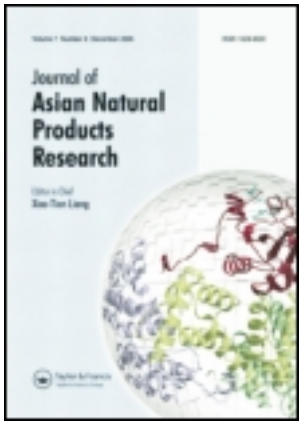

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Practical and efficient approach to the synthesis of guineensine

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A total synthesis of guineensine, a secondary metabolite of the Piperaceae family, has been executed in 12 steps with an overall yield of 27%. Key steps in the synthesis featured novel application of a Julia–Kocienski olefination reaction which effectively constructed alkenamide skeleton. This contributes a unique approach to the synthesis of the piperamide alkaloids.

Keywords: piper amide alkaloids; guineensine; Piperaceae family; Julia–Kocienski olefination; Corey–Fuchs reaction

1. Introduction

Plants of the Piperaceae family are widely distributed throughout tropical and subtropical regions. Piper species have been used in traditional medicinal systems for thousands of years, including the Chinese and the Indian systems of medicine [1]. For years, the chemistry of the Piper species has been widely investigated, and phytochemical studies from all over the world have resulted in the isolation of numerous structurally diverse amides with the wide range of bioactivities such as cytotoxic, stomach aches, insect repellents, anti-inflammatory, insecticidal, and anti-feedant activities [1]. Recently, Matsuda et al. [2] have isolated three new amide alkaloids from the roots of *Piper chaba* and assessed their hepatoprotective activity. Piperamides (alkenamides) share a common skeleton with conjugated linear chain attached both sides with various amides and aromatic ring, which has made them attractive synthetic targets for the last three decades [3]. Structurally, guineensine possesses a highly conjugated isobutyl amide group and an aromatic ring which are linked through a six carbon chain (Figure 1) [4].

The array of conjugated double bonds in a linear structure of **1** has provided us with a strong motive to investigate a novel strategy for an effective construction of the alkenamide core that will enable the synthesis of the diverse class of piperamides for the pharmacological screening. Syntheses of these compounds have generally involved in the construction of linear chain followed by amide formation via the condensation with the cyclic amines or acyclic amines. Recently, Rao et al. [5] have accomplished the first stereoselective synthesis of piperamides in which key reactions are the Wittig reaction, Sharpless asymmetric dihydroxylation, epoxidation, and a *trans*-regioselective opening of 2,3-epoxy alcohol. To date, only two syntheses of the guineensine have been reported,

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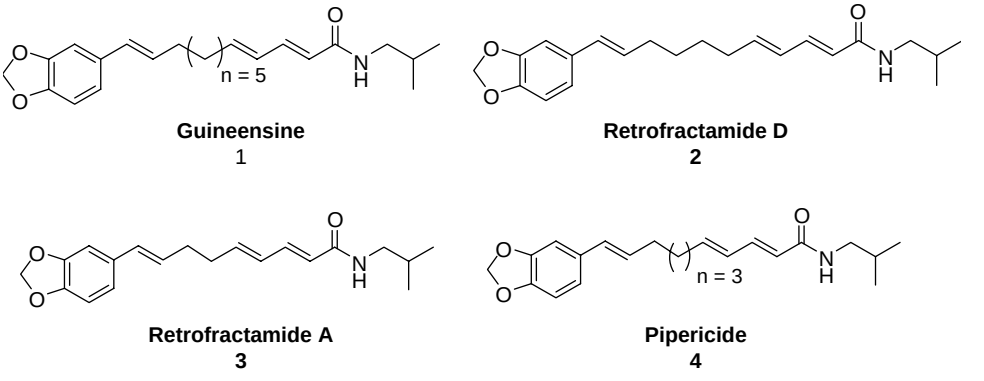


Figure 1. Representative alkenamides of Piperaceae family.

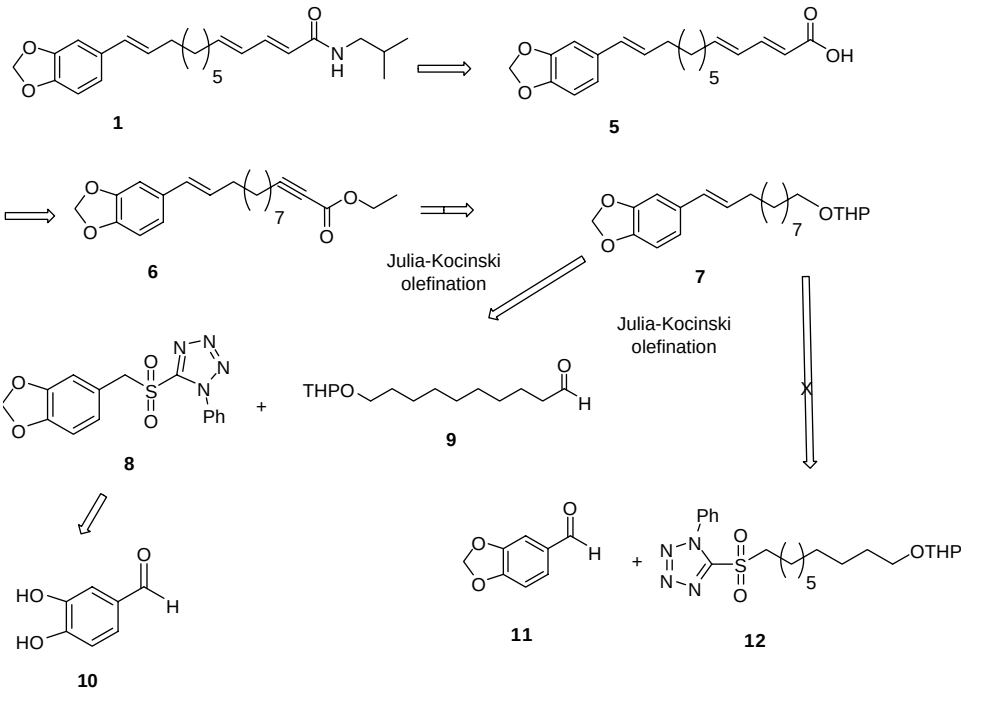
which also utilized the modified Wittig reaction as a key step [3,6]. Given the importance of these types of scaffolds, we were intrigued by the prospect of an alternative route to their synthesis.

During our continuing efforts in the synthesis of alkaloids of natural origin [7], we developed a new and efficient synthetic route to alkenamide skeleton using commercially available starting material, and then by taking advantage of the Julia–Kocienski olefination reaction as a key step, we realized the construction of alkenamide skeleton that represents the core structures of amide type alkaloids of Piperaceae family. In this paper, we report the approach for the construction of the alkenamide core followed by the total synthesis of guineensine (**1**).

2. Results and discussion

As outlined retrosynthetically in Scheme 1, initial disconnection of **1** revealed fragment **5**, which could be subjected to condensation with amine to realize the target molecule. The acid fragment **5**, in turn, was obtained from the key fragment **7** through sequential steps of the Swern oxidation, Corey–Fuchs reaction, and ester hydrolysis. To access the key fragment **7**, initially it was thought that basic alkenamide skeleton would arise from sulfone derivative of mono-THP-protected decanediol (**12**) and pipernal (**11**) via the Julia olefination reaction. Several attempts were made to prepare key fragment from pipernal (**11**) and to employ it as a potential intermediate, but, unfortunately, resulted the products in diminished yields (5–10%).

However, switching solvents and conducting the reaction with more equivalents of sulfone as well as pipernal in the presence of various bases (lithium bis (trimethylsilyl)azide (LHMDS), sodium bis(trimethylsilyl)amide (NaHMDS), lithium diisopropyl amide (LDA), and BuLi) also did not improve the reaction yields. Then, we turned our retrosynthetic strategy to realize that the key fragment was envisaged with the Julia–Kocienski olefination between sulfone derivative of the pipernal **11** and aldehyde **9**. Thus, our present total synthesis will be highlighted by the utilization of Julia olefination which directs the construction of the alkenamide core. More importantly, we have successfully implemented a strategy that minimizes protecting group manipulation in a unique fashion, a common and unavoidable practice in the synthesis of piperamide alkaloids that are reported earlier. The brevity of this analysis along with the structural simplicity of the precursors makes this route attractive for the implementation of the library synthesis of diverse Piperaceae family alkaloids for the

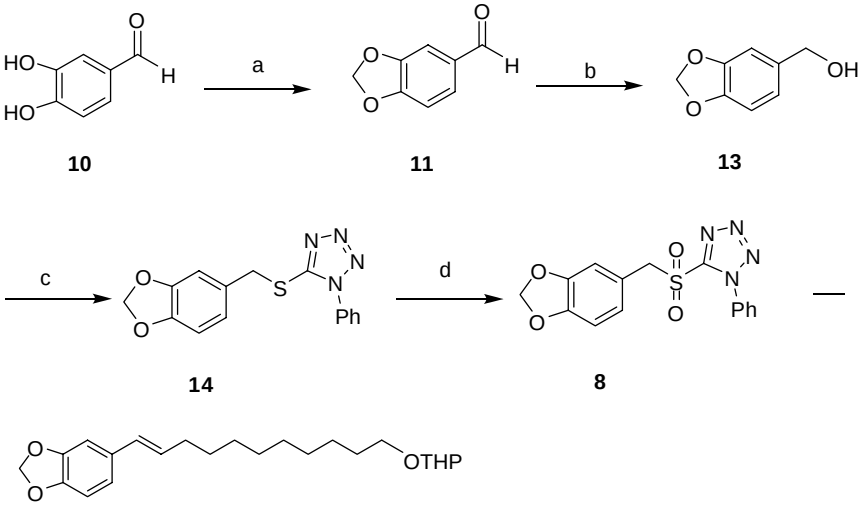


Scheme 1. Retrosynthetic analysis of guineensine.

biological screening and further structure–activity relationship studies.

The total synthesis based on the above-mentioned plan was initiated from commercially available 3,4-dihydroxy benzaldehyde **10** as a synthon. Thus, protection of the 3,4-hydroxyl groups with methylene iodide in the presence of K_2CO_3 in DMF gave its methylenedioxy-protected aldehyde as a pale yellow colored liquid **11** in 80% yield [8], which upon reduction with $NaBH_4$ in methanol led the corresponding alcohol **13** in 98% yield. Conversion of the alcohol **13** into corresponding thioether by Kocienski [9] procedure followed by the Mitsunobu-type reaction with diisopropyl azodicarboxylate, triphenylphosphine, and 1-phenyl-1*H*-tetrazol-5-thiol yielded **14** in 95% yield. Oxidation of **14** with ammonium heptamolybdate and H_2O_2 afforded sulfone derivative **8** with 80% yield. The sulfone **8** was further subjected to Kocienski-modified Julia olefination [10] reaction with the aldehyde **9**[1] in the presence of LiHDMS in dry tetrahydrofuran (THF) at −78°C to room temperature to give the key fragment **7** with the desired *E*-olefin predominately in modest yield (70% yield). The presence of two olefinic proton signals at δ 5.56–5.45 (dd, $J = 15.6$, 10.0 Hz) and 6.17 (d, $J = 15.8$ Hz) with the coupling constant of 15.6 Hz in 300 MHz, ^{1}H NMR spectrum also confirmed the *trans*-geometry of the newly generated double bond (Scheme 2).

Having achieved a reliable synthesis of key fragment **7** of alkenamide skeleton, we proceeded for the preparation of target compound guineensine (**1**). Accordingly, the THP group was removed under acidic conditions [11] using PTSA in MeOH to deliver alcohol **15** in 95%, which upon subjected to IBX [12] oxidation gave the corresponding aldehyde **16**. The modified Corey–Fuchs [13] homologation of aldehyde **16** followed by dibromomethylenation with CBr_4 and PPh_3 furnished the dibromo olefin **17** in essentially quantitative yield. Reaction of this material with *n*-BuLi



Scheme 2. Synthesis of key fragment **7**. Reagents and conditions: (a) CH_2I_2, K_2CO_3, DMF, reflux, 5 h, 80%; (b) $NaBH_4$, MeOH, 0°C, 15 min, 98%; (c) PPh_3, 1-phenyl-1*H*-tetrazol-5-thiol, di isopropylazodicarboxylate (DIAD), dry THF, rt, 0.5 h, 95%; (d) ammonium heptamolybdate tetrahydrate, EtOH, 0°C to rt, 7 h, 80%; (e) aldehyde **9**, LHMDS, THF, −78°C to rt, 12 h, 70%.

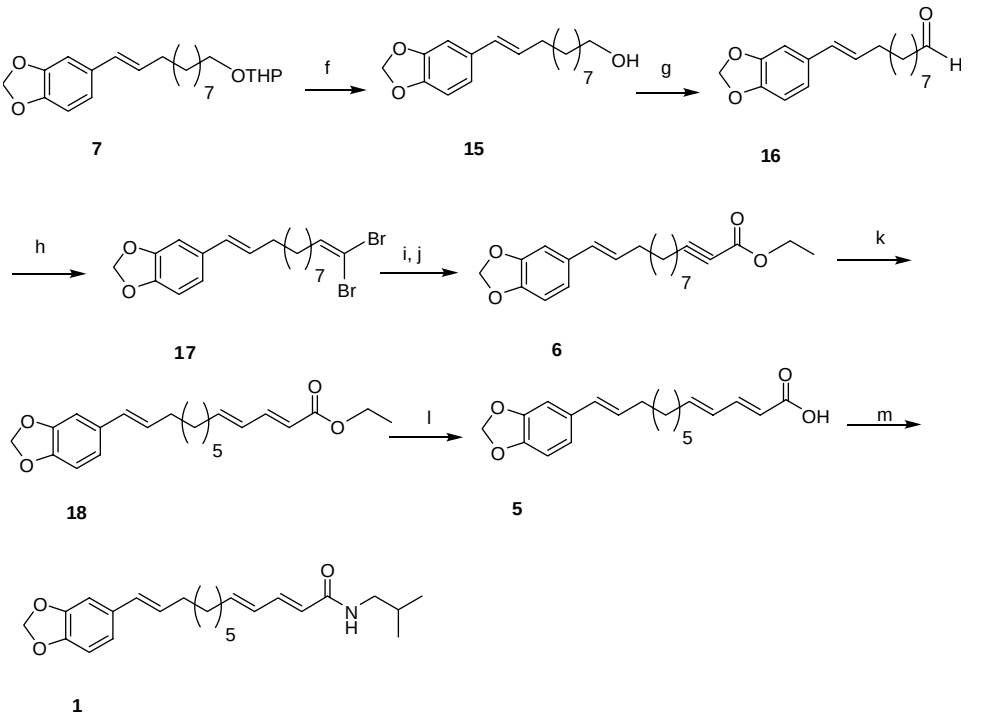
and quenching with chloroethylformate furnished alkynoate **6**. Exposure of alkynoate **6** to the Rychnovsky variant of the Trost isomerization [14], (Ph_3P/PhOH) yielded dienoate **18** in excellent yield (95%) with perfect double bond stereoselectivity. Finally, treatment of dienoate **18** to a mixture of aqueous LiOH and THF saponified the ethyl ester group to the corresponding carboxylic acid, followed by condensation [15] with isobutyl amine in the presence of EDC/HOBt system; guineensine **1** was successfully yielded. All the intermediate compounds including guineensine were well characterized by IR, NMR, and MS spectral data. The spectral data of synthetic guineensine were also comparable to the reported data for natural product [16]. Comparison of our physical and spectroscopic data with the published data confirmed our successful synthesis of guineensine.

In summary, the guineensine synthesis outlined in Schemes 2 and 3 proceeds in 12 simple steps from a commercially available starting material, with an overall yield of 27%. The general approach does, therefore, offer certain advantages over the previous synthesis of the guineensine and related alkenamides of Piperaceae family natural products. The synthesis appears to be general, and it should allow access to the preparation of a variety of structural analogs for investigation of pharmacological structure–activity relationships. In addition, it demonstrates that the formation of core can be accomplished via Julia–Kocienski olefination with reasonable yield, which will allow for facile modification of aliphatic chain. Studies directed toward the preparation of guineensine analogs and their evaluation as cytotoxic and aldose reductase inhibitors are currently underway and will be reported in due course.

3. Experimental

3.1 General experimental procedures

^1H and ^{13}C NMR spectra were recorded either in $CDCl_3$ or in MeOH-d^4 solvent on 300, 500, or 75 MHz spectrometer at ambient temperature. Chemical shifts δ are given in parts per million and coupling



Scheme 3. Synthesis of guineensine (**1**). Reagents and conditions: (f) PTSA, MeOH, 0°C, 45 min, 95%; (g) IBX, DMSO, THF, rt, 98%; (h) CBr_4, TPP, dry DCM, 0°C, 2 h, 95%; (i) *n*-BuLi, dry THF, −78°C; (j) chloroethyl formate, dry THF, −78°C, 2 h, 90%; (k) TPP, phenol, benzene, reflux, 95%; (l) LiOH, THF/H_2O, rt, 12 h, 96%; (m) EDC, HOBt, isobutyl amine, DCM, 0°C to rt, 8 h, 90%.

constants *J* are given in Hertz. The chemical shifts are reported in parts per million on scale downfield from TMS as internal standard and signal patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; br s, broad singlet. FT-IR spectra were recorded as thin films on KBr or neat. For MS and HR-MS, *m/z* ratios are reported as values in atomic mass units. All the reagents and solvents were reagent grade and were used without further purification unless specified otherwise. Technical grade ethyl acetate and hexane used for column chromatography were distilled prior to use. THF when used as solvent for the reactions was freshly distilled from sodium benzophenone ketyl. Column chromatography was carried out using silica gel (60–120 and 100–200 mesh) packed in glass columns. All the reactions were performed under an atmosphere of nitrogen in flame or oven-dried glassware with magnetic stirring.

3.2 Spectral data

3.2.1 Compound 7

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.75–6.65 (3H, m), 6.17 (1H, d, $J = 15.8$ Hz), 5.93 (2H, s), 5.56–5.45 (1H, dd, $J = 15.8$, 10 Hz), 4.54 (1H, t, $J = 3.02$ Hz), 3.86–3.76 (1H, m), 3.73–3.62 (1H, m), 3.50–3.41 (1H, m), 3.36–3.27 (1H, m), 2.33–2.23 (2H, m), 1.72–1.39 (8H, m), 1.33–1.24 (12H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4, 146.1, 131.8, 129.7, 128.7, 122.3, 120.2, 109.0, 108.0, 100.6, 67.2, 61.2, 30.7, 30.0, 29.8, 29.6, 29.6, 29.4, 26.4, 25.7, 19.4; ESI-MS: *m/z* 397.2 $[M + Na]^+$. HR-ESI-MS: *m/z* 397.2316 $[M + Na]^+$ (calcd for $C_{23}H_{34}O_4Na$, 397.2355).

3.2.2 Compound **6**

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.87–6.65 (3H, m), 6.23 (1H, d, $J = 16.3$ Hz), 6.01–5.92 (1H, m), 5.90 (2H, s), 4.18 (2H, q, $J = 6.7$, 14.4 Hz), 2.34–2.25 (2H, m), 2.19–2.12 (2H, m), 1.47–1.27 (12H, m), 0.92 (3H, t, $J = 6.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.1, 148.0, 146.2, 131.7, 129.9, 128.8, 122.4, 120.3, 109.1, 108.2, 108.1, 100.6, 88.2, 73.8, 61.2, 33.1, 30.1, 29.6, 29.3, 27.7, 18.8, 14.3; ESI-MS: *m/z* 357.2042 $[M + H]^+$. HR-ESI-MS: *m/z* 357.2042 $[M + H]^+$ (calcd for $C_{22}H_{29}O_4$, 357.2066).

3.2.3 Compound **5**

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.25 (1H, m), 6.83 (1H s), 6.74–6.66 (2H, m), 6.30–6.10 (3H, m), 6.04–5.90 (3H, m), 5.75 (1H, d, $J = 15.8$ Hz), 2.23–2.10 (4H, m), 1.50–1.27 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 148.0, 147.7, 146.3, 142.7, 132.1, 129.2, 128.8, 128.2, 121.8, 120.1, 119.02, 108.0, 105.1, 100.7, 35.4, 32.7, 30.0, 29.5, 29.2, 28.9, 28.5, 27.4; ESI-MS: *m/z* 329.1701 [M + H]. HR-ESI-MS: *m/z* 329.1701 [M + H] (calcd for $C_{20}H_{25}O_4$, 329.1753).

3.2.4 Compound **14**

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (1H, d, $J = 8.0$ Hz), 7.50 (2H, m), 7.35 (1H, d, $J = 7.8$ Hz), 7.40 (3H, m), 6.89 (1H, s), 5.89 (2H, s), 4.50 (2H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.02, 148.2, 147.8, 136.8, 134.2, 128.5 (2C), 127.8, 124.6 (2C), 120.1, 112.6, 112.0, 100.8, 35.8. ESI-MS: *m/z* 313.2 $[M + H]^+$. HR-ESI-MS: *m/z* 313.0712 $[M + H]^+$ (calcd for $C_{15}H_{13}N_4O_2S$, 313.0759).

3.2.5 Compound **8**

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (1H, d, $J = 8.0$ Hz), 7.53–7.50 (2H, m), 7.30 (1H, d, $J = 7.8$ Hz), 7.40–7.36 (3H, m), 6.70 (1H, s), 5.89 (2H, s), 5.29 (2H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.2, 147.6, 130.1, 128.7 (3C), 128.5, 126.8 (2C), 126.0, 124.6, 112.6, 112.0, 100.8, 62.4. ESI-MS: *m/z* 345.1 $[M + H]^+$. HR-ESI-MS: *m/z* 345.0650 [M + H] (calcd for $C_{15}H_{13}N_4O_4S$, 345.0658).

3.2.6 Compound **15**

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13 (1H, s), 6.83 (1H, d, $J = 4.0$ Hz), 6.72 (1H, d, $J = 4.0$ Hz), 6.68 (1H, d, $J = 8$ Hz), 5.98 (1H, d, $J = 8.0$ Hz), 5.91 (2H, s), 3.60 (2H, t, $J = 6.8$, 12.8 Hz), 2.28 (1H, m), 2.15–2.10 (2H, m), 1.54–1.56 (2H, m), 1.43–1.42 (2H, m), 1.30–1.32 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.8, 147.6, 133.0, 126.8, 126.6, 120.8, 110.1, 109.2, 101.0, 62.0, 34.8, 32.0, 29.7, 29.3 (2C), 22.0 (2C), 25.4. ESI-MS: *m/z* 291.0 $[M + H]^+$. HR-ESI-MS: *m/z* 291.1942 $[M + H]^+$ (calcd for $C_{18}H_{27}O_3$, 291.1960).

3.2.7 Compound **16**

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.72 (1H, s), 7.20 (1H, s), 7.08 (1H, d, $J = 4.0$ Hz), 6.96 (1H, d, $J = 4.0$ Hz), 6.62 (1H, d, $J = 8$ Hz), 6.04 (1H, d, $J = 8$ Hz), 5.91 (2H, s), 2.39–2.42 (2H, m), 2.21–2.24 (4H, m), 1.30–1.36 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.1, 147.8, 147.6, 143.5, 133.0, 126.8, 126.6, 120.8, 110.1, 109.2, 101.0, 34.8, 32.0, 29.7, 29.3 (2C), 28.1, 28.0. ESI-MS: *m/z* 289.0 $[M + H]^+$. HR-ESI-MS: *m/z* 289.1809 $[M + H]^+$ (calcd for $C_{18}H_{25}O_3$, 289.1804).

3.2.8 Compound **17**

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.83 (1H, s), 6.68–6.70 (2H, m), 6.23 (1H, d, $J = 6.0$ Hz), 6.40–6.35 (1H, m), 5.94–6.00 (1H, m), 5.91 (2H, s), 2.16–2.20 (2H, m), 2.09–2.10 (2H, m), 1.43–1.50 (4H, m), 1.33–1.36 (8H, m). ESI-MS: *m/z* 444.7 $[M + H]^+$. ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.2, 148.0, 138.2, 133.0,

132.6, 127.2, 119.7, 101.2, 95.8, 34.8, 29.7 (2C), 29.6 (2C), 29.0 (2C), 28.0, 27.3, 24.1. ESI-MS: *m/z* 444.7 $[M^+ + 2]$. HR-ESI-MS: *m/z* 444.0362 [M + 2] (calcd for $C_{19}H_{26}Br_2O_2$, 444.0300).

3.2.9 Compound **18**

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (1H, dd, $J = 4.0$, 2.5 Hz), 6.83 (1H, s), 6.71 (1H, d, $J = 2.5$ Hz), 6.68 (1H, d, $J = 2.5$ Hz), 5.98–6.0 (2H, m), 5.92 (2H, s), 6.10–6.18 (2H, m), 5.72 (1H, d, $J = 4.8$ Hz), 4.18–4.20 (2H, m), 2.16–2.19 (4H, m), 1.29–1.32 (8H, m), 0.90 (3H, t, $J = 4.6$, 2.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2, 148.2, 148.0, 145.0, 135.0, 133.1, 128.3, 127.0, 124.6, 119.2, 110.6, 108.2, 105.0, 101.2, 61.4, 30.0, 29.9, 29.7 (2C), 29.0 (2C), 14.7. ESI-MS: *m/z* 357.0 $[M + H]^+$. HR-ESI-MS: *m/z* 357.2053 $[M + H]^+$ (calcd for $C_{22}H_{29}O_4$, 357.2066).

3.2.10 Compound **1**

mp 119°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14 (1H, dd, $J = 14.7$, 9.9 Hz), 6.84 (2H, br s), 6.74–6.75 (2H, m), 6.27 (1H, d, $J = 15.9$ Hz), 6.06–6.04 (2H, m), 5.93 (2H, s), 5.73 (1H, d, $J = 15.9$ Hz), 3.15 (2H, dd, $J = 6.6$ Hz), 2.14–1.16 (4H, m), 1.76–1.79 (1H, m), 1.4–1.5 (2H, m), 1.25–1.4 (4H, m), 0.92 (6H, d, $J = 6.6$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 147.8, 146.4, 143.0, 141.2, 132.4, 129.2, 128.2, 121.7, 120.1, 120.0, 108.1, 105.3, 100.8, 46.8, 32.8, 32.7, 30.2, 29.2, 28.9, 28.6, 28.5, 20.2; ESI-MS: *m/z* 384 $[M + H]^+$.

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Note

1. The aldehyde **9** was prepared from commercially available decanediol, in which one of the hydroxyl group was selectively protected as a THP ether (dihydropyran, PTSA, DCM, rt, 3 h) and the resultant THP ether was subjected to Swern oxidation condition.

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