Monatshefte für Chemie - Chemical Monthly (2021) 152:545–549
https://doi.org/10.1007/s00706-021-02762-2

ORIGINAL PAPER

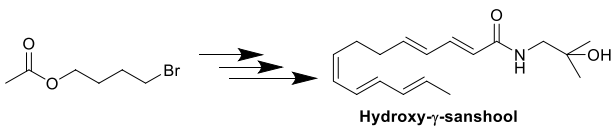
Synthesis of hydroxy-γ-sanshool

Jiyu Gao[1] · Jianjun Zhou[1] · Taiping Chen[1] · Yan Xiao[1] · Zicheng Li[1] · Wencai Huang[1]

Received: 18 January 2021 / Accepted: 29 March 2021 / Published online: 17 April 2021

Abstract
Hydroxy-γ-sanshool was prepared with 19.5% overall yield through eight steps. Wittig reactions of ylides with ethyl 4-oxobut-2-enoate as well as (2*E*,4*E*)-hex-2,4-dienal were key steps to construct a carbon skeleton. The 2*E*,4*Z*-isomer in ethyl 8-hydroxyocta-2,4-dienoate can be isomerized to the desired 2*E*,4*E*-isomer with iodine as a catalyst, and free tetradeca-2,4,8,10,12-pentaenoic acid can be purified through crystallization in 1% ethyl acetate in *n*-hexane. The impurities in other intermediates can be easily removed, the synthetic process can avoid the synthesis or use of 4-bromobutyraldehyde which comes from the oxidation of unstable 4-bromobutan-1-ol, and the work-ups were simple.

Graphic abstract



Keywords Pentaenamide · Total synthesis · Wittig reaction · Isomers

Introduction

Sanshools are isolated from Zanthoxylum bungeanum, mainly including *α*-sanshool, *β*-sanshool, *γ*-sanshool, *δ*-sanshool, and hydroxy-sanshool analogs which contain hydroxyl on amino part (Fig. 1) [1].

Ren et al. found that hydroxy-*γ*-sanshool could activate the mammalian target of rapamycin (mTOR) pathway and improve the metabolism of diabetic rats [2]. Katina et al. proved that hydroxy-*γ*-sanshool was a good antagonist of the cannabinoid 1 (CB1) receptor. Thus, hydroxy-*γ*-sanshool may be a potential candidate for the treatment of type-1 diabetes [3]. In addition, other pharmacological effects had been discovered, such as anesthesia [4] and gastrointestinal regulation [5]. However, the content of hydroxy-*γ*-sanshool in Zanthoxylum bungeanum is very low (less than 0.01%) [1]. Thus, chemical synthesis became only the source of hydroxyl-*γ*-sanshool.

✉ Zicheng Li
sculzc@scu.edu.cn

[1] School of Chemical Engineering, Sichuan University, Chengdu, China

Aoki et al. synthesized hydroxyl-*γ*-sanshool using 4*Z*,6*E*,8*E*-deca-4,6,8-trienenitrile-Fe(CO)$_3$ complex as a key intermediate [6]. Although high yield was achieved, the process involved highly toxic carbonyl iron, and reaction conditions were harsh.

Crombie et al. synthesized hydroxyl-*γ*-sanshool from ethyl (2*E*,4*E*)-8-hydroxyocta-2,4-dienoate by Horner-Wadsworth-Emmons (HWE) reaction. The ethyl (2*E*,4*E*)-8-chloroocta-2,4-dienoate was prepared from 4-chlorobutan-1-ol [7, 8]. But the activity of 8-chloroocta-2,4-dienoate is not satisfactory in the next reaction of forming phosphonium salt.

Xia et al. synthesized *γ*-sanshool and hydroxy-*γ*-sanshool from sorbaldehyde and (6-ethoxy-6-oxohexyl)triphenylphosphonium bromide to construct triene fragment. A three-step Corey-Fuchs reaction was used to reduce the ester to an aldehyde and the aldehyde to the triene [9]. Although a good yield had been achieved, the substrate was expensive and harsh conditions were required.

As one of our projects, we have finished the synthesis of hydroxyl-*α*-sanshool from ethyl 2-oxoacetate and 4-bromobutyl acetate [10], here we reported the synthesis

of hydroxy-γ-sanshool from ethyl 4-oxobut-2-enoate and 4-bromobutyl acetate, the synthetic route was depicted in Scheme 1. The impurities in the process can be separated by utilizing the insolubility of phophonium salts 1 and 5 in ethyl acetate and ethyl ether, most of the 2*E*,4*Z*-isomer in compound 3 can be isomerized into the desired 2*E*,4*E*-structure with iodine as a catalyst and the desired 8*Z*-isomer free acid 7 can be crystallized in 1% ethyl acetate in *n*-hexane.

Results and discussion

The key steps in the preparation of hydroxyl-γ-sanshool were the formation of several double bonds of carbon–carbon. Hydroxyl-γ-sanshool can be synthesized in two routes, one is as the procedures of Xia et al., another is the ylide from ethyl (2*E*,4*E*)-8-bromooct-2,4-dienoate reacted with (2*E*,4*E*)-hex-2,4-dienal followed by amidation. Ethyl (2*E*,4*E*)-8-bromooct-2,4-dienoate can be relatively easily prepared as Fig. 2.

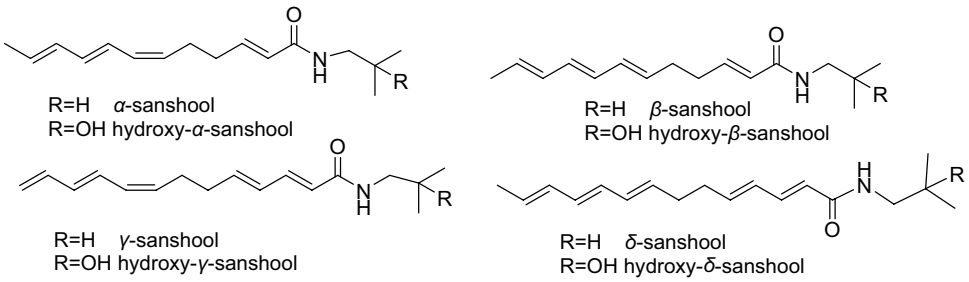


Fig. 1 Chemical structure of sanshools

Scheme 1

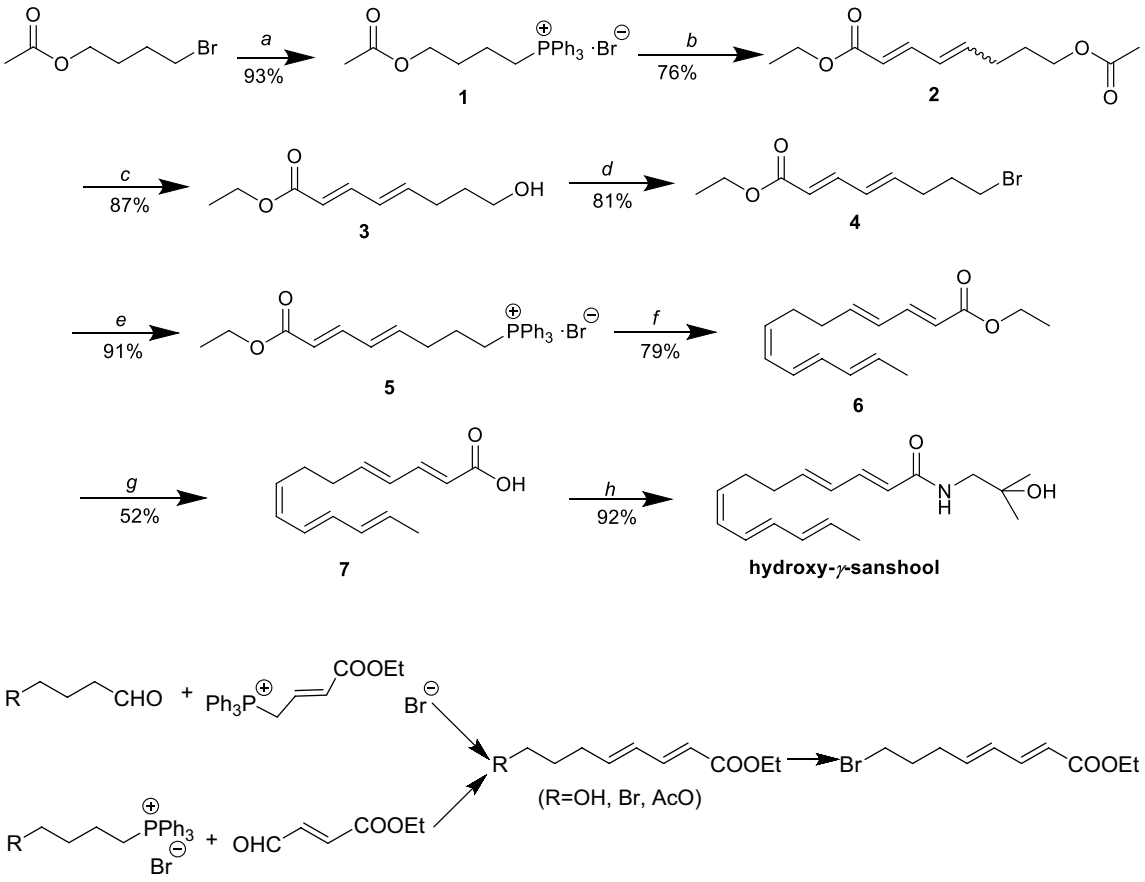


Fig. 2 The synthetic route of ethyl (2*E*,4*E*)-8-bromooct-2,4-dienoat

Initially, 1,4-butanediol or 4-bromobutan-1-ol was chosen to prepare 4-bromobutyraldehyde which involved the oxidation reaction with PCC [11–13]. However, 4-bromobutan-1-ol is unstable during its synthesis, storage, and oxidation. The yield of aldehyde was low and the purification was very difficult. Relatively, 4-bromobutyl acetate can be easily prepared from tetrahydrofuran reacting with acetyl bromide. And 4-bromobutyl acetate can be easily transformed into ylide which was reacted with commercially available ethyl 4-oxobut-2-enoate. Although the 2*E*,4*Z*-isomer was main product, it can be isomerized to its 2*E*,4*E*-isomer. This process can avoid utilizing oxidation reaction with PCC and unstable 4-bromobutan-1-ol.

4-Bromobutyl acetate was reacted with Ph_3P to afford 1, 1 was reacted with ethyl 4-oxobut-2-enoate to give 2, compound 2 was hydrolyzed and 2*E*,4*Z*-3 was isomerized to 2*E*,4*E*-3, 3 was then transferred into 4 with CBr_4 and Ph_3P. All impurities in 4 including those that existed in 4-bromobutyl acetate can be separated during the synthesis of quaternary phosphonium salt 5, because 5 can't be dissolved in ethyl acetate or ether while other compounds can. The 2*E*,4*Z*-isomer in compound 3 was converted into the desired 2*E*,4*E*-isomer with iodine as a catalyst. The initial ratio of 2*E*,4*Z*:2*E*,4*E* in compound 3 was 58:42; after the isomerization, the ratio of 2*E*,4*Z*:2*E*,4*E* was 89.6:10.4.

The phosphonium salt 5 was reacted with (2*E*,4*E*)-hex-2,4-dienal in the presence of Cs_2CO_3 to give 6, the percentage of 2*E*,4*E*,8*Z*,10*E*,12*E*-isomer in 6 was 62% by relative peak area in HPLC. Compound 6 was hydrolyzed with NaOH in a 33% methanol aqueous solution, and pure 7 was obtained by crystallization in 1% ethyl acetate in *n*-hexane. Finally, hydroxy-γ-sanshool was obtained smoothly by the condensation reaction with 1-amino-2-methylpropan-2-ol catalyzed by HBTU.

Conclusion

Hydroxy-γ-sanshool was synthesized with an overall yield of 19.5% including two Wittig reactions to construct carbon skeleton, the process was easily operation, raw materials were available, and work-ups were simple. All intermediates and the target product have been characterized by ^{1}H NMR, ^{13}C NMR, and HRMS.

Experimental

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 or chloroform-*d* solutions at room temperature (20 ± 2 °C). ^{1}H and ^{13}C chemical shifts are quoted in parts per million downfield from TMS. High-resolution mass spectra (HRMS) were obtained on a MicrOTOF-Q II mass spectrometer with an ESI 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. HPLC was performed on LC-3000 HPLC system using a Welchrom C18 column (4.6 mm × 250 mm, 5 μm) or U-3000 HPLC system using a Syncroni C18 column ((4.6 mm × 250 mm, 5 μm).

(4-Acetoxybutyl)triphenylphosphonium bromide (1) [16] A mixture of 15.66 g of 4-bromobutyl acetate (80 mmol) (which was prepared according to the reported procedures [14]) and 21 g of triphenylphosphine (80 mmol) in 100 cm^3 of acetonitrile was refluxed for 12 h under nitrogen [15]. Then it was cooled to room temperature and acetonitrile was removed to obtain a colorless oil. 50 cm^3 of ether was added to the oil and frozen in the refrigerator for 2 h. The mixture was ground to obtain a white granular solid, which was filtered, washed with ether and ethyl acetate, respectively, and dried in vacuum to obtain a white powdery solid, 34.3 g with a yield of 93%. The product can be used directly in the next step without further purification. ^{1}H NMR (DMSO-d_6): δ = 7.85–7.73 (m, 15H, Ar–H), 4.09 (t, J = 7.1 Hz, 2H, -CH_2O-), 3.64 (t, J = 7.2 Hz, 2H, -CH_2-), 2.24 (s, 3H, $COCH_3$), 1.69–1.73 (m, 2H, -CH_2-), 1.18–1.20 (m, 2H, -CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 165.86, 135.29, 130.65, 122.42, 119.06, 60.14, 32.39, 20.89, 20.27, 14.25 ppm.

Ethyl (2*E*,4*Z*/2*E*,4*E*)-8-acetoxyocta-2,4-dienoate (2, $C_{12}H_{18}O_4$) A mixture of 32 g of compound 1 (70.4 mmol), 9 g of ethyl (*E*)-4-oxobut-2-enoate (70.4 mmol) and 46.0 g of Cs_2CO_3 (141 mmol) in 100 cm^3 of CH_2Cl_2 was refluxed for 24 h under nitrogen. After cooling to ambient temperature, the solvent was removed. Then 250 cm^3 of *n*-hexane was added to the residue and stirred for 30 min. The solid was filtered, and washed twice with 200 cm^3 of *n*-hexane. Combined organic layer was evaporated to obtain a yellow oil, 12.1 g, with a yield of 76% (2*E*,4*E*:2*E*,4*Z* = 42:58). The product can be used directly in the next step without further purification. ^{1}H NMR (DMSO-d_6): δ = 7.50 (dd, J = 15.2, 11.8 Hz, 0.42H, = CH-), 7.21 (dd, J = 15.3, 9.5 Hz, 0.58H, = CH-), 6.27 (d, J = 9.1 Hz, 1H, = CH), 6.24–5.93 (m,1H, = CHCO-), 5.87(d, J = 15.3 Hz, 1H, = CH-), 4.12 (q, J = 7.3 Hz, 2H, -OCH_2-), 3.99 (q, J = 6.3 Hz, 2H, -CH_2CO-), 2.37–2.16 (m, 2H, = $CHCH_2$-), 1.99 (s, 3H, -$COCH_3$), 1.66–1.73 (m, 2H, -CH_2-), 1.21 (t, J = 7.1, 3H, -CH_2CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 170.72, 166.62, 145.14, 139.21, 129.06, 119.78, 63.57, 60.11, 29.23, 27.61, 21.00, 14.51 ppm; HRMS (ESI): *m/z* calcd. for $C_{12}H_{18}O_4$ ($[M+Na]^+$) 249.1103, found 249.1106.

Ethyl (2*E*,4E)-8-hydroxyocta-2,4-dienoate (3) [17] A mixture of 11.5 g of compound 2 (50.7 mmol) and 10 g of pre-treated strong acidic styrene type cation exchange resin 732 in 50 cm^3 of ethanol was refluxed for 5 h. After cooling to ambient temperature, the resin was filtered out and washed with ethanol. To the filtrate was added 10 drops of 0.1 g/cm^3 iodine in ethanol solution, the reaction was then refluxed for 12 h. The solvent was evaporated to obtain a brown oil, which was dissolved in 50 cm^3 of CH_2Cl_2, and washed three times with 30 cm^3 of water. After the organic phase was dried over Na_2SO_4, the solvent was evaporated to obtain a yellow oil, 8.2 g with a yield of 87% (2*E*,4*E*:2*E*,4*Z* = 89.6:10.4). The product can be used directly in the next step without further purification. ^{1}H NMR (DMSO-d_6): δ = 7.53 (dd, *J* = 15.2, 11.7 Hz, 0.9H, = CH), 7.22 (dd, *J* = 15.3, 10.0 Hz, 0.1H, = CH), 6.27 (d, *J* = 5.8 Hz, 1H, = CH-), 5.99–5.85 (m, 2H, = CH), 4.46 (s, 1H, -OH), 4.13 (q, *J* = 7.4 Hz, 2H, -OCH_2CH_3), 3.43 (t, *J* = 7.8 Hz, 2H, -CH_2OH), 2.36–2.15 (m, 2H, = $CHCH_2$-), 1.52–1.57 (m, 2H, -CH_2-), 1.22 (t, *J* = 7.1, 3H, -CH_2CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 166.74, 145.44, 145.26, 128.68, 119.44, 60.54, 60.13, 31.99, 29.49, 14.59 ppm; HRMS (ESI): *m/z* calcd. for $C_{10}H_{16}O_3$ ([M + H]$^+$) 185.1178, found 185.1173.

Ethyl (2*E*,4*E*)-8-bromoocta-2,4-dienoate (4) [18] CBr_4 (7.1 g, 21.3 mmol) was added to a solution of 10.8 g of Ph_3P (41.1 mmol) in 100 cm^3 of CH_2Cl_2 cooled in ice bath, and the reaction was stirred for 1 h. To the reaction was added a solution of 7.8 g of compound 3 (42.3 mmol) in 10 cm^3 of CH_2Cl_2, the reaction was stirred for 2 h in ice bath and another 2 h at ambient temperature. The solvent was evaporated to obtain a viscous yellow solid, 50 cm^3 of *n*-hexane was added to the viscous solid and stirred vigorously until the mixture was dispersed into a granular solid, the solid was filtered and washed with *n*-hexane (2 × 20 cm^3). The filtrate was evaporated to give 4 as a light-yellow oil, which was used directly in the next reaction, 8.4 g with a yield of 81%. ^{1}H NMR (DMSO-d_6): δ = 7.53 (dd, *J* = 15.1, 11.9 Hz, 0.05H, = CH-), 7.21 (dd, *J* = 15.4, 10.0 Hz, 0.95H, = CH-), 6.35–6.21 (m, 2H, = CH-), 5.90 (d, *J* = 15.4 Hz, 1H, = CH-), 4.11 (q, *J* = 7.1 Hz, 2H, -CH_2CH_3), 3.53 (t, *J* = 6.6 Hz, 2H, -CH_2-), 2.28 (q, *J* = 7.2 Hz, 2H, = $CHCH_2$-), 1.89–1.96 (m, 2H, -CH_2-) ppm; ^{13}C NMR (DMSO-d_6): δ = 166.72, 145.21, 143.40, 129.45, 119.94, 60.22, 31.61, 31.22, 31.15, 14.64 ppm; HRMS (ESI): *m/z* calcd. for $C_{10}H_{15}BrO_2$ ([M + H]$^+$) 247.0334 and 249.0313, found 247.0336 and 249.0309.

((4*E*,6*E*)-8-Ethoxy-8-oxoocta-4,6-dien-1-yl)triphenylphosphonium bromide (5, $C_{28}H_{30}BrO_2P$) A solution of 8.5 g of Ph_3P (32.4 mmol) and 8.0 g of compound 4 (32.4 mmol) in 30 cm^3 of acetonitrile was refluxed 24 h under nitrogen. The solvent was evaporated to obtain a colorless oil. 20 cm^3 of ether was added to the oil, which was placed in the refrigerator for 2 h, then ground to obtain a white granular solid. The solid was filtered and washed with 20 cm^3 of ether and 20 cm^3 of ethyl acetate, respectively. The obtained solid was dried in vacuum, 14.9 g with a yield of 91%. The product can be used directly in the next step without further purification. ^{1}H NMR (DMSO-d_6): δ = 7.94–7.73 (m, 15H, Ar–H), 7.47 (dd, *J* = 15.2, 11.8 Hz, 0.53H, = $CHCH_2$-), 7.18 (dd, *J* = 15.4, 9.8 Hz, 0.47H), 6.28 (d, *J* = 9.0 Hz, 1H, = CH-), 6.25–5.92 (m, 1H, = CHCO-), 5.96–5.81 (m, 1H, = CH-), 4.12 (dq, *J* = 14.1, 7.1 Hz, 2H, -CH_2CH_3), 3.67 (q, *J* = 6.4 Hz, 2H, = $CHCH_2$-), 1.66 (dt, *J* = 8.9, 4.4 Hz, 2H, -CH_2-), 1.20 (dt, *J* = 8.7, 7.1 Hz, 3H, -CH_3), 1.00–1.13 (m, 2H, -CH_2-) ppm; ^{13}C NMR (DMSO-d_6): δ = 166.70, 145.116, 143.05, 139.67, 135.44, 135.44, 135.41, 134.13, 134.03, 130.82, 130.69, 129.74, 127.88, 122.42, 120.13, 119.31, 118.46, 60.41, 33.31, 28.59, 20.77, 14.66 ppm; HRMS (ESI): *m/z* calcd. for $C_{28}H_{30}O_2P^+$ 429.1983, found 429.2011.

Ethyl (2*E*,4*E*,8*Z*,10*E*,12*E*)-tetradeca-2,4,8,10,12-pentaenoate (6, $C_{16}H_{22}O_2$) A mixture of 14.2 g of compound 5 (27.9 mmol), 2.67 g of (2*E*,4*E*)-2,4-hexadienal (27.8 mol), and 36.4 g of Cs_2CO_3 (55.9 mmol) in 100 cm^3 of CH_2Cl_2 was refluxed for 24 h under nitrogen. After cooling to ambient temperature, 15 g of diatomite was added and stirred for 30 min. The solid was filtered and washed with 20 cm^3 of CH_2Cl_2, combined organic layer was concentrated to obtain a yellow viscous oil. Subsequently 50 cm^3 of *n*-hexane was added to the oil and the mixture was stirred vigorously at ambient temperature for 30 min. The solid was filtered and washed with 60 cm^3 of *n*-hexane, combined organic layer was concentrated to obtain a pale-yellow oil. The crude oil was purified by flash silica gel column chromatography (ethyl acetate-petroleum ether, 1:30) to give a colorless oil, 5.42 g with a yield of 79%. ^{1}H NMR (DMSO-d_6): δ = 7.49 (dd, *J* = 15.2, 11.7 Hz, 0.38H, = CH-), 7.20 (dd, *J* = 15.3, 9.9 Hz, 0.62H, = CH-), 6.74–6.34 (m, 1H, = CH-), 6.35–6.25 (m,1H, = CH-), 6.21 (d, *J* = 11.3, 1H, = CH-), 6.18–6.11 (m, 1H, = CH-), 6.07 (d, *J* = 20.6 Hz, 1H, = CH-), 6.03–5.91 (m, 1H, = CH-), 5.87 (d, *J* = 15.2 Hz, 1H, = CH-), 5.55–5.32 (m 1H, = CH-), 4.09–4.16 (m, 2H, -CH_2CH_3) 2.32 (dt, *J* = 22.7, 7.4 Hz, 2H, = $CHCH_2$-), 2.22 (dt, *J* = 11.3, 5.4 Hz, 2H, = $CHCH_2$-), 1.74 (d, *J* = 6.9 Hz 3H, = $CHCH_3$), 1.21 (td, *J* = 6.8 Hz, 2H, -CH_2CH_3) ppm; ^{13}C NMR (DMSO-d_6): δ = 166.69, 145.28, 139.48, 133.65, 132.36, 130.55, 130.15, 129.79, 129.10, 126.03, 119.74, 60.17, 32.09, 26.92, 18.56, 14.62 ppm; HRMS (ESI): *m/z* calcd. for $C_{16}H_{22}O_2$ ([M + H]$^+$) 247.1698, found 247.1698.

(2*E*,4*E*,8*Z*,10*E*,12*E*)-Tetradeca-2,4,8,10,12-pentaenoic acid (7) [9] A mixture of 5.2 g of compound 6 (20.8 mmol) and 3.2 g of NaOH (80 mmol) in 20 cm^3 of methanol and 40 cm^3 of water was refluxed for 2 h. The solvent was concentrated and 20 cm^3 of water was added to the solution. After washing with ether (3 × 50 cm^3), the aqueous phase was adjust to pH 1 with hydrochloric acid (1 mol/dm^3). Then

the aqueous phase was extracted with CH_2Cl_2 (3×50 cm^3), the combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated to obtain a yellow sticky solid. The solid was recrystallized with 1% ethyl acetate in *n*-hexane solution, 2.4 g with a yield of 52%. ^{1}H NMR ($CDCl_3$): $\delta=7.32$ (dd, $J=15.3$, 9.9 Hz, 1H, =CH-), 6.53–6.23 (m, 1H, =CH-), 6.24–6.19 (m, 1H, =CH-), 6.17 (s, 1H, =CH-), 6.14 (d, $J=4.1$ Hz, 1H, =CH-), 6.08 (dq, $J=11.6$, 2.2 Hz, 1H, =CH-), 6.02 (t, $J=11.0$ Hz, 1H, =CH-), 5.78 (dd, $J=15.3$, 2.2 Hz, 1H, =CH-), 5.74–5.56 (m, 1H, =CH-), 5.57–5.28 (m, 1H), 2.29 (tdd, $J=19.8$, 10.4, 6.4 Hz, 4H, $=CHCH_2$-), 1.76 (td, $J=6.6$, 1.4 Hz, 3H, $-CH_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta=172.74$, 147.44, 145.11, 133.61, 131.85, 130.37, 129.74, 129.58, 128.81, 125.33, 118.72, 33.15, 26.96, 18.51 ppm; HRMS (ESI): *m/z* calcd. for $C_{14}H_{18}O_2$ ($[M+Na]^+$) 241.0728, found 241.0729.

Hydroxy-γ-sanshool [9] Et_3N (5.1 g, 50.4 mmol) and 5.5 g of HBTU (14.4 mmol) were added into a solution of 2.1 g of compound 7 (9.62 mmol) in 50 cm^3 of $CHCl_3$, the reaction was stirred for 30 min in an ice-water bath, then 3.06 g of 1-amino-2-methylpropan-2-ol (34.3 mmol) was added under nitrogen. The reaction was stirred for 1 h in an ice water bath and another 3 h at ambient temperature. 50 cm^3 of water was added to the reaction and stirred for 30 min. After separating the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2×20 cm^3), then the combined organic layer was washed with 1 mol/dm^3 of hydrochloric acid, brine, saturated $NaHCO_3$ solution, and brine. The organic layer was dried over Na_2SO_4 and evaporated to obtain a light yellow oil. 20 cm^3 of petroleum ether was added to the oil, and the mixture was frozen in the refrigerator for 2 h. White granular solid was obtained after vigorous stirring for 10 min, which was collected by filtration and dried under vacuum. 2.57 g, 92% yield. The product has the same retention time as an authentic sample in HPLC. ^{1}H NMR (DMSO-d_6): $\delta=8.03$–7.87 (m, 1H, -NH), 7.50–7.14 (m, 1H, =CH-), 7.03 (s, 1H, =CH-), 6.28 (d, $J=13.5$ Hz, 1H, =CH-), 6.17 (t, $J=5.6$, 1H, =CH-), 6.10 (d, $J=15.1$ Hz, 1H, =CH-), 6.09–5.82 (m, 1H, =CH-), 5.82–5.76 (m, 1H, =CH-), 5.75 (d, $J=6.9$ Hz, 1H, =CH-), 5.63–5.39 (m 1H, =CH-), 3.16 (t, $J=5.9$ Hz, 3H, -OH, $-NHCH_2$-), 2.43–2.30 (m 2H, $=CHCH_2$-), 1.80 (d, $J=7.7$ Hz, 2H, $=CHCH_2$-), 1.25 (d, 3H, $=CHCH_3$), 1.09–1.06 (m, 6H, $-CH_3$, $-CH_3$) ppm; ^{13}C NMR (DMSO-d_6): $\delta=166.01$, 139.58, 138.02, 134.04, 133.65, 132.41, 130.14, 127.66, 126.30, 126.07, 124.13, 69.97, 50.26, 27.71, 20.74, 17.56, 16.99 ppm; HRMS (ESI): *m/z* calcd. for $C_{18}H_{27}NO_2$ ($[M+Na]^+$) 312.1940, found 312.1935.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00706-021-02762-2.

Acknowledgements We thank the State Key Laboratory of Biotherapy, West China Hospital, Sichuan University for ^{1}H NMR, ^{13}C NMR, and HRMS determination. This work was financially supported by the Sichuan Provincial Administration of Traditional Chinese Medicine2018HJZX04.

References

1. Yang X (2008) J Agric Food Chem 56:1689
2. Ren T, Zhu Y, Xia X, Ding Y, Guo J, Kan J (2017) J Mol Endocrinol 58:113
3. Dossou KS, Devkota KP, Morton C, Egan JM, Lu G, Beutler JA, Moaddel R (2013) J Nat Prod 76:2060
4. Rong R, Cui MY, Zhang QL, Zhang MY, Yu YM, Zhou XY, Yu ZG, Zhao YL (2016) J Sep Sci 39:2728
5. Tokita Y, Yamamoto M, Satoh K, Nishiyama M, Iizuka S, Imamura S, Kase Y (2011) J Pharmacol Sci 115:75
6. Aoki K, Igarashi Y, Nishimura H, Morishita I, Usui K (2012) Tetrahedron Lett 53:6000
7. Crombie L, Fisher D (1985) Tetrahedron Lett 26:2477
8. Crombie L, Fisher D (1985) Tetrahedron Lett 26:2481
9. Xia X, Toy PH (2014) Synlett 25:2787
10. Zhou J, Xiao Y, Chen T, Gao J, Huang W, Li Z (2020) J Chem Res 1747519820974323
11. Koley D, Srinivas K, Krishna Y, Gupta A (2014) RSC Adv 4:3934
12. Kad GL, Kaur I, Bhandari M, Singh J, Kaur J (2003) Org Process Res Dev 3:339
13. Khan AA, Kamena F, Timmer MS, Stocker BL (2013) Org Biomol Chem 11:881
14. Cloke JB, Pilgrim FJ (1939) J Am Chem Soc 61:2667
15. Rigatti R, Ost T, Fashena S (2008) Method for pairwise sequencing of double-stranded DNA on clustered arrays. Patent WO 2008/041002 A2, 2008; (2008) Chem Abstr 148:419098
16. Leeson PD, Ellis D, Emmett JC (1988) J Med Chem 31:31
17. Chen X, Zhang Y, Wan H, Wang W, Zhang S (2016) Chem Commun 52:3532
18. Cooper SP, Booker-Milburn KI (2015) Angew Chem 127:6596