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Synthesis of a Family of Epoxyvinyltriflate Stereotetrads from 4-Hydroxycyclohex-2-en-1-one[1]

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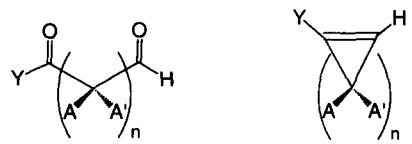
Abstract: 4-Hydroxy cylohex-2-en-1-one can be converted into a family of highly oxygenated cyclohexyl epoxyvinyltriflates by epoxidation, rearrangement, and epoxidation. Furthermore, double stereoselection via Jacobsen epoxidation enables synthesis of compounds such as **20a** which were previously very difficult to prepare.

Because of the desirability of constructing complex organic targets via multiply-convergent strategies, assemblies such as **1** are typically synthesized as logical sub-goals in preparation for assembly of the final target. Acyclic arrays such as **1** have been constructed by schemes featuring cyclic stereoselection followed by ozonolytic cleavage of carbocycles such as **2**.[2] More common approaches to compounds of type **1** including the Evans aldol, Brown/Roush allylborations, and other methods have been incorporated into the lexicon of the organic chemist,[3] yet each of these procedures has its own virtues and limitations. While space constraints do not allow a detailed comparison of the methodologies illustrated in the references, suffice it to say that *there is currently no general synthetic approach for the efficient construction of all members of a family of targets such as* ***1***.

Figure 1



1 A, A' = H, C, N, O 2
Y = leaving group
n = 1 to 6

In the preceding paper we reported an efficient synthesis of symchiral[4] stereotriads based upon the functionalization of achiral cyclohexenone **3**.[5] That study used cyclic, chemospecifically-differentiated dienes to promulgate functionality with simultaneous creation of stereogenic centers, and benefited from the seminal contributions of Hudlicky, Johnson, and Lautens.[2] Asymmetry creation relied upon Jacobsen epoxidation of vinyl triflate **3** to introduce the absolute stereochemistry resident in **4**. While functionalization of **4** provides ready access to epoxides **c,t-6a,b**, the aforementioned strategy does not easily accommodate introduction of additional functionality at the 4-position of epoxyvinyl triflates **c,t-6a,b** (Figure 2).

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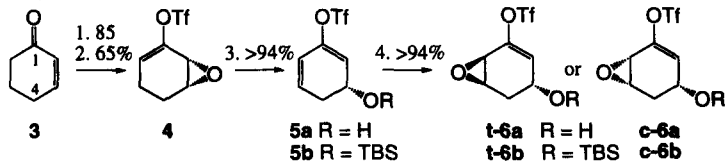
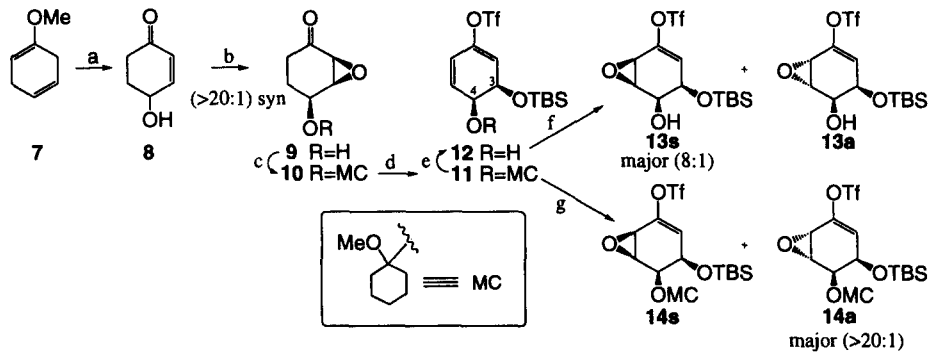
Figure 2



While we ultimately require symchiral compounds bearing four contiguous chiral centers, and methods are available for synthesis of both enantiomers of 4-hydroxycyclohex-2-en-1-one,[6] we initially investigated the chemistry of the more readily available *racemic* 4-hydroxycyclohex-2-en-1-one **dl-8.**

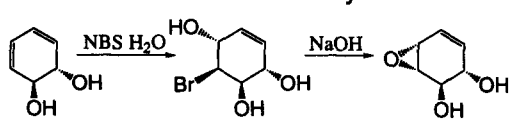
Two of the four desired stereotetrads ($C_{3,4}$-syn) are smoothly generated as shown in Figure 3. Directed epoxidations (reactions b, f, and g) combined with *in situ* formation and fragmentation of epoxyvinyl triflates (reaction d) provides **13s** and **14a** in good to excellent yields.

Figure 3



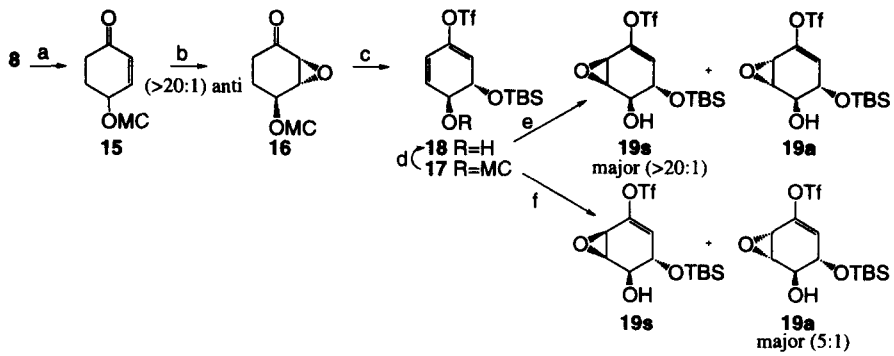
a. i $(CO_2H)_2$,MeOH, H_2O ii MCPBA iii Al_2O_3 73% b.TBHP, Triton B, benzene 75% c. 1-cyclohexenylmethyl ether, TsOH 89% d. i LDA/THF, Tf_2NPyr ii LiHMDS, HMPA iii TBSCl 65% e. $FeCl_3$ SiO_2 quant. f. mCPBA, $NaHCO_3$, CH_2Cl_2 85% g. TFDMDO 85%.

Figure 4 shows the construction of the remaining two stereotetrads ($C_{3,4}$-anti). Again directed epoxidations and one pot multi-step transformations are key to the efficient generation of **19s** and **20a**. Compounds with the stereochemistry of **20a** are known to be difficult to produce by directed epoxidation methods and are usually obtained through formation of the halohydrin formation followed by base-mediated cyclization.[7]



Synthesis of the $C_{3,4}$-anti series (Figure 4) requires protection of the 4-hydroxyl functionality of compound **8** as the MC acetal **15**. This enables anti epoxidation of **15** to afford α-epoxyenone **16** which then serves as progenitor to the remaining targets.

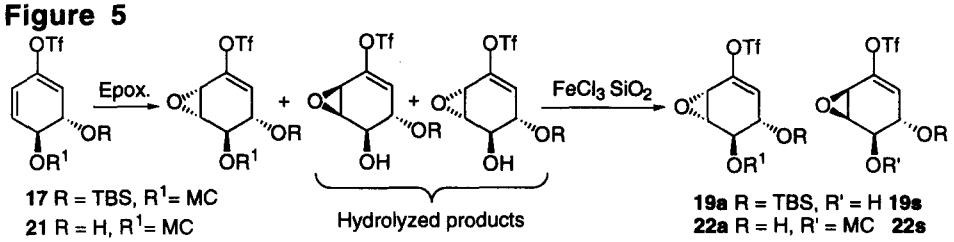
Figure 4



a. 1-cyclohexenylmethyl ether, TsOH 91% b.TBHP, Triton B, benzene 85% c. i LDA/THF, Tf_2NPyr ii LiHMDS, HMPA iii TBSCl 67% d. $FeCl_3$ SiO_2 quant. e. mCPBA, $NaHCO_3$, CH_2Cl_2 84% f. i Jacobsen epox. (RR catalyst), ii $FeCl_3$ SiO_2 74%.

Although reaction *f* currently enjoys the smallest stereocontrol we have obtained in this study, it represents a significant improvement over known methods of achieving similar reactions.[7] Attempts to produce a compound with **19a** stereochemistry via directed epoxidation of homoallyl alcohol **21** lead predominantly to the 4,5 *syn* product **22s**. Sterically directed epoxidation of **17** resulted in nearly the same ratio. Only when optically pure **17** was submitted to Jacobsen epoxidation could compound **19a** be recovered as the major diastereomer in 74% yield. Because the MC protecting group was partially hydrolyzed during the reaction, we believe this to be the source of the unwanted **19s**.

Figure 5



This strategy is a concise and predictable approach for the preparation of highly oxygenated cyclic synthons from readily available starting material. The generality and efficiency of this protocol portend applications for total synthesis of highly oxygenated cyclic and acyclic fragments derived from these intermediates. Studies are currently underway to further expand this concept.

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