

HETEROCYCLES, Vol. 93, No. 1, 2016, pp. 310 - 322. © 2016 The Japan Institute of Heterocyclic Chemistry
Received, 31st August, 2015, Accepted, 10th December, 2015, Published online, 6th January, 2016
DOI: 10.3987/COM-15-S(T)42

FORMAL TOTAL SYNTHESIS OF ARTOCARPIN

Isao Mizota, Kana Taniguchi, and Makoto Shimizu*

Department of Chemistry for Materials, Graduate School of Engineering, Mie University, Tsu, Mie 514-8507, Japan. E-mail: imizota@chem.mie-u.ac.jp, mshimizu@chem.mie-u.ac.jp

Abstract – A formal total synthesis of artocarpin was achieved via selective demethylation, iodination, followed by Suzuki-Miyaura coupling reaction of the key flavone derivative. It took only 7 steps in the overall yield of 55% starting from commercially available 3,5-dimethoxyphenol.

INTRODUCTION

Flavonoids are the aromatic compounds having a phenylchroman frame belonging to polyphenols and are known as the natural pigment compounds widely existing in plant kingdom. They also have various biological activities; in particular, flavones shown in Figure 1 constituted A, B, and C rings have high antioxidative effect.¹ Such an effect is attributed to the structure of several benzene rings which can absorb the unpaired electron of free radicals due to the acceptability for electrons on the benzene ring. It is also well known that the number of hydroxy group of flavone affects the oxidative effect, for the *o*-dihydroxy group of B ring and the carbonyl group of the 4-position of flavone play an important role for the above effect. Recently, this effect has been paid attention to studying the synthesis of bioactive compounds with higher ability by introducing more substituents to the flavone skeleton.

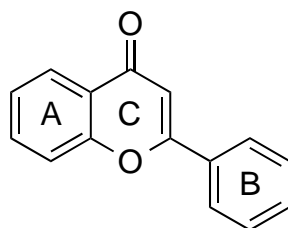


Figure 1. Flavone

Artocarpin (**1**) is isolated from the *Artocarpus incisus* of the moraceous plant and has the flavone skeleton (Figure 2).² Artocarpin (**1**) can inhibit 5 α -reductant enzyme which reduces testosterone to dihydrotestosterone to lead blocking of androgenetic alopecia, prostatic disease, and sexual desire decline

This paper is dedicated to Professor Dr. Lutz F. Tietze on the occasion of his 75th birthday.

caused by excess dihydrotestosterone. As this effect acts with the epidermis in particular an endothelium, artocarpin is a prospective compound for illness on skin. In addition, artocarpin is known to be the anticancer agent—skin cancer. Moreover, it is used as the cyclooxygenase repressor and 5-lipoxygenase repressor utilized to an antiphlogistic balm, an antifebrile and various antiallergic drugs.

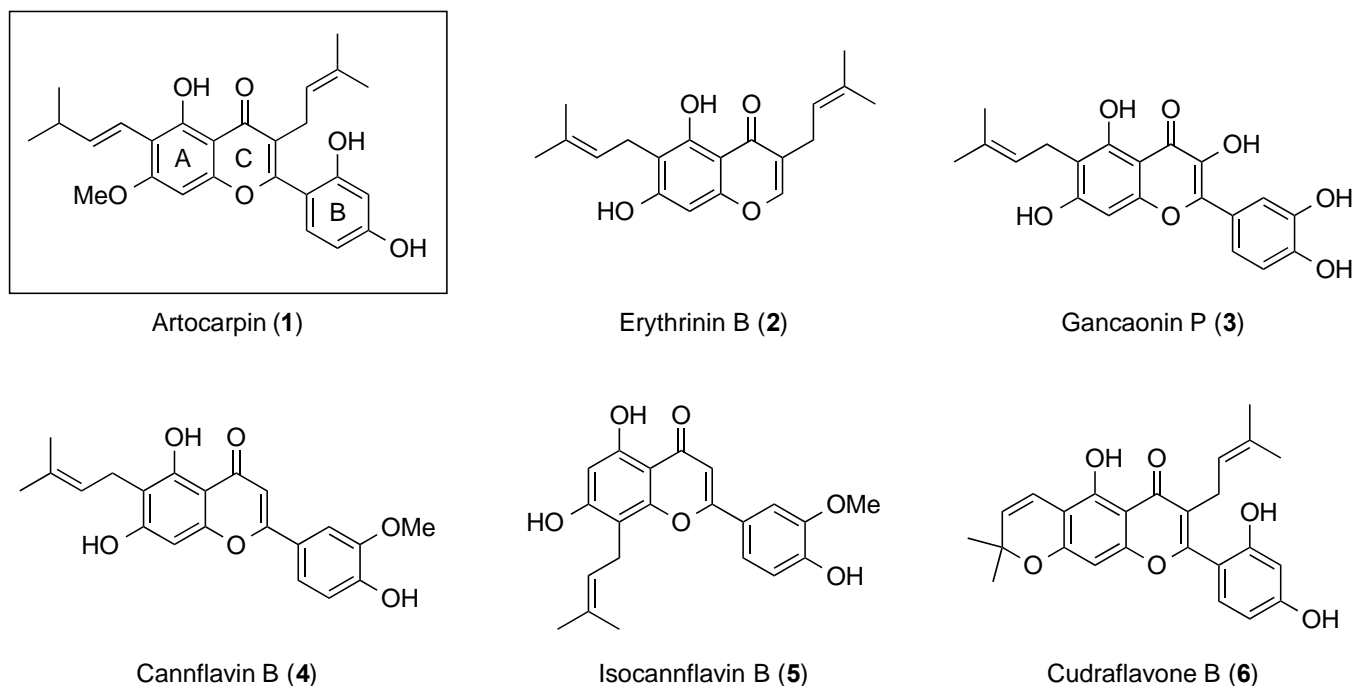


Figure 2. Artocarpin Derivatives

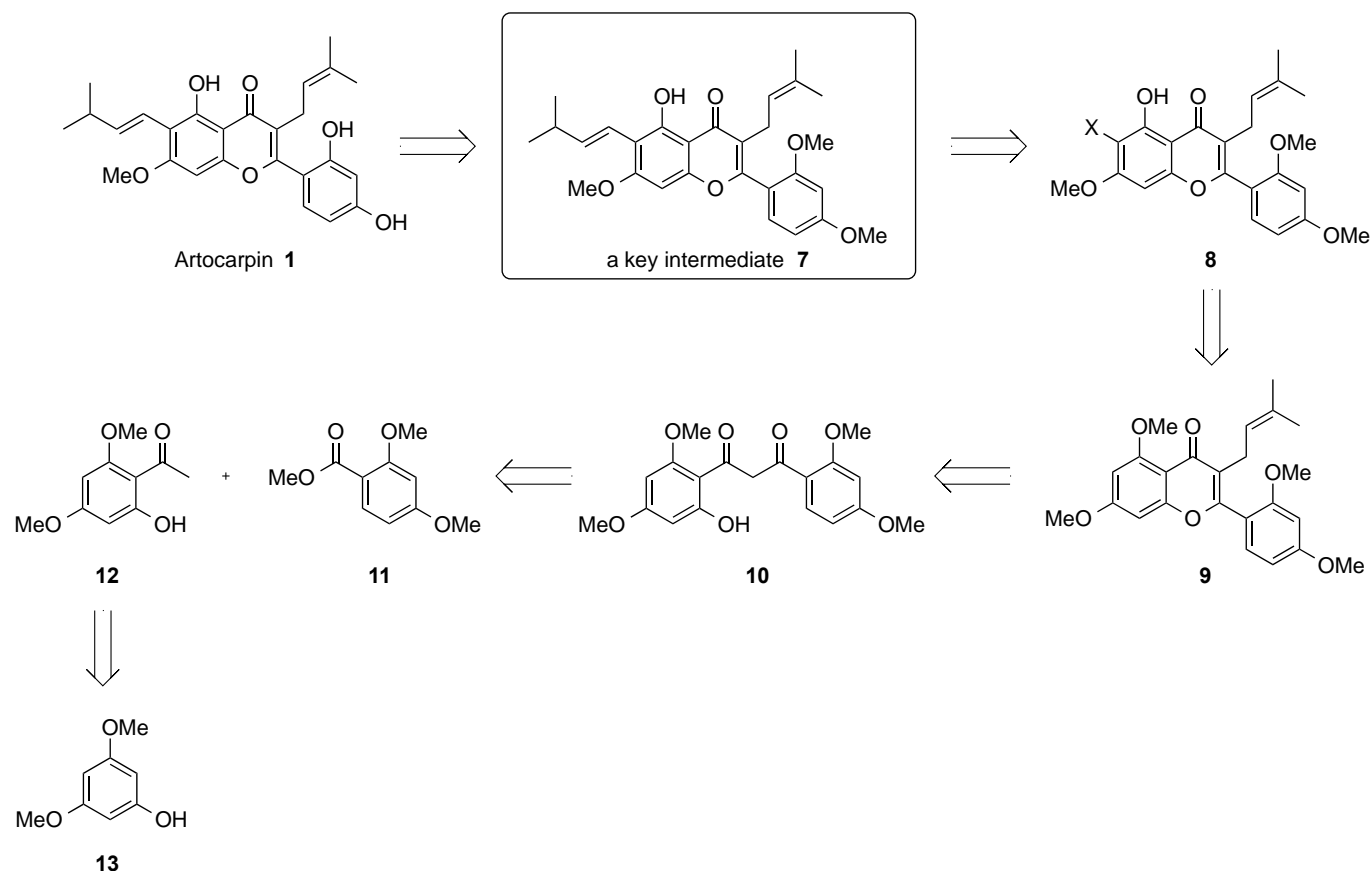
There are various prenylated flavonoids in the natural world as artocarpin derivatives such as erythrinin B (2),³ gancaonin P (3),⁴ cannflavin B (4)⁵ and isocannflavin B (5).⁶ These compounds have strong antioxidative ability due to a prenyl group, which has a double bond in the form and is easy to supplement a radical and promote the antioxidant action. Cudraflavone B (6)⁷ is also an artocarpin derivative which has a strong antiphlogistic agent as well as an antioxidant action. Thus prenylated flavonoids such as artocarpin are strong bioactive compounds including the antioxidative effect. However, there is a problem that the application to pharmaceutical products is difficult because expensive materials are needed in conventional synthetic methods, and therefore, more efficient synthetic methods of prenylated flavonoid are highly required today.^{8,9}

The synthesis of artocarpin had not been reported until recently due to the bad solubility and reactivity of the substrates. However, Hou and coworkers reported the first total synthesis of artocarpin in 2013 via a linear reaction sequence of 12 steps with the overall yield of 3.5%, starting from 1,3,5-trimethoxybenzene.^{2d} In their report, although the total synthesis of artocarpin was achieved via a key intermediate 7 (*vide infra*), they commented that their own synthetic routes were tediously long and inefficient.

Our group has also studied the total synthesis of artocarpin and inspired by this timely report. We have found an alternative synthetic route, which is shorter and more efficient to provide the key intermediate of artocarpin. Herein, we report a formal synthesis of artocarpin providing only 7 steps to its intermediate, in 55% overall yield, including sequential selective demethylation/ regioselective iodination/ Suzuki-Miyaura coupling, starting from commercially available 3,5-dimethoxyphenol.

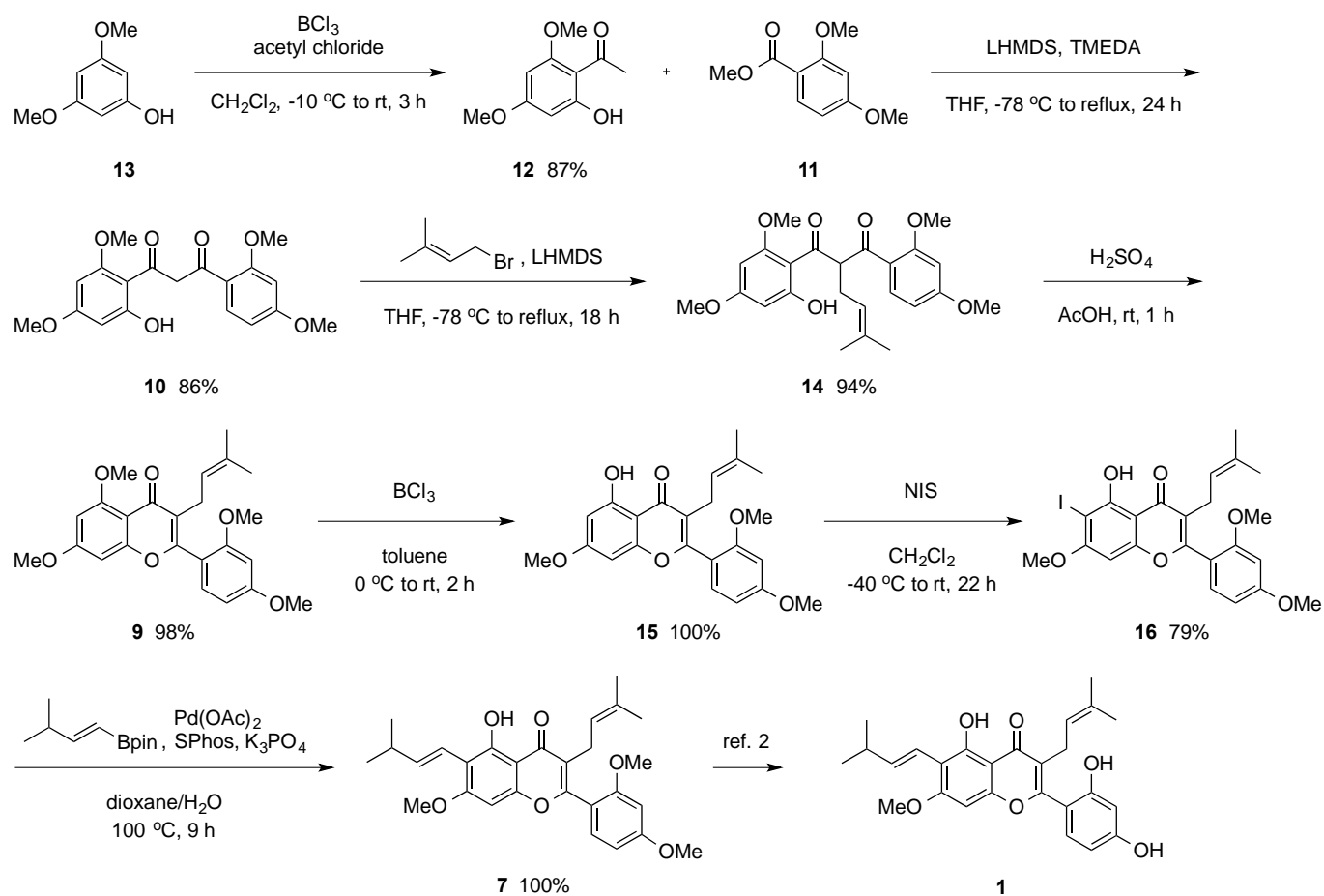
RESULTS AND DISCUSSION

Our retrosynthetic analysis of **1** is shown in Scheme 1. We aimed at the synthesis of **1** via coupling reactions, starting from inexpensive materials. We envisioned that artocarpin **1** could be synthesized by selective demethylation of the precursor **7** as a key intermediate. The precursor **7** could be built from the halogenated flavonoid **8** by a coupling reaction. The flavonoid **8** could be obtained by selective demethylation of **9** followed by selective halogenation, which could be constructed by cyclization of the diketone **10** under acidic conditions. The diketone **10** could be synthesized by Claisen condensation of the hydroxy ketone **12** with the ester **11**. The hydroxy ketone **12** could be obtained from commercially available 3,5-dimethoxyphenol **13**.



Scheme 1. Retrosynthetic Analysis of Artocarpin

Our synthesis of artocarpin **1** began with Friedel-Crafts acylation of 3,5-dimethoxyphenol **13** (Scheme 2). A commercially available compound **13** was readily acylated with acetyl chloride in the presence of BCl_3 to give the hydroxy phenylketone **12** in 87% yield. Among the conditions examined for the Claisen condensation of methyl(2-hydroxy-4,6-dimethoxy)phenyl ketone **12** with dimethoxyphenyl ester **11**, the combination of LHMDS with TMEDA was the most effective to afford the desired diketone **10** in 86% yield, while use of other bases such as LDA, NaHMDS and KHMDS were not effective for this reaction. To construct the prenylated flavonoid **9**, we then examined various conditions and after all we found that the desired flavonoid **9** could be obtained by prenylation of the diketone **10** with the 3,3-dimethylallyl bromide and LHMDS to afford the compound **14** followed by cyclization under the acidic conditions in 92% yield (2 steps). This flavone ring was very stable and the order of the reaction was very important. In fact, cyclization of **10** under the acidic conditions (H_2SO_4 , AcOH, rt, 1 h) proceeded to construct the flavone skeleton in quantitative yield; however, the next prenylation did not take place under various reaction conditions.



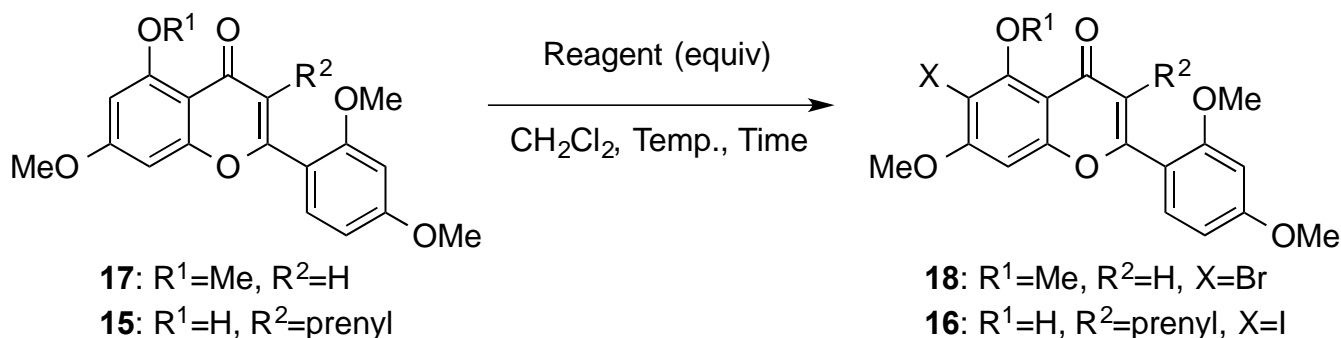
Scheme 2. Synthesis of the Known Artocarpin Precursor **7**

To introduce a prenyl group at the 6-position of the flavonoid utilizing a coupling reaction, a regioselective halogenation of the flavonoid compound was needed.¹⁰ We examined the direct

halogenation of the model substrate **17** having four methoxy groups in the molecule (Table 1). However, the desired halogenated product **18** was not obtained, and instead, the non-selective halogenated product was formed (entries 1 and 2). These results indicated that four methoxy groups increased the electron density of the flavonoid to induce some side reactions. Thus, selective demethylation of the flavonoid **9** was carried out to avoid the formation of by-products. The demethylation with BCl_3 in toluene gave the desired 5-demethylated flavonoid **15** in quantitative yield, while the yield of **15** was low when CH_2Cl_2 or ethyl acetate was used as a solvent.

Next the regioselective halogenation of the partially demethylated derivative **15** was carried out, and parameters involving halogenation reagents, temperatures and reaction times were examined (Table 1, entries 3-5). We found that treating the trimethoxy derivative **15** with NIS effected the selective 6-iodination to afford the iodinated flavonoid **16** in 79% yield (entry 4). This selectivity may be explained in terms of the hydrogen bonding between a hydroxy group and NIS.¹¹

Table 1. Examination of Regioselective Halogenation of Flavonoid



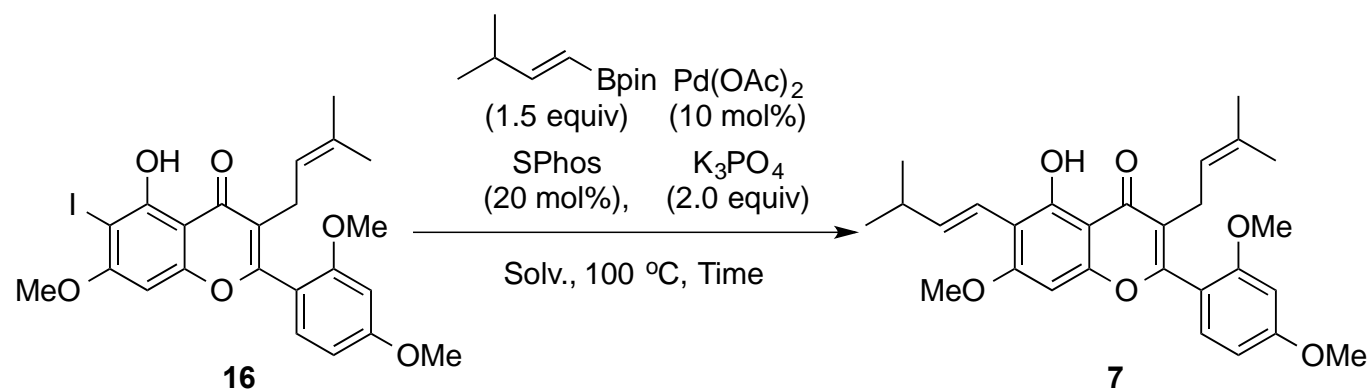
Entry	Substrate	Reagent (eq)	Temp. (°C)	Time (h)	Product	Yield (%)
1 ^a	17	TBATB (1.5)	rt	2	18	0
2	17	NBS (2.3)	0 to rt	12	18	0 ^c
3	15	NIS (1.0)	0 to rt	15	16	52
4 ^b	15	NIS (1.0)	-40 to rt	22	16	79
5	15	DIH (1.0)	0 to rt	18	16	35

^a CHCl_3 was used as a solvent. ^bReagent was put by dropping funnel. ^cTribrominated compound was obtained in 55% yield.

The final step to the artocarpin precurator **7**, a known key intermediate^{2d} was investigated via a coupling reaction. Although various coupling reactions such as Stille-, Heck-, and Sonogashira-couplings were examined, no desired coupled product **7** was obtained.¹² After considerable efforts for the coupling reaction, we found that Suzuki-Miyaura coupling of **16** proceeded to give the desired product **7**. Solvents

systems were screened and the results are shown in Table 2. When the reaction was carried out in the presence of Pd(OAc)₂ (10 mol%) and a SPhos ligand (20 mol%) in the solvent mixture (dioxane/H₂O = 10/1), the reaction took place smoothly to give the desired coupled product **7** in quantitative yield (entry 3), while longer reaction time decreased the yield due to the decomposition of the product (entry 2). Thus, we achieved a formal total synthesis of artocarpin, the synthesis of a key intermediate **7** in only 7 steps in 55% overall yield from 3,5-dimethoxyphenol.

Table 2. Examination of Suzuki-Miyaura Cross Coupling Reaction of **16**



Entry	Solvent	Time (h)	Yield (%)
1	DMF : H ₂ O (10 : 1)	19	23
2	dioxane : H ₂ O (10 : 1)	18	87
3	dioxane : H ₂ O (10 : 1)	9	100
4	H ₂ O	21	53

CONCLUSIONS

In summary, we succeeded in the formal synthesis of artocarpin utilizing regioselective iodination and Suzuki-Miyaura coupling reaction as crucial steps. The artocarpin precursor **7** was synthesized in only 7 steps starting from a commercially available material and the overall yield was 55%. It is apparent that this route provides an extremely effective protocol to synthesize a useful intermediate in comparison with the reported method.¹³

EXPERIMENTAL

General

Infrared spectra were determined on a JASCO FT/IR-460 plus spectrometer. ¹H NMR and ¹³C NMR spectra were recorded with a JEOL ECX-400P, or a JEOL A-500 spectrometer using tetramethylsilane as

an internal standard. Mass spectra were recorded on a JEOL MS-700D spectrometer. Dichloromethane (CH₂Cl₂) and dimethyl formamide (DMF) were distilled from calcium hydride and stored over Molecular Sieves 4Å. Tetrahydrofuran (THF) was distilled from benzophenone ketyl immediately before use. Toluene was dried over calcium chloride, distilled, and stored over Molecular Sieves 4Å. 1,4-Dioxane was distilled from calcium hydride and stored over sodium. Ethyl acetate (AcOEt) was distilled from phosphorus pentoxide and stored over Molecular Sieves 4Å. Acetonitrile (MeCN) was distilled from phosphorus pentoxide and then from calcium hydride, and stored over Molecular Sieves 4Å. Purification of products was performed by column chromatography on silica gel (Kanto Silica Gel 60N) and/or preparative TLC on silica gel (Merck Kiesel Gel GF254).

1-(2-Hydroxy-4,6-dimethoxyphenyl)ethan-1-one (12)¹⁴

In a 200-mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed 3,5-dimethoxyphenol **13** (5.00 g, 32.4 mmol) in CH₂Cl₂ (66 mL) at -10 °C, and to it was added BCl₃ in CH₂Cl₂ (32 mL, 32.4 mmol, 1.0 M, 1.0 equiv) and acetyl chloride (3.0 mL, 42.2 mmol) slowly. After the mixture was stirred for 20 min, the whole mixture was heated at reflux for 3 h. The reaction was quenched with 2*N* HCl (80 mL), and the mixture was extracted with CH₂Cl₂ (20 mL x 3) and dried over anhydrous Na₂SO₄, and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (CH₂Cl₂/MeOH = 100 / 1) to give the title compound **12** (5.49 g, 87%).

1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(2,4-dimethoxyphenyl)propane-1,3-dione (10)

In a 200-mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed LHMDS in THF (39 mL, 51.0 mmol, 1.3 M) at -78 °C, and to it was added **12** (2.00 g, 10.2 mmol) in THF (51 mL). After the mixture was stirred for 1 h at -78 °C and warmed to -10 °C for 1 h, to it were added methyl 2,4-dimethoxybenzoate **11** (2.00 g, 10.2 mmol) in THF (51 mL) and TMEDA (7.6 mL, 51.0 mmol), and the whole mixture was heated at reflux for 24 h. The reaction was quenched reversely by pouring the solution into ice water and 2*N* HCl (50 mL), and the mixture was extracted with CHCl₃ (20 mL x 3). The combined extracts were washed with sat. NaCl aq. (30 mL) and dried over anhydrous Na₂SO₄, and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4 / 1) to give the title compound **10** (3.15 g, 86%). Yield 86%, *keto* : *enol* = 48 : 52; Yellow solid; mp 108-109 °C; ¹H NMR (500 MHz, CDCl₃) δ : 3.59 (s, 1.44H), 3.77 (s, 1.44H), 3.80 (s, 1.44H), 3.81 (s, 1.56H), 3.86 (s, 1.44H), 3.86 (s, 1.56H), 3.89 (s, 1.56H), 3.94 (s, 1.56H), 4.51 (s, 0.96H), 5.86 (d, *J* = 2.5 Hz, 0.48H), 5.97 (d, *J* = 2.5 Hz, 0.52H), 6.07 (d, *J* = 2.5 Hz, 0.48H), 6.09 (d, *J* = 2.5 Hz, 0.52H), 6.44 (d, *J* = 2.5 Hz, 0.48H), 6.50 (d, *J* = 2.5 Hz, 0.52H), 6.56 (dd,

$J = 2.5, 8.6$ Hz, 0.48H), 6.58 (dd, $J = 2.5, 8.6$ Hz, 0.52H), 7.65 (s, 0.52H), 7.93 (d, $J = 8.6$ Hz, 0.48H), 7.95 (d, $J = 8.6$ Hz, 0.52H), 13.5 (s, 0.52H), 13.7 (s, 0.48H); ^{13}C NMR (125 MHz, CDCl_3) δ : 55.3, 55.4, 55.5, 55.5, 55.6, 55.6, 59.7, 90.8, 91.3, 93.7, 94.1, 98.2, 98.9, 101.8, 104.8, 105.1, 105.5, 105.7, 116.1, 120.1, 131.5, 132.9, 160.2, 160.9, 161.7, 162.2, 163.5, 164.8, 165.0, 166.2, 166.6, 167.6, 174.3, 193.3, 193.4, 200.0; IR (neat) : 2942, 2844, 1658, 1597, 1290, 1215, 1159, 1114, 1027, 822 cm^{-1} ; HRMS(EI) : Calcd for $\text{C}_{19}\text{H}_{20}\text{O}_7(\text{M})^+$ 360.1209, found 360.1200.

1-(2,4-Dimethoxyphenyl)-3-(2-hydroxy-4,6-dimethoxyphenyl)-2-(3-methylbut-2-en-1-yl)propane-1,3-dione (14)

In a 30-mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed LHMDS in THF (0.077 mL, 0.100 mmol, 1.3 M) at -78 °C, and to it was added **10** (36.0 mg, 0.100 mmol) in THF (2.0 mL). After the mixture was stirred at -78 °C for 1 h, to it was added 1-bromo-3-methyl-2-butene (0.014 mL, 0.120 mmol) and the whole mixture was heated at reflux for 18 h. The reaction was quenched with sat. NH_4Cl aq. (5.0 mL), and the mixture was extracted with EtOAc (5.0 mL x 3). The combined extracts were washed with sat. NaCl aq. (5.0 mL x 3) and dried over anhydrous Na_2SO_4 , and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4 / 1) to give the title compound **14** (40.2 mg, 94%).

Yield 94%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ : 1.61 (s, 3H), 1.64 (s, 3H), 2.58-2.67 (m, 2H), 3.59 (s, 3H), 3.70 (s, 3H), 3.81 (s, 3H), 3.86 (s, 3H), 5.12 (dddd, $J = 1.2, 1.2, 4.3, 7.3$ Hz, 1H), 5.45 (dd, $J = 6.4, 6.4$ Hz, 1H), 5.88 (d, $J = 2.1$ Hz, 1H), 6.08 (d, $J = 2.1$ Hz, 1H), 6.43 (d, $J = 2.4$ Hz, 1H), 6.56 (dd, $J = 2.4, 8.9$ Hz, 1H), 7.99 (d, $J = 8.9$ Hz, 1H), 13.89 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 17.7, 25.8, 27.3, 55.1, 55.2, 55.5, 55.5, 64.7, 90.7, 93.8, 98.2, 105.4, 105.5, 119.6, 122.7, 132.4, 133.7, 160.4, 161.9, 164.7, 165.8, 167.9, 194.8, 201.9; IR (neat) : 3442, 2939, 2846, 1652, 1599, 1461, 1417, 1273, 1214, 1160, 1113, 1026, 937, 824, 753 cm^{-1} ; HRMS(EI) : Calcd for $\text{C}_{24}\text{H}_{28}\text{O}_7(\text{M})^+$ 428.1835, found 428.1820.

2-(2,4-Dimethoxyphenyl)-5,7-dimethoxy-3-(3-methylbut-2-en-1-yl)-4H-chromen-4-one (9)

In a 50-mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed **14** (130 mg, 0.304 mmol) at room temperature, and to it were added acetic acid (30 mL), sulfuric acid (0.030 mL, 0.547 mmol). After the mixture was stirred at room temperature for 1 h, the reaction was quenched with sat. NaHCO_3 aq. (20 mL), and the mixture was extracted with EtOAc (10 mL x 3). The combined extracts were washed with sat. NaCl aq. (10 mL x 3) and sat. NaHCO_3 aq. (10 mL x 3) and dried over anhydrous Na_2SO_4 , and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (*n*-hexane/ Et_2O = 1 / 1) to give the title compound **9** (122 mg, 98%).

Yield 98%; Yellow solid; mp 144 °C; ^1H NMR (500 MHz, CDCl_3) δ : 1.39 (s, 3H), 1.58 (d, $J = 1.3$ Hz, 3H), 3.00 (d, $J = 6.9$ Hz, 2H), 3.78 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 3.94 (s, 3H), 5.16 (ddt, $J = 1.3, 1.4, 6.9$ Hz, 1H), 6.32 (d, $J = 2.4$ Hz, 1H), 6.39 (d, $J = 1.8$ Hz, 1H), 6.54-6.55 (m, 1H), 6.57 (d, $J = 2.4$ Hz, 1H), 7.25 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 17.5, 24.9, 25.7, 55.5, 55.6, 56.2, 92.4, 95.6, 98.8, 104.5, 108.9, 115.3, 122.3, 123.8, 131.0, 131.4, 157.5, 158.4, 160.1, 161.0, 162.3, 163.5, 177.2; IR (neat) : 2937, 2926, 2583, 1638, 1612, 1507, 1458, 1421, 1348, 1307, 1209, 1161, 1031, 824, 729 cm^{-1} ; HRMS(EI) : Calcd for $\text{C}_{24}\text{H}_{26}\text{O}_6(\text{M})^+$ 410.1729, found 410.1745.

2-(2,4-Dimethoxyphenyl)-5-hydroxy-7-methoxy-3-(3-methylbut-2-en-1-yl)-4H-chromen-4-one (15)

In a 30-mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed **9** (132 mg, 0.322 mmol) in toluene (5.0 mL) at 0 °C, and to it was added BCl_3 in CH_2Cl_2 (0.387 mL, 0.387 mmol, 1.0*N*). After the whole mixture was warmed to room temperature and stirred for 2 h, the reaction was quenched with 2*N* NaOH aq. (5.0 mL), and the mixture was extracted with EtOAc (5.0 mL x 3). The combined extracts were washed with sat. NaCl aq. (5.0 mL x 3) and dried over anhydrous Na_2SO_4 , and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (*n*-hexane/Et₂O = 3 / 1) to give the title compound **15** (127 mg, 100%).

Yield 100%; Yellow solid; mp 123-124 °C; ^1H NMR (500 MHz, CDCl_3) δ : 1.42 (s, 3H), 1.62 (s, 3H), 3.03 (d, $J = 6.9$ Hz, 2H), 3.79 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 5.09 (ddt, $J = 1.5, 1.5, 6.9$ Hz, 1H), 6.33 (d, $J = 2.1$ Hz, 1H), 6.33 (d, $J = 2.4$ Hz, 1H), 6.55 (d, $J = 2.1$ Hz, 1H), 6.58 (dd, $J = 2.4, 8.5$ Hz, 1H), 7.24 (d, $J = 8.5$ Hz, 1H), 13.01 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 17.5, 24.2, 25.6, 55.5, 55.6, 55.6, 91.9, 97.6, 98.7, 104.6, 105.4, 114.9, 121.4, 121.5, 131.3, 131.9, 158.1, 158.3, 160.8, 162.1, 162.7, 165.1, 182.3; IR (neat) : 3430, 3009, 2965, 2934, 2843, 1656, 1621, 1586, 1502, 1443, 1209, 1161, 1036, 829, 756 cm^{-1} ; HRMS(EI) : Calcd for $\text{C}_{23}\text{H}_{24}\text{O}_6(\text{M})^+$ 396.1573, found 396.1566.

2-(2,4-Dimethoxyphenyl)-5-hydroxy-6-iodo-7-methoxy-3-(3-methylbut-2-en-1-yl)-4H-chromen-4-one (16)

In a 50-mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed **15** (426 mg, 1.08 mmol) at -40 °C, and to it was added NIS (243 mg, 1.08 mmol) in CH_2Cl_2 (22 mL) warming to room temperature over 20 h. After the whole mixture was stirred for 2 h, the reaction was quenched with H_2O (5.0 mL), and the mixture was extracted with CH_2Cl_2 (5.0 mL x 3). The combined extracts were washed with sat. NaCl aq. (5.0 mL x 3) and dried over anhydrous Na_2SO_4 , and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (*n*-hexane/ EtOAc = 4 / 1) to give the title compound **16** (447 mg, 79%).

Yield 79%; Red oil; ^1H NMR (500 MHz, CDCl_3) δ : 1.41 (s, 3H), 1.61 (s, 3H), 3.05 (d, $J = 6.4$ Hz, 2H), 3.79 (s, 3H), 3.88 (s, 3H), 3.92 (s, 3H), 5.08 (ddt, $J = 1.2, 1.2, 6.4$ Hz, 1H), 6.40 (s, 1H), 6.55 (d, $J = 2.3$ Hz, 1H), 6.58 (dd, $J = 2.3, 8.4$ Hz, 1H), 7.25 (d, $J = 8.4$ Hz, 1H), 14.05 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 17.6, 24.3, 25.6, 55.6, 56.7, 69.0, 90.2, 98.8, 104.7, 105.6, 114.6, 121.2, 121.7, 131.3, 132.2, 158.4, 158.5, 161.1, 161.2, 162.8, 163.0, 181.5; IR (neat) : 2926, 1627, 1570, 1419, 1263, 1210, 1161, 770, 572, 561 cm^{-1} ; HRMS(EI) : Calcd for $\text{C}_{23}\text{H}_{23}\text{IO}_6(\text{M})^+$ 522.0539, found 522.0568.

2-(2,4-Dimethoxyphenyl)-5-hydroxy-6- $\{(E)\text{-}3\text{-methylbut-1-en-1-yl}\}$ -4H-chromen-4-one (7)^{2d,15}

In a 30-mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon were placed **16** (35.1 mg, 0.0672 mmol), $\text{Pd}(\text{OAc})_2$ (1.5 mg, 0.00672 mmol), SPhos (5.5 mg, 0.0134 mmol) and K_3PO_4 (28.5 mg, 0.134 mmol), and to it was added (*E*)-4,4,5,5-tetramethyl-2-(3-methylbut-1-en-1-yl)-1,3,2-dioxaborolane (19.8 mg, 0.101 mmol) in 1,4-dioxane (1.0 mL) and H_2O (0.10 mL). After the mixture was stirred for 2 min and degassed at room temperature, the whole mixture was warmed to 100 $^\circ\text{C}$ and stirred for 9 h. The reaction was cooled at room temperature and quenched with sat. NaHCO_3 aq. (5.0 mL), and the mixture was extracted with CH_2Cl_2 (5.0 mL x 3). The combined extracts were washed with sat. NaCl aq. (5.0 mL x 3) and dried over anhydrous Na_2SO_4 , and concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (*n*-hexane/ EtOAc = 4 / 1) to give the title compound **7** (36.9 mg, 100%). The spectral properties are identical with the reported ones.^{2d,15}

Yield 100%; Yellow solid; mp 149-150 $^\circ\text{C}$ (lit.¹⁵ 150-152 $^\circ\text{C}$); ^1H NMR (500 MHz, CDCl_3) δ : 1.12 (d, $J = 6.8$ Hz, 6H), 1.40 (s, 3H), 1.61 (s, 3H), 2.49 (ddqq, $J = 1.2, 6.8, 6.8, 6.9$ Hz, 1H), 3.03 (d, $J = 6.7$ Hz, 2H), 3.79 (s, 3H), 3.87 (s, 3H), 3.87 (s, 3H), 5.09 (ddt, $J = 1.2, 1.2, 6.7$ Hz, 1H), 6.34 (s, 1H), 6.54-6.60 (m, 3H), 6.71 (dd, $J = 6.9, 16.2$ Hz, 1H), 7.25 (d, $J = 8.5$ Hz, 1H), 13.70 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 17.6, 22.7, 24.2, 25.6, 33.1, 55.6, 55.8, 89.3, 98.7, 104.6, 105.3, 109.3, 114.9, 115.8, 121.4, 121.5, 131.3, 131.9, 142.2, 156.4, 158.3, 159.0, 160.4, 162.6, 182.4; IR (neat) : 2958, 2927, 2861, 1646, 1616, 1585, 1451, 1352, 1303, 1207, 1160, 1033, 980, 834, 757 cm^{-1} ; HRMS(EI) : Calcd for $\text{C}_{28}\text{H}_{32}\text{O}_6(\text{M})^+$ 464.2199, found 464.2202.

ACKNOWLEDGEMENTS

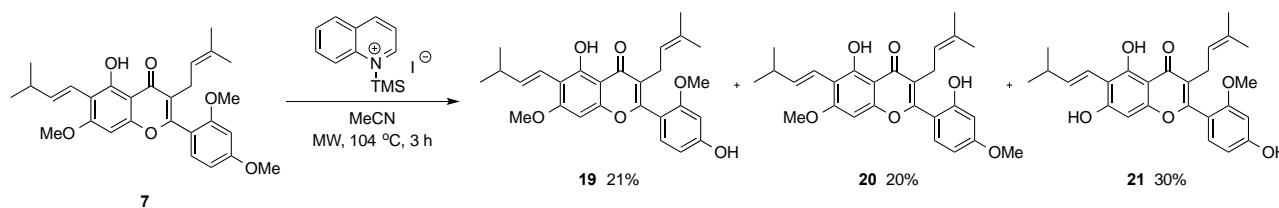
This work was supported by Grants-in-Aid for Scientific Research (B) and on Innovative Areas "Organic Synthesis Based on Reaction Integration, Development of New Methods and Creation of New Substances" from JSPS and MEXT.

REFERENCES

- (a) S. F'guyer, F. Afaq, and H. Mukhtar, *Photodermatol. Photoimmunol. Photomed.*, 2003, **19**, 56; (b) K. Swindells and L. E. Rhodes, *Photodermatol. Photoimmunol. Photomed.*, 2004, **20**, 297; (c) H. Sies and W. Stahl, *Annu. Rev. Nutr.*, 2004, **24**, 173; (d) P. Kullavanijaya and H. W. Lim, *J. Am. Acad. Dermatol.*, 2005, **52**, 937; (e) K. Huvaere, K. Olsen, and L. H. Skibsted, *J. Org. Chem.*, 2009, **74**, 7283.
- (a) W.-C. Lan, C.-W. Tzeng, C.-C. Lin, F.-L. Yen, and H.-H. Ko, *Phytochemistry*, 2013, **89**, 78; (b) C.-W. Lee, H.-H. Ko, C.-C. Lin, C.-Y. Chai, W.-T. Chen, and F.-L. Yen, *Food Chem. Toxicol.*, 2013, **60**, 123; (c) K. Panthong, K. Tohdee, N. Hutadilok-Towatana, S. P. Voravuthikunchai, and S. Chusri, *J. Braz. Chem. Soc.*, 2013, **24**, 1656; (d) W.-J. Zhang, J.-F. Wu, P.-F. Zhou, Y. Wang, and A.-J. Hou, *Tetrahedron*, 2013, **69**, 5850; (e) Z.-P. Zheng, Y. Xu, C. Qin, S. Zhang, X. Gu, Y. Lin, G. Xie, M. Wang, and J. Chen, *J. Agric. Food Chem.*, 2014, **62**, 5519.
- J. Jang, M. Na, P. T. Thuong, D. Njamen, J. T. Mbafor, Z. T. Fomum, E. -R. Woo, and W. K. Oh, *Chem. Pharm. Bull.*, 2008, **56**, 85.
- B. T. Ngadjui, S. F. Kouam, E. Dongo, G. W. F. Kapche, and B. M. Abegaz, *Phytochemistry*, 2000, **55**, 915.
- A. K. Ibrahim, M. M. Radwan, S. A. Ahmed, D. Slade, S. A. Ross, M. A. ElSohly, and I. A. Khan, *Phytochemistry*, 2010, **71**, 1014.
- A. Minassi, A. Giana, A. Ech-Chahad, and G. Appendino, *Org. Lett.*, 2008, **10**, 2267.
- J. Hosek, M. Bartos, S. Chudík, S. Dall'Acqua, G. Innocenti, M. Kartal, L. Kokoska, P. Kollár, Z. Kutil, P. Landa, R. Marek, V. Závalová, M. Zemlicka, and K. Smejkal, *J. Nat. Prod.*, 2011, **74**, 614.
- (a) J. Algar and J. P. Flynn, *Proc. Roy. Irish Acad.*, 1934, **42B**, 1; (b) T. Oyamada, *J. Chem. Soc. Japan*, 1934, **55**, 1256; (c) C. J. Bennett, S. T. Caldwell, D. B. McPhail, P. C. Morrice, G. G. Duthie, and R. C. Hartley, *Bioorg. Med. Chem.*, 2004, **12**, 2079; (d) M. Tsukayama, E. Kusunoki, M. M. Hossain, Y. Kawamura, and S. Hayashi, *Heterocycles*, 2007, **71**, 1589; (e) A. R. Katritzky, N. Shobana, J. Pernak, A. S. Afridi, and W. -Q. Fan, *Tetrahedron*, 1992, **48**, 7817; (f) A. R. Katritzky and A. Pastor, *J. Org. Chem.*, 2000, **65**, 3679; (g) A. Hiza, Y. Tsukaguchi, T. Ogawa, M. Inai, T. Asakawa, Y. Hamashima, and T. Kan, *Heterocycles*, 2014, **88**, 1371.
- For the synthesis of Artocarpin derivative, see: T. -H. Tseng, S. -K. Chuang, C. -C. Hu, C. -F. Chang, Y. -C. Huang, C. -W. Lin, and Y. -J. Lee, *Tetrahedron*, 2010, **66**, 1335.
- (a) P. Bovonsombat, R. Ali, C. Khan, J. Leykajakul, K. P. S. Aphimanchindakul, N. Pungcharoenpong, N. Timsuea, A. Arunrat, and N. Punpongjareorn, *Tetrahedron*, 2010, **66**, 6928; (b) P. Bovicelli, R. Bernini, R. Antonioletti, and E. Mincione, *Tetrahedron Lett.*, 2002, **43**, 5563; (c) G. Righi, R. Antonioletti, I. P. Silvestri, N. D'Antona, D. Lambusta, and P. Bovicelli, *Tetrahedron*,

[2010, 66, 1294.](#)

11. For the selective iodination, see: K. Lu, J. Chu, H. Wang, X. Fu, D. Quan, H. Ding, Q. Yao, and P. Yu, [Tetrahedron Lett., 2013, 54, 6345.](#)
12. (a) T. Kamino, K. Kuramochi, and S. Kobayashi, [Tetrahedron Lett., 2003, 44, 7349](#); (b) B. Liang, M. Huang, Z. You, Z. Xiong, K. Lu, R. Fathi, J. Chen, and Z. Yang, [J. Org. Chem., 2005, 70, 6097](#); (c) M. M. Hossain, Y. Kawamura, K. Yamashita, and M. Tsukayama, [Tetrahedron, 2006, 62, 8625](#); (d) S. Tischer and P. Metz, [Adv. Synth. Catal., 2007, 349, 147](#); (e) H. Lim, S. B. Kim, H. Park, H. W. Chang, and H. P. Kim, [Arch. Pharm. Res., 2009, 32, 1525](#); (f) E. Awuah and A. Capretta, [Org. Lett., 2009, 11, 3210](#); (g) Y. Kohari, Y. Hoshino, H. Matsuyama, and H. Nakano, [Heterocycles, 2010, 81, 1871](#); (h) Q. Yang and H. Alper, [J. Org. Chem., 2010, 75, 948](#); (i) S. Messaoudi, J.-D. Brion, and M. Alami, [Org. Lett., 2012, 14, 1496.](#)
13. In an attempt to achieve the total synthesis of artocarpin via a single step demethylation of the two methoxy groups, the regioselective bis-demethylation of the intermediate **7** was examined under various conditions. This step turned out to be very tedious and it was not easy to demethylate both the methoxy groups of the 2-(2,4-dimethoxy)phenyl moiety in a single operation. For example, the reaction was carried out with an excess TMS-iodoquinoline as a demethylation reagent in acetonitrile at 104 °C in the microwave reactor for 3 h to afford the compounds **19** and **20** demethylated one methoxy moiety on the 2-(2,4-dimethoxy)phenyl group in 21% and 20% yields, respectively. In addition the compound **21** demethylated two of the other methoxy groups was also obtained in 30% yield.



For the selective demethylation, see: (a) F. M. Dean, J. Goodchild, L. E. Houghton, J. A. Martin, R. B. Morton, B. Parton, A. W. Price, and N. Somvichien, [Tetrahedron Lett., 1966, 7, 4153](#); (b) M. Node, K. Nishide, M. Sai, K. Ichikawa, K. Fuji, and E. Fujita, [Chem. Lett., 1979, 97](#); (c) M. Node, K. Nishide, K. Fuji, and E. Fujita, [J. Org. Chem., 1980, 45, 4275](#); (d) K. Lal, S. Ghosh, and R. G. Salomon, [J. Org. Chem., 1987, 52, 1072](#); (e) J. S. Yadav, B. V. S. Reddy, C. Madan, and S. R. Hashim, [Chem. Lett., 2000, 738](#); (f) C. A. Gray, P. T. Kaye, and A. T. Nchinda, [J. Nat. Prod., 2003, 66, 1144](#); (g) S. J. O'Malley, K. L. Tan, A. Watzke, R. G. Bergman, and J. A. Ellman, [J. Am. Chem. Soc., 2005, 127, 13496](#); (h) J. Magano, M. H. Chen, J. D. Clark, and T. Nussbaumer, [J. Org. Chem., 2006, 71, 7103](#); (i) D. Buisson, J. Quintin, and G. Lewin, [J. Nat. Prod., 2007, 70, 1035](#); (j) J. Chae, [Arch. Pharm. Res., 2008, 31, 305](#); (k) Z. Wu, G. Wei, G. Lian, and B. Yu, [J. Org. Chem., 2010, 75,](#)

[5725](#).

14. G. Bringmann, T. F. Noll, T. Gulder, M. Dreyer, M. Grüne, and D. Moskau, [J. Org. Chem., 2007, 72, 3247](#).
15. M. P. S. C. Cunha, A. C. Pinto, and R. Braz-Filho, [J. Braz. Chem. Soc., 1994, 5, 101](#).