Synthesis of hydroxy-α-sanshool

Jianjun Zhou, Yan Xiao, Taiping Chen, Jiyu Gao, Wencai Huang and Zicheng Li

Abstract
Hydroxy-α-sanshool was synthesized in a 13% overall yield through eight steps, which included two Wittig reactions that were used to form the carbon skeleton with ethyl 2-oxoacetate and 2E,4E-hexadienal being reacted with the appropriate ylides. Impurities in the processes could easily be separated. Ethyl 6-hydroxy-2Z-hexenoate was converted to its E-isomer with catalysis by I2 and 2E,6Z,8E,10E-dodecatetraenoic acid was crystallized from a solution in 1% ethyl acetate in n-hexane.

Keywords
Hydroxy-α-sanshool, Wittig reaction, synthesis

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Introduction
The sanshools are representative unsaturated fatty acid amides found in Zanthoxylum (Zanthoxylum bungeanum Maxim.) and include α-sanshool, β-sanshool, γ-sanshool, δ-sanshool, and homologues containing one hydroxy group in the amino fragment (Figure 1).1–3 Hydroxy-α-sanshool is the main numb flavoring substance in Zanthoxylum, and its content directly determines the degree of numbness of Zanthoxylum.4,5 Hydroxy-α-sanshool has been found to have several bioactivities. It acts as an agonist of transient receptor potential vanilloid type-1 (TRPV-1) and transient receptor potential ankyrin-1 (TRPA-1)6 and is a selective blocker of some two-pore domain potassium channels (KCNK): TASK-1 (KCNK3), TASK-3 (KCNK9), and TRESK (KCNK18).7,8

The synthesis of Wu et al. was the easiest to carry out although the preparation of ethyl 6-bromobutyrate is not straightforward. Although 4-bromobutyraldehyde can be prepared by reducing ethyl 4-bromobutyrate, the reaction must be performed in the absence of water and at a low temperature.13–15 An alternative method is the bromination of ethyl 6-hydroxy-2E-hexenoate.16–19 Ethyl 6-hydroxy-2E-hexenoate can be prepared from tetrahydrofuran-2-ol which is obtained by reduction of γ-butyrolactone using diisobutylaluminium hydride (DIBALH) albeit at an extremely low temperature or from 4-hydroxy-1-butyraldehyde. This can be obtained by oxidation of 1,4-butanediol with pyridinium chlorochromate (PCC) or MnO2,20–22 but the yield is low and the purification difficult.

Considering the difficult preparation of 4-bromobutyraldehyde or 4-hydroxybutyraldehyde, a new route starting from glyoxylic acid was designed (Scheme 2). Ethyl (E)-6-bromohex-2-enoate 4 can be prepared from the hydroxyester 3 by bromination. In turn, ester 3 can be prepared by a Wittig reaction involving the phosphonium salt 1 and ethyl 2-oxoacetate, followed by cleavage of the acetate and isomerization of the resulting ester 2 with catalysis by I2.

Therefore, 4-bromobutyraldehyde is difficult to prepare on a large scale.

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Figure 1. The sanshools.

Scheme 1. Reported processes in the literatures
of the alkene. Phosphonium salt 1 can be prepared by PPh₃ reacted with 4-bromobutyl acetate which was synthesized from tetrahydrofuran and acetyl bromide. The isomerization of the Z-isomer of 3 into its E-isomer was catalyzed by iodine. This novel process avoids the use of 4-bromobutyraldehyde. The reaction work-ups are simple, the yields are high, and the starting materials are easily available.

Results and discussion

Chemistry

According to the literature, the impurities in 4-bromobutyl acetate are 1,4-dibromobutane and 1,4-diacetoxybutane. 1,4-Diacetoxybutane can be easily removed following the catalyst. 2E,6Z,8E,10E-Dodecatetraenoic acid was crystallized from a solution in 1% ethyl acetate in n-hexane. The work-ups were simple and the overall yield of the product was high. All the intermediate and target compounds were characterized by ¹H NMR, ¹³C NMR, and MS spectra.

Conclusion

In summary, hydroxy-α-sanshool was synthesized in eight steps using two Wittig reactions as the key assembly steps. The cis-isomer of ethyl 6-hydroxyhex-2-enoate can be isomerized to the desired trans-isomer using I₂ as the catalyst. 2E,6Z,8E,10E-Dodecatetraenoic acid was crystallized from a solution in 1% ethyl acetate in n-hexane. The work-ups were simple and the overall yield of the product was high. All the intermediate and target compounds were characterized by ¹H NMR, ¹³C NMR, and MS spectra.

Experiment

All the reagents were purchased from commercial suppliers without further purification unless otherwise specified. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer. NMR spectra were recorded in DMSO-d₆ solutions at room temperature (20 °C ± 2 °C). ¹H and ¹³C chemical shifts are quoted in parts per million downfield from TMS. Supplemental MS spectra were recorded on a Bruker Esquire 3000 instrument. High-resolution mass spectra (HRMS) were obtained on a MicrOTOF-Q II mass spectrometer with a supplemental source (Waters, Manchester). As for known compounds, only ¹H NMR and ¹³C NMR spectra were confirmed with previously reported literature, and the main intermediates were characterized by ¹H NMR, ¹³C NMR spectra, and mass spectra.

4-Bromobutyl acetate

It was prepared according to the reported procedure. Light yellow liquid 27.6 g, yield 85%. ¹H NMR (400 MHz, DMSO-d₆, ppm) δ 4.03 (t, J = 6.8 Hz, 2H), 3.42 (t, J = 6.4 Hz, 2H), 2.01 (s, 3H), 1.81–1.88 (m, 2H), 1.50–1.57 (m, 2H).
E-isomers was 67:33. 10 Drops of I$_2$ in and was filtered and washed twice with 30 mL ethanol. The solution in 80 mL ethanol and refluxed overnight. The mixture that was refluxed for 3 h. Ethanol was removed to obtain a pale yellow viscous oil. 100 mL CH$_2$Cl$_2$ was added to the oil, which was washed with water (3 × 3 mL). CH$_2$Cl$_2$ was distilled to obtain which was washed with water (3 × 3 mL). The CH$_2$Cl$_2$ was distilled and 250 mL of the mixture was refluxed for 24 h under nitrogen atmosphere. CH$_2$Cl$_2$ was distilled and 250 mL of n-hexane was added, the mixture was frozen for 1 h, to give a white solid, the solid was then filtered and washed with ethyl acetate and ether, respectively, to afford as a colorless powder, 17.9 g, 92%. m.p. 142–144 °C. 1H NMR (400 MHz, DMSO-d$_6$, ppm): δ 7.86–7.72 (m, 15H), 6.86 (d, δ = 15.7, 6.7 Hz, 1H), 5.93–5.82 (d, δ = 15.7, 6.7 Hz, 1H), 4.09 (q, δ = 7.1 Hz, 2H), 3.67–3.59 (m, 2H), 2.40 (m, 2H), 1.76–1.67 (m, 2H), 1.19 (t, δ = 7.1 Hz, 3H). 13C NMR (100 MHz, DMSO-d$_6$, ppm): δ 165.6, 147.4, 135.1, 135.0, 133.8, 133.7, 130.4, 130.3, 122.2, 119.0, 118.1, 59.9, 32.2, 32.0, 28.8, 26.8, 20.8, 14.3. HRMS (Supplemental) m/z: Anal. calcld for C$_{63}$H$_{54}$O$_{2}$Br$_2$ [M + Na]$^+$ 321.0172; found 321.0174.

(Z/E)Ethyl 6-acetoxy-2-hexenoate (2). To a solution of 1 (50 g, 0.11 mol) and ethyl 2-oxoacetate (11.2 g, 0.22 mol) in CH$_2$Cl$_2$ (250 mL) was added Cs$_2$CO$_3$ (71.2 g, 0.22 mol), and the mixture was refluxed for 24 h under nitrogen atmosphere. CH$_2$Cl$_2$ was distilled and 250 mL of n-hexane was added to the residue, the mixture was then stirred for 30 min, and the cake was filtered and washed twice with 200 mL of n-hexane. n-Hexane was distilled to obtain a yellow oil. The oil was distilled under vacuum, and the 120 °C–125 °C fraction (15 torr) was collected to afford as a light yellow oil, which was used directly in the next reaction, 5.4 g, 79%.

Ethyl 6-hydroxy-2E,6Z,8E,10E-hexa-2,4-dodecadienoate (6). To a solution of 5 (14.9 g, 30.76 mmol) and 2,4E-dodecadienyal (3.0 g, 30.76 mmol) in CH$_2$Cl$_2$ (100 mL) was added Cs$_2$CO$_3$ (20.1 g, 61.52 mmol) and stirred for 24 h at 45 °C under nitrogen atmosphere. After cooled to room temperature, celite (10.0 g) was added to the reaction mixture, which was stirred for 1 h and filtered, the cake was washed with CH$_2$Cl$_2$ (3 × 30 mL), and the combined filtrate was concentrated in vacuum. n-Hexane (100 mL) was added to the mixture, the mixture was filtered, the cake was washed with n-hexane (3 × 30 mL), and the solvent was evaporated in vacuum to afford 6 as a colorless oil, which was used directly in the next reaction, 5.4 g, 79% (the percentage of 2E,6Z isomer in the mixture was 56%). 1H NMR (400 MHz, DMSO-d$_6$, ppm): δ 6.92–6.82 (d, δ = 15.5, 6.5 Hz, 1H), 6.27–5.95 (m, 4H), 5.87 (d, δ = 15.7 Hz, 1H), 5.78–5.65 (m, 1H), 5.37 (m, 1H), 4.09 (q, δ = 7.1 Hz, 2H), 2.29 (m, 4H), 1.73 (d, δ = 6.4 Hz, 3H), 1.19 (t, δ = 7.1 Hz, 3H). 13C NMR (100 MHz, DMSO-d$_6$, ppm): δ 166.0, 165.7, 148.3, 147.7, 135.2, 134.0, 133.9, 130.4, 130.3, 122.2, 119.0, 118.4, 59.9, 32.2, 32.0, 28.8, 28.6, 20.8, 14.3. HRMS (Supplemental) m/z: Anal. calcld for C$_{26}$H$_{28}$O$_2$P$^+$ 403.1821; found 403.1819.

Ethyl 6-bromo-2E-hexenoate (4). CBr$_4$ (4.4 g, 12.64 mmol) was added to a solution of PPh$_3$ (13.2 g, 50.56 mmol) in 50 mL CH$_2$Cl$_2$ cooled in ice bath, and the reaction was stirred for 1 h. To the reaction was added a solution of compound 3 (8.0 g, 50.56 mmol) in 10 mL CH$_2$Cl$_2$, the reaction was stirred for 2 h in ice salt bath and then another 2 h at room temperature. The solvent was distilled off to obtain a viscous yellow solid, to the viscous solid was added 50 mL n-hexane and stirred vigorously until the mixture was dispersed into a granular solid, the solid was filtered and washed with n-hexane (2 × 20 mL), and n-hexane was evaporated under vacuum to give 4 as a light yellow oil, which was used directly in the next reaction, 9.1 g, 81%.

1H NMR (600 MHz, DMSO-d$_6$, ppm): δ 7.85–7.73 (m, 15H), 4.13–4.06 (t, J = 7.1 Hz, 2H), 2.05–1.71 (s, 3H), 1.71–1.53 (m, 2H), 1.19 (m, 4H). 13C NMR (151 MHz, DMSO-d$_6$, ppm) δ 165.8, 147.6, 135.2, 134.0, 133.9, 130.6, 122.4, 119.0, 118.4, 60.1, 32.3, 20.8, 20.2, 14.5.

1H NMR (400 MHz, DMSO-d$_6$, ppm): δ 7.86–7.72 (m, 15H), 6.86 (d, δ = 15.7, 6.7 Hz, 1H), 5.86 (d, δ = 15.6, 6.7 Hz, 1H), 4.17 (q, δ = 7.1 Hz, 2H), 3.40 (t, δ = 6.5 Hz, 2H), 2.40–2.32 (m, 2H), 2.03–1.97 (m, 2H), 1.27 (t, δ = 7.2 Hz, 3H). 13C NMR (100 MHz, CDCl$_3$, ppm): δ 166.2, 146.6, 122.4, 60.1, 32.4, 30.6, 30.2, 14.1. HRMS (Supplemental) m/z: Anal. calcld for C$_{63}$H$_{54}$O$_{2}$P$^+$ 321.0172; found 321.0174.

Ethyl 6-hydroxy-2E,6Z,8E,10E-hexa-2,4-dodecadienoate (5). Compound 4 (8.8 g, 39.98 mmol) and PPh$_3$ (10.5 g, 39.98 mmol) were added to 50 mL acetonitrile, and the reaction mixture was refluxed overnight. Acetonitrile was distilled off under reduced pressure to obtain a pale yellow viscous oil. 100 mL ether was added to the oil and frozen for 1 h in the refrigerator. The solid was filtered and washed twice with ethyl acetate and ether, respectively, to afford as a white powder, 17.9 g, 92%. m.p. 142–144 °C. 1H NMR (400 MHz, DMSO-d$_6$, ppm): δ 7.86–7.72 (m, 15H), 6.86 (d, δ = 15.7, 6.7 Hz, 1H), 5.93–5.82 (d, δ = 15.7, 6.7 Hz, 1H), 4.09 (q, δ = 7.1 Hz, 2H), 3.67–3.59 (m, 2H), 2.40 (m, 2H), 1.76–1.67 (m, 2H), 1.19 (t, δ = 7.1 Hz, 3H). 13C NMR (100 MHz, DMSO-d$_6$, ppm): δ 165.6, 147.4, 135.1, 135.0, 133.8, 133.7, 130.4, 130.3, 122.2, 119.0, 118.1, 59.9, 32.2, 32.0, 28.8, 26.8, 20.8, 14.3. HRMS (Supplemental) m/z: Anal. calcld for C$_{63}$H$_{54}$O$_{2}$P$^+$ 403.1821; found 403.1819.
149.1, 133.7, 132.3, 130.2, 130.1, 129.9, 126.0, 121.8, 60.1, 31.8, 26.2, 18.5, 14.5. HRMS (Supplemental) m/z: Anal. calcd for C₁₄H₂₀O₂ [M + Na]+ 243.1356; found 243.1359.

2E,6Z,8E,10E-dodecatetraenoic acid (7). Compound 6 (5.0 g, 22.70 mmol) and NaOH (1.8 g, 45.39 mmol) were added to a mixture of 120 mL water and 60 mL methanol and refluxed for 2 h. After cooled to room temperature, methanol was removed, and the reaction mixture was extracted with diethyl ether (3 × 50 mL). The aqueous phase was acidified with 1 mol/L HCl to pH = 1, which was then extracted with CH₂Cl₂ (3 × 50 mL). The organic layer was washed with brine, and dried over Na₂SO₄. CH₂Cl₂ was concentrated in vacuum to afford a yellowish viscous solid. The crude product was recrystallized twice from 1% ethyl acetate in hexane to obtain 7 as a white solid, 2.0 g with 45% yield (the purity of 2E,6Z-isomer was 99%).¹² m.p. 93.5–95.5°C (lit. 93.5–95°C); ¹H NMR (400 MHz, DMSO-d₆ ppm): δ 12.11 (s, 1H), 6.81 (dt, J = 15.6, 6.5 Hz, 1H), 6.46–6.35 (m, 1H), 6.23–6.11 (m, 2H), 6.02 (t, J = 11.0 Hz, 1H), 5.81–5.69 (m, 2H), 5.36 (dt, J = 7.7–7.2 Hz, 1H), 2.34–2.23 (m, 4H), 1.76–1.72 (d, J = 7.1 Hz, 3H). ¹³C NMR (100 MHz, DMSO-d₆ ppm): δ 167.1, 148.0, 133.3, 131.9, 129.9, 129.7, 129.5, 125.6, 122.3, 31.4, 25.9, 18.1. HRMS (Supplemental) m/z: Anal. calcd for C₁₂H₁₆O₂ [M + Na]+ 215.1048; found 215.1051.

Hydroxy-α-sanshool (8). To a mixture of 7 (1.7 g, 8.84 mmol), 1-amino-2-methyl-2-propanol (1.2 g, 13.46 mmol), and triethylamine (3.5 g, 34.59 mmol) in CH₂Cl₂ (20 mL) was added HBTU (4.9 g, 12.92 mmol) and stirred for 1 h at room temperature. 50 mL water was added to the reaction mixture, which was then extracted with CH₂Cl₂ (3 × 30 mL), the organic phase was washed with 1 mol/L HCl, 5% NaHCO₃, and brine, respectively, and dried with Na₂SO₄. CH₂Cl₂ was evaporated to afford a colorless solid. Petroleum ether (20 mL) was added to the oil, the mixture was placed for 2 h in the refrigerator, which was then violently stirred for 10 min, the formed solid was filtered and dried in vacuum to obtain 8 as a white solid, 1.9 g, 82%.¹² The solid turned brown during heating and dissolves at 84–90°C. ¹H NMR (400 MHz, DMSO-d₆ ppm): δ 7.76–7.71 (m, 1H), 6.65–6.57 (m, 1H), 6.45–6.34 (m, 1H), 6.29–5.94 (m, 4H), 5.73 (dq, J = 13.8, 6.8 Hz, 1H), 5.43–5.33 (m, 1H), 4.44 (s, 1H), 3.08 (d, J = 6.0 Hz, 2H), 2.25 (dq, J = 13.8, 7.5 Hz, 4H), 1.74 (d, J = 6.8 Hz, 3H), 1.04 (s, 6H). ¹³C NMR (101 MHz, DMSO-d₆ mm): δ 165.3, 141.7, 133.7, 132.0, 130.2, 129.7, 129.4, 125.7, 125.1, 69.6, 49.8, 31.5, 27.4, 27.4, 26.4, 18.2. HRMS (Supplemental) m/z: Anal. calcd for C₁₆H₂₅NO₂ [M + Na]+ 286.1778; found 286.1781.

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Supplemental material

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