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Oxymercuration of Homoallylic Alcohol Derived Hemiacetals: Diastereoselective Synthesis of Protected 1,3-Diols

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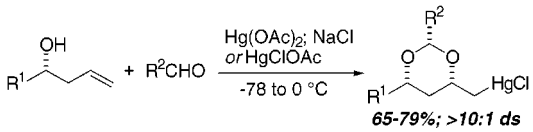
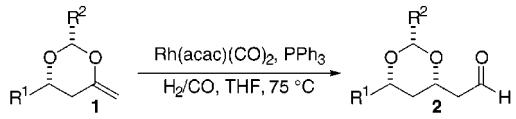
ABSTRACT



Protected 1,3-diol synthons may be synthesized efficiently from homoallyic alcohols and simple aldehydes by oxymercuration of the derived hemiacetals. The reactions are diastereoselective and proceed without the use of solvent. Both $Hg(OAc)_2$ and HgClOAc are effective in the reaction, and the latter produces isolable organomercurial chlorides directly.

We have been engaged in the development of stereoselective methods for the synthesis of (1,3,5...)-polyols,[1] as such structural units are found widely in biologically active natural products.[2] One approach focused on the rhodium-catalyzed hydroformylation of enol acetals **1** (Scheme 1). While this

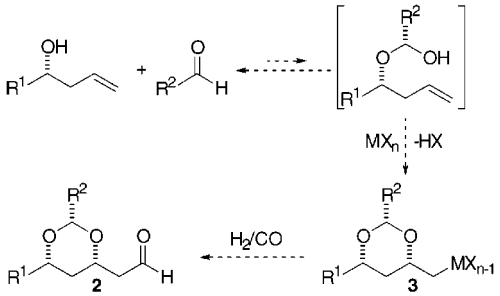
Scheme 1



methodology was found to be quite effective in producing aldehydes **2**, its utility in polyol synthesis is ultimately limited by the difficulty in synthesizing large quantities of the enol acetals.[3]

Mechanistic analysis of the hydroformylation process suggests the intermediacy of alkylrhodium **3** (M = Rh; Scheme 2). In devising an alternate approach to the synthesis of aldehydes **2**, it occurred to us that access to a species such as **3** might be secured by oxymetalation of homoallylic alcohol derived hemiacetals as outlined in Scheme 2. In principle, such a reaction could lead to a one-pot conversion of homoallylic alcohols to aldehydes **2**. Herein we report the successful development of an oxymercuration of homoallylic alcohol derived hemiacetals.[4]

Scheme 2



(1) (a) Leighton, J. L.; O'Neil, D. N. *J. Am. Chem. Soc.* **1997**, *119*, 11118−11119. (b) Leighton, J. L.; Chapman, E. *J. Am. Chem. Soc.* **1997**, *119*, 12416−12417. (c) Sarraf, S. T.; Leighton, J. L. *Tetrahedron Lett.* **1998**, *39*, 6423−6426.

(2) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021−2040.

(3) We have employed the method of Petasis: Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1996**, *37*, 141−144. While effective, the method is less amenable to larger scales.

(4) For reviews of oxymercuration reactions, see: (a) Larock, R. C. *Solvomercuration/Demercuration Reactions in Organic Synthesis*; Springer: New York, 1986. (b) Larock, R. C. In *Comprehensive Organometallic Chemistry II*; McKillop, A., Vol. Ed., and Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, U.K., 1995; Vol. 11, pp 389−435.

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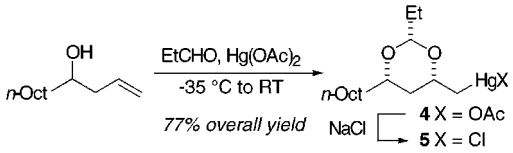
In 1974 Overman reported that stable hemiacetals derived from allylic and homoallylic alcohols and chloral undergo smooth oxymercuration when subjected to the action of Hg-$(OCOCF_3)_2$.[5,6] More recently, Bloodworth has shown that hemiperacetals derived from allylic hydroperoxides and aliphatic aldehydes undergo oxymercuration in moderate yields.[7] It could reasonably be postulated that the success of these methods derives from the high concentrations of hemiacetal that obtain in both cases. Indeed, Overman reported that the use of benzaldehyde instead of chloral resulted in drastically lower yields of the desired products. Nevertheless, it was of interest to revisit the possibility of using simple aliphatic aldehydes rather than chloral, as this would contribute greatly to the utility of the method.

With these design considerations in mind, we began our investigation with 1-dodecen-4-ol (Scheme 3). Treatment of

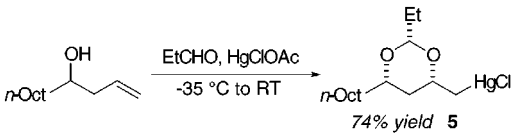
Scheme 3



this alcohol with 1.5 equiv of propionaldehyde and 1.0 equiv of $Hg(OAc)_2$ in THF led to formation of alkylmercury acetate **4**, along with a lesser amount of a diastereomer and several other unidentified products, as judged by ^{1}H NMR spectroscopy of the unpurified reaction mixture. Addition of brine to the unpurified reaction mixture then allowed the isolation of alkylmercury chloride **5**.[8] After some experimentation, it was discovered that the reaction was best carried out under solvent-free conditions at reduced temperatures. Under optimized conditions, the overall diastereoselectivity was >10:1 and the major product **5** could be isolated in 77% yield.

In an effort to minimize handling of organomercurial intermediates, it was of interest to investigate the use of HgClOAc[9,10] in the cyclization, as this would lead to the direct synthesis of the alkylmercury chlorides without the need for anion exchange. Indeed, we have found that HgClOAc is generally as effective as $Hg(OAc)_2$ in inducing the desired cyclization (Scheme 4). Furthermore, the unpuri-

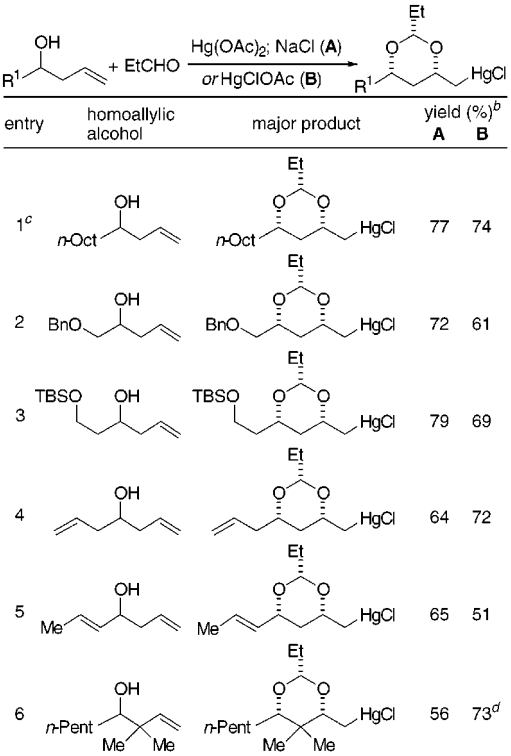
Scheme 4



fied reaction mixture is simply subjected to chromatographic purification to give the cyclized products directly with a minimum of handling and manipulation. In this fashion alkylmercury chloride **5** could be synthesized directly in 74% yield.

With these initial results established, we endeavored to delineate the scope of the reaction (Table 1). In every case

Table 1. Oxymercuration of Homoallylic Alcohol Derived Hemiacetals[a]



[a]Method A: 3.0 equiv EtCHO, 1.0 equiv $Hg(OAc)_2$, -78 °C to RT. Method B: 3.0 equiv EtCHO, 1.0 equiv HgClOAc, -78 °C to RT. [b]Isolated yield of purified major product. [c]-35 °C to RT. [d]1.2 equiv HgClOAc.

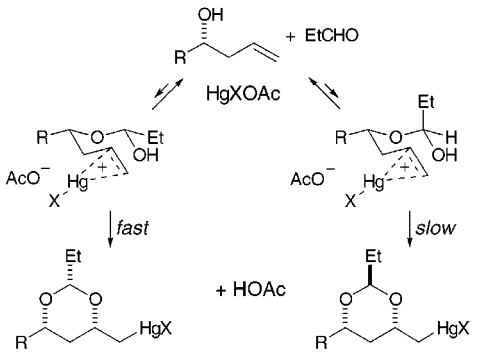
the diastereoselectivity was found to be at least 10:1 in favor of the *all-cis* product, as measured by ^{1}H NMR spectroscopy of the unpurified reaction mixtures. Benzyloxy, silyloxy, and alkenyl groups, likely to be of considerable utility in polyol synthesis, are all well-tolerated (entries 2−4). Alkene substitution can lead to good chemoselectivity in diene substrates (entry 5), and substitution in the allylic position is also well-tolerated (entry 6), although this latter reaction is significantly slower than the other examples. Propionaldehyde has become the aldehyde of choice simply for its convenience; however, other alkanals work equally well.

(5) Overman, L. E.; Campbell, C. R. *J. Org. Chem.* **1974**, *39*, 1474−1481.
(6) A related example involving ketone hemiacetals has been recorded. See: Kitching, W.; Lewis, J. A.; Fletcher, M. T.; de Voss, J. J.; Drew, R. A. I.; Moore, C. J. *J. Chem. Soc., Chem. Commun.* **1986**, 855−856.
(7) (a) Bloodworth, A. J.; Shah, A. *J. Chem. Soc., Chem. Commun.* **1991**, 947−948. (b) Bloodworth, A. J.; Tallant, N. A. *J. Chem. Soc., Chem. Commun.* **1992**, 428−429.
(8) All new compounds were characterized spectroscopically. Stereochemical determinations were derived from NOE experiments. See the Supporting Information for details.
(9) Bowmaker, G. A.; Churakov, A. V.; Harris, R. K.; Oh, S.-W. *J. Organomet. Chem.* **1998**, *550*, 89−99.
(10) We have developed an alternative procedure for the preparation of HgClOAc. See the Supporting Information for details.

Interestingly, benzaldehyde performs poorly in this reaction, in agreement with the original Overman observation. The use of acetone does not lead to the production of significant amounts of the desired acetonide product, presumably because of greatly reduced hemiacetal concentration.

It is of interest to understand whether the observed diastereoselectivity is a result of kinetic or thermodynamic factors.[11] A plausible scenario for kinetic control is outlined in Scheme 5. Rapid and reversible hemiacetal formation and

Scheme 5



mercurinium ion formation are followed by rate- and product-determining cyclization, wherein the lowest energy pathway is controlled by minimization of steric strain.

Control experiments support this mechanistic postulate. A mixture of $Hg(OAc)_2$ and EtCHO was treated with 1-dodecen-4-ol according to the procedure described above. Upon completion of the reaction, MeCHO (3.0 equiv) was added and the mixture was stirred for an additional period of 1.5 h. No incorporation of MeCHO into the organomercury product was observed, indicating irreversibility in the cyclization step. In a related experiment, organomercury chloride **5** was treated with AcOH and MeCHO and, as before, no incorporation of MeCHO into **5** was observed.

The reported reactions are efficient, diastereoselective, and experimentally simple, delivering useful polyol synthons from simple reagents. In addition, it may prove possible to develop in situ derivitization methods for the alkylmercury products, thus eliminating all handling of potentially toxic intermediates. Our efforts to achieve such a process in the arena of carbonylation are in progress and will be reported separately.

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

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(11) In the Overman study of chloral-derived hemiacetals, the oxymercuration step was determined to be reversible.[5]