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Short communication

Syntheses and biological evaluation of C-3′-N-acyl modified taxane analogues from 1-deoxybaccatin-VI

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ABSTRACT

A series of side-chain modified taxane analogues were synthesized and their *in vitro* anticancer activities against four human cancer cell lines: MDA-MB-231 (human breast cancer), PC-3 (human prostatic cancer), HepG2 and H460 (human hepatoma) were studied. The three hydroxyl groups at C-7, C-9 and C-10 enable the behavior of these compounds to be evidently distinct from other similar compounds. The strong cytotoxicity in the four cell lines showed by the newly synthesized taxane analogues **13a** and **13d** indicated them as potential lead compounds for anticancer drug design.

1. Introduction

Paclitaxel **1** (**Fig. 1**), a diterpenoid natural compound was isolated from the stem bark of *Taxus brevifolia*, has preeminent antitumor activities against a range of cancers, including breast, ovarian, germ cell, lung and esophageal cancers [1–5]. The activity is believed to be related to its binding to polymerize tubulin, to promote microtubule assembly and to stabilize microtubule by bundle formation [6]. Numerous structure-activity-relationship studies (SARs) indicated that the C-13 side chain is an indispensable part for its antitumor activity, Ojima et al. synthesized a variety of C-3′-N-acyl modified paclitaxel analogues by employing β-lactam four-membered ring which can be coupled to baccatin III through coupling reaction as a side chain precursor to produce paclitaxel analogues. Respectively, these C-3′-N-acyl (2-furyl, 2-thienyl, p-fluorophrnyl and p-methoxyphenyl) modified paclitaxel analogues exhibited similar or lower IC_{50} comparing with paclitaxel against J774.1 and J7.DEF3 [7–9]. The structure-activity-relationship studies (SARs) also showed that the 1-hydroxyl group is not crucial for the tubulin assembly activities of paclitaxel [10–13].

Starting from 1-deoxybaccatin-VI **3** (**Fig. 1**), which is readily available from *Taxus chinensis*, *Rehd. Var. mairei* in good yield [14,15], Kingston synthesized several 1-deoxybaccatin-VI analogues and reported that compound **4** (**Fig. 1**) (IC_{50} = 0.0315 μM) had an IC_{50} value 11-fold greater than that of paclitaxel (IC_{50} = 0.0028 μM) in the HCT116 cell line evaluated [16]. In our previous study, we also presented the detailed design and synthesis of 1-deoxypaclitaxel [17]; in the A549 cell line evaluated by us 1-deoxypaclitaxel **5** (Fig. 1) (IC50 = 0.062 μM) had an IC_{50} value 10-fold greater than that of paclitaxel (IC50 = 0.0063 μM). According to the two studies, both of the two compounds indicated a significant loss in cytotoxicity. However, in our further investigation of 1-deoxypaclitaxel analogues [18], we discovered that compound **6** (Fig. 1) (IC_{50} = 0.11 ng/mL) had the same IC_{50} value as that of paclitaxel (IC_{50} = 0.13 ng/mL) in the A2780 cell line evaluated, while this compound (IC_{50} = 0.18 ng/mL) even had an IC_{50} value 1.6-fold lower than that of paclitaxel (IC_{50} = 0.29 ng/mL) in the A549 cell line evaluated. Compared to the compound **4** and 1-deoxypaclitaxel **5**, compound **6** is structurally distinctive due to the three hydroxyls at the C-7, C-9 and C-10 positions.

As an ongoing part of our research on 1-deoxypaclitaxel analogues [17,18], we have become interested in developing the syntheses and biological activities of a series of 1-deoxypaclitaxel analogues bearing different substituted groups at the C-3′-N-Acyl position and three hydroxyls at the C-7, C-9 and C-10 positions from 1-deoxybaccatin VI. The activities of these newly synthesized compounds against four cancer cell lines and cell survival data are reported in this paper.

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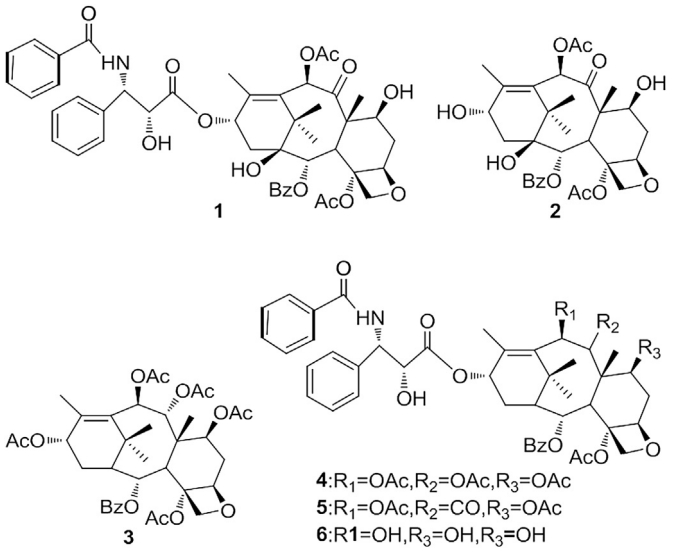


Fig. 1. Paclitaxel and 1-deoxybaccatin III analogues.

2. Results and discussion

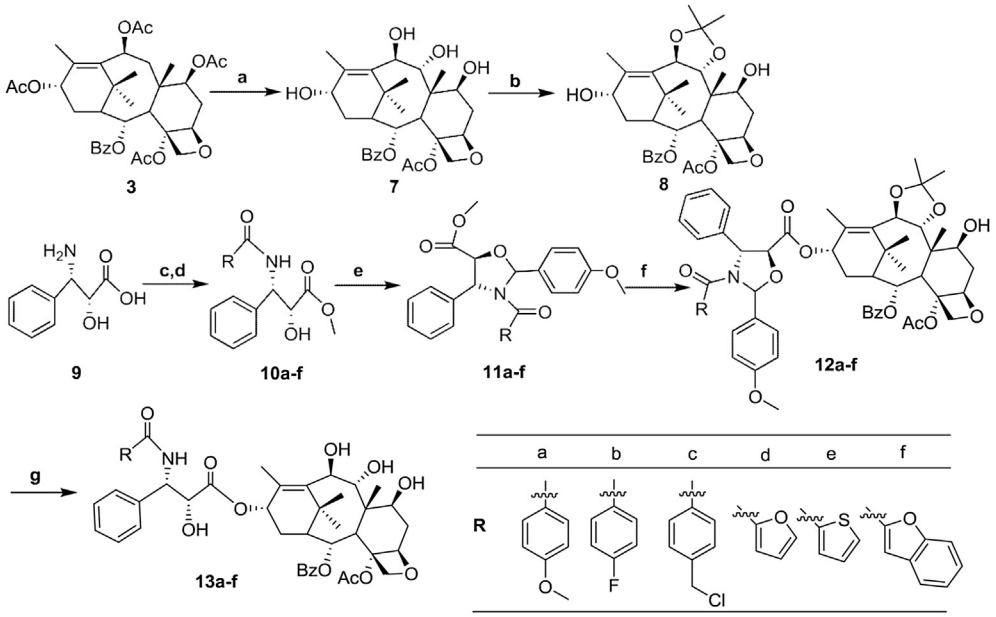
2.1. Chemistry

As previously reported, paclitaxel side chains were synthesized by different methods [19–26]. In this study, we applied the method which was recently described by Yoshio Hayashi et al. [25,26] to synthesize the oxazoline side chain precursor by using (2R,3S)-3-Phenylisoserine **9** with natural configuration (Scheme 1).

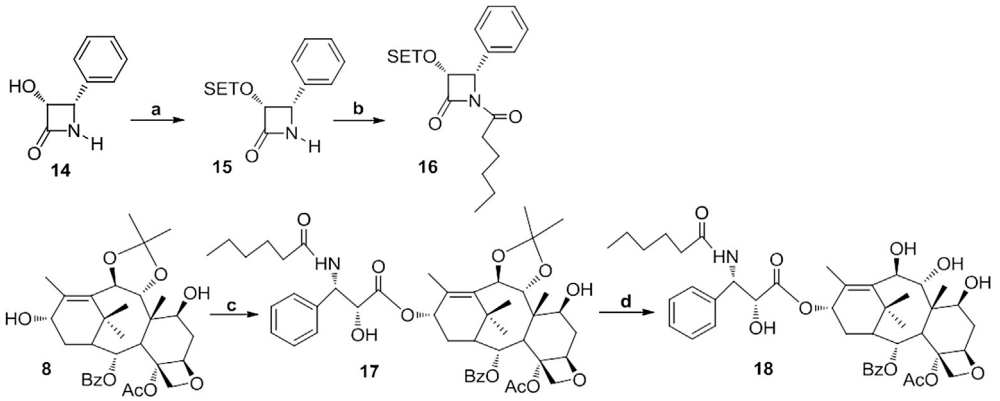
The synthesis of compounds **13a-f** is shown in Scheme 1. The starting material 1-deoxybaccatin VI **3** was selectively deacetylated at the C-7, C-9, C-10 and C-13 acetoxyl groups without concomitant deacylation of the C-2 and C-4 acyloxy groups. Subsequent protection of the C-9 and C-10 hydroxyl groups using 2,2-dimethoxypropane gave compound **8**, in which only two hydroxyls remained at the C-7 and C-13 positions after deprotection. However, the C-13 hydroxyl group is more active compared with the C-7 hydroxyl group due to the huge stereo-hindrance effect on the C-7 hydroxyl group caused by the acetal protection at the C-9 and C-10 positions. Therefore, the corresponding carboxylic acid can be immediately coupled with compound **8** by the DDC-DMAP method in toluene.

The key step is the synthesis of the corresponding carboxylic acid, starting from commercially available material (2R,3S)-3-Phenylisoserine **9** with natural configuration as outlined in Scheme 1. Compound **9** was first transformed into **10a-f** after protection of the amine moiety by the acyl chloride and formation of the methyl ester. The next cyclic protection used 4-methoxy benzaldehyde dimethyl acetal in the presence of a catalytic amount of pyridinium p-toluenesulfonate (PPTS), yielding compounds **11a-f**. Compounds **11a-f**, after saponification to the corresponding carboxylic acid without further purification, were then coupled with compound **8** in the present of DCC and DMAP to smoothly provide the corresponding cyclic ester intermediates **12a-f** with good to excellent yield (80–91%). After hydrolysis of the two acetonide protecting groups under strongly acidic conditions, the final products **13a-f** were afforded (Scheme 2).

Further investigation of the modification of the side chain revealed it is difficult to modify the C-3-N'-acyl position using the corresponding alkanoic acid, such as n-hexylic and n-butyric acid, through the DDC-DMAP coupling method. However, the novel taxoid bearing a n-hexane group at the C-3-N′-Acyl position was reported to exhibit excellent antitumor activities [27], which interested us in the design and synthesis of n-hexanoyl-modified 1-deoxypaclitaxel analogues via a β-lactam four-membered ring-opening coupling protocol [28–32]. The synthesis of the compound **18** is illustrated in Scheme 2. Starting from the commercially available β-lactam **14** with high enantiomeric purity, protection of the hydroxyl group of β-lactam **14** at low temperature as a triethylsilyl (TES) ether afforded 3-OTES-β-lactam **15** in 76% yield. Treatment of 3-OTES-β-lactam **15** with n-hexanoyl chloride in



Scheme 1. Reagents and conditions: (a) $NH_2NH_2 \cdot H_2O$, EtOH, rt, 82%; (b) 2,2-dimethoxypropane, montmorillonite K10, CH_2Cl_2, rt, 97%; (c) $SOCl_2$, MeOH, 0 °C to rt, overnight; (d) carbonyl chloride, THF, sat. $NaHCO_3$, 0 °C to rt, 3 h; (e) 4-methoxybenzaldehyde dimethyl acetal, PPTS, toluene, 110 °C, 90%; (f) (1) KOH, MeOH, rt, 2 h; (2) DCC, DMAP, CH_2Cl_2, 50 °C, 2 h; (g) PTS, MeOH, rt, 5 h, 20–30%.



Scheme 2. Reagents and conditions: (a) TESCl, imidazole, CH_2Cl_2, 0 °C to rt, 87%; (b) NEt_3, RCOCl, CH_2Cl_2, 0 °C to rt, 65%; (c) **16**, NaHMDS, THF, −30 °C; then 0.04 N HCl, CH_3OH, rt, 50%; (d) 0.04 N HCl, CH_3OH, 60 °C, 92%.

dichloromethane for 2 h at room temperature afforded N-hexanoyl-β-lactam **16**. The coupling of compound **8** with N-hexanoyl-β-lactam **16** was carried out under standard conditions using LiHMDS in THF at −40 °C, followed by deprotection with 0.3 N HCl/CH_3OH, to afford the corresponding new taxoid **17** (Scheme 2). Finally, compound **17** was treated with 0.3 N HCl at 60 °C for 6 h to obtain product **18**.

To compare with these compounds **13a-f**, **17** and **18** with three hydroxyl groups on the parent skeleton, we also became interested in the synthesis of the compound **20**, as presented in Scheme 3.

Starting from compound **19**, which was reported in our previous work [17], compound **20** was successfully synthesized by the β-lactam four-membered ring-opening coupling protocol which is illustrated in detail above.

2.2. Cytotoxicity assay

2.2.1. Cytotoxicity to MDA-MB-231 and PC-3 cell lines

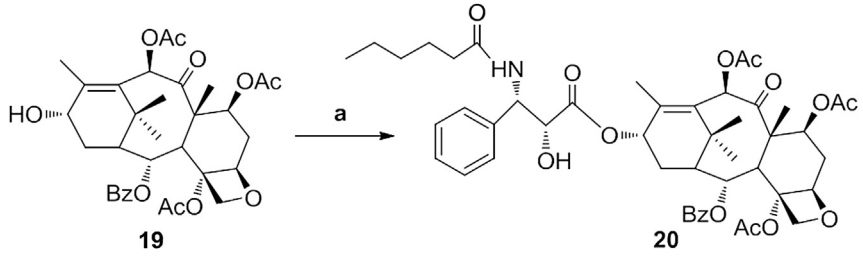
The *in vitro* antitumor activities of the newly synthesized compounds **13a-f**, **17**, **18** and **19** were evaluated in a cytotoxicity assay employing MDA-MB-231 (human breast cancer cells) cell line and PC-3 (human prostatic cancer cells) cell line by MTT method. The inhibitory activities (IC_{50}) are summarized in Table 1.

As reported in Table 1, it was observed that most of compounds exhibited similar cytotoxicities against two human cancer cell lines in comparison with paclitaxel. In particular, 1-dexoypaclitaxel analogues **13d** was about as active as paclitaxel in both cell lines with IC_{50} values in the range of 0.001–0.004 μM. Although most of the newly synthesized compounds showed similar antitumor activities, some compounds exhibited selectivity between the two human cancer cell lines. For the MDA-MB-231 cell line, the 3′-N-substituted 1-dexoypaclitaxel analogues **13a**, **13b**, **13d** and **18** were about as active as paclitaxel with IC_{50} values less than 0.001 μM. In the PC-3 cell line, all the compounds displayed the similar inhibitory activity with IC_{50} values in the range of 0.004–0.09 μM except for compounds **13e**, **17** and **20c**.

The notable compound **18** with alkyl substituents at the C-3′-N also showed potent cytotoxicity against the two human cancer cell lines. In comparison with the compound **17**, compound **18** has the three hydroxyl groups at the C-7, C-9 and C-10 positions instead of the acetal group of compound **17**. In the two cell lines evaluated by us, compound **18** had IC_{50} values that were, on average, 0.1-fold and 0.05-fold lower than that of compound **17**. Interestingly, compound **20** in general had an IC_{50} values 270-fold and 30-fold greater than that of compound **18** in the MDA-MB-231 cell line and the PC-3 cell line evaluated, respectively. The results are consistent with our previous report and Kingston's investigations [13–15]. As illustrated by the results above, it was evident that these 1-dexoypaclitaxel analogues with three hydroxyls at the C-7, C-9 and C-10 positions have an obvious advantage in cytotoxicity.

The dose–response curves for paclitaxel and compounds **13a-f**, **17** and **18** are shown in Fig. 2. All exponentially growing human tumor cell lines exposed for 72 h to paclitaxel and the compounds formulated in DMSO solution (MTT method) exhibited characteristic dose–response curves. In the two cell lines evaluated, the maximal antiproliferative response to either paclitaxel or **18** was 40–50% inhibition of cell survival by 72 h; thus, the efficacy of both compounds was equivalent. However, the maximal reduction in cell survival elicited by other compounds (**13a-f**) in a 72 h incubation was approximately 90–99%, as shown in Fig. 2.

In MDA-MB-231 cell lines, all of the compounds exhibited greater inhibition of cell survival than paclitaxel when the concentration was 10–100 μM. This implied that each of the compounds exhibited better efficacy at this range of concentration (10–100 μM) than paclitaxel. Generally speaking, the newly synthesized compounds can effectively inhibit the growth of MDA-MB-231 tumor at this range of concentration (10–100 μM); the inhibition was similar in the PC-3 cell lines. Interestingly, most of the



Scheme 3. Reagents and conditions: (a) **16**, NaHMDS, THF, −30 °C; 0.04 N HCl, CH_3OH, rt.

Table 1
Cytotoxicity (IC_{50}[a]) values for paclitaxel and its analogues **13a-f**, **17**–**18** and **21a-b**.

Compounds	MDA-MB-231[b]	PC-3[c]
	IC_{50} (μM)	IC_{50} (μM)
13a	<0.001	0.01
13b	<0.001	0.02
13c	0.03	0.09
13d	<0.001	0.004
13e	1.26	1.63
13f	0.02	0.07
17	0.01	0.21
18	<0.001	0.01
20	0.27	0.33
Paclitaxel	<0.001	<0.001

[a] Cytotoxicity (IC_{50}) was assayed by MTT method under growing human tumor cell lines were exposed for 72 h.
[b] Human breast cancer cell line.
[c] Human prostatic cancer cell line.

compounds also exhibited greater inhibition of cell survival than that of paclitaxel when the concentration was 100 μM and showed similar inhibition of cell survival at lower concentrations (0.001–1 μM) in the two cell lines. This curve demonstrated a plateau in survival at concentrations of above 0.001–1 μM; no additional obvious cytotoxicity was observed in any of the cell lines exposed to paclitaxel for 72 h in the concentrations range from 0.001 to 10 μM. It is notable that some compounds still exhibited greater inhibition of cell survival even at low concentrations (0.001 μM), especially in MDA-MB-231, as shown in Fig. 2(a). The three hydroxyl groups at the C-7, C-9 and C-10 positions are a possible explanation of this phenomenon.

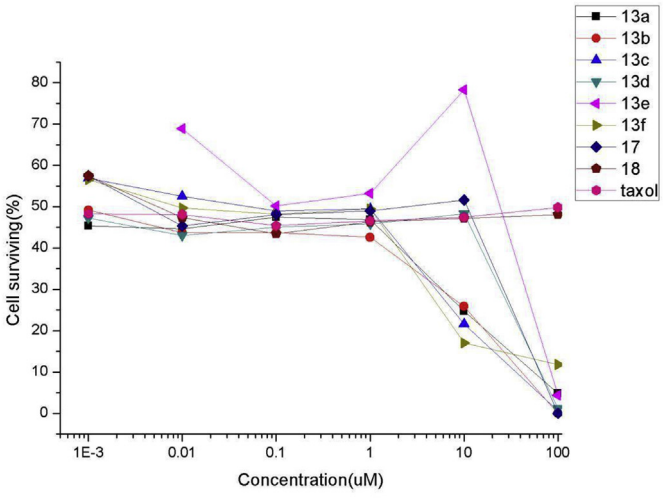


Fig. 2. Survival of two human tumor cell lines after exposure to compounds and paclitaxel for 72 h. (**a**) MDA-MB-231 (human breast cancer) cell line; (**b**) PC-3 (human prostatic cancer) cell line.

2.2.2. Cytotoxicity to HepG2 and H460 cell lines

As we known, though paclitaxel has been used to in treatment against breast, ovarian, germ cell, lung and esophageal cancers [1–5], few paclitaxel analogues have been used to against to hepatic carcinoma. In our study, however, we found that the newly synthesized taxane analogues also had good activity to against hepatic carcinoma. As shown in Table 2, the cytotoxicity of paclitaxel and its analogues against hepatic carcinoma were evaluated by CCK-8 method employing HepG2 and H460 cell lines. As reported in Table 2, compounds **13a** and **13d** indicated more potent cytotoxicity activities than that of paclitaxel in the assay, especially compound **13a** which exhibited excellent cytotoxicity activities in both cell lines. This result, which has important implications for curing other cancers such as liver cancer, indicated that the newly synthesized taxane analogues **13a** and **13d** showed outstanding cytotoxicity activities in MDA-MB-231 and PC-3 cell lines as well as in hepatic carcinoma cell lines.

3. Conclusion

In summary, a series of polyhydroxy taxane derivatives were synthesized and their cytotoxicities were evaluated. The new taxoids bearing different substituted groups at the C-3′-N-Acyl position showed degrees of cytotoxicity which differed significantly. Most of the compounds exhibited potent cytotoxicity to the MDA-MB-231 (human breast cancer cells) cell line and PC-3 (human prostatic cancer cells) cell line and exhibited greater inhibition of cell survival than paclitaxel when the concentration was 10–100 μM in the two cell lines. Compounds **13a**, **13d** and **18** exhibited excellent cytotoxicity in MDA-MB-231 and PC-3 cell lines as well as hepatic carcinoma cell lines. The IC_{50} values of compound **20** and compound **18** illustrated obviously the advantage of three hydroxyl groups at the C-7, C-9 and C-10 positions. Further modifications of these and other lead structures with the aim of improving the potency *in vitro* as well as the efficacy *in vivo* are in progress.

4. Experimental section

4.1. General chemical procedures

Commercially available reagents were purchased and were used without further purification unless otherwise mentioned. ^{1}H NMR

Table 2
Cytotoxicity (IC_{50}[a]) values for paclitaxel and its analogues **13a**, **13d** against hepatic carcinoma.

Compounds	HepG2[b]	H460[c]
	IC_{50} (μM)	IC_{50} (μM)
13a	0.567	0.199
13d	2.02	0.289
Paclitaxel	1.217	4.287

[a] Cytotoxicity (IC_{50}) was assayed by CCK-8 method under which growing human tumor cell lines were exposed for 48 h.
[b] HepG2 hepatoma cell lines.
[c] H460 hepatoma cell lines.

and ^{13}C NMR spectra were recorded on a Bruker Avance (500 MHz) spectrometer in $CDCl_3$ or DMSO-d_6, unless otherwise noted. Chemical shifts are reported in parts per million (ppm) and coupling constants (J) are reported in Hertz (Hz). Coupling patterns are described by abbreviations: s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad). Chemical shifts in $CDCl_3$ were reported in the scale relative to $CHCl_3$ (7.26 ppm) for ^1H NMR, and to $CDCl_3$ (77.16 ppm) for ^{13}C NMR, as internal references. The center line of the multiplets of DMSO-d_6 was defined as 2.50 for ^1H NMR. Mass spectra were recorded using an EI source (Agilent 5975N instrument). Silica gel plate GF254 was used for thin layer chromatography (TLC) and silica gel H or 300–400 mesh was used for flash column chromatography. Yields are shown in terms of those of isolated pure materials.

4.2. Synthetic procedures

4.2.1. Synthesis of 7,9,10,13-tetradeacetyl-1-deoxybaccantin **7** [18]

Compound **3** (3 g, 1.0 mmol) was dissolved in 95% ethanol (40 mL) and treated with hydrazine hydrate (86 mL) at 26 °C for 12 h. After careful neutralization (1 N HCl, pH = 7), the mixture was extracted with EtOAc and worked up in the usual manner, then recrystallized from a mixture of methanol and water to yield **7** (2 g, 78%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.01 (s, 3H), 1.59 (s, 6H), 1.64–1.67 (m, 2H), 1.72 (dd, *J* = 8.7 and 0.8 Hz, 1H), 1.84 (s, 3H), 2.15 (s, 3H), 2.26–2.37 (m, 2H), 2.87 (d, *J* = 5.3 Hz, 1H), 3.95 (d, *J* = 8.0 Hz, 1H), 4.01–4.08 (br, 1H), 4.15 (d, *J* = 8.0 Hz, 1H), 4.22 (t, *J* = 8.2 and 8.4 Hz, 1H), 4.26–4.45 (m, 2H), 4.68 (d, *J* = 10.4 Hz, 1H), 4.90 (d, *J* = 9.1 Hz, 1H), 4.99 (d, *J* = 4.6 Hz, 1H), 5.58 (dd, *J* = 4.4 and 1.7 Hz, 1H), 6.08 (br, 1H), 6.27 (br, 1H), 7.58 (m, 2H), 7.69 (m, 1H), 8.02 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 13.01, 15.53, 23.04, 27.07, 30.34, 32.13, 37.82, 38.14, 43.85, 44.22, 47.64, 65.66, 70.83, 72.22, 73.42, 76.24, 78.97, 81.03, 83.71, 129.34, 129.73, 130.05, 134.03, 136.25, 138.42, 164.85, 169.57.

4.2.2. Synthesis of compound **8** [18]

To a solution of **7** (265.3 mg, 0.5 mmol) in a mixture of CH_2Cl_2 (20 mL) and CH_3OH (0.5 mL) were added 2,2-DMP (0.37 mL, 3 mmol) followed by Montmorillonite K10 (40 mg), and the reaction mixture was vigorously stirred for 4 h at 26 °C. The solution was filtered and evaporated to a white residue, which was recrystallized from acetonitrile, affording compound **8** (276.8 mg, 97%). ^1H NMR (500 MHz,$CDCl_3$) δ (ppm): 1.09 (s, 3H), 1.52 (s, 6H), 1.54–1.57 (m, 1H), 1.70 (s, 3H), 1.75 (s, 3H),1.85–1.88 (m, 1H), 1.91 (d, *J* = 8.7 Hz, 1H), 2.04 (s, 3H), 2.10 (d, *J* = 7.6 Hz, 1H), 2.26 (s, 3H), 2.58–2.61 (m, 2H), 2.81 (d, J = 5.4 Hz, 1H), 4.14 (d, *J* = 8.3 Hz, 1H), 4.31 (t, *J* = 8.7 and 8.4 Hz, 1H), 4.36 (d, *J* = 8.3 Hz, 1H), 4.54 (d, *J* = 9.9 Hz, 1H), 4.63 (d, *J* = 8.5 Hz, 1H), 4.92 (d, *J* = 8.7 Hz, 1H), 5.03 (d, *J* = 9.9 Hz, 1H), 5.0 (s, 1H), 5.78 (dd, *J* = 5.4 and 2.0 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 8.08 (dd, *J* = 8.1 and 1.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 12.94, 15.72, 22.94, 25.84, 26.97, 27.13, 30.52, 31.75, 36.81, 38.23, 41.75, 42.57, 47.65, 67.72, 71.64, 72.25, 74.86, 76.57, 81.81, 83.87, 84.68, 107.33, 128.67, 129.84, 132.75, 133.58, 143.23, 165.19, 171.56.

4.2.3. General procedure for synthesis of compounds ***10a-f***

To a solution of (2R,3S)-3-Phenylisoserine **9** (100 mg, 0.52 mmol) in anhydrous MeOH (3 mL), thionyl chloride ($SOCl_2$, 0.05 mL, 0.79 mmol) was added drop-wise at 0 °C. The reaction mixture was stirred overnight at room temperature and the reaction was monitored by TLC. After the completion of the reaction, the reaction was quenched with $NaHCO_3$. The solution was evaporated under reduced pressure and diluted with H_2O. The water phase was extracted with EtOAc three times, the combined organic solution was dried over Na_2SO_4 and the solvent was removed under reduced pressure, resulting in an oil. To a solution of the resulting oil in a mixture of THF (10 mL) and saturated $NaHCO_3$ (10 mL), one of a series of different carbonyl chlorides (3 mmol) was added drop-wise at 0 °C, respectively. The whole mixture was stirred vigorously at room temperature for 3 h. The desired compound was extracted with EtOAc. The organic solution was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure, and the resulting oil was purified by silica gel column chromatography (EtOAc: hexane = 1:3), yielding a product **10** (80–90%).

*4.2.3.1. Compound **10a**.* White solid; m.p.: 141–146 °C; Yield: 80%; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.85 (s, 3H), 3.87 (s, 3H), 4.65 (s, 1H), 5.74 (d, *J* = 9.3 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 3H), 7.32 (t, *J* = 15.3 Hz, 1H), 7.38 (t, *J* = 15.2 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 29.70, 53.29, 54.81, 55.44, 73.31, 113.84, 126.27, 126.89, 127.91, 128.54, 128.75, 128.93, 138.86, 162.71, 166.38, 173.43.

*4.2.3.2. Compound **10b**.* White solid; m.p.: 150–157 °C; Yield: 85%; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.83 (s, 3H), 4.64 (d, *J* = 2.2 Hz, 1H), 4.60 (s, 1H), 5.74 (dd, *J* = 2.3 and 2.5 Hz, 1H), 7.08 (t, *J* = 18.5 Hz, 2H), 7.31 (t, *J* = 15.0 Hz, 1H), 7.37 (t, *J* = 15.5 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.76–7.80 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 53.23, 55.02, 73.25, 115.57, 126.91, 128.00, 128.76, 129.47, 129.54, 130.13, 130.15, 138.59, 163.88, 165.89, 166.01,173.39.

*4.2.3.3. Compound **10c**.* White solid; m.p.: 139–144 °C; Yield: 90%; ^1H NMR (500 MHz, $CDCl_3$) (ppm): 3.84 (s, 3H), 4.60 (s, 1H), 4.65 (d, *J* = 1.0 Hz, 1H), 5.75 (d, *J* = 9.5 Hz, 1H), 7.13 (d, *J* = 9.0 Hz, 1H), 7.3 (t, *J* = 14.4 Hz, 1H), 7.38 (t, *J* = 15.6 Hz, 2H), 7.45 (t, *J* = 16.0 Hz, 4H), 7.77 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 45.33, 53.27, 54.98, 73.25, 126.91, 127.60, 128.00, 128.77, 133.93, 138.57, 141.16, 166.44, 173.38.

*4.2.3.4. Compound **10d**.* White solid; m.p.: 138–143 °C; Yield: 82%; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.37 (d, *J* = 3.3 Hz, 2H), 3.86 (s, 3H), 4.63 (br, 1H), 5.72 (dd, *J* = 2.0 and 2.2 Hz, 1H), 6.51 (dd, *J* = 2.0 and 1.0 Hz, 1H), 7.12 (d, *J* = 4.5 Hz, 2H), 7.19 (br, 1H), 7.32 (t, *J* = 15.5 Hz, 1H), 7.38 (t, *J* = 15.0 Hz, 2H), 7.46–7.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 53.31, 55.08, 112.23, 114.89, 126.95, 128.00, 128.76, 138.62, 144.19, 147.43, 157.64, 173.26.

*4.2.3.5. Compound **10e**.* White solid; m.p.: 177–181 °C; Yield: 85%; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.35 (d, *J* = 3.0 Hz, 2H), 3.74 (s, 3H), 4.63 (br, 1H), 5.35 (dd, *J* = 2.0 and 2.2 Hz, 1H), 6.21 (dd, *J* = 2.5 and 1.0 Hz, 1H), 7.20 (d, *J* = 4.0 Hz, 2H), 7.30 (br, 1H), 7.35 (t, *J* = 15.5 Hz, 1H), 7.51 (t, *J* = 15.3 Hz, 2H), 7.52–7.56 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 29.71, 53.35, 54.83, 73.18, 126.92, 127.71, 128.00, 128.54, 128.77, 130.46, 138.24, 138.61, 161.28, 173.29.

*4.2.3.6. Compound **10f**.* White solid; m.p.: 183–187 °C; Yield: 87%; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.87 (s, 3H), 4.67 (d, *J* = 2.0 Hz, 1H), 5.79 (d, *J* = 9.5 Hz, 1H), 7.29–7.35 (m, 2H), 7.38–7.46 (m, 3H), 7.49–7.54 (m, 4H), 7.67 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 30.33, 53.33, 54.36, 73.19, 111.15, 111.94, 122.74, 123.77, 127.01, 128.08, 128.80, 138.49, 148.09, 158.28, 173.19.

4.2.4. General procedure for synthesis of compounds ***11a-f***

The resulting solid **10** (1 mmol) and pyridinium p-toluenesulfonate (PPTS) (0.1 mmol) were dissolved in anhydrous toluene (30 mL), and 4-methoxybenzaldehyde dimethyl acetal (1.5 mmol) was subsequently added drop-wise under an argon atmosphere. Following 40 min of heating at reflux, the reaction mixture was allowed to cool to ambient temperature and was diluted with Et_2O. The organic layer was washed successively with water, saturated

$NaHCO_3$, water and brine; the solution was dried over Na_2SO_4; and solvents were removed under reduced pressure. The resulting oil was purified by silica gel column chromatography (EtOAc: hexane = 1:4), yielding a product **11** (74–84%).

*4.2.4.1. Compound **11a**.* Slight yellow oil; Yield: 84%; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.77 (s, 3H), 3.82 (s, 6H), 4.86 (d, J = 3.5 Hz), 5.47 (br, 1H), 6.72 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.5 Hz, 2H), 6.94 (br, 1H), 7.29–7.35 (m, 6H), 7.48 (br, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 14.43, 52.27, 55.29, 113.50, 127.03, 127.69, 128.01, 128.69, 128.73, 129.30, 130.08, 159.88, 161.61, 170.53.

*4.2.4.2. Compound **11b**.* Slight yellow oil; Yield: 75%; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.82 (s, 3H), 3.84 (s, 3H), 4.89 (br, 1H), 5.45 (br, 1H), 6.87 (d, J = 8.5 Hz, 2H), 6.92 (t, J = 17.5 Hz, 2H), 7.25–7.36 (m, 7H), 7.43 (br, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 52.78, 55.27, 113.58, 115.46, 127.04, 128.76, 128.78, 129.43, 129.50, 129.65, 131.77, 160.01, 170.41; HR-MS: calcd for $C_{25}H_{22}FNO_5$ ($[M+H]^+$), 436.1380; found, 436.1554.

*4.2.4.3. Compound **11c**.* Slight yellow oil; Yield: 78%; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.79 (s, 3H), 3.82 (s, 3H), 4.50 (s, 2H), 4.89 (br, 1H), 5.42 (br, 1H), 6.85 (s, 2H), 7.18–7.36 (m, 9H), 7.43 (br, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 14.20, 21.02, 45.39, 52.75, 55.26, 60.36, 113.55, 127.41, 128.14, 128.42, 128.79, 135.64, 159.98, 170.39; HR-MS: calcd for $C_{26}H_{24}ClNO_5$ ($[M + H]^+$), 466.1241; found, 466.1415.

*4.2.4.4. Compound **11d**.* Slight yellow oil; Yield: 80%; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.80 (s, 3H), 3.84 (s, 3H), 4.95 (br, 1H), 5.84 (br, 1H), 6.37 (dd, J = and 1.0 Hz, 1H), 6.88 (d, J = 10.5 Hz, 2H), 6.94 (d, J = 2.4 Hz, 2H), 7.02 (s, 1H), 7.29–7.37 (m, 6H), 7.50 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 14.20, 21.03, 52.82, 55.26, 60.38, 63.90, 64.02, 111.67, 113.48, 117.57, 127.95, 128.57, 128.79, 128.97, 129.72, 144.98, 147.01, 158.91, 159.97, 170.42.

*4.2.4.5. Compound **11e**.* Slight yellow oil; Yield: 75%; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.8 (s, 3H), 3.84 (s, 3H), 4.96 (d, J = 2.5 Hz, 1H), 5.76 (d, J = 2.3 Hz, 1H), 6.85 (t, J = 9.8 Hz, 1H), 6.90 (d, J = 16.0 Hz, 2H), 6.99 (s, 1H), 7.05 (d, J = 4.0 Hz, 1H), 7.34–7.39 (m, 5H), 7.43 (d, J = 5.5 Hz, 1H), 7.55 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 52.88, 55.29, 64.91, 91.81, 113.52, 126.92, 127.49, 128.26, 128.88, 129.15, 129.52, 129.93, 131.22, 138.37, 139.02, 160.07, 163.90, 170.39; HR-MS: calcd for $C_{23}H_{21}NO_5S$ ($[M + H]^+$), 424.1038; found, 424.1212.

*4.2.4.6. Compound **11f**.* Slight yellow oil; Yield: 82%; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.80 (s, 3H), 3.85 (s, 3H), 5.01 (s, 1H), 5.95 (br, 1H), 6.90 (d, J = 8.5 Hz, 2H), 7.13 (br, 1H), 7.20–7.24 (m, 2H), 7.30–7.39 (m, 4H), 7.45 (d, J = 7.4 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 14.22, 21.03, 52.84, 55.25, 60.37, 64.35, 91.78, 111.88, 113.34, 113.56, 122.62, 123.72, 126.69, 127.12, 128.06, 128.64, 129.03, 147.85, 154.87, 160.06, 170.36; HR-MS: calcd for $C_{27}H_{23}NO_6$ ($[M + H]^+$), 458.1423; found, 458.1597.

*4.2.5. General procedure for synthesis of compounds **12a-f***

A solution of KOH (1.1 mmol) in water (4 mL) was added slowly at room temperature to a stirred solution of **11** in MeOH (30 mL). The reaction mixture was stirred for 2 h. After the completion of the reaction, MeOH was evaporated under reduced pressure. The residual mixture successively was diluted with water, washed with Et_2O, acidified with 1 N HCl, and extracted with EtOAc successively. The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The resulting solid (2.0 mmol), compound **8** (1.0 mmol), DCC (2.0 mmol) and DMAP (1.0 mmol) were dissolved in anhydrous toluene (6 mL), and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with EtOAc and washed with saturated NH_4Cl, water, saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The resulting oil was purified by silica gel column chromatography (EtOAc: hexane = 1:3), yielding **12** as a white solid (80–91%).

*4.2.5.1. Compound **12a**.* White solid; m.p.: 150–156 °C; Yield: 91%; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.27 (s, 3H), 1.54 (s, 3H), 1.55 (s, 3H), 1.65–1.69 (m, 1H), 1.71 (s, 3H), 1.83 (s, 3H), 1.85–1.88 (m, 1H), 1.98 (s, 3H), 2.03 (s, 3H), 2.30 (s, 3H), 2.45–2.53 (m, 1H), 2.59–2.66 (m, 1H), 2.76 (d, J = 6.5 Hz, 1H), 3.76 (s, 3H), 3.84 (s, 3H), 4.09–4.15 (m, 2H), 4.32–4.37 (m, 2H), 4.60 (d, J = 11.2 Hz, 1H), 4.91 (d, J = 9.5 Hz, 2H), 4.94 (br, 1H), 5.07 (d, J = 12.3 Hz, 2H), 5.61 (br, 1H), 5.8 (dd, J = 1.3 Hz, J = 2.0 Hz, 1H), 6.17 (t, J = 18.5 Hz, 1H), 6.72 (d, J = 9.4 Hz, 2H), 6.89 (d, J = 8.0 Hz, 2H), 7.01 (br, H), 7.29–7.35 (m, 6H), 7.44–7.49 (m, 3H), 7.59 (t, J = 15.5 Hz, 1H), 8.05 (d, J = 6.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 13.02, 14.19, 15.60, 21.45, 22.03, 24.95, 26.52, 26.78, 26.90, 27.11, 31.96, 36.71, 38.64, 41.88, 42.36, 47.82, 55.30, 60.38, 71.70, 72.09, 74.38, 76.36, 81.13, 83.77, 84.553, 107.42, 113.48, 113.54, 127.17, 127.61, 128.17, 128.63, 128.79, 128.87, 129.32, 129.54, 129.79, 130.02, 133.61, 133.65, 138.81, 159.91, 161.53, 161.58, 165.05, 169.33, 170.87.

*4.2.5.2. Compound **12b**.* White solid; m.p.: 102–107 °C; Yield: 90%; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.28 (s, 3H), 1.55 (s, 3H), 1.56 (s, 3H), 1.66–1.70 (m, 1H), 1.71 (s, 3H), 1.84 (s, 3H), 1.85–1.88 (m, 1H), 1.99 (s, 3H), 2.01 (s, 3H), 2.45–2.53 (m, 1H), 2.59–2.66 (m, 1H), 2.76 (d, J = 6.5 Hz, 1H), 3.83 (s, 3H), 4.09–4.15 (m, 3H), 4.32–4.37 (m, 2H), 4.61 (d, J = 11.5 Hz, 1H), 4.90 (d, J = 10.3 Hz, 1H), 4.94 (br, 1H), 5.07 (d, J = 12.5 Hz, 2H), 5.58 (br, 1H), 5.04 (dd, J = 3.5 and 2.4 Hz, 1H), 6.87–6.93 (m, 4H), 7.28–7.38 (m, 6H), 7.47 (t, J = 16.5 Hz, 3H), 7.60 (t, J = 14.5 Hz, 1H), 8.05 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 13.01, 14.20, 15.55, 21.04, 22.07, 26.50, 26.77, 26.90, 27.11, 31.95, 36.73, 38.66, 41.90, 42.37, 47.79, 60.38, 71.66, 71.75, 72.12, 74.37, 81.19, 83.76, 88.51, 107.52, 113.64, 115.26, 115.44, 128.39, 128.63, 128.88, 128.90, 129.44, 129.52, 129.56, 129.80, 133.63, 133.83, 160.06, 165.04, 169.33, 170.68; HR-MS: calcd for $C_{56}H_{60}FNO_{13}$ ($[M + Na]^+$), 996.3938; found, 996.3941.

*4.2.5.3. Compound **12c**.* White solid; m.p.: 136–143 °C; Yield: 80%; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.28 (s, 3H), 1.33–1.45 (m, 1H), 1.55 (s, 3H), 1.56 (s, 3H), 1.65–7.71 (m, 1H), 1.72 (s, 3H), 1.84 (s, 3H), 1.99 (s, 3H), 2.01 (s, 3H), 2.46–2.67 (m, 2H), 2.76 (d, J = 2.3 Hz, 1H), 3.83 (s, 3H), 4.11–4.26 (m, 1H), 4.32–4.36 (m, 2H), 4.52 (t, J = 17.3 Hz, 3H), 4.61 (d, J = 1.0 Hz, 1H), 4.90 (d, J = 1.2 Hz, 1H), 4.97 (br, 1H), 5.07 (s, 1H), 6.17 (t, J = 16.3 Hz, 1H), 6.89 (br, 2H), 7.22–7.36 (m, 10H), 7.47 (t, J = 15.3 Hz, 3H), 7.60 (t, J = 16.5 Hz, 1H), 8.05 (d, t, J = 7.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 13.02, 15.56, 22.09, 24.95, 26.50, 26.91, 27.12, 31.96, 33.92, 36.74, 38.66, 41.89, 42.37, 45.39, 47.79, 55.30, 71.66, 72.12, 74.38, 76.37, 81.18, 83.76, 84.51, 107.50, 113.53, 113.63, 127.45, 128.39, 128.64, 128.86, 128.93, 129.52, 129.80, 133.81, 135.54, 138.64, 165.05, 169.33, 170.67; HR-MS: calcd for $C_{57}H_{62}ClNO_3$ ($[M + Na]^+$), 1026.3808; found, 1026.3802.

*4.2.5.4. Compound **12d**.* White solid; m.p.: 140–147 °C; Yield: 85%; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.26 (s, 3H), 1.53 (s, 6H), 1.65–1.69 (m, 1H), 1.71 (s, 3H), 1.83 (s, 3H), 1.84–1.89 (m, 1H), 1.95 (s, 3H), 2.01 (s, 3H), 2.48–2.55 (m, 1H), 2.61–2.67 (m, 1H), 2.77 (d, J = 5.5 Hz, 2H), 3.82 (s, 3H), 4.32–4.37 (q, J = 22.5 Hz, 2H), 4.60 (d, J = 10.6 Hz, 1H), 4.91 (d, J = 9.7 Hz, 1H), 5.03–5.09 (m, 2H), 5.08 (s, 3H), 5.82 (d, J = 6.5 Hz, 1H), 5.98 (s, 1H), 6.17 (t, J = 17.6 Hz, 1H), 6.36 (dd, J = 1.0 and 1.2 Hz, 1H), 6.87 (d, J = 9.5 Hz, 2H), 6.95 (d,

J = 3.4 Hz, 1H), 7.18 (s, 1H), 7.30–7.35 (m, 4H), 7.40–7.51 (m, 6H), 7.59 (t, J = 15.5 Hz, 1H), 8.05 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 13.01, 14.02, 15.48, 21.04, 22.03, 26.54, 26.85, 26.88, 27.10, 31.92, 36.74, 38.65, 41.89, 42.35, 47.85, 55.26, 60.37, 71.68, 71.92, 72.13, 74.35, 76.36, 81.14, 83.75, 84.52, 91.84, 107.44, 111.74, 128.63, 128.98, 129.53, 133.63, 133.70, 138.59, 145.02, 146.86, 159.98, 165.04,169.46.

4.2.5.5. Compound ***12e***. White solid; m.p.: 130–136 °C; Yield: 87%; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.26 (s, 3H), 1.53 (s, 3H), 1.55 (s, 3H), 1.65–1.69 (m, 1H), 1.71 (s, 3H), 1.83 (s, 3H),1.84–1.89 (m, 1H), 1.95 (s, 3H), 2.05 (s, 3H), 2.48–2.55 (m, 1H), 2.61–2.67 (m, 1H), 2.77 (d, J = 5.5 Hz, 2H), 3.84 (s, 3H), 4.09–4.15 (m, 3H), 4.32–4.37 (q, J = 26.6 Hz, 2H), 4.60 (d, J = 10.5 Hz, 1H), 4.91 (d, J = 9.5 Hz, 1H), 5.03–5.09 (m, 3H), 5.82 (d, J = 6.2 Hz, 1H), 5.91 (s, 1H), 6.18 (t, J = 20.5 Hz, 1H), 6.86 (t, J = 9.7 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 3.5 Hz, 1H), 7.14 (s, 1H), 7.37–7.49 (m, 8H), 7.54–7.61 (m, 3H), 8.05 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 13.04, 14.20, 15.63, 21.04, 22.03, 26.55, 26.84, 26.90, 27.11, 31.96, 36.72, 38.65, 41.87, 42.37, 47.85, 55.29, 60.38, 65.35, 71.72, 71.95, 72.08, 74.36, 76.37, 81.14, 83.77, 84.56, 92.08, 107.44, 113.58, 127.07, 127.49, 128.37, 128.62, 128.93, 129.23, 129.55, 129.81, 130.00, 131.24, 133.61, 133.70, 138.15, 138.64, 160.09, 163.46, 15.06, 169.41, 171.00; HR-MS: calcd for $C_{54}H_{59}NO_{13}S$ ($[M + H]^+$), 984.3598; found, 984.3599.

4.2.5.6. Compound ***12f***. White solid; m.p.: 145–150 °C; Yield: 83%; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.28 (s, 3H), 1.54 (s, 3H), 1.56 (s, 3H), 1.65–1.69 (m, 1H), 1.71 (s, 3H), 1.84 (s, 3H), 1.87–1.94 (m, 1H), 1.98 (s, 3H), 2.01 (s, 3H), 2.46–2.53 (m, 1H), 2.58–2.66 (m, 1H), 2.75 (d, J = 5.5 Hz, 2H), 3.83 (s, 3H), 4.32–4.36 (m, 2H), 4.60 (d, J = 10.2 Hz, 1H), 4.90 (d, J = 8.2 Hz, 1H), 4.96 (br, 1H), 5.07 (s, 1H), 5.82 (d, J = 6.5 Hz, 1H), 6.17 (t, J = 18.6 Hz, 1H), 6.89 (br, 2H), 7.14 (d, J = 4.5 Hz, 2H), 7.31–7.39 (m, 7H), 7.46 (t, J = 15.4 Hz, 3H), 7.59 (t, J = 15.5 Hz, 1H), 8.05 (d, J = 8.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 13.01, 14.26, 15.55, 21.05, 22.09, 26.50, 26.76, 27.12, 30.95, 36.73, 38.66, 41.90, 42.37, 47.78, 55.31, 60.38, 71.64, 72.13, 74.37, 76.36, 76.87, 77.13, 77.38, 81.19, 83.76, 84.50, 107.51, 113.66, 128.42, 128.71, 128.96, 129.44, 129.52, 129.80, 133.47, 133.64, 133.86, 134.38, 160.09, 163.03, 169.34, 170.63; HR-MS: calcd for $C_{54}H_{59}NO_{13}S$ ($[M + Na]^+$), 1018.3947; found, 1018.3984.

4.2.6. General procedure for synthesis of compounds ***13a-f***

The resulting solid **12** (1.0 mmol) was dissolved in MeOH (5 mL) and p-toluenesulfonic acid (0.7 mmol) was added. After stirring for 5 h at room temperature, the reaction mixture was diluted with EtOAc and washed three times with saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The resulting oil was purified by silica gel column chromatography (EtOAc: hexane = 2:3), and the unreacted minor diastereomer was discarded, yielding **13** as a white powder (20–30%).

4.2.6.1. Compound ***13a***. White solid; m.p.: 159–163 °C; Yield: 20%; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.15 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.41–1.71 (m, 1H), 1.75 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 1.92–1.95 (m, 2H), 2.27 (s, 3H, CH_3), 2.51–2.63 (m, 2H), 3.46 (br, 1H), 3.80 (s, 3H), 4.20 (d, J = 8.0 Hz, 1H), 4.26–4.30 (m, 2H), 4.36 (d, J = 8.0 Hz, 1H), 4.65 (br, 1H), 4.76 (d, J = 2.5 Hz, 1H), 4.83 (d, J = 10.5 Hz, 2H), 4.95 (d, J = 2.5 Hz, 2H), 5.07 (br, 3H), 5.74 (dd, J = 5.5 and 1.5 Hz, 1H), 5.88 (dd, J = 9.5 and 2.5 Hz, 1H), 5.90–5.94 (m, 1H), 6.92 (d, J = 3.3 Hz, 2H), 7.30–7.43 (m, 4H), 7.30–7.40 (m, 3H), 7.64 (t, J = 7.3 Hz, 1H), 7.70 (d, J = 7.5 Hz, 2H), 8.07 (d, J = 7.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 12.62, 14.11, 16.12, 21.10, 22.67, 26.45, 26.72, 29.32, 37.84, 37.91, 43.92, 44.52, 47.11, 54.40, 55.41, 60.44, 71.35, 71.31, 73.94, 74.07, 76.85, 77.24, 79.07, 82.65, 83.87, 113.88, 125.93, 127.28, 127.94, 128.67, 128.94, 129.51, 129.75, 133.64, 133.91, 138.38, 138.54, 162.41, 165.04, 166.17, 171.17, 171.37; HR-MS: calcd for $C_{46}H_{53}NO_{13}$ ($[M + H]^+$), 828.3595; found, 828.3574.

4.2.6.2. Compound ***13b***. White solid; m.p.: 186–191 °C; Yield: 30%; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.08 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 1.86–1.98 (m, 2H), 2.29 (s, 3H, CH_3), 2.10–2.16 (m, 1H), 2.56–2.70 (m, 2H), 3.86 (s, 1H), 3.96 (s, 1H), 4.05 (d, J = 8.5 Hz, 1H), 4.19–4.27 (m, 2H), 4.42 (dd, J = 8.3 Hz, 1H), 4.71 (d, J = 2.2 Hz, 1H), 4.96 (d, J = 2.5 Hz 1H), 4.77 (br, 1H), 4.83 (d, J = 10.0 Hz, 2H), 4.92–4.97 (d, J = 2.6 Hz, 2H), 5.3 (s, 3H, CH_3), 5.74 (dd, J = 5.5 and 1.5 Hz, 1H), 5.88 (dd, J = 9.5 and 2.5 Hz, 1H), 5.9–5.94 (m, 1H), 7.13–7.16 (t, 2H), 7.30–7.43 (m, 4H), 7.30–7.40 (m, 4H), 7.88 (m, 2H), 8.07 (d, J = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 12.61, 14.12, 14.19, 15.12, 19.16, 22.69, 26.45, 26.72, 29.36, 29.66, 29.70, 31.68, 31.92, 38.00, 43.95, 44.63, 47.15, 54.53, 60.43, 71.21, 71.26, 71.33, 73.83, 74.16, 76.86, 77.22, 78.98, 82.68, 83.82,126.61, 127.32, 128.14, 128.65, 128.70, 129.52, 129.76, 131.92, 132.63, 133.64, 133.81, 138.18, 138.47, 165.61, 165.55, 171.19, 171.27; HR-MS: calcd for $C_{45}H_{50}FNO_{12}$ ($[M + Na]^+$), 838.3215; found, 838.3183.

4.2.6.3. Compound ***13c***. White solid; m.p.: 146–153 °C; Yield: 25%; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.16 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.71 (s, 2H), 1.41–1.71 (m, 2H), 1.76 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 1.84–1.95 (m, 2H), 2.28 (s, 3H, CH_3), 2.52–2.67 (m, 4H), 2.83 (t, 1H), 3.36 (br, 1H), 4.20 (d, J = 8.5 Hz, 1H), 4.26–4.30 (m, 2H), 4.36 (d, J = 8.0 Hz, 2H), 4.62 (s, 2H), 4.76 (d, J = 2.5 Hz, 1H), 4.83 (d, J = 10.3 Hz, 1H), 4.97 (t, J = 15.6 Hz, 2H), 5.05 (d, J = 3.6 Hz, 2H), 5.88 (dd, J = 9.5 and 2.5 Hz, 1H), 5.91 (m, 2H), 7.31–7.41 (m, 3H), 7.46–7.65 (m, 6H), 7.82 (d, J = 2.5 Hz, 2H), 8.07 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 12.65, 14.12, 15.08, 20.45, 21.47, 22.69, 25.60, 26.49, 29.69, 31.67, 31.92, 32.72, 37.89, 38.07, 43.92, 44.56, 47.19, 53.26, 54.50, 71.29, 73.29, 73.92, 74.04, 76.78, 77.03, 77.24, 77.29, 79.02, 82.62,83.91, 126.90, 127.05, 127.16, 127.29, 128.01, 128.65, 128.76, 128.82, 129.35, 129.55, 129.77,130.01, 130.86, 133.63, 133.93, 138.47, 142.42, 165.06, 166.65, 171.13, 171.38; HR-MS: calcd for $C_{46}H_{52}ClNO12$ ($[M + Na]^+$), 868.3076, found 868.3071.

4.2.6.4. Compound ***13d***. White solid; m.p.: 155–161 °C; Yield: 27%; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.15 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.46–1.73 (m, 2H), 1.75 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 1.92–1.98 (m, 2H), 2.27 (s, 3H, CH_3), 2.4–2.6 (m, 2H), 3.44 (br, 1H), 3.84 (m, 1H), 4.22 (d, J = 8.5 Hz, 1H), 4.26–4.30 (m, 2H), 4.36 (d, J = 8.0 Hz, 1H), 4.68 (br, 1H), 4.74 (d, J = 2.5 Hz, 1H), 4.83 (d, J = 10.5 Hz, 1H), 4.85 (d, J = 2.7 Hz, 2H), 4.97 (d, J = 2.5 Hz, 1H), 5.06 (br, 1H), 5.79 (dd, J = 5.5 and 1.5 Hz, 1H), 5.90–5.94 (m, 1H), 6.51 (m, 1H), 7.13 (d, 2H), 7.30–7.39 (m, 3H), 7.46–7.52 (m, 4H), 7.64 (t, J = 10.6 Hz, 1H), 8.07 (d, J = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 12.64, 14.12, 15.11, 21.02, 22.65, 26.41, 26.75, 31.68, 37.98, 43.98, 44.65, 47.15, 53.81, 60.46, 71.14, 71.27, 71.33, 74.07, 76.88, 77.24, 79.05, 82.78, 83.88,112.38, 115.08, 127.34, 128.0, 128.65, 129.35, 129.76, 133.68, 133.98, 138.38, 138.42, 144.38, 147.47, 157.68, 165.04, 170.97,171.25; HR-MS: calcd for $C_{43}H_{49}NO_{13}$ ($[M + Na]^+$), 810.3102, found 810.3070.

4.2.6.5. Compound ***13e***. White solid; m.p.: 148–153 °C; Yield: 27%; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.16 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.54–1.70 (m, 1H), 1.76 (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 1.86–1.97 (m, 2H), 2.27 (s, 3H, CH_3), 2.4–2.6 (m, 2H), 2.85 (d, J = 2.5 Hz, 1H), 3.36 (br, 1H), 4.20 (d, J = 8.5 Hz, 1H), 4.26–4.30 (m, 2H), 4.36 (d, J = 8.6 Hz, 1H), 4.66–4.77 (m, 3H), 4.83 (d, J = 10.5 Hz, 1H), 4.97 (d, J = 2.2 Hz, 2H), 5.76 (dd, J = 5.5 and 1.5 Hz, 1H), 5.83 (dd, J = 9.5 and 2.5 Hz, 1H), 5.9–5.94 (m, 1H), 7.08 (t, J = 10.7 Hz, 1H), 7.31–7.40 (d, J = 3 Hz, 4H), 7.46–7.53 (m, 4H), 7.56–7.64 (m, 2H), 8.07 (d,

J = 7.9 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 12.64, 15.33, 22.62, 26.45, 29.7,31.74, 31.85, 38.16, 43.98, 44.63, 47.27, 54.57, 71.29, 71.32, 73.90, 74.14, 76.81, 77.27, 79.07, 82.77,83.97, 127.31, 127.70, 128.17, 128.63,128.74, 129.54, 129.75, 130.58, 133.64, 133.97, 138.21, 138.48, 138.57, 161.14, 165.08, 171.08, 171.60; HR-MS: calcd for $C_{43}H_{49}SO_{12}$ ($[M + H]^+$), 804.3053, found 804.3060.

*4.2.6.6. Compound **13f**.* white solid; m.p.: 160–166 °C; yield: 23%; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.14 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.71 (s, 2H), 1.41–1.71 (m, 1H), 1.76 (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 1.84–1.95 (m, 2H), 2.28 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 2.4–2.6 (m, 2H), 2.83 (d, J = 2.4 Hz 1H), 3.36 (br, 1H), 4.20 (d, J = 8.5 Hz, 1H), 4.26–4.30 (m, 2H), 4.36 (d, J = 8.0 Hz, 1H), 4.6 (br, 1H), 4.76 (d, J = 2.5 Hz, 1H), 4.83 (d, J = 10.0 Hz, 1H), 4.92–4.97 (d, J = 2.7 Hz, 2H), 5.3 (s, 3H, CH_3), 5.74 (dd, J = 5.5 and 1.5 Hz, 1H), 5.88 (dd, J = 9.5 and 2.5 Hz, 1H), 5.90–5.94 (m, 1H), 7.31–7.52 (m, 7H), 7.55 (d, d, J = 9.8.0 Hz, 2H), 7.60–7.69 (m, 3H), 7.85 (d, J = 2.5 Hz, 1H), 8.07 (d, J = 5.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 12.54, 14.11, 23.10, 25.55, 31.65, 37.8,8 38.04, 43.97, 44.65, 47.14, 54.15, 71.15, 71.20, 76.85, 77.14, 79.06, 82.65, 83.88, 111.10, 111.80, 122.74, 123.87, 126.97, 127.37, 127.57, 128.14, 128.67, 129.57, 129.78, 133.68, 133.91, 138.14, 138.47, 148.17, 154.72, 158.12, 165.08, 170.87, 171.14; HR-MS: calcd for $C_{47}H_{51}NO_{13}$ ($[M + Na]^+$), 860.3258, found 860.3244.

*4.2.7. Synthesis of compound **15** [33,34]*

Compound **14** (100 mg, 0.6 mmol), triethylsilane (142 mg, 1.23 mmol) and 1H-imidazole (125 mg, 1.84 mmol) were dissolved in dry CH_2Cl_2 (6 mL) under 0 °C. After stirring under nitrogen atmosphere for 0.5 h, the reaction was quenched by with saturated NH_4Cl, the solvent was removed under reduced pressure. The water layer was extracted with EtOAc, the organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The resulting oil was purified by silica gel column chromatography (EtOAc: hexane = 1: 15), yielding **15** as a colorless oil (150 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.35–0.48 (m, 6H), 0.76 (t, J = 7.9 Hz, 9H), 4.78 (d, J = 4.7 Hz, 1H), 5.07 (dd, J = 4.7 and 2.7 Hz, 1H), 6.44 (s, 1H), 7.28–7.36 (m, 5H).

*4.2.8. Synthesis of compound **16** [33,34]*

Compound **15** (150 mg, 0.6 mmol), triethylsilane (109 mg, 1.08 mmol), and DMAP (66.5 mg, 0.54 mmol) were dissolved in dry CH_2Cl_2 (6 mL), and hexanoyl chloride (24.39 mg, 0.81 mmol) was slowly added to the mixture at 0 °C. After stirring under nitrogen atmosphere for 2 h, the reaction was quenched with water and the solvent was removed under reduced pressure. The water layer was extracted with EtOAc, the organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The resulting oil was purified by silica gel column chromatography (EtOAc: hexane = 1:8), yielding **16** as a colorless oil (130 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.37–0.51 (m, 6H), 0.77 (t, J = 7.9 Hz, 9H), 0.89 (t, J = 7.0 Hz, 3H), 1.33 (q, J = 7.2, 3.6 Hz, 4H), 1.64–1.69 (m, 2H), 2.68–2.76 (m, 1H), 2.76–2.84 (m, 1H), 5.09 (d, J = 5.9 Hz, 1H), 5.14 (d, J = 5.9 Hz, 1H), 7.22–7.23 (m, 2H), 7.28–7.34 (m, 3H).

*4.2.9. Synthesis of compound **17***

Compound **16** (130 mg, 0.6 mmol) and compound **8** (131 mg, 0.23 mmol) were dissolved in dry THF (6 mL), and sodium bis(-trimethylsilyl) amide (63.47 mg, 0.35 mmol) was slowly added to the mixture at 0 °C. After stirring under nitrogen atmosphere for 2 h, the reaction was quenched with saturated NH_4Cl and the solvent was removed under reduced pressure. The water layer was extracted with EtOAc and the organic layer was dried over Na_2SO_4. The resulting intermediate was dissolved in 2 mL MeOH and 0.04 N HCl was slowly added until the pH of the mixture measured 3–4. After stirring at 40 °C for 3 h, saturated $NaHCO_3$ solution was added to bring the pH of the mixture to 7. The solvent was removed under reduced pressure, the resulting mixture was extracted with EtOAc, the solution was dried over Na_2SO_4, and the resulting oil was purified by silica gel column chromatography (EtOAc: hexane = 1:1), yielding **17** as a white solid (100 mg, 50%); m.p.: 155–163 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.87 (t, J = 6.9 Hz, 3H), 1.18 (s, 3H), 1.22–1.31 (m, 4H), 1.53 (s, 6H), 1.53–1.62 (m, 3H), 1.65 (s, 3H), 1.69 (s, 3H), 1.78 (s, 3H), 1.84 (dd, J = 15.3 and 9.2 Hz, 1H), 1.99 (d, J = 8.7 Hz, 1H), 2.18–2.23 (m, 2H), 2.24 (s, 3H), 2.55–2.64 (m, 2H), 2.68 (d, J = 5.5 Hz, 1H), 4.14 (d, J = 8.8 Hz, 1H), 4.21 (t, J = 8.5 Hz, 1H), 4.34 (d, J = 8.4 Hz, 1H), 4.53 (d, J = 9.8 Hz, 1H), 4.66 (d, J = 2.3 Hz, 1H), 4.92 (d, J = 8.7 Hz, 1H), 4.96 (d, J = 9.8 Hz, 2H), 5.62 (dd, J = 9.3 and 8.0 Hz, 1H), 5.79 (dd, J = 5.4 and 1.7 Hz, 1H),5.9 (t, J = 8.5 Hz, 1H), 6.57 (d, J = 9.3 Hz, 1H), 7.29 (t, J = 7.2 Hz, 1H), 7.36 (t, J = 7.5 Hz, 2H), 7.43 (d, J = 7.3 Hz, 2H), 7.47 (t, J = 7.8 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 8.06 (d, J = 7.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 13.12, 14.00, 15.62, 22.34, 22.77, 25.41, 26.07, 26.95, 27.00, 27.10, 29.81, 31.50, 31.95, 36.67, 36.82, 36.84, 38.64, 41.80, 42.55, 47.67, 54.14, 54.55, 71.38, 71.64, 72.27, 73.60, 74.57, 76.55, 82.25, 83.74, 84.47, 107.56, 127.08, 127.38, 127.90, 128.04, 128.87, 128.70, 128.81, 129.54, 129.91, 133.81, 134.24, 138.67, 138.64, 165.40, 170.87, 171.64, 172.74; HR-MS: calcd for $C_{47}H_{61}NO_{12}$ ($[M + H]^+$), 832.4272, found 832.4253.

*4.2.10. Synthesis of compound **18***

Compound **17** (40 mg, 0.048 mmol) was dissolved in MeOH (6 mL) and 0.04 N HCl was slowly added to the mixture until pH of the mixture measured 3–4. After stirring at 60 °C for 6 h, saturated $NaHCO_3$ solution was added to bring the pH of the mixture to 7. The solvent was removed under reduced pressure, the products extracted with EtOAc and dried over Na_2SO_4, and the resulting oil was purified by silica gel column chromatography (EtOAc: hexane = 2:1), yielding **18** as a white powder (35 mg, 92%); m.p.: 171–176 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.82 (t, J = 7.1 Hz, 3H), 1.18 (s, 3H), 1.23–1.31 (m, 4H), 1.52–1.58 (m, 2H), 1.58–1.64 (m, 1H), 1.66 (s, 3H), 1.74 (s, 3H), 1.75 (s, 3H), 1.93 (dd, J = 14.6 and 10.6 Hz, 1H), 1.99 (d, J = 8.8 Hz, 1H), 2.12 (t, J = 7.0 Hz, 2H), 2.26 (s, 3H), 2.40–2.50 (m, 1H), 2.51–2.60 (m, 1H), 2.83 (d, J = 5.7 Hz, 1H), 3.77 (s, 1H), 4.16 (d, J = 8.4 Hz, 1H), 4.27 (dd, J = 21.2 and 9.7 Hz, 2H), 4.34 (d, J = 8.4 Hz, 1H), 4.71 (s, 1H), 4.85 (s, 1H), 4.89–4.95 (m, 2H), 5.39 (s, 1H), 5.62 (dd, J = 9.4 and 1.4 Hz, 1H), 5.72 (dd, J = 5.7 and 1.4 Hz, 1H), 5.90 (t, J = 8.0 Hz, 1H), 6.7 (d, J = 9.4 Hz, 1H), 7.28 (t, J = 7.2 Hz, 1H), 7.34 (t, J = 7.4 Hz, 2H), 7.40 (d, J = 7.4 Hz, 2H), 7.46 (t, J = 7.8 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 8.04 (d, J = 7.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 12.64, 14.11, 14.32, 15.22, 21.31, 22.44, 22.70, 25.41, 26.45, 26.94, 29.47, 29.95, 31.55, 31.74, 36.67, 37.94, 38.45, 44.27, 44.50, 47.34, 53.94, 71.65, 71.54, 71.74, 73.50, 74.14, 79.04, 82.47, 84.18, 127.17, 128.04, 128.88, 128.67, 129.67, 129.94, 133.61, 134.57, 138.17, 138.67, 165.0, 170.61, 172.87; HR-MS: calcd for $C_{44}H_{57}NO_{12}$ ($[M + H]^+$), 792.3959, found 792.3949.

*4.2.11. Synthesis of compound **20***

Compound **19** (30 mg, 0.049 mmol) and compound **16** (27.7 mg, 0.074 mmol) were dissolved in dry THF (2 mL), and sodium bis(-trimethylsilyl) amide (0.04 mL, 0.074 mmol) was slowly added to the mixture at 0 °C. After stirring under nitrogen atmosphere for 2 h, the reaction was quenched with saturated NH_4Cl, and the solvent was removed under reduced pressure. The water layer was extracted with EtOAc and the organic layer was dried over Na_2SO_4. The resulting intermediate was dissolved in 2 mL MeOH, and 0.04 N HCl was slowly added until the pH of the mixture measured 3–4. After stirring at 40 °C for 3 h, saturated $NaHCO_3$ solution was added to bring the pH of the mixture to 7. The solvent was removed under reduced pressure, the resulting mixture was extracted with EtOAc, the solution was dried over Na_2SO_4, and the resulting oil was

purified by silica gel column chromatography (EtOAc: hexane = 1:1), yielding **20** as a white solid (20.1 mg, 47%). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 0.82 (t, J = 6.9 Hz, 3H), 1.15 (s, 3H), 1.21–1.26 (m, 7H), 1.50–1.61 (m, 2H), 1.69 (dd, J = 15.1, 8.8 Hz, 1H), 1.78 (s, 3H), 1.82 (dd, J = 14.3, 12.0 Hz, 1H), 1.87 (s, 3H), 2.02 (s, 3H), 2.05 (d, J = 9.4 Hz, 1H), 2.13–2.20 (m, 5H), 2.33 (s, 3H), 2.50–2.63 (m, 2H), 3.73 (d, J = 6.7 Hz, 1H), 3.76 (d, J = 4.4 Hz, 1H), 4.13 (d, J = 8.5 Hz, 1H), 4.37 (d, J = 8.6 Hz, 1H), 4.68 (s, 1H), 4.97 (d, J = 9.1 Hz, 1H), 5.53–5.60 (m, 2H), 5.63 (dd, J = 6.7, 2.8 Hz, 1H), 5.93 (t, J = 8.9 Hz, 1H), 6.20 (s, 1H), 6.45 (d, J = 9.1 Hz, 1H), 7.29 (t, J = 6.9 Hz, 1H), 7.37 (td, J = 15.2, 7.4 Hz, 4H), 7.48 (t, J = 7.7 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 8.05 (d, J = 7.3 Hz, 2H); ^{13}C NMR (125 Hz, $CDCl_3$) δ ppm: 13.99, 14.74, 20.85, 21.20, 22.42, 22.62, 25.49, 25.66, 26.38, 29.87, 31.41, 33.60, 36.67, 38.50, 45.00, 54.43, 56.46, 60.52, 71.46, 71.84, 72.02, 73.22, 75.67, 76.67, 81.10, 83.93, 127.13, 128.19, 128.81, 128.93, 129.40, 129.94, 132.70, 133.77, 138.39, 138.94, 165.08, 169.14, 170.27, 170.63, 172.69, 173.05, 202.68; ESI Full MS m/z: $[M + Na]^+$ 896, 595.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2015.09.019.

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