# A NEW ROUTE TO A-NORSTEROID KETONES: SYNTHESIS OF A-NORTESTOSTERONE

Enrico Mincione*, Paolo Bovicelli, Maria Luigia Forcellese and Augusto Gambacorta

Istituto di Chimica Organica, Università degli Studi di Roma 00185, Roma Italy.

Received 12-5-83

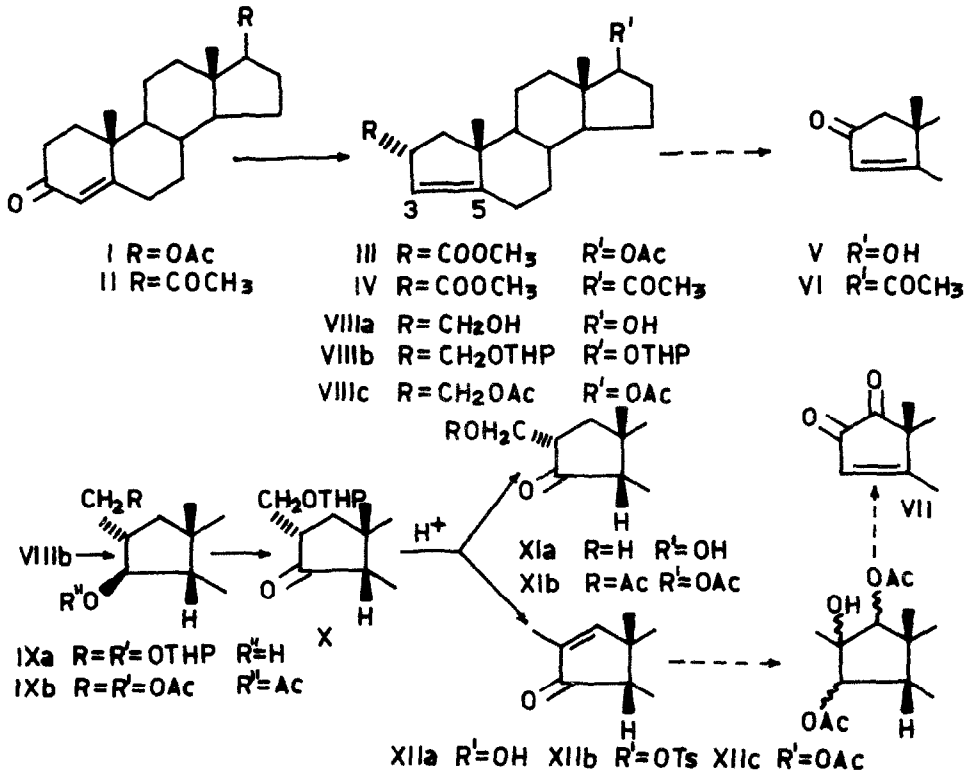
ABSTRACT

A new useful synthetic route to A-nortestosterone via $\Delta^{3(5)}$ A-norsteroids is described.

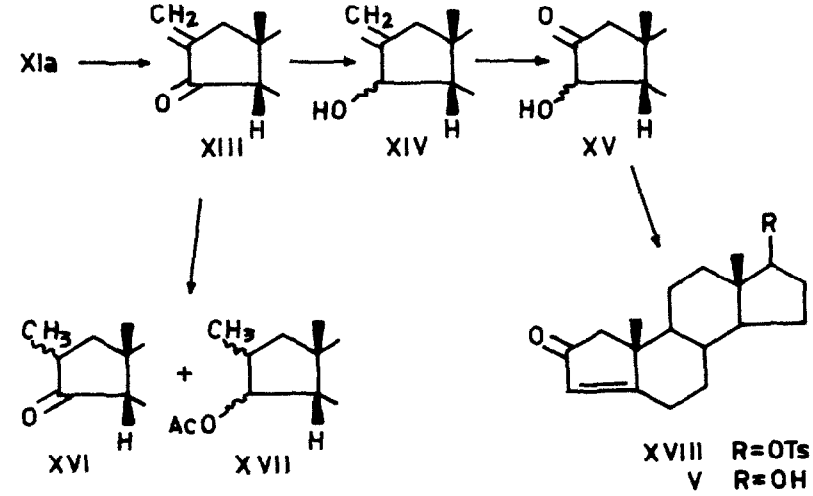
We previously reported (1) that the $\Delta^4$ -3-keto steroids (I) and (II) are converted in "one step" to the corresponding $\Delta^{3(5)}$ A-norsteroid esters (III) and (IV) (Scheme 1) by thallium (III) nitrate in high yields (75%).

These novel compounds appear to be useful intermediates for a new synthetic route to the A-norsteroid ketones (V), (VI) and (VII) which exhibit antihormonal activity(2).

We now report the conversion of compound (III) to A-nortestosterone (V). Compound (III), by reduction with lithium aluminum hydride, gave quantitatively the corresponding diol (VIIIa) which was converted into the ditetrahydropyranylether (VIIIb) (Scheme 1). The latter compound, after hydroboration with borane-methyl sulfide and subsequent oxidation with $H_2O_2$, gave the corresponding 3$\beta$ -alcohol (IXa) as the main product (80%) together with a minor amount of the epimeric 3$\alpha$-alcohol. The preferred formation of epimer (IXa) is in agreement with an attack of the 3,5-double bond from the sterically favoured $\beta$-side of the molecule. Oxidation of (IXa) with chromium anhydride-pyridine gave in good yields (90%) the 3-keto derivative




SCHEME 1




SCHEME 2

(X) which afforded the keto diol (XIa) (75%) by hydrolysis in mild conditions. Under more severe hydrolytic conditions the unsaturated ketone (XIIa) was obtained from compound (X) as the only product. The structure of the latter compound was confirmed by its NMR spectrum where both vinylic methyl group and a strongly deshielded vinylic proton were observed,as well as by the absorbance in the UV spectrum of the enonic group.

The enone (XII) appears as a useful starting material for the synthesis of A-nor compound (VII) (Scheme 1) which exhibits antihormonal activity (2). The next step, the conversion of compound (XIa) into the methylene ketone (XIII), was accomplished in "one step" (70% yield) by tosylation of the alcoholic functions (Scheme 2). During the work up of the reaction mixture the primary tosylate group was selectively eliminated to give directly compound (XIII). Reduction of enone (XIII) to the allylic alcohol (XIV), ozonization of the methylenic double bond to afford the ketol (XV) and dehydration of the latter to A-nortestosterone tosylate (XVIII) were planned as a synthetic sequence from compound (XIII) to compound (XVIII).

However, the reduction of compound (XIII) with the usual reagents (sodium borohydride, lithium aluminum hydride) then acetylation,afforded a mixture of the 2-methyl-3-keto derivative (XVI) and the 2-methyl-3-acetoxy derivative (XVII) arising from the 1,4 reduction of the enonic system. Compound (XIV) was obtained finally in satisfactory yields (65%) by reduction of (XIII) with sodium borohydride in the presence of cerium trichloride (3) which prevents the hydride addition to the methylenic carbon.

Ozonolysis of the allylic alcohol (XIV) afforded the keto-alcohol (XV). Dehydration of ketol (XV) with phosphorus oxychloride-pyridine gave the tosyloxy derivative (XVIII). The alkaline hydrolysis of the latter compound afforded finally A-nortestosterone (V), identical (NMR, IR, mp) to an authentic specimen (4).

## EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. IR spectra ($CHCl_3$) were recorded on a Perkin-Elmer 257 spectrophotometer and NMR spectra ($CDCl_3$) were obtained on a Perkin-Elmer R 32 (90 MHz) spectrometer, using tetramethylsilane as internal standard. Mass spectra were recorded with an AEI MS 12 spectrometer. UV spectra were recorded on a Perkin-Elmer 137 instrument. Chromatographies were performed with Merck $SiO_2$ gel and TLC with Merck $HF_{254}$ $SiO_2$ gel. Specific rotations were determined on a Galileo polarimeter N° 130224 at 25°C.

17β -Hydroxy-2α -hydroxymethyl-A-norandrost-3(5)-en-2-one (VIIIa). A solution of compound (III) (4 g in 272 ml of anhydrous diethyl ether) was added in ten minutes to a suspension of tithium aluminum hydride (2.4 g) in anhydrous diethyl ether (200 ml) and stirred overnight. After cooling with an ice bath, ethyl acetate (6.5 ml), methanol (6.5 ml) and water (6.5 ml) were added and stirring was continued for 3 h. The mixture was filtered, the residual solid washed with hot chloroform and the resulting solution dried over anhydrous sodium sulfate. Solvent removal gave 3.0 g (98%) of diol (VIIIa): needles from chloroform-hexane, mp 183-185°C, $[\alpha]_D$ = +62 ($CHCl_3$). IR 3380 (hydroxyl), 1630 (C=C) $cm^{-1}$. NMR ($C_5H_5N$-d): δ 0.95 (3H, s, 18-Me), 1.0 (3H, s, 19-Me), 3.1 (1H, m, 17-H), 3.8 (2H, m, 2-$CH_2$OH), 5.45 (1H, b.s., 3-H).

Anal. Caldc. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41.
Found C, 78.40; H, 10.32%.

Compound (VIIIa) was characterized by acetylation, in the

usual manner, to the diacetate (VIIIc): IR 1730 (acetate C=O), 1630 (C=C) $cm^{-1}$. NMR: $\delta$ 0.8 (3H, s, 18-Me), 0.95(3H, s, 19-Me), 2.0 (6H, s, 2-$CH_2$OCO Me and 17-OCO Me), 3.95 (2H, d, 2-$CH_2$OCO Me), 4.55 (1H, b.s. 17-H), 5.05 (1H, b.s., 3-H).

17$\beta$-Hydroxy-2$\alpha$-(2'-tetrahydropyranyl)oxymethyl-A-norandrost-3(5)-en-2-one 17-(2'-tetrahydropyranyl) ether (VIIIb). Dihydropyran (21.5 ml) and some crystals of p-toluenesulfonic acid were added to compound (VIIIa) (3.3 g). The suspension was stirred until solution was complete and then warmed on a water bath at 100°C for 4 h. After cooling, sodium carbonate (5.2 g) was added, the suspension was stirred for 30 min and the mixture was extracted with diethyl ether. The organic phase was washed with water until neutral, dried with anhydrous sodium sulfate and the solvent was evaporated. The residue was adsorbed on basic $Al_2O_3$ B III and eluted first with petroleum ether (bp 40-70°C) and then with petroleum ether-diethyl ether 90:10 to give 5.2 g (100%) of the ditetrahydropyranylether (VIIIb) as a liquid $[\alpha]_D$ = +11 ($CHCl_3$). NMR: $\delta$ 0.80 (3H, s, 18-Me), 0.95 (3H, s, 19-Me), 3.5, 3.8, 4.5, 4.9 (9H, m, superimposed ethereal protons), 5.2 (1H, b.s., 3-H).

Anal. Calcd. for $C_{29}H_{46}O_4$ : C, 75.94; H, 11.11.
Found C, 75.52; H, 10.43%.

17$\beta$-Hydroxy-2$\alpha$-hydroxymethyl-A-nor-5$\beta$-androstan-3-one (XIa). Compound (VIIIb) (2.1 g) was dissolved in anhydrous tetrahydrofuran (23.2 ml); a solution of borane-dimethylsulfide (3.5 ml in 10.7 ml of anhydrous tetrahydrofuran) was added under stirring in a nitrogen atmosphere at room temperature during 30 min and stirring was continued overnight. The solution was cooled with an ice bath and water (3.61 ml), sodium acetate (42.5 ml of a 5M solution) and $H_2O_2$ (21.5 ml of a 30% solution) were added in succession under vigorous stirring. After 1 h the mixture was extracted with diethyl ether and the ethereal extract was washed until neutral, dried and evaporated. The residue was chromatographed on basic alumina B III by eluting with benzene to afford 1.7 g (80%) of the 3$\beta$-alcohol (IXa). IR 3400 $cm^{-1}$ (hydroxyl). NMR: $\delta$ 0.75 (3H, s, 18-Me), 1.05(3H, s, 19-Me), 3.3-4.7 (superimposed signals).
The identity of compound (IXa) was confirmed by hydrolysis

with HCl in water-ethanol (rt, 4h) to the corresponding triol, and then acetylation in the usual manner ($Ac_2O$, pyridine, rt, 24 h) to give the known triacetate (IXb) (1). Compound (IXa) (5.1 g) was dissolved in 4.8 ml of pyridine and a suspension of 6.51 g of chromic anhydride in 92.9 ml of pyridine was added under stirring. The mixture was left overnight, then diethyl ether and water were added and the mixture was filtered. The ethereal extract was evaporated to dryness to give 4.63 g of crude product (X), which IR spectrum showed a signal at 1735 $cm^{-1}$ for a ketone on a five-membered ring. This crude product was dissolved in ethanol (155 ml), then water (7.98 ml) containing conc HCl (3.5 ml) was added under stirring. After 4 h, saturated sodium carbonate solution was added until neutral. The ethanol was eliminated by distillation under reduced pressure, the residue was extracted with diethyl ether and the ethereal extracts were washed, dried and evaporated to give 2.4 g (75%) of the keto diol (XIa), plates from diethyl ether-hexane, mp 68-71°C. IR 3430 (hydroxyl), 1730 $cm^{-1}$ (ketone C=O); NMR: $\delta$ 0.75 (3H, s, 18-Me), 1.2 (3H, s, 19-Me), 3.15 (1H, m 17-H), 3.65 (2H, m, 2-$CH_2$OH). (XIa) was acetylated to (XIb); $[\alpha]_D$=+36 ($CHCl_3$). NMR: $\delta$ 0.8 (3H, s, 18-Me), 1.2 (3H, s, 19-Me), 2.0 (6H, s, 2-$CH_2$OCOMe and 17-OCOMe), 4.2 (2H, m, 2-$CH_2$OCOMe), 4.5 (1H, m, 17-H).

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78.
Found C, 70.55; H, 8.34%.

17 $\beta$ -Hydroxy-2-methyl-A-nor-5 $\beta$ -androst-1-en-3-one 17-tosylate (XIIb). Compound (X) (0.35 g) was dissolved in 12 ml of ethanol. Water (0.6 ml) and conc HCl (0.25 ml) were added under stirring and the solution was refluxed for 4h. After cooling, a saturated solution of sodium chloride and sodium carbonate was added until neutral. After the usual work up, the crude product was chromatographed on silica gel by eluting with benzene-diethyl ether 95:5 to give 0.18 g(70%)of compound (XIIa). IR 3450 (hydroxyl), 1700 (ketone C=O), 1640 $cm^{-1}$ (C=C) NMR: $\delta$ 0.75 (3H, s, 18-Me), 1.2 (3H, s, 19-Me), 1.75 (3H, d, 2-Me), 3.5 (1H, m, 17-H), 7.25(1H, b.s., 3-H). This latter compound was characterized as the tosylate (XIIb) and acetate (XIIc) as follow. Compound (XIIa) was dissolved in pyridine (2 ml), 0.174 g of tosyl chloride was added and the solution was left at room temperature for 36 h. Ice and water were added and the mixtu-

re was extracted with diethyl ether. The extracts were washed with 1N HCl, then 1N NaOH, neutralized, dried and evaporated. Chromatography on silica gel of the residue (benzene as eluent) afforded the tosylate (XIIb) (0.12 g, 80%) prisms from diethyl ether, mp 175-177°C. $[\alpha]_D$ =+28 ($CHCl_3$). IR 1700 (ketone C=O), 1640 (C=C), 1600 $cm^{-1}$(aromatic C=C). NMR: $\delta$ 0.8 (3H, s, 18-Me), 1.1 (3H, s, 19-Me), 1.7 (3H, d, 2-Me), 2.4 (3H, s, Me-Ph), 4.18 (1H, m, 17-H), 7.18 (1H, m, 1-H), 7.16-7.74 (4H, m, aromatic protons). UV: $\lambda$ max 228nm ($\varepsilon$ =37,700 in ethanol).

Anal. Calcd. for $C_{26}H_{34}O_4S$: C, 70.56; H, 7.74.
Found C, 70.27; H, 7.90%.

Acetilation of compound (XIIa) in the usual manner gave the acetate (XIIc). IR 1735 (acetate C=O), 1700 (ketone C=O), 1640 (C=C). NMR: $\delta$ 0.78 (3H, s, 18-Me), 1.18 (3H, s, 19-Me), 1.75 (3H, d, 2-Me), 1.95 (3H, s, 17-OCOMe), 4.50 (1H, m, 17-H), 7.18 (1H, m, 1-H).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15.
Found C 75.97; H, 8.95%.

17 $\beta$ -Hydroxy-2-methylene-A-nor-5 $\beta$ -androstan-3-one 17-tosylate (XIII). Compound (XIa) (0.7 g) was tosylated in the usual manner, then $Na_2CO_3$ 2N was added and the alkaline mixture extracted with diethyl ether. The ethereal extracts were washed with cold 1N HCl, then with water until neutral and the solvent was evaporated (5); the crude mixture obtained was purified by chromatography on silica gel by eluting with benzene to give the enone (XIII) (0.8 g, 70%); plates from methylene chloride-methanol mp 164-167°C $[\alpha]_D$ =+76 ($CHCl_3$). IR 1730 (ketone C=O), 1650 (C=C), 1600 $cm^{-1}$(aromatic C=C). NMR: $\delta$ 0.8 (3H, s, 18-Me), 1.12 (3H,s, 19-Me), 2.4 (3H, s, Me-Ph), 4.18 (1H, m, 17-H), 5.25 and 6.0 (2H, b.s., 2-$H_2$C=C), 7.16-7.74 (4H, m, aromatic protons). UV: $\lambda$ max 228 nm ($\varepsilon$ = 6140 in ethanol).

Anal. Calcd. for $C_{26}H_{36}O_4S$: C, 70.24; H, 8.16.
Found C, 69.94; H, 8.35%.

3 ξ , 17 β -Dihydroxy-2-methylene-A-nor-5 β -androstane 17-tosylate (XIV). Compound (XIII) (0.082 g) was dissolved in 4.8 ml of a 0.4 M methanolic solution of cerous chloride heptahydrate. Then dioxane (0.5 ml) was added and sodium borohydride (0.076 g) was added under stirring during five min. water was added and the reaction mixture was extracted with diethyl ether. After the usual work up and chromatographic purification on silica gel, 0.054 g (65%) of compound (XIV) was obtained as an uncrystallizable substance. $[\alpha]_D$ =+9.6 ($CHCl_3$). IR 3430 (hydroxyl) 1650(C=C) 1600 $cm^{-1}$ (aromatic C=C). NMR: δ 0.8 (3H, s, 18-Me), 1.2 (3H, s, 19-Me), 2.41 (3H, s, Me-Ph), 4.2 (1H, m, 17-H), 4.45 (1H, d, 3-H), 5.03 and 5.13 (2H, b.s., 2-$H_2$C=C), 7.16-7.74 (4H, m, aromatic protons).

Anal. Calcd. for $C_{26}H_{36}O_4S$: C, 70.24; H, 8.16.
Found C, 69.96; H, 7.98%.

17 β -Hydroxy-2 ξ -methyl-A-nor-5 β -androstan-3 one 17- tosylate (XVI) and 3 ξ , 17β -dihydroxy-2 ξ -methyl-A-nor-5-androstane 17-tosylate (XVII). A solution of compound (XIII) (0.11 g) in dioxane (17 ml) was added to a solution of sodium borohydride (0.07 g) in dioxane-methanol 1:1(3.6 ml) and water (0.15 ml). After two h, the reaction mixture was worked up and acetylated with acetic anhydride in pyridine as usual. Chromatographic separation on silica gel by eluting with hexane-diethyl ether 90:10 afforded 0.06 g of compound (XVI) and 0.03 of compound (XVII). Compound (XVI): IR 1730 (ketone C=O), 1600 $cm^{-1}$ (aromatic C=C).NMR: δ 0.8 (3H, s, 18-Me), 1.15 (3H, s, 19-Me), 1.1 (3H, d, 2-Me), 2.41 (3H, s, Me-Ph), 4.2 (1H, m, 17-H), 7.27-7.75 (4H, m, aromatic proton).

Anal. Calcd. for $C_{16}H_{36}O_4S$: C, 70.24; H, 8.16.
Found C, 70.26; H, 8.30%.

Compound (XVII): IR 1725 (acetate C=O), 1600 $cm^{-1}$ (aromatic C=C). NMR: δ 0.81 (3H, s, 18-Me), 0.98 (3H, s, 19-Me), 1.12 (3H, d, 2-Me), 2.0 (3H, s, 3-OCOMe), 2.41 (3H, s, Me-Ph), 4.2 (1H, m, 17-H), 4.9 (1H, m, 3-H), 7.27-7.75 (4H,m, aromatic protons).

Anal. Calcd. for $C_{28}H_{40}O_5S$: C, 68.83; H, 8.25.
Found C, 68.63; H, 8.14%.

3ζ, 17β-Dihydroxy-A-nor-5β-androstan-2-one 17-tosylate (XV). Compound (XIV) (0.07 g) was dissolved in $CHCl_3$ (3.5 ml) then submitted to ozonization (7.000V, $O_2$ flux 8 ml/h, -55°C) with an Ozo-B instrument (s.r.l. Elbe -Milano - Italy), monitoring the reaction with a 10% aqueous KI solution. Excess ozone was eliminated by a nitrogen stream and 0.8 ml of glacial acetic acid and 0.371 g of powdered zinc were added during 30 min. The reaction mixture was filtered and the resulting solution was rinsed with diethyl ether, washed to neutrality with sodium carbonate solution, dried and evaporated. The crude reaction product was chromatographed on silica gel by eluting with benzene-diethyl ether 80:20 to give the ketol (XV) (0.04g, 60%) needles from hexane-diethyl ether, mp 127 - 129°C; $[\alpha]_D$ = -76 ($CHCl_3$). IR 3420 (hydroxyl), 1735 $cm^{-1}$ (ketone C=O). NMR: δ ($CDCl_3$) 0.8 (3H, s, 18-Me), 1.12 (3H, s, 19-Me), 2.42 (3H, s, Me-Ph), 4.18 (1H, m, 17-H), 4.5 (1H, d, 3-H), 7.27-7.75 (4H, m, aromatic protons).

Anal. Calcd. for $C_{25}H_{34}O_5S$: C, 67.24; H, 7.68.
Found C, 67.09; H, 7.51%.

17β-Hydroxy-A-norandrost-3(5)-en-2-one 17- tosylate (XVIII). Compound (XV) (0.1 g) was dissolved in anhydrous pyridine (1.5 ml) and phosphorus oxychloride (0.05 ml) was added. The solution was warmed to 125°C for 30 min and after cooling, water, ice and 1N HCl were added. Extraction with diethyl ether, washing with 2N HCl, saturated $NaHCO_3$ solution and water, drying and evaporation gave compound (XVIII) (0.060 g, 65%), plates from ethyl ether mp 151-154°C, $[\alpha]_D$ = -8.6 ($CHCl_3$). IR 1680 (ketone C=O), 1630 (C=C), 1600 $cm^{-1}$ (aromatic C=C). NMR: δ ($CDCl_3$) 0.82 (3H, s, 18-Me), 1.15 (3H, s, 19-Me), 2.42 (3H, s, Me-Ph), 4.25 (1H,m, 17-H), 5.7 (1H, s, 3-H), 7.27-7.75 (4H, m, aromatic protons).

Anal. Calcd. for $C_{25}H_{32}O_4S$: C, 70.07; H, 7.53.
Found C, 70.15; H, 7.70%.

17β-Hydroxy-A-norandrost-3(5)-en-2-one (V). Compound (XVIII) (0.080 g) was dissolved in 10 ml of a 5% solution of KOH in ethanol-water (1:1) and refluxed for 4 h. After cooling and extraction with diethyl ether, the ethereal

extracts were washed until neutral, dried and evaporated. Chromatographic purification on silica gel (benzene: diethyl ether 60:40 as eluent) gave compound (V) (0.040 g, 75%), prisms from ethyl acetate-hexane, mp 173-176°C (lit. (6) mp 175-176°C), $[\alpha]_D$ = -20 (ethanol ) (lit (6) $[\alpha]_D$ = = -22 ) identical to an authentic sample of A-nortestosterone (mixed melting point, IR and NMR spectra) (4).

ACKNOWLEDGMENTS

We thank Dr. F.L.Weisenborn of the Squibb Institute for Medical Research for a kind gift of A-nortestosterone and the Italian CNR for financial support of this work.

REFERENCES

1. Mincione, E., Barraco, P. and Forcellese, M. L., GAZZ. CHIM. ITAL., 110, 515 (1980).
2.a)Marshall, P. G., in "Rodd's Chemistry of Carbon Compounds", vol II chapter 16 (Coffey, S., Editor), ELSEVIER PUBLISHING CO, Amsterdam (1970) p 281; b) Dauben, W. G., Boswell, G. A. and Templeton, W. H. J. AMER. CHEM. SOC., 83, 5006 (1961).
3. Luche, J. L., Rodriguez-Hahn, L., and Crabbè, P., J. CHEM. SOC. CHEM. COMM., 14, 601 (1978).
4. Supplied by Dr. F. L. Weisenborn of the Squibb Institute for Medical Research, Princetown, N.J.
5. It is necessary to make basic the reaction mixture with 2N $Na_2CO_3$ to eliminate p-toluensulfonic acid which can isomerize the exocyclic diene (XIII) to the endocyclic diene (XII).
6. Weisenborn, F. L. and Applegate, H. E., J. AMER. CHEM. SOC., 81, 1960 (1959).