

FIRST PREPARATION OF (+)-SPATHULENOL.  
REGIO- AND STEREOSELECTIVE OXIDATION OF (+)-AROMADENDRENE WITH OZONE.

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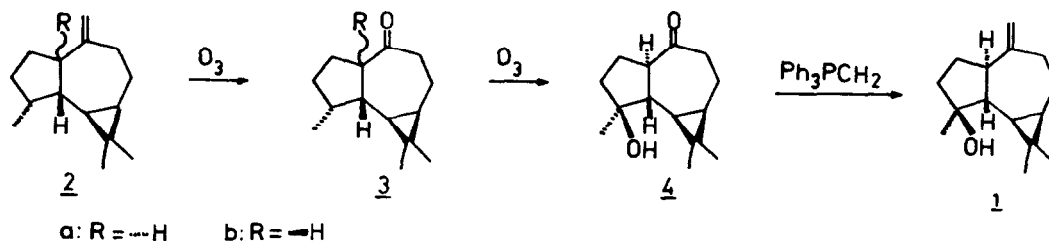
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**Abstract:** (+)-Spathulenol was prepared for the first time in three reaction steps from (+)-aromadendrene by two subsequent ozonizations the second of which was regio- and stereoselective, followed by a Wittig reaction. The overall recycle yield was 13%.

(+)-Spathulenol (1), a sesquiterpene alcohol with an azulene skeleton, has been identified as a constituent of many essential oils such as Eucalyptus spathulata var. grandiflora<sup>1</sup> and Chamomille<sup>2</sup>. Maurer<sup>3</sup> and ter Heide<sup>4</sup> found that (+)-spathulenol is also present in Clary Sage Oil. The presence of 1 in Spike Lavender Oil spanish has also been demonstrated by ter Heide<sup>5</sup>. As these essential oils are important for the flavour and fragrance industry, and the isolated spathulenol had interesting olfactive properties, we decided to synthesize (+)-spathulenol.

The only synthesis of spathulenol described in the literature was reported by Surburg<sup>6</sup>, who obtained (-)-spathulenol in an 18-steps synthesis from (-)- $\beta$ -pinene. The overall yield of this laborious preparation was 0.2%.

(+)-Aromadendrene (2a) would appear to be a more attractive starting material for the synthesis of (+)-spathulenol. It is present in the distillation tails of the oil of Eucalyptus globulus, which is commercially available<sup>7</sup>. One should be able to prepare 1 by regio- and stereoselective oxidation of 2a.



One of the methods recently published for the oxidation of a compound with a tertiary hydrogen atom to the corresponding tertiary alcohol is by reaction with ozone<sup>8</sup>. It is also known that the hydroxylation proceeds with an almost complete retention of configuration<sup>9</sup>.

It was recognized that the presence of the exocyclic double bond would complicate the ozonization of 2a. Difficulty might also be expected by the presence of other tertiary hydrogen atoms. Among its impurities, (+)-aromadendrene 2a contains 12% of 2b<sup>10</sup>.

Ozonization of (+)-aromadendrene 2a in ethanol followed by reduction with triethyl phosphite gave a 4 : 1 mixture of the ketones 3a<sup>12</sup> and 3b in a yield of 87%. The ketone 3a was purified by crystallization.

Apoaromadendrone 3a was oxidized by ozone using cyclohexane as solvent until achieving a conversion of 50%<sup>13</sup>. Hydroxyketone 4 was obtained in a yield of 9% (recycle 18%).

Hydroxy ketone 4 was converted in 79% yield to (+)-spathulenol (1) using methylene triphenyl phosphorane<sup>14</sup> as described by Surburg and Moudon<sup>6</sup> for (-)-spathulenol.

#### References and notes

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- 10 The composition of the aromadendrene used: 58% (+)-aromadendrene, 12% allo-aromadendrene 2b and 16% numerous sesquiterpenes in small quantities.
- 11 A solution of 150 g aromadendrene<sup>10</sup> in 1000 g of ethanol was ozonolyzed at 5°C until no further ozone was absorbed. The resulting solution of the peroxides was reduced by the addition of 200 ml of triethyl phosphite (exothermal reaction). After evaporating the solvent, the residu was cooled for three hours at 5°C. Compound 3a solidified out of the mixture and was filtered. The yield was 84 g of 3a in a purity of 90% (87%).
- 12 G. Büchi, W. Hofheinz, and J.V. Pakstelis, *J. Amer. Chem. Soc.* **91**, 6473 (1969).
- 13 A solution of 50 g of ketone 3a in 500 ml of cyclohexane was saturated with ozone for 6 hours at 5°C. The excess of ozone was removed by a nitrogen purge. The mixture was treated with 10 ml of triethyl phosphite. The solution was washed three times with aqueous NaOH (5%) to remove the organic acids formed. After it was washed with brine and the solvent was evaporated, the residue was distilled (bp<sub>2 mm Hg</sub> 150-160°). Direct yield 4.5 g (9%) of 4. 25 g of the starting material was recovered, so the recylce yield of 4 was 18%.
- 14 The product 1 obtained after distillation was further purified by SLC (SiO<sub>2</sub>/pentane ether) [ $\alpha$ ] 20/D = 5.0°.

(Received in UK 4 March 1985)