Structure and Synthesis of (±)-Wuweizisu C

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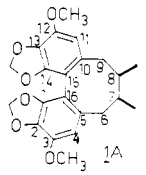
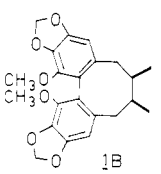
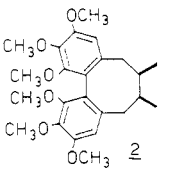
The natural ketone 3-methoxy-4,5-(methylenedioxy)propiophenone (crocatone), a constituent of *Oenanthe crocata*, was readily obtained from vanillin and converted in five steps to (±)-wuweizisu C, a pharmacologically active dibenzocyclooctene lignan constituent of *Schizandra chinensis*. Support for the structure *cis*-6,7,8,9-tetrahydro-1,14-dimethoxy-2,3,12,13-bis(methylenedioxy)-7,8-dimethyldibenzo[*a*,*c*]cyclooctene (**1B**) of this product is provided.

The dibenzocyclooctene class of lignans is now well recognized and has about 3 dozen known natural representatives. A subclass comprises members possessing only methyl substituents on the cyclooctene ring, at least eight of which are known to be naturally occurring. These are (+)-deoxyschizandrin[1,2,4,5] (wuweizisu A[3]), (±)-γ-schizandrin[2,4] (wuweizisu B[3]), (−)-pseudo-γ-schizandrin,[2] (−)-wuweizisu C,[3,4] (−)-gomisin J,[6,7] (−)-gomisin N[8,9] (possibly the same as pseudo-γ-schizandrin), (−)-gomisin K_1,[10] (+)-gomisin K_2,[10] and (+)-gomisin K_3[10] (probably the same as schisanthenol[11]). These compounds have been isolated from the fruit, leaves, and seeds of *Schizandra* species. Extracts, which have long been used in Asia for medicinal purposes, are a source of a drug known as Wu-Wei-Zi in China and Kita-gomisi in Japan.

The pharmacologically active product (−)-wuweizisu C was isolated by Chen and co-workers[3] by ethanol extraction of the kernels of *Fructus schizandrae* (the dried whole fruit of *Schizandra chinensis*). They established the dibenzocyclooctene carbon skeleton and symmetrical disposition of the aryl ring substituents of this substance and suggested, mainly on the basis of spectrometric data and the apparent close relationship to the congener deoxyschizandrin (**2**), that it had the structure (**1A**). The


1A


1B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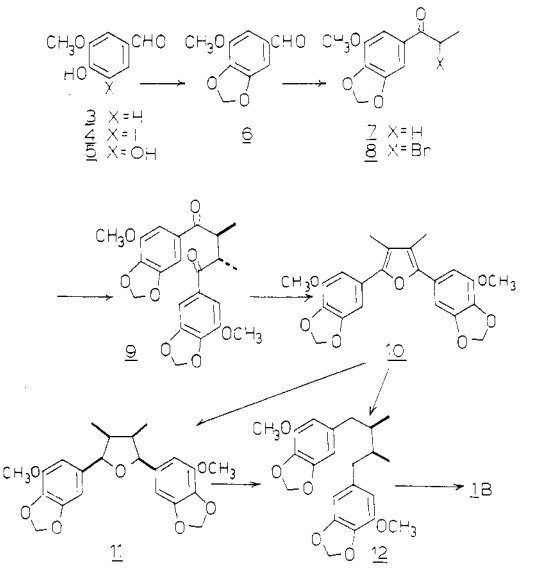
constitution of deoxyschizandrin has now been well established by unequivocal syntheses.[12,13] Although not specifically considered in this paper,[3,14] an alternative (**1B**) was not excluded by any chemical evidence and was in fact subsequently promulgated by Liu and co-workers[4] from consideration of solvent shift and nuclear Overhauser effects of the proton magnetic resonance spectrum. The synthesis of (±)-wuweizisu C which we report here does not by itself distinguish between these structures. Recently, however, Ikeya, Taguchi and their co-workers[15] have presented a detailed ^{13}C NMR spectral analysis of dibenzocyclooctene lignans, which permits elucidation of the positions of functional groups on the aromatic rings, and the spectrum of our synthetic product clearly confirms the structure (**1B**); i.e., wuweizisu C has the structure *cis*-6,7,8,9-tetrahydro-1,14-dimethoxy-2,3:12,13-bis(methylenedioxy)-7,8-dimethyldibenzo[*a*,*c*]cyclooctene.

In general, the synthesis plan was based upon our earlier successful synthesis of (±)-deoxyschizandrin[13] with appreciable path shortening as developed here.

The requisite starting material, 3-methoxy-4,5-(methylenedioxy)propiophenone (**7**) has been reported as a

Scheme I



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(14) Two of the aryl methoxyl groups (at C-1,14) of deoxyschizandrin exhibit high-field NMR chemical shifts (δ 3.60) attributable to aryl ring shielding in the nonplanar biphenyl system. The shifts for the methoxyl group in wuweizisu C at δ 3.84 would by this criterion favor **1A** rather than **1B**, and in a preliminary account of part of this work (*Chem. Ind.* **1980**, 538) we represented the (±) synthetic product by Chen's formula (**1A**). It is now apparent that such high shielding at positions 1 and 14 results only if the methoxyl group is buttressed by an adjacent methoxyl group and that a methylenedioxy group does not produce the same effect. A relevant and clear example is afforded by gomisin N,[8,9] which has methoxyl groups at C-1 and 14 but only *one* shielded methoxyl signal (δ 3.55), since one methoxyl group is adjacent to a methylenedioxy group and the other has an *o*-methoxyl substituent.
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Table I. ^{13}C Spectral Data[a]

	range	found
axial *sec*-Me group (e.g., at C-7)	12.7 ± 0.2	12.6
equatorial *sec*-Me group (at C-8)	21.7 ± 0.2	21.7
$ArCH_2$ adjacent to Me-eq (C-9)	35.4 ± 0.2	35.4
$ArCH_2$ adjacent to Me-ax (C-6)	39.1 ± 0.2	38.9
CH-ax Me (C-7)	33.7 ± 0.1	33.7
CH-eq Me (C-8)	40.8 ± 0.2	40.8
OMe adjacent to Ar H (3,12-OMe in 1A)	55.9 ± 0.2	
OMe lacking adjacent Ar H (1,14-OMe in 1B)	60.5 ± 1.0	59.6

[a] Given as δ values for $CDCl_3$ solutions.

natural product from *Oenanthe crocata* L. and named crocatone,[16,17] but it has apparently not been previously synthesized. It was made readily from vanillin (**3**) by treatment with iodine monochloride to give 5-iodovanillin (**4**)[18] which on being heated with sodium hydroxide and cupric sulfate solution[19] yielded 3,4-dihydroxy-5-methoxybenzaldehyde (**5**). Methylenation of **5** by a recently described procedure[20] (CH_2Cl_2–KF–$HCONMe_2$) afforded the aldehyde **6** in 65% yield, and conversion to crocatone (**7**) was effected by the standard procedure of oxidation of the alcohol obtained by addition of ethylmagnesium bromide (Scheme I).

Crocatone (**7**) cleanly afforded the α-bromo derivative **8** by bromination in chloroform solution, and alkylation of the sodium enolate of **7** with **8** in liquid ammonia gave the racemic diaroylbutane **9** in over 80% yield. The racemic configuration assigned to this product was anticipated from the earlier work on deoxyschizandrin synthesis[13] and is supported by the characteristic chemical shift (δ 1.28) of the secondary methyl group.[21] Brief treatment with methanolic hydrogen chloride sufficed to convert the 1,4-diketone **9** essentially quantitatively to the 2,5-diaryl-3,4-dimethylfuran **10**, catalytic hydrogenation of which in ethyl acetate gave in excellent yield the *meso-cis*-tetrahydrofuran **11**.

We have now found that the tetrahydrofuran **11** undergoes hydrogenolysis with 10% palladium/carbon if very high catalyst/substrate ratios are employed. From the mixture of products obtained, that fraction which remains adsorbed to the catalyst contains more than 90% of the desired *meso*-diarylbutane (**12**), and this could be similarly obtained directly from the furan **10**. As anticipated from earlier work, oxidation of such diarylbutanes with vanadium oxytrifluoride yields dibenzo[*a*,*c*]cyclooctenes, and treatment of **12** with this reagent yielded (±)-wuweizisu C (**1B**) with a ^1H NMR spectrum in excellent agreement with that reported for the natural enantiomer.

A comparison of the ^{13}C chemical shifts of the synthetic wuweizisu C with those expected for formulas **1A** and **1B** from the Ikeya–Taguchi data[15] as tabulated in Table I clearly supports formula **1B**.

Experimental Section

NMR spectra were determined for solutions in [^2H]chloroform with tetramethylsilane as internal standard. Melting points were determined with a Fisher-Johns and/or a Gallenkamp apparatus. Analytical TLC was carried out on Eastman Chromagram sheets (13181 silica gel and 13252 alumina, both with fluorescent indicator). Preparative TLC was conducted with Whatman silica gel (PLK5F). For column chromatography, alumina (Fisher, 60–200 mesh) and silica gel (Merck, silica gel 60, 230–400 mesh) were employed.

4-Hydroxy-5-iodo-3-methoxybenzaldehyde (5-iodovanillin, 4) was prepared as previously described[18] in 81% yield by treatment of vanillin with iodine monochloride and isolated as prisms from ethanol: mp 180–181 °C (lit.[18] mp 181–182 °C); ^1H NMR [$(CD_3)_2SO$] δ 3.91 (s, 3 H, OMe), 7.48 (d, 1 H, J = 2 Hz, H-2), 7.92 (d, 1 H, J = 2 Hz, H-6), 9.83 (s, 1 H, CHO), 10.74 (s, 1 H, OH).

3,4-Dihydroxy-5-methoxybenzaldehyde (5) was prepared as previously described[19] in 68% yield by heating 5-iodovanillin with sodium hydroxide and copper sulfate solution and isolated as plates from benzene: mp 133–134 °C (lit.[19] mp 133–134 °C); ^1H NMR [$(CD_3)_2SO$] δ 3.85 (s, 3 H, OMe), 7.06 (s, 2 H, H-2 and H-6), 9.68 (s, 1 H, CHO); ^1H NMR [$(CD_3)_2CO$–$CDCl_3$] δ 3.92 (s, 3 H, OMe), 7.08 (d, 1 H, J = 2 Hz, H-2), 7.13 (d, 1 H, J = 2 Hz, H-6), 7.80 (br s, 1 H, OH), 8.00 (br s, 1 H, OH), 9.78 (s, 1 H, CHO).

3-Methoxy-4,5-(methylenedioxy)benzaldehyde (6). Potassium fluoride (14.0 g) and methylene chloride (75 mL) were added to a solution of 3,4-dihydroxy-5-methoxybenzaldehyde (9.0 g) in dimethylformamide (300 mL), and the mixture was heated under reflux with stirring under a nitrogen atmosphere for 1.5 h. It was then diluted with water (ca. 200 mL) and extracted with ether (3 × 200 mL), and the extract was washed successively with 5% aqueous sodium hydroxide solution (3 × 150 mL), water, and brine. Evaporation of the dried ($MgSO_4$) extract yielded a residue, which on crystallization from methanol gave the methoxy(methylenedioxy)benzaldehyde **6** as prisms: 6.15 g; mp 131–132 °C (lit.[22] mp 130 °C); ^1H NMR δ 3.98 (s, 3 H, OMe), 6.10 (s, 2 H, OCH_2O), 7.06 (d, 1 H, J = 2 Hz, Ar H), 7.08 (d, 1 H, J = 2 Hz, Ar H), 9.84 (s, 1 H, CHO).

3-Methoxy-4,5-(methylenedioxy)propiophenone (Crocatone, 7). A solution of 3-methoxy-4,5-(methylenedioxy)benzaldehyde (3.53 g) in ether (150 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 30 min and then worked up in the usual way to give the intermediate alcohol as a colorless oil: 3.17 g; ^1H NMR δ 0.89 (t, 3 H, J = 7 Hz, Me), 1.68 (q, 2 H, J = 7 Hz, CH_2), 2.28 (br s, 1 H, OH), 3.88 (s, 3 H, OMe), 4.46 (t, 1 H, CHOH), 5.93 (s, 2 H, OCH_2O), 6.53 (s, 2 H, H-2 and H-6). To a solution of this alcohol (3.0 g) in acetone (25 mL) at 0–5 °C was added Jones reagent (1.4 M, 8 mL) dropwise over 10 min, the mixture was stirred at room temperature for 30 min, and then 2-propanol (3 mL) was added. It was worked up by aqueous dilution, concentration, and ether extraction. The washed and dried ether extract yielded crocatone (**7**) as needles (2.23 g) from petroleum ether: mp 88–89 °C (lit.[16] mp 89 °C); ^1H NMR δ 1.22 (t, 3 H, J = 7 Hz, Me), 2.92 (q, 2 H, J = 7 Hz, CH_2), 3.96 (s, 3 H, OMe), 6.05 (s, 2 H, OCH_2O), 7.15 (d, 1 H, J = 2 Hz, Ar H), 7.28 (d, 1 H, J = 2 Hz, Ar H). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.8. Found: C, 63.4, H, 5.9.

α-Bromo-3-methoxy-4,5-(methylenedioxy)propiophenone (8). To a solution of the ketone **7** (2.0 g) in chloroform (12 mL) was added dropwise with stirring a solution of bromine (1.4 g) in chloroform (7 mL), and the mixture was allowed to stand for 1.5 h. It was then washed with water (25 mL) and saturated sodium bicarbonate solution (2 × 25 mL), dried, and evaporated to give the bromo ketone **8** as long white needles (2.20 g) from ethanol: mp 114.5–115 °C; ^1H NMR δ 1.88 (d, 3 H, J = 7 Hz, Me), 3.86 (s, 3 H, OMe), 5.20 (q, 1 H, J = 7 Hz, CHBr), 6.09 (s, 2 H, OCH_2O), 7.22 (d, 1 H, J = 2 Hz, Ar H), 7.37 (d, 1 H, J = 2 Hz, Ar H). Anal. Calcd for $C_{11}H_{11}O_4Br$: C, 46.0; H, 3.9. Found: C, 46.3; H, 4.0.

(±)-2,3-Bis[3-methoxy-4,5-(methylenedioxy)benzoyl]butane (9). To liquid ammonia (ca. 50 mL) were added ferric chloride (ca. 5 mg) and sodium (300 mg) at −78 °C (external acetone–CO_2 bath), and the solution was stirred for ca. 2 h (gray

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sodamide visible). A solution of the ketone **7** (1.50 g) in tetrahydrofuran (20 mL) was then added dropwise over 10 min, and the mixture was stirred for a further 10 min, after which a solution of the bromo ketone **8** (2.06 g) in tetrahydrofuran (60 mL) was added dropwise over 30 min. After a further 45 min, ammonium chloride (1.5 g) was added, the ammonia allowed to evaporate at room temperature, and the resultant solution filtered and evaporated under reduced pressure. A solution of the residue was dissolved in petroleum ether–dichloromethane (3:1) and chromatographed on a column (2 × 15 cm) of alumina. Elution with the same solvent (ca. 600 mL) gave the (±) diketone **9** as short needles (2.46 g) from dichloromethane–methanol: mp 166–167 °C; ^{1}H NMR δ 1.28 (d, 6 H, J = 7 Hz, Me), 3.46–3.86 (m, 2 H, COCH), 3.94 (s, 6 H, OMe), 6.06 (s, 4 H, OCH_2O), 7.22 (d, 2 H, J = 1.5 Hz, Ar H), 7.30 (d, 2 H, J = 1.5 Hz, Ar H). Anal. Calcd for $C_{22}H_{22}O_8$: C, 63.8; H, 5.35. Found: C, 63.8; H, 5.5.

3,4-Dimethyl-2,5-bis[3-methoxy-4,5-(methylenedioxy)-phenyl]furan (10). To a solution of the (±) diketone **9** (1.94 g) in dichloromethane (40 mL) was added 40 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 1 h, concentrated, and cooled to yield the furan **10** as plates: 1.46 g; mp 143.5–144 °C (unchanged on crystallization from methanol–dichloromethane); ^{1}H NMR δ 2.19 (s, 6 H, Me), 3.98 (s, 6 H, OMe), 6.02 (s, 4 H, OCH_2O), 6.88 (s, 4 H, Ar H). Anal. Calcd for $C_{22}H_{20}O_7$: C, 66.7; H, 5.1. Found: C, 66.9; H, 5.3.

***c*-3,*c*-4-Dimethyl-*r*-2,*c*-5-bis[3-methoxy-4,5-(methylenedioxy)phenyl]tetrahydrofuran (11).** A solution of the furan **10** (300 mg) in ethyl acetate (40 mL) was stirred with palladium/carbon (10% 400 mg) under hydrogen for 20 h. After filtration and evaporation, the residual oil (247 mg) was dissolved in petroleum ether–dichloromethane (1:1) and filtered through a column (1 × 15 cm) of alumina. Crystallization of the eluate from methanol gave the tetrahydrofuran **11** as fine needles: 224 mg; mp 95.5–96 °C; ^{1}H NMR δ 0.62 (d, 6 H, J = 7 Hz, Me), 2.38–2.80 (m, 2 H, H-3 and H-4), 3.94 (s, 6 H, OMe), 5.09 (d, 2 H, J = 7 Hz, H-2 and H-5), 6.00 (s, 4 H, OCH_2O), 6.64 (s, 4 H, Ar H). Anal. Calcd for $C_{22}H_{24}O_7$: C, 66.0; H, 6.0. Found: C, 65.8; H, 6.2.

***meso*-1,4-Bis[3-methoxy-4,5-(methylenedioxy)phenyl]-2,3-dimethylbutane (12).** (a) A solution of the tetrahydrofuran **11** (180 mg) in ethyl acetate (40 mL) was stirred with palladium/carbon (10%, 800 mg) under hydrogen overnight and then filtered. The filtrate was then extracted (Soxhlet, 2 h) with chloroform, evaporation of which yielded the crude butane **12** as an oil: 78 mg; ^{1}H NMR δ 0.84 (d, 6 H, J = 6 Hz, Me), 1.5–2.0 (m, 2 H, CHMe), 2.2–2.9 (m, 4 H, Ar CH_2), 3.89 (s, 6 H, OMe), 5.92 (s, 4 H, OCH_2O), 6.32 (d, 2 H, J = 1.5 Hz, Ar H), 6.36 (d, 2 H, J = 1.5 Hz, Ar H); mass spectrum, calcd for $C_{22}H_{26}O_6$ m/e 386.1729, found m/e 386.1744. This preparation, which contained 5–10% unchanged tetrahydrofuran, was used without further purification. Evaporation of the original filtrate gave a residual oil (80 mg) which was a mixture containing about 75% butane **12** by NMR examination.

(b) A solution of the furan **10** (400 mg) in ethyl acetate (50 mL) in the presence of palladium carbon (10%, 1.2 g) was hydrogenated and worked up as in method a. From the extracted catalyst there was obtained the butane **12** (140 mg) of >95% purity and from the filtrate a mixture (240 mg) containing about 30% of the butane.

(±)-Wuweizisu C (1B). A mixture of anhydrous trifluoroacetic acid (5 mL) and dichloromethane (16 mL) was added to a solution of the diaryldimethylbutane **12** (130 mg) in dichloromethane (30 mL) at −78 °C and the mixture stirred for 10 min. Vanadium oxyfluoride (300 mg) was then added with stirring at the same temperature for 30 min and at room temperature for a further 30 min. Saturated aqueous sodium carbonate was then added, and the organic phase was successively washed with sodium carbonate solution (50 mL), brine (50 mL), and water. The dried (Na_2SO_4) extract was concentrated to ca. 10 mL, filtered through a short column of alumina, and evaporated. The residual oil (105 mg) on TLC (silica gel; toluene–ethyl acetate, 9:1) gave a front-running zone, which on elution and crystallization from methanol–dichloromethane gave ***cis*-6,7,8,9-tetrahydro-1,14-dimethoxy-2,3:12,13-bis(methylenedioxy)-7,8-dimethyldibenzo[*a*,*c*]cyclooctene (1)** as rectangular prisms: mp 160–161 °C; mass spectrum, calcd for $C_{22}H_{24}O_6$ m/e 384.1573, found m/e 384.1575; ^{1}H NMR δ 0.72 (d, 3 H, J = 7 Hz, Me), 0.96 (d, 3 H, J = 7 Hz, Me), 1.6–2.7 (m, 6 H, $ArCH_2CH$), 3.84 (s, 6 H, OMe), 5.96 (s, 4 H, OCH_2O), 6.51 (s, 2 H, Ar H). These data are in excellent agreement with those reported for the natural (−) isomer.[3]

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Registry No. (±)-**1B**, 77647-22-4; **3**, 121-33-5; **4**, 5438-36-8; **5**, 3934-87-0; **6**, 5780-07-4; **7**, 19937-86-1; (±)-**8**, 77589-55-0; (±)-**9**, 75470-83-6; **10**, 75470-84-7; *meso*-**11**, 75470-85-8; *meso*-**12**, 75470-86-9; (±)-1-[3-methoxy-4,5-(methylenedioxy)benzyl]propanol, 77589-56-1; ethyl bromide, 74-96-4.