# Synthesis of (±)-Deoxyschizandrin [1]

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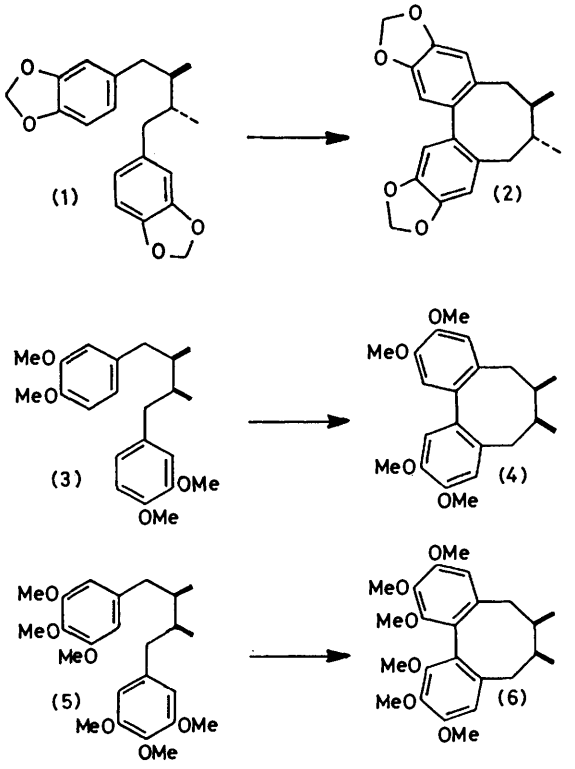
1,4-Diarylbutanes undergo intramolecular oxidation with vanadium oxytrifluoride to yield dibenzo[*a,c*]cyclo-octenes. Two short synthetic routes to the lignan, (±)-deoxyschizandrin have been developed from 3,4,5-trimethoxypropiophenone.

OVER twenty naturally occurring bisbenzocyclo-octenes have been isolated and are now recognized as a subgroup of lignans. They include the schizandrins,[2,3] the gomisins,[4] the steganes,[5] and kadsurins.[6] The significant therapeutic activity already reported for several of these products has promoted much recent activity in both synthesis and structure elucidation, and syntheses of (±)-steganacin,[7,8] (±)-steganol,[7,8] (±)-steganone,[7-9] (±)-deoxyschizandrin,[10] and (±)-kadsurin [11] have been reported within the last two years. Other significant approaches to the bisbenzocyclo-octene skeleton have also been described recently.[12-14] We report here a short synthesis of (±)-deoxyschizandrin,[15] a constituent of the seed oil of *Schizandra chinensis* Baill. (Magnoliaceae).

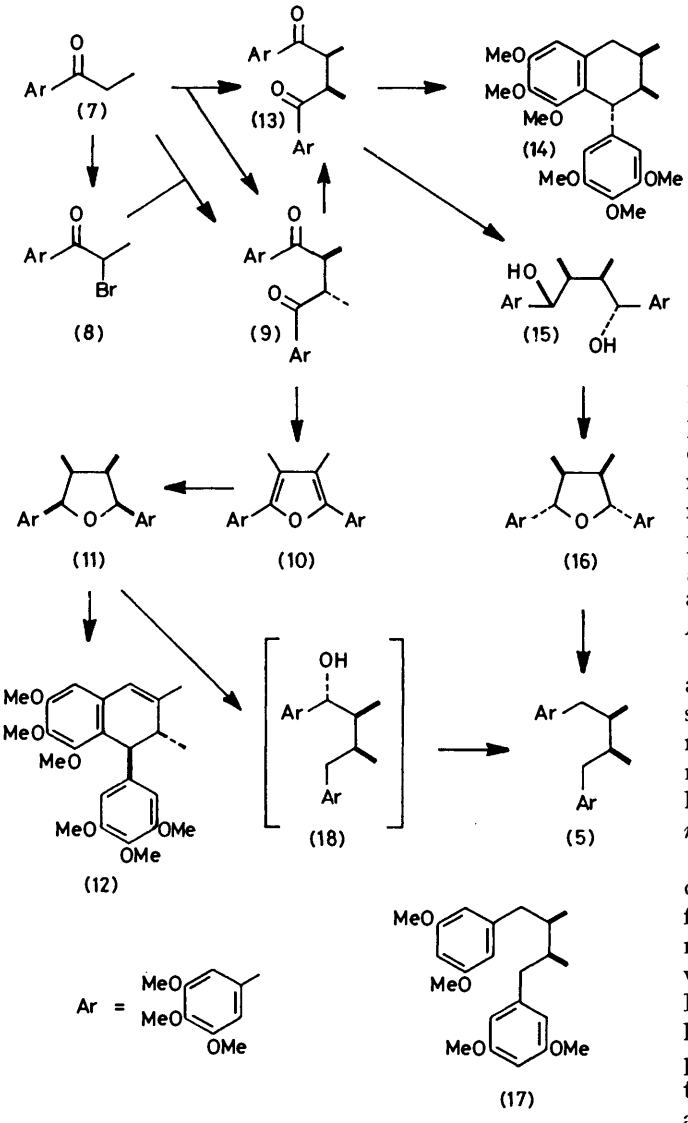
The introduction of vanadium oxytrifluoride as a reagent for the intramolecular oxidation of non-phenolic substrates [16] prompted preliminary experiments to ascertain if the lignan bisbenzocyclo-octene skeleton might be simply assembled from a 1,4-diarylbutane. Accordingly, the bis-methylenedioxyphenylbutane (1), previously prepared [17] in confirmation of the structure of (±)-austrobilignan-5,[18] was treated with vanadium oxytrifluoride and afforded in 60% yield a high-melting product whose $^1$H n.m.r. spectrum was in complete agreement with the dibenzo[*a,c*]cyclo-octene structure (2). Similar oxidation of *meso*-dihydroguaiaretic acid dimethyl ether (3), of well established configuration,[19] yielded the tetramethoxy analogue (4).




Further information essential for a synthesis of (±)-deoxyschizandrin was forthcoming from these successful intramolecular oxidations. Whereas the proton chemical shifts of the *trans*-6,7-dimethyl groups in (2) are identical (δ 1.03), they are non-equivalent (δ 0.80 and 1.05) in the *cis*-6,7-dimethyl product (4). While this is readily understandable as a consequence of the restricted rotation of the biphenyl, the striking agreement between the values of the latter and those reported for (±)-deoxyschizandrin indicate that the *trans*-dimethyl structure proposed [15] for the natural product must be incorrect and that it should be formulated as the *cis*-isomer (6). This conclusion, which has also been reached independently,[10] necessitated the preparation of *meso*-1,4-bis-(3,4,5-trimethoxyphenyl)-2,3-dimethylbutane (5) as the immediate synthetic precursor.

The required starting ketone, 3,4,5-trimethoxypropiophenone (7) was readily obtained by addition of ethylmagnesium bromide to 3,4,5-trimethoxybenzaldehyde followed by Jones oxidation, and yielded the α-bromo-derivative (8) as previously described.[20] Alkylation of the sodium enolate of (7) with (8) in liquid ammonia gave in 93% yield the diaroylbutane (9) whose expected [17,19] racemic configuration was confirmed by the characteristic chemical shift (δ 1.32) of the methyl group. This diketone was quantitatively converted to the diaryldimethylfuran (10) by brief treatment with methanolic hydrogen chloride and thence to the *meso-cis*-tetrahydrofuran (11) by catalytic hydrogenation in acetic acid. The symmetry of (11) is readily established from the $^1$H n.m.r. spectrum and the *cis* methyl–aryl configuration revealed by the resonance (δ 0.67) of the methyl groups, highly shielded by the aryl rings. It had been hoped that catalytic hydrogenolysis of (11) would yield the *meso*-butane (5) directly, since such a reduction had been reported for the veratryl analogue.[19] We were, however, unsuccessful in attempts to accomplish this under a variety of hydrogenation conditions, which led us to seek an alternative route. The instability of the tetrahydrofuran towards acid was shown by conversion to the known [21] aryldihydronaphthalene (12) by treatment with perchloric acid–acetic acid at room temperature.

A recently reported method for the synthesis of 1,4-diketones involves oxidative coupling of a ketone enolate with cupric chloride [22] or cupric trifluoromethanesulphonate.[23] We have found that oxidation of the




anion of 3,4,5-trimethoxypropiophenone (7), prepared in di-isopropylamine–tetrahydrofuran, with cupric trifluoromethanesulphonate gave in excellent yield a mixture of the (±)-diketone (9) and the *meso*-diketone (13) in the ratio *ca.* 3 : 2. The separation of these isomers was particularly simple due to the *meso*-diketone being fortuitously insoluble in ether and separating at the ether–water interface of the usual work-up, leaving the (±)-diketone in the ether phase. This observation further indicated that base-catalysed isomerization of the (±)-diketone in ether solvent would result in precipitation of the desired *meso*-diketone, and such conversion was effected in over 90% yield. An attempt to transform the diaroylbutane (13) to the desired dibenzylbutane (5) directly by hydrogenolysis was again unsuccessful. From the mixture obtained under hydrogenation conditions in tetrahydrofuran, the only crystalline product isolated had an empirical formula $C_{24}H_{32}O_4$, and on the basis of the $^1$H n.m.r. spectrum is most reasonably formulated as the aryltetralin (14) in which the 1-aryl group adopts the more stable axial conformation (*trans* to the C-3 equatorial methyl group).

Reduction of the diketone (13) with lithium aluminium hydride gave a diol. Of the two configurational possibilities, the symmetrical (*meso*) or unsymmetrical (racemic) structure, the former is clearly excluded by the $^1$H n.m.r. spectrum. The diol, which could have been formed by an intramolecular hydride transfer from the intermediate alkoxymetal hydride, is accordingly formulated as (15). Attempted conversion of this diol to the methanesulphonate ester derivative and to the derived dibromide by treatment with triphenylphosphine dibromide resulted in each case in dehydration to the known [21] *meso-trans*-tetrahydrofuran (16) as the principal product. Again, this tetrahydrofuran was resistant to catalytic hydrogenolysis, but was successfully cleaved by reduction with sodium in liquid ammonia to yield the required *meso*-diaryldimethylbutane (5). A minor by-product, readily separated by thin-layer chromatography was the analogue (17) in which reductive dealkoxylation of the *p*-methoxy functions had occurred. Ample precedent for this behaviour exists.[24]

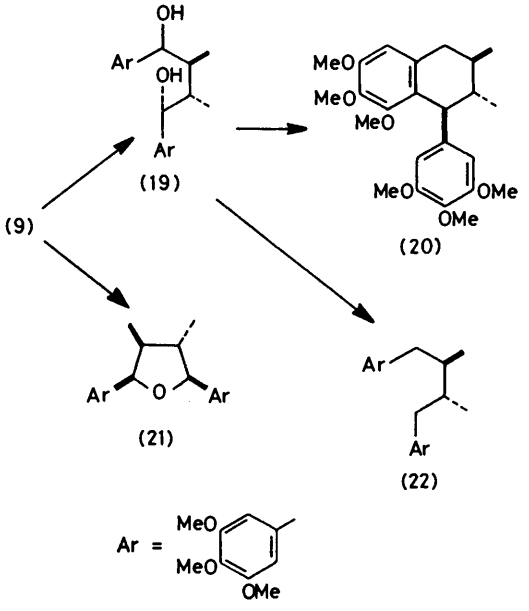
The *meso-cis*-tetrahydrofuran (11) was consequently also subjected to sodium–ammonia reduction under the same conditions. The crude product could most reasonably be formulated, by consideration of the $^1$H n.m.r. spectrum as the alcohol (18), and as expected on hydrogenation in acetic acid yielded the same required *meso*-diarylbutane (5).

The final step in the synthesis of (±)-deoxyschizandrin consisted of oxidation of (5) with vanadium oxytrifluoride to give the dibenzo[*a*,*c*]cyclo-octene (6) with m.p. and $^1$H n.m.r. spectrum in excellent agreement with the racemic product, reported by Ghera, Ben-David, and Becker in a fifteen-step synthesis, and which had been identified with the natural product by comparison of i.r., u.v., and $^1$H n.m.r. spectra.[10] We believe that this five-step synthesis should be of general applicability and affords considerable economy of effort.

Some additional experiments were performed on the (±)-diketone (9). On reduction with lithium aluminium hydride, of the two possible diol products, a racemic unsymmetrical diol and a racemic symmetrical diol, the former (19) was obtained, and on catalytic hydrogenation in ethanol yielded the all-*trans*-aryltetralin (20). Catalytic hydrogenation of the diketone (9) in ethanol yielded the known diaryltetrahydrofuran (21). Sodium–ammonia reduction of (21) or catalytic hydrogenolysis of the diol (19) in acetic acid both yielded the (±)-diaryldimethylbutane (22).

Since considerable uncertainty exists regarding the configurations at C-6,7 of several other *Schizandra* products (compare refs. 2 and 4 with 6 and 25), these procedures also open the way for proof by synthesis.

In the Chinese work,[25] deoxyschizandrin (named Wuweizisu A) was isolated from the fruit of the plant and was assigned the same C-6,7 *cis*-configuration as adduced here.




EXPERIMENTAL

N.m.r. spectra were determined for solutions in [$^2$H]-chloroform with tetramethylsilane as internal standard. M.p.s were determined with a Fisher–Johns apparatus. Analytical and preparative t.l.c. were carried out on Polygram Sil G (Macherey–Nagel) and silica gel 60 PF-254 + 366 (Merck). Column chromatography procedures were carried out on silica gel 60 (70—230 mesh, Merck) or alumina grade III (Woelm).

*Action of Vanadium Oxytrifluoride on* (±)-2,3-*Dimethyl*-1,4-*bis*-(3,4-*methylenedioxyphenyl*)*butane* (1).—Vanadium oxytrifluoride (0.5 g) was added to a solution of the butane (1) (220 mg) and trifluoroacetic acid (6 ml) in dichloromethane (55 ml) at 0 °C. The mixture was stirred at 0 °C for 1 h and at room temperature for a further 3 h. Citric acid (3 g) was then added, followed by water, and the separated organic layer washed with water and 10% w/v aqueous sodium carbonate. Evaporation of the dried ($Na_2SO_4$) extract gave a residual brown solid (210 mg) which was dissolved in benzene and filtered through Florisil (F-101) to yield a solid (129 mg) which crystallized from methanol to give trans-5,6,7,8-*tetrahydro*-6,7-*dimethyl*-2;3;10,11-*bismethylenedioxydibenzo*[a,c]*cyclo-octene* (2) as long prisms, m.p. 251—252° (Found: C, 74.1; H, 6.4. $C_{20}H_{20}O_4$ requires C, 74.05; H, 6.22%), δ (200 MHz) 1.03 (6 H, d, *J* 6 Hz, sec. $CH_3$), 1.25br (2 H, s, MeC*H*), 2.23 and 2.31 (4 H, 6-line m, $J_{gem}$ 14 Hz, $J_{vic}$ 9.5 and 1 Hz, $ArCH_2$), 5.94 (4 H, s, $OCH_2O$), 6.70 (2 H, s, ArH), and 6.74 (2 H, s, ArH).

*Action of Vanadium Oxytrifluoride on* meso-*Dihydroguaiaretic Acid Dimethyl Ether* (3).—To a solution of the ether (3) (180 mg, 0.5 mmol) in dichloromethane (10 ml) containing trifluoroacetic anhydride (0.5 ml) was added vanadium oxytrifluoride (372 mg, 3 mmol) in dichloromethane (10 ml) containing trifluoroacetic acid (1 ml) over 10 min at 5 °C. The mixture was stirred at room temperature for 2 h, poured onto ice, and the separated organic layer washed with saturated sodium hydrogencarbonate solution, dried ($Na_2SO_4$), and evaporated. The residue was chromatographed on a column of alumina (Grade III), elution with ether–light petroleum (1 : 4) giving a fraction (80 mg) which crystallized from the same solvents to give cis-2,3,10,11-*tetramethoxy*-6,7-*dimethyl*-5,6,7,8-*tetrahydrodibenzo*[a,c]*cyclo-octene* (4) as needles, m.p. 175—177° (Found: C, 74.3; H, 7.6. $C_{22}H_{28}O_4$ requires C, 74.15; H, 7.9%), δ 0.80 (3 H, d, *J* 6 Hz, sec. $CH_3$), 1.05 (3 H, d, *J* 6 Hz, sec. $CH_3$), 1.04—2.0 (2 H, m, MeC*H*), 2.05—2.66 (4 H, m, $ArCH_2$), 3.88 (6 H, s, ArOMe), 3.93 (6 H, s, ArOMe), and 6.75 (4 H, s, ArH).

3,4,5-*Trimethoxypropiophenone* (7).—A solution of 3,4,5-trimethoxybenzaldehyde (15 g) in ether (100 ml) was added to a solution of ethylmagnesium bromide [from magnesium (2.75 g), Vitride (Eastman) (1 ml), ethyl bromide (10 ml), and ether (100 ml). The mixture was stirred for 15 min, then worked up in the usual way to give the intermediate alcohol as an oil (17 g), δ 0.95 (3 H, t, *J* 7 Hz, Me), 1.6—1.9 (2 H, m, $CH_2$), 2.03 (1 H, s, OH), 3.87 (3 H, s, 4-OMe), 3.89 (6 H, s, 3- and 5-OMe), 4.45 (1 H, t, *J* 7 Hz, ArCH), and 6.62 (2 H, s, ArH). To a solution of this alcohol in acetone (100 ml) at 0 °C was added Jones reagent (1.4M; 60 ml), the mixture stirred at room temperature for 1 h, then worked up by aqueous dilution and extraction with ether to yield the ketone (7) as long needles (14.2 g), m.p. 52—53° (from light petroleum), δ 1.22 (3 H, t, *J* 7 Hz, Me), 2.97 (2 H, q, *J* 7 Hz, $CH_2$), 3.92 (9 H, s, ArOMe), and 7.27 (2 H, s, ArH). The ketone with same m.p. was prepared less conveniently from diethylcadmium and 3,4,5-trimethoxybenzoyl chloride as previously described.[26]

α-*Bromo*-3,4,5-*trimethoxypropiophenone* (8).—Bromination of the ketone (7) (4.48 g) in chloroform solution as previously described [20] gave the bromo-ketone (8) as needles (5.3 g), m.p. 84—85° (from methanol) (lit.,[20] 83—84°), δ 1.87 (3 H, d, *J* 7 Hz, Me), 3.93 (9 H, s, ArOMe), 5.15 (1 H, q, *J* 7 Hz, CHBr), and 7.35 (2 H, s, ArH).

(±)-2,3-*Bis*-(3,4,5-*trimethoxybenzoyl*)*butane* (9).—To liquid ammonia (50 ml) was added ferric chloride (25 mg) followed by sodium (400 mg), and the mixture stirred until disappearance of the blue colour. The ketone (7) (2.6 g) was added with continued stirring for 15 min, followed by the bromo-ketone (8) (3.5 g). After a further hour, ammonium chloride (3 g) and dichloromethane (50 ml) were added, the ammonia allowed to evaporate, and the mixture filtered and washed with dichloromethane (25 ml). The combined filtrate was diluted with methanol and concentrated to yield the *racemic diketone* (9) as long needles (4.8 g), m.p. 165—166°, ν(KBr) 1 660 $cm^{-1}$ (Found: C, 64.45; H, 6.85. $C_{24}H_{30}O_8$ requires C, 64.55; H, 6.75%), δ 1.32 (6 H, d, *J* 7 Hz, sec. Me), 3.92 (18 H, s, ArOMe), and 7.28 (4 H, s, ArH).

3,4-*Dimethyl*-2,5-*bis*-(3,4,5-*trimethoxyphenyl*)*furan* (10).—To a solution of the racemic diketone (9) (700 mg) in dichloromethane (4 ml) was added 4 ml of an aqueous methanolic hydrogen chloride solution (made by diluting 5 ml of concentrated hydrochloric acid to 100 ml with methanol). The mixture was heated under reflux for 10 min, and cooled, to yield the furan (10) as prisms (653 mg), m.p. 155—157° (Found: C, 67.35; H, 6.4. $C_{24}H_{28}O_7$ requires C, 67.25; H, 6.6%), δ 2.23 (6 H, s, Me), 3.91 (6 H, s, 4-ArOMe), 3.94 (12 H, s, 3- and 5-ArOMe), and 6.91 (4 H, s, ArH).

Treatment of the *meso*-diketone (13) (500 mg, prepared

as below) under the same conditions yielded the same furan (460 mg).

c-3,c-4-*Dimethyl*-r-2,c-5-*bis*-(3,4,5-*trimethoxyphenyl*)*tetrahydrofuran* (11).—A solution of the furan (10) (1.5 g) in acetic acid (20 ml) was stirred with palladium–carbon (10%; 3.5 g) under hydrogen for 16 h. After filtration and evaporation, the residual oil (1.26 g) was crystallized from ether to yield the meso-cis-*tetrahydrofuran* (11) as prisms, m.p. 109—110° (Found: C, 66.85; H, 7.5. $C_{24}H_{32}O_7$ requires C, 66.65; H, 7.45%), δ 0.67 (6 H, d, *J* 7 Hz, C-3 and -4 Me), 3.88 (18 H, s, ArOMe), 5.15 (2 H, d, *J* 7 Hz, H-2 and -5), and 6.70 (4 H, s, ArH).

Under a variety of catalytic hydrogenation conditions in tetrahydrofuran solution at pressures up to 2 000 lb $in^{-2}$, (11) was recovered unchanged.

*Action of Perchloric Acid on the* meso-cis-*Tetrahydrofuran* (11).—Perchloric acid (70%, 4 ml) was added to a solution of (11) (200 mg) in acetic acid (4 ml). The mixture was stirred for 30 min, then neutralized with sodium hydroxide solution and extracted with ether. Evaporation of the washed and dried extract gave a solid (126 mg) which on purification by t.l.c. ($R_F$ 0.6, benzene–ether 4 : 1) and crystallization from methanol gave *trans*-1,2-dihydro-6,7,8-trimethoxy-2,3-dimethyl-1-(3,4,5-trimethoxyphenyl)naphthalene (12) as prisms, m.p. 108—109° (lit.,[21] 105—106°), δ 1.08 (3 H, d, *J* 7 Hz, 2-Me), 1.80 (3 H, d, *J* 1.5 Hz, 3-Me), 2.1—2.4 (1 H, m, H-2), 3.62 (3 H, s, 8-OMe), 3.73 (6 H, s, 3- and 5-OMe), 3.77, 3.83, and 3.85 (each 3 H, s, OMe), 4.05br (1 H, H-1), 6.12 (1 H, d, *J* 1.5 Hz, H-4), 6.35 (2 H, s, H-2 and -6), and 6.45 (1 H, s, H-5).

meso-2,3-*Bis*-(3,4,5-*trimethoxybenzoyl*)*butane* (13).—(*a*) n-Butyl-lithium (9.1 ml; 2.2M in hexane) was added to a solution of di-isopropylamine (2.94 ml) in tetrahydrofuran (18.6 ml) under nitrogen, stirred at 0 °C for 15 min, then cooled to −78 °C. A solution of the propiophenone (7) (4 g) in tetrahydrofuran (30 ml) was added with stirring for 1 h followed by a solution of copper(I) trifluoromethanesulphonate (7.18 g) in acetonitrile (20 ml). After stirring for a further hour at −78 °C and 30 min at room temperature, ammonium chloride (6 g) was added and the mixture poured into ice–water and extracted with ether. The solid which precipitated at the interfacial layer was collected and recrystallized from dichloromethane–methanol to give the meso-*diketone* (13) as long needles (1.3 g), m.p. 194—196° (Found: C, 64.4; H, 6.8. $C_{24}H_{38}O_8$ requires C, 64.55; H, 6.75%), δ 1.17 (6 H, d, *J* 7 Hz, sec. Me), 3.97 (18 H, s, ArOMe), and 7.33 (4 H, s, ArH).

Evaporation of the washed and dried ether layer yielded the (±)-diketone (9) (2.1 g), identical to that prepared by alkylation of the ketone (7) with the bromo-ketone (8).

(*b*) A solution of sodium methoxide (90 mg) in methanol (10 ml) was added to a solution of the (±)-diketone (9) in tetrahydrofuran–diethyl ether (70 ml; 2 : 5 v/v) and the mixture stirred at room temperature overnight, when the precipitated *meso*-diketone (302 mg, m.p. 196—197°) was collected. Concentration of the filtrate gave, after one day, a further 72 mg of the same product. The *meso*-diketone was also rather soluble in methanol, cyclohexane, and acetic acid.

*Reduction of* meso-2,3-*Bis*-(3,4,5-*trimethoxybenzoyl*)*butane* (13).—(a) *By catalytic hydrogenation*. A solution of the *meso*-diketone (250 mg) in tetrahydrofuran (75 ml) was stirred with palladium–carbon (10%; 1.6 g) under hydrogen for 18 h. After filtration and evaporation, the residual oil (200 mg) was purified by t.l.c. [$R_F$ 0.45 (benzene–ether 4 : 1)] and crystallized from hexane to give 1,2,3,4-*tetrahydro*-6,7,8-*trimethoxy*-t-2,t-3-*dimethyl*-r-1-(3,4,5-*trimethoxyphenyl*-*naphthalene* (14) as prisms (98 mg), m.p. 105—107° (Found: C, 69.4; H, 7.8. $C_{24}H_{32}O_6$ requires C, 69.2; H, 7.75%), δ 0.90 (3 H, d, *J* 6 Hz, 2- or 3-Me), 0.93 (3 H, d, *J* 7 Hz, 3- or 2-Me), 1.6—2.1 (2 H, m, H-2 and -3), 2.2—2.8 (2 H, m, $ArCH_2$), 3.40 (3 H, s, 8-OMe), 3.75 (6 H, s, 2 × ArOMe), 3.81 (6 H, s, 2 × ArOMe), 3.87 (3 H, s, ArOMe), 4.02 (1 H, d, *J* 2.5 Hz, H-1), 6.22 (2 H, s, H-2 and -5), and 6.47 (1 H, s, H-5).

(b) *By lithium aluminium hydride*. Lithium aluminium hydride (0.5 g) was added to a solution of the *meso*-diketone (410 mg) in tetrahydrofuran, stirred at room temperature for 1 h, then worked up as usual to give the racemic unsymmetrical diol (1RS,2SR,3RS,4RS)-2,3-*dimethyl*-1,4-*bis*-(3,4,5-*trimethoxyphenyl*)*butane*-1,4-*diol* (15) as an amorphous solid (Found: C, 64.0; H, 7.6. $C_{24}H_{34}O_8$ requires C, 64.0; H, 7.6%), δ 0.66 (3 H, d, *J* 7 Hz, sec. Me), 0.92 (3 H, d, *J* 7 Hz, sec. Me), 1.8—2.2 (2 H, m, H-2 and -3), 3.83 (18 H, s, 6 × ArOMe), 4.2—4.4 (1 H, m, ArC*H*OH–), 4.6—4.9 (1 H, m, ArC*H*OH–), and 6.52 (4 H, s, ArH).

*Dehydration of the Racemic Unsymmetric Diol* (15).—(a) *With methanesulphonyl chloride*. Methanesulphonyl chloride (1 ml) was added to a solution of the diol (15) (650 mg) in pyridine (20 ml) at room temperature. The mixture was stirred for 20 h, then worked up *via* ether to yield a light brown oil (475 mg) which crystallized from ether–light petroleum to yield the *meso-trans*-tetrahydrofuran, *t*-3,*t*-4-dimethyl-*r*-2,*c*-5-bis-(3,4,5-trimethoxyphenyl)tetrahydrofuran (16) (308 mg), m.p. 90—92° (lit.,[21] m.p. 90—90.5°), δ 1.07 (6 H, d, *J* 7 Hz, 3- and 4-Me), 2.5—2.6 (2 H, m, H-3 and -4), 3.85 (18 H, s, 6 × OMe), 4.52 (2 H, d, *J* 6 Hz), and 6.70 (4 H, s, ArH). Inspection of the $^1H$ n.m.r. spectrum of the crude product indicated it was a mixture of the *meso-trans* (16) and *meso-cis* (11) isomers in a 7 : 1 ratio. The same result was obtained by carrying out the reaction for 15 min at 0 °C with dichloromethane–tri-n-butylamine as solvent. The *meso-trans*-tetrahydrofuran was recovered unchanged from attempted catalytic hydrogenolysis with palladium–carbon in tetrahydrofuran.

(b) *With triphenylphosphine dibromide*. A solution of the diol (15) (500 mg) in acetonitrile (5 ml) was added dropwise at room temperature to a solution of triphenylphosphine dibromide, prepared at 0 °C by addition of bromine (360 mg) to triphenylphosphine (620 mg) in acetonitrile (10 ml). The mixture was stirred for 10 min, then filtered and evaporated. The residue was dissolved in benzene–ether (4 : 1) and filtered through a silica column (4 × 1/2 in diam.). Elution with the same solvent (80 ml) gave an oil (62 mg) followed by the *meso-trans*-tetrahydrofuran (16) (367 mg) eluted by the next 200 ml of solvent.

*Sodium–Ammonia Reduction of* meso-trans-*Tetrahydrofuran* (16).—To liquid ammonia (100 ml), sodium (0.1 g) was added, followed by a solution of the *meso-trans*-tetrahydrofuran (16) (720 mg) in 1,2-dimethoxyethane. More sodium (0.3 g) was then added and the mixture stirred for 15 min. After addition of water (8 ml), the ammonia was allowed to evaporate, and dichloromethane (65 ml) was added to the residue. The mixture was filtered, the filtrate evaporated, and the product subjected to preparative t.l.c. (benzene–ether 85 : 15). The front-running zone ($R_F$ 0.75) gave meso-1,4-*bis*-(3,5-*dimethoxyphenyl*)-2,3-*dimethylbutane* (17) (51 mg) as an oil, which did not crystallize from the common solvents, δ 0.87 (6 H, d, *J* 6 Hz, 2- and 3-Me), 1.5—2.0 (2 H, m, H-2 and -3), 2.2—2.9 (4 H, m, $ArCH_2$),

3.77 (12 H, s, 4 × ArOMe) and 6.33 (6 H, s, 6 × ArH). An intermediate zone ($R_F$ 0.55) yielded 173 mg of an unidentified mixture. The third zone ($R_F$ 0.33) gave meso-1,4-*bis*-(3,4,5-*trimethoxyphenyl*)-2,3-*dimethylbutane* (5) as short prisms (394 mg) from methanol, m.p. 87—89° (Found: C, 68.8; H, 8.25. $C_{24}H_{34}O_6$ requires C, 68.85; H, 8.2%), δ 0.88 (6 H, d, *J* 6 Hz, 2- and 3-Me), 1.5—2.0 (2 H, m, H-2 and -3), 2.2—2.9 (4 H, m, $ArCH_2$), 3.85 (18 H, s, 6 × ArOMe), and 6.38 (4 H, s, 4 × ArH).

(±)-*Deoxyschizandrin* (6).—Trifluoroacetic acid–methylene chloride (1 : 4; 10 ml) was added to a solution of the hexamethoxydiarylbutane (5) (54 mg) in methylene chloride (15 ml) at −78 °C and the mixture stirred for 10 min. Vanadium oxytrifluoride (100 mg) was then added with stirring at the same temperature for 30 min and at room temperature for a further 30 min. After removal of solvent, concentrated ammonium hydroxide solution (3 ml) was added and the mixture extracted with ether. Evaporation of the washed and dried extract gave a solid (49 mg) which on t.l.c. (ether–light petroleum 1 : 1) gave a front-running zone, which on elution and crystallization from methanol gave *cis*-5,6,7,8-tetrahydro-1,2,3,10,11,12-hexamethoxy-6,7-dimethyldibenzo[*a*,*c*]cyclo-octene (deoxyschizandrin) (6) as short prisms (29 mg) from methanol, m.p. 114—115° (lit.,[10] 112—113°), δ 0.73 (3 H, d, *J* 7 Hz, sec. Me), 1.00 (3 H, d, *J* 7 Hz, sec. Me), 1.9—2.1 (2 H, m, H-6 and -7), 2.2—2.7 (4 H, m, 2 × $ArCH_2$), 3.60 (6 H, s, 2 × ArOMe), 3.90 (12 H, s, 4 × ArOMe), and 6.55 (2 H, s, 2 × ArH).

*Hydrogenolysis of the* meso-cis-*Tetrahydrofuran* (11).—The *meso-cis*-tetrahydrofuran (740 mg) was treated with sodium and ammonia in the same manner as the *meso-trans* isomer, and gave an oil (602 mg) which on t.l.c. (ether–light petroleum 1 : 1) gave an oil (310 mg) considered to be the alcohol (18), δ 0.66 (3 H, d, *J* 7 Hz, sec. Me), 0.91 (3 H, d, *J* 7 Hz, sec. Me), 1.7—2.3 (2 H, m), 3.95 (18 H, s 6 × ArOMe), 4.40 (1 H, d, ArCHO–), 6.47 (2 H, s, 2 × ArH), and 6.57 (2 H, s, 2 × ArH). A solution of this product (250 mg) in acetic acid (50 ml) was stirred under hydrogen with palladium–carbon (10%; 250 mg) for 20 h. Work-up in the usual way gave the *meso*-diarylbutane (5) (166 mg).

r-2,c-5-*Bis*-(3,4,5-*trimethoxyphenyl*)-t-3,c-4-*dimethyltetrahydrofuran* (21).—A solution of the racemic diketone (9) (1.0 g) in ethanol (100 ml) was stirred with palladium–carbon (10%; 0.5 g) at room temperature under hydrogen for 20 h. The residue obtained after filtration and removal of solvent was crystallized from ether–light petroleum to yield the tetrahydrofuran (21) as prisms (630 mg), m.p. 89—91° (lit.,[21] 90—91°) (Found: C, 66.75; H, 7.45. Calc. for $C_{24}H_{32}O_7$: C, 66.65; H, 7.45%), δ 0.72 (3 H, d, *J* 7 Hz, 4-Me), 1.12 (3 H, d, *J* 6 Hz, 3-Me), 1.60—1.94 (1 H, m, H-3), 2.05—2.45 (1 H, m, H-4), 3.83, 3.85, and 3.87 (6 H, each s, ArOMe), 4.44 (1 H, d, *J* 8.5 Hz, H-2), 5.13 (1 H, d, *J* 8 Hz, H-5), 6.61 (2 H, s, ArH), and 6.78 (2 H, s, ArH).

*Reduction of* (±)-2,3-*Bis*-(3,4,5-*trimethoxybenzoyl*)*butane* (9) *with Lithium Aluminium Hydride*.—A solution of the racemic diketone (9) (0.5 g) in tetrahydrofuran (30 ml) was added to lithium aluminium hydride (0.5 g) in the same solvent (10 ml), the mixture stirred at room temperature for 1 h, then worked up in the usual way. Trituration of the product with chloroform–light petroleum gave the racemic unsymmetrical diol (1SR,2SR,3SR,4RS)-1,4-*bis*-(3,4,5-*trimethoxyphenyl*)-2,3-*dimethylbutane*-1,4-*diol* (19) as a solid of indefinite m.p. (softening *ca.* 135—140° with clearing *ca.* 165—176°) (Found: C, 63.9; H, 7.7. $C_{24}H_{34}O_8$ requires C, 64.0; H, 7.6%), δ 0.72 (3 H, d, *J* 7 Hz, sec. Me), 1.08 (3 H, d, *J* 7 Hz, sec. Me), 2.0—2.25 (2 H, m, H-2 and -3), 3.82 and 3.85 (18 H, each s, 6 × ArOMe), 4.2—4.7 (2 H, m, ArC*H*OH–), 6.48 (2 H, s, ArH), and 6.62 (4 H, s, ArH).

(±)-1,4-*Bis*-(3,4,5-*trimethoxyphenyl*)-2,3-*dimethylbutane* (22).—(*a*) A solution of the (±)-unsymmetrical diol (19) (350 mg) in acetic acid (20 ml) was stirred with palladium–carbon (10%; 0.3 g) under hydrogen for 72 h. After filtration and evaporation, the residue was crystallized from methanol to give the (±)-dimethylbutane (22) as prisms, m.p. 126—128° (lit.,[21] 129—130°) (Found: C, 68.95; H, 8.25. Calc. for $C_{24}H_{34}O_6$: C, 68.85; H, 8.2%), δ 0.86 (6 H, d, *J* 6 Hz, 2- and 3-Me), 1.5—2.0 (2 H, m, H-2 and -3), 2.35—2.65 (4 H, m, $ArCH_2$), 3.76 (12 H, s, 4 × ArOMe), 3.79 (6 H, s, 2 × ArOMe), and 6.30 (4 H, s, ArH).

(*b*) To liquid ammonia (100 ml), sodium (*ca.* 70 mg) was added, followed by a solution of the tetrahydrofuran (21) (700 mg) in 1,2-dimethoxyethane (30 ml). More sodium (240 mg) was then added and the mixture stirred for 10 min. After addition of water (6 ml), the ammonia was allowed to evaporate and the dimethoxyethane removed under reduced pressure. The residue was dissolved in dichloromethane, washed with water, dried, and evaporated to yield a mixture of products (580 mg) which was chromatographed on alumina (Grade 3). Elution with ether–light petroleum (1 : 5) gave, after one crystallization, the same (±)-dimethylbutane (100 mg), m.p. 125—127°, as obtained in (*a*).

1,2,3,4-*Tetrahydro*-6,7,8-*trimethoxy*-t-2,c-3-*dimethyl*-r-1-(3,4,5-*trimethoxyphenyl*)*naphthalene* (20).—A solution of the (±)-unsymmetrical diol (19) (1 g) in ethanol (100 ml) was stirred with palladium–carbon (10%; 2 g) under hydrogen for 2 days. Removal of solvent and catalyst and crystallization of the residue from methanol gave the aryltetrahydronaphthalene (20) as needles (198 mg), m.p. 136—137° (lit.,[21] 133—134°).

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