When this occurred, the pH of the dilute solutions was adjusted using microliter amounts of 1 *N* NaOH or 1 *N* HCl. pH readings were generally taken after each run and agreement with the initial reading was usually ±0.03 pH units. Differences between pH readings of the buffer solutions used for a single-buffer plot were usually ±0.03. pD readings were taken as pH meter reading +0.4.[14]

Most reactions were followed through at least 3 half-lives and showed good first-order behavior. Rate constants for these reactions were calculated on a Wang 700 programmable computer using a nonlinear regression analysis program. For some of the slower reactions, the reaction was followed to about 2% completion and the rate constant was determined from the known value of the total absorbance change for the complete reaction.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We are also grateful to Dr. C. E. Stauffer for sending us his original data and samples used in his work.

Supplementary Material Available. Data of imidazole-catalyzed hydrolysis of *p*-nitro-2,2,2-trifluoroacetanilide will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-75-377.

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(9) We used samples of both these anilides supplied to us by Stauffer as well as a sample of trifluoroacetanilide synthesized by us.
(10) Our rate constants for the hydrolysis reaction agree well with those obtained by Stauffer.[4]
(11) A recent claim[8] that tetrahedral intermediates accumulate during the alkaline hydrolysis of anilides has also been shown to be incorrect.[12]
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Bis Annelations *via* 6-Methyl-2-vinylpyridine.[1a-c] An Efficient Synthesis of *dl-D*-Homoestrone

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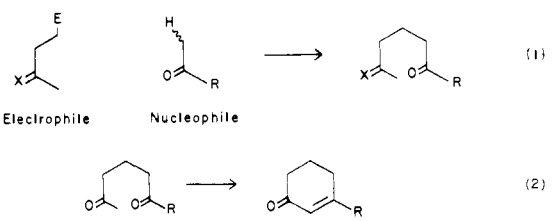
Abstract: The synthetic equivalence of 6-methyl-2-vinylpyridine with 3-vinylcyclohex-2-en-1-one has been demonstrated. The vinylpicoline is attached at the position α to a ketone by Michael addition. The cyclohex-2-en-1-one system bearing the substituent RCH_2 at the 3-position is elaborated from the 2-picoline bearing the substituent RCH_2 at the 6-position by a sequence involving metal–ammonia reduction, hydrolysis, and aldolization. An efficient conversion of the Wieland–Miescher ketone to *dl-D*-homoestrone, *via* this strategy is described.

The synthetic logic inherent in the methyl vinyl ketone (MVK) approach to the construction of cyclohexenones[2-4] has found extensive application in the synthesis of polycyclic natural products. While a wide assortment of variations has been introduced into the framework of this strategy, such annelations are characterized by two stages. The first involves the merger of an enolate (or enol) nucleophile with the electrophilic terminus (E) of an annelating agent. The agent is so constructed that the carbon-bearing function X is transformable to a ketone. In the final stage, a 1,5-hexanedione system undergoes intramolecular aldolization. In this cyclization, the nucleophilic enolate (or enol) is derived from the annelating agent, while the receptor carbonyl group arises from what was originally the nucleophile.

The modifications have dealt primarily with variations in the nature of the electrophilic terminus and with new methods for unraveling the 1,5-hexanedione required for cyclization. The researches of the Stork school[6a-d] have been particularly instrumental in expanding the feasibility of cyclohexenone annelations through a series of ingenious "oxobutyl" equivalents.



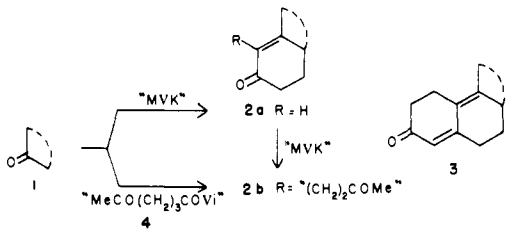
(1)

(2)

Another important advance in cyclohexenone syntheses arises from building into the annelating agent a substitution mode such that the α carbon of the enone, produced upon cyclization, emerges in a constructively functionalized form. The use of ethyl vinyl ketone,[4a,7,8] or its equivalent, in place of methyl vinyl ketone represents an example of this type of strategy. The Wenkert syntheses of the resin acids

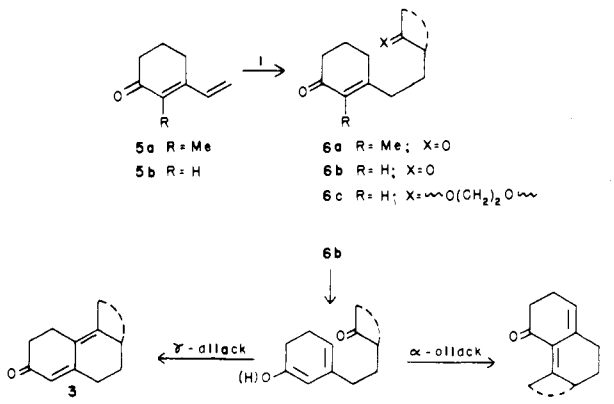
and valeranone[9a,b] and the Roussel synthesis of steroids[4c] involve steps which are illustrative of more complex functionalization schemes.

A special but important instance where it is desirable to produce α-substituted cyclohexenones arises when the objective is to use this functionality to elaborate still another cyclohexenone. The goal represented by the transformation of structure **1** to **3** is termed bis annelation. In principle, the problem of bis annelation may be approached from the standpoint of two successive cyclohexenone annelations.[7,8] Schematically this involves the sequence **1** → **2a** → **2b** → **3**. It is recognized that the methyl vinyl ketone equivalent ("MVK") used in going from **1** to **2a** need not be the one employed in going from **2a** to **2b**.



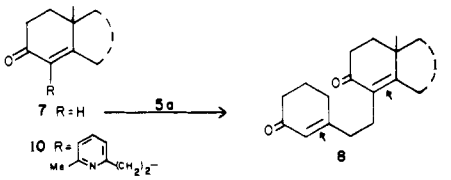
To circumvent the need for a separate conversion of **2a** to **2b**, a bis annelating agent, **4**[10,11] may be useful. System **4**, denoted as "$MeCO(CH_2)_3COVi$", corresponds to a synthetic equivalent of oct-7-ene-2,6-dione. Thus, it allows for the direct conversion of **1** to **2b**. Examples of bis annelating agents have been reported by Stork[6c,12] and by Ireland.[13]

Another specific example of **4** is encountered in the use of 3-vinylcyclohexenones. These systems constitute internally cyclized versions of the generalized annelating agent, **4**. Annelation commences with an extended (1,6) Michael reaction. The adduct **6** so produced is converted to the desired hexalone **3** by vinylogous aldolization. This approach was first reduced to practice by Eschenmoser and coworkers[14] using **5a** R = Me.[15] It will be noted that in this case, the mode of cyclodehydration of intermediate adduct **6a**, involving the γ carbon of the dienol as the nucleophile, is defined by the substitution at the α carbon. The alternative mode, utilizing the α carbon of the dienol as the nucleophile, cannot be consummated by a β-elimination reaction. Subsequent to the preliminary account of our studies in this area,[1a] the utilization of **5b**[16] was reported. In consonance with our observations (*vide infra*), it was found that even in the *a priori* ambiguous case of **6b**, aldolization occurs *via* the γ carbon.



Nevertheless, the direct use of systems such as **5a** or **5b** appeared to us to constitute an unsatisfactory general solution to the problem of bis annelation. Thus, the preparations of such compounds are rather cumbersome.[14-16] Furthermore, the only reports of successful 1,6-additions to 3-vinylcyclohexenones involve the use of β-dicarbonyl systems as nucleophiles. Hence, the application of **5** to the bis annelation of simple ketones is questionable.

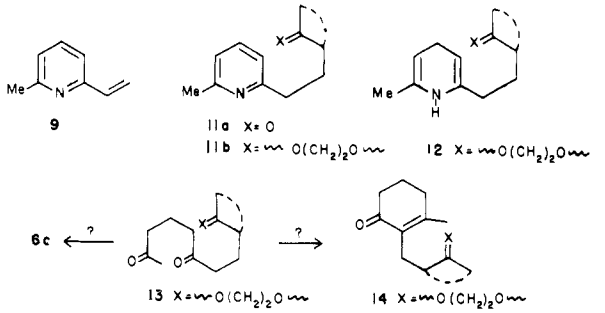
Furthermore, a fundamental difficulty arises when the possibilities of using 3-vinylcyclohexenones as bis annelating agents for enones such as **7** are examined. The enone system might, in principle, be used to direct alkylation by dienone **5** in the desired, α, sense. A system such as **8** would be produced. The problems of executing selective reduction (catalytic or chemical) on the bicyclic enone in the presence of the pendant cyclohexenone (see arrows) could well prove unmanageable.[17,18]



With these considerations in mind, it appeared that 6-methyl-2-vinylpyridine (**9**) has many commendable features as a bis annelating agent. It is preparable, in bulk, from the tar base 2,6-lutidine by hydroxymethylation and dehydration.[19,20] Furthermore, Michael additions of nucleophiles,[21] including enolates derived from simple ketones,[22] are known for 2- and 4-vinylpyridines. Hence, one could readily envision the preparation of α-picolylethylated ketones of the type **11a** including, in principle, α-picolylethylated enones such as **10**. No difficulty in the conversion of **10** → **11** *via* catalytic reduction would be expected.

The unraveling sequence was formulated with a major reliance on a Birch-type reduction of the pyridine.[23-25] The dihydro product **12**,[26] after hydrolysis of its two enamine linkages, would give rise to the 1,5-diketone **13**. Cyclization of **13** could afford **6c** which after deketalization would lead to **6b**. Vinylogous aldolization might then lead to the desired **3**. The ketal protection was deemed to be necessary to sustain the required keto level functionality through the Birch reduction. It appeared most convenient to introduce the ketal at the stage of **11b**.

The requirement that the postulated diketone **13** cyclize so as to produce a trisubstituted cyclohexenone of the type **6c** represented, at the outset, the element of the proposal most open to question. It is evident that this mode of cyclization of **13** must compete, *a priori*, with an alternative mode which would afford **14**. While we have found only one instance, uncomplicated by other unsymmetrical substitutions, where this ambiguity was encountered in a cyclohexenone cyclization,[27] this precedent suggested that the tetrasubstituted product such as **14** would be expected. In the possibly related situation of cyclopentenone formation *via* aldolization of diketones of the type $MeCO(CH_2)_2COCH_2R$, there is a long line of precedents[28,29] all pointing in the direction of tetrasubstituted products.



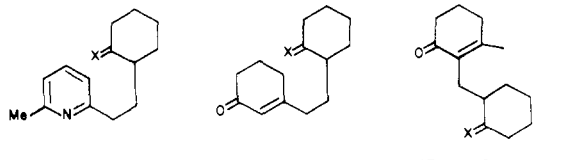
Discussion of Results

Model Studies with Cyclohexanone. To confront the ques-

tions of the mode of aldolization of systems such as **13** and the ambiguities, discussed above, associated with the cyclization of **6b**, we first undertook the annelation of cyclohexanone *via* MVP (**9**). Picolylethylation was achieved through the enamine method which we had adapted to this problem some years ago.[30] Upon hydrolysis, compound **15a** was obtained in 54% yield and converted (75%) to its dioxalane derivative **15b**. Our approach at the outset was to avoid attempted isolation of intermediates such as **12**[26] and even **13**. Furthermore, the ketal protection was to be maintained through the first aldolization (*cf.* **13** → **6c**).

Addition of 2.2 equiv of sodium to a solution of **15b** in liquid ammonia–ether–ethanol was followed by evaporation of the volatiles under a stream of nitrogen. The residue so produced was treated with aqueous ethanolic sodium hydroxide. The ketal blocking group was then removed, and the reaction mixture was separated into basic and neutral components. From the acid-soluble fraction, 24% of the starting material in the form of ketone **15a** was recovered. Chromatography of the neutral fraction afforded two isomeric enediones. The major compound, 52% isolated yield, is clearly the desired **16a**. The minor component, 14% isolated yield, is the tetrasubstituted cyclohexenone **17a**. The structures of both compounds follow unambiguously from their spectral properties (see Experimental Section). The ratio of isolated yields agrees quite closely with the 3.8:1 ratio of glc (uncalibrated) peak areas. The column chromatographic separation is clean cut with no complicating mixture fractions; thus the ratio of the isomers isolated in this way is an accurate reflection of their relative abundance.

The ratio **16a:17a** stands in contrast to predictions based on analogies relating to cyclenone formation by base-catalyzed closure of systems of the type $MeCO(CH_2)_n$-$COCH_2R$. These analogies point in the direction of tetrasubstituted enone.[27-29] Therefore, it was important to ascertain that the enones were actually formed during the base-induced aldolization rather than the acid-catalyzed stage of the reaction sequence. Accordingly, compound **15b** was treated with sodium–ammonia–ethanol and the dihydro product,[26] so produced, was exposed to aqueous ethanolic sodium hydroxide. In this fashion, the enoneketals **16b** and **17b** were isolated in a ratio of 3.8:1 in a combined yield of 72%. Therefore, the enones are indeed being elaborated in base. The reproducibility of this finding is seen in the fact that in a large number of runs starting with **15b**, where the ratio of enones was established either by analytical glc, isolation by preparative tlc, or isolation by column chromatography of either the ketoenones (**16a:17a**) or the ketalenones (**16b:17b**), the ratio of trisubstituted cyclenones varied only from 3.3 to 3.8:1.



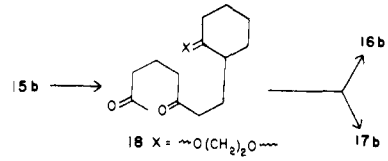
Since this distribution is contrary to precedents,[27-29] the formulation of pyridine (**11**) → dihydropyridine (**12**) → diketone (**13**) → cyclenone (**14**) to the case at hand was subjected to closer scrutiny. In particular, the viability of diketoneketal **18** as an actual intermediate in the formation of enones **16** and **17** was tested.

Toward this objective, compound **15b** was treated with sodium–ammonia–ethanol, and the dihydropyridine[26] (1,4- or 3,4-) assumed to be present was hydrolyzed under nearly neutral conditions with a view toward avoiding premature aldolization and deketalization. It is important to postpone aldolization till the conditions could be arranged to simulate those used in the conversion of **15b** to enones **16a** and **17a**. The ketal linkage was maintained so that the issue of aldolization would be focused on the acyclic ketones only.

In practice, it was possible to isolate diketoneketal **18** in 37% yield from **15b**. While obtained as an oil, its spectra and tlc behavior suggested it to be homogeneous. It will be noted that the mere isolation of **18** does not, *per se*, define its role as the sole product-determining intermediate in the production of enones **16b** and **17b**. Diketone **18** was isolated in substantially lower (37 *vs.* 72%) yield than was realized for enones **16b** and **17b**. Furthermore, the conditions of its isolation differed from those used in the generation of these enones.

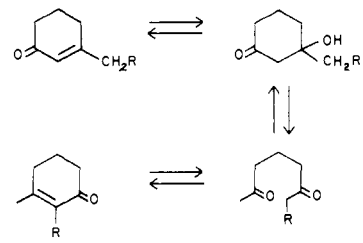
Treatment of **18** with aqueous ethanolic sodium hydroxide at room temperature gave, in 95% combined yield after chromatography, a 3.8:1 ratio of **16b:17b**. *To our knowledge, this result constitutes the first demonstration of preferential formation of trisubstituted cyclenone relative to its tetrasubstituted isomer from an internal aldolization reaction.*

The precise structural factors which are responsible for this favorable result have not, as yet, been determined. Preliminary studies[1b,c] have suggested that the formation of tetrasubstituted product (*cf.* **14**) may be discouraged, at least at the kinetic level, by the steric congestion between the substituents at the 2- and 3-positions of the cyclohexenone. Indeed, it has been found[1c] that the room temperature aldolization of 2,6-octanedione affords a 19:1 ratio of 2,3-dimethylcyclohexenone:3-ethylcyclohexenone, a result very much in keeping with the trend found in cyclopentenone formation.



While the distribution of enones (trisubstituted predominant over tetrasubstituted) was quite favorable for our synthetic purposes, the effects of changing reaction conditions was examined in greater detail. Diketone **18** was subjected to cyclodehydration using aqueous ethanolic sodium hydroxide, as before, except at reflux temperature. An aliquot of the reaction mixture was removed after 15 min. Glc analysis (uncalibrated) revealed a ratio **16b:17b** ~ 3.8:1. Thus no obvious temperature effect on the distribution of products at the kinetic level is observed. However, when heating under reflux was continued for 50 hr, ketalenones **16b:17b** were now isolated in a 1:3.4 ratio (combined yield = 80%).

This result is most readily interpreted by invoking the well-known reversibility of the aldol condensation.[28,31] The route shown below is precedented[32] for the interconversion of cyclohexenones.



Apparently under the particular reaction conditions, the tetrasubstituted isomer is more stable. This transformation was demonstrated more convincingly by starting with pure

ketalenone **16b**. When this substance was heated under the same conditions in aqueous ethanolic alkali, a 1:3.4 mixture of **16b**:**17b** was isolated (80% yield).

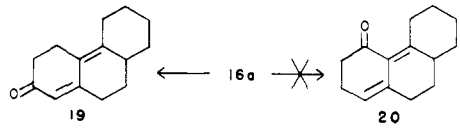
In the light of this isomerization reaction, it was not surprising to find that the reduction-cyclization route starting with **15b** could be modified so as to produce **17b** as the major product. Thus after treatment of **15b** with sodium-ammonia-ethanol, the residue produced upon removal of the volatiles was treated with aqueous ethanolic alkali under reflux for 60 hr. Work-up and chromatography gave a 15% yield of **16b** and a 49% yield of **17b**.

We shall return briefly to the question of aldolization of diketones leading to cyclohexenones for the case of **29**. For the moment, it is seen that considerable control can be exercised over the ratio of cyclohexenones **16b** and **17b** *via* temperature adjustments. Of course, the purpose of bis annelation is well served by bypassing diketones **18** as well as the ketalenones **16b** and **17b** and proceeding directly (after chromatography) to **16a** in 52% yield as described above.

The success of the bis annelation scheme now depended on the direction of vinylogous aldolization of seco system **16a**. In principle, two types of cyclization may be envisioned for this compound. Cyclization toward the γ carbon produces, after β elimination, an extended dienone (*cf.* **19**). Cyclization toward the α carbon followed by β elimination (possible only when R = H) gives a cross conjugated product (*cf.* **20**).[33,34]

It was of considerable encouragement to find that cyclodehydration of enone **16a** using *p*-toluenesulfonic acid-acetic acid (TsOH-AcOH) gave the crystalline extended dienone **19** in 84% yield.[35] The structure of **19** follows unequivocally from its spectral properties and combustion analysis (see Experimental Section). Examination of the crude reaction mixture, from which **19** was obtained in crystalline form, failed to disclose the presence of any other related products in terms of R_f. The purpose of the chromatography (see Experimental Section) was to remove small amounts of impurities which had no tlc mobility in a solvent system (3:2 benzene:ethyl acetate) where the R_f of **19** is 0.47. While the point cannot be made with complete rigor, it appears to us that in the conversion of **16a** to **19**, there is no competition from formation of **20** nor from any obviously derivable transformation product of **20**.

The unidirectionality in the internal aldolization of **16a** allowed for a modification in the procedure by which **15b** is converted to **19**. Thus, after Birch reduction of **15b** followed by hydrolysis, cyclization, and deketalization, the mixture of **16a** and **17a** so produced is treated directly with TsOH-AcOH to give crystalline **19** in 50% yield after chromatography and crystallization.

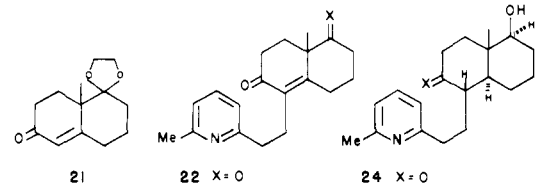


A Total Synthesis of *dl-D*-Homoestrone. The successful bis annelation of cyclohexanone included two aldolization precedents which augured well for the total synthesis of steroids. With the purpose of studying the utility of the bis-annelation reaction, we defined as our objective the total synthesis of *dl-D*-homoestrone (**31**). It was already known[36] that **31** could be obtained from dienedione **30**.[37] It will be noted that **30** is the bis-annelation product of the trans-dihydro product derivable from the Wieland-Miescher ketone.[38] Our approach to the synthesis involved exploiting the enone functionality of the Wieland-Miescher system to direct picolylethylation in the desired sense. With this accomplished, the double bond would be removed by catalytic reduction.[39] In the light of the known lability of the Wieland-Miescher ketone toward cleavage[40] of its vinylogous β-dicarbonyl system, protection of the saturated ketone was required. Monoketal **21** was thus the starting material.[41a,b]

MVP was smoothly appended to **21** by Michael addition. The extended dienolate required for reaction was generated from **21** through the action of potassium *tert*-amyl oxide-*tert*-amyl alcohol. The ketal was removed as part of the work-up procedure thus affording **22**. That coupling had taken place is assured by the mass spectrum of **22**, *m/e* (parent) 297. The presence of conjugated enone functionality is supported by its infrared spectrum (λ_{max} ($CHCl_3$) 1709, 1663, 1595, 1582 cm^{-1}). The absence of a signal characteristic of an α proton of an enone (τ 4.0-4.4) establishes that alkylation had indeed occurred in the α position. *To our knowledge, the conversion of* **21** *to* **22** *represents the first instance of alkylation of a conjugated enone with a vinylpyridine. The yield of* **22** *is 80%.*

Through this alkylation, all 19 carbon atoms required for the final objectives, **30** and **31**, were properly joined. Preparations for the crucial reductive cyclization commenced with selective sodium borohydride reduction of enedione **22**, thereby affording the crystalline enone alcohol **23**, mp 103-104°, in 80% yield from **21**. The β stereochemistry for the alcohol is formulated on the basis of precedent.[42]

Similarly abundant precedent[43] supports the notion that catalytic reduction of the double bond of Δ^4-3-ketones bearing large alkyl substituents at C_4, such as is the case for **23**, leads predominantly to trans-fused decalones. Accordingly, compound **23** was subjected to hydrogenation over a 10% Pd/C catalyst in ethyl acetate containing a trace of triethylamine. The semicrystalline dihydro product **24**, thus generated, was subjected directly to acid-catalyzed ketalization using ethylene glycol-*p*-TsOH in toluene under reflux. After chromatography, the nicely crystalline hydroxyketal **25**, mp 128-130°, was obtained in 58% yield. While this disappointingly low yield might have been explained by postulating nonstereospecificity in the catalytic hydrogenation, the mother liquors from which **25** was obtained comprised only 10% of the reaction mixture. Analysis of this material by nmr indicates it to contain (*ca.* 50%) more of **25**. Hence, only a 5% loss may be ascribed to nonstereospecificity in the reduction. Unfortunately, we are unable to account for the major source (*ca.* 30%) of attrition *via* material which is not mobile under the conditions of chromatography.



Compound **25** was treated with sodium-ammonia-ethanol under conditions identical with those used for **15b**. The residue remaining after evaporation of the ammonia, was subjected to the action of aqueous ethanolic sodium hydroxide at room temperature. Deketalization as part of the work-up method gave neutral material in 93% yield. Though this neutral product was not subjected to further purification, its nmr spectrum and tlc properties showed the presence of only one product. The spectral properties (see Experimental Section) are completely consistent with structure **26** and inconsistent with structure **28**. Furthermore, Jones oxidation of **26** afforded the crystalline enedione **27**, mp 101-102°, in 84% yield (*i.e.*, 78% from **25**).

These results differ in two important respects from the

results encountered in the reductive cyclization of the model ketal **15b**. First, the yield (93%) of the primary product, **26** arising from **25**, is significantly higher than the combined yields (72%) of **16b** and **17b**. We believe this favorable difference to be a consequence of superior solubility properties arising from the hydroxyl group of **25**.

Another important difference is seen in the fact that for the case of **25**, the only enone produced is **26**, whereas in the case of **15b**, a mixture (**16b** and **17b**) is obtained (albeit the major product, **16b** is of the same type as **26**). At no stage was there any indication for the formation of tetrasubstituted enone **28**. There is every reason to believe that were this compound present to the extent of *ca.* 5% in a mixture with **26**, it would have been detected by nmr analysis (vinylic methyl signal in the region of $\delta \sim 2$–2.2 ppm (*cf.* **17a**). Furthermore, none of the steps taken in the work-up or the isolation of **26** was such as to lead to the selective loss of **28** were it present.

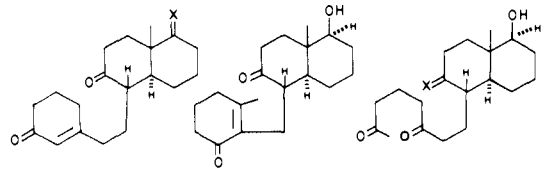
As in the case of **15b**, it was thus of interest to see whether diketoneketal **29** constitutes a viable intermediate in the production of **26**. Accordingly, ketal **25** was reduced with sodium–ammonia–ethanol. The residue from evaporation of the ammonia was treated with dilute ethanolic sodium hydroxide at room temperature for 5 min. In this manner, the diketoneketal **29** was obtained in 43%[44] yield after preparative tlc purification.

Treatment of **29** with aqueous ethanolic sodium hydroxide was followed by acidic deketalization. On the basis of tlc and nmr analysis, it is concluded that the product of this reaction is **26**. No evidence was encountered for the formation of **28**. Its presence in trace quantities cannot be ruled out since we did not have an authentic sample of this compound available. It will be recognized that this result stands in contrast to the result obtained in the case of diketoneketal **18** where a mixture (**16b** and **17b**) was obtained.

An even more striking contrast was observed when **29** was subjected to cyclodehydration at reflux temperature for 17 hr. Again, after acidic deketalization, compound **26** was the only detectable product by tlc and nmr analysis. It will be recalled that in the case of diketone **18** these conditions led predominantly (3.4:1) to the tetrasubstituted product **17b** relative to the trisubstituted isomer **16b** presumably through enone equilibration. The conversion of enone **16b** to a mixture of **16b** and **17b** in which the latter predominates was, in fact, demonstrated. In the case at hand, clearly no such isomerization occurs for the ketal precursor of **26**.

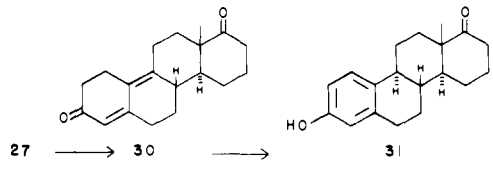
It must be emphasized that the failure to achieve isomerization may reflect the need for different reaction conditions for equilibration. One cannot conclude with certainty that in this series the trisubstituted enone is actually the thermodynamically preferred product.

Nevertheless, the results speak for the unidirectional formation of the trisubstituted isomer at least at the kinetic level. The contrast between this situation and that for isomers **16b** and **17b** may be the consequence of even more serious steric crowding in tetrasubstituted cyclohexenone **28** than is the case for **17b**. A systematic study of those structural factors which are influential at the kinetic level in cyclohexenone formation and which influence the thermodynamic stability of the isomeric cyclohexenones is in progress.



The total synthesis of *dl-D*-homoestrone was completed in two steps from the *seco* system **27**. The tetracyclic dienone **30** was obtained from **27** in 66% yield through the action of tosyl acid in acetic acid. The same reaction was executed in 44% yield,[1b] *via* the action of sodium methoxide–methanol. While these yields are not as good as those encountered in the case of **16a**, there was no indication of competition from α attack (*cf.* enol derived from **6b**).

The dienedione **30** was converted to *dl-D*-homoestrone (**31**) through the action of acetyl bromide–acetic anhydride[36] followed by saponification of the intermediate phenolic acetate. The yield for this final step is 82%. The overall yield of the *dl-D*-homoestrone (**31**) from the *dl*-monoketal **21** is 15%.[45] Further applications of this method of bis annelation will be reported shortly.



Experimental Section[46]

Preparation of 2-[2-(6-Methyl-2-pyridyl)ethyl]cyclohexanone (15a). A solution of 52 g (0.436 mol) of 6-methyl-2-vinylpyridine (**9**) and 133 g (0.88 mol) of 1-pyrrolidinocyclohexene in 100 ml of dry diethylcarbitol (bp 188°) was heated under reflux for 16 hr under a nitrogen atmosphere. After cooling, 50 ml of water was added, and the two-phase system was stirred for 2 hr at room temperature. To this was added 200 ml of 10% aqueous HCl, and the resulting mixture was extracted with 100 ml of ether. The acidic layer was made basic by cautious addition of excess solid potassium carbonate. This mixture was extracted three times with 100-ml portions of methylene chloride. After the mixture was dried, the solvent was concentrated at the water pump and the residue distilled from an oil-jacketed flask (0.1 mm). A major fraction, 51 g (54%), was collected from 103–105°: λ_{max} ($CHCl_3$) 1709, 1597, 1582 cm^{-1}; δ ($CDCl_3$) 7.33–7.63 (m, 1 H), 7.03–6.82 (m, 2 H), 2.94–1.1 (m, 16 H containing t $\sim$ 3 H at δ 2.81 and s $\sim$ 3 H at δ 2.48).

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.19; H, 9.00; N, 6.53.

Preparation of the Ethylene Ketal of 2[2-(6-Methyl-2-pyridyl)ethyl]cyclohexanone (15b). A solution of 20 g (0.094 mol) of ketone **15a**, 29.2 g (0.470 mol) of ethylene glycol, and 1.79 g (0.0094 mol) of *p*-TsOH in 100 ml of xylene was heated under reflux under N_2 in a flask equipped with a Dean-Stark trap. Aliquots of the reaction were checked for disappearance of the band (1709 cm^{-1}) due to the carbonyl group of **15a**. After disappearance of this peak, the solution was cooled and extracted with 2% sodium hydroxide. The xylene was distilled under reduced pressure and the residue distilled from an oil-jacketed flask (*ca.* 0.08 mm). A major fraction of **15b** (18.4 g; 75% yield) was collected from 115–122°: λ_{max} ($CHCl_3$) 1584 cm^{-1}; δ ($CDCl_3$) 7.48–7.20 (m, 1 H), 6.95–6.68 (m, 2 H), 3.82 (s, 4 H), 2.87–1.15 (m, 16 H containing t $\sim$ 2 H at δ 2.30 and s $\sim$ 3 H at δ 2.43).

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.54; H, 8.61; N, 5.48.

Reductive Cyclization of 15b. Formation of Enediones 16a and 17a. To a solution containing 1.48 g (5.67 mmol) of ketal **15b**, 1.03 g (22.4 mmol) of absolute ethanol, and 4.0 ml of anhydrous ether in 50 ml of dry liquid ammonia (freshly distilled from sodium) was slowly added 285 mg (12.32 g-atoms) of sodium metal. The solution was stirred for 15 min and the ammonia evaporated under a stream of nitrogen. To the residue was added 26 ml of ethanol followed by 13 ml of H_2O containing 560 mg of sodium hydroxide. This solution was stirred for 2.5 hr at room temperature. The reaction mixture was acidified with 10% aqueous HCl and stirred 20 min at room temperature. The reaction mixture was diluted with 10 ml of H_2O and extracted with five 20-ml portions of CH_2Cl_2. The organic extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvents afforded 823 mg of an oil. Chromatography on 100 g of silica gel using 3:1 hexane:ethyl acetate as the eluent af-

forded 167 mg (13.5%) of **17a** as an oil: λ_{max} ($CHCl_3$) 1703, 1652 cm^{-1}; λ_{max} (95% EtOH) 249 mμ (ε 7100); δ ($CDCl_3$) 1.1–3.0 (m, containing singlet at δ 2.02); *m/e* (P), 137, 111, 98.

An analytical sample was prepared using preparative glc on 10 ft × 0.5 in. 3% SE 30 on a Suppelcoport column at 180°.

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.22; H, 9.24.

After continuing elution with the same solvent system, compound **16a** (642 mg; 52%) was obtained as an oil: λ_{max} ($CHCl_3$), 1703, 1661, 1620 cm^{-1}; λ_{max} (95% EtOH) 234 mμ (ε 7200); δ ($CDCl_3$) 1.0–2.5 (m, 19 H), 5.67 (s, 1 H); *m/e* 220 (P) 125, 110, 94.

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.40; H, 9.20.

Neutralization of the acidic layer followed by extraction with methylene chloride and drying (Na_2SO_4) afforded pyridine ketal **15a**, 304 mg, 24%.

Reductive Cyclization of 15b. Formation of Enoneketals 16b and 17b. To a solution containing 1.22 g (4.67 mmol) of ketal **15b**, 8.59 mg (18.68 mmol) of absolute ethanol, and 4 ml of anhydrous ether in 50 ml of anhydrous liquid ammonia (freshly distilled from sodium) was added 236 mg (10.28 g-atoms) of a freshly cut sodium metal in small pieces. After the resulting solution was stirred for 15 min, the ammonia was evaporated in a stream of nitrogen. The residue was taken up in 18 ml of ethanol, and a solution of 476 mg (11.7 mmol) of NaOH in 9 ml of H_2O was added. After the resulting solution was stirred for 2.5 hr at room temperature, 10 ml of H_2O was added and the solution extracted with five 15-ml portions of CH_2Cl_2. The combined extracts were dried over anhydrous Na_2SO_4, and the solvent was removed to afford 1.16 g of an oil. Chromatography of the oil on 100 g of silica gel using 4:1 benzene:ethyl acetate as the eluent afforded 176 mg (14%) of ketal **17b** as an oil: λ_{max} ($CHCl_3$) 1645, 1607 cm^{-1}; λ_{max} (95% EtOH) 248 mμ (ε 7200); δ ($CDCl_3$) 1.2–2.9 (m, containing a singlet at δ 2.01), 3.90 (s, 4 H); *m/e* 264 (P) 154, 94.

An analytical sample was prepared using preparative glc on a 10 ft × 0.5 in. 3% SE 30 on a Suppelcoport column at 200°.

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.13. Found: C, 72.70; H, 9.13.

Continued elution with the same solvent system gave enoneketal **16b** (708 mg; 58%) as an oil: λ_{max} ($CHCl_3$) 1650, 1620 cm^{-1}; λ_{max} (95% EtOH) 235 mμ (ε 7200); δ ($CDCl_3$) 1.0–2.9 (m, 19 H), 3.88 (s, 4 H), 5.78 (s, 1 H); *m/e* 264 (P) 141 (base peak).

An analytical sample was prepared as described for **17b** above.

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.64; H, 9.16.

Reduction of Pyridine Ketal 15b. Cyclodehydration at Reflux Temperatures. Formation of 17b as the Major Product. To a solution containing 283.4 mg (1.05 mmol) of ketal **15b**, 198 mg (4.32 mmol) of absolute ethanol, and 1.0 ml of anhydrous ether in 10 ml of anhydrous liquid ammonia (freshly distilled from sodium) was added 55 mg (2.38 g-atoms) of sodium. After the solution was stirred 15 min, the ammonia was evaporated in a stream of nitrogen, the residue was taken up in 4 ml of ethanol, and a solution of 100 mg (2.5 mmol) of NaOH in 2 ml of H_2O was added. The resulting solution was refluxed for 60 hr under an atmosphere of nitrogen, cooled to room temperature, and diluted with 5 ml of H_2O. The mixture was extracted with four 5-ml portions of CH_2Cl_2, the organic layers were dried over anhydrous Na_2SO_4, and the solvents were removed to afford 278 mg of yellow oil. Chromatography of the oil on 15 g of silica gel using 4:1 benzene:ethyl acetate as the eluent afforded 138 mg (49%) of **17b**, 41.3 mg (14.5%) of **16b**, and 25.7 mg of the starting ketal **15b**.

Cyclodehydration of Diketoneketal 18. Formation of Enoneketals 16b (Major) and 17b (Minor). To a solution containing 47.3 mg (0.166 mmol) of dione **18** in 0.64 ml of EtOH was added a solution of 25 mg of NaOH in 0.30 ml of H_2O. The resulting solution was stirred for 2.5 hr at room temperature under an atmosphere of nitrogen. The reaction mixture was diluted with 2 ml of H_2O and the mixture extracted four times with 5-ml portions of CH_2Cl_2. The organic extracts were dried over anhydrous Na_2SO_4 and the solvents evaporated to yield 45 mg of oil. Chromatography on 5 g of silica gel using 4:1 benzene:ethyl acetate as the eluent afforded 9 mg (20%) of ketal **17b** and 34 mg (76%) of ketal **16b**.

Cyclodehydration of Dione 18 at Reflux. Formation of Enoneketals 16b (Minor) and 27b (Major). To a solution containing 33.3 mg (0.117 mmol) of **18** in 0.60 ml of EtOH was added 14.5 mg of NaOH in 0.30 ml of H_2O. The resulting solution was refluxed 50 hr under an atmosphere of nitrogen. After being cooled to room temperature, the reaction mixture was diluted with 2 ml of H_2O and extracted with four 3-ml portions of CH_2Cl_2. The combined extracts were dried over anhydrous Na_2SO_4 and the solvents evaporated to afford 31 mg of crude oil. Chromatography on 5 g of silica gel using 4:1 benzene:ethyl acetate as eluent afforded 19.2 mg (62%) of ketal **17b** and 5.6 mg (18%) of ketal **16b**.

Treatment of Enoneketal 16b with Aqueous Ethanolic Alkali under Reflux Formation of a Mixture of 16b and 17b. To a solution containing 105 mg (0.399 mmol) of ketal **16b** in 2 ml of ethanol was added a solution of 50 mg of NaOH in 1 ml of H_2O. The resulting solution was refluxed for 55 hr under an atmosphere of nitrogen. After the solution was cooled to room temperature, 3 ml of H_2O was added and the mixture extracted with four 5-ml portions of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, the solvents were removed, and the residue was chromatographed on 10 g of silica gel using 4:1 benzene:ethyl acetate as the eluent to afford 71 mg (68%) of **17b** and 21 mg (19%) of ketal **16b**.

Cyclodehydration of Enedione 16a. Formation of 2,3,4,5,6,7,8,9,10,14-Decahydrophenenthren-2-one (19). A solution containing 200 mg (0.909 mmol) of enedione **16a** and 75 mg of *p*-toluenesulfonic acid in 4 ml of glacial acetic acid under an atmosphere of nitrogen was heated for 25 min on a steam bath. After the solution was cooled to room temperature, 5 ml of H_2O was added and the resulting emulsion extracted with three 5-ml portions of CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, the solvents were removed, and the residue was chromatographed on 20 g of silica gel using 6:1 benzene:ethyl acetate as the eluent to afford 165 mg of an oil. Trituration with ether afforded 153 mg (84%) of **19**, mp 59–60°; mp of 2,4-DNP (95% EtOH) 176–177° [lit.[35] 175°; λ_{max} ($CHCl_3$) 1647, 1610 cm^{-1}; λ_{max} (95% EtOH) 303 mμ (ε 15,000); δ ($CDCl_3$) 1.2–3.0 (m, 17 H), 5.63 (s, 1 H); *m/e* 184 (P).

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.03; H, 8.49.

Conversion of 15b to 19 without Purification of Any Intermediates. To a solution containing 1.52 g (5.82 mmol) of ketal **15b**, 1.07 g (23.2 mmol) of absolute ethanol, and 4 ml of anhydrous ether in 50 ml of anhydrous liquid ammonia was added 294 mg (12.8 g-atoms) of Na metal. After the addition was complete, the solution was stirred for 15 min and the ammonia evaporated under a stream of nitrogen. The residue was taken up in 20 ml of ethanol, a solution of 582 mg (14.5 mmol) of NaOH in 10 ml of H_2O was added, and the resulting solution was stirred for 2.5 hr under an atmosphere of nitrogen at room temperature. The reaction mixture was acidified with 10% aqueous HCl and stirred for 20 min. To this was added 10 ml of H_2O, and the mixture was extracted with five 20-ml portions of CH_2Cl_2. The organic extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvents afforded 810 mg of an oil which was shown by analytical glc (10 ft, 2% Dexsil on Gas-chrom Q, 60–80 mesh; temperature programmed from 70 to 300° at 10°/min) to be a 3.8:1 mixture of enediones **16a**:**17a**. The crude product was taken up in 8 ml of glacial acetic acid. To this solution was added 400 mg of *p*-toluenesulfonic acid, and the reaction mixture was heated on a steam bath under a nitrogen atmosphere for 25 min. After addition of 5 ml of H_2O and extraction with 3 × 15 ml of CH_2Cl_2, the organic extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvents and chromatography on 50 g of silica gel using 6:1 benzene:ethyl acetate as the eluent afforded 193 mg of enedione **17a** and 554 mg (52%) of dienone **19**.

Picolylethylation of Enoneketal 21. Formation of Octalindione 22. To a solution containing 0.848 g (0.0216 g-atom) of potassium metal dissolved in 200 ml of dry *tert*-amyl alcohol (freshly distilled from sodium) was slowly added under nitrogen 4.8 g (0.0216 mol) of monoketal **21** in 50 ml of *tert*-amyl alcohol. After the solution was stirred for 0.5 hr, 5.02 g (0.0475 mol) of 6-methyl-2-vinylpyridine was added. The mixture was stirred at room temperature for 0.5 hr and then heated under reflux for 12 hr. After cooling to room temperature, the solution was acidified with 10% aqueous HCl and stirred for 1 hr. After neutralization with $NaHCO_3$, the mixture was extracted five times with 50-ml portions of CH_2Cl_2, and the combined organic extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvents and chromatography of the

residue on 500 g of silica gel using 1:1 hexane:ethyl acetate as the eluent afforded 5.15 g (80%) of the picolylethylated octalindione **22**: λ_{max} ($CHCl_3$) 1709, 1663, 1595, 1582 cm^{-1}; δ ($CDCl_3$) 1.36 (s, 3 H), 1.9–3.0 (m, 17 H, containing a singlet at δ 2.50), 6.94 (t, 2 H), 7.36 (t, 1 H); *m/e* 297 (P).

Selective Reduction of Octalindione 22. Formation of Hydroxyoctalone 23. To a solution of 5.15 g (0.0175 mol) of enedione **22** in 200 ml of absolute ethanol maintained under an atmosphere of nitrogen at 0° was slowly added 340 mg (0.0088 mol) of $NaBH_4$. The solution was stirred at 0° for 0.5 hr and then at room temperature for 1.5 hr. The reaction mixture was poured into 100 ml of H_2O and extracted with five 100-ml portions of CH_2Cl_2, and the combined organic layers were dried over anhydrous $NaSO_4$. After evaporation of the solvents, the oily residue was triturated with ether to afford 1.9 g of white crystalline **23**. Chromatography of the mother liquor on 100 g of silica gel using 3:2 ethyl acetate:hexane as the eluent afforded 2.50 g of pale yellow oil which when triturated with ether afforded 2.26 g of **23** as white crystals (total yield = 4.16 g; 80%), mp 103–104°: λ_{max} ($CHCl_3$) 3600, 3400, 1650, 1590, 1575 cm^{-1}; λ_{max} (95% EtOH) 251 mμ (ϵ 11,700), 210 (8600); δ ($CDCl_3$) 1.10 (s, 3 H) 1.5–3.0 (m, 17 H containing s at δ 2.50), 3.33 (t, 1 H), 4.0 (s, 1 H, hydroxyl), 6.94 (t, 2 H), 7.36 (t, 1 H); *m/e* 299 (P).

Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42. Found: C, 76.09; H, 8.23.

Catalytic Reduction of 23. Formation of Hydroxydecalone 24. To a solution containing 3.27 g (0.0109 mol) of eneketol **23** in 105 ml of ethyl acetate was added 70 mg of triethylamine and 650 mg of 10% palladium on carbon. The mixture was stirred under a hydrogen atmosphere for 40 hr. The mixture was filtered and the catalyst thoroughly washed with hot ethyl acetate. Evaporation of the combined washings afforded 3.25 g of the dihydro product **24** as a semisolid: λ_{max} ($CHCl_3$) 3400, 1703, 1590, 1575 cm^{-1}; δ ($CDCl_3$) 1.07 (s, 3 H), 1.1–3.0 (m, 19 H, containing a singlet at δ 2.50), 3.17 (t, 1 H), 3.90 (s, 1 H), 6.97 (t, 2 H), 7.36 (t, 1 H); *m/e* 301.

Ketalization of 24. Formation of Hydroxyketal 25. To a solution containing 3.25 g (10.7 mmol) of crude ketol **24** in 70 ml of toluene was added 100 mg of *p*-toluenesulfonic acid and 20 ml of ethylene glycol. The mixture was heated under reflux with azeotropic removal of the water for 48 hr. After cooling of the mixture to room temperature, 30 ml of 5% $NaHCO_3$ was added, the reaction mixture was extracted four times with 25-ml portions of ether, and the combined extracts were dried over anhydrous Na_2SO_4. Following removal of the solvents, the residue was chromatographed on 150 g of silica gel. Elution with 1:1 hexane:ethyl acetate afforded 3.76 g of an oil which when triturated with ether afforded 3.34 g (58%) of hydroxyketal **25** as white crystals, mp 128–130°: λ_{max} ($CHCl_3$) 3600, 3500, 1575, 1590, cm^{-1}; δ ($CDCl_3$) 0.88 (s, 3 H), 1.0–2.0 (m, 15 H), 2.51 (s, 3 H), 2.80 (t, 2 H), 3.17 (t, 1 H), 3.98 (s, 4 H), 6.93 (d, 2 H), 7.42 (t, 1 H); *m/e* 345 (P).

Anal. Calcd for $C_{21}H_{31}O_3N$: C, 73.01; H, 9.04; N, 4.05. Found: C, 72.84; H, 9.17; N, 3.91.

Reductive Cyclization of 25. Formation of Hydroxyenedione 26. To a solution containing 1.98 g (5.74 mmol) of hydroxyketal **25**, 1.06 g (22.96 mmol) of absolute EtOH, and 5 ml of anhydrous ether in 50 ml of anhydrous liquid ammonia (freshly distilled from sodium) was slowly added 290 mg (12.6 g-atoms) of freshly cut sodium. The resulting solution was stirred for 15 min. The ammonia was evaporated in a stream of nitrogen and the residue taken up in 22 ml of EtOH. To this was added a solution prepared from 574 mg (14.35 mmol) of NaOH in 11 ml of H_2O. After stirring for 2.5 hr at room temperature, the reaction mixture was acidified with 10% HCl and stirred for 25 min. Extraction with five 50-ml portions of CH_2Cl_2 followed by drying the combined organic extracts over anhydrous Na_2SO_4 and evaporation of the solvents afforded 1.62 g (93%) of **26** as a pale yellow oil: λ_{max} ($CHCl_3$) 3400, 1695, 1660 cm^{-1}; δ ($CDCl_3$) 1.10 (s, 3 H), 1.2–2.5 (m, 22 H), 3.25 (t, 1 H), 3.97 (s, 1 H), 5.81 (s, 1 H).

Jones Oxidation of 26. Formation of Enedione 27. To a solution containing 1.28 g (4.2 mmol) of hydroxyenedione **26** in 200 ml of acetone was slowly added Jones reagent (prepared by the addition of 2.62 g chromium trioxide to 2.3 ml of concentrated H_2SO_4 and 7.7 ml of H_2O) until the solution turned dark brown. After being stirred at room temperature for 1t min, the mixture was filtered and the acetone evaporated. The residue was taken up in 50 ml of ether and washed twice with 15-ml portions of 5% $NaHCO_3$ and the ether layer dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded 1.12 g of yellow oil which, when triturated with ether, afforded 1.05 g (84%) of enetrione **27** as white crystals, mp 101–102°: λ_{max} ($CHCl_3$) 1695, 1660, 1615 cm^{-1}; δ ($CDCl_3$) 1.35 (s, 3 H), 1.5–2.7 (m, 23 H), 5.81 (s, 1 H); *m/e* 302; λ_{max} (95% EtOH) 234 mμ (ϵ 9700).

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.22; H, 8.59.

Conversion of Pyridineketal 25 to Diketoneketal 29. To a solution of 345 mg (1.0 mmol) of **25**, 184 mg (4.0 mmol) of absolute ethanol, and 1 ml of anhydrous ether in *ca.* 10 ml of anhydrous ammonia was added 51 mg (2.2 mmol) of sodium. After disappearance of the blue color, the ammonia was evaporated, and to the residue was added a solution prepared from 1.72 ml of 5% aqueous sodium hydroxide and 3.45 ml of ethanol. The mixture was stirred for 5 min at room temperature, poured into 5 ml of water, and extracted three times with 25 ml of methylene chloride. The organic layers were combined and dried over sodium sulfate. Evaporation of the solvent gave 226 mg of a yellow oil. Preparative tlc of 115 mg of this residue using ether as the element gave 81 mg (*ca.* 43% yield) of **29**, R_f 0.6: λ_{max} ($CHCl_3$) 1729 cm^{-1}; δ ($CDCl_3$) 3.93 (broad singlet, 4 H), 3.2–0.7 (*ca.* 30 H, containing ~3 H singlets at δ 2.10 and 0.82); *m/e* 366 (P), 99 (base peak).

Cyclization of Diketoneketal 29. Formation of Hydroxyenedione 26. (i) **At Room Temperature.** To a solution of 80 mg (0.218 mmol) of diketalketone **29** in 1.0 ml of ethanol was added a solution of 29.4 mg (0.735 mmol) of sodium hydroxide in 0.590 ml of water. The solution was stirred under nitrogen for 2.5 hr at room temperature. The solution was then acidified with 10% aqueous HCl, stirred for 15 min at room temperature, and then extracted with 3 × 20 ml of methylene chloride. The organic layers were combined and dried over sodium sulfate. Evaporation of the solvent left a residue of 55 mg (83% crude yield) of a residue characterized as **26** by the identical tlc properties [one spot, R_f 0.25 (ether)] and nmr spectrum with those of the authentic material.

(ii) **Under Reflux.** To a solution of 140 mg (0.382 mmol) of diketoneketal **29** in 2 ml of ethanol was added a solution of 51.6 mg (1.28 mmol) of sodium hydroxide in 1.05 ml of water. This solution was heated under reflux for 17 hr. After being cooled, the solution was acidified with 10% aqueous HCl and then stirred for 15 min at room temperature. This reaction mixture was poured into 3 ml of water and extracted three times with 20 ml of methylene chloride. The combined organic layers were dried over sodium sulfate. Evaporation of the solvent left 120 mg of a residue (100% crude yield) characterized as **26** by the identity of its tlc and nmr spectrum with those of authentic material.

Cyclodehydration of 27. Formation of Dienedione 30. A solution containing 772 mg (2.57 mmol) of enetrione **27** and 250 mg of *p*-toluenesulfonic acid in 27 ml of glacial acetic acid, under a nitrogen atmosphere, was heated on a steam bath for 45 min. After the solution was cooled to room temperature, 20 ml of H_2O was added, and the resulting solution was extracted with 4 × 25 ml of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4. After evaporation of the solvents, the residue was taken up in 50 ml of ether and washed twice with 10-ml portions 5% $NaHCO_3$. The ether layer was dried over anhydrous Na_2SO_4, and after evaporation of the solvent, the residue was chromatographed on 50 g of silica gel using 1:1 hexane:ethyl acetate as the eluent to afford 524 mg of an oil. Crystallization from hexane–ether afforded 487 mg (66%) of crystalline *D*-homoestra-4,9$^{(10)}$-diene-3,17a-dione, mp 161–163° [lit.[37] 165–167°]: λ_{max} ($CHCl_3$) 1695, 1645, 1605 cm^{-1}; δ ($CDCl_3$) 1.38 (s, 3 H), 1.4–3.1 (m, 22 H), 5.58 (s, 1 H); *m/e* 284; λ_{max} (95% EtOH) 306 nm (ϵ 19,500) [lit. −306 (20,000)].

Isomerization of 30.[36] Formation of *dl-D*-Homoestrone (31). A solution containing 125 mg (0.44 mmol) of dienedione **30**, 84 mg of acetyl bromide, and 108 mg of acetic anhydride in 0.5 ml of CH_2Cl_2 was stirred under an atmosphere of nitrogen for 1 hr. To the reaction mixture was slowly added 5 ml of 5% $NaHCO_3$ and the mixture extracted three times with 5-ml portions of Et_2O. After drying and evaporation of the solvents, the residue was taken up in 30 ml of MeOH, 5 ml of H_2O and 400 mg of K_2CO_3 were added, and the solution was stirred at room temperature for 1 hr. After neutralization with 10% HCl, the methanol was evaporated, the remaining water layer was extracted three times with 10-ml portions of CH_2Cl_2, and the combined extracts were dried over an-

hydrous Na_2SO_4. Evaporation of the solvents afforded 113 mg of the desired *D*-homoestrone as yellow crystals which when recrystallized from hexane–ether afforded 103 mg (82%) of *D*-homoestrone, mp 220–223° (lit.[47] 225–227°): λ_{max} ($CHCl_3$) 3590, 3450, 1695 cm^{-1}; δ ($CDCl_3$) 1.12 (s, 3 H), 1.3–3.0 (m, 18 H), 6.53 (m, 2 H), 7.06 (d, 1 H); λ_{max} (95% EtOH) 278 nm (ϵ 1670) [lit. λ_{max} (95% EtOH) 278 (2,000), 286 (1900)][3].

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References and Notes

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(45) It should be noted that this yield was defined by using only purified intermediates **22–27** and **30** on the way to **31.** Also intermediates **23, 25, 27,** and **30** were moved into the next step only after crystallization. Hence, it would appear likely that a higher overall yield could be realized by consolidating purifications after several steps.
(46) Microanalyses were conducted by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were measured on a Perkin-Elmer 137 infracord spectrophotometer or on a Perkin-Elmer 247. Nmr spectra were obtained at 60 MHz (Varian Associates T-60 or A 60-D) using tetramethylsilane (TMS) internal standard. Chemical shifts are reported in parts per million (δ) from TMS. Mass spectra were obtained by direct insertion on an LKB-9000 combined glc–mass spectrometer. Ultraviolet spectra were obtained on a Perkin-Elmer Model 124 spectrophotometer. Melting and boiling points are uncorrected.
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