The structure and synthesis of 2-hydroxy-4-methoxy-6-methylphenyl 3-hydroxy-5-methylphenyl ether (LLV125?), a fungal diaryl ether

5 AUTHORS, INCLUDING:

Jack Richard Cannon

The Umnversity of Western Australia, Crawl…

48 PUBLICATIONS **709** CITATIONS

SEE PROFILE

The Structure and Synthesis of 2-Hydroxy-4-methoxy-6-methylphenyl 3-Hydroxy-5-methylphenyl Ether (LL-V125α), a Fungal Diaryl Ether †

By **J. R. Cannon, T. M. Cresp, B. W. Metcalf,** and **M. V. Sargent,*** Department of Organic Chemistry, University of Western Australia, Nedlands, Western Australia
J. A. Elix, Chemistry Department, School of General Studies, Australian National University, Canberra, Australia

The Structure and Synthesis of 2-Hydroxy-4-methoxy-6-methylphenyl 3-Hydroxy-5-methylphenyl Ether (LL-V125α), a Fungal Diaryl Ether †

By J. R. Cannon, T. M. Cresp, B. W. Metcalf, and M. V. Sargent,* Department of Organic Chemistry, University of Western Australia, Nedlands, Western Australia

J. A. Elix, Chemistry Department, School of General Studies, Australian National University, Canberra, Australia

A fungal diaryl ether, LL–V125α, has been identified as 2-hydroxy-4-methoxy-6-methylphenyl 3-hydroxy-5-methylphenyl ether (4), contrary to a previous suggestion. This assignment has been confirmed by synthesis. A number of modifications of the Ullmann diaryl ether synthesis have been investigated.

THE diaryl ether function is common in complex natural products such as depsidones and bisbenzylisoquinoline alkaloids, but simple naturally occurring diaryl ethers are rare.[1] The report by McGahren et al.[1] that a diaryl ether, LL-V125α, occurred as a metabolite of a fungus of the order Sphaeropsidales attracted our attention, since we have been engaged in the synthesis of diaryl ethers in connection with our work on both depsidones [2] and robustol.[3]

McGahren et al.[1] considered structures (1), (4), and (5) for LL-V125α chiefly on the grounds that cleavage by sodium and liquid ammonia of the di-O-methyl ether of the natural product gave 3-hydroxy-5-methoxytoluene (9) and 3,5-dimethoxytoluene (10), whereas similar cleavage of the di-O-ethyl ether gave 3-ethoxy-5-hydroxytoluene (11) and 3-ethoxy-5-methoxytoluene (12). Structures (4) and (5) for LL-V125α were rejected since the di-O-methyl ether (m.p. 91—92°) was claimed [1]

† Preliminary communication, J. R. Cannon, T. M. Cresp, B. W. Metcalf, M. V. Sargent, and J. A. Elix, Chem. Comm., 1971, 473.

[1] W. J. McGahren, W. W. Andres, and M. P. Kunstmann, J. Org. Chem., 1970, **35**, 2433.

[2] S. Kurokawa, J. A. Elix, P. L. Watson, and M. V. Sargent, J. Japan. Botany, 1971, **46**, 33; T. M. Cresp, J. A. Elix, and M. V. Sargent, unpublished results.

[3] J. R. Cannon, P. W. Chow, B. W. Metcalf, A. J. Power, and M. W. Fuller, Tetrahedron Letters, 1970, 325.

to be different from tri-*O*-methylalectol (6) (m.p. 96°), a depsidone degradation product synthesised by Asahina and Fuzikawa,[4] although no direct comparison was made. The di-*O*-methyl ether of LL-V125α apparently was not oxidised by dichromate and the aryl ether linkage was not cleaved on fusion with potassium hydroxide, as reported by Asahina and Fuzikawa for tri-*O*-methylalectol (6).[4] On demethylation LL-V125α gave a trihydric phenol which was assigned structure (3) and which exhibited in its n.m.r. spectrum a multiplet centred at τ 3·73 due to the five aromatic protons. It appeared to us that the n.m.r. spectrum of this compound would be better accommodated by structure (7), since in the n.m.r. spectrum of compound (3) two of the aromatic protons should be equivalent and give rise to a singlet. Hence either structure (4) or (5) follows for LL-V125α.
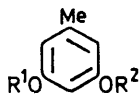
Further evidence adduced by McGahren *et al.*[1] for structure (1) was that one of the new *O*-methyl resonances which appeared in the n.m.r. spectrum of the
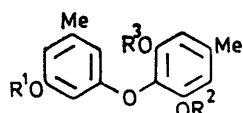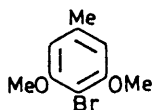

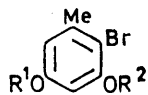(1) R¹ = R² = H, R³ = Me
(2) R¹ = R² = R³ = Me
(3) R¹ = R² = R³ = H
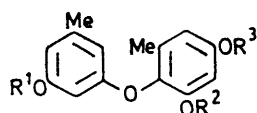
(4) R¹ = R² = H, R³ = Me
(5) R¹ = R³ = H, R² = Me
(6) R¹ = R² = R³ = Me
(7) R¹ = R² = R³ = H
(8) R¹ = R² = CH₂Ph, R³ = Me

(9) R¹ = H; R² = Me
(10) R¹ = R² = Me
(11) R¹ = H; R² = Et
(12) R¹ = Me; R² = Et
(13) R¹ = CH₂Ph, R² = H

(14)

(15) R¹ = R² = Me
(16) R¹ = Me, R² = CH₂Ph

product obtained on methylation of LL-V125α was coincident with the *O*-methyl resonance initially present in the n.m.r. spectrum of LL-V125α. However it seemed to us that this coincidence could also arise if LL-V125α had structure (4). This latter evidence we tentatively regarded as favouring structure (4) rather than (5) for LL-V125α.

The synthesis of the diaryl ether (2), having the structure proposed by McGahren *et al.*[1] for the methyl ether of LL-V125α, was undertaken first. The classical Ullmann condensation of 3-hydroxy-5-methoxytoluene (9)[5] and 4-bromo-3,5-dimethoxytoluene (14)[5] gave the diaryl ether (2) in only 10% yield. Methods for increasing this yield were sought and various modifications of the classical Ullmann condensation were investigated. Bacon's modification[6] gave the diaryl ether (2) in 5%

yield and that of Williams *et al.*[7] gave only a 2% yield. The modification of Tomita *et al.*[8] in which pyridine is used as solvent, copper(II) oxide as catalyst, and potassium carbonate as base, however, gave the diaryl ether (2) in 18% yield. This compound had m.p. 141—142° and was different from LL-V125α di-*O*-methyl ether. On demethylation it gave the trihydric phenol (3), m.p. 148—150°, different from the oil obtained by McGahren *et al.*[1] by demethylation of the natural product.

Asahina and Fuzikawa[4] synthesised tri-*O*-methylalectol (6) in 0·2% yield by the classical Ullmann reaction between 3-hydroxy-5-methoxytoluene (9) and 2-bromo-3,5-dimethoxytoluene (15). In our hands this method gave tri-*O*-methylalectol (6) in 19% yield, and the Tomita modification afforded a 22% yield of this product. This material had an i.r. spectrum identical with that of the di-*O*-methyl ether of LL-V125α. Demethylation of the synthetic product gave alectol (7) as an oil.

3-Benzyloxy-5-hydroxytoluene (13) and 3-benzyloxy-2-bromo-5-methoxytoluene (16), both available by conventional methods, on Ullmann condensation gave the di-*O*-benzyl compound (8). On hydrogenolysis this furnished LL-V125α, identical (mixed m.p., i.r. and mass spectra) with the natural product, thus confirming structure (4).

EXPERIMENTAL

General directions have been given previously.[5]

2,6-Dimethoxy-4-methylphenyl 3-Methoxy-5-methylphenyl Ether (2).—(a) 3-Hydroxy-5-methoxytoluene[5] (4·0 g) was added to potassium methoxide [from potassium (1·05 g) and absolute methanol (10 ml)] and the methanol was evaporated off under dry nitrogen. Benzene (30 ml) was added and the evaporation was repeated, then 4-bromo-3,5-dimethoxytoluene[5] (6·7 g) and copper bronze (30 mg) were added and the mixture was stirred and heated at 210° (bath) for 3·5 h under dry nitrogen. The cooled melt was dissolved in ether; the solution was filtered through kieselguhr, washed with aqueous 5% sodium hydroxide, water, and saturated brine, and finally dried (Na₂SO₄). Removal of the ether left a dark brown residue which was chromatographed over alumina (90 g; Alcoa grade 1) with benzene–ether (4 : 1) as eluant. The *diphenyl ether* (850 mg, 10%) formed prisms (from methanol), m.p. 141—142° (Found: C, 70·4; H, 7·0%; *M*, 288. C₁₇H₂₀O₄ requires C, 70·8; H, 7·0%; *M*, 288); τ (CCl₄) 3·65 (2H, s, ArH), 3·80 (1H, m, ArH), 3·93 (2H, m, ArH), 6·30 (6H, s, 2 × OMe), 6·33 (3H, s, OMe), and 7·70 and 7·78 (each 3H, s, Me).

(b) 3-Hydroxy-5-methoxytoluene (1·3 g) was added to a solution of sodium methoxide [from sodium (0·21 g) and methanol (10 ml)]. The methanol was evaporated off under nitrogen and the residue dried at 25° and 0·1 mmHg for 5 min. Copper(I) oxide (0·65 g), 4-bromo-3,5-dimethoxytoluene (2·1 g), and *NN*-dimethylacetamide (10 ml) were

[4] Y. Asahina and F. Fuzikawa, *Ber.*, 1934, **67**, 163.
[5] J. R. Cannon, T. M. Cresp, B. W. Metcalf, M. V. Sargent, G. Vinciguerra, and J. A. Elix, *J. Chem. Soc. (C)*, 1971, 3495.
[6] R. G. R. Bacon and H. A. O. Hill, *J. Chem. Soc.*, 1964, 1108; R. G. R. Bacon and O. J. Stewart, *ibid.*, 1965, 4953.

[7] A. L. Williams, R. E. Kinney, and R. F. Bridger, *J. Org. Chem.*, 1967, **32**, 2501; see also M. J. Rance and J. C. Roberts, *Tetrahedron Letters*, 1970, 2799.
[8] M. Tomita, K. Fujitani, and Y. Aoyagi, *Chem. and Pharm. Bull. (Japan)*, 1965, **13**, 1341.

added and the mixture was stirred and heated under reflux under dry nitrogen for 60 h. The cooled mixture was filtered and the filtrate poured into dilute hydrochloric acid and extracted with ether. The extract was washed with aqueous 5% sodium hydroxide then with water, and dried (Na_2SO_4). Removal of the solvent left a brown oil (880 mg) which on chromatography as in (a) afforded the product, m.p. 141—142° (131 mg, 5%).

(c) A solution of sodium methoxide (475 mg) in methanol (46 ml) and benzene (20 ml) was added to 3-hydroxy-5-methoxytoluene (3·0 g) with stirring under an atmosphere of dry nitrogen. The solvents were removed by distillation; benzene (20 ml) was then added and removed by evaporation. Pyridine (20 ml), 4-bromo-3,5-dimethoxytoluene (4·75 g), and copper(I) chloride (1·0 g) were added. The mixture was heated under reflux with stirring under dry nitrogen for 28 h. After cooling, the crude product was isolated as in (b) and the brown oil (3·45 g) was preadsorbed from benzene on to silica gel and chromatographed over a column of silica gel (total 3 × 24 cm) with light petroleum–ethyl acetate (19 : 1) as eluant (100 ml fractions were collected). Fractions 16—21 afforded the diphenyl ether (120 mg, 2%) as prisms (from methanol), m.p. 141—142°.

(d) 3-Hydroxy-5-methoxytoluene (4·20 g), 4-bromo-3,5-dimethoxytoluene (5·50 g), finely divided anhydrous potassium carbonate (5 g), and pyridine (15 ml) were gradually heated to 130° (bath) with stirring under dry nitrogen. Copper(II) oxide (1 g) was added and the mixture was then stirred for 21 h at 150—160° (bath) under dry nitrogen, cooled, and dissolved in ether. The solution was filtered through Kieselguhr and washed in turn with dilute hydrochloric acid, aqueous 5% sodium hydroxide, water, and saturated brine. The product, isolated as before, formed prisms (1·236 g, 18%) (from methanol), m.p. 141—142°.

2,6-*Dihydroxy-4-methylphenyl* 3-*Hydroxy-5-methylphenyl Ether* (3).—The foregoing diaryl ether (2) (300 mg) and pyridine hydrochloride (29 g) were heated at 160—170° with stirring in an all-glass apparatus for 6 h under dry nitrogen. The melt was cooled, treated with water, and extracted with ethyl acetate. The extract was washed with brine, dried (Na_2SO_4) and evaporated to leave the *phenol* (230 mg, 90%), which crystallised from methanol as prisms, m.p. 148—150° (Found: M, 246·0893. $^{12}C_{14}{}^{1}H_{14}{}^{16}O_4$ requires M, 246·0892); τ 3·69br (5H, s, 2ArH and 3OH exchangeable with D_2O), 3·80 (3H, m, ArH), and 7·87 and 7·97 (each 3H, s, Me).

2,4-*Dimethoxy-6-methylphenyl* 3-*Methoxy-5-methylphenyl Ether* (*Tri-O-methylalectol*) (6).—(a) Potassium methoxide [from potassium (0·71 g) and absolute methanol (15 ml)] was added to 3-hydroxy-5-methoxytoluene (2·70 g) under an atmosphere of dry nitrogen. The methanol was removed by distillation and the residue dried at 25° and 0·1 mmHg for 10 min. 2-Bromo-3,5-dimethoxytoluene [5] (4·5 g) and copper bronze (20 mg) were added and the mixture was stirred and heated at 210° (bath) for 3·5 h under dry nitrogen. The cooled melt was treated as before and the crude product (3·45 g) was preadsorbed from benzene on to silica gel and chromatographed over a column of silica gel with light petroleum–ethyl acetate (19 : 1) as eluant (150 ml fractions were collected). Fractions 9—16 yielded the product (1·077 g, 19%) as plates, m.p. 94·5—96° (from methanol) (lit.,[4] 96°) (Found: M, 288. Calc. for $C_{17}H_{20}O_4$: M, 288); τ 3·67 (5H, m, ArH), 6·25 (3H, s, OMe), 6·31 (6H, s, 2 × OMe), and 7·77 and 7·87 (each 3H, s, Me). The i.r.

spectrum (Nujol) was identical with that of an authentic sample of LL-V125α di-O-methyl ether.

(b) 2-Bromo-3,5-dimethoxytoluene (3·2 g), 3-hydroxy-5-methoxytoluene (1·9 g), finely divided potassium carbonate (4·0 g), and pyridine (15 ml) were heated to 130° (bath) with stirring under dry nitrogen; copper(II) oxide (0·6 g) was added and the mixture was heated for 20 h at 150° (bath). The product (883 mg, 22%), isolated as before, formed plates (from methanol), m.p. 94·5—96°.

2,4-*Dihydroxy-6-methylphenyl* 3-*Hydroxy-5-methylphenyl Ether* (*Alectol*) (7).—Demethylation of the foregoing diaryl ether (6), as before, gave the *phenol* (200 mg, 80%), which was purified by layer chromatography and was obtained as a viscous oil (Found: M, 246·0893. $^{12}C_{14}{}^{1}H_{14}{}^{16}O_4$ requires M, 246·0892); τ 3·18br (2H, s, D_2O-exchangeable OH), 3·74 (6H, m, 5ArH and D_2O-exchangeable OH), and 7·82 and 8·02 (each 3H, s, Me).

3,5-*Dibenzyloxytoluene*.—Orcinol monohydrate (16 g) was heated under reflux in benzene in a Dean–Stark apparatus until no more water passed over. The benzene was removed under reduced pressure and the residue in dry NN-dimethylformamide (175 ml) was stirred at 100° with anhydrous potassium carbonate (32 g) and benzyl chloride (30·8 g) for 4 h. The mixture was cooled, diluted with water, and extracted exhaustively with ethyl acetate. The extract was washed with water and with saturated brine, and dried (Na_2SO_4). Removal of the solvent left a dark brown oil which was chromatographed over silica gel (3·7 × 44 cm) with light petroleum–ethyl acetate (17 : 1) as eluant to give the *benzyl ether* (32·5 g, 95%) as prisms, m.p. 47—48° (from light petroleum) (Found: C, 82·5; H, 6·7%; M, 304. $C_{21}H_{20}O_2$ requires C, 82·85; H, 6·6%; M, 304); τ 2·78 (10H, m, 2 × Ph), 3·61 (3H, m, 2-, 4-, and 6-H), 5·23 (4H, s, 2 × CH_2), and 7·84 (3H, s, Me).

3-*Benzyloxy-5-hydroxytoluene* (13).—The foregoing benzyl ether (32·5 g) in ethyl acetate (300 ml) was shaken in an atmosphere of hydrogen in the presence of 10% palladised charcoal (3·2 g) until 1 mol. equiv. of hydrogen had been absorbed. Filtration and evaporation left an oily residue which was dissolved in benzene; the solution was extracted exhaustively with aqueous 5% sodium hydroxide. The benzene layer was washed with water, and with saturated brine, and dried (Na_2SO_4). Removal of the solvent left the starting benzyl ether (14·4 g, 44%). The basic extract was acidified with concentrated hydrochloric acid at 0° and then extracted exhaustively with ether. The ethereal extract was washed in turn with water and saturated brine, and finally dried (Na_2SO_4). The brown oily residue left on removal of the ether was chromatographed over silica gel (3·7 × 50 cm) with light petroleum–ethyl acetate (9 : 1) as eluant to give the *monobenzyl ether* (8·95 g, 39%) as rods, m.p. 61·5—62·5° (from light petroleum) (Found: C, 78·35; H, 6·75. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·6%); τ 2·73 (5H, m, Ph), 3·71 (3H, m, 2-, 4-, and 6-H), 5·18 (2H, s, CH_2), and 7·87 (3H, s, Me).

3-*Benzyloxy-2-bromo-5-methoxytoluene* (16).—2-Bromo-3-hydroxy-5-methoxytoluene [5] (10·0 g) in dry NN-dimethylformamide (120 ml) was stirred with anhydrous potassium carbonate (32 g) and benzyl chloride (5·1 g) for 18 h at room temperature. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and with saturated brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed over a column of silica gel (3·7 × 50 cm) with light petroleum (1 l) then light petroleum–ethyl acetate (35 : 1) as eluants

(200 ml fractions were collected). Early fractions afforded a little benzyl chloride and fractions 14—17 furnished the *benzyl ether* (9·8 g, 69%) as an oil, b.p. 180—190° (bath) at 1 mmHg (Found: C, 58·1; H, 4·7; Br, 25·9. $C_{15}H_{15}BrO_2$ requires C, 58·65; H, 4·9; Br, 26·0%. Found: M, 306·0257. $^{12}C_{15}{}^{1}H_{15}{}^{79}Br^{16}O_2$ requires M, 306·0256); τ 2·71 (5H, m, Ph), 3·70br (2H, s, 4- and 6-H), 5·11 (2H, s, CH_2), 6·43 (3H, s, OMe), and 7·79 (3H, s, Me).

2-Benzyloxy-4-methoxy-6-methylphenyl 3-Benzyloxy-5-methylphenyl Ether (8).—Potassium methoxide [from potassium (0·52 g) and absolute methanol (80 ml)] was added to 3-benzyloxy-5-hydroxytoluene (3·0 g) under an atmosphere of dry nitrogen. The solution was distilled to dryness and benzene (30 ml) was added. The solution was again distilled to dryness and then dried at 25° and 0·1 mmHg for 5 min. 3-Benzyloxy-2-bromo-5-methoxytoluene (4·3 g) and copper bronze (100 mg) were then added and the mixture was stirred and heated at 180—190° (bath) for 4·5 h, under dry nitrogen. The cooled melt was worked up as usual and the crude product (4·3 g) was preadsorbed from chloroform on to silica gel and chromatographed over a column of silica gel (3·7 × 53 cm) with light petroleum–ethyl acetate (38 : 1) as eluant (100 ml fractions were collected). Fractions 32 and beyond contained the *diphenyl ether* (1·46 g, 22%) which formed fine needles (from light petroleum), m.p. 86—87° (Found: C, 78·75; H, 6·55%; M, 440. $C_{29}H_{28}O_4$ requires C, 79·05; H, 6·4%;

M, 440); τ 2·70 and 2·84 (each 5H, s, Ph), 3·66 (5H, m, ArH), 5·09 (4H, s, 2 × CH_2), 6·31 (3H, s, OMe), and 7·78 and 7·87 (each 3H, s, Me).

2-Hydroxy-4-methoxy-6-methylphenyl 3-Hydroxy-5-methylphenyl Ether (LL-V125α) (4).—The foregoing dibenzyl ether (500 mg) was dissolved in ethyl acetate (25 ml) and shaken with hydrogen in the presence of palladium chloride (30 mg) and 10% palladised charcoal (100 mg) until hydrogen absorption ceased. The filtered solution was evaporated and the residue was crystallised from light petroleum to afford the *product* (289 mg, 98%) as rosettes of needles, m.p. and mixed m.p. 121—122° (lit.,[1] 121·5—122·5°) (Found: C, 68·85; H, 6·2%; M, 260. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·2%; M, 260); τ 3·72 (5H, m, ArH), 4·42br and 4·62br (each 1H, s, OH), 6·23 (3H, s, OMe), and 7·78 and 7·94 (each 3H, s, Me). The mass and i.r. (Nujol) spectra were virtually identical with those of the natural material. The *diacetate* formed prisms (from light petroleum), m.p. 72—73° (lit.,[1] 75—76°) (Found: C, 66·6; H, 5·9%; M, 344. $C_{19}H_{20}O_6$ requires C, 66·25; H, 5·85%; M, 344); τ 3·41 (5H, m, ArH), 6·17 (3H, s, OMe), 7·67 and 7·73 (each 3H, s, OAc), and 7·81 and 7·92 (each 3H, s, Me).