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Synthesis and cytotoxic activity evaluation of dihydrocucurbitacin B and cucurbitacin B derivatives

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ABSTRACT

Two cucurbitacins, dihydrocucurbitacin B (**1**) and cucurbitacin B (**2**), which can be obtained in large amounts from the roots of *Wilbrandia ebracteata* and from the fruits of *Luffa operculata*, respectively, were used as starting materials for the preparation of a library of 29 semi-synthetic derivatives. The structural changes that were performed include the removal, modification or permutation of functional groups in rings A and B as well as in the side chain. All new semisynthetic compounds, as well as **1** and **2**, were tested in vitro for their cytotoxic effects on non-small-cell lung cancer cells (A549 cells). Some of these compound displayed potent to moderate activity against A549 tumor cells, especially those cucurbitacin B derivatives which were modified at ring A.

1. Introduction

In recent years, new chemical entities derived from natural products have gained importance in the search for therapeutic drugs. In this context, we have investigated the cucurbitacins as natural product scaffolds for the preparation of new bioactive substances.[1,2] The cucurbitacins are highly oxygenated triterpene derivatives, based on the cucurbitane skeleton, 19-(10→9β)-abeo-10-lanost-5-ene, which are known for their bitter taste.[3] These compounds are predominantly found in different species of the Cucurbitaceae family.[4] The main components of this family are cucurbitacins A–T, and there are hundreds of derivatives which have been classified according to structural features in ring A, side chain modifications and stereochemistry considerations. These compounds can be found in free or glycosylated forms.[3–5] Recent works have reported that cucurbitacins B, D, E, I, Q, and related compounds are active against different tumor cell lines, via suppression of STAT3 (Signal Transducer and Activator of Transcription-3) phosphorylation.[6] STAT3 is constitutively activated in multiple human cancers including ovarian, breast, prostate and lung, playing a pivotal transcriptional role in cancer cell progression, differentiation and survival by up-regulating several genes, including those that encode for anti-apoptotic proteins such as mcl-1 and bcl-xL, and the cell cycle regulators cyclin D1 and c-Myc.[7] Thus, since the most of chemotherapeutic strategies aim to initiate apoptosis, it is now generally accepted that STAT3 represents a valid target for novel anticancer drug design.[8] Some authors also reported that cucurbitacins can directly modulate the actin cytoskeleton. Duncan[9e] demonstrated that cucurbitacin E acts as a potent disruptor of cytoskeletal integrity by increasing the filamentous or polymerized actin fraction in prostate carcinoma cells. Other studies carried out with cucurbitacin B also showed the aggregation of F-actin in various human cancer cell lines.[9]

In the literature there are three important publications on the synthesis and modifications of cucurbitacins: the preparation of hexanorcucurbitacin analogues by Ahn,[10] the semisynthetic study, biological evaluation and QSAR analysis by Halaweish[11] and the first approximation to the total synthesis of the cucurbitane core by Jung.[12] To the best of our knowledge, there are no studies of the preparation of cucurbitacin derivatives in which structural changes were made by removal, modification or permutation of functional groups in order to explore the influence of modifications in the carbon skeleton, conformation, polarity or solubility on the biological activity.

Our research group is interested in the preparation of semisynthetic analogues of bioactive compounds from natural sources with the aim of improving their biological activity.[13] We began our work with two species of Cucurbitaceae, *Wilbrandia ebracteata* Cogn. and *Luffa operculata* (L.) Cogn. which are known for the production of a

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wide variety of cucurbitacin derivatives, with predominance of dihydrocucurbitacin B (**1**) and cucurbitacin B (**2**), Figure 1.

Both compounds have several oxygenated functional groups, making them particularly suitable substrates for semisynthetic modifications, as well as a challenge in terms of chemo- and regioselectivity. Herein, we describe our results in the semisynthesis of several cucurbitacin derivatives and the evaluation of their in vitro cytotoxic activity against lung cancer cells (A549). We designed analogues bearing modifications at positions 2, 3, 7, 16, 20, 22, and 25 of cucurbitacin B and dihydrocucurbitacin B, as well as by molecular simplification of the natural products. A preliminary structure–activity relationship (SARs) is also discussed.

2. Results and discussion

2.1. Chemistry

In a previous report, fractionation of the dichloromethane extract of the roots of *W. ebracteata* led to the isolation of several cucurbitane-type triterpenoids with cytotoxic properties.[14] Two of the active compounds, dihydrocucurbitacin B (**1**) and cucurbitacin B (**2**) could be obtained with good yields from the roots of *W. ebracteata* (2.0 g from 3.7 kg) and from the fruits of *L. operculata* (2.5 g from 2 kg), respectively, and were used to prepare semisynthetic derivatives.

2.1.1. Modifications at C-2 and C-16

The first attempted modifications at C-2 and C-16 were oxidations (Scheme 1). The reaction of **1** with PCC yielded the unexpected compound **3**, instead of the diketone as major compound. Treatment of the α-hydroxy ketones **1** and **3** with KOH in MeOH–DMF, following the procedure used with triterpenoids having a similar A-ring structure, such as maslinic and corosolic acids, afforded the diosphenols **4** and **5**, respectively.[15] This sequence is a simple and practical route to synthesize diosphenol derivatives from natural abundant cucurbitacins.

In order to protect the hydroxyl groups at C-2 and C-16, compounds **1** and **2** were treated with acetic anhydride to yield diesters **6** and **8**, and with succinic anhydride to yield diester **7**. In the same way, acylation of **1** with benzoyl chloride yielded two new ester derivatives: the benzoyl monoester **9** and diester **10**. In order to explore the use of carbamates, the disubstituted derivative **11** was prepared by treatment with 1,1′-carbonyldiimidazol (Scheme 2).

2.1.2. Modifications of the α-hydroxy ketone group in ring A

As it is well known, the α-hydroxy ketone group is present in the most active compounds of the cucurbitacin B family. In order to study the biological importance of this functionality in ring A, we performed structural modifications by substitution at C-2. Ten derivatives were obtained by nucleophilic substitution using the tosylate as leaving group in a regioselective way, as shown in Scheme 3. Compounds **1** and **2** were converted to the sulphonates **12** and **14** by reaction with 4-toluenesulfonyl chloride in the presence of DABCO at low temperatures.[16] The secondary hydroxyl at C-16 in compound **12** was acetylated to yield **13** under standard conditions. These intermediates were treated under S_N2 conditions with a variety of nucleophilic reagents: sulfur nucleofiles like thiophenol to give compounds **15** and **16**, thioacetate to yield compound **17** and thiourea to obtain **18** and **19** aminothiazoles under microwave conditions. All the above mentioned products were synthesized with reasonable yields, between 57 and 84%. Analysis of the ^{1}H NMR spectra of the products revealed that the coupling constants of H-2 were identical as in the starting substances (J = 5.0, 14.0 Hz). Confirmatory NOESY experiments were performed in the case of the thiophenol **15**. A NOE correlation was observed between H-2 (4.07 ppm) and the C-28 methyl (1.29 ppm), which are both located at the α face of the molecule. These facts indicate that the substituent at C-2 is at the β face and that inversion of configuration at C-2 did not take place. It is believed that the presence of a vicinal carbonyl group at C-3 was responsible for this result, leading to the more stable intermediate with a pseudo-equatorial substituent at C-2 due to enolization under the reaction conditions.

Reaction of sulfonates **12–14** with $(Bu)_4NBr$ yielded the brominated analogues **20** and **21**, while treatment with sodium azide in DMF, afforded the enamino ketones **22**, **23** and **24** (Scheme 4). In the last case the reaction proceeds by base-promoted loss of the acidic H-2 with a subsequent irreversible nitrogen loss.[17]

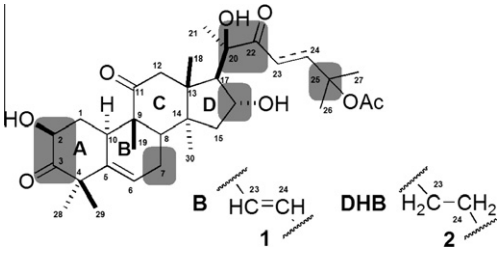


Figure 1. Modifications on Cucurbitacin B and DHB.

2.1.3. Deoxygenation reactions

As the natural bioactive cucurbitacins have hydroxyls at positions 2 and 16, the next goal was to study the influence of dehydroxylation at these positions on the biological activity. To synthesize these compounds, a modified Barton-McCombie deoxygenation reaction was used.[18] For this purpose, the mono and dithiocarbonyl intermediates **25** and **26** were prepared from 1. Treatment of these intermediates with diphenylsilane and lauroyl peroxide in refluxing toluene yielded the 2-deoxy (**27**) and 2,16-dideoxy (**28**) dihydrocucurbitacin B analogues (Scheme 5).

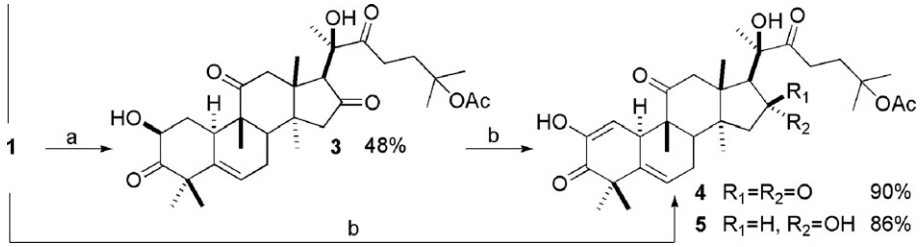
2.1.4. Cleavage of the side chain

The presence of an unstauration in the side chain of cucurbitacin B results in this compound having a much higher cytotoxic activity than dihydrocucurbitacin B.[12] In order to study the influence of the side chain on the biological activity of cucurbitacins, a molecular simplification strategy was applied to obtain new analogues. Starting from **1**, the dibenzoyl ester was obtained and reduced with lithium tri-tert-butoxyaluminium hydride to yield the vicinal diol derivative **29**.[19] An oxidative cleavage of the α-diol on the side chain was performed using periodic acid to give intermediate **30**,[20] which was then oxidized with PCC to give the 3-keto compound **31** (Scheme 6).

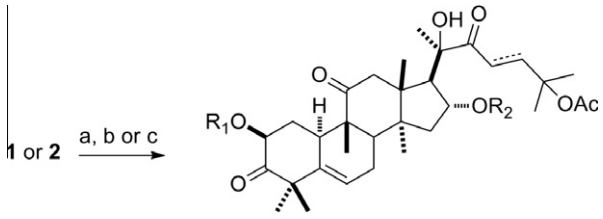
To avoid the isomerization of C-17, the C-20 ketone was protected as the ethylene glycol acetal. The benzoates at C-2 and C-16 were then removed under basic conditions and finally the carbonyls were deprotected with dilute HCl, yielding hexanorcucurbitacin I **33** and hexanorcucurbitacin F **35**.[21]

2.1.5. Modifications in the side chain

In order to observe the importance of some key functionalities of the side chain, the α,β-unsaturated ketone, the tertiary hydroxyl at C-20 and the ester at C-25 were modified (Scheme 7). Luche reduction of **2** yielded the allylic alcohol **36**.[22] The tertiary hydroxyl at C-20 in compound **6** was then protected as a triflouroacetate ester to obtain **37**.[23] The acetate at C-25 was subjected to elimination conditions using the Alvarez-Manzaneda protocol yielding the alkene **38**.[24]



Scheme 1. (a) PCC, $BaCO_3$, CH_2Cl_2; (b) KOH, MeOH, DMF.



Scheme 2. (a) Ac_2O, Py, DMAP; (b) Succinic anhydride, Py, DMAP; (c) BzCl, Py, CH_2Cl_2; (d) CDI, THF, 70 °C.

2.1.6. Introduction of α,β-unsaturated ketones

The α,β-unsaturated ketone in the side chain appears to have a direct relationship with the strong cytotoxicity of some natural cucurbitacins.[9b,25] In order to explore this observation, this functionality was introduced in other parts of the molecule, such as rings A and B (Scheme 8). Selective oxidation of **15** with potassium peroxymonosulfate (Oxone®)[26] produced the sulfoxide, which was then converted to the 1-ene-3-one compound **39** by elimination. The 5-ene-7-one derivative **40** was synthesized from **6** by an allylic oxidation with CrO_3 in pyridine.[27]

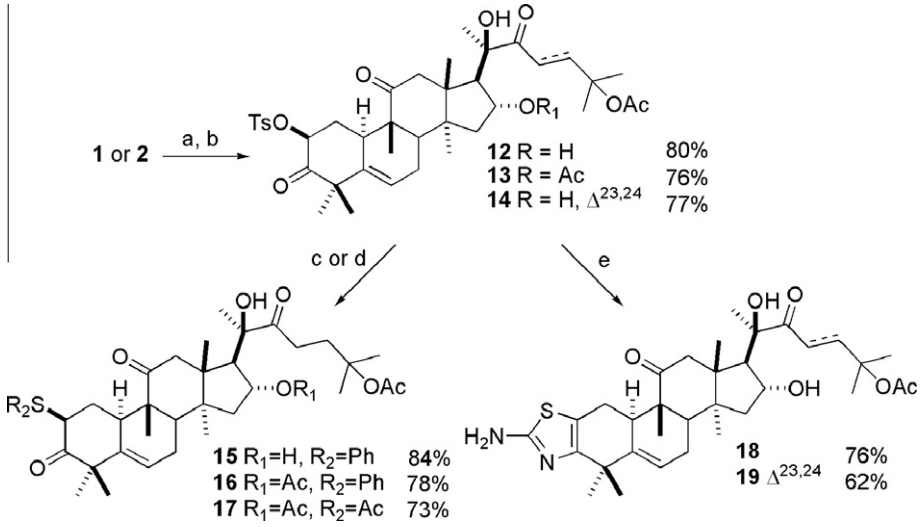
3. Cytotoxic activity

Current in vitro screening methods of cytotoxic effects with the use of human tumor cells are important tools for research and development of new drugs. They allow the evaluation of various types of cancer cells providing leads for the discovery of drugs with high specificity.[28,29]

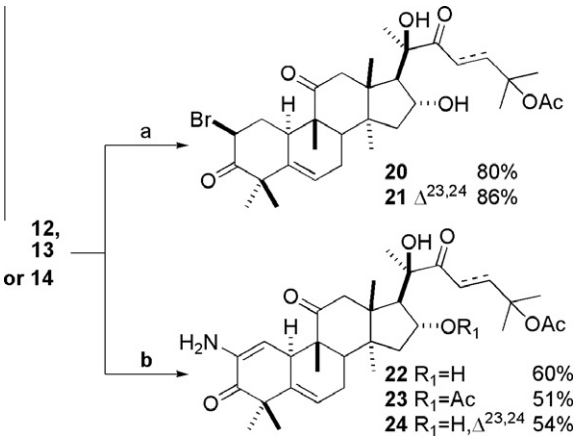
In this work, the cytotoxic activity of the novel synthesized compounds was evaluated against non-small-cell lung cancer (A549 cells) using the MTT colorimetric assay.[30] The activity is expressed as 50% growth inhibitory concentration (IC_{50}) values at 48 h and 72 h, and the results are presented in Table 1.

Derivatives of dihydrocucurbitacin B in which both 2-OH and 16-OH were esterified (compounds **6**, **7**, **8** and **10**) together with the carbamate (compound **11**), showed lack of cytotoxic effects. Compound **3** (16-oxo dihydrocucurbitacin B) was less cytotoxic than the precursor (compound **1**) (26.49 vs 12.09 μM) and the biological activity was lost when the 2-OH of this compound was esterified or converted to an enol (compound **4**). The influence of these two hydroxyl groups could also be observed through the deoxygenation of C-2 and C-16 to give compounds **27** and **28**. The 2-deoxy-dihydrocucurbitacin B (compound **27**) showed a reduction in its cytotoxic activity, while 2,16-dideoxy-dihydrocucurbitacin B (compound **28**) showed an IC_{50} value comparable to the parent compound **1**. Further studies should be made combining the deoxygenation of position 16 and the presence of other molecular modifications to explore the influence of this functionality.

The derivatives of cucurbitacin B with substitution at C-2 (compounds **19**, **21** and **24**) showed significant cytotoxic effects, although somewhat lower than the precursor (compound **2**). Despite the loss of the hydroxyl group at C-2 and the decrease in cytotoxicity, the presence of the nitrogenated groups in the case of **19** and **24** opened the possibility to synthesize new derivatives with higher solubility in biological media. Compound **20**, 2-bromo-dihydrocucurbitacin B derivative, showed moderate activity, about two-fold lower than compound **1** (29.09 vs 12.09 μM).



Scheme 3. Substitution at C-2 with sulphur nucleophiles. Reagents and conditions: (a) 4-toluenesulfonyl chloride, DABCO, CH_2Cl_2, 0 °C; (b) $(CH_3CO)_2O$, Py, DMAP; (c) C_6H_5SH, THF, NaH; (d) CH_3COSK, acetone; (e) $SC(NH_2)_2$, EtOH, MW, 100 °C.



Scheme 4. Substitution at C-2. Reagents and conditions: (a) $(Bu)_4N^-Br^+$, DMF; (b) NaN_3, DMF, 70 °C.

For cucurbitacin B, there are several reports on its cytotoxic[9a,31,32] and antitumoral[6f,33] properties, including some examples where these compounds work in association with other chemotherapeutic agents.[5,31,34–37] Preliminary analyses of structure–activity relationship pointed out the relevance of the α,β-unsaturated ketone in the side chain of cucurbitacin B for its cytotoxic activity.[11,38,39] In an attempt to explore this tendency, derivatives with an α,β-unsaturated ketone were obtained in other positions of the molecule, specifically in rings A (compound **39**) and B (compound **40**). Compound **39** presented a weak activity, while compound **40** was inactive, confirming the importance of the α,β-unsaturated ketone location in the side chain. In the same way, the elimination of this functionality in the side chain (compound **36**) also resulted in an inactive product. When compound **2** was acetylated, product **8** showed less cytotoxicity (2.64 vs 0.04 μM), although the cytotoxic activity remained high. Modifications on the side chain of compound **1** were conducted to give compounds **37** and **38**, but only **38** showed moderate activity.

Taking into account the side chain relevance for the cytotoxic activity of cucurbitacins, compounds **33** and **35** were obtained. These compounds can also be found in natural sources,[40] usually at such low concentrations that hinder biological experimentation. When the cytotoxicity of both compounds (**33** and **35**) was evaluated, the activity was lost suggesting once more that the side chain structure has a huge influence on the cytotoxic activity of this class of compounds. Compound **5** can also be found in natural sources and was already reported as active against U937 tumor cell lines,[40] NUCG-3 and HONE-1,[41] but was inactive in our experiments with A549 cells.

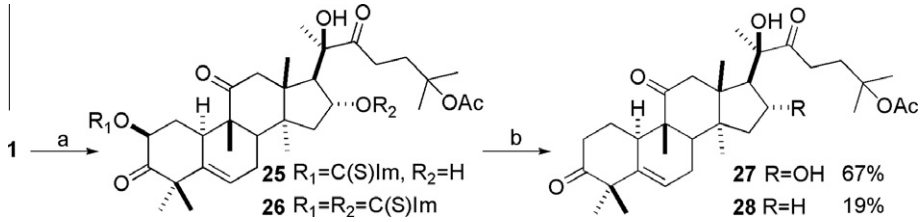
In summary, we describe here the synthesis of new analogues of natural products dihydrocucurbitacin B (**1**) and cucurbitacin B (**2**) including structural variations at different positions. From these results, it is evident that small changes can significantly alter the cytotoxic effects of cucurbitacins. Among the 29 semisynthetic compounds tested, some displayed potent to moderate activity against A549 tumor cells, in particular cucurbitacin B derivatives **8**, **19**, **21** and **24**.

These results allowed a preliminary structure–activity relationship (SAR) evaluation. Further analysis concerning the mechanistic basis of the cytotoxic activity and a quantitative structure–activity relationship (QSAR) are being conducted.

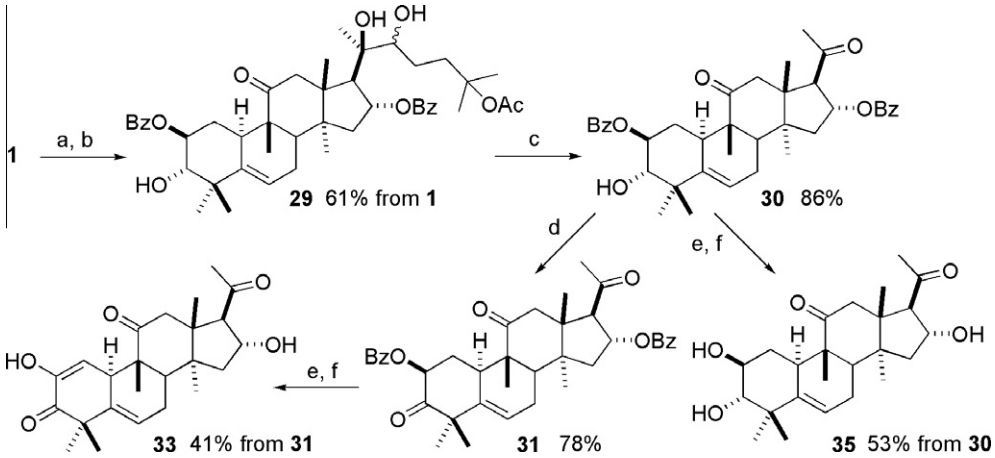
4. Experimental

4.1. General methods

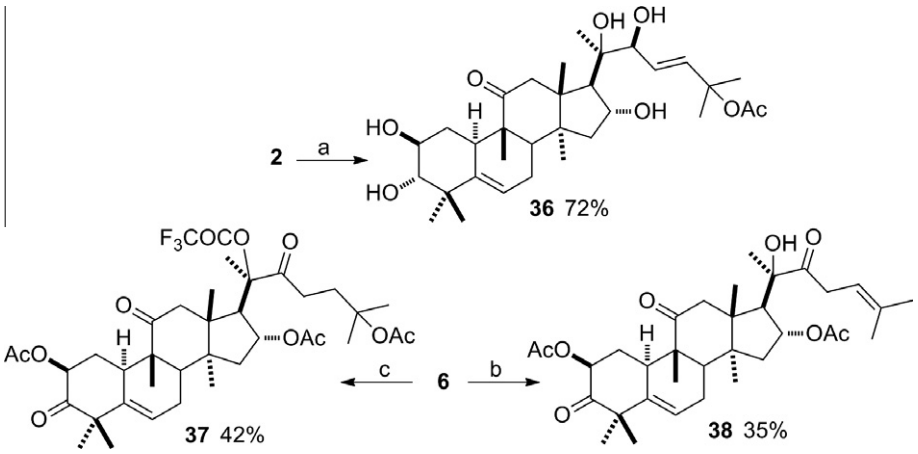
All reactions were followed by analytical thin-layer chromatography (TLC, Merck Silica Gel 60G F_{254}) with visualization under UV



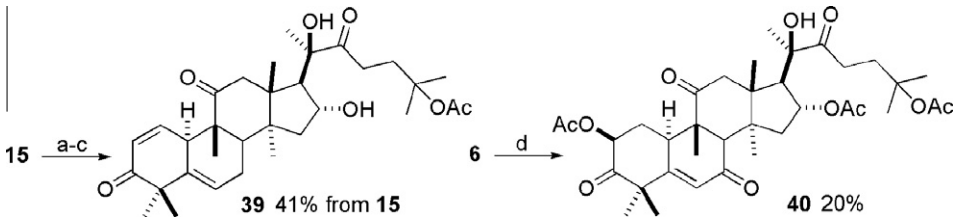
Scheme 5. Reagents and conditions: (a) 1,1′-thiocarbonyldiimidazol, Et_2Cl_2, 60 °C; (b) $[CH_3(CH_2)_{10}CO]_2O_2$, Ph_2SiH_2, toluene, 115 °C.



Scheme 6. Reagents and conditions: (a) C_6H_5COCl, Py, CH_2Cl_2; (b) $C_{12}H_{28}AlO_3Li$, THF, 0 °C; (c) H_5IO_6, MeOH; (d) PCC, $BaCO_3$, CH_2Cl_2; (e) ethylene glycol, $HC(OEt)_3$, TsOH; f) (i) KOH, MeOH, (ii) HCl, Et_2O.



Scheme 7. Reagents and conditions: (a) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, −30 °C; (b) I_2, Ph_3P, CH_2Cl_2; (c) TFAA, DBU, CH_2Cl_2, 0 °C.



Scheme 8. Reagents and conditions: (a) C_6H_5SH, THF, NaH; (b) Oxone, MeOH, H_2O; (c) TEA, toluene, MW, 120 °C, 5 min.; (d) Cr_3O, Py, CH_2Cl_2.

Table 1
Inhibitory effect of dihydrocucurbitacin B and cucurbitacin B analogues on proliferation of A549 cells

Compound	IC_{50}[a]				Increase toxicity (CC_{48}/CC_{72})
	48 h	95% Confidence interval	72 h	95% Confidence interval	
1	19.91	16.32–24.87	12.09	10.26–14.25	1.6
2	0.13	0.09–0.19	0.04	0.03–0.07	3.3
3	54.42	35.65–83.09	26.49	19.80–35.45	2.1
4	>100	–	>100	–	–
5	>100	–	>100	–	–
6	>100	–	72.52	53.46–98.38	–
7	>100	–	>100	–	–
8	14.65	10.90–19.70	2.64	1.89–3.70	5.5
9	>100	–	>100	–	–
10	>100	–	>100	–	–
11	>100	–	>100	–	–
16	>100	–	>100	–	–
17	>100	–	>100	–	–
18	>100	-	>100	–	–
19	28.80	18.98–43.71	11.52	6.80–19.52	2.5
20	34.93	31.40–38.85	29.09	25.21–33.58	1.2
21	1.33	0.452–3.94	0.12	0.07–0.20	11.1
22	>100	–	>100	–	–
23	>100	–	55.19	33.09–92.02	–
24	0.42	0.16–1.13	0.12	0.06–0.23	3.5
26	14.65	10.90–19.69	6.90	4.49–10.60	2.1
27	>100	–	66.74	51.56–86.39	–
28	>100	–	11.47	8.99–14.62	–
30	>100	–	>100	–	–
33	>100	–	>100	–	–
35	>100	–	>100	–	–
36	>100	–	>100	–	–
37	>100	–	>100	–	–
38	>100	–	42.6	26.33–68.93	–
39	87.77	75.08–102.62	77.74	62.83–96.18	1.1
40	>100	–	>100	–	–
Doxorubicin	3.69	2.34–5.82	1.18	0.89–1.55	3.1
Paclitaxel	1.16	0.73–1.84	0.19	0.11–0.32	6.1

[a] IC_{50}: 50% inhibitory concentration (μM); For determination of IC_{50}, data sets from cytotoxicity experiments were analyzed by non-linear regression and calculated using log(compound) compared with normalized response (variable slope), by GraphPad Prism software.

light and by spraying phosphoric vanillin, followed by heating. Uncorrected melting points were determined by using a MQAPF-301 apparatus. IR spectra (KBr) were obtained on a Shimadzu Prestige 2 instrument. NMR spectra were recorded on a Bruker Avance 2 500 MHz spectrometer and on a Varian NMR AS 400. The 2D NMR spectra were obtained using standard pulse sequences. High-resolution ESI (ESI-HR-MS) mass spectra were recorded on a Bruker-Daltonics MicroTOF—Q II mass spectrometer. Column chromatography was performed using silica gel (Merck®). The solvents were purchased from Tedia®, purified and dried before use. All other reagents were purchased from Sigma–Aldrich®.

4.2. Material

Dried and powdered roots of *W. ebracteata* (3.7 kg) were exhaustively extracted with 10 L CH_2Cl_2 of (3×) at room temperature, as previously described.[14] The isolation procedures resulted in the purification of 2.0 g of dihydrocucurbitacin B (**1**).

Additionally, fruits of *L. operculata* (2 kg) were powdered and exhaustively extracted with CH_2Cl_2 (3 × 4 L) at room temperature for 5 days. The extract was filtered and taken to dryness under reduced pressure and temperature below 45 °C generating the dichloromethane extract (9 g). This extract was subjected to vacuum liquid column chromatography (12 cm id × 15 cm) on silica gel: activated charcoal (1:1) using MeOH (500 mL), MeOH:EtOAc (1:1, 500 mL) and EtOAc (500 mL) as eluent. Fraction EtOAc (4 g) was subjected to CC using silica gel as adsorbent (particle size 63–200 μm) and hexane/EtOAc 50% as mobile phase (2 L) providing 2.5 g of cucurbitacin B (**2**).

4.3. Preparation of cucurbitacin analogues

4.3.1. Preparation of 3

A mixture of PCC (582 mg, 3.57 mmol) and $BaCO_3$ (706 mg, 3.57 mmol) in dry CH_2Cl_2 (2.0 mL) was stirred for 5 min. Compound **1** (500 mg, 0.89 mmol) dissolved in 2 mL of CH_2Cl_2 was then added and the reaction was stirred for 2 h. The reaction mixture was diluted with diethyl ether (30.0 mL) and poured through a short column of Florisil®. The solvent was removed under vacuum and the residue was purified by column chromatography (50% ethyl acetate/hexane) to give pure product **3** (240 mg, 48% yield) as white solid. Mp: 108–109 °C; IR (KBr): 3445, 2975, 1367, 1266, 1254, 1206, 1125 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.81 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 4.45 (1H, dd, *J* = 5.9, 13.0 Hz, H-2), 3.61 (1H, s, H-17), 3.36 (1H, d, *J* = 15.0 Hz, H-12a), 2.80 (1H, m, H-10), 2.75 (1H, d, *J* = 15.0 Hz, H-12b), 2.74 (2H, m, H-23), 2.52 (1H, m, H-7b), 2.34 (1H, ddd, *J* = 3.6, 6.1, 13.0, Hz, H-1), 2.25 (1H, d, *J* = 8.0 Hz, H-8), 2.14 (1H, d, *J* = 18 Hz, H-15b), 2.06 (1H, d, *J* = 18 Hz, H-15a), 2.04 (2H, m, H-24), 1.98 (3H, s, Me-32), 1.97 (1H, m, H-7a), 1.47 (3H, s, Me-26), 1.46 (3H, s, Me-27), 1.36 (3H, s, Me-28), 1.34 (3H, s, Me-30), 1.29 (3H, s, Me-21), 1.28 (3H, s, Me-29), 1.28 (1H, ddd, *J* = 13.0, 13.0, 13.0 Hz, H-1b), 1.16 (3H, s, Me-19), 1.13 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 216.1 (C-16), 213.9 (C-22), 212.6 (C-3), 210.3 (C-11), 170.4 (C-31), 140.7 (C-5), 119.9 (C-6), 81.4 (C-25), 80.0 (C-20), 71.5 (C-2), 61.7 (C-17), 50.3 (C-4), 49.5 (C-9), 48.8 (C-15), 47.7 (C-13), 47.0 (C-12), 44.5 (C-14), 42.0 (C-8), 35.9 (C-1), 34.9 (C-24), 33.7 (C-10), 30.2 (C-23), 29.3 (C-28), 25.9 (C-26), 25.8 (C-27), 24.0 (C-7), 23.4 (C-21), 22.4 (C-32), 21.2 (C-29), 20.0 (C-19), 19.6 (C-18), 19.2 (C-30); ESI-MS (negative ion mode) *m*/*z* 557.3143 $[M-H]^+$ (calcd for $C_{32}H_{45}O_8$ 557.3119).

4.3.2. Preparation of 4

To a solution of **3** (100 mg, 0.179 mmol) in MeOH (0.5 mL) and DMF (0.5 mL) was added KOH (65 mg, 1.79 mmol) with stirring at 20 °C. After 1 h, the reaction mixture was evaporated under reduced pressure and the residue was purified by chromatography on silica gel (40% ethyl acetate/hexane) affording **4** (90 mg, 90% yield) as a white solid. Mp: 97–98 °C; IR (KBr): 3444, 3974, 1738, 1731, 1714, 1693, 1665, 1397, 1368, 1267, 1252, 1228, 1206, 1127, 1044 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.96 (1H, dd, *J* = 0.4, 2.7 Hz, H-1), 5.79 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 3.60 (1H, s, H-17), 3.54 (1H, m, H-10), 3.34 (1H, dd, *J* = 0.9, 14.8 Hz, H-12a), 2.78 (1H, d, *J* = 14.8 Hz, H-12b), 2.73 (2H, dt, *J* = 6.0, 8.5 Hz, H-23), 2.49 (1H, ddt, *J* = 2.5, 8.5, 19.5 Hz, H-7b), 2.30 (1H, d, *J* = 8.5, H-8), 2.15 (1H, d, *J* = 18 Hz, H-15b), 2.09 (1H, d, *J* = 18 Hz, H-15a), 2.05 (2H, dt, *J* = 6.0, 8.5 Hz, H-24), 1.98 (1H, m, H-7a), 1.97 (3H, s, CH_3CO_2), 1.47 (3H, s, Me-26), 1.46 (3H, s, Me-27), 1.37 (3H, s, Me-29), 1.37 (3H, s, Me-30), 1.29 (3H, s, Me-20), 1.26 (3H, s, Me-28), 1.15 (3H, s, Me-19), 1.11 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 216.1 (C-16), 213.8 (C-22), 210.9 (C-11), 198.4 (C-3), 170.4 (C-31), 144.7 (C-2), 137.1 (C-5), 120.2 (C-6), 114.1 (C-1), 81.4 (C-25), 79.9 (C-20), 61.8 (C-17), 49.9 (C-9), 49.1 (C-15), 47.8 (C-13), 47.6 (C-4), 47.2 (C-12), 44.6 (C-14), 41.3 (C-8), 35.0 (C-24), 34.7 (C-10), 30.2 (C-23), 27.9 (C-28), 25.9 (C-26), 25.8 (C-27), 23.8 (C-7), 23.4 (C-20), 22.4 (C-32), 20.2 (C-29), 20.1 (C-18), 19.7 (C-19), 18.8 (C-30); ESI-MS (negative ion mode) *m*/*z* 555.2984 $[M-H]^-$ (calcd for $C_{32}H_{43}O_8$ 555.2963).

4.3.3. Preparation of 5

Following the procedure described for **4**, compound **5** was obtained in 86% yield from **1.** Mp: 222–223 °C; IR (KBr): 3547, 2978, 1729, 1712, 1693, 1666, 1660, 1371, 1261, 1231, 1124 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 5.95 (1H, d, *J* = 2.5 Hz, H-1), 5.77 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 4.33 (1H, m, H-16), 3.51 (1H, m, H-10), 3.23 (1H, d, *J* = 14.5 Hz, H-12a), 2.82 (1H, ddd, *J* = 6.0, 10.0, 17.5 Hz), 2.73 (1H, d, *J* = 14.5 Hz, H-12b), 2.53, 2.51 (1H, d, *J* = 6.9 Hz, H-17), 2.52 (1H, m, H-23b), 2.39 (1H, m, H-7b), 2.05 (2H, m, H-24), 2.02 (1H, d, *J* = 8.0 Hz, H-8), 1.97 (1H, m, H-7a), 1.96 (3H, Me-32), 1.86 (1H, dd, *J* = 9.0, 13.0 Hz, H-15b), 1.46 (3H, Me-26), 1.44 (3H, Me-27), 1.42 (3H, Me-21), 1.40 (3H, Me-30), 1.36 (3H, Me-28), 1.25 (3H, Me-29), 1.03 (3H, Me-19), 0.99 (3H, Me-18).[42]

4.3.4. Preparation of 6

A mixture of **1** (300 mg, 0.54 mmol), dry pyridine (2.0 mL), acetic anhydride (2.0 mL) and catalytic amount of DMAP was stirred at 20 °C during 2 h. The mixture was then diluted with 50.0 mL of EtOAc, washed with HCl 1 M solution (3 × 30.0 mL), dried over anhydrous Na_2SO_4 and filtered. The crude product was purified by column chromatography (40% ethyl acetate/hexane) to afford **6** (290 mg, 84% yield) as a white solid. Mp: 131–132 °C. IR (KBr) 3445, 2984, 1731, 1698, 1374, 1245, 1029 cm^{-1}; ^1H NMR (400 MHz,): δ = 5.78 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 5.48 (1H, dd, *J* = 5.5, 13.0 Hz, H-2), 5.14 (1H, m, H-16), 3.25 (1H, d, *J* = 14.5 Hz, H-12a), 2.80 (1H, m, H-10) 2.74 (1H, d, *J* = 14.5 Hz, H-12b), 2.71 (1H, d, *J* = 7.5, H-17), 2.65 (2H, m, H-23), 2.44 (1H, m, H-7b), 2.15 (3H, s, Me-2′), 2.12 (1H, overlapped, H-1a), 2.04 (1H, overlapped, H-15b), 2.04 (2H, m, H-24), 2.02 (1H, d, *J* = 7.5 Hz, H-8), 1.99 (3H, s, Me-32), 1.95 (3H, s, Me-2″), 1.93 (1H, m, H-7a), 1.52 (1H, ddd, *J* = 13.0, 13.0, 13.0 Hz, H-1b), 1.49 (3H, s, Me-27), 1.46 (3H, s, Me-26), 1.45 (3H, s, Me-21), 1.41 (1H, m, H-15a), 1.31 (3H, s, Me-28), 1.31 (3H, s, Me-30), 1.29 (3H, s, Me-29), 1.10 (3H, s, Me-19), 1.02 (3H, s, Me-18); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.3 (C-22), 211.7 (C-11), 205.6 (C-3), 170.1 (C-31), 170.1 (C-1′), 170.0 (C-1″), 139.7 (C-5), 120.4 (C-6), 81.0 (C-25), 78.6 (C-20), 74.0 (C-16), 73.2 (C-2), 54.0 (C-17), 51.2 (C-4), 49.9 (C-13), 48.6 (C-12), 48.4 (C-9), 47.9 (C-14), 43.2 (C-15), 42.0 (C-8), 35.1 (C-24), 34.3 (C-10), 32.0 (C-1), 30.4 (C-23), 28.7 (C-28), 26.0 (C-26), 25.8 (C-27), 24.2 (C-21), 23.7 (C-7), 22.4 (C-32), 21.3 (C-29), 20.0 (C-19), 19.6 (C-18), 18.8 (C-30); ESI-MS (negative ion mode) *m*/*z* 643.3511 $[M-H]^-$ (calcd for $C_{36}H_{51}O_{10}$ 643.3488).

4.3.5. Preparation of 7

To a solution of **1** (100 mg, 0.18 mmol) in CH_2Cl_2 (3.0 mL) and pyridine (0.15 mL, 1.8 mmol) was added succinic anhydride (180 mg, 1.8 mmol) and a catalytic amount of DMAP with stirring at 20 °C. After 24 h, the mixture was diluted with CH_2Cl_2 (20.0 mL) and washed with HCl 1 M (2 × 20.0 mL). The organic phase was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting crude product was purified by column chromatography on silica gel (20% ethyl acetate/hexane), to give the hemisuccinate **7** (95 mg, 70% yield) as a white solid. Mp: 101–102 °C; IR (KBr): 3450, 3200, 2978, 2669, 1746, 1729, 1713, 1370, 1250, 1164, 1017, 980 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.80 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 5.51 (1H, dd, *J* = 13.5, 5.3 Hz, H-2), 5.23 (1H, m, H-16), 3.29 (1H, d, *J* = 14.8 Hz, H-12a), 2.84 (1H, m, H-10), 2.75 (1H, d, *J* = 14.8 Hz, H-12b), 2.74 (1H, d, *J* = 7.5, H-17), 2.72 (2H, m, H-23), 2.72 (2H, m, H-3′), 2.68 (2H, m, H-3″), 2.60 (2H, m, H-2′) 2.45 (2H, m, H-2″), 2.43 (1H, m, H-7b), 2.12 (2H, m, H-1a), 2.03 (2H, m, H-24), 2.01 (1H, overlapped, H-15b), 2.02 (1H, d, *J* = 8.0 Hz, H-8), 2.0 (1H, overlapped, H-15b), 1.99 (3H, s, Me-32), 1.95 (1H, m, H-7a), 1.53 (1H, ddd, *J* = 13.5, 13.5, 13.5 Hz, H-1b), 1.48 (3H, s, Me-27), 1.47 (3H, s, Me-26), 1.45 (3H, s, Me-21), 1.41 (1H, overlapped, H-15a), 1.32 (3H, s, Me-29), 1.31 (3H, s, Me-30), 1.28 (3H, s, Me-28), 1.09 (3H, s, Me-19), 1.0 (3H, s, Me-18); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.0 (C-22), 212.6 (C-11), 205.9 (C-3), 174.6 (C-4′), 174.4 (C-4″), 171.8 (C-1′), 171.7 (C-1″), 170.7 (C-31), 139.3 (C-5), 120.4 (C-6), 81.2 (C-25), 78.6 (C-20), 74.3 (C-16), 73.5 (C-2), 54.1 (C-17), 51.2 (C-4), 50.0 (C-13), 48.4 (C-12), 48.3 (C-9), 47.6 (C-14), 42.9 (C-15), 41.9 (C-8), 35.1 (C-24), 34.0 (C-10), 31.9 (C-1), 30.7 (C-23), 29.0 (C-3′), 28.8 (C-3″), 28.4 (C-28), 25.7 (C-2′), 25.6 (C-2″), 24.2 (C-21), 23.6 (C-7), 22.2 (C-32), 21.1 (C-29), 19.8 (C-19), 19.6 (C-18), 18.6 (C-30); ESI-MS (negative ion mode) *m/z* 759.3612 $[M-H]^-$ (calcd for $C_{40}H_{55}O_{14}$ 759.3597).

4.3.6. Preparation of 8

Following the procedure described for **6**, compound **8** was obtained in 80% yield from **2.** Mp: 121–122 °C; IR (KBr): 3439, 2979, 1738, 1728, 1690, 1633, 1367, 1241, 1131, 1024 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$): δ = 7.15 (1H, d, *J* = 15.6 Hz, H-24), 6.40 (1H, d, *J* = 15.6, H-23), 5.77 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 5.47 (1H, dd, *J* = 5.2, 13.5 Hz, H-2), 5.17 (1H, m, H-16), 3.24 (1H, d, *J* = 14.6 Hz, H-12a), 2.80 (1H, m, H-10), 2.74 (1H, d, *J* = 14.6 Hz, H-12b), 2.69 (1H, d, *J* = 7.5 Hz, H-17), 2.41 (1H, ddt, *J* = 2.5, 8.0, 19.0 Hz, H-7b), 2.14 (3H, s, Me-2′), 2.11 (1H, overlapped, H-1a), 2.03 (3H, s, Me-32), 1.97 (1H, d, *J* = 8.0 Hz, H-8), 1.97 (1H, m, H-7a), 1.91 (1H, overlapped, H-15b),1.86 (3H, s, Me-2″), 1.58 (3H, s, H-27), 1.57 (3H, s, H-26), 1.52 (1H, ddd, *J* = 13.0, 13.0, 13.0 Hz, H-1b), 1.42 (3H, s, Me-21), 1.38 (1H, d, *J* = 13.0 Hz, H-15a), 1.31 (3H, s, H-30), 1.30 (3H, s, H-28), 1.28 (3H, s, H-29), 1.09 (3H, s, H-19), 1.02 (3H, s, H-18); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 211.8 (C-11), 205.6 (C-3), 200.8 (C-22), 170.3 (C-31), 170.1 (C-1′), 169.6 (C-1″), 152.7 (C-24), 139.7 (C-5), 120.4 (C-6), 119.2 (C-23), 79.1 (C-25), 77.6 (C-20), 73.5 (C-16), 73.3 (C-2), 54.1 (C-17), 51.2 (C-4), 49.9 (C-13), 48.6 (C-12), 48.4 (C-9), 48.0 (C-14), 43.1 (C-15), 42.1 (C-8), 34.3 (C-10), 31.9 (C-1), 28.8 (C-28), 26.6 (C-26), 26.3 (C-27), 23.7 (C-21), 23.6 (C-7), 21.9 (C-32), 21.3 (C-29), 20.7 (C-2′), 20.6 (C-2″), 19.9 (C-19), 19.7 (C-18), 18.7 (C-30); ESI-MS (positive ion mode) *m/z* 660.3742 $[M+NH_4]^+$ (calcd for $C_{36}H_{54}NO_{10}$ 660.3742).

4.3.7. Preparation of 9 and 10

To a solution of compound **1** (1.0 g, 1.79 mmol) in CH_2Cl_2 (10.0 mL) and pyridine (5.0 mL), benzoyl chloride (0.41 mL, 3.57 mmol) was added dropwise under nitrogen atmosphere, at 0 °C. The reaction was kept at 20 °C for 4 h, diluted by adding 50 mL of CH_2Cl_2 and washed with HCl 1 M (3 × 30 mL). The organic phase was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting crude product was purified by chromatography on silica gel (40% ethyl acetate/hexane) to give **9** as a minor product (230 mg, 19% yield), together with **10** as a major product (900 mg, 65% yield) as white solids. (**9**) Mp: 135–136 °C; IR (KBr): 3526, 3440, 2975, 1736, 1698, 1370, 1316, 1270, 1208, 1177, 1123, 1027, 979, 713 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.07 (2H, dd, *J* = 8.4, 1.3 Hz, H-3′/H-7′), 7.56 (1H, m, H-5′), 7.44 (2H, t, *J* = 8.4, Hz, H-4′/H-6′), 5.82 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 5.72 (1H, dd, *J* = 5.5, 13.6 Hz, H-2), 4.31 (1H, m, H-16), 3.28 (1H, d, *J* = 14.6 Hz, H-12a), 2.91 (1H, m, H-10), 2.83 (1H, m, H-23a), 2.71 (1H, d, *J* = 14.6 Hz, H-12b), 2.55 (1H, d, *J* = 6.9 Hz, H-17), 2.52 (1H, m, H-23b), 2.43 (1H, ddt, *J* = 2.5, 8.0, 19.5 Hz, H-7b), 2.27 (1H, ddd, *J* = 3.6, 5.5, 13.0, Hz, H-1a), 2.06 (2H, m, H-24), 2.0 (1H, d, *J* = 8.0 Hz, H-8), 1.98 (1H, m, H-7a), 1.96 (3H, s, Me-32), 1.85 (1H, dd, *J* = 9.0, 13.0 Hz, H-15b), 1.69 (1H, ddd, *J* = 13.0, 13.0, 13.0 Hz, H-1b), 1.46 (3H, s, Me-27), 1.44 (3H, s, Me-30), 1.42 (3H, s, Me-26), 1.40 (1H, m, H-15a), 1.40 (3H, s, Me-21), 1.39 (3H, s, Me-28), 1.32 (3H, s, Me-29), 1.13 (3H, s, Me-19), 0.98 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 213.9 (C-22), 212.3 (C-11), 205.5 (C-3), 170.3 (C-31), 165.7 (C-1′), 139.8 (C-5), 133.2 (C-5′), 129.9 (C-3′/C-7′), 129.5 (C-2′), 128.3 (C-4′/6′), 120.6 (C-6), 81.3 (C-25), 78.9 (C-20), 73.9 (C-2), 71.0 (C-16), 57.8 (C-17), 51.4 (C-4), 50.7 (C-13), 48.8 (C-12), 48.5 (C-9), 48.4 (C-14), 45.5 (C-15), 42.4 (C-8), 34.8 (C-24), 34.4 (C-10), 32.1 (C-1), 30.7 (C-23), 28.8 (C-28), 26.2 (C-26), 25.9 (C-27), 24.5 (C-21), 23.9 (C-7), 22.4 (C-32), 21.3 (C-29), 20.0 (C-19), 19.9 (C-18), 18.7 (C-30); ESI-MS (negative ion mode) *m/z* 663.3557 $[M-H]^-$ (calcd for $C_{39}H_{51}O_9$ 663.3539). (**10**) Mp: 122–123 °C; IR (KBr): 2978, 1737, 1723, 1714, 1696, 1369, 1268, 1176, 1115, 1068, 1024, 978 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.07 (2H, dd, *J* = 8.5, 1.3 Hz, H-3′/H-7′), 7.92 (2H, dd, *J* = 8.5, 1.3 Hz, H-3″/H-7″), 7.57 (2H, m, H-5′/H-5″), 7.44 (4H, m, H-4′/H-4″/H-6′/H-6″), 5.78 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 5.74 (dd, *J* = 13.0, 5.5 Hz, H-2), 5.53 (1H, m, H-16), 3.34 (1H, d, *J* = 14.7 Hz, H-12a), 2.93 (1H, m, H-10), 2.92 (2H, d, *J* = 7.2 Hz, H-17), 2.80 (1H, d, *J* = 14.6 Hz, H-12b), 2.63 (1H, ddd, *J* = 17.5, 10.0, 6.0 Hz, H-23a), 2.52 (1H, m, H-23b), 2.45 (1H, ddt, *J* = 2.5, 8.0, 19.0 Hz, H-7b), 2.30 (1H, ddd, *J* = 3.6, 5.5, 13.0 Hz, H-1a), 2.13 (1H, dd, *J* = 13.8, 9.0 Hz, H-15b), 2.08 (1H, d, *J* = 8.0 Hz, H-8), 1.96 (1H, dd, *J* = 5.0, 19.0 Hz, H-7a), 1.95 (3H, s, Me-32), 1.77 (1H, m, H-24a), 1.72 (1H, ddd, *J* = 13.0, 13.0, 13.0 Hz, H-1b), 1.54 (1H, m, H-24b), 1.52 (1H, d, *J* = 13.8 Hz, H-15a), 1.47 (3H, s, H-30), 1.44 (3H, s, H-27), 1.39 (3H, s, H-26), 1.30 (3H, s, H-21), 1.27 (3H, s, H-28), 1.27 (3H, s, H-29), 1.16 (3H, s, H-19), 1.10 (3H, s, H-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 212.5 (C-22), 211.8 (C-11), 205.4 (C-3), 170.2 (C-31), 165.7 (C-1″), 165.5 (C-1′), 139.8 (C-5), 133.2 (C-5′/C-5″), 129.8 (C-3′/C-7′), 129.4 (C-3″/C-7″), 128.5 (C-4′/C-6′), 128.4 (C-4′/C-6″), 120.5 (C-6), 80.9 (C-25), 78.9 (C-20), 74.4 (C-16), 73.8 (C-2), 54.7 (C-17), 51.4 (C-4), 50.4 (C-13), 48.7 (C-12), 48.4 (C-9), 48.0 (C-14), 43.5 (C-15), 42.0 (C-8), 35.3 (C-24), 34.4 (C-10), 32.1 (C-1), 30.5 (C-23), 28.8 (C-28), 25.8 (C-26), 25.5 (C-27), 24.3 (C-21), 23.8 (C-7), 22.4 (C-32), 21.3 (C-29), 20.1 (C-19), 19.8 (C-18), 18.7 (C-30); ESI-MS (negative ion mode) *m/z* 767.3803 $[M-H]^-$ (calcd for $C_{46}H_{55}O_{10}$ 767.3801).

4.3.8. Preparation of 11

To a solution of **1** (100 mg, 0.18 mmol) in THF (3.0 mL), 1,1′-carbonyldiimidazole (120 mg, 0.72 mmol) was added and the mixture was heated at 70 °C. After 4 h, the reaction was diluted by adding 30 mL of diethyl ether and washed with brine (2 × 30.0 mL). The organic phase was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting crude product was purified by chromatography on silica gel (70% ethyl acetate/hexane) to give **11** (67 mg, 50% yield) as a white solid. Mp: 148–149 °C; IR (KBr): 2935, 1758, 1727, 1395, 1370, 1316, 1289, 1240, 1223, 1172, 1041, 1002, 938 cm^{-1}; ^1H NMR^1H NMR (400 MHz, $CDCl_3$): δ = 8.17 (1H, m, H-4′), 8.07 (1H, m, H-4″), 7.45 (1H, s, H-2′), 7.37

(1H, s, H-2″), 7.09 (2H, m, H-3′/H-3″), 5.84 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 5.65 (1H, dd, *J* = 5.0, 13.0 Hz, H-2), 5.63 (1H, m, H-16), 3.31 (1H, d, *J* = 14.5 Hz, H-12a), 2.91 (1H, d, *J* = 7.2 Hz, H-17), 2.87 (1H, m, H-10), 2.80 (1H, d, *J* = 14.5 Hz, H-12b), 2.65 (2H, m, H-23), 2.48 (1H, ddt, *J* = 2.5, 8.0, 19.0 Hz, H-7b), 2.37 (1H, ddd, *J* = 3.6, 5.5, 13.0 Hz, H-1a), 2.15 (1H, dd, *J* = 13.8, 9.0 Hz, H-15b), 2.10 (1H, d, *J* = 8.0 Hz, H-8), 1.99 (1H, dd, *J* = 5.0, 19.0 Hz, H-7a), 1.98 (3H, s, Me-32), 1.75 (1H, overlapped, H-15a), 1.73 (2H, m, H-24), 1.68 (1H, ddd, *J* = 13.0, 13.0, 13.0 Hz, H-1b), 1.50 (3H, s, Me-30), 1.39 (3H, s, Me-27), 1.37 (3H, s, Me-26), 1.37 (3H, s, Me-21), 1.34 (3H, s, Me-29), 1.32 (3H, s, Me-28), 1.17 (3H, s, Me-19), 1.08 (3H, s, Me-18); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 213.4 (C-22), 211.3 (C-11), 204.0 (C-3), 170.2 (C-31), 147.8 (C-1′), 147.7 (C-1″), 139.0 (C-5), 137.2 (C-4′), 136.8 (C-4″), 130.8 (C-3′), 130.6 (C-3″), 120.9 (C-6), 117.2 (C-2′), 117.0 (C-2″), 80.9 (C-25), 78.9 (C-20), 78.5 (C-2), 76.6 (C-16), 54.7 (C-17), 51.3 (C-4), 50.2 (C-13), 48.4 (C-12), 48.2 (C-9), 47.9 (C-14), 43.0 (C-15), 41.9 (C-8), 35.0 (C-24), 34.1 (C-10), 31.8 (C-1), 31.0 (C-23), 28.5 (C-28), 25.7 (C-26), 25.6 (C-27), 24.3 (C-21), 23.7 (C-7), 22.3 (C-32), 21.1 (C-29), 20.2 (C-19), 19.7 (C-18), 18.7 (C-30); ESI-MS (positive ion mode) *m/z* 749.3754 $[M+H]^+$ (calcd for $C_{40}H_{53}N_4O_{10}$ 749.3756).

4.3.9. Preparation of 12

To a solution of compound **1** (1.0 g, 1.79 mmol) in CH_2Cl_2 (8.0 mL), DABCO (1.0 g, 8.95 mmol) was added and the mixture was cooled at 0 °C. *p*-Toluenesulfonyl chloride (1.36 g, 7.16 mmol) was then added (3 × 1.3 mmol each 15 min). After 15 min of the last addition the mixture was diluted by adding 60.0 mL of cold CH_2Cl_2, washed with cold HCl 1 M (3 × 50.0 mL) and cold brine (3 × 50.0 mL). The organic phase was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting crude product was purified by chromatography on silica gel (40% ethyl acetate/hexane) to afford **12** (1.02 g, 80% yield) as a white solid. Mp: 122–123 °C; IR (KBr): 3549, 3449, 1279, 1732, 1697, 1598, 1370, 1357, 1179, 967, 889 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (2H, d, *J* = 8.4 Hz, H-3′/H-5′), 7.35 (2H, *J* = 8.4 Hz, H-2′/H-6′), 5.79 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 5.39 (1H, dd, *J* = 13.0, 6.0 H-2), 4.31 (1H, m, H-16), 3.25 (1H, d, *J* = 14.5, H-12a), 2.82 (1H, m, 23a), 2.81 (1H, m, H-10), 2.70 (1H, d, *J* = 14.5, H-12b), 2.54 (1H, d, *J* = 8.2 Hz, H-17), 2.53 (1H, overlapped, H-23b), 2.45 (3H, s, Me-7′), 2.40 (1H, m, H-7b), 2.24 (1H, ddd, *J* = 13.0, 6.1, 3.6 Hz, H-1a), 2.06 (2H, m, H-24), 1.99 (1H, m, H-7a), 1.98 (1H, d, *J* = 8.5 Hz, H-8), 1.96 (3H, s, Me-32), 1.55 (1H, ddd, *J* = 13.0, 13.0, 13.0 Hz, H-1b), 1.85 (1H, dd, *J* = 13.0, 9.0 Hz, H-15b), 1.47 (3H, s, Me-27), 1.45 (3H, s, Me-26), 1.43 (3H, s, Me-21), 1.40 (1H, m, H-15a), 1.35 (3H, s, Me-30), 1.27 (3H, s, Me-28), 1.26 (3H, s, Me-29), 1.24 (1H, m, H-1α), 1.03 (3H, s, Me-19), 0.97 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 213.9 (C-22), 211.8 (C-11), 203.9 (C-3), 170.4 (C-31), 144.9 (C-4′), 138.9 (C-5), 133.9 (C-1′), 129.7 (C-3′/C-5′), 127.9 (C-2′/C-6′), 121.0 (C-6), 81.3 (C-25), 78.9 (C-2), 78.8 (C-20), 71.0 (C-16), 57.7 (C-17), 51.5 (C-4), 50.6 (C-13), 48.7 (C-12), 48.3 (C-9), 48.3 (C-14), 45.4 (C-15), 42.3 (C-8), 34.8 (C-24), 34.2 (C-10), 33.5 (C-1), 30.7 (C-23), 28.5 (C-28), 26.1 (C-26), 25.8 (C-27), 24.4 (C-21), 23.8 (C-7), 22.4 (C-32), 21.7 (C-29), 21.3 (C-2″), 19.9 (C-19), 19.8 (C-18), 18.6 (C-30); ESI-MS (positive ion mode) *m/z* 732.3780 $[M+NH_4]^+$ (calcd for $C_{39}H_{58}NO_{10}S$ 749.3776).

4.3.10. Preparation of 13

Following the procedure described for **6**, compound **13** was obtained in 95% yield from **12**. Mp: 121–122 °C; IR (KBr) 3315, 2979, 1735, 1697, 1369, 1254, 1175, 1091, 1014, 970 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85 (2H, d, *J* = 8.4 Hz, H-3′/H-5′), 7.35 (2H, d, *J* = 8.4 Hz, H-2′/H-6′), 5.77 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 5.70 (1H, dd, *J* = 13.0, 6.0 Hz, H-2), 5.14 (1H, m, H-16), 3.25 (1H, d, *J* = 14.7 Hz, H-12a), 2.79 (1H, m, H-10), 2.75 (1H, d, *J* = 14.7 Hz, H-12b), 2.71 (1H, d, *J* = 7.5 Hz, H-17), 2.69 (2H, m, H-23), 2.45 (3H, s, Me-7′), 2.40 (1H, ddt, *J* = 19.5, 8.5, 2.5 Hz, H-7b), 2..24 (1H, m, H-1a), 2.04 (2H, m, H-24), 2.0 (1H, m, H-15b), 2.0 (1H, d, *J* = 8.5 Hz, H-8), 1.99 (3H, s, Me-32), 1.94 (3H, s, Me-2″), 1.92 (1H, m, H-7a), 1.50 (3H, s, Me-26), 1.47 (3H, s, Me-27), 1.45 (3H, s, Me-21), 1.40 (1H, dd, *J* = 14.0, 1.0 Hz, H-15a), 1.29 (3H, s, Me-30), 1.25 (3H, s, Me-28), 1.25 (3H, s, Me-29), 1.04 (3H, s, Me-19), 1.01 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 212.5 (C-22), 211.4 (C-11), 203.9 (C-3), 170.3 (C-31), 170.1 (C-1″), 145.0 (C-4′), 139.1 (C-5), 134.1 (C-1′), 129.8 (C-3′/C-5′), 128.0 (C-2′/C-6′), 121.1 (C-6), 81.2 (C-25), 78.8 (C-2), 78.7 (C-20), 74.2 (C-16), 54.2 (C-17), 51.7 (C-4), 50.0 (C-13), 48.8 (C-12), 48.4 (C-9), 48.0 (C-14), 43.3 (C-15), 42.1 (C-8), 35.3 (C-24), 34.4 (C-10), 33.6 (C-1), 30.6 (C-23), 28.6 (C-28), 26.2 (C-26), 26.0 (C-27), 24.4 (C-21), 23.8 (C-7), 22.5 (C-32), 21.9 (C-7′), 21.5 (C-29), 21.1 (C-2″), 20.1 (C-19), 19.8 (C-18), 18.9 (C-30). ESI-MS (positive ion mode) *m/z* 779.3436 $[M+Na]^-$ (calcd for $C_{41}H_{56}Na_{11}S$ 779.3435).

4.3.11. Preparation of 14

Following the procedure described for **12**, compound **14** was obtained in 77% yield from **2**. Mp: 133–134 °C; IR (KBr): 3450, 3279, 1738, 1730, 1693, 1632, 1368, 1250, 1175, 1126, 1092, 968, 891, 679, 560 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85 (2H, d, *J* = 8.4 Hz, H-3′/H-5′), 7.34 (2H, d, *J* = 8.4 Hz, H-2′/H-6′), 7.07 (1H, d, *J* = 15.6 Hz, H-24), 6.48 (1H, d, *J* = 15.6 Hz, H-23), 5.78 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 5.40 (1H, dd, *J* = 13.0, 6.0 Hz, H-2), 4.35 (1H, m, H-16), 3.24 (1H, d, *J* = 14.7 Hz, H-12a), 2.81 (1H, m, H-10), 2.70 (1H, d, *J* = 14.7 Hz, H-12b), 2.50 (1H, d, *J* = 7.1 Hz, H-17), 2.45 (3H, s, H-7′), 2.38 (1H, ddt, *J* = 19.5, 8.2, 2.4 Hz, H-7b), 2.24 (1H, ddd, 12.5, 5.5, 3.7 Hz, H-1a), 2.03 (3H, s, Me-32), 1.97 (1H, d, *J* = 8.5 Hz, H-8), 1.96 (1H, m, H-7a), 1.86 (1H, dd, *J* = 13.3, 9.3, H-15b), 1.58 (3H, s, Me-26), 1.56 (1H, overlapped, H-1a), 1.55 (3H, s, Me-26), 1.45 (3H, s, Me-26), 1.42 (1H, overlapped, H-15b), 1.42 (3H, s, Me-21), 1.26 (3H, s, Me-28), 1.26 (3H, s, Me-29), 1.03 (3H, s, Me-19), 0.97 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 211.8 (C-11), 203.9 (C-3), 202.4 (C-22), 170.2 (C-31), 152.0 (C-24), 144.8 (C-4′), 138.9 (C-5), 134.0 (C-1′), 129.6 (C-3′/C-5′), 127.9 (C-2′/C-6′), 121.1 (C-6), 120.2 (C-23), 79.3 (C-25), 78.8 (C-2), 78.1 (C-20), 71.3 (C-16), 58.2 (C-17), 51.5 (C-4), 50.6 (C-13), 48.7 (C-12), 48.4 (C-9), 48.0 (C-14), 45.3 (C-15), 42.3 (C-8), 34.2 (C-10), 33.5 (C-1), 28.5 (C-28), 26.4 (C-27), 25.9 (C-26), 23.9 (C-21), 23.8 (C-7), 22.0 (C-32), 21.7 (C-7′), 21.4 (C-29), 19.9 (C-18), 19.9 (C-19), 18.6 (C-30); ESI-MS (positive ion mode) *m/z* 730.3613 $[M+NH_4]^+$ (calcd for $C_{39}H_{56}NO_{10}S$ 730.3619).

4.3.12. Preparation of 15

To a solution of **12** (80 mg, 0.11 mmol) in anhydrous THF (1.0 mL), thiophenol (0.01 mL, 10.3 mmol) was added with stirring at 20 °C under nitrogen atmosphere. After 2 h, the reaction was diluted by adding 20 mL of CH_2Cl_2 and washed with NaOH 20% (2 × 25 mL). The organic phase was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting crude product was purified by chromatography on silica gel (30% ethyl acetate/hexane) to afford **15** (62 mg, 84% yield) as a white solid. Mp: 105–106 °C; IR (KBr): 3454, 2976, 1730, 1713, 1704, 1694, 1470, 1462, 1366, 1252, 1210, 1174, 1128, 1022, 749, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.40 (2H, m, H-2′/H-6′), 7.30 (2H, m, H-3′/H-5′), 7.26 (1H, m, H-4′), 5.78 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 4.30 (1H, m, H-16), 4.07 (1H, dd, *J* = 13.5, 5.3 Hz, H-2), 3.18 (1H, d, *J* = 14.6 Hz, H-12a), 2.80 (1H, m, H-23a), 2.63 (1H, d, *J* = 14.6 Hz, H-12b), 2.62 (1H, m, H-10), 2.51 (1H, d, *J* = 7.1 Hz, H-17), 2.50 (1H, m, H-23b), 2.40 (ddt, *J* = 19.6, 8.5, 2.9 Hz, H-7b), 2.26 (1H, ddd, *J* = 13.5, 5.3, 3.6 Hz, H-1a), 2.05 (2H, m, H-24), 1.97 (1H, overlapped, H-7a), 1.96 (3H, s, Me-32), 1.95 (1H, d, *J* = 8.0 Hz, H-8), 1.83 (1H, dd, *J* = 12.7, 9.5 Hz, H-15b), 1.54 (1H, ddd, *J* = 13.5, 13.5, 13.5 Hz, H-1b), 1.45 (3H, s, Me-26), 1.43 (3H, s, Me-27), 1.39 (3H, s, Me-21), 1.37 (1H, d, *J* = 12.7 Hz, H-15a), 1.33 (3H, s, Me-29),

1.29 (3H, s, Me-28), 1.05 (3H, s, Me-19), 0.94 (3H, s, Me-18). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 213.9 (C-22), 212.2 (C-11), 208.2 (C-3), 170.3 (C-31), 140.3 (C-5), 133.8 (C-1′), 132.5 (C-3′/C-5′), 129.0 (C-2′/C-6′), 127.5 (C-4′), 120.1 (C-6), 81.2 (C-25), 78.9 (C-20), 71.0 (C-16), 57.7 (C-2), 54.6 (C-17), 51.7 (C-4), 50.6 (C-13), 48.7 (C-9), 48.6 (C-12), 48.4 (C-14), 45.5 (C-15), 42.3 (C-8), 36.4 (C-10), 34.8 (C-24), 33.7 (C-1), 30.6 (C-23), 28.7 (C-28), 26.1 (C-26), 25.8 (C-27), 24.4 (C-21), 23.8 (C-7), 23.1 (C-29), 22.4 (C-32), 19.8 (C-19), 19.8 (C-18), 18.7 (C-30); ESI-MS (positive ion mode) *m/z* 675.3349 $[M+Na]^+$ (calcd for $C_{38}H_{52}NaO_7S$ 675.3326).

4.3.13. Preparation of 16

Following the procedure described for **15**, compound **16** was obtained in 78% yield from **13**. Mp: 101–102 °C; IR (KBr): 2978, 1738, 1730, 1714, 1684, 1370, 1250, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.40 (2H, dd, *J* = 8.0, 1.5 Hz, H-2′/H-6′), 7.30 (2H, m, H-3′/H-5′), 7.26 (1H, m, H-4′), 5.76 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 5.12 (1H, m, H-16), 4.05 (1H, dd, *J* = 13.2, 5.3 Hz, H-2), 3.17 (1H, d, *J* = 14.6 Hz, H-12a), 2.68 (1H, d, *J* = 7.2 Hz, H-17), 2.67 (1H, d, *J* = 14.6 Hz, H-12b), 2.58 (2H, m, H-23), 2.57 (1H, m, H-10), 2.40 (ddt, *J* = 19.6, 8.5, 2.9 Hz, H-7b), 2.26 (1H, ddd, *J* = 13.2, 5.3, 3.6 Hz, H-1a), 2.02 (2H, m, H-24), 2.0 (1H, overlapped, H-15b), 1.99 (3H, s, Me-32), 1.97 (1H, d, *J* = 8.0 Hz, H-8), 1.96 (3H, s, Me-2″), 1.90 (1H, ddd, *J* = 13.2, 6.0, 1.5 Hz, H-7a), 1.54 (1H, ddd, *J* = 13.2, 13.2, 13.2 Hz, H-1b), 1.48 (3H, s, Me-26), 1.45 (3H, s, Me-27), 1.41 (3H, s, Me-21), 1.37 (1H, dd, *J* = 14.0, 1.0 Hz, H-15a), 1.32 (3H, s, Me-29), 1.28 (3H, s, Me-28), 1.26 (3H, s, Me-30), 1.06 (3H, s, Me-19), 0.98 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 212.3 (C-22), 211.6 (C-11), 208.1 (C-3), 170.0 (C-31), 140.3 (C-5), 133.7 (C-1′), 132.6 (C-3′/C-5′), 129.0 (C-2′/C-6′), 127.6 (C-4′), 120.1 (C-6), 81.0 (C-25), 78.6 (C-20), 74.0 (C-16), 54.5 (C-2), 54.0 (C-17), 51.6 (C-4), 49.9 (C-13), 48.6 (C-9), 48.5 (C-12), 47.9 (C-14), 43.2 (C-15), 42.1 (C-8), 36.4 (C-10), 35.1 (C-24), 33.6 (C-1), 30.4 (C-23), 28.6 (C-28), 26.0 (C-26), 25.8 (C-27), 24.2 (C-21), 23.7 (C-7), 23.2 (C-29), 22.3 (C-32), 20.9 (C-2″), 19.9 (C-19), 19.6 (C-18), 18.8 (C-30); ESI-MS (negative ion mode) *m/z* 693.3459 $[M-H]^-$ (calcd for $C_{40}H_{53}O_8S$ 663.3467).

4.3.14. Preparation of 17

To a solution of **13** (80 mg, 0.106 mmol) in anhydrous acetone (1.0 mL), potassium thioacetate (121 mg, 1.06 mmol) was added with stirring at 20 °C under nitrogen atmosphere. After 8 h, the mixture was filtered and evaporated under reduced pressure. The resulting crude product was purified by column chromatography on silica gel (30% ethyl acetate/hexane), to give **17** (51 mg, 73% yield) as a white solid. Mp: 113–114 °C; IR (KBr): 3479, 2978, 1737, 1730, 1714, 1693, 1682, 1369, 1249 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.78 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 5.14 (1H, ddd, *J* = 1.2, 7.6, 9.3 Hz, H-16), 4.58 (1H, dd, *J* = 5.0, 14.0 Hz, H-2), 3.30 (1H, dd, *J* = 0.6, 14.6 Hz, H-12a), 2.85 (1H, m, H-10), 2.75 (1H, d, *J* = 14.6 Hz, H-12b), 2.72 (1H, d, *J* = 7.6 Hz, H-17), 2.66 (2H, m, H-23), 2.41 (1H, ddt, *J* = 2.5, 8.0, 19.5 Hz, H-7b), 2.36 (3H, s, Me-2′), 2.13 (1H, ddd, *J* = 5.0, 8.5, 13.0 Hz, H-1a), 2.05 (2H, m, H-24), 2.01 (1H, overlapped, H-15b), 2.0 (3H, s, Me-32), 1.99 (1H, d, *J* = 8.0 Hz, H-8), 1.95 (3H, s, Me-2″), 1.93 (1H, m, H-7a), 1.51 (1H, ddd, *J* = 13.0, 13.0, 13.0 Hz, H-1b), 1.50 (3H, s, Me-26), 1.47 (3H, s, Me-27), 1.45 (3H, s, Me-21), 1.40 (1H, dd, *J* = 1.2, 14.2, H-15a), 1.36 (3H, s, Me-28), 1.33 (3H, s, Me-30), 1.31 (3H, s, Me-29), 1.06 (3H, s, Me-19), 1.01 (3H, br s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 212.4 (C-22), 211.7 (C-11), 206.7 (C-3), 194.6 (C-1′), 170.1 (C-31), 170.0 (C-1″), 140.2 (C-5), 120.3 (C-6), 81.0 (C-25), 78.6 (C-20), 74.1 (C-16), 54.0 (C-17), 51.9 (C-4), 50.6 (C-2), 50.0 (C-13), 48.7 (C-12), 48.6 (C-9), 47.9 (C-14), 43.3 (C-15), 42.1 (C-8), 36.5 (C-10), 35.2 (C-24), 33.8 (C-1), 30.6 (C-2′), 30.4 (C-23), 29.3 (C-28), 26.0 (C-26), 25.8 (C-27), 24.2 (C-21), 23.8 (C-7), 22.4 (C-29), 22.3 (C-32), 20.9 (C-2″), 19.8 (C-19), 19.6 (C-18), 18.8 (C-30); ESI-MS (negative ion mode) *m/z* 659.3264 $[M-H]^-$ (calcd for $C_{36}H_{51}O_9S$ 559.3259).

4.3.15. Preparation of 18

A sealed 10 mL glass tube containing thiourea (213 mg, 2.8 mmol) and compound **12** (100 g, 0.140 mmol) in EtOH was introduced in the cavity of a microwave reactor (CEM Co., Discover) and irradiated with stirring under a maximum potency (300 W) for 10 min. The temperature was raised up to 100 °C. After cooling of the mixture to room temperature, the reaction vessel was opened and the product was evaporated under reduced pressure. The resulting crude product was purified by chromatography on Florisil® (50% ethyl acetate/hexane) to afford **18** (64 mg, 76% yield) as a white solid. Mp: 142–143 °C; IR (KBr): 3445, 3354, 2978, 1730, 1713, 1693, 1681, 1652, 1534, 1531, 1372, 1262, 1208, 1128, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 5.76 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 4.31 (1H, t, *J* = 7.5 Hz, H-16), 3.24 (1H, d, *J* = 14.5 Hz, H-12a), 2.82 (1H, ddd, *J* = 6.8, 9.0, 17.5 Hz, H-23a), 2.67 (1H, *J* = 14.5 Hz, H-12b), 2.59 (1H, m, H-10), 2.54 (d, *J* = 7.5 Hz, H-17), 2.51 (1H, m, H-23), 2.45 (1H, overlapped, H-2), 2.41 (1H, m, H-7b), 2.39 (1H, overlapped, H-2), 1.98 (1H, m, H-7a), 1.97 (3H, s, Me-32), 1.96 (1H, d, *J* = 8.5 Hz, H-8), 1.89 (1H, ddd, *J* = 14.0, 9.0, 4.5 Hz, H-1a), 1.84 (1H, m, H-15b), 1.82 (1H, overlapped, H-15a), 1.51(1H, m, H-1b), 1.46 (3H, s, Me-27), 1.44 (3H, s, Me-26), 1.42 (3H, s, Me-21), 1.37 (3H, s, Me-30), 1.27 (3H, s, Me-29), 1.24 (3H, s, Me-28), 1.09 (3H, s, Me-19), 0.97 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 213.9 (C-3), 213.6 (C-11), 213.0 (C-22), 170.3 (C-31), 165.6 (C-1′), 140.7 (C-5), 119.7 (C-6), 115.6 (C-2), 81.2 (C-25), 78.9 (C-20), 71.1 (C-16), 57.7 (C-17), 50.9 (C-4), 50.7 (C-14), 49.0 (C-9), 48.8 (C-12), 48.4 (C-13), 45.6 (C-15), 42.3 (C-8), 38.0 (C-2), 36.0 (C-10), 34.8 (C-24), 30.6 (C-23), 28.5 (C-28), 26.1 (C-26), 25.8 (C-27), 24.5 (C-1), 24.4 (C-21), 23.9 (C-7), 22.9 (C-29), 22.4 (C-32), 19.8 (C-18), 19.6 (C-19), 18.7 (C-30); ESI-MS (negative ion mode) *m/z* 599.3188 $[M-H]^-$ (calcd for $C_{33}H_{47}N_2O_6S$ 599.3160).

4.3.16. Preparation of 19

Following the procedure described for **18**, compound **19** was obtained in 62% yield from **14**. Mp: 198–199 °C; IR (KBr): 3642, 3467, 3363, 2972, 1727, 1691, 1613, 1537, 1370, 1289, 1257, 1127, 990 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 7.02 (1H, d, *J* = 15.6 Hz, H-24), 6.50 (1H, d, *J* = 15.6, H-23), 4.36 (1H, t, *J* = 7.1 Hz, H-16), 3.40 (2H, s, NH_2), 3.16 (1H, d, *J* = 14.8 Hz, H-12a), 2.62 (1H, m, H-10), 2.60 (1H, d, *J* = 14.5 Hz, H-12b), 2.50 (1H, d, *J* = 7.1 Hz, H-17), 2.47 (1H, overlapped, H-1a), 2.46 (1H, overlapped, H-7b), 2.35 (1H, dd, *J* = 15.2, 11.5 Hz, H-1b) 2.02 (1H, m, H-7a), 2.01 (3H, s, Me-32), 1.98 (1H, d, *J* = 8.5 Hz, H-8), 1.87 (1H, dd, *J* = 13.3, 9.3, H-15b), 1.55 (3H, s, Me-26), 1.54 (3H, s, Me-27), 1.43 (3H, s, Me-21), 1.41 (3H, s, Me-28), 1.37 (3H, s, Me-29), 1.33 (3H, s, Me-30), 1.33 (1H, overlapped, H-15a) 1.18 (3H, s, Me-19), 0.95 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 214.1 (C-11), 202.8 (C-22), 170.5 (C-32), 166.0 (C-1′), 151.3 (C-24), 150.6 (C-2), 141.0 (C-5), 120.3 (C-23), 120.2 (C-6), 115.3 (C-3), 79.5 (C-25), 78.3 (C-20), 70.7 (C-16), 57.8 (C-17), 50.4 (C-14), 48.5 (C-9), 48.0 (C-12), 47.9 (C-13), 45.0 (C-15), 43.0 (C-8), 39.8 (C-4), 36.1 (C-10), 31.8 (C-28), 27.6 (C-29), 26.7 (C-26), 26.1 (C-227), 25.8 (C-21), 23.7 (C-7), 23.5 (C-1), 22.9 (C-32), 21.7 (C-32), 20.4 (C-19), 19.6 (C-18), 18.9 (C-30); ESI-MS (positive ion mode) *m/z* 599.3135 $[M+H]^+$ (calcd for $C_{33}H_{47}N_2O_6S$ 599.3149).

4.3.17. Preparation of 20

To a solution of **12** (100 mg, 0.140 mmol) in DMF (1.0 mL), $(Bu)_4N^-Br^+$ (91 mg, 2.80 mmol) was added with stirring at 20 °C. After 35 h, the reaction was diluted by adding 20 mL of diethyl ether and washed with brine (2 × 25 mL). The organic phase was dried with anhydrous sodium sulfate and evaporated under

reduced pressure. The resulting crude product was purified by chromatography on silica gel (40% ethyl acetate/hexane) to afford **20** (70 mg, 80% yield) as a white solid. Mp: 113–114 °C; IR (KBr): 3289, 2978, 1730, 1697, 1368, 1260, 1218, 1128, 1021 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 5.81 (1H, ddd, J = 2.0, 2.0, 6.0, H-6), 4.85 (1H, dd, J = 5.2, 11.5 Hz, H-2), 4.31 (1H, t, J = 7.1 Hz, H-16), 3.22 (1H, d, J = 14.7 Hz, H-12a), 2.82 (1H, m, H-23a), 2.70 (1H, m, H-10), 2.70 (1H, d, J = 14.5 Hz, H-12b), 2.52 (1H, m, H-23b), 2.53 (1H, d, J = 7.1 Hz, H-17), 2.52 (1H, m, H-1a), 2.41 (1H, m, H-7b), 2.06 (2H, m, H-24), 2.01 (3H, s, Me-32), 1.98 (1H, d, J = 7.8 Hz, H-8), 1.99 (1H, m, H-7a), 1.86 (1H, ddd, J = 13.0, 13.0, 13.0 Hz, H-1b), 1.85 (1H, dd, J = 9.0, 13.0 Hz, H-15b), 1.46 (3H, s, Me-27), 1.44 (3H, s, Me-26), 1.42 (3H, s, Me-21), 1.40 (1H, m, H-15a), 1.34 (3H, s, Me-30), 1.38 (3H, s, Me-29), 1.29 (3H, s, Me-28), 1.10 (3H, s, Me-19), 0.97 (3H, s, Me-18); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 213.9 (C-22), 212.2 (C-11), 203.6 (C-3), 170.3 (C-31), 139.4 (C-5), 120.8 (C-6), 81.3 (C-25), 78.9 (C-20), 71.0 (C-16), 57.8 (C-17), 52.8 (C-2), 51.9 (C-4), 50.6 (C-13), 48.8 (C-12), 48.5 (C-14), 48.3 (C-9), 45.5 (C-15), 42.4 (C-8), 37.9 (C-1), 37.1 (C-10), 34.8 (C-24), 30.7 (C-23), 28.9 (C-28), 26.2 (C-27), 25.9 (C-26), 24.5 (C-21), 23.8 (C-7), 23.2 (C-29), 22.4 (C-32), 20.0 (C-19), 19.9 (C-18), 18.7 (C-30); ESI-MS (negative ion mode) m/z 621.2409 $[M-H]^-$ (calcd for $C_{32}H_{46}BrO_7$ 621.2432).

4.3.18. Preparation of 21

Following the procedure described for **20**, compound **21** was obtained in 86% yield from **14**. Mp: 131–132 °C; IR (KBr): 3510, 2978, 1729, 1693, 1633, 1370, 1250, 1125 cm^{-1}; ^1H-NMR ($CDCl_3$): δ = 7.06 (1H, d, J = 15.6 Hz, H-24), 6.47 (1H, d, J = 15.6, H-23), 5.81 (1H, ddd, J = 2.0, 2.0, 6.0, H-6), 4.86 (1H, dd, J = 5.5, 13.0 Hz, H-2), 4.36 (1H, t, J = 7.1 Hz, H-16), 3.21 (1H, d, J = 14.5 Hz, H-12a), 2.72 (1H, m, H-10), 2.68 (1H, d, J = 14.5 Hz, H-12b), 2.51 (1H, ddd, J = 3.6, 6.1, 13.0, Hz, H-1a), 2.49 (1H, d, J = 7.1 Hz, H-17), 2.41 (1H, m, H-7b), 2.01 (3H, s, Me-32), 1.99 (1H, m, H-7a), 1.97 (1H, d, J = 8.0 Hz, H-8), 1.88 (1H, dd, J = 7.1, 13.0 Hz, H-15b), 1.86 (1H, ddd, J = 13.0, 13.0, 13.0 Hz, H-1b), 1.57 (3H, s, Me-27), 1.55 (3H, s, Me-26), 1.44 (3H, s, Me-21), 1.43 (1H, d, J = 13.0 Hz, H-15a), 1.38 (3H, s, Me-29), 1.33 (3H, s, Me-30), 1.29 (3H, s, Me-28), 1.09 (3H, s, Me-19), 0.98 (3H, s, Me-18); ^{13}C NMR ($CDCl_3$): δ = 212.1 (C-11), 203.7 (C-3), 202.4 (C-22), 170.2 (C-31), 152.0 (C-24), 139.4 (C-5), 120.9 (C-6), 120.3 (C-23), 79.3 (C-25), 78.2 (C-20), 71.3 (C-16), 58.2 (C-17), 52.8, (C-2), 51.9 (C-4), 50.6 (C-14), 50.2 (C-4), 48.7 (C-12), 48.5 (C-9), 48.1 (C-13), 45.3 (C-15), 42.5 (C-8), 37.9 (C-1), 37.1 (C-10), 28.9 (C-28), 26.4, (C-27), 26.0 (C-26), 24.0 (C-21), 23.8 (C-7), 23.3 (C-29), 22.0 (C-32), 20.0 (C-19), 19.9 (C-18), 18.8 (C-30); ESI-MS (negative ion mode) m/z 619.2292 $[M-H]^-$ (calcd for $C_{32}H_{44}BrO_7$ 619.2276).

4.3.19. Preparation of 22

To a solution of **15** (80 mg, 0.11 mmol) in DMF (1.0 mL), sodium azide (72 mg, 1.11 mmol) was added. The mixture was heated at 70 °C and after 1 h was diluted by adding 20.0 mL of diethyl ether and washed with brine (2 × 25.0 mL). The organic phase was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting crude product was purified by chromatography on silica gel (50% ethyl acetate/hexane) to afford **22** (37 mg, 60% yield) as a white solid. Mp: 133–134 °C; IR (KBr): 3452, 3347, 2925, 1727, 1694, 1582, 1368, 1260, 1022 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 5.73 (1H, ddd, J = 2.5, 2.5, 5.0, H-6), 5.64 (1H, d, J = 2.5 Hz, H-1), 4.33 (1H, t, J = 7.1 Hz, H-16), 3.47 (1H, br s, H-10), 3.25 (1H, d, J = 14.7 Hz, H-12a), 2.83 (1H, ddd, J = 17.4, 10.0, 6.0, H-23a), 2.71 (1H, d, J = 14.5 Hz, H-12b), 2.53 (1H, d, J = 7.1 Hz, H-17), 2.53 (1H, m, H-23b), 2.36 (1H, m, H-7b), 2.07 (2H, m, H-24), 2.02 (1H, d, J = 7.8 Hz, H-8), 1.96 (3H, s, Me-32), 1.99 (1H, m, H-7a), 1.85 (1H, dd, J = 9.0, 13.0 Hz, H-15b), 1.46 (3H, s, Me-27), 1.44 (3H, s, Me-26), 1.43 (1H, m, H-15a), 1.42 (3H, s, Me-21), 1.40 (3H, s, Me-30), 1.32 (3H, s, Me-29), 1.24 (3H, s, Me-28), 0.99 (3H, s, Me-19), 0.98 (3H, s, Me-18); ^{13}C NMR ($CDCl_3$): δ = 213.9 (C-22), 213.6 (C-11), 198.6 (C-3), 170.3 (C-31), 137.6 (C-5), 136.9 (C-2), 119.6 (C-6), 112.9 (C-1), 81.2 (C-25), 78.9 (C-20), 71.1 (C-16), 57.8 (C-17), 51.9 (C-4), 50.6 (C-13), 49.2 (C-9), 48.9 (C-12), 48.4 (C-14), 48.0 (C-4) 45.7 (C-15), 41.6 (C-8), 34.8 (C-24), 34.0 (C-10), 30.6 (C-23), 27.9 (C-28), 26.1 (C-27), 25.8 (C-26), 24.5 (C-21), 23.6 (C-7), 22.4 (C-32), 20.5 (C-29), 19.9 (C-19), 19.8 (C-18), 18.3 (C-30); ESI-MS (negative ion mode) m/z 556.3280 $[M-H]^-$ (calcd for $C_{32}H_{46}NO_7$ 556.3280).

4.3.20. Preparation of 23

Following the procedure described for **22**, compound **23** was obtained in 51% yield from **16** as a white solid. Mp: 129–130 °C; IR (KBr): 3458, 3363, 2978, 1740–1640, 1372, 1260, 1022 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 5.71 (1H, ddd, J = 2.5, 2.5, 5.0, H-6), 5.64 (1H, d, J = 2.5 Hz, H-1), 5.16 (1H, m, H-16), 3.45 (1H, m, H-10), 3.23 (1H, d, J = 14.3 Hz, H-12a), 2.75 (1H, d, J = 14.5 Hz, H-12b), 2.71 (1H, d, J = 7.7 Hz, H-17), 2.64 (1H, ddd, J = 17.4, 10.0, 6.0, H-23a), 2.37 (ddt, J = 19.6, 8.5, 2.9 Hz, H-7b), 2.05 (2H, m, H-24), 2.04 (1H, d, J = 8.5 Hz, H-8), 2.03 (1H, overlapped, H-15b), 1.98 (3H, s, Me-32), 1.95 (3H, s, H-2′), 1.96 (1H, m, H-7a), 1.49 (3H, s, Me-26), 1.46 (3H, s, Me-27), 1.45 (3H, s, Me-21), 1.44 (1H, overlapped, H-15a), 1.35 (3H, s, Me-30), 1.31 (3H, s, Me-29), 1.23 (3H, s, Me-28), 1.03 (3H, s, Me-18), 1.00 (3H, s, Me-19); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 213.0 (C-11), 212.3 (C-22), 198.4 (C-3), 170.1 (C-31), 170.0 (C-1′), 137.6 (C-5), 136.9 (C-2), 119.6 (C-6), 112.6 (C-1), 81.0 (C-25), 78.6 (C-20), 74.1 (C-16), 54.1 (C-17), 50.0 (C-4), 49.1 (C-9), 48.8 (C-12), 47.9 (C-13), 47.9 (C-14), 43.5 (C-15), 41.3 (C-8), 35.1 (C-24), 34.9 (C-10), 30.4 (C-23), 27.8 (C-28), 26.0 (C-27), 25.7 (C-26), 24.3 (C-21), 23.5 (C-7), 22.3 (C-32), 20.9 (C-2′), 20.5 (C-29), 19.9 (C-19), 19.6 (C-18), 18.4 (C-30); ESI-MS (negative ion mode) m/z 598.3391 $[M-H]^-$ (calcd for $C_{34}H_{48}NO_8$ 598.3385).

4.3.21. Preparation of 24

Following the procedure described for **22**, compound **24** was obtained in 54% yield from **14**. Mp: 121–122 °C; IR (KBr): 3468, 2979, 1733, 1695, 1651, 1371, 1254, 1127 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.06 (1H, d, J = 15.6 Hz, H-24), 6.47 (1H, d, J = 15.6, H-23), 5.80 (1H, ddd, J = 2.5, 2.5, 5.0, H-6), 5.73 (1H, m, H-1), 4.37 (1H, m, H-16), 3.49 (1H, s, H-10), 3.25 (1H, d, J = 14.7 Hz, H-12a), 2.71 (1H, d, J = 14.5 Hz, H-12b), 2.49 (1H, d, J = 7.0 Hz, H-17), 2.36 (1H, m, H-7b), 2.02 (1H, d, J = 7.8 Hz, H-8), 2.01 (1H, m, H-7a), 1.99 (3H, s, Me-32), 1.88 (1H, dd, J = 9.0, 13.0 Hz, H-15b), 1.57 (3H, s, Me-27), 1.54 (3H, s, Me-26), 1.56 (1H, overlapped, H-15a), 1.44 (3H, s, Me-21), 1.39 (3H, s, Me-30), 1.32 (3H, s, Me-29), 1.25 (3H, s, Me-28), 1.0 (3H, s, Me-19), 0.99 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 213.9 (C-11), 202.5 (C-22), 198.8 (C-3), 170.3 (C-31), 151.9 (C-24), 137.4 (C-5), 137.3 (C-2), 120.4 (C-23), 120.4 (C-6), 119.9 (C-1), 79.3 (C-25), 78.2 (C-20), 71.4 (C-16), 58.2 (C-17), 50.8 (C-14), 49.2 (C-9), 48.9 (C-12), 48.1 (C-13), 48.0 (C-4), 45.6 (C-15), 41.6 (C-8), 35.0 (C-10), 27.9 (C-28), 26.4 (C-27), 25.9 (C-26), 24.0 (C-21), 23.6 (C-7), 22.0 (C-32), 20.4 (C-29), 20.0 (C-19), 19.9 (C-18), 18.4 (C-30); ESI-MS (negative ion mode) m/z 554.3121 $[M-H]^-$ (calcd for $C_{32}H_{44}NO_7$ 554.3123).

4.3.22. Preparation of 25 and 26

To a solution of 1 (400 mg, 0.71 mmol) in 1,2-dichloroethane (6.0 mL), 1,1′-thiocarbonyldiimidazole (1.0 g, 5.68 mmol) was added and the mixture was heated at 70 °C. After 6 h, the reaction was cooled down, evaporated under reduced pressure and subjected to column chromatography on silica gel (30% ethyl acetate/hexane) to give 25 (200 mg, 42% yield) and 26 (250 mg, 45% yield) as white solids. (25): Mp: 122–123 °C; IR: 3140, 2974,

1733, 1712, 1700, 1464, 1388, 1334, 1286, 1234, 986 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.41 (1H, s, H-4′), 7.66 (1H, s, H-2′), 7.06 (1H, s, H-3′), 6.22 (1H, dd, *J* = 5.5, 13.6 Hz, H-2), 5.85 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 4.32 (1H, m, H-16), 3.30 (1H, d, *J* = 14.5 Hz, H-12a), 2.92 (1H, m, H-10), 2.83 (1H, m, H-23a), 2.71 (1H, d, *J* = 14.5 Hz, H-12b), 2.52 (1H, d, *J* = 6.9 Hz, H-17), 2.52 (1H, m, H-23b), 2.43 (1H, m, H-7b), 2.37 (1H, m, H-1a), 2.05 (2H, m, H-24), 2.0 (1H, d, *J* = 8.0 Hz, H-8), 1.97 (3H, s, Me-32), 1.91 (1H, m, H-7a), 1.83 (1H, m, H-15b), 1.77 (1H, ddd, *J* = 13.0, 13.0, 13.0 Hz, H-1b), 1.46 (3H, s, Me-27), 1.44 (3H, s, Me-30), 1.44 (3H, s, Me-26), 1.39 (3H, s, Me-21), 1.39 (3H, s, Me-28), 1.33 (3H, s, Me-29), 1.28 (1H, overlapped, H-15a), 1.14 (3H, s, Me-19), 0.89 (3H, s, Me-18); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 213.7 (C-22), 212.3 (C-11), 203.3 (C-3), 183.2 (C-1′), 170.3 (C-31), 138.9 (C-5), 136.9 (C-4′), 130.3 (C-3′), 121.2 (C-6), 118.0 (C-2′), 81.2 (C-25), 81.2 (C-16), 78.9 (C-20), 70.6 (C-2), 57.7 (C-17), 51.5 (C-4), 50.5 (C-13), 48.7 (C-12), 48.3 (C-9), 48.2 (C-14), 45.4 (C-15), 42.2 (C-8), 34.7 (C-24), 34.2 (C-10), 31.9 (C-1), 30.7 (C-23), 28.1 (C-28), 26.1 (C-26), 25.8 (C-27), 24.5 (C-21), 23.8 (C-7), 22.4 (C-32), 21.1 (C-29), 20.0 (C-19), 19.9 (C-18), 18.6 (C-30); ESI-MS (positive ion mode) *m/z* 671.3353 $[M+H]^+$ (calcd for $C_{36}H_{51}N_2O_8S$ 671.3361). (26) Mp: 134–135 °C; IR: 3130, 2974, 1728, 1712, 1697, 1464, 1393, 1329, 1286, 1246, 1231, 981, 734 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.49 (1H, s, H-4″), 8.40 (1H, s, H-4′), 7.69 (1H, s, H-2″), 7.59 (1H, s, H-2′), 7.10 (2H, s, H-3′/H-3″), 6.22 (1H, dd, *J* = 5.0, 13.0 Hz, H-2), 6.04 (1H, m, H-16), 5.83 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 3.37 (1H, d, *J* = 14.5 Hz, H-12a), 3.08 (1H, d, *J* = 5.5 Hz, H-17), 2.92 (1H, m, H-10), 2.81 (1H, d, *J* = 14.5 Hz, H-12b), 2.63 (2H, m, H-23a), 2.5 (1H, overlapped, H-7b), 2.45 (1H, overlapped, H-1a), 2.1 (1H, d, *J* = 8.0 Hz, H-8), 2.05 (2H, m, H-24), 1.97 (3H, s, Me-32), 1.91 (1H, m, H-7a), 1.83 (1H, m, H-15b), 1.73 (1H, ddd, *J* = 13.0, 13.0, 13.0 Hz, H-1b), 1.97 (3H, s, Me-32), 1.50 (3H, s, Me-30), 1.39 (3H, s, Me-21), 1.39 (3H, s, Me-26), 1.35 (3H, s, Me-21), 1.33 (1H, overlapped, H-15a), 1.31 (3H, s, Me-28), 1.31 (3H, s, Me-29), 1.17 (3H, s, Me-19), 1.08 (3H, s, Me-18); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 214.2 (C-22), 211.4 (C-11), 203.1 (C-3), 183.2 (C-1′), 182.4 (C-1″), 170.1 (C-31), 139.0 (C-5), 136.9 (C-4′), 136.9 (C-4″), 136.6 (C-), (C-), 130.6 (C-3′), 130.5 (C-3″), 120.8 (C-6), 118.0 (C-2′), 117.4 (C-2″), 83.6 (C-2), 80.9 (C-16), 80.8 (C-25), 79.2 (C-20), 54.9 (C-17), 51.4 (C-4), 50.0 (C-13), 48.4 (C-12), 48.1 (C-9), 47.7 (C-14), 42.7 (C-15), 41.9 (C-8), 34.8 (C-24), 34.1 (C-10), 31.8 (C-1), 31.5 (C-23), 27.9 (C-28), 25.5 (C-26), 25.4 (C-27), 24.5 (C-21), 23.7 (C-7), 22.3 (C-32), 21.0 (C-29), 20.0 (C-19), 19.7 (C-18), 18.7 (C-30); ESI-MS (positive ion mode) *m/z* 781.3302 $[M+H]^+$ (calcd for $C_{40}H_{53}N_4O_8S_2$ 781.3299).

4.3.23. Preparation of 27

To a solution of **25** (190 mg, 0.28 mmol) in toluene (7 mL), diphenylsilane (0.4 mL, 2.24 mmol) and lauroyl peroxide (6 × 0.2 mL of a solution 0.160 g/mL in toluene, each 15 min) were added. The reaction mixture was stirred under argon atmosphere at 115 °C for 1.5 h. After cooling, the solution was evaporated under reduced pressure and subjected to column chromatography on silica gel to obtain **27** (45 mg, 67% yield) as a white solid. Mp: 108–109 °C; IR (KBr): 3439, 2974, 1730, 1714, 1693, 1370, 1254, 1213, 1123, 1020, 950 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.77 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 4.31 (1H, m, H-16), 3.24 (1H, d, *J* = 14.5 Hz, H-12a), 2.82 (1H, m, H-23a), 2.67 (1H, d, *J* = 14.3 Hz, H-12b), 2.59 (1H, m, H-10), 2.53 (1H, d, *J* = 7.5 Hz, H-17), 2.51 (1H, m, H-23b), 2.46 (1H, overlapped, H-2a), 2.40 (1H, overlapped, H-7b), 2.39 (1H, overlapped, H-2b), 2.06 (2H, m, H-24), 1.98 (1H, ddd, *J* = 19.6, 5.0, 1.5 Hz, H-7a), 1.96 (3H, s, Me-32), 1.96 (1H, d, *J* = 8.5 Hz, H-8), 1.89 (1H, m, H-1a), 1.85 (1H, dd, *J* = 13.3, 9.0 Hz, H-15b), 1.53 (1H, m, H-1b), 1.46 (3H, s, Me-26), 1.44 (3H, s, Me-27), 1.42 (3H, s, Me-21), 1.41 (1H, d, *J* = 13.3 Hz, H-15a), 1.37 (3H, s, Me-30), 1.27 (3H, s, Me-29), 1.24 (3H, s, Me-28), 1.09 (3H, s, Me-19), 0.97 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 213.9 (C-3), 213.6 (C-11), 213.0 (C-22), 170.3 (C-31), 140.7 (C-5), 119.7 (C-6), 81.2 (C-25), 78.9 (C-20), 71.1 (C-16), 57.7 (C-17), 50.9 (C-4), 50.7 (C-13), 49.0 (C-9), 48.8 (C-12), 48.4 (C-14), 45.6 (C-15), 42.3 (C-8), 38.0 (C-2), 36.0 (C-10), 34.8 (C-24), 30.6 (C-23), 28.5 (C-28), 26.1 (C-26), 25.8 (C-27), 24.5 (C-1), 24.5 (C-21), 23.9 (C-7), 22.9 (C-29), 22.4 (C-32), 19.8 (C-18), 19.6 (C-19), 18.7 (C-30); ESI-MS (negative ion mode) *m/z* 543.3353 $[M-H]^-$ (calcd for $C_{32}H_{47}O_7$ 543.3327).

4.3.24. Preparation of 28

Following the procedure described for **27**, compound **28** was obtained in 19% yield from **26** as a colourless oil. Mp: 98–99 °C; IR (KBr): 3439, 2974, 1730, 1714, 1693, 1370, 1254, 1213, 1123, 1020, 950 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.76 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 3.12 (1H, dd, *J* = 0.8, 14.3 Hz, H-12a), 2.67 (1H, *J* = 14.3 Hz, H-12b), 2.56 (1H, overlapped, H-10), 2.54 (2H, overlapped, H-23), 2.40 (2H, overlapped, H-2), 2.40 (1H, overlapped, H-7b), 2.35 (1H, t, *J* = 7.5 Hz, H-17), 2.04 (2H, overlapped, H-24), 2.02 (1H, m, H-8), 1.99 (1H, m, H-7a), 1.97 (3H, s, Me-32), 1.86 (1H, ddd, *J* = 14.0, 9.0, 4.5 Hz, H-1a), 1.64 (1H, overlapped, H-16), 1.52 (1H, m, H-1b), 1.47 (3H, s, Me-27), 1.44 (3H, s, Me-26), 1.42 (3H, s, Me-21), 1.39 (2H, m, H-15), 1.36 (1H, m, H-16), 1.27 (3H, s, Me-29), 1.23 (3H, s, Me-28), 1.13 (3H, s, Me-30), 1.09 (3H, s, Me-19), 0.99 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 213.9 (C-3), 213.7 (C-11), 213.1 (C-22), 170.4 (C-31), 140.8 (C-5), 120.1 (C-6), 81.3 (C-25), 80.1 (C-20), 51.0 (C-4), 50.5 (C-14), 49.1 (C-13), 49.0 (C-9), 49.0 (C-12), 48.8 (C-17), 42.5 (C-8), 38.2 (C-2), 36.2 (C-10), 35.3 (C-24), 34.1 (C-15), 30.3 (C-23), 28.5 (C-28), 26.1 (C-26), 26.0 (C-27), 24.7 (C-21), 24.5 (C-1), 24.0 (C-7), 23.2 (C-29), 22.5 (C-32), 21.5 (C-16), 19.6 (C-19), 19.0 (C-18), 18.4 (C-30). ESI-MS (positive ion mode) *m/z* 551.3343 $[M+Na]^+$ (calcd for $C_{32}H_{48}NaO_6$ 551.3342).

4.3.25. Preparation of 29

A solution of compound 10 (800 mg, 1.04 mmol) in anhydrous THF (15.0 mL) was cooled at 0 °C and stirred for 5 min. Lithium tri-tert-butoxyaluminium hydride (1.59 g, 6.24 mmol) was then added and the mixture was stirred on an ice bath under nitrogen atmosphere. After 2 h, the mixture was diluted by adding 100.0 mL of EtOAc, washed with of saturated solution of sodium potassium tartrate (3 × 50.0 mL) and water (2 × 40.0 mL). The organic phase was then dried with Na_2SO_4 and evaporated under reduced pressure. The resulting crude product was purified by chromatography on silica gel (70% ethyl acetate/hexane) to afford 29 (750 mg, 93% yield) as a white solid. Mp: 137–138 °C; IR (KBr): 3515, 2975, 1722, 1713, 1694, 1688, 1601, 1583, 1371, 1315, 1275, 1214, 1175, 1113, 1070, 1025, 966, 714 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.02 (4H, m, H-3′/H-7′/H-3″/H-7″), 7.58 (2H, m, H-5′/H-5″), 7.45 (4H, m, H-4′/H-4″/H-6′/H-6″), 5.75 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 5.71 (1H, dd, *J* = 7.5, 7.5 Hz, H-16), 5.12 (1H, ddd, *J* = 11.5, 10.0, 4.3 Hz, H-2), 3.33 (1H, d, *J* = 10.0 Hz, H-3), 3.23 (1H, dd, *J* = 10.0, 1.3 Hz, H-22), 3.19 (1H, d, *J* = 12.7 Hz, H-12a), 2.90 (1H, d, *J* = 7.7 Hz, H-17), 2.67 (1H, d, *J* = 12.7 Hz, H-12b), 2.50 (1H, m, H-10), 2.43 (1H, ddt, *J* = 19.6, 8.5, 2.9 Hz, H-7b), 2.12 (1H, dd, *J* = 14.0, 7.5 Hz, H-15b), 2.01 (1H, overlapped, H-1a), 2.0 (1H, d, *J* = 8.5 Hz, H-8), 1.94 (3H, s, Me-32), 1.93 (1H, overlapped, H-7a), 1.74 (1H, m, H-23a), 1.61 (1H, overlapped, H-23b), 1.60 (1H, overlapped, H-24a), 1.59 (1H, d, *J* = 14 Hz, H-15a), 1.44 (1H, m, H-24b), 1.36 (3H, Me-26), 1.36 (3H, Me-27), 1.35 (3H, Me-30), 1.32 (1H, overlapped, H-1b), 1.31 (3H, Me-21), 1.22 (3H, Me-28), 1.12 (3H, Me-19), 1.05 (3H, Me-29), 1.04 (3H, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 212.6 (C-11), 170.4 (C-31), 166.9 (C-1″), 166.0 (C-1′), 140.0 (C-5), 133.2 (C-5″), 133.2 (C-5′), 130.3 (C-2″), 130.0 (C-2′), 129.7 (C- C-3″/C-7″), 129.3 (C- C-3′/C-7′), 128.6 (C- C-4″/C-6″), 128.3 (C-4′/C-6′), 119.6 (C-6), 82.1 (C-25), 79.3 (C-22), 78.4 (C-3), 76.0 (C-20), 75.8 (C-16), 74.9 (C-2),

52.5 (C-17), 50.6 (C-13), 48.9 (C-12), 48.1 (C-9), 47.6 (C-14), 44.0 (C-15), 42.6 (C-8), 42.4 (C-4), 38.7 (C-23), 33.8 (C-10), 30.6 (C-1), 26.1 (C-26), 25.7 (C-27), 24.5 (C-28), 23.7 (C-7), 22.6 (C-32), 22.4 (C-21), 21.5 (C-29), 20.2 (C-19), 19.8 (C-18), 18.5 (C-30); ESI-MS (positive ion mode) *m/z* 795.4088 $[M+Na]^+$ (calcd for $C_{46}H_{60}NaO_{10}$ 795.4079).

4.3.26. Preparation of 30

To a solution of **29** (700 mg, 0.91 mmol) in MeOH (14.0 mL), H_5IO_6 (622 mg, 2.73 mmol) was added with stirring at 20 °C. After 1 h, the reaction was diluted with 50.0 mL of EtOAc and poured over aq 5% $NaHSO_3$. The organic phase was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting crude product was purified by chromatography on silica gel (60% ethyl acetate/hexane) to afford **30** (480 g, 86% yield) as a white solid. Mp: 129−130 °C; IR (KBr): 3449, 2979, 1737, 1730, 1714, 1693, 1368, 1247, 1118, 1022, 950 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.04 (2H, dd, *J* = 8.5, 1.3 Hz, H-3′/H-7′), 7.99 (2H, dd, *J* = 8.5, 1.3 Hz, H-3″/H-7″), 7.59 (2H, m, H-5′/H-5″), 7.44 (4H, m, H-4′/H-4″/H-6′/H-6″), 5.90 (1H, ddd, *J* = 9.0, 6.5, 1.2 Hz, H-16), 5.78 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 5.13 (1H, ddd, *J* = 11.5, 10.0, 4.3 Hz, H-2), 3.48 (1H, d, *J* = 6.5 Hz, H-17), 3.34 (1H, dd, *J* = 10.0, 3.5 Hz, H-3), 3.30 (1H, dd, *J* = 14.5, 0.8, Hz, H-12a), 2.52 (1H, m, H-10), 2.52 (1H, d, *J* = 14.5 Hz, H-12b), 2.47 (ddt, *J* = 19.5, 7.8, 3.0 Hz, H-7b), 2.20 (3H, Me-21), 2.16 (1H, dd, *J* = 14.0, 9.0 Hz, H-15b), 2.0 (1H, *J* = 7.8 Hz, H-8), 2.0 (1H, overlapped, H-1a), 1.97 (1H, overlapped, H-7a), 1.70 (1H, br d, *J* = 14.0 Hz, H-15a), 1.36 (3H, Me-30), 1.33 (1H, ddd, *J* = 13.0, 13.0, 13.0 Hz, H-1b), 1.25 (3H, Me-28), 1.13 (3H, Me-19), 1.07 (3H, Me-29), 0.76 (3H, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 210.9 (C-11), 206.1 (C-20), 167.1 (C-1″), 166.0 (C-1′), 140.3 (C-5), 133.3 (C-5″), 133.3 (C-5′), 130.1 (C-2′), 130.1 (C-2″), 129.8 (C-3′/C-7′), 129.7 (C-3″/C-7″), 128.6 (C-4′/C-6′), 128.5 (C-4″/C-6″), 119.5 (C-6), 78.5 (C-3), 75.5 (C-16), 75.0 (C-2), 64.2 (C-17), 49.9 (C-13), 48.8 (C-9), 48.6 (C-14), 47.1 (C-12), 43.5 (C-15), 43.0 (C-8), 42.8 (C-4), 33.9 (C-10), 31.6 (C-21), 30.7 (C-1), 24.7 (C-28), 24.0 (C-7), 21.6 (C-29), 20.3 (C-19), 20.0 (C-18), 18.9 (C-30); ESI-MS (negative ion mode) *m/z* 611.3014 $[M-H]^-$ (calcd for $C_{38}H_{43}O_7$ 611.3014).

4.3.27. Preparation of 31

A mixture of PCC (200 mg, 1.23 mmol) and $BaCO_3$ (250 mg, 1.23 mmol) in dry CH_2Cl_2 (5.0 mL) was stirred for 5 min. Compound **30** (250 mg, 0.41 mmol) dissolved in 2 mL of CH_2Cl_2 was then added and the reaction was stirred at 20 °C. After 20 h the reaction mixture was diluted with diethyl ether (30.0 mL) and poured through a short column of Florisil®. The solvent was removed under vacuum and the residue was purified by column chromatography on silica (50% ethyl acetate/hexane) to give pure product **31** (195 mg, 78% yield) as a white solid. Mp: 156–157 °C; IR (KBr): 2974, 1973, 1917, 1737, 1720, 1699, 1692, 1275, 1205, 1175, 1114, 1026, 978, 713 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.1 (2H, dd, *J* = 8.5, 1.3 Hz, H-3′/H-7′), 8.03 (2H, dd, *J* = 8.5, 1.3 Hz, H-3″/H-7″), 7.60 (2H, m, H-5′/H-5″), 7.47 (4H, m, H-4′/H-4″/H-6′/H-6″), 5.91 (1H, ddd, *J* = 8.6, 6.5, 1.2 Hz, H-16), 5.82 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 5.75 (dd, *J* = 13.0, 5.5 Hz, H-2), 3.50 (1H, d, *J* = 6.5 Hz, H-17), 3.36 (1H, dd, *J* = 14.5, 0.9 Hz, H-12a), 2.93 (1H, m, H-10), 2.61 (1H, d, *J* = 14.5 Hz, H-12b), 2.49 (ddt, *J* = 19.6, 8.5, 2.9 Hz, H-7b), 2.28 (1H, ddd, *J* = 13.0, 5.5, 3.5 Hz, H-1a), 2.22 (3H, s, Me-21), 2.19 (1H, dd, *J* = 13.8, 9.0 Hz, H-15b), 2.07 (1H, d, *J* = 8.0 Hz, H-8), 2.02 (1H, ddd, *J* = 19.5, 6.0, 1.1 Hz, H-7a), 1.74 (1H, overlapped, H-15a), 1.72 (1H, ddd, *J* = 13.0, 13.0, 13.0 Hz, H-1b), 1.45 (3H, s, Me-30), 1.39 (3H, s, Me-28), 1.32 (3H, s, Me-29), 1.16 (3H, s, Me-19), 0.8 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 210.7 (C-11), 205.8 (C-20), 205.3 (C-3), 165.9 (C-1''), 165.7 (C-1′), 139.8 (C-5), 133.3 (C-5′), 133.2 (C-5''), 129.9 (C-2″), 129.9 (C-3″/C-7″), 129.5 (C-2′), 129.5 (C-3′/C-7′), 128.5 (C-4″/C-6″), 128.4 (C-4′/C-6′), 120.3 (C-6), 75.4 (C-16), 73.7 (C-2), 64.0 (C-17), 51.4 (C-4), 49.7 (C-14), 48.8 (C-9), 48.5 (C-13), 46.9 (C-12), 43.3 (C-15), 42.7 (C-8), 34.4 (C-10), 32.1 (C-1), 31.5 (C-21), 28.7 (C-28), 23.9 (C-7), 21.3 (C-29), 20.1 (C-19), 19.9 (C-18), 18.7 (C-30); ESI-MS (positive ion mode) *m/z* 633.2838 $[M+Na]^+$ (calcd for $C_{38}H_{42}NaO_7$ 633.2823).

4.3.28. Preparation of 32

Compound **31** (180 mg, 0.29 mmol) was stirred at 20 °C with triethyl orthoformate (0.96 mL, 5.8 mmol), ethylene glycol (0.65 mL, 11.6 mmol) and a catalytic amount of *p*-toluenesulfonic acid. After 3 h the reaction mixture was diluted with EtOAc and washed with brine (2 × 25.0 mL) and water (2 × 25.0 mL). The organic phase was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting crude product was purified by chromatography on silica gel (40% ethyl acetate/hexane) to afford **32** (160 mg, 79% yield) as white solid. Mp: 152–153 °C; IR (KBr): 2983, 1721, 1714, 1696, 1271, 1173, 1115, 714 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.07 (2H, m, H-3′/H-7′), 8.03 (2H, m, H-3″/H-7″), 7.56 (2H, m, H-5′/H-5″), 7.44 (4H, m, H-4′/H-4″/H-6′/H-6″), 5.79 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 5.76 (1H, m, H-16), 5.75 (1H, dd, *J* = 6.0, 13.0 Hz, H-2), 4.04 (2H, m, H-1‴), 3.80 (2H, m, H-2‴), 3.18 (1H, d, *J* = 15.0, H-12a), 2.93 (1H, d, *J* = 6.7 Hz, H-17), 2.91 (1H, m, H-10), 2.70 (1H, d, *J* = 14.8 Hz, H-12b), 2.46 (ddt, *J* = 19.5, 8.0, 2.9 Hz, H-7b), 2.29 (1H, ddd, *J* = 13.0, 6.0, 3.5 Hz, H-1b), 2.14 (1H, dd, *J* = 9.0, 14.0, Hz, H-15b), 2.08 (1H, d, *J* = 8.0 Hz, H-8), 1.99 (1H, ddd, *J* = 20.0, 6.0, 1.5 Hz, H-7a), 1.71 (1H, ddd, *J* = 13.0, 13.0, 13.0 Hz, H-1b), 1.60 (1H, d, *J* = 14.0 Hz, H-15a), 1.43 (3H, s, Me-30), 1.39 (3H, s, Me-28), 1.32 (3H, s, Me-21), 1.30 (3H, s, Me-29), 1.15 (3H, s, Me-19), 0.94 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 212.5 (C-11), 205.5 (C-3), 166.1 (C-1''), 165.7 (C-1′), 139.8 (C-5), 133.2 (C-5′), 132.9 (C-5″), 130.5 (C-2′), 129.9 (C-3″/C-7″), 129.5 (C-3′/C-7′), 129.5 (C-), 128.4 (C-), 128.3 (C-), 120.5 (C-), 110.6 (C-20), 75.2 (C-16), 73.9 (C-2), 65.2 (C-1‴), 62.8 (C-2‴), 57.2 (C-17), 51.4 (C-4), 48.8 (C-12), 48.5 (C-13), 47.8 (C-14), 47.7 (C-9), 43.7 (C-15), 42.4 (C-8), 34.4 (C-10), 32.2 (C-1), 28.7 (C-28), 24.5 (C-21), 23.9 (C-7), 21.3 (C-29), 20.1 (C-19), 19.3 (C-18), 18.4 (C-30); ESI-MS (positive ion mode) *m/z* 655,3282 $[M+H]^+$ (calcd for $C_{30}H_{47}O_8$ 655.3265).

4.3.29. Preparation of 33

Compound **32** (100 mg, 0.143 mmol) was dissolved in 1 M KOH methanolic solution (3.0 mL) with stirring at 20 °C. After 1 h, the reaction was diluted with EtOAc and washed with brine (2 × 25.0 mL), water (2 × 25.0 mL) and 1 M HCl solution (3 × 30.0 mL). The organic phase was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting crude product was purified by chromatography on silica gel (50% ethyl acetate/hexane) to afford **33** (30 mg, 52% yield) as a white solid. Mp: 95–96 °C; IR (KBr): 3563, 3458, 2978, 1704, 1692, 1650, 1399, 1362, 1219, 1191, 1100, 1089, 1039, 1025 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 5.90 (1H, d, *J* = 2.4 Hz, H-1), 5.78 (1H, ddd, *J* = 2.5, 2.5, 5.0 Hz, H-6), 4.98 (1H, ddd, *J* = 1.2, 6.5, 9.0 Hz, H-16), 3.53 (1H, m, H-10), 3.29 (1H, dd, *J* = 1.1, 14.3 Hz, H-12a), 3.16 (1H, d, *J* = 6.5 Hz, H-17), 2.56 (1H, *J* = 14.3 Hz, H-12b), 2.40 (ddt, *J* = 2.9, 8.5, 19.6 Hz, H-7b), 2.18 (3H, s, Me-21), 2.02 (ddd, *J* = 1.5, 4.9, 19.6 Hz, H-7a), 2.01 (d, *J* = 8.5 Hz, H-8), 1.95 (ddd, *J* = 0.7, 9.2, 13.5 Hz, C-15b), 1.56 (dd, *J* = 1.2, 13.5 Hz, C-15a), 1.42 (3H, s, Me-30), 1.36 (3H, s, Me-29), 1.26 (3H, s, Me-28), 1.03 (3H, s, Me-19), 0.7 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 211.8 (C-11), 207.9 (C-20), 198.7 (C-3), 144.7 (C-2), 137.0 (C-5), 120.7 (C-1), 114.6 (C-6), 71.8 (C-16), 67.6 (C-17), 50.0 (C-9), 49.4 (C-13), 48.9 (C-14), 47.7 (C-4), 47.4 (C-12), 45.3 (C-15), 42.1 (C-8), 34.8 (C-10), 31.6 (C-21), 28.0 (C-28), 23.8 (C-7), 20.3 (C-29), 20.2 (C-19), 19.9 (C-18), 18.5 (C-30); ESI-MS (positive ion mode) *m/z* 401.2324 $[M+H]^+$ (calcd for $C_{24}H_{33}O_5$ 401.2322).

4.3.30. Preparation of 34

Following the procedure described for **32**, compound **34** was obtained in 88% yield from **30**. Mp: 145–146 °C; IR (KBr): 3563, 2978, 1713, 1694, 1601, 1581, 1378, 1314, 1278, 1177, 1114, 1068, 886, 711 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.04 (2H, dd, *J* = 8.5, 1.3 Hz, H-3′/H-7′), 8.03 (2H, dd, *J* = 8.5, 1.3 Hz, H-3″/H-7″), 7.56 (2H, m, H-5′/H-5″), 7.44 (4H, m, H-4′/H-4″/H-6′/H-6″), 5.76 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 5.73 (1H, m, H-16), 5.13 (1H, ddd, *J* = 4.5, 10.0, 12.0 Hz, H-2), 4.04 (2H, m, H-1‴), 3.79 (2H, m, H-2‴), 3.32 (1H, d, *J* = 10.0 Hz, H-3), 3.11 (1H, d, *J* = 14.8, H-12a), 2.91(1H, d, *J* = 6.5 Hz, H-17), 2.61 (1H, d, *J* = 14.8 Hz, H-12b), 2.50 (1H, m, H-10), 2.44 (ddt, *J* = 19.5, 8.0, 2.9 Hz, H-7b), 2.10 (1H, dd, *J* = 9.0, 14.0, Hz, H-15b), 2.0 (1H, d, *J* = 8.0 Hz, H-8), 1.99 (1H, overlapped, H-1a), 1.94 (1H, dd, *J* = 19.5, 5.5 Hz, H-7a), 1.57 (1H, d, *J* = 14.0 Hz, H-15a), 1.35 (3H, s, Me-30), 1.32 (1H, ddd, *J* = 13.0, 13.0, 13.0 Hz, H-1b), 1.30 (3H, s, Me-21), 1.23 (3H, s, Me-28), 1.12 (3H, s, Me-19), 1.06 (3H, s, Me-29), 0.90 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 212.6 (C-11), 167.0 (C-1''), 166.2 (C-1′), 140.1 (C-5), 133.1 (C-5′), 132.9 (C-5″), 130.6 (C-2′), 130.0 (C-2″), 129.7 (C-3″/C-7″), 129.5 (C-3′/C-7′), 128.4 (C-4″/C-6″), 128.3 (C-4′/C-6′), 119.5 (C-6), 110.7 (C-20), 78.5 (C-3), 75.2 (C-16), 75.0 (C-2), 65.2 (C-1‴), 62.8 (C-2‴), 57.2 (C-17), 48.8 (C-13), 48.3 (C-14), 47.8 (C-12), 47.6 (C-9), 43.7 (C-15), 42.6 (C-8), 33.8 (C-10), 30.6 (C-1), 24.5 (C-21), 24.5 (C-28), 23.8 (C-7), 21.5 (C-29), 20.2 (C-19), 19.2 (C-18), 18.5 (C-30); ESI-MS (positive ion mode) *m/z* 657.3441 $[M+H]^+$ (calcd for $C_{40}H_{49}O_8$ 657.3422).

4.3.31. Preparation of 35

Compound **34** (150 mg, 0.23 mmol) was dissolved in 1 M KOH methanolic solution (3.0 mL) with stirring at 20 °C. After 1 h, the reaction was diluted with EtOAc and washed with brine (2 × 25.0 mL), water (2 × 25.0 mL) and 1 M HCl solution (3 × 30.0 mL). The organic phase was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting crude product was purified by chromatography on silica gel (50% ethyl acetate/hexane) to afford **35** (60 mg, 64% yield) as a white solid. Mp: 145–146 °C; IR (KBr): 3491, 1695, 1681, 1363, 1267, 1192, 1092, 1058, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.74 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 4.95 (1H, ddd, *J* = 9.1, 6.5, 1.6 Hz, H-16), 3.60 (1H, ddd, *J* = 4.3, 9.2, 9.2 Hz, H-2), 3.25 (1H, dd, *J* = 1.15, 14.3 Hz, H-12a), 3.15 (1H, d, *J* = 6.5 Hz, H-17), 2.98 (1H, d, *J* = 9.2 Hz, H-3), 2.45 (1H, d, *J* = 14.3 Hz, H-12b), 2.42 (1H, m, H-7b), 2.36 (1H, m, H-10), 2.16 (3H, s, Me-21), 1.95 (1H, m, H-7a), 1.94 (1H, dd, *J* = 9.0, 13.0 Hz, H-15b), 1.90 (1H, *J* = 7.5 Hz, H-8), 1.90 (1H, m, H-1a), 1.50 (1H, dd, *J* = 7.1, 13.0 Hz, H-15a), 1.30 (3H, s, Me-30), 1.21 (3H, s, Me-28), 1.10 (1H, m, H-1b), 1.10 (3H, s, Me-19), 0.97 (3H, s, Me-29), 0.66 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 211.6 (C-11), 208.1 (C-20), 140.7 (C-5), 119.1 (C-6), 80.9 (C-3), 71.7 (C-16), 70.9 (C-2), 67.6 (C-17), 49.9 (C-13), 48.8 (C-9), 48.6 (C-14), 47.1 (C-12), 45.0 (C-15), 43.0 (C-8), 41.9 (C-4), 33.9 (C-10), 33.3 (C-1), 31.5 (C-21), 24.6 (C-28), 23.8 (C-7), 21.5 (C-29), 20.4 (C-19), 19.7 (C-18), 19.1 (C-30); ESI-MS (negative ion mode) *m/z* 405.2616 $[M-H]^-$ (calcd for $C_{24}H_{37}O_5$ 405.2635).

4.3.32. Preparation of 36

A mixture of **2** (100 mg, 0.18 mmol) and $CeCl_3.7H_2O$ (200 mg, 0.537 mmol) in MeOH (2.5 mL) was cooled at -30 °C and $NaBH_4$ (81 mg, 2.15 mmol) was then added. After stirring for 2 h, the reaction was diluted by adding 20.0 mL of EtOAc and washed with brine (2 × 20.0 mL). The organic phase was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting crude product was purified by chromatography on silica gel using ethyl acetate as mobile phase to afford **36** (72 mg, 72%) as a white solid. Mp: 199–200 °C; IR (KBr): 3448, 3279, 1732, 1717, 1698, 1567, 1556, 1403, 1281, 1128, 1081, 750 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ = 5.92 (1H, dd, *J* = 16.0, 1.2 Hz, H-24), 5.77 (1H, dd, *J* = 16.0, 6.0 Hz, H-23), 5.76 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 4.63 (1H, m, H-16), 3.97 (1H, dd, *J* = 6.0, 1.2 Hz, H-22), 3.55 (1H, ddd, *J* = 11.5, 9.3, 4.2 Hz, H-2), 3.24 (1H, d, *J* = 14.6 Hz, H-12a), 2.86 (1H, d, *J* = 9.3, H-3), 2.49 (1H, m, H-10), 2.48 (1H, d, *J* = 14.6 Hz, H-12b), 2.43 (1H, m, H-7b), 2.37 (1H, d, *J* = 6.5 Hz, H-17), 2.0 (1H, overlapped, H-7a), 1.96 (3H, s, Me-32), 1.95 (1H, d, *J* = 8.2 Hz, H-8), 1.89 (1H, dd, *J* = 12.2, 9.0 Hz, H-15b), 1.78 (1H, dt, *J* = 12.4, 4.2 Hz, H-1a), 1.53 (3H, s, Me-27), 1.52 (3H, s, Me-26), 1.50 (1H, overlapped, H-15a), 1.30 (3H, s, Me-30), 1.23 (3H, s, Me-21), 1.18 (3H, s, Me-28), 1.07 (3H, s, Me-19), 0.96 (3H, s, Me-29), 0.94 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, CD_3OD): δ = 216.6 (C-11), 171.9 (C-31), 142.7 (C-5), 137.4 (C-24), 128.8 (C-23), 120.0 (C-6), 81.9 (C-3), 81.5 (C-22), 77.2 (C-20), 72.3 (C-16), 71.6 (C-2), 56.4 (C-17), 52.5 (C-13), 50.0 (C-9), 49.6 (C-12), 49.1 (C-14), 45.6 (C-15), 44.2 (C-8), 43.4 (C-4), 34.9 (C-10), 34.7 (C-1), 27.5 (C-26), 27.3 (C-27), 25.3 (C-28), 24.8 (C-7), 24.2 (C-21), 22.3 (C-32), 22.3 (C-29), 20.4 (C-19), 20.3 (C-18), 19.6 (C-30); ESI-MS (negative ion mode) *m/z* 561.3438 $[M-H]^-$ (calcd for $C_{32}H_{49}O_8$ 561.3433).

4.3.33. Preparation of 37

To a solution of **6** (100 mg, 0.15 mmol) in anhydrous CH_2Cl_2, DBU (1.16 mL,7.75 mmol) and trifluoroacetic anhydride (1.08 mL, 7.75 mmol) were added with stirring at 0 °C under nitrogen atmosphere. After 10 h, the reaction was diluted by adding icewater (20.0 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were washed with HCl 1 M (2 × 25.0 mL) and brine (2 × 25.0 mL). The organic phase was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting crude product was purified by chromatography on silica gel (40% ethyl acetate/hexane) to afford **37** (48 mg, 42% yield) as a white solid. Mp: 86–87 °C; IR (KBr): 2976, 1788, 1741, 1731, 1695, 1369, 1246, 1215, 1170, 1149, 1113, 1082, 1048, 1028, 977 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.79 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 5.48 (1H, dd, *J* = 5.5, 13.0 Hz, H-2), 5.28 (1H, m, H-16), 3.27 (1H, d, *J* = 14.5 Hz, H-12a), 2.79 (1H, m, H-10) 2.75 (1H, d, *J* = 7.5, H-17), 2.66 (H, d, *J* = 14.5 Hz, H-12b), 2.60 (1H, m, H-23a), 2.53 (1H, m, H-23b), 2.45 (1H, m, H-7b), 2.15 (3H, s, Me-2′), 2.12 (1H, overlapped, H-1a), 2.06 (1H, overlapped, H-15b), 2.04 (2H, m, H-24), 2.02 (1H, d, *J* = 7.5 Hz, H-8), 1.99 (3H, s, Me-32), 1.96 (1H, m, H-7a), 1.95 (3H, s, Me-2″), 1.94 (3H, s, Me-21), 1.54 (1H, ddd, *J* = 13.0, 13.0, 13.0 Hz, H-1b), 1.48 (3H, s, Me-27), 1.46 (1H, m, H-15a), 1.45 (3H, s, Me-26), 1.32 (3H, s, Me-30), 1.31 (3H, s, Me-28), 1.29 (3H, s, Me-29), 1.10 (3H, s, Me-19), 1.02 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 210.8 (C-11), 205.4 (C-3), 202.1 (C-22), 170.2 (C-31), 170.1 (C-1′), 169.7 (C-1″), 155.5 (C-1‴), 139.7 (C-5), 120.3 (C-6), 114.3 (C-2‴), 90.6 (C-20), 80.9 (C-25), 73.1 (C-2), 73.1 (C-16), 55.0 (C-17), 51.2 (C-4), 50.2 (C-13), 48.6 (C-12), 48.3 (C-9), 47.6 (C-14), 43.1 (C-15), 42.1 (C-8), 34.6 (C-24), 34.3 (C-10), 32.1 (C-23), 31.9 (C-1), 28.7 (C-28), 26.0 (C-26), 25.8 (C-27), 23.6 (C-7), 22.3 (C-32), 21.3 (C-29), 21.0 (C-20), 20.9 (C-2″), 20.6 (C-2′), 20.0 (C-19), 19.8 (C-18), 18.4 (C-30); ESI-MS (negative ion mode) *m/z* 739. 3280 $[M-H]^-$ (calcd for $C_{38}H_{50}F_3O_{11}$ 739.3311).

4.3.34. Preparation of 38

Iodine (79 mg, 0.31 mmol) was added to a solution of Ph_3P (81 mg, 0.31 mmol) in CH_2Cl_2 (0.5 mL) and the mixture was stirred at room temperature for 10 min. A solution of **6** (100 mg, 0.155 mmol) in CH_2Cl_2 (1.0 mL) was then added and the mixture was stirred at room temperature. After 8 h, Aq 5% $NaHSO_3$ was added and the reaction was stirred for 10 min. The mixture was then diluted with CH_2Cl_2 (20.0 mL) and washed with H_2O (2 × 15.0 mL) and brine (2 × 15.0 mL). The organic phase was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting crude product was purified by chromatography on

silica gel (40% ethyl acetate/hexane) to afford **38** (32 mg, 35%) as a white solid. Mp: 119–120 °C; IR (KBr): 3445, 2979, 1738, 1731, 1696, 1373, 1238, 1110, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.78 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 5.48 (1H, dd, *J* = 5.5, 13.5 Hz, H-2), 5.34 (1H, m, H-24), 5.13 (1H, ddd, *J* = 1.5, 8.2, 9.5 Hz, H-16), 3.37 (1H, m, H-23a), 3.27 (1H, m, H-23b), 3.24 (1H, d, *J* = 15.0 Hz, H-12a), 2.80 (1H, m, H-10), 2.75 (1H, d, *J* = 8.2 Hz, H-17), 2.74 (1H, d, *J* = 15.0 Hz, H-12b), 2.43 (1H, ddt, *J* = 2.5, 8.0, 19.5 Hz, H-7b), 2.15 (3H, s, Me-2′), 2.13 (1H, overlapped, H-1a), 2.02 (1H, d, *J* = 8.0 Hz, H-8), 2.0 (1H, m, H-15b), 1.95 (1H, m, H-7a), 1.90 (3H, s, Me-2″), 1.76 (3H, d, *J* = 1.5 Hz, Me-26), 1.67 (3H, br s, Me-27), 1.53 (1H, ddd, *J* = 13.0, 13.0, 13.0 Hz, H-1b), 1.46 (3H, s, Me-21), 1.40 (1H, dd, *J* = 1.5, 14.0, H-15a), 1.32 (3H, s, Me-28), 1.31 (3H, s, Me-30), 1.29 (3H, s, Me-29), 1.10 (3H, s, Me-19), 1.02 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 211.8 (C-11), 211.3 (C-22), 205.6 (C-3), 170.2 (C-1′), 170.1 (C-1″), 139.7 (C-5), 135.5 (C-25), 120.4 (C-6), 115.5 (C-24), 78.5 (C-20), 73.9 (C-16), 73.3 (C-2), 54.0 (C-17), 51.3 (C-4), 49.9 (C-13), 48.6 (C-12), 48.4 (C-9), 47.9 (C-14), 43.2 (C-15), 42.1 (C-8), 35.2 (C-23), 34.3 (C-10), 32.0 (C-1), 28.7 (C-28), 25.7 (C-26), 24.0 (C-21), 23.7 (C-7), 21.3 (C-29), 20.8 (C-2″), 20.7 (C-2′), 20.0 (C-18), 19.6 (C-19), 18.9 (C-30), 18.3 (C-27); ESI-MS (negative ion mode) *m/z* 585.3421 $[M-H]^-$ (calcd for $C_{34}H_{49}O_8$ 585.3422).

4.3.35. Preparation of 39

To a solution of compound **15** (150 mg, 0.224 mmol) in methanol (2.0 mL), a suspension of Oxone® (179 mg, 0.29 mmol) in water (2.0 mL) was added at 0 °C. After 5 min, a saturated solution of sodium bisulfite (5.0 mL) was added. After evaporation under reduced pressure, the crude mixture was dissolved in water and extracted with diethyl ether (2 × 20 mL). The organic phase was then dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting crude product was purified by chromatography on silica gel (40% ethyl acetate/hexane) to afford the mixtures of sulfoxides (86 mg, 57% yield) Major isomer ^1H NMR ($CDCl_3$) δ = 7.65 (2H, dd, *J* = 8.0, 1.5 Hz, H-2′/H-6′), 7.56 (2H, m, H-3′/H-7′), 7.53 (1H, m, H-4′), 5.80 (1H, ddd, *J* = 2.0, 2.0, 6.0, H-6), 4.28 (1H, m, H-16), 6.43 (1H, dd, *J* = 13.2, 6.0 Hz, H-2), 3.06 (1H, d, *J* = 14.6 Hz, H-12a), 2.78 (1H, m, H-23a), 2.56 (1H, d, *J* = 14.6 Hz, H-12b), 2.51 (1H, m, H-10), 2.49 (1H, overlapped, H-23b), 2.46 (1H, d, *J* = 7.2 Hz, H-17), 2.41 (1H, overlapped, H-7b), 2.03 (2H, m, H-24), 1.96 (1H, d, *J* = 8.0 Hz, H-8), 1.96 (1H, m, H-7a), 1.95 (3H, s, Me-32), 1.91 (2H, m, H-1), 1.80 (1H, dd, *J* = 9.0, 13.5 Hz, H-15b), 1.44 (3H, s, Me-26), 1.42 (3H, s, Me-27), 1.37 (1H, m, H-15a), 1.35 (3H, s, Me-20), 1.32 (3H, s, Me-29), 1.27 (3H, s, Me-30), 1.22 (3H, s, Me-28), 1.11 (3H, s, Me-19), 0.92 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 213.8 (C-22), 211.8 (C-11), 207.6 (C-3), 142.3 (C-1′), 139.3 (C-5), 131.2 (C-4′), 129.1 (C-3′/C-5′), 124.6 (C-2′/C-6′), 121.0 (C-6), 81.2 (C-25), 78.9 (C-20), 71.0 (C-16), 71.0 (C-2), 57.7 (C-17), 51.6 (C-4), 50.4 (C-13), 48.8 (C-12), 48.7 (C-9), 48.3 (C-14), 45.5 (C-15), 42.3 (C-8), 35.3 (C-10), 34.8 (C-24), 30.6 (C-23), 27.9 (C-28), 26.1 (C-26), 25.8 (C-27), 24.4 (C-20), 23.8 (C-7), 23.2 (C-29), 21.7 (C-1), 19.9 (C-20), 19.8 (C-18), 18.6 (C-30), CH_3CO_2 (170.3, 22.4); ESI-MS (positive ion mode) *m/z* 669.3470 $[M+H]^+$ (calcd for $C_{38}H_{53}O_8S$ 669.3456).

A sealed 10 mL glass tube containing the mixture of isomers (80 mg, 0.12 mmol) and triethylamine (0.03 mL, 0.24 mmol) in toluene was introduced in the cavity of a microwave reactor (CEM Co., Discover) and irradiated with stirring under a maximum potency (300 W) for 5 min. The temperature was raised up to 120 °C. After cooling the mixture to 20 °C, the reaction vessel was opened and the product was evaporated under reduced pressure. The resulting crude product was purified by chromatography on silica (40% ethyl acetate/hexane) to afford **39** (46 mg, 71% yield) as a white solid. Mp:133–134 °C; IR (KBr): 3420, 1972, 1931, 1723, 1702, 1698, 1694, 1674, 1661, 1366, 1275, 1217, 1210, 1181, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 6.70 (1H, dd, *J*=2.1, 10.4 Hz, H-2), 5.98 (1H, dd, *J* = 3.0, 10.4 Hz, H-2), 5.79 (1H, ddd, *J* = 2.5, 2.5, 5.0, H-6), 4.34 (1H, t, *J* = 7.0 Hz, H-16), 3.36 (1H, m, H-10), 3.26 (1H, d, *J* = 15.0 Hz, H-12a), 2.83 (1H, ddd, *J* = 6.5, 9.0, 17.5 Hz, H-23a), 2.75 (1H, d, *J* = 15.0 Hz, H-12b), 2.54 (1H, d, *J* = 7.0 Hz, H-17), 2.52 (1H, m, H-23b), 2.36 (1H, ddt, *J* = 3.0, 8.5, 19.5 Hz, H-7b), 2.06 (2H, overlapped, H-24), 2.03 (1H, overlapped, H-7a), 2.02 (1H, d, *J* = 8.5 Hz, H-8), 1.96 (3H, s, Me-32), 1.87 (1H, *J* = 9.0, 13.0 Hz, H-15b), 1.47 (1H, overlapped, H-15a), 1.46 (3H, s, Me-26), 1.44 (3H, s, Me-27), 1.42 (3H, s, Me-21), 1.41 (3H, s, Me-30), 1.29 (3H, s, Me-29), 1.20 (3H, s, Me-28), 1.01 (3H, s, Me-19), 1.00 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 213.8 (C-22), 213.1 (C-11), 202.4 (C-3), 170.3 (C-31), 145.7 (C-2), 137.2 (C-5), 127.3 (C-1), 120.5 (C-6), 81.2 (C-25), 78.9 (C-20), 71.0 (C-16), 57.8 (C-17), 50.6 (C-), 49.0 (C-12), 48.8 (C-4), 48.4 (C-14), 48.3 (C-9), 45.7 (C-15), 41.5 (C-8), 36.5 (C-10), 34.8 (C-24), 30.7 (C-23), 27.4 (C-28), 26.1 (C-27), 25.8 (C-26), 24.5 (C-21), 23.6 (C-7), 22.4 (C-32), 20.2 (C-29), 20.0 (C-19), 19.9 (C-18), 18.1 (C-30); ESI-MS (negative ion mode) *m/z* 541.3146 $[M-H]^-$ (calcd for $C_{32}H_{45}O_7$ 541.3171).

4.3.36. Preparation of 40

CrO_3 (46 mg, 0.47 mmol) was dissolved in a mixture of pyridine (0.4 mL, 0.31 mmol) and CH_2Cl_2 (1.0 mL). After stirring for 10 min, a solution of **9** (100 mg, 0.16 mmol) in 0.5 mL of CH_2Cl_2 was added slowly. The mixture was stirred at room temperature for 72 h, filtered and the filtrate was neutralized with 5% HCl, washed (NaCl, $NaHCO_3$, and water), dried with anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was subjected to column chromatography (40% ethyl acetate/hexane) to give **44** (20 mg, 20% yield) as a white solid. Mp: 131–132 °C; IR (KBr) 3445, 2984, 1731, 1698, 1374, 1245, 1029 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 6.23 (1H, d, *J* = 2.2 Hz, H-6), 5.52 (1H, dd, *J* = 13.0, 5.3 Hz, H-2), 5.19 (1H, m, H-16), 3.24 (1H, d, *J* = 15.5 Hz, H-12a), 3.19 (1H, ddd, *J* = 13.0, 3.8, 2.2 Hz, H-10), 2.86 (1H, d, *J* = 15.5 Hz, H-12b), 2.66 (1H, d, *J* = 7.5 Hz, H-17), 2.63 (2H, m, H-23), 2.59 (1H, s, H-8), 2.45 (1H, dd, *J* = 15.2, 9.0 Hz, H-15b), 2.31 (1H, ddd, = 13.0, 5.3, 3.8 Hz, H-1a), 2.18 (CH_3COO), 2.03 (2H, m, H-24), 1.98 (3H, s, Me-2′), 1.92 (3H, s, Me-2″), 1.72 (1H, ddd, *J* = 13.0, 13.0, 13.0 Hz, H-1b), 1.48 (3H, s, Me-26), 1.46 (3H, s, Me-27), 1.45 (3H, s, Me-21), 1.44 (3H, s, Me-28), 1.41 (3H, s, Me-29), 1.34 (3H, s, Me-30), 1.33 (1H, overlapped, H-15a), 1.15 (3H, s, Me-19), 1.05 (3H, s, Me-18); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 212.0 (C-22), 209.5 (C-11), 202.9 (C-3), 198.3 (C-7), 170.4 (C-1′), 170.0 (C-31), 169.5 (C-1″), 163.9 (C-5), 125.1 (C-6), 81.0 (C-25), 78.5 (C-20), 73.6 (C-16), 72.4 (C-2), 57.2 (C-8), 53.9 (C-17), 52.0 (C-4), 49.5 (C-13), 48.8 (C-9), 48.6 (C-12), 47.5 (C-14), 43.1 (C-15), 36.5 (C-10), 35.2 (C-24), 30.5 (C-23), 30.2 (C-1), 29.7 (C-28), 26.0 (C-26), 25.8 (C-27), 24.3 (C-21), 22.4 (C-2′), 21.1 (C-29), 21.0 (C-19), 20.8 (C-2″), 20.6 (C-32), 19.7 (C-18), 19.2 (C-30); ESI-MS (positive ion mode) *m/z* 681.3280 $[M+Na]^+$ (calcd for $C_{36}H_{50}NaO_{11}$ 681.3245).

4.4. Biological activity

4.4.1. Cell line

Human non-small-cell lung cancer A549 cells were kindly provided by Dr. Rosina Gironès from Microbiology Department of University of Barcelona, Spain. A549 cells (American Type Culture Collection [ATCC] CCL185) were grown in Minimal Essential Medium supplemented with 10% fetal bovine serum, 100 U/mL penicillin G, 100 μg/mL streptomycin and 25 μg/mL amphotericin B in a humidified 5% CO2 atmosphere at 37 °C.

4.4.2. Cell viability assay

The effect of compounds treatment on the viability of A549 cells was measured by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) (Sigma, MO, USA) assay based on the ability

of live cells to cleave the tetrazolium ring to a molecule that absorb at 540 nm.[30] Briefly, cells were plated in 96-well culture plates ($1x10^4$ cells/well). After 24 h incubation, the cells were treated with different concentrations of the compounds. After 48 h and 72 h at 37 °C, the medium was removed and 50 μL of MTT reagent (1 mg/mL) was added to each well, and cells were further incubated at 37 °C for 4 h. The MTT solution was removed, 100 μL of dimethyl sulfoxide (Merck, Germany) was added to each well to dissolve formazan crystals, and the plates were gently shaken, whereby crystals were completely dissolved, followed by reading on a scanning multiwell spectrophotometer (Infinite 1200 TECAN, Grödje, Austria). The 50% inhibition concentration (IC_{50}) was defined as the concentration that inhibited cell proliferation by 50% when compared to untreated controls. Untreated cells were used as controls. Paclitaxel (Glenmark, Brazil) (at 0–10 μM) and doxorubicin (Zodiac, Brazil) (at 0–10 μM) were used as positive control (purity > 98%). The final concentration of DMSO showed no interference with the growth of cells.

4.5. Statistical analysis

The IC_{50} values and 95% confidence intervals of the tested compounds on A549 cells were calculated with a log (compound) versus normalized response (variable slope) curve fit (GraphPad Prism, Software Inc., San Diego, CA).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2012.03.001.

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