A Formal Regio- and Stereoselective Total Synthesis of Estrone. A Convenient Synthesis of *D*-Homoestrone

Sir:

The synthesis of estrone (**24**) has held a special fascination for organic chemists, and many types of approaches have been reported toward this natural sex hormone.[1] In the last decade, interest has focused on developing asymmetric syntheses of estrone and related compounds.[2-4]

In connection with our interest[5,6] in the synthetic development of cycloaddition of electrocyclic reaction[7] starting from *o*-quinodimethanes based on benzocyclobutenes,[8] we investigated a new synthesis of estrone (**24**) through *O*-methyl-*D*-homoestrone (**22**) via the intramolecular cycloaddition reaction **20** → **22**. The present communication reports a synthesis of *D*-homoestrone (**23**), which constitutes a formal total synthesis of estrone (**24**).

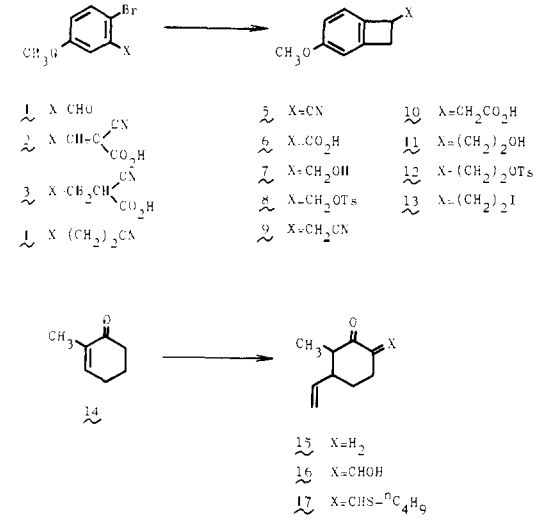
2-Bromo-5-methoxybenzaldehyde (**1**) was subjected to Knoevenagel reaction[9] with cyanoacetic acid to give cinnamic acid **2** (mp 227–228°; 85.3%),[10,11] which was reduced ($NaBH_4$, aqueous $NaHCO_3$)[12] to hydrocinnamic acid **3** (mp 111–112°; 66.2%).[10,11] Decarboxylation[13] of **3** (DMA; 170–180°) afforded phenylpropiononitrile (**4**) (bp 158–160° (5 mmHg); 76%),[10,11] which was cyclized (xs $NaNH_2$, liquid NH_3)[14] to furnish benzocyclobutene (**5**) (mp 89–92°; 64.5%).[10,11] Hydrolysis[15] of **5** (KOH) yielded carboxylic acid **6** (mp 85–86°; 80.5%),[10,11] whose reduction ($LiAlH_4$), followed by tosylation (TsCl, pyridine) of alcohol **7** (oil; *m/e* 164 (M^+)),[11] gave tosylate **8** (mp 60–63°; 76%).[10,11] Cyanation (NaCN, Me_2SO)[16] of **8**, followed by basic hydrolysis[15] of nitrile **9** (oil; *m/e* 173 (M^+)),[11] yielded carboxylic acid **10** (mp 62–65°; 83%),[10,11] which on reduction ($LiAlH_4$) and then tosylation of alcohol **11** (oil; *m/e* 178 (M^+))[11] gave tosylate **12** (mp 61–64°; 44%).[10,11] The tosylate **12** was converted (NaI, Me_2CO) to iodide **13** (yellow oil; 92%; *m/e* 288 (M^+)).[11]

On the other hand, 1,4-addition[17] of vinylmagnesium bromide to 2-methylcyclohexenone (**14**) (CuI, THF; −78°) gave 3-vinylcyclohexanone (**15**) (bp 63–65° (4 mmHg); 66%; *m/e* 138 (M^+)),[11] which was characterized as 6-benzylidene derivative (mp 70–72°; *m/e* 226 (M^+)).[10,11] Formylation (HCO_2Et, NaH, benzene) of **15** gave 6-hydroxymethylene derivative **16**, which was converted (*n*-BuSH, TsOH, benzene)[18] into 6-*n*-butylthiomethylenecyclohexanone (**17**) (bp 155–160° (5 mmHg); 62%; *m/e* 238 (M^+)).[10,11]

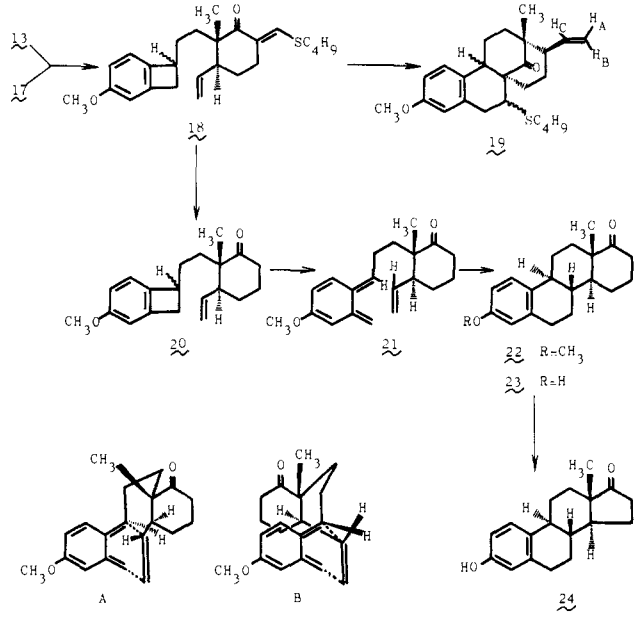
Condensation (*t*-BuOK, *t*-BuOH; 20°, 16 h) of the two components **13** and **17** afforded the 1,1-disubstituted cyclohexanone **18**[25] (oil; 16%, not optimized; NMR (CCl_4) 0.95 (3 H, s, CH_3), 5.0 (dd, J = 2 and 17 Hz), 5.03 (dd, J = 2 and 8.5 Hz), 5.75 (m, J = 8.5 and 17 Hz); *m/e* 398 (M^+)).[10,11] Heating[19] **18** in *o*-dichlorobenzene at 180° overnight gave the cyclized product **19** (viscous syrup; *m/e* 398 (M^+); ir ($CHCl_3$) 1705 cm^{-1}; NMR (CCl_4) 4.90 (1 H, dd, J = 2 and 17 Hz, H_A), 4.95 (1 H, dd, J = 2 and 10 Hz, H_B), 5.73 (1 H, m, J = 10 and 17 Hz, H_C)).[10,11] The appearance of the vinyl protons of **19** at a higher field than those of **18** suggested that the relative configuration between the 2-methyl and the 3-vinyl groups would be cis because the vinyl group in **19** was located over the carbonyl group in the cis, based on a consideration of the Dreiding model. Hydrolysis (KOH, diethylene glycol; 100°)[18] of **18** afforded the key intermediate **20** (oil; *m/e* 298 (M^+); ir ($CHCl_3$) 1685 cm^{-1}; NMR (CCl_4) 0.96 (3 H, s), 3.70 (3 H, s); 44.5%, not optimized).[10,11] This compound transformed smoothly in boiling *o*-dichlorobenzene[19] for 4 h to the crystalline *O*-methyl-*D*-homoestrone (**22**) (mp 160–162° (lit., mp 155–157°,[20] mp 158–160°,[21] mp 162–163°[21]); *m/e* 298 (M^+); ir 1690 cm^{-1}; NMR (CCl_4), 1.08 (3 H, s), 3.69 (3 H, s), 6.50 (1 H, d, J = 2 Hz, H_4), 6.57 (1 H, dd, J = 2 and 8 Hz, H_3), 7.10 (1 H, d, J = 8 Hz, H_1); 95% yield),[10,11] which displayed identical ir ($CHCl_3$) and NMR (CCl_4) spectra as an authentic sample prepared from natural estrone.[22] The stereocontrolled formation of **22** can be explained as follows. The four-membered ring in **20** opens preferentially to form the sterically favored *E*-oriented *o*-quinodimethane **21**,[19] whose synchronous cycloaddition proceeds regiospecifically through the more stable exo transition state A rather than endo state B which has steric repulsion between the aromatic and the cyclohexanone ring. Demethylation (pyridine·HCl)[20] of **22** gave *D*-homoestrone (**23**) (mp 218–222° (lit.,[4] mp 220–223°)]. *O*-Methyl-*D*-homoestrone (**22**) has previously been correlated to estrone **24**,[20,21,23] so this work constitutes a total synthesis of estrone.

Our synthetic method of *D*-homoestrone provides a new approach based on an effective stereospecific cycloaddition reaction and has a high possibility for further development.

Scheme I



Scheme II



References and Notes

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(10) Elemental analytical data in excellent accord with theory were obtained for this substance.
(11) The ir and NMR spectra were in agreement with the assigned structure.
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(24) Communications concerning this paper should be directed to Professor T. Kametani.
(25) All the compounds in the synthetic sequence are racemic. To clarify the stereochemical presentation, only one enantiomer is depicted.

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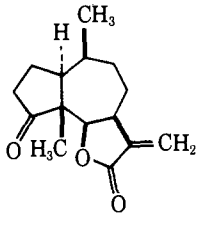
The Total Synthesis of (±)-Damsin

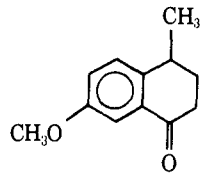
Sir:

The cytotoxic[1] compound damsin (**1**) is a representative[2] of the pseudoguaianolide family of sesquiterpenes which contains more than 50 known members.[3] Although several reports have recently appeared concerning synthetic approaches to the pseudoguaianolide sesquiterpenes,[4] no synthetic entry to this group of compounds has yet been described. We now wish to report the first total synthesis of (±)-damsin (**1**).

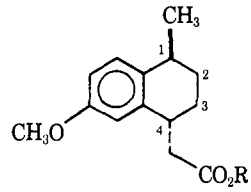


1

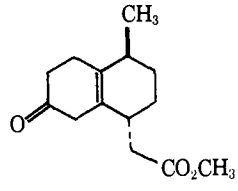
The Reformatsky reaction of 4-methyl-7-methoxytetralone (**2**)[5] with ethyl bromoacetate (zinc, 1:1 ether–benzene, reflux, 2.5 h) followed by hydrogenolysis in ethanol over 5% palladium on carbon gave an 88% yield of a single ester **3a**,[6] bp 145° (0.5 mm). The stereochemistry of **3a** follows from the observation that the lanthanide shift reagent Eu(fod)$_3$ preferentially associates with the carboethoxy group in carbon tetrachloride solution and causes a downfield shift in the NMR which is 12.7% greater for the C-1 hydrogen signal than for that of the C-1 methyl group. Saponification of **3a** with 10% ethanolic potassium hydroxide then afforded the corresponding acid **3b**,[6] mp 81–82.5°. Reduction of **3b** with lithium and liquid ammonia in the presence of *tert*-butyl alcohol and tetrahydrofuran, followed by treatment with aqueous oxalic acid and esterification with ethereal diazomethane, afforded a quantitative yield of β,γ-unsaturated ketone **4**,[6] bp 137° (0.6 mm).



2

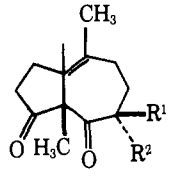


3a, R = C_2H_5
b, R = H

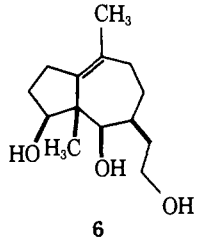


4

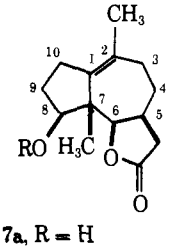
Ozonolysis of **4** at −86° in 1:1 methanol–methylene chloride followed by a reductive workup with trimethyl phosphite and a subsequent alkylation with methyl iodide (potassium carbonate, acetone, 4 hr reflux) afforded in 63% yield a 2:1 mixture of **5a**,[6] mp 87–89.5°, and **5b**,[6] mp 139–140°, which could be separated by a combination of column chromatography (silica gel) and fractional crystallization. Reduction of **5a** with sodium borohydride in methanol at 0° gave triol **6**,[6] mp 109.5–111.5°, in 62% yield. Catalytic oxidation[7] of **6** over platinum (oxygen gas, aqueous acetone, 57°, 5 h) then afforded a 96% yield of hydroxy lactone **7a** which was characterized as phenylurethane **7b**, mp 152–153°. The stereochemistry of **7a** at C-6, C-7, and C-8 follows from the fact that a nuclear Overhauser effect could not be observed in the NMR spectrum for the C-6 and C-8 hydrogens upon saturation of the C-7 methyl signal. In contrast, a NOE of 7 and 11% was observed for the C-6 and C-8 hydrogens, respectively, of the isomeric hydroxy lactone **8**,[6] mp 114–116°, which was obtained directly by reduction of **5b** with sodium borohydride in methanol at 0°. Lactone **7a** could not, however, be obtained directly by reduction of **5a** with sodium borohydride.



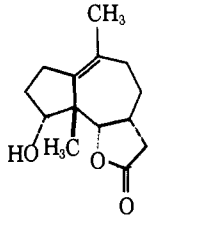
5a, $R^1 = CH_2CO_2CH_3$; R^2 = H
b, R^1 = H; $R^2 = CH_2CO_2CH_3$



6



7a, R = H
b, R = $CONHC_6H_5$



8

Catalytic hydrogenation of **7a** in ethanol over 5% palladium on carbon followed by oxidation with Jones reagent[8] gave a 46% yield of ketone **9**: mp 112–113.5°; ir (CCl_4) 1746, 1783 cm^{-1}; NMR (CCl_4) δ 1.08 (d, 3 H, J = 6.5 Hz), 1.18 (s, 3 H), 4.55 (d, 1 H, J = 6.4 Hz); mass spectrum m/e 236 (M^+). Ketone **9** was then converted to the corresponding ketal **10** (ethylene glycol, *p*-toluenesulfonic acid catalyst, benzene, 2.5 h