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# Design, syntheses, and biological evaluations of squamostolide and its related analogs

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**Abstract**—Squamostolide and its related analogs were designed and synthesized for biological evaluation. All these compounds were tested for growth inhibition activities against human tumor cell lines, in which one of the compounds showed the most potent cytotoxicity among these derivatives against a full panel of 60 human cancer cell lines. The same compound also showed G2/M phase arrest and a weak apoptotic effect during flow cytometric analysis.


## 1. Introduction

The annonaceous acetogenins, isolated from plant genus Annonaceae, a class of naturally occurring polyketides, has attracted worldwide attention for their special structures and manifold biological properties such as immunosuppressive, insecticidal, antiparasitic and antitumor activities.[1] The remarkable antitumor activity of acetogenins was caused by the inhibition of complex I in the mitochondrial electron transport system (ETS)[2a,2b] and NADH oxidase of the plasma membrane of cancer cells.[2c,2d] Inhibition of both enzymes would result in decreasing oxidative cytosolic ATP production and subsequent programmed cell death (apoptosis).[3] Rollicosin **1**,[4a] isolated from *Rollina mucosa*, a compound in the new subtype of acetogenins, possessed a special feature of two lactone moieties on both sides of an aliphatic chain and showed a potent inhibitory activity on the growth of human cancer cell lines. Squamostolide **2a**,[4b] which was isolated from *Annona squamosa* bearing similar structure with compound **1** but lacking the C4 hydroxyl group, exhibited significant biological activities. Both of them may be generated from oxidative degradation of classical acetogenins consisted of THF rings. It is considered that the new type of acetogenin will receive attention due to the attractive chemical probing and biological activities. However, until now, only two approaches for the synthesis of these new skeletons were reported.[5a,b] To probe the synthetic approach toward these structures, we have discovered a general method for the synthesis of squamostolide **2a**. To obtain more insight into constructing the SARs of these new bioactive molecules, compound **2a** and its derivatives **2b–e** based on changing the length of the carbon chain between the lactone rings and the stereochemistry of the chirality centers were designed and synthesized for evaluation of their biological activities.

## 2. Results

### 2.1. Chemistry

As illustrated in Scheme 1, the retrosynthetic analysis of squamostolide **2a** is based on a convergent process including palladium-catalyzed coupling reaction of two building blocks, which are terminal alkyne **3a** and vinyl iodide **4a**. The terminal alkyne **3a** could be prepared from 5-hexyn-1-ol and the vinyl iodide **4a** could be

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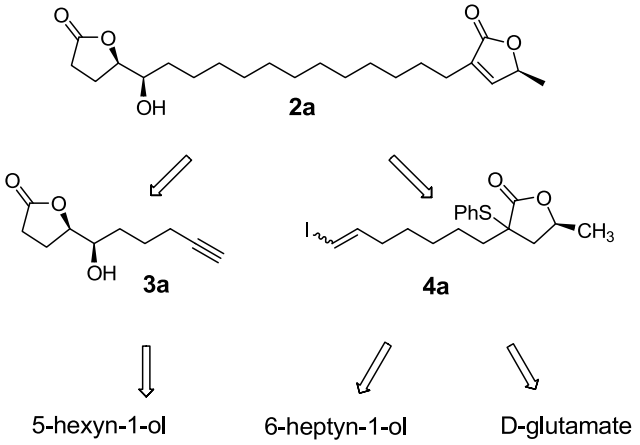



**Scheme 1.**

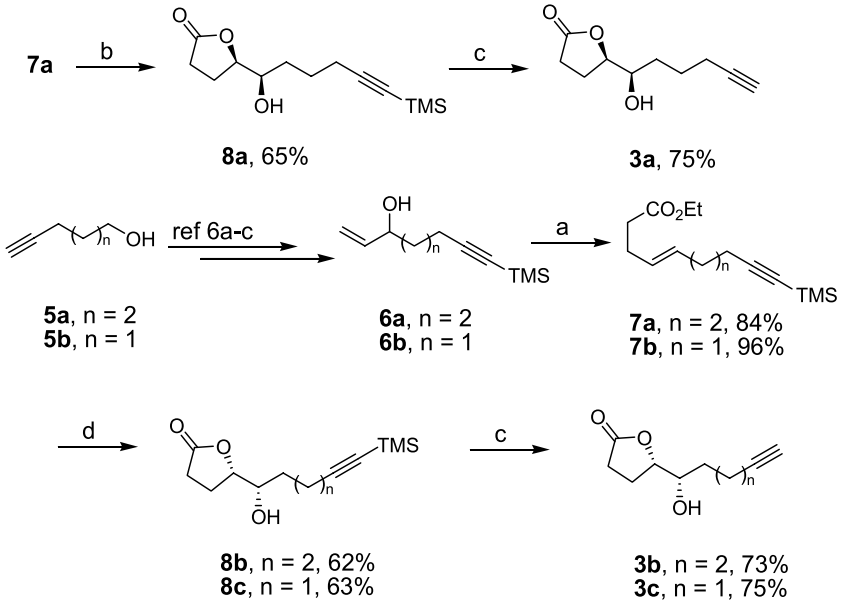
accomplished by using 6-heptyn-1-ol and D-glutamate as the starting materials.

The synthesis of lactones **3a**–**c** is outlined in Scheme 2. The starting allylic alcohols **6a**[6c] and **6b**,[6c] which were prepared from 5-hexyn-1-ol (**5a**) and 4-pentyn-1-ol (**5b**), were treated with triethyl orthoacetate[7] and propionic acid to afford the γ,δ-unsaturated esters **7a** and **7b** in 84% and 96% yields, respectively. Sharpless asymmetric dihydroxylation[8] of **7a** using AD-Mix-β gave lactone **8a** in 65% yield and 99% ee after chromatography. Finally, the TMS group was removed by treatment of **8a** with tetra-*n*-butylammonium fluoride at 0 °C to give lactone **3a** in 75% yield. Compounds **3b** and **3c** were prepared by the same processes from allylic alcohols **6a** and **6b** except using AD-Mix-α as the dihydroxylating agent. The overall yields were obtained in 38% and 45%, respectively.

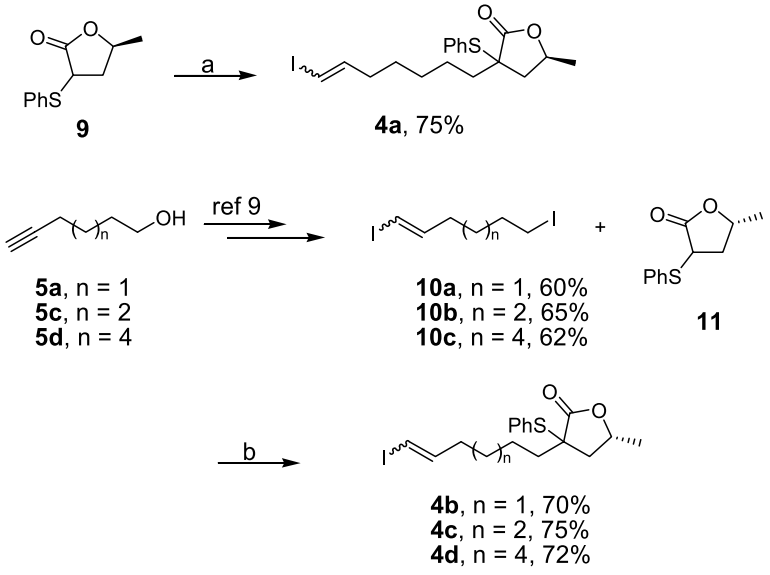
The butanolide moieties **4a**–**d** of the target molecules were achieved by alkylation of lactones[5a,5c] **9** and **11** with di-iodides **10a**–**c** as shown in Scheme 3. The di-iodides **10a**–**c** were synthesized according to the process reported by Keinan[9] using ynols **5a**, **5c** and **5d** as the starting materials in four steps, including protection of the alcohol as silyl ether, hydrostannylation of the terminal acetylene, desilylation, and ionidation to give the di-iodides **10a**–**c**. Finally, the butanolide **4a** was accomplished by treatment of lactone **9** with LDA, following the addition of di-iodide **10b** in 75% yield. The analogs **4b**–**d** were obtained by alkylation of lactone **11** with di-iodides **10a**–**c** in 70–75% yields by similar procedures.

To construct the whole structure of the target molecule, palladium-catalyzed coupling reaction of vinyl iodide **4a** with terminal alkyne **3a** revealed to be the most efficient way.[10] Thus, compounds **3a** and **4a** were mixed together using $Pd(PPh_3)_2Cl_2$ as a catalyst in the presence of copper iodide and $Et_3N$ as the solvent to give eneyne **12a** in 65% yield. Hydrogenation of eneyne **12a** using Wilkinson's catalyst at room temperature in benzene/methanol (1:1) for 24 h gave the saturated product **13a** in 86% yield. Compound **13a** was converted to sulfoxide using *m*-CPBA as an oxidizing agent in $CH_2Cl_2$. Without further purification, the sulfoxide intermediate was then dissolved in toluene and heated to reflux for 2 h to give the squamostolide **2a** in 45% yield as shown in Scheme 4.

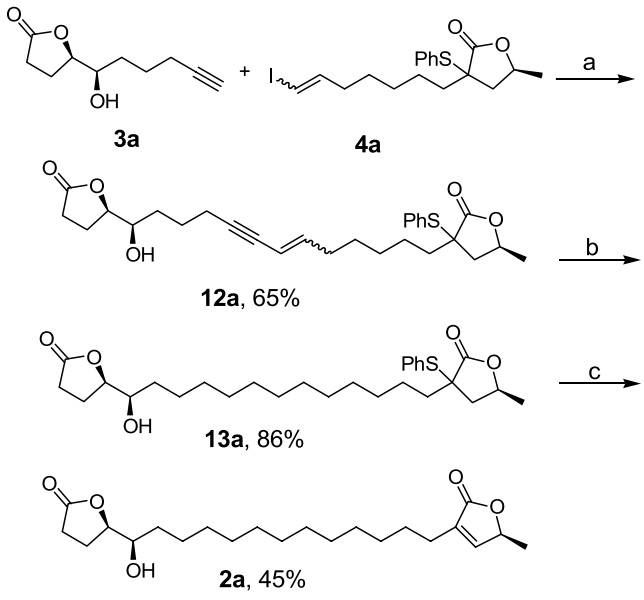
The analogs **2b**–**e** were prepared by similar methods as shown in Scheme 5. Palladium-catalyzed coupling reaction of compound **3b** with **4c** gave **12d** in 67% yield. Eneynes **12b**, **12c** and **12e** were synthesized by coupling reactions of lactone **3c** with vinyl iodides **4b**, **4c** and **4d** under the same reaction conditions in 52%, 57% and 63% yields, respectively. Hydrogenation of eneynes **12b**–**e** using Wilkinson's catalyst at room temperature in benzene/methanol (1:1) for 24 h gave the saturated



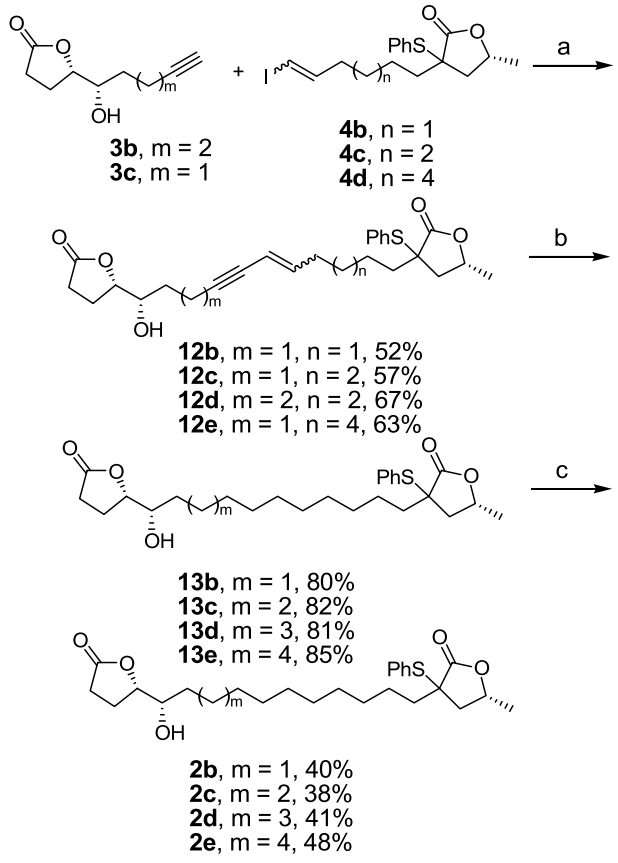

**Scheme 2.** Reagents and conditions: (a) $CH_3CH_2COOH$, $CH_3C(OEt)_3$, 180 °C, 2 h; (b) AD-MIX-β, $CH_3SO_2NH_2$, *t*-BuOH/$H_2O$, 0 °C, 24 h; (c) TBAF, THF, 0 °C, 5 h; (d) AD-MIX-α, $CH_3SO_2NH_2$, *t*-BuOH/$H_2O$, 0 °C, 24 h.




**Scheme 3.** Reagents and conditions: (a) i—LDA, THF, 30 min, 0 °C; ii—HMPA, **10b**, reflux, 2 h; (b) i—LDA, THF, **11**, 30 min, 0 °C, ii—HMPA, **10a–c**, reflux, 2 h.




**Scheme 4.** Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, CuI, $Et_3N$, 24 h; (b) $RhCl(PPh_3)_3$, $H_2$, benzene/MeOH 1:1, 24 h; (c) i—*m*-CPBA, $CH_2Cl_2$, 30 min, ii—toluene, reflux, 2 h.




**Scheme 5.** Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, CuI, $Et_3N$, 24 h; (b) $RhCl(PPh_3)_3$, $H_2$, benzene/MeOH 1:1, 24 h; (c) i—*m*-CPBA, $CH_2Cl_2$, 30 min, ii—toluene, reflux, 2 h.

products **13b–e** in 80–85% yields. Finally, compounds **13b–e** were treated with *m*-CPBA in $CH_2Cl_2$; again the initially formed sulfoxide intermediates were not purified and took for further thermal elimination reactions to give the final products **2b–e** in 40%, 38%, 41% and 48% yields, respectively. All of these compounds were obtained as white powder and the absolute configuration of **2d** was unambiguously determined by X-ray crystallographic analysis.[5a]

## 2.2. Cytotoxicity

Compound **2a** has been evaluated for the growth inhibition activities on several human cancer lines, in which compound **2a** displayed cytotoxicities against WiDr (human colon adenocarcinoma), A-549 (human lung carcinoma) and MCF-7 (human breast adenocarcinoma) with $GI_{50}$ values as 38.7, 33.1 and 41.1 μM, respectively. Compounds **2b–e** have been tested for the primary anticancer activity in the standard three-cell

**Table 1.** In vitro one dose primary anticancer assay[a] of compounds **2b–e**

| Compound | Growth percentages | | |
|---|---|---|---|
| | (Lung) NCI-H460 | (Breast) MCF7 | (CNS) SF-268 |
| **2b** | 68 | 58 | 73 |
| **2c** | 25 | 46 | 88 |
| **2d** | 34 | 67 | 85 |
| **2e** | 72 | 122 | 107 |

[a] One dose of **2b–e** at $10^{-4}$ M concentration.

line panel consisting of the NCI-H460 (lung), MCF7 (breast) and SF-268 (CNS). The results are described in Table 1. The preliminary data showed that compounds **2c** and **2d** exhibited selective growth inhibition against NCI-H460 cancer cell line. Compound **2c** has been evaluated for the NCI in vitro antitumor screen consisting of 60 human tumor cell lines and tested at a minimum of five concentrations at 10-fold dilution. A 48 h continuous drug exposure protocol was used and a sulforhodamine B (SRB) protein assay was used to estimate cell viability or growth. These results are summarized in Table 2. Compound **2c** possessed cytotoxic potency against many cell lines. The $GI_{50}$ values of compound **2c** against leukemia cancer CCRF-CEM, K-562 and MOLT-4 are 17.6, 20.4 and 21.6 μM, respectively. In non-small cell lung cancer panel, the growth of NCI-H226, NCI-H23 and NCI-H522 cell lines was affected by compound **2c** with $GI_{50}$ values as 15.9, 24.2 and 15.9 μM. Among the seven cancer cell lines in the colon cancer panel, compound **2c** exhibited the best inhibitory activity against colon cancer HCC-2998 with the $GI_{50}$ value as 2.3 μM. The $GI_{50}$ values of CNS cancer cell SF-295 and U-251 are 19.8 and 24.5 μM, respectively. In melanoma cancer panel, the growth of MALME-3M, M14, SK-MEL-5 and UACC-62 was inhibited by **2c** at 14.5–25.1 μM concentrations. The $GI_{50}$ values of **2c** against the growth of ovarian cancer IGROV1, OVCAR-3 and OVCAR-8 are 13.7, 16.4 and 23.4 μM, respectively. Compound **2c** also showed cytotoxic potency against 786-0, A498, ACHN, SN12C, TK-10 and UO-31 with a mean $GI_{50}$ value of 22.5 μM in the renal cancer panel. The $GI_{50}$ values of compound **2c** on two prostate cancer cell lines, PC-3 and DU-145, are 30.5 and 24.1 μM and on the breast cancer panel cell lines, NCI/ADR-RES, MDA-MB-231/ATCC and MDA-MB-435, are 12.1, 19.4 and 24.3 μM, respectively. It was noted that most of the $LC_{50}$ values of compound **2c** for the 60 cancer cell lines were higher than 100 μM, which suggested that **2c** showed growth inhibitory activities to human tumor cells and caused neither normal nor cancer cells' death even when the concentration of drug was as high as 100 μM. This phenomenon was meaningful to the advancement of medical therapies of human cancer diseases, while drugs with higher cytotoxicity always followed the higher damages to normal cells.

### 2.3. Cell cycle analysis of compound 2c

To obtain more insight into the role of analog **2c** in affecting whole cells, human leukemia K-562 cell was

**Table 2.** The $IC_{50}/LC_{50}$ values (μM) of cytotoxic activities of compound **2c**[a]

| Panel/cell line | **3** $GI_{50}$[b]/$LC_{50}$[c] |
|---|---|
| *Leukemia* | |
| CCRF-CEM | 17.6/> 100.0 |
| K-562 | 20.4/> 100.0 |
| MOLT-4 | 21.6/83.8 |
| *Non-small cell lung cancer* | |
| A549/ATCC | 38.1/>100.0 |
| EKVX | 33.2/>100.0 |
| HOP-62 | 40.2/>100.0 |
| NCI-H226 | 15.9/>100.0 |
| NCI-H23 | 24.2/>100.0 |
| NCI-H322M | 42.4/>100.0 |
| NCI-H460 | 31.2/>100.0 |
| NCI-H522 | 15.9/>100.0 |
| *Colon cancer* | |
| COLO 205 | 19.1/86.3 |
| HCC-2998 | 2.26/>100.0 |
| HCT-116 | 28.0/>100.0 |
| HCT-15 | 25.5/>100.0 |
| HT29 | 42.4/>100.0 |
| KM12 | 23.6/>100.0 |
| SW-620 | 37.6/>100.0 |
| *CNS cancer* | |
| SF-268 | 40.3/>100.0 |
| SF-295 | 19.8/>100.0 |
| SF-539 | 38.8/>100.0 |
| SNB-19 | 86.5/>100.0 |
| SNB-75 | >100.0/>100.0 |
| U251 | 24.5/>100.0 |
| *Melanoma* | |
| MALME-3M | 19.1/>100.0 |
| M14 | 25.1/>100.0 |
| SK-MEL-2 | 40.8/>100.0 |
| SK-MEL-28 | 78.3/>100.0 |
| SK-MEL-5 | 14.5/>54.2 |
| UACC-257 | 43.2/>100.0 |
| UACC-62 | 21.2/>100.0 |
| *Ovarian cancer* | |
| IGROV1 | 13.7/>100.0 |
| OVCAR-3 | 16.4/>100.0 |
| OVCAR-4 | >100.0/>100.0 |
| OVCAR-5 | NT/>100.0 |
| OVCAR-8 | 23.4/>100.0 |
| SK-OV-3 | 51.7/>100.0 |
| *Renal cancer* | |
| 786-0 | 23.6/>100.0 |
| A498 | 25.6/>100.0 |
| ACHN | 17.9/>100.0 |
| CAKI-1 | 35.8/>100.0 |
| RXF393 | 47.2/>100.0 |
| SN12C | 25.3/>100.0 |
| TK-10 | 22.9/>100.0 |
| UO-31 | 20.1/>100.0 |
| *Prostate cancer* | |
| PC-3 | 30.5/94.3 |
| DU-145 | 24.1/>100.0 |
| *Breast cancer* | |
| MCF7 | 39.2/>100.0 |
| NCI/ADR-RES | 12.1/95.1 |
| MDA-MB-231/ATCC | 19.4/>100.0 |

(*continued on next page*)

**Table 2** (*continued*)

| Panel/cell line | **3** $GI_{50}$[b]/$LC_{50}$[c] |
|---|---|
| MDA-MB-435 | 24.3/>100.0 |
| BT-549 | 47.4/>100.0 |
| T-47D | 32.7/>100.0 |

[a] Data obtained from the NCI's in vitro human tumor cell screen.
[b] The concentration produces 50% reduction in cell growth.
[c] The concentration produces 50% cells kill.

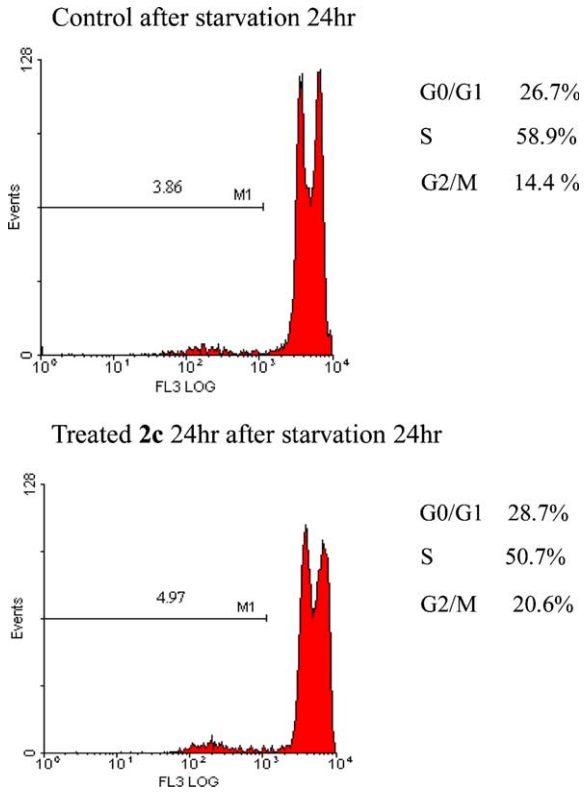



**Figure 1.** The results of flow cytometric analysis of DMSO and derivative **2c**.

used, and the growth characteristics of cells treatment with **2c** were measured (Fig. 1). As shown in Figure 1, cancer cells were exposed to the vehicle solvent (DMSO) as control, and 50 μM of **2c** was added to the cell line. After exposure to the compounds for 24 h, attached cells were analyzed by flow cytometry. The majority of control cells exposed to DMSO were in either the G0/G1 phase (26.7%) or S phase (58.9%) of the cell cycle, and only a few cells in the G2/M phase were detected (14.4%). After treatment of K-562 cell with compound **2c** for 24 h, the percentage of cell at G0/G1 changed to 28.7%, S phase to 50.7%, and G2/M phase to 20.6%.The proportion of G2/M phase cells increased, and a slightly apoptotic effect was observed (4.97%).

## 3. Conclusion

Based upon the above results of the cytotoxic activities of compounds **2b**–**e**, a preliminary picture with the structure–activity relationship could be achieved. It was demonstrated that **2c** displayed more potent biological activity than the other three analogs **2b**, **2d** and **2e** during the evaluation course. On the other hand, the flow cytometric assay indicated that the series of squamostolide structures could cause the G2/M phase blockage and slight apoptotic effect. The profiles suggested that the source of cytotoxicities of these squamostolide analogs was dependent on the length of carbon chain linking the two γ-lactone subdomains. It was thought that a certain aliphatic spacer was necessary for these analogs to bind with the active site in situ. Although their actual targets and mechanisms were still under investigation, the alkylating effect from the γ-butenolide portion of these compounds and coordination with metal ions was considered; however, much evidence is necessary to support the prediction.

In conclusion, this study provides a probing to the undiscovered fields of the new acetogenin structures, and has revealed a lead compound with growth inhibition effects on a full panel of 60 human tumor cell lines in low micro-concentrations along with G2/M phase arrest and apoptosis. These new investigations will be helpful in further elucidation of undiscovered biological properties of these novel acetogenins.

## 4. Experimental

### 4.1. Cell cycle analysis

Flow cytometry was used to measure cell cycle profile and apoptosis. For cell cycle analysis, K-562 cell treated with compound **2c** (50 μM) for 24 h was harvested by centrifugation. After being washed with PBS, the cell was fixed with ice-cold 70% ethanol for 30 min, washed with PBS, and then treated with 1 mL of 1 mg/ml of RNase A solution at 37 °C for 30 min. Cells were harvested by centrifugation at 1000 rpm for 5 min and further stained with 250 μl DNA staining solution (10 mg propidium iodide [PI], 0.1 mg trisodium citrate, and 0.03 mL Triton X-100 dissolved in 100 mL $H_2O$) at room temperature for 30 min in the dark. After loading 500 μL of PBS, the DNA contents of 10,000 events were measured by FACScan (Elite ESP, Beckman Coulter, Brea, CA) and the cell cycle profile was analyzed from the DNA content histograms by using WinCycle software. When cells were apoptosis the containing DNA were digested by endonuclease then the sub G1 pick appear. The percentage in sub G1 was analyzed by gating on cell cycle dot blots using Windows Multiple Document Interface software (WinMDI).

**4.1.1. (*trans*)-Ethyl-10-trimethylsilyl-4-ene-9-decaynoate (7a).** To a solution of Compound **6a** (1.96 g, 10 mmol) in triethyl orthoacetate (3.19 g, 20 mmol) was added propionic acid (0.07 g, 0.01 mmol) and the mixture was reacted at 180 °C for 2 h. The resultant ethanol was removed in vacuum and the residue was purified by flash column chromatography on silica gel to produce **7a** (2.23 g, 84%) as a yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 5.46–5.39 (m, 2 H), 4.11 (q, 2H, $J$ = 7.2 Hz), 2.35–2.25 (m, 4H), 2.18 (t, 2H,

$J$ = 7.2 Hz), 2.10–2.01 (m, 2H), 1.54 (quin, 2H, $J$ = 7.2 Hz), 1.24 (t, 3H, $J$ = 7.2 Hz), 0.12 (s, 9H). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 173.1, 130.5, 129.0, 107.2, 84.5, 60.2, 34.3, 31.4, 28.2, 27.9, 19.1, 14.2, 0.1 (3C). HRMS (EI) Calcd for $C_{15}H_{26}O_2Si$ 266.1702. Found: 266.1697.

**4.1.2. (*trans*)-Ethyl-9-trimethylsilyl-4-ene-8-nonaynoate (7b).** This compound was obtained as a yellow oil with 96% yield. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 5.46–5.38 (m, 2H), 4.08 (q, 2H, $J$ = 7.2 Hz), 2.32–2.21 (m, 4H), 2.20–2.13 (m, 4H), 1.20 (t, 3H, $J$ = 7.2 Hz), 0.10 (s, 9H). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 172.9, 129.5, 129.4, 106.7, 84.6, 60.1, 34.1, 31.6, 27.8, 20.1, 14.2, 0.1 (3C). HRMS (EI) Calcd for $C_{14}H_{24}O_2Si$ 252.1546. Found: 252.1550.

**4.1.3. 5R-(1*R*-Hydroxy-6-trimethylsilyl-hex-4-ynyl)-dihydro-furan-2-one (8a).** Compound **7a** (1.33 g, 5 mmol) was added to a cold (0 °C) solution of AD-mix-α (7.0 g) and $MeSO_2NH_2$ (0.475 g, 5 mmol) in *tert*-butyl alcohol–water (1:1, 20 mL). The mixture was stirred at 0 °C for 24 h and then worked up by addition of sodium sulfite (7.5 g) and extracted with ethyl acetate. The combined organic extracts were then extracted with 2 N KOH (50 mL). Solvents were removed in vacuum and the residue was purified by flash column chromatography on silica gel to afford **8a** (0.82 g, 65% yield, >99% ee based on NMR using $Eu(fod)_3$ as the shift reagent) as a yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 4.41 (td, 1H, $J$ = 7.6 Hz, 4.8 Hz), 3.67–3.58 (m, 1H), 2.64–2.48 (m, 2H), 2.29–2.21 (m, 2H), 2.14–2.04 (m, 2H), 1.76–1.59 (m, 4H), 0.13 (s, 9H). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 177.2, 106.7, 85.2, 83.1, 73.0, 31.6, 28.6, 24.2, 24.0, 19.4, 0.1 (3C). HRMS (EI) Calcd for $C_{13}H_{22}O_3Si$ 254.1338. Found: 254.1339.

**4.1.4. 5*S*-(1*S*-Hydroxy-6-trimethylsilyl-hex-5-ynyl)-dihydro-furan-2-one (8b).** This compound was obtained as a yellow oil with 62% yield (>99% ee based on NMR using $Eu(fod)_3$ as the shift reagent). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 4.40 (td, 1H, $J$ = 7.6 Hz, 4.8 Hz), 3.67–3.58 (m, 1H), 2.64–2.49 (m, 2H), 2.29–2.21 (m, 2H), 2.14–2.06 (m, 2H), 1.76–1.59 (m, 4H), 0.13 (s, 9H). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 177.0, 106.6, 85.2, 83.0, 73.0, 31.6, 28.6, 24.2, 24.0, 19.5, 0.1 (3C). MS (EI) $m/z$: (239, $M^+$-$CH_3$, 21%), 169 (20), 129 (40), 85 (75). HRMS (EI) Calcd for $C_{12}H_{19}O_3Si$ ($M^+-CH_3$) 239.1103. Found 239.1098.

**4.1.5. 5*S*-(1*S*-Hydroxy-5-trimethylsilyl-pent-4-ynyl)-dihydro-furan-2-one (8c).** This compound was obtained as a yellow oil with 63% yield (88% ee based on NMR using $Eu(fod)_3$ as the shift reagent). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 4.44 (td, 1H, $J$ = 7.2 Hz, 4.4 Hz), 3.76–3.70 (m, 1H), 2.64–2.39 (m, 4H), 2.27–2.21 (m, 1H), 2.18–2.11 (m, 1H), 1.77–1.70 (m, 2H), 0.12 (s, 9H). $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$: 177.5, 106.1, 85.5, 82.8, 72.2, 31.6, 28.5, 23.9, 16.1, 0.1 (3C). HRMS (EI) Calcd for $C_{12}H_{20}O_3Si$ 240.1182. Found: 240.1171.

**4.1.6. 5*R*-(1*R*-Hydroxy-hex-5-ynyl)-dihydro-furan-2-one (3a).** To a cold solution (0 °C) of **7a** (0.76 g, 3 mmol) in dry THF (10 mL) was added *tetra*-*n*-butylammonium fluoride (1 M in THF, 3 mL) and the mixture was stirred at 0 °C for 5 h and then worked up with ether and water. The aqueous layer was extracted with diethyl ether and the combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. After filtration and removal of solvent in vacuum, the residue was purified by flash column chromatography on silica gel to give **3a** (0.41 g, 75%). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 4.40 (td, 1H, $J$ = 7.6 Hz, 4.8 Hz), 3.61–3.56 (m, 1H), 2.64–2.47 (m, 2H), 2.28–2.20 (m, 2H), 2.15–2.05 (m, 2H), 1.95 (t, 1H, $J$ = 2.4 Hz), 1.77–1.61 (m, 4H). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 177.4, 83.9, 83.1, 73.0, 68.8, 31.6, 28.6, 24.2, 24.0, 18.0. HRMS (EI) Calcd for $C_{10}H_{14}O_3$ 182.0943. Found: 182.0944.

**4.1.7. 5*S*-(1*S*-Hydroxy-hex-5-ynyl)-dihydro-furan-2-one (3b).** This compound was obtained as a yellow oil with 73% yield. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 4.41 (td, 1H, $J$ = 7.6 Hz, 4.8 Hz), 3.62–3.58 (m, 1H), 2.61–2.49 (m, 2H), 2.28–2.21 (m, 2H), 2.15–2.05 (m, 2H), 1.96 (t, 1H, $J$ = 2.4 Hz), 1.79–1.61 (m, 4H). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 177.1, 83.8, 83.1, 73.1, 68.9, 31.6, 28.6, 24.2, 24.1, 18.1. HRMS (EI) Calcd for $C_{10}H_{14}O_3$ 182.0943. Found 182.0965.

**4.1.8. 5*S*-(1*S*-Hydroxy-pent-4-ynyl)-dihydro-furan-2-one (3c).** This compound was obtained as a yellow oil with 75% yield. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$: 4.40 (td, 1H, $J$ = 7.2 Hz, 4.6 Hz), 3.81–3.72 (m, 1H), 2.64–2.52 (m, 2H), 2.47–2.10 (m, 4H), 1.98 (t, 1H, $J$ = 2.6 Hz), 1.80–1.70 (m, 2H). $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$: 177.2, 83.3, 82.8, 72.1, 69.2, 31.5, 28.6, 23.9, 14.7. HRMS (EI) Calcd for $C_9H_{12}O_3$ 168.0786. Found: 168.0756.

**4.1.9. (*E*,*Z*,*RS*,5*S*)-3-(7-Iodohept-6-enyl)-5-methyl-3-(phenylsulfonyl)-tetrahydrofuran-2-one (4a).** Lithium diisopropylamide (2 M, 2 mmol, 1 mL) was added to a cold (0 °C) solution of lactone **9** (0.42 g, 2 mmol) in THF (5 ml) and the mixture was stirred at 0 °C for 0.5 h. A solution of **10b** (0.70 g, 2 mmol) in HMPA (0.7 ml, 4 mmol) was added and the mixture was warmed to room temperature and heated under reflux for 2 h. The mixture was worked up with saturated aqueous $NH_4Cl$ and extracted with ether. The combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. After filtration and removal of solvent in vacuum, the residue was purified by flash column chromatography on silica gel to give **4a** (0.64 g, 75%) as a yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.56–7.50 (m, 2H), 7.41–7.32 (m, 3H), 6.47 (dt, 0.8H, $J$ = 14.4 Hz, 7.2 Hz), 6.19–6.11 (m, 0.4H), 5.96 (dt, 0.8H, $J$ = 14.4 Hz, 1.2 Hz), 4.50–4.40 (m, 1H), 2.54–2.46 (m, 1H), 2.13–1.93 (m, 3H), 1.78–1.73 (m, 2H), 1.62–1.53 (m, 2H), 1.44–1.24 (m, 4H), 1.24 (d, 3H, $J$ = 6.4 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 177.0, 146.2, 136.8 (2C), 130.3, 129.7, 129.0 (2C), 74.6, 73.1, 56.1, 40.1, 36.3, 35.7, 28.7, 28.0, 24.3, 21.5. HRMS (EI) Calcd for $C_{18}H_{23}IO_2S$ 430.0464. Found: 430.0465.

**4.1.10. (*E*,*Z*,3*RS*,5*R*)-3-(6-Iodohex-5-enyl)-5-methyl-3-(phenylsulfonyl)-tetrahydrofuran-2-one (4b).** This compound was obtained as a yellow oil with 70% yield. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.58–7.51 (m, 2H), 7.42–7.33 (m, 3H), 6.47 (dt, 0.8H, $J$ = 14.4 Hz, 7.2 Hz), 6.20–6.10 (m, 0.4H), 5.97 (dt, 0.8H, $J$ = 14.4 Hz, 1.6 Hz), 4.52–4.43 (m, 1H), 2.56–2.46 (m, 1H), 2.16–1.91 (m, 3H), 1.81–1.71 (m, 2H), 1.66–1.52 (m, 2H), 1.46–1.31 (m, 2H), 1.21 (d, 3H, $J$ = 6.4 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 176.9, 145.9, 137.1 (2C), 130.3, 129.7, 129.0 (2C), 74.6, 74.0, 56.0, 40.2, 36.0, 35.6, 27.8, 23.9, 21.5. HRMS (EI) Calcd for $C_{17}H_{21}IO_2S$ 416.0307. Found: 416.0322.

**4.1.11. (*E*,*Z*,3*RS*,5*R*)-3-(7-Iodohept-6-enyl)-5-methyl-3-(phenylsulfonyl)-tetrahydrofuran-2-one (4c).** This compound was obtained as a yellow oil with 75% yield.$^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.58–7.50 (m, 2H), 7.42–7.33 (m, 3H), 6.47 (dt, 0.8H, $J$ = 14.4 Hz, 7.2 Hz), 6.20–6.10 (m, 0.4H), 5.97 (dt, 0.8H, $J$ = 14.4 Hz, 1.6 Hz), 4.52–4.40 (m, 1H), 2.56–2.46 (m, 1H), 2.14–1.94 (m, 3H), 1.80–1.71 (m, 2H), 1.61–1.50 (m, 2H), 1.43–1.25 (m, 4H), 1.19 (d, 3H, $J$ = 6.4 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 176.9, 146.3, 136.8 (2C), 130.3, 129.7, 129.0 (2C), 74.6, 73.2, 56.0, 40.2, 36.3, 35.8, 28.7, 28.0, 24.3, 21.5. HRMS (EI) Calcd for $C_{18}H_{23}IO_2S$ 430.0464. Found: 430.0469.

**4.1.12. (*E*,*Z*,3*RS*,5*R*)-3-(9-Iodonon-8-enyl)-5-methyl-3-(phenylsulfonyl)-etrahydrofuran-2-one (4d).** This compound was obtained as a yellow oil with 72% yield. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.58–7.50 (m, 2H), 7.42–7.26 (m, 3H), 6.48 (dt, 0.8H, $J$ = 14.4 Hz, 7.2 Hz), 6.18–6.08 (m, 0.4H), 5.96 (dt, 0.8H, $J$ = 14.4 Hz, 1.6 Hz), 4.52–4.40 (m, 1H), 2.56–2.46 (m, 1H), 2.08–1.94 (m, 3H), 1.80–1.72 (m, 2H), 1.65–1.52 (m, 2H), 1.41–1.23 (m, 8H), 1.19 (d, 3H, $J$ = 6.0 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 176.9, 146.6, 136.8 (2C), 130.4, 129.7, 129.0 (2C), 74.4, 73.2, 56.2, 40.1, 36.5, 36.0, 29.7, 29.4, 28.7, 28.2, 24.6, 21.5. HRMS (EI) Calcd for $C_{20}H_{27}IO_2S$ 458.0776. Found: 458.0779.

**4.1.13. (*E*,*Z*,3*RS*,5*S*)-3-[6-Enyl-8-tridecaynyl-13*R*-hydroxy-13-(5*R*-dihydro-furan-2-onyl)]-5-methyl-3-(phenylsulfonyl)-tetrahydrofuran-2-one (12a).** To a solution of **4a** (0.22 g, 0.5 mmol) in $Et_3N$ (1 mL) under $N_2$ were added $Pd(PPh_3)_2Cl_2$ (26 mg, 0.0375 mmol) and CuI (21 mg, 0.12 mmol). The mixture was stirred at room temperature for 0.5 h and to it was added a solution of **3a** (0.091 g, 0.5 mmol) in $Et_3N$ (1 ml). The reaction mixture was stirred at room temperature for 24 h and concentrated. The residue was purified by flash column chromatography to produce **19a** (0.16 g, 65%) as a yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.55–7.50 (m, 2H), 7.38–7.30 (m, 3H), 5.97 (dt, 1H, $J$ = 15.6 Hz, 7.2 Hz), 5.38 (dt, 1H, $J$ = 15.6 Hz, 1.6 Hz), 4.48–4.37 (m, 2 H), 3.60–3.55 (m, 1H), 2.64–2.44 (m, 4H), 2.40–2.31 (m, 2H), 2.29–2.20 (m, 1H), 2.17–1.85 (m, 4H), 1.78–1.55 (m, 5H), 1.41–1.23 (m, 6H), 1.18 (d, 3H, $J$ = 6.4 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 177.3, 177.0, 143.1, 136.6 (2C), 130.2, 129.6, 128.9 (2C), 109.8, 87.8, 83.0, 79.6, 73.2, 73.1, 56.1, 40.0, 36.2, 32.6, 31.7, 28.9, 28.6, 28.4, 24.5, 24.3, 24.0, 21.4, 19.0. HRMS (EI) Calcd for $C_{28}H_{36}O_5S$ 484.2283. Found: 484.2285.

**4.1.14. (*E*,*Z*,3*RS*,5*R*)-3-[(5-Enyl-7-undecaynyl-11*S*-hydroxy-11-(5*S*-dihydro-furan-2-onyl)]-5-methyl-3-(phenylsulfonyl)-tetrahydrofuran-2-one (12b).** This compound was obtained as a yellow oil with 52% yield. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.56–7.50 (m, 2H), 7.41–7.31 (m, 3H), 6.01 (dt, 1H, $J$ = 15.6 Hz, 7.2 Hz), 5.42 (dt, 1H, $J$ = 15.6 Hz, 1.6 Hz), 4.49–4.41 (m, 2H), 3.79–3.71 (m, 1H), 2.62–2.47 (m, 5H), 2.28–2.21 (m, 1H), 2.16–2.05 (m, 4H), 1.98–1.93 (m, 1H), 1.78–1.71 (m, 4H), 1.64–1.55 (m, 1H), 1.40–1.30 (m, 3H), 1.19 (d, 3H, $J$ = 6.4 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 177.0 (2C), 143.1, 136.8 (2C), 130.3, 129.7, 129.0 (2C), 110.0, 87.3, 82.8, 80.1, 73.2, 72.4, 56.0, 40.1, 36.2, 32.5, 31.7, 28.6 (2C), 24.0 (2C), 21.5, 15.6. HRMS (EI) Calcd for $C_{26}H_{32}O_5S$ 456.1970. Found 456.1961.

**4.1.15. (*E*,*Z*,3*RS*,5*R*)-3-[6-Enyl-8-dodecaynyl-12*S*-hydroxy-12-(5*S*-dihydro-furan-2-onyl)]-5-methyl-3-(phenylsulfonyl)-tetrahydrofuran-2-one (12c).** This compound was obtained as a yellow oil with 57% yield. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.56–7.50 (m, 2H), 7.41–7.31 (m, 3H), 6.00 (dt, 1H, $J$ = 15.6 Hz, 7.2 Hz), 5.40 (dt, 1H, $J$ = 15.6 Hz, 1.6 Hz), 4.49–4.40 (m, 2H), 3.79–3.73 (m, 1H), 2.61–2.54 (m, 1H), 2.49–2.41 (m, 4H), 2.30–2.21 (m, 1H), 2.18–2.02 (m, 4H), 1.97–1.90 (m, 1H), 1.81–1.68 (m, 4H), 1.61–1.50 (m, 1H), 1.40–1.22 (m, 5H), 1.17 (d, 3H, $J$ = 6.4 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 177.2, 177.0, 143.5, 136.7 (2C), 130.3, 129.7, 129.0 (2C), 109.7, 87.2, 82.8, 80.1, 73.2, 72.3, 56.1, 40.0, 36.3, 32.6, 31.7, 28.9, 28.6, 28.3, 24.4, 24.0, 21.4, 15.6. HRMS (EI) Calcd for $C_{27}H_{34}O_5S$ 470.2127. Found: 470.2120.

**4.1.16. (*E*,*Z*,3*RS*,5*R*)-3-[6-Enyl-8-tridecaynyl-13*S*-hydroxy-13-(5*S*-dihydro-furan-2-onyl)]-5-methyl-3-(phenylsulfonyl)-tetrahydrofuran-2-one (12d).** This compound was obtained as a yellow oil with 67% yield. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.55–7.50 (m, 2H), 7.41–7.32 (m, 3H), 6.00 (dt, 1H, $J$ = 15.6 Hz, 7.2 Hz), 5.43 (dt, 1H, $J$ = 15.6 Hz, 1.6 Hz), 4.50–4.39 (m, 2H), 3.63–3.56 (m, 1H), 2.64–2.46 (m, 4H), 2.36–2.30 (m, 2H), 2.29–2.21 (m, 1H), 2.17–1.85 (m, 4H), 1.78–1.55 (m, 5H), 1.41–1.23 (m, 6H), 1.18 (d, 3H, $J$ = 6.4 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 177.0, 176.9, 143.1, 136.7 (2C), 130.3, 129.6, 128.9 (2C), 109.9, 87.8, 83.0, 79.7, 73.2, 73.0, 56.2, 40.1, 36.3, 32.6, 31.9, 28.9, 28.6, 28.4, 24.5, 24.4, 24.0, 21.4, 19.0. HRMS (EI) Calcd for $C_{28}H_{36}O_5S$ 484.2283. Found: 484.2264.

**4.1.17. (*E*,*Z*,3*RS*,5*R*)-3-[8-Enyl-10-tetradecaynyl-14*S*-hydroxy-14-(5*S*-dihydro-furan-2-onyl)]-5-methyl-3-(phenylsulfonyl)-tetrahydrofuran-2-one (12e).** This compound was obtained as a yellow oil with 63% yield. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$: 7.56–7.51 (m, 2H), 7.39–7.28 (m, 3H), 5.99 (dt, 1H, $J$ = 15.6 Hz, 7.2 Hz), 5.45 (dt, 1H, $J$ = 15.6 Hz, 1.6 Hz), 4.52–4.39 (m, 2H), 3.63–3.52 (m, 1H), 2.63–2.42 (m, 5H), 2.32–1.24 (m, 20H), 1.18 (d, 3H, $J$ = 6.4 Hz). $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$: 177.1 (2C), 143.9, 136.7 (2C), 130.4, 129.7, 129.0 (2C), 109.5,

87.0, 82.8, 80.2, 73.2, 72.4, 56.2, 40.1, 36.4, 32.8, 31.8, 29.6, 29.4, 29.1, 28.8, 28.6, 24.6, 24.0, 21.4, 19.0. HRMS (FAB) Calcd for $C_{29}H_{39}O_5S$ 499.2519. Found: 499.2519.

**4.1.18. (3*RS*,5*S*)-3-[13-Hydroxytridecanyl-13*R*-(5*R*-dihydro-furan-2-onyl)]-5-methyl-3-(phenylsulfonyl)-tetrahydrofuran-2-one (13a).** To a solution of **12a** (97 mg, 0.2 mmol) in benzene/methanol (1:1 2 mL) was added chlorotris(triphenylphosphine)-rhodium (0.2 g, 0.2 mmol). The resulting mixture was then stirred at room temperature under hydrogen (1 atm) for 24 h. Solvents were removed under reduced pressure and the residue was purified by flash column chromatography to produce **13a** (84 mg, 86%) as a brown oil. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.56–7.50 (m, 2H), 7.40–7.31 (m, 3H), 4.49–4.38 (m, 2H), 3.59–3.53 (m, 1H), 2.64–2.46 (m, 3H), 2.27–2.07 (m, 3H), 1.97–1.91 (m, 1H), 1.77–1.71 (m, 2H), 1.57–1.31 (m, 21H), 1.15 (d, 3H, $J$ = 6.4 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 177.3, 177.1, 136.7 (2C), 130.4, 130.0, 128.9 (2C), 82.9, 73.5, 73.2, 56.3, 40.0, 36.4, 32.9, 30.4, 29.6, 29.4 (2C), 29.3, 29.2, 28.6, 28.4, 25.5, 25.4, 24.6, 24.0, 21.4. HRMS (EI) Calcd for $C_{28}H_{42}O_5S$ 490.2753. Found: 490.2750.

**4.1.19. (3*RS*,5*R*)-3-[11*S*-Hydroxyundecanyl-11-(5*S*-dihydro-furan-2-onyl)]-5-methyl-3-(phenylsulfonyl)-tetrahydrofuran-2-one (13b).** This compound was obtained as a brown oil with 80% yield. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$: 7.56–7.50 (m, 2H), 7.41–7.29 (m, 3H), 4.56–4.39 (m, 2H), 3.61–3.54 (m, 1H), 2.64–2.51 (m, 3H), 2.38–1.93 (m, 3H), 1.80–1.62 (m, 3H), 1.57–1.41 (m, 4H), 1.39–1.26 (m, 14H), 1.16 (d, 3H, $J$ = 6.4 Hz). $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$: 177.2, 177.1, 136.8 (2C), 130.4, 130.0, 129.0 (2C), 82.9, 73.5, 73.2, 56.3, 40.0, 36.4, 32.9, 30.4, 29.5, 29.4, 29.3, 28.6, 28.5, 25.5, 25.4, 24.6, 24.0, 21.4. HRMS (EI) Calcd for $C_{26}H_{38}O_5S$ 462.2440. Found: 462.2470.

**4.1.20. (3*RS*,5*R*)-3-[12*S*-Hydroxydodecanyl-12-(5*S*dihydro-furan-2-onyl)]-5-methyl-3-(phenylsulfonyl)-tetrahydrofuran-2-one (13c).** This compound was obtained as a brown oil with 82% yield. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.56–7.50 (m, 2H), 7.40–7.31 (m, 3H), 4.50–4.38 (m, 2H), 3.60–3.52 (m, 1H), 2.63–2.47 (m, 3H), 2.28–2.06 (m, 3H), 1.98–1.91 (m, 1H), 1.80–1.70 (m, 3H), 1.57–1.41 (m, 4H), 1.39–1.26 (m, 15H), 1.16 (d, 3H, $J$ = 6.4 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 177.2, 177.1, 136.8 (2C), 130.4, 130.0, 129.0 (2C), 82.9, 73.5, 73.2, 56.3, 40.0, 36.4, 32.9, 30.4, 29.5, 29.4, 29.3 (2C), 28.6, 28.5, 25.5, 25.4, 24.6, 24.0, 21.4. HRMS (EI) Calcd for $C_{27}H_{40}O_5S$ 476.2596. Found: 476.2596.

**4.1.21. (3*RS*,5*R*)-3-[13*S*-Hydroxytridecanyl-13-(5*S*-dihydro-furan-2-onyl)]-5-methyl-3-(phenylsulfonyl)-tetrahydrofuran-2-one (13d).** This compound was obtained as a brown oil with 81% yield. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.56–7.50 (m, 2H), 7.40–7.31 (m, 3H), 4.49–4.38 (m, 2H), 3.60–3.53 (m, 1H), 2.64–2.47 (m, 3H), 2.27–2.07 (m, 3H), 1.97–1.91 (m, 1H), 1.79–1.71 (m, 2H), 1.57–1.30 (m, 21H), 1.15 (d, 3H, $J$ = 6.4 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 177.3, 177.2, 136.7 (2C), 130.4, 129.6, 128.9 (2C), 82.9, 73.5, 73.2, 56.3, 40.0, 36.4, 32.9, 30.4, 29.6, 29.4 (2C), 29.3, 29.2, 28.6, 28.4, 25.5, 25.4, 24.6, 24.0, 21.4. HRMS (EI) Calcd for $C_{28}H_{42}O_5S$ 490.2753. Found 490.2755.

**4.1.22. (3*RS*,5*R*)-3-[14*S*-Hydroxytetradecanyl-14-(5*S*-dihydro-furan-2-onyl)]-5-methyl-3-(phenylsulfonyl)-tetrahydrofuran-2-one (13e).** This compound was obtained as a brown oil with 85% yield. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$: 7.57–7.50 (m, 2H), 7.40–7.31 (m, 3H), 4.50–4.37 (m, 2H), 3.59–3.53 (m, 1H), 2.63–2.45 (m, 3H), 2.27–1.19 (m, 6H), 1.82–1.73 (m, 3H), 1.57–1.25 (m, 23H), 1.15 (d, 3H, $J$ = 6.2 Hz). $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$: 177.1, 174.1, 136.8 (2C), 130.5, 129.7, 129.0 (2C), 82.9, 73.6, 73.2, 56.3, 40.1, 36.5, 33.0, 29.7, 29.5 (3C), 29.4 (3C), 29.3 (2C), 28.7, 25.4, 24.7, 24.1, 21.5. HRMS (FAB) Calcd for $C_{29}H_{45}O_5S$ 505.2989. Found: 505.2989.

### 4.2. Squamostolide (2a)

*m*-CPBA (16 mg, 0.1 mmol) was added to a solution of **13a** (49 mg, 0.1 mmol) in $CH_2Cl_2$ (1 mL) at 0 °C and the mixture was stirred at this temperature for 30 min. It was then worked-up with saturated aqueous $NaHCO_3$ and extracted with $CH_2Cl_2$. The combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. After filtration and removal of solvent in vacuum, the residue was refluxed in toluene (2 mL) for 2 h. Solvent was removed again and the residue was purified by flash column chromatography to produce **2a** (17 mg, 45%) as a white powder. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 6.98 (d, 1H, $J$ = 1.6 Hz), 5.01–4.95 (m, 1H), 4.41 (td, 1H, $J$ = 7.6 Hz, 4.4 Hz), 3.58–3.53 (m, 1H), 2.65–2.48 (m, 2H) 2.28–2.20 (m, 3H), 2.14–2.06 (m, 1H), 1.80 (br, 1H), 1.57–1.42 (m, 6H), 1.38 (d, $J$ = 6.8 Hz, 3 H), 1.37–1.19 (m, 16H). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 177.2, 173.9, 148.9, 134.2, 82.9, 77.4, 73.5, 32.9, 29.5 (3C), 29.4 (3C), 29.2, 29.1, 28.6, 27.3, 25.4, 25.1, 24.0, 19.2. HRMS (EI) Calcd for $C_{22}H_{36}O_5$ 380.2563. Found 380.2563, mp 96–97 °C, $[\alpha]_D^{25}$ −2.9 (*c* 0.4, acetone), $^{lit}[\alpha]_D^{24}$ −3.3 (*c* 0.122, acetone).

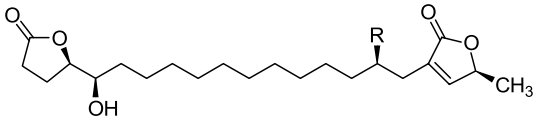
**4.2.1. 3-[11*S*-Hydroxyundecanyl-11-(5*S*-dihydro-furan-2-onyl)]-5*R*-methyl-5*H*-furan-2-one (2b).** This compound was obtained as a white powder with 40% yield. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 6.98 (d, 1H, $J$ = 1.6 Hz), 5.01–4.92 (m, 1H), 4.41 (td, 1H, $J$ = 7.6 Hz, 4.4 Hz), 3.58–3.51 (m, 1H), 2.64–2.49 (m, 2H), 2.28–2.20 (m, 3H), 2.16–2.09 (m, 1H), 1.56–1.44 (m, 6H), 1.40 (d, 3H, $J$ = 6.8 Hz), 1.28–1.19 (m, 13H). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 177.1, 174.0, 148.9, 134.3, 82.9, 77.4, 73.6, 32.9, 29.4 (3C), 29.2 (2C), 29.1, 28.7, 27.3, 25.4, 25.1, 24.0, 19.2. HRMS (EI) Calcd for $C_{20}H_{32}O_5$ 352.2250. Found: 352.2256, mp 90–91 °C, $[\alpha]_D^{25}$ −9.2 (*c* 1.0, $CHCl_3$).

**4.2.2. 3-[12*S*-Hydroxydodecanyl-12-(5*S*-dihydro-furan-2-onyl)]-5*R*-methyl-5*H*-furan-2-one (2c).** This compound was obtained as a white powder with 38% yield. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 6.98 (d, 1H, $J$ = 1.6 Hz), 5.01–4.93 (m, 1H), 4.40 (td, 1H, $J$ = 7.6 Hz, 4.4 Hz), 3.58–3.50 (m, 1H), 2.65–2.48 (m, 2H), 2.28–2.20 (m, 3H), 2.16–2.06 (m, 1H) 1.90 (br, 1H) 1.56–1.41 (m, 5H), 1.39 (d, 3H, $J$ = 6.8 Hz), 1.28–1.19 (m, 15H). $^{13}$C

NMR ($CDCl_3$, 100 MHz) $\delta$: 177.2, 173.9, 148.9, 134.2, 82.9, 77.4, 73.5, 32.9, 29.5 (3C), 29.4 (2C), 29.2, 29.1, 28.7, 27.3, 25.4, 25.1, 24.0, 19.2. HRMS (EI) Calcd for $C_{21}H_{34}O_5$ 366.2406. Found: 366.2409, mp 65–66 °C, $[\alpha]_D^{25}$ −7.5 (*c* 1.0, $CHCl_3$).

**4.2.3. 3-[13*S*-Hydroxytridecanyl-13-(5*S*-dihydro-furan-2-onyl)]-5*R*-methyl-5*H*-furan-2-one (2d).** This compound was obtained as a white powder with 41% yield. $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 6.98 (d, 1H, $J$ = 1.6 Hz), 5.01–4.95 (m, 1H), 4.41 (td, 1H, $J$ = 7.6 Hz, 4.4 Hz), 3.58–3.54 (m, 1H), 2.60–2.48 (m, 2H) 2.28–2.21 (m, 3H), 2.15–2.08 (m, 1H), 1.73 (br, 1H), 1.57–1.41 (m, 6H), 1.39 (d, $J$ = 6.8 Hz, 3H), 1.37–1.19 (m, 16H). $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$: 177.2, 173.9, 148.9, 134.2, 82.9, 77.4, 73.6, 32.9, 29.5 (3C), 29.4 (3C), 29.2, 29.1, 28.6, 27.3, 25.4, 25.1, 24.0, 19.2. HRMS (EI) Calcd for $C_{22}H_{36}O_5$ 380.2563. Found: 380.2559, mp 103–104 °C, $[\alpha]_D^{25}$ −13.6 (*c* 1.0, $CHCl_3$).

**4.2.4. 3-[14*S*-Hydroxytetradecanyl-14-(5*S*-dihydro-furan-2-onyl)]-5*R*-methyl-5*H*-furan-2-one (2e).** This compound was obtained as a white powder with 48% yield. $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 6.98 (d, 1H, $J$ = 1.6 Hz), 5.02–4.96 (m, 1H), 4.41 (td, 1H, $J$ = 7.6 Hz, 4.4 Hz), 3.58–3.54 (m, 1H), 2.62–2.12 (m, 6H), 1.57–1.40 (m, 7H), 1.39 (d, $J$ = 6.8 Hz, 3H), 1.36–1.15 (m, 19H). $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$: 177.3, 173.9, 148.9, 134.3, 82.9, 76.4, 73.6, 32.9, 29.5 (3C), 29.4 (3C), 29.2 (2C), 29.1, 28.7, 27.4, 25.4, 25.1, 24.0, 19.2. HRMS (FAB) Calcd for $C_{23}H_{39}O_5$ 395.2799. Found: 395.2804, mp 80–81 °C, $[\alpha]_D^{25}$ −10.3 (*c* 1.0, $CHCl_3$).




**1** Rollicosin (R = OH)
**2a** Squamostolide (R = H)

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## References and notes

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