Synthesis of (±)-Dibenzocyclooctadiene Lignans, (±)-Isoschizandrin, and Their Stereoisomers, Utilizing the Samarium-Barbier Reaction

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Several (±)-dibenzocyclooctadiene lignans, (±)-isoschizandrin (1a), 1b, 2a, and 2b, were synthesized by the samarium-Barbier reaction of the phenylpropenes 4 and the phenylacetone 5 to give the *erythro*- and *threo*-butanols 6 and 7, followed by oxidative aryl–aryl coupling reaction of each butanol.

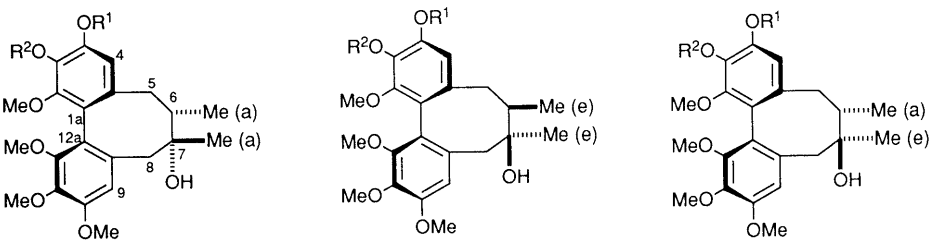
Keywords synthesis; lignan; dibenzocyclooctadiene; samarium-Barbier reaction; oxidative aryl–aryl coupling reaction

In the preceding paper,[1] we reported a concise synthesis of (±)-schizandrin (**3a**), (±)-gomisin A (**3b**) and related stereoisomers belonging to the dibenzocyclooctadiene (DBCO) lignan group, utilizing the recently developed samarium-Grignard reaction. These DBCO lignans can be classified into two types according to the configuration of the C-6 and C-7 methyl groups on the DBCO ring, namely, compounds having *cis* relative configuration, such as **3a** and **3b**, and compounds having *trans* configuration, such as **1** and **2**. The latter lignans can be subdivided into two types, that is, one in which, the methyl groups at C-6 and C-7 have each axial configuration, such as **1**, and one in which they each have equatorial configuration, such as **2**. Almost a dozen such lignans have been isolated from the fruits of *Schizandra chinesis* BAILLON (Schizandraceae) to date.[2]

During further investigation of samarium(II)-catalyzed reductive coupling reactions of the phenylpropenes **4** and the phenylacetone derivative **5** following the samarium-Grignard experiments reported in the previous paper,[1] we found that the *threo*-products **7** are formed in preference to the *erythro*-products **6**. This paper deals with the synthesis of the DBCO lignans **1** and **2**, including (±)-isoschizandrin (**1a**), through formation of the *threo*-butanols **7**, followed by oxidative aryl–aryl coupling reactions.

The phenylpropenes (*E*)-**4a**[3a] and (*E*)-**4b**[3b] were synthesized by the reaction of 3,4,5-trimethoxybenzaldehyde or 3-methoxy-4,5-methylenedioxybenzaldehyde with ethylmagnesium bromide followed by dehydration of the resultant propanol with $KHSO_4$ in the presence of *p-tert*-butylcatechol. A mixture of (*E*)- and (*Z*)-**4b** (*E*/*Z* ratio = 3 : 2) was prepared by the Wittig reaction of 3-methoxy-4,5-methylenedioxybenzaldehyde and (ethyl)-triphenylphosphonium bromide using *n*-butyl lithium. The samarium-Barbier-type reactions of the phenylpropenes **4** with the phenylacetone **5**[4] were performed by utilizing the methods of Inanaga *et al.*[5] and Curran and Totleben.[6] The best result was obtained in the reaction of (*E*)-**4b** and **5** in the ratio of (*E*)-**4b** : **5** : 0.1 M SmI_2 in tetrahydrofuran (THF) = 4 : 1 : 4 in the presence of hexamethylphosphoramide (HMPA) and *tert*-BuOH under an argon stream to give selectively the cross coupling products **6b** and **7b** (*erythro*/*threo* ratio = 7 : 93, as determined by analytical HPLC with MeOH : H_2O = 6 : 4 as the eluent) in 38% yield. Similar reaction of (*E*)-**4a** or a mixture of (*E*)- and (*Z*)-**4b** with **5** was performed and the results are shown in Table I. Less selectivity in the *erythro*/*threo* ratio of the product was observed in the reaction of a mixture of (*E*)- and (*Z*)-**4b** with **5**. The structures of the coupling products **6** and **7** were clarified in the preceding paper.[1]

We were particularly interested in stereoselective formation of the *threo*-butanol **7** in the above samarium-Barbier reactions even though the chemical yields are not high, and since we wished to use these *threo* compounds for synthesis of DBCO lignans in which the C-6 and C-7 methyl groups are relatively *trans*, such as **1** and **2**. Oxidative coupling reactions were performed on the isobutyrates **8**, because oxidation of the alcohol **7** may give only the spirodienone, as reported previously.[1] Several reagent systems based on iron(III) salts were examined for oxidative coupling reaction of **8** as shown in Table II, and we found that a) the best yields were obtained in the reactions with the reagent system $Fe(ClO_4)_3 \cdot 9H_2O$–CH_2Cl_2–MeCN, b) two coupling products **9a** and **10a** were generated in the reactions of **8a**,

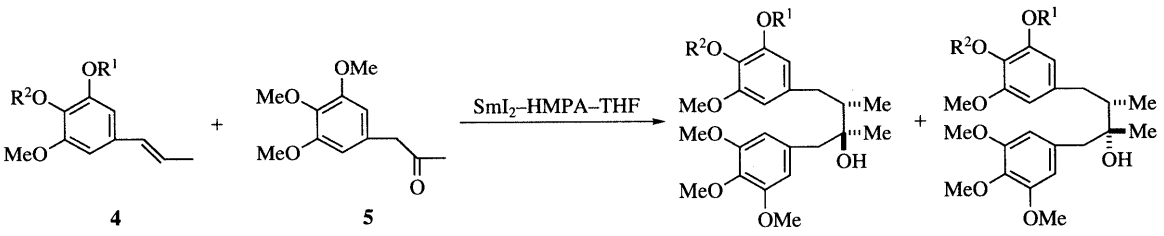


1a : R^1=R^2=Me (isoschizandrin) **2a** : R^1=R^2=Me **3a** : R^1=R^2=Me

1b : R^1+R^2=CH_2 **2b** : R^1+R^2=CH_2 **3b** : R^1+R^2=CH_2

Chart 1

TABLE I. Cross Coupling Reactions of Phenylacetone and Phenylpropenes in the SmI_2–HMPA–THF System



Run	Phenylpropene	Yield (%)	Product	Ratio (6:7)[a]
1	(*E*)-**4a**: $R^1=R^2=Me$	32	**6a**+**7a**	(10:90)
2	(*E*)-**4b**+(*Z*)-**4b**: $R^1+R^2=CH_2$	36	**6b**+**7b**	(14:86)
3	(*E*)-**4b**: $R^1=R^2=CH_2$	38	**6b**+**7b**	(7:93)

a) The *erythro*/*threo* ratios were determined by HPLC analysis.

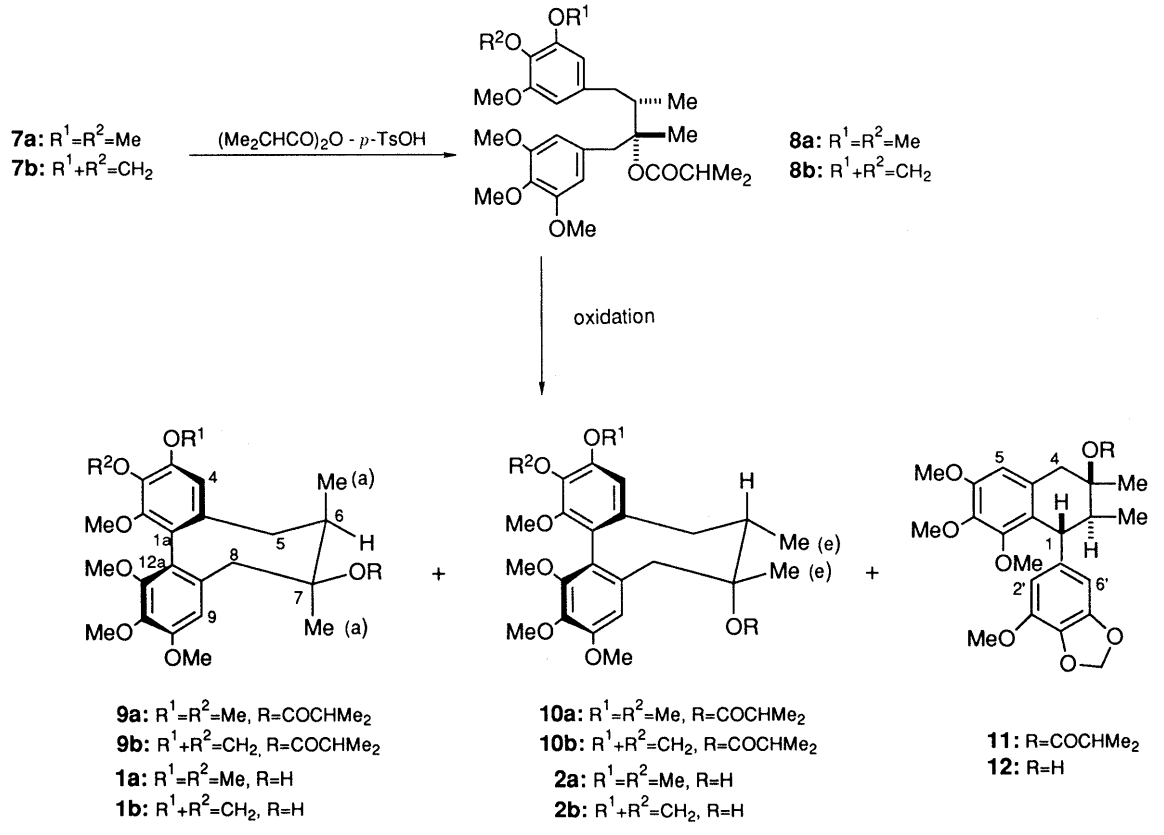


Chart 2

TABLE II. Oxidative Aryl–Aryl Coupling Reaction of **8a** and **8b**

Run	Substrate	Reagent	Yield (%)	Product	Ratio (9:10:11)[a]
1	**8a**	A	36.0	(**9a**+**10a**)	(85:15)
2	**8a**	B	21.8	(**9a**+**10a**)	(85:15)
3	**8a**	C	5.0	(**9a**+**10a**)	(85:15)
4	**8b**	A	55.8	(**9b**+**10b**+**11**)	(38:11:51)
5	**8b**	B	22.0	(**9b**+**10b**+**11**)	(38:11:51)
6	**8b**	D	34.0	(**9b**+**10b**+**11**)	(32: 9:59)

a) The ratio of the products were obtained after hydrolysis of the coupling products. Reagent A, $Fe(ClO_4)_3\cdot 9H_2O$–CH_2Cl_2–MeCN; B, $Fe(ClO_4)_3\cdot 9H_2O$–MeCN; C, $FeCl_3$–MeCN; D, $Fe(ClO_4)_3\cdot 9H_2O$–CF_3CO_2H–CH_2Cl_2–MeCN.

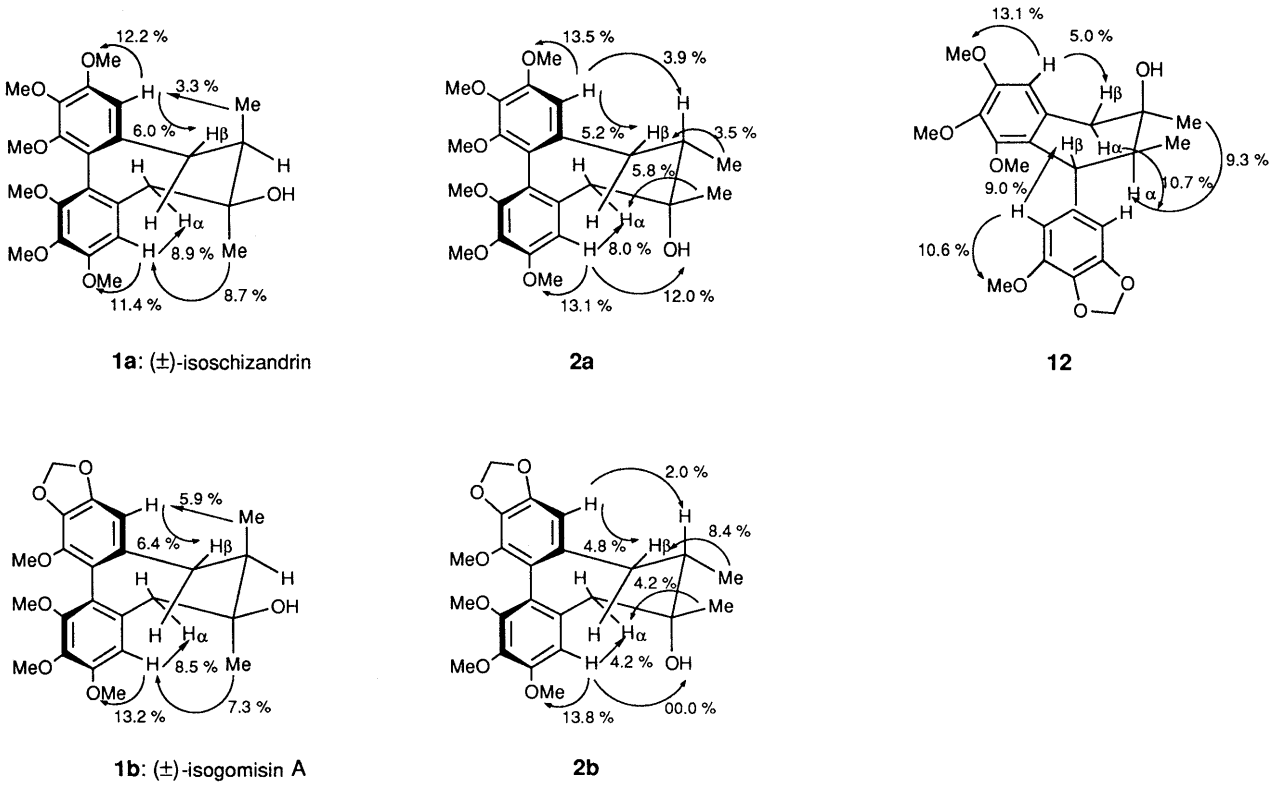
and **9a** was formed in preference to **10a**, c) three products were produced in the reactions of **8b**, namely, two DBCO lignans **9b** and **10b** and the 1-aryltetralin **11**, and the yield of the tetralin **11** was increased in the oxidation with the reagent D system, including CF_3CO_2H in the solvent.

The coupling products were subsequently hydrolyzed with 10% KOH to give the corresponding alcohols **1a**, **1b**, **2a**, **2b**, and **12**. The structure of **1a**, (±)-isoschizandrin, mp 89—90 °C, was identified by direct comparison of the physical data with those of synthetic (−)-isoschizandrin.[7] The structure of **2a** was also identified by direct comparison of the physical data (Tables III and IV) with reported

TABLE III. ^{1}H-NMR Spectral Data for the Lignans

	1a[a]	**1a**[b]	**1b**[a]	**1b**[b]	**2a**[a]	**2a**[b]	**2b**[a]	**2b**[b]
H-9	6.62	6.46	6.48	6.41	6.68	6.63	6.68	6.60
H-4	6.54	6.39	6.63	6.50	6.56	6.51	6.49	6.49
H-8α	2.33, d	2.23, d	2.31, d	2.19, d	2.57, d	2.59, d	2.59, d	2.55, d
(*J*=Hz)	(13.0)	(13.1)	(12.8)	(13.2)	(13.0)	(13.5)	(13.4)	(13.1)
H-8β	2.82, d	2.97, d	2.84, d	2.97, d	2.64, d	2.72, d	2.64, d	2.67, d
(*J*=Hz)	(13.0)	(13.5)	(13.4)	(13.2)	(13.0)	(13.5)	(13.4)	(13.1)
H-5α	2.47—2.58	2.63, dd	2.47—2.49	2.55, dd	2.22, dd	2.32, dd	2.05—2.22	2.22, dd
(*J*=Hz)	(m)	(14.0)	(m)	(13.7)	(14.2)	(13.7)	(m)	(13.7)
		(2.2)		(1.5)	(9.6)	(10.4)		(10.3)
H-5β	2.47—2.58	2.38, dd	2.47—2.49	2.30, dd	2.15, dd	2.10, d	2.05—2.22	1.99, d
(*J*=Hz)	(m)	(14.0)	(m)	(13.7)	(14.2)	(13.7)	(m)	(13.2)
		(7.9)		(10.1)	(2.0)			
H-6 (m)	1.80—1.95	1.83—1.95	1.82—1.95	1.60—1.75	1.58—1.70	1.58—1.69	1.51—1.66	1.46—1.57
C-7-OH (s)	1.36	1.45	1.60	1.37	1.57	1.43	1.51	1.55
C-7-Me (s)	1.20	1.20	1.17	1.07	1.29	1.23	1.27	1.18
C-6-Me	0.89, d	0.90, d	0.89, d	0.90, d	1.10, d	1.12, d	1.07, d	1.02, d
(*J*=Hz)	(7.1)	(7.0)	(7.3)	(7.3)	(7.1)	(7.0)	(7.0)	(7.0)
Ar-OMe	3.56	3.45	3.50	3.42	3.635	3.40	3.61	3.37
	3.57	3.46	3.862	3.53	3.639	3.46	3.87	3.63
	3.882	3.62	3.887	3.84	3.89	3.71	3.90	3.87
	3.893	3.64	3.891	3.88	(×2)	3.73	3.91	3.89
		3.85			3.90	3.86		
		3.86			(×2)	3.87		
OCH_2O	—	—	5.96, d	5.28, d	—	—	5.95, d	5.29, d
(*J*=Hz)			(1.6)	(1.5)			(1.5)	(1.5)
			5.98, d	5.31, d			5.96, d	5.35, d
			(1.6)	(1.5)			(1.5)	(1.5)

a) δ in $CDCl_3$; ^{1}H-NMR at 270 MHz. *b*) δ in C_6D_6; ^{1}H-NMR at 270 MHz.



1a: (±)-isoschizandrin **2a** **12**

1b: (±)-isogomisin A **2b**

Chart 3. ^{1}H-NOE Data for Synthetic Dibenzocyclooctadiene Lignans **1a**, **1b**, **2a**, **2b**, and **12** in C_6D_6

values.[5] The structure of a new compound (**1b**) was confirmed by comparison of the ^{1}H-NMR data with those of **1a** and analysis of ^{1}H-nuclear Overhauser effect (^{1}H-NOE) (Chart 3). The aryl–aryl coupling in **1b** was confirmed to be between C(1a) and C(12a) by the following facts: namely, when the signal at C(9)-H δ 6.41 was irradiated, a 13.2% increment of the C(10)-OMe signal was observed, but irradiation of C(4)-H at δ 6.50 had no

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

Carbon No.	1a	1b	2a	2b
1a	122.8	121.9	122.0	121.0
1	151.7	141.3	151.1	140.7
2	140.3	135.2	140.0	136.9
3	151.8	147.8	153.1	148.9
4a	133.6	133.8	138.1	134.7
4	110.3	106.0	107.3	103.1
5	35.4	34.9	36.8	36.6
6	40.7	40.9	46.2	46.1
7	74.1	74.0	70.2	70.1
8a	133.6	132.2	131.6	131.8
8	42.1	41.8	45.7	45.6
9	110.5	110.7	110.1	110.2
10	152.0	151.9	152.4	152.4
11	140.4	140.4	140.8	140.7
12a	123.2	123.2	124.0	123.9
12	151.7	151.8	151.8	151.9
6-Me	13.5	13.3	18.9	18.8
7-Me	29.3	29.2	30.6	30.5
Ar-OMe	60.64	61.1	60.9	61.0
	60.62	60.6	60.6	60.7
	60.99	59.7	56.0	59.6
	60.98	55.9	55.9	55.9
	55.92			
	55.91			
OCH_2O	—	100.9	—	100.8

a) δ in $CDCl_3$; ^{13}C-NMR at 125.65 MHz.

TABLE V. ^{1}H-NMR Spectral Data for the Lignans

	11[a]	12[a]	12[b]
H-2′ (J=Hz)	6.40, d (1.5)	6.36, d (1.5)	6.53, d (1.5)
H-6′ (J=Hz)	6.30, d (1.5)	6.30, d (1.5)	6.48, d (1.5)
H-5 (s)	6.37	6.41	6.23
H-1 (J=Hz)	3.65—3.90 (m)	3.59, d (9.2)	3.77, d (8.9)
H-2 (m)	1.55—1.75	1.60—1.75	2.58—2.72
H-4α (J=Hz)	3.65—3.90 (m)	3.06, d (15.8)	2.78, d (15.8)
H-4β (J=Hz)	2.89, d (16.2)	2.74, d (15.9)	2.50, d (15.8)
C-3-OH (s)	—	1.42	1.30
C-3-Me (J=Hz)	1.10, d (6.7)	1.06, d (6.8)	1.09, d (6.7)
C-4-Me (s)	1.62	1.33	1.16
Ar-OMe	3.21	3.20	3.32
	3.70	3.74	3.40
	3.81	3.84	3.51
	3.88	3.88	3.66
OCH_2O	5.90, d (1.5)	5.89, d (1.5)	5.32, d (1.5)
(J=Hz)	5.92, d (1.5)	5.90, d (1.5)	5.35, d (1.5)
CO-CH- (m)	2.18—2.29	—	—
CH-Me_2	0.70, d (6.7)	—	—
(J=Hz)	0.82, d (6.7)		

a) δ in $CDCl_3$; ^{1}H-NMR at 270 MHz. b) δ in C_6D_6; ^{1}H-NMR at 270 MHz.

influence on any of the aromatic-OMe signals. The stereochemistry of **1b** was also elucidated by means of the following ^{1}H-NOE experiment. Namely, a) upon irradiation of the signal of C(9)-H at δ 6.41, a 8.5% increment of the C(8)-αH signal was observed, but irradiation of the C(7)-OH had no influence, b) upon irradiation of the signal of C(4)-H at δ 6.50, the signal of C(5)-βH was increased 6.4%, c) upon irradiation of the signal of C(7)-Me at δ 1.07, a 7.3% increment of the signal of C(9)-H was observed, d) the dihedral angle between C(5)-βH and C(6)-αH may be about 0° because the coupling constant between these two protons was 10.1 Hz, and the dihedral angle between C(5)-αH and C(6)-βH may be about 90° because the coupling constant between these two protons was 1.5 Hz. Thus, the DBCO ring of **1b** may have a twist-boat-chair form and the C(6)-Me and C(7)-Me groups may both be axial, as shown in Chart 3. Although the new compound **1b** obtained in this investigation has not yet been isolated yet from nature, this compound may be named as (±)-isogomisin A (**1b**), being related to (±)-isoschizandrin (**1a**). The structure of **2b** is considered to have the DBCO ring in twist-boat-chair form and C(6)-Me and C(7)-Me groups in equatorial conformation based on a similar analysis to that in the case of **1b**.

Finally, the structure of the tetralin **12** was also elucidated by analysis of the ^{1}H-NMR data and a ^{1}H-NOE. experiment (Table V and Chart 3). In addition to the ^{1}H-NOE experiment (Chart 3), it can be postulated that the dihedral angle between C(1)-βH and C(2)-αH may be about 180° because the coupling constant of these two protons was 8.9 Hz. These analyses imply that the structure of the 1-aryltetralin **12** may be represented as shown in Chart 3.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded with a JASCO IR-700 spectrometer, ^{1}H- and ^{13}C-NMR spectra with JEOL JNM-EX90, JNM-GX270 and JNM-GSX500 spectrometers with tetramethylsilane as an internal standard ($CDCl_3$ and C_6D_6 solution). Mass spectra were recorded on a JEOL JMS-D300 spectrometer. Elemental analyses were done using a Yanaco CHN-MT-3 apparatus. Wako Silica gel C-200 (200 mesh) and Merck Kieselgel $60F_{254}$ were used for column chromatography and thin-layer chromatography (TLC), respectively. The organic extract was dried over Na_2SO_4. High-performance liquid chromatography (HPLC) was performed a Wakosil 5C4-200 column (25 cm × 4.6 mm i.d. for analytical scale or 25 cm × 20 mm i.d. for preparative scale) with aqueous methanol (40—60%), using a Shimadzu LC-6A apparatus for monitoring at 254 nm.

General Procedure for the Coupling Reactions of the Ketone (5) and the Phenylpropenes (4a, 4b) in the SmI_2–HMPA–THF System A solution of the phenylpropene **4** (4 mmol) and the ketone **5** (1 mmol) in dry THF (2 ml) and *tert*-BuOH (0.2 ml) was added over 1—2 min to a 0.1 M solution of SmI_2 in THF (40 ml)[8] and HMPA (4 ml). The mixture was stirred at 25 °C for 5 min, then the reaction was quenched with 0.5 N HCl (6 ml) and the whole was extracted with hexane–ether (1 : 1). The organic extracts were combined and washed with H_2O (2×) and brine. The organic layer was dried and concentrated. The residue was subjected to silica gel column chromatography, eluted successively with CH_3CO_2Et–hexane (3 : 10; for the mixture of **6a** and **7a**) and CH_3CO_2Et–hexane (1 : 4, for the mixture of **6b** and **7b**). The inseparable mixture was further separated by preparative HPLC with MeOH–H_2O (60 : 40, v/v).

6a and **7a**[1] were prepared from **5** and (*E*)-**4a**.

6a: Colorless prisms, mp 138—139 °C (ether–hexane). *Anal.* Calcd for $C_{24}H_{34}O_7$: C, 66.34; H, 7.89. Found: C, 66.38; H, 8.00. MS *m/z*: 434 (M^+).

7a: Colorless prisms, mp 119—120 °C (ether–hexane). *Anal.* Calcd for $C_{24}H_{34}O_7$: C, 66.34; H, 7.89. Found: C, 66.15: H, 7.90. MS *m/z*: 434 (M^+).

6b and **7b**[1] were prepared from **5** and (*E*)-**4b** or a mixture of (*E*)- and (*Z*)-**4b**.

6b: Colorless crystals, mp 128—128.5 °C ($CHCl_3$–ether). *Anal.* Calcd for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 65.85; H, 7.27. MS *m/z*: 418 (M^+).

7b: Colorless prisms, mp 86.5—87.0 °C ($CHCl_3$–ether). *Anal.* Calcd for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 66.00; H, 7.19. MS *m/z*: 418 (M^+).

***threo*-2-Isopropylcarbonyloxy-2,3-dimethyl-1,4-bis(3,4,5-trimethoxyphenyl)butane (8a)** *p*-Toluenesulfonic acid (400 mg) was added to a solution of the *threo*-butanol **7a** (868 mg, 2 mmol) in isobutyric anhydride (15 ml), and the mixture was stirred at room temperature for 1.5 h. The

reaction mixture was poured into ice-water and extracted with ether. The ether layer was washed with saturated $NaHCO_3$ and H_2O, then dried and concentrated. The residue was subjected to silica gel column chromatography. The eluate with hexane–ether–$CHCl_3$ (5 : 1 : 1, v/v) gave 847 mg (84%) of **8a** as colorless crystals, mp 88—89 °C (ether–hexane). IR (KBr) 1710 cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, d, J=6.7 Hz, C3-Me), 1.14 and 1.16 (each 3H, d, J=7.0 Hz, CH-$\underline{Me}_2$), 1.15 (3H, s, C2-Me), 2.15 (1H, dd, J=13.0, 11.6 Hz, C4-H), 2.44—2.54 (1H, m, –CO–C$\underline{H}$), 2.78—2.86 (1H, m, C3-H), 2.96 (1H, dd, J=13.0, 1.6 Hz, C4-H), 3.04 and 3.22 (each 1H, d, J=14.4 Hz, Cl-H), 3.83 (3H, s, Ar-OMe), 3.84 (9H, s, 3 × Ar-OMe), 3.85 (6H, s, 2 × Ar-OMe), 6.32 and 6.47 (each 2H, s, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 14.1 (C3-$\underline{Me}$), 19.1 and 19.2 (–CH$\underline{Me}_2$), 21.1 (C2-$\underline{Me}$), 35.3 (–CO–$\underline{C}$H), 38.2 (C4), 41.2 (C1), 41.3 (C3), 56.06, 56.08, 60.85, 60.88, and 60.8 (each Ar-O$\underline{Me}$), 86.9 (C2), 105.9, 107.9, 132.8, 136.2, 136.8, 152.7, and 153.1 (each Ar-C), 176.4 (–$\underline{C}$O–CH). *Anal.* Calcd for $C_{28}H_{40}O_8$: C, 66.64; H, 7.99. Found: C, 66.64; H, 7.92. MS *m/z*: 504 (M^+).

***threo*-2-Isopropylcarbonyloxy-4-(3-methoxy-4,5-methylenedioxyphenyl)-2,3-dimethyl-1-(3,4,5-trimethoxyphenyl)butane (8b) 8b**, colorless plates, mp 78—78.5 °C, was synthesized from **7b** in 82% yield by a procedure similar to that used for **8a**. IR (Nujol): 1718, 1636, 1580 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, d, J=6.7 Hz, C3-Me), 1.13 and 1.15 (each 3H, d, J=7.0 Hz, CH-$\underline{Me}_2$), 1.14 (3H, s, C2-Me), 2.13 (1H, dd, J=13.0, 11.6 Hz, C4-H), 2.43—2.53 (1H, m, –CO–C$\underline{H}$), 2.74—2.81 (1H, m, C3-H), 2.93 (1H, dd, J=13.0, 1.6 Hz, C4-H), 2.99 and 3.23 (each 1H, d, J=14.0 Hz, Cl-H), 3.83 (9H, s, 3 × Ar-OMe), 3.88 (3H, s, Ar-OMe), 5.93 (2H, s, OCH_2O), 6.30, 6.34 (each 1H, s, Ar-H), 6.41 (2H, s, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 13.9 (C3-$\underline{Me}$), 19.1 and 19.2 (–CH$\underline{Me}_2$), 21.1 (C2-$\underline{Me}$), 35.2 (–CO–$\underline{C}$H), 37.8 (C4-Me), 41.3 (C3), 41.4 (C1), 56.1, 56.5, and 60.9 (each Ar-O$\underline{Me}$), 86.8 (C2), 103.1, 107.9, 108.1, 132.8, 133.4, 135.5, 136.7, 143.4, 148.7, and 152.7 (each Ar-C), 176.4 (–$\underline{C}$O–CH). *Anal.* Calcd for $C_{27}H_{36}O_8$: C, 66.37; H, 7.43. Found: C, 66.51; H, 7.52. MS *m/z*: 488 (M^+).

Oxidation of 8a with the Reagents A, B, C and Hydrolysis of the Coupling Products Method A: With $Fe(ClO_4)_3 \cdot 9H_2O$–CH_2Cl_2–MeCN (Reagent A): A solution of the ester **8a** (202 mg, 0.4 mmol) in anhydrous MeCN (1 ml) and CH_2Cl_2 (1 ml) was added to a solution of $Fe(ClO_4)_3 \cdot 9H_2O$ (516 mg, 1 mmol) in anhydrous MeCN (3 ml) and CH_2Cl_2 (3 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 column chromatography. The eluate with ether–hexane–$CHCl_3$ (1 : 6 : 1, v/v) gave 72 mg (35.8%) of a mixture of **9a** and **10a**. A solution of the above mixture (72 mg) in 10% alcoholic KOH (20 ml) was refluxed for 24 h. The reaction mixture was poured into ice-water, acidified with aqueous 10% HCl and then extracted with $CHCl_3$. The organic layer was washed with H_2O, dried and concentrated. The residue was subjected to silica gel column chromatography. The first eluate with ether–hexane (3 : 2, v/v) gave 50 mg (79%) of 6(*RS*),7(*SR*)-5,6,7,8-tetrahydro-7-hydroxy-1,2,3,10,11,12-hexamethoxy-6,7-dimethyldibenzo[*a*,*c*]cyclooctene, *RS*-biar (**1a**) as colorless crystals ($CHCl_3$–ether), mp 89—90 °C. IR (KBr): 3450, 1590 cm^{-1}. *Anal.* Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.67; H, 7.70. MS *m/z*: 432 (M^+).

The second eluate gave 8.6 mg (14%) of 6(*SR*),7(*RS*)-5,6,7,8-tetrahydro-7-hydroxy-1,2,3,10,11,12-hexamethoxy-6,7-dimethyldibenzo-[*a*,*c*]cyclooctene, *RS*-biar (**2a**) as colorless crystals ($CHCl_3$–ether), mp 103—104 °C. IR (KBr): 3480, 1594 cm^{-1}. *Anal.* Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.59; H, 7.47. MS *m/z*: 432 (M^+). ^{1}H- and ^{13}C-NMR data are listed in Tables III, IV, and V.

Method B: With $Fe(ClO_4)_3 \cdot 9H_2O$–MeCN (Reagent B): A solution of **8a** (202 mg, 0.4 mmol) in anhydrous MeCN (2 ml) was added to a solution of $Fe(ClO_4)_3 \cdot 9H_2O$ (516 mg, 1 mmol) in anhydrous MeCN (6 ml), and the whole was stirred at room temperature for 15 min. The reaction mixture was worked up as described in method A to give 44 mg (21.8%) of a mixture of **9a** and **10a**. The above mixture (44 mg) was hydrolyzed and worked up as described in method A to give 30 mg (79%) of **1a** and 5 mg (13%) of **2a**.

Method C: With $FeCl_3$–MeCN (Reagent C): A solution of **8a** (202 mg, 0.4 mmol) in dry MeCN (6 ml) was added to a solution of $FeCl_3$ (584 mg, 3.6 mmol) in dry MeCN (6 ml), and the whole was stirred at room temperature for 1 min. The reaction mixture was worked up as described in method A to give 10 mg (5.0%) of a mixture of **9a** and **10a**. The above mixture (10 mg) was hydrolyzed and worked up as described in method A to give 6.8 mg (78%) of **1a** and 1.2 mg (14%) of **2a**.

Oxidation of 8b with the Reagents A, B, D and Hydrolysis of the Coupling Products Method A: With $Fe(ClO_4)_3 \cdot 9H_2O$–CH_2Cl_2–MeCN (Reagent A): Oxidation of **8b** was carried out by the procedure described for the oxidation of **8a** with reagent A, to give 6(*RS*),7(*SR*)-5,6,7,8-tetrahydro-7-hydroxy-1,10-11,12-tetramethoxy-6,7-dimethyl-2,3-methylenedioxydibenzo[*a*,*c*]cyclooctene, *RS*-biar (**1b**), 6(*SR*),7(*RS*)-5,6,7,8-tetrahydro-7-hydroxy-1,10,11,12-tetramethoxy-6,7-dimethyl-2,3-methylenedioxydibenzo[*a*,*c*]cyclooctene, *RS*-biar (**2b**), and *t*-3-hydroxy-*t*-2,*c*-3-dimethyl-*r*-1-(3-methoxy-4,5-methylenedioxyphenyl)-tetralin (**12**).

1b: Colorless needles ($CHCl_3$–ether), mp 148—149 °C. IR (KBr): 3496, 1618, 1594 cm^{-1}. *Anal.* Calcd for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78. Found: C, 66.22; H, 6.67. MS *m/z*: 416 (M^+).

2b: Colorless needles ($CHCl_3$–ether), mp 118—118.5 °C. IR (KBr): 3490, 1609, 1599 cm^{-1}. *Anal.* Calcd for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78. Found: C, 66.49; H, 6.79. MS *m/z*: 416 (M^+).

12: As colorless prisms ($CHCl_3$–ether), mp 138—139 °C. IR (KBr): 3520, 1628, 1596 cm^{-1}. *Anal.* Calcd for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78. Found: C, 66.35; H, 6.79. MS *m/z*: 416 (M^+). Yields and physical data are listed in Tables II, III, IV, and V.

Method B: With $Fe(ClO_4)_3 \cdot 9H_2O$–MeCN (Reagent B): Oxidation of **8b** was carried out by the procedure described for the oxidation of **8a** with reagent B, to give **1b**, **2b**, and **12**.

Method C: With $Fe(ClO_4)_3 \cdot 9H_2O$–CF_3CO_2H–CH_2Cl_2–MeCN (Reagent D): A solution of **8b** (98 mg, 0.2 mmol) in anhydrous MeCN (1 ml) and CH_2Cl_2 (1 ml) was added to a solution of $Fe(ClO_4)_3 \cdot 9H_2O$ (259 mg, 0.5 mmol) in anhydrous MeCN (1.5 ml), CH_2Cl_2 (1.5 ml), and CF_3CO_2H (0.3 ml) and the whole was stirred at room temperature for 1.5 min. The reaction mixture was poured into ice-water and extracted with ether. The organic layer was washed with saturated $NaHCO_3$ and H_2O, then dried and concentrated. The reaction mixture was hydrolyzed and worked up as described in method A to give **1b**, **2b**, and **12**.

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