Synthesis C. Mugnaini, F. Corelli Paper

Total Synthesis of δ-Sanshool and Analogues Thereof

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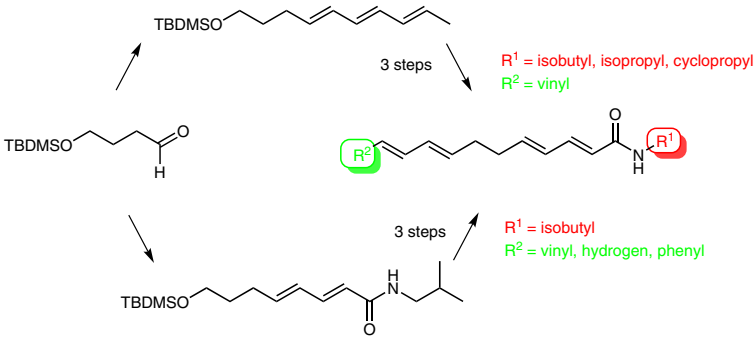

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Abstract Two simple synthetic approaches were developed for the total synthesis of δ-sanshool, an isobutylamide characterized by a C_{14} pentaunsaturated chain with all *trans* double bonds and proposed as a promising lead for the treatment of type-1 diabetes due to its dual activity on cannabinoid (CB) receptors. The syntheses are based on a suitably protected core fragment derived from 1,4-butanediol. These strategies also enable the preparation of small libraries of chemical analogues modified at either the polyunsaturated alkyl chain or the amidic head for use in SAR studies.

Key words sanshools, alkamides, trienes, Horner–Wadsworth–Emmons reaction, cannabinoid receptors

The genus *Zanthoxylum* belongs to the family Rutaceae and is represented by 250 species, mainly distributed in North America and in East Asia. Many of these species have been used widely in traditional medicine to treat toothache and as food spices for their ability to evoke a tingling and pungent sensation.[1] This pharmacological activity is believed to be predominantly elicited by the sanshools (Figure 1) present in the traditional medicine.[2]

Sanshools are a family of polyunsaturated fatty acid amides (FAA) which differ in the length and in the double bond geometry of the polyunsaturated chain, and in the potential presence of a hydroxylated isobutyl chain linked to the amide moiety.[3]

δ-Sanshool, an isobutylamide characterized by a C_{14} all-*trans* pentaunsaturated chain, was isolated for the first time in 1997 from Budo-Zanthoxylum fruit and its structure was assigned by spectral examination.[4] Due to its ability to activate the TRPV1 receptor, δ-sanshool exhibits a pungent taste[5] and has been proposed as an ingredient in formulations to stimulate digestion and enhance nutrient absorption.[6] More recently, starting from extracts from *Zantoxylum bungeanum*, Moaddel and co-workers have identified δ-sanshool as a molecule with the desired dual activity, as a CB1 antagonist and CB2 agonist,[7] for the possible therapeutic treatment of type-1 diabetes.[8]

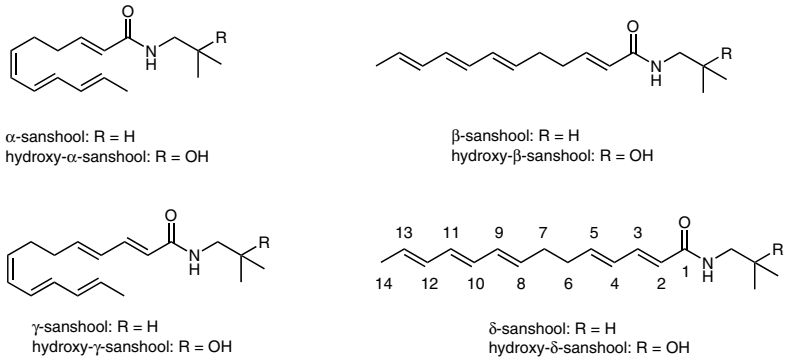
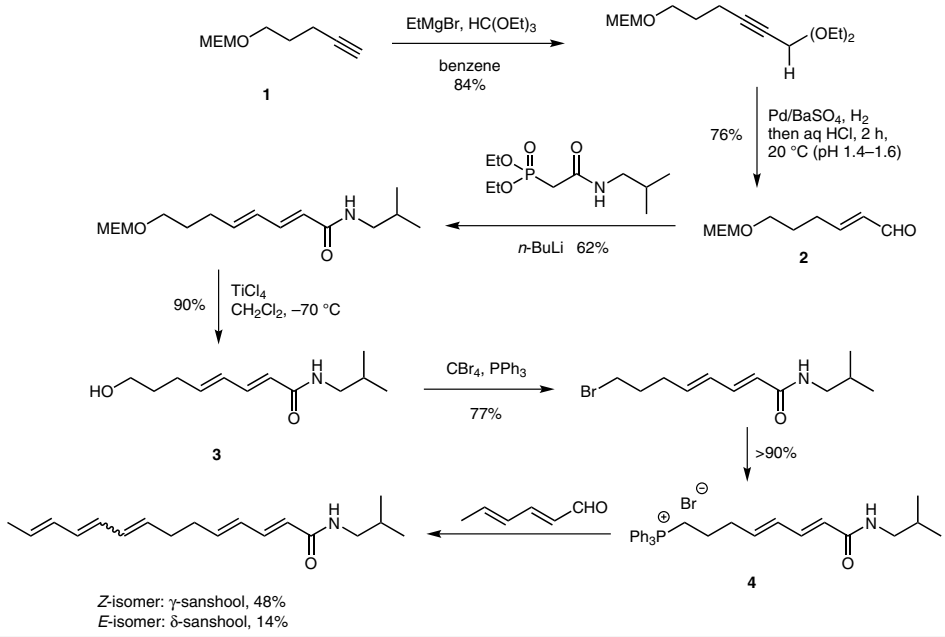


Figure 1 Examples of sanshools



Scheme 1 Synthesis of γ- and δ-sanshool according to Crombie and Fisher[9]

For this reason, a larger amount of the identified sanshool was needed to continue with biological investigations. However, due to the lack of synthetic procedures for the preparation of δ-sanshool, a reliable synthetic protocol needed to be established which could be exploited not only for the preparation of the target molecule, but also for the creation of a small library of chemical congeners to be used as SAR probes.

In 1985, twelve years before its isolation and characterization, δ-sanshool was described by Crombie and Fisher as a side product in the preparation of γ-sanshool, differing from its δ-isomer by the *Z* geometry of the C8–C9 double bond (Scheme 1).[9] In this procedure, MEM-protected 4-pentyn-1-ol **1** was elaborated, in two steps, into MEM-protected (*E*)-6-hydroxyhex-2-enal **2** via reaction with ethyl orthoformate in the presence of a Grignard reagent and subsequent stereoselective reduction of the triple bond and pH-controlled deacetalization. Wadsworth–Emmons condensation followed by alcohol deprotection gave the key intermediate **3**, which was readily converted into the corresponding phosphonium salt **4**. Wittig reaction with (2*E*,4*E*)-hexa-2,4-dienal afforded the desired product, γ-sanshool, in 48% yield and the side product, δ-sanshool, in 14% yield. Therefore, δ-sanshool was obtained in 3% overall yield in seven steps.

However, the experimental protocol was not included in the published manuscript. As a result, the synthesis of δ-sanshool has never been reported in detail.

The synthesis of γ-sanshool proposed by Crombie and Fisher presented the generation of the C2–C3, C4–C5 and C8–C9 double bonds by means of a stereoselective hydrogenation, a Wadsworth–Emmons reaction and a Wittig reaction, respectively, as the key steps. Thus, in this work, a similar disconnection approach was maintained. Three main issues were considered: the attainment of the *E*-geometry at the C8–C9 double bond, the commercial availability of the main building blocks, and the possibility to obtain analogues modified at both the polyunsaturated alkyl chain and the amide head.

On this basis, a suitably protected core fragment arising from 1,4-butanediol (fragment B in Figure 2) was selected as the starting material to be functionalized via two Wadsworth–Emmons reactions to install the A and C fragments (Figure 2).

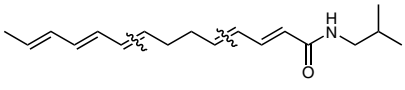
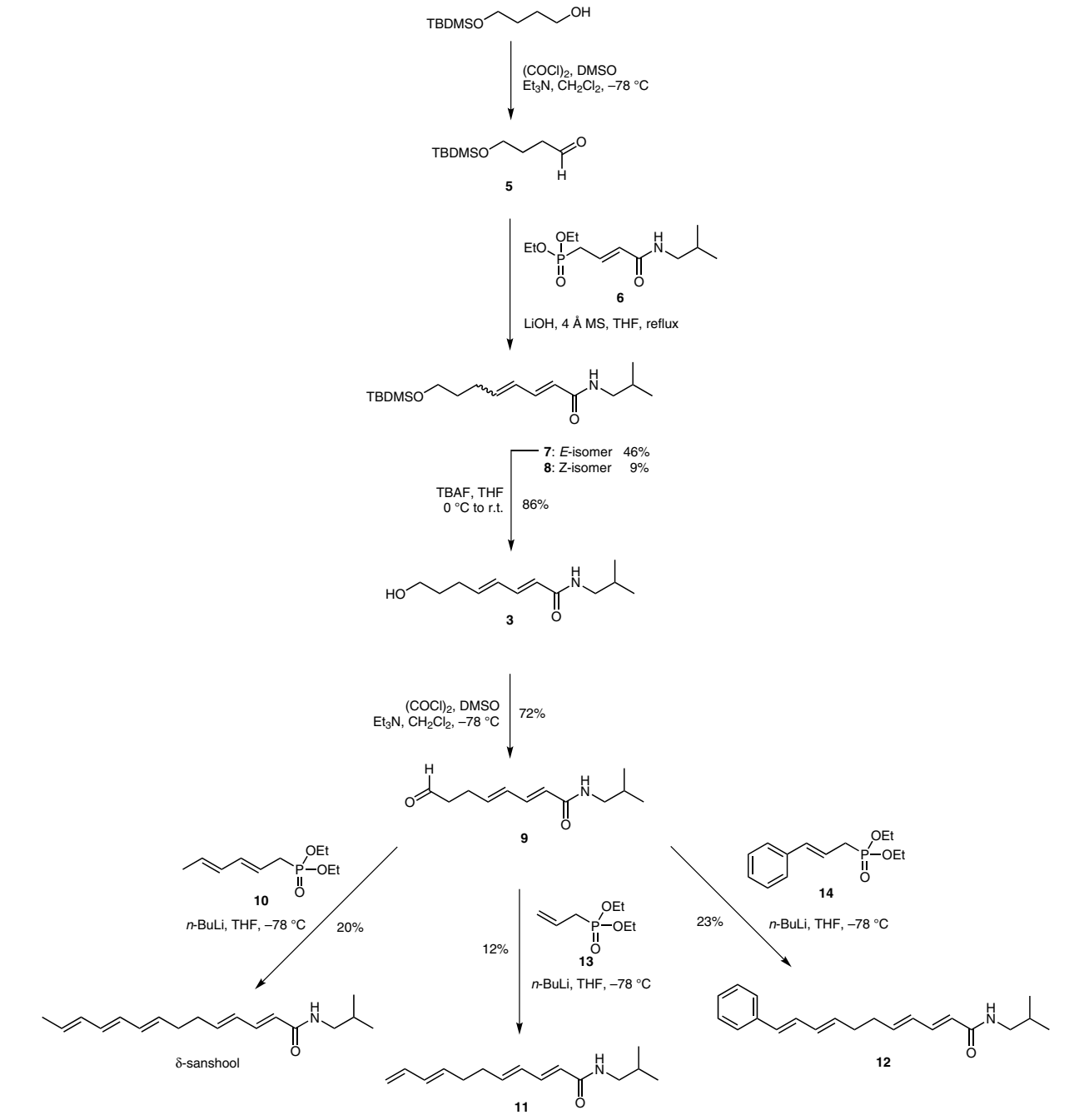


Figure 2 Disconnection approach

In a first approach, the introduction of the amide head and the triene moiety in a C + B + A sequence was pursued. Introducing the triene moiety at the end of the synthesis has important advantages including the chemical stability of the intermediates[10,11] and the possibility to produce structural modifications at the alkyl chain level, while keeping the amide head unchanged. In particular, the key synthon **5**[12] (Scheme 2) was obtained by Swern oxidation of commercially available 4-[(*tert*-butyldimethyl)silyl]oxybu-

tan-1-ol, which without further purification was condensed with phosphonate **6**[13] in the presence of LiOH in THF at reflux temperature[11] to give a mixture of the dienes **7** and **8**. The ratio of dienes **7**/**8**, evaluated by ^{1}H NMR analysis of the crude mixture, was 5:1 with a total yield of 46% of the *E*-isomer **7** (calculated over two steps).

After chromatographic separation, compound **7** was deprotected with TBAF and the resulting alcohol **3** was converted into the corresponding aldehyde **9** by Swern oxidation. δ-Sanshool was obtained in 20% yield as a single isomer by reacting **9** with phosphonate **10**[14] in the presence of *n*-BuLi in THF at –78 °C. This approach provided the target compound, δ-sanshool, in five steps and 7% overall yield, starting from 4-[(*tert*-butyldimethyl)silyl]oxybutan-1-ol.

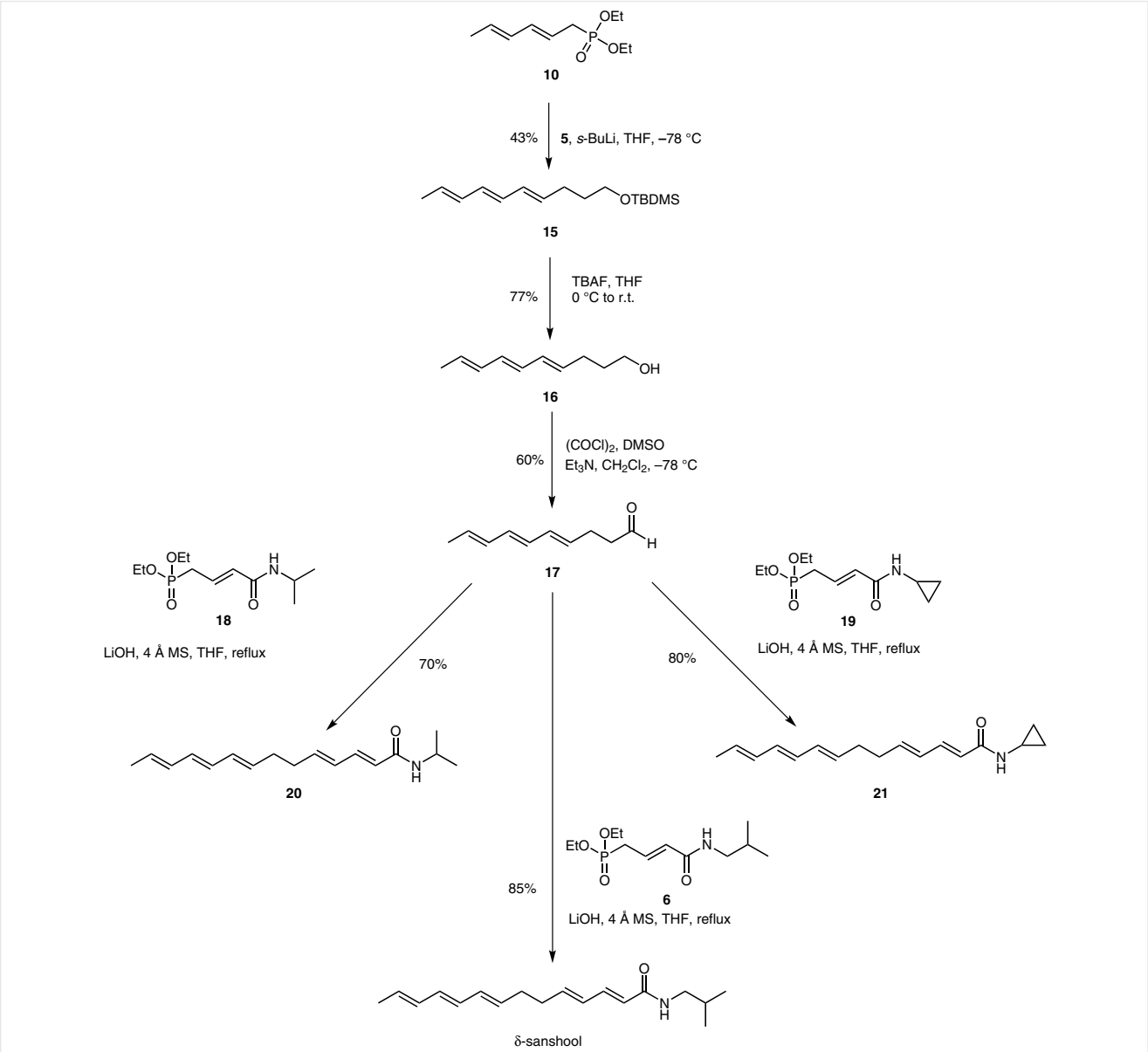


Scheme 2 Synthesis of δ-sanshool and analogues **11** and **12** via the C + B + A sequence

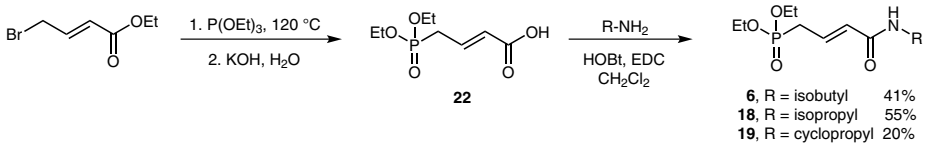
Similarly, compounds **11** and **12**, characterized by a modification of the triene portion of δ-sanshool, were obtained by reacting the common intermediate **9** with the commercially available phosphonates **13** and **14**, respectively. Both reactions gave the *E*-isomer as the sole product in 12% and 23% yields, respectively. The low yields of the Horner–Wadsworth–Emmons reactions leading to δ-sanshool, **11** and **12** are due to the formation of degradation products whose synthesis could not be avoided even on slightly changing the reaction conditions.

In a second approach, δ-sanshool was obtained according to the same disconnection route but combining the three fragments in an A + B + C fashion (Scheme 3). This ensured the possibility to introduce different amide heads as the final step of the synthesis. Accordingly, phosphonate **10** (Scheme 3) was condensed with aldehyde **5** using *sec*-BuLi as the base. All-*trans* triene **15**, obtained as the exclusive isomer, was deprotected with TBAF and the resulting alcohol **16** was oxidized using Swern conditions to give the aldehyde **17**.

Condensation of aldehyde **17** with phosphonate **6** using LiOH in THF at reflux afforded δ-sanshool in 85% yield (14% overall yield in four steps starting from phosphonate **10**). The putative *cis* isomer was obtained in trace amount after chromatographic purification and was not characterized. Similarly, condensation of aldehyde **17** with phosphonates



Scheme 3 Synthesis of δ-sanshool and analogues **20** and **21** via the A + B + C sequence



Scheme 4 Synthesis of phosphonates **6**, **18** and **19**

18 and **19** allowed the preparation of two analogues of δ-sanshool modified at the amide level (compounds **20** and **21**, respectively).

This second approach, though preferable in terms of stereoselectivity and general yields, proved to be less convenient because of the chemical instability of the intermediates. These had to be stored at low temperature in the absence of light and oxygen, and had to be prepared and used rapidly in subsequent reactions.

Phosphonates **6**, **18** and **19** were prepared from ethyl 4-bromocrotonate by an Arbuzov reaction,[13] hydrolysis of the ester moiety[15] and subsequent reaction of carefully dried acid **22** with the appropriate amine in the presence of EDC and HOBt (Scheme 4).[11]

The double bond geometry of the new compounds was assigned by decoupling experiments and comparison of the ^{1}H NMR spectrum of synthesized δ-sanshool with data reported in the literature (see the Supporting Information).

In conclusion, for the first time, a simple synthetic approach has been described for the total synthesis of δ-sanshool and the preparation of derivatives modified either at the lipophilic tail of the molecule or at the amide head. However, the newly synthesized compounds proved to be extremely unstable even when stored at –15 °C under nitrogen and in the absence of light. This behavior raises the issue of their biological evaluation which must be performed rapidly on freshly purified materials in order to ensure the robustness of the experimental outcomes. Additional studies to modify the structural skeleton of δ-sanshool are ongoing in our laboratories with the aim of obtaining molecules endowed with increased chemical stability.

Reagents were purchased from commercial suppliers and were used without further purification. Anhydrous reactions were run under dry N_2 (positive pressure). Merck silica gel 60 was used for flash chromatography (23–400 mesh). Melting points were determined on a Gallenkamp apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz on a Bruker Avance DPX400 spectrometer. Chemical shifts are reported relative to tetramethylsilane at 0.00 ppm. Mass spectral (MS) data were obtained using an Agilent 1100 LC/MSD VL system (G1946C) with a 0.4 mL/min flow rate using a binary solvent system of MeOH–H_2O (95:5). Mass spectra were acquired either in positive or in negative mode scanning over the mass range of 105–1500. UV detection was monitored at 254 nm. GC–MS data were collected on a Varian Saturn 2000 GC–MS equipped with a VF-5 ms capillary column, using the following conditions: gas flow = 0.8 mL/min; temperature: 80 °C (5 min), 80–280 °C (10 °C/min), 280 °C (10 min). Elemental analysis was performed using a Perkin-Elmer PE 2004 elemental analyzer and the obtained data for C, H, and N are within 0.4% of the calculated values.

(2*E*,4*E*)-8-[(*tert*-Butyldimethylsilyl)oxy]-*N*-isobutylocta-2,4-dienamide (7) and (2*E*,4*Z*)-8-[(*tert*-Butyldimethylsilyl)oxy]-*N*-isobutylocta-2,4-dienamide (8)

Oxalyl chloride (9.7 mL, 2 M in CH_2Cl_2, 19.5 mmol) was diluted in CH_2Cl_2 (100 mL) and the reaction mixture was cooled to –78 °C. DMSO (2.8 mL, 39 mmol) was slowly added followed, after 15 min, by the dropwise addition of 4-[(*tert*-butyldimethylsilyl)oxy]butan-1-ol (3.0 mL, 13 mmol) in CH_2Cl_2 (15 mL). After the solution had been stirred for 45 min at –78 °C, Et_3N (8.1 mL, 58.5 mmol) was added. After 1 h, the mixture was allowed to warm gradually to 0 °C, kept at this temperature for an additional 30 min, and then quenched by the addition of sat. aq $NaHCO_3$ solution (50 mL). The mixture was allowed to rest overnight and the two phases were separated. The aq layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent evaporated to give aldehyde **5** (yellow oil, 3.0 g), which was used in the next reaction without further purification. A solution of phosphonate **6** (5.4 g, 19.5 mmol) in THF (50 mL) was added to a suspension of LiOH (1.6 g, 39.0 mmol) in dry THF (50 mL) in the presence of 4 Å molecular sieves. After 10 min, a solution of aldehyde **5** (3.0 g) in THF (15 mL) was added and the mixture was heated at reflux temperature for 2.5 h. After cooling, the mixture was filtered and evaporated to dryness. The crude residue was purified by column chromatography (PE–Et_2O, 2:1) to give compounds **7** (1.9 g, 6.0 mmol) and **8** (390 mg, 1.2 mmol) in 46% and 9% yields, respectively.

Compound 7

White solid; mp 78–80 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (dd, *J* = 14.5 Hz, *J* = 10.1 Hz, 1 H), 6.11–5.96 (m, 2 H), 5.68 (d, *J* = 15.0 Hz, 1 H), 5.45 (br s, 1 H), 3.64 (t, *J* = 6.2 Hz, 2 H), 3.10 (t, *J* = 6.1 Hz, 2 H), 2.15 (q, *J* = 7.1 Hz, 2 H), 1.73 (sept, *J* = 6.7 Hz, 1 H), 1.56 (quin, *J* = 7.0 Hz, 2 H), 0.86 (s, 3 H), 0.85 (s, 3 H), 0.82 (s, 9 H), –0.03 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 142.4, 141.2, 128.5, 121.9, 62.3, 46.9, 31.8, 29.2, 28.6, 25.9, 20.1, 18.3, –5.3.

GC–MS: t_R = 23.18 min, *m*/*z* = 268 [M – *t*-Bu]$^+$.

Anal. Calcd for $C_{18}H_{35}NO_2Si$: C, 66.41; H, 10.84; N, 4.30. Found: C, 66.52; H, 10.85; N, 4.29.

Compound 8

Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (dd, *J* = 14.5 Hz, *J* = 11.7 Hz, 1 H), 6.00 (t, *J* = 11.1 Hz, 1 H), 5.77 (d, *J* = 14.8 Hz, 1 H), 5.73–5.67 (m, 1 H), 5.59 (br s, 1 H), 3.54 (t, *J* = 6.4 Hz, 2 H), 3.09 (t, *J* = 6.4 Hz, 2 H), 2.27 (q, *J* = 7.5 Hz, 2 H), 1.73 (sept, *J* = 6.7 Hz, 1 H), 1.60–1.51 (m, 2 H), 0.85 (s, 3 H), 0.84 (s, 3 H), 0.81 (s, 9 H), –0.03 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 139.3, 135.7, 126.6, 124.0, 62.5, 47.0, 32.6, 28.6, 25.9, 24.6, 20.1, –5.3.

GC–MS: t_R = 22.46 min, *m*/*z* = 268 [M – *t*-Bu]$^+$.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{18}H_{35}NO_2Si$: 325.24; found: 325.25.

(2*E*,4*E*)-8-Hydroxy-*N*-isobutylocta-2,4-dienamide (3)

TBAF (1.9 mL, 1 M in THF, 1.9 mmol) was added at 0 °C to a solution of compound **7** (305 mg, 0.9 mmol) in THF (10 mL). After 5 min, the reaction mixture was allowed to warm to r.t. and stirred for 3 h. After evaporation of the solvent, the resulting dark yellow oil was purified by column chromatography (EtOAc–PE, 2:1 → EtOAc) to give compound **3** (170 mg, 0.8 mmol) as a white solid in 86% yield.

Mp 82–84 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (dd, *J* = 14.9 Hz, *J* = 10.4 Hz, 1 H), 6.12–5.96 (m, 2 H), 5.72 (d, *J* = 15.0 Hz, 1 H), 5.67 (br s, 1 H), 3.58 (t, *J* = 6.4 Hz, 2 H), 3.09 (t, *J* = 6.2 Hz, 2 H), 2.18 (q, *J* = 7.2 Hz, 2 H), 1.93 (br s, 1 H), 1.73 (sept, *J* = 6.7 Hz, 1 H), 0.86 (s, 3 H), 0.84 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 142.0, 141.1, 128.8, 122.1, 62.1, 47.0, 31.7, 29.2, 28.6, 20.1.

GC–MS: t_R = 9.82 min, *m*/*z* = 142 [M – 69]$^+$.

Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.35; H, 9.99; N, 6.62.

(2*E*,4*E*)-7-Formyl-*N*-isobutylhepta-2,4-dienamide (9)

Oxalyl chloride (590 µL, 2 M in CH_2Cl_2, 1.2 mmol) was diluted in CH_2Cl_2 (7 mL) and the mixture was cooled to –78 °C. DMSO (170 µL, 2.3 mmol) was slowly added followed, after 15 min, by the dropwise addition of compound **3** (165 mg, 0.8 mmol) in CH_2Cl_2 (3 mL). After the solution had been stirred for 45 min at –78 °C, Et_3N (490 µL, 3.5 mmol) was added. After 1 h, the reaction mixture was allowed to warm gradually to 0 °C, kept at this temperature for an additional 30 min and then quenched by the addition of sat. aq $NaHCO_3$ solution (10 mL). The mixture was allowed to rest overnight and the two phases were separated. The aq layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent evaporated. The crude residue was purified by column chromatography (EtOAc–PE, 2:1) to give **9** (117 mg, 0.5 mmol) as a white solid in 72% yield.

Mp 80–82 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.61 (s, 1 H), 6.98 (dd, *J* = 15.0 Hz, *J* = 10.8 Hz, 1 H), 6.35 (br s, 1 H), 6.04–5.98 (m, 1 H), 5.88–5.80 (m, 1 H), 5.76 (d, *J* = 15.0 Hz, 1 H), 2.98 (t, *J* = 6.4 Hz, 2 H), 2.43 (t, *J* = 7.1 Hz, 2 H), 2.34–2.28 (m, 2 H), 1.64 (sept, *J* = 6.7 Hz, 1 H), 0.76 (s, 3 H), 0.74 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.1, 166.1, 140.4, 139.5, 129.4, 123.0, 46.9, 42.7, 28.6, 25.3, 20.1.

MS (ESI): *m*/*z* = 210 [M + H]$^+$, 232 [M + Na]$^+$.

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.95; H, 9.16; N, 6.68.

δ-Sanshool, Compounds 11 and 12; General Procedure

n-BuLi (1.1 mL, 1.6 M in hexane, 1.74 mmol) was added dropwise at –78 °C to a solution of the appropriate phosphonate **10**, **13**, or **14** (1.74 mmol) in THF (10 mL). After stirring for 30 min, a solution of aldehyde **9** (280 mg, 1.34 mmol) in THF (4 mL) was added. The reaction mixture was kept at –78 °C for 15 min, and was then allowed to warm to r.t. during the night. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and the aq phase was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed under vacuum. The crude residue was purified by column chromatography.

δ-Sanshool

Yield: 73 mg (20%) (eluent: PE–EtOAc, 7:3); white solid; mp 129–132 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.02 (dd, *J* = 15.1 Hz, *J* = 10.6 Hz, 1 H), 6.17–6.11 (m, 1 H), 6.04–5.90 (m, 5 H), 5.86 (d, *J* = 15.1 Hz, 1 H), 5.63–5.53 (m, 2 H), 2.99 (d, *J* = 7.0 Hz, 2 H), 2.20–2.14 (m, 4 H), 1.76–1.66 (m, 4 H), 0.85 (s, 3 H), 0.84 (s, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 167.7, 141.6, 140.6, 132.1, 131.7, 131.3, 131.1, 130.1, 128.8, 128.3, 122.0, 46.6, 32.4, 31.7, 28.3, 19.1, 16.9.

GC–MS: t_R = 14.50 min, *m*/*z* = 213 [M – 60]$^+$.

Anal. Calcd for $C_{18}H_{27}NO$: C, 79.07; H, 9.95; N, 5.12. Found: C, 78.95; H, 9.97; N, 5.13.

(2*E*,4*E*,8*E*)-*N*-Isobutylundeca-2,4,8,10-tetraenamide (11)

Yield: 37 mg (12%) (eluent: PE–EtOAc, 7:3); white solid; mp 98–100 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (dd, *J* = 14.8 Hz, *J* = 10.4 Hz, 1 H), 6.27–6.18 (m, 1 H), 6.11–5.95 (m, 3 H), 5.68 (d, *J* = 15.0 Hz, 1 H), 5.64–5.57 (m, 1 H), 5.38 (br s, 1 H), 5.03 (d, *J* = 17.0 Hz, 1 H), 4.91 (d, *J* = 10.1 Hz, 1 H), 3.10 (t, *J* = 6.5 Hz, 2 H), 2.25–2.14 (m, 4 H), 1.78–1.68 (m, 1 H), 0.86 (s, 3 H), 0.85 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 141.7, 141.0, 137.0, 133.7, 131.7, 128.7, 122.2, 115.4, 46.9, 32.5, 31.8, 28.6, 20.1.

GC–MS: t_R = 20.83 min, *m*/*z* = 233 [M]$^+$.

Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.38; H, 9.91; N, 5.99.

(2*E*,4*E*,8*E*,10*E*)-*N*-Isobutyl-11-phenylundeca-2,4,8,10-tetraenamide (12)

Yield: 95 mg (23%) (eluent: PE–EtOAc, 4:1); pale yellow solid; mp 147–149 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.29 (m, 2 H), 7.24–7.20 (m, 2 H), 7.14–7.09 (m, 2 H), 6.66 (dd, *J* = 15.6 Hz, *J* = 10.4 Hz, 1 H), 6.38 (d, *J* = 15.7 Hz, 1 H), 6.18–6.05 (m, 2 H), 6.01–5.95 (m, 1 H), 5.78–5.70 (m, 3 H), 3.08 (t, *J* = 6.4 Hz, 2 H), 2.21 (s, 4 H), 1.76–1.67 (m, 1 H), 0.85 (s, 3 H), 0.84 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 141.5, 140.8, 137.5, 134.0, 131.3, 130.6, 129.1, 128.9, 128.6, 127.2, 126.4, 126.2, 122.5, 47.0, 32.7, 32.1, 28.6, 20.1.

MS (ESI): *m*/*z* = 310 [M + H]$^+$, 332 [M + Na]$^+$.

Anal. Calcd for $C_{21}H_{27}NO$: C, 81.51; H, 8.79; N, 4.53. Found: C, 81.34; H, 8.80; N, 4.54.

[(4*E*,6*E*,8*E*)-Deca-4,6,8-trienyloxy](*tert*-butyl)dimethylsilane (15)

sec-BuLi (10 mL, 1.4 M in cyclohexane, 14 mmol) was added dropwise at –78 °C to a solution of phosphonate **10** (2.94 g, 14 mmol) in THF (60 mL). After 20 min, a solution of aldehyde **5** (2.26 g, 11 mmol) in THF (20 mL) was added to the yellow solution. The reaction mixture turned red and was allowed to warm up gradually to r.t. After 15 h, the mixture was quenched with sat. NH_4Cl solution (50 mL) and the aq phase was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was

removed under vacuum. The crude residue was purified by column chromatography (PE–Et_2O, 99:1) to give 1.25 g of **15** (4.7 mmol, 43% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.00–5.96 (m, 4 H), 5.62–5.56 (m, 2 H), 3.54 (t, *J* = 6.3 Hz, 2 H), 2.10–2.04 (m, 2 H), 1.69 (d, *J* = 6.7 Hz, 3 H), 1.57–1.47 (m, 2 H), 0.82 (s, 9 H), –0.03 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.5, 131.8, 130.7, 130.5, 128.8, 62.5, 32.4, 30.9, 29.1, 25.9, 18.2, –5.3.

GC–MS: t_R = 17.17 min, *m*/*z* = 209 [M – *t*-Bu]$^+$.

MS (ESI): *m*/*z* [M]$^+$ calcd for $C_{16}H_{30}OSi$: 266.21; found: 266.23.

(4*E*,6*E*,8*E*)-Deca-4,6,8-trien-1-ol (16)

TBAF (7.5 mL, 1 M in THF, 7.5 mmol) was added to a solution of compound **15** (1.0 g, 3.8 mmol) in THF (30 mL) at 0 °C. After 5 min, the temperature was allowed to warm to r.t. and the mixture was stirred overnight. After solvent evaporation, the crude residue was purified by column chromatography (Et_2O–PE, 2:1) to give compound **16** (443 mg, 2.9 mmol) as a white solid in 77% yield.

Mp 56–57 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.06–5.94 (m, 4 H), 5.64–5.55 (m, 2 H), 3.58 (t, *J* = 6.1 Hz, 2 H), 2.14–2.08 (m, 2 H), 1.69 (d, *J* = 6.9 Hz, 3 H), 1.63–1.56 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.1, 131.7, 131.2, 131.1, 130.3, 129.1, 62.4, 32.2, 29.1, 18.2.

GC–MS: t_R = 13.29 min, *m*/*z* = 152 [M]$^+$.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C 79.01; H, 10.56.

(4*E*,6*E*,8*E*)-Deca-4,6,8-trienal (17)

Oxalyl chloride (2.5 mL, 2 M in CH_2Cl_2, 4.9 mmol) was diluted in CH_2Cl_2 (10 mL) and the mixture was cooled to –78 °C. DMSO (0.8 mL, 9.5 mmol) was slowly added followed, after 15 min, by the dropwise addition of compound **16** (250 mg, 1.6 mmol) in CH_2Cl_2 (5 mL). After the solution had been stirred for 45 min at –78 °C, Et_3N (2.3 mL, 16 mmol) was added. After 1 h, the reaction mixture was allowed to warm gradually to 0 °C, kept at this temperature for an additional 30 min and then quenched by the addition of sat. aq $NaHCO_3$ solution (15 mL). The mixture was allowed to rest overnight and the two phases were separated. The aq layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent evaporated. The crude residue was purified by column chromatography (PE–Et_2O, 4:1) to give **17** (144 mg, 0.9 mmol) as a colorless oil in 60% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.69 (s, 1 H), 6.07–5.93 (m, 4 H), 5.65–5.51 (m, 2 H), 2.46 (t, *J* = 6.9 Hz, 2 H), 2.37–2.32 (m, 2 H), 1.69 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.8, 133.9, 131.7, 131.6, 131.0, 129.8, 129.6, 43.3, 25.3, 18.2.

MS (ESI): *m*/*z* = 151 [M + H]$^+$, 173 [M + Na]$^+$.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{10}H_{14}O$: 150.1; found: 150.11.

Phosphonates 6, 18 and 19; General Procedure

HOBt (304 mg, 2.2 mmol) and EDC (862 mg, 4.5 mmol) were added to a solution of **22** (500 mg, 2.2 mmol) in CH_2Cl_2 (15 mL). After 5 min, the appropriate amine (4.4 mmol) was added and the reaction mixture was stirred at r.t. for 3 h. Next, H_2O (10 mL) was added, the two phases were separated and the aq phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude residue was purified by column chromatography (EtOAc–MeOH, 10:1) to give the corresponding amide.

Diethyl (*E*)-3-(Isobutylcarbamoyl)allylphosphonate (6)

Yield: 250 mg (41%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.67–6.57 (m, 1 H), 5.92–5.87 (m, 1 H), 5.49 (br s, 1 H), 4.04 (q, *J* = 7.1 Hz, 4 H), 3.09–3.06 (m, 2 H), 2.61 (d, *J* = 7.7 Hz, 1 H), 2.66 (d, *J* = 7.7 Hz, 1 H), 1.76–1.69 (m, 1 H), 1.18 (t, *J* = 7.2 Hz, 6 H), 0.85 (d, *J* = 6.7 Hz, 6 H).

GC–MS: t_R = 20.70 min, *m*/*z* = 222 [M – 55]$^+$.

Diethyl (*E*)-3-(Isopropylcarbamoyl)allylphosphonate (18)

Yield: 318 mg (55%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.69–6.59 (m, 1 H), 5.86 (dd, *J* = 4.5 Hz, *J* = 15.4 Hz, 1 H), 5.40 (br s, 1 H), 4.06–4.02 (m, 4 H), 2.66 (d, *J* = 7.7 Hz, 1 H), 2.60 (d, *J* = 7.7 Hz, 1 H), 1.27–1.23 (m, 7 H), 1.11 (s, 3 H), 1.09 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.1, 131.6, 131.5, 129.0, 128.9, 62.1, 41.1, 30.7, 22.4, 16.3.

GC–MS: t_R = 19.44 min, *m*/*z* = 264 [M + 1]$^+$.

MS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{22}NO_4P$: 263.13; found: 263.11.

Diethyl (*E*)-3-(Cyclopropylcarbamoyl)allylphosphonate (19)

Yield: 181 mg (20%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.75–6.66 (m, 1 H), 5.87 (dd, *J* = 4.7 Hz, *J* = 15.6 Hz, 1 H), 5.66 (br s, 1 H), 4.12–4.03 (m, 4 H), 2.87–2.72 (m, 1 H), 2.69 (d, *J* = 7.7 Hz, 1 H), 2.63 (d, *J* = 7.7 Hz, 1 H), 1.29 (t, *J* = 7.0 Hz, 6 H), 0.88–0.71 (m, 2 H), 0.57–0.49 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.5, 132.0, 129.0, 62.2, 32.7, 25.8, 16.3, 7.6.

GC–MS: t_R = 20.78 min, *m*/*z* = 149 [M – 112]$^+$.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{21}NO_4P$: 262.11; found: 262.

δ-Sanshool, Compounds 20 and 21; General Procedure

A solution of the appropriate phosphonate **6**, **18**, or **19** (0.4 mmol) in THF (1 mL) was added to a suspension of LiOH (34 mg, 0.8 mmol) in dry THF (5 mL) in the presence of 4 Å molecular sieves. After 20 min, a solution of aldehyde **17** (30 mg, 0.2 mmol) in THF (1 mL) was added and the reaction mixture was heated at reflux temperature for 3 h. After cooling, the mixture was filtered and evaporated to dryness. The crude residue was purified by column chromatography (CH_2Cl_2–MeOH, 98:2).

δ-Sanshool

Yield: 46 mg (85%) (eluent: PE–EtOAc, 7:3).

The analytical data was consistent with that obtained according to the procedure outlined in Scheme 2.

(2*E*,4*E*,8*E*,10*E*,12*E*)-*N*-Isopropyltetradeca-2,4,8,10,12-pentaenamide (20)

Yield: 36 mg (70%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12–7.06 (m, 1 H), 6.09–5.96 (m, 6 H), 5.72–5.68 (m, 1 H), 5.61–5.58 (m, 2 H), 5.16 (br s, 1 H), 4.10–5.07 (m, 1 H), 2.16–2.09 (m, 4 H), 1.70 (d, *J* = 6.7 Hz, 3 H), 1.11 (d, *J* = 6.4 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 141.0, 139.9, 132.4, 131.7, 131.4, 131.3, 130.1, 129.5, 129.2, 121.7, 44.7, 33.0, 23.2, 18.3.

MS (ESI): *m*/*z* = 260 $[M + H]^+$, 282 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{25}NO$: C, 78.72; H, 9.71; N, 5.40. Found: C, 78.59; H, 9.72; N, 5.41.

(2*E*,4*E*,8*E*,10*E*,12*E*)-*N*-Cyclopropyltetradeca-2,4,8,10,12-pentaenamide (21)

Yield: 41 mg (80%); white solid.

^{1}H NMR (400 MHz, MeOD): δ = 7.03 (dd, *J* = 10.5 Hz, *J* =15.1 Hz, 1 H), 6.08–5.94 (m, 6 H), 5.77 (d, *J* = 15.1 Hz, 1 H), 5.58–5.52 (m, 2 H), 2.73–2.70 (m, 1 H), 2.20–2.14 (m, 4 H), 1.67 (d, *J* = 6.8 Hz, 3 H), 0.86–0.75 (m, 2 H), 0.36–0.30 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 142.0, 141.1, 132.4, 131.7, 131.4, 131.3, 130.1, 129.2, 128.7, 121.7, 32.7, 32.0, 28.6, 22.7, 18.3.

MS (ESI): *m*/*z* = 258 $[M + H]^+$, 280 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C 79.42; H, 8.99; N, 5.43.

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Supporting Information

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