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NEW RESULTS IN THE TOTAL SYNTHESIS OF 19-NORSTEROIDS

G. SAUCY, B. BANNER, R. BORER, N. COHEN, W. EICHEL, S. KWOH, D. R. PARRISH, M. ROSENBERGER and R. D. YOUSSEFYEH*

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, N.J. 07110, U.S.A.

SUMMARY

Recent endeavors in the field of steroid total synthesis have led to several new approaches which utilize the principle of asymmetric induction. Important developments will briefly be reviewed, followed by a presentation of two novel routes to estrone. The first is based on the use of (−)-(5S)-5-hydroxy-9-oxodecanoic acid lactone which is transformed in several steps to d-(−)-estra-4,9-diene-3,17-dione and thence to estrone. The second, altogether different route starts with (+)-(7aS)-7,7a-dihydro-7a-methyl-1,5(6H)-indandione and involves the preparation of a 9,10-*seco* ACD-tricyclic intermediate and its conversion into d-(+)-estrone methyl ether.

INTRODUCTION

The efficient preparation of the natural enantiomer of a given steroid rather than the racemate is a requirement for any modern total synthesis [1]. In the past, the synthesis of an optically active steroid relied on *classical resolution* of the final steroid or a suitable precursor. An elegant and noteworthy exception to this inherently inefficient and often wasteful approach is the high yield stereospecific microbiological reduction [2] of the prochiral Torgov–Smith β-diketone intermediate I to give the chiral hydroxyketone II and thence the optically active steroid [3]. Chemical versions of the same concept were later also achieved [4, 5]. Together with these selective transformations, the Torgov–Smith synthesis allows the preparation of optically active estrone and analogs in a rather efficient manner [1].

In the last few years, new approaches to optically active estrone and 19-norsteroids have been developed which utilize the principle of *diastereoselective synthesis* [6] (asymmetric induction). These routes are outlined below.†

RESULTS

Several diastereoselective syntheses of 19-norsteroids [7] evolved logically from the fortuitous observation [8] that the dienolether IV is formed from the hydroxy vinylketone III (R=C_2H_5) with high asymmetric induction. It is postulated that the dihydropyran V, which has a prochiral center, is the crucial intermediate in the diastereoselective step. The second and most remarkable example of an asymmetric synthesis is the cyclization of the prochiral triketone VI with catalytic amounts of S-proline, leading to aldol VII of very high optical purity, and thence to the key CD-bicyclic product VIII [9]. Combination of S-proline with perchloric acid directly gives VIII, again of very high optical purity [10]. The analogy between the postulated enolether V and the (hypothetical) enamine IX appears obvious, although a more complex mechanism for the transformation VI → VII probably obtains [9]. The ready accessibility of the optically active CD-intermediate VIII has prompted the development of several promising routes to estrone and 19-norsteroids.

An efficient synthesis of the $\Delta^{4,9}$-dien-3-one XIII (precursor of estrone) and its deconjugated isomer [7, 9(11)-diene] from the optically active keto lactone X *via* diene XI has been achieved [11]. The lactone X was readily obtained by regio- and stereoselective microbiological reduction of 5,9-dioxodecanoic acid. The double cyclization of the tetraketone XII (readily available from XI) was performed with piperidine acetate.

In another application of the diastereoselective transformation of the type III → IV, the estrone precursor XVII could be prepared from the lactone XIV *via* intermediates XV and XVI‡ [12].

A straightforward and high yield route [13] to d-(+)-estrone from the key indane VIII involves conjugate addition of the Grignard reagent XVIII to the α-methylene ketone XIX [readily accessible in five stages from VIII [14]]. This process results in a high yield of the ACD-tricyclic intermediate XX which is easily cyclized to the 9(11)-dehydro estrone derivative XXI, a convenient precursor for the preparation of d-(+)-estrone.§ As an interesting side result, d-(+)-equilenin methyl ether was also obtained [13] from XXI upon treatment with trifluoroacetic acid followed by oxidation.

* Present address Syntex Laboratories, Inc., Palo Alto, CA 94300, U.S.A.

† New routes leading to racemic steroids only are not covered in this short review.

‡ An alternate asymmetric synthesis of enedione XVI has been reported by another group [10].

§ A related, equally efficient total synthesis of d-(+)-estrone starting from VIII has been reported [15].

DISCUSSION

In contrast to the usually wasteful process of classical resolution, the principle of diastereoselective synthesis [6] is inherently superior. Its application to the total synthesis of optically active steroids (estrone and 19-norsteroids) results in the expected improvements, as described above. A very promising new development is based on the elegant and most efficient asymmetric cyclization of the prochiral triketone VI, which makes the key indane VIII very accessible. As a consequence, all routes to steroids based on this CD-intermediate are of obvious attraction.

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