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Solid Phase Synthesis of 17α-*E*/*Z*-(X-Phenyl)-Vinyl Estradiols Using the Stille Coupling Reaction

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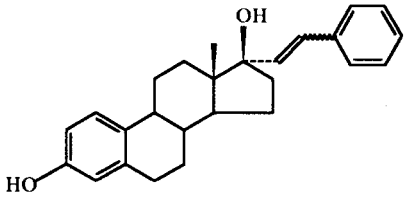
Abstract—As a continuation of our program to develop probes for the hormone binding domain (HBD) of the estrogen receptor (ER), we designed a series of novel 17α-*E*/*Z*-(X-phenyl)-vinyl estradiols. Based upon our experience with solution chemistry we applied solid phase synthesis using carboxylated resins to synthesize the new compounds. The Stille coupling reaction permitted the introduction of a variety of functional groups and positional isomers on the terminal phenyl group. Subsequent cleavage from the resin generated a series of novel estradiol derivatives.

Introduction

As a part of our ongoing program to design and develop new therapeutic agents for the treatment of breast cancer, we have focused on new steroidal derivatives that interact at the hormone binding domain (HBD) of the estrogen receptor (ER). While many of our initial studies confirmed the established estrogen receptor structure activity relationships, derivatives with the *E*- and *Z*-X-vinyl group at the 17α-position particularly demonstrated unusual properties.[1] Further explorations with phenylvinyl (I) and phenylselenovinyl (II) estradiol suggested that receptor affinities comparable to estradiol itself could be maintained in spite of the apparent steric bulk of the 17α substituent.[2] Recent publications of the crystal structure of the liganded HBD of the ER[3] suggested that the 17α groups project into a region that may accommodate significant steric tolerance. We have elected to develop new estradiol derivatives that could exploit that tolerance.



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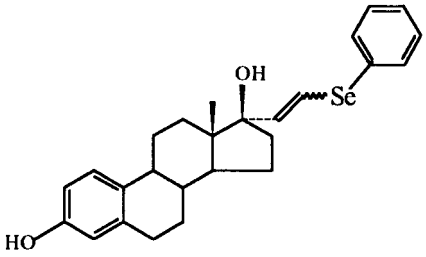

II

The synthesis of our target compounds to date had relied on traditional solution phase chemistry. In order to prepare new derivatives containing a variety of functional groups or existing as positional isomers, we considered approaches that could generate a large number of compounds more easily. The logical choice was solid phase synthesis. We envisioned that we could append our steroid to the inert polymer support, divide it into discrete aliquots, perform the requisite synthetic transformation, remove its individual products from the support and then characterize them. While a significant body of literature existed for solid phase synthesis (SPS) with steroids[4–9] and for Stille coupling,[10–12] there were no prior reports on the specific application that we wished to carry out. For example, Poirer et al., has described solid phase transformations of both androstanes and 16α-substituted estradiols,[4] however, neither employed transformations comparable to those we would require. Similarly, several groups have reported the use of the Stille reaction to couple aromatic and alkyl groups[10–12] but with fewer structural constraints than those imposed by the estrogen scaffold. Therefore, this work involved developing new methods to achieve our objectives.

Keywords: solid phase synthesis; estrogen receptor probes; carboxylation; hydrostannylation; Stille reaction.

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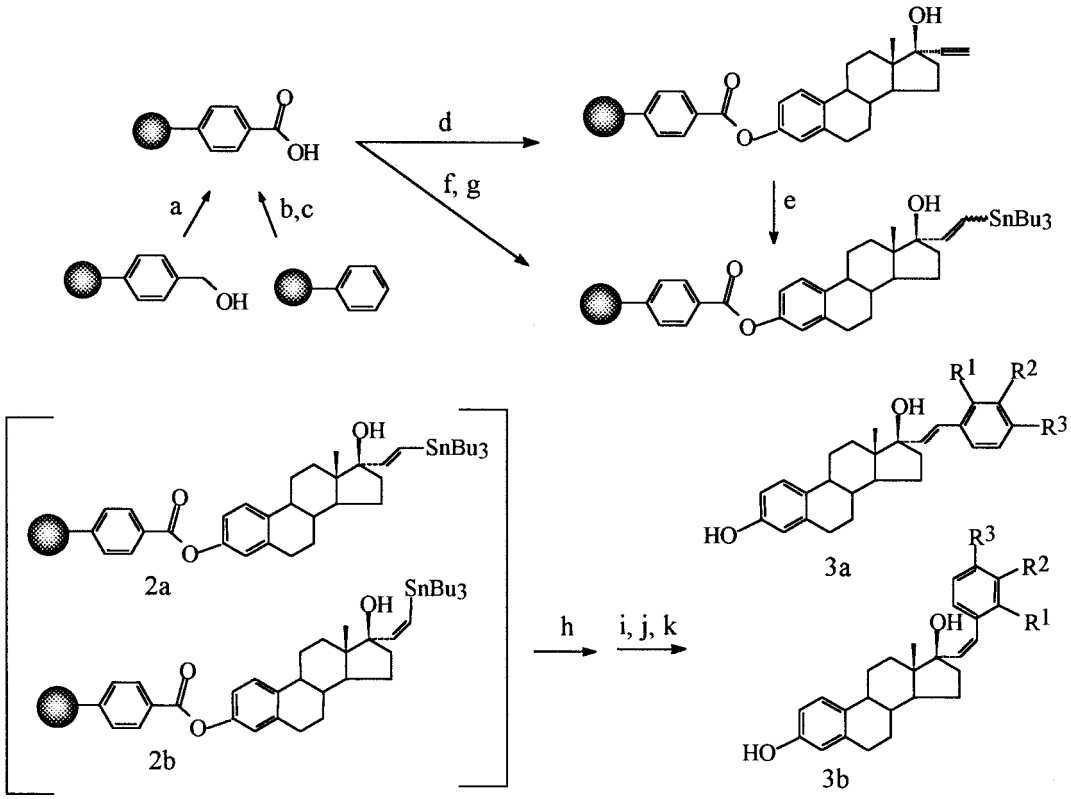


Scheme 1. Reagent: (a) Jones reagent ($H_2Cr_2O_4$, H_2SO_4, acetone); (b) *n*-BuLi, TMEDA, cyclohexane, 50°C; (c) Dry ice, THF; (d) 17α-Ethynyl estradiol, DCC, DMAP, CH_2Cl_2; (e) $HSnBu_3$, Et_3B, THF, 50–60°C; (f) 17α-Ethynyl estradiol, $HSnBu_3$, Et_3B, THF, 50–60°C; (g) DCC, DMAP, CH_2Cl_2; (h) R-Aryl-X, Pd $(PPh_3)_4$, BHT, toluene, N_2, reflux; (i) 5 N-NaOH in CH_3OH–Dioxane (1:3); (j) 5%-CH_3COOH; (k) 10%-$NaHCO_3$.

In this report we demonstrate our approach to developing the solid phase synthesis of the 17α-substituted phenylvinyl estradiols. This involved coupling the steroid intermediates to the resin, identifying appropriate reaction conditions and cleaving the final products from the resin. The result is a reliable method for generating a novel series of functionalized estradiols which can be evaluated for their biological properties.

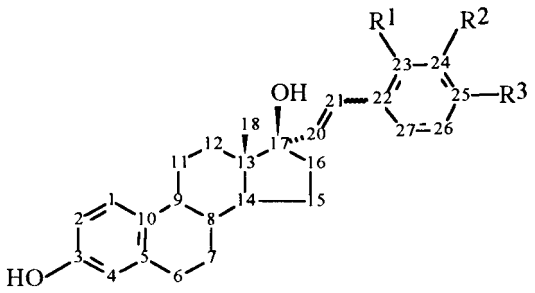
The approach that we selected incorporated several features. First, we chose the carboxylated resins because the estrogen could be selectively coupled through its phenolic linkage to the polymer and the ultimate cleavage of the ester bond at the end of the synthetic sequence would pose few problems. Use of an ether linkage would require either acidic or reductive cleavage, which would not be compatible with the functional groups present in the intermediates or final products. Similarly, amides, carbamates and photolabile links could also present potential problems at various steps of the process. Esterification at the 3-position, however, would not interfere with either the hydrostannylation or the palladium (0) catalyzed coupling reactions that would occur at the 17α-position. The integrity of the tertiary alcohols, *E*/*Z*-styryl groups, or functionality on the terminal phenyl group would be compromised if conditions other than a mild base were used to remove the product from the resin.

Results and Discussion

One of the key elements of the synthetic scheme was the selection of a linker that could be both formed and cleaved under mild conditions. This was based on our observations that 17α-substituted estradiols were unstable under strongly acidic conditions such as those frequently used to release products from the resins. Therefore our resin of choice was carboxylated polystyrene which could be esterified under neutral conditions and ultimately cleaved with mild base. Our first example (compound **8a**) was prepared using the carboxylated resin obtained either by oxidation of a Wang resin using Jones reagent[13] or by carboxylation of a polystyrene resin via lithiation with *n*-butyl lithium.[14] The reactions for both methods were easily monitored by the appearance of the 1700 cm^{-1} absorption in the FT-IR spectrum. The loading capacity of our carboxylated resins was determined by coupling 17α-ethynyl estradiol onto the resins using DCC in the presence of catalytic amount of DMAP and measuring its subsequently cleaved estradiol derivatives from the aliquot of the resins. The loading[15] of oxidized Wang resin was 0.4–0.6 mmol g^{-1} and that of carboxylated polystyrene was 1.5–1.9 mmol g^{-1}. Once we confirmed the utility of coupling through the ester linkage using carboxy polystyrene resin we employed the commercially available carboxy polystyrene for the remainder of our studies. The loading yield of the reaction using the resins with already known loading capacity (2.47 mmol g^{-1}) was 82%. The yield was determined by 'cleave and characterize' methods.

Synthesis of the analogs (Scheme 1) commenced by coupling the 3-phenolic group of 17α-ethynyl estradiol to the carboxy polystyrene resin. An antimony (III) chloride

Table 1. Yields (%) of Stille coupling reaction using solid phase synthesis



Compound	R^1 (*ortho*)	R^2 (*meta*)	R^3 (*para*)	Yield (%)
4a:*E*	CF_3	H	H	38
5a:*E*	H	CF_3	H	33
6a:*E*	H	H	CF_3	49
6b:*Z*	H	H	CF_3	17
7a:*E*	CH_3	H	H	38
8a:*E*	H	CH_3	H	75
8b:*Z*	H	CH_3	H	54
9a:*E*	H	H	OCH_3	36

assay confirmed the presence of the steroids on the resins.[16–18] The absence of color change with bromocresol green suggested that no free carboxylic acid groups remained on the resin.[19] The appearance of a peak at 3301 cm^{-1} in the IR spectrum, corresponding to the C–H stretch of the ethynyl group, also confirmed the reaction and a shift of carbonyl absorption to higher frequency (from 1690 to 1734 cm^{-1}) was also observed.

The subsequent hydrostannylation step incorporated either the use of hydrostannylation of bound ethynyl estradiol (Method A) or hydrostannylation of ethynyl estradiol in solution phase synthesis followed by coupling to the resin (Method B). The resin-bound 17α-ethynyl estradiol was hydrostannylated with tributyltin hydride using triethylborane as a radical initiator[20] to afford a mixture of the 17α-*E*/*Z*-tri-*n*-butylstannylvinyl estradiol in 20–30% (0.12 mmol g^{-1} of *E*, 0.01 mmol g^{-1} of *Z*) loading yields. Varying the reaction conditions, e.g. different solvents, temperatures, or reaction times, did not improve the yields. Therefore, a direct coupling of 17α-*E*/*Z*-tri-*n*-butylstannylvinyl estradiols used to overcome the low efficiency of this step. 17α-Ethynyl estradiol was hydrostannylated at 60°C and the crude mixture was directly transferred to the resin slurry in CH_2Cl_2. The mixture was treated with a 2–3 fold excess of DCC and a catalytic amount of DMAP was added. The loading yield for the coupling reaction was 0.59 mmol g^{-1} with a *Z*/*E* ratio=1:20. The low loading yield was due to use of the acetic acid for the protonation of phenoxide ion after cleavage, subjecting the products to protiodestannylation and reducing the expected loading yield. Because the cleavage after hydrostannylation did not provide a precise loading yield, we subsequently used the dry weight difference between pre- and post-reaction to determine the loading yield. Using the dry weight difference method, the yield for the hydrostannylation reaction was 1.55 mmol g^{-1} for both *E*- and *Z*-isomers. Because hydrostannylation on the resin did not afford satisfactory yields, Method B was the method of choice. As we have previously reported[21] the ratio of *E* and *Z* isomers is a function of the reaction temperature, time and stoichiometric ratio of tributyltin hydride to alkyne. At 60°C the reaction generated greater than 20:1 (*E*/*Z*) ratio bound to the solid phase. To increase the ratio of the *Z*-isomer, triethylborane was used as a radical initiator and the reaction was run at low temperature. The proportion of the *Z*-isomer (*Z*/*E*=1:10) increased, however, the reaction required a longer time and the loading yield for the hydrostannylation was slightly lower than at higher temperature (1.44 mmol g^{-1} by the dry weight difference method) because of more unreacted 17α-ethynyl estradiol in the reaction mixture.

The resin-bound hydrostannnylated estradiol was subjected to the Stille coupling reaction[22] using a variety of substituted aryl halides to generate the target compounds (Table 1). As shown in Scheme 1, $Pd(PPh_3)_4$ was used as the catalyst for the reaction and 3,5-di-*t*-butyl-4-hydroxytoluene (BHT) was added as a scavenger. The use of $Pd(PPh_3)_4$ generated an insoluble by-product that caused coloration of the resin, however, it was easily removed by rinsing it through the built-in filter (50–70 μm). After completion of all the reaction steps, the product was cleaved from the resin by saponification with 5 N NaOH dissolved in CH_3OH–Dioxane (1:3).

As shown in Table 1, the unoptimized yields of the Stille reactions on solid phase ranged from 17–75%, comparable to those observed for solution phase synthesis.[23] Compounds **5a** (*para*-trifluoromethylphenyl, *E*-isomer) and **5b** (*para*-trifluoromethylphenyl, *Z*-isomer) were isolated from the Stille reaction in a ratio of 98:2. Compound **7a** (*meta*-methylphenyl, *E*-isomer) and **7b** (*meta*-methylphenyl, *Z*-isomer) were also obtained in a ratio of 96:4. Although the *Z*-tri-*n*-butylstannyl vinyl estradiol was initially present on the resin, no *Z*-isomers of compound **3a**, **4a**, **6a** or **8a** were isolated from the Stille coupling, instead, 17α-vinyl estradiol, resulting from protiodestannylation was recovered as a side product. Because an excess of reagent was used to drive the reaction to completion, unreacted hydrostannylated 17α-*E*/*Z*-(tri-*n*-butylstannyl)-vinyl estradiol was not detected after the Stille reaction. It is possible that the *Z*-isomers either isomerized to thermodynamically more stable *E*-isomers under the conditions required for the Stille reaction or underwent protiodestannylation. As previously observed, the *Z*-isomer is much more susceptible to protiodestannylation than the *E*-isomer and the appearance of the side product under either solid phase or solution phase synthesis was approximately the same.

The isolated product were characterized by standard spectroscopic methods (FT-IR, ^1H and ^{13}C NMR) and analytical methods. The data were consistent with the proposed structures. Stereochemical assignments for compounds **5a** and **5b** were based on the C_{20}, C_{21} olefinic proton coupling constants for which *E*=16 Hz and *Z*=12.9 Hz, respectively. For compounds **7a** and **7b**, the observed coupling constants were 18.2 Hz for the C_{20} *E*-vinyl proton and 13.1 Hz for the C_{20} *Z*-vinyl proton. In ^{13}C NMR, long range couplings were observed for the compounds **3a**–**5a** and **5b** containing the trifluoromethyl group. Coupling with strongly electronegative fluorine was found at the carbon directly attached to the fluorine ($^1J_{C-F}$) and one ($^2J_{C-F}$) and two carbons distant ($^3J_{C-F}$). The carbons appeared as quartets and the coupling constants

were approximately $^{1}J_{C-F}$=270 Hz, $^{2}J_{C-F}$=32 Hz, $^{3}J_{C-F}$ =3–5 Hz, respectively.

Initial biological evaluation of these compounds indicates that they retain substantial affinity for the ER-LBD (results to be published elsewhere). Because both the properties of the aryl substitutent and its position on the ring (*o*/*m*/*p*) appear to affect the receptor binding, a more extensive evaluation of the derivatives is required.

In conclusion, we have applied the Solid Phase Synthesis methodology using carboxylated resins to generate a series of novel ER-LBD ligands. The initial objectives of this study, the simplification of the purification steps and the simultaneous production of both *E*- and *Z*-isomers, were largely achieved. The products were in acceptable yields, however no attempt had been made at this point to optimize conditions and clearly the yields could be improved. Analysis of the products indicated that the initial method provided only the *E*-isomer for most of the target compounds even though both *E* and *Z*-isomers were present after hydrostannylation reaction. We anticipate that modifications in both the coupling and cleavage steps would improve the yields for the chemically more sensitive *Z*-isomers. Nevertheless, this study has demonstrated the feasibility of solid phase synthesis for generating a variety of functionalized estradiol derivatives. Based on our preliminary biological results, we anticipate that further modifications of the phenyl group will yield promising results and we intend to adapt these methods for use in a combinatorial approach to generate diverse target compounds as ER-LBD ligands.

Experimental

Materials

Reagents and solvents were obtained from commercial sources (Aldrich and Sigma) and were used without further purification. Wang resins and carboxylated polystyrene resins were obtained from Novabiochem. The loading capacities of the resins, 0.75 mmol g^{-1} for the Wang resin and 2.47 mmol g^{-1} for the polystyrene resin, were determined by the manufacturer.

General methods

A specially designed flask which had a glass frit, through which the reaction mixture could be filtered by applying pressure, was used for the solid phase synthesis. Purifications for the intermediates were done by rinsing resins three times with the following solvents: CH_2Cl_2, THF, DMF, MeOH, CH_2Cl_2. The cleaved products were purified on a silica gel column chromatography using the appropriate solvents and were characterized by melting point, NMR, IR and elemental analysis. Melting points were determined in open capillary on an Electrothermal Melting Point Apparatus and were uncorrected. IR spectra were recorded on a Perkin–Elmer Model 1600 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were obtained with a Varian XL-300 NMR spectrometer at 300 MHz in $CDCl_3$, acetone-d_6, or DMSO-d_6 as a solvent. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA). As on-resin reaction monitoring methods, color tests and FT-IR methods were used. Bomocresol green (0.5% in ethanol, pH=8) was used to assay for free carboxylic acids.[18] The color of the stock solution was dark blue and changed to yellow in the presence of free carboxy groups. Antimony (III) chloride solution (25% in CCl_4) was also used to determine whether the steroid (17α-ethynyl estradiol) was coupled to the resin and a positive test result for the presence of estradiol was indicated by the color purple.[16–18] In addition, a spectroscopic method (FT-IR) was facilitated to detect chromophore change by reaction.

Preparation of the carboxylated resin

(Method A). The Wang resins (1 g, 0.75 mmol) were swelled in the CH_2Cl_2 overnight and rinsed twice with THF, CH_3OH, CH_2Cl_2 and acetone. Acetone (5 mL) was added to the swelled resins. To the slurry was added 1 mL of Jones reagent[13] in a dropwise manner. The mixture was allowed to stand at room temperature for 24 h. The resin mixture was rinsed twice with water–acetone (1:1), CH_3OH, DMF, DMSO and CH_2Cl_2 and dried in vacuo. The loading capacity after the carboxylation reaction was 0.4–0.6 mmol g^{-1}, which was determined with the coupling of 17α-ethynyl estradiol to the resin. The aliquot of the resins was characterized by FT-IR. FT-IR (KBr) ν: 3000–3500 (OH, broad), 1690 (C=O, broad), 1603, 1492, 1452 (aromatic ring), 1279 (C–O).

(**Method B**). The carboxylation of a polystyrene resin was accomplished using the method described by Farrall et al.[14] FT-IR (KBr) ν: 3420 (OH, broad), 1630 (C=O, broad), 1200–1400 (C–O, broad). Loading capacity: 1.5–1.9 mmol g^{-1}.

Coupling 17α-ethynyl estradiol to the resins

The carboxylated Wang resin (2.3 g) or polystyrene resin (2.5 g) was placed in the reactor equipped with a magnetic stirrer. The resin was swelled in the CH_2Cl_2 for 5 h and washed sequentially with THF, DMF, CH_3OH, THF and CH_2Cl_2. To the resin was added 0.23 g (1.1 mmol) of dicyclohexylcarbodiimide (DCC) and 5 mL of CH_2Cl_2 and the mixture was mildly stirred for 10 min. To the slurry was added 0.75 g (2.6 mmol) of 17α-ethynyl estradiol dissolved in 10 mL of CH_2Cl_2–DMF (9:1) solvent and catalytic amount of 4-dimethylaminopyridine (DMAP). The reaction mixture was stirred for 5 min and then allowed to stand at room temperature for 24 h. The resin was washed three times with CH_2Cl_2, CH_3OH, IPA (60°C), THF and DMF (60°C).[24] The rinsed resin was dried under vacuum for 5 h. The actual loading of the resin was determined by quantitative measurement of the material by cleavage from known weight of resin using 5 N-NaOH in CH_3OH–dioxane (1:3). The resin-bound steroids were characterized by FT-IR and the cleaved compounds by ^{1}H and ^{13}C NMR before proceeding to the next step. The loading capacity of each resin was shown in Method A and B; FT-IR (KBr) ν: 3437 (17β-OH), 3301 (17α-C≡C–H), 1735 (C=O), 1607, 1493, 1452 (aromatic ring), 1216(C–O).

Hydrostannylation

(Method A). The 17α-ethynyl estradiol coupled to the resin (0.49 g, 0.57 mmol g^{-1}) was placed in a dry 25 mL reaction flask equipped with a reflux condenser and a magnetic stirrer and was swelled in THF for 1 h. To the slurry in the dry THF were treated triethylborane (0.7 mL) and tributyltin hydride (1 mL).[20] The mixture was allowed to stand at 60–70°C for 48 h under a nitrogen atmosphere. The reaction mixture was washed three times each with CH_2Cl_2, CH_3OH, DMF, CH_2Cl_2 and ethyl acetate and the resultant resin was dried in vacuo. An aliquot of the resins was cleaved with 5 N NaOH in CH_3OH–CH_2Cl_2 (1:2) to afford a mixture of *E*- and *Z*-isomers. The mixture was separated by chromatography on the silica gel to give a 23% (0.13 mmol g^{-1}) yield of products, consisting of 21% (0.12 mmol g^{-1}) of the *E*-isomer and 2% (0.01 mmol g^{-1}) of the *Z*-isomer. R_f (*Z*-isomer)=0.58 (hexane–ethyl acetate, 4:1); R_f (*E*-isomer)=0.44 (hexane–ethyl acetate, 4:1); Amorphous; ^{1}H NMR ($CDCl_3$, 300 MHz, δ), 0.88 (s, 3H, C_{18}-methyl-H), 1.2–2.4 (m, steroid envelope and tributyl-stannyl-H), 2.7–2.9 (m, 2H, C_6-H), 6.06 (d, 1H, *J*=19.4 Hz, C_{21} vinyl-H), 6.22 (d, 1H, *J*=19.4 Hz, C_{20} vinyl-H), 6.79 (d, 1H, *J*=2.4 Hz, C_4-H), 6.84 (dd, 1H, *J*=2.6, 8.4 Hz, C_2-H), 7.28 (d, 1H, *J*=8.8 Hz, C_1-H); ^{13}C NMR ($CDCl_3$), 9.6 (C_{22}, 4C), 13.7 (C_{24}, 4C), 14.2 (C_{18}), 23.4 (C_{15}), 26.4 (C_{11}), 27.3 (C_{25}, 4C), 27.4 (C_7), 29.2 (C_{23}, 4C), 29.6 (C_6), 32.4 (C_{12}), 35.9 (C_{16}), 39.4 (C_8), 43.8 (C_9), 46.7 (C_{13}), 49.0 (C_{14}), 85.6 (C_{17}), 112.6 (C_2), 115.2 (C_4), 124.6 (C_{21}), 126.5 (C_1), 132.7 (C_{10}), 138.3 (C_5), 152.4 (C_{20}), 153.3 (C_3); FT-IR (KBr) ν: 3445 (17β-OH, broad), 1719 (C=O), 1653 (C=C), 1607, 1493, 1451 (aromatic ring), 1217 (C–O).

(Method B). The 17α-ethynyl estradiol (3 g, 10 mmol) was dissolved in THF and treated with triethylborane (2 mL, 17 mmol) and tributyltin hydride (3 g, 11 mmol). The mixture was stirred with a magnetic stirrer at 60°C for 16 h. The crude mixture (7.73 g) was evaporated to dryness, redissolved in the CH_2Cl_2, and transferred to the swelled resin (5 g) in CH_2Cl_2 in the presence of DCC. A catalytic amount of DMAP was added to the mixture, which was allowed to stand for 24 h. The resultant functionalized resin was treated as previously described. The total loading for both *E*- and *Z*-isomers was 0.59 mmol g^{-1} with 0.56 mmol g^{-1} of *E*-isomer and 0.03 mmol g^{-1} of *Z*-isomer, however, by the dry weight difference between pre- and post-reaction, the loading for both *E*- and *Z*-isomers was 1.55 mmol g^{-1}.

Electrophilic destannylation on the resin

The Stille reaction was used to couple the anchored *E*- and *Z*-stannylvinyl estradiol to aryl halides. The resin was added to the reaction flask, swelled in the CH_2Cl_2, subsequently treated with 10 mL of anhydrous toluene. To the resultant slurry was added a 3–4 fold excess of the functionalized aryl halide, 1–2 crystals of 3,5-di-*t*-butyl-4-hydroxytoluene (BHT), and $Pd(PPh_3)_4$.[13–15] The reaction was allowed to proceed at 90–100°C for 24 h. After cooling, the resin was washed as previously described, dried in vacuo and weighed.

Cleavage

The resin was swelled in CH_2Cl_2 (10 mL) containing 3 mL of 5 N-NaOH in CH_3OH–Dioxane (1:3), and stirred for 1 h. This cleavage step was repeated three times. Most of the product was collected from the first attempt, a small amount by second hydrolysis and almost none from the third trial. The fractions were combined, evaporated to dryness and partitioned between ethyl acetate and water. Acetic acid (1 mL, 5%) was added. The organic phase was washed with 10% aqueous $NaHCO_3$ to remove the residual acetic acid, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by silica gel column chromatography or by recrystallization from the appropriate solvent.

17α-20*E*-21-(2-Trifluoromethylphenyl)-19-norpregna-1,3,5(10),20-tetraene-3,17β-diol (17α-*E*-(2-trifluoro methylphenyl)-vinyl estradiol) (4a). Yield=38%; R_f=0.19 (hexane–ethyl acetate, 4:1); mp 224–225°C; ^{1}H NMR (300 MHz, Acetone-d_6, δ) 1.02 (s, 3H, C_{18} methyl-H), 1.2–2.4 (m, steroid envelope), 2.7–2.9 (m, 2H, C_6-H), 3.98(s, 1H, 17β hydroxyl-H), 6.53 (d, 1H, *J*=2.3 Hz, C_4-H), 6.58 (dd, 1H, *J*=2.6, 8.5 Hz, C_2-H), 6.64 (d, 1H, *J*=15.7 Hz, C_{20} vinyl-H), 7.0 (dd, 1H, *J*=2.5, 15.8 Hz, C_{21} vinyl-H), 7.07 (d, 1H, *J*=8.7 Hz, C_1-H), 7.42 (t, 1H, *J*=7.8 Hz, C_{26}-H), 7.60 (t, 1H, *J*=7.3 Hz, C_{25}-H), 7.69 (d, 1H, *J*=7.8 Hz, C_{27}-H), 7.81 (d, 1H, *J*=8.3 Hz, C_{24}-H), 7.98 (s, C_3 hydroxy-H); ^{13}C NMR (75.4 MHz, Acetone-d_6, δ) 14.7 (C_{18}), 24.1 (C_{15}), 27.2 (C_{11}), 28.3 (C_7), (C_6), 33.4 (C_{12}), 37.5 (C_{16}), 40.7 (C_8), 44.6 (C_9), 48.4 (C_{13}), 50.0 (C_{14}), 84.3 (C_{17}), 113.5 (C_2), 115.9 (C_4), 123.4 (C_{21}), 125.6 (q, *J*=273.2 Hz, C_{28}:CF_3), 126.4 (q, *J*=5.8 Hz, C_{24}), 127.0 (C_1), 127.4 (q, *J*=29.4 Hz, C_{23}), 127.8 (C_{26}), 128.6 (C_{27}), 132.0 (C_{25}), 133.2 (C_{10}), 137.9 (C_{22}), 139.1 (C_5), 142.4 (C_{20}), 155.9 (C_3); Anal. Calcd for $C_{27}H_{29}O_2F_3$: C, 73.30; H, 6.56. Found: C, 73.04; H, 6.68.

17α-20*E*-21-(3-Trifluoromethylphenyl)-19-norpregna-1,3,5(10),20-tetraene-3,17β-diol (17α-*E*-(3-trifluoro methylphenyl)-vinyl estradiol) (5a). Yield=33%; R_f (*E*-isomer)=0.19 (hexane–ethyl acetate, 4:1); mp 244–246°C; ^{1}H NMR (300 MHz, Acetone-d_6, δ), 1.01 (s, 3H, C_{18}-methyl), 1.2–2.4 (m, steroid envelope), 2.7–2.9 (m, 2H, C_6-H), 3.98 (s, 1H, 17β hydroxyl-H), 6.53 (d, 1H, *J*=2.6 Hz, C_4-H), 6.58 (dd, 1H, *J*=2.6, 8.3 Hz, C_2-H), 6.74 (d, 1H, *J*=16 Hz, C_{21} vinyl-H), 6.84 (d, 1H, *J*=16 Hz, C_{20} vinyl-H), 7.06 (d, 1H, *J*=8.3 Hz, C_1-H), 7.54–7.56 (m, 2H, C_{25}, C_{27}-H), 7.75–7.79 (m, 2H, C_{23}, C_{26}-H), 7.93 (s, C_3-hydroxy-H); ^{13}C NMR (75.4 MHz, Acetone-d_6, δ), 14.7 (C_{18}), 24.1 (C_{15}), 27.3 (C_{11}), 28.3 (C_7), (C_6), 33.5 (C_{12}), 37.5 (C_{16}), 40.7 (C_8), 44.6 (C_9), 48.4 (C_{13}), 50.1 (C_{14}), 84.2 (C_{17}), 113.5 (C_2), 115.9 (C_4), 123.6 (q, *J*=5.6 Hz, C_{25}), 124.1 (q, *J*=3.7 Hz, C_{23}), 125.4 (q, *J*=271 Hz, C_{28}:CF_3), 126.0 (C_{26}), 127.0 (C_1), 130.2 (C_{21}), 130.7 (C_{27}), 131.2 (q, *J*=32 Hz, C_{24}), 132.0 (C_{10}), 138.4 (C_5), 139.7 (C_{20}), 139.9 (C_{22}), 155.9 (C_3); Anal. Calcd for $C_{27}H_{29}O_2F_3$: C, 73.30; H, 6.56. Found: C, 73.42; H, 6.68.

17α-20*E*-21-(4-Trifluoromethylphenyl)-19-norpregna-1,3,5(10),20-tetraene-3,17β-diol (17α-*E*-(4-trifluoro methylphenyl)-vinyl estradiol) (6a). Yield=49%; R_f= 0.15 (hexane–ethyl acetate, 4:1); mp 215–217°C; ^{1}H

NMR (Acetone-d_6, 300 MHz, δ), 1.02 (s, 3H, C_{18} methyl-H), 1.2–2.4 (m, steroid envelope), 2.7–2.9 (m, 2H, C_6-H), 3.90 (s, 1H, 17β hydroxyl-H), 6.53 (d, 1H, J=2.6 Hz, C_4-H), 6.58 (dd, 1H, J=2.6, 8.4 Hz, C_2-H), 6.73 (d, 1H, J=16 Hz, C_{21} vinyl-H), 6.85 (d, 1H, J=16 Hz, C_{20} vinyl-H), 7.07 (d, 1H, J=8.3 Hz, C_1-H), 7.64 (d, 2H, J=8.7 Hz, C_{23}, C_{27}-H), 7.70 (d, 2H, J=8.6 Hz, C_{24}, C_{26}-H), 8.0 (s, C_3-hydroxy-H); ^{13}C NMR (75.4 MHz, Acetone-d_6, δ) 14.7 (C_{18}), 24.1 (C_{15}), 27.3 (C_{11}), 28.3 (C_7), (C_6), 33.5 (C_{12}), 37.6 (C_{16}), 40.7 (C_8), 44.6 (C_9), 48.5 (C_{13}), 50.2 (C_{14}), 84.2 (C_{17}), 113.5 (C_2), 115.9 (C_4), 125.4 (q, J=270.6 Hz, C_{28}:CF_3), 126.0 (C_{21}), 126.2 (q, J=3.5 Hz, C_{26}), 126.2 (q, J=3.5 Hz, C_{24}), 127.0 (C_1), 127.6 (C_{23}, C_{27}), 128.9 (q, J=32 Hz, C_{25}), 132.0 (C_{10}), 138.4 (C_5), 140.6 (C_{20}), 142.7 (C_{22}), 155.9 (C_3); Anal. Calcd for $C_{27}H_{29}O_2F_3$: C, 73.30; H, 6.56. Found: C, 73.36; H, 6.79.

17α-20*Z*-21-(4-Trifluoromethylphenyl)-19-norpregna-1,3,5(10),20-tetraene-3,17β-diol (17α-*Z*-(4-trifluoro methylphenyl)-vinyl estradiol) (6b). Yield=17%; R_f= 0.29 (hexane–ethyl acetate, 4:1); ^{1}H NMR (300 MHz, Acetone-d_6, δ) 0.97 (s, 3H, C_{18} methyl-H), 1.2–2.4 (m, steroid envelope), 2.7–2.9 (m, 2H, C_6-H), 3.89 (s, 1H, 17β hydroxyl-H), 6.12 (d, 1H, J=12.9 Hz, C_{21} vinyl-H), 6.48–6.62 (m, 3H, C_2, C $_4$, C_{20} vinyl-H), 7.11 (d, 1H, J=8.1 Hz, C_1-H), 7.59 (d, 2H, J=8.4 Hz, C_{23}, C_{27}-H), 7.80 (d, 2H, J=8.4 Hz, C_{24}, C_{26}-H), 7.95 (s, C_3 hydroxy-H).

17α-20*E*-21-(2-Methylphenyl)-19-norpregna-1,3,5(10), 20-tetraene-3,17β-diol (17α-*E*-(2-methylphenyl)-vinyl estradiol) (7a). Yield=38%; R_f=0.18 (hexane–acetone, 4:1); mp 199–200°C; ^{1}H NMR (Acetone-d_6, 300 MHz, δ), 1.01 (s, 3H, C_{18} methyl-H), 1.2–2.4 (steroid envelope), 2.34 (s, 3H, C_{28} methyl-H), 2.7–2.9 (m, 2H, C_6-H), 3.84 (s, 1H, 17β hydroxyl-H), 6.44 (d, 1H, J=16 Hz, C_{21} vinyl-H), 6.52–6.63 (m, 2H, C_2, C_4-H), 6.83 (d, 1H, J=16 Hz, C_{20} vinyl-H), 7.07 (d, 1H, J=8.3 Hz, C_1-H), 7.10–7.15 (m, 3H, C_{24}, C_{25}, C_{26}-H), 7.48 (d, 1H, J=6.8 Hz, C_{27}-H), 7.97 (s, C_3 hydroxy-H); ^{13}C NMR (75.4 MHz, Acetone-d_6, δ) 14.7 (C_{18}), 19.9 (C_{28}: methyl), 24.1 (C_{15}), 27.3 (C_{11}), 28.3 (C_7), (C_6), 33.5 (C_{12}), 37.5 (C_{16}), 40.7 (C_8), 44.7 (C_9), 48.2 (C_{13}), 50.1 (C_{14}), 84.2 (C_{17}), 113.5 (C_2), 115.9 (C_4), 125.4(C_{26}), 126.5 (C_{25}), 126.9 (C_{24}), 127.0 (C_1), 127.7 (C_{21}), 130.8 (C_{27}), 132.0 (C_{10}), 135.9 (C_{20}), 137.9 (C_{22}), 138.4 (C_5), 138.8 (C_{23}), 155.9 (C_3); Anal. Calcd for $C_{27}H_{32}O_2$: C, 83.51; H, 8.25. Found: C, 83.79; H, 8.65.

17α-20*E*-21-(3-Methylphenyl)-19-norpregna-1,3,5(10), 20-tetraene-3,17β-diol (17α-*E*-(3-methylphenyl)-vinyl estradiol) (8a). Yield=75%; R_f=0.17 (hexane–acetone, 4:1); mp 204–205°C; ^{1}H NMR (300 MHz, Acetone-d_6, δ), 1.00 (s, 3H, C_{18} methyl-H), 1.2–2.4 (m, steroid envelope), 2.31 (s, 3H, C_{28} methyl-H), 2.7–2.9 (m, 2H, C_6-H), 3.74 (s, 1H, 17β hydroxyl-H), 6.52–6.63 (m, 4H, C_4, C_2, C_{21} vinyl, C_{20} vinyl-H), 7.03 (d, 1H, J=7.3 Hz, C_{25}-H), 7.07 (d, 1H, J=8.7 Hz, C_1-H), 7.16–7.31 (m, 3H, J=7.4 Hz, C_{23}, C_{26}, C_{27}-H), 7.93 (s, 1H, C_3 hydroxy-H); ^{13}C NMR (75.4 MHz, Acetone-d_6, δ) 14.8 (C_{18}), 21.4 (C_{28}: methyl), 24.1 (C_{15}), 27.3 (C_{11}), 28.4 (C_7), (C_6), 33.5 (C_{12}), 37.4 (C_{16}), 40.8 (C_8), 44.7 (C_9), 48.3 (C_{13}), 50.2 (C_{14}), 84.2 (C_{17}), 113.6 (C_2), 116.0 (C_4), 124.4 (C_{27}), 127.0 (C_1), 127.7 (C_{25}), 127.8 (C_{26}), 128.5 (C_{21}), 129.2 (C_{23}), 132.2 (C_{10}), 137.0 (C_{20}), 138.4 (C_5), 138.7 (C_{22}, C_{24}), 155.9 (C_3); Anal. Calcd for $C_{27}H_{32}O_2$: C, 83.51; H, 8.25. Found: C, 83.23; H, 8.42.

17α-20*Z*-21-(3-Methylphenyl)-19-norpregna-1,3,5(10), 20-tetraene-3,17β-diol (17α-*Z*-(3-methylphenyl)-vinyl estradiol) (8b). Yield=54% (0.01 g); R_f=0.25 (hexane–acetone, 4:1); ^{1}H NMR (300 MHz, Acetone-d_6, δ) 0.95 (s, 3H, C_{18} methyl-H), 1.2–2.4 (m, steroid envelope), 2.31 (s, 3H, C_{28} methyl-H), 2.7–2.9 (m, 2H, C_6-H), 3.27 (s, 1H, 17β hydroxyl-H), 5.96 (d, 1H, J=13.1 Hz, C_{21} vinyl-H), 6.44 (d, 1H, J=13.1 Hz, C_{20} vinyl-H), 6.53 (d, 1H, J=2.6 Hz, C_4-H), 6.60 (dd, 1H, J=2.6, 8.3 Hz, C_2-H), 7.03 (d, 1H, J=7.3 Hz, C_{25}-H), 7.11 (d, 1H, J=8.3 Hz, C_1-H), 7.17 (t, 1H, J=7.6 Hz, C_{26}-H), 7.38–7.43 (m, 2H, C_{23}, C_{27}-H), 7.95 (s, 1H, C_3 hydroxy-H); ^{13}C NMR (75.4 MHz, Acetone-d_6, δ) 14.58 (C_{18}), 21.42 (C_{28}:methyl), 23.85 (C_{15}), 27.40 (C_{11}), 28.30 (C_7), (C_6), 32.97 (C_{12}), 38.4 (C_{16}), 40.9 (C_8), 44.7 (C_9), 48.8 (C_{13}), 50.1 (C_{14}), 84.3 (C_{17}), 113.6 (C_2), 116.0 (C_4), 127.1 (C_1), 127.8 (C_{27}), 128.1 (C_{25}), 128.3 (C_{26}), 129.7 (C_{21}), 131.4 (C_{23}), 132.0 (C_{10}), 137.1 (C_{20}), 137.6 (C_{24}), 138.45 (C_5) 138.5 (C_{22}), 155.9 (C_3); Anal. Calcd for $C_{29}H_{36}O_3$: C, 80.55; H, 8.33. Found: C, 80.00; H, 8.41.

17α-20*E*-21-(4-Methoxyphenyl)-19-norpregna-1,3,5,(10), 20-tetraene-3,17β-diol (17α-*E*-(4-methoxyphenyl)-vinyl estradiol) (9a). Yield=36%; R_f=0.23 ($CHCl_3$–CH_3OH, 99:1); ^{1}H NMR (300 MHz, Acetone-d_6, δ) 0.99 (s, 3H, C_{18} methyl-H), 3.68 (s, 1H, 17β hydroxy-H), 3.78 (s, 3H, C_{28}:methoxy-H), 6.46 (d, 1H, J=16.1 Hz, C_{21}-H), 6.51–6.59 (m, 3H, C_2, C_4, C_{20}-H), 6.88 (d, 2H, J=8.8 Hz, C_{24}, C_{26}-H); 7.07 (d, 1H, J=8.3 Hz, C_1-H); 7.39 (d, 2H, J=8.8 Hz, C_{23}, C_{27}-H), 7.95 (s, 1H, C_3 hydroxy-H); ^{13}C NMR (75.4 MHz, Acetone-d_6, δ) 14.7 (C_{18}), 24.1 (C_{15}), 27.3 (C_{11}), 28.3 (C_7), (C_6), 33.4 (C_{12}), 37.3 (C_{16}), 40.7 (C_8), 44.7 (C_9), 48.2 (C_{13}), 50.0 (C_{14}), 55.5 (C_{28}:methoxy), 84.1 (C_{17}), 113.5 (C_2), 114.7 (C_{24}, C_{26}), 115.9 (C_4), 127.0 (C_1), 127.0 (C_{21}), 128.3 (C_{23}, C_{27}), 131.4 (C_{22}), 132.1 (C_{10}), 134.9 (C_{20}), 138.4 (C_5), 155.9 (C_3), 159.9 (C_{25}).

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