Tetrahedron Letters,Vol.26,No.9,pp 1137-1140,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF 11β-HYDROXY-18-ETHYNYLPROGESTERONE: AN INHIBITOR OF ALDOSTERONE BIOSYNTHESIS

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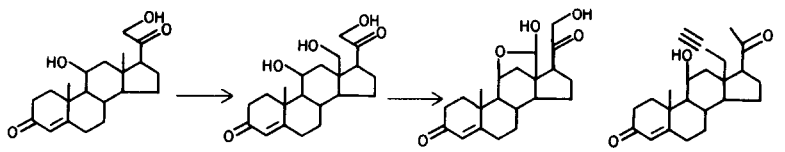
Abstract: The title compound was prepared by thermolysis of a C20 cyanohydrin peracetate to yield a C18 nitrile which was subsequently converted to an acetylene.

The principle mineral corticoid, aldosterone (1), is synthesized in the zona glomerulosa cells of the adrenal cortex from corticosterone (2) apparently via sequential cytochrome P-450-mediated hydroxylations at C18 (2→3→1).[1] As we[2] and others[3,4] had shown earlier that 19-ethynylandrost-4-ene-3,17-dione is a potent suicide inactivator of aromatase, an enzyme which carries out sequential hydroxylations at C19 of the steroid nucleus, a logical synthetic target for the inhibition of 18-hydroxylase became the 11β-hydroxy-18-ethynylprogesterone 4. The proposed mechanism of inactivation involves oxygen donation from activated heme to the triple bond of 4, leading ultimately to heme alkylation. A similar mechanism has been proven operative for the inactivation of hepatic cytochrome P-450 by acetylene itself.[5]

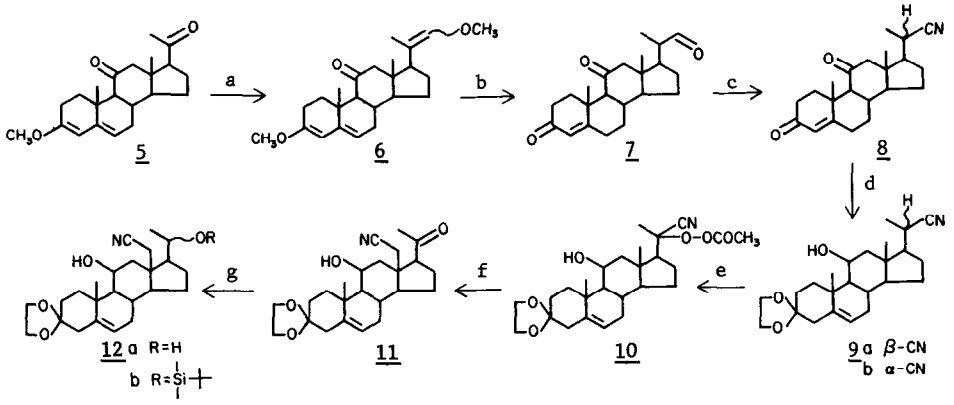


2 3 1 4

Functionalization of C18 on the steroid nucleus has been achieved by intramolecular free radical reactions initiated by free radical formation at the 11-hydroxy[6,7] or 20-hydroxy groups.[8] The Barton photolysis of 11β-hydroxynitrite esters[6] leads to oxime formation at C18 and the Kalvoda-Botta acetyl hypoiodite procedure using a 20-hydroxy precursor generates a C18 iodide.[7] Alternatively, the C20 cyanohydrin leads, under these conditions, to the C18 nitrile.[8] While these procedures may provide eventual access to 4, we elected to use 11β-hydroxy-20-cyanosteroid 9 as the key intermediate. It was anticipated that either photolysis[9] or thermolysis[10] of the derived perester 10 would lead to 11β-hydroxy-18-cyano-20-ketosteroid 11 which would be a convenient intermediate for later transformations to the target acetylene 4.

The synthesis of 11β-hydroxy-18-cyano-20-ketosteroid 11 is outlined in Scheme 1. Commercially available 11-ketoprogesterone was converted to dienol ether 5,[11] (mp 120-128°C) and treated with methoxymethylenetriphenylphosphorane (1.5 eq.) in toluene[12] to form dienol ether 6. Acid hydrolysis of crude 6 then liberated diketoaldehyde 7 [17] (mp 143.5-144°C) in overall 30-40% yield from 11-ketoprogesterone. Diketoaldehyde 7 was then converted to monooximes which were dehydrated using carbonyldiimidazole[13] in CH_2Cl_2 to afford nitrile 8 (mp 169-180°C), isomeric at C20, in 82% yield. Ketalization of 8 followed by reduction at elevated temperatures with sodium borohydride in THF/aq. NaOH then gave 11β-hydroxy-20-nitriles 9.[14] Isomeric nitriles 9 (9a, mp 190.5-192.5°C; 9b mp 204-205°C) could be separated by flash chromatography, and their conversion to peroxyesters 10 studied individually. While one of these isomers formed a dianion when treated with LDA at -70°, which could be trapped with oxygen and the resultant hydroperoxy anion acylated with acetyl chloride at -70° to afford 10, the other isomer required the use of the less hindered potassium diethylamide at -40°C for conversion to the dianion.[18] Subsequently, the isomeric mixture was subjected to the latter conditions. Radical decomposition of 10 in hot pyridine[10] led directly to the 18-cyano-20-ketone 11 (mp 219.5-222°C) in 40-60% yield from the mixture of nitriles 9.[19] Ketone 11 was reduced to 12a (mp 209-212°C) then silylated to 12b (mp 193-197°C).

Scheme 1[16]

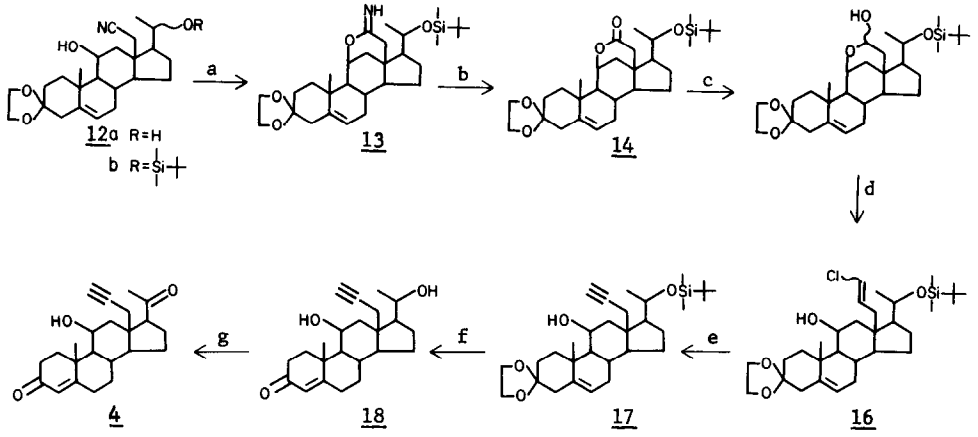


Reagents: (a) $Ph_3PCHOCH_3/PhCH_3$; (b) 2:1 dioxane:1N HCl, 71%; (c) (i) $H_2NOH{\cdot}HCl/C_5H_5N$, 0°C; (ii) CDI/CH_2Cl_2, 82%; (d) (i) $HOCH_2CH_2OH/pTSA/C_6H_6$, 81%; (ii) $NaBH_4$/THF/aq. NaOH, 90%; (e) (i) KDEA/THF/HMPA, -45°C; (ii) O_2; (iii) CH_3COCl; (f) C_5H_5N, 100°C, 40-60%; (g) (i) $NaBH_4/CH_3OH$, 0°C, 86%; (ii) TBDMSCl/DMAP/Et_3N/DMF, 85%.

The conversion of 12b to the target 18-ethynylsteroid 4 is shown in Scheme 2. On exposure to sodium hydride 12b was transformed to the imidate 13 which, on hydrolytic workup, afforded lactone 14 in 94% yield from the nitrile 12b. Lactone 14, on treatment with diisobutylaluminum hydride, gave lactol 15. Even though Drieding models of the lactol 15 and its corresponding open hydroxyaldehyde form demonstrated that the aldehyde function was considerably encumbered, a Wittig reaction under vigorous conditions using chloromethylenetriphenylphosphorane afforded a mixture of vinyl chlorides 16[17] in 76% yield with a 10% recovery of 15. Dehydrochlorination of 16 afforded acetylene 17[17] in greater than 90% yield. When subjected to acid conditions, 17 underwent simultaneous deprotection at C3 and at C20 to give 18,[17] which was oxidized to the target 4 using the Swern procedure.[15,20]

Biosynthesis of aldosterone from corticosterone in zona glomerulosa cells from beef adrenals was inhibited by 4 and this will be reported elsewhere.

Scheme 2[16]



Reagents: (a) NaH/THF; (b) NaOAc/aq. HOAc, pH 5-6, 65°C, 94%; (c) DIBAL/$PhCH_3$, 96%; (d) Ph_3PCHCl/THF, 66°C, 76%; (e) LDA/THF, 90%; (f) 95:5 CH_3OH:1N HCl, 74%; (g) (i) ClCOCOCl/DMSO/CH_2Cl_2; (ii) Et_3N, 62%.

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16. Satisfactory spectral and analytical data were obtained for all compounds unless otherwise noted.
17. Satisfactory microanalysis was not obtained for this compound.
18. We assign the β-stereochemistry to 9a based on analogy to 11-desoxy-9 which we prepared from commercially available 3-oxopregn-4-ene-20β-carboxaldehyde. This material underwent deprotonation with LDA at -70°, leading ultimately to desoxy-11.
19. Mild acid hydrolysis of 11 produced the known 11β-hydroxy-18-cyanopregn-4-ene-3,20-dione.[7]
20. Spectral data confirming the structure of 4 are: ^{1}H NMR (90MHz, $CDCl_3$) δ 5.60 (broad s, 1H, enone), 4.38 (m, 1H, 11α-), 2.30 (s, acetylene), 2.19 (s, 21-CH_3), 1.37 (S, 19-CH_3); IR (KBr) 3430, 3270, 2120, 1715, 1660 cm^{-1}; MS (e.i.) m/e 354 ($M^{+\cdot}$), 43 (100%).

(Received in USA 5 November 1984)