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Communication

First Total Synthesis of Cryptopyranmoscatone A2 from D-Ribose

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Abstract: First total synthesis of a naturally occuring styryl lactone, cryptopyranmoscatone A2 has been achieved from inexpensive and highly abundant D-ribose. The key features of the synthetic strategy are the utilization of oxa-Michael addition, asymmetric allylation and metathesis reactions.

Naturally occuring styryllactones are reported to possess significant cytotoxicity toward human tumor cell lines.[1] They have been traditionally used for the treatment of edema and rheumatism.[2] Other applications include their use as painkillers[3] and mosquito repellants.[4] Cryptopyranmoscatones A1, A2, A3, B1, B2 and B4 (Figure 1, **1-6**),[5] a series of styryllactones along with other cryptocarya pyrones were isolated from the branch and stem bark of *Cryptocarya moschata*, Lauraceae, a tree growing up to 30-40m high, found in the Atlantic Forest, mainly in the Southeastern Region of Brazil. The structures of these compounds were established by spectroscopic studies. Some of these cryptocarya pyrones possessed biological activities. For example, cryptomoscatone D2 has been identified as a highly efficacious inhibitor of the G2 check point,[6] which can enhance killing of cancer cells by ionizing radiation and DNA-damaging chemotherapeutic agents, particularly in cells lacking p53 function. This styryl lactone also displayed high dose- and time dependent antiproliferative activity against HeLa, SiHa, C33A and MRC-5 cell lines.[7] Cryptofolione[5,8] displayed activity towards *Trypanosoma cruzi*, trypomastigotes, reducing their number by 77% at 250 µg mL-1. Cryptocarya species showed outstanding equipotent activity towards COX-1 and COX-2.[9] *C. moschata* is recognized as an important alimentary food source for primates such as *Brachyteles arachnoids*. The striking structural motif of cryptopyranmoscatones, coupled with their scarcity, prompted us to pursue their syntheses, and rendering them readily available for biological investigations. Karlotoxin-2,[10] a marine cytotoxic polyketide also possess a similar tetrahydropyran core.

As part of our program on the synthesis of biologically active natural lactones,[11] our group reported the first total syntheses of cryptopyranmoscatone B1[12] and A1[13] in 2010 and 2011 respectively. Now, we herein disclose our first stereoselective total synthesis of cryptopyranmoscatone A2 from readily available D-ribose using oxa-Michael, ring-closing metathesis (RCM) and cross-metathesis (CM) reactions as key steps.

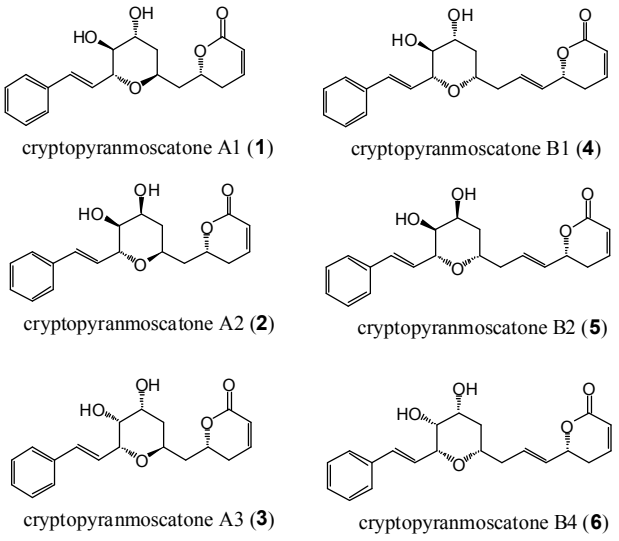

Figure 1. Structures of natural cryptopyranmoscatones **1-6**

Results and Discussion

Our retrosynthetic strategy for cryptopyranmoscatone A2 is depicted in Scheme 1. We envisaged that cryptopyranmoscatone A2 could be obtained from an intermediate **7** through oxa-Michael addition reaction (Scheme 1). Cryptopyranmoscatone A2 (**2**) could be prepared by first elaborating the right side and then to the left side of the oxa-Michael product, 2,6-*trans*-tetrahydropyran **9**, performing RCM and cross-metathesis reactions as the key steps. In turn, the intermediate **7** could be accessible from D-ribose *via* lactone **10** (Scheme 1).

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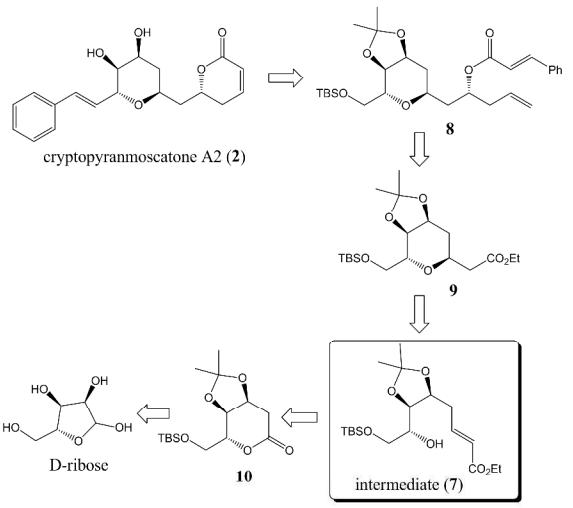
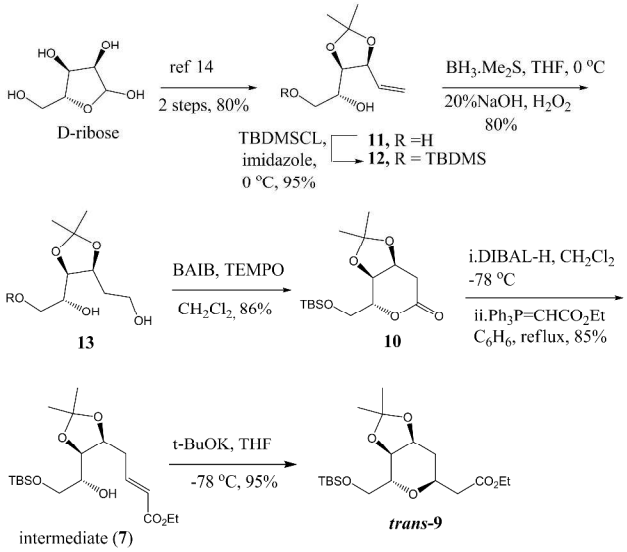
Electronic supplementary information (ESI) available: spectral data of all compds and copies of ^{1}H and ^{13}C NMR spectra of all compds



Scheme 1. A retrosynthetic approach for cryptopyranmoscatone A2 (**2**)

The synthesis of 2,6-*trans*-tetrahydropyran core of **2** is illustrated in Scheme 2. It was initiated from compound **11**, which was synthesized in two steps from commercially available D-ribose following a known protocol.[14] The primary alcohol **11** was protected with TBSCl/imidazole to give silyl ether **12** in 95% yield. Hydroboration[15] of **12** with $BH_3 \cdot Me_2S$ followed by oxidative workup afforded 1,5-diol **13** in 80% yield. Oxidative cyclization of diol **13** with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and [bis(acetoxy)iodo]benzene [$(PhI(OAc)_2$) (BAIB)][16] produced the desired δ-lactone **10** in 86% yield. The intermediate **7** could be made from **10** by lactone opening. Thus, lactone **10** was reduced to lactol using DIBAL-H and subjected to Wittig olefination using stabilized ylide to furnish α,β-unsaturated ester **7** in 85% overall yield (Scheme 2).



Scheme 2. Synthesis of *trans*-tetrahydropyran core (**9**)

Cis- or *trans*- 2,6-tetrahydropyran core can be synthesized from an intermediate **7** based on different reaction conditions. Since, we need a *trans*-tetrahydropyran unit, the hydroxy ester 7 was subjected to Intramolecular oxa-conjugate cyclization (oxa-Michael reaction)[17] by exposure to KO^t-Bu in THF at -78 °C for 30 min, which gave rise to 2,6-*trans*-tetrahydropyran (*trans*-**9**) in 95% yield with high diastereoselectivity (dr = 20:1) (Scheme 2).

This *trans*-stereochemistry of the newly generated ring-junction of tetrahydropyran **9** was assigned based on ^{1}H NMR (600 MHz, $CDCl_3$) data and assignments were made with the aid of TOCSY and NOESY experiments (Figure 2). The medium NOE between C2H/C6H suggested that both the protons are *anti* to each other (*trans* related). This was further supported by NOE correlation between C2H/Me-a, C4H/C6H, C2H/C5H and C3H/C4H, confirming the structure. The energy minimized structure is also shown in Figure 3.

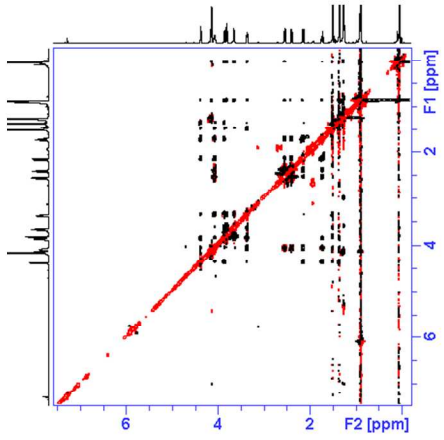


Figure 2. NOESY spectrum showing the characteristic NOE correlations of compound **9**

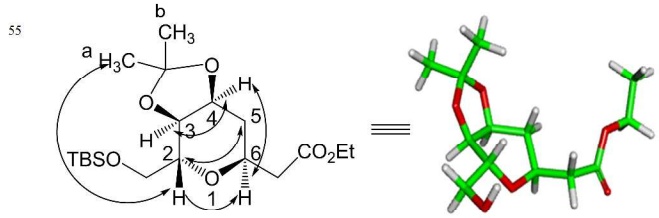
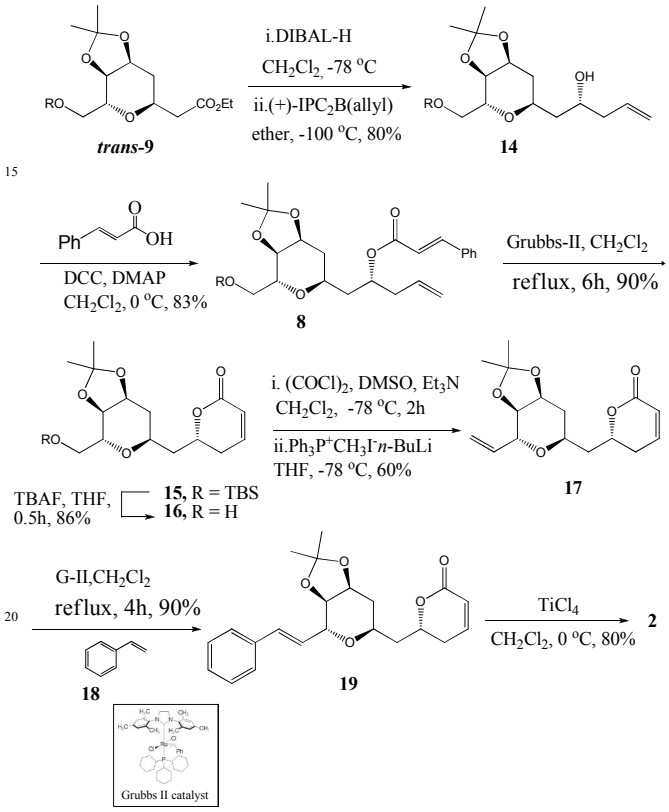


Figure 3. Chemical and energy-minimized structure of **9**

Completion of the total synthesis of cryptopyranmoscatone A2 (**2**) is illustrated in Scheme 3. Diisobutylaluminium hydride (DIBAL-H) Reduction of ester in *trans*-**9** furnished an aldehyde, which was subjected to Brown asymmetric allylation[18] with (+)-Ipc_2B-allyl at -100 °C to give homoallyl alcohol **14** in 80% yield. Stereochemical assignment at the newly created hydroxy bearing center was confirmed at the later stage after converting into ester. Acylation of **14** with cinnamic acid under DCC−DMAP conditions provided compound **8** in 83% yield with dr 99:1 (by HPLC).[19] Treatment of **8** with second-generation Grubbs' catalyst[20] (10 mol%) in CH_2Cl_2 at reflux temperatures afforded

lactone **15** in 90% yield. Removal of the TBS group with TBAF in THF gave primary alcohol **16**. Alcohol **16** was oxidized under Swern conditions to give an aldehyde, which was subjected to Wittig olefination with to give an olefinic lactone **17** in 60% yield over two steps. The cross-metathesis reaction of olefin **17** with styrene **18** using Grubbs' second generation carbene catalyst[20] in CH_2Cl_2 under reflux conditions for 4 h afforded **19** in 90% yield. Finally deprotection of the acetonide group in compound **19** using conc $TiCl_4$[21] completed the first total synthesis of cryptomoscatone A2 (**2**) in 80% yield. Spectral and analytical data of our synthetic compound were all in good agreement with those of the natural cryptomoscatone A2 (**2**).[5]



Scheme 3. Total Synthesis of Cryptopyranmoscatone A2 (**2**)

Conclusions

In conclusion, we have achieved the first total synthesis of cryptopyranmoscatone A2. D-ribose has been used as the starting material. The key steps in the synthesis involved are oxa-Michael, asymmetric allylation and metathesis reactions.

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} $degcm^2g^{-1}$. 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. ^1H NMR spectra were recorded at 300, 400, 500 and ^{13}C NMR spectra 75 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*)-2-((tert-butyldimethylsilyl)oxy)-1-((4*R*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)ethanol (12): To a stirred solution of diol **11** (5.0 g, 16.50 mmol) and imidazole (3.6 g, 52.87 mmol) in dry CH_2Cl_2 (30 mL) was added TBDMS-Cl (3.6 g, 24.0 mmol) portion wise at 0 °C. The reaction mixture was stirred at the same temperature for 2 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2. The extract was washed with water and brine, dried over anhydrous Na_2SO_4, the solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography (hexane/EtOAc, 9:1) to furnish pure compound **12** (7.6 g, 95% yield) as a colorless liquid. $[\alpha]_D^{25}$: -12.6 (*c* = 0.08, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 6.09-5.96 (m, 1H), 5.41 (dt, *J* = 16.9, 1.5 Hz, 1H), 5.28 (dt, *J* = 10.3, 1.3 Hz 1H), 4.68 (tt, *J* = 1.3, 7.7 Hz, 1H), 4.05 (dd, *J* = 6.4, 8.8 Hz, 1H), 3.80 (dd, J = 3.0, 9.8 Hz, 2H), 3.71-3.59 (m, 2H), 2.53 (d, *J* = 5.2 Hz, 1H), 1.46 (s, 3H), 1.35 (s, 3H), 0.91(s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 134.0, 117.4, 108.6, 78.6, 77.3, 69.4, 64.3, 27.7, 25.8, 25.3, 18.2, -5.4, -5.5; IR (neat): 3480, 2954, 2930, 1463, 1381, 1255, 1059, 837, 779 cm^{-1}; HRMS (ESI) for $C_{15}H_{30}O_4SiNa$ $[M+Na]^+$ found 325.1811 calcd 325.1806

(*R*)-2-((tert-butyldimethylsilyl)oxy)-1-((4*R*,5*S*)-5-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (13): To compound **12** (7.5 g, 23.40 mmol) in dry THF (50 mL) was added TBDMSCl (12.4 mL, 2M solution in THF) for over a period of 10 min maintaining the temperature at 0 °C. The reaction mixture was brought to rt and stirred for a period of 8 h. This was then treated with a very slow addition of 3N NaOH until the reaction mixture was basic at 0 °C. To this was added H_2O_2 (30% solution in H_2O, 50 mL) and the reaction mixture was stirred for over a period of 3 h and then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography (hexane/EtOAc, 8:2) to furnish the diol **13** (6.3 g, 80% yield) as colorless liquid. $[\alpha]_D^{25}$: -1.58 (*c* = 0.12, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 4.41-4.35 (m, 1H), 3.98 (dd, *J* = 5.6, 9.0 Hz, 1H), 3.90-3.75 (m, 3H), 3.71-3.63 (m, 2H), 2.79 (br.s, 1H), 2.10-2.04 (m, 1H), 1.93-1.85 (m, 1H), 1.42 (s, 3H), 1.32 (s, 3H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 108.1, 77.7, 77.1, 68.9, 64.3, 61.4, 31.5, 28.1, 25.8, 25.6, -5.4, -5.5; IR (neat): 3486, 2988, 2927, 1372, 1230, 1086, 835, 768 cm^{-1}; HRMS (ESI) for $C_{15}H_{32}O_5SiNa$ $[M+Na]^+$ found 343.1916 calcd 343.1904

(3a*S*,4*R*,7a*S*)-4-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethyldihydro-3aH-[1,3]dioxolo[4,5-c]pyran-6(4H)-one (10): BAIB (6.6g, 20.4 mmol) was added to a solution of diol **13** (6.0 g, 18.9 mmol) and TEMPO (0.29 g, 1.85 mmol) in 20 ml of

CH_2Cl_2. The rection mixture was stirred until the alcohol was no longer detectable (TLC), and then it was diluted with CH_2Cl_2 (20 mL). The mixture was washed with a saturarated aqueous solution of $Na_2S_2O_3$ (20 mL) and extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extracts were washed with aqueous $NaHCO_3$ (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure and purified by silica gel column chromatography (hexane/EtOAc = 7:3) to afford **10** as a light yellow coloured liquid (5.0 g, 86%) $[\alpha]_D^{25}$: +33.9 (*c* = 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.64-4.55 (m, 1H), 4.39-4.33 (m,1H), 4.31-4.25 (m, 1H), 3.99 (dd, *J* = 2.6, 11.3 Hz, 1H), 3.87 (dd, *J* = 3.7, 11.3 Hz, 1H), 3.06 (dd, *J* = 6.0, 15.8 Hz, 1H), 2.67 (dd, *J* = 5.2, 15.8 Hz, 1H), 1.48 (s, 3H), 1.37 (s,3H), 0.90 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.5, 110.2, 80.2, 71.2, 70.7, 63.0, 34.9, 26.8, 25.8, 24.5, 18.3, -5.5, -5.6; IR (neat): 3488, 2932, 2858, 1756, 1256, 1067, 838, 779 cm^{-1}; HRMS (ESI) for $C_{15}H_{28}O_5SiNa$ $[M+Na]^+$ found 339.1604 calcd 339.1615

(*E*)-ethyl 4-((4*S*,5*R*)-5-((*R*)-2-((tert-butyldimethylsilyl)oxy)-1-hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate (7): A stirred solution of lactone **10** (4.8 g, 12.3 mmol) in CH_2Cl_2 (30 mL) was cooled to -78 °C, then DIBAL–H (23.4 mL, 1.6 M solution in toluene) was added slowly. After 1 h, the reaction was quenched with methanol (10 mL) and potassium sodium tartrate (15 mL), and stirred at room temperature for 0.5 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 X 50 mL). The combined organic layers were washed with brine (2 X 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude lactol. This was used for the next step without further purification.To a solution of the above lactol in C_6H_6 (30 mL) was added Ph_3P=CHCOOEt (7.9 g, 22.7 mmol) and the reaction mixture was stirred for 4 h at reflux condition. After completion of the reaction, monitored by TLC, C_6H_6 was removed under reduced pressure, residue was dissolved in ether, and petroleum ether was added to it. The triphenylphosphineoxide crystallized out was filtered off and the filtrate was concentrated to dryness. The crude product was purified by column chromatography (hexane/EtOAc, 7:3) to afford the pure α,β-unsaturated ester **7** (4.9 g, 85%) as a colorless oil. $[\alpha]_D^{25}$: -38.9 (*c* = 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.05 (dt, *J* = 7.1, 15.7 Hz, 1H), 5.93 (dt, *J* = 1.3, 15.7 Hz, 1H), 4.32-4.27 (m, 1H), 4.19 (q, *J* = 7.0, 14.2 Hz 2H), 3.99 (dd, *J* = 5.7, 9.1 Hz, 1H), 3.86-3.81 (m, 1H), 3.70-3.64 (m, 2H), 2.74-2.68 (m, 1H), 2.62 (br.s, 1H), 2.51-2.43 (m, 1H), 1.42 (s, 3H), 1.32 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.92 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.5, 110.2, 80.2, 71.2, 70.7, 63.0, 34.8, 26.8, 25.7, 24.5, 18.2, -5.5, -5.6; IR (neat): 3490,2927,2882,1698,1383,1256, 1218,1046,759 cm^{-1}; HRMS (ESI) for $C_{19}H_{36}O_6SiNa$ $[M+Na]^+$ found 411.2175 calcd 411.2168.

ethyl 2-((3a*S*,4*R*,6*S*,7a*S*)-4-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl)acetate (9): To a solution of alcohol 7 (4.6 g, 11.8 mmol) in THF (20 mL) at –78 °C was added *t*-BuOK (1.46 g, 13.02 mmol). After 0.5 h stirring at -78 °C, a saturated solution of NH_4Cl (10 mL) was added and the mixture warmed up to rt. Extraction was carried out with Et_2O (3 X 20 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The purification of the residue by flash column chromatography (hexane/EtOAc, 8:2) furnished cyclic compound **9** (4.3 g, 95%) as a colorless oil. $[\alpha]_D^{25}$: +39.5 (*c* = 0.23, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.39-4.32 (m, 1H), 4.13 (*q*, *J* = 6.8 Hz, 2H), 4.09-4.0 (m, 1H), 3.84 (dd, *J* = 4.5, 9.0 Hz, 1H), 3.80 (dd, *J* = 1.5, 11.3 Hz, 1H), 3.63 (dd, *J* = 5.3, 11.3 Hz, 1H), 3.38-3.31 (m, 1H), 2.53 (dd, *J* = 7.5, 15.1 Hz, 1H), 2.37 (dd, *J* = 5.3, 15.1Hz, 1H), 2.13 (dt, *J* = 2.2, 15.1 Hz, 1H), 1.77-1.65 (m, 1H), 1.48 (s, 3H), 1.35 (s, 3H), 1.25 (t, *J* = 7.5 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.7, 108.7, 78.8, 71.8, 70.3, 68.9, 63.4, 60.3, 40.7, 325, 28.2, 26.1, 25.8, 18.3, 14.0, -5.3; IR (neat): 3445, 2933, 1731, 1382, 1254, 1098, 837, 759 cm^{-1}; HRMS (ESI) for $C_{19}H_{36}O_6SiNa$ $[M+Na]^+$ found 411.2211calcd 406.2195.

(*R*)-1-((3a*S*,4*R*,6*R*,7a*S*)-4-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl)pent-4-en-2-ol (14): To a stirred solution of acetonide protected ester *trans*-**9** (4.0 g, 10.3 mmol) in dry CH_2Cl_2 (20 mL) was added DIBAL-H (7.7 mL, 1.6 M solution in toluene) dropwise over a period of 10 min under nitrogen atmosphere at -78 °C. After stirring for 2 h at the same temperature, dry methanol (10 mL) was added and the reaction mixture was allowed to warm to room temperature. Saturated aqueous solution of sodium potassium tartarate (10 mL) was added and the resulting mixture was stirred vigorously until the two layers were separated. The organic layer was separated and the aqueous layer was extracted with additional CH_2Cl_2 (2 x 40 mL). The combined organic filtrates were washed with H_2O (2 X 10 mL) and brine (2 X 10 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford the crude aldehyde. This was used for the next step without further purification.

To a solution of (+)-IPC_2B(allyl) (1.0 M in pentane, 12.4 mL) in diethyl ether (10 mL) was cooled to -100 ºC and a solution of above crude aldehyde in 10 ml of diethyl ether was added slowly. The mixture was stirred at -100 ºC for 2 h and then warmed to 0 ºC. The reaction was quenched by the dropwise addition of 3 mL of 30% H_2O_2 (aq) and 3 ml of 1N NaOH. The mixture was diluted with 20 mL of ethyl acetate and the layers were separated. The aqueous layer was extracted with (3 X 10 mL) ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated. The crude reaction mixture was further purified by silicagel column chromatography (hexane/EtOAc, 7:3) to give homoallyl alcohol **14** (3.1g, 80%) as a clear liquid. $[\alpha]_D^{25}$: +24.0 (*c* = 0.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.92-5.75 (m, 1H), 5.15-5.04 (m, 2H), 4.41-4.34 (m, 1H), 3.97-3.86 (m, 2H), 3.82 (dd, *J* = 1.8, 11.1 Hz, 1H), 3.77 (dd, *J* = 4.9, 9.2 Hz, 1H), 3.59 (dd, *J* = 6.6, 11.1 Hz, 1H), 3.36 (dd, *J* = 2.0, 9.0 Hz, 1H), 2.78 (br.s, 1H), 2.32-2.22 (m, 1H), 2.08-1.99 (m, 1H), 1.84-1.60 (m, 4H), 1.51 (s, 3H), 1.36 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.1, 117.3, 108.9, 79.0, 72.0, 70.9, 69.9, 68.3, 63.7, 41.7, 40.8, 33.2, 28.3, 26.3, 25.9, 18.3; IR (neat): 3453, 2929, 1640, 1381, 1251, 1086, 835, 778 cm^{-1}; HRMS (ESI) for $C_{20}H_{38}O_5SiNa$ $[M+Na]^+$ found 409.2378 calcd 409.2382.

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(*R*)-1-((3a*S*,4*R*,6*R*,7a*S*)-4-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl)pent-4-en-2-yl cinnamate (8): Cinnamic acid (1.72 mL, 8.7 mmol) was added dropwise under N_2 to a solution of **14** (3.0 g, 5.8 mmol), DCC (3.20 g, 11.6 mmol) in CH_2Cl_2 (15 mL), and catalytic amount of DMAP was added to it. The mixture was stirred at 0 °C for 0.5 h. After completion, the mixture was poured into brine (5 mL), and extracted with CH_2Cl_2 (2 X 10 mL). The organic phase was washed with 1M aq. HCl, dried (Na_2SO4), and concentrated. The crude product purified by column chromatography (hexane/EtOAc, 8:2) to afford the corresponding acrylic ester **8** (3.3 g, 83%) as a colorless oil. $[\alpha]_D^{25}$: -32.7 (c = 0.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.66 (d, *J* = 16.0 Hz, 1H), 7.56-

7.49 (m, 2H), 7.42-7.36 (m, 3H), 6.42 (d, J = 15.8 Hz, 1H), 5.87-5.72 (m, 1H), 5.33-5.23 (m, 1H), 5.14-5.03 (m, 2H), 4.40-4.34 (m, 1H), 3.91 (dd, J = 5.1, 9.4 Hz, 1H), 3.83 (dd, J = 2.0, 11.5 Hz, 1H), 3.66 (dd, J = 5.1, 11.5 Hz, 2H), 3.29-3.21 (m, 1H), 2.4-2.38 (m, 2H), 2.05 (dt, J = 2.4, 14.9 Hz, 1H), 1.77-1.63 (m, 3H), 1.45 (s,3H), 1.34 (s,3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.3, 144.5, 134.4, 133.5, 130.1, 128.8, 128.0, 118.4, 117.8, 108.7, 78.6, 72.2, 70.7, 70.5, 69.0, 63.4, 39.7, 39.1, 33.5, 28.3, 26.3, 25.94, 18.5, -5.2; IR (neat): 3443, 2928, 1714,1638,1252,1170, 835, 768 cm^{-1}; HRMS (ESI) for $C_{29}H_{44}O_6SiNa$ $[M+Na]^+$ found 539.2812 calcd 539.2799.

(*R*)-6-(((3a*S*,4*R*,6*R*,7a*S*)-4-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl)methyl)-5,6-dihydro-2H-pyran-2-one (15): A solution of Grubbs' second-generation catalyst G-II (0.033 g, 0.0419 mmol, 10 mol%) in CH_2Cl_2 (10 mL) was added dropwise to a solution of acrylic ester **8** (0.250 g, 0.419 mmol) in CH_2Cl_2 (60 mL) at rt., and stirring was continued for 5 h at reflux condition. The solvent was evaporated and the crude product purified by column chromatography (hexane/EtOAc, 75:25) to give lactone **15** (0.219 g, 92% yield) as a pale yellow oil. $[\alpha]_D^{25}$: +70.6 (c = 0.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.86 (qd, J = 2.4, 9.6 Hz, 1H), 6.01 (dd, J = 2.4, 9.6 Hz, 1H), 4.76-4.65 (m, 1H), 4.39-4.33 (m, 1H), 3.97-3.86 (m, 1H), 3.82 (dd, J = 2.1, 11.7 Hz, 1H), 3.74 (dd, J = 5.1, 9.6 Hz, 1H), 3.58 (dd, J = 6.8, 11.5 Hz, 1H), 3.36 (dd, J = 2.0, 9.0 Hz, 1H), 2.50-2.39 (m, 1H), 2.38-2.29 (m, 1H), 2.08 (dt, J = 1.9, 14.5 Hz, 1H), 1.95-1.86 (m, 1H), 1.77-1.66 (m, 2H), 1.50 (s, 3H), 1.35 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.5, 145.0, 117.6, 110.2, 80.2, 74.4, 71.2, 70.7, 69.2, 63.0, 34.9, 26.8, 29.4, 25.7, 24.5, -5.5,-5.6; IR (neat): 3437, 2932, 1694, 1638, 1377, 1218, 1053, 835, 756 cm^{-1}; HRMS (ESI) for $C_{21}H_{36}O_6SiNa$ $[M+Na]^+$ found 430.2632 calcd 430.2619.

(*R*)-6-(((3a*S*,4*R*,6*R*,7a*S*)-4-(hydroxymethyl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl)methyl)-5,6-dihydro-2H-pyran-2-one (16): To a solution of **15** (3.0 g, 7.2 mmol) in anhydrous THF (15 mL) was added TBAF (7.2 mL, 7.2 mmol, 1M soln. in THF) dropwise at 0 °C, and the mixture was stirred for 30 min. H_2O (2 mL) was added, and the mixture was extracted with EtOAc. The org. extracts were washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography (hexane/EtOAc 6:4) to furnish the alcohol **16** (2.1 g, 90% yield) as colorless liquid. $[\alpha]_D^{25}$: +30.4 (c = 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.91-6.86 (m, 1H), 6.04-6.0 (m, 1H), 4.76-4.66 (m, 1H), 4.40-4.36 (m, 1H), 4.22-3.95 (m, 3H), 3.86-3.75 (m, 1H), 3.64-3.51 (m, 1H), 2.45-2.32 (m, 2H), 2.15-2.09 (m, 1H), 1.96-1.89 (m, 1H), 1.76-1.65 (m, 2H), 1.53 (s, 3H), 1.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.7, 146.5, 115.7, 109.2, 78.3, 75.3 72.0, 71.7, 70.9, 63.1, 38.6, 32.7, 30.3, 28.2, 26.2; IR (neat): 3498, 2925, 1705,1637, 1249, 1173, 1055, 767 cm^{-1}; HRMS (ESI) for $C_{15}H_{22}O_6Na$ $[M+Na]^+$ found 321.1317 calcd 321.1321.

(*R*)-6-(((3a*S*,4*R*,6*R*,7a*S*)-2,2-dimethyl-4-vinyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl)methyl)-5,6-dihydro-2H-pyran-2-one (17): A solution of oxalyl chloride (0.8 mL, 13.4 mmol) in 10 mL of freshly distilled CH_2Cl_2 was cooled to −78 °C, and anhydrous DMSO (1.4 mL, 26.8 mmol) was added dropwise. The mixture was stirred 30 min at −78 °C upon which alcohol **16** (2.0 g, 6.7 mmol) in 10 mL CH_2Cl_2 was added dropwise. The reaction was stirred 45 min at −78 °C then triethylamine (neat, 4.0 mL, 40.2 mmol) was added dropwise. The mixture was stirred 30 min at −78 °C then washed with 10 mL for each of H_2O, 1 N HCl, saturated sodium bicarbonate, then brine. Each wash was back-extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was used for the next step without further purification

In a reaction flask, a 2.5 M solution of *n*-BuLi in hexane (8.1 mL, 20.1 mmol) was added under N_2 atmosphere to a stirred suspension of methyltriphenylphosphonium iodide (8.3 g, 20.1 mmol) in dry THF (100 mL) at -78 °C. The mixture was allowed to warm to room temperature, stirred for 1 h, and cooled to -78 °C again. To this mixture a solution of above crude aldehyde in dry THF (10 mL) was added dropwise, and the resulting mixture was stirred at room temperature for 2 h, quenched with aqueous NH_4Cl, and extracted with EtOAc (2 X 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 8:2) to give compound **17** (0.8 g, 60% over 2 steps) as liquid. . $[\alpha]_D^{25}$: +62.7 (c = 0.16, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.89-6.85 (m, 1H), 6.02 (dd, J = 1.6, 9.9 Hz, 1H), 5.92-5.82 (m, 1H), 5.33 (dt, J = 1.3, 17.3 Hz, 1H), 5.22 (dt, J = 1.5, 10.6 Hz, 1H), 4.73-4.66 (m, 1H), 4.40-4.34 (m, 1H), 4.02-3.97 (m, 1H), 3.81 (dd, J = 5.3, 9.1 Hz, 1H), 3.72 (dd, J = 4.7, 9.3 Hz, 1H), 2.44-2.29 (m, 2H), 2.11 (dt, J = 1.8, 14.9 Hz, 1H), 1.95-1.89 (m, 1H), 1.76-1.67 (m, 2H), 1.52 (s, 3H), 1.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.3, 145.0, 135.9, 121.4, 116.4, 109.1, 77.9, 74.8, 74.6, 72.0, 68.2, 41.2, 33.4, 29.9, 28.3, 26.2; IR (neat): 3432, 2986, 1696, 1357, 1254, 1073, 839, 756 cm^{-1}; HRMS (ESI) for $C_{16}H_{22}O_5Na$ $[M+Na]^+$ found 295.1538 calcd 295.1529.

(*R*)-6-(((3a*S*,4*R*,6*R*,7a*S*)-2,2-dimethyl-4-((*E*)-styryl)tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl)methyl)-5,6-dihydro-2H-pyran-2-one (19): A solution of Grubbs' second-generation catalyst G-II (86 mg, 0.10 mmol, 10 mol%) in CH_2Cl_2 (1 mL) was added dropwise to a solution compound **17** (300 mg, 1.01 mmol) and the styrene **18** (320 mg, 3.03 mmol) in CH_2Cl_2 (10 mL) at r.t., and the mixture was refluxed for 5 h. The solvent was evaporated and the crude product purified by column chromatography (hexane/EtOAc, 7:3) to give lactone **19** (0.3 g, 90% yield) as a pale yellow oil. $[\alpha]_D^{25}$: +36.7 (c = 0.23, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42-7.38 (m, 2H), 7.32-7.26 (m, 2H), 7.24-7.20 (m, 1H), 6.88 (dq, J = 2.1, 9.6 Hz, 1H), 6.65 (d, J = 16.0 Hz, 1H), 6.24 (dd, J = 5.6, 16.1 Hz, 1H), 6.03 (dd, J = 1.6, 9.7 Hz, 1H), 4.78-4.71 (m, 1H), 4.43-4.39 (m, 1H), 4.09-4.03 (m, 1H), 4.0 (dd, J = 5.6, 9.1 Hz, 1H), 3.82 (dd, J = 4.8, 9.3 Hz, 1H), 2.46-2.30 (m, 2H), 2.15 (dt, J = 2.1, 15.1 Hz, 1H), 1.95 (ddd, J = 2.3, 9.3, 14.6 Hz, 1H), 1.79-1.71 (m, 2H), 1.56 (s,3H), 1.39 (s,3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.2, 145.0, 136.6, 131.3, 128.4, 127.6, 127.2, 126.5, 121.4, 109.2, 77.8, 75.1, 74.6, 72.1, 68.3, 41.2, 33.4, 29.9, 28.3, 26.2; IR (neat): 3442, 2985, 2927, 1721, 1378, 1247, 1046, 968, 749 cm^{-1}; HRMS (ESI) for $C_{22}H_{26}O_5Na$ $[M+Na]^+$ found 393.1668 calcd 393.1659.

(*R*)-6-(((2*S*,4*S*,5*S*,6*R*)-4,5-dihydroxy-6-((*E*)-styryl)tetrahydro-2H-pyran-2-yl)methyl)-5,6-dihydro-2H-pyran-2-one [cryptopyranmoscatone A2 (1)]: To a stirred solution of compound **19** (100 mg, 0.25 mmol) in anhydrous CH_2Cl_2 (5 mL), $TiCl_4$ (0.03 mL, 0.25 mmol) was added at 0 °C and the reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was quenched with solid $NaHCO_3$ and filtered. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (50% EtOAc/Hexane) to afford **2** (48 mg, 80%) as a colourless oil.

$[\alpha]_D^{25}$: +9.5 (c = 0.26, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44-7.39 (m, 2H), 7.37-7.31 (m, 2H), 7.27-7.25 (m, 1H), 6.86 (dq, J = 2.4, 9.6 Hz, 1H), 6.71 (d, J = 16.0 Hz, 1H), 6.21 (dd, J=16.0, 7.3 Hz, 1H), 6.01 (dd, J = 2.5, 9.7 Hz, 1H), 4.75-4.67 (m, 1H), 4.23-4.19 (m, 3H), 3.42 (dd, J = 9.6, 2.8 Hz 1H), 2.44-2.31 (m, 2H), 1.97-1.92 (m, 1H), 1.79-1.50 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.4, 145.1, 136.1, 133.8, 128.6, 128.0, 126.8, 126.6, 121.4, 76.5, 74.9, 71.3, 67.0, 66.8, 41.0, 38.0, 29.9; IR (neat:) 3420, 2924, 2854, ss1719, 1384, 1253, 1071, 755 cm^{-1}; HRMS (ESI) for $C_{19}H_{22}O_5Na$ $[M+Na]^+$ found 353.1365 calcd 353.1358.

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