Total Synthesis of (±)-Petasitolone and (±)-Fukinone

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Abstract: An efficient, general, and fully stereocontrolled synthesis of eremophilane-type compounds is disclosed. The approach features a highly diastereoselective Diels–Alder/aldol sequence to give a common intermediate, which is subsequently exploited to produce (±)-petasitolone and (±)-fukinone in a short sequence.

Key words: eremophilane, Diels–Alder reactions, aldol reactions, condensation

The decahydronaphthalene (Decalin) skeleton is one of the most prevalent structural motifs in numerous natural products.[1–3] In particular, terpenoids possessing the decahydronaphthalene moiety display a wide variety of biological activities that may have medicinal potential.[3] Owing to their importance in nature, the synthesis of decahydronaphthalenes has become a major focal point of synthetic chemistry. The structural complexity of the isolated natural products demands the development of new and efficient strategies to construct stereochemically rich and multifunctional decahydronaphthalenes. For this reason, there has been a great deal of interest in developing methods for their synthesis, as reflected by the flurry of reports in this area from various groups around the globe over the last decade.[4]

The eremophilane-type sesquiterpenes (±)-petasitolone (**1**)[5] and (±)-fukinone (**2**)[6] have been isolated from rhizomes of *Petasites japonicus* Maxim. These natural products possess three stereogenic centers, two methyl groups, and a hydrogen atom on a *cis*-decahydronaphthalene-related skeleton (Figure 1). The diverse biological properties of these eremophilanes, combined with their unique structural and conformational challenges, have attracted considerable synthetic attention.[7,8] Recently, we developed an efficient, short, and highly stereocontrolled route to the *cis*-decahydronaphthalene system and applied this method in the synthesis of (±)-eremophilenolide, (±)-eremophiledinone, and (±)-deoxyeremopetasidione.[9] In this paper, we report the total synthesis of (±)-petasitolone (**1**) and (±)-fukinone (**2**) using this methodology.[10]

Retrosynthetically, we envisaged that (±)-petasitolone (**1**) and (±)-fukinone (**2**) could be derived from the common intermediate **5**. Compound **5** would be prepared from acetal **6** by intramolecular aldol condensation. Diels–Alder adduct **8**, obtained from (*E*)-2-methylbut-2-enal (tiglic aldehyde, **9**) and diene **10**, would serve as a precursor for the synthesis of **6** via intermediate **7** (Scheme 1).

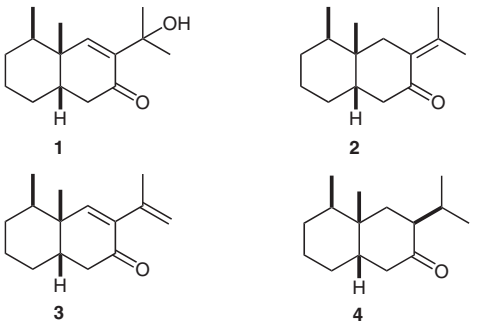
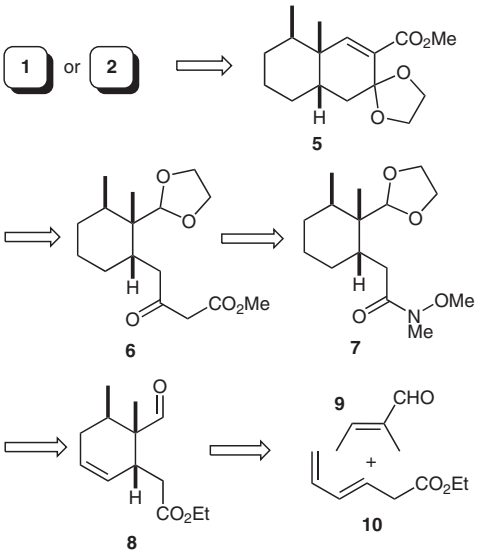


Figure 1 Selected eremophilanes possessing a *cis*-decahydronaphthalene-related skeleton



Scheme 1 Retrosynthesis of (±)-petasitolone and (±)-fukinone

In accordance with the synthetic plan, our synthesis began with the Lewis acid ($BF_3{\cdot}OEt_2$) mediated Diels–Alder reaction between known diene **10** and commercially available (*E*)-2-methylbut-2-enal (**9**). The reaction occurred with excellent stereoselectivity[11] to give adduct **8** containing the desired stereocenters. Protection of the aldehyde as acetal **11**, followed by the removal of the unwanted double bond in the presence of 10% palladium on carbon in methanol, produced saturated ester **12**. Lithium hydroxide mediated hydrolysis of the ester resulted in acid **13**,

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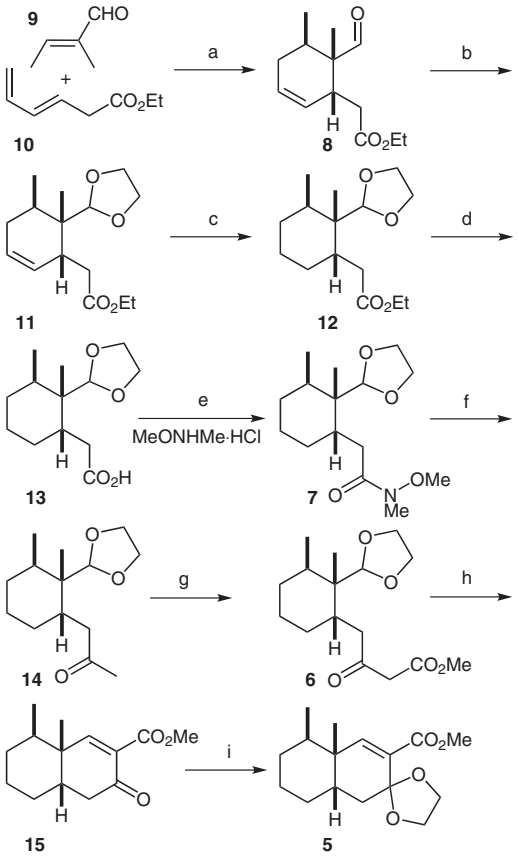
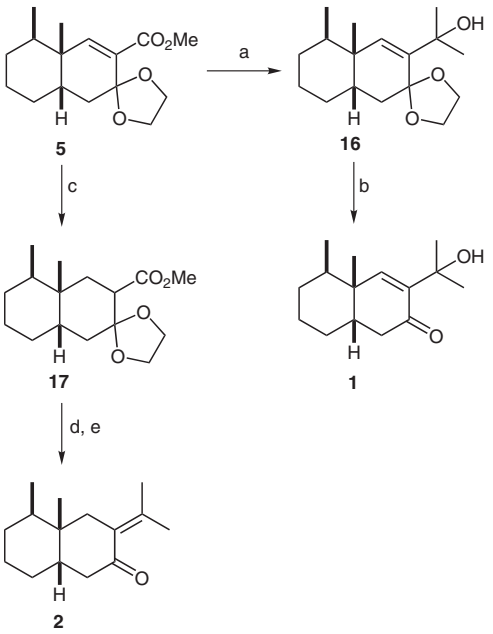
and coupling between the acid and *N*,*O*-dimethylhydroxylamine hydrochloride yielded Weinreb amide **7**. Grignard addition to the amide gave methyl ketone **14**. The subsequent treatment of the methyl ketone with methyl chloroformate in the presence of lithium hexamethyldisilazide gave the desired carbon-chain-elongated[12] product **6**. To our expectation, when we exposed compound **6** to 6 M hydrochloric acid in dichloromethane for the deprotection of the aldehyde moiety, *cis*-decahydronaphthalene derivative **15** was isolated in 80% yield as a result of an in-situ acid-mediated aldol condensation. The protection of the ketone functionality as a ketal produced the common intermediate **5** (Scheme 2).



Scheme 2 Reagents and conditions: (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C to r.t., 75% yield; (b) $(CH_2OH)_2$, PTSA (cat.), benzene, 81% yield; (c) 10% Pd/C, MeOH, 90% yield; (d) aq LiOH, THF, MeOH, 85% yield; (e) EDC, 1*H*-benzotriazol-1-ol, Et_3N, CH_2Cl_2, 90% yield; (f) MeMgCl, THF, 0 °C, 90% yield; (g) LiHMDS, methyl chloroformate, THF, –78 °C, 87% yield; (h) 6 M HCl, CH_2Cl_2, reflux, 30 min, 80% yield; (i) $(CH_2OH)_2$, PTSA (cat.), benzene, 90% yield

A Grignard reaction between resulting ketal **5** and methylmagnesium chloride, followed by the deprotection of ketal **16** using 6 M hydrochloric acid, allowed us to accomplish the total synthesis of (±)-petasitolone (**1**) (Scheme 3).

The synthesis of (±)-fukinone (**2**) began by the removal of the double bond in ketal **5** in the presence of 10% palladium on carbon in methanol to yield product **17**. Compound **17** was reacted with methylmagnesium chloride, and this was followed by subsequent treatment with 6 M hydrochloric acid in *N*,*N*-dimethylformamide to yield (±)-fukinone **2** (Scheme 3).



Scheme 3 Reagents and conditions: (a) MeMgCl, THF, 0 °C, 1 h, 92% yield; (b) 6 M HCl, CH_2Cl_2, reflux, 1 h, 80% yield; (c) 10% Pd/C, MeOH, 1 h, 85% yield; (d) MeMgCl, THF, 0 °C, 1 h; (e) DMF, 6 M HCl, r.t., 30 min, 64% yield over two steps

In conclusion, we have accomplished the total synthesis of (±)-petasitolone (**1**) in 11 steps (17% overall yield) and (±)-fukinone (**2**) in 12 steps (13% overall yield). The applied Lewis acid mediated Diels–Alder reaction and the aldol condensation strategy remain the key steps in our synthesis.

Infrared spectra were recorded on a Shimadzu IR Prestige 21 FT-IR spectrometer. The ^1H NMR (400 MHz) and ^{13}C NMR (50 MHz) spectra were determined in $CDCl_3$ soln on Varian Mercury Plus (400 MHz) and Gemini 2000 (200 MHz) spectrometers, respectively. Proton chemical shifts are relative to TMS as the internal standard and are expressed in ppm. Melting points were determined using a Buchi Melting Point B-540 melting point apparatus and are uncorrected. Mass spectrometry was performed on a Perkin-Elmer API 3000 instrument using ESI. Column chromatography was carried out using silica gel, grade 100–200 mesh. The reactions were monitored by TLC on silica gel plates (60 F254), visualizing with UV light, I_2 spray, or $KMnO_4$ charing. Unless stated otherwise, the reactions were performed under argon. The solvents THF, CH_2Cl_2, and benzene were obtained from a dry solvent system. All other reagents were purchased from Aldrich at the highest commercial quality and were used without further purification.

Ethyl [(1*R,5*R**,6*S**)-6-Formyl-5,6-dimethylcyclohex-2-enyl]acetate (8)**

To a solution of diene **10** (7.5 g, 53.6 mmol) and (*E*)-2-methylbut-2-enal (**9**) (11.2 g, 134.0 mmol) in dry CH_2Cl_2 (265 mL) was added $BF_3{\cdot}OEt_2$ (15.5 g, 107.1 mmol) dropwise at –78 °C. The mixture was allowed to warm to r.t. and was stirred overnight. The CH_2Cl_2 layer was washed with 10% $NaHCO_3$ (3 × 100 mL) followed by H_2O (100 mL) and brine (100 mL), and then was dried ($MgSO_4$) and

concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, EtOAc–hexane, 0.2:99.8) to afford adduct **8**. Yield: 9.0 g (75%); light-brown oil.

IR (neat): 2978, 1732, 1174 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.60 (s, 1 H), 5.71–5.66 (m, 1 H), 5.64–5.97 (m, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 2.65–2.59 (m, 1 H), 2.45 (dd, *J* = 5.4, 15.8 Hz, 1 H), 2.37–2.30 (m, 1 H), 2.25–2.18 (m, 1 H), 2.17–2.05 (m, 1 H), 1.79–1.72 (m, 1 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 1.08 (s, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 206.6, 172.6, 127.4, 126.1, 60.4, 49.6, 37.6, 35.6, 30.65, 29.5, 15.7, 15.6, 13.9.

ESI-MS: *m*/*z* = 225 $[M + H]^+$.

Ethyl [(1*R,5*R**,6*S**)-6-(1,3-Dioxolan-2-yl)-5,6-dimethylcyclohex-2-enyl]acetate (11)**

To a solution of aldehyde **8** (5.8 g, 25.9 mmol) and ethane-1,2-diol (3.2 g, 51.6 mmol) in benzene (52 mL) was added a catalytic amount of PTSA (0.24 g, 1.29 mmol), and the mixture was heated under reflux using Dean–Stark apparatus. After 2 h, the organic layer was washed with sat. $NaHCO_3$ (2 × 25 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated in vacuo to give an oil, which was purified by flash column chromatography (silica gel, EtOAc–hexane, 5:95) to give acetal **11**. Yield: 5.6 g (81%); colorless oil.

IR (neat): 2978, 2883, 1732, 1091 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.66–5.63 (m, 1 H), 5.56–5.53 (m, 1 H), 4.71 (s, 1 H), 4.13 (q, *J* = 7.0 Hz, 2 H), 3.95–3.88 (m, 2 H), 3.82–3.76 (m, 2 H), 2.72 (dd, *J* = 4.2, 15.2 Hz, 1 H), 2.56–2.52 (m, 1 H), 2.21 (dd, *J* = 4.2, 15.2 Hz, 1 H), 2.21–2.12 (m, 1 H), 1.97–1.93 (m, 1 H), 1.74–1.69 (m, 1 H), 1.26 (t, *J* = 7.0 Hz, 3 H), 0.94 (d, *J* = 6.9 Hz, 3 H), 0.88 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.6, 128.5, 126.0, 107.1, 64.6, 64.4, 60.1, 40.6, 38.6, 36.5, 31.5, 30.6, 16.3, 14.4, 14.3.

ESI-MS: *m*/*z* = 269 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{24}O_4$: 269.1759; found: 269.1759.

Ethyl [(1*S,2*S**,3*R**)-2-(1,3-Dioxolan-2-yl)-2,3-dimethylcyclohexyl]acetate (12)**

A mixture of acetal **11** (2.0 g, 7.5 mmol), 10% Pd/C (0.4 g), and abs MeOH (23 mL) was stirred under hydrogen at atmospheric pressure for 1 h at r.t. The mixture was then filtered on a pad of Celite, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc–hexane, 5:95) to afford saturated ester **12**. Yield: 1.8 g (90%); colorless oil.

IR (neat): 2932, 1733, 1160, 1094, 1035 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.83 (s, 1 H), 4.10 (q, *J* = 7.1 Hz, 2 H), 3.93–3.87 (m, 2 H), 3.80–3.77 (m, 2 H), 2.63 (dd, *J* = 3.6, 15.2 Hz, 1 H), 2.32 (dd, *J* = 10.9, 15.2 Hz, 1 H), 2.17–2.11 (m, 1 H), 1.91–1.87 (m, 1 H), 1.63–1.54 (m, 2 H), 1.53–1.45 (m, 2 H), 1.38–1.27 (m, 2 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 0.91 (d, *J* = 6.7 Hz, 3 H), 0.89 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.4, 107.6, 64.6, 64.4, 59.9, 41.9, 37.3, 34.9, 32.6, 29.7, 26.7, 20.3, 16.2, 15.5, 14.4.

ESI-MS: *m*/*z* = 271 $[M + H]^+$.

[(1*S,2*S**,3*R**)-2-(1,3-Dioxolan-2-yl)-2,3-dimethylcyclohexyl]acetic Acid (13)**

To a stirred solution of saturated ester **12** (5.0 g, 18.5 mmol) in THF (32 mL) and MeOH (32 mL) was added aq LiOH (32 mL, 37.0 mmol) at 0 °C. The resulting mixture was stirred for 5 h at r.t. and then was concentrated under reduced pressure. The residue was acidified to pH 2 with 2 M HCl. The aqueous layer was extracted with EtOAc (3 × 100 mL), and the combined organic layers were washed with H_2O (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, EtOAc–hexane, 10:90) to give acid **13**. Yield: 3.8 g (85%); colorless oil.

IR (neat): 2932, 1704, 1410, 1093 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.83 (s, 1 H), 3.95–3.89 (m, 2 H), 3.83–3.77 (m, 2 H), 2.73 (dd, *J* = 3.4, 15.6 Hz, 1 H), 2.37 (dd, *J* = 10.7, 15.6 Hz, 1 H), 2.17–2.13 (m, 1 H), 1.94–1.85 (m, 1 H), 1.69–1.60 (m, 1 H), 1.59–1.46 (m, 3 H), 1.44–1.38 (m, 1 H), 1.30–1.25 (m, 1 H), 0.92 (d, *J* = 6.8 Hz, 3 H), 0.91 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 175.2, 102.3, 59.2, 59.0, 36.0, 31.6, 29.2, 27.2, 24.2, 21.3, 14.9, 10.8, 10.2.

ESI-MS: *m*/*z* = 243 $[M + H]^+$.

[(1*S,2*S**,3*R**)-2-(1,3-Dioxolan-2-yl)-2,3-dimethylcyclohexyl]-*N*-methoxy-*N*-methylacetamide (7)**

To a solution of acid **13** (4.00 g, 16.52 mmol) in CH_2Cl_2 (84 mL) was added EDC (4.74 g, 24.75 mmol) and 1*H*-benzotriazol-1-ol (3.34 g, 24.78 mmol) at 0 °C. To this mixture was then added *N*,*O*-dimethylhydroxylamine hydrochloride (1.61 g, 16.52 mmol) followed by Et_3N (3.47 mL, 24.78 mmol). The resulting solution was allowed to stir overnight at r.t., and then the mixture was diluted with CH_2Cl_2 (84 mL) and successively washed with 10% citric acid (2 × 100 mL), sat. aq $NaHCO_3$ (2 × 100 mL), H_2O (100 mL), and brine (100 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash column chromatography (silica gel, EtOAc–hexane, 10:90) to give amide **7**. Yield: 4.24 g (90%); colorless oil.

IR (neat): 2933, 1660, 1093 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.89 (s, 1 H), 3.93–3.85 (m, 2 H), 3.83–3.78 (m, 2 H), 3.68 (s, 3 H), 3.17 (s, 3 H), 2.65 (dd, *J* = 3.4, 15.1 Hz, 1 H), 2.56–2.54 (m, 1 H), 2.24–2.21 (m, 1 H), 1.96–1.91 (m, 1 H), 1.64–1.58 (m, 2 H), 1.54–1.47 (m, 2 H), 1.39–1.25 (m, 2 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 0.91 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 175.0, 107.6, 76.4, 64.5, 64.3, 61.0, 41.4, 36.5, 32.7, 31.9, 29.6, 26.6, 20.4, 16.2, 15.5.

ESI-MS: *m*/*z* = 286 $[M + H]^+$.

1-[(1*S,2*S**,3*R**)-2-(1,3-Dioxolan-2-yl)-2,3-dimethylcyclohexyl]propan-2-one (14)**

To a solution of amide **7** (2.0 g, 7.0 mmol) in THF (21 mL) at 0 °C was added 3 M MeMgCl in THF (3.5 mL, 10.5 mmol) dropwise. After 1 h at 0 °C, the reaction was quenched with sat. aq NH_4Cl (20 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with H_2O (2 × 50 mL) and brine (50 mL), dried (anhyd $MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc–hexane, 5:95) to afford methyl ketone **14**. Yield: 1.5 g (90%); colorless oil.

IR (neat): 2929, 2877, 1714, 1354, 1091 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.79 (s, 1 H), 3.93–3.81 (m, 2 H), 3.80–3.76 (m, 2 H), 2.76 (dd, *J* = 3.4, 16.6 Hz, 1 H), 2.41 (dd, *J* = 9.8, 16.6 Hz, 1 H), 2.25–2.19 (m, 1 H), 2.12 (s, 3 H), 1.90–1.85 (m, 1 H), 1.63–1.39 (m, 4 H), 1.30–1.22 (m, 2 H), 0.92 (d, *J* = 6.8 Hz, 3 H), 0.89 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 209.7, 107.8, 64.6, 64.3, 44.2, 41.4, 36.0, 32.5, 30.2, 29.7, 26.9, 20.4, 16.4, 15.4.

ESI-MS: *m*/*z* = 241 $[M + H]^+$.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{24}O_3$: 241.1804; found: 241.1797.

Methyl 4-[(1*S,2*S**,3*R**)-2-(1,3-Dioxolan-2-yl)-2,3-dimethylcyclohexyl]-3-oxobutanoate (6)**

To a solution of methyl ketone **14** (3.0 g, 12.5 mmol) in dry THF (63 mL) under nitrogen at –78 °C was added 1 M LiHMDS in hexane (31.5 mL, 37.5 mmol) dropwise over a 10-min period, and the resulting mixture was stirred at the same temperature for 1 h. Methyl chloroformate (1.5 mL, 15.0 mmol) was then added in one portion and the mixture was stirred at the same temperature for a further 1 h. The reaction was quenched with aq NH_4Cl (30 mL) and the mixture was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with H_2O (40 mL) and brine (40 mL), dried (anhyd $MgSO_4$), and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (silica gel, EtOAc–hexane, 7:93) to afford ester **6**. Yield: 3.2 g (87%); colorless oil.

IR (neat): 2931, 1749, 1716, 1091 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.77 (s, 1 H), 3.93–3.82 (m, 2 H), 3.80–3.75 (m, 2 H), 3.73 (s, 3 H), 3.45 (s, 2 H), 2.90 (dd, *J* = 3.9, 16.9 Hz, 1 H), 2.49 (dd, *J* = 9.3, 16.9 Hz, 1 H), 2.26–2.23 (m, 1 H), 1.88–1.86 (m, 1 H), 1.62–1.40 (m, 4 H), 1.30–1.25 (m, 2 H), 0.91 (d, *J* = 7.0 Hz, 3 H), 0.89 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 203.0, 167.73, 107.7, 64.5, 64.2, 52.1, 49.1, 43.8, 41.3, 35.64, 32.4, 29.6, 26.9, 20.4, 16.3, 15.4.

ESI-MS: *m*/*z* = 299 [M + H]$^+$.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{26}O_5$: 299.1858; found: 299.1849.

Methyl (4a*S,8*R**,8a*S**)-8,8a-Dimethyl-3-oxo-3,4,4a,5,6,7,8,8a-octahydronaphthalene-2-carboxylate (15)**

To a solution of ester **6** (1.50 g, 5.03 mmol) in CH_2Cl_2 (25.16 mL) was added 6 M HCl (25.16 mL), and the mixture was heated under reflux for 30 min. The mixture was then cooled to r.t. and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were washed with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude compound was purified by flash column chromatography (silica gel, EtOAc–hexane, 10:90) to afford bicyclic compound **15**. Yield: 0.95 g (80%); colorless oil.

IR (neat): 1749, 1716, 1091 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (s, 1 H), 3.81 (s, 3 H), 2.73 (dd, *J* = 12.5, 16.8 Hz, 1 H), 2.32 (dd, *J* = 4.4, 16.8 Hz, 1 H), 2.12–2.08 (m, 1 H), 1.89–1.84 (m, 1 H), 1.78–1.70 (m, 1 H), 1.59–1.42 (m, 2 H), 1.40–1.25 (m, 3 H), 1.19 (s, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 195.1, 166.3, 165.2, 130.1, 52.0, 40.1, 39.5, 39.2, 35.4, 35.0, 29.6, 26.8, 20.1, 15.8.

ESI-MS: *m*/*z* = 237 [M + H]$^+$.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{20}O_3$: 237.1491; found: 237.1484.

Methyl (4a′*S,5′*R**,8a′*S**)-4a′,5′-Dimethyl-4a′,5′,6′,7′,8′,8a′-hexahydro-1′*H*-spiro[1,3-dioxolane-2,2′-naphthalene]-3′-carboxylate (5)**

To a mixture of oxo ester **15** (1.50 g, 6.35 mmol) and ethane-1,2-diol (0.87 g, 12.70 mmol) in benzene (32 mL) was added a catalytic amount of PTSA (0.12 g, 0.63 mmol), and the mixture was heated under reflux using Dean–Stark apparatus. After 2 h, the organic layer was washed with sat. $NaHCO_3$ (2 × 15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated in vacuo to give an oil, which was purified by flash column chromatography (silica gel, EtOAc–hexane, 5:95) to give ketal **5**. Yield: 1.60 g (90%); white solid; mp 87–88 °C.

IR (KBr): 2926, 1728, 1259, 1058 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03 (s, 1 H), 4.26–4.20 (m, 2 H), 4.05–3.94 (m, 2 H), 3.72 (s, 3 H), 2.16 (t, *J* = 13.7 Hz, 1 H), 1.90–1.85 (m, 1 H), 1.78–1.72 (m, 2 H), 1.52 (dd, *J* = 2.4, 12.8 Hz, 2 H), 1.50–1.37 (m, 3 H), 1.25–1.21 (m, 1 H), 1.04 (s, 3 H), 0.89 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.9, 155.4, 128.6, 106.9, 65.8, 65.0, 51.4, 38.6, 38.0, 37.2, 34.1, 30.6, 27.4, 21.2, 19.0, 16.3.

ESI-MS: *m*/*z* = 281 [M + H]$^+$.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{24}O_4$: 281.1753; found: 281.1763.

2-{(4a′*S,5′*R**,8a′*S**)-4a′,5′-Dimethyl-4a′,5′,6′,7′,8′,8a′-hexahydro-1′*H*-spiro[1,3-dioxolane-2,2′-naphthalene]-3′-yl}propan-2-ol (16)**

To a solution of ketal **5** (570 mg, 2.03 mmol) in THF (10 mL) at 0 °C was added 3 M MeMgCl in THF (72.7 mL, 8.12 mmol) dropwise. After 1 h at 0 °C, the reaction was quenched with sat. aq NH_4Cl (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O (2 × 10 mL) and brine (10 mL), dried (anhyd $MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc–hexane, 12:88) to afford alcohol **16**. Yield: 520 mg (92%); white solid; mp 121–122 °C.

IR (KBr): 3491, 2922, 1369, 1165 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.60 (s, 1 H), 4.20–3.96 (m, 4 H), 2.03 (t, *J* = 13.2 Hz, 1 H), 1.86–1.75 (m, 2 H), 1.71–1.62 (m, 2 H), 1.48 (dd, *J* = 2.4, 12.8 Hz, 2 H), 1.41 (s, 3 H), 1.40 (s, 3 H), 1.37–1.31 (m, 2 H), 1.24–1.16 (m, 1 H), 0.98 (s, 3 H), 0.85 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.6, 136.9, 110.9, 72.8, 63.9, 62.8, 37.9, 37.2, 35.4, 34.9, 31.2, 30.9, 30.0, 27.9, 21.6, 19.6, 16.2.

ESI-MS: *m*/*z* = 281 [M + H]$^+$.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{28}O_3$: 281.2117; found: 281.2129.

(4a*S,5*R**,8a*S**)-3-(2-Hydroxypropan-2-yl)-4a,5-dimethyl-4a,5,6,7,8,8a-hexahydronaphthalen-2(1*H*)-one [(±)-Petasitolone, 1]**

To a solution of ketal **16** (120 mg, 0.43 mmol) in CH_2Cl_2 (2.2 mL) was added 6 M HCl (2.2 mL), and the mixture was heated under reflux for 1 h. The mixture was then cooled to r.t. and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with H_2O (2 × 10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude compound was purified by flash column chromatography (silica gel, EtOAc–hexane, 10:90) to afford (±)-petasitolone (**1**). Yield: 101 mg (80%); colorless oil.

IR (neat): 3446, 2964, 2926, 1654, 1355 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.70 (s, 1 H), 4.53 (br s, 1 H), 2.70 (dd, *J* = 12.5, 17.3 Hz, 1 H), 2.26 (dd, *J* = 4.6, 17.3 Hz, 1 H), 2.08–2.01 (m, 1 H), 1.82–1.69 (m, 2 H), 1.57–1.54 (m, 1 H), 1.53–1.28 (m, 10 H), 1.22 (s, 3 H), 0.92 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.6, 154.9, 141.0, 71.7, 40.6, 39.4, 38.5, 35.6, 30.1, 29.3, 29.1, 26.8, 20.6, 20.4, 15.9.

ESI-MS: *m*/*z* = 219 [M – OH]$^+$.

ESI-HRMS: *m*/*z* [M – OH]$^+$ calcd for $C_{15}H_{23}O$: 219.1749; found: 219.1750.

Methyl (4a′*S,5′*R**,8a′*S**)-4a′,5′-Dimethyloctahydro-1′*H*-spiro[1,3-dioxolane-2,2′-naphthalene]-3′-carboxylate (17)**

A mixture of unsaturated ketal **5** (500 mg, 1.78 mmol), 10% Pd/C (100 mg), and abs MeOH (9 mL) was stirred under hydrogen at atmospheric pressure for 1 h at r.t. The mixture was then filtered on a pad of Celite, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc–hexane, 15:85) to afford saturated ketal **17**.

Yield: 430 mg (85%); colorless oil.

IR (neat): 3435, 2926, 2870, 1701 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.99 (dd, *J* = 3.6, 8.4 Hz, 2 H), 3.73 (dd, *J* = 4.4, 8.8 Hz, 2 H), 3.72 (s, 3 H), 2.65 (d, *J* = 17.6 Hz, 1 H), 2.38 (dd, *J* = 6.8, 18.0 Hz, 1 H), 2.12–2.07 (m, 1 H), 1.85 (d, *J* = 17.2 Hz, 1 H), 1.72–1.69 (m, 2 H), 1.56–1.49 (m, 4 H), 1.33–1.21 (m, 3 H), 0.90 (d, *J* = 6.4 Hz, 3 H), 0.89 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 168.2, 161.2, 107.7, 69.9, 60.9, 51.4, 35.8, 34.5, 34.0, 33.9, 29.7, 29.4, 28.1, 23.5, 20.5, 15.0.

ESI-MS: *m*/*z* = 283 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{26}O_4$: 283.1909; found: 283.1896.

(4a*S,5*R**,8a*S**)-3-Isopropylidene-4a,5-dimethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-one [(±)-Fukinone, 2]**

To a solution of ketal **17** (90 mg, 0.32 mmol) in THF (3 mL) at 0 °C was added 3 M MeMgCl in THF (0.43 mL, 1.28 mmol) dropwise. After 1 h at 0 °C, the reaction was quenched with sat. aq NH_4Cl (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H_2O (2 × 5 mL) and brine (5 mL), dried (anhyd $MgSO_4$), and concentrated under reduced pressure. The crude alcohol was dissolved in DMF (2 mL), and to this solution was added 6 M HCl (2 mL) and the mixture was stirred at r.t. for 30 min. Then, H_2O (5 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H_2O (2 × 10 mL) and brine (10 mL), dried (anhyd $MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc–hexane, 5:95) to afford (±)-fukinone (**2**). Yield: 45 mg (64%); colorless oil.

IR (neat): 2927, 2865, 1686, 1448 cm^{-1}.

1H NMR (400 MHz, $CDCl_3$): δ = 2.74 (d, *J* = 14.5 Hz, 1 H), 2.55 (dd, *J* = 10.7, 16.3 Hz, 1 H), 2.26 (dd, *J* = 5.6, 16.3 Hz, 1 H), 2.00–1.88 (m, 1 H), 1.94 (s, 3 H), 1.79 (s, 3 H), 1.77–1.66 (m, 4 H), 1.55–1.23 (m, 4 H), 0.96 (s, 3 H), 0.85 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 206.0, 139.9, 131.2, 44.0, 41.3, 40.6, 36.7, 32.3, 30.1, 29.6, 27.2, 22.5, 21.5, 20.9, 16.0.

ESI-MS: *m*/*z* = 221 $[M + H]^+$.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{24}O$: 221.1905; found: 221.1898.

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