STEREOSELECTIVE EPOXIDATION OF 5(10)-ENE OF 11β-FUNCTIONATED STEROIDS AND EFFECT OF 5(10)-EPOXY GROUP ON REACTION OF 11β-SUBSTITUTE[1]

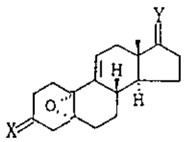
Yang Suming, Yang Zhengyu, Xia Yi, and Xia Peng*

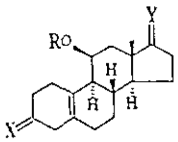
Department of Organic Chemistry, School of Pharmacy, Shanghai Medical University, Shanghai 200032, P.R.China

Abstract- A route for synthesis of steroidal 5(10)α-epoxy-9(11)-ene from 11β-functionalized estr-5(10)-ene *via* epoxidation of 5(10)-ene and then introduction of 9(11)-ene was reported. The effect of 11β-hydroxy and acyloxy groups on stereoselective epoxidation of 5(10)-ene as well as the effect of 5(10)-epoxide configuration on some reactions of corresponding 11β-substitutes were described. A 11β-phenyl-4,9-estradiene compound has been synthesized from the 9(11)-ene-5(10)α-epoxide intermediate obtained by this route.

Steroidal 5(10)α-epoxy-9(11)-ene (6) is a key intermediate for synthesis of 11β-aryl-19-norsteroids which was found to be active as anti-progestin agents.[2,3] We have developed a new method for synthesis of compound (6) by epoxidation of 11β-functionalized 5(10)-ene compound (3) and then introduction of 9(11)-ene, rather than the already established method by direct epoxidation of steroidal 5(10),9(11)-diene in which some particular reagents such as CF_3COCF_3 are required to get high regioselectivity for the epoxidation of 5(10)-ene.[4,5]

The new method involves a stereoselective epoxidation directed by 11β-functional group. It appears to be prospective because different 11β-functional group will have





6 X=ketal; Y=O, ketal

3 X=$-(OMe)_2$; Y=$-OCH_2CH_2O-$
a R=H
b R=Ac
c R=PhCO

different stereoselectivity in the epoxidation of 5(10)-ene. The α:β ratio of the epoxidation of compounds (3a,3b) was calculated with the following formula:

$$\alpha:\beta=\frac{[\alpha]_m-[\alpha]_\beta}{[\alpha]_\alpha-[\alpha]_m}$$

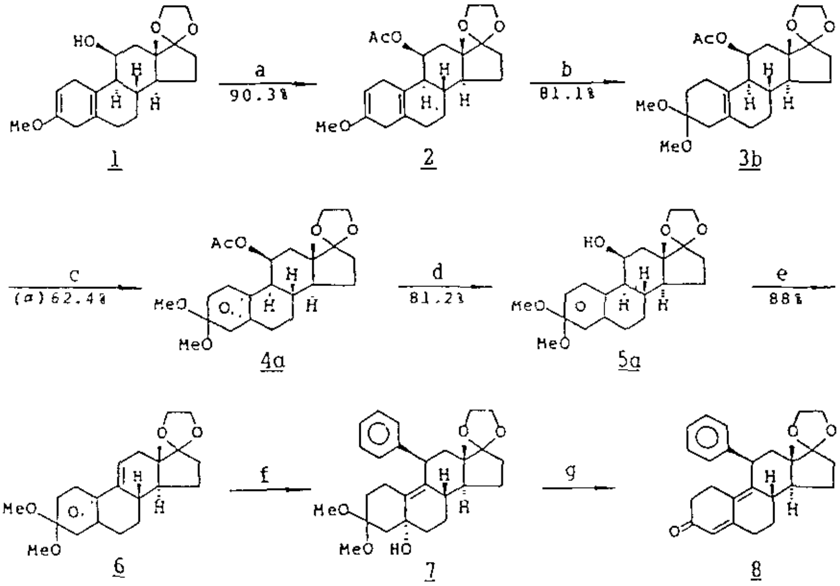
$[\alpha]_m$: specific rotation of the mixed products of epoxidation;
$[\alpha]_\alpha$: specific rotation of the corresponding α-epoxide;
$[\beta]_\beta$: specific rotation of the corresponding β-epoxide.

Compound (3a) can be epoxidized to the 5(10)-β-epoxide in high selectivity with either Cl_3CCN/H_2O_2 (α:β about 9:91) or CF_3COCF_3/H_2O_2 (5:95) because of the directive effect of 11β-hydroxyl group. However epoxidation of compound (3b) gives a mixture of 5(10)-α- and β-epoxides in a ratio(α/β) about 55:45 with Cl_3CCN/H_2O_2 in CH_2Cl_2 and 59:41 in AcOEt but 36:64 with CF_3COCF_3/H_2O_2 in CH_2Cl_2. To our surprise, the reaction of compound (3b) with CF_3COCF_3/H_2O_2 in AcOEt at the same conditions resulted in recovery of starting material without any perceptible epoxidized product.

A further preliminary experiment shows a higher α:β ratio in epoxidation of compound (3c) with Cl_3CCN/H_2O_2 in AcOEt than that of 3b.

Another key step in the method is the conversion of 11β-hydroxy group into 9(11)ene without effect on both 5(10)-epoxy and 3-ketal groups which are very sensitive to usual conditions for the hydroxy group elimination. Though the known mild reagents (*p*-TsCl/PY) can eliminate 11β-hydroxy group of compound (3a) it couldn't do well with the epoxide (5α). Fortunately we found that *p*-dimethylaminopyridine (DMAP) as catalyst instead of pyridine can successfully reach this goal in quite high yield. DMAP can be recovered conveniently and recycled.

We also have examined some different effects of 5(10)α- or β-epoxy group on the reaction of 11β-substitute. 11β-Hydroxy group in compound (5α) is easily eliminated to 9(11)-ene or acylated; while that of compound (5β) [5(10)β-epoxy] is reluctant to eliminate or acylated at the same condition. 11β-Acyloxy group of compound (4β) [5(10)β-epoxy] *can be smoothly* hydrolyzed with sodium hydroxide in methanol to 11β-hydroxy group at room temperature; while the same reaction with compound (4α) requires heating to complete. These variations obviously showed the considerable space interaction between 11β-functional group and 5(10)-epoxy group.



a: Ac_2O, Py, DMAP
b: MeOH, PPTS, Et_2O
c: H_2O_2, Cl_3CCN, AcOEt
d: KOH, MeOH
e: *p*-TsCl, DMAP, CH_2Cl_2
f: PhMgBr, CuCl, THF
g: MeOH, HCl

It is worthy to note that compound (4α) can be easily and quite completely crystallized from the mixture of 5(10)-α- and β-epoxide; however, compound (4β) is difficult to crystallize even though in the quite pure form. This provides a convenient separation method of these two diastereoisomers. Compound (6) had been synthesized from compound (1) *via* five steps with overall yield 32.6% and from this intermediate 11β-phenyl-19-norsteroid derivative (8) has been prepared.

EXPERIMENTAL

General Details

Melting points were obtained in capiliary tubes and uncorrected. The ir spectra were obtained in potassium bromide discs on a Perkin-Elmer 783 spectrophotometer. The ^1H and ^{13}C nmr spectra were obtained in deuteriochloroform on JNM-FX-90Q spectrometer with TMS as internal reference. The ms spectra were obtained on JMS-D300C instrument. The uv spectra were obtained on Shimadzu UV-260 spectrophotometer. Specific rotations were determined in ethylene chloride containing 0.5% triethylamine on WXG-4 instrument. All reactions were monitored by tlc on silica gel plate. The yields were not optimized. The starting steroid (1)[6] was synthesized in our laboratory and identified.

11β-Acyloxy-17-cyclic ethylenedioxo-3-methoxy-2,5(10)-estradiene(2):

To a solution of 1.00 ml of pyridine, 0.9 ml of acetic anhydride and 25 mg of DMAP, 17-cyclic ethylenedioxo-11β-hydroxy-3-methoxy-2,5(10)-estradiene(1) (250 mg, 0.72 mmol, mp 149-153°C) was added. The dissolved mixture was placed at 8-9°C for 24 h and then was poured into 100 ml of cooled aqueous sodium carbonate (4%). The precipitated solid was filtered off, washed with water and dried to yield 280 mg of crude product. It was crystallized from ethyl acetate to give 2, 253 mg (90.34%); mp 180-185°C. Recrystallization from ethyl acetate afforded the sample for analysis; mp 184-186°C;

[α]: +52.9°(c=0.50 g/10.0 ml); ms: m/z 388, 328, 266, 227; ir: 1725 cm^{-1}. Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.11; H, 8.30. Found: C, 70.98; H, 8.44.

11β-Acyloxy-17-cyclic ethylenedioxo-3,3-dimethoxy-5(10)-estrene(3b):

To a solution of 2 (1.96 g, 5.05 mmol, mp 180-185°C) in 80 ml of anhydrous ether, pyridinium *p*-toluenesulfonate(PPTS) (75 mg, 0.30 mmol) in 3.00 ml of anhydrous methanol was added. The mixture was stirred at room temperature for 8 h, then 100 ml of ether was added, and washed twice with saline water. The ether layer was separated, dried with anhydrous sodium sulfate and the solvent was evaporated to give 3b, 1.72 g (81.07%); mp 106-113°C. It was recrystallized twice from ether for analysis; mp 120-122°C; [α]: +61.12°(c=0.50 g/10.0 ml); ^{1}H nmr: δ 0.96(s,3H), 2.00(s,3H), 3.16(s,3H), 3.22(s,3H), 3.81(s,2H), 3.83(s,2H), 5.31(s,1H); ms: m/z(%) 420(0.001), 388(29), 328(27), 267(26), 227(29), 99(100); ir: 1725 cm^{-1}. Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.55; H, 8.63. Found: C, 68.48; H, 8.76.

General Procedure for Epoxidation of Steroidal 5(10)-ene:

11β-Acyloxy-17-cyclic ethylenedioxo-3,3-dimethoxy-5(10)α-epoxyestrane(4a):

To a solution of 3b (2.79 g, 6.64 mmol, mp 106-113°C) in 60 ml of ethyl acetate added 5.00 ml of a freshly prepared solution of aqueous hydrogen peroxide (30%) containing 1.00 g of dipotassium hydrogen phosphate and then a solution of 1.00 ml of trichloroacetonitrile in 10.0 ml of ethyl acetate was added dropwise over 80 min and stirred at room temperature for 7 h. The solution was diluted with 100 ml of ethyl acetate and washed with 50 ml of aqueous sodium thiosulfate(25%), 50 ml of aqueous potassium hydroxide(5%) and water until pH about 7. The organic layer was dried with anhydrous sodium sulfate and evaperated. The residue was crystallized from ether and n-pentane to yield 4a, 1.74 g (62.36%); mp 105-108°C. Recrystallization twice from ether and acetone afforded the analytical sample; mp 176-179°C; ^{1}H nmr: δ 0.96(s,3H), 2.08(s,3H), 3.08(s,3H), 3.16(s,3H), 3.80(s,2H), 3.84(s,2H), 5.20(s,1H); ms: m/z(%)

436(4), 404(3), 386(8), 264(14), 99(100); ir: 1735 cm^{-1}. Anal. Calcd for $C_{24}H_{36}O_7$: C, 66.03; H, 8.31. Found: C, 65.90; H, 8.17.

17-Cyclic ethylenedioxo-3,3-dimethoxy-5(10)α-epoxy-11β-hydroxyestrane(5α):

A solution of 4α (1.50 g, 3.44 mmol, mp 105-108°C), potassium hydroxide(7.5 g, .134 mmol) in methanol(60.0 ml) was stirred at room temperature for 17 h and refluxed for 1 h, to which 50 ml of water was added. The solution was concentrated to about 45 ml and poured into 150 ml of ice-water. The precipitated solid was filtered off and dried to give 1.10 g of 5α (81.21%); mp 179-181°C. Recrystallization from ethyl acetate to give the analytical sample; mp 180-182°C; [α]: +59.52°(c=0.50 g/10.0 ml); ^{1}H nmr: δ 1.10(s,3H), 3.14(s,3H), 3.18(s,3H), 3.80(s,2H), 3.84(s,2H), 4.40(s,1H); ms: m/z(%) 394(2), 362(4), 344(7), 99(100); ir: 3500, 1665(week) cm^{-1}. Anal. Calcd for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found: C, 66.93; H, 8.78.

17-Cyclic ethylenedioxo-3,3-dimethoxy-5(10)α-epoxy-9(11)-estrene(6):

To a solution of *p*-toluenesulfonyl chloride(3.60 g, 18.88 mmol) and DMAP(6.60 g) in 10 ml of methylene chloride, 5α (2.50 g, 6.33 mmol, mp 179-181°C) was added. After it was dissolved, the solution stood at room temperature for 8 days and then diluted with 400 ml of ether , washed with 40 ml of a buffer solution of dipotassium hydrogen phosphate(2%) and potassium dihydrogen phosphate(2%) for 3 times. After removal of the solvent, the residual solid was smashed in n-hexane and filtered off to give 2.10 g (88.0%) of 6; mp 102-109°C. Recrystallization from isopropyl ether afforded the sample for analysis; mp 116-119°C; ^{1}H nmr: δ 0.86(s,3H), 3.13(s,3H), 3.19(s,3H), 3.88(s,2H), 3.90(s.2H), 6.00(s,1H); ^{13}C nmr: δ 14.7(q), 22.3(t), 24.3(t), 24.9(t), 32.0(t), 32.4(t), 33.4(t), 38.0(d), 39.2(t), 44.3(s), 45.5(d), 47.5(q), 60.4(s), 60.8(s), 64.3(t), 65.0(t), 98.3(s), 118.7(s), 126.2(d), 135.8(s); ms: m/z(%) 376(3), 344(9), 282(7), 243(8), 99(100); ir: 1640(week) cm^{-1}. Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.19; H, 8.57. Found: C, 69.85; H, 8.62.

17-Cyclic ethylenedioxo-3,3-dimethoxy-5α-hydroxy-11β-phenyl-9(10)-estrene(7):

To a suspension of small pieces of magnesium (80 mg, 3.29 mmol) in dry THF (3 ml), under refluxing a solution of 0.4 ml(3.81 mmol) bromobenzene in dry THF (10 ml) was added slowly. After refluxing for 0.5 h, the solution was cooled to room temperature. Then 20 mg of cuprous chloride was added, stirred for 10 min. A solution of 6 (240 mg, 0.64 mmol, mp 102-109°C) in 8 ml of THF was added. It was placed at room temperature for 3 days, poured into 150 ml of saturated aqueous ammonium chloride and extracted with ether. The organic layer was dried with anhydrous sodium sulfate and evaporated. The residue was purified by column chromatography with benzene-acetone (9:1) as an eluent to give 150 mg (51.8%) of 7; mp 161-164°C. Recrystallization from isopropyl ether afforded the analytical sample; mp 166-169°C; ^{1}H nmr: δ 0.49(s,3H), 3.20(s,6H), 3.85(s,4H), 4.28(d, J=7.2 Hz, 1H), 4.45(s,1H), 7.20(s,5H); ms: m/z(%) 454(1), 436(2), 422(9), 404(55), 343(27), 99(100); ir: 3565, 1600 cm^{-1}. Anal. Calcd for $C_{28}H_{38}O_5$: C, 73.98; H, 8.42, Found C, 73.69; H, 8.68.

17-cyclic ethylenedioxo-11β-phenyl-4(5),9(10)estradien-3-one(8):

The unpurified residue (7) obtained in previous reaction was dissolved in 15 ml of methanol and 5 drops of 2N hydrochloric acid was added. The solution was stirred at room temperature for 1 h, neutralized with ten drops of aqueous sodium hydrogen carbonate (5%) to pH 6-7, then concentrated to 6-7 ml and cooled. After filtration 60 mg of 8 (24.14% calculated from 6) was obtained; mp 274-277°C. Recrystallization from ethanol-chloroform afforded the sample for analysis; mp 277-279°C; ^{1}H nmr: δ 0.51(s,3H), 3.88(s,4H), 4.40(d, J=7.2 Hz, 1H), 5.75(s,1H), 7.18-7.20(m,5H); ms: m/z(%) 390(100), 328(48), 99(63); ir: 1650, 1600, 1590 cm^{-1}; uv: ($CHCl_3$) 301 (ε: 2560) nm. Anal. Calcd for $C_{26}H_{30}O_3$: C, 80.00; H, 7.74. Found: C, 80.25; H, 7.88.

ACKNOWLEDGMENT

We are grateful to the Fund of Chinese Academy of Sciences for financial support of

this work.

REFERENCES

1. This paper is dedicated to Professor Rolf Huisgen at the occasion of his 75th birthday.
2. G. Teutsch, Antiprogestin Steroid RU486 Hum. Fertil. Control, [Proc. Conf. Antiprogestational Compd. RU 486] 1984 (Pub.1985), 27-47(Eng). Edited by E. E. Baulieu *and S. J. Segal, Plenum: New York*, N.Y. (*Chem*. Abstr., 1986, 105, 165029r)
3. A. Belanger and G. Teutsch, Steroids, 1981, 37, 361.
4. G. Costeronsse and G. Teutsch (Roussel-UCLAF), EP. 0,005,100 (1979) (Chem. Abstr., 1980, 93, 186,675x)
5. R. Rohde, G. Neef, G. Sauer, and R. Wiechert, Tetrahedron Lett., 1985, 26, 2069.
6. P. D. Klimstra and J. Daran (Searle, G.D.,and Co.), US. 3,338,929 (1967) (Chem. Abstr., 1968, 69, 77594d)

Received, 10th March, 1994