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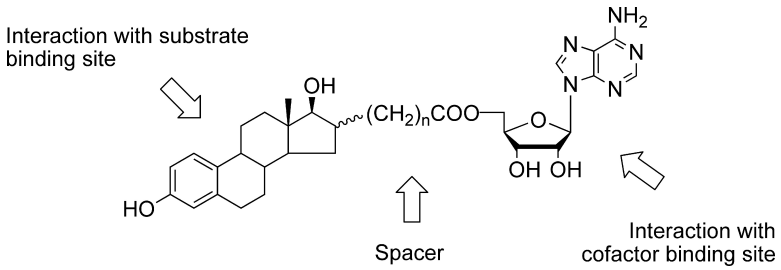
J. Med. Chem., **2005**, 48 (26), 8134-8147• DOI: 10.1021/jm058235e • Publication Date (Web): 18 November 2005



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Estradiol−Adenosine Hybrid Compounds Designed to Inhibit Type 1 17β-Hydroxysteroid Dehydrogenase

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Received June 15, 2005

The steroidogenic enzyme type 1 17β-hydroxysteroid dehydrogenase (17β-HSD) is involved in the synthesis of estradiol (E_2), a hormone well-known to stimulate the growth of estrogen-sensitive tumors. To obtain compounds able to control E_2 formation, two moieties were linked with a methylene side chain: an adenosine moiety for interacting with the cofactor-binding site and an E_2 moiety for interacting with the substrate-binding site. When tested as inhibitors of type 1 17β-HSD, the hybrid compounds inhibited the reductive activity (E_1 into E_2) with IC_{50} values ranging from 52 to 1000 nM. The optimal side-chain length was determined to be eight methylene groups for a 16β-orientation. The presence of two components (E_2 and adenosine) is essential for good inhibition, since 16β-nonyl-E_2 and 5-nonanoyl-*O*-adenosine, two compounds having only one of the components, did not inhibit the enzyme. Moreover, the 3D-structure analysis of EM-1745 complexed with type 1 17β-HSD showed key interactions with both substrate- and cofactor-binding sites.

Introduction

The estrogens and androgens are known to play a crucial role in the regulation of physiological effects.[1] Because it controls the formation and inactivation of estrogen estradiol (E_2) and androgen testosterone, the 17β-hydroxysteroid dehydrogenase (17β-HSD) enzyme family constitutes a logical target for drugs designed to treat estrogen- and androgen-sensitive diseases, such as breast and prostate cancers.[2] Furthermore, 17β-HSDs are widespread in human tissues, not only in classic steroidogenic tissues but also in a large series of peripheral tissues.[3] Until now, 12 isoforms have been found to be involved in the interconversion of 17-ketosteroids and 17β-hydroxysteroids.[4] Although in vitro the reductive or oxidative reactions catalyzed by all 17β-HSDs are reversible, recent data clearly showed that in intact cells, an experimental system that more closely reflects the physiological conditions, the activity catalyzed by each type of 17β-HSD is almost exclusively unidirectional.[5]

In our efforts to develop therapeutic agents against breast cancer and other estrogen-sensitive diseases,[6] we focused on type 1 17β-HSD or human estradiol dehydrogenase [E.C.1.1.1.62].[7] This enzyme is responsible for the transformation of estrone (E_1), the less active estrogen, into E_2, the most potent estrogen, using reduced nicotinamide adenine dinucleotide, phosphorylated (NADPH) or not (NADH), as cofactor (Figure 1). Type 1 17β-HSD is also responsible for the transformation of dehydroepiandrosterone (DHEA) into the weak estrogen 5-androstene-3β,17β-diol (Δ^5-diol).[8] The importance of type 1 17β-HSD activity in breast tumor development and growth is indicated by the increased levels of E_2 in tumor.[9] The conversion of E_1 into E_2 has been observed in normal human breast,[10] benign breast tumors,[11] and malignant breast tumors,[12] but the reductive activity is more important in breast tumors than in normal breast tissue.[13] To better control E_2 formation, we are interested in developing potent inhibitors of type 1 17β-HSD. Such inhibitors could be used alone or as a complementary approach to the treatment of breast cancer by a pure antiestrogen.

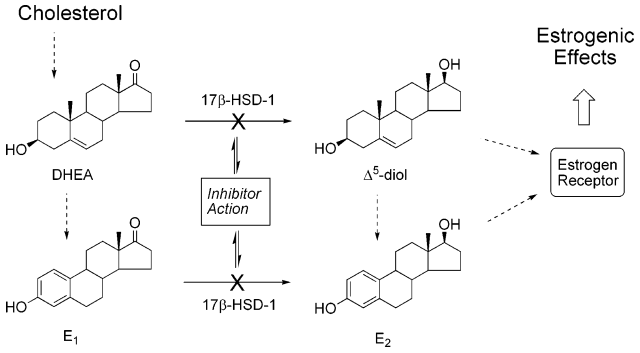

Figure 1. The key role of type 1 17β-HSD in the activation of DHEA and E_1 into more estrogenic compounds Δ^5-diol and E_2.

Although type 1 17β-HSD activity was reported 50 years ago in human tissues,[14] no inhibitor is yet used in a therapy. The inhibitors of this isoform are nonetheless the most important in number and variety among the inhibitors of 17β-HSDs reported in the literature.[15] Briefly, irreversible inhibitors include the affinity-labeling substrates developed for the structural analysis of the enzyme,[16] the suicide substrate 16-methylene-E_2 and analogue compounds,[17] 16-(halogenoalkyl)-E_2,[18] and 16-oxoestrone (under basic pH (8.5) conditions).[19] These inhibitors contain a functional group that reacts with an amino acid residue to form a stable covalent bond inactivating the enzyme. On the other hand, inhibitors

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10.1021/jm058235e CCC: $30.25
Published on Web 11/18/2005

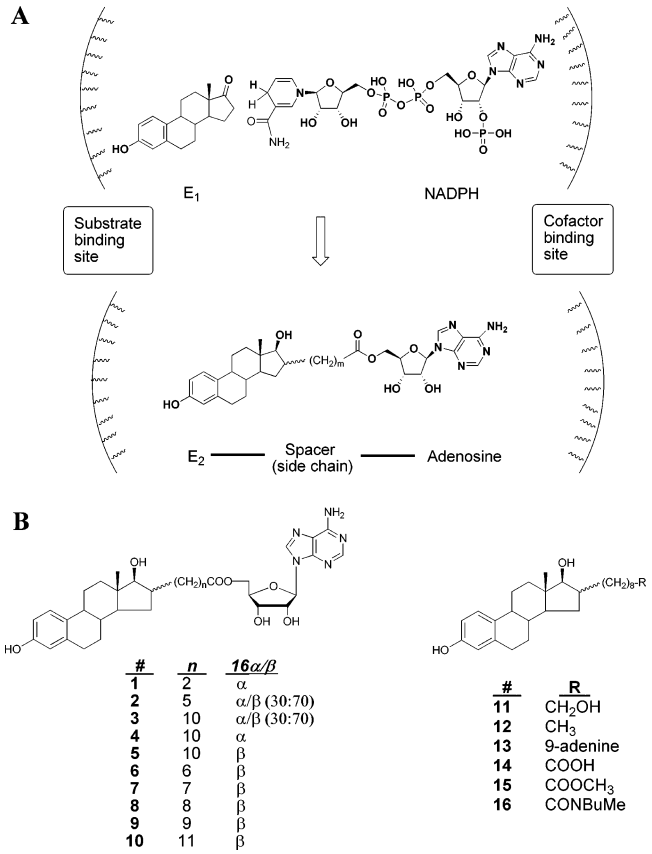


Figure 2. (A) Representation of the natural substrate E_1 (left) and cofactor NAD(P)H (right) involved in the formation of E_2 catalyzed by type 1 17β-HSD and schematic representation of proposed estradiol−adenosine hybrid inhibitors designed to interact with two binding sites of the enzyme. (B) Chemical structure of inhibitors synthesized and tested.

of the second category are reversible and are represented by E_1 derivatives with pyrazole or isoxazole fused to D-ring positions 16 and 17,[20] E_2 derivatives bearing a long alkanamide side chain at position 7α or 6β,[21] and various phytoestrogens and analogues.[22] The exact mechanism of action is not known for all of the above-mentioned inhibitors, but they probably interact with only one site of the enzyme, typically the substrate-binding one. Two affinity-labeling compounds have also been synthesized to interact with the cofactor-binding site.[16j,k] Recently, 16β-derivatives of E_1 designed to interact with the substrate-binding site and the cofactor were reported as potent inhibitors of type 1 17β-HSD.[23] Through the use of molecular modeling studies, it was proposed that the 16β-side chain functionalities were responsible for additional interactions with the nicotinamide portion and a phosphate oxygen of the cofactor whereas the E_1 nucleus binds to the substrate binding site. However, no example of 17β-HSD inhibitors designed to interact with two binding sites (Figure 2), namely, the substrate- and cofactor-binding sites, has been described.

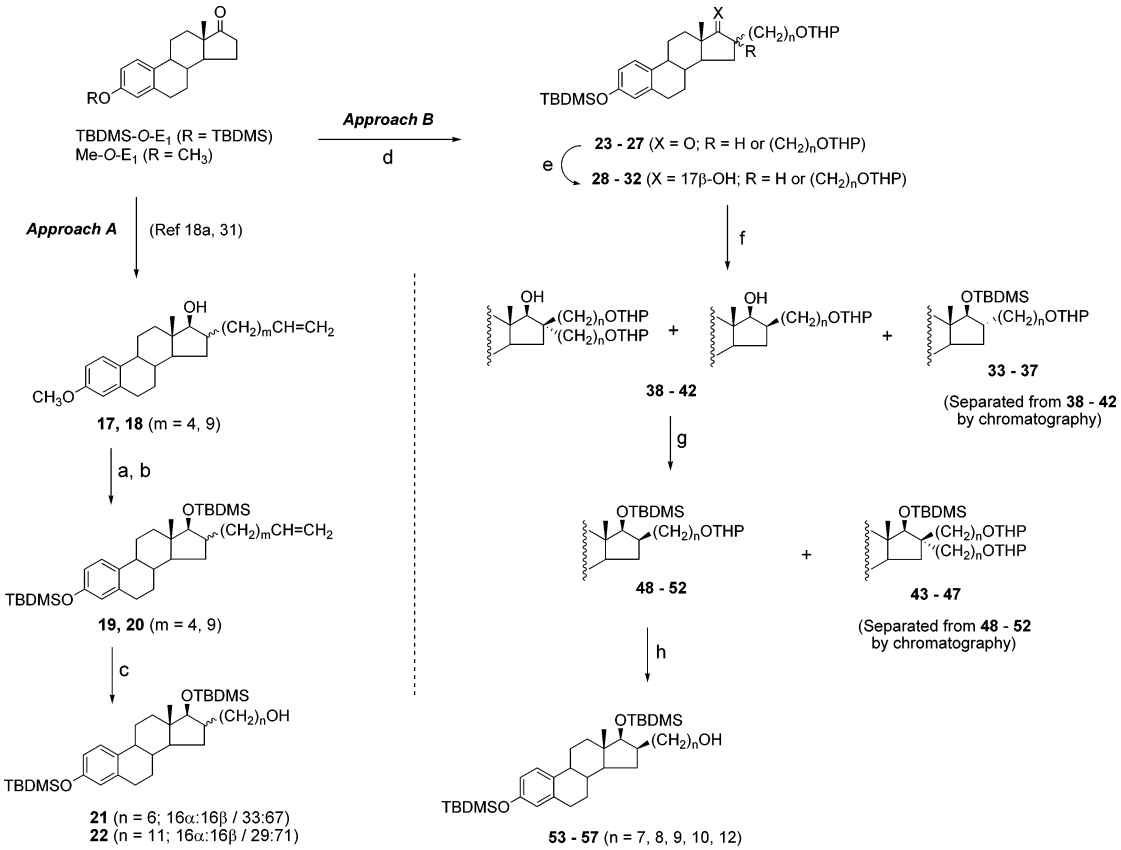
Type 1 17β-HSD was the first steroidogenic enzyme to be crystallized and to have its 3D-structure analyzed. Thus, the report of three-dimensional structures of the apoenzyme (type 1 17β-HSD only),[24] the binary complex (enzyme/steroid),[25] and the ternary complex (enzyme/steroid/$NADP^+$)[26] provided additional data for the design of inhibitors. Binding studies also showed that ADP and $NADP^+$ have similar affinities for type 1 17β-HSD (S.-X. Lin, unpublished results). Furthermore the nicotinamide ring has weaker electron density than the rest of the cofactor apparently due to a lack of direct interaction with the active site.[26a] Taken together, these results suggest that the entire cofactor NAD(P)H moiety could be substituted by adenosine only. Considering the information reported above and previous structure−activity relationship (SAR) results on 17β-HSDs inhibitors,[18,27] novel E_2−adenosine hybrids were designed to interact with two binding sites of the enzyme (Figure 2A): the adenosine moiety for interacting with the cofactor-binding site and the E_2 moiety for interacting with the substrate-binding site. The E_2 and adenosine moieties were linked with a methylene side-chain spacer. Following our first report of the modeling study and crystallographic analysis of such a potent hybrid inhibitor complexed with the enzyme,[28] we now report the full details of the chemical synthesis and structure−activity study that make possible the realization of this new family of dual-site inhibitors of type 1 17β-HSD (Figure 2B).

Results and Discussion

Chemistry. Overview. The novel inhibitors have two important moieties, an enzyme substrate (E_2) and a cofactor fragment (adenosine). To optimize the affinity of each moiety to their respective binding site, the OHs of the steroid as well as the NH_2 and secondary OHs of the adenosine must be free. The primary alcohol of the adenosine was thus retained for the formation of a covalent ester bond with the C16-steroid side chain (Figure 2). First, to rapidly determine whether the strategy of hybrid inhibitors is viable, two E_2−adenosine hybrids, compounds **2** and **3**, were synthesized as a mixture of 16α and 16β isomers starting from key alcohols **21** and **22**. To explore the chemical synthesis, we had previously prepared the E_2−adenosine hybrid **1** bearing as a spacer a side chain that was too short (only two methylenes).[29] After the feasibility of hybrid inhibitors was established and since the 16β-orientation gave better inhibitory activity than the corresponding 16α-oriented side chain (compare **4** and **5**, in Table 1), we generated inhibitors in a pure 16β−isomeric form, compounds **6**−**10**, starting from key alcohols **53**−**57**.

Synthesis of Alcohols 21 and 22. Alkylation with lithium diisopropylamide is a widely used method for introducing an alkyl side chain in the α position of several ketones. For hindered steroidal C17-ketones however,[30] this reaction is limited to activated electrophiles and consequently was not appropriate for introducing the long alkyl side chains required for the synthesis of steroidal compounds **2**−**16**. Two other approaches (A and B, Scheme 1) were therefore developed for the synthesis of key alcohol intermediates **21**, **22**, and **53**−**57**, respectively, from methyl-*O*-estrone (Me-*O*-E_1) and *tert*-butyldimethylsilyl-*O*-estrone (TBDMS-*O*-E_1). For the synthesis of **21** and **22** (approach A), the first steps follow a sequence of reactions previously developed by us for introducing a long alkyl side chain.[18a,31] The sequence involves an activation of the steroidal C17-ketone by adding a methoxycarbonyl group at C16, an alkylation at C16 using 6-bromohexene or 11-bromoundecene and KH as base, a decarboalkoxy-

Scheme 1. Synthesis of Alcohols **21** and **22** (Approach A) and **53**−**57** (Approach B) from E_1[a]



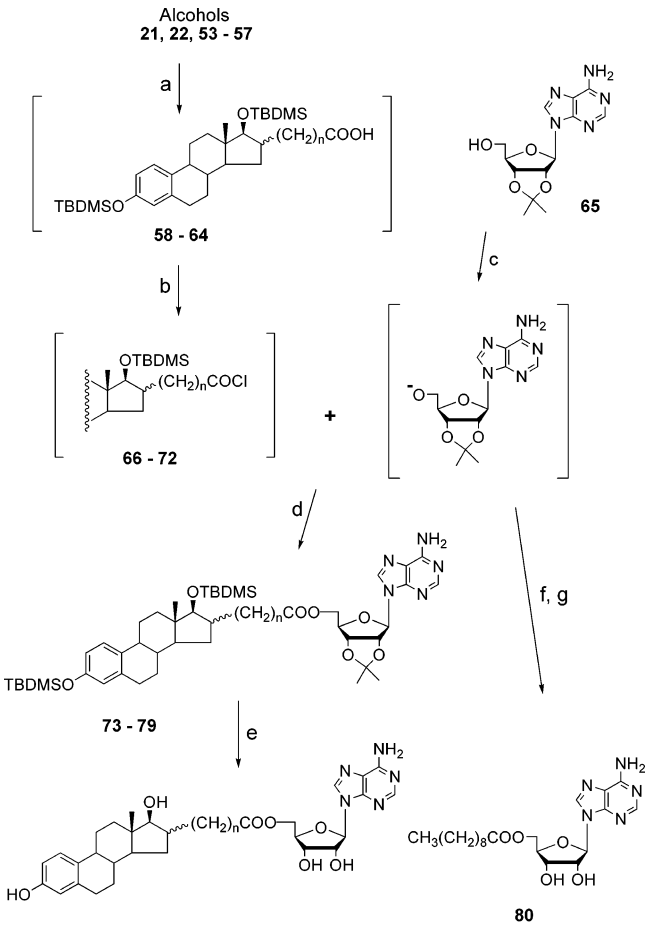
[a] The reagents and conditions are as follows: (a) EtSNa, DMF, reflux, 1 h; (b) TBDMS-OTf, 2,6-lutidine, CH_2Cl_2, rt, overnight; (c) i. BH_3-THF, THF, 0 °C, 3 h; ii. NaOH, H_2O_2, 0 °C−rt, 1 h; (d) LiHMDS, $Br(CH_2)_nOTHP$ [n = 7, 8, 9, 10, 12], THF, reflux, 12 h; (e) $LiAlH_4$, THF, −78 °C, 1.5 h; (f) TBDMS-Cl, imidazole, DMF, rt, 12 h; (g) TBDMS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h; (h) *p*-TSA, MeOH, acetone, rt, 2 h.

lation, and a stereoselective $LiAlH_4$ reduction of C17 ketone to give the 17β-alcohols **17** and **18** as a mixture of two isomers. Both isomers were easily identified, and 16α/16β ratios were determined by NMR spectroscopy. For the 16β isomer, the 18-CH_3 signal is shifted (0.77 ppm) compared to that of the 16α isomer (0.80 ppm). On the other hand, the 17-CH signal of the 16α isomer is shifted (3.27 ppm) compared to that of the 16β-isomer (3.74 ppm). In ^{13}C NMR, the 17-CH signal values of **17** and **18** (88.20 and 88.16 ppm for 16β-R or 82.48 and 82.47 ppm for 16α-R) are also very specific indicators of the C16 and C17 stereochemistry, as we previously demonstrated in our NMR study of D-ring substitution.[32] The methoxy group of alkenes **17** and **18** was next cleaved to the corresponding phenolic compound, the 3-OH and 17β-OH of which were protected, yielding di-TBDMS derivatives **19** and **20**. These two alkenes were then submitted to an oxidative hydroboration producing alcohols **21** and **22**.

Synthesis of Alcohols 53−57. For the synthesis of alcohols **53**−**57** as pure 16β-isomers, a new strategy was developed (approach B, Scheme 1). To this end, the activation and decarboalkoxylation steps were eliminated by choosing a strong base (LiHMDS) for the alkylation at C16, but a mixture of three compounds was thus generated. The mixtures of two monoalkylated (16α and 16β) and dialkylated derivatives, compounds **23**−**27**, were then treated with $LiAlH_4$ to stereoselectively reduce the ketone into alcohols **28**−**32**. Because the mixtures of three C16-alkylated compounds represented by ketones **23**−**27** and alcohols **28**−**32** were not separable by chromatography, a four-step sequence was developed to obtain only the pure 16β-derivatives **53**−**57**. The sequence involves a selective TBDMS protection (TBDMS−Cl, imidazole) of the less hindered OH group among mixtures **28**−**32** (that of the α-monoalkylated compound), a flash chromatography to eliminate **33**−**37** (16α-isomer), a TBDMS protection (TBDMS−OTf, lutidine) of mixtures **38**−**42**, and a flash chromatography to separate **43**−**47** (dialkylated compounds) from **48**−**52** (16β-isomer). In a final step, the THP group of **48**−**52** was removed under mild acid conditions to give alcohols **53**−**57**. The 16β-configuration of **53**−**57** was easily confirmed using the ^{1}H and ^{13}C NMR probes discussed above.

Synthesis of Adenosine Derivatives 2−10 and 80. The methodology that we developed for the preparation of **1**[29] was used with success in the preparation of **2**−**10** from alcohols **21** and **22**, as well as **53**−**57** (Scheme 2). Briefly, the latter were oxidized into carboxylic acids with Jones' reagent, and the acids **58**−**64** were transformed by a treatment with oxalyl chloride into acid chlorides **66**−**72**; these were added to the anionic form of isopropylidene adenosine (**65**) to give esters **73**−**79**. The same conditions allowed the synthesis of ester **80** after hydrolysis of the isopropylidene group. The three protective groups (isopropylidene and two TBDMS) of esters **73**−**79** need to be carefully removed by a sequential treatment of gaseous HCl and tetrabutylammonium fluoride (TBAF) to generate **2**, **3**, and **6**−**10**. Herein, the

Scheme 2. Synthesis of Estradiol−Adenosine Hybrids **2**−**10** and Adenosine Derivative **80**[a]



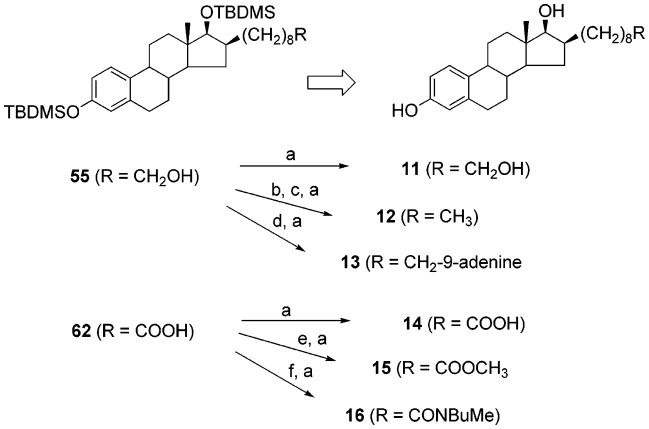
2 - 10 (n = 5α/β, 10α/β, 10α, 10β, 6β, 7β, 8β, 9β, 11β)

[a] The reagents and conditions are as follows: (a) Jones' reagent, acetone, 0 °C, 1 h; (b) $(COCl)_2$, CH_2Cl_2, rt, 1.5 h; (c) NaH, THF, rt, 0.5 h; (d) THF, −20 °C, 45 min; (e) i. HCl(g) in CH_2Cl_2, rt, 15−105 min; ii. TBAF, THF, 60 °C, 2 h; (f) nonanoyl chloride, THF, −20 °C, 2 h; (g) HCl(g) in CH_2Cl_2, rt, 100 min.

TBAF treatment allowed the removal of the more stable 17β-TBDMS group, which was not cleaved by HCl treatment. Surprisingly, when we started the deprotective sequence of reactions by a TBAF treatment followed with gaseous HCl, we did not observe the trideprotected compound. Moreover, the final trideprotection did not work for a 16β-oriented two-methylene side chain, although it gave a satisfactory yield with the 16α-analogue.[29] In the first case, the anchimeric assistance of 17β-OH probably promotes the hydrolysis of the ester bond within the 16β-side chain. This reaction was however not observed for all longer β-oriented side chains, and final E_2−adenosine hybrid compounds **2**, **3**, and **6**−**10** were obtained in acceptable yields. Compounds **4** and **5** were obtained after HPLC purification of **3**, which consisted in a mixture of 16α/16β isomers. IR, ^{1}H NMR, ^{13}C NMR, and HRMS data agree with expected structures of compounds **2**−**10** and clearly show the characteristics of both E_2 and adenosine components.

Synthesis of Compounds 11−16. After the optimal spacer length (eight CH_2) was determined, compounds **11**−**16** were synthesized to complement our SAR study (Scheme 3). Alcohol **11** was obtained from **55** after removal of di-TBDMS groups with TBAF at 60 °C. 16β-

Scheme 3. Synthesis of Diversified Compounds **11**−**16**[a]



[a] The reagents and conditions are as follows: (a) TBAF, THF, 60 °C, 20 h; (b) MsCl, Et_3N, CH_2Cl_2, rt, 2 h; (c) $LiAlH_4$, THF, rt, −78 °C−rt, 24 h; (d) adenine, PPh_3, DEAD, dioxane, rt, 6 h; (e) $TMSCHN_2$, MeOH−benzene, rt, 45 min; (f) i. *i*-BuOCOCl, Bu_3N, CH_2Cl_2, −10 °C, 30 min; ii. BuMeNH, rt, overnight.

Nonyl-E_2 (**12**) was synthesized from alcohol **55** by a classic two-step sequence involving the formation of an intermediate mesylate and its substitution by a hydride followed by a di-TBDMS hydrolysis. Adenine was linked to alcohol **55** under Mitsunobu conditions (PPh_3 and diethyl azodicarboxylate, DEAD), and the di-TBDMS groups of the resulting amine were removed with TBAF giving **13**. Acid **14** was generated simply by removing the di-TBDMS of **62**, whereas methyl ester **15** was recovered after methylation and di-TBDMS hydrolysis. The butyl,methyl amide **16** was synthesized from acid **62** through the formation of a mixed anhydride reacting with BuMeNH.

Efficiency of the Inhibitors. Human placenta was the usual source of type 1 17β-HSD activity in the past, but transfected cells recently offered a valuable alternative. In our enzymatic assay, we used a homogenate of transfected HEK-293 cells that overexpress type 1 17β-HSD activity as a source of enzyme.[33] Since E_2 is a more potent estrogen than E_1, the natural reductive enzyme activity transforming E_1 into E_2 was favored by adding an excess of NADH as cofactor. Moreover, pH and temperature close to physiological conditions (pH = 7.4 and T = 37 °C) were used for the assay. After measuring the radioactivity associated with the newly formed [^{14}C]-E_2 and the remaining [^{14}C]-E_1, we calculated the percentage of transformation and thereafter the percentage of inhibition or IC_{50} values of the tested compounds.

A series of three compounds was first synthesized and tested to rapidly determine the worth of the designed E_2−adenosine hybrid inhibitors (Table 1, assay A). Compounds **1** and **2** with two and five methylenes as spacer, respectively, weakly inhibited the type 1 17β-HSD activity (IC_{50} = 13.5 and 6.9 μM, respectively). This result agrees with a screening study showing a weak inhibitory activity on type 1 17β-HSD by a series of 16α-E_2 derivatives.[18e] Furthermore, by a 3D-structure analysis of the enzyme, it was observed that adding a side chain at position 16α creates a steric hindrance that decreases the binding affinity (unpublished results). Nonetheless, compound **3** with the longer spacer (n = 10) was a better inhibitor (8-fold) than unlabeled E_1 despite the presence of a long side chain. This result suggests additional interactions between the adenosine

Table 1. Inhibition of Type 1 17β-HSD by Estradiol−Adenosine Hybrids **1**−**10**[a]

compd	C16 orientation, α, β, or both	spacer length, n	assay A, IC_{50} (nM)	assay B, IC_{50} (nM)	assay C, IC_{50} (nM)
1	α	2	13500		
2	α/β (37: 63)	5	6900		
3	α/β (30: 70)	10	90		144
E_1			700		
4	α	10		310	
5	β	10		120	
9	β	9		140	
10	β	11		1000	
E_1				600	
6	β	6			430
7	β	7			93
8	β	8			52
E_1					810

[a] For the transformation of [^{14}C]-E_1 (0.1 μM) into [^{14}C]-E_2. The enzyme source was a homogenate of transfected HEK-293 cells overexpressing type 1 17β-HSD.

moiety and the enzyme that counterbalance the negative steric influence of a C16-substituent on the E_2 nucleus. But it appeared that the side-chain length is a crucial parameter. Thus, without an appropriate spacer length, the adenosine residue cannot interact efficiently with the cofactor-binding site and no improvement of inhibitory activity is obtained. Consequently, we observed a decrease of inhibiting potency, as compared to that of E_1, due to steric hindrance of the adenosine and spacer for compounds **1** and **2**. For compound **3**, however, the steric hindrance of a long hydrophobic spacer composed of 10 methylene groups was counterbalanced by the presence of the adenosine residue, which probably interacts with the cofactor-binding site.

Considering the good results obtained with **3** and to study the effect of side-chain orientation, the isomeric mixture was submitted to HPLC. Compounds **4** and **5**, the 16α- and 16β-isomer, respectively, were then isolated and tested, and IC_{50} values were determined (Table 1, assay B). Thus, for a spacer length of 10, compound **5** with a β-oriented side chain is a better inhibitor than its 16α analogue **4** (IC_{50} = 120 and 310 nM, respectively). We next focused on the 16β-stereoisomers with the aim of optimizing the side-chain length. The E_2−adenosine hybrid compounds **6**−**10** inhibited the enzyme activity with IC_{50} values ranging from 52 to 1000 nM (Table 1, assays B and C). The optimal side-chain length was determined to be eight methylene groups (compound **8**, EM-1745, IC_{50} = 52 nM); that is to say, this length allows optimal interactions of the E_2 and adenosine moieties with the enzyme substrate- and cofactor-binding sites. It is noteworthy that EM-1745 also is a much more potent inhibitor than two previously described inhibitors, EM-678[21c] and EM-251[6a] (89%, 34%, and 19% inhibition, respectively, when tested at 10 nM using the same enzymatic assay).

Next, to confirm the key role of the E_2 and adenosine interacting components, a new series of compounds with a spacer consisting of eight methylene groups were tested as inhibitors of type 1 17β-HSD (Figure 3). Clearly, the presence of the two components (E_2 and adenosine) is an important requirement for a strong enzyme inhibition, as seen for compound **8**, the E_2−adenosine hybrid inhibitor. In fact, 5-nonanoyl-*O*-adenosine (**80**) did not inhibit the enzyme more than E_1

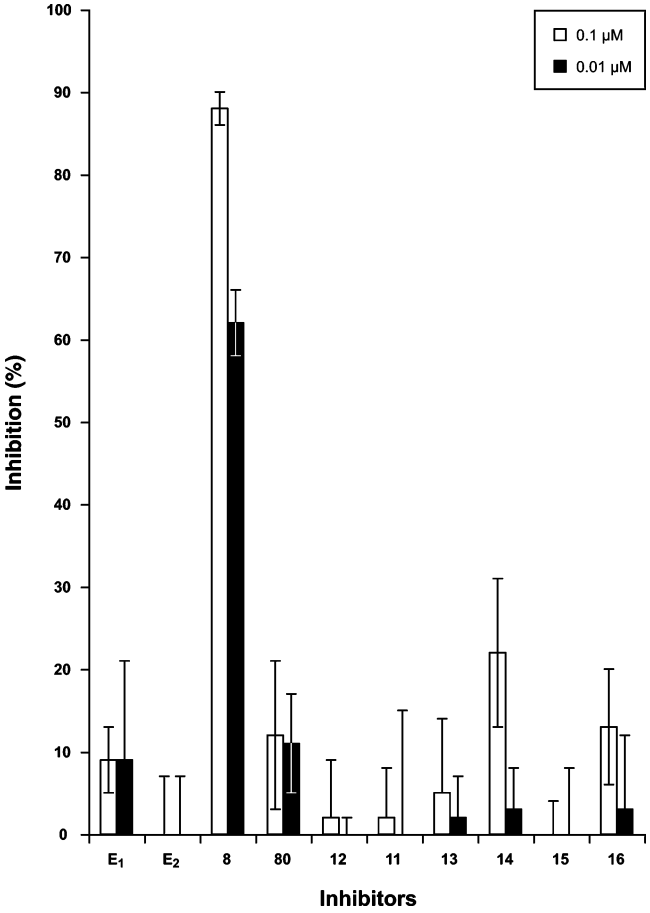


Figure 3. Inhibition of type 1 17β-HSD by compounds **8**, **11**−**16**, **80**, unlabeled E_2, and unlabeled E_1 at two concentrations, 0.01 and 0.1 μM. See Experimental Section for the conditions used in this enzymatic assay.

did at the higher concentration tested (0.1 μM), and the same result was obtained for 16β-nonyl-E_2 (**12**). Other chemical groups, such as hydroxymethyl, *N*-adenine, carboxyl, methoxycarbonyl, and *N*-methyl-*N*-butyl carbamide, were also added at the end of the optimized side chain (compounds **11** and **13**−**16**), but no interesting inhibition resulted from these modifications.

The conclusions resulting from the present SAR study were later confirmed by the crystallization of a complex of EM-1745 and type 1 17β-HSD at a 1.6 Å resolution (Figure 4). Furthermore, the crystal structure analysis of the complex allowed the identification of a series of hydrogen bonds with the E_2 (O3/His221, O17/Ser142, and O17/Tyr155) and the adenosine (NH_2/Asp65, N/Val66, O/Gly92, and OHs/Ser11) moieties (Figure 5). The results from the previously reported crystallographic study (see ref 28 for a fully detailed discussion) clearly demonstrated that the hybrid compound **8** (EM-1745) is an efficient inhibitor with high enzyme affinity, thus supporting our initial hypothesis for the design.

In conclusion, a new family of potent inhibitors of type 1 17β-HSD was developed by linking E_2 and adenosine with a methylene spacer. The chemical synthesis started from E_1 and necessitated the introduction of an alkyl side chain at position 16β before adding the adenosine moiety and performing the final trideprotection. These E_2−adenosine hybrid compounds were tested using a homogenate of HEK-293 cells expressing the type 1 17β-HSD activity, and the compound bearing a spacer of

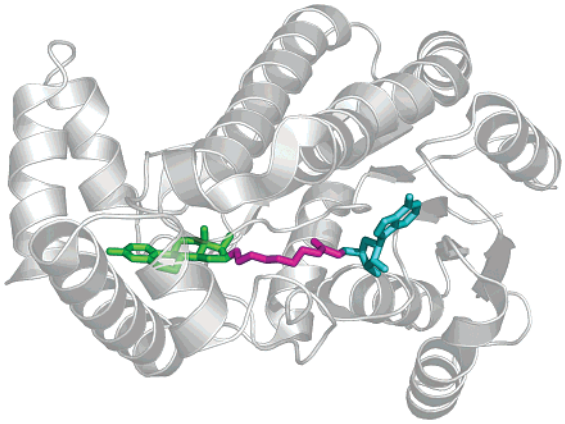


Figure 4. Cartoon representation of crystal structure of type 1 17β-HSD complexed with hybrid inhibitor EM-1745 (compound **8**). The three components of the inhibitor are shown in green (estradiol), red (spacer or side chain), and blue (cofactor fragment adenosine). This figure was generated by PyMol (DeLano, W. L. *The PyMOL Molecular Graphics System*; DeLano Scientific: San Carlos, CA, 2002; http://www.pymol.org).

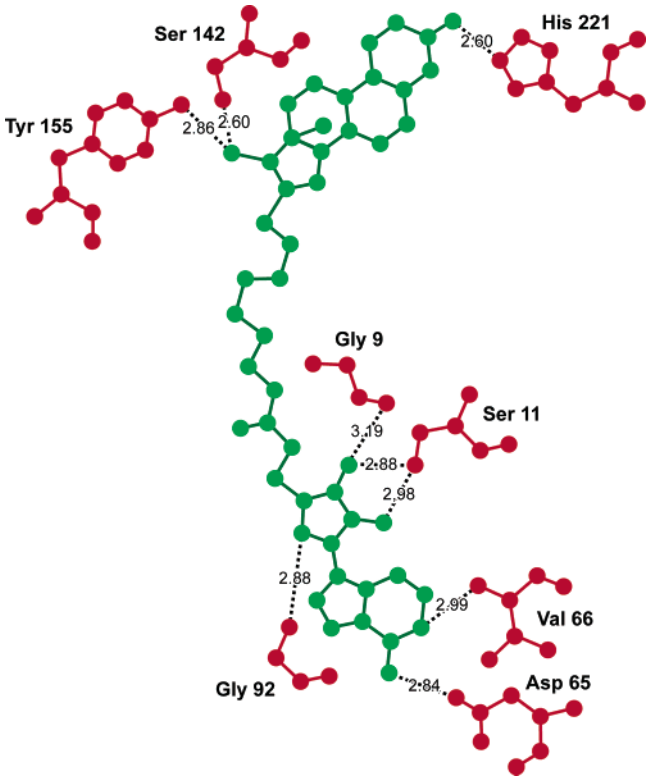


Figure 5. Schematic diagram of the most important hydrogen bonds between EM-1745 (compound **8**, in green) and certain amino acid residues (in red) of type 1 17β-HSD. The hydrogen bonds are represented by dashed lines, and their lengths are given in Å. For a more detailed version of this diagram showing all hydrogen bonds and hydrophobic contacts, see Figure 7 of ref 28.

eight methylene groups (**8**, EM-1745) was the most potent inhibitor (IC_{50} = 52 nM) of the transformation of E_1 into E_2. A complementary series of compounds having the adenosine moiety replaced by a simple chemical group clearly showed the crucial role of adenosine (compounds **11**−**16**). Moreover, the synthesis of the adenosine derivative **80** with an alkyl side chain but without an E_2 nucleus produced a compound with no inhibitory activity, thus showing that the E_2 moiety also appears essential in the inhibitory process. Taken together, these SAR results confirm that both the E_2 and adenosine moieties of the hybrid inhibitor are required for a potent inhibitory activity, suggesting key interactions between the substrate- and cofactor-binding sites of the enzyme. Furthermore, the crystal structure analysis of the complex of EM-1745 and type 1 17β-HSD confirmed the efficiency of the inhibitor.[28] Although bisubstrate inhibitors of steroidogenic enzymes estrogen sulfotransferase and 5α-reductase were recently reported,[34] our series of E_2−adenosine hybrid compounds represents to the best of our knowledge the first bisubstrate inhibitors designed for the broad family of hydroxysteroid dehydrogenases.

Experimental Section

General Information. Methyl-*O*-estrone (Me-*O*-E_1) and *tert*-butyldimethylsilyl-*O*-estrone (TBDMS-*O*-E_1) were used as starting material and synthesized from E_1 (Sigma, St-Louis, MO) as previously reported.[18b] Chemical reagents were purchased from Aldrich Chemical Co. (Milwaukee WI), and solvents were obtained from Fisher Scientific (Montréal, Canada). THF was distilled from sodium benzophenone ketyl. Anhydrous reactions were carried out under an argon atmosphere in oven-dried glassware. Thin-layer chromatography (TLC) was performed on 0.20-mm silica gel 60 F_{254} plates (E. Merck, Darmstadt, GE). All flash column chromatography was performed on 230−400 mesh ASTM silica gel 60 (E. Merck, Darmstadt, GE), unless stated otherwise. Infrared spectra (IR) were obtained on a Perkin-Elmer 1600 (series FTIR) spectrophotometer and expressed in cm^{-1}. ^1H and ^{13}C NMR spectra are expressed in ppm and were recorded on a Bruker AC/F 300 at 300 and 75 MHz, respectively. Assignment of NMR signals was done using 1D and 2D NMR experiments (COSY, HSQC, HMBC, DEPT). High-resolution mass spectra (HRMS) and CHN analyses were provided by the Regional Laboratory for Instrumental Analysis (Université de Montréal, Montréal, Canada). High-performance liquid chromatography (HPLC) analyses were carried out using a Waters Associates system (Milford, MA).

Synthesis of Intermediate Alcohols 21 and 22 (Approach A). Synthesis of Alkenes 17 and 18. They were prepared from Me-*O*-E_1 using our previously reported approach.[18a,31] The sequence of reactions involves a methoxycarbonylation at position 16, an alkylation with KH and bromohexene or bromoundecene, a decarboalkoxylation, and a stereoselective C17-carbonyl reduction with $LiAlH_4$. Compounds **17** and **18** were thus obtained and next used as a mixture of 16β (major) and 16α (minor) isomers.

6-[3′-Methoxy-17′β-hydroxy-1′,3′,5′(10′)-estratrien-16′α/β-yl]-hexene (17). Colorless oil. IR (film): 3450 (OH), 1640 (C=C). ^1H NMR ($CDCl_3$): 0.77 and 0.80 (2s, 18′-CH_3, 16′β/16′α 67:33), 2.85 (m, 6′-CH_2), 3.27 and 3.74 (2d, J = 7.4 and 10.0 Hz, 17′α-CH, respectively, for 16′α and 16′β isomers), 3.78 (s, CH_3O), 4.95 (d, J = 10.3 Hz, 1H of CH=CH_2), 5.01 (d, J = 18.7 Hz, 1H of CH=CH_2), 5.82 (m, CH=CH_2), 6.63 (d, J = 2.5 Hz, 4′-CH), 6.72 (dd, J_1 = 2.5 Hz and J_2 = 8.5 Hz, 2′-CH), 7.21 (d, J = 8.5 Hz, 1′-CH). ^{13}C NMR ($CDCl_3$): 11.89, 12.36, 26.23, 26.30, 27.23, 27.47, 27.92, 28.13, 29.13, 29.69, 29.82, 30.15, 31.31, 32.40, 33.79, 35.60, 36.81, 37.72, 38.36, 38.64, 39.98, 44.00, 44.09, 44.15, 48.38, 48.58, 55.19, 82.48, 88.20, 111.44, 113.82, 114.21, 126.24, 132.74, 137.94, 139.09, 157.44. HRMS: calcd for $C_{25}H_{36}O_2$ $[M]^+$ 368.27155, found 368.26970.

11-[3′-Methoxy-17′β-hydroxy-1′,3′,5′(10′)-estratrien-16′α/β-yl]-undecene (18). White solid. IR (film): 3466 (OH), 1640 (C=C). ^1H NMR ($CDCl_3$): 0.77 and 0.80 (2s, 18′-CH_3, 16′β/16′α 65:35), 2.85 (m, 6′-CH_2), 3.27 and 3.74 (2d, J = 7.3 and 10.0 Hz, 17′α-CH, respectively, for 16′α and 16′β isomers), 3.78 (s, CH_3O), 4.93 (d, J = 10.3 Hz, 1H of CH=CH_2), 4.99 (d, J = 17.1 Hz, 1H of CH=CH_2), 5.82 (m, CH=CH_2), 6.64 (s_{app}, 4′-CH), 6.71 (dd, J_1 = 2.6 Hz and J_2 = 8.5 Hz, 2′-CH), 7.21 (d, J = 8.6 Hz, 1′-CH). ^{13}C NMR ($CDCl_3$): 11.86, 12.35, 26.29, 27.23,

27.45, 28.44, 28.66, 28.92, 29.13, 29.47, 29.59, 29.65, 29.81, 29.87, 30.12, 31.46, 32.40, 33.79, 35.78, 36.81, 37.71, 38.34, 38.62, 40.01, 43.99, 44.12, 48.38, 48.56, 55.15, 82.47, 88.16, 111.41, 113.79, 114.07, 126.26, 132.72, 137.90, 139.20, 157.40. HRMS: calcd for $C_{30}H_{46}O_2$ $[M]^+$ 438.34979, found 438.35000.

Protecting Group Modification (Synthesis of 19 and 20). To a solution of methoxy derivatives **17** or **18** (400−877 mg, 1.09−2.00 mmol) in dry DMF (30−35 mL) was added sodium ethanethiolate (1.37−2.53 g, 16.3−30.1 mmol), and the mixture was heated at reflux for 1 h. Thereafter, the reaction was quenched by addition of water, and the resulting solution was acidified with aqueous 10% HCl before successive extraction with CH_2Cl_2 and EtOAc. The combined organic phase was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude diols (271−735 mg, 0.73−1.73 mmol) were dissolved in CH_2Cl_2 (20−50 mL), and 2,6-lutidine (0.86−2.05 mL, 7.3−17.3 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMS-OTf) (0.84−1.99 mL, 3.68−8.65 mmol) were successively added. The reaction was stirred at room-temperature overnight. The resulting mixture was then poured into diethyl ether, washed with water, and dried over $MgSO_4$. After filtration and evaporation of solvent, the crude compound was purified by flash chromatography with hexanes to give di-TBDMS compounds **19** or **20** (425−744 mg, 0.73−1.14 mmol).

6-[3′,17′*β*-(Di-*tert*-butyldimethylsilyloxy)-1′,3′,5′(10′)-estratrien-16′α/*β*-yl]-hexene (19). White solid (67%). IR (film): 1640 (C=C). ^{1}H NMR ($CDCl_3$): 0.055, 0.058, and 0.070 (3s, 17′-Si(CH_3)$_2$), 0.20 (s, 3′-Si(CH_3)$_2$), 0.75 and 0.79 (2s, 18′-CH_3, 16′*β*/16′α 67:33), 0.92 and 0.94 (s, 17′-SiC(CH_3)$_3$), 0.99 (s, 3′-SiC(CH_3)$_3$), 2.80 (m, 6′-CH_2), 3.22 and 3.66 (2d, J = 7.3 and 9.2 Hz, 17′α-CH, respectively, for 16′α and 16′*β* isomers), 4.95 (d, J = 9.9 Hz, 1H of CH=CH_2), 5.01 (d, J = 17.7 Hz, 1H of CH=CH_2), 5.84 (m, CH=CH_2), 6.56 (d, J = 2.1 Hz, 4′-CH), 6.62 (dd, J_1 = 2.6 Hz and J_2 = 8.3 Hz, 2′-CH), 7.12 (d, J = 8.4 Hz, 1′-CH). ^{13}C NMR ($CDCl_3$): −4.57, −4.39, −4.03, −3.94, 12.26, 12.77, 18.17, 18.24, 25.71, 25.98, 26.35, 27.26, 27.47, 28.00, 29.11, 29.22, 29.47, 29.71, 31.96, 32.37, 33.79, 33.86, 34.67, 37.49, 38.19, 38.46, 38.71, 40.70, 43.75, 44.06, 44.14, 44.27, 44.37, 48.29, 48.57, 82.60, 88.10, 114.10, 117.10, 119.90, 126.08, 133.30, 137.88, 139.20, 153.25. HRMS: calcd for $C_{36}H_{63}Si_2O_2$ $[M + H]^+$ 583.43665, found 583.43560.

11-[3′,17′*β*-(Di-*tert*-butyldimethylsilyloxy)-1′,3′,5′(10′)-estratrien-16′α/*β*-yl]-undecene (20). White solid (57%). IR (film): 1641 (C=C). ^{1}H NMR ($CDCl_3$): 0.040 and 0.055 (2s, 17′-Si(CH_3)$_2$), 0.18 (s, 3′-Si(CH_3)$_2$), 0.73 and 0.77 (2s, 18′-CH_3, 16′*β*/16′α 72:28), 0.90 and 0.93 (s, 17′-SiC(CH_3)$_3$), 0.98 (s, 3′-SiC(CH_3)$_3$), 2.79 (m, 6′-CH_2), 3.21 and 3.64 (2d, J = 7.3 and 9.2 Hz, 17′α-CH, respectively, for 16′α and 16′*β* isomers), 4.93 (d, J = 10.6 Hz, 1H of CH=CH_2), 4.99 (d, J = 17.0 Hz, 1H of CH=CH_2), 5.82 (m, CH=CH_2), 6.55 (d, J = 2.3 Hz, 4′-CH), 6.61 (dd, J_1 = 2.5 Hz and J_2 = 8.4 Hz, 2′-CH), 7.12 (d, J = 8.4 Hz, 1′-CH). ^{13}C NMR ($CDCl_3$): −4.58, −4.40, −3.97, 12.27, 12.77, 18.15, 18.25, 25.71, 25.98, 26.36, 27.26, 27.47, 28.42, 28.51, 28.94, 29.15. 29.53, 29.60, 29.65, 29.87, 32.12, 32.39, 33.82, 34.79, 37.49, 38.19, 38.45, 38.71, 40.75, 43.77, 44.06, 44.15, 44.24, 44.36, 48.29, 48.57, 82.63, 88.09, 114.06, 117.09, 119.90, 126.08, 133.33, 137.90, 139.26, 153.24. HRMS: calcd for $C_{41}H_{71}Si_2O_2$ $[M + H]^+$ 651.49927, found 651.50020.

Oxidative Hydroboration of Double Bond (Synthesis of 21 and 22). To a stirred solution of di-TBDMS derivatives **19** or **20** (375−685 mg, 0.64−1.05 mmol) dissolved in dry THF (20−50 mL) was added dropwise, at 0 °C, a solution of borane in THF (1.5−2.4 mL, 1.5−2.4 mmol), and the mixture was allowed to react 3 h under argon. Then, a solution of 3 N NaOH (0.54−0.88 mL) and 30% H_2O_2 (0.23−0.37 mL) was added at 0 °C, and the mixture was left at room temperature for 1 h. The resulting mixture was quenched by addition of water and extracted with EtOAc. The combined organic phase was washed with water and a saturated solution of NaCl, and dried over $MgSO_4$. The crude compound was purified by flash chromatography with hexanes/EtOAc (92:8) as eluent to give alcohols **21** or **22** (337−610 mg, 0.56−0.91 mmol).

6-[3′,17′*β*-(Di-*tert*-butyldimethylsilyloxy)-1′,3′,5′(10′)-estratrien-16′α/*β*-yl]-hexanol (21). White solid (87%). IR (film): 3346 (OH). ^{1}H NMR ($CDCl_3$): 0.035, 0.042, 0.050, and 0.054 (4s, 17′-Si(CH_3)$_2$), 0.18 (s, 3′-Si(CH_3)$_2$), 0.73 and 0.77 (2s, 18′-CH_3, 16′*β*/16′α 67:33), 0.90 and 0.92 (s, 17′-SiC(CH_3)$_3$), 0.97 (s, 3′-SiC(CH_3)$_3$), 2.79 (m, 6′-CH_2), 3.21 (d, J = 7.2 Hz, 0.3H of 17′α-CH, 16′α isomer), 3.64 (m, CH_2OH and 0.7H of 17′α-CH, 16′*β* isomer), 6.55 (s_{app}, 4′-CH), 6.61 (dd, J_1 = 2.5 Hz and J_2 = 8.3 Hz, 2′-CH), 7.11 (d, J = 8.3 Hz, 1′-CH). ^{13}C NMR ($CDCl_3$): −4.56, −4.40, −4.04, −3.96, 12.25, 12.77, 18.16, 18.25, 25.71, 25.97, 26.35, 27.26, 27.45, 28.39, 28.48, 29.44, 29.67, 32.09, 32.39, 32.80, 34.73, 37.47, 38.18, 38.44, 38.69, 40.73, 43.75, 44.07, 44.12, 44.25, 44.35, 48.29, 48.57, 63.10, 82.61, 88.08, 117.10, 119.90, 126.09, 133.31, 137.89, 153.25. HRMS: calcd for $C_{36}H_{63}Si_2O_3$ $[M - H]^+$ 599.43158, found 599.42920.

11-[3′,17′*β*-(Di-*tert*-butyldimethylsilyloxy)-1′,3′,5′(10′)-estratrien-16′α/*β*-yl]-undecanol (22). White solid (87%). IR (film): 3346 (OH). ^{1}H NMR ($CDCl_3$): 0.044 and 0.056 (2s, 17′-Si(CH_3)$_2$), 0.18 (s, 3′-Si(CH_3)$_2$), 0.73 and 0.77 (2s, 18′-CH_3, 16′*β*/16′α 71:29), 0.90 and 0.93 (2s, 17′-SiC(CH_3)$_3$), 0.98 (s, 3′-SiC(CH_3)$_3$), 2.79 (m, 6′-CH_2), 3.21 (d, J = 7.4 Hz, 0.3H of 17′α-CH, 16′α isomer), 3.64 (t_{app}, CH_2OH and 0.7H of 17′α-CH, 16′*β* isomer), 6.55 (d, J = 2.2 Hz, 4′-CH), 6.61 (dd, J_1 = 2.5 Hz and J_2 = 8.4 Hz, 2′-CH), 7.11 (d, J = 8.5 Hz, 1′-CH). ^{13}C NMR ($CDCl_3$): −4.54, −4.36, −4.02, 3.93, 12.26, 12.79, 18.18, 18.26, 25.73, 26.00, 26.38, 27.29, 27.48, 28.44, 28.55, 29.45, 29.63, 29.84, 29.90, 32.14, 32.42, 32.84, 34.81, 37.50, 38.21, 38.48, 38.73, 40.77, 43.79, 44.09, 44.16, 44.27, 44.37, 48.31, 48.60, 63.12, 82.65, 88.10, 117.11, 119.92, 126.10, 133.34, 137.91, 153.26. HRMS: calcd for $C_{41}H_{73}Si_2O_3$ $[M - H]^+$ 669.50983, found 669.51280.

Synthesis of Intermediate Alcohols 53−57 (Approach B). Procedures for Alkylation of TBDMS-*O*-E$_1$ at C-16 and Carbonyl Reduction (Synthesis of 28−32). TBDMS-*O*-E$_1$ (3.8−5.0 g, 9.90−13.02 mmol) was dissolved in dry THF (200 mL), and the solution was cooled to −78 °C. A solution of lithium bis(trimethylsilyl)amide (LiHMDS) in THF (13 mL, 13.0 mmol) was added, and the reaction mixture was stirred at 0 °C for 1 h after which it was cooled to −78 °C and Br(CH_2)$_n$OTHP (n = 7, 8, 9, 10, 12)[35] (8.5−12.0 g, 28.6−39.1 mmol) solubilized in dry THF (20 mL) was added dropwise. The solution was heated to reflux and stirred overnight. Then, a saturated aqueous solution of NH_4Cl (100 mL) was added, and the mixture was extracted with EtOAc, washed with brine, and dried over $MgSO_4$. Solvent was evaporated, and the crude product was purified by flash chromatography (hexanes/CH_2Cl_2, 5:5, followed by hexanes/EtOAc, 85:15) to give a mixture of mono (α and *β*) and dialkylated E$_1$ derivatives **23**−**27** (2.22−4.47 g) in variable proportions (approximately 2:2:1) and starting material (0.6−2.8 g, 16−56%). Under argon atmosphere, ketones **23**−**27** (2.1−4.0 g) were dissolved in dry THF (100−300 mL), and the solution was cooled at −78 °C. $LiAlH_4$ (183−391 mg) was added, and the suspension was allowed to stir for 2 h at −78 °C. Acetone and $Na_2SO_4 \cdot 10H_2O$ were added, and the mixture was stirred overnight. $MgSO_4$ was added, and the resulting suspension was filtered on Celite and washed with acetone, and the resulting filtrate was concentrated. The crude compounds were purified by flash chromatography using hexanes/EtOAc (95:5) as eluent to give alcohols **28**−**32** (1.9−3.9 g).

Selective Protection of α-Monoalkylated Alcohols Among Mixtures 28−32 to Produce 33−37. The mixtures of E$_2$ derivatives **28**−**32** (1.8−4.8 g) were dissolved in dry DMF (75−150 mL) under an atmosphere of argon. Imidazole (2.0−4.3 g) and *tert*-butyldimethylsilyl chloride (TBDMS-Cl) (2.9−4.8 g) were added, and the reaction mixture was stirred at room temperature. After 5 h, water (25 mL) was added, and the reaction mixture was extracted with EtOAc. The combined organic layer was washed with brine and dried over $MgSO_4$, and the solvent was evaporated. The residues were purified by flash chromatography (hexanes/EtOAc, 95:5) to give the 16α-isomers **33**−**37** (0.87−1.88 g) as 3,17*β*-diTBDMS derivatives and alcohols **38**−**42** (0.55−1.40 g) as a mixture of 16*β*-isomer and dialkylated compounds.

Procedure for the Protection of 17β-Alcohols of 38−42 (16β-Monoalkylated and 16α/16β-Dialkylated Derivatives). Under an atmosphere of argon, the mixtures of alcohols **38**−**42** (0.76−1.39 g) dissolved in dry CH_2Cl_2 (50 mL) were treated with 2,6-lutidine (540−1010 μL) and TBDMS-OTf (532−997 μL), and the solution was stirred for 2−4 h at 0 °C. A solution of aqueous 5% $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2. The combined organic phase was washed with water and brine, dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The dialkylated derivatives **43**−**47** (75−577 mg) and 16β-monoalkylated derivatives **48**−**52** (575−907 mg) were separated by flash chromatography (hexanes/EtOAc, 98:2).

16′β-[7-(Tetrahydropyranyloxy)-heptyl]-3′,17′β-(di-*tert*-butyldimethylsilyloxy)-1′,3′,5′(10′)-estratriene (48). Colorless gummy oil. IR (film): no OH band. ^{1}H NMR (300 MHz, $CDCl_3$): 0.037 and 0.041 (2s, 17′-Si$(CH_3)_2$), 0.18 (s, 3′-Si$(CH_3)_2$), 0.73 (s, 18′-CH_3), 0.92 (s, 17′-SiC$(CH_3)_3$), 0.97 (s, 3′-SiC$(CH_3)_3$), 2.79 (m, 6′-CH_2), 3.38 and 3.73 (2m, CH_2O of side chain), 3.51 and 3.88 (2m, CH_2O of THP), 3.65 (d, J = 9.3 Hz, 17′α-CH), 4.57 (t, J = 4.3 Hz, OCHO of THP), 6.54 (d, J = 2.3 Hz, 4′-CH), 6.60 (dd, J_1 = 2.7 Hz and J_2 = 8.3 Hz, 2′-CH), 7.12 (d, J = 8.5 Hz, 1′-CH). ^{13}C NMR (75 MHz, $CDCl_3$): −4.59, −4.40, 12.75, 18.16, 18.23, 19.69, 25.50, 25.69 (3×), 25.97 (3×), 26.22, 26.34, 27.44, 28.46, 29.53, 29.77 (2×), 30.79, 32.10, 32.38, 38.17, 38.43, 40.71, 44.13, 44.34, 48.55, 62.32, 67.70, 82.60, 98.82, 117.08, 119.88, 126.07, 133.30, 137.87, 153.22.

16′β-[8-(Tetrahydropyranyloxy)-octyl]-3′,17′β-(di-*tert*-butyldimethylsilyloxy)-1′,3′,5′(10′)-estratriene (49). Colorless gummy oil. IR (film): no OH band. ^{1}H NMR (300 MHz, $CDCl_3$): 0.038 and 0.041 (2s, 17′-Si$(CH_3)_2$), 0.18 (s, 3′-Si$(CH_3)_2$), 0.73 (s, 18′-CH_3), 0.92 (s, 17′-SiC$(CH_3)_3$), 0.97 (s, 3′-SiC$(CH_3)_3$), 2.79 (m, 6′-CH_2), 3.38 and 3.73 (2m, CH_2O of side chain), 3.50 and 3.88 (2m, CH_2O of THP), 3.64 (d, J = 9.3 Hz, 17′α-CH), 4.58 (t, J = 3.5 Hz, OCHO of THP), 6.55 (d, J = 2.2 Hz, 4′-CH), 6.60 (dd, J_1 = 2.5 Hz and J_2 = 8.4 Hz, 2′-CH), 7.12 (d, J = 8.5 Hz, 1′-CH). ^{13}C NMR (75 MHz, $CDCl_3$): −4.58, −4.39, 12.76, 18.16, 18.24, 19.69, 25.51, 25.70, 25.98, 26.26, 26.35, 27.45, 28.51, 29.49, 29.65, 29.74, 29.83 (2×), 30.79, 32.12, 32.38, 38.17, 38.43, 40.72, 44.13, 44.34, 48.56, 62.31, 67.69, 82.61, 98.80, 117.08, 119.89, 126.08, 133.30, 137.89, 153.22.

16′β-[9-(Tetrahydropyranyloxy)-nonyl]-3′,17′β-(di-*tert*-butyldimethylsilyloxy)-1′,3′,5′(10′)-estratriene (50). Colorless gummy oil. IR (film): no OH band. ^{1}H NMR (300 MHz, $CDCl_3$): 0.06 (s, 17′-Si$(CH_3)_2$), 0.20 (s, 3′-Si$(CH_3)_2$), 0.75 (s, 18′-CH_3), 0.94 (s, 17′-SiC$(CH_3)_3$), 0.99 (s, 3′-SiC$(CH_3)_3$), 2.80 (m, 6′-CH_2), 3.39 and 3.75 (2m, CH_2O of side chain), 3.51 and 3.89 (2m, CH_2O of THP), 3.66 (d, J = 9.1 Hz, 17′α-CH), 4.60 (t, J = 2.3 Hz, OCHO of THP), 6.56 (d, J = 2.2 Hz, 4′-CH), 6.62 (dd, J_1 = 2.5 Hz and J_2 = 8.4 Hz, 2′-CH), 7.13 (d, J = 8.5 Hz, 1′-CH). ^{13}C NMR (75 MHz, $CDCl_3$): −4.59, −4.40, 12.76, 18.14, 18.24, 19.67, 25.50, 25.70, 25.98, 26.24, 26.35, 27.45, 28.51, 29.51 (2×), 29.61 (2×), 29.74, 29.85, 30.78, 32.11, 32.38, 38.17, 38.43, 40.73, 44.12, 44.34, 48.54, 62.26, 67.67, 82.60, 98.79, 117.07, 119.88, 126.07, 133.28, 137.85, 153.21.

16′β-[10-(Tetrahydropyranyloxy)-decyl]-3′,17′β-(di-*tert*-butyldimethylsilyloxy)-1′,3′,5′(10′)-estratriene (51). Colorless gummy oil. IR (film): no OH band. ^{1}H NMR (300 MHz, $CDCl_3$): 0.05 (s, 17′-Si$(CH_3)_2$), 0.19 (s, 3′-Si$(CH_3)_2$), 0.74 (s, 18′-CH_3), 0.94 (s, 17′-SiC$(CH_3)_3$), 0.98 (s, 3′-SiC$(CH_3)_3$), 2.80 (m, 6′-CH_2), 3.39 and 3.74 (2m, CH_2O of side chain), 3.51 and 3.88 (2m, CH_2O of THP), 3.65 (d, J = 9.0 Hz, 17′α-CH), 4.56 (t, J = 3.6 Hz, OCHO of THP), 6.55 (d, J = 2.2 Hz, 4′-CH), 6.61 (dd, J_1 = 2.3 Hz and J_2 = 8.4 Hz, 2′-CH), 7.12 (d, J = 8.5 Hz, 1′-CH). ^{13}C NMR (75 MHz, $CDCl_3$): −4.60, −4.41, 12.74, 18.14, 18.22, 19.67, 25.49, 25.68, 25.96, 26.23, 26.33, 27.44, 28.51, 29.48, 29.60 (2×), 29.65 (2×), 29.74, 29.86, 30.77, 32.10, 32.37, 38.16, 38.43, 40.71, 44.12, 44.34, 48.54, 62.28, 67.67, 82.60, 98.80, 117.07, 119.87, 126.06, 133.28, 137.85, 153.21.

16′β-[12-(Tetrahydropyranyloxy)-dodecyl]-3′,17′β-(di-*tert*-butyldimethylsilyloxy)-1′,3′,5′(10′)-estratriene (52). Colorless gummy oil. IR (film): no OH band. ^{1}H NMR (300 MHz, $CDCl_3$): 0.05 (s, 17′-Si$(CH_3)_2$), 0.19 (s, 3′-Si$(CH_3)_2$), 0.74 (s, 18′-CH_3), 0.93 (s, 17′-SiC$(CH_3)_3$), 0.98 (s, 3′-SiC$(CH_3)_3$), 2.79 (m, 6′-CH_2), 3.39 and 3.74 (2m, CH_2O of side chain), 3.51 and 3.87 (2m, CH_2O of THP), 3.65 (d, J = 9.3 Hz, 17′α-CH), 4.58 (t, J = 3.4 Hz, OCHO of THP), 6.55 (d, J = 2.3 Hz, 4′-CH), 6.61 (dd, J_1 = 2.4 Hz and J_2 = 8.4 Hz, 2′-CH), 7.12 (d, J = 8.5 Hz, 1′-CH). ^{13}C NMR (75 MHz, $CDCl_3$): −4.57, −4.39, 12.77, 18.17, 18.25, 19.70, 25.52, 25.71, 25.99, 26.26, 26.36, 27.47, 28.54, 29.51, 29.63 (3×), 29.70 (3×), 29.90, 30.79, 32.12, 32.39, 38.18, 38.45, 40.73, 44.15, 44.35, 48.57, 62.32, 67.70, 82.63, 98.83, 117.09, 119.90, 126.09, 133.33, 137.90, 153.24.

Procedure for Hydrolysis of THP (Synthesis of 53−57). Tetrahydropyranyl derivatives **48**−**52** (525−800 mg; 0.68−1.10 mmol) were solubilized in acetone (75−100 mL), and *p*-TSA (130−209 mg, 0.68−1.10 mmol) was added at room temperature. MeOH (0.5−1.0 mL) was added dropwise, and the mixture was allowed to stir for 3−5 h. Thereafter a solution of aqueous 5% $NaHCO_3$ was added, acetone was partially evaporated, and the mixture was extracted with EtOAc. The combined organic layer was dried ($MgSO_4$) and concentrated under vacuum. The residues were purified by flash chromatography using hexanes/EtOAc (95:5) as eluent to give alcohols **53**−**57** (401−608 mg; 83−88%) and starting material (4−8%).

7-[3′,17′β-(Di-*tert*-butyldimethylsilyloxy)-1′,3′,5′(10′)-estratrien-16′β-yl]-heptanol (53). White solid (88%). IR (film): 3325 (OH). ^{1}H NMR (300 MHz, $CDCl_3$): 0.045 and 0.051 (2s, 17′-Si$(CH_3)_2$), 0.19 (s, 3′-Si$(CH_3)_2$), 0.74 (s, 18′-CH_3), 0.93 (s, 17′-SiC$(CH_3)_3$), 0.98 (s, 3′-SiC$(CH_3)_3$), 2.79 (m, 6′-CH_2), 3.64 (t, J = 6.6 Hz, CH_2OH), 3.65 (d, J = 9.6 Hz, 17′α-CH), 6.54 (d, J = 2.2 Hz, 4′-CH), 6.61 (dd, J_1 = 2.2 Hz and J_2 = 8.5 Hz, 2′-CH), 7.12 (d, J = 8.5 Hz, 1′-CH). ^{13}C NMR (75 MHz, $CDCl_3$): −4.55, −4.36, 12.76, 18.17, 18.25, 25.70, 25.97, 26.35, 27.45, 28.44, 29.46, 29.71, 29.83, 32.10, 32.38, 32.82, 38.17, 38.42, 40.72, 44.12, 44.34, 48.55, 63.08, 82.59, 117.08, 119.89, 126.08, 133.29, 137.87, 153.23.

8-[3′,17′β-(Di-*tert*-butyldimethylsilyloxy)-1′,3′,5′(10′)-estratrien-16′β-yl]-octanol (54). White solid (83%). IR (film): 3335 (OH). ^{1}H NMR (300 MHz, $CDCl_3$): 0.038 and 0.042 (2s, 17′-Si$(CH_3)_2$), 0.18 (s, 3′-Si$(CH_3)_2$), 0.73 (s, 18′-CH_3), 0.92 (s, 17′-SiC$(CH_3)_3$), 0.97 (s, 3′-SiC$(CH_3)_3$), 2.79 (m, 6′-CH_2), 3.64 (t, J = 6.6 Hz, CH_2OH), 3.65 (d, J = 10.3 Hz, 17′α-CH), 6.54 (d, J = 2.3 Hz, 4′-CH), 6.60 (dd, J_1 = 2.5 Hz and J_2 = 8.4 Hz, 2′-CH), 7.11 (d, J = 8.5 Hz, 1′-CH). ^{13}C NMR (75 MHz, $CDCl_3$): −4.57, −4.39, 12.77, 18.18, 18.25, 25.71, 25.99, 26.36, 27.48, 28.52, 29.44, 29.66, 29.72, 29.82, 32.12, 32.39, 32.80, 38.18, 38.43, 40.73, 44.13, 44.35, 48.57, 63.09, 82.61, 117.09, 119.90, 126.09, 133.31, 137.88, 153.24.

9-[3′,17′β-(Di-*tert*-butyldimethylsilyloxy)-1′,3′,5′(10′)-estratrien-16′β-yl]-nonanol (55). White solid (86%). IR (film): 3341 (OH). ^{1}H NMR (300 MHz, $CDCl_3$): 0.055 and 0.058 (2s, 17′-Si$(CH_3)_2$), 0.20 (s, 3′-Si$(CH_3)_2$), 0.75 (s, 18′-CH_3), 0.94 (s, 17′-SiC$(CH_3)_3$), 0.99 (s, 3′-SiC$(CH_3)_3$), 2.80 (m, 6′-CH_2), 3.65 (t, J = 6.6 Hz, CH_2OH), 3.66 (d, 17′α-CH), 6.56 (d, J = 2.5 Hz, 4′-CH), 6.61 (dd, J_1 = 2.6 Hz and J_2 = 8.4 Hz, 2′-CH), 7.13 (d, J = 8.5 Hz, 1′-CH). ^{13}C NMR (75 MHz, $CDCl_3$): −4.59, −4.40, 12.75, 18.15, 18.24, 25.70, 25.97, 26.34, 27.45, 28.51, 29.44, 29.60 (2×), 29.70, 29.85, 32.10, 32.37, 32.78, 38.16, 38.43, 40.72, 44.12, 44.34, 48.54, 63.06, 82.60, 117.07, 119.88, 126.06, 133.29, 137.85, 153.21.

10-[3′,17′β-(Di-*tert*-butyldimethylsilyloxy)-1′,3′,5′(10′)-estratrien-16′β-yl]-decanol (56). White solid (84%). IR (film): 3334 (OH). ^{1}H NMR (300 MHz, $CDCl_3$): 0.038 and 0.041 (2s, 17′-Si$(CH_3)_2$), 0.18 (s, 3′-Si$(CH_3)_2$), 0.73 (s, 18′-CH_3), 0.92 (s, 17′-SiC$(CH_3)_3$), 0.97 (s, 3′-SiC$(CH_3)_3$), 2.78 (m, 6′-CH_2), 3.64 (t, J = 6.6 Hz, CH_2OH), 3.65 (d, J = 9.8 Hz, 17′α-CH), 6.54 (d, J = 2.5 Hz, 4′-CH), 6.60 (dd, J_1 = 2.4 Hz and J_2 = 8.4 Hz, 2′-CH), 7.11 (d, J = 8.5 Hz, 1′-CH). ^{13}C NMR (75 MHz, $CDCl_3$): −4.57, −4.40, 12.77, 18.16, 18.24, 25.71, 25.99, 26.36, 27.45, 28.54, 29.44, 29.61 (2×), 29.71, 29.88, 32.12, 32.39, 32.83, 38.18, 38.44, 40.73, 44.13, 44.35, 48.57, 63.10, 82.63, 117.10, 119.89, 126.09, 133.33, 137.90, 153.24.

12-[3′,17′β-(Di-*tert*-butyldimethylsilyloxy)-1′,3′,5′(10′)-estratrien-16′β-yl]-dodecanol (57). Colorless gummy oil (87%). IR (film): 3339 (OH). ^{1}H NMR (300 MHz, $CDCl_3$): 0.043 (s, 17′-Si$(CH_3)_2$), 0.18 (s, 3′-Si$(CH_3)_2$), 0.73 (s, 18′-CH_3), 0.93 (s, 17′-SiC$(CH_3)_3$), 0.98 (s, 3′-SiC$(CH_3)_3$), 2.79 (m, 6′-CH_2), 3.64

(t, J = 6.6 Hz, CH_2OH), 3.65 (d, J = 10.8 Hz, 17′α-CH), 6.54 (d, J = 2.3 Hz, 4′-CH), 6.60 (dd, J_1 = 2.4 Hz and J_2 = 8.4 Hz, 2′-CH), 7.12 (d, J = 8.5 Hz, 1′-CH). ^{13}C NMR (75 MHz, $CDCl_3$): −4.57, −4.39, 12.77, 18.22 (2×), 25.71, 25.99, 26.36, 27.46, 28.53, 29.44, 29.69 (3×), 29.90, 32.12, 32.39, 32.83, 38.18, 38.44, 40.73, 44.13, 44.34, 48.57, 63.10, 82.62, 117.09, 119.90, 126.09, 133.33, 137.90, 153.23.

Synthesis of Adenosine Derivatives 2−10 and 80. Oxidation of Alcohols to Carboxylic Acids 58−64 and Esterification to 73−79. To a solution of alcohols **21**, **22**, and **53−57** (360−550 mg, 0.57−0.85 mmol) in acetone (10−50 mL), Jones' reagent (0.42−0.82 mL of a CrO_3−H_2SO_4, 2.7 M solution) was added dropwise at 0 °C and allowed to stir for 0.25−2.0 h. Then, 2-propanol (a few drops) and brine were added, acetone was partially evaporated under reduced pressure, and the mixture was extracted with EtOAc, and the organic layer was dried with $MgSO_4$. Solvent was removed, and the crude acids **58−64** were dissolved in CH_2Cl_2 (20−40 mL) and treated 1.5 h at room temperature with an excess of oxalyl chloride (2.5−10 mL). After evaporation of solvent and azeotropic removal of exceeding reagent with benzene, acyl chlorides **66−72** were used for the next step without any purification. To a suspension of NaH (60% in mineral oil; 133-219 mg, 3.32−5.48 mmol) in dry THF (40 mL) and under an atmosphere of argon was added a solution of 2′,3′-isopropylidene-adenosine (**65**) (285−468 mg, 0.93−1.52 mmol) in dry THF (25−40 mL), and the mixture was stirred for 30 min at room temperature. Then the reaction mixture was cooled at −20 °C, and a solution of crude acyl chlorides **66−72** in dry THF (10 mL) was added dropwise. After 1−2 h, *p*-TSA (458−753 mg, 2.41−3.96 mmol) was added, and the temperature was allowed to rise to 0 °C before the addition of water. The mixture was then extracted with EtOAc (2×) and $CHCl_3$ (2×), and the organic layers were dried with $MgSO_4$. After solvent evaporation, a flash chromatography with $CHCl_3$/MeOH (99:1 to 90:10) afforded esters **73−79** (293−471 mg) in 47−75% yields. Starting material (23−30%) was also recovered during the formation of **73**, **74**, and **78**.

5′-*O*-{6-[3′,17′*β*-(Di-*tert*-butyldimethylsilyloxy)-1′,3′,5′-(10′)-estratrien-16′α/*β*-yl]-hexanoyl} 2′,3′-*O*-Isopropylideneadenosine (73). White solid (57%). IR (film): 3330 and 3183 (NH_2), 1738 (C=O, ester), 1641 (C=N). ^{1}H NMR ($CDCl_3$): 0.023, 0.035, and 0.047 (3s, 17′-Si(CH_3)$_2$), 0.18 (s, 3′-Si(CH_3)$_2$), 0.72 and 0.76 (2s, 18′-CH_3, 16′*β*/16′α 68:32), 0.89 and 0.91 (2s, 17′-SiC(CH_3)$_3$), 0.97 (s, 3′-SiC(CH_3)$_3$), 1.40 and 1.62 (2s, 2 × CH_3 of isopropylidene), 2.24 (t, J = 7.5 Hz, CH_2COO), 2.78 (m, 6′-CH_2), 3.19 and 3.63 (2d, J = 7.3 and 9.1 Hz, respectively, for 17′α-CH of 16′α and 16′*β* isomers), 4.22 and 4.36 (2m, 5′-CH_2 of ribose), 4.47 (m, 4′-CH of ribose), 5.05 (dd, J_1 = 3.4 Hz and J_2 = 6.3 Hz, 3′-CH of ribose), 5.47 (dd, J_1 = 2.0 Hz and J_2 = 6.3 Hz, 2′-CH of ribose), 5.76 (s, NH_2), 6.10 (d, J = 2.1 Hz, 1′-CH of ribose), 6.54 (d, J = 2.6 Hz, 4′-CH), 6.60 (dd, J_1 = 2.6 Hz and J_2 = 8.4 Hz, 2′-CH), 7.11 (d, J = 8.5 Hz, 1′-CH), 7.89 and 8.36 (2s, 2 × CH of adenine). ^{13}C NMR ($CDCl_3$): −4.59, −4.54, −4.39, −4.03, −3.96, 12.23, 12.75, 18.17, 18.23, 24.79, 24.85, 25.39, 25.71, 25.96, 26.34, 27.16, 27.45, 28.11, 28.19, 29.38, 29.69, 31.97, 32.35, 33.95, 37.45, 38.16, 38.42, 38.69, 40.67, 44.11, 44.35, 48.55, 63.85, 81.75, 82.56, 88.02, 84.25, 85.03, 91.08, 114.57, 117.10, 119.89, 120.35, 126.06, 133.27, 137.89, 139.66, 149.31, 153.24, 155.51, 173.23. HRMS: calcd for $C_{49}H_{78}Si_2N_5O_7$ [M + H]$^+$ 904.54401, found 904.54200.

5′-*O*-{11-[3′,17′*β*-(Di-*tert*-butyldimethylsilyloxy)-1′,3′,5′-(10′)-estratrien-16′α/*β*-yl]-undecanoyl} 2′,3′-*O*-Isopropylideneadenosine (74). White solid (47%). IR (film): 3328 and 3180 (NH_2), 1740 (C=O, ester), 1651 (C=N). ^{1}H NMR ($CDCl_3$): 0.037 and 0.048 (2s, 17′-Si(CH_3)$_2$), 0.18 (s, 3′-Si(CH_3)$_2$), 0.73 and 0.77 (2s, 18′-CH_3, 16′*β*/16′α 72:28), 0.89 and 0.92 (2s, 17′-SiC(CH_3)$_3$), 0.97 (s, 3′-SiC(CH_3)$_3$), 1.40 and 1.62 (2s, 2 × CH_3 of isopropylidene), 2.22 (t, J = 7.5 Hz, CH_2COO), 2.78 (m, 6′-CH_2), 3.20 and 3.64 (2d, J = 6.4 and 9.1 Hz, respectively, for 17′α-CH of 16′α and 16′*β*?-isomers), 4.22 and 4.36 (2m, 5′-CH_2 of ribose), 4.48 (m, 4′-CH of ribose), 5.05 (dd, J_1 = 3.4 Hz and J_2 = 6.2 Hz, 3′-CH of ribose), 5.48 (dd, J_1 = 1.9 Hz and J_2 = 6.2 Hz, 2′-CH of ribose), 5.59 (s, NH_2), 6.11 (d, J = 1.7 Hz, 1′-CH of ribose), 6.54 (s_{app}, 4′-CH), 6.60 (dd, J_1 = 2.6 Hz and J_2 = 8.3 Hz, 2′-CH), 7.11 (d, J = 8.5 Hz, 1′-CH), 7.89 and 8.37 (2s, 2 × CH of adenine). ^{13}C NMR ($CDCl_3$): −4.55, −4.37, −4.03, −3.95, 12.26, 12.78, 18.17, 18.27, 24.80, 25.23, 25.40, 25.73, 25.85, 25.99, 26.37, 27.17, 27.47, 28.47, 28.56, 29.12, 29.25, 29.49, 29.62, 29.71, 29.90, 32.14, 32.41, 33.97, 34.81, 37.49, 38.20, 38.46, 38.72, 40.75, 43.80, 44.15, 44.27, 44.36, 48.29, 48.59, 63.83, 81.75, 82.65, 88.10, 84.27, 85.03, 91.15, 114.60, 117.10, 119.92, 120.34, 126.10, 133.35, 137.93, 139.76, 149.30, 153.17, 153.26, 155.38, 173.26. HRMS: calcd for $C_{54}H_{88}Si_2N_5O_7$ [M + H]$^+$ 974.62225, found 974.62460.

5′-*O*-{7-[3′,17′*β*-(Di-*tert*-butyldimethylsilyloxy)-1′,3′,5′-(10′)-estratrien-16′*β*-yl]-heptanoyl} 2′,3′-*O*-Isopropylideneadenosine (75). White solid (70%). IR (film): 3324 and 3160 (NH_2), 1742 (C=O, ester), 1644 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$): 0.021 and 0.031 (2s, 17′-Si(CH_3)$_2$), 0.18 (s, 3′-Si(CH_3)$_2$), 0.72 (s, 18′-CH_3), 0.91 (s, 17′-SiC(CH_3)$_3$), 0.97 (s, 3′-SiC(CH_3)$_3$), 1.40 and 1.62 (2s, 2 × CH_3 of isopropylidene), 2.23 (t, J = 7.6 Hz, CH_2COO), 2.78 (m, 6′-CH_2), 3.63 (d, J = 9.1 Hz, 17′α-CH), 4.19−4.39 (2m, 5′-CH_2 of ribose), 4.49 (m, 4′-CH of ribose), 5.05 (dd, J_1 = 3.4 Hz and J_2 = 6.3 Hz, 3′-CH of ribose), 5.47 (dd, J_1 = 1.7 Hz and J_2 = 6.2 Hz, 2′-CH of ribose), 5.93 (s, NH_2), 6.11 (d, J = 1.6 Hz, 1′-CH of ribose), 6.54 (d, J = 2.5 Hz, 4′-CH), 6.60 (dd, J_1 = 2.5 Hz and J_2 = 8.4 Hz, 2′-CH), 7.11 (d, J = 8.5 Hz, 1′-CH), 7.90 and 8.36 (2s, 2 × CH of adenine). ^{13}C NMR (75 MHz, $CDCl_3$): −4.57, −4.40, 12.75, 18.15, 18.24, 24.77, 25.39, 25.70, 25.96, 26.33, 27.14, 27.44, 28.34, 29.19, 29.50, 29.69, 32.08, 32.36, 33.97, 38.15, 38.42, 40.67, 44.12, 44.34, 48.54, 63.83, 81.73, 82.57, 84.25, 85.02, 91,11, 114.58, 117.09, 119.89, 120.49, 126.08, 133.29, 137.87, 139.76, 149.29, 152.93, 153.23, 155.42, 173.24.

5′-*O*-{8-[3′,17′*β*-(Di-*tert*-butyldimethylsilyloxy)-1′,3′,5′-(10′)-estratrien-16′*β*-yl]-octanoyl} 2′,3′-*O*-Isopropylideneadenosine (76). White solid (75%). IR (film): 3324 and 3161 (NH_2), 1741 (C=O, ester), 1649 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$): 0.024 and 0.033 (2s, 17′-Si(CH_3)$_2$), 0.18 (s, 3′-Si(CH_3)$_2$), 0.72 (s, 18′-CH_3), 0.91 (s, 17′-SiC(CH_3)$_3$), 0.97 (s, 3′-SiC(CH_3)$_3$), 1.40 and 1.62 (2s, 2 × CH_3 of isopropylidene), 2.23 (t, J = 7.6 Hz, CH_2COO), 2.78 (m, 6′-CH_2), 3.64 (d, J = 9.0 Hz, 17α-CH), 4.20−4.39 (2m, 5′-CH_2 of ribose), 4.48 (m, 4′-CH of ribose), 5.05 (dd, J_1 = 3.3 Hz and J_2 = 6.0 Hz, 3′-CH of ribose), 5.47 (d, J = 5.8 Hz, 2′-CH of ribose), 6.07 (s, NH_2), 6.11 (s, 1′-CH of ribose), 6.54 (d, J = 2.2 Hz, 4′-CH), 6.60 (dd, J_1 = 2.2 Hz and J_2 = 8.6 Hz, 2′-CH), 7.11 (d, J = 8.5 Hz, 1′-CH), 7.91 and 8.36 (2s, 2 × CH of adenine). ^{13}C NMR (75 MHz, $CDCl_3$): −4.61, −4.43, 12.73, 18.12, 18.21, 24.77, 25.36, 25.68, 25.95, 26.31, 27.12, 27.42, 28.45, 29.09, 29.29, 29.67 (2×), 32.08, 32.33, 33.92, 38.13, 38.39, 40.67, 44.09, 44.31, 48.51, 63.81, 81.70, 82.55, 84.24, 84.99, 91,09, 114.55, 117.06, 119.87, 120.27, 126.05, 133.27, 137.85, 139.77, 149.17, 152.80, 153.19, 155.42, 173.24.

5′-*O*-{9-[3′,17′*β*-(Di-*tert*-butyldimethylsilyloxy)-1′,3′,5′-(10′)-estratrien-16′*β*-yl]-nonanoyl} 2′,3′-*O*-Isopropylideneadenosine (77). White solid (47%). IR (film): 3324 and 3161 (NH_2), 1742 (C=O, ester), 1644 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$): 0.028 and 0.035 (2s, 17′-Si(CH_3)$_2$), 0.18 (s, 3′-Si(CH_3)$_2$), 0.72 (s, 18′-CH_3), 0.91 (s, 17′-SiC(CH_3)$_3$), 0.97 (s, 3′-SiC(CH_3)$_3$), 1.40 and 1.62 (2s, 2 × CH_3 of isopropylidene), 2.23 (t, J = 7.6 Hz, CH_2COO), 2.78 (m, 6′-CH_2), 3.63 (d, J = 9.1 Hz, 17′α-CH), 4.20−4.38 (2m, 5′-CH_2 of ribose), 4.49 (m, 4′-CH of ribose), 5.05 (dd, J_1 = 3.3 Hz and J_2 = 6.3 Hz, 3′-CH of ribose), 5.47 (dd, J_1 = 1.9 Hz and J_2 = 6.2 Hz, 2′-CH of ribose), 6.00 (s, NH_2), 6.11 (d, J = 2.0 Hz, 1′-CH of ribose), 6.54 (d, J = 2.3 Hz, 4′-CH), 6.60 (dd, J_1 = 2.5 Hz and J_2 = 8.4 Hz, 2′-CH), 7.11 (d, J = 8.5 Hz, 1′-CH), 7.90 and 8.36 (2s, 2 × CH of adenine). ^{13}C NMR (75 MHz, $CDCl_3$): −4.59, −4.42, 12.75, 18.13, 18.22, 24.76, 25.37, 25.69, 25.97, 26.33, 27.12, 27.43, 28.49, 29.09, 29.21, 29.49, 29.69, 29.80, 32.10, 32.36, 33.93, 38.16, 38.41, 40.70, 44.10, 44.32, 48.54, 63.80, 81.71, 82.58, 84.23, 85.01, 91,10, 114.56, 117.07, 119.88, 120.28, 126.06, 133.29, 137.86, 139.71, 149.21, 152.91, 153.20, 155.42, 173.22.

**5′-*O*-{10-[3′,17′*β*-(Di-*tert*-butyldimethylsilyloxy)-1′,3′,5′-(10′)-estratrien-16′*β*-yl]-decanoyl} 2′,3′-*O*-Isopropyli-

deneadenosine (78). White solid (52%). IR (film): 3324 and 3172 (NH_2), 1742 (C=O, ester), 1643 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$): 0.028 and 0.034 (2s, 17′-Si(CH_3)$_2$), 0.18 (s, 3′-Si(CH_3)$_2$), 0.73 (s, 18′-CH_3), 0.92 (s, 17′-SiC(CH_3)$_3$), 0.97 (s, 3′-SiC(CH_3)$_3$), 1.40 and 1.62 (2s, 2 × CH_3 of isopropylidene), 2.23 (t, J = 7.5 Hz, CH_2COO), 2.78 (m, 6′-CH_2), 3.63 (d, J = 9.2 Hz, 17′α-CH), 4.20−4.38 (2m, 5′-CH_2 of ribose), 4.49 (m, 4′-CH of ribose), 5.04 (dd, J_1 = 3.4 Hz and J_2 = 6.3 Hz, 3′-CH of ribose), 5.47 (dd, J_1 = 1.9 Hz and J_2 = 6.2 Hz, 2′-CH of ribose), 5.97 (s, NH_2), 6.11 (d, J = 1.7 Hz, 1′-CH of ribose), 6.54 (d, J = 2.5 Hz, 4′-CH), 6.60 (dd, J_1 = 2.5 Hz and J_2 = 8.4 Hz, 2′-CH), 7.11 (d, J = 8.5 Hz, 1′-CH), 7.91 and 8.36 (2s, 2 × CH of adenine). ^{13}C NMR (75 MHz, $CDCl_3$): −4.57, −4.40, 12.77, 18.15, 18.25, 24.77, 25.37, 25.71, 25.99, 26.35, 27.14, 27.45, 28.53, 29.10, 29.27, 29.46, 29.66, 29.71, 29.87, 32.12, 32.37, 33.95, 38.18, 38.43, 40.72, 44.12, 44.34, 48.55, 63.81, 81.70, 82.60, 84.28, 85.02, 91,15, 114.61, 117.09, 119.89, 120.24, 126.08, 133.31, 137.89, 139.83, 149.20, 152.62, 153.21, 155.25, 173.24.

5′-*O*-{12-[3′,17′*β*-(Di-*tert*-butyldimethylsilyloxy)-1′,3′,5′-(10′)-estratrien-16′*β*-yl]-dodecanoyl} 2′,3′-*O*-Isopropylideneadenosine (79). Colorless gummy oil (71%). IR (film): 3324 and 3172 (NH_2), 1740 (C=O, ester), 1651 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$): 0.033 and 0.036 (2s, 17′-Si(CH_3)$_2$), 0.18 (s, 3′-Si(CH_3)$_2$), 0.73 (s, 18′-CH_3), 0.92 (s, 17′-SiC(CH_3)$_3$), 0.97 (s, 3′-SiC(CH_3)$_3$), 1.40 and 1.62 (2s, 2 × CH_3 of isopropylidene), 2.23 (t, J = 7.5 Hz, CH_2COO), 2.78 (m, 6′-CH_2), 3.63 (d, J = 9.2 Hz, 17′α-CH), 4.20−4.38 (2m, 5′-CH_2 of ribose), 4.49 (m, 4′-CH of ribose), 5.04 (dd, J_1 = 3.4 Hz and J_2 = 6.3 Hz, 3′-CH of ribose), 5.47 (dd, J_1 = 1.9 Hz and J_2 = 6.2 Hz, 2′-CH of ribose), 5.97 (s, NH_2), 6.11 (d, J = 1.7 Hz, 1′-CH of ribose), 6.54 (d, J = 2.5 Hz, 4′-CH), 6.60 (dd, J_1 = 2.5 Hz and J_2 = 8.4 Hz, 2′-CH), 7.11 (d, J = 8.5 Hz, 1′-CH), 7.91 and 8.36 (2s, 2 × CH of adenine). ^{13}C NMR (75 MHz, $CDCl_3$): −4.60, −4.42, 12.74, 18.21 (2×), 24.75, 25.36, 25.68, 25.96, 26.33, 27.12, 27.42, 28.51, 29.07, 29.22, 29.44, 29.63 (2×), 29.68 (2×), 29.88, 32.10, 32.35, 33.92, 38.14, 38.40, 40.69, 44.09, 44.31, 48.52, 63.80, 81.69, 82.58, 84.25, 85.00, 91,12, 114.55, 117.06, 119.87, 120.27, 126.05, 133.28, 137.85, 139.77, 149.17, 152.81, 153.18, 155.39, 173.21.

Procedure for the Final Trideprotection of 73−79 (Synthesis of 2, 3, and 6−10). At room temperature, gaseous hydrogen chloride was bubbled for 15−105 min (successive 15 min bubbling and reactions monitored by TLC except for **73** and **74**) in a solution of protected esters **73**−**79** (14−426 mg, 0.016−0.464 mmol) dissolved in dry CH_2Cl_2 (5−75 mL). The solvent was then evaporated, and the crude monoprotected intermediates (17β-TBDMS derivatives) were dissolved in dry THF (2−40 mL) and treated at 60 °C with tetrabutylammonium fluoride (1 M in THF; 39−930 μL, 0.039−0.930 mmol). After 2−6 h, the solvent was removed under vacuum; the residues were preadsorbed on C_{18} silica gel and filtered on a C_{18} silica gel column (reverse phase) with MeOH/H_2O (70:30 or 55:45) as eluent. The compounds were next purified by flash chromatography (normal phase) using $CHCl_3$/MeOH (96:4 to 92:8) as eluent to give the desired final compounds **2**, **3**, and **6**−**10** in 23−46% yields. Starting material (27% and 41%) was recovered for **2** and **3** because the HCl bubbling time was too short.

5′-*O*-{6-[3′,17′*β*-Dihydroxy-1′,3′,5′(10′)-estratrien-16′α/*β*-yl]-hexanoyl} adenosine (2). White solid (46%). IR (KBr): 3344 and 3214 (OH and NH_2), 1731 (C=O, ester), 1645 (C=N). ^{1}H NMR (CD_3OD): 0.74 and 0.78 (2s, 18′-CH_3, 16′β/16′α 63:37), 2.34 (t, J = 7.4 Hz, CH_2COO), 2.74 (m, 6′-CH_2), 3.16 and 3.64 (2d, J = 7.6 and 9.6 Hz, respectively, for 17′α-CH of 16′α and 16′β isomers), 4.26 (m, 4′-CH of ribose), 4.38 (m, 5′-CH_2 and 3′-CH of ribose), 4.72 (t_{app}, J = 4.7 Hz, 2′-CH of ribose), 6.02 (d, J = 4.3 Hz, 1′-CH of ribose), 6.47 (s_{app}, 4′-CH), 6.52 (dd, J_1 = 2.5 Hz and J_2 = 8.5 Hz, 2′-CH), 7.06 (d, J = 8.5 Hz, 1′-CH), 8.20 and 8.26 (2s, 2 × CH of adenine). ^{13}C NMR (CD_3OD): 12.60, 13.23, 25.99, 27.58, 28.50, 28.73, 29.10, 29.37, 30.31, 30.73, 32.73, 33.57, 34.91, 36.69, 38.15, 39.08, 39.99, 40.32, 41.50, 44.14, 45.18, 45.42, 49.28 (under solvent peaks), 49.84, 64.55, 71.77, 75.29, 83.31, 88.91, 83.44, 90.50, 113.70, 116.03, 120.60, 127.15, 132.73, 138.83, 141.10, 150.56, 153.94, 155.88, 157.34, 175.10. HRMS: calcd for $C_{34}H_{46}N_5O_7$ $[M + H]^+$ 636.33972, found 636.33610.

5′-*O*-{11-[3′,17′*β*-Dihydroxy-1′,3′,5′(10′)-estratrien-16′α/*β*-yl]-undecanoyl} Adenosine (3). White solid (28%). IR (KBr): 3350 broad (OH and NH_2), 1736 (C=O, ester), 1648 (C=N). ^{1}H NMR (CD_3OD): 0.75 and 0.79 (2s, 18′-CH_3, 16′β/16′α 70:30), 2.31 (t, J = 7.3 Hz, CH_2COO), 2.75 (m, 6′-CH_2), 3.17 and 3.67 (2d, J = 7.3 and 9.7 Hz, respectively, for 17′α-CH of 16′α and 16′β-isomers), 4.26 (m, 4′-CH of ribose), 4.38 (m, 5′-CH_2 and 3′-CH of ribose), 4.73 (t_{app}, J = 4.7 Hz, 2′-CH of ribose), 6.01 (d, J = 4.3 Hz, 1′-CH of ribose), 6.46 (s_{app}, 4′-CH), 6.52 (dd, J_1 = 2.3 Hz and J_2 = 8.8 Hz, 2′-CH), 7.05 (d, J = 8.5 Hz, 1′-CH), 8.20 and 8.25 (2s, 2 × CH of adenine). ^{13}C NMR (CD_3OD): 12.61, 13.23, 25.99, 27.60, 28.52, 28.76, 29.54, 29.84, 30.10, 30.32, 30.53, 30.63, 30.73(2×), 31.00, 32.96, 33.64, 34.91, 36.94, 38.18, 39.11, 40.02, 40.35, 41.66, 44.22, 45.19, 45.46, 49.29 (under solvent peaks), 50.01, 64.55, 71.77, 75.22, 83.38, 88.98, 83.43, 90.49, 113.70, 116.04, 120.61, 127.17, 132.73, 138.84, 141.17, 150.57, 153.93, 155.89, 157.34, 175.08. HRMS: calcd for $C_{39}H_{56}N_5O_7$ $[M + H]^+$ 706.41797, found 706.41630. Anal. ($C_{39}H_{55}N_5O_7$) C,H,N.

5′-*O*-{7-[3′,17′*β*-Dihydroxy-1′,3′,5′(10′)-estratrien-16′*β*-yl]-heptanoyl} Adenosine (6). White solid (23%). IR (KBr): 3356 broad (OH and NH_2), 1730 (C=O, ester), 1642 (C=N). ^{1}H NMR (300 MHz, CD_3OD): 0.73 (s, 18′-CH_3), 2.31 (t, J = 7.3 Hz, CH_2COO), 2.74 (m, 6′-CH_2), 3.65 (d, J = 9.8 Hz, 17′α-CH), 4.25 (m, 4′-CH of ribose), 4.38 (m, 5′-CH_2 and 3′-CH of ribose), 4.73 (t, J = 4.7 Hz, 2′-CH of ribose), 6.02 (d, J = 4.2 Hz, 1′-CH of ribose), 6.46 (d, J = 2.3 Hz, 4′-CH), 6.52 (dd, J_1 = 2.6 Hz and J_2 = 8.4 Hz, 2′-CH), 7.05 (d, J = 8.5 Hz, 1′-CH), 8.20 and 8.25 (2s, 2 × CH of adenine). ^{13}C NMR (75 MHz, CD_3OD): 13.23, 25.98, 27.58, 28.75, 29.62, 30.12, 30.55, 30.74, 32.86, 33.60, 34.91, 39.08, 39.99, 41.59, 45.17, 45.43, 49.99, 64.51, 71.76, 75.26, 83.34, 83.43, 90.47, 113.70, 116.03, 120.57, 127.16, 132.73, 138.83, 141.11, 150.56, 153.92, 155.88, 157.34, 175.10. HRMS: calcd for $C_{35}H_{48}N_5O_7$ $[M + H]^+$ 650.35483, found 650.35478. Anal. ($C_{35}H_{47}N_5O_7$) C,H,N.

5′-*O*-{8-[3′,17′*β*-Dihydroxy-1′,3′,5′(10′)-estratrien-16′*β*-yl]-octanoyl} Adenosine (7). White solid (33%). IR (KBr): 3335 broad (OH and NH_2), 1730 (C=O, ester), 1642 (C=N). ^{1}H NMR (300 MHz, CD_3OD): 0.75 (s, 18′-CH_3), 2.32 (t, J = 7.2 Hz, CH_2COO), 2.76 (m, 6′-CH_2), 3.67 (d, J = 9.7 Hz, 17′α-CH), 4.26 (m, 4′-CH of ribose), 4.38 (m, 5′-CH_2 and 3′-CH of ribose), 4.74 (t, J = 4.7 Hz, 2′-CH of ribose), 6.01 (d, J = 4.3 Hz, 1′-CH of ribose), 6.46 (d, J = 2.5 Hz, 4′-CH), 6.52 (dd, J_1 = 2.6 Hz and J_2 = 8.4 Hz, 2′-CH), 7.06 (d, J = 8.5 Hz, 1′-CH), 8.20 and 8.26 (2s, 2 × CH of adenine). ^{13}C NMR (75 MHz, CD_3OD): 13.26, 25.92, 27.51, 28.69, 29.71, 30.07, 30.31, 30.69, 30.74, 32.86, 33.56, 34.88, 38.98, 39.86, 41.50, 45.09, 45.30, 49.88, 64.51, 71.67, 75.22, 83.29 (2×), 90.43, 113.67, 116.02, 120.64, 127.13, 132.66, 138.74, 140.98, 150.41, 153.83, 155.74, 157.19, 175.03. HRMS: calcd for $C_{36}H_{50}N_5O_7$ $[M + H]^+$ 664.37048, found 664.37053. Anal. ($C_{36}H_{49}N_5O_7$) C,H,N.

5′-*O*-{9-[3′,17′*β*-Dihydroxy-1′,3′,5′(10′)-estratrien-16′*β*-yl]-nonanoyl} Adenosine (8). White solid (31%). IR (film): 3345 broad (OH and NH_2), 1735 (C=O, ester), 1647 (C=N). ^{1}H NMR (300 MHz, CD_3OD): 0.75 (s, 18′-CH_3), 2.32 (t, J = 7.1 Hz, CH_2COO), 2.76 (m, 6′-CH_2), 3.67 (d, J = 9.8 Hz, 17′α-CH), 4.26 (m, 4′-CH of ribose), 4.38 (m, 5′-CH_2 and 3′-CH of ribose), 4.74 (t, J = 4.8 Hz, 2′-CH of ribose), 6.01 (d, J = 4.3 Hz, 1′-CH of ribose), 6.47 (d, J = 2.2 Hz, 4′-CH), 6.52 (dd, J_1 = 2.5 Hz and J_2 = 8.5 Hz, 2′-CH), 7.06 (d, J = 8.5 Hz, 1′-CH), 8.20 and 8.26 (2s, 2 × CH of adenine). ^{13}C NMR (75 MHz, CD_3OD): 13.26, 25.98, 27.59, 28.75, 29.81, 30.09, 30.30, 30.55, 30.74, 30.89, 32.94, 33.63, 34.91, 39.08, 40.00, 41.63, 45.17, 45.43, 50.00, 64.55, 71.77, 75.22, 83.37, 83.43, 90.49, 113.71, 116.04, 120.57, 127.17, 132.74, 138.83, 141.16, 150.55, 153.92, 155.85, 157.34, 175.13. HRMS: calcd for $C_{37}H_{51}N_5O_7$ Na $[M + Na]^+$ 700.36807, found 700.36900. HPLC purity of 99%.

5′-*O*-{10-[3′,17′*β*-Dihydroxy-1′,3′,5′(10′)-estratrien-16′*β*-yl]-decanoyl} Adenosine (9). White solid (30%). IR (KBr): 3365 broad (OH and NH_2), 1735 (C=O, ester), 1642 (C=N). ^{1}H NMR (300 MHz, CD_3OD): 0.76 (s, 18′-CH_3), 2.32 (t, J =

7.1 Hz, CH_2COO), 2.76 (m, 6′-CH_2), 3.67 (d, J = 9.7 Hz, 17′α-CH), 4.26 (m, 4′-CH of ribose), 4.38 (m, 5′-CH_2 and 3′-CH of ribose), 4.74 (t, J = 4.7 Hz, 2′-CH of ribose), 6.01 (d, J = 4.3 Hz, 1′-CH of ribose), 6.46 (d, J = 2.5 Hz, 4′-CH), 6.52 (dd, J_1 = 2.6 Hz and J_2 = 8.4 Hz, 2′-CH), 7.06 (d, J = 8.4 Hz, 1′-CH), 8.20 and 8.26 (2s, 2 × CH of adenine). ^{13}C NMR (75 MHz, CD_3OD): 13.30, 25.97, 27.57, 28.75, 29.87, 30.12, 30.34, 30.56, 30.72 (2×), 31.00, 32.96, 33.64, 34.91, 39.05, 39.94, 41.60, 45.15, 45.37, 49.96, 64.56, 71.75, 75.27, 83.36 (2×), 90.47, 113.72, 116.06, 120.57, 127.16, 132.70, 138.77, 141.07, 150.49, 153.91, 155.82, 157.29, 175.07. HRMS: calcd for $C_{38}H_{54}N_5O_7$ $[M + H]^+$ 692.40178, found 692.40230. Anal. ($C_{38}H_{53}N_5O_7$) C,H,N.

5′-*O*-{12-[3′,17′β-(Dihydroxy)-1′,3′,5′(10′)-estratrien-16′β-yl]-dodecanoyl} Adenosine (10). White solid (42%). IR (KBr): 3348 broad (OH and NH_2), 1736 (C=O, ester), 1648 (C=N). ^{1}H NMR (300 MHz, CD_3OD): 0.76 (s, 18′-CH_3), 2.32 (t, J = 7.1 Hz, CH_2COO), 2.77 (m, 6′-CH_2), 3.68 (d, J = 9.8 Hz, 17′α-CH), 4.25 (m, 4′-CH of ribose), 4.38 (m, 5′-CH_2 and 3′-CH of ribose), 4.73 (t, J = 4.7 Hz, 2′-CH of ribose), 6.01 (d, J = 4.3 Hz, 1′-CH of ribose), 6.46 (d, J = 2.4 Hz, 4′-CH), 6.52 (dd, J_1 = 2.6 Hz and J_2 = 8.4 Hz, 2′-CH), 7.06 (d, J = 8.5 Hz, 1′-CH), 8.20 and 8.25 (2s, 2 × CH of adenine). ^{13}C NMR (75 MHz, CD_3OD): 13.24, 25.86, 27.45, 28.65, 29.77, 30.03, 30.24, 30.46, 30.64 (2×), 30.94, 32.84, 33.53, 34.84, 38.93, 39.80, 41.48, 45.05, 45.27, 49.84, 64.49, 71.58, 75.18, 83.22 (2×), 90.40, 113.62, 115.98, 120.64, 127.09, 132.62, 138.71, 140.88, 150.50, 153.77, 155.66, 157.12, 174.98. HRMS: calcd for $C_{40}H_{58}N_5O_7$ $[M + H]^+$ 720.43308, found 720.43330. Anal. ($C_{340}H_{57}N_5O_7$) C,H,N.

HPLC Separation of Isomeric Mixture 3 to Obtain 4 and 5. The separation of isomers **4** and **5** from the epimeric mixture **3** was carried out by preparative HPLC with a Guard-Pak cartridge (Nova-Pak HR C_{18}, 40 mm × 10 mm) and a Prep-Pak cartridge (Nova-Pak HR C_{18}, 40 mm × 100 mm) using UV detector at 205 nm. Compounds were eluted from a gradient using CH_3CN/H_2O/MeOH (30:28:42) at a flow rate of 13 mL/min. The HPLC resolution was very low; consequently few pure fractions of **4** and **5** were recovered for analysis. Retention times of 14.1 and 16.2 min were observed for **4** and **5**, respectively, with an analytic HPLC (Nova-Pak C_{18}, 3.9 mm × 150 mm, CH_3CN/H_2O/MeOH (35:29:36) at 1 mL/min flow rate).

5′-*O*-{11-[3′,17′β-dihydroxy-1′,3′,5′(10′)-estratrien-16′α-yl]-undecanoyl} Adenosine (4). White solid. IR (film): 3355 broad (OH and NH_2), 1730 (C=O, ester), 1648 (C=N). ^{1}H NMR (300 MHz, CD_3OD): 0.79 (s, 18′-CH_3), 2.32 (t, J = 7.5 Hz, CH_2-COO), 2.75 (m, 6′-CH_2), 3.18 (d, J = 7.6 Hz, 17′α-CH), 4.25 (m, 4′-CH of ribose), 4.37 (m, 5′-CH_2 and 3′-CH of ribose), 4.75 (t, J = 4.7 Hz, 2′-CH of ribose), 6.01 (d, J = 4.3 Hz, 1′-CH of ribose), 6.46 (d, J = 2.2 Hz, 4′-CH), 6.52 (dd, J_1 = 2.2 Hz and J_2 = 8.2 Hz, 2′-CH), 7.06 (d, J = 8.4 Hz, 1′-CH), 8.20 and 8.26 (2s, 2 × CH of adenine). ^{13}C NMR (75 MHz, CD_3OD): 12.61, 25.98, 27.52, 28.51, 29.53, 30.09, 30.31, 30.52, 30.62, 30.71-(2×), 31.03, 34.90, 36.92, 38.18, 40.35, 44.21, 45.23, 45.44, 49.28 (under solvent peaks), 64.55, 71.78, 75.21, 83.43, 88.97, 90.49, 113.70, 116.04, 120.60, 127.14, 132.65, 138.83, 141.16, 150.56, 153.92, 155.91, 157.34, 175.07. HRMS: calcd for $C_{39}H_{56}N_5O_7$ $[M + H]^+$ 706.41743, found 706.41738.

5′-*O*-{11-[3′,17′β-Dihydroxy-1′,3′,5′(10′)-estratrien-16′β-yl]-undecanoyl} Adenosine (5). White solid. IR (film): 3355 broad (OH and NH_2), 1730 (C=O, ester), 1648 (C=N). ^{1}H NMR (300 MHz, CD_3OD): 0.76 (s, 18′-CH_3), 2.32 (t, J = 7.5 Hz, CH_2-COO), 2.77 (m, 6′-CH_2), 3.68 (d, J = 9.8 Hz, 17′α-CH), 4.25 (m, 4′-CH of ribose), 4.38 (m, 5′-CH_2 and 3′-CH of ribose), 4.73 (t, J = 4.7 Hz, 2′-CH of ribose), 6.01 (d, J = 4.3 Hz, 1′-CH of ribose), 6.47 (d, J = 2.7 Hz, 4′-CH), 6.52 (dd, J_1 = 2.6 Hz and J_2 = 8.5 Hz, 2′-CH), 7.06 (d, J = 8.5 Hz, 1′-CH), 8.20 and 8.26 (2s, 2 × CH of adenine). ^{13}C NMR (75 MHz, CD_3OD): 13.23, 25.98, 27.60, 28.75, 29.83, 30.09, 30.31, 30.52, 30.62, 30.72-(2×), 30.99, 32.95, 33.63, 34.90, 39.10, 40.01, 41.66, 45.18, 45.45, 50.01, 64.55, 71.78, 75.21, 83.37, 83.43, 90.49, 113.70, 116.03, 120.61, 127.16, 132.74, 138.83, 141.16, 150.56, 153.92, 155.88, 157.34, 175.07. HRMS: calcd for $C_{39}H_{56}N_5O_7$ $[M + H]^+$ 706.41743, found 706.41968.

Synthesis of 5′-Nonanoyl-*O*-adenosine (80). 2′,3′-Isopropylidene adenosine (**65**) (695 mg, 2.26 mmol) was added to a suspension of NaH (60% in mineral oil; 316 mg, 7.92 mmol) in dry THF (60 mL) under argon atmosphere and mixed 30 min at room temperature. A solution of nonanoyl chloride (200 mg, 1.13 mmol) in dry THF (15 mL) was then added to the reaction mixture, first cooled at −20 °C. After 2 h, *p*-TSA (1.11 g, 5.65 mmol) was added. After addition of water, the mixture was extracted with EtOAc and $CHCl_3$, dried over $MgSO_4$, and evaporated to dryness. The crude material was purified by flash chromatography ($MeOH/CH_2Cl_2$, 7:93) to afford the 5′-nonanoyl-*O*-adenosine 2′,3′-isopropylidene (392 mg) as a white foam in 78% yield (calculated from nonanoyl chloride). This intermediate compound (62 mg, 0.14 mmol) was dissolved in dry CH_2Cl_2 and gaseous HCl was bubbled approximately 100 min at room temperature. The solvent was evaporated, and the crude residue was purified by flash chromatography ($MeOH/CH_2Cl_2$, 5:95 to 10:90) to give ester **80** (16 mg) in 28% yield. White solid. IR (film): 3331 and 3107 (OH and NH_2), 1731 (C=O, ester), 1666 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): 0.84 (t, J = 6.7 Hz, CH_2CH_3), 1.21 (m, 5 × CH_2 of alkyl side chain), 1.47 (m, CH_2CH_2COO), 2.28 (dd, J_1 = 6.4 Hz, J_2 = 7.6 Hz, CH_2COO), 4.07 (m, 4′-CH of ribose), 4.17−4.37 (m, 3′-CH and 5′-CH_2 of ribose), 4.66 (t, J = 4.9 Hz, 2′-CH of ribose), 5.38 (d, J = 5.4 Hz, OH of 3′-CH of ribose), 5.58 (d, J = 5.3 Hz, OH of 2′-CH of ribose), 5.90 (d, J = 4.9 Hz, 1′-CH of ribose), 7.34 (s, NH_2), 8.15 and 8.32 (2s, 2 × CH of adenine). ^{13}C NMR (75 MHz, DMSO-d_6): 13.98, 22.08, 24.38, 28.40, 28.53, 28.64, 31.21, 33.31, 63.71, 70.16, 72.74, 81.43, 87.70, 119.10, 139.72, 149.30, 152.60, 156.20, 172.79. HRMS: calcd for $C_{19}H_{29}N_5O_5$ $[M]^+$ 407.2168, found 407.2176. HPLC purity of 90%.

Diversification of Compounds with the Optimal Nonyl Spacer (Compounds 11−16). Synthesis of Triol 11. Alcohol **55** (200 mg, 0.31 mmol) was dissolved in dry THF (20 mL) and treated with a solution of tetrabutylammonium fluoride (1.25 mL, 1.25 mmol) for 20 h at 60 °C. A saturated aqueous solution of $NaHCO_3$ (20 mL) was then added, and the mixture was extracted with EtOAc. The combined organic layer was washed with brine and dried with $MgSO_4$, the solvent was removed, and the compound was purified by flash chromatography using hexanes/EtOAc (75:25) as eluent to give **11** in 58% yield.

16β-(9′-Hydroxynonanyl)-1,3,5(10)-estratriene-3,17β-diol (11). White solid. IR (film): 3376 (OH). ^{1}H NMR (300 MHz, acetone-d_6): 0.79 (s, 18-CH_3), 2.77 (m, 6-CH_2), 3.42 (d, J = 4.8 Hz, OH), 3.53 (dd, J_1 = 4.2 Hz and J_2 = 5.7 Hz, CH_2-OH), 3.72 (dd, J_1 = 5.3 Hz and J_2 = 9.6 Hz, 17α-CH), 6.53 (d, J = 2.3 Hz, 4-CH), 6.58 (dd, J_1 = 2.5 Hz and J_2 = 8.4 Hz, 2-CH), 7.09 (d, J = 8.4 Hz, 1-CH), 7.94 (s, phenol-OH). ^{13}C NMR (75 MHz, acetone-d_6): 13.00, 26.54, 27.11, 28.24, ∼30 (5 × CH_2 under solvent peaks), 30.63, 32.57, 33.25, 33.63, 38.60, 39.41, 41.22, 44.81, 44.85, 49.47, 62.34, 82.21, 113.45, 115.81, 126.85, 132.00, 138.27, 155.83. HRMS: calcd for $C_{27}H_{42}O_3Na$ $[M + Na]^+$ 437.30262, found 437.30363. HPLC purity of 98%.

Synthesis of Nonyl Derivative 12. To a solution of alcohol **55** (55 mg, 0.086 mmol) dissolved in dry CH_2Cl_2 (5 mL) and cooled in an ice bath was added with stirring dry Et_3N (39 μL, 0.28 mmol) and methane sulfonyl chloride (MsCl; 20 μL, 0.20 mmol). The solution was stirred at 25 °C for 2 h and then poured into water and extracted with CH_2Cl_2. The organic extract was dried with $MgSO_4$ and concentrated under reduced pressure. The crude mesylate derivative was solubilized in dry THF (10 mL), cooled at −78 °C, and treated with $LiAlH_4$ (10 mg, 0.26 mmol). The suspension was stirred and allowed to warm to room temperature for 24 h. Acetone and $Na_2SO_4 \cdot 10H_2O$ were then added, and the resulting suspension was stirred overnight. $MgSO_4$ was added, and the solution was filtered on Celite and washed with acetone. After the solvent was evaporated, the crude nonyl intermediate was dissolved in THF (10 mL) and treated 22 h at 60 °C with a solution of

tetrabutylammonium fluoride in THF (520 μL, 0.52 mmol) to hydrolyze the two TBDMS groups. After the usual workup (as described for compound **11**), the residue was purified by flash chromatography (hexanes/EtOAc, 90:10) to give **12** in 61% yield (three steps).

16β-Nonyl-1,3,5(10)-estratriene-3,17β-diol (12). White solid. IR(film): 3464 (OH). ^{1}H NMR (300 MHz, acetone-d_6): 0.78 (s, 18-CH_3), 0.88 (t, J = 6.8 Hz, $(CH_2)_3CH_3$), 2.76 (m, 6-CH_2), 3.53 (d, J = 5.3 Hz, OH), 3.72 (dd, J_1 = 5.4 Hz and J_2 = 9.6 Hz, 17α-CH), 6.53 (d, J = 2.3 Hz, 4-CH), 6.59 (dd, J_1 = 2.6 Hz and J_2 = 8.4 Hz, 2-CH), 7.09 (d, J = 8.4 Hz, 1-CH), 7.96 (s, OH). ^{13}C NMR (75 MHz, acetone-d_6): 13.22, 14.47, 23.44, 27.35, 28.47, ∼30 (5 × CH_2 under solvent peaks), 30.89, 32.76, 32.85, 33.50, 38.85, 39.64, 41.47, 45.06, 45.11, 49.71, 82.31, 113.58, 115.95, 127.14, 132.27, 138.55, 155.94. HRMS: calcd for $C_{27}H_{42}O_2Na$ $[M + Na]^+$ 421.30770, found 421.30870. HPLC purity of 95%.

Synthesis of Adenine Derivative 13. To a suspension of **55** (108 mg, 0.168 mmol), adenine (68 mg, 0.50 mmol), and PPh_3 (132 mg, 0.50 mmol) in dry dioxane (9 mL) at room temperature under argon was added a solution of diethyl azodicarboxylate (DEAD) (79 μL, 0.50 mmol) in dry dioxane (3 mL) over a period of 30 min. The resulting mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure, and the residue was directly purified on silica gel ($CHCl_3$/MeOH, 98:2) to afford in 92% yield the protected adenine derivative. This compound (118 mg, 0.155 mmol) was treated with a solution of tetrabutylammonium fluoride in THF (930 μL, 0.93 mmol) under the same conditions described for alcohol **11** to give, after a reversed-phase chromatography on C_{18} silica gel (MeOH/H_2O, 70:30), **13** in 57% (two steps).

9-[9′-(3″,17″β-Dihydroxy-1″,3″,5″(10″)-estratrien-16″b-yl)nonyl]-9*H*-purin-6-ylamine (13). White solid. IR (film): 3315 and 3134 (OH, NH_2). ^{1}H NMR (300 MHz, CD_3OD): 0.76 (s, 18″-CH_3), 2.77 (m, 6″-CH_2), 3.68 (d, J = 9.8 Hz, 17″α-CH), 4.23 (t, J = 7.2 Hz, CH_2N), 6.47 (d, J = 2.4 Hz, 4″-CH), 6.52 (dd, J_1 = 2.4 Hz and J_2 = 8.4 Hz, 2″-CH), 7.07 (d, J = 8.4 Hz, 1″-CH), 7.90 (s, NH_2), 8.12 and 8.20 (2s, 2 × CH of adenine). ^{13}C NMR (75 MHz, CD_3OD): 13.25, 27.58 (2×), 28.76, 29.84, 30.12, 30.52, 30.62, 30.75, 30.96, 31.02, 32.98, 33.62, 39.08, 40.01, 41.63, 44.97, 45.17, 45.44, 49.97, 83.34, 113.70, 116.02, 120.01, 127.18, 132.67, 138.80, 142.75, 150.60, 153.61, 155.90, 157.30. HRMS: calcd for $C_{32}H_{46}N_5O_2$ $[M + H]^+$ 532.36460, found 532.36455. Anal. ($C_{32}H_{45}N_5O_2$) C,H,N.

Synthesis of Acid 14. The acid **62** (60 mg, 0.091 mmol) was dissolved in THF (10 mL) and treated 3.5 h at 60 °C with a solution of tetrabutylammonium fluoride in THF (200 μL, 0.20 mmol) to hydrolyze the two TBDMS groups. After the usual workup (as reported for **11**), the crude product was purified by flash chromatography ($CHCl_3$/MeOH, 95:5) to give acid **14** in 69% yield.

9-(3′,17′β-Dihydroxy-1′,3′,5′(10′)-estratrien-16′β-yl)Nonanoic Acid (14). White solid. IR (KBr): 3412 broad (OH), 1702 (C=O, acid). ^{1}H NMR (300 MHz, acetone-d_6): 0.78 (s, 18′-CH_3), 2.29 (t, J = 7.4 Hz, CH_2COO), 2.76 (m, 6′-CH_2), 3.72 (d, J = 9.6 Hz, 17′α-CH), 6.53 (d, J = 2.5 Hz, 4′-CH), 6.59 (dd, J_1 = 2.7 Hz and J_2 = 8.3 Hz, 2′-CH), 7.10 (d, J = 8.4 Hz, 1′-CH). ^{13}C NMR (75 MHz, CD_3OD): 13.23, 26.17, 27.60, 28.77, 29.87, 30.28, 30.46, 30.68, 30.76, 31.02, 32.99, 33.62, 36.00, 39.09, 40.01, 41.66, 45.18, 45.45, 49.99, 83.36, 113.69, 116.00, 127.17, 132.68, 138.80, 155.88, 177.89. HRMS: calcd for $C_{27}H_{40}O_4Na$ $[M + Na]^+$ 451.28188, found 451.28201. HPLC purity of 92%.

Synthesis of Ester 15. To a solution of acid **62** (60 mg, 0.091 mmol) dissolved in MeOH (1 mL) and benzene (4 mL) was added trimethylsilyldiazomethane ($TMSCHN_2$; 2 M in hexanes; 60 μL, 0.12 mmol) in benzene (1 mL). The mixture was stirred for 45 min at room temperature and concentrated to obtain the methyl ester intermediate, which was deprotected in THF (10 mL) with a solution of tetrabutylammonium fluoride in THF (320 μL, 0.32 mmol) for 18 h at 60 °C. After the usual workup (as reported for **11**), the crude residue was purified by flash chromatography (hexanes/EtOAc, 60:40) to give ester **15** in 50% (two steps).

Methyl 9-(3′,17′β-Dihydroxy-1′,3′,5′(10′)-estratrien-16′β-yl) Nonanoate (15). White solid. IR (film): 3417 (OH), 1716 (C=O, ester). ^{1}H NMR (300 MHz, acetone-d_6): 0.78 (s, 18′-CH_3), 2.29 (t, J = 7.4 Hz, CH_2COO), 2.76 (m, 6′-CH_2), 3.52 (d, J = 5.3 Hz, OH), 3.61 (s, $COOCH_3$), 3.71 (dd, J_1 = 2.6 Hz and J_2 = 9.6 Hz, 17′α-CH), 6.53 (d, J = 2.3 Hz, 4′-CH), 6.58 (dd, J_1 = 2.6 Hz and J_2 = 8.4 Hz, 2′-CH), 7.10 (d, J = 8.4 Hz, 1′-CH), 7.93 (s, OH). ^{13}C NMR (75 MHz, CD_3OD): 13.23, 26.04, 27.60, 28.77, 29.84, 30.19, 30.38, 30.62, 30.75, 30.99, 32.98, 33.62, 34.80, 39.08, 40.01, 41.66, 45.17, 45.46, 49.99, 51.96, 83.35, 113.69, 116.00, 127.17, 132.69, 138.80, 155.88, 176.03. HRMS: calcd for $C_{28}H_{42}O_4Na$ $[M + Na]^+$ 465.29753, found 465.29768. HPLC purity of 87%.

Synthesis of Amide 16. To a suspension of acid **62** (100 mg, 0.15 mmol) and Bu_3N (127 μL, 0.53 mmol) in CH_2Cl_2 (10 mL) at −10 °C under argon was added *i*-BuOCOCl (60 μL, 0.46 mmol), and the resulting mixture was stirred for 30 min at −10 °C. Then, BuMeNH (180 μL, 1.5 mmol) was added, and the solution was allowed to warm at room-temperature overnight. CH_2Cl_2 (20 mL) was added; the organic layer was washed with 1 M HCl solution, a saturated aqueous solution of $NaHCO_3$, and water, dried over $MgSO_4$, and concentrated to obtain the crude amide. The latter was then solubilized in THF (10 mL) and treated for 24 h with a solution of tetrabutylammonium fluoride in THF (334 μL, 0.33 mmol) at 60 °C. After the usual workup (as reported for **11**), final flash chromatography was performed using hexanes/EtOAc (50:50) to give the amide **16** in 41% yield (two steps).

***N*-Methyl,*N*-butyl 9-(3′,17′β-Dihydroxy-1′,3′,5′(10′)-estratrien-16′β-yl) Nonamide (16).** White solid. IR (film): 3320 (OH), 1614 (C=O, amide). ^{1}H NMR (300 MHz, $CDCl_3$): 0.76 (s, 18′-CH_3), 0.93 (m, $(CH_2)_3CH_3$), 2.30 (m, CH_2COO), 2.81 (m, 6′-CH_2), 2.91 and 2.97 (2s, NCH_3), 3.25 and 3.36 (2t, J = 7.5 Hz, NCH_2), 3.73 (dd, J_1 = 7.5 Hz and J_2 = 9.8 Hz, 17′α-CH), 6.57 (d, J = 2.7 Hz, 4′-CH), 6.63 (dd, J_1 = 2.7 Hz and J_2 = 8.3 Hz, 2′-CH), 7.15 (d, J = 8.4 Hz, 1′-CH). ^{13}C NMR (75 MHz, $CDCl_3$): 12.38, 13.86, 19.97 (20.08), 25.13, 25.50, 26.31, 27.41, 28.61, 29.43 (30.66), 29.48, 29.64, 29.80, 31.44, 32.41, 33.02, 33.68, 33.37 (35.40), 37.72, 38.34, 39.99, 44.00, 44.13, 47.45-(49.80), 48.57, 82.52, 112.64, 115.21, 126.47, 132.66, 138.23, 153.44, 173.10. HRMS: calcd for $C_{32}H_{52}NO_3$ $[M + H]^+$ 498.39417, found 498.39549. HPLC purity of 91%.

Enzymatic Assay (Inhibition of Type 1 17β-HSD). Human embryonic kidney (HEK)-293 cells transfected with type 1 17β-HSD cDNA fragment were kindly provided by Dr. Van Luu-The.[33] Heat shock was performed in 50 mM sodium phosphate buffer (pH 7.4), containing 20% glycerol and 1 mM EDTA to obtain cellular fragmentation (−80 to 37 °C, three times, 5 min). The cytosol fraction containing the enzyme was isolated as the supernatant after centrifugation (100 000*g*, 5 min, 4 °C). The enzymatic reaction was performed at 37 °C for 2 h in 1 mL of a solution that included 780 μL of 50 mM sodium phosphate buffer (pH 7.4, 20% glycerol, and 1 mM EDTA), 100 μL of 10 mM NADH in phosphate buffer, 10 μL of approximately 10 μM of [^{14}C]-estrone in ethanol (59.6 mCi/mmol, Dupont NEN Products, Boston), 10 μL of the indicated inhibitor dissolved in ethanol, and 100 μL of diluted enzymatic source in phosphate buffer. Afterward, radiolabeled steroids were extracted twice from the reaction mixture by 2 mL of diethyl ethyl, and solvent was evaporated to dryness. Steroids were dissolved in 50 μL of CH_2Cl_2 and applied on 0.20 mm TLC plates (Kieselgel 60 F 254). Plates were developed in a mixture of toluene/acetone (4:1). Radioactivity signals were detected and quantified using a PhosphoImager (Sunny Vale, CA). The percentage of transformation of [^{14}C]-E_1 into [^{14}C]-E_2 was calculated as follows: % transf. = 100 × ([[^{14}C]-E_2]/([[^{14}C]-E_1] + [[^{14}C]-E_2])), and subsequently, % inh. = 100 × (% transf. of control − % transf. of compound)/(% transf. of control). The IC_{50} values were calculated using an unweighted iterative least-squares method for four-parameters logistic curve fitting (DE_{50} program, CHUL Research Center, Québec, Canada).

Acknowledgment. This work was supported by a Collaborative Project Grant from the Natural Sciences

and Engineering Research Council of Canada (NSERC). We thank the Oncology and Molecular Endocrinology Research Center for providing chemical and biological facilities. We are grateful to Dr. Van Luu-The for judicious advice regarding the enzymatic assay and for providing HEK-293 cells overexpressing type 1 17β-HSD. We also thank Ms. Sylvie Méthot for careful revision of the manuscript.

Supporting Information Available: Inhibition curves obtained with inhibitors **1**−**10** and unlabeled E_1 (Figures 6−8), ^{13}C NMR signal assignment of estradiol−adenosine hybrids **2**−**10** (Table 2), and data on the purity of tested compounds **2**−**16** and **80** (Table 3, HPLC chromatograms, and ^1H NMR spectra). This material is available free of charge via the Internet at http://pubs.acs.org.

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JM058235E