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A Practical Synthesis of *d,l*-Dibenzocyclooctadiene Lignans, *d,l*-Deoxyschizandrin, *d,l*-Wuweizisu C, and Their Stereoisomers

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Several (±)-dibenzocyclooctadiene lignans, (±)-deoxyschizandrin (**2a**), (±)-wuweizisu C (**2b**), and their stereoisomers **3a**, **3b**, and **3b**-TBC, were synthesized stereospecifically from corresponding phenylacetones **5a** and **5b** in four steps.

Keywords——dibenzocyclooctadiene lignan, deoxyschizandrin, wuweizisu C, practical synthesis, oxidative aryl–aryl coupling

More than 30 dibenzocyclooctadiene lignans, unique constituents of the fruits of *Schizandra chinensis* BAILLON (Schizandraceae), have been isolated since 1961.[1] It has been reported that these lignans, in particular, gemisin A (**1**), deoxyschizandrin (**2a**), and wuweizisu C (**2b**), show significant antihepatotoxic activity against the liver injuries induced by various chemicals (CCl_4, D-galactosamine, α-naphthylisothiocyanate (ANIT), and orotic acid) in biochemical and histopathological investigations.[2] Further, the antihepatotoxic actions of the lignans were confirmed in an *in vivo* study using mice[3] and an *in vitro* study using primary cultured rat hepatocytes.[4] Although these lignans have been already synthesized,[5] a practical synthesis is required in view of their interesting pharmacological activities. We report herein a practical synthesis of several lignans, racemic **2a** and **2b** and their stereoisomers **3a**, **3b**, and **3b**-TBC.

The present synthetic plan consists of reductive coupling and dehydroxylation of the phenylacetone **5** to give the symmetrical olefins **8** and **9**, followed by hydrogenation and oxidative aryl–aryl coupling reaction to construct the desired lignans as shown in Chart 1.

The phenylacetones **5a**, mp 57—59 °C, and **5b**, mp 49—50 °C, were synthesized by reduction and hydrolysis with Fe–$FeCl_3$/conc. HCl of the nitrostyrenes **4a** and **4b**, which were prepared from the corresponding benzaldehydes in yields 64% and 65%, respectively. Reductive couplings of the phenyl acetones **5a** and **5b** with $TiCl_4$–Zn in tetrahydrofuran (THF) afforded diastereoisomeric mixtures of the butanediols **6a**, mp 154—155 °C, and **6b**, mp 145—147 °C, in yields of 88% and 88%.[6] Treatment of the diol **6a** or **6b** with ethyl orthoformate in the presence of benzoic acid[7] afforded the corresponding (*Z*)- and (*E*)-butenes (through **7a** and **7b**) **9a**, mp 119—121 °C, and **8a**, bp 210—220 °C (3 mm), or **9b**, mp 111—113 °C, and **8b**, bp 235—240 °C (3 mm), in yields of 45% and 45% or 46% and 46%, respectively. These (*Z*)- and (*E*)-olefins, **8a** and **9a** or **8b** and **9b**, can be separated easily by simple recrystallization from EtOH. Further, the (*Z*)- and (*E*)-olefins are interconvertible by irradiation with a low-pressure ultraviolet (UV) lamp in cyclohexane. Catalytic reduction of the butenes **8a** and **9a** with Pt black in AcOH gave the *meso*-1,4-bisphenylbutanes **10a**, mp 115—117 °C, and *d,l*-**11a**, mp 125—127 °C, in yields of 72% and 82%, respectively. Similarly, catalytic reductions of **8b** and **9b** with 5% Rh/C in AcOH at 120—135 kg/cm^2 gave the *meso*-butanes **10b**, mp 86—88 °C, and *d,l*-**11b**, oil, in yields of 72%.

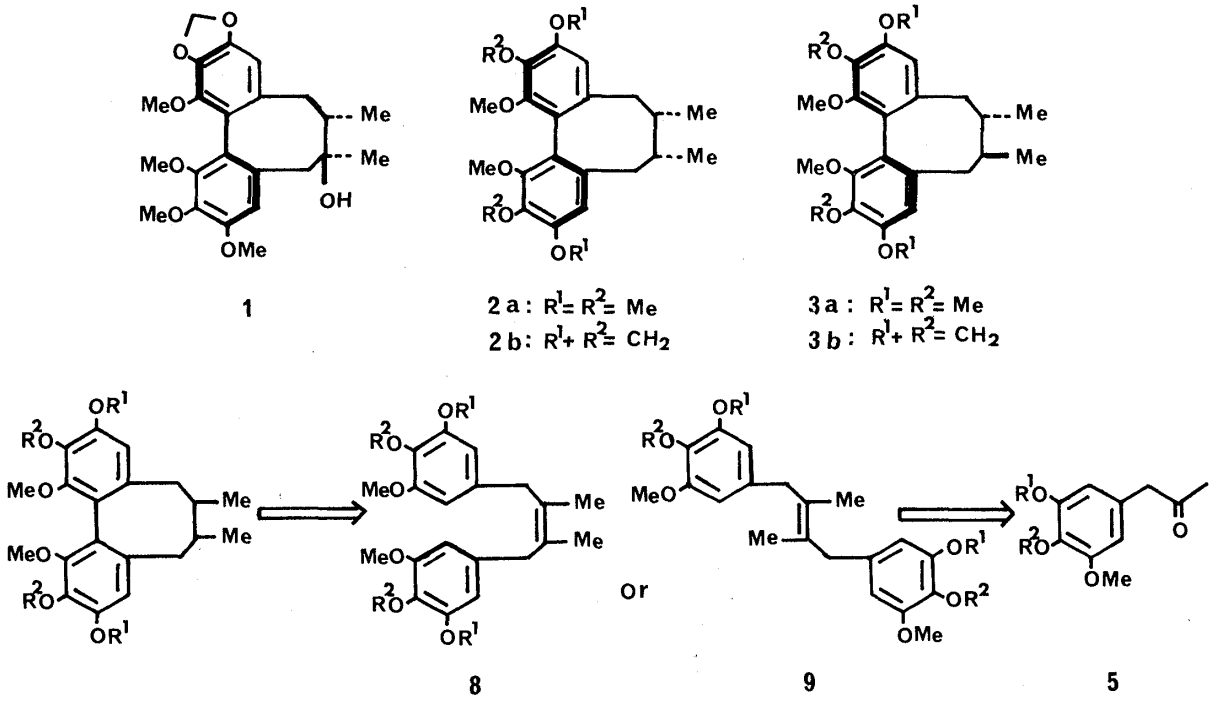

Chart 1

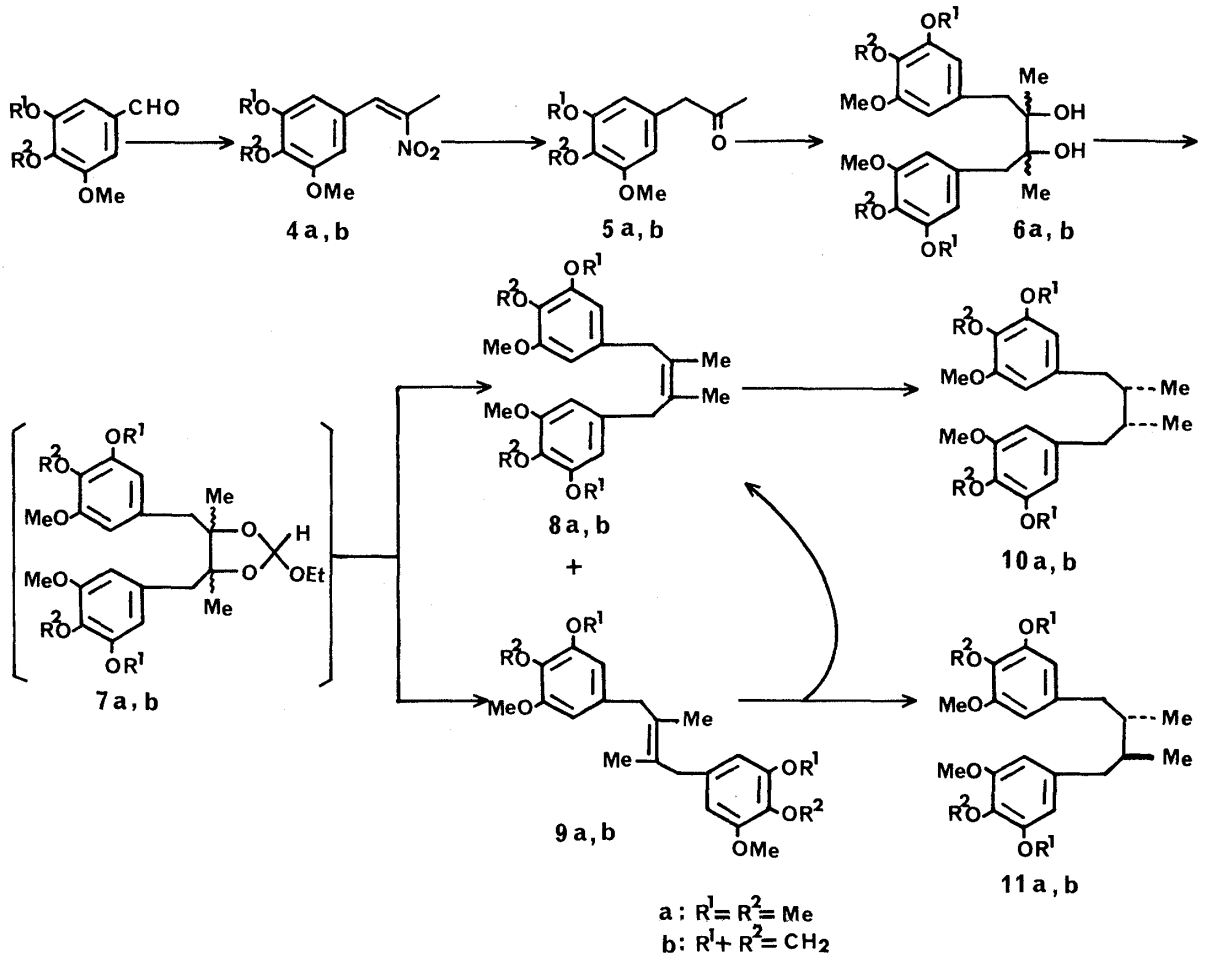

Chart 2

TABLE I. Oxidative Coupling Reaction of the 1,4-Bisphenylbutanes

Substrate	Reagent	Product	Yield (%)
10a	A	**2a**	9.0
	B	**2a**	8.5
	C	**2a**	9.2
	D	**2a**	32.0
	E	**2a**	9.0
11a	A	**3a**	9.1
	B	**3a**	9.1
	C	**3a**	9.8
	D	**3a**	35.2
	E	**3a**	9.5
10b	D	**2b**	Trace
	E	**2b**	46.2
11b	D	**3b**+**3b**-TBC	Trace
	E	**3b**+**3b**-TBC	35.0+10.2

Reagent A, VOF_3; B, anodic oxidation; C, $[Mn(Ac_2O)_3]$ $(ClO_4)_3$; D, $[FeCl_2(Ac_2O)_2]$ $(FeCl_4)$; E, $[Fe(H_2O)_x(MeCN)_y]$ $(ClO_4)_3$. $x+y=6$.

Finally, oxidative aryl–aryl coupling reactions of **10a** and **10b** with various reagents to give the desired *d,l*-dibenzocyclooctadiene lignans, deoxyschizandrin (**2a**) and wuweizisu C (**2b**), were investigated. The results are shown in Table I; the best result was obtained by oxidation with $FeCl_2(Ac_2O)_2$ $(FeCl_4)$, prepared from $FeCl_3$ with Ac_2O, in the case of **10a** and with $Fe(H_2O)_x(CH_3CN)_y$ $(ClO_4)_3$; $(x+y=6)$, prepared from $Fe(ClO_4)_3 \cdot 6H_2O$ with CH_3CN, in the case of **10b**. All physical data for these synthetic lignans **2a** and **2b** were identical with those of the natural products except for the optical rotations.

On the other hand, oxidations of **11a** and **11b** with various reagents gave the lignans **3a**, **3b**, and **3b**-TBC (unknown in nature) in the yields shown in Table I. Though it is known that the C(13) and C(14) methyl groups have a *cis* relationship and take quasi-equatorial and quasi-axial configurations, respectively, and the eight-membered ring has a twist-boat-chair form in both deoxyschizandrin (**2a**)[1c,d] and wuweizisu C (**2b**),[1k,5g,8] the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra of **3a**, **3b**, and **3b**-TBC showed major differences as compared with those of **2a** and **2b** as listed in Table II.

The structures of **3a**, **3b**, and **3b**-TBC were examined from the following three points of view, namely, (i) the aryl–aryl coupling position, (ii) the relative configuration of the C(13) and C(14) methyl groups, and (iii) the conformation of the eight-membered ring. First of all, the ^{13}C-NMR spectra show that these compounds have symmetrical structures because only half of the carbon signals were observed with respect to the molecular formulas. The carbon signals of aromatic methoxyl groups in **3b** and **3b**-TBC were observed at 59.5 and 59.6 ppm in the ^{13}C-NMR spectra. In contrast, the carbon signals of the C(3) and C(10) methoxy groups were observed at 55.7 ppm and the signals of other methoxyl groups at 60.3 and 60.7 ppm in deoxyschizandrin (**2a**). This suggests that the methoxyl groups are not adjacent to a tertiary carbon atom.[9] Further, no solvent shift of the signals of aromatic methoxyl groups by C_6D_6 was found in the proton nuclear magnetic resonance (^{1}H-NMR) spectra.[8a] Thus, the aryl–aryl coupling positions in these three compounds can be presumed to be at C(1a) and C(12a).

Secondly, the relative configuration of the C(13) and C(14) methyl groups was assigned on the basis of the following evidence. It has already been established that the axial C(14) and the equatorial C(13) methyl groups are responsible for the signals at 12.6 and 21.7 ppm in the ^{13}C-NMR spectra of **2a** and **2b**, respectively.[1k,9] The C(13) and C(14) methyl signals of these compounds, **3a**, **3b**, and **3b**-TBC, were observed as one signal at 23.7, 23.5, and 20.5 ppm,

TABLE II. ^{13}C-NMR Spectral Data for the Lignans[a)]

Carbon No.	**2a**	**3a**	**2b**	**3b**	**3b**-TBC
1a	123.2	122.7 (×2, C-12a)	122.2	121.5 (×2, C-12a)	122.4 (×2, C-12a)
1	151.5	151.1 (×2, C-12)	141.1	140.9 (×2, C-12)	141.2 (×2, C-12)
2	139.6	140.0 (×2, C-11)	134.4	136.9 (×2, C-11)	134.9 (×2, C-11)
3	151.4	152.8 (×2, C-10)	147.6	148.6 (×2, C-10)	147.5 (×2, C-10)
4	110.3	107.7 (×2, C-9)	106.0	103.3 (×2, C-9)	106.1 (×2, C-9)
4a	133.5	137.9 (×2, C-8a)	132.7	134.5 (×2, C-8a)	133.0 (×2, C-8a)
5	39.0	42.8 (×2, C-8)	38.7	42.7 (×2, C-8)	35.9 (×2, C-8)
6	33.7	40.9 (×2, C-7)	33.7	40.7 (×2, C-7)	32.8 (×2, C-7)
7	40.6		40.8		
8	35.5		35.4		
8a	138.8		134.4		
9	107.0		103.1		
10	152.7		148.7		
11	139.9		138.2		
12	151.5		141.3		
12a	122.2		121.1		
13	12.6	23.7 (×2, C-14)	12.6	23.5 (×2, C-14)	20.5 (×2, C-14)
14	21.7		21.7		
OMe C-1,12	60.3 (×2)	60.5 (×2)	59.6	59.5	59.6
C-2,11	60.7 (×2)	60.7 (×2)			
C-3,10	55.7 (×2)	55.9 (×2)			
OCH_2O			100.7 (×2)	100.6 (×2)	100.7 (×2)

a) δ in $CDCl_3$; ^{13}C, 25 MHz at 25°.

respectively, in the ^{13}C-NMR spectra. Furthermore, the C(14) and C(13) methyl group signals of **2a** and **2b** were observed at 0.73, 1.00 ppm and 0.73, 0.96 ppm, respectively, each as two doublets, in the ^{1}H-NMR spectra (Table III). On the other hand, the corresponding signals of **3a**, **3b**, and **3b**-TBC were found at 1.05, 1.01, and 0.84 ppm, each as one doublet. These results suggest that the C(13) and C(14) methyl groups in **3a**, **3b**, and **3b**-TBC may possess *trans*, diequatorial configurations.

Compounds **3b** and **3b**-TBC, therefore, may be conformational isomers of the eight-membered ring system. The proton signals (1.55—1.82 ppm) of C(6)- and C(7)-H in **3b**-TBC were observed at lower field in the ^{1}H-NMR spectra as compared with the signal at 1.0—1.3 ppm in **3b**, presumably due to the shielding effect of the benzene ring. In measurements of nuclear Overhauser effect (NOE), a 9.5% increment of the integrated intensity of C(4)- and C(9)-H in **3b** was found on irradiation of C(6)- and C(7)-H (at δ 1.15), but only a 2% increment of the intensity in **3b**-TBC on irradiation at δ 1.72. These results suggest that C(6)- and C(7)-H of **3b** are closer to the benzene ring than is the case in **3b**-TBC. Furthermore, the

TABLE III. ^{1}H-NMR Spectral Data for the Lignans[a)]

	2a	2b	3a	3b	3b-TBC
Me-14	0.73 (d, J=7)	0.73 (d, J=7)			
			1.05 (d, J=4.5)	1.01 (d, J=4.5)	0.84 (d, J=7.3)
Me-13	1.00 (d, J=7)	0.96 (d, J=7)			
H-6,7	1.90 (center, m)	1.82 (center, m)	1.20 (center, m)	1.15[b)] (center, m)	1.72[c)] (center, m)
H-8	2.55 (center, m)	2.51 (center, m)	2.15 (dd, J=13.2, 8.5 H-8β,5α)	2.10 (dd, J=13.2, 9 H-8β,5α)	2.25 (dd, J=13.4, 8 H-8β,5α)
H-5	2.27 (dd, J=13.2, 9) 2.02 (dd, J=13.2, 1)	2.06 (center, m)	2.38 (dd, J=13.2, 1 H-8α,5β)	2.32 (dd, J=13.2, 1 H-8α,5β)	2.45 (dd, J=13.4, 2 H-8α,5β)
H-4,9	6.55 (s)	6.51 (s)	6.57 (s)	6.48 (s)	6.46 (s)

a) δ in $CDCl_3$; ^{1}H-NMR at 100 MHz (J=Hz). *b*) Results of NOE measurements in **3b**: H-6,7 $\xrightarrow[\text{(irrad. at 1.15)}]{9.5\%}$ H-4,9. *c*) NOE in **3b**-TBC: H-6,7 $\xrightarrow[\text{(irrad. at 1.72)}]{2\%}$ H-4,9.

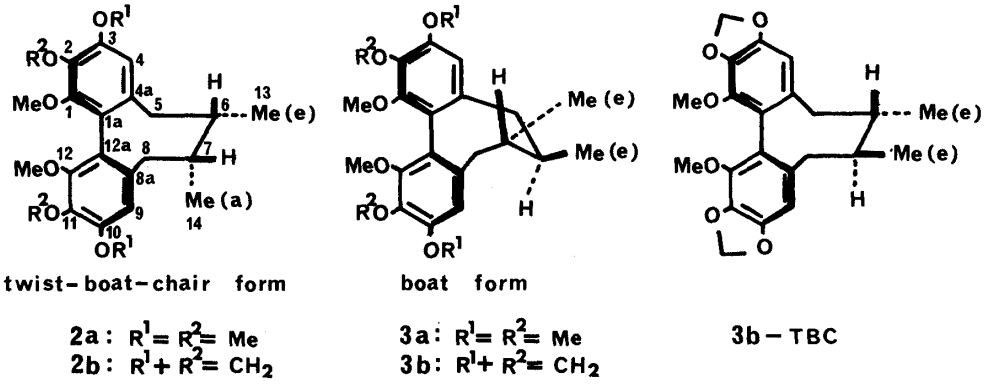

Chart 3

coupling constants between C(5)-αH and C(6)-H, and C(8)-βH and C(7)-H were each 9 Hz, and those between C(5)-βH and C(6)-H, and C(8)-αH and C(7)-H were each 1 Hz in the ^{1}H-NMR spectrum of **3b**. These values suggest that the bond angles between C(5)-αH and C(6)-H, and C(8)-βH and C(7)-H may each be near to 0°, and those between C(5)-βH and C(6)-H, and C(8)-αH and C(7)-H may each be about 120° in **3b**. On the other hand, the bond angles between C(5)-αH and C(6)-H, and C(8)-βH and C(7)-H may each be about 150°, and those between C(5)-βH and C(6)-H, and C(8)-αH and C(7)-H may each be about 90° in **3b**-TBC as judged similarly from the corresponding coupling constants in the ^{1}H-NMR spectrum. The spectrum of **3a** is very similar to that of **3b**. Hence, the structures of **3a**, **3b**, and **3b**-TBC can be illustrated as shown in Chart 3, where **3a** and **3b** both take a boat form and **3b**-TBC has a twist-boat-chair form of the eight-membered ring, and the two methyl groups at C(13) and C(14) have equatorial configurations in all three compounds.

These syntheses of **2a** and **2b** consist of four steps from the corresponding phenylacetones **5a** and **5b** and given overall yields of *ca.* 18% and 27% (assuming that complete inter-

conversions of **9a** to **8a** and **9b** to **8b** are achieved).

A comparative study of pharmacological action between synthetically prepared racemic lignans **2a** and **2b** and the natural lignans by examining antihepatotoxic action on CCl_4-induced liver injury showed that **2b** is superior to **2a** in terms of potency and that the efficacy of the synthesized product is comparable with that of the natural one.[10]

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded with a Hitachi 260-10 spectrometer, ^{1}H- and ^{13}C-NMR spectra with a JEOL JNM-FX 100 spectrometer with tetramethylsilane as an internal standard ($CDCl_3$ or C_6D_6 sol.) and mass spectra (MS) with a JEOL JMS-D 300 spectrometer. Elemental analyses were done by Ms. A. Sakamoto and Ms. M. Takeda, Kissei Pharmaceutical Company, Matsumoto, Japan. Wako Silica gel C-200 (200 mesh) and Merck Kieselgel 60 F_{254} were used for column chromatography and thin-layer chromatography (TLC), respectively.

1-(3,4,5-Trimethoxyphenyl)-2-nitropropene (4a)——A solution of 3,4,5-trimethoxybenzaldehyde (33 g, 0.167 mol), nitroethane (37.5 g, 0.5 mol), and piperidine (2 ml) in benzene (400 ml) was refluxed for 24—30 h until no more water was separated by a water separator. After the solvent had been removed under reduced pressure, the residue was recrystallized from MeOH to yield 25.5 g (60%) of **4a** as yellow crystals, mp 90—92 °C. IR (KBr) cm^{-1}: 1640, 1580, and 1520. ^{1}H-NMR ($CDCl_3$) δ: 2.50 (3H, d, J=1.5 Hz, olefinic-Me), 3.95 (9H, s, 3×ArOMe), 6.65 (2H, s, ArH), and 8.05 (1H, br s, olefinic-H). *Anal.* Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. MS *m/e*: 253.0951. Found: C, 56.68; H, 6.00; N, 5.50. MS *m/e*: 253.0953.

1-3-Methoxy-4,5-(methylenedioxy)phenyl-2-nitropropene (4b)——**4b**, mp 106—108 °C (MeOH), was synthesized from 3-methoxy-4,5-methylenedioxybenzaldehyde by a procedure similar to that used for **4a** in 60% yield. IR (KBr) cm^{-1}: 1640, 1600, and 1520. ^{1}H-NMR ($CDCl_3$) δ: 2.48 (3H, d, J=1.5 Hz, olefinic-Me), 3.95 (3H, s, ArOMe), 6.05 (2H, s, $-OCH_2O-$), 6.65 (2H, s, ArH), and 8.00 (1H, br s, olefinic-H). *Anal.* Calcd for $C_{11}H_{11}NO_5$: C, 55.69; H, 4.67; N, 5.91. MS *m/e*: 237.0637. Found: C, 55.67; H, 4.77; N, 5.88. MS *m/e*: 237.0643.

1-(3,4,5-Trimethoxyphenyl)-2-propanone (5a)——Hot H_2O (500 ml) was added to a hot solution of the nitropropene **4a** (49.8 g, 0.197 mol) in EtOH (400 ml), then Fe powder (63 g) and hydrate $FeCl_3$ (2.5 g) were added with heating and vigorous stirring, and finally conc. HCl (32 ml) was added slowly. The addition of HCl caused a violent reaction which subsided after 5 min, then the solution was refluxed with stirring for 3 h, and the whole was distilled under reduced pressure until about 500 ml of distillate was collected. The residue was filtered, and the fluffy iron oxide was washed throughly with hot H_2O and with $CHCl_3$. The combined filtrate and washing were acidified strongly with HCl and then extracted with $CHCl_3$. The organic layer was dried and concentrated. The residue was recrystallized from ether–$CHCl_3$ to yield 35.3 g (80%) of **5a** as colorless crystals, mp 57—59 °C. IR (Nujol) cm^{-1}: 1700 and 1580. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s, COMe), 3.52 (2H, s, $ArCH_2$), 3.77 (9H, s, 3×ArOMe), and 6.28 (2H, s, ArH). *Anal.* Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. MS *m/e*: 224.1049. Found: C, 64.26; H, 7.37. MS *m/e*: 224.1055.

1-[3-Methoxy-4,5-(methylenedioxy)phenyl]-2-propanone (5b)——**5b**, mp 49—50 °C, was synthesized from **4b** by a procedure similar to that used for **5a** in 80% yield. IR (Nujol) cm^{-1}: 1969 and 1620. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, s, COMe), 3.52 (2H, s, $ArCH_2$), 3.90 (3H, s, ArOMe), 5.98 (2H, s, $-OCH_2-$), and 6.40 (2H, s, ArH). *Anal.* Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. MS *m/e*: 208.0734. Found: C, 63.50; H, 5.90. MS *m/e*: 208.0727.

1,4-Bis(3,4,5-trimethoxyphenyl)-2,3-dimethyl-2,3-butanediol (6a)——Zn powder (22.5 g, 0.34 mol) was added slowly under a nitrogen atmosphere to a mixture of the ketone **5a** (25.5 g, 0.114 mol) and $TiCl_4$ (32.4 g, 0.17 mol) in dry THF (400 ml), and the whole was refluxed for 3 h. The reaction mixture was cooled, and alkaline hydrolysis was performed with 10% aqueous K_2CO_3. The precipitates were separated from the solution by filtration and the filtrate was extracted with $CHCl_3$. The organic layer was washed with H_2O, then dried and concentrated. The residue was recrystallized from ether to yield 22.5 g (88%) of **6a** as colorless crystals, mp 154—155 °C. IR (KBr) cm^{-1}: 3450 and 1600. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (6H, s, 2×Me), 2.10 (2H, br s, 2×OH), 2.65 (2H, d, J=13.67 Hz, $ArCH_2$), 3.10 (2H, d, J=13.67 Hz, $ArCH_2$), 3.85 (9H, s, 3×ArOMe), 3.87 (9H, s, 3×ArOMe), and 6.48 (4H, s, ArH). *Anal.* Calcd for $C_{24}H_{34}O_8$: C, 63.98; H, 7.61. MS *m/e*: 450. 2253. Found: C, 64.00; H, 7.74. MS *m/e*: 450.2259.

1,4-Bis[3-methoxy-4,5-(methylenedioxy)phenyl]-2,3-dimethyl-2,3-butanediol (6b)——**6b**, mp 145—147 °C (ether), was synthesized from **5b** by a procedure similar to that used for **6a** in a yield of 88%. IR (Nujol) cm^{-1}: 3510 and 1620. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (6H, d, J=1.5 Hz, 2×Me), 2.00 (2H, br s, 2×OH), 2.55 (2H, d, J=12 Hz, $ArCH_2$), 3.05 (2H, d, J=12 Hz, $ArCH_2$), 3.88 (6H, s, 2×ArOMe), 5.94 (4H, s, 2×$-OCH_2O-$), and 6.45 (4H, br s, ArH). *Anal.* Calcd for $C_{22}H_{26}O_8$: C, 63.14; H, 6.26. MS *m/e*: 418.1628. Found: C, 63.07; H, 6.37. MS *m/e*: 418.1640.

(*Z*)-1,4-Bis(3,4,5-trimethoxyphenyl)-2,3-dimethyl-2-butene (8a) and (*E*)-1,4-Bis(3,4,5-trimethoxyphenyl)-2,3-dimethyl-2-butene (9a)——A mixture of the butanediol **6a** (4.32 g, 9.6 mmol), ethyl orthoformate (4.03 g, 27 mmol), and benzoic acid (0.8 g, 6.5 mmol) was heated at 100—105 °C for 2 h while ethanol was distilled from the mixture. The

solution was cooled, and additional benzoic acid (0.4 g, 3.27 mmol) was added, then the mixture heated at 180 °C for 4 h while a further amount of EtOH was distilled off and CO_2 was evolved. The residue was dissolved in CH_2Cl_2, washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was recrystallized from EtOH to yield 1.8 g (45%) of **9a** as colorless crystals, mp 119—121 °C. IR (Nujol) cm^{-1}: 1590. ^{1}H-NMR ($CDCl_3$) δ: 1.80 (6H, s, 2 × olefinic-Me), 3.42 (4H, s, 2 × $ArCH_2$), 3.82 and 3.85 (18H, each s, 6 × ArOMe), and 6.42 (4H, s, ArH). *Anal.* Calcd for $C_{24}H_{32}O_6$: C, 69.20; H, 7.74. MS *m/e*: 416.2197. Found: C, 68.90; H, 7.86. MS *m/e*: 416.2181.

The above mother liquor of recrystallization was concentrated and the residue was distilled in a bulb-to-bulb distillation apparatus to yield 1.8 g (45%) of **8a** as a colorless oil: bp 210—220 °C (3 mm). IR (Nujol) cm^{-1}: 1600. ^{1}H-NMR ($CDCl_3$) δ: 1.72 (6H, s, 2 × olefinic-Me), 3.50 (4H, s, 2 × $ArCH_2$), 3.80 and 3.82 (18H, each s, 6 × ArOMe), and 6.40 (4H, s, ArH). *Anal.* Calcd for $C_{24}H_{32}O_6$: C, 69.20; H, 7.74. MS *m/e*: 416.2199. Found: C, 68.91; H, 7.88. MS *m/e*: 416.2212.

(*Z*)-1,4-Bis[3-methoxy-4,5-(methylenedioxy)phenyl]-2,3-dimethyl-2-butene (8b) and (*E*)-1,4-Bis[3-methoxy-4,5-(methylenedioxy)phenyl]-2,3-dimethyl-2-butene (9b)——**8b** and **9b** were synthesized from **6b** by procedures similar to those used for **8a** and **9a** in yields of 46%. **9b**, mp 111—113 °C (EtOH), colorless crystals. IR (Nujol) cm^{-1}: 1630. ^{1}H-NMR ($CDCl_3$) δ: 1.74 (6H, s, 2 × olefinic-Me), 3.38 (4H, s, 2 × $ArCH_2$), 3.90 (6H, s, 2 × ArOMe), 5.97 (4H, s, 2 × $-OCH_2-$), and 6.40 (4H, s, ArH). *Anal.* Calcd for $C_{22}H_{24}O_6$: C, 68,73; H, 6.29. MS *m/e*: 384.1574. Found: C, 68.85; H, 6.37. MS *m/e*: 384.1586. **8b**, bp 235—240 °C (3 mm), colorless oil. IR (film) cm^{-1}: 1630. ^{1}H-NMR ($CDCl_3$) δ: 1.70 (6H, s, 2 × olefinic-Me), 3.43 (4H, s, 2 × $ArCH_2$), 3.88 (6H, s, 2 × ArOMe), 5.95 (4H, s, 2 × $-OCH_2O-$), and 6.38 (4H, br s, ArH). *Anal.* Calcd for $C_{22}H_{24}O_6$: C, 68.73; H, 6.29. MS *m/e*: 384.1571. Found: C, 68.72; H, 6.39. MS *m/e*: 384.1568.

Isomerization of the (*E*)-Butene 9a to the (*Z*)-Butene 8a——A solution of the (*E*)-butene **9a** (100 mg) in cyclohexane (100 ml) was irradiated with the 100 W low-pressure UV lamp for 1 h in the presence of I_2 (10 mg). Gas chromatographic measurement showed that this solution consisted of *ca.* 60% (*E*)-isomer and 40% (*Z*)-isomer.

***meso*-1,4-Bis(3,4,5-trimethoxyphenyl)-2,3-dimethylbutane (10a)**——The (*Z*)-butene **8a** (1 g, 24 mmol) was hydrogenated in the presence of PtO_2 (600 mg) in ArOH (50 ml). The catalyst was removed, and the filtrate was concentrated. The residue was recrystallized from MeOH to give 0.723 g (72%) of **10a** as colorless crystals, mp 115—117 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (6H, d, J=6 Hz, 2 × Me), 1.5—2.0 (2H, m, 2 × C<u>H</u>–Me), 2.2—2.8 (4H, m, 2 × $ArCH_2$), 3.85 (18H, s, 6 × ArOMe), and 6.38 (4H, s, ArH). *Anal.* Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. MS *m/e*: 418.2354. Found: C, 68.92; H, 8.25. MS *m/e*: 418.2342.

(±)-1,4-Bis(3,4,5-trimethoxyphenyl)-2,3-dimethylbutane (11a)——The (*E*)-butene **9a** (1 g, 2.4 mmol) was hydrogenated in the presence of PtO_2 (600 mg) in AcOH (50 ml). The solution was worked up, then the residue was recrystallized from MeOH to yield 0.823 g (82%) of **11a** as colorless crystals, mp 125—127 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (6H, d, J=6 Hz, 2 × Me), 1.6—2.0 (2H, m, C<u>H</u>–Me), 2.30—2.65 (4H, m, 2 × $ArCH_2$), 3.79 (12H, s, 4 × ArOMe), 3.82 (6H, s, 2 × ArOMe), and 6.28 (4H, s, ArH). *Anal.* Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. MS *m/e*: 418.2354. Found: C, 68.59; H, 8.39. MS *m/e*: 418.2348.

***meso*-1,4-Bis[3-methoxy-4,5-(methylenedioxy)phenyl]-2,3-dimethylbutane (10b)**——The (*Z*)-butene **8b** (1.2 g, 3.1 mmol) was hydrogenated in the presence of 5% Rh/C in AcOH (50 ml) at 120—135 psi for 20 h. The catalyst was filtered off and washed with $CHCl_3$ several times, then the filtrate was neutralized with 10% NaOH aq. and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried and concentrated. The residue was recrystallized from MeOH to give 0.87 g (72%) of **10b** as colorless crystals, mp 86—88 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (6H, d, J=6 Hz, 2 × Me), 1.5—2.0 (2H, m, 2 × C<u>H</u>–Me), 2.15—2.90 (4H, m, 2 × $ArCH_2$), 3.88 (6H, s, 2 × ArOMe), 5.93 (4H, s, 2 × $-OCH_2O-$), 6.32 (2H, d, J=1.5 Hz, ArH), and 6.36 (2H, d, J=1.5 Hz, ArH). *Anal.* Calcd for $C_{22}H_{26}O_6$: C, 68.37; H, 6.78. MS *m/e*: 386.1727. Found: C, 68.36; H, 6.85. MS *m/e*: 386.1726.

(±)-1,4-Bis[3-methoxy-4,5-(methylenedioxy)phenyl]-2,3-dimethylbutane (11b)——**11b**, an oil, was synthesized from the (*E*)-butene **9b** by a procedure the similar to that used for **10b** in 72% yield. ^{1}H-NMR ($CDCl_3$) δ: 0.82 (6H, d, J=6 Hz, 2 × Me), 1.5—2.0 (2H, m, 2 × C<u>H</u>–Me), 2.2—2.80 (4H, m, $ArCH_2$), 3.90 (6H, s, 2 × ArOMe), 5.95 (4H, s, 2 × $-OCH_2O-$), 6.32 (2H, d, J=1.5 Hz, ArH), and 6.36 (2H, d, J=1.5 Hz, ArH). *Anal.* Calcd for $C_{22}H_{26}O_6$: C, 68.37; H, 6.78. MS *m/e*: 386.1727. Found: C, 68.56; H, 6.90. MS *m/e*: 386.1730.

Oxidation of *meso*-1,4-Bis(3,4,5-trimethoxyphenyl)-2,3-dimethylbutane (10a)——Method A. With $Fe(ClO_4)_3 \cdot 9H_2O$ in MeCN: A solution of the *meso*-diaryldimethylbutane **10a** (376 mg, 0.9 mmol) in dry MeCN (9 ml) was added to a solution of $Fe(ClO_4)_3 \cdot 9H_2O$ (1.32 g, 2.5 mmol) in dry MeCN (15 ml), and the whole was stirred at room temperature for 1 min. The reaction mixture was poured into ice-water and extracted with ether. The organic layer was washed with H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The eluate with 20% ether in petroleum ether gave 34 mg (9%) of (±)-deoxyschizandrin, *cis*-5,6,7,8-tetrahydro-1,2,3,10,11,12-hexamethoxy-6,7-dimethyldibenzo[*a*,*c*]cyclooctene (**2a**), as colorless crystals, mp 112—113 °C (MeOH). IR (Nujol) cm^{-1}: 1600. ^{1}H-NMR ($CDCl_3$) δ: 0.73 [3H, d, J=7 Hz, C(14)-Me], 1.00 (3H, d, J=7 Hz, C(13)-Me], 1.80—2.0 [2H, m, C(6)- and C(7)-H], 2.02 [1H, dd, J=13.5 and 1 Hz, C(5)β-H], 2.27 [1H, dd, J=13.2 and 9 Hz, C(5)α-H], 2.45—2.65 [2H, m, C(8)α- and C(8)β-H], 3.58 (6H, s, 2 × ArOMe), 3.90 (12H, s, 4 × ArOMe), and 6.55 (2H, s, ArH). *Anal.* Calcd for $C_{24}H_{32}O_6$: C, 69.20; H, 7.74; MS *m/e*: 416.2199. Found: C, 69.18; H, 7.88. MS *m/e*: 416.2217.

Method B. With $FeCl_3$ in Ac_2O: A solution of **10a** (501.6 mg, 1.2 mmol) in Ac_2O (16 ml) was added to a solution

of $FeCl_3$ (1.8 g, 11 mmol) in Ac_2O (15 ml), and the whole was stirred at room temperature for 2 min. The reaction mixture was poured into ice-water and extracted with ether. The organic layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was purified as in method A to give 160 mg (32%) of **2a**.

Method C. With VOF_3 in CF_3CO_2H: VOF_3 (300 mg) was added to a solution of **10a** (130 mg) in CF_3CO_2H (5 ml) and CH_2Cl_2 (40 ml) at −78 °C under a nitrogen atmosphere, and the whole was stirred at −78 °C for 30 min then at room temperature for an additional 30 min. Sat. Na_2CO_3 was added to the solution, and the organic layer was successively washed with sat. Na_2CO_3, brine and H_2O, then dried and concentrated. The residue was purified as in method A to yield 11.6 mg (9%) of **2a**.

Method D. With $Mn(ClO_4)_2 \cdot 6H_2O$–$KMnO_4$ in Ac_2O: A solution which was prepared by addition of a solution of $KMnO_4$ (197.5 mg, 1.25 mmol) in Ac_2O (75 ml) to a solution of $Mn(ClO_4)_2 \cdot 6H_2O$ (1.68 g, 5 mmol) in Ac_2O (5 ml) was added to a solution of **10a** (501.6 mg, 1.2 mmol) in Ac_2O (10 ml) with stirring at room temperature, and the whole was stirred for 20 min. The reaction mixture was worked up as in method B to yield 34.4 mg (9.2%) of **2a**.

Method E. By Anodic Oxidation: **10a** (100 mg) was oxidized in the presence of Et_4NClO_4 (800 mg) as an electrolyte in MeCN (35 ml) at 1.05 V (SCE) using platinum electrodes and a Hg–Hg_2Cl_2 reference electrode for 15 min. The reaction mixture was worked up as in method A to give 8.5 mg (8.5%) of **2a**.

Oxidation of (±)-Bis(3,4,5-trimethoxyphenyl)-2,3-dimethylbutane (11a)——Method A. With $Fe(ClO_4)_3 \cdot 9H_2O$ in MeCN: A solution of the (±)-diaryldimethylbutane **11a** (376 mg, 0.9 mmol) in dry MeCN (9 ml) was added to a solution of $Fe(ClO_4)_3 \cdot 9H_2O$ (1.32 g, 2.5 mmol) in dry MeCN (15 ml), and the whole was stirred at room temperature for 1 min. The reaction mixture was poured into ice-water and extracted with ether. The organic layer was washed with H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The eluate with 20% ether in petroleum ether gave 35.5 mg (9.5%) of *trans*-5,6,7,8-tetrahydro-1,2,3,10,11,12-hexamethoxy-6,7-dimethyldibenzo[*a*,*c*]cyclooctene (**3a**) as colorless crystals, mp 129—131 °C (MeOH). IR (Nujol) cm^{-1}: 1600. ^1H-NMR ($CDCl_3$) δ: 1.05 [6H, d, J=4.5 Hz, C(13)- and C(14)-Me], 1.0—1.4 [2H, m, C(6)- and C-(7)-H], 2.15 [2H, dd, J=13.2 and 8.5 Hz, C(8)β- and C(5)α-H], 2.38 [2H, dd, J=13.2 and 1 Hz, C(8)α- and C(5)β-H], 3.64 [6H, s, C(1)- and C(12)-OMe], 3.89 (12H, s, 4×ArOMe), and 6.57 [2H, s, C(4)- and C(9)-H]. *Anal.* Calcd for $C_{24}H_{32}O_6$: C, 69.20; H, 7.74. MS *m/e*: 416.2199. Found: C, 68.91; H, 7.89. MS *m/e*: 416.2189.

Method B. With $FeCl_3$ in Ac_2O: A solution of **11a** (501.6 mg, 1.2 mmol) in Ac_2O (16 ml) was added to a solution of $FeCl_3$ (1.8 g, 11 mmol) in Ac_2O (15 ml), and the whole was stirred at room temperature for 2 min. The reaction mixture was poured into ice-water and extracted with ether. The organic layer was washed with sat. $NaHCO_3$ aq. and H_2O, then dried and concentrated. The residue was purified as in method A to give 175 mg (35%) of **3a**.

Method C. With VOF_3 in CF_3CO_2H: VOF_3 (300 mg) was added to a solution of **11a** in CF_3CO_2H (5 ml) and CH_2Cl_2 (30 ml) under a nitrogen atmosphere at −78 °C, and the solution was stirred at the same temperature for 30 min then at room temperature for a further 30 min. Sat. Na_2CO_3 was then added to the solution, and the organic layer was successively washed with sat. Na_2CO_3 aq., brine, and H_2O, then dried and concentrated. The residue was purified as in method A to yield 12.3 mg (9.5%) of **3a**.

Method D. With $Mn(ClO_4)_2 \cdot 6H_2O$–$KMnO_4$ in Ac_2O: A solution which was prepared by addition of a solution of $KMnO_4$ (197.5 mg, 1.25 mmol) in Ac_2O (75 ml) to a solution of $Mn(ClO_4)_2 \cdot 6H_2O$ (1.68 g, 5 mmol) in Ac_2O (5 ml) was added to a solution of **11a** (501.6 mg, 1.2 mmol) in Ac_2O (10 ml) at room temperature, an the whole was stirred for 20 min. The reaction mixture was worked up as in method B to yield 49 mg (9.8%) of **3a**.

Method E. By Anodic Oxidation: **11a** (100 mg) was oxidized in the presence of an electrolyte Et_4NClO_4 (800 mg) in MeCN (35 ml) at 1.05 V (SCE) using platinum electrodes and a reference electrode of Hg–Hg_2Cl_2 for 15 min. The reaction mixture was worked up as in method A to give 9 mg (9.1%) of **3a**.

Oxidation of *meso*-1,4-Bis[3-methoxy-4,5-(methylenedioxy)phenyl]-2,3-dimethylbutane (10b)——Method A. With $Fe(ClO_4)_3 \cdot 9H_2O$ in MeCN: A solution of the *meso*-diaryldimethylbutane **10b** (347 mg, 0.9 mmol) in dry MeCN (9 ml) was added to a solution of $Fe(ClO_4)_3 \cdot 9H_2O$ (1.32 g, 2.5 mmol) in dry MeCN (15 ml), and the whole was stirred at room temperature for 1 min. The reaction mixture was poured into ice-water and extracted with ether. The organic layer was washed with H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The eluate with 20% ether in petroleum ether gave 162 mg (47%) of (±)-wuweizisu C, *cis*-5,6,7,8-tetrahydro-1,12-dimethoxy-2,3 : 10,11-bis(methylenedioxy)-6,7-dimethyldibenzo[a,*c*]cyclooctene (**2b**), as colorless crystals, mp 158—160 °C (MeOH). IR (KBr) cm^{-1}: 1615. ^1H-NMR ($CDCl_3$) δ: 0.73 [3H, d, J=7 Hz, C(14)-Me], 0.96 [3H, d, J=7 Hz, C(13)-Me], 1.6—2.7 (6H, m, 2×ArC$\underline{H}_2$C$\underline{H}$), 3.84 (6H, s, 2×ArOMe), 5.96 (4H, s, 2×–OC$\underline{H}_2$O–), and 6.51 (2H, s, ArH). *Anal.* Calcd for $C_{22}H_{24}O_6$: C, 68.73; H, 6.29. MS *m/e*: 384.1593. Found: C, 68.70; H, 6.34. MS *m/e*: 384.1583.

Method B. With $FeCl_3$ in Ac_2O: A solution of **10b** (347 mg, 0.9 mmol) in Ac_2O (15 ml) was added to a solution of $FeCl_3$ (1.46 g, 9 mmol) in Ac_2O (15 ml), and the whole was stirred at room temperature for 2 min. The reaction mixture was poured into ice-water and extracted with ether. The organic layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was purified as in method A to give a trace amount of **2b**.

Oxidation of (±)-1,4-Bis[3-methoxy-4,5-(methylenedioxy)phenyl]-2,3-dimethylbutane (11b)——Method A. With $Fe(ClO_4)_3 \cdot 9H_2O$ in MeCN: A solution of the (±)-diaryldimethylbutane **11b** (347 mg, 0.9 mmol) in dry MeCN (9 ml) was added to a solution of $Fe(ClO_4)_3 \cdot 9H_2O$ (1.32 g, 2.5 mmol) in dry MeCN (15 ml), and the whole was stirred at room temperature for 1 min. The reaction mixture was poured into ice-water and extracted with ether. The organic

layer was washed with H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The eluate with 20% ether in petroleum ether gave 38.5 mg (10%) of *trans*-5,6,7,8,-tetrahydro-1,12-dimethoxy-2,3 : 10,11-bis(methylenedioxy)-6,7-dimethyldibenzo[*a*,*c*]cyclooctene (**3b**-TBC) as colorless crystals, mp 238—240 °C ($CHCl_3$–ether). IR (Nujol) cm^{-1}: 1605. ^{1}H-NMR ($CDCl_3$) δ: 0.84 [6H, d, J=7.3 Hz, C(13)- and C(14)-Me], 1.55—1.82 [2H, m, C(6)- and C(7)-H], 2.25 [2H, dd, J=13.4 and 8 Hz, C(8)β- and C(5)α-H], 2.45 [2H, dd, J=13.4 and 2 Hz, C(8)α- and C(5)β-H], 3.80 [6H, s, C(1)- and C(12)-OMe], 5.92, 5.95 (each 2H, d, J=1.22 Hz, 2×–OCH_2O–), and 6.46 (2H, s, C(4)- and C(9)-H]. *Anal.* Calcd for $C_{22}H_{24}O_6$: C, 68.73; H, 6.29. MS *m/e*: 384.1572. Found: C, 68.47; H, 6.34. MS *m/e*: 384.1562.

The above mother liquor of recrystallization was concentrated and the residue was recrystallized from MeOH to give 135 mg (35%) of *trans*-5,6,7,8-tetrahydro-1,12-dimethoxy-2,3 : 10,11-bis(methylenedioxy)-6,7-dimethyldibenzo[*a*,*c*]cyclooctene (**3b**) as colorless crystals, mp 193—195 °C. IR (Nujol) cm^{-1}: 1620. ^{1}H-NMR ($CDCl_3$) δ: 1.01 [6H, d, J=4.5 Hz, C(13)- and C(14)-Me], 1.0—1.30 [2H, m, C(6)- and C(7)-H], 2.10 [2H, dd, J=13.2 and 9 Hz, C(8)β- and C(5)α-H], 2.32 [2H, dd, J=13.2 and 1 Hz, C(8)α- and C(5)β-H], 3.87 [6H, s, C(1)- and C(12)-OMe], 5.90 (4H, s, 2×–OCH_2O–), and 6.48 [2H, s, C(4)- and C(9)-H]. *Anal.* Calcd for $C_{22}H_{24}O_6$: C, 68.73; H, 6.29. MS *m/e*: 384.1570. Found: C, 68.70; H, 6.35. MS *m/e*: 384.1557.

Method B. With $FeCl_3$ in Ac_2O: A solution of **11b** (347 mg, 0.9 mmol) in Ac_2O (15 ml) was added to a solution of $FeCl_3$ (1.46 g, 9 mmol) in Ac_2O, and the whole was stirred at room temperature for 2 min. The reaction mixture was poured into ice-water and extracted with ether. The organic layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was purified as in method A to yield a trace amount of **3b** and **3b**-TBC.

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