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Direct Introduction of CH_2OH by Intermolecular Trapping of CO

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Summary: Alkyl iodides are converted to the corresponding hydroxymethyl compounds in good yield by treatment with catalytic triphenylgermane-$NaBH_3CN$-AIBN in benzene-THF under an atmosphere of CO at high pressure. This methodology is used for the synthesis of an analogue of the B ring of the calicheamicin oligosaccharide in which the hydroxylamine at C4 is replaced by a hydroxymethyl group.

Calicheamicin γ^1 (Figure 1) is an antitumor antibiotic that has attracted a great deal of attention recently because it cleaves DNA site selectively.[1] It consists of a chromophore attached to a very unusual oligosaccharide chain. The oligosaccharide chain contains a hydroxylamine glycosidic linkage which we have suggested is critical for effective DNA binding.[2] To test this hypothesis, we decided to "mutate" the N-O linkage to a C-O linkage and assay the effects on DNA binding. This requires making the C4 hydroxymethyl monosaccharide 4 (Scheme 2) and incorporating it into our synthesis of the calicheamicin oligosaccharide. Although monosaccharide 4 appears to be a simple target, we soon found out that introducing hydroxymethyl (or formyl) equivalents into sugars is a formidable challenge. Below we report a direct and efficient method for introducing hydroxymethyl units into organic molecules, including sugars, using intermolecular radical trapping of CO and *in situ* reduction.

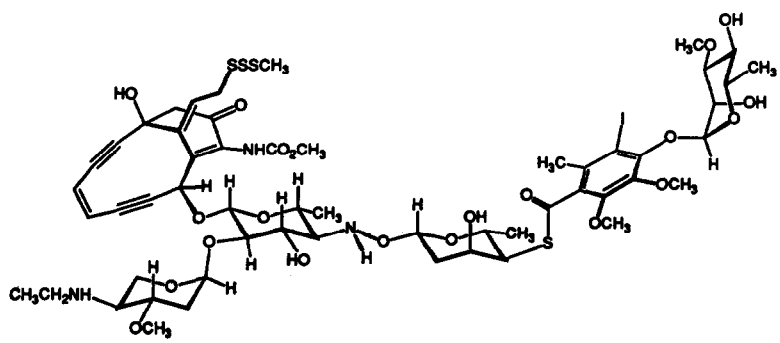
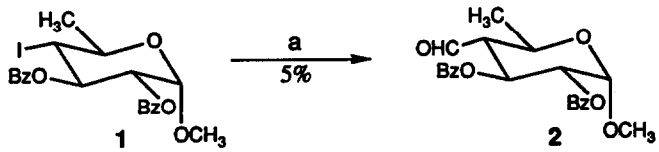


Figure 1. Calicheamicin γ^1

The radical trapping grew out of efforts to introduce the desired carbon-carbon bond via S_N2 displacement. An enormous amount of effort has gone into developing methods to introduce hydroxymethyl (or formyl) equivalents

into organic molecules using S_N2 chemistry in the past three decades and there are numerous conditions and reagents available.[3] Unfortunately, none of the methods we tried worked on protected sugar substrates. S_N2 displacements can be extremely difficult in sugars because the subtrates are inductively deactivated and the nucleophiles are often very basic; the result is that elimination often predominates over displacement. This is what happened in the cases we examined. Radical methods offer a potential solution to the problem of unwanted elimination.[4]

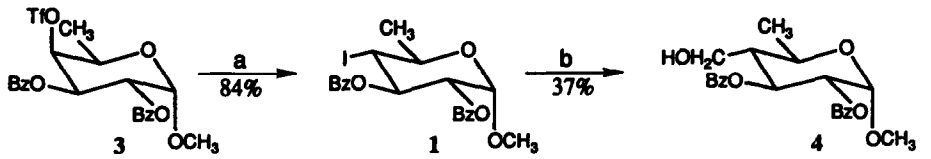
Ryu *et al.* recently reported Bu_3SnH/AIBN induced addition of CO to alkyl radicals under high pressure to form the corresponding aldehydes.[5] We examined this reaction, which works for simple alkyl halides, and found that it gives only a 5% yield for the formylation of a secondary sugar radical (Scheme1). The major product of this reaction was reduction of the alkyl halide to the corresponding alkane, presumably because quenching of the alkyl radical is faster than the trapping of CO to form the acyl radical.



Scheme 1. a) Bu_3SnH (2 eq), AIBN (0.1 eq), Benzene, 1200 psi CO, 105 °C, 8 hr.

It seemed that it should be possible to minimize the reduction product using a strategy, first investigated by Corey, to generate a hydride donor at low concentration *in situ*.[6] Since *in situ* generation of a hydride donor requires the presence of a reducing agent, we anticipated being able to go directly from the appropriate alkyl halide to the desired primary alcohol.

The desired transformation was accomplished by combining sugar iodide **1** (0.510 g, 1 eq), triphenylgermane (0.031 g, 0.1 eq),[7] $NaBH_3CN$ (0.187 g, 2.9 eq), and AIBN (0.017 g, 0.1 eq) in 37 mL of benzene/THF (40 : 1) in a glass tube, which was inserted in a 300 mL autoclave (Scheme 2).[8] The solution was degassed and then stirred at 105 °C under 1400 psi of CO. After 12 hrs, the reaction was cooled to room temperature and CO was released slowly. The desired hydroxymethyl monosaccharide **4** was isolated after aqueous workup and purification by flash chromatography on silica gel (25% ethyl acetate, petroleum ether) in 37% yield. It is worth noting that the intermolecular trapping proceeds stereoselectively (20:1) to give the equatorial isomer. In direct contrast, anomeric sugar (C1) radicals trap to give the axial isomer stereoselectively.[9] It is not clear whether the stereoselectivity in this



Scheme 2. a) NaI (1.5 eq), acetone, 25 °C, 6 hr b) Ph_3GeH (0.1eq), AIBN (0.1 eq), $NaBH_3CN$ (2.9 eq), Benzene-THF (50:1), 1400 psi CO, 105 °C, 12 hr.

case results from trapping of the sterically less hindered equatorial acyl radical or from enhanced stability or reactivity of the C4 equatorial alkyl radical relative to the axial radical.

Considering the difficulty of the case the results were encouraging. In the only other report of an intermolecular trapping of a C4 sugar radical (with acrylonitrile), Giese obtained a 30% yield.[10] We have

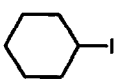
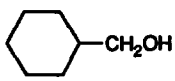
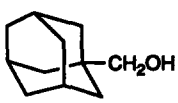
Entry	Substrate	Product	Yield[11] (%)
1	$CH_3(CH_2)_9I$	$CH_3(CH_2)_9CH_2OH$	59
2			62
3			75

Table 1.

investigated the reaction with some more standard alkyl iodides and the results demonstrate that it is an efficient method for introducing hydroxymethyl groups (Table 1).

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11. Yields refer to isolated purified product. All new compounds were characterized by ^{1}H and ^{13}C NMR and FAB MS.

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