Journal of Steroid Biochemistry, 1975, Vol. 6, pp. 177–181. Pergamon Press. Printed in Great Britain

AN EXPEDITIOUS SYNTHESIS OF ESTRONE

S. DANISHEFSKY* and P. CAIN

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, U.S.A.

SUMMARY

The Tris annelating agent, 6-(2-methyl-6-pyridyl-hex-1-ene-3-one), has been synthesized in four steps from the readily available 2,6-lutidine. To this 12-carbon ensemble is added, in a Michael fashion, 2-methycyclopentane-1,3-dione. The prochiral pyridyltrione, so produced, can be cyclized to afford 4-(2-α-picolylethyl)-hydrind-4-ene-3,7-dione (I). Using conventional acidic catalysis, compound I is obtained as the racemate. However, under the influence of L-phenylalanine, an 86% enrichment (*i.e.* 93% 13S; 7% 13R) of the desired enantiomer is realized. The key reaction in the steroid synthesis involves Birch reduction of the pyridine ring followed by hydrolytic ring opening, recyclization *via* the aldol route, deketalization and vinylogous aldol cyclization.

INTRODUCTION

For the past 40 years, the steroids have been the recipients of intense interest from synthetic organic chemists [1]. This attention is the result of a productive confluence of biology and chemistry. Though the extent of the diversity of the physiological activity of steroids still awaits full definition, the application of steroids and modified steroids to medical objectives ranging from anti-inflammation to contraception has, no doubt, been a positive factor in initiating and sustaining research directed toward their total synthesis [2]. Chemically, the steroids along with their biogenetically related terpenes, have provided the arena in which have been developed many of the key reactions of alicyclic synthesis.

In formulating a program addressed to steroid total synthesis, one can't help but be cognizant of the many successes which have already been recorded in this area [1]. Obviously, two of the classical reasons for undertaking a total synthesis, *i.e.* proof of structure and sheer demonstration of a feasibility are no longer, on the whole, appropriate to this class of natural products. Nevertheless, we were attracted to steroids as devices for testing a new synthetic strategy, namely, the conversion of a picolyl moiety to cyclohexenone.

In choosing steroid synthesis as the setting in which to demonstrate this synthetic equivalency, we were mindful of what is perhaps the ultimate rationale for the total synthesis of products already known from nature, *i.e.* the possibility of increasing their availability in a meaningful way.

The availability of estrone or its derivative 19-norsteroids, by partial synthesis from sterols or sapogenins, is clearly a time-variable concept [2, 3]. Among the factors which might influence this type of availability are the abundance of the natural source, the feasibility of extraction of the natural product from the natural source, and the ease of the chemical manipulations in the partial synthesis process. The precise calculation of the efficiency required of a total synthesis of estrone, such that the total synthesis is competitive with partial synthesis (or indeed, with other total syntheses), is beyond the competence of our laboratory. Nevertheless, it is possible to identify certain general criteria which must be faced if a total synthesis is to be even worthy of consideration as a potential source of steroids. The total synthesis should occur in good overall yield. It should begin with a readily available starting material, which is converted to the final product *via* inexpensive reagents. In this spirit, one should be particularly wary of syntheses which involve various operations which are themselves more costly than the end products under pursuit. Along the synthetic pathway, useful intermediates should be readily separable from unwanted byproducts.

The importance of producing the final steroid in antipodally pure form, corresponding in absolute configuration to that required for biological function, has already been stressed [4]. In principle, this may be achieved in three ways. The possibility of starting with a naturally occurring precursor whose chirality is appropriate to that required in the final steroid, should be considered. This approach is, of course, implicit in all the partial synthesis strategies [3], and one could envision its extension to non-steroidal starting materials. Another attractive possibility involves asymmetric synthesis [5, 6]. In this approach, the desired chirality is induced into the synthetic stream by judicious (more often, adventitious) use of chiral reagents. Finally, there is the possibility of resolution. At this stage of steroid synthesis, it is generally felt that recourse to resolution, in itself, constitutes a serious, if not fatal, impediment to the prospects of practical application.

The chemical logic of our plan is set forth in Fig. 1. Two electron reduction of picolyl derivative **1** might give the dihydro derivative **2**. System **2** is hydrolytically related to the 1,5-diketone **3**. The latter may be envisioned as an aldol type precursor

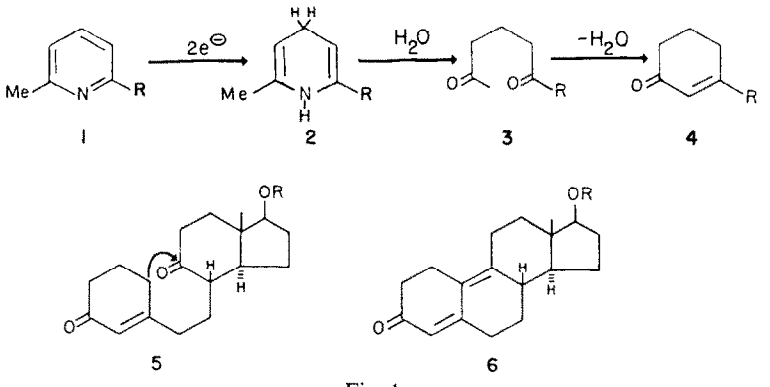

Fig. 1.

of cyclohexenone **4.** It is recognized that, in principle, a wide latitude of functionality may be encompassed in the formalism *R*. Included among these, is the possibility that *R* represents the CD system of a potential steroid appended *via* an *ethano* linkage. In that event, system **4** may be expanded to **5**. It will be seen that **5** might be induced to undergo further aldolization, in a vinylogous sense, to give rise to **6**. Compound **6** can be converted to 19-norsteroids *via* chemical reduction, or to estrone itself by armotization.

RESULTS

Previous research in our laboratory has resulted in the experimental realization of the essential features of this scheme. Early studies were initiated on cyclohexanone. Picolylethylation of the pyrrolidine enamine of cyclohexanone with 2-methyl-6-vinylpyridine followed by ketalization gave intermediate **7**. The ketalization was, of course, necessary to avoid reduction of the carbonyl group concurrent with reduction of the pyridine. Intermediate **7** was subjected to reduction with sodium–ammonia–ethanol. The dihydropyridine, so produced, was exposed, *in situ*, to hydrolytic cyclization and the presumed diketone system (cf. 3) was, *in situ*, aldolyzed. Deketalization produced intermediate **8**. The latter underwent very smooth vinylogous aldolization to give model dienone **9**.

With these favorable precedents secured, we then turned to the total synthesis of dl-D-homoestrone [8]. The synthesis started with the well known racemic monoketal **10** of the Wieland–Miescher ketone. Base induced picolylethylation, using potassium-tert-butoxide/2-methyl-6-vinylpyridine was followed by deketalization and selective (sodium borohydride) reduction to give the crystalline hydroxyenone, **11**. In recent experimentation, an 80% yield has been realized for the three step preparation of **11** [8].

Compound **11** was primed for reductive annelation, first by catalytic reduction and then by ketalization. The conversion of **11** → **12** has been executed in 82% yield by the use of Pd/C in 90% ethanol containing 0·1 eq of $HClO_4$ in the catalytic reduction step. This constitutes a significant improvement over what has been previously reported [8]. Intermediate **12**, was subjected to chemical reduction (sodium–ammonia–ethanol), hydrolytic-cyclization (sodium hydroxide aqueous ethanol-room temperature) and deketalization (aqueous acid-room temperature). The resultant hydroxyenedione, **13a**, was oxidized (Jones), whereupon the crystalline *seco*-steroid **13b**, was obtained. The yield of **12** → **13b** is 75%. The remaining two steps from **13b** → dl-D-homoestrone (**15**) were easily performed. Thus, cyclization with tosyl

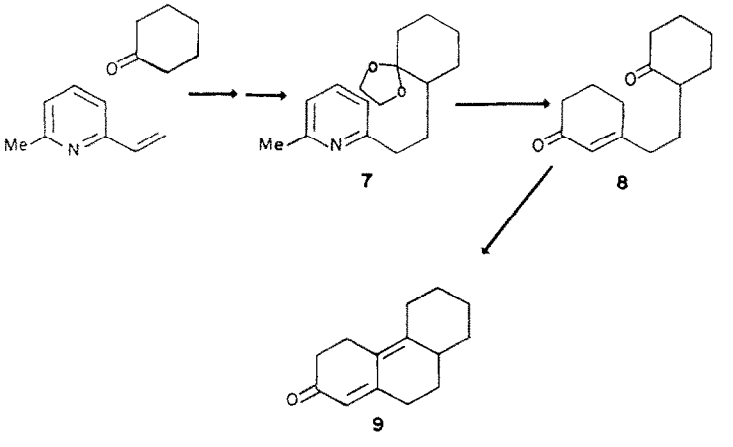

Fig. 2.

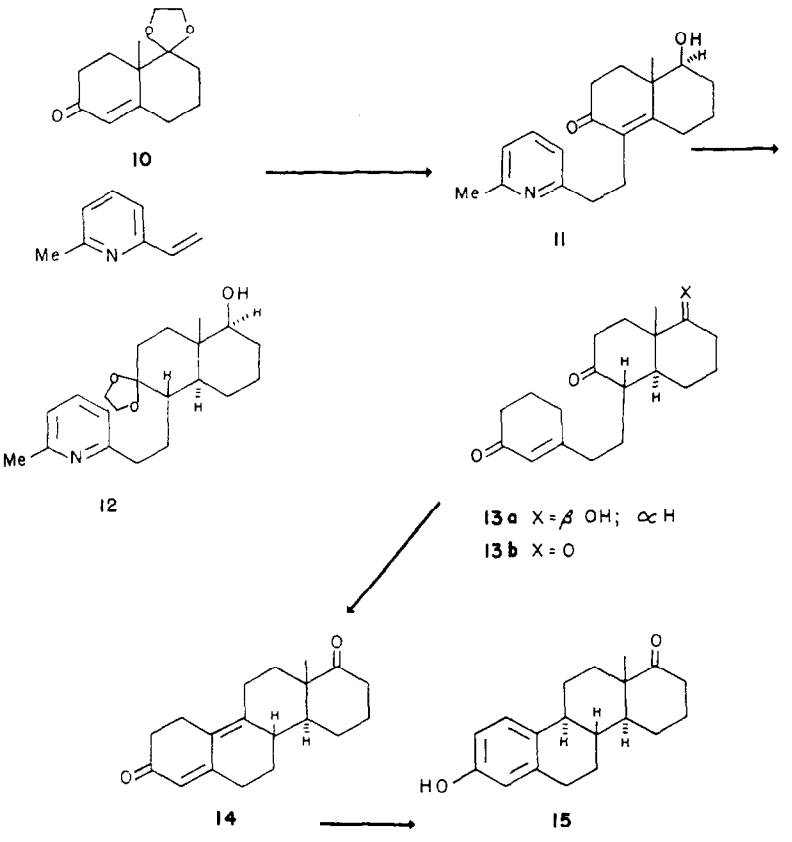

Fig. 3.

acid-acetic acid gave dienedione **14**. This was converted to dl-D-homoestrone (**15**) through the action of acetyl bromide-acetic anhydride. The overall transformation of **10**→**15** has now been achieved in 18% yield.

Prior to applying this methodology to the total synthesis of estrone itself, we undertook a major simplification in the preparation of picolyethylated bicyclenones such as **11**. The approach used in the exploratory D-homoseries started with the monocyclic 2-methyl-1,3-dione of the general type **16**. The sequence from **16**→**11** involves a minimum of five stages: (i) Robinson type annelation; (ii) selective protection; (iii) picolylethylation; (iv) deprotection; and (v) selective reduction. A rather more attractive possibility presented itself, *i.e.* recourse to a Tris annelating agent, **17**. This compound is then used to annelate **16**. Selective reduction affords system **11** in two steps.

The desireability of this process is closely tied to the availability of the Tris annelating agent, **17**. In practice this compound can be prepared in 4 steps (56% overall yield) from the readily available 2,6-lutidine [9]. This is achieved by alkylating its conjugate base (derived *via* phenyllithium) with 3-chloropropionaldehyde diethylacetal followed by acidic work-up. The aldehyde (71% yield) is subjected to the action of vinylmagnesium chloride and the intermediate allylic alcohol is oxidized with activated manganese dioxide to give **17** (80% yield for the last two steps).

Compound 17 has been used to annelate 2-methylcyclopentane-1,3-dione to give hydrindenedione **18a** in 93% yield. This is reduced with sodium borohydride to give the hydroxyenone **18b** in 89% yield.

The synthesis of dl-estrone was achieved as follows: catalytic reduction (H_2/Pd/C–$HClO_4$–EtOH) of **18b** gave a mixture of dihydro compounds. Unfortunately, the saturation of the double bond is also accompanied by *ca.* 21% hydrogenolysis of the keto function. The stereospecific (14α) saturation of the double bond of **18b** represents, at this time, the most serious obstacle to the expeditions total synthesis of estrone. Ketalization of the dihydro mixture was then followed by chromatographic separation of the desired (14α) hydroxyketal, **19**. Unfortunately, the conversion of **18b** to pure **19** is only 45%. The active search for a more satisfactory solution to this problem is very much in progress.

With compound **19** in hand, the route to dl-estrone was clearly defined. In our preliminary studies we have, already, worked out conditions whereby **19** is converted to estrone (**20**) in four operational steps, without recourse to any chromatography save for the final purification, in 38% yield. As, in the model studies, compound **19** was subjected in sequence to the following steps: (i) reduction with sodium–ammonia–ethanol; (ii) hydrolytic cyclization with aqueous sodium hydroxide–ethanol; (iii) deketalization *via* aqueous acid; (iv) Jones oxidation; (v) vinylogous aldolization (tosyl acid–acetic acid); and (vi) aromatization (acetyl bromide–acetic anhydride).

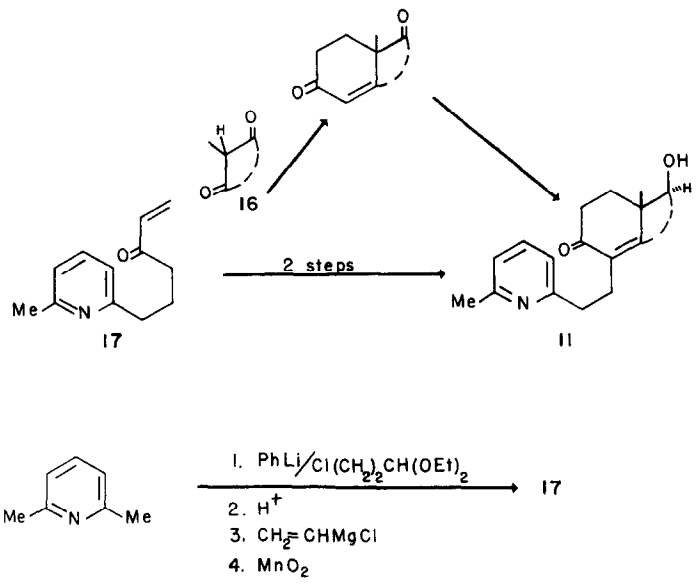

Fig. 4.

The correspondence of the chromatographic properties, infrared and nmr spectra of the dl estrone (**20**), thus obtained, with those of the natural, optically active material, leave no doubt as to the identity (except for antipodal state) of the synthetic and natural materials.

Though the problem of the introduction of the required 14α-stereochemistry (**18b** → **19**) has not been solved in a completely satisfactory fashion, we felt, nevertheless, that the progress thus far achieved warranted an attack on the other central stereochemical challenge in the total synthesis of steroids. *i.e.* control over absolute configuration. Our strategy in this regard was to prepare the desired 13S-antipode by combination of 2-methylcyclopentane-1,3-dione with the Tris annelating agent **17** under asymmetric induction. In pursuing this objective, a knowledge of the sign and magnitude of optical rotation of the pure 13S antipode of **18** (a or b) was seen to be of considerable importance.

One of the great triumphs of the discipline of asymmetric induction was recorded in the synthesis of hydrindenedione **22a** through cyclization of the prochiral trione **21** with L-proline [5, 6]. Previously, the pure 13S hydroxyketone **22b** had been obtained *via* resolution, and the dextrorotary isomer, $[\alpha]_D^{benzene} = +90{\cdot}6°C$ had been converted to steroidal products of unambiguous (13S) configuration (10). Hence, there can be no doubt that the dextrorotary antipode of **22b** corresponds, in its absolute configuration, to that required for steroids.

We prepared trione **21** by the condensation of 2-methycyclopentane-1,3-dione with methyl vinyl ketone. Cyclization under the Schering[5] conditions, using L-proline, gave **22a** ($[\alpha]_D^{benzene} = +360°C$, lit = +363°C). Selective reduction with lithium tri-*tert*-butoxyaluminum hydride gave **22b** $[\alpha]_D^{benzene} = +89{\cdot}5°C$, lit = +90·6°C. Compound **22b** was then converted to its *t*-butyl ether derivative, **22a** m.p. 64–65°C, under the same conditions described by Roche workers in the dl-series [11]. Compound **22c** was subjected to picolylethylation using potassium tert butoxide/*t*-butanol/2-methyl-6-vinylpyridine. The intermediate *t*-butylether was then cleaved under the influence of acid to give optically pure **18b** $[\alpha]_D = +28{\cdot}4°C$. Oxidation of **18b** with Jones reagent gave optically pure **18a**, $[\alpha]_D = +200{\cdot}2°C$. It should be noted that this method might, itself, be an attractive one for the synthesis of estrone were it not for the inefficiency of the picolylethylation (46%). Nevertheless, for our purposes, it provided the crucial rotation data necessary to monitor the efficacy of our own attempts at asymmetric induction.

An important advance in the pyridine route to optically active estrone was achieved by the discovery that treatment of 2-methylcyclopentane-1,3-dione with **17** (Et_3N–EtOAC) gave a nearly quantitative yield of prochiral trione **24**. It will be immediately recognized that **23** is conceptually quite related

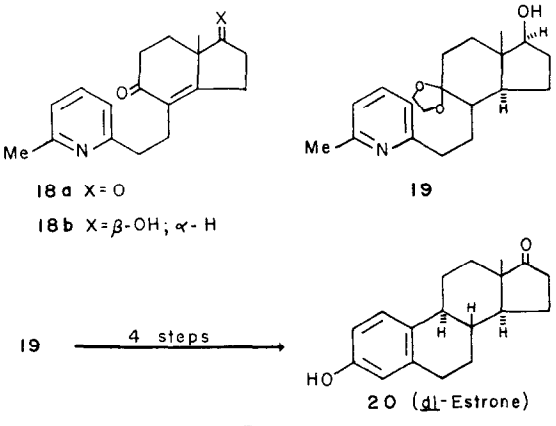

Fig. 5.

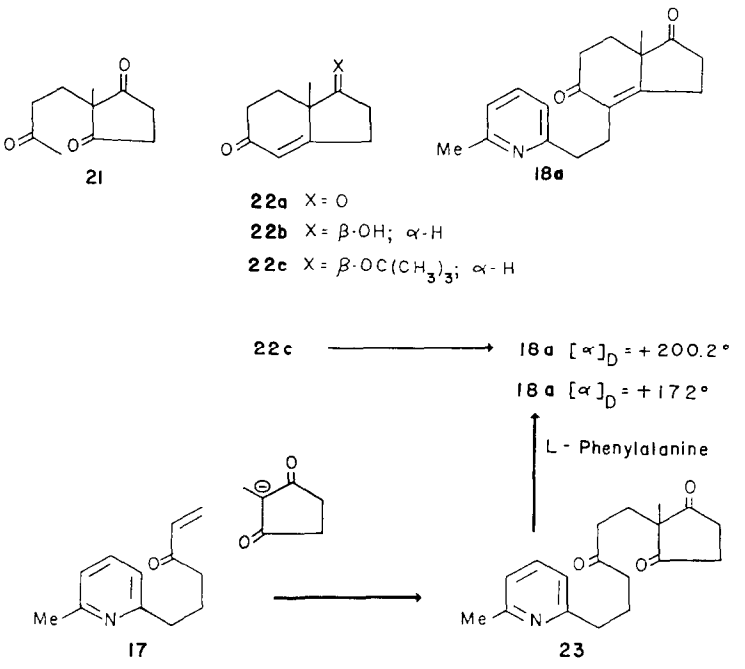

Fig. 6.

to **21** in that, in principle, chirality can be induced at the methyl-bearing carbon by some process which selects among the two cyclopentanone carbonyl groups during an internal aldolization reaction.

Early attempts at utilizing L-proline under conditions similar to those used in the case of **17** were generally disappointing. However, it was found that when the amino acid L-phenylalanine was used, the prochiral **24** was converted to enedione **18a** of optical rotation $[\alpha]_D = +172°C$. Since $[\alpha]_D$ for optically pure **18a** has been determined to be $+200·2°C$, it is seen that the efficiency of the asymmetric induction is currently 86%.

While the cause of the dramatic increase in the efficiency of the asymmetric induction *via* L-phenylalanines is not understood, it is clear that a highly promising laboratory synthesis of optically active estrone and 19-norsteroids is at hand.

Acknowledgement—This research has been supported by funds from the National Cancer Institute and the National Institute for Child Health Development.

REFERENCES

1. Akhrem A. A. and Titov Y. A.: In *Total Steroid Synthesis.* Plenum Press, N.Y., N.Y. (1970).
2. For a review of recent applications of steroids see: Wiechert R.: *Angew. Chem. Int.* **9** (1970) 321–332.
3. Applezweig N. A.: In *Steroid Drugs.* McGraw Hill, N.Y., (1962).
4. Saucy G. and Cohen N.: *MTP International Review of Science,* Series One, Vol. 8, Steroids, (Edited by W. F. Johns). Butterworths, London (1973) pp. 1–26.
5. Eder U., Sauer G. and Wiechert R.: *Agnew. Chem. Int.* **10** (1971) 496–497.
6. Hajos Z. G. and Parrish D. R.: *J. org. Chem.* **39** (1974) 1615–1621.
7. Daninshefsky S. and Cavanaugh R.: *J. Am. chem. Soc.* **90** (1968) 2806–2807.
8. Danishefsky S. and Nagel A.: *J. chem. Soc., Chem. Commun.* (1972) 372–373. A full accounting of this work, describing substantially improved yield, will appear shortly: Danishefsky S., Cain P. and Nagel A.: *J. Am. chem. Soc.* **97** (1975) 380–387.
9. Danishefsky S. and Cain P.; *J. org. Chem.* **39** (1974) 2925.
10. Hajos Z. G., Parrish D. R. and Oliveto: *Tetrahedron* (1968) 2039–2046.
11. Hajos Z. G., Parrish D. R. and Oliveto: *J. org. Chem.* **32** (1967) 3008–3010.