First Total Synthesis of Cryptopyranmoscatone A3 and Cryptopyranmoscatone B4

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Received: 04.10.2017
Accepted after revision: 20.01.2018
Published online: 27.02.2018

DOI: 10.1055/s-0036-1591931; Art ID: so-2017-d0044-op

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Abstract The first total synthesis of cryptopyranmoscatones A3 and B4 has been accomplished from D-ribose or but-3-ynol. The key steps involved in the synthesis are oxa-Michael addition, highly diastereoselective Brown allylation, and ring closing metathesis (RCM) and cross metathesis (CM) reactions.

Key words oxa-Michael addition, Brown asymmetric allylation, ring-closing metathesis, cross metathesis

Natural products possessing α,β-unsaturated δ-lactone moieties have attracted considerable attention because of their promising pharmacological properties, which include anticancer,1,2 antimicrobial,3 antifungal,4 and insecticidal activity.5 Cryptopyranmoscatones A1, A2, A3, B1, B2, and B4 (1–6; Figure 1) were isolated by Cavalheiro and Yoshida6 from the branch and stem bark of Cryptocarya moschata, Lauraceae in 2000, together with other representative structures. This tree grows up to 30–40 m high, mainly in the Southeastern Region of Brazil. The structures of these compounds were established by spectroscopic methods. Based on circular dichroism measurements, the authors were able to set the absolute configuration at C6 as R. Structurally, these styryl lactones incorporate a dihydro-α-pyrone moiety as well as a tetra-substituted tetrahydropyran ring. In preliminary biological studies, the cryptomoscatone family of compounds showed G2 checkpoint inhibitory properties7 and cytotoxicity against human cervical carcinoma cell lines.8 Cryptocaryalactones belonging to this group are natural germination inhibitors, although they have no effect on corn.9 Extracts of Cryptocarya species have shown cyclooxygenase-1 and -2 inhibition.10 At least some of these pharmacological effects may be related to the presence of the conjugated double bond, which acts as a Michael acceptor. The biological activity of the cryptopyranmoscatones has not been studied, presumably because of the limited supply from natural sources. The fascinating structural architecture and scarcity of these natural products have attracted our attention with the aim to develop a general synthetic strategy to prepare them.

As part of our continued efforts towards the synthesis of biologically active natural lactones,11 we have already reported the first total synthesis of cryptopyranmoscatones A1,12 A2,13 and B1.14 In the present communication, we herein report the first stereoselective total synthesis of cryptopyranmoscatones A3 and B4 either from but-3-ynol or from D-ribose in a synthetic pathway via an intermediate from which both cryptopyranmoscatone A3 and B4 could be obtained.

Our retrosynthetic strategy for cryptopyranmoscatone A3 and B4 is depicted in Scheme 1. We envisaged that both cryptopyranmoscatone A3 and B4 could be synthesized from bis-olefin 8 by utilizing a ring closing metathesis reaction, while the bis-olefin itself could be obtained from 9 by successive reactions involving oxidation and allylation followed by acrylation. The 2,6-trans-tetrahydro-γ-pyrone 11 could be constructed from a common intermediate 7. In turn, intermediate 7 could be obtained via lactone 15 through a phenylacetylene addition reaction of the aldehyde, produced from the corresponding primary alcohol 13, which could be derived from D-ribose. Cryptopyranmoscatone B4 (6) could be prepared from compound 10 by performing a cross-metathesis reaction as the key step; whereas, the precursor, 2,6-trans-tetrahydro-γ-pyrone 11 could be obtained from intermediate 7.
The synthesis of the key intermediate 7 started with the known alcohol 13 (Scheme 2). Initially, we planned to prepare 13 from benzoate diol 12 in a three-step sequence by protecting group manipulations involving TBS protection followed by removal of the benzoyl and benzyl groups. The known benzoate diol 12 could be prepared in five steps by following reported procedures. However, bearing in mind the number of steps involved and overall yield in obtaining alcohol 13, it was alternatively prepared from D-ribose in five steps in an overall yield of 70%. After protecting the free hydroxy group in 13 as its pivaloyl ether 16, the TBS group was removed with tetrabutylammonium fluoride (TBAF) to yield the corresponding alcohol 17. Oxidation of alcohol 17 with 2-iodoxybenzoic acid (IBX) gave an aldehyde that was subjected to Grignard addition with phenyl acetylene to give propargyl alcohol 18 as a mixture of diastereomers in 88:12 ratio (determined by chiral HPLC). This inseparable mixture was carried on to the preparation of ketone intermediate keto 7. Thus, partial reduction of the triple bond in 18 with Red-Al furnished diol 19. Oxidative cyclization of 1,5-diol 19 with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and [bis(acetoxy)iodo]benzene (BAIB) produced the desired δ-lactone 15 in 86% yield. Lactone 15 was reduced to the lactol using diisobutylaluminum hydride (DIBAL-H) and subjected to Wittig olefination using the two carbon stabilized ylide to furnish α,β-unsaturated ester 20 in 78% overall yield (Scheme 2). IBX oxidation of 20 furnished the key intermediate 7, from which both target molecules cryptopyranmoscatone A3 and B4 could be synthesized by adopting a chemoselective reduction of the keto group.

![Figure 1 Structures of natural cryptopyranmoscatones](image-url)
Accordingly, the synthesis of A3 (3) commenced with stereoselective reduction of the keto group in 7 using NaBH₄ in the presence of CeCl₃·7H₂O at –78 °C in MeOH to furnish the syn alcohol 21, the properties of which correlated with those reported. The hydroxyester 21, on exposure to t-BuOK in THF at –78 °C, readily underwent intramolecular oxa-Michael reaction to afford 2,6-trans tetrahydropyran 9 as a single diastereomer (>20:1) in 95% yield (Scheme 3).
The trans-stereochemistry of the newly generated ring junction of tetrahydropyran 9 was assigned based on 1H NMR (600 MHz, CDCl3) data and assignments were made with the aid of TOCSY and NOESY experiments (see SI, Figure 2). The medium NOE enhancement between C2H/C6H suggested that both protons are anti to each other (trans related). This was further supported by the NOE correlations between C2H/Me-a, C4H/C6H, C2H/C5H, and C3H/C4H, confirming the structure.

After establishing the structure, the ester group in 9 was converted into a terminal alkene by reduction using DIBAL-H in CH2Cl2 followed by Wittig reaction to afford 10. Cross-metathesis24 reaction of terminal alkene with the known vinyl lactone 25 was carried out using Grubbs’ second generation catalyst in CH2Cl2 under refluxing conditions for 4 h to afford the desired lactone 26. Finally, removal of the acetonide was achieved by treatment with TFA in CH2Cl2 at 0 °C to room temperature for 0.5 h to give the cryptopyranmoscatone B4 (6) in 80% yield. The spectroscopic and physical data of synthetic 6 are in agreement with those of the natural compound, thereby confirming its structure and absolute stereochemistry.

In conclusion, we have achieved the first total synthesis of cryptopyranmoscatones A3 and B4. The key steps involved in the synthesis are oxa-Michael addition, asymmetric allylation, and metathesis reactions.

All reactions were performed under inert atmosphere. All glassware used for performing the reactions was oven- or flame-dried. Anhydrous solvents were distilled prior to use: THF from Na and benzo-phenone; CH2Cl2 from CaH2; MeOH from Mg. Commercial reagents were used without purification. Column chromatography was carried out 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). Specific rotations [α]D were measured with a polarimeter and given in 10−1 deg cm2 g−1. Infrared spectra were recorded in CHCl3, or as KBr discs (as mentioned) and reported in wavenumber (cm−1). High-resolution mass spectra (HRMS)
[ESI+] were obtained by using either a TOF or a double focusing spectrometer. 1H NMR spectra were recorded at 300, 400, 500 MHz and
13C NMR spectra were obtained at 75, 100, 125 MHz in CDCl3 solution unless otherwise mentioned. Chemical shifts are reported 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.

Ethyl (E)-4-(((4R,5R)-5-Cinnamoyl-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate (7)
To an ice-cooled solution of 2-(iodooxy)benzoic acid (1.8 g, 6.5 mmol) in anhydrous CH2CN (20 mL) was added a solution of alcohol
methyl-1,3-dioxolan-4-yl)but-2-enoate (21)
Yield: 1.3 g (90%); liquid; \([\text{hexane/EtOAc}, 8:2]\) to give 7.

Yield: 1.3 g (90%); liquid; \([\alpha]_D^{25} +9.5 (c = 0.26, \text{CHCl}_3)\).

Ethyl (E)-4-(((4R,5S)-5-([\alpha]-1-Hydroxy-3-phenylallyl]-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate (21)
A stirred solution of \(\alpha\)-hydroxy-3-phenylallyl alcohol (30 mg, 0.08 mmol) in anhydrous CH2Cl2 (10 mL) was cooled to −78 °C, then DIABAL (1.6 M in toluene, 2.2 mL) was added slowly. After 1 h, the reaction was quenched with MeOH (2 mL) and sodium potassium tartrate (15 mL) and stirred at r.t. for 0.5 h. The layers were separated and the aqueous layer was extracted with CH2Cl2 (3 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na2SO4, filtered, and concentrated in vacuo to afford pure \(\alpha,\beta\)-unsaturated ester 24.

Yield: 1.6 g (85%); pale-yellow oil; \([\alpha]_D^{25} +27.3 (c = 0.2, \text{CHCl}_3)\).

Ethyl (E)-4-(((4R,5S)-5-([\beta]-1-Hydroxy-3-phenylallyl]-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate (24)
A stirred solution of 7 (0.6 g, 1.7 mmol) in CH2Cl2 (10 mL) was cooled to −78 °C, then DIABAL (1.6 M in toluene, 2.2 mL) was added slowly. After 1 h, the reaction was quenched with MeOH (10 mL) and sodium potassium tartrate (15 mL) and stirred at r.t. for 0.5 h. The layers were separated and the aqueous layer was extracted with CH2Cl2 (3 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na2SO4, filtered, and concentrated in vacuo to afford pure \(\alpha,\beta\)-unsaturated ester 24.

Yield: 1.6 g (85%); pale-yellow oil; \([\alpha]_D^{25} +27.3 (c = 0.2, \text{CHCl}_3)\).

Ethyl (E)-4-(((4S,5S)-5-([\gamma]-1-Hydroxy-3-phenylallyl]-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate (24)
A stirred solution of 7 (0.6 g, 1.7 mmol) in CH2Cl2 (10 mL) was cooled to −78 °C, then DIABAL (1.6 M in toluene, 2.2 mL) was added slowly. After 1 h, the reaction was quenched with MeOH (10 mL) and sodium potassium tartrate (15 mL) and stirred at r.t. for 0.5 h. The layers were separated and the aqueous layer was extracted with CH2Cl2 (3 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na2SO4, filtered, and concentrated in vacuo to afford pure \(\alpha,\beta\)-unsaturated ester 24.

Yield: 1.6 g (85%); pale-yellow oil; \([\alpha]_D^{25} +27.3 (c = 0.2, \text{CHCl}_3)\).

Ethyl (E)-4-(((4R,5S)-5-([\delta]-1-Hydroxy-3-phenylallyl]-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate (24)
A stirred solution of 7 (0.6 g, 1.7 mmol) in CH2Cl2 (10 mL) was cooled to −78 °C, then DIABAL (1.6 M in toluene, 2.2 mL) was added slowly. After 1 h, the reaction was quenched with MeOH (10 mL) and sodium potassium tartrate (15 mL) and stirred at r.t. for 0.5 h. The layers were separated and the aqueous layer was extracted with CH2Cl2 (3 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na2SO4, filtered, and concentrated in vacuo to afford pure \(\alpha,\beta\)-unsaturated ester 24.

Yield: 1.6 g (85%); pale-yellow oil; \([\alpha]_D^{25} +27.3 (c = 0.2, \text{CHCl}_3)\).

Ethyl (E)-4-(((4R,5S)-5-([\epsilon]-1-Hydroxy-3-phenylallyl]-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate (24)
A stirred solution of 7 (0.6 g, 1.7 mmol) in CH2Cl2 (10 mL) was cooled to −78 °C, then DIABAL (1.6 M in toluene, 2.2 mL) was added slowly. After 1 h, the reaction was quenched with MeOH (10 mL) and sodium potassium tartrate (15 mL) and stirred at r.t. for 0.5 h. The layers were separated and the aqueous layer was extracted with CH2Cl2 (3 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na2SO4, filtered, and concentrated in vacuo to afford pure \(\alpha,\beta\)-unsaturated ester 24.

Yield: 1.6 g (85%); pale-yellow oil; \([\alpha]_D^{25} +27.3 (c = 0.2, \text{CHCl}_3)\).

Ethyl (E)-4-(((4R,5S)-5-([\zeta]-1-Hydroxy-3-phenylallyl]-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate (24)
A stirred solution of 7 (0.6 g, 1.7 mmol) in CH2Cl2 (10 mL) was cooled to −78 °C, then DIABAL (1.6 M in toluene, 2.2 mL) was added slowly. After 1 h, the reaction was quenched with MeOH (10 mL) and sodium potassium tartrate (15 mL) and stirred at r.t. for 0.5 h. The layers were separated and the aqueous layer was extracted with CH2Cl2 (3 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na2SO4, filtered, and concentrated in vacuo to afford pure \(\alpha,\beta\)-unsaturated ester 24.

Yield: 1.6 g (85%); pale-yellow oil; \([\alpha]_D^{25} +27.3 (c = 0.2, \text{CHCl}_3)\).
Funding Information

The authors thank the Council of Scientific and Industrial Research (CSIR), New Delhi, India, for financial support as part of a five year programme under the title ORIGIN (CSC-0108). A.M. thanks the Council of Scientific and Industrial Research (CSIR), New Delhi, India, for financial assistance in the form of a Research Fellowship.

Supporting Information

Experimental procedures, spectroscopic data, copies of 1H NMR 13C NMR and NOESY spectra are available. Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591931.

References

(17) The diastereomeric ratio of the product was determined by using a Shimadzu high-performance liquid-chromatography (HPLC) system equipped with a chiral HPLC column (Chiralcel OD) and a UV detector at an absorbance of 254 nm. Eclipse XDB C18 (150 × 46 mm, 5 (m column) and a solvent system of 60% acetonitrile in 0.1% FA at a flow rate of 1.0 mL/min were used. tr: 7.8 and 8.4 min.