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Synthesis of ustalic acid, an inhibitor of Na^+,K^+-ATPase

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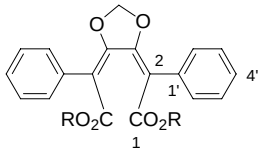
Abstract— Ustalic acid, an inhibitor of Na^+,K^+-ATPase isolated from a poisonous mushroom, was synthesized in 8 steps using the Suzuki–Miyaura coupling and oxidation of methylene acetal as key steps.

1. Introduction

Ustalic acid (**1**) was isolated from a poisonous mushroom, *Tricholoma ustale* (Kakishimeji in Japanese) by Kawagishi et al. in 2002 (Fig. 1).[1] Ustalic acid (**1**) inhibited Na^+,K^+-ATPase; IC_{50} values of ustalic acid (**1**) against the commercially available enzyme purified from porcine cerebral cortex and the crude enzyme from mouse intestinal mucosal cells were 5.2 and 0.77 mM, respectively. In 2006, Nishikawa et al. first achieved the total synthesis of ustalic acid dimethyl ester (**2**).[2] We planned an efficient synthesis of ustalic acid (**1**), which will provide a practical supply for further biological studies. We report here the first synthesis of ustalic acid (**1**) in 8 steps using Suzuki–Miyaura coupling[3] as a key step. Recently, Takahashi et al. have reported the total synthesis of a similar compound vialinin A, by a similar cross-coupling strategy.[4]

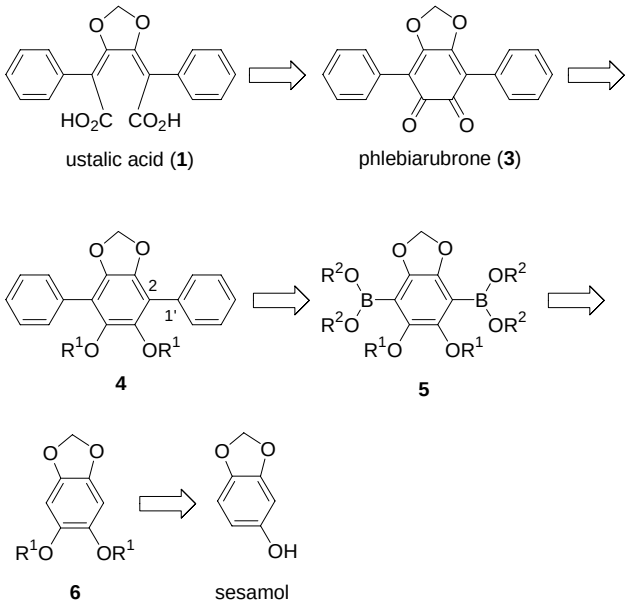


R = H; ustalic acid (**1**)
R = Me (**2**)

Figure 1. Structures of ustalic acid (**1**) and derivative.

2. Results and discussions

Our synthetic plan of ustalic acid (**1**) is shown in Scheme 1. Our synthetic route to ustalic acid (**1**) involved the Suzuki–Miyaura coupling[3] at C-2–C-1'. We therefore synthesized organoboron compound **5**.



Scheme 1. Retrosynthetic analysis of ustalic acid (**1**).

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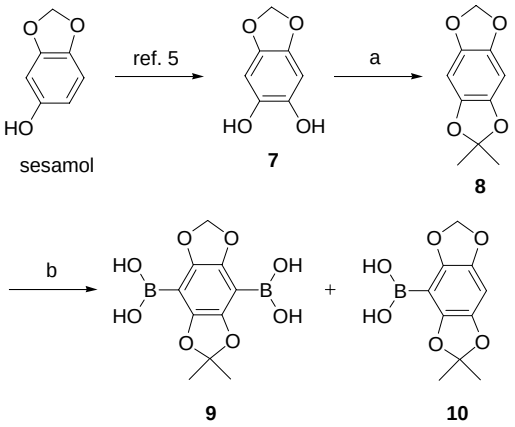
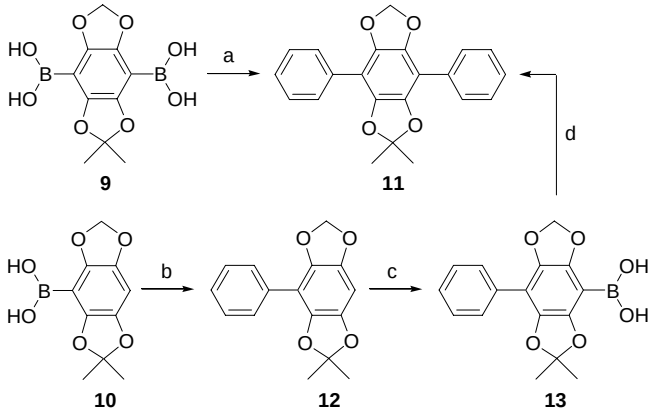
Synthesis of the ustalic acid (**1**) started from commercially available sesamol (Scheme 2). Sesamol was transformed into catechol **7**,[5] and the hydroxyl group of **7** was then protected as an acetonide. The introduction of two boronic acid moieties into **8** was accomplished through a double lithiation by using *n*-BuLi and TMEDA at –78 °C and trapping with $B(OMe)_3$ to give diboronic acid **9** and monoboronic acid **10**.



Scheme 2. Synthesis of organoboronic acids. Reagents and conditions: a) PPTS, isopropenyl methyl ether, benzene, reflux, 96%, b) *n*-BuLi, TMEDA, $B(OMe)_3$, THF, Et_2O, -78 °C to rt, **9**: 33%, **10**: 24%.

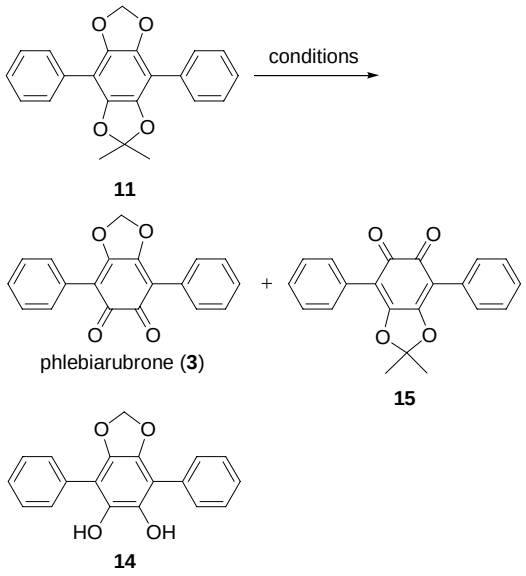
We tried the Suzuki–Miyaura coupling[3] with diboronic acid **9** and iodobenzene (Scheme 3). The coupling reaction with $Pd(PPh_3)_4$ and Na_2CO_3 in dioxane afforded diphenyl compound **11** in one step, but the yield was low (25%). In contrast, the cross-coupling reaction of monoboronic acid **10** with iodobenzene proceeded by the same conditions to give monophenyl compound **12** in 71% yield. Compound **12** was converted into boronic acid **13** by lithiation followed by treatment with $B(OMe)_3$. The coupling reaction of **13** with iodobenzene was subjected to the same conditions to give diphenyl compound **11**.



Scheme 3. Study of Suzuki–Miyaura coupling. Reagents and conditions: a) PhI, $Pd(PPh_3)_4$, Na_2CO_3, dioxane, rt, 25%; b) PhI, $Pd(PPh_3)_4$, Na_2CO_3, dioxane, rt, 71%; c) *n*-BuLi, TMEDA, $B(OMe)_3$, THF, Et_2O, -78 °C to rt, 49%; d) PhI, $Pd(PPh_3)_4$, Na_2CO_3, dioxane, rt, 40%.

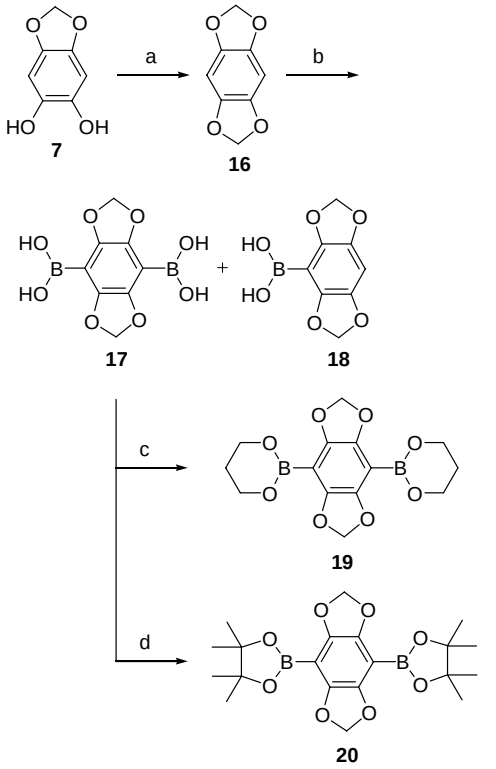
The investigation of removal of the acetonide group in **11** is summarized in Table 1. Acidic hydrolysis of **11** gave phlebiarubrone (**3**), an oxidative compound of catechol **14** (entry 1), which was isolated from the culture of the fungus *Phlebia strigozonata*.[6] Synthetic phlebiarubrone (**3**) gave spectral data (^1H NMR, ^{13}C NMR, and HRMS) in full agreement with those of the natural one.[7] Because catechol **14** readily accepted air oxidation, **14** was not isolated. Because of the irreproducible yield, we tried to synthesize *ortho*-quinone **3** by selective oxidation (entries 2–5). The reaction of **11** with DDQ gave only the undesired *ortho*-quinone **15** (entry 2). The oxidation by ammonium cerium(IV) nitrate (CAN) afforded the desired *ortho*-quinone **3** (12% yield) and the undesired *ortho*-quinone **15** (35% yield) (entry 3). The reactions at low temperature increased the selectivity of *ortho*-quinone **3** (entries 4 and 5). However, we could not satisfy the yield and selectivity in this transformation; therefore, we next tried oxidation of protected catechol by two methylene acetal groups.

Table 1. Study of the removal of the acetonide group in **11**.



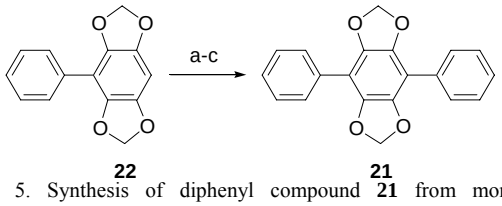
Entry	Conditions	**14**	**3**	**15**	**11**
1	6 M HCl, THF-MeOH, 100 ºC	0%	~59%	0%	0%
2	DDQ, CH_2Cl_2-H_2O, rt, 2 days	–	0%	37%	50%
3	CAN, MeCN-H_2O, 0 ºC, 5 min.	–	12%	35%	0%
4	CAN, MeCN-H_2O, −20 ºC, 5 min.	–	31%	47%	0%
5	CAN, MeCN-H_2O, −40 ºC, 10 min.	–	27%	25%	0%

The hydroxyl groups of catechol **7** were protected by the second methylene acetal (Scheme 4).[8] The bis-methylene acetal **16** was converted to diboronic acid **17** by double lithiation followed by treatment with B(O-*i*Pr)$_3$. Another borate reagent, B(OMe)$_3$, was less effective in this case. Furthermore, the bis-methylene acetal **16** was converted to boronate **19** and pinacolborane **20** by sequential boronation and esterfication.



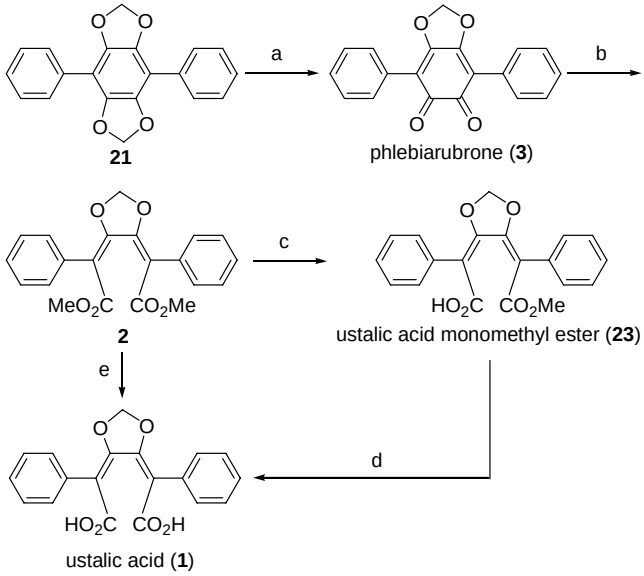
Scheme 4. Synthesis of boronate compounds. Reagents and conditions: a) CH_2Br_2, Cs_2CO_3, DMF, 90 °C, 46% (from sesamol); b) *n*-BuLi, TMEDA, B(O-*i*Pr)$_3$, Et_2O, -78 °C to rt, **17**: 55%, **18**: 12%, recovered **16**: 21%; c) trimethylene glycol, toluene, reflux; d) pinacol, $MgSO_4$, CH_2Cl_2, rt.

Next, we attempted a Suzuki–Miyaura coupling,[3] as depicted in Table 2. A cross-coupling reaction between diboronic acid **17** and iodobenzene with $Pd(PPh_3)_4$ or $PdCl_2$(dppf) afforded monophenyl compound **22** and bis-methylene acetal **16** (entries 1 and 2). An attempt at a cross-coupling reaction of the diboronic acid **17** with $PdCl_2(PPh_3)_2$ and Cs_2CO_3 in DMF at room temperature gave the desired diphenyl compound **21**, but the yield was low (8%) (entry 3). The reaction at 90 °C afforded the desired diphenyl compound **21** in 30% yield along with monophenyl compound **22** (18%) and bis-methylene acetal **16** (4%) (entry 4). The cross-coupling reaction of the boronate **19** with $PdCl_2(PPh_3)_2$ and Cs_2CO_3 in DMF afforded the desired diphenyl compound **21** in 43% yield (entry 5). Treatment of pinacolborane **20** under the same conditions gave the desired diphenyl compound **21** in 62% yield (entry 6). In entries 5 and 6, the crude boronic esters **19** and **20** were employed, and the yields were calculated from **16** in 3 steps. Thus, this cross-coupling was the most efficiently effected by using pinacolborane **20**. Also, monophenyl compound **22** was transformed into the desired diphenyl compound **21** by the same reactions (Scheme 5).



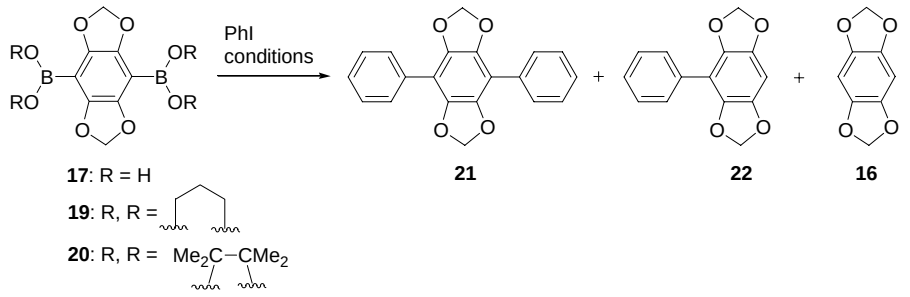
Scheme 5. Synthesis of diphenyl compound **21** from monophenyl compound **22**. Reagents and conditions: a) *n*-BuLi, TMEDA, B(O-*i*Pr)$_3$, Et_2O, -78 °C to rt; b) pinacol, $MgSO_4$, CH_2Cl_2, rt; c) PhI, $PdCl_2(PPh_3)_2$, Cs_2CO_3, DMF, 90 °C, 27% in 3 steps, (recovered **16**: 27%).

Since the diphenyl compound **21** has been synthesized in an available yield, we attempted oxidation of **21**. Oxidation of **21** with CAN gave phlebiarubrone (**3**) in quantitative yield (Scheme 6). To convert phlebiarubrone (**3**) to ustalic acid dimethyl ester (**2**), we followed the procedure reported by Nishikawa et al.[2] with a modification. Phlebiarubrone (**3**) was treated with $Pb(OAc)_4$ (20 equiv) in MeOH and toluene in the presence of K_2CO_3 (2.1 equiv) to give ustalic acid dimethyl ester (**2**). This modification increased the yield of the ustalic acid dimethyl ester (**2**) to 11%. Hydrolysis of the ustalic acid dimethyl ester (**2**) with 3 M KOH aq. in DMSO at room temperature for 1 day afforded the ustalic acid monomethyl ester (**23**). The monomethyl ester **23** was treated under the same conditions for 4 days to give ustalic acid (**1**) in 38% yield. The reaction at 70 °C for 39 h gave ustalic acid (**1**) in 23% yield. Synthetic ustalic acid (**1**) gave spectral data (^{1}H NMR, ^{13}C NMR, IR, and HRMS) in full agreement with those of the natural one,[1] thus completing the total synthesis.



Scheme 6. Synthesis of ustalic acid (**1**). Reagents and conditions: a) CAN, MeCN-H_2O, 0 °C, quant.; b) $Pb(OAc)_4$, K_2CO_3, toluene, MeOH, rt, 11%; c) 3 M KOH aq., DMSO, rt; d) 3 M KOH aq., DMSO, rt, 38% in 2 steps; e) 3 M KOH aq., DMSO, 70 °C, 23%.

Table 2. Study of Suzuki–Miyaura coupling.



		Conditions				Yield		
Entry	Substrate	Catalyst	Solvent	Base	Temp.	**21**	**22**	**16**
1	**17**	$Pd(PPh_3)_4$	1,4-dioxane	Na_2CO_3 *aq*	rt	0%	16%	31%
2	**17**	$PdCl_2(dppf)$	DME	K_3PO_4 *aq*	60 °C	0%	43%	8%
3	**17**	$PdCl_2(PPh_3)_2$	DMF	Cs_2CO_3 *aq*	rt	8%	13%	11%
4	**17**	$PdCl_2(PPh_3)_2$	DMF	Cs_2CO_3 *aq*	90 °C	30%	18%	4%
5*	**19**	$PdCl_2(PPh_3)_2$	DMF	Cs_2CO_3	rt	43%	16%	32%
6*	**20**	$PdCl_2(PPh_3)_2$	DMF	Cs_2CO_3	90 °C	62%	3.2%	0%

* Isolated yields calculated from **16** (in 3 steps).

3. Conclusion

In summary, we achieved the first synthesis of ustalic acid (**1**) by using the Suzuki–Miyaura coupling as a key step. Further structure–activity relationship studies are now in progress.

4. Experimental

4.1 General methods.

^{1}H NMR spectra were recorded on a JEOL JNM-EX270 (270 MHz), or a Bruker AVANCE 500 (500 MHz) spectrometer. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm) downfield from tetramethylsilane as the internal standard, and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. ^{13}C NMR spectra were recorded on a JEOL JNM-EX270 (67.8 MHz), or a Bruker AVANCE 500 (125 MHz) spectrometer. Chemical shifts for ^{13}C NMR are reported in ppm, relative to the central line of a triplet at 77.0 ppm for deuteriochloroform. IR spectra were recorded on a JASCO FT/IR-300 instrument and are reported in wavenumbers (cm^{-1}). ESI mass spectra were recorded on a Applied Biosystems QStar/Pulsar *i* spectrometer. Elemental analyses were recorded on a Yanaco CHN CORDER MT-6. TLC analysis were conducted on E. Merck precoated silica gel 60 F_{254} (0.25 mm layer thickness). Fuji Silysia silica gel BW-820 MH was used for column chromatography unless otherwise noted. Organic solvents for moisture-sensitive reactions were distilled from the following drying agents: THF, Et_2O, DME, and 1,4-dioxane (Na-benzophenone ketyl), benzene and toluene (Na). Anhydrous acetone, MeOH, CH_2Cl_2 and DMF were purchased from Kanto Chemical Co., Inc., or Wako Pure Chemical Industries, Ltd., and used without further drying. All moisture-sensitive reactions were performed under an atmosphere of argon or nitrogen, and the starting materials were azeotropically dried with benzene before use. All new compounds were determined to be >95% pure by ^{1}H NMR unless otherwise noted.

*4.2 Bis-methylene acetal **16.***

To a stirred solution of catechol **7** (1.02 g, 6.62 mmol) and Cs_2CO_3 (2.67 g, 8.19 mmol) in DMF (10 mL) was added CH_2Br_2 (0.71 mL, 9.93 mmol) at room temperature, and the mixture was stirred at 90 °C for 19 h. After cooling to room temperature, the mixture was diluted with Et_2O (30 mL), filtrated with Celite, and this Celite was rinsed with Et_2O (3×6 mL). The filtrate and rinse were washed with

H_2O (3×10 mL), and the aqueous layer was extracted with Et_2O (3×6 mL). The combined organic layers were washed with 1 M NaOH aq. (×3), H_2O (×2), and brine (×1); dried (Na_2SO_4); and concentrated. The residual oil was purified by column chromatography on silica gel (15 g, *n*-hexane–EtOAc 30:1→10:1) to give bis-methylene acetal **16** (489 mg, 46%.) as a white solid: colorless crystals; Mp 139-140 °C (*n*-hexane–CH_2Cl_2); ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.48 (s, 2H), 5.86 (s, 4H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 141.1, 101.0, 93.0; *Anal.*Calcd. for $C_8H_6O_4$: C, 57.84; H, 3.64; O, 38.52%. Found: C, 57.76; H, 3.76; O, 38.57%.

*4.3 Diphenyl compound **21**.*

To a stirred solution of bis-methylene acetal **16** (400 mg, 2.41 mmol) in Et_2O (10 mL) at 0 °C were added TMEDA (1.0 mL, 6.71 mmol) and *n*-BuLi (1.61 M solution in *n*-hexane, 4.5 mL, 7.25 mmol) under nitrogen flow, and the resultant mixture was stirred at 0 °C for 30 min. After cooling to –78 °C, B(O-*i*Pr)$_3$ (2.8 mL, 12.2 mmol) in Et_2O (4.2 mL) was added, and the resultant mixture was stirred at –78 °C for 1 h. The mixture was stirred at room temperature for 17 h, diluted with 1 M HCl to pH 1, and extracted with $CHCl_3$ (4×15 mL). The combined extracts were dried (Na_2SO_4) and concentrated to afford crude diboronic acid **17** (670 mg), which was used for the next reaction without further purification.

The crude diboronic acid **17** (670 mg), pinacol (2.26 g, 19.1 mmol), and $MgSO_4$ (1.30 g, 10.8 mmol) were dissolved in CH_2Cl_2 (16 mL), and the resultant mixture was stirred at room temperature for 17.5 h. The mixture was filtrated with Celite, and this Celite was rinsed with CH_2Cl_2 (3×5 mL). The filtrate and rinse were combined and concentrated to afford crude diboronic pinacol ester **20** (1.28 g), which was used for the next reaction without further purification.

All solvents were degassed by freeze-thawing. To a stirred solution of crude diboronic pinacol ester **20** (1.28 g) and iodobenzene (0.8 mL, 7.18 mmol) in DMF (10 mL) were added $PdCl_2(PPh_3)_2$ (190 mg, 0.24 mmol) and Cs_2CO_3 (2.34 g, 7.18 mmol) at room temperature in a glove box. The mixture was stirred at 90 °C for 14 h under nitrogen flow and diluted with H_2O (10 mL) at room temperature. The resultant mixture was filtrated with Celite, and this Celite was rinsed with Et_2O (3×10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3×15 mL). The combined Et_2O layers were washed with 1 M HCl (×2), H_2O (×1), and brine (×1); dried (Na_2SO_4); and concentrated. The residual solid was purified by recrystallization from *n*-hexane−CH_2Cl_2 to give diphenyl compound **21** (451 mg, 59% in 3 steps) as colorless crystals. The mother liquid was concentrated, and the residual solid was purified by recycle HPLC [JAIGEL-1H-40 (600×20 mm) and JAIGEL-2H-40 (600×20 mm); flow rate 3.8 mL/min; detection, UV 254 nm; solvent $CHCl_3$] to give diphenyl compound **21** (21.7 mg, 2.8% in 3 steps; total 473 mg, 62% in 3 steps) and monophenyl compound **22** (18.7 mg, 3.2% in 3 steps) as colorless crystals, respectively: Diphenyl compound **21**: Mp 204-205 °C (*n*-hexane–CH_2Cl_2); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.82-7.86 (m, 4H), 7.42-7.48 (m, 4H), 7.31-7.37 (m, 2H), 6.00 (s, 4H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 139.0, 131.2, 128.8, 128.2, 127.8, 107.8, 100.8; *Anal.*Calcd. for $C_{20}H_{14}O_4$: C, 75.46; H, 4.43; O, 20.10%. Found: C, 75.19; H, 4.57; O, 20.24%; Monophenyl compound **22**: Mp 138-139 °C (*n*-hexane–CH_2Cl_2); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.78-7.83 (m, 2H), 7.41-7.47 (m, 2H), 7.31-7.37 (m, 1H), 6.49 (s, 1H), 5.93 (s, 4H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 141.4, 138.7, 131.2, 128.7, 128.2, 127.8, 108.9, 101.0, 92.1; *Anal.*Calcd. for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16; O, 26.42%. Found: C, 69.25; H, 4.26; O, 26.49%.

*4.4 phlebiarubrone (**3**).*

To a stirred solution of diphenyl compound **21** (410 mg, 1.28 mmol) in acetonitrile (97 mL) was added CAN (1.0 M solution in H_2O, 3.9 mL, 3.90 mmol) at 0 °C, and the mixture was stirred at 0 °C for 3 min. The mixture was diluted with H_2O (80 mL) and extracted with $CHCl_3$ (3×15 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (10 g, *n*-hexane–EtOAc 10:1→4:1) to give red solid. The red solid was purified by recrystallization from *n*-hexane−CH_2Cl_2 to give phlebiarubrone (**3**) (389 mg, quant.) as red crystals: Mp 248-250 °C (*n*-hexane–CH_2Cl_2); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.60-7.65 (m, 4H), 7.34-7.48 (m, 6H), 6.13 (s, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 175.9, 156.1, 129.4, 128.7, 128.6, 128.1, 113.7, 102.7; HRESIMS *m/z* 327.0636, calcd for $C_{19}H_{12}NaO_4$ $[M+Na]^+$ 327.0633.

*4.5 ustalic acid dimethyl ester (**2**).*

Phlebiarubrone (**3**) (100 mg, 0.329 mmol), $Pb(OAc)_4$ (2.92 g, 6.59 mmol), and K_2CO_3 (96.2 mg, 0.696 mmol) were dissolved in toluene (8.2 mL) and MeOH (5.8 mL). The resultant mixture was stirred at room temperature for 47 h, diluted with H_2O (15 mL) and ethylene glycol (a few drops), and filtrated with Celite. The filtrate was extracted with Et_2O (4×15 mL). The combined extracts were washed with H_2O, saturated aqueous $NaHCO_3$, and H_2O; dried (Na_2SO_4); and concentrated. The residual oil was purified by column chromatography on silica gel (8.0 g, *n*-hexane–EtOAc 5:1→2:1), preparative TLC (CH_2Cl_2), and preparative TLC (*n*-hexane–EtOAc 2:1) to give ustalic acid dimethyl ester (**2**) (13 mg, 11%) as a yellow solid: IR (film) 1718, 1637 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.31-7.42 (m, 10H), 5.41 (s, 2H), 3.73 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 167.5, 148.6, 134.4, 129.8, 127.9, 127.8, 115.2,

95.9, 52.2; HRESIMS *m/z* 389.0998, calcd for $C_{21}H_{18}NaO_6$ $[M+Na]^+$ 389.1001.

*4.6 ustalic acid (**1**).*

The ustalic acid dimethyl ester (**2**) (2.6 mg, 7.10 μmol) was treated with 3 M KOH aq.–DMSO (1:1, 0.45 mL) at room temperature for 24 h. The mixture was diluted with saturated NaH_2PO_4 to pH 3 and extracted with $CHCl_3$ (×4). The combined extracts were dried (Na_2SO_4) and concentrated to afford crude ustalic acid monomethyl ester (**23**) (2.3 mg), which was used for the next reaction without further purification.

The crude ustalic acid monomethyl ester (**23**) (2.3 mg) was treated with 3 M KOH aq.–DMSO (1:1, 0.45 mL) at room temperature for 4 days. The mixture was diluted with saturated NaH_2PO_4 to pH 3 and extracted with $CHCl_3$ (×4). The combined extracts were dried (Na_2SO_4) and concentrated to afford crude ustalic acid (**1**). The residual oil was purified by HPLC (Develosil ODS-HG-5 (250×20 mm), flow rate 5 mL/min; detection, UV 254 nm; solvent 50% MeOH/0.1% TFA) to give ustalic acid (**1**) (0.9 mg, 38%, retention time 91.2 min) as a white solid: IR (film) 1698, 1630 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.29-7.41 (m, 10H), 5.46 (s, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 174.2, 149.2, 133.4, 129.9, 128.2, 127.9, 115.0, 96.3; HRESIMS *m/z* 361.0686, calcd for $C_{19}H_{14}NaO_6$ $[M+Na]^+$ 361.0688.

Acknowledgments

This work was supported in part by Grants-in-Aid for Scientific Research on Priority Area (No. 16073204, ‘‘Creation of Biologically Functional Molecules’’); and by the 21st COE program from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan. We would like to thank Mr. Ikuo Iida (University of Tsukuba) for the elemental analyses.

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