

TOTAL SYNTHESIS OF VERTICILLENE, THE PUTATIVE  
BIOGENETIC PRECURSOR OF THE TAXANE ALKALOIDS

Christopher B. Jackson and Gerald Pattenden\*

Department of Chemistry, The University, Nottingham, NG7 2RD

Summary: Intramolecular reductive coupling of the bis-aldehyde (14) in the presence of Ti(0), followed by 1,4-reduction of the resulting tetraene (16) using sodium in ammonia, provides a facile synthesis of E,E-verticillene (2), the putative biogenetic precursor of the taxane family of alkaloids e.g. (3).

The novel bicyclo[9.3.1]pentadecatrienol (1), known as verticillol, is a constituent of the wood of the conifer Sciadopitys verticillata (Taxodiaceae).<sup>1</sup> The hydrocarbon (2), corresponding to (1), and designated verticillene, is the putative biogenetic precursor of the taxane group of alkaloids which show structures, e.g. (3), based on the tricyclo[10.3.1.0<sup>4,6</sup>]pentadecene ring system (4).<sup>2</sup> Verticillene (2) has its origins in geranylgeranyl pyrophosphate, and correlates with cembrene (5), also a constituent of conifer wood,<sup>3</sup> and with casbene (6) produced by seedlings of Ricinus communis (Euphorbiaceae).<sup>4</sup> Although a number of syntheses of cembrene and casbene have now been described,<sup>5</sup> the synthesis of verticillene (2) has not hitherto been accomplished.<sup>6</sup> In this Letter we outline a total synthesis of E,E-verticillene (2), and in the accompanying Letter we summarise our investigations of transannular cyclisations of both (2) and verticillol (1) in order to vindicate the biosynthetic speculation mentioned above.

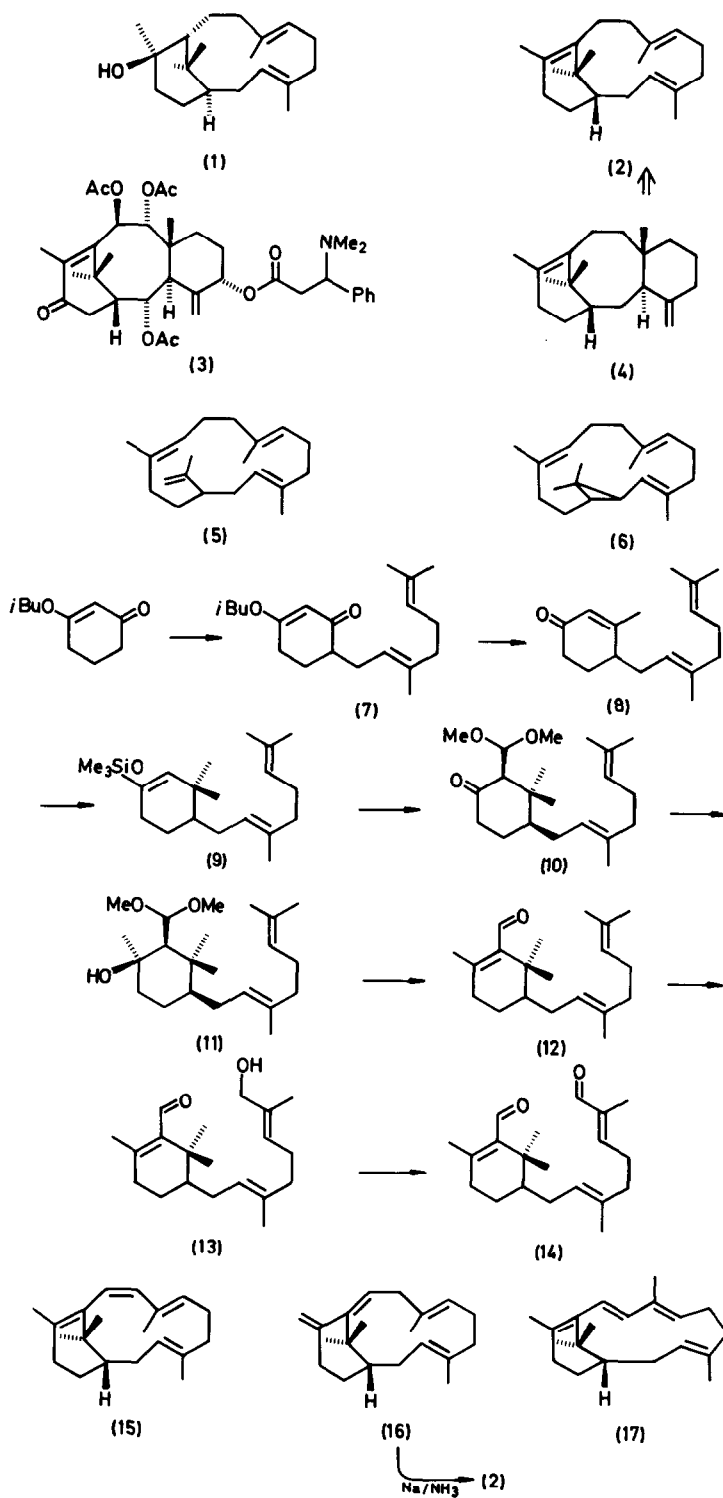
Our synthesis of verticillene (2) features intramolecular reductive coupling of the bis-aldehyde (14) in the presence of Ti(0),<sup>7</sup> with concomitant 1,5-H sigmatropic rearrangement, to elaborate the twelve membered ring, followed by 1,4-reduction of the resulting tetraene (16) using sodium in ammonia. Thus, alkylation of the enolate derived from 3-isobutoxycyclohexenone (LDA, THF; -78°C) with E-3,7-dimethylocta-2,6-dienyl bromide, first gave the 4-substituted 1,3-dione enol ether (7) which, after addition of methyl lithium and hydrolysis (dilute HCl) provided the disubstituted cyclohexenone (8) (76%)<sup>8</sup>, b.p. 145-6°C at 0.1 mmHg,  $\nu_{\max}$  1675 cm<sup>-1</sup>. The cyclohexenone (8) was next added to a solution of lithium dimethylcuprate, and the resulting enolate was quenched at -78°C with chlorotrimethylsilane

to give the corresponding silyl enol ether (9) (88%), b.p. 114-5°C at 0.5mmHg.

When the silyl enol ether (9) and trimethyl orthoformate were added concurrently over 2 min to titanium tetrachloride in dichloromethane, separation and chromatography led to the cis-ketoacetal (10) (58%) as a colourless oil. Addition of methylmagnesium iodide to the ketoacetal (10) then provided the tertiary alcohol (11) (98%) which upon dehydration ( $\text{POCl}_3\text{-C}_5\text{H}_5\text{N}$ ; 65°C, 1.5h) gave a mixture of positional isomers of the unsaturated aldehyde (12). Equilibration of the mixture of isomers in the presence of methanolic potassium hydroxide provided the pure aldehyde (12) (93% overall),  $\nu_{\text{max}}$  1675 $\text{cm}^{-1}$ ;  $\delta$  1.11(Me), 1.29(Me), 1.63(2x:CMe), 1.7(:CMe), 1.6-2.4(m, 11H), 2.1(:CMe), 5.15br (2x:CH), 10.17(CH<sub>2</sub>O). Oxidation of the trienal (12) with catalytic selenium dioxide ( $\text{SeO}_2, \text{t-BuO}_2\text{H}, \text{CH}_2\text{Cl}_2, 25^\circ\text{C}, 3\text{h}$ ) was found to be regioselective, and gave the E,E-allylic alcohol (13),  $\delta$  1.1(Me), 1.28(Me), 1.62(:CMe), 1.68(:CMe), 2.1(:CMe), 1.5-2.7(m, 12H), 4.0(CH<sub>2</sub>OH), 5.15br(:CH), 5.43br(:CH), 10.2(CH<sub>2</sub>O), which on oxidation with manganese dioxide provided the key bis-aldehyde (14)  $\delta$  1.12(Me), 1.30(Me), 1.67(:CMe), 1.7(:CMe), 2.13(:CMe), 1.5 - 2.7(m, 11H), 5.25br(:CH), 6.55br(:CH), 9.5(CH<sub>2</sub>O), 10.25(CH<sub>2</sub>O);  $\delta$ (carbon) 195.0(d), 192.6(d), 155.3(d), 154.3, 140.9, 139.5, 134.4, 125.5(d), 46.5(d), 38.2(t), 36.4, 35.1(t), 27.8(t), 27.4(t), 26.1(q), 22.6(t), 21.1(q), 19.4(q), 16.0(q).

Addition of a solution of (14) in dimethoxyethane, via a syringe pump over 22h, to a slurry of titanium trichloride and Zn-Cu couple<sup>7</sup> in dimethoxyethane led to a mixture of three hydrocarbons in a combined yield of 40%, which was separated by chromatography on silica gel impregnated with silver nitrate. The major product (25%) showed spectral data,  $\delta$  1.06(Me), 1.18(Me), 1.57(:CMe), 1.73(:CMe), 1.55-2.56m(12H), 3.46(t, J12, CH), 4.64(m, CHH), 5.02(m, :CHH), 5.37(dd, J12 and 4, :CH.CH<sub>2</sub>);  $\delta$  carbon 146.7, 145.6, 135.1, 132.3, 126.7(d), 126.1(d), 120.2(d), 111.4(t), 46.6(d), 40.7, 40.2(t), 38.3(t), 34.2(t), 32.3(t), 30.5(q), 29.4(t), 25.9(q), 23.3(t), 17.3(q), 15.5(q), consonant with the tetraene (16) resulting from 1,5-H sigmatropic rearrangement of the initial coupled product (15). We assume that the driving force for the rearrangement is provided by migration of the bridgehead double bond from the six-ring to the twelve-ring in the bicycle (15). The structure and stereochemistry of one of the minor products (7%) resulting from intramolecular reductive coupling of (14) was established as (15) by X-ray crystallography<sup>9</sup>, whereas the other minor product (6%) is assigned as (17) from comparative spectral data and specific n.m.r. decoupling experiments.

The synthesis of E,E-verticillene (2) was completed by treating the tetraene (16) with sodium in liquid ammonia<sup>10</sup> for 0.5h followed by quenching with ammonium chloride. This procedure gave the hydrocarbon (78%) as a colourless oil,  $\delta$  0.87(Me), 0.97(Me), 1.55(2x:CMe), 1.7(:CMe), 1.5 - 2.9(m, 15H), 4.76(br, :CH), 5.2(br, :CH);  $\delta$  carbon 132.8, 131.5, 128.6(d), 126.8(d),



126.3, 42.9(d), 30.2(t), 39.5(t), 37.0, 34.2(t), 32.9(q), 31.5(t), 27.5(t), 26.1(t), 26.0(t), 24.6(q), 21.7(q), 16.6(q), 15.4(q). Comparison between these n.m.r. data and those of natural verticillol (1), whose structure has been firmly established by x-ray crystallography<sup>1</sup>, confirmed the gross structure of the verticillene, and furthermore confirmed its E,E-geometry.

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9. We thank M.J. Begley for this information which will be published separately.
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