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Total synthesis of 14,21-diepi-squamocin-*K*

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ABSTRACT

A new method to prepare annonaceous acetogenins is described in the synthesis of the 14,21-diepimer (**14**) of *squamocin-K*. The synthesis utilized the controlled sequence of ring-closing metathesis (RCM) and cross metathesis (CM) reactions to incorporate the stereocenters and skeleton from (3*R*,4*R*)-1,5-hexadiene-3,4-diol and 10-chloro-1-decene. The lactone moiety was attached through nucleophilic substitution and achieved the desymmetrization. Inhibitory activities of **14** against human hormone-refractory prostate cancer cell line (PC-3) were also evaluated.

1. Introduction

Annonaceous acetogenins are a large family of natural products, widely found in the tropical plant family of Annonaceae.[1] These compounds are potent inhibitors of mitochondrial complex I and have profound biological effects, such as cytotoxic, antitumor, antiparasitic, pesticidal, antimicrobial, and immunosuppressive activities.[2] Recent research also showed that they are toxic to cortical neurons and linked to some neurodegenerative disorders.[3]

The structure of annonaceous acetogenins is characterized by the long-chain (C32 or C34) fatty acids ending with an unsaturated γ-lactone and a hydrophilic central core constituted of cyclic ethers and hydroxyl groups. Based on the structure of their central core, these acetogenins are classified as mono-tetrahydrofuran (THF), adjacent bis-THF, and others.[2b] Most of the known annonaceous acetogenins belong to the subgroup of the adjacent bis-tetrahydrofurans, which in general, are also more potent in biological studies than the other two types.[4] The stereochemistry of the bis-THF core was reported to affect the anticancer activity of these compounds.[4h] Thus, many synthetic efforts for preparing or mimicking such acetogenins have been developed.[5–7]

Recently, we reported that the C_2 symmetrical (3*R*,4*R*)-1,5-hexadiene-3,4-diol (**1**)[8] could be the sole source for the key skeleton and stereocenters of the adjacent bis-THF core of annonaceous acetogenins, and the formal synthesis of asimicin.[9] Here, we report our progress in applying this strategy, which is exemplified in the total synthesis of 14,21-diepi-squamocin-*K* (Fig. 1).

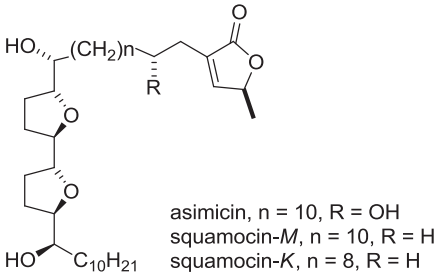

Fig. 1. Representative annonaceous acetogenins.

2. Results and discussion

The retrosynthetic analysis is shown in Scheme 1. We planned to assemble the molecular skeleton by controlled ring-closing metathesis (RCM) and cross metathesis (CM),[10] which extended the C_2 symmetry of diene-diol **1**. Desymmetrization and the incorporation of the lactone moiety were to be achieved by an S_N2 reaction.

Diene-diol **1** was converted to bis-methoxymethyl ether **2**, which was treated with boron trichloride followed by diisopropylethylamine (DIPEA) and two additional units of **1** to give diol **3** (Scheme 2). The remaining hydroxyl groups of **3** were protected by benzyl (Bn) or

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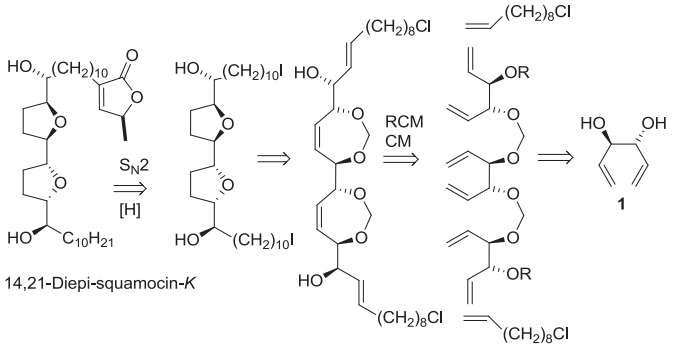
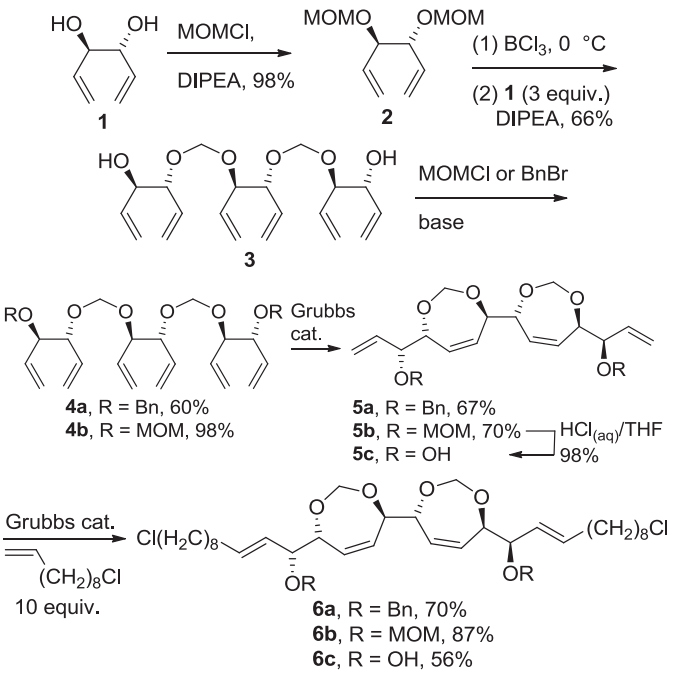


Scheme 1. Retrosynthetic analysis of 14,21-diepi-squamocin-*K*.



Scheme 2. Synthesis of 14,21-diepi-squamocin-*K*.

methoxymethyl (MOM) groups (**4a** and **4b**, respectively). Although the attempted RCM reaction of **3** with the second generation Grubbs catalyst gave the complicated mixture due to the competitive pathways between RCM and CM (Table 1, entry 1),[11] the RCM reactions of the protected **4a** and **4b** were successful to provide bis-4,7-dihydro-1,3-dioxepines **5a** and **5b** (Table 1, entries 2 and 3). Hydrolysis of **5b** afforded **5c**. Both MOM-protected **5b** and diol **5c** smoothly underwent intermolecular CM reactions with excess 10-chloro-1-decene to give **6b** and **6c**, respectively (entries 4, 5). In contrast, the CM reaction of Bn-protected **5a** was sluggish (entries 6 and 7). Fortunately, a satisfactory yield (70%) for the CM process of **5a** to **6a** was obtained in refluxing 1,2-dichloroethane (entry 8). The observed reactivity differences between **5a**–**c** in CM are explained by the differing affinities of the allylic substituents for the ruthenium catalyst (OH≈OMOM>OBn).[12] The development of practical RCM and CM conditions for the benzyl-protected substrates **4a** and **5a** was useful because the OBn group was stable to the strongly acidic conditions needed for the later hydrolysis of the methylene acetals (vide infra).[13] Consequently, compound **6a** was adopted for the synthesis of **14**.

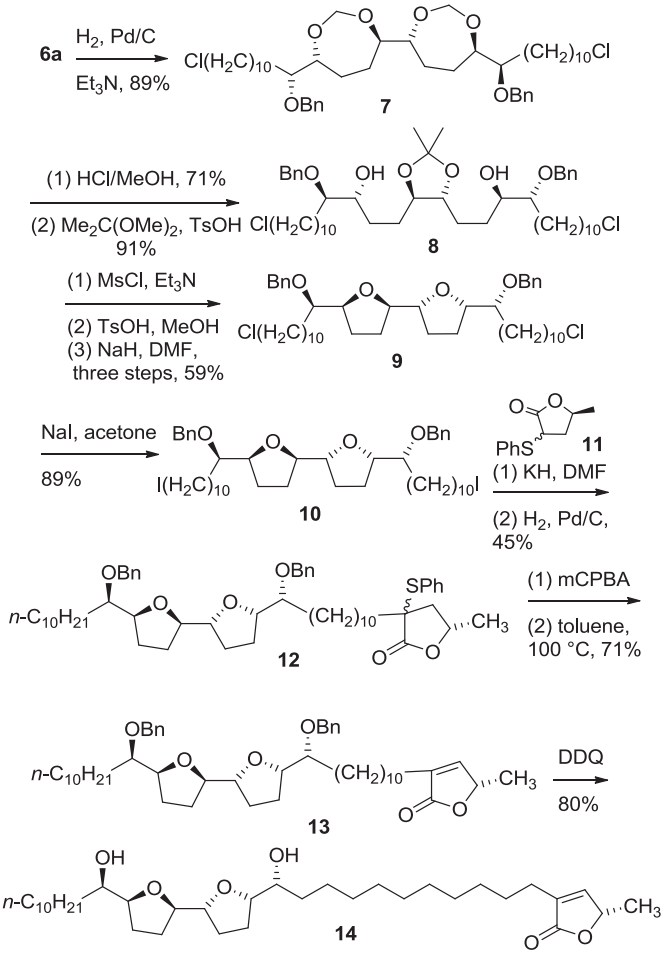
Tetraene **6a** was hydrogenated to **7**[14] and subsequent removal of the methylene acetal and formation of the acetonide gave diol **8**, in which the hydroxyl groups along the C_2 symmetrical axis are differentiated (Scheme 3). Mesylation, deprotection, and cyclization of

Table 1
Reaction conditions for the metathesis reactions of **3**–**5**

Entry	Reactant	Product	Solvent	Temp (°C)	Time (h)	Yield (%)
1[a]	**3**	**5c**	Toluene	70	3	0
2[a]	**4a**	**5a**	Toluene	75	3	67
3[a]	**4b**	**5b**	Toluene	70	3	70
4[b]	**5b**	**6b**	CH_2Cl_2	40	16	87
5[b]	**5c**	**6c**	CH_2Cl_2	40	16	56
6[b]	**5a**	**6a**	CH_2Cl_2	40	16	0
7[b]	**5a**	**6a**	Toluene	70	16	43
8[b]	**5a**	**6a**	$(CH_2Cl)_2$	84	16	70

[a] Ring-closing metathesis.
[b] Cross metathesis with 10-chloro-1-decene (10 equiv).

8 generated bis-THF derivative **9** with the stereochemistry *erythro*/*cis*/*threo*/*cis*/*erythro*. This was converted to the more reactive diiodide **10** for the subsequent nucleophilic substitution reaction. Although the reaction using lactone **11** as the nucleophile has been widely applied in related syntheses,[6] we found that nucleophilic substitution involving **10** and **11** was challenging as previously reported by Brown's and Tanaka's groups.[6j,15] After screening many reaction conditions, we found that the use of *N*,*N*-dimethylformamide (DMF) as the solvent and potassium hydride as the base yielded the mono-alkylation product **12** in a satisfactory yield (51%).[16] The remaining iodo group in **12** was reduced to give **13**, and the unsaturated lactone **14** was produced after the oxidation of phenyl sulfide and elimination of the corresponding sulfoxide. The 14,21-diepi-squamocin-*K* (**14**) was produced after removal of the benzyl groups by reaction with 2,3-dichloro-5,6-dicyano-*p*-



Scheme 3. Synthesis of 14,21-diepi-squamocin-*K* (continued).

benzoquinone (DDQ).[17] Preliminary assay of **14** against the cell proliferation of human hormone-refractory prostate cancer cell line (PC-3) showed moderate activity (IC_{50} 19.9 μM).

3. Conclusion

In summary, we have developed a total synthesis to prepare annonaceous acetogenins having an adjacent bis-THF core. Our approach uses the C_2 diene-diol **1** as the only source of stereocenters, which circumvents formation of the chiral centers by stereoselective oxidations of olefins as is often seen in other syntheses of such acetogenins.[6] The sequence of the controlled RCM and CM on compounds **4** and **5** built the molecular skeleton and negated the use of protecting groups on the terminal olefins.[9] A new reaction condition was developed for the nucleophilic substitution of **11** to diiodide **10**. The desymmetrization by S_N2 reaction avoided the low efficiency in applying CM for this purpose.[6m,18] For further applications, the diol **8** could be used to prepare other diastereomers because its hydroxyls groups are differentiated, and the remaining iodo group after the reaction of **10** and **11** could allow further conjugation.

4. Experimental section

4.1. General method

All purchased chemicals were used without further purification. Anhydrous solvents were distilled prior to use: THF and diethyl ether from sodium benzophenone ketyl; CH_2Cl_2 and DMF from calcium hydride. ^1H and ^{13}C NMR spectra were obtained on 300 or 500 MHz spectrometers and referenced to TMS or residual $CHCl_3$. Column chromatography was conducted using silica gel (230–400 mesh). TOF analyzer type was used for the HRMS (ESI) measurement. Double focusing mass spectrometer was used for the HRMS (EI) and HRMS (FAB) measurement.

*4.1.1. (5R,6R)-5,6-Divinyl-2,4,7,9-tetraoxadecane (**2**).* Chloromethyl methyl ether (MOMCl, 2.35 g, 29.2 mmol) was added to a solution of **1** (1.1 g, 9.7 mmol), diisopropylethylamine (6.3 g, 48.6 mmol), and dichloromethane (25 mL) at 0 °C. The reaction mixture was refluxed for 16 h, quenched with satd $NH_4Cl_{(aq)}$ (30 mL), and extracted with ether (50 mL×3). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:5; R_f 0.55) to give **2** (1.93 g, 9.53 mmol, 98%) as a light yellow oil. $[\alpha]_D^{20}$ −167.9 (*c* 2.96, $CHCl_3$) ^1H NMR ($CDCl_3$, 300 MHz) δ 3.35 (s, 6H), 4.08–4.10 (m, 2H), 4.59 (d, *J*=6.8 Hz, 2H), 4.69 (d, *J*=6.8 Hz, 2H), 5.25–5.32 (m, 4H), 5.74–5.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.6, 79.1, 94.2, 118.7, 134.8; HRMS (EI) calcd for $[M]^+$ ($C_{10}H_{18}O_4$) 202.1205, found 202.1205; IR (neat) 3081, 2950, 2890, 1745, 1425, 1236, 1150, 1101, 1033, 922 cm^{-1}.

*4.1.2. (3R,4R,8R,9R,13R,14R)-4,8,9,13-Tetravinyl-5,7,10,12-tetraoxahexadeca-1,15-diene-3,14-diol (**3**).* Boron trichloride (6.6 mL, 6.7 mmol) was added to a solution of **2** (1.68 g, 8.3 mmol) and dichloromethane (12 mL) at 0 °C under nitrogen. The reaction mixture was stirred for 0.5 h at 0 °C, at rt for another 2 h, and then concentrated to give (3*R*,4*R*)-3,4-bis(chloromethoxy)hexa-1,5-diene. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.25–4.29 (m, 2H), 5.38–5.45 (m, 6H), 5.55–5.59 (m, 2H), 5.68–5.77 (m, 2H).

The crude (3*R*,4*R*)-3,4-bis(chloromethoxy)hexa-1,5-diene was diluted with dichloromethane (40 mL), and the solution was added dropwise to a solution of **1** (2.84 g, 24.9 mmol), diisopropylethylamine (5.36 g, 41.5 mmol), and dichloromethane (100 mL) at 0 °C. The reaction mixture was heated at reflux for 16 h, quenched with $NaHCO_{3(aq)}$ (2%, 100 mL), and extracted with dichloromethane (30 mL×3). The combined organic layers were washed with satd $NaCl_{(aq)}$ (30 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:3; R_f 0.39) to give **3** (2.02 g, 5.5 mmol, 66%; two steps) as a colorless oil. $[\alpha]_D^{20}$ −200.1 (*c* 1.76, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.32 (d, *J*=3.6 Hz, 2H), 4.05–4.07 (m, 4H), 4.21–4.23 (m, 2H), 4.65–4.72 (m, 4H), 5.15–5.38 (m, 12H), 5.63–5.81 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 74.7, 79.1, 82.1, 89.4, 116.7, 119.7, 119.9, 133.8, 134.3, 136.6; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{20}H_{30}O_6Na$) 389.1940, found 389.1936; IR (neat) 3475, 3081, 2983, 2896, 1743, 1645, 1425, 1024, 927, 702 cm^{-1}.

*4.1.3. (3R,4R,8R,9R,13R,14R)-1,16-Diphenyl-3,4,8,9,13,14-hexavinyl-2,5,7,10,12,15-hexaoxahexadecane (**4a**).* Compound **3** (443 mg, 1.21 mmol) in *N*,*N*-dimethylformamide (DMF, 2.5 mL) was added to a slurry of sodium hydride (290 mg, 7.24 mmol) in DMF (4 mL) at 0 °C, and the mixture was stirred for 1 h at 0 °C. Benzyl bromide (1.24 g, 7.24 mmol) was added, and this mixture was stirred for another 2 h. It was then concentrated, quenched with satd $NH_4Cl_{(aq)}$ (10 mL), and extracted with ethyl acetate (10 mL×3). The combined organic layers were washed with water (5 mL×3), satd $NaCl_{(aq)}$ (10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:5; R_f 0.34) to give **4a** (376.1 mg, 0.69 mmol, 60%) as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.82–3.86 (m, 2H), 4.16–4.24 (m, 4H), 4.40 (d, *J*=12.0 Hz, 2H), 4.62 (d, *J*=12.0 Hz, 2H), 4.69 (m, 4H), 5.17–5.31 (m, 12H), 5.75–5.88 (m, 6H), 7.24–7.30 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 70.5, 78.1, 78.3, 82.0, 88.9, 118.7, 119.3, 127.4, 127.6, 128.2, 134.2, 134.6, 135.1, 138.5; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{34}H_{42}O_6Na$) 569.2879, found 569.2870; IR (neat) 3079, 3027, 2952, 2892, 1643, 1496, 1454, 1423, 1027, 927, 736 cm^{-1}.

*4.1.4. (5R,6R,10R,11R,15R,16R)-5,6,10,11,15,16-Hexavinyl-2,4,7,9,12,14,17,19-octaoxaicosane (**4b**).* Chloromethyl methyl ether (MOMCl, 2.35 g, 29.2 mmol) was added to a solution of **3** (1.1 g, 9.7 mmol), diisopropylethylamine (6.3 g, 48.6 mmol), and dichloromethane (25 mL) at 0 °C. The reaction mixture was refluxed for 16 h, quenched with satd $NH_4Cl_{(aq)}$ (30 mL), and extracted with ether (50 mL×3). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:5; R_f 0.55) to give **4b** (4.33 g, 9.53 mmol, 98%) as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.32 (d, *J*=3.6 Hz, 2H), 4.05–4.07 (m, 4H), 4.21–4.23 (m, 2H), 4.65–4.72 (m, 4H), 5.15–5.38 (m, 12H), 5.63–5.81 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 74.7, 79.1, 82.1, 89.4, 116.7, 119.7, 119.9, 133.8, 134.3, 136.6; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{24}H_{38}O_8Na$) 477.2464, found 477.2462.

*4.1.5. (4R,4′R,7R,7′R)-7,7′-Bis((R)-1-(benzyloxy)allyl)-4,4′,7,7′-tetrahydro-4,4′-bi(1,3-dioxepine) (**5a**).* A reaction mixture comprising **4a** (81.7 mg, 0.149 mmol), Grubbs second generation catalyst (12.6 mg, 0.015 mmol), and toluene (7.5 mL) was stirred at 75 °C under an atmosphere of nitrogen for 3 h and then concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:5; R_f 0.45) to give **5a** (49.0 mg, 0.10 mmol, 67%) as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.85–3.89 (m, 2H), 4.40 (d, *J*=12.3 Hz, 4H), 4.49 (s, 2H), 4.66 (d, *J*=12.0 Hz, 2H), 4.90–4.94 (m, 4H), 5.28–5.36 (m, 4H), 5.75–5.86 (m, 6H), 7.25–7.32 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 70.3, 76.8, 80.8, 95.2, 119.6, 127.6, 127.8, 128.3, 131.7, 132.4, 134.7, 138.1; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{30}H_{34}O_6Na$) 513.2253, found 513.2258; IR (neat) 3031, 2787, 1496, 1454, 1126, 1066, 933, 738 cm^{-1}.

*4.1.6. (4R,4′R,7R,7′R)-7,7′-Bis((R)-1-(methoxymethoxy)allyl)-4,4′,7,7′-tetrahydro-4,4′-bi(1,3-dioxepine) (**5b**).* The reaction mixture

comprising **4b** (183.2 mg, 0.404 mmol), Grubbs second generation catalyst (34 mg, 0.04 mmol), and toluene (20 mL) was stirred at 70 °C under an atmosphere of nitrogen for 3 h and then concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:3; R_f 0.55) to give **5b** (111.4 mg, 0.283 mmol, 70%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.36 (s, 6H), 4.13–4.17 (m, 4H), 4.42 (s, 2H), 4.52 (s, 2H), 4.57 (d, J=3.5 Hz, 2H), 4.70 (d, J=3.3 Hz, 2H), 4.92 (m, 4H), 5.27–5.35 (m, 4H), 5.75–5.85 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.6, 76.6, 76.7, 78.3, 94.0, 95.2, 119.5, 132.0, 132.4, 134.3; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{20}H_{30}O_8Na$) 421.1838, found 421.1837.

*4.1.7. (1R,1′R)-1,1′-((4R,4′R,7R,7′R)-4,4′,7,7′-Tetrahydro-[4,4′-bi(1,3-dioxepine)]-7,7′-diyl)bis(prop-2-en-1-ol) (**5c**).* A solution of **5b** (75.8 mg, 0.19 mmol), hydrochloric acid (6 N, 2 mL), THF (4 mL), and water (4 mL) was stirred at rt for 24 h. The reaction mixture was concentrated, satd $NaHCO_{3(aq)}$ (5 mL) was added, and the mixture was extracted with ethyl acetate (5 mL×3). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:1; R_f 0.20) to give **5c** (64.3 mg, 0.19 mmol, 99%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.66 (br, 2H), 4.08 (t, J=6.5 Hz, 2H), 4.24–4.27 (m, 2H), 4.51 (t, J=1.5 Hz, 2H), 4.96 (s, 4H), 5.27–5.43 (m, 4H), 5.77 (s, 4H), 5.80–5.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 74.5, 76.7, 78.5, 95.0, 118.5, 131.4, 132.2, 136.1; HRMS (ESI) calcd for $[M+Na^+]$ ($C_{16}H_{22}O_6Na$) 333.1314, found 333.1321.

*4.1.8. (4R,4′R,7R,7′R)-7,7′-Bis((R,E)-1-(benzyloxy)-11-chloroundec-2-en-1-yl)-4,4′,7,7′-tetrahydro-4,4′-bi(1,3-dioxepine) (**6a**).* Grubbs second generation catalyst, (8.5 mg, 0.01 mmol) was added to a solution of 10-chloro-1-decene (174.7 mg, 1.0 mmol) and 1,2-dichloroethane (1 mL). The reaction mixture was warmed to 40 °C and stirred for 20 min under an atmosphere of nitrogen. Compound **5a** (49.1 mg, 0.1 mmol) in 1,2-dichloroethane (2 mL) was then added dropwise. The reaction mixture was heated to reflux for 16 h and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:5; R_f 0.45) to give **6a** (54.9 mg, 0.07 mmol, 70%) as a light yellow oil. $[\alpha]_D^{20}$ +67.4 (c 0.63, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28–1.40 (m, 20H), 1.70–1.76 (m, 4H), 2.02–2.09 (m, 4H), 3.51 (t, J=6.6 Hz, 4H), 3.77–3.81 (m, 2H), 4.37–4.41 (m, 4H), 4.51 (m, 2H), 4.63 (d, J=12.3 Hz, 2H), 4.90–4.94 (m, 4H), 5.40–5.48 (m, 2H), 5.65–5.80 (m, 6H) 7.26–7.31 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.0, 28.8, 29.0, 29.1, 29.2, 32.5, 32.8, 45.3, 70.1, 76.8, 78.1, 80.1, 95.3, 126.6, 127.6, 128.0, 128.4, 131.7, 132.8, 137.0, 138.7; HRMS (ESI) calcd for $[M+Na^+]$ ($C_{46}H_{64}O_6Cl_2Na$) 805.3978, found 805.3981; IR (neat) 3031, 2927, 2856, 1455, 1124, 1086, 735 cm^{-1}.

*4.1.9. (4R,4′R,7R,7′R)-7,7′-Bis((R,E)-11-chloro-1-(methoxymethoxy) undec-2-en-1-yl)-4,4′,7,7′-tetrahydro-4,4′-bi(1,3-dioxepine) (**6b**).* Grubbs second generation catalyst (17.6 mg, 0.02 mmol) was added to the solution of 10-chloro-1-decene (364 mg, 2.08 mmol) and dichloromethane (2 mL). The reaction mixture was warmed to 40 °C and stirred for 20 min under an atmosphere of nitrogen. Compound **5b** (64.6 mg, 0.208 mmol) in dichloromethane (2 mL) was then added dropwise. The reaction mixture was heated at reflux for 16 h and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:3; R_f 0.32) to give **6b** (124.5 mg, 0.18 mmol, 87%) as a light yellow oil. $[\alpha]_D^{20}$ +58.7 (c 0.73, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20–1.45 (m, 20H), 1.61–1.89 (m, 4H), 1.95–2.10 (m, 4H), 3.49 (t, J=6.8 Hz, 4H), 4.01–4.13 (m, 2H), 4.30–4.40 (m, 2H), 4.47–4.55 (m, 4H), 4.68–4.70 (d, J=6.9 Hz, 2H), 4.92 (dd, J=8.7 Hz, J=4.5 Hz, 4H), 5.28–5.47 (m, 2H), 5.62–5.89 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.8, 28.6, 28.8, 28.9, 29.2, 32.2, 32.6, 45.0, 55.4, 76.7, 78.0, 93.5, 95.2, 125.9, 131.7, 132.6, 136.9; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{36}H_{60}Cl_2O_8Na$) 713.3563, found 713.3561.

*4.1.10. (1R,1′R,2E,2′E)-1,1′-((4R,4′R,7R,7′R)-4,4′,7,7′-Tetrahydro-[4,4′-bi(1,3-dioxepine)]-7,7′-diyl)bis(11-chloroundec-2-en-1-ol) (**6c**).* Grubbs second generation catalyst, (32.9 mg, 0.037 mmol) was added to the solution of 10-chloro-1-decene (641.2 mg, 3.67 mmol) and dichloromethane (3 mL). The reaction mixture was warmed to 40 °C and stirred for 20 min under an atmosphere of nitrogen. Compound **5c** (120.1 mg, 0.367 mmol) in dichloromethane (3 mL) was then added dropwise. The reaction mixture was heated at reflux for 16 h and concentrated. The crude product was purified by column chromatography to give **6c** (124.0 mg, 0.205 mmol, 56%) as a colorless oil. $[\alpha]_D^{20}$ +42.0 (c 0.23, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20–1.45 (m, 20H), 1.68–1.80 (m, 4H), 1.90–2.15 (m, 4H), 3.49–3.53 (t, J=6.6 Hz, 4H), 4.00 (m, 2H), 4.20–4.21 (m, 2H), 4.51 (m, 2H), 4.97–5.00 (m, 4H), 5.43–5.47 (m, 2H), 5.74–5.83 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.8, 28.7, 28.8, 28.9, 29.2, 32.3, 32.5, 45.1, 74.5, 76.7, 79.1, 95.1, 127.7, 131.5, 132.0, 136.2; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{32}H_{52}Cl_2O_6Na$) 625.3039, found 625.3038.

*4.1.11. (4R,4′R,7R,7′R)-7,7′-Bis((R)-1-(benzyloxy)-11-chloroundecyl)-4,4′-bi(1,3-dioxepane) (**7**).* A suspension of **6a** (47.2 mg, 0.060 mmol), triethylamine (3.3 mg, 0.03 mmol), and palladium (10% on activated carbon, 3.4 mg, 0.003 mmol) was stirred at rt for 3 h under a hydrogen atmosphere (1 atm). The suspension was filtered and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:5; R_f 0.45) to give **7** (39.5 mg, 0.05 mmol, 83%) as a light yellow oil. $[\alpha]_D^{20}$ +28.7 (c 0.87, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23–1.39 (m, 32H), 1.70–1.76 (m, 12H), 3.31–3.35 (m, 2H), 3.51 (t, J=13.5 Hz, 4H), 3.64–3.65 (m, 2H), 3.78–3.81 (m, 2H), 4.55 (s, 4H), 4.79–4.84 (m, 4H), 7.26–7.31 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.9, 26.8, 28.8, 29.4, 29.5, 29.7, 30.0, 32.3, 32.6, 45.1, 72.5, 76.6, 78.7, 81.4, 93.3, 127.5, 127.7, 127.9, 128.2, 138.7; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{46}H_{72}Cl_2O_6Na$) 813.4604, found 813.4601; IR (neat) 3029, 2925, 2856, 1455, 1361, 1120, 1055, 734 cm^{-1}.

*4.1.12. (3R,3′R,4R,4′R)-1,1′-((4R,5R)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(4-(benzyloxy)-14-chlorotetradecan-3-ol) (**8**).* A solution of **7** (544.9 mg, 0.688 mmol), methanol (25 mL), and concd hydrochloric acid (3.2 mL) was heated at reflux for 5 h. The reaction mixture was concentrated, satd $NaHCO_{3(aq)}$ (20 mL) was added, and the mixture was extracted with ethyl acetate (10 mL×3). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:1; R_f 0.39) to give the tetraol (375.1 mg, 0.488 mmol, 71%) as a light yellow gel. $[\alpha]_D^{20}$ +1.1 (c 0.64, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25–1.37 (m, 28H), 1.46–1.76 (m, 8H), 1.69–1.76 (m, 8H), 3.24–3.28 (m, 2H), 3.38 (m, 2H), 3.49 (t, J=16.8 Hz, 4H), 3.53–3.58 (m, 2H), 4.45–4.49 (m, 2H), 4.60–4.67 (m, 2H), 7.31 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.9, 21.3, 25.3, 25.8, 27.1, 29.0, 29.6, 30.1, 30.4, 32.8, 45.3, 72.7, 73.1, 74.9, 82.7, 128.1, 128.5, 128.7, 138.5; HRMS (FAB) calcd for $[M+Na]^+$ ($C_{44}H_{73}O_6Cl_2$) 767.4783, found 767.4787.

p-Toluenesulfonic acid monohydrate (8.1 mg, 0.043 mmol) was added to a solution of the intermediate tetraol (667.1 mg, 0.85 mmol), 2,2-dimethoxypropane (266.3 mg, 2.56 mmol), and dichloromethane (5.1 mL). After being stirred at rt for 16 h, the reaction mixture was diluted with dichloromethane (10 mL), washed with $NaOH_{(aq)}$ (1 *N*, 5 mL×3), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:3; R_f 0.36) to give **8** (626.5 mg, 0.775 mmol, 91%) as a light yellow oil. $[\alpha]_D^{20}$ +14.2 (c 0.72, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26–1.38 (m, 34H), 1.61–1.63 (m, 8H), 1.96 (m, 8H), 3.24–3.31 (m, 2H), 3.51 (t, J=16.5 Hz, 4H), 3.58–3.60 (m, 4H), 4.46–4.50 (m, 2H), 4.60–4.66 (m, 2H), 7.26–7.36 (m, 10H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.8, 25.4, 27.0, 27.5, 29.0, 29.6, 29.7, 30.1, 30.2, 32.8, 45.3, 72.5, 80.9, 82.5, 83.5, 108.2, 127.9, 128.0, 128.6, 138.6; HRMS (FAB) calcd for $[M+Na]^+$ ($C_{47}H_{76}Cl_2O_6Na$) 829.4917, found 829.4908; IR (neat) 3467, 3029, 2927, 2856, 1720, 1496, 1259, 1070, 736 cm^{-1}.

*4.1.13. (2R,2′R,5S,5′S)-5,5′-Bis((R)-1-(benzyloxy)-11-chloroundecyl) octahydro-2,2′-bifuran (**9**).* Methanesulfonyl chloride (67.3 mg, 0.588 mmol) was added to the solution of **8** (158.4 mg, 0.196 mmol), triethylamine (118.7 mg, 1.175 mmol), and dichloromethane (0.5 mL) at 0 °C. The reaction mixture was stirred at rt for 5 h, quenched with satd $NaHCO_{3(aq)}$ (1 mL), and extracted with dichloromethane (2 mL×3). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:3; R_f0.49) to give the dimesylate (175.8 mg, 0.182 mmol, 93%) as a colorless oil. $[\alpha]_D^{20}$ +16.0 (*c* 1.81, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25–1.38 (m, 34H), 1.55–1.66 (m, 8H), 1.72–1.84 (m, 8H), 2.9 (s, 6H), 3.51 (t, *J*=11.7 Hz, 4H), 3.58 (m, 4H), 4.55–4.59 (m, 4H), 4.72 (m, 2H), 7.27–7.33 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.7, 24.9, 25.4, 26.9, 27.3, 28.9, 29.5, 29.7, 31.5, 31.6, 32.7, 38.5, 45.2, 60.4, 72.5, 79.4, 79.9, 108.3, 127.5, 128.0, 128.5, 138.0.

A solution of the above dimesylate (140.1 mg, 0.145 mmol), *p*-toluenesulfonic acid monohydrate (47.5 mg, 0.250 mmol), methanol (14.4 mL), and water (1.6 mL) was stirred at 60 °C for 5 h. The reaction mixture was concentrated, satd $NaHCO_{3(aq)}$ (15 mL) was added, and the mixture was extracted with ethyl acetate (15 mL×3). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was redissolved in DMF (1 mL), and the solution was transferred into a flask containing a suspension of sodium hydride (14 mg, 0.58 mmol) and DMF (3 mL) at 0 °C. The mixture was stirred at rt for 16 h, quenched with satd $NH_4Cl_{(aq)}$ (5 mL), diluted with water (10 mL), and extracted with ether (50 mL). The organic layer was washed with water (10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:3; R_f 0.48) to give **9** (66.9 mg, 0.091 mmol, 63%) as a light yellow oil. $[\alpha]_D^{20}$ +3.9 (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (m, 28H), 1.39–1.42 (m, 8H), 1.72–1.94 (m, 8H), 3.51 (t, *J*=12.3 Hz, 4H), 3.61 (m, 2H), 3.76 (m, 2H), 3.93–3.95 (m, 2H), 4.57 (d, *J*=11.4 Hz, 2H), 4.75 (d, *J*=11.4 Hz, 2H), 7.25–7.32 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.7, 24.8, 25.7, 26.9, 28.2, 28.9, 29.5, 31.6, 32.2, 32.7, 45.2, 73.4, 80.3, 82.3, 82.6, 127.3, 127.7, 128.2, 139.4; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{44}H_{68}Cl_2O_4Na$) 753.4392, found 753.4394; IR (neat) 3029, 2925, 2854, 1733, 1458, 1261, 1068, 734 cm^{-1}.

*4.1.14. (2R,2′R,5S,5′S)-5,5′-Bis((R)-1-(benzyloxy)-11-iodoundecyl)octahydro-2,2′-bifuran (**10**).* A solution of **9** (497.7 mg, 0.68 mmol), sodium iodide (2.04 g, 13.63 mmol), and acetone (23 mL) was heated at reflux for 16 h. The reaction mixture was concentrated, water (10 mL) and ether (10 mL) were added, and the mixture was extracted with ethyl acetate (10 mL×3). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:3; R_f 0.45) to give **10** (553.6 mg, 0.61 mmol, 89%) as a light yellow oil. $[\alpha]_D^{20}$ +2.35 (*c* 0.74, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24 (m, 32H), 1.50–1.54 (m, 4H), 1.78–1.81 (m, 8H), 3.16 (t, *J*=13.8 Hz, 4H), 3.6 (m, 2H), 3.76 (m, 2H), 3.94–3.95 (m, 2H), 4.57 (d, *J*=11.4 Hz, 2H), 4.74 (d, *J*=11.4 Hz, 2H), 7.26–7.34 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.34, 14.1, 22.7, 25.7, 28.2, 28.5, 29.4, 29.5, 29.7, 30.5, 32.1, 33.6, 73.3, 80.4, 82.3, 82.6, 127.3, 127.7, 128.3, 139.4.

Compound **12**. A solution of diiodide **10** (70.0 mg, 0.076 mmol) and lactone **11** (12.7 mg, 0.061 mmol) in DMF (0.5 mL) was added to a suspension of potassium hydride (4.2 mg, 0.1039 mmol) in DMF (0.5 mL) at 0 °C. The reaction mixture was stirred for 16 h at rt, quenched with satd $NH_4Cl_{(aq)}$ (1 mL) and water (2 mL), and extracted with ether (10 mL). The organic layer was washed with water (2 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:5; R_f 0.32) to give the iodo-lactone (38.8 mg, 0.039 mmol, 51%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15–1.43 (m, 31H), 1.49–1.59 (m, 8H), 1.69–1.81 (m, 6H), 1.82–1.97 (m, 3H), 2.35–2.53 (m, 1H), 3.16 (t, *J*=14.1 Hz, 2H), 3.60–3.61 (m, 2H), 3.75 (m, 2H), 3.92–3.96 (m, 2H), 4.43–4.70 (m, 3H), 4.74 (d, *J*=9.3 Hz, 2H), 7.30–7.32 (m, 13H), 7.49–7.55 (m, 2H).

A suspension of the iodo-lactone (38.8 mg, 0.039 mmol), triethylamine (7.9 mg, 0.078 mmol), and palladium (10% on activated carbon, 8.3 mg, 0.008 mmol) was stirred at 40 °C for 2 h under a hydrogen atmosphere (1 atm). The suspension was filtered and concentrated to give **12** (29.8 mg, 0.034 mmol, 88%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80–0.90 (m, 3H), 1.15–1.43 (m, 33H), 1.43–1.54 (m, 8H), 1.72–1.81 (m, 4H), 1.84–1.97 (m, 3H), 2.26–2.52 (m, 1H), 3.59–3.61 (m, 2H), 3.75–3.77 (m, 2H), 3.91–3.96 (m, 2H), 4.45–4.58 (m, 3H), 4.72 (d, *J*=11.7 Hz, 2H), 7.30–7.32 (m, 13H), 7.52–7.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.7, 24.3, 24.6, 25.6, 25.9, 27.3, 27.9, 28.2, 28.6, 29.5, 32.6, 34.6, 36.4, 40.1, 42.4, 56.0, 56.2, 73.2, 73.6, 80.3, 80.8, 82.3, 127.2, 127.6, 128.2, 128.3, 129.0, 129.7, 129.9, 130.4, 136.8, 137.1, 177.1; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{55}H_{80}O_6SNa$) 891.5573, found 891.5565.

*4.1.15. (S)-3-((R)-11-(Benzyloxy)-11-((2R,2′R,5S,5′S)-5′-((R)-1-(benzyloxy)undecyl)octahydro-[2,2′-bifuran]-5-yl)undecyl)-5-methylfuran-2(5H)-one (**13**).* 3-Chloroperoxybenzoic acid (*m*CPBA, 0.7 mg, 0.0041 mmol) was added to a solution of **12** (3.4 mg, 0.0039 mmol) and dichloromethane (1 mL) at 0 °C. After being stirred for 20 min at 0 °C, satd sodium thiosulfate$_{(aq)}$ (0.5 mL) and satd $NaHCO_{3(aq)}$ (0.5 mL) were added, and the mixture was extracted with ethyl acetate (1 mL×3). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was redissolved in toluene (1 mL), and the solution was heated in at 100 °C for 3 h and then concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:5; R_f 0.41) to give **13** (2.1 mg, 0.0028 mmol, 71%) as a light yellow oil. $[\alpha]_D^{20}$ +3.28 (*c* 0.83, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.80–0.90 (m, 3H), 1.23–1.44 (m, 33H), 1.50 (m, 8H), 1.74–1.98 (m, 6H), 2.24 (t, *J*=7.4 Hz, 2H), 3.62 (m, 2H), 3.75 (m, 2H), 3.90–3.96 (m, 2H), 4.56 (d, *J*=11.55 Hz, 2H), 4.74 (d, *J*=11.6 Hz, 2H), 4.96–4.98 (m, 1H), 6.95 (s, 1H), 7.25–7.32 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 15.3, 19.2, 22.7, 25.2, 25.6, 26.9, 27.4, 28.2, 29.2, 29.3, 29.5, 29.6, 29.7, 31.9, 32.2, 73.3, 77.4, 80.3, 82.3, 82.6, 127.3, 127.6, 127.7, 128.0, 128.2, 129.2, 134.3, 139.4, 148.8, 173.9; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{49}H_{74}O_6Na$) 781.5383, found 781.5378.

*4.1.16. 14,21-Diepi-squamocin-K (**14**).* 2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ, 5.0 mg, 0.022 mmol) was added to the mixture of **13** (2.1 mg, 0.0028 mmol), 1,2-dichloromethane (0.5 mL), and buffer solution (pH 7.0, 50 mM, sodium phosphate, 0.02 mL). The reaction mixture was heated in a 50 °C oil bath for 3 h, satd $NaCl_{(aq)}$ (0.5 mL) was added, and the mixture was extracted with ether (1 mL×3). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:1; R_f 0.60) to give **14** (1.3 mg, 0.0022 mmol, 80%) as a light yellow oil. $[\alpha]_D^{20}$ −4.4 (*c* 0.34, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.80–0.90 (m, 3H), 1.23–1.44 (m, 33H), 1.50 (m, 8H), 1.74–1.98 (m, 8H), 2.28 (t, *J*=7.8 Hz, 2H), 3.91–3.97 (m, 6H), 4.99–5.05 (m, 1H), 7.00–7.01 (d, *J*=1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 19.2, 22.7, 23.7, 25.1, 26.0, 29.0, 29.1, 29.3, 29.49, 29.53, 29.6, 29.7, 32.7, 72.2, 77.3, 80.8, 83.2, 134.3, 148.8, 173.9; HRMS (ESI) calcd for $[M+Na]^+$ ($C_{35}H_{62}O_6Na$) 601.4444,

found 601.4440; IR (neat) 3440, 2925, 2854, 1755, 1261, 1080, 800 cm^{-1}.

The sulforhodamine B assay for measurement of cell proliferation was performed in human hormone-refractory prostate cancer cell line PC-3.

4.2. Sulforhodamine B (SRB) assay

Cells were seeded in 96-well plates in medium with 5% FBS. After 24 h, cells were fixed with 10% trichloroacetic acid (TCA) to represent cell population at the time of compound addition (T0). After additional incubation of DMSO or test compound for 48 h, cells were fixed with 10% TCA and SRB at 0.4% (w/v) in 1% acetic acid was added to stain cells. Unbound SRB was washed out by 1% acetic acid and SRB bound cells were solubilized with 10 mM Trizma base. The absorbance was read at a wavelength of 515 nm. Using the following absorbance measurements, such as time zero (T0), control growth (C), and cell growth in the presence of the compound (Tx), the percentage growth was calculated at each of the compound concentrations levels. Percentage growth inhibition was calculated as: $[1-(Tx-T0)/(C-T0)]\times100\%$. Growth inhibition of 50% (IC_{50}) is determined at the compound concentration, which results in 50% reduction of total protein increase in control cells during the compound incubation.

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Supplementary data

^{1}H and ^{13}C NMR spectra of all new compounds are available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.02.015. These data include MOL files and InChIKeys of the most important compounds described in this article.

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