First highly stereoselective synthesis of (+)-dihydrosesamin, a trisubstituted tetrahydrofuran-type of lignan, by using highly *erythro*-selective aldol condensation

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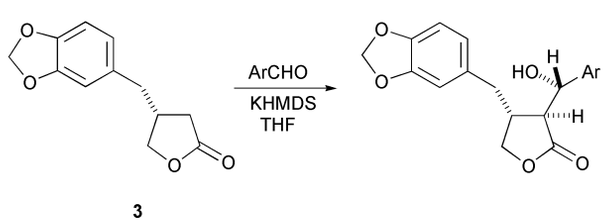
A 2,3,4-tri-substituted tetrahydrofuran-type lignan, (+)-dihydrosesamin **2**, was stereoselectively synthesized by using *erythro*-selective aldol condensation of the potassium enolate from (3*R*)-3-(3,4-methylenedioxyphenyl)-4-butanolide **3** with piperonal as a key reaction. This is the first stereoselective synthesis of (+)-dihydrosesamin, which is the enantiomer of the natural product.

Introduction

A 2,3,4-trisubstituted tetrahydrofuran lignan, (−)-dihydrosesamin **1**,[1] has been isolated from *Daphne tangutica* which had been used as an abortifacient and a medicine for rheumatism and toothache. Though the biological activity of (−)-dihydrosesamin **1** is unknown, tetrahydrofuran lignans are known to be antioxidants, PAF inhibitors and stress compounds in plants.[2] Synthetic research into **1** and its stereoisomers is very important in the study of structure–activity relationships of tetrahydrofuran lignans. The stereoselective introduction of three substituents onto a tetrahydrofuran ring is also an interesting topic. Some racemic syntheses of dihydrosesamin have been reported;[3] however, there is no report on the synthesis of the optically active compound. This paper is the first report of a stereoselective synthesis of (+)-dihydrosesamin **2** which is the enantiomer of the natural product (Fig. 1).

In this research, the *erythro*-selective aldol condensation using the potassium enolate of γ-butyrolactone[4] was employed as a key reaction to obtain the stereochemistry at the 2- and 3-position of (+)-dihydrosesamin. It has been previously reported that aldol condensation of the potassium enolate of (3*R*)-3-(3,4-methylenedioxybenzyl)-4-butanolide[5] **3** with some tri/dimethoxybenzaldehydes preferentially gave the *erythro* aldol product (Scheme 1).



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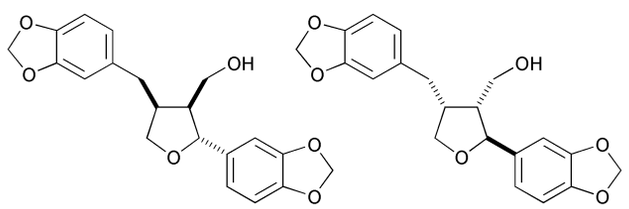
Scheme 1 *erythro*-Selective aldol condensation.

If the aldol condensation of the butanolide **3**[5] with piperonal gave the *erythro* aldol product **4** (2*S*,2′*S*) in high selectivity, this aldol product would be transformed into diol **5** which could be converted into the tetrahydrofuran-ring system **6** by S_N2 cyclization with retention of the stereochemistry at the benzylic position. In this plan, the steric configuration at the 2- and 3-position of the tetrahydrofuran ring in **6** would depend on the stereochemistry at the 2- and 2′-position of aldol product **4**, respectively, and the steric configuration of the 3-position of the butanolide **3**, whose preparation from L-glutamic acid has been reported,[5] would be that of the 4-position of the tetrahydrofuran ring in **6** (Scheme 2).



(–)-dihydrosesamin (**1**) (+)-dihydrosesamin (**2**)

Fig. 1

Results and discussion

Aldol condensation of the butanolide **3**[5] with piperonal using potassium bis(trimethylsilyl)amide as a base gave *erythro* aldol product **4** (2*S*,2′*S*) as a single isomer in 78% yield. Butanolide **3** was recovered to the extent of 14%. The coupling constant of 2-H with the proton of the benzyl substituent at C-2′ (2.9 Hz) revealed the product to be the *erythro* isomer (2*S*,2′*S*).[6] This coupling constant was due to the axial–equatorial relationship of 2-H and 2′-H in the six-membered ring formed by a hydrogen bond between the hydroxy group and the carbonyl group. In the case of the *threo* isomer, this coupling constant would be 6–9 Hz because of the resulting diaxial relationship.

After protection of the hydroxy group as a triethylsilyl (TES) group using triethylsilyl trifluoromethanesulfonate (TESOTf)[7] and 2,6-dimethylpyridine (2,6-lutidine) (84%), the lactone **7** was reduced to diol **8** by lithium aluminium hydride in 100% yield. An S_N2 cyclization was then adopted to produce the tetrahydrofuran ring. Thus diol **8** was converted into dimesyl derivative **9** by employing methanesulfonyl chloride and triethylamine, in 93% yield. This resulting unstable dimesyl diester was exposed to desilylation using tetra-*n*-butylammonium fluoride.[8] In this stage, intramolecular S_N2 cyclization occurred to give the (methylsulfonyloxymethyl)tetrahydrofuran **10** in 90% yield. This unstable monomesyl ester was treated with aq. sodium hydroxide in DMF to give (+)-dihydrosesamin **2** {$[a]_D^{20}$ +15.9, *c* 0.75 in pyridine; (−)-dihydrosesamin **1**: $[a]_D^{20}$ −15.9, *c* 0.67 in pyridine[1]}. An NOE experiment showed the correlation of the methylene protons of the hydroxymethyl group (3′-H_2) with the benzylic protons on the 4-position (4′-H_2) and with

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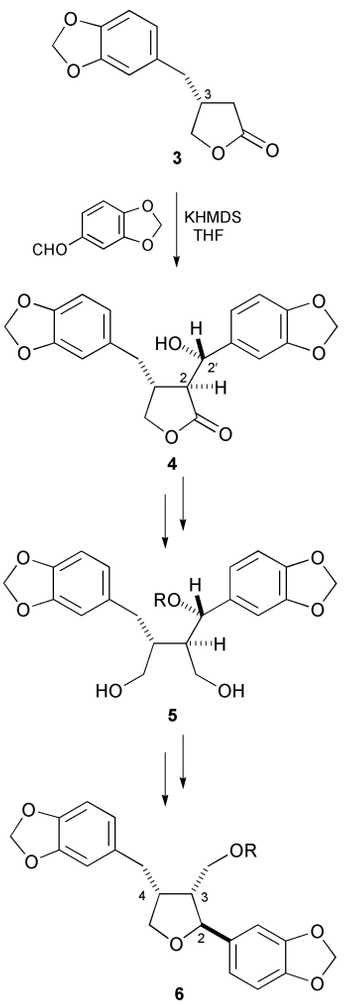
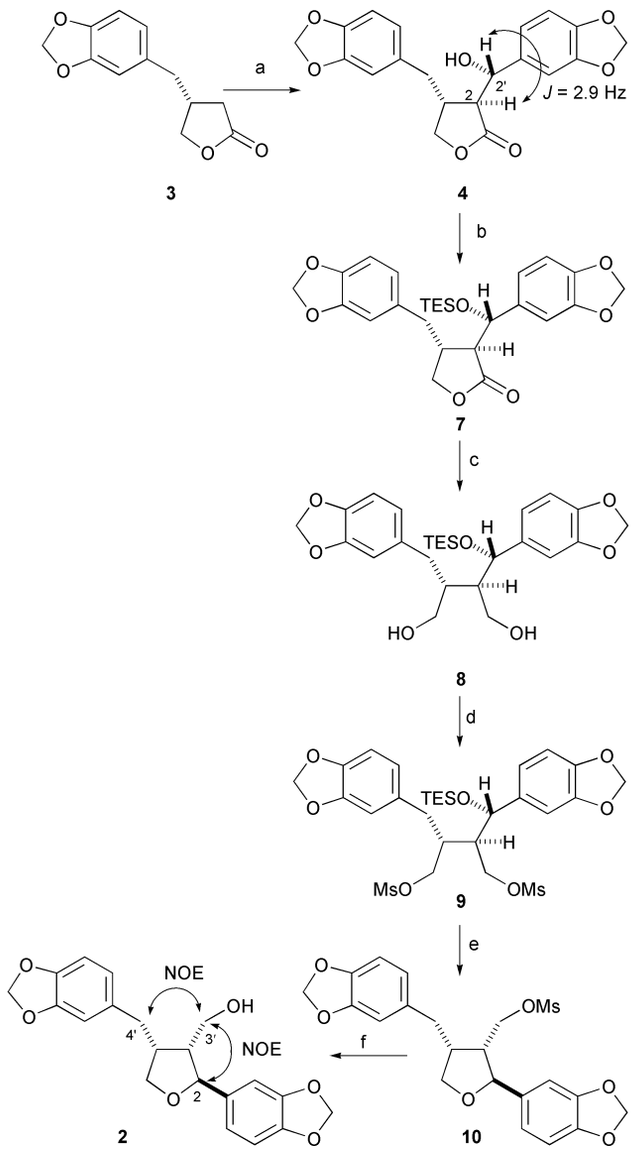


Scheme 2 Synthetic plan of (+)-dihydrosesamin.

2-H (Scheme 3). The NMR and IR data of the synthesized (+)-dihydrosesamin **2** agreed with those of natural (−)-dihydrosesamin **1** [1,3]

(+)-Dihydrosesamin **2** was therefore stereoselectively synthesized from the butanolide **3** in 6 steps in 37% overall yield. In this process, *erythro*-selective aldol condensation of butanolide **3** with piperonal was employed for stereoselective introduction of substituents.



Scheme 3 Synthesis of (+)-dihydrosesamin **2**. *Reagents and conditions (yields)*: (a) piperonal, KHMDS, THF, −75 °C, 1 h (78%); (b) TESOTf, 2,6-lutidine, CH_2Cl_2, rt, 1 h (84%); (c) $LiAlH_4$, THF, 0 °C, 1 h (100%); (d) MsCl, Et_3N, CH_2Cl_2, rt, 1 h (93%); (e) *n*-Bu_4NF, THF, 0 °C, 1.5 h (90%); (f) 1 M aq. NaOH, DMF, 120 °C, 16 h (68%).

Experimental

All melting-point (mp) data are uncorrected. NMR data were measured by a JNM-EX400 spectrometer. EIMS data were measured with an Hitachi M-80B and optical rotations were evaluated with an Horiba SEPA-200, $[\alpha]_D$-values are in units of 10^{-1} deg cm^2 g^{-1}. The silica gel used was Wakogel C-300 (Wako, 200–300 mesh), and preparative TLC was conducted with Merck silica gel 60 F_{254} (0.5 mm thickness, 20 × 20 cm). The numbering of compounds was changed to follow IUPAC nomenclature rules.

(2*S*,3*R*)-2-[(1*S*)-1-Hydroxy-1-(3,4-methylenedioxyphenyl)-methyl]-3-(3,4-methylenedioxybenzyl)-4-butanolide 4

To a solution of KHMDS (0.5 M in toluene; 21.8 ml, 10.9 mmol) in THF (80 ml) was added a solution of the butanolide **3** (2.00 g, 9.08 mmol) in THF (10 ml) at −75 °C. After the solution had been stirred at −75 °C for 30 min, a solution of piperonal (1.57 g, 10.5 mmol) in THF (20 ml) was added. The reaction mixture was stirred at −75 °C for 1 h before the addition of saturated aq. NH_4Cl and EtOAc. The organic solution was separated, washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography (10% EtOAc–benzene) to give *erythro-aldol product* **4** (2.62 g, 78%) as a colorless oil, $[\alpha]_D^{20}$ −44.6 (*c* 0.92, $CHCl_3$); $\nu_{max}(CHCl_3)$/cm^{-1} 3500, 2899, 1755, 1611, 1505, 1445, 1042; $\delta_H(CDCl_3)$ 2.27 (1H, dd, *J* 13.7, 7.8 Hz, ArCH_2), 2.42 (1H, dd, *J* 13.7, 8.1 Hz, ArCH_2), 2.58 (1H, dd, *J* 5.9, 2.9 Hz, 2-H), 2.79 (1H, m, 3-H), 2.82 (1H, s, OH), 3.94 (1H, dd, *J* 8.8, 5.9 Hz, 4-H), 4.32 (1H, dd, *J* 8.8, 8.3 Hz, 4-H), 5.24 (1H, br s, by D_2O-exchange d, *J* 2.9 Hz, ArC*H*OH), 5.89 (1H, d, *J* 1.5 Hz, OC*H*HO), 5.92 (1H, d, *J* 1.5 Hz, OCH*H*O), 5.95 (1H, d, *J* 1.5 Hz, OC*H*HO), 5.96 (1H, d, *J* 1.5 Hz, OCH*H*O), 6.30–6.34 (2H, m, ArH), 6.61 (1H, d, *J* 7.8 Hz, ArH), 6.72 (3H, s, ArH); $\delta_C(CDCl_3)$ 36.3, 39.4, 52.8, 71.8, 72.7, 100.9, 101.1, 105.8, 108.1, 108.6, 118.3, 121.5, 131.5, 134.9, 146.1, 146.9, 147.6, 147.8, 178.3; *m*/*z* (EI, 20 eV) 370 (M^+, 11%), 220 (23), 135 (100) [Found (HRMS): M^+, 370.1048. $C_{20}H_{18}O_7$ requires *M*, 370.1051].

(2*S*,3*R*)-3-(3,4-Methylenedioxybenzyl)-2-[(*S*)-(3,4-methylene-dioxyphenyl)(triethylsilyloxy)methyl]-4-butanolide 7

To an ice-cooled solution of aldol product **4** (2.30 g, 6.21 mmol) and 2,6-lutidine (1.81 ml, 15.5 mmol) in CH_2Cl_2

(10 ml) was added TESOTf (1.62 ml, 7.16 mmol). The reaction solution was stirred at room temperature for 1 h before addition of saturated aq. $NaHCO_3$. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After evaporation, the residue was purified by silica gel column chromatography (40% EtOAc–hexane) to give *silyl ether* **7** (2.53 g, 84%) as colorless crystals, mp 114–115 °C (30% EtOAc–hexane), $[\alpha]_D^{20}$ −54.3 (*c* 0.92, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2880, 1763, 1611, 1505, 1443, 1042; $\delta_H(CDCl_3)$ 0.56 (6H, q, *J* 7.8 Hz, $SiCH_2CH_3$), 0.88 (9H, t, *J* 7.8 Hz, $SiCH_2CH_3$), 2.23 (1H, dd, *J* 13.7, 9.3 Hz, $ArCH_2$), 2.41 (1H, dd, *J* 3.9, 2.0 Hz, 2-H), 2.49 (1H, dd, *J* 13.7, 7.3 Hz, $ArCH_2$), 2.81 (1H, m, 3-H), 3.98 (1H, dd, *J* 8.5, 3.7 Hz, 4-H), 4.39 (1H, dd, *J* 8.5, 7.8 Hz, 4-H), 5.27 (1H, d, *J* 2.0 Hz, ArCHOH), 5.89 (1H, d, *J* 1.5 Hz, OCHHO), 5.91 (1H, d, *J* 1.5 Hz, OCHHO), 5.95 (1H, d, *J* 1.5 Hz, OCHHO), 5.97 (1H, d, *J* 1.5 Hz, OCHHO), 6.21 (1H, d, *J* 1.5 Hz, ArH), 6.27 (1H, dd, *J* 7.8, 1.5 Hz, ArH), 6.56 (1H, d, *J* 7.8 Hz, ArH), 6.64–6.65 (3H, m, ArH); $\delta_C(CDCl_3)$ 4.6, 6.7, 35.9, 39.9, 54.3, 73.2, 73.3, 100.9, 101.1, 105.7, 107.8, 107.9, 108.6, 118.2, 121.7, 131.6, 135.9, 146.0, 146.7, 147.5, 178.1; *m*/*z* (EI, 20 eV) 484 (M^+, 5%), 455 (22), 265 (100), 135 (33) (Found: C, 64.31; H, 6.52. $C_{26}H_{32}O_7Si$ requires C, 64.44; H, 6.66%).

(2*R*,3*R*)-2-(3,4-Methylenedioxybenzyl)-3-[(*S*)-(3,4-methylenedioxyphenyl)(triethylsilyloxy)methyl]butane-1,4-diol 8

To a suspension of $LiAlH_4$ (0.13 g, 3.43 mmol) in THF (5 ml) was added a solution of lactone **7** (1.10 g, 2.27 mmol) in THF (10 ml) at 0 °C. After the reaction mixture had been stirred at room temperature for 1 h, saturated aq. $MgSO_4$ and K_2CO_3 were added. The mixture was stirred at room temperature for 30 min before filtration. The filtrate was concentrated. The residue was subjected to silica gel column chromatography (EtOAc–hexane 1 : 2) to give diol **8** (1.11 g, 100%) as a colorless oil, $[\alpha]_D^{20}$ −60.0 (*c* 0.85, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3425, 2880, 1609, 1505, 1443, 1042, 939; $\delta_H(CDCl_3)$ 0.52 (6H, q, *J* 7.8 Hz, $SiCH_2CH_3$), 0.87 (9H, t, *J* 7.8 Hz, $SiCH_2CH_3$), 1.79 (1H, m), 2.29 (1H, m), 2.38 (1H, dd, *J* 13.7, 8.3 Hz, $ArCH_2$), 2.50–2.70 (1H, br, OH), 2.66 (1H, dd, *J* 13.7, 7.1 Hz, $ArCH_2$), 3.46 (1H, dd, *J* 11.0, 7.1 Hz, CH_2OH), 3.53 (1H, dd, *J* 11.0, 4.6 Hz, CH_2OH), 3.65 (1H, dd, *J* 11.1, 2.5 Hz, CH_2OH), 3.77 (1H, dd, *J* 11.1, 5.6 Hz, CH_2OH), 3.80–4.00 (1H, br, OH), 4.92 (1H, d, *J* 6.3 Hz, ArCHOH), 5.90 (2H, s, OCH_2O), 5.95 (2H, d, *J* 3.4 Hz, OCH_2O), 6.44 (1H, s, ArH), 6.46 (1H, d, *J* 7.8 Hz, ArH), 6.64 (1H, d, *J* 7.8 Hz, ArH), 6.68–6.70 (3H, m, ArH); $\delta_C(CDCl_3)$ 4.7, 6.7, 36.8, 39.4, 50.0, 59.5, 61.5, 73.7, 100.7, 100.9, 106.9, 107.6, 107.9, 109.2, 119.7, 121.8, 134.0, 137.2, 145.6, 146.5, 147.4, 147.5; *m*/*z* (EI, 20 eV) 488 (M^+, 0.2%), 265 (100), 135 (62) (Found: C, 64.26; H, 6.54. $C_{26}H_{36}O_7Si$ requires C, 63.91; H, 7.43%).

(2*S*,3*R*,4*R*)-3-Hydroxymethyl-4-(3,4-methylenedioxybenzyl)-2-(3,4-methylenedioxyphenyl)tetrahydrofuran [(+)-dihydrosesamin] 2

To an ice-cooled solution of diol **8** (0.55 g, 1.13 mmol) and Et_3N (0.33 ml, 2.37 mmol) in CH_2Cl_2 (10 ml) was added MsCl (0.19 ml, 2.45 mmol). After the reaction solution had been stirred at room temperature for 1 h, saturated aq. $NaHCO_3$ and CH_2Cl_2 were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Evaporation and silica gel column chromatography (EtOAc–hexane 1 : 2) gave unstable dimesyl derivative **9** (0.68 g, 93%) as a colorless oil, $\delta_H(CDCl_3)$ 0.53 (6H, q, *J* 7.8 Hz), 0.89 (9H, t, *J* 7.8 Hz), 2.08 (1H, m), 2.42 (1H, m), 2.53 (1H, dd, *J* 13.7, 9.3 Hz), 2.79 (1H, dd, *J* 13.7, 6.1 Hz), 3.00 (3H, s, OMs), 3.01 (3H, s, OMs), 4.23 (2H, d, *J* 6.4 Hz), 4.31 (1H, dd, *J* 9.3, 6.3 Hz), 4.47 (1H, dd, *J* 9.3, 4.6 Hz), 4.86 (1H, d, *J* 4.9 Hz), 5.92 (2H, s), 5.97 (2H, d, *J* 2.4 Hz), 6.39 (1H, s), 6.45 (1H, d, *J* 8.3 Hz), 6.63 (1H, d, *J* 8.3 Hz), 6.61 (1H, s), 6.67 (1H, d, *J* 8.3 Hz), 6.70 (1H, d, *J* 8.3 Hz); $\delta_C(CDCl_3)$ 4.7, 6.8, 35.7, 37.2, 37.4, 46.3, 67.7, 70.7, 73.4, 100.9, 101.1, 106.4, 107.8, 108.0, 108.9, 119.4, 121.9, 132.2, 136.0, 146.0, 146.9, 147.6.

To an ice-cooled solution of this dimesyl compound (0.68 g, 1.05 mmol) in THF (10 ml) was added *n*-Bu_4NF (1 M in THF; 1.05 ml, 1.05 mmol). After the reaction solution had been stirred at 0 °C for 1.5 h, saturated aq. NH_4Cl and EtOAc were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Evaporation and silica gel column chromatography (EtOAc–hexane 1 : 2) gave the unstable (methylsulfonyloxymethyl)tetrahydrofuran **10** (0.41 g, 90%) as a colorless oil, $\delta_H(CDCl_3)$ 2.49–2.58 (2H, m), 2.74 (1H, m), 2.85 (1H, dd, *J* 13.4, 5.1 Hz), 3.01 (3H, s, OMs), 3.71 (1H, dd, *J* 8.8, 7.1 Hz), 4.07 (1H, dd, *J* 8.8, 6.8 Hz), 4.29 (1H, dd, *J* 10.0, 8.6 Hz), 4.45 (1H, dd, *J* 10.0, 8.6 Hz), 4.80 (1H, d, *J* 5.9 Hz), 5.94 (2H, s), 5.95 (2H, s), 6.61–6.69 (2H, m), 6.73–6.81 (4H, m); $\delta_C(CDCl_3)$ 33.0, 37.5, 42.1, 49.5, 67.2, 72.6, 82.4, 100.9, 101.1, 106.1, 108.1, 108.3, 108.8, 119.1, 121.4, 133.2, 135.8, 147.2, 147.9.

A reaction solution of the (methylsulfonyloxymethyl)-tetrahydrofuran **10** (0.41 g, 0.98 mmol) in DMF (0.5 ml) and 1 M aq. NaOH (0.5 ml) was stirred at 120 °C for 16 h before additions of water and EtOAc. The organic solution was separated, washed with brine, dried (Na_2SO_4), and evaporated. The residue was applied to silica gel TLC plates (benzene–EtOAc 5 : 1) to give (+)-dihydrosesamin **2** (0.24 g, 68%) as colorless crystals, mp 97–98 °C; $[\alpha]_D^{20}$ +15.9 (*c* 0.75, pyridine); $\nu_{max}(CHCl_3)/cm^{-1}$ 3437, 2888, 1611, 1505, 1445, 1042, 938; $\delta_H(CDCl_3)$ 1.60 (1H, br s, OH), 2.35 (1H, m, 3-H), 2.53 (1H, dd, *J* 13.4, 10.5 Hz, $ArCH_2$), 2.70 (1H, m, 4-H), 2.87 (1H, dd, *J* 13.4, 5.1 Hz, $ArCH_2$), 3.72 (1H, dd, *J* 8.3, 6.4 Hz, 5-H), 3.76 (1H, dd, *J* 10.7, 6.8 Hz, CH_2OH), 3.89 (1H, dd, *J* 10.7, 6.8 Hz, CH_2OH), 4.04 (1H, dd, *J* 8.3, 6.6 Hz, 5-H), 4.79 (1H, d, *J* 6.4 Hz, 2-H), 5.93 (2H, s, OCH_2O), 5.94 (2H, s, OCH_2O), 6.64 (1H, d, *J* 7.8 Hz, ArH), 6.68 (1H, s, ArH), 6.73 (1H, d, *J* 7.8 Hz, ArH), 6.76 (2H, s, ArH), 6.83 (1H, s, ArH); $\delta_C(CDCl_3)$ 33.2 ($ArCH_2$), 42.3 (4-C), 52.6 (3-C), 60.9 (CH_2OH), 72.9 (5-C), 82.9 (2-C), 100.9 (OCH_2O), 101.0 (OCH_2O), 106.3, 108.0, 108.3, 108.9, 119.0, 121.4, 134.1, 137.0, 145.9, 146.9, 147.7, 147.8; *m*/*z* (EI, 20 eV) 356 (M^+, 65%), 135 (100) [Found (HRMS): M^+, 356.1252. $C_{20}H_{20}O_6$ requires *M*, 356.1258].

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