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A NEW APPROACH TO CORTICOID TOTAL SYNTHESIS

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We have recently published (1,2), a useful method for angular alkylation in position 10 of the 5(10), 9(11) estradiene derivatives. Thus, the diene I treated with organic peracids gives mainly the mono-epoxide II together with the two isomers III and IV. When the 5α, 10α-epoxy compound is subjected to the methyl Grignard reagent at room temperature, a trans diaxial opening of the oxirane ring occurs which permits the stereospecific introduction of the 10β-methyl group in very good yields.

These results prompted us to reinvestigate the synthesis of pregnanes from the appropriate estrane derivatives. For this purpose, the optically active dienic ketal V, (3), readily available by an industrial total synthesis elaborated in our research center (4) was transformed to the cyanohydrin VI with an excellent yield (90 %, m.p. =233-234°, $[\alpha]_D$ = + 175°) (5). The reaction was performed under equilibrium conditions (excess potassium cyanide in acetic acid and methanol). The less soluble cyanohydrin, with the nitrile group in the β-configuration precipitates, thus shifting the equilibrium in its favor.

The assignment of the configuration is based on the reaction of VI with methyl lithium in ethyl ether which gives the known ketol (VII) (3). Treatment of the cyanohydrin VI in methylene chloride with m-chloro perbenzoic acid leads to the expected epoxide VIII (m.p. = 215°, $[\alpha]_D$ = -21°) with a small amount of 5α, 10α and 9β, 11β isomeric epoxides, analogous to III and IV. In comparison with the results observed earlier in the epoxidation of the dienic benzoate I, the percentage of the desired 5α, 10α-epoxide from VI is increased (65 instead of 50). The 17β-cyano 17α-hydroxy group directs the attack of peracid towards the α-side of the steroid molecule and preferably on the 5(10) double bond.

For the following step of the synthesis, it is necessary to protect the hydroxyl function of the cyanohydrin group from the action of the Grignard reagents. The trimethylsilyl ether X (m.p. =166°, $[\alpha]_D$ = + 16°) was used. It was easily prepared by the action of chlorotrimethylsilane in pyridine ; this ether can be formed before or after epoxidation.

Thence, a one step procedure leads to the pregnane structure, for, when the epoxide X is treated with methylmagnesium bromide in tetrahydrofuran under reflux overnight, two simultaneous reactions occur : 1° - the opening of the oxirane ring with stereospecific introduction of the 19-methyl group ; 2° - condensation of the Grignard reagent with the nitrile, thus building up the pregnane side-chain. Treatment of the crude product with ammonium chloride in aqueous solution allows the concomitant hydrolysis of the intermediate imine and of the trimethylsilyl ether. In this way, the compound XI (m.p. =213°, $[\alpha]_D$ = -19°), a versatile intermediate for the synthesis of corticoids, is obtained from VIII with an overall yield of about 66 %. Upon treatment with aqueous acid, XI gives rise to the conjugated ketone XII already described (6).

In the Grignard reaction, it is possible to stop it at the first step, i.e. the opening of the epoxide, and to isolate the compound XIII (m.p. = 165°, $[\alpha]_D$ = -4°) with an excellent yield (95 %) by performing the reaction at room temperature. In this case, during subsequent hydrolysis in ammonium chloride, the trimethylsilyl ether bond is preserved.

This allowed us to perform the synthesis of 19-alkyl pregnane derivatives by reacting at first an alkyl magnesium halide (with alkyl $\neq$ methyl) with the epoxide X, at room temperature, followed by the reaction with methylmagnesium bromide in tetrahydrofuran at reflux in order to build up the pregnane side-chain.

The details of our study will be published later.

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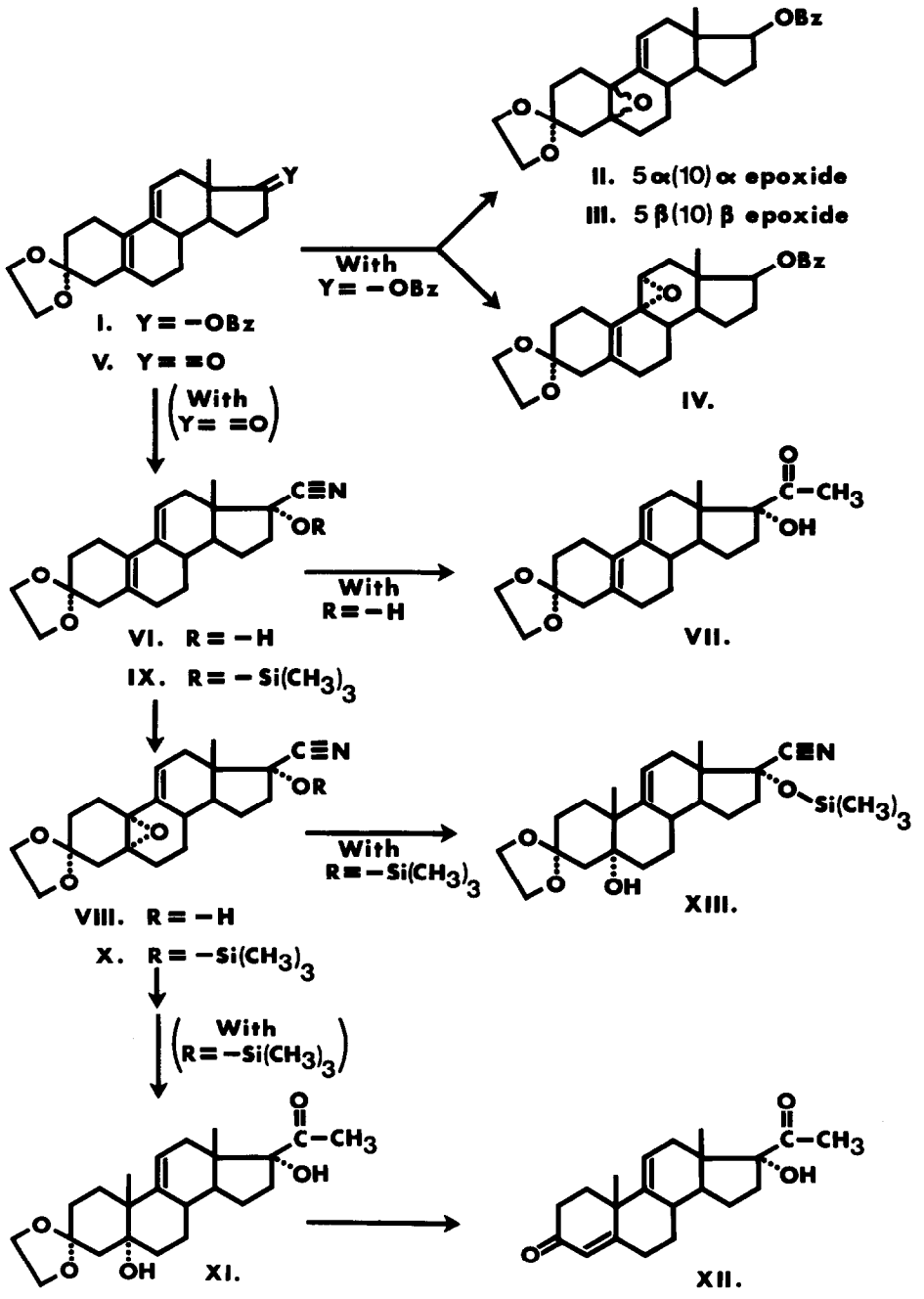
OBz
II. 5α(10)α epoxide
III. 5β(10)β epoxide
Y
With
Y = −OBz
I. Y = −OBz
V. Y = =O
With
Y = =O
OBz
IV.
C≡N
OR
With
R = −H
VI. R = −H
IX. R = −Si(CH3)3
C−CH3
OH
VII.
C≡N
OR
With
R = −Si(CH3)3
VIII. R = −H
X. R = −Si(CH3)3
C≡N
O−Si(CH3)3
OH
XIII.
With
R = −Si(CH3)3
C−CH3
OH
OH
XI.
C−CH3
OH
XII.

(1) L. Nédélec, Bull. Soc. Chim. France, 2548 (1970).

(2) L. Nédélec and J.C. Gasc, Bull. Soc. Chim. France, 2556 (1970).

(3) M. Vignau, R. Bucourt, J. Tessier, G. Costerousse, J.C. Gasc, L. Nédélec, R. Joly, J. Warnant and B. Goffinet, Canadian Patent 801 724 (Roussel-Uclaf) .

(4) a) L. Velluz, G. Nominé, G. Amiard, V. Torelli and J. Cérède, C. R. Acad. Sci., 257, 3086 (1963).

b) L. Velluz, J. Valls and G. Nominé, Angew. Chem., 77, 185 (1965).

(5) The structures of all compounds were established by elementary analysis and from spectroscopic data and the results were in agreement with the assigned structures. Specific rotations were determined in chloroform.

(6) J. Fried, J.E. Herz, E.F. Sabo, A. Borman, F.M. Singer and P. Numerof, J. Am. Chem. Soc., 77, 1068 (1955).