Synthesis of *cis*- and *trans*-Davanoids: Artemone, Hydroxydavanone, Isodavanone, and Nordavanone

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Received: 19.02.2013; Accepted after revision: 27.03.2013

This paper is dedicated to Prof. Christopher T. Walsh on the occasion of his retirement in 2013.

Abstract: A concise and versatile synthesis of both *cis* and *trans* diastereomers of the natural products artemone, hydroxydavanone, isodavanone, and nordavanone has been accomplished. The preparation of *trans*-davanone is also described. Each synthesis is six to eight steps from geranyl acetate, with differentiation between *cis* and *trans* products occurring through a diastereoselective cyclization prior to derivatization. Many of these compounds are minor components of davana oil and have now been synthesized for the first time.

Key words: davanone, terpenoids, total synthesis, stereoselective synthesis, green chemistry, asymmetric allylic O-alkylation

Davana oil, the essential oil of the Indian sage *Artemisia pallens*, contains over 30 terpenoid natural products (Figure 1).[1] The most abundant of these is *cis*-davanone,[2] which is reported to have antifungal,[3] antispasmodic,[4] and antibacterial[5] properties. Indeed, *cis*-davanone has been the target of several synthetic studies.[6] Other davanoids (compounds with structures related to davanone) have received much less attention in synthetic and bioactivity studies, perhaps due to their relative scarcity in davana oil.[1]

Among the davanoids that have never before been prepared stereoselectively (if at all) are *trans*-davanone, *trans*-nordavanone, *trans*-artemone, *cis*- and *trans*-hydroxydavanone, and *cis*- and *trans*-isodavanone. The most compelling target among these is *cis*-hydroxydavanone, whose antifungal activity is four-fold greater than that of davanone against a range of fungi.[3] Driven by the possibility of discovering more potent antifungal agents and the lack of stereoselective syntheses of many of these compounds, we adapted our enantioselective seven-step synthesis of *cis*-davanone[6g] to these other davanoids.

We previously reported five-step syntheses of *cis*- and *trans*-davana acid ethyl esters (**1** and **2**) using Pd_2dba_3 and either C_3-(*S*)-TunePhos or C_3-(*R*)-TunePhos, respectively.[6g] These esters were treated with prenylmagnesium chloride to produce *cis*- and *trans*-artemone directly (**3** and **4**, see Scheme 1). The γ-prenylated products **3** and **4** did not undergo a second Grignard addition to the ketone, as Baran et al. observed for a similar reaction.[7] Our six-step synthesis of *cis*-artemone (**3**) is significantly shorter than the only previous stereoselective route, a 20-step achievement by Honda et al.[6e] A nonstereoselective preparation of artemones has been reported by Naegeli et al.[8]

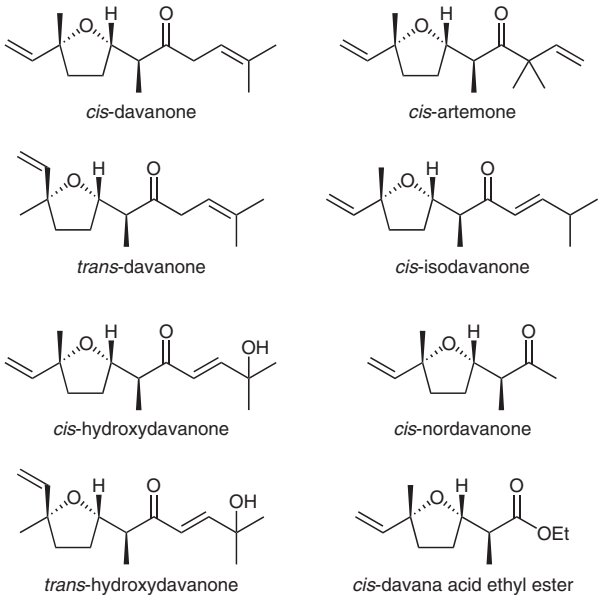
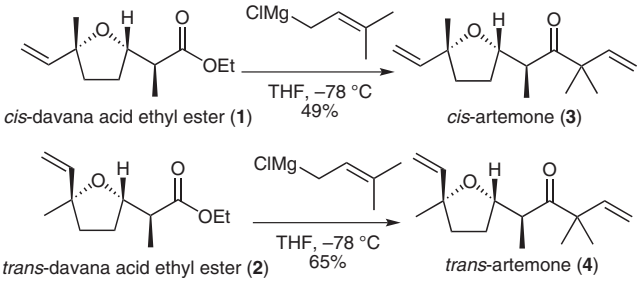


Figure 1 Structures of davanoids mentioned in this article that are found in davana oil from *Artemesia pallens*. Of these, only davanone and hydroxydavanone are known to naturally occur in both *cis* and *trans* forms.[1]



Scheme 1 Preparation of *cis*- and *trans*-artemone

In order to prepare other davanoids, *cis* and *trans* esters **1** and **2** were converted into the corresponding Weinreb amides **5**[6g] and **6**, respectively (Scheme 2). From these Weinreb amides, *cis*- and *trans*-nordavanone (**7** and **8**) were readily generated with methylmagnesium chloride. Likewise, *trans*-davanone (**9**) was obtained after reaction of **6** with prenylmagnesium chloride.

SYNTHESIS 2013, 45, 1541–1545
Advanced online publication: 24.04.2013
DOI: 10.1055/s-0033-1338429; Art ID: SS-2013-M0146-OP
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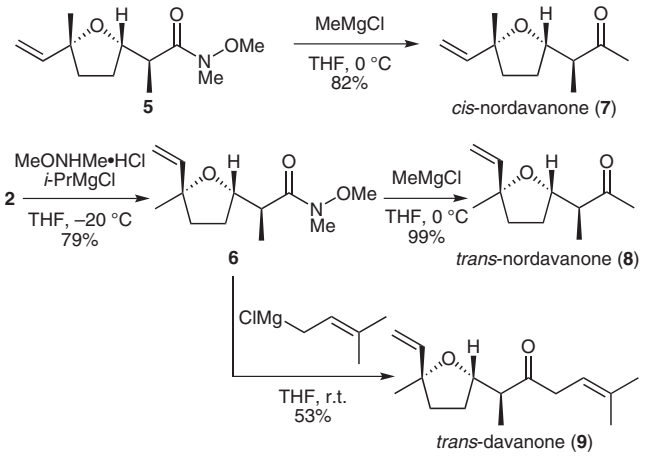
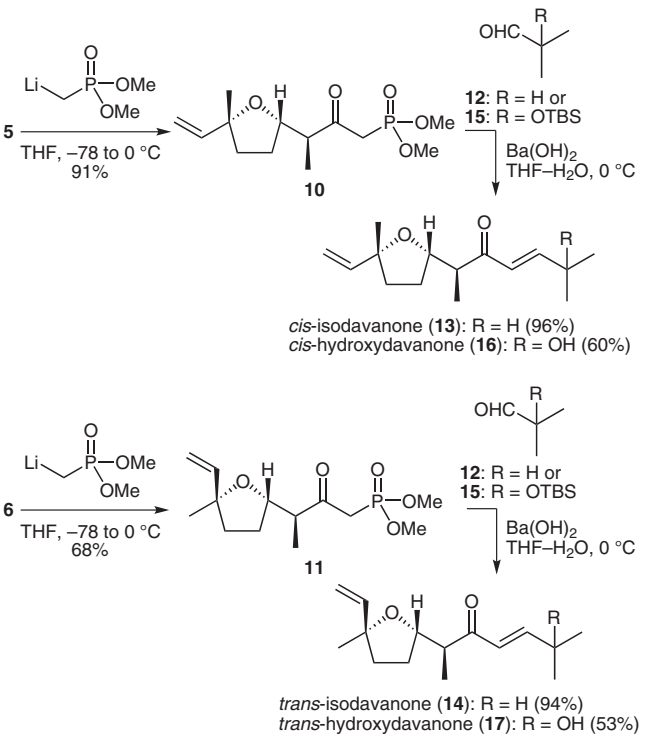


Scheme 2 Synthesis of *cis*-nordavanone, *trans*-nordavanone, and *trans*-davanone

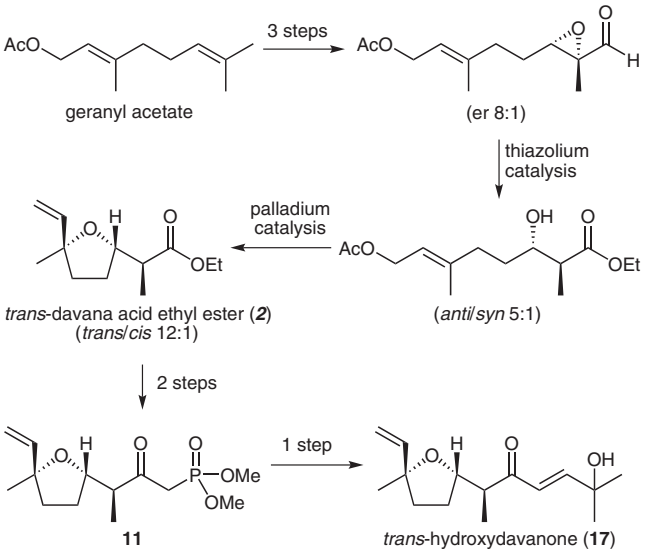
Previously, the nordavanones had been synthesized non-stereoselectively by Thomas and Ozainne as a complex mixture of eight stereoisomers.[9] The only reported stereoselective synthesis of *cis*-nordavanone (**7**) was by Sabitha et al. in 2010.[6h] We are the first to report the stereoselective syntheses of *trans*-nordavanone (**8**) and *trans*-davanone (**9**).[10]

The α,β-unsaturated isodavanones and hydroxydavanones were prepared using Horner–Wadsworth–Emmons reactions. First, the Weinreb amides **5** and **6** were treated with dimethyl lithiomethylphosphonate to give ketophosphonates **10** and **11**, respectively (Scheme 3). Condensation of **10** and **11** with isobutyraldehyde (**12**) was facile using barium hydroxide in wet THF,[11] resulting in *cis*- and *trans*-isodavanone (**13** and **14**), respectively. To our great delight, these same aqueous basic conditions with the known TBS-protected aldehyde **15**[12] directly produced *cis*- and *trans*-hydroxydavanone (**16** and **17**), conveniently removing the silyl group following condensation.[13] These are the first stereoselective preparations of the isodavanones and hydroxydavanones; the longest linear sequence to each of these four davanoids from geranyl acetate requires only eight steps (Scheme 4). Neither *cis*-hydroxydavanone (**16**) nor *trans*-hydroxydavanone (**17**) has ever been synthesized previously, and the only reported synthesis of isodavanones is the complex mixture of stereoisomers obtained by Ohloff and Giersch on their way to davanone.[6b]

In conclusion, we have built upon our recent synthesis of *cis*-davanone[6g] to selectively prepare nine other davanoids. This is the first systematic approach to any of the *trans*-davanoids. All five *trans* isomers plus *cis*-isodavanone (**13**) and *cis*-hydroxydavanone (**16**) have now been made stereoselectively[14] for the first time. Each synthesis avoids separate protecting group steps along its longest linear path, maintains redox economy,[15] and is shorter than any previous stereoselective route. In the cases of



Scheme 3 Synthesis of *cis*- and *trans*-isodavanones and hydroxydavanones



Scheme 4 Overview of the eight-step synthesis of *trans*-hydroxydavanone

trans-davanone (**9**) and *cis*- and *trans*-artemone (**3** and **4**), all of the carbons in our synthetic sesquiterpene products ultimately derive from intact prenyl units. Preliminary antifungal screens indicate that *cis*-isodavanone and *trans*-hydroxydavanone have promising bioactivity,[16] and we are eager to fully test and report the antifungal properties of all of these davanoids in due course.

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All reactions, unless otherwise noted, were carried out under an atmosphere of argon using oven-dried glassware and magnetic stirring. Anhyd CH_2Cl_2 and THF were obtained from a SolvPure anhyd solvent system using activated Al_2O_3. Reactions were monitored with TLC on glass plates coated with mesh 400 silica gel and visualized using UV and either anisaldehyde or $Ce(SO_4)_2$ stain. Column chromatography was performed using mesh 60 silica gel. IR spectra were recorded on a Thermo Scientific Nicolet iS5 FT-IR spectrometer using an iD5 diamond ATR accessory. GC-MS was performed with an Agilent 5975C using electron impact ionization. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker Avance 400 spectrometer at ambient temperature. Chemical shifts are expressed in ppm (δ) using TMS as the internal standard. For ^{13}C spectra, chemical shifts are referenced to $CDCl_3$ at 77.0 ppm. Optical rotation measurements were made using a Jasco P-1010 polarimeter. High-resolution mass spectrometry (HRMS) was performed using either an electron ionization (EI) source on a double-focusing, magnetic sector mass spectrometer, or a chemical ionization (CI) source on a time-of-flight mass spectrometer.

Ethyl (2*S*)-2-[(2*S*,5*S*)-5-Methyl-5-vinyltetrahydrofuran-2-yl]propanoate (*trans*-Davana Acid Ethyl Ester, 2)

Following the procedure of Morrison et al.,[6g] *trans*-davana acid ethyl ester (**2**)[17] was obtained as a colorless oil (66%); R_f = 0.75 (hexanes–EtOAc, 3:1); $[\alpha]_D^{23}$ +15 (*c* 0.31, $CHCl_3$).

IR (ATR): 1734 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.84 (dd, *J* = 17, 10 Hz, 1 H), 5.18 (dd, *J* = 17, 2 Hz, 1 H), 4.98 (dd, *J* = 10, 2 Hz, 1 H), 4.18 (m, 1 H), 4.16 (d, *J* = 7 Hz, 2 H), 2.59 (dq, *J* = 7, 7 Hz, 1 H), 1.83–1.99 (m, 2 H), 1.65–1.75 (m, 2 H), 1.30 (s, 3 H), 1.26 (t, *J* = 7 Hz, 3 H), 1.12 (d, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.0, 143.6, 111.31, 83.0, 79.8, 60.3, 45.0, 36.9, 28.2, 27.0, 14.2, 12.8.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{12}H_{20}O_3$: 212.1412; found: 212.1418.

(2*S*)-4,4-Dimethyl-2-[(2*S*,5*R*)-5-methyl-5-vinyltetrahydrofuran-2-yl]hex-5-en-3-one (*cis*-Artemone, 3)

Prenylmagnesium chloride was generated by adding 1-chloro-3-methylbut-2-ene (0.45 mL, 4.022 mmol) dropwise over ca. 3 min to a stirred suspension of Mg turnings (542 mg, 22.3 mmol) in THF (8.15 mL) at r.t. After stirring for 10 min, the liquid portion was cannulated into a stirred solution of **1** (75.1 mg, 0.35 mmol) in THF (1.63 mL) at –78 °C over 15 min, followed by a THF rinse (0.5 mL). This mixture was stirred at –78 °C for 21 h before it was quenched with brine (25 mL). The resulting mixture was extracted with Et_2O (3 × 15 mL), washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (hexanes → 10:1 hexanes–Et_2O) to afford **3** (41 mg, 0.17 mmol, 49%) as a yellow oil; R_f = 0.82 (hexanes–EtOAc, 3:1); $[\alpha]_D^{25}$ +36.9 (*c* 1.0, $CHCl_3$).

IR, GC-MS (EI), and ^{1}H NMR data match published values.[8]

^{13}C NMR (100 MHz, $CDCl_3$): δ = 216.0, 145.2, 142.8, 114.6, 111.4, 81.3, 51.8, 46.4, 37.9, 30.7, 29.7, 26.8, 23.6, 23.5, 15.6.

(2*S*)-4,4-Dimethyl-2-[(2*S*,5*S*)-5-methyl-5-vinyltetrahydrofuran-2-yl]hex-5-en-3-one (*trans*-Artemone, 4)

Using the same procedure as for the *cis* compound, *trans* ester **2** (98.8 mg, 0.465 mmol) was converted into *trans*-artemone (**4**). The crude mixture was purified by flash chromatography (50:1 hexanes–Et_2O → Et_2O) to afford **4** (71.8 mg, 0.304 mmol, 65%) as a colorless oil; R_f = 0.85 (hexanes–EtOAc, 3:1); $[\alpha]_D^{25}$ +39.6 (*c* 1.0, $CHCl_3$).

IR (ATR): 1711, 1635 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.98 (dd, *J* = 17, 11 Hz, 1 H), 5.79 (dd, *J* = 18, 11 Hz, 1 H), 5.19 (dd, *J* = 16, 1 Hz, 1 H), overlapping with 5.16 (dd, *J* = 10, 1 Hz, 1 H), 5.11 (dd, *J* = 17, 2 Hz, 1 H), 4.94 (dd, *J* = 11, 2 Hz, 1 H), 4.07 (td, *J* = 8, 7 Hz, 1 H), 3.05 (qd, *J* = 8, 7 Hz, 1 H), 1.92–2.01 (m, 1 H), 1.80–1.90 (m, 1 H), 1.60–1.73 (m, 2 H), 1.26 (s, 3 H) with overlappings at 1.25 (s, 3 H), 1.22 (s, 3 H), 0.95 (d, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 216.0, 144.1, 142.8, 114.5, 111.6, 83.1, 81.2, 51.8, 46.3, 37.4, 30.1, 29.2, 27.3, 23.5, 15.4.

HRMS (CI): *m*/*z* calcd for $C_{15}H_{25}O_2$: 237.1849; found: 237.1847 [MH$^+$].

(2*S*)-*N*-Methoxy-*N*-methyl-2-[(2*S*,5*S*)-5-methyl-5-vinyltetrahydrofuran-2-yl]propanamide (6)

The HCl salt of *N*,*O*-dimethylhydroxylamine (4.10 g, 42.0 mmol) was added to a solution of **2** (849 mg, 4.00 mmol) in THF (108 mL). Upon cooling the stirred solution to –20 °C in a NaCl/ice bath, a 2.0 M solution of isopropylmagnesium chloride was added dropwise (55.8 mL, 84.0 mmol). After 50 min, the reaction was quenched with sat. aq NH_4Cl (100 mL), and extracted with Et_2O (4 × 50 mL). The combined Et_2O layers were washed with brine (150 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (5:1 hexanes–EtOAc) to afford *trans* Weinreb amide **6** (720 mg, 3.17 mmol, 79%) as a colorless oil; R_f = 0.15 (hexanes–EtOAc, 3:1); $[\alpha]_D^{24}$ +7.6 (*c* 1.39, $CHCl_3$).

IR (ATR): 1660 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.84 (dd, *J* = 17, 11 Hz, 1 H), 5.17 (dd, *J* = 17, 2 Hz, 1 H) 4.96 (dd, *J* = 11, 2 Hz, 1 H), 4.14–4.22 (m, 1 H), 3.72 (s, 3 H), 3.21 (s, 3 H), 3.06 (m, 1 H), 1.96–2.02 (m, 1 H), 1.86–1.96 (m, 1 H), 1.67–1.79 (m, 2 H), 1.29 (s, 3 H), 1.08 (d, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.8, 143.6, 111.4, 82.7, 79.9, 61.4, 40.7, 37.1, 29.2, 28.6, 27.0, 13.2.

HRMS (CI): *m*/*z* calcd for $C_{12}H_{22}NO_3$: 228.1594; found: 228.1596 [MH$^+$].

(3*S*)-3-[(2*S*,5*R*)-5-Methyl-5-vinyltetrahydrofuran-2-yl]butan-2-one (*cis*-Nordavanone, 7)

MeMgCl (0.88 mL, 2.64 mmol, 3.0 M in THF) was added dropwise over 5 min to a solution of *cis* Weinreb amide **5** (95.8 mg, 0.440 mmol) in THF (8.36 mL) at 0 °C. The resulting solution was stirred at 0 °C for 3 h. Additional MeMgCl (0.59 mL, 1.76 mmol) was added to the reaction mixture to achieve full conversion. The mixture was stirred at 0 °C for another 90 min, and then it was quenched with cold, sat. aq NH_4Cl (20 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (50:1 hexanes–Et_2O) to give *cis*-nordavanone (**7**) as a colorless oil (63.1 mg, 0.346 mmol, 82%); R_f = 0.57 (hexanes–EtOAc, 2:1); $[\alpha]_D^{24}$ +43.3 (*c* 1.0, $CHCl_3$).

IR, ^{1}H NMR, ^{13}C NMR, and GC-MS (EI) data match published values.[6h]

(3*S*)-3-[(2*S*,5*S*)-5-Methyl-5-vinyltetrahydrofuran-2-yl]butan-2-one (*trans*-Nordavanone, 8)

Using the same procedure as for the *cis* compound, *trans* Weinreb amide **6** (76.6 mg, 0.337 mmol) was converted into *trans*-nordavanone (**8**). The crude mixture was purified by flash chromatography (4:1 hexanes–EtOAc) to afford **8** as a colorless oil (60.9 mg, 0.334 mmol, 99%); R_f = 0.50 (hexanes–EtOAc, 4:1); $[\alpha]_D^{24}$ +28.8 (*c* 4.6, $CHCl_3$).

IR (ATR): 1714, 1626 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82 (dd, *J* = 18, 11 Hz, 1 H), 5.15 (dd, *J* = 17, 2 Hz, 1 H) 4.97 (dd, *J* = 11, 2 Hz, 1 H), 4.03–4.11 (m, 1 H), 2.58–2.70 (m, 1 H), 2.21 (s, 3 H), 1.94–2.04 (m, 1 H), 1.84–1.91 (m, 1 H), 1.67–1.75 (m, 1 H), 1.59–1.67 (m, 1 H), 1.29 (s, 3 H), 1.08 (d, *J* = 7 Hz, 3 H).

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^{13}C NMR (100 MHz, $CDCl_3$): δ = 221.9, 143.7, 111.5, 83.2, 80.5, 52.8, 36.9, 29.7, 29.3, 27.3, 12.9.

HRMS (CI): *m*/*z* calcd for $C_{11}H_{19}O_2$: 183.1380; found: 183.1381 [MH^+].

(2*S*)-6-Methyl-2-[(2*S*,5*S*)-5-methyl-5-vinyltetrahydrofuran-2-yl]hept-5-en-3-one (*trans*-Davanone, 9)

1-Chloro-3-methylbut-2-ene (0.60 mL, 5.3 mmol) was added dropwise over ca. 3 min to a suspension of Mg turnings (25.60 g, 1.05 mol) and 1,2-dibromoethane (0.2 mL) in THF (34.6 mL) at r.t. When the mixture became warm, the reaction flask was immediately cooled to 0 °C. The mixture was stirred for 15 min and 4 mL of this mixture was added to a solution of *trans* Weinreb amide **6** (15.3 mg, 0.067 mmol) in THF (4.0 mL) over 5 min at r.t. After 2 h, the reaction was quenched with brine (15 mL) and extracted with Et_2O (3 × 15 mL). The combined Et_2O extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated. The crude mixture was purified by flash chromatography (hexanes → 40:1 hexanes–Et_2O) to afford *trans*-davanone (**9**) as a colorless film (8.4 mg, 0.036 mmol, 53%); R_f = 0.71 (hexanes–EtOAc, 4:1); $[\alpha]_D^{23}$ +30.0 (*c* 0.59, $CHCl_3$).

IR (ATR): 1715 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.83 (dd, *J* = 17, 11 Hz, 1 H), 5.35 (m, 1 H), 5.16 (dd, *J* = 17, 2 Hz, 1 H), 4.98 (dd, *J* = 11, 2 Hz, 1 H), 4.07 (m, 1 H), 3.27 (m, 2 H), 2.72 (m, 1 H), 2.00 (m, 1 H), 1.88 (m, 1 H), 1.66–1.78 (m, 1 H) with overlappings at 1.77 (3 H), 1.56–1.65 (m, 1 H) with overlappings at 1.64 (3 H), 1.28 (s, 3 H), 1.03 (d, *J* = 8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.2, 143.7, 135.5, 116.2, 111.5, 83.1, 80.7, 51.3, 42.9, 36.9, 29.4, 27.3, 25.9, 18.2, 13.0.

HRMS (CI): *m*/*z* calcd for $C_{15}H_{25}O_2$: 237.1849; found: 237.1857 [MH^+].

Dimethyl {(3*S*)-3-[(2*S*,5*R*)-5-Methyl-5-vinyltetrahydrofuran-2-yl]-2-oxobutyl}phosphonate (10)

n-BuLi (1.5 mL, 2.64 mmol, 1.75 M in hexanes) was added dropwise to a solution of dimethylmethyl phosphonate (0.33 mL, 0.44 mmol) in THF (6.23 mL) at –78 °C over 2 min. After stirring at –78 °C for 35 min, a solution of *cis* Weinreb amide **5** (100.8 mg, 0.44 mmol) in THF (1.56 mL) was added via cannula over 2 min, followed by a THF rinse (0.2 mL). After 1 h, the reaction was allowed to warm to 0 °C and quenched with ice and sat. aq NH_4Cl (4 mL). The resulting mixture was extracted with EtOAc (3 × 40 mL), the combined Et_2O layers were washed with brine (50 mL), dried ($MgSO_4$), and concentrated. The crude product was purified via flash chromatography (1:1 hexanes–EtOAc) to obtain *cis*-ketophosphonate **10** as a yellow oil (116.1 mg, 0.40 mmol, 91%); R_f = 0.16 (hexanes–EtOAc, 1:1); $[\alpha]_D^{23}$ +127.1 (*c* 1.0, $CHCl_3$).

IR (ATR): 1714 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.92 (dd, *J* = 17, 11 Hz, 1 H), 5.12 (dd, *J* = 17, 2 Hz, 1 H), 4.97 (dd, *J* = 11, 2 Hz, 1 H), 3.95 (m, 1 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 3.52 (dd, *J* = 23, 14 Hz, 1 H), 3.17 (dd, *J* = 22, 14 Hz, 1 H), 2.91 (m, 1 H), 1.99–2.08 (m, 1 H), 1.87–1.96 (m, 1 H), 1.69–1.78 (m, 1 H), 1.56–1.68 (m, 1 H), 1.26 (s, 3 H), 1.04 (d, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.9, 144.8, 111.9, 83.8, 81.9, 53.4, 52.9, 43.1, 41.8, 37.7, 30.8, 26.9, 13.2.

HRMS (CI): *m*/*z* calcd for $C_{13}H_{24}O_5P$: 291.1356; found: 291.1355 [MH^+].

Dimethyl {(3*S*)-3-[(2*S*,5*S*)-5-Methyl-5-vinyltetrahydrofuran-2-yl]-2-oxobutyl}phosphonate (11)

Employing the same procedure as for the *cis* compound, *trans* Weinreb amide **6** (127.0 mg, 0.53 mmol) was converted into *trans*-ketophosphonate **11** as a yellow oil (104.6 mg, 0.36 mmol, 68%); R_f = 0.16 (hexanes–EtOAc, 1:1); $[\alpha]_D^{24}$ +83.8 (*c* 4.4, $CHCl_3$).

IR (ATR): 1714, 1642 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81 (dd, *J* = 17, 11 Hz, 1 H), 5.12 (dd, *J* = 17, 2 Hz, 1 H), 4.97 (dd, *J* = 11, 2 Hz, 1 H), 3.98 (m, 1 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.49 (dd, *J* = 23, 14 Hz, 1 H), 3.18 (dd, *J* = 22, 14 Hz, 1 H), 2.91 (m, 1 H), 1.99–2.07 (m, 1 H), 1.82–1.93 (m, 1 H), 1.71–1.80 (m, 1 H), 1.63–1.71 (m, 1 H), 1.32 (s, 3 H), 1.05 (d, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.8, 143.8, 111.8, 83.8, 81.7, 53.4, 53.3, 43.3, 42.1, 36.9, 30.4, 27.6, 13.2.

HRMS (CI): *m*/*z* calcd for $C_{13}H_{24}O_5P$: 291.1356; found: 291.1364 [MH^+].

(4*E*,2*S*)-2-[(2*S*,5*R*)-5-Methyl-5-vinyltetrahydrofuran-2-yl]-6-methylhept-4-en-3-one (*cis*-Isodavanone, 13)

Activated $Ba(OH)_2$ (110.0 mg, 0.64 mmol)[11] was added to a solution of *cis*-ketophosphonate **10** (116.1 mg, 0.400 mmol) in THF (1.2 mL), and the mixture was stirred vigorously at r.t. for 30 min. It was then cooled to 0 °C, and a solution of isobutyraldehyde (**12**; 73 μL, 0.80 mmol) in THF–H_2O (40:1, 1.20 mL) was then added. The reaction mixture was stirred at 0 °C and rapidly formed a colorless gel. The gel was broken up with a spatula, and the mixture was stirred for an additional 30 min. The reaction was then quenched with CH_2Cl_2/sat. aq $NaHCO_3$ (1:1, 4 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL), the combined CH_2Cl_2 layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (50:1 hexanes–Et_2O) to provide *cis*-isodavanone (**13**) as a clear oil (90.7 mg, 0.384 mmol, 96%); R_f = 0.42 (hexanes–EtOAc, 6:1); $[\alpha]_D^{24}$ +20.9 (*c* 1.0, $CHCl_3$).

IR (ATR): 1693, 1670, 1672 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85 (dd, *J* = 16, 7 Hz, 1 H), 6.16 (dd, *J* = 17, 2 Hz, 1 H), 5.90 (dd, *J* = 17, 11 Hz, 1 H), 5.18 (dd, *J* = 17, 2 Hz, 1 H), 4.97 (dd, *J* = 11, 2 Hz, 1 H), 4.23 (m, 1 H), 2.98 (m, 1 H), 2.48 (m, 1 H), 1.94–2.03 (m, 1 H), 1.84–1.93 (m, 1 H), 1.71–1.79 (m, 1 H), 1.60–1.70 (m, 1 H), 1.26 (s, 3 H), 1.08 (s, 3 H), 1.07 (s, 3 H), 1.04 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.5, 154.0, 145.1, 127.5, 111.8, 83.3, 80.9, 49.4, 38.0, 31.4, 29.6, 27.0, 21.8, 21.7, 13.5.

HRMS (CI): *m*/*z* calcd for $C_{15}H_{25}O_2$: 237.1849; found: 237.1852 [MH^+].

(4*E*)-(2*S*)-2-[(2*S*,5*S*)-5-Methyl-5-vinyltetrahydrofuran-2-yl]-6-methyl-4-hepten-3-one (*trans*-Isodavanone, 14)

Following the same procedure as for the *cis* compound, *trans*-ketophosphonate **11** (137.0 mg, 0.472 mmol) was converted into *trans*-isodavanone (**14**) as a clear oil (105.0 mg, 0.444 mmol, 94%); R_f = 0.56 (hexanes–EtOAc, 6:1); $[\alpha]_D^{24}$ +17.5 (*c* 2.4, $CHCl_3$).

IR (ATR): 1693, 1669, 1627 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85 (dd, *J* = 16, 7 Hz, 1 H), 6.16 (dd, *J* = 17, 2 Hz, 1 H), 5.83 (dd, *J* = 17, 11 Hz, 1 H), 5.16 (dd, *J* = 17, 2 Hz, 1 H), 4.96 (dd, *J* = 11, 2 Hz, 1 H), 4.16 (m, 1 H), 2.97 (dq, *J* = 7, 7 Hz, 1 H), 2.47 (m, 1 H), 1.91–1.99 (m, 1 H), 1.82–1.91 (m, 1 H), 1.65–1.75 (m, 2 H), 1.29 (s, 3 H), 1.07 (d, *J* = 7 Hz, 6 H), 1.06 (d, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.7, 153.5, 143.6, 126.8, 111.3, 82.9, 79.9, 48.9, 37.1, 31.1, 28.5, 27.0, 21.32, 21.28, 12.5.

HRMS (CI): *m*/*z* calcd for $C_{15}H_{25}O_2$: 237.1849; found: 237.1851 [MH^+].

(4*E*,2*S*)-6-Hydroxy-6-methyl-2-[(2*S*,5*R*)-5-methyl-5-vinyltetrahydrofuran-2-yl]hept-4-en-3-one (*cis*-Hydroxydavanone, 16)

Activated $Ba(OH)_2$ (134.7 mg, 0.78 mmol)[11] was added to a solution of *cis*-ketophosphonate **10** (152.6 mg, 0.525 mmol) in THF (1.6 mL), and the mixture was stirred vigorously at r.t. for 30 min. It was then cooled to 0 °C, and a solution of aldehyde **15**[12] (211.1 mg, 1.033 mmol) in THF–H_2O (40:1, 1.6 mL) was added. The reaction

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mixture was stirred at 0 °C and it immediately formed an orange heterogeneous mixture. The mixture was stirred for an additional 90 min, and then warmed to r.t. and stirred for 3 h. The reaction was then quenched with CH_2Cl_2/sat. aq $NaHCO_3$ (1:1, 4 mL) and the resulting mixture was extracted with CH_2Cl_2 (6 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (50:1 → 5:1 hexanes–Et_2O) to obtain *cis*-hydroxydavanone (**16**) as a yellow oil (79.7 mg, 0.316 mmol, 60%); R_f = 0.16 (hexanes–EtOAc, 5:1); $[\alpha]_D^{24}$ +35.8 (*c* 1.69, $CHCl_3$).

IR (ATR): 3443, 1680, 1630 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.93 (d, *J* = 16 Hz, 1 H), 6.43 (d, *J* = 16 Hz, 1 H), 5.91 (dd, *J* = 17, 11 Hz, 1 H), 5.19 (dd, *J* = 17, 2 Hz, 1 H), 4.98 (dd, *J* = 11, 2 Hz, 1 H), 4.24 (m, 1 H), 2.95 (m, 1 H), 1.97–2.07 (m, 1 H), 1.87–1.95 (m, 1 H), 1.72–1.82 (m, 1 H), 1.59–1.71 (m, 1 H), 1.40 (s, 6 H), 1.28 (s, 3 H), 1.05 (d, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.3, 152.9, 145.0, 125.6, 111.9, 83.5, 80.9, 71.2, 50.3, 38.0, 29.8, 29.7, 26.9, 13.5.

HRMS (CI): *m*/*z* calcd for $C_{15}H_{25}O_3$: 253.1798; found: 253.1803 [MH^+].

(4*E*,2*S*)-6-Hydroxy-6-methyl-2-[(2*S*,5*S*)-5-methyl-5-vinyltetrahydrofuran-2-yl]hept-4-en-3-one (*trans*-Hydroxydavanone, 17)

Following the same procedure as for the *cis* compound, *trans*-ketophosphonate **11** (175 mg, 0.602 mmol) was converted into *trans*-hydroxydavanone (**17**). Following flash chromatography (50:1 hexanes–Et_2O → Et_2O), **17** was obtained as a yellow oil (80.0 mg, 0.317 mmol, 53%); R_f = 0.36 (hexanes–EtOAc, 3:1); $[\alpha]_D^{24}$ +14.7 (*c* 0.49, $CHCl_3$).

IR (ATR): 3446, 1667, 1629 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.92 (d, *J* = 16 Hz, 1 H), 6.44 (d, *J* = 16 Hz, 1 H), 5.84 (dd, *J* = 17, 11 Hz, 1 H), 5.17 (dd, *J* = 17, 2 Hz, 1 H), 4.98 (dd, *J* = 11, 2 Hz, 1 H), 4.19 (m, 1 H), 2.96 (m, 1 H), 1.94–2.02 (m, 1 H), 1.84–1.93 (m, 1 H), 1.72–1.81 (m, 1 H), 1.66–1.71 (m, 1 H), 1.41 (s, 6 H), 1.31 (s, 3 H), 1.09 (d, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.2, 152.7, 144.0, 125.6, 111.7, 83.4, 80.3, 71.4, 50.3, 37.3, 30.0, 29.8, 29.3, 27.5, 12.9.

HRMS (CI): *m*/*z* calcd for $C_{15}H_{25}O_3$: 253.1798; found: 253.1802 [MH^+].

Acknowledgment

This work was supported by an Arnold and Mabel Beckman Scholars Award (to K.K.W.), a Camille and Henry Dreyfus Foundation Faculty Startup Award, the Sherman Fairchild Foundation, National Science Foundation REU Grant CHE-1005253, the John Stauffer Charitable Trust, the Harvey Mudd College Department of Chemistry, and the Christian Scholars Foundation. We thank Dr. Richard W. Kondrat and Ronald B. New at the University of California, Riverside for exact mass measurements and Karen C. Morrison for helpful comments on the manuscript.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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