

First total synthesis of Artekeiskeanol B and D

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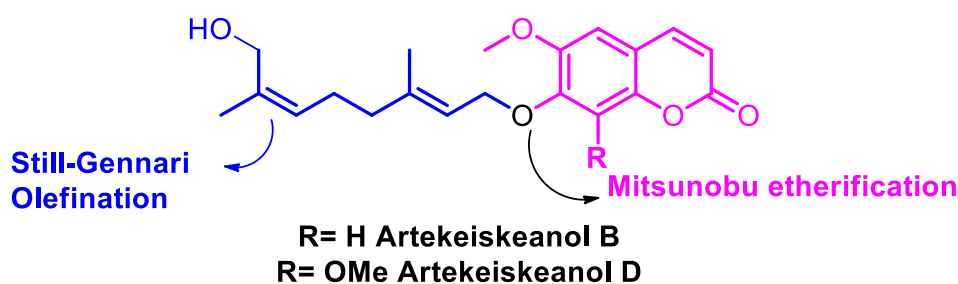
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Abstract

Synthesis of natural products, Artekeiskeanol B and D are described. The important protocols involved in the synthesis are oxidative C-C bond cleavage, Still-Gennari olefination, debenzylation and Mitsunobu etherification. The synthesis was started from commercially available Geraniol and 2,4-dihydroxy benzaldehyde.



Keywords: Traditional medicine, coumarins, reduction, etherification

Introduction

Coumarins and their derivatives are abundantly available as natural products, particularly from plant plethora.¹⁻⁶ Coumarins, were first isolated by Vogel and Guibourt, independently in 1820, from tonka beans and melilot flowers respectively and the first synthesis was reported by Perkin in 1868. The coumarin derivatives have occupied a huge space in pharmaceuticals and also in other areas like cosmetics.⁷⁻⁹ Artekeiskeanol A-D (Figure 1) are coumarin derivatives, isolated from *Artemisia keiskeana*, a traditional medicinal plant.¹⁰⁻¹² The biological importance and their structural fascination attracted us to carry out their synthesis. As part of our regular research program, in the synthesis of biologically active natural products,¹³⁻¹⁹ we have already reported the total synthesis of Artekeiskeanol A and C.²⁰ Whereas, in this report, presenting the total synthesis of Artekeiskeanol B and D.

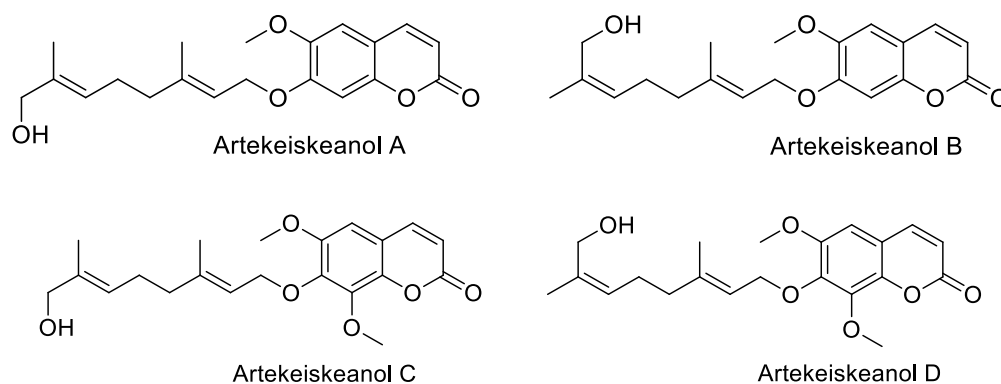
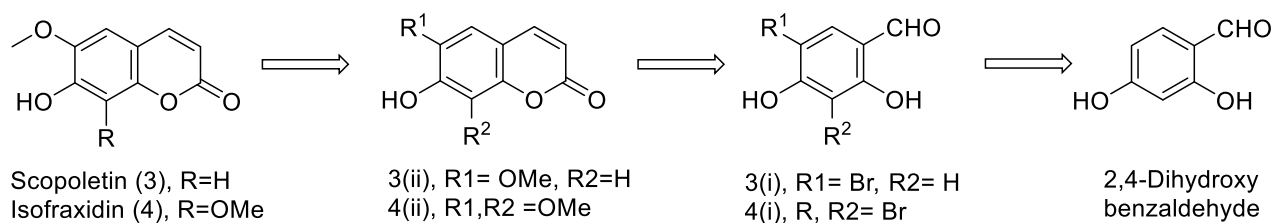


Figure 1. Isolated natural products Artekeiskeanol A-D.

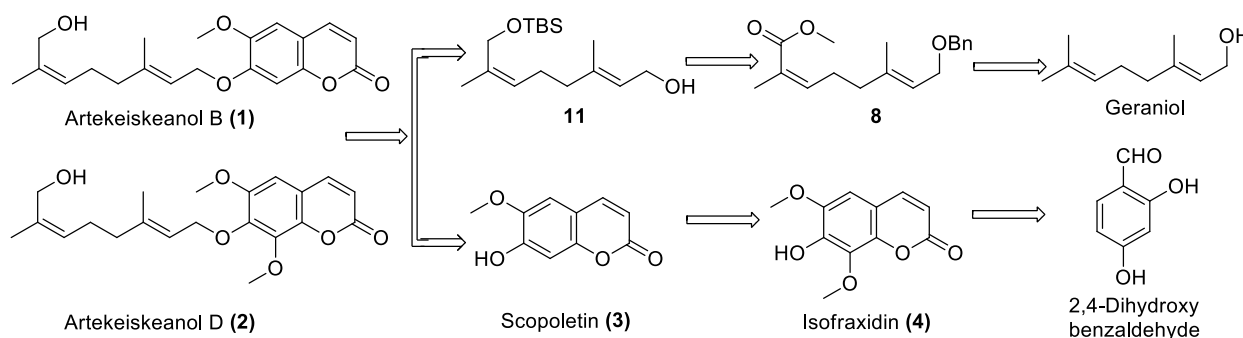
In this work, we have followed, our previous protocol (Scheme 1)²⁰ for the synthesis of 7-hydroxy coumarin's entitled as isofraxidin and scopoletin, which are the main intermediates for Artekeiskeanol A - D. (Figure 1).



Scheme 1. Retrosynthesis of Scopoletin (3) and Isofaxidin (4).

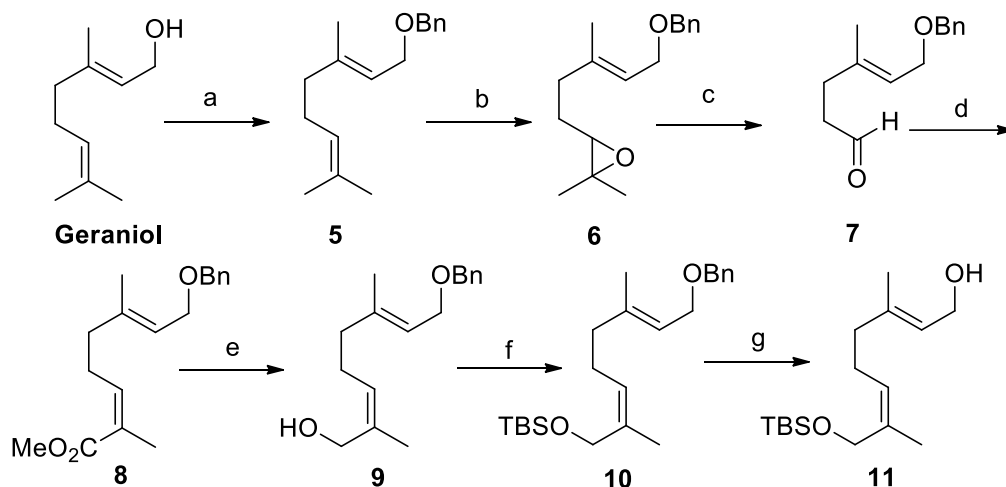
Results and Discussion

Herein, we report the synthesis of Artekeiskeanol B and D, respectively as shown in the scheme-2, as a prolongation to our previous work reported earlier.²⁰ The key steps in our convergent strategy involve Still-Gennari olefination and Mitsunobu reaction. The Key precursor (11) could be synthesized from commercially available geraniol.



Scheme 2. Retrosynthetic analysis of Artekeiskeanol B and D.

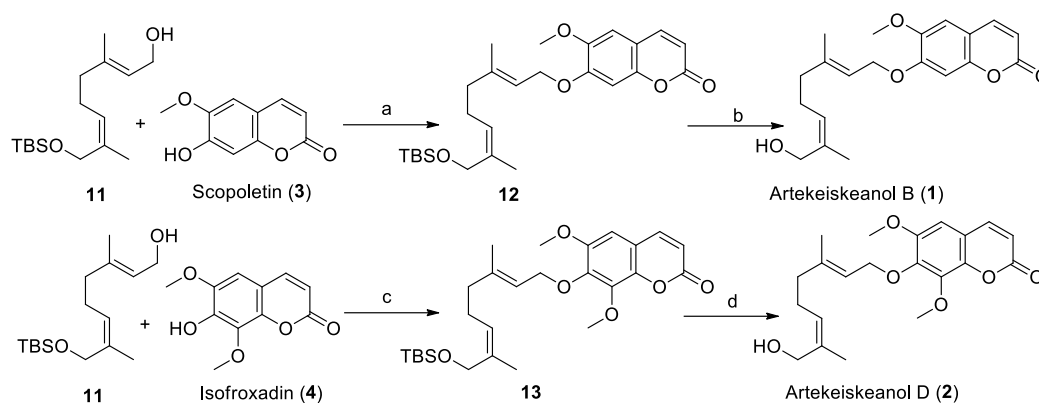
The synthesis of key intermediate **11** was begun with commercially available starting material geraniol as shown in the scheme-3. Geraniol was subjected to benzylation by using benzyl bromide to afford the corresponding benzyl ether **5** and followed by the selective epoxidation at C-6, gave the epoxide **6**. Thus obtained epoxide (**6**) was subjected for oxidative cleavage with periodic acid to get the aldehyde **7**. Still-Gennari olefination of aldehyde (**7**) afforded the key intermediate ester **8** with excellent selectivity in good yields.²¹⁻²⁵ The configuration of olefins at C-2 and C-6 of the ester **8** was confirmed as *2E* and *6Z*, based on the 2D-NOE correlation spectral studies of H-1/10, H-6/9,¹¹ as shown in the (Figure 2) and also mentioned in the table-1. Later, the ester **8** was reduced to furnish alcohol **9**, which was protected with TBS-Cl, gave silyl ether **10**. Thus obtained compound, on reductive cleavage of benzyl ether with lithium-naphthalene,^{26, 27} yielded the aliphatic fragment **11**.



Reagents and conditions: (a) NaH, BnBr, *tetra*-butylammoniumiodide, THF, 0 °C - r.t, 3h, 95%. (b) *m*-CPBA, CH₂Cl₂, 0 °C - r.t, 2h, 77%. (c) H₅IO₆, THF - H₂O, 0 °C, 30 min, 95%. (d) Methyl-2-(bis(2,2,2-trifluoroethoxy) phosphoryl)propanoate, 18-crown-6, potassium *bis*(trimethylsilyl)amide, THF, -78 °C, 30min, 88%. (e) DIBAL-H, CH₂Cl₂, -78 °C, 1h, 71%. (f) TBS-Cl, imidazole, CH₂Cl₂, r.t, 30min, 86%. (g) Li-Naphthalene, THF, -45 °C, 1h, 89%.

Scheme 3. Synthesis of fragment 11.

The coumarin derivatives, Scopoletin (**3**) and Isofroxadin (**4**) were synthesized by following our earlier protocol (Scheme 1).²⁰ Formation of C-O bond between fragment **11** and **3** and also between fragment **11** and **4** was achieved with Mitsunobu conditions,²⁸ followed by desilylation with operationally simple catalyst TBAF to afford the target natural products,²⁹ Artekeiskeanol B (**1**) and Artekeiskeanol D (**2**), in excellent yields, as shown in the scheme-4. Spectroscopic data of the synthetic products **1** and **2** are in consistency with the data reported for the natural products, as depicted in table 2 and table 3.



Reagents and conditions: (a) Triphenylphosphine, Diisopropyl azodicarboxylate, THF, 0 °C- r.t, 2h, 80%. (b) Tetra-*n*-butylammoniumfluoride, THF, 0 °C- r.t, 2h, 82%. (c) Triphenylphosphine, Diisopropylazodicarboxylate, THF, 0 °C-r.t, 2h, 81%. (d) Tetra-*n*-butylammoniumfluoride, THF, 0 °C - r.t, 2h, 77%.

Scheme 4. Synthesis of Artekeiskeanol-B & D.

All the synthesized products were characterized by their ¹H NMR, ¹³C NMR, IR and mass spectral analysis and compared with literature reports¹¹.

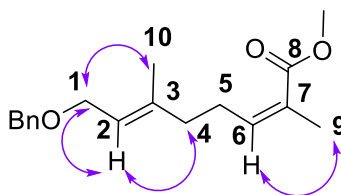
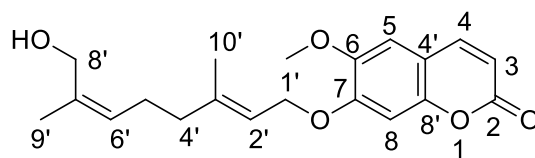


Figure 2

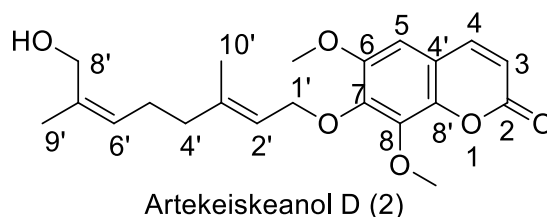
Table 1. 2D NOE correlations of compound **8**

Position	NOE correlations of compound 8
1	H-10
2	H-1,4
4	H-2
6	H-9
9	H-6
10	H-1

Table 2. Comparative ^1H & ^{13}C NMR data for the natural & synthetic Artekeiskeanol B

Artekeiskeanol B (1)

$^1\text{H} / ^{13}\text{C}$	Artekeiskeanol B, natural product		Artekeiskeanol B, synthetic product	
Position	$\delta ^1\text{H}$ (J Hz) (in CDCl_3)	$\delta ^{13}\text{C}$	$\delta ^1\text{H}$ (J Hz) (in CDCl_3)	$\delta ^{13}\text{C}$
2		161.5 (s)		161.4
3	6.25 (d, 9.3)	113.3 (d)	6.29 (d, 9.4)	113.3
4	7.59 (d, 9.3)	143.3 (d)	7.62 (d, 9.5)	143.3
4*		111.3 (s)		111.3
5	6.82 (s)	107.9 (d)	6.85 (s)	108.0
6		146.5 (s)		146.5
7		151.9 (s)		152.0
8	6.79 (s)	101.1 (d)	6.83 (s)	101.1
8*		149.8 (s)		149.6
1'	4.65 (d, 6.5)	66.2 (t)	4.68 (d, 6.5)	66.2
2'	5.44 (tdd, 6.5, 2.5, 1.5)	118.8 (d)	5.47 (tdd, 6.5, 2.5, 1.5)	118.8
3'		141.6 (s)		141.6
4'	2.07 (br t, 7.5)	39.5 (t)	2.10 (br t, 7.4)	39.5
5'	2.18 (br q, 7.5)	25.6 (t)	2.20 (br q, 7.5)	25.6
6'	5.21 (br t, 7)	127.2 (d)	5.25 (br t, 7)	127.1
7'		134.9 (s)		134.9
8'	4.09 (s)	61.5 (t)	4.12 (s)	61.5
9'	1.73 (d, 0.8)	21.1 (q)	1.76 (d, 0.8)	21.1
10'	1.74 (s)	16.9 (q)	1.77 (s)	16.9
OCH_3 -6	3.88 (s)	56.3 (q)	3.91 (s)	56.3

Table 3. Comparative ^1H & ^{13}C NMR data for the natural & synthetic Artekeiskeanol D

^1H / ^{13}C	Artekeiskeanol D, Natural product		Artekeiskeanol D, Synthetic product	
Position	δ ^1H (J = Hz) (in CDCl_3)	δ ^{13}C	δ ^1H (J = Hz) (in CDCl_3)	δ ^{13}C
2		160.6 (s)		160.6
3	6.31 (d, 9.7)	115.1 (d)	6.35 (d, 9.4)	115.2
4	7.58 (d, 9.7)	143.5 (d)	7.62 (d, 9.6)	143.5
4*		114.4 (s)		114.5
5	6.63 (s)	103.5 (d)	6.66 (s)	103.6
6		150.6 (s)		150.6
7		144.7 (s)		144.8
8		141.7 (s)		141.7
8*		142.9 (s)		143.0
1'	4.62 (d, 7)	70.1 (t)	4.66 (d, 7.2)	70.1
2'	5.51 (tdd, 7.3, 2.4, 1.5)	120.0 (d)	5.55 (tdd, 7.3, 2.4, 1.5)	120.1
3'		142.1 (s)		142.1
4'	2.03 (br t, 7.3)	39.5 (t)	2.06 (br t, 7.3)	39.6
5'	2.13 (br q, 7.5)	25.8 (t)	2.16 (br q, 7.5)	25.8
6'	5.21 (br t, 7.2)	127.3 (d)	5.24 (br t, 7.1)	127.4
7'		134.8 (s)		134.9
8'	4.07 (s)	61.4 (s)	4.10 (s)	61.5
9'	1.75 (d, 1)	21.2 (q)	1.78 (d, 1)	21.2
10'	1.67 (s)	16.4 (q)	1.70 (s)	16.4
OCH_3 -6	3.86 (s)	56.2 (q)	3.89 (s)	56.3
OCH_3 -8	4.00 (s)	61.7 (q)	4.03 (s)	61.8

Conclusions

In summary, we report the first total synthesis of Artekeiskeanol B and D in 9 steps with an overall yield, 13.6% each. The key reactions involved in this synthesis are oxidative cleavage of olefin, selective debenzoylation, Still-Gennari olefination for the synthesis of aliphatic side chain **11** with desired *cis* and *trans* configuration respectively at C-6/C-2 and Mitsunobu etherification for coupling of sidechain with scopoletin (**3**) and isofroxadin (**4**) to achieve the targets Artekeiskeanol B and D.

Experimental Section

General. All the air and moisture sensitive reactions were carried out under inert atmosphere (nitrogen or argon). Oven-dried glass apparatus were used to perform all the reactions. Freshly distilled anhydrous solvents were used for air and moisture sensitive reactions. Commercially available reagents were used as such. Purification of compounds was carried out via column chromatography by using silica gel (60-120 mesh) packed in glass columns. ^1H NMR and ^{13}C NMR were recorded in CDCl_3 on 100 MHz and 400 MHz spectrometer, using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer FT-RT 240-c Spectrophotometer using Thin Film optics. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70eV. High resolution mass spectra (HRMS) [ESI+] were obtained using TOF spectrometer.

(E)-{[(3,7-Dimethylocta-2,6-dien-1-yl)oxy]methyl}benzene (5). To a stirred solution of geraniol (5g, 32.41 mmol) in dry THF (30 mL) was added NaH (0.93g, 38.89 mmol) and benzyl bromide (6.09g, 35.65 mmol) dropwise at 0 °C and stirred for 5 min, then added TBAI (0.2g) and allowed to stir at room temperature for 3h. After the completion of the reaction (monitored by TLC), the reaction mixture was quenched with ice cooled water, added EtOAc (100 mL). The organic layer was rinsed with brine, dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by column chromatography on silica gel (60-120 mesh), by eluting with EtOAc-Hexane (1:4) mixture to afford, compound **5**, in 7.52g (95%) as a yellow oil.

IR (neat): ν 3062, 1454, 1217, 1103, 770 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 7.37 - 7.26 (m, 5H), 5.40 (t, 1H, J = 6.7 Hz), 5.10 (t, 1H, J = 6.7 Hz), 4.50 (s, 2H), 4.04 (d, 2H, J = 6.72 Hz), 2.14 - 2.09 (m, 2H), 2.06 - 2.03 (m, 2H), 1.68 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 140.3, 138.6, 131.7, 129.1, 128.8, 128.4, 127.8, 127.5, 124.1, 120.9, 71.9, 66.6, 39.6, 26.4, 25.7, 17.7, 16.5. HRMS: m/z $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{17}\text{H}_{28}\text{ON}$: 262.21647; found: 262.21654.

(E)-3-(5-(Benzyloxy)-3-methylpent-3-en-1-yl)-2,2-dimethyloxirane (6). To a stirred solution of *m*-CPBA (2.82g, 16.39 mmol) in dry CH_2Cl_2 (30 mL) under inert atmosphere at 0 °C was added compound **5** (5g, 20.49 mmol), which is dissolved in dry CH_2Cl_2 (20 mL). Then the reaction mixture was warmed to room temperature and allowed to stir for 2h. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with NaOH (3x20 mL, 1M) solution, followed by water, then dried over Na_2SO_4 . The solvent was distilled off in vacuum to give crude compound, which was then purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-Hexane (1:1) mixture to afford, epoxide **6** (4.1g, 77%) as a yellow oil.

IR (neat): ν 2963, 1452, 1251, 1076, 740 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 7.35 - 7.25 (m, 5H), 5.46 - 5.43 (m, 1H), 4.50 (s, 2H), 4.02 (d, 2H, J = 6.7 Hz), 2.71 (t, 1H, J = 6.2 Hz), 2.22 - 2.19 (m, 1H), 2.17 - 2.14 (m, 1H), 1.67 - 1.65 (m, 5H), 1.30 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 139.1, 138.3, 128.1, 127.5, 127.3, 121.2, 72.0, 66.3, 63.7, 58.0, 36.0, 27.0, 24.6, 18.5, 16.3. HRMS: m/z $[\text{M}+\text{NH}_4]^+$ calcd for $\text{C}_{17}\text{H}_{28}\text{O}_2\text{N}$: 278.21119; found: 278.21125.

Methyl-(2Z,6E)-8-(benzyloxy)-2,6-dimethylocta-2,6-dienoate (8). To a stirred solution of epoxide **6** (3g, 1.11 mmol) in dry THF (16 mL) was added a solution of H_5IO_6 (3.9g, 17.3 mmol), which was dissolved in water (8 mL) at 0 °C and the resulting mixture was stirred for 30 min. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with sat. NaHCO_3 and stirred for 30 min. The aqueous layer was extracted with EtOAc (2x30 mL) and the combined organic layer was washed with brine, dried over Na_2SO_4 , concentrated under reduced pressure. The obtained aldehyde **7** (95%), which was used as such for further reaction without purification.

To a stirred solution of 18-crown-6-ether (5.6g, 21.10 mmol) and methyl 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)propanoate (4.2g, 12.66 mmol) in dry THF (15 mL) at -78 °C was added a solution of KHMDS (2.52g, 12.66 mmol) and stirred for 20 min, then crude aldehyde **7**, in dry THF was added and stirred for another 30 min at the same temperature. After completion of the reaction (confirmed by TLC), the reaction mixture was quenched with sat. ammonium chloride. The aqueous layer was extracted with hexane (2x30 mL) and the combined organic layers were washed with brine, dried over Na₂SO₄. The solvent was evaporated under reduced pressure to give crude compound, which was then purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-Hexane (1:9) mixture to afford, compound **8** (2.77g, 88%) as a yellow oil over two steps.

IR (neat): ν 2951, 1726, 1452, 1274, 1130, 767 cm⁻¹ ¹H NMR (400 MHz, CDCl₃): δ 7.34 - 7.26 (m, 5H), 5.93 (t, 1H, J = 7.4 Hz), 5.42 (t, 1H, J = 6.6 Hz), 4.50 (s, 2H), 4.04 (d, 2H, J = 6.9 Hz), 3.72 (s, 3H), 2.60 (q, 2H, J = 7.4 Hz), 2.14 (t, 2H, J = 7.7 Hz), 1.88 (s, 3H), 1.65 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 168.3, 142.6, 139.5, 138.5, 128.3, 127.8, 127.5, 121.4, 71.9, 66.4, 51.2, 39.0, 27.6, 20.6, 16.3. HRMS: m/z [M+NH₄]⁺ calcd for C₁₈H₂₈O₃N: 306.20634; found: 306.20642.

((2Z,6E)-8-(Benzyloxy)-2,6-dimethylocta-2,6-dien-1-ol (9)). To a stirred solution of compound **8** (2.5 g, 8.68 mmol) in dry CH₂Cl₂ (30 mL) at -78 °C was added DIBAL-H (2.71g, 19.09 mmol, 1M, Hexane) slowly and stirred for 1h. The completion of reaction was confirmed by TLC, and then reaction mixture was quenched with sat. Sodium potassium tartrate (Rochelle salt) and stirred until the reaction mixture turns into clear solution. The aqueous layer was extracted with CH₂Cl₂ (3x30 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (2:8) mixture to give **9** (1.59 g, 71%) as a yellow oil.

IR (neat): ν 3420, 2956, 1527, 1431, 1328, 1216, 744 cm⁻¹ ¹H NMR (400 MHz, CDCl₃): 7.35 - 7.26 (m, 5H), 5.38 (t, 1H, J = 6.8 Hz), 5.25 (t, 1H, J = 7.4 Hz), 4.50 (s, 2H), 4.08 (s, 2H), 4.0 (d, 2H, J = 6.8 Hz), 2.17 (q, 2H, J = 7.3 Hz), 2.05 (t, 2H, J = 7.3 Hz), 1.79 (s, 3H), 1.64 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 140.1, 138.3, 135.1, 128.3, 127.8, 127.5, 127.2, 121.3, 72.1, 66.3, 61.3, 39.4, 25.7, 21.2, 16.5. HRMS: m/z [M+NH₄]⁺ calcd for C₁₇H₂₈O₂N: 278.21119; found: 278.21125.

{[(2Z,6E)-8-(Benzyloxy)-2,6-dimethylocta-2,6-dien-1-yl]oxy}(tert-butyl)dimethylsilane (10). A solution of alcohol **9** (1.5g, 0.60 mmol) in dry CH₂Cl₂ (5 mL) was stirred for 10 min at 0 °C and then added TBS-Cl (0.78g, 5.17 mmol) and imidazole (0.43g, 6.38 mmol) was allowed to stir for 30 min at room temperature. After the completion of reaction (confirmed by TLC), quenched with ice cooled water and extracted with CH₂Cl₂ (3x20 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-Hexane (1:9) mixture to give **10** (1.85g, 86%) as a yellow oil.

IR (neat): ν 2925, 1512, 1461, 1264, 1086, 920, 849, 770 cm⁻¹ ¹H NMR (400 MHz, CDCl₃): 7.35 - 7.26 (m, 5H), 5.40 (t, 1H, J = 7.7 Hz), 5.19 (t, 1H, J = 7.1 Hz), 4.50 (s, 2H), 4.14 (s, 2H), 4.04 (d, 2H, J = 6.6 Hz), 2.17 (q, 2H, J = 7.4 Hz), 2.10 (t, 2H, J = 8.5 Hz), 1.73 (s, 3H), 1.64 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 140.0, 138.5, 135.1, 128.3, 127.8, 127.5, 125.8, 121.0, 72.0, 66.5, 61.8, 39.7, 25.9, 25.8, 21.1, 18.5, 16.5, -5.3. HRMS: m/z [M+NH₄]⁺ calcd for C₂₃H₄₂O₂SiN: 392.29945; found: 392.29793.

(2E,6Z)-8-[(tert-Butyldimethylsilyl)oxy]-3,7-dimethylocta-2,6-dien-1-ol (11). To a stirred solution of naphthalene (4.9g, 38.5 mmol) in dry THF (50 mL) was added lithium (0.17g, 24.06 mmol) at room temperature and stirred for 2 h. Then, added compound **10** (1.8g, 4.81 mmol), which was dissolved in dry THF (10 mL) at -45 °C and stirred for 1h at the same temperature. After completion of the reaction (confirmed by TLC), the reaction mixture was quenched with sat.NH₄Cl and the aqueous layer was extracted with EtOAc

(3x20 mL). The combined organic layer was washed with brine, dried over Na₂SO₄ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (1:9) mixture to give **11** (1.21g, 89%) as a yellow oil.

IR (neat): ν 3538, 2945, 1720, 1560, 1467, 1259, 1085, 848, 774 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 5.40 (t, 1H, J = 7.1 Hz), 5.16 (t, 1H, J = 7.2 Hz), 4.12 (s, 4H), 2.14 (q, 2H, J = 7.4 Hz), 2.02 (t, 2H, J = 7.2 Hz), 1.72 (s, 3H), 1.65 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 138.7, 135.1, 125.7, 123.8, 61.8, 59.1, 39.5, 29.6, 25.9, 25.7, 20.9, 18.3, 16.1, -5.3. HRMS: m/z [M+H]⁺ calcd for C₁₆H₃₃O₂Si: 285.22443; found: 285.22474.

7-[[[(2E,6Z)-8-((tert-Butyldimethylsilyl)oxy)-3,7-dimethylocta-2,6-dien-1-yl]oxy]-6-methoxy-2H-chromen-2-one (12). To a stirred solution of Scopoletin **3** (0.3g, 1.56 mmol) and alcohol **11** (0.46g, 1.71 mmol) in dry THF (10 mL) was added PPh₃ (0.34g, 1.35 mmol). The solution was cooled to 0 °C and DIAD (0.28g, 1.48 mmol) was added slowly. The reaction mixture was stirred at 0 °C for 10 min and allowed to warm to room temperature. After stirring at room temperature for 2h, the reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (2:8) mixture to give **12** (0.59 g, 80%) as a yellow oil.

IR (neat): ν 3058, 1541, 1424, 1360, 1215, 1138, 1056, 980, 863, 741 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.63 (d, 1H, J = 9.4 Hz), 6.86 (s, 1H), 6.84 (s, 1H), 6.29 (d, 1H, J = 9.5 Hz), 5.49 (t, 1H, J = 6.7 Hz), 5.18 (t, 1H, J = 8.3 Hz), 4.69 (d, 2H, J = 6.5 Hz), 4.14 (s, 2H), 3.92 (s, 3H), 2.18 (q, 2H, J = 7.7 Hz), 2.10 (t, 2H, J = 6.9 Hz), 1.78 (s, 3H), 1.72 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 161.5, 152.1, 149.9, 146.6, 143.3, 141.7, 135.4, 125.4, 118.6, 113.4, 111.4, 108.0, 101.2, 66.3, 61.7, 56.4, 39.7, 25.9, 25.7, 21.1, 18.4, 16.8, -5.2. HRMS: m/z [M+H]⁺ calcd for C₂₆H₃₈O₅Si: 459.25671; found: 459.25622.

7-[[[(2E,6Z)-8-Hydroxy-3,7-dimethylocta-2,6-dien-1-yl]oxy]-6-methoxy-2H-chromen-2-one (1). To the stirred solution of compound **12** (0.3g, 0.65 mmol) in dry THF (5 mL) was added TBAF (0.16g, 0.61 mmol) slowly at 0 °C, and the reaction mixture was allowed to stirred for 2h at 0 °C to r.t. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with sat. NaHCO₃ and the aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layer was washed with brine, dried over Na₂SO₄ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (1;1) mixture to give **1** (0.18g, 82%) as a colorless solid.

IR (neat): 3382, 2924, 1702, 1459, 1310, 1118, 1080, 690 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.62 (d, 1H, J = 9.5 Hz), 6.85 (s, 1H), 6.83 (s, 1H), 6.29 (d, 1H, J = 9.4 Hz), 5.47 (t, 1H, J = 6.5, 2.5, 1.5 Hz), 5.25 (t, 1H, J = 7.0 Hz), 4.68 (d, 2H, J = 6.5 Hz), 4.12 (s, 2H), 3.91 (s, 3H), 2.20 (q, 2H, J = 7.6 Hz), 2.10 (t, 2H, J = 7.3 Hz), 1.77 (s, 3H), 1.76 (d, 3H, J = 0.8 Hz). ¹³C NMR (100 MHz, CDCl₃): δ 161.4, 152.0, 149.6, 146.5, 143.3, 141.6, 134.9, 127.1, 118.8, 113.3, 111.3, 108.0, 101.1, 66.2, 61.5, 56.3, 39.5, 25.6, 21.1, 16.9. HRMS: m/z [M+H]⁺ calcd for C₂₀H₂₄O₅: 345.15667; found: 345.15862.

7-[[[(2E,6Z)-8-((tert-Butyldimethylsilyl)oxy)-3,7-dimethylocta-2,6-dien-1-yl]oxy]-6,8-di methoxy-2H-chromen-2-one (13). To stirred solution of Isofroxadin **4** (0.3 g, 1.35 mmol) and alcohol **11** (0.42 g, 1.48 mmol) in dry THF (10 mL) was added PPh₃ (0.34 g, 1.35 mmol). The solution was cooled to 0 °C and DIAD (0.28 g, 1.48 mmol) was added slowly. The reaction mixture was stirred at 0 °C for 10 min and allowed to warm to room temperature and stirred for 2h, the reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (2:8) mixture to give **13** (0.58 g, 81%) as a yellow oil.

IR (neat): ν 3023, 2813, 1726, 1530, 1421, 1326, 1216, 1167, 1052, 945, 740 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.62 (d, 1H, J = 9.5 Hz), 6.66 (s, 1H), 6.36 (d, 1H, J = 9.5 Hz), 5.56 (t, 1H, J = 7.6 Hz), 5.16 (t, 1H, J = 6.9 Hz), 4.69 (d, 2H, J = 7.0 Hz), 4.14 (s, 2H), 4.04 (s, 3H), 3.89 (s, 3H), 2.18 - 2.13 (m, 1H), 2.08 - 2.05 (m, 3H), 1.72 (s, 3H),

1.70 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 160.6, 150.6, 144.9, 143.5, 142.1, 141.7, 135.2, 125.6, 119.9, 115.2, 114.4, 103.6, 70.3, 61.7, 60.4, 56.3, 39.7, 25.8, 21.07, 18.4, 16.3, -5.2. HRMS: m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{27}\text{H}_{40}\text{O}_6\text{Si}$: 489.17762; found: 489.17526.

7-[[*(2E,6Z)*-8-Hydroxy-3,7-dimethylocta-2,6-dien-1-yl]oxy]-6,8-dimethoxy-2*H*-chromen-2-one (2). To the stirred solution of compound **13** (0.3 g, 0.61 mmol) in dry THF (5 mL) was added TBAF (0.16 g, 0.61 mmol) slowly at 0 °C. The reaction mixture was allowed to stir for 2 h at r.t. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with sat. sodium bicarbonate and the aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (1:1) mixture to give **2** (0.17 g, 77%) as a yellow solid.

IR (neat): ν 3460, 3022, 1725, 1543, 1423, 1306, 1215, 1067, 982, 742 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 7.62 (d, 1H, $J = 9.6$ Hz), 6.66 (s, 1H), 6.35 (d, 1H, $J = 9.4$ Hz), 5.55 (t, 1H, $J = 7.3$, 7.24, 1.5 Hz), 5.24 (t, 1H, $J = 7.1$ Hz), 4.66 (d, 2H, $J = 7.2$ Hz), 4.10 (s, 2H), 4.03 (s, 3H), 3.89 (s, 3H), 2.16 (q, 2H, $J = 7.5$ Hz), 2.06 (t, 2H, $J = 7.3$ Hz), 1.78 (d, 3H, $J = 1.0$ Hz), 1.70 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 160.6, 150.6, 144.8, 143.5, 143.0, 142.1, 141.7, 134.9, 127.3, 120.1, 115.2, 114.5, 103.6, 70.1, 61.8, 61.5, 56.3, 39.6, 25.8, 21.2, 16.4. HRMS: m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{27}\text{O}_6$: 375.18022; found: 375.18177.

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Supplementary Material

^1H and ^{13}C NMR spectra of compounds **1**, **2**, **5**, **6**, **8-13** are available in the Supplementary Material File associated with this paper.

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