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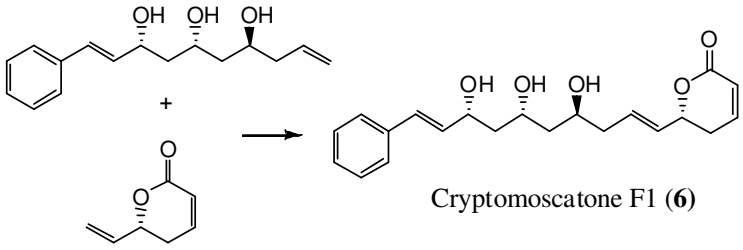
Graphical Abstract

First Total Synthesis of Cryptomoscatone F1

Atla Raju and Gowravaram Sabitha,[a]*



Cryptomoscatone F1 (**6**)

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Communication

First Total Synthesis of Cryptomoscatone F1

Atla Raju and Gowravaram Sabitha*

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Abstract— Total synthesis of cryptomoscatone F1 has been accomplished for the first time. The strategy involves chelation-controlled allylation, the addition of alkylzinc to an aldehyde and olefin cross-metathesis reactions as key steps. A new route to a vinyl lactone was explored.

Styryllactones such as cryptomoscatones D1,[1] D2, E1, E2 (cryptofolione), E3, and F1[2] were isolated from branch and stem bark of *Cryptocarya mandiocanna*, *and C. moschata* Lauraceae. Their structures were established by spectroscopic methods. *C moschata* Nees is an arboreal species that is widely spread in the Atlantic forests of Brazil. It is recognised as an important food source for primates such as *Brachyteles arachnoids* E.Geoffroy, 1806. *Cryptocarya* is one of the largest pantropical genera in Lauraceae. The genus includes about 350 species, and lactones isolated from these species have been shown to exhibit several bi ological activities.[3] Cryptomoscatone D2 possesses high dose-dependent and time-dependent cytotoxicity in HeLa, SiHa, C33A, and MRC-5 cell lines.[4] Cryptofolione showed activity towards *Trypanosoma cruzi* trypomastigotes, reducing their number by 77% at 250 μg mL^{-1}.[5]

Thus, interesting biological activities of cryptomoscatones, along with limited availability from natural sources, impelled us to undertake a total synthesis of cryptomoscatone F1. We have reported the synthesis of cryptomoscatone D2[6a] and cryptofolione.[7] Recently, similar cryptomoscatones[6b,c,d] have attracted the attention of other synthetic research groups. Now, we describe herein the first total synthesis of cryptomoscatone F1 (**6**). It was proposed a threo relationship between OH-4' and OH-6' and erythro relationship between OH-6' and OH-8'.

Our synthetic plan toward **6** is summarized in Scheme 1. We envisaged that F1 could be derived from the triol **7** and the vinyl lactone **8** via olefin cross-metathesis (CM). While vinyl lactone **8** could be prepared from commercially available (*R*)-2,3-*O*-cyclohexylidene glyceraldehyde[8] by a new synthetic route.

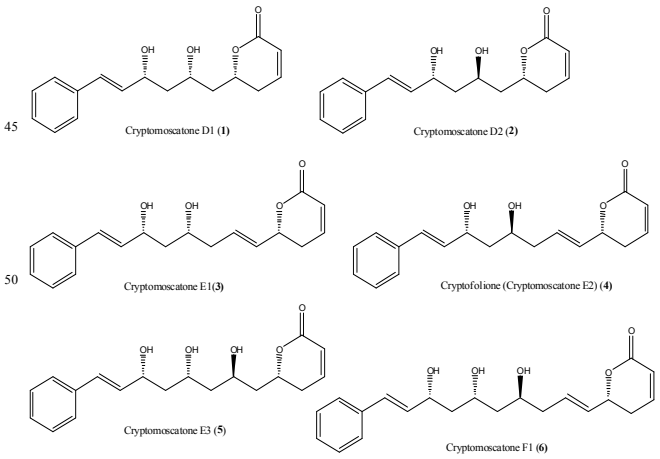
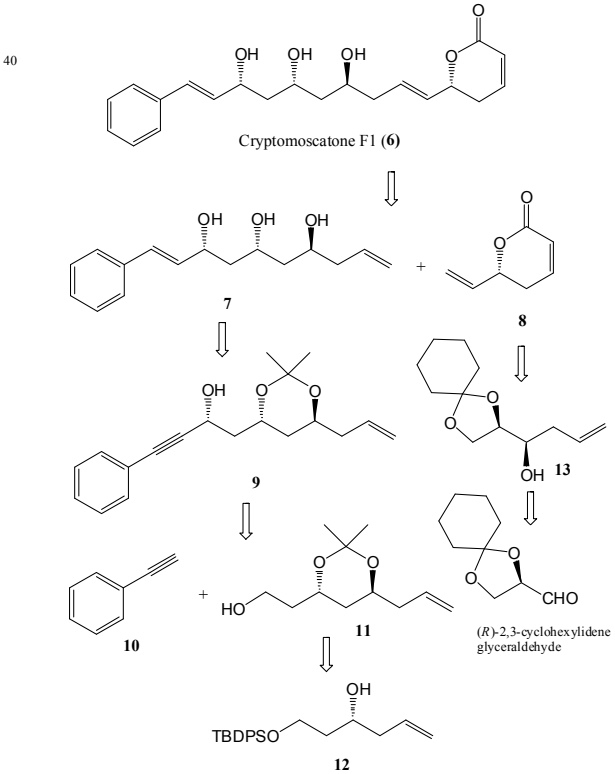


Figure 1. Natural Cryptomoscatones **1-6**



Scheme 1. Retrosynthetic analysis for **6**

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†Electronic supplementary information (ESI) available: spectral data of all compds and copies of ^{1}H and ^{13}C NMR spectra of all compds

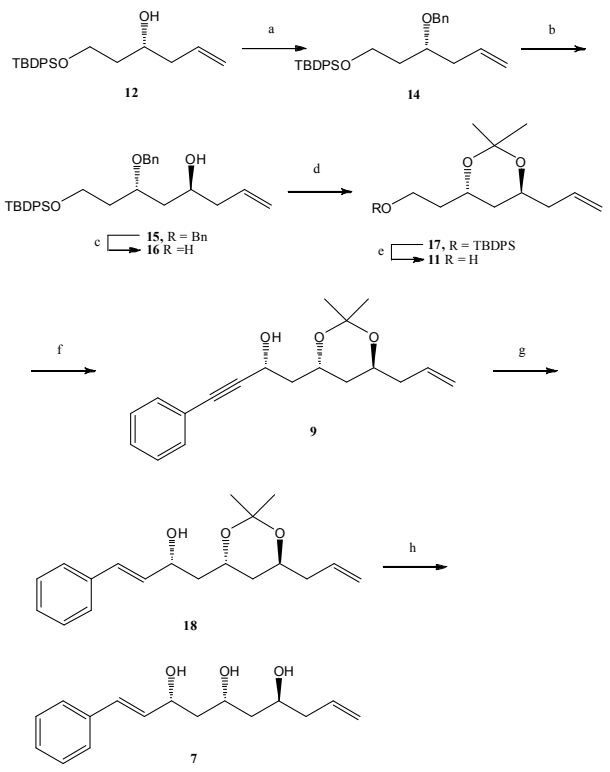
Results and Discussion

The synthesis of triol **7**, depicted in Scheme 2, started with protection of **12** [(*S*)-enantiomer] (prepared as reported for its known *R*-enantiomer)[9] as its benzyl ether using benzyl trichloroacetamidate and CSA in CH_2Cl_2 to give **14** in 84% yield. To establish the second stereogenic center with the required stereochemistry, it was thought worthwhile to adopt a chelation-controlled stereoselective allylation reaction occurring through 1,3-induction. Accordingly, oxidative cleavage of the olefin in compound **14** under Jin's one-pot conditions[10] using OsO_4–$NaIO_4$ and 2,6-lutidine in dioxane–water (3:1) furnished the corresponding aldehyde, which was immediately treated with allyltrimethyl silane in the presence of $MgBr_2.OEt_2$[11] in CH_2Cl_2 at 0^0C to afford homoallyl alcohol **15** in 86 % yield with a diastereomeric ratio of 20:1. The benzyl group was deprotected with Li/Naphthalene in dry THF to give diol **16**, which was subsequently transformed into isopropylidene derivative **17** with dimethoxypropane and a catalytic amount of PPTS in 90% yield. The TBDPS group in compound **17** was removed with TBAF in THF and the *anti* geometry was assigned to 1,3-diol group in compound **11** by Rychnovsky method.[12] In the ^{13}C NMR spectrum of **11**, the resonance arising from the acetonide methyl groups appeared at δ = 24.64 and 24.75 ppm and that of the quaternary carbon atom at δ = 100.29 ppm, indicating a 1,3-*anti* relationship.

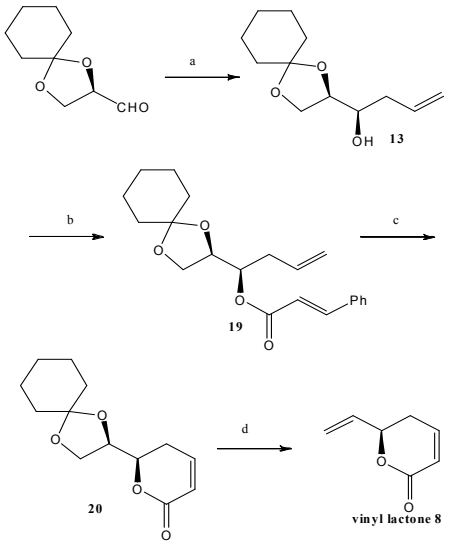
After confirming the sterocenters, compound **11** on oxidation with IBX in CH_3CN gave an aldehyde. Next, we planned to introduce C8' chiral center by asymmetric alkynylzinc addition reaction to aldehyde.[13] Thus, addition of phenylacetylene to an aldehyde in the presence of diethylzinc, (*S*)-BINOL, and $Ti(O^iPr)_4$ generated chiral propargyl alcohol with dr 95:5.[14]

Stereochemical assignment at the newly created hydroxy bearing center in **9** (C8'-OH in target molecule) was established as *R* by preparing *R* and *S*-mandelic esters. A reduction of the triple bond in compound **9** to the corresponding double bond was accomplished using Red-Al to give **18** in 92% yield. The acetonide group was removed upon treatment with $CuCl_2.2H_2O$ in CH_3CN at 0 ^{o}C to afford triol compound **7** in 90% yield.

The synthesis of vinyl lactone, other synthon was initiated from (*R*)-2,3-*O*-isopropylidene glyceraldehyde, which was subjected to 1,2-chelation-controlled allylation[15] in the presence of $Mg.Br_2.(OEt)_2$, allyltributyltin to afford *syn* homoallylic alcohol **13** in 86% yield and dr 97:3.[16] The diastereomeric ratio was determined by chiral HPLC column in the next step after conversion of homoallylic alcohol **13** into cinnamoyl ester. Thus, esterification of homoallylic alcohol **13** with cinnamoyl chloride furnished the corresponding ester, which was subjected to Ring-closing metathesis (RCM) using Grubbs Ist generation catalyst to afford unsaturated lactone. The cyclohexylidene protecting group was easily removed with 80% TFA in CH_2Cl_2 to obtain diol, which on treatment with PPh_3-imidazole-iodine[17] in refluxing toluene converted to the terminal olefin affording vinyl lactone (**8**).



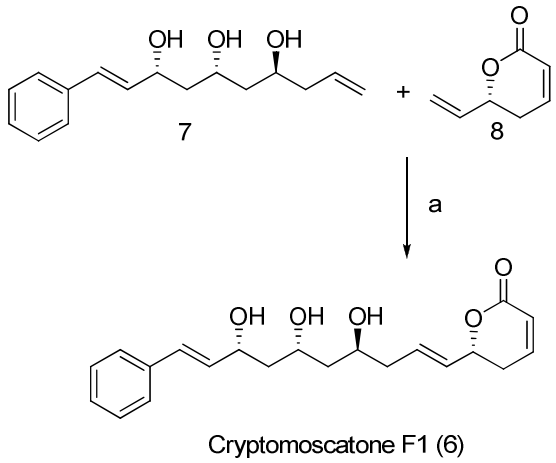
Scheme 2.Synthesis of triol 7. reagents a) $BNOC(NH)CCl_3$, CSA, CH_2Cl_2, rt, 12 h, 84%; b) (i)OsO_4, $NaIO_4$, 2,6-Lutidine, 1,4-Dioxane/H_2O, rt, 2 h; (ii) $allylSiMe_3$, $MgBr_2.Et_2O$, CH_2Cl_2, 0 °C, 12 h,76% (over 2 steps); c) Li/Naphthalene, dry THF, 1 h, -10 ^{o}C, 85%; d) 2,2-DMP, PPTS, 0 °C-rt,10 h, 94%; e) TBAF, THF, 0 °C, 3 h, 90%; f) IBX, AcCN, reflux, 1 h (ii) Phenylacetylene, Et_2Zn, (*S*)-BINOL, $Ti(OiPr)_4$, toluene, dry CH_2Cl_2, 6 h, 74% (over 2 steps); g) Red-Al, THF, 0 °C, 3 h, 93%; h) $CuCl_2.2H_2O$, AcCN, 0 °C, 1 h, 90%.



Scheme 3. Synthesis of vinyl lactone 8. reagents: a) allyltributyltin, $MgBr_2.Et_2O$, CH_2Cl_2, -78 ^{o}C to -20 ^{o}C,16 h, 86%; b) (*E*)-Cinnamoyl chloride, Et_3N, DMAP, CH_2Cl_2, 0 °C, 12 h, 85%; c) G-I Catalyst, dry CH_2Cl_2, reflux, 24 h, 92%; d) (i) 80% TFA, CH_2Cl_2, 0 °C , 2 h, (ii) PPh_3, Im, I_2, toluene, reflux, 3 h, 68% (over 2 steps).

Having both fragments **7** and **8** in hand, we proceeded for olefin cross-metathesis reaction. Thus, triol **7** was subjected to cross-

metathesis coupling with vinyl lactone **8** in the presence of Grubbs' second generation catalyst[18] in refluxing CH_2Cl_2 for 1 h to afford the target, cryptomoscatone F1 in 89% yield (Scheme 4). The ^1H and ^{13}C NMR of our synthetic **6** are in full agreement with the reported spectra of natural product. NOESY experiment was also performed in order to confirm the *E* configuration of the double bonds in compound **6** (Figure 2).



Scheme 4. Synthesis of cryptomoscatone F1.reagents a) G-II catalyst,CH_2Cl_2, reflux**,** 1 h, 89%.

Determining the *E*-Configuration of C1′=C2′ and C9′=C10′ double bonds based on ^1H NMR (500 MHz, $CDCl_3$) data and assignments were made with the aid of NOESY experiments (Figure 2). The medium NOE correlation observed between C1′H/C5H, C1′H/C3′H determining the *E*-Configuration of C1′=C2′ double bond. The medium NOE correlation observed between $C9^1H/C7^1H$, and strong NOE correlation between C9′H/PhH, C10′H/PhH determining the E-Configuration of C9′=C10′ double bond. Since the remaining double bond geometry was deduced by ^1H-^1H coupling constants($J_{H\text{-}3,\ H\text{-}4}$ = 9.9 Hz (*Z*)-Configuration).

This was further supported by ^1H-^1H coupling constants.

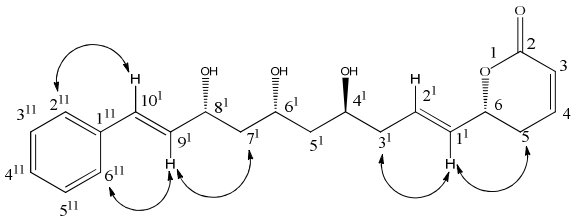


Figure 2. NOESY characteristic NOE correlations of compound **6.**

J H-3, H-4 = 9.9Hz (Z)-Configuration,

J H-1^1, H-2^1 = 15.5Hz (E)-Configuration,

J H-9^1, H-10^1 = 15.8Hz (E)-Configuration

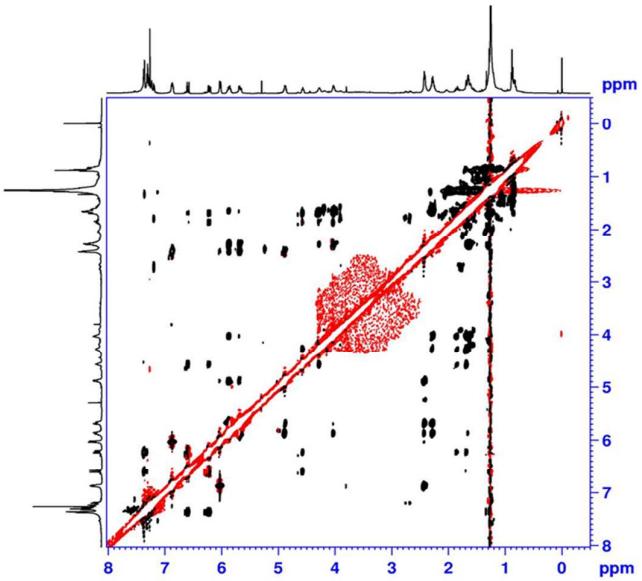


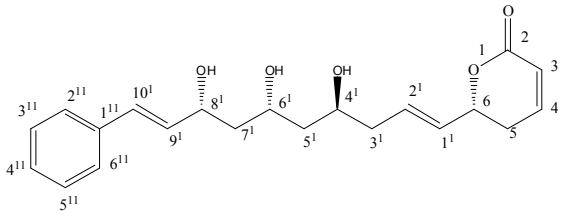
Figure 3. NOESY spectrum showing the characteristic NOE correlations of compound **6**

Conclusions

In conclusion, we have accomplished the first total synthesis of cryptomoscatone F1 (**6**) in 13 steps with an overall yield of 11.57%.

Comparative data for the natural and synthetic compound was provided in Table 1.

TABLE1. COMPARATIVE DATA OF NATURAL PRODUCT[2] AND SYNTHETIC COMPOUND (6)



^{1}H NMR				^{13}C NMR	
	NATURAL PRODUCT	SYNTHETIC PRODUCT		NATURAL PRODUCT	SYNTHETIC PRODUCT
H			**C**		
3	6.00(dt, J =10,1 Hz)	6.03(dt, J =9.9,1.6 Hz)	2	164.1	164.2
4	6.80(dt, J =10,4 Hz)	6.91-6.85 m	3	121.4	121.3
5	2.40 m	2.47-2.39 m	4	144.8	144.9
6	4.90 (br q, J =6 Hz)	4.93-4.86 m	5	29.7	29.6
1^1	5.70 (dd,J =16,6 Hz)	5.69 (dd, J =15.5,6.5 Hz)	6	77.9	77.9
2^1	5.90(dt, J =16,7 Hz)	5.92-5.84 m	1^1	129.7	129.5
3^1	2.30 (t ,J = 7 Hz)	2.35-2.22 m	2^1	131.4	131.4
4^1	4.00 m	4.08-4.01 m	3^1	40.3	40.2
5^1	1.70 m	1.92-1.82 m,1H	4^1	68.1	67.9
6^1	4.30 m	4.33-4.24 m	5^1	42.3	42.4
7^1	1.70 m	1.75-1.60 m,3H	6^1	70.0	69.6
8^1	4.60 m	4.62-4.56 m	7^1	42.9	42.9
9^1	6.20 (dd, J =16,6 Hz)	6.23 (dd, J = 15.8,6.5 Hz)	8^1	73.6	73.3
10^1	6.60 (d, J =16 Hz)	6.60 (d, J =15.8 Hz)	9^1	130.2	130.0
Ph	7.30 m	7.41-7.22 m,5H	10^1	131.6	131.6
			1^{11}	136.5	136.5
			$2^{11}/6^{11}$	126.5	126.4
			$3^{11}/5^{11}$	*128*.6	*128*.5
			4^{11}	127.8	127.6

Experimental Section:

General: All reactions were performed under inert atmosphere. All glassware apparatus used for reactions are perfectly oven/flame dried. Anhydrous solvents were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2, DMSO from CaH_2; MeOH from Mg cake. Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (60–120 mesh) unless otherwise mentioned. Analytical thin layer chromatography (TLC) was run on silica gel 60 F254 pre-coated plates (250 μm thickness). Optical rotations $[\alpha]_D$ were measured on a polarimeter and given in 10^{-1} degcm^{2}g^{-1}. Infrared spectra were recorded in $CHCl_3$/KBr (as mentioned) and reported in wave number (cm^{-1}). Mass spectral data were obtained using MS (EI) ESI, HRMS mass spectrometers. High resolution mass spectra (HRMS) [ESI+] were obtained using either a TOF or a double focusing spectrometer. ^{1}H NMR spectra were recorded at 300, 500 and ^{13}C NMR spectra 75,125 MHz in $CDCl_3$ solution unless otherwise mentioned, chemical shifts are in ppm downfield from tetramethylsilane and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

(*R*)-1-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)but-3-en-1-ol (13): To a solution of crude aldehyde (0.8 g, 4.7 mmol) in dry CH_2Cl_2 (8 mL) was added $MgBr_2.Et_2O$ (1.46 g, 5.64 mmol). After stirring for 15 min and cooling to -78 ^oC allyl tributyl tin (1.6 mL, 5.17 mmol) was added; stirring was continued for 16 h while the temperature slowly rose to -20 ^oC. The mixture was poured into 10% aq HCl (10 mL). The water phase was extracted with CH_2Cl_2 (3 x 10mL). The combined organic extracts were washed with sat. aq $NaHCO_3$ (10 mL) and brine, dried, the solvent was evaporated and the residue purified by column chromatography (30% Hexane/EtOAc) to give **13** (0.858 g, 86%) as a colorless liquid. $[\alpha]_D^{25}$: +1.72 (*c* 1.2, $CHCl_3$). IR (neat) ν_{max}: 3435, 2935, 2860, 1640, 1163, 1100, 1044 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) : δ 5.91-5.75 (m, 1H), 5.20-5.09 (m, 2H), 4.05-3.87 (m, 3H), 3.83-3.73 (m, 1H), 2.38-2.12 (m, 2H), 1.69-1.49 (m, 6H), 1.45-1.22 (m, 4H). **^{13}C NMR** ($CDCl_3$,125 MHz) : δ 133.9, 118.1, 109.5, 77.6, 70.3, 64.7, 37.5, 36.1, 34.7, 25.0, 23.9, 23.7. **HRMS** (ESI) for $C_{12}H_{20}O_3Na$ $[M + Na]^+$ found 235.1345 calcd 235.1340.

(*R*)-1-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)but-3-en-1-yl cinnamate (19): To the solution of alcohol 13 (0.76 g, 3.58 mmol) was dissolved in 10 mL of CH_2Cl_2 and cooled to 0 ^oC and (0.895 mg, 5.37 mmol) of cinnamoyl chloride, (1mL, 7.16 mmol) of Et_3N, and (35 mg 0.29 mmol) DMAP were added, warmed to room temperature and stirred overnight. The mixture was then poured into brine and extracted with CH_2Cl_2 (2 x 10 mL). The organic phases were washed with 1 M aq. HCl (5 mL) and brine (8 mL), dried over Na_2SO_4. The solvent was removed under aspirator vacuum, and the crude product was purified by column chromatography silica gel (20 % Hexane/EtOAc), to obtain 0.999 g (85%) of **19**. $[\alpha]_D^{25}$: +8.09 (*c* 0.8, $CHCl_3$). IR (neat) ν_{max}: 3081, 2936, 2861, 1714, 1638, 1449, 1202, 1166, 1100, 767 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) : 7.69 (d, *J* = 16.0 Hz, 1H), 7.55-7.50 (m, 2H), 7.41-7.36 (m, 3H), 6.44 (d, *J* = 16.0 Hz, 1H), 5.86-5.77 (m, 1H), 5.18-5.06 (m, 3H), 4.24-4.19 (m, 1H), 4.09-4.04 (m, 1H), 3.89-3.84 (m, 1H), 2.56-2.49 (m, 1H), 2.47-2.39 (m, 1H), 1.65-1.53 (m, 6H), 1.44-1.23 (m, 4H). **^{13}C NMR** ($CDCl_3$, 75 MHz) : δ 166.1, 145.2, 134.2, 131.1, 130.3, 128.8, 128, 118, 117.7, 110.1, 75.8, 73, 65.8, 36, 35.3, 34.8, 25.1, 23.9, 23.7. **HRMS** (ESI) for $C_{21}H_{26}O_4Na$ $[M + Na]^+$ found 365.1728 calcd 365.1721.

(*R*)-6-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)-5,6-dihydro-2*H*-pyran-2-one (20): Grubbs' first-generation catalyst (0.225 g, 0.27 mmol) was added to a solution of **19** (0.9 g, 2.74 mmol) in dry CH_2Cl_2 (100 mL) at reflux, over 24 h. After completion of the reaction (TLC), the solvent was removed under reduced pressure and the residue was purified by column chromatography (40% Hexane/EtOAc) to give **20** (0.6 g, 92%) as a colorless liquid. $[\alpha]_D^{25}$: +15.8 (*c* 1.3, $CHCl_3$). IR (neat) ν_{max}: 2935, 2860, 1738, 1247, 1099, 1054, 816 cm^{-1}.**^{1}H NMR** (300 MHz, $CDCl_3$) : δ 6.96-6.86 (m, 1H), 6.01 (dd, *J* = 9.8, 1.7 Hz, 1H), 4.31-3.98 (m, 4H), 2.67-2.55 (m, 1H), 2.52-2.38 (m, 1H), 1.64-1.49 (m, 8H), 1.48-1.27 (m, 2H). **^{13}C NMR** ($CDCl_3$,75 MHz) : δ 163, 144.9, 121.1, 110.4, 78, 75.6, 66.5, 36.4, 34.4, 26.2, 24.9, 23.9, 23.6. **HRMS** (ESI) for $C_{13}H_{18}O_4Na$ $[M + Na]^+$ found 261.1097 calcd 261.1096.

(*R*)-6-vinyl-5,6-dihydro-2H-pyran-2-one (8): Compound **20** (0.545 g, 2.28 mmol) was dissolved in 80% aq CF_3COOH (1 mL) at 0 ^oC and the mixture was stirred at the same temperature for 2 h. The reaction mixture was then extracted with CH_2Cl_2 (3 x 5 mL). The collected organic layers were combined,washed with 10% $NaHCO_3$ (3 x 5 mL), water, and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was taken as such for the next step without further purification.To a solution of crude diol (0.3 g, 1.89 mmol) in dry toluene (5 mL) was added triphenylphosphine (1.989 g, 7.59 mmol) followed by imidazole (0.517 g, 7.59 mmol) and stirred vigorously. To the resulting solution was added iodine (0.722 g, 5.69 mmol) and the mixture was refluxed at 110 ^0C for 3 h. The reaction mixture, after bringing to room temperature, was decanted into excess sat. aq $Na_2S_2O_3$ (5 mL) and sat. aq $NaHCO_3$ (5 mL) in a separatory funnel. The residue in the reaction flask was extracted with EtOAc (3 x 5 mL). These extracts were combined with the material in the separatory funnel and shaken until the iodine was consumed. The organic phase was washed with H_2O (1 x 5 mL), dried, and concentrated. The crude residue was chromatography(30% Hexane/EtOAc), to obtain **8** (0.193 g, 68% (over 2 steps).as liquid. $[\alpha]_D^{25}$: +80.6 (*c* 0.9, $CHCl_3$). IR (neat) ν_{max}: 1723, 1385, 1248, 1033, 817 cm^{-1}. **^{1}H NMR (**500 MHz, $CDCl_3$): δ 6.88 (ddd, *J* = 9.7, 5.4, 3.0 Hz, 1H), 6.04 (td, *J* = 9.7, 1.2 Hz, 1H), 5.94 (ddd, *J* = 17.0, 10.6, 5.7 Hz, 1H), 5.40 (dd, *J* = 17.2, 0.9 Hz, 1H), 5.29 (dd, *J* =10.5, 0.9 Hz, 1H), 4.95-4.90 (m, 1H), 2.51-2.38 (m, 2H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 163.3, 144.0, 134.2, 120.9, 117.3, 76.1, 28.7. **HRMS** (ESI) for $C_7H_8O_2Na$ $[M + Na]^+$ found 147.0422 calcd 147.0422.

(*R*)-((3-(benzyloxy)hex-5-en-1-yl)oxy)(tert-butyl)diphenylsilane (14): To a stirring solution of alcohol **12** (2 g, 5.64 mmol), freshly prepared benzyl trichloroacetimidate (2.14 g, 8.47 mmol), and CH_2Cl_2 (10 mL) in a 50 mL round bottom flask, under an atmosphere of N_2, was added (±)-camphor-10-sulfonic acid (131 mg, 0.56 mmol) in one portion. The reaction was allowed to proceed for 12 h at rt, after which time TLC analysis indicated essentially complete consumption of starting material. The reaction mixture was concentrated under reduced pressure, diluted with 20% Hexane/EtOAc (30 mL), filtered over a pad of Celite, and concentrated under reduced pressure to give a red slurry. Purification was accomplished by column chromatography (5% Hexane/EtOAc), collecting 8 mL fractions.

The product containing fractions were combined and concentrated under reduced pressure to give benzyl ether **14** (2.1 g, 84% yield) as colorless oil. $[\alpha]_D^{25}$: +13.8 (*c* 1.5, $CHCl_3$). IR (neat) ν_{max}: 3069, 2956, 2932, 2891, 1639, 1427, 1109, 735, 701 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) : δ 7.72-7.69 (m, 4H), 7.44-7.33 (m, 11H), 5.88-5.79 (m, 1H), 5.10-5.04 (m, 2H), 4.78 (s, 2H), 3.86-3.78 (m, 1H), 3.77-3.70 (m, 2H), 2.36-2.31 (m, 2H), 1.80-1.75 (m, 2H), 1.10 (s, 9H). **^{13}C NMR** ($CDCl_3$, 75 MHz) : δ 138.4, 135.8, 135.1, 134.7, 134.5, 129.6, 129.5, 127.6, 127.5, 127.4, 127.3, 72.6, 70.2, 66.8, 41.5, 36.0, 26.5, 18.9. **HRMS** (ESI) for $C_{29}H_{36}O_2SiNa$ $[M + Na]^+$ found 467.2376 calcd 467.2373.

(4*S*,6*S*)-6-(benzyloxy)-8-((tert-butyldiphenylsilyl)oxy)oct-1-en-4-ol (15): To a solution of **14** (2.01 g, 4.52 mmol) in 1,4-dioxane/water (3:1; 12 mL), 2,6-lutidine (1.1 mL, 9.05 mmol), OsO_4 (4.6mL , 0.09 mmol) followed by $NaIO_4$ (3.87 g, 18.1 mmol) were sequentially added at room temperature, and the mixture was stirred for 2 h. After completion of the reaction (monitored by TLC), 1,4-dioxane was removed under reduced pressure, and the residue was diluted with CH_2Cl_2 (20 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were quickly washed with 1 N HCl (2 x 5 mL) to remove excess 2,6-lutidine followed by brine (2 x 5 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude aldehyde **.** To a solution of crude aldehyde (1.8 g, 4.03 mmol) in CH_2Cl_2 (15 mL) at 0 ^oC were added $MgBr_2{\cdot}OEt_2$ (2.08 g, 8.07 mmol), and allyltrimethylsilane (3.2 mL, 20,17 mmol). The resultant mixture was stirred at 0 ^oC overnight before being quenched with 1 N aq. HCl solution. The resultant mixture was warmed to room temperature and extracted with EtOAc. The organic layer was washed successively with sat. aq $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography silica gel (20% Hexane/EtOAc) to give homoallylic alcohol **15** (1.693 g, 76.5% (over 2 steps) as a colorless oil. $[\alpha]_D^{25}$: +25.6 (*c* 1.3, $CHCl_3$). IR (neat) ν_{max}: 3432, 3069, 2932, 2857, 1639, 1427, 1108, 702 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) : δ 7.68-7.63 (m, 4H), 7.45-7.25 (m, 1H), 5.85-5.75 (m, 1H), 5.12-5.06 (m, 2H), 4.5 (s, 2H), 4.00-3.89 (m, 2H), 3.83-3.69 (m, 2H), 2.23-2.16 (m, 2H), 2.00-1.92 (m, 1H), 1.80-1.70 (m, 1H), 1.63-1.57 (m, 2H), 1.05 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz) : δ 138.1, 135.5, 134.8, 134.7, 133.6, 129.6, 128.3, 127.8, 127.6, 117.4, 74.2, 71.4, 67.7, 60.4, 42.1, 39.5, 36.5, 26.8, 19.1. **HRMS** (ESI) for $C_{31}H_{40}O_3$ SiNa $[M + Na]^+$ found 511.2638 calcd 511.2623.

(3*S*,5*S*)-1-((tert-butyldiphenylsilyl)oxy)oct-7-ene-3,5-diol (16): To a stirred solution of naphthalene (2.6 g, 20.28 mmol) in THF (10 mL) were added lithium granules (165 mg, 23.66 mmol) at room temperature, and the solution was allowed to stir at room temperature for 30 min to generate Li naphthalenide. To the resulting dark green solution was added benzyl ether **15** (1.65 g, 3.38 mmol) at -10 ^oC, and the mixture was allowed to stir at the same temperature for 30 min,quenched with aqueous NH_4Cl, extracted into EtOAc (3 x 50 mL), dried over Na_2SO_4, concentrated, and purified on silica gel (40% Hexane/EtOAc) to give diol **16** (1.143 g, 85%) as a colorless liquid. $[\alpha]_D^{25}$: −14.9 (*c* 1.2, $CHCl_3$). IR (neat) ν_{max}: 3416, 2931, 2857, 1428, 1109, 1083, 740, 704 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) : δ 7.69-7.65 (m, 4H), 7.47-7.37 (m, 6H), 5.89-5.79 (m, 1H), 5.16-5.09 (m, 2H), 4.30-4.22 (m, 1H), 4.05-3.98 (m, 1H), 3.90-3.85 (m, 2H), 3.78 (br.s, 1H), 2.30-2.25 (m, 2H), 1.92-1.78 (m, 1H), 1.70-1.56 (m, 3H), 1.05 (s, 9H). **^{13}C NMR** ($CDCl_3$, 75 MHz) : δ 135.4, 134.8, 132.8, 132.6, 129.8, 127.7, 117.6, 69.5, 67.9, 63.6, 42.2, 42, 38.1, 26.7, 18.9. **HRMS** (ESI) for $C_{24}H_{34}O_3SiNa$ $[M + Na]^+$ found 421.2169 calcd 421.2158.

(2-((4*S*,6*S*)-6-allyl-2,2-dimethyl-1,3-dioxan-4-yl)ethoxy)(tert-butyl)diphenylsilane (17) : 2,2-Dimethoxypropane (0.7 mL, 5.52mmol) and catalytic PPTS (83 mg, 0.33 mmol) were added successively to a solution of diol **16** (1.1 g, 2.76 mmol) in a CH_2Cl_2 (8 mL). The solution was stirred for 10 h at room temperature and then quenched with solid $NaHCO_3$. The crude compound was concentrated in vacuo and purified by column chromatography (15% Hexane/EtOAc) to afford the acetonide product **17** (1.137 g, 94%) as a colorless liquid. $[\alpha]_D^{25}$: +27.8 (*c* 0.8, $CHCl_3$). IR (neat) ν_{max}: 2934, 2858, 1379, 1223, 1110, 739, 704 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) : δ 7.69-7.63 (m, 4H), 7.44-7.35 (m, 6H), 5.84-5.75 (m, 1H), 5.13-5.02 (m, 2H), 4.13-4.05 (m, 1H), 3.89-3.75 (m, 2H), 3.72-3.66 (m, 1H), 2.36-2.88 (m, 1H), 2.22-2.15 (m, 1H), 1.77-1.54 (m, 4H), 1.35 (s, 3H), 1.33 (s, 3H), 1.04 (s, 9H).
^{13}C NMR ($CDCl_3$, 75 MHz) : δ 135.4, 134.4, 133.8, 129.5, 127.5, 116.7, 100.1, 66.1, 63.3, 60, 40.1, 38.8, 38, 26.8, 24.8, 19.1. **HRMS** (ESI) for $C_{27}H_{38}O_3SiNa$ $[M + Na]^+$ found 461.2482 calcd 461.2471.

2-((4*S*,6*S*)-6-allyl-2,2-dimethyl-1,3-dioxan-4-yl)ethanol (11): A 1 M solution of TBAF in THF (4.56 mL, 4.56 mmol) was added to a solution of compound **17** (1 g, 2.28 mmol) in dry THF (5 mL) at 0 ^oC. The mixture was stirred at room temperature for 3 h. After completion of the reaction, the mixture was diluted with EtOAc (15 mL). The combined organic layers were washed with brine, and the mixture was extracted with EtOAc (3 x 10 mL), dried over Na_2SO_4. The solvent was removed under reduced pressure, and the mixture was purified by column chromatography (20% Hexane/EtOAc) to afford **11** (410 mg, 90%) as a colorless liquid. $[\alpha]_D^{25}$: +40.6 (*c* 1.6, $CHCl_3$). IR (neat) ν_{max}: 3422, 2987, 2939, 1643, 1308, 1224, 1168, 1054, 761 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) : δ 5.83-5.73 (m, 1H), 5.12-5.03 (m, 2H), 4.08-4.01 (m, 1H), 3.91-3.84 (m, 1H), 3.78-3.72 (m, 2H), 2.55 (br.s, 1H), 2.34-2.77 (m, 1H), 2.23-2.16 (m, 1H), 1.77-1.70 (m, 2H), 1.69-1.61 (m, 2H), 1.37 (s, 3H), 1.35 (s, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz) : δ 134.2, 117, 100.4, 66.5, 66.1, 40, 37.6(2C), 24.8, 24.7. **HRMS** (ESI) for $C_{11}H_{20}O_3Na$ $[M + Na]^+$ found 223.1312 calcd 223.1310.

(*R*)-1-((4*S*,6*S*)-6-allyl-2,2-dimethyl-1,3-dioxan-4-yl)-4-phenylbut-3-yn-2-ol (9): To the solution of alcohol **11** (0.3 g, 1.50 mmol) in anhydrous CH_3CN (5 mL) IBX (0.63 g, 2.25 mmol) was added and the resulting suspension was vigorously stirred at reflux condition for 1 h,. and the reaction was allowed to cool to rt, filtered through Celite. The residue was washed with EtOAc (3 × 5 mL) and the combined filtrate was concentrated to give the crude aldehyde, which was directly used for the next reaction without further purification. In 25 mL flask, 1 mL toluene solution of phenylacetylene(0.56 mL, 5.09 mmol) and diethylzinc(5.1 ml, 5.09 mmol) was refluxed for 1hour under nitrogen. After the solution was cooled to room temperature, (*S*)-BINOL (360 mg, 1.27 mmol), diethyl ether (8 mL) and $Ti(O^iPr)_4$ (0.37 mL, 1.27 mmol) were added sequentially. The solution was stirred for another 1 h, and aldehyde (252 mg, 1.27 mmol) was added. After additional 4 h, the reaction was quenched with saturated ammonium chloride. The resulting mixture was extracted with $CH_2Cl_2$and concentrated under vacuum. Purification of the residue by passing through a short silica gel column (20% Hexane/EtOAc) afforded the pure propargylic alcohol product **9** (335mg, 74.8% ,over 2 steps) as a colorless liquid. $[\alpha]_D^{25}$: +9.1 (*c* 0.6, $CHCl_3$). IR (neat) ν_{max} : 3412, 3078, 2986, 2926, 1638, 1490, 1381, 1223, 1025, 756 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) : δ 7.44-7.41 (m, 2H), 7.33-7.28 (m, 3H),

5.84-5.75 (m, 1H), 5.13-5.04 (m, 2H), 4.48-4.79 (m, 1H), 4.18-4.11 (m, 1H), 3.90 (qt, *J* = 14.1, 7.0 Hz, 1H), 2.98 (d, *J* = 2.7 Hz, 1H), 2.35-2.28 (m, 1H), 2.24-2.17 (m, 1H), 2.10-2.02 (m, 1H), 1.97-1.91 (m, 1H), 1.70 (t, 2H), 1.40 (s, 3H), 1.37 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 134.2, 131.6, 128.3, 128.2, 117, 100.6 (2C), 89.3, 66.1, 66, 43.2, 40, 37.8, 24.9, 24.6. **HRMS** (ESI) for $C_{19}H_{24}O_3Na$ $[M + Na]^+$ found 323.1623 calcd 323.1621.

(*R*)-(*R*,*E*)-1-((4*R*,6*S*)-6-allyl-2,2-dimethyl-1,3-dioxan-4-yl)-4-phenylbut-3-en-2-yl 2-methoxy-2-phenylacetate: To a solution of propargylic alcohol **9** (12 mg, 0.066 mmol) in dry CH_2Cl_2 (5 mL), DMAP catalytic, (*R*)-*O*-methylmandelic acid (9 mg, 0.079 mmol) and DCC (12 mg, 0.099 mmol) were added and the mixture was stirred at room temperature for 60 minutes under argon. The reaction was diluted with DCM and filtered through Celite. The filtrate was concentrated under reduced pressure and purified by column chromatography (5-10% hexane/ethyl acetate) to afford *O*-methylmandelate as a colorless oil (15 mg, 85%). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.49-7.43 (m, 2H), 7.38-7.26 (m, 8H), 5.82-5.74 (m, 1H), 5.11-5.03 (m, 2H), 4.81 (s, 1H), 4.13-4.06 (m, 1H), 3.89-3.82 (m, 1H), 3.45 (s, 3H), 3.44-3.40 (m, 1H), 2.33-2.25 (m, 1H), 2.21-2.14 (m, 1H), 2.07-1.92 (m, 2H), 1.66-1.58 (m, 2H), 1.35 (s, 3H), 1.33 (s, 3H).

(*S*)-(*R*,*E*)-1-((4*R*,6*S*)-6-allyl-2,2-dimethyl-1,3-dioxan-4-yl)-4-phenylbut-3-en-2-yl 2-methoxy-2-phenylacetate: To a solution of propargylic alcohol **9** (10 mg, 0.066 mmol) in dry CH_2Cl_2 (5 mL), DMAP catalytic, (*S*)-*O*-methylmandelic acid (6 mg, 0.079 mmol) and DCC (10 mg, 0.099 mmol) were added and the mixture was stirred at room temperature for 60 minutes under argon. The reaction was diluted with DCM and filtered through Celite. The filtrate was concentrated under reduced pressure and purified by column chromatography (5-10% hexane/ethyl acetate) to afford *O*-methylmandelate as a colorless oil (13 mg, 87%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50-7.27 (m, 10H), 5.79-5.70 (m, 1H), 5.10-5.01 (m, 2H), 4.81 (s, 1H), 4.17-4.07 (m, 1H), 4.02-3.95 (m, 1H), 3.82-3.76 (m, 1H), 3.43 (s, 3H), 2.34-2.32 (m, 1H), 2.17-2.10 (m, 1H), 1.92-1.8 (m, 1H), 1.65-1.50 (m, 3H), 1.30 (s, 3H), 1.29 (s, 3H).

(*R*,*E*)-1-((4S,6S)-6-allyl-2,2-dimethyl-1,3-dioxan-4-yl)-4-phenylbut-3-en-2-ol (18): To a cold (0 ^oC) solution of propargylic alcohol **9** (0.2 g, 0.66 mmol) in THF (5 mL) was added Red-Al (0.32 mL, 70 wt% in toluene, 0.99 mmol) dropwise. After 3h at 0 ^oC, the reaction mixture was quenched carefully by dropwise addition of saturated aqueous sodium sulphate (Caution: vigorous evolution of H_2 may result). EtOAc was added and the mixture was allowed to warm to rt. The organic layer was washed with brine and the combined aqueous layer was extracted several times with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (30% Hexane/EtOAc) to provide (187 mg ,93% yield) of allylic alcohol **18** as a colorless oil. $[\alpha]_D^{25}$: +24.5 (*c* 0.9, $CHCl_3$). IR (neat) ν_{max} : 3437, 3026, 2986, 2937, 1641, 1449,1380, 1223, 1166, 1123, 968, 749 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) : δ 7.42-7.18 (m, 5H), 6.61 (d, *J* = 15.8 Hz, 1H), 6.18 (dd, *J* = 15.8, 6.4 Hz, 1H), 5.87-5.71 (m, 1H), 5.14-5.02 (m, 2H), 4.53-4.44 (m, 1H), 4.16-4.03 (m, 1H), 3.95-3.84 (m, 1H), 3.43 (br.s, 1H), 2.37-2.14 (m, 2H), 1.83-1.57 (m, 4H), 1.41 (s, 3H), 1.38 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz) : δ 136.7, 134.1, 131.6, 129.8, 128.4, 127.4, 126.3, 117, 100.6, 72.2, 66.9, 66, 42.7, 39.9, 38, 24.9, 24.6. **HRMS** (ESI) for $C_{19}H_{26}O_3Na$ $[M + Na]^+$ found 325.1779 calcd 235.1770.

(3*R*,5*R*,7*S*,*E*)-1-phenyldeca-1,9-diene-3,5,7-triol (7) : To a solution that was cooled in an ice bath of compound **18** (0.1 g, 0.33 mmol) in CH_3CN (5 mL) was added $CuCl_2 \cdot 2H2O$ (112 mg, 0.66 mmol) as a solid. The reaction mixture was stirred at 0 ^oC for 1 h. The reaction mixture was quenched with solid $NaHCO_3$ (2 g), and the resulting mixture was filtered. The filtrate was concentrated under reduced pressure, and the crude product was purified by column chromatography (60% Hexane/EtOAc) to afford triol **7** (78 mg, 90%) as a colorless oil. $[\alpha]_D^{25}$: +42.7 (*c* 0.5, $CHCl_3$). IR (neat) ν_{max} : 3369, 3080, 3027, 2939, 1640, 1433, 1070, 967, 749 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) : δ 7.43-7.16 (m, 5H), 6.60 (d, *J* = 15.8 Hz, 1H), 6.22 (dd, *J* = 15.8, 6.7 Hz, 1H), 5.89-5.73 (m, 1H), 5.20-5.08 (m, 2H), 4.63-4.53 (m, 1H), 4.35-4.23 (m, 1H), 4.02 (qt, *J* = 12.8, 6.7 Hz, 1H), 2.32-2.22 (m, 2H), 1.90-1.59 (m, 4H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 136.5, 134.5, 131.6, 129.8, 128.5, 127.6, 126.4, 117.9, 73, 69.4, 67.7, 43.1, 42.4, 42. **HRMS** (ESI) for $C_{16}H_{22}O_3Na$ $[M + Na]^+$ found 285.1461 calcd 285.1461.

(*R*)-6-((1*E*,4*S*,6*R*,8*R*,9*E*)-4,6,8-trihydroxy-10-phenyldeca-1,9-dien-1-yl)-5,6-dihydro-2H-pyran-2-one (6) (Cryptomoscatone F1): A soln of Grubbs II catalyst (3 mg, 0.003 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a soln of the triol 7 (16 mg, 0.061 mmol) and vinyl lactone **8** (11 mg, 0.091 mmol) in CH_2Cl_2 (1 mL) at r.t., and the mixture was refluxed for 1 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (80% Hexane/EtOAc) to give viscous liquid (19 mg , 89%). $[\alpha]_D^{25}$: +35.0 (*c* 1.0, $CHCl_3$). IR (neat) ν_{max} : 3405, 2925, 2854, 1713, 1384, 1250, 1054, 753 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) : δ 7.41-7.22 (m, 5H), 6.91-6.85 (m, 1H), 6.60 (d, *J* = 15.8 Hz, 1H), 6.23 (dd, *J* = 15.8, 6.7 Hz, 1H), 6.03 (dt, *J* = 9.9, 1.6 Hz, 1H), 5.92-5.84 (m, 1H), 5.69 (dd, *J* = 15.5, 6.5 Hz, 1H), 4.93-4.86 (m, 1H), 4.62-4.56 (m, 1H), 4.33-4.24 (m, 1H), 4.08-4.01 (m, 1H), 2.47-2.39 (m, 2H), 2.35-2.22 (m, 2H), 1.92-1.82 (m, 1H), 1.75-1.60 (m, 3H).**^{13}C NMR** ($CDCl_3$, 125 MHz) : δ 164.2, 144.9, 136.5, 131.6, 131.4, 130, 129.5, 128.5, 127.6, 126.4, 121.3, 77.9, 73.3, 69.6, 67.9, 42.9, 42.4, 40.2, 29.6 . HRMS: calcd. for $C_{21}H_{26}O_5Na$ $[M + NH_4]^+$: 381.1678: found: 381.1674.

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