



SELECTIVE DIHYDROXYLATION OF NON-CONJUGATED DIENES IN FAVOR OF THE TERMINAL OLEFIN

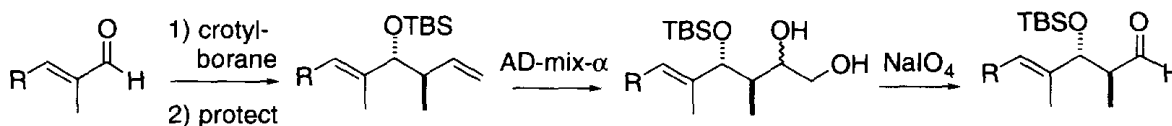
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Abstract: Non-conjugated dienes were dihydroxylated using the commercially available osmium tetroxide AD-mix- α reagent resulting in highly regioselective dihydroxylation of the terminal olefin rather than the internal, more substituted olefin. These findings now allow for the use of allylmetal reagents on substrates where preexisting internal olefins are present. The resultant diol can be cleaved to the aldehyde allowing for subsequent transformations. This selectivity is controlled by a steric effect imposed by the allylic silyl ether adjacent to the internal olefin. © 1997 Elsevier Science Ltd.

Recently we reported the synthesis of stipiamide, a new multi-drug resistance reversal agent, together with 6,7-dehydro-stipiamide, a non-natural and more potent variant.¹ The *anti*-1,2-hydroxymethyl functionality was made using Brown's crotyl boration procedure.² It was found to be superior in yield and selectivity to analogous asymmetric aldol methods³ (sch. 1). Selective cleavage of the primary olefin in the presence of the tri-substituted olefin then became a necessity. Previous osmium tetroxide dihydroxylation studies of simple non-conjugated dienes by Sharpless,⁴ Corey⁵ and others⁶ have shown conclusively that the more substituted, internal olefin is selectively oxidized. Selective diene oxidation in favor of the least substituted olefin has been reported by Danishefsky using stoichiometric osmium tetroxide.⁷ More recently, a catalytic version with NMO (N-methylmorpholine N-oxide) has been used with moderate selectivity.⁸ When this procedure resulted in poor yield and selectivity with our substrate, we reasoned that use of a larger ligand on osmium might favor oxidation

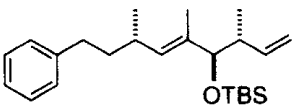
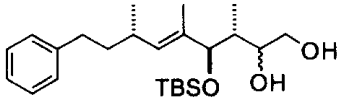
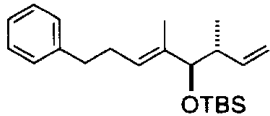
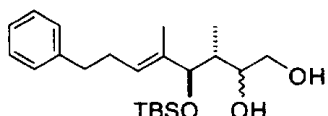
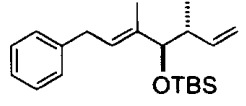
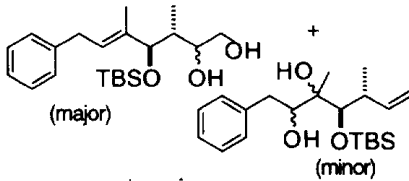
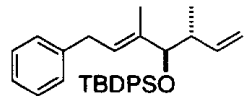
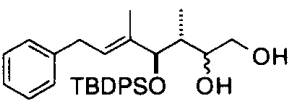
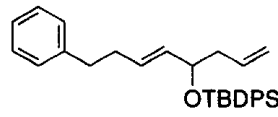
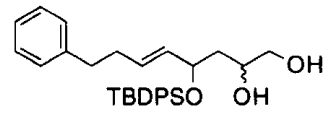
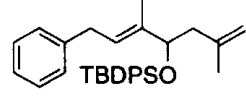
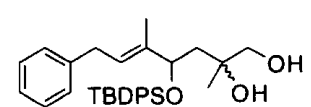
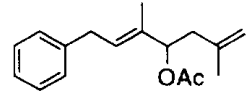
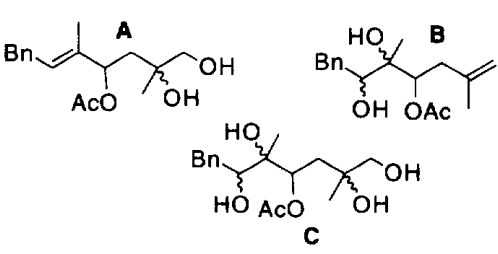
Scheme 1



of the terminal olefin. The Sharpless AD-mix reagent⁹ was found to selectively dihydroxylate the terminal olefin allowing for treatment with periodate to give the needed aldehyde. This paper will explore some of the factors contributing to this selectivity and extend the generality of this useful transformation.

The stipiamide substrate (Table 1, entry 1) cleanly underwent terminal olefin oxidation using the commercially available AD-mix- α in 1:1 H₂O/*t*-BuOH at room temperature using the conditions of Sharpless.¹⁰ This reaction was

Table 1. Dihydroxylation of non-conjugated dienes using AD-mix- α .^a

entry	Substrate	Product(s)	yield (de)
1			86% (1:1)
2			61% (1:1) 86% (1:1) ^b
3			87% (1:1) 15:1 major:minor
4			86% (1:1) ^c
5			63% (1:1) ^d
6			70% (1:1) ^d
7			30% A:B:C 3:1:1

^aUnless otherwise indicated, all reactions were run at rt for 24 h according to the procedure of Sharpless. ^bThis reaction was run using AD-mix- β . ^c12 h, the yield is based on recovered starting material. ^dYield based on recovered starting material.

performed on 10 g scale numerous times during the course of our synthesis giving consistent yields of 85-87% (1:1 de) with no internal dihydroxylation or tetrahydroxylation products (>20:1).¹¹

It appears that steric hindrance incurred by the large silyl ether adjacent to the internal olefin prevents dihydroxylation of the internal olefin due to an unfavorable interaction with the bis-cinchona complexed osmium tetroxide.¹² Use of osmium tetroxide with added quinuclidine or triethylamine gave mixtures of internal, terminal diol, and tetraol in low yield. Entry 2, lacking the allyl methyl group, reacted with high selectivity with AD-mix- β giving product in higher yield compared to AD-mix- α . The origin of the enhanced yield is unknown at this time. The simplified substrate, entry 3, lacking the allylic methyl group gave terminal diol product in a diminished ratio of 15:1.¹³ The larger *t*-butyldiphenylsilyl (TBDPS) protecting group, entry 4, restored the high selectivity consistent with the proposed hindrance model.

High selectivity was also found in the case of mono- versus disubstituted olefin as shown in entry 5. With simple diene substrates, lacking the silylether, Sharpless has shown that internal dihydroxylation predominates (13:1, 56% yield).^{4a} Now with entry 5, the terminal olefin was dihydroxylated with no observable internal dihydroxylation product after 24 h at rt. Initially the reaction was run at 0 °C for 3 d giving 20% yield of the terminal diol with 54% recovered starting material. The yield was significantly improved by reaction at rt for 12 h giving a 63% yield based on recovered starting material. In the case of terminal di- versus internal trisubstituted olefin, entry 6, exclusive preference for terminal olefin oxidation was found giving diol in 70% yield with no other oxidation products observable. Acetate, entry 7, in addition to being sterically smaller, is more electron withdrawing relative to a silylether.⁵ These two factors combined to erode the regioselectivity giving a 3:1:1 mixture of terminal diol, internal diol, and tetraol products.

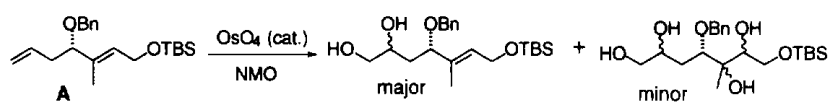
In conclusion, "reverse" Sharpless selectivity for terminal dihydroxylation of non-conjugated dienes can be performed with high selectivity using the AD-mix reagent provided the internal olefin is hindered by an adjacent group of sufficient size. These findings significantly extend the scope and utility of asymmetric allylmetal reagents.

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References and Notes

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Optimal osmylation conditions gave products 5:1 (major/minor) in 73% overall yield. Preliminary reactions with our substrate (table 1, entry 1) proceeded slowly and with low selectivity using these conditions.

9. Use of the AD-mix reagent has been reported for the selective oxidation of a terminal olefin in the presence of a cyclic disubstituted olefin. see: Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106.
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11. All new compounds were characterized by ^1H and ^{13}C NMR. In addition, select compounds were subject to combustion analysis or high resolution mass spectrometry with satisfactory results. Yields were determined by product isolation after silica gel chromatography.
12. Kolbe, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483 (table 20 and figure 7). Also see: Park, C. Y. Ph. D. Thesis, Massachusetts Institute of Technology, 1991, where allyl alcohols react 23x faster than the corresponding allyl methyl ethers suggestive of a hydrogen bonding effect.
13. This ratio was determined by further reacting the isolated crude with sodium periodinate to obtain the corresponding aldehydes (85%). ^1H NMR of the crude periodinate reaction gave a simple spectrum allowing for determination of the dihydroxylation product distribution.

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