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Deoxygenative divergent synthesis: en route to quinic acid chirons

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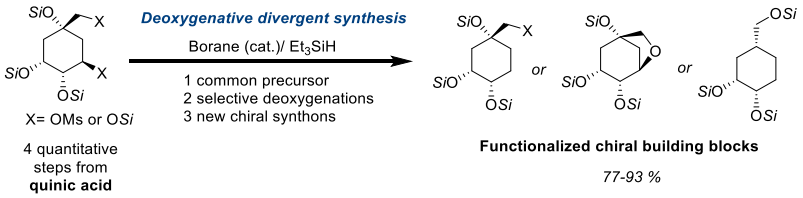
Supporting Information Placeholder



ABSTRACT: The installation of vicinal mesylate and silyl ether groups in a quinic acid derivative, generates a system prone for stereoselective borane-catalyzed hydrosilylation through a siloxonium intermediate. The diversification of the reaction conditions allowed the construction of different defunctionalized fragments foreseen as useful synthetic fragments. The selectivity of the hydrosilylation was rationalized based on deuteration experiments and computational studies.

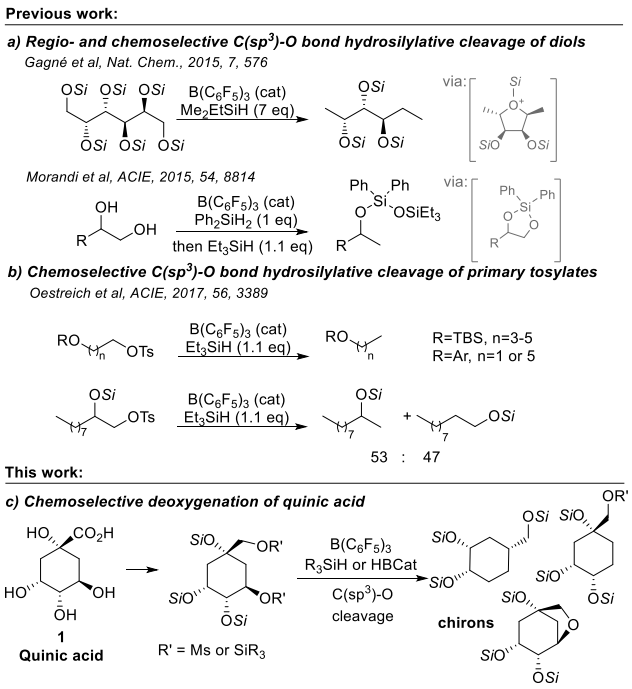
Synthetic strategies remain critically dependent on hemisynthesis or chiral pool despite the plethora of currently available catalytic asymmetric transformations.[1] The contemporary mandatory transition from fossil to bio-based carbon resources calls for the development of synthetic transformations that maximize the full potential of chemical entities or fragments created by Nature. Saccharides are the main components of biomass and the efforts done for their integration in biorefineries have augmented the development of methods for removal of their oxygen functionalities.[2] Dehydration[3] and selective cleavage of C–O bonds[4] of saccharides have been explored in the expansion of the biomass-derived chemical space.[5] The Yamamoto´s seminal $B(C_6F_5)_3$-catalyzed hydrosilylation of C–O bonds[6] has been used in the extensive deoxygenation of saccharides[7] and recently in the regioselective deoxygenation of saccharides,[8] and polyols[8c] to provide new chiral entities (Scheme 1a). Alternative boron catalysts such as Piers' borane ($HB(C_6F_5)_2$)[9] and more recently $B(3,5\text{-}CF_3)_2C_6H_3)_3$,[10] have been demonstrated to catalyze the silylative deoxygenation of biomass-derived sugars.[11] The outcome of this deoxygenation method depends on several stereochemical and electronic parameters: first and foremost is the structure of the oxygenated substrate,[8a] as vicinal groups can assist the C–O bond cleavage.[8c] The second parameter is the hydrosilane employed,[8b, 8c] and the third is the fluoroarylborane catalyst.[12] Gagné and co-workers have recently progressed the field by replacing hydrosilanes by hydroboranes as precursors of H-$B(C_6F_5)_3^-$ hydride in the C–O bond cleavage with different selectivities than the ones observed in the hydrosilylation.[13]

Morandi[14] and Oestreich[15] have expanded the $B(C_6F_5)_3$-catalyzed hydrosilylation of C(sp^3)–O bonds to 1,2-diols and primary tosylates, respectively. Both methods are effective in cleaving the terminal C–O bond, the former due to the formation of a cyclic siloxane intermediate and the latter due to the higher reactivity of the tosylate compared with the silyl ether. Although suitable for the cleavage of primary tosylates containing a primary silyl ether (Scheme 1b, R=TBDMS, n=3-5), or an aryl ether (Scheme 1b, R=Ar, n=1 or 5), rearranged products from anchimeric assistance were observed for 1,2-diols (Scheme 1b, bottom). Indeed, the non-selective opening of a three-membered silyloxonium ion leads to the indiscriminate formation of a primary and secondary silyl ether. Substituents' migration competing with direct deoxygenation processes was further explored by Morandi, providing a reductive pinacol-type rearrangement of vicinal diols.[16] On a related note, the $B(C_6F_5)_3$-catalyzed hydrosilylation of tetrasubstituted epoxides leads to a migratory ring-opening process after the formation of a silyloxonium ion intermediate.[17] While the $B(C_6F_5)_3$-catalyzed hydrosilylation of C–O bonds has been rapidly expanding the accessibility to saccharides-derived chiral fragments for synthesis,[8c,10-11,13,18] we envisioned that different chiral synthons[19] could be reached by focusing on natural cyclitols.

Quinic acid **1** was provisionally considered as one suitable feedstock for the bio-based benzoic acid production[20] or other aromatics.[21] However, high cost associated with the use of

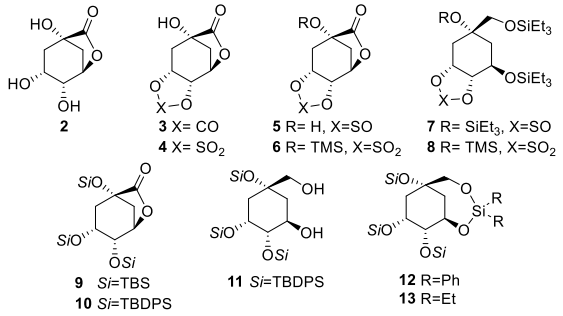
glucose as feedstock for bacterial production of quinic acid [22] has again relegated this cyclitol to the chiral pool.[23] Nevertheless, quinic acid and its acyl-derivatives are widespread secondary metabolites of the shikimic acid pathway[24] in plants and can be obtained for instance from coffee beans, plants, fruits and even food wastes.[25] Herein we present our efforts towards the selective cleavage of C(sp^3)–O bonds of a common quinic acid-derived precursor with judiciously selected *O*-substituents, into diverse chiral fragments (Scheme 1c).

Scheme 1. $B(C_6F_5)_3$-catalyzed selective deoxygenation of 1,2-diols and primary alkyl tosylates.



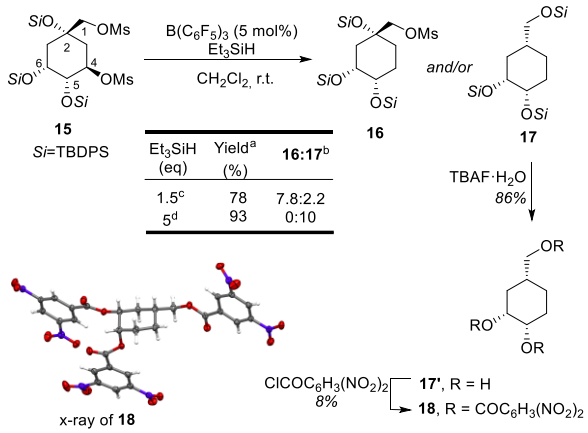
Aware of putative effects imposed by the diverse conformations of cyclitols on the regioselectivity of deoxygenation using the $B(C_6F_5)_3$/SiH system, the vicinal *cis* diol moiety of quinide **2** was derivatized to several functional groups. Besides conferring the desired conformational effect, further deprotection after deoxygenation would provide substrates prone to typical C-C oxidative cleavage and subsequently give chiral linear C_7 fragments. Attempts on the hydrosilylation of cyclitol derivatives **3-13** (Scheme 2) failed in providing any deoxygenated products (see supporting information section 1 for complete rationale).

Scheme 2. Quinic acid derivatives explored in $B(C_6F_5)_3$-catalyzed hydrosilylation



The discouraging lack of reactivity of the silylated quinic acid derivatives prompted us to explore the anchimeric assistance by silyl ethers in the C–O bond cleavage of tosylates, as previously reported by Oestreich and co-workers.[15] Excellent chemoselectivity was reported for the deoxygenation of primary alkyl tosylates from non-vicinal diol derivatives. However, the formation of a three-membered silyloxonium ion intermediate resulted in rearranged products and lack of regioselectivity was observed when considering aliphatic 1,2-vicinal diol systems. Gratifyingly, treatment of **15** with different catalyst loadings and amounts of triethylsilane resulted in formation of **16** and/or **17** in different ratios (Scheme 3 and Table S1 in SI for further experiments). Silyl ethers derived from primary and secondary alcohols have been reported to be more reactive towards $B(C_6F_5)_3$-catalyzed reduction with hydrosilanes than the ones derived from tertiary homologs.[6c, 6d] On the other hand, the neighboring group assistance can deeply impact the regioselectivity. Notably, cleavage of the primary mesylate in **15** was accompanied by stereospecific migration of the silyloxy group from the vicinal tertiary carbon to provide **17** (Scheme 3). The absolute configuration of the deoxygenated product was determined through x-ray diffraction analysis of the 3,5-dinitrobenzoyl derivative **18**, obtained after desilylation of **17** and benzoylation of the triol **17'**.

Scheme 3. Deoxygenation of quinic acid derivative 15

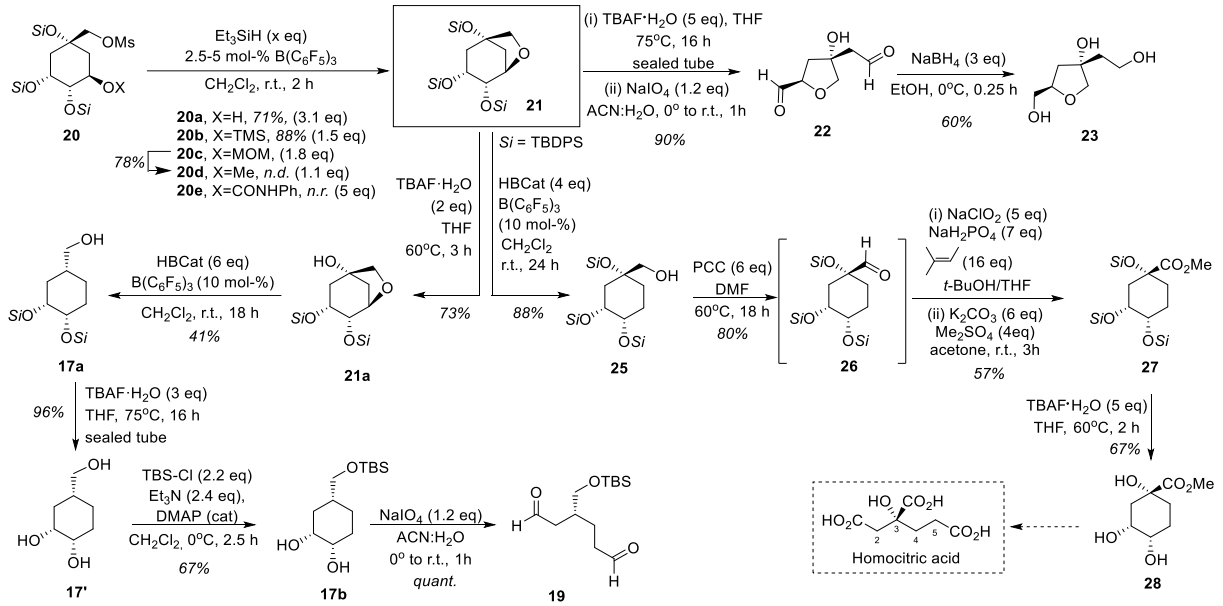


Et_3SiH (eq)	Yield[a] (%)	16:17[b]
1.5[c]	78	7.8:2.2
5[d]	93	0:10

[a] **15** (0.14 mmol) and $B(C_6F_5)_3$ in CH_2Cl_2, at r.t. followed by addition of Et_3SiH; [b] ratio determined from isolated yields; [c] [**15**] = 0.05 M; [d] [**15**] = 0.3 M

Attempts to overcome the higher propensity of C4 towards deoxygenation, by replacing the mesylate with protecting groups proved futile. Instead, $B(C_6F_5)_3$/SiH treatment of **20** having the secondary hydroxyl protected as silyl ether (**20b**) resulted in the fast intramolecular cyclization to bicyclic compound **21** in up to 88% yield (Scheme 4). Exposure of MOM-ether **20c** to the same conditions resulted in the formation of compound **20d** in 78% yield (Scheme 5). Treatment of methyl ether **20d** with additional triethylsilane (1.1 equivalents) in presence of $B(C_6F_5)_3$ led to formation of cyclic ether **21**, as deduced from crude NMR. Carbamoyl protected **20e** was unreactive towards $B(C_6F_5)_3$-catalyzed hydrosilylation, and only starting material was recovered, despite the harsh reaction conditions used (20 mol% catalyst, excess of silane and refluxing toluene). The structural complexity of compound **21**[26] was broken down through oxidative cleavage of the C-C bond upon desilylation and oxidation of the *cis* glycol moiety via Malaprade oxidation to

Scheme 4. Formation and controlled cleavage of bicyclic tetrahydrofuran 21



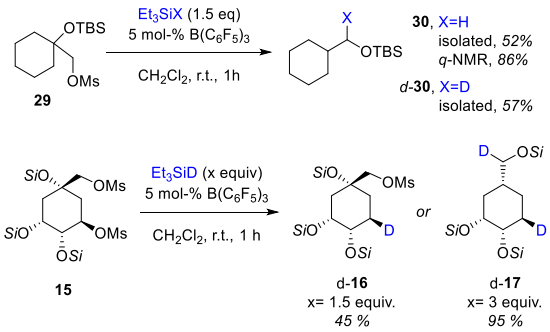
(n.d = yield not deternined; n.r. = no reaction)

provide dialdehyde **22** in excellent yield. The cyclic ethers **22** and **23**, are envisioned as interesting synthetic intermediates due to the presence of oxygen functionality-containing substituents at C1 and C3 positions of the tetrahydrofuran core.[27] The selective deprotection of the tertiary silyl ether of **21** followed by similar cleavage with catechol borane and desilylation also provided compound **17a**. A sequence of silyl ethers' cleavage and primary alcohol protection resulted in **17b** that was submitted to Malaprade oxidation providing dialdehyde **19**, envisioned as a rich fragment for stereoselective synthesis due to the three functionalities and structural similarities with Perlin aldehydes.[28] Impelled by the bicyclic skeleton of **21**, the controlled modification of its stereogenic carbons was attempted. The lack of reactivity of **21** towards cleavage of the O-Si bond by $B(C_6F_5)_3$-catalyzed hydrosilylation was overcome by reduction with catechol borane, as recently developed by Gagne,[13] resulting in the selective cleavage of the C–O bond from the secondary carbon to provide **25** in 87% yield.

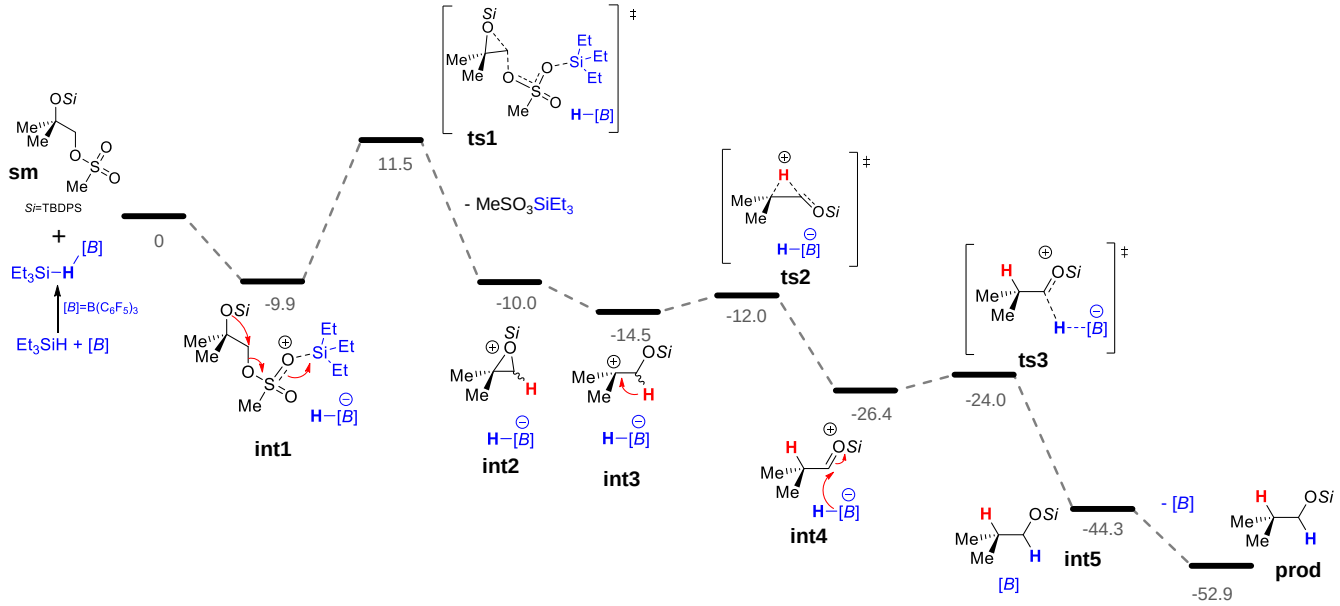
Selective oxidation of primary alcohol moiety of **25** followed by one-pot esterification and desilylation led to **28**, a known intermediate in the synthesis of homocitric acid.[29] Even though not attempted, it is worth noticing that the use of deuteriocatecholborane in the manipulation of **21** would provide an entry for the preparation of labeled homocitrate. Although of potential interest for biological studies, deuterium labeling at position 5 remains unveiled.[29a, 30].

The observed preferred chemoselectivity for C–O bond cleavage of the secondary carbon over the primary mesylate in **15**, suggests the formation of the three-membered silyloxonium ion as proposed previously by Oestreich. The higher propensity of C4 for deoxygenation compared to C1 is justified by the easier formation of the strained three-membered silyloxonium ion in C4-C5 than in C1-C2, as the later will turn C2 into a spiro carbon. Such event should become less energy demanding after removal of one of the carbocycle substituents. Additionally, the easier access of the hydride to C4 over C5 renders this process highly regioselective in the opening of the siloxonium. Motivated by the excellent regioselectivity in opening of the putative three-membered silyloxonium ion with hydrosilanes, compound **29**, an analog of **15**, was submitted to similar deoxygenation protocol. The treatment of cyclohexanol derivative **29** with $B(C_6F_5)_3$ and silyl hydrides resulted in cleavage of the C–O bond and migration of the silyl ether moiety to the primary carbon (Scheme 5), contrasting with the previously reported lack of selectivity for deoxygenation of primary tosylates vicinal to a secondary silyl ether.[15] While no alkyl migration was observed in the deoxygenations of quinic acid derivatives, which was expected given the precedents on the hydrosilylation of epoxides in acyclic systems[17] the migration of hydride from the primary to tertiary carbon was considered.[31] When using Et_3SiD as a reducing agent, the deuteration occurred selectively at the primary carbon, affording *d*-**30** in 57% after isolation. Similar behavior was observed in the hydrosilylation of **15** with Et_3SiD. The delivery of the deuteride to the opposite face of the silyl ethers of the cyclohexane derivative (absolute configuration determined from inspection of vicinal coupling constants) seems to indicate a different mechanism when comparing with the tertiary silyl ether/primary mesylate counterpart.

Scheme 5. $B(C_6F_5)_3$-catalyzed siloxonium opening with Et_3SiD.



Scheme 6. Free energy profile (M06-2X/6-311++G//M06-2X/6-31G**) and mechanistic representation for deoxygenation of model substrate sm, via siloxonium and 1,2-hydride shift. Values are presented in kcal/mol, referring to the initial pair of sm and Et_3Si-H-$B(C_6F_5)_3$**



In order to get further insight on the formation of the silyloxonium intermediate and its regioselective opening, a simplified system was studied by means of Density Functional Theory[32] (Scheme 6), and geometries of the transition states calculated (please consult Figure S1 and full computational account in SI).The energetically favorable interaction of the mesylate group of **sm** with silylium ion in **int1** increases the electrophilic character of the primary carbon, triggering the formation of the silyloxonium ion **int2** through a 21.4 kcal/mol energy barrier. C–O bond lengths in the siloxonium **int2** differ by 0.05 Å, with the most substituted bond being elongated. The equilibration of the siloxonium to **int3**, where the abovementioned C–O bond is clearly broken ($d_{C\text{-}O}$=2.385 Å), is energetically more favorable by 4.5 kcal/mol. The 1,2-hydride shift for neutralization of the positive charge on the tertiary carbon is a favorable process with **int4** being 11.9 kcal/mol more stable than **int3**. Additionally, the energy barrier for the 1,2-hydride migration through **ts2** is only 2.5 kcal/mol. The hydride delivery from the hydridoborate anion to the electrophilic carbon of the oxocarbenium is almost spontaneous and **int4** can simply overcome the barely existent energy barrier of 2.4 kcal/mol for **ts3** to ultimately form the very stable silyl ether **int5**. The overall process is energetically favored as demonstrated by the ΔG_f of **prod** (52.9 kcal/mol) with the rate limiting step being the formation of the siloxonium **int2**.

In conclusion, we have described the $B(C_6F_5)_3$-catalyzed defunctionalization of a cyclitol through hydride delivery to three-membered silyloxonium ions. The success of the deoxygenation of quinide and derivatives using this hydrosilylation depends on the protecting groups. Nevertheless, the achieved deoxygenations proved highly stereoselective and allowed the diversification of chiral fragments that can be obtained from quinic acid. The expansion of this transition-metal free deoxygenation protocol to cyclitols had diversified the array of molecules and fragments that can be obtained from biorenewables.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental details, preliminary studies on hydrosilylation and characterization data of all synthetic intermediates, full accounts on computational calculations and ^{1}H and ^{13}C NMR copies of spectra for all reported compounds. (PDF)

X-ray structure of **18** (CIF)

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Author Contributions

The manuscript was written through contributions of all authors.

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