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[A035]

Areno annelated Estranes by Intermolecular Cycloaddition

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Keywords: Synthesis, Estranes, Ring annelation, Cycloaddition

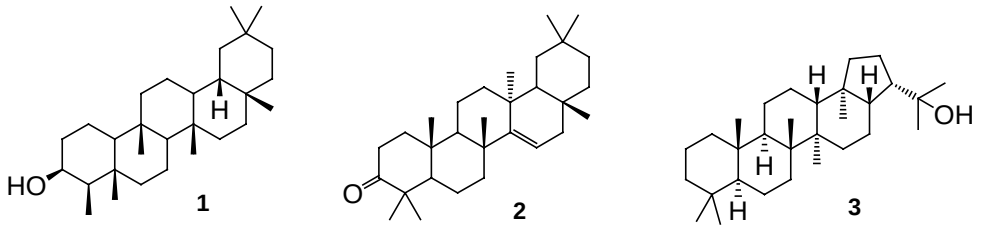


Figure 1

Introduction. Pentacyclic triterpenoids are naturally occuring compounds. Typical examples are taxarenes, friedelanes (of the baccharane group) hopanes of the lupine group (Figure 1). More recently, pentacyclic triterpenoids with an aromatic *E*-ring have been isolated from the Palauan sponge *Haliclona* (aka *Adocia*) (Figure 2).[1,2] These have been found to have inhibitory activity of the reverse transcriptase of the human

immunodeficiency virus and of kinesin motor proteins.[3]

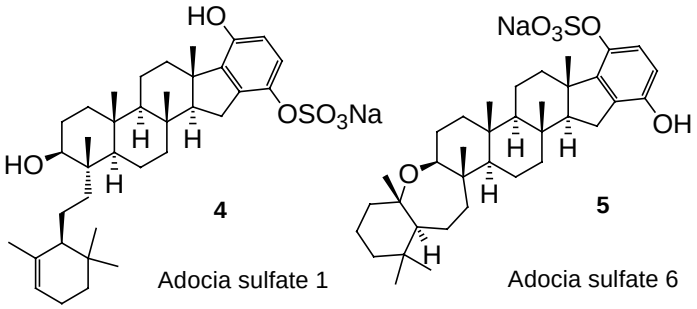
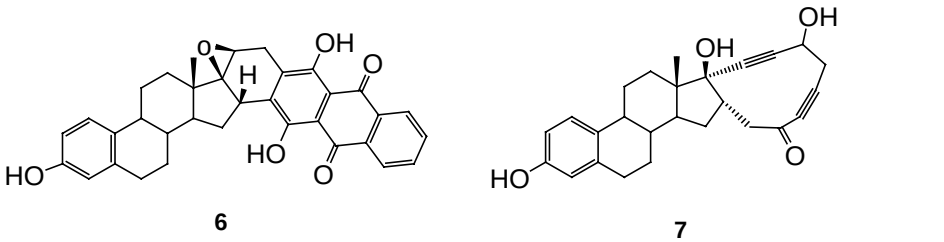


Figure 2 [Kalaitzis 1999, see also Blackburn 2000]

Synthetic steroid derived pentacyclic molecules with the ring annelation at C16/C17 have been prepared and tested for their anti-inflammatory activity (azasteroidal [16,17-*c*]pyrazoles,[4] cyclohexeno annelated steroids[5]) and their inhibitory activity towards 17β-dehydrogenase ([16,17-*c*]pyrazoloestrane)[6]. Annelation at C16/C17 has also been used to prepare hybrids of steroids and organic moieties of known biological activity (Figure 3).[7]

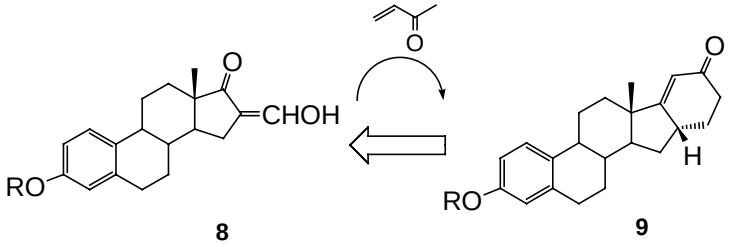


Estrarubicin [de Riccardis 1998] Estradiol diyne hybrid [Jones 2001]

Figure 3

Furthermore, certain 7α and 11β-substituted pentacyclic estranes show a good binding

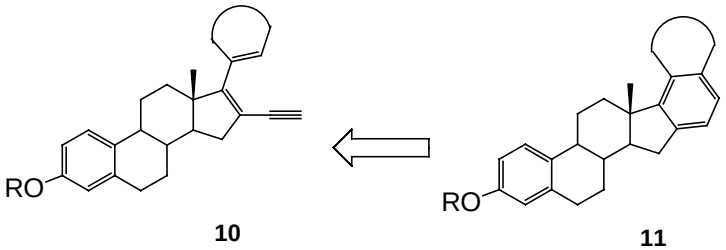
affinity to the human estradiol and progesterone receptors and derivatives can act as inhibitors of oesteoporosis.[8] In our efforts to evaluate estrane derived pentacyclic compounds with the annelation at C16/C17 as to their binding to the estrogen receptor *ER*α, in order to develop new therapeutic agents as well as diagnostica for breast cancer, we have synthesized a larger number of *E*-ring annelated estranes.[9-11]



8 **9**

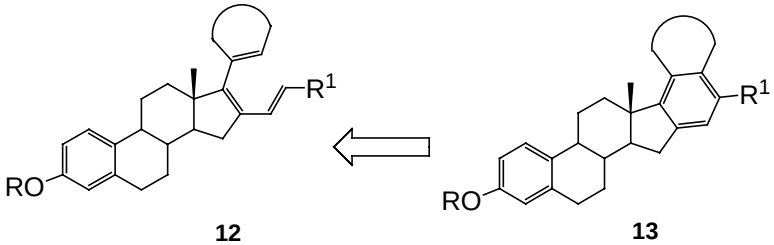
[Allison 1967]

Scheme 1 Ring Fusion to Estranes via Robinson Annelation



10 **11**

[Watanabe, Thiemann et al., ref. 10]



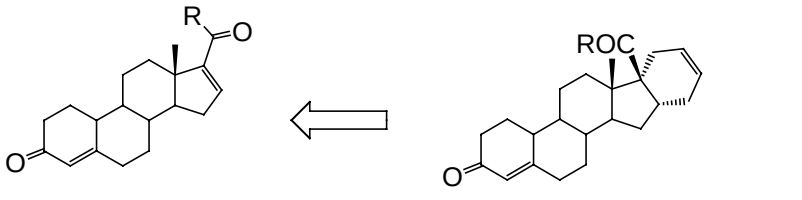
12 **13**

[Watanabe, Thiemann et al., ref. 11]

Scheme 2 Ring Annelation of Estranes via Intramolecular cyclization reactions

A number of strategies for the construction of alicyclic and aromatic ring annelations of

steroids have been forwarded., among them Robinson annelation of 16-formyl-17-ketosteroids[12] (Scheme 1) and other polar cyclocondensation reactions.[13] Recently, the authors themselves have communicated steroidal ring annelation by intramolecular methods, namely be triene cyclization reaction[9a,b,11] and by diene-yne cyclization (Scheme 2).[10]



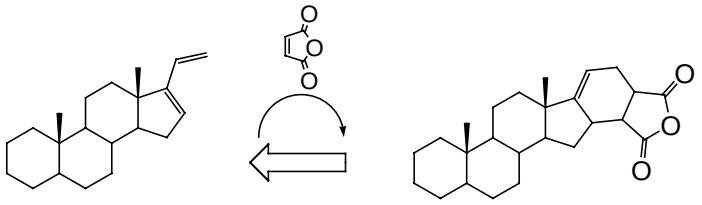
14 **15**

[Kasch 1990, Ponsold 1987]

Scheme 3 Steroids as dienophiles in [4 + 2]-cycloaddition reactions

As a further approach, the [4 + 2] cycloaddition reaction has been used. Here, initial reports showed the use of the steroid as the dienophile, where steroids with an unsaturation at C16/C17 were employed (Scheme 3).[14] It must be noted that in general estra-1,3,5(10),16-tetraenes are quite inreactive as dienes and only an electron withdrawing substituent at the olefinic moiety C16/C17, such as in **14** (Scheme 3), makes them attractive components in DA reactions, where even then Lewis acids have to be utilized to further activate the steroid as ene-component. Only more recently, steroidal dienes have also been subjected to ring annelation.[7a,15] The dienes used are

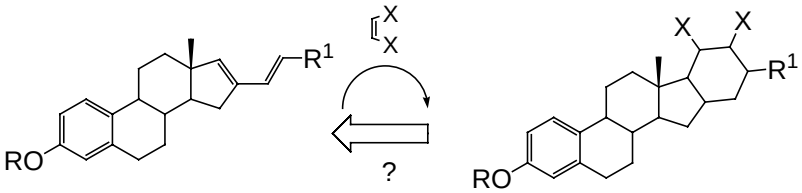
17-vinyl substituted steroidal 16,17-enes (Scheme 4). In this contribution, the authors communicate a ring annelation reaction of estrone derived steroids by [4+2]-cycloaddition of 16-vinyl substituted estra-1,3,5(10),16-tetraenes.



16 **17**

[Skoda-Foeldes 1996, 1997]

17-Vinylsteroids as dienes in D-A reactions



18 **19**

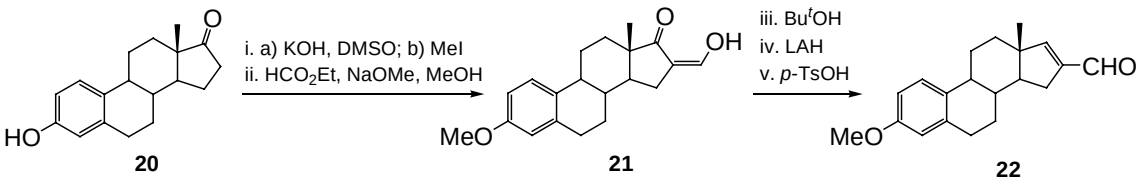
16-Vinylestranes as dienes in D-A reactions
= content of the present communication

Scheme 4

Results and Discussion

The best starting material for 17-non-substituted 16-vinylestra-1,3,5(10),16-tetraenes was deemed to be the known[16] 3-*O*-methyl-16-formylestra-1,3,5(10),16-tetraen-3-ol (**22**). Commercially available estrone (**20**) was protected at C3 as a methyl ether [a] KOH, DMSO; b] MeI[17]]. Reaction of 3-*O*-methylestrone with ethyl formate under basic

conditions provides after work-up 16-formylestrone **21**, which is a common precursor for a number of ring annelation procedures (see also Scheme 1). In most solvents, **21** exists in its tautomeric hydroxy-enol form. The enol can be alkylated and transformed to the corresponding 3-*O*-methyl-16-(*tert*-butoxymethylene)estra-1,3,5(10)-trien-3-ol -17-one. The *tert*-butyl group is sufficiently bulky to force the subsequent reduction step ($LiAlH_4$) to occur 1,2 rather than 1,4. Hydrolysis of the intermediately formed 3-*O*-methyl-16-(*tert*-butoxymethylene)estra-1,3,5(10)-trien-3,17-diol (*p*-TsOH) results in the desired aldehyde **22**.

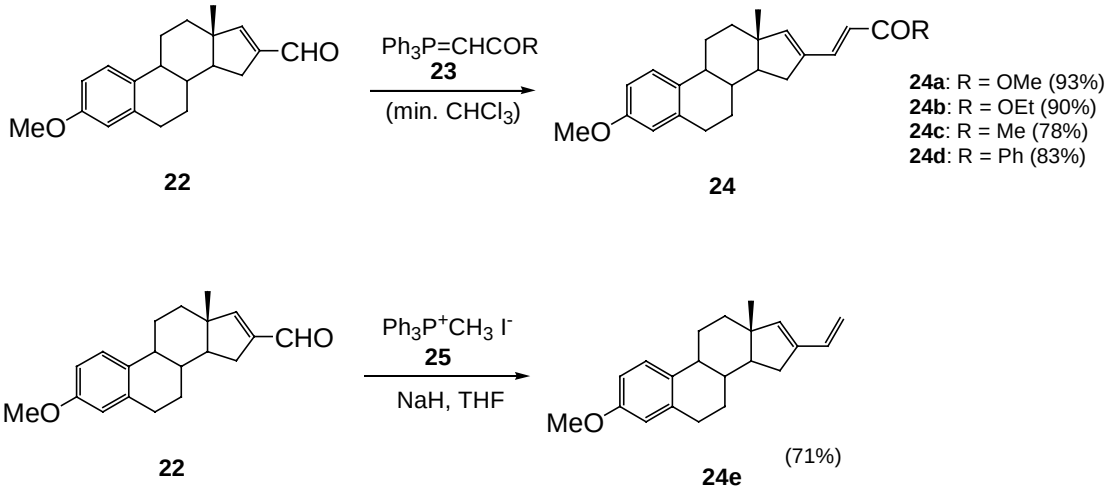


Synthetic route to 3-*O*-Methyl-16-formylestra-1,3,5(10),16-tetraen-3-ol (**22**)

Scheme 5

The introduction of the (substituted) vinyl functionality at C-16 was to proceed via Wittig olefination reaction. Initially, aldehyde **22** was reacted with a number of stabilized phosphoranes according to a method developed recently.[18] The phosphoranes included alkoxycarbonylmethylidene-, acetylmethylidene-, and benzoyl-methylidenetriphenylphosphorane. It could be shown that all of these phosphoranes

react with most aldehydes in a minimum amount of solvent (for carbaldehydes with a melting point above 70ºC) or under solventless conditions (for carbaldehydes that are liquids or possess a melting point that is below 70ºC). No special precautions need to be used, where the reaction mixture is simply heated to 100ºC. Although the authors often deaerate the sample before the reaction, the transformation can also be carried out in the presence of air. No precautions have to be taken to dry the sample. In the case of solid **22**, a minimum amount of chloroform was used to help mix phosphorane and steroidal aldehyde prior to the reaction. After the olefination had been performed (1h – 90 min), the crude mixture was subjected to a quick column filtration to give the Wittig products **24** (Scheme 6).



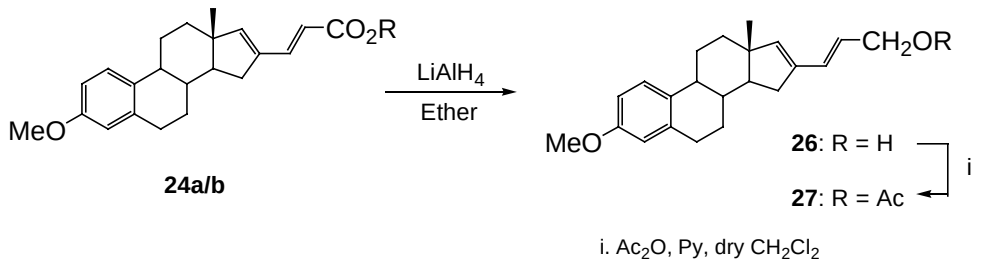
Preparation of 16-vinylestra-1,3,5(10),16-tetraenes by Wittig olefination of steroidal aldehyde **22**

Scheme 6

In the case of the preparation of the unsubstituted 3-*O*-methyl-16-vinylestra-

1,3,5(10),16-tetraen-3-ol (**24e**), where steroidal aldehyde **22** was reacted with the more reactive methylidenetriphenylphosphorane, a mixture of aldehyde, phosphonium salt **25** and NaH as base were reacted under an inert atmosphere in dry THF as solvent. 3-*O*-Methyl-16-vinylestra-1,3,5(10),16-tetraen-3-ol **24e** had been prepared earlier by reductive elimination of a steroidal diol monoester.[19]

The push-pull dienes **24** do not undergo Diels-Alder type reactions with ease, although a limted number of DA reactions with donor-acceptor substituted dienes are known.[20] Nevertheless, **24d** could be subjected to DA reaction with *N*-phenylmaleimide with some success, but this will be described elsewhere. Rather, Wittig products **24** were reduced to the corresponding alcohols. As an example, **24a** was reacted with $LiAlH_4$ in ether to give the hydroxymethyl- substituted steroidal diene **26**. The hydroxy group in **26** was protected with the acetyl group (Ac_2O, py, CH_2Cl_2 to give **27** (Scheme 7).



24a/b

Scheme 7 Preparation of diene **27**

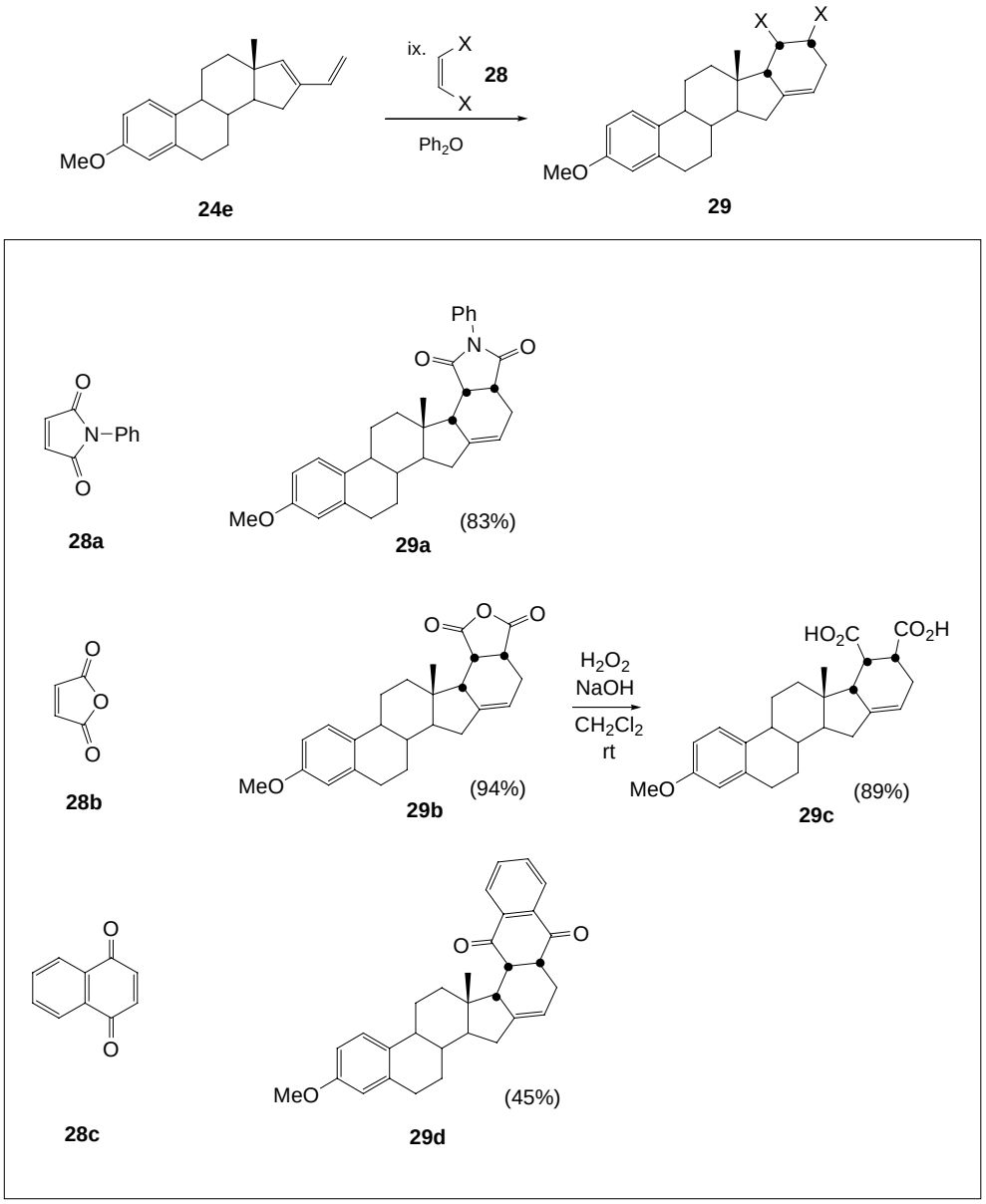
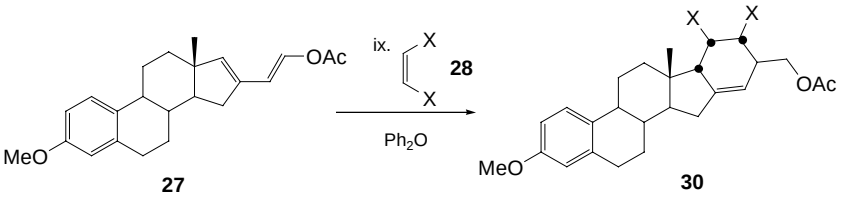


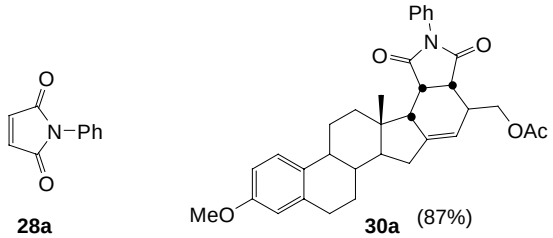
Table 1 DA reaction of steroidal diene 16-vinylestra-1,3,5(10),16-tetraen-3-ol **24e**

With **24e** and **27** in hand, two viable 16-vinylestra-1,3,5(10),16-tetraenes were available as potential steroidal dienes. Indeed, both **24e** and **27** could be reacted with a number of doubly activated (two electron-withdrawing substituents) alkenes (Tables 1 and 2) to produce cycloadducts in excellent yield. The cycloaddition reactions were found to be stereoselective except for the reaction of **27** with maleic anhydride, which produced a

stereoisomeric mixture (9:1).

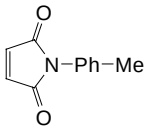


27 **30**

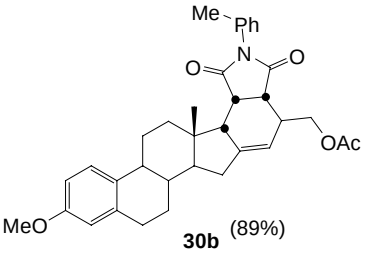


28a

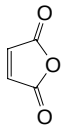
30a (87%)



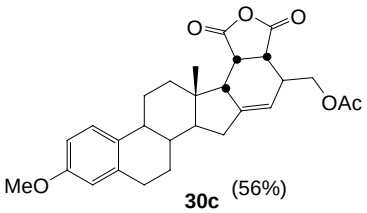
28d



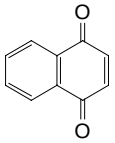
30b (89%)



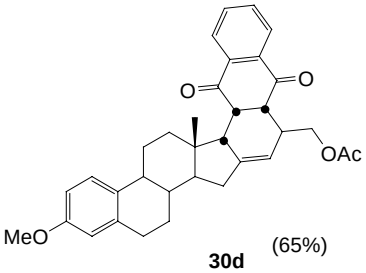
28b



30c (56%)



28c



30d (65%)

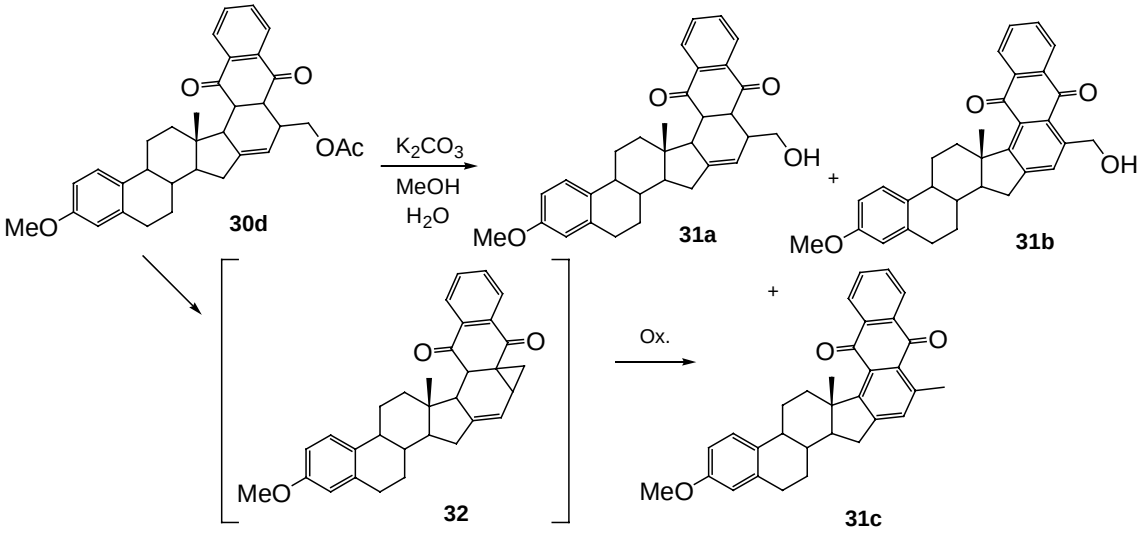
Table 2 DA reaction of steroidal diene **27**

For the most part, the cycloadducts are purified by column chromatography, in the case of the reaction of either **24e** or **27** with maleic anhydride, the correspnoding cycloadducts **29b** and **30c** can be obtained by direct precipitation from the reaction mixture by addition of ether/hexane.

In the cycloaddition, the authors used diphenyl ether as solvent. Diphenyl ether has been found to be superior[21] to decaline in many of the reactions performed at high temperatures (140 – 180ºC). Diphenyl ether can be completely separated from the reaction mixture by eluting the mixture off a column of silica gel with hexane as eluant. Diphenyl ether solubilizes many compounds much better than decaline and thus much less polymerisation occurs due to the reaction of starting material aggregates often found in decaline. A drawback of diphenyl ether that it is an irritant substance.

It is interesting to note that base catalysed hydrolysis of the acetoxy group in the cycloadducts leads to partial loss of the hydroxy function altogether. An example is shown in Scheme 8. In fact, the aim of the hydrolysis was to transform the acetyloxy group into a better leaving group (eg., mesylate) in order to induce an intramolecular substitution with a concomittant ring closure to the spirocyclopropane function. The spirocyclopropane function is known to be associated with biological activity as spirocyclopropane containing molecules can alkylate specific functionalities in

biomolecules leading to their inhibition. The occurrence of the methyl substituent in product **31c** may mean that surprisingly also under the conditions of the hydrolysis a ring closure occurred leading to possible intermediate **32**. An analogous methyl substituted product was found in the hydrolysis of **30a**.



Scheme 8 Surprising loss of the acetyloxy function during base catalysed deprotection of the steroidal acetate

Conclusion.

With steroidal dienes **24e** and **27** it could be shown that ring annelation at positions C16/C17 of ring D can be achieved by cycloaddition of 16-vinylestra-1,3,5(10),16-tetraenes with doubly activated dienophiles, where diphenyl ether is a beneficial solvent for the reaction. The scope of the reaction and further transformations of the cycloadducts, especially in view of spirocyclopropane containing compounds, is currently under investigation.

Experimental

General remarks: Melting points were measured on a Yanaco microscopic hotstage and are uncorrected. Infrared spectra were measured with JASCO IR-700 and Nippon Denshi JIR-AQ2OM instruments. ^{1}H and ^{13}C NMR spectra were recorded with a JEOL EX-270 spectrometer (^{1}H at 270 MHz, ^{13}C at 67.8 MHz). In some cases, a JEOL Lambda 400 FT-NMR spectrometer (^{1}H at 395.7 MHz, ^{13}C at 99.45 MHz) or a JEOL 600 (^{1}H at 600.2 MHz, ^{13}C at 150.91 MHz) were used as noted in the experimental section for the compounds involved. The chemical shifts are relative to TMS (solvent $CDCl_3$, unless otherwise noted). Mass spectra were measured with a JMS-01-SG-2 spectrometer. Column chromatography was carried out on Wakogel 300. For the heating experiments, an electric oven, EYELA NDO-450N, preheated at 100 ºC, was used.

Estrone (WAKO) was acquired commercially. 3-*O*-Methylestrone was synthesized (KOH, DMSO, MeI) according to Johnstone and Rose.[17] Although commercially available, phosphoranes **23**[23] as well as methyltriphenylphosphonium iodide (**25**)[24] were prepared by standard procedures.

Selected synthetic procedures and physical and spectroscopic data of the new

compounds:

Typical procedure of a Wittig olefination of a steroidal carbaldehyde with a stabilized phosphorane with a minimal amount of solvent:

3-*O*-Methyl-16-(*E*)-ethoxycarbonylethenylestra-1,3,5(10),16-tetraen-3-ol (**24b**). – A mixture of 3-*O*-methyl-16-formylestra-1,3,5(10),16-tetraen-3-ol (**22**) (296 mg, 1.0 mmol), ethoxycarbonylmethylidenetriphenylphosphorane (1.5 mmol) in $CHCl_3$ (0.5 mL) was left to react in an electric oven at 100ºC for 1h. Direct column chromatography of the reaction mixture on silica gel (hexane/$CHCl_3$/ether 6:1:1) gave **24b** (331 mg, 90%) as a colorless solid, mp. 111ºC; IR (KBr) ν 2928, 2846, 1718, 1634, 1612, 1503, 1308, 1251, 1171, 1003, 841, 826 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.84 (s, 3H, CH_3), 1.30 (t, 3H, ^3J 7.3 Hz), 1.39 – 2.45 (m, 11H), 2.89 (m, 2H), 3.78 (s, 3H, OCH_3), 4.22 (q, 2H, ^3J 7.3 Hz, $OC\underline{H}_2$), 5.79 (d, 1H, ^3J 15.7 Hz), 6.29 (s, 1H), 6.64 (d, 1H, ^4J 2.7 Hz), 6.71 (dd, 1H, ^3J 8.9 Hz, ^4J 2.7 Hz), 7.18 (d, 1H, ^3J 8.9 Hz), 7.44 (d, 1H, ^3J 15.7 Hz);^{13}C NMR (67.8 MHz, $CDCl_3$, DEPT 90, DEPT 135) δ 14.31 (+, CH_3), 16.73 (+, CH_3), 26.36 (-), 27.81 (-), 29.68 (-), 30.61 (-), 35.35 (-), 37.34 (+, CH), 44.28 (+, CH), 46.98 (C_{quat}), 54.74 (+,CH), 55.19 (+, OCH_3), 60.19 (-), 111.44 (+, CH), 113.85 (+, CH), 118.03 (+, CH), 125.95 (+, CH), 132.68 (C_{quat}), 137.82 (C_{quat}), 140.24 (C_{quat}), 141.76 (+, CH), 151.58 (+, CH), 157.49 (C_{quat}) , 167.38 (C_{quat}, CO); MS (FAB, 3-nitrobenzyl

alcohol) *m/z* (%) 366 (M^+, 100). HRMS Found: 366.2200. Calcd. for $C_{24}H_{30}O_3$: 366.2195. Calcd. for $C_{24}H_{30}O_3$: C, 78.65; H, 8.25%. Found C, 78.71; H, 8.29%.

Analogous reaction procedures gave the following products:

3-*O*-Methyl-16-(*E*)-methoxycarbonylethenylestra-1,3,5(10),16-tetraen-3-ol (**24a**). – colorless solid, mp. 141ºC; IR (KBr) ν 2918, 1700, 1624, 1257, 1039 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.85 (s, 3H, CH_3), 1.38 – 2.45 (m, 11H), 2.89 (m, 2H), 3.75 (s, 3H, $CO_2C\underline{H}_3$), 3.78 (s, 3H, OCH_3), 5.79 (d, 1H, ^3J 15.7 Hz), 6.30 (s, 1H), 6.64 (d, 1H, ^4J 2.7 Hz), 6.71 (dd, 1H, ^3J 8.6 Hz, ^4J 2.7 Hz), 7.18 (d, 1H, ^3J 8.6 Hz), 7.45 (d, 1H, ^3J 15.7 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 16.73, 26.38, 27.83, 29.69, 30.62, 35.37, 37.38, 44.31, 47.02, 51.46, 54.78, 55.21, 111.47, 113.89, 117.55, 125.96, 132.69, 137.83, 140.22, 142.05, 151.79, 157.53, 167.82; MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 353 (MH^+, 5). HRMS Found: 353.2125. Calcd. for $C_{23}H_{29}O_3$: 353.2117 (MH^+, FAB).

3-*O*-Methyl-16-acetylethenylestra-1,3,5(10),16-tetraen-3-ol (**24c**). - colorless solid; mp. 155ºC; IR (KBr) ν 3006, 2930, 1658, 1614, 1497, 1363, 1282, 1255, 1218, 1178, 1051, 969, 865, 810 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.86 (s, 3H, CH_3), 1.37 – 2.45 (m, 11H), 2.30 (s, 3H, CH_3), 2.90 (m, 2H), 3.78 (s, 3H, OCH_3), 6.07 (d, 1H, ^3J 15.7 Hz),

6.38 (s, 1H), 6.65 (d, 1H, ^4J 2.7 Hz), 6.72 (dd, 1H, ^3J 8.4 Hz, ^4J 2.7 Hz), 7.19 (d, 1H, ^3J 8.4 Hz), 7.29 (d, 1H, ^3J 15.7 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 16.70, 26.34, 27.12, 27.79, 29.66, 30.60, 35.28, 37.32, 44.26, 47.14, 54.72, 55.19, 111.46, 113.82, 125.95, 127.43, 132.59, 137.82, 140.63, 140.73, 152.92, 157.47, 198.98; MS (EI, 70 eV) 336 (M^+, 100), 321 (M^+-CH_3, 33), 293 (9), 241 (12). HRMS Found: 336.2087. Calcd. for $C_{23}H_{28}O_2$: 336.2089.

3-*O*-Methyl-16-benzoylethenylestra-1,3,5(10),16-tetraen-3-ol (**24d**). – colorless solid; mp. 164ºC; IR (KBr) ν 3050, 3012, 2926, 2848, 1657, 1589, 1495, 1449, 1323, 1307, 1280, 1257, 1233, 1206, 1179, 1037, 1019, 977, 707 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (s, 3H, CH_3), 1.43 – 2.39 (m, 10H), 2.53 (dd, 1H, ^2J 14.3 Hz, ^3J 6.4 Hz), 2.91 (m, 2H), 3.78 (s, 3H, OCH_3), 6.43 (s, 1H), 6.65 (d, 1H, ^4J 2.7 Hz), 6.72 (dd, 1H, ^3J 8.6 Hz, ^4J 2.7 Hz), 6.85 (d, 1H, ^3J 15.1 Hz); 7.19 (d, 1H, ^3J 8.6 Hz), 7.45 – 7.59 (m, 3H), 7.59 (d, 1H, ^3J 15.1 Hz), 7.94 (m,. 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$, DEPT 90, DEPT 135) δ 16.71 (+, CH_3), 26.36 (-), 27.87 (-), 29.68 (-), 30.79 (-), 35.32 (-), 37.39 (+, CH), 44.29 (+, CH), 47.19 (C_{quat}), 54.78 (+, OCH_3), 55.20 (CH), 111.43 (+, CH), 113.89 (+, CH), 122.20 (+, CH), 125.98 (+, CH), 128.38 (+, CH), 128.50 (+, CH), 132.48 (+, CH), 132.66 (C_{quat}), 137.79 (C_{quat}), 139.39 (C_{quat}), 140.95 (C_{quat}), 142.08 (+, CH), 153.61 (+,

CH), 157.51 (C_{quat}), 191.09 (C_{quat}, CO); MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 399 (MH^+, 100). HRMS Found: 399.2318. Calcd. for $C_{28}H_{31}O_2$: 399.2324 (MH^+, FAB).

3-*O*-Methyl-16-(3'-hydroxyprop-1'-en-1'-yl)estra-1,3,5(10),16-tetraen-3-ol (**26**). – **24b** (331 mg, 0.9 mmol) was added slowly to a suspension of $LiAlH_4$ (30 mg, 0.8 mmol) in dry ether (10 mL). The reaction mixture was kept at reflux for 1.5 h. To the cooled solution was carefully added water (2.5 mL) and 2N aq. HCl (2 mL). Then the mixture was diluted with additional water (10 mL) and extracted with $CHCl_3$ (3 X 15 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the crude material on silica gel (ether/hexane/$CHCl_3$) gave **26** (228 mg, 78%) as a colorless solid, mp. 114ºC; IR (KBr) ν 3370 (bs), 3018, 2928, 2846, 1649, 1612, 1496, 1459, 1279, 1157, 1129, 1052, 1037, 1010, 961 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.82 (s, 3H, CH_3), 1.35 – 2.28 (m, 10H), 2.35 (m, 2H), 2.89 (m, 2H), 3.78 (s, 3H, OCH_3), 4.22 (m, 2H), 5.75 (dt, 1H, ^3J 15.7 Hz, ^3J 6.8 Hz), 5.88 (s, 1H), 6.42 (d, 1H, ^3J 15.7 Hz), 6.65 (d, 1H, ^4J 2.7 Hz), 6.71 (dd, 1H, ^3J 8.6 Hz, ^4J 2.7 Hz), 7.19 (d, 1H, ^3J 8.6 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 17.06, 26.46, 27.87, 29.74, 30.98, 35.80, 37.37, 44.40, 46.24, 54.91, 55.19, 63.77, 111.37, 113.82, 125.97, 128.14, 129.37, 132.94, 137.91, 140.73, 143.20, 157.36; MS (EI, 70 eV) *m/z* (%) 324 (M^+, 100),

309 (25), 293 (44), 227 (23), 213 (36), 173 (80). HRMS Found: 324.2085. Calcd. for $C_{22}H_{28}O_2$: 324.2089.

3-*O*-Methyl-16-(3'-acetoxyprop-1'-en-1'-yl)estra-1,3,5(10),16-tetraen-3-ol (**27**). – To a solution of **26** (163 mg, 0.5 mmol) in dry CH_2Cl_2 (5 mL) was given successively dry pyridine (197 mg, 2.5 mmol) and acetic anhydride (255 mg, 2.5 mmol). The resulting mixture was stirred at rt for 10h. Thereafter, the solution was transferred directly to a column and separated on silica gel (hexane / $CHCl_3$ / ether 3 : 1 :1) to give **27** (170 mg, 93%) as an oil. IR (KBr) ν 2924, 1740, 1611, 1501, 1238, 1037 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.82 (s, 3H, CH_3), 1.30 – 2.45 (m, 11H), 2.08 (s, 3H, $COC\underline{H}_3$), 2.89 (m, 2H), 3.78 (s, 3H, OCH_3), 4.62 (d, 2H, ^3J 6.8 Hz), 5.70 (dt, 1H, ^3J 15.6 Hz, ^3J 6.8 Hz), 5.92 (s, 1H), 6.46 (d, 1H, ^3J 15.6 Hz), 6.65 (d, 1H, ^4J 2.7 Hz), 6.71 (dd, 1H, ^3J 8.6 Hz, ^4J 2.7 Hz), 7.19 (d, 1H, ^3J 8.6 Hz), ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 17.00, 21.02, 26.44, 27.85, 29.72, 30.89, 35.74, 37.35, 44.38, 46.30, 54.91, 55.19, 65.20. 111.37, 113.83, 122.71, 125.96, 132.23, 132.90, 137.89, 140.49, 144.20, 157.42, 170.80; MS (EI, 70 eV) *m/z* (%) 366 (M^+, 46), 173 (100). HRMS Found: 366.2201. Calcd. for $C_{24}H_{30}O_3$: 366.2195.

3-*O*-Methyl-*N*-tolyl-6-acetoxymethyl-1,8-diketoisoindolino(3,4:17,16)estra-1,3,5(10),1

6(17*H*)-tetraen-3-ol (**30b**) – typical example of a DA-reaction of a 16-vinylestra-1,3,5(10),16-tetraen-3-ol. – A solution of **27** (135 mg, 0.37 mmol) and *N*-tolylmaleimide (**28d**) (120 mg, 0.64 mmol) in diphenylether (800 mg, 4.7 mmol) was kept at 135ºC for 14h. Thereafter the solution was transferred directly to a column and separated over silica gel (initially hexane to elute the diphenyl ether; then hexane/$CHCl_3$/ether 1:1:1) to give **30b** (116 mg, 89%) as a colorless solid; mp. 234ºC; IR (KBr) ν 3034, 2918, 2860, 1742, 1704, 1513, 1500, 1394, 1226, 1211, 1181, 1036, 840, 812 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.95 (s, 3H, CH_3), 1.33 – 2.90 (m, 15H), 2.08 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.36 (dd, 1H, ^3J 8.4 Hz, ^3J 7.3 Hz), 3.51 (dd, 1H, ^3J 8.4 Hz, ^3J 5.4 Hz), 3.76 (s, 3H, OCH_3), 4.42 (dd, 1H, ^2J 11.4 Hz, ^3J 7.9 Hz), 4.67 (dd, 1H, ^2J 11.4 Hz, ^3J 6.5 Hz), 5.62 (m, 1H), 6.61 (d, 1H, ^4J 2.7 Hz), 6.69 (dd, 1H, ^3J 8.4 Hz, ^4J 2.7 Hz), 7.01 (d, 2H, ^3J 8.4 Hz), 7.21 (d, 1H, ^3J 8.4 Hz), 7.23 (d, 2H, ^3J 8.4 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$, DEPT 90, DEPT 135) δ 20.99 (+, CH_3), 21.17 (+, CH_3), 22.50 (+, CH_3), 26.83 (-), 27.97 (-), 29.84 (-), 31.15 (-), 31.85 (-), 37,15 (+, CH), 39.01 (+, CH), 42.71 (+, CH), 42.92 (+, CH), 42.97 (C_{quat}), 49.28 (+, CH), 53.57 (+, CH), 55.14 (+, OCH_3), 64.59 (-), 111.38 (+, CH), 113.69 (+, CH), 118.51 (+, CH), 126.34 (2C, +, CH), 126.40 (C_{quat}), 129.27 (+, CH), 129.76 (2C, +, CH), 132.93 (C_{quat}), 137.99 (C_{quat}), 138.86 (C_{quat}), 149.02 (C_{quat}), 157.30 (C_{quat}, CO), 175.76 (C_{quat}, CO), 177.16

(C_{quat}, CO); MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 554 (MH^+, 25), 494 (21). HRMS Found: 553.2823. Calcd. for $C_{35}H_{39}O_5N$: 553.2828. Calcd. for $C_{35}H_{39}NO_5$: C, 75.92; H, 7.10; N 2.53%. Found C, 75.67; H, 7.06; N 2.52%.

Typical products of the base catalysed hydrolysis of the acetates:

3-*O*-Methyl-hydroxymethylanthraquinoestra-1,3,5(10),16-tetraen-3-ol **31b**; pale yellow solid, mp. 141ºC; IR (KBr) ν 3430 (bs, OH), 2924, 1672, 1500, 1271, 1063, 1036, 722 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.21 – 2.97 (m, 13H), 1.27 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 3.98 (t, 1H), 4.78 (m, 2H), 6.67 (d, 1H, ^4J 2.7 Hz), 6.75 (dd, 1H, ^3J 8.6 Hz, ^4J 2.7 Hz), 7.24 (d, 1H, ^3J 8.6 Hz), 7.69 (s, 1H), 7.77 (m, 2H), 8.18 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.81, 26.88, 27.80, 29.70, 32.61, 33.35, 37.70, 43.77, 49.22, 55.21, 56.77, 65.62, 111.52, 113.81, 126.11, 126.38, 126.77, 131.22, 132.27, 132.51, 132.69, 133.53, 133.83, 133.94, 134.46, 137.67, 142.65, 152.71, 155.92, 157.54, 185.55, 186.78; MS (FAB, 3-nitrobenzyl alcohol) m/z (%) 479 (MH^+, 1.4). 478 (M^+, 0.6). HRMS Found: 478.2147. Calcd. for $C_{32}H_{30}O_4$: 478.2144.

3-*O*-Methyl-methylanthraquinoestra-1,3,5(10),16-tetraen-3-ol **31c**; IR (KBr) ν 2918, 1666, 1592, 1497, 1343, 1254, 1153, 1036, 907, 725 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$)

δ 1.23 – 2.97 (m, 13H), 1.34 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.67 (d, 1H, ^4J 2.7 Hz), 6.73 (dd, 1H, ^3J 8.6 Hz, ^4J 2.7 Hz), 7.25 (d, 1H, ^3J 8.6 Hz), 7.44 (s, 1H), 7.73 (m, 2H), 8.17 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.91, 24.13, 26.73, 27.84, 29.75, 32.40, 33.42, 37.73, 43.84, 49.02, 55.21, 56.86, 111.50, 113.83, 126.05, 126.14, 126.56, 130.68, 132.45, 132.64, 133.24, 133.35, 133.94, 134.39, 134.51, 137.70, 141.03, 151.20, 154.14, 157.51, 185.53, 186.20; MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 463 (MH^+, 1.4), 462 (M^+, 1.2). HRMS Found: 462.2203. Calcd. for $C_{32}H_{30}O_3$: 462.2195.

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