Pergamon

Tetrahedron Letters 40 (1999) 1277–1280

TETRAHEDRON LETTERS

# Solid-Phase Synthesis of Phenolic Steroids: Towards Combinatorial Libraries of Estradiol Derivatives

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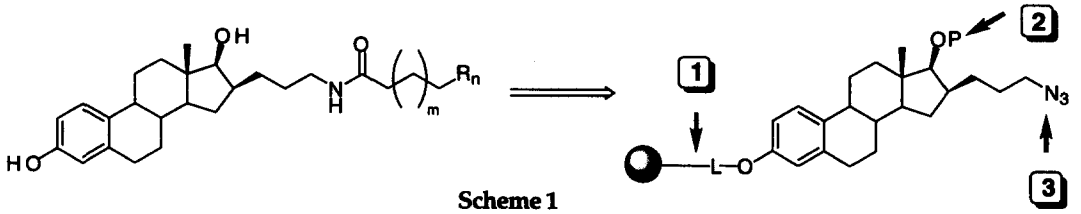
Received 24 November 1998; accepted 9 December 1998

**Abstract.** The 16β-(azidopropyl) derivative of estradiol (**7**) was synthesized and coupled to aminomethyl resin via a photolabile *o*-nitrobenzyl linker. Condensation of the corresponding iminophosphorane with activated acids successfully gave amides. Photocleavage resulted in good yield recovery of estradiol derivatives **15** and **16** in acceptable purities for biological screening.


In our study aimed at the development of therapeutic agents for the treatment of hormone-sensitive diseases, we are interested in the combinatorial synthesis of androsterone [1] and estradiol [2] derivatives. Among promising lead compounds, we found that estradiol derivatives containing various functionalized side chains at position 16 showed interesting biological properties [3]. We then needed powerful synthetic methods to prepare functionally diverse estradiol derivatives. The retrosynthetic plan shown in Scheme 1 illustrates the three key features of our strategy: 1) the estradiol derivative should be linked to the resin through its phenolic functionality rather than to the 17β-hydroxy group because of a possibility of steric hinderance from the polymer during the derivatization of the 16β-side-chain, 2) the 17β-hydroxy protecting group should be compatible with the subsequent sequence of reactions and could be deprotected on support to allow an additional combinatorial level, 3) an amine could lead to several derivatives and could be generated from an azide, which is easily monitored by infrared spectroscopy.

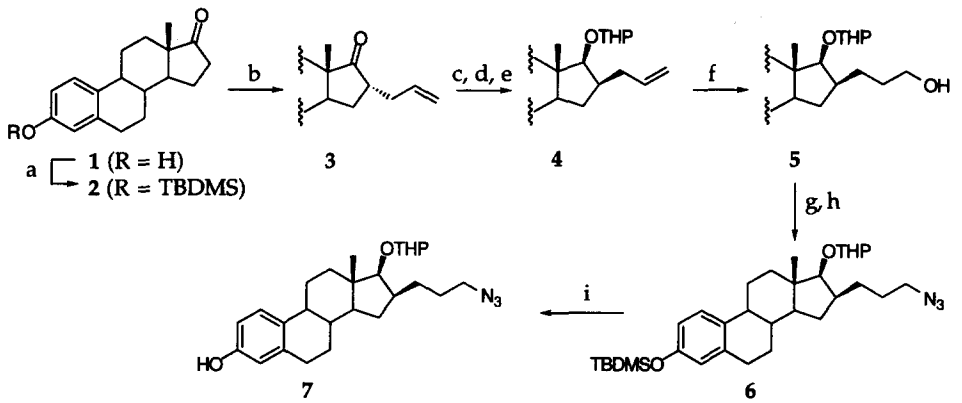



**Scheme 1**

While the straightforward synthetic sequence illustrated in Scheme 2 was performed to generate multigram scale of precursor **7** without difficulty, the choice of solid support was clearly the bottom line of the synthesis. Unfortunately, the literature

0040-4039/99/$ - see front matter 
*PII:* S0040-4039(98)02640-9

contains few reports of synthetic transformations of polymer-bound steroids [4-10] and only one report concerning the coupling of phenolic steroids on carboxypolystyrene [5]. There is clearly a lack of systematic studies on the linkage of steroids through functions other than amides and esters.

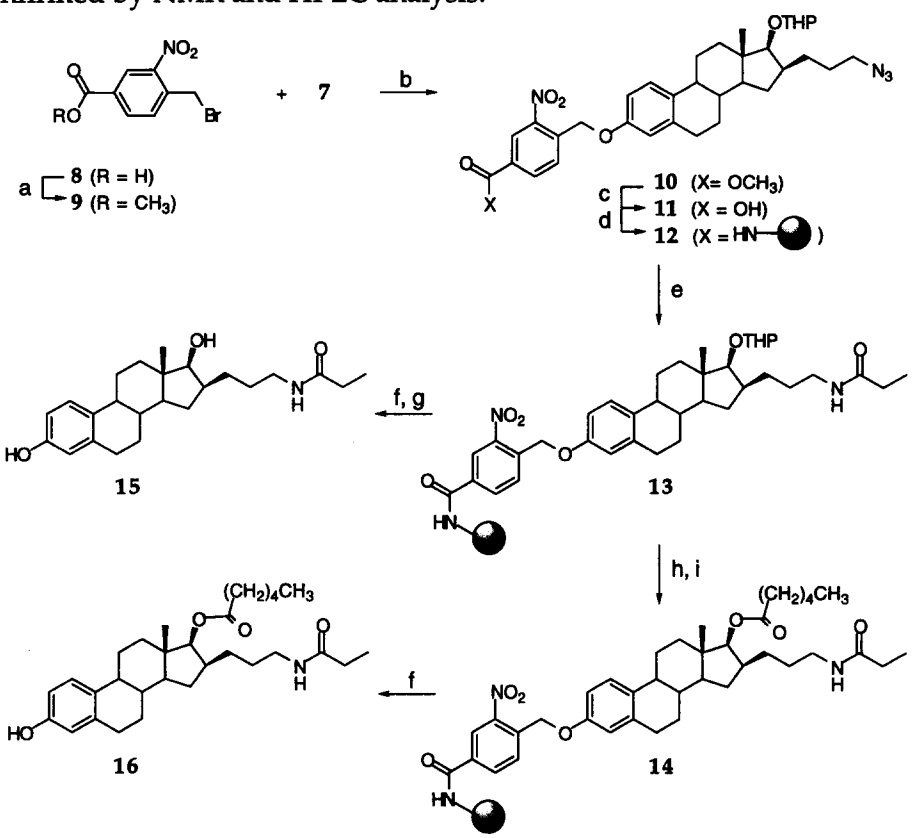



**Scheme 2** *Reagents and conditions:* (a) TBDMS-Cl, imidazole, DMF, rt; (b) *i.* LDA, THF -78 °C *ii.* $BrCH_2CH{=}CH_2$ (78%, two steps); (c) *i.* LDA, THF -78 °C *ii.* MeOH; (d) $LiAlH_4$, THF, -78 °C; (e) DHP, *p*-TSA, $CH_2Cl_2$, rt (89%, three steps); (f) *i.* $BH_3$.THF, 0°C *ii.* NaOH, $H_2O_2$ (79%); (g) Tos-Cl, pyridine, 0°C; (h) $NaN_3$, DMF, rt (87%, two steps); (i) TBAF, THF, 0°C (98%).

First, we tried to attach the phenol function of estrone (**1**) to several resins that have been previously used for phenol attachment; namely, Merrifield [11], Wang [12-14], hydroxymethylphenoxyacetyl (HMP)-AM [15-18], and dihydropyranyl (DHP)-HM [19, 20]. The coupling reactions of estrone as well as precursor **7** to Merrifield's resin (NaH, DMF, 60°C) were found to be very effective (>90%). The cleavage of estrone linked to Merrifield's resin needed drastic conditions ($TFA:H_2O:Me_2S$, 95:5:10) and resulted in 50% recovery of purified material. On the other hand, the final cleavage of Merrifield-bound N-acylated derivative of **7** gave only 20% of isolated product after alkaline hydrolysis of the corresponding 17-trifluoromethyl acetate, which resulted from TFA cleavage. We then tried milder cleavage conditions by using more acid-labile linkers. However, the final cleavage of estrone attached via a 4-alkoxybenzyl ether (Wang or HMP-AM resins), using a wide range of TFA-containing deprotection cocktails (1% to 95% TFA with $Me_2S$ as scavenger), was always accompanied by 50% alkylation of positions 2 or 4 of estrone by the linker through its benzylic carbon. Other acidic conditions (10% $H_2SO_4$ in dioxane; $SnCl_4$ in $CH_2Cl_2$) gave the same results. We also tried the THP linker because of its high sensitivity to acids, but loading of estrone onto such a resin was clearly unsatisfactory (<40%, established after deprotection step on a gram scale of resin).

Taking into account the previous limitations due to the particular nature of precursor **7** (phenol and 17β-OH), we found that the *o*-nitrobenzyl ether photolabile group [21-23] was a convenient linker for our purpose. Thus, we added the linker to precursor **7** before its coupling to aminomethyl polystyrene resin using the synthetic transformations illustrated in Scheme 3. To illustrate the suitability of our approach

towards combinatorial synthesis of estradiol derivatives, we performed the synthesis of two model compounds from resin **12**. As indicated in Scheme 3, the synthetic sequence led to N-substituted aminopropyl estradiol having free or acylated 17β-OH (compounds **15** and **16**, respectively). The key step of this synthesis is the transformation of the azide group into the amide via the condensation of its corresponding iminophosphorane with an activated acid [24, 25]. Compounds **15** and **16**, obtained in overall yields of 20-30 % (4-5 steps) after photocleavage, were characterized by $^1$H NMR, $^{13}$C NMR, IR, and mass spectra [26]. High purities (>90%) were confirmed by NMR and HPLC analysis.




**Scheme 3** *Reagents and conditions:* (a) $TMSCHN_2$, benzene/MeOH (4:1), rt (96%); (b) $Cs_2CO_3$, $CH_3CN$/DMF (4:1), rt (67%); (c) LiOH aq, THF, rt (83%); (d) Aminomethyl resin (1.0 mmol/g), DIPC, HOBt, DMF, rt; (e) propionic acid, EDC, HOBt, dioxane, then $Bu_3P$ in toluene, rt; (f) hν (350 nm), MeOH, rt; (g) 2% HCl, MeOH, rt; (h) *p*-TSA, 1-butanol/$ClCH_2CH_2Cl$ (1:1), rt; (i) hexanoic acid, DIPC, DIPEA, DMAP, $CH_2Cl_2$, rt.

In summary, we have described a convenient synthesis of estradiol derivatives using solid-phase methodology. Almost all suitable linkers for attachment of phenols to solid support were investigated. However, TFA-mediated cleavage was shown to provoke numerous side-reactions on our substrate. This observation led us to consider a photolabile linker, which we successfully used to perform the first reported solid-phase synthesis of estradiol derivatives with acceptable purities and two diversity

levels. Studies are now in progress to extend this synthesis into a split-and-pool format.

**Acknowledgments:** Financial support from the Medical Research Council of Canada, Fonds pour la Recherche en Santé du Québec, Le Fonds FCAR, and Natural Sciences and Engineering Research Council of Canada. We are also grateful to Mr. Roch P. Boivin for batch synthesis of **7**.

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[26] Compound **15**: IR (KBr, $cm^{-1}$): 3350 (OH, NH), 1630 (C=O, amide); $^1H$ NMR ($CD_3OD$): 0.77 (s, 18-$CH_3$), 1.12 (t, J = 7.6 Hz, $CH_3CH_2$), 2.17 (q, J = 7.6 Hz, $CH_3CH_2CO$), 2.77 (m, 6-$CH_2$), 3.30 (m, $CH_2N$), 3.70 (d, J = 9.7 Hz, 17α-CH), 6.47 (d, J = 2.4 Hz, 4-CH), 6.53 (dd, $J_1$ = 8.5 Hz and $J_2$ = 2.4 Hz, 2-CH), 7.06 (d, J = 8.5 Hz, 1-CH); $^{13}C$ NMR ($CD_3OD$): 10.62, 13.20, 27.57, 28.75, 29.63, 30.25, 30.30, 30.74, 33.57, 39.04, 40.01, 40.72, 41.35, 45.20, 45.43, ~49.0 (under solvent), 83.19, 113.72, 116.03, 127.17, 132.68, 138.80, 155.90, 177.00; LRMS [M+H$^+$]: 386 m/z.
Compound **16**: IR (film, $cm^{-1}$): 3300 (OH and NH), 1730 (C=O, ester), 1655 (C=O, amide); $^1H$ NMR ($CDCl_3$): 0.78 (s, 18-$CH_3$), 0.90 (t, J = 6.6 Hz, $CH_3CH_2$), 1.16 (t, J = 7.5 Hz, $CH_3CH_2$), 2.20 (q, J = 7.5 Hz, $CH_3CH_2CO$), 2.35 (t, J = 6.6 Hz, $CH_2CH_2CO$), 2.80 (m, 6-$CH_2$), 3.23 (m, $CH_2N$), 4.71 (d, J = 9.9 Hz, 17α-CH), 6.58 (d, J = 2.3 Hz, 4-CH), 6.63 (dd, $J_1$ = 8.4 Hz and $J_2$ = 2.3 Hz, 2-CH), 7.11 (d, J = 8.4 Hz, 1-CH); $^{13}C$ NMR ($CDCl_3$): 9.94, 13.34, 13.92, 22.32, 24.80, 26.11, 27.33, 28.32, 28.85, 29.57, 29.78, 31.36, 32.06, 34.48, 37.61, 38.04, 38.18, 39.52, 43.50, 43.75, 48.67, 83.22, 112.74, 115.26, 126.40, 132.18, 137.97, 153.74, 174.11, 186.77; LRMS [M+H$^+$]: 484 m/z.