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Total synthesis of cryptomoscatones D1 and D2: stereochemical assignment of cryptomoscatone D1

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ABSTRACT

The first total synthesis and structural elucidation of cryptomoscatone D1, and a novel synthetic approach for cryptomoscatone D2 were achieved in 30% and 29% overall yield, respectively. The synthesis relied on the use of a key Mukaiyama aldol reaction followed by a diastereoselective carbonyl reduction that allowed the preparation of four cryptomoscatone isomers in a stereochemically divergent manner. Comparison of NMR data and CD curves of the synthetic stereoisomers and natural products confirmed the stereochemical nature of cryptomoscatone D2, and led to establishing the absolute configuration of cryptomoscatone D1.

1. Introduction

The genus *Cryptocarya* comprises around 350 species distributed around the world with 18 of them described in South America.[1,2] Among the secondary metabolites isolated from these species, the dihydropyranones have been shown to display promising biological activities[3a] including inhibition of G2 checkpoint and of nuclear export.[3b] Recently, the total synthesis of natural dihydropyran-2-ones has been described in the literature.[3c,d]

Cryptocarya mandiocanna, is found in southeast Brazil and has been extensively studied.[4–6] In 2000, Cavalheiro and Yoshida reported the isolation from the bark of *C. mandiocanna* (first named as *Cryptocarya moschata*)[4,7] of several styrenic dihydropyran-2-ones with different lengths and degrees of oxidation of the unsaturated tether. However, they were not able to unambiguously establish the absolute configuration of the carbinolic stereocenters in the tether linking the dihydropyran-2-one and the styrenic moiety. Their relative configuration was suggested as 1,3-*anti* and 1,3-*syn* for cryptomoscatone D1 (**1**) (wrongly denominated as cryptofolione)[4] and D2 (**2**), respectively. The authors assigned the absolute configuration of the stereogenic center at the dihydropyran-2-one moiety (C-6) as *R* based on the observation of a positive Cotton effect on CD spectra (Fig. 1).

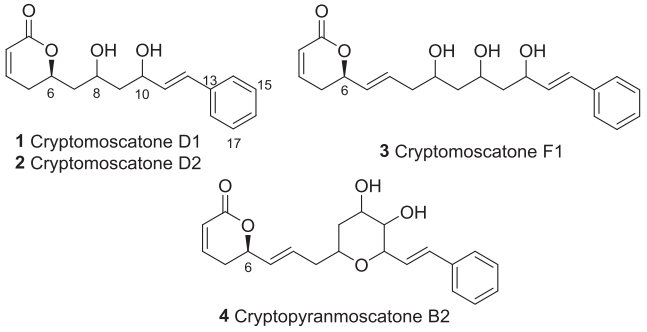

Fig. 1. Some dihydropyran-2-ones isolated from *C. mandiocanna* with unknown absolute configuration.

Recently, Yadav and co-workers reported the first total synthesis of cryptomoscatone D2 (**2**), together with the syntheses of (5*R*,7*S*)-kurzilactone and (+)-cryptofolione.[8] The two stereogenic centers of the tether linking the styrenic and dihydropyran-2-one moieties were generated by enantioselective $TiCl_4$-promoted thiazolidine-2-thione acetate aldol reactions while the one at C-6 was set in place by Brown's asymmetric allylation, which set the stage for the construction of the dihydropyran-2-one ring toward the end of the synthetic plan. Yadav and co-workers provided the specific optical rotation of synthetic cryptomoscatone D2 (**2**), while only the Cotton effect observed in the CD analysis was reported in the original

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publication of its isolation. Interestingly, the isomer claimed to be cryptomoscatone D2 (**2**) by Yadav and co-workers displayed *anti* relative configuration for the two carbinolic stereogenic centers present in the tether chain (Fig. 2) while Cavalheiro and Yoshida had originally assigned a *syn* relationship for this pair of stereogenic centers.[4]

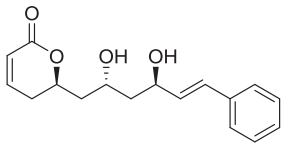


Fig. 2. Structure of cryptomoscatone D2 (**2**) as established by Yadav and co-workers.[8]

Considering the difference in the ^{13}C NMR chemical shifts observed for natural and synthetic cryptomoscatone D2 (**2**), particularly for the stereogenic centers at C-8 and C-10 (Fig. 3) and the absence so far of a total synthesis of cryptomoscatone D1 (**1**), which would allow to unravel its absolute configuration, we decided to synthesize the four stereoisomers of the aforementioned cryptomoscatones bearing *R* configuration at the dihydropyran-2-one stereogenic center (C-6) for comparison with the spectral data of natural compounds.[4]

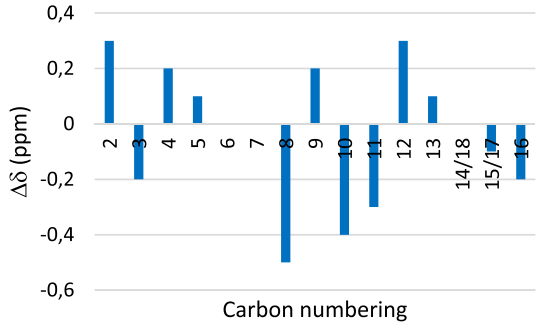
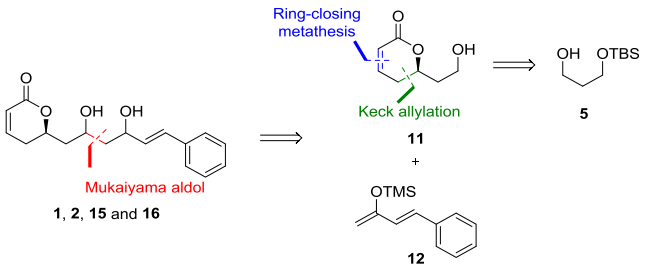


Fig. 3. Comparison of the ^{13}C NMR data ($\Delta\delta$) of natural and Yadav's synthetic cryptomoscatone D2 (**2**).[8]

2. Results and discussion

Assuming the absolute stereochemistry at C-6 as *R*, we planned a divergent strategy based on the coupling of two fragments by a Mukaiyama aldol reaction followed by a diastereoselective carbonyl reduction in order to access the four cryptomoscatone isomers (Scheme 1).



Scheme 1. Retrosynthetic plan for cryptomoscatones D1, D2, and isomers.

Our synthesis began with the preparation of alcohol **11**. Swern oxidation of commercially available alcohol **5**, followed by asymmetric allylation under Keck's conditions[9] provided allylic alcohol **7** in 78% overall yield (two steps) and 95:5 enantiomeric ratio. The stereochemistry of the major isomer was assigned as *R* after preparation of the corresponding α-methoxy(trifluoromethyl)phenylacetic (MTPA) esters and application of Mosher's model (Scheme 2).[10] Lactone **10** was readily prepared after conversion of homoallylic alcohol **7** to the corresponding acrylate **9**, followed by ring-closing metathesis with first generation Grubbs catalyst[11] in 76% overall yield. Deprotection of the silyl ether group of lactone **10** furnished the desired alcohol **11** (80% yield), which was synthesized from alcohol **5** in five steps and 47% overall yield (Scheme 2).

Silyl enol ether **12** was prepared from the corresponding methylketone as described by Jung and Novack,[12] and the Mukaiyama aldol reaction was performed with freshly prepared aldehyde derived from the oxidation of alcohol **11** using Dess–Martin periodinane under similar conditions to those described by Yadav and co-workers.[13] The Lewis acid employed was $BF_3{\cdot}Et_2O$[13] at −50 °C, and after 4 h at the same temperature, the reaction yielded diastereoisomers **13** and **14** in 90% yield from alcohol **11**, in a 70:30 *anti*/*syn* ratio (Scheme 3). After separation by semi-preparative HPLC, the NMR data of **13** and **14** were shown to be identical to those described by Jiang and Chen[14] for kurzilactone and its epimer at C-8.

The two dihydropyran-2-ones **13** and **14** underwent stereoselective carbonyl reduction to provide the four possible diastereoisomers (**1**, **2**, **15**, and **16**) displaying *R* configuration at C-6 (Scheme 4). Reduction of ketone **13** under chelation control using the protocol by Prasad et al. ($LiBH_4$, Et_2BOMe)[15] afforded *syn* diols **1** and **16** in excellent yield and diastereoselectivity (Scheme 4). The *syn* relative configuration was confirmed upon converting alcohols **1** and **16** into the corresponding 2,2-dimethyl ketals **17** and **18**, respectively (Scheme 5). Inspection of their ^{13}C NMR spectra revealed a significant chemical shift difference for the two methyl groups in the ketal groups ($\Delta\delta \approx 10$ ppm), which is in full agreement with Rychnovsky's model[16,17] for a 1,3-*syn* relationship of the diols in dihydropyran-2-ones **1** and **16**. Additionally, NOESY experiments revealed the expected correlations between H_a, H_b, and H_c for acetonide **17** and between $H_{a'}$, $H_{b'}$, and $H_{c'}$ for acetonide **18** (Scheme 5).

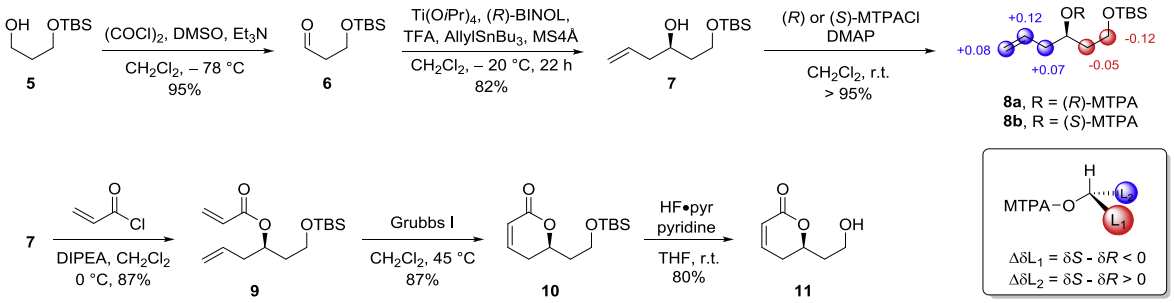
A directed hydride transfer using the protocol by Evans et al.[18] provided *anti* diols **2** and **15** also in excellent yield and selectivity (Scheme 4).

Comparison of the ^1H and ^{13}C NMR spectra of the four diol diastereoisomers with the data available for natural cryptomoscatone D2, revealed that the spectroscopic data for synthetic **2** nicely fit the one reported for the natural product, while the differences in the ^{13}C chemical shifts for stereoisomers **1**, **15**, and **16** could not be reconciled with the data of the natural product (Fig. 4).

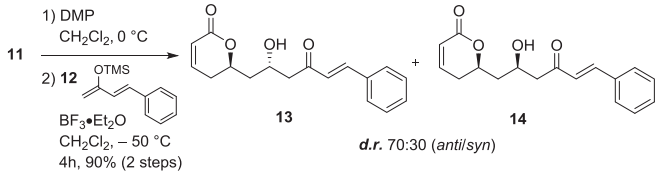
Our results therefore confirm the absolute configuration established by Yadav et al. for cryptomoscatone D2 (6*R*,8*R*,10*R*-**2**).[8]

As to cryptomoscatone D1, comparison of ^{13}C NMR data of the synthetic 1,3-diols with those of the natural product revealed that the ^{13}C NMR for synthetic **1** nicely fit the data reported for cryptomoscatone D1 except for the carbonyl carbon. A close inspection of the original ^{13}C NMR spectrum for natural cryptomoscatone D1 revealed that the carbonyl signal was originally misassigned, as it was not possible to distinguish it from the baseline noise[21] On the other hand, large differences in the ^{13}C NMR chemical shifts were observed for diastereoisomers **2**, **15**, and **16**, particularly for C-6, C-8, and C-10 (Fig. 5). Therefore, cryptomoscatone D1 (**1**) should be assigned the 6*R*,8*R*,10*S* absolute configuration.

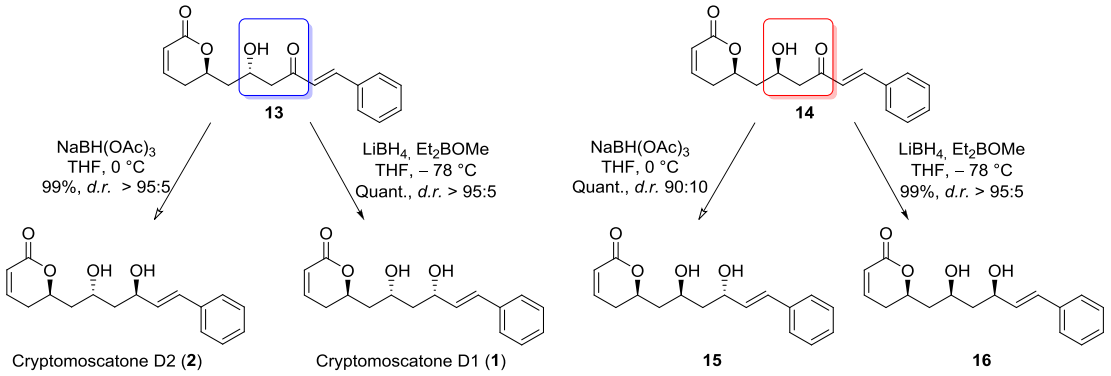
Synthetic cryptomoscatones D1 (**1**) and D2 (**2**) also displayed positive Cotton effects at 254–272 nm, in accordance with those described for the correspondent natural products (see Supplementary data for CD spectra).[4]



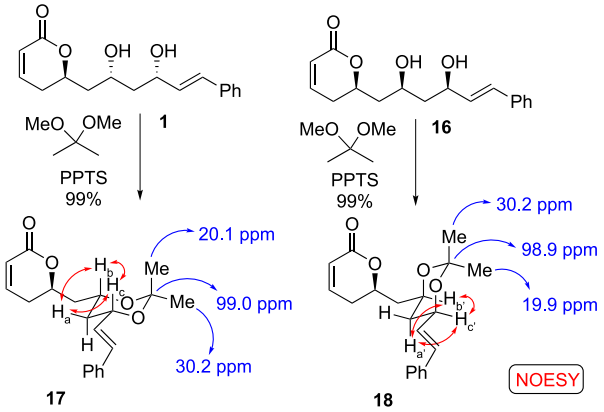
Scheme 2. Preparation of alcohol **11**.



Scheme 3. Preparation of *anti*-kurzilactone (**13**) and *syn*-kurzilactone (**14**).



Scheme 4. 1,3-Reduction of aldol adducts **13** and **14**.



Scheme 5. Preparation of cyclic acetals **17** and **18** and some NOESY correlation.

3. Conclusions

A straightforward synthesis of the natural products cryptomoscatones D1 (**1**) and D2 (**2**) has been developed. An eight-step synthesis, involving an asymmetric allylation, ring-closing metathesis, and a Mukaiyama aldol reaction furnished the natural products in 30% and 29% overall yield, respectively. Comparison of the NMR and CD spectra of the natural products with the four synthetic diastereoisomers unequivocally established the 6*R*,8*R*,10*S* configuration for cryptomoscatone D1 (**1**) and confirmed the 6*R*,8*R*,10*R* configuration of cryptomoscatone D2 (**2**), as proposed by Yadav and co-workers.

4. Experimental section

4.1. General

Starting materials and reagents were obtained from commercial sources and used as received unless otherwise specified. Dichloromethane was treated with calcium hydride and distilled before use. Tetrahydrofuran was treated with metallic sodium and benzophenone and distilled before use. Anhydrous reactions were carried out with continuous stirring under atmosphere of dry nitrogen. Progress of the reactions was monitored by thin-layer chromatography (TLC) analysis (Merck, silica gel 60 F^{254} on aluminum plates). ^{1}H NMR and ^{13}C NMR were recorded on Bruker 250, 500, or 600, the chemical shifts (δ) were reported in parts per million (ppm) relative to deuterated solvent as the internal standard ($CDCl_3$ 7.26 ppm, 77.00 ppm), coupling constants (J) are in hertz (Hz). Mass spectra were recorded on a Waters Xevo Q-Tof apparatus operating in electrospray mode (ES). Infrared spectra with Fourier transform (FTIR) were recorded on a Therm Scientific Nicolet iS5, the principal absorptions are listed in cm^{-1}. The values of optical rotation were measured at 25 °C in a polarimeter Perkin–Elmer 341, with sodium lamp, the measure is described as follow $[\alpha]_D$ (c (g/100 mL), solvent). IUPAC names of the compounds were generated using ChemBioDraw Ultra 13.0. The HPLC analyses

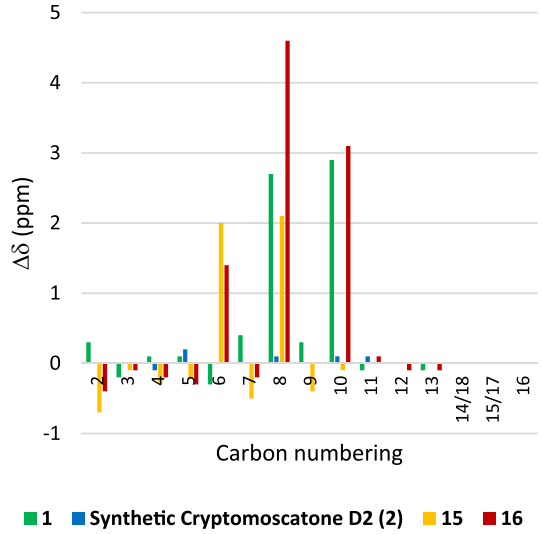


Fig. 4. Comparison of the ^{13}C NMR data ($\Delta\delta$) of natural and synthetic cryptomoscatone D2 (**2**) and its diastereoisomers **1**, **15**, and **16**.

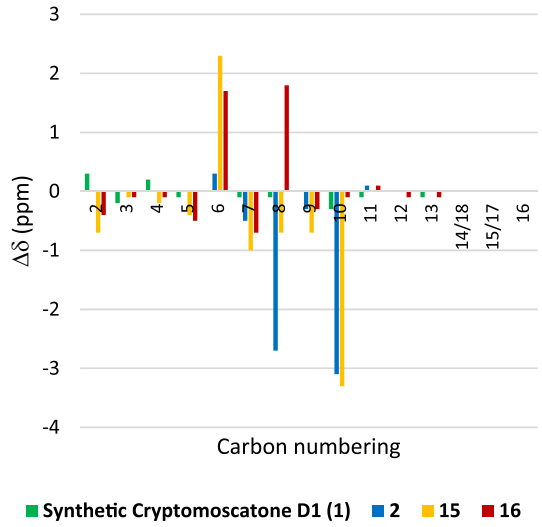


Fig. 5. Comparison of the ^{13}C NMR data ($\Delta\delta$) of natural and synthetic cryptomoscatone D1 (**1**) and its diastereoisomers **2**, **15**, and **16**.

were carried out using Waters 2695 Alliance® equipment. Semi-preparative HPLC was performed on Waters 1525, all experiments were realized at room temperature with a photodiode array detector. NMR spectra were processed using ACD/NMR Processor Academic Edition version 12.01. The circular dichroism (CD) analyses were performed on J720-Jasco ORD 306 spectropolarimeter, using methanol as solvent.

4.2. 3-((*tert*-Butyldimethylsilyl)oxy)propanal (6)

DMSO (2.13 mL, 30 mmol, 1.5 equiv) was added to a solution of oxalyl chloride (2.25 mL, 26 mmol, 1.3 equiv) in CH_2Cl_2 (90 mL) at −78 °C, the mixture was stirred for 15 min and then a solution of alcohol **5** (3807 mg, 20 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added to the reaction at −78 °C and the mixture was stirred for 1 h. Triethylamine (13 mL) was added to the reaction at −78 °C and the cooling bath was removed. After the mixture reach room temperature, it was diluted with Et_2O (50 mL) and the organic phase was washed with water (50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated. The product was purified by flash chromatography (hexanes/EtOAc 95:5) to furnish the aldehyde (3570 mg, 19 mmol, 95% yield) as a colorless oil. R_f 0.50 (hexanes/EtOAc 90:10). ^1H NMR (250 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.85 (s, 9H), 2.56 (td, J=5.8, 1.9 Hz, 2H), 3.95 (t, J=6.0 Hz, 2H), 9.77 (d, J=1.6 Hz, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −5.5 ($2CH_3$), 18.1 (C), 25.7 ($3CH_3$), 46.5 (CH_2), 57.3 (CH_2), 201.8 (CH).

4.3. (*R*)-1-((*tert*-Butyldimethylsilyl)oxy)hex-5-en-3-ol (7)

In a flask were added crushed molecular sieves 4 Å (7.5 g), (*R*)-BINOL (630 mg, 2.2 mmol, 0.2 equiv), CH_2Cl_2 (15 mL), TFA (2.5 μL, 33 μmol, 3 mequiv), and Ti(O*i*Pr)$_4$ (336 μL, 1.1 mmol, 0.1 equiv), this mixture was refluxed for 1 h to result a dark red suspension that was cooled to rt. A solution of aldehyde **6** (2134 mg, 11.3 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added to the dark red mixture via cannula, this mixture was stirred for 10 min at rt and it was cooled to −50 °C, then allyltributylstannane (5.27 mL, 16.5 mmol, 1.5 equiv) was added dropwise and the temperature was slowly increased to −20 °C. The reaction was stirred for 22 h, then brine (30 mL) was added and the mixture was stirred at rt for 1 h. The molecular sieves were removed by filtration, the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2×30 mL). The organic phases were combined, dried (Na_2SO_4), and concentrated. The product was purified by flash chromatography (hexanes/EtOAc 90:10) to furnish the alcohol (2075 mg, 9.0 mmol, 82% yield) as a colorless oil. R_f 0.34 (hexanes/EtOAc 90:10). $[\alpha]_D^{25}$ +7 (*c* 1.0, $CHCl_3$), $[\alpha]_{D,lit}^{25}$ +7.8 (*c* 1, $CHCl_3$).[19] ^1H NMR (250 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.88 (s, 9H), 1.62–1.69 (m, 2H), 2.21–2.27 (m, 2H), 3.32 (d, J=2.2 Hz, 1H), 3.74–3.92 (m, 3H), 5.05–5.12 (m, 2H), 5.83 (ddt, J=17.1, 10.2, 7.1 Hz, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −5.6 ($2CH_3$), 18.1 (C), 25.8 ($3CH_3$), 37.8 (CH_2), 41.9 (CH_2), 62.5 (CH_2), 71.1 (CH), 117.2 (CH_2), 135.0 (CH).

4.4. (*R*)-1-((*tert*-Butyldimethylsilyl)oxy)hex-5-en-3-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (8a)

DMAP (9.3 mg, 75 μmol, 1.5 equiv) was added to a solution of alcohol **7** (11.5 mg, 50 μmol, 1 equiv) in CH_2Cl_2 (1 mL) at rt, then (*S*)-(+)-MTPA chloride (14.2 μL, 75 μmol, 1.5 equiv) was added to the reaction and the mixture was stirred for one day at the same temperature. The product was directly purified by flash chromatography (hexanes/EtOAc 90:10) to furnish the ester (21.2 mg, 47.4 μmol, 95% yield) as a colorless oil. R_f 0.51 (hexanes/EtOAc 90:10). $[\alpha]_D^{25}$ −2 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.89 (s, 9H), 1.80–1.90 (m, 2H), 2.35–2.47 (m, 2H), 3.54 (s, 3H), 3.61–3.69 (m, 2H), 5.01–5.06 (m, 2H), 5.28–5.35 (m, 1H), 5.66 (ddt, J=17.2, 9.9, 7.2 Hz, 1H), 7.36–7.42 (m, 3H), 7.52–7.56 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.4 ($2CH_3$), 18.2 (C_0), 25.9 ($3CH_3$), 36.2 (CH_2), 38.3 (CH_2), 55.4 (CH_3), 59.0 (CH_2), 73.8 (CH), 84.6 (q, J^{C-F}=27 Hz, C), 118.5 (CH_2), 123.4 (q, J^{C-F}=289 Hz, C_0), 127.5 (CH), 128.3 (2CH), 129.5 (2CH), 132.3 (C), 132.7 (CH), 166.1 (C). ^{19}F NMR (235 MHz, $CDCl_3$) δ −71.4. IR (film, NaCl) 776, 835, 1019, 1099, 1169, 1257, 1746, 2857, 2929, 2954 cm^{-1}. HRMS $[C_{22}H_{33}O_4F_3Si+H]^+$ calculated 447.2178, found 447.2171.

4.5. (*R*)-1-((*tert*-Butyldimethylsilyl)oxy)hex-5-en-3-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (8b)

DMAP (9.3 mg, 75 μmol, 1.5 equiv) was added to a solution of alcohol **7** (11.5 mg, 50 μmol, 1 equiv) in CH_2Cl_2 (1 mL) at rt, then (*R*)-(−)-MTPA chloride (14.2 μL, 75 μmol, 1.5 equiv) was added to the reaction at rt and the mixture was stirred for one day at the same temperature. The product was directly purified by flash chromatography (hexanes/EtOAc 90:10) to furnish the ester (21.3 mg, 47.6 μmol, 95% yield) as a colorless oil. R_f 0.51 (hexanes/EtOAc 90:10). R_f 0.51 (hexanes/EtOAc 90:10). $[\alpha]_D^{25}$ −62 (*c* 0.5, $CHCl_3$). ^1H

NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.01 (s, 3H), 0.87 (s, 9H), 1.80 (q, J=6.5 Hz, 2H), 2.42–2.52 (m, 2H), 3.47–3.57 (m, 2H), 3.55 (s, 3H), 5.09–5.14 (m, 2H), 5.32 (quint, J=6.4 Hz, 1H), 5.77 (ddt, J=16.8, 10.7, 7.2 Hz, 1H), 7.36–7.41 (m, 3H), 7.53–7.56 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.4 ($2CH_3$), 18.2 (C), 25.9 ($3CH_3$), 36.3 (CH_2), 38.6 (CH_2), 55.5 (CH_3), 58.9 (CH_2), 73.9 (CH), 84.5 (q, J^{C-F}=27 Hz, C), 118.5 (CH_2), 123.4 (q, J^{C-F}=289 Hz, C), 127.4 (CH), 128.3 (2CH), 129.5 (2CH), 132.4 (C), 133.1 (CH), 166.1 (C). ^{19}F NMR (235 MHz, $CDCl_3$) δ −71.3. IR (film, NaCl) 834, 1019, 1098, 1169, 1182, 1747, 2856, 2929, 2955 cm^{-1}. HRMS $[C_{22}H_{33}O_4F_3Si+H]^+$, calculated 447.2178, found 447.2181.

4.6. (*R*)-1-((*tert*-Butyldimethylsilyl)oxy)hex-5-en-3-yl acrylate (9)

DIPEA (1.41 mL, 8 mmol, 2 equiv) was added to a solution of alcohol **7** (922 mg, 4 mmol, 1 equiv) in CH_2Cl_2 (40 mL) at 0 °C, then acryloyl chloride (0.51 mL, 6 mmol, 1.5 equiv) was added to the reaction at 0 °C and the mixture was stirred for 3 h at the same temperature. Brine (40 mL) was added, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (40 mL). The organic phases were combined, dried (Na_2SO_4), and concentrated. The product was purified by flash chromatography (hexanes/EtOAc 90:10) to furnish the acrylate (986 mg, 3.47 mmol, 87% yield) as a colorless oil. R_f 0.69 (hexanes/EtOAc 90:10). $[\alpha]_D^{25}$ −33 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.86 (s, 9H), 1.77–1.83 (m, 2H), 2.32–2.42 (m, 2H), 3.64 (td, J=6.4, 2.9 Hz, 2H), 5.03–5.08 (m, 2H), 5.10 (qt, J=6.3 Hz, 1H), 5.75 (ddt, J=17.1, 10.1, 7.1 Hz, 1H), 5.78 (dd, J=10.4, 1.4 Hz, 1H), 6.08 (dd, J=17.3, 10.6 Hz, 1H), 6.36 (dd, J=17.3, 1.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.5 ($2CH_3$), 18.2 (C), 25.8 ($3CH_3$), 36.5 (CH_2), 38.7 (CH_2), 59.3 (CH_2), 70.9 (CH), 117.8 (CH_2), 128.8 (CH), 130.3 (CH_2), 133.5 (CH), 165.6 (C). IR (film, NaCl) 776, 836, 1096, 1293, 1406, 1726, 2857, 2929, 2956 cm^{-1}. HRMS $[C_{15}H_{28}O_3Si+Na]^+$, calculated 307.1705, found 307.1687.

4.7. (*R*)-6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-5,6-dihydro-2*H*-pyran-2-one (10)

Grubbs' catalyst first generation (237 mg, 0.28 mmol, 0.1 equiv) was added to a solution of acrylate **9** (882 mg, 3.1 mmol, 1 equiv) in CH_2Cl_2 (300 mL) at 40 °C, the mixture was stirred at the same temperature for 3 h, then the solvent was removed in vacuo. The product was purified by flash chromatography (hexanes/EtOAc 75:25) to furnish the lactone (688 mg, 2.68 mmol, 87% yield) as a brown oil. R_f 0.50 (hexanes/EtOAc 75:25). $[\alpha]_D^{25}$ +50 (*c* 1.24, $CHCl_3$), $[\alpha]_{D,lit}^{25}$ +44.9 (*c* 0.98, $CHCl_3$).[20] ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.85 (s, 9H), 1.77–2.03 (m, 2H), 2.32–2.38 (m, 2H), 3.69–3.85 (m, 2H), 4.53–4.64 (m, 1H), 5.98 (dt, J=9.8, 1.8 Hz, 1H), 6.86 (dt, J=9.6, 4.3 Hz, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −5.5 ($2CH_3$), 18.1 (C), 25.8 ($3CH_3$), 29.5 (CH_2), 37.7 (CH_2), 58.3 (CH_2), 75.0 (CH), 121.3 (CH), 145.2 (CH), 164.3 (CH).

4.8. (*R*)-6-(2-Hydroxyethyl)-5,6-dihydro-2*H*-pyran-2-one (11)

A solution of HF·pyridine (1.91 mL) and pyridine (4.15 mL, 51.2 mmol, 16 equiv) in THF (10 mL) was added to a solution of silyl ether **10** (821 mg, 3.2 mmol, 1 equiv) in THF (25 mL) at 0 °C, the mixture was stirred for 4 h at rt. Saturated aqueous solution of $NaHCO_3$ (30 mL) was added to the reaction and the mixture was extracted with EtOAc (10×30 mL). The organic phases were combined, dried (Na_2SO_4), and concentrated. The product was purified by flash chromatography (EtOAc) to furnish the alcohol (365 mg, 2.6 mmol, 80% yield) as a colorless oil. R_f 0.36 (EtOAc). $[\alpha]_D^{25}$ +90 (*c* 1.0, $CHCl_3$), $[\alpha]_{D,lit}^{25}$ +119.6 (*c* 0.54, $CHCl_3$).[20] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.78–1.81 (m, 1H), 1.88–1.91 (m, 1H), 2.24–2.35 (m, 2H), 3.32 (br s, 1H), 3.65–3.73 (m, 2H), 4.53–4.58 (m, 1H), 5.88 (d, J=9.8 Hz, 1H), 6.83 (ddd, J=9.3, 5.5, 2.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.2 (CH_2), 37.1 (CH_2), 57.6 (CH_2), 75.3 (CH), 120.6 (CH), 145.8 (CH), 164.6 (C).

4.9. (*E*)-Trimethyl((4-phenylbuta-1,3-dien-2-yl)oxy)silane (12)[12]

Triethylamine (0.77 mL, 5.5 mmol, 2.6 equiv) was added to a solution of (*E*)-4-phenyl-3-buten-2-one (310 mg, 2.1 mmol, 1 equiv) in THF (5 mL) at 0 °C, the mixture was stirred for 5 min and then TMSOTf (0.54 mL, 2.9 mmol, 1.4 equiv) was added to the reaction at 0 °C and the mixture was stirred for 3 h at the same temperature. A mixture of Et_2O (20 mL) and pH 7 buffer solution (20 mL) was added, then the temperature was increased to rt. The organic phase was separated and washed with pH 7 buffer solution (3×20 mL). The organic phase was dried ($MgSO_4$) and concentrated. The product was purified by flash chromatography (hexanes) to furnish the silyl enol ether (380 mg, 1.7 mmol, 83% yield) as a colorless oil. R_f 0.90 (hexanes/EtOAc 90:10). ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.36 (s, 9H), 4.52 (d, J=9.0 Hz, 2H), 6.65 (d, J=15.8 Hz, 1H), 6.90 (d, J=15.6 Hz, 1H), 7.26–7.41 (m, 3H), 7.46–7.51 (m, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 0.1 ($3CH_3$), 97.0 (CH_2), 126.5 (CH), 126.8 (2CH), 127.7 (CH), 128.6 (2CH), 129.3 (CH), 136.8 (C), 155.1 (C).

4.10. (*R*)-6-((*S*,*E*)-2-Hydroxy-4-oxo-6-phenylhex-5-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (13) and (*R*)-6-((*R*,*E*)-2-hydroxy-4-oxo-6-phenylhex-5-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (14)

Dess–Martin periodinane (603 mg, 1.4 mmol, 1.4 equiv) was added to a solution of alcohol **11** (142 mg, 1 mmol, 1 equiv) in CH_2Cl_2 (5 mL) at 0 °C. The reaction was stirred at 0 °C for 2 h and then aqueous solution of $NaHCO_3$ (1 mL) and $Na_2S_2O_3$ (1 mL) was added. The mixture was extracted with CH_2Cl_2 (2×25 mL), the organic phases were combined, dried (Na_2SO_4), and concentrated at 100 mbar and rt. After solvent removal, the crude aldehyde was immediately diluted in dry CH_2Cl_2 (20 mL) and this solution was transferred via cannula to a solution of silyl enol ether **12** (437 mg, 2 mmol, 2 equiv) in CH_2Cl_2 (20 mL) at −50 °C. Then $BF_3{\cdot}Et_2O$ was added to the mixture and the reaction was stirred at the same temperature for 4 h. Aqueous solution of $NaHCO_3$ (20 mL) was added and the mixture was extracted with CH_2Cl_2 (2×30 mL), the organic phases were combined, dried (Na_2SO_4), and concentrated. The products were purified by flash chromatography (hexanes/EtOAc 60:40 to EtOAc) to furnish the mixture of diastereoisomers **13**/**14** in a ratio 70:30 (257 mg, 0.9 mmol, 90% yield) as a colorless oil. The two diastereoisomers were separated by semi-preparative HPLC using a column of C18 and water/CH_3CN 75:25 as eluent. Compound **13**: R_f 0.34 (hexanes/EtOAc 30:70). t_R (HPLC/C18) 26.6 min. $[\alpha]_D^{25}$ +62 (*c* 1.0, $CHCl_3$), $[\alpha]_{D,lit}^{25}$ +84 (*c* 0.231, $CHCl_3$).[14] ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.75–1.95 (m, 2H), 2.27–2.46 (m, 2H), 2.79 (dd, J=17.4, 8.7 Hz, 1H), 2.92 (dd, J=17.4, 3.2 Hz, 1H), 3.61 (br s, 1H), 4.43–4.52 (m, 1H), 4.70–4.81 (m, 1H), 6.00 (dt, J=9.8, 0.9 Hz, 1H), 6.71 (d, J=16.3 Hz, 1H), 6.87 (ddd, J=9.6, 5.4, 3.0 Hz, 1H), 7.36–7.41 (m, 3H), 7.50–7.61 (m, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 29.9 (CH_2), 41.7 (CH_2), 46.9 (CH_2), 64.0 (CH), 74.9 (CH), 121.3 (CH), 126.1 (CH), 128.5 (2CH), 129.0 (2CH), 130.9 (CH), 134.1 (C), 143.9 (CH), 145.4 (CH), 164.3 (C), 200.4 (C). Compound **14**: R_f 0.34 (hexanes/EtOAc 30:70). t_R (HPLC/C18) 24.9 min. $[\alpha]_D^{25}$ +40 (*c* 1.0, $CHCl_3$), *ent*-**14** $[\alpha]_{D,lit}^{25}$ −60.8 (*c* 1.0, $CHCl_3$).[14] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.93 (ddd, J=14.3, 6.0, 4.0 Hz, 1H), 2.14 (ddd, J=14.5, 7.9, 6.6 Hz, 1H), 2.48–2.53 (m, 2H), 2.95 (dd, J=17.6, 8.4 Hz, 1H), 3.01 (dd, J=17.6, 3.5 Hz, 1H), 3.51 (d, J=2.4 Hz, 1H), 4.41–4.47 (m, 1H), 4.78–4.84 (m, 1H), 6.08 (dt, J=9.8, 1.7 Hz, 1H), 6.78 (d, J=16.2 Hz, 1H), 6.95 (ddd, J=9.5, 5.0, 3.7 Hz, 1H), 7.43–7.47 (m, 3H), 7.58–7.62 (m, 2H), 7.64 (d, J=16.3 Hz, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 29.1 (CH_2), 40.6 (CH_2), 46.5 (CH_2), 64.5 (CH), 75.5 (CH), 121.3

(CH), 126.0 (CH), 128.5 (2CH), 129.0 (2CH), 130.9 (CH), 134.0 (C), 144.0 (CH), 145.3 (CH), 164.2 (C), 200.5 (C).

4.11. Cryptomoscatone D2 (2)

Sodium triacetoxyborohydride (125 mg, 0.56 mmol, 8 equiv) was added to a solution of β-hydroxy ketone **13** (20 mg, 70 μmol, 1 equiv) in THF (2 mL) at 0 °C, then acetic acid (25 mg, 0.42 mmol, 6 equiv) was added and the mixture was stirred for one day at 0 °C. Aqueous solution of $NaHCO_3$ (10 mL) was added and the mixture was extracted with Et_2O (2×20 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated. The product was purified by flash chromatography (EtOAc) to furnish the diol **2** (20 mg, 69 μmol, 99% yield) as a colorless oil. R_f 0.22 (hexanes/EtOAc 30:70). $[\alpha]_D^{25}$ +60 (*c* 1.0, $CHCl_3$), $[\alpha]_{D,lit}^{26}$ +65.3 (*c* 2.6, $CHCl_3$).[8] ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.79–1.89 (m, 3H), 1.93 (ddd, *J*=14.4, 9.4, 2.5 Hz, 1H), 2.38–2.41 (m, 2H), 4.41 (tt, *J*=9.0, 2.8 Hz, 1H), 4.67–4.69 (m, 1H), 4.78 (tdd, *J*=9.5, 6.2, 3.1 Hz, 1H), 6.04 (dt, *J*=9.8, 1.6 Hz, 1H), 6.32 (dd, *J*=15.9, 6.3 Hz, 1H), 6.66 (d, *J*=15.8 Hz, 1H), 6.90–6.93 (m, 1H), 7.24–7.27 (m, 1H), 7.34 (t, *J*=7.6 Hz, 2H), 7.39–7.43 (m, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 29.9 (CH_2), 42.4 (CH_2), 43.2 (CH_2), 64.8 (CH), 70.6 (CH), 75.0 (CH), 121.3 (CH), 126.5 (2CH), 127.8 (CH), 128.6 (2CH), 130.4 (CH), 131.5 (CH), 136.5 (C), 145.4 (CH), 164.5 (C). IR (film, NaCl) 695, 1056, 1259, 1392, 1448, 1699, 2917, 3396 (br) cm^{-1}. HRMS $[C_{17}H_{20}O_4-H_2O+H]^+$, calculated 271.1334, found 271.1329.

4.12. Cryptomoscatone D1 (1)

A solution of Et_2BOMe in THF (1 M, 0.16 mL, 0.16 mmol, 3.6 equiv) was added to a solution of β-hydroxy ketone **13** (12.9 mg, 45 μmol, 1 equiv) in THF/MeOH (2.5 mL, 80:20) at −78 °C, the resulting mixture was stirred for 20 min. Then a solution of $LiBH_4$ (3.9 mg, 0.16 mmol, 3.6 equiv) in THF (1 mL) was added to the reaction at −78 °C and the mixture was stirred for 3 h. Buffer (pH 7) solution (8 mL), MeOH (10 mL), and H_2O_2 30% (1 mL) were added sequentially at 0 °C. The resulting mixture was stirred for 1 h at 0 °C, then the mixture was diluted with water (10 mL) and extracted with EtOAc (3×30 mL). The organic phases were combined, dried (Na_2SO_4), and concentrated. The product was purified by flash chromatography (hexanes/EtOAc 30:70) to furnish the diol **1** (13 mg, 45 μmol, quantitative yield) as a colorless oil. R_f 0.21 (hexanes/EtOAc 30:70). $[\alpha]_D^{25}$ +55 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.72–1.80 (m, 3H), 1.90 (ddd, *J*=14.3, 9.8, 2.4 Hz, 1H), 2.32–2.42 (m, 2H), 4.34 (tt, *J*=9.8, 2.4 Hz, 1H), 4.59–4.63 (m, 1H), 4.78 (tdd, *J*=10.4, 5.0, 2.9 Hz, 1H), 6.03 (dd, *J*=9.2, 1.2 Hz, 1H), 6.23 (dd, *J*=15.9, 6.7 Hz, 1H), 6.60 (d, *J*=15.9 Hz, 1H), 6.90 (ddd, *J*=9.7, 5.6, 2.9 Hz, 1H), 7.24–7.27 (m, 1H), 7.32 (t, *J*=7.4 Hz, 2H), 7.37–7.40 (m, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 29.8 (CH_2), 42.8 (CH_2), 43.5 (CH_2), 67.4 (CH), 73.4 (CH), 74.7 (CH), 121.1 (CH), 126.5 (2CH), 127.8 (CH), 128.6 (2CH), 130.2 (CH), 131.5 (CH), 136.4 (C), 145.6 (CH), 164.8 (C). IR (film, NaCl) 751, 969, 1058, 1259, 1393, 1707, 2921, 3397 (br) cm^{-1}. HRMS $C_{17}H_{20}O_4-H_2O+H]^+$, calculated 271.1334, found 271.1329.

4.13. (*R*)-6-((2*S*,4*S*,*E*)-2,4-Dihydroxy-6-phenylhex-5-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (15)

Sodium triacetoxyborohydride (45 mg, 0.20 mmol, 8 equiv) was added to a solution of β-hydroxy ketone **14** (7.2 mg, 25 μmol, 1 equiv) in THF (2 mL) at 0 °C, then acetic acid (9 mg, 0.15 mmol, 6 equiv) was added and the mixture was stirred for one day at 0 °C. Saturated aqueous $NaHCO_3$ solution (10 mL) was added and the mixture was extracted with Et_2O (2×20 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated. The product was purified by flash chromatography (EtOAc) to furnish the diol **15** (7.2 mg, 25 μmol, quantitative yield) as a colorless oil. R_f 0.25 (hexanes/EtOAc 30:70). $[\alpha]_D^{25}$ +30 (*c* 0.37, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.79–1.85 (m, 2H), 1.92 (ddd, *J*=14.5, 8.8, 3.5 Hz, 1H), 2.08–2.16 (m, 1H), 2.41–2.47 (m, 2H), 2.66 (br s, 1H), 3.10 (br s, 1H), 4.28 (tt, *J*=8.8, 2.9 Hz, 1H), 4.66–4.76 (m, 2H), 6.04 (d, *J*=9.9 Hz, 1H), 6.30 (dd, *J*=15.9, 6.1 Hz, 1H), 6.65 (d, *J*=16.0 Hz, 1H), 6.87–6.93 (m, 1H), 7.24–7.27 (m, 1H), 7.33 (t, *J*=7.5 Hz, 2H), 7.37–7.42 (m, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 29.5 (CH_2), 41.9 (CH_2), 42.8 (CH_2), 66.8 (CH), 70.4 (CH), 77.0 (CH), 121.2 (CH), 126.5 (2CH), 127.8 (CH), 128.6 (2CH), 130.3 (CH), 131.5 (CH), 136.5 (C), 145.2 (CH), 163.8 (C). IR (film, NaCl) 750, 1229, 1711, 2921, 3425 cm^{-1}. HRMS $[C_{17}H_{20}O_4-H_2O+H]^+$, calculated 271.1334, found 271.1329.

4.14. (*R*)-6-((2*S*,4*R*,*E*)-2,4-Dihydroxy-6-phenylhex-5-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (16)

A solution of Et_2BOMe in THF (1 M, 0.10 mL, 0.10 mmol, 3.6 equiv) was added to a solution of β-hydroxy ketone **14** (8.0 mg, 28 μmol, 1 equiv) in THF/MeOH (2.5 mL, 80:20) at −78 °C, the resulting mixture was stirred for 20 min. Then a solution of $LiBH_4$ (2.4 mg, 0.10 mmol, 3.6 equiv) in THF (1 mL) was added to the reaction at −78 °C and the mixture was stirred for 3 h. pH 7 buffer solution (8 mL), MeOH (10 mL) and H_2O_2 30% (1 mL) were added sequentially at 0 °C. The resulting mixture was stirred for 1 h at 0 °C, then the mixture was diluted with water (10 mL) and extracted with EtOAc (3×30 mL). The organic phases were combined, dried (Na_2SO_4), and concentrated. The product was purified by flash chromatography (hexanes/EtOAc 30:70) to furnish the diol **16** (8.0 mg, 28 μmol, 99% yield) as a colorless oil. R_f 0.21 (hexanes/EtOAc 30:70). $[\alpha]_D^{25}$ +70 (*c* 0.27, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.74–1.86 (m, 3H), 2.08 (dt, *J*=14.5, 7.8 Hz, 1H), 2.42–2.46 (m, 2H), 2.83 (br s, 1H), 3.60 (br s, 1H), 4.23 (tt, *J*=8.7, 3.2 Hz, 1H), 4.57–4.63 (m, 1H), 4.70 (qd, *J*=7.2, 5.6 Hz, 1H), 6.03 (dt, *J*=9.9, 1.8 Hz, 1H), 6.23 (dd, *J*=15.9, 6.6 Hz, 1H), 6.61 (d, *J*=15.9 Hz, 1H), 6.90 (dt, *J*=9.7, 4.2 Hz, 1H), 7.24–7.27 (m, 1H), 7.32 (t, *J*=7.6 Hz, 2H), 7.37–7.40 (m, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 29.4 (CH_2), 42.2 (CH_2), 43.2 (CH_2), 69.3 (CH), 73.6 (CH), 76.4 (CH), 121.2 (CH), 126.5 (2CH), 127.8 (CH), 128.6 (2CH), 130.4 (CH), 131.4 (CH), 136.4 (C), 145.3 (CH), 164.1 (C). IR (film, NaCl) 1068, 1260, 1636, 1700, 2852, 2923, 3955, 3425 (br) cm^{-1}. HRMS $[C_{17}H_{20}O_4-H_2O+H]^+$, calculated 271.1334, found 271.1329.

4.15. (*R*)-6-(((4*S*,6*S*)-2,2-Dimethyl-6-((*E*)-styryl)-1,3-dioxan-4-yl)methyl)-5,6-dihydro-2*H*-pyran-2-one (17)

PPTS (0.7 mg, 2.8 μmol, 0.1 equiv) was added to a solution of diol **1** (8.0 mg, 28 μmol, 1 equiv) in 2,2-dimethoxypropane (1 mL) at rt in an open flask. The mixture was stirred for 5 h, then the solvent was removed in vacuo, and the product was purified by flash chromatography (hexanes/EtOAc 60:40) to furnish the acetonide (9.0 mg, 27 μmol, 99% yield) as a colorless oil. R_f 0.40 (hexanes/EtOAc 60:40). $[\alpha]_D^{25}$ +20 (*c* 0.46, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.37–1.44 (m, 1H), 1.44 (s, 3H), 1.54 (s, 3H), 1.63 (dt, *J*=13.0, 2.5 Hz, 1H), 1.73 (ddd, *J*=14.4, 9.9, 2.6 Hz, 1H), 1.91 (ddd, *J*=14.4, 9.7, 2.2 Hz, 1H), 2.30–2.35 (m, 1H), 2.35–2.41 (m, 1H), 4.29–4.33 (m, 1H), 4.55–4.58 (m, 1H), 4.68–4.72 (m, 1H), 6.04 (dd, *J*=9.8, 1.7 Hz, 1H), 6.17 (dd, *J*=16.0, 6.2 Hz, 1H), 6.61 (d, *J*=16.0 Hz, 1H), 6.89 (ddd, *J*=9.6, 5.9, 2.5 Hz, 1H), 7.23 (t, *J*=7.3 Hz, 1H), 7.30 (t, *J*=7.6 Hz, 2H), 7.38 (d, *J*=7.3 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.1 (CH_3), 30.0 (CH_2), 30.2 (CH_3), 37.4 (CH_2), 42.0 (CH_2), 64.4 (CH), 70.0 (CH), 74.2 (CH), 99.0 (C), 121.5 (CH), 126.5 (2CH), 127.7 (CH), 128.5 (2CH), 129.6 (CH), 130.9 (CH), 136.6 (C), 145.1 (CH), 164.3 (C). IR (film, NaCl) 749, 820, 967, 1163, 1201, 1252, 1383, 1721, 2852, 2921, 2992 cm^{-1}. HRMS $[C_{20}H_{24}O_4-C_3H_6O+H]^+$, calculated 271.1334, found 271.1328.

4.16. (*R*)-6-(((4*R*,6*R*)-2,2-dimethyl-6-((*E*)-styryl)-1,3-dioxan-4-yl)methyl)-5,6-dihydro-2*H*-pyran-2-one (18)

PPTS (0.7 mg, 2.8 μmol, 0.1 equiv) was added to a solution of diol **16** (8.0 mg, 28 μmol, 1 equiv) in 2,2-dimethoxypropane (1 mL) at rt

in an open flask. The mixture was stirred for 5 h, then the solvent was removed in vacuo, and the product was purified by flash chromatography (hexanes/EtOAc 60:40) to furnish the acetonide (9.0 mg, 27 μmol, 99% yield) as a colorless oil. R_f 0.40 (hexanes/EtOAc 60:40). $[\alpha]_D^{25}$ +21 (*c* 0.60, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 1.42–1.47 (m, 1H), 1.45 (s, 3H), 1.52 (s, 3H), 1.71 (dt, *J*=13.0, 2.5 Hz, 1H), 1.80 (dt, *J*=14.3, 5.5 Hz, 1H), 2.11 (dt, *J*=14.3, 7.0 Hz, 1H), 2.36–2.41 (m, 1H), 2.43–2.49 (m, 1H), 4.24–4.28 (m, 1H), 4.56 (ddt, *J*=10.2, 6.2, 1.4 Hz, 1H), 4.61–4.66 (m, 1H), 6.04 (ddd, *J*=9.8, 2.6, 0.9 Hz, 1H), 6.16 (dd, *J*=16.0, 6.2 Hz, 1H), 6.60 (d, *J*=16.0 Hz, 1H), 6.91 (ddd, *J*=9.6, 6.0, 2.4 Hz, 1H), 7.23 (tt, *J*=7.2, 1.4 Hz, 1H), 7.29–7.31 (m, 2H), 7.36–7.38 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 19.9 (CH_3), 29.3 (CH_2), 30.2 (CH_3), 36.7 (CH_2), 40.8 (CH_2), 64.8 (CH), 70.0 (CH), 74.6 (CH), 98.9 (C), 121.3 (CH), 126.6 (2CH), 127.7 (CH), 128.5 (2CH), 129.5 (CH), 130.9 (CH), 136.6 (C), 145.3 (CH), 164.4 (C). IR (film, NaCl) 721, 1200, 1248, 1381, 1719, 2920 cm^{-1}. HRMS $[C_{20}H_{24}O_4-C_3H_6O+H]^+$, calculated 271.1334, found 271.1329.

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Supplementary data

^1H and ^{13}C NMR spectra for all synthesized compounds, including COSY and NOESY analyzes for compounds **17** and **18**. CD spectra for natural and synthetic **1** and **2**. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.07.025.

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21. We compared the data of synthetic **1** with the data provided by Professor A. Cavalheiro for natural cryptomoscatone D1 and confirmed the identity of both samples, except for the chemical shift of the carbonyl carbon, which could not be distinguished from the baseline noise in the ^{13}C NMR spectrum of the natural compound.