C7-Substituted Estranes and Related Steroids

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Abstract: C7-substituted steroids, especially C7-substituted estradiol derivatives, have been the subject of intensive interdisciplinary studies encompassing the fields of chemistry, biochemistry and medicine. While showing the more pertinent structures with their physiological characteristics, this review will focus on the synthetic approaches to these molecules.

Keywords: Steroids, estrogens, antiestrogens, estradiol, radiodiagnostics, breast cancer.

1. INTRODUCTION

In recent years, the study of estrogens and antiestrogens has gained importance in such varied but interacting fields as radiodiagnostic agents for minimal breast cancer [1], estrogen receptor positive breast cancer therapy [2] and hormone replacement therapy [3] as well as the systematic study of the action of environmental hormones on the human endocrinal system and their effect on wildlife [4]. Although compounds possessing estrogenic or antiestrogenic character can be of a variety of structures, one of the important classes of compounds constitutes estradiol derivatives. 3,17β-Estradiol itself is the natural human estrogen with such diverse functions as of the reproductive organs, maintaining the bone structure, and regulating plasma levels of HDL cholesterol, thus playing a role in protecting against cardiovascular disease. Much of the action of estradiol and other estrogens proceeds through their interaction with the estrogen receptor ERα. A number of diseases have been found to be estrogen mediated, among them is estrogen receptor positive breast cancer. This, however, could open up the chance to target this type of cancer with both steroidal diagnostics as well as therapeutic agents. In the last 35 years, a number of research has been devoted to the development of novel synthetic steroids in this area. Especially, C7-substituted steroids have been at the forefront of this development, ever since early research has shown that C7 substitutents can increase the binding of the steroid to the estrogen receptor, which has led to a number of antiestrogens used as lead structures (see below). The following contribution discusses the synthesis of C7-substituted estradiol derivatives.

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2. BRIEF OVERVIEW AND CATEGORIZATION OF SYNTHETIC STRATEGIES

Decades ago, after the first steroidal contraceptives had been put onto the market, it was realized that 7α-methyl substituted steroids can bind more strongly to steroidal receptors than their non-substituted counterparts. This was also recognized for the 7α-methylestradiols, which show a good receptor binding affinity (RBA) to the estrogen receptor ERα (see below). The finding quickly led to applications such as the development of radioimaging agents and the antiestrogens for cancer therapy. Industrial interest quickly followed and a number of drugs [RU 45144 (**4**), ICI-164384 (**5**), ICI-182780 (other names: Faslodex, Fulvestrant, ZD 9238) (**6**) and EM-139 (**7**)] were forwarded [5-15] [for a more complete reading, see ref. 16], where ICI 164384 and ICI 182780 act as pure antiestrogens. ICI 182780 is a drug that blocks estrogen activity in the body and is used in the therapy of estrogen-dependent tumors such as breast cancer [2,11,12]. These molecules have also been derivatised. Thus, 16α-halo derivatives of ICI 164384 have been studied in detail [13]. Studies with radiolabeled ICI 182780 (^{14}C and other labels) have been carried out [17].

The strategies used to prepare C7-substituted estranes can be divided into three main categories: a.) the *De Novo* synthetic approach utilizing a preformed C-7 substituent in one of the fragments used to build the steroidal frame; b.) the introduction of the C7-substituent to derivatives of another steroidal series and the subsequent transformation of these compounds to derivatives of the estrane series; c.) the addition of the C7 substituent to a compound of the estrane series, in which the C7 position has been activated in an earlier step. The following review is structured according to the above named general categorization of synthetic approaches, where sections a.) – d.) deal with the introduction of C-substituents, while sections e.) deals with heterofunctionalization at C-7. Finally a brief, personal view of future possibilities in this area is given.

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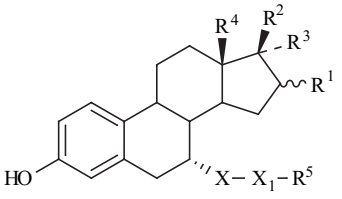
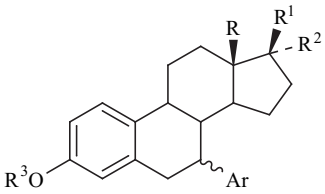


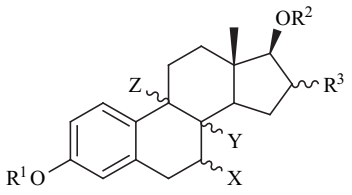
1

General formulation of Eur. Pat. EP 138.504
(J. Bowler, B. S. Taite [ICI] **1985**)
Steroids as antiestrogens



2

General formulation of Eur. Pat. Appl. EP 280.614
(F. Nique, L. Nedelec, M. M. Bouton, D. Philibert [Roussel-UCLAF] **1988**)
7-Aryl-19-norsteroids as antiproliferates, antiestrogens and/or estrogens



3

General formulation of Ger. Offenl. DE 4.018.828
(H. Kuenzer, R. Bohlmann [Schering A.-G.]) **1990**
Preparation of substituted Estra-1,3,5(10)-trienes

specifically mentioned:
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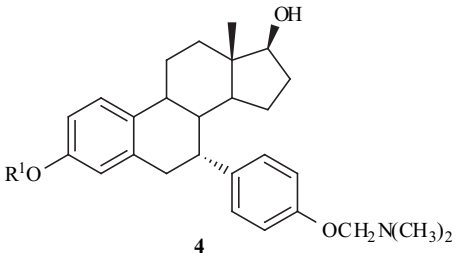

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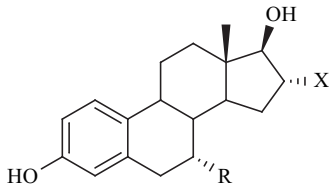


5: X = H, R = $(CH_2)_{10}CON(n\text{-}C_4H_9)CH_3$ (ICI 164384)
6: X = H, R = $(CH_2)_9SO(CH_2)_3CF_2CF_3$ (ICI 182780)
7: X = Cl, R = $(CH_2)_{10}CON(n\text{-}C_4H_9)CH_3$ (EM-139)

Fig. (1). Examples of Patent Applications in the area of C-7 substituted Estra-1,3,5(10)-trienes.

3. SYNTHESES OF C7-SUBSTITUTED ESTRANES

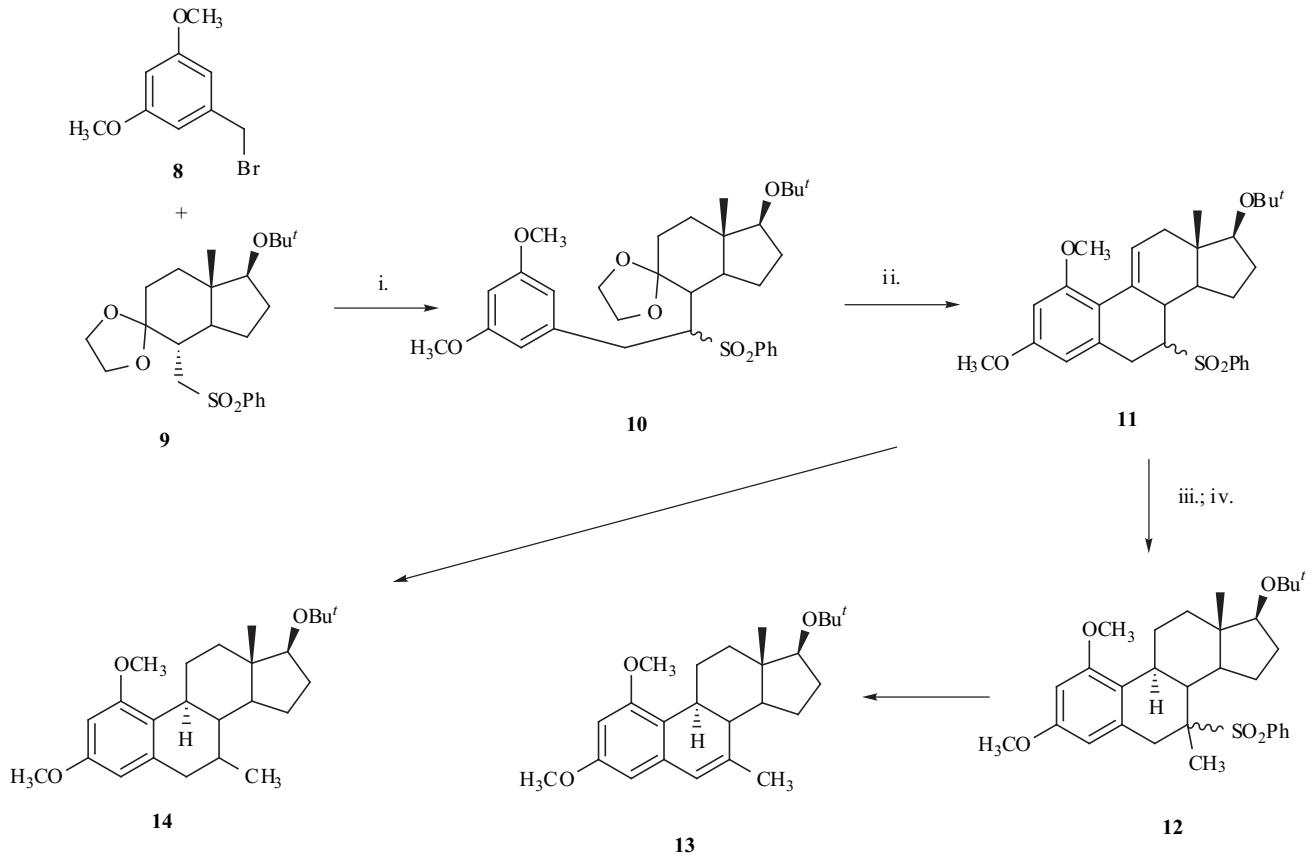
a.) *De Novo* Syntheses

In principle, *de novo* syntheses have been accomplished through key ring closure reactions of rings B, C, B / C, and B / C / D. All of these strategies have been utilized in the preparation of C7-substituted steroids.

i. Closure Reactions of Ring B as Key Step

In 1971, Schering has patented 1,3-diacetoxy-17α-ethynyl-7α-methylestra-1,3,5(10)-trien-17β-ol as a strong estrogen [18]. At first the compound was prepared in a partial synthesis [27]. Later, a total synthesis was forwarded based on a nucleophilic substitution reaction of a lithiated homochiral 1,2,3,3a,4,5,7,7a-octahydro-4-(phenylsulfonyl) methyl-5*H*-inden-5-one (**9**) with an appropriately substituted benzyl bromide (e.g., **8**) and a subsequent acid catalyzed *Friedel-Crafts* type closure of ring B of the steroidal frame [19-23]. This approach has been used by G. Sauer, R. Wiechert *et al.* for the preparation of other synthetic steroids [22, 24-26]. The methyl group is introduced in **11** by lithiation at the C7-position, taking advantage of the acidity of C7 (position α to the electron withdrawing phenyl-sulfonyl group). The anion is reacted with methyl iodide leading to the 7α-methyl substituted estradiol **12** as the major product. Steric reasons are given for the high stereoselectivity noted in the reaction (Scheme **1**). The reductive removal of the auxiliary sulfonyl yields a mixture of 7α- and 7β-methylestra-1,3,5(10)-trien-17β-ol derivatives **14**, the ratio of which depends on the reductant used. Both the reduction with K/Hg in a mixture of ethanol/toluene 4:1 and the electrochemical reduction at the Hg cathode ($LiClO_4$ [electrolyte], MeOH [solvent], non-divided cell, ratio 9:1) show high stereoselectivity. Both epimeric sulfones as starting material gave the same diastereoisomeric mixture within experimental error. This process was also patented.

Not only the 4-phenylsulfonylmethyl substituted 1,2,3,3a,4,5,7,7a-octahydro- 5*H*-inden-5-one is a suitable starting material for this process, but also the corresponding 4-cyanomethyl substituted 1,2,3,3a,4,5,7,7a-octahydro-5*H*-inden-5-one has been used successfully. Here, the electron-



Scheme 1.

withdrawing cyano group takes the place of the electron-withdrawing phenylsulfonyl group and the cyclization leads to a 7-cyano substituted estra-1,3,5(10)-triene system. The cyano group can be reduced with DIBAH to an aldehyde function [28] and the aldehyde itself can be converted to a methyl group by *Wolff-Kishner* reduction. A third approach combines the *de novo* synthesis of an estrone with the subsequent functionalization at C7 *via* a 6-keto group [27,29]. Here, the 1,2,3,3a,4,5,7,7a-octahydro-4-(phenyl-sulfonyl)methyl-5*H*-inden-5-one is reacted with dimethoxy-acetonitrile instead of with dimethoxybenzyl bromide. This leads to a primary estra-1,3,5(10)-triene stemming from the cyclization reaction that has a cyano group at C6. The cyano group is oxidatively cleaved under phase transfer conditions to yield a 6-ketoestra-1,3,5(10)-triene-1,3,17-triol. A C7 methyl group is introduced [27,29] following reaction conditions described in section b.

In a related reaction sequence, *Hajos-Parrish* ketol **15** is reacted with 3',5'-dimethoxy-α-bromopropiophenone (**16**) [NaH, THF] [30] to give **17**. **17** is ring closed to furan **18**, which allows for a selective hydrogenation of the furan moiety to provide a tetrahydrofuranyl moiety which is opened under acid catalysis (1N HCl) to give after a second hydrogenation of the crude material β-hydroxy compound **19**. Oxidation to ketone **20** is achieved with *Jones* reagent. Then, **20** is submitted to a *Friedel-Crafts* type reaction with concomitant dehydration to give **21** (Scheme **2**) [30a].

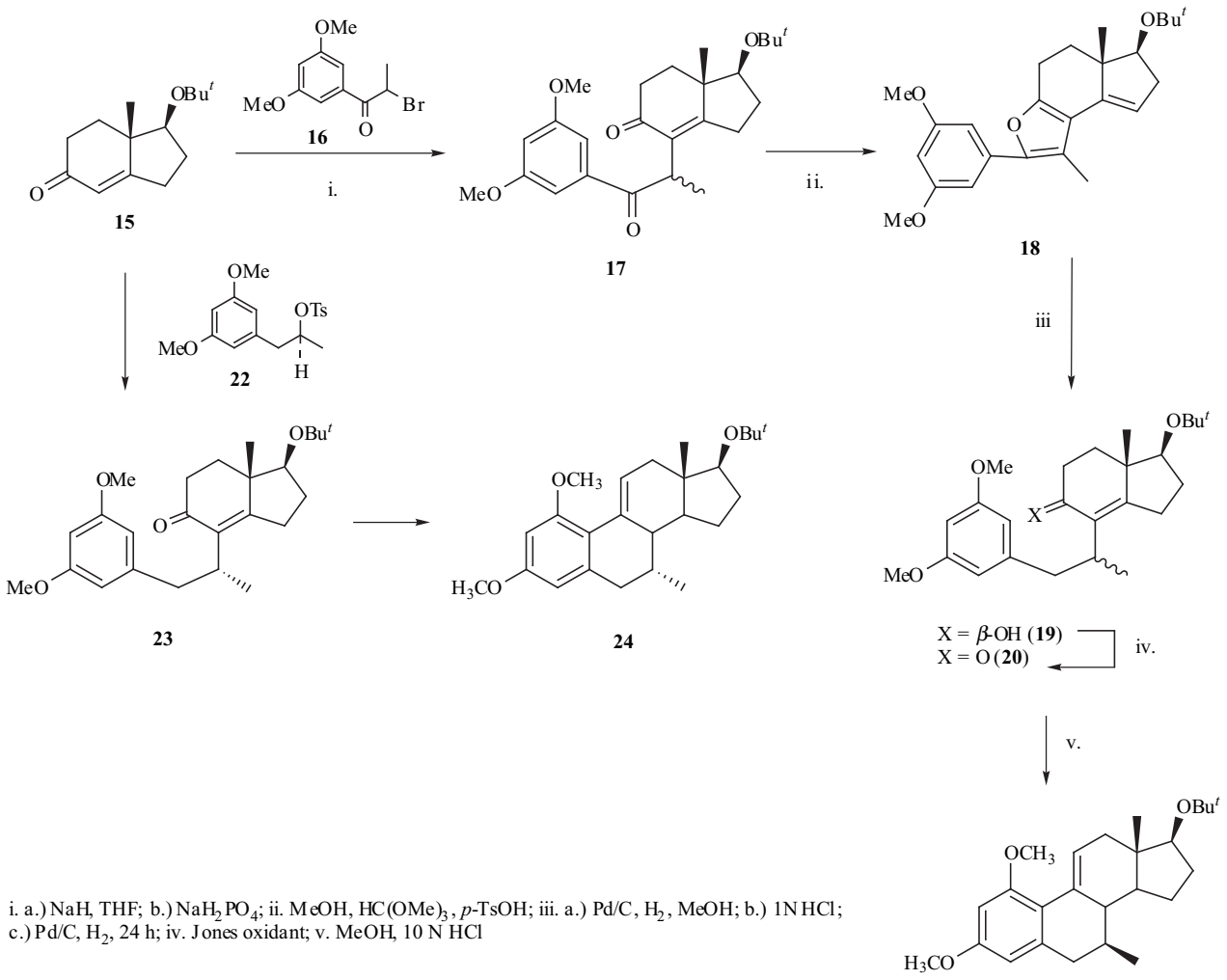
A slightly different approach has been used by Z. Cai *et al.* [31] which reacted with the indane system as C/D fragment with the tosylate of enantiomerically pure 1-(3'-methoxyphenyl)propan-2-ol, which they derived from 3'-methoxyphenylpropan-2-one by enzymatic reduction.

ii. Closure Reactions of Ring C as Key Step

D. Lednicer *et al.* [32] used a Torgov approach [33] to 7,7-dimethylestradiol derivatives **29**/**30**. The starting material of the synthesis, 3,3-dimethyl-1-tetralone **25**, easily accessible from 3-methoxybenzyl chloride and diethyl isopropylidenemalonate in 4 steps, is reacted with vinylmagnesium bromide to the allyl alcohol **26**, which is transformed with 2-methylcyclopentane-1,3-dione (**27**) to the seco steroidal derivative **28**. **28** could be ring-closed to **29** by treatment with conc. HCl in EtOH (Scheme **3**). Here, other acidic catalysts, such as *p*-toluenesulfonic acid, were not successful and mostly led to double isomerization in the seco structure. It is important to note that product **29**, which shows an unsaturation at C15/16, is an isomer of the normal Torgov cyclization product, where the unsaturation can be found at C14/15. This difference in reaction outcome is thought to be the result of steric constraints imposed by the C7 dimethyl group.

iii. Closure Reactions of Rings B/C as Key Step

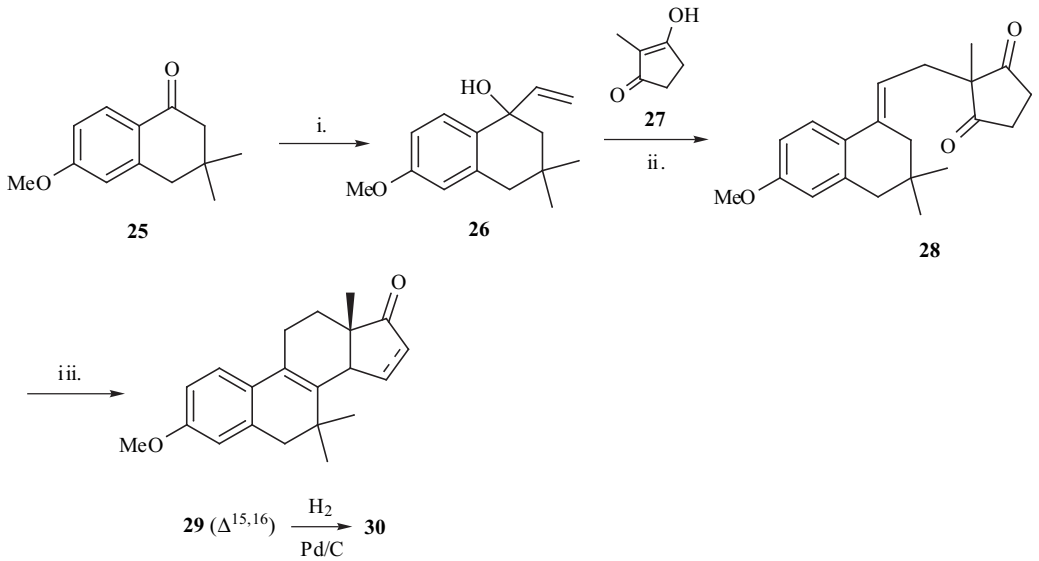
T. Takahashi *et al.* [34] used the *Kametani* method of retrocyclization of the benzocyclobutene **34** to an inter-



i. a.) NaH, THF; b.) NaH_2PO_4; ii. MeOH, $HC(OMe)_3$, *p*-TsOH; iii. a.) Pd/C, H_2, MeOH; b.) 1N HCl; c.) Pd/C, H_2, 24 h; iv. Jones oxidant; v. MeOH, 10 N HCl

U. Eder *et al*. **1977**, **1979**

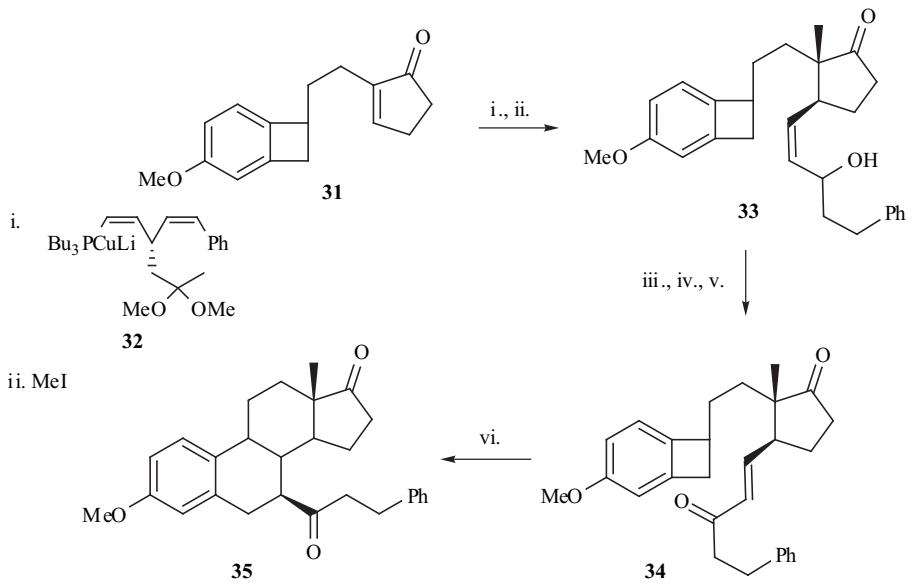
Scheme 2.



i. VinylMgBr, THF; ii. KOH, MeOH; iii. 8.5N HCl, 10 min., rt

D. Lednicer *et al.* **1971**

Scheme 3.



iii. Me-C_6H_4SOCl, Et_3N; iv. MeO_3P, MeOH; v. Swern-oxidation; vi. 180°C

Takahashi *et al.* **1980**

Scheme 4.

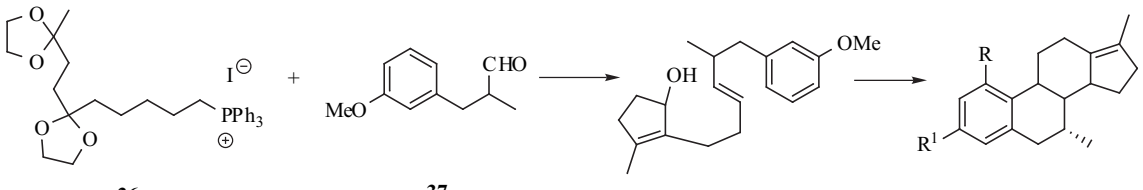
mediate *o*-quinodimethane which undergoes an intermolecular cycloaddition with a double bond in the tether of the molecule (Scheme **4**). This, T. Takahashi *et al.* combined with their process of a stereoselective methylation of the intermediate adduct of a previous *Michael* addition step (**31** - **33**), where a carbon nucleophile (in this case the modified cuprate **32**) adds to a cyclopent-2-enone unit (in **31**). The olefinic moiety in the tether, which is an allyl alcohol, is *cis*/*trans* isomerized in 2 steps and the alcohol function is converted to a keto group by *Swern* oxidation (**33** – **34**). The *Kametani* benzocyclobutane-*o*-diquinomethane reversion / intramolecular cycloaddition step is carried out in *o*-dichlorobenzene at 180ºC [34]. The stereochemistry of the C7 substituent ($PhCH_2CH_2CO$) in this case is β (Scheme **4**).

iv. Closure Reactions of Rings B/C/D as Key Step

In 1978, M. B. Groen and F. Zeelen [35] published a total synthesis of racemic 7α-methyl substituted estra-1,3,5(10),15(17)-tetraen-3-ols **39** (Scheme **5**). The key step is the *Domino*-type cyclization of **38** in the presence of $SnCl_4$ at –70ºC. The *Friedel-Crafts* alkylation of the anisyl moiety leads to a mixture of the two possible regioisomers **39**. **38** itself was prepared by *Wittig* reaction, acetal cleavage and subsequent condensation to form the cyclopentenyl-moiety of the molecule. Later, the synthesis was patented to encompass estra-1,3,5(10),15(17)-tetraenes that do not possess an alkyl substituent at C17 (Scheme **5**).

b) Transformation of Other Steroidal Series to Estrones

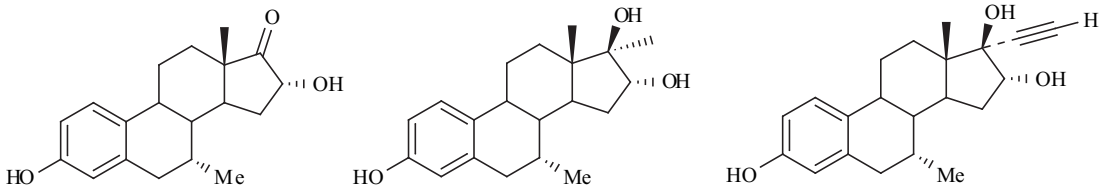
Perhaps one of the earliest systematic studies of any C7-substituted estrones have been published by G. Anner *et al.* of the Ciba-Geigy Laboratories [36-41]. G. Anner *et al.* synthesized 7α-methylestrone and derivatives thereof from testosterone. The main step involved the Cu-1 mediated 1,6-addition [37] of methylmagnesium bromide to the dienone **44** (Scheme **6**). The subsequent aromatization to the estrone series was carried out with loss of the C18 methyl group. Later, 7α-methylestrone (**47**), 6α-hydroxy-7α-methylestrone (**40**), 17α-ethynyl- 7α-methylestra-3,17β-diol (**42**), 7α,17α-dimethylestra-3,17β-diol (**41**) (Fig. **2**) and intermediates of their synthesis were patented as highly active estrogens with antigonadotropic activity [38-41,42]. In later years, numerous reports have appeared on the binding characteristics of the 7α-methyl substituted estra-3,17β-diols. Thus, F. J. Zeelen and E. W. Bergink [43] carried out a mapping of the dependence of the binding affinity of the molecules to the estrogen receptor on the position of the methyl substituent. The authors found that methyl



R = OMe, R^1 = H, and R = H, R^1 = OMe

Groen and Zeelen **1978**

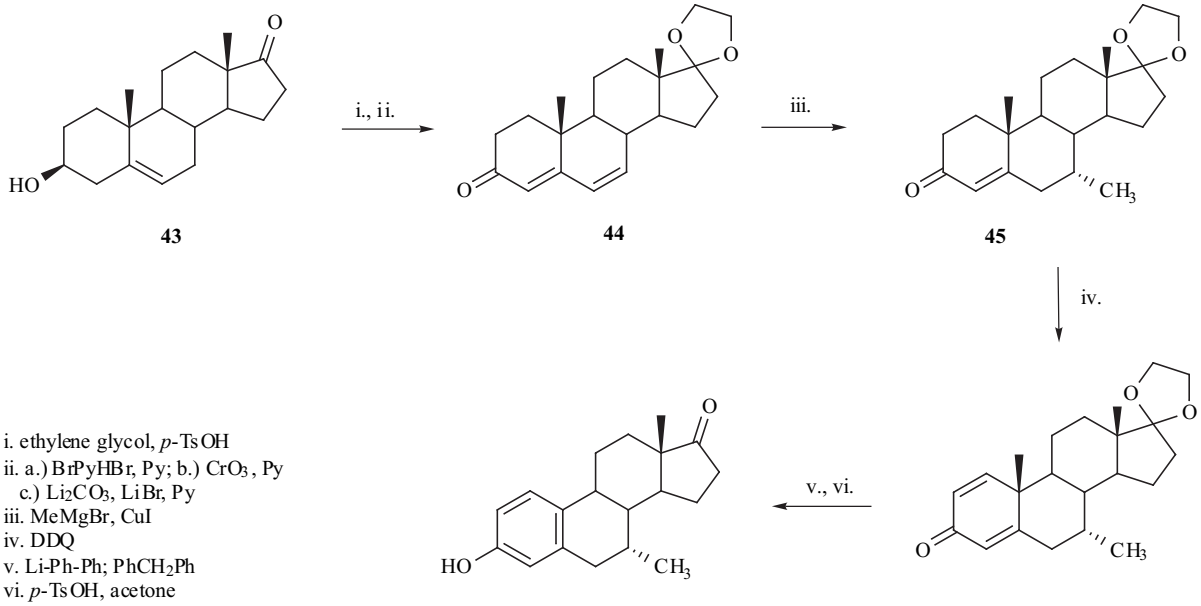
Scheme 5.



40 **41** **42**

G. Anner *et al.* (CIBA Corp.)
US Pat. 3318926, 3318928, and 3318925

Fig. (2).



i. ethylene glycol, *p*-TsOH
ii. a.) BrPyHBr, Py; b.) CrO_3, Py
c.) Li_2CO_3, LiBr, Py
iii. MeMgBr, CuI
iv. DDQ
v. Li-Ph-Ph; $PhCH_2Ph$
vi. *p*-TsOH, acetone

G. Anner *et al.* **1967**

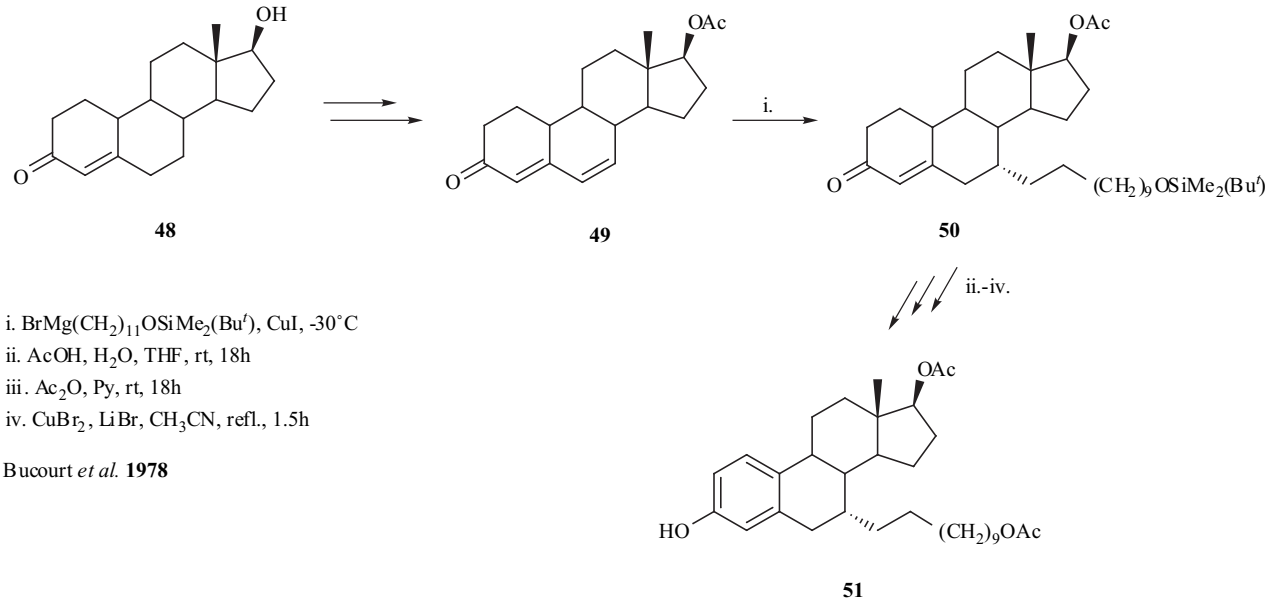
43 **44** **45** **46** **47**

Scheme 6.

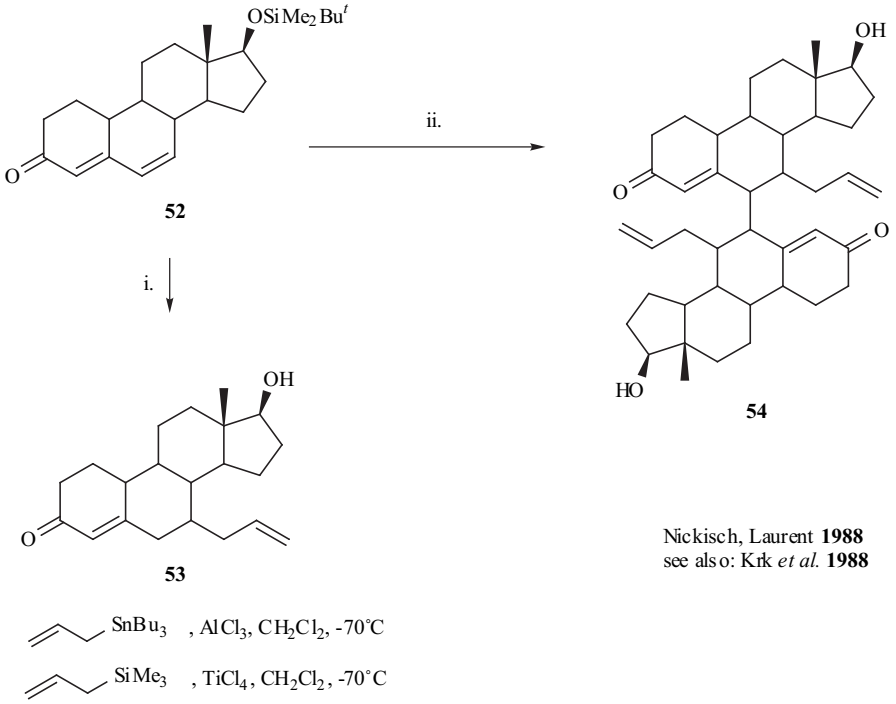
substitution at positions C1, C2, C6α, C15α, C15β, and C18 is detrimental to the binding [43]. Substitution at positions C7α, C11β, and C17β is advantageous for the binding [44]. Finally, 7α-methylestrone (**47**) was also used as a precursor of a 7α-methyl-D-homoestra-1,3,5(10)-triene derivative, where Me_3SiCN was added to the C17 keto group. The introduced cyano group was reduced to an amino group. A *Tiffeneau-Demjanov* rearrangement furnished the D-homoestra-1,3,5(10)-triene derivative [45].

In 1978, R. Bucourt *et al.* [46] reported on the use of 7-alkylestradiols as biospecific adsorbents for the chromatographic purification of the estradiol receptor ERα. Again, the synthesis of these C7-substituted estradiols is based on a Homo-*Michael* addition of alkyl *Grignard* reagents to 17β-acetoxy-19-norandrosta-4,6-dien-3-one (**49**), a reaction which is run under Cu(I) catalysis. **49** can be prepared in 2 steps from the commercially available, albeit expensive 19-nortestosterone (**48**) (Scheme **7**). In case of an introduction of longer alkyl chains, the preparation of the corresponding *Grignard* reagents necessitates long reaction times, where the use of ultrasonication has been found to be beneficial. Restrictions due to the *Grignard* reaction itself limit the choice of functional groups at the chain terminus that can be introduced directly in this step. This limitation makes further transformations of functional groups necessary. In the case of the introduction of a hydroxy function as the terminal substituent, it has to be protected, e.g., as a silyl ether. As the best results in the Homo-*Michael* addition are achieved with an excess of nucleophile, the separation of addition product from non-reacted nucleophilic reagent is often tedious. The addition product may be aromatized to the estrane derivative with $CuBr_2$/LiBr in acetonitrile. Further elaboration to the target compounds involve functional group interconversions including the manipulation of protective groups at C17 within the steroidal frame, as well as the terminus of the C7 side chain. A number of groups[47-53] have prepared 7α-substituted estra-1,3,5(10)-trien-3,17β-diols in this fashion. The *Bucourt* method has been used in the synthesis of a number of patented structures [54, in part 47].

An allyl substituent can be introduced at C7 of a 17β-O-protected 19-norandrost-4-en-17-ol-3-one, when reacting 17β-*O*-protected 19-norandrost-4,6-dien-17-ol-3-one (e.g. **52**) with allyltrimethylsilane under F^- catalysis (TBAF, DMF, HMPA) or under $BF_3 \cdot Et_2O$ catalysis (Scheme **8**) [54,55]. In the first case, much 1,2-addition product is isolated, while in the latter case the reaction temperature plays a significant role for the outcome of the reaction. While the reaction at



Scheme 7.

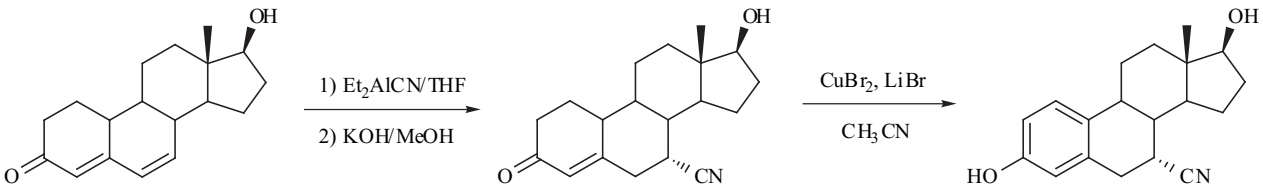


Scheme 8.

–78ºC mainly gives the desired 1,6-adduct, at –15ºC a dimeric steroidal structure, **54**, is the main product, where the X-ray crystal structure has been determined [54b]. K. Nickisch and H. Laurent [55] isolated exclusively the dimer under similar conditions ($BF_3 \cdot Et_2O$, CH_2Cl_2, -70ºC), but noted the formation of the 1,6-adduct upon using allyltrimethylstannane instead of allyltrimethylsilane.

A cyano group can be introduced at C7α with ease by reacting 4,6-estradien-17β-ol-3-one **55** with diethylaluminum cyanide (THF) (Scheme **9**) [56]. For the subsequent aromatization of ring A in **56**, 3 different methods were evaluated (SeO_2, Bu^tOH [25%] or i. Ac_2O-py-AcCl; ii. NBS, DMF; iii. HCl, acetone; iv. 5% KOH in MeOH [60%]), where treatment of **56** with Cu(II)Br_2 and LiBr in acetonitrile at rt gave the best result (80%) [56]. Further elaborations of **57** have been performed [57].

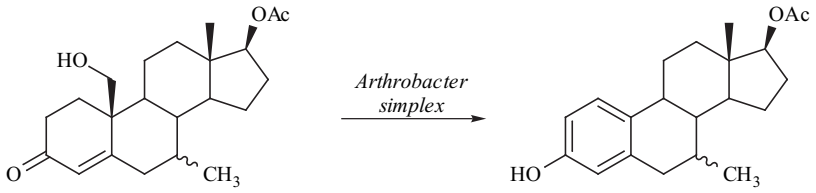
It must be noted that other methods of aromatization of ring A have been studied, where steroids of the testosterone series can be transformed enzymatically (Scheme **10**) to the estrane series as shown by N. Yi *et al.,* which reacted form 7α-methyl-19-hydroxymethyltestosterone 17-acetate (**58**) with *Arthrobacter simplex* to form 17-*O*-acetyl 7α-methylestra-3,17β-diol (**59**) (Scheme **10**) [58]. Another example of an enzymatic transformation is the aromatization of 7α-methyl-19-nortestosterone (**60**) to 7α-methylestra-



55 **56** **57**

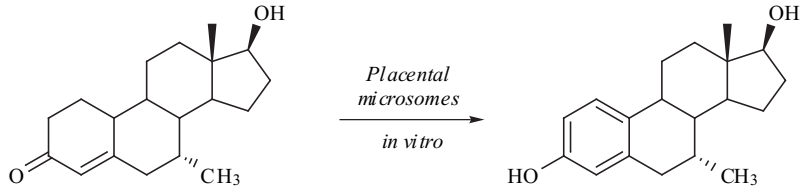
H. Ali, J. E. van Lier *et al.* **2002/2003**

Scheme 9.



58 **59** 85%

Y. Ni *et al.* (**1983**)



60 **47**

A. LaMorte *et al.* (**1994**)

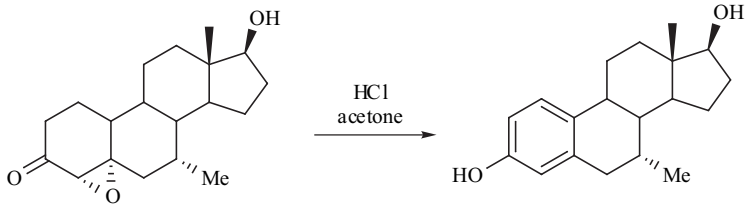
Scheme 10.

3,17β-diol (**47**) by human placental microsomes *in vitro* [59].

A further, purely chemical way of aromatization employs an epoxidation of the 4(5) olefinic moiety after the 1,6-addition of the C-nucleophile (to C7) with subsequent acid catalyzed ring opening of the epoxide and dehydration of the resulting alcohol (Scheme **11**) [60].

c) Direct Addition of Substituents to C7 of Estranes

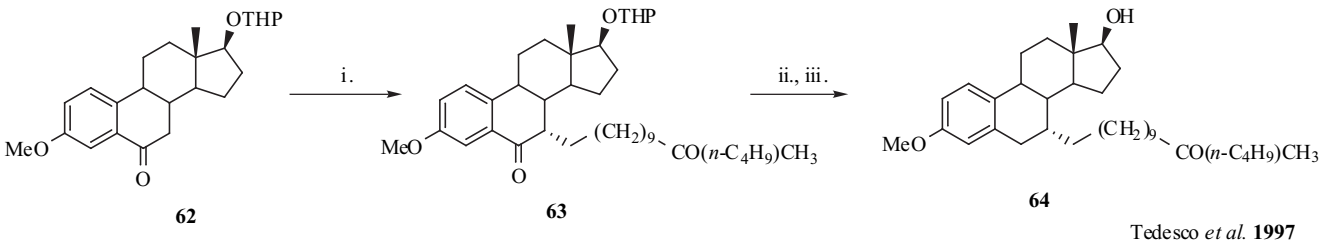
When the C7 position of an estrane is activated, then it is also possible to add the substituent directly to the steroid. The best way to activate the C7 position is *via* transformation of the benzylic C6 position. Thus, a number of ways are known to oxidize C-6 [61] either directly to a keto functionality or to a hydroxy function (by hydroxylation *via* lithiation at C6, transformation to the boronic ester by reaction with trimethylborate, and subsequent oxidative cleavage) [62]. When the 6-keto derivative is brominated, the ensuing 7-bromo-6-ketoestrane can be methylated [27] at C7 by reaction with methyl iodide in the presence of zinc. However, with the keto group in position at C6, C7 lends itself also to direct substitution by conjugate addition [63]. In this way, both carbon and heteroatomic nucleophiles can be added [64-73]. The enolates of the 6-ketoestrane derivatives are formed with $KOBu^t$ or similar bases. The



61 **47**

J. Ma and Z. Li **1987**

Scheme 11.



62 **63** **64**

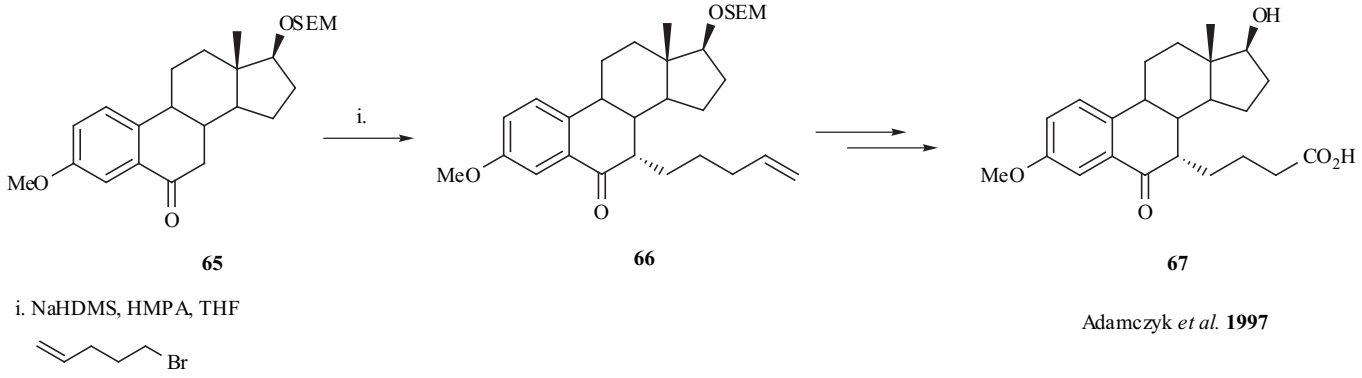
Tedesco *et al.* **1997**

i. $KOBu^t$, $CH_3(n\text{-}C_4H_9)NCO(CH_2)_{10}I$
ii. $BF_3{\cdot}Et_2O$, Et_3SiH
iii. MeONa, MeOH

Scheme 12.

enolate in THF forms a dark, deep red solution. The addition of the alkyl halides, preferably the iodides, are initially performed at –78ºC with the reaction mixture gradually warming to rt. The additions usually yield a mixture of 7α- and 7β-substituted products, with the 7α-isomer being the main product (Scheme **12**). Identification of the stereochemistry may best be carried out by analysis of the coupling constant $J_{H7\text{-}H8}$. A number of functional groups can be incorporated with the introduced chain. α,ω-iodoalkylamides and nitriles can be reacted without difficulty [70,71]. Aldehyde and alcohol functionalities can also be introduced, when suitably protected (e.g., as an acetal [aldehyde] or a siloxy ether [alcohol]).

In general, the yields of the alkylations by conjugate addition in these cases are not very high, although much of the starting material can be recovered and recycled. Adamczyk *et al.* [65] have reported on the alkylation of 3,17β - *bis* (2-trimethylsilyl) - ethoxymethylestra -1,3,5(10)-trien-6-one (**65**) with 5-bromo-1-pentene in the presence of NaHDMS as base (Scheme **13**). The yield of **66** was 21% and the use of different bases (e.g., LDA, LiHDMS, KHDMS) have not been more successful [65].



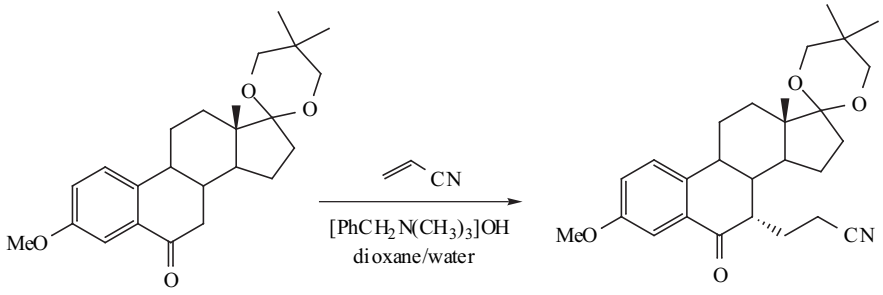
65 **66** **67**

i. NaHDMS, HMPA, THF

Adamczyk *et al.* **1997**

Scheme 13.

The carbon number *m* of the alkyl iodides used in these conjugate addition reactions can be varied considerably; *m* = 2, however, evidently gives poor results if the corresponding ethyl iodide carries an electron withdrawing group (carboxylic ester, carboxamide, cyano) and is reacted under the conditions mentioned above ($KOBu^t$, THF). In these cases, it is often advisable to carry out a *Michael* addition with the group to be introduced acting as *Michael* acceptor



68 **69**

Thiemann *et al.* **2001**

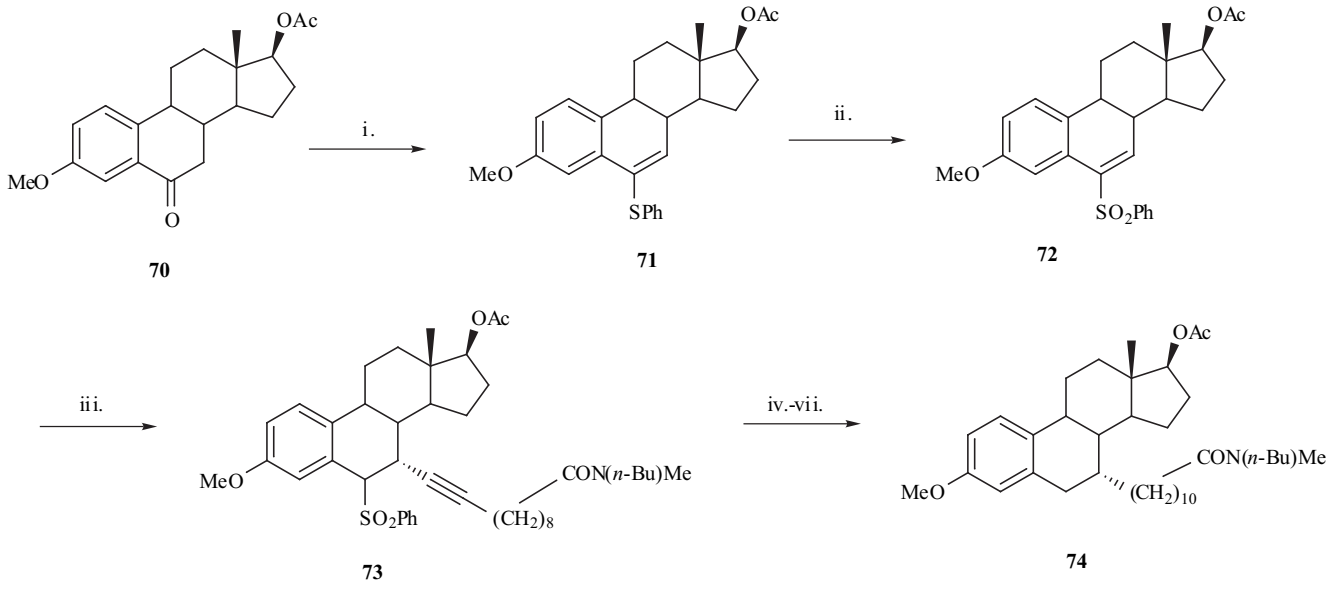
Scheme 14.

(e.g., reaction of the enolate of **68** with acrylonitrile, see Scheme **14**) [73]. Here, the use of a two-phase system with trimethylbenzylammonium hydroxide acting as both base and phase transfer catalyst (PTC) is advisable. Also in the *Michael* addition reactions, although carried out at higher temperatures (up to 50ºC) than the conjugate addition reactions as discussed above, the main product is the corresponding 7α-alkylated estrane, e.g., **69** (Scheme **14**). 7,7-Bisalkylated products as by products have also been found in these reactions, but usually in small amounts.

For m = 1, a typical *Mannich* reaction has been carried out with 3-*O*-methyl-6-ketoestra-3,17β-diol. The corresponding 7-dialkylaminomethylestra-3,17β-diols can be isolated as their hydrochlorides [74].

A complementary reaction, which uses the steroidal system as a *Michael* acceptor and alkyllithium reagents as C-electrophiles, has been developed by Künzer *et al.* in their synthesis of ICI 164384. Here, the ketone **70** is transformed to the thioenol ether **71** with thiophenol in THF [64] in the presence of triethylamine as base and $TiCl_4$ as Lewis acid catalyst (Scheme **15**). The actual *Umpolung* of the molecule takes place in the oxidation of the thioenol ether the ene-sulfone **72**, which then serves as the *Michael* acceptor. The synthesis encompasses more synthetic steps. The reductive elimination of the sulfone moiety in **73** with sodium amalgam, however, provides an alternative to the reduction of ketones with complex hydrides in the presence of Lewis acids to acquire the C7α-alkylsubstituted estra-1,3,5(10)-trienes (see below). Ultimately, the 3-methyl ether in **74** is cleaved by the reaction with sodium methylmercaptide in DMF at 130ºC, an alternative to the cleavage with BBr_3 [64], which in many cases does not lead to good results.

The keto functionality at C6, which has been used in most of the reactions described above as an auxiliary for the activation of C7, can be removed under reductive conditions (complex metal hydride in presence of a Lewis acid) or can be transformed to yield a C6/C7 olefinic moiety giving C7-substituted estra-1,3,5(10),6-tetraenes (either by reduction to a 6-hydroxy function with subsequent acid catalyzed [68-72] or thermally induced [73] elimination of water or, especially in the case of m = 2, by *Shapiro* reaction of the C6 tosylhydrazone, e.g., **75** (Scheme **16**), formed in 2 steps from the 6-ketone).

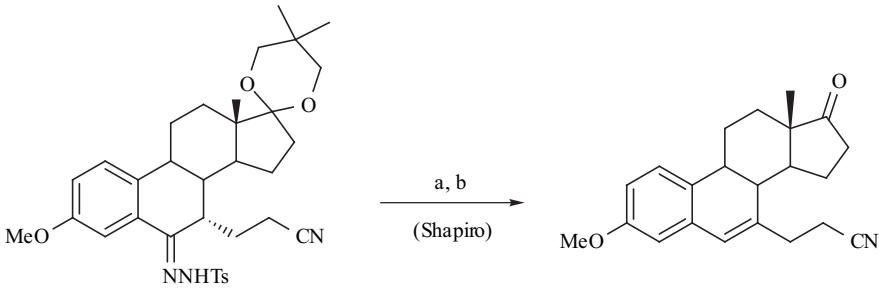


70 **71** **72** **73** **74**

Kuenzer **1994**

i. $TiCl_4$, THF, 0˚C, thiophenol, triethylamine, rt; AcOH, $NaBO_3$, rt; iii. RLi, THF; iv. MeOH, NaOH
v. EtOAc, Pd/C, H_2; vi. MeOH, 3% Na(Hg), NaH_2PO_4; vii. DMF, $NaSCH_3$, 130˚C

Scheme 15.

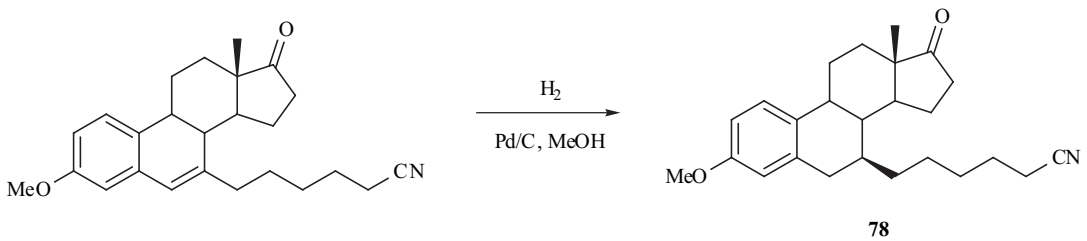


75 **76**

a.) Celite, $KOBu^t$; 10 mBar; 150˚C; b.) *p*-TsOH, acetone, rt

Thiemann *et al.* **2001**

Scheme 16.



77 **78**

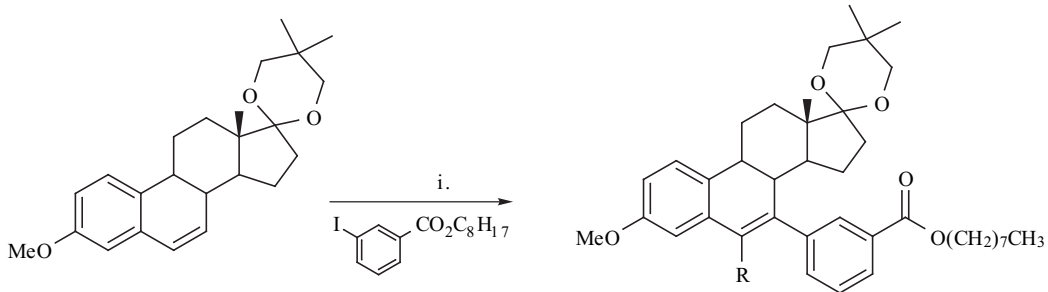
Yamamoto, Thiemann *et al.* **2004**

Scheme 17.

Interestingly, hydrogenation of the C-7 substituted estra-1,3,5(10),6-tetraenes, e.g., of **77**, with H_2 using Pd/C as catalyst leads selectively to the 7β-substituted estra-1,3,5(10)-trienes as could be ascertained by X-ray crystal structural analysis of 6-[3-hydroxy-17-oxoestra-1,3,5(10)-trien-7β-yl]hexanenitrile (**78**) (Scheme **17**) [75].

It should be possible to utilize C7-non-substituted estra-1,3,5(10),6-tetraene derivatives for an entry into the C7-substituted estranes. A number of synthetic strategies of estra-1,3,5(10),6-tetraenes has been attempted by *Heck* reaction of **79** with octyl *m*-iodobenzoate. Here, the C7 substituted estra-1,3,5(10),6-tetraene **80** formed albeit in mediocre yield and with the double arylation product as a by product (Scheme **18**) [76].

The complexation of estranes with tricarbonylchromium(0) is known [77,78]. Also, estra-1,3,5(10),6-tetraene **81** forms the corresponding η^6-chromiumtricarbonyl(0) complex **82** (Scheme **19**) [79,80]. It is interesting to note that while



79 **80a/b**

i. $Pd(OAc)_2$, $NaHCO_3$, Bu_4NCl, $CHCl_3$ or DMF

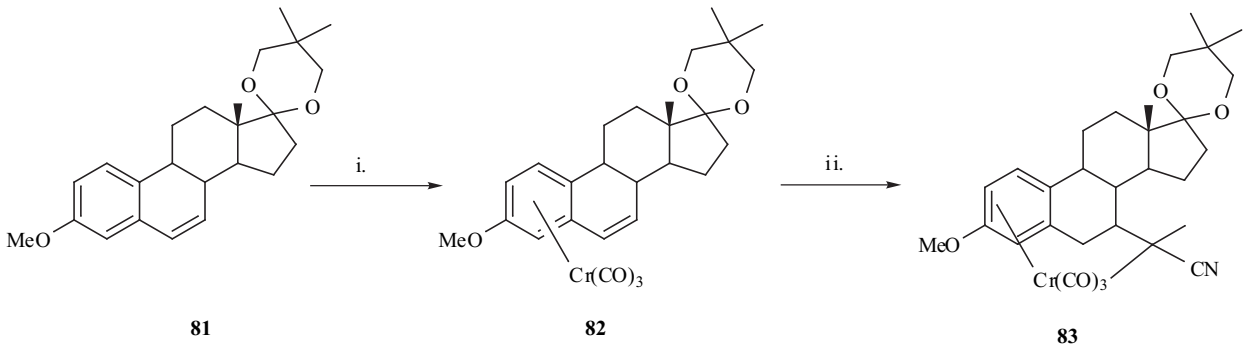
Thiemann **2000**

R = H or Ph-CO-$(CH_2)_7CH_3$

Scheme 18.

suggest themselves, however, more work has to be carried out to discern whether these are indeed viable routes to C-7 substituted estranes. Direct addition of C-nucleophiles to C7

η^6-chromiumtricarbonyl(0) complexes of estra-1,3,5(10)-trien-3,17β-diol derivatives form in a 1:1 mixture of α- and β-π-facial isomers, **82** forms exclusively as the more



81 **82** **83**

i. $Cr(CO)_6$, Bu_2O/THF, 130-140°C (quant); ii. $(CH_3)_2C(Li)CN$ (trace)

M. C. Melo e Silva, K. G. Dongol, T. Thiemann **1999** and **2003**

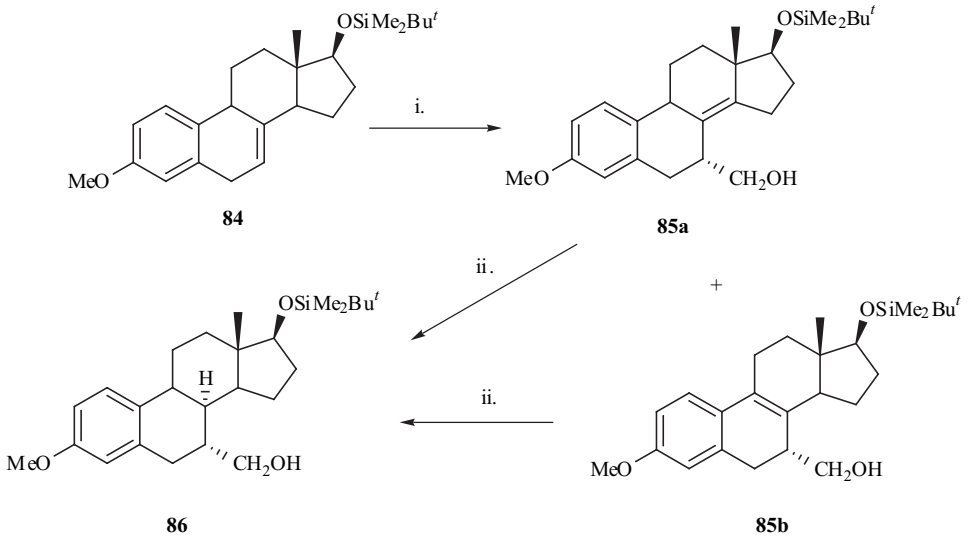
Scheme 19.

sterically congested β-isomer. It is thought that the 6,7-olefinic moiety in **81** exerts a directing effect in the complexation.

Due to the strong electron withdrawing character of the chromiumtricarbonyl moiety, the C-7 position of the estra-1,3,5(10),6-tetraene should be sufficiently electrophilic to react with a C-nucleophile in an addition reaction. M. F. Semmelhack *et al.* [81] have carried out such reactions with η^6-dihydronaphthalene chromium complexes and a limited number of C-nucleophiles. In the case of the estra-1,3,5(10),6-tetraene complex, the addition products, *cf.* **83**, can also be detected, but the yield of these adducts is low. The stereochemistry at C7 of the products has not yet been determined [79].

Estra-1,3,5(10),6-tetraenes can be transformed to the corresponding 6,7-epoxides. The epoxides have been converted to the 7-ketoestrane derivatives, which themselves have been submitted to *Wittig* olefination reactions [82]. To date, the control of a regioselective ring opening of the epoxides with *Grignard* reagents to have a direct access to C7-substituted estranes has proven to be difficult.

Lastly, 7α-hydroxymethylestra-3,17β-diol **86** is accessible through a *Prins* reaction starting from equilin. Two homoallylic alcohols, **85a**/**b**, are formed in a 6 : 1 ratio. They can be separated, however, both can be hydrogenated over Pd/C to give the same isomer **86** (Scheme **20**) [83].



i. $Al(CH_3)_2Cl$, $(HCHO)_n$; ii. H_2, Pd/C

Kuenzer *et al.* **1991**

Scheme 20.

d.) Functionalization and Functional Transformation of the C7 Side Chain in Estranes

Once the chain is introduced at C7 of the estrane derivative, it can be functionally transformed [48-50,70-72,84,85], depending on the substituents that have been concomitantly introduced. The conditions of linking the chain to the steroidal frame often make it impossible to introduce formyl, alcohol or amine functions directly with the introduction of the chain. However, acetals, silyl ethers and olefinic moieties are all compatible. From these, carbaldehydes (deprotection of the acetals, deprotection of the alcohols and oxidation, hydroboration of terminal olefinic moieties with oxidative work-up) can be obtained. Moreover, J. N. da Silva and J. E. van Lier have shown how to optimally derivatize the 11α-hydroxyundecylestradiol, prepared by the method of Bucourt *et al.* (see above). Thus, the hydroxy function can be transformed easily to a chloro- or bromo group (CCl_4/PPh_3 or CBr_4/PPh_3). The bromo functionality can be substituted for an iodo group (NaI/butanone or acetone) or a fluoro group (n-Bu_4NF). Phenolic ethers can be prepared (phenol, $NaHCO_3$, DMF). As the direct introduction of a cyano group is compatible with the reaction conditions of the conjugate addition of alkyl iodides to 6-ketoestra-1,3,5(10)-trienes, this opens new opportunities for functionalization of the chain terminus, as the versatile cyano group can easily be transformed to an amino group, to a carbaldehyde function (reduction with diisobutylaluminum hydride), to a free amide (partial hydrolysis with H_2O_2/NaOH under phase transfer conditions at rt) or to a carboxylic acid (complete hydrolysis) [70-73]. Potentially, the free amide can be alkylated.

B. Muehlenbruch *et al.* [84] have coupled fluorescein-amine *via* the DCC method to 7α-carboxybutyl-estra-1,3,5(10)-trien-3-ol to give compound **87** as a fluorescent marker. Compounds similar to **87** have been prepared (Fig. **3**) [84]. *In vitro*, these compounds still possess an appreciable binding affinity to the estrogen receptor ERα. A further fluorescent conjugate, **88**, has been forwarded by A. N. French *et al.* (Fig. **3**) [86]. Here, the fluorescent moiety was coupled to a 7α-aminoalkyl substituted estradiol derivative, prepared *in situ* from the corresponding 7α-azidoalkyl derivative. The chemiluminescent estradiol conjugate **89** was prepared from 7α-(3'-carboxypropyl)-estra-3,17β-diol and an N^{10}-(3-sulfopropyl) acridinium-9-carboxamide by the DCC method (Fig. **3**) [87].

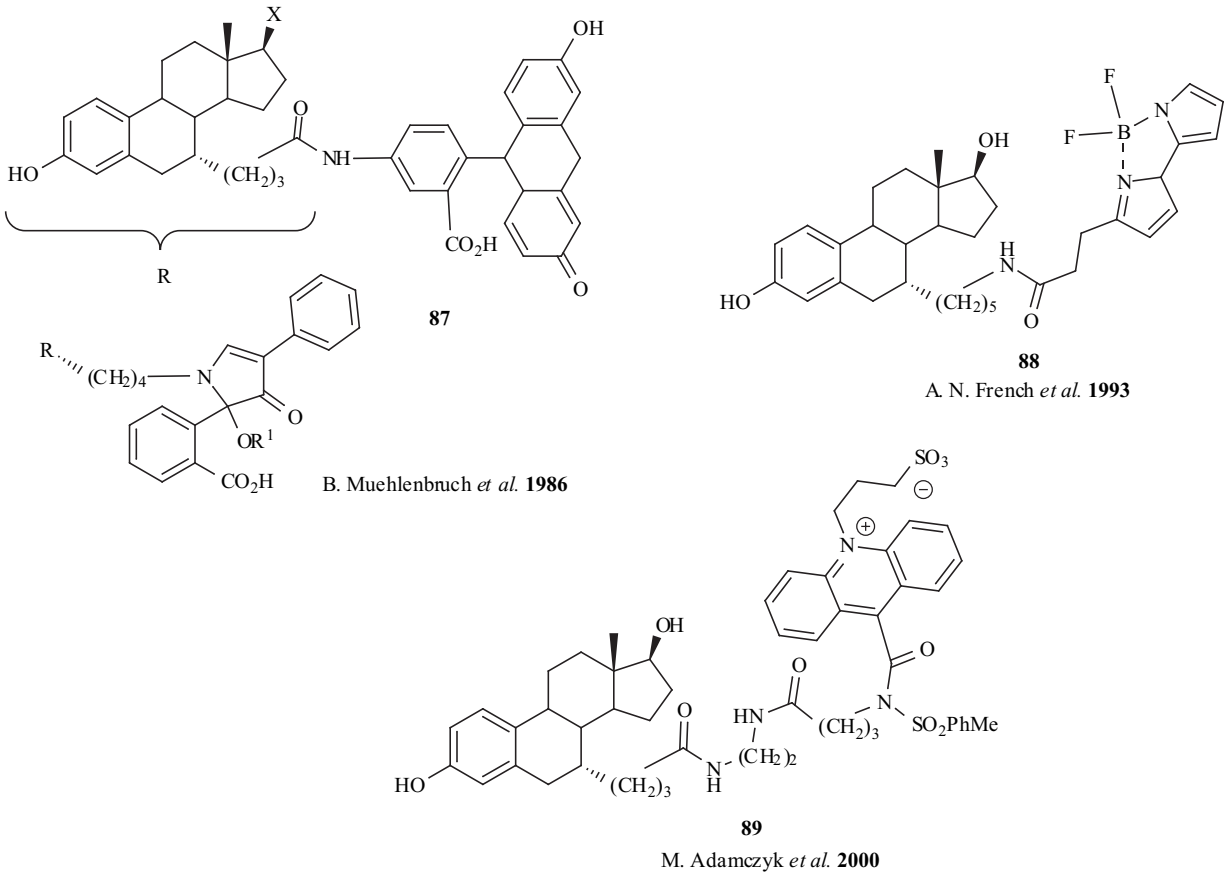
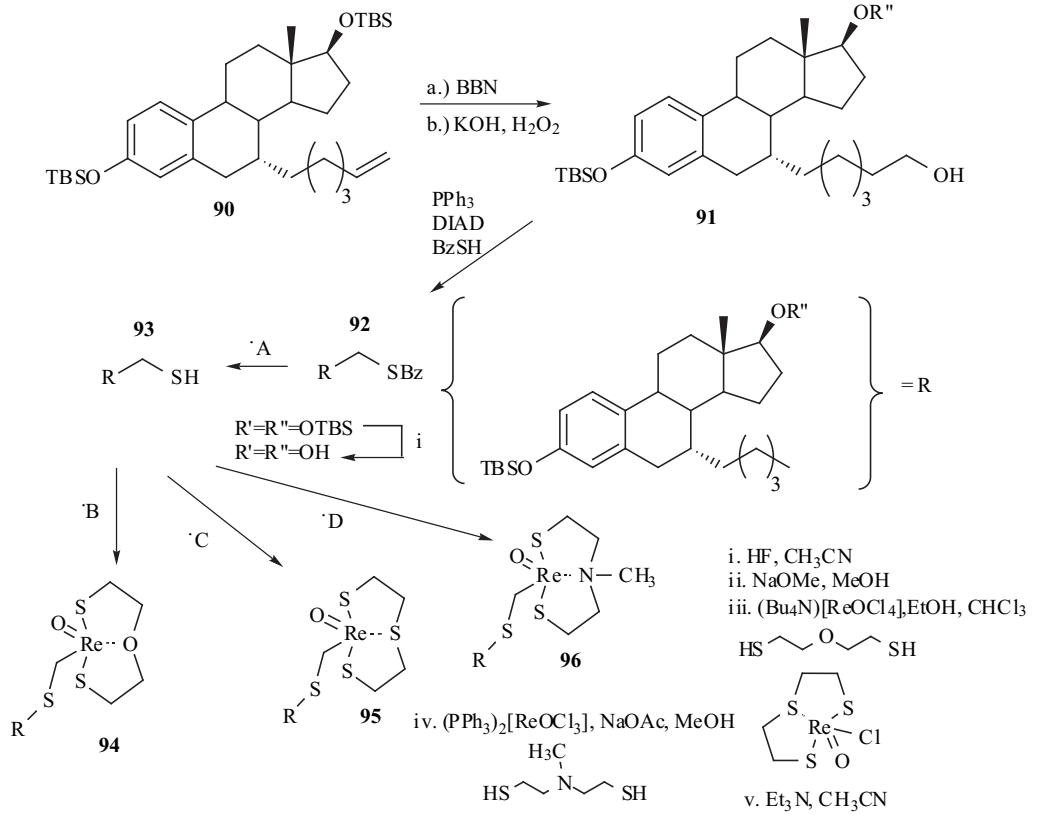
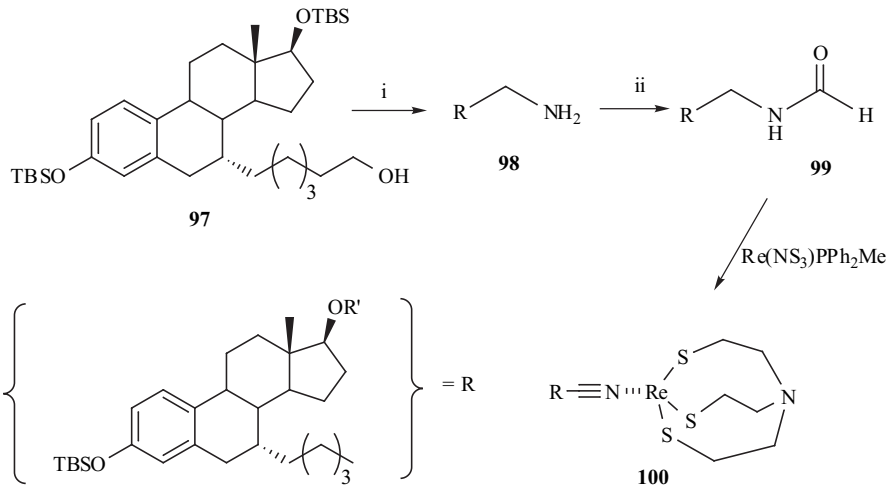


Fig. (3).



Rhenium containing radioimaging agents on basis of C7α-substituted estradiols
Skaddan, Wuest, Katzenellenbogen **1999**.

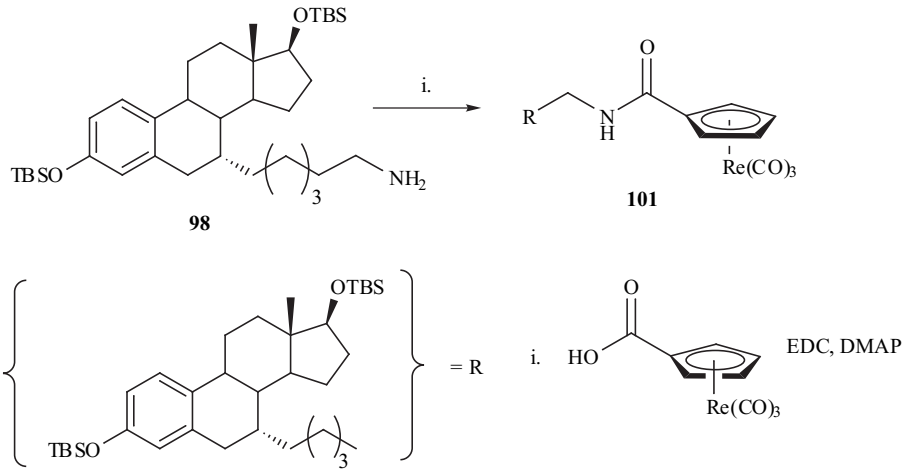
Scheme 21.



Rhenium containing radioimaging agents on basis of C7α-substituted estra-3,17β-diols

Skaddan, Wuest, Katzenellenbogen **1999**

Scheme 22.



Rhenium containing radioimaging agents on basis of C7α-substituted estra-3,17β-diols

Skaddan, Wuest, Katzenellenbogen **1999**

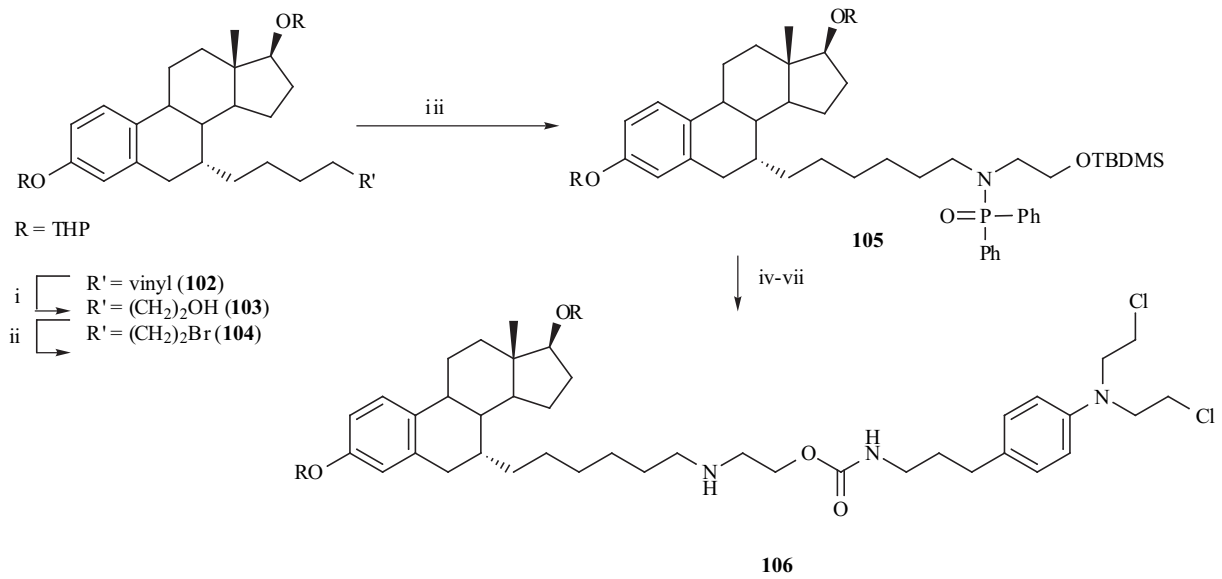
Scheme 23.

J. A. Katzenellenbogen *et al.* [66,68,88] have shown that facile derivatization of the terminal functional group in the introduced C7 carbon chain leads to various possibilities of ligand formation, which facilitate the binding of metals to the steroid (Schemes **21**-**23**). These metals can be rhenium or technetium, i.e., metals that can be used as radioligands in radioimaging agents. It must be stressed that while 7α-methyl groups in estradiols have led to a better binding of the molecule to the receptor, longer C7 chains may carry larger substituents without interfering substantially with the binding of the molecule, as it is considerd that long chains outreach the confines of the ligand receptor complex, so that these larger substituents on the chains find themselves outside of the ligand receptor complex.

The coupling of bioactive residues to estradiols using the C7 tether is also possible. This has been demonstrated by J. M. Essigmann, R. G. Croy *et al.* [89], who synthesized estradiol-mustard conjugates such as **106** (Scheme **24**, for bioactive residues, including mustards linked at positions other than C7, [see ref. 118i].The mustard residue is to act as a genotoxin that helps destroy estrogen receptor-positive breast cancer cells, where the estradiol is responsible for the binding affinity of the molecule to the estrogen receptor [89].

e.) Heteroatom Functionalization at C7

The strategies for heterofunctionalization at C7 resemble those of C7 alkyl functionalization. In the cases of A-ring aromatization after introduction of a hetero-functionality at C7, especially of a hydroxy function, often leads *via* aromatization of both the A and the B ring to the equilin series. A typical example is given by the transformation by



i. BH_3, THF, KOH/H_2O_2; ii. MsCl, LiBr; iii. $Ph_2P(O)NH(CH_2)_2OTBDMS$, NaH, cat. Bu_4NBr; iv. TBAF; v. *p*-nitrophenylchloroformate, DIEA; vi. 4-(*N*,*N-bis*-2-chloroethylaminophenyl)propylamine, DIEA; vii. H^+

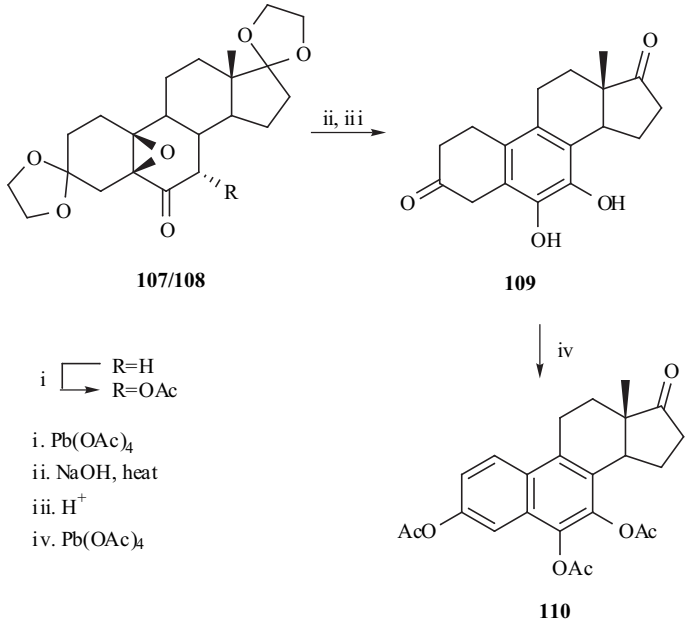
J. E. Essigmann and R. G. Croy *et al.* **2002**

Scheme 24.

Mihailovic *et al.* [90]. Here, the α,β-epoxyketone **107** is acetylated α to the keto group (C7) with $Pb(OAc)_4$. Heating the compound **108** in aq. NaOH leads to **109** *via* aromatization of the B-ring. The protective acetal groups are cleaved at C3 and C17. Then, ring A is aromatized with $Pb(OAc)_4$ to yield 6,7-diacetoxyequilin (**110**) (Scheme **25**) [90].

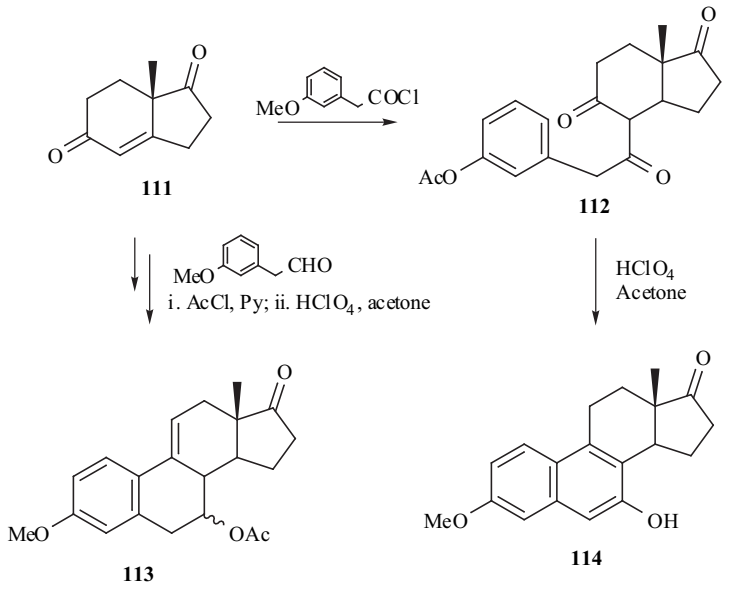
The *Friedel-Crafts* type cyclization of **112** also leads to the equilin series. **112** can be prepared from the *Hajos-Parrish* diketone (**111**) in 1 step. Analogous to **112**, also, the alcohol can be prepared from **111** in 1 step. It can be acetylated and ring-closed with $HClO_4$ in acetone to give a mixture of 7α- and 7β-acetoxy-3-methoxy-estra-1,3,5(10), 9(11)-tetraenes **113**, from which the β-isomer can be crystallized [91].

Most likely not by design was the outcome of the bromination of **115** with tribromoacetic acid (140ºC, 20 min, N_2) which yields 7,16-dibromo-1-methyl-estra- 1,3, 5(10)-triene-6,17-dione (**116**) [92]. 7-Bromoestra-1,3,5(10)-triene-6,17-diol derivatives, furnished by bromination of 6-ketoestradiol derivatives, have been known for some time.



M. Lj. Mihailovic *et al.* **1978**

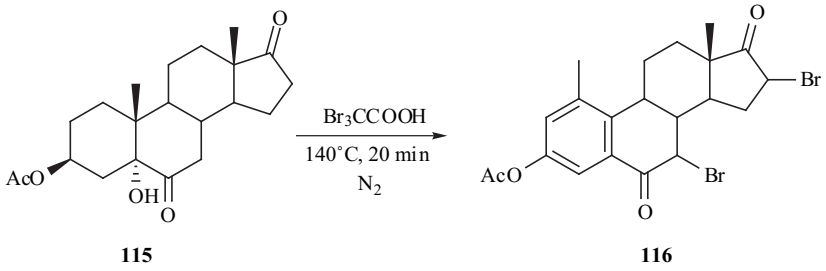
Scheme 25.



111 **112** **113** **114**

Daniweski, Kiegiel **1988**

Scheme 26.



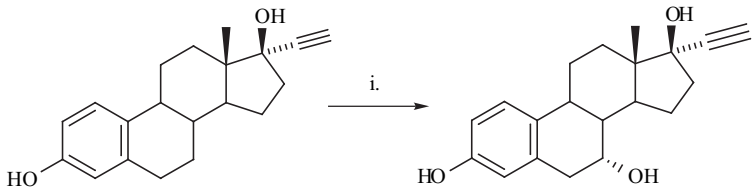
115 **116**

W. J. Szczepek **1981**

Scheme 27.

In 1976, Schering A.-G. patented a number of C7α hydroxylated estradiols as estrogens. The preparative procedure followed a microbial oxidation using *Diplodia natalensis* ATCC 9055 (Scheme **28**) [93]. The hydroxy group was functionalized in various ways (etherification; mesylation). Experiments on estra-3,7α,17β-triol itself, though, have shown that hydroxylation at C-7α decreases both the activity of the molecule as a post-coital contraceptive as well as its receptor binding affinity to ERα (estrogenicity: estra-3,17β-diol >> 11β-hydroxy- = 6β-hydroxy- > 16α-hydroxy- > 7α-hydroxy > 16β-hydroxyestra-3,17β-diol; contraceptive action: estra-3,17β-diol >> 11β-hydroxy- > 7α-hydroxyestra-3,17β-diol) [94-96]. Estra-3,7α,17β-triol has been found as a metabolite in the brain of rats [97] and in the liver microsomes of juvenile rainbow trout [98].

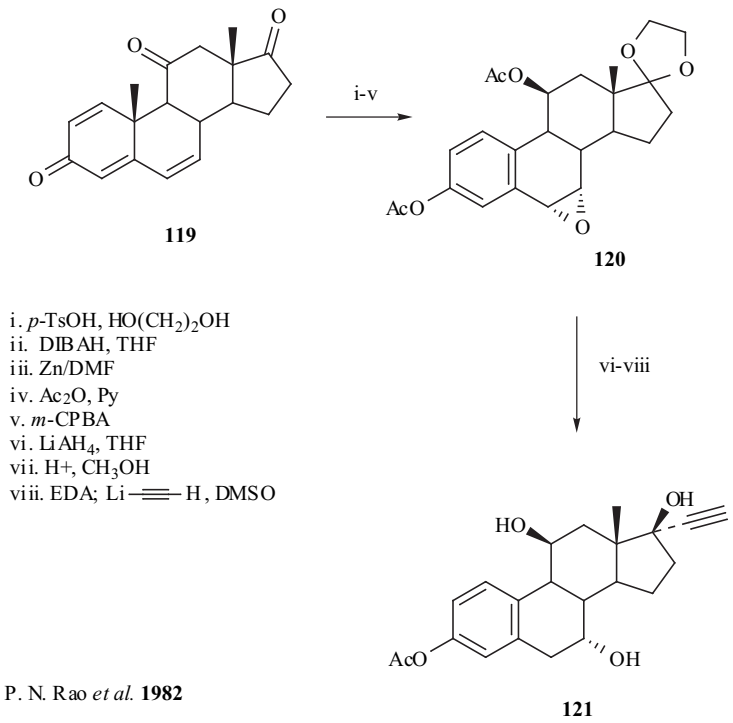
Subsequently, the 17α-ethynyl-estra-1,3,5(10)-triene-3,7α,11β,17β-tetraol **121** was synthesized with the idea that while the 7α-hydroxy group lowers the estrogenicity of this type of molecules, the postcoital antifertility of the derivative may still be adequate. The introduction of the 7α-hydroxy group was accomplished by reduction of the 6,7-epoxide **120**. Access to the estrane series was given through



117 **118**

i. *Diplodia natalensis*
Schering A.-G. **1976**

Scheme 28.



Scheme 29.

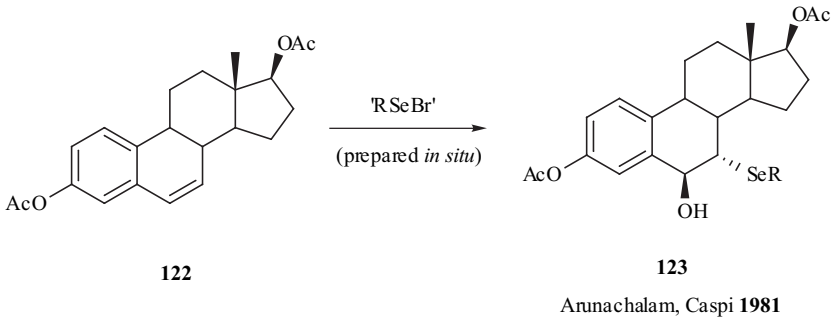
aromatization with Zn/DMF (concomitant loss of C18 methyl) [99].

Methyl and phenylselenyl bromide has been added to estra-1,3,5(10),6-tetraene-3,17β-diol 3,17β-diacetate (**122**) to give after work-up the corresponding C7α-alkyl/arylselenyl-estra-1,3,5(10)-trien-3,6β,17β-triol 3,6β,17β-triacetates **123**. While the steroids have been saponified with 5% KOH in EtOH, no additional transformation using these compounds were published. Oxidation of the compounds with H_2O_2 in THF yielded after acidic work-up 3,17β-di-*O*-acetoxy-6-ketoestra-3,17β-diol [100]. The 7α-methylselenyl derivative was found to bind poorly to the estrogen receptor ERα – here, the 16α- and 17α-methylselenyl and the 16α-phenylselenyl derivatives gave better results (around 30% of estra-3,17β-diol itself) [101].

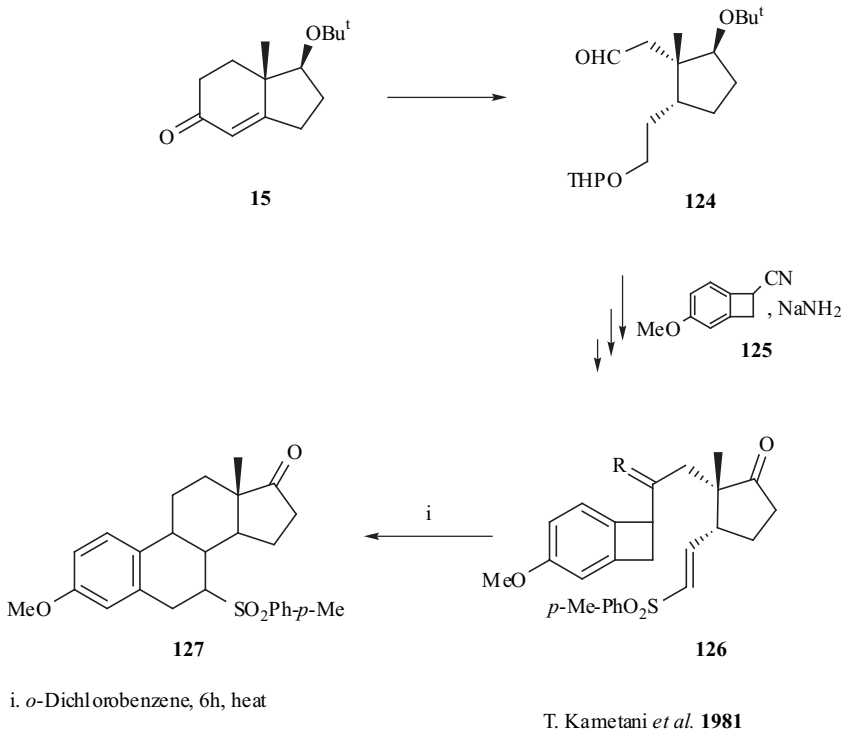
In situ prepared 'BrOMe' also adds to estra-1,3,5(10),6-tetraene derivatives in a regio- and stereoselective fashion to give 7α-bromo-6β-methoxy-adducts [102].

A *De Novo* synthesis of 7-phenylsulfonylestra-3,17β-diols **127** has been devised by T. Kametani *et al.* and is a pendant to the *De Novo* synthesis of G. Sauer *et al.* from Schering A.-G. T. Kametani *et al.* [103], who operate with a benzocyclobutene–*o*-quinodimethane ring opening / [4 + 2]-cycloaddition strategy as their terminal key step, and can control the regiochemistry of the benzo(A-ring)-annelation without reverting to a symmetrically substituted benzo group (i.e., dimethoxybenzo- as in the case of G. Sauer *et al.*) The synthetic route is very long, however, no effort has been undertaken to functionalize the molecules further utilizing the C7-phenylsulfonyl moiety.

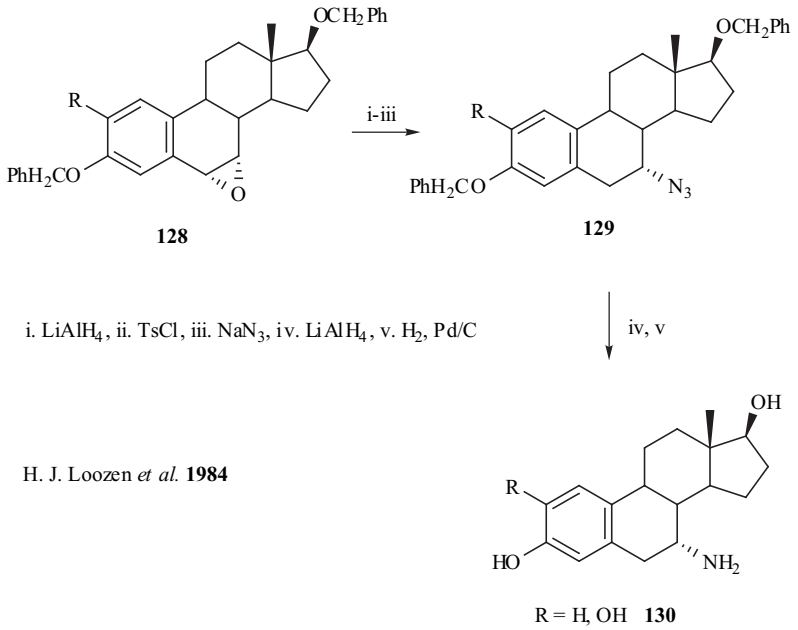
H. J. Loozen *et al.* [104] have prepared the 7-amino-estradiols **130**. These were synthesized *via* the 6,7-epoxy-estradiols **128**. Reduction with $LiAlH_4$ leads to the 7α-alcohol, which is converted into its tosylate. Reaction with sodium azide in a nucleophilic substitution gives the 7-azido compound **129**, which is reduced to the amino product with $LiAlH_4$ (Scheme **32**). Catalytic debenzylation furnishes



Scheme 30.



Scheme 31.



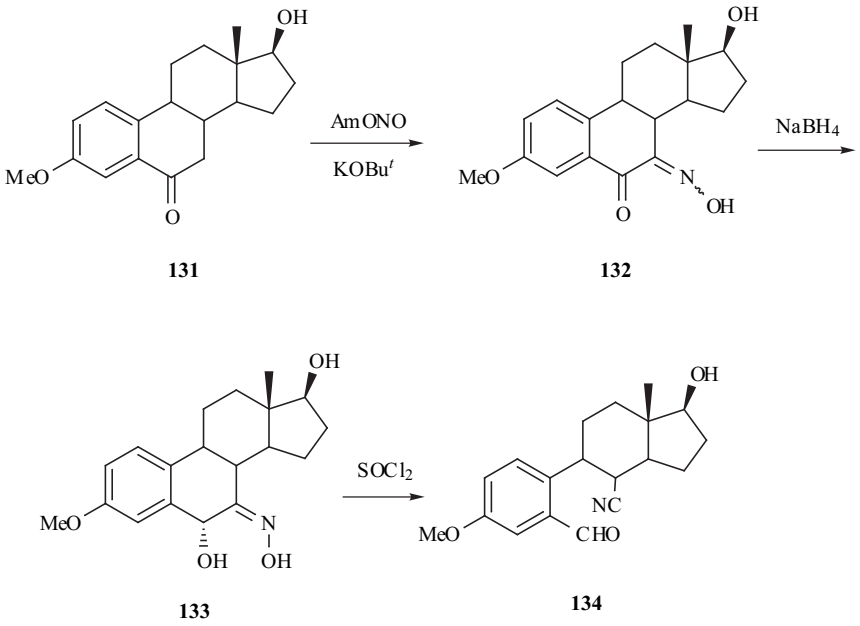
Scheme 32.

the 7-aminoestra-3,17β-diol. An analogous sequence has also been carried out to give the 7-aminoestra-2,3,17β-triol [104].

Also, the 7-oxime of the 6-ketoestra-3,17β-diol **132** has been prepared by standard methods (AmONO, KOBu^t). Thus far it has not been found to be a versatile starting material for further transformations in C7-substituted estra-1,3,5(10)-triene series. When the 6-keto group is reduced, a subsequent *Beckmann* reaction on the triol 7-oxime **133** leads to a *Beckmann* fragmentation and to the unexpected 9-methoxy-6-oxo-17β-hydroxy- 6,7-secoestra-1,3,5(10)-trien-7-nitrile (**134**) [105].

7-Alkylthio-substituents as thioethers[106,107] can readily be synthesized by reaction of 7α-bromo-6-ketoestra-3,17β-diol 3,17-diacetate with a thiophenol. The thiophenol may carry a leaving group (i.e., a triflate or a halide) that can be used in further elongation of the C7 chain by metal catalyzed coupling reaction.

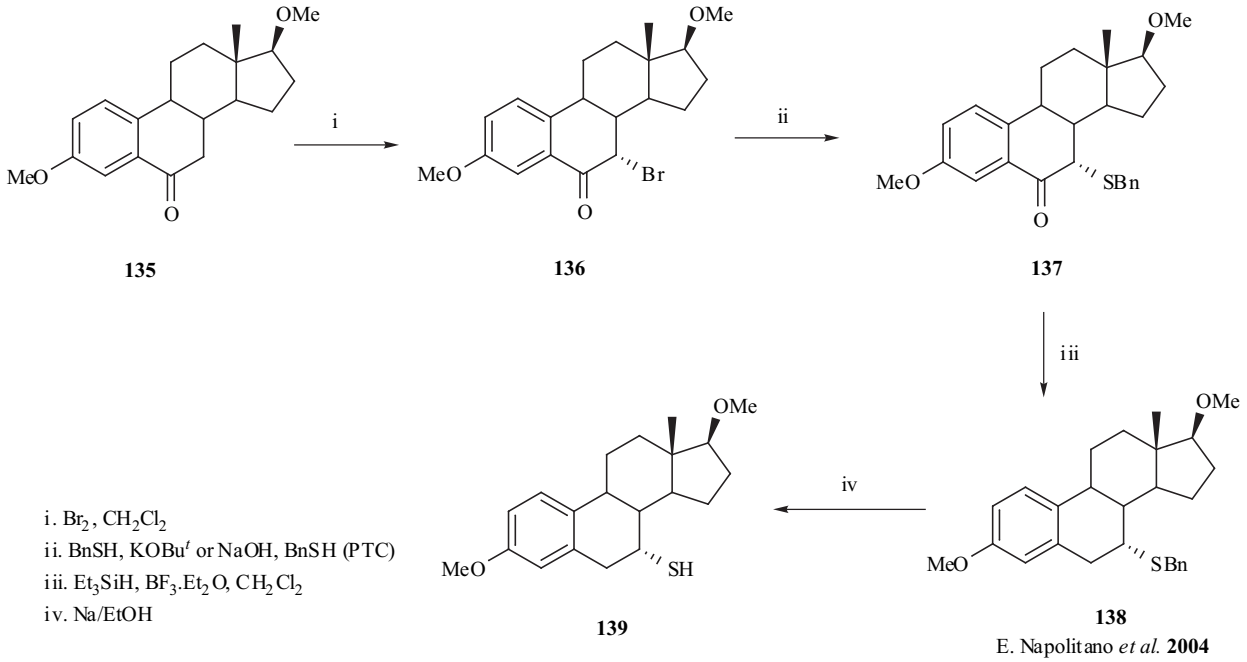
A mercapto group can be introduced at C7α by submitting 7α-bromo-6-ketoestra- 3,17β-diol derivative **136** to a substitution reaction with benzylthiol (KOBu^t, DMF or aq. NaOH, Bu_4NHSO_4, benzene [PTC]) [108] substitution reaction, which gives the benzylsulfide **137** with retention of configuration. Deoxygenation of C6 with Et_3SiH, $BF_3{\cdot}Et_2O$



131 **132** **133** **134**

V. M. Pejanovic *et al.* **1995**

Scheme 33.



135 **136** **137** **138** **139**

E. Napolitano *et al.* **2004**

Scheme 34.

to **138** is followed by debenzylation with Na, resulting in the 7α-mercaptoestradiol **139**.

4. OUTLOOK

Many of the new developments in synthetic organic and in synthetic medicinal chemistry are reflected in the directions taken in the preparation of new steroidal ligands for the estrogen receptor ERα. Thus, combinatorial chemistry has found its way into this field. This can involve the linking of a steroidal system on a solid phase for the synthesis [109,110], as well as the synthesis of linkers [111] themselves on a solid phase.

Interesting new research is taking place in radiolabeling C7 substituted estradiols, where more emphasis is put on technetium and rhenium radioisotopes [112]. However, fluoro- and iodo radioisotopes are also studied. Nevertheless, the development of radioimaging agents based on radiolabeled steroids, i.e., on substituted estradiols, remains a difficult problem to solve. This is in part because of the poor biodistribution of many of the compounds, mostly due to their lipophilicity. More success will be seen in the

further use of antiestrogens for tumor therapy. The last 5-6 years have seen a trend towards using derivatives of the original ICI-182780 [113-116]. Though it has been noted that a dual functionalization at C7α and C11β can be detrimental to the binding affinity of the molecule to the receptor, some of the more recently designed antiestrogens, substituted at C7α, carry a fluoro substituent at C11β [114]. It must also be pointed out that there is a significant effort to develop further antiestrogens or selective estrogen modulators (SEMs) on the basis of non-steroidal structures.

The more immediate future may also see a greater development in using C7 substituted estradiols as carriers of anti-tumor compounds for the treatment of estrogen positive breast cancer [117-119]. Competition may come from certain techniques using anti-tumor agents linked to antibodies.

Undoubtedly, however, the interest in the preparation and application of novel 7-substituted estradiols and their derivatives will remain high.

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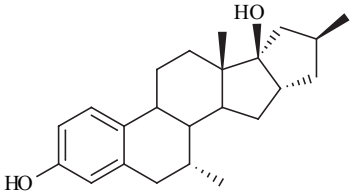

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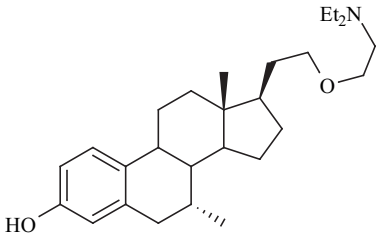

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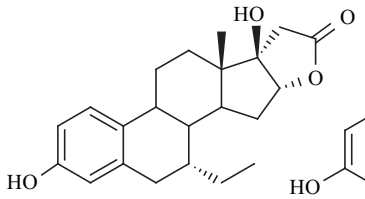

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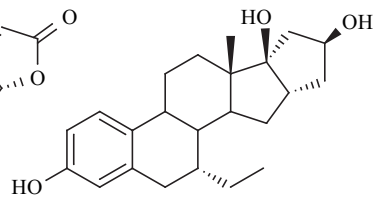

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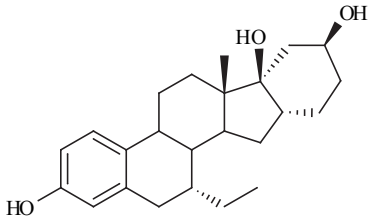

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