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C7-SUBSTITUTED ES TRA-1,3,5(10)-TRIENES - SYNTHESIS an OVERVIEW

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This contribution is to give a comprehensive review of preparations of C7-substituted estranes.

Introduction

In recent times the study of estrogens and antiestrogens, both naturally occuring and synthetic, has gained importance in such diverse but interlinked fields as the development of radiodiagnostica for breast cancer,[1] the advancement of both chemical cancer therapy[2] and hormone replacement therapy as well as the systematic study of the action of environmental hormones on the human endocrinal system and their effect on wildlife. Although compounds that possess estrogenic or antiestrogenic character can be of a variety of structures, the natural human estrogen is the steroid estra-3,7β-diol. In the last 3 decades a lot of research has been devoted to the development of new steroids with applications in the fields mentioned above. Especially, C7-substituted steroids have been at the forefront of that development. The following review focuses on the synthesis of C-7 substituted estrane derivatives.

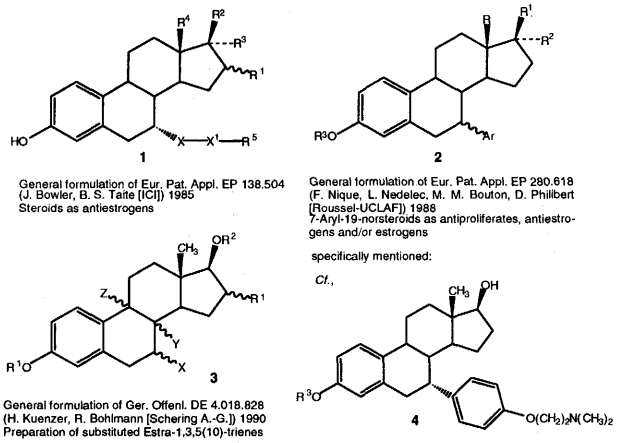

Figure 1 Examples of Patent Applications in the area of C-7 substituted Estra-1,3,5(10)-trienes

Decades ago, after the first steroidal contraceptives were put onto the market, it had been 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 (ICI 164384 (**5**), EM-139, ICI-182780 (**6**) and RU-45144) were forwarded,[3-12] where ICI 164384 (**5**) and ICI 182780 (**6**) 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.[2,9-10] These molecules have also been derivatised. Thus, the 16α-halo derivatives of ICI 164384 have been

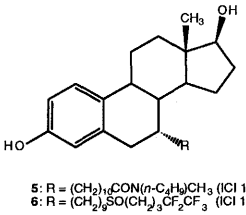

Figure 2. Industrially synthesized Antiestrogens

studied in detail.[11] Studies with radiolabelled ICI 182780 (^{14}C and other labels) have been carried out.[12]

The strategies used to prepare C7-substituted estranes can be roughly divided into three main categories: a.) the approach using a *De Novo* synthetic strategy that already includes 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 categorisation of synthetic approaches, where sections a.)-d.) deal with the introduction of C-substituents, while section e.) deals

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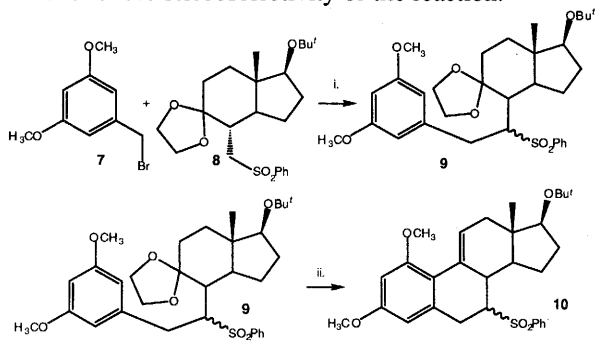
with heterofunctionalisation at C-7. Section f.) gives a brief, personal view of future possibilities in this area.

a.) De Novo Syntheses

In 1971 Schering has patented 1,3-diacetoxy-17α-ethynyl-7α-methylestra-13,5,(10)-triene-17β-ol as a strong estrogen.[14] At first the compound was prepared in a partial synthesis. 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 (**8**) with an appropiately substituted benzylbromide and a subsequent acid catalysed Friedel Crafts type closure of ring B of the steroidal frame.[16-19] This approach has been used by G. Sauer, R. Wiechert et al. for the preparation of other synthetic steroids.[18,20-22] The methyl group is introduced by lithiation of the C-7 position, taking advantage of the acidity of C-7 (allylic position; position α to the electron withdrawing phenylsulfoxy group). The anion is reacted with methyl iodide, furnishing as the major product the 7α-methyl substituted estradiol. The authors give steric reasons for the stereoselectivity of the reaction.



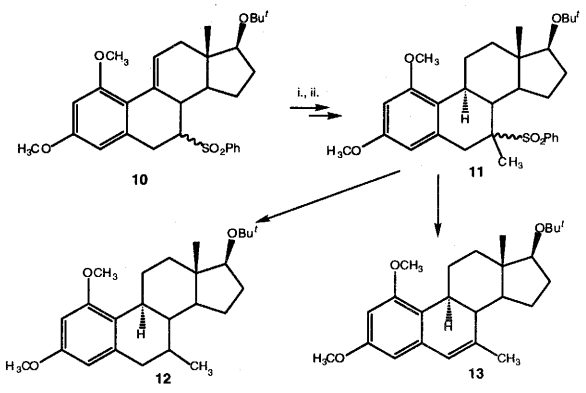
i. LDA, THF; ii. TFA; CF_3COOH; toluene G. Sauer, R. Wiechert, et al. 1982

Scheme 1. *De Novo* Approach to 7α-Methylestradiols - Part A: Construction of the Steroidal Frame

The reductive removal of the auxiliary sulfonyl group yields a mixture of 7α- and 7β-methylestra-1,3,5(10)-triene-17β-ol derivatives, the ratio of which depends on the reductant used. Both the reduction with K/Hg in a mixture of ethanol and toluene (4:1) and the electrochemical reduction at a mercury cathode ($LiClO_4$ [electrolyte], MeOH [solvent], non-divided cell, ratio 9:1) showed high stereoselectivity.

Both epimeric sulfones **11** as starting material gave the same diasteroisomeric 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-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[24] and the

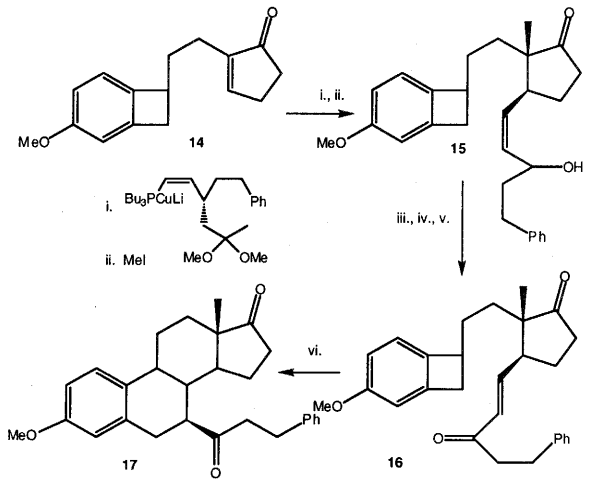


i. LDA, CH_3I; ii. H_2, Pd/C, EtOH G. Sauer, R. Wiechert, et al. 1982

Scheme 2. Part B: Derivatisation at C-7

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 functionalisation at C-7 via a 6-keto group.[23,25] Here, 1,2,3,3a,4,5,7,7a-octahydro-4-(phenylsulfonyl)methyl-5*H*-inden-5-one is reacted with dimethoxyphenylacetonitrile instead of with dimethoxybenzyl bromide. This leads to a primary estra-1,3,5(10)-triene, stemming from the cylization reaction, that has a cyano group at C-6. 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 C-7 methyl group is introduced[23,25] following reaction conditions described in section b.)

A slightly different approach has been used by Z. Cai et al.,[26] who reacted the indane system as the C/D fragment with the tosylate of enantiomerically pure 1-(*m*-methoxyphenyl)propan-2-ol, which they derived from *m*-methoxyphenylpropan-2-one by enzymatic reduction.

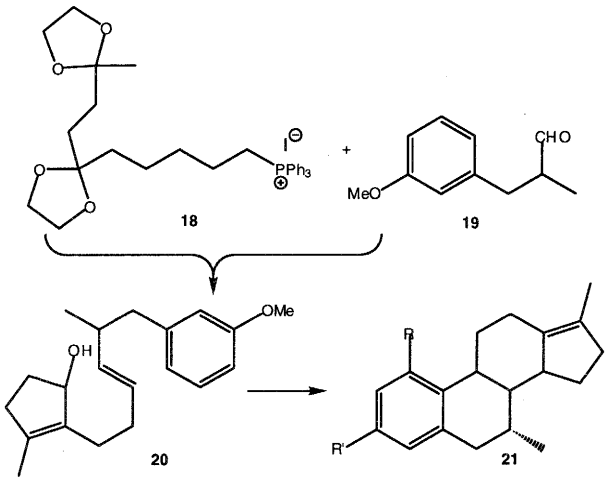


iii. Me-PhSOCl, Et_3N; iv. Me_3OP, MeOH; v. Swern-Oxidation; vi. 180°C

Scheme 3 Takahashi 1990

T. Takahashi et al.[27] used the Kametani method of retrocyclisation of a benzocyclobutene **16** to an intermediate *ortho*-quinodimethane which under an intramolecular cycloaddition with a double bond in the tether of the molecule. This, T. Takahashi et al. combined with their process of stereoselective methylation of an

intermediate adduct of a previous Michael addition step, where a carbon nucleophile (in this case a modified cuprate) adds to a cyclopent-2-enone. The olefinic moiety in the tether, which is an allyl alcohol, is cis/trans isomerized in two steps and the alcohol function is converted to a keto group by Swern oxidation. The Kametani benzocyclobutene - *o*-diquinomethane reversion / intramolecular cylcoaddition step is carried out in *o*-dichlorobenzene at 180℃.[27] The stereochemistry of the C7-substituent ($PhCH_2CH_2CO$) in this case is β.

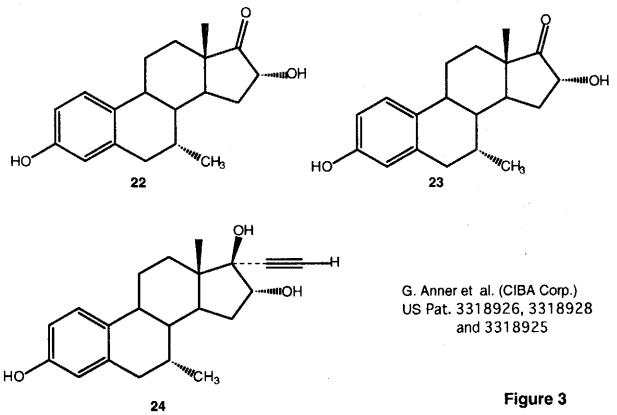


Groen and Zeelen 1978

R = OMe, R' = H and R = H, R' = OMe

Scheme 4

In 1978, M. B. Groen and F. J. Zeelen[28,29] published a total synthesis of racemic 7α-methyl substituted estra-1,3,5(10),15(17)-tetraen-3-ol **21**. The key step is the Domino-type cyclization of **20** in the presence of $SnCl_4$ at -70℃. The Friedel-Crafts alkylation of the anisyl moiety leads to a mixture of the two possible regioisomers. **20** itself was prepared by Wittig-reaction, acetal cleavage and subsequent condensation to form the cyclopentenyl-moiety of the molecule. Later, this synthesis was patented to encompass estra-1,3,5(10),15(17)-tetraenes that do not possess an alkyl-substituent at C-17.



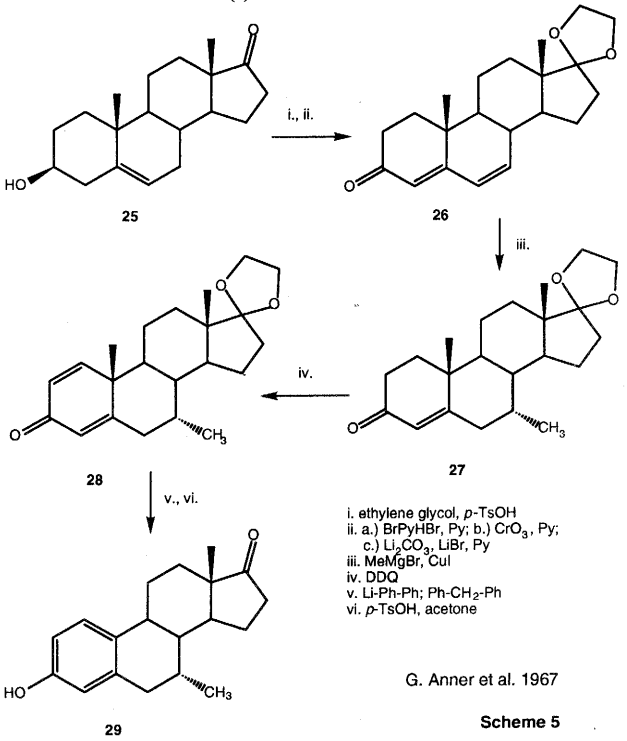
G. Anner et al. (CIBA Corp.)
US Pat. 3318926, 3318928 and 3318925

Figure 3

b.) *Transformation of other Steroidal Series to Estranes*

Perhaps one of the earliest systematic studies of any C7 substituted estrones have been by G. Anner et al. of the CIBA Geigy Laboratories.[30-35]

G. Anner et al. synthesized 7α-methylestrone and derivatives thereof from testosterone. The main step involved the Cu(I) mediated 1,4-addition[31] of



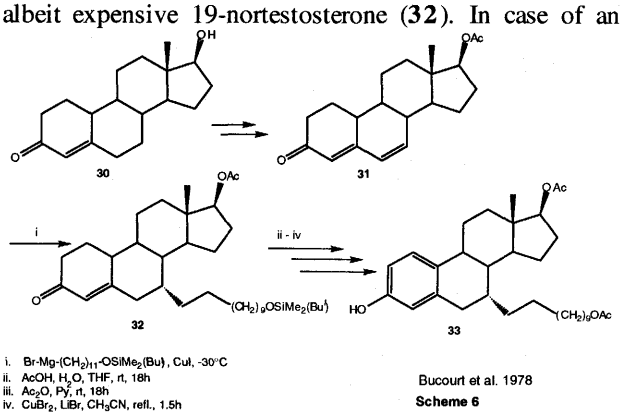
G. Anner et al. 1967

Scheme 5

methylmagnesium bromide to the dienone **28** (also, see below). The subsequent aromatisation to the estrone series was carried out with loss of the C-18 methyl group. Later 7α-methylestrone, 16α-hydroxy--7α-methylestrone, 17α-ethynyl-7α-methylestra-3,17β-diol, 7α,17α-dimethyl-estra-3,17β-diol and intermediates of their syntheses were patented as highly active estrogens with antigonadotropic activity. In later years, numerous reports have appeared on the binding characteristics of 7α-methyl substituted estra-3,17β-diols. Thus, F. J. Zeelen and E. W. Bergink[37] carried out a mapping of the dependence of the binding affinity of the molecules to the estrogen receptor on the position of the methyl substitutent. The authors found that methyl substitution at positions 1, 2, 6α, 15α, 15β and 18 is detrimental to the binding,[38] substitution at positions 7α, 11β and 17β is advantageous for the binding. Finally, 7α-methylestrone was also used as a precursor for a 7α-methyl-*D*-homoestra-1,3,5(10)-triene derivatives, where Me_3SiCN was added to the 17-keto group, the introduced azido function reduced to an amino group. A Tiffeneau-Demjanov type rearrangement furnished the D-homoestra-1,3,5(10)-triene derivative.[39]

In 1978, R. Bucourt et al. reported on the use of 7-alkylestradiols as biospecific adsorbents[40] 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 (**31**), a reaction which is run under Cu(I) catalysis. **31** can

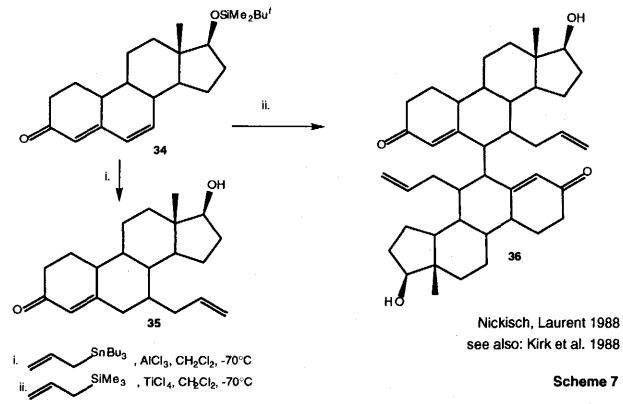
be prepared in two steps from the commercially available, albeit expensive 19-nortestosterone (**32**). In case of an



i. Br-Mg-$(CH_2)_{11}$-$OSiMe_2(Bu^t)$, CuI, -30°C
ii. AcOH, H_2O, THF, rt, 18h
iii. Ac_2O, Py^2, rt, 18h
iv. $CuBr_2$, LiBr, CH_3CN, refl., 1.5h

Bucourt et al. 1978
Scheme 6

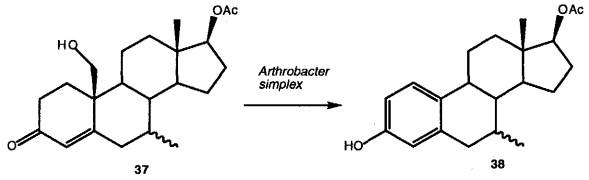
introduction of longer alkyl chains, the preparation of the corresponding Grignard reagents necessitates long reaction times, where the use of ultrasonication has been found to be beneficial. Restrictions due to the Grignard reaction itself limit the choice of functional groups at the (other) chain terminus that can be introduced directly in this step. This limitation makes further transformation of the functional group necessary. In the case of the introduction of a hydroxy function as the terminal substituent, it has to be protected, e.g. as a silylether. As the best results in the *Homo-Michael* addition reaction are achieved with an excess of the nucleophile, the separation of the addition product from non-reacted nucleophilic reagent may become tedious. The addition product may be aromatised to the estrane derivative with $CuBr_2$/LiBr in acetonitrile. Further elaboration to the target compounds involve functional group transformations including the manipulation of protective groups at C-17 within the steroidal frame as well as at the terminus of the C7 side-chain. A number of groups[41-48] have prepared 7α-substituted estra-1,3,5(10)-trien-3,17β-diols in this fashion. The Bucourt method has been by many groups and a number of structures have been patented that have been made this way.[49, in part 41]



Nickisch, Laurent 1988
see also: Kirk et al. 1988
Scheme 7

An allyl substituent can be introduced at C-7 of 17β-acetoxyestra-4-en-3-one, when reacting 17β-acetoxyestra-4,6-dien-3-one with allyltrimethylsilane under F^- catalysis (TBAF, DMF, HMPA) or under $BF_3{\cdot}Et_2O$ catalysis.[49] 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 -78°C mainly gives the desired 1,6-adduct, at -15°C a dimeric steroidal structure is the main product. K. Nickisch and H. Laurent[50] isolated exclusively the dimer under similar conditions ($BF_3{\cdot}Et_2O$, CH_2Cl_2, -70°C), but noted the formation of the 1,6-adduct upon using allyltimethylstannane instead of allyltrimethylsilane.

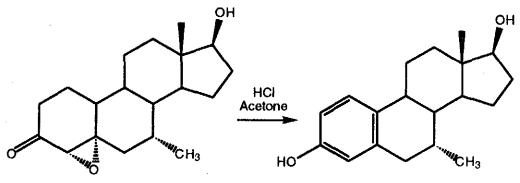
Steroids of the testosterone series can also be transformed enzymatically to the estrane series as shown by N. Yi et al., who reacted 7α-methyl-19-hydroxymethyltestosterone 17-acetate with *Arthrobacter simplex* to 7α-methylestra-1,3,5-trien-3,17β-diol 17-acetate.[51]



Scheme 8

85% Y. Ni et al. (1983)

A further, purely chemical way of aromatisation employs an epoxidation of the 4(5) olefinic moiety after the 1,6-addition of the C-nucleophile (to C-7) with subsequent acid catalysed ring opening of the epoxide and dehydration of the resulting alcohol.[52]



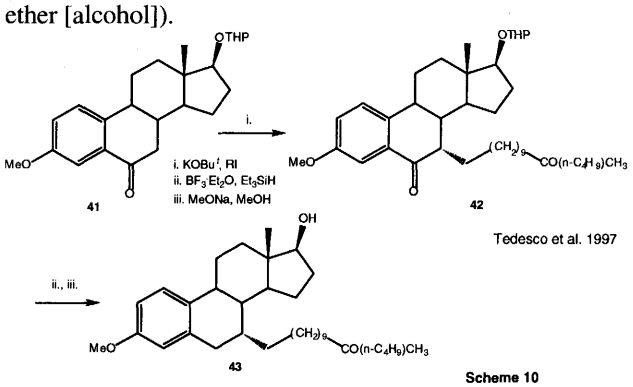
Scheme 9

J. Ma, Z. Li 1987

c.)*Direct Addition of Substituents to C-7 of Estranes*

When the C-7 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 C-7 position is via transformation of the benzylic C-6 position. Thus, a number of ways are known to oxidize C-6[53] either to a keto functionality or to a hydroxy function[54] (by hydroxylation). When the 6-ketoderivative is brominated, the ensuing 7-bromo-6-ketoestrane can be methylated[23] at C-7 by reaction with methyl iodide in the presence of zinc. However, with the keto group in position at C-6, C-7 lends itself also to direct substitution by conjugate addition.[55] In this way, both carbon and heteroatomic nucleophiles can be added.[56-65] The enolate of the 6-keto-estrane derivatives is formed with $KOBu^t$ or similar bases. Great care must be taken to exclude all oxygen (and water) from the reaction mixture. The enolate in THF forms a dark, deep red solution. The addition of the alkyl halides, preferably of the iodides, initially is performed at -78°C with the reaction mixture gradually warming up to room temperature. The additions usually yield a mixture of 7α and 7β substituted products, with the 7α-isomer being the

main product. 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.[63,64] Aldehyde and alcohol-functionalities can also be introduced, when suitably protected (e.g., as an acetal [aldehyde] or a siloxy-ether [alcohol]).

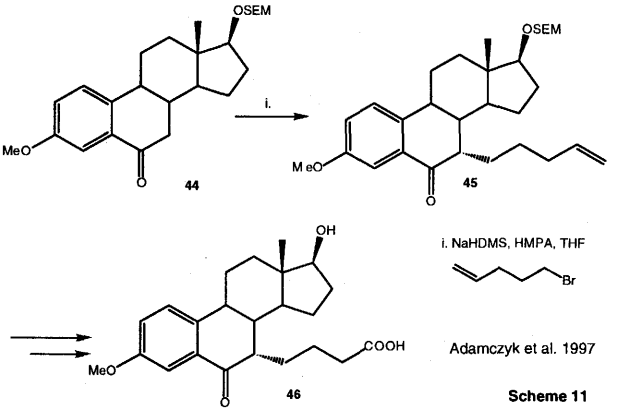


Tedesco et al. 1997

Scheme 10

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.[57] have reported on the alkylation of 3,17β-bis(2-trimethylsilyl)ethoxymethylestra-1,3,5(10)-trien-6-one (**44**) with 5-bromo-1-pentene in the presence of NaHDMS as base. The yield of **45** was 21% and the use of different bases (e.g., LDA, LiHMDS, KHDMS) have not been more successful.[57]

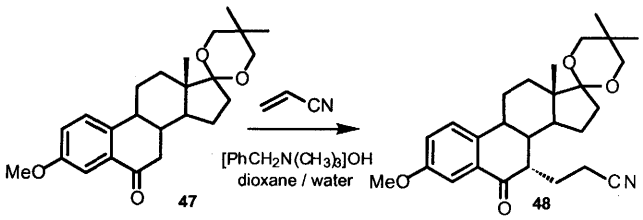
The carbon number m in these conjugate addition reactions can be varied considerably, when an n-alkyliodide is to be added; m = 2, however, evidently gives poor results when the corresponding ethyliodide carries an electron withdrawing group (carboxylic ester, carboxamide, cyano) and is reacted under the conditions mentioned above (KOBu^t THF). In these cases,[65] it often is advisable to carry out a Michael addition with the group to be introduced acting as Michael acceptor (e.g., reaction of the



Adamczyk et al. 1997

Scheme 11

enolate of **47** with acrylonitrile). Then 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 50°C), the main product is the 7α-alkylated estrane **48**. 7,7-Bisalkylated products as side products have also been found, albeit in much smaller amounts.



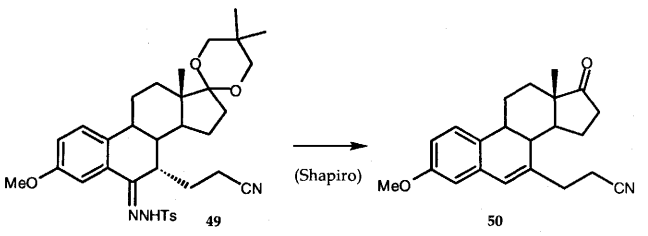
Thiemann et al. 2001

Scheme 12

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.[66]

A complementary reaction which uses the steroidal system as a Michael acceptor and alkyllithium reagents as C-electrophiles as the Michael donors, has been developed by Kuenzer et al. in their synthesis of ICI 164384. Here, the 6-keto group is transformed to a thioenol ether with thiophenol in THF[56] in the presence of triethylamine as base and $TiCl_4$ as Lewis acid catalyst. The actual Umpolung of the molecule takes place in the oxidation of the thioenol ether to the ene-sulfone **53**, which then serves as the Michael acceptor. The synthesis encompasses more synthetic steps; the reduction of the sulfone **54** to **55** with sodium almagam, however, provides an alternative to the reduction of the ketones with complex hydrides in the presence of Lewis acids (see below). The 3-methyl ether is cleaved by the reaction with sodium methylmercaptide in DMF at 130°C, an alternative to the cleavage with BBr_3, which in many cases does not lead to good results.

The keto functionality at C-6 which has been used as auxiliary for the activation of C-7 can be removed under reductive conditions (complex metal hydride in presence of a Lewis acid) or can be transformed to yield a C-6-C-7 olefinic moiety (either by reduction to a 6-hydroxy function with subsequent acid catalysed elimination or, especially in the case m = 2 by Shapiro reaction of the C-6 tosylhydrazone, formed in two steps from the 6-ketone).[65]



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

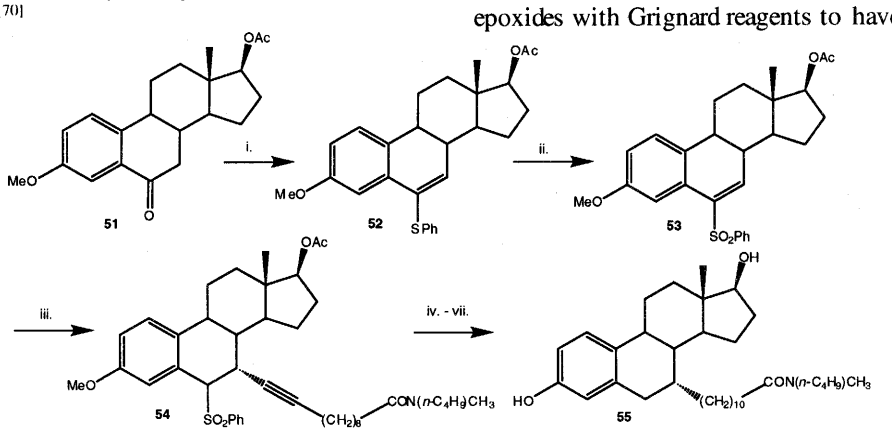
Thiemann et al. 2001

Scheme 13

It should be possible to utilize estra-1,3,5(10),6-tetraene derivatives, *i.e.*, an olefinic moiety at C6/C7, for an entry into the C-7 substituted estranes. A number of synthetic

strategies 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 at C-7 of estra-1,3,5(10),6-tetraenes has been attempted by Heck reaction of **5 6** with butyl *p*-iodobenzoate. Here, the C-7 substituted estra-1,3,5(10),6-tetraene formed, albeit in mediocre yield and with the double arylation product as a side product.[67]

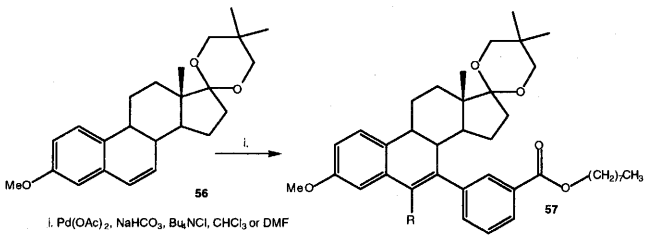
The complexation of estranes with chromiumtricarbonyl(0) is known[68,69] Also, estra-1,3,5(10),6-tetraene **58** forms the corresponding η^6-chromiumtricarbonyl(0) complex.[70]



i. $TiCl_4$, THF, 0°C, thiophenol, triethylamine, rt; ii. AcOH, $NaBO_3$, rt; iii. RLi, THF; iv. MeOH, NaOH v. EtOAc, Pd/C, H_2; vi. MeOH, 3% Na(Hg), $NaHPO_4$; vii. DMF, $NaSCH_3$ 130°C.

Kuenzer 1994

Scheme 14

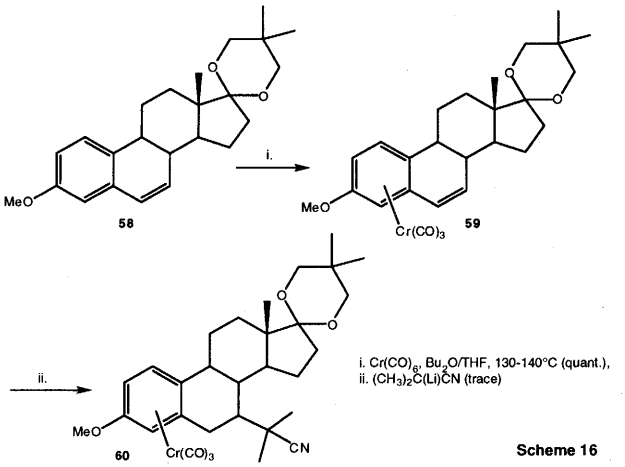


i. $Pd(OAc)_2$, $NaHCO_3$, Bu_4NCl, $CHCl_3$ or DMF

Thiemann 2000

R = H or Ph-CO-$(CH_2)_7CH_3$ **Scheme 15**

Due to the strong electron withdrawing character of the chromiumtricarbonyl moiety, the C-7 position of the

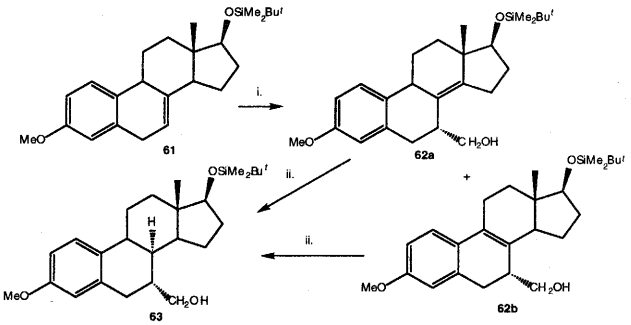


i. $Cr(CO)_6$, Bu_2O/THF, 130-140°C (quant.), ii. $(CH_3)_2C(Li)CN$ (trace)

Scheme 16

estra-1,3,5(10),6-tetraene derivative should be sufficiently electrophilic to react with a C-nucleophile in an addition reaction. M. F. Semmelhack et al.[69] have carried out such reactions with 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 can also be detected, but the yield of these adducts is low. Neither the stereochemistry of the complex used nor that of the addition product has been determined yet.[70]

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.[71] The control of a regioselective ring opening of the epoxides with Grignard reagents to have a direct access to C-7 substituted estranes has proven to be difficult to date. Lastly, 7α-hydroxymethylestradiol is also accessible via *Prins* reaction starting from equilinin. Two homoallylic alcohols are formed in a 6:1 ratio, which can be separated. However, both can be hydrogenated over palladium on charcoal (Pd/C) to give the same isomer **6 3**.[72]



i. $Al(CH_3)_2Cl$, $(HCHO)_n$

ii. H_2, Pd/C

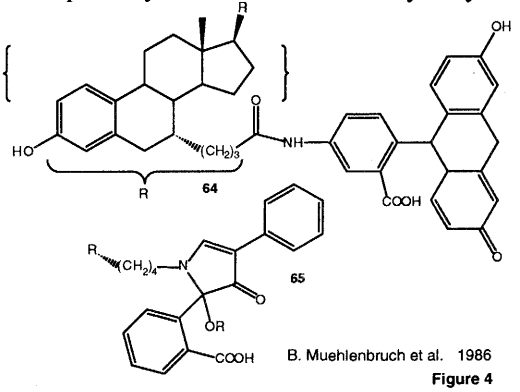
Künzer et al. 1991

Scheme 17

d.) *Functionalisation and Functional Transformations of C-7 Side Chain of Estranes*

Once the chain is introduced at C-7 of the estrane derivative, it can be functionally transformed,[42-44,47,63-65,73,74] 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, silylethers and olefinic moities are all compatible. From these carbaldehydes (deprotection of the acetals, deprotection of

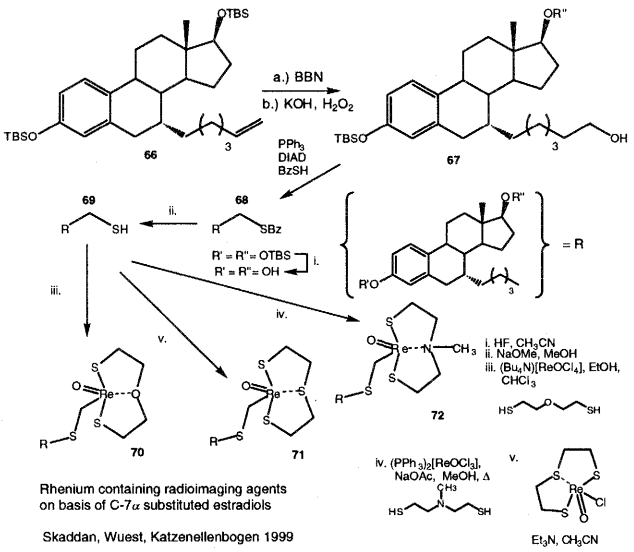
the alcohols and oxidation, hydroboration of terminal olefinic moieties with oxidative work-up) can be obtained. Moreover, J. N. da Silva and J. E. van Lier have shown how to optimally derivatise the 11α-hydroxyundecyl-



B. Muehlenbruch et al. 1986

Figure 4

estradiol, prepared by the method of Bucourt et al. (see above). Thus, the hydroxy function can be transformed easily to a chloro- or a bromo-group (CCl_4/PPh_3 or CBr_4/PPh_3). The bromo-functionality can be substituted for an iodo group (NaI/butanone) or a fluoro group (n-Bu_4F). Phenolic ethers can be prepared (phenol, $NaHCO_3$, DMF). Also 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.



Rhenium containing radioimaging agents on basis of C-7α substituted estradiols

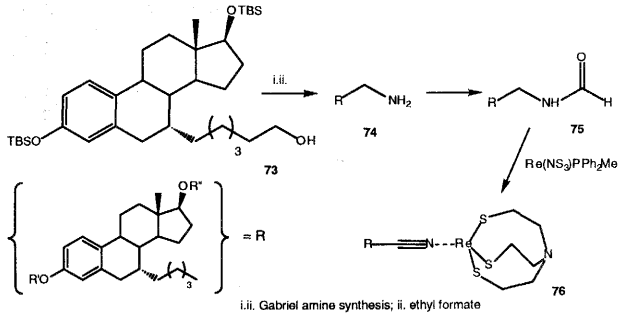
Skaddan, Wuest, Katzenellenbogen 1999

Scheme 18

The versatile cyano group can be easily transformed to an amino group, to a carbaldehyde (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).[63-65] Potentially the free amide can be alkylated.

B. Muehlenbruch et al. have coupled fluoresceinamine via the DCC method[74] to 7-α-carboxybutyl-estra-1,3,5(10)-trien-3-ol to give compound **64** as a fluorescent marker. Similar compounds such as **65** have been prepared.[74] *In vitro*, these compounds still possess a marked binding affinity to the estrogen receptor ERα.

J. A. Katzenellenbogen et al.[60,61] have shown that facile derivatisation of the terminal functional group in the introduced C-7 carbon chain leads to various possibilities of ligand formation, which facilitate the binding of metals to the steroid. 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 estrones have led to a better binding of the molecule to the receptor, longer C-7 chains may carry



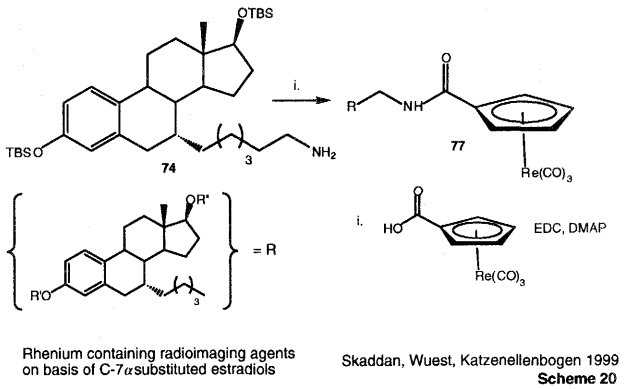
i.ii. Gabriel amine synthesis; ii. ethyl formate

Rhenium containing radioimaging agents on basis of C-7α substituted estradiols

Skaddan, Wuest, Katzenellenbogen 1999

Scheme 19

larger substituents without interfering substantially with binding of the molecule, as it is thought that long chains



Rhenium containing radioimaging agents on basis of C-7αsubstituted estradiols

Skaddan, Wuest, Katzenellenbogen 1999

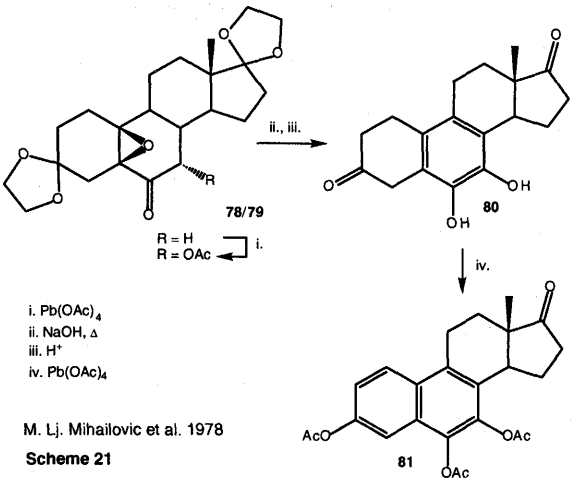
Scheme 20

outreach the confines of the ligand receptor complex, so that these larger substituents on the chains find themselves outside of the ligand receptor complex.

e.) *Heteroatom-functionalisation at C-7.*

The strategies for heterofunctionalisation at C-7 resemble those of C-7 functionalisation with a carbon substituent. In the cases of A-ring aromatisation after introduction of a hetero-functionality at C-7, especially of a hydroxy function, often leads via aromatisation of both the A and the B ring to the equilin series. A typical example is given by the transformation by Mihailovic et al. Here, the α,β-epoxyketone **78** is acetylated α to the keto group (C-7) with $Pb(OAc)_4$. Heating the compound in aq. NaOH leads to aromatisation of the B-ring. The protective acetal groups are cleaved at C-3 and C-17. Then ring A is aromatised with $Pb(OAc)_4$ to yield 6,7-diacetoxyequilin **81**.[75] The Friedel-Crafts type cyclization of **92** also leads to the equilin series. **92** can be prepared from the *Hajos-Parrish* diketone (**91**) in 1 step. Also the alcohol can be prepared from **91** in 1 step. It can be acetylated and ring-closed

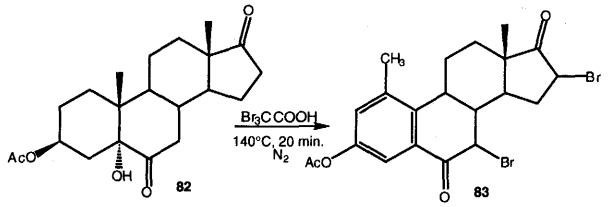
with $HClO_4$ in acetone to give a mixture of 7α- and 7β-acetoxy-3-methoxyestra-1,3,5(10),9(11)-tetraenes **94**, from which the β-isomer can be crystallized.[76]



M. Lj. Mihailovic et al. 1978

Scheme 21

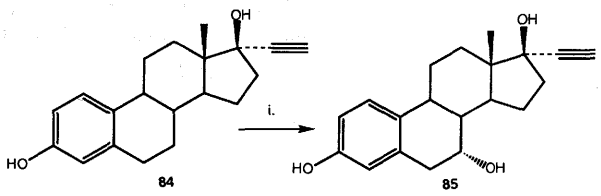
Most likely not by design was the outcome of the bromination of **82** with tribromoacetic acid (140°C, 20 min, N_2), which yields 7,16-dibromo-1-methyl-estra-1,3,5(10)-trien-6,17-dione (**83**).[77] 7-Bromoestra-1,3,5-(10)-trien-6-on-3,17-diol derivatives, furnished by bromination of 6-ketoestradiol derivatives, have been known for some time.



W. J. Szczepek 1981

Scheme 22

In 1976 Schering A.-G. patented a number of C-7α hydroxylated estratriols as estrogens. The preparative procedure followed a microbial oxidation using *Diplodia natalensis* ATCC 9055.[78] The hydroxy groups 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—hydroxy; contraceptive action: estra-3,17β-diol>> 11β-hydroxy>7α-hydroxy). Estra-3,7α,17β-triol has been found as a metabolite in the brain of rats and in the liver microsomes of juvenile rainbow trout.[80,82] Subsequently, the 17α-ethynyl-estra-1,3,5(10)-trien-3,7α,11β,17β-tetraol 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. Access to the estrane series was given

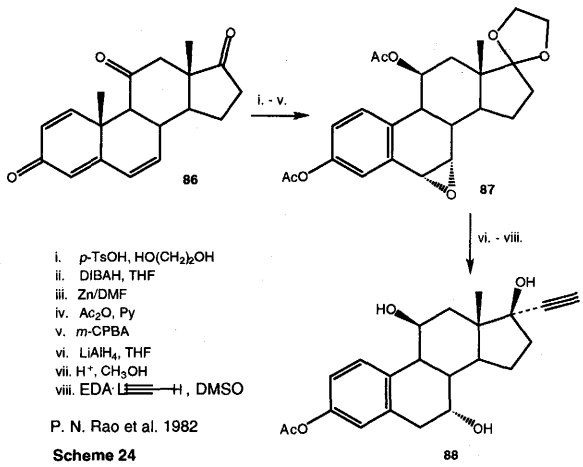


i. Diplodia natalens

Schering A.-G. 1976

Scheme 23

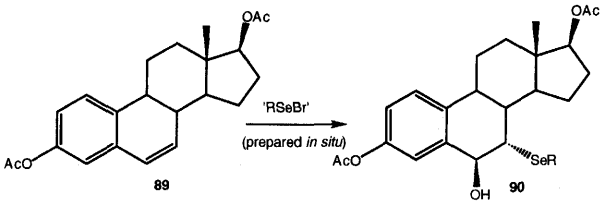
through aromatisation with Zn/DMF (concomitant loss of C-18 methyl).[84]



P. N. Rao et al. 1982

Scheme 24

Methyl and phenylselenyl bromide has been added to estra-1,3,5(10),6-tetraen-3,17β-diacetate to give after work-up the corresponding C-7α-alkyl/arylselenylestra-1,3,5(10)-trien-3,6β,17β-triacetates. While the steroids have been saponified with 5% KOH in EtOH, no additional transformations using these compounds were



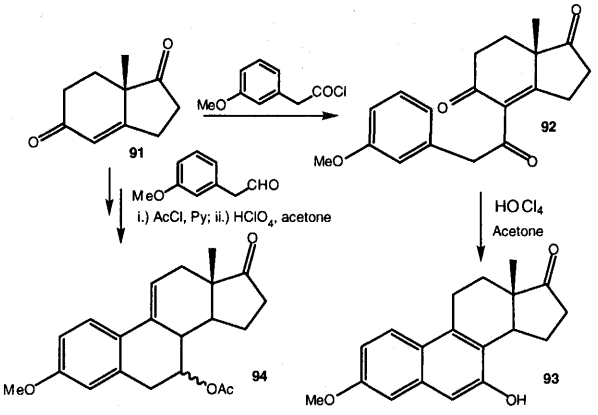
Scheme 25

Arunachalam, Caspi 1981

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.[85] 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).[86]

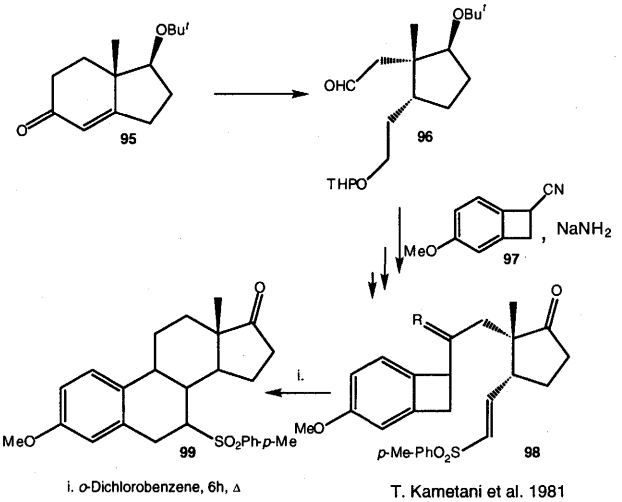
In situ prepared 'BrOMe' also adds to estra-1,3,5(10),6-tetraene derivatives in a regio- and stereoselective fashion to give 7α-bromo-6β-methoxy-adducts.[87]

A *De Novo* synthesis of 7-phenylsulfonylestra-3,17β-diols 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.,[88] who operate with a benzocyclobutene - *ortho*-quinodimethane ring opening / [4 + 2]-cycloaddition strategy as their terminal key step,



Scheme 26 Daniewski, Kiegiel 1988

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, and no effort has been undertaken to functionalize the molecules further utilizing the C7-phenylsulfonyl moiety.



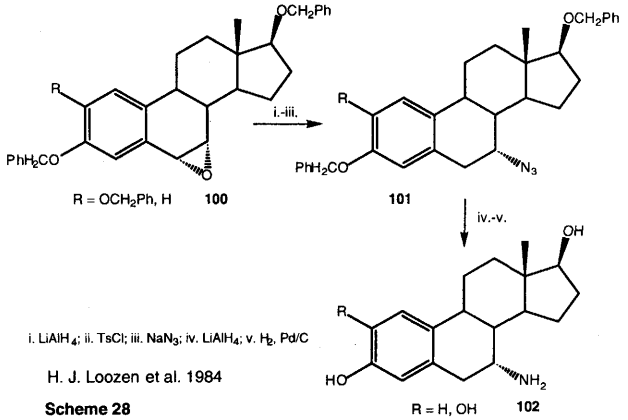
i. *o*-Dichlorobenzene, 6h, Δ T. Kametani et al. 1981

Scheme 27

H. J. Loozen et al.[89] have prepared the 7-aminoestradiols. These were synthesized via the 6,7-epoxy estradiols. Reduction with $LiAlH_4$ leads to the 7α-alcohol, which is converted into the tosylate. Reaction with sodium azide in a nucleophilic substitution gives the 7-azido compound, which is reduced to the amino product with $LiAlH_4$. Catalytic debenzylation furnishes the 7-aminoestra-3,17β-diol. An analogous sequence has also been carried out to give the 7-aminoestra-2,3,17β-triol.

Also the 7-oxime of the 6-ketoestradiol 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 the 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 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.[90]

7-Alkylthio-substituents as thioethers[91,92] can readily 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 C-7 chain by metal catalysed coupling reactions.



H. J. Loozen et al. 1984

Scheme 28

e.) *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. Thus, combinatorial chemistry has found its way also into this field. This can involve the linking of a steroidal system on a solid phase for the synthesis[93,94] as well as the synthesis of linkers[95] themselves on a solid phase.

Interesting new research is taking place in radiolabelling C-7 substituted estradiols, where more emphasis is put on technetium and rhenium as radioisotopes[96] rather than on fluoro- or iodo-substituents. Nevertheless, the development of radioimaging agents based on radiolabelled steroids, i.e., on substituted estradiols, remains a difficult problem to solve. This is in part because of the bad tissue distribution of many of the compounds, mostly due to their lipophilicity. More success will be seen in the further use of antiestrogens for tumour therapy. The last 3-4 years have seen a trend back towards using derivatives of the original ICI-182780.[97-99] Though it has been noted that a dual functionalisation at C-7α and C-11β can be detrimental to the binding affinity of the molecule, to the receptor, some of the more recent designed antiestrogens, substituted at C-7α, carry a fluoro-substituent at C-11β.[99]

The more immediate future may also see a greater development in using C-7 substituted estradiols as carriers of anti-tumour compounds for the treatment of estrogen positive breast cancer.[100] Competition may come from certain techniques using anti-tumour agents linked to antibodies.

Undoubtedly, however, the interest in the preparation and application of novel 7α-substituted estra-1,3,5(10)-trienes will remain high.

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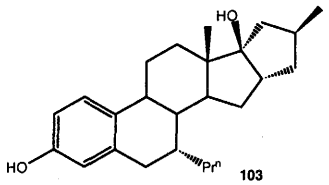

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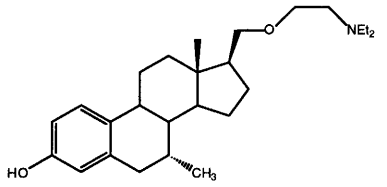

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