JOC*Note*

General Strategy for Stereoselective Synthesis of 1-Substituted *Exo,Endo*-2,6-Diaryl-3,7-dioxabicyclo[3.3.0]octanes: Total Synthesis of (±)-Gmelinol

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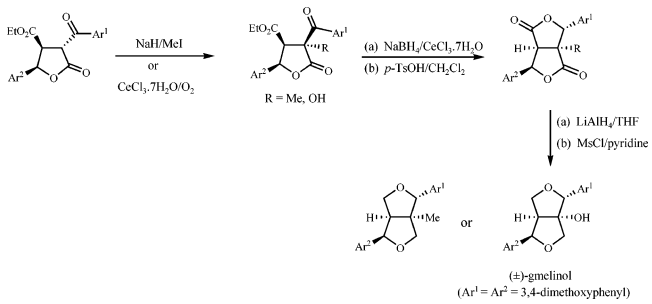
Received September 13, 2005



A general strategy for stereoselective synthesis of 1-substituted *exo,endo*-2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes including (±)-gmelinol from (2,3-*trans*)-(4,5-*cis*)-α-aroylparaconic esters, which are readily obtained from the reaction of vicinal dianions derived from α-aroylsuccinic esters with aromatic aldehydes, is described. The synthetic sequence involves α-methylation or α-hydroxylation, reduction, bislactonization, and reduction followed by furofuran formation.

Furofurans containing the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]-octane skeleton are an important class of natural lignans that have shown a wide range of biological activities, such as antitumor, antihypertensive, anti-inflammatory, insecticidal, and platelet-activating factor antagonist activities.[1−3] These types of compounds possess the 2,6-diaryl substituents on the exo,-exo; exo,endo; or endo,endo face of the 3,7-dioxabicyclo[3.3.0]-octanes. Furofurans with a hydroxy group at the bridgehead position such as compounds **1**−**4** (Figure 1) have also been found in nature.[4−7]

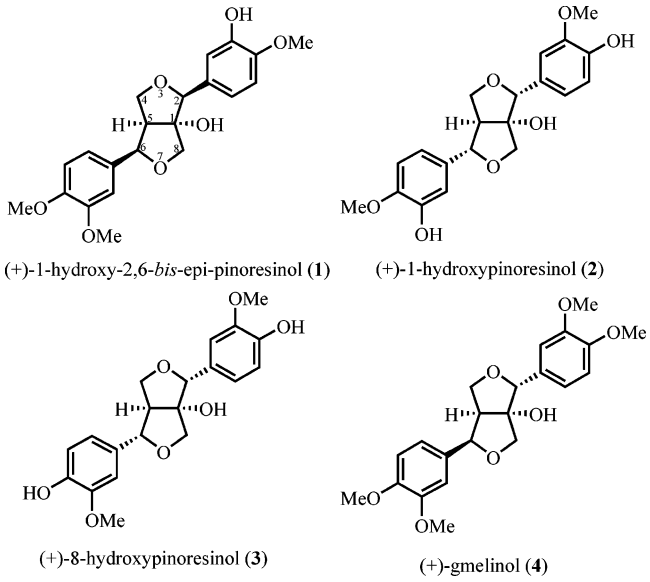


FIGURE 1. Representative 1-hydroxyfurofuran lignans.

Because of interesting structural features and their biological importance, a number of synthetic methodologies of the furofurans have been reported.[3] However, only a few approaches have been on the 1-hydroxyfurofurans.[8−12] As part of our ongoing research on the synthetic utilization of vicinal dianions derived from α-aroylsuccinates, a general route to (3,4-*trans*)-(4,5-*cis*)-α-aroylparaconic esters **6** from these vicinal dianions with aromatic aldehydes in the presence of $ZnCl_2$ has been reported.[13] Compounds of type **6** have been shown as versatile precursors for the preparation of α-arylidene-γ-butyrolactones,[13a] (±)-thuriferic acid ethyl ester, its analogues, and (±)-picropodophyllone.[13c] In this note, we report an efficient and general stereoselective strategy to 1-hydroxy-*exo*,*endo*-2,6-furofurans, (±)-gmelinol (**4**), and its derivatives as well as to 1-methylated analogues, starting from (3,4-*trans*)-(4,5-*cis*)-α-aroylparaconic esters **6** (TC-isomers).

Our investigation began with the synthesis of TC-**6a**−**c** by reacting vicinal dianions derived from the corresponding α-aroylsuccinic esters **5a**,**b** with aromatic aldehydes. The desired α-aroylparaconic esters **6a**−**c** were obtained as a mixture of

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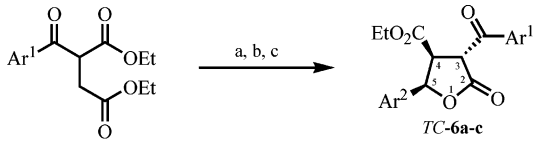
10.1021/jo0519110 CCC: $33.50
Published on Web 12/01/2005

TABLE 1. Preparation of (3,4-*trans*)-(4,5-*cis*)-α-Aroylparaconic Esters 6a−c

5	Ar^2CHO	6 (% yield, diastereomeric ratio)[a]	TC-6, % yield[b]
5a	benzaldehyde	**6a**, (80, 77:7:14:2)	60
5b	3,4-dimethoxybenzaldehyde	**6b**, (70, 83:1:13:3)	57
5b	3,4-methylenedioxybenzaldehyde	**6c**, (77, 82:trace:15:3)	65

[a] Isolated yield and ratios determined by ^1H NMR (see also the Supporting Information). [b] Yield of the pure (3,4-trans)-(4,5-cis) isomer of **6** (TC-**6**) obtained after recrystallization.

SCHEME 1 [a]



5a Ar^1 = Phenyl
5b Ar^1 = 3,4-Dimethoxyphenyl

6a $Ar^1 = Ar^2$ = Phenyl
6b $Ar^1 = Ar^2$ = 3,4-Dimethoxyphenyl
6c Ar^1 = 3,4-Dimethoxyphenyl; Ar^2 = 3,4-Methylenedioxyphenyl

[a] Reagents and conditions: (a) 2 LDA, THF, −78 °C, 1 h; (b) Ar^2CHO, $ZnCl_2$, −78 °C to room temperature, overnight; (c) 2 N HCl.

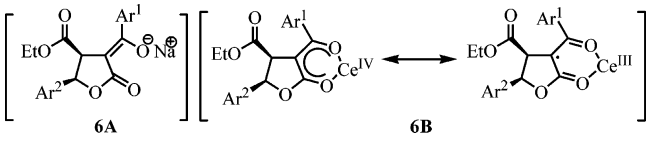


FIGURE 2. Enolate anion **6A** and the proposed cerium complex intermediate **6B** of compound **6**.

diastereomers in 70, 80, and 77% yields, respectively. The pure TC-**6a**−**c** were obtained after recrystallization in 60, 57, and 65% yields, respectively, as shown in Scheme 1 and Table 1.

Having the required starting α-aroylparaconic esters **6** in hand, we carried out the synthesis of *exo*,*endo*-furofurans of types **15** (R = Me) and **16** (R = OH) by base-catalyzed methylation of TC-**6a**−**c** employing NaH and CH_3I in THF[13c] to afford the expected products **7a**−**c** in good yields as a single stereoisomer. The stereoselective methylation of the enolate anion **6A** (Figure 2) derived from TC-**6** occurs from the less-hindered side, to avoid the steric interaction with the carboethoxy group at the 4-position. Similarly, α-hydroxylation of TC-**6a**−**c** could be achieved by treatment with O_2 in the presence of $CeCl_3 \cdot 7H_2O$ in *i*-PrOH[14,15] (for **6a**) or in a 1:1 mixture of *i*-PrOH and DMF (for **6b**,**c**) at 65 °C for 20 h to furnish a single stereoisomer of the corresponding α-hydroxylated products **8a**−**c** in moderate to good yields. This could be explained by the fact that oxygen reacts exclusively with a cerium complex intermediate **6B** (Figure 2) from the less-hindered side.[15] The results are summarized in Scheme 2 and Table 2.

Our next task was to study stereoselective reduction of γ-lactones **7** and **8** to the required hydroxy derivatives **9** and **10** which were expected to undergo lactonization to yield *exo*,*endo*-bislactones **11** and **12**. Good yields of highly stereoselective reduction of **7a** leading to a mixture of hydroxy γ-lactone **9a** and *exo*,*endo*-bislactone **11a** were achieved by using $NaBH_4$ (3 equiv) and $CeCl_3 \cdot 7H_2O$ (1 equiv) in a 1:1 mixture of CH_2Cl_2/MeOH at 0 °C for 3 h. Both compounds were obtained as a single diastereomer after chromatography. Careful workup of the reaction provided only the hydroxy γ-lactone **9a** in 80% yield after chromatography. By using the same reduction conditions, we prepared hydroxy γ-lactones **9b**,**c** and **10a**−**c** from the corresponding **7b**,**c** and **8a**−**c** in moderate to good yields, as listed in Table 2. Lactonization of **9a**−**c** and **10a**−**c** in the presence of a catalytic amount of *p*-TsOH in CH_2Cl_2 at room temperature furnished the desired *exo*,*endo*-bislactones **11a**−**c** and **12a**−**c** in moderate to excellent yields (Table 2). The relative stereochemistry at positions 5 and 6 of the *exo*,*endo*-bislactones **11a** was assigned by nuclear Overhauser effect (NOE) experiments (Figure 3). A single-crystal X-ray crystallography finally confirmed the relative stereochemistry of **11a**.[16]

TABLE 2. Results Obtained from Scheme 2

TC-6	7 or 8 (%)[a]	9 or 10 (%)[a]	11 or 12 (%)[a]	13 or 14 (%)[a]	15 or 16a and 4 (%)[a]
TC-**6a**	**7a** (95)	**9a** (80)	**11a** (99)	**13a** (65)	**15a** (65)
TC-**6b**	**7b** (74)	**9b** (86)	**11b** (77)	**13b** (63)	**15b** (47)
TC-**6c**	**7c** (90)	**9c** (57)	**11c** (57)	[b]	[b]
TC-**6a**	**8a** (79)	**10a** (80)	**12a** (86)	**14a** (59)	**16a** (62)
TC-**6b**	**8b** (71)	**10b** (73)	**12b** (74)	**14b** (60)	**4** (63)
TC-**6c**	**8c** (48)	**10c** (49)	**12c** (52)	[b]	[b]

[a] Isolated yield. All products were obtained as a single stereoisomer. [b] The reactions were not performed.

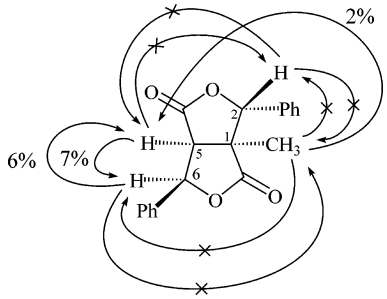


FIGURE 3. Observed NOE for **11a**.

To complete the synthesis of the furofurans **15**, **16a**, and (±)-gmelinol (**4**), reduction of *exo*,*endo*-bislactones **11a**,**b** and **12a**,**b** to tetraols **13a**,**b** and pentaols **14a**,**b**, followed by cyclization to the expected furofurans, has to be achieved. Thus, from reduction of **11a**,**b** and **12a**,**b**, the compounds **13a**,**b** and **14a**,**b**, respectively, were obtained in 59−65% yields by employing lithium aluminum hydride in refluxing tetrahydrofuran. Cyclization of **13a** to the expected furofurans was first attempted with methanesulfonyl chloride in a mixture of pyridine and CH_2Cl_2[17] at 0 °C to provide *exo*,*endo*-furofuran **15a** in 65% yield

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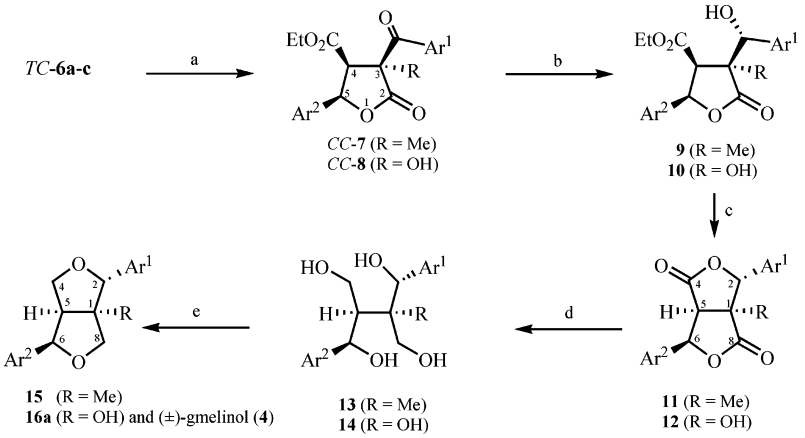
SCHEME 2. Synthesis of Compounds 7−16[a]



[a] Reagents and conditions: (a) 1 equiv of NaH, 0 °C, 1 h, then 2 equiv of MeI, 0 °C to room temperature, 16 h for the preparation of **7**, and 40 mol % of $CeCl_3 \cdot 7H_2O$, O_2, *i*-PrOH/DMF (1:1), reflux, 20 h for the preparation of **8**; (b) 3 equiv of $NaBH_4$, 1 equiv of $CeCl_3 \cdot 7H_2O$, 65 °C, CH_2Cl_2/MeOH (1:1), 0 °C, 3 h; (c) *p*-TsOH (cat.), CH_2Cl_2, room temperature, 24 h; (d) 10 equiv of $LiAlH_4$, THF, 65 °C, 5 h; (e) 5 equiv of MsCl, pyridine, CH_2Cl_2, 0 °C to room temperature, 16 h.

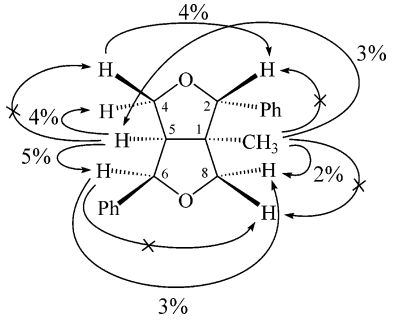


FIGURE 4. Observed NOE for **15a**.

after purification. A low yield of **15a** was achieved when *p*-toluenesulfonyl chloride in a mixture of pyridine and CH_2Cl_2 was used. Under the standard conditions, 1-substituted *exo*,*endo*-furofurans **15a**,**b**, **16a**, and **4** were prepared in 47−65% yields. The relative stereochemistries at positions 5 and 6 of **15a**,**b**, **16a**, and **4** were assigned by analysis of the coupling constants between H-5 and H-6 (J_{cis} = 6.2−6.5 Hz) that appeared as doublets for each proton at δ 4.99−5.27 ppm in the ^{1}H NMR spectra. The exo,endo stereochemistry of **15a** was supported by NOE experiments (Figure 4), and single X-ray crystallographic data of **4** confirmed its relative stereochemistry.[16]

The spectral data (^{1}H and ^{13}C NMR, IR) of our synthetic product (±)-*exo*,*endo*-furofuran **4** are identical with those of the antimalarial agent gmelinol, previously isolated from the heartwood of *Gmelina vitiensis*.[5,6]

In conclusion, we have developed a general method for the preparation of 1-methylated and 1-hydroxylated *endo*,*exo*-furofurans, including (±)-gmelinol (**4**) starting from (3,4-*trans*)-(4,5-*cis*)-α-aroylparaconic esters. This method is amenable to a considerable variation because both aryl groups of α-aroylparaconic esters can be varied, and the introduction of an α-substituent at the 3-position of these compounds can be easily prepared with high diastereoselectivity. The syntheses of other furofuran lignans both in racemic and enantiomeric forms related to gmelinol are in progress.

Experimental Section

Preparation of Ethyl (2*R,3*R**,4*R**)-4-Hydroxy-4-(3,4-dimethoxybenzoyl)-2-(3,4-dimethoxyphenyl)-5-oxotetrahydrofuran-3-carboxylate (8b).** A pure diastereomer TC-**6b** (212.2 mg, 0.4629 mmol) was added to a suspension of $CeCl_3 \cdot 7H_2O$ (69.0 mg, 0.1852 mmol) in 2-propanol (1.5 mL) and DMF (1.5 mL). The flask was evacuated twice and flushed with O_2 each time, and the reaction mixture was stirred for 20 h at 65 °C under flush of O_2. The mixture was diluted with water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the crude product was purified by preparative thin-layer chromatography (SiO_2, 40% EtOAc in hexanes) to give a white solid of CC-**8b** [156.7 mg, 71% yield; mp 178−179 °C (EtOAc −hexanes)]. IR (Nujol): ν_{max} 3294s, 1789s, 1720s, 1655m, 1593m, 1578m, 1518s, 1464s cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD): δ 7.95 (dd, J = 8.6, 2.0 Hz, 1H), 7.64 (d, J = 2.0 Hz, 1H), 6.90−6.75 (m, 4H), 5.97 (d, J = 6.0 Hz, 1H), 3.90, 3.88, 3.85, 3.81 (each s, 3H), 3.70 (d, J = 6.0 Hz, 1H), 3.63 (q, J = 7.1 Hz, 2H), 0.77 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD): δ 192.9, 172.2, 168.6, 154.3, 149.7, 149.4, 149.0, 127.7, 127.4, 126.8, 118.8, 113.3, 111.5, 110.4, 109.5, 84.6, 79.3, 61.6, 60.1, 56.6, 56.5, 56.4, 13.9. MS: *m*/*z* (%) relative intensity 475 (M^+ + 1, 4), 474 (M^+, 16), 236 (15), 182 (15), 166 (29), 165 (100). HRMS (ESI-TOF): calcd for $C_{24}H_{26}O_{10}Na$ (M^+ + Na), 497.1424; found, 497.1418.

Preparation of Ethyl (2*R,3*R**,4*R**)-4-Hydroxy-4-[α-(*R**)-hydroxy-3,4-dimethoxybenzyl]-2-(3,4-dimethoxyphenyl)-5-oxotetrahydrofuran-3-carboxylate (10b).** A solution of $CeCl_3 \cdot 7H_2O$ (1.7479 g, 4.6913 mmol) in methanol (4.5 mL) was added to a solution of CC-**8b** (1.4856 g, 3.1312 mmol) in a mixture of methanol (15 mL) and CH_2Cl_2 (15 mL). $NaBH_4$ (355.5 mg, 9.3973 mmol) was then slowly added at 0 °C under an argon atmosphere. After stirring for 3 h at 0 °C, the reaction mixture was quenched with a saturated NH_4Cl solution (25 mL) and diluted with water (50 mL), and 2 N HCl was added until the reaction mixture became clear. The mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 40% EtOAc in hexanes) to give a white solid of **10b** as a single isomer [1.0833 g, 73% yield; mp 189−190 °C (EtOAc−hexanes)]. IR (Nujol): ν_{max} 3482s, 1782s, 1723s, 1606w, 1593w, 1514s, 1463s cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD): δ 7.21 (app. d, J = 1.4 Hz, 1H), 7.13−7.09 (m, 1H),

7.00−6.93 (m, 4H), 5.91 (d, J = 5.4 Hz, 1H), 5.11 (s, 1H), 3.87 (s, 3H), 3.83 (s, 6H), 3.82 (s, 3H), 3.80−3.68 (m, 2H), 3.50 (d, J = 5.4 Hz, 1H), 0.84 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): δ 173.9, 169.1, 148.7, 148.7, 148.6, 148.3, 130.7, 127.1, 120.8, 117.9, 111.7, 110.8, 110.4, 108.6, 80.6, 79.1, 72.8, 60.7, 57.9, 55.7, 55.7, 13.3. MS: *m*/*z* (%) relative intensity 474 (M^+, 0.1), 310 (45), 219 (30), 191 (100), 167 (45), 166 (56), 165 (89), 151 (59), 139 (47). Anal. Calcd for $C_{24}H_{28}O_{10}$: C, 60.50; H, 5.92. Found: C, 60.20; H, 5.92.

Preparation of (1*R,2*R**,5*R**,6*R**)-2,6-Bis(3,4-dimethoxyphenyl)-1-hydroxy-4,8-dioxo-3,7-dioxabicyclo[3.3.0]octane (12b).** A solution of **10b** (1.0833 g, 2.2832 mmol) in CH_2Cl_2 (22 mL) and a catalytic amount of *p*-TsOH·H_2O (183.2 mg, 0.9631 mmol) was stirred at room temperature overnight (16 h) under an argon atmosphere. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 40% EtOAc in hexanes) to give a white solid of **12b** [0.8054 g, 74% yield; mp 208−209 °C (EtOAc−hexanes)]. IR (Nujol): ν_{max} 3411w, 1770s, 1609w, 1594w, 1524s, 1463s cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD): δ 7.05−6.94 (m, 2H), 6.93−6.80 (m, 4H), 5.73 (s, 1H), 5.68 (d, J = 5.3 Hz, 1H), 3.87 and 3.86 (each s, 3H), 3.85 (s, 3H), 3.60 (d, J = 5.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): δ 174.4, 173.0, 149.8, 149.7, 149.4, 149.0, 129.2, 124.2, 119.4, 118.7, 111.1, 111.0, 110.0, 108.7, 84.4, 81.1, 79.7, 77.2, 55.9, 55.8, 55.7. MS: *m*/*z* (%) relative intensity 430 (M^+, 5), 428 (53), 234 (47), 218 (61), 205 (44), 204 (42), 203 (32), 167 (38), 165 (100). HRMS (ESI-TOF): calcd for $C_{22}H_{22}O_9Na$ (M^+ + Na), 453.1162; found, 453.1146.

Preparation of (1*R,2*S**,3*R**,4*R**)-2,3-Bis(hydroxymethyl)-1,4-bis(3,4-dimethoxyphenyl)- 2-hydroxybutane-1,4-diol (14b).** A solution of **12b** (63.9 mg, 0.1485 mmol) in THF (2 mL) was slowly added to a suspension of $LiAlH_4$ (56.3 mg, 1.4846 mmol) in THF (2 mL) at 65 °C under an argon atmosphere. After refluxing for 5 h, the reaction mixture was allowed to cool to 0 °C, quenched with 10% NaOH (3 mL) and water (15 mL), and stirred for an additional 10 min. The insoluble materials were filtered through a Celite pad and eluted with THF. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 40% EtOAc in hexanes) to give a yellow solid of **14b** [38.9 mg, 60% yield; mp 182−183 °C (EtOAc−hexanes)]. IR (Nujol): ν_{max} 3553s, 3261s, 1610w, 1592m, 1516s, 1464s cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD): δ 7.21 (s, 1H), 7.07−6.85 (m, 5H), 5.34 (s, 1H), 4.95 (s, 1H), 3.92 (dd, J = 12.4, 6.9 Hz, 1H), 3.87−3.77 (m, 1H), 3.84, 3.82, 3.81 and 3.80 (each s, 3H), 3.62 (d, J = 11.7 Hz, 1H), 3.57 (d, J = 11.7 Hz, 1H), 2.33 (app. d, J = 6.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD): δ 150.2, 149.84, 149.79, 149.1, 139.3, 135.2, 122.2, 118.9, 113.6, 112.6, 112.0, 110.8, 79.0, 76.6, 72.4, 65.7, 59.3, 56.6, 56.5, 56.4, 53.3. MS: *m*/*z* (%) relative intensity, 438 (M^+ + 1, 0.1), 177 (33), 167 (100), 166 (50), 151 (37), 139 (82). HRMS (ESI-TOF): calcd for $C_{22}H_{30}O_9Na$ (M^+ + Na), 461.1788; found, 461.1788.

Preparation of (1*R,2*R**,5*R**,6*R**)-2,6-Bis(3,4-dimethoxyphenyl)-1-hydroxy-3,7-dioxabicyclo[3.3.0]octane [(±)-gmelinol][5] (4).** To a solution of **14b** (74.0 mg, 0.1688 mmol) in CH_2Cl_2 (2 mL) containing a pyridine (0.2 mL, 2.4955 mmol) was added a solution of MsCl (0.1 mL, 1.3196 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred and slowly warmed to room temperature overnight (16 h). The mixture was diluted with NH_4Cl (10 mL) and water (10 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 60% EtOAc in hexanes) to give a white solid of (±)-gmelinol (**4**) [43.1 mg, 63% yield; mp 153−154 °C (EtOAc−hexanes)]. IR (Nujol): ν_{max} 3544s, 1607w, 1590m, 1519s, 1461s cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.00−6.80 (m, 6H), 5.23 (d, J = 6.3 Hz, 1H), 4.60 (s, 1H), 4.23 (d, J = 9.3 Hz, 1H), 3.98 (dd, J = 9.3, 9.3 Hz, 1H), 3.92 and 3.91 (each s, 3H), 3.90 (s, 6H), 3.72 (d, J = 9.3 Hz, 1H), 3.32 (dd, J = 9.3, 9.3 Hz, 1H), 3.18−3.08 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.5, 149.5, 149.0, 148.2, 130.6, 127.7, 119.1, 117.7, 111.5, 111.2, 110.1, 109.0, 90.9, 88.9, 81.3, 75.9, 68.5, 57.4, 56.0, 55.99, 55.95. MS: *m*/*z* (%) relative intensity 403 (M^+ + 1, 15), 402 (M^+, 65), 221 (57), 179 (58), 177 (100), 166 (46), 165 (89), 151 (87).

Acknowledgment. We thank the Thailand Research Fund for financial support to M.P. (BRG/22/2544) and P.K. (TRF4780020 and RSA4780020), as well as for the award of a Senior Research Scholar to V.R. Thanks are also made to the Higher Education Development Project, Postgraduate Education and Research Program in Chemistry (PERCH), for support.

Supporting Information Available: General experimental details and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0519110