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CATALYTIC OSMYLATION OF CONJUGATED DIENES: A ONE-POT STEREOSELECTIVE SYNTHESIS OF POLYOLS

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Abstract: Conjugated dienes have been hydroxylated with catalytic amounts of osmium tetroxide. The reaction can be highly stereoselective depending on the nature of the terminal substituents, leading to polyols of predictable configurations.

Recently we reported a uniquely practical and highly enantioselective asymmetric dihydroxlyation (ADH) of olefins using a catalytic amount of OsO_4 and derivatives of the cinchona alkaloids.[1] Since the discovery of this new process, a number of improvements, including enhanced reaction rates and higher enantioselectivity, have been realized through the modification of various elements of the reaction.[2] As part of our continuing efforts to broaden the scope of this reaction, we have focused our attention on the hydroxylation of conjugated olefins.

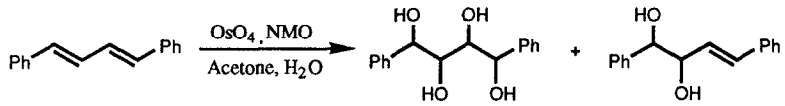
Studies on dihydroxylation of allylic alcohols and allylic ethers abound in the literature. However, the osmylation of 1,3-dienes or 1,3,5-trienes in connection with α,β- dihydroxy olefins has received little attention, despite its potential utility in the synthesis of polyhydroxylated compounds.

1,4-Diphenyl-1,3-butadiene was chosen as the substrate for the initial study; the aim was to obtain 1,2-dihydroxy-1,4-diphenyl-3-butene by treatment of the diene with a catalytic amount of OsO_4, and one equivalent of *N*-methylmorpholine *N*-oxide (NMO) (based on mmol of diene). Since the resulting diol would be sterically and electronically deactivated relative to the diene, it should be less reactive toward the OsO_4.

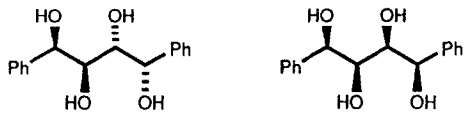
Instead, 1,2,3,4-tetrahydroxy-1,4-diphenyl-butane, 2, was obtained as the major product, with only a trace amount of the diol 3. This unexpected rate acceleration exhibited by the diol will be discussed in a later communication; we will focus here on the stereoselectivity of the reaction. We noted that the tetrol that was obtained was formed in a diastereomeric ratio of 16:1. The structure of the major diastereomer was determined by X-ray crystallography of the corresponding acetate to

be the 1,2-*syn*-2,3-*anti*-3,4-*syn*-isomer; the minor product was the 1,2-*syn*-2,3-*syn*-3,4-*syn*-isomer. When the same reaction was carried out in the presence of dihydroquinidine *p*-chlorobenzoate, only a 6:1 ratio was observed for the 2,3-*anti*/2,3-*syn* tetrols.

Scheme 1



1 **2** **3**

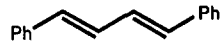
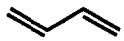
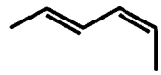


2a **2b**

The procedure for a typical reaction is as follows: The olefin was placed in a round-bottomed flask and charged with enough acetone to make the solution 0.5M in olefin. NMO (60% by weight solution in H_2O) and OsO_4 (stock solution in toluene or acetonitrile, 0.4-0.5M) were added; the flask was then capped with a rubber septum and allowed to stand at 25 °C until TLC showed complete consumption of the starting olefin. The reaction was quenched by the addition of $Na_2S_2O_5$. The mixture was then diluted with an equal volume of CH_2Cl_2, stirred for 1 hour, concentrated *in vacuo*; benzene was then added, and the remaining water was removed azeotropically on a rotary evaporator. The resulting solids were placed under vacuum (0.04 to 0.1 mm Hg) 12 to 18 hours. The solids were treated with 8 equivalents acetic anhydride, 8 equivalents 4-dimethylaminopyridine, CH_2Cl_2, and refluxed 4 hours. After cooling to 25 °C the mixture was poured into H_2O, extracted three times with ether, then washed with H_2O and 10% aqueous H_2SO_4. The organic phase was concentrated and filtered through a silica gel plug. Diastereomeric ratios were determined from GC analysis.

The tetrol obtained through this method is extremely crystalline, and can easily be obtained in high diastereomeric purity (96% d.e.) by simply filtering the precipitates formed from the reaction and washing the solids with organic solvents (typically a combination of CH_2Cl_2 and EtOAc).[3] The 2,3-anti array in 2a is consistent with the findings of other groups in the addition of OsO_4 to allylic alcohols and allylic ethers [4] and cyclic dienes.[5] A variety of acyclic dienes were subjected to the same reaction conditions; the results are shown in Table 1.

Table 1. Diastereoselectivity of Polyol Formation

Entry	Substrate	Yield	Ratio (2,3 - *anti*, 2,3 -*syn*)
1		87%	16:1
2		80%	5:1
3		72%	10:1
4		95%	2:1
5		95%	7:4:1 *

* ratio (2,3- *anti*, 4,5 -*anti*)/ (2,3- *anti*, 4,5-*syn*)/ 2,3-*syn*, 4,5-*syn*)

As is shown in Table 1, the diastereoisomeric ratios for the all-*trans* conjugated dienes ranged from good to excellent, with 1,4-diphenyl-1,3-butadiene giving the highest ratio. Selectivities for the aliphatic dienes were also good. In the case where both 1 and 4 positions are E-substituted with aliphatic groups the selectivity remains high (10:1, Entry 3). When less substituted (Entry 2) or *cis* double bonds (Entry 4) are involved, however, the selectivity drops. As is apparent from the osmylation of 1,6-diphenyl-1,3,5-hexatriene, the reaction of more highly conjugated olefins proceeds in a less stereoselective manner. The 2,3-*anti*-4,5-*anti*-relationship of the major product was again confirmed by X-ray crystallographic analysis.

We had hoped to extend this method to long chain polyenes, thus constituting a method for the synthesis of stereoregular polyhydroxylated carbon chains. Unfortunately, the selectivity drops precipitously when the starting compound contains four double bonds.[6] Nevertheless, this new method offers a way to introduce, in one step, four to six new contiguous stereogenic centers in one molecule.

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[3] We found the corresponding acetates to be much more soluble in organic solvents.

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[6] We tested this reaction with 1,8-diphenyl-1,3,5,7-octatetraene.

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