Stereospecific Total Synthesis of (+)-Davana Acid, (+)-Nordavanone and (+)-Davanone

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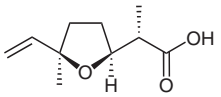
Received 4 November 2009; revised 10 November 2009

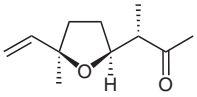
Abstract: A short, total synthesis of (+)-davana acid, (+)-nordavanone and (+)-davanone, which are principle components of davana oil, is described. The notable features are the use of the Evans *syn* aldol reaction and cyclic ether formation by an intramolecular S_N2 displacement reaction as key steps.

Key words: Evans aldol, cyclic ether, (–)-linalool, natural product, davana oil

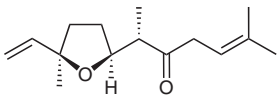
A number of novel sesquiterpenoids[1] such as davana acid (**1**), nordavanone (**2**), and davanone (**3**) have been isolated from the davana oil of *Artemisia pallens*, a plant grown in south India (Figure 1). Davanone **3** was also found in another plant: *Tanacetum vulgare*.[2] The structures of these compounds were assigned on the basis of spectroscopic and degradation studies.[1c,3] In view of the importance of davana oil in the perfume industry, *A. pallens* is under commercial cultivation in India. Tremendous interest in the oil has been aroused in the European countries, the USA and Japan because of its use in the flavouring of cakes, tobacco and in some costly beverages.[4] For this reason, the chemical composition of the davana oil from *A. pallens* and has been investigated by a number of research groups.[5]



davana acid (**1**)



nordavanone (**2**)

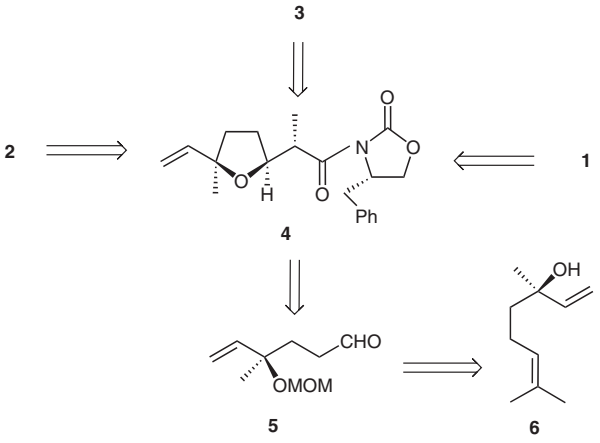


davanone (**3**)

Figure 1

(+)-Davanone is the principle component of davana oil and exhibits antifungal[6] and antispasmodic activities.[7] However, in spite of their importance in the perfume industry, apart from racemic syntheses,[8] there have been few reports[9] on the preparation of **1**, **2** or **3** (Figure 1). One recent synthesis of (+)-davanone[10] also reports the isolation of four diastereomeric davana acid ethyl esters as intermediates. Therefore, we undertook the stereospecific synthesis of these natural products; the results are reported here.

According to the retrosynthetic analysis depicted in Scheme 1, compounds **1**, **2** and **3** could all be obtained from the key central intermediate **4**, which, in turn, could be prepared from aldehyde **5** by the Evans *syn* aldol reaction and cyclic ether formation. Aldehyde **5** could be made from (–)-linalool (**6**).

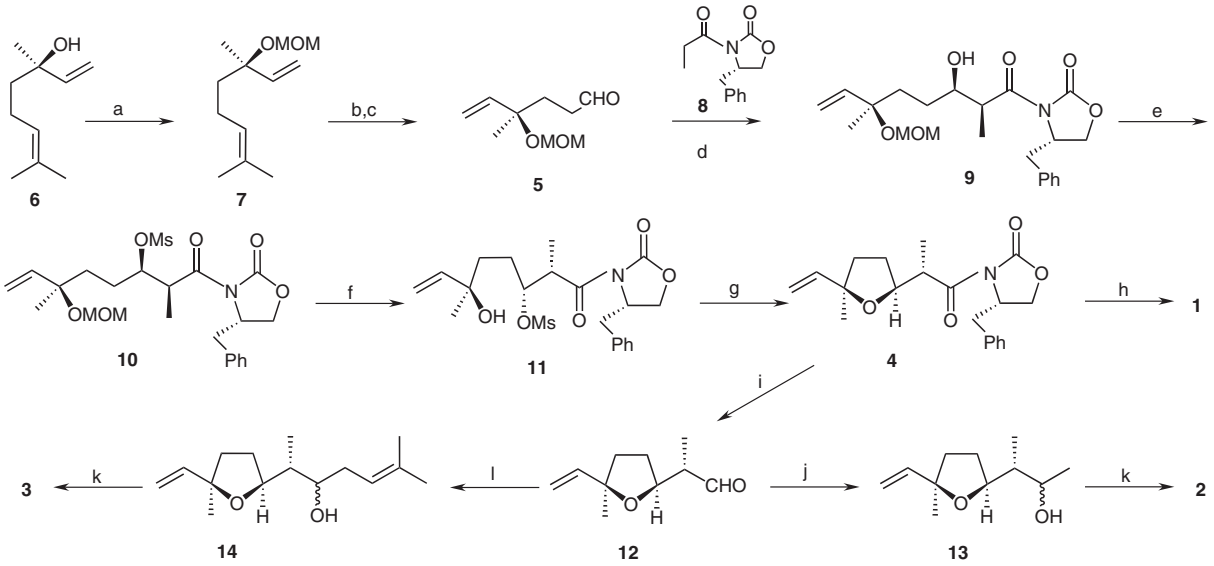


Scheme 1 Retrosynthetic analysis

The synthesis began with commercially available (–)-linalool (**6**), which was converted into its methoxymethyl (MOM) ether **7** using MOM-Cl, and Hunig's base in dichloromethane (Scheme 2). Next, a two-step sequence, comprising chemoselective dihydroxylation[11] of the more electron-rich C–C double bond in compound **7** [OsO_4, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*-BuOH, H_2O] and vicinal diol cleavage ($NaIO_4$, H_2O, Me_2CO) furnished the required aldehyde **5** in good yield.

Aldehyde **5** was subjected to the Evans *syn* aldol[12] reaction with the enolate of chiral *N*-propionyl oxazolidinone **8** to furnish the aldol adduct **9** with high diastereoselectivity (de 98%) in 87% yield. Subsequent mesylation of the secondary hydroxy group (MsCl, Et_3N, 96%) afforded mesylate-protected compound **10**, which was selectively MOM-deprotected (HCl, THF, 90%) to give hydroxy mesylate **11**. On treatment with 2,6-lutidine at 120 °C, **11** rapidly cyclised to the cyclic ether *anti*,*cis*-**4** as a single

SYNTHESIS 2010, No. 5, pp 0807–0810
Advanced online publication: 11.12.2009
DOI: 10.1055/s-0029-1218603; Art ID: Z23809SS



Scheme 2 *Reagents and conditions*: (a) Hunig's base, MOM-Cl, CH_2Cl_2, 0 °C→r.t., 1 h, 88%; (b) OsO_4, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*-BuOH, H_2O; (c) $NaIO_4$, H_2O, Me_2CO, 80% (over 2 steps); (d) $(n\text{-}Bu)_2BOTf$, Et_3N, CH_2Cl_2, –78 °C, 87%; (e) MsCl, Et_3N, 0 °C, 0.5 h, 96%; (f) HCl, THF, r.t., 1 h, 90%; (g) 2,6-lutidine, 120 °C, 1 h, 93%; (h) H_2O_2, LiOH, H_2O–THF, 82%; (i) DIBAL-H, CH_2Cl_2, –78 °C, 88%; (j) MeMgI, Et_2O, 0 °C, 85%; (k) IBX, DMSO, CH_2Cl_2, 2 h, 0 °C→r.t; (l) C_5H_9ZnBr, HMPA, THF, reflux, 78%.

isomer in 93% yield through an S_N2-type substitution (Scheme 2).

Hydrolysis of **4** with LiOH and H_2O_2 in THF–H_2O (1:1) afforded, after an acidic workup, the target davana acid **1** in 82% yield, whereas cleavage of the oxazolidinone in **4** using DIBAL-H provided aldehyde **12** in 88% yield, which was used immediately for the next reaction. The Grignard reaction of aldehyde **12** with methylmagnesium iodide provided secondary alcohol **13** as a diastereomeric mixture in a ratio of 1:1, which used in the next step without further purification. Oxidation of alcohol **13** with IBX in DMSO provided (+)-nordavanone (**2**) in 82% yield. Alternatively, prenylation[13] of aldehyde **12** with prenylzinc bromide in the presence of HMPA in THF, furnished secondary alcohol **14** as a diastereomeric mixture (1:1) in 78% yield. Alcohol **14** was oxidized with IBX to yield (+)-davanone (**3**) in 80% yield. Analytical data for the synthetic material proved to be identical to those reported previously.[10]

In summary, a concise, asymmetric total synthesis of (+)-davana acid, (+)-nordavanone and (+)-davanone has been accomplished using the Evans *syn* aldol reaction and stereospecific cyclic ether formation as key steps.

Reactions were conducted under N_2 in anhydrous solvents. All reactions were monitored by TLC (Merck 60 F-254 silica gel plates, visualized under UV irradiation). *n*-Hexane (bp 60–80 °C) was used. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous material. Air-sensitive reagents were transferred by syringe or double-ended needle. Evaporation of solvents was performed at reduced pressure with a Büchi rotary evaporator. IR data were collected on a Perkin-Elmer FTIR-240 spectrophotometer. ^1H and ^{13}C NMR spectra of samples in $CDCl_3$ were recorded on Varian FT-200 MHz (Gemini) and Bruker UXNMR FT-300 MHz (Avance) spectrometers. Chemical shifts (δ) are reported relative to TMS (δ = 0.0 ppm) as an internal standard. Mass spectra (EI) were recorded at 70 eV on an LC-MSD (Agilent technologies) spectrometer. Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co., India. Optical rotations were measured with a JASCO DIP-370 Polarimeter.

(3*R*)-3-(Methoxymethoxy)-3,7-dimethyl-1,6-octadiene (7)

To a solution of alcohol **6** (5 g, 32.4 mmol) in anhydrous CH_2Cl_2 (30 mL) at 0 °C, were successively added DIPEA (8.4 mL, 48.6 mmol), catalytic DMAP (10 mg), and MOM-Cl (3.36 mL, 42.12 mmol). The mixture was stirred for 3 h at 25 °C then quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4 (2 g), and concentrated in vacuo. The crude residue was purified by column chromatography (EtOAc–hexane, 1:9) to afford the MOM ether **7**.

Yield: 5.6 g (88%); light-yellow oil.

IR (neat): 2975, 2927, 1640, 1449, 1375, 1146, 1036, 922 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.88–5.73 (m, 1 H), 5.21–5.02 (m, 3 H), 4.63 (ABq, *J* = 6.9 Hz, 2 H), 3.35 (s, 3 H), 2.06–1.92 (m, 2 H), 1.67 (s, 3 H), 1.59 (s, 3 H), 1.58–1.49 (m, 2 H), 1.30 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.8, 131.4, 124.3, 114.4, 91.5, 78.4, 55.2, 40.9, 25.6, 22.8, 22.4, 17.5.

MS (EI): *m*/*z* = 221 $[M + Na]^+$.

(4*S*)-4-Benzyl-3-[(2*S*,3*R*,6*R*)-3-hydroxy-6-(methoxymethoxy)-2,6-dimethyl-7-octenoyl]-1,3-oxazolan-2-one (9)

To a mixture of **7** (5.2 g, 26.2 mmol) in *t*-BuOH (50 mL) and H_2O (50 mL) were added $K_3Fe(CN)_6$ (25.9 g, 78.6 mmol), K_2CO_3 (10.8 g, 78.6 mmol), $MeSO_2NH_2$ (2.48 g, 26.2 mmol), and OsO_4 (1 mL, 4% in H_2O) at r.t. The mixture was stirred for 12 h, quenched with solid Na_2SO_3 (2 g), and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with aq KOH (2 N, 2 × 15 mL) and brine (2 × 20 mL), dried (Na_2SO_4), filtered, and concentrated to give the crude diol, which was used directly in the next step without further purification. The above crude diol was dissolved in acetone (15 mL) and $NaIO_4$ (9.9 g, 46.2 mmol) was added. H_2O was added dropwise until the $NaIO_4$ was completely dissolved. The resultant solution was stirred for 1 h and quenched with sat. aq

$Na_2S_2O_3$ (25 mL). After removing the acetone under reduced pressure, the residue was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, concentrated and the residue was purified by column chromatography to give aldehyde **5** (3.6 g, 80% over 2 steps), which was used for the next reaction immediately.

To a solution of 4-benzyl-3-propionyl-1,3-oxazolidin-2-one (**8**; 4.05 g, 17.4 mmol) in anhydrous CH_2Cl_2 (36 mL), was added di-*n*-butylboryl triflate (1 M in CH_2Cl_2, 17.4 mL, 17.4 mmol) at 0 °C. The resulting brown solution was stirred for 10 min, then Et_3N (5.09 mL, 36.2 mmol) was added (the colour changed from red to light-yellow during the addition). The mixture was stirred for 1 h at 0 °C then cooled to –78 °C and a solution of the above aldehyde **5** (2.5 g, 14.5 mmol) in anhydrous CH_2Cl_2 (10 mL) was added. Stirring was continued for 1 h at –78 °C, then the reaction mixture was allowed to warm to 0 °C and stirred for 30 min at this temperature. The reaction was quenched with pH 7 phosphate buffer (15 mL), MeOH (50 mL) was added, then the mixture was finally treated with a mixture of MeOH–H_2O_2 (2:1, 35 mL). The mixture was allowed to warm to r.t. and stirred for 1 h. Most of the organic solvents were removed by rotary evaporation and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined extracts were washed with sat. $NaHCO_3$ (2 × 10 mL), brine (2 × 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc–hexane, 3:7) to afford the aldol product **9**.

Yield: 5.1 g (87%); colourless gummy oil; $[\alpha]_D^{25}$ +18.1 (*c* 1.0, $CHCl_3$).

IR (neat): 3475, 2935, 1780, 1695, 1211 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.17 (m, 5 H), 5.80 (dd, *J* = 17.9, 10.5 Hz, 1 H), 5.18 (m, 1 H), 5.14–5.12 (m, 1 H), 4.70–4.57 (m, 3 H), 4.23–4.13 (m, 2 H), 3.90–3.80 (m, 1 H), 3.72 (dq, *J* = 3.0, 6.9 Hz, 1 H), 3.35 (s, 3 H), 3.28 (dd, *J* = 13.4, 2.8 Hz, 1 H), 2.72 (dd, *J* = 13.2, 9.8 Hz, 1 H), 1.93–1.42 (m, 4 H), 1.30 (s, 3 H), 1.24 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.1, 153.1, 142.6, 135.0, 129.5, 128.9, 127.4, 114.8, 91.6, 78.5, 71.8, 66.2, 55.4, 55.2, 42.4, 37.8, 37.0, 28.1, 23.2, 10.5.

MS (EI): *m*/*z* = 428 $[M + Na]^+$.

(1*R*,4*R*)-1-(1*S*)-2-[(4*S*)-4-Benzyl-2-oxo-1,3-oxazolan-3-yl]-1-methyl-2-oxoethyl-4-(methoxymethoxy)-4-methyl-5-hexenyl Methanesulfonate (10)

To a stirred solution of **9** (4.2 g, 10.3 mmol) and Et_3N (2.8 mL, 20.6 mmol) in anhydrous CH_2Cl_2 (25 mL) at 0 °C, was added MsCl (0.96 mL, 12.4 mmol). The mixture was stirred at r.t. for 1 h and extracted with CH_2Cl_2 (2 × 25 mL). The extract was washed with H_2O (2 × 15 mL) and brine (2 × 15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the residual oil by column chromatography (EtOAc–hexanes, 2:8) gave mesylate **10**.

Yield: 4.8 g (96%); colourless oil; $[\alpha]_D^{25}$ +42.7 (*c* 1.0, $CHCl_3$).

IR (neat): 3097, 2933, 1775, 1699, 1353, 1172, 915 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.16 (m, 5 H), 5.82 (dd, *J* = 17.6, 10.2 Hz, 1 H), 5.28–5.02 (m, 3 H), 4.65–4.52 (m, 3 H), 4.28–4.10 (m, 2 H), 3.96 (dq, *J* = 3.0, 6.9 Hz, 1 H), 3.35 (s, 3 H), 3.28 (dd, *J* = 13.0, 2.9 Hz, 1 H), 2.99 (s, 3 H), 2.74 (dd, *J* = 12.9, 9.5 Hz, 1 H), 1.84–1.56 (m, 4 H), 1.28 (s, 3 H), 1.22 (d, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 153.6, 142.1, 135.2, 129.3, 128.8, 127.2, 115.0, 91.5, 81.7, 77.8, 66.5, 55.8, 55.2, 41.5, 38.5, 37.7, 36.1, 27.2, 23.4, 9.4.

MS (EI): *m*/*z* = 506 $[M + Na]^+$.

(1*R*,4*R*)-1-(1*S*)-2-[(4*S*)-4-Benzyl-2-oxo-1,3-oxazolan-3-yl]-1-methyl-2-oxoethyl-4-hydroxy-4-methyl-5-hexenyl Methanesulfonate (11)

To a solution of **10** (4 g, 8.27 mmol) in THF (20 mL), was added aq HCl (15%, 10 mL), and the reaction mixture was stirred at r.t. for 1 h. After completion of the reaction, the reaction mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with H_2O (2 × 15 mL), brine (2 × 15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography to afford **11**.

Yield: 3.2 g (90%); colourless oil; $[\alpha]_D^{25}$ +29.3 (*c* 1.0, $CHCl_3$).

IR (neat): 3509, 2975, 1776, 1699, 1386, 1354, 1172, 915 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.15 (m, 5 H), 5.93–5.77 (m, 1 H), 5.29–5.0 (m, 3 H), 4.63–4.51 (m, 1 H), 4.31–4.04 (t, *J* = 8.3 Hz, 1 H), 4.13 (dd, *J* = 2.2, 8.3 Hz, 1 H), 4.03–3.93 (m, 1 H), 3.29 (dd, *J* = 3.0, 13.5 Hz, 1 H), 3.0 (s, 3 H), 2.74 (dd, *J* = 9.8, 12.8 Hz, 1 H), 1.85–1.57 (m, 5 H), 1.30 (s, 3 H), 1.23 (d, *J* = 7.5 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 153.6, 144.2, 135.1, 129.3, 128.7, 127.1, 112.2, 81.7, 72.6, 66.4, 55.7, 41.6, 38.4, 37.6, 37.0, 28.2, 27.4, 9.4.

MS (EI): *m*/*z* = 462 $[M + Na]^+$.

(4*S*)-4-Benzyl-3-(2*S*)-2-[(2*S*,5*R*)-5-methyl-5-vinyltetrahydro-2-furanyl]propanoyl-1,3-oxazolan-2-one (4)

A solution of **11** (3 g, 6.8 mmol) in 2,6-lutidine (10 mL) was stirred under N_2 in a 120 °C oil bath until the reaction was complete (monitored by TLC). After cooling to 25 °C, the reaction mixture was diluted with EtOAc (100 mL) and washed with aq sat. $CuSO_4$ (2 × 25 mL). The combined organic phases were washed with H_2O (2 × 25 mL), brine (2 × 15 mL), and dried over anhydrous Na_2SO_4. The residue was purified by chromatography on silica gel (*n*-hexane–EtOAc, 8:2) to give **4**.

Yield: 2.17 g (93%); colourless oil; $[\alpha]_D^{25}$ +59.5 (*c* 1.0, $CHCl_3$).

IR (neat): 2972, 2999, 2876, 1780, 1699, 1210 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.18 (m, 5 H), 5.83 (dd, *J* = 17.5, 10.9 Hz, 1 H), 5.09 (dd, *J* = 17.5, 1.4 Hz, 1 H), 4.94 (dd, *J* = 10.9, 1.4 Hz, 1 H), 4.73–4.67 (m, 1 H), 4.27–4.09 (m, 3 H), 3.94–3.86 (m, 1 H), 3.30 (dd, *J* = 13.1, 2.9 Hz, 1 H), 2.72 (dd, *J* = 13.9, 9.5 Hz, 1 H), 2.09–2.02 (m, 1 H), 1.96–1.90 (m, 1 H), 1.79–1.65 (m, 2 H), 1.26 (s, 3 H), 1.15 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.1, 153.2, 144.3, 135.5, 129.4, 128.9, 127.3, 111.7, 83.1, 80.8, 66.1, 55.5, 43.3, 37.9, 37.5, 29.6, 26.3, 14.4.

MS (EI): *m*/*z* = 366 $[M + Na]^+$.

(2*S*)-2-[(2*S*,5*R*)-5-Methyl-5-vinyltetrahydro-2-furanyl]propanoic Acid (1)

H_2O_2 (30% solution in H_2O, 1.32 mL, 11.6 mmol) and LiOH (1 N, 2.9 mL, 2.9 mmol) were added sequentially to a solution of **4** (0.5 g, 1.45 mmol) in THF (20 mL) and H_2O (6 mL), and the mixture was stirred in an ice-water bath. When the reaction was complete (indicated by TLC), aq sat. $Na_2S_2O_3$ (3 mL) was added, followed by H_2O (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 6 mL) and the aqueous phase was acidified to pH 1, extracted with EtOAc (3 × 5 mL), and dried over anhydrous Na_2SO_4. The organic layer was concentrated in vacuo and purified by column chromatography (EtOAc–hexanes, 4:6) to yield compound **1**.

Yield: 0.21 g (82%); colourless liquid; $[\alpha]_D^{25}$ +21.3 (*c* 1.0, $CHCl_3$).

IR (neat): 3400, 2925, 2855, 1711, 1220 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.91 (dd, *J* = 17.6, 10.4 Hz, 1 H), 5.24 (dd, *J* = 17.6, 1.6 Hz, 1 H), 5.03 (dd, *J* = 10.4, 1.6 Hz, 1 H),

4.21–4.14 (m, 1 H), 2.60–2.52 (m, 1 H), 2.13–2.04 (m, 1 H), 2.01–1.90 (m, 1 H), 1.85–1.77 (m, 1 H), 1.72–1.64 (m, 1 H), 1.34 (s, 3 H), 1.15 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.6, 143.8, 112.2, 84.0, 80.3, 45.5, 37.6, 29.9, 26.6, 13.2.

MS (EI): *m*/*z* = 207 $[M + Na]^+$.

(3*S*)-3-[(2*S*,5*R*)-5-Methyl-5-vinyltetrahydro-2-furanyl]butan-2-one (2)

To a cooled (–78 °C) solution of **4** (1.8 g, 5.2 mmol) in CH_2Cl_2 (20 mL), was added DIBAL-H (1 M in CH_2Cl_2, 5.72 mL, 5.72 mmol). The solution was stirred for 15 min at –78 °C and then quenched by the addition of EtOAc (3 mL). Potassium sodium tartrate (Rochelle salt; 0.5 M, 50 mL) was added and the mixture was stirred for 1 h at 25 °C. The organic phase was separated and the aqueous phase was extracted with Et_2O (150 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (EtOAc–hexanes, 3:7) gave **12** (0.77 g, 88%) as a light-yellow oil. This aldehyde was immediately used for the next reaction. To a suspension of Mg (57 mg, 2.38 mmol) in anhydrous Et_2O (1 mL), MeI (0.15 mL, 2.38 mmol) was added dropwise under a nitrogen atmosphere at 0 °C. It was allowed to stir for ~1 h at r.t. Aldehyde **12** (0.2 g, 1.19 mmol) in anhydrous Et_2O (1 mL) was then added dropwise at 0 °C and the mixture was stirred at 25 °C for ~30 min. After completion of the reaction, sat. aq NH_4Cl (5 mL) was added and the mixture was extracted with EtOAc (3 × 5 mL). The organic layer was washed with brine (2 × 5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (silica gel; EtOAc–hexanes, 3:7) afforded **13** (0.18 g, 85%) as a yellow oil.

To an ice-cooled solution of 2-(iodooxy)benzoic acid (0.36 g, 1.28 mmol) in anhydrous DMSO (1 mL), was added a solution of alcohol **13** (0.15 g, 0.88 mmol) in anhydrous CH_2Cl_2 (4 mL). The mixture was stirred at 25 °C for 2 h and then filtered through a Celite pad and washed with Et_2O (2 × 5 mL). The combined organic filtrates were washed with H_2O (2 × 5 mL) and brine (2 × 3 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (EtOAc–hexane, 2:8) to afford nordavanone **2**.

Yield: 0.12 g (82%); colourless oil; $[\alpha]_D^{22}$ +14.6 (*c* 0.5, $CHCl_3$).

IR (neat): 2925, 2854, 1712, 1243 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.89 (dd, *J* = 17.1, 10.5 Hz, 1 H), 5.19 (dd, *J* = 17.1, 1.7 Hz, 1 H), 4.98 (dd, *J* = 10.5, 1.7 Hz, 1 H), 4.15–4.06 (m, 1 H), 2.70–2.59 (m, 1 H), 2.23 (s, 3 H), 2.07–1.97 (m, 1 H), 1.95–1.86 (m, 1 H), 1.80–1.70 (m, 1 H), 1.66–1.52 (m, 1 H), 1.27 (s, 3 H), 1.01 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.5, 144.5, 111.4, 83.0, 80.7, 52.6, 37.5, 29.7, 29.6, 26.5, 12.9.

MS (EI): *m*/*z* = 205 $[M + Na]^+$.

(2*S*)-6-Methyl-2-[(2*S*,5*R*)-5-methyl-5-vinyltetrahydro-2-furanyl]-5-hepten-3-one (3)

To a suspension of zinc (0.93 g, 14.28 mmol) in anhydrous THF (10 mL), was added 4-bromo-2-methylbut-2-ene (1.06 g, 7.14 mmol) and the solution was stirred at 25 °C for 1 h. The solution was treated with aldehyde **12** (0.2 g, 1.19 mmol) and HMPA (2 mL, 11.9 mmol) and was heated to reflux for 72 h. Sat. aq NH_4Cl (4 mL) was added to the reaction mixture and the solution was diluted with EtOAc (5 mL), washed with brine (5 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (EtOAc–hexane, 3:7) to give alcohol **14** as a colourless oil (0.22 g, 78%). The alcohol **14** (0.15 g, 0.63 mmol) was subjected to oxidation with IBX and DMSO following the procedure described above for compound **2**, to yield davanone **3**.

Yield: 0.118 g (80%); colourless oil; $[\alpha]_D^{22}$ +63.4 (*c* 0.5, $CHCl_3$).

IR (neat): 2928, 2853, 1709, 1214, 1030 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.89 (dd, *J* = 17.2, 10.4 Hz, 1 H), 5.30–5.35 (m, 1 H), 5.18 (dd, *J* = 17.2, 1.6 Hz, 1 H), 4.96 (dd, *J* = 10.4, 1.6 Hz, 1 H), 4.14–4.06 (m, 1 H), 3.32–3.16 (m, 2 H), 2.72–2.64 (m, 1 H), 2.04–1.96 (m, 1 H), 1.93–1.82 (m, 1 H), 1.76–1.66 [m, 1 H, with overlapping s at 1.73 (3 H)], 1.63–1.51 [m, 1 H, with overlapping s at 1.60 (3 H)], 1.23 (s, 3 H), 0.99 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.3, 144.6, 135.2, 116.0, 111.4, 83.1, 80.8, 51.3, 42.5, 37.4, 30.0, 26.8, 25.6, 18.0, 13.2.

MS (EI): *m*/*z* = 259 $[M + Na]^+$.

Acknowledgment

M.N.P. and M.B. thank CSIR, New Delhi for the award of fellowships.

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