# Ring A aromatic steroids in the pregnane series

**Cavit Uyanik[a]*, Aslihan Malay[b], James R. Hanson[c], Peter B. Hitchcock[c] and Serpil Tiryakioglu[c]**

[a]*Department of Chemistry, University of Kocaeli, Izmit 41380, Kocaeli, Turkey*

[b]*Department of Chemistry, Gebze Institute of Technology, P.K. 141, Gebze, 41400, Kocaeli, Turkey*

[c]*Department of Chemistry, University of Sussex, Brighton, Sussex BN1 9QJ, UK*

4-Methylpregna-1,3,5(10)-trien-20-one and 4-methylpregna-1,3,5(10),16-tetraen-20-one have been obtained by a dienol: benzene type of rearrangement of 5α,6α-epoxypregnanes possessing a further double bond equivalent on ring A. The crystal structure of 4-methyl-19-norpregna-1,3,5(10)-trien-20-one is reported.

**Keywords** pregna-1,3,5(10)-triene, pregna-1,3,5(10),16-tetraene, rearrangements, epoxides

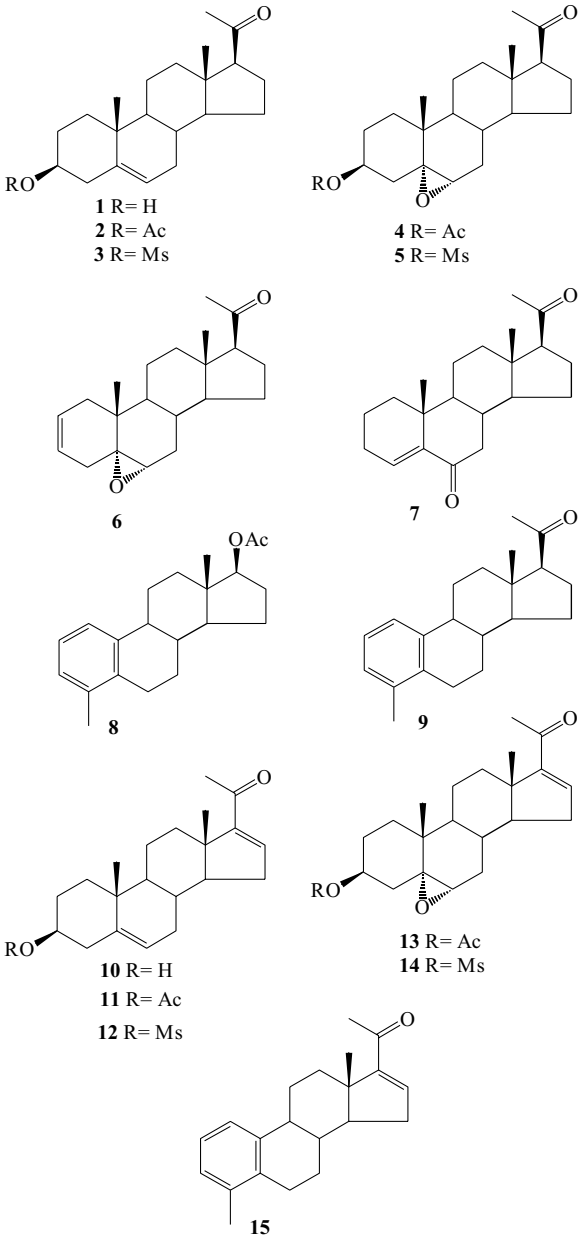
The ring A binding: ring D acting model for steroids binding to the steroidal nuclear receptors can be used to rationalise structure: activity relationships. Binding to the estrogen receptor is associated with an aromatic ring A.[1] Recently there has been considerable interest in the synthesis of modified steroids that bind to the estrogen receptor in the context of chemotherapy of breast cancer.[2] Consequently it was of interest to synthesise some steroids possessing an aromatic ring A and a progestogen side chain. Such compounds might bind to the estrogen receptor but not exhibit estrogenic activity. The dienol: benzene rearrangement is a general reaction in which androstanes possessing two double bond equivalents and a carbonium ion source at centres close to ring A are converted to methylestratrienes in the presence of hydrobromic acid in acetic acid.[3] We now report the extension of the rearrangement to a number of pregnanes to provide 4-methylpregna-1,3,5(10)-trien-20-ones. 4-Methylpregna-1,3,5(10)-trien-20-one was obtained previously[4] as a product of the reaction of progesterone with acetyl bromide.

Pregnenolone **1** was converted to its 3β-acetate **2** and to the 3β-methanesulfonate **3**.[5] Each was then epoxidised with *m*-chloroperbenzoic acid to give the 5α,6α-epoxides, **4** and **5** ($\delta_H$ 2.9, $J$ = 4.4 Hz, H-6). The crude material contained a small amount of the β-epoxide ($\delta_H$ 3.1). Treatment of both the 3β-acetoxy and 3β-methanesulfonyloxy-5α,6α-epoxides **4** and **5**, with hydrobromic acid in glacial acetic acid gave 4-methyl-19-norpregna-1,3,5(10)-trien-20-one **9** ($\delta_H$ 7.16 and 7.00, each d, $J$ = 7.5 Hz, 1- and 3-H; $\delta_H$ 7.04, t, $J$ = 7.5 Hz, 2-H; $\delta_H$ 2.20, (3H, s, 4-Me).[4,6] On one occasion some 17β-acetoxy-4-methylestra-1,3,5(10)-triene **8** was obtained from the rearrangement, possibly arising from a Baeyer–Villiger oxidation of the C-20 ketone during the epoxidation reaction.

The X-ray crystal structure of 4-methyl-19-norpregna-1,3,5(10)-trien-20-one **9** (see Fig. 1) confirmed the structure and established that no isomerisation had taken place at other centres in the molecule as a possible result of backbone or other acid-catalysed rearrangements during the course of the dienol: benzene rearrangement. Although there are quite close contacts between C-1 and C-11 and between the C-4 methyl group and C-6 (2.948 and 2.906Å respectively) both rings B and C remain in half-chair and chair conformations.

Elimination of the 3β-methanesulfonate group from 3β-methanesulfonyloxy-5α,6α-epoxypregnane-20-one **5** with collidine gave 5α,6α-epoxypregn-2-en-20-one ($\delta_H$ 5.60, 2H, m, 2-H and 3-H).[7] This was accompanied by a small amount of pregn-4-ene-6,20-dione **7** ($\delta_H$ 6.21, t, $J$ = 6.8 Hz, 4-H). Treatment of the 5α,6α-epoxypregn-2-en-20-one **6** with hydrobromic acid in glacial acetic acid gave a good yield of the 4-methyl-19-norpregna-1,3,5(10)-trien-20-one **9**.

16-Dehydropregnenolone **10** is a readily available pregnane starting material in which the 16-double bond provides access to steroids that are modified on ring D. Consequently it was of interest to see if this double bond withstood the conditions of the dienol: benzene rearrangement. Both the 3β-acetate **11**[9] and 3β-methanesulfonate **12** were converted to the 5α,6α–epoxides **13** and **14**, with *m*-chloroperbenzoic acid ($\delta_H$ 2.86, d, $J$ = 4.4 Hz, 6-H). The 16-ene remained intact ($\delta_H$ 6.63). These epoxides were treated with hydrobromic acid in glacial acetic acid. Careful chromatography of the products yielded




**1** R= H
**2** R= Ac
**3** R= Ms

**4** R= Ac
**5** R= Ms

**6**

**7**

**8**

**9**

**10** R= H
**11** R= Ac
**12** R= Ms

**13** R= Ac
**14** R= Ms

**15**

* Correspondent. E-mail: cuyanik@kou.edu.tr

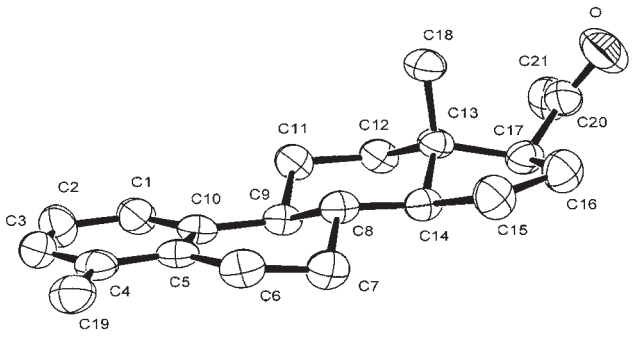



**Fig. 1** X-ray structure of **9**.

4-methyl-19-norpregna-1,3,5(10),16-tetraen-20-one **15** in reasonable yield (66%). The tetraene possessed NMR signals at $\delta_H$ 7.00 and 7.18, each d, $J$ = 7.5 Hz, and $\delta_H$ 7.4, t, $J$ = 7.5 Hz, Ar-H; $\delta_H$ 2.28, Ar-Me; $\delta_H$ 6.68, t, $J$ = 5.0 Hz, 16-H.

In conclusion we have shown that the generalised dienol: benzene rearrangement can be applied to 5α,6α-epoxides in the pregnane series which also contain a further carbonium ion source. The conditions do not lead to epimerisation at other centres *e.g.* C-9 and C-17 and they can be applied to steroids possessing a 16,17-double bond.

## Experimental

*General experimental details*

Silica for chromatography was Merck 9385. Light petroleum refers to the fraction b.p. 60– 80°C. $^1$H and $^{13}$C NMR spectra were determined at 300 and 75 MHz respectively using a Bruker AMX 300 spectrometer for solutions in deuteriochloroform. IR spectra were measured using nujol mulls on a Perkin-Elmer 1710 FTIR. High-resolution mass spectra were obtained on a Bruker Daltonics Apex III mass spectrometer operating in the electrospray mode by adding Na to the sample. Extracts were dried over anhydrous sodium sulfate.

3β-Methanesulfonoxypregn-5-en-20-one **3,** prepared from pregnenolone **1** with methanesulfonyl chloride in pyridine, had m.p. 123–126°C (lit.,[5] 116–118°C); $\nu_{max}$: 1693, 1174 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 0.59 (3H, s,18-H), 0.98 (3H, s,19-H), 1.0–2.10 (20H, overlapping multiplets), 2.09 (3H, s, 21-H), 2.50 (1H, t, $J$ = 8.8 Hz, 17-H), 2.98 (3H, s, 3β-OMs), 4.47 (1H, tt, $J$ = 5.6 and 11.2 Hz, 3α-H), 5.38 (1H, d, $J$ = 4.7 Hz, 6-H).

3β-Methanesulfonyloxy derivative **12,** prepared from 16-dehydropregnenolone **10** with methanesulfonylchloride in pyridine, had m.p. 140–142°C; $\nu_{max}$: 1700, 1660 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 0.85 (3H, s,18-H), 1.00 (3H, s, 19-H), 2.16 (3H, s, 21-H), 1.00–2.50 (17H, overlapping multiplets), 2.95 (3H, s, 3β-OMs), 4.57 (1H, m, 3α-H), 5.36 (1H, d, $J$ = 4.4 Hz, 6-H), 6.65 (1H, t, $J$ = 5.0 Hz, 16-H); HRMS: $M^+$, found 415.1840. $C_{22}H_{32}O_4SNa$ requires 415.1880).

*Epoxidation reactions*

3β-Methanesulfonyloxy derivative **3** (3 g) in chloroform (40 cm$^3$) at 0°C for 15 minutes and then at room temperature for 2 h. The solution was diluted with chloroform, washed with aqueous sodium sulfite, aqueous sodium hydrogen carbonate, water and brine, and dried. Evaporation of the solvent gave a residue which was purified by recrystallisation to give 5α,6α-epoxy-3β-methanesulfonoxypregnan-20-one **5** (2.0 g) as needles, m.p. 170–172°C (lit.,[7] 173–175°C); $\nu_{max}$: 1694, 1166 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 0.83 (3H, s,18-H), 1.05 (3H, s, 19-H), 2.08 (3H, s, 21-H), 1.0–2.5 (20H, overlapping multiplets), 2.90 (1H, d, $J$ = 4.4 Hz, 6-H), 2.96 (3H, s, 3β-OMs), 4.80 (1H, m, 3α-H), HRMS: $M^+$, found 433.202. $C_{22}H_{34}O_5SNa$ requires 433.202).

3β-Acetoxy-5α,6α-epoxypregnan-20-one **4**, prepared under similar conditions, had m.p. 163–165°C (lit.,[11] 165–166°C); $\nu_{max}$: 1727, 1700 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 0.53 (3H, s, 18-H), 1.05 (3H, s, 19-H), 2.00 (3H, s, 3β-OAc), 2.08 (3H, s, 21-H), 0.65–2.15 (20H, overlapping multiplets), 2.89 (1H, d, $J$ = 4.4 Hz, 6-H), 4.93 (1H, m, 3α-H).

3β-Methanesulfonyloxy derivative **14,** prepared under similar conditions, had m.p. 154–156°C; $\nu_{max}$: 1698, 1666 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 0.80 (3H, s,18-H), 1.08 (3H, s, 19-H), 2.21 (3H, s, 21-H), 0.80–2.40 (17H, overlapping multiplets), 2,91 (1H, d, $J$ = 4.4 Hz, 6-H), 2.96 (3H, s, 3β-OMs), 4.80 (1H, m, 3α-H), 6.64 (1H, t, $J$ = 5.0 Hz, 16-H); $\delta_C$ (75 MHz, $CDCl_3$) 16.15, 20.65, 28.00, 28.85, 31.33, 32.35, 35.37, 37.69, 38.84, 41.87, 42.94, 46.37, 56.51, 59.27, 60.58, 65.43, 65.61, 71.08, 79.92, 144.54, 155.40, 197.14; HRMS: $M^+$, found 431.1863 $C_{22}H_{32}O_5SNa$ requires 431.1882).

3β-Acetoxy-5α,6α-epoxypregn-16-en-20-one **13,** prepared under similar conditions, had m.p. 142–144°C; $\nu_{max}$: 1732, 1701, 1659 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 0.80 (3H, s,18-H), 1.06 (3H, s, 19-H), 1.98 (3H, s, 3β-OAc), 2.19 (3H, s, 21-H), 0.70–2.30 (17H, overlapping multiplets), 2,86 (1H, d, $J$ = 4.4 Hz, 6-H), 4.93 (1H, m, 3α-H), 6.63 (1H, t, $J$ = 5.0, 16-H); HRMS: $M^+$, found 395.2186 $C_{23}H_{32}O_4Na$ requires 395.2191).

*Elimination reaction with collidine*

3β-Methanesulfonyloxy derivative **5** (3.0 g) was dissolved in collidine (30 cm$^3$) and heated under reflux for 2 h. The solution was cooled, poured into dilute hydrochloric acid and extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid, water and dried. The solvent was evaporated and the residue chromatographed on silica. Elution with 10% ethyl acetate in light petroleum gave 5α,6α-epoxypregn-2-en-20-one **6** (1.75 g, 76%), m.p. 208–209°C (lit.,[7] 208–210°C); $\nu_{max}$: 1730, 1650 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 0.83 (3H, s,18-H), 1.12 (3H, s, 19-H), 2.09 (3H, s, 21-H), 1.10–2.25 (18H, overlapping multiplets), 2,87 (1H, d, $J$ = 4.4 Hz, 6-H), 5.60 (2H, m, 2- and 3-H). Further elution with 15% ethyl acetate in light petroleum gave pregn-4-ene-6,20-dione **7** (150 mg, 6.5%), m.p. 108–109°C(lit.,[7] 208–210°C); $\nu_{max}$: 1730, 1704, 1630 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 0.87 (3H, s,18-H), 1.18 (3H, s, 19-H), 2.12 (3H, s, 21-H), 0.70–2.20 (20H, overlapping multiplets), 6.37 (1H, t, $J$ = 3.5 Hz, 4-H); HRMS: $M^+$, found 337.2141 $C_{21}H_{30}O_2Na$ requires 337.2138).

*Aromatisation reactions*

3β-Acetoxy-5α,6α-epoxypregnan-20-one **4** (1 g) was suspended in a mixture of 48% hydrobromic acid (2.5 cm$^3$) and glacial acetic acid (9 cm$^3$) and heated under reflux for 15 min. The solution was cooled and neutralised with aqueous sodium hydrogen carbonate. The products were extracted with ethyl acetate. The extract was washed with water, dried and the solvent was evaporated to give a residue which was chromatographed on silica. Elution with 10% ethyl acetate in light petroleum gave 17β-acetoxy-4-methyestra-1,3,5(10)-triene **8** (70 mg, 8%), m.p. 185–187°C (lit.,[6] 186–188°C); $\nu_{max}$: 1729, 1582 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 0.84 (3H, s, 18-H), 2.07 (3H, s, 17β-OAc), 2.23 (3H, s, 4-Me), 1.20–2.72 (15H, overlapping multiplets), 4.70 (1H, t, $J$ = 8.2 Hz, 17α-H), 7.02 (1H, d, $J$ = 7.5 Hz, 1-H), 7.04 (1H, t, $J$ = 7.5 Hz, 2-H), 7.16 (1H, d, $J$ = 7.5 Hz, 3-H). Further elution with 20% ethyl acetate in light petroleum gave 4-methyl-19-norpregna-1,3,5(10)-trien-20-one **9** (550 mg, 59%) which was crystallised from ethyl acetate as needles, m.p. 165–167°C (lit.,[4] 170°C); $\nu_{max}$: 1701, 1582 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 0.62 (3H, s, 18-H), 2.14 (3H, s, 21-H), 2.20 (3H, s, 4-Me), 1.20–2.90 (16H, overlapping multiplets), 7.00 (1H, d, $J$ = 7.5 Hz, 3-H), 7.04 (1H, t, $J$ = 7.5 Hz, 2-H), 7.16 (1H, d, $J$ = 7.5 Hz, 1-H); $\delta_C$ (75 MHz, $CDCl_3$) 13.76, 20.23, 23.25, 24.55, 27.13, 27.53, 28.14, 31.92, 38.21, 39.47, 44.66, 44.77, 56.24, 64.26, 123.41, 125.74, 127.76, 135.54, 136.88, 140.39, 209.95; HRMS: $M^+$, found 319.2038. $C_{21}H_{28}ONa$ requires 319.2034).

Under similar conditions 3β-methanesulfonyloxy derivative **5** (1.0 g) gave 4-methyl-19-norpregna-1,3,5(10)-trien-20-one **9** (390 mg, 54%) which was identified by its $^1$H NMR spectrum.

Under similar conditions 5α,6α-epoxypregn-2-en-20-one **6** (1.0 g) gave 4-methyl-19-norpregna-1,3,5(10)-trien-20-one **9** (560 mg, 59%) which was identified by its $^1$H NMR spectrum.

Under similar conditions 3β-acetoxy-5α,6α-epoxypregn-16-en-20-one **13** (1.0 g) gave 4-methyl-19-norpregna-1,3,5(10),16-tetraen-20-one **15** (490 mg, 66%), m.p. 176–178°C; $\nu_{max}$: 1715, 1661, 1586 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 0.91 (3H, s, 18-H), 2.21 (3H, s, 21-H), 2.28 (3H, s, 4-Me), 1.20–2.72 (13H, overlapping multiplets), 6.68 (1H, t, $J$ = 5.0 Hz, 16-H), 6,98 (1H, d, $J$ = 7.5 Hz, 3-H), 7.05 (1H, t, $J$ = 7.5 Hz, 2-H), 7.18 (1H, d, $J$ = 7.5 Hz, 1-H); $\delta_C$ (75 MHz, $CDCl_3$) 16.26, 20.24, 26.91, 27.38, 27.56, 28.25, 32.39, 35.27, 36.46, 45.33, 46.73, 56.15, 123.30, 125.78, 127.73, 135.34, 136.75, 140.77, 144.73, 155.93, 197.23; HRMS: $M^+$, found 317.1871 $C_{21}H_{26}ONa$ requires 317.1874).

Under similar conditions 3β-methanesulfonyloxy derivative **14** (1.0 g) gave 4-methyl-19-norpregna-1,3,5(10),16-tetraen-20-one **15** (395 mg, 54.4%) which was identified by its $^1$H NMR spectrum.

*X-ray crystallographic data and structure determination*
4-Methyl-19-norpregna-1,3,5(10)-trien-20-one **9**, $C_{21}H_{28}O$, $M_r$ 296.43, crystal system, tetragonal, space group $P4_1$ (No.76), $a$ = 7.6459(3), $c$ = 28.7940(8) Å, $V$ = 1683.29(10) Å$^3$, $Z$ = 4, $D_{calc}$ = 1.17 g cm$^{-3}$, $\mu$ = 0.07 mm$^{-1}$, F(000) = 648. Data were collected on a Kappa CCD diffractometer using a crystal of size 0.4 × 0.2 × 0.2 mm$^3$ for $5.52<\theta<25.01°$ and $-9 \le h \le 5$; $-9 \le k \le 9$, $-22 \le l \le 34$. A total of 7233 reflections were collected. There were 2487 independent reflections and 2179 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods using SHELXS-97and refined using SHELXL-97 by full matrix least-squares on $F^2$. The final R indices were [$I > 2\sigma(I)$], $R_1$ = 0.041, $wR_2$ = 0.105 and (all data), $R_1$ = 0.051, and $wR_2$ = 0.112. The goodness-of-fit on $F^2$ was 1.047 and the largest difference peak and hole was 0.11 and –0.10 eÅ$^{-3}$.

The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC No 249903).

*Received 2 October 2005; accepted 20 January 2006*
*Paper 05/3556*

## References

1 G.M. Anstead, K.E. Carlson and J.A: Katzenellenbogen, *Steroids*, 1997, **62**, 268.
2 A.M.H. Brodie and V.C.O. Njar, *Steroids*, 2000, **65**, 171.
3 for a review see M.P. Hartshorn and D.N. Kirk, *Steroid Reaction Mechanism*, Elsevier, Amsterdam, 1968, p. 283.
4 J. Schmitt, J.J. Panouse, P.J. Cornu, A. Hallot, H. Pluchet and P. Comoy, *Bull. Soc. Chim. (France)*, 1965, 1934.
5 R.J. Ryan, G. Bourgery and S. Julia, *Bull. Soc. Chim. (France)*, 1972, 1415.
6 J.R. Hanson, P.B. Reese and I.H. Sadler, *J. Chem. Soc., Perkin Tarns. 1*, 1984, 2937.
7 J.R. Hanson and I. Kiran, *J. Chem. Research (S),* 1999, 594; *(M)*, 1999, 2532.
8 M.B. Rubin and A.P. Brown, *J. Org. Chem*., 1968, **33**, 2794.
9 R.E. Marker, R.B. Wagner, P.R. Ulshafer, E.L. Wittbecker, D.P.J. Goldsmith and C.H. Ruof, *J. Am. Chem. Soc.,* 1943, **65**, 1199.