Tetrahedron Letters,Vol.27,No.42,pp 5133-5134,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A NOVEL CYCLOPENTANE ANNULATION REACTION : NEW SYNTHESIS OF ESTRONE

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Abstract : Novel cyclopropanol synthesis and cyclopentane annulation reaction lead to a new synthesis of estrone.

A new, simple and commercially viable synthesis of estrone[1], the starting material for important contraceptic drugs, is described in the present communication.

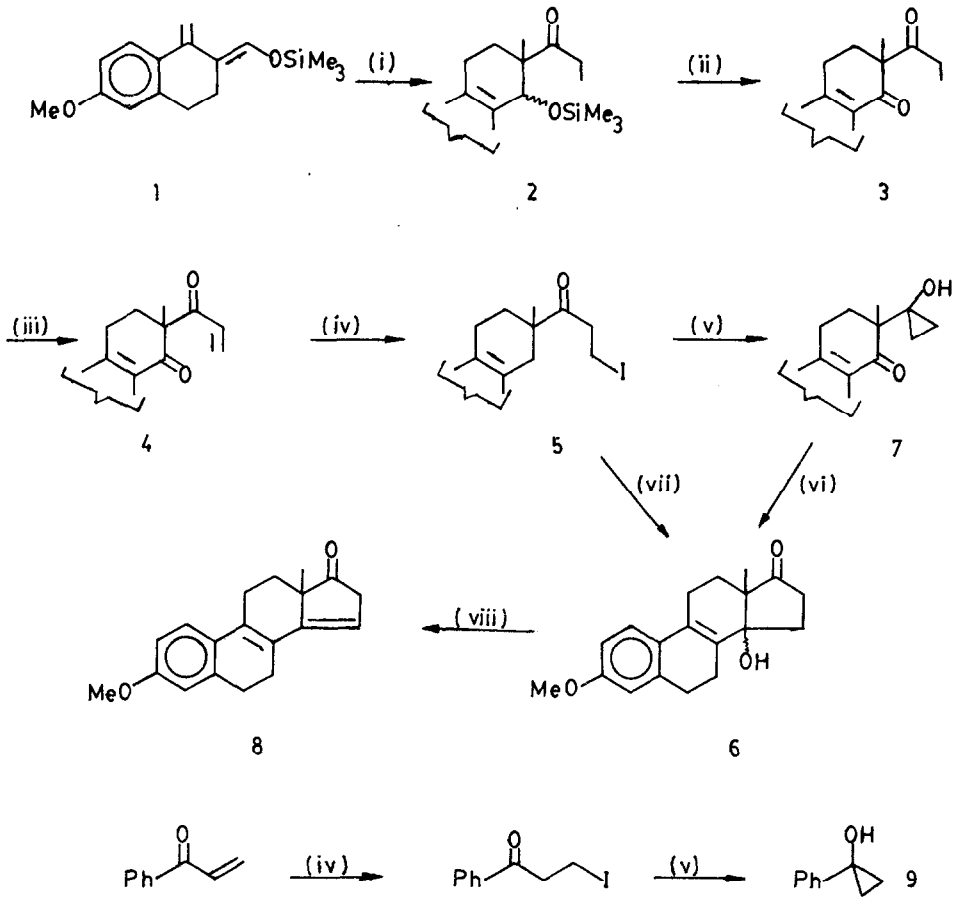
The key steps in the synthesis, delineated below, are :
(i) formation of the C ring by a Diels-Alder reaction on the diene (1) using ethyl isopropenyl ketone as the dienophile, a strategy similar to the one used earlier by us for the synthesis of equilenin[2], leading to an adduct which had all the carbon atoms needed for the construction of ring D, (ii) formation of a cyclopropanol derivative from an α,β-unsaturated ketone via the β-iodo compound (5), by treatment of the latter with $Zn/ClSiMe_3$ in refluxing THF[3], and (iii) ring expansion of the cyclopropanol (7) to the hydroxy cyclopentanone (6) by treatment with NaH in THF.

The new cyclopentane annulation reaction lead to construction of the D ring, by cyclisation between C-14 and C-15 (steroid numbering), not reported so far in estrone synthesis. The synthesis is of significance since dehydration of the cyclopentanol followed by reduction would lead to transfused cyclopentanone, especially when an alkyl group is present at the ring junction.

Cyclopentane annulation via cyclopropyl derivatives has been reported by others[4]. The methodology reported here, however, is new.

The cyclopropanol formation, reported here, is also new and general. Thus phenylvinylketone, was converted to the phenyl cyclopropanol (9) via the corresponding β-iodoketone.

It was also possible to obtain the hydroxy cyclopentanone (6), from the β-iodoketone (5), by an intramolecular Grignard reaction, using active Mg[5]. However the yield was only 30%.



(i) $H_2C{=}C(CH_3)COCH_2CH_3$, PhH, △, 40 h; 95% (ii) DDQ; 95% (iii) a. PhSeCl, CH_2Cl_2, RT, 20 h b. 30% H_2O_2-AcOH; 80% (iv) 57% HI; quant. (v) Zn, TMSCl, THF, △, 2 h, 68% (vi) NaH, THF, RT, 3 h, 90% (vii) active Mg, THF, 10°, 30% (viii) p-TSA, PhH, △, 2 min, quant.

Acknowledgement : We thank DST for funds, CSIR for a fellowship to PAP and Prof. L.N. Mander (Research School of Chemistry, Australian National University, Canberra) for a sample of Torgov's compound.

References and Notes

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(Received in UK 21 July 1986)