Syntheses of Lignans from 2,3-Diaroylbutanes

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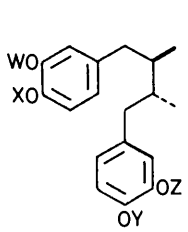
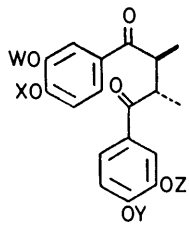
2,3-Diaroylbutanes can be selectively converted with high stereospecificity into 2,5-diaryl-3,4-dimethylfurans or 2,3-diarylbutanes. The racemic forms of the dibenzylbutane lignans, dihydroguaiaretic acid dimethyl ether (2), austrobilignan-5 (12), and austrobilignan-6 (14) and the diaryltetrahydrofuran lignans, veraguensin (3) and its piperonyl analogue (10) have been readily synthesized. A short convenient synthesis of the aryltetralin lignan, galbulin (5) and the all-*trans*-tetrahydrofuran lignan, galbelgin (6) are also reported.

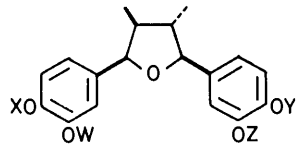
A HIGHLY efficient preparation of (±)-2,3-bis-(3,4-dimethoxybenzoyl)butane (1), involving alkylation of the sodium enolate of propioveratrone in liquid ammonia,[1] was developed for the synthesis of the food antioxidant nordihydroguaiaretic acid. We describe here the conversion of this diketone and analogues to representative members of the diarylbutane, tetrahydrofuran, and aryltetralin classes of lignans by one or two step procedures.



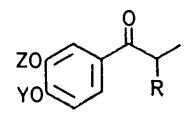
(2) W = X = Y = Z = Me
(14) X = H, W = Me, YZ = CH_2



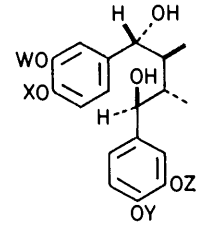
(1) W = X = Y = Z = Me
(9) WX = YZ = CH_2
(18) X = $PhCH_2$, W = Me, YZ = CH_2



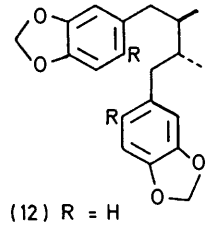
(3) W = X = Y = Z = Me
(10) WX = YZ = CH_2
(15) X = H, Y = Me, YZ = CH_2
(16) X = W = Me, YZ = CH_2
(19) WX = CH_2, Y = H, Z = Me
(20) X = Ac, W = Me, YZ = CH_2
(21) WX = CH_2, Y = Ac, Z = Me



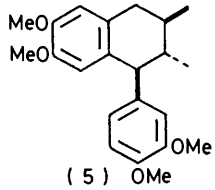
(7) YZ = CH_2, R = H
(8) YZ = CH_2, R = Br
(17) Y = $PhCH_2$, Z = Me, R = H



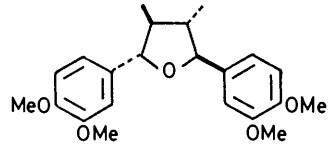
(4) W = X = Y = Z = Me
(11) XW = YZ = CH_2



(12) R = H
(13) R = Br



(5)



(6)

Catalytic hydrogenation of (1) with palladium–carbon, using a high catalyst : substrate ratio, gave by direct crystallization from the reaction mixture (±)-dihydroguaiaretic acid dimethyl ether (2), previously synthesized by a less direct Stobbe synthesis pathway.[2] In contrast, when this reduction was performed with a lower catalyst substrate ratio, the product, isolated in *ca.* 60% yield, was readily identified from the highly characteristic n.m.r. spectrum as the tetrahydrofuran lignan, (±)-veraguensin (3), which had previously been synthesized in very low yield [3] or by a more involved pathway.[4] (+)-Veraguensin was first isolated [5] from the wood *Ocotea veraguensis* and subsequently [6] from the leaves of *Trimenia papuana*.

Reduction of the racemic diketone (1) with lithium aluminium hydride yielded a diol whose n.m.r. spectrum exhibited non-equivalent secondary methyl groups, and

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is accordingly formulated as (4). The n.m.r. spectrum of the non-crystalline diacetate derivative also revealed non-equivalent methyl and acetoxy groups. On hydrogenation of this diol in acetic acid, two products were readily isolated by crystallization. The first, obtained in 22% yield, and identified as the aryltetralin (±)-galbulin (5) had previously been synthesized [7] prior to the isolation of the (−)-form, as a constituent of the bark of *Himantandra baccata*.[8] Several other syntheses of this product or interconversions from other lignans of known structure have been reported.[9-13] The second, a dehydration product obtained in *ca.* 50% yield was identified as (±)-galbelgin [10] (6), the all-*trans* substituted tetrahydrofuran isomer of veraguensin, which has also been obtained previously in low yield [3] or by a more circuitous route.[14]

Alkylation of 3,4-methylenedioxypropiophenone (7) with the α-bromo-derivative (8) yielded (±)-2,3-bis-(3,4-methylenedioxybenzoyl)butane (9). When this was hydrogenated in acetic acid solution, it behaved in an analogous manner to the veratroyl analogue, to give *r*-2,*c*-5-bis(3,4-methylenedioxyphenyl)-*t*-3,*c*-4-dimethyltetrahydrofuran (10), readily identified from the n.m.r. spectrum. This particular stereoisomer has not yet been reported as a natural product. The all-*trans* isomer is known, however, in both (−)- [8] and (+)-forms [15] and both *meso*-forms have been synthesized.[16] The diketone (9), when an increased catalyst ratio was used, similarly gave the butane (12), the (−)-enantiomer of which has recently been isolated from *Austrobaileya scandens* and designated as austrobilignan-5.[17] The hydrogenolysis product (12) is accordingly formulated as (±)-austrobilignan-5. Like the natural product, it was isolated as an oil, but was readily characterized as a crystalline dibromo-derivative. When the diketone was reduced with lithium aluminium hydride it gave the diol (11) which on hydrogenolysis in acetic acid also yielded (12), unexpectedly in view of the previous result, (4) ⟶ (5) + (6). The diarylbutane, austrobilignan-6 (14) and the tetrahydrofuran, austrobilignan-7 (15) whose structure had been established [17] by conversion into calopiptin (16), a constituent of *Piptocalyx moorei* Oliv.,[5,18] represent lignans with dissimilar aryl ring substitution. We wished to determine if the foregoing general procedures were readily adapted to synthesis of such structures. The required diaroylbutane intermediate (18) was obtained by reaction of the methylenedioxyphenyl bromo-ketone (8) with the anion derived from 4-benzyloxy-3-methoxypropiophenone (17).[19] When this was mixed rapidly with (8) there was obtained a mixture of all three diketones (1), (9), and (18). On the presumption that the symmetrical diketones had been formed as a consequence of competitive displacement on bromine *versus* carbon,[20] the complication was consequently readily obviated by slow addition of the bromo-ketone after which the desired unsymmetrical diketone (18) was isolated in 77% yield. Hydrogenation of this diketone in acetic acid with a high catalyst : substrate ratio readily gave the vanillylpiperonylbutane with a ^{1}H n.m.r. spectrum identical to that reported for austrobilignan-6(14).

When the reduction was performed with a lower catalyst : substrate ratio, *i.e.* conditions conducive to tetrahydrofuran formation, the crude product had a ^{1}H n.m.r. spectrum in excellent agreement with that that reported for austrobilignan-7, except for the appearance of two methoxy signals in a 1 : 1 ratio. It was concluded that the formation of (15) was accompanied, as would be expected, by the closely related structural analogue (19) with identical configuration. Our attempts at chromatographic separation of these isomers (silica, alumina, and polyamide) were unsuccessful. A partial separation of the acetate derivatives (20) and (21) was effected on silica gel, but neither was obtained crystalline or pure. We conclude that this methodology of synthesis of dissimilar substituted 2,5-diaryltetrahydrofurans will be limited by the isomer formation and separation difficulty. With similar or dissimilar aryl substitution, hydrogenolysis of 2,3-diaroylbutanes with catalyst : substrate ratio of 1 : 4 provides an excellent pathway to diarylbutane lignans, whereas a ratio of *ca.* 1 : 2 leads stereospecifically to 2,5-diaryl-3,4-dimethyltetrahydrofuran lignans.

EXPERIMENTAL

N.m.r. spectra were determined for solutions in [^{2}H]-chloroform with tetramethylsilane as internal standard. Peak integrated intensities were consistent with assigned numbers of protons.

(±)-*Dihydroguaiaretic Acid Dimethyl Ether* (2).—Palladium–charcoal (10%; 500 mg) was added to a solution of the diketone (1) (500 mg) in ethanol (50 ml) and stirred under hydrogen for 20 h. On crystallization of the residue, obtained by removal of catalyst and solvent, from methanol gave 1,4-bis(4-hydroxy-3-methoxyphenyl)-2,3-dimethylbutane (2) as prisms (260 mg), m.p. 71 °C (lit.,[2] m.p. 70.4—71.2 °C), δ 0.84 (d, *J* 6.5 Hz, 2 × sec-Me), 1.5—1.95 (m, 2 × C*H*Me), 2.3—2.65 (m, 4 benzylic H), 3.80 (s, 2 × OMe), 3.82 (s, 2 × OMe), and 6.55—6.85 (m, 6 × ArH).

(±)-*Veraguensin* (3).—Treatment of the diketone (1) (500 mg) in acetic acid (25 ml) with palladium–charcoal (10%, 200 mg) as above gave (±)-veraguensin (280 mg),

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m.p. and mixed m.p. 120—122 °C, on one crystallization from methanol, with a n.m.r. spectrum identical to that reported.[4]

2,3-*Dimethyl*-1,4-*diveratrylbutane*-1,4-*diol* (4).—Lithium aluminium hydride (0.5 g) in tetrahydrofuran (10 ml) was added to a solution of the diketone (1) (500 mg) in the same solvent; the mixture was stirred at room temp. for 1 h and then worked up in the usual way. Crystallization of the product (500 mg), once from ethanol, then from chloroform–light petroleum, yielded the *diol* (4) as flakes, m.p. 125—126 °C (Found: C, 67.6; H, 7.7. $C_{22}H_{30}O_6$ requires C, 67.7; H, 7.7%), δ 0.59 (d, *J* 7 Hz, sec-Me), 1.05 (d, *J* 7 Hz, sec-Me), 1.80—2.45 (m, 2 × C*H*Me), 3.88 (s, 4 × OMe), 4.2—4.7 (m, 2 ArC*H*OH–), and 6.65—6.95 (m, 6 × ArH).

Acetylation with acetic anhydride–pyridine gave a non-crystalline diacetate, δ 0.66 (d, *J* 7 Hz, sec-Me), 1.03 (d, *J* 7 Hz, sec-Me), 2.03 (s, OAc), 2.07 (s, OAc), 3.78, 3.82, and 3.88 (all s, 1, 1 and 2 OMe respectively), 5.51 (d, *J* 3.5 Hz, ArCH), 5.67 (d, *J* 3.5 Hz, ArCH), and 6.58—6.86 (m, 6 × ArH).

Hydrogenation of 2,3-*Dimethyl*-1,4-*diveratrylbutane*-1,4-*diol* (4).—Palladium–charcoal (10%, 120 mg) was added to a solution of the diol (4) (150 mg) in acetic acid (12 ml) and stirred under hydrogen at room temperature for 24 h. The catalyst and solvent were removed, and the residue crystallized from methanol to give (±)-galbulin (5) as short needles (30 mg), m.p. 116—118 °C (lit.,[12] m.p. 116—117 °C), δ 0.87 (d, *J* 5.5 Hz, 2-Me), 1.08 (d, *J* 5.5 Hz, 3-Me), 2.65 (m, $ArCH_2$), 3.57, 3.81, 3.84, and 3.87 (all s, 4 × OMe), 6.23 (s, 8-H), and 6.60—6.82 (m, 4 × ArH).

Evaporation of the filtrate and crystallization of the residue from diethyl ether–light petroleum gave (±)-galbelgin (6) as prisms (70 mg), m.p. 125—127 °C (lit.,[14] m.p. 124—127 °C) with concordant n.m.r. spectrum.

3,4-*Methylenedioxypropiophenone* (7).—A solution of piperonal (40 g) in ether (100 ml) was added during 15 min to a solution of ethylmagnesium bromide, prepared from magnesium (7.6 g), and ethyl iodide (31 ml) in ether (100 ml). The mixture was stirred for an additional 15 min, worked up, and the product (45.9 g) dissolved in acetone (200 ml) and oxidized with an excess of Jones reagent (1.4M). The dark oil product (35.5 g) was distilled at 120 °C/25 mmHg to give the ketone (7) as a white solid (31 g), m.p. 38—39 °C (lit.,[21] m.p. 38—39 °C), δ 1.20 (t, *J* 7 Hz, Me) 2.91 (q, *J* 7 Hz, CH_2), 6.03 (s, OCH_2O), and 6.73—7.65 (m, 3 × ArH).

α-*Bromo*-3,4-*methylenedioxypropiophenone* (8) prepared in quantitaive yield by bromine addition in chloroform solution, crystallized from methanol as needles, m.p. 54—55° (lit.,[22] m.p. 52—53 °C), δ 1.89 (d, *J* 7 Hz, Me), 5.56 (q, *J* 7 Hz, COCHBr), 6.07 (s, OCH_2O), and 6.82—7.78 (m, 3 × ArH).

(±)-2,3-*Bis*-(3,4-*methylenedioxybenzoyl*)*butane* (9).—To liquid ammonia (*ca.* 100 ml), ferric chloride (a few mg) was added, followed by sodium (430 mg); the mixture was stirred until disappearance of the blue colour when the ketone (7) (3.0 g) in tetrahydrofuran (100 ml) was added to it and stirred for 15 min; this was followed by the addition of the solid bromo-ketone (8) (4.35 g). Stirring was continued for 1 h after which solid ammonium chloride was added; the ammonia was then allowed to evaporate off. The mixture was filtered, washed with chloroform, and the solvents removed. Crystallization of the gum from methylene chloride–methanol gave the *diketone* (9) as fine needles (3.0 g), m.p. 206—207 °C (Found: C, 67.8; H, 5.2. $C_{20}H_{18}O_6$ requires C, 67.8; H, 5.1%), δ 1.26 (d, *J* 7 Hz, 2 × sec-Me), 3.67—4.03 (m, 2 × COCH), 6.05 (s, 2 × OCH_2O), and 6.82—7.77 (m. 6 × ArH).

r-2,c-5-*Bis*-(3,4-*methylenedioxyphenyl*)-t-3,c-4-*dimethyltetrahydrofuran* (10).—To a solution of the diketone (9) (500 mg) in acetic acid (100 ml) was added palladium–charcoal (10%; 250 mg); the mixture was stirred under hydrogen for 2½ h and then worked up. Crystallization of the product from ether–hexane gave the *tetrahydrofuran* (10) as needles (250 mg), m.p. 113—114 °C (Found: C, 70.4; H, 6.0. $C_{20}H_{20}O_5$ requires C, 70.6; H, 5.9%), δ 0.65 (d, *J* 7 Hz, 4-Me), 1.02 (d, *J* 6 Hz, 3-Me), *ca.* 1.8 (m, 2 × C*H*Me), 4.33 (d, *J* 9 Hz, 2-H), 5.08 (d, *J* 9 Hz, 5-H), 5.97 (s, 2 × OCH_2O), and 6.75—7.08 (m, 6 × ArH).

2,3-*Dimethyl*-1,4-*dipiperonylbutane*-1,4-*diol* (11).—A suspension of the diketone (9) (1.0 g) in tetrahydrofuran (20 ml) was added to lithium aluminium hydride (1.0 g) in the same solvent (20 ml) and the mixture was stirred for 1 h and then worked up. Crystallization of the product from chloroform–hexane afforded the *diol* (11) as rosette clusters (650 mg), m.p. 141—142° (Found: C, 67.0; H, 6.25. $C_{20}H_{22}O_6$ requires C, 67.0; H, 6.2%), δ 0.54 (d, *J* 7 Hz, sec-Me), 1.02 (d, *J* 7 Hz, sec-Me), 2.00—2.57 (m, 2 × C*H*Me), 4.32 (d, *J* 9 Hz, ArC*H*OH), 4.53 (d, *J* 8 Hz, ArCHOH), 5.93 and 5.97 (both s, 2 × OCH_2O), and 6.67—6.95 (m, 6 × ArH).

(±)-1,4-*Bis*(3,4-*methylenedioxyphenyl*)-2,3-*dimethylbutane* [(±)-Austrobilignan-5] (12). (a) A solution of the diol (11) (300 mg) in acetic acid (50 ml) was stirred under hydrogen with palladium–charcoal (10%; 200 mg) overnight, and worked up to yield (±)-austrobilignan-5 (12) as an oil, the n.m.r. spectrum of which was in excellent agreement with that reported for (—)-austrobilignan-5.

A solution of bromine (2 equiv.) in chloroform was added to (12) (260 mg) in the same solvent and the mixture heated under reflux for 5 min., treated with charcoal, filtered, and evaporated. Crystallization of the product from methanol gave (±)-1,4-*bis*-(2-*bromo*-4,5-*methylenedioxyphenyl*)-2,3-*dimethylbutane* (13) as prisms (150 mg), m.p. 135—136 °C (Found: C, 49.6; H, 4.2. $C_{20}H_{20}Br_2O_4$ requires C, 49.6; H, 4.2%), δ 0.88 (d, *J* 7 Hz, 2 × sec-Me), 1.50—2.25 (m, 2 × C*H*Me), 2.33—3.00 (m, 2 × $ArCH_2$), 5.93 (s, 2 × OCH_2O), 6.60 (s, 2 × 6-ArH) and 6.97 (s, 2 × 3-ArH).

(b) Hydrogenation of the diketone (9) (201 mg) in acetic acid (50 ml) with palladium–carbon (10%; 460 mg) gave (12), identical to that prepared in (a).

(±)-2-(4-*Benzyloxy*-3-*methoxybenzoyl*)-3-(3,4-*methylenedioxy*)*butane* (18).—To liquid ammonia (250 ml), ferric chloride (20 mg) was added, followed by sodium (880 mg) and the mixture was stirred until the blue colour disappeared. A solution of 4-benzyloxy-3-methoxypropiophenone [19] (9.3 g) in tetrahydrofuran (150 ml) was then added and stirred for 15 min. A solution of the bromoketone (8) (9.8 g) in tetrahydrofuran (100 ml) was added dropwise during 90 min and stirred for a further 30 min before ammonium chloride (4 g) was added, and the ammonia allowed to evaporate. The mixture was filtered, washed with tetrahydrofuran (50 ml), and the combined filtrate evaporated under reduced pressure to give a residual light brown solid (16.3 g), a portion of which (10.5 g) was dissolved in benzene (*ca.* 50 ml) and chromatographed on a column (12 in × 1½ in diameter) of silica gel (Merck 60). The column was eluted with benzene (100 ml) and the benzene–chloroform (25 : 2, 500 ml), to give a gum (2.04 g, not further examined); benzene–

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ethyl acetate (1 : 1, 500 ml) gave a solid (7.6 g) which on crystallization from methanol gave the *butane* (18) as spiked prisms (7.1 g), m.p. 113—116 °C (Found: C, 72.4; H, 5.9. $C_{27}H_{26}O_6$ requires C, 72.6; H, 5.9%), δ 1.25 (d, *J* 6 Hz, 2 × sec-Me), 3.67—4.17 (m, 2 × COCH), 3.88 (s, ArOMe), 5.22 (s, OCH_2Ph), 5.98 (s, 2 × OCH_2O), and 6.78—7.77 (m, 11 × ArH).

In an experiment in which the bromo-ketone was added in one portion, the three diketones (1), (9), and (18) were detected in the residual product. On chromatography on alumina, elution with benzene–chloroform (10 : 1 to 4 : 1) gave the dipiperonylbutane (9) and with chloroform a mixture of (1) and (18), readily separated by fractional crystallization from methanol, (18) being the more soluble constituent.

(±)-1-(4-*Hydroxy*-3-*methoxyphenyl*)-4-(3,4-*methylenedioxyphenyl*)-2,3-*dimethylbutane* [(±)-*Austrobilignan*-6] (14).—A solution of the diketone (18) (510 mg) in acetic acid (100 ml) was stirred with palladium–carbon (10%, 2 g) under hydrogen for 3½ hr. Filtration and solvent removal gave (±)-austrobilignan-6 (14) as a gum (390 mg); the ^1H n.m.r. spectrum was identical to that reported in the literature.[17]

Attempted Synthesis of Austrobilignan-7 (15).—A solution of the diketone (18) (2 g) in acetic acid (200 ml) was stirred with palladium–carbon (10%; 800 mg) under hydrogen for 3½ h, filtered, and evaporated to give a pale yellow gum (1.65 g), which was purified by t.l.c. [benzene–ether (2 : 1), saturated with ammonia]. The n.m.r. spectrum was similar to that reported for (15), except that in addition to an OMe signal at δ 3.87, another of equal intensity at δ 3.90 [attributed to the OMe of (19)] was found. Attempted separation by chromatography on silica, alumina, and polyamide with a variety of solvent systems was unsuccessful. Acetylation with pyridine and acetic anhydride gave a gum with n.m.r. spectrum similar to that reported of austrobilignan-7 acetate (20) except that in addition to an OMe signal at δ 3.83, another at δ 3.87 [attributed to the OMe of (21)] was present. A partial separation of these was obtained by t.l.c. on silica gel [benzene–ether (15 : 1)] with the ratio of (20) : (21) increasing in the lower third of the plate and decreasing in the top third (as measured by methoxy integration). Neither fraction could be crystallized.

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