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Studies on Steroidal Plant Growth Regulators 22. Osmium Tetroxide Catalyzed Asymmetric Dihydroxylation of the (22E, 24R)- and the (22E, 24S)-24-Alkyl Steroidal Unsaturated Side Chain

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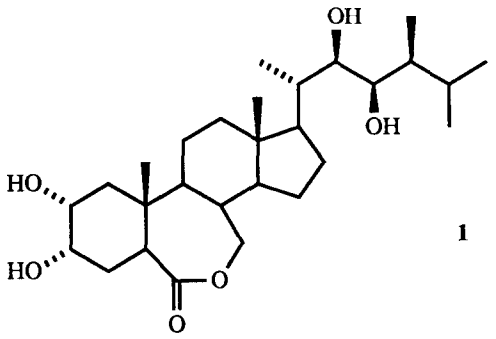
Abstract: The osmium tetroxide catalyzed asymmetric hydroxylation of the (22E, 24R)- and (22E, 24S)-24-alkyl steroidal unsaturated side chain are described. High stereoselectivity was obtained on dihydroxylation of these unsaturated side chains, when the 24-alkyl is methyl, while in the case of a 24-ethyl substituent the chiral ligand would be the dihydroquinine p-chlorobenzoate (DHQ).

Since the structure and stereochemistry of brassinolide [**1**, (22R, 23R, 24S) -2α, 3α, 22, 23-tetrahydroxy-24-methyl-B-homo-7-oxa-5-cholestan-6-one] has been determined,[1] a number of brassinosteroids with and without hydroxyl groups or an alkyl substituent in their side chain were synthesised.[2]



1

The alkyl substituent at C-24 has significant influence on the hydroxylation of the C-22 double bond with osmium tetroxide determining the ratio of (22R, 23R)- and (22S, 23S)-22, 23-diols. The steroids with (24S)-24-methyl group or without a methyl substituent at C-24 yielded mainly the unnatural (22S, 23S)-isomers, while with (24R)-24-methyl group a mixture of isomers in ratio of 1:1 was obtained. For the steroid with a (24S)-24-ethyl group oxidation yielded mainly the unnatural (22S, 23S)-isomers.[2c] Isomers with the unnatural (22S,

23S)-22, 23- dihydroxyl groups were inactive or less potent against the plant growth regulator activity,[2b,2c] so an improved method for obtaining the natural (22R, 23R)-22, 23-dihydroxyl isomers as the major products is required.

Very recently, Sharpless and his co-workers reported a very high enantioselectivity of the osmium-catalyzed asymmetric dihydroxylation of olefins[3] by using potassium ferricynide as the cooxidant.[4] We now make a successful application of this reaction for the first time to higher olefins, the (22E)-24-alkyl steroidal unsaturated side chains, providing the (22R, 23R)-22, 23-dihydroxy isomers as the major products in three examples (table 1, entry 1-3, method A). Method A[3] for the dihydroxylation of this unsaturated side chain is not perfect (entry 5-6), although it is much better than the old one (method C).[2] As is shown in Table 1, an unexpected 8:1 ratio of (22R, 23R) and (22S, 23S) was obtained from the (24S)-24-methyl substituted steroidal side chain (entry 3) in contrast to the old method (entry 4, method C). It is worthy to note that the 8:1 ratio of (22R, 23R) and (22S, 23S) was also formed in the (24R)-24-methyl substituted steroidal side chain (entry 1-2, method A). When the chiral ligand, dihydroquinine-p-chrolobenzoate (DHQ) was used instead of DHQD for the dihydroxylation of the (22E, 24R)- or (22E, 24S)-24-methyl steroids (entry 2-3, method B), the opposite ratio of (22R, 23R) and (22S, 23S) was obtained as expected.[3] While dihydroxylation of the (22E, 24S)-24-ethyl steroid (entry 5, method B) produces the (22S, 23S)-22, 23-diols as essentially the sole product. It is obvious that from an inspection of molecular models that the (24S)-24-ethyl and ring D of the steroid nucleus greatly hinder a front side attack of bulky oxmium tetraoxide complexed reagent onto the side chain.

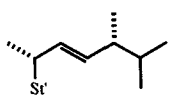
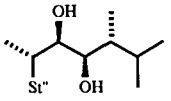
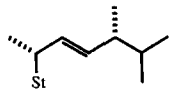
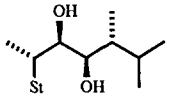
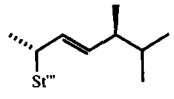
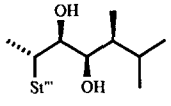
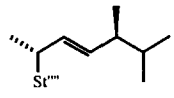
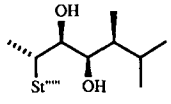
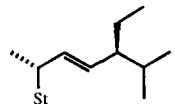
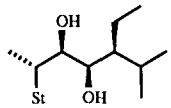
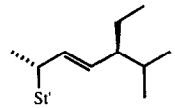
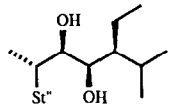
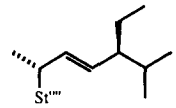
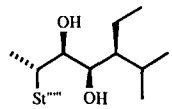
This highly effective new oxidation method is proving useful for the preparation of the (22R, 23R)-configured bioactive isomer in spite of (24S) or (24R)-oriented methyl group existed in the unsaturated side chain. In the case of 22E, 24S)-24-ethyl substituted side chain, the (22S, 23S)-configured isomer was obtained as the sole product.

Although this catalytic asymmetric dihydroxylation of olefins is very effective,[5] it is known to be not ideal for higher olefins.[4] However, we found that in the dihydroxylation of the present examples the rate of reaction and stereoselectivity could be greatly enhanced by addition of larger amounts of OsO_4 (0.005- 0.01 equiv) and chiral ligand (0.1-0.2 equiv).[3]

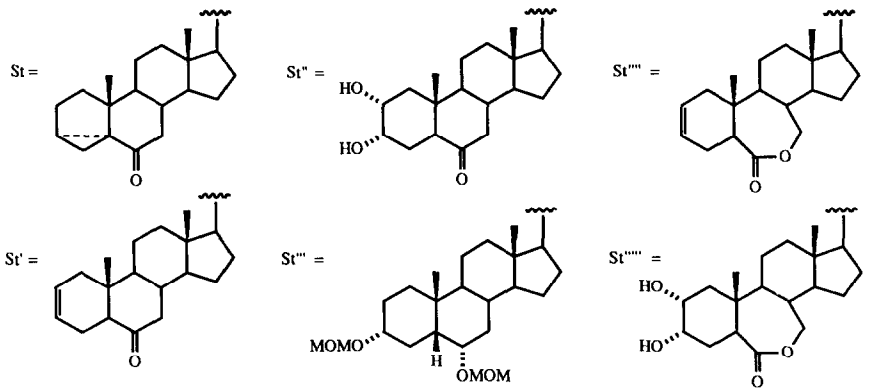
Further extending this uniquely practical highly enantioselective asymmetric dihydroxylation to other higher olefins is in progress.

Acknowledgement: The investigation was supported by the National Sciences Foundation and Chinese Academy of Sciences.

Table 1: OsO_4 catalysed asymmetric dihydroxylation of (22E, 24R)- and (22E, 24S)-24-alkyl steroidal unsaturated side chains.[a]

Entry	Olefin	Products	Methods: product ratio[f] (yields[e]) A[b]	B[c]	C[d]
1			8 : 1 (90%)		3 : 5 (80%)
2			8 : 1 (94%)	1 : 9 (84%)	
3			8 : 1 (70%)	22S,23S (82%)	
4					1 : 4[2c]
5			1.5 : 1 (93%)	22S,23S (83%)	
6			1.3 : 1 (89%)		
7					1 : 9[2c] 1 : 5[2h] (95%)

a) The reaction was carried out at room temperature in tertbutyl alcohol-water, 1:1 v/v, using dihydroquinidine-p-chlorobenzoate (DHQD, 0.1-0.2 equiv.) or dihydroquinine-p-chlorobenzoate (DHQ, 0.1-0.2 equiv.), $K_3Fe(CN)_6$ (0.3-1.2 equiv.), OsO_4 (0.005-0.01 equiv.) and olefin (0.2mmol.). The reaction mixture was stirred at r.t. for 3-5 days. b) Method A: OsO_4-$K_3Fe(CN)_6$-DHQD. c) Method B: OsO_4-DHQ-$K_3Fe(CN)_6$. d) Method C: OsO_4-NMMNO. e) Isolated yield by flash chromatography. f) (22R,23R) : (22S,23S).



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