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Stereoselective total synthesis of cryptopyranmoscatone A1

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ABSTRACT

The first total synthesis of cryptopyranmoscatone A1 isolated from *Cryptocarya moschata* has been accomplished from 3,4,6-tri-*O*-acetyl-D-glucal. In addition to the RCM and cross-metathesis (CM) reactions, the synthesis features a highly diastereoselective Brown's allylation reaction and sets the absolute stereochemistry of the natural product.

Cryptopyranmoscatones A1, A2, A3, B1, B2, and B4 (**1–6**), goniothalamin (**7**), and cryptofolione (**8**) (Fig. 1) are a group of α-pyrones isolated from the branch and stem bark of *Cryptocarya moschata*, Lauraceae, by Cavalheiro et al.[1] The common feature of these pyrones is that they all contain a styryl group; however, they have varying carbon skeletons. The structures of these compounds were established by spectroscopic studies. *Cryptocarya* species showed outstanding equipotent activity toward COX-1 and COX-2.[2] Some of the *Cryptocarya* pyrones have been identified as highly efficacious inhibitors of the G2 check point, which can enhance killing of cancer cells by ionizing radiation and DNA-damaging chemotherapeutic agents, particularly in cells lacking p53 function.[3] The highly unique structures and the impressive levels of biological activities make them as attractive targets for total synthesis. Earlier, we have reported the synthesis of goniothalamin[4a,b] and cryptofolione.[4b] Quite recently, the first synthesis of cryptopyranmoscatone B1 (**4**) was reported by our group,[5] where we have demonstrated tandem stereoselective oxocarbenium cation formation/reduction reaction to get the 2,6-*syn* tetrahydropyran (THP) ring with the required allyl side chain. Now, we herein report the first total synthesis of cryptopyranmoscatone A1 (**1**) from 3,4,6-tri-*O*-acetyl-D-glucal by using oxa-Michael addition reaction as the key step to achieve the 2,6-*anti* THP ring in addition to the RCM and CM reactions in combination with Brown's asymmetric allylation.

Retrosynthetic analysis is depicted in Scheme 1. We envisaged that the target molecule **1** can be accomplished through RCM and cross-metathesis reactions of tetrasubstituted pyran **9** and pyran **9** could be prepared from derivative **10** by Brown's asymmetric allylation. The ester **10** is accessible from **11** by utilizing oxa-Michael addition reaction, whereas the lactone intermediate **11** could be made from 3,4,6-tri-*O*-acetyl-D-glucal 12 by functional group manipulations.

The synthesis of cryptopyranmoscatone A1 **1** was started from the commercially available tri-*O*-acetyl-D-glucal 12 by selective silylation at position 6, followed by MOM protection at position 3 and position 4, removal of the silyl protecting group, converting into alkene, subsequent PCC oxidation as reported in our earlier report[5] to obtain lactone **11**. The lactone **11** was reduced to lactol using DIBAL-H and subjected to Wittig olefination using stabilized ylide to furnish α,β-unsaturated ester **13** in 85% overall yield (Scheme 2). The hydroxy ester **13** on exposure to *t*-BuOK in THF at −78 °C readily underwent intramolecular oxa-Michael reaction[6] to afford 2,6-*trans* tetrahydropyran **10** as a single diastereomer (>20:1) in 95% yield.

The structure of compound **10** was characterized by NMR experiments including 2-D nuclear Overhauser enhance spectroscopy (NOESY) and double quantum filtered correlation spectroscopy (DQFCOSY). From the one dimensional ^{1}H NMR experiments, $^3J_{H1(Pro\text{-}R)\text{-}H2}$ = 8.6, $^3J_{H1(Pro\text{-}S)\text{-}H2}$ = 5.6, $^3J_{H2\text{-}H3(Pro\text{-}R)}$ = 4.0, $^3J_{H2\text{-}H3(Pro\text{-}S)}$ = 7.3, $^3J_{H3(Pro\text{-}R)\text{-}H4}$ = 4.0, $^3J_{H3(Pro\text{-}S)\text{-}H4}$ = 6.5, $^3J_{H4\text{-}H5}$ = 5.4, $^3J_{H5\text{-}H6}$ = 5.4, $^3J_{H6\text{-}H7}$ = 6.2, $^3J_{H7\text{-}H8}$ = 10.5 and $^3J_{H7\text{-}H8}$ = 17.2 Hz, were determined. By NOESY cross peaks H1(*Pro-R*)/H3(*Pro-S*), H1(*Pro-S*)/H3(*Pro-S*), H1(*Pro-S*)/H6, H1(*Pro-R*)/H6, H1(*Pro-R*)/H4, H1(*Pro-S*)/

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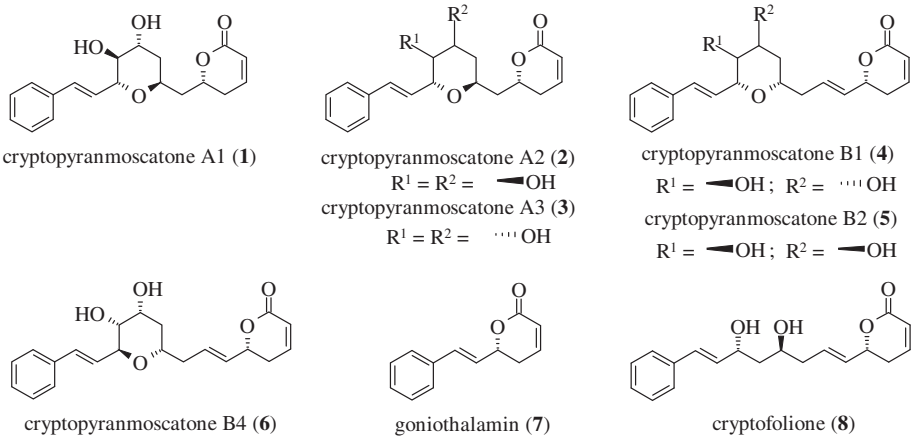
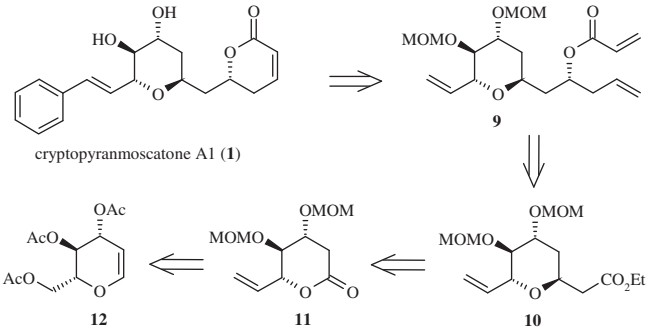


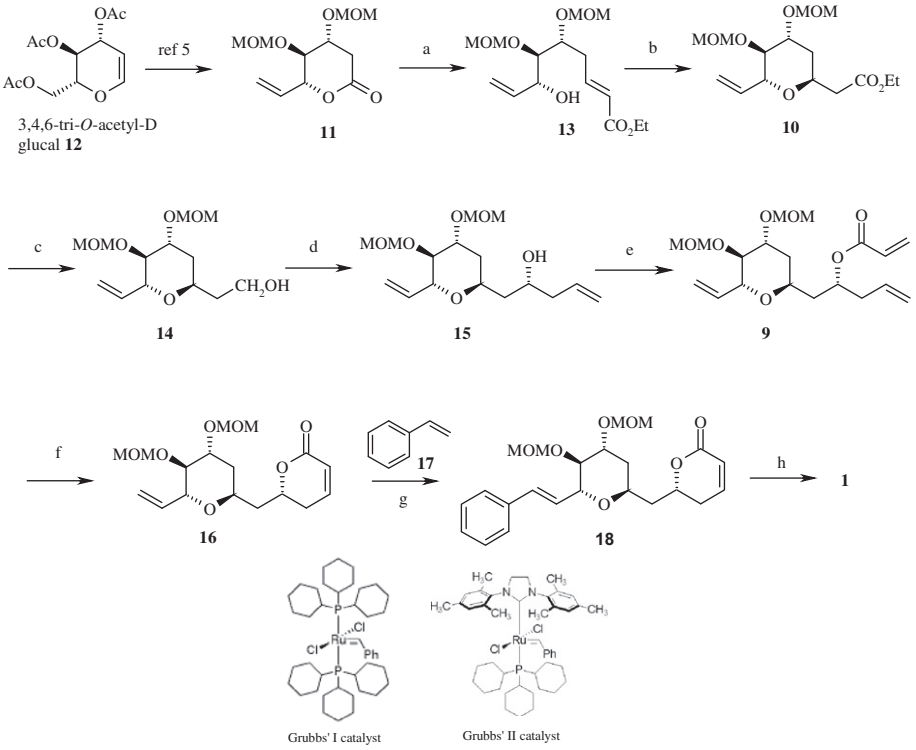
Figure 1. Styryl lactones.



Scheme 1. Retrosynthetic analysis for cryptopyranmoscatone A1.

H4, H5/H7, and H4/H6, along with the couplings support the energy minimized structure shown in Figure 2.

Reduction of ester group in compound 10 with DIBAL-H in CH_2Cl_2 at 0 °C gave alcohol **14** in 84% yield (Scheme 2). Alcohol **14** was oxidized using IBX followed by Brown's asymmetric allylation[7] with B-allyldiisopinocampheylborane to furnish the homoallyl alcohol (**15**, 91% de) in 82% overall yield for the two step-sequence. The homoallyl alcohol was converted into its acryloyl ester **9** and subsequent ring closing metathesis (RCM)[8] using the first-generation Grubbs' catalyst that yielded lactone **16** exclusively. The cross-metathesis reaction of olefin 16 with styrene **17** using Grubbs' second generation carbene catalyst[9] in benzene at 55 °C for 8 h afforded **18**. Finally, cleavage of MOM groups using 4 N HCl in CH_3CN/H_2O (4:1) at 0 °C for 3 h furnished the target lactone, cryptopyranmoscatone A1 (**1**) in 80% yield. The spectral



Scheme 2. Reagents and conditions: (a) (i) Dibal-H, CH_2Cl_2, 0 °C, 1 h; (ii) $Ph_3P{=}CHCOO_2Et$, C_6H_6, reflux, 4 h, 85% (over two steps); (b) *t*-BuOK (1.1 equiv), THF, −78 °C, 0.5 h, 95% (20:1 dr); (c) Dibal-H, CH_2Cl_2, 0 °C, 1 h, 84%; (d) (i) IBX, DMSO, CH_2Cl_2, 0 °C to rt, 4 h; (ii) (+)-IPC_2B(allyl) 1.0 M in pentane, ether, −100 to 0 °C, 2 h, 82% (over two steps), (91% de); (e) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, 85%; (f) Grubbs' 1st generation catalyst (10 mol%), CH_2Cl_2, reflux, 6 h, 91%; (g) Grubbs' 2nd generation catalyst (10 mol%), C_6H_6, 55 °C, 8 h, 87%; (h) 4 N HCl, $CH_3CN{:}H_2O$ (4:1), 0 °C, 3 h, 80%.

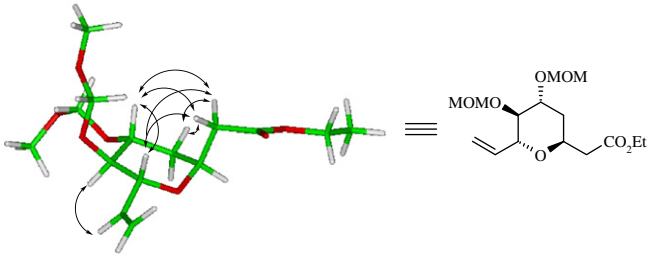


Figure 2. Energy minimized structure and chemical structure of **10**.

(IR, ^{1}H, ^{13}C NMR, and mass) data[10] of **1** were found to be identical in all respects with those reported by Cavalheiro et al. for the natural product[1] thereby confirming its structure and absolute stereochemistry.

In conclusion, we have accomplished the first stereoselective total synthesis of cryptopyranmoscatone A1 starting from relatively cheap and commercially available tri-*O*-acetyl-D-glucal utilizing Brown's asymmetric allylation in addition to RCM, cross-metathesis, and oxa-Michael reactions. This report provides an attractive method for the preparation of other natural analogs, which is underway in our lab and the results will be published in due course.

Acknowledgments

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10. *Ethyl 2-[(2S,4R,5R,6R)-4,5-di(methoxymethoxy)-6-vinyltetrahydro-2H-2-pyranyl]-acetate* (**10**): To a solution of alcohol **13** (1.0 g, 3.14 mmol) in THF (10 mL) at −78 °C was added *t*-BuOK (387 mg, 3.44 mmol). After 0.5 h stirring at −78 °C, a saturated solution of NH_4Cl (5 mL) was added and the mixture warmed up to rt. Extraction was carried out with Et_2O (3 × 10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The purification of the residue by flash column chromatography (eluent:PE–EtOAc, 8:2) furnished cycloadduct **10** in 95% yield (950 mg) as a colorless oil. R_f = 0.6 (PE–EtOAc, 8:2); $[\alpha]_D^{25}$: +48 (*c* = 0.0125 g/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.09–5.95 (m, 1H), 5.32 (dt, *J* = 17.3, 1.5 Hz, 1H), 5.19 (dt, *J* = 10.5, 1.5 Hz, 1H), 4.73–4.59 (m, 4H), 4.47–4.36 (m, 1H), 4.19–4.07 (m, 3H), 3.89–3.79 (m, 1H), 3.44–3.38 (m, 1H), 3.35 (d, *J* = 3.0 Hz, 6H), 2.64 (dd, *J* = 15.1, 8.3 Hz, 1H), 2.40 (dd, *J* = 15.1, 6.0 Hz, 1H), 1.96–1.84 (m, 1H), 1.80–1.69 (m, 1H), 1.26 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 171, 135.1, 117.3, 96.4, 95.5, 75.9 (d, 2C), 72.8, 65.3, 60.5, 55.9, 55.5, 39.4, 32.7, 14.2; IR (Neat): 2927, 1734, 1644, 1446, 1151, 1034, 921 cm^{-1}; ESIMS: *m/z* 341 $[M+Na]^+$; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{15}H_{26}O_7Na$: 341.1576; found: 341.1587; *(2R)-1-[(2R,4R,5R,6R)-4,5-di(methoxymethoxy)-6-vinyltetrahydro-2H-2-pyranyl]-4-penten-2-ol* (**15**): $[\alpha]_D^{25}$: +45 (*c* = 0.01 g/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.15–6.01 (m, 1H), 5.89–5.72 (m, 1H), 5.33 (d, *J* = 17.3 Hz, 1H), 5.23 (d, *J* = 10.5 Hz, 1H), 5.12–5.01 (m, 2H), 4.73–4.59 (m, 4H), 4.29–4.13 (m, 2H), 3.91–3.78 (m, 2H), 3.48–3.41 (m, 1H), 3.35 (d, *J* = 5.2 Hz, 6H), 2.33–2.11 (m, 2H), 1.95–1.60 (m, 2H), 1.54–1.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 135.0, 134.8, 117.7, 117.3, 96.3, 95.5, 76.0, 75.5, 72.6, 71.3, 68.9, 55.8, 55.6, 41.8, 39.6, 33.4; IR (Neat): 3450, 2929, 1638, 1438, 1149, 1035, 918 cm^{-1}; ESIMS: *m/z* 339 $[M+Na]^+$; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{16}H_{28}O_6Na$: 339.1783; found: 339.1778; *(6R)-6-[(2S,4R,5R,6R)-4,5-di(methoxymethoxy)-6-vinyltetrahydro-2H-2-pyranyl]methyl-5,6-dihydro-2H-2-pyranone* (***16***): $[\alpha]_D^{25}$: +91 (*c* = 0.0115, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.88–6.80 (m, 1H), 6.21–6.07 (m, 1H), 5.99 (dt, *J* = 9.8, 1.5 Hz, 1H), 5.31–5.16 (m, 2H), 4.74–4.53 (m, 5H), 4.23–4.07 (m, 1H), 3.90–3.81 (m, 1H), 3.49–3.31 (m, 8H), 2.47–2.13 (m, 3H), 1.98–1.67 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 164.4, 145.2, 135.2, 121.2, 117.8, 96.3, 95.6, 76.3, 75.5, 75.1, 72.6, 63.8, 55.8, 55.6, 38.4, 33.0, 28.7; IR (Neat): 2927, 1721, 1636, 1386, 1249, 1035, 920 cm^{-1}; ESIMS: *m/z* 365 $[M+Na]^+$; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{17}H_{26}O_7Na$: 365.1576; found: 365.1576; *(6R)-6-((2S,4R,5S,6R)-4,5-dihydroxy-6-[(E)-2-phenyl-1-ethenyl]tetrahydro-2H-2-pyranylmethyl)-5,6-dihydro-2H-2-pyranone* (**1**): $[\alpha]_D^{25}$: +45 (*c* = 0.0095 g/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42–7.20 (m, 5H), 6.90–6.82 (m, 1H), 6.68 (d, *J* = 15.8 Hz, 1H), 6.21 (dd, *J* = 15.8, 6.9 Hz, 1H), 6.00 (dt, *J* = 9.8, 1.5 Hz, 1H), 4.59–4.47 (m, 1H), 4.32–4.21 (m, 1H), 4.00 (t, *J* = 7.5 Hz, 1H), 3.94–3.84 (m, 1H), 3.32–3.23 (m, 1H), 2.54–2.30 (m, 3H), 2.01–1.68 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 164.5, 145.3, 136.1, 133.7, 128.6, 128.0, 126.6, 126.1, 121.2, 75.9, 75.3, 74.5, 68.9, 68.3, 35.8, 35.6, 28.5; IR (Neat): 3388, 2927, 1707, 1388, 1256, 1056, 816, 749, 694 cm^{-1}; ESIMS: *m/z* 353 $[M+Na]^+$; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{19}H_{22}O_5Na$: 353.1364; found: 353.1369.