Synthesis, Separation, and Theoretical Studies of Chiral Biphenyl Lignans (α- and β-DDB)

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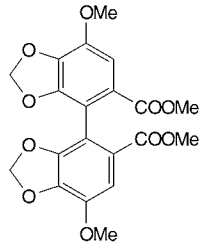
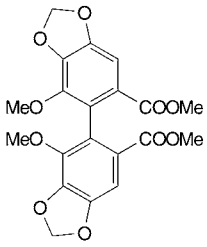
Two biphenyl lignans, α- and β-DDB (**1** and **2**, respectively) were efficiently synthesized without contamination by other regio-isomers. The different yields of the *Ullmann* coupling reactions for the synthesis of **1** and **2** were rationalized by calculating steric hindrance, stability, entropy change, and heat-of-formation values. The enantiomers of **1** and **2** were readily separated by HPLC on a chiral stationary phase. Their configurations were assigned based on the *Cotton* effect of the authentic natural products.

Introduction. – Lignans, natural products with a broad range of biological activities, have attracted much attention over the years. The fruits of *Schizandra chinensis* (Schizandraceae) have been used as a tonic and astringent drug in traditional Chinese medicine. Its constituents, schizandrin and deoxyschizandrin are antihepatotoxic (liver injury), anticonvulsive (cerebral protection), and exhibit antitumor, anti-HIV, and antifungal activities, among other properties.

The biphenyl unit of these natural products is crucial for their pharmacological activity [1–6]. The racemic mixture of 'dimethyl 4,4′-dimethoxy-5,6,5′,6′-dimethylenedioxybiphenyl-2,2′-dicarboxylate' (α-DDB; **1**)[1]) exhibits significant antiheptotoxic activity and effectively lowers the serum-transaminase level. The corresponding two regioisomers **2** and **3** (β- and γ-DDB, respectively) were isolated as by-products during the synthesis of **1**. The pure enantiomers have not been separated so far. Since the



1 (α-DBB)



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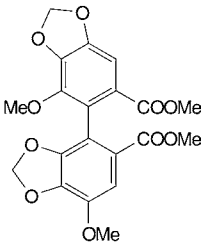


3 (γ-DBB)

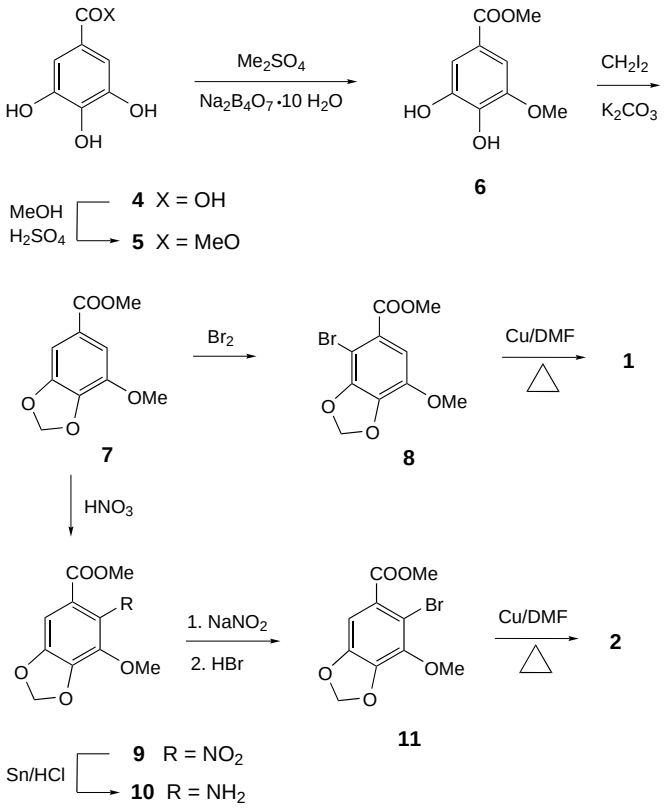
[1]) Systematic names: dimethyl 7,7′-dimethoxy-[4,4′]bi[1,3-benzodioxolyl]-5,5′-dicarboxylate (**1**), dimethyl 4,4′-dimethoxy-[5,5′]bi[1,3-benzodioxolyl]-6,6′-dicarboxylate (**2**), and dimethyl 7,4′-dimethoxy-[4,5′]bi[1,3-benzodioxolyl]-5,6′-dicarboxylate (**3**).

single enantiomers of these lignans could display different biological activities and because the key intermediates can be used for the synthesis of *Schizandra* derivatives and as chiral-recognition agents, it was of interest to further study the synthesis, separation and properties of these compounds.

Here, we describe a convenient synthesis of **1** (α-DDB) and **2** (β-DDB). The AM1 semi-empirical method was used to calculate the corresponding heat of formation (ΔH_f°) to rationalize the different yields obtained in the *Ullmann* coupling reactions. Both enantiomers of **1** and **2** were effectively resolved by HPLC on cellulose tris(3,5-dimethylphenylcarbamate) as the chiral stationary phase. Solvent effects on chiral resolution are also detailed. The optical properties of the pure enantiomers was confirmed by their circular dichroism (CD).

Results and Discussion. – The lignans **1** and **2** were synthesized from gallic acid (**4**) (*Scheme*). Esterification of **4**, followed by selective monomethylation of **5**, yielded compound **6**, which was reacted with CH_2I_2 under weakly basic conditions to afford methyl 7-methoxy-1,3-benzodioxole-5-carboxylate (**7**). Bromination of **7** generated the corresponding 4-bromo derivative **8** as the only product. *Ullmann* coupling of monomer **8** using copper as a catalyst finally afforded **1** in 40% overall yield.

Scheme



Unfortunately, the 6-bromo derivative **11** could not be prepared by direct bromination of **7**. Therefore, another approach was taken. Nitration of **7** produced predominantly the 6-nitro compound **9**. The NO_2 group was reduced with $SnCl_2$, and the resulting amino derivative **10** was converted to **11** *via Sandmeyer* reaction. *Ullmann* coupling of **11** then generated the desired lignan **2** in 52% overall yield, from gallic acid in pure form.

The structural difference between **1** and **2** lies in their different substitution patterns with respect to the biphenyl moiety. β-DDB (**2**) corresponds to schizandrin C [7][8]. The two MeO groups are in *ortho* position relative to the biphenyl axis, and one might assume that **2** is sterically more hindered than **1**. The *Ullmann* coupling of **8** should then give higher yields of **1** than that of **11** for the synthesis of **2**. However, the opposite is true!

To better understand these results, we determined the enthalpy changes (ΔH_f°) of α-DDB (**1**) and β-DDB (**2**) by means of AM1 calculations [9]. The conformations of the monomers **8** and **11**, as well as those of **1** and **2**, were also calculated. *Fig. 1* depicts the optimized structures of **1** and **2**, and *Fig. 2* shows their conformational preferences. The

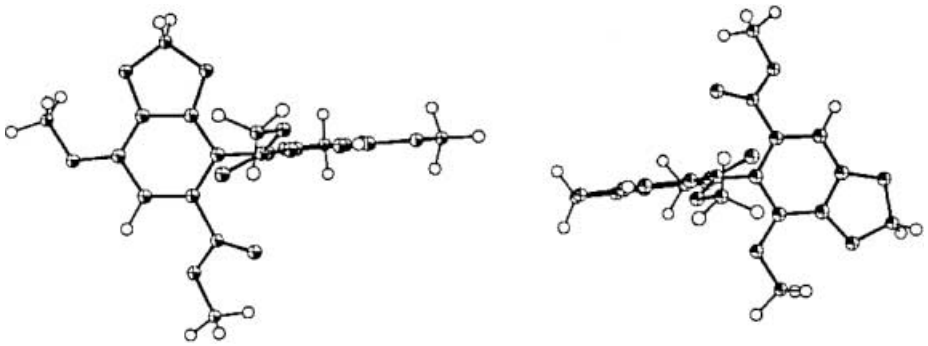


Fig. 1. *Calculated lowest-energy conformations of α-DDB* (**1**; left) *and β-DDB* (**2**; right)

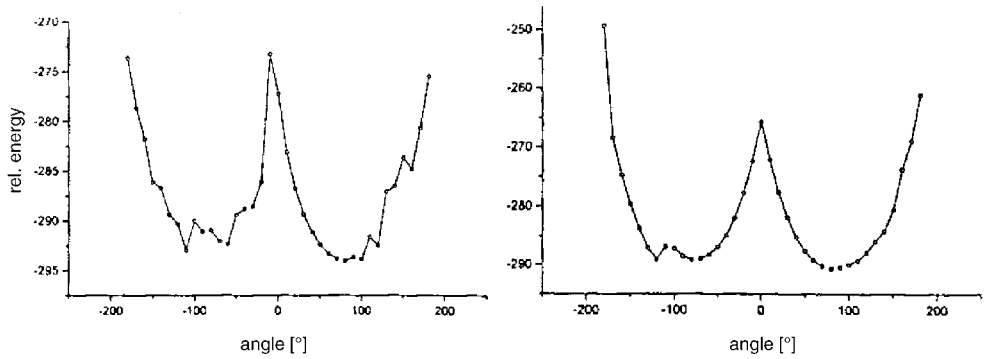


Fig. 2. *Calculated relative energies of α-DDB* (**1**; left) *and β-DDB* (**2**; right) *as a function of the dihedral angles between the two respective phenyl rings*

results indicate that the benzodioxolane ring is perfectly planar. Orthogonal conformations with the two phenyl rings perpendicular to each other possess the lowest energy. Therefore, steric hindrance may have little influence on the *Ullmann* coupling.

The ΔH_f° values for **1** and its precursor **8** are *ca.* −596 and −1229 kJ/mol, and those for **2** and **11** *ca.* −575 and −1216 kJ/mol, respectively. With a ΔH_f° value of −138 kJ/mol, for $CuBr_2$, the enthalpic change for the synthesis of **1** from **8** is *ca.* −176 kJ/mol, while that for **2** from **11** is −203 kJ/mol, which might explain the higher yield for **2** in the *Ullmann* coupling.

Statistic studies indicated that 98.8% of 534 different kinds of natural and semi-synthetic drugs analyzed possess stereogenic centers, and that most of the corresponding enantiomers show different pharmacological, toxicological, and therapeutic properties [10–12]. We, therefore, attempted to separate the enantiomers of **1** and **2** by HPLC using tris(3,5-dimethylphenylcarbamate)-functionalized cellulose (CDMPC) on aminopropylated spherical silica gel as the chiral stationary phase. Combinations of different alcohols were used as mobile phases. The effects of primary, secondary, and tertiary alcohols on the separation of **1** and **2** are shown in the *Table*. α-DDB (**1**) has a higher retention time than **1**. The retention times t_2 for the corresponding enantiomers of **1** and **2** increase, with increasing chain length of the primary alcohols, but decreases after PrOH. Secondary and tertiary alcohols further increase t_2 although chain length hardly affects the retention time. X-Ray analysis confirmed that the chiral stationary CDMPC phase has a levorotatory threefold axis, resulting in a helical structure containing enantiomorphic sites formed by phenylaminocarbamate [13–15]. The chiral-recognition ability of the stationary phase is based mainly on the formation of H-bonds, dipole/dipole and π/π interactions. In addition, the highly ordered structure of cellulose plays an important role in the separation of enantiomers because it allows only molecules with appropriate enantiomorphic shapes, to pass through the cellulose phase. *Fig. 3* shows schematically possible interactions between DDB and the cellulose stationary phase. The alcohol in the mobile phase competes with DDB for H-bond interactions with the carbamate NH groups. Because PrOH is less polar than MeOH and EtOH, its competitive interaction with cellulose is weaker, and, thus, t_2 increases in the order MeOH < EtOH < PrOH. BuOH and pentanol give rise to lower

Table. *Effect of Different Mobile Phases on the Enantiomer Separation of* **1** *and* **2**. Retention times t_1 and t_2 (in min) refer to the pertinent enantiomers. The separation factor α corresponds to t_2/t_1.

Mobile Phase	**1**			**2**		
	t_1	t_2	α	t_1	t_2	α
MeOH/EtOH 1:1	9.43	15.1	1.60	4.39	7.73	1.58
EtOH	9.80	16.3	1.66	4.40	8.37	1.90
PrOH	13.5	23.1	1.73	4.87	12.4	2.55
BuOH	10.8	17.5	1.62	4.28	9.88	2.31
Pentanol	8.33	13.2	1.59	4.62	6.91	1.50
i-PrOH	21.9	38.8	1.77	6.47	19.8	3.06
i-BuOH	22.5	39.4	1.75	6.66	21.3	3.20
Isopentanol	19.0	33.4	1.76	9.30	21.4	2.30
t-BuOH	31.2	52.7	1.69	10.3	35.2	2.31

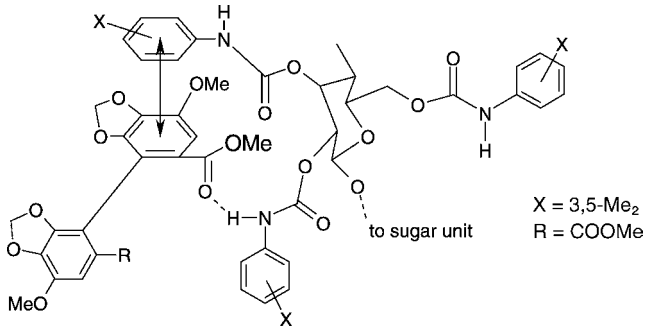


Fig. 3. *Interactions between DDB and functionalized cellulose* (CDMPC)

t_2 values because their polarities are similar to that of PrOH, but also due to higher steric hindrance. The mobile phases also have a similar effect on the separation factors α. PrOH and BuOH give rise to larger α values for **2**, while the secondary and tertiary alcohols are more powerful for the resolution of **1**.

The enantiomers of **1** and **2** were successfully separated by chiral HPLC (*Fig. 4*) and assigned according to their CD spectra (*Fig. 5*). The first fraction showed a positive *Cotton* effect at 258 nm, while the second fraction exhibited a negative *Cotton* effect at the same wavelength. By comparing with the CD spectra of the natural product, it was concluded that the first fraction of **1** and **2** corresponds to the (*R*)-configuration, and the second to the (*S*)-configuration [16–18]. Because compound **1** is sterically less hindered than **2**, it is conformationally unstable. Although its conformation could be initially confirmed by CD spectroscopy, it gradually epimerized upon standing at room temperature.

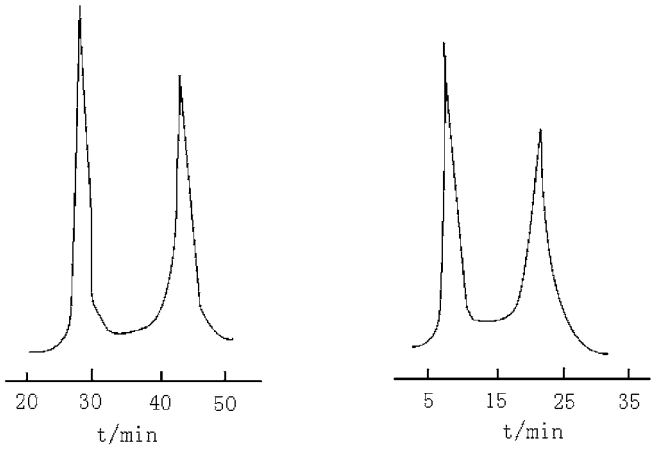


Fig. 4. *HPLC Enantiomer separation of* **1** (left) *and* **2** (right). Conditions: 2.62M PrOH in hexane; flow rate 1 ml/min; CDMPC column.

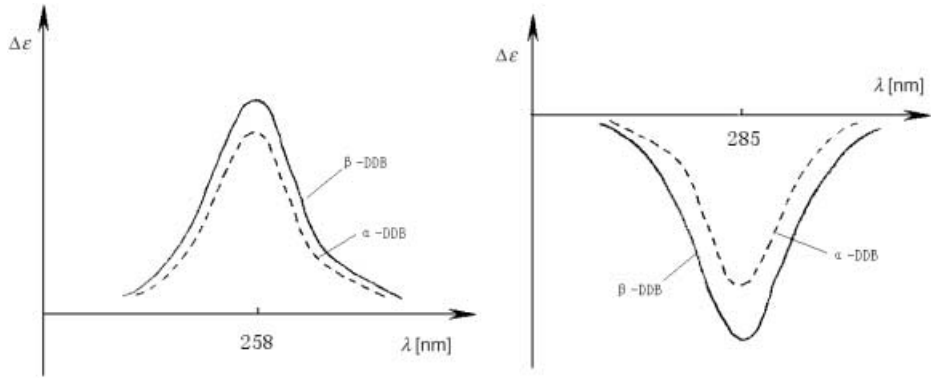


Fig. 5. *Circular dichroism spectra of α- and β-DDB*

Conclusions. – We have developed a convenient method for the preparation of biphenyl lignans α-DDB (**1**) and β-DDB (**2**) among other lignan derivatives. The yields of the crucial *Ullmann* coupling were rationalized by AM1 semi-empirical calculations. The enantiomers of **1** and **2** were successfully separated by HPLC on CDMPC as the chiral stationary phase and configurationally assigned by means of CD spectroscopy relative to the authentic natural products.

Experimental Part

General. Silica gel *G* and GF_{254} were used for column and thin-layer chromatography. Melting points were measured on a *Reichert* microscope, uncorrected. CD Spectra were recorded on a *JASCO J-20C* spectropolarimeter. IR Spectra were recorded on a *Perkin-Elmer 580B* spectrophotometer. ^{1}H-NMR spectra were recorded on a *Bruker AM-500* spectrospin spectrometer in $CDCl_3$ with Me_4Si as internal standard. Mass spectra were recorded on a *Shimadzu ZAB-2B* spectrometer. Elemental analyses were performed on a *Carlo-Erba 1106*.

Methyl 3,4-Dihydroxy-5-methoxybenzoate (**6**). A mixture of **5** (25.0 g, 0.136 mol) in 5% aq. borax soln. was treated with 60 ml of DMSO and 100 ml of 25% aq. NaOH soln. at r.t. The mixture was stirred for 6 h, cooled to 0° in an ice bath, and then acidified to pH *ca*. 2 by dropwise adding conc. H_2SO_4. The precipitate was filtered off, and the crude product was recrystallized from EtOH, providing 20.1 g (75%) of **6**. Needles. M. p. 111–113° (lit. 112–113° [19]).

Methyl 7-Methoxy-1,3-benzodioxole-5-carboxylate (**7**). To a soln. of **6** (10.0 g, 50.5 mmol) in 300 ml of acetone were added 45 g of CH_2I_2 and 50 g of K_2CO_3. The resulting mixture was refluxed for 4 h. The excess solid K_2CO_3 was filtered off, and the solvent was evaporated under reduced pressure. The residue was poured into ice-water. Upon standing overnight, the crude product precipitated and was recrystallized from EtOH, providing 8.2 g (77.3%) of **7**. Brilliant needles. M.p. 88–89° (lit. 86–88°, [8]). ^{1}H-NMR ($CDCl_3$): 3.85 (*s*, MeO); 3.89 (*s*, *Me*OAr); 6.09 (*s*, OCH_2O); 7.10 (*d*, $J = 1.5$, 2 arom. H). Anal. calc. for $C_{10}H_{10}O_5$: C 57.14, H 4.80; found: C 57.23, H 4.82.

Methyl 4-Bromo-7-methoxy-1,3-benzodioxole-5-carboxylate (**8**). Br_2 (16.8 g, 0.21 mol) was added dropwise to a soln. of **7** (22.0 g, 0.105 mol) in 130 ml of Ac_2O over 2 h at 12–15°. The mixture was poured into ice-water and extracted with AcOEt. The solvent was evaporated to provide 28 g (92%) of **8**. White solid. M.p. 104–105°. ^{1}H-NMR ($CDCl_3$): 3.85 (*s*, MeO); 4.10 (*s*, *Me*OAr); 6.10 (*s*, OCH_2O); 7.50 (*s*, arom. H). Anal. calc. for $C_{10}H_9O_5Br$: C 41.55, H 3.14; found: C 41.58, H 3.12.

Dimethyl 7,7′-Dimethoxy-[4,4′]bi[1,3-benzodioxolyl]-5,5′-dicarboxylate (**1**). A mixture of **8** (0.8 g, 2.76 mmol), activated Cu powder (0.8 g), and anh. DMF (4 ml) was heated to reflux for 4 h under vigorous stirring. After cooling to 100°, the mixture was poured into ice-water, and the precipitate was collected. The crude product was purified by FC (Al_2O_3; hexanes/$CHCl_3$) to afford 0.23 g (39.8%) of **1**. ^{1}H-NMR ($CDCl_3$): 3.67

(*s*, 3 H); 3.69 (*s*, 3 H); 3.87 (*s*, 6 H); 5.96 (*s*, 2 H); 5.99 (*s*, 2 H); 7.28 (*s*, 1 H); 7.33 (*s*, 1 H). Anal. calc. for $C_{20}H_{18}O_{10}$: C 57.42, H 4.34; found: C 57.48, H 4.30.

Methyl 7-Methoxy-6-nitro-1,3-benzodioxole-5-carboxylate (**9**). Conc. HNO_3 (100 ml) was added dropwise to a stirred suspension of **7** (10 g, 47.6 mmol) in 50 ml of Ac_2O over a period of 1 h at a temp. of 0°. The mixture was stirred for an additional hour and then poured into ice-water. The precipitate was collected and recrystallized from AcOEt to yield 11.2 g (91.8%) of **9**. Yellowish needles. M.p.126–128°. ^{1}H-NMR ($CDCl_3$): 3.97 (*s*, MeO); 4.17 (*s*, *Me*OAr); 6.24 (*s*, OCH_2O); 7.24 (*s*, arom. H). Anal. calc. for $C_{10}H_9NO_7$: C 47.07, H 3.55; found: C 47.10, H 3.53.

Methyl 6-Amino-7-methoxy-1,3-benzodioxole-5-carboxylate (**10**). A suspension of $SnCl_2 \cdot H_2O$ (5.0 g) in 50 ml of conc. HCl was heated until becoming a homogeneous soln. and cooled to 40°. Then, **9** (5.0 g, 19.6 mmol) was added. The mixture was refluxed for 30 min, cooled, neutralized with 10% aq. NaOH soln., and extracted with $CHCl_3$. The usual workup provided 3.0 g (68%) of **10**. Needles. M.p. 90–91°. IR: 3300–3500*s* ($ArNH_2$). ^{1}H-NMR ($CDCl_3$): 3.82 (*s*, MeO); 3.99 (*s*, *Me*OAr); 5.00 (br., $ArNH_2$, exchangeable with D_2O); 5.88 (*s*, OCH_2O); 7.01 (*s*, arom. H). Anal. calc. for $C_{10}H_{11}O_5N$: C 53.33, H 4.92; found: C 53.38, H 4.89.

Methyl 6-Bromo-7-methoxy-1,3-benzodioxole-5-carboxylate (**11**). $CuSO_4$ (2.0 g) and KBr (1.0 g) were dissolved in 10 ml of H_2O. The mixture was heated to 50°, and a soln. of NaOH (0.6 g) and $NaHSO_3$ (0.6 g) in H_2O (2 ml) was added. The mixture was stirred to afford CuBr. A suspension of CuBr in 40% HBr was prepared for the next step. A suspension of **10** (1.0 g, 4.44 mmol) in 40% HBr (5 ml) was cooled to 0–5°, and a soln. of $NaNO_2$ (0.5 g, 7.2 mmol) in 15 ml of H_2O was added. The resulting diazonium salt was slowly added to the above suspension of CuBr in 40% HBr. The mixture was stirred overnight at 5°. The orange-red color faded gradually. The mixture was heated to 50–60° for 30 min, and was washed with H_2O and 10% aq. $NaHCO_3$ soln. to yield 0.9 g (70%) of **11** as a solid. M.p. 82–83°: ^{1}H-NMR ($CDCl_3$): 3.91 (*s*, MeO); 4.04 (*s*, *Me*OAr); 6.07 (*s*, OCH_2O); 7.04 (*s*, arom. H). Anal. calc. for $C_{10}H_9O_5Br$: C 41.55, H 3.14; found: C 41.56, H 3.16.

Dimethyl 4,4′-Dimethoxy-[5,5′]bi[1,3-benzodioxolyl]-6,6′-dicarboxylate (**2**). A mixture of **11** (1.0 g, 3.46 mmol), activated Cu powder (1.0 g), and anh. DMF (5 ml) was refluxed for 4 h under vigorous stirring. The mixture was filtered, and the filtrate was concentrated. The resulting residue was purified by FC (Al_2O_3; hexanes → hexanes/$CHCl_3$) to afford 375 mg (52%) of **2** as a solid. M.p. 207–208°. ^{1}H-NMR ((D_6)-acetone): 3.56 (*s*, 2 MeO); 3.74 (*s*, 2 *Me*OAr); 6.16 (*s*, 2 OCH_2O); 7.16 (*s*, 2 arom. H). Anal. calc. for $C_{20}H_{18}O_{10}$: C 57.42, H 4.34; found: C 57.45, H 4.35.

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