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Anti-Kishi Selective Dihydroxylation of Allylic Alcohol Derivatives

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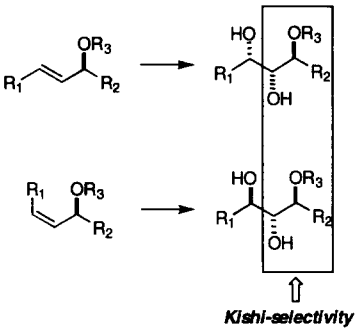
Abstract: A highly diastereoselective dihydroxylation protocol has been developed for acyclic allylic alcohol derivatives leading to triol derivatives with diastereoselectivity reversed to the classical osmylation (anti-Kishi). Selectivities are acceptable for *E*-allylic derivatives **1**, and high for those derived from *Z*-derivatives **4**. © 1997 Elsevier Science Ltd.

Polyhydroxylated natural compounds have gained intensive interest during the past decades.[1] The preparation of polyol fragments consisting of contiguous hydroxylated chiral centers has remained a persisting challenge for synthetic chemists. Dihydroxylation of allylic alcohols with achiral osmium tetroxide (OsO_4), as developed by Kishi and co-workers, is the most reliable and versatile method for the preparation of triols.[2] Related substrate-controlled oxidations have also been reported by several other groups.[3] Although these methods are very useful, the stereoselectivity is always controlled in the anti-sense relative to the allylic substituents (Kishi-selectivity, Scheme 1). An empirical rule on the stereoselectivity of the OsO_4-mediated dihydroxylation of chiral olefins bearing allylic alkoxy-substituents has been formulated by the Kishi group,[1] and theoretical evaluation has also been described.[4]

Scheme 1.

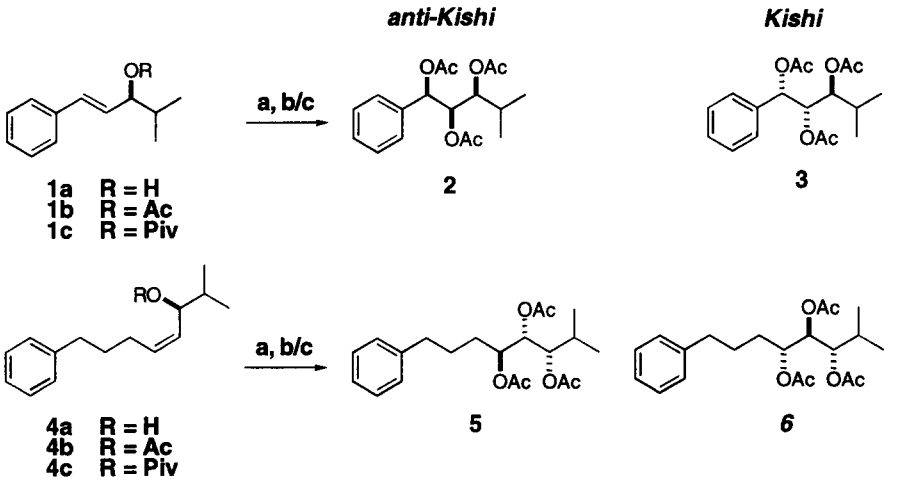


As the Kishi-selectivity leads to *anti*-addition, the problem of *syn*-selective dihydroxylation of allylic alcohol derivatives has recently been attacked by means of Sharpless asymmetric dihydroxylation (AD), but in the 'mismatched' cases the results have been modest at best.[5] We now wish to report a new convenient approach to anti-Kishi triols by Woodward oxidation.[6]

The reaction of olefins with iodine and silver acetate in moist acetic acid is a much overlooked method for the preparation of *cis*-diols with the hydroxyl groups on the more hindered side of the molecule.[7] In the literature we found only few examples where this method was applied for allylic alcohols but the results were controversial.[8] Since no systematic study was available in this field we decided to investigate the reaction of

simple acyclic allylic alcohol derivatives **1a-c** and **4a-c** under the Woodward conditions[9] and determine the stereochemical outcome.

Scheme 2.



Reagents: a) I_2, AgOAc,CH_3COOH; H_2O, 90 °C, 3h; b) for **1a** and **1b**: Ac_2O, DMAP, pyr; c) for **1c**: DIBAL-H, THF -78 °C; Ac_2O, DMAP, pyr.

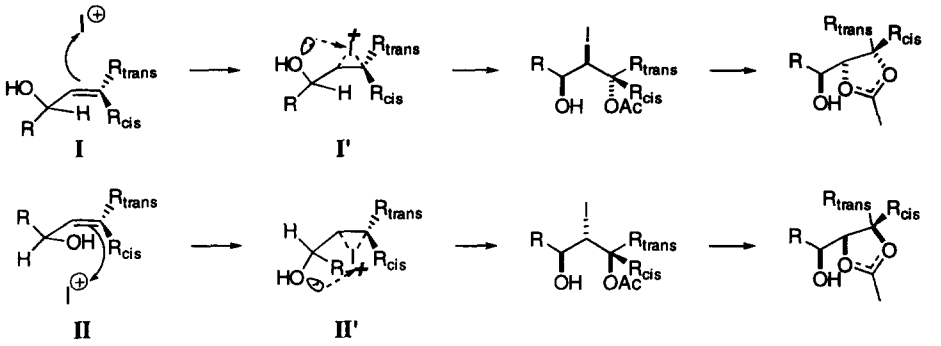
The Woodward oxidations of unprotected alcohols **1a** and **4a** gave *anti*-addition as main products (Table 1, entries 1 and 4).[10] Apparently the electrophilic attack on the double bond proceeds in such a manner that the inside position for the OH is preferred on stereoelectronic grounds.[4a] The attack of the I^+ electrophile occurs *syn* to OH in the H in-plane conformer **I** or *syn* to H in the OH in-plane conformer **II** leading to two possible onium ion diastereomers (**I'** and **II'**, respectively) which are stabilized by interactions between the developing positive charge and the oxygen lone pairs (Scheme 3).[11] The sense of internal asymmetric induction can be reversed if substituents at the *cis*-position of the double bond destabilize the O-inside transition state **II** due to allylic 1,3-strain or the bulky allylic substituents destabilize the forming onium ion **II'**. On steric grounds, the transition state **II'** is disfavored compared to **I'**, which leads triols **3** and **6** via *trans*-iodoacetate and dioxolane intermediates. Our experimental results are in accordance with the theory.

Table 1. Diastereoselectivities of the *cis*-hydroxylations of the compounds **1-4.**

Entry	*Compound*	*Anti-Kishi:Kishi*	*Yield*[b]
1	1a	1:12[a]	-
2	1b	2.5:1[a]	71
3	1c	4:1[a]	65
4	4a	1:2.6[c]	75
5	4b	14.3:1[c]	90
6	4c	12.4:1[c]	85

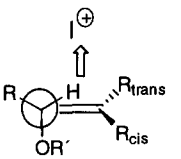
[a]The ratio was determined by 1H NMR.[12]
[b]Crude yield.
[c]The ratios were determined by HPLC and the stereochemistry was determined by converting triols to corresponding acetonides.[13]

Scheme 3.



The diastereoselectivity of the dihydroxylation was reversed when the alcohol group was protected, and for the *trans* compounds **1b** and **1c** the selectivity was improved when the size of the protecting group was increased (Table 1, entries 2 and 3). Apparently, the directing effect caused by complexation of the oxygen lone pair and electrophile lessened in the ester derivatives. Thus, the electrophile attacks the more accessible face of the double bond giving rise to *syn-syn*-triols **2b,c** as the major products. Though one should not expect that steric and electronic effects will without exception result in the same transition state geometry regardless of the electrophilic reactant,[4b,c] transition state **III** (large allylic oxygen function *anti*, alkyl outside and H in sterically most demanding position inside) would explain our experimental results.

Scheme 4.



III

For the *cis*-allylic compounds **4b** and **4c** the transition state conformation **III** is strongly favored due to allylic 1,3 strain.[14] The selectivity is improved compared to the *trans* isomers **1b,c** but the size of the protection group had no significant effect (Table 1, entries 5 and 6). Clearly the direction of the asymmetric induction is not solely a function of the sizes of the allylic groups.

Based on these results we believe that this method has great synthetic value. Further studies are needed before firm conclusions can be drawn concerning all the steric and electronic factors controlling the diastereoselectivity. This method is now being applied in our laboratories for the synthesis of 1-deoxy-castanospermine and related compounds and the results will be reported in due course.

ACKNOWLEDGEMENTS: Financial support from the Academy of Finland is gratefully acknowledged.

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9. Typical experimental procedure: To a solution of the allylic ester **1b** (150 mg, 0.69 mmol, 100 mol%) in acetic acid (5 ml), iodine (183.8 mg, 0.72 mmol, 105 mol%) and silver acetate (258.7 mg, 1.55 mmol, 225 mol%) were added and the resulting mixture was stirred at r.t. until all iodine was consumed. Distilled water (12.5 µL, 12.4 mg, 0.69 mmol, 100 mol%) was added and the temperature was raised to 80 °C and the reaction mixture was stirred for 3 hours. The yellowish precipitate was the filtered off and washed with toluene. The combined organic solvents were evaporated under reduced pressure and the product was further dried *in vacuo*. The product was acetylated directly without further purification.
10. All new compounds gave satisfactory spectral and analytical data.
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12. The assignment of the stereochemistry was based on the analogy of the OsO_4 mediated cis-hydroxylation which gave 1:12 selectivity and determination of the ratios was done by integration of the carbinol proton signals.
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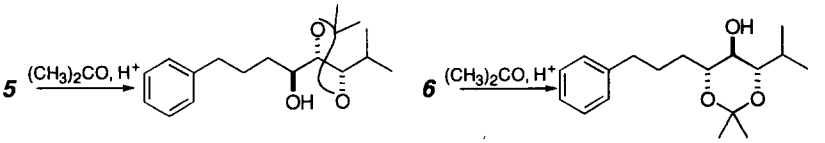

The ^1H chemical shifts of the acetonide methyl signals are informative of the structure and thus the relative stereochemistry of the compounds. In the 5-membered ring, the methyl groups are magnetically equivalent and should give only one signal (1.38 ppm) whereas in the 6-membered ring we two signals from axial and equatorial methyl groups are discernible (1.45 ppm and 1.39 ppm).

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