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Syntheses and Biological Evaluation of New Glyco-modified Angucyclin-antibiotics

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Abstract—The synthesis of novel aquayamycin-derived angucycline antibiotics **13a–d** has been achieved. Glycosylation of aquayamycin (**6**) using 2-selenoglycosyl acetate **7** as glycosyl donor proceeded in excellent yield but attempts to reductively remove the selenyl group led to rearrangement or further aromatization of the aglycon. As a consequence of these results, it became possible to prepare urdamycinone B (**10**) starting from aquayamycin (**6**). In addition, silyl protected D-olivals **12a**,**b** were attached to the C-glycoside domain of aquayamycin (**6**) under protic conditions. As expected, the hydroxy and phenol groups of the benz[*a*]anthracene framework of **6** did not react under the glycosylation conditions employed. Stepwise removal of the silyl protecting group starting with tetrabutyl ammonium fluoride followed by use of the HF/pyridine complex suppressed a possible rearrangement of the aglycon and successfully terminated the sequence. The new angucycline-antibiotics **13a** and **13b** are some of the most potent xanthine oxidase inhibitors known and show cytotoxic activity with ED_{50}-values in the range of $12.6–2.9\times10^{-6}$ M

Introduction

The angucycline group of antibiotics comprises a rapidly growing class of secondary metabolites from microbial sources[1] of which the first member was discovered in 1966.[2] Since the classification of the angucyclines is linked to the tetracyclic benz[*a*]anthracene (**1**) system, this class is clearly distinguished from the anthracycline group of antibiotics (Fig. 1).[3] The angucyclines not only display anticancer activity but also a multitude of other activities such as antibacterial, antiviral, and enzyme inhibitory properties. Most of them, such as urdamycin A (**2**) or landomycin A (**3**), are glycoconjugates containing one or more sugars attached at different positions of the angucyclinone framework. In fact, 2,6-dideoxy and 2,3, 6-trideoxy sugars, like D-olivose (**4**) and L-rhodinose (**5**), respectively, are present in many examples.[4]

Carbohydrate containing antibiotics and antitumor agents have been known for decades and extensive research has been directed toward the aglycon moieties and to their interaction with oligonucleotides.[5] However, only a few studies have been devoted to the fact that it was the deoxysugar domains which endow the system with clinically useful biological activity. The rigid character of the pyran rings along with the flexibility located in the glycosidic linkages give these compounds the ability of preorganization. Also, a delicate balance between hydrophilic and hydrophobic domains is an additional feature of deoxygenated carbohydrates.[6] Moreover, recent studies clearly show that deoxygenated oligosaccharides in natural products from microbial sources can act as recognition elements in the mode of action of drugs.[7] In many instances, the aglycon alone is not active, typical examples being erythromycin and amphotericin B.[8] The recent interest in the glycopeptide antibiotic vancomycin led to the important observation that a modification of the aminodeoxy sugar vancosamine can dramatically increase the activity against vancomycin-resistant strains.[9] For this reason, and since the first total syntheses of a few angucyclines have recently been disclosed,[10] we chose to focus our study on the chemical modification of the carbohydrate domain of the angucycline antibiotic aquayamycin (**6**) and to assess the biological properties of the new glycoconjugates.[11] This project posed an interesting challenge from several standpoints. A synthetic strategy would be required which circumvented the difficulties associated with the chemical

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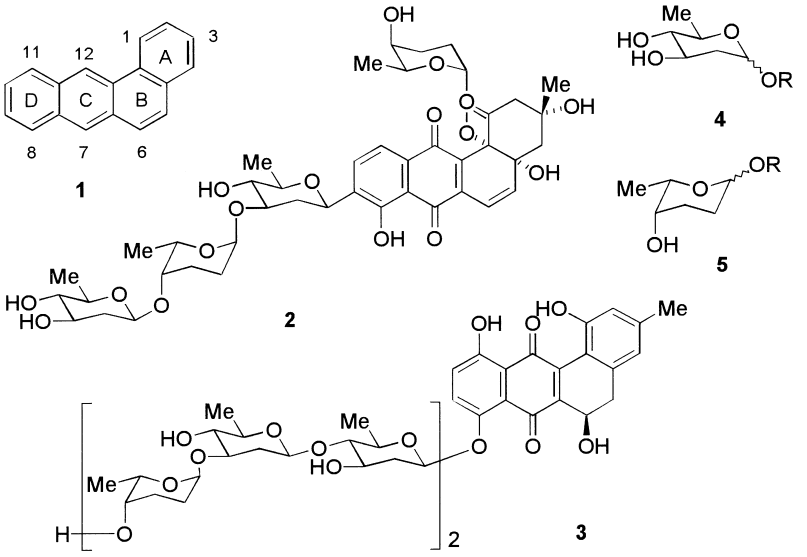


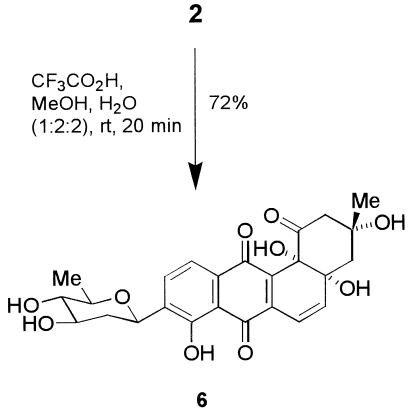
Figure 1. Structures of the tetracyclic backbone **1** of angucycline antibiotics, urdamycin (**2**) and landomycin A (**3**) and deoxygenated glycosides derived from D-olivose (**4**) and L-rhodinose (**5**).

lability of the benz[*a*]anthracene aglycon in angucycline antibiotics. In fact, Umezawa and co-workers observed skeletal rearrangement of aquayamycin to the corresponding naphthacenequinone in the presence of base or upon thermal treatment.[12] A similar rearrangement also occurs under photochemical conditions; however, anthracyclines are the products generated. Finally, acidic reaction conditions either favor dehydration of **6** to the corresponding benz[*a*]anthraquinone or ring opening of the angular ring and subsequent formation of anthraquinones.[12] Therefore, our strategy required a careful selection of a glycosyl donor along with an appropriate glycosidation procedure. Moreover, all resident protecting groups must be removed under conditions which would allow isolation of the intact target angucyclines. From synthetic studies on anthracycline antibiotics[13] and other natural products,[14] it was known that 2-deoxy-glycosyl acetates as well as glycals could function as suitable donors for this new class of aglycon 'acceptor'. No member of the urdamycin group of antibiotics contains a D-olivosyl group attached at O-3 or O-4 of the *C*-glycoside. Instead, most commonly L-rhodinose (**5**) and other biosynthetically therefrom derived 2,3,6-trideoxy hexoses serve as the *O*-glycosidically linked second sugar. On the other hand, diolivosyl units are an integral part of various angucycline antibiotics like landomycin **3**,[1] so that we chose this 2,6-deoxysugar as a glycosyl donor leading to new angucyclines that have structural relationship to both the landomycines as well as urdamycin A (**2**).

Results and Discussion

Glycosylation of aquayamycin

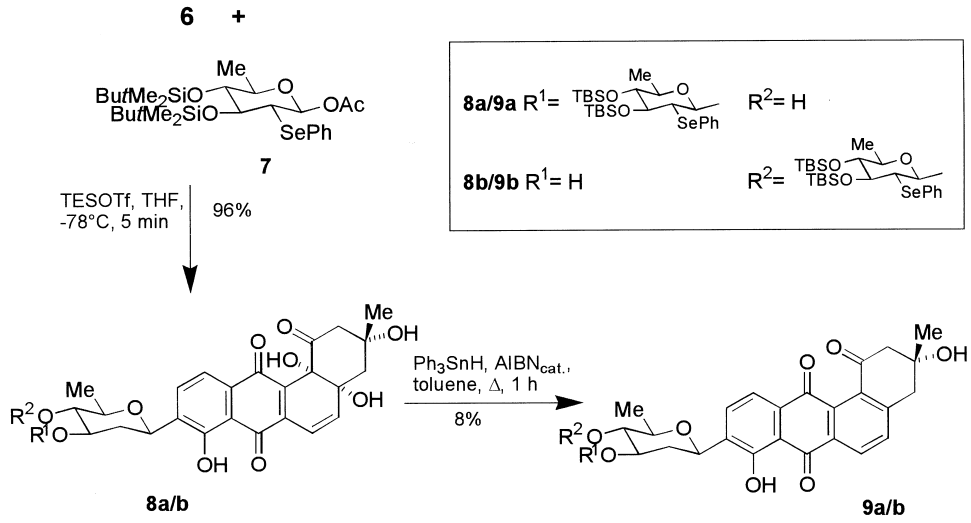
In the first phase of the project, we required a gram amount of aquayamycin (**6**), which was prepared from urdamycin A (**2**) by hydrolytic removal of the three *O*-glycosidically linked deoxysugars under acidic conditions.[15] Prior to this transformation, compound **2** was harvested in excellent yield (540 mg/L) after fermentation of *Streptomyces fradiae* (Tü 2717).[16] The improvement in yield was mainly achieved by an altered work up procedure of the fermentation broth (Scheme 1).[17]



Scheme 1. Preparation of aquayamycin (**6**).

Although aquayamycin contains six functional groups, which are potential glycosyl acceptors, we anticipated that only the two equatorial alcohols of the *C*-saccharide would be involved in glycosylation reactions. The remaining hydroxy groups should show reduced nucleophilicity due to chelation via hydrogen bonding to the quinone carbonyl, or reduced reactivity due to a sterically congested environment. Therefore, selective protection of the benz[*a*]anthracene hydroxy groups was thought to be unnecessary and elongation of the carbohydrate domain becomes feasible.

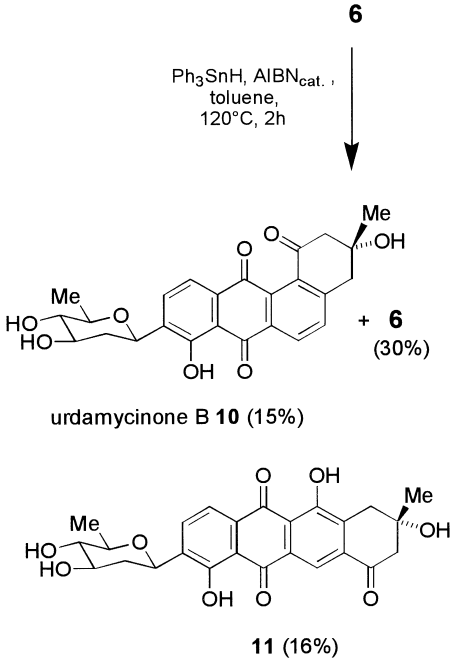
In a primary experiment, we employed 2-phenylselenoolivosyl acetate (**7**),[14] an ideal glycosyl donor for selectively constructing 2-deoxy-β-glycosides.[18] Silicon-based protection groups were chosen, since preliminary experiments with ester groups revealed that final ester



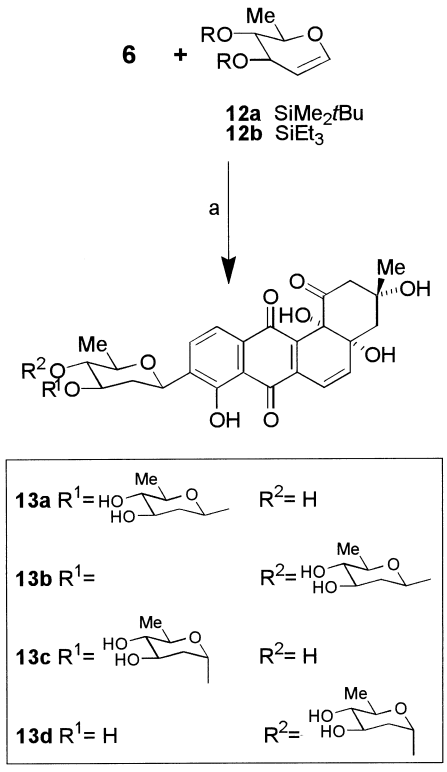
Scheme 2. Glycosylation of aquayamycin (**6**) using glycosyl donor **7**.

hydrolysis led to decomposition of the aglycon.[19] Thus, 2,6-dideoxy glucosyl donor **7** was coupled with aquayamycin (**6**) in the presence of an equimolar amount of glycosyl promoter (TESOTf) at −78 °C (Scheme 2). The reaction afforded an inseparable mixture of position isomers **8a** and **8b** in excellent yield. However, reductive deselenylation using Ph_3SnH did not furnish the desired silyl-protected β-olivosides of aquayamycin. The NMR spectra of one major reduction product clearly indicated that reduction had taken place between the A and B rings of the aglycons, leading to the corresponding olivosides **9a** and **9b** of urdamycinone B. In this respect the signals at 8.31 and 7.86 ppm (for 11-H and 6-H) in the ^1H NMR spectrum are diagnostic. This interpretation was confirmed when aquayamycin (**6**) was subjected to identical reaction conditions (Scheme 3). Now, the reduction products **10** and **11** were identified along with recovered starting material (30%). The formation and isolation of urdamycinone B (**10**) is remarkable in two aspects. Firstly, this transformation is the shortest chemical route[20] to this known angucycline antibiotic[1b] and, secondly, under the harsh reaction conditions no aromatization of the A ring took place. The rearranged aglycon **11** is also a known angucycline antibiotic which is formed by UV irradiation of aquayamycin at room temperature.[12]

As a consequence, we turned our attention to the use of glycals as glycosyl donors. Thus, glycosylation of compound **6** was achieved in dichloromethane with silyl-protected D-olivals **12a** and **12b** in the presence of anhydrous (D/L)-camphor-10-sulfonic acid (CSA)[21] as activator (Scheme 4). Due to the low solubility of **6** in this solvent the reaction had to be carried out under very dilute conditions. Although the question of solubility can be overcome by performing the reaction in dry THF, the proton source is not sufficiently active under these conditions for promoting glycosylation. Similarly, triphenyl phosphine hydrobromide (TPHB),[22] another suitable protic source,[14] does not mediate glycosylation here, but reacts with the aglycon in an unspecified manner. The complex mixture of isomers showed a 1.4:1 ratio of α and β anomers and 2:1 ratio of 3-OH and 4-OH glycosides. It should be noted that similar studies have been conducted by Krohn and Bäuerlein.[23] The mixture of glycosides was partially purified by flash gel filtration and directly desilylated. Due to the highly reactive aglycon, suitable desilylation conditions had to be found. Hydrofluoride in acetonitrile effectively removes silyl groups, but it is also able to cleave 2-deoxy sugars such as the olivosyl moiety.[19] The HF/pyridine complex in THF does not have sufficient reactivity to promote desilylation before substantial chemical alteration in the benz[*a*]anthracene framework occurs. Tetra-*n*-butyl ammonium fluoride (TBAF), however, is too basic and only the more reactive β-olivosyl moieties are deprotected prior to decomposition of the aglycon.



Scheme 3. Formation of urdamycinone B by radical promoted reduction of **6**.



Scheme 4. Preparation of new angucycline antibiotics **13a–d**. (a) For **12a**: (1) anhydr, CSA, CH_2Cl_2, rt, 6 h, 93%; (2) Bu_4NF, THF, 0 °C, 30 min; (3) HF/pyr, THF, rt, 7 days (**13**: 42% for two steps; **6**: 29%); for **12b**: (1) anhydr, CSA, CH_2Cl_2, rt, 14 h, 83%; (2) Bu_4NF, THF, 0 °C, 30 min (**13**: 76%).

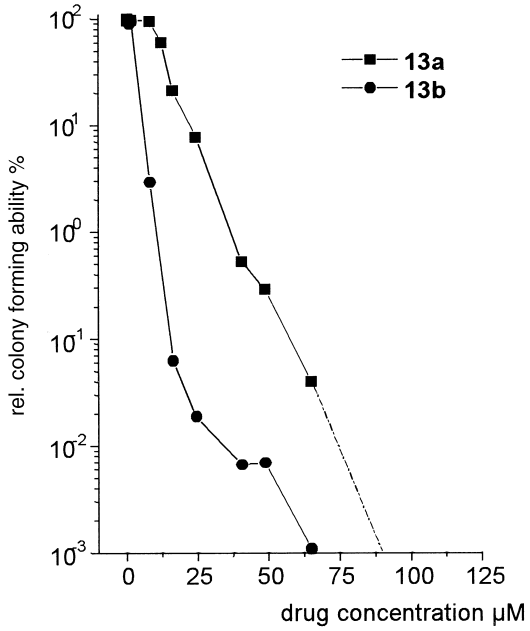


Figure 2. Cytotoxic effects of the compounds **13a** and **13b** as determined by the colony-forming ability assay. Human bronchial carcinoma cells of line A549 were incubated serum-free with **13a** and **13b** for 24 h, postincubated in culture medium for 12 days at 37 °C and 7.5% CO_2. The colonies were fixed and counted. The effects were compared to untreated controls as rel. clone forming rates. All survival points were done in triplicate, and experiments were conducted two times.

Therefore, we used a combination of two reagents by first employing TBAF in THF at 0 °C for 30 min. After terminating the reaction, the deblocked β-glycosylated aquayamycin derivatives **13a** and **13b** were separated by flash chromatography from the protected α-isomers. These were deprotected using a large excess of the HF/pyridine complex to afford α-glycoside **13c**. Under these harsh reaction conditions it was not possible to suppress glycosidic cleavage of **13d**. Instead, only aquayamycin (**6**) was isolated as a byproduct. However, the efficiency of this sequence was improved when 3,4-di-*O*-triethylsilyl protected glycal **12b** served as glycosyl donor. Due to enhanced lability of the triethylsilyl protection under acidic conditions the proton-assisted coupling with **6** proceeded in slightly reduced yield. But final desilylation was achieved under milder conditions and with satisfactory yield. HPLC-assisted separation of the glycosylated aquayamycins finally allowed the isolation of **13d** as a 1:1 mixture with **13c**. The structures of **13a–c** were comprehensively determined from the analyses of the NMR spectra (COSY, HETCOR and HMBC). Additional structural data were gained by recording FAB mass spectra.

Biological results

Preliminary cytotoxicity tests with the new angucycline antibiotics **13a** and **13b** were conducted, using human bronchial carcinoma cells of line A549.[24] The new angucyclines showed in vitro cytotoxicity with ED_{50} values[25] of 12.6 µM for **13a** and 2.9 µM for **13b** (Fig. 2). Drugs in clinical use commonly show a 100-fold higher antiproliferative activity compared to the values described above. Moreover, **13a–c** displayed good cytophatic effects against L-929 mouse fibroblast cells, K562 human leukemia cells and HeLa cells (Table 1).[26]

13a–c showed no antiviral activity by testing cytopathic effects with *Cocksackie virus* B3, *Influenca virus* and *Herpes simplex virus* Type 1. All three compounds displayed significant antibacterial activities in preliminary agar diffusion assays against *Bacillus subtilus* (ATCC 6633) and *Staphylococcus aureus* (SG 511).[26] In addition, compounds **13a–c** inhibited xanthine oxidase with an efficiency superior to allopurinol, so far the therapeutically most potent inhibitor of this enzyme known.[27] Thus in the cell-free system the three compounds suppressed chemiluminescence (CL) induced by xanthine oxidase and enhanced by lucigenin (Table 2). Concentration dependent suppression of CL was observed with IC_{50} = g/mL (0.42 µM) for **13a** + **b** and IC_{50} = 0.28 µg/mL

Table 1. Cytotoxic effects of the title compounds on various cell lines

Cell line	IC_{50} (µM)		
	13a	**13b**	**13c**
Human bronchial carcinoma A549	12.6[a]	2.9[a]	n.d.
Adherent mouse fibroblasts L929	6.6	2.4	16.7
Human leukemia K562	6.2	3.6	23.4
Human cervix carcinoma/HeLa	12.7	6.0	30.0

[a]Effective concentration expressed as EC_{50}.

Table 2. Lucigenin enhanced inhibition of xanthine oxidase

Concentration (μg/mL)	Suppression of chemoluminescence (%)			
	13a	**13b**	**13c**	Allopurinol
0.2	61.1	62.2	62.6	58.4
0.4	22.3	20.5	31.3	44.0
0.8	5.4	3.4	5.3	31.9

(0.46 μM) for **13c** compared to $IC_{50} = 0.32$ μg/mL (2.3 μM) for allopurinol.

It is evident that compounds **13a**–**c** inhibit the enzyme activity of xanthine oxidase and do not simply prevent the lucigenin reaction by scavenging superoxide anion radicals. This interpretation gained support when a luminol enhanced horseradish peroxidase assay was carried out. Here, the glyco-modified aquayamycin derivatives showed just weak activity as radical scavenger.[28]

Conclusion

In summary, we developed a route for preparing new angucycline antibiotics by fermentation followed by glycosylation which contain novel carbohydrate patterns. Our work evaluated the scope and limitations of different glycosylation methods with respect to the aglycon, which will ease future work for modifying the carbohydrate portion of angucycline antibiotics. Furthermore, all new angucycline-antibiotics are potent xanthine oxidase inhibitors and show strong cytotoxic activity.

Experimental

General remarks

All temperatures quoted are uncorrected. Optical rotations given in 10^{-1} °cm^2 g^{-1}: Perkin–Elmer 141 polarimeter. CD spectra: Jasco J 500 A (given in °cm^2 10^{-1} mol^{-1}). ^{1}H NMR, ^{13}C NMR, ^{1}H, ^{1}H- and ^{1}H, ^{13}C-COSY, HETCOR, as well as HMBC spectra: Bruker AMX 300, ARX 400 and Varian VXR 500 spectrometer. ^{13}C NMR multiplicities: DEPT 135 method. ^{1}H Multiplicities are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, br = broad. ^{13}C Multiplicities are reported using the following abbreviations: s = singlet (due to quaternary carbon), d = doublet (methine), q = quartet (methyl), t = triplet (methylene). MS: Finnigan MAT 95, 20 kV (FAB–MS) and 200 eV (DCI–MS; NH_3). Unless otherwise stated, all reactions were run under a nitrogen atmosphere. All solvents used were of reagent grade and were further dried. Reactions were monitored by TLC on silica gel 60 PF^{254} (E. Merck, Darmstadt) and spots were detected either by UV-absorption or by staining with H_2SO_4/4-methoxy benzaldehyde in ethanol. Preparative column chromatography (CC): silica gel 60 (E. Merck, Darmstadt). Preparative HPLC: Abimed/Gilson. Aquayamycin was prepared according to ref 15 in 72% yield. Details for the preparation of compound **7** have been reported previously.[14,18]

3′-[3″,4″-Di-*O*-(*tert*-butylsilyl)-6″-deoxy-2″-phenylselenyl-β-D-arabino-pyranosyloxy]-aquayamycin (8a) and 4′-[3″,4″-di-*O*-(*tert*-butylsilyl)-6″-deoxy-2″-phenylselenyl-β-D-arabino-pyranosyloxy]-aquayamycin (8b). To a solution of **6** (9.2 mg, 18.9 μmol) and **7** (13.5 mg, 23.6 μmol) in dry THF (1 mL) under nitrogen at −78 °C was added TESOTf (18.9 μmol; 1 vol% in diethyl ether). After 5 min a mixture of aqueous NH_4Cl solution and CH_2Cl_2 (1:4; 15 mL) was added at −78 °C. The aqueous layer was washed with CH_2Cl_2 (2×) and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was subjected to column chromatography (CH_2Cl_2:MeOH 9:1) to afford a 2:1 mixture of position isomers **8a**,**b** (17.0 mg, 17.5 μmol; 96%) along with aquayamycin (**6**, 0.3 mg, 0.6 μmol; 3%). The separation of the isomeric mixture and further characterization of the pure isomers was not attempted.

3′-[3″,4″-Di-*O*-(*tert*-butylsilyl)-6″-deoxy-2″-phenylselenyl-β-D-arabino-pyranosyloxy]-urdamycinone B (9a) and 4′-[3″,4″-di-*O*-(*tert*-butylsilyl)-6″-deoxy-2″-phenylselenyl-β-D-arabino-pyranosyloxy]-urdamycinone B (9b). To a solution of **8a,b** (22.6 mg, 22.2 μmol) in dry toluene (0.5 mL) under nitrogen was added Ph_3SnH (8.5 mg, 24.4 μmol) and a catalytic amount of AIBN and the temperature was raised to 120 °C. After 1 h the solvent was removed under reduced pressure and the crude product was twice subjected to column chromatography (CH_2Cl_2:MeOH 19:1 and petroleum ether:EtOAc 1:1).

Among some not identifiable but selenium containing fractions, a pure sample of **9a,b** (1.8 mg, 1.9 μmol; 8%) could be obtained as a 2:1* mixture of the position isomers.

9a,b: amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 12.69 (s, 1H, 8-OH), 12.64 (s, 1H*, 8-OH*), 8.31 (d, J = 8.0 Hz, 1H, 11-H), 8.31 (d, J = 8.0 Hz, 1H*, 11-H*), 7.86 (d, J = 8.0 Hz, 1H*, 6-H*), 7.85 (d, J = 8.0 Hz, 1H, 6-H), 7.69 (d, J = 8.0 Hz, 1H, 10-H), 7.68 (d, J = 8.0 Hz, 1H*, 10-H*), 7.59–7.52 (m, 4H, 4H*, 5-H, 5-H*, SePh, SePh*), 7.11–7.03 (m, 2H, 2H*, SePh, SePh*), 5.02 (d, J = 7.5 Hz, 1H*, 1″-H*), 5.01 (d, J = 7.5 Hz, 1H, 1″-H), 4.87 (br d, J = 11.2 Hz, 1H*, 1′-H*), 4.83 (br d, J = 11.2 Hz, 1H, 1′-H), 4.31 (br d, J = 4.0 Hz, 1H*, 3″-H*), 4.22 (br d, J = 4.0 Hz, 1H, 3″-H), 3.95–3.91 (m, 1H, 1H*, 3′-H, 3′-H*), 3.62 (m, 1H, 1H*, 5″-H, 5″-H*), 3.57 (br d, J = 4.4 Hz, 1H*, 4″-H*), 3.55 (br d, J = 4.4 Hz, 1H, 4-H″), 3.46 (m, 1H, 1H*, 5′-H, 5′-H*), 3.23 (d, J = 7.5 Hz, 1H*, 2″-H*), 3.20–3.16 (m, 2H, 4′-H, 2″-H), 3.16 (br s, 2H, 2H*, 2-H_{ax}, 2-H_{eq}, 2-H^*_{ax}, 2-H^*_{eq}), 3.13 (d, J = 14.8 Hz, 1H*, 4-H^*_a), 3.11 (d, J = 14.8 Hz, 1H, 4-H_a), 3.06 (dd, J = 9.0, 9.0 Hz, 1H*, 4′-H*), 3.01 (d, J = 14.8 Hz, 1H*, 4-H^*_b), 3.01 (d, J = 14.8 Hz, 1H, 4-H_b), 2.52 (br dd, J = 5.0, 12.6 Hz, 1H*, 2′-H^*_{eq}), 2.26 (br dd, J = 5.0, 12.6 Hz, 1H, 2′-H_{eq}), 1.51 (s, 3H, CH_3), 1.50 (s, 3H*, CH^*_3), 1.40 (br d, J = 6.0 Hz, 6H*, 6′-H*, 6″-H*), 1.37 (br d, J = 6.0 Hz, 6H, 6′-H, 6″-H), 1.36–1.26 (m,

1H, 1H*, 2′-H_{ax},2′-H^*_{ax}), 0.94 (br s, 9H, 9H*, $C(CH_3)_3$, $C(CH_3)^*_3$), 0.84 (br s, 9H, 9H*, $C(CH_3)_3$, $C(CH_3)^*_3$), 0.10–0.04 (8 s, 4*3H, 4*3H*, 2*$Si(CH_3)_2$, 2*$Si(CH_3)^*_2$). $C_{49}H_{66}O_{11}SeSi_2$ (966.17): (DCI-MS), *m/z* (%) = 984.5 (100) [M + NH_4^+], 966.6 (88) [M^+].

Radical reduction of aquayamycin (6). To a solution of **6** (5.0 mg, 10.3 μmol) in dry toluene (0.5 mL) under nitrogen was added Ph_3SnH (5.4 mg, 15.3 μmol) and a catalytic amount of AIBN and the temperature was raised to 120 °C. After 1 h the solvent was removed under reduced pressure and the crude product was subjected to column chromatography (CH_2Cl_2:MeOH 14:1). Final purification was achieved by HPLC (55% MeOH, 45% H_2O; 5 mL/min; RP_{18}).

1st fraction (R_t = 4.58 min): **6** (1.5 mg, 3.1 μmol; 30%).

2nd fraction *urdamycinone B* (**10**) (R_t = 6.67 min): (0.7 mg, 1.5 μmol; 15%). [α] $\Theta_{216.6\,nm}$ = 4400 °, $\Theta_{268.6\,nm}$ = −1200 ° (sh), $\Theta_{407.6\,nm}$ = 1060 ° (*c* = 0.0261 mM in MeOH, 22 °C). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.33 (d, *J* = 8.0 Hz, 1H, 11-H), 8.01 (d, *J* = 8.0 Hz, 1H, 6-H), 7.72 (d, *J* = 8.0 Hz, 1H, 10-H), 7.75 (d, *J* = 8.0 Hz, 1H, 5-H), 4.94 (dd, *J* = 2.0, 11.0 Hz, 1H, 1′-H), 3.85 (ddd, *J* = 5.0, 9.0, 11.2 Hz, 1H, 3′-H), 3.53 (dq, *J* = 6.0, 9.0 Hz, 1H, 5′-H), 3.22 (dd, *J* = 9.0, 9.0 Hz, 1H, 4′-H), 3.17 (s, 2H, 2-H_{ax}, 2-H_{eq}), 3.13 (d, *J* = 14.8 Hz, 1H, 4-H_a), 3.02 (d, *J* = 14.8 Hz, 1H, 4-H_b), 2.52 (ddd, *J* = 2.0, 5.0, 12.6 Hz, 1H, 2′-H_{eq}), 1.52 (s, 3H, CH_3), 1.48 (ddd, *J* = 11.2, 11.2, 12.6 Hz, 1H, 2′-H_{ax}), 1.41 (d, *J* = 6.0 Hz, 3H, 6′-H). $C_{25}H_{44}O_8$ (452.45): (DCI-MS), *m/z* (%) = 469.5 (26) [M + NH_3^+], 452.5 (16) [M^+], 434.6 (100) [M−H_2O^+].

3rd fraction (3*R*)-9-(6*R*,5*S*,4*R*,2*R*)-4,5-Dihydroxy-6-methyl-tetrahydro-pyran-2-yl-3,5-dihydroxy-3-methyl-3,4-dihydro-2*H*-naphthacene-1,6,11-triene (**11**) (R_t = 13.09 min): (0.8 mg, 1.7 μmol; 16%). $C_{25}H_{24}O_9$ (468.45): (DCI-MS), *m/z* (%) = 451.4 (100) [M−H_2O + H^+]. Neg. FAB–MS: 468.3 (100) [M^-], 467.3 (31) [M−H^+]. Physical and spectroscopic data are in accordance with ref 12.

Coupling of glycals 12a,b with aquayamycin (6). To a suspension of **6** (96 mg, 0.197 mmol) in dry CH_2Cl_2 (15 mL) under nitrogen at 0 °C was added anhydrous camphor sulfonic acid (51 mg, 0.220 mmol) and glycal **12a** (90 mg, 0.251 mmol). The temperature was raised to rt and the reaction mixture was stirred until the suspension turned to a clear orange solution. After six hours, saturated aqueous $NaHCO_3$ solution was added. The aqueous layer was washed with ethyl acetate (3×) and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was subjected to column chromatography (CH_2Cl_2:MeOH 19:1).

1st fraction: **6** (6 mg, 0.012 mmol; 6%).

2nd fraction (R_f = 0.25–0.16; CH_2Cl_2:MeOH 19:1): mixture of silyl-protected 2″,6″-dideoxy-D-*arabino*-pyranosyloxy-aquayamycin (155 mg, 0.183 mmol; 93%), amorphous orange solid. $C_{43}H_{64}O_{13}Si_2$ (845.13): (DCI-MS), *m/z* (%) = 862.6 (100) [M + NH_3^+].

Employing the procedure described above, aquayamycin (**6**, 418 mg, 0.86 mmol), glycal **12b** (339 mg, 0.95 mmol) and a catalytic amount of anhydrous camphor sulfonic acid (10 mg) in dry CH_2Cl_2 (100 ml) were used to prepare the primary glycosylation products (606 mg, 0.72 mmol, 83%) along with the starting material **6** (65 mg, 0.13 mmol, 15%).

3′-(2″,6″-Dideoxy-β-D-arabino-pyranosyloxy)-aquayamycin (13a) and 4′-(2″,6″-dideoxy-β-D-arabino-pyranosyloxy)-aquayamycin (13b). The crude glycosylation product obtained from the glycosylation described above (155 mg, 0.183 mmol) was treated with tetrabutyl ammonium fluoride in absolute THF (0.1 M, 2 mL, 1.1 equ.) under nitrogen at 0 °C. After 30 min, saturated aqueous NH_4Cl solution was added whereby the color of the solution changed from deep blue to orange. The aqueous layer was washed with ethyl acetate (3×) and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The deprotected β-glycosides (R_f = 0.38; CH_2Cl_2:MeOH 9:1) were separated from the unprotected angucyclines (R_f = 0.63; CH_2Cl_2:MeOH 9:1) by subjecting the crude product to column chromatography (CH_2Cl_2:MeOH 19:1). The starting material was reisolated (82 mg, 0.097 mmol; 53%) and the two deprotected β-adducts were separated by HPLC (30% CH_3OH, 70% H_2O; 5 mL/min; RP18).

1st fraction (R_f = 7.68 min) **13a** (12.3 mg, 0.02 mmol; 11%). Amorphous solid. [α] $\Theta_{218.6\,nm}$ = 20900 °, $\Theta_{234.0\,nm}$ = 10300 °, $\Theta_{252.8\,nm}$ = −3690 °, $\Theta_{273.2\,nm}$ = −10400°, $\Theta_{403.6\,nm}$ = −5270 °, $\Theta_{469.4\,nm}$ = 273° (*c* = 0.0267 mM in MeOH, 22 °C). ^{1}H NMR (300 MHz, $CO(CD_3)_2$, 25 °C): δ = 12.35 (s, 1H, 8-OH), 7.89 (br d, *J* = 7.4 Hz, 1H, 10-H), 7.56 (br d, *J* = 7.4 Hz, 1H, 11-H), 6.82 (br d, *J* = 9.6 Hz, 1H, 6-H), 6.44 (br d, *J* = 9.6 Hz, 1H, 5-H), 5.20 (s, 1H, OH), 4.85 (br d, *J* = 11.4 Hz, 1H, 1′-H), 4.76 (dd, *J* = 1.8, 9.8 Hz, 1H, 1″-H), 4.73 (s, 1H, OH), 4.61 (s, 1H, OH), 4.58 (s, 1H, OH), 4.20, 4.07 (2d, *J* = 4.6 Hz, 2H, 3″-OH, 4″-OH), 3.76 (ddd, *J* = 5.0, 8.6, 11.4, 1H, 3′-H), 3.64–3.50 (m, 1H, 3″-H), 3.44 (dq, *J* = 6.2, 9.2 Hz, 1H, 5″-H), 3.39 (dq, *J* = 6.2, 9.2 Hz, 1H, 5′-H), 3.04 (dd, *J* = 8.6, 9.2 Hz, 1H, 4′-H), 2.97 (d, *J* = 12.6 Hz, 1H, 2-H_{ax}), 2.97 (ddd, *J* = 4.6, 8.6, 9.2 Hz, 1H, 4″-H), 2.67 (dd, *J* = 2.8, 12.6 Hz, 1H, 2-H_{eq}), 2.43 (ddd, *J* = 1.8, 5.0, 12.8 Hz, 1H, 2′-H_{eq}), 2.24 (d, *J* = 14.8 Hz, 1H, 4-H_{ax}), 2.13 (ddd, *J* = 1.8, 4.8, 12.4 Hz, 1H, 2″-H_{eq}), 2.06 (dd, *J* = 2.8, 14.8 Hz, 1H, 4-H_{eq}), 1.51 (ddd, *J* = 9.8, 11.6, 12.4 Hz, 1H, 2″-H_{ax}), 1.38 (ddd, *J* = 11.2, 11.4, 12.8 Hz, 1H, 2′-H_{ax}), 1.33 (d, *J* = 6.2 Hz, 3H, 6′-H), 1.29 (d, *J* = 6.2 Hz, 3H, 6″-H), 1.22 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CO(CD_3)_2$, 25 °C): δ = 206.3 (s, C-1), 190.1 (s, C-7), 183.2 (s, C-12), 158.8 (s, C-8), 146.6, (s, C-5), 140.5 (s, C-12a), 139.6 (s, C-6a), 138.9 (s, C-9a), 134.5 (d, C-10), 132.1 (s, C-11a), 119.9 (d, C-11), 117.8 (d, C-6), 114.3 (s, C-7a), 100.7 (d, C-1″), 83.7 (d, C-3′), 81.9 (s, C-4a), 78.3, 78.2 (2s, C-12b, C-3), 77.9 (d, C-4″), 77.5 (d, C-5′), 76.4 (d, C-4′), 73.3 (d, C-5″), 72.0 (d, C-1′, C-3″), 53.0 (t, C-2), 44.6 (t, C-4), 40.7 (t, C-2″), 38.9 (t, C-2′), 30.0 (q, 3-CH_3), 18.8 (q, C-6′), 18.3 (q, C-6″). $C_{31}H_{36}O_{13}$ (616.61): (FAB–MS, negative mode), *m/z* (%) = 616.4 (100) [M^-], 615.5 (24) [M−H^-].

2nd fraction (R_f = 9.72 min): **13b** (12.5 mg, 0.02 mmol; 11%). Amorphous solid. [α] $\Theta_{218.6\,nm}$ = 20 700°, $\Theta_{234.0\,nm}$ = 10 000° (sh), $\Theta_{252.6\,nm}$ = −3330°, $\Theta_{272.0\,nm}$ = 8720°, $\Theta_{406.2\,nm}$ = −3800°, $\Theta_{455.8\,nm}$ = 230° (*c* = 0.0284 mM in MeOH, 23 °C). ^{1}H NMR (300 MHz, $CO(CD_3)_2$, 25 °C): δ = 12.33 (s, 1H, 8-OH), 7.88 (br d, *J* = 7.8 Hz, 1H, 10-H), 7.56 (br d, *J* = 7.8 Hz, 1H, 11-H), 6.82 (br d, *J* = 9.6 Hz, 1H, 6-H), 6.44 (br d, *J* = 9.6Hz, 1H, 5-H), 5.20 (s, 1H, OH), 4.87 (dd, *J* = 1.8, 11.2 Hz, 1H, 1′-H), 4.73 (s, 1H, OH), 4.72 (dd, *J* = 2.0, 9.8 Hz, 1H, 1″-H), 4.60 (s, 1H, OH), 4.55 (s, 1H, OH), 4.23, 4.13 (2d, *J* = 4.6 Hz, 2H, 3″-OH, 4″-OH), 3.72 (ddd, *J* = 5.2, 8.6, 11.4, 1H, 3′-H), 3.59 (dddd, *J* = 4.6 5.2, 8.8, 11.6 Hz, 1H, 3″-H), 3.54 (dq, *J* = 6.2, 9.2 Hz, 1H, 5″-H), 3.40 (dq, *J* = 6.2, 9.2 Hz, 1H, 5′-H), 3.10 (dd, *J* = 8.6, 9.2 Hz, 1H, 4′-H), 2.99 (ddd, *J* = 4.6, 8.8, 9.2 Hz, 1H, 4″-H), 2.98 (d, *J* = 12.6 Hz, 1H, 2-H_{ax}), 2.67 (dd, *J* = 3.0, 12.6 Hz, 1H, 2-H_{eq}), 2.42 (dd, *J* = 1.8, 5.0, 12.8 Hz, 1H, 2′-H_{eq}), 2.26 (d, *J* = 14.0 Hz, 1H, 4-H_{ax}), 2.25 (ddd, *J* = 2.0, 5.2, 12.4 Hz, 1H, 2″-H_{eq}), 2.07 (dd, *J* = 3.0, 14.8 Hz, 1H, 4-H_{eq}), 1.53 (ddd, *J* = 9.8, 11.6, 12.4 Hz, 1H, 2″-H_{ax}), 1.33 (d, *J* = 6.2 Hz, 3H, 6′-H), 1.28 (ddd, *J* = 11.2, 11.4, 12.8 Hz, 1H, 2′-H_{ax}), 1.28 (d, *J* = 6.2 Hz, 3H, 6″-H), 1.22 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CO(CD_3)_2$, 25 °C): δ = 206.3 (s, C-1), 190.1 (s, C-7), 183.2 (s, C-12), 158.5 (s, C-8), 146.6, (s, C-5), 140.4 (s, C-12a), 139.6 (s, C-6a), 139.0 (s, C-9a), 134.2 (d, C-10), 132.1 (s, C-11a), 119.8 (d, C-11), 117.8 (d, C-6), 115.3 (s, C-7a), 102.1 (d, C-1″), 89.4 (d, C-4′), 82.0 (s, C-4a), 78.2, 78.0 (2s, C-12b, C-3), 77.6 (d, C-4″), 75.6 (d, C-5′), 73.4 (d, C-5″), 72.0 (d, C-3″), 71.8 (d, C-1′), 71.5 (d, C-3′), 53.0 (t, C-2), 44.6 (t, C-4), 40.4, 40.3 (2t, C-2′, C-2″), 30.0 (q, 3-CH_3), 18.5 (q, C-6′), 18.3 (q, C-6″). $C_{31}H_{36}O_{13}$ (616.61): (FAB–MS, negative mode), *m*/*z* (%) = 616.4 (100) [M^-], 615.5 (21) [$M-H^-$], 598.4 (29) [$M-H_2O^-$].

3′-(2″,6″-Dideoxy-α-D-arabino-pyranosyloxy)-aquayamycin (13c) and 4′-(2″,6″-dideoxy-α-D-arabino-pyranosyloxy) - aquayamycin (13d). The fraction of protected glycoconjugates obtained after the TBAF-mediated desilylation (41 mg, 0.048 mmol) were dissolved in dry THF (5 mL) in a polyethylene flask and treated with small portions of HF/pyridine complex (0.4 mL). After 7 days the reaction mixture was neutralized with aqueous $NaHCO_3$ solution and the resulting solution was washed with ethyl acetate (3×). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (CH_2Cl_2:MeOH 19:1) afforded two fractions.

1st fraction (R_f = 0.2; CH_2Cl_2:MeOH 19:1): **13c** (6 mg, 0.01 mmol; 20%). Amorphous solid. [α] $\Theta_{219\,nm}$ = 21500°, $\Theta_{230.8\,nm}$ = 13500° (sh), $\Theta_{253.2\,nm}$ = −1600°, $\Theta_{271.4\,nm}$ = 8780°, $\Theta_{398.0\,nm}$ = −2570°, $\Theta_{456.2\,nm}$ = 1070° (*c* = 0.0302 mM in MeOH, 25 °C). ^{1}H NMR (300 MHz, $CO(CD_3)_2$, 25 °C): δ = 12.35 (s, 1H, 8-OH), 7.89 (br d, *J* = 7.8 Hz, 1H, 10-H), 7.56 (br d, *J* = 7.8 Hz, 1H, 11-H), 6.81 (br d, *J* = 9.8 Hz, 1H, 6-H), 6.44 (br d, *J* = 9.8 Hz, 1H, 5-H), 5.20 (s, 1H, OH), 5.13 (br d, *J* = 3.8 Hz, 1H, 1″-H), 4.87 (dd, *J* = 1.8, 11.2 Hz, 1H, 1′-H), 4.73 (s, 1H, OH), 4.60 (s, 1H, OH), 4.40 (s, 1H, OH), 4.30–3.90 (br s, 2H, 3″-OH, 4″-OH), 3.76–3.64 (m, 2H, 3′-H, 3″-H), 3.51 (dq, *J* = 6.4, 9.2 Hz, 1H, 5″-H), 3.51 (dq, *J* = 6.0, 9.2 Hz, 1H, 5′-H), 3.16 (dd, *J* = 8.8, 9.2 Hz, 1H, 4′-H), 2.98 (d, *J* = 12.6 Hz, 1H, 2-H_{ax}), 2.92 (dd, *J* = 8.8, 9.2 Hz, 1H, 4″-H), 2.67 (dd, *J* = 3.0, 12.6 Hz, 1H, 2-H_{eq}), 2.53 (ddd, *J* = 1.8, 5.0, 12.8 Hz, 1H, 2′-H_{eq}), 2.25 (d, *J* = 14.8 Hz, 1H, 4-H_{ax}), 2.15 (ddd, *J* = 0.8, 5.0, 12.8 Hz, 1H, 2″-H_{eq}), 2.06 (dd, *J* = 3.0, 14.8 Hz, 1H, 4-H_{eq}), 1.53 (ddd, *J* = 3.8, 11.8, 12.8 Hz, 1H, 2″-H_{ax}), 1.39 (ddd, *J* = 11.2, 11.4, 12.8 Hz, 1H, 2′-H_{ax}), 1.33 (d, *J* = 6.0 Hz, 3H, 6′-H), 1.22 (s, 3H, CH_3), 1.13 (d, *J* = 6.4 Hz, 3H, 6″-H). ^{13}C NMR (125 MHz, $CO(CD_3)_2$, 25 °C): δ = 206.3 (s, C-1), 189.4 (s, C-7), 182.5 (s, C-12), 157.8 (s, C-8), 145.9, (s, C-5), 139.8 (s, C-12a), 138.8, 138.5 (2s, C-6a, C-9a), 133.6 (d, C-10), 131.3 (s, C-11a), 119.1 (d, C-11), 117.1 (d, C-6), 114.6 (s, C-7a), 100.1 (d, C-1″), 81.3 (s, C-4a), 80.7 (d, C-3′), 78.3 (d, C-4″), 77.2 (s, C-12b), 76.8 (s, C-3), 76.8 (d, C-5′), 76.4 (d, C-4′), 71.3 (d, C-1′), 68.9 (d, C-3″), 68.4 (d, C-5″), 52.3 (t, C-2), 43.9 (t, C-4), 39.5 (t, C-2′), 38.5 (t, C-2″), 30.0 (q, 3-CH_3), 18.8 (q, C-6′), 18.2 (q, C-6″). $C_{31}H_{36}O_{13}$ (616.61): (FAB–MS, negative mode), *m*/*z* (%) = 616.4 (100) [M^-], 615.5 (27) [$M-H^-$].

2nd fraction: **6** (7.2 mg, 0.014 mmol; 29%). In addition, the triethylsilyl protected glycosylation products (1.45 g, 1.70 mmol) were used to prepare the title compounds **13a–d** (800 mg, 1.30 mmol, 76%) after treatment with dry Bu_4NF (14 ml; 1 M in THF) in THF (60 mL) for 30 min at 0 °C. Work-up and chromatographic separation proceeded as described above. After HPLC purification, this sequence allowed us to isolate **13a** and **13b** as well as **13d**, which was present in a 1:1 mixture with **13c**.

13c and **13d*** (R_f = 0.2; CH_2Cl_2:MeOH 19:1), amorphous solid. ^{1}H NMR (200 MHz, $CO(CD_3)_2 + D_2O$, 25 °C): δ = 7.89 (d, *J* = 7.8 Hz, 1H, 1H*, 10-H, 10-H*), 7.55 (d, *J* = 7.8 Hz, 1H, 1H*, 11-H, 10-H*), 6.81 (d, *J* = 9.8 Hz, 1H, 1H*, 6-H, 6-H*), 6.44 (d, *J* = 9.8 Hz, 1H, 1H*, 5-H, 5-H*), 5.48 (d, *J* = 3.5 Hz, 1H*, 1″-H*), 5.13 (d, *J* = 3.5 Hz, 1H, 1″-H), 4.87 (dd, *J* = 1.8, 11.2 Hz, 1H, 1′-H), 4.84 (dd, *J* = 1.8, 11.1 Hz, 1H*, 1′-H*), 3.87 (ddd, *J* = 11.3, 8.8, 4.8 Hz, 1H*, 3′-H*), 3.80–3.64 (m, 2H, 1H*, 3′-H, 3″-H, 3″-H*), 3.60–3.43 (m, 2H, 2H*, 5′-H, 5′-H*, 5″-H, 5″-H*), 3.22 (t, *J* = 9.0 Hz, 1H*, 4′-H*), 3.14 (t, *J* = 9.0 Hz, 1H, 4′-H), 2.96 (t, *J* = 9.0 Hz, 1H*, 4″-H*), 2.95 (d, *J* = 12.6 Hz, 1H, 1H*, 2-H_{ax}, 2-H^*_{ax}), 2.93 (t, *J* = 9.0 Hz, 1H, 4″-H), 2.67 (dd, *J* = 3.0, 12.6 Hz, 1H, 1H*, 2-H_{eq}, 2-H^*_{eq}), 2.50 (ddd, *J* = 1.8, 5.0, 12.8 Hz, 1H, 2′-H_{eq}), 2.37 (ddd, *J* = 2.0, 5.0, 12.8 Hz, 1H*, 2′-H^*_{eq}), 2.25–2.00 (m, 3H, 3H*, 4-H_{ax}, 4-H^*_{ax}, 2″-H_{eq}, 2″-H^*_{eq}, 4-H_{eq}, 4-H^*_{eq}, $CO(CD_3)$), 1.57 (ddd, *J* = 4.1, 11.8, 12.8 Hz, 1H*, 2″-H^*_{ax}), 1.54 (ddd, *J* = 3.8, 11.8, 12.8 Hz, 1H, 2″-H_{ax}), 1.48–1.30 (m, 1H, 1H*, 2′-H_{ax}, 2′-H^*_{ax}), 1.35 (d, *J* = 6.0 Hz, 3H*, 6′-H*), 1.33 (d, *J* = 6.0 Hz, 3H, 6′-H), 1.21 (s, 3H, 3H*, CH_3, CH_3^*), 1.12 (d, *J* = 6.0 Hz, 3H*, 6″-H*), 1.12 (d, *J* = 6.4 Hz, 3H, 6″-H).

Cell culture and colony-forming assay

Biological effects of the compounds were tested in a colony-forming assay according to the published procedure with the following modifications. Briefly, after seeding A549 cells in six-well multiplates the desired concentrations of freshly diluted drugs in DMSO (1% final concentration in the culture wells) were added and

incubated for 24 h in a serum-free medium UltraCulture (BioWhittaker). Before and after drug exposure cells were washed in the UltraCulture medium to remove serum of the culture medium.

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