Tetrahedron Letters,Vol.26,No.17,pp 2069-2072,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

STEREOSELECTIVE EPOXIDATION OF 5(10),9(11)-ESTRADIENES

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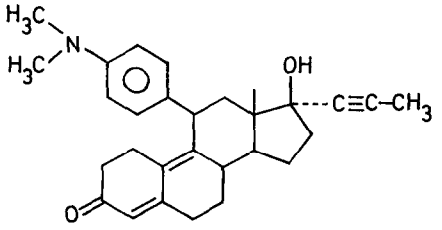
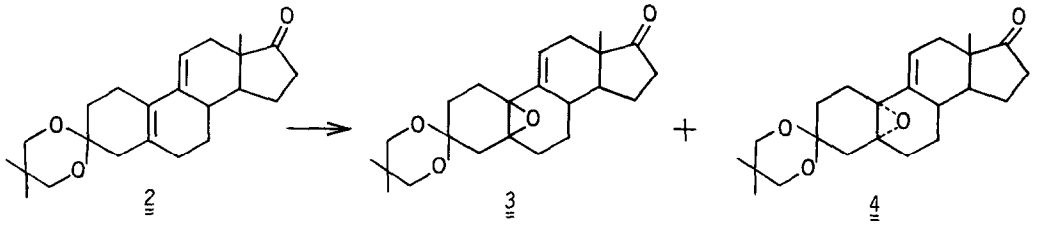
Summary: 3,3-(2,2-Dimethyltrimethylene-1,3-dioxy)-5(10),9(11)-estradien-17-one is converted to its 5α,10α-epoxide by iron phthalocyanine/iodosylbenzene in a highly stereoselective manner.

During the past few years 11ß-aryl-estradienes, especially RU 38 486 (1), have received remarkable interest due to their potent antiprogestational activities[1].



1

The key intermediates leading to these compounds are 5α,10α-epoxy-9(10)-estrenes which allow the stereospecific introduction of 11ß-substituents by conjugate opening with Cu(I) modified Grignard reagents or lithium cuprates[2,3]. The procedure employed for the epoxidation of diene ketal 2 by Teutsch et al.[4,5] is distinguished by high regioselectivity. However, the stereoselectivity of this process is unsatisfactory as a mixture of isomers is formed containing 35 per cent of 5ß,10ß-epoxide 3 and 65 per cent of 5α,10α-epoxide 4, chromatographic separation of which is rather tedious.



2 3 4

Our own interest in 11ß-substituted steroids prompted us to look for a more stereoselective approach. Since a variety of commonly used epoxidation reagents[6], applied to compound 2, failed to improve the α/ß ratio, we turned our attention to oxygen transferring processes catalyzed by transition metal complexes.

In recent years iron and manganese porphyrins[7] and complexes like $[Fe_3O(piv)_6(MeOH)_3]Cl$[8] and [Cr(III)(salen)][9], an analogue of the long-known salcomines[10], have been thoroughly investigated as simple models for the heme-containing monooxygenase cytochrome P-450 and related enzymes. The most studied application of these reagents in non biological systems is the epoxidation of olefins in the presence of oxygen donors like alkyl hydroperoxides, periodates and iodosylbenzene.

Carrying out experiments with diene 2 and these catalysts we found that the oxoiron complex[8] and the salcomines in the presence of different oxygen sources (e.g. O_2, H_2O_2, PhIO) did not improve the α/ß ratio between 3 and 4. Chloro-tetraphenylporphyrinato iron (III) and iodosylbenzene in dichloromethane, however, resulted in a considerably increased α-stereoselectivity (α : ß = 10 : 1) but gave only low yields of the desired α-epoxid due to incomplete conversion of the starting material and to the formation of undefined side products.

Another group of oxygen transferring compounds whose catalytic qualities have been widely investigated are the transition metal phthalocyanines[11]. We, therefore, examined the behaviour of a selected number of these compounds (Cu(II), Ni(II), Co(II), Mn(II) and Fe(II)) towards diene 2 using different oxygen sources.

Generally no reaction could be observed with molecular oxygen, metal peroxides, nitrosobenzene, pyridine-N-oxide and N-methyl-morpholine-N-oxide. Hydrogen peroxide and tert.butylhydroperoxide decomposed very quickly under the influence of the phthalocyanines giving only small quantities of the epoxide 4 accompanied by unreacted starting material and large amounts of side products. At last iodosylbenzene turned out to be the oxygen source of choice, as far as reactivity and stability were concerned.

Using iodosylbenzene as oxygen donor we compared the different phthalocyanines with respect to stereoselectivity, conversion rate and ratio between epoxides 3 and 4 and side products. In a group consisting of the above mentioned phthalocyanines, the iron complex clearly proved to be the best.

Finally the influence of the solvent was examined. While no reaction could be ascertained in ethylacetate, as well as N-methyl-pyrrolidone, tertiary amines, pyridine and DMSO, slow reaction took place in tetrahydrofurane and other ethers, dichloromethane, chloroform, DMF and ethanol; short reaction times were observed in acetone, nitromethane, methanol and acetonitrile, best results being obtained in acetonitrile.

Thus Fe(II)-phthalocyanine/iodosylbenzene in acetonitrile turned out to be the best suited epoxidation reagent for diene 2, resulting in a chemical yield greater than 80 % and a stereoselectivity of 11 : 1 in favour of the desired α-epoxid 4.

In a typical experiment a suspension of 1,0 g (2,8 mmol) 3,3-(2,2-dimethyltrimethylene-1,3-dioxy)-5(10),9(11)-estradien-17-one, 1,5 g (6,8 mmol) iodosylbenzene and 0,2 g (0,35 mmol) iron(II)-phthalocyanine in 10 ml of dry acetonitrile was stirred at room temperature for 3,5 h. The reaction mixture was then filtered through Celite, washed thoroughly and concentrated. The residue was chromatographed over Al_2O_3 (ICN, act.III, neutral) with a mixture of n-hexane and ethylacetate (92,5 : 7,5), yielding 0,07 g of 3,3-(2,2-dimethyltrimethylene-1,3-dioxy)-5ß,10ß-epoxy-9(11)-estrene-17-one 3 (6,7 %), m.p. 203-205°C, $[\alpha]_D^{25}$ +66,9° ($CHCl_3$, c=0,5) and 0,77 g of 3,3-(2,2-dimethyltrimethylene-1,3-dioxy)-5α,10α-epoxy-9(11)-estrene-17-one 4 (73,7 %), m.p. 124-126°C, $[\alpha]_D^{25}$ +130,7° ($CHCl_3$, c=0,5).

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(Received in Germany 13 February 1985)