Simple and Efficient Asymmetric Synthesis of Furofuran Lignans Yangambin and Caruilignan A

Naoki Mori,[a] Hidenori Watanabe,*[a] Takeshi Kitahara[a,b]

[a] Department of Applied Biological Chemistry, Graduate School of Agricultural and Life Sciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-8657, Japan

[b] Laboratory of Natural Product Chemistry, Center for Basic Research, The Kitasato Institute, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8642, Japan

Fax +81(3)58418019; E-mail: ashuten@mail.ecc.u-tokyo.ac.jp

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Abstract: A novel asymmetric dimerization of cinnamic acid derivative was achieved in high efficiency and high stereoselectivity. By using the reaction as a key step, two furofuran lignans, yangambin and caruilignan A were synthesized in optically pure form in only 5 and 6 steps, respectively.

Key words: asymmetric synthesis, oxidative dimerization, furofuran lignan, yangambin, caruilignan

Lignans belong to a family of dimeric phenylpropanoids. Their diverse structures, incorporating additional oxygen bridge(s), and their variety of bioactivities have fascinated organic chemists and a large number of compounds have been isolated and synthesized up to the present.[1] Yangambin (**1**) was first obtained as a dimethylated derivative of lirioresinol-B[2] isolated from tulip tree, *Liriodendron tulipifera* L., and then isolated from Chinese medicinal plant, *Magnolia fargesii*[3,4] (Figure 1).

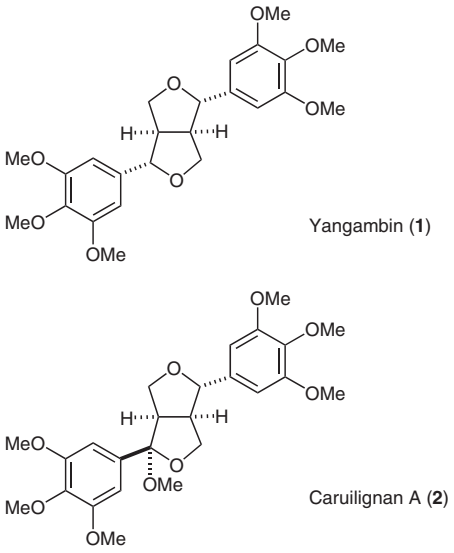
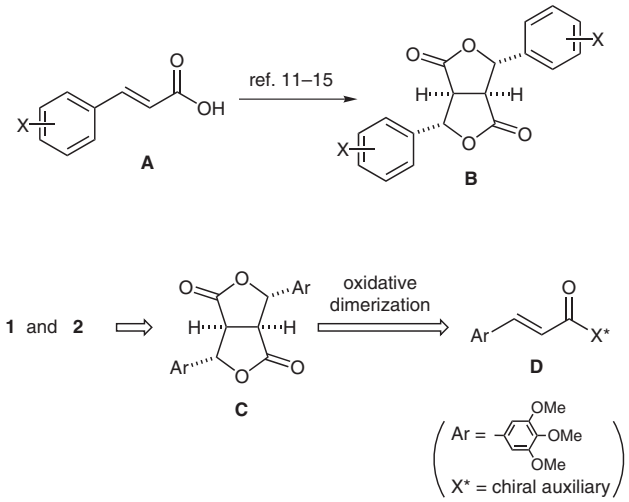


Figure 1

Despite the various pharmacological activities, such as selective inhibition against platelet activating factor,[5] protective effects against cardiovascular collapse and anaphylactic shock, anti-allergic properties, analgesic activity, depressant effect in the central nervous system[6] and apoptosis induction,[7] only one racemic synthesis has been reported.[8] Caruilignan A (**2**) was isolated from the extract of traditional Chinese medicine, *Artemisia caruifolia*, and exhibits a cytotoxicity against Meth-A cells.[9] We report here a short step synthesis of the enantiomerically pure furofuran lignans (**1** and **2**) by employing a novel asymmetric dimerization of cinnamic acid derivative.



Scheme 1

The most straightforward approach to furofuran lignans is a biomimetic and oxidative dimerization of derivatives of cinnamyl alcohol or cinnamic acid. Although four reagents [$FeCl_3$–O_2,[10] $Tl(OCOCF_3)_3$,[11] PbO_2,[12] $NaIO_4$[13]] are known to oxidize cinnamic acids **A** to racemic furofuran-type dilactones **B** (Scheme 1), yields of the product (**B**) are unsatisfactory and asymmetric versions under these conditions have not been developed yet. Oxidation of **A** with plant-originated peroxidases is also reported to give optically active products.[13–15] However, they are not valuable for practical use due to the low chemical/optical yields or low availability of the enzyme. We therefore de-

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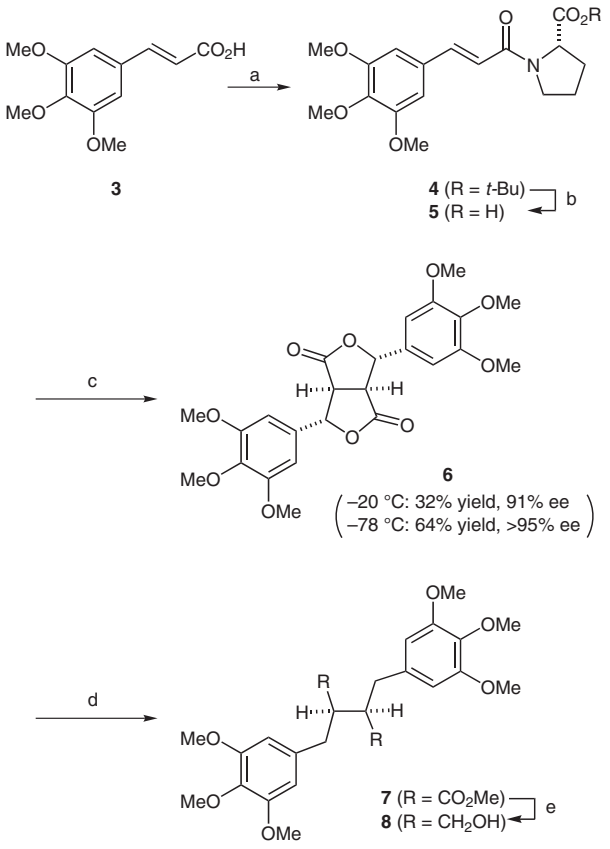
signed to equip the carboxyl group with a chiral auxiliary to control the newly introduced four asymmetric centers (**D** to **C**).

L-Proline was chosen as a chiral auxiliary and the commercially available 3,4,5-trimethoxycinnamic acid (**3**) was converted into amide **5** in two steps via **4** as shown in Scheme 2. Treatment of **5** with PbO_2 and trifluoroacetic acid (TFA) in CH_2Cl_2 at –20 °C afforded dilactone **6** in 32% yield. This result surprised us because the chiral auxiliary was removed during the reaction and the product was identical to a compound obtained from the free acid **3**.[12] In addition, the yield was much higher than that of the original reaction (14% from **3**),[12] and moreover, enantiomeric purity of **6** was quite high (91% ee). The reaction was then carried out at lower temperature (–78 °C), and the chemical yield as well as the enantiomeric purity was found to improve considerably (64% yield, > 95% ee). On the other hand, other oxidizing agents, such as $FeCl_3$–O_2[10] and $Tl(OCOCF_3)_3$,[11] did not afford **6**. Interestingly, L-valine derivative instead of L-proline afforded an antipode of **6**, but it was less reactive and both chemical and optical yields were much lower (21%, 68% ee). Optical purity of the products was determined by chiral HPLC analysis of **7**, which was obtained from **6** by hydrogenolysis and methyl ester formation. The absolute stereochemistry was determined by comparing the sign of specific rotation with known antipodal compound of **8**.[16]



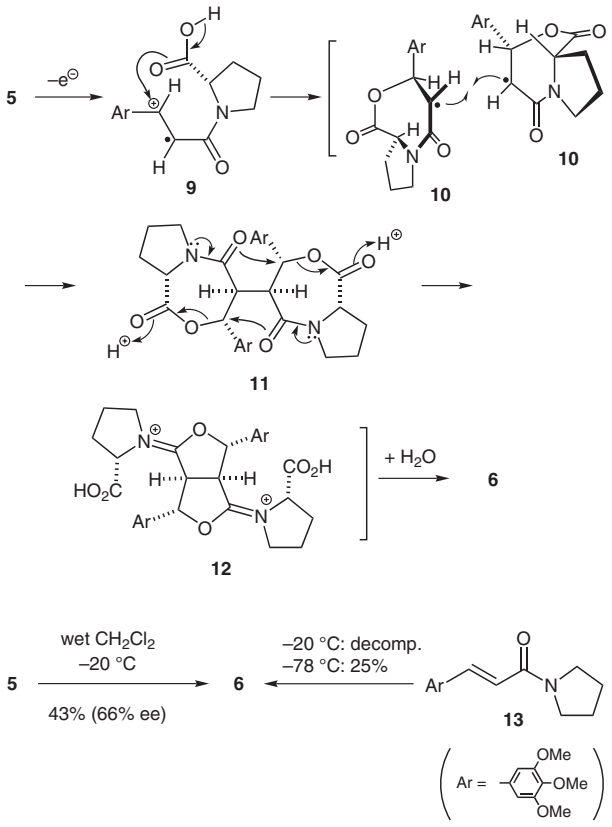
Scheme 2 *Reagents and conditions*: a) L-Proline *tert*-butyl ester, HOBt, DCC, THF (80%); b) TFA, 0 °C (82%); c) PbO_2, TFA, Celite, CH_2Cl_2; d) H_2, Pd-C, EtOH–AcOH then CH_2N_2, Et_2O–MeOH (80%); e) $LiAlH_4$, THF (92%).

The presumed mechanism of the asymmetric induction is illustrated in Scheme 3. The first step of the reaction is a one-electron oxidation to generate a radical cation (**9**), which was trapped intramolecularly by the carboxyl group from α-face to form a radical of seven-membered lactone (**10**). Since the sp^2 nature of the amide radical and the pyrrolidine ring strictly fix the conformation of **10**, most atoms of the fused rings are almost on the same plane except the OC=O group of the lactone. Radical-radical coupling of **10** takes place on the opposite side of the OC=O group to give **11**. We initially expected that **11** would be obtained as a product. But fortunately, strong acidic conditions with TFA caused the reconstruction of the ring system (**11** to **12**) and **6** was obtained by hydrolytic loss of proline during aqueous workup.

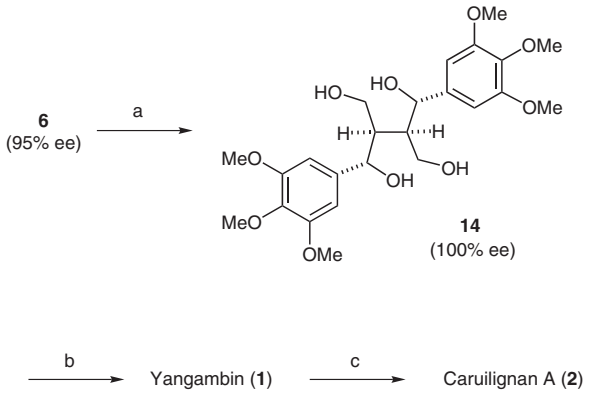
Our presumption that the carboxyl group plays an important role in the reaction was supported by the negative effect of water on the enantiomeric purity of the product. When aqueous dichloromethane was used as a solvent, enantiomeric purity of **6** dropped to 66% ee. Competitive addition of water to **9** was thought to make the reaction nonstereoselective or only poorly so. In addition to that, a simple pyrrolidine amide (**13**) showed quite low reactivity under the same conditions and **6** was obtained in poor yield. This result also strongly supports the importance of the carboxylic group.

To complete the synthesis, dilactone **6** (95% ee) was first reduced to tetraol **14** with $CaBH_4$ in ethanol (Scheme 4). Other reducing agents, such as $LiAlH_4$, DIBAL-H, $NaBH_4$, AlH_3 and $LiBH_4$, could not complete the reaction and gave a mixture of partially reduced products even when an excess of the reducing agent was used. Tetraol **14** was a highly crystalline compound and its enantiomeric purity could be enhanced to 100% ee by simple recrystallization. Selective mesylation of primary alcohols of **14** caused subsequent ether formation smoothly and yangambin (**1**) was obtained in an excellent yield. Transformation of **1** into caruilignan A (**2**) was performed by oxidation with DDQ in the presence of methanol. By quenching the reaction at a low level of conversion (20%), overoxidation to dimethoxy compound was avoided, and **2** was obtained in quantitative yield based on the recovery of **1**. The spectroscopic data of our synthetic **1** and **2** were in good accordance with those reported in the literature.[8,17]

In summary, we have developed a simple and efficient asymmetric approach to furofuran lignans, and yangambin (**1**) and caruilignan A (**2**) were synthesized in optically pure form. The overall yields of **1** and **2** were 30% over five steps and 30% over six steps, respectively. After the completion of this work, we found that PbO_2 was not strong enough to oxidize cinnamic amides with two or less oxygen atoms on the benzene ring and electrolysis is more effective for these substrates. Those results and the application to the syntheses of other furofuran lignans will be reported in due course.



Scheme 3



Scheme 4 *Reagents and conditions*: a) $Ca(BH_4)_2$, EtOH, then recrystallization (74%); b) MsCl (3 equiv), DMAP, Py, 0 °C → r.t. (96%); c) DDQ, CH_2Cl_2, MeOH (19%, quant. based on recovery).

Optical rotations were recorded with a Jasco DIP-1000 polarimeter. IR spectra were measured with a Jasco FT/IR-230 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Jeol JNM AL300 spectrometer. Mass spectra were recorded on a Jeol JMS-700T spectrometer. Column chromatography was performed using Merck silica gel 60 (0.060–0.200 mm). Microanalyses were performed on a Perkin-Elmer CHN analyzer (GC 15806). TLC was carried out on Merck glass plates precoated with silica gel 60 F_{254} (0.25 mm). HPLC was performed using a Showa Denko shodex DS-4 instrument. Melting points were measured with a Yanaco micro melting point apparatus and are uncorrected.

***tert*-Butyl (*S*)-1-[(*E*)-3-(3,4,5-Trimethoxyphenyl)propenoyl]pyrrolidine-2-carboxylate (4)**

To a solution of HOBt (2.56 g, 19.0 mmol), L-proline *tert*-butyl ester (2.50 g, 14.6 mmol), **3** (3.48 g, 14.6 mmol) in THF (50 mL) was added DCC (3.92 g, 19.0 mmol) at 0 °C. After stirring at r.t. for 3 h, the reaction mixture was filtered through Celite®. The filtrate was poured into sat. $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with sat. NH_4Cl solution and brine, dried with anhyd $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–EtOAc (3:1–1:1) gave **4** (4.56 g, 80%) as colorless crystals; mp 44–46 °C; $[\alpha]_D^{17}$ –61 (c = 0.9, $CHCl_3$).

IR (KBr): 2975, 1736, 1652, 1582, 1506, 1413, 1331, 1153, 1126, 1005 cm^{-1}.

Major Rotamer

^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 [s, 9 H, $C(CH_3)_3$], 1.86–2.20 (m, 4 H, H-3, H-4), 3.66–3.78 (m, 1 H, H_a-5), 3.80–3.92 (m, 1 H, H_b-5), 3.87 (s, 3 H, OCH_3), 3.90 (s, 6 H, OCH_3), 4.43–4.52 (m, 1 H, H-2), 6.63 (d, J = 15.3 Hz, 1 H, H-2′), 6.74 (s, 2 H, ArH), 7.63 (d, J = 15.3 Hz, 1 H, H-3′).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.6, 27.8, 29.1, 47.0, 55.9, 56.3, 59.8, 81.2, 104.9, 117.4, 130.8, 139.4, 142.6, 153.3, 164.6, 171.4.

Minor Rotamer

^1H NMR (300 MHz, $CDCl_3$): δ = 1.44 [s, 9 H, $C(CH_3)_3$], 1.86–2.20 (m, 4 H, H-3, H-4), 3.66–3.78 (m, 1 H, H_a-5), 3.80–3.92 (m, 1 H, H_b-5), 3.87 (s, 3 H, OCH_3), 3.89 (s, 6 H, OCH_3), 4.43–4.52 (m, 1 H, H-2), 6.47 (d, J = 15.3 Hz, 1 H, H-2′), 6.71 (s, 2 H, ArH), 7.61 (d, J = 15.3 Hz, 1 H, H-3′).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.7, 27.6, 31.4, 46.8, 55.8, 56.2, 59.7, 82.1, 104.8, 117.5, 130.6, 139.4, 142.3, 153.3, 165.1, 171.7.

Anal. Calcd for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47; N, 3.58. Found: C, 64.16; H, 7.46; N, 3.48.

(*S*)-1-[(*E*)-3-(3,4,5-Trimethoxyphenyl)propenoyl]pyrrolidine-2-carboxylic Acid (5)

A solution of **4** (769 mg, 1.97 mmol) in TFA (8 mL) was stirred at 0 °C for 4 h. The reaction mixture was concentrated in vacuo and the residue was chromatographed over silica gel. Elution with EtOAc gave **5** (543 mg, 82%) as colorless crystals; mp 100–102 °C; $[\alpha]_D^{17}$ –216 (c = 1.0, $CHCl_3$).

IR (KBr): 2941, 1735, 1646, 1583, 1505, 1455, 1333, 1243, 1125, 1002 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.90–2.03 (m, 1 H, H_a-3), 2.07–2.13 (m, 2 H, H-4), 2.64 (br d, J = 12.3 Hz, 1 H, H_b-3), 3.65–3.74 (m, 1 H, H_a-5), 3.77–3.82 (m, 1 H, H_b-5), 3.89 (s, 3 H, OCH_3), 3.90 (s, 6 H, OCH_3), 4.76 (d, J = 8.1 Hz, 1 H, H-2), 6.58 (d, J = 15.3 Hz, 1 H, H-2′), 6.77 (s, 2 H, ArH), 7.76 (d, J = 15.3 Hz, 1 H, H-3′).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.7, 27.4, 47.8, 55.9, 56.4, 60.6, 105.4, 115.5, 129.9, 140.1, 145.1, 153.4, 167.6, 172.4.

Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.42; H, 6.58; N, 4.24.

(1*S*,4*S*,5*S*,8*S*)-4,8-Bis(3,4,5-trimethoxyphenyl)-3,7-dioxabicyclo[3.3.0]octane-2,6-dione (6)

To a solution of **5** (20.0 mg, 0.059 mmol) in CH_2Cl_2 (1.5 mL) were added Celite® (100 mg), TFA (40 μL, 0.519 mmol) and PbO_2 (70.0 mg, 0.295 mmol) at –78 °C. After stirring at –78 °C for 14 h, the reaction mixture was filtered through Celite®. The filtrate was poured into water and extracted with Et_2O. The organic layer was washed with sat. $NaHCO_3$ solution and H_2O, dried with anhyd $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–EtOAc (2:3) gave **6** (9.0 mg, 64%). Re-

crystallization from hexane–THF gave colorless crystals; mp 179–180 °C; $[\alpha]_D^{22}$ +37 (*c* = 1.0, $CHCl_3$).

IR (KBr): 2944, 2841, 1769, 1594, 1509, 1466, 1427, 1364, 1334, 1241, 1128, 1002 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.55 (s, 2 H, H-1, H-5), 3.81 (s, 6 H, OCH_3), 3.86 (s, 12 H, OCH_3), 5.87 (s, 2 H, H-4, H-8), 6.49 (s, 4 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 48.5, 56.3, 60.8, 81.5, 101.3, 133.6, 138.4, 153.9, 174.9.

Anal. Calcd for $C_{24}H_{26}O_{10}$: C, 60.76; H, 5.52. Found: C, 60.91; H, 5.44.

Dimethyl (2*R*,3*R*)-Bis(3,4,5-trimethoxyphenylmethyl)butanedioate (7)

To a solution of **6** (non-recrystallized, 115 mg, 0.243 mmol) in EtOH–AcOH (8 mL, 1:1) was added 10% Pd/C (230 mg) and the mixture was stirred at r.t. for 2 d under H_2 atmosphere. The mixture was filtered through Celite® and concentrated in vacuo. The residue was dissolved in MeOH (10 mL) and treated with a solution of CH_2N_2 in Et_2O at 0 °C. After addition of few drops of AcOH to destroy the unreacted CH_2N_2, the reaction mixture was concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–EtOAc (2:1–1:2) gave crude **7** (98.0 mg, 80%, > 95% ee). Recrystallization from hexane–EtOAc gave pure **7** (> 99% ee) as colorless crystals. HPLC [column: Daicel Chiralcel OD (0.46 cm × 25 cm), eluent: hexane–*i*-PrOH (2.5:1), flow rate: 0.9 mL/min, detection: UV (254 nm)]: t_R = 15.7 min [(*R*,*R*)-isomer]; t_R = 18.8 min [(*S*,*S*)-isomer]; mp 100–102 °C; $[\alpha]_D^{21}$ –39 (*c* = 1.0, $CHCl_3$).

IR (KBr): 2943, 2834, 1734, 1589, 1509, 1456, 1437, 1243, 1167, 1002 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.90–3.30 (m, 6 H, H-2, H-3, CH_2Ar), 3.66 (s, 6 H, $COOCH_3$), 3.78 (s, 12 H, OCH_3), 3.80 (s, 6 H, OCH_3), 6.29 (s, 4 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.9, 47.5, 51.8, 60.0, 60.8, 105.8, 134.2, 136.5, 153.1, 173.6.

Anal. Calcd for $C_{26}H_{34}O_{10}$: C, 61.65; H, 6.77. Found: C, 61.67; H, 6.71.

(2*R*,3*R*)-Bis(3,4,5-trimethoxyphenylmethyl)butane-1,4-diol (8)

To a solution of **7** (72.3 mg, 0.143 mmol) in THF (5 mL) was added $LiAlH_4$ (20.0 mg, 0.527 mmol) at 0 °C. The reaction mixture was stirred at r.t. for 2 h, and then cooled to 0 °C. H_2O and 3 N HCl were added to the mixture and the reaction mixture was extracted with $CHCl_3$. The organic layer was dried with anhyd $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with EtOAc gave **8** (58.9 mg, 92%). Recrystallization from hexane–EtOAc gave colorless crystals; mp 146–149 °C; $[\alpha]_D^{21}$ –30 (*c* = 1.0, $CHCl_3$), {Lit.[16] (*S*,*S*)-**8**: $[\alpha]_D^{23}$ +23.6 (*c* = 0.11, $CHCl_3$)}.

IR (KBr): 3503, 2933, 2835, 1593, 1508, 1462, 1422, 1238, 1133, 1039, 1007 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.87–1.93 (m, 2 H, H-2, H-3), 2.68 (dd, *J* = 6.3, 13.8 Hz, 2 H, CH_aAr), 2.78 (dd, *J* = 7.8, 13.8 Hz, 2 H, CH_bAr), 3.56 (dd, *J* = 3.9, 11.4 Hz, 2 H, H_a-1, H_a-4), 3.80 (s, 12 H, OCH_3), 3.81 (s, 6 H, OCH_3), 3.81–3.86 (m, 2 H, H_b-1, H_b-4), 6.35 (s, 4 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.6, 43.7, 56.1, 60.6, 60.8, 105.9, 136.2, 136.3, 153.1.

Anal. Calcd for $C_{24}H_{34}O_8$: C, 63.98; H, 7.61. Found: C, 63.69; H, 7.58.

(1*S*,2*R*,3*R*,4*S*)-2,3-Bis(hydroxymethyl)-1,4-bis(3,4,5-trimethoxyphenyl)butane-1,4-diol (14)

$CaCl_2$ (1.26 g, 11.4 mmol) and $NaBH_4$ (860 mg, 22.7 mmol) were added to EtOH (20 mL). After stirring at r.t. for 15 min, **6** (770 mg, 1.62 mmol) in EtOH (5 mL) was added to the mixture. After stirring at r.t. overnight, the reaction mixture was poured into diluted HCl and extracted with $CHCl_3$. The organic layer was washed with sat. $(NH_4)_2SO_4$ solution, dried with anhyd $MgSO_4$ and concentrated in vacuo. Recrystallization from EtOAc gave **14** (580 mg, 74%) as colorless crystals; mp 204–205 °C; $[\alpha]_D^{23}$ –31 (*c* = 1.0, MeOH).

IR (KBr): 3481, 2938, 1595, 1507, 1460, 1420, 1329, 1233, 1127, 999 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 2.20–2.25 (m, 2 H, H-2, H-3), 3.72 (s, 18 H, OCH_3), 3.72–3.88 (m, 4 H, CH_2OH), 4.80 (d, *J* = 3.9 Hz, 2 H, H-1, H-4), 6.37 (s, 4 H, ArH).

^{13}C NMR (75 MHz, CD_3OD): δ = 46.1, 56.2, 61.0, 61.8, 74.2, 103.9, 137.2, 141.3, 153.9.

Anal. Calcd for $C_{24}H_{34}O_{10}$: C, 59.74; H, 7.10. Found: C, 59.34; H, 7.03.

(1*S*,3a*R*,4*S*,6a*R*)-1,3a,4,6a-Tetrahydro-1,4-bis(3,4,5-trimethoxyphenyl)-3*H*,6*H*-furo[3,4-*c*]furan (1, Yangambin)

To a solution of **14** (100 mg, 0.207 mmol) in pyridine (1.8 mL) were added DMAP (4.3 mg) and MsCl (48 μL, 0.622 mmol) at 0 °C. After stirring at 0 °C for 6 h, the mixture was warmed to r.t. and stirring was continued for 2 d. The reaction mixture was poured into H_2O and extracted with EtOAc. The organic layer was dried with anhyd $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane–EtOAc (1:1) gave **1** (88.9 mg, 96%). Recrystallization from EtOAc gave colorless crystals; mp 119–120 °C; $[\alpha]_D^{23}$ +44 (*c* = 1.0, $CHCl_3$) {Lit.[17] $[\alpha]_D^{29}$ +46 (*c* = 0.4, $CHCl_3$)}.

IR (KBr): 2952, 2824, 1588, 1510, 1464, 1422, 1329, 1238, 1131, 998 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.09–3.13 (m, 2 H, H-3a, H-6a), 3.83 (s, 6 H, OCH_3), 3.87 (s, 12 H, OCH_3), 3.93 (dd, *J* = 3.6, 9.3 Hz, 2 H, H_a-3, H_a-6), 4.31 (dd, *J* = 6.6, 9.3 Hz, 2 H, H_b-3, H_b-6), 4.75 (d, *J* = 3.3 Hz, 2 H, H-1, H-4), 6.57 (s, 4 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 54.3, 56.1, 60.8, 71.9, 85.9, 102.7, 136.7, 137.4, 153.4.

Anal. Calcd for $C_{24}H_{30}O_8$: C, 64.56; H, 6.77. Found: C, 64.75; H, 6.75.

(1*R*,3a*R*,4*S*,6a*R*)-1,3a,4,6a-Tetrahydro-1,4-bis(3,4,5-trimethoxyphenyl)-1-methoxy-3*H*,6*H*-furo[3,4-*c*]furan (2, Caruilignan A)

To a solution of **1** (20 mg, 0.045 mmol) in CH_2Cl_2 (2 mL) were added DDQ (10.2 mg, 0.045 mmol) and MeOH (0.1 mL) at 0 °C. After stirring at 0 °C for 3 h, the remaining DDQ was destroyed by the addition of $NaBH_4$ (ca. 10 mg). The reaction mixture was poured into H_2O and extracted with Et_2O. The organic layer was dried with anhyd $MgSO_4$ and concentrated in vacuo. The residue was purified by preparative TLC [hexane–EtOAc (1:1)] to give **2** (4.0 mg, 19%) as an amorphous solid with recovery of **1** (16.2 mg, 81%); $[\alpha]_D^{27}$ +86 (*c* = 0.93, $CHCl_3$) {Lit.[9] $[\alpha]_D^{24}$ +62 (*c* = 0.83, $CHCl_3$)}.

IR (KBr): 2939, 1593, 1506, 1460, 1415, 1342, 1234, 1126, 1005 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.99 (s, 3 H, OCH_3-1), 3.04 (m, 1 H, H-3a), 3.10 (t, *J* = 8.7 Hz, 1 H, H_a-6), 3.31 (q, *J* = 8.7 Hz, 1 H, H-6a), 3.83 (s, 3 H, $ArOCH_3$), 3.86 (m, 1 H, H_b-6), 3.87 (s, 9 H, $ArOCH_3$), 3.89 (s, 6 H, $ArOCH_3$), 4.06–4.16 (m, 2 H, H-3), 4.48 (d, *J* = 6.6 Hz, 1 H, H-4), 6.57 (s, 2 H, ArH), 6.72 (s, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 48.8, 52.9, 56.1, 56.2, 56.8, 60.8, 60.9, 69.6, 70.4, 87.9, 103.0, 103.9, 110.2, 133.2, 136.6, 137.6, 137.7, 153.1, 153.4.

HRMS–FAB: *m/z* $[M + H]^+$ calcd for $C_{25}H_{33}O_9$: 477.2125; found: 477.2085.

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References

(1) Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75.
(2) Dickey, E. E. *J. Org. Chem.* **1958**, *23*, 179.
(3) Hirose, M.; Satoh, Y.; Hagitani, A. *Nippon Kagaku Zasshi* **1968**, *89*, 887.
(4) Kakisawa, H.; Chen, Y. P.; Hsu, H. Y. *Phytochemistry* **1972**, *11*, 2289.
(5) (a) Castro-Faria-Neto, H. C.; Bozza, P. T.; Cruz, H. N.; Silva, C. L. M.; Violante, F. A.; Barbosa-Filho, J. M.; Cordeiro, R. S. B.; Tibiriçá, E. V. *Planta Med.* **1995**, *61*, 101. (b) Castro-Faria-Neto, H. C.; Bozza, P. T.; Cruz, H. N.; Silva, C. L. M.; Violante, F. A.; Barbosa-Filho, J. M.; Cordeiro, R. S. B.; Tibiriçá, E. V. *Planta Med.* **1995**, *61*, 106.
(6) Marques, R. C. P.; de Medeiros, S. R. B.; Dias, C. S.; Barbosa-Filfo, J. M.; Agenz-Lima, L. F. *Mutat. Res.* **2003**, *536*, 117; and references cited therein.
(7) Hausott, B.; Greger, H.; Marian, B. *J. Cancer Res. Clin. Oncol.* **2003**, *129*, 569.
(8) Suginome, H.; Orito, K.; Yorita, K.; Ishikawa, M.; Shimoyama, N.; Sasaki, T. *J. Org. Chem.* **1995**, *60*, 3052.
(9) Ma, C.-M.; Nakamura, N.; Min, B. S.; Hattori, M. *Chem. Pharm. Bull.* **2001**, *49*, 183.
(10) Cartwright, N. J.; Haworth, R. D. *J. Chem. Soc.* **1944**, 535.
(11) Taylor, E. C.; Andrade, J. G.; Rall, G. J. H.; Steliou, K.; Jagdmann, G. E. Jr.; McKillop, A. *J. Org. Chem.* **1981**, *46*, 3078.
(12) Yuzikhin, O. S.; Vasil'ev, A. V.; Rudenko, A. P. *Russ. J. Org. Chem.* **2000**, *36*, 1743.
(13) Tazaki, H.; Taguchi, D.; Hayashida, T.; Nabeta, K. *Biosci., Biotechnol., Biochem.* **2001**, *65*, 2613.
(14) Takahashi, H.; Matsumoto, K.; Ueda, M.; Miyake, Y.; Fukuyama, Y. *Heterocycles* **2002**, *56*, 245.
(15) Ou, L.; Kong, L.-Y.; Zhang, X.-M.; Niwa, M. *Biol. Pharm. Bull.* **2003**, *26*, 1511.
(16) Shibuya, H.; Takeda, Y.; Zhang, R. S.; Tanitame, A.; Tsai, Y. L.; Kitagawa, I. *Chem. Pharm. Bull.* **1992**, *40*, 1639.
(17) Lee, C. K.; Chang, M. H. *J. Chin. Chem. Soc. (Taipei)* **2000**, *47*, 555.