Protosappanins E-1 and E-2, Stereoisomeric Dibenzoxocins Combined with Brazilin from Sappan Lignum

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An inseparable mixture of two new dibenz[*b*,*d*]oxocins combined with brazilin, named protosappanins E-1 (1) and E-2 (2), was obtained from the heartwood (Sappan Lignum) of *Caesalpinia sappan* L. (Leguminosae). They were separated from each other as isomeric hexamethyl ethers $C_{38}H_{38}O_{11}$, $[\alpha]_D^{23}$ −80.8° (3) and $[\alpha]_D^{24}$ −9.6° (4). The mixture of 1 and 2 afforded brazilin and protosappanin B on reductive cleavage with sodium borohydride in alkaline methanol. On acid treatment, one of the hexamethyl ethers (3) yielded the other hexamethyl ether (4), *l*-11b-hydroxybrazilin trimethyl ether (13), and the dimethylacetal (11) of the trimethyl ether of protosappanin C. Compounds 1 and 2 were concluded to consist of protosappanin C combined with 11b-hydroxybrazilin through an acetal linkage and to be stereoisomeric in respect of the acetal carbon. The stereochemistries at the acetal carbons of 3 and 4 were determined by means of nuclear magnetic resonance (nuclear Overhauser effect) experiments.

Keywords *Caesalpinia sappan*; Leguminosae; Sappan Lignum; protosappanin E-1; protosappanin E-2; dibenz[*b*,*d*]oxocin

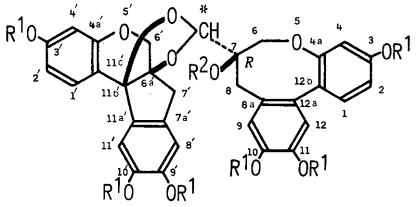
Sappan Lignum, the heartwood of *Caesalpinia sappan* L. (Leguminosae) contains several kinds of phenolic components, such as brazilin, chalcones, dibenz[*b*,*d*]oxocins, homoisoflavones and so on.[1-3] We have reported the isolation and structural elucidation of sappanchalcone[3] and dibenz[*b*,*d*]oxocins (protosappanins A, B, and C).[2] In the course of our chemical investigations, we obtained an inseparable mixture of two new dibenz[*b*,*d*]oxocins, designated protosappanin E-1 (**1**) and protosappanin E-2 (**2**). This paper deals with the structure determination of these compounds.

The mixture of protosappanins E-1 (**1**) and E-2 (**2**) was isolated as a light reddish brown powder, which showed a single spot on a silica gel thin layer chromatogram (TLC). In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum, the mixture showed complicated signals, and neither acetyl nor methoxy signals were observed. The mixture, after methylation with diazomethane, was separated into the two components as their hexamethyl ethers (**3** and **4**). The two components in the mixture which yielded **3** and **4** upon methylation were designated **1** and **2**, respectively.

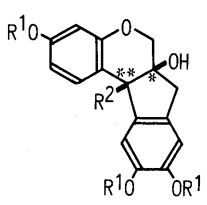
Protosappanin E-1 hexamethyl ether (**3**), an amorphous powder, $[\alpha]_D^{23}$ −80.8° ($CHCl_3$), showed absorptions due to a hydroxy group at 3500 cm^{-1} and aromatic rings at 1610 and 1495 cm^{-1} in the infrared (IR) spectrum. The high-resolution mass spectrum (MS) indicated the molecular ion at *m*/*z* 670.242, corresponding to $C_{38}H_{38}O_{11}$, and prominent fragment ions at *m*/*z* 355 (base ion) and *m*/*z* 310 were observed in the electron impact mass spectrum (EI-MS). The carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum of **3** exhibited thirty-two signals along with six methoxy signals, assignable to four benzene rings (fourteen singlets and ten doublets), four methylenes, three quaternary carbons joined to oxygen atoms, and an acetal carbon.

Protosappanin E-2 hexamethyl ether (**4**), an amorphous powder, $[\alpha]_D^{24}$ −9.6° ($CHCl_3$), has the same molecular formula as that of **3** ($C_{38}H_{38}O_{11}$) from the analysis of its high-resolution MS. The IR spectrum and the EI-MS of **4** were almost superimposable on those of **3**, and moreover its ^{13}C-NMR spectrum indicated that **4** has the same carbon system as **3** in the molecule (Table I). Therefore **4** was presumed to be a stereoisomer of **3**.

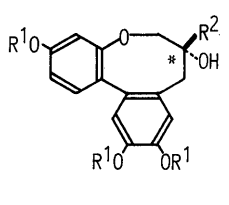
The mixture of **1** and **2** was unstable to weak alkali (such as 1% sodium carbonate), while the hexamethyl ethers (**3** and **4**) were stable even to strong alkali such as 20% sodium hydroxide in hot methanol. So, the mixture was treated with sodium borohydride in methanolic sodium carbonate to give two products, **5** and **7**, in almost equal yields. On methylation with diazomethane, **5** afforded a trimethyl ether (**6**), mp 138—140 °C, $[\alpha]_D^{20}$ +137.5° ($CHCl_3$), which was identical with brazilin trimethyl ether. The other product (**7**) was found to be identical with protosappanin B by direct



protosappanin E-1 (**1**):
$R^1=R^2=H$, $*=S$ configuration
protosappanin E-2 (**2**):
$R^1=R^2=H$, $*=R$ configuration
3: $R^1=CH_3$, $R^2=H$, $*=S$
4, **12**: $R^1=CH_3$, $R^2=H$, $*=R$
9: $R^1=CH_3$, $R^2=Ac$, $*=S$



brazilin (**5**): $R^1=R^2=H$, $*=S$, $**=R$
6: $R^1=CH_3$, $R^2=H$
13: $R^1=CH_3$, $R^2=OH$



protosappanin B (**7**):
$R^1=H$, $R^2=CH_2OH$, $*=S$
8: $R^1=CH_3$, $R^2=CH_2OH$
protosappanin C (**10**):
$R^1=H$, $R^2=CHO$, $*=R$
11: $R^1=CH_3$, $R^2=CH(OCH_3)_2$

Chart 1

TABLE I. ^{13}C-NMR Data (in $CDCl_3$)

Compound	3	4	6	8	9	11	13
C-1	131.5	131.0		131.4	130.7	131.9	
C-2	109.9	110.3		110.1	110.7	110.0	
C-3	158.7	158.8		158.5	159.2	158.8	
C-4	106.7	106.4		106.5	107.0	106.6	
C-4a	160.7[a]	160.6[a]		160.5	160.6[a]	160.4	
C-6	77.0	77.5		78.6	75.9	77.6	
C-7	71.2	71.8		74.2	82.2	73.8	
C-8	38.2	38.1		38.9	35.5	38.3	
C-8a	126.2	126.0		126.1	126.7	126.5	
C-9	115.6	115.5		114.9[a]	113.0	115.3[a]	
C-10	148.4[b]	148.2[b]		148.1[b]	147.9[b]	148.0[b]	
C-11	148.1[b]	147.9[b]		147.9[b]	147.7[b]	147.8[b]	
C-12	113.6	113.3		113.3[a]	114.8	113.1[a]	
C-12a	131.7[c]	131.6[c]		131.5	132.5[c]	131.5	
C-12b	124.8	125.4		124.9	126.3	125.1	
7-C	105.5	107.1		67.2	102.0	109.2	
AcO-					170.8		
					22.3		
C-1′	129.0	129.1	130.9		128.9		129.6
C-2′	109.8	109.9	109.5		109.7		109.5
C-3′	155.4	155.4	154.3		155.9		154.5
C-4′	102.3	101.9	101.9		102.2		101.3
C-4a′	160.5[a]	160.5[a]	159.3		160.4[a]		160.4
C-6′	69.9	67.8	70.2		70.1		69.0
C-6a′	88.1	88.7	77.3		87.9		77.9
C-7′	38.9	39.1	41.4		39.0		39.2
C-7a′	132.8[c]	134.5[c]	130.6		132.8[c]		130.9
C-8′	107.7	108.0	108.5[a]		107.6		108.5[a]
C-9′	151.0	150.6	148.7[b]		150.9		150.0[b]
C-10′	149.7[b]	149.3[b]	148.4[b]		149.6[b]		148.8[b]
C-11′	107.5	107.7	107.8[a]		107.5		107.8[a]
C-11a′	132.9[c]	131.7[c]	136.2		131.2[c]		136.5
C-11b′	87.2	87.8	50.4		87.6		78.1
C-11c′	117.4	116.7	114.4		117.5		117.7
CH_3O-	55.4	55.4×2	55.3	55.3	55.4	55.3	55.2
	55.5	56.0	56.2×2	56.0	55.5	55.9×2	56.0
	56.0	56.1		56.1	56.0×2	57.7×2	56.1
	56.1	56.2×2			56.3×2		
	56.3						
	56.4						

a—*c*) Assignments may be interchanged in each column.

TABLE II. ^{1}H-NMR Date for Compounds **3** and **4** (in $CDCl_3$)

	3	4
1-H	7.17, d, J=8.6	7.18, d, J=8.5
2-H	6.80, dd, J=2.4, 8.6	6.72, dd, J=2.4, 8.5
4-H	6.59, d, J=2.4	6.45, d, J=2.4
6-H_2	4.33, d, J=12.5	4.22, d, J=12.5
	3.98, d, J=12.5	a)
8-H_2	2.80, d, J=14.0	a)
	2.69, d, J=14.0	a)
9-H	6.75, s	6.75, s
12-H	6.81, s	6.80, s
Acetal-H	4.83, s	5.27, s
1′-H	7.74, d, J=8.8	7.69, d, J=8.5
2′-H	6.66, dd, J=2.7, 8.8	6.67, dd, J=2.4, 8.5
3′-H	6.47, d, J=2.7	6.44, d, J=2.4
6′-H_2	4.29, d, J=11.0	3.99, d, J=10.9
	a)	a)
7′-H_2	3.32, d, J=17.0	3.29, d, J=16.7
	3.25, d, J=17.0	3.17, d, J=16.7
8′-H	6.68, s	6.68, s
11′-H	7.10, s	7.02, s
CH_3O–	3.76, 3.82	3.74, 3.79
	3.85, 3.88	3.83, 3.84
	3.89, 3.92	3.85, 3.88

a) Masked by other signals.

comparison. The absolute structures of brazilin[1e] and protosappanins[2c] have recently been determined to be as illustrated in Chart 1.

In the molecule of **3** there is an acetal carbon resonating at 105.5 ppm in the ^{13}C-NMR spectrum (*vide supra*), and its molecular formula contains four fewer hydrogens than the sum of brazilin trimethyl ether (**6**) and protosappanin B trimethyl ether (**8**). These chemical and spectral findings suggested that **1** (and also **2**) consists of 11b-hydroxybrazilin and protosappanin C linked with each other through an acetal linkage. A Dreiding model showed two possible structures **1** and A (Chart 2) except for their stereochemistry. Both candidates might be expected to afford **5** and **7** on treatment with sodium borohydride in alkali solution (*vide supra*) through brazilein and protosappanin C (**10**) as transient intermediates: a probable degradation mechanism for the case of **1** is shown in Chart 3. In order to identify the correct structure of **1**, its hexamethyl ether (**3**) was derived into an acetate with acetic anhydride in pyridine. The acetylation was accomplished under forcing reaction conditions of a raised temperature (120 °C) for a prolonged time (20 h), affording a monoacetate (**9**) as an amorphous powder, $C_{40}H_{40}O_{12}$, $[\alpha]_D^{24}$ −71.7° ($CHCl_3$). In the IR

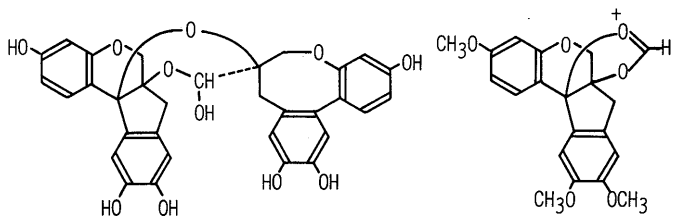
spectrum of **9** no hydroxyl absorption was observed. From a comparison of the ^{13}C-NMR spectra, acetylation of the hydroxyl group of **3** to give **9** caused a downfield shift of 11.0 ppm for the oxygenated quaternary carbon (C-7) and upfield shifts of 1.1, 2.7 and 3.5 ppm for an oxygenated methylene (C-6), a methylene (C-8) and an acetal carbon, respectively. Chemical shifts of other signals were almost unchanged. These acetylation shifts indicated that the more probable structure for protosappanin E-1 is **1** in Chart 1. This conclusion was also supported by a base ion peak (*m/z* 355) in the EI-MS of **3** due to ion a (Chart 2), which corresponds to the base ion at *m/z* 75 in the case of the dimethylacetal (**11**) of protosappanin C trimethyl ether.[2c]

The acetal linkage of **3** was cleaved with *p*-TsOH in MeOH to afford three products, **11**, **12** and **13**, along with recovered **3**. The former two products **11**, an amorphous powder, $[\alpha]_D^{23}$ −71.0° and **12**, an amorphous powder, $[\alpha]_D^{24}$ −9.3°, proved to be identical with the dimethylacetal of protosappanin C trimethyl ether and protosappanin E-2 hexamethyl ether (**4**) on direct comparison with authentic samples. The third product **13**, an amorphous powder, $[\alpha]_D^{20}$ −32.0°, showed a molecular ion at *m/z* 344 ($C_{19}H_{20}O_6$) in the EI-MS and its ^{13}C-NMR spectrum revealed that **13** is identical with *l*-11b-hydroxybrazilin, whose *dl*-form has been synthesized from brazilin through trimethylbrazilone by Perkin *et al.*[5] We synthesized *dl*-**13** according to them, and *l*-**13** from brazilin as an amorphous powder, $[\alpha]_D^{27}$ −29° ($CHCl_3$). The fact that **3** afforded **11**, **12** (=**4**) and **13** indicated that the acetal linkage of **3** was cleaved or epimerized by the acid catalyst, suggesting that protosappanin E-1 hexamethyl ether has structure **3** and that protosappanin E-2 hexamethyl ether is the epimer of **3** in respect to the configuration of the acetal carbon.

Next, ^{1}H-NMR nuclear Overhauser effect (NOE) experiments (in d_5-pyridine) were carried out on **3** and **4** to determine the stereochemistry of their acetal carbons. On irradiation at one (δ_H 3.19) of the methylene protons at C-8 of **4**, 10% enhancement was observed for one (δ_H 3.51) of the methylene protons at C-7′, while in the case of **3** no effect was observed between the corresponding protons. Applying these results to the Dreiding models of the two epimers (**3** and **4**), it was found that 8-H and 7′-H are able to come sufficiently close to each other in the case of **4** having *R* configuration at the acetal carbon, and its probable conformation is shown in Fig. 1. In the case of *S* configuration 7′-H and 8-H can not approach as closely as in the case of *R* configuration in any possible conformation. Therefore, the absolute stereochemistries at the acetal carbons of **3** and **4** were determined as *S* and *R*, respectively. There is a sigma bond between the acetal carbon and C-7 in both **3** and **4**, but rotation around this bond must be suppressed in **4** because of the presence of the hydrogen bond between the hydroxyl at C-7 and the ethereal oxygen(s), which forces **4** to take the preferential conformation illustrated in Fig. 1.

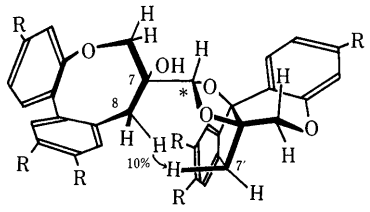
Consequently, the structures of protosappanins E-1 hexamethyl ether and E-2 hexamethyl ether were established as **3** and **4**, respectively, and it follows that protosappanins E-1 and E-2 can be represented as **1** and **2**, respectively, in Chart 1.

Dewick has already proposed a biosynthetic route to brazilin from a chalcone (sappanchalcone)[3] *via* homoisoflavones.[6] We have also discussed the biogenetic relationship between sappanchalcone and brazilin,[2a] and that between sappanchalcone and protosappanins.[2c] We summarize the overall relationships in Chart 4. According to our hypothetical biosynthetic scheme (Chart 4), the



A ion a (*m/z* 355)

Chart 2



*=*R* configuration
R=OCH$_3$

Fig. 1. Probable Conformation of Protosappanin E-2 Hexamethyl Ether (**4**)
The arrow refers to the observed NOE.

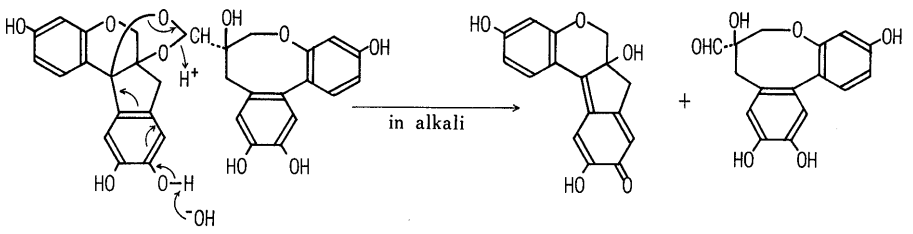


Chart 3

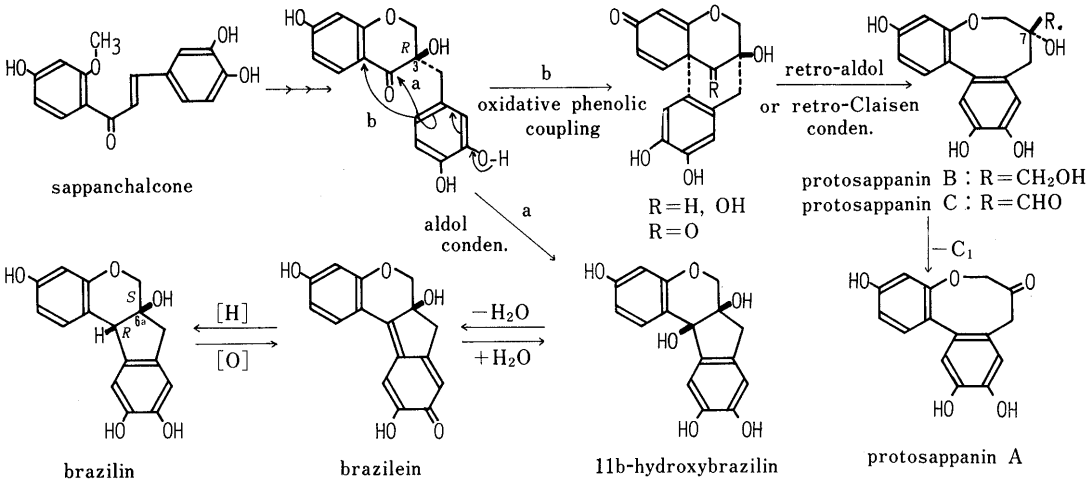


Chart 4. Hypothetical Biogenetic Relationships of Brazilin-Related Compounds in Sappan Lignum

tertiary carbinol carbons at C-6a in brazilin and C-7 in protosappanins derive from the common carbon C-3 of an intermediate homoisoflavone (such as sappanone B[7]). In fact, those asymmetric carbons have the same stereochemical relationship.[1e,2c] Protosappanins E-1 (**1**) and E-2 (**2**) seem to be dimeric products formed from brazilein and protosappanin C (**10**).

Experimental

All melting points were taken on a Yanagimoto melting point determination apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-181 automatic polarimeter in a 1 dm tube. IR spectra were obtained with a Shimadzu IR-400 spectrometer. Ultraviolet (UV) spectra were recorded on a Shimadzu UV-250. NMR spectra were recorded with a JEOL JNM-FX-100 or JNM-GX-400 spectrometer with tetramethylsilane as an internal standard; chemical shifts are given on the δ scale (ppm), coupling constants (J values) are expressed in hertz (Hz), and the following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet and m=multiplet. MS were recorded with a JEOL JMS-D 300 machine. Thin-layer chromatography (TLC) was performed on Kieselgel 60 F_{254} precoated plates (Merck) and detection was carried out by UV absorption measurement.

Extraction and Isolation The extraction and separation procedures were as described in the previous paper where the mixture of protosappanins E-1 (**1**) and E-2 (**2**) was referred to as "an unknown compound" in the experimental section.[2c]

Methylation of the Mixture of 1 and 2 An excess of diazomethane in ether was added to a solution of a mixture of **1** and **2** (350 mg) in MeOH (50 ml), and the reaction mixture was allowed to stand overnight at room temperature. The solvent was evaporated off and the residue was methylated again under the same condition until the methylation was completed as judged by TLC. The reaction product was chromatographed over silica gel. Elution with hexane–EtOAc (1 : 1) afforded **3** (210 mg) and **4** (93 mg). TLC (benzene–EtOAc (1 : 1)): Rf 0.31 (**3**), 0.27 (**4**).

Protosappanin E-1 Hexamethyl Ether (3) An amorphous powder, $[\alpha]_D^{23}$ $-80.8°$ ($c=0.74$, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3500 (OH), 1610, 1495 (arom.). EI-MS m/z: 670 (M^+), 355 (base ion, ion a in Chart 2), 310, 309. High MS m/z: Calcd for $C_{38}H_{38}O_{11}$ (M^+), 670.242; $C_{20}H_{19}O_6$, 355.118; $C_{19}H_{18}O_4$, 310.120. Found 670.242, 355.120, 310.119. UV λ_{max}^{MeOH} nm ($\log\varepsilon$): 215 (end absorption, 4.73), 247 (4.31), 287 (4.14). ^{1}H-NMR (C_5D_5N) δ: 3.17, 3.27 (each 1H, d, $J=13.8$, 8-H_2), 3.38, 3.45 (each 1H, d, $J=16.9$, 7′-H_2), 4.31, 4.44 (each 1H, d, $J=10.7$, 6′-H_2), 4.50, 4.79 (each, 1H, d, $J=12.3$, 6-H_2). No nuclear Overhauser effect (NOE) was observed among 6-H_2, 8-H_2, 7′-H_2 and 6′-H_2.

Protosappanin E-2 Hexamethyl Ether (4) An amorphous powder, $[\alpha]_D^{24}$ $-9.6°$ ($c=2.0$, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3450, 1610, 1500. High MS m/z: Calcd for $C_{38}H_{38}O_{11}$ (M^+) 670.242. Found 670.241. EI-MS m/z 670 (M^+), 355, 310, 309. ^{1}H-NMR (C_5D_5N) δ: 3.08, 3.19 (each 1H, d, $J=18.9$, 8-H_2), 3.51 (1H, d, $J=17.7$, one of 7′-H_2),[8] 4.31, 4.48 (each 1H, d, $J=10.9$, 6′-H_2), 4.32, 4.70 (each 1H, d, $J=12.4$, 6-H_2).

Reductive Cleavage of 1 and 2 with Alkali Sodium borohydride was added in small portions to a solution of a mixture of **1** and **2** (120 mg) in MeOH saturated with Na_2CO_3 (3 ml) with stirring until the red-colored solution changed into an almost colorless one. The reaction mixture was allowed to stand overnight at room temperature. Several drops of AcOH and H_2O (30 ml) were added to the solution, and then the MeOH was evaporated off under reduced pressure. The residual solution was extracted with EtOAc (30 ml × 3). The extract was applied to a column of silica gel and the column was eluted with benzene–EtOAc–MeOH (25 : 25 : 1) to afford **5** (18 mg) and **7** (13 mg) as an amorphous powder. **5** was identical with brazilin on TLC, and its trimethyl ether (**6**), mp 138—140 °C (hexane–benzene), $[\alpha]_D^{20}$ $+137.5°$ ($c=0.5$, $CHCl_3$) was identical with brazilin trimethyl ether on the basis of IR, NMR and MS comparisons. **7**, $[\alpha]_D^{20}$ $-15.5°$ ($c=0.7$, MeOH) was identical with protosappanin B as judged from comparisons of their TLC behavior and IR, NMR and MS data.

Acetylation of 3 In a sealed tube **3** (100 mg) was treated with Ac_2O (1 ml) in pyridine (1 ml) at 120 °C for 20 h. After usual work-up the reaction mixture was applied to a silica gel column. Elution with benzene–EtOAc (4 : 1) afforded an acetate (**9**, 75 mg) and the starting material (5 mg). **9**, an amorphous powder, $[\alpha]_D^{24}$ $-71.7°$ ($c=1.4$, $CHCl_3$). EI-MS m/z: 712 (M^+), 652 (M^+-AcOH), 355 (ion a, in Chart 2), 327, 310. High MS m/z: Calcd for $C_{40}H_{40}O_{12}$ (M^+) 712.252. Found: 712.252. ^{1}H-NMR ($CDCl_3$) δ: 1.97 (3H, s, AcO–).

Acid Treatment of 3 A solution of **3** (50 mg) and p-TsOH (20 mg) in anhydrous MeOH was heated under reflux for 4 h. After addition of H_2O (10 ml) to the solution, the MeOH was evaporated off under reduced pressure. The residual aqueous solution was extracted with EtOAc and the EtOAc layer was shaken vigorously with water (5 ml) containing p-TsOH (5 mg) for 5 min,[9] washed with water, and then dried over anhydrous Na_2SO_4, successively. After concentration of the EtOAc solution, the residue was applied to a column of silica gel and eluted with benzene–EtOAc (4 : 1) to afford **3** (the starting material, 8 mg), **12** (7 mg), **11** (13 mg), and **13** (15 mg). **12**, powder, $[\alpha]_D^{24}$ $-9.3°$ ($c=1.6$, $CHCl_3$); **11**, powder, $[\alpha]_D^{23}$ $-71.0°$ ($c=1.0$, $CHCl_3$); and **13**, powder, $[\alpha]_D^{20}$ $-32.0°$, were identical with authentic samples of **4**, **11**, and **13** (*vide infra*), respectively, on the basis of TLC, MS, IR and NMR comparisons.

***dl*-11b-Hydroxybrazilin Trimethyl Ether (*dl*-13) from 6 i) Trimethylbrazilone (14)** According to the method of Perkin *et al.*, **14** was prepared from brazilin trimethyl ether. **14**, mp 184—185.5° (dec.). (lit. 184—187 °C).[4] EI-MS m/z: 342 (M^+), 324, 191, 164.

ii) *dl*-11b-Hydroxybrazilin Trimethyl Ether (*dl*-13) According to the method of Perkin *et al.*, *dl*-**13** was prepared from trimethylbrazilone. *dl*-**13**, mp 166—167 °C (hexane). (lit., 167—168 °C).[5] EI-MS m/z: 344 (M^+), 326, 310, 298, 297, 267. ^{13}C-NMR (Table I).

***l*-11b-Hydroxybrazilin Trimethyl Ether (*l*-13)** A solution of brazilein (120 mg) in 1% NaOH was shaken for 8 min, then acidified with 1% HCl. The reaction mixture was filtered to remove precipitates and extracted with EtOAc (20 ml × 3). The combined EtOAc solution was washed with H_2O and dried over anhydrous Na_2SO_4, and then MeOH (30 ml) was added to the solution after removal of Na_2SO_4. The mixture was treated with ethereal diazomethane solution in the same way as described for methylation of the mixture of **1** and **2**. The product was applied to a column of silica gel with benzene–EtOAc (3 : 2) as the solvent to afford

l-**13**, which we could not crystallize. *l*-**13**, $[\alpha]_D^{27}$ −29° ($CHCl_3$) was identical with *dl*-**13** on the basis of TLC, MS, NMR and IR (in $CHCl_3$) comparisons.

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References and Notes

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8) The signal of the other proton of 7′-H_2 was masked by other signals (see also Table II).
9) If this procedure was omitted, 11b-methoxybrazilin trimethyl ether was obtained in place of 11b-hydroxybrazilin trimethyl ether.