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Efficient synthesis of γ-DDB

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Abstract—Synthesis of **γ-DDB**, which is another family member of **α-DDB** (dimethyl 4,4′-dimethoxy-5,6,5′,6′-dimethylenedioxybiphenyl-2,2′-dicarboxylate), is described. The unsymmetric isomer (**γ-DDB**) was constructed by a linker-directed intramolecular Ullmann coupling reaction, followed by the cleavage of the linker and re-esterification.

1. Introduction

Schisandrin-type lignans, which are predominantly isolated from schisandraceae, have the structural feature of dibenzocyclooctandiene.[1–9] The benzene rings of these compounds are normally substituted with six alkoxy groups as shown in compounds (**A**) and (**B**) (Fig. 1). The corresponding acyclic compounds: **α-DDB** (dimethyl-4,4′-dimethoxy-5,6,5′,6′-dimethylene dioxybiphenyl-2,2′-dicarboxylate) and **β-DDB**, have been synthesized for their conversion to the corresponding natural products and other analogs. The preparation of those compounds can be achieved by symmetrically coupling two bromobenzene derivatives and some of the resulted analogs have shown interesting biological activities as antihepatotoxic and anticancer agents.[10–18] Similarly, it

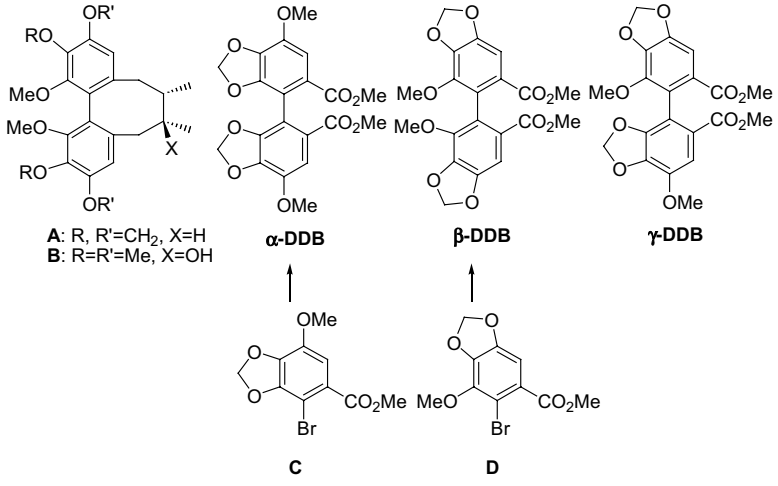

Figure 1.

Keywords: γ-DDB; Ullmann; Unsymmetrical.
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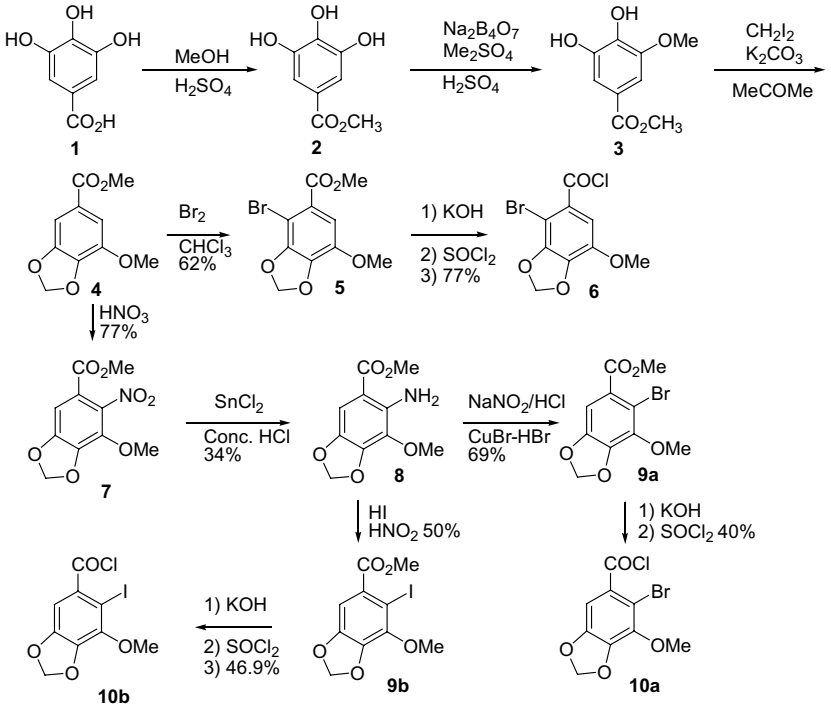


Scheme 1.

can be assumed that asymmetrical structure **γ-DDB** is a desirable starting material to be converted to the related analogs for their biological studies. We report here a synthetic procedure for preparing **γ-DDB** by using the key step of a salicylic alcohol-directed intramolecular Ullmann coupling reaction.

It can be observed from the symmetric structures of **α-DDB** and **β-DDB** that methyl 2-bromo-3,4-methylenedioxy-5-methoxybenzoate (**C**) can react with copper via the Ullmann coupling reaction to give **α-DDB**, and methyl 2-bromo-3-methoxy-4,5-methylenedioxybenzoate (**D**) can give **β-DDB**. The corresponding intermolecular Ullmann coupling reactions of the above mentioned two bromides (**C**) and (**D**) in one reaction process could not give **γ-DDB** cleanly, but produce a mixture of three DDB compounds (α-, β-, and γ-isomers). It is, however, hoped that a linker can be used to connect two different phenyl bromides together, and intramolecular coupling reaction shall give the unsymmetrical compound such as **γ-DDB**.

Compound **4**, which was prepared in three steps from myristicinic acid **4**, was easily brominated to compound **5**[14] and then converted to the desired chloride **6**. Alternatively, the nitration of compound **4** proceeded smoothly to give compound **7**, which was reduced to 6-amino derivative **8**. The Sandmeyer reactions of **8** gave bromo-derivative (**9a** mp 86.5 °C) and iodo-derivative (**9b** mp 89 °C), which were converted to the corresponding halides **10a** and **10b**, respectively. Since NMR spectroscopic data of bromides **5** and **9a** are very similar in terms of patterns and chemical shifts, the compound identities have been investigated. Firstly, the ^{1}H NMR spectroscopy of the mixture of compounds **5** and **9a** with the ratio of 2:1 presented two

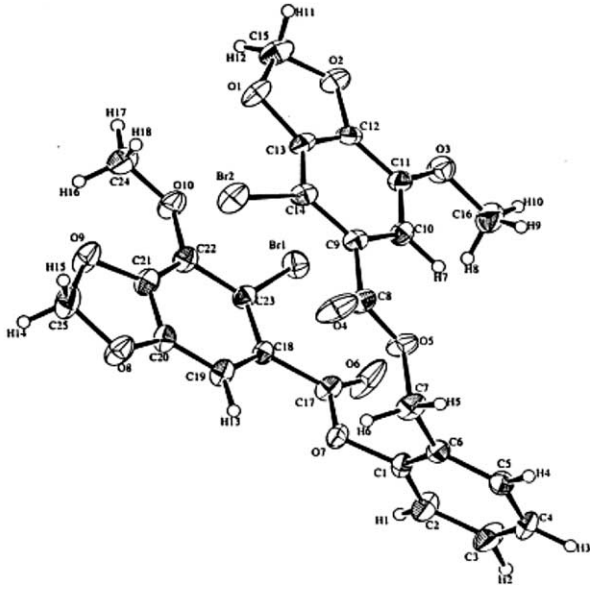
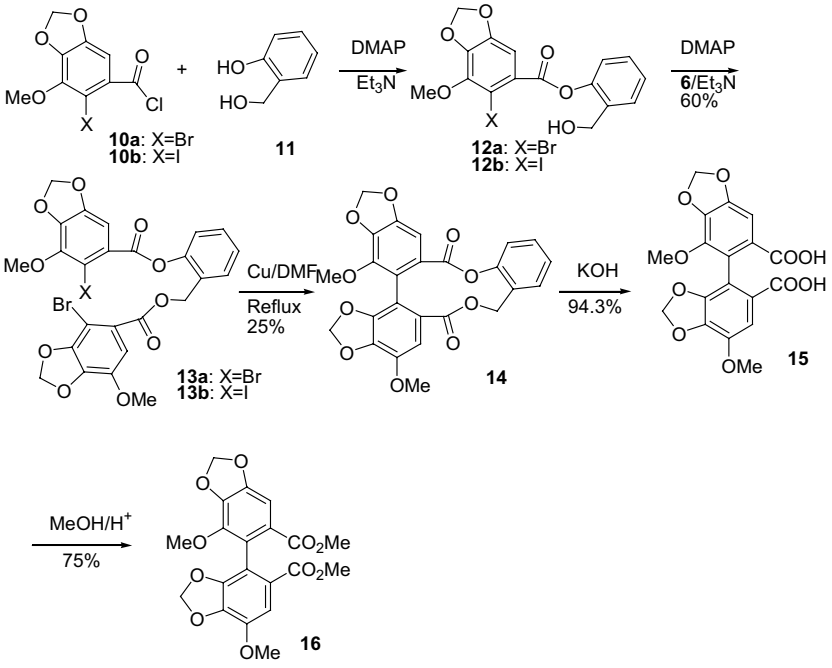


Figure 2.

sets of hydrogen atoms with the integration ratio of 2:1, confirming compounds **5** and **9a** to be different. Secondly, the intermolecular Ullmann coupling reaction of **9a** proceeded smoothly to give the corresponding **β-DDB** and the ^{1}H NMR data of **β-DDB** is consistent with those reported in the literature (Scheme 1).[14]

The Ullmann coupling reactions of diester **13a** (Fig. 2) proceeded in the presence of activated copper powder in DMF after refluxing for 3 h to result in the formation of **14**. By using **10b** instead of **10a**, the same diester **14** was produced in slightly improved yield and the structure of cou-



Scheme 2.

pling product **14** was confirmed by high resolution MS and ^{1}H NMR. The intramolecular coupling product **14** was hydrolyzed by KOH solution to afford γ-dicarboxylic acid **15**. The desired **γ-DDB 16** was obtained by acid-catalyzed esterification of compound **15** in MeOH (Scheme 2).

2. Experimental section

The melting point (mp) was taken on XT-4 microscope an uncorrected. IR was recorded on Perkin–Elmer 683 infrared spectrometer. H NMR data were obtained on a Bruker DPX-400 spectrometer. Mass spectra was recorded on a ZAB-HS mass spectrometer.

2.1. Methyl 2-bromo-3,4-dimethylenedioxy-5-methoxy benzoate (5)

To the solution of methyl 3,4-dimethylenedioxy-5-methoxy benzoate (22 g, 0.105 mmol) in acetic acid (130 ml) was added dropwise the mixture of bromine (16.8 g, 0.21 mmol) in acetic acid (60 mL) at low temperature (12–15 °C). The resulting solution was stirred for 2 h at room temperature and was poured into ice water to provide solid materials. Then the solid materials were filtered, washed with water, and dried over $MgSO_4$ to give crude products (28 g), which were recrystallized from ethanol twice to give compound **5** (19 g, 62%), mp 104–106 °C (reference value[19]) 106.5 °C.

2.2. 2-Bromo-3,4-dimethylenedioxy-5-methoxy benzoic acid chloride (6)

To compound **5** (5 g, 18.1 mmol) was added KOH solution (150 mL, 5%). The mixture was heated to reflux for 5 h. The solution was cooled to room temperature and acidified with concentrated hydrochloric acid to pH 2 to provide white powder. Then the powder was collected and dried (4.27, 90%, mp 240–242 °C). To the obtained acid (4 g, 14.5 mmol) was added thionyl chloride (15 mL). The mixture was heated to reflux for 4 h and was cooled to room temperature to provide solid materials. The $SOCl_2$ solution was partially removed under reduced pressure to provide more solid materials. The combined solid materials were washed with cyclohexane to give compound **6** (3.3 g, 77%), 146–148 °C. MS (m/z, %), 294 (M^+, 24), 257 (M^+–Cl, 90), 77 (C_6H_5, 100).

2.3. Methyl 3,4-dimethylenedioxy-5-methoxy-6-nitro-benzoate (7)

To concentrated HNO_3 (100 mL, $d = 1.45$, 65%, 1.5 mmol) was added compound **4** (10 g, 47.6 mmol) within 1 h at 5 °C. The mixture was stirred for 1 h at 0 °C and was poured into the crushed ice (400 g) to provide yellow solid materials. The solid materials were filtered, washed with water, and dried to give crude products (11.2 g). The crude products were recrystallized from ethyl acetate to give compound **7** (9.4 g, 77%), mp 124–126 °C (Ref. 14 126–128 °C). ^{1}H NMR ($CDCl_3$) δ 7.241 (s, 1H, ArH), 6.242 (s, 2H, OCH_2O), 4.175 (s, 3H, OCH_3), 3.969 (s, 3H, $COOCH_3$).

2.4. Methyl 6-amino-3,4-dimethylenedioxy-5-methoxy benzoate (8)

To $SnCl_2{\cdot}2H_2O$ (5 g, 22 mmol) was added concentrated hydrochloric acid (50 mL). The mixture was heated to melt completely and compound **7** (5 g, 19.6 mmol) was

then added at 40 °C. The nitro-compound was heated to reflux for 0.5 h and cooled to room temperature. The solvent was removed to provide solid materials, which was neutralized with NaOH solution (10%) to provide white solid materials. The white solid materials were mostly dissolved in cyclohexane and filtered. Filtrate solution precipitates compound **8** (1.5 g, 34%), mp 88–90 °C (Ref. 14 90–91 °C). ^{1}H NMR ($CDCl_3$) δ 7.01 (s, 1H, ArH), 5.883 (s, 2H, OCH_2O), 3.99 (s, 3H, OCH_3), 3.82 (s, 3H, $COOCH_3$), 5.0 (br, 2H, $ArNH_2$).

2.5. Methyl 6-bromo-3,4-dimethylenedioxy-5-methoxy benzoate (9a)

To $CuSO_4 \cdot 5H_2O$ (2 g, 8 mmol) were added potassium bromide(1 g, 8.4 mmol) and water (10 mL). After heating the mixture to become melted, NaOH solution (0.6 g, 15 mmol) and $NaHSO_3$ solution (0.6 g, 5.7 mmol) were sequentially added. The resulting solution was stirred to provide CuBr, which was washed with water three times and mixed with hydrobromic acid (5 mL, 40%) for the next step.

To compound **8** (1 g, 4.44 mmol) in hydrobromic acid (5 mL, 40%), was added dropwise sodium nitrite solution (0.5 g, 10.6 mmol) in 2.5 mL water at 0–5 °C until KI-starch paper showed light purple. The resulting solution was poured into a suspension of CuBr. Upon standing overnight, materials were extracted with benzene, washed with $NaHCO_3$ solution (10%), and dried with anhydrous $CaCl_2$ to provide crude products (0.9 g). The crude products were recrystallized from ethanol to give compound **9a** (0.89 g, 69%), mp 80–82 °C (Ref. 14 82–83 °C). ^{1}H NMR ($CDCl_3$) δ 7.03 (s, 1H, ArH), 6.07 (s, 2H, OCH_2O), 4.04 (s, 3H, OCH_3), 3.90 (s, 3H, $COOCH_3$), MS (m/z, %) 288 (M^+, 30), 257 (M–OCH_3, 87).

2.6. Methyl 6-iodo-3,4-dimethylenedioxy-5-methoxy benzoate (9b)

To compound **8** (6 g, 26 mmol) was added concentrated hydrochloric acid (5 mL). To the mixture was added dropwise sodium nitrite solution at 0–5 °C until KI-starch paper showed purple. The resulting solution was added KI solution to provide black solid materials. After extracting with benzene, the solution was washed with NaOH solution twice, and with brine once. The benzene solution was then dried over anhydrous $CaCl_2$ to provide crude products. The crude products were recrystallized from anhydrous ethanol to give compound **9b** (0.5 g, 50%), MS (m/z, %), 336 (M^+, 100), 305 (M^+–OCH_3, 77).

2.7. 6-Bromo-3,4-dimethylenedioxy-5-methoxy benzoyl chloride (10a)

To compound **9a** (2 g, 6.92 mmol) was added KOH solution (50 mL, 5%). The mixture was heated to reflux for 5 h and was added concentrated hydrochloric acid (pH = 2) to give powder, which was filtrated to give 6-bromo-3,4-dimethylenedioxy-5-methoxy benzoic acid (1.55 g, 81%), mp 188–190 °C. IR ($\gamma_{c=0}$, 1700 cm^{-1}). To this acid (2 g, 7.27 mmol) was added thionyl chloride (6 mL). The mixture was stirred for 5 h at 50 °C. Removal of thionyl chloride under reduced pressure gave yellow solid materials, which were filtered to give compound **10a** (0.86 g, 40%), mp 136–138 °C. IR ($\gamma_{c=0}$ 1750 cm^{-1}).

2.8. 6-Iodo-3,4-dimethylenedioxy-5-methoxy benzoyl chloride (10b)

To compound **9b** (1 g, 3 mmol) was added KOH (30 mL, 5%). The mixture was refluxed for 4 h. The solution was acidified with concentrated HCl to give white powder. The powder was filtered and dried to provide 6-iodo-3,4-dimethylenedioxy-5-methoxy benzoic acid (0.8 g, 88%), mp 178–180 °C, IR ($\gamma_{c=0}$ 1700 cm^{-1}). To this acid (0.8 g, 2.38 mmol) was added thionyl chloride (2.8 mL). The mixture was stirred for 5.5 h at 50 °C. Removal of thionyl chloride under reduced pressure gave compound **10b** (0.38 g, 46.9%), mp 145–147 °C. IR ($\gamma_{c=0}$ 1752 cm^{-1}).

2.9. Salicylalcohol diester (13a)

To dried DMF (20 mL) were added salicylalcohol (100 mg, 0.8 mmol), triethylamine (1 mL), DMAP, and compound **10a** (236 mg) at $-20 \sim -30$ °C. The mixture was stirred for 1 h at $-20 \sim -30$ °C and another 6 h at room temperature. Compound **6** was then added at $-20 \sim -30$ °C and stirred for 0.5 h at this temperature and for additional 12 h at rt. The solution was poured into water to provide solid. The solid materials were mixed with ethyl acetate, which was washed with brine. The organic phase was dried over anhydrous magnesium sulfate. After filtration, removal of solvents gave solid materials, which was recrystallized from chloroform–methanol to give compound **13a** (0.34 g, 60%), mp 160–162 °C. Anal. Calcd for $C_{25}H_{18}O_{10}Br_2C$: 47.03, H: 2.84; found C: 47.18, H: 2.70. MS (m/z, %) 638 (M^+, 6), 558 (M^+–Br, 1), 259 ($C_9H_6O_4Br^+$, 100), 179 ($C_9H_6O_4^+$, 22). ^{1}H NMR (DMSO-d_6) δ ppm 7.63 (d, 1H, ArH), 7.51 (m, 1H, ArH), 7.53 (s, 1H, ArH), 7.36 (m, 2H, ArH), 6.85 (s, 1H, ArH), 6.237 (s, 2H, OCH_2O), 6.13 (s, 2H, OCH_2O), 5.31 (s, 2H, $ArCH_2$), 3.91 (s, 3H, $ArOCH_3$), 3.86 (s, 3H, $ArOCH_3$).

X-ray structural determination crystal data compound **13a**: $C_{25}H_{18}O_{10}Br_2$ M = 638.22 A = 9.442(4) Å B = 29.93(1) Å C = 8.869(3) Å β = 100.21(2) °V = 2467(1) $Å^3$ primitive monoclinic cell $P2_1/C$(#14) Z = 4 Dx = 1.72 g/cm^3 μ(MoKα) = 33.53 cm^{-1} F(000) 1272.00. The diffraction experiment was carried out using a colorless transparent prisma with dimension of 0.60 × 0.40 × 0.30 mm. The diffractometer RAX1S-IV was used with graphite monochromated MoKα radiation (λ = 0.71070 nm). The structure was solved by a direct method using teXsan and Fourier method. The

refinement of atomic parameters was carried out using full-matrix least-squares methods with anisotropic temperature factors. Throughout the refinement, the function $\Sigma w(|F_o| - |F_c|)^2$ was minimized. The weighting scheme of $w = 1/\sigma^2(F_o)$ was used during the final refinement stage. The final R value is 0.054 ($R_w = 0.077$). Atomic coordinates and esd 's have been deposited at the Cambridge Crystallographic Data Center.

2.10. Salicylalcohol diester (13b)

To dried DMF (20 mL) were added salicylalcohol (100 mg, 0.8 mmol), triethylamine (1 mL), DMAP, and compound **10b** (236 mg) at $-20 \sim -30$ °C. The mixture was stirred for 1 h at $-20 \sim -30$ °C and another 6 h at room temperature. Compound **6** was then added at $-20 \sim -30$ °C and stirred for 0.5 h at this temperature for additional 12 h at rt. The solution was poured into water to provide solid, which was mixed with ethyl acetate. After the ethyl acetate was washed with brine, the organic phase was dried over anhydrous magnesium sulfate. Removal of solvents gave solid materials, which were recrystallized from chloroform–methanol to give compound **13b** (0.35 g, 60%), mp 160–162 °C. ^{1}H NMR (Acetone-d_6) δ ppm 7.66 (d, 1H, ArH), 7.50 (t, 1H, ArH), 7.35 (m, 2H, ArH), 7.573 (s, 1H, ArH), 6.913 (s, 1H, ArH), 6.13 (s, 2H, OCH_2O), 6.22 (s, 2H, OCH_2O), 5.37 (s, 2H, $ArCH_2$), 3.93 (s, 3H, $ArOCH_3$), 3.94 (s, 3H, $ArOCH_3$).

2.11. Biphenyl lactone (14)

A mixture of **13a** (200 mg, 0.31 mmol), activated Cu powder (600 mg), and anhydrous DMF (1.0 mL) was heated to reflux for 4 h under vigorous stirring. After cooling to room temperature, acetone was added. Solid was removed and the filtrate was concentrated. The crude product was purified by flash chromatography on silica gel (AcOEt–CH_2Cl_2) to afford 112 mg (25.0%) of **14**, mp 202–204 °C. ^{1}H NMR (Acetone-d_6) ppm 7.54 (d, 1H, ArH), 7.47 (m, 1H, ArH), 7.32 (m, 2H, ArH), 7.18 (s, 1H, ArH), 6.70 (s, 1H, ArH), 6.13 (d, 2H, OCH_2O), 6.09 (d, 2H, OCH_2O), 5.96 (d, 1H, $J = 11.6$Hz, $ArCH_2$), 4.64 (d, 1H, $J = 11.6$Hz, $ArCH_2$), 3.89 (s, 3H, $ArOCH_3$), 3.98 (s, 3H, $ArOCH_3$). HR-FAB Ms Obsd; m/z 479.0958, Calcd for $C_{25}H_{18}O_{10}$ m/z 479.0960 $(M+H)^+$.

2.12. 7,4′-Dimethoxy-[4,5′]bi[1,3-benzodioxolyl]-5,6′-dicarboxylic acid (15)

A mixture of **14** (100 mg, 0.21 mmol), KOH (200 mg), acetone (1 mL) and H_2O (0.5 mL) was refluxed for 2 h under vigorous stirring. The solvent was evaporated under reduced pressure and then acidified to pH 1 by dropwise adding 10% HCl. The mixture was extracted with AcOEt. The solvent was evaporated to provide 75 mg (94.3%) of **15**, which was recrystallized from CH_3OH–$CHCl_3$ (870 mg, mp 260 °C). Anal. Calcd for $C_{18}H_{14}O_{10}$: C, 55.39; H, 3.62. Found: C, 55.28; H, 3.70. ^{1}H NMR (Acetone-d_6) ppm 7.25 (s, 1H, ArH), 7.11 (s, 1H, ArH), 6.00 (d, 2H, OCH_2), 5.82 (d, 2H, OCH_2O), 3.82 (s, 3H, OCH_3).

2.13. Dimethyl 7,4′-dimethyl-[4,5′]bi[1,3-benzodioxolyl]-5,6-dicarboxylate(r-DDB, 16)

A mixture of **15** (50 mg, 0.13 mmol), CH_3OH (10 mL) and Concd H_2SO_4 (0.1 mL) was refluxed for 5 h under vigorous stirring. The mixture was poured into ice-water and extracted with AcOEt. The solvent was evaporated to provide 40 mg (75%) of **16**. Mp 150–152 °C. Anal. Calcd for $C_{20}H_{18}O_{10}$: C, 57.42; H, 4.34 Found: C, 57.32; H, 4.43. ^{1}H NMR ($CDCl_3$). δ ppm 7.16 (s, 1H, ArH), 7.35 (s, 1H, ArH), 5.97 (s, 2H, –OCH_2O–), 6.14 (s, 2H, –OCH^2O–), 3.57 (s, 3H, –OCH_3), 3.59 (s, 3H, –OCH_3), 3.76 (s, 3H, $ArOCH_3$), 3.96 (s, 3H, $ArOCH_3$).

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