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THE FIRST TOTAL SYNTHESES OF SCHOLAREINS A, C, AND D EMPLOYING 2ND GENARATION PALLADIUM-CATALYZED CYCLOALKENYLATION

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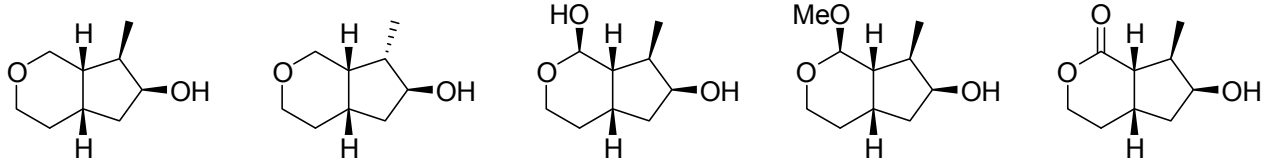
Abstract – (±)-Scholareins A (**1**), C (**3**), and D (**4**) have been synthesized for the first time by a 2nd generation palladium-catalyzed cycloalkenylation. In addition, total synthesis of (±)-boonein (**5**) has also been achieved by applying the same catalytic cyclization as the key step.

INTRODUCTION

In 1983, boonein (**5**), a possible precursor in the indole alkaloid biogenesis, was isolated from the bark of *Alstonia boonei*.[1] Structurally similar 11-noriridoids, scholareins A (**1**), B (**2**), C (**3**), and D (**4**) were also isolated in 2008 from EtOH extract of the bark of *Alstonia scholaris*, which is widely distributed in the tropical regions of Africa and Asia.[2] While two research groups have independently achieved total syntheses of boonein (**5**),[3] no laboratory synthesis of scholareins has been described (Figure 1).

As part of our ongoing program on the synthesis of biologically active iridolactones via the 2nd generation palladium-catalyzed cycloalkenylation developed by us,[4] we undertook the synthesis of boonein (**5**) and scholareins A-D (**1**-**4**). Herein, we disclose the first total syntheses of 11-noriridoids, scholareins A (**1**), C (**3**), and D (**4**), using the 2nd generation palladium-catalyzed cycloalkenylation.



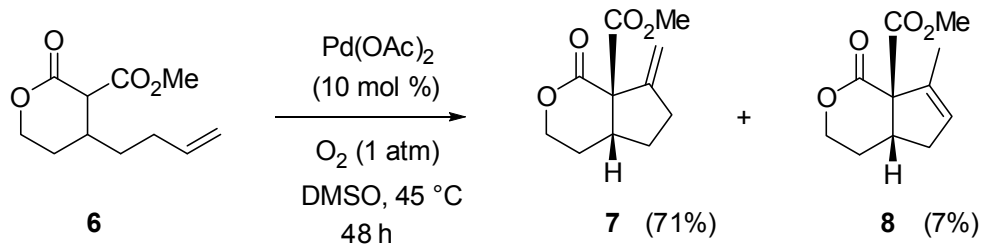
scholarein A (**1**) scholarein B (**2**) scholarein C (**3**) scholarein D (**4**) boonein (**5**)

Figure 1

Dedicated to Professor Ei-ichi Negishi on the occasion of his 77th birthday

RESULTS AND DISCUSSION

Since we have already demonstrated a 2nd generation palladium-catalyzed cycloalkenylation of olefinic lactone ester **6** in total syntheses of onikulactone and mitsugashiwalactone,[5] we next focused on developing a concise method for transformation of **7** into further oxidized iridoids, such as boonein (**5**) and scholareins (**1**-**4**) (Scheme 1). It should be noted that the yield and the product ratio (**7** versus **8**) of the 2nd generation palladium-catalyzed cycloalkenylation of **6** could be increased after a prolonged reaction time.

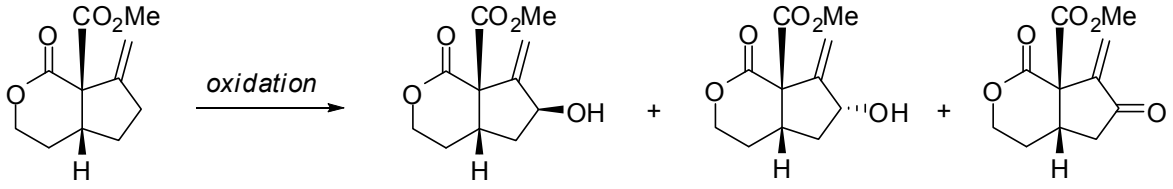


6 **7** (71%) **8** (7%)

Scheme 1

After separation of compounds **7** and **8**, exo-olefin **7** was subjected to allylic oxidation under a variety of conditions. Some of the conditions and yields examined for allylic oxidation of **7** are listed in Table 1. Although no allylic alcohol was obtained using SeO_2 in CH_2Cl_2-AcOH, enone **11** was produced in 14% yield (entry 1). Allylic alcohols **9** and **10** were produced in 52% yield as an 11:9 separable mixture when the reaction was performed in the presence of 6.0 equivalents of SeO_2 in CH_2Cl_2-AcOH-H_2O (entry 2). The best result, 80% yield (based upon recovered starting material **7**), was obtained for the reaction using 1.4 equivalents of SeO_2 and 6.4 equivalents of *tert*-butyl hydroperoxide in CH_2Cl_2-THF-HMPA (3.8:8.5:1 v/v) as solvent (entry 3). The relative stereochemistry of **10** was established on the basis of NOE correlation as depicted in Figure 2. It should be noted that the reaction solvent is a critical factor in the allylic oxidation. Investigations into the solvent effect are underway.

With allylic alcohol **9** in hand, a stereoselective hydrogenation was next conducted in the presence of a catalytic amount of Rh-Al_2O_3 in EtOH to lead to a 4:1 separable mixture of **12** and **13** in nearly quantitative yield. The relative stereochemistry of the major product **12** was elucidated by the NOE correlation shown in Figure 3. Finally, **12** was transformed into (±)-boonein (**5**) after removal of the ester moiety under the Krapcho reaction conditions (Scheme 2).[6] The ^1H and ^{13}C NMR spectra of the synthetic (±)-boonein (**5**) were identical to those reported.[1]

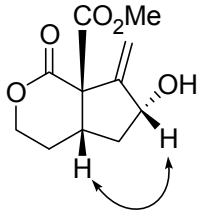


7 **9** **10** **11**

entry	reagent (equiv)	solvent	temperature (°C)	time (h)	yield (%)		
					9 + **10** (**9** : **10**)		**11**
1	SeO_2 (6.0)	CH_2Cl_2-AcOH (30 : 1)	60	24	0		14
2	SeO_2 (6.0)	CH_2Cl_2-AcOH-H_2O (45 : 1.6 : 1)	30	62	52	(9 : 11)	6
3	SeO_2 (1.4) ^{t}BuOOH (6.4)	CH_2Cl_2-THF-HMPA (3.8 : 8.5 : 1)	80	24	80[a]	(1 : 1)	0

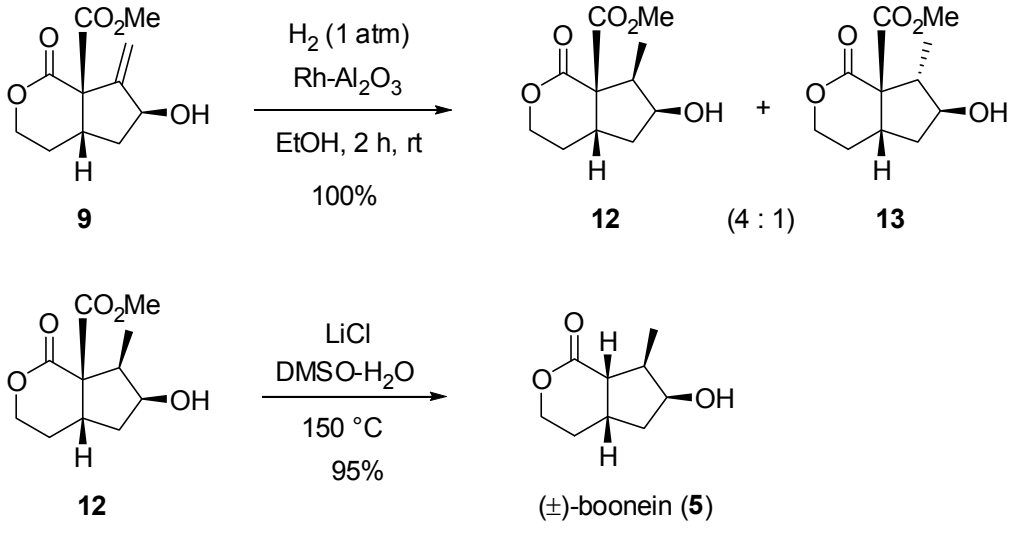
a) based upon recovered starting material **7**.

Table 1



10

Figure 2



9 **12** **13**

12 (±)-boonein (**5**)

Scheme 2

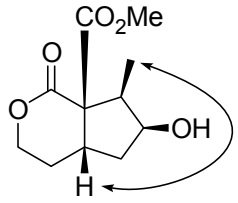


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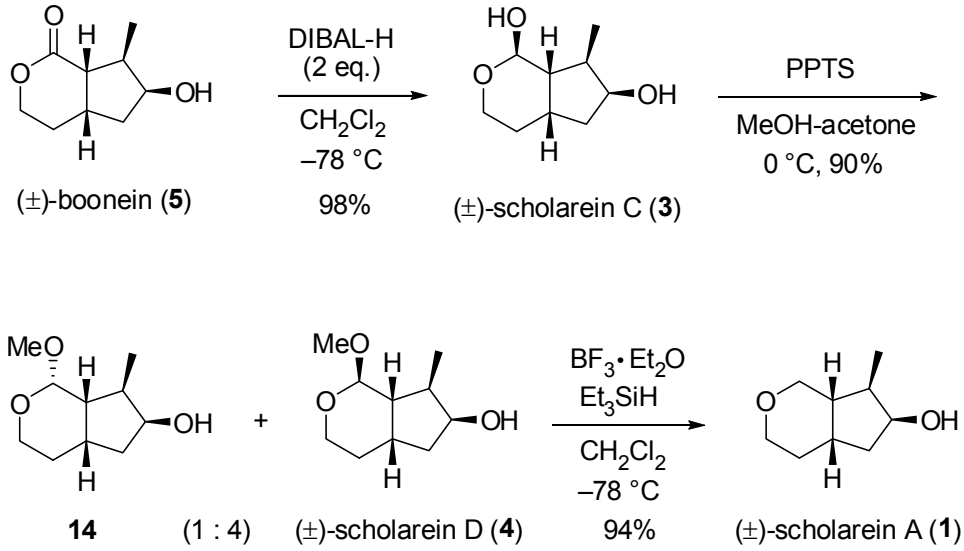
Figure 3

To assemble (±)-scholareins A (**1**), C (**3**), and D (**4**), (±)-boonein (**5**) was reduced with 2 equivalents of DIBAL-H to give rise to (±)-scholarein C (**3**) in 98% yield. Upon treatment of **3** with PPTS in MeOH-CH_2Cl_2 at 0 °C, (±)-scholarein D (**4**) was afforded as a major acetal together with **14**. Although (±)-scholarein D (**4**) was easily separable, (±)-scholarein A (**1**) was directly produced from a mixture of (±)-scholarein D (**4**) and **14** in 94% yield when the mixture was treated with boron trifluoride etherate in the presence of triethylsilane (Scheme 3).[7] The spectral properties of the synthetic compounds **1**, **3** and **4** were identical to the corresponding previously reported spectra.[2]



Scheme 3

In conclusion, we have achieved the first total synthesis of (±)-scholareins A (**1**), C (**3**), and D (**4**) by means of 2nd generation palladium-catalyzed cycloalkenylation. The methodology developed here should also provide access to synthetic analogues of scholareins.

EXPERIMENTAL

Unless otherwise noted, all reactions were performed in an oven-dried glassware, sealed with a rubber septum under an atmosphere of argon. Anhydrous THF, CH_2Cl_2, and Et_2O were purchased from Kanto Chemical Co., Inc. DMSO and HMPA were distilled from CaH_2 under reduced pressure. Unless otherwise mentioned, materials were obtained from commercial suppliers and used without further purification. Flash column chromatography was carried out using Cica 60 N (spherical / 40-50 μm) silica gel. Reactions and chromatography fractions were analyzed employing precoated silica gel 60 F_{254} plates (Merck). Compounds were visualized using an ultraviolet lamp (254 nm) and/or by staining with *p*-anisaldehyde (in EtOH), phosphomolybdic acid (in EtOH), ammonium molybdate (in 10% H_2SO_4), or potassium permanganate (in water containing NaOH and K_2CO_3). IR spectra were measured on a SHIMADZU FT-IR 8300 spectrophotometer. ^{1}H NMR spectra were recorded on Varian 400 MR (400 MHz), JEOL AL-400 (400 MHz) or JEOL JX-500 (500 MHz) spectrometers with tetramethylsilane (δ 0), $CHCl_3$ (δ 7.26), C_6H_6 (δ 7.16), or CH_3COCH_3 (δ 2.05) as an internal standard. ^{13}C NMR spectra were recorded on Varian 400 MR (100 MHz) spectrometers with $CDCl_3$ or Acetone-d_6 as an internal standard. Mass spectra were recorded on JEOL JMS-DX 303, JEOL JMS-AX 500, or JEOL JMS-AX 700 spectrometers. All melting points were determined on Yanaco micro melting point apparatus and are uncorrected. Analytical and semipreparative HPLC separation were performed by using a HPLC system composed of a Jacso PU-2086 pump, a Jasco UV-2075 detector, and a Jasco RI-2031 detector.

(1*SR*,6*RS*)-Methyl 9-methylene-2-oxo-3-oxabicyclo[4.3.0]nonane-1-carboxylate (7) and (1*SR*,6*RS*)-Methyl 9-methyl-2-oxo-3-oxabicyclo[4.3.0]non-8-en-1-carboxylate (8): To a solution of **6** (50 mg, 0.24 mmol) in DMSO (0.50 mL), $Pd(OAc)_2$ (5.39 mg, 0.024 mmol) was added at rt, and then the resulting mixture was stirred at 45 °C for 48 h under an atmosphere of oxygen. To the reaction mixture was added saturated aqueous $NaHCO_3$ solution, and then the mixture was extracted three times with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, and evaporated to afford a crude oil. The crude product was purified by flash column chromatography with hexane-EtOAc (3:1 v/v) as an eluent, giving **7** (35.9 mg, 71%) as a pale yellow oil and **8** (3.5 mg, 7%) as a pale yellow oil.

Data for **7**: IR (neat) 1745, 1730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (1H, dd, *J* = 2.0, 2.0 Hz), 5.33 (1H, dd, *J* = 2.0, 2.0 Hz), 4.36 (1H, ddd, *J* = 11.5, 4.8, 4.4 Hz), 4.42 (1H, ddd, *J* = 11.4, 10.2, 3.0 Hz), 3.77 (3H, s), 3.01 (1H, ddd, *J* = 13.3, 8.7, 6.8 Hz), 2.56-2.50 (2H, m), 2.08-1.94 (2H, m), 1.68 (1H, dddd, *J* = 14.3, 10.2, 8.6, 4.0 Hz), 1.53 (1H, dddd, *J* = 12.8, 7.8, 7.8, 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 168.3, 146.7, 113.6, 67.7, 63.7, 53.4, 42.9, 31.4, 30.3, 27.2. Data for **8**: IR (neat) 1745, 1730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 (1H, br s), 4.35 (1H, ddd, *J* = 11.2, 7.6, 3.2 Hz), 4.28 (1H, dddd, *J* = 11.2, 7.2, 2.8, 0.4 Hz), 3.78 (3H, s), 3.08-3.01 (1H, m), 2.79-2.70 (1H, m), 2.22-2.06 (2H, m), 1.87 (3H,

br s), 1.77-1.69 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 168.3, 137.0, 131.4, 67.7, 66.9, 53.1, 41.1, 38.1, 29.4, 14.8.

(1*SR*,6*SR*,8*SR*)-Methyl 8-hydroxy-9-methylene-2-oxo-3-oxabicyclo[4.3.0]nonane-1-carboxylate (9) and (1*SR*,6*SR*,8*RS*)-Methyl 8-hydroxy-9-methylene-2-oxo-3-oxa-bicyclo[4.3.0]nonane-1-carboxylate (10). To a suspension of selenium oxide (22.2 mg, 0.20 mmol) in CH_2Cl_2 (1.5 mL), ^{t}BuO$_2$H (0.13 mL, 0.92 mmol) was added dropwise at rt. After 20 min of vigorous stirring, a solution of **7** (30 mg, 0.14 mmol) in THF (3.4 mL) and HMPA (5.0 mL, 28.7 mmol) was added to the mixture. The resulting mixture was heated at 80 °C and stirred at the same temperature for 24 h. After cooling to rt, a saturated aqueous solution of $NaHCO_3$/Na_2SO_3 was added, and then the resulting mixture was stirred for 30 min. The mixture was extracted three times with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$, and evaporated to afford a crude oil. The crude product was purified by flash column chromatography with hexane-EtOAc (1:3 v/v) as an eluent, giving a separable mixture of **9** and **10** (18.2 mg, 80%, based on recovered starting material) as a pale yellow oil. Data for **9**: IR (neat) 3437, 1728, 1267 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (2H, d, *J* = 7.2 Hz), 4.62-4.58 (1H, m), 4.37-4.25 (2H, m), 3.81 (3H, s), 3.23 (1H, dddd, *J* = 7.2, 7.2, 7.2, 7.2 Hz), 2.22-2.14 (2H, m), 2.04 (1H, ddd, *J* = 13.6, 7.6, 3.2 Hz), 1.78 (1H, ddd, *J* = 13.6, 8.0, 5.6 Hz), 1.66 (1H, ddd, *J* = 14.6, 7.6, 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 168.3, 149.2, 114.3, 73.0, 67.0, 61.2, 53.5, 38.6, 38.3, 27.7; LRMS *m/z* 167 [(M-CO_2CH_3)$^+$]; HRMS calcd for $C_{11}H_{14}O_5$ (M^+) 226.0841, $C_9H_{11}O_3$ [(M-CO_2CH_3)$^+$] 167.0708, found 167.0718. Data for **10**: IR (neat) 3438, 1731, 1269 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (2H, dd, *J* = 2.0, 2.0 Hz), 4.62-4.57 (1H, m), 4.39 (1H, ddd, *J* = 11.4, 6.4, 3.6 Hz), 4.23 (1H, ddd, *J* = 10.4, 10.0, 2.8 Hz), 3.77 (3H, s), 2.94 (1H, dddd, *J* = 7.6, 7.6, 7.6, 7.6 Hz), 2.32 (1H, ddd, *J* = 13.2, 7.2, 7.2 Hz), 2.21-2.12 (2H, m), 1.88-1.79 (1H, m), 1.49 (1H, ddd, *J* = 7.6, 7.6, 13.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 167.7, 148.9, 117.8, 74.5, 67.1, 61.9, 53.8, 40.2, 39.3, 27.3; LRMS *m/z* 167 [(M-CO_2CH_3)$^+$]; HRMS calcd for $C_{11}H_{14}O_5$ (M^+) 226.0841, $C_9H_{11}O_3$ [(M-CO_2CH_3)$^+$] 167.0708, found 167.0710. Data for **(1*SR*,6*SR*,8*RS*)-Methyl 2,8-dioxo-9-methylene-3-oxabicyclo[4.3.0]-nonane-1-carboxylate (11):** IR (neat), 1730, 1647 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (1H, s), 6.03 (1H, s), 4.45- 4.42 (2H, m), 3.82 (3H, s), 3.19-3.12 (1H, m), 2.73 (1H, dd, *J* = 18.4, 8.4 Hz), 2.29 (1H, dd, *J* = 18.4, 3.2 Hz), 2.13-2.06 (1H, m), 1.73-1.63 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 167.7, 148.9, 117.8, 74.5, 67.1, 61.9, 53.8, 40.2, 39.3, 27.3; LRMS *m/z* 165 [(M-CO_2CH_3)$^+$]; HRMS calcd for $C_{11}H_{12}O_5$ (M^+) 224.0685, $C_9H_9O_3$ [(M-CO_2CH_3)$^+$] 165.0552, found 165.0552.

(1*SR*,6*SR*,8*SR*,9*SR*)-Methyl 8-hydroxy-9-methyl-2-oxo-3-oxabicyclo[4.3.0]nonane-1-carboxylate (12) and (1*SR*,6*SR*,8*SR*,9*RS*)-Methyl 8-hydroxy-9-methyl-2-oxo-3-oxabicyclo[4.3.0]nonane-1-carboxylate (13). To a stirred solution of **9** (32.0 mg, 0.14 mmol) in EtOH (3.0 mL), rhodium-alumina (10.3 mg, 0.050 mmol) was added. The mixture was stirred at rt under an atmosphere of hydrogen. After 2 h,

the reaction mixture was filtered through Celite® and the filtrate was concentrated *in vacuo* to afford a crude oil. The crude product was purified by flash column chromatography with hexane-EtOAc (1:3 v/v) as an eluent, giving **12** (25.6 mg, 80%) as a colorless oil and **13** (6.40 mg, 20%) as a colorless oil. Data for **12**: IR (neat) 3471, 1730, 1263 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.35 (1H, ddd, *J* = 11.6, 2.8, 2.8 Hz), 4.07-4.01 (2H, m), 3.82 (3H, s), 3.25-3.18 (1H, m), 2.78-2.70 (1H, m), 2.31-2.21 (2H, m), 1.62-1.47 (2H, m), 1.20 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 171.3, 75.8, 67.7, 62.0, 53.8, 47.6, 43.2, 42.7, 30.7, 11.0; LRMS *m/z* 169 [$(M\text{-}CO_2CH_3)^+$]; HRMS calcd for $C_{11}H_{16}O_5$ (M^+) 228.0998, $C_9H_{13}O_3$ [$(M\text{-}CO_2CH_3)^+$] 169.0865, found 169.0861. Data for **13**: IR (neat) 3459, 1730, 1271 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.45-4.34 (2H, m), 4.03 (1H, br s), 3.78 (3H, s), 3.04-2.97 (2H, m), 2.32-2.23 (2H, m), 2.06 (1H, dddd, *J* = 15.6, 8.8, 1.2, 1.2 Hz), 1.85 (1H, ddd, *J* = 13.7, 8.6, 4.8 Hz), 1.66 (1H, dddd, *J* = 14.0, 6.4, 6.4, 3.2 Hz), 1.05 (3H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 168.9, 78.3, 67.3, 62.7, 53.7, 49.1, 39.4, 38.7, 27.9, 15.6; LRMS *m/z* 169 [$(M\text{-}CO_2CH_3)^+$]; HRMS calcd for $C_{11}H_{16}O_5$ (M^+) 228.0998, $C_9H_{13}O_3$ [$(M\text{-}CO_2CH_3)^+$] 169.0865, found 169.0861.

(±)-Boonein (5). A mixture of **12** (5.3 mg, 0.023 mmol), lithium chloride (10.0 mg, 0.23 mmol), and one drop of H_2O in DMSO (0.30 mL) was stirred at 150 °C for 2 h. After cooling to rt, H_2O was added, and the resulting mixture was extracted three times with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, and evaporated to afford a crude oil. The crude product was purified by flash column chromatography with hexane-EtOAc (1:3 v/v) as an eluent, giving **5** (3.7 mg, 95%) as a colorless solid; mp 92 °C. Data for (±)-boonein (**5**): IR (neat) 3415, 1698, 1273 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.32 (1H, ddd, *J* = 11.2, 6.0, 3.2 Hz), 4.21 (1H, ddd, *J* = 11.2, 8.8, 2.4 Hz), 4.15-4.13 (1H, m), 2.93-2.82 (1H, m), 2.66 (1H, dd, *J* = 10.8, 10.8 Hz), 2.29-2.20 (1H, m), 2.14-2.06 (2H, m), 1.53-1.45 (2H, m), 1.24 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 75.4, 67.1, 47.3, 44.2, 41.2, 34.0, 29.6, 13.9; LRMS *m/z* 170 (M^+); HRMS calcd for $C_9H_{14}O_3$ (M^+) 170.0943, found 170.944.

(±)-Scholarein C (3). To a stirred solution of **5** (12.5 mg, 0.073 mmol) in CH_2Cl_2 (3.7 mL) was added dropwise DIBAL-H (1.02 M solution in hexane, 0.14 mL, 0.15 mmol) at –78 °C. After 1 h of stirring at –78 °C, H_2O was added dropwise over 5 min. The resulting mixture was slowly warmed to rt, and then hexane and EtOAc were added. The solution was cooled to 0 °C, and $MgSO_4$ was added. After 30 min of stirring, the resulting suspension was filtered through Celite®. The filtrate was concentrated to afford a crude oil. The crude product was purified by flash column chromatography with hexane-EtOAc (1:3 v/v) as an eluent, giving **3** (12.3 mg, 98%) as a colorless solid; mp 103 °C. Data for (±)-scholarein C (**3**): IR (neat) 3362 cm^{-1}; ^1H NMR (400 MHz, Acetone-d_6) δ 4.93 (1H, br s), 4.17-4.13 (1H, m), 3.87 (1H, ddd, *J* = 11.4, 11.4, 3.2 Hz), 3.37 (1H, ddd, *J* = 11.4, 3.6, 3.6 Hz), 2.41-2.32 (1H, m), 1.97-1.91 (1H, m), 1.80-1.61 (3H, m), 1.50-1.42 (1H, m), 1.34-1.27 (1H, m), 0.98 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, Acetone-d_6) δ 93.6, 73.6, 58.7, 48.8, 42.5, 39.5, 32.2, 30.1, 13.1; HRMS (FAB^+) calcd for $C_9H_{15}O_3$

$[(M-H)]^+$ 171.1021, found 171.1018.

(±)-Scholarein D (4). To a solution of **3** (16.0 mg, 0.093 mmol) in MeOH (5.0 mL) and acetone (0.10 mL), PPTS (1.2 mg, 4.7×10^{-3} mmol) was added at 0 °C. After 1 h of stirring at 0 °C, saturated aqueous $NaHCO_3$ solution was added and the resulting mixture was extracted three times with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, and evaporated to afford a crude oil. The crude product was purified by flash column chromatography with hexane-EtOAc (1:1 v/v) as an eluent, giving **4** (12.5 mg, 72%) as a colorless oil and **14** (3.1 mg, 18%) as a colorless oil. Data for (±)-scholarein D (**4**); IR (neat) 3426 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.54 (1H, br s), 4.27-4.22 (1H, m), 3.73 (1H, dddd, *J* = 11.6, 11.6, 2.8, 0.4 Hz), 3.49 (1H, ddd, *J* = 11.2, 4.8, 2.8 Hz), 3.38 (3H, s), 2.41-2.33 (1H, m), 2.07 (1H, ddq, *J* = 12.0, 6.8, 6.8, Hz), 1.86 (1H, ddd, *J* = 14.4, 6.4, 2.4 Hz), 1.76-1.69 (2H, m), 1.53-1.47 (1H, m), 1.40-1.29 (2H, m), 1.04 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.7, 74.2, 58.4, 54.9, 46.7, 42.0, 38.4, 31.4, 28.9 12.3; HRMS (FAB^+) calcd for $C_{10}H_{17}O_3$ $[(M-H)]^+$ 185.1178, found 185.1176. Data for **14**; IR (neat) 3434 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.59 (1H, d, *J* = 4.0 Hz), 4.25-4.21 (1H, m), 3.90 (1H, ddd, *J* = 11.2, 4.8, 2.8 Hz), 3.49 (1H, ddd, *J* = 11.2, 11.2, 3.6 Hz), 3.42 (3H, s), 2.33-2.17 (2H, m), 1.96 (1H, ddd, *J* = 9.6, 8.0, 3.6 Hz), 1.79-1.75 (2H, m), 1.59-1.43 (2H, m), 1.32 (1H, br s) 1.07 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.5, 75.3 63.2, 56.2, 47.5, 41.4, 37.3, 34.2, 28.5, 14.0; HRMS (FAB^+) calcd for $C_9H_{16}O_3$ $[(M-H)]^+$ 185.1178, found 185.1183.

(±)-Scholarein A (1). To a stirred solution of a mixture of **4** and **14** (7.0 mg, 0.036 mmol) and Et_3SiH (11.0 μL, 0.072 mmol) in CH_2Cl_2 (3.6 mL), $BF_3\cdot OEt_2$ (9.0 μL, 0.072 mmol) was added dropwise at –78 °C. After 0.5 h of stirring at –78 °C, saturated aqueous $NaHCO_3$ solution was added. The resulting mixture was allowed to warm to rt with vigorous stirring and then the mixture was extracted three times with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$, and evaporated to afford a crude oil. The crude product was purified by flash column chromatography with hexane-EtOAc (1:1 v/v) as an eluent, giving **1** (5.3 mg, 94%) as a colorless oil. Data for (±)-scholarein A (**1**); IR (neat) 3416 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.29-4.25 (1H, m), 3.85-3.80 (2H, m), 3.68 (1H, dd, *J* = 12.0, 3.6 Hz), 3.33 (1H, ddd, *J* = 11.6, 11.6, 2.4 Hz), 2.26-2.17 (1H, m), 2.10 (1H, ddq, *J* = 10.8, 6.8 6.8 Hz), 1.85 (1H, ddd, *J* = 14.4, 6.4, 3.2 Hz), 1.77 (1H, ddd, *J* = 14.8, 7.6, 3.2 Hz), 1.64-1.49 (2H, m) 1.43-1.32 (2H, m) 1.01 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.8, 67.4 67.0, 43.3, 41.7, 37.8, 34.0, 30.3, 11.9; HRMS (FAB^+) calcd for $C_9H_{15}O_3$ $[(M-H)]^+$ 155.1072, found 155.1070.

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