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Mild Reductive Opening of Aryl Pyranosides Promoted by Scandium(III) Triflate

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Scandium(III) complexes have increasingly found use as promoters in a variety of organic transformations.[1] While the majority of available methods draw upon the ability of scandium to activate C═X π-bonds toward nucleophilic additions, more recent studies have shown that scandium complexes may also activate C−X σ-bonds.[2] Though still underdeveloped, this mode of activation holds considerable potential in chemical synthesis.

Recent efforts in our laboratories have focused on the design and development of a range of chiral organosilane reagents for the synthesis of functionalized pyrans through a stereoselective [4+2]-annulation.[3] Herein, we report a mild and efficient reductive opening of aryl pyranosides obtained from our annulation methodology, using scandium(III) triflate in the presence of a hydride source (Et_3SiH). The reaction results in the efficient reduction of the benzylic C−O σ-bond with formation of a stereochemically well-defined acyclic system (Scheme 1).

Historically, the opening of cyclic ethers has relied on hydrogenation employing high pressure, temperature, or strong acids, limiting the reaction scope.[4] Dissolving metal reduction has also been employed with some degree of success,[5] and conditions utilizing trialkylsilanes have also been described. However, strong acidic conditions[6] or activated substrates[7] are typically needed to achieve conversion.

Accordingly, a range of Lewis acids were screened in the presence of Et_3SiH with the hope of providing acyclic substrates.[8] This survey identified $Sc(OTf)_3$ as the only reliable promoter, giving the desired acyclic congener in moderate yields (Table 1, entry 1). Increasing the catalyst loading to 2 equiv gave excellent yields of the desired acyclic product after 24 h (entry 2). Decreasing the amounts of triethylsilane slowed the reaction rate and lowered the yield (entry 3). Finally, it was found that 2 equiv of scandium triflate and 5 equiv of triethylsilane gave the best results under ambient conditions (entry 4). Microwave irradiation was also considered to expedite the reaction. A significant reduction in reaction time (24 h to 100 min) with minimal loss of chemical yield was achieved (entry 5). In addition, the quantities of $Sc(OTf)_3$ for the reaction could be lowered to substoichiometric amounts.

To determine functional group compatibility, a series of aryl pyranosides were subjected to both room temperature and microwave ring-opening conditions (Table 2). Aromatic nitro groups (entry 3) and basic nitrogens (entry 4) were tolerated. Aromatic halogens, which may be lost under normal hydrogenation, remained intact (entries 5 and 8). Aromatic and aliphatic methyl ethers tolerated the reduction (entries, 3, 5, 8−10, and 12); however, TBS ethers are cleaved under the described conditions to give the acyclic product as its triol (entry 10). No stereochemical dependency was observed in either the 2,6-*trans* or *cis*-tetrahydropyran giving excellent yields of the opened form (entries 1−8 trans, 9−12 cis). The methodology was also extended to 1-aryl deoxyribose (entry 11) and aryl C-glycosides (entry 12) to give highly oxygenated acyclic products.

Scheme 1. Reductive Opening of Aryl Pyranoside

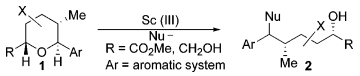
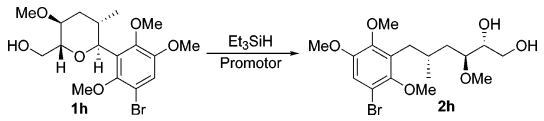


Table 1. Reduction Promoted by $Sc(OTf)_3$



entry[a]	promotor	equiv	equiv Et_3SiH	time	isolated yield (%)[b]
1	$Sc(OTf)_3$	1	20	24 h	61
2	$Sc(OTf)_3$	2	20	24 h	88
3	$Sc(OTf)_3$	2	2	24 h	67
4	$Sc(OTf)_3$	2	5	24 h	88
5[c]	$Sc(OTf)_3$	0.25	5	100 min	80

[a] Reactions were run in DCM at 25 °C for 24 h unless otherwise noted. [b] All yields are based on isolated product after purification by chromatography. [c] Reaction was irradiated under microwave conditions (DCM, 300 W, 70 PSI, 100 °C).

Table 2. Scope of $Sc(OTf)_3$ Promoted Ring-Opening Reaction

Entry	Cyclic ether **1**	Acyclic Product **2**	% Yield[a]
	Ar / R	R	RT[b] μ[c]
1	**1a** Ph	H	**2a** 67 (71)
2	**1b** 2-Napthyl	H	**2b** 83 (86)
3	**1c** 5-NO_2-2,3,6-$(MeO)_3C_6H$	OMe	**2c** 82
4	**1d** 4-Me_2N-C_6H_4	H	**2d** 73
5	**1e** 5-Br-2,3,6-$(MeO)_3C_6H$	OMe	**2e** 87 (89)
6	**1f** Ph	H	**2f** 78 (71)
7	**1g** 1-Napthyl	H	**2g** 93 (89)
8	**1h** 5-Br-2,3,6-$(MeO)_3C_6H$	OMe	**2h** 88 (80)
9	**1i** 4-Me-2,3,5,6-$(OMe)_4C_6$		**2i** 78
10	**1j** 4-Me-2,3,5,6-$(OMe)_4C_6$		**2j** 62
11	**1k** Ph		**2k** 50 (51)
12	**1l** 2,4,6-$(OMe)_3C_6H_2$		**2l** 65 (61)

[a] All yields are based on isolated product after purification by chromatography. [b] Reactions were run in DCM using 5 equiv of Et_3SiH in the presence of $Sc(OTf)_3$ (2.0 equiv) at 25 °C. [c] Reactions were run in DCM using $Sc(OTf)_3$ (0.25−2 equiv) and 5 equiv of silane at 300 W, 70 PSI, and 100 °C.

Having optimized the reductive opening of a number of aryl pyranosides using Et_3SiH, other nucleophiles were evaluated to widen the scope of the reaction (Table 3). We were pleased to find

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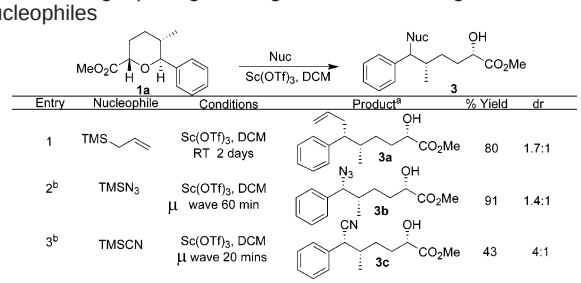
Table 3. Ring-Opening Utilizing Carbon and Nitrogen Nucleophiles



[a] All yields are based on isolated product after purification by chromatography and dr determined by ^{1}H NMR. [b] Reactions were irradiated under microwave conditions (DCM, 300 W, 70 PSI, 100 °C).

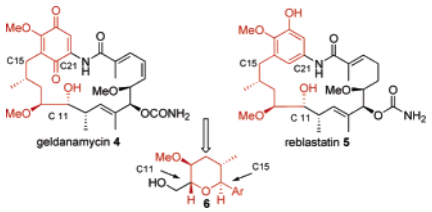


Figure 1. Related ansamycin antibiotics.

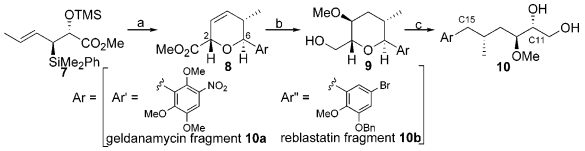
that both nitrogen and carbon-based nucleophiles[9] participated in the opening to give substitution on the benzylic position (entries 1−3). For example, **1a** in the presence of allylsilane provided allyl derivative **3a** in 80% yield (entry 1). Utilizing trimethylsilyl azide gave **3b** in similar yields and selectivity (entry 2). Finally, TMSCN provided **3c** in lower yield but at a useful level of selectivity (entry 3). Initial experiments utilizing the described reaction conditions gave acyclic products with moderate levels of selectivity (dr = 1.4−4:1) and provided the basis for the introduction of useful functional groups at the benzylic carbon.[10]

Our immediate plan is to use this methodology in the synthesis of geldanamycin **4**, a potent inhibitor of heat-shock protein 90 (HSP 90). HSP 90 has been of great interest since the discovery of the ATPase binding regions' role in cancer and protein maintenance.[11] Many inhibitors of HSP 90 are currently known, of which the ansamycins antibiotics have received notable attention not only for their potential role in cancer treatment but also for their synthetically challenging molecular architecture.[12]

In that context, we have completed the synthesis of reblastatin **5**, a benzenoid ansamycin-like cell cycle inhibitor.[13] Our initial route utilized an awkward deoxygenation of the C15 carbon. Since geldanamycin and reblastatin share several structural features, the development of a more efficient method that addresses benzylic (C15) deoxygenation would be useful in accessing these molecules (Figure 1). We envisioned that activation of the pyran C−O σ-bond of pyran **6**, presumably through metal complexation, and nucleophilic opening should allow for a concise synthesis of the C11−C21 portion of the ansamycins and circumvent the need for deoxygenation strategies.

This is showcased in the synthesis of the C11−C21 fragments of both geldanamycin **4** and reblastatin **5** (Scheme 2). Applying our [4+2]-annulation strategy utilizing enantioenriched (*E*)-crotylsilane **7** generated the required dihydropyran core systems **8a** and **8b** in excellent yield and selectivity. Selective hydroboration of the cyclic double bond provided a secondary alcohol, which was subsequently methylated with Meerwein's reagent. Ester reduction with $LiBH_4$ provided primary alcohols **9a** and **9b**. Reductive opening with $Sc(OTf)_3/Et_3SiH$ gave the C11−C21 fragments of both geldanamycin **10a**[14] and reblastatin **10b**[10] as previously reported. In regards to functional group compatibility, it is interesting to note that the benzyl ether of **10b** was preserved under the described conditions.

Scheme 2. C11−C21 Fragments of Reblastatin and Geldanamycin



[a] Reagents and conditions: (a) ArCHO, TfOH, DCM, −78 °C, **8a** Ar′ = 63% 2,6-trans/cis = 3:1, **8b** Ar″ = 87% 2,6-trans/cis = 20:1. (b) (i) $BH_3{\cdot}SMe_2$, H_2O_2, THF; (ii) Me_3OBF_4, DCM; (iii) $LiBH_4$, Et_2O, three steps, **9a** Ar′ = 68%, dr = 4:1, **9b** Ar″ = 56%, dr = 3:1. (c) $Sc(OTf)_3$, Et_3SiH, DCM, **10a** Ar′ = 84%, **10b** Ar″ = 63%.

In conclusion, an efficient method for the nucleophilic ring opening of stereochemically well-defined aryl pyranosides is presented. The reaction effects a formal deoxygenation of the benzylic position to provide useful, enantioenriched, building blocks. Future work will include further determination of the reaction scope and application of the present methodology in natural product synthesis.

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Supporting Information Available: Experimental details and selected spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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