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BIOMIMETIC TOTAL SYNTHESIS OF 14α-METHYL-19-NORSTEROIDS STEREOSELECTIVE EPOXIDATIONS WITH $Mo(CO)_6$ / t-BuOOH.

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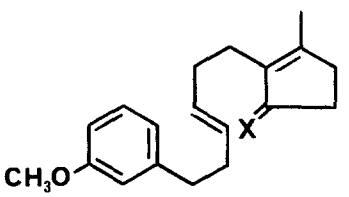
Summary: A total synthesis of the novel steroids DL-14α-methylestradiol (9) and DL-14α-methyl-19-nortestosterone (11) via cationic cyclization is described. Advantage was taken of the unusual stereoselectivity of $Mo(CO)_6$ /t-BuOOH epoxidations.

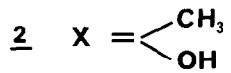
In the past two decades 14α-methyl steroids have received considerable attention due to the fact that they may be formed in nature by a pathway deviating from the normal biosynthesis of steroids from lanosterol[1]. In contrast to 14α-methyl derivatives of the other major sex hormones[2] to date 14α-methyl estradiol (9) is still an unknown compound, in spite of various attempts at its synthesis.[1, 3, 4]

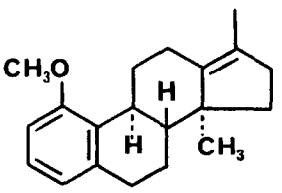
Since the synthesis of 9 and related compounds is still actively being pursued[5] we would like to report the synthesis of 9 and 14α-methyl-19-nortestosterone (11) in racemic form based on Johnson's biomimetic route.[6]

The known compound 1[6], upon reaction with methyl lithium produced the cyclopentenol 2, which was immediately cyclized (H COOH/ CH_2Cl_2 2:1, 0-5°C, 30 min) to give the tetracyclic products 3, mp 103-104.5°C, and 4b, mp 59.5-60.5°C, in 27 and 47% yield, respectively.



1 X = O

2 X = 



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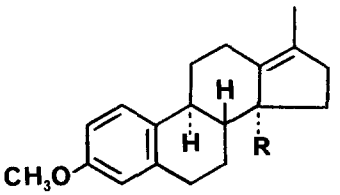
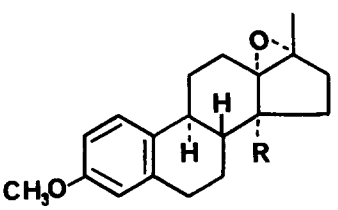


4a R = H

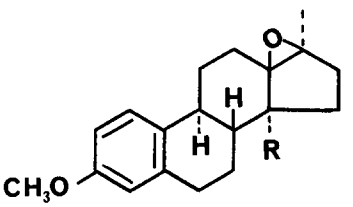
4b R = CH_3

While compounds like 4a can be converted into the corresponding 13α, 17α-epoxides in modest yield via chloro- or bromohydrin intermediates[6] compounds analogous to 4b reportedly fail to form halohydrin derivatives.[4]

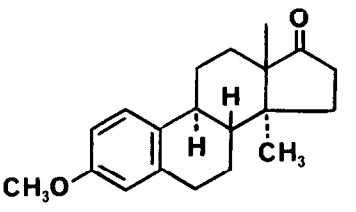
Therefore successful completion of the synthesis hinged on finding ways to intoduce the epoxy group in the sterically hindered 13α, 17α-position. A number of methods were tested for this purpose, initially with the estrone intermediate 4a as the substrate. Nearly quantitative conversion of 4a into the epoxides 5a and 6a was observed with dry t-butylhydroperoxide (~1,5 equivalents) in the presence of a catalytic amount of molybdenum hexacarbonyl (5% on a molar basis) in benzene or toluene (80°C, 1-2 h).[8] More importantly 5a and 6a were formed in a ratio of 5:1, the exact opposite of what was observed in the peracid oxidation of 4a.[6] Recrystallization of the crude mixture gave the desired epoxide 5a in yields up to 80%, a dramatic improvement over the reported method.[6]



5a R = H
5b R = CH_3



6a R = H
6b R = CH_3



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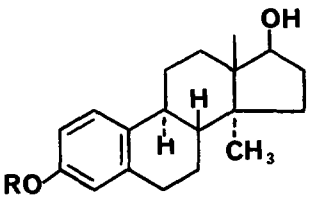
Surprisingly the observed stereoselectivity was fully preserved, when 4b was subjected to the reaction conditions mentioned above, 5b and 6b being produced in a 5:1 ratio in almost quantitative yield.[9] This remarkable stereoselectivity is reminiscent of that observed in the reaction of analogous compounds with osmium tetroxide.[10] An attractive explanation for this similarity is the assumption that the molybdenum catalysed epoxidation, like the osmylation, proceeds via a 5-membered ring incorporating the metal atom, as suggested by Mimoun.[11]

Rearrangement of 5b ($BF_3.Et_2O$, 0.6 equiv., toluene, 0-5°C, 40 min) produced DL-14α-methylestrone 3-methyl ether, 7, mp 129-130°C, in 42% yield, based on 4b.

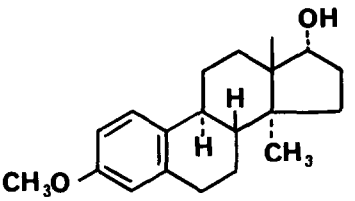
Reduction of 7 with sodium (5 equiv) in toluene / i-propanol (10:1, 100°C, 2h) afforded 8, mp 130-132°, as the major product (84% yield) while the less polar 17α-isomer, mp 125-127°C, was isolated as a minor product (6% yield).

Demethylation (pyridine. HCl, 15 equiv., 200°C, 1 h) of 8 produced DL-14α-methylestradiol 9, mp 230-231°C, in 53% yield.

Birch reduction of 8 (Li, 17 equiv., NH_3, -60°C, 1.5h) followed by acid treatment (1 N HCl in H_2O/THF 1:1, 60°C, 1.5 h) gave DL-14α-methyl-19-nortestosterone, 11, mp 143-145°C, in 81% yield.



8 R=CH_3
9 R=H



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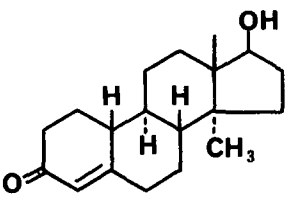

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Table 1

^{1}H-NMR data [a]

chemical shifts (from TMS)

compd.	CH_3 at C-14 [b]	CH_3 at C-13 [b] or C-17	H at C-17
3	0.94	1.60	
4b	0.93	1.60	
5b	1.01	1.33	
6b	0.91	1.38	
7	0.89 (0.922)	1.02 (1.014)	
8	0.89 (0.88)	0.89 (0.88)	4.16 (dd, J = 6, 8.5)
9	0.89 (0.88)	0.89 (0.88)	4.13 (dd, J = 6, 8.5)
10	1.13 (1.114)	0.80 (0.806)	3.94 (dd, J = 1.5, 8)
11	0.79	0.94 (0.925)	4.15 (dd, J = 6, 8.5)

a) $CDCl_3$-solution, 90 M Hz

b) Calculated values [13] in brackets

The increment for the C-13 methyl group caused by the C-14 methyl substituent and vice versa (0.125 ppm) and the contribution of the aromatic A ring (0.03 ppm) were taken from the literature. [14, 15]

The structures of the new products were confirmed by ^{1}H-NMR spectral data. Chemical shifts of the angular methyl groups were calculated for the compounds 7 - 10, using literature data and assuming that the effect of a C-17 substituent on the C-14 methyl shift is the same as that of a C-15 substituent on the C-13 methyl shift. The validity of this assumption has been demonstrated for related compounds.[12]

References and notes

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