Supplementary Material

An Improved and Practical Method for Synthesizing of α-Sanshools and Spilanthol

Akira Nakamura1, Kazuki Mimaki1, Ken-ichi Tanigami1, Tomohiro Maegawa1\*

1 School of Pharmaceutical Sciences, Kindai University, 3-4-1 Kowakae, Higashi-osaka, Osaka 577-8502, Japan.

# EXPERIMENTAL SECTION

All chemicals were obtained from Sigma Aldrich, TCI, Nakarai Chemical or FUJIFILM Wako chemical as reagent grade and were used as received. Column chromatography and TLC were performed on Merck Silica gel 60 (230‒400 mesh) and Merck Silica gel F254 plates (0.25 mm), respectively. 1H and 13C NMR spectra were recorded on the JEOL JMN-400 spectrometer in CDCl3. Chemical shifts (δ) are reported in ppm downfield from the internal standard tetramethylsilane (TMS). High-resolution electrospray ionization mass spectrometry (HRESIMS) was measured by Exactive Plus mass spectrometer (Thermo Fisher Scientific Inc.).

**Methyl (*E*)-6-bromohex-2-enoate (3)1**

To a solution of 4-bromobutan-1-ol (2.14 g, 14.0 mmol) and AZADOL (21.5 mg, 0.140 mmol) in CH2Cl2 (35 mL), saturated NaHCO3 aq. (15 mL) containing KBr (167 mg, 1.40 mmol) and *n*-Bu4NBr (226 mg, 0.701 mmol) was added. While the reaction mixture was vigorously stirred at 0 °C, a premixed solution of aqueous NaOCl･5H2O (2.30 g, 14.0 mmol) and saturated NaHCO3 aq. (20 mL) was added dropwise over 10 min. After stirring for 2 h at 0 °C, the reaction mixture was separated, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na2SO4, and partially concentrated under reduced pressure. To the concentrated solution methyl (triphenylphosphoranylidene)acetate (5.15 g, 15.4 mmol) was added and stirred at room temperature for 2 h. The solution was concentrated under reduced pressure, and purified by silica gel column chromatography (hexane/AcOEt = 5:1) to give **3** (2.32 g, 80%) as colorless oil. 1H NMR (CDCl3) δ 1.99-2.06 (m, 2H), 2.36-2.42 (m, 2H), 3.42 (t, *J* = 6.6 Hz, 2H), 3.74 (s, 3H), 5.89 (dt, *J* = 15.6, 1.6 Hz, 1H), 6.93 (dt, *J* = 15.2, 6.8 Hz, 1H).

**Methyl (*E*)-6-iodohex-2-enoate (7)2**

To a solution of **3** (2.30 g, 11.1 mmol) in acetone (23 mL) was added NaI (2.50 g, 16.7 mmol). After stirring at 55 °C for 7 h, the reaction mixture was quenched with saturated NH4Cl aq. and then extracted with AcOEt. The organic layer was dried over Na2SO4 and concentrated under reduced pressure to give **7** (2.68 g, 95%) as colorless oil that was used without further purification. 1H NMR (CDCl3) δ 1.99 (m, 2H), 2.35 (m, 2H), 3.20 (t, *J* = 6.6 Hz, 2H), 3.72 (s, 3H), 5.90 (dt, *J* = 15.6, 1.5 Hz, 1H), 6.92 (dt, *J* = 15.6, 7.2 Hz, 1H).

**(*E*)-(6-Methoxy-6-oxohex-4-en-1-yl)triphenylphosphonium iodide (4d)**

A mixture of **7** (730 mg, 2.87 mmol) and PPh3 (791 mg, 3.02 mmol) in acetonitrile (3 mL) was heated at 50 °C for 24 h. The solvent was removed under reduced pressure and the crude product was triturated with AcOEt and stirred for 15 min. The insoluble white powder was filtered, washed with AcOEt, and dried in vacuo to give **4d** (1.28 g, 86%) as white solid. mp 223-224 oC. 1H NMR (CDCl3) δ 1.75-1.77 (m, 2H), 2.65-2.67 (m, 2H), 3.63 (s, 3H), 3.74-3.81 (m, 2H), 5.79-5.84 (d, *J* = 7.8 Hz, 1H), 6.73-6.81 (m, 1H), 7.65-7.69 (5H, m), 7.73-7.81 (m, 10H). 13C NMR (CDCl3) δ 21.2 (d, *J* = 4.2 Hz) 22.4 (d, *J* = 51.1 Hz), 32.1 (d, *J* = 17.3 Hz), 51.4, 117.8 (d, *J* = 86.5 Hz), 122.6, 130.5 (d, *J* = 12.4 Hz), 133.6 (d, *J* = 10.7 Hz), 135.1 (d, *J* = 3.3 Hz), 146.5, 166.7. HRMS (ESI+) m/z calcd for C23H27O2NaP [M+Na]+: 389.1665, found: 389.1652.

**Methyl (2*E*,6*Z*,8*E*,10*E*)-dodeca-2,6,8,10-tetraenoate (8)1**

A mixture of **4d** (103 mg, 0.200 mmol) in dry THF (1.0 mL) was cool to -78 °C under an argon atmosphere. KHMDS (0.48 mL of 0.5 M toluene solution, 0.240 mmol) was added dropwise to the solution over 2 min. After stirring at -78 °C for 0.5 h, (2*E*,4*E*)-2,4-hexadienal **9** (44.2 µL, 0.300 mmol) was added. After stirring for 2 h at -40 °C, the reaction mixture was quenched with saturated NH4Cl aq. and then extracted with AcOEt. The organic layer was dried over Na2SO4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/AcOEt = 1:1) and (hexane/AcOEt = 10:1) to give **8** (34.2 mg, 83%) as yellow oil. 1H NMR (CDCl3) δ 1.78 (d, *J* = 6.8 Hz, 3H), 2.27-2.38 (m, 4H), 3.72 (s, 3H), 5.32-5.43 (m, 1H), 5.69-5.77 (m, 1H), 5.85 (d, *J* = 16.0 Hz, 1H), 6.00-6.21 (m, 3H), 6.29-6.55 (m, 1H), 6.98 (dt, *J* = 15.6,6.8 Hz, 1H).

**(2*E*,6*Z*,8*E*,10*E*)-Dodeca-2,6,8,10-tetraenoic acid (10)1**

A mixture of **8** (150 mg, 0.720 mmol) and NaOH (144 mg, 3.60 mmol) in water (1.4 mL) was stirred at 70 °C for 3 h. After cooling to room temperature, the reaction mixture was extracted with AcOEt, and then acidified with aqueous 1N HCl to pH = 2. The organic layer was washed with brine, dried with Na2SO4 and concentrated under reduced pressure to afford **10** (115 mg, 83%) as white solid. 1H NMR (CDCl3) δ 1.76 (d, *J* = 7.2 Hz, 3H), 2.30-2.36 (m, 4H), 5.30-5.36 (m, 1H), 5.71 (dq, *J* = 14.4, 6.8 Hz, 1H), 5.83 (d, *J* = 15.6 Hz, 1H), 6.00-6.20 (m, 3H), 6.29-6.35 (dd, *J* = 14.0, 11.2 Hz, 1H), 7.06 (dt, *J* = 15.6, 6.8 Hz, 1H).

**Hydroxyl-α-sanshool (1)1**

To a mixture of **10** (28.8 g, 0.150 mmol), 1-amino-2-methyl-2-propanol (21 l, 0.225 mmol) and triethylamine (0.6 mL, 4 mmol) in MeCN (0.3 mL) and CH2Cl2 (0.15 mL), was added HBTU (114 mg, 0.300 mmol). After 1 h, the reaction mixture was diluted with AcOEt, and washed with 1N HCl, saturated NaHCO3 aq., and brine. The organic layer was dried over Na2SO4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (AcOEt) to afford **1** (35.7 mg, 88%) as a colorless oil. 1H NMR (CDCl3) δ 1.21 (s, 6H), 1.76 (d, *J* = 6.8 Hz, 3H), 2.25-2.34 (m, 4H), 2.78 (s, 1H), 3.31 (d, *J* = 6.0 Hz, 2H), 5.32-5.38 (m, 1H), 5.71 (dq, *J* = 14.4, 6.8 Hz, 1H), 5.82 (d, *J* = 15.2 Hz, 1H), 5.88 (brs, 1H), 6.00 (dd, *J* = 11.2, 11.2 Hz, 1H), 6.06-6.19 (m, 2H), 6.27-6.34 (m, 1H), 6.84 (dt, *J* = 16.0, 6.0 Hz, 1H). 13C NMR (CD3OD) 18.4, 27.2, 27.6, 33.1, 51.1, 71.6, 125.1, 126.5, 130.4, 130.6, 130.9, 133.2, 134.7, 145.1, 169.0. HRMS (ESI+) m/z calcd for C16H25NO2Na [M+Na]+: 286.1783, found: 286.1778.

**α-Sanshool (11)3**

To a mixture of **10** (28.8 mg, 0.150 mmol), isobutylamine (23 l, 0.225 mmol) and triethylamine (42 L, 0.300 mmol) in MeCN (0.3 mL) and CH2Cl2 (0.15 mL), was added HBTU (114 mg, 0.300 mmol). After 1 h, the reaction mixture was diluted with AcOEt, and washed with 1N HCl, saturated NaHCO3 aq., and brine. The organic layer was dried over Na2SO4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/AcOEt = 1:1) to afford α-Sanshool (34.0 mg, 92%) as a colorless oil. 1H NMR (CDCl3) δ 0.89 (d, *J* = 6.4 Hz, 6H), 1.78-1.73 (m, 4H), 2.21-2.32 (m, 4H), 3.11 (t, *J* = 6.0 Hz, 2H), 5.33-5.37 (m, 1H), 5.55 (brs, 1H), 5.68 (dq, *J* = 14.4, 6.8 Hz, 1H), 5.77 (d, *J* = 15.2 Hz, 1H), 5.99 (dd, *J* = 11.2, 11.2 Hz, 1H), 6.04-6.18 (m, 2H), 6.30 (dd, *J* = 14.0, 11.2 Hz, 1H), 6.80 (dt, *J* = 15.6, 6.8 Hz, 1H). 13C NMR (CDCl3) 18.3, 20.1, 26.5, 28.6, 32.0, 46.8, 124.2, 125.2, 129.5, 129.6, 130.1, 131.7, 133.4, 143.4, 165.9. HRMS (ESI+) m/z calcd for C16H25NONa [M+Na]+: 270.1834, found: 270.1832.

**Methyl (2*E*,6*Z*,8*E*)-deca-2,6,8-trienoate (12)**

A mixture of **4d** (1.03 g, 2.00 mmol) in dry THF (10 mL) was cool to -78 °C under an argon atmosphere. KHMDS (4.4 mL, 2.20 mmol) was added dropwise to the solution over 2 min. After stirring at -78 °C for 0.5 h, crotonaldehyde (0.34 mL, 3.00 mmol) was added. After stirring for 2 h at -40 °C, the reaction mixture was quenched with saturated NH4Cl aq. and then extracted with AcOEt. The organic layer was dried with Na2SO4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ AcOEt = 1:1) and (hexane/ AcOEt = 10:1) to give **12** (342 mg, 95%) as colorless oil. 1H NMR (CDCl3) δ 1.76 (d, *J* = 6.8 Hz, 3H), 2.26-2.32 (m, 4H), 3.71 (s, 3H), 5.20-5.26 (m, 1H), 5.71 (dq, *J* = 14.4, 6.8 Hz, 1H), 5.83 (d, *J* = 15.6 Hz, 1H), 5.96 (dd, *J* = 10.8, 10.8 Hz, 1H), 6.23-6.29 (m, 1H), 7.06 (dt, *J* = 15.6, 6.4 Hz, 1H). 13C NMR (CDCl3) δ 18.1, 26.0, 32.1, 51.2, 121.2, 126.5, 127.0, 129.0, 129.9, 148.4, 166.8. HRMS (ESI+) m/z calcd for C11H17O2Na [M+H]+: 181.1229, found: 181.1220.

**(2*E*,6*Z*,8*E*)-Deca-2,6,8-trienoic acid (13)**

A mixture of **12** (300 mg, 1.66 mmol) and NaOH (333 mg, 8.32 mmol) in water (3.3 mL) was stirred at 70 °C for 3 h. After cooling to room temperature, the reaction mixture was extracted with AcOEt, and then acidified with aqueous 1N HCl to pH = 2. The organic layer was washed with brine, dried over Na2SO4, filtered, and concentrated under reduced pressure to afford **13** (263 mg, 91%) as white solid. 1H NMR (CDCl3) δ ppm 1.76 (d, *J* = 6.8 Hz, 3H), 2.30-2.36 (m, 4H), 5.20-5.24 (m, 1H), 5.71 (dq, *J* = 14.4, 6.8 Hz, 1H), 5.84 (d, *J* = 16.0 Hz, 1H), 5.97 (dd, *J* = 10.8, 10.8 Hz, 1H), 6.23-6.30 (m, 1H), 7.06 (dt, *J* = 15.6, 6.4 Hz, 1H), 11.3 (brs, 1H). 13C NMR (CDCl3) 18.2, 25.9, 32.3, 121.1, 126.5, 126.9, 129.7, 130.1, 151.2, 172.1. HRMS (ESI+) m/z calcd for C10H14O2Na [M+Na]+: 189.0891, found: 189.0885.

**Spilanthol4**

To a mixture of **13** (106 mg, 0.638 mmol), isobutylamine (96 l, 0.957 mmol) and triethylamine (0.18 mL, 1.23 mmol) in MeCN (1.3 mL) and CH2Cl2 (0.6 mL), was added HBTU (363 mg, 0.957 mmol). After 1 h, the reaction mixture was diluted with AcOEt, and washed with 1N HCl, saturated NaHCO3 aq. and brine. The organic layer was dried over Na2SO4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/AcOEt = 2:1) to afford spilanthol (116 mg, 84%) as a colorless oil. 1H NMR (CDCl3) δ 0.90 (d, *J* = 6.4 Hz, 6H), 1.74-1.76 (m, 4H), 2.23-2.31 (m, 4H), 3.13 (t, *J* = 6.4 Hz, 2H), 5.21-5.27 (m, 1H), 5.43 (brs, 1H), 5.68 (dq, *J* = 14.8, 6.8 Hz, 1H), 5.76 (d, *J* = 14.4 Hz, 1H), 5.95 (dd, *J* = 9.6, 9.6 Hz, 1H), 6.23-6.30 (m, 1H), 6.80 (dt, *J* = 15.6, 6.8 Hz, 1H). 13C NMR (CDCl3) 18.2, 20.0, 26.3, 28.5, 32.0, 46.8, 124.1, 126.6, 127.5, 129.3, 129.8, 143.3, 166.0. HRMS (ESI+) m/z calcd for C14H23NONa [M+Na]+: 244.1677, found: 244.1673.

1 Wu, B., Kun L., and Toy, P. H. (2012) Synthesis of hydroxy-α-sanshool. Synlett 23, 2564–2566. doi: 10.1055/s-0032-1317172

2 Lautens, M., Paquin, J.-F., Piguel, S., and Dahlmann, M. (2001). Palladium-catalyzed sequential alkylation-alkenylation reactions and their application to the synthesis of fused aromatic rings. J. Org. Chem. 66, 8127-8134. doi: 10.1021/jo0107296

3 Igarashi, Y. (2012). Alkynes and their use for preparation of sanshools in high stereoselectivity. Jpn. Kokai Tokkyo Koho Patent. P2012-116786A

4 Barbosa, A. F., de Carvalho, M. G., Smith, R. E., and Sabaa-Srur, A. U. O. (2016) Spilanthol: occurrence, extraction, chemistry and biological activities. Rev. Bras. Farmacogn. 26, 128–133. doi: 10.1016/j.bjp.2015.07.024

**3** 1H NMR



**7** 1H NMR



**4d** 1H NMR



**4d** 13C NMR



**8** 1H NMR



**8** 13C NMR



**10** 1H NMR



**1** 1H NMR



**1** 13C NMR



**11** 1H NMR

****

**11** 13C NMR



**12** 1H NMR



**12** 13C NMR



**13** 1H NMR

**13** 13C NMR



**Spilanthol** 1H NMR



**Spilanthol** 13C NMR



****