Revised Structure of Alboctalol

Robert B. Bates,*,† Sriyani Caldera,† V. H. Deshpande,‡ B. L. Malik,§ and S. K. Paknikar§

Chemistry Department, University of Arizona, Tucson, Arizona 85721, National Chemical Laboratory, Pune 411008, India, and Chemistry Department, Goa University, Goa 403203, India

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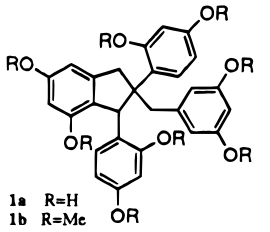
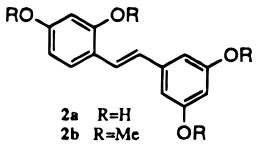
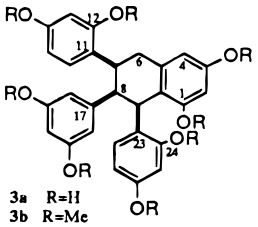
A revised structure was deduced for alboctalol from NMR studies. Racemic alboctalol octamethyl ether was synthesized by treatment of oxyresveratrol tetramethyl ether with acid.

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.

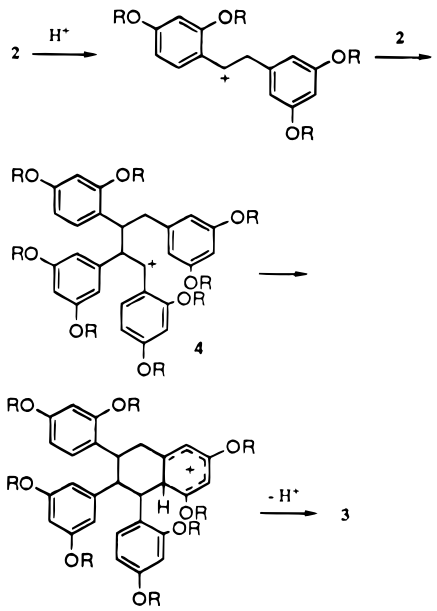






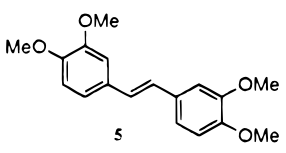
The ^{13}C NMR spectrum of alboctalol octamethyl ether[1] did not show two methylenes, one methinyl, and one quaternary sp^3 carbons as required for structure **1b**, but instead one methylene and three methinyls as in **3b**. The 500 MHz ^1H NMR spectrum showed the coupling constants and chemical shifts 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 δ5.74) 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.

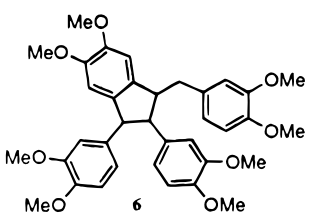
Scheme 1. Possible Biosynthesis of **3**



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 Binks[2] 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.





* Address for correspondence.
† University of Arizona.
‡ National Chemical Laboratory.
§ Goa University.
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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 ^{1}H 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}; ^{1}H 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, ^{1}H NMR, and ^{13}C NMR data identical with those of the natural product.

References and Notes

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