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Facile photochemical synthesis of mixed siloxyacetal glycosides as potential pH-sensitized prodrugs for selective treatment of solid tumors†

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Photochemical reactions of a variety of acylsilanes with peracetylated free glycosides in anhydrous benzene at ambient temperature yielded novel, highly acid-sensitive siloxyacetal glycosides in 75–90% yields with complete retention of configuration at the anomeric center. Subsequent deacetylation of triisopropylsiloxy- and *tert*-butyldimethylsiloxy derivatives with sodium methoxide in methanol afforded deprotected siloxyacetal glycosides in nearly quantitative yields. Acid hydrolysis of trimethylsilyl siloxyacetals proceeded with a half-life of 17.5 minutes at pH 6.2 which is vastly superior to the decomposition rate of conventional acetals under similar conditions. The structure of one of the novel siloxyacetals was confirmed by X-ray crystallography. *In vitro* biological studies showed that glucose-derived siloxyacetals may serve as potential pH-activated prodrugs for selective treatment of solid tumors.

Introduction

The ultimate goal of cancer drug research is to develop therapies that can selectively kill tumor cells without adverse effects on the host.[1] To address this issue, considerable efforts have been made to utilize some of the distinctions between normal and tumor cells. Traditionally, cancer has been thought of as a disease of abnormal cell proliferation. This belief has provided a basis for the development of most of the currently used chemotherapeutic agents that achieve selectivity as a result of the drugs being taken up to a greater extent by the rapidly proliferating cancer cells. The recent advances in molecular biology has allowed development of a number of mechanism-based drugs. These drugs potentially offer greater selectivity and reduced toxicity as they attempt to target specific biochemical or molecular pathways inherent to the malignant phenotype. However, most of these drugs still remain dose-limiting due to extreme cytotoxicity.

While most of the latest attempts for selective cancer treatment are focused on the molecular target approaches, the profound microphysiological differences discovered by Warburg[2] more than seven decades ago received much less attention.[3] It is now well recognized that the tumor microenvironment is characterized by dramatically increased glucose intake, slow blood flow, hypoxia, and low extracellular pH (pH_e).[4–6] The functional vasculature of tumors is often inadequate to supply the nutritional needs of the rapidly expanding population of cells, leading to deficiency in oxygen and many other nutrients. As a result, production of lactic acid under anaerobic conditions and the hydrolysis of ATP in the energy-deficient environment contribute to the acidic microenvironment found in many types of tumors.[7–10] Non-invasive pH measurements reveal the presence of large regions of acidic pH_e in tumors, with the intracellular pH (pH_i) being maintained in the neutral to alkaline range.[10] The standard pH difference between normal tissues and tumors is rather small at 7.4 *versus ca.* 6.9–7.0 pH units. However, this differential can be enhanced by as much as 1–1.5 units by hyperthermia,[11] and/or glucose administration[12,13] without affecting pH of the surrounding normal tissues. Therefore, any therapy that exploits this marginal, yet conceptually significant, pH difference could be interesting to explore.

One of the modern approaches that takes advantage of tumor acidity is the targeting of malignant cells through the use of ionophores that equilibrate pH_e and pH_i and thus selectively inhibit the growth of tumor cells.[14] The tumor pH gradient was also exploited to selectively increase uptake of weakly acidic drugs into tumors compared to the normal tissues.[15] pH-responsive micelles loaded with anticancer drugs have also been explored.[16]

It is well known that acetals reveal virtually unlimited stability to basic conditions while being quite fragile towards acids,[17] a property that makes them interesting candidates for pH-based therapies. In a recent study, proteins were encapsulated within acetal cross-linked hydrogels which, at acidic pH, released the entrapped molecules, while, at neutral pH, the cross-linker remained largely intact.[18] In another example, acid-degradable polyacetal–doxorubicin conjugates were used for improved tumor targeting.[19] Yet another approach involves designing appropriate non-toxic acid-labile agents that are stable at physiological pH but are cleaved rapidly at slightly acidic pH with the liberation of cytotoxic compounds. The progress in the development of such "proton-activated prodrugs" has been recently reviewed by Tietze and Feuerstein.[20] Thus, the utility of conventional acid-labile acetals, ketals and acetal glycosides for selective treatment of solid tumors had been explored.[21–24] These acetal glycosides could be chemisensitized at pH 6.2 with a release of cytotoxic aldehydes. Although the rates of acid-catalyzed hydrolysis were relatively low at pH 6.2 ($t_{1/2}$ = 2–76 hours) some of these compounds exhibited nearly no toxicity at physiological pH while at pH 6.2 the survival rate of cancer cells decreased by a factor of 50000.[25] Another interesting use of acetals in nucleoside prodrug design has been recently described by Matsuda *et al.*[22]

For this promising approach to be successful, it is crucial to develop agents that are cleaved as quickly as possible at pH 6.2 in order to avoid their excessive circulation prior to activation. Considerable efforts have been undertaken to synthesize acetal glycosides with appropriate acid lability.[25] However, the conventional acetal glycosides have insurmountable limitations

† Electronic supplementary information (ESI) available: Materials and Methods and characterization data for compounds **24**, **25**, **29**–**34**. See http://www.rsc.org/suppdata/ob/b4/b405786d/

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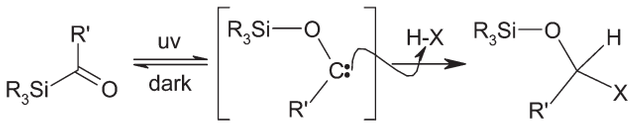
with respect to the further increases of their hydrolysis rates. In this paper we present a facile and general photochemical synthesis of a novel class of highly acid-sensitive siloxyacetal glycosides which are stable under physiological pH but are rapidly transformed into cytotoxic aldehydes at slightly acidic conditions found in extracellular environment of solid tumors. Hydrolysis and *in vitro* biological activity of these novel carbohydrate derivatives are also discussed.

Results and discussion

A. Synthesis of acylsilanes

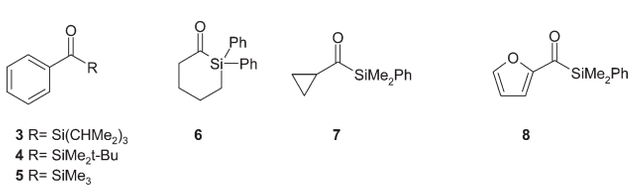
Since their first synthesis by Brook[26] nearly 50 years ago, acylsilanes (α-silyl ketones) have attracted considerable interest not only because of their special physical properties, but also because of the synthetic utility of these compounds due to the unusual reactivity of the carbonyl group located alpha to the silicon atom. Numerous synthetic transformations that are pertinent to the acylsilane functionality have been recently reviewed.[27–30] In addition, acylsilanes show photochemistry that is not possible with other carbonyl compounds, such as the [1,2]-silyl shift to form highly reactive siloxycarbenes.[31–35] These carbenes are extremely labile and react by intramolecular insertion into H–X bonds of polar reagents (HOAc, HCN, pyrrole, HSPh, HCl, HOR)[36] and electron-poor olefins.[37] In the dark or in the absence of polar traps, siloxycarbenes rapidly rearrange into the original acylsilanes (eqn. 1).[32] For example, with alcohols as solvents, mixed acetals of an aldehyde with 1 mol each of silanol and alcohol were formed in 60–100% yields.[38] These acetals were highly sensitive towards acid-catalyzed solvolysis and could be isolated only in the presence of base.[31]



(1)

Although numerous methods for the synthesis of acylsilanes have appeared in the literature in recent years,[29] the original dithiane route developed simultaneously by Brook *et al.*[39] and by Seebach and coworkers[40] remains quite general and convenient for the preparation of a great variety of acylsilanes. We have chosen this method, with slight modifications, for the preparation of sterically crowded acylsilanes **3** and **4** (Scheme 1) from commercially available 2-phenyl-1,3-dithiane (**1**). Dithiane **1** was first silylated with TIPS-triflate or TBDMS-Cl[41] and then hydrolyzed with chloramine-T[42] to afford the corresponding acylsilanes **3** and **4** in good overall yields. Benzoyltrimethylsilane (**5**) was readily prepared from benzyltrimethylsilyl ether *via* dibromination with two equivalents of *N*-bromosuccinimide followed by hydrolysis with silver acetate in acetone–ethanol–water.[43] The cyclic 1,1-diphenyl-1-silacyclohexanone-2 (**6**) was synthesized starting from 5-chloro-1-pentyne as previously described by Brook and Pierce[44] and by Benkeser and Cunico[45] Synthesis of cyclopropoyldimethylphenylsilane (**7**) and 2-furoyldimethylphenylsilane (**8**) was accomplished by reaction of cyclopropanecarbonyl chloride and 2-furoyl chloride, respectively, with dimethylphenylsilyl–zinc cyanocuprate acting as a silyl anion source.[46]

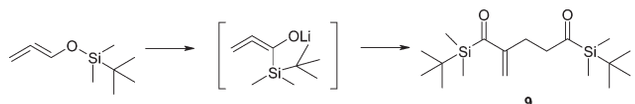
Attempted preparation of the α,β-unsaturated vinyl acylsilane by hydrolysis of the intermediate lithium silaacrolein enolate anion (obtained from *tert*-butyldimethylsilyl allene)[47] following the literature procedure[48] failed yielding instead an interesting and previously unreported bi-functional acylsilane **9** as a sole product (eqn. 2).



3 R= Si(CHMe$_2$)$_3$
4 R= SiMe$_2$t-Bu
5 R= SiMe$_3$

6 **7** **8**

Scheme 1



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(2)

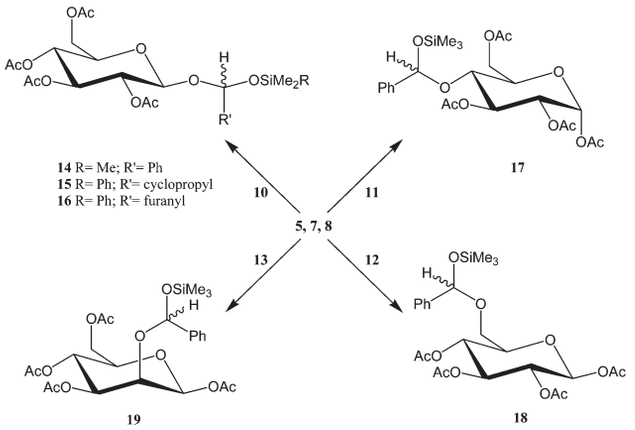
B. Synthesis of siloxyacetal glycosides

The photoreaction of acylsilanes with various peracetylated free glucopyranosides was carried out in a solution or suspension of these substrates in anhydrous benzene, with or without trace amounts of pyridine added to stabilize the acid-sensitive acetal glycosides from solvolysis by the photogenerated acids.[31] Progress of the photoreaction was monitored either by TLC or by the disappearance of the brightly colored acylsilanes. In general, a solution of 2 equivalents of the free glycoside and 1 equivalent of acylsilane in anhydrous benzene in the presence of a catalytic amount of dry pyridine in a Pyrex® tube was purged with dry argon and irradiated at λ_{max} = 350 nm using a Rayonet photochemical chamber reactor RPR-100. The reaction was usually complete within 30 min. The reaction solution was evaporated to dryness and the residue purified by flash-chromatography using eluants containing 0.3% Et_3N for stabilization of the acid-sensitive acetal glycosides from decomposition on the slightly acidic silica gel. The siloxyacetal glycosides were obtained in 70–90% yields.

Since original reports by Brook *et al* indicated the highly unstable nature of siloxyacetals formed by reacting acylsilanes with simple primary alcohols,[31] we set out to explore the stability of siloxyacetals formed at different positions on the sugars. First, three positional isomers **14**, **17**, and **18** were prepared by reacting 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside,[49] (**10**) 1,2,3,6-tetra-*O*-acetyl-α-D-glucopyranoside[49] (**11**) and 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranoside[49] (**12**) with benzoyltrimethylsilane **5**. The photoadduct **18** of the primary alcohol **12** was too unstable to be isolated and partially decomposed on silica gel even in the presence of stabilizing triethylamine. At the same time, adduct **17** of the secondary alcohol **11** was isolated as a stable oil and could be stored indefinitely at −20 °C without any signs of decomposition. Remarkably, the photoadduct **14**, with a 1,1′-diacetal structure, not only was exceptionally stable but also was isolated in a solid form and could be recrystallized from hot ethanol solution. The 1,1′-diacetal structures are known to be difficult to synthesize by conventional organic methods and supposedly they must be more acid-labile than corresponding monoacetals.[21]

In addition, glucopyranoside **10** was reacted with acylsilanes **7** and **8** to afford photoadducts **15** and **16**, respectively. Photoadduct **15** survived purification on silica gel but decomposed slowly on storage without added base, while adduct **16** could not survive even purification on silica gel. Finally, stable mannose-derived photoadduct **19** was prepared from 1,3,4,6-tetra-*O*-acetyl-β-mannopyranoside[50] (**13**) and acylsilane **5** (Scheme 2).

All of the siloxyacetal glycosides were isolated as 1 : 1 inseparable mixtures of diastereomers at the acetal center. ^{1}H NMR spectra were consistent with the structures of acetals, *i.e.* the presence of characteristic singlets at 5–6 ppm of a hydrogen attached to the acetal carbon.[31] The stereochemistry at the anomeric center of the adducts **14** and **15** remained unchanged, as judged by the NMR spectroscopy. All of the above siloxyacetals gave satisfactory elemental analyses. However, FAB mass spectra of trimethylsiloxy acetals failed to give the molecular ion signals (see Experimental section). Therefore, the structure and relative stereochemistry of the crystalline diacetal photoproduct **14** was unambiguously determined by the X-ray crystal structure analysis (Fig. 1).



Scheme 2

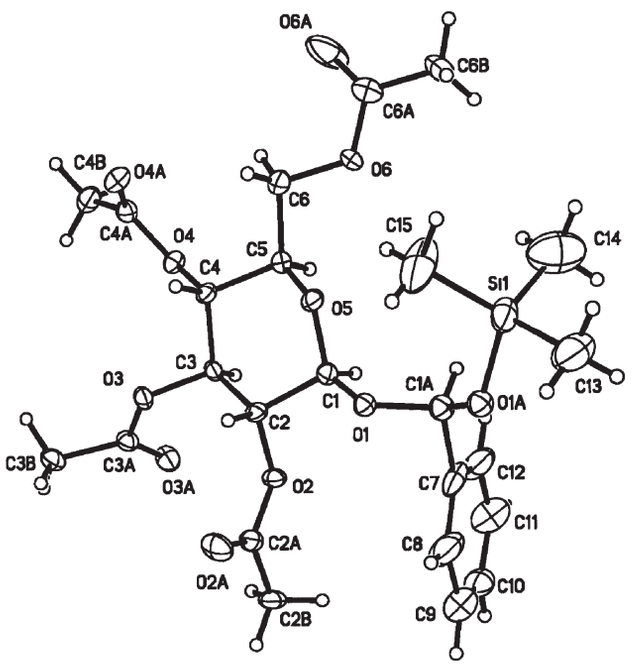
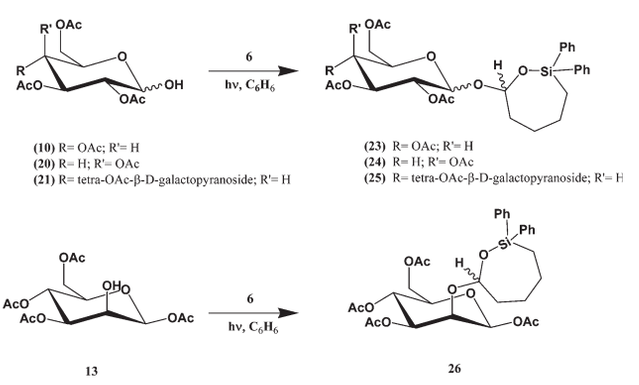


Fig. 1 X-Ray crystal structure of photoadduct **14**. Displacement ellipsoid plot is drawn at the 50% probability level. There is some disorder (65/35) of the atoms O1, O1A and C1A and only the major form is shown. HFIX 33 was used to generate the coordinates; it is likely that the methyl H atoms are incorrectly oriented.

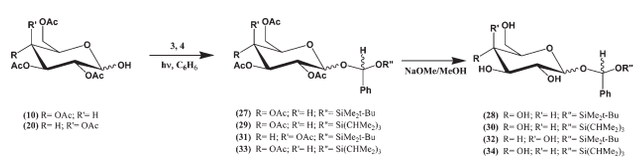
A series of seven-member ring cyclic photoadducts **23**–**26** was prepared by reaction of glucopyranoside **10**, 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranoside (**20**), lactose heptaacetate (**21**), and mannopyranoside **13** with cyclic acylsilane **6** (eqn. 3). Interestingly, the photoreaction of **6** was much more efficient than that of **5** with completion times of less than 20 min and with nearly quantitative yields. This can be explained by greater tendency of cyclic acylsilanes to react *via* siloxycarbenes compared to their acyclic analogs that are also known to react *via* radical pathways.[31] All cyclic photoadducts were separated as 1 : 1 mixtures of diastereomers at the acetal center, were exceptionally stable towards separation on silica gel and could be stored neat or in solution at room temperature without any decomposition.



(3)

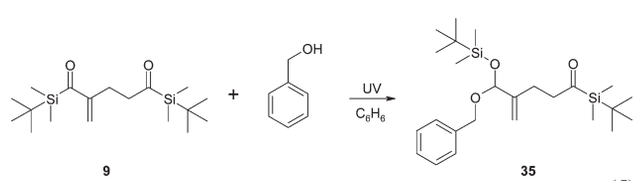
The critical stage in the synthesis was the deacetylation of the trimethyl- and the cyclic diphenyl siloxyacetal glycosides. Since potassium carbonate in anhydrous alcohols was used in the earlier work of Brook *et al.* to stabilize photochemically generated trimethylsiloxyacetals of simple alcohols,[31] it was expected that the silyl functionality would remain intact during the deacetylation procedure using catalytic K_2CO_3 in anhydrous methanol.[17] However, all our attempts to deacetylate compounds **14**–**19** and **23**–**26** with K_2CO_3 in anhydrous methanol led to decomposition of the acetal functionality. A variety of other literature methods for the mild basic deprotection of acetyl groups were attempted; all of which also led to the rapid destruction of the acetal functionality, presumably *via* nucleophilic attack at the vulnerable silicon center (see Experimental section). For example, deacetylation of **14** and **23** also failed using a basic ion-exchange resin in water-free methanol with ultrasound as developed by Tietze and Fischer-Beller specifically for deacetylation of acid-labile glycosides.[23]

This has led us to use other more sterically hindered trialkylsilyl groups that are more resistant to the basic conditions used during the deacetylation procedures. To this end, we have synthesized a series of sterically-crowded siloxyacetal glycosides **27**–**33** *via* reaction of acylsilanes **3** and **4** with glycopyranosides **10** and **20** (eqn. 4). These siloxyacetal glycosides could be easily deprotected with catalytic sodium methoxide in methanol to give compounds **28**–**34** in nearly quantitative yields. In contrast to the trimethylsilyl derivatives, all of the triisopropyl and *tert*-butyldimethyl siloxyacetals gave consistent elemental analyses and FAB mass spectra (see Experimental section).



(4)

Interestingly, photoreaction of the novel bi-functional acylsilane **9** with benzyl alcohol evidently led to the photoadduct **35** (eqn. 5) in which only the unsaturated side of the acylsilane functionality reacted with the OH-bond, leaving the unsaturated segment intact.

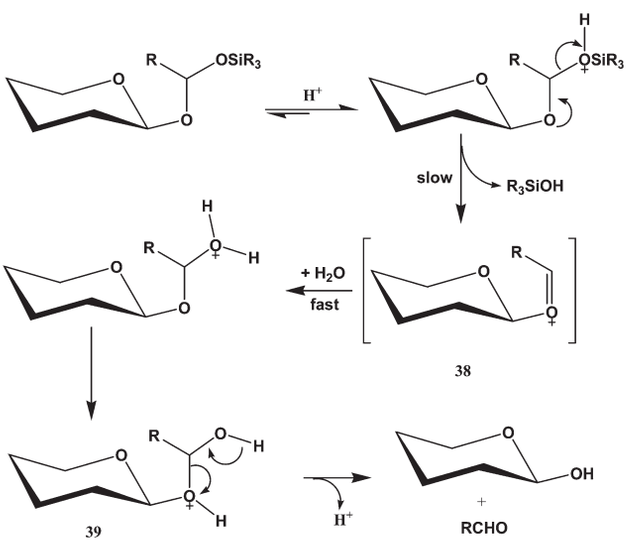


(5)

C. Hydrolysis studies

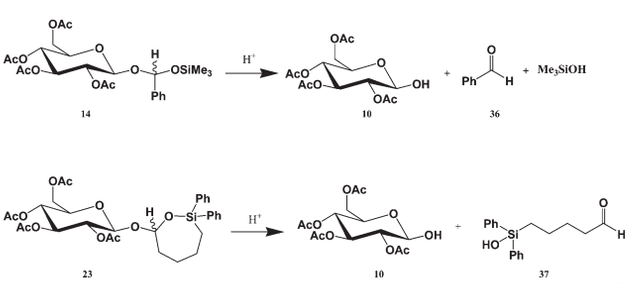
There is substantial evidence that the specific acid-catalyzed hydrolysis of acetals, ketals, and orthoesters proceeds by an A-1 mechanism.[51] The siloxyacetals are not an exception. The precedent for the studies of the rate of hydrolysis of mixed acetals of silanol, simple alcohols, and an aldehyde may be found in the earlier work of Brook *et al.*[31] For example, the kinetics of decomposition of $Ph_3SiOCHPh(OMe)$ siloxyacetal was determined at 0 °C and the plot of log of concentration *vs.* time was linear in accordance with the pseudo first-order kinetics required by the A-1 mechanism (Scheme 3). The first step is the equilibrium protonation of the siloxy-oxygen followed by rate-limiting loss of silanol (C–O bond cleavage) to give a resonance-stabilized oxocarbenium ion **38** which then suffers nucleophilic attack by water with the release of a sugar and an aldehyde *via* breakdown of the highly unstable hemiacetal

39. A second mode of decomposition is believed to involve a Si–O bond cleavage *via* nucleophilic attack on the silicon atom by water; in this case hemiacetal **39** is formed without the intermediacy of the oxocarbenium ion **38**.[31] In both cases, however, the observed pseudo first-order rate constant depends only on pH with no catalysis by undissociated acids.[51] The advantage of siloxyacetals over conventional acetals can be explained by the much higher basicity of the silicon-bound oxygen atom relative to carbon-bound oxygen.[28] This causes the protonation equilibrium to shift towards the protonated form of the acetal which in turn will effectively increase the rate of formation of the oxocarbenium ion **38**. The higher nucleophilicity of the siloxy oxygen atom is attributed to the large inductive effect due to low electronegativity of silicon (1.8) relative to carbon (2.5), and by the larger mass of silicon;[28] the same reason responsible for the unusual reactivity of α-silyl ketones compared to conventional ketones.



Scheme 3

We first investigated the products of acid-catalyzed degradation of acyclic siloxyacetal **14** and cyclic siloxyacetal **23**. Thus, the siloxyacetals were completely hydrolyzed in chloroform solution by addition of a catalytic amount of 1 M HCl. The hydrolysis was followed by TLC and was usually complete within a few minutes. The products of decomposition were separated by flash-column chromatography and identified by TLC, NMR and by comparing to the literature data. It was found that **14** decomposes with a release of glucopyranoside **10**, benzaldehyde, and trimethylsilanol, which under acidic conditions spontaneously dehydrates to yield siloxane $Me_3SiOSiMe_3$. Cyclic siloxyacetal **23** gave exclusively glucopyranoside **10** and a known 5-(diphenylhydroxysilyl) pentanal[52] **37** (eqn. 6).



(6)

The rate of hydrolysis of siloxyacetal **14** at different pHs was measured spectrophotometrically by following the absorbance increase due to the appearance of benzaldehyde at λ_{max} = 250 nm. McIlvaine buffers (phosphate–citrate) at pH 4.3, 6.2, 6.98 and 7.4, with constant ionic strength, were used in the studies.[53] The ionic molarity of all buffers was maintained constantly at 0.5 M with KCl. Stock solutions of the substrate **14** were prepared in acetonitrile. Kinetic runs were initiated by injecting the stock solution into a temperature equilibrated buffer directly into the UV cuvette to make the final concentration of the substrate 10^{-8} M. Fig. 2 shows the results of the kinetic runs at different pH values. The kinetic trace at pH 6.2 was fitted linearly in accordance with the first-order kinetics law to give the rate constant for the hydrolysis $k = 3.94 \times 10^{-2}$ min^{-1}, which corresponds to a half-life of only 17.5 minutes at ambient temperature. The acid lability of benzaldehyde acetals can be either increased or decreased by introducing electon-donating or electron-withdrawing substituents, respectively, in the *para* position of the phenyl ring. For example, the half-life of benzaldehyde acetals was reduced by as much as 200 times simply by reducing a *p*–NO_2 group to an amine.[22]

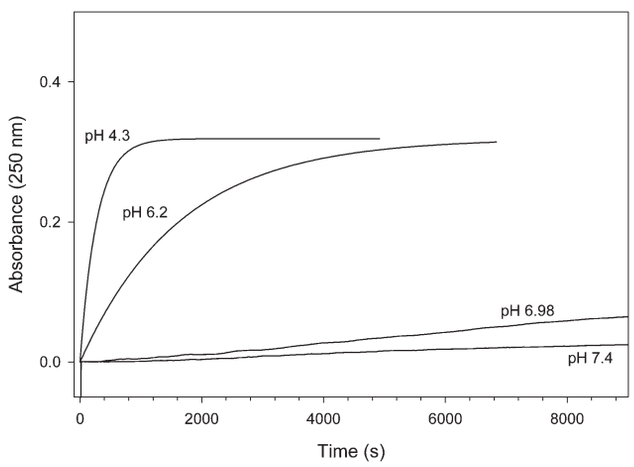


Fig. 2 Kinetics of acid-catalyzed hydrolysis of adduct **14** in McIlvaine buffer monitored by the appearance of benzaldehyde at λ_{max} = 250 nm.

D. Biological activity

In vitro anticancer evaluation of siloxyacetal glycosides **14** (NSC 725089), **23** (NSC 725091), **24** (NSC 725090), and **25** (NSC 725092) was performed in the NCI's three cell line prescreen assay against two standard drugs with well-documented activity, namely 5-fluorouracil (NSC 19893) and adriamycin (NSC 123127). The three cell lines were MCF-7 (breast cancer), NCI-H460 (lung cancer), and SF-268 (CNS tumor), and the tests were performed according to the protocol outlined in the Materials and Methods section.†

The results of the testing are shown in Table 1. It is evident that benzaldehyde-bearing siloxyacetal **14** was completely inactive against all tested cell lines. Among the cyclic acetals **23**–**25**, which bear masked lipophilic 5-(diphenylhydroxy)silyl pentanal **37**, on the other hand, only glucoside **23** appeared to be effective against the MCF-7 cell line (inhibiting cell growth to 31% relative to control) while galactoside **24** and lactoside **25** analogs had very little if any cytotoxic effect (see Table 1).

Since an accelerated rate of glucose transport is one of the most prominent biomarkers of many tumor tissues,[54] we assume that the relative efficiency of siloxyacetal **23** compared to **24** and **25** may be attributed to the preferential uptake of this compound by MCF-7 cells. The inactivity of **14** *versus* **23**, in turn, may be explained by low cytotoxicity of benzaldehyde *versus* lipophilic silyl-terminated pentanal **37**. The cyto- and genotoxic activity of aliphatic aldehydes is well documented.[55] For example, studies on cyto- and genotoxicity of *n*-alkanals have shown that these aldehydes are markedly toxic to human and rodent cells and that the toxicity increases with increasing chain length (lipophilicity).[56] Thus, hexanal and nonanal have been found to be extremely toxic but not mutagenic, while propanal, butanal, and pentanal, in addition to being toxic, were able to cause DNA mutations.[56] In contrast, to our knowledge, no studies exist on the antitumor activity of aromatic aldehydes since they are rarely observed in natural systems.

Table 1 Percent growth of cells treated with 100 μM solutions of the selected siloxyacetal glycosides relative to controls

Cell line	Compound (14)	(23)	(24)	(25)
NCI-H460	109[a]	88	98	93
MCF-7	91	31	80	82
SF-268	111	110	104	101

[a] Percent = growth treated/growth controls.

Conclusions

In summary, a series of highly acid-sensitive siloxyacetal glycosides have been synthesized *via* facile photochemical insertion of siloxycarbenes into the OH-bond of a variety of carbohydrates. Although siloxyacetals of simple alcohols have been prepared before, their low stability without added base prevented them from being useful synthetic intermediates. In contrast, siloxyacetal glycosides reported in this study, especially those having 1,1′-diacetal structure, proved to be exceptionally stable and could be stored indefinitely without added base. These physical properties may potentially lead to their use as orthogonal protecting groups in oligosaccharide synthesis. In addition, it was shown that one glucose derivative had moderate activity against the MCF-7 breast cancer cell line. At the same time, similar lactose and galactose derivatives were completely inactive. Further extension of this study to include more cytotoxic aldehydes may provide a novel potent class of anti-cancer agents that function by pH difference.

Experimental

General procedure for the synthesis of siloxyacetal glycosides 14–19, 23–27, 29, 31, 33

All photoreactions were carried out in the Rayonet Photochemical Chamber Reactor Model RPR-100 equipped with RPR-3500A lamps (λ_{max} = 350 nm) under argon atmosphere in anhydrous benzene at ambient temperature. The progress of the reactions was monitored by TLC (thin layer chromatography), IR (disappearance of the OH-bond in excess of acylsilanes), and visually (disappearance of bright yellow acylsilanes in excess of peracetylated free glycosides).

General procedure for deacetylation of triisopropyl- and *tert*-butyldimethylsilyl acetals 27, 29, 31, 33

A solution of 0.17 mmol of a siloxyacetal in 5–10 ml of anhydrous MeOH (Aldrich) was treated with 2–3 drops of 25% v/v NaOMe–MeOH (Aldrich). After 30 min the reaction was carefully neutralized with weakly acidic ion-exchange resin (Amberlite® IRC-50), filtered, evaporated and separated by FCC (flash column chromatography) with 10% MeOH in CH_2Cl_2.

2-Phenyl-2-triisopropylsilyl-1,3-dithiane 2a

A solution of 2 g (10.2 mmol) of 2-phenyl-1,3-dithiane (PDT) in 16 ml THF was cooled to 0 °C. A solution of 1.6 M *n*-BuLi in hexanes (9.5 ml, 15.2 mmol, 1.5 equiv.) was added dropwise to the solution of PDT. After 10 min, 3.12 g (10.2 mmol) of TIPSOTf was added at once. After stirring for 30 min at 0 °C, the reaction was slowly warmed to ambient temperature. After an additional 30 min the reaction was carefully quenched with sat. NH_4Cl, diluted with EtOAc, washed 2 times with water and dried over $MgSO_4$. After evaporation, the residue was separated by FCC with 50 : 1 to 40 : 1 hexanes–EtOAc to give 2.5 g (70%) of crystalline product. R_f 0.8 (4 : 1 hexanes–EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02–8.06 (m, 2H, Ph), 7.31–7.37 (m, 2H, Ph), 7.12–7.17 (m, 1H, Ph), 1.80–2.80 (m, 6H, $S(CH_2)_3S$), 1.25–1.38 (m, 3H, $Si(CHMe_2)_3$), 1.10 (d, 18H, J = 7.42 Hz, $Si(CHMe_2)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.4, 130.7, 128.2, 125.3, 49.9, 25.4, 25.3, 19.7, 12.0; FAB MS *m*/*z* 309 ($MH^+ - C_3H_8$), 352.1 (M^+), MW 352.7. Anal: calcd for $C_{19}H_{32}S_2Si$: C, 64.71; H, 9.15; found: C 64.87; H 9.25%.

2-Phenyl-2-*tert*-butyldimethylsilyl-1,3-dithiane 2b[42]

Compound **2b** was prepared similarly to compound **2a** in 92% yield.

Benzoyltriisopropylsilane 3[58]

A solution of 2.5 g (7.08 mmol) of **2a** in 40 ml of acetone was treated with 11 g (39.15 mmol) of chloramine-T in 80 ml of 80 : 20 MeOH–H_2O. The reaction solution immediately turned fluorescent yellow. After 15 min, 20 ml of 10% NaCl was added followed by 20 ml of 0.5 M $NaHCO_3$. The product was extracted with hexanes until no yellow color remained in the aqueous phase. The hexane extracts were evaporated and purified by FCC to give 1.45 g (78%) of acylsilane **3** as a bright yellow liquid.

Benzoyl-*tert*-butyldimethylsilane 4[42]

Compound **4** was prepared from **2b** according to the preparation of **3** above in 73% yield.

1,5-Bis-(*tert*-butyldimethylsilyl)-2-methylene-pentane-1,5-dione 9

A solution of 220 mg (1.29 mmol) of *tert*-butyldimethylsilylallenyl ether[48] in 4 ml of THF was slowly treated with 0.7 ml (1.15 mmol) of 1.7 M solution of *tert*-butyllithium in pentane at −78 °C. The solution became light yellow. After 40 minutes, the reaction was warmed to room temperature and quenched with a solution of 1.25 ml 1 M H_2SO_4 in 10 ml THF. The reaction was diluted with 1 : 1 hexane–diethyl ether, washed with water and brine and dried over $MgSO_4$. Evaporation of the solvents followed by FCC with 15 : 1 hexanes–diethyl ether afforded 160 mg (73%) of **9** as a bright yellow viscous liquid. R_f 0.5 (10 : 1 hexanes–diethyl ether); IR (neat) 1752, 1642 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.89 (s, 1H, $C=CH_2$), 5.79 (s, 1H, $C=CH_2$), 2.52 (m, 2H, $-CH_2-$), 2.23 (m, 2H, $-CH_2-$), 0.750 (s, 9H, *t*-Bu), 0.747 (s, 9H, *t*-Bu), 0.09 (s, 6H, $SiMe_2$), 0.0 (s, 6H, $SiMe_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 250.5 ($TBDMSC(O)CH_2$), 241.2 ($TBDMSC(O)C=CH_2$), 154.6 ($C=CH_2$), 129.6 ($C=CH_2$), 49.0, 26.9, 26.6, 22.6, 16.9, 16.7, −4.3, −6.8. FAB MS *m*/*z* (relative intensity) 341.2 (MH^+), MW 340.7. Anal: calcd for $C_{18}H_{36}O_2Si_2$: C, 63.47; H, 10.65; found: C 63.70; H 10.63%.

Photoreaction of acylsilane 9 with benzyl alcohol. 35

To a solution of 25 mg (0.07 mmol) of **9** in 5 ml of anhydrous benzene was added 50 mg (0.40 mmol, 5.7 equiv.) of anhydrous benzyl alcohol followed by 1 drop of pyridine for stabilization purposes. The solution was purged with argon for 20 min, sealed and placed in a photoreactor. In *ca.* 10–20 min the reaction was complete. Separation of the products on silica gel with 10 : 1 hexanes–diethyl ether gave 20 mg (64%) of **35** as a clear oil. R_f 0.60 (5 : 1 hexanes–diethyl ether); IR (neat) 2930, 2858, 1752 (TBDMSC=O), 1691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.17–7.32 (m, 5H, Ph), 5.11 (s, 1H, acetal CH), 5.07 (s, 1H, $=CH_2$), 4.85 (s, 1H, $=CH_2$), 4.43 (ABq, 2H, J = 11.71 Hz, $PhCH_2O$), 2.78 (m, 2H, $CH_2C=O$), 2.30 (m, 2H, $CH_2=CCH_2-$), 0.8–0.9 (m, 18H, 2 × $SiCMe_3$), 0.0–0.1 (m, 12H, 2 × $SiMe_2$). Anal: calcd for $C_{25}H_{44}O_3Si_2$: C, 66.91; H, 9.88; found: C 66.70; H 9.82%.

1-(Trimethylsiloxy-phenyl-methoxy)-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside 14

A 1 : 1 mixture of two diastereomers at the acetal center (designated arbitrarily as *R*(*S*) and *S*(*R*)). Yield 70%. R_f 0.5

(*tert*-butylmethyl ether–petroleum ether). White crystals‡, mp 95–97 °C; IR (neat) 1040, 1222, 1367, 1756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.41–7.30 (m, 5H, aromatic), 6.05 (s, 1H, PhCH (*S*(*R*)epimer), 5.93 (s, 1H, PhCH (*R*(*S*)-epimer)), 4.91 (d, 0.5H, H-1 (*S*(*R*)) epimer), 4.56 (d, 1H, H-1 (*R*(*S*)) epimer), 4.25–4.06 (m, 2H, H-6), 3.72 (ddd, 0.5H, H-5 (*S*(*R*)) epimer), 3.58 (ddd, 1.1H, H-5 (*R*(*S*)) epimer), 2.08, 2.07, 2.03, 2.01, 2.00, 1.98, 1.90 (s, 12H, $CH_3C(O)$), 0.17 (s, 1H, $SiMe_3$), 0.11 (s, 1H, $SiMe_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.4 ($CH_3C(O)$, (*S*(*R*))), 170.3 ($CH_3C(O)$, (*R*(*S*))), 170.1 ($CH_3C(O)$, (*S*(*R*))), 170.0 ($CH_3C(O)$, (*R*(*S*))), 169.2 ($CH_3C(O)$, (*S*(*R*))), 169.1 ($CH_3C(O)$, (*R*(*S*))), 169.0 ($CH_3C(O)$, (*S*(*R*))), 168.8 ($CH_3C(O)$, (*R*(*S*))), 139.9 (C-1, Ph, (*S*(*R*))), 139.8 (C-1, Ph, (*R*(*S*)), 128.6 (C-4, Ph, (*R*(*S*))), 128.4 (Ph, (*S*(*R*))), 128.0 (C-3,5, Ph, (*R*(*S*))), 127.9 (Ph, (*S*(*R*))), 126.0 (C-2,6, Ph, (*R*(*S*))), 97.8, 97.1, 94.8, 93.9, 72.8, 72.6, 71.7, 71.5, 71.1, 70.8, 68.3, 68.2, 61.8 (C-6, *S*(*R*)), 61.8 (C-6, *R*(*S*)), 20.5, 20.4, 20.32, 20.3, 20.28, ($CH_3C(O)$), 0.02 ($SiMe_3$, (*S*(*R*)), 0.00 ($SiMe_3$, (*R*(*S*))). Anal: calcd for $C_{24}H_{34}O_{11}Si$ C, 54.74; H, 6.51; found: C, 54.81; H 6.51%.

4-(Trimethylsiloxy-phenyl-methoxy)-1,2,3,6-tetra-*O*-acetyl-α-D-glucopyranoside 17

A 1 : 1 mixture of two diastereomers at the acetal center. Clear oil. Yield 60%. R_f 0.2 (1 : 1 benzene–EtOAc); IR (neat) 1751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.33 (m, 5H, Ph), 6.22 (m, 1H, H-1), 5.68, 5.49 (s, 2 × 0.5H, PhC*H*), 5.44–5.54 (m, 1H, H-4), 4.95–5.03 (m, 1H, H-3), 3.77–4.62 (m, 4H, H-2, H5, H-6ab), 1.94–2.10 (s, 12H, Ac), 0.02, 0.01 (s, 9H, $SiMe_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 170.4, 170.1, 170.0, 169.9, 169.4, 168.9, 168.9, 140.5, 140.3, 129.0, 129.0, 128.5, 128.4, 128.4, 126.0, 125.9, 125.8, 125.8, 98.6, 98.2, 89.2, 89.1, 72.1, 72.0, 71.7, 71.1, 71.0, 69.9, 69.7, 69.4, 62.8, 61.7, 21.2, 20.9, 20.9, 20.8, 20.8, 20.5, 20.5, 14.1, 0.2, 0.04, 0.00. Anal: calcd for $C_{24}H_{34}O_{11}Si$: C, 54.74; H, 6.51; found: C, 54.88; H 6.51%.

2-(Trimethylsiloxy-phenyl-methoxy)-1,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside 19

A 1 : 1 mixture of two diasteromers at the acetal center (arbitrarily designated as *R*(*S*) and *S*(*R*)). Glassy solid. Yield 63%. R_f 0.35 (1 : 1 hexanes–ethyl acetate + 0.6% Et_3N); IR (neat) 1034, 1216, 1368, 1743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.43–7.48 (m, 2H, aromatic), 7.29–7.37 (m, 3H, aromatic), 2.19, 2.12, 2.11, 2.04, 2.04, 2.03, 2.02, 1.99 (s, 12H, AcO), 5.91 (*R*(*S*)), 5.89 (*S*(*R*)) (s, 1H, PhCH), 5.78 (*S*(*R*)), 5.74 (*R*(*S*)) (d, 1H, H-1), 5.37, 5.34 (t, 1H, *J* = 9.51 Hz, H-4), 5.0 (dd, 1H, *J* = 3.03, 9.73 Hz, H-3(*R*(*S*))), 4.90 (dd, 1H, *J* = 3.34, 9.75 Hz, H-3(*S*(*R*))), 4.34 (dd, 1H, *J* = 1.17, 3.27 Hz, H-2), 4.23 (d, 1H, H-6a), 4.18 (d, 1H, *J* = 5.32, H-6b), 3.72–3.78 (m, 1H, H-5), 0.16 (*R*(*S*)), 0.09(*S*(*R*)) (s, 9H, $SiMe_3$), ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.6, 170.2, 169.7, 169.3, 169.3, 168.6, 168.4 ($C(O)CH_3$), 140.6, 140.2, 129.6, 128.9, 128.7, 128.5, 128.0, 127.9, 126.5, 126.4, 98.1, 97.8 (PhCH), 92.4, 92.0 (2′C), 73.1, 73.0, 72.1, 69.4, 69.2, 65.8, 65.5 (sugar CH′s), 62.2 (6′C), 21.0, 20.9, 20.8, 20.6, 20.57, 20.55, 20.53 ($C(O)CH_3$), 0.16, 0.00 ($SiMe_3$). Anal: calcd for $C_{24}H_{34}O_{11}Si$ C, 54.74; H, 6.51; found: C, 54.90; H 6.53%.

1-(*tert*-Butyldimethylsiloxy-phenyl-methoxy)-2,3,4,6-tetra-*O*-acetyl-α,β-D-glucopyranoside 27

A mixture of four diastereomers at the anomeric and acetal centers (NMR of β-anomer given). Clear oil. Yield 78%. R_f 0.45 (2 : 1 hexanes–ethyl acetate + 0.3% NEt_3); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.46 (m, 5H, Ph), 5.00–5.20 (m, 3H, H-2, H-3, H-4), 4.61 (d, 1H, *J* = 7.81 Hz, βH-1), 4.08–4.15 (m, 2H, H-6), 2.12, 2.04, 2.02, 1.94 (s, 4 × 3H, Ac), 0.93 (s, 9H, Si(*tert*-Bu)), 0.19, 0.14 (s, 2 × 3H, $SiMe_2$). ^{13}C NMR data (100 MHz, $CDCl_3$) δ = 175.72, 175.40, 174.47, 174.20, 145.35, 133.92, 133,86, 133.28, 131.44, 131.33, 103.13, 101.99, 100.09, 99.68, 78.08, 76.82, 76.39, 73.64, 67.07, 30.78, 25.82, 25.70, 25.65, 23.18, 0.79, 0.00. FAB MS *m*/*z* 607.3 (MK^+), MW 568.7. Anal: calcd for $C_{27}H_{40}O_{11}Si$ C, 57.02; H, 7.09; found: C, 57.23; H 7.14%.

1-(*tert*-Butyldimethylsiloxy-phenyl-methoxy)-α,β-D-glucopyranoside 28

A mixture of four diastereomers at the anomeric and acetal centers. Glassy solid. Yield 95%. R_f 0.32 (10% MeOH in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.30–7.54 (m, 5H, Ph), 6.04 (s, 0.3H, PhCH), 6.00 (s, 0.2H, PhCH), 5.93 (s, 0.2H, PhCH), 5.88 (s, 0.3H, PhCH), 2.8–5.4 (11H, sugar ring protons), 0.86 (9H, Si(*tert*-Bu)), 0.00–0.19 (6H, $SiMe_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.8, 145.7, 145.5, 133.7, 133.3, 133.2, 131.5, 131.4, 131.3, 131.2, 105.1, 103.5, 102.4, 102.3, 100.2, 99.5, 81.3, 80.6, 79.2, 78.3, 77.9, 77.0, 76.8, 76.6, 76.5, 74.1, 66.3, 30.7, 23.1, 0.6, 0.6, 0.30, 0.27, 0.2, 0.00. FAB MS *m*/*z* 439.3 ($M + K^+$), MW 400.5. Anal: calcd for $C_{19}H_{32}O_7Si$: C, 56.97; H, 8.05; found: C 56.34; H 7.95%.

1-(2,2-Diphenyl-1-oxa-2-silacyclohept-7-yl)-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside 23

Two diastereomers at the acetal center (arbitrarily assigned as *R*(*S*) and *S*(*R*)). Glassy solid. Yield 90%. R_f 0.38 (*R*(*S*) epimer), 0.33 (*S*(*R*) epimer) (2 : 1 hexanes–ethyl acetate + 1% Et_3N); IR (neat) 1748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.57–7.67 (m, 4H, aromatic), 7.31–7.43 (m, 6H, aromatic), 5.16 (t, 1H, *J* = 9.55 Hz, acetal H), 4.77 (d, 1H, *J* = 7.88 Hz, β-1′H), 2.01, 2.00, 1.99, 1.86 (s, 12H, Ac); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.7, 170.3, 169.4, 169.2, 136.0, 135.6, 134.3, 134.2, 134.1, 134.04, 129.9, 129.8, 128.1, 128.0, 127.9, 127.8, 101.3, 99.0, 72.9, 72.0, 71.6, 68.3, 62.1, 37.6, 25.4, 23.1, 20.8, 20.63, 20.6, 20.5, 14.5. FAB MS *m*/*z* 615.3 (MH^+), MW 614.7. Anal: calcd for $C_{31}H_{38}O_{11}Si$: C, 60.57; H, 6.23; found: C 60.60; H 6.27%.

2-(2,2-Diphenyl-1-oxa-2-silacyclohept-7-yl)-1,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside 26

A 3 : 2 mixture of two diastereomers at the acetal center. Glassy solid. Yield 86%. R_f 0.55 (1 : 1 hexanes–ethyl acetate); IR (neat) 1033, 1052, 1216, 1368, 1747, 2937 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.74–7.68 (m, 1H, aromatic), 7.68–7.62 (m, 1H, aromatic), 7.58–7.51 (m, 2H, aromatic), 7.43–7.30 (m, 6H, aromatic), 5.77 (d, *J* = 1.39 Hz, 0.6H (*R*(*S*)), H-1), 5.76 (d, *J* = 0.76 Hz, 0.4H (SI), H-1), 5.40 (t, *J* = 9.72 Hz, 0.4H (SI), H-4), 5.30 (t, *J* = 9.33 Hz, 0.6H (*R*(*S*)), H-4), 5.23 (dd, *J* = 7.63, 1.35 Hz, 0.4H, acetal H(SI)), 5.19 (dd, *J* = 6.55, 1.73 Hz, 0.6H, acetal H (*R*(*S*))), 5.12 (dd, *J* = 9.48, 2.93 Hz, 0.6H, H-3 (*R*(*S*)), 4.93 (dd, *J* = 9.96, 3.32 Hz, 0.4H, H-3 (SI)), 4.42 (d, *J* = 2.93 Hz, 0.4H, H-2(SI)), 4.37 (q, *J* = 1.37 Hz, 0.6H, H-2(*R*(*S*))), 4.3–4.11 (m, 2H, H-6), 3.75 (m, 1H, H-5), 2.07, 2.03, 2.02, 1.94 (s, 12H, $CH_3C(O)$), 1.73, 1.58, 1.54, 2.1–1.18 (m, 8H, aliphatic ring); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.9, 170.7, 169.8, 169.7, 169.4, 168.6, 136.3, 136.2, 136.1, 136.0, 134.5, 134.4, 134.3, 134.2, 130.1, 130.09, 130.0, 129.97, 128.5, 128.2, 128.14, 128.11, 128.0, 101.2, 100.5, 92.4, 92.0, 73.5, 73.4, 72.7, 72.0, 71.3, 70.8, 66.6, 65.8, 62.7, 62.6, 37.72, 37.65, 25.9, 25.8, 23.6, 23.5, 21.0, 20.96, 20.9, 20.8, 20.6, 15.2, 15.0. FAB MS *m*/*z* 615.3 (MH^+); MW 614.7. Anal: calcd for $C_{31}H_{38}O_{11}Si$: C, 60.57; H, 6.23; found: C 60.32; H 6.21%.

In vitro biological activity studies

Siloxyacetals were solubilized in dimethyl sulfoxide and stored frozen. Compounds were then diluted with complete media with 0.1% gentamicin, and 20 µl of this solution was dispensed into test wells containing 50 µl of cell suspension to yield a test concentration of 100 µM. After compound addition, plates were in-

‡ CCDC reference number 246339. See http://www.rsc.org/suppdata/ob/b4/b405786d for crystallographic data in .cif or other electronic format.

cubated at standard conditions for 48 hours. Following this, 10 µl per well Alamar Blue was added and the plates were incubated for an additional 4 hours. Fluorescence was measured using an excitation wavelength of 530 nm and an emission wavelength of 590 nm. Percent test cell (PTC) growth/control (untreated) cell growth (T/C) was calculated on a plate-by-plate basis for test wells relative to control wells. Percent growth is expressed as the ratio of fluorescence of the test well to the average fluorescence of the control wells.[57]

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