Synthesis E. Srinivas et al. Paper

Stereoselective Total Synthesis of Cryptomoscatone F1

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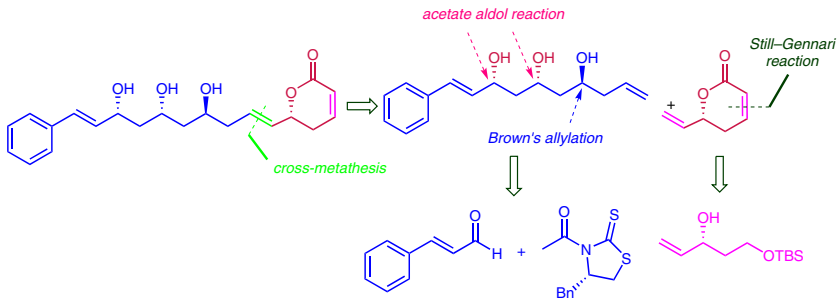

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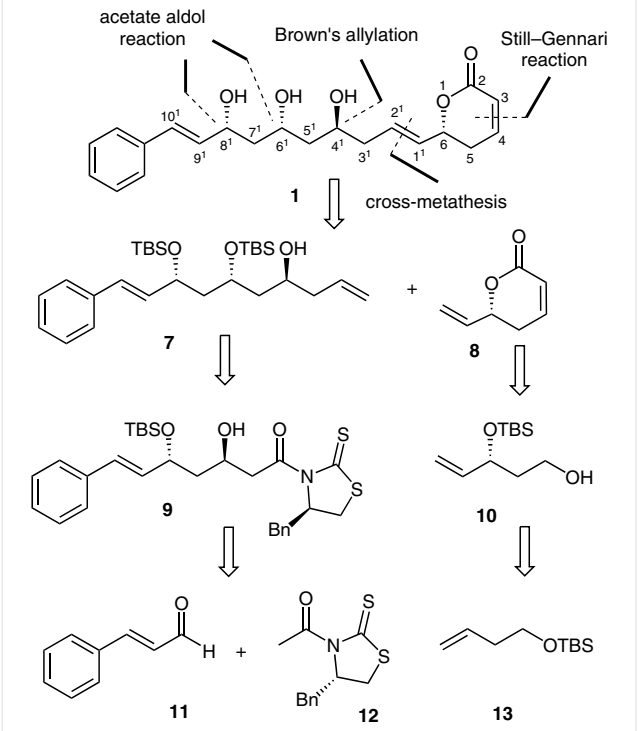
Abstract A concise stereoselective total synthesis of cryptomoscatone F1 has been accomplished by utilization of asymmetric acetate aldol reaction, Brown's asymmetric allylation, and olefin cross-metathesis as key transformations.

Key words cryptomoscatone F1, acetate aldol reaction, Brown's asymmetric allylation, olefin cross-metathesis

Naturally occurring 6-substituted 5,6-dihydro-α-pyrones have been observed in several botanical families and fungi species. Among them 6-(ω-arylalkenyl)-5,6-dihydro-α-pyrones bearing no substituent at C4 are characteristic of *Cryptocarya* species (Lauraceae).[1,2] These α-pyrones are structurally characterized by 5,6-dihydro-α-pyrone, 1,3-diol or 1,3,5-triol, and *trans*-styryl skeletons. Cryptomoscatone F1 (**1**, Figure 1), a class of 6-(ω-arylalkenyl)-5,6-dihydro-α-pyrones, has been isolated from branch and stem bark of *Cryptocarya* species such as *Cryptocarya mandiocanna*,[3] and *C. moschata* Lauraceae. Lactones isolated from these species have been shown to exhibit several biological activities such as anti-inflammatory,[4] antiproliferative activity,[5] and inhibition of the growth of breast-cancer cell lines.[6]

Thus, the interesting biological features and our ongoing research on the synthesis of biologically active lactone-containing natural products,[7,8] prompted us to explore the synthesis of cryptomoscatone F1 (**1**). Earlier we reported the synthesis of cryptomoscatone D2 (**4**), cryptomoscatone E1 (**2**), and (+)-cryptofolione (**5**).[8] Sabitha and Raju reported the first total synthesis of cryptomoscatone F1 (**1**)[9] and Ramesh et al. have also accomplished the synthesis of cryptomoscatone F1.[10] Herein we disclose a concise convergent strategy for the synthesis of cryptomoscatone F1.

Our retrosynthetic strategy is outlined in Scheme 1. Initial disconnection was made at the 1^1–2^1 *trans*-olefinic double bond of cryptomoscatone F1 (**1**) and the reconnection was planned via cross-metathesis[11] between the two key intermediates **7** and vinyl lactone **8**. While the key intermediate **7** could be synthesized from commercially available *trans*-cinnamaldehyde (**11**) by employing iterative acetate aldol reactions with (4*S*)-3-acetyl-4-benzylthiazolidine-2-thione (**12**) for the creation of two stereocenters fol-



Scheme 1 Retrosynthetic analysis of cryptomoscatone F1

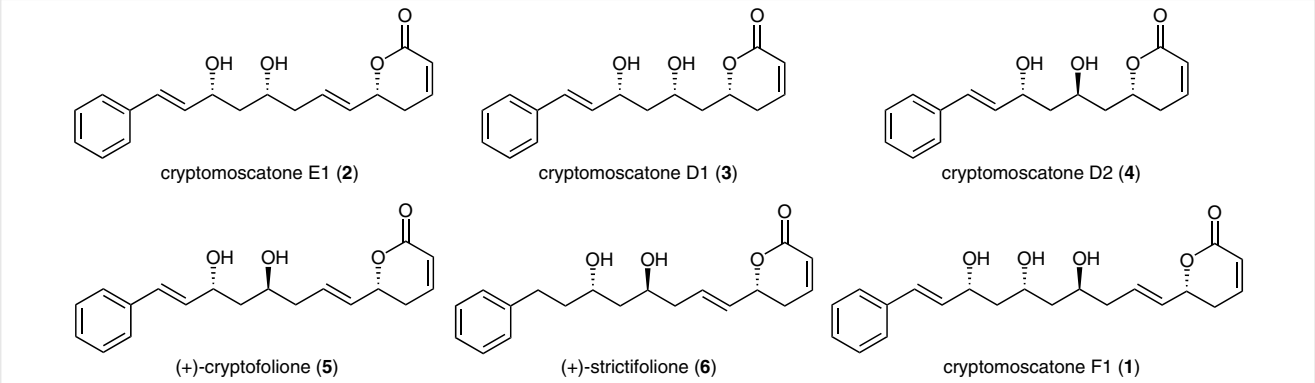
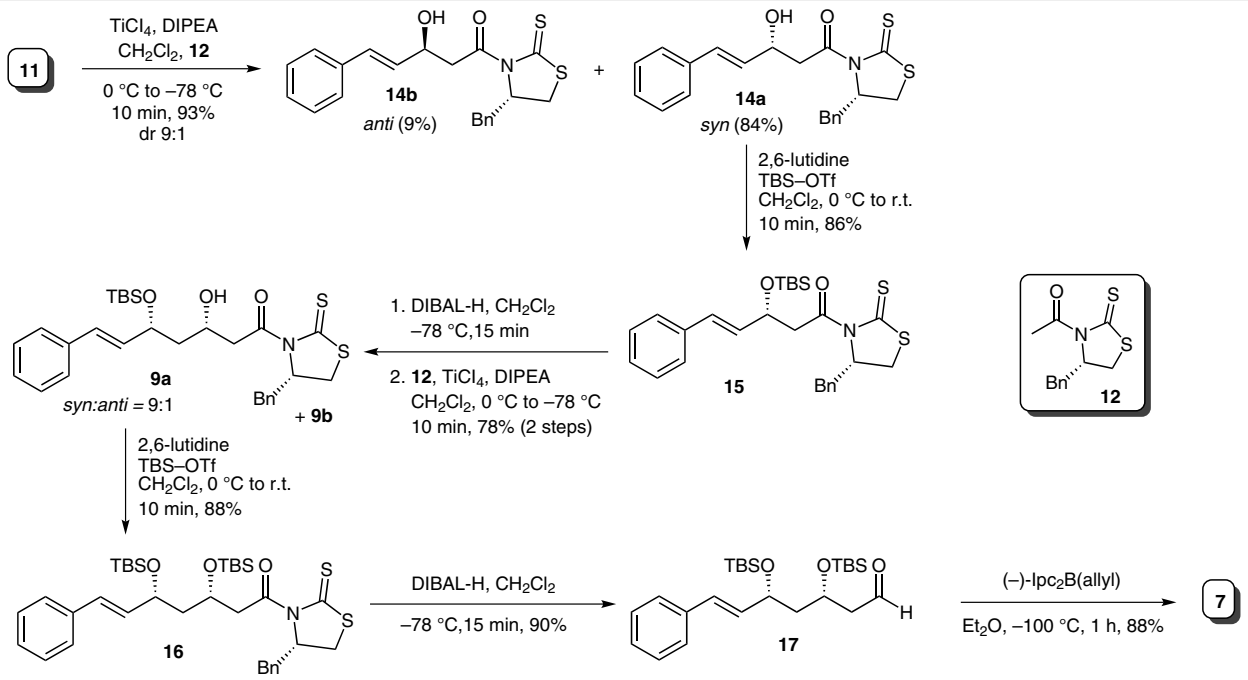


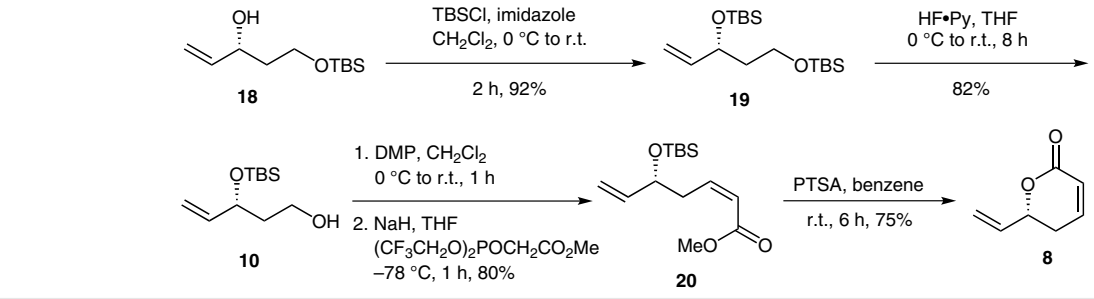
Figure 1 Natural products containing styrylpyrones

lowed by Brown's asymmetric allylation for the creation of an additional stereogenic center. Vinyl lactone **8** could be obtained from the known TBS ether[12] **13** of homoallyl alcohol using key reactions such as Jacobsen's kinetic resolution,[13] Still–Gennari olefination,[14] and finally lactonization.

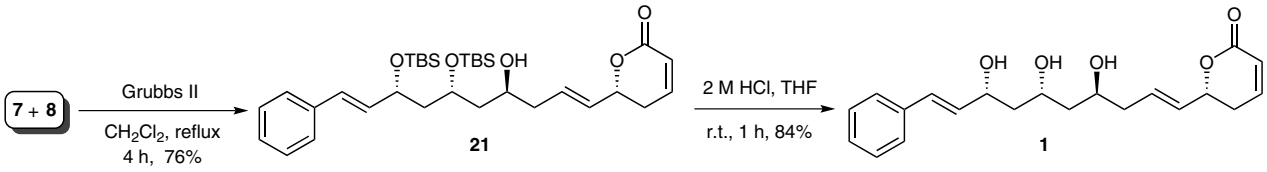
Our forward synthesis towards the total synthesis of cryptomoscatone F1 (**1**), started with titanium-mediated asymmetric acetate aldol[15b–e] addition reaction between *trans*-cinnamaldehyde (**11**) and (4*S*)-3-acetyl-4-benzylthiazolidine-2-thione (**12**)[15a] that produced column chromatographically separable diastereomers **14a** and **14b** in a 9:1 ratio (Scheme 2), the acetate aldol product **14a** was obtained in 84% isolated yield with high diastereoselectivity. Protection of the secondary hydroxy group in **14a** as its corresponding TBS ether was accomplished by the treatment with TBSOTf and 2,6-lutidine in dichloromethane at 0 °C to afford **15** in 86% yield. Reductive cleavage of the chiral auxiliary in compound **15** was achieved using DIBAL-H at –78 °C in dichloromethane to give an intermediate aldehyde that was used directly in the next step without further purification. Iteration of the acetate aldol reaction with aldehyde, obtained in the previous step, was carried out with auxiliary **12** in a similar way to afford **9a** as the major diastereomer (**9a**/**9b** 9:1 after chromatographic separation) in 78% yield over two steps. The secondary hydroxy group in compound **9a** was protected as its TBS ether to obtain **16** in 88% yield. Reductive removal of chiral auxiliary with DIBAL-H furnished aldehyde **17** in 90% yield, and the aldehyde was



Scheme 2 Synthesis of key intermediate **7**



Scheme 3 Synthesis of vinyl lactone



Scheme 4 Synthesis of cryptomoscatone F1

subjected to Brown's asymmetric allylation[16] with (–)-*B*-allyldiisopinocampheylborane [(–)-Ipc_2B(allyl)] in Et_2O at –100 °C to give the desired key intermediate **7** in 88% yield as a single diastereomer.

Vinyl lactone **8**, the cross-metathesis partner of **7**, was synthesized from the known chiral allyl alcohol **18**[12] (Scheme 3). Compound **18** was protected as its TBS ether using TBSCl and imidazole in CH_2Cl_2 to give disilylated compound **19** in 92% yield. The selective deprotection[17] of primary TBS ether was carried out with HF·Py in THF to afford primary alcohol **10** in 82% yield. Dess–Martin periodinane (DMP) oxidation of alcohol **10** gave the corresponding aldehyde, which was directly subjected to Still–Gennari reaction with methyl *P*,*P*-bis(2,2,2-trifluoroethyl) phosphonoacetate and NaH to furnish *cis*-olefinic ester **20** in 80% yield over two steps. Cyclization of the ester **20** was carried out with PTSA in benzene to afford vinyl lactone **8** in 75% yield.[18]

With the two key fragments **7** and **8** in hand, the next concern was to couple them by olefin cross-metathesis reaction (Scheme 4). Thus, the cross-metathesis reaction between olefins **7** and **8** (1:4) ratio in the presence of Grubbs II catalyst in CH_2Cl_2 at reflux for 4 hours gave the desired α,β-unsaturated δ-lactone **21** in 76% yield. Finally, the silyl groups in lactone **21** were deprotected upon treatment with 2 M HCl in THF to afford cryptomoscatone F1 (**1**) in 84% yield. The ^1H NMR and ^{13}C NMR spectra and optical rotation were found to be identical with the data from the literature.[9,10]

In conclusion, we have achieved a short and convergent synthesis of cryptomoscatone F1 in 9 steps involving asymmetric acetate aldol reactions, Brown's asymmetric allylation, and olefin cross-metathesis as key steps with an overall yield of 25%.

Unless otherwise mentioned, all reactions were carried out under an inert atmosphere of argon or N_2 using standard syringe, septa, and cannula techniques. Commercial reagents were used without further purification. All solvents were purified by standard techniques. IR spectra were recorded with a Perkin-Elmer 683 spectrophotometer with NaCl optics and the spectra were calibrated against the polystyrene absorption at 1610 cm^{-1}. Samples were scanned neat, as KBr wafers, or as a thin film in $CHCl_3$. Optical rotations were obtained with a Jasco DIP-360 digital polarimeter. NMR spectra were recorded in $CDCl_3$ with a Bruker 300, Varian Unity 500 NMR spectrometer. Column chromatographic separations were carried out on silica gel (60–120 mesh). Mass spectra were obtained on a Finnigan MAT1020B or micro mass VG 70-70H spectrometer operating at 70 eV using a direct inlet system.

(4*S*)-4-Benzyl-3-[(3*R*,4*E*)-3-hydroxy-5-phenylpent-4-enoyl]thiazolidine-2-thione (14a)

To a stirred solution of (4*S*)-3-acetyl-4-benzylthiazolidine-2-thione (**12**, 3.0 g, 11.95 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added $TiCl_4$ (1.57 mL, 14.34 mmol) dropwise. The yellow thick suspension was stirred for 10 min, and then DIPEA (2.4 mL, 14.34 mmol) was added dropwise at 0 °C. The mixture was stirred for 10 min at 0 °C, then cooled to –78 °C followed by the addition of freshly distilled *trans*-cinnamaldehyde (**11**, 1.6 mL, 11.95 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred for 10 min, quenched with sat. NH_4Cl and warmed to r.t. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried (anhyd Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 5% EtOAc–hexane) to furnish aldol product **14a** (3.87 g, 84%) as a yellow liquid and **14b** (0.39 g, 9%) as a yellow liquid; $[\alpha]_D^{25}$ +128.2 (*c* 1.34, $CHCl_3$).

IR (neat): 3391, 3026, 1688, 1344, 1162, 749, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.14 (m, 10 H), 6.65 (d, *J* = 15.4 Hz, 1 H), 6.24 (dd, *J* = 5.8, 15.4 Hz, 1 H), 5.36 (m, 1 H), 4.83 (br m, 1 H), 3.69 (dd, *J* = 17.3, 2.9 Hz, 1 H), 3.34–3.44 (m, 2 H), 3.24 (dd, *J* = 3.8, 12.5 Hz, 1 H), 3.04 (dd, *J* = 1.9, 10.6 Hz, 1 H), 2.88 (d, *J* = 11.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.3, 172.4, 136.4, 136.3, 130.6, 129.8, 129.4, 129.0, 128.5, 127.8, 127.3, 126.5, 68.6, 68.3, 45.7, 36.8, 32.1.

MS (ESI): *m*/*z* = 406 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{21}NO_2S_2Na$: 406.0911; found: 406.0906.

(4*S*)-4-Benzyl-3-[(3*R*,4*E*)-3-(*tert*-butyldimethylsiloxy)-5-phenylpent-4-enoyl]thiazolidine-2-thione (15)

2,6-Lutidine (1.3 mL, 11.2 mmol) was added to a solution of alcohol **14a**■■*OK?*■■ (3.3 g, 8.62 mmol) in anhyd CH_2Cl_2 (35 mL) at 0 °C. After 5 min, TBSOTf (3.0 mL, 12.92 mmol) was added dropwise and the mixture was stirred at 0 °C for 5 min. The mixture was quenched with sat. $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine solution, dried (anhyd Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 2% EtOAc–hexane) to give **15** (3.7 g, 86%) as a yellow solid; mp 78–79 °C; $[\alpha]_D^{25}$ +165.2 (*c* 1.28, $CHCl_3$).

IR (KBr): 3453, 2953, 2929, 2855, 1697, 1255, 1161, 834 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.16 (m, 10 H), 6.56 (d, *J* = 15.8 Hz, 1 H), 6.21 (dd, *J* = 6.8, 15.8 Hz, 1 H), 5.21 (m, 1 H), 4.97–4.86 (m, 1 H), 3.80–3.69 (m, 1 H), 3.36–3.16 (m, 3 H), 3.02 (dd, *J* = 2.3, 10.6 Hz, 1 H), 2.86 (d, *J* = 11.3 Hz, 1 H), 0.89 (s, 9 H), 0.11 (s, 3 H), 0.08 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.1, 171.3, 136.5, 131.7, 129.8, 129.3, 128.8, 128.5, 127.5, 127.1, 126.4, 70.5, 68.6, 46.7, 36.5, 32.1, 25.7, 18.0, –4.2, –4.9.

MS (ESI): *m*/*z* = 520 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{27}H_{35}NO_2S_2SiNa$: 520.1776; found: 520.1779.

(3*S*,5*R*,*E*)-1-[(*S*)-4-Benzyl-2-thioxothiazolidin-3-yl]-5-(*tert*-butyldimethylsiloxy)-3-hydroxy-7-phenylhept-6-en-1-one (9a)

To a stirred solution of **15** (2.7 g, 5.42 mmol) in anhyd CH_2Cl_2 (35 mL) at –78 °C was added a 25 wt% solution of DIBAL-H in toluene (7.3 mL, 10.84 mmol) dropwise over 10 min and the mixture was stirred at –78 °C for 10 min. The mixture was quenched with sat. aq sodium potassium tartrate solution (10 mL) and the mixture was stirred vigorously at r.t. for a further 1 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine solution, dried (anhyd Na_2SO_4), filtered, and concentrated under reduced pressure to give the crude aldehyde, which was used in the next step without further purification.

To a stirred solution of (4*S*)-3-acetyl-4-benzylthiazolidine-2-thione (**12**, 1.45 g, 5.78 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added $TiCl_4$ (0.7 mL, 6.35 mmol) dropwise. The thick yellow suspension was stirred for 10 min and then DIPEA (1.1 mL, 6.35 mmol) was added dropwise at 0 °C. The dark red solution was stirred for 10 min at 0 °C and then cooled to –78 °C. To the mixture was added a solution of the aldehyde (1.5 g, 5.78 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred for 15 min and then it was quenched with sat. aq NH_4Cl solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried (anhyd Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 5% EtOAc–hexane) to give **9a** as yellow solid (2.2 g, 78%, 2 steps); mp 92–93 °C; the diastereomer **9b** was also obtained (0.2 g, 7%, two steps); $[\alpha]_D^{25}$ –10.6 (*c* 0.48, $CHCl_3$).

IR (KBr): 3486, 2953, 2930, 2856, 1689, 1258, 1161, 835, 751 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.15 (m, 10 H), 6.54 (d, *J* = 15.9 Hz, 1 H), 6.17 (dd, *J* = 15.9, 7.3 Hz, 1 H), 5.39 (ddd, *J* = 10.6, 7.1, 3.9 Hz, 1 H), 4.59 (dd, *J* = 13.2, 7.0 Hz, 1 H), 4.43 (dd, *J* = 17.4, 9.6 Hz, 1 H), 3.71–3.14 (m, 5 H), 3.13–2.95 (m, 1 H), 2.88 (d, *J* = 11.6 Hz, 1 H), 1.99–1.83 (m, 1 H), 1.75 (ddd, *J* = 14.0, 5.5, 3.2 Hz, 1 H), 0.92 (s, 9 H), 0.10 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.2, 172.4, 136.5, 136.4, 132.0, 130.1, 129.4, 128.8, 128.5, 127.6, 127.2, 126.4, 73.3, 68.3, 66.4, 46.1, 44.2, 40.1, 36.7, 32.0, 25.8, 18.0, –3.9, –4.8.

MS (ESI): *m*/*z* = 564 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{29}H_{39}NO_3S_2SiNa$: 564.2038; found: 564.2034.

(3*S*,5*R*,*E*)-1-[(*S*)-4-Benzyl-2-thioxothiazolidin-3-yl]-3,5-bis(*tert*-butyldimethylsiloxy)-7-phenylhept-6-en-1-one (16)

2,6-Lutidine (0.28 mL, 2.41 mmol) was added to a solution of alcohol **9a**■■*OK?*■■ (1 g, 1.85 mmol) in anhyd CH_2Cl_2 (10 mL) at 0 °C. After 15 min, TBSOTf (0.64 mL, 2.78 mmol) was added dropwise and the mixture was stirred at 0 °C for 5 min. The mixture was quenched by the addition of sat. $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine solution, dried (anhyd Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 2% EtOAc–hexane) to give **16** (1.07 g, 88%) as a yellow liquid; $[\alpha]_D^{25}$ +116.4 (*c* 0.44, $CHCl_3$).

IR (KBr): 2955, 2928, 2854, 1703, 1364, 1255, 1157, 1070, 834 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.19 (m, 10 H), 6.54 (d, *J* = 15.9 Hz, 1 H), 6.19 (dd, *J* = 15.9, 6.7 Hz, 1 H), 5.24 (ddd, *J* = 10.6, 6.9, 3.8 Hz, 1 H), 4.55–4.44 (m, 1 H), 4.39 (dd, *J* = 12.8, 6.4 Hz, 1 H), 3.69–3.53 (m, 1 H), 3.38–3.19 (m, 3 H), 3.03 (dd, *J* = 13.0, 10.8 Hz, 1 H), 2.86 (d, *J* = 11.5 Hz, 1 H), 1.92 (td, *J* = 13.4, 6.7 Hz, 1 H), 1.82–1.69 (m, 1 H), 0.92 (d, *J* = 2.9 Hz, 9 H), 0.86 (s, 9 H), 0.11 (m, 6 H), 0.06 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.0, 172.0, 136.9, 136.6, 132.7, 129.6, 129.4, 128.9, 128.5, 127.4, 127.2, 126.4, 70.8, 68.7, 66.7, 46.4, 46.2, 36.5, 32.2, 25.9, 25.8, 18.2, 18.0, –4.1, –4.3, –4.5, –4.7.

MS (ESI): *m*/*z* = 679 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{35}H_{53}NO_3S_2Si_2Na$: 678.2903; found: 678.2891.

(4*S*,6*R*,8*R*,*E*)-6,8-Bis(*tert*-butyldimethylsiloxy)-10-phenyldeca-1,9-dien-4-ol (7)

A 25% solution of DIBAL-H in toluene (1.6 mL, 2.38 mmol) was slowly added over 5 min to a stirred solution of **16** (0.78 g, 1.19 mmol) in anhyd CH_2Cl_2 (10 mL) at –78 °C, and the mixture was stirred at –78 °C for 10 min. After completion of the reaction, sat. aq potassium sodium tartrate solution (5 mL) was added and the mixture was stirred vigorously at r.t. for additional 1 h. The mixture was then extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic layers were washed with brine solution (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 3% EtOAc–hexane) to give **17** (0.48 g, 90%) as a clear liquid.

To a stirred solution of 1.0 M solution of (–)-Ipc$_2$B(allyl) in pentane (0.6 mL, 0.62 mmol) and anhyd Et$_2$O (3 mL) at –100 °C was added a solution of the aldehyde **17** (0.250 g, 0.56 mmol) in Et$_2$O (5 mL) dropwise. The mixture was stirred at –100 °C for 1 h and then warmed to 0 °C. The mixture was quenched by dropwise addition of 30% aq H_2O_2 (1 mL) and 1 M aq NaOH (1 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic layers were washed with brine solution (6 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude product was purified by column chromatography (silica gel, 5% EtOAc–hexane) to give **7** (0.24 g, 88%) as a clear liquid; $[\alpha]_D^{25}$ +18.6 (*c* 0.46, $CHCl_3$).

IR (KBr): 3453, 2953, 2931, 2857, 1070, 834, 773 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.18 (m, 5 H), 6.48 (d, *J* = 15.9 Hz, 1 H), 6.13 (dd, *J* = 15.9, 6.9 Hz, 1 H), 5.83 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1 H), 5.11 (ddd, *J* = 9.9, 2.6, 1.5 Hz, 2 H), 4.37–4.27 (m, 1 H), 4.18–4.08 (m, 1 H), 3.89–3.79 (m, 1 H), 3.35 (s, 1 H), 2.33–2.17 (m, 2 H), 1.94–1.82 (m, 2 H), 1.65 (ddd, *J* = 14.7, 9.2, 4.7 Hz, 1 H), 1.52 (dt, *J* = 14.3, 9.2 Hz, 1 H), 0.91 (s, 9 H), 0.90 (s, 9 H), 0.13 (s, 6 H), 0.06 (s, 3 H), 0.03 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.7, 134.9, 132.8, 129.5, 128.5, 127.5, 126.3, 117.2, 71.0, 68.8, 67.7, 44.5, 42.3, 40.2, 25.8, 25.7, 18.1, 17.9, –3.9, –4.6, –4.8, –4.9.

MS (ESI): *m*/*z* = 513 [M + Na]$^+$.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{50}O_3Si_2Na$: 513.3196; found: 513.3178.

(*R*)-1,3-Bis(*tert*-butyldimethylsiloxy)pent-4-ene (19)

To a stirred solution of alcohol **18** (1.2 g, 5.55 mmol) in CH_2Cl_2 (12 mL) at 0 °C, imidazole (0.75 g, 11.11 mmol) and TBSCl (0.91 g, 6.11 mmol) were added and the mixture was stirred for 2 h at r.t. The mixture was diluted with CH_2Cl_2 and washed with water (20 mL), brine solution (15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, 4% EtOAc–hexane) to furnish bis(silyl ether) **19** (1.68 g, 92%) as a colorless liquid; $[\alpha]_D^{25}$ –2.5 (*c* 1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.86–5.76 (m, 1 H), 5.18–4.99 (m, 2 H), 4.27 (q, *J* = 6.1 Hz, 1 H), 3.72–3.60 (m, 2 H), 1.76–1.60 (m, 2 H), 0.89 (s, 18 H), 0.07–0.02 (m, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.6, 113.5, 70.7, 59.4, 41.1, 29.7, 25.9, 25.8, –4.4, –4.9, –5.3.

MS (ESI): *m*/*z* = 331 [M + H]$^+$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{39}O_2Si_2$: 331.2488; found: 331.2475.

(*R*)-3-(*tert*-Butyldimethylsiloxy)pent-4-en-1-ol (10)

To a stirred solution of **19** (1.5 g, 4.53 mmol) in THF (15 mL) at 0 °C was added HF·Py in THF (0.68 mL, 4.53 mmol) and the mixture was stirred for 8 h at r.t. The mixture was quenched with sat. $NaHCO_3$ solution (15 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The organic extract was washed with brine solution (10 mL), dried (Na_2SO_4), concentrated, and purified by column chromatography (silica gel, 6% EtOAc–hexane) to afford **10** (0.8 g, 82%) as a colorless liquid; $[\alpha]_D^{25}$ +5.6 (*c* 0.5, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.91–5.78 (m, 1 H), 5.26–5.10 (m, 2 H), 4.45–4.39 (m, 1 H), 3.87–3.78 (m, 1 H), 3.76–3.68 (m, 1 H), 2.49 (br s, 1 H), 1.90–1.80 (m, 1 H), 1.76–1.68 (m, 1 H), 0.90 (s, 9 H), 0.10 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.5, 114.3, 73.2, 60.0, 39.1, 25.8, –4.4, –5.0.

MS (ESI): *m*/*z* = 217 [M + H]$^+$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{25}O_2Si$: 217.1618; found: 217.1613.

Methyl (*Z*,*R*)-5-(*tert*-Butyldimethylsiloxy)hepta-2,6-dienoate (20)

To a stirred solution of alcohol **10** (0.24 g, 1.11 mmol) in dry CH_2Cl_2 (4 mL) was added Dess–Martin periodinane (0.710 g, 1.66 mmol) at 0 °C, and the mixture was stirred for 1 h at r.t. The mixture was quenched with sat. $Na_2S_2O_3$ and $NaHCO_3$ solns (1:1 mixture, 5 mL) and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with H_2O (10.0 mL) and brine (10.0 mL), dried (Na_2SO_4), and concentrated to furnish the corresponding aldehyde as a yellow liquid, which was directly used in the next reaction.

To a stirred solution of $(CF_3CH_2O)_2POCH_2CO_2Me$ (0.5 mL, 2.21 mmol) in anhyd THF (3 mL) was added NaH (66 mg, 1.66 mmol) at –78 °C. The temperature was raised to 0 °C and the mixture was stirred for 0.5 h. To the mixture, the aldehyde (0.237 g, 1.11 mmol) dissolved in THF (3 mL) was added at –78 °C. The mixture was stirred for 3 h at r.t.■■*–78 °C, 1 h in Sch.3*■■, quenched with sat. NH_4Cl solution (5 mL), and extracted with EtOAc (2 × 8 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), concentrated, and purified by column chromatography (silica gel, 5% EtOAc–hexane) to give **20** (0.24 g, 80% over 2 steps) as a yellow syrup; $[\alpha]_D^{25}$ –9.6 (*c* 1.5, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.34 (dt, *J* = 7.1, 4.4 Hz, 1 H), 5.88–5.76 (m, 2 H), 5.20 (dt, *J* = 3.2, 1.5 Hz, 1 H), 5.07 (dt, *J* = 3.0, 1.5 Hz, 1 H), 4.29–4.19 (m, 1 H), 3.71 (s, 3 H), 2.90–2.84 (m, 2 H), 0.89 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 146.3, 140.7, 120.5, 114.2, 72.5, 50.9, 37.1, 29.6, 25.7, –4.5, –4.9.

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

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{27}O_3Si$: 271.1729; found: 271.1718.

(*R*)-6-Vinyl-5,6-dihydro-2*H*-pyran-2-one (8)

To a stirred solution of **20** (0.25 g, 0.925 mmol) in distilled benzene was added a catalytic amount of PTSA and the mixture was stirred at r.t. for 6 h. Solid $NaHCO_3$ (0.02 g) was added to quench the PTSA and the mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by column chromatography (silica gel, 20% EtOAc–hexane) to afford vinyl lactone **8** (0.086 g, 75%) as a yellow liquid; $[\alpha]_D^{25}$ +91.3 (*c* 0.3, $CHCl_3$).

IR (neat): 1726, 1463, 1284, 1214 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.92–6.86 (m, 1 H), 6.08–6.04 (m, 1 H), 6.0–5.92 (m, 1 H), 5.41 (m, 1 H), 5.30 (m, 1 H), 4.97–4.90 (m, 1 H), 2.50–2.42 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.7, 144.3, 134.8, 121.6, 117.8, 77.7, 29.3.

MS (ESI): *m*/*z* = 125 [M + H]$^+$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_7H_9O_2$: 125.0602; found: 125.0595.

(*R*)-6-[(1*E*,4*S*,6*R*,8*R*,9*E*)-6,8-Bis(*tert*-butyldimethylsiloxy)-4-hydroxy-10-phenyldeca-1,9-dien-1-yl]-5,6-dihydro-2*H*-pyran-2-one (21)

To a stirred solution of homoallylic alcohol **7** (0.04 g, 0.082 mmol) and vinyl lactone **8** (0.04 g, 0.326 mmol) in dry CH_2Cl_2 under argon atmosphere, Grubbs II catalyst (7 mg, 10 mol%) was added. The resulting mixture was stirred at reflux for 4 h. After completion of the reaction,

the solvent was evaporated and the crude residue was purified by column chromatography (silica gel, 15% EtOAc–hexane) to afford **21** (0.036 g, 76%) as a dark brown oil; $[\alpha]_D^{25}$ +56.2 (*c* 2.0, $CHCl_3$).

IR (KBr): 3486, 2953, 2930, 2856, 1689, 1258, 1161, 835, 751 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.19 (m, 5 H), 6.93–6.82 (m, 1 H), 6.49 (d, *J* = 15.9 Hz, 1 H), 6.20–6.00 (m, 2 H), 5.97–5.82 (m, 1 H), 5.69 (dd, *J* = 15.5, 6.6 Hz, 1 H), 4.88 (dd, *J* = 14.5, 7.3 Hz, 1 H), 4.35–4.16 (m, 2 H), 4.05 (s, 1 H), 3.70 (dd, *J* = 13.8, 6.1 Hz, 1 H), 2.44 (dd, *J* = 8.1, 3.7 Hz, 2 H), 2.37–2.19 (m, 3 H), 2.02–1.75 (m, 3 H), 0.90 (d, *J* = 1.2 Hz, 18 H), 0.19–0.06 (m, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.9, 144.6, 136.7, 132.7, 131.6, 129.8, 129.3, 128.6, 127.6, 126.4, 121.6, 78.0, 71.0, 69.0, 67.8, 44.4, 40.8, 40.5, 29.7, 25.9, 25.8, 18.1, 17.9, –3.9, –4.6, –4.7, –4.8.

MS (ESI): *m*/*z* = 609 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{54}O_5Si_2Na$: 609.3427; found: 609.3402.

Cryptomoscatone F1 (1)

To a stirred solution of lactone **21** (15 mg, 0.026 mmol) in THF (1 mL) at 0 °C was added a few drops of 2 M HCl. The mixture was warmed to r.t. and then stirred for 3 h■■*1 h in Sch4*■■. The reaction was then quenched with sat. $NaHCO_3$ solution and layers were separated. The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic layers were washed with brine solution, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, 75% EtOAc–hexane) to give **1** (7 mg, 84%) as a brown liquid; $[\alpha]_D^{25}$ +31.4 (*c* 0.64, $CHCl_3$) {Lit.[9] $[\alpha]_D^{25}$ +35.0 (*c* 1.0, $CHCl_3$)}.

IR (neat): 3402, 2930, 2856, 1713, 1384, 1258, 1054, 751 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.21 (m, 5 H), 6.89 (ddd, *J* = 13.8, 9.6, 4.2 Hz, 1 H), 6.61 (d, *J* = 15.9 Hz, 1 H), 6.23 (dd, *J* = 15.9, 6.5 Hz, 1 H), 6.07–6.02 (m, 1 H), 5.93–5.85 (m, 1 H), 5.70 (dd, *J* = 15.4, 6.4 Hz, 1 H), 4.91 (dd, *J* = 14.9, 6.5 Hz, 1 H), 4.60 (t, *J* = 7.0 Hz, 1 H), 4.34–4.27 (m, 1 H), 4.05 (dd, *J* = 14.4, 9.4 Hz, 1 H), 2.47–2.41 (m, 2 H), 2.30 (dd, *J* = 15.2, 7.9 Hz, 2 H), 1.87 (dt, *J* = 14.4, 10.1 Hz, 1 H), 1.74–1.65 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.0, 144.7, 136.5, 131.6, 131.1, 130.3, 129.9, 128.6, 127.8, 126.5, 121.6, 77.8, 73.8, 70.0, 68.1, 42.9, 42.3, 40.3, 29.7.

MS (ESI): *m*/*z* = 358 $[M + H]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{26}O_5$: 358.2014; found: 358.2007.

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Supporting Information

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