

Regio- and Stereo-specific Allylic Oxidation of Germacrane-type Sesquiterpene Lactones with Selenium Dioxide and *t*-Butyl Hydroperoxide

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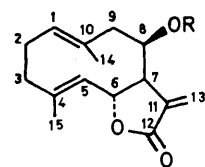
Summary The regio- and stereo-specific allylic oxidation of the germacrane-type sesquiterpene lactones epitulipinolide (1), eupatoriopicrin acetonide (2), and the *O*-methanesulphonate (3) with SeO₂ and *t*-butyl hydroperoxide is discussed.

RECENTLY, many highly oxygenated melampolide and *cis,cis*-germacranolide-type sesquiterpene lactones possessing potent physiological activity have been isolated from plants of the family Compositae.¹ However, the only oxidation

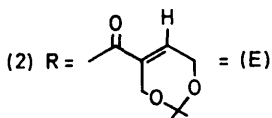
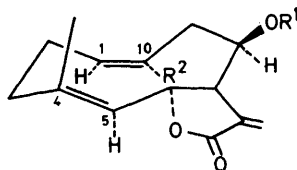
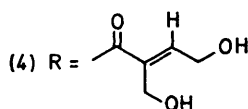
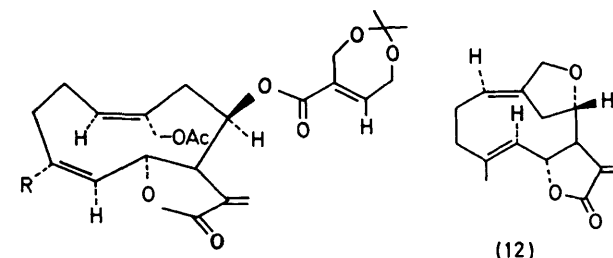
reactions of germacrane-type sesquiterpene lactones which have been investigated have been epoxidations. We describe here the regio- and stereo-specific allylic oxidation of the simple germacranolides epitulipinolide (1),[†] eupatoriopicrin acetonide (2) and the methanesulphonate (3) with SeO₂ and *t*-butyl hydroperoxide.³

Allylic oxidation of epitulipinolide (1) and eupatoriopicrin acetonide (2) [which was obtained from eupatoriopicrin (4)⁴ by acetalization with *p*-MeC₆H₄SO₃H and acetone] with 0.5 mol. equiv. of SeO₂ and 2 mol. equiv. of 70% *t*-butyl

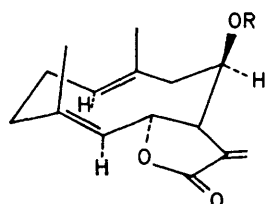
[†] This compound was isolated from *Liliodendron tulipifera* (Magnoliaceae) (ref. 2).



(1) R = Ac

(3) R = SO₂Me(5) R¹ = Ac, R² = CH₂OH(6) R¹ = (E), R² = CH₂OH(7) R¹ = Ac, R² = CHO(8) R¹ = (E), R² = CHO(9) R¹ = (E), R² = CH₂OAc(10) R = CH₂OH

(11) R = CHO



(13) R = Ac or (E)

hydroperoxide in anhydrous CH₂Cl₂ at room temperature for 2 h afforded the desired alcohols (5) (90%)[‡] and (6) (85%), respectively, along with the melampolide-type aldehydes (7) (5%) and (8) (7%), respectively. The alcohols (5) and (6) were completely converted with activated MnO₂ in ether into compounds (7) and (8), respectively. Furthermore, allylic oxidation of the acetate (9), obtained by acetylation of (6) with Ac₂O-pyridine, under the same conditions as above gave the *cis,cis*-germacranolide-type alcohol (10) (45%) and the aldehyde (11) (5%).

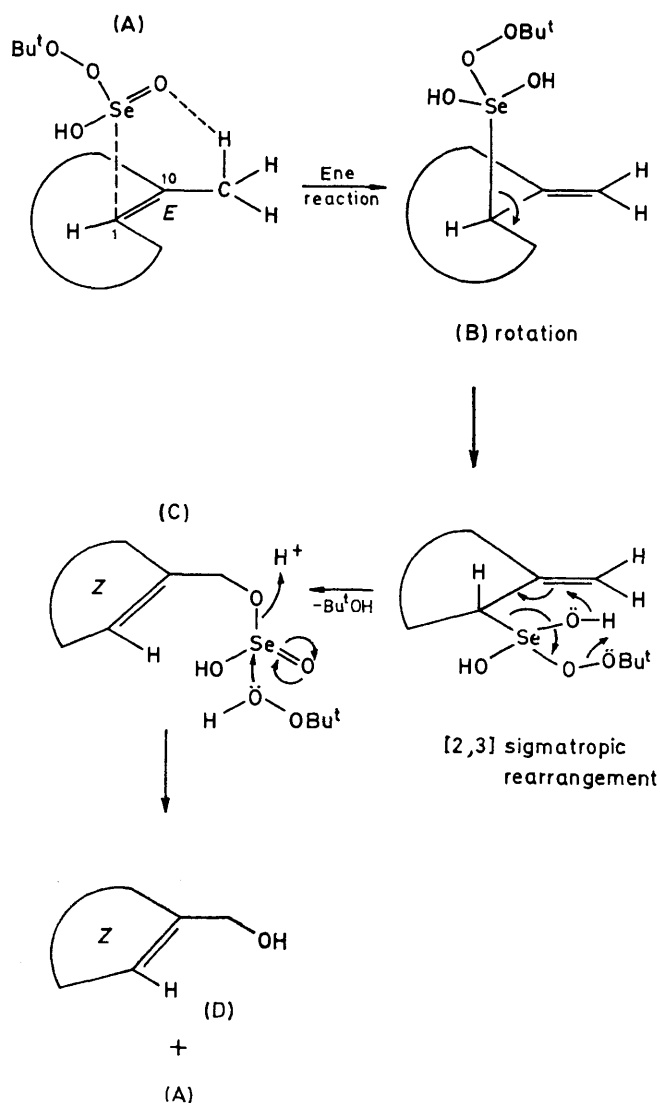
The ester (3), which was obtained from eupatoriopicrin (4) by alkaline hydrolysis followed by mesylation with methanesulphonyl chloride and pyridine, was also regio- and stereo-

[‡] Satisfactory analytical and spectroscopic data were obtained for all new compounds.

[§] The out-of-plane bending (*ca.* 15°) of the 1(10) double bond is smaller than that (*ca.* 25–30°) of the 4(5) double bond in germacranolides.⁶ In addition, the allylic hydrogens of the 10-methyl group have the most favourable orientation, which is approximately orthogonal to the olefinic plane in the six-membered transition state of the ene reaction.

specifically oxidized at C-14. Treatment of the reaction product with silica gel gave the tetrahydrofuran derivative (12) in 65% yield.

The above results show that allylic oxidation of germacran-type sesquiterpene lactones with SeO₂ and *t*-butyl hydroperoxide occurs regio- and stereo-specifically at C-14 as expected from the chair-chair-conformation (13) of the ten-membered ring of (1) or (2) in solution.⁵ We suggest the mechanism shown in the Scheme.



SCHEME

The initial step in this mechanism is formation of the selenium *t*-butyl hydroperoxide moiety (A) as an activating agent which undergoes an ene reaction at the *E*-1(10) double bond[§] according to the soft-soft affinity between the double bond and selenium. The resulting allylselenenic

ester (B) undergoes rearrangement *via* a five-membered transition state ([2,3]sigmatropic rearrangement) to the ester (C) which is hydrolysed by 1 mol. equiv. of *t*-butyl hydroperoxide to the alcohol (D) containing a *Z* double bond in the ten-membered ring, and the activating agent (A) is regenerated. Consequently, catalytic amounts of SeO₂ suffice for this reaction.

We have thus found the oxidized products (5), (6), and (12) to be potential key intermediates for the preparation of highly oxygenated sesquiterpene lactones.

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¹ H. D. Fischer, N. H. Fischer, R. W. Frank, and E. J. Oliver, 'Progress in the Chemistry of Organic Natural Products,' Springer-Verlag, Vienna and New York, 1979, Vol. 38, p. 1.

² R. W. Duskotch and F. S. El-Ferally, *J. Org. Chem.*, 1970, **35**, 1928.

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

⁴ K. Ito, Y. Sakakibara, and M. Haruna, *Chem. Lett.*, 1979, 1503.

⁵ K. Tori, I. Horibe, Y. Tamura, and H. Tada, *J. Chem. Soc., Chem. Commun.*, 1973, 620; see also refs. 2 and 4.

⁶ A. T. McPhail and K. D. Onan, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1798. P. Coggon, A. T. McPhail, and G. A. Sim, *J. Chem. Soc. B*, 1970, 1024; R. J. McClure, G. A. Sim, P. Coggon, and A. T. McPhail, *Chem. Commun.*, 1970, 128.