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Synthesis of hydroxy-α-sanshool

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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 2*E*,4*E*-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 I_2 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, so establishing the quality of the 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 process of separating hydroxy-α-sanshool from Zanthoxylum is tedious and gives low yields.[9]

Igarashi et al.[10] synthesized hydroxy-α-sanshool using a Suzuki–Miyaura coupling (SMC) (see Scheme 1). This SMC-based route involved the synthesis of complex building blocks and involved non-readily available starting materials. Sonnet et al.[11] synthesized α-sanshool using ethyl 4,6,8-decatrienoate as an intermediate although the process needs harsh conditions and involved the reduction of an acid to an aldehyde. Wu et al.[12] synthesized hydroxy-α-sanshool using 4-bromobutyraldehyde as a key intermediate. However, the starting material 4-bromo-1-butanol is unstable during its preparation, storage, and oxidation; therefore, 4-bromobutyraldehyde is difficult to prepare on a large scale.

The synthesis of Wu et al. was the easiest to carry out although the preparation of ethyl 6-bromo-2E-hexenoate 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-2*E*-hexenoate.[16–19] 6-Hydroxy-2*E*-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 MnO_2,[20–22] but the yield is low and the purification difficult.

Considering the difficult preparation of 4-bromobutyraldehyde or 4-hydoxybutyraldehyde, 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

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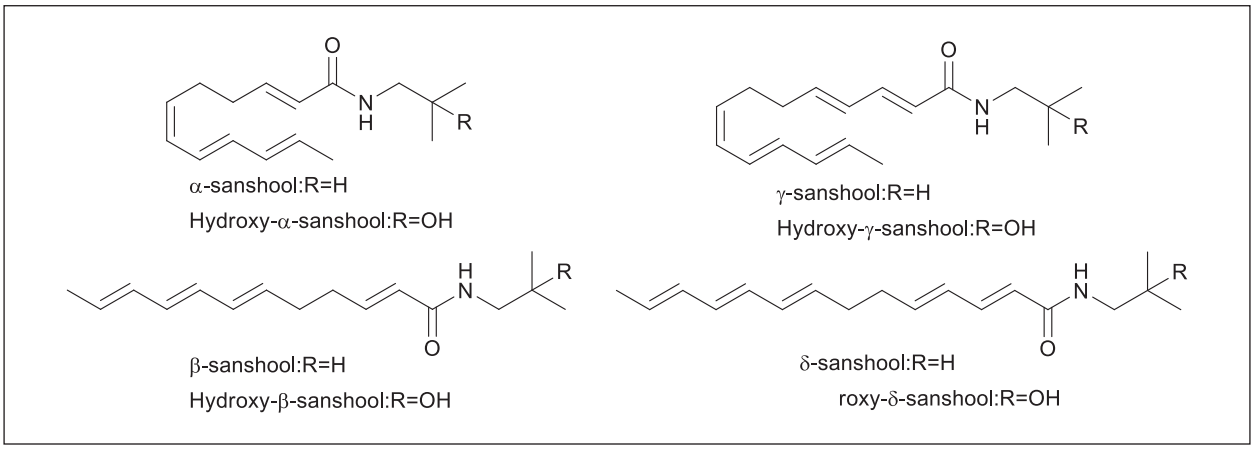
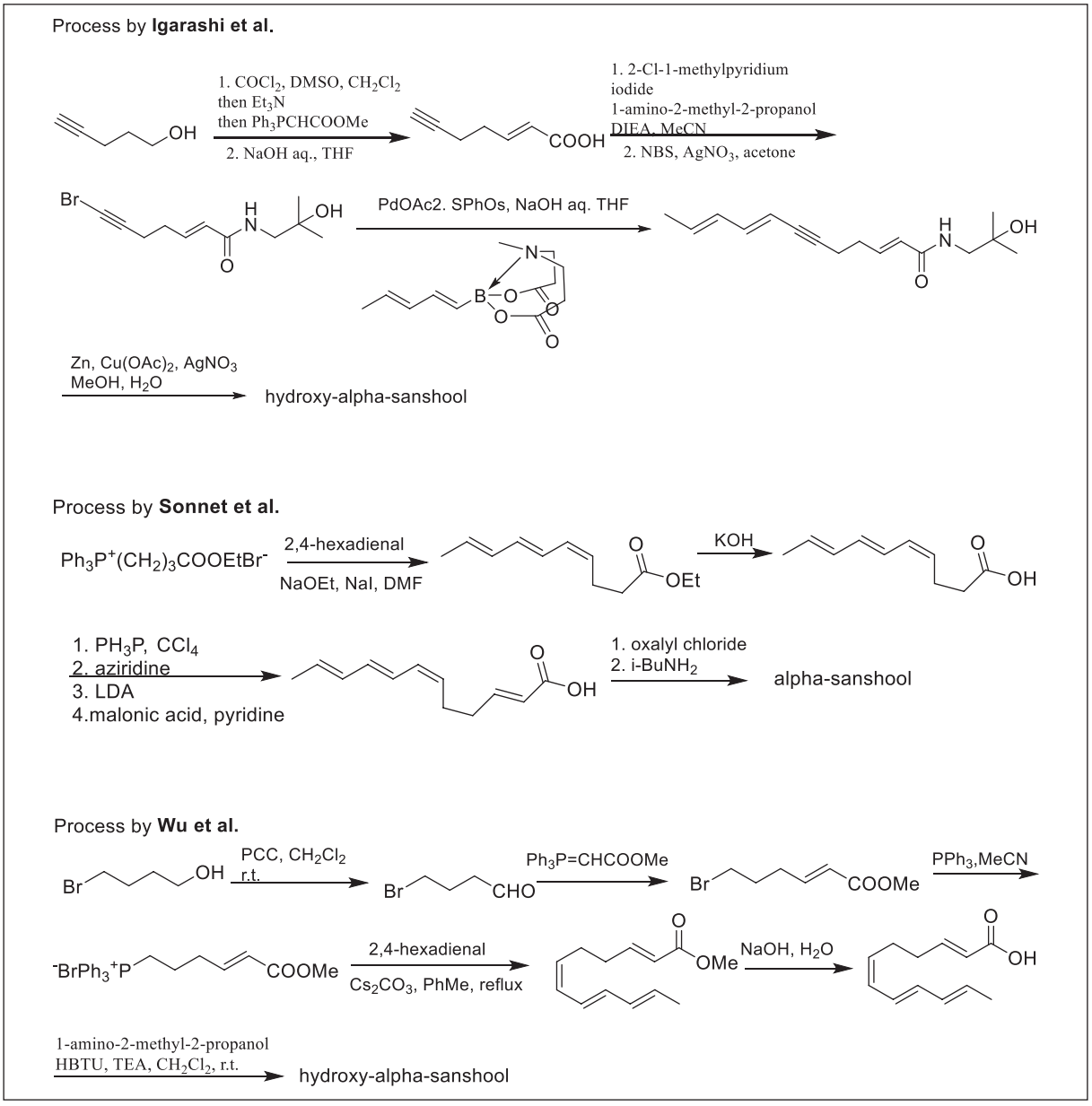
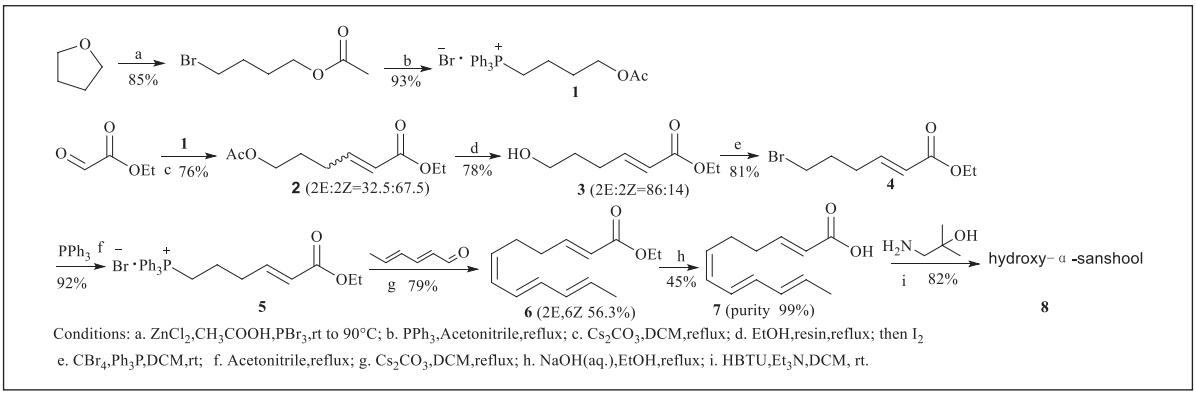


Figure 1. The sanshools.



Scheme 1. Reported processes in the literatures



Scheme 2. Designed synthetic route in our work

of the alkene. Phosphonium salt 1 can be prepared by PPh_3 reacted with 4-bromobutyl acetate which was synthesized from tetrahydrofuran and acetyl bromide.[23] 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,[23] the impurities in 4-bromobutyl acetate are 1,4-dibromobutane and 1,4-diacetoxybutane. 1,4-Diacetoxybutane can be easily removed following the preparation of the quaternary phosphonium salt **1**. The 1,4-dibromobutane was transferred into a mixture of a single quaternary phosphonium salt and a double quaternary phosphonium salt. The mono quaternary phosphonium salt leads to the target intermediate **4** after isomerization. The double quaternary phosphonium salt may participate in a single Wittig reaction to give a product that can be removed from the reaction mixture because of its insolubility in *n*-hexane and in a double Wittig reaction whose product can be separated in the subsequent preparation of phosphonium salt **5**. Other impurities can also be easily removed during the preparation of the quaternary phosphonium salt **5**.

The phosphonium salt **1** was obtained in a 93% yield from 4-bromobutyl acetate and PPh_3.[24] Hex-2-enoate **2** was obtained through the Wittig reaction of phosphonium salt **1** and ethyl 2-oxoacetate in a 76% yield (2*E*:2*Z* = 32:68). The hex-2-enoate **2** was ethanolyzed and the product isomerized to ethyl (*E*)-6-hydroxyhex-2-enoate **3** in a 78% yield (2*E*:2*Z* = 86:14). The hydroxyester **3** was reacted with CBr_4 and PPh_3 to give the corresponding bromoester **4** in a 81% yield.[24] This bromoester **4** was reacted with PPh_3 in acetonitrile to give the phosphonium salt **5** in a 92% yield and the long-chain ester **6** was prepared from phosphonium salt **5** and 2*E*,4*E*-hexa-2,4-dienal in the presence of Cs_2CO_3 in a 79% yield (2*E*,6*Z*: 2*E*,6*E* = 56:44). The ester **6** was hydrolyzed and the product crystallized to afford 2*E*,6*Z*-acid **7** in a 45% yield and a 2*E*,6*Z*-purity of 99%. Finally, hydroxy-α-sanshool **8** was obtained in a 82% yield by the coupling reaction of the acid **7** with 1-amino-2-methyl-2-propanol catalyzed by 2-1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium (HBTU) and Et_3N.

We tried to record the nuclear magnetic resonance (NMR) spectrum of our synthetic hydroxy-α-sanshool **8** in $CDCl_3$ to compare it with the data reported in the literature. However, in our hands, hydroxy-α-sanshool **8** is unstable in this solvent. However, the high-performance liquid chromatography (HPLC) of our synthetic sanshool **8** was consistent with that of the natural product and the NMR spectrum of our sample in dimethyl sulfoxide (DMSO)-d_6 was supportive of the assigned structure.

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 I_2 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 ^{1}H NMR, ^{13}C NMR, and MS spectra.

Experiment

All the reagents were purchased from commercial suppliers without further purification unless otherwise specified. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer. NMR spectra were recorded in DMSO-d_6 solutions at room temperature (20 °C ± 2 °C). ^{1}H and ^{13}C 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 ^{1}H NMR and ^{13}C NMR spectra were confirmed with previously reported literature, and the main intermediates were characterized by ^{1}H NMR, ^{13}C NMR spectra, and mass spectra.

4-Bromobutyl acetate

It was prepared according to the reported procedure.[23] light yellow liquid 27.6 g, yield 85%. ^{1}H NMR (400 MHz, DMSO-d_6, 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). ^{13}C NMR (101 MHz, DMSO-d_6, ppm) δ 171.2, 67.7, 36.0, 31.6, 29.9, 25.8.

[4-(Acetyloxy)butyl]triphenylphosphonium bromide *(1)*. 4-Bromobutyl acetate (23.5 g, 0.12 mol) and PPh3 (30 g, 0.12 mol) were added to 250 mL acetonitrile and refluxed overnight. Acetonitrile was distilled off under reduced pressure to obtain a pale yellow viscous oil. After 150 mL ether 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 **1** as a white powder, 51.3 g, 93%.[24] 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). ^{13}C 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.

(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, 0.11 mol) in CH_2Cl_2 (250 mL) was added Cs_2CO_3 (71.2 g, 0.22 mol), and the mixture was refluxed for 24 h under nitrogen atmosphere. CH_2Cl_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 **2** as a colorless oil, 16.6 g, 76% (2*E*:2*Z* = 32:68).[16] 1H NMR (400 MHz, DMSO-d_6, ppm): δ (*E*)-isomer 6.89 (dt, J = 15.7 Hz, 6.9 Hz, 1H), 5.88 (d, J = 15.7 Hz, 1H), 4.15–4.09 (q, 2H), 3.99 (t, J = 6.5 Hz, 2H), 2.29–2.21 (m, 2H), 2.00 (s, 3H), 1.73 (p, J = 6.9 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 170.8, 166.0, 148.9, 121.8, 63.5, 60.2, 28.5, 26.9, 21.1, 14.5. HRMS (Supplemental) m/z: Anal. calcd for $C_{10}H_{16}O_4$ $[M+Na]^+$ 223.0941; found 223.0943.

Ethyl 6-hydroxy-2*E*-hex-2-enoate *(3)*. The strong acidic styrene type cation exchange resin 732 (15 g) was added into a solution of compound **2** (14.5 g, 71.92 mmol) dissolved in 80 mL ethanol and refluxed overnight. The reaction was cooled to room temperature, and then the resin was filtered and washed twice with 30 mL ethanol. The ratio of *E*- and *Z*-isomers was 67:33. 10 Drops of I_2 in ethanol solution (0.1 g/mL) were added to the reaction mixture that was refluxed for 3 h. Ethanol was removed to afford a brown oil. 100 mL CH_2Cl_2 was added to the oil, which was washed with water (3 × 20 mL), and the organic phase was dried over anhydrous sodium sulfate. The CH_2Cl_2 was distilled to obtain **3** as a light yellow oil (*E:Z* = 86:14), which could be used directly in the next reaction, 8.9 g, 78% (2*E*:2*Z*=86:14).[15] 1H NMR (400 MHz, $CDCl_3$, ppm): δ 6.93 (dt, J = 15.7, 6.9 Hz, 1H), 5.80 (d, J = 15.6 Hz, 1H), 4.19–4.11 (q, J = 7.1 Hz, 2H), 3.61 (t, J = 5.4 Hz, 2H), 2.26 (m, 2H), 1.73–1.64 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.6, 148.5, 121.4, 61.5, 60.1, 30.7, 28.3, 14.0. HRMS (Supplemental) m/z: Anal. calcd for $C_8H_{14}O_3$ $[M+H]^+$ 159.0140; found 159.0141.

Ethyl 6-bromo-2*E*-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_2Cl_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_2Cl_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%.[12] 1H NMR (400 MHz, $CDCl_3$, ppm): δ 6.89 (dt, J=15.7, 7.0 Hz, 1H), 5.86 (d, J=15.6 Hz, 1H), 4.17 (q, J=7.1 Hz, 2H), 3.40 (t, J=6.5 Hz, 2H), 2.40–2.32 (m, 2H), 2.03–1.97 (m, 2H), 1.27 (t, J=7.2 Hz, 3H). ^{13}C 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. calcd for $C_8H_{13}BrO_2$ $[M+H]^+$ 221.0172; found 221.0174.

(6-Ethoxyl-6-oxo-4*E*-hexenyl)triphenylphosphonium bromide *(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 **5** as a white powder, 17.9 g, 92%.[12] m.p. 142–144 °C. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 7.86–7.72 (m, 15H), 6.86 (dt, J=15.7, 6.7 Hz, 1H), 5.93–5.82 (d, J=15.7 Hz, 1H), 4.09 (q, J=7.1 Hz, 2H), 3.67–3.59 (m, 2H), 2.40 (m, 2H), 1.76–1.67 (m, 2H), 1.19 (t, J=7.1 Hz, 3H). ^{13}C 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, 28.6, 20.8, 14.3. HRMS (Supplemental) m/z: Anal. calcd for $C_{26}H_{28}O_2P^+$ 403.1821; found 403.1819.

Ethyl *2E,6Z,8E,10E*-dodecatetraenoate *(6)*. To a solution of **5** (14.9 g, 30.76 mmol) and 2*E*,4*E*-hexadienal (3.0 g, 30.76 mmol) in CH_2Cl_2 (100 mL) was added Cs_2CO_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_2Cl_2 (3 × 50 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 × 20 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 2*E*,6*Z* isomer in the mixture was 56%).[12] 1H NMR (400 MHz, DMSO-d_6, ppm): δ 6.92–6.82 (dt, J=15.5, 6.5 Hz, 1H), 6.27–5.95 (m, 4H), 5.87 (d, J=15.7 Hz, 1H), 5.78–5.65 (m, 1H), 5.37 (m, 1H), 4.09 (q, J=7.1 Hz, 2H), 2.29 (m, 4H), 1.73 (d, J=6.4 Hz, 3H), 1.19 (t, J=7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 166.0,

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 $C_{14}H_{20}O_2$ $[M+Na]^+$ 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 CH_2Cl_2 (3×50 mL). The organic layer was washed with brine, and dried over Na_2SO_4. CH_2Cl_2 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 2*E*,6*Z*-isomer was 99%).[12] m.p. 93.5–95 °C (lit.11 93.5–95 °C); ^{1}H NMR (400 MHz, DMSO-d_6, 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, 6.2 Hz, 1H), 2.34–2.23 (m, 4H), 1.76–1.72 (d, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 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 $C_{12}H_{16}O_2$ $[M+Na]^+$ 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 CH_2Cl_2 (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 CH_2Cl_2 (3×30 mL), the organic phase was washed with 1 mol/L HCl, 5% $NaHCO_3$, and brine, respectively, and dried with Na_2SO_4, CH_2Cl_2 was evaporated to afford a colorless oil. 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 dark brown during heating and dissolves at 84–90 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 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). ^{13}C NMR (101 MHz, DMSO-d_6, ppm): δ 165.3, 141.7, 133.3, 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 $C_{16}H_{25}NO_2$ $[M+Na]^+$ 286.1778; found 286.1781.

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Supplemental material

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