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Reductive Desilanolation as a Route to Benzonitriles. An Application to a Concise Synthesis of the Aromatic Sector of Calicheamicin.

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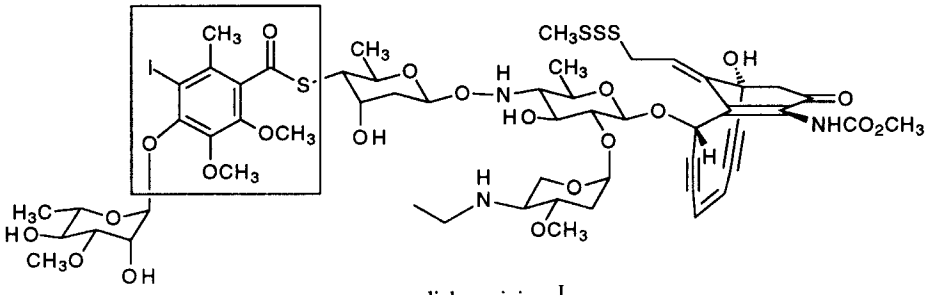
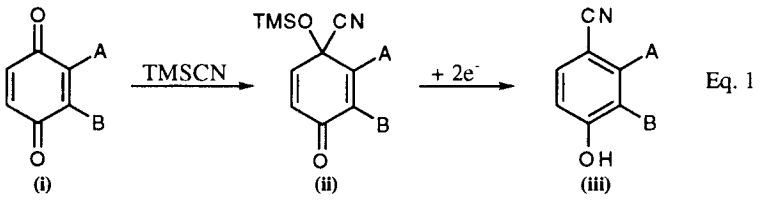
Abstract: The TMS-cyanohydrins of quinones undergo reductive desilanolation in the presence of samarium iodide to form hydroxybenzonitriles. Benzoquinone **1** was converted to the hexasubstituted aromatic fragment of calicheamicin **4** by this method.

When the enediyne antibiotics esperamicin and calicheamicin were discovered and disclosed, primary attention was quite naturally directed to the effector region of the molecules. Given the structural novelty of the aglycone and its unique ignition mechanism, this early emphasis is hardly surprising.[1] However, continuing research enabled by synthetic advances from the laboratories of Nicolaou[2] and Kahne,[3] as well as our own,[4] have revealed the critical role of the aryl-tetrasaccharide domain of the drug. This carbohydrate segment in of itself (as the methyl glycoside) and within the drug, has remarkable DNA binding properties.[5] Possibilities for exploring DNA-carbohydrate interactions in transcriptional modulation are currently being pursued.[6]



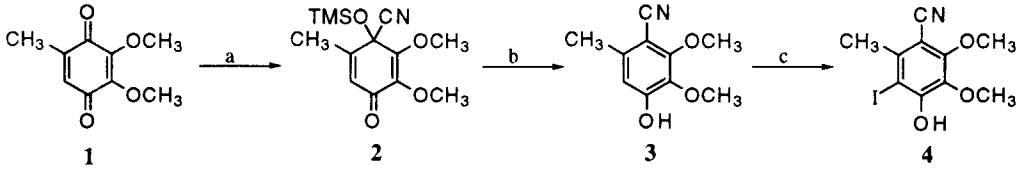
calicheamicin γ_1^I

The structural reasons for the DNA recognition properties of the aryl-tetrasaccharide domain and the specific role that the aromatic sector plays is a matter of continuing interest.[7] The first preparation of the aromatic sector was described by Nicolaou.[8] While this chemistry was important in facilitating synthetic progress in the area, possibilities for an alternate approach with improvements in terms of conciseness, potential control in placement of the iodine, and avoidance of expensive reagents could be entertained. In particular, we wondered about the possibility of converting *p*-quinones to *p*-hydroxybenzonitriles by the paradigm implied in Equation 1. The success of such a venture would, in each case, depend on the selectivity of TMS-cyanohydrin formation (see formation of **ii** rather than its regioisomer). Another critical question was the feasibility of reductive "silanolate" ejection in contrast to reductive de-cyanation.

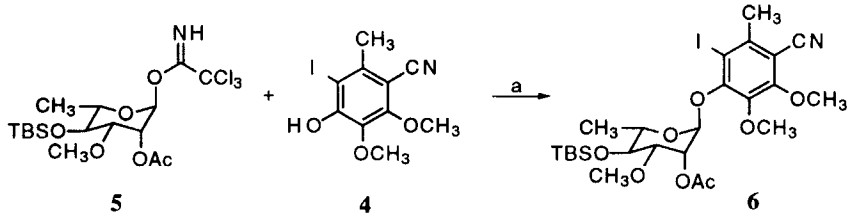


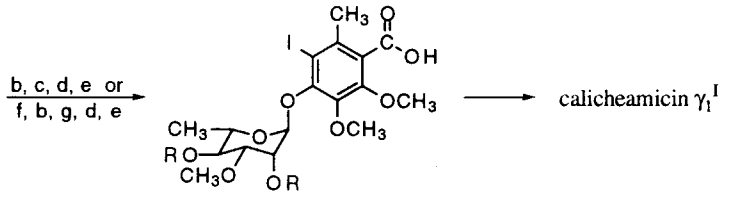
Eq. 1

To explore these matters, we set as our first goal the synthesis of compound **4**. Following the precedents of Evans[9] and Hegedus,[10] commercially available quinone **1** was converted to the TMS-cyanohydrin **2**. Treatment of this compound with samarium iodide[11] afforded **3**,[12] which upon iodination (ICl)[8b,13] gave a 76% overall yield of **4**. The latter was smoothly glycosylated with the previously described[4b] donor **5** to afford a 95% yield of compound **6**. The acid **7b**[14] derived from nitrile **6** was utilized in a convergent total synthesis of calicheamicin γ_1^I.[15]



Scheme 1: a) TMSCN, KCN/18-crown-6 b) SmI_2, THF, MeOH, 82% c) ICl, CH_3CN, 93%





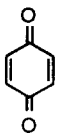
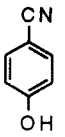
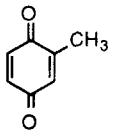
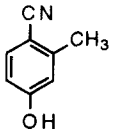
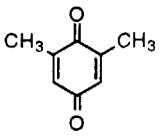
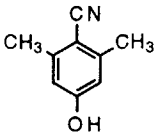
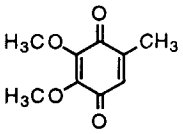
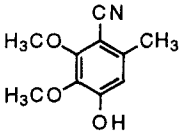
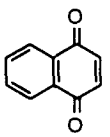
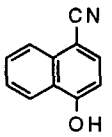
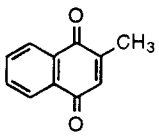
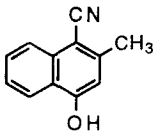
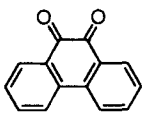
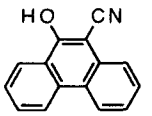
7a R = TBS (71% from **6**)
7b R = TES (72% from **6**)

Scheme 2: a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 95% b) NaOMe, MeOH c) TBSOTf, DMAP, pyridine, CH_2Cl_2 d) DIBAL, hexanes e) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF, H_2O f) $Bu_4N^+F^-$, THF g) TESOTf, DMAP, pyridine, CH_2Cl_2

To demonstrate the general utility of the method, we prepared a variety of aryl nitriles from their respective quinones. The results are outlined in Table 1. Successful results were obtained for a number of benzoquinones

and naphthoquinones.[16] The ratios of regioisomeric products were dictated by the selectivity of TMS-cyanohydrin formation and were nearly identical to those observed by Evans.[9] In addition, the conversion of phenanthrenequinone to 10-hydroxy-phenanthrene-9-nitrile suggests the possibility of using *ortho*-quinones for a similar transformation.[17]

Table 1 The Preparation of Hydroxylbenzonitriles

Quinone	Product	Yield[a]	Ratio of Regioisomers[b]
		80%	--
		78%	10:1
		82%	20:1
		82%	20:1
		75%	--
		84%	10:1
		89%	--

[a] The yields are based upon pure isolated material.

[b] The ratios were determined by NMR analysis of the crude benzonitriles.

In a typical reaction, the quinone (ca. 0.5 mmol) was dissolved in CH_2Cl_2 (1.0 mL[18]) and stirred at room temperature. Trimethylsilyl cyanide (1.2 equiv) and potassium cyanide/18-crown-6 complex (ca. 1 mg) were

added. The reaction was usually complete after 20 minutes. The solvent was removed *in vacuo* and the crude cyanohydrins were dissolved in THF (1.5 mL) and methanol (0.75 mL). The solution was cooled to -78 °C and samarium(II) iodide in THF (0.1 M, ca. 2 equiv) was slowly added until the reaction was complete by TLC. The mixture was added to saturated aqueous NH_4Cl (10 mL) and extracted with diethyl ether (2 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography.

Acknowledgments: This work was supported by NIH Grant No. CA-28824.

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12. Small amounts (~ 5%) of the corresponding hydroquinone were isolated, but it is unclear whether it arose from less than ideal selectivity in the reduction of the TMS-cyanohydrin or from direct reduction of quinone starting material still remaining in the crude cyanohydrin mixture.
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16. Competitive bis-cyanohydrin formation was sometimes observed in small scale reactions or when an excess of catalyst was used.
17. We should note that two attempted examples did not work well. In the cases of 1,2-naphthoquinone and 9,10-anthracenequinone, competition from the bis-cyanohydrin formed was quite serious.
18. Less soluble quinones such as phenanthrenequinone required more dilute conditions.

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