O,O-Silyl Group Migrations in Quinic acid derivatives: An Opportunity for Divergent Synthesis

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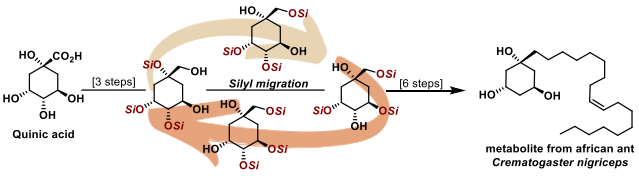
Supporting Information Placeholder



ABSTRACT: The *O,O*-silyl group migrations on a quinic acid-derived cyclitol have been studied and the ease of migration observed to be dependent on the silicon substituents and reaction conditions. Conditions were found to improve the formation of a main isomer during the *O,O*-silyl group migrations that could be integrated into the formal synthesis of vitamin D receptor modulator VS-105 and in the first total synthesis of a metabolite from African ants *Crematogaster nigriceps.*

The chiron approach in organic synthesis enables the planning of concise and efficient routes towards stereoselective total syntheses of natural products by recognition of the chiral substructures as fragments of the target molecule.[1] The advantages of using chiral building blocks from nature are numerous, particularly because of the diversity of carbon frameworks containing specific stereochemistries as well as the global need of decreasing the use of carbon from non-renewable fossil resources.[2] Notwithstanding the high synthetic value of chiral carbohydrates and derived polyols, their usage is often disadvantageous since the use of protective groups is required to allow differentiation on the reactivity of hydroxy groups.[3] While strategies to segregate the reactivity of similar functionalities are limited, such problem is often obviated by exploring the selective protection of functional groups and functional group rearrangement (*i.e.* migration).[3d, 4]

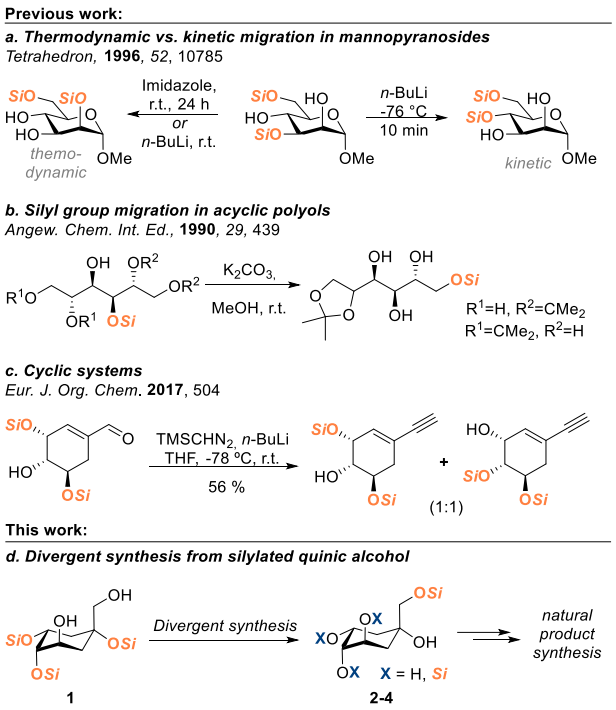
Silyl ethers are commonly used as protecting groups of alcohols to suppress their reactivity.[5] Moreover the steric and electronic properties of the silyl ether molecule, and subsequently their reactivity, is dependent on the silyl group employed.[5a, 6] Thus, despite the emerging trend of protecting group-free syntheses,[7] the use of such tool can occasionally warrant structural diversification, especially when considering the vast knowledge gathered on the selective formation[4b, 8] and cleavage[9] of silyl ethers. Although relatively stable in basic media, silyl ethers vicinal to a hydroxy group can undergo 1,4-*O,O*-silyl migration in good yields. This can proceed via a putative pentacoordinate intermediate formed upon alkoxide attack to silicon,[10] which seems to be hampered under Luche reduction conditions.[11] Such type of migration in carbohydrates and derivatives is widely acknowledged.[12]

Despite its common occurrence in carbohydrates, only a few of the reported 1,4-*O,O*-silyl migrations have been methodically studied.[13] The regioselectivity of α-D-pyranosides reactions with *tert*-butyldimethylsilyl (TBDMS) and *tert*-butyldiphenylsilyl (TBDPS) chlorides was observed to be dependent on the reaction conditions. The combination of imidazole in DMF promotes *O,O*-silyl migrations under kinetic control and does not result in the formation of the most stable regioisomer, while harder bases change the isomer distribution profile (Scheme 1a).[13b] Similar intramolecular silyl migrations under basic conditions have also been observed for polyols (Scheme 1b),[14] although in acyclic systems the 1,5-*O,O*-silyl migration competes with the 1,4-migratory process.[15] Besides carbohydrates and their derivatives, the *O,O*-silyl group migration in cyclic systems has been somewhat overlooked. Ferrero and co-workers reported the occasionally competitive 1,4-*O,O*-silyl migration during a Colvin rearrangement step in the synthesis of a previtamin D_3 analog from shikimic acid (Scheme 1c).[16] The fluctuating regioselectivities were attributed to the different batches of *n*-BuLi, containing different amounts of lithium hydroxide.

During our previous studies on the modification of quinic acid,[17] when attempting to convert a primary hydroxyl function of trisilylated quinic alcohol **1** into a sulfonate moiety, we observed multiple silyl migrations as an untraceable mixture of products. Considering that the diversification of a common precursor into several synthetic intermediates is a powerful tool

to synthesize molecules otherwise difficult or impossible to reach, and the limited number of studies on the *O*-silyl migration in carbacyles, we set to improve the selectivity of the migration process (Scheme 1d). This approach would provide us synthetically rich intermediates in a divergent synthesis strategy.[18]

Scheme 1. *O*,*O*-Silyl migrations in polyols.

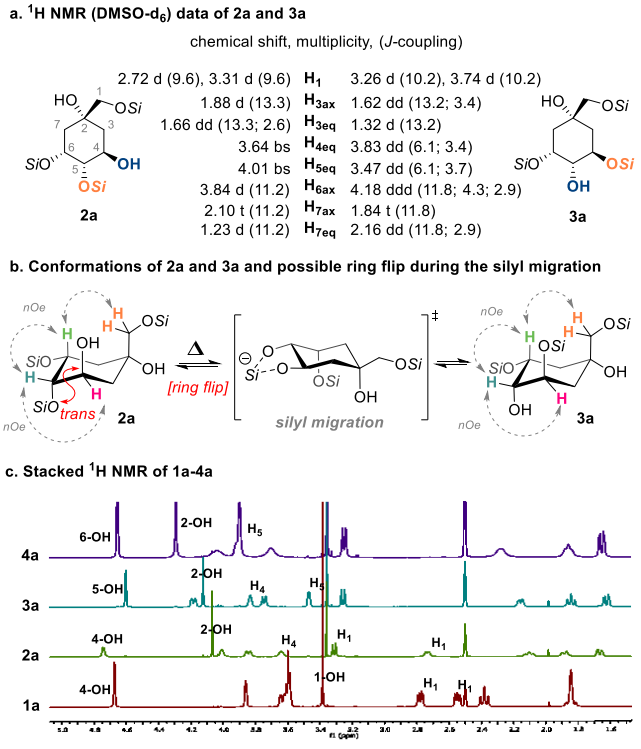


To study the silyl group migration reaction in quinic acid derivatives, trisilylated diols **1a** and **1b** were synthesized and subjected to different bases and solvents (Table 1). We were pleased to notice the exclusive formation of **2**, regardless of the different silyl ethers, upon treatment with imidazole as a base for 6 hours (Table 1, entry 1). Intriguingly, when attempting to push the secondary→secondary *O*,*O*-silyl migration (5-*O*→4-*O*) by elongating the reaction time and increasing the amount of imidazole, the migration took place with TBPDS-protected derivative whilst no **3b** or **4b** were detected with less bulky TBDMS-group (entry 2). While targeting a better selectivity towards **3** or **4**, other bases were screened (entries 3-6). DMAP was also able to provide isomer **2a** from the TBDPS-protected derivative **1a**, but the TBDMS congener **1b** undergone migration in only 20% to the corresponding isomer **2b** (entry 3). Surprisingly, the use of stronger base Et_3N proved futile with the exclusive isolation of recovered starting material (entry 4). Treatment of **1a** with even stronger bases KHMDS and NaH promoted the formation of both 4-*O*-TBDPS protected isomers **3a** and **4a** (entries 5-6), although in lower overall yield than when comparing with prolonged use of imidazole (entry 2). Sodium hydride has been previously used in silyl migrations of sugar derivatives with great overall yields though full selectivity has not been reached.[12b, 19] Lowering the temperature when using NaH, to minimize the formation of other unknown side products, did not return the desired isomers (data not shown). Replacement of THF by toluene (entry 7) allowed some formation of **3a** together with **4a,** and the selectivity towards the former was greatly improved by elongating the reaction time and increasing the amount of base (entry 8).

Although **3a** could be obtained in 78% yield, the analogous reaction from TBDMS-derivative returned only 25% of **3b** and traces of **4b**, clearly indicating the importance of the silane substituents on the migratory process. Further increase of the temperature using DMF as solvent (entry 9) resulted in the formation of **4a** in higher yield but still in moderate regioselectivity. Using methanol as solvent together with Et_3N resulted in room temperature selective 2-*O*→1-*O* silyl group migration to primary silyl ethers **2a** and **2b** (entry 10), in contrast with the lack of reactivity observed in refluxing THF (entry 4). Notably, **3** and **4** were not observed under these conditions, although secondary→secondary silyl migration was reported for nucleosides.[20] Invigorated by this, other bases were tested with MeOH (entries 11-13), allowing the formation of **4** in moderate yields (**4a** 35% and **4b** 27 %) using a combination of bases in a sealed tube (entry 13).

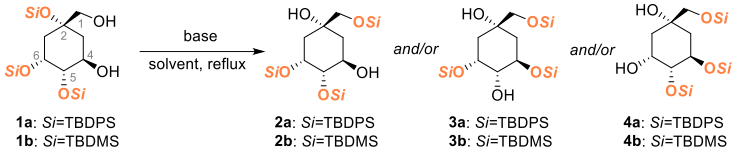
Contrasting to the facile 2-*O*→1-*O* silyl group migration to form **2a**, the silyl shifts within the six-membered ring required harsher reaction conditions and were never observed in the absence of tertiary→primary migration. A more difficult 5-*O*→4-*O* silyl group migration would be expectable given the relative *trans* position of the oxygen atoms. This aspect was confirmed by a careful NMR-analysis of NOESY and other multidimensional experiments of TBDPS-containing compounds **1a-4a** in DMSO-d_6 (Scheme 2, also see Supporting Information). The spectra of **2a** and **3a** point to a preferable conformation in which the primary silyl ether occupies axial positions, thus requiring interconversion to a more suitable conformation for the migration to take place (Scheme 2b).

Scheme 2. Selected ^{1}H NMR data of TBDPS-derivatives.



Having in hand suitable conditions for the formation of regioisomers **2-4**, we envisioned their suitability for divergent synthesis approaches. The structural similarities between **2** and **4** and biologically relevant compounds is evident. For instance,

Table 1. Optimization of silyl migration.



Entry[a]	Solvent	Base (eq.)	Time (h)	*Si*=TBDPS[b]			*Si*=TBDMS[b]		
				2a	**3a**	**4a**	**2b**	**3b**	**4b**
1 [c]	THF	Imidazole (2.0)	6	95	nd	nd	95	nd	nd
2	THF	Imidazole (3.0)	72	14	63	23	92	nd	nd
3	THF	DMAP (2.0)	18	81	traces	nd	20	nd	nd
4	THF	Et_3N (2.0)	18	traces	nd	nd	nd	nd	nd
5	THF	KHMDS (2.0)	18	traces	51	15	-	-	-
6	THF	NaH (3.0)	18	traces	57	17	-	-	-
7[d]	Toluene	Imidazole (2.0)	6	93	7	traces	99	nd	nd
8[d]	Toluene	Imidazole (5.0)	56	traces	78	16	66	25	traces
9[e]	DMF	Imidazole (2.0)	18	5	62	33	-	-	-
10[d], [f]	MeOH	Et_3N (1.0)	18	98	nd	nd	>99	nd	nd
11[d]	MeOH	Imidazole (2.0)	18	78	11	traces	-	-	-
12	MeOH	DMAP (2.0)	18	traces	65	28	82	12	traces
13[g]	MeOH	Imidazole (2.0) + Et_3N (2.0)	18	5 (traces)	56 (50)	29 (35)	68 (14)	22 (49)	8 (27)

[a] All reactions were carried out at 0.2 M of **1** in refluxing temperature, except indicated otherwise. [b]Isolated yield. [c] Substrate was used at 0.4 M; [d] Substrate was used at 0.1 M. [e] Carried out at 120 °C. [f] Carried out at room temperature; [g] in parenthesis are presented the results from a reaction in a sealed tube at 100 °C. n.d. – not detected

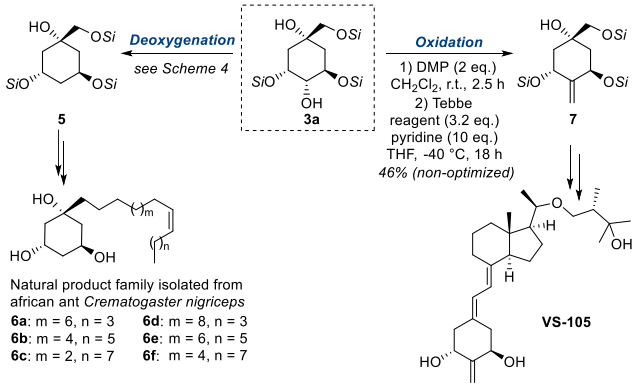
their oxidized forms could be useful in the preparation of carbasugars,[21] the ketonic form of **2** could become a synthetic intermediate in in the recent synthesis of (–)-pseudohygrophorones[22] while the deoxygenation of **4** could provide the unusual hydroxylated ring of hydroisoflavone B.[23] Despite such possibilities, we decided to explore regioisomer **3a** in divergent synthesis by changing the oxidation state of C-5 (Scheme 3). Such strategy would provide us the possibility to prepare the compound **7**, a synthetic intermediate of vitamin D receptor agonist VS-105 (a kidney disease drug that completed phase 1 clinical trials),[24] and to perform the first total synthesis of a metabolite isolated from African ants of species *Crematogaster nigriceps*. These ants were found to produce a family of 1-alk(en)yl-1,3,5-trihydroxycyclohexanes (**6a–6f**), isolated and characterized by Braekman *et al.* in 2003.[25] The long carbon chains of the natural products **6a**–**6f** are derived from common fatty acids and have a mutual cyclitol backbone that could be built from **3a** after deoxygenation into **5** and further synthetic manipulation.

Gladly, the Dess-Martin periodinane oxidation of **3a** gave ketone in an excellent 98% yield, which was further transformed into the exocyclic alkene **7** using Tebbe´s reagent (Scheme 3). The olefination took place despite the congestion around the secondary alcohol caused by the TBDPS groups, similarly to the reported olefination of TBDMS-protected quinic acid ester derivative.[26]

We envisioned that the syntheses of the family of natural products **6** could be easily achieved by selective epoxide opening of key intermediate **10** with organometallic reagent derived from corresponding fatty acid, after deoxygenation of **3a** (Scheme 4a). To avoid regio- and diastereoselective issues in the opening of a cyclic siloxonium ion, we decided to proceed with the Barton-McCombie deoxygenation of **3a** instead of using the previously explored borane-catalyzed deoxygenation with hydrosilanes.[17]

The introduction of the *O*-thiocarbonyl group showed to be challenging due to the required use of a base and subsequent *O*,*O*-silyl group migrations. After failed attempts in preparing the thiocarbonylimidazolide or methyl xanthate from **3a**, phenyl thionocarbonate **8** could be prepared in 89% yield (Scheme 4b) due to the high electrophilicity of phenyl chlorothionocarbonate.

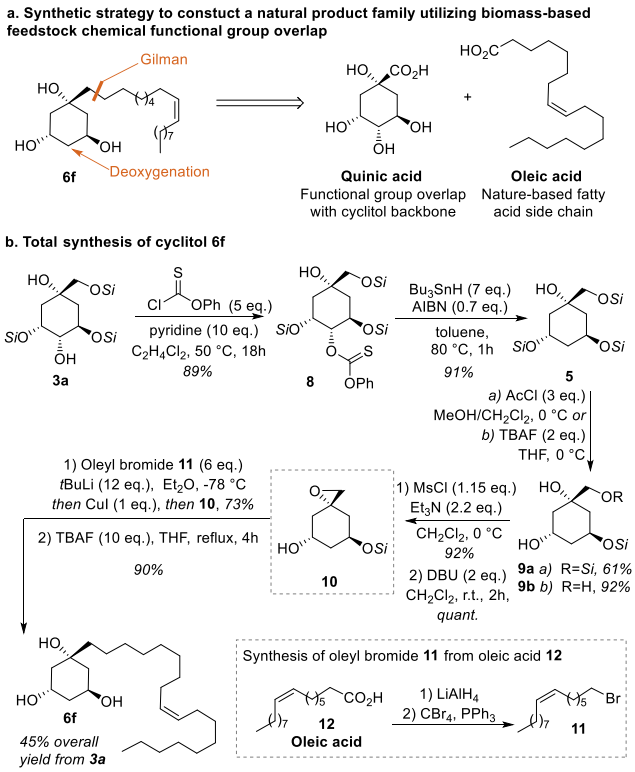
Scheme 3. Divergent modification of 3a and preparation of VS-105 precursor.



Alcohol **5** was cleanly obtained in 91% yield after Barton-McCombie deoxygenation. Despite the myriad of conditions tested for the selective deprotection of the primary TBDPS-group in **5**, cleavage of the secondary silyl ether was always observed. Treatment of **5** with excess acetyl chloride provided

alcohol **9a**, whose structure was elucidated from nOe contacts between the secondary and tertiary hydroxy groups. The use of 2 equivalents of TBAF promoted the secondary and primary TBDPS-groups cleavage to **9b** in 92% yield. Chemoselective mesylation of primary alcohol over secondary and tertiary hydroxy groups of triol **9b** followed by treatment with DBU for intramolecular S_N reaction resulted in the formation of epoxide **10**, a key intermediate in the synthesis of the 1-alk(en)yl-1,3,5-trihydroxycyclohexanes **6** metabolites family. This synthetic approach was showcased for the preparation of the oleic acid derivative **6f**. Hence, oleic acid was reduced to the corresponding alcohol with $LiAlH_4$ followed by conversion of the alkyl bromide **11** through Appel reaction, as previously reported.[27] After unsuccessful attempts on opening the epoxide with the organomagnesium compound, the *in situ* generation of a Gilman reagent by treatment of **11** with *t*-BuLi followed by addition of CuI, promoted the desired formation of the tertiary alcohol in 73%. Cleaving the secondary TBDPS-group led to the formation of the African ants cyclitol **6f** in 90% yield which structure was verified by comparison with previously reported data of the isolated natural product.

Scheme 4. Synthesis of oleyl derivative of trihydroxycyclohexane metabolite from African ants *Crematogaster nigriceps*.



In summary, we herein present the protective group migrations across a quinic acid-derived cyclitol backbone, as an opportunity for the diverse syntheses of high-added-value molecules. The ease of *O,O*-silyl group migration was observed to depend on the silicon substituents in the cyclitol system, with the TBDPS being easier to migrate than less bulky TBDMS. The diol obtained after 2-*O*→1-*O* and 5-*O*→4-*O* silyl groups migration from easily accessible **1a**, was incorporated in the first total synthesis of a metabolite from African ants *Crematogaster nigriceps* in 45% overall yield (10 steps, 34% overall yield from quinic acid).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and characterization data of all synthetic intermediates, ^1H and ^{13}C NMR copies of spectra for all reported compounds. (PDF)

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Notes

The authors declare no competing financial interest.

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