A series of 7-ω-carboxamidoalkyl-substituted estra-1,3,5(10),6-tetraenes

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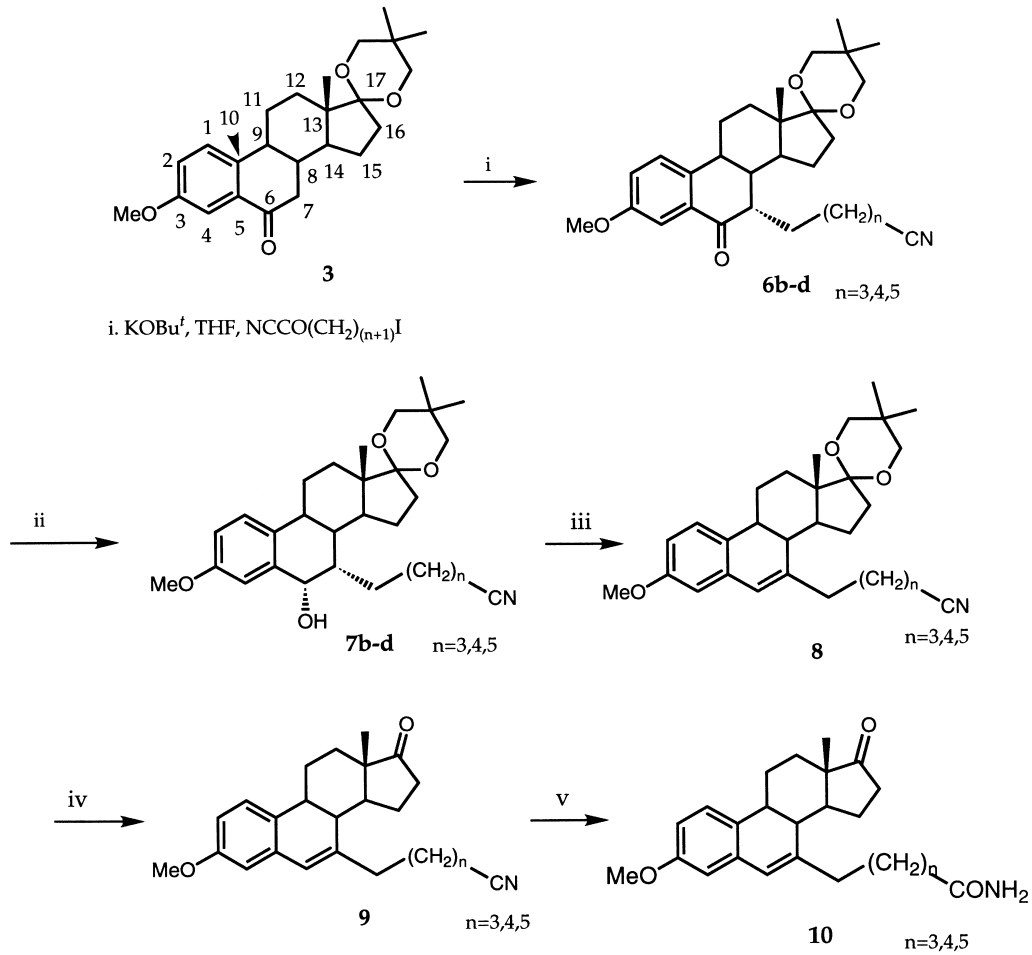
Thies Thiemann[a]*, Kuniharu Umeno[b], Eiko Inohae[b], Masao Imai[b], Yuji Shima[b] and Shuntaro Mataka[a]

[a]Institute of Advanced Material Study and [b]Graduate School of Engineering, Kyushu University, 6-1, Kasuga-koh-en, Kasuga-shi, Fukuoka 816-8580, Japan

A number of 7-ω-carboxamidoalkyl-substituted estra-1,3,5(10),6-tetraenes as potential ligands for the estrogen receptor ERα have been prepared using either a conjugate addition of α,ω-iodoalkanenitriles or a Michael addition to steroidal ketone **3** as the key step.

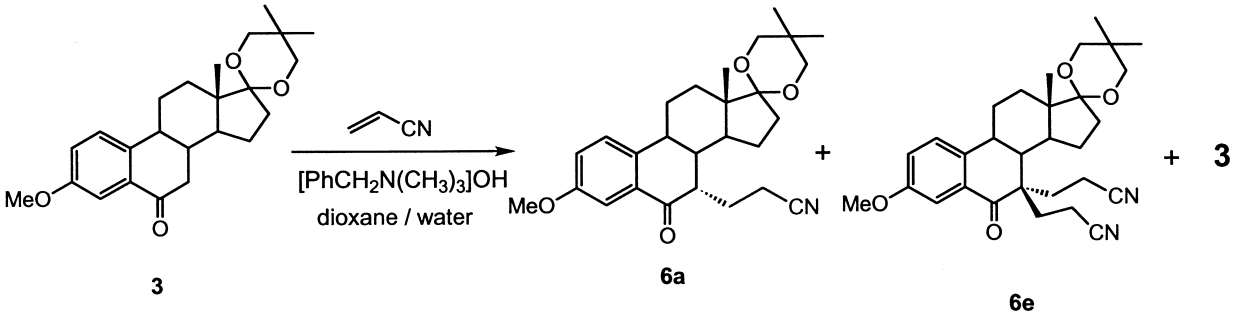
Keywords: steroids, estrogens, estrone, Shapiro reaction, conjugate addition, Wittig-olefination, phosphorane, phase transfer catalysis

The synthesis and evaluation of novel synthetic ligands for the estrogen receptor ERα has become important in the development of hormone replacement therapy as well as in the development of new radiodiagnostics for the early detection of breast cancer. A large percentage of breast cancer cells have a heightened concentration of estrogen receptor ERα and worldwide studies are underway to find a ligand that can be radiolabelled and that has a high and selective binding affinity to ERα, an acceptable metabolism (with an acceptable clearance from blood and muscle tissue) and shows a good biodistribution. A larger number of steroidal and non-steroidal compounds have been evaluated as to their suitability as ligands for ERα. It has been found that within the estradiol-series a substituent at C-7α or C-11β can be advantageous for the binding affinity of the molecule to the receptor.[3] Only a little work has been done as to the effect of structural changes within the steroidal framework on the receptor binding affinity (RBA) of the steroid. Recently, the authors have prepared



Scheme 1

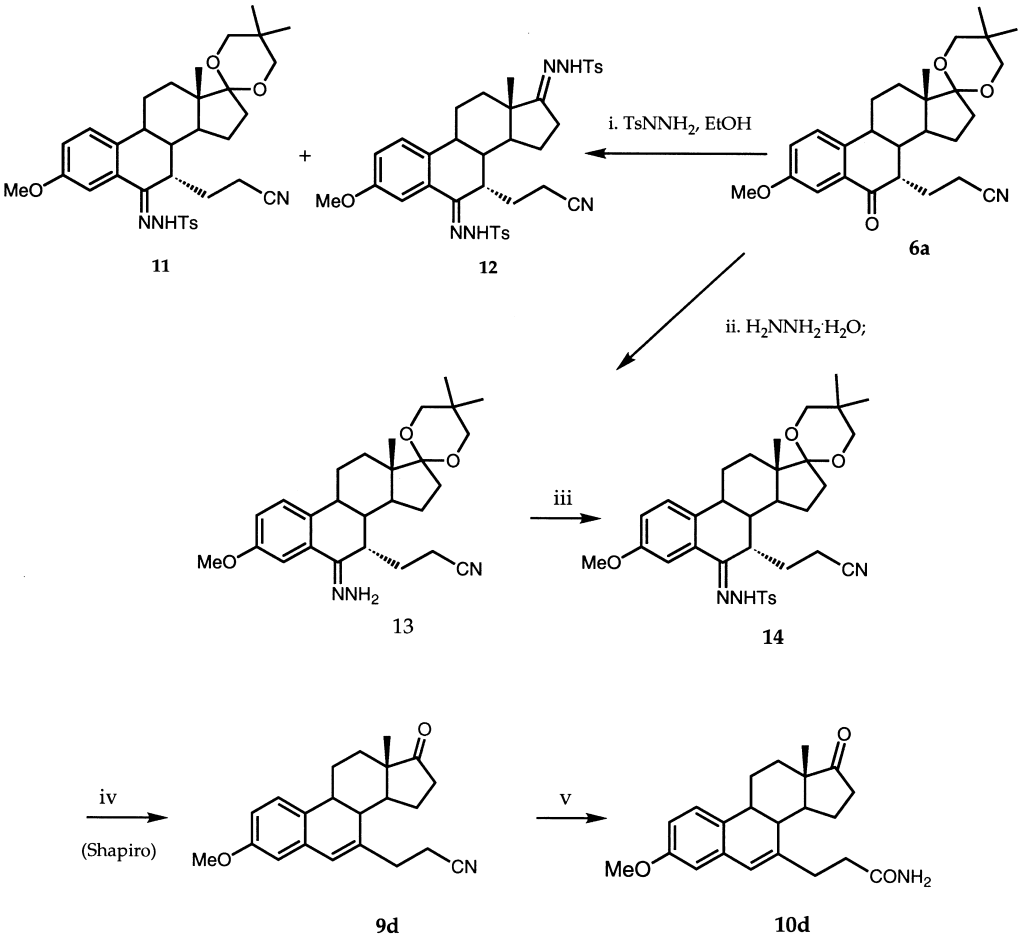
* To receive any correspondence. E-mail: thies@cm.kyushu-u.ac.jp



	−EWG	Yield of **B**	Yield of **C**	recovered Yield
a	−CN	47%	11%	33%

Scheme 2

estra-1,3,5(10),6-tetraene derivatives. RBA studies, albeit with the 3-methoxy substituted estratetraenes, have shown a promising receptor binding affinity of these molecules when compared to the respective saturated 3-methoxy substituted estra-1,3,5(10)-trienes. Biodistribution studies[5] with both [^{125}I](*E*)- and [^{125}I](*Z*)-3-methoxy-17α-iodovinylestra-1,3,5(10),6-tetraen-17β-ol in mice have provided preliminary insights into the distribution in tissues of the parent estra-1,3,5(10),6-tetraenes, but have also shown that a better target to non-target ratio in uptake of these radio-compounds is required in order to obtain a promising estrogen receptor-imaging agent. This might be achieved by C-7 substitution of the parent compounds, where amido, sulfoxy and other polar functionalities near the terminus of the C-7 chain seem preferable for a good RBA of the molecule to the receptor.



iii. *p*-TsCl, Py; iv. a.) Celite, KOBu^t; 10 mBar; 150°C; b.) *p*-TsOH, acetone, rt; v. Bu_4NHSO_4, CH_2Cl_2, H_2O_2, PTC, rt

Scheme 3

For this purpose, a number of 7-ω-carboxamidoalkyl-substituted estra-1,3,5(10),6-tetraenes have been prepared, the synthesis of which is described in this paper. While in the conjugate addition[8-10] of α,ω-iodoalkanenitriles to steroidal ketone **3**[17] 7α-(ω-cyanoalkyl)estra-1,3,5(10)-triene derivatives **6** are formed, the 7α-cyanoethyl derivative **6a** can best be synthesised by a Michael addition of the enolate of **3** to acrylonitrile under phase transfer conditions.[18] The preparation of the estra-1,3,5(10),6-tetraenes is achieved by reduction of the keto-functionality at C-6 to alcohols **7** and subsequent elimination acid catalysed. This sequence does not proceed for **7a** (*n*=1). In this case, **6a** has to be converted into a tosylhydrazone which is subjected to a Shapiro reaction. The terminal cyano group is hydrolysed to the amide function under phase transfer catalysis (PTC) in the last stage.[24] The cyano group can also be used for further chain-elongation. Reduction of the cyano group in **9d** with DIBAL-H leads to the the corresponding aldehyde **15**. Compound **15** can be subjected to a Wittig olefination with phosphoranes of type **16**[25] to form a number of different C-7 substituted estratetraenes. One such example is shown here. A facile linkage of a 7-formylalkyl substituted estra-1,3,5(10),6-tetraene to moities with cytostatic activity as by the Wittig-olefination described here may lead to the use of such a steroid as a drug delivery system for future applications in breast cancer therapy.

Techniques used: IR, ^{1}H NMR, ^{13}C NMR, elemental analysis, LRMS, HRMS, column chromatography

References: 25

Schemes: 5

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