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A STEREOCONTROLLED TOTAL SYNTHESIS OF 2β,3β,20β-TRIACETOXY-5α-PREGNAN-6-ONE — A TOTAL SYNTHESIS OF 20-HYDROXYECDYSONE

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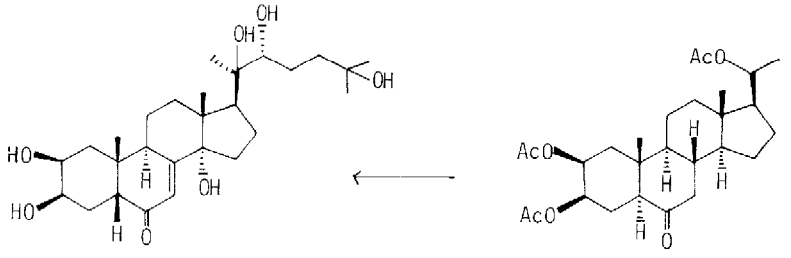
Summary: The stereoselective total synthesis of 2β,3β,20β-triacetoxy-5α-pregnan-6-one (2) via acetylene-cation cyclization of 7, which was readily derived from the D-ring aromatic steroid 3, is described and this constitutes a total synthesis of 20-hydroxyecdysone (1).

20-Hydroxyecdysone (1), the first crustacean molting hormone,[1] has attracted much attention[2-5] mainly because of its highly oxidized structure and biological activity as an insect molting hormone Nakanishi speculated in his paper[6] describing the synthesis of 20-hydroxyecdysone that the use of ecdysteroid in the silk industry would lead to the production of larger quantities of high-quality silk. Although there have been many reports on the synthesis of ecdysteroid,[6-8] naturally occurring steroids have been used as starting materials. Here we wish to describe a total synthesis of triacetate (2)[5] which effects a total synthesis of 20-hydroxyecdysone (1).

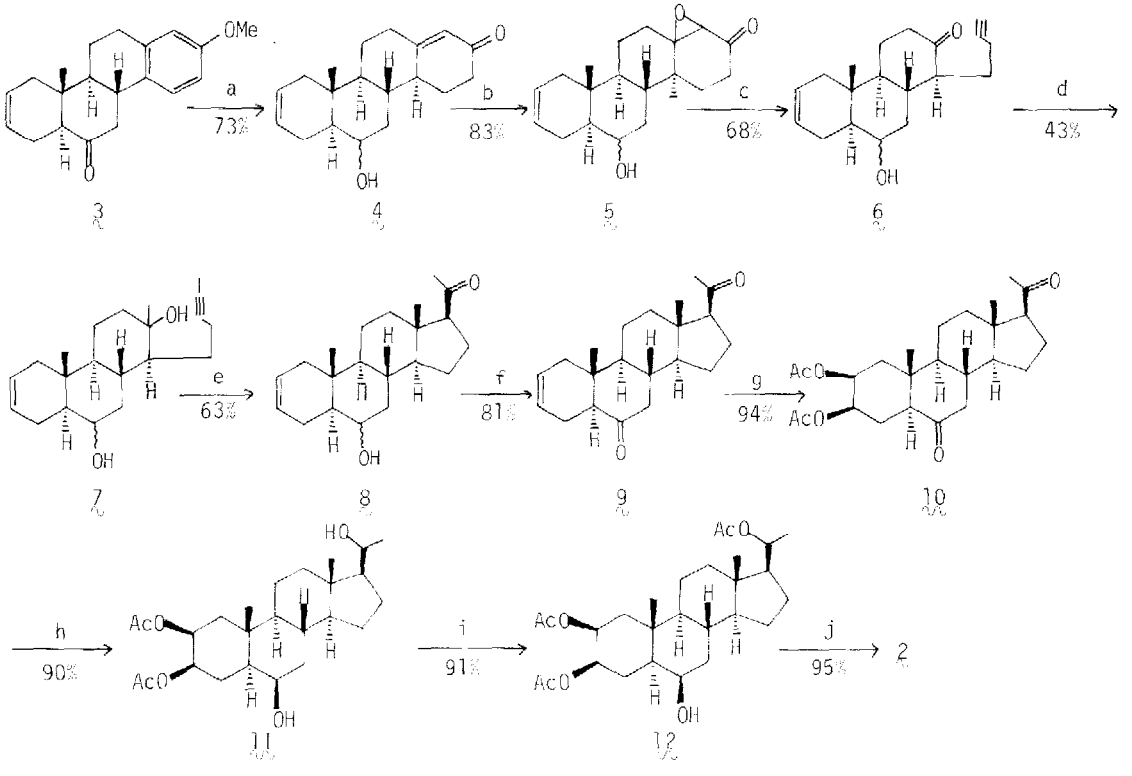


1 2

As outlined in scheme 2, the starting material for the sequence is the D-ring aromatic steroid (3).[9] The enone (4), prepared from (3) by reduction with sodium borohydride and followed by Birch reduction and acid treatment, was converted into the epoxide (5) by treatment with 30 % hydrogen peroxide in 10 % aqueous sodium hydroxide and methanol. The acetylenic ketone (6) [i.r. ($CHCl_3$) 3300 (C≡CH) and 1700 cm^{-1} (C=O); m/e 286 (M^+)] resulting from Eschenmoser ring opening reaction of (5), using p-toluenesulfonyl hydrazide in acetic acid and dichloromethane, was treated with methyllithium in tetrahydrofuran followed by methyl iodide in the presence of lithium amide in liquid ammonia to give the acetylenic alcohol (7) [i.r. ($CHCl_3$) 3620 cm^{-1} (OH); m/e 316 (M^+)]. Cyclization of (7), to produce compound (8) [i.r. ($CHCl_3$) 1695 cm^{-1} (C=O); m/e 316 (M^+)], was effected by treatment with trifluoroacetic acid and trifluoroacetic anhydride followed by hydrolysis with 10 % potassium hydroxide in ethanol. Prévost-Woodward reaction, using silver acetate and iodine in wet acetic acid, of the olefinic diketone (9) [i.r. ($CHCl_3$) 1695 cm^{-1} (C=O); n.m.r. (CCl_4) 0.62 (3H, s, Me), 0.7 (3H, s, Me), 2.03 (3H, s, Me), and 5.6 (2H, br s, olefinic protons); m/e 314 (M^+)] which was obtained by Jones' oxidation of (8), furnished the diacetate (10) [m/e

432 (M^+)]. Successive treatment of (10) with sodium borohydride in methanol and dichloromethane and then acetic anhydride in pyridine yielded the monoalcohol (12) [m/e 478 (M^+)] which was finally subjected to Jones' oxidation, resulting in formation of the target compound (2). Compound (2) thus obtained was identified with an authentic sample[5] by i.r. ($CHCl_3$) and n.m.r. ($CDCl_3$) spectral comparison.

Scheme 2



Reagents a: (i) $NaBH_4$, MeOH, 0°C; (ii) Li, liq. NH_3, ^tBuOH, THF, -78°C, (iii) TsOH, $(CH_3)_2C=O$, reflux. b: 30 % H_2O_2, 10 % NaOH, MeOH, 0°C. c: $TsNHNH_2$, CH_2Cl_2, AcOH, -20°C to RT. d; (i) MeLi, THF. 0°C; (ii) $LiNH_2$, liq. NH_3, MeI, -78°C. e: (i) $(CF_3CO)_2O$, -10°C to RT; (ii) KOH, EtOH, RT. f: Jones' reagent, $(CH_3)_2C=O$, 0°C. g: (i) AgOAc, I_2, wet AcOH, 45°C; (ii) Ac_2O, C_5H_5N, RT. h: $NaBH_4$, MeOH, CH_2Cl_2, 0 C. i: Ac_2O, C_5H_5N, RT. j: Jones' reagent, $(CH_3)_2C=O$, 0°C.

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References

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