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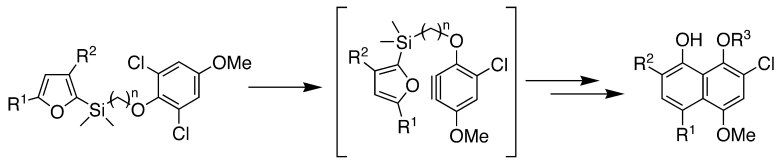

n = 1, 2; R^1, R^2 = H, Sug combinations; R^3 = H, Me

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Regioselective Synthesis of Unsymmetrical *C*-Aryl Glycosides Using Silicon Tethers as Disposable Linkers

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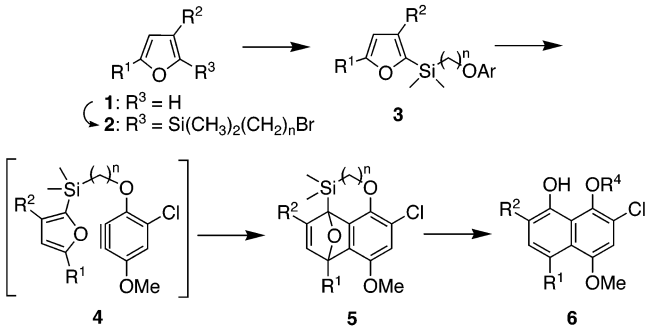
C-Aryl glycoside antibiotics comprise an important subclass of the *C*-glycoside family of natural products, a group of compounds that has attracted considerable interest because of their range of significant biological activities and resistance to enzymatic hydrolysis.[1,2] We recently disclosed two general approaches to prepare the four major classes of *C*-aryl glycosides.[3,4] The first of these involved the acid-catalyzed ring openings of the cycloadducts obtained from the Diels−Alder reaction of benzynes with glycosyl furans, and the other featured the palladium-catalyzed S_N2'-type ring opening of benzyne-furan cycloadducts with iodoglycals followed by appropriate adjustment of oxidation levels.

In these studies, symmetrical benzynes were universally employed as reaction partners, so the regiochemistry of the cycloaddition was never an issue. Although unsymmetrical benzynes are known to undergo regioselective Diels−Alder reactions,[5] such cycloadditions typically proceed with poor regioselectivity.[6] This problem became manifest during recent work that culminated in a formal synthesis of the *C*-aryl glycoside galtamycinone.[7] Hence, to apply our methodology to the synthesis of naturally occurring *C*-aryl glycosides, it is essential to control the regiochemistry of the pivotal benzyne-furan cycloadditions. We now report that disposable silicon tethers may be exploited to control the regiochemistry of benzyne-furan cycloadditions that lead to the major groups of *C*-aryl glycosides.[8]

Two protocols differing only in the number of carbon atoms in the tether were developed as outlined in Scheme 1. Regioselective metalation of glycosyl furan derivatives **1** followed by reaction with an appropriate chlorosilane and refunctionalization as needed leads to the silanes **2**, which are coupled with halophenols to give **3**. Selective deprotonation of **3** generates the benzynes **4**, and subsequent intramolecular Diels−Alder reaction then occurs spontaneously to furnish the cycloadducts **5**. On the basis of the prior art of Rickborn and Stork,[9] we anticipated that fluoride would induce the cleavage of the silicon−carbon bonds in the tethers in **5** to give intermediates that could undergo acid-catalyzed opening of the oxabicycloheptadiene ring to deliver either the glycosyl naphthols **6** (R^4 = H or Me), depending on the nature of the tether and the precise tactics used to effect its removal.

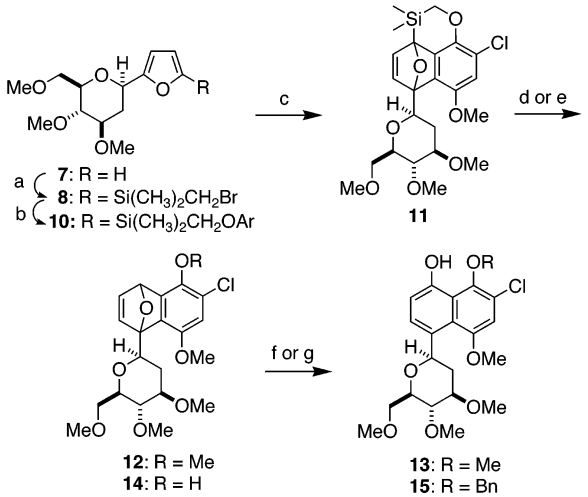
Scheme 1[a]



[a] n = 1, 2; R^1, R^2 = H, sugar combinations; Ar = 2,6-Cl_2-4-MeO-C_6H_2; R^4 = H, Me.

The use of silicon tethers to access *C*-aryl glycosides belonging to Group I[4] may be exemplified by two related strategies that differ in the number of carbon atoms that are present in the connecting chain. In the first of these, the known glycosyl furan **7**[3] was converted into the furylsilane **8** by sequential metalation (*n*-BuLi, THF, −78 °C) and reaction with bromomethylchlorodimethylsilane (Scheme 2).[10] *O*-Alkylation of 2,6-dichloro-4-methoxyphenol (**9**)[11] with **8** then provided the Diels−Alder precursor **10**. When **10** was treated with *s*-BuLi in THF at −95 °C, facile deprotonation ortho to one of the chlorine atoms ensued. The resultant anion underwent elimination upon warming to generate an intermediate benzyne that then cyclized via an intramolecular Diels−Alder reaction with the pendant glycosyl furan to provide cycloadduct **11** as a diastereomeric mixture.

Scheme 2[a]



[a] Reaction conditions: (a) LDA, THF, −78 °C; $Me_2Si(Cl)CH_2Br$, 73%; (b) **9**, Bu_4NI, K_2CO_3, Me_2CO, 83%; (c) *s*-BuLi, THF −95 °C; warm to −5 °C, 68%; (d) Bu_4NF, DMF, 79%; (e) Bu_4NF, THF; H_2O_2, MeOH, 62%; (f) TFA, CH_2Cl_2, ca. 100%; (g) NaH, BnBr, 95%; TFA, CH_2Cl_2, 90%.

Two tactics were developed for converting the cycloadduct **11** into substituted naphthols. In the event, reacting **11** with excess Bu_4NF (TBAF) in DMF cleaved both carbon−silicon bonds to afford dimethyl ether **12**, which underwent acid-catalyzed ring opening to furnish **13**, a representative *C*-aryl glycoside of Group I. Alternatively, when **11** was treated with TBAF in THF, only the bridgehead carbon−silicon bond was cleaved; subsequent Tamao oxidation furnished the phenol **14**.[12,13] *O*-Alkylation of **14** followed by acid-catalyzed ring opening gave **15** in which each of the phenolic oxygens is differentiated for subsequent transformations.

We found that *O*-alkylations of other phenols with bromomethylsilanes such as **8** may be problematic because of competing nucleophilic attack on silicon.[14] We developed a solution to this

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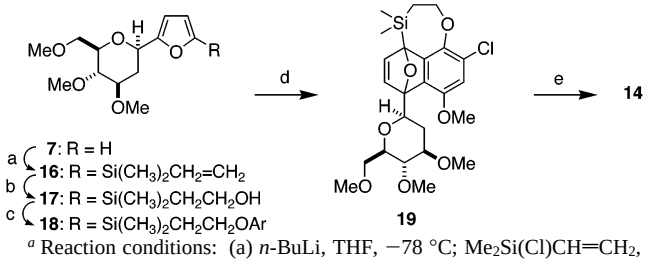
problem that features use of a tether containing an additional carbon atom. Thus, **7** was converted into the silyl alcohol **17** by metalation and reaction with chlorodimethyl-vinylsilane followed by regioselective hydroboration and oxidation (9-BBN, THF; NaOOH)[15] of the intermediate vinylsilane **16** (Scheme 3). Mitsunobu[16] coupling of **17** with **9** then afforded **18**. Deprotonation of **18** with *t*-BuLi led to the formation of an intermediate benzyne that underwent cycloaddition to deliver **19**. When **19** was treated with TBAF in DMF at 70 °C, the tether, which resembles a SEM protecting group,[17] was cleaved, and **14** was obtained in 80% yield.

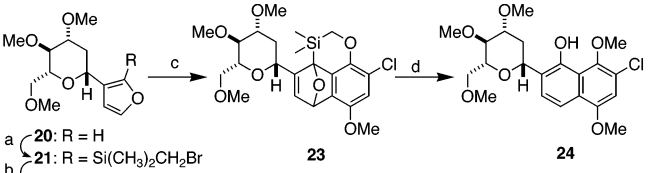
Scheme 3[a]



[a] Reaction conditions: (a) *n*-BuLi, THF, −78 °C; $Me_2Si(Cl)CH{=}CH_2$, 88%; (b) 9-BBN, THF; H_2O_2, NaOH, 88%; (c) **9**, DIAD, PPh_3, THF, 75%; (d) *t*-BuLi, THF, −95 °C; warm to −10 °C, 81%; (e) Bu_4NF, DMF, 70 °C, 80%.

Having developed an effective regioselective strategy for preparing Group I *C*-aryl glycosides, it remained to extend this approach to representative glycosides of Groups II and III.[4] Toward this end, the known glycosyl furan **20**[3] was converted into **21** by directed metalation (LDA, THF, −78 °C) and reaction with bromomethylchlorodimethylsilane (Scheme 4). *O*-Alkylation of phenol **9** with **21** afforded **22**. Deprotonation of **22** occurred selectively on the phenyl ring, and the benzyne that formed upon warming cyclized to provide cycloadduct **23** in 91% yield as a mixture of diastereomers. Cleavage of both carbon−silicon bonds using TBAF in DMF provided an intermediate dimethyl ether that underwent ring opening upon exposure to TFA to afford naphthol **24** as a single isomer.

Scheme 4[a]

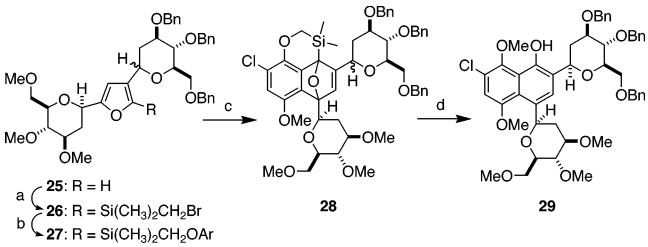


[a] Reaction conditions: (a) LDA, THF, −78 °C; $Me_2Si(Cl)CH_2Br$, 88%; (b) **9**, K_2CO_3, Bu_4NI, Me_2CO, 78%; (c) *s*-BuLi, THF, −95 °C; warm to −30 °C, 91%; (d) Bu_4NF, DMF, room temperature, TFA, CH_2Cl_2, −5 °C to room temperature, 71%.

A regiochemical controlled entry to Group III *C*-aryl glycosides commenced with converting the glycosyl furan **25**, which was prepared as a mixture (ca. 6:1) of epimers as reported previously,[3] into the furylsilane **26** by metalation and silylation (Scheme 5). *O*-Alkylation of the phenol **9** with **26** produced **27**, which was transformed into a mixture of diastereomeric cycloadducts **28** via benzyne formation-cycloaddition. Exhaustive cleavage of the carbon−silicon bonds as before followed by acid-catalyzed ring opening delivered the naphthol **29** as a single diastereomer.

We have thus demonstrated the utility of silicon tethers to control the regiochemistry of Diels−Alder cycloadditions of substituted benzynes and glycosyl furans to provide ready access to unsymmetrical representatives of the three major groups of *C*-aryl glycosides. The application of this novel methodology to the efficient synthesis of naturally occurring *C*-aryl glycoside antibiotics

Scheme 5[a]



[a] Reaction conditions: (a) LDA, THF, −78 °C; $Me_2Si(Cl)CH_2Br$, 82%; (b) **9**, K_2CO_3, Bu_4NI, Me_2CO, 88%; (c) *t*-BuLi, THF, −90 °C to −10 °C, 61%; (d) Bu_4NF, DMF, room temperature; TFA, CH_2Cl_2, 0 °C to room temperature, 72%.

is the subject of several active investigations in our laboratories, the results of which will be disclosed in due course.

Acknowledgment. We thank the National Institute of General Medical Sciences (GM 31077), the Robert A. Welch Foundation, Pfizer, Inc., and Merck Research Laboratories for their generous support of this research.

Note Added after ASAP. In the version posted 10/4/03, there was an error in the reaction conditions given in Scheme 5. The version posted 10/9/03 and the print version are correct.

Supporting Information Available: Copies of ^1H NMR spectra of all new compounds and representative experimental procedures for preparing **13** from **7** and **14** from **16** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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