First Total Synthesis of Mappain with a Prenylated and Geranylated Stilbene

by **Lakkoju Chakrapani**, **Eun Mi Jung**, and **Yong Rok Lee***

School of Chemical Engineering and Technology, Yeungnam University, Gyeongsan 712-749, Korea
(phone: +82-53-810–2529; fax: +82-53-810-4631; e-mail: yrlee@yu.ac.kr)

The first total synthesis of naturally occurring mappain has been achieved by a convergent sequence. The key strategy involved in the synthesis of mappain was a (*E*)-stilbene formation by *Horner–Wadsworth–Emmons* reaction of the corresponding prenylated benzaldehyde with a geranylated benzyl phosphonate.

Introduction. – Molecules bearing the stilbene moiety are widely found in nature [1], and have a variety of interesting biological activities and properties, including antimicrobial [2], antimalarial [3], antioxidant [4], antileukemic [5], anti-platelet aggregative [6], anticarcinogenic [7], anti-HIV [8], protein tyrosine kinase inhibitory [9], anti-inflammatory [10], antimutagenic [11], antifungal [12], and hepatoprotective [13] activities. In the course of the investigation to identify new anticancer lead compounds from Asian botanical sources, mappain (**1**) with a prenylated and geranylated stilbene was isolated from the leaves of *Macaranga mappa* (*Fig.*) [14]. The lipophilic crude extract of these leaves has shown potent cytotoxicity against both drug-resistant (SKVLB-1) and drug-sensitive (SK-OV-3) ovarian cancer cell lines with an IC_{50} value of 3.5 μg/ml [14].

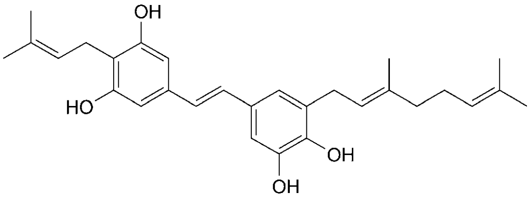


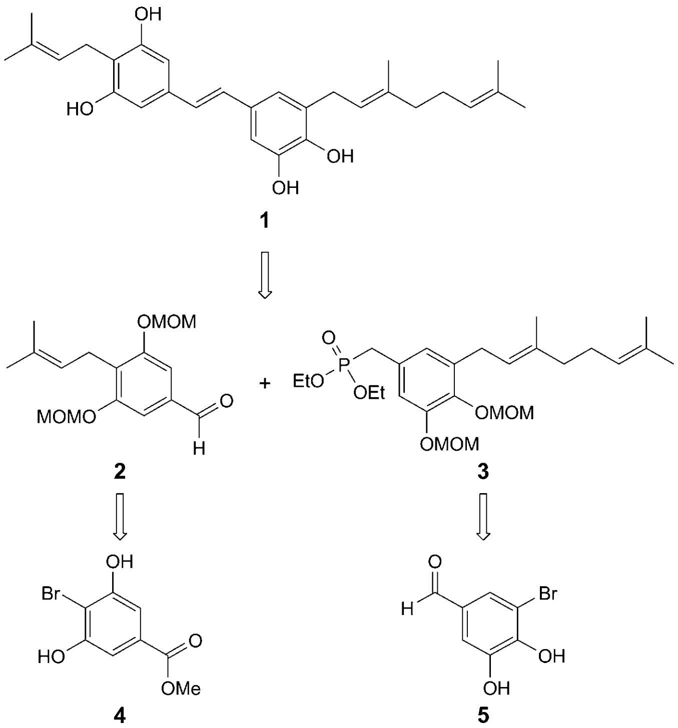
Figure. *Structure of mappain* (**1**)

This range of important biological activities and properties has stimulated research of the total synthesis of mappain (**1**). Even though the structure of this natural product was well-established by spectroscopic analysis, its total synthesis remained unreported.

Recently, we developed efficient and useful synthetic routes for preparing stilbenes [15]. As part of an ongoing study of the efficacy of this synthetic approach, the synthesis of **1** with a prenylated and geranylated stilbene moiety has been attempted. Herein, the first total synthesis of the naturally occurring mappain (**1**) is reported.

Results and Discussion. – In *Scheme 1*, the retrosynthetic analysis for mappain (**1**) through disconnection is shown. Mappain (**1**) could be prepared by a *Horner–Wadsworth–Emmons* reaction of the arene-carbaldehyde **2** and the benzyl phosphonate **3**. Benzaldehyde **2** can be prepared from readily available methyl 4-bromo-3,5-dihydroxybenzoate (**4**), while phosphonate **3** can be derived from 3-bromo-4,5-dihydroxybenzaldehyde (**5**).

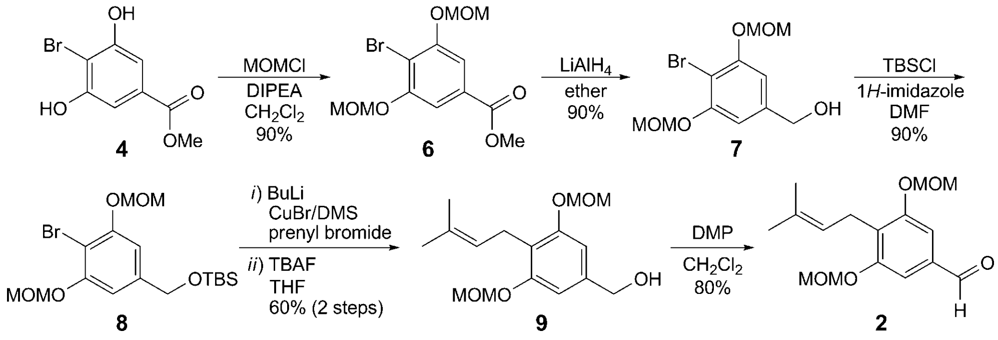
Scheme 1



The synthetic approach of benzaldehyde **2** as the left half of **1** is shown in *Scheme 2*. Protection of ester **4** with methoxymethyl chloride (MOMCl) in the presence of *N*,*N*-diisopropylethylamine (DIPEA) to give **6**, followed by reduction with LiAlH$_4$, provided benzyl alcohol **7** in 81% yield (two steps). Reaction of **7** with ^{t}BuMe$_2$SiCl (TBSCl) proceeded smoothly to afford silyl ether **8** in 90% yield. Transmetallation of **8** with BuLi in the presence of CuBr/dimethyl sulfide complex [16], followed by addition of prenyl bromide to trap the intermediate anion derived from halogen–metal exchange, afforded the expected prenylated compound, which was cleavaged with Bu$_4$NF (TBAF) to give benzyl alcohol **9** in 60% yield (two steps). Oxidation of **9** with *Dess–Martin* periodinane (DMP) finally provided benzaldehyde **2** in 80% yield (*cf.* [17]).

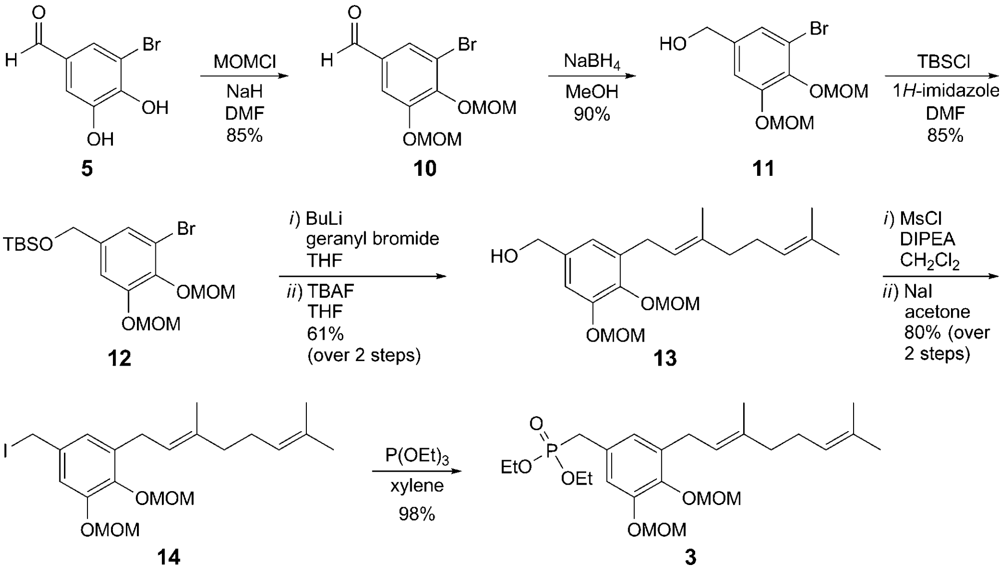
As shown in *Scheme 3*, the synthesis of phosphonate **3** as the right half of **1** began with the readily available 3-bromo-4,5-dihydroxybenzaldehyde (**5**). Reaction of **5** with 2.2 equiv. of MOMCl in the presence of NaH afforded compound **10** in 85% yield.

Scheme 2



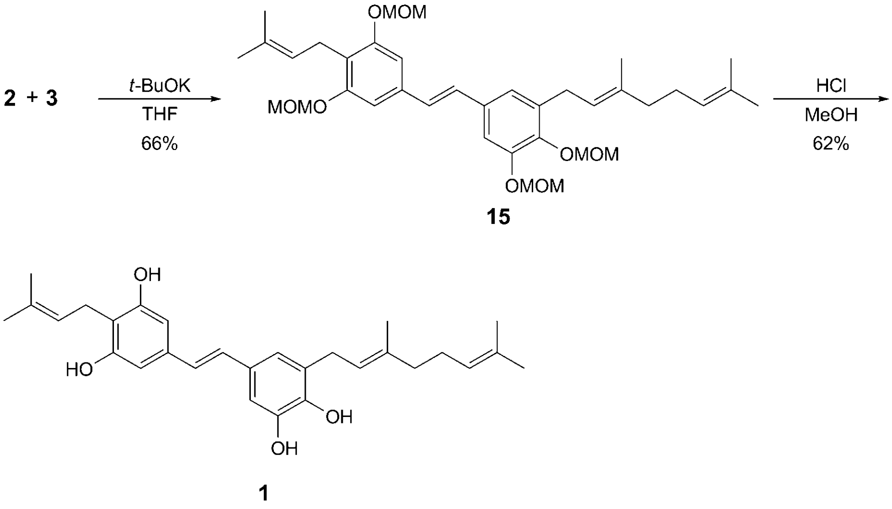
Reduction of **10** with $NaBH_4$ in MeOH gave benzyl alcohol **11** in 90% yield. Treatment of **11** with TBSCl in the presence of 1*H*-imidazole gave silyl ether **12** in 85% yield. Compound **13** was produced in 61% yield (two steps) by halogen–metal exchange and alkylation reaction using BuLi with geranyl bromide in THF, followed by cleavage of the silyl ether with TBAF in THF. Alcohol **13** was then converted to the corresponding iodide **14** (80%, two steps) by formation of the methanesulfonate, followed by displacement with NaI. Reaction of **14** with $P(OEt)_3$ in refluxing xylene for 12 h afforded the desired phosphonate **3** in 98% yield (*cf.* [18]).

Scheme 3



To complete the total synthesis of natural mappain (**1**), stilbene formation was carried out as shown in *Scheme 4*. The *Horner–Wadsworth–Emmons* reaction of benzaldehyde **2** with phosphonate **3** in the presence of *t*-BuOK in THF gave the desired (*E*)-stilbene **15** in 66% yield (*cf.* [19]). Deprotection of the four MOM ether groups of compound **15** with concentrated HCl in MeOH at room temperature for 12 h afforded mappain (**1**) in 62% yield. The spectral data of synthetic material **4** were in agreement with those reported in [14].

Scheme 4



Conclusions. – The first total synthesis of mappain (**1**) has been accomplished by a convergent sequence. The key strategy for the synthesis of mappain (**1**) was the (*E*)-stilbene formation by a *Horner–Wadsworth–Emmons* reaction of benzaldehyde **2** and phosphonate **3**, synthesized from readily available benzoate **4** and 3-bromo-4,5-dihydroxybenzaldehyde (**5**), respectively, in a straightforward fashion.

This work was supported by grant No. RTI04-01-04 from the *Regional Technology Innovation Program of the Ministry of Knowledge Economy* (*MKE*).

Experimental Part

General. All experiments were carried out under N_2. Anal. TLC: *Merck* pre-coated SiO_2 plates (Art. 5554) with a fluorescent indicator. Flash column chromatography (FCC): SiO_2 *9385*. IR Spectra: *Jasco FTIR 5300* spectrophotometer. ^1H- and ^{13}C-NMR spectra: *Bruker Model ARX* (300 and 75 MHz, resp.) spectrometer; in $CDCl_3$ as the solvent. HR Mass spectra were recorded at the *Korea Basic Science Institute.*

Methyl 4-Bromo-3,5-bis(methoxymethoxy)benzoate (**6**). $MeOCH_2Cl$ (3.0 g, 37.5 mmol) was added to a soln. of **4** (3.70 g, 15.0 mmol) and DIPEA ($EtN(i\text{-}Pr)_2$; 9.675 g, 75.0 mmol) in dry CH_2Cl_2 (50 ml) at r.t. The mixture was refluxed for 6 h, and then H_2O (50 ml) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 ml), and the combined org. extracts were washed with sat. NH_4Cl soln. (50 ml) and then H_2O (30 ml). The org. layers were dried (anh. Na_2SO_4), and removal of solvent at reduced pressure left an oily residue, which was then purified by CC (SiO_2; hexane/AcOEt 5 :1) to give **6** (4.50 g, 90%). Solid. M.p. 128–129°. IR (KBr): 2938, 2834, 1722, 1592, 1436, 1320, 1242, 1156, 1045, 903, 762. ^1H-NMR ($CDCl_3$, 300 MHz): 7.46 (*s*, 2 H); 5.28 (*s*, 4 H); 3.88 (*s*, 3 H); 3.50 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 166.1; 154.8; 130.3; 109.9; 109.4; 95.05; 56.5; 52.4. HR-MS: 334.0050 (M^+, $C_{12}H_{15}BrO_6^+$; calc. 334.0052).

[4-Bromo-3,5-bis(methoxymethoxy)phenyl]methanol (**7**). To a soln. of **6** (3.35 g, 10.0 mmol) in dry Et_2O (20 ml), $LiAlH_4$ (0.76 g, 20.0 mmol) was added carefully at 0°, and the mixture was stirred at r.t. for 2 h. The reaction was quenched by the addition of H_2O (40 ml), and the mixture was extracted with AcOEt (3 × 30 ml). The org. layer was washed with sat. NH_4Cl soln. (30 ml), then dried (anh. Na_2SO_4), and concentrated under reduced pressure to afford the crude residue. The resulting residue was purified by FCC (SiO_2; hexane/AcOEt 3 : 1) to give **7** (2.76 g, 90%). Liquid. IR (neat): 3252, 3150, 2953, 1592, 1443, 1311, 1243, 1157, 1041, 916, 831, 692, 645. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.30 (*s*, 2 H); 5.72 (*s*, 4 H); 5.06 (*s*, 2 H); 4.00 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 154.7; 141.8; 107.5; 102.5; 94.8; 64.4; 56.3. HR-MS: 306.0101 (M^+, $C_{11}H_{15}BrO_5^+$; calc. 306.0103).

*{[4-Bromo-3,5-bis(methoxymethoxy)benzyl]oxy}(*tert*-butyl)dimethylsilane* (**8**). To a soln. of **7** (1.53 g, 5.0 mmol) in dry DMF (10 ml), 1*H*-imidazole (0.85 g, 12.5 mmol), and TBSCl (^{t}BuMe$_2$SiCl; 0.90 g, 6.0 mmol) were added. The mixture was stirred for 10 h. The reaction was quenched by the addition of H_2O (40 ml), and the mixture was extracted with AcOEt (3 × 30 ml). The org. layer was washed with sat. NH_4Cl soln. (30 ml), dried (anh. Na_2SO_4), and concentrated under reduced pressure to afford the crude residue. The resulting residue was purified by FCC (SiO_2; hexane/AcOEt 7 : 1) to give **8** (1.80 g, 90%). Liquid. IR (neat): 2952, 1677, 1589, 1445, 1255, 1157, 1103, 1051, 922, 843, 779, 684. ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.82 (*s*, 2 H); 5.21 (*s*, 4 H); 4.65 (*s*, 2 H); 3.47 (*s*, 6 H); 0.91 (*s*, 9 H); 0.06 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 154.6; 142.4; 106.8; 101.4; 94.9; 64.3; 56.2; 25.7; 18.2; − 5.4. HR-MS: 420.0969 (M^+, $C_{17}H_{29}BrO_5Si^+$; calc. 420.0968).

[3,5-Bis(methoxymethoxy)-4-(3-methylbut-2-en-1-yl)phenyl]methanol (**9**). To a soln. of **8** (0.42 g, 1.0 mmol) in dry THF (10 ml) at − 78°, BuLi (0.48 ml, 2.5M in hexane, 1.2 mmol) was added, and the mixture was stirred for 1 h. Then, CuBr/DMS complex (0.205 g, 1.0 mmol) was added in one portion, the resulting soln. was stirred for 20 min, and then prenyl bromide (0.224 g, 1.5 mmol) was added dropwise. The mixture was stirred at − 78° for 2 h and allowed to stirred for 10 h at r.t. The org. layer was washed with sat. NH_4Cl soln. (30 ml), dried (anh. Na_2SO_4) and concentrated under reduced pressure to afford a crude residue. To the soln. of the crude residue in THF (10 ml), TBAF (1.5 mmol) was added at 0°, and the mixture was stirred at r.t. for 3 h. The reaction was quenched by the addition of sat. NH_4Cl soln. (30 ml), and the mixture was extracted with AcOEt (3 × 30 ml). The org. layer was washed with H_2O (30 ml), dried (anh. Na_2SO_4), and concentrated under reduced pressure to afford the crude residue, which was purified by CC (SiO_2; hexane/AcOEt 4 : 1) to afford **9** (0.178 g, 60%). Liquid. IR (neat): 3432, 2917, 1593, 1439, 1294, 1153, 1047, 927, 845, 693. ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.78 (*s*, 2 H); 5.17 – 5.13 (*m*, 1 H); 5.14 (*s*, 4 H); 4.56 (*s*, 2 H); 3.44 (*s*, 6 H); 3.35 (*d*, $J = 7.2$, 2 H); 1.76 (*s*, 3 H); 1.63 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 155.6; 140.0; 131.0; 122.7; 119.2; 106.3; 94.2; 65.3; 55.9; 25.7; 22.6; 17.7. HR-MS: 296.1626 (M^+, $C_{16}H_{24}O_5^+$; calc. 296.1624).

3,5-Bis(methoxymethoxy)-4-(3-methylbut-2-en-1-yl)benzaldehyde (**2**). To a stirred soln. of **9** (0.318 g, 1.1 mmol) in dry CH_2Cl_2 (10 ml) was added *Dess–Martin* periodane (0.458 g, 1.1 mmol) at 0°, and the mixture was stirred at r.t. for 3 h. The reaction was quenched with sat. $NaHCO_3$ soln. (30 ml), and the mixture was extracted with CH_2Cl_2 (3 × 30 ml). The org. layers were washed with sat. sodium thiosulfate soln. (20 ml) and H_2O (30 ml), dried (anh. Na_2SO_4), and concentrated under reduced pressure to afford a crude residue. The resulting residue was purified by CC (SiO_2; hexane/AcOEt 9 : 1) to afford **2** (0.235g, 80%). Liquid. IR (neat): 3380, 2917, 2832, 2728, 1697, 1585, 1444, 1381, 1295, 1156, 1050, 934, 852, 732, 658. ^{1}H-NMR ($CDCl_3$, 300 MHz): 9.85 (*s*, 1 H); 7.28 (*s*, 2 H); 5.24 (*s*, 4 H); 5.13 (*t*, $J =$ 7.0, 1 H); 3.46 (*s*, 6 H); 3.41 (*d*, $J = 7.0$, 1 H); 1.77 (*s*, 3 H); 1.64 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 191.7; 155.9; 135.4; 132.2; 127.3; 121.3; 108.8; 94.3; 56.1; 25.8; 23.2; 17.8. HR-MS: 294.1469 (M^+, $C_{16}H_{22}O_5^+$; calc. 294.1467).

3-Bromo-4,5-bis(methoxymethoxy)benzaldehyde (**10**). To a stirred soln. of *5-bromo-3,4-dihydroxybenzaldehyde* (**5**; 2.0 g, 9.2 mmol) in dry DMF (40 ml) at 0° was added NaH (2.20 g, 92.0 mmol), and the soln. was stirred for 10 min. To the mixture, MOMCl (1.840 g, 23.0 mmol) was added slowly, and the reaction was run for 1 h. The reaction was quenched by the addition of H_2O (30 ml), and the mixture was extracted with AcOEt (3 × 50 ml). The org. layer was washed with sat. NH_4Cl soln. (30 ml), dried (anh. Na_2SO_4), and concentrated under reduced pressure to afford a crude residue. FCC (SiO_2; hexane/AcOEt 5 : 1) afforded **10** (2.380 g, 85%). Liquid. IR (neat): 2956, 2833, 1696, 1568, 1478, 1380, 1276, 1158, 1082, 1011, 936, 745, 669. ^{1}H-NMR ($CDCl_3$, 300 MHz): 9.80 (*s*, 1 H); 7.70 (*s*, 1 H); 7.57 (*s*, 1 H); 5.26 (*s*, 2 H);

5.22 (*s*, 2 H); 3.61(*s*, 3 H); 3.46 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 189.5; 151.1; 149.2; 133.1; 128.7; 118.3; 115.2; 98.8; 95.1; 58.0; 56.5. HR-MS: 303.9948 (M^+, $C_{11}H_{13}BrO_5^+$; calc. 303.9946).

[3-Bromo-4,5-bis(methoxymethoxy)phenyl]methanol (**11**). To a stirred soln. of **10** (1.0 g, 3.3 mmol) in MeOH at 0° was added $NaBH_4$ (0.186 g, 4.9 mmol) in small portions, and the reaction was run for 1 h. The reaction was quenched by the addition of H_2O (30 ml), and the mixture was extracted with AcOEt (3 × 40 ml). The org. layer was washed with sat. NH_4Cl soln. (40 ml), dried (anh. Na_2SO_4), and concentrated under reduced pressure to afford a crude residue. FCC (SiO_2; hexane/AcOEt 3:1) afforded **11** (0.90 g, 90%). Liquid. IR (neat): 3430, 2935, 1569, 1481, 1275, 1157, 1006, 949, 852, 676. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.17 (*s*, 1 H); 7.05 (*s*, 1 H); 5.15 (*s*, 2 H); 5.13 (*s*, 2 H); 4.54 (*s*, 2 H); 3.62 (*s*, 3 H); 3.45 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 150.9; 143.2; 138.4; 124.5; 117.8; 114.2; 98.8; 95.2; 64.1; 57.9; 56.4. HR-MS: 306.0103 (M^+, $C_{11}H_{15}BrO_5^+$; calc. 306.0103).

*{[3-Bromo-4,5-bis(methoxymethoxy)benzyl]oxy}(*tert*-butyl)dimethylsilane* (**12**). To a stirred soln. of **11** (0.80 g, 2.6 mmol) in dry DMF (10 ml) at 0° was added 1*H*-imidazole (0.443 g, 6.5 mmol), and the mixture was stirred for 10–15 min. TBSCl (0.471 g, 3.1 mmol) was added carefully, and the mixture was allowed to stirred at r.t. for 10 h. The reaction was quenched by the addition of H_2O (30 ml), and the mixture was extracted with AcOEt (3 × 30 ml). The org. layer was washed with sat. NH_4Cl soln. (30 ml), dried (anh. Na_2SO_4), and concentrated under reduced pressure to give a crude residue. FCC (SiO_2; hexane/AcOEt 4:1) afforded **12** (0.932 g, 85%). Liquid. IR (neat): 2952, 1570, 1479, 1262, 1158, 1093, 1011, 954, 842, 675. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.14 (*s*, 1 H); 7.06 (*s*, 1 H); 5.15 (*s*, 2 H); 5.14 (*s*, 2 H); 4.61 (*s*, 2 H); 3.63 (*s*, 3 H); 3.46 (*s*, 3 H); 0.92 (*s*, 9 H); 0.07 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 150.8; 142.7; 138.9; 123.6; 117.5; 113.5; 98.8; 95.2; 63.9; 57.9; 56.2; 25.9; 18.3; −5.3. HR-MS: 420.0970 (M^+, $C_{17}H_{29}BrO_5Si^+$; calc. 420.0968).

*{3-[(2*E*)-3,7-Dimethylocta-2,6-dien-1-yl]-4,5-bis(methoxymethoxy)phenyl}methanol* (**13**). To a soln. of **12** (0.80 g, 1.9 mmol) in dry THF (10 ml) at −78° was added BuLi (0.9 ml, 2.5M in hexane, 2.3 mmol), and the mixture was stirred for 1 h. To the mixture was added geranyl bromide (0.618 g, 2.85 mmol) slowly *via* syringe, and the reaction was run at the same temp. for 2 h. Then, the mixture was stirred at 0° for 12 h, and the reaction was quenched by the addition of H_2O (30 ml), and the mixture was extracted with AcOEt (3 × 30 ml). The org. layer was washed with sat. NH_4Cl soln. (30 ml), dried (anh. Na_2SO_4), and concentrated under reduced pressure to afford a crude residue. To the soln. of the crude residue in THF (10 ml) was added TBAF (1.9 ml, 1.9 mmol, 1.0M in THF) at 0°, and the soln. was stirred at r.t. for 3 h. The reaction was quenched by the addition of sat. NH_4Cl soln. (30 ml), and the mixture was extracted with AcOEt (3 × 30 ml). The org. layer was washed with H_2O (30 ml), dried (anh. Na_2SO_4), and concentrated under reduced pressure to give a crude residue, which was purified by CC (hexane/AcOEt 4:1) to afforded **13** (0.423 g, 61%). Liquid. IR (neat): 3456, 2924, 1597, 1447, 1297, 1155, 1042. ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.98 (*s*, 1 H); 6.81 (*s*, 1 H); 5.28 (*t*, $J = 7.2$, 1 H); 5.16 (*s*, 2 H); 5.07 (*s*, 3 H); 4.55 (*s*, 2 H); 3.57 (*s*, 3 H); 3.47 (*s*, 3 H); 3.40 (*d*, $J = 7.2$, 2 H); 2.14–1.98 (*m*, 4 H); 1.69 (*s*, 3 H); 1.65 (*s*, 3 H); 1.57 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 149.6; 143.9; 137.0; 136.1; 135.9; 131.2; 124.1; 122.4; 121.4; 112.6; 98.9; 94.9; 64.8; 57.3; 56.0; 39.6; 28.3; 26.5; 25.5; 17.5; 16.0. HR-MS: 364.2252 (M^+, $C_{21}H_{32}O_5^+$; calc. 364.2250).

*1-[(2*E*)-3,7-Dimethylocta-2,6-dien-1-yl]-5-(iodomethyl)-2,3-bis(methoxymethoxy)benzene* (**14**). To a soln. of **13** (0.75 g, 2.1 mmol) in CH_2Cl_2 (10 ml) at 0° was added DIPEA (1.329 g, 10.3 mmol), and the soln. was stirred for few min. To the mixture was added MsCl (0.934 g, 8.2 mmol) slowly, and the reaction was continued for 4 h. The reaction was quenched by the addition of H_2O (30 ml), and the mixture was extracted with CH_2Cl_2 (3 × 30 ml). The org. layer was washed with sat. NH_4Cl soln. (30 ml), dried (anh. Na_2SO_4), and concentrated under reduced pressure to afford a crude residue. To the soln. of crude residue in dry acetone (10 ml) was added NaI (1.54 g, 10.3 mmol), and the mixture was stirred at r.t. for further 24 h. The reaction was quenched by the addition of H_2O (30 ml), and the mixture was extracted with AcOEt (3 × 30 ml). The org. layer was washed with sat. $NaHSO_3$ soln. (30 ml), dried (anh. Na_2SO_4), and concentrated under reduced pressure to afford a crude residue. The resulting residue was purified by CC (SiO_2; hexane/AcOEt 10:1) to afford **14** (0.78 g, 80%). Liquid. IR (neat): 2920, 1587, 1481, 1295, 1157, 1036, 968, 652. ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.98 (*d*, $J = 2.0$, 1 H); 6.83 (*d*, $J = 2.0$ Hz, 1 H); 5.27 (*t*, $J = 7.0$, 1 H); 5.15 (*s*, 2 H); 5.09 (*t*, $J = 6.9$, 1 H); 5.07 (*s*, 2 H), 4.37 (*s*, 2 H); 3.57 (*s*, 3 H);

3.50 (*s*, 3 H); 3.36 (*d*, *J* = 7.0, 2 H); 2.11 – 2.01 (*m*, 4 H); 1.68 (*s*, 3 H), 1.67 (*s*, 3 H), 1.59 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 149.6; 144.4; 136.6; 136.3; 134.9; 131.4; 124.2; 123.4; 122.1; 114.5; 98.9; 95.1; 57.4; 56.2; 39.7; 28.3; 26.6; 25.7; 17.7; 16.1; 6.2.

*Diethyl {3-[(2*E*)-3,7-Dimethylocta-2,6-dien-1-yl]-4,5-bis(methoxymethoxy)benzyl}phosphonate* (**3**). To a soln. of **14** (0.50 g, 1.1 mmol) in xylene was added $P(OEt)_3$ (0.266 g, 1.6 mmol), and the mixture was refluxed for 12 h. After the mixture was allowed to cool to r.t., the extra $P(OEt)_3$ was removed under high vacuum. The crude yellow oil was purified by CC (SiO_2; hexane/AcOEt 1 : 2) to afford **3** (0.50 g, 98%). Liquid. IR (neat): 2948, 1590, 1484, 1254, 1158, 1035, 968.5, 799.5, 674.6. ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.90 (*t*, *J* = 2.4, 1 H); 6.71 (*t*, *J* = 2.4, 1 H); 5.25 (*t*, *J* = 7.0, 1 H); 5.13 (*s*, 2 H); 5.08 – 5.03 (*m*, 1 H); 5.03 (*m*, 2 H); 4.04 – 3.93 (*m*, 4 H); 3.55 (*s*, 3 H); 3.45 (*s*, 3 H); 3.35 (*d*, *J* = 7.0, 2 H); 2.98 (*d*, *J* = 21.3, 2 H); 2.07 – 1.97 (*m*, 4 H); 1.66 (*s*, 3 H); 1.63 (*s*, 3 H); 1.55 (*s*, 3 H); 1.23 – 1.18 (*m*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 149.3; 143.4; 135.9; 135.8; 130.9; 127.1; 124.1; 123.9; 122.2; 115.3; 98.7; 94.8; 61.7; 61.6; 57.0; 55.8; 39.4; 33.9; 32.1; 28.0; 26.3; 25.3; 17.3; 16.0; 15.8. HR-MS: 484.2593 (M^+, $C_{25}H_{41}O_7P^+$; calc. 484.2590).

*5-{(*E*)-2-[3,5-Bis(methoxymethoxy)-4-(3-methylbut-2-en-1-yl)phenyl]ethenyl}-1-[(2*E*)-3,7-dimethylocta-2,6-dien-1-yl]-2,3-bis(methoxymethoxy)benzene*; **15**). To a soln. of **2** (0.191 g, 0.4 mmol) in dry THF (10 ml), *t*-BuOK (0.219 g, 2.0 mmol) was added in one portion, and the mixture was stirred for few min at 0°. To the mixture was added **3** (0.127 g, 0.4 mmol) in THF (1 ml) slowly, and the mixture was stirred at r.t. for 10 h. The reaction was quenched by the addition of H_2O (30 ml), and the mixture was extracted with AcOEt (3 × 30 ml). The org. layers were washed with sat. NH_4Cl soln. (30 ml), dried (anh. Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by CC (SiO_2; hexane/AcOEt 1 : 1) to give **15** (0.097 g, 66%). Liquid. IR (neat): 2921, 1583, 1673, 1444, 1158, 1049, 1099, 970, 856, 740. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.13 (*s*, 1 H,); 6.95 – 6.89 (*m*, 5 H); 5.32 (*t*, *J* = 6.9, 1 H); 5.21 (*s*, 6 H); 5.20 – 5.15 (*m*, 2 H); 5.10 (*s*, 2 H); 3.55 (*s*, 3 H); 3.51 (*s*, 3 H); 3.49 (*s*, 6 H); 3.41 (*d*, *J* = 6.9, 2 H); 3.37 (*d*, *J* = 6.9, 2 H); 2.11 – 2.03 (*m*, 4 H); 1.76 (*s*, 3 H); 1.73 (*s*, 3 H); 1.66 (*s*, 3 H); 1.65 (*s*, 3 H); 1.59 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 155.7; 149.9; 144.3; 136.4; 136.1; 133.5; 131.4; 131.0; 128.0; 127.9; 124.2; 122.7; 122.5; 121.7; 119.7; 111.6; 108.0; 106.1; 99.0; 95.0; 94.4; 57.5; 56.2; 55.9; 39.7; 29.2; 26.6; 25.8; 25.7; 22.7; 17.7; 17.6; 16.2. HR-MS: 624.3660 (M^+, $C_{37}H_{52}O_8^+$; calc. 624.3662).

Mappain (*=5-{(*E*)-2-[3,5-Dihydroxy-4-(3-methylbut-2-en-1-yl)phenyl]ethenyl}-3-[(2*E*)-3,7-dimethylocta-2,6-dien-1-yl]benzene-1,2-diol*; **1**). To a stirred soln. of **15** (0.058 g, 0.1 mmol) in MeOH (5 ml) were added 5 drops of conc. HCl at 0°, and the mixture was stirred at r.t. for 12 h. The mixture was diluted with sat. $NaHCO_3$ soln. (30 ml) and extracted with AcOEt (3 × 30 ml). Removal of solvent at reduced pressure left an oily residue, which was then purified by CC (SiO_2; hexane/AcOEt 3 : 1) to give **1** (0.025 g, 62%). Solid. M.p. 99 – 101°. IR (KBr): 3461, 2923, 1611, 1505, 1441, 1044, 852, 740. ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.91 (*d*, *J* = 1.8, 1 H); 6.83 (*d*, *J* = 16.2, 1 H); 6.75 (*d*, *J* = 1.8, 1 H); 6.71 (*d*, *J* = 16.2, 1 H); 6.51 (*s*, 2 H); 5.48 (*s*, 1 H); 5.33 – 5.23 (br. *s*, 2 H), 5.05 – 5.01 (*m*, 1 H), 3.39 (*d*, *J* = 7.0, 2 H); 3.36 (*d*, *J* = 7.0, 2 H); 2.14 – 2.06 (*m*, 4 H); 1.81 (*s*, 3 H); 1.77 (*s*, 3 H); 1.74 (*s*, 3 H); 1.67 (*s*, 3 H); 1.59 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz,): 155.1; 144.3; 142.0; 138.6; 137.1; 135.2; 132.0; 130.0; 128.4; 127.5; 126.1; 123.8; 121.5; 121.4; 120.5; 112.9; 110.6; 106.1; 39.6; 29.6; 26.4; 25.8; 25.7; 22.5; 17.8; 17.7; 16.2. HR-MS: 448.2617 (M^+, $C_{29}H_{36}O_4^+$; calc. 448.2614).

REFERENCES

[1] J. Gorham, M. Tori, Y. Asakawa, 'The Biochemistry of the Stilbenoids', Chapman & Hall, London, 1995; S. He, B. Wu, Y. Pan, L. Jiang, *J. Org. Chem.* **2008**, *73*, 5233; T. Ito, T. Tanaka, M. Iinuma, I. Iliya, K. Nakaya, Z. Ali, Y. Takahashi, R. Sawa, Y. Shirataki, J. Murata, D. Dardaedi, *Tetrahedron* **2003**, *59*, 5347; S. Sotheeswaran, V. Pasupathy, *Phytochemistry* **1993**, *32*, 1083; E.-K. Seo, H. Chai, H. L. Constant, T. Santisuk, V. Reutrakul, C. W. W. Beecher, N. R. Farnsworth, G. A. Cordell, J. M. Pezzuto, A. D. Kinghorn, *J. Org. Chem.* **1999**, *64*, 6976; J.-R. Dai, Y. F. Hallock, J. H. Cardellina II, M. R. Boyd, *J. Nat. Prod.* **1998**, *61*, 351.

[2] M. A. Ali, K. Kondo, Y. Tsuda, *Chem. Pharm. Bull.* **1992**, *40*, 1130.

[3] C. Boonlaksiri, W. Oonanant, P. Kongsaeree, M. Kittakoop, Y. Tanticharoen, Y. Thebtaranonth, *Phytochemistry* **2000**, *54*, 415.

[4] H. Matsuda, T. Morikawa, I. Toguchida, J.-Y. Park, S. Harima, M. Yoshikawa, *Bioorg. Med. Chem.* **2001**, *9*, 41; J.-G. Fang, M. Lu, Z.-H. Chen, H.-H. Zhu, L. Yang, L.-M. Wu, Z.-L. Liu, *Chem. – Eur. J.* **2002**, *8*, 4191.

[5] J. Zheng, V. D. Ramirez, *Biochem. Biophys. Res. Commun.* **1999**, *261*, 499.

[6] F. Orsini, F. Pelizzoni, L. Verotta, T. Aburjai, *J. Nat. Prod.* **1977**, *60*, 1082; T. A. Aburjai, *Phytochemistry* **2000**, *55*, 407.

[7] L.-M. Yang, S.-J. Lin, F.-L. Hsu, T.-H. Yang, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1013.

[8] L.-X. Wang, A. Heredia, H. Song, Z. Zhang, B. Yu, C. Davis, R. Redfield, *J. Pharm. Sci.* **2004**, *93*, 2448; K. Likhitwitayawuid, B. Sritularak, K. Benchanak, V. Lipipun, J. Mathew, R. F. Schinazi, *Nat. Prod. Res.* **2005**, *19*, 177.

[9] K. Thakkar, R. L. Geahlen, M. Cushman, *J. Med. Chem.* **1993**, *36*, 2950.

[10] K.-S. Huang, M. Lin, L.-N. Yu, M. Kong, *Tetrahedron* **2000**, *56*, 1321.

[11] F. Uenobe, S. Nakamura, M. Miyazawa, *Mutat. Res.*, *Fundam. Mol. Mech. Mutagen.* **1997**, *373*, 197.

[12] M. Bokel, M. N. C. Diyasena, A. A. L. Gunatilaka, W. Kraus, S. Sotheeswaran, *Phytochemistry* **1988**, *27*, 377.

[13] Y. Oshima, K. Namao, A. Kamijou, S. Matsuoka, M. Nakano, K. Terao, Y. Ohizumi, *Cell. Mol. Life Sci.* **1995**, *51*, 63.

[14] J. E. van der Kaaden, T. K. Hemscheidt, S. L. Mooberry, *J. Nat. Prod.* **2001**, *64*, 103.

[15] L. Xia, Y. R. Lee, *Synlett* **2008**, 1643; H. J. Lee, Y. R. Lee, S. H. Kim, *Helv. Chim. Acta* **2009**, *92*, 1404.

[16] S. Takaoka, K. Nakade, Y. Fukuyama, *Tetrahedron Lett.* **2002**, *43*, 6919.

[17] H. Tohma, Y. Kita, *Adv. Synth. Catal.* **2004**, *346*, 111.

[18] S. Gronowitz, K. Stenhammar, L. Svensson, *Heterocycles* **1981**, *15*, 947.

[19] T. Smith, D. A. Modarelli, *Tetrahedron Lett.* **2008**, *49*, 526.

Received September 3, 2009