Ring D 16,17-heteroannelated estranes

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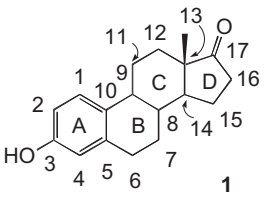
The synthesis of estranes bearing an additional heterocyclic ring attached to C-16 and C-17 is reviewed. Potential applications and biological activities of the compounds are described.

Keywords: steroids, synthetic estranes, cyclisation, cyclocondensation, heteroannelation

In recent years, significant synthetic effort has been devoted to the preparation of ring annelated estranes in the search for steroidal derivatives with useful biological activity. The objective has been to introduce novel biological activity and reduce estrogenic activity. In this regard, ring annelation has also been used to link known bioactive residues to the estrane skeleton. Although a larger number of 2,3-ring annelated estranes have also been prepared, this review focusses exclusively on 16,17-heteroannelated estranes.



1

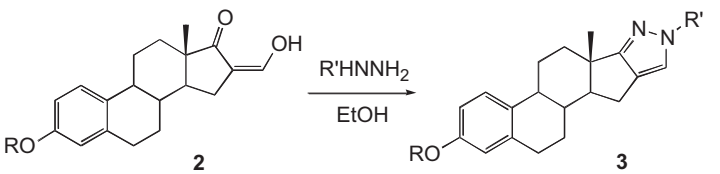
Fig. 1. Naturally occuring estrone with atom numbering and denotation of rings A – D

16,17-Heterocyclo- and heteroareno annelated estranes

Estrane[17,16-*c*]pyrazoles **3** were the first of a series of 16,17-heteroarenoannelated estrane derivatives in which separate studies by Robinson[1] and de Ruggieri[2] showed that compounds such as **3** (R = R' = Me) lowered the level of serum cholesterol (hypocholesterolemic activity) without having undesirable estrogenic activity.[1] Estrane[17,16-*c*]pyrazoles were prepared by the reaction of 16-formyl-estra-1,3,5(10)-trien-3-ol-17-one (**2**) with hydrazines in refluxing ethanol.[1,2] In general, **2** is a key intermediate for the synthesis of both 16,17-heteroareno- and 16,17-arenoannelated estranes. It can be prepared easily by formylation of suitably 3-*O*-protected estrone (**1**) [HCO_2Et, $NaOCH_3$, benzene]. Further syntheses of related estrane[17,16-*d*]pyrazoles along these lines have been described subsequently.[3,4]

In **3c**, subsequent *N*-alkylation can lead to a mixture of the 1'-alkylpyrazole and the 2'-alkylpyrazole derivatives. Guided by the knowledge that steroids possessing a pyrazole fused to ring A (*eg.* the non-androgenic anabolic steroid Stanozol USP) can be powerful inhibitors of the human endocrine system, Sweet *et al.*[4] studied 3-methoxyestra-1,3,5(10)-triene-[17,16*c*]-pyrazole (**3c**). It was found to be a competitive inhibitor of the human estradiol 17β-dehydrogenase [E_2-17βDH], where an intermolecular hydrogen bonding is thought to stabilise the steroid-[E_2-17βDH] complex. This finding was taken further by Potter *et al.*[5] with a novel series of 5'-alkylamidoestrane[17,16-*c*]pyrazoles **8**. Thus replacement of the 16-formyl group in **2** with a 16-keto functionality as in **6** can be used in the transformation **6**–**7**. Reaction of 16-methoxycarbonylestradiol (**4**) with hydrazine proceeds to give pyrazolone **5**,[6] of which two possible tautomeric forms are the isopyrazole **5a** and pyrazole **5b**. An ester function at the 5'-position of the pyrazole unit in **7** gives the possibility to functionalise the molecules further. On this basis Potter *et al.*[5b] have built libraries of 5'-alkylamidoestrane [17,16-*c*]pyrazoles **8**. These molecules hold great promise as estradiol dehydrogenase type 1 (17β-HSD1) inhibitors.[8] 17β-HSD1 is an oxidoreductase that converts estrone to estradiol and is overexpressed in certain types of breast cancer cells. Inhibition of this enzyme may lead to a method of cancer chemotherapy.

A further route to estrane[17,16-*c*]pyrazoles was achieved through the BF_3 catalysed cyclisation of the secoaldehyde **10**[8] with substituted phenylhydrazines. Initially, hydrazones were formed. In a second step these were transformed with $BF_3{\cdot}Et_2O$ to azomethine imines which, as reactive intermediates, undergo an intramolecular 1,3-dipolar cycloaddition with the olefinic moiety of the allyl substituent at C-16, to yield in a double ring closure reaction estrane-[17,16]-pyrazolines **11b**. These were oxidised under the reaction conditions to the pyrazoles **11a** (Scheme 3).[9] Reaction of **10** with hydrazine itself and subsequent treatment of the dimeric hydrazone with $BF_3{\cdot}Et_2O$ gave the dimer **12** (Scheme 3).[9] A similar reaction of **10** with hydroxylamine furnished estrane[17,16]isoxazolidines **13** via the corresponding oxime (Scheme 3).[9] Estrane



2

2a: R = H
2b: R = CH_3

3

3a: R = H, R' = H; **3b**: R = H, R' = CH_3
3c: R = CH_3, R' = H; **3d**: R = CH_3, R' = CH_3

See refs. 1, 2 and 4.

Scheme 1

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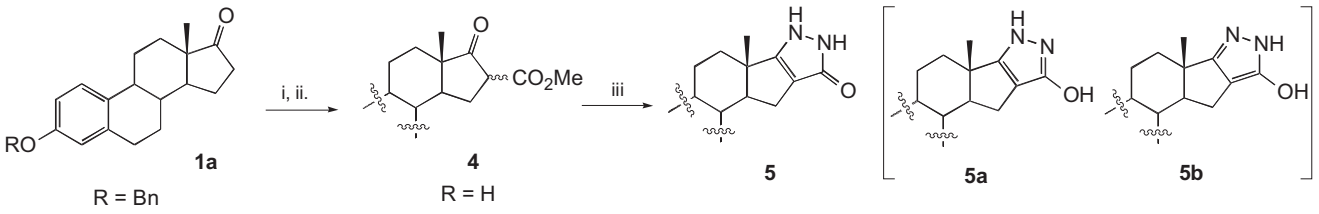
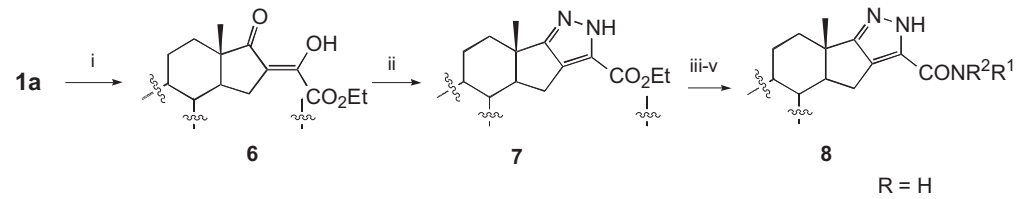
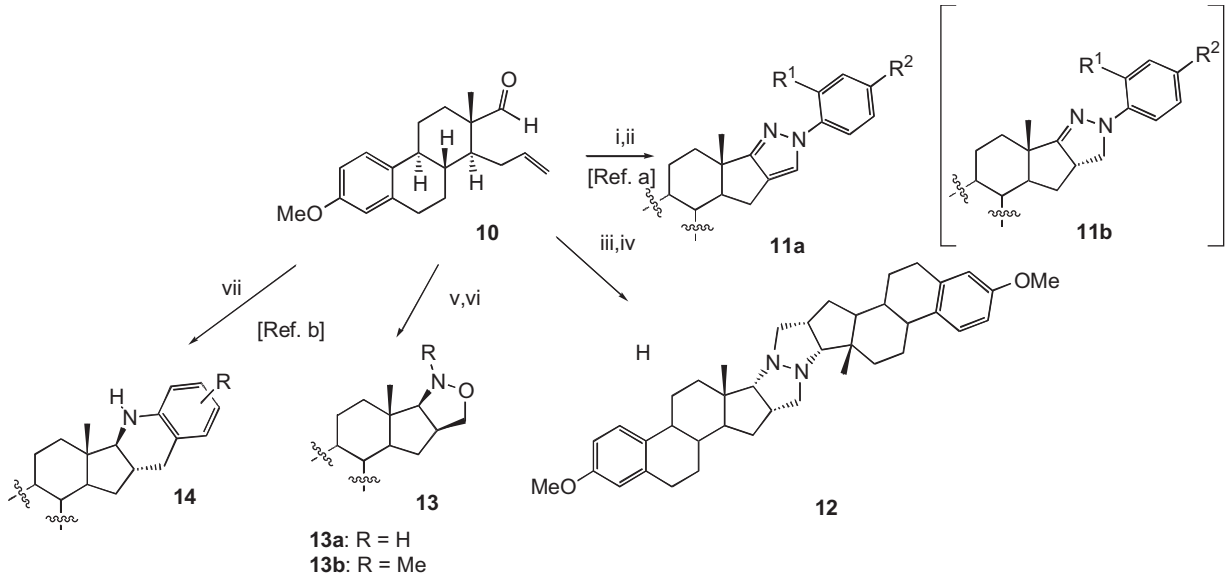


i, $MeOCO_2Me$, NaH, THF, Δ; ii, Pd/C, H_2, THF, rt; iii, $H_2NNH_2{\cdot}H_2O$, toluene, Δ.[1,2,4]



i, $(CO_2Et)_2$, $KOBu^t$, toluene; ii, $H_2NNH_2{\cdot}H_2O$, EtOH/CH_2Cl_2, refl., then rt; iii, NaOH, EtOH, refl.; iv, DMAP, EDC, Et_3N, R^1NHR^2; v, Pd/C, H_2, EtOH–THF.[5a]

Scheme 2



i, $R^1R^2PhNHNH_2$, EtOH, cat. HOAc; ii, $BF_3{\cdot}Et_2O$, toluene or $CHCl_3$; iii, H_2NNH_2, EtOH, cat. HOAc; iv, $BF_3{\cdot}Et_2O$, toluene v, for R = H: $H_2NOH{\cdot}HCl$, NaOH, MeOH, refl.; vi, $BF_3{\cdot}Et_2O$, toluene; v,vi. for R = Me: $MeNHOH{\cdot}HCl$, NaOH, MeOH, refl.; vii, R-Ph-NH_2, CH_2Cl_2; molecular sieves; then $BF_3{\cdot}Et_2O$.[10a,10b]

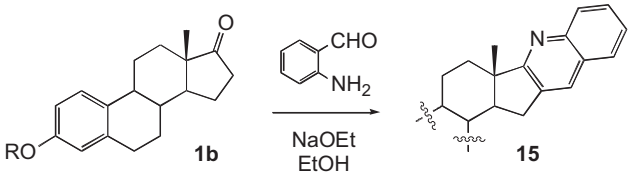
Scheme 3

[17,16-*d*]isoxazole derivatives have been prepared previously by reaction of **2** with hydroxylamine hydrochloride in refluxing ethanol.[4]

When the secoaldehyde **10** was reacted with substituted anilines and the ensuing imines were treated with $BF_3{\cdot}Et_2O$, estranetetrahydroquinolines **14** were formed (Scheme 3).[10] X-ray crystallographic analyses have been carried out on 11a[11] and 14a.[12]

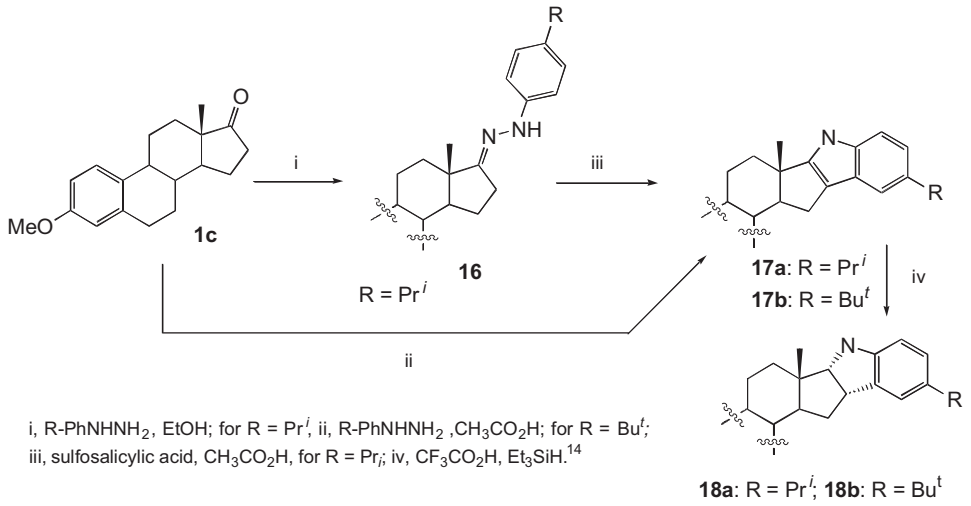
The synthesis of estrane[17,16-*b*]quinolines of type **15** takes advantage of a simple base catalysed Friedlander cyclocondensation of a suitably protected estrone **1b** with *o*-aminobenzaldehydes (Scheme 4).[13]

Estrane[17,16]indolines have been examined as chain-breaking antioxidants, inhibiting the oxidation of low density lipoproteins (LDLs) in blood plasma that would lead to the release of foam cells, a process closely associated with atherosclerosis.[14] It has been shown by Sainsbury *et al*.[14] that **18a** and **18b** bind selectively to LDLs rather than very low density lipoproteins (VLDLs), but the overall



Scheme 4

incorporation into the proteins is too low. Compounds **18a**/**b** were synthesised from 3-*O*-methylestrone via indoles **17a**/**b** by Fischer indole synthesis, either directly or by a two step sequence, where the initially formed hydrazone was isolated.[14] The indoles **17a**/**b** were reduced with a mixture of triethylsilane and trifluoroacetic acid, to the indolines **18a**/**b** (Scheme 5). Compound **18b** was characterised by single crystal X ray structural analysis.[14]



Scheme 5

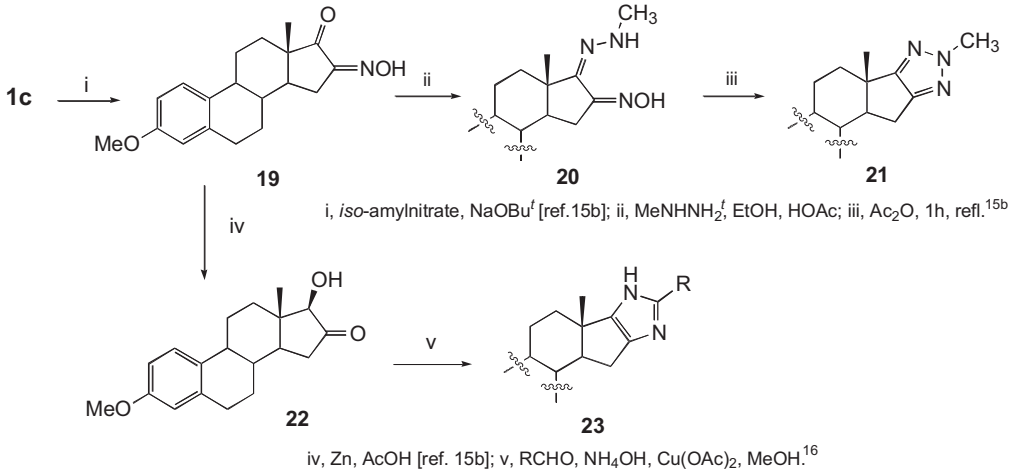
The 3-*O*-methylestra-1,3,5(10)-trien-3-ol-16,17-dione 16-oxime (**19**)[15a] is a suitable substrate for the preparation of the estrane[17,16-*d*]triazole **21** (Scheme 6),[15b] when it is condensed with methylhydrazine via the corresponding *N*-methylhydrazone **20**. Compound **21** has also been proposed by Roussel-UCLAF as a compound with hypo-cholesterolemic activity.[15b]

Compound **19** can also be used as a key intermediate in the preparation of estrane[17,16-*d*]imidazoles.[16] The synthesis proceeds via estra-1,3,5(10)-triene-3,17β-diol-16-one (**22**), which is treated with a substituted aldehyde and ammonia in the presence of $Cu(OAc)_2$ as catalyst (Scheme 6).[16]

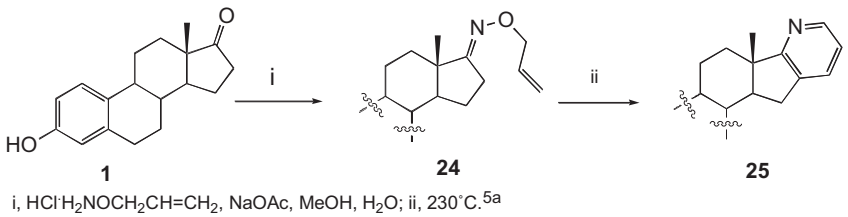
Synthesis of the estrane[17,16-*b*]-pyridine **25** has been accomplished via the thermal rearrangement of the *O*-allyl oxime **24**, obtained from estrone (**1**) with *O*-allylhydroxylamine hydrochloride (Scheme 7).[5a]

The steroidal ketoenamine **26**, resulting from the reaction of *N*-methylphenylammonium trifluoroacetate with 16-formyl-estra-1,3,5(10)-trien-17-one (**2**), has also been used as a precursor of heteroannelated estranes. In **2**, as a ketoenol, the carbonyl reactivity of formyl and keto-groups towards nucleophiles is lowered by internal hydrogen bonding. Thus, the use of **26**, replacing **2** as starting material, can be advantageous. As an example, the condensation of the enamine **26** with guanidinium hydrochloride under basic conditions yields estratetraeno[17,16-*e*]-2'-aminopyrimidine **27** (Scheme 8).[17] Compound **27** has been reacted further to give steroidal-peptide hybrids, useful as ligands for radiolabels rhenium and technetium. An X-ray crystal structural analysis has been carried out on **27**.[18]

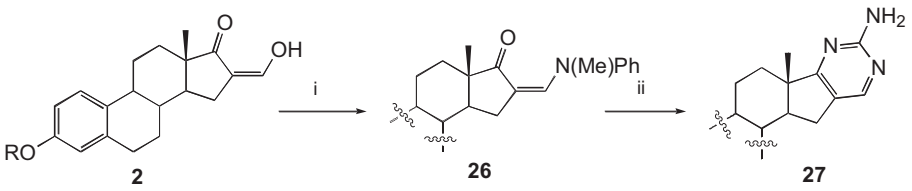
1',4'-Pyrazino-[2',3': 16,17]-3-*O*-methylestra-1,3,5(10)-trien-3-ol (**30**) has been synthesised from 3-*O*-methylestra-1,3,5(10)-trien-16,17-dione (**28**) and ethylenediamine with



Scheme 6



Scheme 7



2 **26** **27**

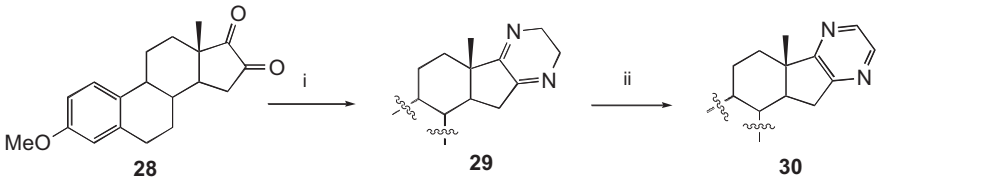
i, TFA·MeNPh, benzene; ii, guanidine hydrochloride, ^{i}PrOH, NaOMe.[17a]

Scheme 8

subsequent oxidative dehydrogenation using Pd/C in toluene (Scheme 9).[19] The dimeric steroidal pyrazine synthesised recently by *Lotowski et al*.[21] is of interest as a potentially bioactive molecules due to a certain structural relationship to the natural cephalostatins,[20a] isolated from the marine tube worm *Cephalodiscus gilchristi,* and ritterazines,[20b] isolated from the tunicate *Ritteralla tokioka*. The synthesis of the *cis* and *trans* isomers of ring D-linked bis-estrane-pyrazine has been achieved by treatment of 16α-bromo-estrone with gaseous ammonia and successive air oxidation (Scheme 9).[21]

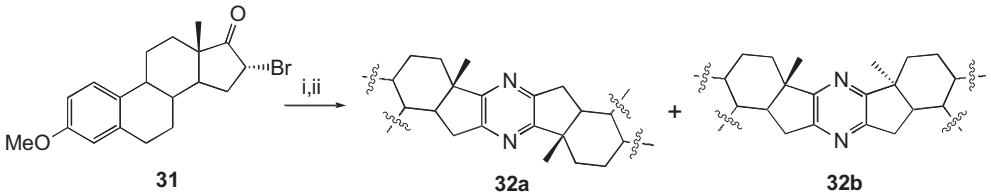
A substitute for the 16-formylestrone **2** as a starting material for ring annelation, in addition to the enamine **26**, is the steroidal ketene thioacetal **33**. This is directly accessible from **1c** by base catalysed reaction with carbon disulfide (Scheme 10).[22] Compound **33** can be reacted with guanidine nitrate to give aminopyrimidine derivative **34**, with hydrazine to give the pyrazole **35**, and with hydroxylamine hydrochloride to give isoxazole **36** (Scheme 10).[22] The reaction of **33** with the anion of indole-3-acetonitrile leads to carbazole **37**.[23a] Treatment of **33** with the anion of 2-methylindole, which is protected (*n*-BuLi, CO_2) and finally deprotected during the acid catalysed cyclisation, leads to a reaction at the 17-keto group of **33** to give a 1,2 addition product. This product is subjected to acid catalysed cyclisation to **38**.[23b] Compound **33** can also be used to prepare areno annelated estranes.[22]

Isoxazolino[4,5 : 16,17]estranes are formed by the [3 + 2] cycloaddition of nitrile oxides to estra-1,3,5(10),16-tetraenes. Thus, Gerali *et al*.[24] have prepared isoxazolines **40** from



28 **29** **30**

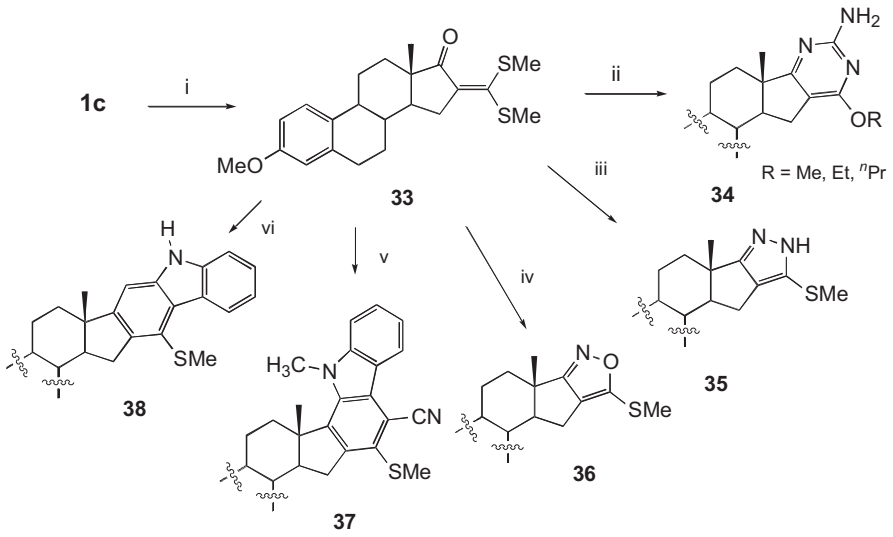
i, $H_2N(CH_2)_2NH_2$, EtOH, refl.; ii, Pd./C, toluene.[19]



31 **32a** **32b**

i, NH_3, benzene, BuOH; ii, O_2, H_2O.[21]

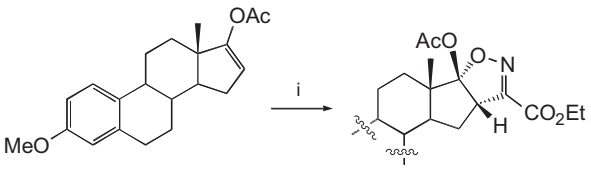
Scheme 9



33 **34** **35** **38** **36** **37**

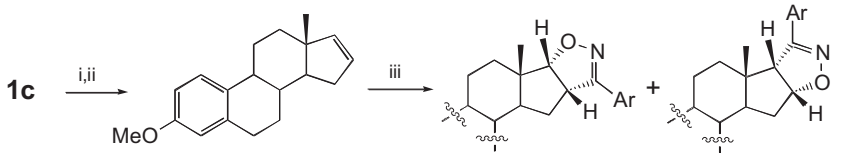
i, (a) Na^{t}BuO, CS_2, THF; (b) MeI; ii, guanidinium nitrate, NaOR, ROH, refl.; iii, $N_2H_4 \cdot H_2O$,EtOH, refl.; iv, $NH_2OH \cdot HCl$, NaOEt, EtOH, refl.; v, (a.) indole-3-acetonitrile, NaH, DMF; (b.) *p*-TsOH, benzene, refl.; vi, (a.) 2-methylindole, *n*-BuLi; (b.) CO_2; (c.)^{t} BuLi; vii. H_3PO_4, 110°C.[22,23a,23b]

Scheme 10



39 **40**

i, ethyl chlorohydroxyliminoacetate, Et_3N, ether.[24]



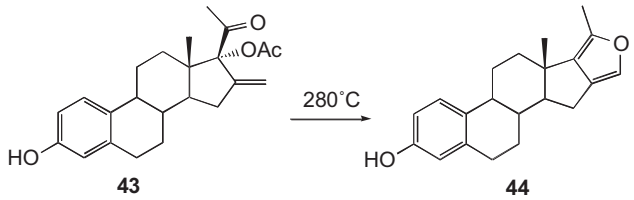
41 **42a** **42b**

i, p-$TsNHNH_2$, HOAc, CH_2Cl_2; ii, MeLi, ether, THF; iii, RC=N(Cl)OH, where R = Ph, thieynl, *p*-NO_2-phenyl.[25]

Scheme 11

17-*O*-acetyl-3-*O*-methylestra-1,3,5(10),16-tetraene-3,17-diol and ethyl chlorohydroxyiminoacetate in the presence of triethylamine as a base (Scheme 11).[24] The reaction is regio- and stereoselective. Arylnitrile oxides have been added to 3-*O*-methylestra-1,3,5(10),16-tetraene (**41**), which was obtained from estrone **1c** by the Shapiro reaction via estrone-17-tosylhydrazone. For the most part, the [3 + 2] cycloaddition of **41** with the arylnitrile oxides gives both regioisomers **42a** and **42b**, where again the newly formed isoxazoline is joined to the steroid from the α-face (Scheme 11).[25]

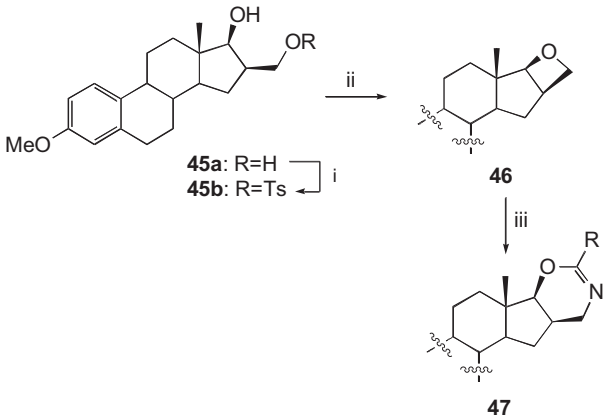
A 2'-methylfuran system has been fused to ring D of estrone. Thus estra-1,3,5(10)-triene-[17,16-c]-2'-methylfuran **44** has been synthesised through pyrolysis of **43** (Scheme 12).[26]



43 **44**

See ref. 26.

Scheme 12



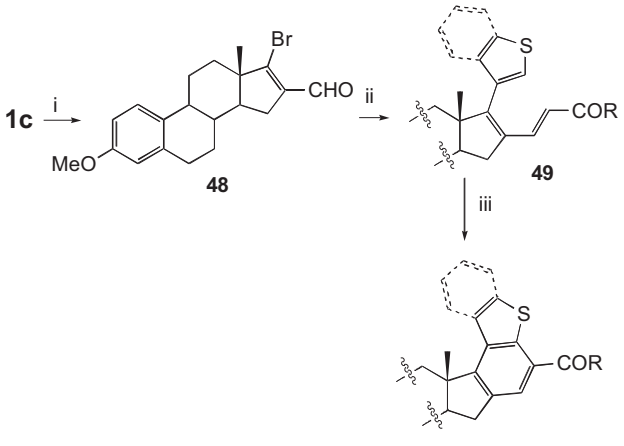
i, *p*-TsCl, py; ii, NaOMe, MeOH, reflux; iii, RCN, HBF_4, Et_2O.[27]

Scheme 13

Estrane oxetanes **46**, which are easily prepared from the *p*-toluenesulfonate **45b** of 16β-hydroxymethyl-3-*O*-methylestra-1,3,5(10)-triene-3,17β-diol (**45a**) with base, have been found to be suitable precursors for the preparation of dihydro-oxazine-fused estranes via Ritter reaction.[27] Compound **46**, when reacted with aliphatic or aromatic nitriles in the presence of HBF_4 in ether, gives the dihydro-oxazine **47** (Scheme 13). An X-ray crystal structural analysis has been carried out of compound **47a**.[28]

Benzothienyl- and dibenzothienyl moities can be annelated to ring D of estranes by cyclisation of trienes **49**. These are prepared from the Arnold-Vilsmeier product, β-bromo-α,β-enaldehyde **48**,[29] by Wittig olefination with conjugated phosphoranes and concomitant Suzuki–Miyaura coupling in one pot.[30] The triene cyclisation can be achieved at 135°C in diphenyl ether to give **50** (Scheme 14).[30]

Alternatively, dibenzothieno-annelated estranes can also be prepared via ruthenium catalysed hetarene-ene-yne cyclisation of **55**. Two routes are known to **53**, a key intermediate in the synthesis of the hetarene-ene-ynes **55**. The first made use of **48**, which was subjected to a Suzuki–Miyaura reaction (Scheme 15). In the second route, **2**, was converted to its *tert*-butyl ether **51**, and reacted with the α-lithiated

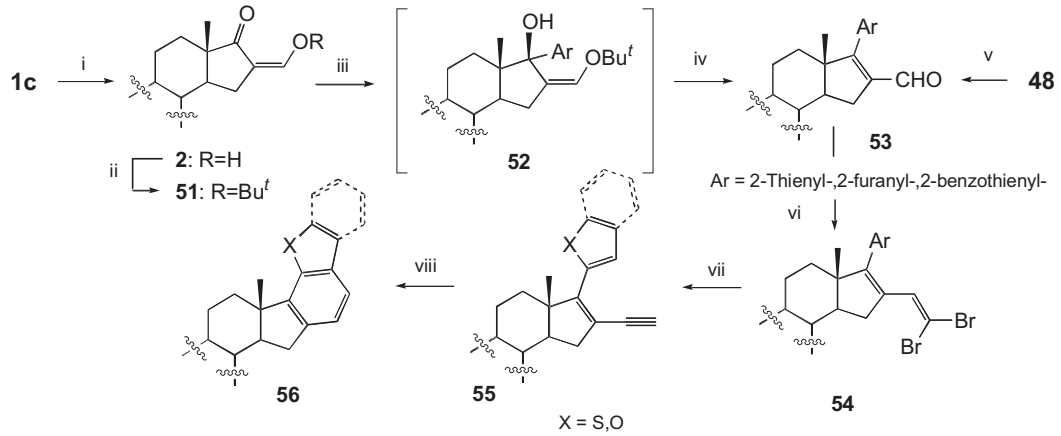


48

i, BBr_3, DMF, $CHCl_3$; ii, Ph_3P=CHCOR, 

, $Pd(PPh_3)_4$, DME, aq. Na_2CO_3; iii, diphenyl ether, 135˚C.[30]

Scheme 14



i, HCO_2Et, NaOMe, DMF; ii, *p*-TsOH, Bu^{t}OH, benzene; iii, *n*-BuLi, Ar-Br or furan, THF or ether; iv, *p*-TsOH; v, Ar-B(OH)$_2$, DME, Na_2CO_3, $Pd(PPh_3)_4$; vi, CBr_4, PPh_3; vii, *n*-BuLi or TBAF; viii, Ru(*p*-cymene)Cl_2PPh_3, NH_4PF_6, CH_2Cl_2 or Ru/CNF, $ClCH_2CH_2Cl$;[31]

Scheme 15

heterocycle to give the carbinol **52**.[31] This was immediately hydrolysed with *p*-TsOH to yield **53**. This was converted to the dibromoethenyl derivative **54**, which then underwent dehydrobromination to **55**. Compound **55** can be cyclised by using Ru(*p*-cymene)Cl_2PPh_3 as a catalyst under homogenous reaction conditions (Scheme 15).[31] The cyclisation has also been shown to proceed with ruthenium immobilised on carbon materials, such as on carbon nanofibres, under heterogenous reaction conditions. The reaction sequence can also be carried out to produce benzofurano- and benzothieno annelated estranes (Scheme 15).[31]

In this review we have described the synthesis of a range of heterocyclic steroids with a diverse and potentially useful biological activity.

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