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Total synthesis of prenylated acylphloroglucinols: faberiones A, B, and E

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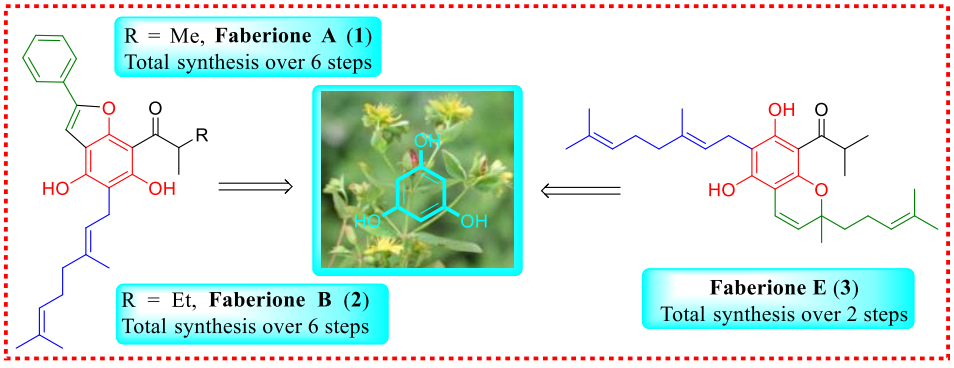
Abstract

The first total synthesis of acylphloroglucinol-based natural products faberiones A, B, and E is reported, which were isolated from *Hypericum faberi*. Total syntheses of faberiones A and B are accomplished in six linear steps from commercially accessible 1,3,5-trimethoxybenzene (methyl protected form of phloroglucinol) in overall yields of 31 and 33% respectively, *via* simple and straightforward approaches that include acylation, *o*-methoxy deprotection, selective iodination and tandem-Sonogashira cyclization followed by C-geranylation. Faberione E is achieved in two linear steps from acylphloroglucinol with an overall yield of 57% *via* geranylation followed by benzopyran formation reaction.



Keywords: Phloroglucinol, faberiones, natural products, geranylation, tandem-Sonogashira

Introduction

In the ancient past, natural products worked as a major source of drugs, and many of the pharmaceutical compounds today are derived from natural products.[1] They have been proven to be a noble source of biologically active compounds for centuries.[2] Varieties of plant materials have been traditionally used to make tea and tonics for the cure of illnesses by indigenous societies; plants also produce a great number of health-promoting products, such as minerals, proteins, vitamins, and many polyphenol derivatives like phloroglucinol.[3-5]

Phloroglucinol based natural products are a major class of secondary metabolites with various biological properties such as antimicrobial, anticancer, antiviral, antibacterial, anti-analgesic, etc.[6] They are widely present in various families like Guttiferae, Hypericaceae, Euphorbiaceae, Myrtaceae, Cannabinaceae, Aspidiaceae, Clusiaceae, Lauraceae, Fagaceae, etc.[5-7]

Recently, Gang Xu and coworkers isolated six new acylphloroglucinol based natural products faberiones A-F (**1-6**, Figure1) from the whole plant of *Hypericum faberi*. Out of these, faberiones A-D (**1**-**4**) considered as rare styrene substituted acylphloroglucinol based natural products. Faberione B (**2**) was found to be cytotoxically active against the pancreatic cell line (PANC-1) with IC_{50} value of 6.2 μM.[8]

Due to prominent biological properties and attractive skeleton of these natural products, we were prompted to explore the chemical synthesis of faberiones A, B and E. Herein, we describe efficient and straight forward approaches with good overall yields.

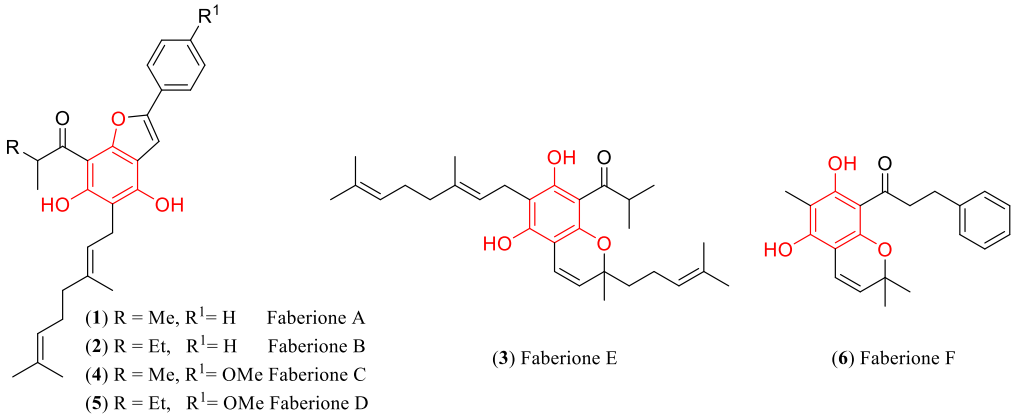
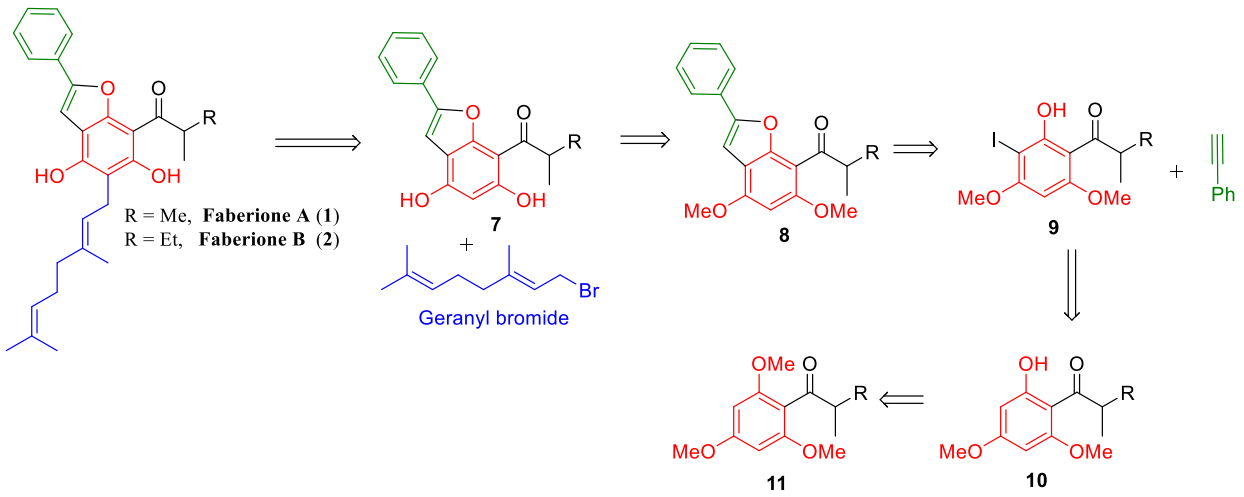


Figure 1. Structures of faberiones A-F (**1-6**).

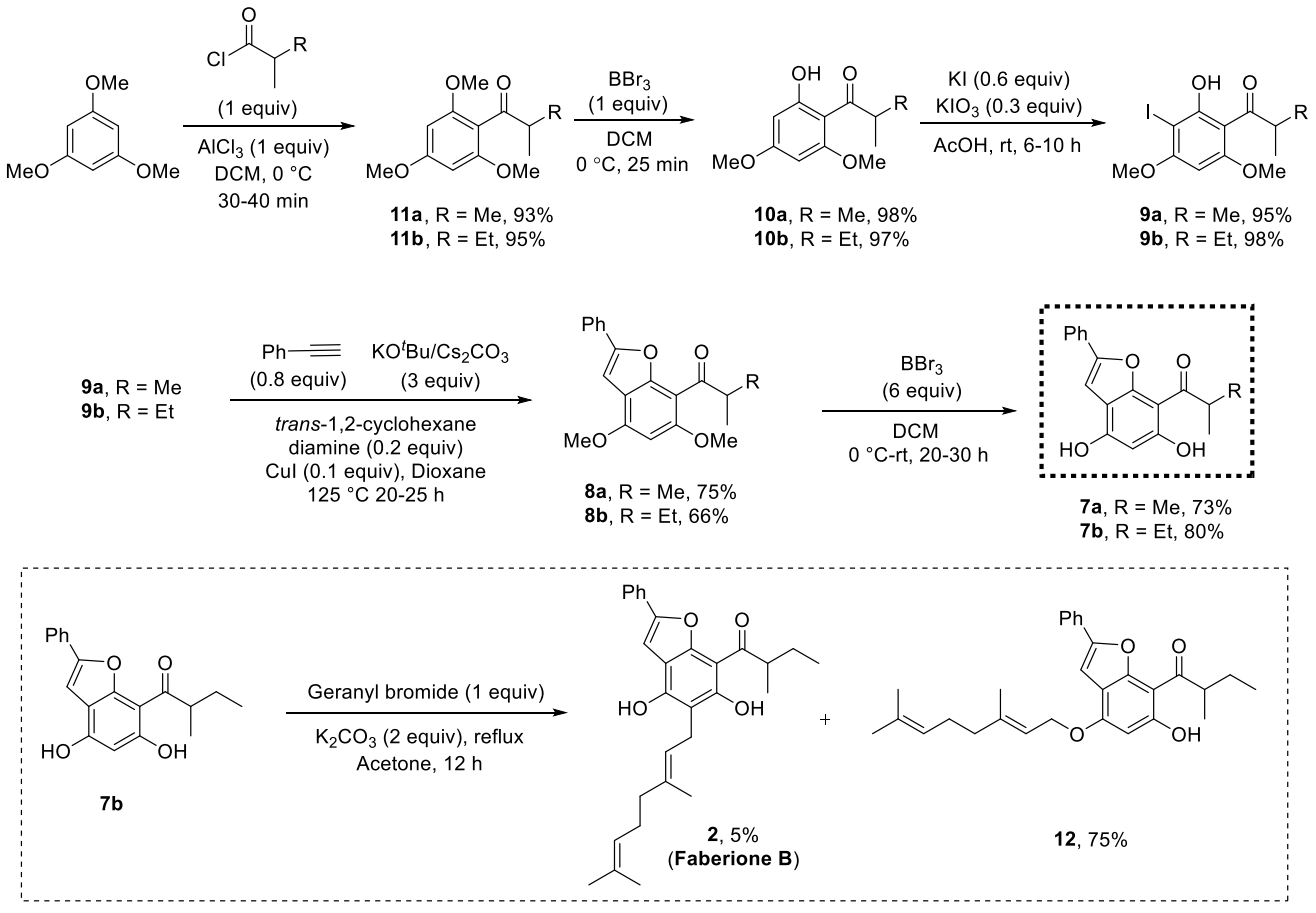
Results and Discussion

Retrosynthetic analysis of **1** and **2** is depicted in Scheme 1. Faberiones A and B could be achieved *via* C-geranylation of **7** and it was expected to be obtained from **8** by usual demethylation of aromatic methoxy groups. Polysubstituted benzofuran **8** could be derived from **9** by tandem Sonogashira cyclization with phenylacetylene. Compound **9** could be synthesized *via* selective iodination of **10**, which could be obtained by *ortho*-demethylation of **11**.



Scheme 1. Retrosynthetic analysis of faberiones A and B.

As shown in Scheme 2, we began our synthetic investigation toward faberiones A and B using commercially accessible 1,3,5-trimethoxybenzene (methyl protected form of phloroglucinol). Synthesis of compound **11a/11b** from 1,3,5-trimethoxybenzene *via* acylation in presence of isobutyryl or 2-methylbutanoyl chloride with $AlCl_3$ in DCM was accomplished in good yield (93/95%) by following reported protocol.[9,10]

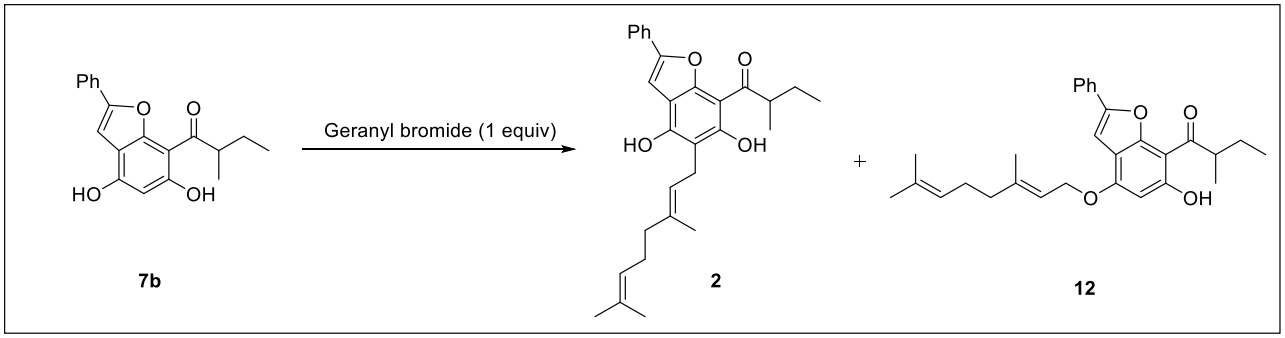


Scheme 2. Synthesis of compounds **7a** and **7b.**

The acylated product **11a/11b** was subjected to *ortho*-demethylation in presence of BBr_3 in DCM at 0 °C to give **10a/10b** in excellent yield (98/97%).[11.12] The selective iodination of **10a/10b** occurred using KI and KIO_3 in AcOH at room temperature to produce **9a/9b** in good yield (95/98%).[13,14] The polysubstituted benzofuran **8a/8b** was prepared in 75/64% yield *via* copper catalyzed tandem-Sonogashira reaction between **9a/9b** and phenylacetylene in dioxane as solvent at 125 °C (Scheme 2).[15]

Compound **8a/8b** was demethylated in presence of BBr_3 in DCM at 0 °C to room temperature to give **7a/7b** in 73/77% yield.[16,17] When **7b** was treated with geranyl bromide in presence of K_2CO_3 in acetone as solvent at reflux,[18] it was observed that reaction yielded two products **2** (faberione B) and **12** (Scheme 2). The desired product **2** was obtained in 5% while *O*-geranylation in 75% yields respectively. They were distinguished on the basis of ^1H and ^{13}C NMR spectra in which geranyl-CH_2 peak was observed at 3.54 ppm and 39.7 in case of **2**, due to C-C connectivity. However, O-C connectivity in product **12**, it was observed at 4.70 ppm and 65.7.
In order to get the C-alkylated product in good yield, we optimized geranylation reaction using compound **7b** with geranyl bromide to obtain C-alkylated compound as major product. When compound **7b** reacted with geranyl bromide in presence of K_2CO_3 (1 equiv) and acetone as solvent at room temperature, both C-alkylated **2** and O-alkylated **12** products were obtained in 12 and 35% yields respectively (Table 1, entry 1). Using 2.5 equivalents of K_2CO_3 at room temperature, yielded **2** and **12** in 41% and 15% yields (entry 2). When the solvent was switched to THF, improvement in the formation of **2** was observed (entry 3). With an effort to improve yield of **2**, other bases (LiOH, DBU and $Cs_2CO_{3)}$ were tried but unfortunately no significant result was observed with respect to yield of **2** (entries 4-6). The notable result was observed, when NaI (1 equiv) was used with K_2CO_3 (2.5 equiv) in THF at room temperature, yielded compound **2** in 70% due to *insitu* exchange of bromide by iodide as leaving group (entry 7). Moreover, excess NaI (2.5 equiv) also tested and **2** along with **12** were obtained in 62 and 7% yields respectively (entry 8).

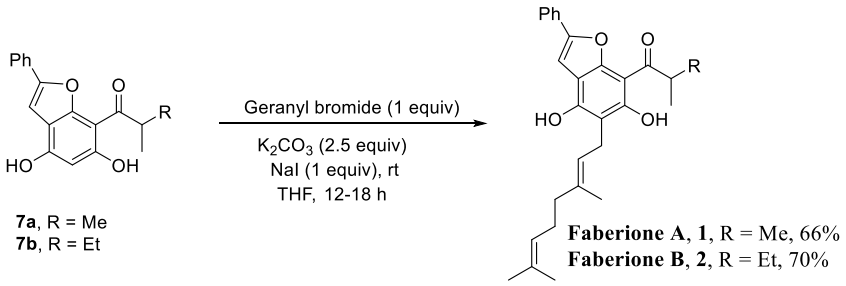
Table 1. Optimization for C-alkylation[a,b]



S.No	Base (equiv)	Solvents (dry)	Temperature	**2** (%)[b]	**12** (%)[b]
1	K_2CO_3 (1)	Acetone	rt	12	35
2	K_2CO_3 (2.5)	Acetone	rt	41	15
3	K_2CO_3 (2.5)	THF	rt to reflux	48	16
4	LiOH (1)	THF	rt	trace	18
5	DBU (2.5)	THF	rt	24	52
6	Cs_2CO_3 (2.5)	THF	rt	39	40
7	K_2CO_3 (2.5) + NaI (1)	THF	rt	70	trace
8	K_2CO_3 (2.5) + NaI (2.5)	THF	rt	62	7

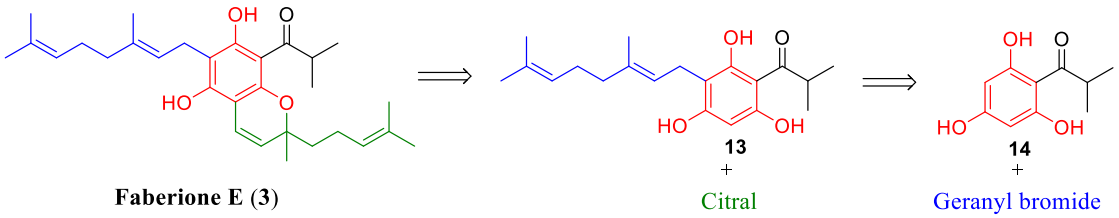
[a]Reaction conditions: **13** (0.15 mmol), Prenyl bromide (0.15), anhydrous solvents. [b]Isolated yield.

Among the optimized conditions, entry 7 was found to be best for the selective synthesis of C-alkylated product **2**. Using optimized conditions, biologically active natural products faberiones A and B were synthesized from **7a/7b** in 66 and 70% yields respectively (Scheme 3).



Scheme 3. Synthesis of faberiones A and B.

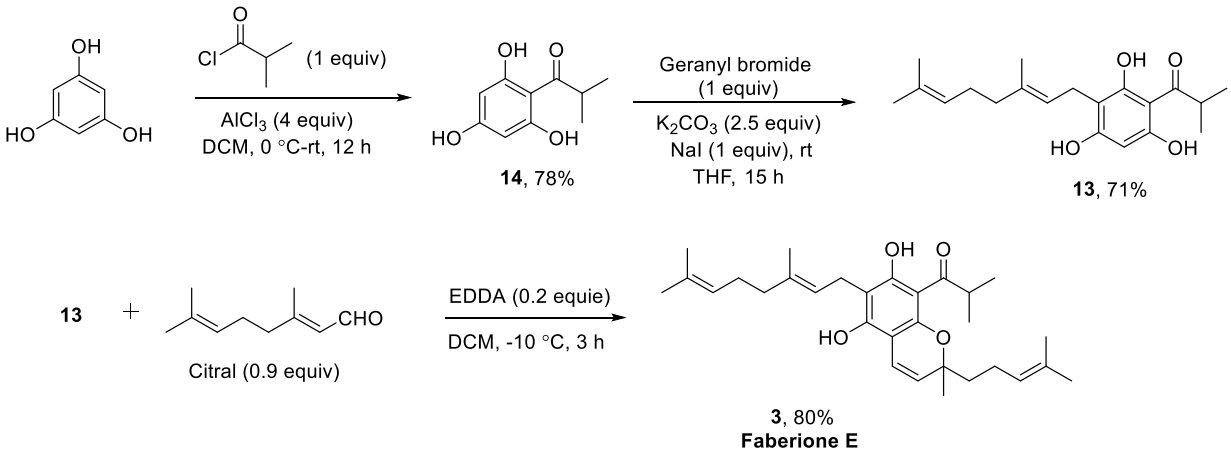
Retrosynthetic analysis of **3** is depicted in Scheme 4. Faberione E could be achieved from **13** *via* benzopyran formation with citral. Compound **13** could be derived from **14** by the geranylation of acylated phloroglucinol **14** (Scheme 4).



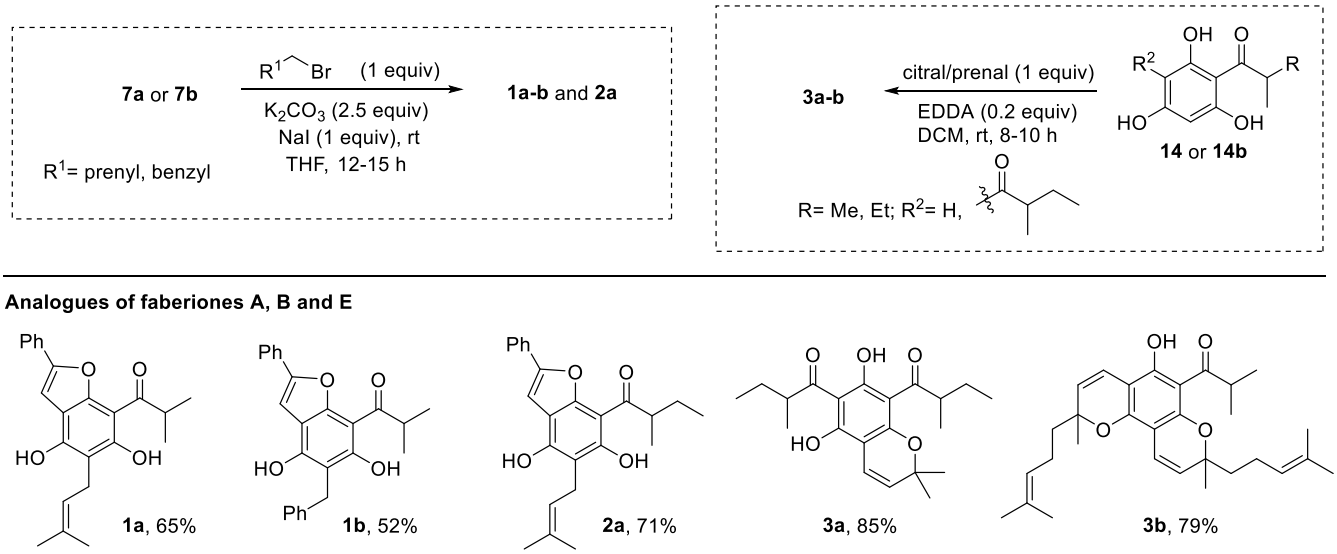
Scheme 4. Retrosynthetic analysis of faberione E.

As shown in Scheme 5, we commenced our synthetic investigation toward faberione E using commercially available phloroglucinol, which was converted to acylated phloroglucinol **14** in presence of $AlCl_3$ in 78% yield by following reported protocol.[19,20] Compound **13** was prepared by the geranylation of **14** using K_2CO_3/NaI with geranyl bromide in THF at room temperature. Then, compound **13** was subjected for the synthesis of faberione E *via* benzopyran ring formation in presence of citral and EDDA at room temperature.[21,22] Faberione E was obtained in overall yield of 57% (Scheme 5).

Due to interesting biological properties and attractive structures of faberiones A, B and E, we were interested in synthesizing their analogues. Here, **1a** and **1b** were synthesized *via* alkylation of **7a** and **2b** from **7b** using optimized condition. Derivatives **3a** and **3b** were prepared from **14** and **14b** by following benzopyran ring formation protocol (Scheme 6).



Scheme 5. Synthesis of faberione E.



Scheme 6. Synthesis of analogues of faberiones A, B and E.

Conclusions

In conclusion, we have accomplished the total synthesis of faberiones A, B six linear steps and E over two linear steps with overall yields of 31, 33 and 57% from commercially accessible starting materials. Five analogues of faberiones A, B and E were synthesized in moderate to good yields by following standard reaction conditions.

Experimental Section

General. All reactions were performed using oven-dried glassware. Commercial grade solvents and reagents were distilled before use. The reaction progress was examined by TLC by using silica gel GF 254 on a microscopic glass slide coated with silica gel. Melting points were recorded in open capillary tubes using

electrothermal melting point apparatus. Purification of products were carried out by flash chromatography using Merck silica gel with ethyl acetate and hexane solvent mixture as eluent. ^{1}H and ^{13}C NMR spectrum were recorded at ambient temperature using Bruker 400 and 600 MHz spectrometers. The samples were prepared by dissolving the compounds in $CDCl_3$/DMSO-D_6 and TMS as internal standard. Chemical shift (δ) in ppm and coupling constant (*J*) in Hz are reported. HRMS was recorded on an Agilent spectrometer using electrospray ionization (ESI-TOF).

Synthesis of 11a and 11b

To a stirred solution of 1,3,5-trimethoxybenzene (1equiv, 7.9 mmol) in DCM (15 ml) was added $AlCl_3$ (1 equiv, 7.9 mmol) followed by isobutyryl chloride/2-methylbutanoyl chloride (1 equiv, 7.9 mmol) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 30-40 min (monitored by TLC). The reaction mixture quenched by crushed ice and extracted by EtOAc (3 x 50 ml). The combined organic layers were washed by brine, dried over Na_2SO_4 and concentrated under reduce pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc:Hex) to give acylated products **11a/11b**.

Compound 11a. R_f = 0.40 (10% EtOAc:Hex, silica gel TLC). White solid in 93% (1.75gm) yield. MP= 61-63 °C. ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 6.11 (s, 2H), 3.82 (s, 3H), 3.76 (s, 6H), 3.01 (sept, *J* = 7.0 Hz, 1H), 1.12 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.7, 162.0, 158.0, 113.2, 92.9, 90.6, 55.7, 55.4, 42.1, 17.8. IR (Neat):2965, 1695, 1594, 1459, 1211, 1131,975 cm^{-1}. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd. for $C_{13}H_{18}NaO_4^+$ 261.1097, found 261.1111.

Compound 11b. R_f = 0.50 (10% EtOAc:Hex, silica gel TLC). Gummy liquid in 95% (1.89gm) yield. 1H NMR (600 MHz, CDCl3) *δ* 6.10 (s, 2H), 3.82 (s, 3H), 3.76 (s, 6H), 2.92 – 2.83 (m, 1H), 1.83 – 1.76 (m, 1H), 1.42 – 1.33 (m, 1H), 1.10 (d, J = 7.0 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.3, 162.0, 158.2, 113.6, 90.6, 55.7, 55.4, 48.9, 25.4, 15.1, 11.7. IR (Neat): 2961, 1694, 1596, 1458, 1211, 1132, 966, 814 cm^{-1}. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd. for $C_{14}H_{21}O_4^+$ 253.1434, found 253.1433.

Synthesis of 10a and 10b

To a stirred solution of **11a/11b** (1equiv, 6.3 mmol) in DCM (20 ml) was slowly added BBr_3 (0.9 equiv, 5.67 mmol) at 0 °C under nitrogen atmosphere and stirred for 25-30 min (monitored by TLC). The reaction mixture was quenched by crushed ice and extracted by DCM (3 x 50 ml). The combined organic layers were washed by brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc:Hex) to give **10a/10b**.

Compound 10a. R_f = 0.60 (10% EtOAc:Hex, silica gel TLC). Yellow liquid in 98% (1.39 gm) yield. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 14.08 (s, 1H), 6.07 (d, *J* = 2.4 Hz, 1H), 5.93 (d, *J* = 2.4 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.77 – 3.72 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3, 168.0, 165.7, 162.4, 105.1, 93.8, 90.9, 55.6, 55.5, 39.5, 19.2. IR (Neat): 2967, 1596, 1420, 1215, 1156, 1115, 823 cm^{-1}. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd. for $C_{12}H_{17}O_4^+$ 225.1121, found 225.1139.

Compound 10b. R_f = 0.70 (10% EtOAc:Hex, silica gel TLC). Yellow liquid in 97% (1.45 gm) yield. ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 14.14 (s, 1H), 6.07 (s, 1H), 5.93 (d, *J* = 2.3 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.65 – 3.56 (m, 1H), 1.84 – 1.76 (m, 1H), 1.42 – 1.34 (m, 1H), 1.14 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.0, 167.9, 165.7, 162.4, 105.6, 93.8, 90.9, 55.6, 55.5, 46.2, 27.0, 16.5, 12.0. IR (Neat): 2963, 1583, 1454, 1416, 1208, 1154, 1112, 821 cm^{-1}. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd. for $C_{13}H_{19}O_4^+$ 239.1278, found 239.1291.

Synthesis of 9a and 9b

To a stirred solution of **10a/10b** (1 equiv, 4.5 mmol) in acetic acid (15 ml) was added KI (0.66 equiv, 2.97 mmol) and KIO_3 (0.33 equiv, 1.48 mmol) followed by dil.HCl addition at room temperature under nitrogen atmosphere. The reaction mixture was stirred at room temperature up to completion of starting material (monitored by TLC). The reaction mixture filtered through vacuum filtration and provided **9a/9b**.

Compound 9a. R_f = 0.40 (10% EtOAc:Hex, silica gel TLC). Yellow solid in 95% (1.59 gm) yield. MP= 108-110 ^oC. ^1H NMR (600 MHz, $CDCl_3$) δ 14.84 (s, 1H), 6.02 (s, 1H), 3.95 (d, *J* = 6.3 Hz, 6H), 3.75 (sept, *J* = 6.7 Hz, 1H), 1.16 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.3, 165.2, 163.9, 163.6, 105.6, 86.8, 67.3, 56.4, 55.8, 39.6, 19.2. IR (Neat): 3488, 2939, 2666, 1616, 1561, 1409, 1219, 1129, 911, 790 cm^{-1}. HRMS (ESI-TOF) *m/z* $[M+NH_4]^+$ calcd. for $C_{12}H_{19}INO_4^+$ 368.0353, found 368.0324.

Compound 9b. R_f = 0.50 (10% EtOAc:Hex, silica gel TLC). Yellow solid in 98% (1.61 gm) yield. MP= 80-82 ^oC. ^1H NMR (600 MHz, $CDCl_3$) δ 14.90 (s, 1H), 6.02 (s, 1H), 3.95 (d, *J* = 2.7 Hz, 6H), 3.62-3.59 (m, 1H), 1.82-1.78 (m, 1H), 1.40-1.35 (m, 1H), 1.14 (d, *J* = 6.7 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.0, 165.1, 163., 163.6, 106.1, 86.8, 67.2, 56.4, 55.9, 46.3, 27.0, 16.5, 12.0. IR (Neat): 3448, 2957, 2874, 1620, 1557, 1403, 1218, 1126, 967, 786 cm^{-1}. HRMS (ESI-TOF) *m/z* $[M+2Na]^{2+}$ calcd. for $C_{13}H_{17}INaO_4^{2+}$ 204.9978, found 204.9973.

Synthesis of 8a and 8b

Compound **9a/9b** (1 equiv, 2.8 mmol), phenylacetylene (0.83 equiv, 2.32 mmol),KOtBu/Cs_2CO_3 (3 equiv, 8.4 mmol), trans-1,2- diaminocyclohexane (20 mol %), CuI (10mol %) and 1,4- dioxane (5 mL) were taken in a 50 mL sealed tube. The sealed tube was evacuated and backfilled with nitrogen. The reaction mixture was heated to 125 ^oC up to the completion of starting material (monitored by TLC). After the completion of SM, reaction mixture was quenched by water and extracted by EtOAc (3 x 50 ml). The combined organic layers were washed by brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc:Hex) to give **8a/8b**.

Compound 8a. R_f = 0.30 (10% EtOAc:Hex, silica gel TLC). Gummy yellow-brown in 75% (680 mg) yield. ^1H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.00 (s, 1H), 6.31 (s, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.57 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.24 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.5, 157.8, 155.2, 154.5, 154.2, 130.2, 128.8, 128.2, 124.4, 113.7, 108.0, 98.2, 90.7, 56.9, 55.7, 41.1, 18.5. IR (Neat): 2963, 1677, 1597, 1455, 1327, 1203, 1108, 756 cm^{-1}. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd. for $C_{20}H_{21}O_4^+$ 325.1434, found 325.1420.

Compound 8b. R_f = 0.40 (10% EtOAc:Hex, silica gel TLC). Gummy yellow in 66% (624 mg) yield. ^1H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.2 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.02 (s, 1H), 6.34 (s, 1H), 3.97 (s, 3H), 3.91 (s, 3H), 3.43 (h, *J* = 6.8 Hz, 1H), 1.93 – 1.84 (m, 1H), 1.54 – 1.46 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.0, 157.6, 155.1, 155.0, 154.2, 130.3, 128.8, 128.2, 124.5, 113.8, 108.7, 98.2, 90.8, 56.9, 55.7, 47.9, 26.4, 15.9, 11.8. IR (Neat): 2959, 1677, 1598, 1454, 1328, 1202, 1109, 754 cm^{-1}. HRMS (ESI-TOF) *m/z* $[M]^+$ calcd. for $C_{21}H_{22}O_4^+$ 338.1518, found 338.1502.

Synthesis of 7a and 7b

To a stirred solution of **8a/8b** (1 equiv, 1.2 mmol) in DCM (20 ml) was slowly added BBr_3 (6 equiv, 7.2 mmol) at 0 ^oC under nitrogen atmosphere and stirred for the complete conversion of starting material (monitored by TLC). After the completion of SM, reaction mixture was quenched by crushed ice and extracted by DCM (3 x 30 ml). The combined organic layers were washed by brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (30% EtOAc:Hex) to give **7a/7b**.

Compound 7a. R_f = 0.50 (30% EtOAc:Hex, silica gel TLC). Yellow solid in 73% (260 mg) yield. MP= 182-184 °C. ^{1}H NMR (400 MHz, $DMSO_6$) *δ* 13.64 (s, 1H), 11.53 (s, 1H), 7.81 (d, *J* = 8.1 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.39 (s, 1H), 7.35 (t, *J* = 6.9 Hz, 1H), 6.24 (s, 1H), 4.00 – 3.89 (m, 1H), 1.26 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $DMSO_6$) δ 206.9, 165.5, 158.91, 154.9, 153.3, 130.0, 129.6, 128.7, 124.2, 112.5, 100.3, 100.1, 98.5, 38.7, 19.2. IR (Neat): 2931, 2862, 1609, 1455, 1214, 1112, 819, 757 cm^{-1}. HRMS (ESI-TOF) *m/z* $[M+NH_4]^+$ calcd. for $C_{18}H_{20}NO_4^+$ 314.1387, found 314.1392.

Compound 7b. R_f = 0.60 (30% EtOAc:Hex, silica gel TLC). Yellow solid in 80% (298 mg) yield. MP= 160-162 °C. ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 14.05 (s, 1H), 7.72 (d, *J* = 7.3 Hz, 2H), 7.44 (t, *J* = 7.3 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.05 (s, 1H), 6.32 (s, 1H), 3.94-3.91 (m, 1H), 2.01-1.94 (m, 1H), 1.64 – 1.55 (m, 1H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.02 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.7, 165.3, 156.2, 155.2, 154.0, 130.0, 129.0, 128.3, 124.2, 112.2, 101.9, 98.9, 98.6, 45.5, 26.5, 16.3, 11.9. IR (Neat): 3287, 2968, 1610, 1414, 1209, 1152, 822, 753 cm^{-1}. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd. for $C_{19}H_{19}O_4^+$ 311.1278, found 311.1264.

Synthesis of 2 and 12

To a stirred solution of **7b** (1 equiv, 0.16 mmol) in acetone (2 ml) was added K_2CO_3 (2 equiv, 0.32 mmol) at room temperature then refluxed for 12 h. After the completion of SM (monitored by TLC), solvent evaporated on rota vapor then diluted by water and extracted by EtOAc (3 x 10 ml). The combined organic layers were washed by brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15% EtOAc:Hex) to give **2** and **12**.

Faberione B (2). R_f = 0.40 (15% EtOAc:Hex, silica gel TLC). Yellow gummy in 5% (3.8 mg) yield. ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 14.38 (s, 1H), 7.75 (d, *J* = 7.2 Hz, 2H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.03 (s, 1H), 6.76 (s, 1H), 5.36 (t, *J* = 7.3 Hz, 1H), 5.07 (t, *J* = 6.2 Hz, 1H), 3.96-3.99 (m, 1H), 3.54 (brd, *J* = 7.2 Hz, 2H), 2.14 (dd, *J* = 14.5, 5.7 Hz, 4H), 2.02-1.96 (m, 1H), 1.86 (s, 3H), 1.70 (s, 3H), 1.61 (s, 3H), 1.61-1.57 (m, 1H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.03 (t, *J* = 7.4 Hz, 3H). IR (Neat): 3363, 2966, 2920, 1606, 1416, 1220, 1112, 810, 753 cm^{-1}. HRMS (ESI-TOF) *m/z* $[M]^{2+}$ calcd. for $C_{29}H_{34}O_4^{2+}$ 223.1228, found 223.1230.

Compound 12. R_f = 0.70 (15% EtOAc:Hex, silica gel TLC). Yellow gummy in 75% (53.4 mg) yield. ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 13.95 (s, 1H), 7.74 – 7.71 (m, 2H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.07 (s, 1H), 6.30 (s, 1H), 5.54-5.52 (m, 1H), 5.12-5.09 (m, 1H), 4.70 (d, *J* = 6.6 Hz, 2H), 3.94 (dd, *J* = 13.4, 6.7 Hz, 1H), 2.18-2.09 (m, 5H), 2.00-1.95 (m, 1H), 1.77 (s, 3H), 1.68 (s, 3H), 1.62 (s, 3H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.2, 166.2, 158.5, 154.4, 153.6, 142.3, 132.0, 130.2, 128.9, 128.1, 124.0, 123.7, 118.4, 113.0, 101.7, 99.3, 96.0, 65.7, 45.5, 39.6, 26.5, 26.3, 25.7, 17.7, 16.8, 16.4, 12.0. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd. for $C_{29}H_{35}O_4^+$ 447.2530.

Synthesis of faberiones A and B

To a stirred solution of **7a/7b** (1 equiv, 0.15) in THF (2 ml) was added NaI (1 equiv, 0.15) followed by K_2CO_3 (2 equiv, 0.3) and stirred at room temperature. After the completion of SM (monitored by TLC), diluted by water and extracted by EtOAc (3 x 20 ml). The combined organic layers were washed by brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15% EtOAc:Hex) to give **1/2**.

Faberione A (1). R_f = 0.30 (15% EtOAc:Hex, silica gel TLC). Yellow gummy in 66% (43 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 14.28 (s, 1H), 7.75 (d, *J* = 7.4 Hz, 2H), 7.45 (t, *J* = 7.0 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.03 (s, 1H), 6.72 (s, 1H), 5.36 (t, *J* = 7.5 Hz, 1H), 5.06 (t, *J* = 5.4 Hz, 1H), 4.12 – 4.04 (m, 1H), 3.54 (d, *J* = 7.2 Hz, 2H), 2.20 – 2.07 (m, 4H), 1.86 (s, 3H), 1.70 (s, 3H), 1.61 (s, 3H), 1.37 (d, *J* = 6.8 Hz 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.6, 163.2, 155.3, 153.5, 153.5, 140.5, 132.4, 130.2, 129.0, 128.1, 124.1, 123.6, 121.5, 111.8, 108.3, 101.1, 98.6,

39.7, 38.9, 26.2, 25.8, 22.0, 19.0, 17.8, 16.3. IR (Neat): 3366, 2970, 2923, 1609, 1412, 1230, 1114, 757 cm^{-1}. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd. for $C_{28}H_{33}O_4^+$ 433.2373, found 433.2347.

Faberione B (2). R_f = 0.40 (15% EtOAc:Hex, silica gel TLC). Yellow gummy in 70% (47 mg) yield. ^1H NMR (600 MHz, $CDCl_3$) *δ* 14.38 (s, 1H), 7.75 (d, *J* = 7.2 Hz, 2H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.03 (s, 1H), 6.76 (s, 1H), 5.36 (t, *J* = 7.3 Hz, 1H), 5.07 (t, *J* = 6.2 Hz, 1H), 3.96-3.99 (m, 1H), 3.54 (brd, *J* = 7.2 Hz, 2H), 2.14 (dd, *J* = 14.5, 5.7 Hz, 4H), 2.02 – 1.96 (m, 1H), 1.86 (s, 3H), 1.70 (s, 3H), 1.61 (s, 3H), 1.61 – 1.57 (m, 1H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.03 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.5, 163.2, 155.3, 153.6, 153.5, 140.4, 132.4, 130.2, 128.9, 128.1, 124.1, 123.6, 121.5, 111.8, 108.4, 101.6, 98.6, 45.5, 39.7, 26.6, 26.2, 25.7, 22.0, 17.8, 16.6, 16.3, 12.0. IR (Neat): 3363, 2966, 2920, 1606, 1416, 1220, 1112, 810, 753 cm^{-1}. HRMS (ESI-TOF) *m/z* $[M]^{2+}$ calcd. for $C_{29}H_{34}O_4^{2+}$ 223.1228, found 223.1230.

Synthesis of 13

Compounds **14** and **14a** were prepared according to the literature protocol.[20-23] To a stirred solution of **14** (1 equiv, 2.5 mmol) in THF (2 ml) was added NaI (1 equiv, 2.5 mmol) followed by K_2CO_3 (2 equiv, 5.0 mmol) and stirred at room temperature. After the completion of SM (monitored by TLC), diluted by water and extracted by EtOAc (3 x 20 ml). The combined organic layers were washed by brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15% EtOAc:Hex) to give **13**.

Compound 13. R_f = 0.40 (15% EtOAc:Hex, silica gel TLC). Yellow gummy in 71% (590 mg) yield. ^1H NMR (600 MHz, $CDCl_3$) *δ* 6.38 (s, 1H), 5.87 (s, 1H), 5.25 (t, *J* = 7.7 Hz, 1H), 5.05 (t, *J* = 7.5 Hz, 1H), 3.91 (dt, *J* = 13.5, 6.7 Hz, 1H), 3.37 (d, *J* = 7.0 Hz, 2H), 2.13 – 2.06 (m, 4H), 1.81 (s, 3H), 1.67 (s, 3H), 1.59 (s, 3H), 1.18 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.0, 162.5, 160.9, 160.1, 140.0, 132.2, 123.6, 121.5, 105.7, 104.2, 95.5, 39.7, 39.3, 26.3, 25.7, 21.6, 19.3, 17.7, 16.2. IR (Neat): 3313, 2971, 2926, 1614, 1433, 1235, 825 cm^{-1}. HRMS (ESI-TOF) *m/z* $[M]^{2+}$ calcd. for $C_{20}H_{28}O_4^{2+}$ 166.0994, found 166.0975.

Synthesis of faberione E

To a stirred solution of **8** (1 equiv, 0.1 mmol) in DCM (2 ml) was added citral (0.9 equiv, 0.09 mmol) followed by EDDA (0.2 equiv, .2 mmol) and stirred at -10 °C. After the completion of SM (monitored by TLC), diluted by water and extracted by EtOAc (3 x 20 ml). The combined organic layers were washed by brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc:Hex) to give faberione E.

Faberione E (3). R_f = 0.55 (10% EtOAc:Hex, silica gel TLC). Yellow gummy in 80% (37.4 mg) yield. ^1H NMR (600 MHz, $CDCl_3$) *δ* 14.29 (s, 1H), 6.61 (d, *J* = 10.0 Hz, 1H), 6.34 (s, 1H), 5.40 (d, *J* = 10.0 Hz, 1H), 5.27 (t, *J* = 7.3 Hz, 1H), 5.11 (d, *J* = 7.2 Hz, 1H), 5.04 (t, *J* = 6.8 Hz, 1H), 3.91 (sept, *J* = 6.7 Hz, 1H), 3.41-3.39 (m, 2H), 2.17 – 2.06 (m, 6H), 1.85 (m, 1H), 1.82 (s, 3H), 1.68 (brs, 7H), 1.60 (s, 3H), 1.58 (s, 5H), 1.42 (s, 3H), 1.19 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.7, 163.4, 157.4, 154.9, 140.2, 132.4, 132.1, 123.8, 123.5, 123.2, 121.9, 117.3, 105.2, 104.7, 101.7, 80.5, 41.6, 39.7, 39.3, 26.5, 26.1, 25.72, 25.68, 23.2, 21.6, 19.7, 19.4, 17.74, 17.6, 16.1. IR (Neat): 3380, 2969, 2923, 1602, 1425, 1373, 1235, 1134, 881 cm^{-1}. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd. for $C_{30}H_{42}NaO_4^+$ 489.2975, found 489.3004.

Synthesis of 1a, 1b and 2b

To a stirred solution of **7a/7b** (1 equiv, 0.1 mmol) in THF (2 ml) was added NaI (1 equiv, 0.1 mmol) followed by K_2CO_3 (2 equiv, 0.2 mmol) and stirred at room temperature. After the completion of SM (monitored by TLC), diluted by water and extracted by EtOAc (3 x 20 ml). The combined organic layers were washed by brine, dried

over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15% EtOAc:Hex) to give **1a/1b/2a**.

Compound 1a. R_f = 0.35 (15% EtOAc:Hex, silica gel TLC). Yellow solid in 65% (24 mg) yield. MP= 158-160 °C. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 14.26 (s, 1H), 7.77 – 7.73 (m, 2H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.37 – 7.31 (m, 1H), 7.04 (s, 1H), 6.67 (s, 1H), 5.36 (t, *J* = 7.3 Hz, 1H), 4.08 (dt, *J* = 13.6, 6.8 Hz, 1H), 3.52 (d, *J* = 7.3 Hz, 2H), 1.88 (s, 3H), 1.81 (s, 3H), 1.36 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.6, 163.2, 155.0, 153.5, 136.7, 130.2, 129.0, 128.1, 124.1, 121.5, 111.7, 108.4, 101.1, 98.5, 38.9, 25.9, 22.0, 19.0, 18.0. IR (Neat): 3370, 2976, 2927, 1615, 1409, 1233, 1150, 1117, 757 cm^{-1}. HRMS (ESI-TOF) *m/z* $[M+2NH_4]^{2+}$ calcd. for $C_{23}H_{32}N_2O_4^{2+}$ 200.1175, found 200.1164.

Compound 1b. R_f = 0.30 (10% EtOAc:Hex, silica gel TLC). Pale yellow solid in 52% (20 mg) yield. MP= 188-190 °C. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 14.26 (s, 1H), 7.74 (d, *J* = 8.7 Hz, 2H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.38-7.26 (m, 5H), 7.23-7.21 (m, 1H), 7.01 (s, 1H), 5.80 (s, 1H), 4.14 (s, 2H), 4.13 – 4.04 (m, 1H), 1.38 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.72, 171.03, 163.55, 161.03, 153.81, 152.87, 139.40, 130.03, 129.01, 128.86, 128.34, 128.29, 126.61, 124.13, 111.49, 109.49, 98.15, 38.95, 28.31, 19.02. IR (Neat): 3366, 2973, 2928, 1613, 1229, 1116, 754, 696 cm^{-1}. HRMS (ESI-TOF) *m/z* $[M+NH_4]^+$ calcd. for $C_{25}H_{26}NO_4^+$ 404.1856, found 404.1826.

Compound 2a. R_f = 0.40 (15% EtOAc:Hex, silica gel TLC). Yellow solid in 71% (27 mg) yield. MP= 174-176 °C. ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 14.36 (s, 1H), 7.75 (d, *J* = 7.2 Hz, 2H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.04 (s, 1H), 6.69 (bs, 1H), 5.36 (t, *J* = 7.3 Hz, 1H), 4.00-3.94 (m, 1H), 3.53 (d, *J* = 7.3 Hz, 2H), 2.01 – 1.96 (m, 1H), 1.88 (s, 3H), 1.81 (s, 3H), 1.61 – 1.58 (m, 1H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.02 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.5, 163.3, 154.9, 153.6, 153.5, 136.5, 130.2, 128.9, 128.1, 124.1, 121.6, 111.7, 108.5, 101.7, 98.5, 45.5, 26.5, 25.82, 22.0, 18.0, 16.5, 11.2. IR (Neat): 3356, 3052, 2972, 1612, 1264, 730 cm^{-1}. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd. for $C_{24}H_{27}O_4^+$ 379.1904, found 379.1884.

Synthesis of 3a

To a stirred solution of **14a** (1 equiv, 0.1 mmol) in DCM (2 ml) was added prenal (1 equiv, 0.1 mmol) followed by EDDA (0.2 equiv, 0.2 mmol) at room temperature. After the completion of SM (monitored by TLC), diluted by water and extracted by EtOAc (3 x 20 ml). The combined organic layers were washed by brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc:Hex) to give **3a**.

Compound 3a. R_f = 0.40 (10% EtOAc:Hex, silica gel TLC). Yellow gummy in 85% (31.5 mg) yield. ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 15.29 (s, 1H), 6.67 (d, *J* = 10.0 Hz, 1H), 5.47 (d, *J* = 10.0 Hz, 1H), 3.83 (dd, *J* = 13.2, 6.4 Hz, 1H), 3.72 (dd, *J* = 13.5, 6.7 Hz, 1H), 1.90-1.81 (m, 2H), 1.53 (d, *J* = 5.7 Hz, 6H), 1.47 – 1.37 (m, 2H), 1.20 – 1.15 (m, 6H), 0.95 – 0.91 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.5, 210.8, 171.2, 167.0, 160.6, 124.1, 116.2, 104.3, 103.5, 101.5, 79.9, 46.1, 46.1, 28.3, 26.8, 26.8, 26.7, 17.0, 16.4, 12.0, 11.9. HRMS (ESI-TOF) *m/z* $[M+K]^+$ calcd. for $C_{21}H_{28}KO_5^+$ 399.1568, found 399.1622.

Synthesis of 3b

To a stirred solution of **14** (1 equiv, 0.1 mmol) in DCM (2 ml) was added citral (1 equiv, 0.1 mmol) followed by EDDA (0.2 equiv 0.2 mmol) at room temperature. After the completion of SM (monitored by TLC), diluted by water and extracted by EtOAc (3 x 20 ml). The combined organic layers were washed by brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10% EtOAc:Hex) to give **3b**.

Compound 3b. R_f = 0.50 (10% EtOAc:Hex, silica gel TLC). Yellow gummy in 79% (36.6 mg) yield. ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 14.17 (s, 1H), 6.70 (d, *J* = 10.1 Hz, 1H), 6.63 (d, *J* = 10.6 Hz, 1H), 5.42 – 5.37 (m, 2H), 5.09 (bs, 2H),

3.85 (dt, *J* = 13.5, 6.7 Hz, 1H), 2.16-2.08 (m, 4H), 1.90 – 1.81 (m, 1H), 1.75-1.72 (m, 1H), 1.69 – 1.64 (m, 8H), 1.57 (s, 3H), 1.56 (s, 3H), 1.43 (d, *J* = 2.2 Hz, 3H), 1.41 (d, *J* = 9.3 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.4, 161.1, 156.4, 155.0, 132.1, 131.8, 124.2, 123.9, 123.7, 123.1, 117.1, 116.8, 116.7, 104.4, 102.2, 101.6, 81.0, 80.5, 41.7, 39.3, 27.0, 26.9, 26.7, 25.7, 23.2, 22.6, 19.7, 19.6, 19.3, 17.6. IR (Neat): 2970, 2921, 1592, 1424, 1369, 1140, 889, 709 cm^{-1}. HRMS (ESI-TOF) *m/z* $[M+2H]^{2+}$ calcd. for $C_{30}H_{42}O_4^{2+}$ 233.1536, found 233.1536.

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Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra of all new compounds are given in the Supplementary Material file associated with this manuscript.

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