

**Tobacco Chemistry 31. (1*S*,4*S*,8*R*,11*S*,12*R*)-8,12-Epoxy-2*E*,6*E*-thunbergadiene-4,11-diol, a New Constituent of Greek Tobacco**

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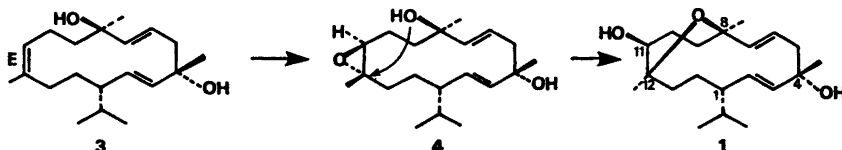
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As part of a general study of tobacco isoprenoids and their degradation products, we have recently determined the absolute configuration of the tobacco thunberganoids and shown the chirality at the carbon carrying the isopropyl group, C(1), to be *S* in these compounds as well as in several tobacco nor-thunberganoids.<sup>1</sup>

Further examination of Greek tobacco has now resulted in the isolation of a new thunberganoid (*1*), obtained in minute quantities as the corresponding mono-acetate (*2*) (3.5 mg, 12 ppb) after acetylation and chromatography of a medium-volatile fraction of an ether extract.<sup>2</sup> Its composition C<sub>20</sub>H<sub>34</sub>O<sub>3</sub> (MS), and the presence of an isopropyl group [ $\delta$  0.85 (d) and 0.88 (d);  $\nu_{\max}$  1370 and 1390 cm<sup>-1</sup>] and three methyl groups [ $\delta$  1.09 (s), 1.18 (s) and 1.34 (s)], probably linked to oxygenated carbons,

implied a diterpenoid structure. A tertiary ( $\nu_{\max}$  3480 cm<sup>-1</sup> in *2*) and a secondary hydroxy group [ $\delta$  3.52 (1 H, m) in *1* shifted to  $\delta$  4.85 in *2*], accommodated two of the three oxygens. This left an ether moiety extending from two fully substituted carbons to account for the third oxygen since there were no further -CHO resonances in the <sup>1</sup>H NMR spectrum. <sup>1</sup>H NMR resonances corresponding to four olefinic protons indicated the presence of two *trans* disubstituted double bonds, one of which was flanked by a methine group and a fully substituted carbon atom, -CH-CH=CH-C- (AB-part of an ABX-system at  $\delta$  5.13 and 5.34,  $J_{AB}$  15.5,  $J_{AX}$  7.5 Hz;  $\nu_{\max}$  979 cm<sup>-1</sup>). The new compound should thus be carbo-monocyclic and the presence of the isopropyl and three methyl substituents suggests that the remaining fourteen carbon atoms are joined in one ring, incorporating the two double bonds and an ether bridge extending between two of the methyl substituted carbon atoms. Although these results implied a thunberganoid structure, the scarce amount of the new compound excluded <sup>13</sup>C NMR and correlative chemical studies and its structure and relative stereochemistry was determined by X-ray diffraction analysis of the monoacetate.

Intensity data for the acetate, which crystallizes in the orthorhombic space group *P*2<sub>1</sub>2<sub>1</sub>2 with  $a = 18.190$  (7),  $b = 12.199$  (2) and  $c = 9.839$  (2) Å, were collected on the Philips computer-controlled PW 1100 diffractometer. An  $\bar{E}$  map with structure-factor phases determined by direct methods displayed all non-hydrogen



Scheme 1. Probable biogenesis of compound *1*.

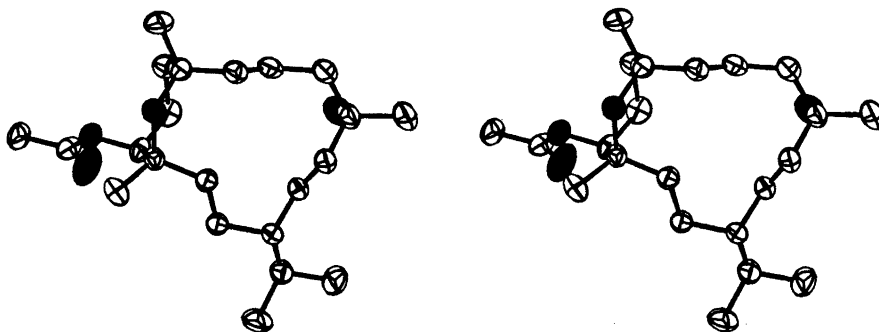


Fig. 1. Stereoscopic view of (1*S*,4*S*,8*R*,11*S*,12*R*)-8,12-epoxy-11-acetoxy-2*E*,6*E*-thunbergadiene-4-ol (*2*).

atoms, while all hydrogen atoms were located from a difference Fourier synthesis. The structure was refined to an *R* value of 0.040 with anisotropic thermal parameters assigned to the carbon and oxygen atoms, and fixed isotropic temperature factors assigned to the hydrogen atoms. A stereoscopic view of the acetate (oxygen atoms shaded) summarising the X-ray results to be discussed in detail elsewhere,<sup>3</sup> is given in Fig. 1.

The absolute configuration of the new thunberganoid (1*S*,4*S*,8*R*,11*S*,12*R*) was inferred from the CD-curves of the corresponding 11-*O*-benzoate and 11-*O*-*p*-nitrobenzoate. These displayed positive <sup>1</sup>*L*<sub>a</sub> bands at 227 (MeOH, Δε<sub>227</sub> ≈ 0.1) and 260 nm (MeOH, Δε<sub>260</sub> ≈ 0.2), respectively, in compliance with the fact that C(12), which is vicinal to the benzyloxyated C(11) and carries the ether oxygen, occurs in a positive sector when a Dreiding model of the benzoate possessing the stereostructure and conformation shown in Fig. 1 is aligned according to the benzoate sector rule.<sup>4,5</sup>

Since the new compound (1) possesses the expected 1*S*-configuration and the chirality at C(4) is *S*, it is likely to be derived from the known tobacco diol (3) (cf. Scheme 1). Similar to other ether bridged tobacco thunberganoids of established absolute configuration, whose formation can be viewed as a result of an oxidative attack on the 11,12-double bond from the α-side of the appropriate 4,8-diols and anchimeric assistance by the 8-hydroxy-group in the formation of the 8,11-ether bridge, it can be inferred from the 11-*S*,12-*R*-configuration of 1 that it is formed in a corresponding manner involving the 11*S*,12-*S*-epoxide (4) or related species as intermediate.

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## Alkylation of Enamines. A Convenient Route to 1,4-Dicarbonyl Compounds

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Methods for preparation of 1,4-dicarbonyl compounds are of current interest, and have been subject to a recent review.<sup>1</sup> Alkylation of enamines with α-halocarbonyl compounds have been reported previously, although these reports deal with enamines derived from cyclic ketones and aldehydes.<sup>2-5</sup>

In the present investigation we have studied the reactions of enamines derived from acyclic aliphatic ketones towards several α-bromocarbonyl compounds, as a possible route to acyclic 1,4-dicarbonyl compounds. The enamines used were the morpholino, dimethylamino and pyrrolidino derivatives of methyl isopropyl ketone and methyl *tert*-butyl ketone (pinacolone), respectively. The α-bromocarbonyl compounds used were bromomethyl isopropyl ketone,<sup>6</sup> bromomethyl *tert*-butyl ketone,<sup>7</sup> bromomethyl phenyl ketone,<sup>8</sup> and ethyl bromoacetate. The reactions were carried out using equimolar amounts or excess of enamine, without any solvent present.

**Results and discussion.** The yields of the 1,4-dicarbonyl compounds obtained in the reactions of α-bromocarbonyl compounds with the enamines are summarized in Table 1 (calculated from <sup>1</sup>H NMR spectra). Physical data are summarized in Table 2. The reaction mechanism is under consideration and will be reported later.

**Experimental.** The IR spectra were obtained on neat samples using a Perkin Elmer 257 spectrometer, the <sup>1</sup>H NMR spectra were recorded on a JEOL C60-HL spectrometer and the <sup>13</sup>C NMR spectra were recorded on a JEOL PFT-60HL spectrometer. TMS was used as internal standard. Deuteriochloroform (<sup>1</sup>H NMR) was used as solvent, and the sample concentrations were ca. 1 M. <sup>13</sup>C NMR spectra were obtained using neat samples and a D<sub>2</sub>O capillary. Probe temperature 23 °C.

**Alkylation of enamines.** A typical procedure was: Bromomethyl *tert*-butyl ketone, 1.90 g (10.6 mmol), was placed in an Erlenmeyer flask equipped with a magnetic stirrer, dropping funnel and reflux condenser fitted with a CaCl<sub>2</sub> drying tube. 2-Dimethylamino-3-methyl-1-butene, 6.3 g (56 mmol, excess), was added in portions to the stirred bromoketone, the stirring being continued for 0.5 h to ensure complete reaction. The precipitated ketoimmonium salt was hydrolyzed with 20 ml of acidulated (HCl) water and stirred for an additional 0.5 h. The aqueous phase was extracted with 2 × 50 ml of ether, and the combined ethereal layers were treated with 10 ml