(16) There are several nomenclatures used to describe the isomers of a linear tetradentate chelate. The one employed here was first used for EDDA chelates by Jordan and Douglas [*Inorg. Chem.*, **12**, 403 (1973)]. It is based on the arrangement of positions on the octahedron not occupied by the tetradentate.
(17) P. F. Coleman, J. I. Legg, and J. Steele, *Inorg. Chem.*, **9**, 937 (1970), and references therein.
(18) J. L. Sudmeier and G. Occupati, *Inorg. Chem.*, **7**, 2524 (1968).
(19) D. A. Buckingham, L. G. Marzilli, and A. M. Sargeson, *J. Am. Chem. Soc.*, **89**, 5133 (1967).
(20) J. A. McClarin, L. A. Dressel, and J. I. Legg, *J. Am. Chem. Soc.*, **98**, 4150 (1976).

Optically Specific Synthesis of Estrone and 19-Norsteroids from 2,6-Lutidine[1]

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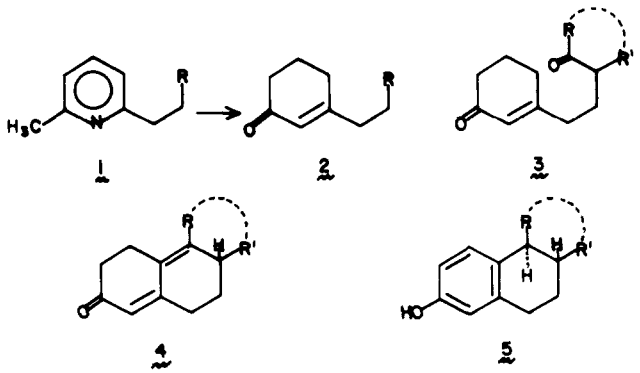
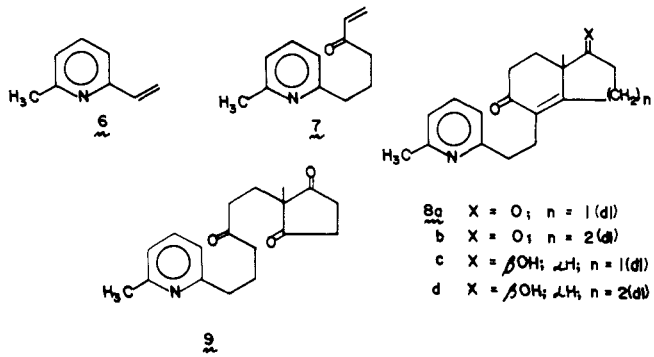
Contribution from the Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260. *Received December 26, 1975*

Abstract: Reaction of 2-methyl-2-[3-oxo-6-(6-methylpyrid-2-yl)hex-1-yl]cyclopentane-1,3-dione with L-phenylalanine and perchloric acid gives 4-[2-(6-methylpyrid-2-yl)ethyl]-7a-methyl-7,7a-dihydro-1,5(6*H*)-indandione with high (85 ± 1%) optical specificity of the 7a*S* enantiomer. The latter is converted to optically pure (+)-estrone and optically pure 19-norandrogens containing the 13*S* configuration, utilizing as key steps reductive hydrolytic cyclization and vinylogous aldolization.

In previous papers in this series, we have demonstrated the convertability of 6-substituted α-picolines of type **1** to 3-substituted cyclohexenones such as **2**.[2-5] The transformation is highly efficient in those cases where R represents a cycloalkanone ketal joined at its α position. The derived enedione **3** suffers smooth vinylogous aldolization to give dienone **4**, which can be isomerized to phenol **5**. This combination of reactions constitutes an attractive route to phenolic steroids such as estrone and its derived 19-norandrogens. The viability of this route to steroids was demonstrated in the context of the total synthesis of *dl*-*D*-homoestrone.[4,5]



In our early studies, systems of the type **1** were assembled by Michael additions to vinylpicoline **6**. An important improvement was achieved when it was found that the tris annelating agent **7** could be readily synthesized (57%) from 2,6-lutidine and that it reacted smoothly with both 2-methylcyclopentane-1,3-dione and 2-methylcyclohexane-1,3-dione to give, directly, 4-alkylated bicyclenones of the type **8**.[6] Moreover it was found that the Michael addition and cyclodehydration stages of the annelation can be decoupled. For instance, reaction of **7** with 2-methylcyclopentane-1,3-dione under the influence of triethylamine in ethyl acetate[7] gave a nearly quantitative yield of the seco system **9**. Experimental details for the synthesis of annelating agent **7**, *dl* systems **8**, and prochiral system **9** have been provided.[5,6]



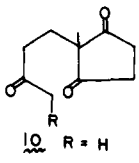
In projecting a total synthesis of estrone from this prior art there remained two major obstacles. For achieving the required stereochemistry, it was crucial to generate the trans C:D junction of steroids by the reduction of **8a** or some suitable, easily accessible derivative. This appeared to be a more complicated proposition than the relatively simple elaboration of the trans C:D system in the *D*-homo series (**8d**). The difficulties associated with the construction of trans hydrindanones from progenitors bearing unsaturation at the junction have been an enduring problem in steroid total synthesis.[8]

The other objective was, of course, the synthesis of estrone in the required antipodal form. Our interest in preparing trione **9** stemmed from the hope that its prochiral nature could be exploited in a chirally specific synthesis of the 13*S*[9] configuration required in the final product. If this asymmetry were to be induced, the possibility of synthesizing optically active steroids without recourse to resolution and with nearly full utilization of intermediates would be within reach.

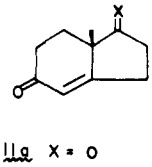
Of course, the feasibility of inducing asymmetry by amino acid promoted aldolization of prochiral precursors was demonstrated concurrently in the laboratories of Z. Hajos at Hoffmann-La Roche[10a] and U. Eder at Schering AG.[10b] Both groups realized high chiral specificity in the cyclization of **10** → **11a** by use of the cyclic amino acid, L-proline.

It should be noted that this easy access to the optically pure **11a** makes this compound per se an attractive intermediate for steroid synthesis. Such routes gain added desirability from the discovery that very high sterospecificities in favor of trans C:D stereochemistry are achieved in the catalytic hydrogenation of hydrindenones **12**[11] (which is prepared from **11a**) and **13**[12] (which is derived from the angular ethyl analogue of **11a**).

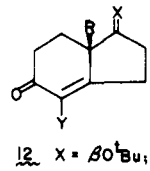
Our interest in preparing optically active **15** and **16** by



10 R = H



11a X = O
b X = βOH; αH
c X = βO^{t}Bu; αH



12 X = βO^{t}Bu; αH
Y = CO_2H R = Me
13 X = O; Y = $CH_2SO_2\phi$
R = Et

chirally specific cyclization of **9** rather than by picolylethylation of a version (cf. **11b** or **11c**) of optically active **11a** arose from difficulties which were first encountered in the *dl* series. Thus, attempts to synthesize *dl*-**8a** by attaching the bis annelating **6** to **11** or its derivatives containing variously modified oxygen functionality at C(1) were achieved only in poor yields. The best results will be described in connection with our synthesis of optically pure **15** and **16** by picolylethylation of **11c** (vide infra).

In this paper we describe (i) a successful solution to the objective of the asymmetrically specific cyclization of **9**, (ii) the results of some investigations into the nature of the intermediates in the cyclization, (iii) a stereoselective (though not completely satisfactory) solution to the establishment of the trans C:D stereochemistry, and (iv) the total synthesis of estrone and 19-norsteroids in the required enantiomeric (13*S*)[9] form.

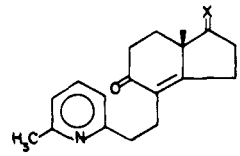
Results

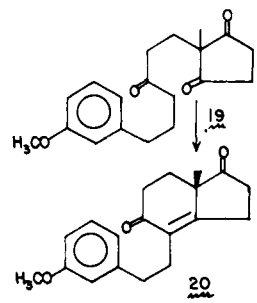
(i) Synthesis of Optically Pure 15 and 16. Already in the *dl* series[6] it had been found that racemic hydrindenedione **8a** and its derived alcohol **8c** were oils which, even in seemingly homogeneous form, defied our best efforts at crystallization. This situation with **8c** stands in sharp contrast to the nicely crystalline character of the *D*-homo precursor **8d**. Accordingly, crystallization did not appear to be an available method for realizing complete optical purity of the picolylethylated hydrindenones of the type required in the synthesis of estrone. We reasoned than an unambiguous knowledge of the optical rotation ($[\alpha]_D$) of optically pure **16** constituted the most straightforward way of determining the efficacy of attempted asymmetric inductions in the cyclization of prochiral **9**.

With this in mind we undertook an unambiguous synthesis of optically pure **16** via its precursor **15**, whose optical purity was also assured. The excellent procedure of Eder[10b] was repeated on trione **10** to afford, after recrystallization, compound **11a** in >99% optical purity. Reduction of **11a** with sodium borohydride according to known procedures gave optically pure **11b**. Using the methodology which Hajos had developed in the *dl* series, **11b** was converted to its *tert*-butyl ether derivative **11c**. Subsequent to our work, optically pure **11c** was reported by a Roche group.[13]

Reaction of **11c** with potassium *tert*-amyl oxide in *tert*-amyl alcohol followed by alkylation of the derived dienolate[5] with **1** gave a 46% yield of the *tert*-butyl ether **14**. While compound **14** was not rigorously purified, its spectral properties supported the assigned structure. That coupling did occur was suggested by its mass spectrum (*m/e* 285; P − isobutylene). The presence of enone functionality is assured by its infrared spectrum ($\nu_{max}^{CHCl_3}$ 1663, 1590, and 1575 cm^{-1}). The position of alkylation was assured by the absence, in its NMR spectrum, of any signals in the region (δ 5.5–6.0) which normally encompasses the resonance of the α proton of an enone.

Hydrolysis of the *tert*-butyl ether gave (86%) optically pure **15** $[\alpha]_D^{C_6H_6}$ 28.1°. Jones oxidation of **15** provided, in 72% yield, optically pure **16**, $[\alpha]_D^{C_6H_6}$ 202.0°. Compounds **15** and **16** were identical in all respects (save optical activity) with racemic compounds **8c** and **8a**, respectively.[6] They were, of course, synthesized in unambiguous fashion by the cyclization of **9**. The structures of **14**, **15**, and **16** are thus proven beyond question and the optical rotations of **15** and **16** are established. The overall chemical yield in going from **11a** → **15** (i.e., **11a** → **11b** → **11c** (+6) → **14** → **15** is only 23%. This underscores the attraction of using the tris annelating agent **7** and the prochiral **9** as intermediates toward **15** and **16**.





11c → 14 X = βO^{t}Bu; αH
15 X = βOH; αH pure 13S
16 X = O pure 13S
9 → 17 X = O 93% 13S; 7% 13R
18 X = βOH; αH 93% 13S; 7% 13R
25 X = O 54% 13S; 46% 13R

19

20

Asymmetric Cyclization of Trione 9. Our first attempts to effect the chirally specific cyclization of **9** involved the use of L-proline in acetonitrile under the influence of perchloric acid. In formulating these experiments, we were mindful of the results of Eder using L-proline–acetonitrile–perchloric acid systems.[10b,14] An apparent decay in the efficacy of asymmetric induction in the cyclization of compounds similar to **10**, but containing a substituent in the center designated as R, emerges from this study.

In practice, cyclization of **9** with L-proline in acetonitrile containing 0.25 equiv of perchloric acid–amino acid gave optically enriched enedione **17**, $[\alpha]_D^{C_6H_6}$ 53.0°. While enriched in the required 13*S*[9] enantiomer, the optical purity of the material so obtained was only 27%, i.e., 13*S*:13*R* = 63.5:36.5.

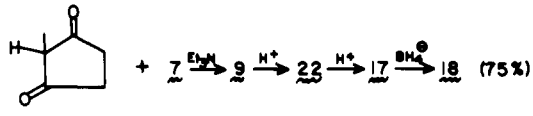
The results of Eder seemed to suggest that the aromatic amino acid L-phenylalanine may be preferred in those cases where R ≠ H. Accordingly, this amino acid was used in cyclization experiments with **9**. Happily it was found that optically enriched **17** was obtained with $[\alpha]_D$ 173.6°, i.e., 13*S*:13*R* = 93:7. This optimal optical purity of 86% in **17** was obtained reproducibly using a ratio of 1 equiv of **9**:1.2 equiv of amino acid:0.5 equiv of perchloric acid in acetonitrile (2.7 ml/mmol of **9**), under reflux for 72 h. The highest optical purity achieved was 86%. The average for many runs under these conditions was 85 ± 1%. It was observed that a decrease in optical specificity (80% optical purity) resulted from the use of 1 equiv of perchloric acid:1.2 equiv of amino acid. On the other hand, the use of a 0.25:1.2 rato of acid:amino acid gave **17** in optical purity of 85%.

The results using a variety of amino acids are summarized in Table I. Since **17** (as is the case with **8a** and **16**) is obtained as an oil, these results are not distorted by the occurrence of any unforeseen enrichments through crystallization. It is seen that optimal specificity is achieved with the aromatic amino acids. The failure of *O*-methyl-L-tyrosine to give a superior result relative to L-phenylalanine suggests that the electron-donating powers of the phenyl ring may not be crucial, though this possibility was not checked further.

It is interesting to note that in the cyclization of the pyridyl trione **9**, the aromatic amino acids phenylalanine, tryptophan, and tyrosine *O*-methyl ether seem to be the most efficacious. Eder has also reported[10b,14] that L-phenylalanine is the most effective amino acid in promoting the chirally specific (79% optical purity) cyclization of **19** → **20**. In this connection, however, it should be mentioned that Hajos reports[10a] that L-phenylalanine is relatively ineffective in promoting the optically specific cyclization to the β-ketol precursor of **11a** (19%). In the light of this confusing set of results it is, at this stage, clearly premature to formulate generalized propositions

Table I. Formation of Optically Enriched **17** by the Cyclodehydration of **9**

Amino acid (1.2 equiv)	$HClO_4$, equiv	$[\alpha]D$, deg	Optical purity of **17**, %	% yield of **17**
L-Phenylalanine	0.5	173.6	86	82
L-Phenylalanine	0.25	172.1	85	82
L-Phenylalanine	1.0	162.3	80	80
L-Tyrosine *O*-methyl ether	0.25	169.5	84	82
D-Tryptophan[15]	0.25	−156.0	78	70
L-Serine	0.25	70.2	35	77
L-Proline	0.25	53.0	26	67
D-Valine[15]	0.25	−41.7	21	72



regarding the relationship of the structure of the amino acid to the nature of its catalytic function in promoting chirally specific aldolization of prochiral triones.

In our own case, the assessment of the optical purity of **17** was supported by its conversion to **18** by reduction with sodium borohydride. The correspondence of the ratio of the optical rotations of **17**:**18** relative to that of **16**:**15** served as an additional confirmation of the purity of our intermediates. For synthetic purposes, a procedure was developed which enables the conversion of 2-methylcyclopentane-1,3-dione and trisannelating agent **7** into **18** of 85% optical purity in 75% chemical yield without purification of prochiral **9**, β-ketol **22** (vide infra), or enone **17**.

(ii) Intermediates in the Conversion of 9 → 17. Under the conditions of Eder[10b] (L-proline–perchloric acid–acetonitrile reflux), no intermediates were described in the conversion of **10** → **11a**. Accordingly, it was of interest to us to obtain a fuller accounting of the steps involved in the transformation of **9** → **17** using essentially the same conditions except for the amino acid (L-phenylalanine). An important step in this pursuit was achieved through a chance observation. In attempting to prepare a sample of **9** for combustion analysis, virtually pure material was subjected to chromatography on silica gel. Far from achieving the intended objective, a new compound, mp 132–134 °C, was obtained in 48% yield. Although no rigorous relative stereochemical assignment is possible, the gross structure of this compound is defined to be the racemic β-ketol **21**. Its infrared spectrum contains OH absorption at 3660 cm^{-1} and two ca. equal intensity bands at 1730 and 1710 cm^{-1}, indicative of the presence of cyclopentanone- and cyclohexanone-type carbonyl systems, respectively.

Treatment of racemic **21** with L-phenylalanine–perchloric acid, to the point where starting **19** was dissipated (~24 h), gave an 88% yield of racemic **8a**. The conditions used simulated those used in the conversion of **9** → **17**. It may be concluded that the process leading from **21** → **8a** is not in competition with any substantial reversion of **21** → **9**, for the latter would have been converted to a product enriched in the 13*S* enantiomer (cf. **17**).

The intermediacy of β-ketol in the amino acid induced conversion of **9** → **17** was supported by its detection (TLC) upon monitoring the reaction progress as a function of time. A buildup of β-ketol as well as its disappearance in favor of **17** was observed concurrently with the steady diminution of **9**. No other TLC mobile components were detected.

It was of interest to assess the optical purity of the β-ketol which is produced under the very same conditions, where enone **17** is being produced with ca. 86% enantiomeric (13*S*)[9] enrichment.

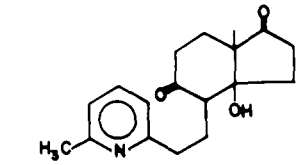
In view of the propensity of the trione **9** to afford racemic β-aldol **21** upon chromatography, it was necessary to await disappearance of **9** before attempting to assess the optical enrichment of the β-ketol produced during amino acid catalyzed production of **17**. In waiting for the disappearance of **9**, the enone **17** rather than the β-ketol becomes the predominant product. However, it was possible to obtain a 19% yield of optically enriched β-ketol **22**, $[\alpha]D$ −47.1°, and a 69% yield of **17**, $[\alpha]D^{C_6H_6}$ 171.4°. The rotation was measured on the total solid chromatographed β-ketol material and is therefore a reliable index of its enrichment.

Several recrystallizations of **22** gave a sample of optically pure β-ketol **23**, $[\alpha]D^{C_6H_6}$ −55.03°. The optical purity of **23** was established by its conversion in a separate reaction with L-phenylalanine–$HClO_4$–acetonitrile to essentially optically pure enone **16**, $[\alpha]D^{C_6H_6}$ 200.2°.

Given $[\alpha]D$ of −55.0° for optically pure **23**, it is seen that the optical enrichment of the β-ketol **22** is 86%. This compares quite closely with the enrichment of 85% of **17**, obtained from the same experiment. *We conclude that in going from* **9** → **17** *under the influence of* L-*phenylalanine, all the optical specificity is built into the same sequence which also provides the β-aldol,* **22**. Furthermore, the route from the β-aldol to the product, **17**, is irreversible with respect to **9** itself or with respect to any other achiral intermediates which lie on the **9** → **17** pathway.

It was of interest to examine the possibility of asymmetric preference in the amino acid induced dehydration of the two enantiomers which comprise racemate **21**. With this in mind, the dehydration of **21** was conducted only partially, giving after chromatographic separation 20% of enone **25** with a rotation, $[\alpha]D^{C_6H_6}$ 16.0°. This constitutes an 8% optical enrichment in the 13*S*[9] enantiomer. A 78% recovery of the β-ketol was achieved. Its observed specific rotation was 1.40°, indicative of a 2.5% enrichment of the 13*R* antipode.

These results demonstrate that there exists a process in which the pre 13*S*[9] β-ketol suffers dehydration with the amino acid–perchloric acid system faster than the pre 13*R* antipode. The recovered β-ketol is therefore enriched in the 13*R* enantiomer. The relative enrichments of 8.0% of the *S* antipode of product **17** and 2.5% of the *R* antipode in "recovered" **24** after 20% reaction are in reasonable agreement with theory, wherein the calculated value would be 2.0% enrichment in **24** given an enrichment of 8.0% in **17** and a 20% extent of reaction (λ = 0.2).[16,17]



9 → **21** (racemate) → Enone **8a**
9 → **22** (92% 13S; 8% 13R) + Enone **17**
22 → **23** (100% 13S) → Enone **16**
21 → 80% **24** (51% 13R; 49% 13S) + 20% Enone **25**

Unfortunately, these data do not allow for the delineation of the origin of this slight optical specificity.[18] It may arise from the acid–base properties of the amino acid–perchloric acid system, which result in kinetic preference in the rate of enolization or oxonium ion formation from the 13*S* enantiomer of **21** during its dehydration. This would lead to enrichment in the 13*R* enantiomer in the recovered ketol (**24**) and enrichment in the 13*S* enantiomer in the enone (**25**) during partial reaction.

Alternatively, it may result from a mechanism of the Spencer type[19a,b] wherein the amino group reacts with the

ketonic group to give an imminium species **27,** which suffers dehydration and hydrolysis to give **17.**

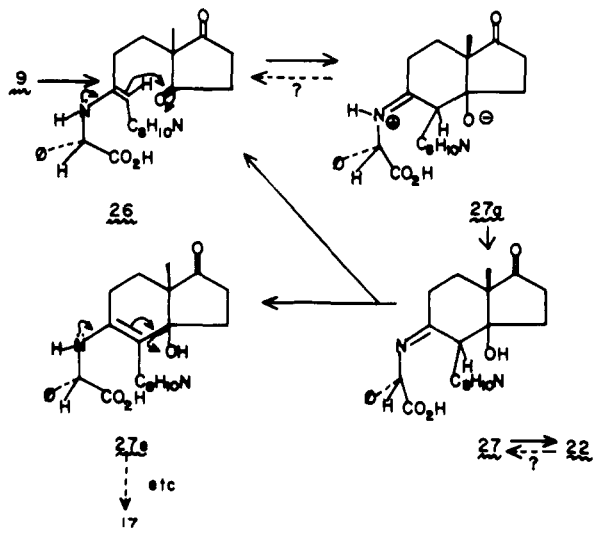
Also, it cannot be said whether the enrichments arise from a single pathway with a kinetic preference ($k_R/k_S = \rho$) of ca. 0.8[16,17] or whether they arise from the combination of totally random ($\rho = 1$) and more selective ($\rho < 0.8$) processes.

It is, however, interesting to note that if enamine **26** is a precursor in the **9** → **17** cyclization, the imminium species **27** would be produced. The latter would be postulated to be in reversible equilibrium with the β-ketol, since **22** is actually isolated from the reaction starting with **9** and itself goes to enone **17.**

If these intermediates be invoked in the cyclization and dehydration pathways, it may be concluded that **27** does not revert to **26.** Were such reversion occurring to any significant extent, the conversion of **21** → **8a** (see above) would not be possible, since enamine **26** would give **17** by this formulation.

It must be emphasized that the argument concerning the nonreversion of **27** → **26** does not apply to the imminium alkoxide species **27a.** Such a species, which need not arise from the acid-catalyzed dehydration starting with **21,** but could arise when the process starts with trione **9,** might well be in Mannich ⇄ reverse Mannich equilibrium with its hypothetical precursor **26** in the **9** → **17** pathway. This is summarized in Scheme I.

Scheme I



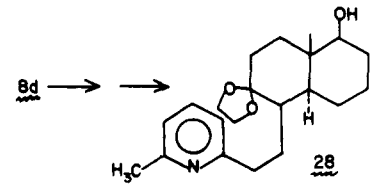
We acknowledge, however, that the fundamental chemical question as to the structural basis for the differentiation (kinetic or thermodynamic) among the diastereotopic carbonyl groups in an intermediate such as **26** has not been addressed. We would venture the opinion that an understanding of the chemical foundation of this effect could well be useful in allowing for its extension to new and structurally varied cases.

(iii) Construction of the Trans C:D Junction. Though the mechanistic details of the asymmetric induction are not well understood, the 86% optical specificity realized in the cyclization of **9** → **17** under the influence of L-phenylalanine represents the most successful induction in the cyclodehydration of a prochiral substrate of the type **10,** where R ≠ H. Accordingly, the possibility of an efficient total synthesis of optically active steroids, without recourse to resolution, presented itself.

Since compounds **17** and **18** are oils, it was decided to advance toward tetracyclic products, which are known for their high degree of crystallinity. In choosing this pathway rather than one involving a search for a crystalline derivative of **17** (or **18**), which would provide a means for elimination of the racemic component (ca. 14%) at an early stage, we were not unmindful of the inefficiency of conducting operations on racemic material which must then be discarded. This issue has been effectively analyzed by Velluz.[20] Nevertheless, it seemed that the avoidance of diversionary exercises and the high crystallinity of the final steroids, with the attendant promise of ready optical purification, warranted such an approach.

Accordingly, the trans-fused ketone **30** became our next objective. In the racemic *D*-homoestrone synthesis, the two-step conversion of **8d** → trans dihydro ketal **28** was achieved in 58% yield using triethylamine in the hydrogenation step. No cis-fused decalin products were isolated after ketalization.

More recently, the reduction of **8d** was carried out using perchloric acid in ethanol[21] containing traces of water. After ketalization, compound **28** was obtained in 82% yield. Accordingly, the optically enriched hydroxyenone **18** was submitted to catalytic hydrogenation under these two sets of conditions.



It was soon found that the catalytic reduction of **18** (or **8c**) is considerably slower than the reduction of **8d** under identical conditions. The use of 3:1 ethyl acetate–triethylamine and a 4:3 ratio (w/w) of enone–10% palladium on charcoal catalyst allows for complete reduction of **18** after 6 days at atmospheric pressure. Observations based on the *dl* (**8c**) and *dl-D*-homo (**8d**) series indicated that separation is most profitably achieved on the corresponding ketals. Accordingly, ketalization of the crude dihydro system was next conducted. TLC analysis showed a ca. 1:1 ratio of dihydro ketals. The mixture was separated by chromatography on silica gel. The faster moving component, obtained in 37% yield, is the cis compound, **29.** The slower moving component, isolated in 44% yield, was the desired trans-fused system, **30.** These stereochemical assignments are fully supported by the successful conversion of **30** into steroids of the natural (i.e., trans C:D junction) stereochemistry.

A more stereoselective preference in favor of the trans product was achieved by conducting the catalytic reduction in acidic medium. Again, separations were conducted after ketalization. Optimum reductive conditions involved the use of perchloric acid in aqueous ethanol[21] with an 8:5 (w/w) ratio of compound–catalyst under 3 atm of hydrogen.

Under these conditions, compounds **29** and **30** were isolated in 17 and 45% yields, respectively. Unfortunately, the use of acid led, in 21% yield, to the product of hydrogenolysis, **31.** Through **31** was not carried any further in the synthesis, its structure follows decisively from its molecular weight (*m/e* 271 = P) and from the absence of bands characteristic of hydroxyl or carbonyl groups in its ir spectrum, as well as the absence of vinylic signals in its NMR spectrum. The degree of competitive hydrogenolysis manifested in the case of **17** is surprising, since it was not cited as a problem in the closely related system **32**[21] and as apparently only a minor problem in the reduction of **13.**[12]

All attempts on our part to diminish the loss of valuable material due to hydrogenolysis and to improve upon the ratio of **30:29** were not successful. The results of catalytic reduction of other 7a-methyl-4-substituted-7,7a-dihydro-5(6*H*)-indanones which have been achieved under varying conditions are included for comparison in Table II.

The chromatographic separation of **30** from **31** is much easier than the separation of **30** from **29.** Therefore, it was operationally preferable to conduct the hydrogenation in acidic

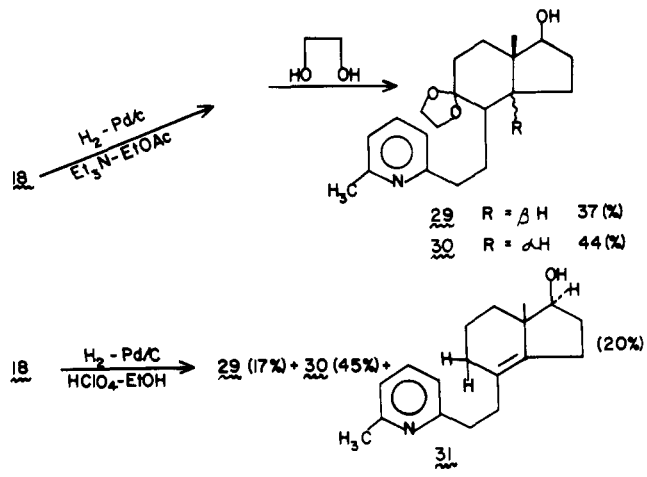
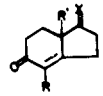


Table II

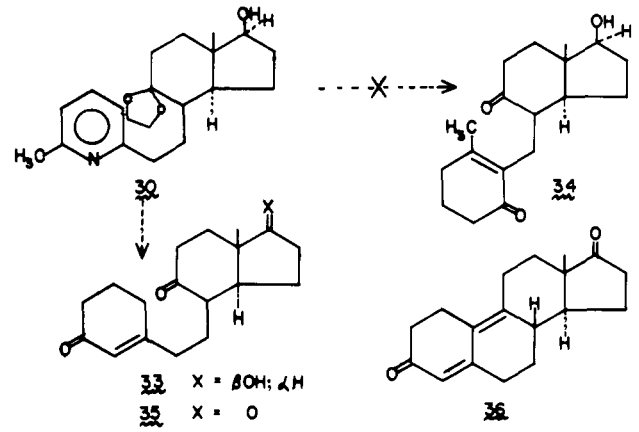
Substrate Undergoing Reduction	Result
	
R = $CH_2CH_2CO_2H$; R'=Me; X=βOH; αH	3aα 60-75%[22]
R = CH_2--CH_2-CH_3; R'=Me; X=βOTHP; αH	3aα >50%[23]
R = CH_2CH_2-$COCH_3$; R'=Me; X=βOH; αH	3aα:3aβ 4:1[24]
R = CH_2(2,4-dimethylisoxazole-3-yl) (32)	3aα:3aβ = 85:15[21]
R = m-methoxyphenethyl; R'=Me; X=βOH; αH	3aα 60%[25,26] (after several steps)
R = CO_2H (12); R'=Me; X=β^{t}Bu; αH (12)	3aα:3β = 94:6[11,13]
R = $CH_2SO_2\phi$; R' = ethyl; X = O (13)	3aα 75%[12]

medium wherein a favorable ratio of **30:29** is established. However, the overall yield in the two-step conversion of **18** → **30** is the same (45%). This yield is clearly a serious impediment to commercial application of the total synthesis herein described.

(iv) Reductive Hydrolytic Cyclization of 30. The Production of Optically Active Steroids. Compound **30**, though homogeneous, was obtained as an oil of enantiomeric enrichment presumably identical with that of precursor **18**. Birch reduction of the pyridine ring was followed by hydrolytic cyclization in alkaline medium. The ketal function was removed via acidic workup. A 90% yield of hydroxyenedione **33** was obtained without purification at any stage. Within the limits of our detection (ca. 5%), there were no complications from the formation of isomeric cyclohexenone **34**. This is totally in line with previous findings in the *dl-D*-homo series.[4,5] Jones oxidation of **33** gave **35** in nearly quantitative yield. Compound **35** and its precursor **33** were obtained as oils. It should be noted that the *D*-homo analogue of **35** is obtained in nicely crystalline form.[5]

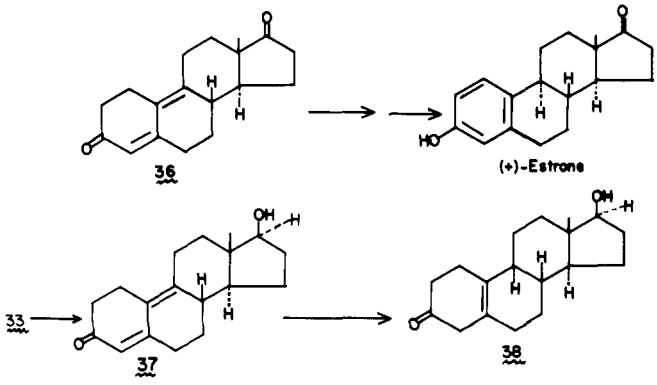
The desired tetracyclic skeleton was established by vinylogous aldolization of **33** under the influence of tosyl acid in acetic acid (100 °C, 1.5 h). The dienedione **36** thus obtained was isomerized to optically enriched estrone by the action of acetyl bromide–acetic anhydride[27] followed by cleavage of the phenolic acetate with potassium carbonate in methanol. The specific rotation (dioxane) of the total crystalline chromatographic fractions which consisted of estrone (48% from **30**) was 138.4°.

A single recrystallization from ether–methanol provided optically pure estrone, $[\alpha]_D$ 160° (authentic sample $[\alpha]_D$ 161°), in 39% chemical yield from **30** (i.e., 13% yield from tris annelating agent **7**). The melting point of the (+)-estrone was 254–255 °C and was undepressed on admixture with an authentic sample, mp 255–256 °C. The NMR spectra ($CDCl_3$) of the synthetic material and authentic sample were superimposable. From the mother liquors of the recrystallization there was obtained 9% (from **30**) of virtually racemic estrone, $[\alpha]_D$ 7.25°.



The route to the 19-norandrogens involved vinylogous aldolization of hydroxyenedione **33** itself with tosyl acid in acetic acid. Optically enriched crystalline hydroxydienone **37**,[28] $[\alpha]_D^{CHCl_3}$ −249.5°, was obtained in 68% yield (based on **30**) after silica gel chromatography. Optically pure **37**, $[\alpha]_D^{CHCl_3}$ −290°, was obtained after one recrystallization from ether–methanol. The melting point of the synthetic **37** was 188–190 °C and was undepressed on admixture with an authentic sample[29] of **38**, mp 187–189 °C, $[\alpha]_D^{CDCl_3}$ −290.2°. The chemical yield of optically pure **37** is 56% from **30** and 18% from **7**.

Optically pure **37** was submitted to Birch reduction by known methodology[28] to give the $\Delta^{5(10)}$-19-norsteroid **38**. Both compounds **37**[28] and **38**[30] have well-known antiovulatory properties. In addition, **38** has been converted to 19-nortestosterone.[31] The total synthesis of estrone and the biologically active 19-norsteroids in chirally specific form, via 2,6-lutidine, is thus complete.[32]



Experimental Section[33]

1. Picolylethylation of 11c. Formation of Optically Pure (+)-(1*S*,7a*S*)-1-*tert*-Butoxy-4-[2-(6-methylpyrid-2-yl)ethyl]-7a-methyl-7,7a-dihydro-5(6*H*)-indanone (14). To a solution of potassium *tert*-amylate in 30 ml of *tert*-amyl alcohol (prepared by dissolving 205 mg (8.83 mol) of potassium in 30 ml of *tert*-amyl alcohol) under an atmosphere of nitrogen was added 1.96 g (8.83 mol) of enone **11c**.[26] After the resulting solution was stirred for 30 min, 2.14 g (18.0 mmol) of freshly distilled 6-methyl-2-vinylpyridine (**6**) was added. The resulting solution was refluxed for 20 h. After cooling to room temperature, 20 ml of H_2O was added and the mixture was extracted five times with 20-ml portions of $CHCl_3$. The combined organic extracts were dried over anhydrous sodium sulfate. After removal of the solvents, chromatography of the crude residue on 300 g of silica gel using 3:2 benzene–ethyl acetate as the eluent afforded 1.18 g (46%) of pi-

colylethylated enone **14** as an oil: $\bar{\nu}$ 1663, 1590, and 1575 cm^{-1}; NMR δ ($CDCl_3$) 0.98 (s, 3), 1.13 (s, 9), 1.4–3.0 (m, 18 containing s, ca. 3, at 2.49), 3.34 (d × d, J = 9 and 8 Hz, 1), 6.89 (t, J = 8 Hz, 2), and 7.41 (t, J = 8 Hz, 1); *m/e* 285 (P − isobutylene) base peak.

2. Cleavage of *tert*-Butyl Ether 14. Formation of Optically Pure (+)-(1*S*,7a*S*)-1-Hydroxy-4-[2-(6-methylpyrid-2-yl)ethyl]-7a-methyl-7,7a-dihydro-5(6*H*)-indanone (15). A solution containing 1.18 g (3.45 mmol) of enone **14** in 40 ml of 5% HCl was heated under reflux for 1 h. After neutralization with $NaHCO_3$, the reaction mixture was extracted three times with 20-ml portions of $CHCl_3$ and the combined organic extracts were dried over anhydrous sodium sulfate. After removal of the solvents, the crude residue was chromatographed on 60 g of silica gel (using 1:1 benzene–ethyl acetate for elution) to afford 795 mg (82%) of hydroxyenone **15** as an oil: $[\alpha]D^{C_6H_6}$ 28.1°; ir $\bar{\nu}$ ($CHCl_3$) 3610, 3420, 1653, 1590, and 1575 cm^{-1}; uv $\lambda_{max}^{95\%EtOH}$ 250 nm (ϵ 12 000) and 210 (9800); NMR δ ($CDCl_3$) 1.03 (s, 3), 1.5–2.9 (m, 18, containing s, ca. 3, at 2.51), 3.63 (t, J = 7 Hz, 1), 4.10 (br s, 1), 6.86 (t, J = 8 Hz, 2), 7.38 (t, J = 8 Hz, 2).

3. Jones Oxidation of Optically Pure 15. Formation of Optically Pure (+)-(7a*S*)-4-[2-(6-methylpyrid-2-yl)ethyl]-7a-methyl-7,7a-dihydro-1,5(6*H*)-indandione (16). To a solution containing 500 mg (1.75 mmol) of hydroxyenone **15** in 100 ml of acetone was added Jones' reagent (freshly prepared by dissolving 2.62 g of CrO_3 in 2.3 ml of H_2SO_4 and 7.7 ml of H_2O), until a brown color remained. After stirring at room temperature for 15 min, isopropyl alcohol was added to remove the brown color and the solution was filtered. The solvents were removed from the filtrate and the residue was taken up in 30 ml of ether and was washed with 10 ml of 5% $NaHCO_3$, 10 ml of H_2O, and finally with 10 ml of saturated NaCl. The ether layer was dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on 50 g of silica gel to afford 363 mg (72.5%) of optically pure enedione **16**, $[\alpha]D$ 202.0°, whose spectral properties were identical with those of an authentic sample of *dl*-**8a**.

4. Cyclization of Prochiral Trione 9 with L-Phenylalanine. Formation of Optically Enriched (+)-(7a*S*)-4-[2-(6-methylpyrid-2-yl)ethyl]-7a-methyl-7,7a-dihydro-1,5(6*H*)-indandione (17). A solution containing 516.2 mg (1.71 mmol) of trione **9**, 338.0 mg (2.05 mmol) of L-phenylalanine, and 0.86 ml of 1 N $HClO_4$ in 4.6 ml of acetonitrile was refluxed under an atmosphere of nitrogen for 40 h. After cooling to room temperature, the solution was filtered and the collected L-phenylalanine was thoroughly washed with $CHCl_3$. The combined filtrate and $CHCl_3$ washings were washed with 5% sodium bicarbonate, water, and finally with saturated NaCl solution. After drying the organic laer over anhydrous sodium sulfate, the solvents were removed to afford 402.1 mg of crude enedione **8a**. Chromatography of the crude material on 20 g of silica gel, using 3:2 benzene–ethyl acetate as the eluent, afforded 397.3 mg (82.1%) of pure enedione **17** as an oil, $[\alpha]D$ 173.6°. The spectral properties of **17** were identical with those of **8a**.[6]

5. Selective Reduction of Enriched Enone 17. Formation of (+)-(1*S*,7a*S*)-1-Hydroxy-4-[2-(6-methylpyrid-2-yl)ethyl]-7a-methyl-7,7a-dihydro-5(6*H*)-indanone (18). To a solution containing 3.43 g (0.0121 mol) of enedione **17**, $[\alpha]D$ 172.1°, in 170 ml of absolute ethanol at 0 °C and maintained under nitrogen, was cautiously added 0.232 g (0.0061 mol) of sodium borohydride. The reaction mixture was then stirred at 0 °C for 1 h. After warming to room temperature, the reaction mixture was slowly poured into 50 ml of water. The resultant mixture was neutralized by the addition of 10% HCl and was then extracted four times with 50-ml portions of $CHCl_3$. The combined organic extracts were washed with saturated NaCl solution and were then dried over anhydrous sodium sulfate. After removal of the solvents, chromatography of the residue on 150 g of silica gel (using 2:1 ethyl acetate–hexane for elution) afforded 2.97 g (88%) of optically enriched hydroxyenone **18**, $[\alpha]D$ 24.1°, as an oil. The infrared and NMR spectra of **18** were identical with those of racemic **8c**.[6]

6. Formation of Enriched (85%) Hydroxyenone 18 from 2-Methylcyclopentane-1,3-dione and Tris Annelating Agent 7 without Purification of Intermediates. In practice, the best chemical yields, without loss of optical efficiency, could be obtained by performing the conversion of 2-methylcyclopentane-1,3-dione → **18** without purification of any of the intermediates. This was carried out as follows.

To a mixture containing 10.07 g (0.0533 mol) of vinyl ketone **7** and 7.16 g (0.064 mol) of 2-methylcyclopentane-1,3-dione in 13 ml of ethyl acetate was added 7.5 ml of a solution of 20% triethylamine in ethyl acetate. The resulting reaction mixture was then stirred under an atmosphere of nitrogen and at room temperature for 36 h. The reaction mixture was poured into 20 ml of water and the mixture was extracted three times with 20-ml portions of $CHCl_3$. The combined extracts were dried over anhydrous sodium sulfate. Removal of the solvents then afforded 15.42 g of crude trione **9**.

A solution containing 15.42 g (0.0512 mol) of **9**, 10.13 g (0.0614 mol) of L-phenylalanine, and 12.8 ml of 1 N $HClO_4$ in 140 ml of CH_3CN was refluxed under an atmosphere of nitrogen for 48 h. After cooling to room temperature, the reaction mixture was filtered and the recovered L-phenylalanine was thoroughly washed with chloroform. The combined filtrate and washings were extracted with 5% sodium bicarbonate solution, then with water, and finally with saturated NaCl solution. The organic fraction was dried over anhydrous sodum sulfate. Evaporation of the solvents afforded 14.22 g of crude optically active enedione **17**.

To a solution containing 14.22 g (0.0502 mol) of crude **17** in 425 ml of absolute ethanol at 0 °C and under an atmosphere of nitrogen was added 949 mg (0.0251 mol) of $NaBH_4$. After being stirred for 1 h at 0 °C, the reaction mixture was poured into 200 ml of H_2O. After neutralization with 10% HCl, the solution was extracted four times with 200-ml portions of $CHCl_3$. The combined organic layers were washed with saturated NaCl solution and then dried over anhydrous sodium sulfate. After removal of the solvents, the residue (14.25 g) was chromatographed on 500 g of silica gel (using 2:1 ethyl acetate–hexane for elution) to afford 11.43 g (75%) of pure hydroxyenone **18** as an oil, $[\alpha]D$ 24.22° (85.3% optically pure). Anal. ($C_{18}H_{23}NO_2$) C, 75.84; H, 8.17; N, 4.90.

7. Formation of Racemic 3aϵ-Hydroxy-4-[2-(6-methylpyrid-2-yl)ethyl]-7a-methyl-3a,4,7,7a-tetrahydro-1,5(6*H*)-indandione (21). To a solution containing 52 mg (2.26 mmol) of sodium hydride in 150 ml of dry DME (freshly distilled from calcium hydride) under a nitrogen atmosphere and at room temperature was added 2.80 g (0.0250 mol) of 2-methylcyclopentane-1,3-dione. After stirring at room temperature for 5 min, a solution containing 4.29 g (0.023 mole) of vinyl ketone **7** in 25 ml of dry DME was added. The resulting solution was then refluxed for 5 h. After this time, TLC (4:4:1 hexane–ethyl acetate–methanol) examination showed the complete disappearance of the starting vinyl ketone **7** (R_f 0.61) and the presence of two new materials (R_f 0.43 and 0.56). The reaction mixture was cooled to room temperature and 50 ml of H_2O was slowly added. The resulting mixture was extracted four times with 50-ml portions of $CHCl_3$. After drying the combined organic layers over anhydrous sodium sulfate, the solvents were removed to afford 6.86 g of crude product. Attempted chromatography on 500 g of silica gel, using 3:2 benzene–ethyl acetate for elution, did not separate the components. Upon standing, a crystalline product formed. Trituration of the chromatographed material with a hexane–ethyl acetate mixture afforded 2.24 g of racemic crystalline β-ketal **21**. Recrystallization (hexane–ethyl acetate) of this crystalline material afforded 2.05 g (30%) of pure β-ketol **21**, mp 132–134 °C. Rechromatography of the mother liquors (4.81 g consisting of mainly trione **9**) afforded, after recrystallization, an additional 1.22 g (18%) of crystalline **21**. The total yield of β-ketol was 3.27 g (48%). The mother liquors consisted mainly of trione 9, but did contain a small amount of **21** as an impurity, as judged by the "angular methyl" NMR signals (δ 1.33 for β-ketol **21**, δ 1.05 for trione **9**); ir $\lambda_{max}^{CHCl_3}$ 3660, 1730, and 1710 cm^{-1}; NMR δ ($CDCl_3$) 1.33 (s, 3), 1.5–3.6 (m, 16), 6.58 (br s, 1), 6.95 (d, J = 8 Hz, 2), 7.12 (d, J = 8 Hz, 1); *m/e* 301 (P). Anal. ($C_{18}H_{23}NO_3$) C, 71.65; H, 7.65; N, 4.50.

8. Complete Dehydration of Racemic 21 with L-Phenylalanine. Formation of Racemic 8a. A solution containing 187 mg (0.620 mmol) of racemic **21**, 122 mg (0.744 mmol) of L-phenylalanine, and 0.2 ml of 1 N $HClO_4$ in 1.7 ml of acetonitrile was heated under reflux under an atmosphere of nitrogen for 24 h. After being cooled to room temperature, the reaction mixture was filtered and the collected L-phenylalanine was thoroughly washed with $CHCl_3$. The combined filtrates were washed with 5% sodium bicarbonate solution, then with water, and finally with saturated NaCl solution. After the organic layers were dried over anhydrous sodium sulfate, the solvents were removed to afford 174 mg of crude enedione **8a**. Chromatography on 10 g of silica gel (using 3:2 benzene–ethyl acetate for elution) afforded 154.0 mg (88%) of enedione **8a**, $[\alpha]D$ 0.00°.

9. Partial Dehydration of β-Ketol 21 under the Influence of L-Phenylalanine. Formation of Enone 25 and β-Ketol 24. A solution containing 201 mg (0.667 mmol) of β-ketol **21**, 132 mg (0.800 mmol) of L-phenylalanine, and 0.17 ml of 1 N $HClO_4$ in 1.8 ml of acetonitrile

was refluxed under an atmosphere of nitrogen for 3 h. After cooling to room temperature, the reaction mixture was filtered and the collected L-phenylalanine was thoroughly washed with $CHCl_3$. The combined filtrates were washed with 5% sodium bicarbonate solution, then with water, and finally with saturated NaCl solution. The organic layer was dried over anhydrous sodium sulfate and the solvents were removed to afford 198 mg of crude material. Chromatography on 25 g of silica gel, using 3:2 hexane–ethyl acetate as the eluent, afforded 156 mg of enedione **8a**, $[\alpha]D$ 16.08°, and 38 mg of **21**, $[\alpha]D^{C_6H_6}$ 1.35°.

10. Reaction of Prochiral Trione 9. Isolation of Optically Enriched β-Ketol 22 and Optically Enriched Enone 17. Formation of Optically Pure β-Ketol 23. A solution containing 4.35 g (0.0145 mol) of trione **9**, 2.87 g (0.0174 mol) of L-phenylalanine, and 3.6 ml of 1 N $HClO_4$ in 39 ml of acetonitrile was refluxed under a nitrogen atmosphere for 30 h. After cooling to room temperature, the reaction mixture was filtered and the collected L-phenylalanine was thoroughly washed with $CHCl_3$. The combined organic filtrates were washed with 5% sodium bicarbonate solution, then with water, and finally with saturated NaCl solution. After drying the organic layer over anhydrous sodium sulfate, removal of the solvents afforded 4.261 g of crude material. Chromatography of this material on 500 g of silica gel, using 3:2 hexane–ethyl acetate as the eluent, afforded 0.823 g (19%) of crystalline β-ketol **22**, $[\alpha]D$ −47.2°. A portion of this material was then recrystallized from hexane–ethyl acetate to give optically pure β-ketol **23** of constant rotation, $[\alpha]D$ −55.03°, mp 157–158 °C. Also obtained from the chromatography was 2.820 g (69%) of enedione **17**, $[\alpha]D$ 171.4°.

11. Complete Dehydration of Optically Enriched (−)-β-Ketol 22 and Optically Pure β-Ketol 23. In separate reactions, samples of β-ketol **22**, $[\alpha]D$ −47.2°, and a sample of β-ketol **23**, $[\alpha]D$ −55.03°, were dehydrated as follows. A solution containing 1.0 equiv of β-ketol, 1.2 equiv of L-phenylalanine, and 0.25 equiv of $HClO_4$ was refluxed in acetonitrile (2.7 ml/mmol) under an atmosphere of nitrogen for 24 h and was worked up as before. In this way, β-ketol **22**, $[\alpha]D$ −47.2°, afforded (88%) enedione **17**, $[\alpha]D$ 171.5°, and β-ketol **25**, $[\alpha]D$ −55.03°, afforded (87%) enedione **16**, $[\alpha]D$ 200.1°.

12. Catalytic Hydrogenation of 18 (in Triethylamine–Ethyl Acetate) Followed by Ketalization. Formation of Optically Enriched (7a*S*)-1β-Hydroxy-4-[2-(6-methylpyrid-2-yl)ethyl]-7a-methyl-3aβ,4ε,7,-7aβ-tetrahydroindan-5(6*H*)-one Ethylene Ketal (29) and 1β-Hydroxy-4-[2-(6-methylpyrid-2-yl)ethyl]-7a-methyl-3aα,4ε,7,-7aβ-tetrahydro- indan-5(6*H*)-one Ethylene Ketal (30). To a solution containing 4.17 g (0.0146 mol) of hydroxyenone **18**, $[\alpha]D$ 24.3°, in 150 ml of a 3:1 solution of ethyl acetate–triethylamine was added 2.80 g of 10% palladium on carbon. The resultant mixture was stirred under an atmosphere of hydrogen at atmospheric pressure and room temperature for 6 days. The reaction mixture was filtered and the collected catalyst was thoroughly washed with absolute ethanol. Removal of the solvents from the combined filtrates afforded 4.02 g of crude dihydro products.

A solution containing 4.02 g of crude dihydro products, 10 ml of ethylene glycol, and 100 mg of *p*-TsOH in 50 ml of toluene was refluxed under an atmosphere of nitrogen for 36 h. After cooling to room temperature, 30 ml of 5% sodium bicarbonate solution was added. The resulting mixture was extracted four times with 60-ml portions of ether. The combined organic extracts were washed with water, then with saturated NaCl solution, and finally were dried over anhydrous sodium sulfate. After removal of the solvents, the residue was chromatographed on 400 g of silica gel (using 1:1 hexane–ethyl acetate for elution) to afford 1.75 g (37%) of cis hydroxy ketal **29**. Continued elution with the same solvent system afforded 2.13 g (44.0%) of trans hydroxy ketal **30**. For **29**: ir $\lambda_{max}^{liq\ film}$ 3333, 1592, and 1574 cm^{-1}; NMR δ 1.07 (s, 3), 1.2–2.3 (m, 13), 2.52 (s, 3), 2.73 (t, J = 8 Hz, 2), 3.6–4.0 (m, 5), 6.97 (d, J = 8 Hz, 2) and 7.47 (t, J = 8 Hz, 1); *m/e* 331 (parent), 107 (base). Anal. ($C_{20}H_{29}NO_3$) C, 72.47; H, 8.86; N, 4.37. For **30**: ir $\lambda_{max}^{liq\ film}$ 3333, 1592, and 1574 cm^{-1}; NMR δ $CDCl_3$ 0.83 (s, 3), 1.2–2.2 (m, 12), 2.52 (s, 3), 2.82 (t, J = 7.5 Hz, 2), 2.98 (br s, 1), 3.68 (t, J = 8 Hz, 1), 3.97 (br s, 4), 6.95 (d, J = 7.5 Hz, 2), and 7.43 (t, J = 7.5 Hz, 1); *m/e* 331 (parent), 107 (base peak). Anal. ($C_{20}H_{29}NO_3$) C, 72.25; H, 8.92; N, 4.32.

13. Catalytic Hydrogenation of 18 in Ethanolic Perchloric Acid Followed by Ketalization. Formation of 29, 30, and Optically Enriched (7a*S*)-1β-Hydroxy-4-[2-(6-methylpyrid-2-yl)ethyl]-7a-methyl-5,6,7,7a-tetrahydroindan (31). To a solution containing 8.24 g (0.0289 mol) of hydroxyenone **18**, $[\alpha]D$ 24.3°, 2.9 ml of 1.0 N $HClO_4$, and 17 ml of H_2O in 260 ml of absolute ethanol was added 5.60 g of 10% palladium on carbon. The resultant mixture was shaken under an atmosphere of hydrogen at 3 atm of pressure and at room temperature for 3 days. The reaction mixture was filtered and the collected catalyst was thoroughly washed with absolute ethanol. After evaporation of the solvents, the residue was taken up in 200 ml of $CHCl_3$. The organic layer was washed with 5% sodium bicarbonate solution, then with water, and finally with saturated NaCl solution. After drying over anhydrous sodium sulfate, removal of the solvents afforded 8.21 g of crude dihydro product.

A solution containing 8.21 g of crude dihydro products, 200 ml of *p*-TsOH·H_2O, and 20 ml of ethylene glycol in 100 ml of toluene was refluxed under an atmosphere of nitrogen for 36 h. During this time, the water which formed in the reaction was removed via a Dean–Stark trap. After cooling to room temperature, 50 ml of 5% sodium bicarbonate solution was added and the mixture was extracted four times with 100-ml portions of ether. The combined ether extracts were washed with water and saturated NaCl. The ether phase was dried over anhydrous sodium sulfate. After removal of the solvents, the crude residue was chromatographed on 700 g of silica gel (using 1:1 hexane–ethyl acetate for elution) to afford 1.63 g (21%) of hydrogenolysis product **31**. Continued elution with the same solvent system then gave 1.74 g (17%) of cis hydroxy ketal **29** and then 4.31 g (45%) of trans hydroxy ketal **30**. The spectral properties of **29** and **30** were the same as those given above. For **31**: ir $\lambda_{max}^{CHCl_3}$ 3550, 3425, 1595, and 1577 cm^{-1}; NMR δ ($CDCl_3$) 0.87 (s, 3), 1.3–2.7 (m, 21 containing s, ca. 3, at 2.47), 3.42 (t, J = 8 Hz, 1), 6.77 (m, 2), and 7.25 (t, J = 7.5 Hz, 1); *m/e* 271 (parent), 107 (base peak).

14. Reductive–Hydrolytic Cyclization of 30. Formation of Optically Enriched 1β-Hydroxy-4ε-[2-(cyclohex-2-en-1-on-4-yl)ethyl]-7aβ-methyl-3a,4,7,7a-tetrahydro-5(6*H*)-indanone (33). To a solution containing 2.10 g (6.34 mmol) of trans hydroxy ktal **30**, 1.16 g (24.36 mmol) of absolute ethanol, and 6.0 ml of anhydrous ether in 60 ml of anhydrous liquid ammonia (freshly distilled from Na) was added 321 mg (13.95 mmol) of sodium metal. After disappearance of the blue color, the ammonia was evaporated under a stream of nitrogen. The residue was taken up in 28 ml of ethanol and a solution containing 700 mg (17.5 mmol) of sodium hydroxide in 14 ml of water was added. The resulting solution was stirred for 2.5 h at room temperature under an atmosphere of nitrogen. The reaction mixture was acidified with 10% HCl and the resulting solution was extracted four times with 50-ml portions of $CHCl_3$. The combined organic extracts were washed with water and then with saturated NaCl solution, and were finally dried over anhydrous sodium sulfate. Removal of the solvent afforded 1.82 g of crude **33**. This material was judged to be suitable for subsequent reactions by its TLC behavior (4:4:1 hexane–ethyl acetate–methanol). Only one spot was evident, R_f 0.42, with the only contamination being a small spot at the origin: ir $\lambda_{max}^{CHCl_3}$ 3597, 3390, 1709, 1664, and 1629 cm^{-1}; *m/e* 290 (P); NMR δ ($CDCl_3$) 1.08 (s, 3), 1.2–2.6 (m, 20), 3.09 (br s, 1), 3.78 (t, J = 7 Hz, 1), and 5.88 (br s, 1).

15. Cyclodehydration of 33. Formation of (−)-Δ$^{9(10)}$-Dehydro-19-nortestosterone (37). A solution containing 1.95 g of **33** and 640 mg of *p*-TsOH·H_2O in 70 ml of glacial acetic acid under an atmosphere of nitrogen was heated at 100 °C for 1.5 h. After cooling to room temperature, the reaction mixture was concentrated to ca. 5 ml. To this concentrate was added 15 ml of H_2O. After neutralization with sodium bicarbonate, the mixture was extracted three times with 25-ml portions of $CHCl_3$. After drying the combined organic extracts over anhydrous sodium sulfate and removal of the solvents, the residue was taken up in 23 ml of 5% methanolic KOH. The resulting solution was stirred under an atmosphere of nitrogen for 1 h. To this was then added 10 ml of H_2O and the solution was then extracted four times with 25-ml portions of $CHCl_3$. The combined organic extracts were washed with water and then with saturated NaCl solution. After drying the organic layer over anhydrous sodium sulfate and removing the solvents, the residue was chromatographed on 75 g of silica gel (using 1:1 hexane–ethyl acetate for elution) to afford 1.26 g (68% from **30**) of optically enriched crystalline dienedione **37**, $[\alpha]D^{CHCl_3}$ −249.5°, lit.[28] $[\alpha]D$ −290.2°. Recrystallization (Et_2O–MeOH) afforded 1.04 g (56% from **30**) of crystalline (−)-**37**, mp 188–189 °C, $[\alpha]D$ −290°, lit.[28] mp 187–189 °C: uv $\lambda_{max}^{95\%\ EtOH}$ 303 nm (ε 20 000); ir $\lambda_{max}^{CHCl_3}$ 3559, 3378, 1650, and 1608 cm^{-1}; *m/e* 272 (P); NMR δ ($CDCl_3$) 0.91 (s, 3), 1.1–3.1 (m, 19), 3.72 (t, J = 8 Hz, 1), 5.69 (br s, 1).

These spectra were identical with the spectra of a sample of optically pure (−)-**38** obtained from Roussel-Uclaf.

16. Reduction of 37. Formation of (13*S*)-(+)-17β-Hydroxyestra-

5(10)-en-3-one (38). To a solution containing 30 ml (4.34 mmol) of lithium in 30 ml of dry liquid ammonia (freshly distilled from lithium) was cautiously added 150.0 mg (0.551 mmol) of fully synthetic dienedione **38** in 15 ml of dry THF (freshly distilled from CaH_2). After stirring the resulting solution for 10 min, NH_4Cl was cautiously added to remove the blue color. After evaporation of the ammonia in a stream of nitrogen, 15 ml of water was added followed by 15 ml of CH_2Cl_2. The organic layer was separated and the aqueous layer was extracted three times with 10-ml portions of CH_2Cl_2. The combined organic layers were dried over anhydrous sodium sulfate and the solvents were removed to afford 149.7 mg of crude dihydro product. Recrystallization from ether afforded 126 mg (83%) of white crystalline 17β-hydroxyestra-5(10)-en-3-one (**38**), mp 179–185 °C, $[\alpha]D^{CHCl_3}$ 189.4°; lit.[30] mp 175–185 °C, $[\alpha]D^{CHCl_3}$ 189.8°.

17. Oxidation of 33. Formation of Optically Enriched (7a*S*)-4-[2-(Cyclohex-2-en-1-on-3-yl)ethyl]-7a-methyl-3aα,4ϵ,7,7a-tetrahydro-1,5(6*H*)-indandione (35). To a solution containing 1.82 g of hydroxyenedione **33** in 300 ml of acetone was slowly added freshly prepared Jones' reagent (prepared by dissolving 262 g of CrO_3 in 2.3 ml of concentrated H_2SO_4 and 7.7 ml of H_2O) until the brown color remained. After stirring at room temperature for 15 min, isopropyl alcohol was added to remove the brown color. The resulting solution was filtered and concentrated to about 25 ml. The solution was then taken up in 100 ml of $CHCl_3$ and was washed with 5% sodium bicarbonate solution, water, and finally with saturated NaCl solution. After drying the organic layer over anhydrous sodium sulfate, the solvents were removed to afford 1.80 g of crude optically active enetrione **35.** The TLC (4:4:1 hexane–ethyl acetate–methanol) behavior of this material indicated a homogeneous material (R_f 0.55) with the only contamination being at the origin: ir $\lambda_{max}^{CHCl_3}$ 1739, 1706, 1661, and 1623 cm^{-1}; NMR δ ($CDCl_3$) 1.18 (s, 3), 1.5–2.8 (m, 20), and 5.87 (br s, 1); *m/e* 288 (parent).

18. Cyclodehydration of 35. Formation of Optically Enriched (13*S*)-$\Delta^{9(10)}$-19-norandrost-4-ene-3,17-dione (36). A solution containing 1.80 g of enetrione **35** and 595 mg of *p*-TsOH·H_2O in 65 ml of glacial acetic acid was heated at 100 °C under an atmosphere of nitrogen for 1.5 h. After cooling to room temperature, the solution was concentrated to about 3 or 4 ml. To this solution was then added 10 ml of H_2O. The aquous solution was then neutralized by the cautious addition of sodium bicarbonate. The resulting mixture was extracted with three 15-ml portions of $CHCl_3$. The combined $CHCl_3$ extracts were dried over anhydrous sodium sulfate. Removal of the solvents afforded 1.68 g of crude dienedione **36.** This material was judged to be homogeneous by TLC behavior (4:4:1 hexane–ethyl acetate–methanol, R_f 0.65) with the only contamination being at the origin: ir $\lambda_{max}^{CHCl_3}$ 1733, 1658, and 1633 cm^{-1}; NMR δ ($CDCl_3$) 1.03 (s, 3), 1.3–3.1 (m, 18), 5.72 (br s, 1); *m/e* 270 (parent).

19. Isomerization of 36. Formation of Optically Pure (13*S*)-(+)-Estrone. To a solution containing 1.60 g of crude dienedione **36** in 7 ml of CH_2Cl_2 under an atmosphere of nitrogen was added 1.53 g of acetic anhydride and 1.19 g of acetyl bromide. The resulting solution was then stirred for 1 h at room temperature. To the reaction mixture was then slowly added 70 ml of 5% sodium bicarbonate solution. The resulting mixture was extracted four times with 50-ml portions of $CHCl_3$. After drying the combined extracts over anhydrous sodium sulfate and removing the solvents, the residue was taken up in 400 ml of methanol. To this solution was added 70 ml of H_2O and 5.65 g of K_2CO_3. The resulting solution was then stirred under an atmosphere of nitrogen at room temperature for 5 h. After neutralization with 10% HCl, the methanol was evaporated and the remaining water layer extracted four times with 100-ml portions of $CHCl_3$. After drying the combined extracts over anhydrous sodium sulfate and removal of the solvents, the residue was chromatographed on 75 g of silica gel (using 2:1 hexane–ethyl acetate for elution) to afford 827 mg (48% from **30**) of crystalline estrone, $[\alpha]D^{dioxane}$ 138.4°, authentic sample $[\alpha]D^{dioxane}$ 161°. Recrystallization from ether–methanol afforded 673 mg (39% from **30**) of synthetic estrone, $[\alpha]D^{dioxane}$ 160°, mp 254–255 °C, authentic sample mp 255–256 °C, undepressed mixture melting point. Evaporation of the mother liquors afforded 154 mg (9% from **30**) of virtually racemic estrone, $[\alpha]D^{dioxane}$ 7.25°. The infrared, NMR, and mass spectra of the synthetic estrone were identical with those of natural (+)-estrone.

Acknowledgment. This research was supported by PHS Grant CA-12107-11. Additional support from the Hoffman-La Roche Corporation is gratefully acknowledged. Acknowledgment is also made to Schering AG for a generous gift of 2-methylcyclopentane-1,3-dione and to Dr. U. Eder for communicating his procedures to us prior to publication. NMR facilities were supported by PHS Grant RR-00292-04.

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(14) We wish to thank Dr. U. Eder of Schering AG for communicating to us the optical purity of **20**[10b] and the experimental procedure for its preparation.
(15) The D-amino acids were obtained through the courtesy of Dr. Malcolm Bell of the Sterling Winthrop Laboratories.
(16) For a racemic mixture undergoing kinetic resolution, it is easily seen that $Y_R/X_S = \lambda/1 - \lambda$, where Y_R is the enantiomeric enrichment of the *R* enantiomer in the starting material and X_S is the enantiomeric enrichment of the *S* enantiomer of the product and λ is the extent of reaction. Since the specific rotation of optically pure **23** is shown to be −55.03°, Y_R for **24** is 2.5%. Given an enantiomeric excess of 8.0% in X_S (i.e., compound **17**), the calculated value for Y_R at $\lambda = 0.2$ is 2.0%. Given the experimental uncertainties in establishing λ (±3%) and in measuring $[\alpha]D$ for only slightly enriched **24** (±10%), the agreement between the calculated and observed values of Y_R must be regarded as satisfactory.
(17) In a racemate undergoing kinetic resolution it is seen that $k_R/k_S = \rho = 1 + (\ln \beta/\ln \alpha)$, where $\beta = (Y_R + 1)/(1 - Y_R)$ and $\alpha = 2(1 - \lambda)/(\beta + 1)$. Given the values X_S, Y_R (calculated), and λ, $\rho = 0.8$.
(18) A recent disclosure (P. Buchsacher, A. Fuerst, and J. A. W. Gutzwiller German Offen. 2 455 372; *Chem. Abstr.*, **83**, 113 377 (1975)) indicates that the racemic β-aldol derived from compound **10** is converted to (+)-**11a** by heating with optically active *S*-proline in DMF. The substrate and the conditions are totally different from those used here, and though the optical specificity and extent ofconversion (kinetic resolution?) are not given, the possibility exists that reversibility of β-aldol → prochiral trione may be realizable under some reaction conditions.
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in parts per million (δ) relative to Me_4Si. Mass spectra were obtained on an LKB 9000A gas chromatography–mass spectrometer by direct probe. All optical rotations were obtained on a Perkin-Elmer 247 polarimeter using a 1 dm cell. The concentration of all samples was 1% and the solvent was benzene unless otherwise indicated. Elemental analyses were conducted by Galbraith Laboratories, Inc., Knoxville, Tenn. Hydrogenations requiring 3 atm of pressure were done on a Parr hydrogenator. Ultraviolet spectra were recorded on a Perkin-Elmer 124 recording spectrophotometer.

Crystal and Molecular Structure of *d,l*-Dethiobiotin. Role of Sulfur in Biotin Stereochemistry[1a]

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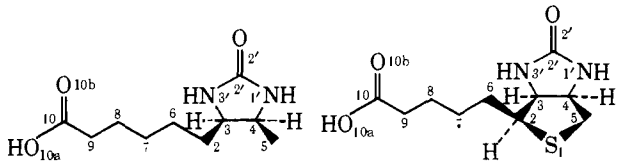
Abstract: The crystal structure of *d,l*-dethiobiotin ($C_{10}H_{18}N_2O_3$) has been accurately determined using x-ray diffraction techniques and refined to a residual of 0.055. The crystals are monoclinic, space group $P2_1/a$, with cell constants (at 22 ± 3 °C) a = 29.9166 (2) Å, b = 4.9990 (1) Å, c = 7.7561 (1) Å, β = 97.855 (2) °, and Z = 4. The ureido moiety in dethiobiotin displays unusual bond lengths for the C=O (1.244 (4) Å) and two C—N bonds (1.346 (4) and 1.347 (4) Å). The ureido oxygen accepts a strong hydrogen bond from the carboxyl group of a neighboring molecule (O···O, 2.633 Å; H···O, 1.83 Å) and is also hydrogen bonded to N(1′). These results lend support to the theory of activation of biotin by increased acidity of the NH groups and the increased nucleophilicity of nitrogen, stabilized by hydrogen bonds to the ureido oxygen. Since both the C–N bond lengths are very nearly equal, the reason for the preferential carboxylation at N(1′) is not electronic but steric, due to a close nonbonded contact (3.042 Å) of a carbon atom of the caproic acid chain to the proximal nitrogen. Lack of sulfur in dethiobiotin does not change the dimensions of the ureido moiety from those observed in biotin, indicating no dominant C···S transannular interaction as suggested by others. The 2-imidazolidone ring in dethiobiotin is markedly nonplanar, and the caproic acid chain is in the trans planar zig-zag conformation, indicating an important role for sulfur in stabilizing both the planarity of the imidazolidone ring and the twisted conformation of the side chain found in biotin.

Dethiobiotin (I) is an intermediate in the biosynthesis of biotin (II).[2] It has been demonstrated that dethiobiotin itself does not serve as a substitute for biotin in carboxylase, decarboxylase, or transcarboxylase systems, but rather is first converted to biotin which is then attached to the appropriate apoenzyme. As a biotin vitamer, it is capable of promoting growth in biotin-deficient systems by conversion to biotin, the essential coenzyme responsible for fixing CO_2 for eventual transfer. It has been observed that dethiobiotin counteracts the tumor promoting effects of biotin in certain systems.[3] It has been suggested[4] that nucleophilic activation of biotin is via hydrogen bond formation with an attendant increase in the double bond character of the carbonyl carbon–nitrogen bonds and a concomitant increase in NH acidity. In a recent paper,[5] structural evidence was presented for the stabilization of the polarization of the ureido carbonyl bond via hydrogen bond formation. In order to investigate the properties of the ureido function more fully, and to determine the role of sulfur on the basic vitamin conformation, the crystal structure of *d,l*-dethiobiotin was determined. This study revealed additional evidence regarding the polarization of the carbonyl bond and shed some light on the role of sulfur in biotin stereochemistry.



I II

Experimental Section

Crystals of *d,l*-dethiobiotin (Nutritional Biochemical Corp.) were grown by slow evaporation from a saturated aqueous solution. A needle-shaped crystal, elongated along the b axis, of dimensions 0.10 × 0.21 × 0.13 mm, was mounted for data collection. Cell constants (Table I) were obtained by a least-squares fit of the 2θ values of 60 high angle reflections for which α_1,α_2 separation could be observed and measured on a GE XRD-5 diffractometer. Unique three-dimensional intensity data (2548 reflections) to the limit $\sin\theta/\lambda = 0.64$ Å^{-1} for Cu Kα radiation (λ 1.540 51 Å) were measured on a GE XRD-5 diffractometer by the stationary crystal–stationary counter method[6] using a 5° take-off angle. Balanced Ni–Co Ross filters were used for effective monochromatization. Reflections (952) which had intensities less than twice the background value in that ($\sin\theta/\lambda$) range were given zero weight during the refinement and for the residual calculation. The anisotropy of absorption was checked for the 020 reflection (χ = 90°) in 10° steps of ϕ, and the crystal showed essentially no variation of absorption as ϕ varied. The data were corrected for Lorentz–polarization effects and processed in the usual way. No detailed absorption correction was applied (μ = 7.64 cm^{-1}).

Structure Determination and Refinement. The crystal structure was determined by routine application of the multi-solution tangent refinement technique, employing the program MULTAN.[7] The 15 nonhydrogen atoms were located in the first E map using the phase set with the highest figure of merit[7] (1.0159), yielding a structure with a residual of 0.26. The atomic positional and individual isotropic thermal parameters of the nonhydrogen atoms were refined by block-diagonal least-squares technique to an R of 0.10. An electron-density difference map at this stage clearly revealed the location of the 18 hydrogen atoms. Continuation of the refinement with individual anisotropic thermal parameters for nonhydrogen atoms and isotropic thermal parameters for hydrogen atoms led to the final R of $(\Sigma(\|F_o| - |F_c\|)/\Sigma|F_o|) = 0.055$. Each of the shifts of the parameters in the final cycle were less than 0.2 of the esd of the corresponding parameter. The function minimized during the refinement was $[w(|F_o| - (1/k)|F_c|)^2]$, using the weighting scheme of Evans.[8] Atomic scattering factors for O, N, and C were those listed in International Tables;[9a] for the hydrogen atoms, the values given in ref 9b were used.

Results

The final positional and thermal parameters are collected in Tables II and III. The observed and calculated structure