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TETRAHEDRON: *ASYMMETRY*

Surprising stereoselectivity in the Payne epoxidation of terpinen-4-ol with acetonitrile/hydrogen peroxide

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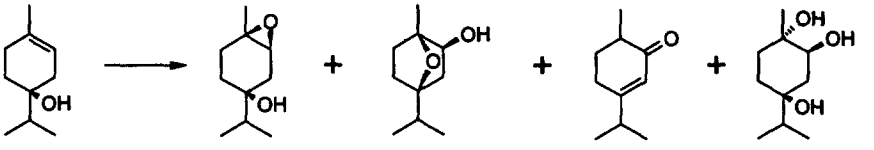
Abstract

A surprisingly high level of *cis*-stereoselectivity in the Payne epoxidation has been identified with the homoallylic alcohol, terpinen-4-ol. Very high efficiencies for hydrogen peroxide are realized under mild conditions. The necessity for peroxyimidic acid stabilization by solvent is replaced by coordination to the directing hydroxyl function, resulting in dramatically improved space yields at up to the one kilogram scale. © 1998 Elsevier Science Ltd. All rights reserved.

Many researchers have explored the stereoselective epoxidation of allylic alcohols using a wide variety of oxidants and/or catalysts.[1] Of these, the vanadium catalyzed epoxidation[2] with TBHP has become the benchmark for both stereoselectivity and economics. Much less effort has been directed toward functional group assisted reactions of homoallylic alcohols.[3] However, at low conversions the V/TBHP reagent has been reported to be successful[1a] and still provides the most attractive general methodology for epoxidation of homoallylic alcohols. In our search for a terpinen-4-ol **I** epoxidation system, we required the total absence of trace proton and/or Lewis acids during the epoxidation and in the product. The reasons were twofold. First, we wanted to minimize the potential for in situ rearrangement into *exo*-2-hydroxy-1,4-cineole **II** and carvenone **III** during preparation of the desired epoxide. Secondly, our major interest during this research was to optimize the acid catalyzed rearrangement of 1,2-epoxyterpinen-4-ol **IV** to *exo*-2-hydroxy-1,4-cineole **II**. This could only be done objectively if no traces of acids of any type were present in the intermediate 1,2-epoxyterpinen-4-ol **IV**. This obviated the use of both Sharpless and peracid based methods.



I IV II III V

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Despite many discussions citing the higher reactivity/lower selectivity of peroxycarboximidic acids relative to their peroxycarboxylic acid counterparts,[4] certain references in the carbohydrate literature suggested some degree of stereoselectivity in nitrile based systems.[4b,5] The results from reactions of Payne type reagents with these multi-oxygenated substrates implied that coordination of the active peroxycarboximidic epoxidizing agent with the allylic oxygen functionality did occur and appeared to direct epoxidation, albeit in most cases, to a limited extent. Even with an anticipated moderate selectivity for *cis* versus *trans* epoxidation on terpinen-4-ol due to high reactivity of the active epoxidation agent, we believed that the epoxide mixture could be separated by conventional means. We felt that the nitrile method would provide us with reasonable quantities of acid-free epoxide to utilize in rearrangement studies.

Table 1
Stereoselectivity of various epoxidation agents[7–9]

Oxidant	Catalyst	% Epoxide Yield	*cis:trans* Ratio	Method Reference
TBHP(1.1eq)	$VO(acac)_2$	90	>90:1	7
CH_3CO_3H	NaOAc	96	3.84	8
CH_3CN/H_2O_2(1.05 eq)	K_2CO_3	96	>90:1	
H_2O_2(1.33 eq)	Na_2WO_4	81	12.50	9

To our surprise (Table 1), reaction of terpinen-4-ol with nitrile/H_2O_2 gave the *cis*-epoxide in yield and selectivity better than with the vanadium catalyzed reaction using TBHP. Both of these methods were far better than the outcome when a buffered peracid system was used. Tungstate catalyzed reactions with hydrogen peroxide led to significant production of the 1,2,4-menthanetriol **V** as a major side-product (Table 1). As a result of our preliminary finding, we scoped the reaction further and found that a wide range of inorganic and organic bases could be used without much impact on the stereoselectivity (Table 2), although stronger bases gave rise to less efficient peroxide utilization. That the active epoxidizing agent coordinates to the hydroxyl is quite clear. In spite of the known high reactivity of peroxycarboximidic acids[4] and the need for its hydrogen bonded stabilization with methanol,[6] only one fifth the level of methanol solvent is necessary with terpinen-4-ol as compared to the well defined procedure for cyclooctene epoxidation utilizing this reagent combination. The reduction in solvent has the multiple benefit of increasing rate, enhancing selectivity to the *cis*-epoxide, and dramatically improving space yield.

Table 2
Impact of base on *cis*-epoxide stereoselectivity

T,°C.	Time, hrs.	Base	% Conversion	% Selectivity
65	1	$KHCO_3$	99.5	96
30	1.5	K_2CO_3	99	>95
60	1	K_2CO_3	93.7	>95
60	3	$NaHCO_3$	64	>95
60	1	$LiOH{\cdot}H_20$	76	>95
60	2	$Mg(OH)_2$	33.1	>95

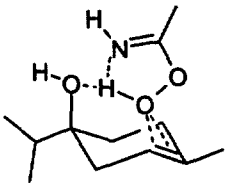
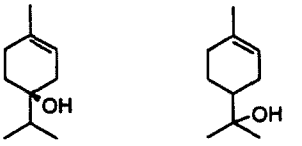


Figure 1.

Table 3
Effect of hydroxyl proximity to olefin

Olefin	Conversion	Time, hours	cis:trans ratio
I	97%	1	>90:1
VI	74%	3.5	7:01
0.5eq I +0.5eq VI	97% for I 3% for VI	1	—

Due to the presence of the bulky C-4 isopropyl group in terpinen-4-ol, the most energetically favorable conformation of the cyclohexene ring places the isopropyl group equatorial, which allows the 4-hydroxyl to be in the more readily accessible axial position. The hydroxyl's cross-ring proximity to the olefin creates an environment that strongly favors intramolecular transfer of the highly reactive peroxycarboximidic acid (Fig. 1). To further explore the hydroxyl impact of directing epoxidation, we compared the terpinen-4-ol results with those of α-terpineol (VI), where the hydroxyl is one carbon–carbon bond further removed from proximity to the olefin (Table 3).



I VI

We saw a relative reduction both in *cis*-selectivity and in hydrogen peroxide usage efficiency. But surprisingly, we still saw higher levels of *cis*-epoxide than that found with peracid epoxidation of terpinen-4-ol. In competitive rate experiments between terpinen-4-ol and α-terpineol (Table 3, entry 3), hydroxyl proximity had a profound impact on reaction rate. There is no reason to suspect that the peroxy coordinates less effectively to α-terpineol than terpinen-4-ol. This leads us to conclude that other side reactions of the peroxycarboximidic acid compete with epoxidation due to the greater distance between olefin and oxidant. This would include intermolecular transfer of coordinated peroxycarboximidic acid to adjacent α-terpineol molecules which would give rise to lower *cis*-epoxide selectivity. This also increases the likelihood that hydrogen peroxide will react with peroxycarboximidic acid to generate acetamide and singlet oxygen.[4a]

This epoxidation has been carried out to prepare greater than one kilogram quantities of epoxide **IV**. The reaction works equally well on both *R* and *S* forms of terpinen-4-ol, as expected. The reagents are much cheaper and more readily available than existing epoxidation agents. Efficiencies on both hydrogen peroxide and nitrile are excellent. As a consequence of this work, we identified not only a viable commercial process with significant reductions in cost relative to V/TBHP methodology, we also obtained a high space yielding reaction and an easily purified epoxide with only acetamide as a by-product.[10] Further, the acetamide was of a purity which evoked interest from commercial manufacturers

of this product. Due to this method's simplicity, non-acid nature, and excellent *cis* stereoselectivity with cycloalkenols, it should be re-discovered as an integral part of the chemist's epoxidation arsenal.

1. Typical preparation

(+)-Terpinen-4-ol (97% purity, 11.3 g, 73 mmol, 57% e.e.), acetonitrile (5.5 g, 134 mmol), and potassium bicarbonate (1.3 g) were added to methanol (10 mL). The mixture was heated to 60–65°C. Hydrogen peroxide (7.9 ml of 30% solution, 82 mmol) was added at a rate of 0.15 mL/min via syringe pump. Fifteen minutes after the addition was completed, the mixture was cooled. The methanol solvent and residual acetonitrile were then evaporated. The remaining organics were dissolved in dichloromethane and washed with a brine solution. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and evaporated to yield a crude product (12.23 g) containing 95.4 wt% (+)-*cis*-1,2-epoxyterpinen-4-ol (57% e.e.) by internal standard GC analysis. The *cis:trans* epoxide ratio was greater than 90:1.

2. Additional data

Epoxide was resolved with a Chiraldex G-TA column (30 m×0.25 mm i.d.); the sample was run through the column at a constant temperature of 90°C; injector temperature=250°C; detector temperature=250°C; head pressure=3 kg/cm; carrier gas=He; total run time=approx. 20 min.

Column and conditions used to resolve starting terpinen-4-ol; column=Cyclodex-B (30 m×0.25 mm i.d., 0.32 μm film); initial temperature=40°C; initial time=5 min; rate=0.5°C/min; injector temperature=220°C; detector temperature=240°C; carrier gas=helium; total time for method=135 min.

Optical rotation measurement specifications: for (+)-*cis*-1,2-epoxyterpin-4-ol: cell path=10 cm; concentration=1.01 g/100 ml; temperature=20°C; α^1=0.088; γ=589 nm; $[\alpha]_{589}^{20}$=+8.73. For (+)-terpinen-4-ol: cell path=10 cm; concentration=1.0563 g/100 ml; temperature=20°C; α^1=0.202; γ=589 nm; $[\alpha]_{589}^{20}$=+19.17.

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