Tetrahedron 67 (2011) 4559–4568

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Biomimetic type approach to the tricyclic core of xyloketals. Application to a short, stereocontrolled synthesis of alboatrin and first synthesis of xyloketal G

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ARTICLE INFO

Article history:
Received 25 January 2011
Received in revised form 19 April 2011
Accepted 22 April 2011
Available online 5 May 2011

Keywords:
Xyloketals
Claisen rearrangement
Intra-molecular cationic cyclization
Alboatrin
Tandem ring-opening and recylisation
Xyloketal G

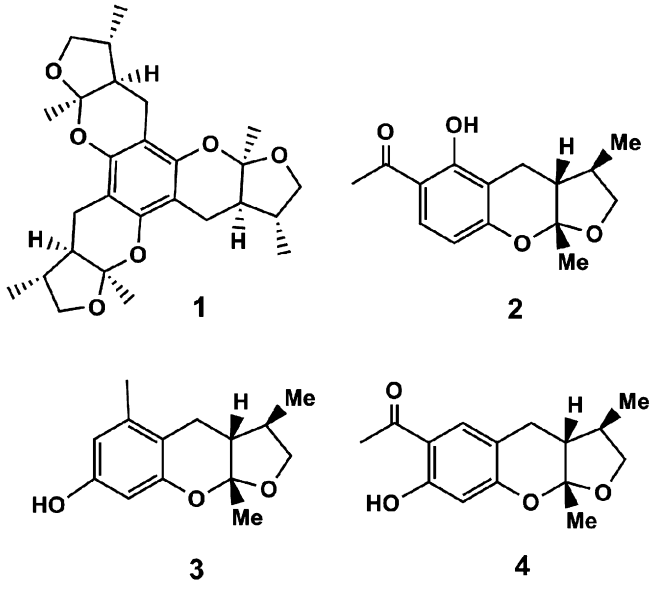
ABSTRACT

A convenient approach to the linear tetrahydrofurano benzopyran ring system of xyloketals is described. An orthoester Claisen rearrangement of a chromenol and an intra-molecular cationic cyclization are the key steps in the synthesis. A short, stereocontrolled and high yield synthesis of the phytotoxic metabolite alboatrin was achieved employing this strategy. A unique case of Lewis acid catalyzed isomerization of *epi*-alboatrin to alboatrin was observed. Subsequently this methodology was extended for the first total synthesis of xyloketal G, where a one pot reaction of three steps viz., acetylation, isomerization and demethylation occurred during acetylation of a mixture of nor-*o*-methyl xyloketal G and nor-*o*-methyl *epi* xyloketal G in presence of $AlCl_3$ to furnish xyloketal G in very good overall yield.

1. Introduction

The impressively diverse structural skeleta that the bountiful nature continues to spawn have never ceased to amaze the organic chemist who continues to draw inspiration from such diversity to bring these molecules within the purview of synthesis. Such diversity has included structural networks that harbour labile and sensitive functionalities, which normally the synthetic chemist will shy away from. An internal ketal in the form of tetrahydrofurano benzopyran, is one such highly labile functionality enshrined in the xyloketals, a group of structurally unique closely related natural products originating from a mangrove fungus of the xylaria species.[1] Xyloketal A **1**, a representative compound belonging to this group was the first one to be isolated and possesses a distinctive C_3-symmmetric molecular structure.

This is also a potent inhibitor of acetyl choline esterase and considered a lead compound in the treatment of Alzheimer's disease. The inimitable characteristic of these molecule is the cis disposition of the three contiguous stereogenic centres in the tetrahydrofuranopyran component. Subsequently a host of related compounds with structural variations involving angular and linear tetrahydrobenzofuranoid systems in their structural inlay were isolated. Xyloketal D **2** is a simpler structural sibling of **1** incorporating a single linear tricyclic network. Xyloketal G **4** is a structural analogue of **2** with a difference



in the substitution of the phenolic hydroxyl group. The unusual structural features and the associated biological properties of the xyloketals have served as attractive targets for synthesis.[2] Our continuing engagements with synthesis of benzoxacyclic natural products with pronounced biological profile[3] have persuaded us to evolve

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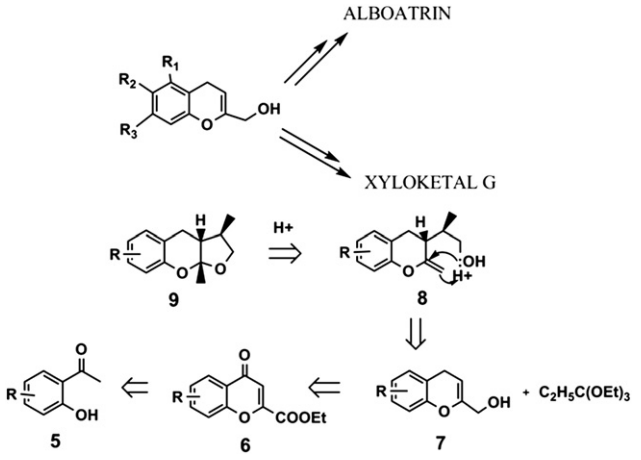
doi:10.1016/j.tet.2011.04.084

a comprehensive program towards the synthesis of xyloketals and related compounds. Primarily, we trained our efforts at developing a convenient method for the linear tricyclic ring system enclosed in these compounds. The core structural motif as in **2** along with identical stereochemical disposition of the three contiguous stereogenic centres is also present in alboatrin **3**, a phytotoxic metabolite isolated from the culture filtrate of *Verticillium alboatrum*.[4] This inhibits the root growth of the host plant (Maris Kabul) and causes vascular-wilt disease in alfalfa. The originally assigned structure was later corrected to **3** involving inversion of the configuration of the secondary methyl group at C-3[5] and representative syntheses of **3** have also been reported.[4,5] We had previously disclosed a synthesis of **3** in which an intra-molecular ketene–alkene cycloaddition followed by an oxidative ring expansion served as the key steps for the development of the tricyclic ring system.[6] This synthesis suffered from low yields in crucial steps and the need to separate the mixture of products in the initial aromatic Claisen rearrangement further impacted the overall yield profile. In this article we describe in detail our successful efforts in developing a convenient alternative and efficient approach to the synthesis of the central tricyclic ring system and its further application to short, stereocontrolled and high yield synthesis of alboatrin.[7] In the course of the synthesis we have also observed a remarkable case of isomerization of the *epi* to the natural isomer, which enabled a further improvement in the total overall yield. The strategy was then applied for the first synthesis of xyloketal G **4**.

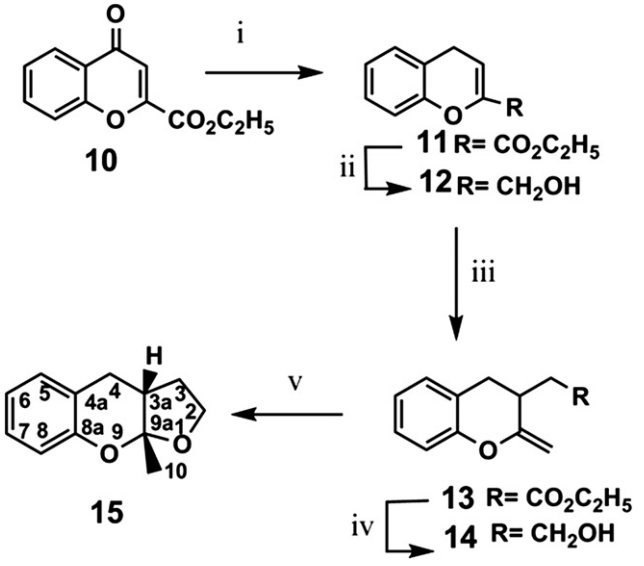
2. Results and discussion

In Scheme 1, is presented the retrosynthetic analysis of our proposed route to the linear tricyclic network contained in the xyloketals. We envisaged the generation of the ring system **9** through a cationic intra-molecular cyclization[8] of a properly hydroxyethyl tethered benzopyran **8**, the annulation providing the thermodynamically more stable cis ring junction in a hydrindane-like system. An orthoester Claisen rearrangement[9] of the chromenol **7** was expected to lead to the alcohol **8** and the chromenol **7** itself was to be rendered from the chromone carboxylate **6**, obtainable from the *o*-hydroxyacetophenone **5** by standard procedure. Before undertaking a synthesis with the properly substituted precursors, it was of interest to test the efficacy of this hypothesis by application to the synthesis of a linear unsubstituted tricyclic model compound.



Scheme 1. Retrosynthetic analysis of the tricyclic core.

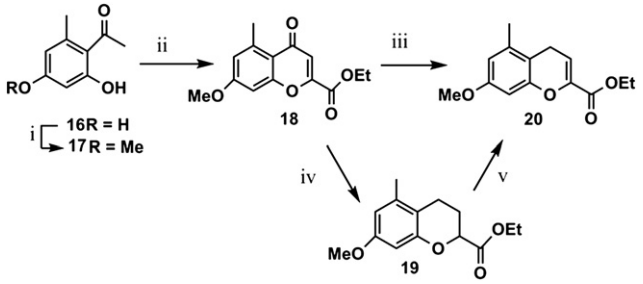
The synthesis began with the ethyl chromone-2-carboxylate **10**.[10] Transformation of this to the requisite allyl alcohol **12** called for a primary chemoselective removal of the carbonyl group. This was achieved employing a combination of sodium cyanoborohydride and boron trifluoride etherate[11] and afforded the chromene carboxylate **11** in about 74% yield. The structure of the chromene carboxylate was supported from the absence of the benzylic ketone in the IR and further endorsed by the ^{1}H NMR spectrum, which showed a doublet at δ 3.53 for the benzylic methylene group. The C-3 olefinic proton consequently appeared as a triplet attesting to the assigned structure. Interaction of this ester with LAH in ether delivered the allylic alcohol **12** in excellent yield. Refluxing a homogenous mixture of this alcohol and triethyl orthoacetate in xylene in presence of a catalytic amount of propionic acid resulted in the expected orthoester Claisen rearrangement to furnish the rearranged ester **13** in 96% yield. The structure of this product was borne out by the appropriate features in the ^{1}H NMR spectrum particularly the two broad singlets at δ 4.27 and 4.60 for the *exo*-methylene protons. The ester function in this was reduced with LAH to the corresponding alcohol **14** in excellent yield. This alcohol was now properly set up for the intra-molecular cyclization envisioned in our proposal. In the event, when a THF solution of this alcohol was subjected to mild acid treatment, it underwent the anticipated cationic cyclization to furnish the tricyclic ketal **15** (Scheme 2).



Scheme 2. Reagents and conditions: (i) $BF_3{\cdot}Et_2O$, $NaCNBH_3$, THF, reflux, 3 h, 74%; (ii) LAH, THF, −40 °C to 0 °C, 1 h, 92%; (iii) $CH_3C(OEt)_3$, C_2H_5COOH (Cat.), xylene, 140 °C, 6 h, 96%; (iv) LAH, THF, 0 °C, 1 h, 97%; (v) H_2SO_4 (Cat.), THF, 0 °C –rt, 2 h, 96%.

The structure of the cyclized product **15** was adequately supported by the appropriate features in the ^{1}H NMR spectrum, which showed a strong singlet at δ 1.58 for the angular methyl group and other relevant features for the methylene protons. The cis ring juncture to this product has been assigned based on previous precedents in the synthesis[1,2] of xyloketals. This conclusion received further support from NOE studies, which showed a strong connection between the angular methyl group and the angular hydrogen at C-3a. The tricyclic ketal **15** incorporated the basic structural network of the xyloketals. The successful synthesis of the basic tricyclic core of the xyloketals secured a potential methodology for the further application to the synthesis of alboatrin **3** and xyloketal G **4**. The synthesis of each called for with suitable variations in the substitution pattern of the starting materials. The synthesis of alboatrin was taken up first. The known resacetophenone **16**[12] was chosen as the appropriate starting point for the synthesis. Interaction of this with iodomethane in refluxing

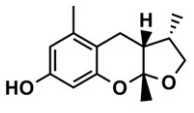
acetone in the presence of potassium carbonate achieved the selective methylation of the less encumbered phenolic group to provide the methyl ether **17**. An intra-molecular hydrogen bonding between the carbonyl oxygen and the adjacently placed phenolic group in **16** renders the distal phenolic function more reactive resulting in this selectivity. Condensation of the methyl ether **17** with diethyl oxalate followed by dehydration of the resultant 2-hydroxy chromanone furnished the desired chromone carboxylate **18** in an overall 90% yield. Banking on the precedent in the case of **10**, this was subjected to reduction with a combination of sodium cyanoborohydride and boron trifluoride etherate to realize the chemoselective deoxygenation of the carbonyl group. Although this afforded the desired chromene carboxylate **20**, the yield was abysmally low (25%).Variations in the reaction parameters involving longer reaction time or excess of the reducing agent did not lead to any improvement in the yield. Hence it became imperative to find suitable alternatives to improve this yield before proceeding further with the synthesis. The carbonyl group being both benzylic and allylic in nature, it was felt that it may be convenient to carry out a hydrogenolysis, which will also result in the reduction of the double bond, which can then be re-introduced taking advantage of the ester functionality employing established procedure. Based on this contention, **18** was subjected to total hydrogenation by exposing to a stream of hydrogen in presence of palladium carbon and furnished the chromane carboxylate **19** in 95% yield. The absence of any carbonyl absorption in the IR and olefinic signals in the ^{1}H NMR spectrum ensured the structure of the product. Reaction of the ester **19** with phenyl selenyl bromide in presence of LDA furnished a selenated ester, which on oxidative elimination employing hydrogen peroxide afforded the olefin re-instated chromene carboxylate **20** in an overall yield of 83% (Scheme 3). Although the whole sequence involved three steps, the overall yield attested to the viability of the modification.



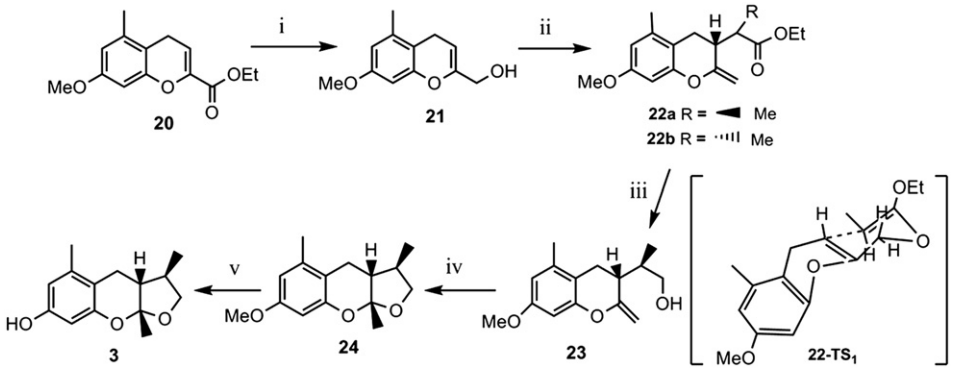
Scheme 3. Reagents and conditions: (i) K_2CO_3, acetone, MeI, reflux, 45 min, 92%; (ii) (a) NaH, $(CO_2C_2H_5)_2$, THF, 0 °C to rt, 8 h; (b) PTSA, C_6H_6, reflux, overall yield 90%; (iii) $BF_3{\cdot}Et_2O$, $NaCNBH_3$, THF, reflux, 4 h, 25%; (iv) Pd/C, H_2, C_2H_5OH, 3 h, 95%; (v) (a) LDA, PhSeBr, THF, −780 °C, 92%; (b) H_2O_2, CH_2Cl_2/THF (2:1), 0 °C to rt, overall yield 90%.

Proceeding with the synthesis, the chromene carboxylate **20** was reduced with LAH and furnished the allylic alcohol **21** in 93% yield. The next step involved an orthoester Claisen rearrangement. At this juncture, it became necessary to look at a sequence, which will also incorporate the required secondary methyl group in a stereocontrolled manner next door to the angular hydrogen in the tetrahydrofurano benzopyran system as present in alboatrin and xyloketals. We decided to carry out the Claisen rearrangement employing triethyl orthopropionate, which will enable the introduction of the requisite secondary methyl group. The Claisen rearrangement is deemed to proceed through a chair-like transition state for the intermediate allyl enol ether.[13,14] An analysis of the purported transition state **22**—TS_1, in our system suggested that the product arising from this will have the cis disposition of the two newly created stereogenic centres as the major if not the only product. Refluxing a homogenous mixture of the alcohol and triethyl orthopropionate in xylene in the presence of catalytic amount of propionic acid delivered the rearranged γ,δ unsaturated ester(s) **22** as a mixture of two diastereomers in 9:1 ratio in 97% total yield. These were separated by column chromatography and the structure of the major isomer was assigned as **22a** based on the arguments discussed above. The final confirmation of the assignment, however, had to await its conversion to alboatrin itself. Reduction of the ester **22a** with LAH furnished the alcohol **23** in 90% yield. When this alcohol was subjected to mild acid treatment, it underwent the intra-molecular cationic cyclization as before to afford the methyl ether **24** of alboatrin as the only isolated product in 96% yield. The melting point and spectral features (^{1}H and ^{13}C NMR) of this material were identical with our previously synthesized sample.[6] Demethylation of this to alboatrin **3** having already been reported,[6] this concluded a short, high yield synthesis of the metabolite (Scheme 4). The synthesis also confirmed the structural and stereochemical assignment to the Claisen rearrangement product **22a**.

Murphy et al., in their synthesis of alboatrin, had obtained *epi*-alboatrin **3a**, as the major product.[5] *epi*-Alboatrin differed from its natural counterpart chiefly in the spectral features. In the ^{1}H NMR spectrum, the C-3 secondary methyl protons displayed an upfield shift, appearing as a doublet at δ 0.88 arising from the shielding by the aromatic ring in the convex conformation of the molecule.



***epi*-Alboatrin 3a**

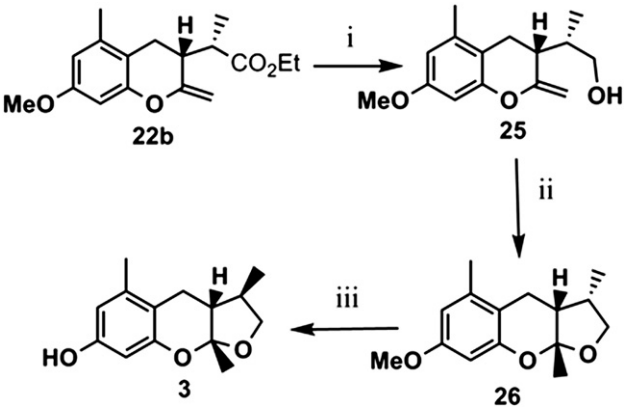


Scheme 4. Reagents and conditions: (i) LAH, THF, −40 °C to 0 °C, 1 h, 93%; (ii) $C_2H_5C(OEt)_3$, C_2H_5COOH (Cat.), xylene, 140 °C, 6 h, 97%; (iii) LAH, THF, 0 °C, 1 h, 90%; (iv) 3 N H_2SO_4 (Cat.), THF, 0 °C to rt, 2 h, 96%; (v) BBr_3, CH_2Cl_2, −78 °C, 1 h, 80%.

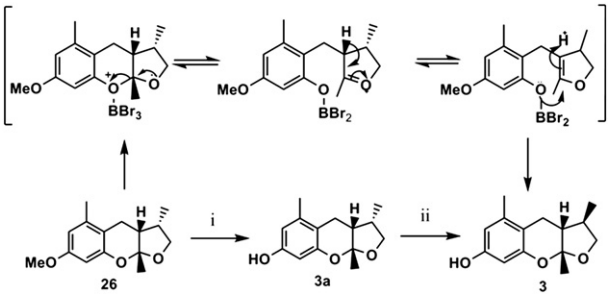
We had obtained the diastereomer **22b** as the minor component in the orthoester Claisen rearrangement and decided to utilize this for a synthesis of *epi*-alboatrin **3a** employing the same sequence of reactions as detailed above for the synthesis of alboatrin. Before that we decided to look at the possible outcome of enolisation and reprotonation of the ester **22a** under various protonation conditions following the experience of Okamoto.[14] If conditions could be developed for epimerization to the trans isomer, it will provide us with a substantial supply of this isomer to carry on with the synthesis of *epi*-alboatrin. Treatment of the ester **22a** with LDA and quenching the enolate with dropwise addition of water at −78 °C furnished a 1:1 mixture of the two diastereomers. When the enolate was quenched with a rapid addition of ethanol, ratio **22a**/**22b** interestingly changed to 1:4. Even more interestingly when *tert*-butanol was employed for quenching the enolate, this ratio shifted to 1:9. We suggest that the less encumbered *exo* face is more accessible in the enolate and the bulky alcohols entail a more preferred *exo* protonation resulting in the ratio of the diastereomers. Thus, we had a procedure for the reversal of the product profile from the Claisen rearrangement and a liberal supply of the desired trans isomer for continuing with the synthesis of *epi*-alboatrin (Scheme 5).

LAH reduction of the ester **22b** furnished the alcohol **25** in 90% yield. Following on the synthesis of alboatrin, this was subjected to mild acid treatment and furnished *O*-methyl-*epi*-alboatrin **26** in near quantitative yield. As anticipated, in the ^{1}H NMR spectrum of **26**, the C-3 secondary methyl protons appeared as a doublet at δ 0.84. Demethylation, as for **24**, was expected to complete the synthesis of *epi*-alboatrin. However, when **26** was subjected to demethylation with BBr_3, the only product isolated in 80% yield was not *epi*-alboatrin **3a**, but alboatrin **3** (Scheme 6).

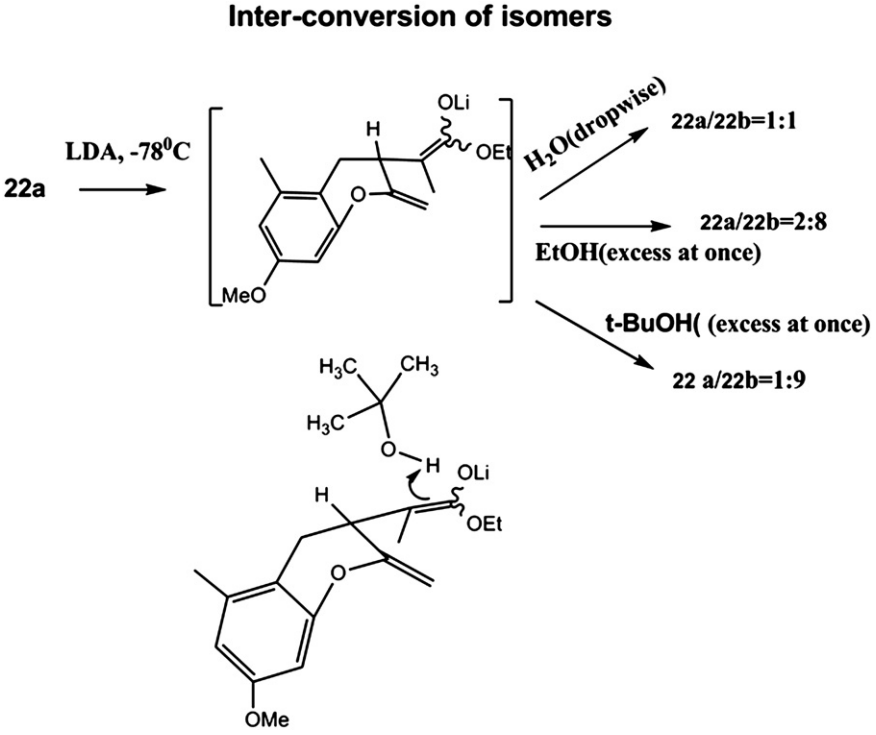
The identity was established from spectral comparison with an authentic sample. This was indeed an unusual and unique case of isomerization and is thought to proceed through a remarkable tandem ring opening and re-cyclization process. We suggest that the primary process is the cleavage of the internal ketal to furnish a dihydrofuran phenol intermediate, which undergoes a protonation with concomitant *anti*-addition of the phenolic moiety to finally deliver **3** (Scheme 7).



Scheme 6. Reagents and conditions: (i) LAH, THF, 0 °C, 1 h, 90%; (ii) H_2SO_4 (Cat.), THF, 0 °C to rt, 2 h, 96%; (iii) BBr_3, CH_2Cl_2, −78 °C, 1 h, 80%.



Scheme 7. Reagents and conditions: (i) EtSNa, DMF, 6 h, 86%; (ii) BBr_3, CH_2Cl_2, −78 °C, 1 h, 92%.



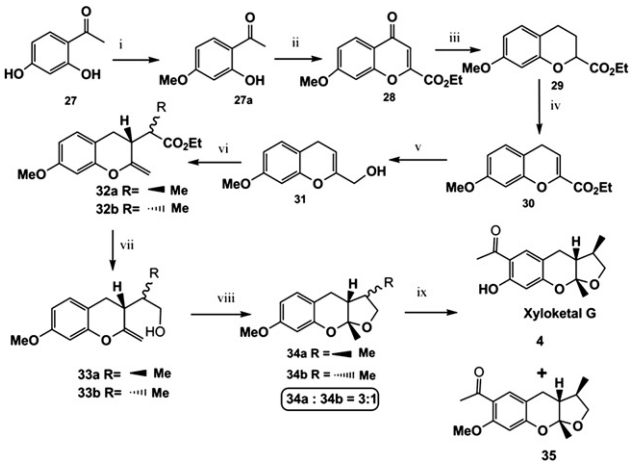
Scheme 5.

Interestingly the protonation takes place *syn* to the secondary methyl group at C-3. Ichihara et al., in their synthesis of **3**,[4] had implicated a similar dihydrofuran intermediate. However, based on the subsequent revision of the configuration of the methyl group at C-3, their conclusion relating to protonation *anti* to this methyl group also needs revision. To secure some support for this proposal, demethylation of **26** was aborted midway. Work up of the reaction furnished a mixture of alboatrin **3** and *o-methyl alboatrin* **24**, indicating a primary ring cleavage followed by re-cyclization prior to demethylation. A similar ring opening and re-cyclization under base catalysis resulting in ring juncture epimerization in a tetrahydro benzopyran system has been reported.[15] Another aspect of great interest and encouragement that emerged from these observations was that the stereochemistry of the Claisen rearrangement product **22** was irrelevant for the final outcome of the synthesis. Indeed when a mixture of both the isomers **22a** and **22b** was subjected to the sequence of reactions involving LAH reduction, acid treatment and demethylation, alboatrin **3** was the sole product isolated in excellent overall yield. Despite these interesting observations, there still remained a need to devise a procedure for the synthesis of *epi*-alboatrin. This called for a deprotection process devoid of any acidic conditions that will circumvent the problem of epimerization. This was achieved by carrying out demethylation of **26** with sodium ethyl mercaptide. This afforded the expected *epi*-alboatrin **3a** in 86% yield as the only product. ^{1}H NMR spectral data fully matched with the reported[5a] values establishing the identity of the product. *epi*-Alboatrin also when treated with BBr_3 under previously stated demethylation conditions fully isomerized to alboatrin.

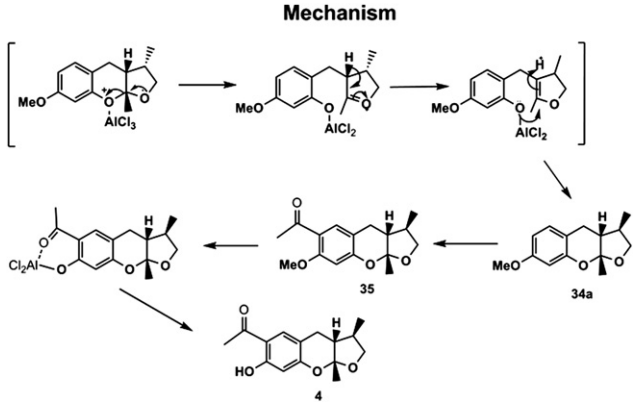
2.1. Synthesis of xyloketal G

The successful synthesis of alboatrin and *epi*-alboatrin laid the foundation for application of the strategy to a synthesis of xyloketal G **4**. Xiongyu et al. reported the isolation of xyloketal G from the marine derived fungus Xylaria species 2508.[1e] This was obtained along with xyloketal D **2**[1] from the seeds of an angiosperm tree in Hongkong. These are regioisomers. Taking up the synthesis, the resacetophenone **27**[16] was subjected to a selective methylation of the less encumbered phenolic group employing iodomethane in presence of potassium carbonate to provide the methyl ether **27a**.[17] This on condensation with diethyl oxalate followed by in situ dehydration of the product furnished the chromone carboxylate **28**.[10] From hereon the sequence of reactions followed the one employed for the synthesis of alboatrin. Hydrogenolysis and subsequent re-instatement of the double bond delivered the chromene carboxylate **30** in an overall yield of 93% (Scheme 8).

Reduction of the ester **29** with LAH furnished the allylic alcohol **31**. This was subjected to an orthoester Claisen rearrangement with triethyl orthopropionate and furnished the rearranged ester(s) **32** as a mixture of diastereomers in 97% yield in a ratio of 3:1. The proportion was arrived at from the integration of the secondary methyl protons in the ^{1}H NMR spectrum and the stereochemistry of the major isomer was assumed based on the arguments in the synthesis of alboatrin. Separation of the isomers was not considered necessary at this stage since, based on previous experience, the final demethylation when carried out with boron tribromide, was expected to lead to the desired xyloketal G **4** from the Lewis acid catalysed isomerization. Hence subsequent steps were carried out on the mixture of isomers. Reduction of the ester(s) with LAH afforded the olefinic alcohol(s) **33**, which on mild acid treatment in THF solution resulted in the anticipated intra-molecular cyclization furnishing a mixture of nor-*O*-methyl xyloketal G **34a** and nor-*epi*-*O*-methyl xyloketal G **34b**. It now remained to carry out an acetylation and demethylation to complete the synthesis. For introduction of the acetyl moiety, the mixture was subjected to a standard Friedel–Crafts acylation with acetyl chloride in presence of anhydrous $AlCl_3$. Work up of the reaction afforded, quite interestingly, xyloketal G **4** and traces of *O*-methyl xyloketal G **35**. It was indeed a case of three reactions, acetylation, isomerization and demethylation occurring in a single pot (Scheme 9). The traces of *O*-methyl xyloketal G **35** indicated the Lewis acid catalyzed isomerization preceding demethylation as in previous case involving alboatrin, although the sequence of acetylation preceding or succeeding isomerization could not, at this point of time, be confirmed. The ready demethylation could be attributed to the proximity effect of the acetyl moiety, allowing the final product to be isolated at the end of the reaction.[18] The ^{1}H and ^{13}C NMR spectra of **4** were fully consonant with those reported,[1e] concluding a short and high yield synthesis of xyloketal G.



Scheme 8. Reagents and conditions: (i) K_2CO_3, acetone, MeI, reflux, 1.5 h, 90%; (ii) (a) NaH, $(CO_2C_2H_5)_2$, THF, 0 °C to rt,18 h; (b) PTSA, C_6H_6, reflux, overall yield 70%; (iii) Pd/C, H_2, C_2H_5OH, 9 h, 90%; (iv) (a) LDA, PhSeBr, THF, −78 to 0 °C, (b) H_2O_2, CH_2Cl_2/THF (2:1), 0 °C to rt, 3 h, overall yield 90%; (v) LAH, THF, −40 °C to 0 °C, 1 h, 93%; (vi) $C_2H_5C(OEt)_3$, C_2H_5COOH (Cat.), xylene, 140 °C, 8 h, 97%; (vii) LAH, THF, 0 °C, 1 h, 85%; (viii) H_2SO_4 (Cat.), THF, 0 °C to rt, 2 h, 96%; (ix) CH_3COCl, $AlCl_3$, DCM, −78 °C to rt, 2 h, 70%.



Scheme 9.

In summary, we have developed a very efficient and stereocontrolled route to the linear tricyclic network of the xyloketals employing a diastereoselective Claisen rearrangement and an intra-molecular cationic cyclization as the key steps and demonstrated its efficacy by applying the methodology to a short, high yield synthesis of the phytotoxic metabolite alboatrin. The synthesis afforded the final product in nine steps from the resacetophenone **27** in an overall yield of 44%. A unique case of isomerization of the *epi* to the natural isomer under Lewis acid conditions was also observed. The strategy was later applied to the first synthesis of xyloketal G, where the use of $AlCl_3$ enabled the one pot occurrence of three reactions to deliver the final product in 30% yield in nine steps from resacetophenone.

3. Experimental

3.1. General

All non aqueous reactions were carried out under an inert atmosphere (argon). Melting points were taken in open capillary tubes in a sulfuric acid bath and are uncorrected. Dry solvents and reagents were prepared from reagent grade materials by conventional methods. Petroleum ether refers to the fraction of bp 60–80 °C. The purity of the products was routinely monitored by TLC. Drying of organic layers was done with sodium sulfate. ^{1}H NMR spectra were recorded at 300 or 500 MHz in $CDCl_3$ solutions. ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at 75 or 125 MHz. Peak positions are indicated in parts per million downfield from an internal TMS standard. IR spectra of liquid products were recorded in thin films or in $CHCl_3$ solution. IR spectra of solids were recorded as KBr pellets. Elemental analysis were recorded in Perkin–Elmer (CHN Analyzer) 2400 series-2.

*3.1.1. Ethyl-4-oxo-4H-chromene-2-carboxylate (**10**).* To a well-stirred solution of NaH (1.13 g) in THF (20 mL) at 0 °C, 2-hydroxy acetophenone (3.22 g, 0.023 mol) and diethyl oxalate (6.4 mL, 0.046 mol) were added followed by stirring for 18 h at room temperature. Then the reaction was quenched with saturated aqueous NH_4Cl solution followed by extraction with ethyl acetate (3×20 mL). The organic part was dried and concentrated to yield a crude alcohol (6.2 g). Without further purification, this alcohol was dissolved in benzene (50 mL), followed by addition of toluene-*p*-sulfonic acid (100 mg) and refluxed using a Dean–Stark water separator for 4 h. The reaction mixture was cooled and concentrated in vacuum and the residue subjected to column chromatography over silica gel. Elution with ethyl acetate/petroleum ether (1:3) furnished the chromone ester **10** (3.5 g, 70%) as colourless crystals. Mp 64–65 °C (lit.[10] mp 63 °C).

*3.1.2. Ethyl-4H-chromene-2-carboxylate (**11**).* To a solution of chromone carboxylate **10** (100 mg, 0.46 mmol) in THF (4 mL), $BF_3{\cdot}OEt_2$ (0.17 mL, 1.38 mmol) and sodium cyanoborohydride (115 mg, 1.832 mmol) were added and refluxed for 3 h. Then the reaction mixture was cooled and quenched by saturated aqueous NH_4Cl solution. The aqueous layer was extracted with ether (3×10 mL) and dried .The solvent was evaporated to get a yellow liquid, which was subjected to chromatography over silica gel. Elution with ethyl acetate/petroleum ether (1:19) furnished the chromene carboxylate **11** as colourless crystals (69 mg, 74%). R_f (20% EtOAc/petroleum ether (60:80)) 0.5; mp 61–63 °C. IR 1729 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16–7.11 (m, 1H); 7.03–7.00 (m, 3H); 6.20 (t, J=3.93 Hz, 1H); 4.28 (q, J=7.1 Hz, 2H); 3.53 (d, J=3.9 Hz, 2H); 1.31 (t, J=5.35 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 151.1, 141.7, 128.9, 127.9, 123.9, 118.1, 117.0, 110.2, 61.4, 24.4, 14.2. HRMS (ESI) M+H$^+$, found: 205.0866; $C_{12}H_{12}O_3$ requires 205.0865.

*3.1.3. (4H-Chromen-2-yl) methanol (**12**).* To a well stirred slurry of LAH (150 mg, 2.17 mmol) in THF (3 mL) at −40 °C, the chromene carboxylate **11** (370 mg, 1.81 mmol) in THF (2 mL) was added slowly via a syringe and stirred for 1 h at the same temperature. The reaction was allowed to attain 0 °C and then quenched with saturated Na_2SO_4 solution. The product was then extracted with ether (3×5 mL) and dried. Removal of the solvent furnished the allylic alcohol **12** as a pale yellow oil, which was subjected to column chromatography using neutral alumina followed by elution with (1:4) ethyl acetate/petroleum ether to furnish the allylic alcohol **12** as a colourless liquid (272 mg, 93%). R_f (20% EtOAc/petroleum ether (60:80)) 0.28; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, J=7.4 Hz, 1H); 7.03–6.96 (m, 2H); 5.01 (s, 1H); 4.13 (br s, 2H); 3.42 (br s, 2H); 1.93 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6, 150.1, 129.2, 127.6, 123.4, 119.6, 116.5, 97.6, 62.8, 23.9. HRMS (ESI) M+Na$^+$, found: 185.0578; $C_{10}H_{10}O_2Na$ requires 185.0578.

*3.1.4. Ethyl 2-(2-methylenechroman-3-yl) acetate (**13**).* A mixture of the allylic alcohol **12** (370 mg, 2.284 mmol), triethyl orthoacetate (3.5 mL, 18.2 mmol) and propionic acid (0.05 mL) was heated with stirring in xylene (7 mL) maintaining the temperature at 140 °C. Heating was continued for 8 h, the reaction mixture was allowed to cool to room temperature and the solvent was removed by distillation under reduced pressure. The residue was purified by column chromatography over silica gel. Elution with ethyl acetate/petroleum ether (1:20) afforded the ester **13** (480 mg, 97%) as a colourless oil. R_f (20% EtOAc/petroleum ether (60:80)) 0.93; IR (neat) 1730 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (t, J=7.5 Hz, 1H); 7.04 (d, J=7.2 Hz, 1H); 6.90 (t, J=7.8 Hz, 2H); 4.60 (s, 1H); 4.27 (s, 1H); 4.17 (q, J=6.9 Hz, 2H); 3.18–3.11 (m, 1H); 2.99 (dd, J=4.8, 15.6 Hz, 1H); 2.65 (dd, J=6.6, 15.6 Hz, 1H); 2.59 (dd, J=6.6, 15.6 Hz, 1H); 2.4 (dd, J=8.0, 15.6 Hz, 1H); 1.25 (t, J=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 157.8, 152.4, 129.2, 127.9, 121.5, 120.7, 115.8, 89.8, 60.7, 37.0, 32.7, 30.6, 14.2. HRMS (EI) M+H$^+$, found: 233.1179; $C_{14}H_{17}O_3$ requires 233.1178.

*3.1.5. 2-(2-Methylenechroman-3-yl)ethanol (**14**).* To a well stirred slurry of LAH (240 mg, 1.04 mmol) in THF (2 mL) at 0 °C, the ester **13** (55 mg, 1.45 mmol) in (2 mL) THF was added slowly via a syringe and stirred for 1 h at the same temperature. The reaction was allowed to attain room temperature and quenched with cold saturated aqueous Na_2SO_4 solution. The product was extracted with ether (3×5 mL) and dried. Removal of the solvent furnished the alcohol **14** as a colourless oil (181 mg, 92%). R_f (20% EtOAc/petroleum ether (60:80)) 0.1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (t, J=7.5 Hz, 1H); 6.9 (d, J=7.5 Hz, 1H); 6.84–6.78 (m, 2H); 4.55 (s, 1H); 4.15 (s, 1H); 3.68 (t, J=6.0 Hz, 2H); 2.96 (dd, J=5.5, 16.0 Hz, 1H); 2.79–2.75 (m, 1H); 2.53 (dd, J=7.5, 15.5 Hz, 1H); 1.74–1.67 (m, 1H); 1.57–1.51 (m, 1H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 158.3, 152.5, 129.3, 127.7, 121.3, 121.01, 115.6, 90.0, 60.5, 34.2, 32.7, 30.9. HRMS (ESI) M+Na$^+$, found: 213.0890; $C_{12}H_{14}O_2Na$ requires 213.0891.

3.1.6. (3aR,9aR*)-9a-Methy-3,3a,4,9a-tetrahydro-2H-furo[2,3-b] chromene (**15**).* To a cooled and stirred solution of the alcohol **14** (40 mg, 0.215 mmol) in THF (2 mL) at 0 °C, a solution of H_2SO_4 (3 N, 0.5 mL) in THF (2 mL) was added and stirred for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with ether (3×3 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution, brine, dried and concentrated. The residue was subjected to column chromatography over silica gel. Elution with ethyl acetate/petroleum ether (1:49) furnished the tricyclic ketal **15** (38 mg, 96%) as a colourless solid. R_f (20% EtOAc/petroleum ether (60:80)) 0.73; mp 44–47 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06–7.14 (m, 2H); 6.83–6.89 (m, 2H); 3.88–4.02 (m, 2H); 3.06 (dd, J=5.7, 16.6 Hz, 1H); 2.79 (d, J=16.6 Hz, 1H); 2.42–2.48 (m, 1H); 2.02–2.07 (m, 1H); 1.73–1.80 (m, 1H); 1.58 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 129.3, 127.7, 120.7, 119.4, 117.0, 107.1, 66.8, 41.1, 28.8, 26.3, 23.2. HRMS (EI) M+H$^+$, found: 191.1071; $C_{12}H_{15}O_2$ requires 191.1072.

*3.1.7. 1-(2-Hydroxy-4-methoxy-6-methylphenyl) ethanone (**17**).* To a solution of **16** (1 g, 0.006 mol) in acetone (15 mL), anhydrous K_2CO_3 (0.8 g, 0.006 mol) and iodomethane (0.7 mL, 0.007 mol) was added and refluxed for 45 min (reaction was monitored with TLC). Then the reaction mixture was cooled and acetone evaporated under vacuum. The reaction mixture was quenched with water and extracted with ether (3×10 mL). The ether extract was dried and concentrated to furnish a yellow solid, which was crystallized from petroleum ether/dichloromethane (1:1) to give colourless crystals of **17** (1.03 g, 92%). Mp 53–54 °C. IR 1637 cm^{-1}. ^{1}H NMR (300 MHz,

$CDCl_3$) δ 13.47 (s, 1H); 6.19 (s, 1H); 6.17 (s, 1H); 3.7 (s, 3H); 2.52 (s, 3H); 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3, 167.5, 164.7, 142.2, 115.5, 112.2, 99.4, 55.7, 33.4, 25.5. HRMS (ESI) M+Na^+, found: 203.0682; $C_{10}H_{12}O_3Na$ requires 203.0684.

*3.1.8. Ethyl 7-methoxy-5-methyl-4-oxo-4H-chromene-2-carboxylate (**18**).* To a cooled (ice-bath), stirred slurry of sodium hydride (0.7 g, 0.028 mol, 50% dispersion in oil) in anhydrous THF (10 mL) under argon, a mixture of 1-(2-hydroxyl-4-methoxy-6-methyl phenyl) ethanone **17** (2.53 g, 0.014 mol) and diethyl oxalate (3.9 mL, 0.028 mol) in THF (20 mL) was added slowly and the reaction mixture left overnight at room temperature. It was then poured into ice-water (70 mL) and acidified with cold dilute HCl (6 N, 20 mL) and extracted with ether (3×40 mL). The ether extract was washed with water (2×20 mL), dried and concentrated. The solid residue was dissolved in benzene (120 mL), toluene-*p*-sulfonic acid (150 mg) was added and refluxed for 8 h, using a Dean–Stark water separator. It was then cooled, washed with saturated aqueous $NaHCO_3$ solution, water, and solvent removed to get a yellowish solid. This was subjected to chromatography over silica gel. Elution with ethyl acetate/petroleum ether (1:4) furnished the chromene carboxylate **18** (3.3 g, 90%) as a colourless solid. R_f (20% EtOAc/petroleum ether (60:80)) 0.44; crystallized from dichloromethane/petroleum ether; mp 132–134 °C; IR 1645, 1737 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (s, 1H); 6.77 (s, 1H); 6.66 (s, 1H); 4.37 (q, *J*=6.9 Hz, 2H); 2.72 (s, 3H); 3.80 (s, 3H); 1.35 (t, *J*=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.4, 163.4, 160.8, 159.5, 150.4, 142.8, 117.4, 117.2, 116.36, 98.8, 62.8, 55.8, 22.9, 14.2. HRMS (EI) M+H^+, found: 263.0920; $C_{14}H_{15}O_5$ requires 263.0919.

*3.1.9. Ethyl-7-methoxy-5-methylchroman-2-carboxylate (**19**).* The chromone carboxylate **18** (260 mg, 1 mmol) was subjected to hydrogenation (60 mmHg) in the presence of palladium charcoal (10%, 80 mg) in ethanol (5 mL) for 9 h. The catalyst was then filtered, the solvent removed and the residue subjected to chromatography over silica gel. Elution with ethyl acetate/petroleum ether (1:4) furnished the chromane carboxylate **19** as a colourless liquid (238 mg, 96%). R_f (20% EtOAc/petroleum ether (60:80)) 0.82; IR (neat) 1755 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (s, 1H); 6.37 (s, 1H); 4.63 (dd, *J*=3.3, 7.8 Hz, 1H); 4.25 (q, *J*=7.2 Hz, 2H); 3.73 (s, 3H); 2.57 (m, 2H); 2.25 (m, 2H); 2.16 (s, 3H); 1.29 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 158.6,154.3, 138.1, 112.3, 109.7, 99.4, 73.5, 61.4, 55.2, 24.9, 20.7, 19.3, 14.2. HRMS (EI) M+H^+, found: 251.1285; $C_{14}H_{19}O_4$ requires 251.1283.

*3.1.10. Ethyl 7-methoxy-5-methyl-4H-chromene-2-carboxylate (**20**).*
(I) *Method* 1: To a solution of chromone carboxylate **18** (100 mg, 0.46 mmol) in THF (4 mL), $BF_3{\cdot}OEt_2$ (0.18 mL, 1.38 mmol) and sodium cyanoborohydride (115 mg, 1.832 mmol) were added and refluxed for 3 h. Then the reaction mixture was cooled and quenched with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with ether (3×10 mL) and dried. The solvent was evaporated to get a yellow liquid, which was subjected to chromatography over silica gel. Elution with ethyl acetate/petroleum ether (3:5) furnished the chromene carboxylate **20** as a colourless liquid (30 mg, 25%). R_f (20% EtOAc/petroleum ether (60:80)) 0.65; IR (neat) 1732 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (s, 1H); 6.37 (s, 1H); 6.13 (t, *J*=4.2 Hz, 1H); 4.23 (q, *J*=7.2 Hz, 2H); 3.66 (s, 3H); 3.29 (d, *J*=4.2 Hz, 2H); 2.09 (s, 3H); 1.28 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 159.2,152.1, 141.8, 138.3, 112.4, 110.6, 109.4, 99.7, 61.8, 55.7, 22.8, 19.6, 14.6. HRMS (ESI) M+Na^+, found: 271.0946; $C_{14}H_{16}O_4Na$ requires 271.0946.

(II) *Method* 2: To a well-stirred solution of LDA, prepared from *n*-butyllithium (0.7 mL of 1.6 M solution in hexane, 0.912 mmol) and diisopropylamine (0.15 mL, 1.06 mmol) in THF (3 mL) at −78 °C, a solution of the chromane carboxylate **19** (190 mg, 0.76 mmol) in THF (2 mL) was added dropwise under argon and the reaction mixture stirred for 30 min. Then the reaction mixture was allowed to warm to −30 °C and kept at that temperature for another 30 min. Again the reaction mixture was cooled to −78 °C and HMPA (0.2 mL) followed by phenyl selenyl bromide (252 mg, 1.4 mmol) in THF (2 mL) were added dropwise. After 2 h the reaction mixture was allowed to attain room temperature and stirred for 1 h. The reaction mixture was then cooled to 0 °C followed by addition of H_2O_2 (5 mL, 30%) and stirred for 3 h and allowed to attain room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with ether (3×15 mL). The combined ethereal extracts were washed with water, dried, and the solvent removed. The residue was subjected to column chromatography over silica gel. Elution with ethyl acetate/petroleum ether (3:5) afforded the chromene carboxylate **20** as a colourless liquid (169 mg, 90%).

*3.1.11. (7-Methoxy-5-methyl-4H-chromen-2-yl) methanol (**21**).* To a well stirred slurry of LAH (60 mg, 1.37 mmol) in THF (3 mL) at −40 °C, the chromene carboxylate **20** (170 mg, 0.68 mmol) in THF (2 mL) was added slowly via a syringe and stirred for 1 h at the same temperature. Then the reaction was allowed to attain 0 °C and quenched with saturated aqueous Na_2SO_4 solution. The reaction mixture was extracted with ether (3×5 mL) and dried. Removal of the solvent furnished the allylic alcohol **21** as a colourless solid (132 mg, 93%); crystallized from dichloromethane/petroleum ether (1:1). Mp 129–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.37 (d, *J*=2.4 Hz, 1H); 6.23 (d, *J*=2.4 Hz, 1H); 4.94 (t, *J*=3.3 Hz, 1H); 4.05 (d, *J*=5.4 Hz, 2H); 3.6 (s, 3H); 3.15 (d, *J*=3.2 Hz, 2H); 2.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 152.5, 149.9, 138.5, 111.4, 109.4, 99.4, 97.9, 63.1, 55.6, 22.2, 19.5. HRMS (ESI) M+Na^+, found: 229.0843; $C_{12}H_{14}O_3Na$ requires 229.0841.

3.1.12. (S)-Ethyl 2-((R*)-7-methoxy-5-methyl-2-methylenechroman-3-yl) propanoate (**22b**).* A mixture of the allylic alcohol **21** (100 mg, 0.48 mmol), triethyl orthopropionate (0.7 mL, 3.4 mmol) and propionic acid (0.06 mL) was heated with stirring in xylene (5 mL) maintaining the temperature at 140 °C. Heating was continued for 8 h; the reaction mixture was allowed to cool to room temperature and the solvent was removed by distillation under reduced pressure (50–60 °C at 20 mmHg). The residue was purified by column chromatography over silica gel. Elution with ethyl acetate/petroleum ether (1:20) afforded the ester **22b** (12 mg, 8.5%) as a colourless oil. R_f (20% EtOAc/petroleum ether (60:80)) 0.76; IR (neat) 1734 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (s, 1H); 6.30 (s, 1H); 4.66 (s, 1H); 4.25 (s, 1H); 4.13 (q, *J*=6.9 Hz, 2H); 3.74 (s, 3H); 2.82–2.87 (m, 1H); 2.73 (dd, *J*=5.1, 16.2 Hz, 1H); 2.61 (dd, *J*=2.1, 16.2 Hz, 2H); 2.43–2.47 (m, 1H); 2.14 (s, 3H); 1.24 (t, *J*=7.2 Hz, 3H); 1.19 (d, *J*=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0,158.8, 155.4, 153.3, 138.1, 111.1, 109.9, 98.7, 92.7, 60.6, 55.3, 39.8, 39.7, 26.3, 19.4, 16.4, 14.4. HRMS (EI) MH^+, found: 291.1598; $C_{17}H_{23}O_4$ requires 291.1596.

3.1.13. (R)-Ethyl 2-((R*)-7-methoxy-5-methyl-2-methylenechroman-3-yl) propanoate (**22a**).* Further elution with ethyl acetate/petroleum ether (1:20) afforded the isomeric ester **22a** (124 mg, 88%) in major amounts as a colourless oil. R_f (20% EtOAc/petroleum ether (60:80)) 0.75; IR (neat) 1732 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (s, 1H); 6.33 (s, 1H); 4.56 (s, 1H); 4.17 (s, 1H); 4.10 (q, *J*=6.9 Hz, 2H); 3.74 (s, 3H); 2.86–2.89 (m, 1H); 2.70 (d, *J*=4.8 Hz, 2H); 2.52–2.57 (m, 1H); 2.2 (s, 3H); 1.26 (t, *J*=7.2 Hz, 3H); 1.16 (d, *J*=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 159.3, 157.3, 153.7, 137.8,111.3, 110.1, 99.1, 90.9, 60.8, 55.6, 41.0, 39.2, 24.1, 19.6, 15.2, 14.5. HRMS (EI) MH^+, found: 291.1589; $C_{17}H_{23}O_4$ requires 291.1596.

3.1.14. (R)-2-((R*)-7-Methoxy-5-methyl-2-methylenechroman-3yl) propan-1-ol (**23**).* To a well stirred slurry of LAH (57 mg, 1.5 mmol) in THF (2 mL) at 0 °C, the ester **22a** (310 mg, 1.07 mmol) in THF

(2 mL) was added slowly via a syringe and stirred for 1 h at the same temperature. Then the reaction was allowed to attain room temperature and quenched with cold saturated aqueous NH_4Cl solution. The reaction mixture was then extracted with ether (3×5 mL) and dried. Removal of the solvent furnished the alcohol **23** (253 mg, 90%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.30 (d, J=1.9 Hz, 1H); 6.22 (d, J=2.2 Hz, 1H); 4.54 (s, 1H); 4.13 (s, 1H); 3.67 (s, 3H); 3.48–3.60 (m, 2H); 2.70 (dd, J=3.3, 15.9 Hz, 1H); 2.58 (dd, J=5.1, 15.9 Hz, 1H); 2.45–2.49 (m, 1H); 2.13 (s, 3H); 1.55–1.61 (m, 1H); 1.53–1.54 (m, 1H); 0.89 (d, J=6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 158.0, 153.6, 137.8, 111.7, 109.8, 98.7, 90.7, 66.5, 55.3, 38.8, 34.8, 24.5, 19.4, 14.8. HRMS (ESI) M+Na^+, found: 270.1309; $C_{15}H_{20}O_3Na$ requires 271.1310.

3.1.15. (3R,3aR*,9aR*)-7-Methoxy-3,5,9a-trimethyl-3,3a,4,9a-tetrahydro-2H-furo [2,3-b]chromene (O-methyl alboatrin) (**24**).* To a cooled and stirred solution of the alcohol **23** (40 mg, 0.16 mmol) in THF (2 mL) at 0 °C, ice-cold H_2SO_4 (3 N, three drops) was added and stirred for 2 h. Then the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with ether (3×3 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution and brine, dried and concentrated. The residue was subjected to column chromatography over silica gel. Elution with ethyl acetate/petroleum ether (1:49) furnished *O*-methyl alboatrin **24** (38 mg, 96%) as a colourless solid. R_f (20% EtOAc/petroleum ether (60:80)) 0.83; mp 54–55 °C (identical with previous sample).[6]

3.1.16. (S)-2-((R*)-7-Methoxy-5-methyl-2-methylenechroman-3-yl) propan-1-ol (**25**).* To a well stirred slurry of LAH (29 mg, 0.78 mmol) in THF (2 mL) at 0 °C, the ester **22b** (130 mg, 0.52 mmol) in THF (2 mL) was added slowly via a syringe and stirred for 1 h at the same temperature. Then the reaction was allowed to attain room temperature and quenched with cold saturated aqueous NH_4Cl solution. The reaction mixture was extracted with ether (3×5 mL) and dried. Removal of the solvent furnished the alcohol **25** as a colourless oil (116 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.36 (s, 1H); 6.29 (d, J=2.2 Hz, 1H); 4.60 (s, 1H); 4.17 (s, 1H); 3.74 (s, 3H); 3.49–3.62 (m, 2H); 2.84 (dd, J=2.7, 16.2 Hz, 1H); 2.69 (dd, J=5.1, 16.2 Hz, 1H); 2.54–2.60 (m, 1H); 2.19 (s, 3H); 1.61–1.65 (m, 1H); 1.52–1.55 (m, 1H); 0.83 (d, J=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 157.4, 153.7, 137.8, 109.6,111.9, 98.7, 91.2, 65.7, 55.3, 38.8, 34.9, 25.1, 19.5, 15.7. HRMS (ESI) M+Na^+, found: 271.1310; $C_{15}H_{20}O_3Na$ requires 271.1310.

3.1.17. (3S,3aR*,9aR*)-7-Methoxy-3,5,9a-trimethyl-3,3a,4,9a-tetrahydro-2H-furo[2,3-b]chromone(O-methyl-epi-alboatrin) (**26**).* To a cooled and stirred solution of the alcohol **25** (65 mg, 0.26 mmol) in THF (2 mL) at 0 °C, ice-cold H_2SO_4 (3 N, four drops) was added and stirred for 2 h. Then the reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with ether (3×3 mL). The combined organic extracts were washed with saturated $NaHCO_3$ and brine, dried and concentrated. The residue was subjected to column chromatography over silica gel. Elution with ethyl acetate/petroleum ether (1:49) furnished *O*-methyl-*epi*-alboatrin **26** (63 mg, 96%) as a colourless solid. R_f (20% EtOAc/petroleum ether (60:80)) 0.82; mp 53–55 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (s, 1H); 6.29 (d, J=2.4 Hz, 1H); 4.12 (t, J=8.1 Hz, 1H); 3.71 (s, 3H); 3.58 (t, J=8.1 Hz, 1H); 2.68–2.70 (m, 2H); 2.43–2.53 (m, 2H); 2.21 (s, 3H); 1.51 (s, 3H); 0.83 (d, J=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 155.2, 136.8, 113.1, 109.4, 107.9, 100.1, 74.8, 55.2, 43.8, 35.5, 24.3, 20.8, 19.4, 14.1. HRMS (EI) MH^+, found: 249.1492; $C_{15}H_{21}O_3$ requires 249.1491.

*3.1.18. Demethylation of O-methyl-epi-alboatrin **26** (**3**).* To a solution of *O*-methyl-*epi*-alboatrin **26** (150 mg, 0.6 mmol) at −78 °C, precooled dichloromethane (5 mL) solution of BBr_3 (10% of 1 M in dichloromethane) was added and stirred for 2 h. Then the reaction mixture was warmed to room temperature and quenched with ice-cooled water followed by extraction with dichloromethane (2×5 mL). The combined organic phases were dried and concentrated in vacuum. The residual crude oil was purified by column chromatography using (1:5) ethyl acetate/petroleum ether to afford **3** (130 mg, 91%) as a colourless solid. R_f (20% EtOAc/petroleum ether (60:80)) 0.34; crystallized from 1:1 (dichloromethane/petroleum ether) to obtain colourless crystals, mp 147–148 °C. This was identified as alboatrin from spectral data and mixed up with a sample synthesized previously.[6]

*3.1.19. epi-Alboatrin (**3a**).* To an ice-cold solution sodium ethyl mercaptide prepared from NaH (6.8 mg, 0.258 mmol) and ethane thiol (0.02 mL, 0.258 mmol) in DMF (3 mL) was added *O*-methyl-*epi*-alboatrin **26** (32 mg, 0.129 mmol) in DMF (1 mL) dropwise under argon atmosphere and then refluxed for 4 h. Then the reaction mixture was cooled to room temperature and quenched with ice-cold water, followed by extraction with ethyl acetate (3×4 mL). The organic phases were concentrated under vacuum to get a yellow oil, which was purified by column chromatography using (1:5) ethyl acetate/petroleum ether to afford **3a** (25 mg, 86%), as a colourless solid. Mp 145–148 °C; R_f (20% EtOAc/petroleum ether (60:80)) 0.35; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (d, J=2.1 Hz, 1H); 6.32 (s, 1H); 5.9 (br s, 1H); 4.12 (t, J=7.9 Hz, 1H); 3.57 (t, J=6.7 Hz, 1H); 2.68–2.69 (m, 2H); 2.44–2.55 (m, 2H); 2.19 (s, 3H); 1.53 (s, 3H); 0.84 (d, J=6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 155.0, 136.8, 112.8, 110.3, 108.1, 102.2, 74.80, 44.0, 35.5, 24.4, 20.6, 19.2, 13.9. HRMS (EI) M+Na^+, found: 257.1151; $C_{14}H_{18}O_3Na$ requires 257.1154.

*3.1.20. Ethyl 7-methoxy-4-oxo-4H-chromene-2-carboxylate (**28**).* To a well-stirred solution of NaH (0.4 g, 0.02 mol) in THF (5 mL) at 0 °C, 4-methoxy-2-hydroxy acetophenone **27** (1 g, 0.006 mol) and diethyl oxalate (1.7 mL, 0.012 mol) were added followed by stirring for 18 h at room temperature. Then the reaction was quenched with saturated aqueous NH_4Cl solution followed by extraction with ethyl acetate (3×20 mL). The organic extract was dried and concentrated to yield an alcohol (2 g). Without further purification, the crude alcohol was dissolved in benzene (10 mL) followed by addition of toluene-*p*-sulfonic acid (100 mg) followed by reflux using a Dean–Stark separator for 4 h. The reaction mixture was cooled and concentrated in vacuum and the residue subjected to column chromatography over silica gel. Elution with ethyl acetate/petroleum ether (3:17) furnished the chromone ester **28** (1.04 g, 70%) as yellowish white crystals. R_f (20% EtOAc/petroleum ether (60:80)) 0.47; mp 109–110 °C (lit.[10] mp 109 °C).

*3.1.21. Ethyl 7-methoxychroman-2-carboxylate (**29**).* The chromone carboxylate **28** (200 mg, 0.9 mmol) was subjected to hydrogenation in the presence of palladium charcoal (10%, 80 mg) in ethanol (5 mL) for 9 h. The catalyst was then filtered and the solvent removed and the residue subjected to chromatography over silica gel. Elution with ethyl acetate/petroleum ether (2:48) furnished the chromane carboxylate **29** as a colourless liquid (191 mg, 90%). R_f (20% EtOAc/petroleum ether (60:80)) 0.7; IR (neat) 1741 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (d, J=8.295 Hz, 1H); 6.53 (d, J=2.4 Hz, 1H); 6.48 (dd, 2.5 Hz, J=8.3 Hz, 1H); 4.72–4.69 (m, 1H); 4.27 (q, J=7.09 Hz, 2H); 3.77 (s, 3H); 2.79–2.66 (m, 2H); 2.29–2.14 (m, 2H); 1.31 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 159.2, 154.1, 129.8, 113.2, 108.0, 101.6, 73.8, 61.3, 55.3, 24.8, 22.6, 14.2. HRMS (EI) M+Na^+, found: 259.0946; $C_{13}H_{16}O_4Na$ requires 259.0946.

*3.1.22. Ethyl 7-methoxy-4H-chromene-2-carboxylate (**30**).* To a well-stirred solution of LDA, prepared from *n*-butyllithium (3.5 mL of

1.6 M solution in hexane, 4.22 mmol) and diisopropylamine (0.8 mL, 5.27 mmol) in THF (3 mL) at −78 °C, a solution of the chromane carboxylate **29** (500 mg, 2.11 mmol) in THF (2 mL) was added in drops under argon and the solution stirred for 30 min. Then the reaction mixture was allowed to warm to −30 °C and kept at that temperature for another 30 min. Again the reaction mixture was cooled to −78 °C and HMPA (0.2 mL) followed by dropwise addition of phenyl selenyl bromide (800 mg, 3.165 mmol) in THF (5 mL). After 2 h the reaction mixture was allowed to attain room temperature and stirred for 1 h. The reaction mixture was cooled to 0 °C followed by addition of H_2O_2 (5 mL, 30%) and stirred for 3 h and then allowed to attain room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with ether (3×15 mL). The combined ethereal extracts were washed with water, dried, and the solvent removed. The residue was subjected to column chromatography over silica gel. Elution with ethyl acetate/petroleum ether (1:19) afforded the chromene carboxylate **30** as a colourless liquid (414 mg, 90%). R_f (20% EtOAc/petroleum ether (60:80)) 0.64; IR (neat) 1732 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.89 (d, J=8.9 Hz, 1H); 6.58 (d, J=6.75 Hz, 1H); 6.2 (t, J=3.97 Hz, 1H); 4.29 (q, J=7.1 Hz, 2H); 3.77 (s, 3H); 3.47 (d, J=3.94 Hz, 2H); 1.31 (t, J=7.08 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 159.4, 151.8, 141.6, 129.4, 111.0, 110.7, 109.9, 101.8, 61.4, 55.4, 23.9, 14.2. HRMS (ESI) M+Na^+, found: 257.0792; $C_{13}H_{14}O_4$ requires 257.0790.

*3.1.23. (7-Methoxy-4H-chromen-2-yl) methanol (**31**).* To a well stirred slurry of LAH (36 mg, 0.94 mmol) in THF (3 mL) at −40 °C, the chromene carboxylate **30** (110 mg, 0.47 mmol) in THF (2 mL) was added slowly via a syringe and stirred for 1 h at the same temperature. Then the reaction was allowed to attain 0 °C and quenched with saturated aqueous Na_2SO_4 solution. The reaction mixture was extracted with ether (3×5 mL) and dried. Removal of the solvent followed by column chromatography of the residual oil using neutral alumina and elution with (1:3) ethyl acetate/petroleum ether furnished the allylic alcohol **31** as a colourless liquid (82 mg, 93%). R_f (20% EtOAc/petroleum ether (60:80)) 0.3; ^1H NMR (300 MHz, $CDCl_3$) δ 6.89 (d, J=8.9 Hz, 1H); 6.58 (d, J=6.75 Hz, 1H); 6.2 (t, J=3.97 Hz, 1H); 4.29 (q, J=7.1 Hz, 2H); 3.77 (s, 3H); 3.47 (d, J=3.94 Hz, 2H); 1.31 (t, J=7.08 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 151.1, 148.7, 131.1, 128.5, 107.3, 100.4, 96.9, 61.7, 54.3, 22.1. HRMS (ESI) M+H^+, found: 193.0866; $C_{11}H_{13}O_3$ requires 193.0865.

3.1.24. (R)-Ethyl 2-((R*)-7-methoxy-2-methylenechroman-3-yl) propanoate (**32a**) and (S*)-ethyl 2-((R*)-7-methoxy-2-methylenechroman-3-yl) propanoate (**32b**).* A mixture of the allylic alcohol **31** (80 mg, 0.37 mmol), triethyl orthopropionate (0.7 mL, 2.97 mmol) and propionic acid (0.06 mL) was heated with stirring in xylene (5 mL) maintaining the temperature at 140 °C. Heating was continued for 8 h after which the reaction mixture was cooled to room temperature and the solvent removed by distillation under reduced pressure. The residue was purified by column chromatography over silica gel. Elution with ethyl acetate/petroleum ether (1:32) afforded the esters **32a** and **32b** (3:1) (99 mg, 97%) as a colourless oil. R_f (20% EtOAc/petroleum ether (60:80)) 0.86; IR (neat) 1736 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) for the diastereomeric mixture δ 6.95–6.89 (m, 1H); 6.52–6.54 (m, 1H); 6.48 (s, 1H); 4.69 (minor isomer) (s, 1H); 4.59 (major isomer) (s, 1H); 4.27 (minor isomer) (s, 1H); 4.20 (major isomer) (s, 1H); 4.12 (q, J=7.08 Hz, 2H); 3.8 (s, 3H); 2.94–2.86 (m, 3H); 2.74–2.67 (m, 2H); 2.62–2.45 (m, 2H); 2.33–2.28 (m, 1H); 1.25 (t, J=6.95 Hz, 3H); 1.17 (d, J=6.95 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.55, 159.7, 157.2, 155.58, 153.39, 130.05, 129.5, 112.503, 112.429, 108.218, 108.112, 101.247, 101.070, 93.133, 91.102, 60.55, 55.49, 40.58, 39.88, 39.49, 39.25, 29.8, 29.06, 26.72, 16.48, 14.7, 14.38, 14.32. HRMS (EI) M+H^+, found: 277.1441; $C_{16}H_{21}O_4$ requires MH^+ 277.1440.

3.1.25. (R)-2-((R*)-7-Methoxy-2-methylenechroman-3-yl) propan-1-ol (**33a**) and (S*)-2-((R*)-7-methoxy-2-methylenechroman-3-yl) propan-1-ol (**33b**).* To a well-stirred solution of LAH (62 mg, 1.62 mmol) in THF (2 mL) at 0 °C, the mixture of esters **32a** and **32b** (300 mg, 1.09 mmol) in THF (2 mL) was added slowly via a syringe and stirred for 1 h at the same temperature. The reaction was allowed to attain room temperature and quenched with cold saturated aqueous NH_4Cl solution. The reaction mixture was extracted with ether (3×5 mL) and dried. Solvent was removed and the residue purified by column chromatography and eluted with (1:9) ethyl acetate/petroleum ether to furnish the mixture of alcohols **33a** and **33b** (3:1) (216 mg, 85%) as a colourless oil. R_f (20% EtOAc/petroleum ether (60:80)) 0.26; ^1H NMR (300 MHz, $CDCl_3$) for the diastereomeric mixtures **33a** and **33b** (3:1) δ 6.89 (dd, J=3.4, 8.2 Hz, 1H); 6.46 (dd, J=2.5, 6.5 Hz, 1H); 6.41 (dd, J=3.9, 5.2 Hz, 1H); 4.61 (major isomer) (s, 1H); 4.2 (major isomer) (s, 1H); 4.16 (minor isomer) (s, 1H); 3.63 (s, 3H); 3.64–3.59 (m, 1H); 3.53–3.48 (m, 1H); 2.86–2.66 (m, 3H); 2.52–2.46 (m, 1H); 1.60–1.57 (m, 1H); 0.90 (d, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 157.8, 153.4, 129.5, 113.2, 113.1, 107.7, 100.9, 100.8, 91.5, 90.9, 66.0, 65.1, 55.2, 38.6, 38.5, 34.4, 34.3, 27.8, 27.1, 14.1, 14.0. HRMS (ESI) M+Na^+, found: 257.1152; $C_{14}H_{18}O_3Na$ requires 257.1154.

3.1.26. (3R,3aR*,9aR*)-Methoxy-3,9a-dimethyl-3,3a,4,9a-tetrahydro-2H-furo[2,3-b] chromene (nor-O-methyl xyloketal G) (**34a**) and (3S*,3aR*,9aR*)-7-methoxy-3,9a-dimethyl-3,3a,4,9a-tetrahydro-2H-furo[2,3-b] chromene (nor-O-methyl epi-xyloketal G) (**34b**).* To a cooled and stirred solution of the alcohols **33a** and **33b** (42 mg, 0.18 mmol) in THF (2 mL) at 0 °C, a solution of H_2SO_4 (3 N, 1 mL) in THF (2 mL) was added and stirred for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with ether (3×3 mL). The combined organic extracts were washed with brine, dried and concentrated. The residue was subjected to column chromatography over silica gel. Elution with ethyl acetate/petroleum ether (1:49) furnished a mixture of nor-*O*-methyl xyloketal G and *O*-methyl *epi*-xyloketal G **34a** and **34b** in the ratio (3:1) (40 mg, 96%) as a colourless solid. Mp 55–56 °C. R_f (20% EtOAc/petroleum ether (60:80)) 0.85; ^1H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, J=8.2 Hz, 1H); 6.45 (dd, J=2.5, 8.2 Hz, 1H); 6.39 (d, J=2.49 Hz, 1H); 4.14 (t, J=8.3 Hz, 1H); 3.73 (s, 3H); 3.42 (t, J=8.3 Hz, 1H); 2.87 (dd, J=5.8, 16.5 Hz, 1H); 2.62 (d, J=16.5 Hz, 1H); 2.11–2.05 (m, 1H); 1.94–1.88 (m, 1H); 1.47 (s, 3H); 1.04 (major isomer) (d, J=6.5 Hz, 3H); 0.86 (minor isomer) (d, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 153.9, 129.7, 128.4, 111.0, 107.9, 107.8, 107.6, 102.5, 101.9, 74.7, 74.1, 55.3, 48.6, 44.5, 35.1, 29.7, 24.9, 23.9, 23.5, 16.0, 13.6. HRMS (EI) M+H^+, found: 235.1335; $C_{14}H_{19}O_3$ requires 235.1334.

3.1.27. 1-((3R,3aR*,9aR*)-7-Hydroxy-3,9a-dimethyl-3,3a,4,9a-tetrahydro-2H-furo[2,3-b]chromen-6yl)ethanone (xyloketal G) (**4**).* To a cooled and stirred solution of $AlCl_3$ (0.057 g, 0.42 mmol) in dichloromethane (2 mL) at −78 °C, the mixture of diastereomers (**34a** and **34b**) (50 mg, 0.213 mmol) in dichloromethane (1 mL) and freshly distilled acetyl chloride (0.02 mL) were added followed by stirring for 2 h at room temperature .The reaction mixture was quenched with 2 N HCl solution and extracted with dichloromethane (3×10 mL). The combined organic extracts were washed with brine, dried and concentrated. The residue was subjected to column chromatography over silica gel. Elution with ethyl acetate/petroleum ether (3.5:46.5) furnished xyloketal G **4** (39 mg, 70%) as a colourless solid. R_f (20% EtOAc/petroleum ether (60:80)) 0.56; crystallized from petroleum ether/dichloromethane (1:1); mp 143–144 °C. Anal. Found: C, 68.88; H, 6.72,

$C_{15}H_{18}O_4$ requires C, 68.68; H, 6.92; IR (KBr) 3423, 1640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 12.36 (s, 1H); 7.46 (s, 1H); 6.36 (s, 1H); 4.16 (t, J=8.19 Hz, 1H); 3.54 (t, J=8.25 Hz, 1H); 2.99 (dd, J=5.16, 16.5 Hz, 1H); 2.75 (d, J=16.4 Hz, 1H); 2.55 (s, 3H); 2.092–2.04 (m, 2H); 1.57 (s, 3H); 1.08 (d, J=6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 163.3, 160.2, 132.1, 114.4, 110.3, 108.9, 104.6, 74.1, 48.1, 34.6, 26.2, 23.7, 23.4, 16.0. HRMS (EI) $M+H^+$, found: 263.1281; $C_{15}H_{19}O_4$ requires 263.1283.

Acknowledgements

We thank the Department of Science and Technology, Govt. of India, New Delhi for financial assistance. D.S. thanks the Council of Scientific and Industrial Research, New Delhi for a Senior Research Fellowship.

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