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A STEREOSELECTIVE TOTAL SYNTHESIS OF Δ^9-PROGESTERONE VIA AN INTRAMOLECULAR CYCLOADDITION REACTION

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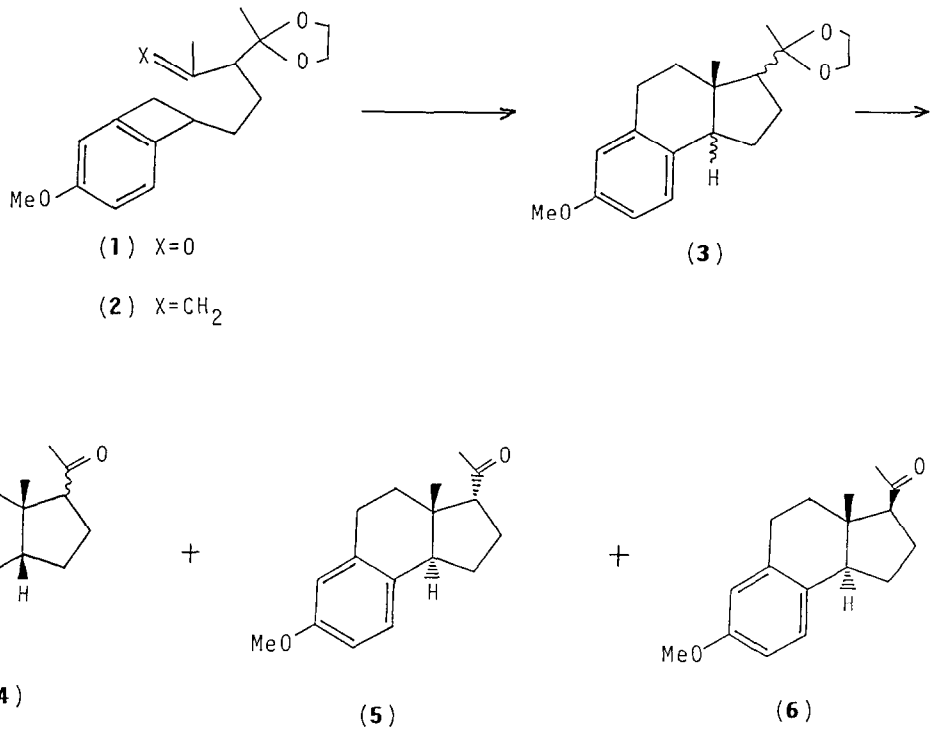
Summary: A stereoselective total synthesis of 19-nor-$\Delta^{9(10)}$-progesterone (**14**) was achieved through des-A B-aromatic steroid (**3**) which was obtained by an intramolecular cycloaddition of the o-quinodimethane generated in situ from the thermolysis of 3-isopropenyl-5-(4-methoxybenzocyclobutenyl)pentan-2-one-2-ethylene ketal (**2**), and the compound (**14**) thus obtained was further converted into Δ^9-progesterone (**18**).

In the course of our synthetic studies of steroids via intramolecular cycloaddition reactions,[1] recently our attention has been focused on the stereoselective construction of des-A B-aromatic steroids[2] because of their potential importance as intermediates for a synthesis of C_{11}-functionallized steroids. Here we wish to report an efficient synthesis of des-A-ring steroid (**6**) via the des-A B-aromatic steroid (**3**) and its conversion into Δ^9-progesterone (**18**).

The mono-ketal (**1**)[2a] was subjected to Nozaki's olefination procedure[3] [Zn, $TiCl_4$, CH_2Br_2, THF, CH_2Cl_2, room temp.] and the reaction was found to proceed in 81% yield giving the isopropenyl derivative (**2**). The thermolysis of **2** was conducted in o-dichlorobenzene under refluxing and the cyclized compound (**3**)(angular methyl resonances at 0.63, 1.06 and 1.16) was obtained in 99% yield as a stereoisomeric mixture, which was successively hydrolized [10% HCl, MeOH, room temp.] to give the ketones (**4**), (**5**), and (**6**) in the ratio of 1:1:10.

The structure of these products was assigned tentatively at this point by comparing with previously obtained compounds[2a] respectively (an angular methyl resonance at 0.95, 0.76 and 0.52 ppm for **4,5 and 6**). Since we could find effective procedures for producing the ketone (**6**) selectively, the conversion of **6** into 19-nor-$\Delta^{9(10)}$-progesterone (**14**) was investigated as follows. The hydroxy compound (**7**) obtained [$NaBH_4$, MeOH, room temp.] from **6** in 99% yield

Scheme 1



(1) X=O

(2) X=CH_2

(3)

(4)

(5)

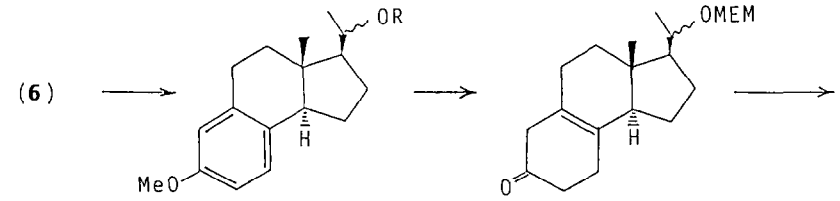
(6)

was converted [MEMCl, Hünig base, CH_2Cl_2, room temp.] in 99% yield into the ether (**8**). The Birch reduction [Li, EtOH, liq. NH_3, THF, -78°] of **8** and an acid hydrolysis [$(CO_2H)_2$, EtOH, H_2O, room temp.] gave the β,γ-unsaturated enone (**9**) [m/e 336 (M^+)] in 82% overall yield. The alkylation of **9** with methyl α-trimethylsilylvinyl ketone[4] under two different conditions, [LDA, HMPA, THF, -78°C; $^nBu_4NF$, THF, room temp.] and [$KN(SiMe_3)_2$, Et_3B, THF, -78°C; n-Bu_4NF, THF, room temp.][5] afforded a mixture of **10**[m/e 476 (M^+)] and **11**[m/e 406 (M^+)] in the ratio of 3:2 in 50% yield and 1:1 in 63 % yield, respectively.

The monoalkylated compound (**11**) was cyclized [t-BuOK, t-BuOH, room temp.] and hydrolized [10% HCl, MeOH, reflux] to give in 27% overall yield the tetracyclic compound (**13**) [m/e 300 (M^+)] via **12**. This product (**13**) was finally oxidised [Jones reagent, acetone, room temp.] to furnish 19-nor-$\Delta^{9(10)}$-progesterone (**14**), which was identified by IR($CHCl_3$) and ^{1}H-NMR($CDCl_3$, 100 MHz) spectral comparison with the authentic sample.[6] Thus, we could determine unambiguously the whole structure of the compound (**6**), whose structure had been previously assigned tentatively.[2a]

The transformation of **14** into Δ^9-progesterone (**18**) was straightforward and as follows. The diketal (**15**) [m/e 386 (M^+)], obtained in 80% yield by ketallization [$HO(CH_2)_2OH$, CSA, benzene, reflux] of **14**, was oxidised [MCPBA, $NaHCO_3$, H_2O, CH_2Cl_2, 0°C] to give in 40% yield the monoepoxide (**16**) [m/e 402 (M^+)] which was then successively reacted with Grignard reagent (MeMgBr, Et_2O,

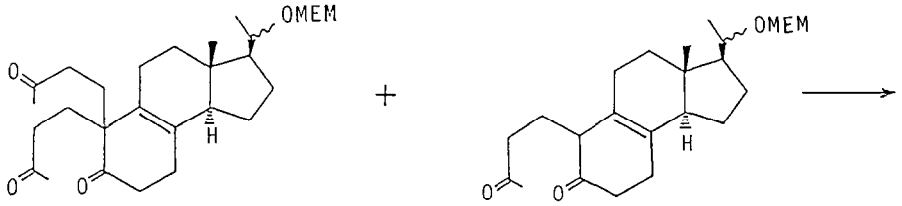
Scheme 2



(7) R=H

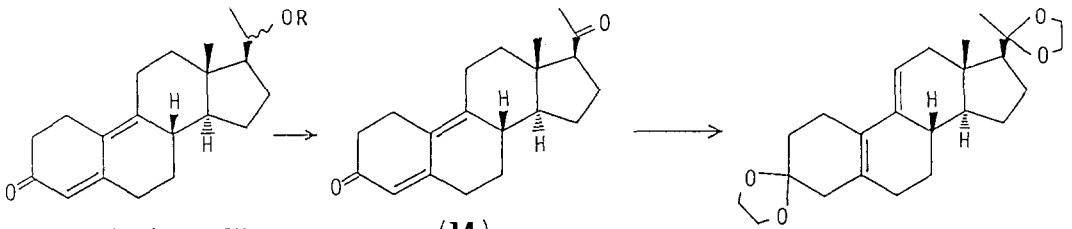
(8) R=MEM

(9)



(10)

(11)

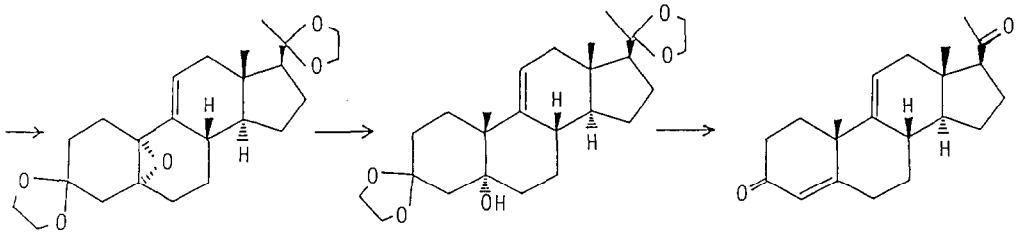


(12) R=MEM

(13) R=H

(14)

(15)



(16)

(17)

(18)

room temp.] and acid treatment [10% HCl, MeOH, reflux] to furnish in 24% overall yield the target compound (**18**) which was identified by IR($CHCl_3$) and ^{1}H-NMR($CDCl_3$, 100 MHz) spectral comparison with the authentic sample.[7]

Thus, we could develop an effective method for the synthesis of Δ^9-progesterone (**18**).

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(7) Commercially available **18** was purified by crystallization(benzene-CH_2Cl_2) and used as an authentic sample.

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