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Asymmetric total synthesis of dihydroisocoumarins: 6-methoxymellein, kigelin and fusarentin 6, 7 dimethyl ether by employing proline catalysed asymmetric α-aminoxylation

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ABSTRACT

A concise asymmetric total synthesis of dihydroisocoumarins such as 6-methoxymellein, kigelin and fusarentin 6,7-dimethyl ether in high enantiopurity have been achieved from non-chiral aldehydes by employing proline catalysed asymmetric α-aminoxylation reaction. The required stereochemistry of hydroxyl group have been generated by alternating L or D proline as a organocatalyst in α-aminoxylation step and lactone ring is assembled by oxa-Pictet-Spengler cyclisation reaction as the key steps.

1. Introduction

The 3,4-dihydroisocoumarin is the fundamental scaffold of various compounds those possess a wide spectrum of biological activity [1]. Mellein (**1**) (pheromone) and its derivatives are most common 3,4-dihydroisocoumarins and known to exhibit an array of biological activities. Most of dihydroisocoumarins are isolated from fungi and plants, mellein (**1**) [2] was isolated from various fungi and several insects; it shows fungicidal, antibacterial, and HCV protease inhibitory activities [3]. The derivatives of mellein, 6-hydroxymellein (**2**) and 6-methoxymellein (**3**) were isolated from phytopathogen, fungi or plant and displayed cytotoxicity, phytotoxicity, and phytoalexin activities [4] (see Fig. 1).

The (−)-kigelin (**4**) was isolated from the root heartwood of *Kigelia pinnata* DC [5a] as well as extracted from fungus *Aspergillus terreus* culture medium [5b]. Kiglin displays significant activity against human pathogenic dermatophytes, *Microsporum canis* and *Trichophyton longifusus* and exhibited potent xanthine oxidase inhibitor activity [6]. Fusarentin ethers **(5)** and **(6)** were isolated along with 7-O-demethylmonocerin (**9**) and (+)-monocerin (**10**) from *fusarium larvarum* [7] it shows various biological activities such as antifungal, insecticidal, plant pathogenic properties and phytotoxic activity [8]. Due to their fascinating structural architecture and the biological significance of this class of compounds there are several total syntheses of these compounds has been reported in literature [9–11]. Most of the reported methods are either based on use of chiron approach, chiral auxiliary or chelation controlled synthesis as well as racemic synthesis. Thus, the development of an efficient organocatalytic stereo divergent protocol for the synthesis of 3,4-dihydroisocoumarin skleton containing molecules from simple staring material is demanding.

Since last few decades, proline and its derivatives have proven to be versatile organocatalyst for the synthesis of structurally diverse molecular architecture [12]. Asymmetric α-aminoxylation of aldehyde is effective method to incorporate hydroxyl group in highly stereo selective fashion [13]. Further, aldehyde functionality was transformed into diol or alkene through $NaBH_4$ reduction and HWE olefination [14]. As part of our research in asymmetric synthesis of bioactive molecules and their key chiral intermediates using proline catalysed reaction [15]. Herein we describe synthesis of 6-methoxymellien **3**, kigelin **4** and fusarentin 6,7-dimethyl ether **5** by employing proline catalysed α-aminoxylation to introduce chiral hydroxyl group in enantioselective manner, HWE olefination or Wittig olefination and oxa-Pictet Spengler reactions as key steps.

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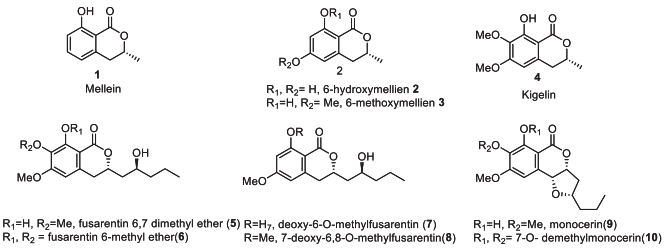
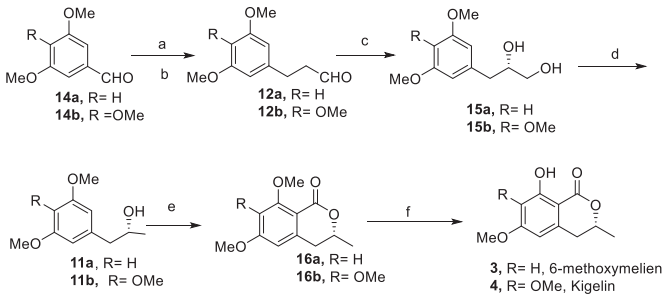


Fig. 1. Structures of dihydroisomarines, 6-methoxymellein, kigelin and fusarentin ether and their analogues.



Scheme 2. Asymmetric synthesis of 6-mehoxymellein and kigelin.

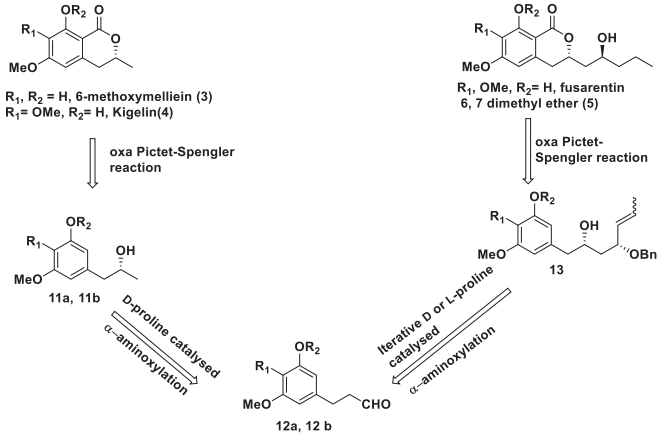
2. Result and discussion

Our envisioned retrosynthetic analysis for dihydroisocoumarins (**3, 4** and **5**) shows straightforward oxa-Pictet-Spengler cyclisation of hydroxy compounds **11a**, **11b** and **13** to obtain target molecules. These hydroxy compounds may be easily accessible through proline catalysed α-aminoxylation of commercially available aldehydes **12a** and **12b** followed by reduction or HWE olefination or Wittig olefination and functional group transformations (Scheme 1).

2.1. Asymmetric synthesis of 6-methoxymellein and kigelin

Based on the above retrosynthetic analysis the total synthesis of 6-methoxymelien **3** and kigelin **4** started with commercially and cheaply available aldehydes as shown in Scheme 2. Our synthesis started from homologation of 3, 5-dimethoxyaldehydes **14a** and 3,4,5-trimethoxybenzaldehyde **14 b** through a 2C-Wittig olefination to obtain desired aldehydes **12a** and **12b**. The α,β-unsaturated esters were reduced using H_2/Pd/C followed by DIBAL-H reduction to corresponding aldehydes **12a** and **12b** in quantitative yield (for details see supporting information). Further D-proline catalysed α-aminoxylation of aldehydes **12a** and **12b** was carried out with PhNO as oxygen source in ACN at −20 °C followed by $NaBH_4$ reduction to get aminoxylated alcohols, which was subjected to O–N bond cleavage to afford enantiomerically pure diols **15a** and **15b** with 70% and 71% yields, respectively [13c]. The selective monotosylation of primary hydroxy group in diols **15a** and **15b** was carried out by using *p*-TsCl (1.1 equiv.) and Et_3N in presence of catalytic amount of Bu_2SnO [16] afforded monotosylated products, which was further treated with $LiAlH_4$ (3.5 equiv.) in THF to afford 2-aryl-propanals **11a** and **11b** in 81% and 83% yields, respectively. Further these 2-arylpropanols were treated under oxa-Pictet -Spengler cyclisation reaction conditions by using $CH(OMe)_3$ and catalytic amount of PTSA in dry DCM to achieve the desired intermediate cyclic acetal. The resulting cyclic acetal subsequently without any purification was treated with Jones reagent in acetone to give pyranolactones **16a** and **16b** in 79% and 81% yields over two steps.[11h] Finally the selective demethylation of valerolactones were done by using BCl_3 (1 M solution in heptane) in DCM at −10 °C for 2h, afforded 6-methoxmellein **3** $[\alpha]_D^{20} = -54$ (c 1, MeOH); lit.[9g] $[\alpha]_D^{20} = -55$ (c 0.23, MeOH) and kigelin **4** $[\alpha]_D^{20} = -78$ (c, 0.5), lit [5a]. $[\alpha]_D^{20} = -79$(*c*1, MeOH) in 69% and 70% yield, respectively. The optical rotations and spectroscopic data were in good agreement with literature reports.[5a, 9g]

Reagents & Conditions (a) ethyl 2-(triphenylphosphoranylidene)acetate, DCM, rt, 12h, 98% yield, (b) i) H_2, Pd/C, MeOH, 100 psi, rt,10h, ii) DIBAL-H, DCM, −78 °C, 2h, 95% over 2 steps. (c) D-proline, PhNO, ACN, −20 °C, 24h ii) $NaBH_4$, MeOH, 0 °C, 30 min, ii) $Cu(OAc)_2$, MeOH, rt, 12h,70% and 71% over 2 steps. (d) i) Bu_2SnO, p-TsCl, Et_3N, DCM, 0 °C,3h, ii) $LiAlH_4$ (3.5 equiv.), THF, rt, 5h, 81% and 83% over 2 steps. (e) PTSA, $CH(OMe)_3$, DCM, 0 °C to rt, 2h, ii) Jones oxidant, acetone, 0 °C to rt, 1h, 79% and 81% over 2 steps. (f) BCl_3, DCM, −10 °C, 69% and 70%, 2h.

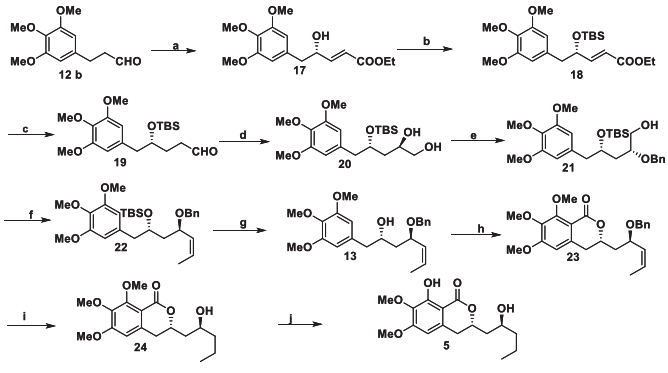


Scheme 1. Retrosynthetic analysis of dihydroisomarines: 6-methoxymellein, kigelin and fusarentin ether.

2.2. Asymmetric synthesis of fusarentin 6,7 -dimethyl ether

After successful synthesis of the 6-methoxymellein **3** and kigelin **4**, we focused our attention towards the most challenging target fusarentin ether, in which two iterative α-aminoxylation reactions were carried out to construct *anti* diol unit in highly diastereoselective manner as shown in Scheme 3.

Reagents and conditions a) PhNO, D-proline, ACN, −20 °C, 24 h, then triethyl phosphonoacetate, DBU, LiCl, 0 °C, 45 min, ii) $Cu(OAc)_2$, MeOH, 12h, rt, 71% b) TBDMSCl, imidazole, DMAP(cat), DMF, rt, 12h, 92% c) i) $NiCl_2$.$6H_2O$, $NaBH_4$, MeOH, 1h 0 °C to rt, ii)



Scheme 3. Asymmetric synthesis of fusarentin 6,7 dimethyl ether.

DIBAL-H, DCM, −78 °C, 1h, 95% (d) i) PhNO, L-proline, ACN, −20 °C, 24h, then $NaBH_4$, MeOH, ii) $Cu(OAc)_2$, MeOH, 12h, rt, 63% e) $PhCH(OMe)_2$, PPTS, benzene, reflux, 1h ii) DIBAL-H, DCM, 0 °C, 12h, 83% f) i) oxalyl chloride, DMSO, DCM, Et_3N, −78 °C, 3h ii) ethyltriphenyl phosphonium bromide, *n*-BuLi, THF, 0 °C to rt, 12h, 70% g) TBAF, THF, rt, 6h, 91%, h) $CH(OMe)_3$, TMSOTf, DCM, rt, 2h, ii) Jones reagent, Acetone, rt, 1h, 85%, (i) H_2, Pd $(OH)_2$/C, 10h, rt, 97%, (j) BCl_3, DCM, −10 °C, 69%.

Our synthetic endeavour (as shown in Scheme 3) began with aldehyde **12b**, which was converted into γ-hydroxy ester **17** by using D-proline catalysed α-aminoxylation followed by HWE olefination in two steps in one pot sequences: i) reaction of aldehyde **12b** with PhNO as oxygen source using D-proline as a organocatalyst to introduce chirality in ACN at −20 °C for 24h. Followed by addition of LiCl, triethylphosphonoacetate and DBU as base at 0 °C, to afford γ-aniloxy ester ii) subsequent O—N bond cleavage was carried out using catalytic $Cu(OAc)_2$ in MeOH yielded γ-hydroxyl ester **17** in 71% yield over two steps and *ee* 99.67% was achieved. The enantiomeric excess was determined by HPLC equipped with Chiralpak IA column (4.6 × 250 nm). The hydroxyl functionality of compound **17** was protected as a TBDMS ether using TBDMSCl and imidazole as a base with catalytic amount of DMAP in DMF at rt for 6 h to afford compound **18** in 92% yield. The reduction of double bond was attempted under hydrogenation condition using H_2/Pd—C. In this step the deprotection of TBDMS group and its lactonisaion product was obtained as a side product. Therefore the selective double bond reduction was carried out using $NiCl_2.6H_2O$/$NaBH_4$ in MeOH to achieve saturated ester. The crude saturated ester was further subjected for DIBAL-H reduction without further purification to yield aldehyde **19** in 95% yield over two steps.

Having sufficient quantity of aldehyde **19** in hand, our next aim was to perform second α-aminoxylation reaction using L-proline as an organocatalyst to introduce hydroxyl group with required stereochemistry. Second α-aminoxylation was carried out over aldehyde **19** using PhNO as an oxidant and L-proline as organocatalyst, followed by reduction with $NaBH_4$ in MeOH to get crude aniloxy alcohol, which was subjected to O—N bond cleavage by using $Cu(OAc)_2$ in MeOH afforded diol **20** in 63% yield over two steps with high diasteroselectivity [13c]. Diasteromerically pure diol functionality of compound **20** was subjected for protection of benzaldehyde dimethyl acetal using catalytic amount of PPTS in benzene under reflux condition afforded 1,2-benzylidine acetal. The crude acetal was further subjected to regioselective reductive opening with DIBAL-H at 0 °C led to desired alcohol **21** in 83% over two steps [17]. The oxidation of primary alcohol to aldehyde under Swern reaction conditions and subsequent treatment of corresponding intermediate aldehyde with Wittig reagent generated from ethyltriphenyl phosphonium bromide and *n*-BuLi as a base, to produce alkene **22** as *cis* isomer in 70% yield. The TBDMS deprotection of alkene **22** was carried out using TBAF in THF to afford free alcohol **13** in 92% yield. After successful construction of monoprotected *anti* 1,3 diol functionality **13** was subjected for oxa-Pictet-Spengler reaction using $CH(OMe)_3$ in presence of catalytic amount of TMSOTf, followed by Jones oxidation protocol afforded γ-valerolactone **23** in 85% yield.[11h] The global double bond reduction and benzyl deprotection was smoothly carried out under hydrogenation conditions using $Pd(OH)_2$ at 100 psi to afford compound **24** in 97% yield. Finally the selective demethylation was carried out using BCl_3 to achieve target molecule fusarentin 6,7-dimethyl ether (**5**) $[\alpha]_D^{20} = -26.9$ (*c* 1.0, $CHCl_3$); lit.[11h] $[\alpha]_D^{20} = -25.8$ (*c* 1.0, $CHCl_3$); lit [7]. $[\alpha]_D^{20} = -29$ (*c* 1.0, $CHCl_3$) as single *anti* diastereomer in 69% yield. The physical and spectroscopic data were in full agreement with reported compound documented in literature.[7, 11h]

3. Conclusion

In summary, we have successfully achieved synthesis of dihydroisocoumarins in high enantiopure form with good overall yield from readily available starting materials. The dihydroiscoumarins such as 6-methoxymellein and kigelin were synthesized in eight steps with 29% and 31% overall yield, respectively. Whereas the synthesis of fusarentin 6,7-dimethyl ether was achieved in 16 steps with 11% yield from commercially available achiral aldehydes. Our synthetic strategy involves use of organocatalyzed (proline) asymmetric α-aminoxylation reaction, which delivers hydroxyl group in highly stereoselective manner with required stereochemistry just by choosing L or D-proline, followed by HWE olefination or Wittig olefination to construct required alkyl chain and oxa-Pictet-Spengler cyclisation to construct lactones are the salient feature of our synthesis. Use of simple, cheaply available achiral starting materials, inexpensive chiral catalyst, simpler reaction procedures are the salient features of our methodology. Further current effort in our group is directed towards the expansion of scope of this synthetic strategy for the preparation of various other dihydroisocoumarins as well as other natural products containing lactone moiety.

4. Experimental section

4.1. General experimental details

All reagents were obtained from commercial suppliers unless otherwise stated and solvents were used as received with the following exceptions. Tetrahydrofuran (THF) was distilled from benzophenone and sodium immediately prior to use. All moisture sensitive reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Reactions were magnetically stirred and monitored by analytical thin-layer chromatography (TLC) E. Merck 0.25 mm silica gel 60 F_{254}. TLC plates were visualized by exposure to ultraviolet light (UV, 254 nm) and/or exposure to an aqueous solution of potassium permanganate ($KMnO_4$), an acidic solution of Ninhydrin or a solution of PMA followed by heating with a heat gun. Chromatography was performed using silica gel (100—200 mesh) with solvents distilled prior to use. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) pure material. All spectra were recorded at 25 °C. ^1H NMR spectra were recorded on 500 MHz and 400 MHz spectrometers and ^{13}C NMR spectra were obtained at 500 NMR (126 MHz) and 400 (101 MHz) spectrometer using $CDCl_3$ as solvent. Tetramethylsilane (0.00 ppm) served as an internal standard in ^1H NMR and $CDCl_3$ (77.0 ppm) in ^{13}C NMR. Chemical shifts were recorded in ppm, and coupling constants (*J*) were in Hz. HRESIMS were taken on Bruker Impact HD quadrupole plus ion trap at CIF, S. P. Pune University. Infrared spectra were recorded on a Nicolet Nexus 470 FT-IR spectrometer. Optical rotations were measured on a digital polarimeter. The following abbreviations are used for the multiplicities: s: singlet, d: doublet, t: triplet, m: multiplet, bs: broad singlet dd: doublet of doublet for proton spectra.

4.2. General procedure for preparation of aldehydes

Aldehyde (2.5 g, 12.5 mmol)) in DCM was added ethyl 2-(triphenylphosphoranylidene)acetate (5.2 g, 15 mmol) and reaction mixture was stirred at rt for 12h after completion of reaction, solvent was evaporated under *vacuo* and purified by using silica gel chromatography using hexane: EtOAc (9:1) gave olefin as white solid in 98% yield.

To a stirred solution of above olefin (1.0 equiv.) in MeOH (50 mL)

was added Pd/C (0.25g, 10%) and reaction mixture was stirred about 10h under hydrogen pressure (100 psi). after completion of reaction (checked on TLC), reaction mass filtered through a celite pad, and MeOH was evaporated under *vacuo* afforded crude saturated ester.

The crude ester was dissolved in DCM (35 mL) and cooled to −78 °C. At this temperature DIBAL-H (13.7 mL, 13.7 mmol, 1 M solution in toluene) was added to the reaction mixture and stirred for 2h. After 2h, reaction was quenched with sat. tartaric acid solution and extracted with DCM (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, evaporated on rotavapour and the crude was purified by column chromatography using pet ether: ethyl acetate (9:1) afforded aldehydes 98% yield as colourless liquid.

Aldehyde **12a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (t, J = 1.3 Hz, 1H), 6.37 (d, J = 2.2 Hz, 2H), 6.34 (d, J = 2.2 Hz, 1H), 3.80 (s, 6H), 2.92 (t, J = 7.5 Hz, 2H), 2.78 (dd, J = 10.8, 4.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.4, 160.9, 142.7, 106.4, 98.1, 55.2, 45.0, 28.4.

Aldehyde **12b:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 6.42 (s, 2H), 3.86 (s, 6H), 3.83 (s, 3H), 2.92 (t, J = 7.4 Hz, 2H), 2.80 (t, J = 7.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.4, 153.2, 136.4, 136.1, 105.2, 60.8, 56.1, 45.3, 28.4.

4.2.1. (S)-3-(3, 5-dimethoxyphenyl)propane-1,2-diol 15a

To stirred solution of PhNO (0.7g, 6.5 mmol) and aldehyde **12a** (1.51g, 7.8 mmol) in ACN (30 mL) was added D-proline (0.15g, 1.3 mmol) at −20 °C, and the reaction mixture was stirred for 24h to same temperature. After 24h warmed to 0 °C and, diluted with MeOH, then $NaBH_4$ was added portion wise to the reaction mixture at 0 °C and stirred it for 30 min. After 30 min reaction mixture quenched with sat. NH_4Cl solution and extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with water, brine dried over Na_2SO_4 and concentrated on rotavapour. The crude was dissolved in MeOH (50 mL), $Cu(OAc)_2$ (0.03 equiv.) was added reaction mixture was stirred for 12h. After completion of reaction, reaction mixture was concentrated on rotavapour. The crude obtained was purified by silica gel column chromatography using Hexane: EtOAc (40:60) afforded diol **15a** as brownish thick liquid (0.97 g, 70%) yield. $[\alpha]_D^{20}$ = −22.64 (c, 0.78) FTIR cm^{-1} 3368, 2935, 2839, 1593, 1258, 1202, 1148; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (d, J = 2.2 Hz, 2H), 6.37 (d, J = 2.2 Hz, 1H), 4.04 (ddd, J = 8.1, 6.2, 4.7 Hz, 1H), 3.80 (s, 6H), 2.84 (s, 2H), 2.71 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9, 140.8, 107.3, 98.4, 72.9, 65.9 55.2, 40.6, HRMS (ESI$^+$) $[M+H]^+$: found 213.1125$C_{11}H_{17}O_4^+$ requires 213.1121.

4.2.2. (R)-1-(3, 5-dimethoxyphenyl) propan-2-ol 11a

To a stirred solution of diol **15a** (0.8 g, 3.3 mmol) and Bu_2SnO (0.08g, 0.3 mol) in DCM was added *p*- TsCl (0.7g, 3.6 mmol), Et_3N (0.92 mL, 6.6 mmol) and DMAP (0.04g, 0.3 mmol) sequentially at 0 °C and stirred at rt for 3h. After completion of reaction (checked on TLC) reaction mixture was quenched with cold water and extracted with EtOAc (3x 40 mL). The combined organic layers washed with brine, dried over Na_2SO_4 and concentrated under *vacuo* to obtain crude product, which was subjected to next step without further purification. To the suspension of $LiAlH_4$ (0.44 g, 11.5 mmol) in THF (20 mL) was added above crude monotosylated compound in THF (10 mL) at 0 °C slowly and reaction mixture was stirred for 5h at room temperature. After completion of reaction, reaction mixture was quenched with aq. NH_4Cl, filtered over celite and extracted with EtOAc (2 x 40 mL). The combined organic layers dried over Na_2SO_4 and concentrated on rotavapour. The crude was purified by silica gel chromatography using hexane: EtOAc (75:25) to obtain alcohol **11a** as yellowish liquid (0.59 g, 81% yield over two steps). $[\alpha]_D^{20}$ = −13.94(c, 0.62), FTIR cm^{-1} 3384, 2964, 2839, 1593, 1201, 1148, 1053; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (d, J = 2.2 Hz, 2H), 6.35 (d, J = 2.2 Hz, 1H), 4.06–4.03 (m, 1H), 3.80 (s, 6H), 2.74 (dd, J = 16, 4.0 Hz, 1H), 2.64 (m, dd, J = 12, 4.0 Hz, 1H); 1.77 (s, 1H), 1.26 (d, J = 8.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9, 140.1, 107.3, 98.4, 68.7, 46.1, 22.8. HRMS (ESI$^+$)$[M+Na]^+$: found 219.0997$C_{11}H_{16}NaO_3^+$ requires 219.0992.

4.2.3. (R)-6, 8-dimethoxy-3-methylisochroman-1-one16a

To a stirred solution of 2-arylpropanol **11a** (0.5g, 2.5 mmol) in DCM (10 mL), was added $CH(OMe)_3$ (2 mL) and PTSA (0.095g,0.5 mmol) at 0 °C and stirred for 2 h at rt. After 2h, reaction mixture was quenched with sat. $NaHCO_3$ and extracted with DCM (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, concentrated under *vacuo* to obtain crude material. Jones oxidant (2 mL, 6 mmol, and 3 M solution) was added to the stirred solution of above crude acetal in acetone at 0 °C and reaction mixture was stirred for 2h at same temperature. After2 h, reaction mixture was quenched with sat. $NaHCO_3$ solution and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated on rotavapour to obtain crude compound. The crude was purified by column chromatography using hexane: EtOAc (65:35) afforded compound **16a** as yellowish sticky liquid (0.44 g, 79% yield over two steps). $[\alpha]_D^{20}$ = -153.89 (c, 0.22), FTIR cm^{-1} 2969, 2927, 1703, 1595, 1245, 1111; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (s, 1H), 6.31 (s, 1H), 4.62–4.28 (m, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 2.84 (dd, J = 15.9, 7.0 Hz, 2H), 1.46 (d, J = 4Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 163.1, 162.7, 143.8, 106.8, 103.8, 97.7, 73.5, 56.1, 55.5, 36.5, 20.6. HRMS (ESI$^+$)$[M+H]^+$: found 223.0961$C_{12}H_{15}O_4^+$ requires 223.0965.

4.2.4. (R)-8-hydroxy-6-methoxy-3-methylisochroman-1-one (6-methoxymellein) 3

To the solution of valerolactone **16a** (0.22g, 1 mmol) in anhydrous DCM was added BCl_3 (1.2 mL, 1.2 mmol, 1 M in heptane) at −10 °C and reaction mixture was stirred for 2h, and then quenched with sat. $NaHCO_3$ and extracted with DCM (3 x 15 mL) and concentrated on rotavapour. The crude was purified by silica gel chromatography in hexane: EtOAc (65:35) afforded 6-methoxymellein **3** as white solid (0.159 g, 70% yield). mp = 76–77 °C, $[\alpha]_D^{20}$ = −54 (c, 0.5), lit.[9g] $[\alpha]_D^{20}$ = −55 (*c* 0.23, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.25 (s, 1H), 6.37 (d, J = 4 Hz, 1H), 6.26 (d, J = 4 Hz, 1H), 4.67 (dd, J = 13.9, 6.8 Hz, 1H), 3.83 (s, 3H), 2.87 (d, J = 7.2 Hz, 2H); 1.51 (d, J = 4 Hz, 3H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 165.8, 164.5, 140.9, 106.1, 101.5, 99.4, 75.5, 55.5, 34.8, 20.6; HRMS (ESI$^+$)$[M+Na]^+$: found 231.0618$C_{11}H_{12}NaO_4^+$ requires 231.0628.

4.2.5. (S)-3-(3, 4, 5-trimethoxyphenyl) propane-1,2-diol 15b

Diol **15b** was synthesized from aldehyde **12b** by using same experimental procedure as used for **15a.** 0.7 g scale (PhNO) afforded diol **15b** as brownish liquid (1.12 g, 71%). $[\alpha]_D^{20}$ = −18.64 (c, 0.4); FTIR cm^{-1} 3383, 2931, 2834, 1591, 1122, 1029, 922, 894; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (s, 1H), 3.94–3.83 (m, 1H), 3.82 (s, 6H), 3.82 (s, 3H), 3.71–3.68 (m,1H), 3.67–3.49 (m, 1H), 2.98 (s, 2H), 2.77–2.64 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2, 136.5, 133.6, 106.2, 73.0, 66.0, 60.8, 56.1, 40.1; HRMS (ESI$^+$)$[M+H]^+$: found 243.1219$C_{12}H_{19}O_5^+$ requires 243.1227.

4.2.6. ((R)-1-(3, 4, 5-trimethoxyphenyl) propan-2-ol 11b

The compound **11b** was synthesized according to procedure used for synthesis of compound **11a.** From diol **15b** (1.0 g scale) afforded **11b** as yellowish liquid (0.88 g, 83% yield). $[\alpha]_D^{20}$ = -2.17 (c, 0.32); FTIR cm^{-1} 3409, 2933, 2837, 1588, 1235, 1119; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (s, 2H), 4.05–4.00 (m, 1H), 3.87 (s, 6H), 3.84 (s, 3H), 2.75 (dd, J = 13.5, 4.3 Hz, 1H), 2.61 (dd, J = 13.5, 8.3 Hz, 1H), 1.90 (s, 1H), 1.28 (d, J = 6.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$)

δ 153.2, 136.6, 134.2, 106.1, 68.8, 60.8, 56.0, 46.1, 22.8. HRMS (ESI^+) $[M+Na]^+$: found 249.1090$C_{12}H_{18}NaO_4^+$ requires 249.1097.

4.2.7. ((R)-6, 7, 8-trimethoxy-3-methylisochroman-1-one 16b

Valerolactone **16b** was synthesized according to procedure used for **16a.** From diol **16b** (0.5 g scale) afforded **16b** as yellowish liquid (0.45 g, 81% yield). $[\alpha]_D^{20}$ = -109.35 (c, 0.24); FTIR cm^{-1} 2966, 2841, 1704, 1587, 1255, 1110; ^1H NMR (400 MHz, $CDCl_3$) δ 6.50 (s, 1H), 4.54 (ttd, J = 12.6, 6.3, 3.6 Hz, 1H), 3.97 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H), 2.91–2.76 (m, 2H), 1.48 (d, J = 6.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 157.5, 156.3, 142.1, 137.0, 111.7, 105.7, 73.9, 61.8, 61.1, 56.1, 36.0, 20.6. HRMS (ESI^+)$[M+H]^+$: found 253.1075$C_{13}H_{17}O_5^+$ requires 253.1071.

4.2.8. (R)-8-hydroxy-6,7-dimethoxy-3-methylisochroman-1-one (kigelin) 4

Same experimental procedure used for the synthesis of kigelin **4** as per procedure used for 6-methoxymellein **3**. From diol **16b** (0.25 g scale) afforded kigelin **4** as pale yellow solid (0.165 g, 70% yield. mp = 143–144 °C; $[\alpha]_D^{20}$ = −78 (c 1, MeOH) lit [5a]. $[\alpha]_D^{20}$ = −79 (c 1, MeOH); FTIR cm^{-1} 2929, 2857, 2356.58, 1655, 1511, 272, 1113, 755; ^1H NMR (400 MHz, $CDCl_3$) δ 11.15 (s, 1H), 6.30 (s, 1H), 4.68 (dt, J = 8.7, 6.2 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 2.86 (d, J = 8.0 Hz, 2H), 1.52 (d, J = 4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 158.4, 156.1, 135.4, 135.3, 102.8, 102.0, 75.8, 60.7, 56.1, 34.6, 20.7; HRMS (ESI^+)$[M+Na]^+$: found 261.0726$C_{12}H_{14}NaO_5^+$ requires 261.0733.

4.2.9. (S,E)-ethyl 4-hydroxy-5-(3,4,5-trimethoxyphenyl)pent-2-enoate 17

To a stirred solution of PhNO (2 g, 18.8 mmol) and aldehyde **12b** (4.7 g, 20.5 mmol) in ACN (50 mL) was added D-proline (0.430 mg, 3.75 mmol) at -20 °C and stirred for 24 h at the same temperature. After 24 h reaction warmed to 0 °C, LiCl (1.190 g, 28.2 mmol), triethyl phosphonoacetate (4.20 g, 28.2 mmol) and DBU (3.42 g, 22.5 mmol) was added sequentially at 0 °C and stirred for additional 1h. After completion of reaction, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under *vacuo* to give a crude α-aminoxy olefinic ester.

To a stirred solution of crude α-aminoxy olefinic ester in MeOH (50 mL) was added $Cu(OAc)_2$ (1.1 g, 0.3 equiv.) and reaction mixture was stirred at rt for 12 h. After completion of the reaction (monitored by TLC), the solvent was evaporated under *vacuo* and crude material was purified by silica gel column chromatography using hexane: EtOAc (7:3) as eluents to afford γ-hydroxy ester **17** (3.3 g, 71% yield) as brown liquid. $[\alpha]_D^{20}$ = +19.59 (*c* 0.34, MeOH); FTIR cm^{-1} 3470, 1712 1589, 1237, 1122, 1036, 1005. ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 (dd, J = 15.6, 4.5 Hz, 1H), 6.45 (s, 2H), 6.09 (dd, J = 15.7, 1.7 Hz, 1H), 4.54 (dtd, J = 6.2, 4.6, 1.7 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.86 (s, 6H), 3.84 (s, 3H), 2.91 (dd, J = 13.7, 4.6 Hz, 1H), 2.73 (dd, J = 13.7, 8.4 Hz, 1H), 2.03 (s, 1H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ, 166.45, 153.35, 148.80, 136.93, 132.46, 120.66, 106.36, 71.63, 60.85, 60.49, 56.11, 43.64, 14.24; HRMS (ESI^+) $[M+H]^+$: found 311.1491$C_{16}H_{23}O_6$ requires 311.1489.

4.2.10. (S,E)-ethyl 4-((tert-butyldimethylsilyl)oxy)-5-(3,4,5tri methoxyphenyl)pent-2-enoate 18

To a stirred solution of γ-hydroxy ester **17** (2.00 g, 6.45 mmol) in DMF (25 mL) were added Imidazole (0.65g, 9.65 mmol), TBDMSCl (1.45 g, 9.65 mmol) and DMAP (catalytic) Sequentially at 0 °C and reaction mixture was stirred at rt for overnight. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with EtOAc (200 mL) and washed with cold water several times then brine and dried over Na_2SO_4 and concentrated under *vacuo*. The obtained crude was purified using silica gel column chromatography using hexane: EtOAc (9:1) to afford compound **18** (2.4 g, 92% yield) as colourless liquid. $[\alpha]_D^{20}$ = −27.2 (*c* 0.20, MeOH); FTIR cm^{-1} 1717, 1590, 1298, 1159,834,776; ^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (dd, J = 15.5, 4.6 Hz, 1H), 6.41 (s, 2H), 6.00 (dd, J = 15.5, 1.6 Hz, 1H), 4.48–4.45 (m, 1H), 4.21 (q, J = 7.1, 2H), 3.86 (s, 6H), 3.84 (s, 3H), 2.81 (dd, J = 13.4, 5.0 Hz, 1H), 2.70 (dd, J = 13.4, 7.7 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H), 0.89–0.85 (m, 9H), −0.04 (s, 3H), −0.17 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.58, 152.99, 150.19, 136.87, 133.37, 120.18, 106.97, 73.07, 60.87, 60.37, 56.09, 44.62, 25.78, 25.64, 18.13, 14.24, 14.19, −4.84, −5.31; HRMS (ESI^+)$[M+Na]^+$: found 447.2178$C_{22}H_{36}NO_6Si$ requires 447.2173.

4.2.11. (R)-4-((tert-butyldimethylsilyl)oxy)-5-(3,4,5-trimethoxy phenyl)pentanal 19

To a stirred solution of compound **18** (2 g, 4.71 mmol) in methanol (30 mL) was added $NiCl_2 \cdot 6H_2O$ (0.220 g, 0.94 mmol), $NaBH_4$ (0.350 g, 9.43 mmol) portion wise subsequently at 0 °C, and stirred at room temperature for 1 h. After completion of the reaction, the reaction mixture was filtered over celite; solvent was evaporated under *vacuo*. The crude was diluted with water and extracted into EtOAc (3 x 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. The crude product was subjected to DIBAL-H reduction without further purification. ^1H of crude; ^1H NMR (400 MHz, $CDCl_3$) δ 6.41 (s, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.94 (dd, J = 6.1, 5.0 Hz, 1H), 3.86 (s, 6H), 3.83 (s, 3H), 2.68 (d, J = 6.2 Hz, 2H), 2.41 ((td, J = 7.4, 1.6 Hz, 2H)), 1.89–1.70 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H), 0.88 (s, 9H), 0.02 (s, 3H), −0.13 (s, 3H).

A solution of crude ester (2.0 g, 1 eq.) in DCM (30 mL) was cooled to − 78 °C. At −78C, DIBAL-H (5.1 mL of a 1 M solution in toluene, 5.1 mmol) was added dropwise and stirred for 1h. After 1h, the reaction mixture was quenched with sat. tartaric acid solution (20 mL) at - 78 °C, warmed to rt and extracted with DCM (3 x 15 mL). The combined organic layers were washed with water, brine and dried over Na_2SO_4 and concentrated under *vacuo*. The crude was purified by silica gel column chromatography using pet ether: ethyl acetate (92: 8) afforded pure aldehyde **19** (1.8 g, 95%) as colourless oil. $[\alpha]_D^{20}$ = −23.44 (*c* 0.25, MeOH); FTIR cm^{-1} 2855, 2716, 1723, 1238, 1125, 831, 774 ^1H NMR (400 MHz, $CDCl_3$) δ 9.80 (t, J = 1.6 Hz, 1H), 6.40 (s, 2H), 3.96 (dd, J = 6.2, 4.7 Hz, 1H), 3.87 (s, 6H), 3.84 (s, 3H), 2.74–2.64 (m, 2H), 2.55 (td, J = 7.4, 1.6 Hz, 2H), 1.86 (ddd, J = 12.2, 7.1, 4.6 Hz, 1H), 1.75 (dt, J = 13.9, 7.3 Hz, 1H), 0.88 (m, 9H), 0.03 (s, 3H), −0.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.42, 153.05, 136.68, 134.37, 106.66, 72.40, 60.88, 56.12, 44.12, 39.65, 28.95, 25.84, 18.01, −4.67, −4.79. HRMS (ESI^+)$[M+H]^+$: found 405.2074$C_{20}H_{35}O_5Si$ requires 405.2068.

4.2.12. (2R,4S)-4-((tert-butyldimethylsilyl)oxy)-5-(3,4,5trimeth oxyphenyl)pentane-1,2-diol 20

Diol **20** was synthesized by using same experimental procedure as used for **15a.** From aldehyde **19** (1.5 g scale) afforded diol **20** as red viscous liquid (0.99 g, 63% yield) (note: L-proline used as organocatalyst) $[\alpha]_D^{20}$ = + 13.84 (*c* 0.25, MeOH); FTIR cm^{-1} 3468, 2931, 2885, 1238, 1124, 1047,831, 773; ^1H NMR (400 MHz, $CDCl_3$) δ 6.40 (s, 2H), 4.27–4.22 (m, 1H), 4.18–4.14 (m, 1H), 3.85 (s, 6H), 3.83 (s, 3H), 3.62 (dd, J = 11.1, 3.4 Hz, 1H), 3.46 (dd, J = 11.1, 6.4 Hz, 1H), 2.87 (dd, J = 13.6, 7.1 Hz, 1H), 2.79 (dd, J = 13.5, 6.3 Hz, 1H), 2.09 (s, 1H), 2.06 (s, 1H), 1.76 (ddd, J = 14.4, 10.5, 3.8 Hz, 1H), 1.52 (ddd, J = 14.4, 4.8, 2.3 Hz, 1H), 0.89 (s, 9H), 0.07 (s, 3H), −0.12 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.13, 136.77, 134.26, 106.66, 72.68, 69.02, 67.11, 60.87, 56.13, 43.42, 37.60, 25.80, 17.92, −4.92, −5.02; HRMS

(ESI$^+$)[M+Na]$^+$: found 423.2179$C_{20}H_{36}NaO_6Si$ requires 423.2173.

4.2.13. (2R,4S)-2-(benzyloxy)-4-((tert-butyldimethylsilyl)oxy)-5-(3,4,5-trimethoxyphenyl)pentan-1-ol 21

To a stirred solution of diol **20** (0.6, g 1.5 mmol) in benzene (50 mL) were added $PhCH(OMe)_2$ (0.25 g, 1.65 mmol) and PPTS (38 mg, 0.15 mmol) and reaction mixture was refluxed for 1h with a Dean−Stark apparatus. After 1 h, reaction was quenched with Et_3N (0.2 mL) and the solvent was removed under *vacuo* to get crude acetal. To the crude solution of acetal in DCM (25 mL), was added DIBAL-H (4.5 mmol, 4.5 ml, 1 M in toluene) at 0 °C and stirred for 12 h at same temperature. After completion of reaction, reaction mixture was quenched with MeOH (1 mL) and saturated tartaric acid solution (5 mL), and extracted with DCM (3 x 50 mL). The combined organic layers were concentrated under *vacuo* to afford crude compound. The crude was purified by silica gel column chromatography using hexane: EtOAc (85: 15) to afford pure compound **21** as a colourless oil (0.60 g, 83%) $[\alpha]_D^{20} = +7.87$ (*c* 0.26, MeOH); FTIR cm^{-1} 3468, 2931, 2885, 1238, 1124, 1047,831, 773; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.26 (m, 5H), 6.36 (s, 2H), 4.52 (d, *J* = 4.1 Hz, 2H), 4.05−4.01 (m, 1H), 3.80−3.69 (m, 10H), 3.68−3.60 (m, 1H), 3.51 (dd, *J* = 11.7, 5.1 Hz, 1H), 2.74−2.66 (m, 2H), 2.06 (s, 1H), 1.83 (ddd, *J* = 14.4, 7.2, 4.5 Hz, 1H), 1.54 (ddd, *J* = 14.4, 7.4, 5.0 Hz, 1H), 0.85 (s, 9H), −0.00 (s, 3H), −0.11 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.00, 138.38, 136.62, 134.39, 128.49, 127.76, 127.53, 106.72, 76.71, 71.08, 70.98, 64.39, 60.87, 56.07, 44.84, 38.95, 25.91, 18.04, −4.42, −4.56 HRMS (ESI$^+$) [M+Na]$^+$: found 513.2649$C_{27}H_{46}NaO_6Si$ requires 513.2642.

4.2.14. (((2S,4R,Z)-4-(benzyloxy)-1-(3,4,5-trimethoxyphenyl) hept-5-en-2-yl)oxy)(tert-butyl)dimethylsilane 22

IBX (0.430 g, 1.53 mmol) was added to the solution of compound **21** (0.5 g, 1.02 mmol) in DMSO (6 mL) and stirred for 4 h at room temperature. After completion of the reaction as observed in TLC, the reaction was quenched with saturated $NaHCO_3$ solution (25 mL) and was extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with brine (30 mL) and dried over Na_2SO_4, concentrated under *vacuo* to obtained crude aldehyde.

To the Wittig salt (1.51 g, 4.08 mmol) in dry THF (10 mL) was added n-BuLi (1.6 mL, 2.5 M in hexane) very slowly at 0 °C and stirred for 30 min at 0 °C to generate Wittig reagent. After 30 min, crude aldehyde in THF (5 mL) was added to the above reaction mixture at 0 °C and stirred at rt for overnight. After completion of reaction mixture, (checked on TLC), quenched with sat. NH_4Cl and extracted with EtOAc (3x 50 mL), the combined organic layer was washed with brine, and concentrated under *vacuo* to obtain crude material. The crude was purified by silica gel column chromatography using hexane: EtOAc (96:4) to afford olefin **22** (0.36 g, 70% yield) as yellow oil. $[\alpha]_D^{20} = +44.91$ (*c* 0.22, MeOH); FTIR cm^{-1} 2930, 2855, 1588, 1238. 1126, 1066, 832, 774; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.29 (m, 5H), 6.41 (s, 2H), 5.77−5.69 (m, 1H), 5.38 (ddd, *J* = 11.0, 9.3, 1.8 Hz, 1H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.42 (td, *J* = 8.8, 4.0 Hz, 1H), 4.33 (d, *J* = 11.4 Hz, 1H), 4.15 (dd, *J* = 5.9, 4.1 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 6H), 2.72 (ddd, *J* = 20.2, 13.7, 6.0 Hz, 2H), 1.86 (ddd, *J* = 13.6, 8.8, 4.6 Hz, 1H), 1.73 (dd, *J* = 7.0, 1.7 Hz, 3H), 1.54 (ddd, *J* = 14.0, 7.3, 4.4 Hz, 1H), 0.89 (s, 9H), 0.04 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ, 152.88, 138.95, 136.49, 134.77, 131.99, 128.28, 127.67, 127.39, 127.24, 106.75, 71.04, 70.18, 69.72, 60.84, 56.00, 44.84, 43.46, 25.88, 18.00, 13.43, −4.55, −4.72; HRMS (ESI$^+$) [M+Na]$^+$: found 523.2855$C_{29}H_{44}NaO_5Si$ requires 523.2850.

4.2.15. (2S,4R,Z)-4-(benzyloxy)-1-(3,4,5-trimethoxyphenyl) hept-5-en-2-ol 13

To the stirred solution of compound **22** (0.35 g, 0.69 mmol) in dry THF (10 mL) was added TBAF (0.9 mmol, 0.9 mL, 1 M solution in THF) and stirred for 6 h at rt. After completion of reaction, reaction mixture was quenched with aq. NH_4Cl and extracted with EtOAc (3x 20 mL). The combined organic layer were washed with brine, dried over Na_2SO_4 and concentrated under *vacuo* to obtain crude material. The crude was purified using by silica gel column chromatography using hexane: EtOAc (80:20) to obtain pure hydroxyl compound **13** (0.245g, 91%) as colourless liquid. $[\alpha]_D^{20} = -22.69$ (*c* 0.23, MeOH); FTIR cm^{-1} 3485, 1588, 1237, 1124, ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.36−7.29 (m, 5H), 6.43 (s, 2H), 1−5.68 (m, 1H), 5.50 (ddd, *J* = 10.9, 9.2, 1.7 Hz, 1H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.56 (td, *J* = 8.5, 3.6 Hz, 1H), 4.36 (d, *J* = 11.7 Hz, 1H), 4.17 (ddd, *J* = 11.8, 8.0, 2.8 Hz, 1H), 3.86 (s, 6H), 3.85 (s, 3H), 2.70 (d, *J* = 6.2 Hz, 2H, and 1H (OH) merged together), 1.84 (ddd, *J* = 14.4, 8.2, 2.7 Hz, 1H), 1.70 (dd, *J* = 8.9, 3.7 Hz, 1H), 1.66 (dd, *J* = 7.0, 1.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.15, 138.36, 136.48, 134.49, 130.96, 128.43, 127.99, 127.77, 127.71, 106.18, 71.43, 70.11, 69.55, 60.84, 56.06, 44.34, 41.63, 13.38; HRMS (ESI$^+$)[M+Na]$^+$: found 409.1990$C_{23}H_{30}NaO_5Si$ requires 409.1985.

4.2.16. (S)-3-((R,Z)-2-(benzyloxy)pent-3-en-1-yl)-6,7,8-trimeth oxyisochroman-1-one 23

The title compound was synthesized by using same experimental procedure as used for **16a.** From compound **13** (0.200 g scale) afforded lactone **23** (0.181 g, 85% yield for two steps) as pale yellow oil: **(**(Note: TMSOTF used as catalyst instead of PTSA) $[\alpha]_D^{20} = -42.81$ (*c* 0.32, MeOH); FTIR cm^{-1} 2937, 1716, 1592, 1254, 1105. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.26 (m, 5H), 6.48 (s, 1H), 5.79−5.71 (m, 1H), 5.39 (ddd, *J* = 11.0, 6.4, 1.8 Hz, 1H), 4.75−4.71 (m, 1H), 4.64 (td, *J* = 8.1, 4.2 Hz, 1H), 4.58 (d, *J* = 11.3 Hz, 1H), 4.37 (d, *J* = 11.3 Hz, 1H), 4.00 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H), 2.93−2.77 (m, 2H), 1.94−1.91 (m, 2H), 1.75 (dd, *J* = 7.0, 1.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.28, 157.53, 156.30, 142.09, 138.61, 137.23, 130.88, 128.33, 128.28, 127.86, 127.56, 111.97, 105.70, 74.37, 70.31, 70.01, 61.87, 61.17, 56.13, 41.13, 34.95, 13.60. HRMS (ESI$^+$)[M+H]$^+$: found 413.1962$C_{24}H_{29}O_6$ requires 413.1958.

4.2.17. (S)-3-((S)-2-hydroxypentyl)-6,7,8-trimethoxyiso chroman-1-one

To the stirred solution of lactone **23** (150 mg, 0.35 mmol) in EtOAc (20 mL), was added $Pd(OH)_2$ (30 mg, 20%) and reaction mixture was stirred at rt under hydrogen pressure (100 psi) in Parr reactor for overnight. After complete consumption of starting material (checked on TLC) reaction mixture was filtered on celite and filtrate was concentrated under *vacuo* to obtain crude material. The crude material was purified by silica gel column chromatography using hexane: EtOAc (65:35), afforded compound **24** (114 mg, 97%) as yellow liquid. $[\alpha]_D^{20} = -64.8$ (*c* 1, $CHCl_3$); FTIR cm^{-1} 3422, 2934, 2872, 1705, 1592, 1257, 1110; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (s, 1H), 4.75−4.69 (m, 1H), 4.08−4.04 (m, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 3.86 (s, 3H), 2.86 (ddd, *J* = 19.1, 16.1, 7.4 Hz, 2H), 2.20 (s, 1H), 1.94 (ddd, *J* = 14.3, 9.6, 2.2 Hz, 1H), 1.71−1.65 (m, 1H), 1.52−1.38 (m, 4H), 0.94 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.39, 157.59, 156.29, 142.03, 137.33, 111.78, 105.73, 74.81, 67.11, 61.84, 61.15, 56.13, 42.24, 40.19, 34.94, 18.74, 14.06.; HRMS (ESI$^+$)[M+H]$^+$: found 325.1643, $C_{17}H_{25}O_6$ requires 325.1646.

4.2.18. (S)-8-hydroxy-3-((S)-2-hydroxypentyl)-6,7-dimethoxy isochroman-1-one (5)

The title compound was synthesized by using same experimental procedure used for compound **3**. From compound **24** (0.1g scale) afforded fusarentin 6,7 dimethyl **5** (66 mg, 70% yield) as a white solid. mp = 101−103 °C; $[\alpha]_D^{25} = -26.9$ (*c* 1, $CHCl_3$); $[\alpha]_D^{20} = -25.8$ (*c* 1, $CHCl_3$); FTIR cm^{-1} 3461, 3388, 2923, 2854, 1650, 1630,

1511, 1272, 1117; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.08 (s, 1H), 6.28 (s, 1H), 4.88–4.81 (m, 1H), 4.07–4.03 (m, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 2.97–2.83 (m, 2H), 1.98 (ddd, J = 14.5, 9.6, 2.3 Hz, 1H), 1.70 (ddd, J = 14.5, 10.2, 3.0 Hz, 1H), 1.52–1.41 (m, 4H), 0.95 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 158.5, 156.2, 135.6, 135.4, 103.0, 102.1, 76.5, 67.1, 60.7, 56.1, 42.3, 40.2, 33.6, 18.7, 14.0; HRMS (ESI^+) $[M+H]^+$: found 311.1485, $C_{16}H_{23}O_6$ requires 311.1489.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2020.131524.

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