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Selenium dioxide *E*-methyl oxidation of suitably protected geranyl derivatives—synthesis of farnesyl mimics

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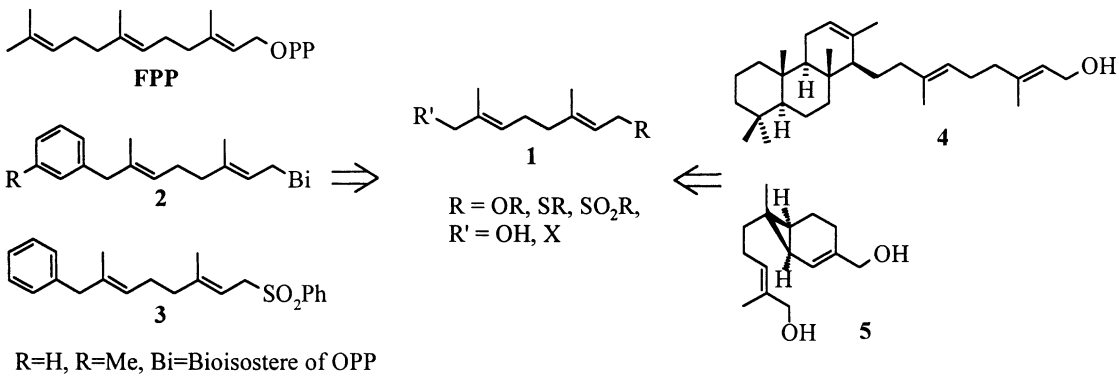
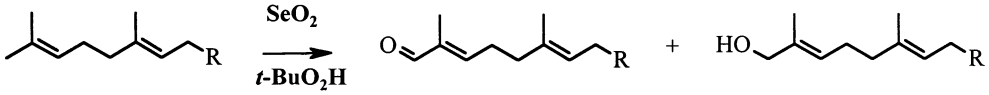
Abstract—Difunctional allylic terpenes are important synthetic building blocks. Functionalisation of protected geranyl derivatives by SeO_2 provides a convenient route to such compounds. The effect of the geranyl protecting group on the oxidation of the terminal *E*-methyl group was systematically investigated. © 2001 Elsevier Science Ltd. All rights reserved.

The synthesis and biological evaluation of mimics of farnesyl diphosphate (FPP) has attracted a considerable amount of attention over the last 10 years, mainly as FPP is used as a substrate by both *Squalene synthase*[1] (SSase) and *Farnesyl-protein transferase*[2,3] (FPTase). Wiemer identified that di-functional terpene derivatives **1** (Scheme 1) are useful intermediates towards the synthesis of a range of farnesyl mimics (**2**).[4] Intermediates, such as **1**, have also been utilised in the synthesis of a large number of natural products.[5] Notable examples include (±)-tricyclohexaprenol[6] **4** and *dl*-Sirenin[7] **5** by Corey.

The synthesis of di-functionalised derivatives **1** are synthetically commonly approached via SeO_2 oxidation of



Scheme 1.



R = OR', SO_2R" or SR"

Scheme 2.

Keywords: allylic oxidation; selenium dioxide; protecting group.

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protected geranyl derivatives (Scheme 2). A well-established oxidation process, we herein report the effect of the allylic protecting group on the '*E*-methyl selective' allylic oxidation[8] of suitably protected/derivatised geranyl analogues.

Various derivatives of commercially available *E*-geraniol (R = OAc **6**, O_2CPh **7**, O_2CCH_2Cl **8**, OMe **9**, OTBDMS **10**, OTBDPS **11**, OBn **12**, OTHP **13**, SO_2Ph **14** and SO_2Me **15**) were synthesised by standard procedures.

In our first oxidation of geranyl acetate **6**, under Sharpless conditions (0.5 equiv. SeO_2 and 2 equiv. *t*-BuO_2H), the reaction ran to completion after 8 hours, although we noted that selenious by-products[9] were formed and present in small quantities even after purification by distillation or chromatography. We also found that trace amounts of selenium were still present after several synthetic steps after the oxidation reaction. As these types of compounds may be used as biological probes or inhibitors, we considered it crucial that these selenious by-products were minimised, allowing the purification of 'selenium-free' products. For the oxidation of **6**, the use of lower molar quantities of SeO_2, typically 1–2 mol%, greatly reduced the selenium by-products, although in our hands these reactions failed to proceed to completion.[5b,10] A compromise of 5 mol% SeO_2 and 3.6 equiv. *t*-BuO_2H led to complete consumption of the acetate **6** starting material, giving the oxidised products **16** and **17** in 52% yield.[11] Reduction of the crude mixture of **16** and **17** using $NaBH_4$ gave pure **17** in 49% yield.[12]

Yields from the oxidation of various geranyl analogues are quite varied and we sought an explanation for this. Wiemer[4a] reported low yields (15–40%) in the allylic oxidation of **11**, **12** and **13**, which are all geranyl ethers. In order to see whether there was a trend, i.e. a contributing effect of the protecting group on the oxidation process, the allylic oxidation of all the geranyl analogues (**7**–**15**) was performed using the modified Sharpless procedure[11] (Table 1).

It was immediately noticeable that the overall oxidation yields of the esters (**16**–**21**) were significantly higher (20–30% higher) than the ethers (**22**–**31**). This led us to believe that the carbonyl function might be involved in stabilising, through hydrogen bonding, the generally accepted six-electron cyclic transition state[13] (I, Fig. 1), whereas the protected ethers weakly possess this ability (compare II and III, Fig. 1). Marshall proposed that oxidation of sulphone **14** was more selective than the analogous oxidation of acetate **6**.[14] This is indeed the

Table 1.

Entry	R	Compound[a]	Yield[b] (%)		Total yield[c] (%)
			Aldehyde	Alcohol	
1	$OCOCH_3$	**16** and **17**	9 (11)	43 (53)	49, **59**
2	$OCOCH_2Cl$	**18** and **19**	0	43[e]	43
3	OCOPh	**20** and **21**	(18)	(38)	54
4	OMe[d]	**22** and **23**	Nd	Nd	19
5	OTBDMS[e]	**24** and **25**	(10)	(26)	31
6	OTBDPS[d]	**26** and **27**	Nd	Nd	28
7	OCH_2Ph[e]	**28** and **29**	22	27	24, **44**
8	OTHP[d]	**30** and **31**	9	31	33
9	SO_2Ph	**32** and **33**	86	6	89, **90**
10	SO_2Me	**34** and **35**	91	0	82
11	SPh[d,f]	**37** and **38**	Nd	Nd	38

[a] Compound numbering; aldehyde and alcohol, respectively.
[b] GC yields of aldehyde and alcohol in parenthesis.
[c] Isolated yields after $NaBH_4$ reduction and purification by distillation or chromatography, selected cases are averages of several runs including the best yield in bold.
[d] The aldehyde/alcohol ratio was not determined (nd).
[e] Similar selenium by-products observed by GC and ^1H NMR, see Ref. 9.
[f] Ref. 5a, 20 mol% SeO_2, 3.6 equiv. *t*-BuO_2H, followed by $LiAlH_4$ reduction.

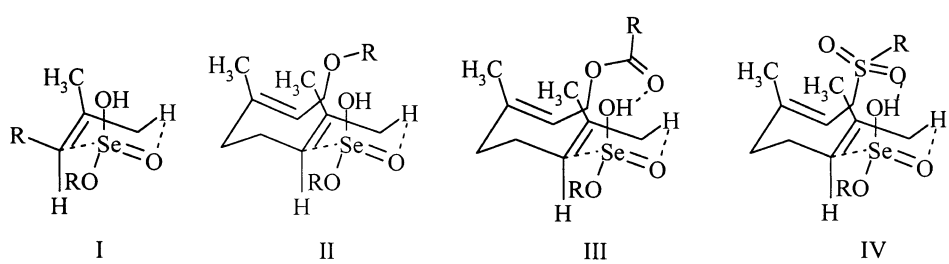
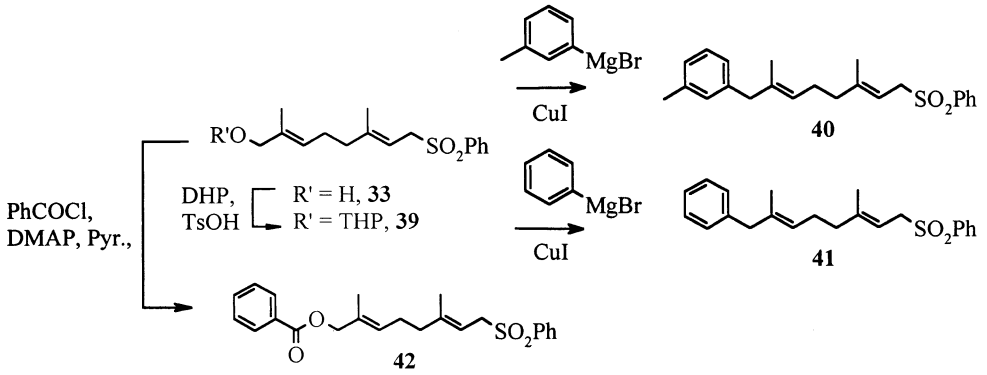


Figure 1.



Scheme 3.

case and we were able to produce **33** in 90% yield. This lends credibility to the idea that the oxygens, in this case of the S=O function, are able to hydrogen bond within the transition state (IV, Fig. 1).

Oxidation of methylsulphone **15** proceeded equally well in 82% yield. Interestingly, the oxidation of thiophenyl geranyl derivative (R = SPh, **36**) is reported to give significantly lower yields of the alcohol product **38**. The results presented here therefore demonstrate that the C=O and S=O functions might be involved in stabilising the intermediate transition state structures.

As we were ultimately interested in the synthesis of farnesyl mimics, it was rationalised that sulphone **33** would serve as an ideal template in which various terminal isoprene mimics could be introduced. It has also been reported that similar SO_2R moieties can act as a biological mimic of the diphosphate group.[15] The protected sulphone derivative **39** was synthesised from the corresponding alcohol **33** in quantitative yield (Scheme 3). To our delight we were able to displace the allylic tetrahydropyranyl moiety to give **40** and **41** in an S_N2 fashion using aryl Gringard reagents in the presence of copper(I)iodide (CuI) in satisfactory yields (40–50%), using the conditions described by Wiemer.[4a–c] Benzoylation of **33** to give **42** in 57% yield was also possible using standard conditions.

In conclusion, the oxidation of suitably functionalised and protected geranyl derivatives with the SeO_2/$^tBuO_2H$ system, originally developed by Sharpless,[8] has been systematically investigated. The chosen protecting group clearly influences the oxidation process. Further studies on the oxidation of smaller tri-substituted isoprenes and the biological activities of the farnesol analogues will be reported in due course.

Acknowledgements

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11. Modified Sharpless procedure (taken from Ref. 8): A stirred mixture containing *t*-BuO_2H (8.27 g, 3.6 equiv.), SeO_2 (0.14 g, 5 mol%) and 4-hydroxybenzoic acid (0.35 g, 10mol%) in CH_2Cl_2 (70mL) was allowed to stir for 1 hour, then compound **6** (5.0 g, 1 equiv.) in CH_2Cl_2 (20 mL) was added dropwise at 0°C and stirred overnight. The mixture was concentrated in vacuo and taken up in diethyl ether (100 mL), and washed successively with 20% aqueous sodium sulphite (2×50 mL) and water (1×50 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford a light green oil, which was purified by flash chromatography. Elution with hexane–diethyl ether (4:1, v/v) gave aldehyde **16** as a light green oil (0.48 g, 9.2%), followed by the alcohol **17** as a clearer green oil (2.33 g, 43.1%). $NaBH_4$ reduction: The crude mixture was taken up in ethanol (50 mL) and stirred at 0°C. $NaBH_4$ (0.97 g, 25.5 mmol, 1 equiv.) was added in small portions over 20 minutes. After 1 hour the reaction was quenched with saturated aqueous ammonium chloride (50 mL) and extracted with diethyl ether (3×100 mL). The combined organic extracts were washed with water (2×100 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo to give the alcohol **17** as a green oil.
12. The overall yield is an average of eight runs on large and small scale; best yield 59%, lowest yield 42%. Reported yields vary between 40 and 76%, depending on the SeO_2 loading and accounting for recovered/recycled starting material.
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