Tetrahedron Letters, Vol.31, No.26, pp 3669-3672, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

CORTICOIDS FROM 17-OXOSTEROIDS

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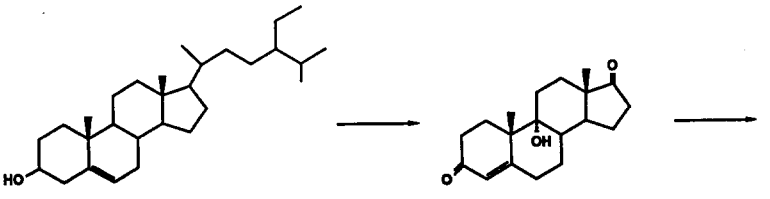
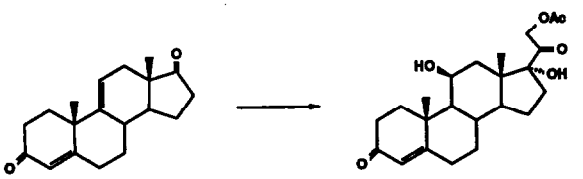
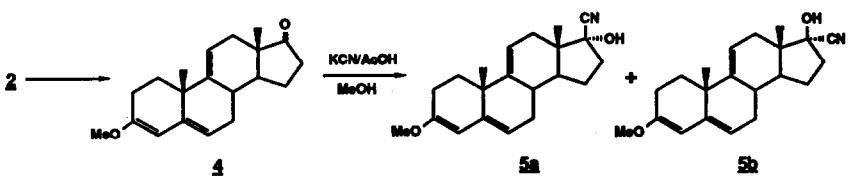
Abstract: Hydrocortisone intermediate 18 can be prepared from 3-methoxyandrost-3,5,9(11)-triene-3,17-dione (4) in 6 steps and in an overall yield of 50-55%. The key steps are the reduction of protected cyanohydrin 6 to aldehyde 7 and the one-pot conversion of 7 to bromoketone 11.

The interconversions of pregnanes and androstanes, i.e., steroids with and without the two-carbon side-chain at the 17-position, have historically been important processes.[1] The relative availability and importance of these two basically different types of steroids have dictated the preferred direction of these interconversions. Recently, the high demand for pregnanes, especially corticoids, and the easy availability of androstanes from biodegradations of a number of abundant natural sterols, have made the androstane to pregnane conversions important commercially.



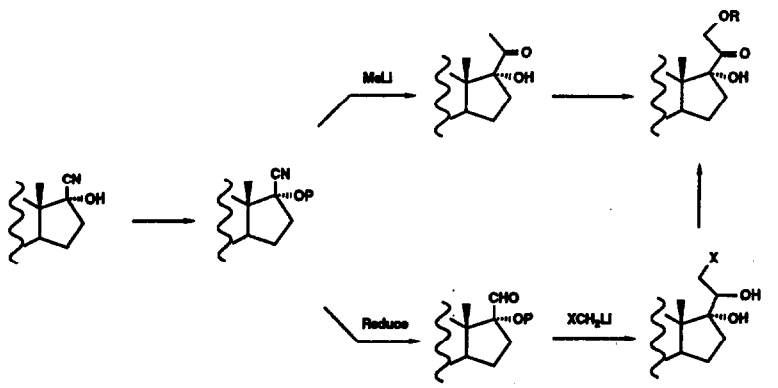


One such androstane is 9α-hydroxyandrost-4-ene-3,17-dione, 1, which is formed in the degradation of β-sitosterol by a mutant of Mycobacterium fortuitum.[2] Dehydration of 1 to $\Delta^{9(11)}$-derivative 2 and the latter's efficient conversion to hydrocortisone acetate, 3, have previously been described.[3] In this Letter we wish to describe an alternative synthesis of 3 starting from methyl enol ether 4, which is available in one step from 2.

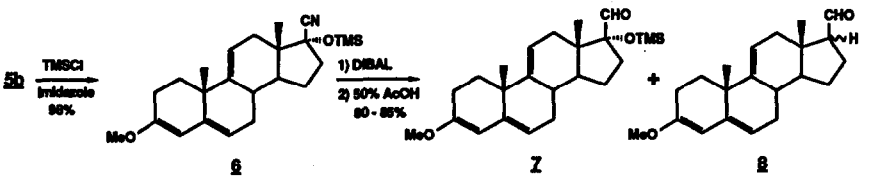


Reaction of hydrogen cyanide with 4 (KCN, AcOH, MeOH) gives a mixture of epimeric cyanohydrins, 5. Although the equilibrium ratio of 5a to 5b when both are in solution is ~1:1, the desired ß-cyano-epimer, 5a, may be formed in 95% yield by selective crystallization under equilibrating conditions.

This strategy for the selective formation of the β-cyano epimer was first reported 35 years ago,[4] but has not received much attention until recently, with their use as intermediates in corticoid syntheses.[5] Generally, following alcohol protection, methyllithium is added to the relatively unreactive nitrile to introduce the second carbon of the side chain. Subsequent oxidation at position-21 can be carried out to afford corticoids. Instead we chose to reduce the protected cyanohydrin to the corresponding aldehyde,[6] which we hoped would be reactive enough to allow addition of a substituted methyllithium. Oxidation of the resulting 20-alcohol to a ketone would then complete the side-chain synthesis.



Cyanohydrin 5b was converted to its trimethylsilyl ether 6 (TMSCl, imidazole, CH_2Cl_2, room temperature) in 98% yield after crystallization from methanol. Reduction of 6 (DIBAL, 5% THF/MTBE, -30°C; 50% aq. acetic acid) gave a nearly quantitative yield of crude aldehyde 7, which was greater than 95% pure by HPLC and TLC analysis. Crystallization from methanol, which was required for storage of this sensitive intermediate, typically gave 80-85% overall yield.

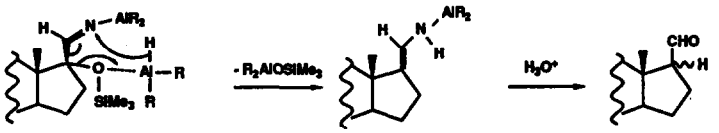


6 7 8

The proper choice of solvent in this reduction was critical. In non-chelating solvents such as toluene or methylene chloride, the level of 17-desoxy impurity 8 (mixture of epimers) ranged from 10-40%. In THF the level of this impurity is <1%, but the reaction is extremely slow, while in methyl t-butyl ether (MTBE) a small, but significant amount of 8 is still

formed. MTBE containing a small amount (5% by volume) of THF gave both a quick (two hours at -30°C) and clean (1-2% 8) reaction.

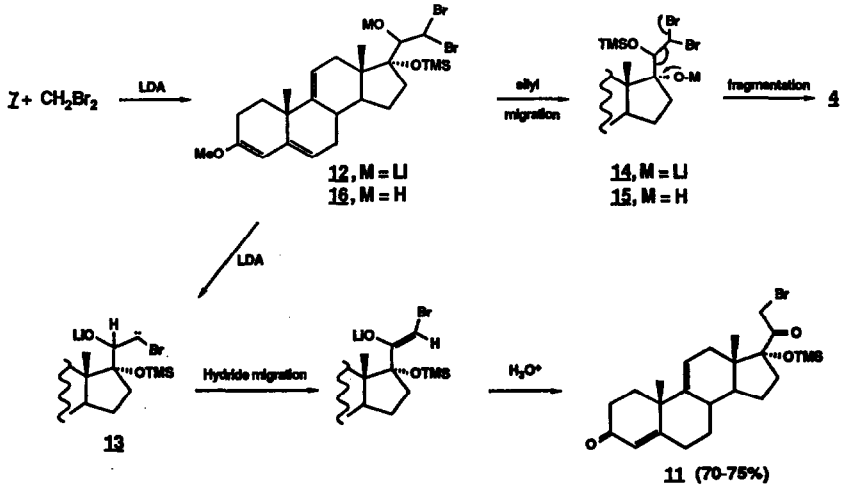
The degree of overreduction leading to 8 correlates well with the Lewis basicity of the solvent, indicating that complexation of the 17-silyloxy by some aluminum species is probably involved in this side-reaction. Complexation of the intermediate aldimine, 9, with a second equivalent of DIBAL, followed by intramolecular conjugate hydride displacement, as depicted below, would give enamine 10, which would lead to 8 upon work-up.



9 10 8

Use of 50% aqueous acetic acid gave very selective hydrolysis of the imine of 7, with no detectable loss of the enol ether or trimethylsilyl protecting groups. It also avoided the problems of insoluble aluminum salts occasionally encountered with aluminum hydride reagents.

Completion of the two-carbon side-chain synthesis, with the desired oxidation state at each carbon, was accomplished in the following manner.[7] Aldehyde 7 and CH_2Br_2 (1.05 equiv.) were dissolved in THF/hexane and cooled to -40°C. A solution of LDA in THF/hexane (1.0 M; 2.8 equiv.) was then added, taking care not to let the temperature go above -30°C. Following addition, the temperature was allowed to increase to -10°C over 30 min. After quenching with aqueous HCl, the main product, bromoketone 11, could be obtained in 70-75% yield following silica gel chromatography.

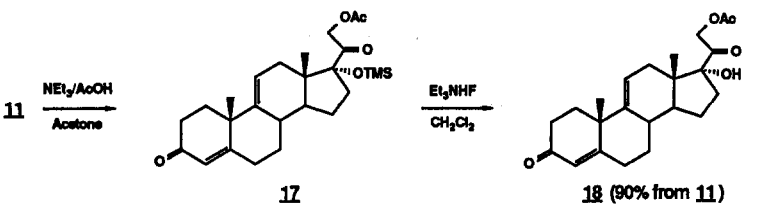


A mechanism for this conversion has been proposed.[7d] The first equivalent of LDA removes a proton from dibromomethane to form dibromomethyllithium, which rapidly adds to

aldehyde 7. The resulting adduct, 12, reacts with a second equivalent of LDA to form carbene 13, which undergoes a hydride migration to give the enolate of the observed product.

Several side-reactions were observed, with the most troublesome being migration of the trimethylsilyl group from the 17-hydroxyl to the 20-hydroxyl in intermediate 12, leading to alkoxide 14. Under conditions where the solvent is predominantly THF, 14 fragments to give 17-ketone derivative 4. As the fraction of hexane in the solvent increases, the rate of fragmentation of 14 decreases, leading to the appearance of 15 (at the expense of 4) in the product.

The total amount of silyl transfer can be minimized by maintaining the temperature of the reaction below -30°C and by keeping the fraction of hexane in the solvent near 50%. When the composition of the solvent is more than 50% hexane, intermediate 12 begins to come out of solution, leading to the presence of 16 in the product.



Conversion of 11 to acetate 17 via bromide displacement was straightforward ($Et_3NH^+OAc^-$, acetone, 56°C). Desilylation of crude 17 (Et_3NHF, CH_2Cl_2, room temperature, 24 hr.) followed by crystallization from acetone/water gave 18 in 90% yield from 11. The conversion of 18 to hydrocortisone acetate has been described previously.[3]

This chemistry provides a short and efficient route from readily available androstanes to high-value corticoids.

References

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(Received in USA 10 April 1990)