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Structure−Activity Relationships of C-17-Substituted Estratriene-3-*O*-sulfamates as Anticancer Agents

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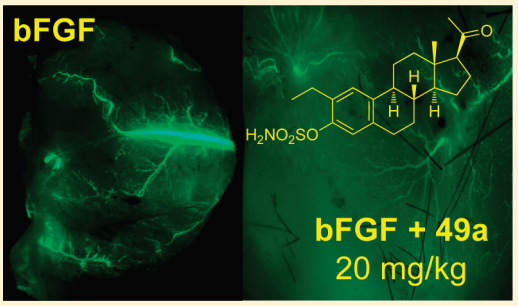
Supporting Information

ABSTRACT: The synthesis and antiproliferative activities of analogues of 2-substituted estradiol-3,17-*O*,*O*-bis-sulfamates (E2bisMATEs) are discussed. Modifications of the C-17 substituent confirm that an H-bond acceptor is essential for high activity; its optimal linkage to C-17 and the local environment in which it resides are defined. In the non-sulfamoylated series 17β-acyl substitution delivers **48b**, the most potent compound identified to date. In the sulfamate series a number of permutations of linker and H-bond acceptor deliver excellent activity, with **55**, **61**, **65**, **49a**, and **49b** proving especially promising. The in vivo potential of these compounds was explored in the NCI hollow fiber assay and also in a mouse Matrigel model of antiangiogenesis in which **49** and **55** show significant inhibitory activity.



INTRODUCTION

The hypothesis that inhibition of angiogenesis, by blocking blood vessel formation and thus the blood supply required to support the growth of solid tumors, might constitute a new strategy for the treatment of cancer was made four decades ago.[1] Recently, a number of drugs disrupting tumor vasculature by targeting vascular endothelial growth factor (VEGF), like the monoclonal antibody bevacizumab[2] and the small molecule vascular endothelial growth factor receptor (VEGFR) inhibitors sorafenib[3] and sunitinib,[4] have gained approval for the treatment of cancer, including various combinations with other anticancer agents.[5] Clinical studies have shown that the success of anti-VEGF therapy is highly dependent on cancer phenotype and clinical history. Through eradicating excess systemic VEGF, bevacizumab treatment initially effects a maturation of the tumor vasculature; this allows for an enhanced delivery of cytotoxic agent to the tumor and, consequently, improved efficacy relative to single agent cytotoxic therapy.[6] However, tumors are able to circumvent blockage of VEGF signaling by, for example, switching to fibroblast growth factor (FGF) to sustain their blood vessel formation:[7] anti-VEGF therapy also results in considerable side effects, and periodic dosing regimes are required to avoid dose limiting toxicity. As a result, rapid tumor regrowth is often observed in the off-dose periods in these regimes after initial tumor regression. In preclinical models there are indications that anti-VEGF therapy may generate more aggressive disease; inhibition of angiogenesis with sunitinib, for example, has been correlated with increased tumor metastasis and decreased overall survival in mice.[8] Nevertheless, the promising results obtained by combining antiangiogenic agents with other anticancer agents encourage studies into compounds that combine an antiangiogenic effect with a second antitumor activity.[5,9] Furthermore, there is considerable interest in the development of agents that cause a disruption of tumor vasculature through alternative, non-VEGF based mechanisms.

In previous studies, we detailed the discovery of a number of sulfamoylated 2-substituted estratriene derivatives that, like the endogenous estrogen metabolite 2-methoxyestradiol **1** (2-MeOE2), inhibit cancer cell proliferation and angiogenesis. 2-Substituted-estradiol-3,17-*O*,*O*-bis-sulfamates **3** (2-MeOE2bisMATE) and **4** (2-EtE2bisMATE),[10] and the 2-substituted-estradiol-3-*O*-sulfamates **5** (2-MeOE2MATE) and **6** (2-EtE2MATE)[11] (Figure 1) are differentiated from **1** by their enhanced biological activities and superior druglike properties. The excellent oral bioavailability of **3** (>85% in rodents),[12] for example, appears to derive from the ability of a sulfamate group both to block inactivating metabolism and deactivating conjugation, while also allowing the molecule to interact reversibly with carbonic anhydrase.[12,13] This latter reversible interaction, which has been characterized by protein crystallography, may minimize first pass liver metabolism through sequestration of the sulfamate drugs in red blood cells.[14] Moreover, as with other aryl sulfamates, **3**−**6** are irreversible inhibitors of steroid sulfatase (STS), itself a target for the treatment of hormone dependent cancer.[15] Although a full mechanistic picture for the activity of these compounds

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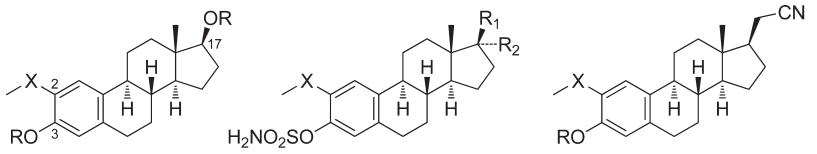


1 X = O, R = H
2 X = CH_2, R= H
3 X = O, R = SO_2NH_2
4 X = CH_2, R = SO_2NH_2
5 X = O, R_1 = OH, R_2 = H
6 X = CH_2, R_1 = OH, R_2 = H
7 X = O, R_1 = R_2 = O
8 X = CH_2, R_1 = R_2 = O
9 X = O, R = H
10 X = CH_2, R = H
11 X = O, R = SO_2NH_2
12 X = CH_2, R = SO_2NH_2

Figure 1. Structures of 2-methoxyestradiol **1**, 2-ethylestradiol **2**, 2-methoxyestradiol-3,17-*O*,*O*-bis-sulfamate **3**, 2-ethylestradiol-3,17-*O*,*O*-bis-sulfamate **4**, 2-methoxyestradiol-3-*O*-sulfamate **5**, 2-ethylestradiol-3-*O*-sulfamate **6**, 2-methoxyestrone-3-*O*-sulfamate **7**, 2-ethylestrone-3-*O*-sulfamate **8**, 2-methoxy-3-hydroxy-17β-cyanomethyl-1,3,5(10)-estratriene **9**, 2-ethyl-3-hydroxy-17β-cyanomethylestra-1,3,5(10)-triene **10**, 2-methoxy-3-*O*-sulfamoyl-17β-cyanomethylestra-1,3,5(10)-triene **11**, 2-ethyl-3-*O*-sulfamoyl-17β-cyanomethylestra-1,3,5(10)-triene **12**.

continues to emerge, it was recently shown that their ability to disrupt the tubulin−microtubule equilibrium in cells is critical for their antitumor activity.[16] It is also important to note, first, that these compounds are not substrates for the P-glycoprotein pump and are thus active against taxane-resistant tumors[17] and, second, that their activity is independent of the estrogen receptor even though they are estrogen derivatives.[18]

The A-ring modified estrogen-3-*O*-sulfamates were initially synthesized with the goal of obtaining potent nonestrogenic, STS inhibitors.[19] It was subsequently discovered that 2-methoxyestrone-3-*O*-sulfamate **7** (2-MeOEMATE) and 2-ethylestrone-3-*O*-sulfamate **8** (2-EtEMATE) (Figure 1) also exhibited an antiproliferative effect against a range of estrogen-independent human cancer cells in vitro.[20] SAR studies on the A-ring estrogen-3-*O*-sulfamates demonstrated that optimal antiproliferative activity is obtained with a 2-methoxy, 2-ethyl, or 2-methylsulfanyl group.[11,21] Further SAR studies focused on D-ring modifications, principally at the C-17 position of the estratriene skeleton. A number of modifications were explored, including variation of the oxidation level of C-17 and substitution at this position. While 17β-hydroxy, 17-keto, and 17-oximino derivatives show similar antiproliferative activity, the 17-deoxy and 17α-benzyl analogues are considerably less active.[22] Sulfamoylation of the 17β-hydroxy group gave the bis-sulfamates **3** and **4** that exhibit slightly enhanced in vitro activity and greatly improved in vivo antitumor effects.[10] It was recently established that deletion or substitution of the C-17-oxygen linker of the 17-*O*-sulfamate group with an electronically neutral methylene group and replacement of the sulfamate's terminal NH_2 with methyl are well tolerated.[16] In addition, an SAR study of C-17 cyanated analogues revealed that 2-methoxy-3-*O*-sulfamoyl-17β-cyanomethylestra-1,3,5(10)-triene **11** and the corresponding 2-ethyl compound **12** offer further enhanced antiproliferative and antiangiogenic activities relative to **3** and **4**.[23] We have also shown that a high level of antiproliferative activity can be retained when a heterocycle possessing a well exposed H-bond acceptor is installed at C-17.[24] All data accrued to date indicate that optimal in vitro activity results from three key pharmacophore elements, namely, the C-2 XMe group (X = O, CH_2 or S), the 3-*O*-sulfamate, and an H-bond acceptor around the C-17 position. Translation of in vitro activities into the in vivo environment is somewhat more complex. For example, when evaluated for activity against the growth of MDA-MB-231 xenografts in female nude athymic mice, **11** proved to be less active than the corresponding bis-sulfamate **3**, despite being 4-fold more potent in vitro. This difference in in vitro and in vivo activities observed for **3** and **11** is dependent on their respective oral bioavailability,

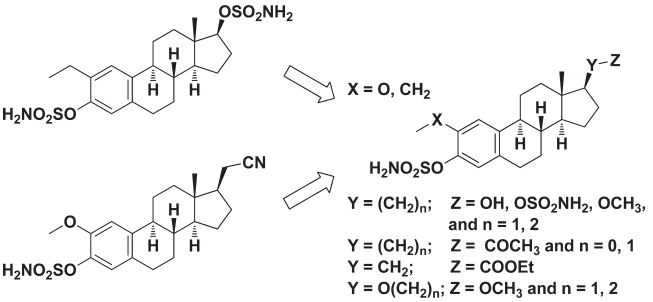
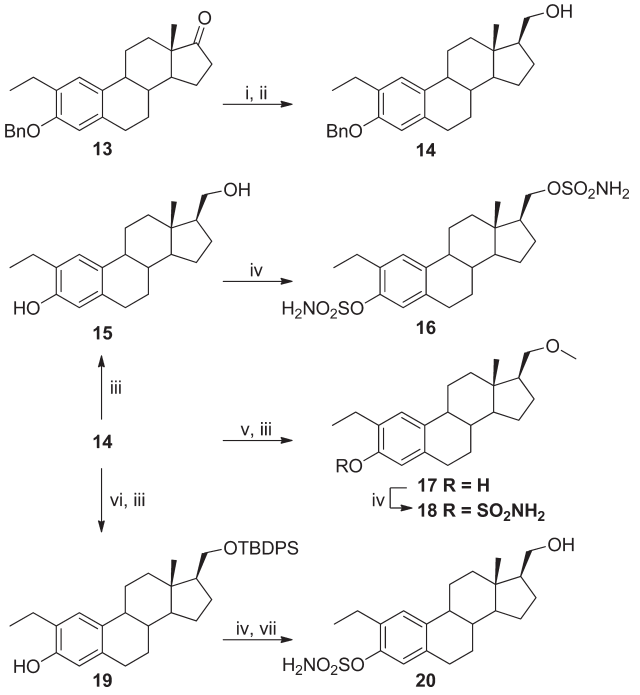


Figure 2. Proposed modifications at C-17 of the 2-substituted estratriene nucleus.

Scheme 1. Synthesis of 17-Hydroxy- and Alkoxymethyl Derivatives[a]



[a] Reagents and conditions: (i) Mg, $TiCl_4$, DCM, THF, 0 °C; (ii) 9-BBN, THF, 0 °C, then 37% H_2O_2, 10% NaOH, 0 °C; (iii) H_2, Pd/C, THF, MeOH, room temp; (iv) H_2NSO_2Cl, DMA, room temp; (v) NaH, MeI, THF, reflux; (vi) TBDPSCl, imidazole, DMF, room temp; (vii) TBAF, THF, room temp.

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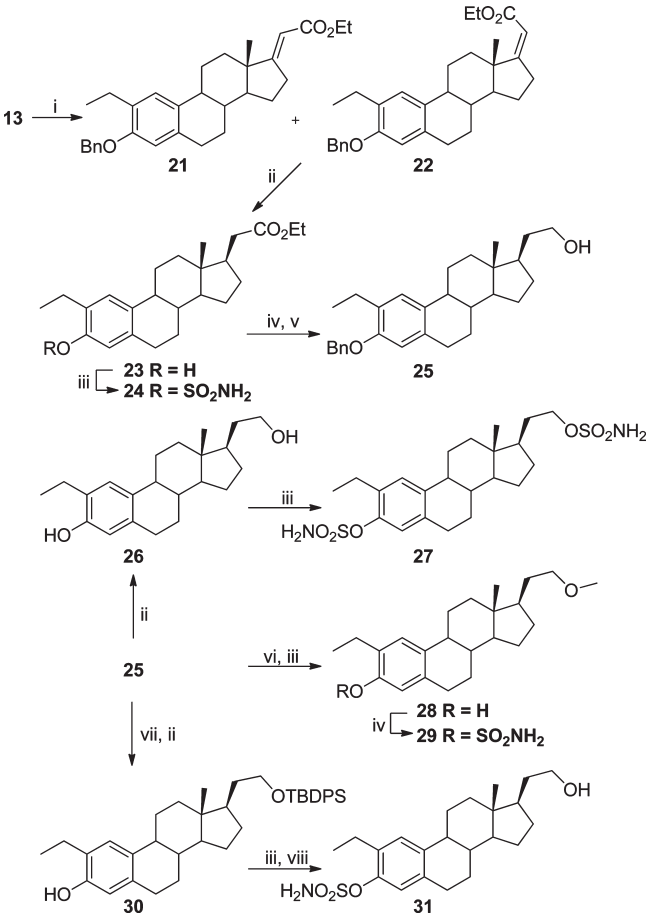
Scheme 2. Synthesis of C-17 Ethyl Derivatives[a]



[a] Reagents and conditions: (i) $(EtO)_2POCH_2CO_2Et$, NaH, THF, reflux; (ii) H_2, Pd/C, THF/MeOH, room temp; (iii) H_2NSO_2Cl, DMA, room temp; (iv) BnBr, K_2CO_3, DMF, room temp; (v) $LiAlH_4$, THF, 0 °C; (vi) MeI, NaH, THF, room temp; (vii) TBDPSCl, imidazole, DMF, room temp; (viii) TBAF, THF, 0 °C.

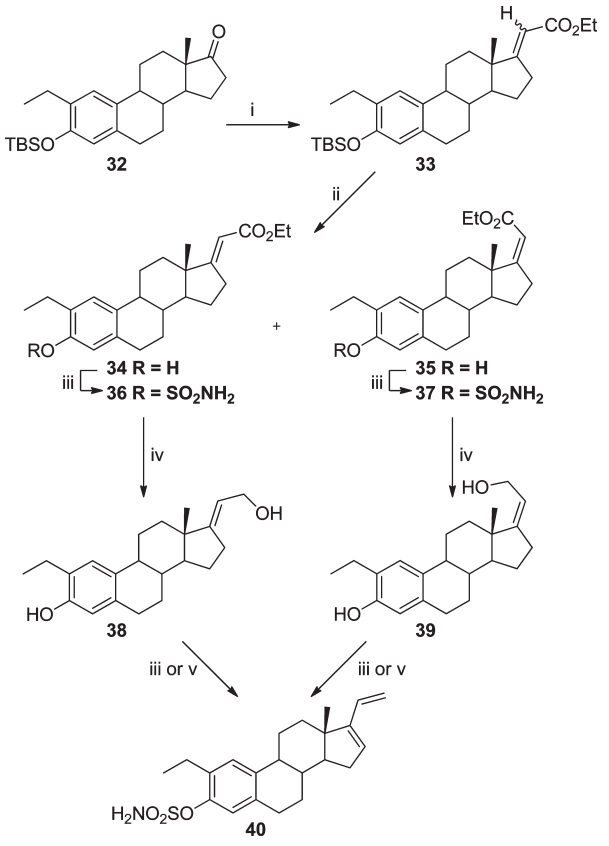
itself a function of their uptake, transport, metabolism, conjugation, and clearance profiles.

In light of these results, we set out to examine whether further C-17 modifications could deliver improvements in both in vitro and, more importantly, in vivo activity and thus embarked on more extensively defining the SAR of this series by synthesizing C-17 modified 2-methoxyestratriene-3-*O*-sulfamates and 2-ethylestratriene-3-*O*-sulfamates projecting an oxygen-containing H-bond acceptor ("Z", see Figure 2) around C-17. The linker "Y" between the estratriene ring system and the H-bond acceptor group was varied in length in order to map onto the region of space occupied by the SO_2 group of the bisMATES **3** and **4** and that of the cyano group of **11** and **12**. We describe here our synthetic approaches to these compounds together with their in vitro biological activities as antiproliferative agents and in vivo data for two selected compounds.

RESULTS AND DISCUSSION

Chemistry. Previous SAR studies on 2-substituted estratriene-3-*O*-sulfamates indicated that an H-bond acceptor around C-17 is required for optimal antiproliferative activity and microtubule

Scheme 3. Synthesis of Various C-17 Olefin Derivatives[a]



[a] Reagents and conditions: (i) $(EtO)_2POCH_2CO_2Et$, NaH, THF, reflux; (ii) TBAF, THF, 0 °C; (iii) H_2NSO_2Cl, DMA, room temp; (iv) DIBAL-H, THF, −78 to 0 °C; (v) H_2NSO_2Cl, 2,6-di-*tert*-butyl-4-methylpyridine, toluene, DCM, room temp.

disruption.[10,11,16,22−25] Aiming to further refine the series, we set out to tether various oxygen-containing H-bond acceptor functions (e.g., OH, OSO_2NH_2, OMe, and $COCH_3$) to C-17 of the estratriene nucleus through short linkers. 2-Ethyl-17β-hydroxymethyl-3-*O*-benzylestra-1,3,5(10)-triene **14** serves as a common intermediate for the synthesis of the 17β-sulfamoyloxy **16**, 17β-methoxymethyl **18**, and the 17β-hydroxymethyl derivatives **20** (Scheme 1). Methylenation of 2-ethyl-3-*O*-benzylestrone **13**[26] followed by a stereoselective hydroboration using 9-BBN yielded **14**. Hydrogenolysis of **14** delivered phenol **15** which was then treated with sulfamoyl chloride to give the bis-sulfamate derivative **16**.[27] Alkylation of **14** with methyl iodide and subsequent hydrogenolysis afforded the 17β-methoxymethylphenol **17** which was then converted to sulfamate **18**. Access to compound **20** first required a sequence of silyl protection of the aliphatic alcohol and debenzylation. This was found to be best achieved with *tert*-butyldiphenylsilyl chloride as silylating agent, as other silyl protecting groups like the TBS and TIPS group proved less stable to the following hydrogenolysis. Phenol **19** was then successively sulfamoylated and desilylated to give the desired sulfamate **20**.

A similar synthetic approach was applied to prepare a series of ether, sulfamate, and hydroxy derivatives incorporating a two-carbon linker to C-17 (Scheme 2). Horner−Wadsworth−Emmons olefination of 2-ethyl-3-*O*-benzylestrone **13** with triethyl phosphonoacetate afforded a 5:1 mixture of olefins **21** and **22** that were

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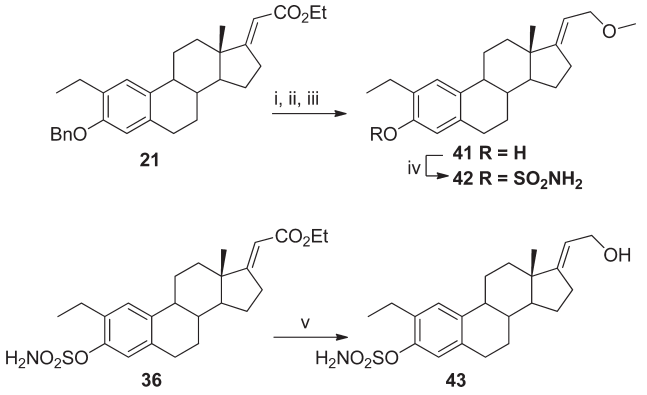
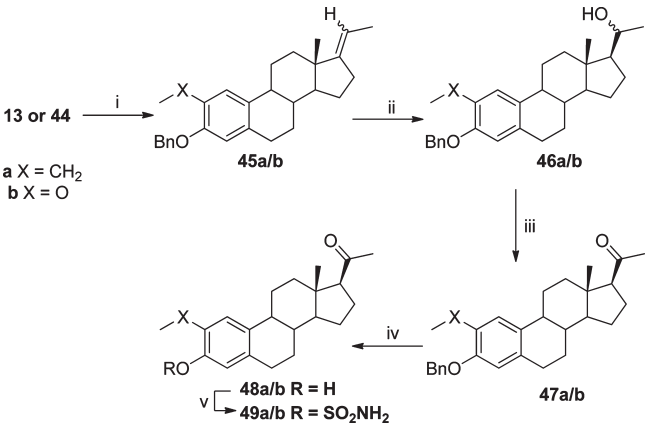
Scheme 4. Synthesis of C-17 Tethered Alkoxy and Hydroxy Derivatives[a]



[a] Reagents and conditions: (i) $LiAlH_4$, THF, 0 °C; (ii) CH_3I, NaH, THF, room temp; (iii) Na, *t*-BuOH, reflux; (iv) H_2NSO_2Cl, DMA, room temp; (v) DIBAL-H, THF, −78 to 0 °C.

Scheme 5. Synthesis of 17β-Acyl Derivatives[a]

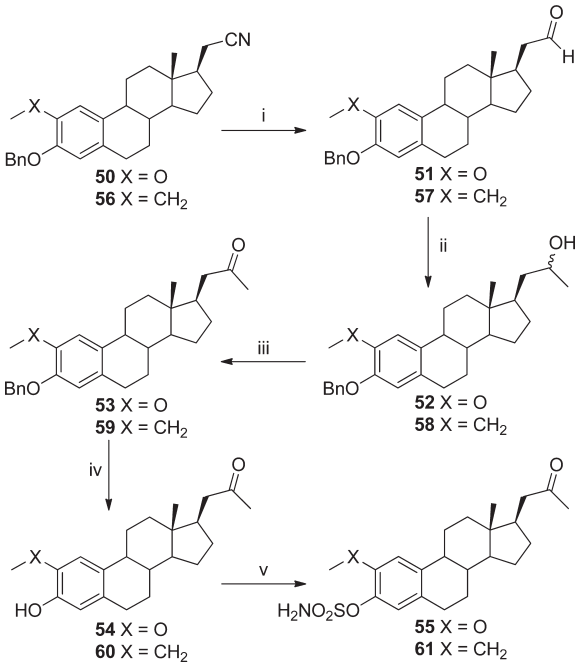


[a] Reagents and conditions: (i) $EtPPh_3I$, NaH, DMSO, 100 °C; (ii) BH_3−THF, THF, 0 °C, then NaOH 30%, H_2O_2, 37%; (iii) Dess−Martin periodinane, DCM; (iv) H_2, Pd/C, THF, MeOH; (v) H_2NSO_2Cl, DMA, room temp.

separable by column chromatography. Concomitant debenzylation and olefin reduction over Pd/C afforded ester **23**. Sulfamoylation of **23** afforded sulfamate **24**. Benzyl reprotection of **23** followed by reduction with $LiAlH_4$ afforded 2-ethyl-17β-(2-hydroxyethyl)-3-*O*-benzylestra-1,3,5(10)-triene **25** that was converted to **27**, **29**, and **31** in a manner analogous to that described for **16**, **18**, and **20** above.

In order to prepare the C-17-C-20 olefinic analogues of **27** and thus explore the effects of the reduced rotational freedom of such compounds on biological activity, 2-ethyl-3-*O*-(*tert*-butyldimethylsilyl)estrone **32** was treated with triethyl phosphonoacetate to give **33** as a mixture of its *E* and *Z* isomers in excellent yield (Scheme 3). Desilylation of **33** afforded phenols **34** and **35** that were separated by flash column chromatography. Each phenol was reacted with sulfamoyl chloride to afford sulfamates **36** and **37**, respectively. Upon reduction with DIBAL-H, **34** and **35** afforded the corresponding alcohols **38** and **39**. Attempts to sulfamoylate both hydroxyl groups with sulfamoyl chloride in DMA[26] or 2,6-di-*tert*-butyl-4-methylpyridine in DCM proved unsuccessful in this case with 17-vinyl-2-ethyl-3-*O*-sulfamoylestra-1,3,5(10),16-tetraene **40**

Scheme 6. Synthesis of C-17 2-Hydroxypropyl and 2-Oxopropyl Derivatives[a]



[a] Reagents and conditions: (i) DIBAL-H, THF, 0 °C to room temp; (ii) MeMgBr, THF, 0 °C; (iii) Dess−Martin periodinane, DCM, 0 °C to room temp; (iv) H_2, Pd/C, THF, MeOH, room temp; (v) H_2NSO_2Cl, DMA, room temp.

being obtained as the sole product. Presumably, the vinyl sulfamate formed in the reaction is unstable to elimination under the reaction conditions.

2-Ethyl-17-(*E*)-(2-methoxyethylidene)-3-*O*-sulfamoylestra-1,3,5(10)-triene **41** was accessed from ester **21** (Scheme 4). Reduction of **21** with $LiAlH_4$ delivered the vinyl alcohol that was methylated and debenzylated to afford phenol **41**. Sulfamoylation of **41** under standard conditions gave **42**. The sulfamoylated ester **36** was reduced with DIBAL-H to afford the 17-(*E*)-hydroxyethylidene derivative **43**.

As mentioned above, the 17β-cyanomethylestra-1,3,5(10)-triene-3-*O*-sulfamates **8** and **9** are particularly potent antiproliferative agents in vitro. We therefore investigated isosteric replacement of the cyano group with a ketone and thus targeted C-17 acylestra-1,3,5(10)-triene-3-*O*-sulfamates **49a** and **49b**. A Wittig reaction between **13** and ethyltriphenylphosphonium iodide in DMSO furnished olefin **45a** as a mixture of *E* and *Z* isomers (Scheme 5). Hydroboration with borane THF afforded the C-17β-isomer of the alcohol **46a** along with a trace amount of the corresponding 17α-isomer which could be removed by chromatography; attempts to achieve complete selectivity with 9-BBN proved unsuccessful in this case. Dess−Martin oxidation afforded compound **47a**, which was converted to the phenol **48a** and sulfamate **49a** under standard conditions. The same set of reactions was also carried out with 2-methoxy-3-*O*-benzylestrone **44** to afford the 2-methoxy analogues **48b** and **49b** for biological evaluation.

Projection of the carbonyl group further from C-17 requires a two-carbon linker, and the 17β-(2-oxopropyl) derivatives **55** and **61** were thus elaborated (Scheme 6). The 17β-cyanomethyl compound **50** was prepared in analogy to the method described

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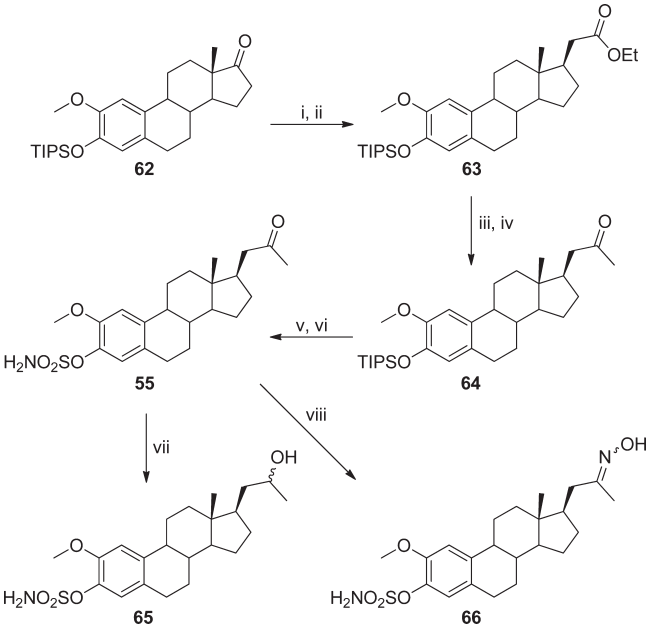
Scheme 7. Improved Approach to 17-(2-Oxopropyl) estratriene Derivatives[a]



[a] Reagents and conditions: (i) $(EtO)_2POCH_2CO_2Et$, NaH, THF, reflux; (ii) H_2, Pd/C, THF, MeOH, room temp; (iii) Tebbe reagent, pyridine, THF, toluene, −78 to 0 °C; (iv) 2 M HCl, room temp; (v) TBAF, THF, room temp; (vi) H_2NSO_2Cl, DMA, room temp; (vii) $NaBH_4$, *i*-PrOH, THF, room temp; (viii) $H_2NOH \cdot HCl$, NaOAc, $MeOH/H_2O$, room temp.

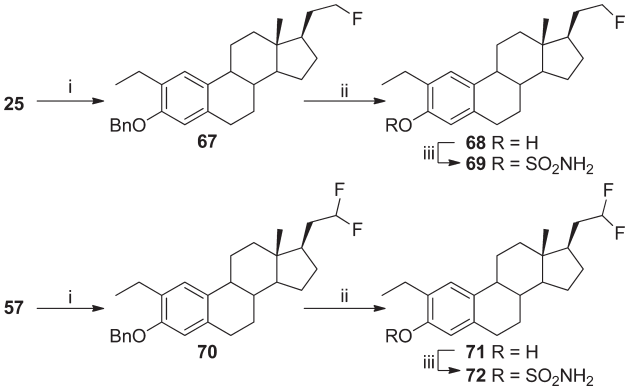
earlier for the synthesis of **56**.[23] A DIBAL-H reduction of **50** then delivered aldehyde **51** in good yield. **51** was reacted with methylmagnesium bromide to afford the secondary alcohol **52** that was then oxidized to ketone **53** with Dess−Martin periodinane. Hydrogenolysis of **53** and subsequent sulfamoylation delivered phenol **54** and sulfamate **55** derivatives. 2-Ethyl-3-*O*-benzyl-17β-cyanomethylestra-1,3,5(10)-triene **56** was transformed to compounds **57**−**61** under analogous conditions.

A shorter and higher yielding route to **55** was later developed (Scheme 7). 2-Methoxy-3-*O*-triisopropylsilyloxyestrone **62** was converted to the ester **63** by sequential Horner−Wadsworth−Emmons olefination and hydrogenation as described above for the synthesis of **23**. A Tebbe methylenation[28] followed by acidic hydrolysis of the intermediate enol ether then delivered ketone **64** in excellent yield. Deprotection of **64** and subsequent sulfamoylation furnished sulfamate **55** in 61% overall yield starting from 2-methoxyestrone. Reduction of **55** with $NaBH_4$ afforded 17β-(2-hydroxypropyl) derivative **65**, while reaction of **55** with hydroxylamine delivered oxime **66**.

We also wished to assess the antiproliferative activity of C-17 fluorinated analogues of sulfamates **31**, **55**, and **61**, since fluorine has long proven to be a successful bioisostere of the hydroxyl in various contexts.[29] We therefore treated compound **25** with DAST to afford **67** that, after successive debenzylation and sulfamoylation, gave access to phenol **68** and sulfamate **69**, respectively (Scheme 8). Similarly, aldehyde **57** could be transformed into the difluoro compounds **70**−**72**.

Biology. To assess their potential as anticancer agents, the series of novel 2-ethyl- and 2-methoxyestratriene derivatives was evaluated for antiproliferative activity against DU-145 (androgen

Scheme 8. Synthesis of 17-(Fluoroethyl)estratriene Derivatives[a]



[a] Reagents and conditions: (i) DAST, THF, 0 °C; (ii) H_2, Pd/C, THF, MeOH, room temp; (iii) H_2NSO_2Cl, DMA, room temp.

receptor negative) prostate cancer cells and MDA-MB-231 (estrogen receptor negative) and MCF-7 (estrogen receptor positive) breast cancer cells in vitro. The results of these assays and comparative data for benchmark compounds **1**−**9** are presented in Table 1.

The bis-sulfamates **3** and **4** (Figure 1) are promising multitargeted antitumor agents that exhibit excellent activity against cancer cell proliferation and angiogenesis in tandem with their high oral bioavailability.[10,12,30] An SAR study on this class of 2-substituted estratriene sulfamates led to the discovery of **11** and **12** and indicated that a sterically unhindered hydrogen bond acceptor attached to C-17 is essential for activity.[23] This finding was confirmed in a further SAR study wherein a systematic substitution or deletion of the constituent atoms the C-17 *O*-sulfamate group, deletion or substitution of the C-17-oxygen linker with an electronically neutral methylene group, and/or replacement of the terminal NH_2 with a methyl group is well tolerated.[16]

As can be seen from data presented in Table 1, activities of the compounds across all three cell lines are generally comparable in magnitude and trend; thus, for clarity, data for antiproliferative activity against DU-145 cells are discussed herein when possible. In agreement with our foregoing studies, the 3-hydroxy derivatives generally exhibit only modest activity when compared with the corresponding 3-*O*-sulfamoyl derivatives. However, a number of functional groups at C-17 are found to confer greater antiproliferative activity than the 17β-hydroxyl of the estradiol derivatives (e.g., 2-MeOE2 **1**). For example, insertion of a two-carbon linker between the hydroxyl group and C-17 (in **26**, **38**, and **39**) delivers a 4- to 15-fold enhancement in antiproliferative activity relative to the parent estradiol derivative **2**. This observation reflects that made for 2-substituted estradiol derivatives **1** and **2** and their 17β-cyanomethyl analogues **9** and **10**,[23] respectively, wherein a two-carbon linker also separates C-17 and the hydrogen bond acceptor. In contrast **16**, which features a one-carbon linker between the H-bond acceptor and C-17, is only equipotent to its parent estradiol derivative **2**, in DU-145 cells. Interestingly, the C-17-(2-fluoroethyl) derivative **68** displays similar activity to the C-17-(2-hydroxyethyl) derivative **26** (albeit the compounds were assessed in different cell lines), indicating that the fluorine is a reasonable bioisostere of hydroxyl in this case. Furthermore, the relative activities of **68** and **71** show

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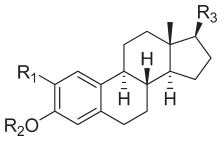
Table 1. Antiproliferative Activities of 2-Ethyl and 2-Methoxyestratriene Derivatives against DU-145, MDA-MB-231, and MCF-7 Human Cancer Cells in Vitro[a]



				GI$_{50}$ (μM)		
					MDA	
compd	R_1	R_2	R_3	DU-145	MB-231	MCF-7
1	MeO	H	OH	1.22	0.94	2.35
2	Et	H	OH	10.3	8.0	10.5
3	MeO	SO_2NH_2	OSO_2NH_2	0.34	0.28	0.25
4	Et	SO_2NH_2	OSO_2NH_2	0.21	0.21	0.07
9	MeO	H	CH_2CN	0.49	0.12	0.30
10	Et	H	CH_2CN	2.5		>100
11	MeO	SO_2NH_2	CH_2CN	0.062	0.071	0.07
12	Et	SO_2NH_2	CH_2CN	0.054	0.141	0.06
15	Et	H	CH_2OH	10.1	6.3	
16	Et	SO_2NH_2	$CH_2OSO_2NH_2$	0.29	0.43	
17	Et	H	CH_2OCH_3	25.3	9.2	
18	Et	SO_2NH_2	CH_2OCH_3	0.33	0.53	
20	Et	SO_2NH_2	CH_2OH	0.10	0.11	
23	Et	H	CH_2CO_2Et			26.4
24	Et	SO_2NH_2	CH_2CO_2Et			4.19
26	Et	H	CH_2CH_2OH			2.52
27	Et	SO_2NH_2	$CH_2CH_2OSO_2NH_2$			5.64
28	Et	H	$CH_2CH_2OCH_3$			24.8
29	Et	SO_2NH_2	$CH_2CH_2OCH_3$	3.4		
31	Et	SO_2NH_2	CH_2CH_2OH			<0.5
34	Et	H	(*E*)-$CHCO_2Et$			30.6
35	Et	H	(*Z*)-$CHCO_2Et$			31.1
36	Et	SO_2NH_2	(E)-$CHCO_2Et$			1.85
38	Et	H	(*E*)-$CHCH_2OH$			0.77
39	Et	H	(*Z*)-$CHCH_2OH$			0.67
41	Et	H	(*E*)-$CHCH_2OCH_3$			>10
43	Et	SO_2NH_2	(*E*)-$CHCH_2OCH_3$			10
48a	Et	H	$COCH_3$	2.0		
49a	Et	SO_2NH_2	$COCH_3$	0.062	0.019	0.026
48b	MeO	H	$COCH_3$	0.30	0.39	
49b	MeO	SO_2NH_2	$COCH_3$	0.046	0.048	
54	MeO	H	CH_2COCH_3	2.4		
55	MeO	SO_2NH_2	CH_2COCH_3	0.089	0.068	<0.005
60	Et	H	CH_2COCH_3	18.9		5.79
61	Et	SO_2NH_2	CH_2COCH_3	0.16	0.18	0.32
65	MeO	SO_2NH_2	$CH_2CH(OH)CH_3$	0.14	0.14	
66	MeO	SO_2NH_2	$CH_2C{=}N(OH)CH_3$	2.09	2.35	
68	Et	H	CH_2CH_2F	3.4		
69	Et	SO_2NH_2	CH_2CH_2F	0.78		
71	Et	H	CH_2CHF_2	60		
72	Et	SO_2NH_2	CH_2CHF_2	1.81		

[a] Data for compounds **1**−**12** are taken from the literature.[14,23,27] GI$_{50}$ values are the mean values obtained from experiments performed in triplicate; SEM, ±7%.

the monofluoro derivative to be superior to the difluoro analogue.

In the case where the hydrogen bond acceptor is a ketone, a one-carbon linker proved optimal (cf. **48a** and **48b** with **60**

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Table 2. GI_{50} and MGM Obtained for Representative Cell Lines in the NCI-60 Screening Panel[a]

	GI_{50} (μM)						
	lung	colon	CNS	melanoma	ovarian	renal	
compd	HOP-62	HCT-116	SF-539	UACC-62	OVCAR-3	SN12-C	MGM (μM)
1	0.7	0.47	0.32	0.36	0.21	0.95	1.3
3	0.051	0.045	0.036	<0.01	<0.01	0.126	0.087
4	<0.01	nd	<0.01	<0.01	<0.01	0.028	0.018
16	0.061	0.038	0.056	0.022	0.019	0.309	0.085
18	0.045	0.022	<0.01	nd	<0.01	0.072	0.042
20	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0.018
24	0.59	0.35	0.22	0.45	0.22	0.63	0.52
29	4.90	2.70	5.01	2.34	4.07	4.68	4.57
31	0.25	0.27	0.35	2.89	11.48	2.45	1.73
43	0.42	0.27	0.22	0.47	0.23	0.58	0.49
49a	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0.015
55	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0.021
65	0.048	0.025	0.023	<0.01	<0.01	0.052	0.028
69	3.72	3.39	5.25	3.89	22.9	7.59	6.31
72	3.89	2.82	1.95	4.90	3.47	5.37	3.09

[a] Results are GI_{50} values in micromolar. Data for compounds **1**−**4** are taken from the literature.[14,21,30] The MGM represents the mean concentration that caused 50% growth inhibition in all 60 cell lines.

and **54**, respectively). The 2-methoxy-17β-acylestratriene derivative **48b** exhibits the best antiproliferative activity of any 3-hydroxy 2-substituted estratriene to our knowledge with a GI_{50} of 300 nM against DU-145 cells, 4-fold better than the activity of 2-MeOE2 **1** and over 30-fold better than 2-MeOE1, which has GI_{50} > 10 μM against this cell line. Likewise, a 5-fold improvement in activity is seen for the corresponding 2-ethyl compound **48a** relative to 2-ethylestradiol **2**. Ketones **54** and **60** in contrast proved to be 2-fold less active the corresponding estradiol derivatives **1** and **2**. The significant antiproliferative activities of compounds such as **26**, **48a**, and **39**, assuming similar cellular uptake properties, are likely to stem from the ability of their C-17 tethered H-bond acceptor groups (CN, OH, C═O) to project into a very specific area of space around C-17 favorable for optimum interaction in the colchicine binding site of tubulin where these compounds are believed to bind. These results suggest that such an interaction is accessible when a one- or two-carbon linker is inserted between C-17 and the H-bond acceptor.

When considering the activities of the 3-*O*-sulfamate derivatives, it is useful to first consider the effect of variation of the linker "Y" while the same hydrogen bond acceptor "Z" is kept constant. In the case where Z is a hydroxyl group, both one- and two-carbon linkers "Y" deliver excellent antiproliferative activity (see **20**, **31**, and **65**). This result reflects the essential equipotency of the cyano and hydroxyl groups as H-bond acceptors[31] and also their ability to access the same interactions around C-17 with these linkers. Methylation of the hydroxyl group proves deleterious to activity, and although this is not as pronounced when the linker "Y" is a methyl group (cf. **20** and **18**), a greater than 6-fold reduction in activity is apparent between **29** and **31** when "Y" is an ethyl group. The negative impact of methylation of the hydroxy group on antitumor activity indicates, as observed in earlier studies,[16,23] that steric bulk around the H-bond acceptor is often detrimental to the necessary interaction in the binding site. Likewise when a one-carbon linker is introduced between the sulfamate and C-17, little difference in antiproliferative activity results (cf. **4** 210 nM and **16** 290 nM) while the corresponding analogue **27** featuring a two-carbon linker displays only modest micromolar activity. In the ketone series (Z equals C═O) both one- and two-carbon linkers are well tolerated though. As with the 3-hydroxy derivatives discussed above, the one-carbon linker appears optimal, for example, with **49b** exhibiting a GI_{50} of 62 nM. In general, a longer linker brings unfavorable steric factors into play, as demonstrated by the activities obtained for compounds such as sulfamate **27** and ester **36**.

The present study also allows for a comparison between hydrogen bond acceptors Z with constant linker Y. One series of compound that is instructive to compare is the two-carbon-linked series of ketone **55**, alcohol **65**, oxime **66**, ester **24**, and methyl ether **29**. The ketone **55** and alcohol **65** with their unsubstituted H-bond acceptors display excellent activity, with **55** proving slightly more active in vitro (GI_{50} = 89 nM). In contrast, the larger oxime, ester, and methyl ether display activity in the low micromolar range, once more illustrating the steric restrictions to interaction around C-17. Similarly, with a one-carbon linker, ketone **49a** and alcohol **20** are of equivalent activity (62 and 100 nM, respectively) while the methyl ether **18** (GI_{50} = 330 nM) is less active. Once more, substitution of the hydrogen bond acceptor proved detrimental to activity, albeit here, with a shorter linker, this substitution is better tolerated than in the longer two-carbon-linked series.

A selection of compounds was also tested in the NCI 60-cell line assay (Table 2) which allows the activity across a wide range of cancer types to be assessed. Data from six cell lines are presented along with the mean activity across the whole panel (MGM value). Screening is conducted at concentrations ranging from 10 nM upward, with maximal activity (where a 50% growth inhibition was obtained in all cell lines at 10 nM) being indicated by an MGM value of 10 nM. The data obtained in the assay are consistent with those obtained in the preliminary antiproliferative screens discussed above and confirm the potential of these compounds against a broad range of cancer phenotypes.

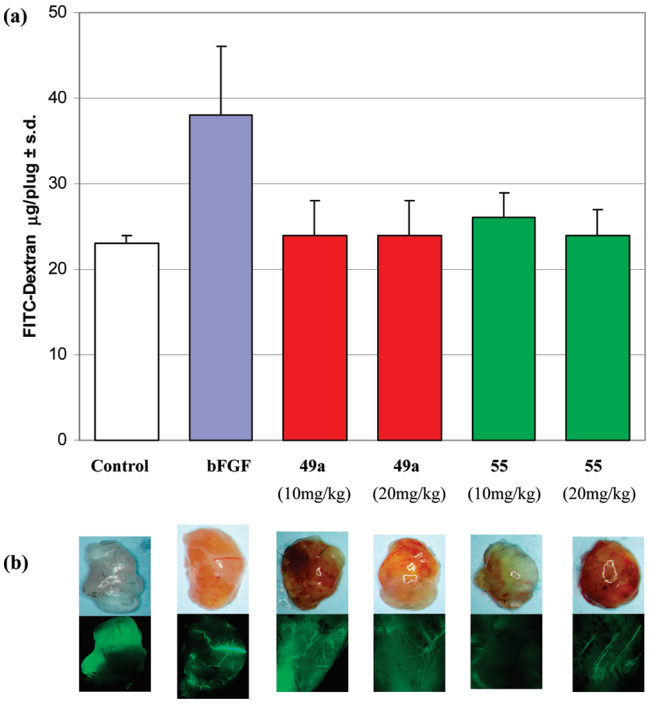

Figure 3. Effect of compounds **49a** and **55** on bFGF induced angiogenesis in Matrigel plugs in mice. Compounds **49a** and **55** were administered orally at the doses indicated for 4 days starting 24 h after Matrigel injection. (a) Quantification of angiogenesis within the Matrigel plugs was achieved after FITC-dextran injection. Compounds **49a** and **55** significantly inhibited FGF-induced angiogenesis at both doses ($p < 0.05$, unpaired t test). (b) Effect of **49a** and **55** on Matrigel plug neovascularization. Normal (upper) and fluorescent (lower) images of excised Matrigel plugs.

A number of compounds proves to be exceptionally active, with six compounds exhibiting an MGM below 100 nM. Of particular note are the C17-hydroxymethyl compound **20**, the ketones **49a** and **55**, and the 2-hydroxypropyl derivative **65**, whose MGM values are all below 30 nM.

On the strength of its in vitro antiproliferative activity **20** was selected for in vivo evaluation at the NCI. Preliminary toxicology showed that the compound is well tolerated by female athymic nude mice at doses up to 400 mg/kg (single ip dose) when formulated in 10% DMSO in saline/Tween 80. Evaluation of **20** in the hollow fiber assay[32] involved assessment of activity against the proliferation of various cancer lines in sealed polyvinylidine fluoride fibers implanted ip or sc. A 50% net cell growth inhibition is awarded a score of 2, and over 48 fibers (12 cell lines × 2 sites × 2 dose levels) a maximum score of 96 is possible. **20** achieved an overall score of 18 with the growth of 25% cells in the ip fibers and 12.5% of the cells in the sc fibers being inhibited by 50% or more. Although this result is promising, a score of 20 or more is required for further NCI development. **20** may potentially suffer inactivating conjugation or metabolism of the C-17 group in vivo, both of which are known issues for the 2-substituted estradiol series.[12,13b] Interestingly, the net score of **20** in this system is equal to that achieved by 2-ethylestrone-3-*O*-sulfamate.[11]

A second evaluation of this class of molecule in vivo was carried out for the ketone derivatives **49a** and **55**. The in vivo antiangiogenic activity of compounds **49a** and **55** was assessed in mice using a Matrigel plug assay in which the bFGF stimulated vessel formation into a Matrigel plug is evaluated in the presence or absence of inhibitor.[30] Mice were thus dosed orally with **49a** and **55** at 10 and 20 mg/kg for 4 days, starting 24 h after Matrigel injection. Visual inspection of the plugs after removal clearly indicated that a marked increased in vascularization, as indicated by increasing red intensity of the plug, occurred in plugs of untreated animals (Figure 3b). For treated animals a noticeable reduction in the level of vascularization was observed and quantification of angiogenesis through FITC staining revealed a very significant inhibitory effect of both **49a** and **55** at 10 and 20 mg/kg (Figure 3a). This study confirms the in vivo antiangiogenic potential of these new derivatives, which reflects observations made for foregoing members of this series such as **3** and **11**.

CONCLUSIONS

In this study we set out to further refine the anticancer activity of 2-substituted estratriene-3-*O*-sulfamates by optimizing the C-17 substituent. Variation of the hydrogen bond acceptor "Z" and the linker group "Y" (Figure 2) that tethers "Z" to C-17 provided further insights into the steric and electronic factors that deliver optimal antiproliferative activity. We have identified a number of C-17 substituents that confer enhanced antiproliferative activity to non-sulfamoylated derivatives relative to the corresponding 2-substituted estradiols; these new derivatives include the 2-methoxy-17β-acyl estratriene **48b** which is the most active D-ring modified 2-methoxyestradiol analogue identified to date. These C-17 substituents could conceivably be combined with alternative C-2 substitution to yield yet more potent non-sulfamoylated estratriene derivatives. Results obtained for the 3-*O*-sulfamates revealed the tolerance to, and benefit of, introducing a linker group between the hydrogen bond acceptor group tethered to C-17. The hydroxymethyl **20**, acyl **49a** and **49b**, 2-hydroxypropyl **65**, and 2-propoxy **55** and **61** derivatives all exhibit excellent antiproliferative activity in vitro across a broad range of cancer cell lines with MGM values below 30 nM across the NCI 60-cell line panel. The potential of three of these compounds as in vivo antitumor and antiangiogenic agents has been established. Promising activity in the NCI hollow fiber assay for compound **20** illustrates in vivo antitumor potential, while **49a** and **55** showed good in vivo antiangiogenic activity. On the basis of these studies, a number of compounds that could supersede **3**, which is currently in preclinical development, are available.

EXPERIMENTAL SECTION

Biology. In Vitro Studies: Cell Lines. DU145 (brain metastasis carcinoma of the prostate) and MDA-MB-231 (metastatic pleural effusion of breast adenocarcinoma) established human cell lines were obtained from ATCC Global Bioresource Center. Cells were maintained in a 5% CO_2 humidified atmosphere at 37 °C in RPMI-1640 medium, supplemented with 10% fetal bovine serum, penicillin, and streptomycin.

Antiproliferative Assays. DU145 and MDA-MB-231 cells were seeded into 96-well microtiter plates (5000 cells/well) and treated with 10^{-9}−10^{-4} M compounds or with vehicle control. At 96 h after treatment, live cell counts were determined by WST-1 cell proliferation assay (Roche, Penzberg, Germany), as instructed by the manufacturer. Viability results were expressed as a percentage of mean control values resulting in the calculation of the 50% growth inhibition (GI_{50}). All experiments were performed in triplicate.

In Vivo Angiogenesis Assay. The Matrigel plug assay was a modified version of previously described methods.[30,33] Briefly, female C57BL/6J mice (6−8 weeks old) were obtained from Charles River UK Ltd. (Margate, Kent, U.K.). Animals were maintained in positive

pressure isolators under a 12 h light−dark cycle and allowed access to food and water ad libitum. The experiments were approved by the Imperial College Animal Ethical Review Committee and met the standards required by the UKCCCR guidelines.[34] Mice were anesthetized, placed on a heated pad (37 °C), and injected subcutaneously into the flanks with 0.5 mL of ice-cold Matrigel (Becton Dickinson, Oxford, Oxon, U.K.) supplemented with 500 ng of basic fibroblast growth factor (bFGF; R&D Systems, Oxford, Oxon, U.K.). Control mice were injected with Matrigel without bFGF. After Matrigel injection they were divided into six groups of five mice: control, bFGF only, bFGF, and **49a** (10 mg/kg, po), bFGF and **49a** (20 mg/kg, po), bFGF and **55** (10 mg/kg, po), and bFGF and **55** (20 mg/kg, po). Control and bFGF only mice were dosed orally with vehicle (10% THF, 90% PG), while the others were dosed every day for 4 days with **49a** or **55** at the indicated dose. Before the end of each study vascularization of Matrigel was quantified by injecting mice with FITC-dextran (125 000 molecular weight, Sigma), 0.1 mL of a 0.25 mg/mL solution intravenously (iv), which allowed blood vessels within plugs to be visualized. Animals were euthanized 20 min after injection, when Matrigel plugs were removed and photographs showing the extent of vascularization taken using a dissecting microscope (Nikon SMZ1500). Photographs of blood vessels within Matrigel plugs were also obtained using a microscope with a fluorescent light source (Zeiss-Axiovert 200). Quantification of FITC-dextran in the Matrigel plugs was achieved by incubating plugs in 1 mL pf Dispase reagent (Becton Dickinson) for 16 h at 37 °C. The resulting mixture was centrifuged in a microfuge at 13 000 rpm for 30 s. The fluorescence of the resulting supernatants was measured using a fluorimeter (Fluostar plus Optima, BCG, Bucks, U.K.), with excitation at 480 nm and measurement at 520 nm, and quantitated against a standard curve of FITC dextran (0.4−25 mg/mL).

Chemistry. All chemicals were either purchased from Aldrich Chemical Co. (Gillingham, U.K.) or Alfa Aesar (Heysham, U.K.). Organic solvents of A.R. grade were supplied by Fisher Scientific (Loughborough, U.K.) and used as supplied. Anhydrous DMA and anhydrous THF were purchased from Aldrich and stored under a positive pressure of N_2 after use. Sulfamoyl chloride was prepared by an adaptation of the method of Appel and Berger[35] and was stored in the refrigerator under positive pressure of N_2 as a solution in toluene as described by Woo et al.[36] An appropriate volume of this solution was freshly concentrated in vacuo immediately before use. Reactions were carried out at room temperature unless stated otherwise. Flash column chromatography was performed on silica gel (Matrex C60).

^{1}H NMR and ^{13}C NMR spectra were recorded with either a JMN-GX 270 at 270 and 67.5 MHz, respectively, or a Varian Mercury VX 400 NMR spectrometer at 400 and 100 MHz, respectively, and chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS) as internal standard. Deuteriochloroform was used as solvent unless otherwise stated. Mass spectra were recorded at the Mass Spectrometry Service Center, University of Bath, U.K. FAB-MS were carried out using *m*-nitrobenzyl alcohol (NBA) as the matrix. Elemental analyses were performed by the Microanalysis Service, University of Bath. Melting points were determined using a Stuart SMP3 melting point apparatus and are uncorrected. All compounds were ≥98% pure by reverse phase HPLC run with acetonitrile/water and methanol/water (Sunfire C18 reverse phase column, 4.6 mm × 150 mm, 3.5 μm pore size).

2-Ethyl-3-*O*-benzyl-17β-hydroxymethylestra-1,3,5(10)-triene 14. Compound **13** (2.35 g, 6 mmol) was added portionwise over 15 min into a mixture of Mg (576 mg, 24 mmol) and $TiCl_4$ (0.63 mL, 6 mmol) in DCM (10 mL) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 2 h and then at room temperature overnight. After cooling to 0 °C, the mixture was neutralized with potassium carbonate (saturated) and extracted with EtOAc (2 × 60 mL). The combined organics were successively washed with water and brine, then dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (hexane/EtOAc 50:1) afforded the alkene as a light yellow oil (1.3 g, 56%). δ_H 0.88 (3H, s), 1.26 (3H, t, *J* 7.4), 1.27−1.70 (7H, m), 1.80−2.05 (3H, m), 2.22−2.68 (5H, m), 2.74 (2H, q, *J* 7.4), 2.87−2.95 (2H, m), 4.74 (2H, m), 5.10 (2H, s), 6.70 (1H, s), 7.19 (1H, s), 7.28−7.50 (5H, m). LC/MS (APCI+): *m*/*z* 387.1 (M^+ + H). A solution of this oil (1.24 g, 3.2 mmol) in THF (10 mL) was added to solution of 9-BBN (1.56 g, 6.4 mmol) in THF (20 mL) at 0 °C, and the mixture was stirred at 0 °C for 5 h. Sodium hydroxide (10%, 20 mL) was cautiously added followed by hydrogen peroxide (37%, 10 mL). The solution was stirred at 0 °C for 2 h and then extracted with EtOAc (2 × 50 mL). The combined organics were washed with water and brine, then dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (hexane/EtOAc 10:1 to 5:1) afforded compound **14** as a white solid (1.05 g, 81%), mp 99−100 °C. δ_H 0.68 (3H, s), 1.20 (3H, t, *J* 7.3 Hz), 1.27−1.70 (8H, m), 1.62−1.90 (4H, m), 1.95−2.04 (1H, m), 2.17−2.36 (2H, m), 2.66 (2H, q *J* 7.3), 2.75−2.90 (2H, m), 3.58 (1H, dd, *J* 10.4, 7.4), 3.76 (1H, dd, *J* 10.4, 6.7), 5.03 (2H, s), 6.63 (1H, s), 7.10 (1H, s), 7.26−7.46 (5H, m). LC/MS (APCI−): *m*/*z* 403.4 (M^- − H).

2-Ethyl-3-hydroxy-17β-hydroxymethylestra-1,3,5(10)-triene 15. A solution of compound **14** (202 mg, 0.5 mmol) in THF (10 mL) and methanol (10 mL) was treated with Pd/C (10%, 30 mg), degassed, then stirred under an atmosphere of hydrogen at room temperature for 24 h. The mixture was filtered through Celite, washed with EtOAc, and concentrated in vacuo. Purification by flash column chromatography (hexane/EtOAc 8:1 to 5:1) afforded compound **15** as a white powder (140 mg, 89%), mp 169−170 °C. δ_H 0.68 (3H, s), 1.20−1.61 (11H, m), 1.65−1.91 (3H, m), 1.94−1.99 (1H, m), 2.14−2.32 (2H, m), 2.58 (2H, q, *J* 7.4), 2.70−2.88 (2H, m), 3.58 (1H, dd, *J* 9.9, 7.9), 3.76 (1H, dd, *J* 9.9, 7.4), 4.65 (1H, s), 6.48 (1H, s), 7.04 (1H, s). HRMS (ES+): *m*/*z* found 315.2324; $C_{21}H_{31}O_2^+$ (M^+ + H) requires 315.2319. Anal. ($C_{21}H_{30}O_2$) C, H, N.

2-Ethyl-3-*O*-sulfamoyl-17β-sulfamoyloxymethylestra-1,3,5(10)-triene 16. Compound **15** (80 mg, 0.25 mmol) was added to solution of sulfamoyl chloride (1.0 mmol) in DMA (1.0 mL) at 0 °C. The reaction mixture was stirred at room temperature for 24 h. Water (10 mL) was added, and the mixture was extracted with EtOAc (2 × 30 mL). The combined organics were successively washed with water and brine, then dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (hexane/EtOAc 3:2) afforded compound **16** as a white powder (90 mg, 76%), mp 167−168 °C. δ_H (acetone-d_6): 0.77 (3H, s), 1.16 (3H, t, *J* 7.4), 1.28−1.55 (7H, m), 1.79−1.97 (3H, m), 2.21−2.41 (2H, m), 2.68 (2H, q, *J* 7.4), 2.76−2.85 (2H, m), 4.08 (1H, dd, *J* 9.4, 6.4), 4.21 (1H, dd, *J* 9.4, 7.4), 6.63 (2H, s, br), 7.07 (1H, s), 7.12 (2H, s, br), 7.23 (1H, s). HRMS (ES+): *m*/*z* found 473.1767; $C_{21}H_{33}N_2O_6S_2^+$ (M^+ + H) requires 473.1775. Anal. ($C_{21}H_{32}N_2O_6S_2$) C, H, N.

2-Ethyl-3-hydroxy-17β-methoxymethylestra-1,3,5(10)-triene 17. A solution of compound **14** (265 mg, 0.65 mmol) in THF (20 mL) was stirred under nitrogen, and sodium hydride (60% suspension in oil, 52 mg, 1.3 mmol) was added portionwise at room temperature. After 15 min iodomethane (0.08 mL, 1.3 mmol) was added and the mixture was heated to reflux for 2 h, cooled to room temperature. Water (5 mL) was added, and the mixture was extracted with EtOAc (2 × 50 mL). The combined organics were washed with water and brine, then dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (hexane/EtOAc 20:1) afforded the methyl ether as a white powder (220 mg, 81%), mp 60−61 °C. δ_H 0.66 (3H, s), 1.21 (3H, t, *J* 7.3), 1.22−1.51 (7H, m), 1.71−2.02 (5H, m), 2.17−2.33 (2H, m), 2.66 (2H, q *J* 7.3), 2.75−2.92 (2H, m), 3.26−3.31 (1H, m), 3.34 (3H, s), 3.47 (1H, dd, *J* 9.3, 6.3), 5.03 (2H, s), 6.63 (1H, s), 7.10 (1H, s), 7.28−7.46 (5H, m). HRMS (ES+): *m*/*z* found 419.2937; $C_{29}H_{39}O_2^+$ (M^+ + H) requires 419.2945. The above methyl ether (190 mg, 0.45

mmol) was treated with Pd/C (10%, 30 mg) in THF (5 mL) and methanol (20 mL) following the method described to access compound **15**. Purification by flash column chromatography (hexane/EtOAc 10:1) afforded compound **17** as a white powder (125 mg, 84%), mp 132−133 °C. δ_H 0.65 (3H, s), 1.19−1.55 (10H, m), 1.70−1.91 (4H, m), 1.95−2.03 (1H, m), 2.14−2.29 (2H, m), 2.56 (2H, q *J* 7.4), 2.69−2.88 (2H, m), 3.27 (1H, dd, *J* 9.2, 7.4), 3.34 (3H, s), 3.47 (1H, dd, *J* 9.2, 6.4), 4.61 (1H, s), 6.48 (1H, s), 7.04 (1H, s). HRMS (ES+): *m/z* found 329.2465; $C_{22}H_{33}O_2^+$ ($M^+ + H$) requires 329.2475. Anal. ($C_{22}H_{32}O_2$) C, H.

2-Ethyl-3-*O*-sulfamoyl-17β-methoxymethylestra-1,3,5(10)-triene 18. Compound **17** (82 mg, 0.25 mmol) was treated with sulfamoyl chloride (0.5 mmol) in DMA (1.0 mL) following the method described to access compound **16**. Purification by flash column chromatography (hexane/EtOAc 5:1) afforded compound **18** as a white powder (80 mg, 79%), mp 132−133 °C. δ_H 0.65 (3H, s), 1.17−1.60 (11H, m), 1.73−2.03 (5H, m), 2.18−2.30 (2H, m), 2.68 (2H, q *J* 7.4), 2.80−2.87 (2H, m), 3.24−3.32 (1H, m), 3.34 (3H, s), 3.46 (1H, dd, *J* 9.4, 6.9), 4.99 (2H, s), 7.06 (1H, s), 7.18 (1H, s). HRMS (ES+): *m/z* found 408.2205; $C_{22}H_{34}NO_4S^+$ ($M^+ + H$) requires 408.2203. Anal. ($C_{22}H_{33}NO_4S$) C, H, N.

2-Ethyl-3-hydroxy-17β-*tert*-butyldiphenylsilyloxymethylestra-1,3,5(10)-triene 19. A solution of compound **14** (404 mg, 1 mmol), *tert*-butyldiphenylsilyl chloride (302 mg, 1.1 mmol), and imidazole (82 mg, 1.2 mmol) in DMF (10 mL) was stirred at room temperature for 4 h. Water (10 mL) was added, and the mixture was extracted with EtOAc (2 × 30 mL). The combined organics were washed with water and brine, then dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (hexane to hexane/EtOAc 25:1) gave the silyl protected alcohol as a colorless oil (600 mg, 93%). δ_H 0.67 (3H, s), 1.06 (9H, s), 1.18−1.58 (11H, m), 1.65−1.92 (4H, m), 2.12−2.36 (3H, m), 2.67 (2H, q *J* 7.4), 2.72−2.92 (2H, m), 3.58 (1H, dd, *J* 10.2, 5.7), 3.73 (1H, dd, *J* 10.2, 7.7), 5.04 (2H, s), 6.64 (1H, s), 7.13 (1H, s), 7.28−7.47 (11H, m), 7.65−7.73 (4H, m). LC/MS (ES−): *m/z* 641.5 (M^- − H). The above silyl protected alcohol (570 mg, 0.89 mmol) was treated with Pd/C (10%, 50 mg) in THF (20 mL) and methanol (20 mL) following the method described to access compound **15**. Purification by flash column chromatography (hexane/EtOAc 25:1 to 20:1) afforded compound **19** as a white powder (430 mg, 88%), mp 63−65 °C. δ_H 0.65 (3H, s), 1.04 (9H, s), 1.17−1.51 (10H, m), 1.71−1.88 (4H, m), 2.08−2.32 (3H, m), 2.58 (2H, q, *J* 7.4), 2.71−2.87 (2H, m), 3.57 (1H, dd, *J* 10.1, 5.9), 3.71 (1H, dd, *J* 10.1, 7.6), 4.44 (1H, s), 6.48 (1H, s), 7.06 (1H, s), 7.35−7.43 (6H, m), 7.66−7.71 (4H, m). HRMS (ES−): *m/z* found 553.3326; $C_{37}H_{47}O_2Si^-$ (M^- − H) requires 551.3340.

2-Ethyl-3-*O*-sulfamoyl-17β-hydroxymethylestra-1,3,5(10)-triene 20. Sulfamoyl chloride (0.5 M in toluene, 2.2 mL, 1.1 mmol) was added to a solution of 2,6-di-*tert*-butyl-4-methylpyridine (275 mg, 1.34 mmol) and compound **19** (370 mg, 0.67 mmol) in DCM (10 mL). The reaction mixture was stirred at room temperature for 5 h. Water (10 mL) was added, and the mixture was extracted with DCM (2 × 30 mL). The combined organics were successively washed with water and brine, then dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (hexane/EtOAc 10:1 to 5:1) afforded the sulfamoylated compound as a white powder (340 mg, 80%), mp 79−81 °C. δ_H 0.66 (3H, s), 1.04 (9H, s), 1.18−1.53 (10H, m), 1.68−1.91 (4H, m), 2.13−2.32 (3H, m), 2.68 (2H, q *J* 7.4), 2.79−2.87 (2H, m), 3.57 (1H, dd, *J* 10.1, 5.9), 3.70 (1H, dd, *J* 10.1, 7.7), 4.94 (2H, s), 7.06 (1H, s), 7.21 (1H, s), 7.34−7.46 (6H, m), 7.66−7.70 (4H, m). HRMS (ES+): *m/z* found 632.3223; $C_{37}H_{50}NO_4SSi^+$ ($M^+ + H$) requires 632.3224. The sulfamoylated compound (200 mg, 0.32 mmol) was stirred in THF (10 mL), cooled to 0 °C, and treated with TBAF in THF (1M, 0.65 mL, 0.65 mmol). The reaction mixture was stirred at room temperature for 7 h. Water (10 mL) was added, and the mixture was extracted with EtOAc (2 × 30 mL). The combined organics were successively washed with water and brine, then dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (hexane/EtOAc 5:1 to 1:1) afforded compound **20** as a white powder (85 mg, 68%), mp 176−177 °C. δ_H (acetone-d_6) 0.58 (3H, s), 1.09 (3H, t, *J* 7.4), 1.15−1.47 (7H, m), 1.57−1.69 (2H, m), 1.75−1.82 (2H, m), 1.87−1.96 (2H, m), 2.12−2.23 (2H, m), 2.59 (2H, q *J* 7.4), 2.70−2.74 (2H, m), 3.44−3.51 (1H, m), 3.60−3.69 (1H, m), 5.93 (2H, s), 6.98 (1H, s), 7.07 (1H, s). HRMS (ES+): *m/z* found 394.2052; $C_{21}H_{32}NO_4S^+$ ($M^+ + H$) requires 394.2047. Anal. ($C_{21}H_{31}NO_4S$) C, H, N.

2-Ethyl-3-benzyloxy-17-(2-ethoxy-2-oxoethylidene)estra-1,3,5(10)-trienes 21 and 22. Sodium hydride (60% dispersion in mineral oil, 0.8 g, 20 mmol) was washed with hexane (3 × 1 mL), then stirred in THF (50 mL) at 0 °C under nitrogen. Triethylphosphonoacetate (4.48 g, 20 mmol) was added dropwise at 0 °C, and the reaction mixture was stirred until gas evolution ceased. Compound **13** (3.9 g, 10 mmol) in THF (10 mL) was added dropwise, and the reaction mixture was heated to reflux for 18 h, then cooled to 0 °C, poured into water (30 mL), and extracted with EtOAc (2 × 50 mL). The combined organics were washed with water and brine, then dried ($MgSO_4$)), filtered, and concentrated in vacuo. Purification by flash column chromatography (hexane to hexane/EtOAc 20:1) successively afforded compounds **22** (590 mg, 13%) and **21** (3.5 g, 75%) as white powders. Compound **21**: mp 61−63 °C. δ_H 0.87 (3H, s), 1.23 (3H, t, *J* 7.4), 1.31 (3H, t, *J* 7.1), 1.30−1.61 (6H, m), 1.84−2.01 (3H, m), 2.19−2.30 (1H, m), 2.41−2.48 (1H, m), 2.67 (2H, q, *J* 7.4), 2.77−2.96 (2H, m), 4.16 (2H, q, *J* 7.1), 5.04 (2H, s), 5.61 (1H, t, *J* 2.3), 6.64 (1H, s), 7.11 (1H, s), 7.28−7.46 (5H, m). HRMS (ES+): *m/z* found 459.2896; $C_{31}H_{39}O_3^+$ ($M^+ + H$) requires 459.2894. Compound **22**: mp 119−120 °C. δ_H 1.05 (3H, s), 1.22 (3H, t, *J* 7.4), 1.30 (3H, t, *J* 7.2), 1.32−1.64 (6H, m), 1.77−1.85 (1H, m), 1.88−1.96 (1H, m), 2.14−2.26 (1H, m), 2.32−2.50 (2H, m), 2.56−2.71 (3H, m), 2.76−2.89 (3H, m), 4.10−4.19 (2H, m), 5.03 (2H, s), 5.69 (1H, t, *J* 1.9), 6.64 (1H, s), 7.11 (1H, s), 7.27−7.46 (5H, m). HRMS (ES+): *m/z* found 459.2907; $C_{31}H_{39}O_3^+$ ($M^+ + H$) requires 459.2894.

2-Ethyl-3-hydroxy-17β-(2-ethoxy-2-oxoethyl)estra-1,3,5(10)-triene 23. Compounds **21** and **22** (3.4 g, 7.4 mmol) were treated with Pd/C (10%, 250 mg) in THF (10 mL) and methanol (50 mL) as described for the synthesis of compound **15**. Purification by flash column chromatography (hexane/EtOAc 20:1 to 10:1) afforded compound **23** as a white powder (2.6 g, 95%), mp 82−84 °C. δ_H 0.62 (3H, s), 1.20 (3H, t, *J* 7.2), 1.25 (3H, t, *J* 7.3), 1.28−1.50 (7H, m), 1.74−1.98 (5H, m), 2.09−2.43 (4H, m), 2.58 (2H, q, *J* 7.3), 2.77−2.86 (2H, m), 4.12 (2H, q, *J* 7.2), 4.77 (1H, s), 6.49 (1H, s), 7.04 (1H, s). HRMS (ES+): *m/z* found 371.2572; $C_{24}H_{35}O_3^+$ ($M^+ + H$) requires 371.2581. Anal. ($C_{24}H_{34}O_3$) C, H.

2-Ethyl-3-*O*-sulfamoyl-17β-(2-ethoxy-2-oxoethyl)estra-1,3,5(10)-triene 24. Compound **23** (100 mg, 0.27 mmol) was treated with sulfamoyl chloride (0.54 mmol) in DMA (1.0 mL) as described for the synthesis of compound **16**. Purification by flash column chromatography (hexane/EtOAc 9:1 to 4:1) afforded compound **24** as a white powder (83 mg, 68%), mp 120−122 °C. δ_H 0.63 (3H, s), 1.21 (3H, t, *J* 7.4), 1.27 (3H, t, *J* 7.0), 1.24−1.50 (7H, m), 1.74−1.98 (5H, m), 2.11−2.42 (4H, m), 2.68 (2H, q, *J* 7.4), 2.82−2.84 (2H, m), 4.12 (2H, q, *J* 7.0), 5.08 (2H, s), 7.05 (1H, s), 7.16 (1H, s). HRMS (FAB+): *m/z* found 450.2313; $C_{24}H_{36}NO_5S^+$ ($M^+ + H$) requires 450.2309. Anal. ($C_{24}H_{35}NO_5S$) C, H.

2-Ethyl-3-*O*-benzyloxy-17β-(2-hydroxyethyl)estra-1,3,5(10)-triene 25. Compound **23** (2.6 g, 7 mmol) was stirred with potassium carbonate (2.75 g, 20 mmol) and benzyl bromide (0.86 mL, 7.2 mmol) in DMF (30 mL) at room temperature for 24 h. Water (50 mL) was added, and the mixture was extracted with EtOAc (2 × 60 mL). The combined organics were washed with water and brine, then dried

($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (hexane/EtOAc 50:1) afforded the phenol as a white powder (3.1 g, 91%), mp 94−95 °C. δ_H 0.64 (3H, s), 1.21 (3H, t, *J* 7.4), 1.27 (3H, t, *J* 7.7), 1.26−1.60 (7H, m), 1.76−2.05 (5H, m), 2.11−2.46 (4H, m), 2.68 (2H, q, *J* 7.7), 2.83 (2H, m), 4.14 (2H, q, *J* 7.4), 5.04 (2H, s), 6.63 (1H, s), 7.11 (1H, s), 7.29−7.47 (5H, m). HRMS (ES+): *m/z* found 461.3057; $C_{31}H_{41}O_3^+$ (M^+ + H) requires 461.3050. A solution of the phenol (2.8 g, 6 mmol) in THF (30 mL) was treated with lithium aluminum hydride (0.45 g, 12 mmol) at 0 °C for 3 h. Ammonium chloride (saturated) was added, and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, then dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (hexane/EtOAc 15:1 to 8:1) afforded compound **25** as a white powder (2.2 g, 88%), mp 98−99 °C. δ_H 0.63 (3H, s), 1.20 (3H, t, *J* 7.4), 1.22−1.58 (9H, m), 1.70−1.92 (5H, m), 2.16−2.34 (2H, m), 2.66 (2H, q, *J* 7.4), 2.82−2.88 (2H, m), 3.64−3.72 (2H, m), 5.03 (2H, s), 6.62 (1H, s), 7.10 (1H, s), 7.28−7.45 (5H, m). HRMS (ES+): *m/z* found 419.2939; $C_{29}H_{39}O_2^+$ (M^+ + H) requires 419.2945.

2-Ethyl-3-hydroxy-17*β*-(2-hydroxyethyl)estra-1,3,5(10)-triene 26. Compound **25** (420 mg, 1.0 mmol) was treated with Pd/C (10%, 40 mg) in THF (5 mL) and methanol (10 mL) as described for the synthesis of compound **15**. Purification by flash column chromatography (hexane/EtOAc 10:1 to 3:1) and crystallization from hexane/EtOAc afforded compound **26** as a white solid (300 mg, 91%), mp 166−167 °C. δ_H 0.62 (3H, s), 1.21 (3H, t, *J* 7.4), 1.23−1.55 (3H, m), 1.70−1.93 (5H, m), 2.13−2.34 (2H, m), 2.58 (2H, q, *J* 7.4), 2.74−2.84 (2H, m), 3.63−3.70 (2H, m), 4.57 (1H, s), 6.49 (1H, s), 7.05 (1H, s). HRMS (ES+): *m/z* found 329.2470; $C_{22}H_{33}O_2^+$ (M^+ + H) requires 329.2475. Anal. ($C_{22}H_{32}O_2$) C, H.

2-Ethyl-17*β*-(2-sulfamoyloxyethyl)estra-3-*O*-sulfamoyl-1,3,5(10)-triene 27. Compound **26** (105 mg, 0.32 mmol) was treated with sulfamoyl chloride (0.54 mmol) in DMA (1.0 mL) as described for the synthesis of compound **16**. Purification by flash column chromatography (hexane/EtOAc 10:1 to 4:1) and crystallization from hexane/EtOAc afforded compound **27** as a white powder (85 mg, 54%), mp 192−194 °C. δ_H (acetone-d_6): 0.69 (3H, s), 1.18 (3H, t, *J* 7.4), 1.29−1.62 (10H, m), 1.76−2.42 (6H, m), 2.70 (2H, q, *J* 7.4), 2.80−2.84 (2H, m), 4.16−4.18 (2H, m), 6.63 (2H, s), 7.09 (1H, s), 7.13 (2H, s), 7.24 (1H, s). HRMS (ES+): *m/z* found 487.1928; $C_{22}H_{35}O_6N_2S_2^+$ (M^+ + H) requires 487.1931. Anal. ($C_{22}H_{34}O_6N_2S_2$) C, H, N.

2-Ethyl-3-hydroxy-17*β*-(2-methoxyethyl)estra-1,3,5(10)-triene 28. Compound **25** (0.42 g, 1 mmol) was treated with NaH (60% dispersion in mineral oil, 0.06 g, 1.5 mmol) and iodomethane (0.12 mL, 2.0 mmol) in THF (30 mL) following the method described for the synthesis of compound **17**. Purification by flash column chromatography (hexane/EtOAc 20:1) afforded the methyl ether as a white powder (415 mg, 96%), mp 70−71 °C. δ_H 0.66 (3H, s), 1.25 (3H, t, *J* 7.4), 1.26−1.60 (9H, m), 1.76−1.96 (5H, m), 2.20−2.42 (2H, m), 2.70 (2H, q, *J* 7.4), 2.82−2.89 (2H, m), 3.38 (3H, s), 3.40−3.46 (2H, m), 5.07 (2H, s), 6.66 (1H, s), 7.15 (1H, s), 7.31−7.50 (5H, m). HRMS (ES+): *m/z* found 433.3101; $C_{30}H_{41}O_2^+$ (M^+ + H) requires 433.3090. The methyl ether (0.4 g, 0.93 mmol) was treated with Pd/C (10%, 30 mg) in THF (5 mL) and methanol (20 mL) as described for the synthesis of compound **15**. Purification by flash column chromatography (hexane/EtOAc 15:1 to 10:1) afforded compound **28** as a white powder (305 mg, 97%), mp 58−59 °C. δ_H 0.62 (3H, s), 1.19−1.56 (12H, m), 1.72−1.91 (5H, m), 2.13−2.34 (2H, m), 2.60 (2H, q, *J* 7.4), 2.73−2.80 (2H, m), 3.37 (3H, s), 3.42−3.48 (2H, m), 5.26 (1H, s), 6.48 (1H, s), 7.06 (1H, s). HRMS (FAB+): *m/z* found 342.2555; $C_{23}H_{34}O_2^+$ (M^+) requires 342.2559. Anal. ($C_{23}H_{34}O_2$) C, H.

2-Ethyl-3-*O*-sulfamoyl-17*β*-(2-methoxyethyl)estra-1,3,5(10)-triene 29. Compound **28** (250 mg, 0.73 mmol) was treated with sulfamoyl chloride (1.5 mmol) in DMA (1.0 mL) as described for the synthesis of compound **16**. Purification by flash column chromatography (hexane/EtOAc 10:1 to 4:1) and crystallization from hexane/EtOAc afforded compound **29** as a white powder (260 mg, 84%), mp 168−169 °C. δ_H 0.61 (3H, s), 1.20 (3H, t, *J* 7.4), 1.22−1.54 (9H, m), 1.70−1.95 (5H, m), 2.15−2.33 (2H, m), 2.68 (2H, q, *J* 7.4), 2.79−2.86 (2H, m), 3.33 (3H, s), 3.35−3.39 (2H, m), 4.95 (2H, s), 7.06 (1H, s), 7.18 (1H, s). HRMS (ES+) *m/z* found 422.2360; $C_{23}H_{36}NO_4S^+$ (M^+ + H) requires 422.2360. Anal. ($C_{23}H_{35}NO_4S$) C, H, N.

2-Ethyl-3-hydroxy-17*β*-(2-*tert*-butyldiphenylsilyloxyethyl) estra-1,3,5(10)-triene 30. Compound **25** (419 mg, 1 mmol), imidazole (136 mg, 2 mmol), and *tert*-butyldiphenylsilyl chloride (300 mg, 1.1 mmol) were stirred in DMF (5 mL) as described for the synthesis of compound **19**. Purification by flash column chromatography (hexane/EtOAc 25:1) afforded the silyl protected alcohol as a white powder (590 mg, 90%), mp 48−50 °C. δ_H 0.63 (3H, s), 1.12 (9H, s) 1.15−1.60 (11H, m), 1.71−2.01 (5H, m), 2.20−2.44 (2H, m), 2.69 (, *J* 7.4), 2.84−2.91 (2H, m), 3.65−3.81 (2H, m), 5.09 (2H, s), 6.68 (1H, s), 7.20 (1H, s), 7.32−7.51 (11H, m), 7.72−7.77 (4H, m). HRMS (ES+): *m/z* found 657.4119; $C_{45}H_{57}O_2Si^+$ (M^+ + H) requires 657.4122. The silyl protected alcohol (550 mg, 0.84 mmol) was treated with Pd/C (10%, 50 mg) in THF (5 mL) and methanol (15 mL) following the method described to access compound **15**. Purification by flash column chromatography (hexane/EtOAc 25:1 to 15:1) afforded compound **30** as a white powder (410 mg, 87%), mp 134−135 °C. δ_H 0.59 (3H, s), 1.08 (9H, s), 1.18−1.56 (12H, m), 1.68−1.89 (5H, m), 2.10−2.33 (2H, m), 2.61 (2H, q, *J* 7.4), 2.73−2.82 (2H, m), 3.61−3.78 (2H, m), 4.71 (1H, s), 6.49 (1H, s), 7.07 (1H, s), 7.36−7.47 (6H, m), 7.68−7.74 (4H, m). HRMS (ES+): *m/z* found 567.3666; $C_{38}H_{51}O_2Si^+$ (M^+ + H) requires 567.3653.

2-Ethyl-3-*O*-sulfamoyl-17*β*-(hydroxyethyl)estra-1,3,5(10)-triene 31. Compound **30** (142 mg, 0.25 mmol) was treated with sulfamoyl chloride (0.5 mmol) in DMA (5 mL) as described for the synthesis of compound **16**. Purification by flash column chromatography (hexane/EtOAc 20:1 to 8:1) afforded the sulfamate as a white powder (115 mg, 70%), mp 185−186 °C. δ_H 0.57 (3H, s), 1.05 (9H, s), 1.18−1.55 (13H, m), 1.68−1.89 (4H, m), 2.15−2.31 (2H, m), 2.68 (2H, q, *J* 7.4), 2.80−2.87 (2H, m), 3.57−3.70 (2H, m), 4.91 (2H, s, br), 7.06 (1H, s), 7.19 (1H, s), 7.34−7.45 (6H, m), 7.64−7.69 (4H, m). HRMS (FAB+): *m/z* found 646.3384; $C_{38}H_{51}NO_4SSi^+$ (M^+ + H) requires 646.3386. The sulfamate (110 mg, 0.17 mmol) was reacted with TBAF (1 M in THF, 0.34 mL, 0.34 mmol) in THF (10 mL) at room temperature for 4 h as described for the synthesis of **20**. Purification by flash column chromatography (hexane/EtOAc 10:1 to 2:1) and crystallization from hexane/EtOAc afforded compound **31** as a white powder (50 mg, 72%), mp 157−158 °C. δ_H: 0.62 (3H, s), 1.17−1.55 (12H, m), 1.70−1.94 (5H, m), 2.16−2.33 (2H, m), 2.68 (2H, q, *J* 7.4), 2.80−2.87 (2H, m), 3.60−3.76 (2H, m), 4.87 (2H, s, br), 7.06 (1H, s), 7.19 (1H, s). HRMS (FAB+): *m/z* found 407.2141; $C_{22}H_{33}NO_4S^+$ (M^+) requires 407.2130. Anal. ($C_{22}H_{33}NO_4S$) C, H, N.

2-Ethyl-17-(2-ethoxy-2-oxoethylidene)-3-*O*-(*tert*-butyldimethylsilyl)estra-1,3,5(10)-triene 33. Compound **32** (4.1 g, 10 mmol) was reacted with triethylphosphonoacetate following the method used for the synthesis of compounds **21** and **22**. Purification by flash column chromatography (hexane to hexane/EtOAc 25:1) afforded compound **33** as a light yellow oil (4.3 g, 89%; mixture of *E* and *Z* isomers). δ_H 0.22 (6H, s), 0.85 (3H, s, major) and 1.03 (3H, s, minor), 0.99 (9H, s), 1.16 (3H, t, *J* 7.4), 1.28 (3H, t, *J* 7.1), 1.31−1.59 (5H, m), 1.82−1.98 (3H,m), 2.13−2.25 (1H, m), 2.37−2.44 (1H, m), 2.55 (2H, q, *J* 7.4), 2.76−2.92 (4H, m), 4.15 (2H, q, *J* 7.1), 5.58 (1H, t, *J* 2.2, major), 5.67 (1H, t, *J* 1.7, minor), 6.48 (1H, s), 7.05 (1 H, s). HRMS (ES+): *m/z* found 483.3279; $C_{30}H_{47}O_3Si^+$ (M^+ + H) requires 483.3289.

2-Ethyl-3-hydroxy-17-(2-ethoxy-2-oxoethylidene)estra-1,3,5(10)-trienes 34 and 35. Compound **33** (4.0 g, 8.3 mmol) was

treated with TBAF (1 M in THF, 9.2 mL, 9.2 mmol) in THF (50 mL) as described for the synthesis of compound **20**. Purification by flash column chromatography (hexane to hexane/EtOAc 10:1) afforded successively the *Z*-isomer **35** (380 mg, 12%) and the *E*-isomer **34** (2.2 g, 72%) as white powders. Compound **34**: mp 85−87 °C. δ_H 0.86 (3H, s), 1.23 (3H, t, *J* 7.4), 1.30 (3H, t, *J* 7.1), 1.33−1.58 (6H, m), 1.85−2.00 (3H, m), 2.18−2.25 (1H, m), 2.39−2.45 (1H, m), 2.60 (2H, q, *J* 7.4), 2.78−2.84 (2H, m), 2.86−2.91 (2H, m), 4.16 (2H, q, *J* 7.1), 4.67 (1H, s), 5.59 (1H, t, *J* 2.3), 6.51 (1H, s), 7.06 (1H, s). HRMS (ES+): *m/z* found 369.2416; $C_{24}H_{33}O_3^+$ (M^+ + H) requires 369.2424. Anal. ($C_{24}H_{32}O_3$) C, H, N. Compound **35**: mp 157−159 °C. δ_H 1.04 (3H, s), 1.22 (3H, t, *J* 7.4), 1.29 (3H, t, *J* 7.2), 1.36−1.62 (6H, m), 1.78−1.84 (1H, m), 1.89−1.95 (1H, m), 2.16−2.23 (1H, m), 2.31−2.37 (1H, m), 2.41−2.49 (1H, m), 2.57−2.65 (3H, m), 2.77−2.84 (3H, m), 4.11−4.20 (2H, m), 4.60 (1H, s, br), 5.68 (1H, t, *J* 1.9), 6.50 (1H, s), 7.05 (1H, s). HRMS (ES+): *m/z* found 369.2419; $C_{24}H_{33}O_3^+$ (M^+ + H) requires 369.2424. Anal. ($C_{24}H_{32}O_3$) C, H, N.

(*E*)-2-Ethyl-3-*O*-sulfamoyl-17-(2-ethoxy-2-oxoethylidene) estra-1,3,5(10)-triene 36. Compound **34** (185 mg, 0.5 mmol) was treated with sulfamoyl chloride (1.5 mmol) in DMA (1.0 mL) as described for the synthesis of compound **16**. Purification by flash column chromatography (hexane/EtOAc 10:1 to 3:1) afforded compound **36** as a white powder (195 mg, 87%), mp 116−118 °C. δ_H 0.86 (3H, s), 1.22 (3H, t, *J* 7.4), 1.29 (3H, t, *J* 7.1), 1.38−1.64 (6H, m), 1.76−2.02 (3H, m), 2.23−2.29 (1H, m), 2.38−2.44 (1H, m), 2.67 (2H, q, *J* 7.4), 2.85−2.91 (4H, m), 4.16 (2H, q, *J* 7.1), 4.98 (2H, s), 5.59 (1H, t, *J* 2.3), 7.09 (1H, s), 7.20 (1H, s). HRMS (ES+): *m/z* found 448.2149; $C_{24}H_{34}NO_5S^+$ (M^+ + H) requires 448.2152. Anal. ($C_{24}H_{33}NO_5S$) C, H, N

(*Z*)- 2-Ethyl-3-*O*-sulfamoyl-17-(2-ethoxy-2-oxoethylidene) estra-1,3,5(10)-triene 37. Compound **35** (170 mg, 0.46 mmol) was treated with sulfamoyl chloride (1.5 mmol) in DMA (1.0 mL) as described for the synthesis of compound **16**. Purification by flash column chromatography (hexane/EtOAc 10:1 to 3:1) afforded compound **37** as a white powder (190 mg, 92%), mp 152−153 °C. δ_H 1.04 (3H, s), 1.22 (3H, t, *J* 7.4), 1.29 (3H, t, *J* 7.2), 1.34−1.64 (6H, m), 1.77−1.85 (1H, m), 1.91−1.97 (1H, m), 2.18−2.27 (1H, m), 2.31−2.38 (1H, m), 2.40−2.49 (1H, m), 2.56−2.74 (3H, m), 2.79−2.88 (3H, m), 4.10−4.18 (2H, m), 4.92 (2H, s), 5.69 (1H, t, *J* 2.1), 7.08 (1H, s), 7.19 (1H, s). HRMS (ES+): *m/z* found 448.2143; $C_{24}H_{34}NO_5S^+$ (M^+ + H) requires 448.2152. Anal. ($C_{24}H_{33}NO_5S$) C, H, N

(*E*)-2-Ethyl-3-hydroxy-17-(2-hydroxyethylidene)estra-1,3, 5(10)-triene 38. A solution of **34** (370 mg, 1.0 mmol) in THF (5 mL) stirred under nitrogen was cooled to −78 °C, and DIBAL-H (1 M in THF, 2.2 mL, 2.2 mmol) was added dropwise. The mixture was stirred at −78 °C for 1 h and then slowly warmed to room temperature and stirred for 30 min. Ammonium chloride (saturated, 5 mL) was added at 0 °C, and the mixture was extracted with EtOAc (2 × 30 mL). The combined organics were washed with water and brine, then dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (hexane to hexane/EtOAc 4:1) afforded compound **38** as a white powder (260 mg, 79%), mp 167−169 °C. δ_H 0.79 (3H, s), 1.21 (3H, t, *J* 7.4), 1.27−1.61 (6H, m), 1.74−1.97 (3H, m), 2.20−2.48 (5H, m), 2.59 (2H, q, *J* 7.4), 2.77−2.83 (2H, m), 4.03−4.12 (2H, m), 4.49 (1H, s), 5.26−5.37 (1H, m), 6.48 (1H, s), 7.06 (1H, s). HRMS (ES+): *m/z* found 349.2129; $C_{22}H_{30}O_2Na^+$ (M^++Na) requires 349.2138. Anal. ($C_{22}H_{30}O_2$) C, H.

(*Z*)-2-Ethyl-3-hydroxy-17- (2-hydroxyethylidene)estra-1,3, 5(10)-triene 39. Compound **35** (180 mg, 0.49 mmol) was treated with DIBAL-H (1 M in THF, 1.0 mL, 1.0 mmol) in THF (5 mL) as described for the synthesis of **38**. Purification by flash column chromatography (hexane to hexane/EtOAc 4:1) afforded compound **39** as a white powder (90 mg, 56%), mp 149−151 °C. δ_H 0.93 (3H, s), 1.23 (3H, t, *J* 7.4), 1.28−1.61 (6H, m), 1.72−1.82 (2H, m), 1.87−1.92 (1H, m), 2.19−2.40 (4H, m), 2.47−2.54 (1H, m), 2.60 (2H, q, *J* 7.4), 2.74−2.83 (2H, m), 4.21 (1H, dd, *J* 12.1, 7.4), 4.35 (1H, dd, *J* 12.1, 7.4), 4.57 (1H, s, br), 5.32−5.37 (1H, m), 6.50 (1H, s), 7.04 (1H, s). HRMS (ES+): *m/z* found 349.2151; $C_{22}H_{30}O_2Na^+$ (M^++Na) requires 349.2138. Anal. ($C_{22}H_{30}O_2$) C, H

2-Ethyl-3-*O*-sulfamoyl-17-vinyl-estra-1,3,5(10),16-tetraene 40. Compound **38** (80 mg, 0.24 mmol) was treated with sulfamoyl chloride (0.5 mmol) in DMA (1.0 mL) as described for the synthesis of compound **16**. Purification by flash column chromatography (hexane/EtOAc 10:1 to 3:1) afforded compound **40** as a colorless oil (52 mg, 56%). δ_H 0.91 (3H, s), 1.21 (3H, t, *J* 7.4), 1.27−1.55 (2H, m), 1.61−1.73 (4H, m), 1.85−2.07 (2H, m), 2.18−2.39 (4H, m), 2.69 (2H, q, *J* 7.4), 2.83−2.92 (2H, m), 4.88−4.97 (1H, m), 4.99 (2H, s), 5.35 (1H, d, *J* 18.0), 5.73 (1H, s, br), 6.32 (1H, dd, *J* 18.0, 11.4), 7.10 (1H, s), 7.18 (1H, s). HRMS (ES+): *m/z* found 388.1937; $C_{22}H_{30}NO_3S^+$ (M^+ + H) requires 388.1941.

Treatment of **39** (80 mg, 0.24 mmol) with sulfamoyl chloride (0.5 mmol) in DMA (1.0 mL) also yielded **40** (70 mg, 74%).

(*E*)-2-Ethyl-3-hydroxy-17-(2-methoxyethylidene)estra-1,3, 5(10)-triene 41. Compound **21** (0.9 g, 1.97 mmol) was treated with lithium aluminum hydride (0.45 g, 12 mmol) in THF (30 mL) at 0 °C as described for the synthesis of compound **25**. Purification by flash column chromatography (hexane/EtOAc 15:1 to 6:1) afforded the allylic alcohol as a white powder (0.75 g, 89%), mp 61−62 °C. δ_H 0.84 (3H, s), 1.20−1.66 (9H, m), 1.82−2.02 (3H, m), 2.21−2.51 (3H, m), 2.71 (2H, q, *J* 7.4), 2.82−2.89 (2H, m), 4.10−4.21 (2H, m), 5.07 (2H, s), 5.28−5.34 (1H, m), 6.66 (1H, s), 7.15 (1H, s), 7.30−7.48 (5H, m). HRMS (ES+): *m/z* found 417.2793; $C_{29}H_{37}O_2^+$ (M^+ + H) requires 417.2788. Method was as for **17** using the allylic alcohol, sodium hydride (60% dispersion in mineral oil, 80 mg, 2 mmol), and iodomethane (0.19 mL, 3.0 mmol) in THF (10 mL) at room temperature for 18 h. Purification by flash column chromatography (hexane/EtOAc 20:1) afforded the methyl ether as a colorless oil (0.59 g, 91%). δ_H: 0.84 (3H, s), 1.24 (3H, t, *J* 7.4), 1.26−1.66 (6H, m), 1.82−2.02 (3H, m), 2.20−2.51 (3H, m), 2.70 (2H, q, *J* 7.4), 2.82−2.89 (2H, m), 3.36 (3H, s), 3.90−3.97 (2H, m), 5.06 (2H, s), 5.24−5.30 (1H, m), 6.66 (1H, s), 7.15 (1H, s), 7.31−7.48 (5H, m). HRMS (ES+): *m/z* found 431.2937; $C_{30}H_{39}O_2^+$ (M^+ + H) requires 431.2945. A solution of the benzyl ether (180 mg, 0.42 mmol) in *t*-BuOH (10 g) was refluxed and treated sodium (∼50 mg). Further chunks of sodium were added every hour until deprotection was complete by TLC (8 h). The mixture was cooled, and the reaction was then quenched with isopropanol. The mixture was then diluted with water. The organics were extracted with ethyl acetate, and the organic layer was washed with water, brine and then evaporated. Purification by flash column chromatography (hexane/EtOAc 15:1 to 8:1) afforded **41** as a white powder (95 mg, 67%), mp 133−134 °C. δ_H 0.79 (3H, s), 1.22 (3H, t, *J* 7.4), 1.28−1.60 (6H, m), 1.75−1.96 (3H, m), 2.18 (1H, m), 2.39 (3H, m), 2.59 (2H, q, *J* 7.4), 2.79 (2H, m), 3.35 (3H, s), 3.90−3.98 (2H, m), 5.11 (1H, s), 5.21−5.28 (1H, m), 6.48 (1H, s), 7.05 (1H, s). HRMS (ES+): *m/z* found 341.2472; $C_{23}H_{33}O_2^+$ (M^+ + H) requires 341.2475. Anal. ($C_{23}H_{32}O_2$) C, H

(*E*)-2-Ethyl-3-*O*-sulfamoyl-17-(2-methoxyethylidene)estra-1,3,5(10)-triene 42. Compound **41** (170 mg, 0.5 mmol) was treated with sulfamoyl chloride (1.0 mmol) in DMA (1.0 mL) as described for the synthesis of compound **16**. Purification by flash column chromatography (hexane/EtOAc 10:1 to 5:1) afforded compound **42** as a white powder (142 mg, 68%), mp 126−127 °C. δ_H 0.79 (3H, s), 1.20 (3H, t, *J* 7.4), 1.22−1.67 (6H, m), 1.78−1.98 (3H, m), 2.17−2.47 (4H, m), 2.68 (2H, q, *J* 7.4), 2.82−2.88 (2H, m), 3.32 (3H, s), 3.87−3.93 (2H, m), 5.14 (2H, s), 5.18−5.24 (1H, m), 7.06 (1H, s), 7.19 (1H, s). HRMS (ES+): *m/z* found 420.2188; $C_{23}H_{34}O_4NS^+$ (M^+ + H) requires 420.2203. Anal. ($C_{23}H_{33}O_4NS$) C, H, N

(*E*)-2-Ethyl-3-*O*-sulfamoyl-17-(2-hydroxyethylidene)estra-1, 3,5(10)-triene 43. Compound **36** (110 mg, 0.25 mmol) was treated with DIBAL-H in (1 M in THF, 0.5 mL, 0.5 mmol) in THF (5 mL)

at −78 °C as described for the synthesis of compound **38**. Purification by flash column chromatography (hexane to hexane/EtOAc 1:1) afforded compound **43** as a white powder (65 mg, 65%) with mp 145−147 °C. δ_H 0.81 (3H, s), 1.22 (3H, t, *J* 7.1), 1.28−1.62 (7H, m), 1.78−2.01 (3H, m), 2.20−2.27 (1H, m), 2.32−2.47 (3H, m), 2.70 (2H, q, *J* 7.1), 2.84−2.88 (2H, m), 4.08−4.21 (2H, m), 5.04 (1H, s, br), 5.29 (1H, t, *J* 6.8), 7.08 (1H, s), 7.20 (1H, s). HRMS (ES+): *m/z* found 388.1932; $C_{22}H_{30}NO_3S^+$ (M^+−OH) requires 388.1941. Anal. ($C_{22}H_{31}O_4NS$) C, H, N

2-Ethyl-3-*O*-benzyl-17-(1-ethenyl)estra-1,3,5(10)-triene 45a. A solution of ethyltriphenylphosphonium iodide (3.75 g, 6.45 mmol) in DMSO (25 mL) was treated with sodium hydride (420 mg, 10.5 mmol, 60% dispersion in mineral oil) and then brought to 100 °C for 0.25 h. 2-Ethyl-3-*O*-benzylestrone (1.85 g, 4.76 mmol) in DMSO (10 mL) was then added to the orange reaction mixture, and heating was continued for a further 16 h. The cooled reaction mixture was then poured onto ice−water (100 mL) and extracted with ether (3 × 100 mL). The organic layers were then washed with water (3 × 100 mL), brine (10 mL), dried, and evaporated. The crude product was purified by column chromatography (hexane/ethyl acetate gradient 100−97%) to give the desired alkene **45a**, as a mixture of geometric isomers, as a clear colorless oil (1.35 g, 71%) which showed significant resonances at δ_H 0.91 and 0.89 (3H, 2*s*, 18-CH_3), 1.22 (3H, t, *J* 7.4, CH_2*Me*), 1.70 (app dt, *J* 7.2 and 1.7,: CH*Me* major isomer), 2.68 (2H, q, *J* 7.4, C*H*$_2$Me), 2.74−2.90 (2H, m, 6-CH_2), 4.98−5.25 (1H, m, CH both isomers), 5.40 (2H, s, OCH_2), 6.64 (1H, s, ArH), 7.12 (1H, s, ArH), and 7.27−7.48 (5H, m). *m/z* (AP+) 401.6 (M^+ + H, 100%) and 309.6 (65%). HRMS (ES+) *m/z* found 401.2839; $C_{29}H_{36}O$ (M^+ + H) requires 401.2834.

2-Ethyl-3-*O*-benzyl-17β-(1-hydroxyethyl) estra-1,3,5(10)-triene 46a. To a room temperature solution of **45a** (700 mg, 1.74 mmol, as a mixture of geometric isomers) was added borane THF (16 mL, 1M). The mixture was stirred for 14 h at room temperature and then treated with sodium hydroxide (20 mL, 10% aqueous) (causing vigorous gas evolution) and then hydrogen peroxide (60 mL, 27.5% aqueous). After 2 h of further stirring the THF was removed on a rotary evaporator and the resultant mixture was extracted into ether (2 × 100 mL). The combined organic layers were then washed with water (2 × 100 mL) and brine (75 mL), dried, and evaporated to give a colorless oil. The crude product was purified by column chromatography to give two fractions. The second fraction (R_f = 0.22 in 15% ethyl acetate/hexane), a clear colorless oil (350 mg, 48%), proved to be the desired alcohol **46a** as a single diastereoisomer with 17β configuration at C-17 (likely (*S*)-configuration at C-20). δ_H 0.65 (3H, s), 1.21 (3H, t, *J* 7.4), 1.18−2.34 (21H, m, including 1.26 (3H, d, *J* 6.2) and 1.20 (3H, t, *J* 7.4)), 2.66 (2H, q, *J* 7.4), 2.76−2.92 (2H, m), 3.69−3.79 (1H, m), 5.04 (2H, s), 6.63 (1H, s), 7.09 (1H, s), and 7.29−7.44 (5H, m). *m/z* (AP+) 419.6 (M^+ + H, 100%) and 401.6 (75%). HRMS (ES+) *m/z* found 419.2945; $C_{29}H_{38}O_2$ (M^+ + H) requires 419.2950.

2-Ethyl-3-*O*-benzyl-17β-(acyl)estra-1,3,5(10)-triene 47a. To a stirred, 0 °C solution of **46a** (330 mg, 0.77 mmol) in dichloromethane (20 mL) was added Dess−Martin periodinane (392 mg, 1.2 equiv, 0.92 mmol) in one portion. The mixture was stirred overnight and then diluted with ether (100 mL) and sodium hydroxide (2 mL, 1 M aqueous) and then stirred for a further 0.5 h prior to washing with water (100 mL) and brine (100 mL), drying, and evaporating. The desired ketone **47a** was isolated by adding hexane to the resultant oil which caused white needles to form (280 mg, 87%), mp 134−135 °C (R_f = 0.45 in 4:1 hexane/ethyl acetate). δ_H 0.65 (3H, s), 1.21 (3H, t, *J* 7.4), 1.25−2.40 (13H, m), 2.15 (3H, s), 2.66 (2H, q, *J* 7.4), 2.59−2.71 (1H, m), 2.76−2.92 (2H, m), 5.04 (2H, s), 6.63 (1H, s), 7.10 (1H, s), and 7.28−7.45 (5H, m). *m/z* (AP+) 417.6 (M^+ + H, 100%).

2-Ethyl-3-*O*-hydroxy-17β-acylestra-1,3,5(10)-triene 48a. A solution of **47a** (260 mg, 0.62 mmol) in THF (3 mL) and methanol (20 mL) was treated with Pd/C (10%, 50 mg) as described for the synthesis of compound **15**. The mixture was then filtered through a pad of Celite and evaporated to give **48a** as a white solid (180 mg, 89%) which was then crystallized from ethyl acetate/hexane to give white needles, mp 197−200 °C. δ_H 0.64 (3H, s), 1.21 (3H, t, *J* 7.4), 1.24−1.90 (9H, m), 2.15 (3H, s), 2.12−2.40 (4H, m), 2.58 (2H, q, *J* 7.4), 2.60 (1H, app t, *J* 9.4), 2.74−2.86 (2H, m), 4.72 (1H, s), 6.49 (1H, s), and 7.03 (1H, s). *m/z* (AP−) 325.6 (M^+, 100%) and 267.5 (75%).

2-Ethyl-3-*O*-sulfamoyl-17β-acylestra-1,3,5(10)-triene 49a. Compound **48a** (80 mg, 0.25 mmol) was treated with sulfamoyl chloride (0.6 mmol) in DMA (2 mL) as described for the synthesis of compound **16**. The desired product 2-ethyl-3-*O*-sulfamoyl-17β-acylestrone was purified by column chromatography (10% acetone in chloroform) to give a white solid (95 mg, 95%). This material was crystallized from ethyl acetate/hexane to give **49a** as fine white needles (73 mg of first crop), mp 192−194 °C. δ_H 0.65 (3H, s, 18-CH_3), 1.21 (3H, t, *J* 7.4), 1.24−1.93 (9H, m), 2.15 (3H, s), 2.15−2.40 (4H, m), 2.60 (1H, dd, *J* 9.4, 9.0), 2.69 (2H, q, *J* 7.4), 2.81−2.87 (2H, m), 4.93 (2H, s), 7.07 (1H, s), and 7.17 (1H, s). *m/z* (AP−) 404.5 (M^+, 100%). HRMS (ES+) *m/z* found 423.2316; $C_{22}H_{31}SO_4N^+$ + NH_4 (or $C_{22}H_{35}SO_4N_2^+$) (M^+ + NH_4) requires 423.2312.

2-Methoxy-3-*O*-benzyl-17-(1-ethenyl)estra-1,3,5(10)-triene 45b. A solution of ethyltriphenylphosphonium iodide (1.25 g, 3 mmol) in DMSO (20 mL) was treated with sodium hydride (120 mg, 3 mmol, 60% dispersion in mineral oil) and then brought to 100 °C for 0.25 h. 2-Methoxy-3-*O*-benzylestrone (390 mg, 1 mmol) was then added to the red reaction mixture, and heating was continued for a further 16 h. The cooled reaction mixture was then poured onto ice−water (50 mL) and extracted with ether (3 × 30 mL). The organic layers were then washed with water (3 × 30 mL), brine (10 mL), dried, and evaporated. The crude product was purified by column chromatography (hexane/ethyl acetate gradient 100−94%) to give the desired alkene **45b** as a mixture of geometric isomers (∼9:1) as a clear colorless oil (200 mg, 57%). δ_H 0.93 and 0.80 (3H, 2s), 1.25−2.54 (14 H, m including 1.70 (app dt, *J* 7.2, 1.7)), 2.68−2.84 (2H, m), 3.88 (3H, s), 5.08−5.23 (1H, m), 5.12 (2H, s), 6.64 (1H, s), 6.87 (1H, s), 7.26−7.48 (5H, m). *m/z* (ES+) 425.2 (M^+ + Na, 100%).

2-Methoxy-3-*O*-benzyl-17β-(1-hydroxyethyl)estra-1,3,5(10)-triene 46b. To an ice cold solution of **45b** (160 mg, 0.39 mmol) in THF (5 mL) was added borane−THF (5 mL, 5 mmol). The mixture was stirred for 14 h at 0 °C, then treated with sodium hydroxide (5 mL, 10% aqueous) and hydrogen peroxide (5 mL, 30% aq). After the mixture was further stirred for 1 h, the THF was removed on a rotary evaporator and the resultant mixture was extracted into ether (2 × 30 mL). The combined organic layers were then washed with water (2 × 20 mL) and brine (25 mL), dried, and evaporated to give a colorless oil. The crude product was purified by column chromatography (4:1 hexane/ethyl acetate) to give the desired alcohol **46b** as a white solid (98 mg, 59%). δ_H 0.66 (3H, s), 1.15−2.30 (17H, m including 1.24 (3H, s)), 2.68−2.80 (2H, m), 3.70−3.83 (1H, m), 3.85 (3H, s), 5.09 (2H, s), 6.61 (1H, s), 6.82 (1H, s), 7.26−7.45 (5H, m). *m/z* (ES+) 443.6 (M^+ + Na, 100%).

2-Methoxy-3-*O*-benzyl-17β-(acyl)estra-1,3,5(10)-triene 47b. To a stirred, 0 °C solution of **46b** (90 mg, 0.21 mmol) in dichloromethane (5 mL) was added Dess−Martin periodinane (109 mg, 1.2 equiv, 0.26 mmol) in one portion. The mixture was stirred for 16 h and then diluted with ether (75 mL) and sodium hydroxide (1 mL, 1 M aqueous) and then stirred for a further 0.5 h prior to washing with water (100 mL) and brine (100 mL), drying, and evaporating. The desired ketone **47b** was obtained as a white solid (70 mg, 80%). δ_H 0.64 (3H, s, 18-CH_3), 1.20−1.95 (10H, m), 2.08−2.34 (6H, m including 2.14 (3H, s)), 2.60 (1H, dd, *J* 9.1, 8.6), 2.70−2.80 (2H, m), 3.85 (3H, s), 5.09 (2H, s), 6.61 (1H, s), 6.82 (1H, s), 7.26−7.45 (5H, s). *m/z* (ES+) 441.6 (M^+ + Na, 100%).

2-Methoxy-3-*O*-hydroxy-17β-acylestra-1,3,5(10)-triene 48b. Compound **47b** (55 mg, 0.13 mmol) in THF (1 mL) and methanol

(5 mL) was treated with Pd/C (10%, 15 mg) as described for the synthesis of compound **15**. The resultant solid was washed with a small volume of ethyl acetate to remove colored impurities, and the resultant white solid was collected by filtration and dried to give **48b** as a white solid (35 mg, 82%), mp 217−219 °C. δ_H 0.65 (3H, s), 1.20−1.91 (10H, m), 2.10−2.34 (6H, m including 2.14 (3H, s)), 2.60 (1H, dd, *J* 8.9, 8.1), 2.72−2.82 (2H, m), 3.89 (3H, s), 5.41 (1H, s, OH), 6.63 (1H, s), 6.77 (1H, s). *m/z* (ES−) 327.6 (M^+ − H), 100%). HRMS (ES+) *m/z* found 329.2122; $C_{21}H_{29}O_3^+$ (M^+ + H) requires 329.2117.

2-Methoxy-3-*O*-sulfamoyl-17β-acylestra-1,3,5(10)-triene 49b. Compound **48b** (22 mg, 0.093 mmol) in DMA (1.5 mL) was added treated with sulfamoyl chloride (0.65 mmol) as described for the synthesis of compound **16**. The desired sulfamate **49b** was crystallized from ethyl acetate/hexane to give fine white needles (15 mg, 40% first crop), mp 178−180 °C. δ_H 0.66 (3H, s, 18-CH_3), 1.30−2.35 (H, m including 2.14 (3H, s)), 2.60 (1H, dd, *J* 9.0, 9.0), 2.82−2.90 (2H, m), 3.87 (3H, s), 4.97 (2H, s), 6.91 (1H, s), 7.02 (1H, s). *m/z* (ES−) 406.6 (M^+, 100%). HRMS (ES+) *m/z* found 425.2105; $C_{21}H_{29}SO_5N^+ + NH_4$ (or $C_{21}H_{33}SO_5N_2^+$) ($M^+ + NH_4$) requires 425.2105.

2-Methoxy-3-benzyloxy-17β-cyanomethylestra-1,3,5(10)-triene 50. Diethyl cyanomethylphosphonate (3.55 g, 20 mmol) in THF (60 mL) was treated with NaH (60% dispersion in mineral oil, 0.4 g, 20 mmol). 2-Methoxy-3-*O*-benzylestrone (3.94 g, 10 mmol) in THF (20 mL) was added dropwise at room temperature, and the solution was stirred for 18 h. The reaction mixture was cooled to 0 °C, and water (30 mL) was added. The mixture was extracted with EtOAc. The organic layer was washed with water and brine, then dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (hexane/EtOAc 25:1 to 6:1) afforded the olefin (mixture of *Z* and *E* isomers). The olefin was treated with Pd/C (10%, 200 mg) in THF (15 mL) and methanol (50 mL) as described for the synthesis of compound **15**. The resultant suspension was filtered through Celite, washed with EtOAc, and concentrated in vacuo. The residue was stirred with potassium carbonate (2.8 g, 20 mmol) and benzyl bromide (1.18 mL, 10 mmol) in DMF (20 mL) for 24 h at room temperature. Water (50 mL) was added, and the mixture was extracted with EtOAc (2 × 80 mL). The combined organics were washed with water and brine, then dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (hexane/EtOAc 20:1 to 5:1) afforded compound **50** as a white solid (3.45 g, 83% over three steps), mp 175−176 °C. δ_H 0.67 (3H, s), 1.21 (3H, t, *J* 7.4), 1.21−1.52 (7H, m), 1.75−1.88 (3H, m), 1.96−2.11 (2H, m), 2.17−2.41 (4H, m), 2.71−2.77 (2H, m), 3.85 (3H, s), 5.10 (2H, s), 6.61 (1H, s), 6.82 (1H, s), 7.25−7.45 (5H, m). LC/MS (ES+): *m/z* 416.2 (M^+ + H).

2-Methoxy-3-benzyloxyestra-1,3,5(10)-triene-17β-acetaldehyde 51. Compound **50** (1.5 g, 3.6 mmol) was treated with DIBAL (1.5 M in THF, 7.2 mL, 10.8 mmol) in THF (30 mL) at 0 °C as described for the synthesis of compound **38**. After addition of HCl (2 M, 20 mL) the mixture was stirred for 0.5 h and then extracted with EtOAc (3 × 30 mL). The combined organics were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford compound **51** as a white powder (1.15 g, 77%), mp 142−144 °C. δ_H 0.64 (3H, s), 1.21−1.52 (7H, m), 1.75−2.05 (5H, m), 2.15−2.35 (3H, m), 2.49−2.57 (1H, m), 2.66−2.78 (2H, m), 3.85 (3H, s), 5.10 (2H, s), 6.61 (1H, s), 6.83 (1H, s), 7.26−7.45 (5H, m), 9.78 (1H, t, *J* 2.2).

2-Methoxy-3-benzyloxy-17β-(2-hydroxypropyl)estra-1,3,5(10)-triene 52. A solution of **51** (420 mg, 1.0 mmol) in THF (10 mL) was stirred under nitrogen, cooled to 0 °C, and treated with methylmagnesium bromide (3 M in diethyl ether, 0.50 mL, 1.5 mmol). The reaction mixture was stirred at 0 °C for 4 h. Ammonium chloride (saturated, 5 mL) was added, and the mixture was extracted with EtOAc (2 × 30 mL). The combined organics were washed with water and brine, then dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (hexane/EtOAc 20:1 to 3:1) afforded compound **52** as a white powder (300 mg, 69%), mp 77−80 °C. δ_H 0.61 and 0.62 (3H, 2s), 1.18−1.60 (13H, m), 1.68−2.00 (4H, m), 2.12−2.28 (2H, m), 2.65−2.83 (2H, m), 3.78−3.87 (3H, m), 5.10 (2H, s), 6.61 (1H, s), 6.84 (1H, s), 7.26−7.45 (5H, m). HRMS (FAB+): *m/z* found 435.2880; $C_{29}H_{39}O_3^+$ (M^+ + H) requires 435.2894.

2-Ethyl-3-benzyloxy-17β-(2-hydroxypropyl)estra-1,3,5(10)-triene 58. Compound **57**[24] (390 mg, 0.94 mmol) was treated with methylmagnesium bromide (3 M in diethyl ether, 0.5 mL, 1.5 mmol) in THF (10 mL) at 0 °C as described for the synthesis of **52**. Purification by flash column chromatography (hexane/EtOAc 20:1 to 10:1) afforded compound **58** as a white powder (310 mg, 77%), mp 66−69 °C. δ_H 0.61 and 0.63 (3H, s), 1.18−1.59 (17H, m), 1.73−1.96 (3H, m), 2.16−2.35 (2H, m), 2.66 (2H, q, *J* 7.4), 2.83 (2H, m), 3.84 (1H, m), 5.03 (2H, s), 6.63 (1H, s), 7.11 (1H, s), 7.27−7.46 (5H, m). HRMS (ES+): *m/z* found 433.3093; $C_{30}H_{41}O_2^+$ (M^+ + H) requires 433.3101.

2-Methoxy-3-benzyloxy-17β-(2-oxopropyl)estra-1,3,5(10)-triene 53. A solution of **52** (250 mg, 0.58 mmol) in DCM (10 mL) was stirred at 0 °C, and Dess−Martin periodinane (293 mg, 0.69 mmol) was added portionwise. The reaction mixture was stirred at 0 °C for 4 h. Then diethyl ether (50 mL) and sodium hydroxide (1 M, 5 mL) were added, and the solution was stirred at 0 °C for 1 h. The organic layer was separated, washed with water and brine, then dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (hexane/EtOAc 10:1 to 5:1) afforded compound **53** as a white powder (165 mg, 66%), mp 120−121 °C. δ_H 0.62 (3H, s), 1.20−1.52 (7H, m), 1.73−2.02 (5H, m), 2.16 (3H, s), 2.20−2.31 (3H, m), 2.52 (1H, dd, *J* 15.8, 3.6), 2.76−2.82 (2H, m), 3.85 (3H, s), 5.09 (2H, s), 6.61 (1H, s), 6.83 (1H, s), 7.28−7.45 (5H, m). HRMS (ES+): *m/z* found 433.2731; $C_{29}H_{37}O_3^+$ (M^+ + H) requires 433.2737.

2-Ethyl-3-benzyloxy-17β-(2-oxopropyl)estra-1,3,5(10)-triene 59. Compound **58** (290 mg, 0.67 mmol) was treated with Dess−Martin periodinane (355 mg, 0.83 mmol) in DCM (20 mL) at 0 °C as described for the synthesis of compound **53**. Purification by flash column chromatography (hexane/EtOAc 10:1 to 5:1) afforded compound **59** as a white powder (220 mg, 76%), mp 46−47 °C. δ_H 0.65 (3H, s), 1.23 (3H, t, *J* 7.3), 1.26−1.58 (7H, m), 1.65−2.05 (5H, m), 2.18 (3H, s), 2.20−2.41 (3H, m), 2.52−2.59 (1H, m), 2.69 (2H, q, *J* 7.3), 2.83−2.88 (2H, m), 5.06 (2H, s), 6.63 (1H, s), 7.13 (1H, s), 7.30−7.48 (5H, m). HRMS (ES+): *m/z* found 431.2937; $C_{30}H_{39}O_2^+$ (M^+ + H) requires 431.2945.

2-Methoxy-3-hydroxy-17β-(2-oxopropyl)estra-1,3,5(10)-triene 54. Compound **53** (155 mg, 0.36 mmol) was treated with Pd/C (10%, 20 mg) in THF (5 mL) and methanol (15 mL) as described for the synthesis of compound **15**. Purification by flash column chromatography (hexane/EtOAc 6:1) afforded compound **54** as a white powder (105 mg, 86%), mp 177−178 °C. δ_H 0.62 (3H, s), 1.20−1.58 (7H, m), 1.72−2.02 (5H, m), 2.16 (3H, s), 2.19−2.32 (3H, m), 2.52 (1H,dd, *J* 15.7, 3.9), 2.72−2.79 (2H, m), 3.84 (3H, s), 5.42 (1H, s), 6.63 (1H, s), 6.77 (1H, s). HRMS (FAB+): *m/z* found 343.2264; $C_{22}H_{31}O_3^+$ (M^+ + H) requires 343.2268. Anal. ($C_{23}H_{30}O_3$) C, H.

2-Ethyl-3-hydroxy-17β-(2-oxopropyl)estra-1,3,5(10)-triene 60. Compound **59** (200 mg, 0.46 mmol) was treated with Pd/C (10%, 30 mg) in THF (5 mL) and methanol (15 mL) as described for the synthesis of compound **15**. Purification by flash column chromatography (hexane/EtOAc 5:1) afforded compound **60** as a white powder (145 mg, 92%), mp 125−126 °C. δ_H 0.63 (3H, s), 1.23 (2H, t, *J* 7.3), 1.27−1.53 (7H, m), 1.74−1.81 (2H, m), 1.84−1.93 (2H, m), 1.95−2.03 (1H, m), 2.18 (3H, s), 2.16−2.24 (1H, m), 2.26−2.33 (1H, m), 2.52−2.58 (1H, m), 2.60 (2H, q, *J* 7.3), 2.74−2.82 (2H, m), 4.99 (1H, s), 6.51 (1H, s), 7.05 (1H, s). HRMS (FAB+): *m/z* found 340.2394; $C_{23}H_{32}O_2^+$ (M^+) requires 340.2402. Anal. ($C_{23}H_{32}O_2$) C, H.

2-Methoxy-3-*O*-sulfamoyl-17β-(2-oxopropyl)estra-1,3,5(10)-triene 55. Compound **54** (70 mg, 0.2 mmol) was treated with sulfamoyl chloride (0.6 mmol) in DMA (1.0 mL) as described for the synthesis of

compound **16**. Purification by flash column chromatography (hexane/EtOAc 5:1 to 3:1) afforded compound **55** as a white powder (70 mg, 66%), mp 186−187 °C. δ_H (acetone-d_6): 0.66 (3H, s), 1.22−1.56 (7H, m), 1.70−1.98 (5H, m), 2.10 (3H, s), 2.22−2.40 (3H, m), 2.57 (1H, dd, *J* 15.9, 3.7), 2.72−2.79 (2H, m), 3.82 (3H, s), 6.90 (2H, s, br), 6.90 (1H, s), 7.01 (1H, s). HRMS (ES+): *m/z* found 422.2002; $C_{22}H_{32}NO_5S^+$ ($M^+ + H$) requires 422.1996. Anal. ($C_{22}H_{31}NO_5S$) C, H, N.

2-Ethyl-3-*O*-sulfamoyl-17β-(2-oxopropyl)estra-1,3,5(10)-triene 61. Compound **60** (100 mg, 0.29 mmol) was treated with sulfamoyl chloride (0.6 mmol) in DMA (1.0 mL) as described for the synthesis of compound **16**. Purification by flash column chromatography (hexane/EtOAc 5:1 to 3:1) afforded compound **61** as a white powder (100 mg, 81%), mp 204−205 °C. δ_H (acetone-d_6): 0.40 (3H, s), 0.94 (3H, t, *J* 7.3), 0.95−1.33 (7H, m), 1.51−1.77 (5H, m), 1.91 (3H, s), 1.99−2.12 (3H, m), 2.28−2.34 (1H, m), 2.45 (2H, q, *J* 7.3), 2.56−2.63 (2H, m), 6.27 (2H, s), 6.84 (1H, s), 6.92 (1H, s). HRMS (FAB+): *m/z* found 419.2123; $C_{23}H_{33}NO_4S^+$ (M^+) requires 419.2130. Anal. ($C_{23}H_{33}NO_4S$) C, H, N.

2-Methoxy-3-(triisopropylsilyloxy)estrone 62. 2-Methoxyestrone (1.801 g, 6.0 mmol) was treated with chlorotriisopropylsilane (1.389 g, 7.2 mmol) and imidazole (1.225 g, 18.0 mmol) in DMF (18 mL) as described for the synthesis of compound **19**. Compound **62** was isolated as a pale yellow oil (3.31 g, >99%). δ_H (0.91 (3H, s), 1.03−1.10 (18H, m), 1.14−1.31 (3H, m), 1.32−1.69 (6H, m), 1.90−2.30 (5H, m), 2.31−2.39 (1H, m), 2.49 (1H, dd, *J* 18.2, 8.3), 2.68−2.87 (2H, m), 3.75 (3H, s), 6.56 (1H, s), 6.74 (1H, s). HRMS (ES+): *m/z* found 457.3125; $C_{28}H_{45}O_3Si^+$ ($M^+ - H$) requires 457.3133.

2-Methoxy-3-(triisopropylsilyloxy)-17β-(2-ethoxy-2-oxoethyl)estra-1,3,5(10)-triene 63. Triethyl phosphonoacetate (3.624 g, 16.2 mmol) in THF (10 mL) was treated with sodium hydride (60%, 661 mg, 16.5 mmol). Compound **62** (3.20 g; 5.8 mmol) in THF (20 mL) was added dropwise, and the mixture was refluxed for 60 h. The reaction mixture was cooled to 0 °C, poured into water (30 mL), and extracted with DCM (4 × 50 mL). The combined organics were washed with ammonium chloride (saturated, 50 mL) and brine, then dried ($MgSO_4$)), filtered, and concentrated in vacuo. Purification by flash column chromatography (hexane to hexane/EtOAc 20:1) gave the olefin as a pale yellow oil (4.68 g, >99%). δ_H 0.85 (3H, s), 1.02−1.09 (18H, m), 1.12−1.63 (12H, m), 1.74−2.04 (3H, m), 2.13−2.39 (2H, m), 2.64−3.03 (4H, m), 3.74 (3H, s), 4.06−4.23 (2H, m), 5.57 (1H × 0.85, t, *J* 2.5, *E*-isomer), 5.66 (1H × 0.15, t, *J* 2.1, *Z*-isomer), 6.55 (1H, s), 6.74 (1H, s). HRMS (ES+): *m/z* found 527.3540; $C_{32}H_{51}O_4Si^+$ ($M^+ - H$) requires 527.3551. The above olefin (4.50 g, 5.6 mmol) was treated with Pd/C (10%, 458 mg) in THF (18 mL) and MeOH (6 mL) as described for the synthesis of compound **15**. Compound **63** was obtained as a pale brown oil (4.31 g, 95%). δ_H 0.63 (3H, s), 1.02−1.10 (18H, m), 1.14−1.51 (12H, m), 1.59−2.02 (6H, m), 2.05−2.28 (3H, m), 2.39 (1H, dd, *J* 14.6, 4.7), 2.61−2.78 (2H, m), 3.74 (3H, s), 4.11 (2H, q, *J* 7.2), 6.54 (1H, s), 6.74 (1H, s). HRMS (ES+): *m/z* found 529.3699; $C_{32}H_{53}O_4Si^+$ ($M^+ - H$) requires 529.3708.

2-Methoxy-3-(triisopropylsilyloxy-17β-(2-oxopropyl)estra-1,3,5(10)-triene 64. Tebbe reagent (0.5 M in toluene, 12.6 mL, 6.3 mmol) was added dropwise over 15 min into a solution of compound **63** (4.20 g, 5.2 mmol) in toluene (17.4 mL), THF (10 mL) and pyridine (0.84 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, then warmed to 0 °C within 2 h. The reaction mixture was poured into HCl (2 M, 400 mL), stirred vigorously at room temperature for 16 h, and extracted with diethyl ether (3 × 100 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 80 g, hexane/diethyl ether 9:1) afforded compound **64** as a light brownish oil (2.504 g, 92% overall from 2-methoxyestrone). δ_H 0.61 (3H, s), 1.02−1.10 (18H, m), 1.12−1.55 (11H, m), 1.71−2.04 (4H, m), 2.15 (3H, s), 2.17−2.35 (3H, m), 2.52 (1H, dd, *J* 15.7, 3.8), 2.62−2.82 (2H, m), 3.74 (3H, s), 6.54 (1H, s), 6.73 (1H, s). HRMS (ES+): *m/z* found 499.3607; $C_{31}H_{51}O_3Si^+$ ($M^+ - H$) requires 499.3602.

2-Methoxy-3-hydroxy-17β-(2-oxopropyl)estra-1,3,5(10)-triene 54. Compound **64** (1.993 g, 4.0 mmol) was treated with TBAF (1 M in THF, 4.4 mL, 4.4 mmol) in THF (7.6 mL) as described for the synthesis of compound **20**. Purification by flash column chromatography (SiO_2, 50 g, hexane/EtOAc 9:1 to 4:1) afforded compound **54** as white solid (1.12 g, 82%). Data are as above.

2-Methoxy-3-*O*-sulfamoyl-17β-(2-oxopropyl)estra-1,3,5(10)-triene 55. By use of the method described for the synthesis of **16**, compound **54** (1.028 g, 3.0 mmol) was reacted with sulfamoyl chloride (9.0 mmol) in DMA (9.0 mL) at room temperature for 2 h. Purification by flash column chromatography (SiO_2, 60 g, chloroform/acetone 9:1) and crystallization from diethyl ether afforded compound **55** as white solid (1.026 g, 81%). Data are as above.

17β-(2-Hydroxypropyl)-2-methoxy-3-*O*-sulfamoylestra-1,3,5(10)-triene 65. Sodium borohydride (15.5 mg, 0.4 mmol) was added to 2-propanol (4.0 mL) under stirring. A solution of compound **55** (84 mg, 0.2 mmol) in THF (2.0 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 2 h. The mixture was then poured into water (40 mL) and ammonium chloride (saturated, 10 mL) and extracted with EtOAc (3 × 30 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 10 g, chloroform/acetone 9:1) afforded compound **65** as a fluffy white solid (63 mg, 75%), mp 170−172 °C. δ_H 0.51 (3H, s), 1.02−1.56 (15H, m), 1.59−1.70 (1H, m), 1.72−1.89 (3H, m), 2.59−2.73 (2H, m), 3.74 (3H, s), 6.26 (2H, s, br), 6.81 (1H, s), 6.93 (1H, s). LC/MS (ES−): *m/z* 422.43 (M^- − H) and 422.50 (M^- − H). HRMS (ES−): *m/z* found 422.2013; $C_{22}H_{32}NO_5S^-$ (M^- − H) requires 422.2006.

17β-(2-Hydroxyiminopropyl)-2-methoxy-3-*O*-sulfamoylestra-1,3,5(10)-triene 66. Compound **55** (84 mg, 0.2 mmol), sodium acetate (165 mg, 2.0 mmol), and hydroxylamine hydrochloride (141 mg, 2.0 mmol) were mixed together and dissolved in methanol (3.6 mL) and water (0.4 mL). The reaction mixture was stirred at room temperature for 2 h and then concentrated in vacuo. Water (20 mL) and ammonium chloride (saturated, 20 mL) were added, and the mixture was extracted with EtOAc (2 × 30 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 10 g, DCM/acetone 4:1) afforded compound **66** as a white wax (mixture of *Z* and *E* isomers) (44 mg, 51%). δ_H ($CDCl_3$/DMSO-d_6) 0.57 (3H × 0.75, s, *E*-isomer), 0.60 (3H × 0.25, s, *Z*-isomer), 1.09−1.51 (7H, m), 1.54−1.85 (6H, m), 1.77 (3H × 0.25, s, *Z*-isomer), 1.79 (3H × 0.75, s, *E*-isomer), 2.04−2.26 (3H, m), 2.63−2.74 (2H, m), 3.74 (3H, s), 6.22 (2H, s, br), 6.81 (1H, s), 6.94 (1H, s), 8.30 (1H, s, br). LC/MS (ES−): *m/z* 435.51 (M^- − H). HRMS (ES−): *m/z* found 435.1952; $C_{22}H_{31}N_2O_5S^-$ (M^- − H) requires 435.1959.

2-Ethyl-3-benzyloxy-17β-(2-fluoroethyl)estra-1,3,5(10)-triene 67. A solution of compound **25** (0.84 g, 2 mmol) in THF (20 mL) was cooled to 0 °C under nitrogen and treated with diethylaminosulfur trifluoride (DAST) (0.40 mL, 3.0 mmol). The reaction mixture was stirred at 0 °C for 4 h. Sodium bicarbonate (saturated, 10 mL) was added, and the mixture was extracted with EtOAc (2 × 30 mL). The combined organics were washed with water and brine, then dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (hexane/EtOAc 50:1) afforded compound **67** as a white powder (0.42 g, 50%), mp 113−114 °C. δ_H 0.66 (3H, s), 1.30 (3H, t, *J* 7.4), 1.32−1.66 (9H, m), 1.81−1.87 (1H, m), 1.92−2.04 (4H, m), 2.25−2.33 (1H, m), 2.39−2.45 (1H, m), 2.76 (2H, q, *J* 7.4), 2.84−2.95 (2H, m), 4.45−4.53 (1H, m), 4.58−4.66 (1H, m), 5.12 (2H, s), 6.72 (1H, s), 7.20 (1H, s), 7.37−7.54 (5H, s). LC/MS (APCI+): *m/z* 421.3 ($M^+ + H$).

2-Ethyl-3-hydroxy-17β-(2-fluoroethyl)estra-1,3,5(10)-triene 68. Compound **67** (420 mg, 1.0 mmol) was treated with Pd/C (10%, 30 mg) in THF (10 mL) and methanol (30 mL) as described for the synthesis of compound **15**. Purification by flash column chromatography (hexane/EtOAc 20:1 to 15:1) afforded compound **68** as a white powder (250 mg 76%), mp 138−139 °C. δ_H 0.63 (3H, s), 1.22

(3H, t, *J* 7.4), 1.25−1.61 (10H, m), 1.73−1.98 (4H, m), 2.14−2.35 (2H, m), 2.59 (2H, q, *J* 7.4), 2.77−2.88 (2H, m), 4.34−4.44 (1H, m), 4.50−4.60 (2H, m), 6.49 (1H, s), 7.05 (1H, s). HRMS (ES+): *m/z* found 331.2432; $C_{22}H_{32}FO^+$ ($M^+ + H$) requires 331.2437. Anal. ($C_{22}H_{31}FO$) C, H.

2-Ethyl-3-*O*-sulfamoyl-17β-(2-fluoroethyl)estra-1,3,5(10)-triene 69. Compound **68** (132 mg, 0.4 mmol) was treated with sulfamoyl chloride (0.5 mmol) in DMA (1.0 mL) as described for the synthesis of compound **16**. Purification by flash column chromatography (hexane/EtOAc 20:1 to 15:1) afforded compound **69** as a white powder (110 mg, 66%), mp 152−153 °C. δ_H 0.63 (3H, s), 1.21 (3H, t, *J* 7.4), 1.23−1.59 (10H, m), 1.73−1.97 (4H, m), 2.16−2.35 (2H, m), 2.68 (2H, q, *J* 7.4), 2.79−2.88 (2H, m), 4.34−4.42 (1H, m), 4.51−4.59 (1H, m), 4.90 (2H, s), 7.11 (1H, s), 7.24 (1H, s). HRMS (ES+): *m/z* found 410.2163; $C_{22}H_{33}FNO_3S^+$ ($M^+ + H$) requires 410.2165. Anal. ($C_{22}H_{32}FNO_3S$) C, H, N.

2-Ethyl-3-benzyloxy-17β-(2,2-difluoroethyl)estra-1,3,5(10)-triene 70. Compound **57** (0.86 g, 2.0 mmol) was treated with diethylaminosulfur trifluoride (DAST) (0.80 mL, 6.0 mmol) in THF (20 mL) as described for the synthesis of compound **67**. Purification by flash column chromatography (hexane/EtOAc 100:1) afforded compound **70** as a white powder (0.42 g, 48%), mp 114−115 °C. δ_H 0.64 (3H, s), 1.22 (3H, t, *J* 7.3), 1.26−2.09 (14H, m), 2.20−2.29 (1H, m), 2.31−2.40 (1H, m), 2.68 (2H, q, *J* 7.3), 2.78−2.89 (2H, m), 5.05 (2H, s), 5.84 (1H, ddt, *J* 57.3, 5.0, 3.7), 6.64 (1H, s), 7.12 (1H, s), 7.29−7.46 (5H, m). LC/MS (APCI+): *m/z* 439.1 ($M^+ + H$).

2-Ethyl-3-hydroxy-17β-(2,2-difluoroethyl)estra-1,3,5(10)-triene 71. Compound **70** (350 mg, 0.8 mmol) was treated with Pd/C (10%, 40 mg) in THF (10 mL) and methanol (30 mL) as described for the synthesis of compound **15**. Purification by flash column chromatography (hexane/EtOAc 50:1 to 40:1) afforded compound **71** as white powder (240 mg, 86%), mp 84−86 °C. δ_H 0.62 (3H, s), 1.21 (3H, t, *J* 7.3), 1.23−2.07 (14H, m), 2.16−2.24 (1H, m), 2.27−2.36 (1H, m), 2.59 (2H, q, *J* 7.3), 2.78 (2H, m), 4.58 (1H, s), 5.84 (1H, ddt, *J* 57.2, 9.2, 5.2), 6.49 (1H, s), 7.05 (1H, s). HRMS (ES+): *m/z* found 349.2340; $C_{22}H_{31}F_2O^+$ ($M^+ + H$) requires 349.2337. Anal. ($C_{22}H_{30}F_2O$) C, H, N.

2-Ethyl-3-*O*-sulfamoyl-17β-(2,2-difluoroethyl)estra-1,3,5(10)-triene 72. Compound **71** (175 mg, 0.5 mmol) was treated with sulfamoyl chloride (0.5 mmol) in DMA (1.0 mL) as described for the synthesis of compound **16**. Purification by flash column chromatography (hexane/EtOAc 15:1 to 10:1) afforded compound **72** as a white powder (155 mg, 72%), mp 164−165 °C. δ_H 0.62 (3H, s), 1.20 (3H, t, *J* 7.3), 1.23−2.08 (17H, m), 2.18−2.35 (2H, m), 2.68 (2H, q, *J* 7.3), 2.82 (2H, m), 4.93 (2H, s, br), 5.82 (1H, tt, *J* 57.0, 4.7), 7.06 (1H, s), 7.18 (1H, s). HRMS (ES+): *m/z* found 428.2068; $C_{22}H_{32}F_2NO_3S^+$ ($M^+ + H$) requires 428.2065. Anal. ($C_{22}H_{31}F_2NO_3S$) C, H, N.

■ ASSOCIATED CONTENT

Supporting Information. Elemental analysis results and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS USED

DAST, diethylaminosulfur trifluoride; VEGF, vascular endothelial growth factor; E2bisMATE, estradiol-3,17-*O*,*O*-bis-sulfamate

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