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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 8521–8524

Novel steroid mimics directed towards the estradiol skeleton

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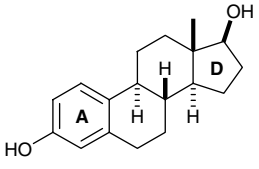
Received 2 September 2005; revised 29 September 2005; accepted 4 October 2005
Available online 19 October 2005

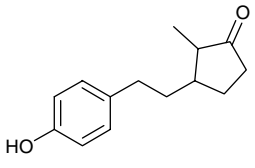
Abstract—A series of non-symmetrical tri- and tetra-substituted ureas have been prepared to mimic the rigid tetracyclic core of estradiol. Tetra-substituted ureas were prepared by a five-step protocol, involving activation and displacement of a carbonyldiimidazole adduct in 48–67% overall yield. This method was unsuccessful for tri-substituted ureas, which were prepared in 42–74% yields by an alternative four-step method, which included a one-pot 4-nitrophenyl carbamate formation/displacement sequence.

Since the first complete structural characterisation of cholesterol in 1932, steroids have distinguished themselves as a class of molecule with an unsurpassed chemical and biological significance.[1] The subsequent discovery that the cyclopentanoperhydrophenanthrene core of cholesterol was shared by a whole family of steroid hormones including the estrogens, androgens, progestins, mineralocorticoids and glucocorticoids as well as the structurally related vitamin D and the bile acids has since established the extreme chemical, clinical and scientific significance of this ring system, which plays a pivotal role in some of the most fundamental biological signalling pathways known.[2]

Steroids elicit their diverse biological actions via different functionality located around the periphery of their rigid tetracyclic core. For example, estradiol **1** can be looked upon as a phenolic and a secondary alcohol that is spatially fixed by a central molecular scaffold. Although steroids are chemically quite simple molecules, with relatively few functional groups, their stereochemical and architectural complexity renders them an exceedingly difficult target for chemical synthesis, which has stretched the minds and ingenuity of numerous scientists over the years.[3] However, from a medicinal point of view, the synthesis of analogues, specifically targeted to probe the structure activity relationship (SAR) of the structure is a slow laborious process. With frequently up to eight contiguous chiral centres it is not surprising that relatively few synthetic drugs have been developed that target this class of receptor. Regarding the steroid nucleus as a rigid molecular scaffold we have initiated a programme to develop a series of steroid mimics aimed at probing nuclear receptor space, targeting known nuclear receptors such as the estrogen receptor,[4] the androgen receptor[5] and the progesterone receptor,[6] with the ultimate goal of finding new ligands and hence the biological significance of some of the orphan nuclear receptors that have been discovered more recently.[7] In this letter we report the preparation of a series of



Estradiol **1**



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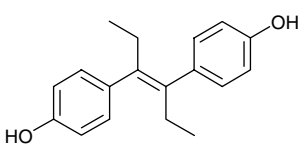
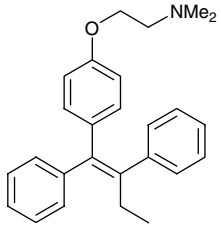


Diethylstilbestrol **3**



Tamoxifen **4**

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doi:10.1016/j.tetlet.2005.10.005

non-symmetrical tri- and tetra-substituted ureas aimed at mimicking molecules with estrogenic properties.

It has been reported that the simplified steroidal structure **2**, which lacks the traditional B and C rings of estrone, shows very little activity as a lipid catabolic agent.[8] This is possibly due to the loss of rotational degrees of freedom of the molecule on complexation with the receptor, rendering the interaction energetically unfavourable. This problem has been overcome by the introduction of unsaturation across the linker, for example, diethylstilbestrol **3** is a good agonist of the estrogen receptor.[9] Although **3** formally has two C–C single bonds within its structure, these are subject to restricted rotation due to the conjugation of the two aromatic rings, rendering the scaffold more rigid. While diethylstilbestrol is not suitable for use in the clinic due to its associated toxicity, the stilbene scaffold has been exploited in the development of Tamoxifen **4**, the drug of choice for the treatment of breast cancer.[10] By consideration of the structure of estradiol, four of the five chiral centres could be removed, and hence the structure greatly simplified, by preparation of urea **10**. We believed that restricted rotation about the two amide bonds of the urea would render the central portion of the molecule less conformationally flexible than the fully saturated system and thus favour binding to the receptor.

Starting from commercially available 4-(methylamino) phenol sulfate **5**, the phenol functionality was protected as its *tert*-butyldimethylsilyl ether **6** under standard conditions (Scheme 1).[11] Treatment of this protected aniline with carbonyldiimidazole gave an intermediate urea **7**, which was activated by reaction with methyl iodide in acetonitrile, in 84% for the two steps.[12] At this point, we were able to introduce diversity into our synthetic sequence by reacting **8** with a variety of proposed D-ring analogues (Fig. 1). These included (3*S*)-pyrrolidinol (−)-**11**, which was prepared in three steps from (*S*)-4-amino-2-hydroxybutyric acid,[13] (3*R*)-pyrrolidinol (+)-**11** and 3-pyrrolidinol (±)-**11**, both of which were commercially available, and 3-pyrrolidinone **12**, which was prepared in four steps from glycine ethyl ester.[14]

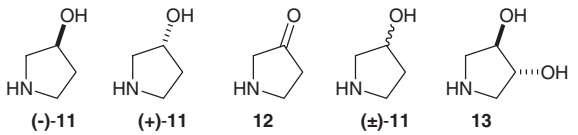


Figure 1. D-ring mimics.

With each of the adducts derived from the pyrrolidines **11** there are two low-energy conformations in which the five-membered ring could sit. The first (**A**), which would map onto the steroidal skeleton as desired and the second (**B**), which would put the D-ring substituent in the pseudo-16-α position of the steroid (Fig. 2). To circumvent this problem, we also prepared (3*R*),(4*R*)-pyrrolidinediol **13** in three steps from (−)-tartaric acid,[15] by a modified route to that reported previously.[16] The inherent C_2 symmetry of **13** means that in both low-energy conformations of the five-membered ring, the molecular structure will be such that the hydroxyl functionalities can be mapped directly onto the estrogen skeleton.

Treatment of the activated urea **8** with (3*S*)-pyrrolidinol (−)-**11** in dichloromethane at room temperature under basic conditions, gave the protected estradiol mimic **9** in 81% yield. Removal of the protecting group to reveal the phenol functionality was carried out in the presence of tetrabutylammonium fluoride to give the desired urea **10** as a colourless solid. The other targets derived from the D-ring mimics **11**–**13** were prepared in a similar manner to give a small targeted library of compounds for biological testing (Table 1).

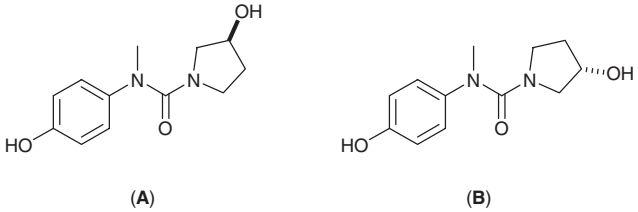
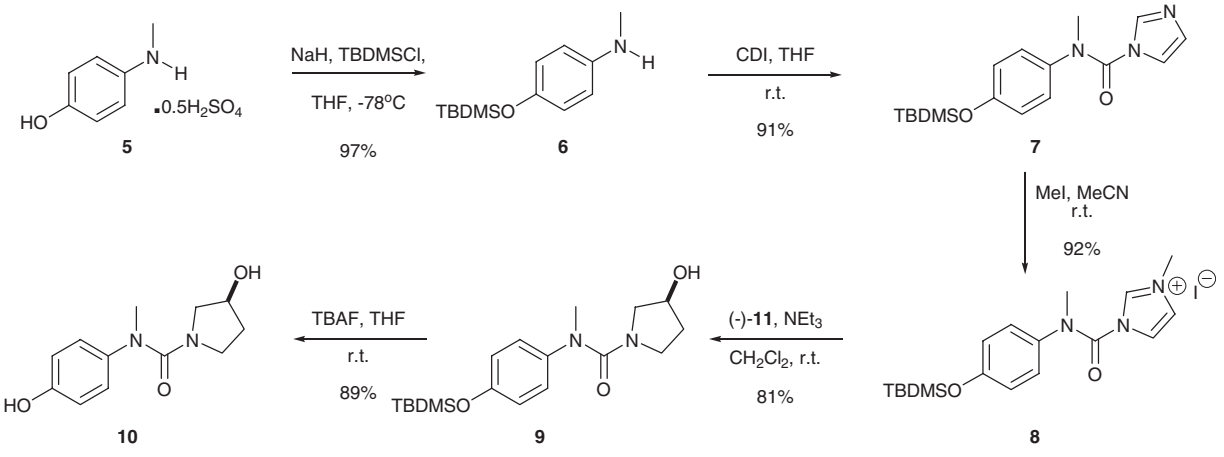


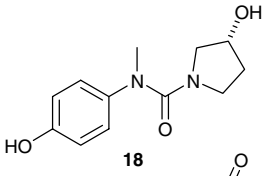
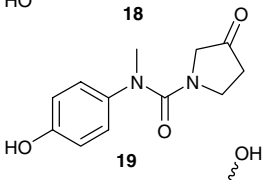
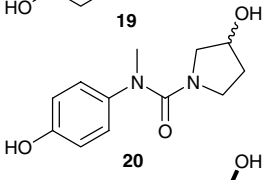
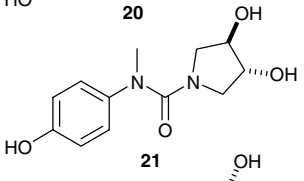
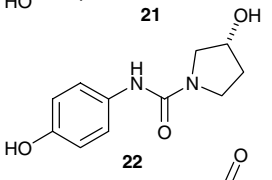
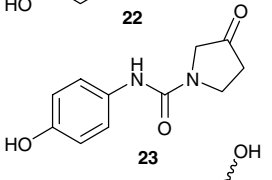
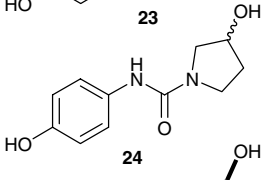
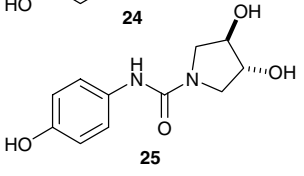
Figure 2. Possible D-ring conformations of estradiol mimic **10**.



Scheme 1. Preparation of tetra-substituted ureas.

This proved to be a general method for the preparation of a variety of non-symmetrical tetra-substituted ureas, however, for the synthesis of tri-substituted ureas (e.g., **16**) an alternative protocol was adopted (Scheme 2).

Table 1. Ureas prepared

A-ring mimic	D-ring mimic	Product	Yield[c] (%)
5[a]	(+)-**11**	 **18**	60
5[a]	**12**	 **19**	48
5[a]	(±)-**11**	 **20**	63
5[a]	**13**	 **21**	67
14[b]	(+)-**11**	 **22**	66
14[b]	**12**	 **23**	42
14[b]	(±)-**11**	 **24**	63
14[b]	**13**	 **25**	74

[a] Method as in Scheme 1.
[b] Method as in Scheme 2.
[c] Yields refer to total overall yield for the whole synthetic sequence.

Protection of 4-nitrophenol **14** followed by reduction of the nitro group gave the protected aniline **15**. Treatment of **15** with 4-nitrophenyl chloroformate in the presence of 1 equiv of triethylamine for 1 h followed by the addition of (3*S*)-pyrrolidinol (−)-**11** and a further equivalent of base led directly to the protected mimic. This one-pot procedure for the synthesis of the urea motif presumably proceeds via an intermediate isocyanate and proved ineffective in the tetra-substituted series, even under forcing conditions. It proved necessary to use this alternative protocol for the synthesis of the tri-substituted mimic **16** as use of carbonyldiimidazole in the coupling led directly to the symmetrical urea **17** as the only isolable product (Fig. 3). Deprotection of the protected phenol in the same manner to that used previously furnished the target compound **16**. This method once again proved to be general and was applicable to the use of **11**–**13** as the prospective D-ring mimics (Table 1).

As can be seen from Table 1, both synthetic sequences to access the tri- and tetra-substituted ureas proved to be amenable to alterations in the D-ring substitute with the target ureas **18**–**25** being isolated in excellent yield over the series, providing access to good quantities of material.

In summary, we have developed the synthesis of a novel molecular scaffold aimed at mimicking the rigid tetracyclic core of a steroidal skeleton. The preparation of the tri-substituted ureas involved the development of a new one-pot reaction sequence via the formation of an activated carbamate, followed by the displacement of 4-nitrophenol with a secondary amine, providing rapid access to this class of compound. This design allows for simple modification of the reactants to introduce a variety of A- and D-ring mimics of the steroidal skeleton by a practically simple protocol, which should be applicable to other steroidal backbones. We are currently evaluating these compounds for biological activity at the estrogen receptor and will report on these findings shortly.

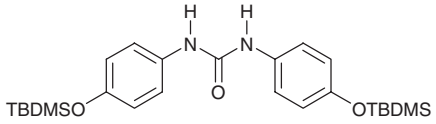


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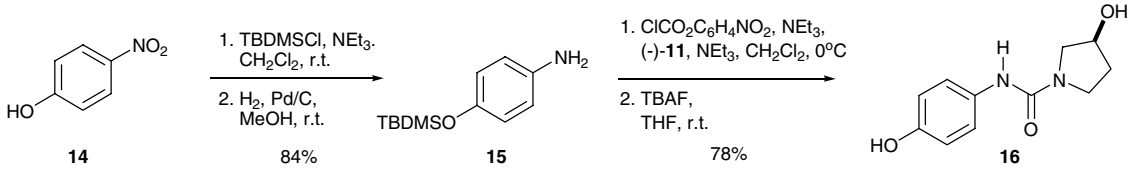
Figure 3. Symmetrical urea prepared by the CDI method.



14 **15** **16**

Scheme 2. Preparation of tri-substituted ureas.

Acknowledgements

The authors wish to thank Dr. Timothy M. Willson (GSK) for helpful discussions, the BBSRC (72/18337) and the Wellcome Trust for financial support, and the HRMS service at Swansea for analyses.

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16. In the reduction of (3*S*),(4*S*)-dihydroxy-1-benzyl-pyrrolidin-2,5-dione we found a modified work-up procedure more convenient than that previously reported (Ref. 15): A solution of (3*S*),(4*S*)-dihydroxy-1-benzylpyrrolidin-2,5-dione (11.54 g, 52.2 mmol) and lithium aluminium hydride (9.92 g, 0.26 mol) in THF (100 mL) was heated at reflux for 12 h. The reaction mixture was allowed to cool to room temperature and was cooled further using an ice bath. The mixture was quenched with water (3 mL) and 5 M NaOH (3 mL) and diluted with ether (50 mL). The resulting mixture was filtered through Celite® and the solids collected were washed with dichloromethane (100 mL). The filtrate was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to give the desired compound (10.01 g, 99%) as a colourless crystalline solid, mp 98–99 °C (lit. mp 98–99 °C);[15] ν_{max} (Nujol)/cm^{-1} 3136 (OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.12 (5H, m), 4.03 (2H, dd, $J = 5.3$, 3.4 Hz), 3.61 (1H, d, $J = 12.9$ Hz), 3.57 (1H, d, $J = 12.9$ Hz), 2.92 (2H, dd, $J = 10.2$, 5.3 Hz), 2.40 (2H, dd, $J = 10.2$, 3.4 Hz), 2.36 (2H, br s); δ_C (100 MHz, $CDCl_3$) δ 138.5, 129.2, 128.7, 127.6, 78.9, 60.6, 60.2; *m/z* (APCI) 194 (MH^+, 100%); HRMS calcd for $C_{11}H_{15}NO_2$ 194.1183 $[M+H]^+$, found 194.1180.