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Total synthesis of cryptopyranmoscatone B1 from 3,4,6-tri-*O*-acetyl-D-glucal

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ABSTRACT

The first stereoselective total synthesis of the natural cryptopyranmoscatone B1 has been accomplished from 3,4,6-tri-*O*-acetyl-D-glucal. In addition to the double cross-metathesis reaction, a tandem nucleophilic addition-diastereoselective reduction of an in situ generated oxocarbenium cation have been used as key steps to assemble the glycoside moiety of the target molecule.

In 2000, Cavalheiro and Yoshida[1] reported the isolation of cryptopyranmoscatones A1, A2, A3, B1, B2, and B4 (**1–6**), goniothalamin (**7**) and cryptofolione (**8**) (Fig. 1) from the branch and stem bark of *Cryptocarya moschata*, Lauraceae, a tree found in the southeastern region of Brazil. The structures were established by spectroscopic studies and these 5,6-dihydro-α-pyrones contain a styryl group attached to the C6 side chain. Styryllactones in general are reported to possess significant cytotoxicity toward several human tumor lines.[2] Some of the *Cryptocarya* pyrones have been identified as highly efficacious inhibitors of the G2 check point, particularly in cells lacking p53 function.[3] The highly unique structure 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] We report herein the first total synthesis of cryptopyranmoscatone B1 (**4**) starting from relatively inexpensive and commercially available 3,4,6-tri-*O*-acetyl-D-

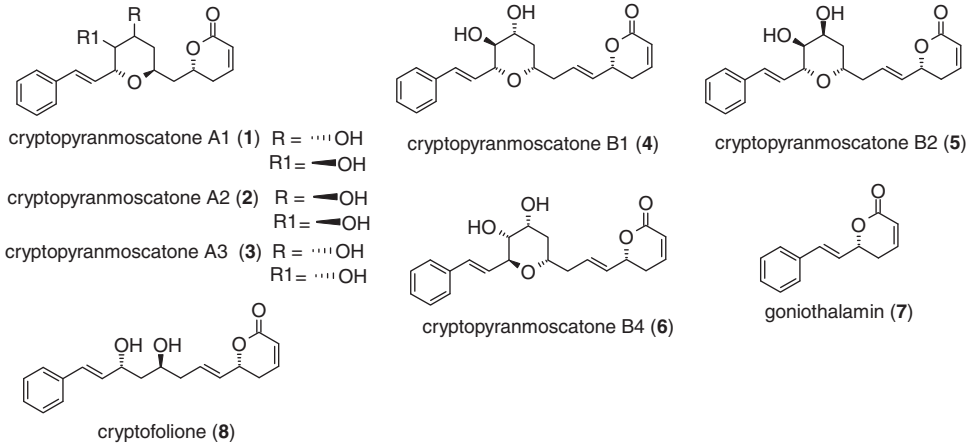

Figure 1. 5,6-Dihydro-α-pyrones.

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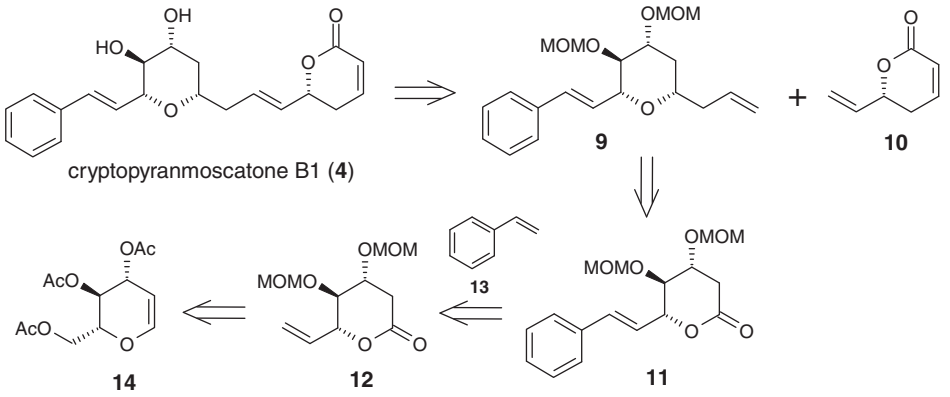
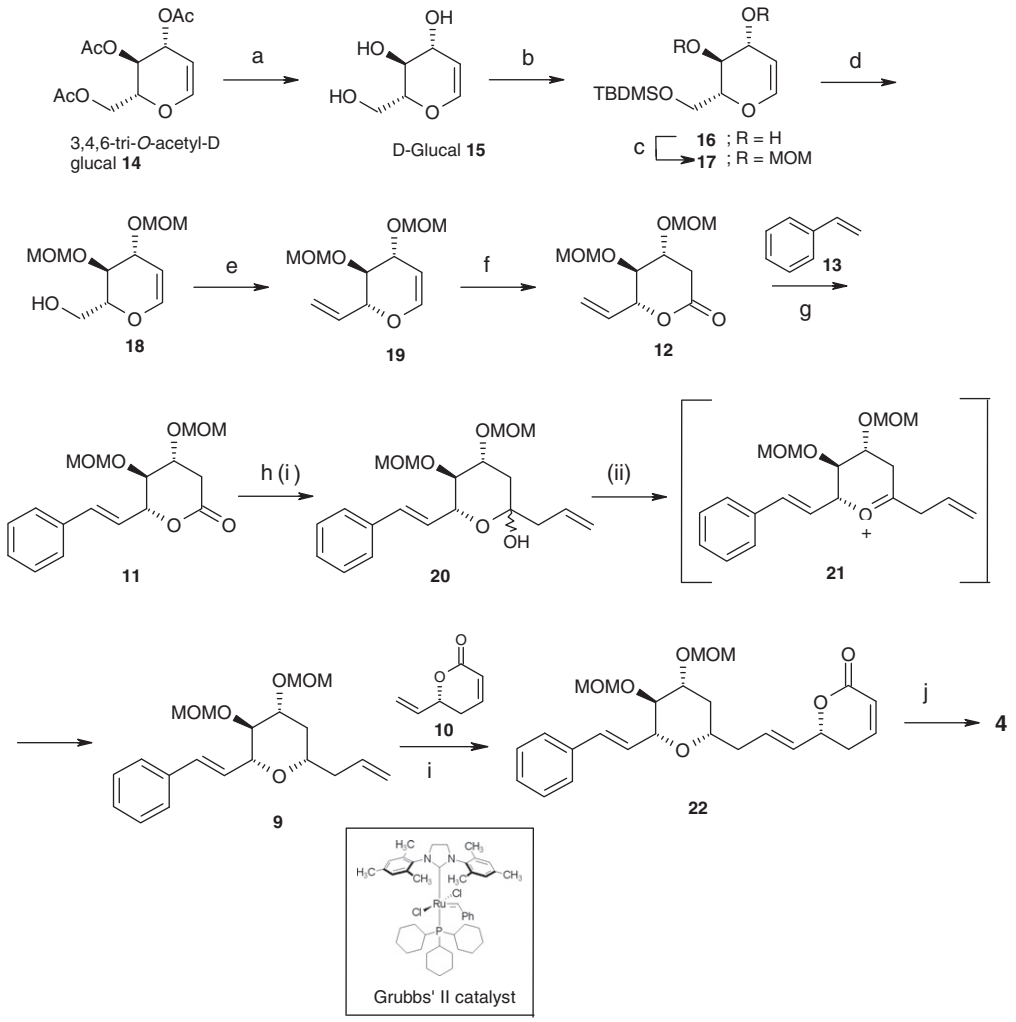


Scheme 1. Retrosynthetic analysis for cryptopyranmoscatone B1.

glucal, the chiral centers present will perfectly match with the target molecule. This synthesis will enable us to evaluate the biological activity of the target molecule.

Retrosynthetic analysis is depicted in Scheme 1. We anticipated that the target molecule can be accomplished through a cross-metathesis reaction of tetrasubstituted pyran **9** with the known vinyl lactone **10**[5] whereas the pyran **9** could be prepared from the lactone derivative **11** which in turn could be made by cross-metathesis reaction of the alkene derivative **12** with styrene **13**. The lactone intermediate **12** could be made from 3,4,6-tri-*O*-acetyl-D-glucal **14** by functional group manipulations, one carbon Wittig reaction and PCC-promoted transformation.



Scheme 2. Reagents and conditions: (a) Ref. 6; (b) TBDMSCl (1.1 equiv), imidazole, DMF, rt, 8 h, 87% over two steps; (c) MOMCl, Hunigs base, CH_2Cl_2, 0 °C to rt, 4 h, 92%; (d) TBAF, THF, rt, 2 h, 70%; (e) (i) IBX, DMSO, DCM, 0 °C to rt, 10 h; (ii) *n*-BuLi, Ph_3PCH_3I, THF, −50 °C to rt, 3 h, 75% over two steps; (f) PCC, silica gel, CH_2Cl_2, 45 °C, 8 h, 83%; (g) Grubbs' catalyst II (10 mol %), C_6H_6, 55 °C, 5 h, 87%; (h) (i) allylMgBr (3 equiv), THF, −78 °C, 1 h, (ii) TFA (4 equiv), Et_3SiH (9 equiv), CH_2Cl_2, −78 °C, 2 h, 68% over two steps; (i) Grubbs' catalyst II (7 mol %), CH_2Cl_2, reflux, 6 h, 87%; (j) 4 N HCl, CH_3CN/H_2O (4:1), 0 °C to rt, 1 h, 79%.

D-Glucal[6] **15**, was prepared from the commercially available tri-*O*-acetyl-D-glucal **14** by de-*O*-acetylation. D-Glucal **15** was selectively silylated at the sixth position to give compound **16**, which was then treated with MOMCl and Hunig's base in CH_2Cl_2 affording fully protected 3,4-di-*O*-MOM-6-*O*-silylated-D-glucal derivative **17** (Scheme 2). Removal of the silyl protecting group of **17** with TBAF provided primary alcohol **18** in 70% yield, which was converted into alkene **19** by subsequent oxidation using IBX in DMSO/CH_2Cl_2 followed by Wittig reaction. This D-glucal derivative **19** was subjected to pyridinium chlorochromate (PCC)-promoted transformation of cyclic enol ether to lactone at 45 °C in the presence of silica gel to give key intermediate **12** in 83% yield. The cross-metathesis reaction of olefin **12** with styrene **13** using Grubbs' second generation carbene catalyst[7] in benzene at 55 °C for 5 h afforded **11**. With the key lactone **11** in hand, our attention was initially focused on the allyl β-*C*-glycoside formation followed by final elaboration of the terminal alkene functional group into the final targeted molecule **4**. Thus, treatment of lactone **11** with excess allylmagnesium bromide in THF at −78 °C readily afforded the lactol intermediate **20** as a mixture of two diastereomers, which readily underwent tandem stereoselective oxocarbenium cation formation/reduction with TFA and Et_3SiH to afford the β-*C*-glycoside **9** in 68% yield from **11** (in >20:1 dr). Presumably, reduction of oxocarbenium cation occurs via axial addition of Et_3SiH to afford the glycoside. This assumption was made based on previous reports.[8]

The second cross-metathesis reaction of terminal alkene **9** with the known vinyl lactone **10** using Grubbs' second generation catalyst in refluxing CH_2Cl_2 for 7 h furnished the required lactone **22** in 87% yield. Finally, removal of MOM groups using 4 N HCl in CH_3CN/H_2O (4:1) at 0 °C for 1 h furnished the target lactone, cryptopyranmoscatone B1 (**4**) in 79% yield. The spectra and physical data of the synthetic **4** are in agreement with those of the natural compound thereby confirming its structure and absolute stereochemistry.[1]

In conclusion, we have accomplished the first stereoselective total synthesis of cryptopyranmoscatone B1 starting from relatively cheap and commercially available tri-*O*-acetyl-D-glucal utilizing double cross-metathesis reaction and the construction of β-*C*-glycoside subunit by a one-pot oxocarbenium cation formation/reduction sequence. This Letter provides an attractive method for the preparation of other natural analogs.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.085.

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