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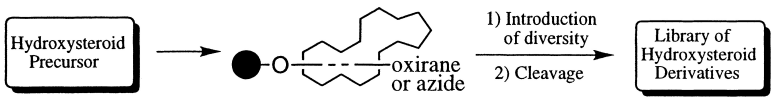

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Solid-Phase Synthesis of Hydroxysteroid Derivatives Using the Diethylsilyloxy Linker

René Maltais, Martin R. Tremblay, and Donald Poirier*

Medicinal Chemistry Division, Oncology and Molecular Endocrinology Research Center, Laval University Medical Center (CHUL), Québec G1V 4G2, Canada

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Four different types of hydroxysteroids (primary alcohol, secondary alcohols, and phenol), bearing either an oxirane or an azide as a precursor of molecular diversity, were linked in good yields to solid support using the butyldiethylsilane polystyrene (PS-DES) resin. These molecules were then used as scaffolds to generate hydroxysteroid derivatives containing two levels of diversity. The proposed libraries were tested by running steroidal alcohols through a model sequence of reactions (solid-phase coupling, aminolysis of oxirane or reduction of azide, amidation, and final cleavage). As a result, two linked secondary alcohols (17β-hydroxy-spiro-3(*R*)-oxirane-5α-androstane and 3β-hydroxy-spiro-17(*S*)-oxirane-5α-androstane) and a primary alcohol (spiro-17(*S*)-oxirane-3-(hydroxymethyl)-1,3,5(10)-estratriene) afforded good overall yields (>45%) and high HPLC purities (>90%) of hydroxysteroids derivatized as alkylamides without purification. One limitation was noted for the fourth library: the phenolic steroid linked by the diethylsilyloxy linker gave a poor overall yield of 8% of the desired model compound. Finally, the diethylsilyloxy linker was used successfully for a rapid solid-phase synthesis of a model library of twenty C19-steroid derivatives (3β-amido-3α-hydroxy-5α-androstane-17-ones), with an average yield of 53% and average HPLC purity of 97% without purification steps.

Introduction

Steroids and their derivatives are potent molecules that are used efficiently to treat many endocrine-related diseases. The rapid generation of a large number of steroidal compounds containing vast molecular diversity could accelerate the identification and optimization of new drug candidates. In our effort to obtain potent inhibitors of key steroidogenic enzymes,[1−5] we became interested in the powerful capacity of combinatorial chemistry to generate steroidal libraries either in solution[6] or on solid phase.[7−9] The description of solid-phase synthetic sequence involving steroids is still rare[7−12] however, and only few combinatorial approaches have been reported.[13−17] The hydroxyl group is certainly one of the most frequently used and chemically accessible functions in the steroidal chemistry. Moreover, its presence is required for the biological activity of various steroids including estrogens, androgens, and progestins. We were thus interested to use the hydroxyl group (primary alcohol, secondary alcohol, or phenol) as a point of attachment to the solid support and to test different solid-phase synthetic sequences of reactions to develop various libraries of hydroxysteroid derivatives. Our targeted libraries A−D (Figure 1) were designed to optimize the inhibitory activity of steroids that we previously identified as lead compounds on different steroidogenic enzymes; namely, type III 17β-hydroxysteroid dehydrogenase (library A),[18] steroid sulfatase (libraries B and C),[1,19] and type I 17β-hydroxysteroid dehydrogenase (library D).[2] The oxirane and the azide groups were chosen as the key precursor functions of the linked steroidal scaffold to provide the diversity of the proposed hydroxysteroid libraries A−D.

Results and Discussion

From the few known examples of hydroxysteroids linked to a solid support,[12,17,20−23] we selected the PS-DES resin[20] and the Ellman's DHP resin[21] for our study. We first tried coupling experiments with 3β-hydroxy-spiro-17(*S*)-oxirane-5α-androstane (**9**) and DHP resin using *p*-TSA or PPTS in 1,2-dichloroethane, but these attempts were unsuccessful due to decomposition of the oxirane group as observed by TLC analysis. Therefore, the diethylsilyloxy linker (PS-DES resin) was chosen over the tetrahydropyranyl linker (DHP resin) because of the nonacidic conditions used during the coupling reaction. This factor was crucial in the case of libraries A−C, because the acid sensitive oxirane function[24] is present on the steroid substrate during the coupling step. Using the PS-DES resin, we then investigated the compatibility of the

* Reprint requests should be sent to Dr. Donald Poirier, Medicinal Chemistry Division, Oncology and Molecular Endocrinology Research Center, Laval University Medical Center (CHUL), 2705 Laurier Boulevard, Québec, Qc G1V 4G2, Canada. Phone: (418) 654-2296. Fax: (418) 654-2761. E-mail: donald.poirier@crchul.ulaval.ca.

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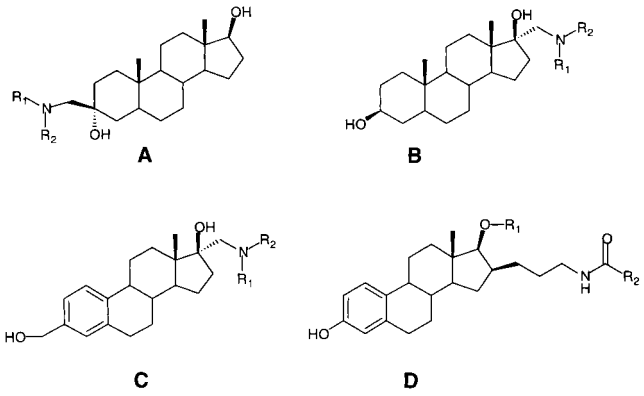


Figure 1. General structures of hydroxysteroid derivatives, members of our targeted libraries A−D containing two levels of molecular diversity.

diethylsilyloxy linker with a sequence of reactions for the synthesis of a model compound for each proposed libraries A−D (Schemes 1−4).

1. Solid-Phase Synthesis of Model Compounds for Libraries A−D. Library A (Scheme 1): The 17β-hydroxy-spiro-3(*R*)-oxirane-5α-androstane (**3**), previously obtained from a stereoselective reaction of dihydrotestosterone (**2**) with dimethylsulfoxonium methylide,[25] was coupled onto PS-DES resin in 60−70% yield with the conditions reported by Hu and co-workers for a less hindered hydroxysteroid, epiandrosterone (77%).[20] The reactive chlorosilyl resin **1b** was generated in situ by a treatment of PS-DES resin (**1a**) with 1,3-dichloro-5,5-dimethylhydantoin.[20] The silyl ether bond formation and the presence of the oxirane group were confirmed by the ^{13}C NMR spectra of resin **4** (Figure 2). The aminolysis of the oxirane **4**, using an excess of either butylamine or heptylamine in ethanol (60 °C) for 3 days, gave the corresponding secondary amines **5a** or **5d**, respectively, containing the first level of diversity (R_1). The next level of diversity (R_2) was introduced by the formation of amides **6a**−**d**. Four different acylation reactions were then realized to demonstrate the interesting diversity of compounds that could be obtained using our synthetic route. These amidations with an acyl chloride, a carboxylic acid, an amino acid, or an α-bromo-acetic acid (as peptoid precursor)[26] led to satisfactory overall yields (45−64%) and high HPLC purities (90−99%) of amides **7a**−**d** after releasing the hydroxysteroid from solid support by a treatment with HF-pyridine.

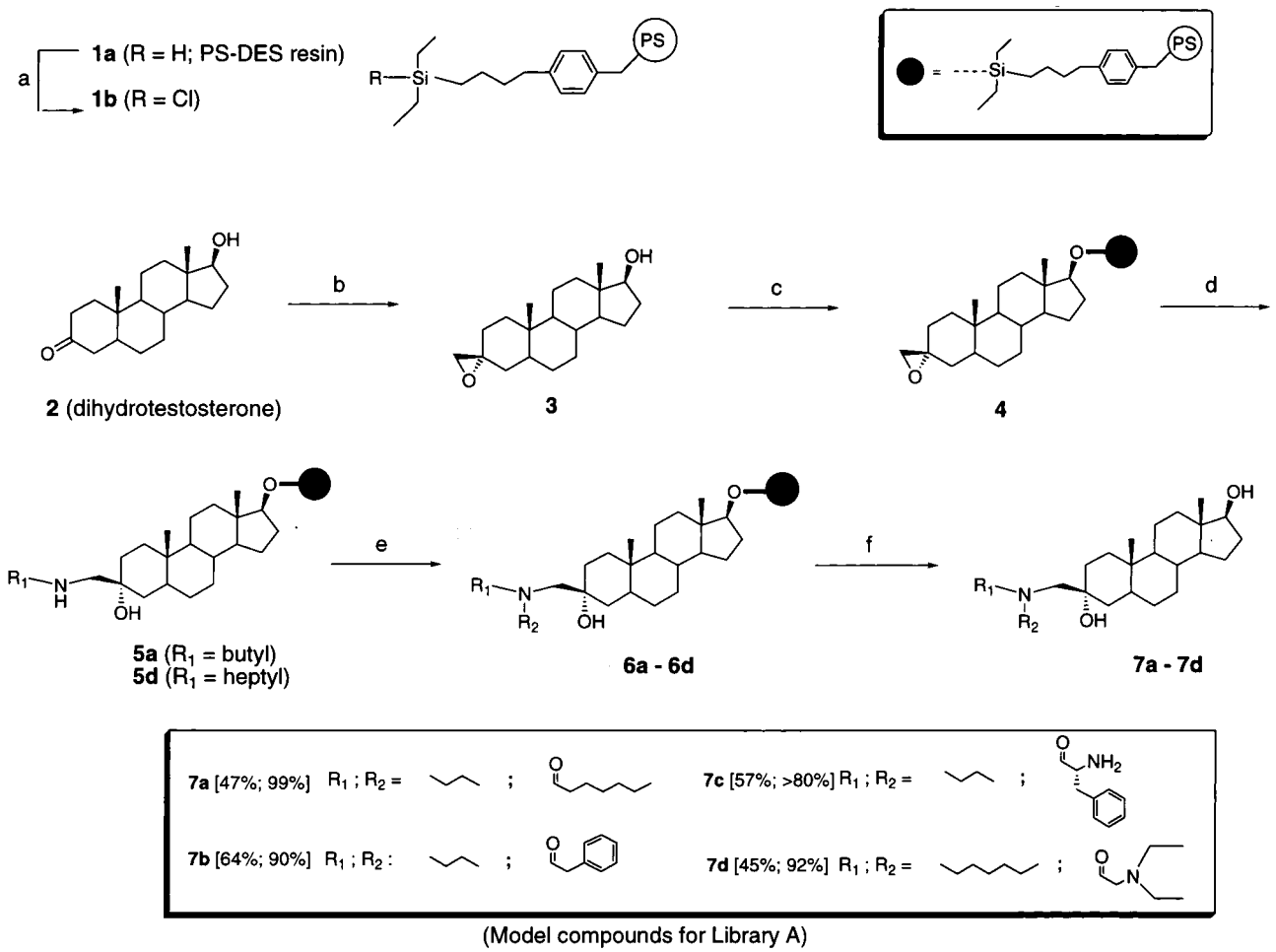
Library B (Scheme 2): Library B was constructed in a manner similar to library A, but the key oxirane function was located at the hindered C17-steroidal position instead of the C3 position. The 3β-hydroxy-17(*S*)-oxirane-5α-androstane (**9**) was first obtained in one step from a stereoselective reaction of epiandrosterone (**8**) and dimethylsulfonium methylide.[27] After coupling the oxirane **9** with chlorosilyl resin **1b** (previously generated in situ from PS-DES resin **1a**), the aminolysis of **10** using butylamine in ethanol (60 °C) followed by amidation with heptanoyl chloride gave the corresponding amide **12**. The latter was submitted to HF-pyridine cleavage condition to afford the desired model compound **13**, in good yield (64%) and excellent HPLC purity (97%) without purification steps.

Library C (Scheme 3): After demonstrating that a secondary hindered C3 or C17 steroidal alcohol linked by a diethylsilyloxy linker is compatible under the nucleophilic and electrophilic conditions needed to prepare libraries A and B, we became interested in extending our strategy to a steroid bearing a primary alcohol. Since this type of steroid is not commercially available, a classical solution-phase synthesis was necessary to obtain precursor **18**. Commercially available estrone (**14**) was first transformed to intermediate estrone triflate[28] and then submitted to a carbonyl insertion reaction[29] to give the carboxylic acid derivative of estrone (compound **15**) in good yield (81%) after recrystallization from the crude reaction mixture. Protection of the C-17 ketone using ethylene glycol and *p*-TSA provided the acetal intermediate **16**. This later was transformed to compound **17** by a sequence of three steps: (*1*) reduction of carboxylic acid to primary alcohol, (*2*) hydrolysis of acetal to ketone, and (*3*) protection of primary alcohol as a *tert*-butyldimethylsilyl (TBDMS) ether derivative. The oxirane formation and TBDMS hydrolysis completed the synthesis of the steroidal primary alcohol **18**, which was coupled to the chlorosilyl resin **1b**. The resin-bound oxirane **19** was then submitted to the strategy established above for libraries A and B. Thus, the aminolysis of **19** using butylamine followed by amidation with heptanoyl chloride gave the amide **21**, which after the final cleavage with HF-pyridine afforded the desired model compound **22** in good yield (44%) and high HPLC purity (92%) without purification steps.

Library D (Scheme 4): Because the TBDMS group and silylated analogues have been extensively used as protecting groups of phenol,[30,2,7,10,27] we decided to evaluate the stability of the diethylsilyloxy linker with a phenolic steroid. In a preliminary study, not reported herein, estrone (**14**) was linked to PS-DES resin using the conditions reported by Hu and co-workers[20] and subsequently recovered in good yield (56%) after a fluoride-mediated cleavage. On the basis of this result, the solid-phase synthesis of a library-D member was started by coupling the steroidal precursor **23** previously synthesized in solution.[7] After attachment of the phenol **23** to PS-DES resin, the azide function of **24** was reduced using a mixture of tin chloride, thiophenol, and triethylamine to obtain the corresponding primary amine. This latter was then submitted to the conditions of amidation. Unfortunately, the phenolic silyl-ether bound was sensitive during the *N*-acylation step with an acyl chloride, resulting in the partial cleavage of the polymer-bound steroid derivative. As a result, the overall yield for the synthesis of steroid **26** (only 8% after flash chromatography) was unsatisfactory, and the sequence of reactions considered to synthesize the library-D member **27** was aborted. It is indeed clear that the diethylsilyloxy linker is less appropriate for phenol than for aliphatic alcohol, with regard to this particular synthetic sequence of reactions. In fact, a photolabile *o*-nitrobenzyl linker was found more suitable for the sequence of reactions leading to **27**,[7] and consequently no additional efforts were tried to optimize the formation of **26**.

2. Solid-Phase Synthesis of a Model Library A. After we established that the diethylsilyloxy linker was suitable

Scheme 1[a,b]



[a] (a) 1,3-Dichloro-5,5-dimethylhydantoin, CH_2Cl_2, rt; (b) NaH, $(CH_3)_3SOI$, DMSO, rt; (c) imidazole, **1b**, CH_2Cl_2, rt; (d) butylamine or heptylamine/EtOH (1:1), 60 °C; (e) **7a**: heptanoyl chloride, pyridine, CH_2Cl_2, rt; **7b**: phenylacetic acid, PyBrOP, HOBt, DIPEA, DMF, rt; **7c**: *N*-Fmoc-Phe, PyBrOP, HOBt, DIPEA, DMF, rt; or **7d**: *1*. bromoacetic acid, DIC, DMF, rt; *2*. diethylamine in DMSO (2.5 M), rt; (f) HF-pyridine, THF, rt. [b]Data between brackets correspond to overall yield and HPLC purity, respectively. The purity of **7c** was estimated by TLC and NMR spectroscopy.

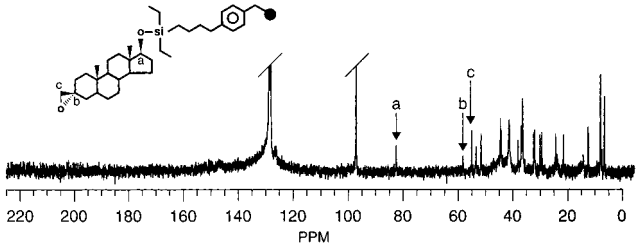


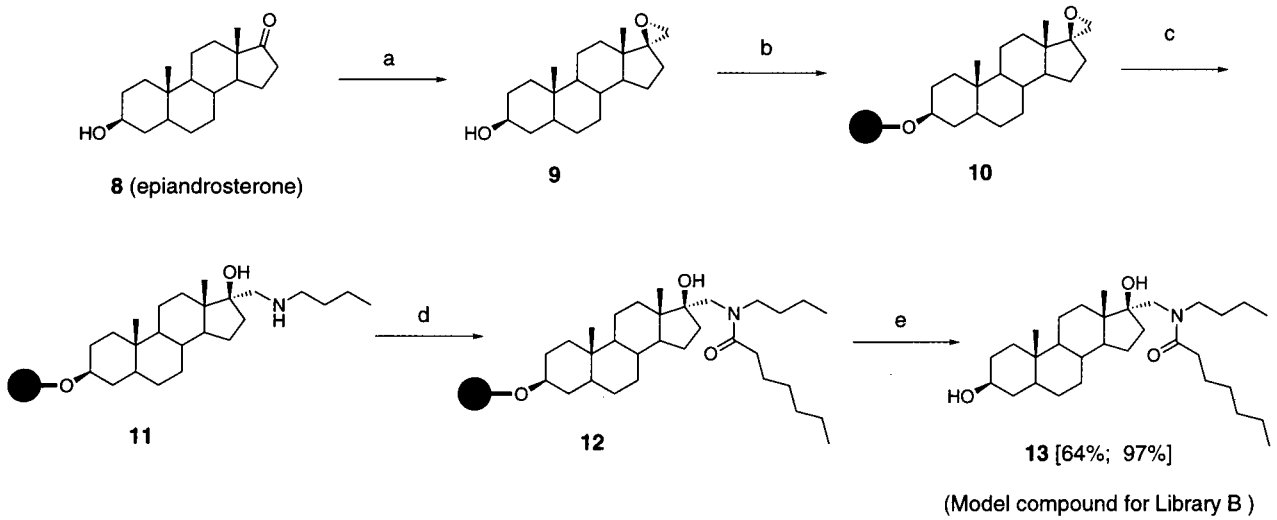
Figure 2. ^{13}C NMR spectrum of resin **4**, the 17β-hydroxy-spiro-3(*R*)-oxirane-5α-androstane (**3**) linked to butyldiethylsilane polystyrene (PS-DES) resin. The spectrum was recorded at 75.5 MHz using 100 mg of resin **4** swelled in 0.6 mL of CCl_4:C_6D_6 (4:1) within a total experiment time of 1 h with the following conditions: $d_1 = 1.0$ s, $p_1 = 30°$ (3.0 μs), aq = 430 ms, RG 800, SI = 32 K.

to attach both secondary (**3** and **9**) and primary (**18**) hydroxysteroids, a small model library of steroid derivatives was generated using the sequence of reactions reported in Scheme 1 for the synthesis of amide **7a**. Using five different alkylamines to introduce the first level of diversity and four different acyl chlorides for the second level, 20 members of library A (compounds **28**−**47**) were easily obtained by solid-phase parallel synthesis (Table 1). The average overall yield (53%) and HPLC purity (97%) were determined with a random sampling of five members and found to be about the same as the yield and purity previously obtained for the model compound **7a**. Mass determination as well as IR and NMR analysis confirmed the formation of compounds **28**−**47**. A series of 3β-amido-3α-hydroxy-5α-androstane-17-ones, representing a family of type III 17β-hydroxysteroid dehydrogenase inhibitors, was thus synthesized in a short period of time. Taking account of the large number of commercially available building blocks (primary amines and acyl chlorides), the model library A exemplified above could be made easily extended by using an automatic synthesizer.

Conclusion

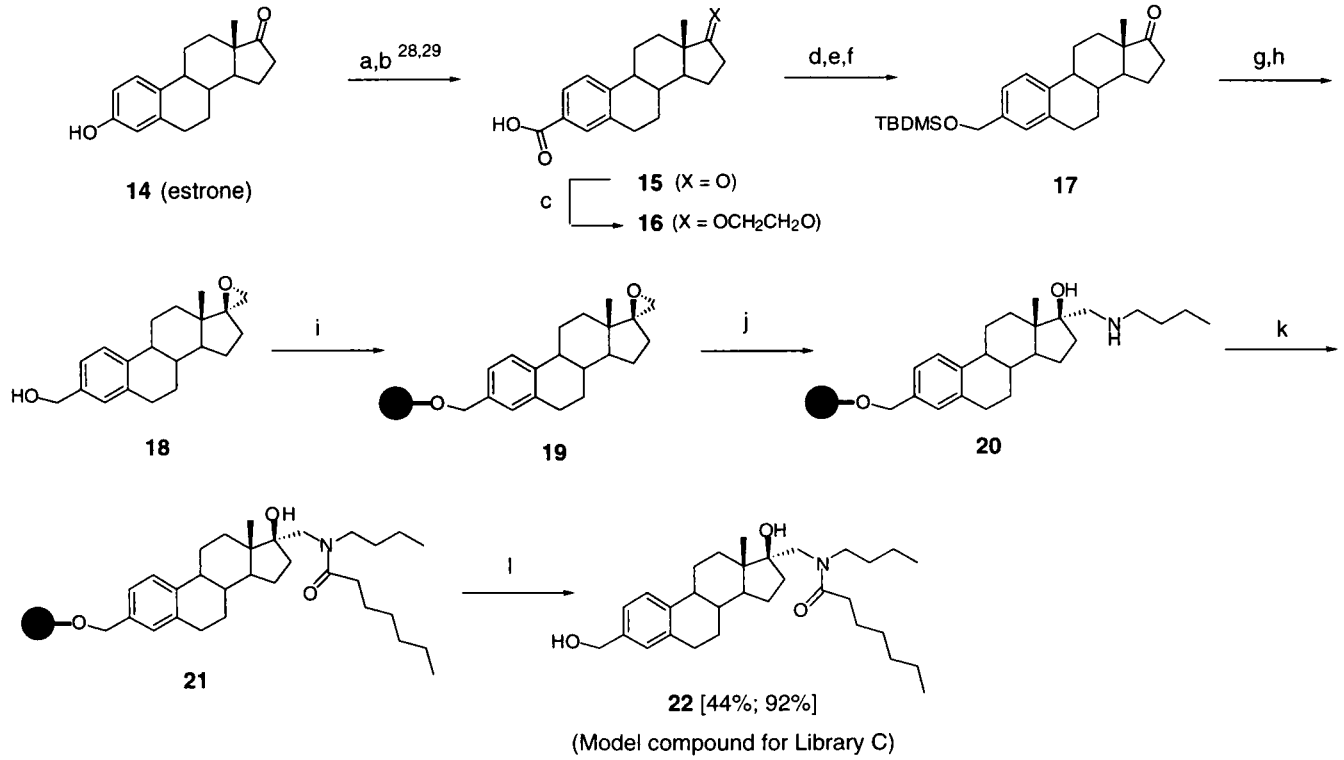
We have performed the solid-phase synthesis of steroid derivatives using four different types of hydroxysteroid scaffolds linked to PS-DES resin. The short sequences of reactions described above provide a model for the development of steroid libraries, which are useful in optimizing or identifying lead compounds for drug discovery. Among the available linkers for alcohols, the diethylsilyloxy linker emerged as the most compatible and versatile linker for the solid-phase synthesis of our model compounds **7a**−**d**, **13**, and **22**. Indeed, the neutral conditions used during the coupling of hydroxysteroids with the chlorosilylated form of PS-DES resin do not affect the oxirane function, the

Scheme 2[a,b]



[a] (a) NaH, $(CH_3)_3SI$, DMSO, rt; (b) imidazole, **1b** [PS-DES resin, 1,3-dichloro-5,5-dimethylhydantoin], CH_2Cl_2, rt; (c) butylamine/EtOH (1:1), 60 °C; (d) heptanoyl chloride, pyridine, CH_2Cl_2, rt; (e) HF-pyridine, THF, rt. [b]Data between brackets correspond to overall yield and HPLC purity, respectively.

Scheme 3[a]

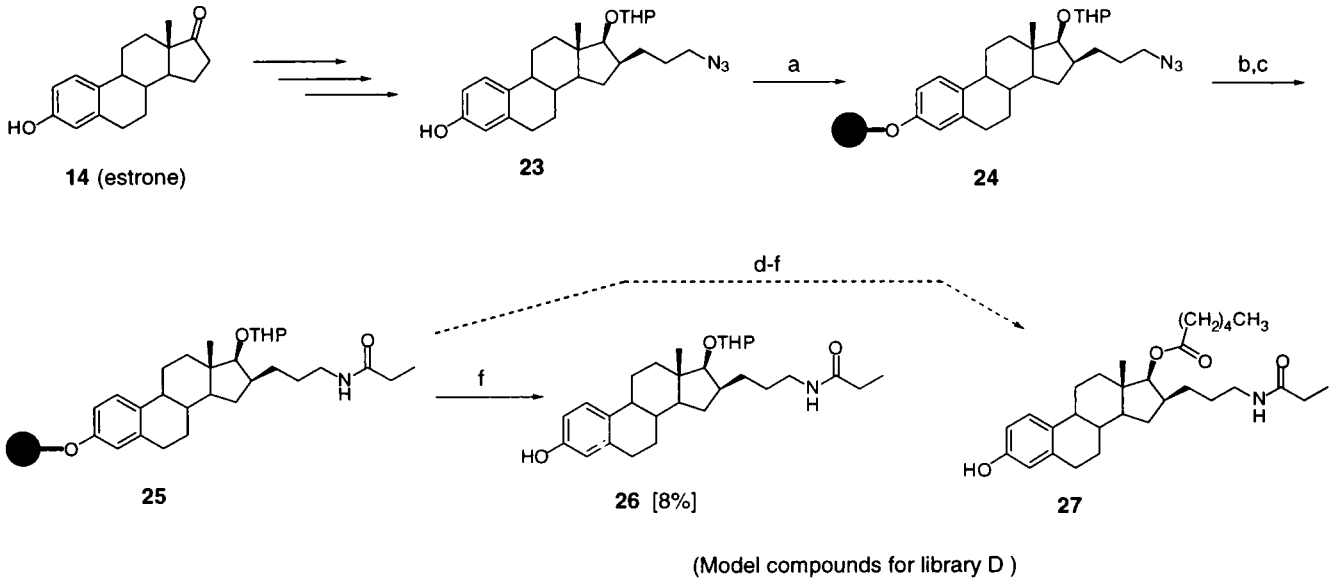


[a] (a) Tf_2O, pyridine, rt; (b) CO, AcOK, $Pd(OAc)_2$, dppf, 60 °C; (c) ethylene glycol, *p*-TSA, toluene, reflux with a Dean−Stark trap; (d) $LiAlH_4$, THF, 0 °C; (e) 6 M HCl, acetone, 0 °C; (f) TBDMS-Cl, imidazole, DMF, rt; (g) NaH, $(CH_3)_3SI$, DMSO, rt; (h) 1 M TBAF in THF, rt; (i) imidazole, **1b** [PS-DES resin, 1,3-dichloro-5,5-dimethylhydantoin], CH_2Cl_2, rt; (j) butylamine/EtOH (1:1), 60 °C; (k) heptanoyl chloride, pyridine, CH_2Cl_2, rt; (l) HF-pyridine, THF, rt. [b]Data between brackets correspond to overall yield and HPLC purity, respectively.

precursor of molecular diversity. Furthermore, the resulting silyl-ether link is stable under nucleophilic or electrophilic conditions. After a model sequence of reactions (four steps), the overall yields (45−64%) obtained with secondary steroidal alcohols (position 3β or 17β) and a primary steroidal benzylic alcohol were satisfactory. The HPLC purities of final compounds released from resin were also excellent (90−99%) without purification steps. This study has shown that the diethylsilyloxy linker possesses many of the characteristics desirable in solid-phase synthesis of either primary or secondary hydroxysteroid derivatives in nonacidic reaction sequences. However, the phenolic steroid linked to PS-DES resin was found very sensitive under acylating conditions, resulting in a poor yield of final compound. After a recent investigation of other available linkers for phenols, our group reported excellent HPLC purities and acceptable overall yields for a typical model sequence of reactions[7] and the elaboration of a library of estradiol derivatives[13] using the photolabile *o*-nitrobenzyl linker.[31−33]

The present study with the diethylsilyloxy linker gave a good idea how the series of hydroxylated steroids linked to a PS-DES resin would behave and offered a starting

Scheme 4[a,b]



[a] (a) Imidazole, **1b** [PS-DES resin, 1,3-dichloro-5,5-dimethylhydantoin] CH_2Cl_2, rt; (b) $SnCl_2$, Et_3N, PhSH, THF, rt; (c) propionyl chloride, DIPEA, CH_2Cl_2, rt; (d) *p*-TSA, butanol/CH_2Cl_2 (1:1), rt; (e) hexanoic acid, DIPC, DIPEA, DMAP, CH_2Cl_2, rt; (f) TBAF, THF, rt. [b]Data between brackets correspond to overall yield after a flash chromatography.

point for the elaboration of many different libraries of hydroxysteroids by solid-phase synthesis. In this regard, a model library of twenty C19-steroid derivatives (compounds **28**−**47**), represented by general formula **7a**, was successfully produced in a short time, in good average yield (53%), and with excellent average HPLC purity (97%) for five selected compounds. This and the other solid-phase reaction sequences reported in this paper (libraries A−C) were suitable for use with an automatic synthesizer that allows the preparation of larger libraries. The preparation of such libraries, more voluminous and designed to target some key enzymes of the steroidogenesis or steroids receptors, is now under progress.

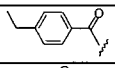
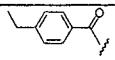
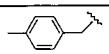
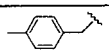
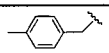
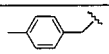
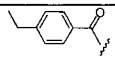
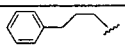
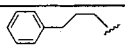
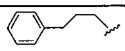
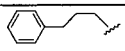
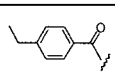
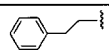
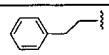
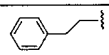
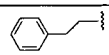
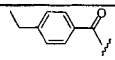
Experimental Section

General Methods. Hydroxysteroids (dihydrotestosterone, epiandrosterone, and estrone) were purchased from Steraloids (Wilton, NH). The butyldiethylsilane polystyrene (PS-DES resin) with a loading of 0.83 or 1.52 mmol/g was supplied by Argonaut Technologies (San Carlos, CA). Chemical reagents were purchased from Sigma-Aldrich Canada Ltd. (Oakville, ON, Canada). The usual solvents were obtained from Fisher Scientific (Montréal, Qc, Canada) and were used as received. Anhydrous dichloromethane (CH_2Cl_2), dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and pyridine were obtained from Sigma-Aldrich. The solid-phase reactions were performed in peptide synthesis vessels with frit (25 mL) equipped for vacuum filtration (ChemGlass Inc.; Vineland, NJ) or in polystyrene PD-10 columns (Amersham Pharmacia Biotech AB; Uppsala, Sweden) coupled with a three-way stopcock (Bio-Rad Laboratories; Hercules, CA). The reaction vessels were shaken with a Burrell wrist-action shaker model 75 (Pittsburgh, PA). Thin-layer chromatography (TLC) and flash-column chromatography were performed on 0.20 mm silica gel 60 F254 plates and with 230-400 mesh ASTM silica gel 60, respectively (E. Merck; Darmstadt, Germany). The purity of final compounds released from solid support was determined by HPLC (Waters Associates, Milford, MA) using a NovaPak C18 reversed-phase column (150 mm × 3.9 mm id) and an ultraviolet detector (205 nM). Infrared spectra (IR) were recorded on a Perkin-Elmer series 1600 FT-IR spectrometer (Norwalk, CT) and the significant bands reported in cm^{-1}. Nuclear magnetic resonance spectra (NMR) were recorded at 300 MHz for ^1H and 75.5 MHz for ^{13}C on a Bruker AC/F300 spectrometer (Billerica, MA) and reported in ppm. Low-resolution mass spectra (LRMS) were recorded on a PE Sciex API-150ex apparatus (Foster City, CA) equipped with a turbo ionspray source.

Library A (Scheme 1): 17β-Hydroxy-spiro-3(*R*)-oxirane-5α-androstane (3). To a solution of trimethylsulfoxonium iodide (15.15 g; 68.8 mmol) in dry DMSO (700 mL) was carefully added sodium hydride 60% in oil (2.75 g; 68.8 mmol) under an atmosphere of argon. The solution was stirred at room temperature for 1 h before adding dihydrotestosterone (**2**) (10.0 g; 34.4 mmol) dissolved in dry THF. The mixture was stirred overnight and then poured in ice/water (1 L) and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated to dryness. Purification of the crude product by flash chromatography (EtOAc:hexane, 1:1) yielded 7.34 g (70%) of oxirane **3**. IR (KBr): 3503 (OH, alcohol). ^1H NMR ($CDCl_3$): 0.74 (s, 3H), 0.85 (s, 3H), 0.80−2.20 (23H), 2.62 (s, 2H), 3.63 (t, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): 11.1, 11.2, 20.5, 23.3, 28.4, 29.1, 30.4, 31.3, 35.4 (2x), 35.8, 35.9, 36.7, 42.9, 43.7, 50.9, 53.5, 54.0, 58.5, 81.7. LRMS for $C_{20}H_{32}O_2 + NH_4$ [M^+]: 322.6 *m/z*.

Coupling of Hydroxysteroid 3 to PS-DES Resin (Synthesis of 4). To dry PS-DES resin **1a** (500 mg; 0.42 mmol) swollen in dry CH_2Cl_2 (2.5 mL) and under an atmosphere of argon was added 1,3-dichloro-5,5-dimethylhydantoin (245 mg; 1.25 mmol) in dry CH_2Cl_2 (2.5 mL). After 2 h, the resulting chlorosilyl resin **1b** was washed under argon with CH_2Cl_2 (3 × 5 mL) and THF (3 × 5 mL). After the

Table 1. Twenty Members of Model Library A

Member	R_1	R_2	Overall Yield (%)[a]	HPLC Purity (%)	LRMS [MH^+] (m/z)
28			50	---	486.5
29			54	---	488.6
30			53	100	522.9
31			55	---	550.5
32			51	---	480.5
33			63	95	482.3
34			54	---	516.7
35			57	---	544.5
36			53	---	494.5
37			58	---	496.6
38			20	---	530.6
39			55	---	558.5
40			57	---	508.5
41			53	95	510.9
42			54	---	544.4
43			56	---	572.6
44			49	96	494.6
45			55	---	496.6
46			62	98	530.4
47			53	---	558.4

[a] The overall yields were calculated for the solid-phase sequence of four steps assuming a complete coupling (theoretical loading of 1.5 mmol/g) of hydroxysteroid **3** on PS-DES resin **1a**.

disappearance of SiH band at 2100 cm^{-1} was confirmed in IR spectrum, the resin was immediately used for the next step. To the resin swollen in dry CH_2Cl_2 (2.5 mL) and kept under an atmosphere of argon was added a solution of imidazole (98 mg; 1.45 mmol) and oxirane **3** (631 mg; 2.08 mmol). The solution was vortexed with a Burrell wrist-action shaker for 4 h at room temperature. The resin was then washed with THF (3 × 5 mL), CH_2Cl_2 (3 × 5 mL), and dried overnight under vacuum to give 567 mg of resin **4**. ^{13}C NMR (CCl_4:benzene-d_6, 80:20): 6.0, 6.9, 7.5, 11.8, 12.0, 13.7, 21.1, 23.5, 24.0, 29.0, 29.6, 31.6, 31.9, 36.0, 36.3, 36.5, 37.7, 40.9, 43.8, 44.1, 51.1, 53.0, 54.6 (CH_2 of oxirane), 57.8 (C of oxirane), 82.1 (CH-OSi) (Figure 2).

Synthesis of Resin 5. A solution of butylamine or heptylamine in ethanol (1:1, v/v) (5 mL) was added to 567 mg of resin **4**. The suspension was stirred with a magnetic stirring bar for 3 days at 60 °C. The resin was then washed with CH_2Cl_2 (3 × 15 mL) and dried under vacuum overnight to give 570 mg of resin **5a** (R_1 = butyl) or **5b** (R_1 = heptyl). The appearance of OH/NH band was observed in IR.

Synthesis of 3β-[*N*-Butyl-*N*-heptanoyl)aminomethyl]-3α,17β-dihydroxy-5α-androstane (7a). To 210 mg of resin **5a** (R_1 = butyl) swollen in dry CH_2Cl_2 (2 mL) and pyridine (42 μL; 0.51 mmol) was added heptanoyl chloride (48 μL; 0.31 mmol), and the mixture was vortexed for 90 min at room temperature. The resin was then washed with CH_2Cl_2, MeOH, and dried under vacuum for 3 h to give resin **6a**. IR (KBr): 3062 (OH, alcohol), 1620 (C═O, amide). The resin was swollen in dry THF (2 mL), and a solution of HF-pyridine (60 μL; 0.3 M final) was added. The resin was

vortexed for 2 h before it was filtered and washed with EtOAc. The filtrate was washed with aqueous $NaHCO_3$ (10%, w/v), evaporated, and dried under vacuum (24 h) to give 36 mg (47% overall yield) of the amide **7a**. IR (KBr): 3425 (OH, alcohols), 1618 (C═O, amide). ^{1}H NMR ($CDCl_3$): 0.71 (s, 3H), 0.76 (s, 3H), 0.87 (t, J = 6.5 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H), 0.80−2.10 (35H), 2.32 (t, J = 7.6 Hz, 2H), 3.30 (m, 4H), 3.61 (t, J = 8.5 Hz, 1H), 4.62 (broad, 1H). ^{13}C NMR ($CDCl_3$): 11.1, 11.3, 13.8, 14.0, 20.0, 20.5, 22.5, 23.3, 25.5, 28.5, 29.1, 30.4, 30.8, 31.4, 31.6, 32.2, 33.0, 33.5, 35.5, 35.9, 36.7, 39.0, 40.3, 42.9, 50.9, 51.0, 54.1, 58.9, 72.6, 81.9, 176.1. LRMS for $C_{31}H_{56}NO_3$ [MH^+]: 490.5 *m*/*z*. HPLC (CH_3CN:H_2O:MeOH, 48:17:35): 99% of purity.

Synthesis of 3β-[*N*-Butyl-*N*-benzylcarbonyl)aminomethyl]-3α,17β-dihydroxy-5α-androstane (7b). To 100 mg of resin **5a** (R_1 = butyl) swollen in DMF (0.5 mL) was added a solution of bromo-tris-pyrolidinophosphonium hexafluorophosphate (PyBrOP) (52 mg; 0.10 mmol), *N*-hydroxybenzotriazole (HOBt) (14 mg; 0.10 mmol), phenylacetic acid (14 mg; 0.10 mmol), and diisopropylamine (33 μL; 0.20 mmol) in DMF (0.5 mL). The mixture was vortexed under an atmosphere of argon for 2 h, and the resin was washed with DMF (3 × 5 mL) and CH_2Cl_2 (3 × 5 mL). The acylation reaction was repeated using the same conditions as above. Thereafter, the resin was swollen in dry THF (1 mL), and a solution of HF-pyridine (60 μL; 0.3 M final) was added. The resin was vortexed for 2 h before it was filtered and washed with EtOAc. The filtrate was washed with aqueous $NaHCO_3$ (10%, w/v), evaporated, and dried under vacuum (24 h) to give 24 mg (64% overall yield) of the amide **7b**. IR (KBr): 3396 (OH, alcohols), 1622 (C═O, amide). ^{1}H NMR ($CDCl_3$): 0.72 (s, 3H), 0.74 (s, 3H), 0.92 (t, J = 7.1 Hz, 3H), 0.80−2.10 (33H), 3.32 (m, 4H), 3.63 (t, J = 8.4 Hz, 1H), 3.74 (s, 2H), 4.44 (broad, 1H), 7.30 (m, 5H). ^{13}C NMR ($CDCl_3$): 11.1, 11.3, 13.8, 20.0, 20.5, 23.4, 28.5, 30.5, 30.7, 31.5, 32.2, 33.5, 35.5, 35.9, 36.7, 39.0, 40.3, 40.8, 43.0, 51.0 (2×), 54.2, 58.7, 72.9, 81.9, 126.9, 128.7 (4x), 134.9, 173.8. LRMS for $C_{32}H_{50}NO_3$ [MH^+]: 496.3 *m*/*z*. HPLC (CH_3CN:H_2O:MeOH, 35:25:40): 90% of purity.

Synthesis of 3β-{[*N*-Butyl-*N*-(2′-amino-3′-phenyl-propionyl)]aminomethyl}-3α,17β-dihydroxy-5α-androstane (7c). To 100 mg of resin **5a** (R_1 = butyl) swollen in DMF (0.7 mL) was added a solution of PyBrOP (168 mg; 0.32 mmol), HOBt (44 mg; 0.32 mmol), *N*-α-Fmoc-L-phenylalanine (126 mg; 0.32 mmol), and diisopropylamine (113 μL; 0.64 mmol) in DMF (0.7 mL). The mixture was vortexed under an atmosphere of argon for 2 h, and the resin was washed with DMF (3 × 5 mL) and CH_2Cl_2 (3 × 5 mL). The acylation reaction was repeated using the same conditions as above. Thereafter, the resin was swollen in dry THF (1 mL), and a solution of HF-pyridine solution (60 μL; 0.3 M final) was added. The resin was vortexed for 2 h before it was filtered and washed with EtOAc. The filtrate was washed with aqueous $NaHCO_3$ (10%, w/v), evaporated, and dried under vacuum (24 h) to give 19 mg (57% overall yield) of the amide **7c**. IR (KBr): 3363 (OH and NH), 1628 (C═O, amide). ^{1}H NMR ($CDCl_3$): 0.72 (s, 3H), 0.74 (s, 3H), 0.90 (t, J = 6.4 Hz, 3H), 0.80−2.20 (28H), 2.6−3.3 (m broad, 6H), 3.61 (m, 3H), 3.85 (t, J = 6.5 Hz, 1H), 7.24 (m, 5H). ^{13}C NMR ($CDCl_3$): 11.1, 11.3, 13.7, 19.9, 20.5, 23.3, 28.4, 30.4, 31.1, 31.5, 32.3, 33.4, 35.5, 35.8, 36.7, 38.6, 40.3, 42.9, 43.1, 50.2, 51.0, 53.4, 54.2, 59.1, 72.8, 81.8, 126.8, 128.6 (2x), 129.3 (2x), 137.6, 177.5. LRMS for $C_{33}H_{53}N_2O_3$ [MH^+]: 525.5 *m*/*z*.

Synthesis of 3β-{[*N*-Heptyl-*N*-(2′-diethylamino-acetyl)]-aminomethyl}-3α,17β-dihydroxy-5α-androstane (7d). To 170 mg of resin **5d** (R_1 = heptyl) swollen in dry DMF (1.7 mL) was added a solution of bromoacetic acid (235 mg; 1.69 mmol) and 1,3-diisopropylcarbodiimide (217 mg; 1.71 mmol). The solution was vortexed under an atmosphere of argon for 30 min, and the resin was washed with DMF (3 × 5 mL), CH_2Cl_2 (3 × 5 mL), and dried under vacuum for 1 h. The acylation reaction was repeated using the same conditions as above. Thereafter, the resin was vortexed in a 2.5 M solution of diethylamine in dry DMSO (2 mL) under an atmosphere of argon at room temperature for 12 h. The resin was washed with DMSO (3 × 5 mL), CH_2Cl_2 (3 × 5 mL), and dried under vacuum for 1 h. Finally, the resin was swollen in dry THF (2 mL), a solution of HF-pyridine (60 μL; 0.3 M final) was added, and the resin was vortexed for 2 h before being filtered and washed with EtOAc. The filtrate was washed with aqueous $NaHCO_3$ (10%, w/v), evaporated, and dried under vacuum (24 h) to give 30 mg (45% overall yield) of the amide **7d**. IR (KBr): 3392 (OH, alcohols), 1623 (C═O, amide). ^{1}H NMR ($CDCl_3$): 0.72 (s, 3H), 0.76 (s, 3H), 0.88 (t, J = 6.5 Hz, 3H), 1.06 (t, J = 6.9 Hz, 6H), 0.80−2.10 (26H), 2.65 (m, 4H), 3.35 (m, 6H), 3.65 (t, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): 10.0, 11.1, 11.4, 11.6, 14.0, 20.5, 22.5, 23.4, 26.8, 28.5, 28.7, 29.1, 30.5, 31.5, 31.7, 32.2, 33.5, 35.6, 35.9, 36.8, 39.1, 40.3, 40.4, 43.0, 47.5, 50.5, 51.0, 54.1, 58.7, 72.8, 81.9, 173.3. LRMS for $C_{33}H_{53}N_2O_3$ [MH^+]: 533.5 *m*/*z*. HPLC (CH_3CN:H_2O:MeOH, 35:35:30): 92% of purity.

Library B (Scheme 2). 3-Hydroxy-spiro-17(*S*)-oxirane-5α-androstane (9). To a solution of trimethylsulfonium iodide (8.43 g; 41.3 mmol) in dry DMSO (350 mL) was carefully added sodium hydride 60% in oil (1.65 g; 41.2 mmol), and the solution was stirred at room temperature under an atmosphere of argon for 1 h. A solution of epiandrosterone (**8**) (2.0 g; 6.89 mmol) in dry THF (60 mL) was then added, and the resulting solution was stirred for 3 h. The solution was poured in ice-water and extracted with EtOAc (150 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated to dryness. Purification of the crude product by flash chromatography (EtOAc:hexane, 1:1) yielded 1.35 g (65%) of oxirane **9**. IR (KBr): 3503 (OH, alcohol). ^{1}H NMR ($CDCl_3$): 0.65 (td, J_1 = 3.9 Hz and J_2 = 11.2 Hz, 1H), 0.82 (s, 3H), 0.87 (s, 3H), 0.90−2.00 (22H), 2.59 and 2.89 (2d of AB system, J = 5.1 Hz, 2 × 1H), 3.58 (m, 1H). ^{13}C NMR ($CDCl_3$): 12.3, 14.3, 20.6, 23.5, 28.5, 29.0, 31.4 (2×), 33.9, 35.5, 35.6, 37.0, 38.1, 40.1, 44.9, 52.8, 53.6, 54.4, 70.5, 71.2. LRMS for $C_{20}H_{32}O_2$ + NH_4 [M^+]: 322.4 *m*/*z*.

Coupling of Hydroxysteroid 9 to PS-DES Resin (Synthesis of 10). To chlorosilyl resin **1b** (300 mg; 0.25 mmol) prepared as above, in dry CH_2Cl_2 (3 mL) and under an atmosphere of argon, was added a solution of imidazole (59 mg; 0.87 mmol) and oxirane **9** (216 mg; 0.74 mmol). The mixture was vortexed for 4 h at room temperature. Next,

the resin was washed with THF (3 × 5 mL) and CH_2Cl_2 (3 × 5 mL) and dried overnight under vacuum to give 350 mg of resin **10**. ^{13}C NMR (CCl_4:benzene-d_6, 80:20): 5.6, 7.1, 12.3, 14.4, 20.6, 23.6, 28.7, 28.9, 31.6, 32.1, 34.1, 35.6(2x), 37.2, 38.8, 40.1, 45.1, 52.5, 52.9 (CH_2 of oxirane), 54.6, 69.6 (C of oxirane), 71.6, (CH−OSi).

Synthesis of Resin 11. A solution of butylamine in ethanol (1:1, v/v) (5 mL) was added to 350 mg of resin **10**. The suspension was stirred with a magnetic stirring bar for 3 days at 60 °C, and the resin was washed with CH_2Cl_2 (3 × 15 mL) and dried overnight under vacuum to give 365 mg of resin **11**. The appearance of OH/NH band was observed in IR.

Synthesis of 17α-[*N*-Butyl-*N*-heptanoyl)aminomethyl]-3β,17β-dihydroxy-5α-androstane (13). To 200 mg of resin **11** swollen in dry CH_2Cl_2 (2 mL) and dry pyridine (42 μL; 0.51 mmol) was added heptanoyl chloride (48 μL; 0.31 mmol). The mixture was vortexed for 90 min at room temperature, and the resin was washed with CH_2Cl_2, MeOH, and then dried under vacuum for 3 h to give resin **12**. IR (KBr): 3359 (OH, alcohol), 1620 (C═O, amide). The resin was swollen in dry THF (2 mL), and a solution of HF-pyridine (60 μL; 0.3 M final) was added. The resin was vortexed for 2 h before being filtered and washed with EtOAc. The filtrate was washed with aqueous $NaHCO_3$ (10%, w/v), evaporated, and dried under vacuum (24 h) to give 43 mg (64% yield) of amide **13**. IR (KBr): 3403 (OH, alcohols), 1618 (C═O, amide). ^1H NMR ($CDCl_3$): 0.60 (m, 1H), 0.85 (s, 3H), 0.89 (t, J = 7.1 Hz, 3H), 1.00 (t, J = 6.5 Hz, 3H), 1.15 (s, 3H), 0.80−2.00 (34H), 2.26 (t, J = 7.3 Hz, 2H), 2.99 and 3.43 (2m, 2 × 1H), 3.52 and 3.84 (2d of AB system, J = 14.0 Hz, 2 × 1H), 3.67 (m, 1H), 4.99 (broad, 1H). ^{13}C NMR ($CDCl_3$): 12.6, 13.9, 14.3, 14.5, 20.4, 21.2, 23.0, 23.9, 25.9, 29.1, 29.5, 31.1, 31.2, 32.1 (2×), 32.3, 33.2, 33.3, 35.9, 36.7, 37.5, 38.9, 45.3, 46.9, 50.6, 51.1, 54.5, 54.9, 71.1, 84.5, 175.6. LRMS for $C_{31}H_{56}NO_3$ [MH^+]: 490.4 *m*/*z*. HPLC (CH_3CN:H_2O:MeOH, 35:25:40): 97% of purity.

Library C (Scheme 3): 17-Dioxolane-1,3,5(10)-estratrien-3-carboxylic Acid (16). To a solution of 17-oxo-1,3,5(10)-estratrien-3-carboxylic acid (**15**)[28,29] (4.87 g; 16.3 mmol) dissolved in toluene were added, at room temperature and under an atmosphere of argon, ethylene glycol (9.13 mL; 163 mmol), and *p*-toluenesulfonic acid (0.30 g; 1.60 mmol). The solution was refluxed in a Dean−Stark apparatus for 90 min. The solution was then diluted with EtOAc (300 mL), washed with water (3 × 250 mL) and dried with Na_2SO_4. The crude product (5.46 g) was purified by flash chromatography with EtOAc/hexane (1:1) as eluent to give 4.46 g (81%) of the acetal **16**. IR (KBr): 2200−3600 (OH, acid) 1684 (C═O, conjugated acid). ^1H NMR ($CDCl_3$): 0.89 (s, 3H), 1.30−2.10 (11 H), 2.42 (m, 3H), 2.92 (m, 2H), 3.92 (m, 4H), 7.39 (d, J = 8.2 Hz, 1H), 7.82 (s, 1H), 7.85 (d, J = 8.2 Hz, 1H). ^{13}C NMR (DMSO-d_6): 14.1, 21.9, 25.3, 26.2, 28.7, 30.3, 33.7, 38.0, 43.9, 45.5, 49.0, 64.1, 64.7, 118.4, 125.6, 126.5, 127.5, 130.1, 137.7, 145.3, 167.4. LRMS for $C_{21}H_{27}O_4$ [MH^+]: 343.1 *m*/*z*.

3-[(*tert*-Butyldimethylsilyloxy)methyl]-1,3,5(10)-estratriene-17-one (17). A sequence of three steps was needed to obtain compound **17**. (*1*) *Reduction of carboxylic acid to primary alcohol*: To a solution of carboxylic acid **16** (13.20 g; 38.5 mmol) in dry THF (1000 mL) was added $LiAlH_4$ (4.38 g; 115.4 mmol) at 0 °C and under an atmosphere of argon. The solution was stirred for 4 h before a dropwise addition of aqueous 1 M Rochelle salt (1500 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 500 mL), and the organic phase was washed with brine (300 mL), dried with Na_2SO_4, filtered, and evaporated under vacuum. The crude pale yellow solid was purified by flash chromatography using EtOAc/hexane (3:7) as eluent to give 10.71 g (85%) of the corresponding steroidal alcohol as a white solid. (*2*) *Hydrolysis of acetal to ketone*: To a solution of steroidal alcohol (2.01 g; 6.1 mmol) in acetone (50 mL) was added at 0 °C an aqueous solution of 6 N HCl (50 mL). The resulting solution was stirred for 1 h at room temperature. A cold solution of aqueous $NaHCO_3$ 10% (w/v) was slowly added until neutralization of the acidic solution. The solution was extracted with EtOAc (2 × 25 mL), washed with brine, and finally dried with $MgSO_4$ to give 1.70 g of the corresponding ketone. IR (KBr): 3373 (OH, alcohol), 1716 (C═O, ketone). (*3*) *Protection of alcohol as a TBDMS derivative*: To the crude primary alcohol (1.70 g; 6.0 mmol) dissolved in dry DMF (100 mL) was added imidazole (2.03 g; 30 mmol) and *tert*-butyldimethylsilyl chloride (1.80 g; 12.0 mmol). The solution was then stirred for 3 h under an atmosphere of argon. The resulting solution was poured in a cold ice/water mixture, and the aqueous phase was extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, and evaporated to give the TBDMS derivative **17** (2.04 g, 84%) after flash chromatography (EtOAc:hexane, 1:9). IR (film): 1736 (C═O, ketone). ^1H NMR ($CDCl_3$): 0.11 (s, 6H), 0.92 (s, 3H), 0.96 (s, 9H), 1.40−2.60 (13H), 2.92 (m, 2H), 4.69 (s, 2H), 7.07 (s, 1H), 7.12 (d, J = 8.1 Hz, 1H), 7.27 (d, J = 7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): 5.2 (2×), 13.8, 18.4, 21.6, 25.7, 26.0 (3×), 26.5, 29.4, 31.6, 35.8, 38.2, 44.3, 48.0, 50.5, 64.7, 123.6, 125.2, 126.7, 136.2, 138.3, 138.8, 220.8. LRMS for $C_{25}H_{38}O_2Si + NH_4$ [M^+]: 416.5 *m*/*z*.

3-(Hydroxymethyl)-spiro-17(*S*)-oxirane-1,3,5(10)-estratriene (18). To a solution of trimethylsulfonium iodide (2.38 g; 11.66 mmol) in dry DMSO (75 mL) was carefully added sodium hydride 60% in oil (468 mg; 11.66 mmol) under an atmosphere of argon, and the solution was stirred for 1 h at room temperature. A solution of primary alcohol **17** in dry THF (60 mL) was then added (1.42 g; 3.89 mmol), and the resulting solution was stirred overnight. The mixture was poured into ice−water and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated to dryness to give a crude oxirane intermediate, which was used for the next step without purification. This later compound was thus dissolved in dry THF (60 mL) and treated with tetrabutylammonium fluoride (5 mL of a 1.0 M solution in THF) at room temperature for 30 min. After usual workup as above and flash chromatography using EtOAc and hexane (3:7), 632 mg (75%, two steps) of alcohol **18** was obtained. IR (KBr): 3434 (OH, alcohol); ^1H NMR ($CDCl_3$): 0.92 (s, 3H), 1.20−2.40 (14H), 2.65 and 2.97 (2d, J = 5.0 Hz, 2 × 1H), 2.89 (m, 2H), 4.62 (d, J = 5.9 Hz, 2H), 7.11 (s,1H), 7.13 (d, J = 8.1 Hz, 1H), 7.28 (d, J = 7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$):

14.3, 23.3, 25.8, 27.1, 29.0, 29.5, 33.9, 38.7, 40.4, 44.2, 51.9, 53.6, 65.2, 70.5, 124.4, 125.6, 127.7, 137.0, 138.2, 139.7. LRMS for $C_{20}H_{26}O_2 + NH_4$ [M^+]: 316.3 *m*/*z*.

Coupling of Hydroxysteroid 18 to PS-DES Resin (Synthesis of 19). To chlorosilyl resin **1b** (300 mg; 0.46 mmol) prepared as above, in dry CH_2Cl_2 (3 mL) and under an atmosphere of argon, was added a solution of imidazole (93 mg; 1.37 mmol) and oxirane **18** (410 mg; 1.37 mmol). The mixture was then vortexed for 4 h at room temperature before being washed with THF (3 × 5 mL) and CH_2Cl_2 (3 × 5 mL) and dried overnight under vacuum to give 535 mg of resin **19**. ^{13}C NMR (CCl_4:benzene-d_6, 80:20): 5.5, 7.4, 14.8, 23.8, 26.3, 27.7, 29.4, 30.0, 34.4, 39.2, 40.7, 44.7, 52.4, 53.1 (CH_2 of oxirane), 65.0 (CH_2−OSi), 70.1 (C of oxirane), 124.2, 125.4, 127.3, 127.7, 136.2, 138.8.

Synthesis of Resin 21. A solution of butylamine in ethanol (1:1, v/v) (7 mL) was added to 535 mg of resin **19**. The suspension was stirred with a magnetic stirring bar for 5 days at 60 °C. The resin was then washed with CH_2Cl_2 (3 × 15 mL) and dried overnight under a vacuum to give 540 mg of resin **20**. To 220 mg of resin **20** in dry CH_2Cl_2 (2.0 mL) and dry pyridine (42 μL; 0.51 mmol) was added heptanoyl chloride (48 μL; 0.31 mmol). The mixture was vortexed for 90 min at room temperature, and the resin was washed with CH_2Cl_2, MeOH, and dried under vacuum for 3 h to give resin **21**.

Synthesis of 17α-[(*N*-Butyl-*N*-heptanoyl)aminomethyl]-3-(hydroxymethyl)-17β-hydroxy-1,3,5(10)-estratriene (22). To 220 mg of resin **21** swollen in dry THF (2 mL) was added a solution of HF-pyridine (60 μL; 0.3 M final), and the mixture was vortexed for 2 h. The resin was then filtered and washed with EtOAc. The filtrate was washed with aqueous $NaHCO_3$ (10%, w/v), evaporated, and dried under vacuum (24 h) to give amide **22** (39 mg, 44%). IR (KBr): 3390 (OH, alcohols), 1618 (C═O, amide). ^1H NMR ($CDCl_3$): 0.80 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 6.0 Hz, 3H), 1.04 (s, 3H), 1.10−2.10 (26H), 2.18 (t, J = 7.4 Hz, 2H), 2.76 (m, 2H), 2.90 and 3.34 (2m, 2H), 3.43 and 3.76 (2d of AB system, J = 14.2 Hz, 2 × 1H), 4.62 (s, 2H), 4.90 (broad, 1H), 7.09 (s,1H), 7.17 (s, 2H). ^{13}C NMR (benzene-d_6): 14.0, 14.3(2×), 20.3, 23.0, 23.6, 25.9, 26.5, 27.9, 29.6, 30.0, 31.0, 31.2, 32.1, 33.2, 33.3, 39.9, 44.7, 47.0, 50.1, 50.6, 54.5, 65.0, 84.6, 124.7, 125.7, 127.9 (under solvent peak), 136.7, 139.4, 139.5, 175.7. LRMS for $C_{31}H_{50}NO_3$ [MH^+]: 484.6 *m*/*z*. HPLC (CH_3CN:H_2O:MeOH, 35:25:40): 92% of purity.

Library D (Scheme 4). Coupling of Hydroxysteroid 23 to PS-DES Resin (Synthesis of 24). To chlorosilyl resin **1b** (500 mg; 0.42 mmol) prepared as above was added a solution of phenol **23**[7] (550 mg; 1.25 mmol) and imidazole (99 mg; 1.45 mmol) in dry DMF (5 mL). The mixture was vortexed for 6 h at room temperature, and the resin was washed with CH_2Cl_2 (3 × 5 mL), DMF:H_2O (1:1) (3 × 5 mL), and THF (4 × 5 mL), and dried overnight under vacuum to give 612 mg of resin **24**. IR (KBr): 2100 (N_3) and no OH band was observed.

Synthesis of Resin 25. The resin **24** (612 mg) was swollen in dry THF (1 mL), 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 an atmosphere of argon for 5 h at room temperature. The resin was then filtered, washed with DMF (4 × 5 mL) and CH_2Cl_2 (4 × 5 mL), and dried under vacuum. The IR spectrum confirmed the disappearance of the azide band (N_3) and a broadening of the NH_2 signal. To the resin (600 mg) in dry 1,2-dichloroethane (4 mL) was added diisopropylethylamine and propionyl chloride to give a final solution of 0.6 and 0.5 M, respectively. The mixture was vortexed overnight at room temperature, filtered, and washed with DMF (5 × 5 mL) and CH_2Cl_2 (5 × 5 mL) to give resin **25**. IR (KBr): 1680 (C═O, amide).

Synthesis of *N*-{3-[3-Hydroxy-17β-(tetrahydro-2*H*-pyran-2-yl-oxy)-1,3,5(10)-estratrien-16β-yl]propyl}-propanamide (26). The resin **25** (535 mg) was swollen in dry THF (4 mL), and a 1.0 M solution of tetrabutylammonium fluoride (800 μL) was added via a syringe. The suspension was vortexed for 90 min at room temperature, and the resin was filtered and washed with CH_2Cl_2 (5 × 5 mL). The filtrate was washed with phosphate buffer (pH 7.2) followed by aqueous HCl (10%, v/v). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. A purification by flash chromatography (hexane:EtOAc, 5:5 to pure EtOAc) was necessary to give 10 mg (8% overall yield) of amide **26**. The full characterization of **26** was already reported by us.[7]

Synthesis of a Model Library (Table 1). The 20-membered model library was prepared according to the sequence of reactions and experimental conditions reported in Scheme 1 for the synthesis of compound **7a** (library A). All compounds were synthesized in parallel, and no purification step was performed after cleavage of the final compounds (**28**−**47**) from solid support. In addition to the mass spectra analysis of all final compounds, five compounds (**30**, **33**, **41**, **44**, and **46**) obtained by a random sampling were characterized by IR and ^1H NMR spectroscopies, and purities determined by HPLC.

3β-[(*N*-Benzoyl-*N*-cyclohexylmethyl)aminomethyl]-3α,-17β-dihydroxy-5α-androstane (30). IR (KBr): 3425 (OH, alcohols), 1594 (C═O, amide). ^1H NMR ($CDCl_3$): 0.60 (m, 1H), 0.73 (s, 3H), 0.80 (s, 3H), 0.75−2.10 (34H), 3.24 (d, J = 6.8 Hz, 2H), 3.54 (s, 2H), 3.65 (t, J = 8.4 Hz, 1H), 7.38 (s, 5H). LRMS for $C_{34}H_{52}NO_3$ [MH^+]: 522.9 *m*/*z*. HPLC (80% of MeOH:H_2O (9:1) and 20% of H_2O, both containing 20 mM of NH_4OAc): 100% of purity.

3β-[(*N*-Benzyl-*N*-*i*-propylcarbonyl)aminomethyl]-3α,-17β-dihydroxy-5α-androstane (33). IR (KBr): 3448 (OH, alcohols), 1624 (C═O, amide). ^1H NMR ($CDCl_3$): 0.72 (s, 3H), 0.73 (s, 3H), 1.12 and 1.13 (2d, J = 6.6 Hz, 6H), 0.75−2.10 (26H), 2.74 (sept, J = 6.7 Hz, 1H), 3.38 (q_{app} of AB system, 2H), 3.63 (t, J = 8.4 Hz, 1H), 4.17 (s, 1H), 4.71 (s, 2H), 7.11 (d, J = 7.3 Hz, 2H). LRMS for $C_{31}H_{48}NO_3$ [MH^+]: 482.3 *m*/*z*. HPLC (CH_3CN:H_2O:MeOH, 35:30:35): 95% of purity.

3β-[(*N*-Phenylpropyl-*N*-*i*-propylcarbonyl)aminomethyl]-3α,17β-dihydroxy-5α-androstane (41). IR (KBr): 3422 (OH, alcohols), 1624 (C═O, amide). ^1H NMR ($CDCl_3$): 0.72 (s, 3H), 0.74 (s, 3H), 1.09 (d, J = 6.6 Hz, 6H), 0.75−2.10 (26H), 2.62 (t and sept (under t), 3H), 3.28 (q_{app}, 2H), 3.34 (t_{app}, 2H), 3.63 (t, J = 8.5 Hz, 1H), 7.18 (d, J = 7.0 Hz,

2H), 7.30 (m, 3H). LRMS for $C_{33}H_{52}NO_3$ [MH^+]: 510.9 *m/z*. HPLC (CH_3CN:H_2O:MeOH, 35:30:35): 95% of purity.

3β-[(*N*-Cyclopropylcarbonyl-*N*-phenylethyl)aminomethyl]-3α,17β-dihydroxy-5α-androstane (44). IR (KBr): 3405 (OH, alcohols), 1618 (C═O, amide). ^{1}H NMR ($CDCl_3$): 0.72 (s, 3H), 0.75 (s, 3H), 0.75−2.10 (29H), 2.94 (t, J = 7.6 Hz, 2H), 3.30 (q_{app} of AB system, 2H), 3.63 (t, J = 8.4 Hz, 1H), 3.75 (m, 2H), 7.17 (d, J = 7.0 Hz, 2H), 7.31 (m, 3H). LRMS for $C_{32}H_{48}NO_3$ [MH^+]: 494.6 *m/z*. HPLC (CH_3CN: H_2O: MeOH, 35: 30: 35): 96% of purity.

3β-[(*N*-Benzoyl-*N*-phenylethyl)aminomethyl]-3α,17β-dihydroxy-5α-androstane (46). IR (KBr): 3422 (OH, alcohols), 1618 (C═O, amide). ^{1}H NMR ($CDCl_3$): 0.73 (s, 3H), 0.80 (s, 3H), 0.80−2.10 (24H), 2.73 (t, J = 7.5 Hz, 2H), 3.57 (m, 5H), 6.86 (d, J = 5.0 Hz, 2H), 7.21 (m, 5H), 7.37 (m, 3H). LRMS for $C_{35}H_{48}NO_3$ [MH^+]: 530.4 *m/z*. HPLC (80% of MeOH:H_2O (9:1) and 20% of H_2O, both containing 20 mM of NH_4OAc): 98% of purity.

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