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THE ASYMMETRIC TOTAL SYNTHESIS OF ESTRADIOL BY AN INTRAMOLECULAR CYCLOADDITION REACTION OF o-QUINODIMETHANE

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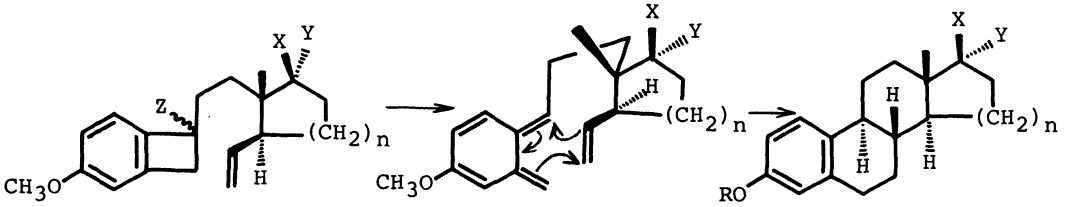
There are many reports on the synthesis of estrone and related compounds[1] and current interest on this field is focussed on an asymmetric[2] and biogenetic synthesis[3] of the above compounds. We have previously revealed[4] that the racemic form of the olefinic benzocyclobutene (1) could be induced to undergo a stereo- and regioselective intramolecular cycloaddition via o-quinodimethane (4)[5] to form O-methyl-D-homoestrone (5) in 95 % yield. In this communication we wish to report a new asymmetric synthesis of estradiol (8) by an asymmetric induction of the optically active cyclopentane derivative along our method.



1 X + Y=O, Z=H, n=2
2 X=O$^{t}C_4H_9$, Y=Z=H, n=1
3 X=O$^{t}C_4H_9$, Y=H, Z=CN, n=1

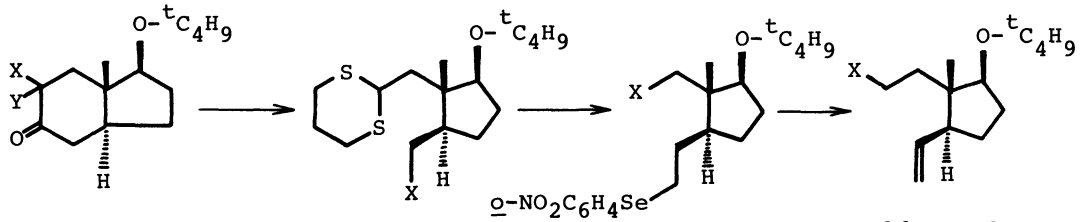
4

5 R=CH_3, X + Y=O, n=2
6 R=CH_3, X=O$^{t}C_4H_9$, Y=H, n=1
7 R=CH_3, X=OH, Y=H, n=1
8 R=Y=H, X=OH, n=1

(1S,3aS,7aS)-1-tert-Butoxy-3a,4,7,7a-tetrahydro-7a-methyl-5(6H)indanone (9)[6] [$(\alpha)_D^{25}$ + 82.2° ($CHCl_3$)] was converted into the ketone thioketal (10) [mp 111 - 113°; 86 %; m/e 328 (M^+); $[\alpha]_D$ + 38.5°][7-9] by the usual way (1. HCO_2Et, NaH;

2. $TsS(CH_2)_3STs$, AcOK), which on alkaline treatment (KOH, t-BuOH) gave the carboxylic acid (11) [oil; 90.5 %; m/e 346 (M^+): ir 1710 cm^{-1}; $[\alpha]_D$ + 24.29°][8,9]. Reduction ($LiAlH_4$) of this, followed by the arylselenation (o-$NO_2C_6H_4SeCN$, n-Bu_3P, THF) of the resulting alcohol (12) [oil; 93.4 %; m/e 332 (M^+); ir 3490 cm^{-1}; NMR ($CDCl_3$) 3.40 - 3.81 (2H, CH_2OH); $[\alpha]_D$ + 22.12][7-9] afforded the selenide (13) [oil; 79.6 %; m/e 517 and 515 (M^+); $[\alpha]_D$ - 12.73°][7-9], whose hydrolysis (MeI, Me_2CO-H_2O) of thioketal group furnished the aldehyde (14) [oil; 94.5 %; m/e 427 and 425 (M^+); ir 1710 cm^{-1}; $[\alpha]_D$ - 11.92°].[7-9] Reduction ($NaBH_4$) of 14 gave the alcohol (15) [oil, 93.3 %; ir 3490 cm^{-1}; $[\alpha]_D$ - 9.5°][7-9], which was converted into the olefin (16) [oil; 75.9 %; m/e 169 (M^+ - 57); NMR ($CDCl_3$) 4.80 - 5.70 (3H, $CH=CH_2$); $[\alpha]_D$ + 49.72°][8,9] by an oxidative deselenation (30 % H_2O_2). Tosylation (TsCl, pyridine) of the olefinic alcohol afforded the tosylate (17) [mp 69 - 71°; 76.5 %; $[\alpha]_D$ + 16.5°][7-9], which was transformed into the iodide (18) (oil; 79.8 %; m/e 280 (M^+ - 56); $[\alpha]_D$ + 30.8°][7-9] by the usual way (NaI, Me_2CO).

Condensation (NaH, DMF; 40°, 45 min) of the iodide (18) with 1-cyano-4-methoxybenzocyclobutene[10] gave the 1,1-disubstituted benzocyclobutene (3) [oil; 48.7 %; m/e 367 (M^+); ir 2230 cm^{-1}][7-9] whose decyanation (Na, liq.NH_3, EtOH, THF) afforded the 1-cyclopentylethylbenzocyclobutene (2) [oil; 85.2 %; m/e 342 (M^+); NMR (CCl_4) 4.70 - 6.10 (3H, $CH=CH_2$)].[7-9] Heating 2 in o-dichlorobenzene at 180° for 3 h in a current of nitrogen afforded the cyclization product (6) [mp 79 - 80°; 77.5 %; m/e 342 (M^+); NMR (CCl_4) 0.75 (3H, s, CH_3), 1.13 (9H, s, $C(CH_3)_3$), 2.65 - 3.0 (3H, benzylic protons), 3.2 - 3.6 (1H, >CH-O-), 3.75 (3H, s, OCH_3); $[\alpha]_D$ + 41°].[8,9,10]



9 X=Y=H

10 X + Y=$S(CH_2)_3S$

11 X=CO_2H

12 X=CH_2OH

13 X=$CH_2SeC_6H_4NO_2$-o

14 X=CHO

15 X=CH_2OH

16 X=OH

17 X=OTs

18 X=I

It is known that an intramolecular cycloaddition of o-quinodimethane with olefin system proceeds stereoselectively to form 1,3,5(10)-tridehydroestrane system under a control by the configuration of substituents on cyclopentane ring.[4,5,11,12] Since we used the optically active starting material (2) whose array on cyclopentane ring is the same with that of estradiol (8), the absolute configuration of our product (6) should be identical with that of natural one. Debutylation (5N HCl, dioxane; 7 h) of 6 gave 3-O-methylestradiol (7) as colorless needles [mp 96 - 97°; (lit.[13] mp 98°); 84 %; ir 3620 cm^{-1}; $[\alpha]_D$ + 69.24°; optical purity 96.8 %, i.e., l : d = 98.4 : 1.6][8,9] which is identical with the sample [mp 96 - 98°] derived from natural estradiol in all aspects except the value of optical rotation. Finally, treatment of 7 with pyridine hydrochloride at 210° for 30 min afforded estradiol (8) [mp 178 - 179°; 80.9 %], not differentiated from natural estradiol in ir (KBr) and NMR spectra. Thus, we have succeeded in the asymmetric total synthesis of estradiol.

Since 1-cyano-4-methoxybenzocyclobutene as a starting material was obtained from m-methoxybenzaldehyde in 31.58 % yield and final estradiol was synthesized from the above compound in 21.85 % yield, a total synthesis has been accomplished from m-methoxybenzaldehyde in 6.9 % yield.

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7 Elemental analytical data in excellent accord with theory were obtained for this substance.

8 The ir and NMR spectra were in agreement with the assigned structure.

9 Rotations were determined with JASCO-PIP-SL automatic polarimeter at 20°C in chloroform.

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