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Communication

Si-Linked Glycomimetics through a Stereoselective Silicon Transfer and Anion Addition

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ABSTRACT: We report a synthesis of silicon-linked glycomimetics, demonstrating unique structural properties and metabolic stability due to the inertness of the C−Si bond. Our method focuses on the stereoselective transfer of silicon and anion addition, revealing that chirality at the silicon atom can be controlled through kinetic resolution. This approach allows for the selective generation of 1,2-*cis* and 1,2-*trans* isomers via the manipulation of C2-protected silicon ethers and nucleophilic opening of glycal epoxides. We achieved high selectivity at the anomeric carbon and expanded the scope to include various saccharides and substituted silanes. Our findings indicate that silicon transfer occurs intramolecularly and is influenced by the nature of the counterion and reaction conditions. Additionally, chiral silanes produced through our method hold promise for medicinal chemistry applications, addressing significant gaps in the synthesis and utility of glycomimetics. This work opens new avenues for the development of bioactive silicon-based molecules.

Glycomimetics, a class of saccharide-derived molecules in which labile functionalities are replaced with more stable units, represent a valuable tool in drug development and in probing fundamental glycobiology.[1] While C-linked saccharides, among others, encompass a broad class of bioactive structures such as antidiabetic drugs and lectin mimetics, studies incorporating other group 14 elements beyond carbon are limited. Specifically, the replacement of exocyclic oxygen

Scheme 1

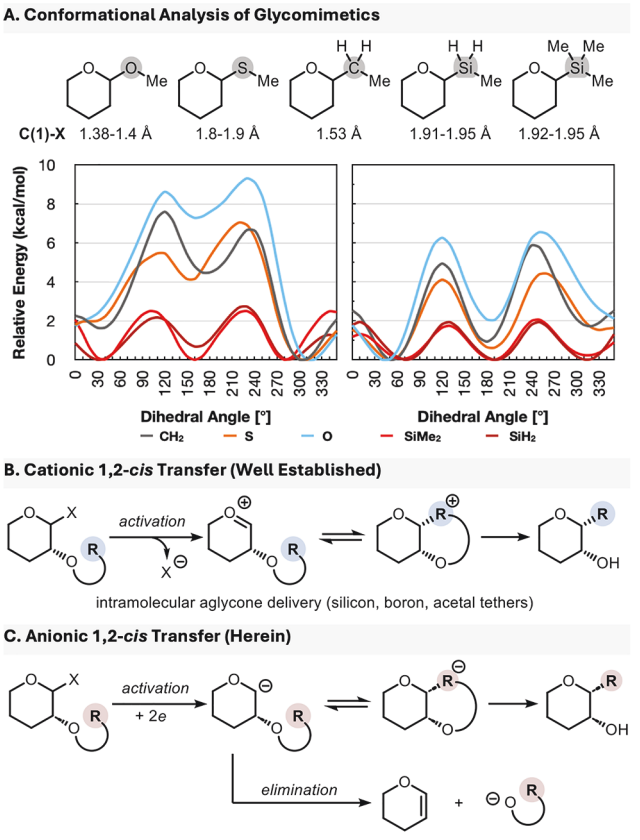
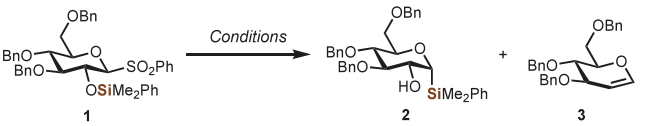


Table 1. Reaction Development[a]



Entry	Reductant	Solvent	Temp [°C]	Time [min]	2 [%]	3 [%]
1	Li/Nap	THF	−78	5	52	19
2	Li/Nap	PhMe	−78	5	N.R.	
3	Na/Nap	Et_2O	−78	5	9	26
4	Na/Nap	2-MeTHF	−78	4	21	35
5	Na/Nap	THF	−78	5	53	28
6	K/Nap	THF	−78	3	64	20
7	K/Nap	THF	−100	5	N.R.	
8	K/Nap	PhMe	−100	30	0	57
9	K/dtbbp	THF	−78	3	49	27

[a]Reagent and conditions: Sulfone **1** (1.00 equiv), solvent (0.035 M), reductant (2.50 equiv, 1.00 M in THF). Yields refer to isolated material after chromatography purification. dtbbp = di-*tert*-butylbiphenyl, Nap = naphthalene. N.R. = no reaction.

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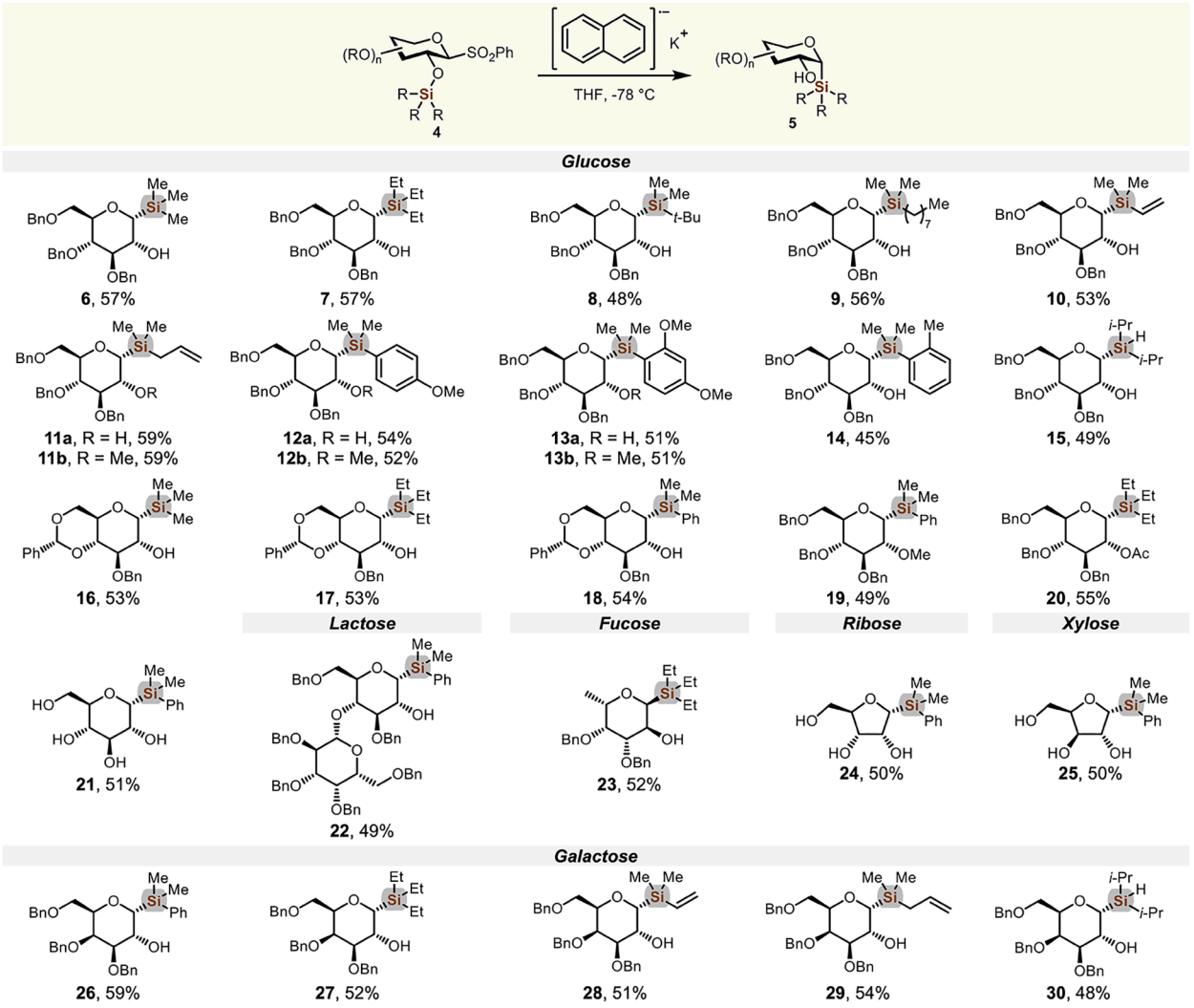
Scheme 2. Scope of 1,2-*cis* Migration under Reductive Conditions[a]



[a]Reagents and conditions: **4** (1 equiv), K/Naphthalenide (2.50 equiv, 1.00 M in THF), THF (0.035 M), −78 °C, 5 min. Only one diastereomer was observed in unpurified reactions mixtures (NMR). Yields refer to homogeneous material isolated after chromatographic purification.

with silicon remains scarcely explored.[2,3] Si-linked glycosides are an intriguing class of glycomimetics due to their much longer C1−Si bonds (∼1.94 Å) compared to C−C single bonds, yet similar to S/Se-linked glycomimetics, and their resistance to oxidation that may occur at the anomeric chalcogen (Scheme 1A). However, unlike other mimetics such as S- and CH_2-linked glycosides, which mimic the conformational behavior of native O-linked glycosides, Si-linked structures are characterized by low barriers of rotation for both axial and equatorial isomers (∼2.0 kcal/mol) with no well-defined single stable rotamer. This novel property of Si-linked glycosides presents an opportunity to create a class of reagents with distinct structural features, high metabolic stability due to the inertness of the C−Si bond, and additional structural diversity resulting from modifications of the silicon atom. Furthermore, organosilicon reagents possess novel medicinal chemistry properties,[4−6] and there is a compelling literature precedent for engaging C1 Si-glycosides in cross-coupling reactions, addressing an important knowledge gap.

In assembling Si-based glycomimetics, we were drawn to the unique properties of anomeric nucleophiles and their synthetic utility in C−C cross-coupling reactions.[7−10] Similar to the preparation of *O*-linked glycosides, controlling the anomeric configuration of glycomimetics remains a central focus, with the challenging 1,2-*cis* configurations receiving special attention.[11] One reliable method to produce 1,2-*cis* linked glycosides capitalizes on intramolecular aglycone delivery[12,13] and a direct transfer from the neighboring C2 position functionalized through silicon,[14−18] boron,[19−24] and acetal tethers.[25,26] Once activated, these produce the putative oxocarbenium intermediate and deliver the "cargo" from the same face as the directing group (Scheme 1B). However, an analogous approach utilizing C1 anomeric nucleophiles has been less studied (Scheme 1C). The anionic transfer faces challenges orthogonal to the Lewis acid pathway, such as harsh reaction conditions for C1 anion generation (metalation) and competitive elimination to glycals. Overcoming these obstacles would constitute a powerful C2 → C1 intramolecular umpolung aglycon delivery strategy complementary to cationic pathways. Inspired by the work of Sinaÿ,[2] we report herein the synthesis of Si-linked glycomimetics and the preparation of 1,2-*cis* and 1,2-*trans* isomers through iterative manipulation of

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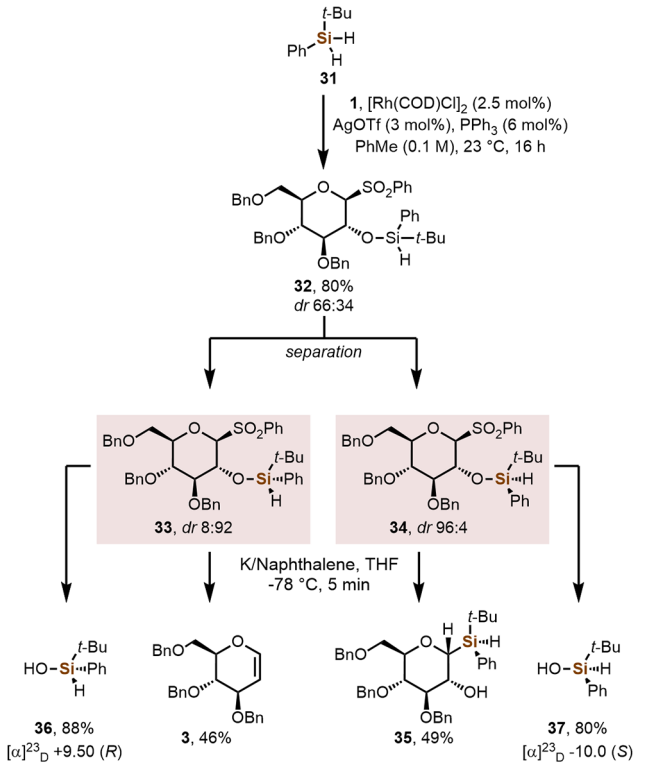
Scheme 3. Kinetic Resolution of Dihydrosilanes



either C2-protected silicon ethers or nucleophilic opening of glycal epoxides with silicon-based anions. We demonstrate exclusive selectivity for the anomeric carbon in each pathway.

Similar to other C1-based nucleophiles, which can be obtained in any anomeric configuration,[7−10] we aimed to access both anomers of Si-substituted glycosides. We first focused on the 1,2-*cis* substituted structures and envisioned that a direct transfer from silicon ethers of C2 could be accomplished under reductive conditions. Unlike the synthesis of C1 stannanes or boronic acids, which may also proceed through an intramolecular transfer from transient ethers, the Si-protected glycosides are stable structures. The results in Table 1 indicate that different reductants and solvents affect the yield of Si-linked glycomimetics. The most effective conditions for the transfer are K naphthalenide in THF at −78 °C for 3 min, yielding 64% of **2** and 20% of **3** (entry 6). Li/Nap in THF also performed well, giving reduced yields of **2** and 19% of **3** (entry 1). Sodium naphthalenide as the reductant in any solvent tested produced moderate yields of both products (entries 3−5). Lowering the temperature to −100 °C with K/Nap resulted in no reaction (entry 7), while using PhMe as a solvent is generally ineffective for **2** but yields 57% of product **3** at −100 °C for 30 min (entry 8). K/dtbbp in THF offers balanced yields of both products (entry 9). Furthermore, highly coordinating additives such as HMPA had also detrimental effects and favored the elimination only. Other potential substrates for the generation of C1 anions such as thioglycosides, sulfoxides and anomeric halides were tested, but due to low yields or practical considerations of their stability, they were deprioritized in the subsequent studies. Analogously, reductive methods with SmI_2 also produced exclusively glucal. Overall, K/Nap in THF at −78 °C was identified as the optimal conditions for high yields, while PhMe can be used for the selective production of **3**.

Scheme 2 lists the scope of the transfer reaction, demonstrating its operational versatility across various saccharides and substituted silanes. Using D-glucose, we established that vinyl **10**, allyl **11**, and aromatic **12**−**14** groups are tolerated. Similar observations were made regarding alkyl groups such as TMS **6**, TES **7**, bulky *tert*-butyl **8**, and long-chain aliphatic **9** indicating that aromatic or unsaturated moieties directly attached to Si were not required. The 1,2-*cis* transfer reaction necessitates a transition state, wherein the putative silacycle intermediate induces planarization and additional strain in the pyranose ring. We hypothesized that constraining the pyranose ring with a 4,6-benzylidene group would facilitate the reorganization of the bicyclic system and favor transfer over the elimination pathway, which could proceed via an acyclic pathway. Testing the transfer reactions with glucose benzylidene substrates revealed that the formation of C1-silyl glycosides **16**−**18** was efficient (51−56%). By analogy to the anomeric assistance of C2 with a carbonyl group, the benzylidene group in glucose and galactose does not prevent the intermediacy of 1,2-*cis* linked structures.

The protection of the hydroxyl groups is also not necessary, as glucose substrates where all of the hydroxyl functionalities were protected as silicon ethers were suitable substrates for the transfer, although all of the silicon ethers were lost during the aqueous workup, producing **21**. Trisubstituted silanes (e.g., **16** and **30**) were also produced in synthetically acceptable yields. Besides glucose, other monosaccharides such as fucose **23**, ribose **24**, xylose **25**, and galactose **26**−**30** transferred the silicon moiety with high efficiency. For the reactions with pentoses **24** and **25**, we utilized tri-O-silyl substrates due to practical considerations and the ease of preparation. In some cases, we also showed that the problematic olefination could be stopped if the reaction mixture was quenched with an electrophile (MeI: **11b**, **12b**, **13b**, **19**; Ac_2O: **20**) without deterioration of the yield. Finally, the reductive conditions are also compatible with disaccharide substrates (lactose **22**). Interestingly, attempted 1,5- and 1,6-transfers from 5′-OTBS D-ribose and 6-OTBS D-glucose substrates resulted in no products. In all of the reactions, we observed the formation of only one diastereomer.

To further expand the utility of the reaction, we wondered if the chiral nature of the saccharide scaffold could be transferred to the chirality of the silicon atom (Scheme 3). Chiral silanes are becoming recognized as valuable synthetic tools,[27−29] and various methods have been developed to introduce an asymmetric silicon,[30−36] including resolution of silicon ethers followed by stereoselective reduction to produce chiral silanes.[37−42] To this end, we first produced a mixture of C2 protected glucose **32** in a reaction with *t*-BuPhSiH$_2$ and a Rh(I) catalyst.[29] This mixture was then separated, and each diastereomer was subjected to reductive conditions at low (−78 °C) and high (23 °C) temperatures. We observed that the fate of the substrate was determined based on the configuration of the silicon center: the R-isomer **33** underwent exclusive elimination producing glucal **3** whereas the S-isomer **34** transferred the silicon group with a high selectivity producing only one diastereomer of trisubsituted monohydrosilane **35** (*dr* > 99:1).[43−45] This novel kinetic resolution was also observed when a 66:34 mixture of **32** was subjected to the reductive conditions although the yield of **35** was low (15%).[46] When the diastereoemerically enriched mixtures of **33** and **34** were subjected to K/Nap at higher temperatures, the corresponding silanols **36** and **37** were produced in 80−

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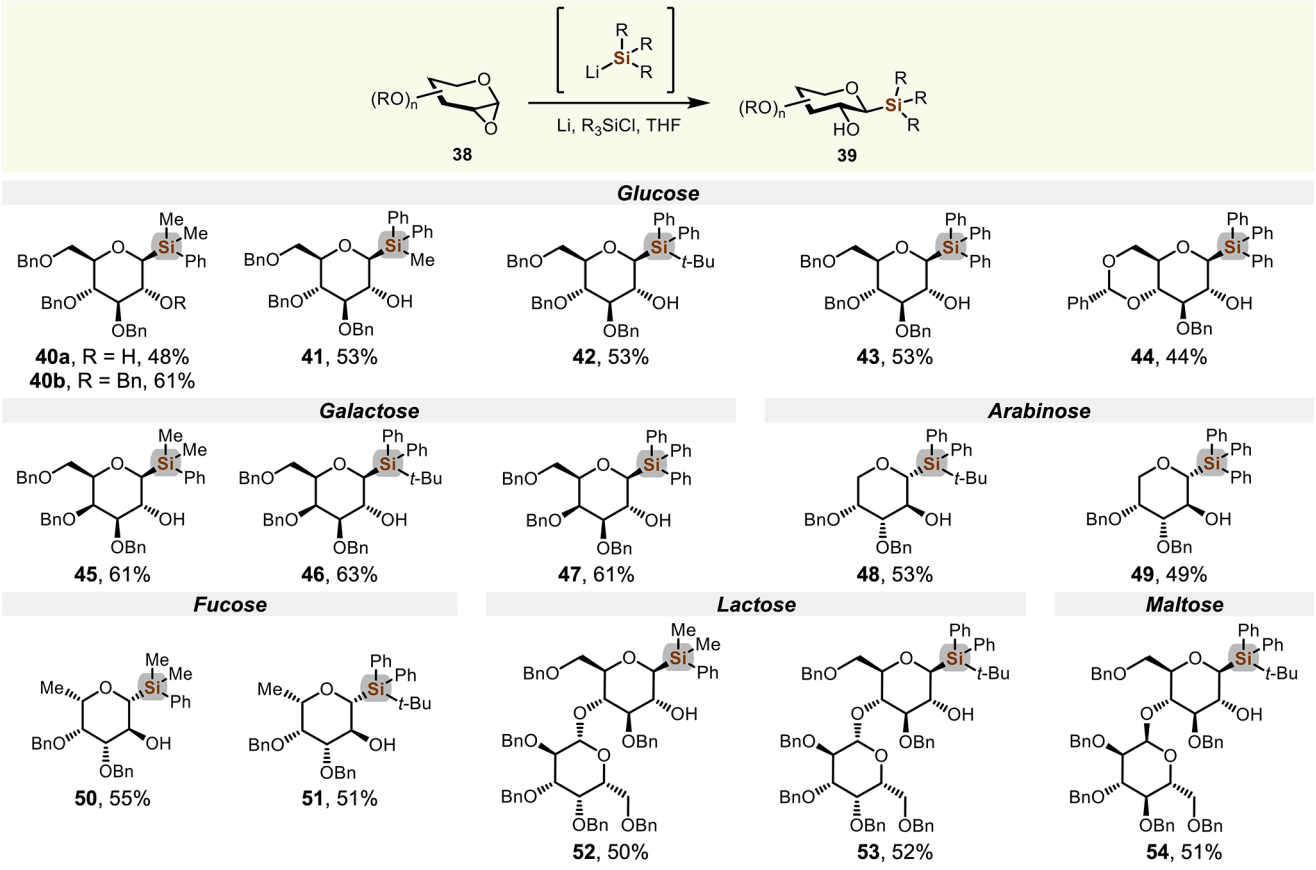
Scheme 4. Scope of 1,2-*trans* Anionic Opening with Silicon Anions[a]



[a]Reagents and conditions: **38** (1 equiv), silyl lithium (2.50 equiv, 1.00 M in THF), THF (0.10 M), 0 to 25 °C, 12 h. Only one diastereomer was observed in unpurified reactions mixtures (NMR). Yields refer to homogeneous material isolated after chromatographic purification.

88% yield, and their optical rotation data were compared to the reported values establishing the absolute configuration at the silicon atom.[47]

To complement the studies on 1,2-*cis* Si-saccharides, we next focused on establishing the 1,2-*trans* relationship by opening of **38** epoxides (Scheme 4). The necessary formation of a stable silicon-centered anion could be accomplished in chlorosilanes with at least one aryl (Ph) group directly attached to Si and Li.[48−58] Unlike the 1,2-*cis* transfer reactions, the problematic Peterson olefination from the resultant alkoxide was not observed, and the isolated products **39** from the nucleophilic additions could be easily converted into C2 ethers (e.g., **40b**).

Several studies were undertaken to better understand the mechanism of the transfer process. We observed that electron-withdrawing groups on the silicon, such as $Si(OR)_3$, promoted exclusive elimination (Scheme S11). For mannose substrates, where both the sulfone and silyl ether are in a *trans* configuration, the reductive conditions produced glucal only (Scheme S12). However, when C2-OH was left free, sulfone reduction provided 1-deoxysaccharide in a high yield (63%, Scheme S16). In a complementary study, we established that the generation of a C1 anion from a free C2 alcohol under reductive conditions (KHMDS followed by K/Nap) and subsequent quenching with a chlorosilane failed to produce the intended **2**, instead yielding 1-deoxysaccharide exclusively (57%). Similarly, a competition experiment with glucose sulfones containing two different silyl ethers provided no evidence of cross-transfer between the anions.

In addition to the experimental studies, free energy profiles were calculated (Scheme 5). First, we optimized individual structures for the transfer (**A**−**E**) and elimination (**F**−**G**) pathways in a tetrahydropyran (THP) model system. The computed free energies indicate that the first step of the transfer is favored over syn elimination by 4.0−4.6 kcal/mol. Furthermore, all starting conformations except for the one with the syn lone pair TMSO and the lone pair in the axial position can proceed through a synclinal elimination transition state. Conversely, cyclic chair intermediates **C** proceeded through energy barriers of 2.6−3.3 kcal/mol to form the transfer product **E**. The optimized geometries for transition state **B** (the carbanion attack) in THP indicate that one of the silicon methyl groups prefers an antiperiplanar orientation. However, the cyclic intermediates **C** and the O−Si cleavage transition states **D** were optimized to geometries with a methyl group and the oxygen at Si in apical orientations. This prompted us to investigate if a possible Berry pseudorotation of the trigonal bipyramid intermediate may be operational in these steps.[59,60] Scans indicated that a stereoretentive Berry pseudorotation is a necessary step to achieve this configuration but proceeds through a negligible barrier (0.7 kcal/mol). The computational search for a stereoinvertive Berry pseudorotation at Si was also performed but revealed a pathway that required a significantly higher barrier of 27.4 kcal/mol. The computational studies therefore support the notion that silicon transfer is a stereoretentive process.

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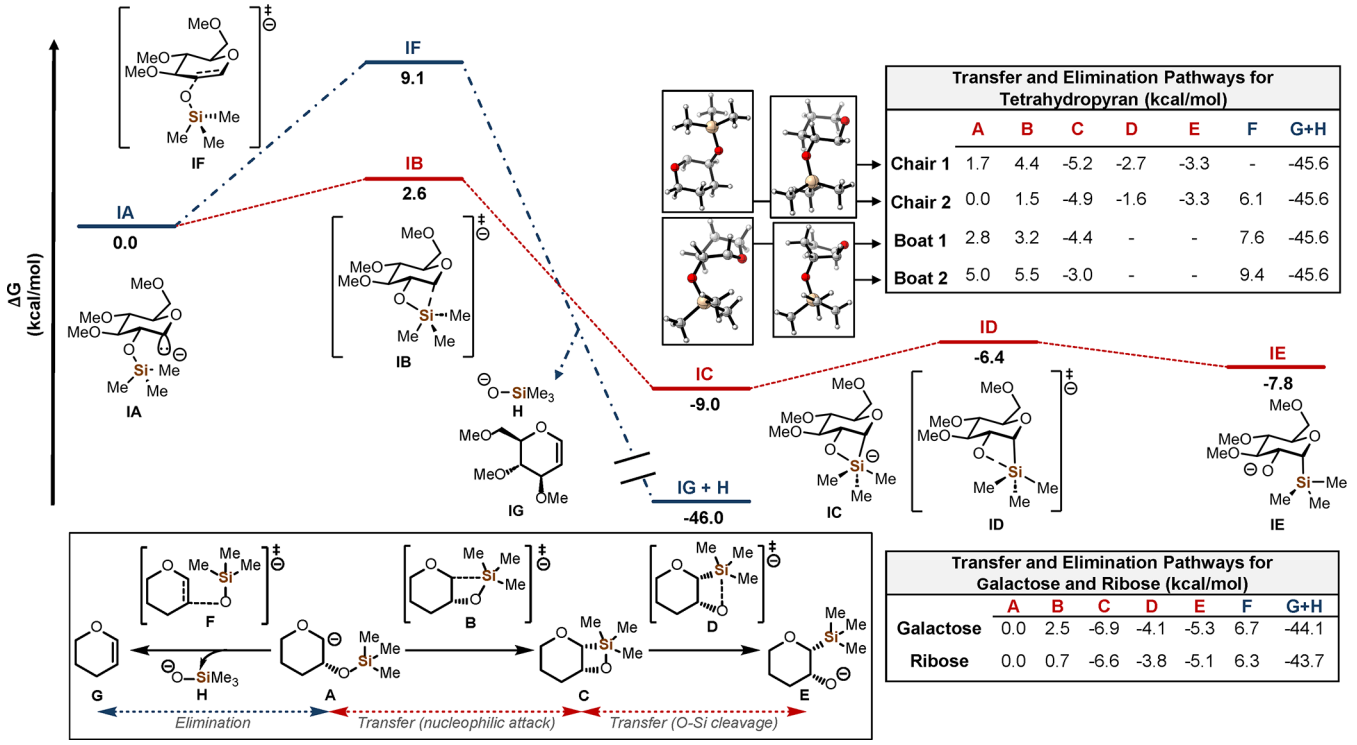
Scheme 5. Computed (DFT) Reaction Profiles for the Migration and Elimination Pathways[a]



Transfer and Elimination Pathways for Tetrahydropyran (kcal/mol)

	A	B	C	D	E	F	G+H
Chair 1	1.7	4.4	-5.2	-2.7	-3.3	-	-45.6
Chair 2	0.0	1.5	-4.9	-1.6	-3.3	6.1	-45.6
Boat 1	2.8	3.2	-4.4	-	-	7.6	-45.6
Boat 2	5.0	5.5	-3.0	-	-	9.4	-45.6

Transfer and Elimination Pathways for Galactose and Ribose (kcal/mol)

	A	B	C	D	E	F	G+H
Galactose	0.0	2.5	-6.9	-4.1	-5.3	6.7	-44.1
Ribose	0.0	0.7	-6.6	-3.8	-5.1	6.3	-43.7

[a]Computed free energy profiles for the proposed transfer and elimination pathways of glucose (IA-IG), galactose, ribose, and different conformations of tetrahydropyran (THP). Optimization and frequency calculations were performed at the SMD-THF-wB97X-D/def2TZVPP level at 1 atm and 298.15 K.

In model glucose, galactose, and ribose systems, the energy barriers for elimination are also higher than the carbanion attack step by approximately 4.2−6.9 kcal/mol. Interestingly, the elimination transition state for glucose and galactose could only be achieved in a twist-boat conformation. The OMe substituents limit the flexibility of the cyclic conformations, and for the elimination to occur, the only possible conformations to align the lone pair and TMSO group could be achieved through a twist-boat. We also calculated a possible transfer from the C5 position in ribose, but the 9.3 and 5.4 kcal/mol energy barriers for the carbanion attack and O−Si cleavage transition states suggest that this reaction is not a feasible pathway, consistent with the experimental data.

In conclusion, we have successfully demonstrated intramolecular umpolung aglycon delivery, producing 1,2-cis substituted silaglycosides with high selectivity. By harnessing the anionic character of the anomeric carbon and silicon reagents, we developed methods for controlling glycosidic linkage configurations, which is a significant advancement over traditional carbon-centered approaches. This study not only fills a gap in the synthetic strategy of glycomimetics but also sets a precedent for the use of silicon in the design of biologically relevant molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c10978.

Detailed experimental procedures, copies of NMR spectra, computational details, and Cartesian coordinates (PDF)

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Notes

The authors declare no competing financial interest.

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