Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Ceric(IV)Ammonium Nitrate Catalyzed Nucleophilic Opening of a Steroidal α,β-Unsaturated Epoxide

G. Neef [a] , E. Ottow [a] , G. Ast [a] & H. Vierhufe [a]
[a] Research Laboratories of Schering AG , D-1000, Berlin, 65, Germany
Published online: 23 Sep 2006.

To cite this article: G. Neef , E. Ottow , G. Ast & H. Vierhufe (1993) Ceric(IV)Ammonium Nitrate Catalyzed Nucleophilic Opening of a Steroidal α,β-Unsaturated Epoxide, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 23:7, 903-911, DOI: 10.1080/00397919308013287

To link to this article: http://dx.doi.org/10.1080/00397919308013287

SYNTHETIC COMMUNICATIONS, 23(7), 903-911 (1993)

CERIC(IV)AMMONIUM NITRATE CATALYZED NUCLEOPHILIC OPENING OF A STEROIDAL α,ß-UNSATURATED EPOXIDE

Günter Neef*, Eckhard Ottow, Gerhard Ast, and Harry Vierhufe

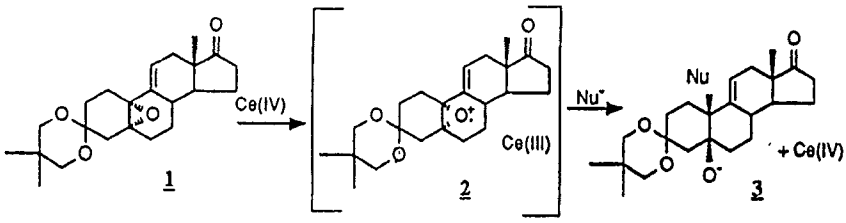
Research Laboratories of Schering AG
D-1000 Berlin 65, Germany

Summary: Ceric(IV) ammonium nitrate catalysis can successfully overcome the unreactivity of 9(11)-unsaturated steroidal 5α, 10α-epoxide 1 towards weakly nucleophilic aniline derivatives.

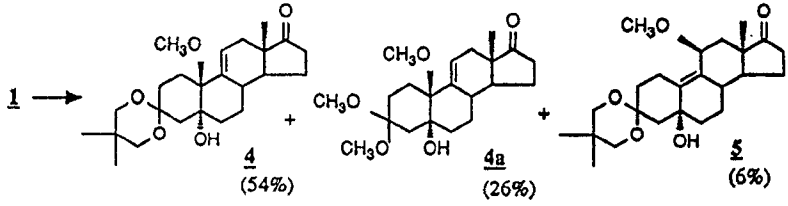
Epoxide **1**[1] is a valuable precursor for a number of structurally uncommon and biologically active steroids. Clean S_N2 opening of **1** is unfortunately limited to quite a small number of highly reactive nucleophiles[2]. Lewis acid support[3] can help to overcome some of the problems, a vast array of interesting nucleophiles, however, remain unreactive, even under most drastic conditions. Despite numerous attempts applying most of the existing methods, we never managed to open epoxide **1** with an aniline derivative in a S_N2 fashion.

A recent report by Iranpoor and Baltork[4] describing a very effective and selective opening of some simple epoxides with alcohols under ceric ammonium nitrate catalysis encouraged us to make a further attempt. An epoxonium radical cation postulated as reactive intermediate can be expected to be trapped by moderately nucleophilic agents. Furthermore, **1** should provide some information about the regioselectivity of nucleophilic attack upon a radical cation derived from an α,ß-unsaturated epoxide.

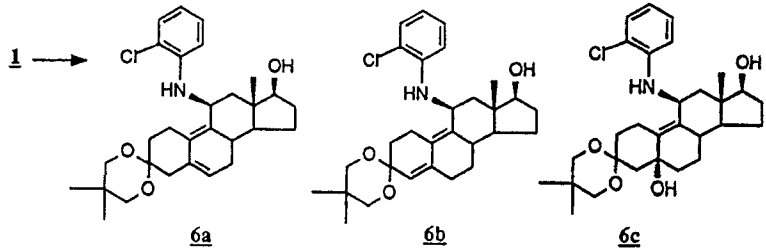
*To whom correspondence should be addressed.

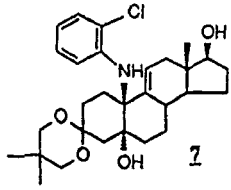


As a first experiment, epoxide 1 was dissolved in methanol and stirred at 0°C with a catalytic amount of ceric ammonium nitrate. Within 90 min the reaction was completed giving the product of S_N2 opening in 54% yield. A major side reaction was trans-ketalization which could be avoided by the use of absolute methanol (boiling with magnesium), thus raising the yield of 4 to 86%. A closer look at the crude product revealed the presence of a small amount of compound 5 (6%) obviously stemming from S_N2' attack.



Replacing methanol with 2-chloro aniline as nucleophile and executing the reaction in methylene chloride solution for 16 hours turned out to give a complex mixture from which four components could be isolated by chromatography and identified.



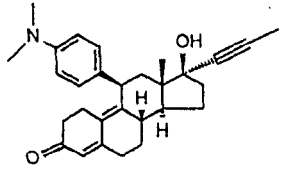


7

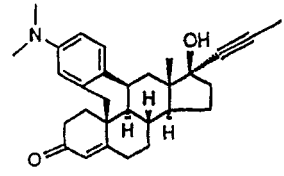
Though at first sight an unattractive result, we were encouraged by the appearance of compound 7 in the product mixture, as in our previous attempts we had never seen a trace of it. Optimization resulted in the finding that the reaction was best carried out using 2-chloro aniline as solvent thereby suppressing formation of dehydration products 6a,b. The approximate 1:1 relationship between S_N2 and S_N2' attack as reflected in products 6c and 7 could not be influenced markedly. Separation of 6c from 7, though tedious, was facilitated by the nice cristallinity of the two compounds. The respective yields could not be made to exceed 20%, however sufficient for further investigations.

The 2-chloro aniline opening of 1 was intended to deliver a key intermediate for the synthesis of final product 9, a molecule of interest with respect to its potential anti-progesterone activity. Since the discovery of RU 486 as the first competitive progesterone antagonist chemical variation has led to a large number of interesting analogues. A clear concept defining the structural requirements for anti-progesterone activity remains to be established.

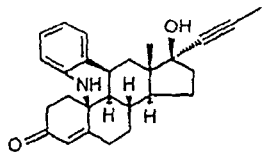
Among others, bridged compounds of type 8[5] turned out to be potent progesterone antagonists with greatly reduced anti-glucocorticoid side effects. Therefore, we concentrated part of our efforts on this type of structure. Replacement of the bridging methylene group by various heteroatoms seemed a worthwhile effort, a NH-group being a favorite candidate for substitution.



RU 38 486

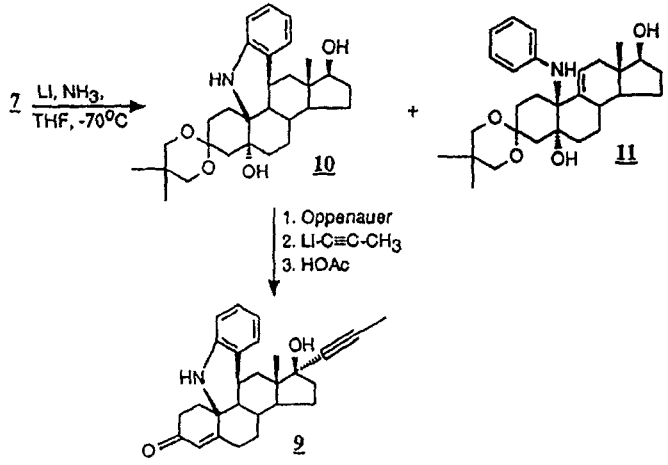


8



9

Intermediate 7 was subjected to the conditions (Li, NH_3) recently described for intramolecular radical cyclization in the analogous benzyl substituted series[5] and again the 6-endo mode of cyclization was observed leading to the amino-bridged compound 10 in about 50% yield. In contrast to the benzyl series, the product of mere dehalogenation (11) was formed in equal amount demonstrating that precursor 7 may be slighly less favorably prepared for intramolecular cylization than the carbon analogue. The ^{1}H-nmr spectrum of 7 reveals a remarkable upfield shift for the signal of the angular C-13-methyl group indicating a preferred orientation of the anilino substituent in such a way that the aromatic nucleus can exert a considerable shielding effect upon the angular methyl group.



Compound 9 was found to have a much lower affinity versus the progesterone receptor than RU 486 and the carbocyclic analogue 8.

Experimental:

General

^{1}H- and ^{13}C-NMR spectra were taken on Bruker AMX-500 and Bruker AC-300 spectrometers using standard software. Chemical shifts are reported in δ values relative to the appropriate reference signals (tetramethylsilane: δ = 0,00 ppm, $CDCl_3$: δ = 77,0 ppm). Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The optical rotations were measured in chloroform with Perkin-Elmer Polarimeter 241. IR-spectra were recorded on an Bruker IFS 25 spectrometer. Mass spectra were taken on a VG 70-70 E (Fisons Instruments). Elemental analyses were performed by the Department of Analytical Chemistry of Schering AG.

a. 3,3-(2,2-Dimethyl-trimethylenedioxy)-5α-hydroxy-10ß-methoxy-9(11)-estren-17-one **4**
3,3-(2,2-Dimethyl-trimethylenedioxy)-5α-hydroxy-11ß-methoxy-9-estren-17-one **5**

Methanol was dried by addition of magnesium (5g/l) to commercial solvent (< 1% H_2O) and distillation. Epoxide **1** (50 g) was dissolved in 250 ml of dry methanol and after addition of ceric(IV)ammonium nitrate (450 mg) stirred for 2,5 h with ice-water cooling. The mixture was poured into $Na_2S_2O_3$-solution (5% in water) and extracted with ethyl acetate. Chromatography on neutral alumina with hexane/ethyl acetate gave two products:

4 (42,5 g), m.p. 167-170°C (from hexane/diisopropyl ether), $[\alpha]_D$ +31,1° ($CHCl_3$, c = 0,520). ^{1}H-nmr (300 MHz, $CDCl_3$): δ = 0,88 ppm (s,3H,H-18); 0,93 (s,3H,ketal-CH_3); 1,00 (s,3H,ketal-CH_3); 2,98 (s,3H,OCH_3); 3,49 (d,J = 11 Hz,1H,ketal-CH_2); 3,53 (s,2H,ketal-CH_2); 3,58 (d,J = 11 Hz,1H,ketal-CH_2); 5,59 (m,1H,H-11).

Anal.calc. for $C_{24}H_{36}O_5$: C 71,26%, H 8,97%, O 19,77%; found: C 71,33%, H 8,37%, O 19,79%.

5 (2,3 g), m.p. 148-150°C (from ethyl acetate/diisopropyl ether), $[\alpha]_D$ -26,8° ($CHCl_3$, c = 0,525). ^{1}H-nmr (300 MHz, $CDCl_3$): δ = 0,93 ppm (s,3H,H-18); 1,05 (s,3H,ketal-CH_3); 1,09 (s,3H,ketal-CH_3); 3,17 (s,3H,OCH_3); 3,48 (d,J = 11

Hz,1H,ketal-CH_2); 3,58 (d,J = 11 Hz,1H,ketal-CH_2); 3,59 (s,2H,ketal-CH_2); 4,42 (m,1H,H-11).

Anal.calc. for $C_{24}H_{36}O_5$: C 71,26%, H 8,97%, O 19,77%; found: C 71,39%, H 8,69%, O 19,78%.

b. 11ß-(2-Chlorophenylamino)-3,3-(2,2-dimethyl-trimethylenedioxy)-4,9-estradiene-17ß-ol **6a**
11ß-(2-Chlorophenylamino)-3,3-(2,2-dimethyl-trimethylen edioxy)-5,9-estradiene-17ß-ol **6b**
10ß-(2-Chlorophenylamino)-3,3-(2,2-dimethyl-trimethylenedioxy)-9(11)-estrene-5α,17ß-diol **7**
11ß-(2-Chlorophenylamino)-3,3-(2,2-dimethyl-trimethylenedioxy)-9-estrene-5α,17ß-diol **6c**

3,3-(2,2-Dimethyl-trimethylenedioxy)-5α,10α-epoxy-9 (11)-estren-17ß-ol **1** (10,0 g) is dissolved in 2-chloroaniline (30 ml). Ceric(IV)ammonium nitrate (4,0 g) is added in small portions at room temperature over a period of 15 min. Stirring is continued for 60 min at ambient temperature. The reaction mixture is then poured into $Na_2S_2O_3$-solution and extracted with ethyl acetate. Excess 2-chloroaniline is removed from the crude product by distillation under reduced pressure (0,5 mmHg). The residue is chromatographed on neutral alumina (3 kg). After elution with hexane/ethylacetate 0-46% two fractions are obtained in the order of polarity. Fraction 1 contains dehydration products **6a,b** (700 mg), fraction 2 (4,1 g) is a mixture of **7** and **6c**.

The product mixtures of fractions 1 and 2 are separately rechromatographed on silica gel (800 g) with dichloromethane/ethyl acetate 0-20% giving in the order of elution:

6a (220mg), brown oil. ^{1}H-nmr (300 MHz, $CDCl_3$): δ = 0,86 ppm (s,3H,H-18); 0,91 (s,3H,ketal-CH_3); 1,08 (s,3H,ketal-CH_3); 3,44 (d,J = 11 Hz,1H,ketal-CH_2); 3,54-3,66 (m,3H,ketal-CH_2); 3,94-4,10 (m,2H,H-17 and NH); 4,46 (broad d,J = 8,5 Hz,1H,H-11); 5,32 (s,1H,H-4); 6,63-7,32 (m,4H,arom.H).

6b (380 mg), brown oil which crystallizes on standing, m.p. 199-201°C (after three recrystallisations from diisopropyl ether/ethyl acetate), $[\alpha]_D$ + 289,9° ($CHCl_3$, c = 0,515). ^{1}H-nmr (300 MHz, $CDCl_3$, D_2O-exchange): δ = 0,88 ppm (s,3H,H-18); 0,90 (s,3H,ketal-CH_3); 1,08 (s,3H,ketal-CH_3); 3,41-3,51

(m,2H,ketal-CH_2); 3,64 (t,J = 10 Hz,2H,ketal-CH_2); 3,83 (d,J = 6 Hz,1H,H-11); 3.94 (t,J = 9 Hz,1H,H-17); 5,60 (d,J = 5 Hz,1H,H-6); 6,59 (dt,J = 7,5 and 2 Hz,1H,arom.H); 6,98 (d,J = 7,5 Hz,1H,arom.H); 7,14 (dt,J = 7,5 and 2 Hz,1H,arom.H); 7,23 (dd,J = 7,5 and 2 Hz,1H,arom.H).

7 (2,36 g from ethyl acetate/dichloromethane), m.p. 275-279°C (decomposition), $[\alpha]_D$ -16,8° ($CHCl_3$, c = 0,505), ^{1}H-nmr (300 MHz, $CDCl_3$): δ = 0,41 ppm (s,3H,H-18); 0,89 (s,3H,ketal-CH_3); 1,02 (s,3H,ketal-CH_3); 3,40-3,62 (m,4H,ketal-CH_2); 3,66-3,78 (m,1H,H-17); 4,38 (s,1H,NH); 4,49 (d,J = 1,2 Hz,1H,5α-OH); 5,77 (m,1H,H-11); 6,53-6,63 (m,1H,arom.H); 6,93-7,03 (m,2H,arom.H); 7,22 (d,J = 7,5 Hz,1H,arom.H).

6c (1,47 g from ethyl acetate), m.p. 225-229 (decomposition), $[\alpha]_D$ -34,0° ($CHCl_3$, c = 0,520), ^{1}H-nmr (300 MHz, $CDCl_3$): δ = 0,86 ppm (s,3H,H-18); 0,95 (s,3H,ketal-CH_3); 1,04 (s,3H,ketal-CH_3); 3,38-3,65 (m,5H,ketal-CH_2,H-17); 4,14 (d,J = 6 Hz,1H,H-11); 4,46 (d,J = 1,2 Hz,1H,5α-OH); 4,53 (broad t,J = 7 Hz,1H,NH); 6,58-6,70 (m,2H,arom.H); 7,14 (t,J = 7,5 Hz,1H,arom.H); 7,24 (dd,J = 7,5 and 1,1 Hz,1H,arom.H).

c. 3,3-(2,2-Dimethyl-trimethylenedioxy)-1',2',3',4'-tetrahydroquinoline-[2',3',4':10ß,9,11ß]-estrane-5α,17ß-diol **10** and 3,3-(2,2-Dimethyl-trimethylenedioxy)-10ß-phenylamino-9(11)-estrene-5α,17ß-diol **11**

Ammonia (105 ml) is condensed into a dry flask cooled to -70°C. Lithium (200 mg) is divided into ten equal portions. A solution is prepared containing 7 (2,1 g) and tert.-butanol (3,5 ml) in dry THF (50 ml). The first portion of lithium is inserted into the liquid ammonia at -70°C, whereupon part of the THF solution is slowly added dropwise until the blue colour is dispersed. The next portion of lithium is added and the procedure repeated until the solution of 7 is consumed. After ammonia evaporation the residual mixture is partitioned between water and ethyl acetate, the organic phase separated and treated as usual. The crude product is chromatographed on neutral alumina using as eluent a hexane/ethyl acetate mixture with the proportion of ethyl acetate increasing from 14 to 28%. In the order of elution two products are obtained: **10** (1,16 g), m.p. 166-169°C (from

diisopropyl ether/ethyl acetate, product is air-sensitive), $[\alpha]_D$ -57,3° ($CHCl_3$, c = 0,520), ^{1}H-nmr (300 MHz, $CDCl_3$): δ = 0,33 ppm (s,3H,H-18); 0,93 (s,3H,ketal-CH_3); 1,01 (s,3H,ketal-CH_3); 3,19 (m,1H,H-11); 3,46-3,74 (m,6H,ketal-CH_2,H-17,NH); 4,36 (d, J = 1,2 Hz,1H,5α-OH); 6,52 (dd,J = 8 and 1,2 Hz,1H,arom.H); 6,68 (dt,J = 8 and 1,2 Hz,1H,arom.H); 6,98 (t,J = 8 Hz,1H,arom.H); 7,27 (d,J = 8 Hz,1H,arom.H).

11 (620 mg), m.p. 249-254°C (decomposition), $[\alpha]_D$ -1,7° ($CHCl_3$, c = 0,515). ^{1}H-nmr (300 MHz, $CDCl_3$): δ = 0,41 ppm (s,3H,H-18); 0,88 (s,3H,ketal-CH_3); 1,03 (s,3H,ketal-CH_3); 3,48-3,62 (m,5H,ketal-CH_2, and NH); 4,43 (s,1H,5α-OH); 5,24 (m,1H,H-11); 6,62-6,75 (m,3H,arom.H); 7.03-7,12 (m,2H,arom.H).

d. 3,3-(2,2-Dimethyl-trimethylenedioxy)-17ß-hydroxy-1',2',3',4 '-tetrahydro-quinoline-[2',3',4':10ß,9,11ß]-estran-17-one

The Oppenauer oxidation (see chapter 3.3.) of **10** (860 mg) with cyclohexanone (2,8 ml) and aluminum triisopropylate (275 mg) in toluene (30 ml) yields, after chromatography on neutral alumina with hexane/ethyl acetate, 17-keto derivative (808 mg), m.p. 259-262 (decomposition) from ethyl acetate/diisopropyl ether, $[\alpha]_D$ -47,4° ($CHCl_3$, c = 0,525), ^{1}H-nmr (300 MHz, $CDCl_3$): δ = 0,46 ppm (s,3H,H-18); 0,93 (s,3H,ketal-CH_3); 1,02 (s,3H,ketal-CH_3); 3,26 (m,1H,H-11); 3,46-3,62 (m,4H,ketal-CH_2); 3,72 (s,1H,NH); 4,39 (d,J = 1,2 Hz,1H,5α-OH); 6,52 (dd,J = 8 and 1,2 Hz,1H,arom.H); 6,69 (dt,J = 8 and 1,2 Hz,1H,arom.H); 6,98 (t,J = 8 Hz,1H,arom.H); 7,28 (d,J = 8 Hz,1H,arom.H).

Anal.calc. for $C_{29}H_{39}N_1O_4$ (465,63): C 74,81%, H 8,44%, O 13,74%, N 3,01%; found: C 74,95%, H 8,17%, O 14,05%, N 3,04%.

e. 3,3-(2,2-Dimethyl-trimethylenedioxy)-1',2',3',4'-tetrahydroquinoline-[2',3',4':10ß,9,11ß]-17α-(1-propynyl)-estrane-5α,17ß-diol

A slow stream of propyne is passed through dry tetrahydrofuran (45 ml) at 0°C until a saturated solution is obtained (20 min). A 1,6 m solution (12 ml) of

n-butyllithium in hexane is slowly added dropwise followed by a solution of the ketone (760 mg) in THF (20 ml). After stirring at ambient temperature for 5 h the mixture is poured into water and extracted with ethyl acetate. Chromatography on neutral alumina with hexane/ethylacetate as eluent gives 17α-propynyl derivative as a viscous, colourless oil (710 mg), $[\alpha]_D$ -81,3° ($CHCl_3$, c = 0,505). ^{1}H-nmr (300 MHz, $CDCl_3$): δ = 0,43 ppm (s,3H,H-18); 0,93 (s,3H,ketal-CH_3); 1,02 (s,3H,ketal-CH_3); 1,90 (s,3H,C≡C-CH_3); 3,26 (m,1H,H-11); 3,43-3,63 (m,4H-ketal-CH_2); 4,43 (d,J = 1,3 Hz,1H,5α-OH); 6,51 (dd,J = 7,5 and 1,3 Hz,1H,arom.H); 6,68 (dt,J = 7,5 and 1,3 Hz,1H,arom.H); 6,98 (t,J = 7,5 Hz,1H,arom.H); 7,27 (d,J = 7,5 Hz,1H,arom.H).

f. 1',2',3',4'-Tetrahydroquinoline-[2',3',4':10ß,9,11ß]-17ß-hydroxy-17α-(1-propynyl)-4-estren-3-one **9**

A solution of propynyl derivative (450 mg) in aqueous acetic acid (70%, 15 ml) is stirred for 7 h at 60°C. The cooled mixture is diluted with water, neutralized with aqueous ammonia and extracted with ethyl acetate. Chromatography on silica gel with hexane/ethyl acetate 0-20% yields unsaturated ketone **9** (300 mg) as a slightly yellow, viscous oil, $[\alpha]_D$ -53,6° ($CHCl_3$, c = 0,505). ^{1}H-nmr (300 MHz, $CDCl_3$): δ = 0,48 ppm (s,3H,H-18); 1,91 (s,3H,C≡C-CH_3); 3,46 (m,1H,H-11); 3,74-4,00 (m,1H,NH); 5,91 (s,1H,H-4); 6,55 (d,J = 7,5 Hz,1H,arom.H); 6,73 (t,J = 7,5 Hz,1H,arom.H); 7,02 (t,J = 7,5 Hz,1H,arom.H); 7,32 (d,J = 7,5 Hz,1H,arom.H).

REFERENCES:

1. Teutsch, G. and Belanger, A. *Tetrahedron Lett.* **1979**, 2051.
2. a) Teutsch, G. *Tetrahedron Lett.* **1982**, 4697.
   b) Nedelec, L. *Bull.Soc.chim.* **1970**, 2548.
3. Chini, M.; Crotti, P. and Macchia, F. *J.Org.Chem. 56*, 5939, **1991**.
4. Iranpoor, N. and Baltork, I.M. *Synth.Comm. 20*, 2789, **1990**.
5. Ottow, E.; Neef, G. and Wiechert, R. *Angew.Chem.Int.Ed.Engl. 28*, 773, **1989**.

(Received in UK 29 September 1992)