Tetrahedron Letters,Vol.23,No.23,pp 2411-2414,1982 0040-4039/82/232411-04$03.00/0
Printed in Great Britain

NEW TOTAL SYNTHESIS OF EQUILENIN AND ESTRONE

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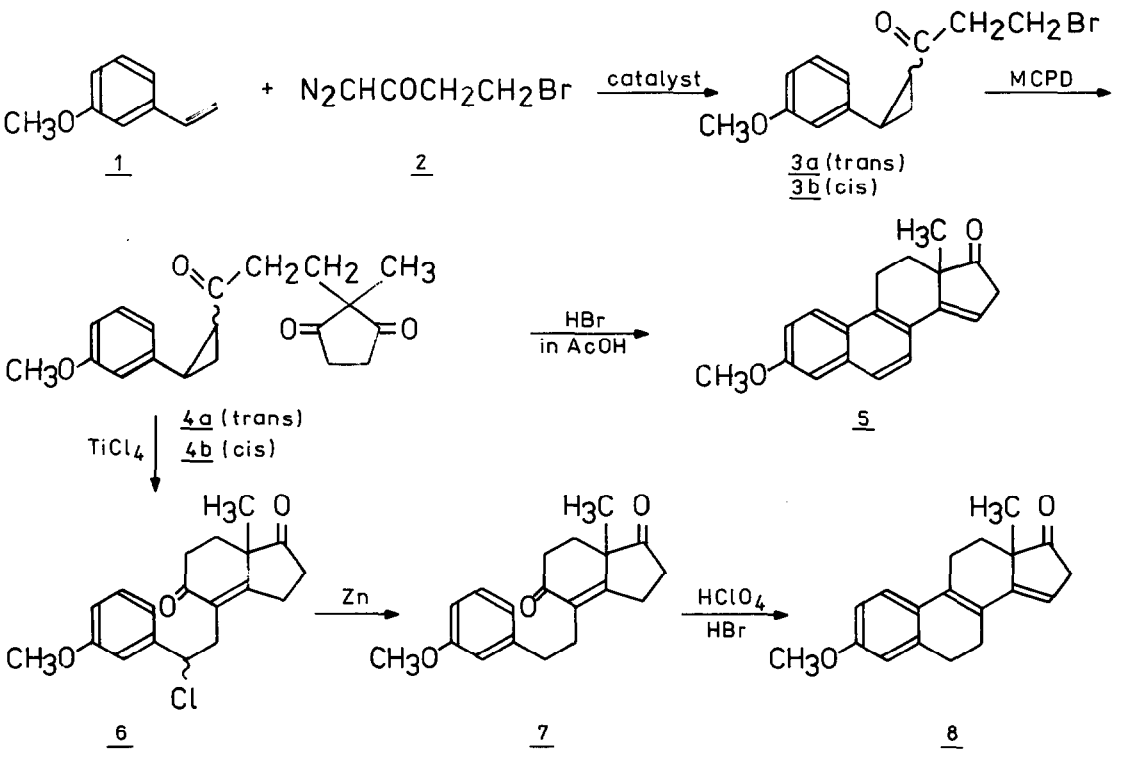
Abstract: The coupling of m-methoxystyrene (1) and diazoketone (2) over copper tartarate gave optically active (46% ee) cyclopropyl derivative (3), which was converted into compounds 5 or 8 with 22% of optical induction.

Since the first synthesis of equilenin in 1939 by Bachman[1], many new approaches[2] towards the total synthesis of estrogens have been elaborated in many laboratories. Because of the importance of these compounds, the efforts to find better methods are continued.

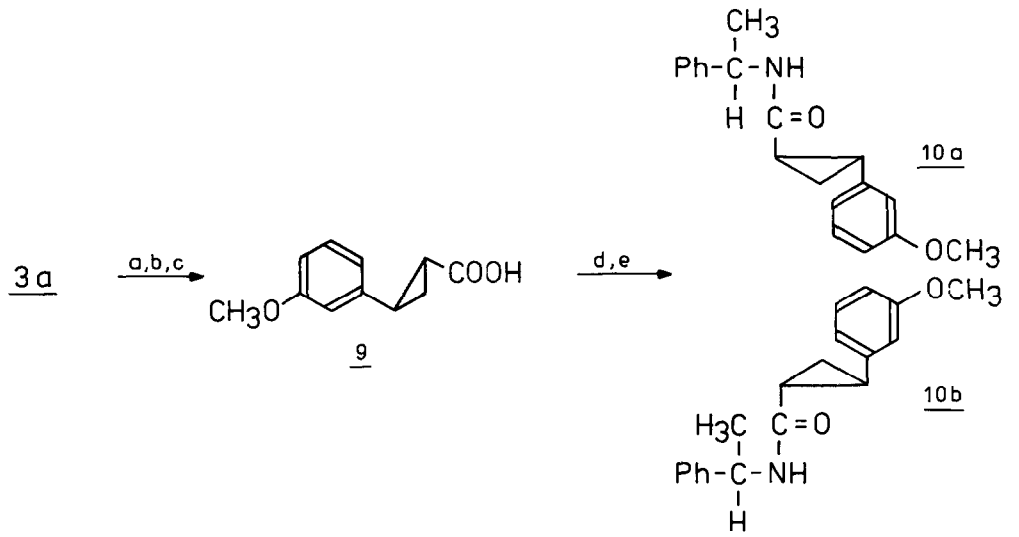
We would like to present our recent results dealing with the total synthesis of estrone and equilenin. The reaction of m-methoxystyrene (1) with diazoketone (2) upon $Pd(AcO)_2$ catalyst gave two bromides 3a (trans) and 3b (cis) which treated with sodium salt of 2-methyl-1,3-cyclopentadione in acetonitrile gave triketones 4a and 4b (60% yield with respect to 2, ratio 4a:4b = 7:1). Cyclization of 4a or 4b in acetic acid with HBr gave methyl ether of 14-dehydroequilenin (5) which can be transformed into equilenin by hydrogenation and demethylation[3]. The triketones 4a and 4b treated with $TiCl_4$ in methylene chloride at room temperature gave tricyclic chloride 6, which without isolation was reduced by zinc to the known unsaturated diketone 7 (85%). The cyclization of 7 in acetic acid with the addition of perchloric acid and hydrobromic acid gave pentaene 8 (80%) which can be converted into estrone or its derivatives by known methods[4]. In order to obtain optically active compounds we carried out the coupling reaction of m-methoxystyrene (1) with diazoketone (2) over copper tartarate as a catalyst, and in this way we obtained compounds 4a and 4b in 30% chemical yield, ratio 4a : 4b = 12 : 1. The



MCPD = 2-methyl-1,3-cyclopentadione

Scheme I

optical rotation of 4a was $[\alpha]_D^{20} = 2.2^\circ$, c 2.21 in ethanol (ee = 46%) and 4b; $[\alpha]_D^{20} = -0.135^\circ$, c 1.2 in ethanol. Compound 4b was isomerized[5] with $PdCl_2 \cdot 2PhCN$ into 4a ; $[\alpha]_D^{20} = 0.416^\circ$, c, 1.3 in ethanol. The optical purity of 4a was determined by chemical transformation shown in Scheme II. An attempt to evaluate the optical purity of 3a or methyl ester of the acid 9 using $Eu(TBC)_3$ failed so that we had to convert the racemic bromoketone 3a as well as the optically active one to diastereoisomeric amides 10a and 10b. In case of racemic bromoketone 3a, two diastereoisomers 10a and 10b were obtained, which were separated by column chromatography. The pure amides 10a and 10b enabled us to measure the optical rotation of defined mixtures of 10a and 10b and then to draw the curve of relationship between the optical rotation and the composition of mixtures 10a and 10b. In case of the optically active bromide 3a the optical rotation of obtained mixture of 10a and 10b was $[\alpha]_D^{20} = 112^\circ$ (c 0.6 in chloroform) which indicated 46% of enantiomer excess. The same optically active bromide 3a was transformed into 4a and cyclized with hydrobromic acid in acetic acid to yield methyl ether of 14-dehydroequilenin (5).



a: Et_3N, b: OsO_4 in pyridine, c: $NaJO_4$, d: $SOCl_2$, e: (+) -phenyloethylamine $[\alpha]_D^{20}$ =+39°

Scheme II

optically inactive. The cyclization of the same 4a with $TiCl_4$ gave chloride 6 which was cyclized to 5 ($[\alpha]_D^{20}$ =4.5°, c 1.1 in chloroform, optical purity 10.9%, lit.[6] $[\alpha]_D^{20}$ = 41°) or reduced with zinc to compound 7 ($[\alpha]_D^{20}$ = 18.5°, c 2.2 in benzene, o.p. 10.22%, lit.[7] $[\alpha]_D^{20}$ = 181°). The cyclization of 7 gave compound 8 ($[\alpha]_D^{20}$ = 10.72, c 1.2 in chloroform, o.p. 10.4%, lit.[8] $[\alpha]_D^{20}$ =103°). We could then compute the optical induction during the cyclization step (4a -->6) which was 22%. The relative configurations of compounds 3a and 3b were determined by a comparison of the NMR spectra of acids 9 (trans and cis) with the spectra of similar compounds known in literature[9].

Acknowledgment: The authors wish to express their thanks to Polish Academy of Sciences for financial support of this work under grant MR.1.12.1.5.1.2.

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(Received in UK 25 March 1982)