

Revised Structure of Alboctalol

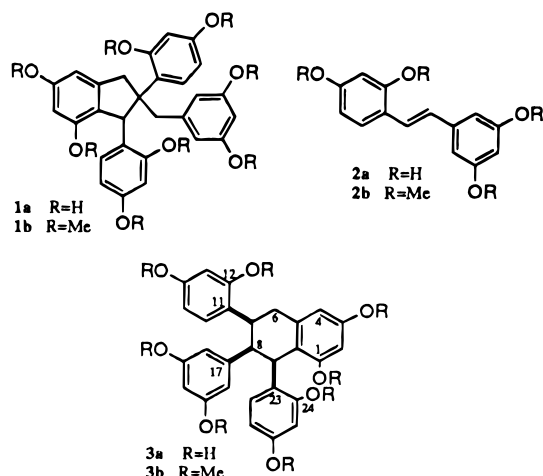
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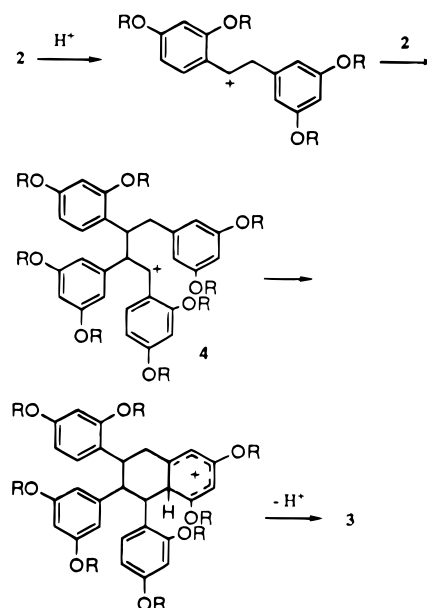
A revised structure was deduced for alboctalol from NMR studies. Racemic alboctalol octamethyl ether was synthesized by treatment of oxyresveratrol tetramethyl ether with acid.

In 1976, alboctalol, a new polyphenol from *Morus alba* (family Moraceae), was assigned structure **1a**.¹ Compound **1a** is apparently a dimer of oxyresveratrol (**2a**), a main constituent of the heartwood of this plant. Alboctalol was not obtained pure, but its octamethyl ether (proposed to be **1b**) was purified through recrystallization. We report spectral data on alboctalol octamethyl ether, which led to revised structures **3a** for alboctalol and **3b** for its octamethyl ether, and that in support of this new structure, racemic alboctalol octamethyl ether **3b** was formed in 6% yield when oxyresveratrol tetramethyl ether (**2b**) was treated with acid.



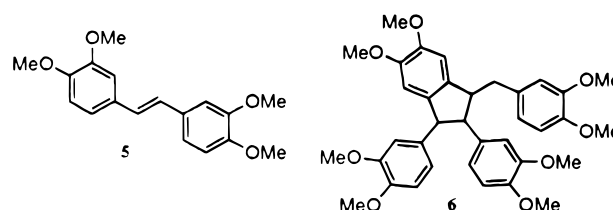
The ¹³C NMR spectrum of alboctalol octamethyl ether¹ did not show two methylenes, one methinyl, and one quaternary sp³ carbons as required for structure **1b**, but instead one methylene and three methinyls as in **3b**. The 500 MHz ¹H NMR spectrum showed the coupling constants and chemical shifts expected for the stereoisomer of **3b** depicted, with the large $J_{6ax,7} = 14.4$ Hz showing the 7-aryl group to be equatorial, and the small $J_{7,8} = 2.9$ Hz showing the 8-aryl group to be axial and requiring the 9-aryl group to be equatorial for the benzocyclohexene half-chair observed to be stable. This conformation has an H8–C8–C9–H9 angle close to 90°, which is consistent with $J_{8,9}$ being too small to observe. It is also supported by the strong upfield shifts (to $\delta 5.74$) observed for H18 and H22, which indicate that, as initially deduced from biosynthetic considerations, the 3,5-dimethoxyphenyl group rather than one of the 2,4-dimethoxyphenyl groups is at position 8.

Scheme 1. Possible Biosynthesis of **3**



The major mass spectral fragments of **3b** (1) are consistent with this structure. Loss of dimethoxyphenyl and H from the molecular ion at m/z 600 (32%) gives a peak at m/z 462 (11%), and loss of dimethoxybenzyl give a peak at 449 (25%). The peaks for about half the dimer at m/z 299 (44%) and 300 (37%) come at least partly through reverse Diels–Alder fragmentation. The base peak at m/z 269 (100%) comes from loss of formaldehyde from a 299 fragment and/or loss of a methoxyl radical from a 300 fragment. The peak at m/z 151 (60%) is due to dimethoxybenzyl and/or dimethoxytropylium cations.

A likely biosynthesis of alboctalol (**3a**) from oxyresveratrol (**2b**) is shown in Scheme 1. Since **3a** is optically active,¹ the acid-catalyzed reactions are probably enzyme-mediated. The final cyclization of intermediate **4** to give a cyclohexane rather than a cyclopentane as reported by Battersby and Binks² in the acid-catalyzed dimerization of 3,4,3',4'-tetramethoxystilbene (**5**) to **6** is readily rationalized on the basis of the relative activation toward electrophilic substitution of the aromatic rings by methoxyl groups.



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We decided to see if racemic alboctalol octamethyl ether (**3b**) could be formed by treatment of oxyresveratrol tetramethyl ether (**2b**) with acid. Compound **2b** was synthesized by a Wittig reaction, but failed to give **3b** under several acidic conditions [P_2O_5 /toluene (2), *p*-toluenesulfonic acid/benzene, trifluoroacetic acid/chloroform] used to dimerize stilbenes. Finally, HCl gas in dry ether gave a 6% yield of **3b**, optically inactive, but with IR and 1H and ^{13}C NMR spectra identical to those of **3b** from methylation of natural **3a**. This synthesis of **3b** supports the view that the 3,5-dimethoxyphenyl group is at position 8 and increases the probability that alboctalol **3a** is indeed a dimer of oxyresveratrol (**2a**). It is likely that other stereoisomers of **3b** are formed in this reaction, but no other product was characterized.

While it is expected from the location of their methoxyl groups that acid-catalyzed dimerization of 4,4'-dimethoxystilbene should give a cyclopentane dimer of type **6**³ and that **2b** should give a cyclohexane dimer **3b**, the cation of type **4** from 3,3',4,4'-tetramethoxystilbene **5** has a choice of similarly activated aromatic rings to give each type of dimer. Though structure **6** has been proposed to be the dimer from **5** by analogy with 4,4'-dimethoxystilbene and this cyclopentane product can be justified as more likely on entropy grounds,² a cyclohexane structure of the **3b** type should still be considered as possible for the dimer of **5**.

Experimental Section

Alboctalol Octamethyl Ether (3b) from Natural Alboctalol (3a). Alboctalol octamethyl ether (**3b**) was prepared from crude natural alboctalol (**3a**) as previously described:¹ mp 168–169 °C; IR (KBr) 2943, 1608, 1550, 1455, 1390, 1292, 1208, 1158, 1045 and 838 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$, TMS, δ) 6.56 (d, 8.4 Hz, H-28), 6.54 (d, 2.4 Hz, H-25), 6.46 (d, 8.4 Hz, H-16), 6.36 and 6.35 (d, 2.5 Hz, H-2 and H-4), 6.34 (d, 2.4 Hz, H-13), 6.33 (dd, 8.4, 2.4 Hz, H-15), 6.27 (dd, 8.4, 2.4 Hz, H-27), 6.20 (t, 2.3 Hz, H-20), 5.74 (d, 2.3 Hz, H-18 and H-22), 4.84 (s, H-9), 3.83 (s, OMe), 3.80 (s, OMe), 3.79 (s, OMe), 3.73 (s, OMe), 3.72 (dt, 14.4, 3.5 Hz, H-7), 3.60 (s, OMe), 3.46 (s, 19-OMe and 21-OMe), 3.39 (s, 1-OMe), 3.27 (d, 2.9 Hz, H-8), 2.85 (dd, 16.8, 14.4 Hz, H-6_{ax}), 2.64 (dd, 16.8, 4.1 Hz, H-6_{eq}); ^{13}C NMR (APT) CH_3 at 2×54.8 , 55.0, 55.2, 2×55.3 , 55.6, and 55.7; CH_2 at 29.9; CH at 31.0, 37.9, 48.0, 97.0, 98.1, 98.3, 2×98.4 , 102.8, 103.1,

104.2, 107.1, 128.1, and 129.2; and C at 119.3, 125.0, 128.8, 140.6, 145.0, 157.7, 157.9, 158.5, 158.6, and 4×159.2 .

Oxyresveratrol Tetramethyl Ether (2b). A mixture of triphenylphosphine (352 mg, 1.34 mmol), 3,5-dimethoxybenzyl chloride (250 mg, 1.33 mmol), and dry C_6H_6 (10 mL) was boiled for 3 h. On cooling, the C_6H_6 was decanted and the solid was washed with benzene (2×10 mL) and dried to give (3,5-dimethoxybenzyl)-triphenylphosphonium chloride (566 mg, 1.3 mmol, 83%). To this salt in dry ether (10 mL) under N_2 was added dropwise over 15 min with stirring KO-*t*-Bu prepared by reacting K (53 mg, 1.34 mmol) with *t*-BuOH (10 mL). After 15 min, a solution of 2,4-dimethoxybenzaldehyde (225 mg, 1.36 mmol) in dry Et_2O (15 mL) was added over 20 min. After 1 h, the reaction mixture was poured onto crushed ice. The Et_2O layer was separated, and the aqueous layer was extracted with Et_2O (3×15 mL). The combined Et_2O extracts were washed with water (2×10 mL) and dried, and the solvent was evaporated. Chromatography of the residual oil on silica gel, with elution with petroleum ether- C_6H_6 (4:1), gave after evaporation **2b** (42 mg, 10%): mp 83–84 °C (lit.⁴ 84 °C).

Racemic Alboctalol Octamethyl Ether (3b). Dry HCl gas was bubbled through dry Et_2O (25 mL) cooled in an ice-salt bath until saturation was complete. **2b** (200 mg, 680 mmol) was added, and the mixture was stirred at 0 °C for 2 h and then at 25 °C for 2 h. The mixture was poured onto ice, and the aqueous layer was neutralized with solid Na_2CO_3 and extracted with Et_2O (3×20 mL). The Et_2O extracts were washed with water (15 mL) and dried, and the solvent was evaporated. The residue was chromatographed on silica gel, with elution with petroleum ether-EtOAc (3:1), to give after evaporation **3b** (12 mg, 6%): mp 166–168 °C; IR, 1H NMR, and ^{13}C NMR data identical with those of the natural product.

References and Notes

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