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An Efficient Synthesis and Biological Activities of 19-Nor-17β-hydroxy-17α-trifluoromethyl-Δ^4-estren-3-one and Its Analogs

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Abstract: 19-Nor-17β-hydroxy-17α-trifluoromethyl-Δ^4-estren-3-one **6** and its analogs **7** and **8** have been synthesized in total yields of 82%, 54% and 27%, respectively, using Me_3SiCF_3 as a trifluoromethylating agent. The three compounds showed high affinity for rat uterus PRc.

Trifluoromethyl-substituted compounds have been examined for their potential as biologically active drugs and agrochemicals.[1] The trifluoromethyl group is one of the most lipophilic substituents and can increase the solubility of drugs in lipids, [1a] thus enhancing their penetrating ability. Since its size is close to that of the methyl group,[2] it does not seriously modify the steric bulk of the steroid, thus ensuring a good fit to the target receptor. The high electron-attracting properties[3] could alter the reactivity of neighbouring groups, causing a possible modification of biological activity of the molecule. So we want synthesis of some trifluoromethyl-substituted steroids to find the new compounds for contraceptive drug.

However, the introduction of a trifluoromethyl group is more difficult than that of a single fluorine atom,[4] thus it is not surprising that only limited number of steroids bearing this group appear in the medicinal chemical literature[5]. The direct introduction of trifluoromethyl group using Me_3SiCF_3 ($TMSCF_3$) reagent has been reported.[6] But this method is not very useful for hindered carbonyl compounds. We have recently reported an improved synthetic method for efficient trifluoromethylation of hindered steroid compounds with $TMSCF_3$ reagent promoted by Me_4NF followed by 40% aq.HF hydrolysis and obtained some trifluoromethyl-substituted steroids in almost quantitative yield.[7]

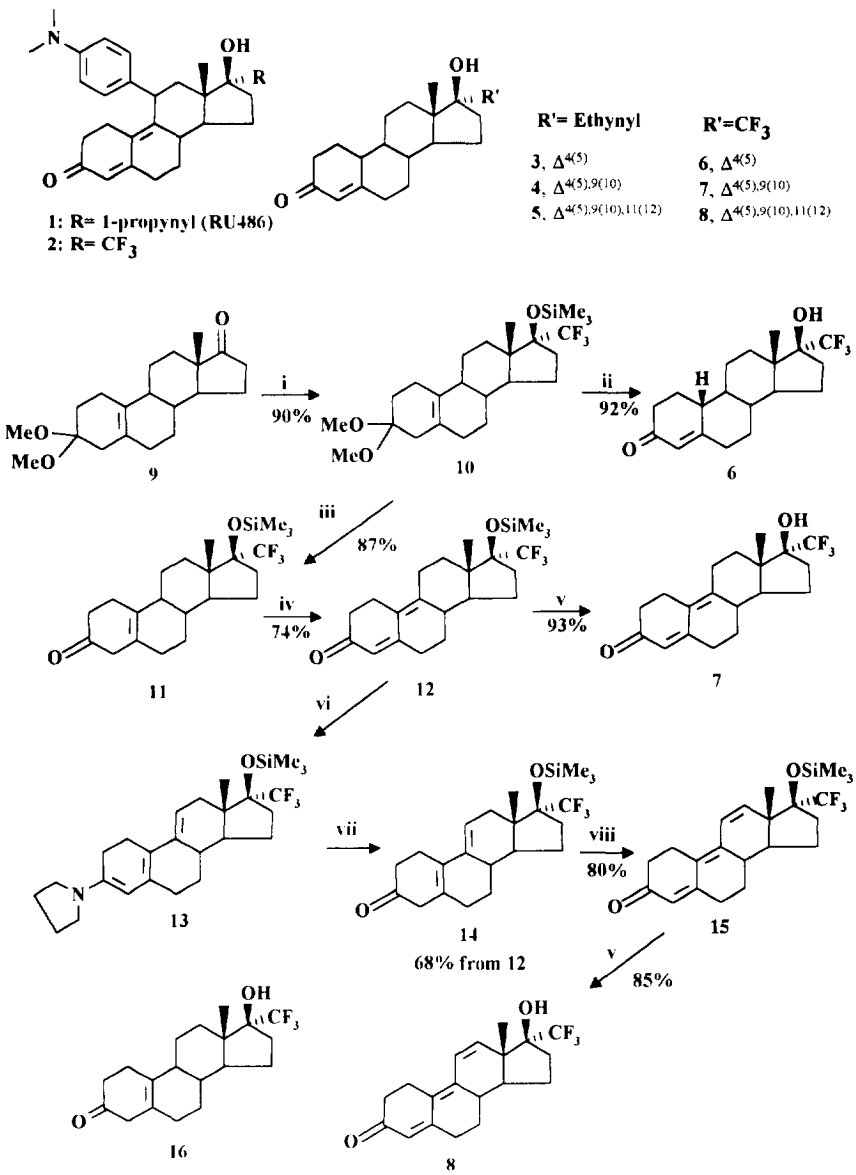
When the useful contraceptive drug 11β-(p-*N,N*-dimethylaminophenyl)-17α-propynyl-estra-4,9-diene-17β-ol-3-one (RU486) (**1**) was modifided by a trifluoromethyl group at the 17-position, the analog **2** exhibited increased bioactivity in biotests, as we have envisaged.[7]

Norethisteron (17α-ethynyl-19-nor-testosterone)(**3**) and some of its derivertives are potent progestogens(such as **4** and **5**) widely used for oral contraception.[8] Recently, the influence of 17-position substituents of these derivatives on the binding affinity to progesterone and androgen receptors have been investigted and some factors were suggested.[9] a): steric changes over the whole molecule may influence the binding affinity; b): the alcohol group at C-17 requires particular consideration and it might be expected that the electron density at O-17, which may be changed by the chemical modifications, is responsibile for the binding affinities.

In this report, we described the synthesis of 19-nor-17β-hydroxy-17α-trifluoromethyl-Δ^4-, -$\Delta^{4,9}$- and -$\Delta^{4,9,11}$-estren-, -estradien- and -estratrien-3-one (**6**, 7 and **8**) (**scheme 1**) as potent bioactive compounds compared with **1** and **2**.

Results and Discussion

Compound **9** was used as starting material due to its ready availability. According to the standard procedure,[7] compound **9** was reacted with $TMSCF_3$ to give the 17β-trimethylsiloxy-17α-



Reagents: i, $TMSCF_3$, TMAF, THF; ii, 40% HF(aq.), THF, then conc. HCl; iii, malonic acid, acetone-H_2O; iv, $C_5H_5N \cdot Br_2 \cdot HBr$, Pyridine; v, 40% aq. HF, THF; vi, Pyrrolidine, CH_3OH; vii, malonic acid, acetone-H_2O, silical gel; viii, DDQ, EtOAc-Benzene.

Scheme 1

trifluoromethyl compound **10** in 90% yield. Compound **10** was not very stable. When **10** was purified by flash chromatography on silica gel using a mixture of petroleum ether and ethyl acetate as an eluent, some parts of products were changed. But if the organic base, Et_3N, was added into the eluent (petroleum ether:EtOAc:Et_3N=100:1:1) for purification, the problem was solved. Desilylation of silyl ether **10** afforded the first target compound **6** in 92% yield by using 40% aq.HF and then conc. HCl. When the treatment with conc HCl was missed, the product was a mixture of **6** and **16**. **16** could be converted to **6** by conc.HCl.

The deprotection of compound **10** was best achieved by using malonic acid and 16% water in acetone as a solvent to give a 87.2% yield of the desired compound **11**. Compound **11** was reacted with pyridinium hydrobromide perbromide (PHP) to afford the conjugated $\Delta^{4,9}$ -diene compound **12** in 74.4% yield. Then **12** was treated with 40% aq.HF to obtain target compound **7** in 93 % yield.

Compound **12** was covnerted to the enamine **13** with pyrrolidine, followed by hydrolysis with a mild condition, malonic acid and silica gel in acetone-water(1:1), to give smoothly key intermediate **14** in 68.4% yield from **12**.

Reaction of **15**, which was generated by treatment of **14** with DDQ in 80% yield, with 40% aq.HF afforded final target compound **8** in 85% yield.

The α-configuration of trifluoromethyl group of 17-position was determined by x-ray crystal diffraction method (Fig.).

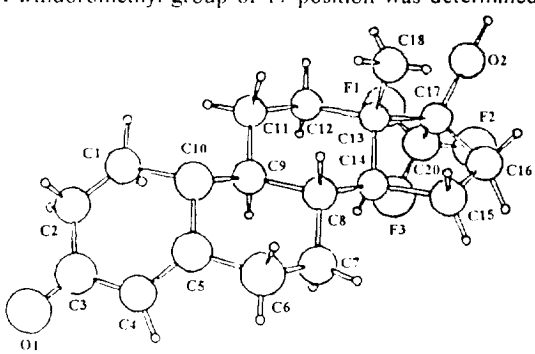


Fig X-ray crystallographic structure of **6**

Compounds **6**, **7** and **8** were synthesized from **9** through 2, 4 and 8 steps and the overall yields were 82%, 54% and 27% respectively.

The competitive inhibitory effect of three steroid compounds on the binding of [^{3}H]R_{5020} to the cytosolic progesterone receptor (PRc) from rat uterus were studied. The results showed that **6**, **7** and **8** had higher competitive inhibitory effects at concentration of 2 X 10^{-9} mol/L. This indicated that the three compounds had higher affinity for rat uterus PRc. The concentrations of the compounds for which the binding of [^{3}H]R_{5020} was inhibited by 50% (IC50) were 1.20 ± 0.3 nmol/L for **6**, 4.50 ± 0.5 nmol/L for **7**, 9.00 ± 1.7 nmol/L for **8**, and 3.50 ± 0.2 nmol/L for RU486. Competition experiments against [^{3}H]R_{5020} showed the specificity of the binding with a sequence in relative affinity for PRc as follows: **6**(291.60) > RU486(100.0) > **7**(77.80) > **8**(38.90) **(see Table 1)** The results suggested that **6** had the highest affinity for rat uterus PRc in this series, but it is neccesary to study **6** further in order to know if **6** has antifertility effect.

Table 1: Relative binding affinities of RU486 and **6-8**

compounds	IC50 (nmol/L)	relative affinity ability (RBA)
RU486	3.5±0.2	100.00
6	1.2±0.3	291.6
7	4.5±0.5	77.8
8	9.0±1.7	38.9

Binding affinity for RU486 was set to 100

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Reference and Notes

1. (a), Banks, R. E., *Organofluorine Compounds and Their Industrial Applications,* Ellis Horword, Chichester, 1979; (b), Filler, R., Kobayashi,Y., *Biomedicinal Aspects of Fluorine Chemistry,* Kodansha Elsevir, New York, 1982; (c) Filler, R., *Biochemistry Involving Carbon-fluorine Bonds,* American Chemistry Society, Washington D.C., 1976.
2. Yokozeki, A. and Baner, S. H., *Top. Curr. Chem.*, 1975, **53**, 71.
3. Yagupolskii, L. M., Ya ll'chenko, A. and Kondratenko, N. V., *Russ.Chem. Rev.* (Engl. Transl.), 1974, **43**, 32.
4. Fried, J. and Abraham, N. A., *Organic Reactions in Steroid Chemistry,* Fried, J. and Edwards, J. A., Ed.; Van Nostrand-Reinhold, New York, 1972, vol.1, p.423.
5. (a), British Drug House Ltd., *Chem. Abstr.*, 1966, **64**, 8266b. (b), Nakanishi, S., Morita, K. -I., Jensen, E. K., *J. Amer. Chem. Soc.*, 1959, **81**, 5259. (c), Godtfredsen, W. O. and Vangedal, S., *Acta Chem. Scand.*, 1961, **15**, 1786. (d), Blazejewski, J. -C., Dorme, R. and Wakselman, C., *J. Chem. Soc., Perkin Tran. 1,* 1986, 337.
6. (a), Prakash, G. K. S., KRISHNAMURTI, R. and Olah, G. A., *J. Am. Chem. Soc.*, 1989, **111,** 393; (b), KRISHNAMURTI, R., Bellew, D. R. and Prakash, G. K. S., *J. Org. Chem.*, 1991, **56**, 984.
7. Zhong-Qi Wang and Ben-Fang Ruan , *J. Fluorine Chem.*, 1994, **69**, 1.
8. Fotherby, K., *Clin. Obster. Gynaecol.*, 1968, **11**, 701.
9. (a), Hammann, P. E., Wöbbeckem, E. and Hoppen, H.-O., *Acta Endocrinol.*, 1987, **115,** 406. (b), Habermahl, G. G., Hammann, P. E. and Wray, V., *Mag. Reson. Chem.*, 1985, **23**, 959. (c), Hammann, P. E., Habermahl, G. G. and Kluge, H., *Mag. Reson. Chem.*, 1988, **26**, 85.

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