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Total Synthesis and Tentative Structural Elucidation of Cryptomoscatone E3: Interplay of Experimental and Computational Studies

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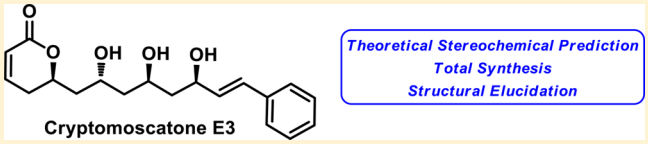
Supporting Information

ABSTRACT: A successful combination of computational chemistry and total synthesis was explored to tentatively elucidate the absolute configuration of cryptomoscatone E3, a polyketide isolated from the Brazilian tree *Cryptocarya mandiocanna*. Two independent synthetic approaches are discussed based on asymmetric allylation, ring closing metathesis, and aldol reactions.



INTRODUCTION

The 5,6-dihydropyran-2-one motif is present in several natural products which display a broad range of biological activities, such as anticancer,[1,2] antimicrobial,[3] antifungal,[4] insecticidal,[5] among others. In previous works, we have contributed to elucidate the stereochemical assignment of molecules with this scaffold, being able to assign the absolute configuration of cryptolatifolione[6] and cryptomoscatone D1[7] and to correct the stereochemical assignment of coibacin A[8] (Figure 1), after total synthesis of the natural products and several diastereoisomers and correlation of the NMR data of synthetic and natural products.

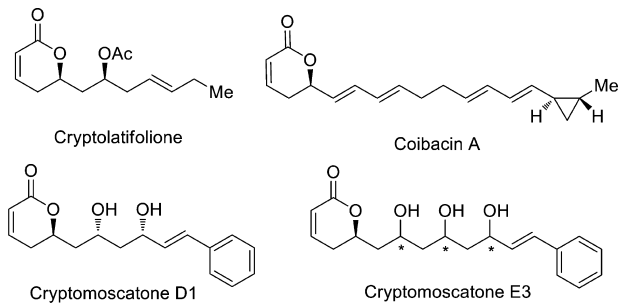


Figure 1. Structures of some natural 5,6-dihydropyran-2-ones.

Surprisingly often, even in the golden age of NMR, structural and stereochemical misassignments are found in the literature.[9] Many of the hundreds of structural revisions published in the last decades started with the total synthesis of the originally proposed (wrong) structure, followed by preparation of other plausible isomers (with the concomitant investment of time, manpower, and funding).[9] Recent years have witnessed an increase in the use of quantum chemistry approaches in solving structural validation problems, mainly through the calculation of NMR shifts.[10] Good correlation between experimental and calculated NMR data provides certainty in the structural proposal. In particular, assignment of the relative stereochemistry of complex molecules represents one of the most important and challenging applications. Smith and Goodman made a contribution in this field by introducing the DP4 probability as a powerful tool to assign one set of experimental data to several plausible structures.[11] The DP4 probability has been used extensively to confirm or propose the structural identification of several complex molecules,[12] though to the best of our knowledge has not guided any total synthesis yet.

Among the plethora of natural products without unambiguous structural assignement, cryptomoscatone E3 (Figure 1) caught our attention. This interesting 6-substituted-5,6-dihydropyran-2-one was isolated by Cavalheiro and Yoshida from the bark of the Brazilian tree *Cryptocarya mandiocanna*, together with other representative structures.[13] Using circular dichroism measurements, the authors were able to set the absolute configuration at C6 as *R*, though they could not unequivocally determine the configuration of the remaining three stereocenters.[13] In this context, we were interested in solving the stereochemical assignment of cryptomoscatone E3 following an in silico-guided total synthesis approach.

Additionally, preliminary studies on the biological properties of the crytomoscatone family of compounds pointed to the G2 checkpoint inhibitory property of some of these dihydropyranones,[14] but a more through study on the biological properties

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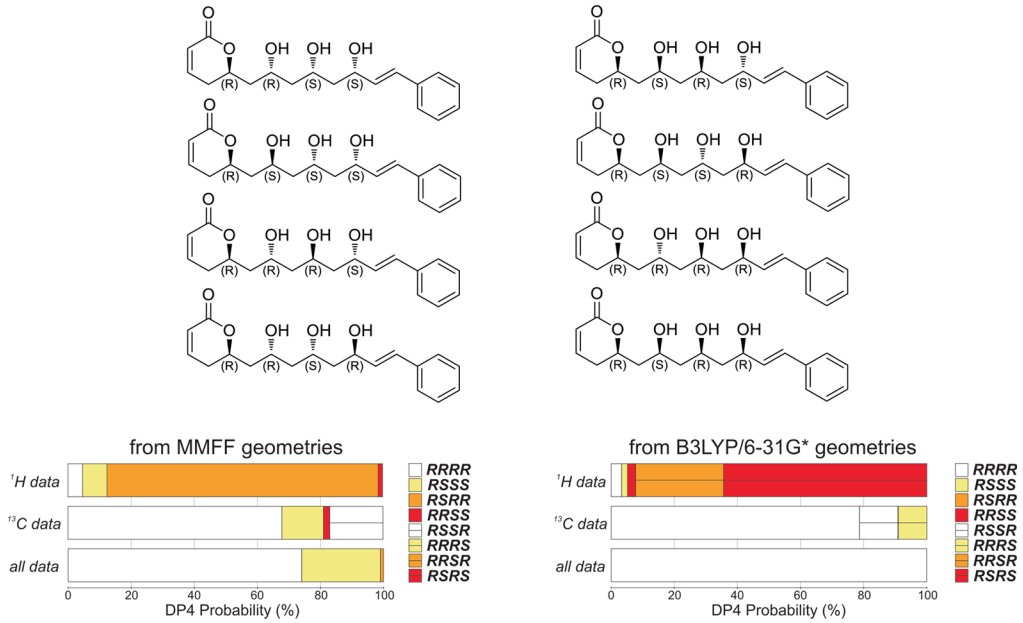


Figure 2. All possible isomers of cryptomoscatone E3, and DP4 probabilities computed from MMFF geometries (left) and B3LYP/6-31G* geometries (right) at the GIAO/B3LYP/6-31G** level of theory.

still awaits a dependable source of this family of natural products.

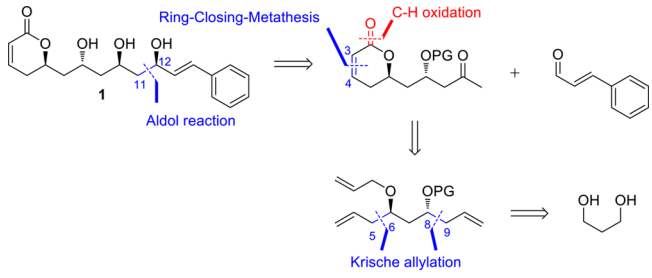
RESULTS AND DISCUSSION

Cryptomoscatone E3 features four stereocenters with unknown configuration for three of them, leading to eight possible isomers (Figure 2). Because the total synthesis of all diastereoisomers would have been highly demanding in terms of resources and time, we speculated to narrow down the possible candidates using quantum chemistry NMR calculations coupled with DP4 probability analysis (see Computational Methods). Thus, each isomer was subjected to an extensive conformational search with the MMFF force field, followed by single-point NMR calculations with the 80−100 lowest-energy conformers from each run at the B3LYP/6-31G** level of theory. The resulting shielding tensors were averaged using the Boltzmann distribution computed from the B3LYP/6-31G**//MMFF energies. With the NMR chemical shifts calculated for the eight plausible isomers, we next computed the DP4 probabilities as originally described by Smith and Goodman (Figure 2).[11]

The combined probabilities for ^{1}H and ^{13}C data (the most recommended for DP4 calculations) pointed toward isomers 6*R*,8*R*,10*R*,12*R* (74% probability) and 6*R*,8*S*,10*S*,12*S* (24% probability). Interestingly, both display the exact opposite configurations at C8, C10, and C12 carbons, suggesting an anti-syn arrangement in the stereotriad of the natural product. To strengthen the confidence of our assignment, we recomputed the DP4 probabilities using a more robust and reliable computational method. Thus, the MMFF geometries of the most stable conformers found for each diastereoisomer (up to 5 kcal/mol from the global minima) were reoptimized at the B3LYP/6-31G* level of theory, and the corresponding NMR shifts were computed at the B3LYP/6-31G** level. To our delight, the new DP4 analysis again identified compound 6*R*,8*R*,10*R*,12*R* as the correct isomer with very high confidence level (99% probability).

With this computational guidance, we directed our synthetic efforts toward cryptomoscatone E3 with 6*R*,8*R*,10*R*,12*R* stereochemistry. The synthesis was first planned based on the coupling of a ketone and cinnamaldehyde by a stereoselective aldol reaction. The lactone ring would be forged by a ring-closing-metathesis reaction followed by a C−H oxidation to install the carbonyl group. The C5−C6 and C8−C9 bonds would be formed by a double Krische allylation of 1,3-propanediol (Scheme 1).

Scheme 1. First Retrosynthetic Analysis to Cryptomoscatone E3



The synthesis started with the enantioselective Krische double allylation reaction of 1,3-propanediol (**2**),[15] which produced diol **3** with high ee and dr.[16] As our first approach to the proposed structure of cryptomoscatone E3 was based on a 1,5-anti diastereoselective boron-mediated aldol reaction which required *p*-methoxylbenzyl protected methyl ketone **13** (Scheme 5), we explored first the ring-closing metathesis reaction on PMB-protected triene **5** (Scheme 2). Based on the results described previously by Brückner and co-workers[17] with a similar substrate, the use of an acylation reaction with acryloyl or crotonoyl chloride as a prelude for the dihydropyranone construction was discarded in favor of an allylation reaction, as the former would furnish preferentially the seven-membered cyclic olefin in the ring-closing metathesis step. In fact, our previous results have shown that the use of acetate **6** afford the

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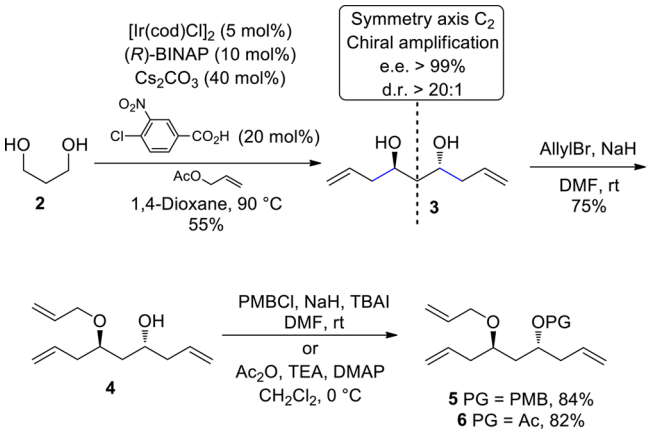
Scheme 2. Synthesis of Trienes 5 and 6



desired dihydropyran **8** in good yield and high selectivity when 1 mol % of Grubbs II catalyst was employed.[6] The implementation of this route required monoallylation of diol **3** with allyl bromide, followed by protection of alcohol **4** with *p*-methoxybenzyl chloride (PMB-Cl).

To forge the six-membered ring of cryptomoscatone E3, triene **5** was subjected to a ring-closing-metathesis (RCM) reaction using five commercially available catalysts to optimize the yield of dihydropyran **7** (Scheme 3, Table 1). While Grubbs

Scheme 3. Ring-Closing-Metathesis Reaction of Trienes 5 and 6

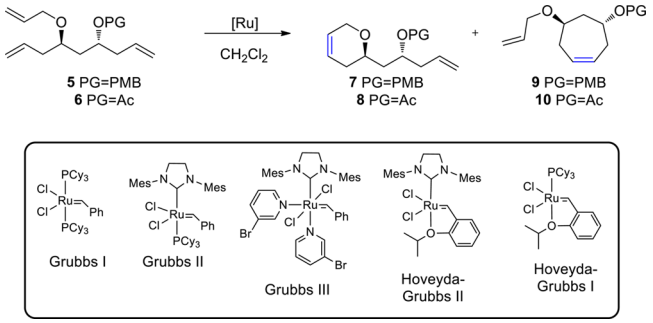


Table 1. Screening of Experimental Conditions for the Preparation of Dihydropyran 7

entry	catalyst[a]	loading (mol %)	temperature (°C)	7:9 ratio	yield (%)[b]
1	Grubbs I	5	40	77:23	95
2	Grubbs I	5	0	75:25	76
3	H-G I	10	40	78:22	82
4	Grubbs II	5	40	> 95:5	80
5	Grubbs II	1	40	> 95:5	85
6	H-G II	5	40	94:6	94
7	Grubbs III	10	40	95:5	93

[a]H-G I = Hoveyda–Grubbs I catalyst, H-G II = Hoveyda–Grubbs II catalyst. [b]Yield after chromatographic purification.

I (entries 1 and 2) and Hoveyda–Grubbs I (entry 3) catalysts did not provide good selectivity in favor of the dihydropyran product, utilization of Grubbs II (entries 4 and 5), Hoveyda–Grubbs II (entry 6), and Grubbs III (entry 7) catalysts furnished high selectivity (94:6 or higher) and good yields (80–94%). For preparative purposes, Grubbs II catalyst was elected as the catalyst of choice.

In the next step, we intended to use a selective allylic radical-based C–H oxidation to convert dihydropyran **7** to dihydropyranone **11** (Scheme 4, Table 2). To predict if C2 would preferentially undergo allylic oxidation, we performed DFT calculations using Gaussian 09.[18] The relative stability of allylic or benzylic radicals were estimated at the UB3LYP/6-31+G** level of theory.[19] Our calculations suggested that the radical centered at C2 would be the most stable radical for dihydropyran **7**. The second most stable radical expected for dihydropyran **7** would be located at C12 (2.7 kcal/mol less stable than the radical centered at C2). Moreover, for dihydropyran **8** the most stable radical would reside at C2, being 6.2 kcal/mol more stable than the radical formed at C5, a prediction which has been experimentally confirmed as previously reported.[6] These results led us to explore different methodologies to selectively oxidize the C2 position of dihydropyran **7**.

Methods based on the use of *tert*-BuOOH as the stoichiometric oxidant and metal catalysts[20] (entries 1–3) were evaluated for compound **7**, but poor yields of dihydropyranonone **11** were obtained (10% or less) with the identification of *p*-methoxybenzaldehyde as a side product resulting from oxidation at C12. Use of reagents based on chromium VI, such as CrO_3, PCC, and PDC (entries 4–8) improved the yield but not beyond 26% (entry 4), again accompanied by the formation of *p*-methoxybenzaldehyde. Use of CrO_3 and 2,2′-bipyridine was not effective (entry 9). A condition explored by Baran and co-workers[19] to improve a challenging allylic oxidation with the unusual Cr (V) reagent[21] (see Scheme 4) was evaluated, but in our hands we observed only trace amounts of the desired product (entry 10). In contrast, the oxidation of dihydropyran **8** was known to proceed cleanly to furnish dihydropyranone **12** in 60–61% with PCC (entries 11 and 12).[6]

Despite the low yield for the preparation of dihydropyranone **11**, terminal alkenes **11** and **12** were subjected to Wacker oxidation[22] which afforded the desired ketones **13** and **15** in 71 and 73% yield, respectively, accompanied by the corresponding aldehydes in 9 and 10% yield, respectively, which could not be separated by conventional flash chromatography. Next, methyl ketone **13** (contaminated with the corresponding aldehyde**14**) was treated with Cy_2BCl and Et_3N to produce the corresponding boron enolate which reacted with cinnamaldehyde to furnish the aldol adduct **17** in good yield and high diastereoisomeric ratio.[23] In contrast, the reaction of methyl ketone **15** (contaminated with the corresponding aldehyde **16**) furnished a complex mixture with no evidence of formation of the desired aldol **18** under otherwise the same reaction conditions (Scheme 5). This observation led us to speculate that the acetate group acts as a leaving group under the basic reaction conditions thus precluding formation of **18**.

At this juncture, we proceeded with our work on the PMB protected aldol adduct **17** which underwent a highly stereoselective carbonyl reduction with Et_2BOMe and $LiBH_4$ to furnish diol **19**.[24] The relative configuration at C10 and C12 was secured as 1,3-syn after derivatization to the corresponding acetonide **20**. Inspection of the ^{13}C NMR spectrum of acetonide **20** showed a difference in the chemical shifts for the two methyl groups ($\Delta\delta$ = 10.3 ppm), which is in concordance with Rychnovsky's model for a 1,3-syn relationship between the oxygens attached to C10 and C12 (Scheme 6).[25]

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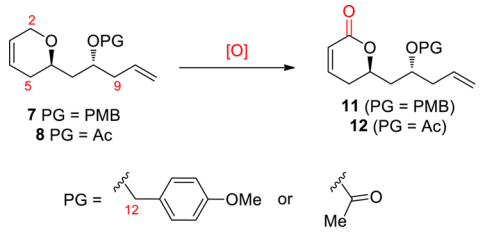
Scheme 4. Allylic Oxidation of Dihydropyrans 7 and 8



PG	Radical position	ΔΔG
PMB	**C2**	**0.0 kcal/mol**
	C5	6.4 kcal/mol
	C9	3.2 kcal/mol
	C12 (PMB)	2.7 kcal/mol
Ac	**C2**	**0.0 kcal/mol**
	C5	6.2 kcal/mol
	C9	6.5 kcal/mol

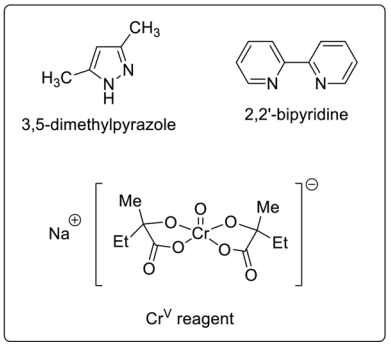


Table 2. Screening of Experimental Conditions for the Allylic Oxidation of Dihydropyrans 7 and 8

entry	PG	oxidizing system	solvent	temperature (°C)	yield (%)[a]
1	PMB	$CuI_{(cat.)}$, ^tBuOOH	MeCN	50	5
2	PMB	$Mn(OAc)_{3(cat.)}$, ^tBuOOH	EtOAc	rt	<5
3	PMB	$Rh_2(OAc)_{4(cat.)}$, ^tBuOOH	CH_2Cl_2	rt	10
4	PMB	PCC	CH_2Cl_2	80	26
5	PMB	PCC, pyridine	CH_2Cl_2	40	25
6	PMB	PCC	$PhCF_3$	70	13
7	PMB	PDC	$(CH_2Cl)_2$	80	21
8	PMB	CrO_3, 3,5-dimethylpyrazole	CH_2Cl_2	−20	24
9	PMB	CrO_3, 2,2′-bipyridine	CH_2Cl_2	−20 to rt	0
10	PMB	Cr^V reagent, 15-crown-5, MnO_2	$PhCF_3$	80	<5
11	Ac	PCC	CH_2Cl_2	80	60
12	Ac	PCC, pyridine	CH_2Cl_2	40	61

[a]Yield determined after chromatographic purification.

Unfortunately, efforts to remove the PMB group in diol **19** or acetonide **20** failed: while Lewis acid-based methods (BF_3·Et_2O, $SnCl_4$, $TiCl_4$) furnished complex mixtures with no evidence for the formation of compound **1** or **22**, radical-based methods (DDQ) induced oxidation at the C12 position, suggesting that the radical produced at C12 is more stable than the benzylic radical at the PMB group (Scheme 6).

Based on these results, a second approach to **1** was designed where the dihydropyran-2-one would be formed last by a ring closing metathesis reaction (C3−C4). The side chain was disconnected at two points: the C10−C11 bond would be constructed by an aldol reaction, while the C8−C9 bond was planned to be formed by an enantioselective allylation (Scheme 7).

This route started with commercially available alcohol **23** which underwent Swern oxidation and Keck asymmetric allylation[26] to give homoallylic alcohol **25** in 71% overall yield and 95:5 enantiomeric ratio determined after ^{19}F NMR analysis of Mosher's ester (Scheme 8).[27]

A reaction sequence including protection of the secondary alcohol as the *tert*-butyldimethylsilyl ether, Upjohn dihydroxylation, and cleavage of the diol product mediated by $NaIO_4$ furnished known aldehyde **27**. Next, a Mukaiyama aldol reaction promoted by BF_3·Et_2O between **27** and the silyl enol ether derived from benzylideneacetone[28] was employed to construct the C10−C11 bond. Aldol product **29** and its epimer at C10 (61:39 dr) was obtained and stereoselectively reduced with Et_2BOMe and $LiBH_4$ to set the stereogenic center at C12 in high selectivity (dr > 95:5). The two diastereoisomers obtained after the reduction step in 71% overall yield, namely (8*S*,10*S*,12*R*)-**30** and (8*S*,10*R*,12*S*)-**30** (60:40 dr), were separated after semipreparative HPLC purification (Scheme 8, see Experimental Section for details).

Prior to the construction of the dihydropyran-2-one ring, diol **30** was protected as the corresponding acetonide, and the primary silyl ether was selectively cleaved by treatment with HF·py (Scheme 9). The stereocenter at C6 was generated by a sequence of Dess−Martin oxidation, followed by Brown asymmetric allylation using (+)-allyl-diisopinocampheylborane.[29] The δ-lactone ring was constructed after esterification of alcohol **32** with acryloyl chloride, and ring closing metathesis reaction mediated by Grubbs I catalyst. Last, complete deprotection under acidic conditions enabled the conclusion of the synthesis of the proposed structure for cryptomoscatone E3 (**1**, Scheme 9).

While the configuration of the stereogenic center at C8 was established at the level of the previously described homoallylic alcohol **25** (Scheme 8),[7,30] inspection of the ^{13}C NMR spectrum of acetonide **31** (Scheme 9) showed a difference in the chemical shifts of the two methyl groups ($\delta_{C22} - \delta_{C23}$ = 10.1 ppm) in accordance with Rychnovsky's model for a 1,3-syn relationship between the oxygens attached to C10 and C12.[25] Therefore, two possibilities remained for the absolute configuration of the stereotriad comprising the stereogenic centers at C8, C10, and C12: either a 8*R*,10*R*,12*R* (8,10-anti/10,12-syn) or 8*R*,10*S*,12*S* (8,10-syn/10,12-syn) stereochemis-

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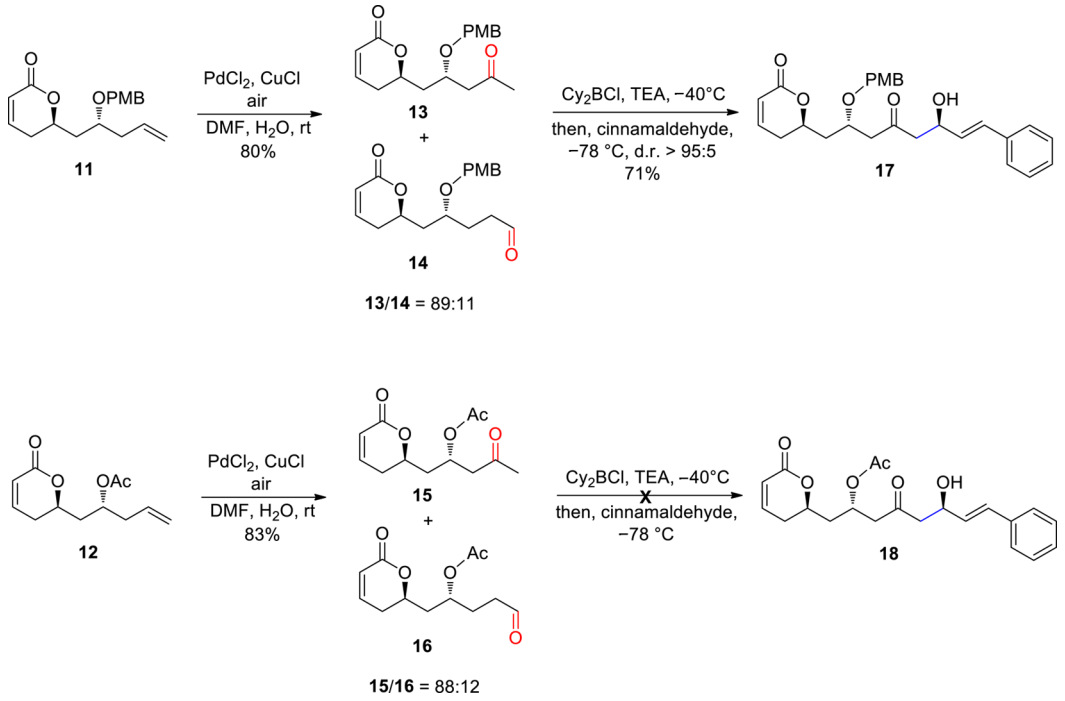
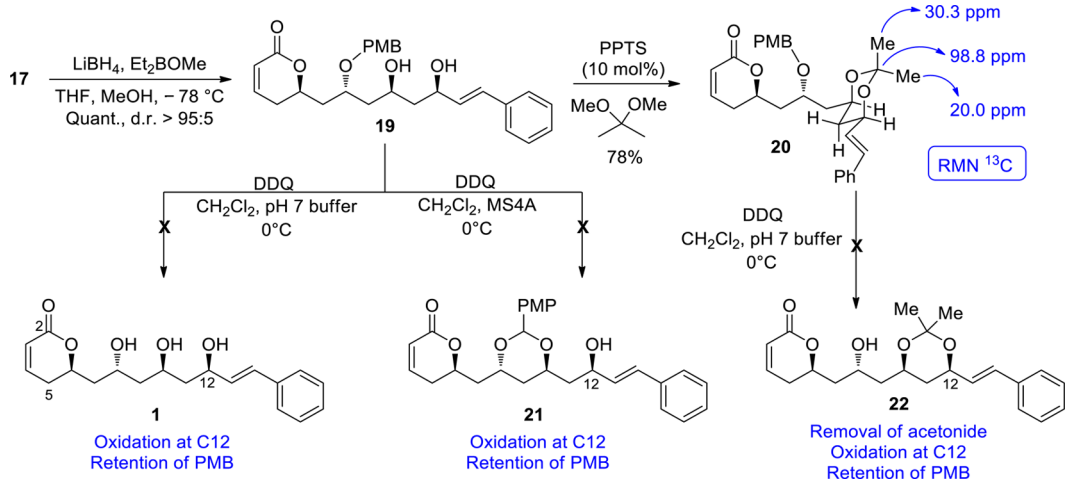
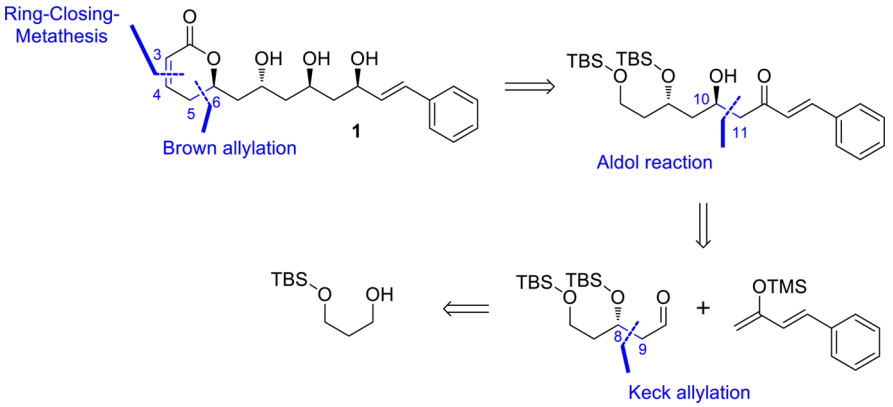
Scheme 5. Attempted Synthesis of Intermediates 17 and 18



Scheme 6. End-Game: First Attempt



Scheme 7. Second Retrosynthetic Analysis for the Proposed Structure for Cryptomoscatone E3



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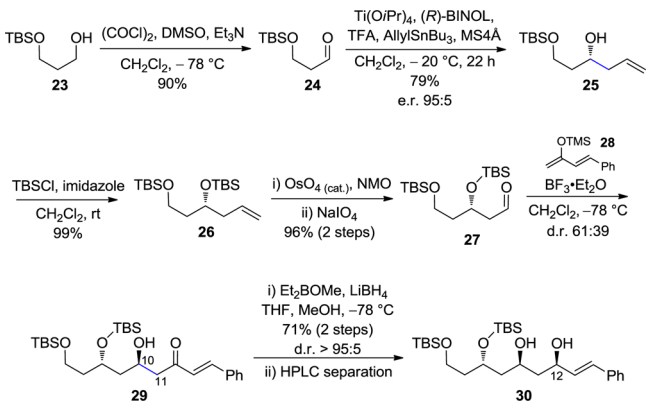
Scheme 8. Synthesis of the Side Chain of the Proposed Structure for Cryptomoscatone E3



try. Upon inspection of the ^{13}C NMR spectrum of synthetic **1** in methanol-d_4, C-10 was observed at 67.4 ppm which nicely fits the expected chemical shift for a 8,10-anti/10,12-syn relationship according to Kishi's model which indicates 68.6 ± 0.5 ppm for the 1,3-anti/3,5-syn and 70.7 ± 0.5 ppm for the 1,3-syn/3,5-syn stereochemistry for a 1,3,5-triol, respectively.[31] Therefore, the relative configuration of the side chain of synthetic **1** was assigned as 8*R*,10*R*,12*R*. The stereocenter of the dihydropyran-2-one was confirmed as *R* by observation of a positive Cotton effect between 254 and 272 nm in the circular dichroism analysis, in concordance with the model of Snatzke (Figure 3).[32]

Finally, an inspection of ^{13}C NMR spectra of synthetic **1** revealed good agreement with natural cryptomoscatone E3[13] (Figure 4), confirming the stereochemistry predicted by GIAO NMR calculation.

CONCLUSIONS

A successful combination of theoretical chemistry and total synthesis enabled the tentative stereochemical assignment of cryptomoscatone E3, a polyketide isolated from *C. moschata*, as 6*R*,8*R*,10*R*,12*R*. This configuration was the one which emerged with the highest DP4 probability computed from MMFF geometries and B3LYP/6-31G* geometries at the GIAO/B3LYP/6-31G** level of theory.

Two synthetic approaches were investigated: while the first one successfully established the required stereocenters based on Krische catalytic double asymmetric allylation, ring closing metathesis reaction, regioselective allylic oxidation, stereoselective boron mediated aldol reaction, and carbonyl reduction, it failed to provide the desired structure by removal of the PMB group. A second approach provided the desired stereoisomer after 14 steps and 9% overall yield, and it was based on a Keck asymmetric allylation, Mukaiyama aldol reaction, stereoselective carbonyl reduction, and ring closing metathesis reaction. All spectroscopic data of synthetic samples prepared in this work matched the data reported for the natural cryptomoscatone E3.

In addition to providing the first total synthesis of cryptomoscatone E3, this work will allow the investigation of the biological properties of this natural product and analogues. These studies are underway in our laboratory.

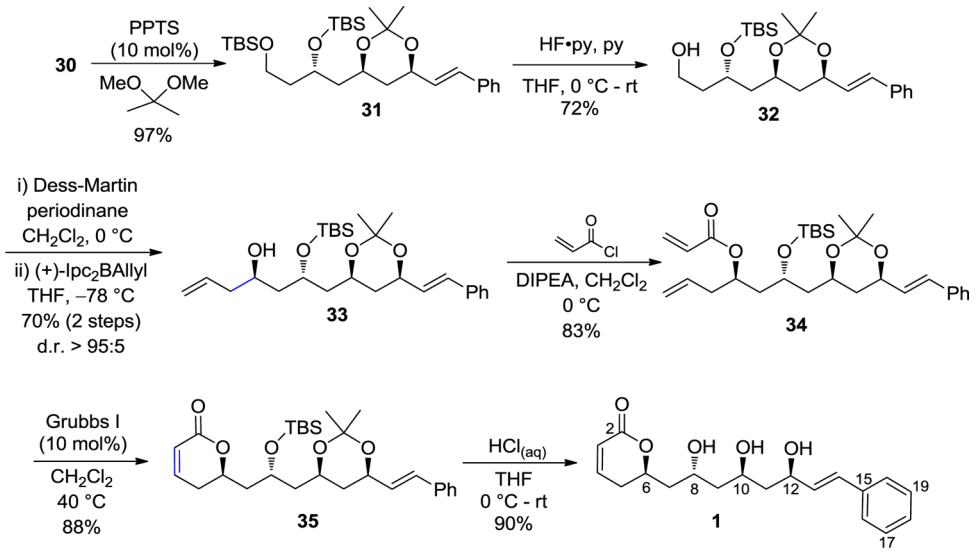
EXPERIMENTAL SECTION

Computational Methods. All the quantum mechanical calculations were performed using Gaussian 09.[18] The conformational search was done in the gas phase using the MMFF force field (implemented in Spartan 08).[33] All conformers within 5 kcal/mol of the lowest energy conformer from each run (80−100 different conformations/diastereoisomer) were subjected to further NMR calculations. The magnetic shielding constants (σ) were computed using the gauge including atomic orbitals (GIAO) method,[34] the method of choice among the different approaches to solve the gauge origin problem, with the B3LYP/6-31G** level of theory in the gas phase. The NMR shielding constants were subjected to Boltzmann averaging over all conformers according to eq 1:

$$\sigma^x = \frac{\sum_i \sigma^x{}_i \exp(-E_i/RT)}{\sum_i \exp(-E_i/RT)} \quad (1)$$

where σ^x is the Boltzmann-averaged shielding constant for nucleus x, $\sigma^x{}_i$ is the shielding constant for nucleus x in conformer i, R is the molar gas constant (8.3145 J K^{-1} mol^{-1}), T is the temperature (298 K), and E_i is the energy of conformer i (relative to the lowest energy conormer) obtained from the single point NMR calculations (B3LYP/6-31G**//MMFF). The chemical shifts were calculated from TMS as

Scheme 9. Conclusion of the Synthesis of Cryptomoscatone E3



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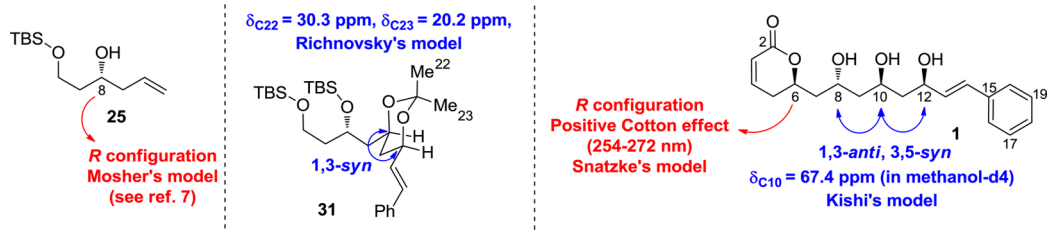

Figure 3. Stereochemical assignment for intermediate **25**, acetonide **31**, and the proposed structure of cryptomoscatone E3 (**1**).

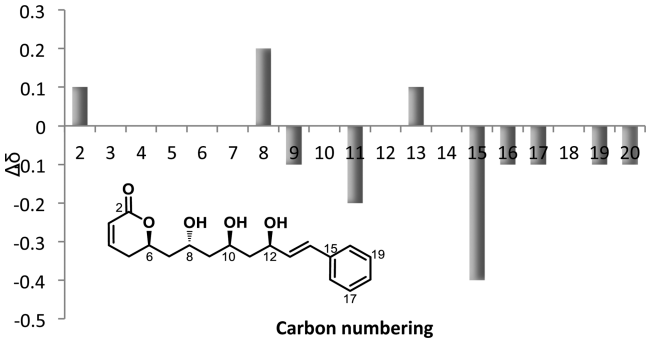

Figure 4. Comparison of ^{13}C NMR data of synthetic and natural cryptomoscatone E3.

reference standard. The systematic errors were removed by empirical scaling according to $\delta_{scaled} = (\delta_{calc} - b)/m$, where m and b are the slope and intercept, respectively, resulting from a linear regression calculation on a plot of δ_{calc} against δ_{exp}.[11]

On the other hand, all conformers within 5 kcal/mol of the lowest energy conformer from each MMFF conformational search were subjected to further reoptimization at the B3LYP/6-31G* level (gas phase). For each diastereoisomer, all conformers within 2 kcal/mol from the B3LYP/6-31G* global minima were subjected to further NMR calculations at the B3LYP/6-31G** level following the same procedure discussed above. The DP4 probabilities were computed as recommended by Smith and Goodman using the statistical values from the original data set.[11]

For the DFT study of the allylic oxidation of dihydropyrans **7** and **8**, conformational searches were performed to locate the minimum energy conformers of all structures. Initially, a large number of geometries were generated using the conformational search module of Hyperchem[35] with the MM+ method. Selected structures were then successively reoptimized at the UB3LYP/6-31G* and UB3LYP/6-31+G** levels of theory.

Geometries for all structures were fully optimized, and the nature of the stationary points found was confirmed by frequency calculations. Reported thermochemical properties include zero-point energies (ZPEs) and Gibbs free energies, computed at 1 atm and 298.15 K and were not scaled.

Materials and Methods. Starting materials and reagents were obtained from commercial sources and used as received unless otherwise specified. Dichloromethane, dichloroethane, triethylamine, and *N*,*N*-diisopropylethylamine were treated with calcium hydride and distilled before use. Tetrahydrofuran, diethyl ether, and 1,4-dioxane were treated with metallic sodium and benzophenone and distilled before use. Acetonitrile and methanol were dried over molecular sieves for at least 1 week before use. Anhydrous ethyl acetate was obtained after treatment with magnesium sulfate and distillation. Anhydrous dimethylformamide, dimethyl sulfoxide, and pyridine were obtained from commercial sources. 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 (silica gel 60 F254 on aluminum plates). ^1H NMR and ^{13}C NMR were recorded on 250, 400, 500, or 600 MHz equipment, the chemical shifts (δ) are reported in parts per million (ppm) relative to deuterated solvent as the internal standard ($CDCl_3$ 7.26 ppm, 77.0 ppm, CD_3OD 3.31 ppm, 49.0 ppm), and coupling constants (J) are in hertz (Hz). Mass spectra were recorded on a Q-Tof apparatus operating in electrospray mode (ES). The principal absorptions of infrared spectra with Fourier transform (FTIR) are listed in cm^{-1}. The values of optical rotation were measured at 25 °C in a polarimeter with a sodium lamp, and described as follows $[\alpha]_{D,T}$ (c (g/100 mL), solvent). IUPAC names of the compounds were generated using ChemBioDraw Ultra 13.0. All HPLC experiments were performed at room temperature with a photodiode array detector. NMR spectra were processed using an ACD/NMR Processor Academic Edition version 12.01. Circular dichroism analyses were performed using methanol as solvent.

*(4R,6R)-Nona-1,8-diene-4,6-diol (**3**).* A pressure tube was charged with $[Ir(cod)Cl_2]$ (104 mg, 150 μmol, 5 mol %), Cs_2CO_3 (393 mg, 1.20 mmol, 40 mol %), 4-chloro-3-nitrobenzoic acid (121 mg, 600 μmol, 20 mol %), and (*R*)-BINAP (189 mg, 300 μmol, 10 mol %). The pressure tube was purged with N_2, and then dry 1,4-dioxane (15 mL) and allyl acetate (3.3 mL, 30 mmol, 10 equiv) were added. The tube was sealed and heated at 90 °C for 30 min to prepare the catalyst in situ. The mixture was cooled to rt, then a solution of 1,3-propanediol (231 mg, 3.00 mmol, 1 equiv) in dry 1,4-dioxane (15 mL) was added to the reaction, which was heated at 90 °C for 3.5 days. The solvent was evaporated in vacuo, and the brown residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 75:25 to 60:40) to give diol **3** (258 mg, 1.65 mmol) as a yellow oil in 55% yield, ee > 99%, dr > 20:1. TLC (SiO_2): R_f = 0.30 (hexanes/EtOAc 60:40). $[\alpha]_D^{25}$ = −30 (c 1.0, $CHCl_3$), for *ent*-**3** $[\alpha]_{D,lit}$ = +35 (c 1.00, $CHCl_3$).[14] The spectral data (^1H and ^{13}C NMR) are in accordance with those reported in literature.[14]

*(4R,6R)-6-(Allyloxy)nona-1,8-dien-4-ol (**4**).* NaH (60% in mineral oil, 360 mg, 9 mmol, 2 equiv) was added to a solution of diol **3** (703 mg, 4.5 mmol, 1 equiv) in dry DMF (20 mL) at rt. After 10 min, allyl bromide (482 μL, 5.4 mmol, 1.2 equiv) was added. After 30 min of stirring, H_2O (100 mL) was added to the reaction, and the mixture was extracted with Et_2O (3 × 50 mL), then the organic phases were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 90:10 to 75:25) to furnish alcohol **4** (662 mg, 3.4 mmol) as a colorless oil in 75% yield. TLC (SiO_2): R_f = 0.50 (hexanes/EtOAc 75:25). $[\alpha]_D^{25}$ = −46 (c 1.0, $CHCl_3$), $[\alpha]_{D,lit}$ = −46 (c 1.0, $CHCl_3$).[6] The spectral data (^1H and ^{13}C NMR) are in accordance with those reported in literature.[6]

*1-((((4R,6R)-6-(Allyloxy)nona-1,8-dien-4-yl)oxy)methyl)-4-methoxybenzene (**5**).* NaH (86.4 mg, 2.2 mmol, 1.8 equiv, 60% in mineral oil) and TBAI (67.2 mg, 0.18 mmol, 0.15 equiv) were added to a solution of alcohol **4** (236 mg, 1.2 mmol, 1 equiv) in dry DMF (25 mL) at rt. After 5 min, PMBCl (332 μL, 2.4 mmol, 2 equiv) was added, and the reaction was stirred for 18 h. H_2O (100 mL) was added to the reaction, the mixture was extracted with ether (100 mL), and then the organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 95:5) to give alcohol **5** (319 mg, 1.0 mmol) as a colorless oil in 84% yield. TLC (SiO_2): R_f = 0.22 (hexanes/EtOAc 95:5). $[\alpha]_D^{25}$ = −82 (c 1.0, $CHCl_3$). IR (NaCl, film): 2917, 2859, 1612, 1513, 1384, 1248, 1076, 915, 756 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 1.58−1.65 (m, 2H), 2.24−2.40 (m, 4H), 3.57−3.87 (m, 3H), 3.80 (s, 3H), 4.06 (ddt, J = 12.5, 5.7, 1.3 Hz, 1H), 4.38 (d, J = 11.1 Hz, 1H), 4.57 (d, J = 11.1 Hz, 1H), 5.01−5.17 (m, 5H), 5.24 (dq,

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J = 17.2, 1.5 Hz, 1H), 5.72−5.98 (m, 3H), 6.85−6.94 (m, 2H), 7.24−7.32 (m, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 38.7, 38.7, 39.9, 55.3, 70.3, 70.8, 74.8, 75.3, 113.9 (2C), 116.5, 117.23, 117.26, 129.5 (2C), 131.1, 134.66, 134.73, 135.4, 159.2. HRMS (ESI) calcd for $C_{20}H_{28}O_3Na$ $[M + Na]^+$: 339.1931, found: 339.1931.

*(4R,6R)-6-(Allyloxy)nona-1,8-dien-4-yl Acetate (**6**).* Et_3N (619 μL, 4.4 mmol, 5 equiv) and DMAP (22 mg, 180 μmol, 20 mol %) were added to a solution of alcohol **4** (173 mg, 880 μmol, 1 equiv) in CH_2Cl_2 (15 mL) at 0 °C. After 5 min, Ac_2O (214 μL, 2.2 mmol, 2.5 equiv) was added, and the reaction was stirred for 2 h. Brine (20 mL) was added to the reaction, the mixture was extracted with CH_2Cl_2 (2 × 20 mL), and then the organic phases were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 90:10) to furnish acetate **6** (172 mg, 720 μmol) as a colorless oil in 82% yield. TLC (SiO_2): R_f = 0.41 (hexanes/EtOAc 90:10). $[\alpha]_D^{25}$ = −75 (*c* 1.0, $CHCl_3$), $[\alpha]_{D,lit.}$ = −75 (*c* 1.0, $CHCl_3$).[6] The spectral data (^{1}H and ^{13}C NMR) are in accordance with those reported in literature.[6]

*(R)-2-((R)-2-((4-Methoxybenzyl)oxy)pent-4-en-1-yl)-3,6-dihydro-2H-pyran (**7**).* Grubbs second generation catalyst (17 mg, 20 μmol, 5 mol %) was added to a solution of allyl ether **6** (127 mg, 400 μmol, 1 equiv) in CH_2Cl_2 (80 mL) at 40 °C. After 60 min, the solvent was removed in vacuo, and the residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 90:10) to furnish dihydropyran **7** (92 mg, 0.32 mmol) as a brownish oil in 80% yield. TLC (SiO_2): R_f = 0.26 (hexanes/EtOAc 95:5). $[\alpha]_D^{25}$ = −14 (*c* 1.0, $CHCl_3$). IR (NaCl, film): 2916, 2834, 1612, 1513, 1384, 1248, 1090, 915, 821 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.60−1.66 (m, 2H), 1.93−2.06 (m, 2H), 2.32−2.40 (m, 2H), 3.71−3.76 (m, 1H), 3.79−3.82 (m, 1H), 3.82 (s, 3H), 4.06−4.18 (m, 2H), 4.43 (d, J = 11.1 Hz, 1H), 4.60 (d, J = 11.1 Hz, 1H), 5.09 (dq, J = 10.4, 0.9 Hz, 1H), 5.13 (dq, J = 17.1, 1.5 Hz, 1H), 5.70−5.75 (m, 1H), 5.79−5.83 (m, 1H), 5.87 (ddt, J = 17.1, 10.0, 7.3 Hz, 1H), 6.88−6.92 (m, 2H), 7.27−7.32 (m, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 31.4, 38.8, 41.1, 55.1, 65.6, 70.0, 71.2, 74.2, 113.6 (2C), 117.1, 124.4, 126.2, 129.4 (2C), 130.9, 134.6, 159.1. HRMS (ESI) calcd for $C_{18}H_{24}O_3Na$ $[M + Na]^+$: 311.1618, found: 311.1646.

*(R)-1-((R)-3,6-Dihydro-2H-pyran-2-yl)pent-4-en-2-yl Acetate (**8**).* Grubbs second generation catalyst (5 mg, 6 μmol, 1 mol %) was added to a solution of allyl ether **6** (143 mg, 600 μmol, 1 equiv) in CH_2Cl_2 (120 mL) at 40 °C. After 60 min, the solvent was removed in vacuo, and the residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 90:10) to furnish dihydropyran **8** (108 mg, 0.51 mmol) as a brownish oil in 85% yield. TLC (SiO_2): R_f = 0.37 (hexanes/EtOAc 90:10). $[\alpha]_D^{25}$ = −5 (*c* 1.0, $CHCl_3$), $[\alpha]_{D,lit.}$ = −5 (*c* 1.0, $CHCl_3$).[6] The spectral data (^{1}H and ^{13}C NMR) are in accordance with those reported in literature.[6]

*(R)-6-((R)-2-((4-Methoxybenzyl)oxy)pent-4-en-1-yl)-5,6-dihydro-2H-pyran-2-one (**11**).* In a pressure tube, PCC (216 mg, 1 mmol, 1 equiv) was added to a solution of dihydropyran **7** (288 mg, 1.0 mmol, 1 equiv) in CH_2Cl_2 (25 mL) at rt, the reaction was stirred for 8 h at 80 °C. Every 8 h, a portion of PCC (216 mg, 1 mmol, 1 equiv) was added to the reaction, until the sixth portion. After the last period of 8 h, the mixture was cooled to rt and filtered through a plug containing a layer of Celite and a layer of silica, and then the plug was flushed with EtOAc. The solvent was removed in vacuo, and the residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 75:25) to furnish dihydropyranone **11** (78.6 mg, 0.26 mmol) as a colorless oil in 26% yield. TLC (SiO_2): R_f = 0.22 (hexanes/EtOAc 75:25). $[\alpha]_D^{25}$ = −40 (*c* 0.37, $CHCl_3$). IR (NaCl, film): 2920, 1721, 1513, 1384, 1247, 1033, 819, 756 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.69 (ddd, J = 14.6, 10.7, 2.6 Hz, 1H), 1.89 (ddd, J = 14.6, 9.9, 2.1 Hz, 1H), 2.26−2.32 (m, 2H), 2.32−2.40 (m, 2H), 3.80 (s, 3H), 3.86−3.93 (m, 1H), 4.39 (d, J = 11.0 Hz, 1H), 4.55−4.60 (m, 1H), 4.61 (d, J = 10.8 Hz, 1H), 5.08−5.15 (m, 2H), 5.82 (ddt, J = 17.1, 10.1, 7.2 Hz, 1H), 6.00 (dt, J = 9.8, 1.7 Hz, 1H), 6.82−6.89 (m, 3H), 7.22−7.27 (m, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 29.9, 38.6, 40.3, 55.3, 71.6, 73.7, 74.7, 113.9 (2C), 117.8, 121.4, 129.6 (2C), 130.5, 133.9, 145.2, 159.3, 164.3. HRMS (ESI) calcd for $C_{18}H_{22}O_4Na$ $[M + Na]^+$: 325.1410, found: 325.1411.

*(R)-1-((R)-6-Oxo-3,6-dihydro-2H-pyran-2-yl)pent-4-en-2-yl Acetate (**12**).* PCC (291 mg, 1.35 mmol, 3 equiv) and pyridine (219 μL, 2.7 mmol, 6 equiv) were added to a solution of dihydropyran **8** (94.6 mg, 450 μmol, 1 equiv) in CH_2Cl_2 (25 mL) at 40 °C. After 12 h, a second portion of PCC (291 mg, 1.35 mmol, 3 equiv) was added to the reaction. After a second period of 12 h, the mixture was filtered through a plug containing a layer of Celite and a layer of silica, and the plug was flushed with EtOAc. The solvent was removed in vacuo, and the residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 75:25) to furnish dihydropyranone **12** (62 mg, 0.28 mmol) as a colorless oil in 61% yield. TLC (SiO_2): R_f = 0.15 (hexanes/EtOAc 75:25). $[\alpha]_D^{25}$ = +22 (*c* 1.0, $CHCl_3$), $[\alpha]_{D,lit.}$ = +22 (*c* 1.0, $CHCl_3$).[6] The spectral data (^{1}H and ^{13}C NMR) are in accordance with those reported in literature.[6]

*(R)-6-((S)-2-((4-Methoxybenzyl)oxy)-4-oxopentyl)-5,6-dihydro-2H-pyran-2-one (**13**).* $PdCl_2$ (35.5 mg, 200 μmol, 1.1 equiv) and CuCl (36.4 mg, 360 μmol, 2 equiv) were added to a solution of alkene **11** (55 mg, 180 μmol, 1 equiv) in a mixture of DMF (14.9 mL) and H_2O (2.1 mL) at rt. After 3 h, H_2O (100 mL) was added to the reaction, the mixture was extracted with EtOAc (2 × 100 mL), and then the organic phases were combined, washed with H_2O (2 × 20 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 60:40) to furnish ketone **13** and aldehyde **14** (46 mg, 140 μmol, ratio 89:11) as a colorless oil in 80% yield. TLC (SiO_2): R_f = 0.20 (hexanes/EtOAc 60:40). $[\alpha]_D^{25}$ = −20 (*c* 0.32, $CHCl_3$). IR (NaCl, film): 3008, 2924, 2854, 1717, 1514, 1384, 1250, 1100, 820, 756 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.70−1.98 (m, 2H), 2.16 (s, 3H), 2.24−2.32 (m, 2H), 2.61 (dd, J = 15.8, 5.8 Hz, 1H), 2.75 (dd, J = 15.9, 5.8 Hz, 1H), 3.77 (s, 3H), 4.17−4.28 (m, 1H), 4.40−4.60 (m, 3H), 5.97 (dt, J = 9.8, 1.6 Hz, 1H), 6.79−6.89 (m, 3H), 7.17−7.25 (m, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 29.7, 31.0, 40.6, 48.7, 55.2, 71.2, 72.1, 74.4, 113.8 (2C), 121.2, 129.5 (2C), 130.1, 145.0, 159.3, 163.9, 206.7. HRMS (ESI) calcd for $C_{18}H_{22}O_5Na$ $[M + Na]^+$: 341.1359, found: 341.1366.

*(S)-4-Oxo-1-((R)-6-oxo-3,6-dihydro-2H-pyran-2-yl)pentan-2-yl Acetate (**15**).* $PdCl_2$ (42.5 mg, 240 μmol, 1 equiv) and CuCl (47.9 mg, 470 μmol, 2 equiv) were added to a solution of alkene **12** (53.1 mg, 240 μmol, 1 equiv) in a mixture of DMF (4.8 mL) and H_2O (800 μL) at rt. After 3 h, H_2O (50 mL) was added to the reaction, the mixture was extracted with EtOAc (3 × 50 mL), and then the organic phases were combined, washed with H_2O (2 × 20 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 50:50 to 30:70) to furnish ketone **15** and aldehyde **16** (47 mg, 200 μmol, ratio 88:12) as a colorless oil in 83% yield. TLC (SiO_2): R_f = 0.31 (hexanes/EtOAc 30:70). $[\alpha]_D^{25}$ = +59 (*c* 1.0, $CHCl_3$). IR (NaCl, film): 2918, 1733, 1717, 1384, 1242, 1045, 821 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.85−2.06 (m, 2H), 1.98 (s, 3H), 2.14 (s, 3H), 2.29−2.36 (m, 2H), 2.77 (d, J = 6.2 Hz, 2H), 4.49 (qd, J = 8.0, 3.7 Hz, 1H), 5.36 (quint., J = 6.3 Hz, 1H), 5.96 (dt, J = 10.0, 1.6 Hz, 1H), 6.84 (dt, J = 9.8, 4.0 Hz, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 20.9, 29.4, 30.4, 39.2, 47.8, 67.1, 74.5, 121.2, 144.8, 163.5, 170.1, 205.2. HRMS (ESI) calcd for $C_{12}H_{16}O_5Na$ $[M + Na]^+$: 263.0890, found: 263.0891.

*(R)-6-((2S,6R,E)-6-Hydroxy-2-((4-methoxybenzyl)oxy)-4-oxo-8-phenyloct-7-en-1-yl)-5,6-dihydro-2H-pyran-2-one (**17**).* Cy_2BCl (76.7 μL, 350 μmol, 2.5 equiv) was added to a solution of ketone **13** (44.6 mg, 140 μmol, 1.0 equiv) in dry Et_2O (5.5 mL) at −40 °C, Et_3N (59.1 μL, 420 μmol, 3 equiv) was added to the reaction, and the mixture was stirred at −40 °C. After 30 min, the reaction was cooled to −78 °C, cinnamaldehyde (71.2 μL, 560 μmol, 4.0 equiv) was added at −78 °C, and the reaction was stirred for 1 h at the same temperature. MeOH (1 mL) was added to the reaction, and the mixture was further stirred for 15 min at rt. Then the reaction contents were concentrated in vacuo. The residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 60:40) to give aldol adduct **17** (45 mg, 100 μmol) as a colorless oil in 71% yield. TLC (SiO_2): R_f = 0.10 (hexanes/EtOAc 60:40). $[\alpha]_D^{25}$ = +3 (*c* 1.0, $CHCl_3$). IR (NaCl, film): 3421 (broad), 2924, 2852, 1717, 1384, 1258, 1032, 803, 755 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.78 (ddd, J = 14.5, 9.2, 3.0 Hz,

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1H), 1.92 (ddd, J = Hz, 14.5, 9.5, 3.8 Hz, 1H), 2.22−2.30 (m, 2H), 2.62−2.85 (m, 4H), 3.19 (br s, 1H), 3.77 (s, 3H), 4.21−4.33 (m, 1H), 4.42−4.60 (m, 3H), 4.70−4.80 (m, 1H), 5.98 (dt, J = 9.9, 1.6 Hz, 1H), 6.18 (dd, J = 16.0, 6.0 Hz, 1H), 6.61 (d, J = 16.0 Hz, 1H), 6.76−6.90 (m, 3H), 7.17−7.40 (m, 7H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 29.7, 40.6, 48.8, 50.4, 55.2, 68.4, 71.2, 72.2, 74.4, 113.8 (2C), 121.2, 126.4 (2C), 127.6, 128.5 (2C), 129.5 (2C), 130.0, 130.2, 136.4, 145.1, 159.3, 164.0, 208.9. HRMS (ESI) calculated for $C_{27}H_{30}O_6Na$ $[M + Na]^+$: 473.1935, found: 473.1881; calculated for $C_{26}{}^{13}CH_{30}O_6Na$ $[M + Na]^+$: 474.1968, found: 474.1946.

*(R)-6-((2R,4S,6R,E)-4,6-Dihydroxy-2-((4-methoxybenzyl)oxy)-8-phenyloct-7-en-1-yl)-5,6-dihydro-2H-pyran-2-one (**19**).* Et_2BOMe solution (1.0 M in THF, 311 μL, 311 μmol, 3.5 equiv) was added to a solution of aldol adduct **17** (40.0 mg, 88.8 μmol, 1.0 equiv) in a mixture of dry THF/MeOH (4:1, 5 mL) at −78 °C. After 20 min, solid $LiBH_4$ (7.5 mg, 311 μmol, 3.5 equiv) was added in a single portion at −78 °C, and the reaction was stirred for 2 h at the same temperature. Phosphate buffer solution (pH 7.0, 8 mL), MeOH (1 mL), and H_2O_2 solution (30%, 0.5 mL) were added to the reaction, and the mixture was further stirred for 1 h at 0 °C. Then the reaction contents were diluted with H_2O (10 mL), the mixture was extracted with EtOAc (3 × 30 mL), and the organic phases were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 30:70) to give diol **19** (40.2 mg, 88.8 μmol) as a colorless oil in quantitative yield. TLC (SiO_2): R_f = 0.20 (hexanes/EtOAc 30:70). $[\alpha]_D{}^{25}$ = −14 (c 1.0, $CHCl_3$). IR (NaCl, film): 3405 (broad), 2920, 1710, 1513, 1384, 1249, 1033, 819, 752 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.56−1.75 (m, 2H), 1.81−1.97 (m, 4H), 2.28−2.34 (m, 2H), 3.63 (br s, 1H), 3.78 (s, 3H), 3.87 (br s, 1H), 4.05−4.15 (m, 1H), 4.15−4.27 (m, 1H), 4.43−4.66 (m, 4H), 6.00 (dt, J = 9.9, 1.7 Hz, 1H), 6.21 (dd, J = 15.8, 6.3 Hz, 1H), 6.61 (d, J = 16.0 Hz, 1H), 6.81−6.89 (m, 3H), 7.20−7.41 (m, 7H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 29.8, 40.2, 40.7, 44.1, 55.2, 69.1, 72.2, 72.89, 72.94, 74.7, 114.0 (2C), 121.3, 126.4 (2C), 127.5, 128.5 (2C), 129.8, 129.8, 129.9 (2C), 131.9, 136.7, 145.1, 159.5, 164.1. HRMS (ESI) calculated for $C_{27}H_{32}O_6Na$ $[M + Na]^+$: 475.2091, found: 475.2105.

*(R)-6-((R)-3-((4R,6R)-2,2-Dimethyl-6-((E)-styryl)-1,3-dioxan-4-yl)-2-((4-methoxybenzyl)oxy)propyl)-5,6-dihydro-2H-pyran-2-one (**20**).* Pyridinium p-toluenesulfonate (PPTS, 1.5 mg, 5.8 μmol, 10 mol %) was added to a solution of diol **19** (26.0 mg, 57.5 μmol, 1 equiv) in 2,2-dimethoxypropane (2,2-DMP, 2.3 mL) at rt. After 5 h, the solvent was removed in vacuo, and the residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 75:25) to furnish acetonide **20** (22.0 mg, 44.7 μmol) as a colorless oil in 78% yield. TLC (SiO_2): R_f = 0.18 (hexanes/EtOAc 75:25). $[\alpha]_D{}^{25}$ = −2 (c 1.0, $CHCl_3$). IR (NaCl, film): 2991, 2918, 1718, 1513, 1384, 1248, 1034, 818, 749 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.48 (s, 3H), 1.53 (s, 3H), 1.56−1.77 (m, 5H), 1.90−2.04 (m, 1H), 2.26−2.35 (m, 1H), 3.80 (s, 3H), 4.00−4.20 (m, 2H), 4.47−4.62 (m, 4H), 6.00 (dt, J = 9.8, 1.7 Hz, 1H), 6.17 (dd, J = 16.0, 6.2 Hz, 1H), 6.61 (d, J = 16.1 Hz, 1H), 6.80−6.91 (m, 3H), 7.20−7.41 (m, 7H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 20.0, 29.8, 30.3, 37.6, 41.6, 43.0, 55.3, 65.3, 70.0, 71.3, 72.7, 74.6, 98.8, 113.9 (2C), 121.3, 126.5 (2C), 127.6, 128.4 (2C), 129.5 (2C), 129.8, 130.6, 130.7, 136.6, 145.1, 159.3, 164.3. HRMS (ESI) calculated for $C_{30}H_{36}O_6Na$ $[M + Na]^+$: 515.2404, found: 515.2398.

*3-((tert-Butyldimethylsilyl)oxy)propanal (**24**).* DMSO (1.69 mL, 23.8 mmol, 1.5 equiv) was added to a solution of oxalyl chloride (1.78 mL, 20.6 mmol, 1.3 equiv) in CH_2Cl_2 (70 mL) at −78 °C, the mixture was stirred for 15 min, and a solution of alcohol **23** (3019 mg, 15.9 mmol, 1 equiv) in CH_2Cl_2 (30 mL) was added to the reaction at −78 °C. This mixture was stirred for 1 h. Triethylamine (11.2 mL, 79.3 mmol, 5 equiv) was added to the reaction at −78 °C, and the cooling bath was removed. After the mixture has reached room temperature, Et_2O (50 mL) was added and the organic phase was washed with saturated aqueous solution of NH_4Cl (50 mL), dried ($MgSO_4$), and concentrated. The product was purified by flash chromatography (SiO_2, hexanes:EtOAc, 95:5) to furnish aldehyde **24** (2700 mg, 14.3 mmol) as a colorless oil in 90% yield. TLC (SiO_2): R_f = 0.50 (hexanes/EtOAc 90:10). The spectral data (^{1}H and ^{13}C NMR) are in accordance with those reported in literature.[7]

*(R)-1-((tert-Butyldimethylsilyl)oxy)hex-5-en-3-ol (**25**).* Powdered molecular sieves 4 Å (7.5 g), (*R*)-BINOL (639 mg, 2.2 mmol, 0.2 equiv), dry CH_2Cl_2 (15 mL), TFA (2.6 μL, 34 μmol, 3 mequiv), and $Ti(OiPr)_4$ (340 μL, 1.1 mmol, 0.1 equiv) were added to a flask, and this mixture was refluxed for 1 h to result in a dark red suspension that was cooled to rt. A solution of aldehyde **24** (2100 mg, 11.2 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added to the dark red mixture via cannula, this mixture was stirred for 5 min at rt, and after cooling to −50 °C, allyltributylstannane (5.35 mL, 16.7 mmol, 1.5 equiv) was added dropwisely, with slow increasing of the temperature to −20 °C. The reaction was stirred for 22 h, 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 (SiO_2, hexanes:EtOAc, 90:10) to furnish alcohol **25** (2020 mg, 8.8 mmol) as a colorless oil in 79% yield. Enantiomeric ratio of alcohol **25** was determined to be 95:5, after derivatization to the corresponding Mosher ester (see ref 7). TLC (SiO_2): R_f = 0.34 (hexanes/EtOAc 90:10). $[\alpha]_D{}^{25}$ = +8 (c 1.0, $CHCl_3$), $[\alpha]_{D,lit.}$ = +7.8 (c 1.0, $CHCl_3$).[29] The spectral data (^{1}H and ^{13}C NMR) are in accordance with those reported in literature.[7]

*(R)-5-Allyl-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (**26**).* To a solution of alcohol **25** (1701 mg, 7.31 mmol, 1 equiv) in anhydrous CH_2Cl_2 (45 mL) were added imidazole (1005 mg, 14.6 mmol, 2 equiv) and TBSCl (1704 mg, 11.0 mmol, 1.5 equiv). The reaction was stirred for 1 day when H_2O (75 mL) and CH_2Cl_2 (100 mL) were added to the reaction. The organic phase was separated, dried (Na_2SO_4), and concentrated in vacuo. The product was purified by flash chromatography (SiO_2, hexanes:EtOAc, 95:5) to furnish TBS-ether **26** (2500 mg, 7.25 mmol) as a colorless oil in 99% yield. TLC (SiO_2): R_f = 0.57 (hexanes/EtOAc 97:3). $[\alpha]_D{}^{25}$ = −20 (c 1.0, $CHCl_3$), $[\alpha]_{D,lit.}$ = −20 (c 1.11, $CHCl_3$).[36] The spectral data (^{1}H and ^{13}C NMR) are in accordance with those reported in literature.[36]

*(S)-3,5-Bis((tert-butyldimethylsilyl)oxy)pentanal (**27**).* 4-Methylmorpholine 4-oxide (NMO, 315 mg, 2.61 mmol, 1.2 equiv) and OsO_4 solution (0.1 M in *t*-BuOH, 870 μL, 43.5 μmol, 2 mol %) were added to a solution of alkene **26** (750 mg, 2.17 mmol, 1 equiv) in a mixture of THF/H_2O (3:1, 12 mL) at rt. After 12 h, solid Na_2SO_3 (200 mg) was added in a single portion at rt, and the mixture was stirred for 30 min at the same temperature. The reaction contents were diluted with H_2O (30 mL), the mixture was extracted with EtOAc (2 × 30 mL), and the organic phases were combined, dried (Na_2SO_4), and concentrated in vacuo to furnish crude diol that was used in next step without further purification.

$NaIO_4$ (1175 mg, 5.44 mmol, 2.5 equiv) was added to a solution of the crude diol in THF/H_2O (3:1, 24 mL) at rt. After 1 h at rt, H_2O (30 mL) was added, the resulting mixture was extracted with EtOAc (3 × 30 mL), and then the organic phases were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 97:3) to give aldehyde **27** (721 mg, 2.08 mmol) as a pale brown oil in 96% yield for two steps. TLC (SiO_2): R_f = 0.90 (hexanes/EtOAc 90:10). $[\alpha]_D{}^{25}$ = −7 (c 1.0, $CHCl_3$), $[\alpha]_{D,lit.}$ = −7.9 (c 1.23, $CHCl_3$).[36] The spectral data (^{1}H and ^{13}C NMR) are in accordance with those reported in literature.[36]

*(3R,5S,7S,E)-7,9-Bis((tert-butyldimethylsilyl)oxy)-1-phenylnon-1-ene-3,5-diol (**30**).* $BF_3{\cdot}Et_2O$ (321 μL, 2.6 mmol, 1.3 equiv) was added to a solution of aldehyde **27** (693 mg, 2.0 mmol, 1 equiv) and silyl enol ether **28** (568 mg, 2.6 mmol, 1.3 equiv) in CH_2Cl_2 (20 mL) at −78 °C. The reaction was stirred for 2 h and then quenched by addition of saturated aqueous solution of $NaHCO_3$ (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the organic phases were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was partially purified by flash chromatography (SiO_2, hexanes:EtOAc, 90:10 to 75:25) to give impure aldol adduct **29**; dr 61:39 was checked by ^{1}H NMR.

Et_2BOMe solution (1.0 M in THF, 4.0 mL, 4.0 mmol, 2 equiv) was added to a solution of impure aldol adduct **29** in a mixture of dry

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THF/MeOH (4:1, 20 mL) at −78 °C. After 30 min, solid $LiBH_4$ (147 mg, 6.0 mmol, 3 equiv) was added in a single portion at −78 °C, and the reaction was stirred for 2.5 h at the same temperature. Phosphate buffer solution (pH 7.0, 10 mL), MeOH (12 mL), and H_2O_2 solution (30%, 1.2 mL) were added to the reaction, and the mixture was further stirred for 1 h at 0 °C. Then the reaction contents were diluted with H_2O (15 mL), the mixture was extracted with EtOAc (3 × 30 mL), and the organic phases were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 80:20) to give diol **30** (430 mg, 0.87 mmol) as a colorless oil in 43%% yield for two steps after semipreparative HPLC on a silica column (dimensions 19 mm × 100 mm, particle size 5 μm and 99:1 hexanes/IPA as eluent, flow 10 mL/min t_R = 12.33 min (major isomer), t_R = 13.18 min (minor isomer). The following data refer to diol **30** after HPLC purification. TLC (SiO_2): R_f = 0.23 (hexanes/EtOAc 80:20). $[\alpha]_D^{25}$ = −8 (*c* 1.0, $CHCl_3$). IR (NaCl, film): 3385 (broad), 2954, 2928, 2856, 1384, 1255, 1093, 836, 776 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 0.06 (s, 6H), 0.11 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H), 0.91 (s, 9H), 1.55−1.90 (m, 6H), 3.66 (t, *J* = 6.2 Hz, 2H), 3.90−4.35 (m, 4H), 4.53−4.61 (m, 1H), 6.21 (dd, *J* = 15.8, 6.2 Hz, 1H), 6.62 (d, *J* = 15.8 Hz, 1H), 7.17−7.40 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: − 5.4 (2C), − 4.84, − 4.80, 17.8, 18.1, 25.7 (3C), 25.8 (3C), 38.9, 42.2, 44.3, 59.5, 68.9, 69.3, 72.7, 126.4 (2C), 127.3, 128.4 (2C), 129.3, 132.1, 136.9. HRMS (ESI) calculated for $C_{27}H_{50}O_4Si_2Na$ $[M + Na]^+$: 517.3140, found: 517.3126.

*(S)-5-(((4S,6R)-2,2-Dimethyl-6-((E)-styryl)-1,3-dioxan-4-yl)-methyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (**31**).* Pyridinium *p*-toluenesulfonate (PPTS, 10.3 mg, 40 μmol, 10 mol %) was added to a solution of diol **30** (198 mg, 400 μmol, 1 equiv) in 2,2-dimethoxypropane (2,2-DMP, 5 mL) at rt. After 3 h, the solvent was removed in vacuo, and the residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 95:5) to furnish acetonide **31** (207.6 mg, 388 μmol) as a brownish oil in 97% yield. TLC (SiO_2): R_f = 0.90 (hexanes/EtOAc 90:10). $[\alpha]_D^{25}$ = +24 (*c* 1.0, $CHCl_3$). IR (NaCl, film): 2992, 2928, 2856, 1383, 1255, 1096, 835, 775 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 0.08 (s, 6H), 0.11 (s, 6H), 0.92 (s, 9H), 0.93 (s, 9H), 1.29−1.80 (m, 6H), 1.47 (s, 3H), 1.54 (s, 3H), 3.69 (t, *J* = 6.5 Hz, 2H), 4.01−4.15 (m, 2H), 4.50−4.60 (m, 1H), 6.19 (dd, *J* = 15.9, 6.2 Hz, 1H), 6.62 (d, *J* = 15.9 Hz, 1H), 7.18−7.42 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: − 5.3 (2C), − 4.5, − 4.1, 18.0, 18.2, 20.2, 25.9 (6C), 30.3, 37.8, 41.0, 44.8, 59.4, 65.5, 66.0, 70.0, 98.6, 126.5 (2C), 127.5, 128.4 (2C), 130.0, 130.5, 136.7. HRMS (ESI) calculated for $C_{30}H_{54}O_4Si_2Na$ $[M + Na]^+$: 557.3453, found: 557.3460.

*(S)-3-((tert-Butyldimethylsilyl)oxy)-4-((4S,6R)-2,2-dimethyl-6-((E)-styryl)-1,3-dioxan-4-yl)butan-1-ol (**32**).* Pyridine (1.86 mL, 23 mmol, 100 equiv) was added to a solution of TBS-ether **31** (123 mg, 230 μmol, 1 equiv) in dry THF (10 mL) at 0 °C. After 5 min, HF·py (750 μL, 29 mmol, 125 equiv) was added dropwisely at 0 °C, and the reaction was stirred for 2.5 h at rt. Saturated aqueous solution of $NaHCO_3$ (50 mL) was added to the reaction, the mixture was extracted with EtOAc (3 × 25 mL), and then the organic phases were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 75:25) to give the alcohol **32** (70.0 mg, 166 μmol) as a colorless oil in 72% yield. TLC (SiO_2): R_f = 0.20 (hexanes/EtOAc 95:5). TLC (SiO_2): R_f = 0.40 (hexanes/EtOAc 75:25). $[\alpha]_D^{25}$ = +20 (*c* 1.0, $CHCl_3$). IR (NaCl, film): 3418 (broad), 2992, 2950, 2856, 1382, 1254, 1093, 965, 836, 775 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 0.10 (s, 3H), 0.12 (s, 3H), 0.91 (s, 9H), 1.26−1.92 (m, 6H), 1.45 (s, 3H), 1.52 (s, 3H), 2.54 (br s, 1H), 3.69−3.88 (m, 2H), 3.99−4.15 (m, 2H), 4.49−4.58 (m, 1H), 6.16 (dd, *J* = 15.9, 6.2 Hz, 1H), 6.60 (d, *J* = 15.9 Hz, 1H), 7.18−7.42 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: − 4.6, − 4.3, 17.9, 20.1, 25.8 (3C), 30.2, 37.7, 39.1, 43.9, 59.4, 65.6, 67.8, 69.9, 98.7, 126.4 (2C), 127.6, 128.4 (2C), 129.7, 130.7, 136.6. HRMS (ESI) calculated for $C_{24}H_{40}O_4SiNa$ $[M + Na]^+$: 443.2588, found: 443.2603.

*(4R,6S)-6-((tert-Butyldimethylsilyl)oxy)-7-((4S,6R)-2,2-dimethyl-6-((E)-styryl)-1,3-dioxan-4-yl)hept-1-en-4-ol (**33**).* Dess−Martin periodinane (24.7 mg, 56.4 μmol, 1.2 equiv) was added to a solution of alcohol **32** (19.8 mg, 47.0 μmol, 1 equiv) in dry CH_2Cl_2 (5 mL) at 0 °C. The reaction was stirred at 0 °C for 2 h, solvent was removed in vacuo, and the aldehyde was partially purified by flash chromatography (SiO_2, CH_2Cl_2).

For application of Brown allylation, the reagent (+)-Ipc_2BAllyl was prepared as follows. Solid (+)-Ipc_2BCl (338 mg, 1.0 mmol) was added to anhydrous THF (18.7 mL), this solution was cooled to −78 °C, and allylMgBr solution (1.0 M, 1.0 mL, 1.0 mmol) was added, after 30 min at −78 °C, and was stirred for 4 h at rt. The concentration of (+)-Ipc_2BAllyl was considered as 0.05 M.

A solution of (+)-Ipc_2BAllyl (0.05 M, 1.5 mL, 75 μL, 1.5 equiv) was added dropwisely to a solution of aldehyde in dry THF (12 mL) at −78 °C. After 1 h at −78 °C, H_2O (20 mL) and $NaBO_3{\cdot}4H_2O$ (500 mg) were added, and the resulting mixture was warmed to rt and stirred further for 90 min. The mixture was extracted with EtOAc (2 × 20 mL), and then the organic phases were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 90:10) to give the alcohol **33** (15.2 mg, 33.0 μmol) as a colorless oil in 70% yield for two steps, and dr > 95:5. TLC (SiO_2): R_f = 0.35 (hexanes/EtOAc 85:15). $[\alpha]_D^{25}$ = +20 (*c* 1.0, $CHCl_3$). IR (NaCl, film): 2992, 2929, 2856, 1383, 1255, 1090, 939, 836, 776 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 0.11 (s, 3H), 0.14 (s, 3H), 0.91 (s, 9H), 1.44 (s, 3H), 1.51 (s, 3H), 1.57−1.78 (m, 6H), 2.12−2.32 (m, 2H), 3.41 (br s, 1H), 3.95−4.11 (m, 2H), 4.16−4.27 (m, 1H), 4.49−4.58 (m, 1H), 5.05−5.15 (m, 2H), 5.85 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H), 6.16 (dd, *J* = 16.1, 6.3 Hz, 1H), 6.60 (d, *J* = 15.9 Hz, 1H), 7.18−7.41 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: − 4.7, − 4.2, 17.9, 20.2, 25.8 (3C), 30.3, 37.7, 42.0, 42.3, 43.6, 65.6, 67.9, 68.6, 69.9, 98.7, 117.2, 126.5 (2C), 127.7, 128.5 (2C), 129.8, 130.8, 135.0, 136.6. HRMS (ESI) calculated for $C_{27}H_{44}O_4SiNa$ $[M + Na]^+$: 483.2901, found:483.2887.

*(4R,6R)-6-((tert-Butyldimethylsilyl)oxy)-7-((4S,6R)-2,2-dimethyl-6-((E)-styryl)-1,3-dioxan-4-yl)hept-1-en-4-yl Acrylate (**34**).* DIPEA (222 μL, 1.26 mmol, 40 equiv) was added to a solution of alcohol **33** (14.5 mg, 31.5 μmol, 1 equiv) in dry CH_2Cl_2 (5 mL) at 0 °C. After 5 min, acryloyl chloride (96 μL, 1.13 mmol, 36 equiv) was added, and the reaction was stirred for 2 h at 0 °C. Brine (10 mL) was added to the reaction, the mixture was extracted with Et_2O (2 × 10 mL), and then the organic phases were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 95:5) to give the acrylate **34** (13.5 mg, 26.2 μmol) as a colorless oil in 83% yield. TLC (SiO_2): R_f = 0.20 (hexanes/EtOAc 95:5). $[\alpha]_D^{25}$ = +7 (*c* 1.0, $CHCl_3$). IR (NaCl, film): 2952, 2928, 2856, 1724, 1383, 1196, 966, 836, 775 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 0.05 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.44 (s, 3H), 1.51 (s, 3H), 1.54−1.90 (m, 6H), 2.35−2.43 (m, 2H), 3.88−4.08 (m, 2H), 4.48−4.58 (m, 1H), 5.02−5.13 (m, 3H), 5.69−5.85 (m, 1H), 5.80 (dd, *J* = 10.3, 1.6 Hz, 1H), 6.10 (dd, *J* = 17.2, 10.3 Hz, 1H), 6.16 (dd, *J* = 15.9, 6.2 Hz, 1H), 6.38 (dd, *J* = 17.2, 1.6 Hz, 1H), 6.60 (d, *J* = 15.9 Hz, 1H), 7.18−7.41 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: − 4.3 (2C), 18.0, 20.1, 25.9 (3C), 30.3, 37.7, 38.9, 41.9, 45.1, 65.6, 66.3, 70.0, 71.2, 98.6, 118.0, 126.5 (2C), 127.6, 128.5 (2C), 128.9, 129.9, 130.3, 130.7, 133.3, 136.7, 165.6. HRMS (ESI) calculated for $C_{30}H_{46}O_5SiNa$ $[M + Na]^+$: 537.3007, found:537.2990.

*Cryptomoscatone E3 (**1**).* Grubbs catalyst first generation (2.1 mg, 2.5 μmol, 10 mol %) was added to a solution of acrylate **34** (13.0 mg, 25 μmol, 1 equiv) in dry CH_2Cl_2 (5 mL) at 40 °C. After 4 h, the solvent was removed in vacuo, and the residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 90:10 to 75:25) to give the dihydropyranone **35** (10.8 mg, 22 μmol) as a brownish oil in 88% yield. The product was considered pure and was immediately used in next step.

A solution of aqueous HCl (3.5 M, 100 μL) was added to a solution of lactone **35** (4.9 mg, 10 μmol, 1 equiv) in THF (2 mL) at 0 °C, the temperature was increased to rt, and the reaction was stirred for 2 h. Solid $NaHCO_3$ (100 mg, 1.2 mmol) was added to the reaction, and the mixture was directly purified by flash chromatography (SiO_2, EtOAc) to give cryptomoscatone E3 (**1**, 3.0 mg, 9.0 μmol) as a colorless oil in 90% yield. TLC (SiO_2): R_f = 0.24 (EtOAc). $[\alpha]_D^{25}$ = −5 (*c* 0.3, MeOH). IR (NaCl, film): 3384 (broad), 2919, 2850, 1704, 1384, 1259, 1056, 810, 751 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 1.57−2.12 (m, 9H), 2.33−2.42 (m, 2H), 4.27−4.40 (m, 2H), 4.55−

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4.64 (m, 1H), 4.69−4.82 (m, 1H), 6.02 (dt, J = 9.6, 1.6 Hz, 1H), 6.23 (dd, J = 15.9, 6.5 Hz, 1H), 6.60 (d, J = 15.9 Hz, 1H), 6.89 (ddd, J = 9.5, 4.6, 3.9 Hz, 1H), 7.22−7.41 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 29.9, 42.4, 42.9, 43.1, 64.7, 70.2, 73.8, 75.1, 121.3, 126.5 (2C), 127.8, 128.6 (2C), 130.4, 131.5, 136.4, 145.5, 164.6. ^{13}C NMR (62.9 MHz, methanol-d_4) δ: 30.9, 44.2, 46.1, 46.5, 64.8, 67.4, 72.1, 76.7, 121.4, 127.5 (2C), 128.5, 129.6 (2C), 131.6, 133.3, 138.4, 148.5, 166.9. HRMS (ESI) calculated for $C_{19}H_{24}O_5Na$ $[M + Na]^+$: 355.1516, found: 355.1504.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01956.

HPLC chromatograms, H^{1}NMR, C^{13}NMR, and CD spectra, and computational data (PDF)

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Notes

The authors declare no competing financial interest.

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