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RECENT ADVANCES IN THE TOTAL SYNTHESIS OF STEROIDS VIA INTRAMOLECULAR CYCLOADDITION REACTIONS

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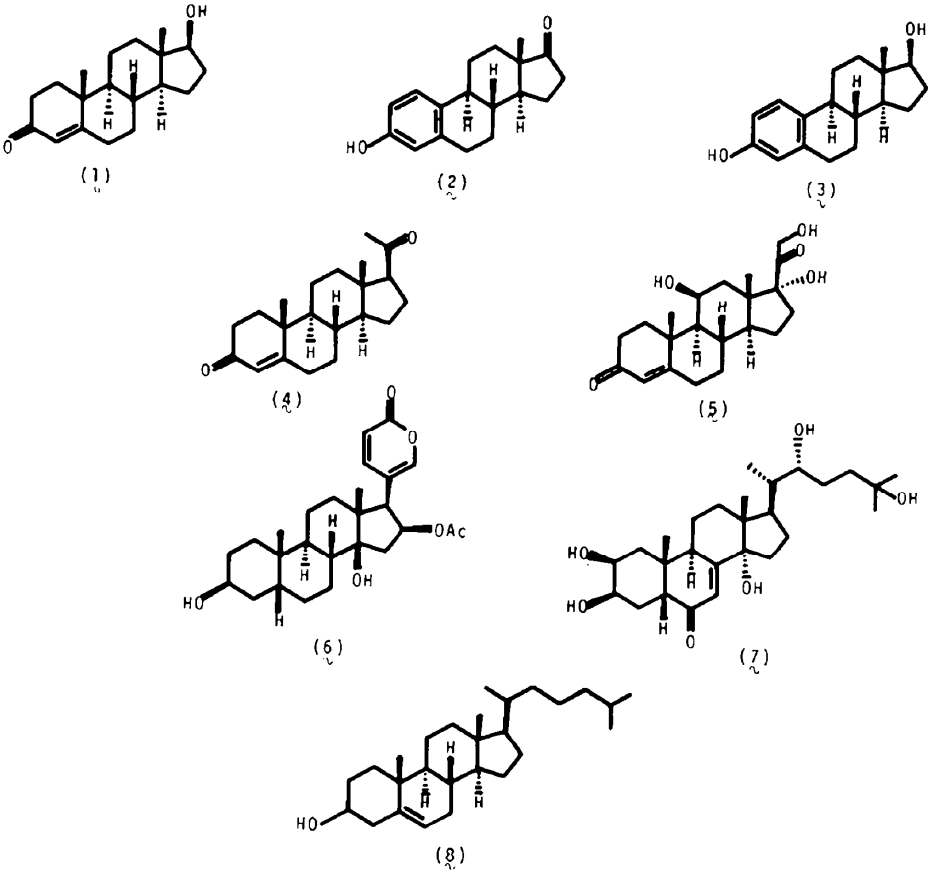
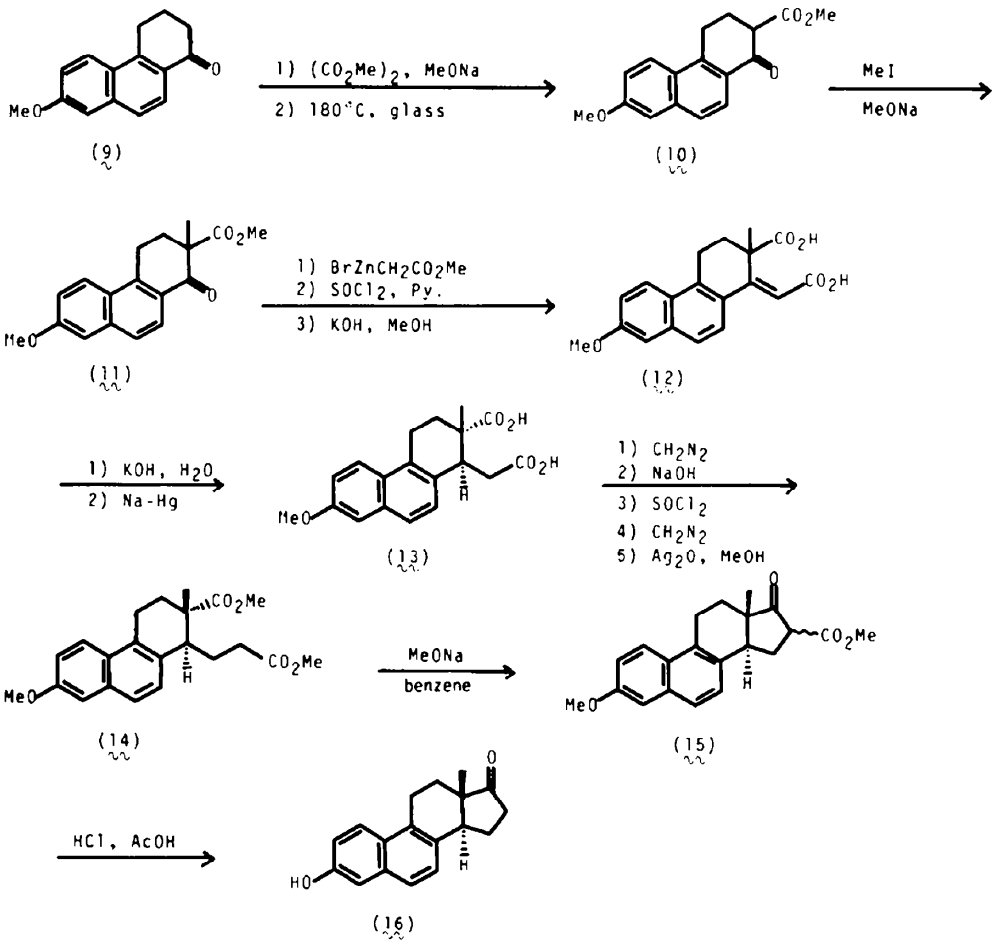
CONTENTS

INTRODUCTION

Steroids are widely distributed in nature and play an important role in the vital activity of the living organism: for example, testosterone (**1**) is the male sex hormone, estrone (**2**), estradiol (**3**), and progesterone (**4**) are female sex hormones which have cycle-regulating and pregnancy-maintaining effects, and hydrocortisone (**5**) is a hormone of the adrenal cortex whose anti-inflammatory effect is used therapeutically. Bufotalin (**6**) is a famous bufadienolide and α-ecdysone (**7**) shows an insect

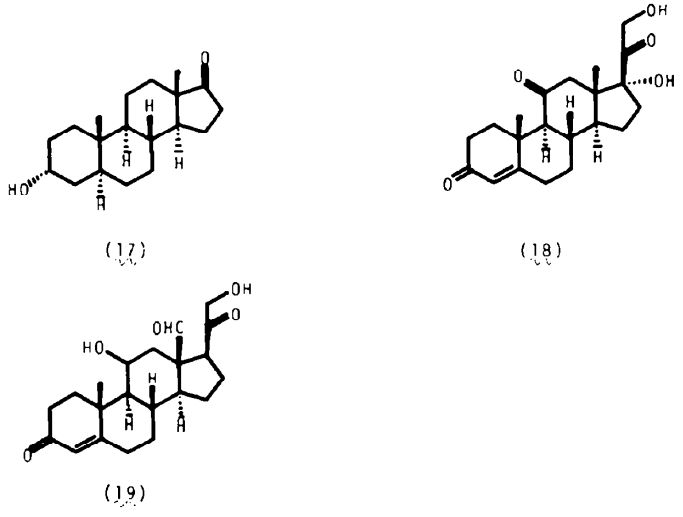


Scheme 1



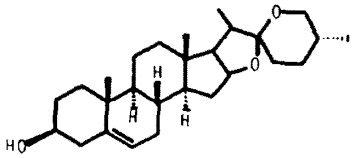
Scheme 2

moulting activity. Historically, investigations in the field of total synthesis of steroids began after the precise formula of cholesterol (**8**) had been established in 1932. The simplest representative of the natural steroids, equilenin (**16**) was first synthesised by Bachmann in 1939,[1] as shown in Scheme 2, starting from Butenandt's ketone (**9**). Equilenin (**16**) has only two chiral centers which simplified the stereochemical problems and made it possible to use classical methods for ring construction. An



Scheme 3

attempt by Bachmann[2] to synthesize estrone (**2**), which has two more chiral centers than equilenin (**16**), along the same lines resulted in the formation of a stereoisomer. Thus, the first synthesis of estrone (**2**) was achieved by Anner and Miescher[3] by using different reaction sequences. After this pioneering work was reported, many papers on steroid synthesis appeared in the literature. Included in these are the total synthesis of androsterone (**17**), cholesterol (**8**), and cortisone (**18**) by Robinson[4-6] and Woodward,[7-10] which can be claimed to be among the greatest victories of synthetic organic chemistry. Also noteworthy are the synthesis of all eight racemates of estrone (**2**)[11-13] and the total synthesis of aldosterone (**19**),[14-18] the most powerful known natural mineral-corticoid. Each of these syntheses reflects the level of knowledge of synthetic organic chemistry at the time. The possibility of scarcity of raw materials in the future, such as diosgenin (**20**), cholesterol (**8**), stigmasterol (**21**), sitosterol (**22**), and cholic acid (**23**), for the semi-synthetic production of other steroids, and the importance of modern ovulation inhibitors, e.g. (+)-norgestrol (**24**) which can only be efficiently produced by total synthesis, make steroid total synthesis an extremely important field of research at the present time. Prospect for the further development of the total synthesis of steroids are dependent on the viability of industrial application.



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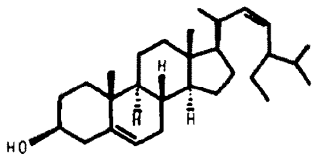

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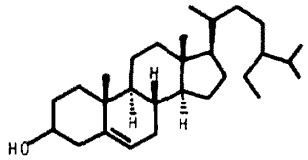

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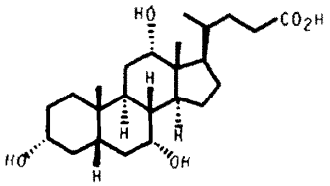

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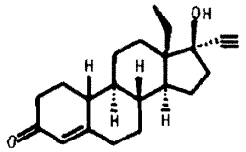
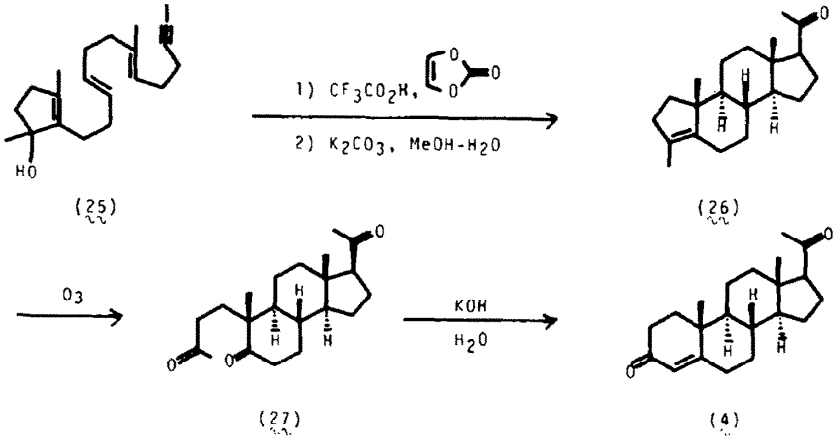


(24)

Scheme 4

Thus, synthetic routes which involve the introduction of protecting groups and their subsequent removal are unsuitable, and each reaction in the sequence should proceed stereospecifically in order to avoid laborious and costly procedures for separation and purification of intermediates and to increase the yield of the final "natural" product. Many procedures which are in accord with the above



(25) (26) (27) (4)

Scheme 5

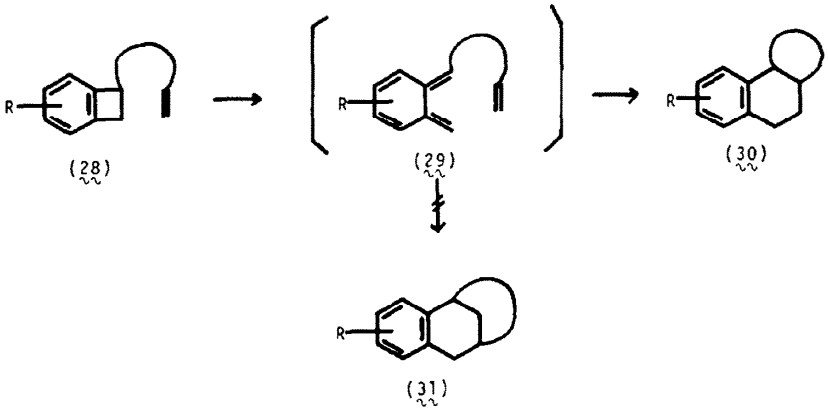
restrictions have been reported.[19-25] Recent advances in the total synthesis of steroids include acetylenic participation in polyolefinic cyclization developed by Johnson[26,27] and represented in a fascinating total synthesis of (±)-progesterone (**4**).[28,29] Acid catalyzed cyclization of acetylenic polyolefin (**25**) produced the steroid via **26** and **27** as outlined in Scheme 5.

Also noteworthy among recent advances is the application of annelation reactions using heterocyclic compounds,[30] developed by Stork and Danishefsky to the synthesis of steroids.

STEROID SYNTHESIS INVOLVING CYCLOADDITION REACTIONS

In contrast to other methods of cyclization, formation of the new ring by a cycloaddition reaction occurs simultaneously with the introduction of all the necessary carbons for steroid constraction. This reaction has been widely used in the total synthesis of steroidal compounds.[31]

Cycloaddition reactions involving participation of an aromatic system, in the form of *o*-quinodimethanes (**29**) derived *in situ* from the corresponding benzocyclobutenes (**28**) constitute another synthetic route to steroids. Since the history and reactions of *o*-quinodimethanes have already been considered in recent reviews,[36-38] we want to summarize here only the intramolecular cycloaddition reactions of *o*-quinodimethanes which have been used in studies directed towards the total synthesis of steroids in our laboratory. This intramolecular reaction proceeds via a primary reversible opening of the butene ring to E-*o*-quinodimethane (**29**) which undergoes irreversible cycloaddition to the multiple bond in the chain forming the annelated tricyclic system (**30**) rather than



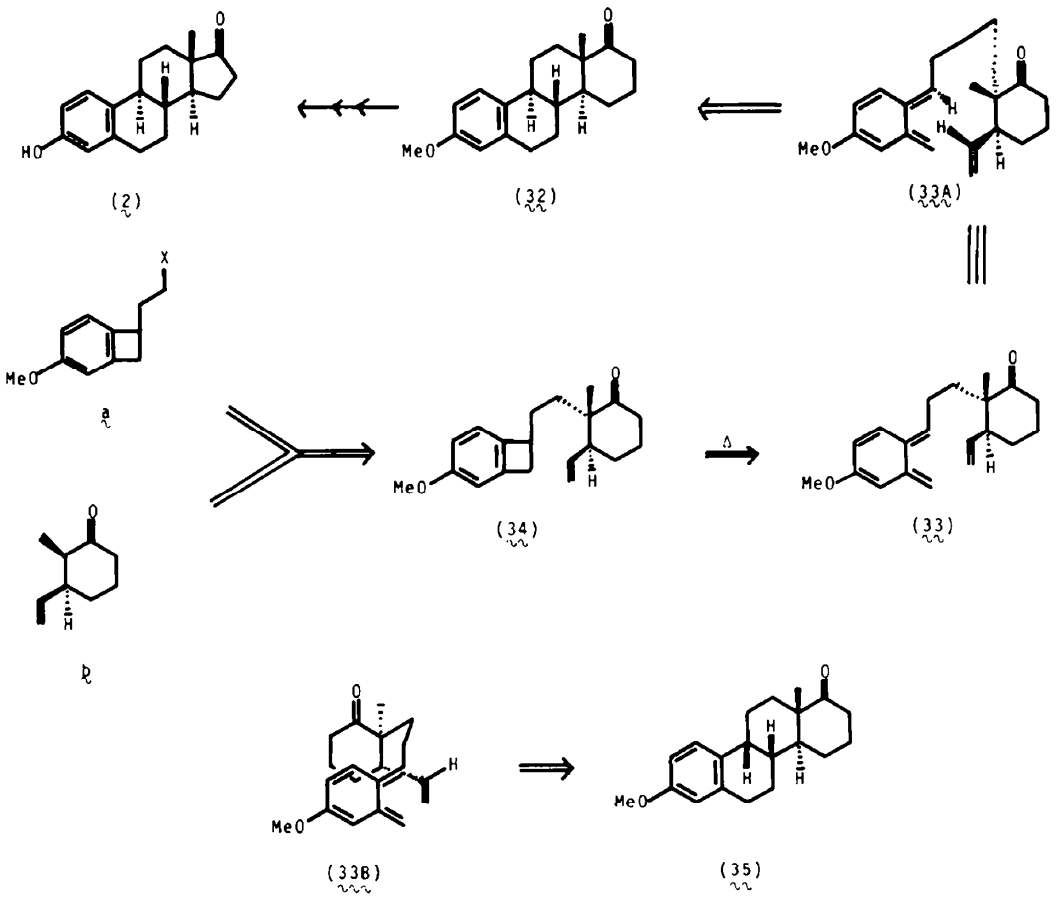
Scheme 6

compound **31**. Advantages of this cycloaddition reaction are in smooth cycloaddition even with unreactive dienophiles, ready accessibility of benzocyclobutenes, and chemical inertness of benzocyclobutenes permitting chemical manipulation.

TOTAL SYNTHESIS OF A-RING AROMATIC STEROIDS

This type of cycloaddition reaction was first applied to steroid synthesis in a total synthesis of D-homoestrone methyl ether (**32**) by us.[39,40] The synthesis was planned on the basis of the reaction sequence outlined in Scheme 7. It was assumed that cycloaddition reaction of the olefinic *o*-quinodimethane (**33**), generated by thermolysis of benzocyclobutene (**34**), would proceed in a stereoselective manner through the sterically favored *exo*-transition state **33A** leading to **32**, rather than through the *endo*-transition state **33B** (leading to **35**) which has steric repulsion between the aromatic and cyclohexane rings. The olefinic benzocyclobutene (**34**) could be derived by alkylation of cyclohexanone derivatives such as 2-methyl-3-vinylcyclohexanone (**b**) with benzocyclobutenylethyl halides such as **a**, under basic conditions.

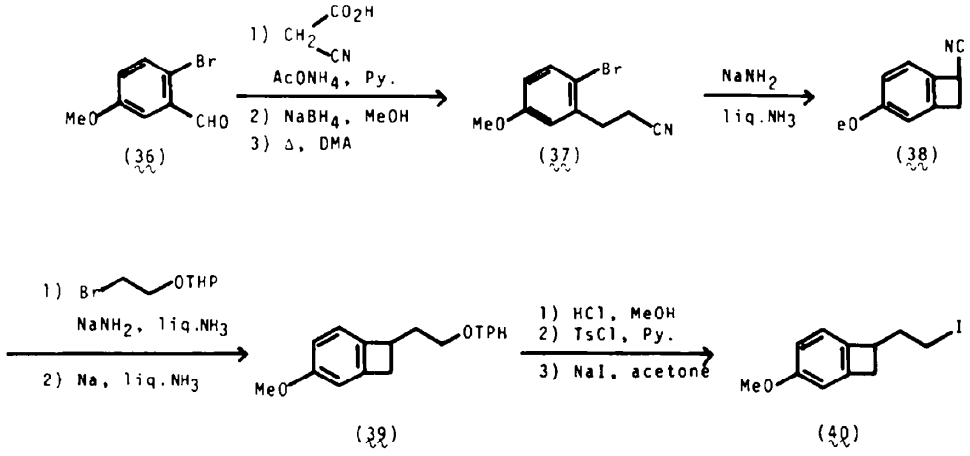
The reaction sequences leading to benzocyclobutenes **38** and **40** are shown in Scheme 8. These sequences can be applied for the synthesis of benzocyclobutenes variously substituted on the aromatic ring, and with various side-chains on the cyclobutene ring, and are adaptable to large scale production. Knoevenagel reaction of 2-bromo-5-methoxybenzaldehyde (**36**) with cyanocetic acid



Scheme 7

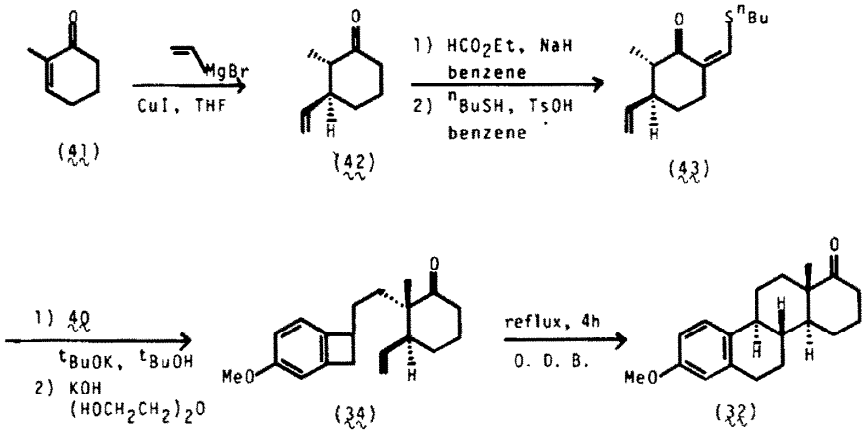
followed by reduction and decarboxylation afforded the phenylpropiononitrile (**37**) which was cyclized to furnish the benzocyclobutene (**38**). Condensation of **38** with the tetrahydropranyl ether of ethylene bromohydrin afforded the ethylated benzocyclobutene which was subjected to reductive decyanation using sodium in liquid ammonia to give compound **39**. Finally, the tosylate which was derived from **39** by cleavage of the tetrahydropranyl group followed by tosylation, was converted into the benzocyclobutenylethyl iodide (**40**).

With this iodide (**40**) in hand, synthesis of **32** was carried out as shown in Scheme 9. Conjugate addition of a vinyl group to 2-methylcyclohexenone (**41**) gave the 3-vinylcyclohexanone (**42**).



Scheme 8

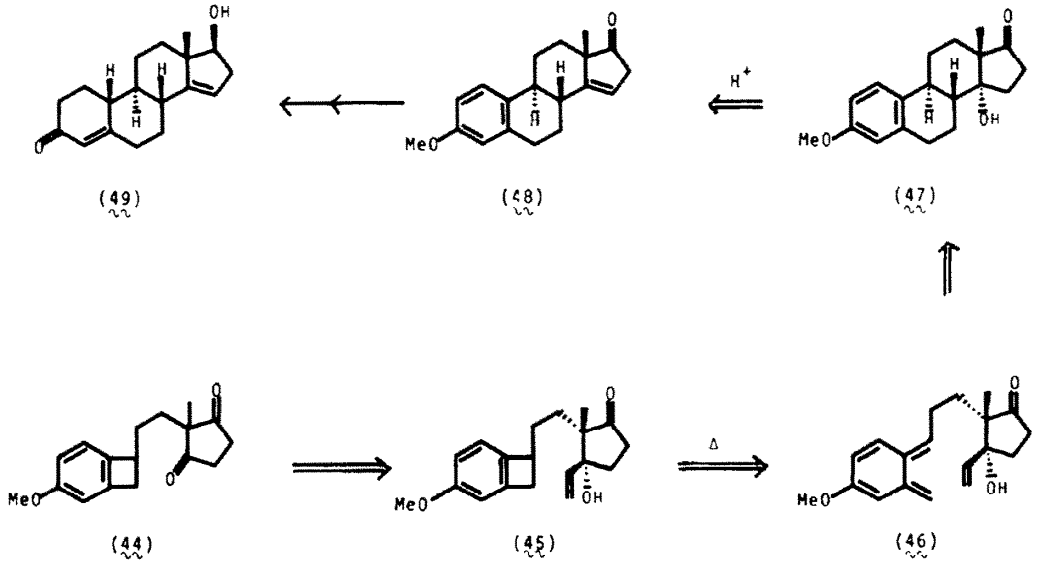
Formylation of **42** followed by treatment with *n*-butylmercaptan afforded compound **43**. Condensation of the two components **40** and **43** followed by hydrolysis furnished the key intermediate **34**, which on refluxing in *o*-dichlorobenzene (ODB) was converted to the crystalline O-methyl-D-homoestrone (**32**) in almost quantitative yield. Demethylation of **32** gave D-homoestrone. As O-methyl-D-homoestrone **32** has previously been correlated to estrone (**2**), this work constitutes a total synthesis of estrone (**2**).



Scheme 9

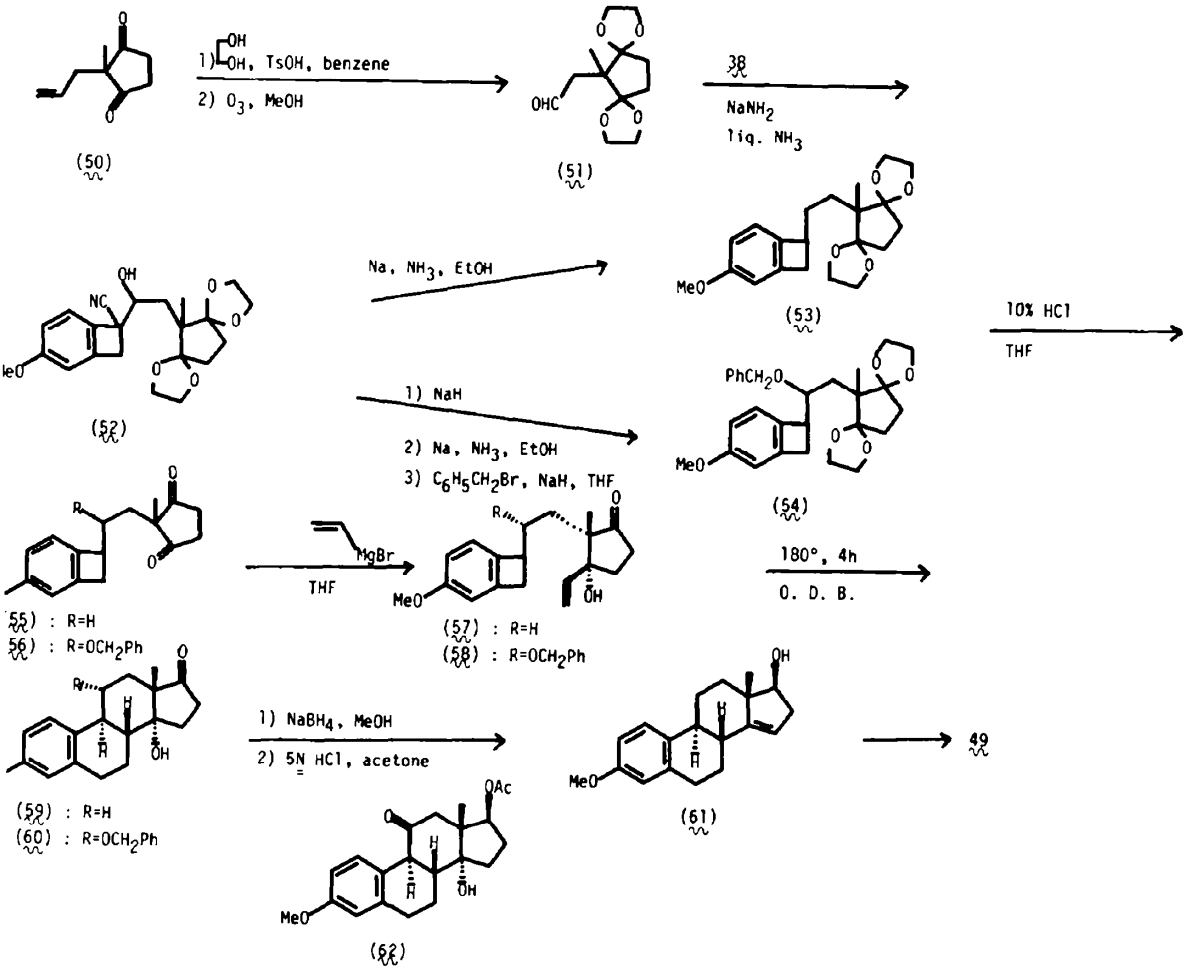
Thus it was confirmed that the cycloaddition reaction of *o*-quinodimethane (**33**) proceeded along the reaction pathway proposed in Scheme 7, namely that the configuration of substituents on the cyclohexanone ring controlled the stereochemistry of the B,C ring junction in the product (**32**) and that the stereochemistry of the butene ring in **34** did not affect that of the product.

This stereoselective synthesis of estrone (**2**) by *o*-quinodimethane cycloaddition opened up a new entry into the total synthesis of various types of steroids. In order to further investigate the stereochemical course of *o*-quinodimethane cycloaddition, we chose as the next target molecule 14α-hydroxyestrone methyl ether.[41,42] The synthetic precursor of this steroid, *o*-quinodimethane (**46**), has an extra substituent, a OH group, on the cyclopentane ring and it was of interest to compare the stereochemical results. Dehydration of **47** is expected to give the 14-dehydro derivative (**48**) which has been synthesised[43] from estrone (**2**) in many steps and correlated with 14-dehydro-19-nortestosterone (**49**), a steroid which was found to show about one hundred times as much androgenic activity as testosterone.[44] The synthesis of **49** was planned as outlined in Scheme 10.



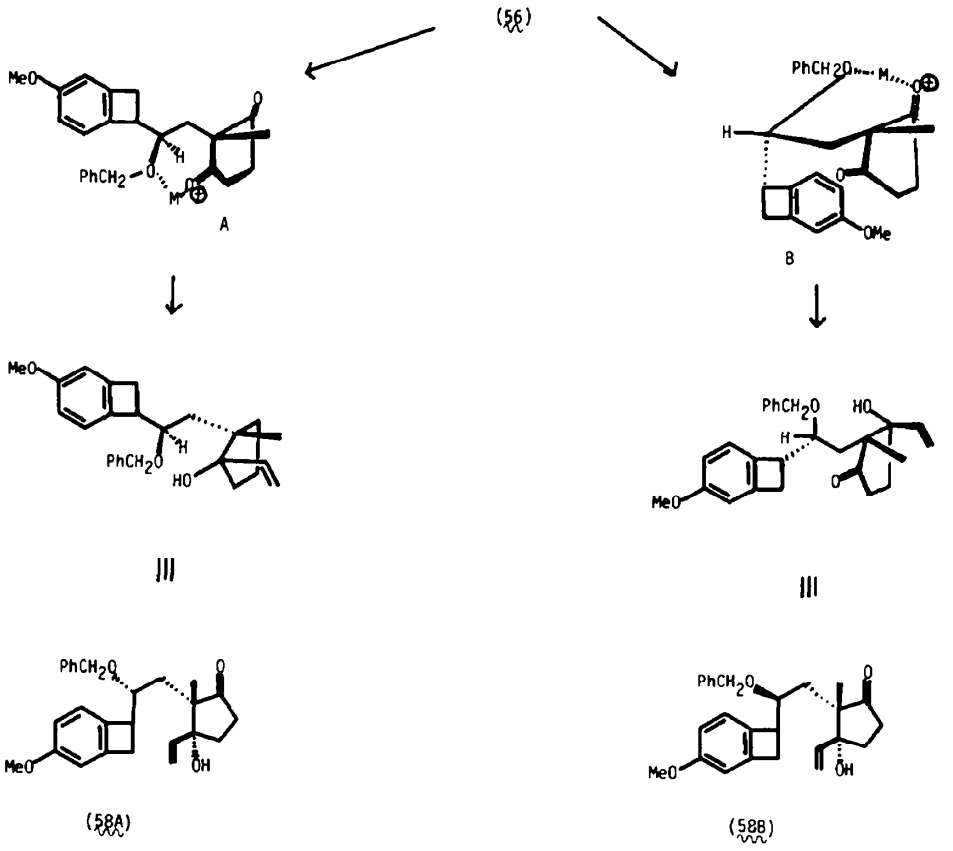
Scheme 10

The aldehyde **51** obtained from the cyclopentadione **50** by ketalization followed by ozonolysis was condensed with 1-cyano-4-methoxybenzocyclobutene (**38**) to give the hydroxycyano compound (**52**) as a diastereoisomeric mixture. Reduction of **52** with sodium in liquid ammonia and ethanol afforded directly the compound **53**. On the other hand, reduction of the sodium salt of **52** gave the hydroxy compound which was converted into its benzyl ether (**54**). Firstly the former reduction product (**53**) was used for the synthesis of **49**. Thus the diketone (**55**) resulting from acid treatment of **53** reacted with vinymagnesium bromide to give stereoselectively the olefinic compound **57** which on thermolysis yielded compound (**59**) as a single product. This reaction sequence demonstrated that intramolecular cycloaddition of *o*-quinodimethanes proceeded in a stereoselective manner even when the extra OH group was present in the cyclopentane moiety. Compound **59** was then converted into **61** on successive treatment with sodium borohydride and 5 N HCl. Since **61** has already been transformed into **49**,[43] this work constitutes a total synthesis of 14-dehydro-19-nortestosterone (**49**). Using the same reaction sequence as described above, 17-O-acetyl-14α-hydroxy-3-O-methyl-11-oxo-estradiol (**62**) which could be an important precursor in the synthesis of 11-oxidized steroids, was prepared as follows.[45] The compound (**60**), resulting from thermolysis of **58**, was converted into **62** by successive reduction, selective acetylation of the 17-OH group, reductive debenzylation, and Jones oxidation.



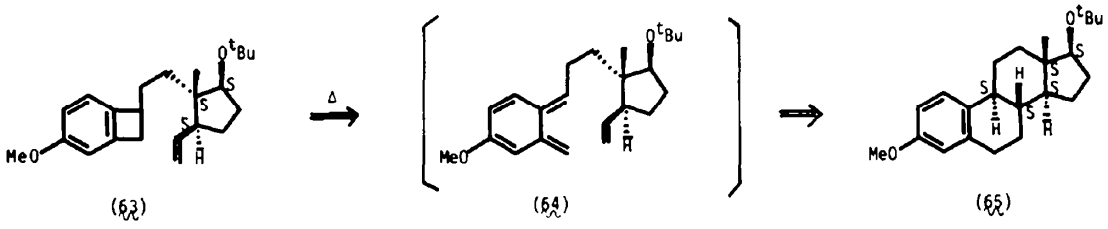
Scheme 11

The stereoselectivity in the formation of **58** can be explained by assuming the reaction sequence summarized in Scheme 12. Of the two possible metal-chelated reaction intermediates **A** and **B**, the latter, which would be the intermediate for the formation of **58B**, is the unfavorable conformer because of severe steric repulsion between the cyclopentane and benzocyclobutene moieties. On the other hand, the intermediate **A**, which would lead to the formation of isomer **58A**, has no such severe steric interactions and the reaction therefore proceeded along this route.



Scheme 12

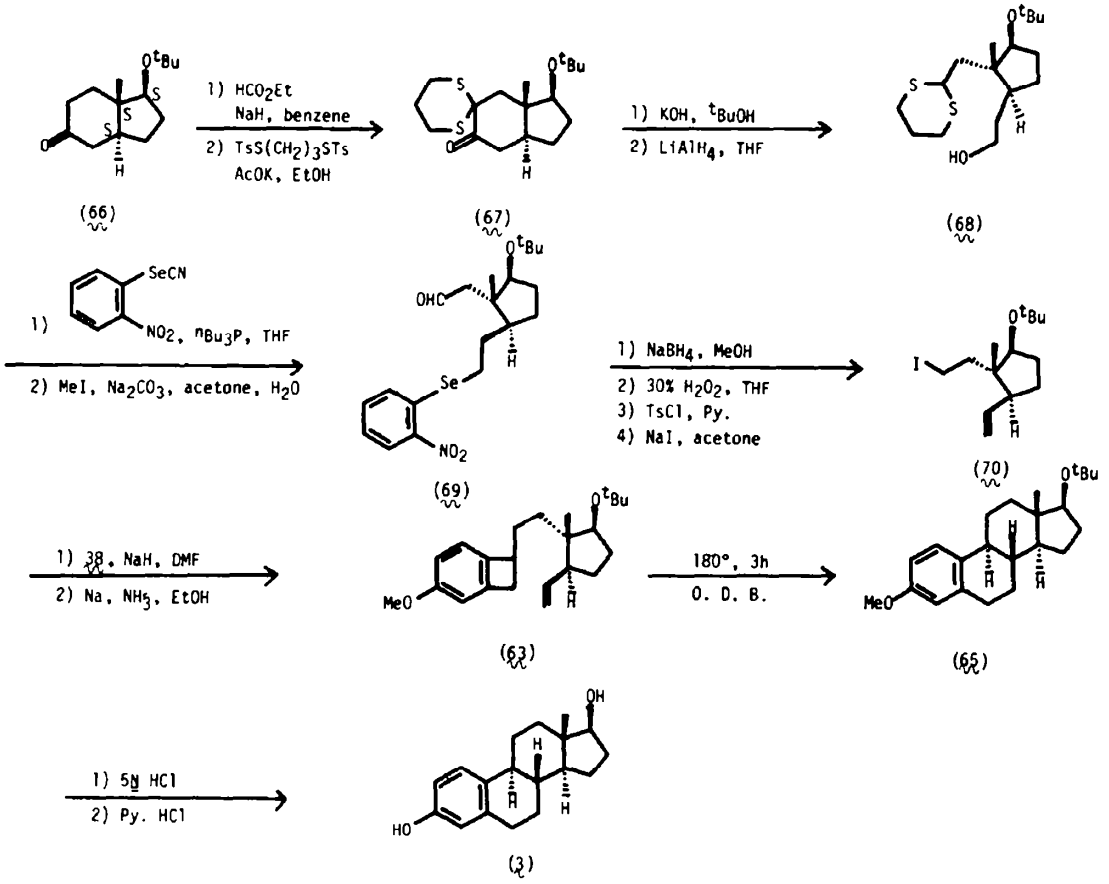
The remarkable stereoselectivity shown in the previous Schemes offered the possibility of the synthesis of optically active steroid hormones and it was towards this goal that our attention then turned. Our first target was the total synthesis of optically active estradiol (**3**)[46] and the synthetic plan is shown in Scheme **13**. It is easily seen that asymmetric induction at C-8 and C-9 of compound **65** might occur as shown by the stereoselective intramolecular cycloaddition of the olefinic *o*-quinodimethane (**64**), resulting from thermolysis of the benzocyclobutene (**63**) in which all the chiral centers in the cyclopentane moiety are S.



Scheme 13

The synthesis of optically active benzocyclobutene (**63**) and its thermolysis were carried out as follows. The optically active indanone (**66**), the absolute configuration of which is known to be all S,[47] was chosen as the starting material. The ketone thioketal (**67**), obtained by successive treatment of **66** with ethyl formate and propane-1,3-dithiol di-*p*-toluenesulfonate, was converted to the ring-opened carboxylic acid which was then reduced to furnish the alcohol **68**. The *o*-nitrophenylseleno compound **69**, prepared by treatment of **68** with *o*-nitrophenylselenocyanide and subsequent treatment of the resulting selenide with methyl iodide in aqueous acetone, was converted into the optically active iodoethylcyclopentane (**70**) in the usual manner. Condensation of **38** with this iodide (**70**) followed by reductive decyanation afforded the optically active olefinic benzocyclobutene (**63**), thermolysi

furnished the optically active estradiol derivative (**65**). The optical purity of 3-O-methylestradiol obtained by acid treatment of **65** was found to be 96.8% and subsequent demethylation produced estradiol (**3**). Thus the total synthesis of optically active estradiol (**3**) was accomplished.



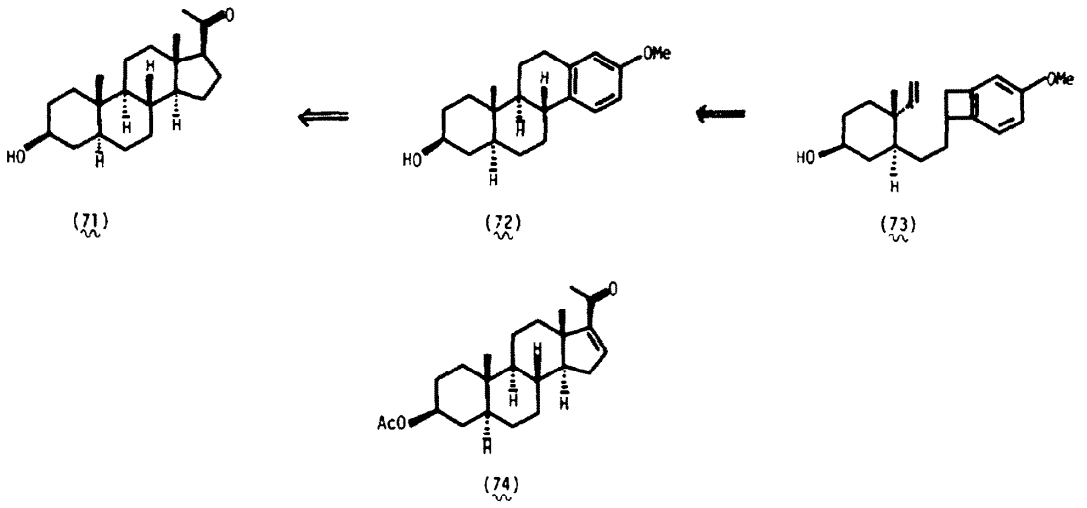
Scheme 14

TOTAL SYNTHESIS OF PREGNANE TYPE STEROIDS

Several total syntheses of A-ring aromatic steroids involving the same type of cycloaddition reaction have been reported by other groups.[48,49]

Although the cycloaddition reactions of *o*-quinodimethanes have been used to achieve the stereoselective total synthesis of a range of substituted A-ring aromatic steroids, none of these methods has provided an efficient route to pregnane type steroids in either racemic or optically active form. Pregnane type steroids not only constitute an important class of steroid hormones but could be key intermediates in the synthesis of other types of steroid hormones.[50] We therefore planned a total synthesis of (+)-5α-dihydropregnenolone (**71**),[51,52] a known metabolite of progesterone, whose acetate is an important synthetic intermediate for cholesterol,[6-10] via the D-ring aromatic steroid (**72**) as outlined in Scheme 15. The latter steroid is also known as a synthetic intermediate for 5α-Δ^{16}-pregnen-3β-ol-20-one acetate (**74**).[53]

The ketal alcohol (**76**), prepared from the optically active diketone[54] (**75**) by ketallization and enone reduction, was converted into the acetoxy enone (**77**) on successive treatment with 10% hydrochloric acid, acetic anhydride, bromine, and lithium carbonate and lithium bromide. The acetylenic aldehyde (**78**), obtained by the Corey modification of the Eschenmoser ring opening reaction of the corresponding epoxide of acetoxy enone (**77**), was partially reduced to the olefinic aldehyde (**79**). Condensation of **79** with the cyanobenzocyclobutene (**38**), followed by reductive elimination of the cyanohydroxy group furnished the optically active olefinic benzocyclobutene (**73**). Alternatively, **73** was synthesised in high yield by condensation of **38** with with the iodide (**80**),

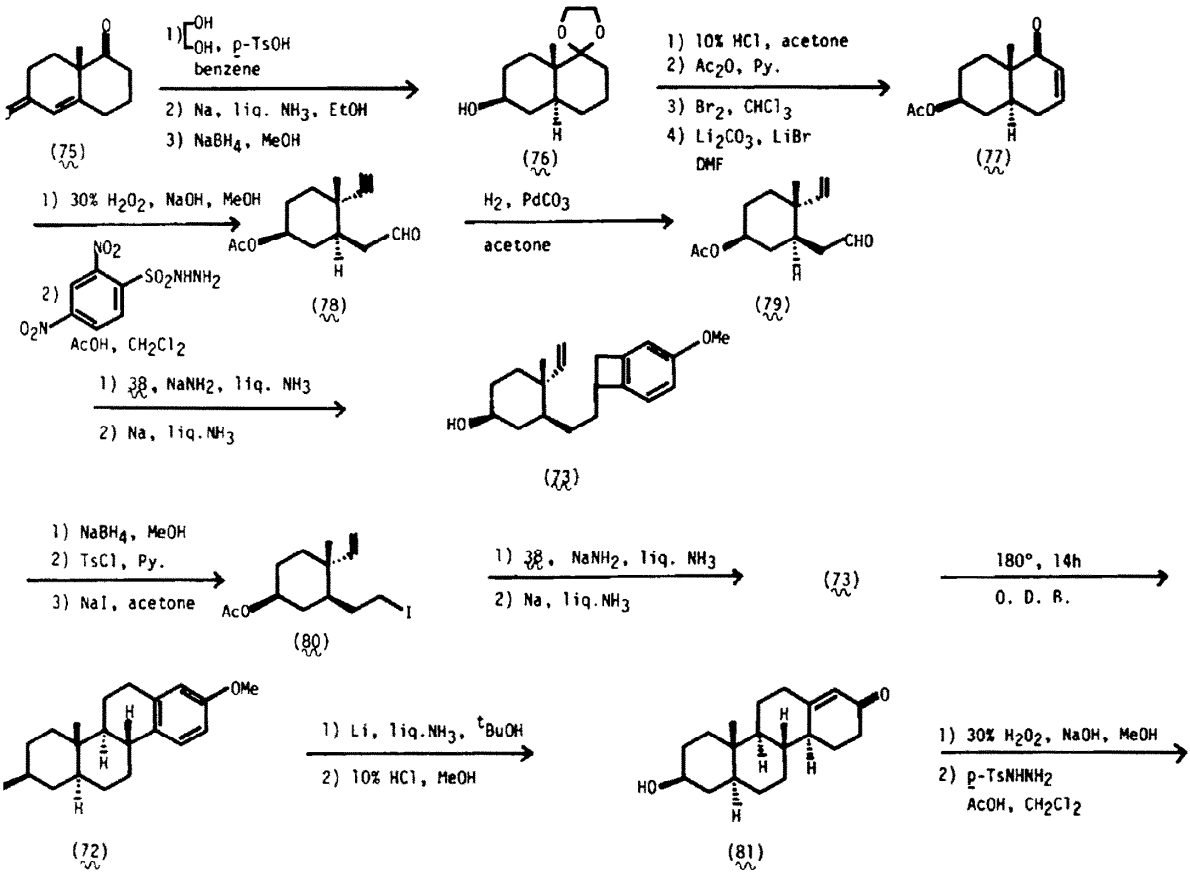


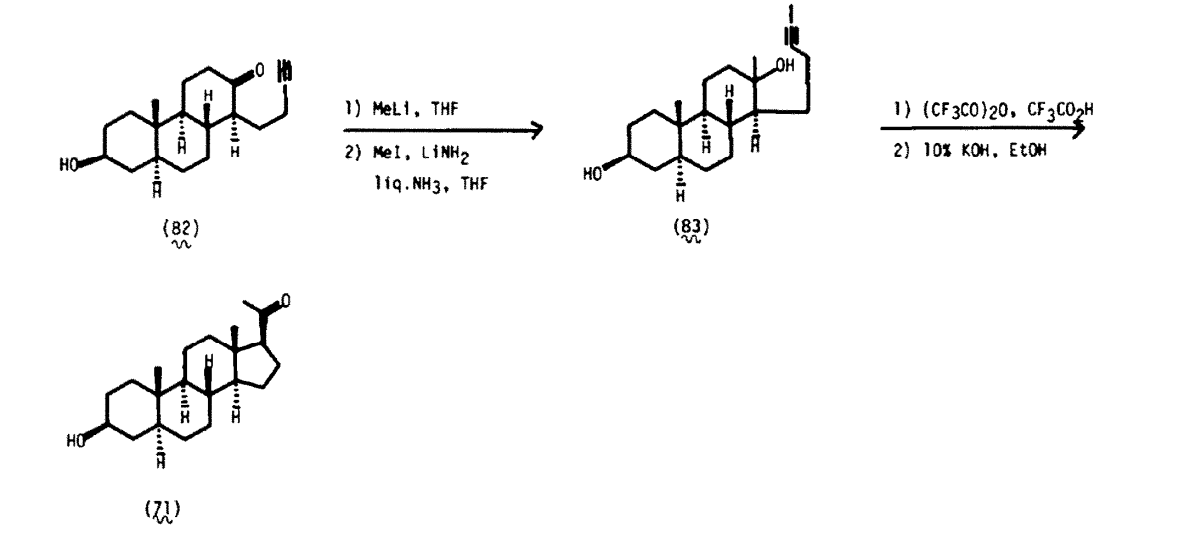
Scheme 15

prepared from olefinic aldehyde (**79**) in the usual manner, followed by reductive decyanation Thermolysis of **73** stereoselectively afforded the D-ring aromatic steroid (**72**) which was then converted into the enone (**81**) by Birch reduction followed by acid treatment. Although the transformation of **81** into the pregnane type of steroid **74** has already been reported,[53] we carried out the following sequence of reactions in order to obtain a more efficient conversion into the pregnane type steroid. The acetylenic ketone (**82**) resulting from Eschenmoser ring opening reaction of the corresponding epoxide of **81**, was converted into the acetylenic alcohol (**83**) by successive treatment with methyllithium and methyl iodide in the presence of sodium amide in liquid ammonia. Cyclization[55] of **83** was effected using trifluoroacetic anhydride and trifluoroacetic acid to furnish (+)-5α-dihydropregnenolone (**71**), the optical purity of which was found to be 91.4%. With an effective synthesis of D-ring aromatic steroids and an efficient procedure for their conversion to pregnane type steroids in hand, we planned a stereoselective total synthesis of β-ecdysone (**84**), via **85**[56] and **86**[57], the latter of which could be derived by thermolysis of benzocyclobutene **88** via **87**

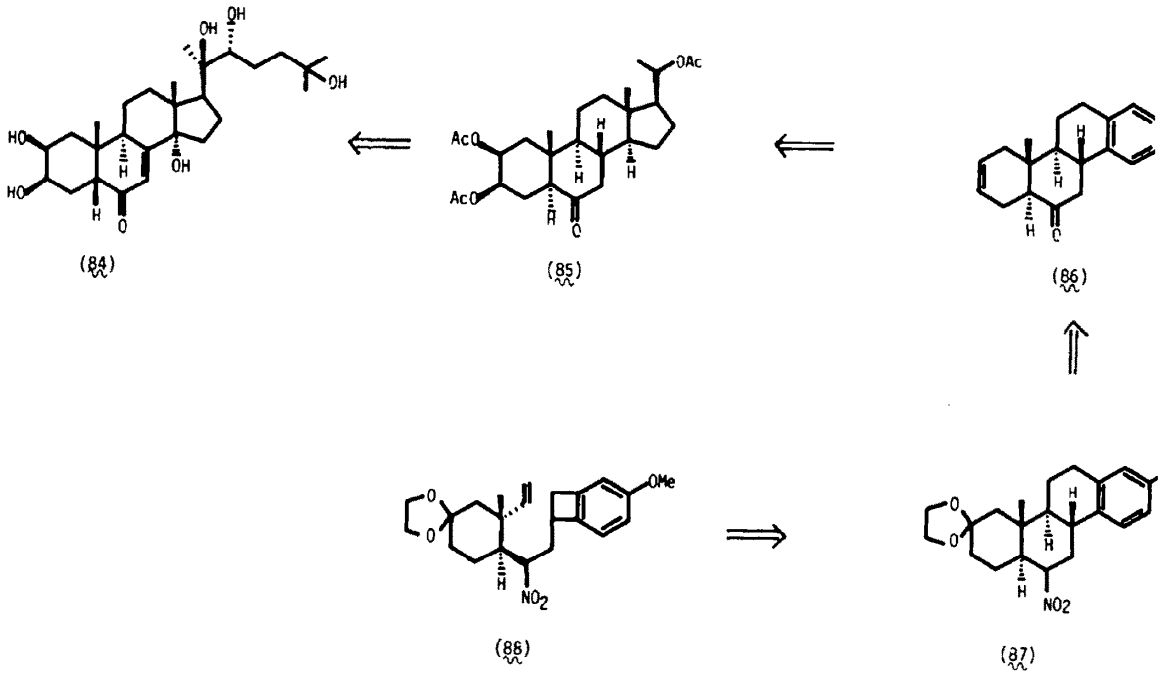
The olefinic ester (**90**), prepared by conjugate addition of a vinyl group to enone (**89**) followed by ketallization, was converted into the nitro compound (**91**) by successive reduction of the ester group tosylation of the alcohol group, substitution of tosylate by iodide and of iodide by nitro group. The nitro compound (**91**) on reaction with formalin and diethylamine gave the Mannich base which was treated with hydrogen chloride to afford the nitro olefin (**92**). Michael addition of the cyanobenzocyclobutene **38** to **92** in the presence of sodium amide yielded the key intermediate (**93**) which on heating at 180° for 2 hr afforded the D-ring aromatic steroid (**94**) with a *cis* B,C ring juncture Although the reaction mechanism for this thermolysis is not yet clear, **94** was subjected to the following transformation. The olefinic nitro compound (**95**), obtained from **94** by successive acid treatment, ketone reduction and dehydration, was subjected to modified Nef reaction as developed by McMurry,[58] and subsequent reductive decyanation, followed by Jones' oxidation, and epimerisation at C_5-position, furnished the initial target molecule (**86**), the transformation of which into **85** was carried out as follows.

The olefinic enone (**96**), prepared by reduction with sodium borohydride, Birch reduction, and acid treatment, was converted into the olefinic epoxy ketone (**97**). The acetylenic ketone (**98**) resulting from Eschenmoser ring opening reaction of **97**, was transformed into acetylenic alcohol (**99**) by successive treatment with methyllithium and methyl iodide in the presence of lithium amide in liquid ammonia. Cyclization of **99** using trifluoroacetic anhydride and trifluoroacetic acid afforded the compound (**100**) which was oxidized with Jones' reagent to give **101**. The diacetoxy compound (**102**) obtained from **101** by Prévost–Woodward reaction followed by acetylation, was reduced with sodium borohydride to afford the diol (**103**) which was finally converted into **85** by successive treatment with acetic anhydride in pyridine and Jones' reagent. Since the compound **85** thus obtained has been transformed[59] into β-ecdysone (**84**), this work constitutes a formal total synthesis of β-ecdysone (**84**


1) OH, OH, p-TsOH benzene
2) Na, liq. NH3, EtOH
3) NaBH4, MeOH
1) 10% HCl, acetone
2) Ac2O, Py.
3) Br2, CHCl3
4) Li2CO3, LiBr DMF
1) 30% H2O2, NaOH, MeOH
2) AcOH, CH2Cl2
H2, PdCO3
acetone
1) 38, NaNH2, liq. NH3
2) Na, liq.NH3
1) NaBH4, MeOH
2) TsCl, Py.
3) NaI, acetone
180°, 14h
O. D. R.
1) Li, liq.NH3, tBuOH
2) 10% HCl, MeOH
1) 30% H2O2, NaOH, MeOH
2) p-TsNHNH2
AcOH, CH2Cl2
(75)
(76)
(77)
(78)
(79)
(73)
(80)
(72)
(81)

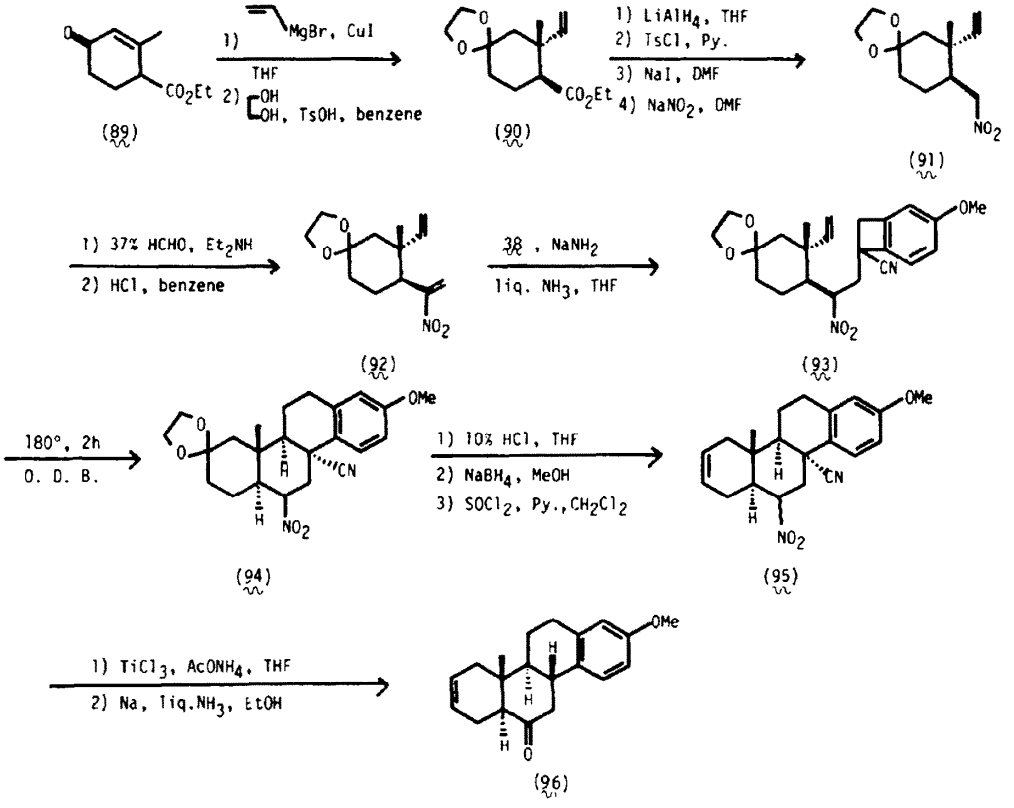

1) MeLi, THF
2) MeI, LiNH2
liq.NH3, THF
1) (CF3CO)2O, CF3CO2H
2) 10% KOH, EtOH
(82)
(83)
(71)

Scheme 16

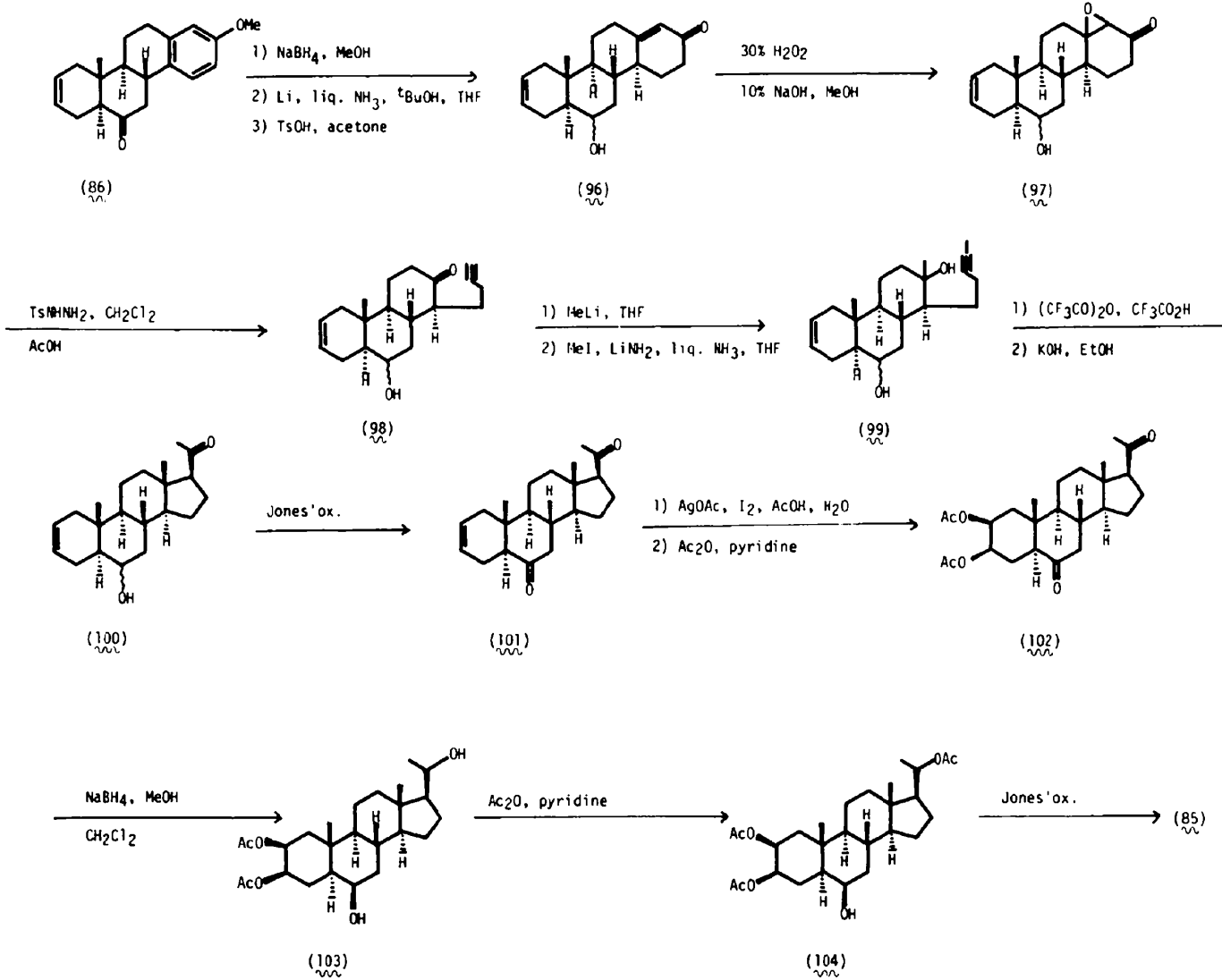


Scheme 17

Since our first introduction of the intramolecular cycloaddition reaction of *o*-quinodimethanes for the synthesis of D-homoestrone, many papers, by several groups including our own, on the synthesis of various types of steroids in which this reaction is the key step, have appeared in the literature. This shows that such reaction may be a general and highly flexible method for steroid synthesis.



Scheme 18


OMe
1) NaBH4, MeOH
2) Li, liq. NH3, tBuOH, THF
3) TsOH, acetone
30% H2O2
10% NaOH, MeOH
TsNHNH2, CH2Cl2
AcOH
1) MeLi, THF
2) MeI, LiNH2, liq. NH3, THF
1) (CF3CO)2O, CF3CO2H
2) KOH, EtOH
Jones' ox.
1) AgOAc, I2, AcOH, H2O
2) Ac2O, pyridine
NaBH4, MeOH
CH2Cl2
Ac2O, pyridine
Jones' ox.
(85)
(86)
(96)
(97)
(98)
(99)
(100)
(101)
(102)
(103)
(104)

Scheme 19

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