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STEREOCONTROLLED SYNTHESIS OF 22-HYDROXY-23-ACETYLENIC STEROIDS, KEY INTERMEDIATES IN STEROID SIDE CHAIN CONSTRUCTION. OBSERVATION OF A DIRECTIVE EFFECT BY AN α-CHIRAL SITE DURING ASYMMETRIC REDUCTION WITH B-3-PINANYL-9-BBN (ALPINE-BORANE)

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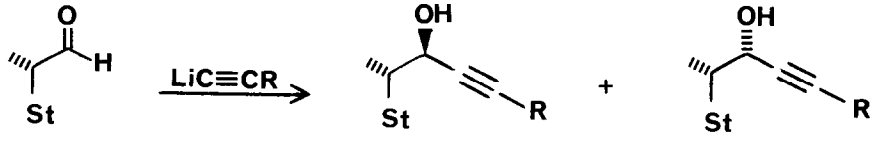
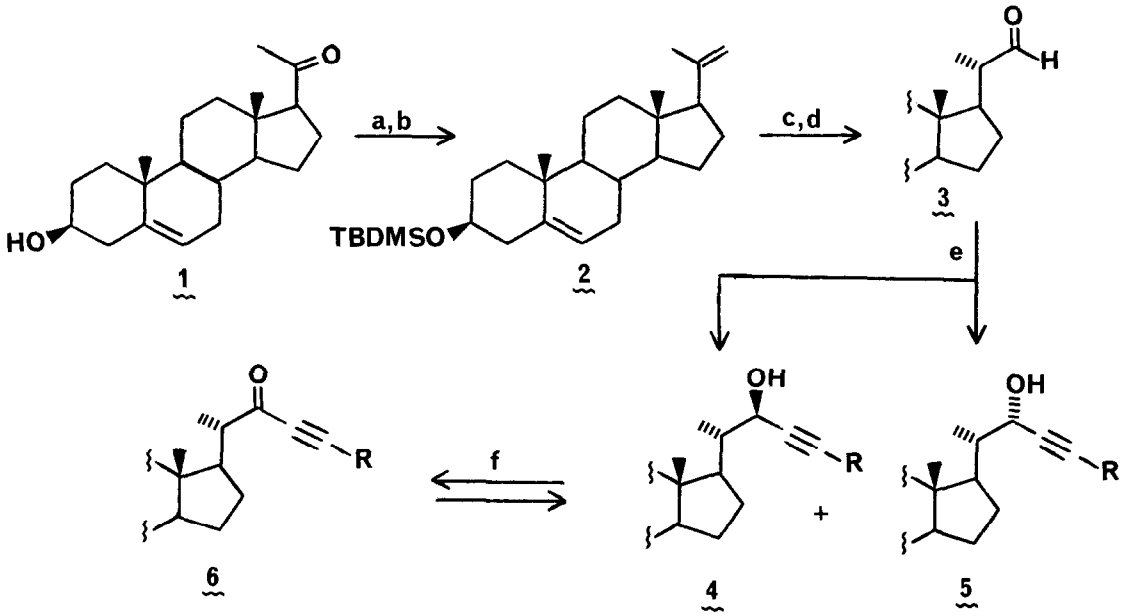
Abstract: An efficient stereoselective synthesis of 22-R- and 22-S-hydroxy-23-acetylenic steroids has been developed using R-Alpine-Borane (125:1, R:S) and L-Selectride (1:11, R:S) to reduce the 22-keto steroid. S-Alpine-Borane provides an unexpectedly low 1:2.7, R:S ratio due to the influence of the α-chiral center at C-20 of the steroid.

The 22-hydroxy-23-acetylenic steroid has often been used as an intermediate in side chain construction.[1] Reduction of the triple bond can provide a cis or trans allylic alcohol (or saturated alcohol). Epoxidation of the resulting allylic alcohol and subsequent opening of the epoxide have been utilized in many syntheses of steroid side chains.[1(c)-(e)] Furthermore, the chirality of the 22-hydroxy center may be stereospecifically transferred through pericyclic processes[2] or S_N2' displacements[1f] to the C-24 position. The acetylenic alcohol is usually prepared by the addition of a lithium acetylide to a C-22 aldehydic steroid. However, the reaction suffers from a low stereoselectivity (often 1:1) and the subsequent need to separate the diastereomeric C-22 alcohols.



We have previously reported the asymmetric reduction of propargyl ketones with B-3-pinanyl-9-BBN (Alpine-Borane).[3] Accordingly, either the 22-R or 22-S-hydroxy-23-acetylenic steroid should be readily prepared by the reduction of a 22-keto-23-acetylenic steroid with R- or S-Alpine-Borane prepared from (+) or (-)-α-pinene, respectively. However, the α-chiral site at C-20 of the steroid may affect the selectivity of the reduction of 22-keto-23-acetylenic steroids with Alpine-Borane. Herein, we report such an α-chiral effect in the reduction of α-chiral alkynyl ketones with Alpine-Borane as well as the stereocontrolled synthesis of 22-hydroxy-23-acetylenic steroids.

Scheme 1



Reducing Agent		4:5	Isolated Yield
R-Alpine-Borane[g]	R = CH_3	125:1	(95%)
	R = $C(CH_3)_2OTHP$	125:1	(96%)
	R = $C(CH_3)_2OTBDMS$	125:1	(96%)
S-Alpine-Borane[g]	R = CH_3	1:2.7	(39%)
S-Alpine-Borane (neat)	R = $C(CH_3)_2OTBDMS$	1:7	(67%)
L-Selectride (-78°)	R = $C(CH_3)_2OTBDMS$	1:11	(100%)

(a) 6 eq. Ph_3PCH_3I, 6 eq. t-BuOK/t-BuOH, THF, reflux, 15h; (b) 2 eq. TBDMSCl, 4 eq. imidazole, DMF, r.t., 17 h, 92% in two steps; (c) 1.6 eq. dicyclohexylborane, 0°C, 17 h, $NaOH/H_2O_2$; (d) 1.6 eq. PCC, r.t. 18 h, 85% in two steps; (e) $LiC{\equiv}C\text{-}R$, -78°, 1 h, RT, 12 h, 98-100% yield; (f) 1.6 eq. PCC, r.t. 18 h, 86%; (g) 2.3 eq. 2.0 M, Alpine-Borane, 92% ee, r.t., 92 h.

Our starting material is the readily available 20-keto steroid, pregnenolone (1). Addition of triphenyl phosphonium methylide and protection of the 3β-hydroxy group gave the 20(22)-methylene steroid 2 (Scheme 1). Hydroboration of 2 with dicyclohexylborane provided the desired 20S-configuration of the alcohol as the predominant product (26:1).[4] Oxidation of the alcohol gave 22-aldehyde 3, from which the minor 20R epimer could be removed by chromatography. The 22-aldehyde steroid is commonly prepared via ozonolysis of stigmasterol.[5] However, the 5(6)-double bond must then be protected. Addition of lithium acetylides gave a diastereomeric mixture of acetylenic alcohols in a ratio of 1:1 to 3:1.[1] This mixture was oxidized to the 22-keto-23-acetylenic steroids 6, which were subsequently reduced with R-Alpine-Borane ((+)-α-pinene, 92% ee). In theory, the maximum asymmetric induction in this reduction would be 92% (24:1 ratio of 4:5). However, HPLC analysis of the reduction mixture indicated that the isomeric ratio of 4:5 had increased to 125:1. This result indicates that the selectivity of asymmetric reduction of 4 seems to be reinforced by the anti-Cram selectivity observed in the reduction of α-chiral ketones with electrophilic reducing reagents.[4] On the other hand, 6 was reduced rather slowly and incompletely (39% reduction after 92 h) by the S-Alpine-Borane reagent (2M in THF) prepared from (-)-α-pinene (92% ee). The S epimer 5 was obtained in a modest 2.7:1 ratio. Using neat S-Alpine-Borane the reaction was 67% complete in 92 h and 5 was obtained in a 7:1 ratio. From the results using 2M reagent one can calculate that the asymmetric induction due to Alpine-Borane proceeds in about an 18:1 ratio while the asymmetric induction due to the α-chiral effect is about 7:1. In the case of R-Alpine-Borane the double asymmetric inductions are working together while in the later case they are working in opposite directions. A similar change in selectivities (13:1 versus 1:2.5 for 4:5) has been observed during the asymmetric reduction of these acetylenic ketones using (+)- and (-)-N-methylephedrine/LAH.[1f]

The observed rate difference (R-Alpine-Borane reduces the ketone much faster than S-Alpine-Borane) suggests that there is a synergistic effect of the two chiral centers on the rate of reduction. This suggests that the C-20 epimer should react slowly with R-Alpine-Borane and it should thus be possible to selectively reduce the S-C-20 epimer in the presence of the R-C-20 epimer with R-Alpine-Borane. However, this hypothesis was not tested.[6]

With a highly selective process for 4 in hand, we sought methods for selectively preparing the epimer 5. Metal hydride reductions of 22-keto steroids are unusual in that the anti-Cram products (i.e., 4) are generally

produced.[1a] However, we found that the highly hindered reagent lithium tri-sec-butylborohydride (L-Selectride)[7] gives the Cram product 5 in acceptable selectivity (11:1) when R is a large group. If R is a methyl group, then 1,4 reduction begins to compete. The use of more hindered trialkylborohydrides leads to slower reactions and lower yield and selectivities.

It has now been demonstrated that an α-chiral site can reinforce or diminish enantioselectivity as well as influence the rate of asymmetric reduction of α-chiral alkynyl ketones with Alpine-Borane. Such an influence on asymmetric induction had not been observed in the reduction of β-chiral alkynyl ketones.[3] The stereocontrol at C-22, which has been void in many stereoselective syntheses,[1(a)-(f),2] will complement stereocontrol of other sites in the steroid side chain.

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