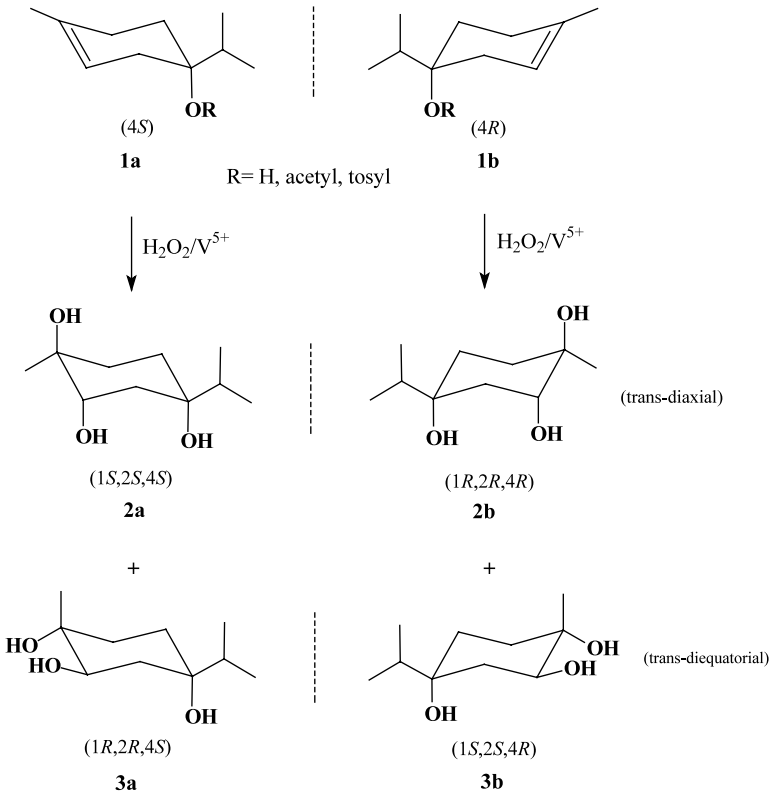
of a vanadium catalyst is more than 1000 times the rate of epoxidation of the parent alkene.[9] In the cyclohexene system the axial homoallylic hydroxyl group directs epoxidation by coordination with the oxidizing agent in the transition state.[10] *trans*-Dihydroxylation of each enantiomer **1a** and **1b**, (R = H) of terpinen-4-ol can furnish two diastereoisomers: **2a** (with *trans* diaxial orientation for new hydroxyl groups) and **3a** (with *trans* diequatorial orientation for new hydroxyl groups), **2b** and **3b**, respectively (see Scheme 1).

High yields and stereoselectivities have been observed in the *trans*-dihydroxylation of terpinen-4-ol: thus, (4*S*)-terpinen-4-ol[11] (**1a**, R = H) was easily reacted with H_2O_2/V^{5+} to give (1*S*,2*S*,4*S*)-*p*-menthane-1,2,4-triol **2a** in about 87% yield and 97% selectivity (see Table 2). The reaction was performed at 55°C in acetone, with stoichiometric amounts of alcohol and H_2O_2 at a concentration of 0.007 M V_2O_5 for 2 h and compound **2a** was obtained in 87% isolated yield. In the same manner, (4*R*)-terpinen-4-ol **1b** (R = H) stereospecifically gave the other enantiomer (1*R*,2*R*,4R)-*p*-menthane-1,2,4-triol **2b**. The literature[12] contains some reports concerning the synthesis of *p*-menthane-1,2,4-triols **2a** and **2b** using peracetic and performic acids, but in very low yield and selectivity (about 30% yield). In the conformational analysis the bulky isopropyl group at C(4) of the terpinen-4-ol is considered to be equatorial and the 4-hydroxyl is in the more readily accessible axial position. As shown in Scheme 2, the high stereoselectivity in the reaction of **1a** can be attributed to the strong coordination of the hydroxyl group to the highly reactive epoxidizing agent, followed by intramolecular oxygen transfer to the double bond of the homoallylic alcohol. The epoxidation is stereoselective and takes place from the face *cis* to hydroxyl, leading to (1*R*,2*S*,4*S*)-1,2-epoxy-*p*-menthane-4-ol (*cis*-epoxide) as the intermediate, which cannot be isolated and readily undergoes ring-opening under acidic conditions. It is well known that unsymmetrical epoxides tend to open under acidic conditions at the more substituted carbon, due to stabilization in the transition state of the partial

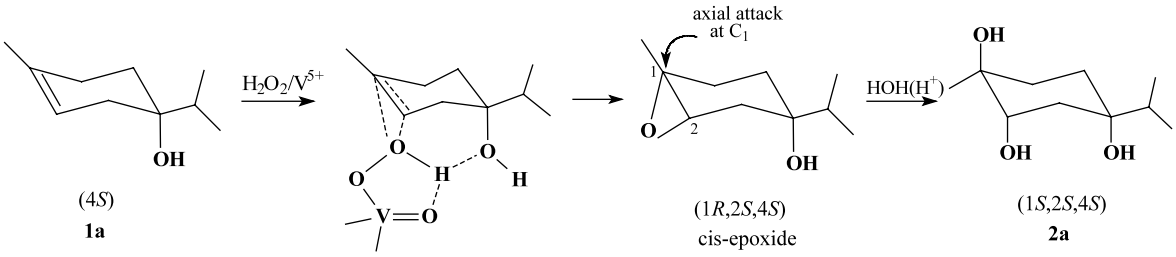


Scheme 1.

Table 2. Stereoselectivity in *trans*-dihydroxylation of **1a** with H_2O_2/V^{5+}

Starting materials[a]	Temp. (°C)	Time (h)	Products[b] ratio **2a**:**3a**	% Yield	% d.e.
1a (R = H)	55	2	97:3	87	94
1a (R = acetyl)	55	3	65:35	70	30
1a (R = tosyl)	55	3	20:80	84	60

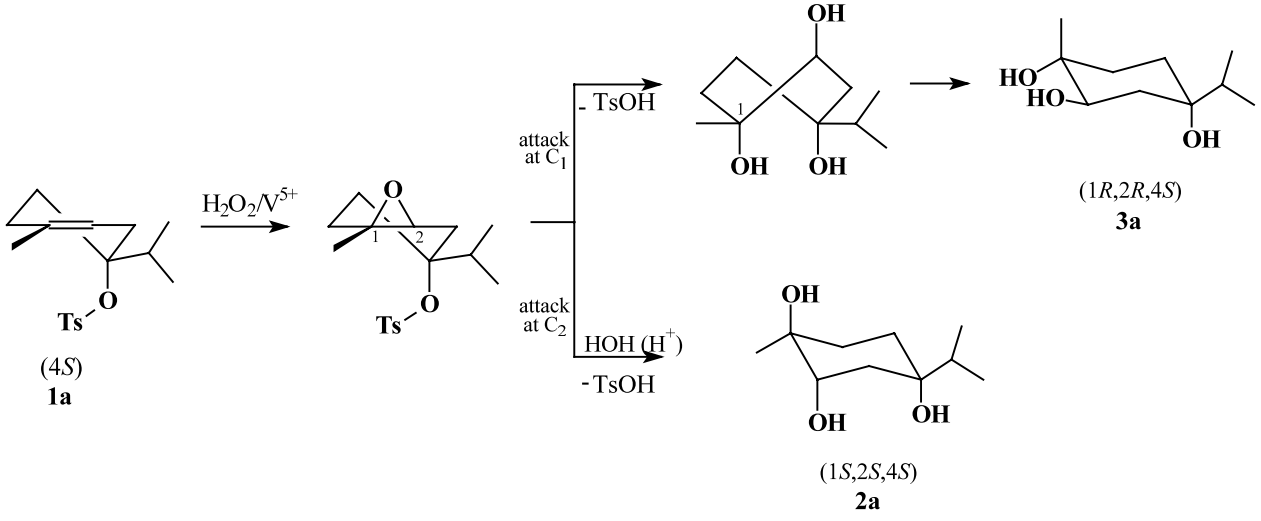
[a] Stoichiometric reactions were carried out in acetone at a concentration of 1.34 M in each reagent and 0.007 M of V_2O_5.
[b] Analyzed by GC–MS.



Scheme 2.

carbenium ion. Opening of cyclohexene oxides generally proceeds in such a fashion that the *trans*-diaxial rather than the *trans*-diequatorial product is obtained (Furst–Plattner rule).[13] In our case, axial-attack of the protonated epoxide at the more substituted carbon, C(1), by a water molecule (S_N2 mechanism) leads to triol **2a** where the two hydroxyl groups have *trans*-diaxial orientation. To confirm this hypothesis, the pure *cis*-epoxide (prepared by the Payne method)[14] was allowed to react under the same conditions with H_2O_2/V^{5+} and only the triol (1*S*,2*S*,4*S*)-**2a** was obtained in 90% yield. Also, we tried to selectively shield the β-face (the same part with OH) and also reducing the coordination with the epoxidizing agent by esterification of the hydroxyl group of terpinen-4-ol with acetyl and tosyl groups: low stereoselectivity was observed in the *trans*-dihydroxylation of terpinen-4-yl acetate and the reaction of (4*S*)-terpinen-4-yl acetate **1a** (R = Ac) with H_2O_2/V^{5+} yielded a mixture of esters, which on alkaline hydrolysis gave triols **2a** and **3a** in a ratio of 65:35 (see Table 2). It is probable that the poor coordination of the acetoxy group with the epoxidizing agent leads to a mixture of two epoxides (*cis* and *trans*), which further hydrolyze to the triols **2a** and **3a**. Very interesting results were obtained in the *trans*-dihydroxylation of terpinen-4-yl tosylate: in this case the other diastereoisomer **3a** was obtained in good yield and high selectivity (see Scheme 3).

trans-Dihydroxylation of the (4*S*)-terpinen-4-yl tosylate **1a** (R = tosyl) with H_2O_2/V^{5+} gave (1*R*,2*R*,4*S*)-*p*-menthane-1,2,4-triol **3a** in much better yield (69%) and diastereoselectivity (d.e. = 80%) than in the reaction of the acetate. The other diastereoisomer **2a** was also obtained as the minor product (15% yield and 20% diastereoselectivity). In the tosylate **1a** (R = tosyl), the tosyl group remains in the axial position (conformational energies for tosyl 0.50 kcal/mol and for isopropyl 2.21 kcal/mol)[13] and exerts steric hindrance on this face. Additionally, coordination with the epoxidizing agent is greatly diminished, so the other face is less hindered and epoxidation takes place *trans* to the tosyl group, leading to the stereoselective formation of a *trans*-epoxide as intermediate. Nucleophilic attack by water upon the protonated epoxide at the more substituted C(1) center gives rise to the diaxially disubstituted twist conformation of the cyclohexane ring which must then subsequently invert to the diequatorially disubstituted chair form of triol **3a**, with *trans*-diequatorial orientation of the new hydroxyl groups. During the reaction the tosyl group is lost. The reaction course for the formation of **2a** (ca. 15%) is best explained by attack of a water molecule at the less substituted C(2) center, but sterically hindered by the tosyl group from C(4), the ring conformation changes smoothly from the half-chair of the epoxide to the chair of triol **2a**. In the same manner, (4*R*)-terpinen-4-yl tosylate **1b**, (R = tosyl) stereospecifically gave the other enantiomer (1*S*,2*S*,4*R*)-*p*-menthane-1,2,4-triol **3b**.



Scheme 3.

Representative procedure for *trans*-dihydroxylation

To a stirred suspension of vanadium pentoxide (0.05 g, 0.27 mmol) in acetone (5 mL), hydrogen peroxide (1 mL) was dropwise added at 30°C for 10 min. After 15 min. V_2O_5 goes promptly into solution to form blood red peroxyvanadic acid. Acetone (20 mL) and (*S*)-(+)-terpinen-4-ol (7.4 g, 47 mmol, 97% purity, 62% e.e., $[\alpha]_D = +21$, $c = 1$) were then added to the reaction mixture. The mixture was heated to 55°C and hydrogen peroxide (4 mL of 35% solution, 47 mmol) was added at a rate of 0.05 mL/min. via syringe pump. After the addition was completed, the mixture was stirred at 55°C for an additional 1 h, the solvent then removed under reduced pressure and the residue diluted with water (30 mL). The white precipitate was filtered off, washed with cold water (10 mL) and dried to yield a crude product (7.6 g, 87% yield and 97% d.e., by GC–MS analysis). Recrystallization from acetone gave (1*S*,2*S*,4*S*)-*p*-menthane-1,2,4-triol **2a**, 6.8 g, 77% yield) as white needles with mp 173°C and $[\alpha]_D = +24$, ($c = 1.5$, EtOH) (lit.[12a] mp 174°C, $[\alpha]_D = +36$ (0.5, EtOH).[16]

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16. (1*R*,2*R*,4*R*)-*p*-Menthane-1,2,4-triol **2b**, $[\alpha]_D = -19.5$ ($c =$ 1.5 EtOH), lit.[12c], $[\alpha]_D = -21.7$ (0.38, EtOH) was obtained in pure form from (*R*)-(–)-terpinen-4-ol (97% purity, 58% e.e., $[\alpha]_D = -19$ ($c = 1$, EtOH). (*S*)-(+)-Terpinen-4-yl tosylate **1a**, (R = tosyl) $[\alpha]_D = +21$, ($c = 1.5$, EtOH) reacted in the same manner to give a mixture of triols **2a** and **3a**, (ratio 20:80 by GC–MS) which was chromatographed on silica gel (CH_2Cl_2–acetone, 3:1) to afford **2a**. Further elution gave (1*R*,2*R*,4*S*)-*p*-menthane-1,2,4-triol **3a** as colorless crystals. Recrystallization from acetone afforded colorless prisms of **3a** with mp 156°C and $[\alpha]_D = +6.5$ ($c = 1$, EtOH). ^{1}H NMR (DMSO-d_6, 300 MHz): 4.05 (1H, d, 7.5, C_2OH), 3.78 (1H, s, C_4OH), 3.55 (1H, s, C_1OH), 3.22 (1H, dd, 11, 4.8, H_2), 1.65 (1H, dd, 6.4, 4, H_{3eq}), 1.58 (1H, dd, 6.5, 4.5, H_{6eq}), 1.45 (1H, dd, 6.5, 4.5, H_{5eq}), 1.38 (1H, hept, 7, H_8), 1.29 (1H, dd, 6.2, 5, H_{3ax}), 1.25 (1H, dd, 14, 5.4, H_{6ax}), 1.20 (1H, dd, 14, 5.4, H_{5ax}), 1.08 (1H, s, CH_3), 0.83 (6H, d, 7, $2CH_3$). ^{13}C NMR: 76.4 (C_2), 74.6 (C_1), 71.1 (C_4), 31.8 (C_7), 37.2 (C_3), 35.4 (C_6), 30.2 (C_5), 27 (C_8), 21.1 (C_9), 20.8 (C_{10}). MS, *m*/*z* (%):127 (50), 117 (35), 109 (46), 55 (62), 43 (100), 41 (52). Anal. calcd for $C_{10}H_{20}O_3$: C, 63.83; H, 10.63; found: C, 63.52; H, 10.27%. (1*S*,2*S*,4*R*)-*p*-Menthane-1,2,4-triol **3b**, $[\alpha]_D =$ -5.5 ($c = 1.5$, EtOH) was obtained in pure form from (*R*)-(–)-terpinen-4-yl tosylate **1b**, R = tosyl, $[\alpha]_D = -17$ ($c = 1.3$, EtOH). Compounds **1a** and **1b** (R = acetyl, tosyl) were synthesized by literature procedures.[15a,b] All specific rotations were performed in EtOH at 20°C.