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Acetal formation by solvolysis of glucal-derived donor–acceptor cyclopropanes

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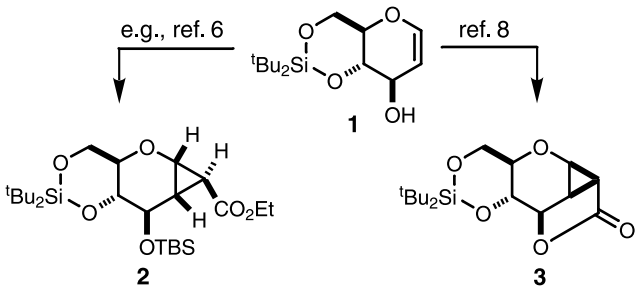
Abstract—The conversion of glucal derived donor–acceptor cyclopropanes to acetals by $TiCl_4$ mediated ring opening and alcohol trapping is described. Good selectivity for the alpha anomer and yields near 90% are consistently observed with aliphatic, benzylic and allylic alcohols, phenols and thiophenols. The utility of this method to prepare oligosaccharides through intermediate *O*,*S*-acetals is illustrated.

1. Introduction

Donor acceptor cyclopropanes are classic synthetic intermediates,[1] and there is great interest in carbohydrate derived cyclopropanes as enzyme inhibitors and as strategic precursors to important C(2) branched sugars.[2,3] Intermolecular glycal cyclopropanations with ethyl diazoacetate have been known for some time (e.g. **1** to **2**, Scheme 1),[4–6] but forcing conditions were required to activate this class of cyclopropanes,[5] and accordingly, their chemistry has remained comparatively underdeveloped.[7] Recently, we demonstrated the first intramolecular glycal cyclopropanation, (e.g. **1** to **3**),[8] with the expectation that the increased ring strain in the resultant cyclopropanes would be sufficiently destabilizing as to engender synthetically useful reactivity.



Scheme 1.

In this paper we report the synthesis of acetals by a $TiCl_4$ mediated ring opening and subsequent solvolysis of glucal-derived cyclopropanes. Alcohols are known to react with various kinds of functionalized cyclopropanes under neutral,[9] photochemical,[10] electrochemical,[11] mercuration,[12] acidic,[13] copper[14] or palladium catalyzed,[15] electrophilic halogenation,[16,17] and miscellaneous conditions.[18] However, of these solvolysis reactions, few of the cyclopropanes were dihydropyran-derived, and a scant number of these were prepared from carbohydrates.[6,15–17,18e] It has been reported that closely related cyclopropanes preferentially undergo ring expansion to seven-membered oxacycles when treated with strong electrophiles, but this mode of ring opening was not observed with cyclopropane **3**.[7]

2. Results and discussion

A variety of Lewis acids were screened for activating the cyclopropane, and $TiCl_4$ appeared to be ideal. When the cyclopropane **3** was treated with 1.6 equiv. of $TiCl_4$, it cleanly converted to a more polar species (as monitored by TLC) that was stable for several hours in the absence of nucleophiles. The stability of the intermediate implicates a chloropyran such as **4** as the likely species (Scheme 2). A subsequent aqueous workup afforded the hemi-acetal **5** in 90% yield. Other Lewis acids that were less effective for the cyclopropane ring opening included: $Ti(OiPr)_4$, $Cl_2Ti(OiPr)_2$, $SnCl_4$, $Sc(OTf)_3$, $ZrCl_4$, $Zr(OTf)_4$ or Et_2AlCl. Treatment of **3** with excess $BF_3{\cdot}OEt_2$ lead to efficient cleavage of the primary silicon oxygen bond to afford **6**,[19] whereas reaction with Me_3SiOTf resulted in the formation of anhydro-sugar **7** after workup with saturated aqueous $NaHCO_3$.[17a]

After activation of cyclopropane **3** with $TiCl_4$ excess methanol was added to access acetal **8a** (Table 1), but low conversion and decomposition plagued this transformation.

Keywords: cyclopropanes; enzyme inhibitors; solvolysis.

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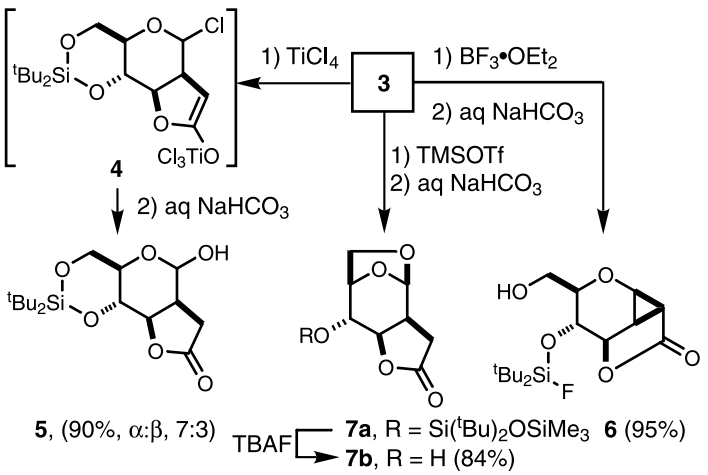
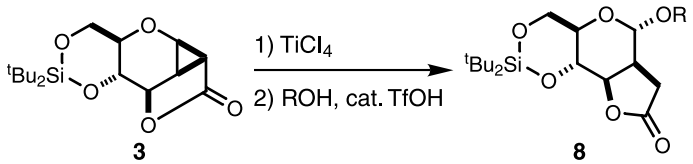


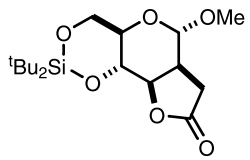
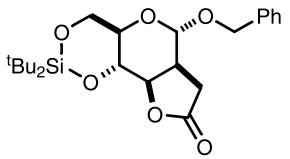
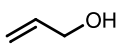
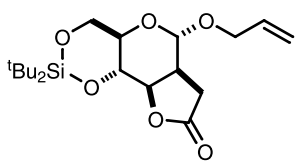
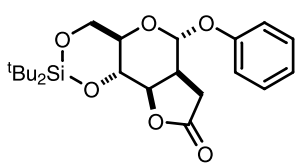
Scheme 2.

Mercury or silver salts are added to promote reactivity in the Köenigs–Knoor glycosidation reaction, but both of these additives are less than ideal. In this regard, it was discovered that the addition of a catalytic amount of strong Brønsted acid, such as trifluoromethanesulfonic acid, resulted in clean solvolysis. Under these conditions, a 6:1 mixture of α and β acetals **8a** was obtained from the reaction with methanol (91%, Table 1, entry a). The selectivity improved slightly to 8:1 with use of benzyl alcohol (entry b), and remarkably, 15:1 selectivity was observed in the addition of allyl alcohol (entry c). Phenols worked equally well as glycosyl acceptors (entry d), and from the reaction with **3** the acetal **8d** was obtained in 87% yield as a 12:1 mixture of diastereomers.

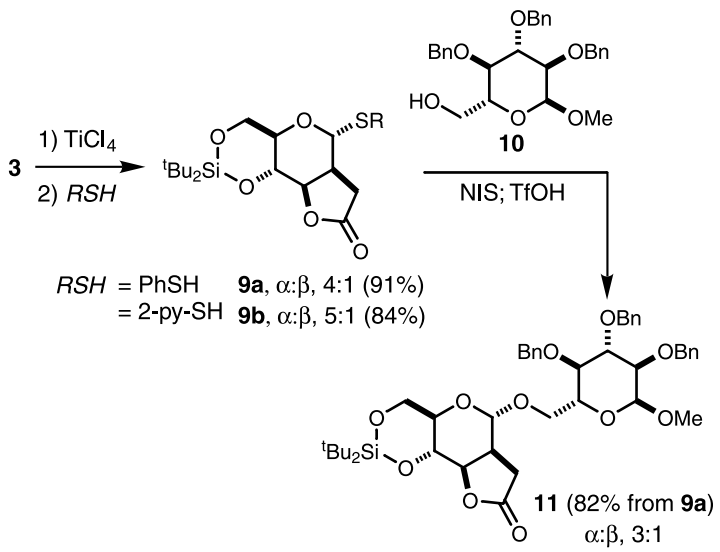
A major disincentive for employing the acetal synthesis as outlined above directly for preparing oligosaccharides is the

Table 1. Acetal formation from cyclopropane **3**



Entry	Alcohol	Product	Ratio α/β	Yield[a] (%)
A	MeOH		6:1	91
B	BnOH		8:1	84
C			15:1	89
D	PhOH		12:1	87

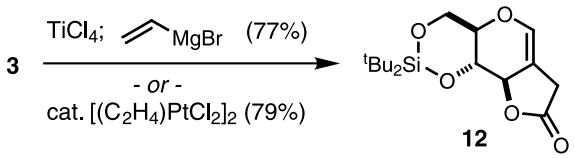
[a] Isolated yield.



Scheme 3.

requirement for excess alcohol to satisfy the electrophilic titanium chloride. However, practical glycosylation can be achieved by a two-step sequence that proceeds through traditional 2-sulfanyl pyran intermediates such as **9** (Scheme 3). The *S*,*O*-acetals **9** were prepared by $TiCl_4$ activation of **3** followed by thiol trapping.[20–22] To illustrate the glycosylation procedure, treatment of **9a** with 2,3,4-tribenzyl methyl pyranoside **10** in the presence of *N*-iodosuccinamide and trifluoromethanesulfonic acid gave the disaccharide **11** (82%) as a 3:1 mixture of diastereomers.[23]

At its present stage of development, the addition of more basic nucleophiles, such as vinyl or alkynyl Grignard reagents, to cyclopropane **3** activated with $TiCl_4$ caused predominately elimination (Scheme 4). The glycal **12** can be prepared more conveniently by a Zeise's dimer catalyzed rearrangement.[15,24]



Scheme 4.

In summary, new and efficient $TiCl_4$ mediated ring opening reactions of glucal-derived donor–acceptor cyclopropanes **3** have been developed for accessing C(2) branched *O*-glycosides **8** and glycals **12**. Glycosidic coupling reactions were achieved through a stepwise process involving intermediate mixed *S*,*O*-acetals **9**. The intramolecular cyclopropanation strategy[8] has proven essential for developing the efficient functionalization chemistry of the glucal-derived cyclopropyl lactones.

3. Experimental

3.1. General

All reactions were run under an atmosphere of argon unless otherwise indicated. Flasks were oven or flamed-dried and allowed to cool in dry box or desiccator prior to use. Solvents and reagents were purified by standard methods.[25]

Thin-layer chromatography (TLC) was performed on EM 250 Kieselgel 60 F254 silica gel plates. The plates were visualized by staining with I_2 on silica, CAM,[26] ninhydrin, or potassium permanganate. Column chromatography was performed with silica gel 60 according to the method of Still.[27]

The ^1H, ^{13}C, ^{31}F NMR data was obtained on a Varian Unity Plus 300 or 400 spectrometer, or a Varian INOVA 500. For ^1H NMR, chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and are, in all cases, referenced to the residual proton resonance peaks: δ 7.24 for $CHCl_3$, δ 2.49 (hept) for DMSO-d_6. The ^{13}C NMR chemical shifts were reported in ppm relative to the center peak of the multiplet for deuterated solvents: δ 77.0 (t) for $CDCl_3$, 39.5 (p) for DMSO-d_6. ^{13}C spectra were routinely acquired with broadband ^1H decoupling. Coupling constants for all spectra are reported in Hertz (Hz). Infrared spectra were measured on a NEXUS 470 FT-IR spectrometer as thin films on sodium bromide plates and are recorded in units of cm^{-1}. HRMS (CI) were made with a VG analytical ZAB2-E instrument.

3.1.1. 8,8-Di-*tert*-butyl-4-hydroxy-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*] naphthalene-2-one (5). To a solution of cyclopropane **3** (250 mg, 0.77 mmol) in Et_2O (13 mL) at rt was added $TiCl_4$ (138 μL, 1.27 mmol, 1.7 equiv.). The mixture was stirred at rt for 2.5–3.0 h until TLC indicated complete consumption of starting material. The dark brown solution was then quickly poured into saturated aqueous $NaHCO_3$ (5 mL). After stirring for 20 min the organic layer was separated and the aqueous layer was extracted with Et_2O (2×8 mL). The combined organic solution was washed with H_2O (2×8 mL), brine (6 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Flash chromatography on silica gel with 5:1 hexanes–EtOAc for elution afforded the title compound as

an inseparable mixture of diastereomers (colorless oil, 237 mg, 90%). R_f 0.51 (50% EtOAc/hexanes); IR (thin film) ν 3600–3250, 1763, 1709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.26 (d, J=3.0 Hz, 1H), 5.17 (dd, J=3.8, 3.8 Hz, 0.44H), 4.64 (dd, J=7.8, 7.8 Hz, 1H), 4.53 (dd, J=7.7, 7.7 Hz, 0.44H), 4.16 (dd, J=10.2, 4.8 Hz, 0.44H), 4.15–4.09 (m, 2H), 4.07 (d, J=3.1 Hz, 0.44H), 4.01 (dd, J=9.9, 4.8 Hz, 1H), 3.89–3.86 (m, 0.44H), 3.73 (d, J=4.1 Hz, 0.44H), 3.44 (ddd, J=10.2, 10.2, 5.1 Hz, 0.44H), 3.24 (d, J=3.1 Hz, 1H), 3.01 (m, 1H), 2.96 (dd, J=21.9, 8.5 Hz, 1H), 2.67–2.61 (m, 0.88H), 2.60–2.50 (m, 2H), 1.82 (s, 1H), 1.05 (s, 13.0H), 1.01 (s, 13.0H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3 (minor), 174.5, 93.1 (minor), 91.8, 82.2 (minor), 80.8, 75.7, 75.5 (minor), 69.3 (minor), 66.5 (minor), 66.4, 64.0, 41.4, 40.7 (minor), 31.3, 28.9 (minor), 27.7, 26.7 (minor), 27.3, 23.1, 20.3; HRMS m/z calcd for $C_{16}H_{29}O_6Si$ $[M+H]^+$ 345.1733, found: 345.1736.

3.1.2. 7-(Di-*tert*-butyl-trimethylsilyoxy)silyoxy-5,10,11-trioxa-tricyclo[6.2.1.0^{2,6}]undecan-one (7a). To a solution of cyclopropane **3** (450 mg, 1.4 mmol) in CH_2Cl_2 (10 mL) at rt was added trimethylsilyl trifluoromethanesulfonate (TMSOTf) (400 μL, 2.1 mmol, 1.5 equiv.). After stirring at rt for 10 h saturated aqueous $NaHCO_3$ (5 mL) was added to the reaction solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×8 mL). The combined organic layer was washed with H_2O (2×8 mL), brine (3 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Purification of the residual oil by flash chromatography on silica gel with 20:1 hexanes–EtOAc for elution afforded the title compound as a colorless syrup (515 mg, 90%). R_f 0.65 (33% EtOAc/hexanes); IR (thin film) ν 1790 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.41 (s, 1H), 4.57 (dd, J=5.8, 1.3 Hz, 1H), 4.41 (ddd, J=4.8, 1.3, 1.3 Hz, 1H), 4.07 (s, 1H), 3.87 (dd, J=7.5, 1.3 Hz, 1H), 3.68 (dd, J=7.5, 5.8 Hz, 1H), 2.68 (ddd, J=8.5, 6.0, 2.5 Hz, 1H), 2.62 (dd, J=17.0, 8.5 Hz, 1H), 2.45 (d, J=17.0 Hz, 1H), 1.00 (s, 9H), 0.97 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 100.7, 79.3, 76.2, 67.5, 64.2, 36.3, 31.2, 27.4, 27.3, 20.6, 20.4, 2.1; HRMS m/z calcd for $C_{19}H_{37}O_6Si_2$ $[M+H]^+$ 417.2129, found: 417.2141.

3.1.3. 7-Hydroxy-5,10,11-trioxa-tricyclo[6.2.1.0^{2,6}]-undecan-one (7b). To a solution of **7a** (380 mg, 0.91 mmol) in THF (8 mL) at 0°C was added Bu^4NF (4.0 mL×1 M, 4.0 mmol, 4.5 equiv.). After stirring at rt for 3 h additional THF (10 mL) was added in to the reaction mixture and the resulting solution was washed with saturated aqueous $NaHCO_3$ (2×5 mL), H_2O (2×8 mL), brine (3 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Purification of the residual oil by flash chromatography on silica gel with 3:1 hexanes–EtOAc for elution afforded the title compound as colorless oil (142 mg, 84%). R_f 0.32 (50% EtOAc/hexanes); IR (thin film) ν 3650–3250, 1779, 1760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.40 (s, 1H), 4.61 (ddd, J=4.4, 1.5, 1.5 Hz, 1H), 4.46–4.44 (m, 1H), 3.96 (dd, J=8.0, 1.2 Hz, 2H), 3.75 (dd, J=8.0, 6.0 Hz, 1H), 2.68–2.56 (m, 2H), 2.49–2.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 101.0, 78.3, 75.6, 66.5, 64.4, 36.2, 31.2; HRMS m/z calcd for $C_8H_{11}O_5$ $[M+H]^+$ 187.0606, found: 187.0607.

3.1.4. 8,8-Di-*tert*-butyl-4-methoxy-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*] naphthalene-2-one (8a)(α). To a solution of cyclopropane **3** (199 mg, 0.61 mmol) in Et_2O (10 mL) at rt was added $TiCl_4$ (108 μL, 1.7 equiv.). The mixture was stirred at rt for 2.5–3.0 h until TLC indicated complete consumption of starting material. To the resulting dark brown solution was then added MeOH (250 μL, 6.1 mmol, 10 equiv.) immediately followed by triflic acid (100 μL×3 M in Et_2O, 0.5 equiv.). The resulting mixture was stirred for 30 min and then poured into saturated aqueous $NaHCO_3$ (10 mL). After stirring for 10 min the organic layer was separated and the aqueous layer was extracted with Et_2O (2×8 mL). The combined organic solution was washed with H_2O (2×8 mL), brine (6 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Purification of the residue by flash chromatography on silica gel with 4:1 hexanes–EtOAc for elution gave the title compound as a colorless oil (173 mg, 78%). R_f 0.71 (50% EtOAc/hexanes); IR (thin film) ν 1783, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.64 (d, J=3.5 Hz, 1H), 4.50 (dd, J=6.8, 6.8 Hz, 1H), 4.18 (dd, J=10.2, 5.1 Hz, 1H), 4.13–4.07 (m, 1H), 3.87 (dd, J=10.1, 10.1 Hz, 1H), 3.48–3.42 (m, 1H), 3.43 (s, 3H), 2.99–2.92 (m, 1H), 2.53 (dd, J=6.8, 3.5 Hz, 2H), 1.06 (s, 9H), 0.98 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 100.3, 82.7, 76.1, 69.6, 67.1, 57.0, 40.3, 29.8, 28.2, 27.8, 23.6, 20.7; HRMS m/z calcd for $C_{17}H_{31}O_6Si$ $[M+H]^+$ 357.1890, found: 359.1890.

3.1.5. 4-Benzyloxy-8,8-di-*tert*-butyl-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*] naphthalene-2-one (8b). The title compounds were prepared from **3** according to the general procedure described for the preparation of **8a**, except that 10 equiv. of benzyl alcohol were used (colorless oil, 210 mg, 84%). R_f 0.65 (50% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5H), 4.80–4.77 (m, 2H), 4.54 (d, J=12.3 Hz, 1H), 4.50 (dd, J=7.5, 7.5 Hz, 1H), 4.18 (dd, J=12.2, 10.6 Hz, 1H), 4.17 (d, J=10.3 Hz, 1H), 3.83 (dd, J=10.3, 10.3 Hz, 1H), 3.43 (ddd, J=10.2, 10.2, 5.3 Hz, 1H), 2.94 (dddd, J=8.6, 8.6, 8.6, 3.4 Hz, 1H), 2.55 (d, J=8.9 Hz, 2H), 1.02 (s, 9H), 0.96 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 136.9, 128.5, 128.0, 127.8, 97.4, 82.2, 75.5, 70.0, 69.2, 66.6, 39.4, 29.1, 27.4, 26.9, 22.7, 19.8; HRMS m/z calcd for $C_{23}H_{35}O_6Si$ $[M+H]^+$ 435.2203, found: 435.2202.

3.1.6. 4-Allyoxy-8,8-di-*tert*-butyl-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*] naphthalene-2-one (8c)(α). The title compound was prepared from **3** according to the general procedure described for the preparation of **8a**, except that 15 equiv. of allyl alcohol were used (white solid, 310 mg, 84%). R_f 0.61 (50% EtOAc/hexanes); IR (thin film) ν 1775, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92–5.82 (m, 1H), 5.29 (dddd, J=17.1, 1.6, 1.6, 1.6 Hz, 1H), 5.22 (dddd, J=10.3, 1.3, 1.3, 1.3 Hz, 1H), 4.82 (s, 1H), 4.59 (dd, J=7.8, 7.8 Hz, 1H), 4.14 (dddd, J=13.0, 5.3, 1.4, 1.4 Hz, 1H), 4.11 (dd, J=9.9, 5.3 Hz, 1H), 3.97 (dddd, J=12.9, 6.2, 1.3, 1.3 Hz, 1H), 3.87 (dd, J=9.9, 9.9 Hz, 1H), 3.80 (dd, J=9.9, 7.8 Hz, 1H), 3.81–3.73 (m, 1H), 2.94 (ddd, J=13.4, 8.6, 8.6 Hz, 1H), 3.53 (dd, J=17.1, 9.0 Hz, 1H), 2.47 (dd, J=17.1, 13.6 Hz, 1H), 1.07 (s, 9H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 132.8, 117.8, 96.2,

80.9, 75.7, 68.2, 66.3, 64.0, 41.4, 31.3, 27.7, 27.3, 23.1, 20.3; HRMS *m/z* calcd for $C_{19}H_{33}O_6Si$ $[M+H]^+$ 385.2045, found: 385.2046.

3.1.7. 8,8-Di-*tert*-butyl-4-phenoxy-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*] naphthalene-2-one (8d)(α). The title compound was prepared from **3** according to the general procedure described for the preparation of **8a**, except that 8.0 equiv. of phenol solution in 0.5 mL of Et_2O were used (colorless syrup, 180 mg, 80%). R_f 0.65 (50% EtOAc/hexanes); IR (thin film) ν 1779, 1713, 1661, 1592 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.26 (m, 2H), 7.04 (dd, *J*=7.4, 7.4 Hz, 1H), 6.98 (d, *J*=7.4 Hz, 2H), 5.43 (d, *J*=3.4 Hz, 1H), 4.66 (dd, *J*=7.4, 7.4 Hz, 1H), 4.38 (dd, *J*=10.2, 6.8 Hz, 1H), 4.18 (dd, *J*=10.2, 4.8 Hz, 1H), 3.84 (dd, *J*=10.1. 10.1 Hz, 1H), 3.66 (ddd, *J*=10.2, 10.2, 4.8 Hz, 1H), 3.19–3.12 (m, 1H), 2.71 (dddd, *J*=17.0, 17.0, 17.0, 8.5 Hz, 2H), 1.06 (s, 9H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 155.7, 129.2, 122.6, 116.3, 96.9, 81.9, 75.3, 69.4, 66.7, 39.1, 29.9, 27.7, 27.3, 23.1, 20.3; HRMS *m/z* calcd for $C_{22}H_{33}O_6Si$ $[M+H]^+$ 421.2046, found: 421.2045.

3.1.8. 8,8-Di-*tert*-butyl-4-phenylsulfanyl-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*] naphthalene-2-one (9a). To a solution of cyclopropane **3** (190 mg, 0.58 mmol) in CH_2Cl_2 (6 mL) at rt was added $TiCl_4$ (103 μL, 0.96 mmol, 1.7 equiv.). The mixture was stirred at rt for 2.0–2.5 h until TLC indicated complete consumption of starting material. To the dark brown solution was added benzenethiol (474 μL, 4.6 mmol, 8.0 equiv.) immediately followed by triflic acid (100 μL×3 M in Et_2O, 0.5 equiv.). The resulting mixture was stirred for 2.0 h and then poured into saturated aqueous $NaHCO_3$ (10 mL). After stirring for 10 min the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic solution was washed with H_2O (2×8 mL), brine (6 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Purification of the residue by flash chromatography on silica gel with 20:1 hexanes–EtOAc for elution gave the title products as colorless syrup: **9a** (β) (46 mg, 18%), **9a** (α) (184 mg, 73%). **9a** (β): R_f 0.71 (25% EtOAc/hexanes); IR (thin film) ν 1779, 1732, 1580 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56–7.41 (m, 2H), 7.36–7.29 (m, 3H), 5.06 (d, *J*=3.4 Hz, 1H), 4.48 (dd, *J*=7.8, 7.8 Hz, 1H), 4.20 (dd, *J*=10.3, 5.1 Hz, 1H), 3.95 (dd, *J*=10.3, 10.3 Hz, 1H), 3.88 (dd, *J*=9.9, 7.8 Hz, 1H), 3.34 (ddd, *J*=10.2, 5.1, 5.1 Hz, 1H), 3.24–3.16 (m, 1H), 2.76 (dd, *J*=7.1, 3.0 Hz, 1H), 2.59 (dd, *J*=17.1, 8.2 Hz, 1H), 1.06 (s, 9H), 0.99 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 132.6, 131.3, 128.8, 127.8, 84.2, 82.3, 75.5, 73.6, 65.9, 42.0, 29.0, 27.7, 27.3, 23.1, 20.3; HRMS *m/z* calcd for $C_{22}H_{33}O_5SiS$ $[M+H]^+$ 437.1818, found: 437.1815. **9a** (α): R_f 0.60 (25% EtOAc/hexanes); IR (thin film) ν 1783, 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.38 (m, 2H), 7.34–7.27 (m, 3H), 5.50 (s, 1H), 4.61 (dd, *J*=7.9, 7.9 Hz, 1H), 4.33 (ddd, *J*=10.2, 10.2, 5.1 Hz, 1H), 4.00 (dd, *J*=10.2, 5.1 Hz, 1H), 3.90–3.81 (m, 2H), 3.08 (ddd, *J*=10.6, 7.9, 0.8 Hz, 1H), 2.63 (d, *J*=10.6 Hz, 2H), 1.04 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 132.8, 132.2, 129.3, 128.3, 84.1, 81.1, 76.5, 66.5, 65.8, 42.2, 33.2, 28.2, 27.8, 23.6, 20.9; HRMS *m/z* calcd for $C_{22}H_{33}O_5SiS$ $[M+H]^+$ 437.1818, found: 437.1819.

3.1.9. 8,8-Di-*tert*-butyl-4-(pyridin-2-ylsulfanyl)-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*] naphthalene-2-one (9b)(α). The title compound was prepared from **3** according to the general procedure described for the preparation of **9a**, except that 6.3 equiv. of 2-mercaptopyridine was used (foamy solid, 301 mg, 70%). R_f 0.66 (25% EtOAc/hexanes); IR (thin film) ν 1782, 1709, 1577, 1556 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (dd, *J*=3.8, 1.0 Hz, 1H), 7.55 (ddd, *J*=7.8, 7.8, 2.0 Hz, 1H), 7.23 (d, *J*=12.6 Hz, 1H), 7.08 (ddd, *J*=5.3, 4.8, 1.0 Hz, 1H), 6.40 (s, 1H), 4.61 (dd, *J*=7.8, 7.8 Hz, 1H), 4.14–4.07 (m, 2H), 4.02 (dd, *J*=10.2, 5.1 Hz, 1H), 3.94–3.83 (m, 2H), 3.23–3.15 (m, 2H), 1.05 (s, 9H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 154.8, 149.3, 136.4, 123.2, 120.7, 80.7, 80.2, 75.9, 67.0, 66.1, 42.3, 32.8, 27.6, 27.3, 23.1, 20.4; HRMS *m/z* calcd for $C_{22}H_{32}O_5NSSi$ $[M+H]^+$ 438.1770, found: 438.1762.

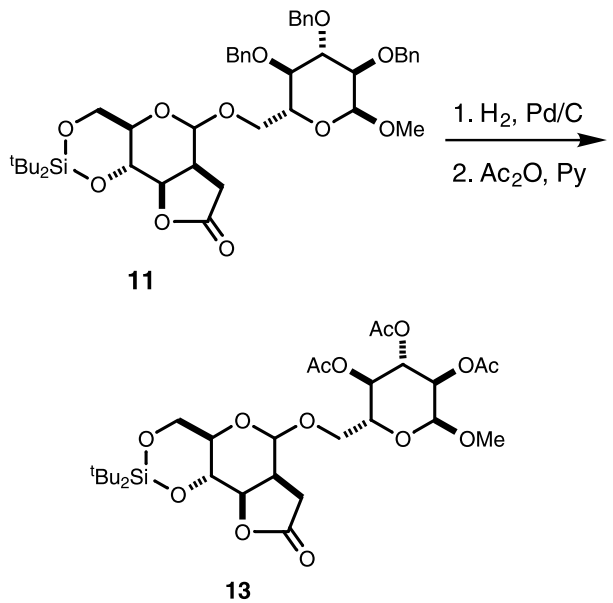
3.1.10. 8,8-Di-*tert*-butyl-4-(3,4,5-tribenzyloxy-6-methoxyl-tetrahydro-pyran-2-ylmethoxy)-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*]naphthalene-2-one (11α). To a 10-mL round-bottomed flask containing **9a** (α) (156 mg, 0.36 mmol) was added *N*-iodosuccinimide (164 mg, 0.73 mmol, 1.5 equiv.) and freshly activated molecular sieves (3 Å, 250 mg). The flask was sealed with a rubber septum, flushed with argon and treated with Et_2O (6 mL). After cooled to −35°C the solution was sequentially treated with **10**10[28] (288 mg, 0.59 mmol, 1.2 equiv., dissolved in 2 mL of Et_2O) and triflic acid (100 μL×1 M in Et_2O, 0.2 equiv.). After 50 min the glycosylation was complete (TLC) and Et_3N (70 μL, 0.50 mmol, 1.0 equiv.) was added. The resulting mixture was stirred for 5 min and poured into saturated aqueous $NaHCO_3$ (5 mL). After 10 min the organic layer was separated and the aqueous layer was extracted with Et_2O (2×8 mL). The combined organic solution was washed with H_2O (2×8 mL), brine (6 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Flash chromatography on silica gel with 10:1 pentanes–Et_2O for elution afforded the title compound as colorless oil (173 mg, 62%). R_f 0.41 (33% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.23 (m, 15H), 4.97 (d, *J*=10.8 Hz, 1H), 4.88 (d, *J*=10.8 Hz, 1H), 4.78 (d, *J*=11.6 Hz, 2H), 4.63 (d, *J*=12.0 Hz, 1H), 4.55 (d, *J*=10.8 Hz, 1H), 4.52–4.48 (m, 2H), 4.06 (dd, *J*=11.6, 3.0 Hz, 1H), 3.98 (dd, *J*=9.2, 9.2 Hz, 1H), 3.85–3.70 (m, 6H), 3.60 (dd, *J*=16.0, 4.1 Hz, 1H), 3.48 (dd, *J*=9.5, 3.4 Hz, 1H), 3.40 (dd, *J*=9.1, 9.1 Hz, 1H), 3.33 (s, 3H), 2.89 (ddd, *J*=13.2, 8.3, 8.3 Hz, 1H), 2.55–2.40 (m, 2H), 1.01 (s, 9H), 0.91 (s, 9H); HRMS *m/z* calcd for $C_{44}H_{57}O_{11}Si$ $[M-H]^+$ 789.3670, found: 789.3666.

3.1.11. 8,8-Di-*tert*-butyl-4-(3,4,5-triacetoxy-6-methoxyl-tetrahydro-pyran-2-ylmethoxy)-hexahydro-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*]naphthalene-2-one (13). To a solution of crude **11** (190 mg, 0.24 mmol) in ethanol (2.5 mL) at rt was added 5% Pd–C (ca. 6 mg). The reaction mixture was stirred under hydrogen atmosphere (balloon) for 2 h and then filtered though a pad of celite. Removal of the solvent under reduced pressure gave the crude product which was immediately dissolved in CH_2Cl_2 (5 mL) and treated sequentially with pyridine (100 μL, 1.1 mmol) and Ac_2O (250 μL, 2.7 mmol). After 15 h at rt the mixture was

poured into saturated aqueous $NaHCO_3$ (20 mL). After stirring for 20 min the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic solution was washed with NH_4Cl solution (4 mL), H_2O (2×8 mL), brine (6 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Flash chromatography on silica gel with 5:1 pentanes–Et_2O for elution afforded the title products as colorless oils: **13** (α) (95, 61%) and **13** (β) (20 mg, 14%). **13** (α): R_f 0.36 (50% EtOAc/hexanes); IR (thin film) ν 1775, 1751, 1709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.46 (dd, J=9.2, 9.2 Hz, 1H), 4.98 (dd, J=9.8, 9.8 Hz, 1H), 4.87–4.80 (m, 3H), 4.53 (dd, J=7.8, 7.8 Hz, 1H), 4.10–4.07 (m, 1H), 3.92 (ddd, J=10.2, 5.8, 2.0 Hz, 1H), 3.85–3.75 (m, 3H), 3.68 (dd, J=11.3, 5.9 Hz, 1H), 3.46 (dd, J=11.0, 2.0 Hz, 1H), 3.37 (s, 3H), 2.92 (ddd, J=16.8, 8.7, 8.7 Hz, 1H), 2.61–2.42 (m, 2H), 2.06 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.02 (s, 9H), 0.97 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 170.2, 170.1, 169.5, 97.7, 96.5, 80.8, 75.6, 70.8, 70.1, 69.1, 67.9, 66.3, 65.6, 63.9, 55.3, 41.0, 30.9, 27.4, 26.9, 22.7, 20.73, 20.69, 20.65, 19.9; HRMS m/z calcd for $C_{29}H_{47}O_{14}Si$ $[M+H]^+$ 647.2735, found: 647.2732. **13** (β): R_f 0.32 (50% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 5.45 (dd, J=9.6, 9.6 Hz, 1H), 4.99–4.87 (m, 2H), 4.80 (dd, J=10.2, 3.8 Hz, 1H), 4.73 (d, J=3.1 Hz, 1H), 4.51 (dd, J=7.8, 7.8 Hz, 1H), 4.17–4.11 (m, 2H), 3.90–3.82 (m, 3H), 3.47–3.34 (m, 2H), 3.37 (s, 3H), 2.92 (dddd, J=8.7, 8.7, 8.7, 3.1 Hz, 1H), 2.67–2.60 (m, 1H), 2.53 (dd, J=17.8, 9.3 Hz, 1H), 2.05 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.03 (s, 9H), 0.97 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 170.1, 170.0, 169.8, 99.2, 96.5, 81.9, 75.4, 70.9, 69.9, 69.1, 69.0, 68.2, 67.2, 66.5, 55.3, 39.4, 30.3, 29.7, 27.4, 27.0, 22.8, 20.69, 20.68, 19.8; HRMS m/z calcd for $C_{29}H_{47}O_{14}Si$ $[M+H]^+$ 647.2735, found: 647.2727 (Scheme 5).

3.1.12. 8,8-Di-*tert*-butyl-5a,6,9a,9b-tetrahydro-3*H*-1,5,7,9-tetraoxa-8-sila-cyclopenta[*a*]naphthalene-2-one (12). To a mixture of cyclopropane **3** (75 mg, 0.23 mmol) and Ziese's dimer (14 mg, 0.02 mmol, 0.1 equiv.) in $ClCH_2CH_2Cl$ (4 mL) was stirred at reflux temperature for 10 h. To the cooled reaction mixture was added CH_2Cl_2 (10 mL). The resulting mixture was washed sequentially with saturated aqueous Na_2CO_3 (2×2 mL), H_2O (2×2 mL), brine (4 mL) and dried ($MgSO_4$). After filtration through a pad of celite, the solvent was removed under reduced pressure. Purification of the residual oil by flash chromatography on silica gel with 5:1 hexanes–EtOAc for elution gave the title compound as colorless oil (59 mg, 79%). R_f 0.74 (50% EtOAc/hexanes); IR (thin film) ν 1785, 1725, 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.28 (s, 1H), 4.88 (dd, J=7.1, 1.0 Hz, 1H), 4.23 (dd, J=10.4, 5.0 Hz, 1H), 4.09 (dd, J=9.9, 7.2 Hz, 1H), 4.00 (dd, J=10.3, 10.3 Hz, 1H), 3.88 (ddd, J=10.3, 10.3, 4.8 Hz, 1H), 3.20 (ddd, J=19.5, 2.2, 2.2 Hz, 1H), 3.05 (d, J=19.5 Hz, 1H), 1.07 (s, 9H), 1.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 138.0, 103.8, 81.1, 73.9, 71.4, 65.8, 31.2, 27.7, 27.2, 23.1, 20.2; HRMS m/z calcd for $C_{16}H_{27}O_5Si$ $[M+H]^+$ 327.1628, found: 327.1616.

Preparation from vinyl magnesium bromide: To a solution of cyclopropane **3** (88 mg, 0.27 mmol) in CH_2Cl_2 (4 mL) at rt was added $TiCl_4$ (29 μL, 0.27 mmol, 1.0 equiv.). After stirred under rt for 2.5 h the solution was cool to 0°C. To the reaction mixture was added vinyl magnesium bromide (1.1 mL×1.0 M in THF, 1.1 mmol, 4.0 equiv.) dropwise until the preformed 1-chloropyran intermediates was completely consumed (TLC). The dark solution was then poured into saturated aqueous $NaHCO_3$ (4 mL). After stirring for 10 min the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic solution was washed with H_2O (2×4 mL), brine (4 mL) and dried ($MgSO_4$). After filtration through a small pad of celite, volatiles were removed under reduced pressure. Purification of the residue by gradient flash chromatography on silica gel with 10:1 to 4:1 hexanes–EtOAc for elution gave the title product as colorless oil (68 mg, 77%).



Scheme 5.

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