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SELECTIVE OXIDATION OF ALLYLIC METHYLS IN MEDIUM RING COMPOUNDS

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Summary: Allylic methyls in medium ring compounds were selectively oxidized to primary alcohols and αβ-unsaturated aldehydes by means of t-butylhydroperoxide and selenium dioxide supported on silica gel.

During our work on the conformational studies of medium ring sesquiterpenes[1] humulene (**1**) and caryophyllene (**4**) we faced a problem to oxidize an allylic methyl group selectively to the corresponding primary allylic alcohol. Oxidation with selenium dioxide in the usual manner proved unsuccessful. The main difficulties associated with these reactions included epoxidations of the double bonds.[2] Some success was achieved with the recently reported method[3] using selenium dioxide together with t-butylhydroperoxide but yields were poor and the reactions were accompanied by undesired epoxidations of double bonds and formation of t-butyl ethers and a complex mixture of oxidation products.[4] We wish to report here a modification of this method to cause the selective oxidation of allylic methyls in medium ring compounds in high yields and quite free from undesired side reactions.

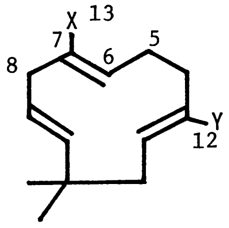
The selectivity and moderation of reactivity of the organic reactions in solid matrix[6] are well known. We found that when selenium dioxide supported on silica gel[7] was used with t-butylhydroperoxide in hexane or dichloromethane as the solvent, only oxidations were observed at allylic methyls to afford the corresponding allylic primary alcohols and α,β-unsaturated aldehydes. Probably when selenium dioxide is supported on silica gel, it aquires selectivity to attack only the methyl groups which are maximum exposed or least hindered, whereas it does not attack the other allylic positions in the medium ring compounds.

The general oxidation procedure utilized in this study involves the stirring of selenium dioxide supported on silica gel[7] (5%, 0.5 g) in dichloromethane or hexane (5 ml) with t-butylhydroperoxide (70%, 3 eq w.r.t substrate) for 15 min at room temperature under argon. This was followed by the dropwise addition of 6,7-diacetoxybicyclohumulene (**16**, 200 mg) in the same solvent (1 ml). After 3 h at room temperature, the reaction mixture was filtered and the residue was washed with dichloromethane. The filtrate and washings were combined, washed with water, brine and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave 6,10-diacetoxybicyclohumulen-12-ol (**17**, 80%) and unchanged substrate (**16**, 20%).

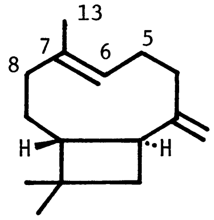
Table

substrate	1		4	6	7	9	11		14	16	18	20	21
weight of substrate (g)	2		1.5	0.5	1	0.3	1		0.5	0.2	0.2	0.5	0.5
impregnated[7)] silica gel (g)	8		2	5	3	0.9	4		1.5	0.5	1.5	5	5
reaction time ‡ (h)	2		0.5	12	2	1	4		3	3	3	12	12
product#	2†	3†	5†,§		8†	10†	12†	13†	15	17§	19§		
yield (%)	30¶	70¶	90¶		70¶	100¶	40¶	60¶	60¶	80	60		

‡During these reaction periods, the major products were allylic alcohols. #All products were characterized spectrally and by combusion analysis. †Geometry of the double bond in allylic alcohol was determined by an analogy with the stereochemistry in reduction of the epoxide of substrate into original olefin. See text. §Configuration of the double bond of allylic alcohol was determined by ^1H NMR. An olefinic proton of trans compound shows double doublet while cis exhibits triplet. ¶Yield is based on total alcohol content obtained after reduction of the crude reaction product with sodium borohydride in methanol at 0 °C.



1 X = Y = CH_3
2 X = CH_2OH, Y = CH_3
3 X = Y = CH_2OH



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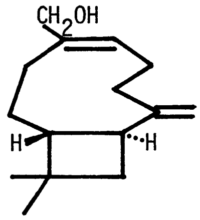

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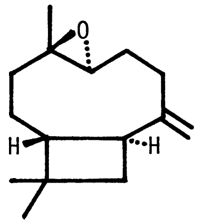

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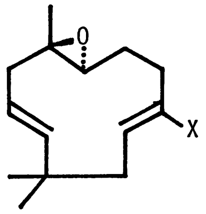

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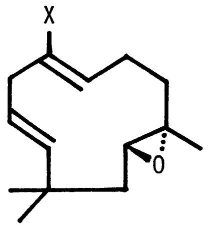
8 X = CH_2OH



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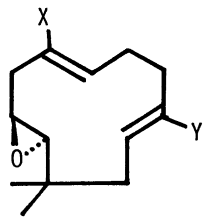
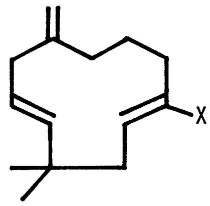


11 X = Y = CH_3
12 X = CH_2OH, Y = CH_3
13 X = Y = CH_2OH



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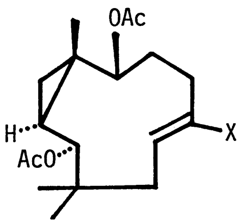
15 X = CH_2OH



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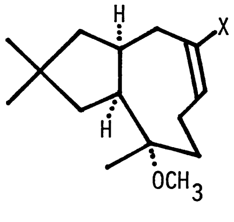
17 X = CH_2OH



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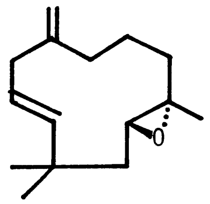

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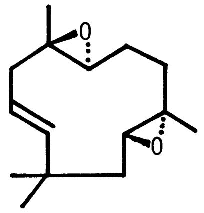

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All the oxidations proceeded smoothly and were almost complete in a period of 2-4 h with formation of alcohols which were sometimes accompanied by α,β-unsaturated aldehydes. When the reaction gave the aldehyde, it was converted to the allylic alcohol by reduction of the crude product with sodium borohydride. The course of the reaction and yields are independent of the solvents used. It is interesting to note that the compounds (**6**, **20** and **21**) remained unchanged under these reaction conditions regardless of their keeping allylic methylene groups. Geometry of the double bond which pariticipated with the reaction was ketp or changed during the oxidation to yield an allylic alcohol which has a stable configuration about the double bond. As a *cis*-cyclooctene **18** was more stable than a trans-isomer, oxidation product **19** was a *cis*-compound, and caryophyllene (**4**) (trans-cyclononene derivative) gave *cis*-caryophyllen-13-ol (**5**) for *cis* was more stable than *trans*-isomer.[8] These observations would be explained by an already proposed mechanism.[10] A species formed by addition of selenium will take more stable conformation around the bond which has originally been the double bond in the substrate to lead a stable allylic alcohol concerning geometry of the double bond.[11] In view of the results listed in Table, the method should prove useful, especiallly because of its specificity and ease of work up.

References

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2) As double bonds of **1** and **4** are strained (dihedral angle 5-6-7-8 = 167.6° for **1**[1a] and 166.5° for **4**[1b]), they are rather susceptible to oxidation to give epoxides. For humulene derivatives: P. S. Kalsi, K. S. Kumar, M. S. Wadia, Chem., Ind., **1971**, 31; G. S. Aulakh, M. S. Wadia, P. S. Kalsi, *ibid*, **1970**, 802.

3) M. A. Umbreit and K. B. Sharpless, J. Am. Chem. Soc., **99**, 5526 (1977).

4) After our work was completed an oxidation of germacranolide under Sharpless conditions[3] was reported.[5] In our experiment under these conditions humulene (**1**) gave humulen-13-ol (**12**) (20%), 12-hydroxyhumulen-13-al (10%), and a mixture of byproducts including an epoxide, and caryophyllene (**4**) yielded a complex mixture of oxidation products instead of caryophyllen-13-ol. Sharpless described about some difficulties for application of his method to medium and small sized cyclic olefin. K. B. Sharpless, T. R. Verhoeven, Aldrichimica Acta, **12**, 63 (1979).

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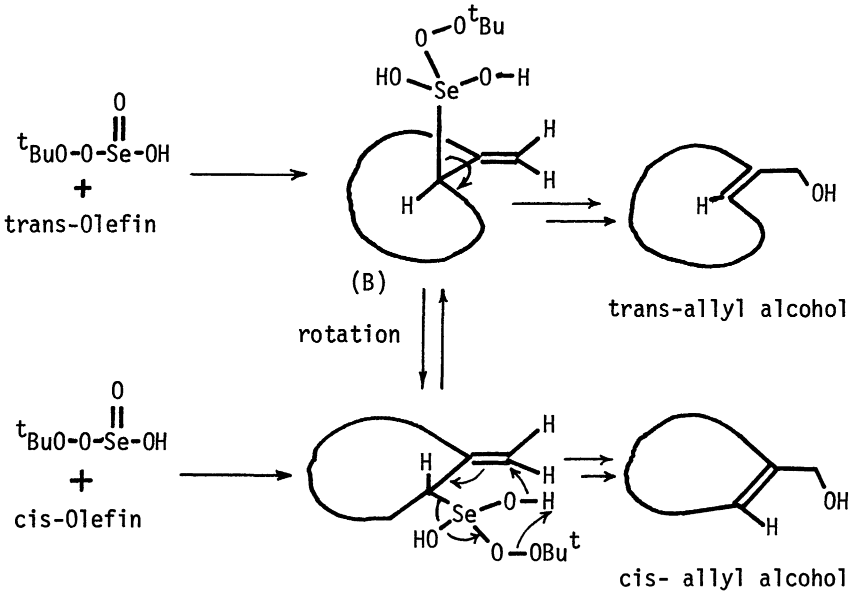
7) Selenium dioxide (5 g) was dissolved in minimum quantity of distilled water and the volume was raised to 150 ml by the addition of methanol to get a clear solution. To this solution was suspended silica gel (100 g, Wako C-200) and a fine slurry was obtained. Methanol-water mixture was evaporated under reduced pressure to get a free flowing powder. This was termed as silica gel impregnated with selenium dioxide.

8) The situation is very similar to the reduction of an epoxide with $TiCl_3$-$LiAlH_4$ 9) to give its original olefin. Epoxide of **18** afforded original *cis* olefin while caryophyllene oxide gave a mixture of *cis* and *trans* (4:1) caryophyllene.

9) J. E. McMurry, M. P. Fleming, J. Org. Chem. **40**, 2555 (1975).

10) N. Rabjohn, Org. React. **24**, 261 (1976). Haruna 5) extended the mechanism to fit with Sharpless conditions.

11) This step corresponds to the stage of "rotation of allylseleninic ester (B)" figured by Haruna et al. 5)



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