Total Synthesis of Hydroxy-*α*- and Hydroxy-*β*-sanshool Using Suzuki–Miyaura Coupling

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Here, we describe the first total synthesis of hydroxyl-*α*- and hydroxyl-*β*-sanshool, which involves Suzuki–Miyaura coupling (SMC). Hydroxy-*α*-sanshool (1) was synthesized by SMC of bromoalkyne 4 with boronate 3 followed by (*Z*)-selective reduction of the triple bond in the coupling product. Hydroxy-*β*-sanshool (2) was synthesized by regio- and (*E*)-selective conversion of 4 to iodoalkene 11 followed by SMC with 3.

Key words hydroxy-*α*-sanshool; hydroxyl-*β*-sanshool; Suzuki–Miyaura coupling; Zanthoxylum Fruit; Daikenchuto

Hydroxy-*α*-sanshool (**1**) was originally isolated as an unstable unsaturated aliphatic amide from the dried fruit of the Japanese pepper (*Zanthoxylum piperitum*).[1] This compound elicits several biological effects such as activation of transient receptor potential channels[2] and inhibition of potassium channels.[3] Hydroxy-*β*-sanshool (**2**), which is a geometric isomer of hydroxyl-*α*-sanshool (**1**), can also be isolated from the same dried fruit.[4] Zanthoxylum Fruit is one of the crude drugs in Kampo formulae 'Daikenchuto.' Moreover, hydroxyl-*α*- and hydroxyl-*β*-sanshool were detected in human plasma and urine after oral administration of Daikenchuto.[5,6] Consequently, in terms of delineating the mechanism of action of Daikenchuto, hydroxyl-*α*- and hydroxyl-*β*-sanshool are considered key compounds. Total synthesis of hydroxyl-*α*- and hydroxyl-*β*-sanshool has not been reported. However, a non-selective Wittig reaction has been used for the synthesis of *α*- and *β*-sanshool, which both lack a hydroxyl group.[7] In this paper, we describe the *E*/*Z*-selective total synthesis of hydroxyl-*α*- and hydroxyl-*β*-sanshool using Suzuki–Miyaura coupling (SMC).

Our synthetic strategy is depicted in Chart 1. Both hydroxyl-*α*-sanshool (**1**) and hydroxyl-*β*-sanshool (**2**) could be synthesized from two common component parts: *N*-methyliminodiacetic acid (MIDA) boronate **3** and amide **4**. After SMC between **4** and **3**, (*Z*)-selective reduction of triple-bond in the resulting coupling product would lead to hydroxyl-*α*-sanshool (**1**). However, conversion of **4** to (*E*)-iodoalkene followed by SMC with **3** would afford hydroxyl-*β*-sanshool (**2**).

Results and Discussion

Hydroxy-*α*-sanshool (**1**) was convergently synthesized from three commercially available reagents; 1,2-epoxy-2-methylpropane (**5**), *trans*-2-bromovinylboronic acid MIDA ester (**7**) and 4-pentyn-1-ol (**8**). The amine fragment **6**[8] was prepared by addition of dibenzylamine to **5** followed by deprotection of the benzyl group in 100% and 99% yield, respectively (Chart 2). The diene fragment **3** (MIDA boronate) was prepared from **7** and *trans*-1-propen-1-ylboronic acid by SMC in 77% yield (Chart 3).[9] Swern oxidation of **8** followed by Wittig reaction with methyl (triphenylphosphoranylidene)acetate was performed in a one-pot reaction in 88% yield.[10–12] This was followed by hydrolysis of the resulting ester to afford carboxylic acid **9** in 93% yield. Condensation[13] of the carboxylic acid **9** with the amine **6** followed by bromination[14] of the alkyne moiety in the amide gave bromoalkyne **4** in 73% and 97% yield, respectively. SMC of bromoalkyne **4** with MIDA boronate **3** afforded diene-yne product **10** in 58% yield. In order to construct the desired (6*Z*,8*E*,10*E*)-triene system, catalytic hydrogenation of **10** in the presence of Lindler catalyst or Pd-$BaSO_4$ was attempted. However, both strategies proved unsuccessful, resulting in over-reduction materials as byproducts. Next, we attempted Zn–Cu–Ag reduction[15] of **10**, and succeeded in the synthesis of the desired hydroxyl-*α*-sanshool (**1**) without the formation of byproducts in 89% yield (Chart 4).

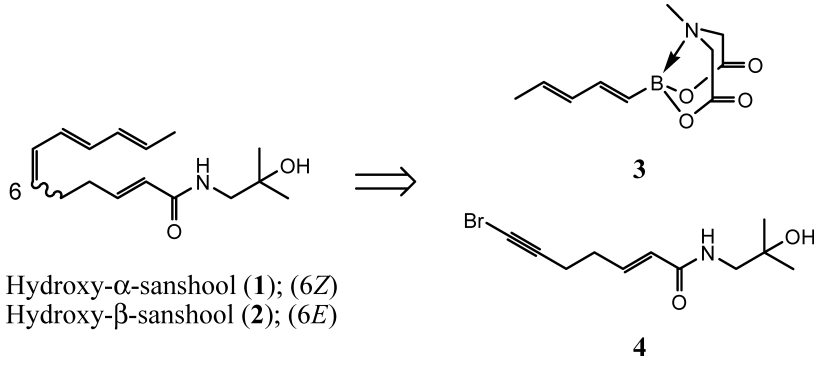

Chart 1. Retrosynthesis of Hydroxy-*α*- and Hydroxy-*β*-sanshool (**1**, **2**)

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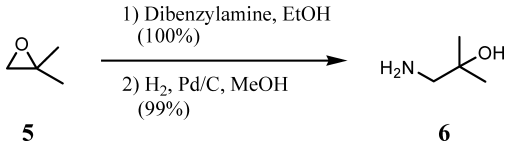

Chart 2. Preparation of Amine Fragment **6**

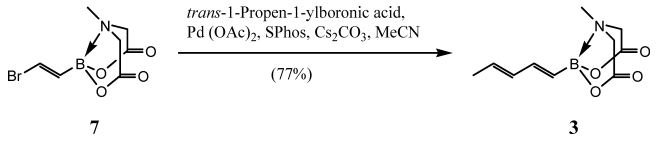

Chart 3. Preparation of Diene Fragment **3**

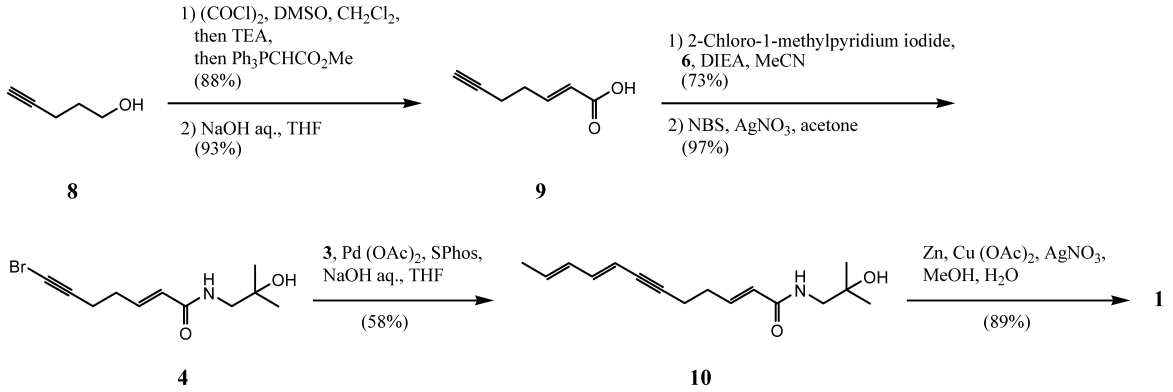

Chart 4. Synthesis of Hydroxy-*α*-sanshool (**1**)

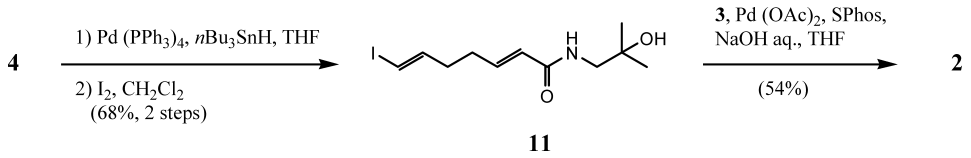

Chart 5. Synthesis of Hydroxy-*β*-sanshool (**2**)

Hydroxy-*β*-sanshool (**2**) was also synthesized from the above intermediate **4**. Initially, we attempted hydrometalation (Zr, Sn or B) of non-substituted alkyne (a condensation product of **9** with **6**) followed by iodination toward (*E*)-7-iodoalkene **11**. However, selective synthesis of (*E*)-7-iodoalkene **11** was not achieved from the non-substituted alkyne, affording instead a regio-isomer (6-iodoalkene) or over-reduction materials as byproducts. Therefore, we attempted hydrostannation of bromoalkyne **4** followed by iodination.[16] As a result, (*E*)-7-iodoalkene **11** was obtained selectively from **4** in 68% yield in 2 steps. Finally, (*E*)-7-iodoalkene **11** was converted to hydroxyl-*β*-sanshool (**2**) by SMC with MIDA boronate **3** in 54% yield (Chart 5).

In conclusion, a concise total synthesis of two sanshools (hydroxyl-*α*- and hydroxyl-*β*-sanshool) has been achieved featuring SMC. Hydroxy-*α*-sanshool (**1**) was synthesized from commercially available alcohol **8** using (*Z*)-selective reduction of the diene-yne intermediate **10** in 6 steps with 30% overall yield. Hydroxy-*β*-sanshool (**2**) was synthesized by regio- and (*E*)-selective iodoalkene conversion of bromoalkyne intermediate **4** in 7 steps with 21% overall yield from **8**.

Experimental

Melting points were measured by the use of a BUCHI Melting Point B-545 and are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL AL-400 (400 MHz) or a Bruker dpx200 (200 MHz) using tetramethylsilane as an internal standard. Infrared spectra were recorded using a JASCO FT/IR-4200. Mass spectra were recorded on a Micromass Q-TOF micro.

2-Hydroxy-2-methylpropylamine (6) A solution of dibenzylamine (18.15 g, 92.00 mmol) and 1,2-epoxy-2-methylpropane (**5**) (24.5 mL, 276.00 mmol) in EtOH (36 mL) was stirred for 72 h at 50°C. The mixture was concentrated under reduced pressure to give *N*,*N*-dibenzyl-2-hydroxy-2-methylamine as a colorless oil (25.56 g, 100%). ^{1}H-NMR ($CDCl_3$, 200 MHz) *δ*: 1.11 (6H, s), 2.43 (1H, s), 2.57 (2H, s), 3.70 (4H, s), 7.20–7.40 (10H, m). +Electrospray ionization (ESI)-MS *m*/*z*: 270 $[M+H]^+$. High resolution (HR)-ESI-MS *m*/*z*: 270.1859 (Calcd for $C_{18}H_{24}NO$, 270.1858).

To a solution of *N*,*N*-dibenzyl-2-hydroxy-2-methylamine (25.56 g, 92.00 mmol) in MeOH (500 mL) was added 10% Pd–C (1 g), and the mixture was stirred under an atmosphere of hydrogen for 24 h at room temperature. The mixture was then filtered through celite with MeOH, and concentrated under reduced pressure to give the desired compound **6** as a colorless oil (8.13 g, 99%). ^{1}H-NMR ($CDCl_3$, 200 MHz) *δ*: 1.17 (6H, s), 2.38 (2H, br s), 2.59 (2H, s), 3.41 (1H, s).

(*N*-*B*)-6-Methyl-2-[(1*E*,3*E*)-penta-1,3-dienyl]-1,3,6,2-dioxazaborocane-4,8-dione (3) A mixture of $Pd(OAc)_2$ (60.6 mg, 0.27 mmol) and 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos, 221.7 mg, 0.54 mmol) in MeCN (7 mL) was stirred for 3 h at room temperature. To a mixture of *trans*-2-bromovinylboronic acid MIDA ester (**7**) (707.2 mg, 2.70 mmol), *trans*-1-propen-1-ylboronic acid (463.9 mg, 5.40 mmol) and Cs_2CO_3 (1.76 g, 5.40 mmol) in MeCN (14 mL) was added the above catalyst solution. The reaction mixture

was stirred for 3 h at 50°C. The mixture was then filtered through celite with EtOAc, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane–EtOAc=1 : 1 then EtOAc–MeOH=100 : 1) to give the desired compound **3** as a colorless solid (461.1 mg, 77%). Recrystallization from EtOAc–hexane afforded colorless crystals: mp 104.4–106.4°C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.78 (3H, d, J=6.5 Hz), 2.83 (3H, s), 3.67 (2H, d, J=16.3 Hz), 3.84 (2H, d, J=16.3 Hz), 5.41 (1H, d, J=17.4 Hz), 5.82 (1H, qd, J=6.5, 15.1 Hz), 6.16 (1H, dd, J=10.1, 15.1 Hz), 6.64 (1H, dd, J=10.1, 17.4 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 18.12, 46.71, 61.39, 132.47, 133.42, 144.95, 167.44. +ESI-MS m/z: 246 $[M+Na]^+$. HR-ESI-MS m/z: 246.0915 (Calcd for $C_{10}H_{14}BNO_4Na$, 246.0914). IR (KBr) cm^{-1}: 1753, 1647, 1604.

(*E*)-Hept-2-en-6-ynoic Acid (9) To a stirred solution of oxalyl chloride (2.44 mL, 28.81 mmol) in dichloromethane (60 mL) at −60°C was added dimethyl sulfoxide (DMSO) (4.09 mL, 57.60 mmol). After 10 min, a solution of 4-pentyn-1-ol (**8**) (2.02 g, 24.01 mmol) in dichloromethane (20 mL) was added to the reaction mixture. After 15 min, the reaction mixture was treated with triethylamine (16.6 mL, 120.1 mmol) and then allowed to warm to 0°C. Methyl (triphenylphosphoranylidene)acetate (9.63 g, 28.81 mmol) was then added to the reaction mixture, and stirred for 1 h at room temperature. The reaction was quenched with water (100 mL), and extracted with dichloromethane (100 mL). The organic extracts were dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane–EtOAc=15 : 1) to give methyl (*E*)-hept-2-en-6-ynoate as a colorless oil (2.92 g, 88%). ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.00 (1H, t, J=2.4 Hz), 2.30–2.50 (4H, m), 3.74 (3H, s), 5.90 (1H, td, J=1.5, 15.7 Hz), 6.99 (1H, td, J=6.6, 15.7 Hz). +ESI-MS m/z: 161 $[M+Na]^+$.

To a solution of methyl (*E*)-hept-2-en-6-ynoate (4.03 g, 29.17 mmol) in tetrahydrofuran (THF) (40 mL) was added a 1 mol–L-NaOH solution (43.8 mL) at room temperature. The reaction mixture was stirred for 1 h at 50°C. The reaction was quenched with 1 mol–L-HCl solution (50 mL), and extracted with EtOAc (100 mL). The organic extracts were dried over Na_2SO_4, and concentrated under reduced pressure to give the desired compound **9** as a colorless solid (3.36 g, 93%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.01 (1H, t, J=2.6 Hz), 2.35–2.40 (2H, m), 2.44–2.50 (2H, m), 5.91 (1H, td, J=1.6, 15.7 Hz), 7.10 (1H, td, J=6.6, 15.7 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 17.30, 31.08, 69.60, 82.45, 121.90, 149.25, 171.53. −ESI-MS m/z: 123 $[M-H]^-$. HR-ESI-MS m/z: 123.0448 (Calcd for $C_7H_7O_2$, 123.0446).

(*E*)-7-Bromo-*N*-(2-hydroxy-2-methylpropyl)hept-2-en-6-ylamide (4) To a solution of **9** (1.00 g, 8.09 mmol), 2-chloro-1-methylpyridium iodide (2.27 g, 8.90 mmol) and *N*,*N*-diisopropylethylamine (4.23 mL, 24.27 mmol) in MeCN (20 mL) was added a solution of **6** (865 mg, 9.71 mmol) in MeCN (10 mL). The reaction mixture was stirred for 1 h at room temperature. The reaction was quenched with water (50 mL), and extracted with EtOAc (50 mL). The organic extracts were dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane/EtOAc = 1/2 to 1/3) to give (*E*)-*N*-(2-hydroxy-2-methylpropyl) hept-2-en-6-ylamide as a colorless solid (1.15 g, 73%). Recrystallization from EtOAc–hexane afforded colorless crystals: mp 62.9–63.5°C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.24 (6H, s), 1.99 (1H, t, J=2.6 Hz), 2.35 (2H, m), 2.43 (2H, m), 2.50 (1H, s), 3.34 (2H, d, J=6.1 Hz), 5.90 (1H, td, J=1.5, 15.4 Hz), 5.99 (1H, br s), 6.88 (1H, td, J=6.5, 15.4 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 17.59, 27.36, 30.93, 50.42, 69.34, 71.06, 82.92, 124.42, 142.61, 166.63. +ESI-MS m/z: 218 $[M+Na]^+$. HR-ESI-MS m/z: 218.1153 (Calcd for $C_{11}H_{17}NO_2Na$, 218.1157). IR (KBr) cm^{-1}: 3313, 3284, 1670, 1626, 1548.

A mixture of (*E*)-*N*-(2-hydroxy-2-methylpropyl)hept-2-en-6-ylamide (646.2 mg, 3.31 mmol), NBS (648.0 mg, 3.64 mmol) and $AgNO_3$ (56.0 mg, 0.331 mmol) in acetone (16 mL) was stirred for 2 h at room temperature. The reaction mixture was then filtered through celite with EtOAc, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane–EtOAc=1 : 3) to give the title compound **4** as a colorless solid (884.2 mg, 97%). Recrystallization from EtOAc–hexane afforded colorless crystals: mp 97.5–98.0°C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.24 (6H, s), 2.34–2.45 (4H, m), 2.54 (1H, s), 3.35 (2H, d, J=6.1 Hz), 5.89 (1H, td, J=1.5, 15.2 Hz), 6.04 (1H, br s), 6.85 (1H, td, J=6.6, 15.2 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 18.87, 27.34, 30.77, 39.24, 50.40, 71.07, 78.76, 124.53, 142.45, 166.58. +ESI-MS m/z: 296 $[M+Na]^+$. HR-ESI-MS m/z: 296.0260 (Calcd for $C_{11}H_{16}BrNO_2Na$, 296.0262). IR (KBr) cm^{-1}: 3289, 1671, 1624, 1548.

(2*E*,8*E*,10*E*)-*N*-(2-Hydroxy-2-methylpropyl)dodeca-2,8,10-trien-6-ynamide (10) A mixture of $Pd(OAc)_2$ (5 mg, 0.0223 mmol) and SPhos (18.3 mg, 0.0446 mmol) in THF (1 mL) was stirred for 1 h at room temperature. To a solution of **4** (61.2 mg, 0.223 mmol) and **3** (69.6 mg, 0.312 mmol) in THF (2.2 mL) was added the above catalyst solution and a 1 mol–L-NaOH solution (1.6 mL). The reaction mixture was stirred for 2 h at 30°C. The mixture was diluted with water (10 mL), and extracted with EtOAc (50 mL). The organic extracts were dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane–EtOAc=1 : 2) to give the desired compound **10** as an unstable colorless solid (33.7 mg, 58%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.24 (6H, s), 1.78 (3H, dd, J=1.0, 6.8 Hz), 2.39 – 2.51 (5H, m), 3.34 (2H, d, J=6.1 Hz), 5.44 (1H, d, J=15.6 Hz), 5.76 (1H, qd, J=6.8, 15.0 Hz), 5.89 (1H, td, J=1.5, 15.4 Hz), 5.93 (1H, br s), 6.07 (1H, m), 6.48 (1H, dd, J=10.9, 15.4 Hz), 6.88 (1H, td, J=6.7, 15.6 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 18.28, 18.79, 27.37, 31.35, 50.42, 71.09, 80.88, 90.19, 108.78, 124.26, 131.05, 131.89, 141.32, 143.03, 166.72. +ESI-MS m/z: 284 $[M+Na]^+$. HR-ESI-MS m/z: 284.1626 (Calcd for $C_{16}H_{23}NO_2Na$, 284.1626). IR (KBr) cm^{-1}: 3353, 1673, 1632, 1548.

Hydroxyl-α-sanshool (1) A suspension of Zn dust (250 mg) in water (1.5 mL) was stirred for 15 min, and then $Cu(OAc)_2$ (25 mg) were added to the suspension at room temperature. After 15 min, $AgNO_3$ (25 mg) were added to the suspension, and the mixture was stirred for 30 min at room temperature. To the activated Zn suspension was added a solution of **10** (28.1 mg, 0.108 mmol) in MeOH (1.5 mL). The reaction mixture was stirred for 20 h at room temperature. The mixture was then filtered through celite with MeOH, and concentrated *in vacuo*. The residue was diluted with EtOAc (10 mL) and saturated NaCl aq. (20 mL), and extracted with EtOAc (20 mL). The organic extracts were dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane–EtOAc=1 : 2)

to give the desired compound **1** as an unstable colorless solid (23.9 mg, 84%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.24 (6H, s), 1.78 (3H, dd, J=1.2, 8.0 Hz), 2.29 (2H, m), 2.35 (2H, m), 2.45 (1H, s), 3.33 (2H, d, J=6.1 Hz), 5.37 (1H, td, J=6.8, 10.9 Hz), 5.73 (1H, qd, J=8.0, 13.5 Hz), 5.84 (1H, td, J=1.5, 15.4 Hz), 5.89 (1H, br t), 6.03 (1H, tt, J=1.5, 10.9 Hz), 6.11 (1H, qdd, J=1.2, 10.5, 13.5 Hz), 6.18 (1H, dd, J=10.5, 14.0 Hz), 6.33 (1H, dd, J=10.9, 14.0 Hz), 6.86 (1H, td, J=6.7, 15.4 Hz).

(2*E*,6*E*)-*N*-(2-Hydroxy-2-methylpropyl)-7-iodohepta-2,6-dienamide (11) To a solution of **4** (125.0 mg, 0.456 mmol) and $Pd(PPh_3)_4$ (53 mg, 0.0456 mmol) in THF (3 mL) was added nBu$_3$SnH (0.25 mL, 0.912 mmol) at 0°C. The reaction mixture was stirred for 30 min at 0°C. The mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexane–EtOAc=1 : 1) to give a (*E*)-vinylstannane (190.5 mg), which was immediately used in the next reaction. To a solution of the (*E*)-vinylstannane (190.5 mg) in dichloromethane (3 mL) was added iodine (116 mg, 0.456 mmol) at 0°C. The reaction mixture was stirred for 1 h at 0°C. The reaction was quenched with saturated $Na_2S_2O_3$ aq. (20 mL), and extracted with EtOAc (50 mL). The organic extracts were dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane–EtOAc=1 : 2) to give the desired compound **11** as a colorless solid (99.9 mg, 68%). Recrystallization from EtOAc–hexane afforded colorless crystals: mp 95.0–96.0°C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.24 (6H, s), 2.22 (2H, m), 2.30 (2H, m), 2.32 (1H, s), 3.34 (2H, d, J=6.1 Hz), 5.83 (1H, td, J=1.5, 15.2 Hz), 5.88 (1H, br s), 6.08 (1H, td, J=1.3, 14.4 Hz), 6.51 (1H, td, J=7.0, 14.4 Hz), 6.83 (1H, td, J=6.6, 15.2 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 27.39, 30.80, 34.58, 50.39, 71.08, 75.86, 124.21, 143.33, 144.73, 166.58. +ESI-MS m/z: 346 $[M+Na]^+$. HR-ESI-MS m/z: 346.0271 (Calcd for $C_{11}H_{18}INO_2Na$, 346.0280). IR (KBr) cm^{-1}: 3362, 3275, 1677, 1635, 1577.

Hydroxyl-*β*-sanshool (2) A mixture of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and SPhos (8.2 mg, 0.02 mmol) in THF (0.5 mL) was stirred for 1 h at room temperature. To a solution of **11** (30.9 mg, 0.0956 mmol) and **3** (32 mg, 0.143 mmol) in THF (1 mL) was added the above catalyst solution and a 1 mol–L-NaOH solution (0.72 mL). The reaction mixture was stirred for 1 h at 30°C. The mixture was diluted with water (10 mL), and extracted with EtOAc (30 mL). The organic extracts were dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane–EtOAc=1 : 2) to give the desired compound **2** as an unstable colorless solid (13.6 mg, 54%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.24 (6H, s), 1.77 (3H, dd, J=1.0, 7.3 Hz), 2.22–2.32 (4H, m), 2.41 (1H, s), 3.33 (2H, d, J=6.1 Hz), 5.59–5.73 (2H, m), 5.82 (1H, td, J=1.5, 15.4 Hz), 5.86 (1H, br t), 6.01–6.14 (4H, m), 6.86 (1H, td, J=6.6, 15.4 Hz).

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