

The Regio- and Stereo-controlled Synthesis of *cis-p*-Menth-3-ene-1,2-diol by means of a 1,2,4-Trioxane Intermediate

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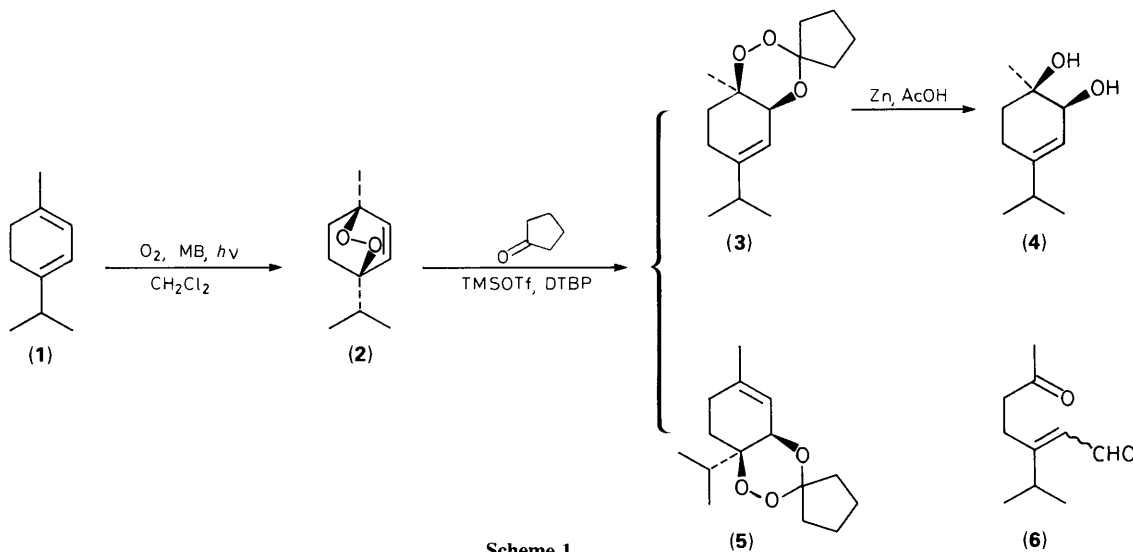
A concise synthesis of (\pm)-*cis-p*-menth-3-ene-1,2-diol from α -terpinene is described which relies on the regio- and stereo-controlled construction of a 1,2,4-trioxane intermediate; structures proposed for two aroma constituents of *Ferula jaeschkeana* oil are revised.

1,2,4-Trioxanes, like certain cyclic peroxides,¹ have potential in organic synthesis.² So far they have been virtually unexploited owing to their limited availability and the belief that they might be unstable. Now that 1,2,4-trioxanes can be prepared conveniently from a variety of electron-rich alkenes and dienes *via* hydroperoxides, 1,2-dioxetanes, and endoperoxides,³ they provide an opportunity for further chemical elaboration. Preliminary studies have shown that the 1,2,4-trioxane ring is sufficiently robust to undergo chemical reaction,⁴ and can also be deployed as an entity of masked, dual functionality.⁵

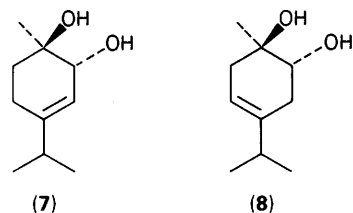
We now describe an application of the aforementioned

chemistry to the synthesis of *cis-p*-menth-3-ene-1,2-diol (**4**), the structure proposed for a recently isolated constituent of the essential oil of the rhizomes of *Ferula jaeschkeana*.⁶ This plant is abundant in the north-west Himalayas and its oil, which contains many oxygenated monoterpenoids, is of importance in Indian perfumery. Interestingly, the diol (**4**) is thought to be one of the components responsible for the exotic aroma of the oil.⁷

Our scheme starts with the commercially available α -terpinene (**1**), which was converted to ascaridole (**2**) by methylene blue (MB)-sensitized photo-oxygenation⁸ in CH_2Cl_2 at -10°C for 14 h. Under these conditions (**2**) was obtained in



Scheme 1



86% yield after chromatography on silica gel. Next, its reaction with cyclopentanone was examined under a variety of conditions. In all instances, incorporation of the ketone function into the ascaridole ring occurred to produce a pair of *cis*-fused 1,2,4-trioxanes (3) and (5). However, the major component[†] was always the angular methyl derivative (3), although variable amounts of its regioisomer (5) and the keto aldehydes (6) were also formed,⁹ depending on the catalyst and temperature (Scheme 1). The highest regioselectivity and efficiency [(3):(5) = 17:1; combined yield 85%] were obtained by allowing (2) to react with 6 mol. equiv. of cyclopentanone in the presence of trimethylsilyl trifluoromethanesulphonate (TMSOTf, 0.25 mol. equiv.) and 2,6-di-*t*-butylpyridine (DTBP, 0.14 mol. equiv.) in CH₂Cl₂ at -78 to -30 °C for 2 h. The isomeric aldehydic byproducts (6) were also formed in ~10% yield together with another, as yet unidentified, minor product. Work-up of the resulting mixture with Et₃N followed by chromatography (silica gel; CH₂Cl₂) afforded pure (3) in 77% yield. Treatment of (3) with zinc powder and glacial acetic acid-ether (1:1) at 0 °C for 15 min gave the *cis*-1,2-diol (4) in 96% yield after chromatography over silica gel.⁵ Comparison of the spectra (360 MHz ¹H and 50 MHz ¹³C NMR) of the resulting racemic (4) with those reported for the purported natural product (4) showed them to be different. Nonetheless, the correctness of our structure (4) was confirmed since its ¹H- and ¹³C-NMR spectra were identical with those of racemic and optically pure samples of (4) prepared chemically¹⁰ and by microbial transformation,¹¹ respectively. We then realized that the spectral properties of the natural product depicted as (4) correspond with those described previously^{10,11} for *trans-p*-menth-3-ene-1,2-diol (7). Moreover, the ¹H- and ¹³C-NMR data reported for another constituent of *F. jaeschkeana* oil, which was previously assigned structure (8) and which also imparts an exotic aroma,^{6,7} are in perfect agreement with structure (4).[‡] In other words, despite these reassignments of structure, our original objective of synthesizing an aroma constituent of *Ferula* oil has been achieved.

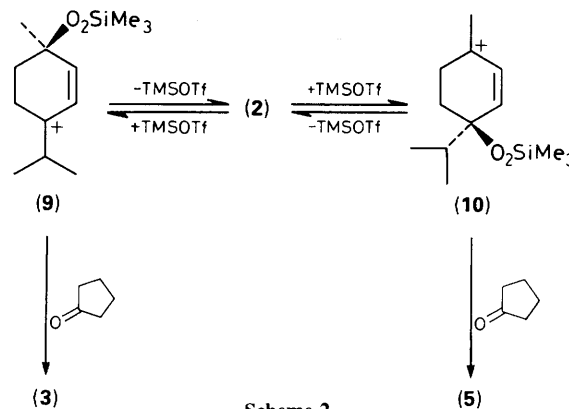
The mechanism by which (2) is converted into (3) and (5) requires comment. Silylation-desilylation undoubtedly generates the isomeric peroxy allylic cations (9) and (10) which are in fast equilibrium through (2).¹² Capture of either by cyclopentanone to produce the *cis*-fused trioxane ring is probably dictated by steric considerations, thereby accounting for the preferred formation of (3) over (5) (Scheme 2).

In conclusion, the synthesis is easy to perform and novel in conception. It demonstrates how an unsymmetrical 1,3-diene can be functionalized in a regio- and stereo-controlled manner.¹³ Formally, a 1,4-endoperoxide is converted to an allylic *cis*-1,2-diol¹⁴ through the agency of the selective formation and reduction of a *cis*-fused 1,2,4-trioxane intermediate.

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[†] New trioxanes (3) and (5) were characterized by their ¹H- and ¹³C-NMR and IR spectra and by elemental analyses.

[‡] Our structural assignments refer to relative configurations.



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