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Total synthesis of ring-A aromatic steroids

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Abstract

A critical examination of the methodologies developed for the synthesis of A-ring aromatic steroids is presented with special emphasis on the synthesis of estrone. Different strategies for the construction of ring systems, control of stereochemistry, resolution and asymmetric synthesis have also been discussed.

Key words: Total synthesis, A-ring steroids, estrone, stereoselectivity, resolution, asymmetric synthesis

1. Introduction

Steroids are cyclopentaphenanthrene derivatives with a broad spectrum of physiological activities. These fascinating polycyclic compounds with rigid molecular structures and unique biological activities compelled the organic chemists to pay intense attention to them. In fact, one of the areas in synthetic organic chemistry that kept the organic chemists engaged for many decades is the synthesis of steroidal hormones. Among all the known steroid hormones, aromatic steroids have attracted special attention because of the interesting physiological properties and considerably easier accessibility for total synthesis, as they contain lesser number of asymmetric centres. These hormones find extensive application in medicine as such and are also important intermediates for the synthesis of 19-nor steroids, a class of potent oral contraceptives and anabolic agents. Excellent reviews dealing with various aspects of the total synthesis of these hormones are available in literature.

The era of steroid total synthesis originated in the early 1930s. Bachmann and collaborators[2] played a vital role in the early development of this field as they were the first to accomplish the total synthesis of equilenin, the simplest of the known steroid hormones. This was followed by the synthesis of estrone by Anner and Miesher[3] in 1948. Since then several syntheses have appeared in literature which have been adequately reviewed. A critical analysis of the methodologies developed for the synthesis of estrone and its related compounds is presented here.

In developing any new synthetic strategy for the total synthesis of steroidal hormones three important factors have to be dealt with with due consideration. They are:

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Construction of ring systems, (b) Control of stereochemistry, and (c) Resolution and asymmetric induction.

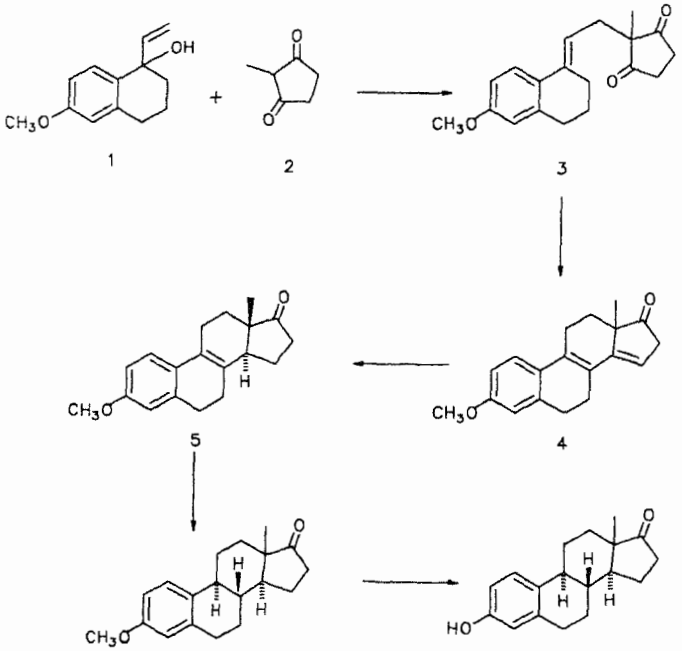
2. Construction of ring systems

Two major approaches have been developed for the construction of A-ring steroid skeleton. These are: (i) alkylation of active methylene compounds or nucleophilic addition of the enolate to a carbon–carbon double bond attached to a carbon bearing a leaving or a carbonyl group, and (ii) intramolecular cycloadditions.

2.1. Alkylation approach

2.1.1. Torgov synthesis

Ananchenko and Torgov[4] developed an elegant and ingenious method for the synth-



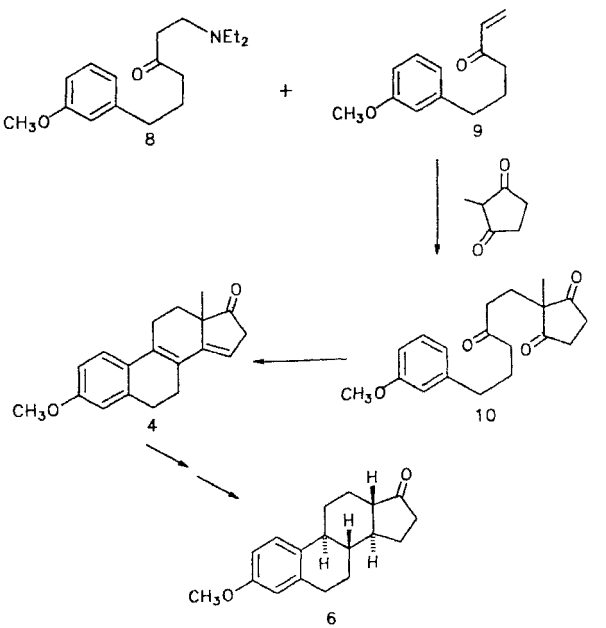
SCHEME 1.

esis of estrone (Scheme 1). Thus, 6-methoxy-1-vinyl-1-tetralol **1** was condensed with 2-methylcyclopenta-1,3-dione **2** to give the intermediate **3**, which was cyclised under acid-catalysed conditions to 3-methoxygona-1,3,5,8,14-pentaene-17-one **4**. Catalytic hydrogenation produced the tetraene **5**, which was subjected to further reduction with potassium in liquid ammonia followed by oxidation to yield the racemic estrone methyl ether **6**. Demethylation of **6** resulted in racemic estrone **7**.

Torgov's strategy is highly versatile and has been used for the synthesis of D-homosteroids[4], a variety of heterosteroids[5], B-homoestrone[6] and B-non-steroids[7].

2.1.2. Smith synthesis

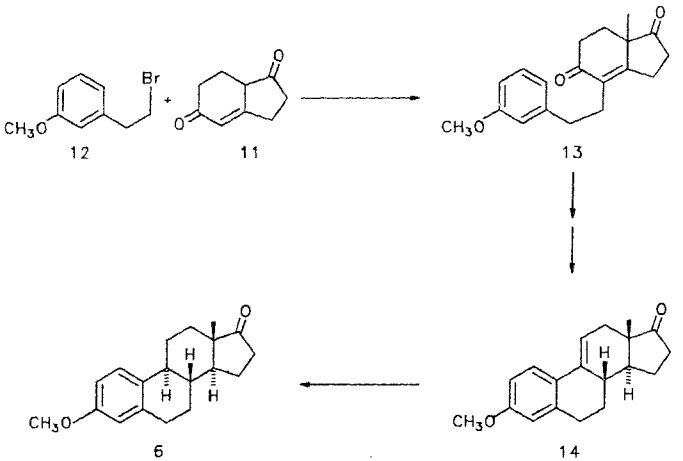
In the first synthesis of Smith[8] reported in 1960 (Scheme 2), a mixture of diethylaminoketone **8** and the unsaturated ketone **9** prepared from 5-(*m*-methoxyphenyl)



SCHEME 2.

penta-2-one, formaldehyde and diethylamine, was treated with 2-methylcyclopenta-1,3-dione **2** in refluxing methanolic potassium hydroxide to give the trione **10**, which was cyclised with PTS to afford the tetracyclic pentaene **4**. This compound **4** was later converted to estrone methyl ether **6** in three steps.

In their second synthesis[9], the enolate of the dione **11**, obtained by using potassium-*t*-butoxide in refluxing benzene, was alkylated with *m*-methoxyphenethyl bromide **12** to furnish the ene-dione **13**. Reduction of the double bond, followed by acid-catalysed cyclisation of **13**, afforded 9,11-dehydroestrone methylether **14**, the hydrogenation of which gave estrone methylether **6** (Scheme 3).

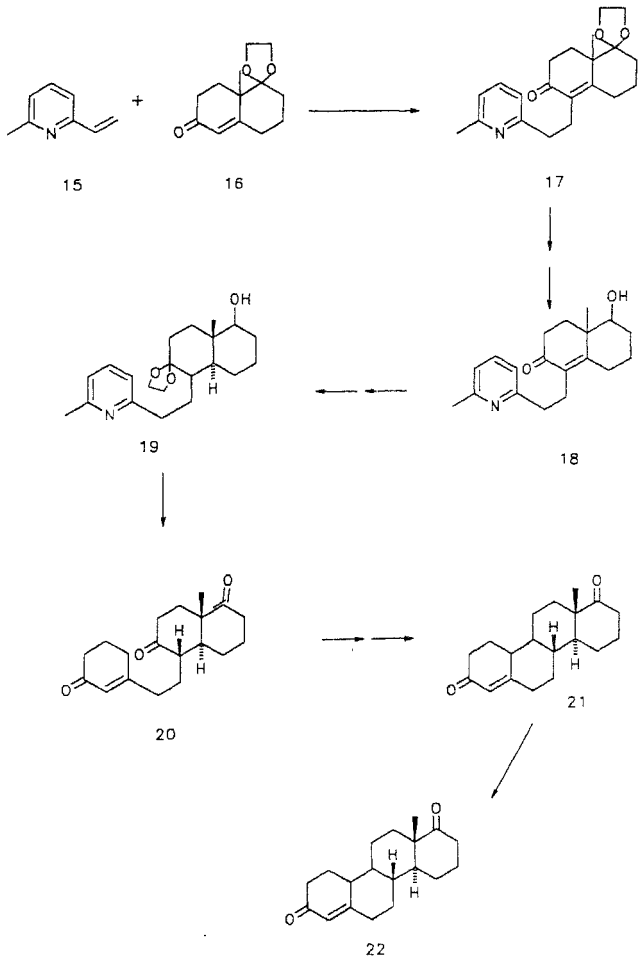


SCHEME 3.

Almost similar or modified approaches were utilized by Wiechert[10], and Cohen[11] and Mander[12] in their synthesis of estrone methyl ether **6**.

2.1.3. Danishefsky synthesis

In 1975, Danishefsky[13] reported a novel synthesis of D-homoestrone involving a pyridine moiety for the construction of the A-ring (Scheme 4). Thus, 6-methyl-2-vinylpyridine **15** was coupled with the mono ketal of the Wieland–Mieschler ketone **16** to give the compound **17**. Deketalisation of **17** followed by sodium borohydride reduction gave the enone alcohol **18**, which after ketalisation followed by the reduction of the double bond afforded the compound **19**. Birch reduction of the pyridine ring of **19** followed by hydrolysis and cyclisation in alkaline medium resulted in the compound **20**, which was converted to D-homoestrone **22** through the compound **21**.

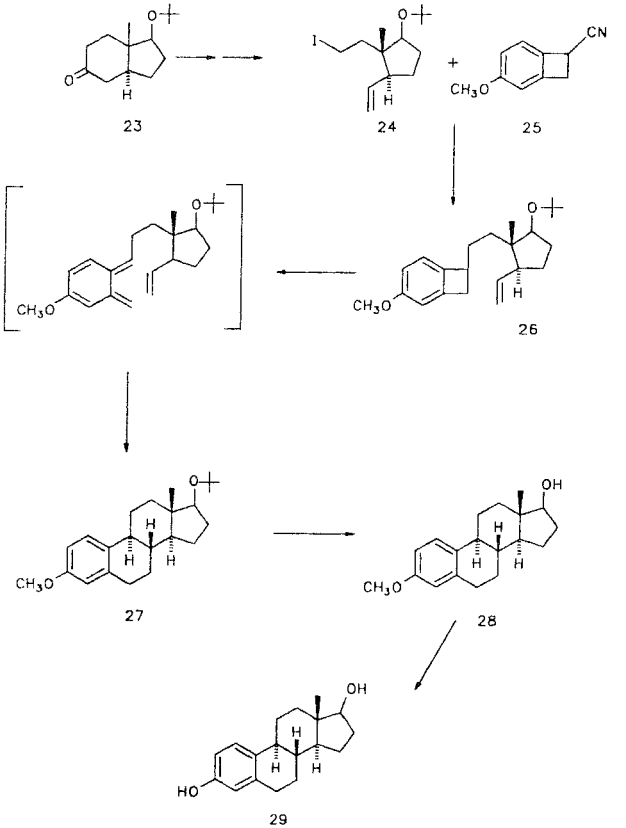


SCHEME 4.

2.2. Intramolecular cycloadditions

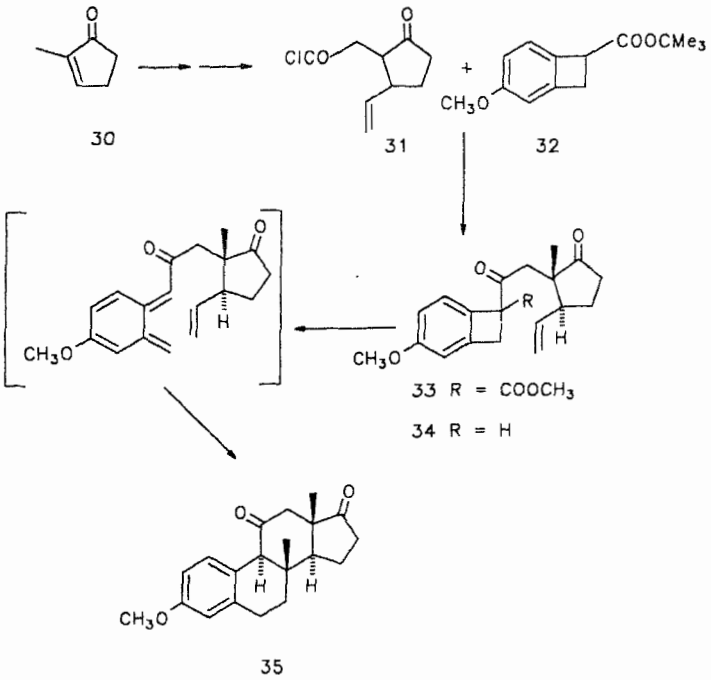
2.2.1. Kametani synthesis

In Kametani's asymmetric synthesis[14] of (+)-estradiol **29**, the chiral hydrindanone **23** was converted to (+)-(1s,2s,3s)-1-*t*-butoxy-2-(-iodoethyl)-2-methyl-2-vinylcyclopentaene



SCHEME 5.

24 by a multistep procedure. Condensation of **24** with **25** followed by hydrogenolysis of the cyano group with sodium in ethanol and liquid ammonia resulted in **26**, which on thermolysis underwent ring opening and cycloaddition affording **27**. Treatment of **27** with dil. *HCl* afforded the optically pure estradiol methylether **28**, which was converted to (+)-estradiol **29** by treating it with pyridinium hydrochloride (Scheme 5).

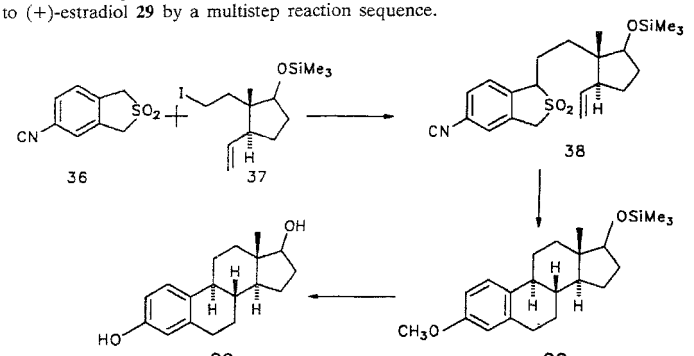


SCHEME 6.

2.2.2. *Oppolzer synthesis*

In Oppolzer's asymmetric synthesis[15] of estrone, the (+)-acid chloride **31**, synthesized from 2-methylcyclopenta-2-ene-1-one **30**, was condensed with benzocyclobutene-*t*-butylester **32** to give the key intermediate **33**, which after hydrolysis and decarboxylation yielded **24**. Thermiolysis of **34** led to the 11-keto steroid **35** (Scheme 6).

Oppolzer also produced orthoquinodimethanes by an alternate approach involving the thermal elimination of sulfurdioxide from the sulfones. In the synthesis[16] of (+)-estradiol **29** (Scheme 7) the adduct **38** was prepared by the alkylation of the sulfone **36** with the iodide **37**. Thermolysis of the adduct **38** in refluxing 1,2,4-trichlorobenzene afforded pure *trans-anti-trans* 3-cyanogona-1,3,5-triene **39**, which was converted to (+)-estradiol **29** by a multistep reaction sequence.



SCHEME 7.

2.2.3. Grieco synthesis

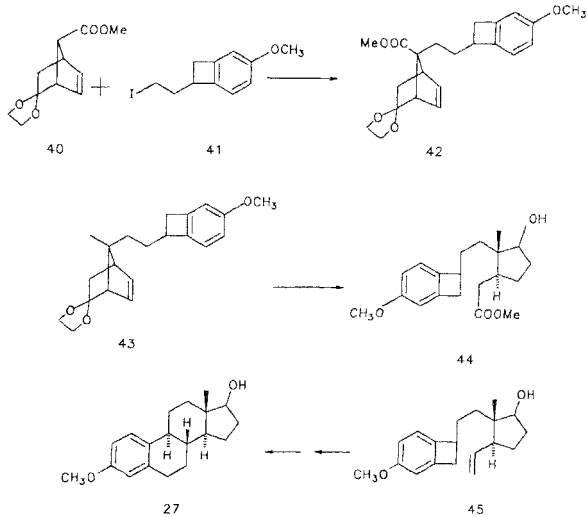
An unusual synthesis[17] of estrone has been developed by Grieco in which the C,D portion of estrone is constructed starting from bicyclo(2.2.1)heptane derivatives, which are readily available from norbornadiene. The bicyclic ketal ester **40** was coupled with benzo-cyclobutene **41** to give the adduct **42**. Through a series of transformations the adduct **42** was converted to **43**, which was then transformed to the vinyl compound **45** *via* the ester **44**. The vinyl compound on thermolysis gave estradiol methyl ether **28** (Scheme 8).

2.2.4. Volhardt synthesis

The only drawback in orthoquinodimethane approach is to obtain the suitably substituted benzocyclobutenes in good yields. To overcome this, Volhardt[18] developed a strategy which involves co-oligomerization of three acetylenic units in the presence of cobalt carbonyl catalyst. Vinyl acetylene **48** was obtained by coupling the iodide **46** with the trimethylsilyl compound **47**. Reaction of vinyl acetylene **48** with ditrimethylsilyl acetylene **49** gave the suitably substituted benzocyclobutene **50** in good yield, which was further converted to estrone **7** *via* thermolysis (Scheme 9).

2.2.5. Quinkert synthesis

Quinkert[19] utilized the photolysis of *ortho* tolyl ketone to generate the required dienol, which could undergo spontaneous cycloaddition resulting in ring closure



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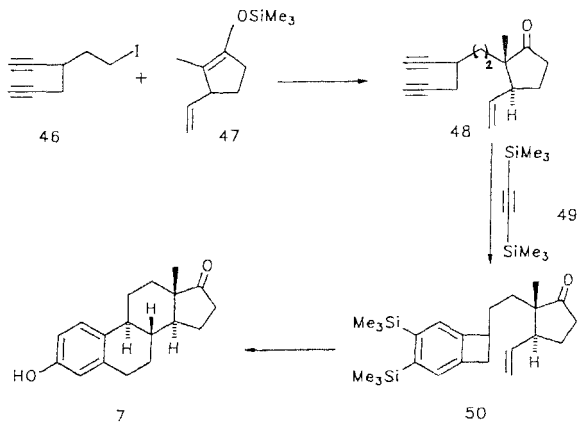
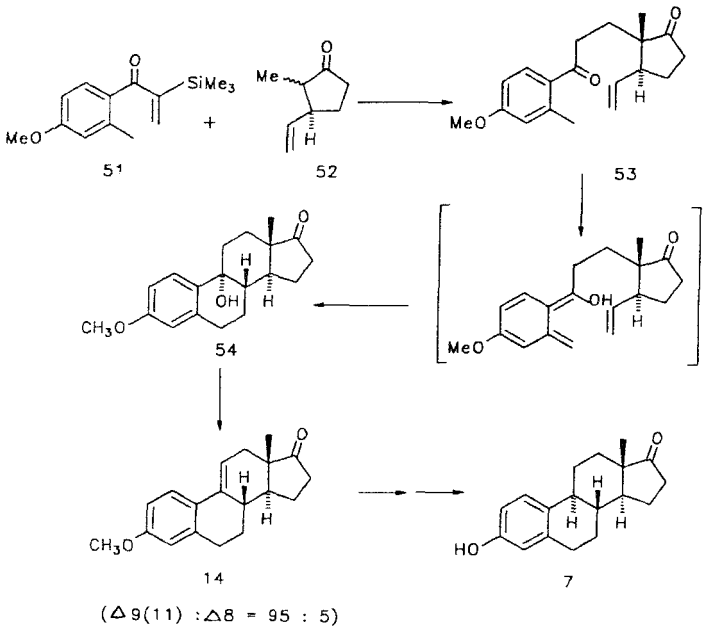


SCHEME 9.

(Scheme 10). The aromatic ketone **51** synthesized from *m*-cresol methyl ether was coupled with the vinylcyclopentanone **52** to yield the adduct **53**, which on exposure to UV light at 98°C yielded **54** with a minor amount of 9β-hydroxy isomer. Dehydration of **54** led to **14** containing 5% of isomeric 8(9)-olefin. Conversion of both these olefins into estrone **7** has already been realized by known methodology.



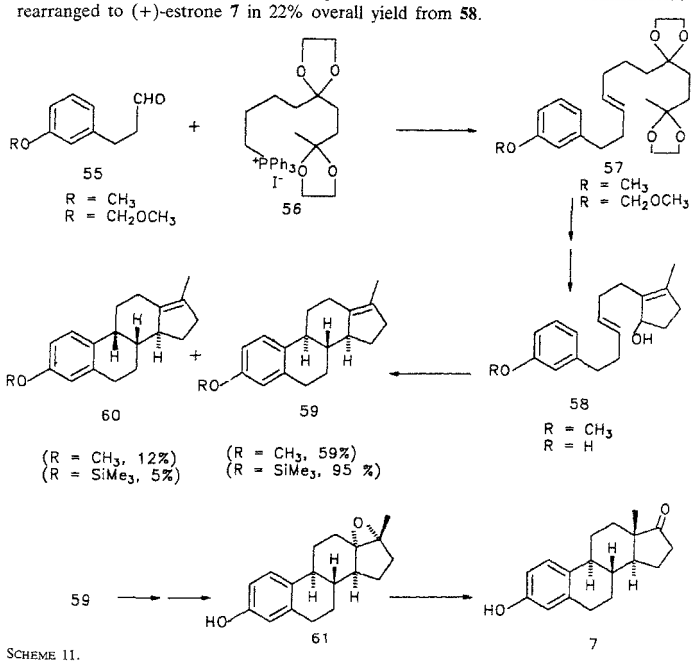
SCHEME 10.

2.3. *Miscellaneous approaches*

2.3.1. *Johnson synthesis*

Johnson utilized cationic cyclisation as a key step to synthesize estrone[20]. In his synthesis (Scheme 11), *m*-alkoxyphenyl propionaldehyde **55** (R=CH_3, CH_2OCH_3) and the phosphonium iodide **56** were condensed by Witting reaction to give the olefin **57** (R=CH_3, CH_2OCH_3). Hydrolysis of the ketal, aldol condensation and reduction of

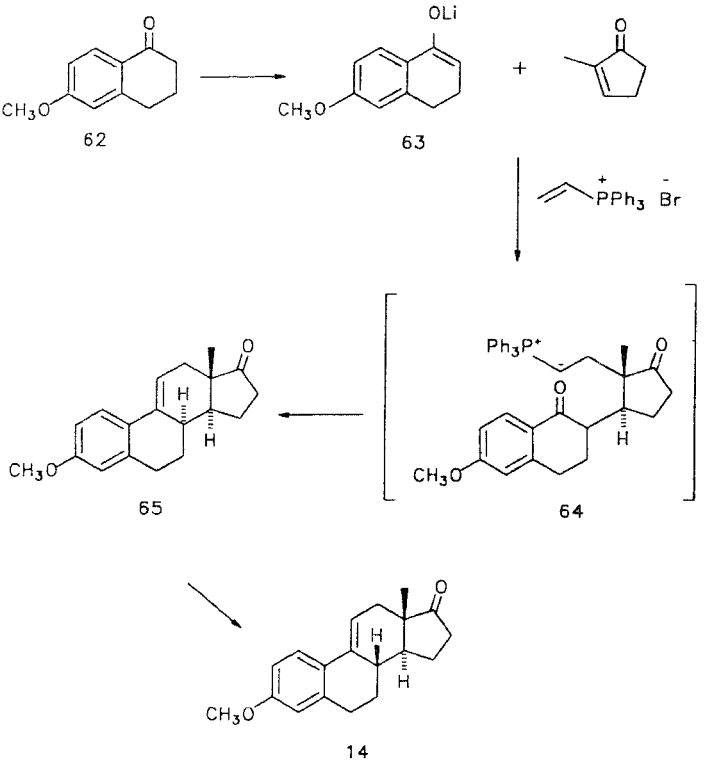
the carbonyl led to key intermediate **58** (R=CH_3,H). Stannic chloride-catalyzed cyclisation of **58** (R=CH_3) in CH_2Cl_2 at −100°C gave the isomeric tetracyclic compounds **59** (R=CH_3) and **60** (R=CH_3) in 71% yield in the ratio of 4.3:1. On the other hand, the 3-trimethylsilyl ether of **58** underwent acid-catalysed cyclisation in quantitative yield resulting in the mixture of **59** (R=$SiMe_3$) and **60** (R=$SiMe_3$) in 20:1 ratio. The olefin **59** was converted to the epoxide **61** *via* its chlorohydrin, since the direct epoxidation mainly gave β-epoxide. The epoxide **61** on treatment with borontrifluoride rearranged to (+)-estrone **7** in 22% overall yield from **58**.



SCHEME 11.

2.3.2. *Posner synthesis*

Posner devised[21] a novel one-pot sequence of two Michael reactions and a Wittig reaction to synthesize estrone methyl ether **6** (Scheme 12). Thus, 6-methoxy-1-tetralone **62** was converted into its lithium enolate **63**, which was coupled sequentially with 2-methyl cyclopent-2-en-1-one and vinyltriphenylphosphonium bromide to yield, *via* the ylide **64**, 9(11)-dehydro-8-isoestrone methylether **65** in 8% yield. Equilibration

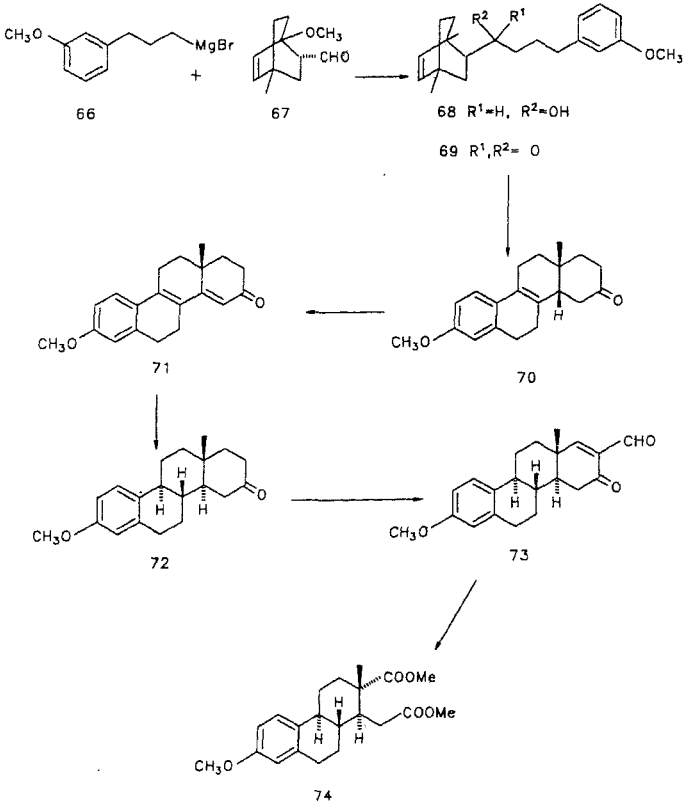


SCHEME 12.

of **65** in refluxing methanolic hydrochloric acid resulted in 3:1 mixture of 9(11)-dehydroestrone methylether **14** and 8-dehydroestrone methylether **5**. Both these isomers have already converted into estrone methylether **6** in good yield.

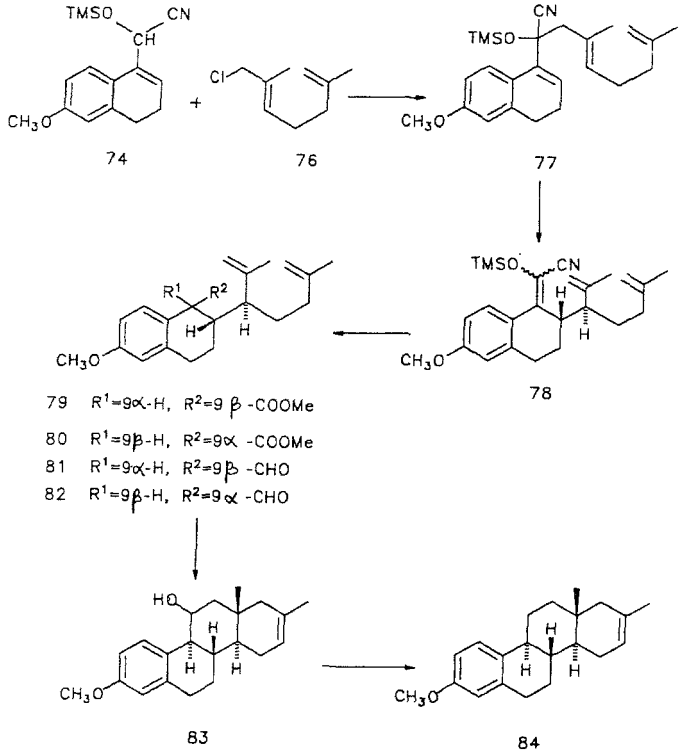
2.3.3. Subba Rao synthesis

In a recently reported[22] synthesis of estrone by Subba Rao *et al* (Scheme 13), the adduct **67**, prepared by the Diels–Alder reaction of 1-methyl-4-methoxy-1,3-cyclohexadiene with acrolein, was coupled with the Grignard reagent **66** resulting in the alcohol **68**. Oxidation of the alcohol **68** with pyridinium chlorochromate yielded the ketone **69**, which on treatment with perchloric acid, underwent rearrangement



SCHEME 13.

followed by ring closure yielding the tetracyclic compound **70**. $PdCl_2$ oxidation of **70** resulted in the pentaenone **71** which on lithium–aniline–liquid ammonia reduction gave the saturated ketone **72**. Hydroxymethylenation of **72** followed by oxidation with selenium dioxide resulted in the unsaturated aldehyde **73**. Oxidative cleavage of the unsaturated aldehyde **73** with potassium permanganate gave the diacid, which on esterification with ethereal diazomethane, yielded the diester **74**, which has been previously converted[23] into estrone methyl ether **6**.



SCHEME 14.

2.3.4. Ziegler synthesis

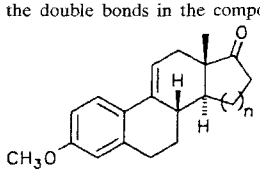
Ziegler reported a novel synthesis of estrone involving a Cope rearrangement,[24] wherein the stereochemistry at C-8 and C-9 is controlled (Scheme 14). The compound **77**, synthesized from the silylcyanohydrin **75** and the chloride **76**, on heating in dimethyl aniline, underwent a Cope rearrangement to the nitrile **78**, the exposure of which to KF in methanol resulted in the methyl esters **79** and **80** (9αH: 9βH=1:4). Conversion of **79** and **80** to the corresponding aldehydes followed by equilibration yielded **81** and **82** (9αH; 9βH=92:8). Cyclisation of the major isomer **81** with $SnCl_4$ produced the 11β-hydroxy compound **83**. Hydrogenolysis of the 11-hydroxyl group by reducing the α-mesylate with lihtium in liquid ammonia resulted in **84**, which had previously been converted[25] into estrone methylether **6** in five steps.

3. Control of stereochemistry

One of the main difficulties in the total synthesis of steroids is the stereoselective introduction of centres of asymmetry by appropriate manipulation of the carbon centres. Most of these transformations involve conversion of trigonal carbon atoms to tetragonal state by employing reactions such as alkylation of enolates, hydrogenation of double bonds and the epimerisation of carbon atoms adjacent to the carbonyl groups, etc. The control of stereochemistry of the centres at C-8, C-9, C-13 and C-14 are dealt herein as they are relevant to the aromatic steroids.

3.1. Control of stereochemistry at C-8 and C-9 positions

In many cases the above centres are formed by the reduction of a 8,9-double bond which essentially is a styrene-type bond. Reduction of these systems with alkali metals in liq. ammonia is generally known to give thermodynamically more stable products and this fact was exploited by Smith[8] and Torgov[4] in their synthesis of estrone methylether and D-homoestrone methylether. They utilized Birch reduction to reduce the double bonds in the compounds **85** and **86** (Scheme 15).



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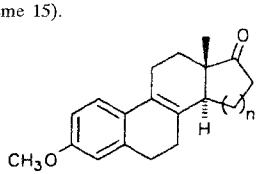

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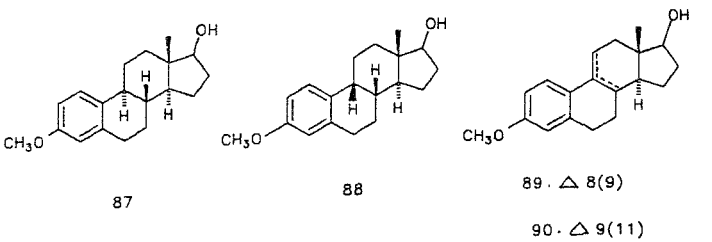
SCHEME 15.

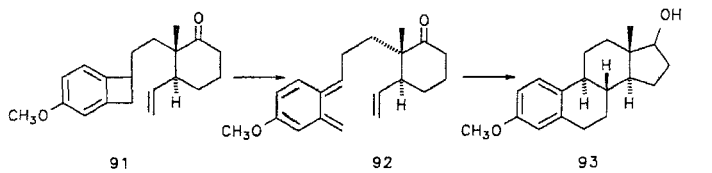
Although Smith and Torgov's synthesis of estrone involves Birch reduction of the styrene double bond, and yield of the final product is low because of the formation of *cis* isomer **88** to a considerable extent. This problem was circumvented by isomerizing the 8,9-double bond into 9,11-position under acidic conditions and hydrogenating the 9,11-dehydrocompound to give exclusively the *trans* isomer **87**. To avoid the



SCHEME 16.

isomerization and hydrogenation steps, a new reduction procedure involving aniline as an external proton source in styrene reductions was developed[8,26]. Reduction in the presence of aniline affords mostly the 9α-isomer and in particular the reduction of **89** and **90** results in the exclusive formation of the required *trans* isomer **87**, thus avoiding the formation of the mixture of stereo isomers (Scheme 16).

Intramolecular Diels–Alder reactions have been used[14,19] extensively for the creation of asymmetric centres at C-8 and C-9. The stereochemistry of these centres was predicted on the basis of the transition state energies as illustrated[27] in the conversion of the benzocyclobutene **91** to D-homoestrone methyl ether **93**. The electrocyclic ring opening of the cyclobutene ring in the conrotatory manner leads to the preferential formation of the sterically favoured E-oriented 6-quinodimethane **92** which undergoes synchronous cycloaddition in a stereospecific manner to give **93** (Scheme 17).



SCHEME 17

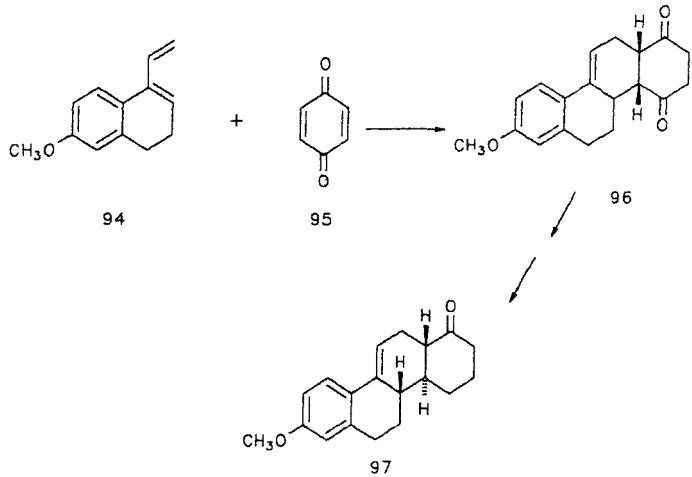
Other methods such as isomerization of double bonds[28] and molecular rearrangements[24] have also been used to control the stereochemistry at the C-8 and C-9 positions.

3.2. Control of stereochemistry at C-13 and C-14

One of the major stereochemical problems in the realization of any total synthesis of a steroid molecule is the formation of a *trans* C,D-ring junction, because the *cis*-

hydrindanes exhibit greater stability over the *trans*-hydrindane systems. In order to over-come this difficulty. Johnson *et al* developed a fundamentally different synthetic stra-tegy called the 'hydrochrysene approach' which involved an initial construction of a *trans*-D-homosteroid by making use of the greater stability of a *trans* decalin system, followed by the conversion of D-homo systems to the natural steroid hormones.

In the synthesis of estrone reported by Johnson[29], the 1,4-diketone **96** was prepared by the cycloaddition of the diene **94** with benzoquinone **95**. The diketone was trans-formed in a few steps into the stable *trans* ketone **97**, which in turn was converted to estrone **7** by sequential transformations (Scheme 18).

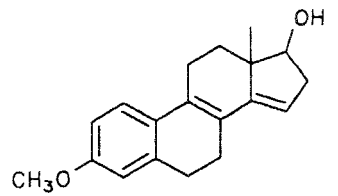


SCHEME 18.

Direct formation of ring D with suitable substituents and a 14,15-double bond followed by stereoselective reduction of the double bond forms yet another method of procuring the *trans*-hydrindane system. This reaction was exploited by Torgov[4], Smith[9] and others[13,26]. They reduced the pentaenes **4** and **98** with 2% Pd–$CaCo_3$ to the corresponding tetraenes **5** and **99** (Scheme 19).

4. Resolution and asymmetric induction

Chemical synthesis of steroids usually produces racemic mixture of products unless a resolution step is introduced at some stage. Resolution can be effected at any stage in a synthesis, but an early resolution will always be advantageous. The resolution



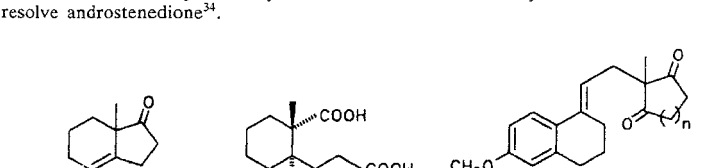
SCHEME 19.

of steroid hormones is generally based on the following methods: (a) Reaction of the racemate with a chiral reagent to produce diastereomers which can be separated by physical methods, and (b) reaction with a chiral reagent to take advantage of its faster reactivity with one enantiomer than with the other.

4.1. Resolution

When a racemic mixture reacts with a chiral reagent it produces diastereomers. These diastereoisomers have different physical properties and can be separated by fractional crystallization, distillation and chromatography, etc. Carboxylic acids are usually resolved by forming salts with optically active amines. For example, in a synthesis leading to estrone, the racemic mixture of **100** was resolved with ephedrine[30]. The racemic mixture of **101** was resolved with brucine[31] (Scheme 20).

Enzymes are chiral reagents that frequently make an absolute differentiation between the enantiomers by being inert towards one of the enantiomers. This fact was exploited in the resolution of seco-dione **102** using the strain *Saccharomyces uvarum*[32] and **103** with *S. carisbergensis*[33] (Scheme 20). In both the above cases optically active alcohols were obtained by specific reduction of the carbonyl group of the enantiomers by the enzyme. Johnson utilized the enzyme *S. cerevisae* to resolve androstenedione[34].



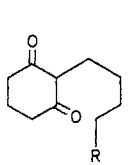
SCHEME 20.

4.2. Asymmetric induction

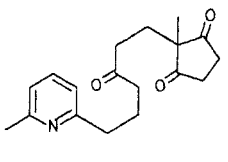
A novel approach to the introduction of optical activity in total synthesis of steroidal hormones without the requirements of either a classical resolution or a microbiological transformation is the asymmetric induction. In this case a new asymmetric centre is created in a molecule during the course of a chemical reaction. Such a transformation may be brought about either by employing a dissymmetric catalyst, or by using a reactant already possessing a dissymmetric centre which during the course of the reaction 'induces' asymmetry at a second centre.

Of the recent methodologies developed for obtaining optically active steroids, chiral aldol cyclisation of a prochiral triketone of the type **104** received immediate attention by various groups of chemists and a large number of experiments were reported in literature. This reaction was first discovered by two groups of workers, Eder[35] and Hajos[36], almost simultaneously. The extent of asymmetric induction in these amino-catalysed cyclisations is removable and often comparable to that achieved by the use of an enzyme.

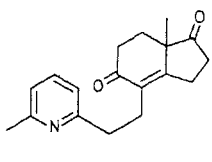
This procedure was adapted by Danishefsky and co-workers in their pursuit towards the synthesis[37] of optically active estrone and 19-nortestosterone. The chiral dione **106** was obtained by the cyclisation of **105** with a chiral aminoacid such as S-phenyl alanine (Scheme 21).



104



105



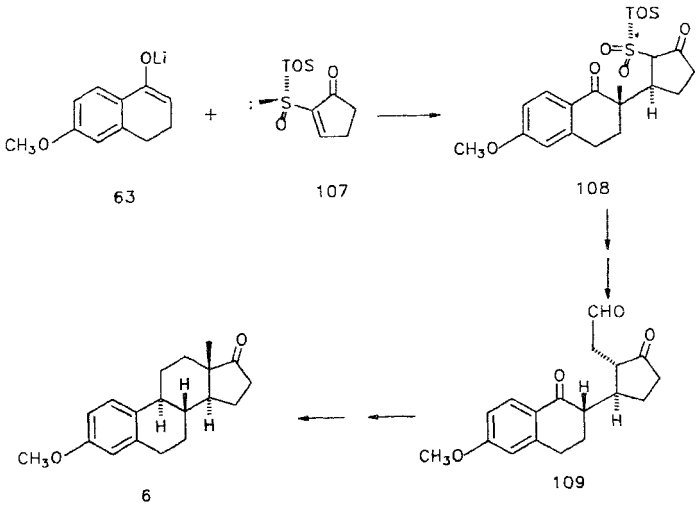
106

SCHEME 21.

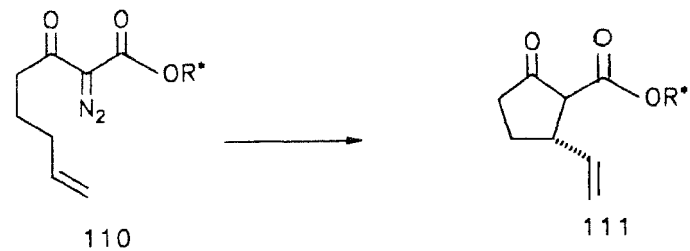
Asymmetric Michael addition was used by Posner and Switzer[38] in their synthesis of (+)-estrone methylether (Scheme 22). The key step is the induction of asymmetry at the prochiral β-carbon atom of an enantiomerically pure α, β-ethylenic sulfoxide.

Conjugate addition of the enolate **63** to enantiomerically pure (s)-(+)-2-(*p*-tolylsulfinyl)-2-cyclopentenone **107** resulted in the ABD intermediate **108**, which was converted to (+)-estrone methyl ether **6**, *via* the intermediate **109**.

Taber's synthesis[39] of (+)-estrone methyl ether **6** involves the rhodium-mediated enantioselective intramolecular C-H insertion reaction to get optically active functionalized cyclopentanone. The chiral R group induces diastereoselectivity in the cyclisation of **110** affording the cyclopentanone **111** (Scheme 23), which was converted to (+)-estrone methylether **6** by multistep reaction sequence.



SCHEME 22.



SCHEME 23.

It is clear from the above that the total synthesis of steroidal hormones still continues to be a challenging problem in terms of: (i) construction of the rings, which demands the conception of more logical and at times fascinating bond-breaking and bond-forming strategies, (ii) control of stereochemistry, having its implications in the field of mechanistic physical organic chemistry, which still has so much to explore,

and (iii) the asymmetric synthesis leading to the required optically pure biologically active enantiomer, which requires the development of more and more new reactions and reagents with commercial viability. Although any area in science in reality is an unfathomable ocean, the area of synthesis of steroidal hormones is a special one, because, in spite of the intense attention it received for many decades, it still continues to demand more and more development, interest and insight and perhaps fits best with what Robert Frost says in his poem,

"The woods are lovely, dark and deep,
But I have promises to keep,
And miles to go before I sleep,
And miles to go before I sleep."

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