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TEMPLATE-DIRECTED EPOXIDATION OF FARNESOL AND OF GERANYLGERANIOL AS CONFORMATIONAL PROBES

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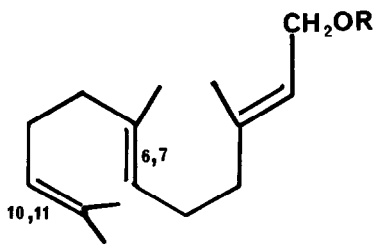
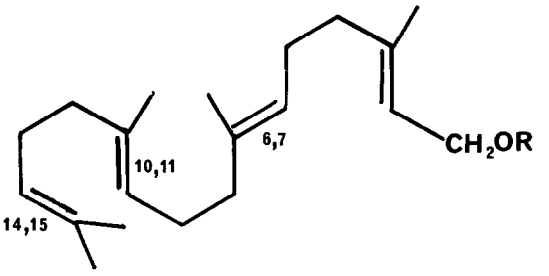
We have described the use of a template to direct the epoxidation of a steroidal diene at a particular double bond, and with stereochemical control.[1] In this process the substrate olefinic alcohol is converted to an ester of a carboxylic acid bearing a phenyldimethylcarbinol group. The hydroxyl group of this template then binds Mo, and directs the Mo catalyzed epoxidation by t-butyl hydroperoxide to a distant double bond which is geometrically accessible to the bound metal. This epoxidation proved to depend very strictly on the precise geometry of the template, since both template and steroid substrate were rigid molecules.

Such selectivity is reminiscent of that we have seen for attack on steroid C-H bonds by rigid attached photoexcited benzophenone groups[2], or aryl iodide templates in steroid halogenations.[3] With these reactions, the use of flexible substrates such as long chain alkanols led to a distribution of reaction products.[4,5] Such a distribution is of no real synthetic use, but furnishes evidence about the conformations of flexible molecules in solution.[5] We now wish to report the application of our template-directed epoxidation reaction to flexible polyenes, specifically all trans farnesol (1)[6] and all trans geranylgeraniol (2)[7]. The results reveal some remarkable features of the conformational preferences of our molecules.

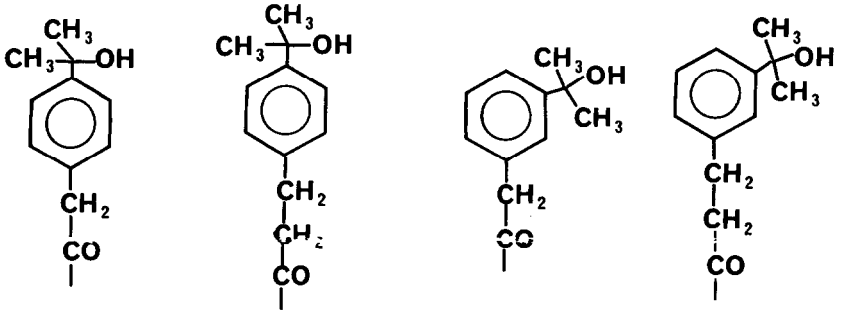
The substrates were converted to esters of template molecules by reaction with an appropriate acetophenone carboxylic acid chloride, then reaction of the resulting ketoesters with CH_3MgI at -35° to afford the final products 3, 4, 5, 6, 7 and 8.



1: R = H
3: R = W
4: R = X
5: R = Y
6: R = Z



2: R = H
7: R = X
8: R = Z



Esters 3-8 were dissolved in benzene and treated with 0.03 equiv. of $Mo(CO)_6$ and 2.0 equiv. of t-butyl hydroperoxide at reflux, as with the steroid examples.[1] In a control reaction compound 4 was allowed to compete with an equal concentration of geranyl benzoate. At a concentration for each of 25 mM, 38% of 4 was epoxidized along with 50% of geranyl benzoate, while at 1.0 mM 43% of 4 was epoxidized, but only 8% of geranyl benzoate. Such controls with 6 also showed negligible attack on geranyl benzoate at 1.0 mM. Thus our reactions are intramolecular at the operating concentration of 1.0 mM. This is also shown in the Table by the fact that cutting the concentration of 6 to 0.5 mM does not affect the product distribution, as it would if there were competing intra- and intermolecular processes yielding different product distributions.

The products of the epoxidation reactions were saponified and acetylated, and the resulting epoxyacetate mixture was cleaved with ethereal periodic acid Controls with authentic geranyl acetate 2,3 epoxide and geranyl acetate 6,7 epoxide established the quantitative formation of 6-methylhept-5-en-2-one and of acetone, respectively. The analysis was by vpc after addition of quantitative reference standards with nearby retention times.

Application of this analytical sequence to the reaction products from 3-8 gave the product distribution data listed in the Table. No significant amount of 2,3 epoxide was ever detected from these intramolecular processes.

Product Distribution from Intramolecular Epoxidation

Substrate[a]	% 6,7 Epoxide	% 10,11 Epoxide	% 14,15 Epoxide
3	43	57	—
4	40	60	—
5	25	75	—
6[b]	17	83	—
7	27	22	51
8	11	36	53

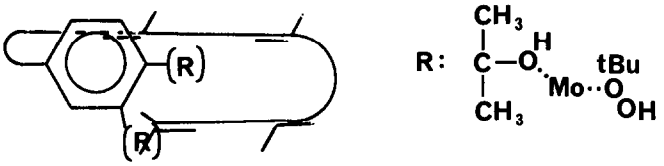
a. At 1.0 mM. b. Identical data also at 0.5 mM.

Molecular models show that if the chain were in an extended conformation the epoxidation of e.g. 3 should have occurred at the 6,7 bond. The large amount of attack at 10,11 indicates that the chain is folded back. In fact in every case there is a preferences for attack at the end of the chain, even in cases such as 7 and 8 in which extensive folding must be required. We have also seen a preference for functionalization near the end of a long chain in our previous benzophenone and directed halogenation studies.[5]

In our steroid halogenation studies[3] we found that a p-iodophenylacetic acid template was equivalent to m-iodophenylpropionic acid; i.e., the shift from p to m, which shortens a template, could be compensated by an additional CH_2 group. It is apparent from the results with 3 and 6 that no such effect operates here. Instead, the m templates in 5, 6, and 8 consistently direct

epoxidation further out, even though they are shorter than the p templates in 3, 4, and 7. The result with 6 at additional dilution shows that no intermolecular reaction is contributing to these results.[8]

The simplest conformation consistent with the data in the Table is one in which the terpene chain is U-shaped, and the template folds back along one leg of the U. If the template is m-attached the bound metal-peroxide may more easily reach the other leg of the U; this contains the topologically more remote 10,11 double bond, although the U shape makes it geometrically close. More complex pictures can also be involved. In any case our results show that even in a benzene solvent the terpene chain is extensively coiled and folded.



Acknowledgements

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8. Intermolecular epoxidation of farnesyl acetate, at 25 mM, in the presence of 1 equiv. of phenyldimethylcarbinol affords 32% of the 6,7 epoxide and 68% of the 10,11 epoxide.