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Homologation of allylic alcohols. An approach to cyclic and acyclic polyoxygenated compounds

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Abstract

The combination of the Sharpless asymmetric epoxidation reaction with a sulfur ylide mediated synthesis of allylic alcohols from epoxides provides a powerful iterative process for the production of polyoxygenated compounds. The alkene installed in the sulfur ylide reaction has also been used in a number of ring closing metathesis reactions to produce highly oxygenated cyclic compounds.

The synthesis of highly oxygenated organic molecules continues to be an area of interest for synthetic chemists. The stereo- and regio-controlled placement of oxygen represents a particular challenge. Recent examples of iterative placement of oxygen have been shown by Hanessian,[1] Lipshutz,[2] McDonald,[3] Sweeney[4] and Rainer.[5] Of particular relevance to the chemistry described herein is the use of silylated epoxides to produce 1,2-diols in an iterative fashion employed by Wicha.[6] We wished to combine two reactions in order to produce a new protocol for directed oxygen placement on a growing alkyl chain. The Sharpless asymmetric epoxidation[7] (SAE) is a well known reaction and has been widely used in organic synthesis for a number of years. It provides reliable, and importantly, predictable levels of enantiomeric excess in the epoxidation of allylic alcohols. Mioskowski has reported the conversion of epoxides to allylic alcohols using a sulfur ylide.[8] The ylide reacts regioselectively at the less hindered end of the epoxide, transfering a methylene group with concomitant loss of dimethyl sulfide. We envisaged that these two reactions could be used in tandem: one produces epoxides from allylic alcohols, the other allylic alcohols from epoxides. The result is then a simple protocol for homologation of allylic alcohols. In addition, we also hoped to use the alkene installed in the sulfur ylide reaction to provide an entry to a number of substrates suitable for ring closing metathesis reactions. This would extend the scope of the protocol to cyclic as well as acyclic targets.

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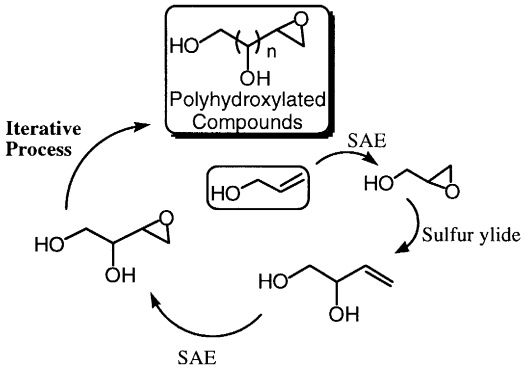
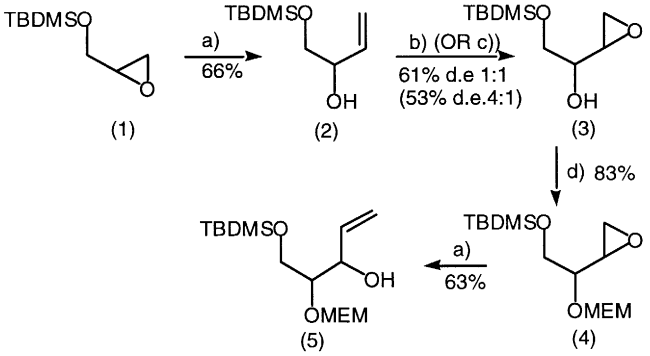


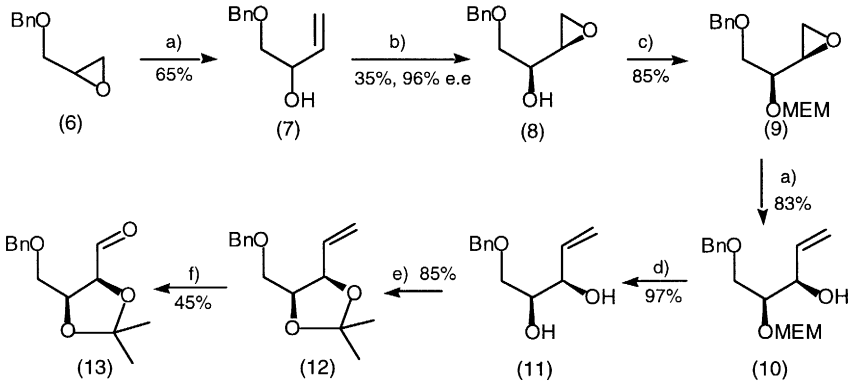
In order to test this proposal, we started with racemic glycidol (Scheme 1). Protection of the primary alcohol as its TBDMS ether (**1**) was followed by the first of the sulfur ylide reactions. As reported by Mioskowski,[8] treatment of trimethylsulfonium iodide with *n*-butyllithium produced the requisite dimethylsulfonium methylidene. Reaction of three equivalents of this with the epoxide gave the allylic alcohol (**2**) in 66% yield.[9] In these early experiments, we used an alternative epoxidation methodology to the Sharpless protocol. Thus, treatment with MCPBA gave the epoxide (**3**) in 61% yield in a diastereoisomeric ratio of ca. 1:1. In order to test the substrate directing effect of the hydroxyl group already in place, we then used $VO(acac)_2/^tBuOOH$. This produced the same product, but with an increased diastereomeric ratio of ca. 4:1. The epoxy alcohol product was now ready to be subjected to a second cycle of the iterative procedure. At this juncture, we were concerned that the acidic proton of the free hydroxyl group may quench the sulfur ylide, and possibly also facilitate a Payne rearrangement of the epoxide from the resultant alkoxide. To prevent this possibility, we decided to protect the alcohol. This protection would also allow for an orthogonal protection strategy on each hydroxyl as the chain grows. Thus, if we were to produce a polyol with this methodology, selective deprotection of the individual alcohols would allow manipulation of selected sites as they were unmasked. At this stage, we chose MEM as a suitable group. A subsequent sulfur ylide reaction produced the allylic diol (**5**) in good yield. Having established that the protocol was viable, we then sought to achieve the sequence in a stereocontrolled manner.



Scheme 1. (a) Me_3SI, BuLi, THF, −25°C; (b) MCPBA, DCM; (c) $VO(acac)_2$, ^tBuOOH; (d) MEMCl, Hunig's base

Starting with benzyl protected racemic glycidol (**6**) (Scheme 2), a sulfur ylide reaction gave the allylic alcohol (**7**), as expected, which was then subjected to a Sharpless kinetic resolution epoxidation. Using standard conditions,[10] one enantiomer of the alcohol was transformed into its epoxide (**8**), while the other was untouched. The enantiomeric excess of the desired product was found to be 96% by HPLC.[11] The

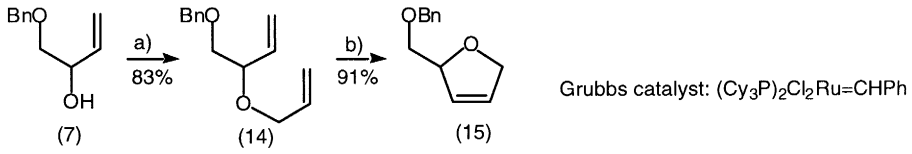
free alcohol was again protected as its MEM ether (**9**) before opening the epoxide with the sulfur ylide to give the allylic alcohol (**10**) in 83% yield.



Scheme 2. (a) Me_3SI, BuLi, THF, −25°C; (b) $Ti(O^iPr)_4$, (+)-diisopropyl tartrate, ^{t}BuOOH; (c) MEMCl, Hunig's base; (d) $TiCl_4$, 0°C, DCM; (e) 2,2-dimethoxypropane; (f) ozone, DCM

Removal of the MEM ether protection and conversion of the diol (**11**) into its dimethyl acetal was carried out before ozonolysis transformed the alkene into the expected carbonyl functionality (**13**). The yield for the ozonolysis was a moderate 43%, but it allowed us to confirm the stereochemistry of the product since this short scheme comprises a synthesis of a protected tetrose.[12] In this short synthetic scheme, we have used Sharpless epoxidation chemistry and the sulfur ylide reaction to build up the molecule in an iterative fashion by homologation of the allyl alcohol functionality. The only other reactions employed in this scheme are protections and deprotections, and the final ozonolysis. It should be noted that this procedure could easily be extended to other longer polyol chains by repeating the iterative cycle an appropriate number of times.

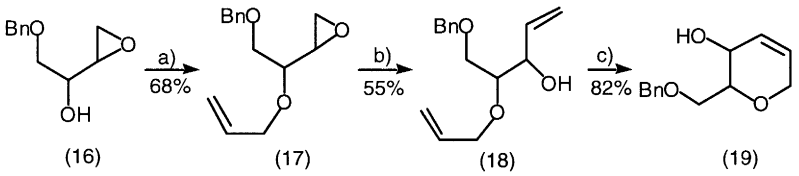
In order to diversify this procedure, and to test the scope of the protocol, we wished to investigate the potential for transformations into other types of skeleton. Since the sulfur ylide reaction introduces a terminal alkene group, we envisaged using a ring closing metathesis[13] to cyclise the chain into oxacycles of varying sizes. In this respect, we took the allylic alcohol (**7**) (Scheme 3) and allylated the hydroxyl group. This diene (**14**) was then cleanly metathesised with Grubbs' catalyst to produce the dihydrofuran (**15**) in an excellent 91% yield.



Scheme 3. (a) NaH, THF, allyl bromide; (b) Grubbs' catalyst, DCM, room temp.

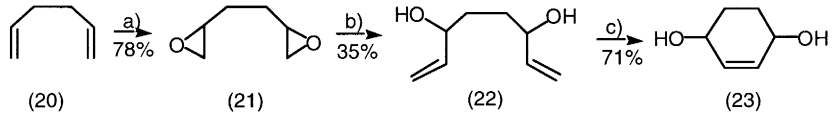
To make a dihydropyran, we extended the chain, as shown in Scheme 4. Allylation of the alcohol (**16**) was achieved at low temperature in order to avoid a Payne rearrangement. The second sulfur ylide reaction proceeded as expected to produce the diene (**18**). Exposing this to Grubbs' catalyst gave the dihydropyran (**19**) in good yield upon stirring at room temperature.

We have also looked at the possibility of attempting the sulfur ylide reaction on a bis epoxide, since this would allow the homologation to proceed in two directions at once (Scheme 5). Epoxidation of 1,5-hexadiene with MCPBA proceeded smoothly to give the expected product (**21**) in good yield. Reaction with excess sulfur ylide gave the diol (**22**) in an unoptimised 35% yield, however, each reaction is



Scheme 4. (a) NaH, THF, allyl bromide, 0°C; (b) Me_3SI, BuLi, −25°C; (c) Grubbs' catalyst, DCM, room temp.

therefore occurring in at least 60% yield. With two terminal alkenes having been placed in the chain, we subjected the diol to a metathesis reaction. Stirring the diene in dichloromethane with Grubbs' catalyst resulted in quantitative conversion to a mixture of the *syn* and *anti* isomers of cyclohexene-1,4-diol (**23**) which were isolated in 71% yield. We were particularly pleased with this result, as it has been reported that Grubbs' catalyst is sensitive to allylic substitution.[14] Here we have two allylic alcohols, and have successfully cyclised the diene without requiring protection of the hydroxyl groups.



Scheme 5. (a) MCPBA, DCM; (b) Me_3SI, BuLi, THF, −25°C; (c) Grubbs' catalyst, DCM, room temp.

Conclusion: We have illustrated a new procedure for homologation of allylic alcohols. The scheme uses two simple reactions to produce a convenient route to densely functionalised organic molecules. We have demonstrated how this can be used to furnish straight chain polyols. In addition, we have utilised the terminal alkene that is installed by the sulfur ylide reaction, and used this in a metathesis approach to oxygenated dihydrofuran, dihydropyran and cyclohexene diol compounds. Application of this protocol to natural product synthesis is underway, and will be reported in due course.

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9. *Preparation of 1-[(phenylmethyl)oxy]but-3-en-2-ol.* To a solution of dimethylsulfonium iodide (7.46 g, 36.58 mmol) in tetrahydrofuran (150 ml) at −25°C was added *n*-butyllithium (14.14 ml, 35.35mmol). The reaction mixture was stirred for 30 minutes prior to the addition of benzylglycidol (2 g, 12.19 mmol) and then allowed to warm to 0°C over approximately 30 minutes. The reaction mixture was then stirred for a further 4 h, cooled to 0°C quenched with water and extracted with diethylether. The organic extracts were combined and dried with magnesium sulfate prior to the solvent being removed under reduced pressure. The crude material was then purified by silica gel chromatography (eluent petrol:diethylether 4:1) to yield 1.41 g (65%) of the title compound as a colourless oil. IR (neat film) 3426, 2860, 1645, 1453, 1104 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.23–7.27 (m, 5H, Ar), 5.80 (ddd, 1H, J=17, 10, 5, -C*H*=CH_2), 5.32 (dt, 1H, J=17, 1, -CH=CH_2), 5.15 (dt, 1H, J=10, 1, -CH=CH_2), 4.52 (s, 2H, ArCH_2), 4.34–4.30 (m, 1H, -C*H*OH), 3.48 (dd, 1H, J=9, 3, -OCH_2), 3.34 (dd, 1H, J=9, 8, -OCH_2). ^{13}C NMR (250 MHz, $CDCl_3$) δ 138.00, 137.00, 136.71, 128.40, 127.75, 116.27, 74.03, 73.29, 71.40. HRMS (EI) calcd for $C_{11}H_{14}O_2$178.09938, found 178.09920.
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