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Solid-Phase Synthesis of Phenolic Steroids: From Optimization Studies to a Convenient Procedure for Combinatorial Synthesis of Biologically Relevant Estradiol Derivatives

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During the course of our studies on therapeutic agents for the treatment of breast cancer, we became interested in the solid-phase combinatorial synthesis of estradiol derivatives that contain a functionalized side chain at either position 16β or 7α. Both types of compounds have already demonstrated inhibitory activity toward both biosynthesis and action of estradiol. As a first step, two versatile precursors bearing an azidoalkyl side chain at either position 16β or 7α of estradiol were synthesized using standard solution-phase methods. Afterward, the effectiveness of five linkers to attach the phenolic function of these estradiol derivatives to a polystyrene resin was investigated; they were benzylic ether (Merrifield), 4-alkoxy-benzylic ethers (Wang, Sheppard), tetrahydropyranyl ether (Ellman), benzoic ester, and *o*-nitrobenzyl ether. To test the linker in a synthetic context, a short sequence of reactions, including reduction of the azide and acylation of the corresponding amine, was performed on the polymer-bound estradiol derivative. While all of the tested linkers proved effective in attaching the phenol functionality of the precursor, only the *o*-nitrobenzyl ether photolabile linker enabled the release of the final products in acceptable purities. Consequently, this linker was used to perform successfully the solid-phase synthesis of four different classes of estradiol derivatives in acceptable yields and excellent purities. This study was preliminary to the combinatorial synthesis of larger libraries of biologically relevant estradiol derivatives.

Introduction

The past decade has witnessed a growing interest for combinatorial chemistry, a new technology that enables the simultaneous chemical synthesis of large libraries of diverse compounds.[1−9] The split-and-pool procedure is one powerful combinatorial method that requires the attachment of the substrate onto a polymer.[10] Solid-phase chemistry, which was initially introduced for the synthesis of peptides and oligonucleotides, has proven valuable in the synthesis of small-molecular-weight structures.[11,12]

During the course of our studies on the development of new therapeutic agents for the treatment of endocrine diseases, we became interested in the solid-phase combinatorial synthesis of steroid derivatives. Unfortunately, the history of polymer-bound steroids is relatively short and few pertinent examples have been reported in the literature (Figure 1). In 1969 and 1973, experiments were performed where estradiol was bound to polyvinyl-, cellulose-, and polyacrylamide-based polymers (**1**), which were used as specific bioadsorbents for the purification of the estrogen receptor.[13,14] In 1983, 3-oxo-steroids, exemplified by the structure **2**, as well as 17-oxo- and 20-oxo-steroids were linked to polystyrene via an acetal function. The linker was introduced into the polymer by a thioether bond.[15] Two years later, attachment of steroids to functionalized polystyrenes through an ester bond via carboxylic acid, alcohol, or phenol groups was reported.[16] Of note, the synthesis of carboxy-polystyrene-bound estrone (**3**) has been described in this paper. Concurrently, 3β-cholestanol was coupled to a polymer-anchored organosilyl (compound **4**) but with only modest yield (11%).[17] In 1990, dehydrocholates were attached via an ester bond to hydroxypolystyrene (compound **5**). Three types of reaction were tested: acetalization, esterification, and hydrazone formation. The corresponding polymer-bound dehydrocholate derivatives were characterized by ^{13}C NMR spectra.[18] In 1994 and 1996, two series of polystyrene-bound peptidosteroidal synthetic receptor libraries (**6** and **7**) were reported.[19,20] In these cases, chenodeoxycholic acid was attached through an amide bound to aminomethyl polystyrene; the resulting peptidosteroids were not, however, released after their solid-phase synthesis. Recently, epiandrosterone was attached via a THP linker to the Merrifield resin (compound **8**) and subsequently removed under mild conditions (*p*-TSA, 1-butanol/1,2-dichloroethane).[21] More recently, the same linker was used for the coupling of an alcohol derivative of chenodeoxycholic acid to polystyrene (compound **9**).[22] A sequence of two reactions

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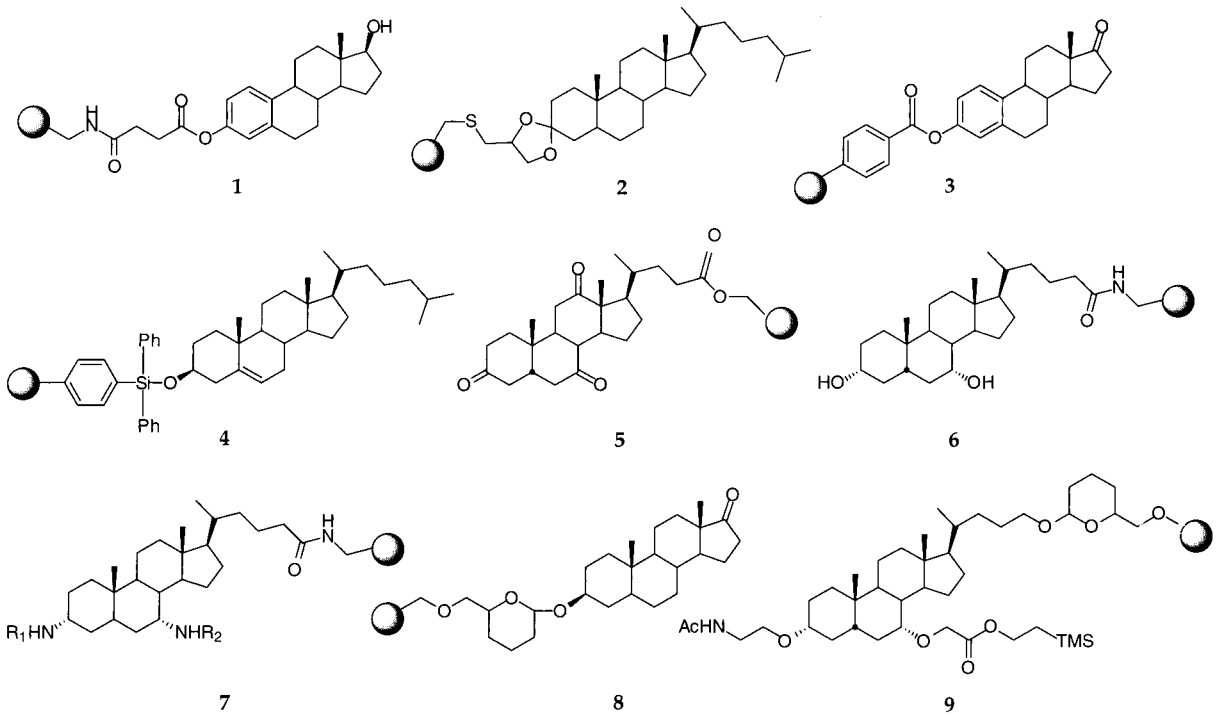


Figure 1. Structures of polymer-bound steroids reported to date. All resins were polystyrene polymers except for structure **1** which was polyacrylamide.

was performed on a support to produce, after an acidic cleavage and purification, the steroid-based scaffold for β-turn mimics (50−90% yields and purities). As can be seen in the literature, there are few reports of synthetic transformations of polymer-bound steroids, and systematic studies concerning the linkage of phenolic steroids such as estradiol, estrone, and their derivatives through functions other than amides and esters are lacking.

Our group is particularly interested in estradiol derivatives bearing substituents at positions 6, 7, 15, 16, and 17.[23−31] These derivatives have presented interesting biological properties as inhibitors of steroid sulfatase and 17β-hydroxysteroid dehydrogenase, key enzymes involved in the biosynthesis of estradiol, whereas some are antagonists of the estrogen receptor. Both 17β-hydroxysteroid dehydrogenase and estrogen receptor proteins accommodate estradiol as the natural ligand/substrate and play predominant roles in estrogen-sensitive diseases such as breast and endometrium cancers.[32−34] In a therapeutic view, estrogen receptor and 17β-hydroxysteroid dehydrogenase could be targeted, by two drugs or ideally one compound blocking these two proteins.[24,26] Combinatorial methods are very powerful means of discovering molecules that can bind to these two proteins without causing harmful biological effects such as the proliferation of breast cancer cells. In preliminary reports, we recently disclosed the solid-phase synthesis of 16β-propylamide[35] and 7α-alkylamide[36] derivatives of estradiol. In the present paper, several procedures used to attach estrone and functionalized estradiol derivatives onto polystyrene resin are reported. This systematic study led to the development of a convenient method, which proved useful for the solid-phase synthesis of biologically relevant libraries of estradiol derivatives.

Results and Discussion

The most potent estrogen, 17β-estradiol, has two important functional groups: a phenolic function at the position 3 and a hydroxyl group at the position 17β. This molecule itself is not a good template for introducing molecular diversity, especially when one of its two functional group must be used to link to the solid support. To generate several derivatives, some versatile functional groups should be added to estradiol prior to its coupling to polymer. The general strategy for introducing molecular diversity into biologically interesting estradiol derivatives is shown in Figure 2. We chose two representative structures of estradiol derivatives having a side chain at either the position 16β or 7α. Both molecules possess the azide function, which was chosen as the amine precursor for its stability in a large range of conditions and because its presence could be easily monitored by infrared spectroscopy. The corresponding amines should be used to introduce commercially available building blocks and enable the production of libraries of estradiol derivatives with structures related to known drug candidates.

1. Chemical Synthesis of Steroidal Precursors 19, 20, and 24 (Schemes 1 and 2). The two precursors were prepared following the synthetic sequences indicated in Schemes 1 and 2. The synthesis of the first precursor was initiated by protection of the phenolic function of estrone (**10**) to the *tert*-butyldimethylsilyl ether **11** before α-alkylation using allyl bromide as the electrophile to yield the 16α-allyl estrone derivative **12**. It is well-known that the major epimer (16α) results from the attack of the corresponding enolate on the electrophile by the less hindered α face of the steroid.[37] We then considered this fact when performing an asymmetric protonation of the enolate giving access to the 16β-epimer with complete inversion of configuration.

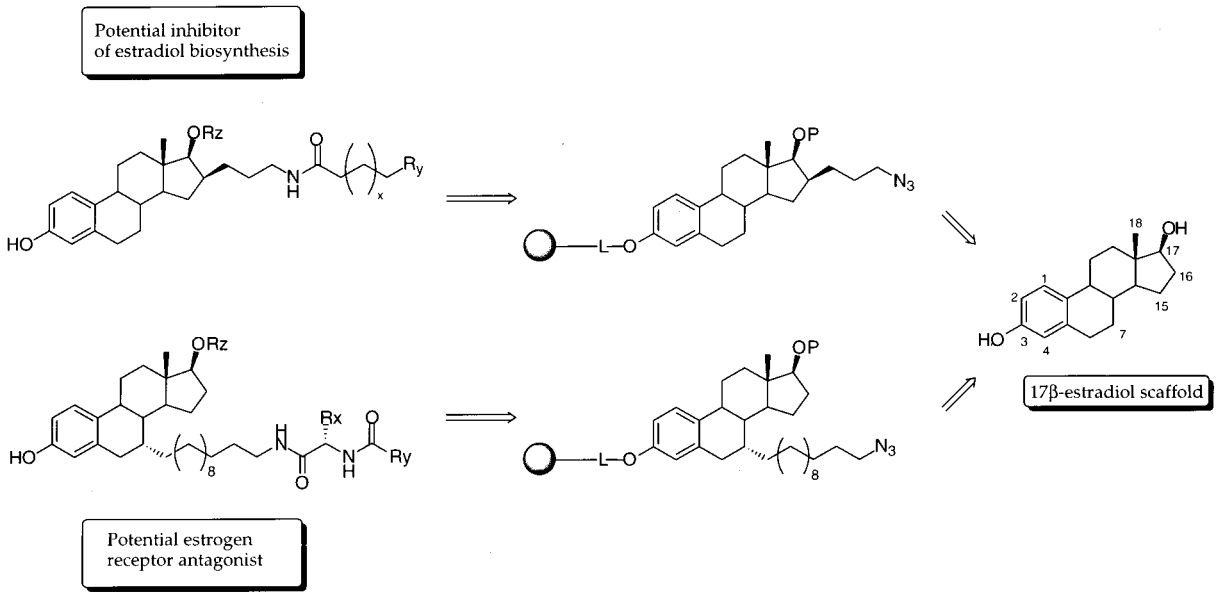
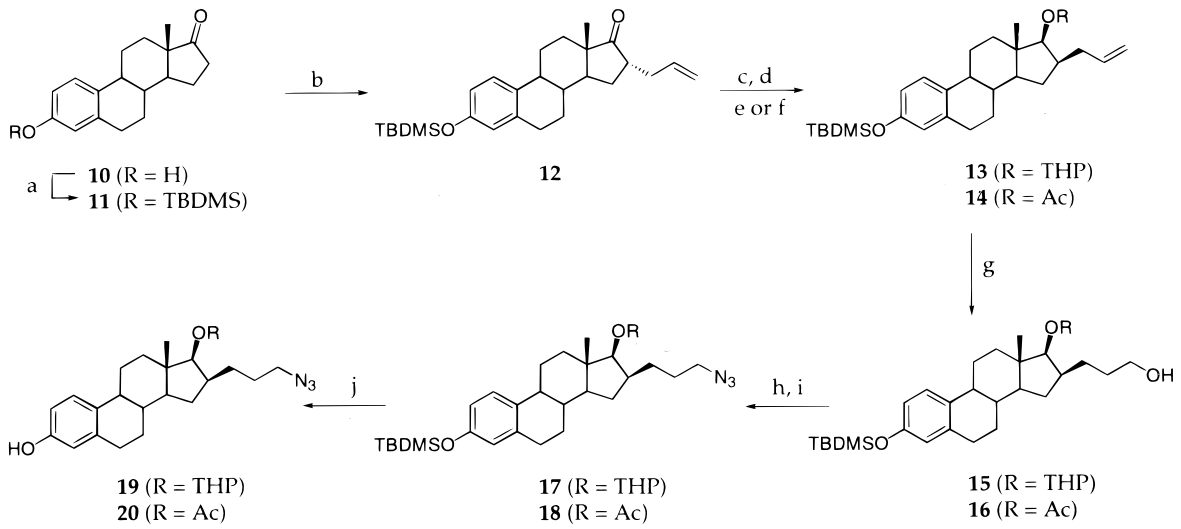


Figure 2. Retrosynthetic strategy for the solid-phase synthesis of diverse estradiol derivatives.

Scheme 1[a]

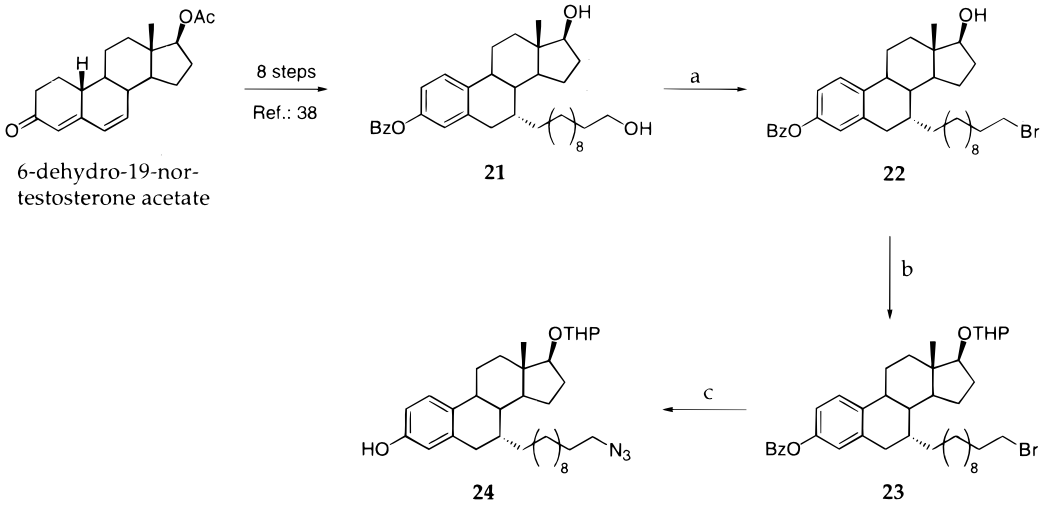


[a] (a) TBDMS-Cl, imidazole, DMF, 25 °C; (b) *i*. LDA, THF, −78 °C; *ii*. $BrCH_2CH{=}CH_2$ (78%, two steps); (c) *i*. LDA, THF −78 °C; *ii*. MeOH; (d) $LiAlH_4$, THF, −78 °C; (e) DHP, *p*-TSA, CH_2Cl_2, 25 °C (for **13**: 89%, three steps); (f) Ac-Cl, DMAP, pyridine, 25 °C (for **14**: 70%, three steps); (g) *i*. BH_3-THF, 0 °C; *ii*. for **15**: NaOH, H_2O_2 (62%) and for **16**: $NaHCO_3$, H_2O_2 (58%); (h) Tos-Cl, pyridine, 0 °C; (i) NaN_3, DMF, 25 °C (for **17**: 83%, two steps; for **18**: 80%, two steps); (j) TBAF, THF, 0 °C, 1 h (for **19**: 90%; for **20**: 85%).

After a highly stereoselective reduction of the 17-ketone, the corresponding 17β-hydroxyl group was protected as the tetrahydropyranyl ether **13** or the acetate **14**. Depending on the chosen linker strategy, these protective groups can be removed either during the final cleavage or directly on the solid support to allow further derivatization for the construction of libraries. Oxidative hydroboration of the terminal alkenes, giving alcohols **15** and **16**, was performed according to two different procedures because the 17β-OAc required mild basic hydrolysis of the boronic intermediate. The alcohols were transformed to the corresponding azides **17** and **18** by the standard tosylate displacement method. Phenols **19** and **20** were generated after a fluoride-mediated cleavage of TBDMS groups. The second precursor (**24**, Scheme 2) was synthesized from the advanced intermediate **21** which is readily available in our laboratory and prepared following the procedure described in the literature.[38] Regioselective bromination of the primary alcohol gave **22**, and the secondary 17β-alcohol was protected as a tetrahydropyranyl ether to provide **23**. Displacement of the primary bromide by azide anion was accompanied by the cleavage of the benzoyl ester when the reaction was heated, thus resulting in the desired precursor **24**.

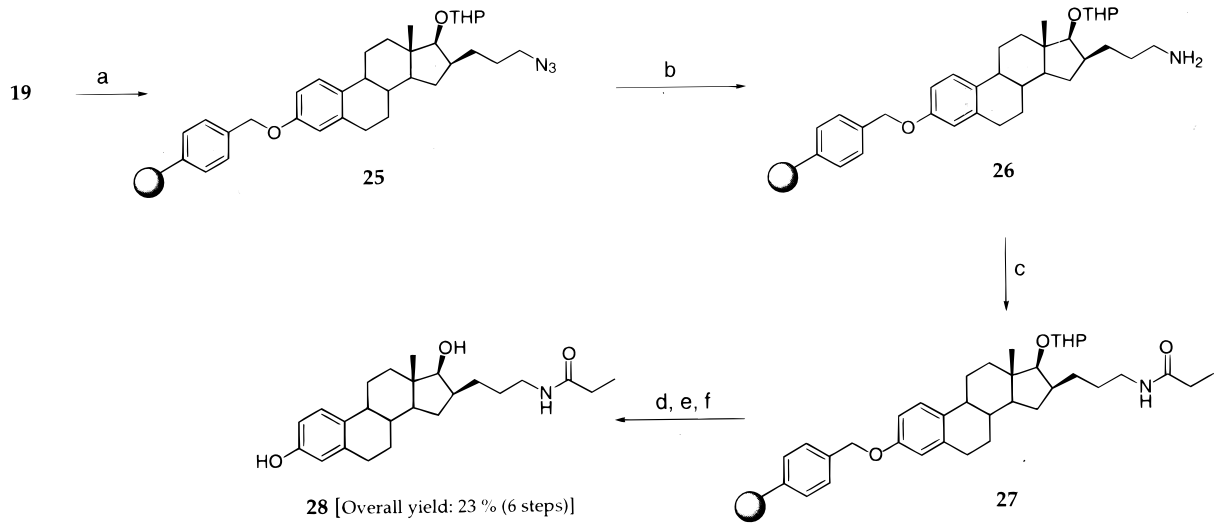
2. Exploration of the Linker Strategy (Schemes 3−5). Before using our synthetic precursors, we wanted to investigate the potential of several linkers to determine what kind of chemistry we would be able to perform on solid support afterward.[39] As mentioned above, there has been only one report of polystyrene-bound estradiol. The following sections describe data that we obtained from studies on several linkers suitable for phenols. In addition, a sequence of three to four chemical transformations was assessed on the polymer to

Scheme 2[a]



[a] (a) CBr_4, PPh_3, CH_2Cl_2, 0 °C (64%); (b) DHP, *p*-TSA, CH_2Cl_2, 25 °C (90%); (c) NaN_3, DMF, 80 °C (77%).

Scheme 3[a]



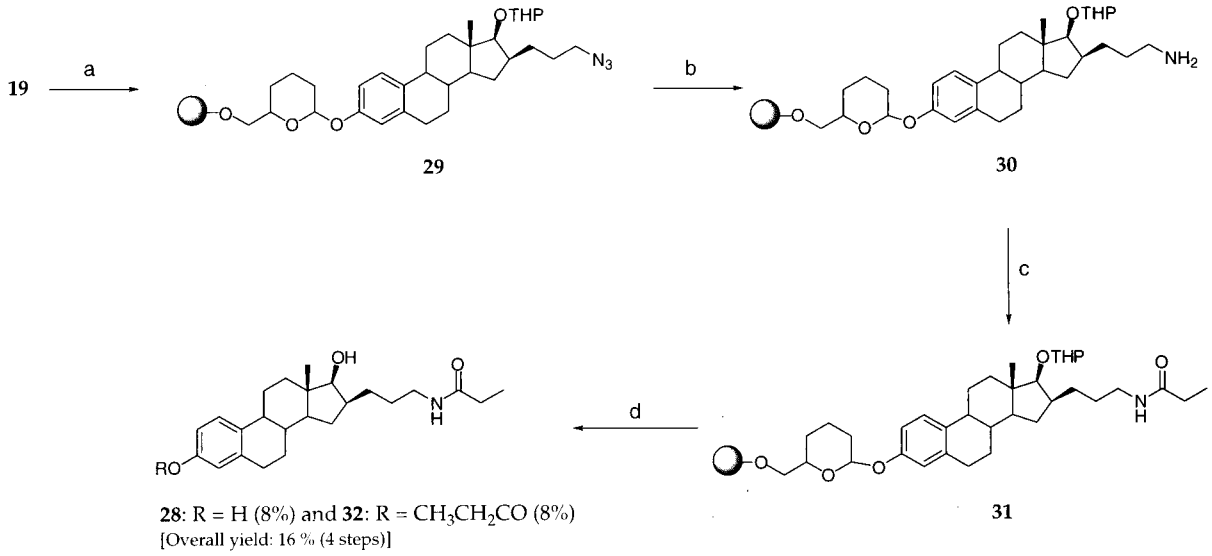
[a] (a) NaH, DMF, Merrifield resin (1.0 mmol/g), 40 °C; (b) $SnCl_2$:Et_3N:HSPh (1:5:4), THF, 25 °C; (c) propionyl-Cl, *i*-Pr_2EtN, $ClCH_2CH_2Cl$, 25 °C; (d) *p*-TSA, 1-butanol:$ClCH_2CH_2Cl$ (1:1), 25 °C; (e) TFA:H_2O:MeSPh (95:5:10), 25 °C; (f) 0.5 N NaOH, THF, 25 °C.

evaluate the scope and limitations of such linkers for the solid-phase synthesis of phenolic steroid derivatives.

Merrifield, Wang, and HMP-AM Resins. Chloromethylpolystyrene is the most well-known and least expensive resin used in solid-phase synthesis.[40] We decided to begin our study by coupling a model phenolic steroid (estrone) to this support. The Merrifield-bound estrone was generated from estrone (**10**) and chloromethylpolystyrene and characterized by Fourier transform infrared spectroscopy (FT-IR) using standard KBr pellets[41] and by gel-phase ^{13}C NMR.[42−44] Afterward, the cleavage of phenolic benzyl ethers was studied either in solution, using estrone 3-benzyl ether as a model, or in solid-phase using Merrifield-bound estrone. Acid-mediated rearrangement of the phenolic benzyl ether was the major side reaction, generating a mixture of 2- and 4-alkylated estrone derivatives when aqueous trifluoroacetic acid (TFA, 95%) was used. In solid-phase, weak recovery of estrone (**10**) suggested that the same rearrangement occurred. This was avoided by the addition of dimethyl sulfide as a carbocation scavenger.[45] Hydrogenolytic conditions, described for the cleavage of benzylic esters on solid support,[46−48] gave satisfactory results in solution, but could not be adapted to the Merrifield-bound substrate. We also tried, without success, ethanethiol-mediated cleavage conditions, which should proceed by a mechanism closer to S_N2 than that of the TFA-mediated cleavage. Finally, tin(IV) chloride, which has been recently reported in the cleavage of phenolic compounds from Merrifield resin,[49] underwent the undesired rearrangement.

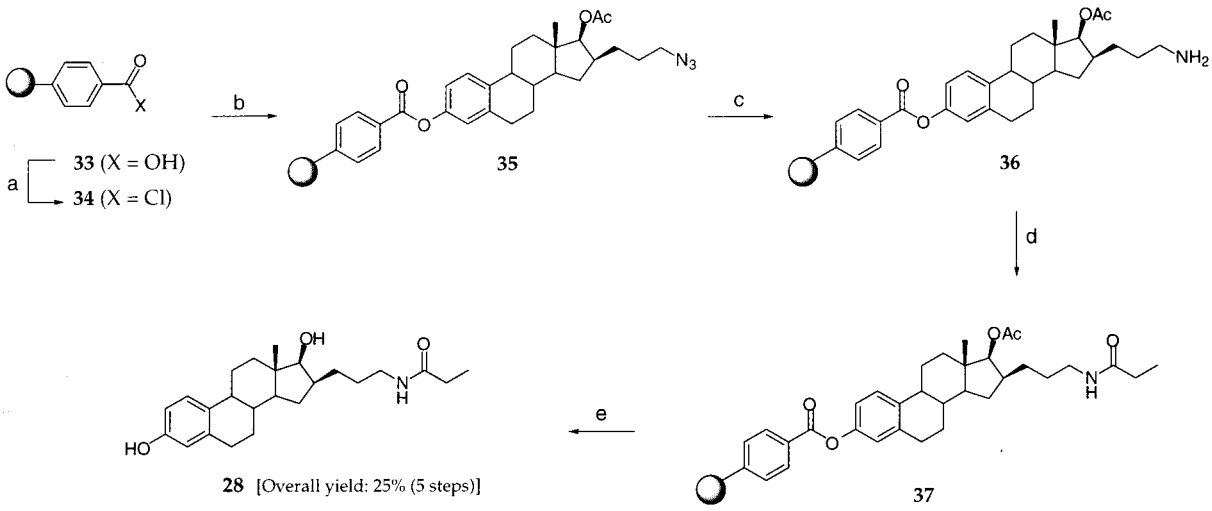
The most widely used linkers for the attachment of phenols to solid supports are 4-alkoxybenzyl derivatives examplified by Wang resin[50−53] and hydroxymethylphenoxy (HMP)-aminomethyl (AM) resin.[54−57] Several authors have reported the cleavage of 4-alkoxybenzyl phenolic ethers using a wide range of TFA-containing deprotection cocktails varying from 1% to 95% TFA. The efficiency of this cleavage and the need for a carbocation scavenger seemed very dependent on the nature of the phenolic derivative. On the other hand, the Mitsunobu procedure is the best method reported for coupling phenols to Wang resin.[52] Unfortunately, this procedure did

Scheme 4[a]



[a] (a) DHP-HM resin (0.68 mmol/g), PPTS, $ClCH_2CH_2Cl$, 80 °C; (b) $SnCl_2$:Et_3N:HSPh (1:5:4), THF, 25 °C; (c) propionyl-Cl, *i*-Pr_2EtN, $ClCH_2CH_2Cl$, 25 °C; (d) PPTS, 1-butanol:$ClCH_2CH_2Cl$ (1:1), 60 °C.

Scheme 5[a]

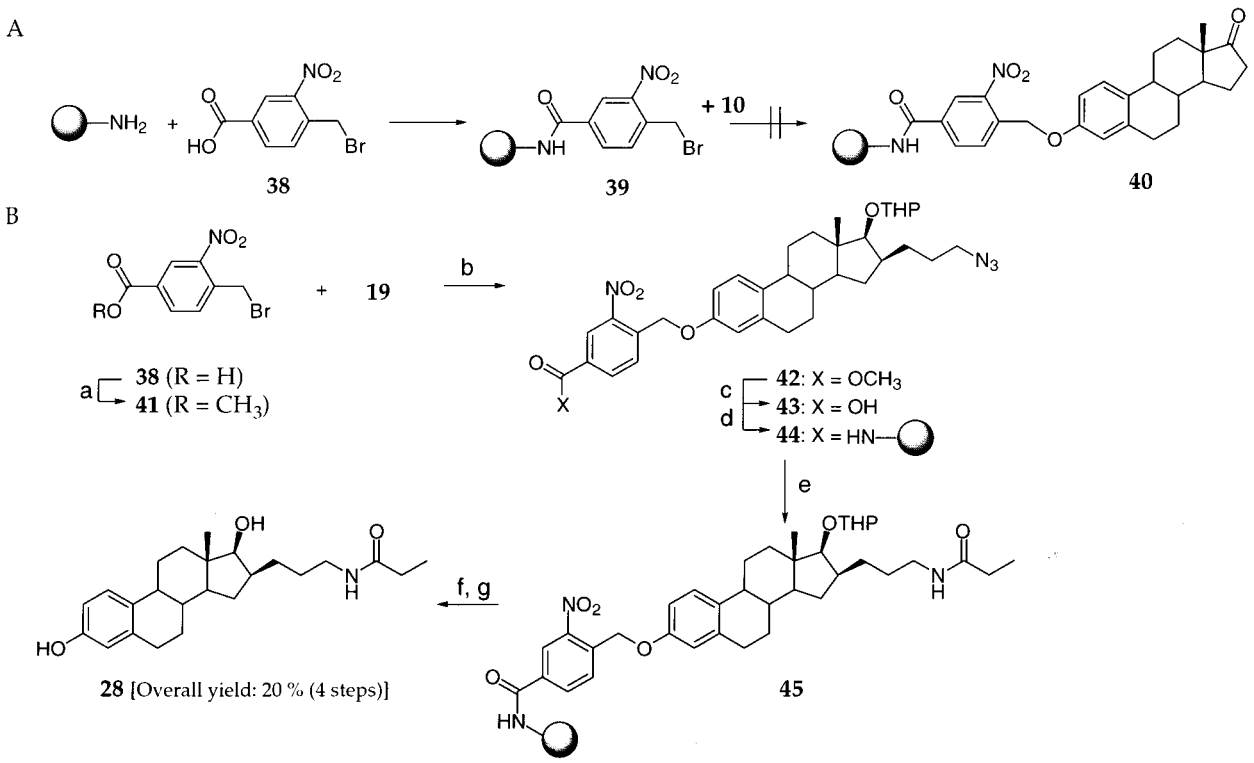


[a] (a) $(COCl)_2$, toluene, 25 °C; (b) **20**, ethylbenzene, DMAP, 136 °C, 16 h; (c) $SnCl_2$:Et_3N:HSPh (1:5:4), THF, 25 °C; (d) propionyl-Cl, *i*-Pr_2EtN, $ClCH_2CH_2Cl$, 25 °C; (e) NaOMe/MeOH, THF, 25 °C.

not work with estrone (**10**), and results were even worse with the 16β-(azidopropyl)-estradiol derivative **19**. Attempts to introduce estrone to mesylate-derived Wang resin[58] and commercially available Wang-Br resin[59] did not give satisfactory coupling yields (<25%). We then synthesized the HMP-AM resin derivative of estrone and used it as a model for investigating several acidic cleavage conditions. Over a broad range of TFA-containing deprotection cocktails, it was found that TFA:H_2O:$PhSCH_3$ (85:5:10) gave 42% of estrone recovery, which needed purification by column chromatography. Since the long synthetic sequence needed to obtain the resin-bound substrate did not improve the recovery and the purity of the released compound, we concluded that the HMP linker was unsuitable for our purposes. Thus, TFA-mediated cleavage of Merrifield-bound substrate using a carbocation scavenger was selected to pursue our goals.

The estradiol derivative **19** was then coupled to the Merrifield resin, under the optimized conditions reported above for estrone (**10**), to give resin **25** (Scheme 3). The presence of the azide group was confirmed by FT-IR. The azide group was reduced to amine **26** according to a procedure first described by Bartra et al.[60] and adapted by Kick et al.[61] In our case, the reaction was completed within 4−5 h of reaction as monitored by the disappearance of the azide stretch in the FT-IR spectrum. The corresponding amine was acylated under standard conditions to yield resin **27**. We found it necessary to remove the THP group before the final TFA-mediated cleavage because, under these conditions, it was transformed to a reactive species that alkylated position 2 of the estradiol derivatives. However, the presence of the free 17β-alcohol during the final cleavage led to the formation of the corresponding trifluoroacetate. Fortunately, it was easily removed by alkaline hydrolysis. The overall yield (23%) of desired purified product **28** was acceptable, but the crude product after the final cleavage was not pure enough to be used as it for biological screening.

Scheme 6[a]



[a] (a) $TMSCHN_2$, benzene/MeOH (4:1), 25 °C (96%); (b) Cs_2CO_3, CH_3CN/DMF (4:1), 25 °C (67%); (c) LiOH aq, THF, 25 °C (83%); (d) aminomethyl resin (1.0 mmol/g), DIPC, HOBt, DMF, 25 °C; (e) propionic acid, EDC, HOBt, dioxane, then Bu_3P in toluene, 25 °C; (f) *hν* (350 m), MeOH, 25 °C; (g) 2% HCl, MeOH, 25 °C.

Therefore, another linker that would allow the cleavage of the final compound under milder conditions warranted investigation.

Dihydropyranyl (DHP) Resin. We tried the tetrahydropyranyl (THP) linker because of its high sensitivity to relatively weak acids. At the moment we began this study, no examples of a phenolic derivative coupled to this resin had been reported, but recently a short paper describing the coupling of phenolic compounds on such resin according to the procedure initially described by Ellman's group[62] has come out. We performed our model synthetic sequence starting by coupling 16β-(azidopropyl)-estradiol derivative **19** on the commercially available DHP resin (Scheme 4). The FT-IR spectrum of resin **29** confirmed the appearance of the azide stretch, while the ^{13}C NMR spectrum did not produce highly resolved signals but nevertheless confirmed that compound **19** was attached to the polymer. Moreover, transacetalization seemed to occur during this coupling reaction. Thus, an important amount of the 16β-(azidopropyl)-estradiol derivative **19** was also coupled via the 17β-OH leaving unprotected 3-OH, resulting in the isolation of 8% of 3-propionyl ester derivative **32** together with 8% of the free phenol **28**. These problems led us to investigate a base-labile linker to synthesize our estradiol derivatives on solid support.

Carboxypolystyrene Resin. The only convenient method reported for coupling estrone to a polymer was the linkage of its phenol group to carboxypolystyrene via an ester bond.[16] Moreover, a multiple phenolic compounds library was produced using this linker.[63] Even though the resulting benzoyl phenolic ester should have been very labile, we decided to test this linker on our model synthetic sequence. The best method reported for the attachment of phenolic steroids to carboxypolystyrene resin was the derivatization of the latter to its corresponding acyl chloride in ethylbenzene and then heating in the presence of estrone.[16] Because we experienced difficulties in reproducing the reported loading with our steroid substrate **20**, we adopted a slightly modified procedure to attach that molecule onto the chlorocarboxypolystyrene resin. As can be seen in Scheme 5, no problem was detected on the sequence of transformations on solid support, and cleavage conditions were mild enough to provide the final compound **28** in an acceptable yield. However, we noticed that the cleavage conditions that gave the best product recovery also gave substantial amounts of nonsteroidal impurities. Although these impurities were removed by chromatography, we did not find that this linker fully met the criteria for minimizing purification steps before biological screening of the final compounds.

***o*-Nitrobenzyl Photolabile Linker.** In light of the studies described above, it is clear that labile linkers for anchoring phenols such as THP reduce the scope of chemical reactions that can be performed on our substrate. On the other hand, acid-mediated cleavages of phenolic benzyl ethers underwent side reactions, which dramatically decrease the yield of the desired product. This fact has also been recognized in solid-phase peptide chemistry, and the *o*-nitrobenzyl photolabile group was then introduced as a linker.[64,65] In addition, tyrosine residues can be protected as *o*-nitrobenzyl ether[66] and this strategy has been extended to the attachment of phenolic compounds onto solid supports.[67,68] Two approaches to produce resins containing phenolic steroids linked by a

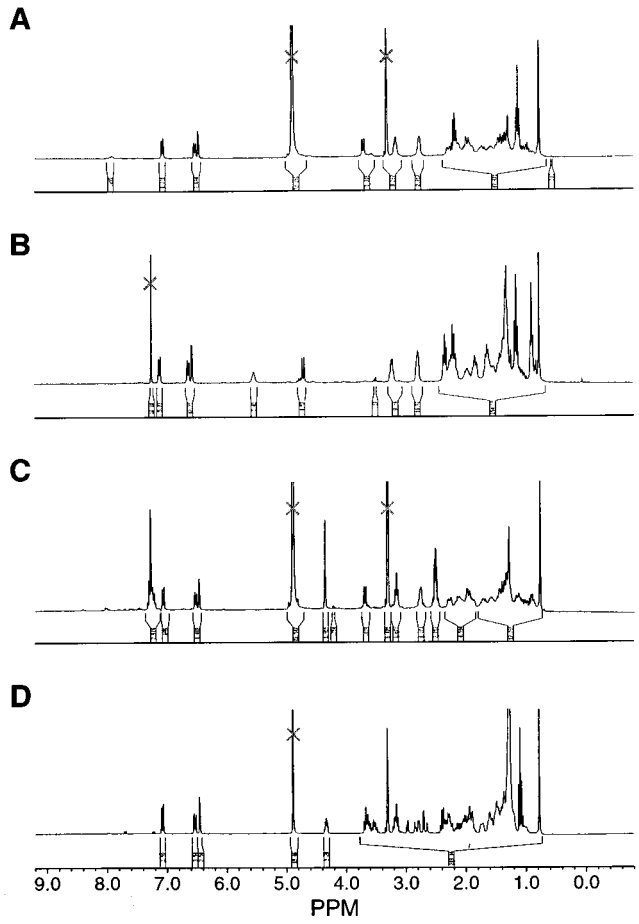
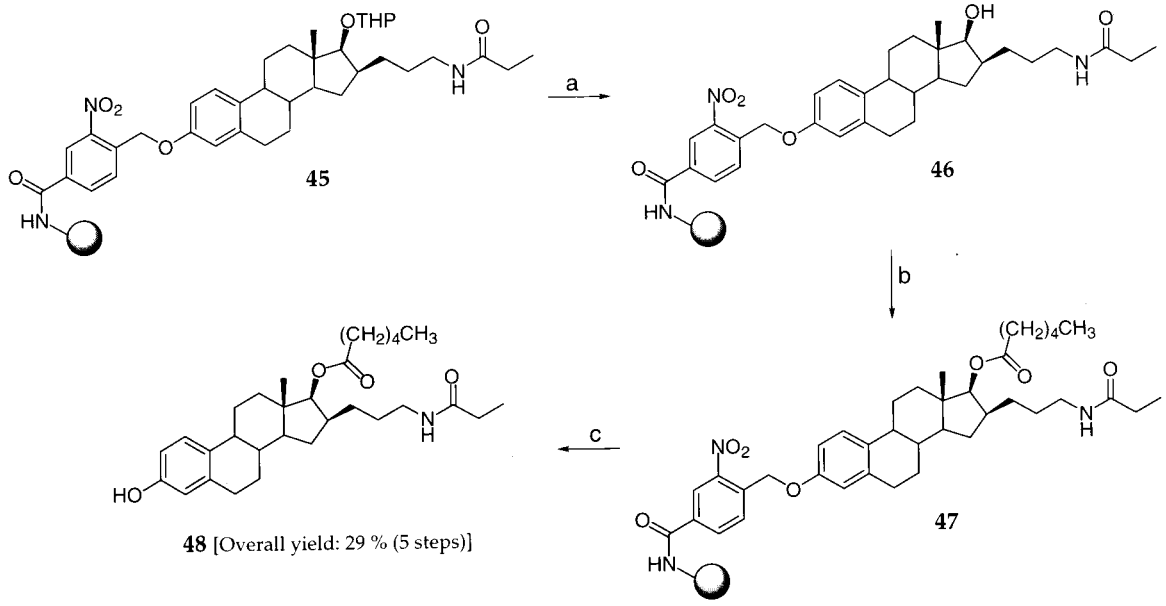


Figure 3. ^{1}H NMR spectra of the crude estradiol derivatives **28** (A), **48** (B), **51** (C), and **58** (D) obtained from the four described synthetic sequences on solid support using the *o*-nitrobenzyl photolabile group as linker (×: signal from NMR solvent).

photolabile linker were considered. First, we synthesized the polystyrene resin **39** having the *o*-nitrobenzyl bromide unit according to the procedure described by Rich and Gurwara (Scheme 6A).[64] However, attempts to directly attach the corresponding sodium or cesium salts of estrone (**10**) did not result in significant increase of the resin weight. Moreover, the FT-IR spectrum did not reveal the presence of the characteristic ketone signal (1735 cm^{-1}) corresponding to **40**. In a second approach (Scheme 6B), we attached the *o*-nitrobenzyl linker **41** to the precursor **19** prior to its coupling to the aminomethyl (AM) resin and then performed the model synthetic sequence. It is noteworthy that the presence of the aromatic nitro group prompted us to make an important modification to the reduction of the azide, which was easily reduced with tin complex in previous sequences. In this particular case, the azide group of **44** was transformed to the iminophosphorane by the Staudinger reaction. Depending on the nature of the acylating agents, the latter was either directly acylated in situ to give the corresponding amide **45** or hydrolyzed to produce the intermediate amine prior to its conversion into amide **45**. This sequence using a photolabile linker resulted in a clean product **28** of acceptable yield (20%) without purification after cleavage (Figure 3A). Thus, the *o*-nitrobenzyl linker met several of the criteria for combinatorial synthesis and was kept in mind for future development of more complex synthetic sequences on phenolic steroids.

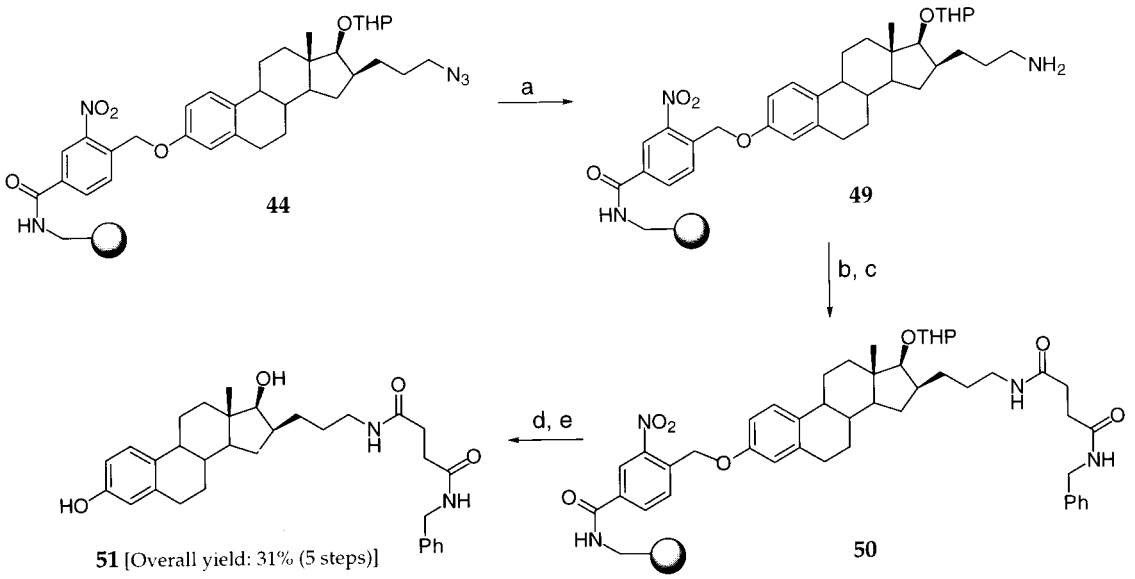
3. Introducing Two Diversity Levels into Estradiol Derivatives: Three Approaches (Schemes 7−9). Three approaches to introduce two diversity levels in our sequence using the *o*-nitrobenzyl photolabile linker were investigated. First, the THP group of resin **45** was removed to generate the free secondary alcohol **46**, which was acylated to yield compound **47**, and **48** after photocleavage (Scheme 7 and Figure 3B). In the second approach (Scheme 8), the azide of resin **44** was reduced according to an adapted procedure initially described by Vaultier et al.[69] and modified by Liang et al.[70] The resulting amine **49** was acylated using succinic anhydride to give the carboxylic acid, which was submitted to a PyBOP-mediated coupling reaction to give the unsymmetric polymer-bound diamide **50**. Although several methods

Scheme 7[a]



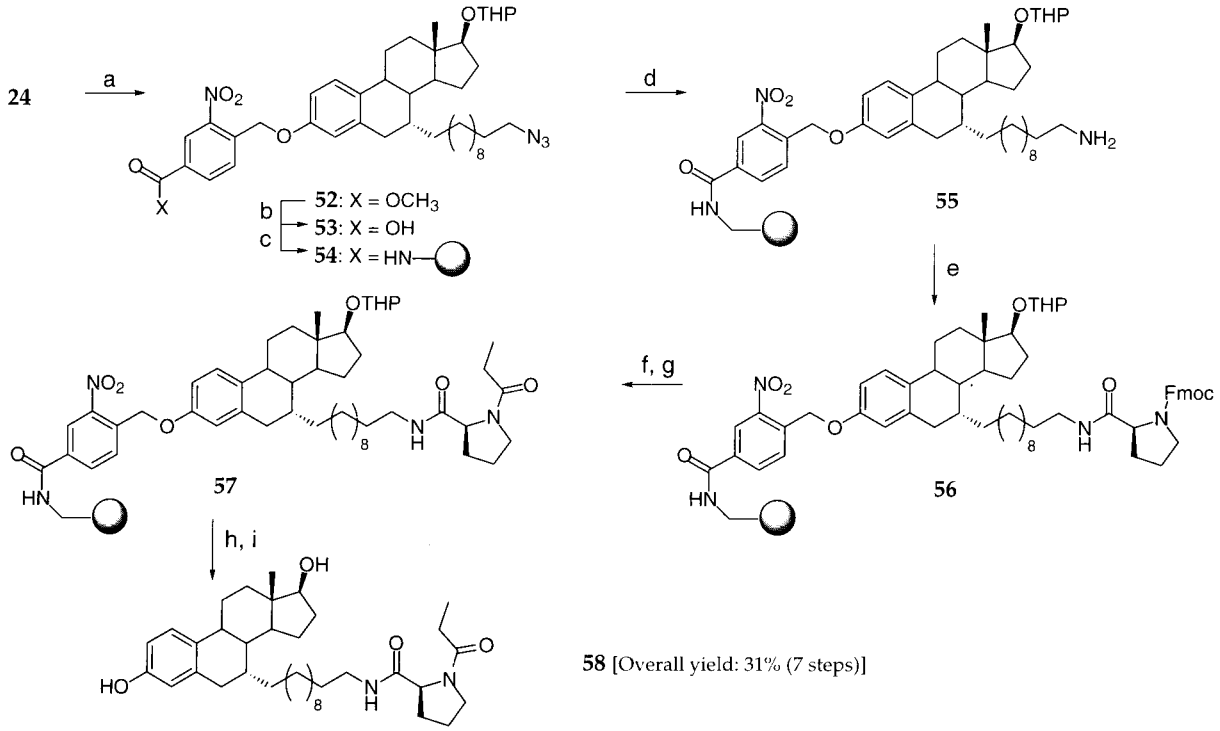
[a] (a) *p*-TSA, 1-butanol/ClCH$_2$CH$_2$Cl (1:1), 25 °C; (b) hexanoic acid, DIPC, *i*-Pr$_2$EtN, DMAP, CH$_2$Cl$_2$, 25 °C; (c) *hν* (350 nm), MeOH, 25 °C.

Scheme 8[a]



[a] (a) *i*. PPh_3, THF, 25 °C; *ii*. H_2O, 70 °C; (b) succinic anhydride, pyridine, 25 °C; (c) $PhCH_2NH_2$, PyBOP, *i*-Pr_2EtN, DMF, 25 °C; (d) *hν* (350 nm), MeOH, 25 °C; (e) 2% HCl, MeOH, 25 °C.

Scheme 9[a]



[a] (a) Cs_2CO_3, **41**, CH_3CN/DMF (4:1), 25 °C (65%); (b) LiOH aq, THF, 25 °C (76%); (c) aminomethyl resin (0.75 mmol/g), EDC, HOBt, DMF, 25 °C; (d) *i*. PPh_3, THF, 25 °C; *ii*. H_2O (e) NHFmoc-Pro-COOH, HBTU, HOBT, *i*-Pr_2EtN, DMF, 25 °C; (f) 20% piperidine, DMF, 25 °C; (g) CH_3CH_2COOH, HBTU, HOBt, *i*-Pr_2EtN, DMF, 25 °C; (h) *p*-TSA, 1-butanol/$ClCH_2CH_2Cl$ (1:1), 25 °C; (i) *hν* (350 nm), MeOH, 25 °C.

were used to perform these two transformations,[71−73] the most appropriate procedure in our case was that developed by Boger's group for the solution-phase synthesis of small-molecule libraries.[74] The photocleavage, and subsequent deprotection of the THP ether, gave the target diamide **51** (Figure 3C) free of either the corresponding cyclic imide or the monoamide, which were side products resulting from other synthetic methods for unsymmetric diamide formation. In the third approach, the estradiol derivative **24** bearing a side chain at position 7α was O-alkylated with the *o*-nitrobenzyl linker prior to its attachment on aminomethyl resin (Scheme 9). Azide **54** was reduced to amine **55** according to the procedure described above. A standard NH-Fmoc amino acid coupling was performed to give the first level of diversity (compound **56**). Then, the Fmoc protecting group was removed to allow a second acylation. Photocleavage and THP acidic hydrolysis gave the acceptably pure compound **58** (Figure 3D). Using this last sequence of transformations, we successfully synthesized a small model library of twenty 7α-alkylamide estradiol derivatives.[36]

Conclusion

We studied several linker strategies to evaluate the scope and limitations during the solid-phase synthesis of estradiol derivatives. Fundamental criteria such as loading capacity, stability during chemical transformations, purity, and recovery of the final product were considered and allowed us to find the most useful linker for our purpose. Benzyl ether (Merrifield) and 4-alkoxybenzyl ether (Wang, HMP) required drastic conditions for the detachment of the final compound which led to undesired side reactions and decreased purity and recovery of the target compound. On the other hand, the THP ether linker was found inappropriate because of an unsatisfactory coupling reaction. Despite the fact that the carboxypolystyrene resin gave interesting loading properties and stability, we found that the cleavage reaction was always accompanied by an important amount of impurities. Finally, we found the *o*-nitrobenzyl photolabile linker convenient, and it enabled the synthesis of four types of estradiol derivatives with acceptable purities without further purification after the final cleavage (Figure 3). Three approaches were successfully used to generate estradiol derivatives with two levels of functional group diversity (Schemes 7−9). The introduction of commercially available building blocks, such as amino acids, acyl chlorides, and anhydrides, on a conviently designed steroidal scaffold gave the desired target compounds with a good degree of molecular diversity. The present paper describes the first step toward the generation of several estradiol-related compounds that could be tested on a variety of biological processes.

Experimental Section

General Methods. Reagents were obtained from Sigma-Aldrich Canada Co. (Oakville, Canada). Estrone was supplied by Steraloids (Wilton, NH). Merrifield resin was purchased from Aldrich (Milwaukee, WI), Wang and aminomethyl resin from Richelieu Technologies (Montréal, Canada) or NovaBiochem (LaJolla, CA), DHP and carboxypolystyrene resins from NovaBiochem. Usual solvents were obtained from Fisher Scientific (Montréal, Canada) and were used as received. Anhydrous dimethylformamide (DMF), methylene chloride (CH_2Cl_2), 1,2-dichloroethane ($ClCH_2CH_2Cl$), benzene, toluene, pyridine, and methanol (MeOH) were obtained from Aldrich in SureSeal bottles, which were conserved under positive argon pressure. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under argon. All anhydrous reactions were performed in oven-dried glassware under positive argon pressure. Solid-phase reactions were almost all performed in peptide-flask fritted glass tubes equipped for vacuum filtration (ChemGlass Inc., Vineland, NJ) and were agitated with a Burrell wrist-action shaker Model 75 (Burrell, Pittsburg, PA). Flash chromatography was performed on E. Merck 60 230−400 mesh silica gel. Thin-layer chromatography was performed on 0.25 mm E. Merck silica gel 60 F_{254} plates and visualized by UV (254 nm) and/or cerium ammonium molybdate. Infrared (IR) spectra were recorded on a Pelkin-Elmer series 1600 FT-IR spectrometer, and the significant bands were reported in cm^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded at 300 MHz for ^1H and 75.5 MHz for ^{13}C on a Bruker AC/F300 spectrometer. Duplication of NMR signals was generally recorded for THP derivatives, but depending the purification method used, the two stereoisomers occurred in varying proportions. The presence of these two stereoisomers increased the complexity of ^{13}C NMR spectra, and additional peaks are written between parentheses. Low-resolution mass spectra were recorded on a API-150ex apparatus equipped with a turbospray source. High-resolution mass spectra were provided by the Centre Régional de Spectrométrie de Masse (Université de Montréal, Montréal, Canada).

Synthesis of 16*β*-(3-Azido-propyl)-estradiol Derivatives 19 and 20 (Scheme 1). 3-*tert*-Butyldimethylsilyloxy-16α-allyl-estra-1,3,5(10)-trien-17-one (12). This compound was prepared as described earlier by our group.[28,75]

3-*tert*-Butyldimethylsilyloxy-17*β*-(tetrahydro-2*H*-pyran-2-yl-oxy)-16*β*-allyl-estra-1,3,5(10)-triene (13). *Inversion of the C16-Configuration*: A solution of diisopropylamine (11 mL; 78.5 mmol) in 175 mL of dry THF was stirred under argon at 0 °C, and 1.6 M *n*-butyllithium (47 mL; 75.5 mmol) was added dropwise. After 30 min, the solution was cooled at −78 °C and the ketone **12** (12.8 g; 30.2 mmol), dissolved in 100 mL of dry THF, was added dropwise to the LDA solution. The mixture was stirred for 1 h at 0 °C before cooling at −78 °C. Then, dry MeOH (3.7 mL; 90.6 mmol) was slowly added to the solution, which was stirred at −78 °C for 1 h. After addition of water, the crude product was extracted with EtOAc. The organic phase was washed with a saturated NaCl solution, dried over $MgSO_4$, and evaporated under reduced pressure. *Reduction:* To a −78 °C solution of the crude ketone (25.2 g; 59.2 mmol) dissolved in 500 mL of dry THF was added lithium aluminum hydride (3.4 g; 89.1 mmol) in small portions, and the resulting mixture was stirred under argon for 4 h at the same temperature. The reaction was quenched by the addition of 3.3 mL of water, followed by 3.3 mL of 15% aqueous NaOH, and an additional 10 mL of water. The crude compound was extracted with EtOAc (3×) from the resulting mixture. The organic layer was washed with brine, dried over $MgSO_4$, and the solvent was evaporated to dryness. *Protection of 17β-Alcohol as a THP*: The crude alcohol (20 g; 46.9 mmol) and 3,4-dihydro-2*H*-pyran (13.7 mL; 150 mmol) were dissolved in 400 mL of anhydrous CH_2Cl_2 under argon. The mixture was cooled at 0 °C, and a catalytic amount of *p*-TSA (892 mg; 4.7 mmol) was added. The reaction was allowed to reach room temperature. After 3 h, a saturated aqueous $NaHCO_3$ solution was added, and extraction was performed with CH_2Cl_2 (3×). The organic phase was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. Purification by flash silica gel chromatography with hexane:EtOAc:Et_3N (98:1:1) as eluent gave 21.8 g (89% yield, three steps) of the diprotected alkene **13**. Amorphous white foam. IR ν (film): no C═O bond. ^1H NMR δ ($CDCl_3$): 0.18 (s, 6H, $Si(CH_3)_2$), 0.80 and 0.85 (2s, 3H, 18-CH_3), 0.98 (s, 9H, $SiC(CH_3)_3$), 2.77 (m, 2H, 6-CH_2), 3.50 and 3.97 (2m, 2H, OCH_2 of THP), 3.75 and 3.83 (2d, J = 9.4 Hz, 1H, 17α-CH), 4.64 and 4.75 (2m, 1H, OCH of THP), 5.00 (m, 2H, CH═CH_2), 5.79 (m, 1H, C*H*═CH_2), 6.54 (d, J = 2.4 Hz, 1H, 4-CH), 6.60 (dd, J_1 = 8.3 Hz and J_2 = 2.4 Hz, 1H, 2-CH), 7.10 and 7.12 (2d, J = 8.3 Hz, 1H, 1-CH). ^{13}C NMR δ ($CDCl_3$): −4.38 (2C),

13.12 (13.23), 18.18, 19.28 (19.68), 25.61, 25.72 (3C), 26.24 (26.35), 27.40, 30.46, 30.73 (31.00), 31.70 (31.99), 35.94, 36.87 (36.96), 37.99 (38.19), 38.94 (39.12), 43.70 (43.88), 44.09 (44.30), 48.85 (49.06), 61.73 (62.56), 85.04 (85.90), 97.66 (98.58), 114.42 (114.63), 117.1, 119.92, 126.09, 133.13 (133.26), 137.85 (138.74), 139.25, 153.27. HRMS: Calcd for $C_{32}H_{50}O_3Si$, 510.3544. Found: 510.3529.

3-*tert*-Butyldimethylsilyloxy-17β-acetoxy-16β-allyl-estra-1,3,5(10)-triene (14). The inversion of the C16-configuration and the reduction of the 17-carbonyl were performed as described above. The protection of 17β-alcohol as an acetate was done as follows: To a solution of the crude alcohol (1.9 g; 4.46 mmol) in 20 mL of dry pyridine at 0 °C were added acetyl chloride (3.2 mL; 44.6 mmol) and (dimethylamino)pyridine (109 mg; 0.39 mmol), and the resulting mixture was stirred for 1 h at 25 °C. Then, EtOAc was added and the organic phase was washed successively with a saturated solution of NH_4Cl, a 1 M aqueous solution of $CuSO_4$, and H_2O. The organic solvent was dried over $MgSO_4$ and evaporated to dryness. Purification by flash silica gel chromatography with hexane:EtOAc (9:1) as eluent gave 1.45 g (70% yield, three steps) of the diprotected alkene **14**. White solid. IR ν (film): 1737 (C=O, ester). ^{1}H NMR δ ($CDCl_3$): 0.18 (s, 6 H, $Si(CH_3)_2$), 0.85 (s, 3H, 18-CH_3), 0.97 (s, 9H, $SiC(CH_3)_3$), 2.09 (s, 3H, CH_3CO), 2.79 (m, 2H, 6-CH_2), 4.80 (d, J = 9.8 Hz, 1H, 17α-CH), 4.99 (m, 2H, CH=CH_2), 5.72 (m, 1H, CH=CH_2), 6.55 (d, J = 2.1 Hz, 1H, 4-CH), 6.60 (dd, J_1 = 7.9 Hz and J_2 = 2.3 Hz, 1H, 2-CH), 7.10 (d, J = 8.4 Hz, 1H, 1-CH). ^{13}C NMR δ ($CDCl_3$): −4.40 (2C), 13.33, 18.16, 21.01, 25.71 (3C), 26.05, 27.41, 29.60, 31.87, 36.35, 37.62, 37.90, 38.02, 43.57, 43.86, 48.82, 82.98, 115.10, 117.16, 119.93, 126.09, 132.93, 137.73, 137.79, 153.33, 171.10. LRMS: Calcd for $C_{29}H_{45}O_3Si$ $[M+H]^+$: 469.3. Found: 469.5 *m*/*z*.

3-[3-*tert*-Butyldimethylsilyloxy-17β-(tetrahydro-2*H*-pyran-2-yl-oxy)-estra-1,3,5(10)-trien-16β-yl]-propanol (15). To a solution of the alkene **13** (21.8 g; 42.7 mmol) dissolved in 450 mL of dry THF at 0 °C was added 1.0 M borane−THF complex (98 mL; 98 mmol) under an argon atmosphere. The mixture was stirred at 0 °C for 3 h. Then, 3 N aqueous NaOH (36 mL; 106.8 mmol) and 30% (w/v) hydrogen peroxide (15 mL; 234.9 mmol) were added. After 2 h at room temperature, the reaction was quenched by the addition of water and the extraction was performed with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The crude compound was purified by flash chromatography (hexane:EtOAc:Et_3N, 89:10:1) to give 13.9 g (62% yield) of the desired alcohol **15**. Amorphous white foam. IR ν (film): 3410 (OH, alcohol). ^{1}H NMR δ ($CDCl_3$): 0.18 (s, 6H, $Si(CH_3)_2$), 0.79 and 0.84 (2s, 3H, 18-CH_3), 0.97 (s, 9H, $SiC(CH_3)_3$), 2.79 (m, 2H, 6-CH_2), 3.49 and 3.96 (2m, 2H, OCH_2 of THP), 3.65 (m, 2H, CH_2OH), 3.73 and 3.79 (2d, J = 9.6 Hz, 1H, 17α-CH), 4.62 and 4.68 (2m, 1H, OCH of THP), 6.55 (d, J = 2.4 Hz, 1H, 4-CH), 6.60 (dd, J_1 = 8.5 Hz and J_2 = 2.4 Hz, 1H, 2-CH), 7.10 and 7.12 (2d, J = 8.5 Hz, 1H, 1-CH). ^{13}C NMR δ ($CDCl_3$): −4.39 (2C), 13.14 (13.20), 18.17, 19.34 (20.27), 25.54, 25.71 (3C), 26.23 (26.32), 27.39, 28.33 (28.43), 29.67, 30.78 (31.14), 31.88, 32.42, 38.02, 38.20 (38.48), 38.87 (39.32), 43.66 (43.88), 44.05 (44.23), 48.78 (49.00), 61.79 (63.04), 63.32, 85.93 (86.14), 97.75 (99.59), 117.11, 119.91, 126.08, 133.10 (133.25), 137.82, 153.27. HRMS: Calcd for $C_{32}H_{52}O_4Si$, 528.3619. Found: 528.3635.

3-(3-*tert*-Butyldimethylsilyloxy-17β-acetoxy-estra-1,3,5(10)-trien-16β-yl)-propanol (16). To a solution of the alkene **14** (715 mg; 1.53 mmol) dissolved in 30 mL of dry THF (10 mL) was added 1.0 M borane−THF complex (6.9 mL; 6.9 mmol) at 0 °C under an argon atmosphere. The mixture was stirred at 0 °C for 3 h. Then, 6 M aqueous NaOAc (1.3 mL; 7.65 mmol) and 30% (w/v) hydrogen peroxide (0.22 mL; 7.65 mmol) were added. After 90 min at room temperature, the reaction was quenched by water and the extraction was performed with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The crude compound was purified by flash chromatography (hexane:EtOAc, 7:3) to give a small amount of the saturated product and 453 mg (58% yield) of the desired alcohol **16**. Amorphous white solid. IR ν (film): 3420 (OH, alcohol), 1735 (C=O, ester). ^{1}H NMR δ ($CDCl_3$): 0.18 (s, 6 H, $Si(CH_3)_2$), 0.84 (s, 3H, 18-CH_3), 0.97 (s, 9H, $SiC(CH_3)_3$), 2.10 (s, 3H, CH_3CO), 2.80 (m, 2H, 6-CH_2), 3.64 (m, 2H, CH_2OH), 4.75 (d, J = 10 Hz, 1H, 17α-CH), 6.55 (d, J = 2.2 Hz, 1H, 4-CH), 6.60 (dd, J_1 = 8.4 Hz and J_2 = 2.4 Hz, 1H, 2-CH), 7.10 (d, J = 8.5 Hz, 1H, 1-CH). ^{13}C NMR δ ($CDCl_3$): −4.40 (2C), 13.36, 18.16, 21.04, 25.71 (3C), 26.05, 27.41, 27.91, 29.60, 31.49, 32.19, 37.65, 38.03, 38.37, 43.50, 43.84, 48.75, 62.96, 83.42, 117.16, 119.92, 126.09, 132.90, 137.69, 153.33, 171.26. LRMS: Calcd for $C_{29}H_{47}O_4Si$ $[M+H]^+$: 487.3. Found: 487.4 *m*/*z*.

3-[3-*tert*-Butyldimethylsilyloxy-17β-(tetrahydro-2*H*-pyran-2-yl-oxy)-estra-1,3,5(10)-trien-16β-yl]-azidopropane (17). Recrystallized tosyl chloride (1.6 g, 8.5 mmol) was added to a cooled solution of the alcohol **15** (3.0 g, 5.7 mmol) in dry pyridine (15 mL) at 0 °C. After 5 h, EtOAc was added, and the organic phase was washed several times with a 1 M solution of $CuSO_4$, then water, and aqueous NaOH (10%, w/v). The basic aqueous phase was re-extracted with EtOAc, and the combined organic layers were successively washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. Sodium azide (924 mg, 14.2 mmol) was added to a solution of the tosylated compound (3.9 g) in dry DMF (15 mL), and the mixture was stirred at room temperature overnight. After completion of the reaction, water was added, and the crude compound was extracted with CH_2Cl_2. The organic phase was washed several times with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Purification by flash chromatography using hexane:EtOAc (9:1) as eluent afforded 2.6 g (83% yield for 2 steps) of the azide **17**. Amorphous white solid. IR ν (film): 2094 (N_3). ^{1}H NMR δ ($CDCl_3$): 0.19 (s, 6H, $Si(CH_3)_2$), 0.80 and 0.85 (2s, 3H, 18-CH_3), 0.98 (s, 9H, $SiC(CH_3)_3$), 2.80 (m, 2H, 6-CH_2), 3.27 (m, 2H, CH_2N_3), 3.51 and 3.96 (2m, 2H, OCH_2 of THP), 3.73 and 3.82 (2d, J = 9.8 Hz, 1H, 17α-CH), 4.62 and 4.72 (2m, 1H, OCH of THP), 6.55 (d, J = 2.4 Hz, 1H, 4-CH), 6.60 (dd, J_1 = 8.5 Hz and J_2 = 2.4 Hz, 1H, 2-CH), 7.10 and 7.12 (2d, J = 8.5 Hz, 1H, 1-CH). ^{13}C NMR δ ($CDCl_3$): −4.41 (2C), 13.12 (13.21), 18.15, 19.29 (19.95), 25.52, 25.70 (3C), 26.18 (26.30), 27.37, 28.00

(28.06), 29.50 (29.63), 30.75 (31.03), 32.13 (32.24), 32.38, 37.65 (37.94), 38.14 (38.22), 39.45 (39.71), 43.63 (43.82), 44.02 (44.15), 48.61 (48.95), 51.69 (51.75), 61.79 (62.93), 85.10 (86.00), 97.74 (98.88), 117.12, 119.91, 126.08, 133.01 (133.17), 137.78, 153.25. HRMS: Calcd for $C_{32}H_{51}O_3N_3Si$, 553.3725. Found: 553.3700.

3-(3-*tert*-Butyldimethylsilyloxy-17*β*-acetoxy-estra-1,3,5-(10)-trien-16*β*-yl]-azidopropane (18). Recrystallized tosyl chloride (2.8 g; 14.8 mmol) was added to a cooled solution of the alcohol **16** (2.4 g; 4.94 mmol) in dry pyridine (20 mL) at 0 °C. After 2 h, tosyl chloride (1 equiv) was added to the mixture at 0 °C. After 4 h, EtOAc was added and the organic phase was washed several times with a 1 M solution of $CuSO_4$, then water, and aqueous NaOH (10%, w/v). The basic aqueous phase was re-extracted with EtOAc, and the combined organic layers were successively washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. Sodium azide (782 mg, 12.0 mmol) was added to a solution of the crude tosylated compound (3.0 g) in dry DMF (20 mL), and the mixture was stirred at room temperature for 6 h. After completion of the reaction, water was added and the crude compound was extracted with CH_2Cl_2. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Purification by flash chromatography (hexane:EtOAc, 95:5) gave 2.0 g (80% yield for two steps) of the azide **18**. Amorphous white solid. IR ν (film): 2095 (N_3), 1735 (C═O, ester). ^{1}H NMR δ ($CDCl_3$): 0.19 (s, 6 H, $Si(CH_3)_2$), 0.85 (s, 3H, 18-CH_3), 0.98 (s, 9H, $SiC(CH_3)_3$), 2.11 (s, 3H, CH_3CO), 2.81 (m, 2H, 6-CH_2), 3.26 (m, 2H, CH_2N_3), 4.77 (d, J = 9.9 Hz, 1H, 17α-CH), 6.55 (d, J = 2.1 Hz, 1H, 4-CH), 6.61 (dd, J_1 = 8.5 Hz and J_2 = 2.4 Hz, 1H, 2-CH), 7.11 (d, J = 8.5 Hz, 1H, 1-CH). ^{13}C NMR δ ($CDCl_3$): −4.43 (2C), 13.33, 18.14, 20.97, 25.68 (3C), 26.02, 27.38, 27.79, 29.00, 29.56, 32.08, 37.61, 37.99, 38.29, 43.50, 43.81, 48.73, 51.56, 83.15, 117.16, 119.90, 126.06, 132.83, 137.64, 153.33, 171.09. LRMS: Calcd for $C_{29}H_{46}N_3O_3Si$ $[M+H]^+$: 512.3. Found: 512.4 *m*/*z*.

3-[3-Hydroxy-17*β*-(tetrahydro-2*H*-pyran-2-yl-oxy)-estra-1,3,5(10)-triene-16*β*-yl]-azidopropane (19). To a cooled solution of the protected derivative **17** (4.1 g; 7.4 mmol) in 30 mL of dry THF at 0 °C was added a 1.0 M solution of tetrabutylammonium fluoride (11.1 mL; 11.1 mmol), and the resulting mixture was stirred at 0 °C for 1 h. Then, a saturated $NaHCO_3$ solution was added, and the crude compound was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Purification by flash chromatography (hexane:EtOAc, 8:2) gave 2.9 g (90% yield) of the desired phenol **19**. Amorphous white solid. IR ν (film): 3350 (OH, phenol), 2095 (N_3). ^{1}H NMR δ ($CDCl_3$): 0.79 and 0.83 (2s, 3H, 18-CH_3), 2.80 (m, 2H, 6-CH_2), 3.26 (m, 2H, CH_2N_3), 3.55 and 3.95 (2m, 2H, CH_2O of THP), 3.73 and 3.81 (2d, J = 10 Hz, 1H, 17α-CH), 4.70 (2m, 1H, CHO of THP), 6.55 (d, J = 2.4 Hz, 1H, 4-CH), 6.62 (dd, J_1 = 8.4 Hz and J_2 = 2.1 Hz, 1H, 2-CH), 7.13 and 7.15 (2d, J = 8.4 Hz, 1H, 1-CH). ^{13}C NMR δ ($CDCl_3$): 13.08 (13.17), 19.24 (19.92), 25.53 (25.64), 26.30 (26.39), 27.30, 28.01 (28.16), 29.48, 29.64, 30.77 (31.04), 32.12 (32.24), 37.92, 38.18 (38.26), 38.87 (39.46), 43.63 (43.75), 43.94 (44.25), 48.71 (48.92), 51.73, 61.80 (62.94), 85.24 (86.11), 97.78 (98.96), 112.68, 115.24, 126.48, 132.74, 138.19, 153.43. LRMS: Calcd for $C_{21}H_{30}N_3O_2$ $[M\text{-}THP+H]^+$: 356.2. Found: 356.4 *m*/*z*.

3-[3-Hydroxy-17*β*-acetoxy-estra-1,3,5(10)-trien-16*β*-yl]-azidopropane (20). To a solution of the protected derivative **18** (2.02 g; 3.95 mmol) in 40 mL of anhydrous THF at 0 °C was added a 1.0 M solution of tetrabutylammonium fluoride (5.9 mL; 5.9 mmol), and the resulting mixture was stirred at 0 °C for 30 min. Then, a saturated $NaHCO_3$ solution was added, and the crude compound was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Purification by flash chromatography (hexane: EtOAc, 8:2) gave 1.33 g (85% yield) of the desired phenol **20**. Amorphous white solid. IR ν (film): 3390 (OH, phenol), 2095 (N_3), 1735 (C═O, ester). ^{1}H NMR δ ($CDCl_3$): 0.83 (s, 3H, 18-CH_3), 2.12 (s, 3H, CH_3CO), 2.81 (m, 2H, 6-CH_2), 3.26 (m, 2H, CH_2N_3), 4.77 (d, J = 10 Hz, 1H, 17α-CH), 5.20 (broad, 1H, OH), 6.57 (d, J = 2.4 Hz, 1H, 4-CH), 6.63 (dd, J_1 = 8.3 Hz and J_2 = 2.5 Hz, 1H, 2-CH), 7.13 (d, J = 8.4 Hz, 1H, 1-CH). ^{13}C NMR δ ($CDCl_3$): 13.29, 21.01, 26.08, 27.29, 27.77, 28.98, 29.54, 32.06, 37.55, 38.00, 38.26, 43.50, 43.72, 48.64, 51.56, 83.27, 112.69, 115.23, 126.46, 132.36, 138.05, 153.46, 171.41. LRMS: Calcd for $C_{23}H_{32}N_3O_3$ $[M+H]^+$: 398.3. Found: 398.2 *m*/*z*.

Synthesis of 7α-(azidoundecanyl)-estradiol Derivatives 24 (Scheme 2). 11-(3-Benzoyloxy-17*β*-hydroxy-1,3,5(10)-estratrien-7α-yl)-bromoundecane (22). A mixture of the starting alcohol **21**[38] (15.1 g; 27.2 mmol), PPh_3 (14.9 mmol; 55.2 mmol), and CBr_4 (18.3 g; 55.2 mmol) in 500 mL of dry CH_2Cl_2 was stirred at 0 °C under argon for 90 min. The crude mixture was preadsorbed on silica gel, and the residue was purified by flash chromatography (CH_2Cl_2:EtOAc, 9:1) to give 10.4 g (64% yield) of the bromide **22**. Amorphous solid. IR ν (film): 3410 (OH, alcohol) and 1737 (C═O, ester). ^{1}H NMR δ ($CDCl_3$): 0.79 (s, 3H, 18-CH_3), 2.86 (ABX system, 2H, 6-CH_2), 3.40 (t, J = 7.0 Hz, 2H, CH_2Br), 3.76 (m, 1H, 17α-CH), 6.93 (d, J = 2.4 Hz, 1H, 4-CH), 6.98 (dd, J_1 = 8.5 Hz and J_2 = 2.4 Hz, 1H, 2-CH), 7.34 (d, J = 8.5 Hz, 1H, 1-CH), 7.50 (t_{app}, J = 7.6 Hz, 2H, *meta*-protons of benzoyl), 7.64 (t_{app}, J = 7.6 Hz, 1H, *para*-proton of benzoyl), 8.19 (d, J = 8.0 Hz, 2H, *ortho*-protons of benzoyl). ^{13}C NMR δ ($CDCl_3$): 11.03, 22.60, 25.64, 27.09, 28.10, 28.16, 28.69, 29.35, 29.44, 29.53, 29.69, 29.92, 30.49, 32.77, 33.08, 34.02, 34.48, 36.84, 38.21, 41.64, 43.28, 46.42, 81.88, 118.68, 122.42, 126.96, 128.48 (2C), 129.66, 130.07 (2C), 133.43, 137.19, 137.28, 148.64, 165.37. LRMS: Calcd for $C_{36}H_{50}O_3Br$ $[M+H]^+$: 609.3 and 611.3. Found: 609.4 and 611.4 *m*/*z*.

11-[3-Benzoyloxy-17*β*-(tetrahydro-2*H*-pyran-2-yl-oxy)-1,3,5(10)-estratrien-7α-yl]-bromoundecane (23). The alcohol **22** (10.4 g; 17.8 mmol) and 3,4-dihydro-2*H*-pyran (5.2 mL; 57.0 mmol) were dissolved in 300 mL of anhydrous CH_2Cl_2 under argon. The mixture was cooled at 0 °C before the addition of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) (338 mg; 1.8 mmol), and the solution was stirred at 0 °C for 1 h. Then, a 5% $NaHCO_3$ aqueous solution was added to the mixture, and the crude compound was extracted

twice with CH_2Cl_2. The combined organic layers were washed with water, dried over $MgSO_4$, and evaporated under reduced pressure. Purification by flash chromatography (hexane:EtOAc, 98:2) gave 11.5 g (90% yield) of the protected compound **23**. Colorless oil. IR ν (film): 1738 (C═O, ester). ^{1}H NMR δ ($CDCl_3$): 0.82 and 0.83 (2s, 3H, 18-CH_3), 2.83 (ABX system, 2H, 6-CH_2), 3.40 (t, J = 6.8 Hz, 2H, CH_2Br), 3.50 and 3.90 (2m, 2H, CH_2O of THP), 3.75 (t, J = 8.5 Hz, 1H, 17α-CH), 4.67 and 4.96 (2m, 1H, CHO of THP), 6.91 (d, J = 2.0 Hz, 1H, 4-CH), 6.97 (dd, J_1 = 8.5 Hz and J_2 = 2.0 Hz, 1H, 2-CH), 7.33 and 7.34 (2d, J = 8.5 Hz, 1H, 1-CH), 7.50 (t_{app}, J = 7.4 Hz, 2H, *meta*-protons of benzoyl), 7.63 (t_{app}, J = 7.4 Hz, 1H, *para*-proton of benzoyl), 8.19 (d, J = 7.5 Hz, 2H, *ortho*-protons of benzoyl). ^{13}C NMR δ ($CDCl_3$): 11.71, 19.31 (19.87), 22.55 (22.67), 25.52 (25.63), 25.63, 27.15, 28.15 (2C), 28.73, 29.39, 29.48, 29.55, 29.67, 29.92, 30.66, 31.05, 32.81, 33.06 (33.15), 34.02, 34.56, 37.35 (37.92), 38.25 (38.34), 41.48, 42.85 (43.36), 46.49, 61.77 (62.70), 84.16 (86.59), 96.54 (99.35), 118.63, 122.41, 126.99, 128.49 (2C), 129.73, 130.08 (2C), 133.41, 137.26 (2C), 148.63, 165.38. LRMS: Calcd for $C_{41}H_{58}O_4$-Br $[M+H]^+$: 693.3 and 695.3. Found: 693.3 and 695.3 *m*/*z*.

11-[3-Hydroxy-17*β*-(tetrahydro-2*H*-pyran-2-yl-oxy)-1,3,5(10)-estratrien-7α-yl]-azidoundecane (24). Sodium azide (4.2 g; 64.4 mmol) was added to a solution of bromide **23** (11.5 g; 16.1 mmol) in 70 mL of dry DMF under argon, and the slurry was heated at 80 °C for 8 h. Then, two portions of sodium azide (2 equiv and 4 equiv, respectively) were added to complete the reaction. Diethyl ether was added next, and the organic layer was washed three times with water, once with brine, dried over $MgSO_4$, and evaporated in vacuo. Purification by flash chromatography (hexane:EtOAc, 95:5) gave the desired compound contaminated with benzoyl azide. A second purification on silica gel (CH_2Cl_2) was needed to provide 4.9 g (77% yield) of the azide **24**. Colorless oil. IR ν (film): 3360 (OH, phenol) and 2095 (N_3). ^{1}H NMR δ ($CDCl_3$): 0.81 and 0.83 (2s, 3H, 18-CH_3), 2.80 (ABX system, 2H, 6-CH_2), 3.26 (t, J = 7.0 Hz, 2H, CH_2N_3), 3.50 and 3.95 (2m, 2H, CH_2O of THP), 3.76 (t, J = 8.5 Hz, 1H, 17α-CH), 4.72 (m, 1H, CHO of THP), 6.0 (broad, 1H, OH), 6.57 (d, J = 2.3 Hz, 1H, 4-CH), 6.60 (dd, J_1 = 8.4 Hz and J_2 = 2.0 Hz, 1H, 2-CH), 7.14 and 7.15 (2d, J = 8.5 Hz, 1H, 1-CH). ^{13}C NMR δ ($CDCl_3$): 11.66, 19.08 (19.71), 22.48 (22.63), 25.52, 26.61, 27.07, 27.26, 28.13, 28.61 (28.73), 29.04, 29.38 (2C), 29.43 (2C), 29.52 (29.65), 29.88, 30.99, 33.08 (33.14), 34.54, 37.30 (37.88), 37.93 (38.03), 41.64 (41.72), 42.84 (43.37), 46.33 (46.39), 51.40, 61.63 (62.63), 84.23 (86.77), 96.43 (99.34), 112.77, 116.10, 126.91, 131.60 (131.73), 137.00, 153.58. LRMS: Calcd for $C_{34}H_{54}N_3O_3$ $[M+H]^+$: 552.4. Found: 552.4 *m*/*z*.

Model Synthetic Sequence Using Merrifield Resin (Scheme 3). To a swollen mixture of Merrifield resin (317 mg; 0.317 mmol) in 2 mL of dry DMF was added a solution of the sodium salt of derivative **19** (349 mg; 0.79 mmol) in 3.5 mL of dry DMF, and the resulting slurry was stirred at 50 °C for 6 h. Then, the resin was filtered, washed successively with dioxane:H_2O (5 × 5 mL), dioxane (5 × 5 mL), H_2O (2 × 5 mL), DMF (5 × 5 mL), CH_2Cl_2 (5 × 5 mL), and MeOH (2 × 5 mL). After drying 16 h under vacuum, 452 mg of resin **25** was recovered corresponding to a quantitative loading yield. IR (KBr): 2092 (N_3). ^{13}C NMR ($CDCl_3$): characteristic signals for the steroidal moiety. This resin (450 mg) was swollen in 1 mL of anhydrous THF, and 5 mL of a freshly prepared solution of $SnCl_2$:HSPh:Et_3N (0.2 M:0.8 M:1.0 M) was added. The resulting mixture was vortexed under argon for 5 h at 25 °C. Then, the resin was filtered and washed with DMF (5 × 10 mL) and CH_2Cl_2 (5 × 10 mL). After drying 16 h under vacuum, 430 mg of resin was weighed. The IR spectrum confirmed the disappearance of the azide band and a broadening of the NH signal. To a swollen mixture of the resin **26** (430 mg) in 3 mL of dry 1,2-dichloroethane were added diisopropylethylamine and propionyl chloride to give 0.6 and 0.5 M solutions, respectively. The mixture was vortexed overnight at 25 °C. The resin was then filtered and washed successively with DMF (5 × 5 mL), CH_2Cl_2 (5 × 5 mL), and MeOH (2 × 5 mL). IR (KBr): 1656 (C═O, amide). ^{13}C NMR ($CDCl_3$): characteristic signals for the steroidal moiety. The resulting resin **27** was suspended in 6 mL of 1-butanol:1,2-dichloroethane (1:1) in the presence of *p*-TSA (57 mg; 0.3 mmol) for 16 h at 25 °C. The resin was filtered, washed with DMF (5 × 5 mL), CH_2Cl_2 (5 × 5 mL), MeOH (5 × 5 mL), and dried under vacuum overnight to yield 416 mg of dry resin. The final cleavage was performed on 300 mg of resin that was stirred in 2.2 mL of a freshly prepared solution of TFA:H_2O:PhSMe (95:5:10) for 2 h at 25 °C. The resin was filtered, washed with TFA (2 × 2 mL) and CH_2Cl_2 (2 × 5 mL), and the resulting filtrate was concentrated to dryness. The resulting crude product was treated with 4 mL of a mixture of 0.5 N NaOH in THF (1:1, v/v) for 30 min at 25 °C. The reaction was neutralized with a 10% aqueous solution of HCl, and the crude product was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Purification by flash chromatography (hexane:EtOAc, 2:8) yielded 27 mg (23% overall yield) of the desired compound **28**.

***N*-[3-(3,17*β*-Dihydroxy-estra-1,3,5(10)-trien-16*β*-yl)-propyl]-propanamide (28).** IR ν (KBr): 3350 (OH, NH), 1630 (C═O, amide). ^{1}H 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_2-CO), 2.75 (m, 6-CH_2), 3.16 (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: Calcd for $C_{24}H_{36}$-NO_3 $[M+H]^+$: 386.3. Found: 386.0 *m*/*z*.

Model Synthetic Sequence Using DHP Resin (Scheme 4). To a swollen mixture of DHP-HM resin (750 mg; 0.51 mmol) in 6 mL of dry 1,2-dichloroethane were added the phenolic derivative **19** (898 mg; 2.0 mmol) and pyridinium *p*-toluenesulfonate (PPTS) (256 mg, 1.0 mmol) in a round-bottom reactor equipped with a condenser. The suspension was vortexed at 80 °C for 16 h. The resin was then filtered and washed with CH_2Cl_2 (5 × 5 mL), DMF:H_2O (1:1) (5 × 5 mL), DMF (5 × 5 mL), and CH_2Cl_2 (5 × 5 mL). After

drying 16 h under vacuum, 880 mg of resin **29** was recovered corresponding to a quantitative loading yield. IR (KBr): 2093 (N_3). This resin (880 mg) was transferred in a peptide-flask and swollen in 2.5 mL of anhydrous THF and 5 mL of a freshly prepared solution of $SnCl_2$:HSPh:Et_3N (0.2 M:0.8 M:1.0 M) was added. The resulting mixture was vortexed under argon for 5 h at 25 °C. Then, the resin was filtered and washed with DMF (3 × 5 mL) and CH_2Cl_2 (5 × 5 mL). The IR spectrum confirmed the disappearance of the azide band and a broadening of the NH signal. After 16 h of drying under vacuum, resin **30** was swollen in 7 mL of dry 1,2-dichloroethane, and diisopropylethylamine and propionyl chloride were added to give a solution of 0.6 and 0.5 M, respectively. The mixture was vortexed overnight at 25 °C. Then, the resin was filtered and washed successively with DMF (5 × 5 mL), CH_2Cl_2 (5 × 5 mL), and MeOH (2 × 5 mL). IR (KBr): 3440 (NH), 1758 (C═O, ester), 1672 (C═O, amide). The resulting resin **31** (900 mg) was suspended in 18 mL of 1-butanol:1,2-dichloroethane (1:1) in the presence of PPTS (154 mg; 0.61 mmol) for 16 h at 60 °C. The resin was filtered with CH_2Cl_2 (7 × 5 mL), and the solvents were evaporated under vacuum. The crude compound was suspended in EtOAc and washed twice with water. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. Purification by flash chromatography (hexane:EtOAc, 5:5 to pure EtOAc) gave 42 mg of a 1:1 mixture of the desired product **28** (8% overall yield) together with its 3-propionyl ester derivative **32** (8% overall yield).

Model Synthetic Sequence Using Carboxypolystyrene (Scheme 5). In a round-bottom flask equipped with a condenser and purged with argon, 485 mg of chlorocarboxypolystyrene **34** (0.60 mmol), prepared from carboxypolystyrene **33** as described by Hodge et al.,[16] was swollen in 1 mL of anhydrous ethylbenzene before adding a solution of phenol **20** (670 mg; 1.69 mmol) in 8 mL of dry ethylbenzene. After the addition of (dimethylamino)pyridine (73 mg; 0.6 mmol), the suspension was stirred for 16 h at 136 °C. The resin was then filtered and washed successively with CH_2Cl_2 (5 × 5 mL), DMF (3 × 3 mL), and CH_2Cl_2 (3 × 5 mL). After 16 h of drying under vacuum, 644 mg of resin was recovered corresponding to 67% of coupling yield. IR (KBr): 2091 (N_3), 1735 (C═O, ester). This resin, **35** (573 mg), was swollen in 1 mL of anhydrous THF, and 4 mL of a freshly prepared solution of $SnCl_2$:HSPh:Et_3N (0.2 M:0.8 M:1.0 M) was added. The resulting mixture was vortexed under argon for 5 h at 25 °C. Then, the resin **36** was filtered and washed with DMF (5 × 3 mL) and CH_2Cl_2 (5 × 3 mL). The IR spectrum confirmed the disappearance of the azide band. To a swollen mixture of the resin **36** (299 mg) in 3 mL of dry dichloromethane were added pyridine and propionyl chloride to give 0.6 and 0.5 M solutions, respectively, as well as a catalytic amount of (dimethylamino)-pyridine (11 mg). The mixture was vortexed for 20 h at 25 °C. The resin was then filtered and washed successively with CH_2Cl_2 (3 × 3 mL), DMF (3 × 3 mL), and CH_2Cl_2 (3 × 3 mL). IR (KBr): 3400 (br, NH amide), 1730 (C═O, ester), 1664 (C═O, amide). The Kaiser test was negative. To the resin **37** (256 mg) swollen in 2 mL of dry THF was added 0.5 mL of a freshly prepared solution of saturated NaOMe in anhydrous MeOH (2 g/8 mL), and the suspension was vortexed for 4 h at 25 °C. The resin was then filtered and washed with THF (2 × 5 mL) and CH_2Cl_2 (4 × 5 mL). After evaporating the organic solvents, the crude compound was extracted three times with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated in vacuo. Purification by flash chromatography (hexane:EtOAc, 2:8 to pure EtOAc) gave 31 mg (25% overall yield) of the desired product **28**.

Model Synthetic Sequence Using *o*-Nitrobenzyl Ether Photolabile Linker (Scheme 6). Methyl 4-{[17*β*-(Tetrahydro-2*H*-pyran-2-yl-oxy)-16*β*-(3-azidopropyl)-estra-1,3,5(10)-trien-3-oxy]methyl}-3-nitrobenzoate (42). In a round-bottom flask purged with argon, the starting phenol **19** (99 mg; 0.23 mmol) was dissolved in 5 mL of dry CH_3CN:DMF (4:1) before adding Cs_2CO_3 (293 mg; 0.90 mmol) and methyl 4-(bromomethyl)-3-nitrobenzoate **41** (184 mg; 0.68 mmol). The mixture was stirred at room temperature for 3 h. CH_3CN was then evaporated under reduced pressure. The crude material was extracted three times with CH_2Cl_2, and the organic phase was washed twice with H_2O, once with brine, and evaporated to dryness. Purification by flash chromatography using LiChroPrep C18 gel (CH_3CN:MeOH:H_2O, 6:3.5:0.5) provided 95 mg (67% yield) of the desired adduct **42**. **Warning**: All *o*-nitrobenzyl ether derivatives should be stored and handled in the absence of light. Amorphous white solid. IR (film): 2095 (N_3), 1731 (C═O, ester), 1535 and 1288 (NO_2). ^{1}H NMR δ ($CDCl_3$): 0.79 and 0.84 (2s, 3H, 18-CH_3), 2.83 (m, 2H, 6-CH_2), 3.27 (m, 2H, CH_2N_3), 3.50 and 3.90 (2m, 2H, CH_2O of THP), 3.73 and 3.81 (2d, J = 10.0 Hz, 1H, 17α-CH), 3.98 (s, 3H, CH_3O), 4.61 and 4.71 (2m, 1H, CH of THP), 5.49 (s, 2H, C*H*$_2$OPh), 6.70 (d, J = 2.5 Hz, 1H, 4-CH), 6.76 (dd, J_1 = 8.6 Hz and J_2 = 2.5 Hz, 1H, 2-CH), 7.20 (d, J = 8.6 Hz, 1H, 1-CH), 8.02 (d, J = 8.2 Hz, 1H, 5-CH of the linker), 8.30 (dd, J_1 = 8.2 Hz and J_2 = 1.3 Hz, 1H, 6-CH of the linker), 8.79 (d, J = 1.3 Hz, 1H, 2-CH of the linker). ^{13}C NMR δ ($CDCl_3$): 13.14, 19.30 (19.92), 25.51, 26.32, 27.32, 28.13, 29.50, 29.77, 31.00, 32.11, 38.12, 38.83, 39.44, 43.75, 44.21, 48.69 (48.91), 51.71, 52.71, 61.81 (62.91), 66.64, 85.07, 98.89, 112.25, 114.79, 126.03, 126.52, 128.85, 130.50, 133.83, 134.39, 138.31, 138.99, 146.70, 155.69, 164.81. LRMS: Calcd for $C_{35}H_{48}N_5O_7$ $[M+NH_4]^+$: 650.4. Found: 650.5 *m*/*z*.

4-{[17*β*-(Tetrahydro-2*H*-pyran-2-yl-oxy)-16*β*-(3-azidopropyl)-estra-1,3,5(10)-trien-3-oxy]methyl}-3-nitrobenzoic Acid (43). To a suspension of the ester **42** (143 mg; 0.23 mmol) in 6 mL of THF:H_2O (2:1) was added LiOH (141 mg; 3.38 mmol). This slurry was warmed at 70 °C for 1 h. The THF was then evaporated, the mixture was neutralized with 10% citric acid, and the crude material was extracted with three portions of $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. Purification by flash chromatography using LiChroPrep C18 gel (CH_3CN:MeOH:H_2O, 6:3.5:0.5) provided 98 mg (70% yield) of the acid **43**. Amorphous white solid. IR (film): 2500−3500 (br OH acid), 2094 (N_3), 1702 (C═O, acid), 1535 and 1280 (NO_2). ^{1}H NMR δ ($CDCl_3$): 0.80 and 0.84 (2s, 3H, 18-CH_3), 2.84 (m, 2H, 6-CH_2), 3.26

(m, 2H, CH_2N_3), 3.52 and 3.90 (2m, 2H, CH_2O of THP), 3.74 and 3.83 (2d, $J = 9.8$ Hz, 1H, 17α-CH), 4.70 and 4.76 (2m, 1H, CH of THP), 5.52 (s, 2H, CH_2OPh), 6.72 (d, J ∼ 2 Hz, 1H, 4-CH), 6.77 (dd, $J_1 = 8.6$ Hz and $J_2 \sim 2$ Hz, 1H, 2-CH), 7.22 (d, $J = 8.6$ Hz, 1H, 1-CH), 8.07 (d, $J = 8.1$ Hz, 1H, 5-CH of the linker), 8.36 (dd, $J_1 = 8.1$ Hz and $J_2 \sim 1$ Hz, 1H, 6-CH of the linker), 8.86 (d, J ∼ 1 Hz, 1H, 2-CH of the linker). ^{13}C NMR δ ($CDCl_3$): 13.09 (13.14), 19.28 (19.92), 25.52 (25.62), 26.24 (26.35), 27.01 (27.27), 28.00 (28.16), 29.50 (29.82), 30.75 (31.00), 32.14 (32.24), 37.69 (37.90), 38.14, 38.30 (38.86), 39.46, 43.63 (43.78), 43.97 (44.25), 48.73 (48.94), 51.72, 61.83 (62.91), 66.68, 85.14 (86.08), 97.81 (98.89), 112.29, 114.81, 119.04 (122.29), 126.64, 128.48 (129.69), 129.07, 133.92, 134.08 (134.89), 138.40, 138.89, 146.83, 155.67, 166.23. LRMS: Calcd for $C_{34}H_{46}N_5O_7$ $[M+NH_4]^+$: 636.3. Found: 636.4 *m*/*z*.

Synthesis of Resin 44. To a solution of acid **43** (415 mg; 0.67 mmol) in 5 mL of dry DMF were successively added diisopropylcarbodiimide (210 μL; 13.4 mmol) and 1-hydroxybenzotriazole (181 mg; 13.4 mmol), and activation of the acid was performed for 30 min at room temperature. Then, the resulting slurry was transferred by syringe to a suspension of aminomethyl resin (255 mg; 0.27 mmol, Richelieu Technologies Ltd., Montreal, Canada) in 2.5 mL of DMF. The suspension was vortexed in absence of light for 28 h at 25 °C. The resin was filtered and washed with CH_2Cl_2 (3 × 5 mL), DMF (3 × 5 mL), CH_2Cl_2 (3 × 5 mL), and MeOH (3 × 5 mL). After 48 h of drying under vacuum, 358 mg (64% weight gain) of resin **44** was recovered. IR (KBr): 3400 (br, NH), 2093 (N_3), 1667 (C═O, amide).

Synthesis of Resin 45. To a suspension of propionic acid (25 μL; 0.33 mmol) and 1-hydroxybenzotriazole (44 mg; 0.33 mmol) in 800 μL of anhydrous 1,4-dioxane was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (63 mg; 0.33 mmol). After stirring for 15 min, the slurry was transferred by a syringe to a suspension of 156 mg of resin **44** (∼0.16 mmol N_3) in 500 μL of 1,4 dioxane followed by a 0.6 M solution of tributylphosphine in toluene (410 μL; 0.25 mmol). The mixture was vortexed in absence of light for 18 h at 25 °C then diluted with DMF and filtered. The resin **45** was washed with DMF (4 × 5 mL), CH_2Cl_2 (4 × 5 mL), MeOH (4 × 5 mL), and dried under vacuum. IR (KBr): 3410 and 3320 (NH), 1660 (C═O, amide).

Synthesis of Amide 28 from Resin 45. A sample of resin **45** (124 mg) was suspended in 2.5 mL of absolute MeOH and placed in a flask surrounded by a jacket containing a 40% $CuSO_4$ solution. Dissolved air was removed from the suspension by passing prepurified argon through the solution for 30 min. The suspension was then irradiated at 350−365 nm with a UVP high-intensity longwave lamp (B-100AP model) for 20 h at room temperature. The resin was filtered and washed with MeOH (2 × 2 mL), CH_2Cl_2 (3 × 2 mL), and MeOH (2 × 2 mL). The solvent was evaporated to dryness, and 5 mL of MeOH containing 2% HCl (v/v) was added. After 30 min of stirring, water was added and MeOH removed. The crude compound was extracted three times with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under vacuum to give 11 mg (20% overall yield) of acceptably pure compound **28** (Figure 3A) without chromatography. The characterization of **28** was reported above.

First Approach for the Synthesis of Estradiol Derivative with Two Diversity Levels: The Case of 17*β*-*O*-Acylated 16*β*-*N*-Alkylamidopropyl-estradiol (Scheme 7). A sample of resin **45** (92 mg) was suspended in 2 mL of a mixture of 1,2-dichloroethane/1-butanol (1:1) and was vortexed with *p*-TSA (8 mg; 0.02 M) in absence of light for 24 h at room temperature. Resin **46** was then filtered and washed with DMF (5 × 3 mL), CH_2Cl_2 (5 × 3 mL), MeOH (5 × 3 mL), and dried 16 h under vacuum to give 87 mg of dried resin. Hexanoic acid (193 μL, 1.61 mmol) was dissolved in 400 μL of dry CH_2Cl_2 at 0 °C in a round-bottom flask and activated with diisopropylcarbodiimide (125 μL; 0.80 mmol). After stirring for 2 min, diisopropylethylamine (280 μL; 1.61 mmol) was added and stirring continued for another 3 min. The activated acid solution was transferred by syringe to a suspension of 67 mg of resin in 200 μL of dry CH_2Cl_2, followed by (dimethylamino)pyridine (20 mg; 0.16 mmol) in 50 μL of CH_2Cl_2. The reaction tube was sealed with Parafilm, wrapped in foil, and vortexed for 18 h at room temperature. The resin was filtered, washed successively with THF (5 × 3 mL), DMF (5 × 3 mL), 20% DIPEA/CH_2Cl_2 (5 × 4 mL), MeOH (4 × 4 mL), and dried under vacuum for 16 h to give 72 mg of resin **47**. This resin was submitted to photocleavage as described above to provide 10 mg (29% overall yield) of acceptably pure compound **48** (Figure 3B) without chromatography.

***N*-{3-[3-Hydroxy-17*β*-(hexanoyloxy)-estra-1,3,5(10)-trien-16*β*-yl]-propyl}-propanamide (48).** IR (film): 3300 (OH and NH), 1730 (C═O, ester), 1655 (C═O, amide). ^{1}H NMR ($CDCl_3$): 0.78 (s, 3H, 18-CH_3), 0.90 (t, $J = 6.6$ Hz, 3H, CH_3CH$_2$), 1.16 (t, $J = 7.5$ Hz, 3H, CH_3CH$_2$), 2.20 (q, $J = 7.5$ Hz, 2H, CH_3CH_2CO), 2.35 (t, $J = 6.6$ Hz, 2H, CH_2CH_2CO), 2.80 (m, 2H, 6-CH_2), 3.23 (m, 2H, CH_2N), 4.71 (d, $J = 9.9$ Hz, 1H, 17α-CH), 5.6 (broad, 1H), 6.58 (d, $J = 2.3$ Hz, 1H, 4-CH), 6.63 (dd, $J_1 = 8.4$ Hz and $J_2 = 2.3$ Hz, 1H, 2-CH), 7.11 (d, $J = 8.4$ Hz, 1H, 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 (2C). LRMS: Calcd for $C_{30}H_{46}NO_4$ $[M+H]^+$: 484.3. Found: 484.0 *m*/*z*.

Second Approach for the Synthesis of Estradiol Derivative with Two Diversity Levels: The Case of Unsymmetric 16*β*-Diamidosuccinyl Derivative of Estradiol (Scheme 8). To swollen resin **44** (205 mg; ∼0.15 mmol) in 3 mL of dry THF was added triphenylphosphine (202 mg; 0.77 mmol), and the mixture was vortexed at room temperature in absence of light. After 24 h, water (750 μL) was added to the suspension, which was gently heated at 70 °C for an additional 16 h. The resulting resin was filtered, washed successively with THF (5 × 2 mL), DMF (5 × 2 mL), CH_2Cl_2 (5 × 2 mL), MeOH (3 × 2 mL), and dried for 16 h to yield 203 mg of resin **49**. The Kaiser test was clearly positive, and the azide stretch had disappeared in the FT-IR spectrum. To a sample of resin **49** (73 mg; ∼0.055 mmol) suspended in 0.8 mL of dry pyridine was added a solution

of succinic anhydride (19 mg; 0.19 mmol) in 150 μL of pyridine, and the resulting mixture was vortexed for 20 h at 25 °C. The resin was filtered, washed with DMF (5 × 2 mL), CH_2Cl_2 (5 × 2 mL), MeOH (3 × 2 mL), and dried for 16 h to give 75 mg of resin. The Kaiser test was negative. The resulting resin (75 mg; ~0.055 mmol) was swollen in 1 mL of dry DMF and treated with benzylamine (30 μL; 0.28 mmol), diisopropylethylamine (98 μL; 0.56 mmol), and a solution of PyBOP (146 mg; 0.28 mmol) in 500 μL of DMF. The mixture was vortexed for 20 h at 25 °C. The resin was filtered, washed with DMF (5 × 2 mL), CH_2Cl_2 (5 × 2 mL), MeOH (3 × 2 mL), and dried for 16 h to give 70 mg of resin **50**. A small portion of this resin (29 mg) was submitted to photocleavage as described above to provide the crude THP protected compound, which was treated with 2% HCl in MeOH as described for compound **28**, to give 3 mg (31% overall yield) of acceptably pure diamide **51** (Figure 3C) without chromatography.

***N*-[3-(3,17*β*-Dihydroxy-estra-1,3,5(10)-trien-16*β*-yl)propyl]-*N′*-(benzyl)-succinic Acid Diamide (51).** IR (film): 3300 (OH and NH), 1640 (C═O, amide). ^{1}H NMR (CD_3OD): 0.77 (s, 3H, 18-CH_3), 2.50 (m, 4H, $COCH_2CH_2CO$), 2.76 (m, 2H, 6-CH_2), 3.15 (m, 2H, CH_2N), 3.69 (d, J = 9.8 Hz, 1H, 17α-CH), 4.36 (s, 2H, PhCH_2), 6.47 (d, J = 2.4 Hz, 1H, 4-CH), 6.52 (dd, J_1 = 8.5 Hz and J_2 = 2.4 Hz, 1H, 2-CH), 7.07 (d, J = 8.5 Hz, 1H, 1-CH), 7.28 (m, 5H, Ph). ^{13}C NMR (CD_3OD): 13.22, 27.57, 28.75, 29.58, 30.27, 30.74, 32.34, 33.54, 39.04, 40.00, 40.76, 41.32, 44.12, 45.19, 45.43, ~ 49.0 (2C, under solvent), 83.20, 113.70, 116.03, 127.17 (2C), 128.14, 128.48, 129.50 (2C), 132.68, 138.79, 139.99, 155.91, 174.49 (2C). LRMS: Calcd for $C_{32}H_{43}N_2O_4$ $[M+H]^+$: 519.3. Found: 519.6 *m*/*z*.

Third Approach for the Synthesis of Estradiol Derivative with Two Diversity Levels: The Case of *N′*-Acyl *N*-Aminoacyl 7α-(Undecanylamino)-estradiol (Scheme 9). Methyl 4-{[17*β*-(Tetrahydro-2*H*-pyran-2-yl-oxy)-7α-(11-azidoundecanyl)-estra-1,3,5(10)-trien-3-oxy]methyl}-3-nitrobenzoate (52). In a round-bottom flask purged with argon, the phenol **24** (4.0 g; 7.31 mmol) was dissolved in 60 mL of a mixture of CH_3CN:DMF (5:1) before the addition of cesium carbonate (9.5 g; 29.2 mmol). The mixture was allowed to stir 30 min at room temperature, then methyl 4-(bromomethyl)-3-nitrobenzoate **41** (6.0 g; 21.9 mmol) dissolved in 4 mL of DMF was added dropwise. The slurry was stirred for 90 min at 25 °C in absence of light. Afterward, EtOAc and water were added successively to the mixture, which was neutralized by adding 10% aqueous citric acid, and the compound was extracted three times with EtOAc. The combined organic layers were washed with 10% aqueous citric acid, dried over $MgSO_4$, and evaporated to dryness. The major contaminant (methyl 4-(bromomethyl)-3-nitrobenzoate) was removed, filtering the crude material on LiChroPrep C18 gel (CH_3CN:MeOH, 1:1 then $CHCl_3$) to produce mainly the desired compound, which was then purified by flash chromatography on SiO_2 (hexane:EtOAc, 9:1) to provide 3.55 g (65% yield) of the pure adduct **52** (**Warning**: all *o*-nitrobenzyl ether derivatives should be stored and handled in the absence of light). Off-white amorphous solid. IR ν (film): 2095 (N_3), 1732 (C═O, ester), 1535 and 1290 (NO_2). ^{1}H NMR δ ($CDCl_3$): 0.80 and 0.82 (2s, 3H, 18-CH_3), 2.80 (ABX system, 2H, 6-CH_2), 3.25 (t, J = 6.9 Hz, 2H, CH_2N_3), 3.48 and 3.92 (2m, 2H, CH_2O of THP), 3.74 (t, J = 8.5 Hz, 1H, 17α-CH), 3.98 (s, 3H, CH_3O), 4.66 (m, 1H, CHO of THP), 5.49 (s, 2H, PhCH_2O), 6.70 (d, J = 2.2 Hz, 1H, 4-CH), 6.77 (dd, J_1 = 8.6 Hz and J_2 = 2.2 Hz, 1H, 2-CH), 7.23 (2d, J = 8.6 Hz, 1H, 1-CH), 8.04 (d, J = 8.2 Hz, 1H, 5-CH of linker), 8.31 (dd, J_1 = 8.1 Hz and J_2 = 1.3 Hz, 1H, 6-CH of linker), 8.80 (d, J = 1.3 Hz, 1H, 2-CH of linker). ^{13}C NMR δ ($CDCl_3$): 11.72, 19.33 (19.91), 22.55 (22.68), 25.63, 26.69, 27.16, 27.26, 28.19, 28.81, 29.12, 29.44, 29.49, 29.59, 29.71 (2C), 29.96, 31.08, 33.10 (33.19), 34.79, 37.36 (37.93), 38.04 (38.13), 41.62 (41.68), 42.90 (43.40), 46.42, 51.46, 52.73, 61.78 (62.72), 66.66, 84.17 (86.59), 96.56 (99.36), 112.39, 115.66, 126.05, 127.12, 128.87, 130.50, 133.26 (133.38), 134.42, 137.37, 139.05, 146.70, 155.72, 164.84. LRMS: Calcd for $C_{43}H_{64}N_5O_7$ $[M+NH_4]^+$: 762.5. Found: 762.7 *m*/*z*.

4-{[17*β*-(Tetrahydro-2*H*-pyran-2-yl-oxy)-7α-(11-azidoundecanyl)-estra-1,3,5(10)-trien-3-oxy]methyl}-3-nitrobenzoic Acid (53). To a solution of the methyl ester **52** (3.4 g; 4.5 mmol) dissolved in a mixture of 150 mL of THF:H_2O (2:1) was added lithium hydroxide (2.8 g; 67.5 mmol), and the resulting suspension was heated gently at 60 °C for 2 h. Then, THF was evaporated, and the reaction was neutralized with 10% aqueous citric acid. The crude material was extracted three times with $CHCl_3$. The combined organic layers were washed with 10% aqueous citric acid, dried over $MgSO_4$, and evaporated in vacuo. Purification using LiChroPrep C18 gel (CH_3CN:MeOH, 1:1) gave 2.4 g (76%) of the desired acid **53**. Off-white amorphous solid. IR (film): 2400−3600 (broad, OH acid), 2095 (N_3), 1710 cm^{-1} (C═O, acid), 1535 and 1280 cm^{-1} (NO_2). ^{1}H NMR δ (acetone-d_6): 0.78 and 0.81 (2s, 3H, 18-CH_3), 2.80 (ABX system, 2H, 6-CH_2), 3.29 (t, J = 6.8 Hz, 2H, CH_2N_3), 3.45 and 3.85 (2m, 2H, CH_2O of THP), 3.68 (m, 1H, 17α-CH), 4.64 (m, 1H, CHO of THP), 5.50 (s, 2H, PhCH_2O), 6.76 (s_{app}, 1H, 4-CH), 6.80 (d_{app}, 1H, 2-CH), 7.20 and 7.22 (2d, J = 8.6 Hz, 1H, 1-CH), 8.04 (d, J = 8.0 Hz, 1H, 5-CH of linker), 8.34 (d_{app}, J = 8.0 Hz, 1H, 6-CH of linker), 8.70 (d, J = 1.3 Hz, 1H, 2-CH of linker). ^{13}C NMR δ (acetone-d_6): 12.31, 20.03 (20.27), 23.33 (23.42), 26.37, 26.49, 27.47, 27.92, 28.20, 28.93 (2C), 29.14, 29.40 to 30.80 (6C under solvent peaks), 31.76 (31.89), 34.13 (35.48), 38.33 (38.67), 39.11 (39.19), 42.79 (43.58), 43.73 (44.17), 47.22 (47.40), 52.01, 61.94 (62.42), 67.36, 84.84 (87.40), 96.98 (99.67), 113.25, 116.49, 126.63, 127.95, 130.01, 132.13, 133.63 (133.69), 135.16, 137.81, 139.43, 148.15, 156.96, 165.73. LRMS: Calcd for $C_{42}H_{62}N_5O_7$ $[M+NH_4]^+$: 748.5. Found: 748.9 *m*/*z*.

Synthesis of Resin 54. To a solution of acid **53** (1.75 g; 2.4 mmol) in 12.5 mL of dry DMF, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (916 mg; 4.8 mmol) and 1-hydroxybenzotriazole (645 mg; 4.8 mmol) were added successively, and activation of the acid was performed for 30 min at room temperature in absence of light. Then, the resulting slurry was transferred by syringe to a suspension of aminomethyl resin (1.6 g; 1.2 mmol, NovaBiochem, LaJolla, CA) in 12.5 mL of DMF. The suspension was vortexed for 28 h at 25 °C. The resin was filtered and washed

with DMF (5 × 10 mL), CH_2Cl_2 (5 × 10 mL), and MeOH (4 × 10 mL). After 48 h of drying under vacuum, 2.47 g (>95% weight gain) of resin **54** was recovered. The Kaiser test was negative. IR (KBr): 2095 (N_3) and 1673 (C═O, amide).

Synthesis of Resin 55. To a sample of resin **54** (485 mg; 0.36 mmol) suspended in 6 mL of dry THF was added triphenylphosphine (477 mg; 1.8 mmol), and the mixture was vortexed at room temperature in the absence of light. After 24 h, water (1.5 mL) was added to the suspension, which was gently heated at 70 °C for an additional 16 h. The resulting resin was filtered, washed successively with THF (5 × 3 mL), DMF (5 × 3 mL), CH_2Cl_2 (5 × 3 mL), MeOH (3 × 3 mL), and dried for 16 h to yield 522 mg of resin **55**. The Kaiser test was clearly positive, and the azide stretch had disappeared in the FT-IR spectrum.

***N*-[11-(3,17*β*-Dihydroxy-estra-1,3,5(10)-trien-7a-yl)-undecanyl]-*N*′-(propionyl)-L-prolylamide (58).** To a solution of NHFmoc-Pro-COOH (337 mg; 1.0 mmol) dissolved in DMF (3 mL) in a dry round-bottom flask, was added successively *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) (380 mg; 1.0 mmol) and 1-hydroxybenzotriazole (HOBt) (135 mg; 1.0 mmol). The activation reaction was allowed to stir for 15 min at 0 °C before adding diisopropylethylamine (355 μL; 2.0 mmol), and the resulting solution was transferred by syringe to a suspension of resin **55** (450 mg; 0.34 mmol). The resulting suspension was vortexed for 1 h at room temperature, and the resin was filtered and then washed with DMF (5 × 3 mL) and CH_2Cl_2 (5 × 3 mL). Resin **56** (450 mg) was suspended in a 2 mL of a mixture of 20% piperidine/DMF and vortexed for 15 min at room temperature. The resin was filtered and suspended again in 2 mL of a mixture 20% piperidine/DMF. After 1 h of mixing, the resin was filtered again and washed with DMF (10 × 3 mL). A sample of the resulting resin (90 mg; 0.067 mmol) was treated with 1.2 mL of 0.17 M of the activated propionic acid prepared as follows: to a solution of CH_3CH_2COOH (63 μL; 0.85 mmol) dissolved in DMF (5 mL) in a dry round-bottom flask were added successively HBTU (324 mg; 0.85 mmol) and HOBt (115 mg; 0.85 mmol). The activation was allowed to stir 15 min before the addition of diisopropylethylamine (297 μL; 1.7 mmol). After 90 min of mixing at room temperature, the resin was filtered, washed with DMF (5 × 2 mL), CH_2Cl_2 (5 × 2 mL), MeOH (5 × 2 mL), and then dried for 16 h under vacuum. Resin **57** was suspended in 2 mL of a 0.07 M of *p*-TSA in a mixture of 1,2-dichloroethane/1-butanol (1:1) for 24 h at room temperature. The resin was then filtered and washed with DMF (5 × 3 mL), CH_2Cl_2 (5 × 3 mL), MeOH (5 × 3 mL), and dried 16 h under vacuum. A sample of the dried resin (72 mg) was submitted to photocleavage as described above in 1.5 mL of oxygen-free MeOH for 24 h. The resin was filtered and washed with CH_2Cl_2 (4 × 2 mL) and MeOH (4 × 2 mL) to give 10 mg (31% overall yield, seven steps) of acceptably pure compound **58** (Figure 3D) without chromatography. Yellow oil. IR (film): 3300 (OH, alcohol and phenol and NH), 1630 (C═O, amide). ^{1}H NMR (CD_3OD): 0.77 (s, 3H, 18-CH_3), 1.09 (m, 4H, C$H_3$$CH_2$ and 15-CH), 2.70 (ABX system, 2H, 6-CH_2), 3.15 (m, 2H, CH_2N of side chain), 3.55 and 3.65 (m, 3H, CH_2N of prolyl and 17α-CH), 4.35 (m, 1H, CHN of prolyl), 6.46 (d, J = 2.3 Hz, 1H, 4-CH), 6.53 (dd, J_1 = 8.4 Hz and J_2 = 2.4 Hz, 1H, 2-CH), 7.07 (d, J = 8.5 Hz, 1H, 1-CH). ^{13}C NMR δ (CD_3OD): 9.09, 11.71, 23.65, 25.67, 26.51, 27.88, 28.49, 28.63, 29.12, 30.37 (2C), 30.65 (4C), 31.01, 33.30, 34.66, 35.78, 38.27, 39.66, 40.38, 43.71, 44.52, 47.82, ∼49.0 (2C, under solvent peak), 61.60, 82.59, 113.92, 116.91, 127.86, 131.83, 137.62, 156.00, 174.75, 175.41. LRMS: Calcd for $C_{37}H_{59}N_2O_4$ $[M+H]^+$: 595.4. Found: 595.6 *m*/*z*.

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