# A Unified Approach to (22*S*)- or (22*R*)-Hydroxy Steroid Side Chain: Lewis Acid-promoted Carbonyl-ene Reaction with α-Alkoxyaldehydes

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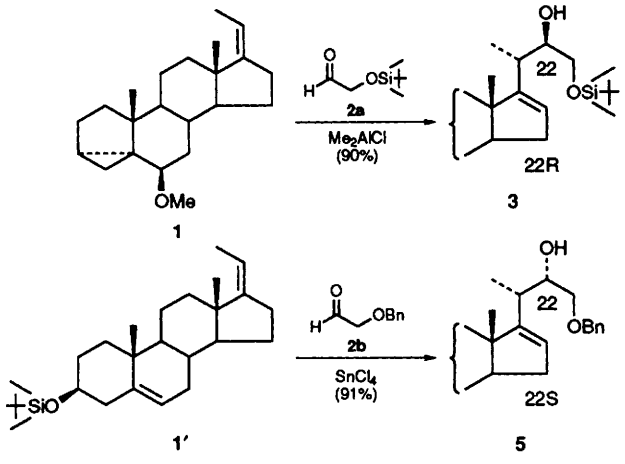
A Lewis acid-promoted carbonyl-ene approach to either (22*S*)- or (22*R*)-hydroxy steroid side chain is described.

Recently, considerable attention has been focused on the development of stereocontrolled syntheses of steroid side chains, particularly the 22-hydroxylated side chains found in ecdysones and brassinolides.[1] We now report a strategy for the stereocontrolled synthesis of either (22*S*)- or (22*R*)-hydroxy steroid side chain, which relies on the concept of the chelation *vs.* non-chelation control[2] of the carbonyl-ene reaction.[3] Judicious choice of Lewis acid and protecting groups of α-alkoxyaldehyde enophiles[4] allows control of the reaction (Scheme 1).




Scheme 1

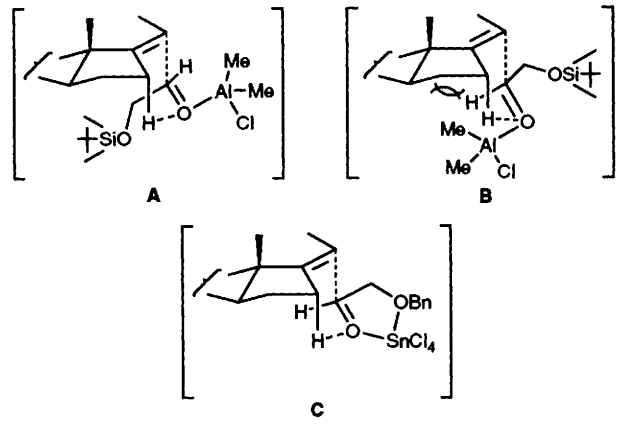



Fig. 1

The starting steroidal olefins (**1** and **1'**) were prepared from 3β-hydroxy-5-androsten-17-one,[5] leading inherently to the 'natural' 20*S*/β chirality.[6]

The ene reaction of the steroidal olefin **1** bearing the cyclic ether moiety with α-silyloxyaldehyde **2a** and $Me_2AlCl$ (1 equiv.) in $CH_2Cl_2$ at −78 °C was found to afford the (22*R*)-hydroxy product **3** as a single stereoisomer in 90% isolated yield. In sharp contrast, the ene reaction of **1** with α-benzyloxyaldehyde (**2b**) and $SnCl_4$ (1 equiv. each) in $CH_2Cl_2$ at −78 °C exhibited complete reversal of diastereoselectivity at C-22 resulting in the formation of the (22*S*)-hydroxy product **4** as a single stereoisomer in 50% isolated yield, albeit, with opening of the acid-labile cyclic ether moiety. Thus, the ene reaction was further examined with 3β-*tert*-butyldimethylsilyloxy olefin **1'** under the same conditions (α-benzyloxyaldehyde **2b**, $SnCl_4$, $CH_2Cl_2$, −78 °C) to give the corresponding ene product (22*S*)-**5** in 91% isolated yield with >99% diastereoselectivity without cleavage of the silyl protecting group.

The stereochemical assignment of the ene products (**3**, **4** and **5**) was made through comparison with the authentic steroids.[7,8] The most distinguishing features are the signals of the olefinic 16-H protons.

We suggest that the ene reaction of α-siloxyaldehyde proceeds preferentially *via* the *endo* transition state **A**, since the *exo* conformer **B** suffers a large steric repulsion between the steroid *D* ring and the Lewis acid complexed to the aldehyde in an *anti* (non-chelation) fashion, see Fig. 1. In fact, the ene reaction of chiral α-*tert*-butyldimethylsilyloxy propanal and isobutene with $Me_2AlCl$ (1 equiv.) gave mainly the non-chelation product, *anti*-**6**; the stereochemical assignment was made after conversion to the boronate **7** which was compared by GLC analysis with the authentic *syn* boronate derived from the *syn*-**8**.[4] By contrast, the ene reaction of α-benzyloxyaldehyde well reflects the chelation situation that the cyclic chelate would possess the sterically favourable *exo* position **C**.[9]

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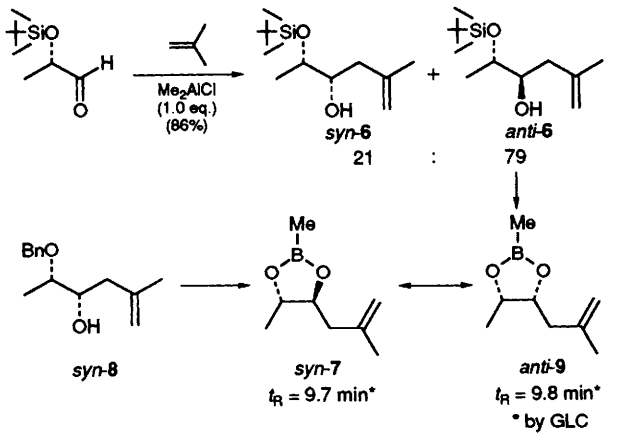


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