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Article

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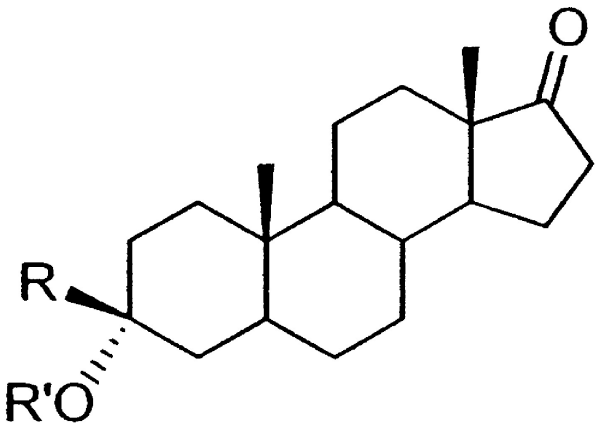

(R = H, alkyls, vinyl, allyl, phenyls
and R' = H, alkyls, allyl)

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Androsterone 3α-Ether-3β-Substituted and Androsterone 3β-Substituted Derivatives as Inhibitors of Type 3 17β-Hydroxysteroid Dehydrogenase: Chemical Synthesis and Structure−Activity Relationship

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Type 3 17β-hydroxysteroid dehydrogenase (17β-HSD) is involved in the biosynthesis of androgen testosterone. To produce potent inhibitors of this key steroidogenic enzyme, we prepared a series of androsterone (ADT) derivatives by adding a variety of substituents at position 3. The 3β-substituted ADT derivatives proved to be good inhibitors (IC_{50} = 57−147 nM) with better inhibitory activities obtained for compounds bearing a propyl, *s*-butyl, cyclohexylalkyl, or phenylalkyl group. With an IC_{50} value of 57 nM, the 3β-phenylmethyl-ADT was 6-fold more potent than ADT, the lead compound, and 13-fold more potent than 4-androstene-3,17-dione, the natural enzyme substrate used itself as inhibitor. The 3α-ether-3β-substituted ADT derivatives had a lower inhibitory activity compared to the 3β-substituted ADT analogues except for the 3β-phenylethyl-3α-methl-*O*-ADT (IC_{50} = 73 nM), which proved to be a more potent inhibitor than 3β-phenylethyl-ADT (IC_{50} = 99 nM). The results of our study identified potent type 3 17β-HSD inhibitors for potential use in the treatment of androgen-sensitive diseases.

Introduction

The last step in the formation of all androgens and estrogens is controlled by the key steroidogenic enzymes 17β-hydroxysteroid dehydrogenases (17β-HSDs).[1−6] Various known isoforms are responsible for the interconversion of 17-ketosteroids (e.g., dehydroepiandrosterone (DHEA), 4-androstenedione (Δ4-dione), and estrone (E_1)) and their corresponding more active 17β-hydroxysteroids (e.g., androst-5-ene-3β,17β-diol (Δ5-diol), testosterone (T), and 17β-estradiol (E_2)). The crucial role played by the 17β-HSD family in steroid biology probably explains the existence of a large series of isoforms having individual cell-specific expression, substrate specificity, and regulatory mechanisms.[7−10] Moreover, it makes this group of enzymes a unique target for the control of the intracellular concentration of all active sex steroids.[11−13]

Among the 17β-HSDs, we are especially interested in the third member of this ubiquitous enzyme family. In fact, type 3 17β-HSD, also referred to as testicular 17β-HSD, is principally found in the microsomal fraction of Leydig cells of the testis, where it reduces Δ4-dione into T using NADPH as a cofactor (Figure 1).[14,15] For this transformation, K_m values of 0.28 and 0.77 μM were determined for rat and human microsomal testis preparations, respectively.[16,17] It was reported that type 3 17β-HSD catalyzes the biosynthesis of approximately 50% of the total amount of androgens in men from the precursor Δ4-dione.[1] The remaining 50% would result from the same enzymatic reaction catalyzed by type 5 17β-HSD,[18] in peripheral tissues.[19] Deficiencies in testicular 17β-HSD (type 3) have been associated with pseudohermaphroditism,[14] thus showing the importance

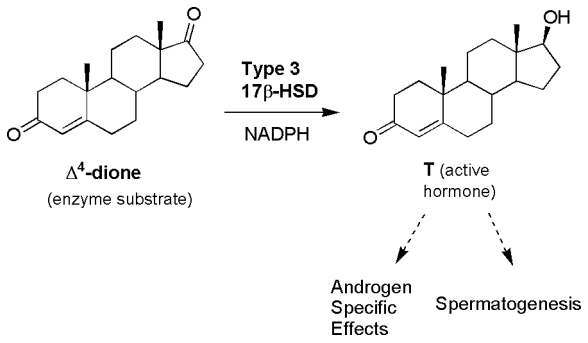

Figure 1. Transformation of 4-androstene-3,17-dione (Δ4-dione) into testosterone (T) catalyzed by type 3 17β-HSD with NADPH as cofactor.

of this enzyme in the production of T from Δ4-dione. It follows that inhibition of this enzyme could block the biosynthesis and, consequently, the action of androgens originating from the testis. On this basis, selective inhibitors of type 3 17β-HSD have the potential for being used in preventing the development of androgen-sensitive diseases such as benign hyperplasia and prostate cancer. These inhibitors could also be used as adjuvants to enhance the efficacy of androgen receptor antagonists. Considering the crucial role of T in spermatogenesis,[20] it would also be interesting to study the potential of such inhibitors as contraceptive agents.

Although several inhibitors of type 1 and type 2 17β-HSDs have been synthesized, few efforts have been made to synthesize inhibitors of type 3 17β-HSD.[11] Pittaway evaluated the ability of 20 steroidal compounds to inhibit type 3 17β-HSD activity in a microsomal preparation of canine testis.[21] This study led him to suggest that a good inhibitor would require the presence of a 17-keto group on a steroidal nucleus having a nonaromatized A-ring. More recently, a screening study led us to consider the 17-ketosteroid andros-

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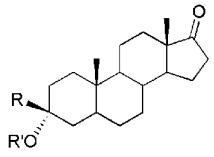
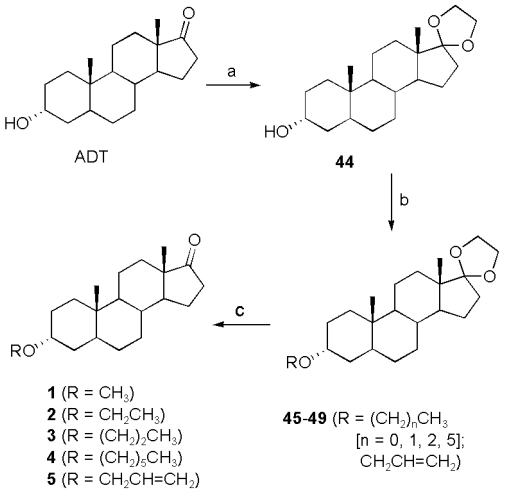


Figure 2. General structure of 3β-substituted ADT derivatives designed to inhibit the steroidogenic enzyme type 3 17β-HSD.

Scheme 1. Chemical Synthesis of ADT 3α-Ether Derivatives **1**−**5**[a]



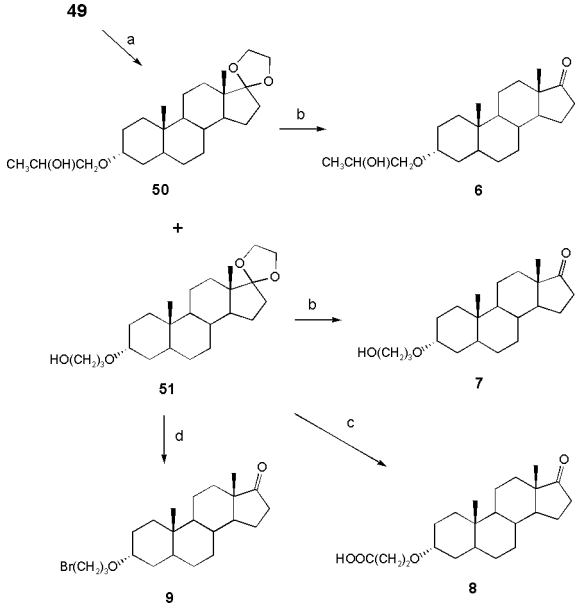
[a] Reagents: (a) $HOCH_2CH_2OH$, *p*-TSA, CH_2Cl_2, reflux; (b) NaH, RI(Br), THF, reflux; (c) aqueous H_2SO_4 (5%), 1,4-dioxane, room temp.

terone (ADT) as a potential nucleus for developing selective inhibitors of this isoform.[22] Following poor results obtained with different kinds of chemical groups at position 16 of ADT,[23] we focused on the opposite steroid nucleus side, obtaining better results by adding a hydrophobic group at position 3.[24−26] Following a preliminary report,[26] we herein present the full details of the chemical synthesis of a series of ADT 3α-ether and/or 3β-substituted derivatives, namely, compounds **1**−**43** (Figure 2), and an assessment of their ability to inhibit type 3 17β-HSD.

Results and Discussion

Chemistry. Synthesis of ADT 3α-Ether Derivatives 1−9 (Schemes 1 and 2). The synthesis of ADT 3α-ether derivatives **1**−**5** is depicted in Scheme 1. To avoid alkylation at position 16 of the keto steroid, the carbonyl of ADT was first protected as ketal with ethylene glycol in the presence of *p*-TSA. The protected form of ADT (compound **44**) was then alkylated in THF at refluxing temperature, using NaH as base and the corresponding alkyl halide (iodide or bromide). The ketals **45**−**49** were thereafter hydrolyzed with a 5% aqueous H_2SO_4 solution in dioxane to afford the desired ADT 3α-ether derivatives **1**−**5**. Other ADT 3α-ether derivatives **6**−**9** were derived from **49**, as depicted in Scheme 2. Reduction of **49** with borane in THF followed by oxidation with H_2O_2 (30%) and NaOH led to a mixture of secondary alcohol **50** and primary alcohol **51** in a ratio of 1:3, which was easily separated by flash

Scheme 2. Chemical Synthesis of ADT 3α-Ether Derivatives **6**−**9**[a]

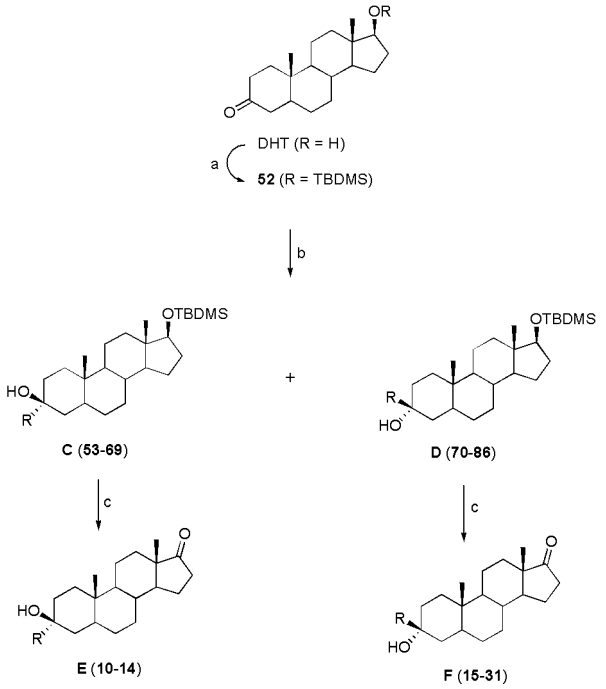


[a] Reagents: (a) (i) BH_3, THF, 0 °C; (ii) H_2O_2, NaOH (3 N); (b) aqueous H_2SO_4 (5%) 1,4-dioxane, room temp; (c) Jones' reagent (2.7 M), acetone, 0 °C; (d) CBr_4, PPh_3, CH_2Cl_2, 0 °C.

chromatography. A sample of the secondary alcohol **50** was coupled to Mosher's acid (*R*-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid) according to the procedure described by Ward and Rhee.[27] As expected, ^1H and ^{19}F NMR spectral analysis of the resulting Mosher's ester revealed that **50** was an epimeric (50/50) mixture of secondary alcohols. The ADT derivatives **6** and **7** were obtained after hydrolysis of the ketal group of **50** and **51**, respectively. Oxidation of alcohol **51** with Jones' reagent in acetone afforded the acid **8**, while submitting this same compound to CBr_4 and PPh_3 in CH_2Cl_2 yielded the bromide **9**.

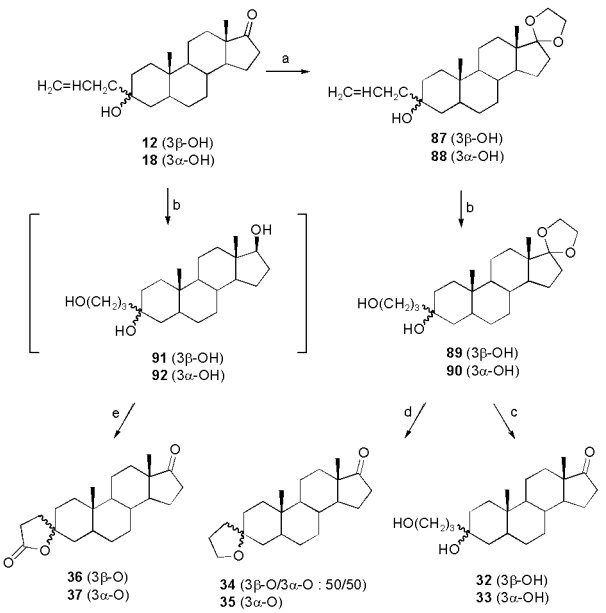
Synthesis of *epi*-ADT/ADT Derivatives 10−37 Substituted at Position 3α or 3β (Schemes 3 and 4). Dihydrotestosterone (DHT) was used as starting material for the synthesis of compounds **10**−**31** (Scheme 3). The 17β-hydroxy group of DHT was first protected as a silylated ether, using TBDMS-Cl and imidazole in DMF, and the carbonyl group at position 3 of **52** was submitted to various alkylating reagents (Table 1). In most cases, a commercially available Grignard reagent was used and the reaction was done at 0 °C in dry THF. In the cases of entries 10 and 13, the Grignard reagent was generated in situ by a well-known procedure described by Smith,[28] using magnesium amalgams and the corresponding halide. Commercially available (entries 4 and 5) and generated (entries 11 and 12) lithium reagents were also used in some cases. When necessary, the lithium reagent was generated in situ in a mixture of diethyl ether and pentane (2:3), *t*-BuLi, and the corresponding bromide according to the procedure described by Bailey and Punzalan.[29] In all cases, a mixture of two stereoisomers at position 3 (Table 1) was obtained, the proportions varying according to the nature of the alkyl group.[30] The β-alkylated isomer was the major compound for entries 1−13, whereas it was the other one when the less nucleophilic Grignard reagents were used (entries 14−17). Both pure stereoisomers

Scheme 3. Chemical Synthesis of *epi*-ADT and ADT Derivatives Substituted at Positions 3α and 3*β* (Compounds **10**−**31** (See Table 1))[a]



[a] Reagents: (a) TBDMS-Cl, imidazole, DMF, room temp; (b) (i) RMgBr(Cl) or RLi, THF, 0 °C; (ii) flash chromatography; (c) (i) MeOH/HCl (2%), room temp or TBAF, THF, reflux; (ii) Jones' reagent (2.7 M), acetone, 0 °C or PCC, CH_2Cl_2, room temp.

Scheme 4. Chemical Synthesis of *epi*-ADT and ADT Derivatives Substituted at Positions 3α and 3*β* (Compounds **32**−**37**)[a]



[a] Reagents: (a) $HOCH_2CH_2OH$, *p*-TSA, CH_2Cl_2; (b) (i) BH_3, THF, 0 °C; (ii) H_2O_2, NaOH (3 N); (c) H_2SO_2 (5%), 1,4-dioxane, room temp; (d) CBr_4, PPh_3, CH_2Cl_2, 0 °C; (e) Jones' reagent (2.7 M), acetone, 0 °C.

were obtained after a separation by flash chromatography and were differentiated by TLC (silica gel normal phase), the 3*β*-substituted derivative being the less polar one (higher R_f value) (Table 1). In addition to their characteristic chromatographic properties, the stereoisomers were identified by the ^{13}C NMR signal of their tertiary alcohol at C3, the signal of which was always lower in ppm for the 3*β* isomer (axial 3α-OH) than for the 3α isomer (equatorial 3*β*-OH). This result agrees with literature data on ADT (3α-OH) and *epi*-ADT (3*β*-OH) derivatives.[30] As a typical example, chemical shifts (*δ*) of 71.22 and 72.42 ppm were observed for **81** (3*β*-alkylated and 3α-OH) and **64** (3α-alkylated and 3*β*-OH), respectively.

The TBDMS groups of 3α-alkylated compounds **53**, **55**, **56**, **62**, and **64** and of all 3*β*-alkylated compounds **70**−**86** were removed by hydrolysis (2% HCl in MeOH or TBAF) and the corresponding alcohols were oxidized (Jones' reagent or PCC) to afford in very good yields the final ketones **10**−**31**, which were characterized by IR, ^1H NMR, ^{13}C NMR, and elemental analyses. A representative 3α derivative of ADT, compound **14**, was also analyzed using X-ray crystallography (Figure 3) in order to confirm unambiguously the C3 stereochemistry previously determined on the basis of TLC characteristics and ^{13}C NMR signal at C3.

Compounds **32**−**37** were obtained from **12** and **18** following the sequences of reactions depicted in Scheme 4. After protection of the C17-ketone as a 1,3-dioxolane derivative, oxidative hydroboration (BH_3 in THF followed by H_2O_2 and NaOH) of the double bond of **87** and **88** yielded **89** and **90**, respectively. Hydrolysis of the ketal afforded the desired *epi*-ADT and ADT derivatives **32** and **33**. On the other hand, submitting **89** and **90** to bromination conditions (CBr_4 and PPh_3) led in both cases to a cyclization with epimerization around C3. In addition, the hydrolysis of the ketal group occurred during this reaction. Separation by flash chromatography allowed us to obtain an epimeric (50/50) mixture of **34** and the ADT derivative **35** alone, and the identification was made on the basis of ^{13}C NMR data. Compounds **12** and **18** were also submitted to oxidative hydroboration conditions (BH_3 in THF followed by H_2O_2 and NaOH) to yield the corresponding triols **91** and **92**, which were directly oxidized with Jones' reagent in acetone to afford the lactones **36** and **37**, respectively.

Synthesis of ADT 3α-Ether-3*β*-Substituted Derivatives 38−**43 (Scheme 5).** The ethers were formed from intermediate compounds **81**, **83**, and **84** using NaH and the corresponding iodide or bromide in refluxing THF. Then the TBDMS protective group of compounds **93**−**98** was hydrolyzed with a 2% methanolic HCl solution. The resulting 17*β*-alcohol was directly submitted to Jones' oxidation to afford the desired ADT 3α-ether-3*β*-substituted derivatives **38**−**43**.

Inhibition of Type 3 17*β*-HSD (SAR Results). The inhibitory activity of ADT derivatives **1**−**43** was determined for the transformation of labeled Δ^4-dione (0.1 *μ*M) into T catalyzed by a homogenate of HEK-293_17*β*-HSD3 cells that overexpress type 3 17*β*-HSD. As reported in the literature,[31] the cells were obtained by transfecting a pCMV-neo_17*β*-HSD3 vector containing the coding region of human type 3 17*β*-HSD gene into wild-type HEK-293 cells, which only express low levels of steroidogenic enzymes. A screening study was first performed at two concentrations of inhibitor (0.3 and 3 *μ*M) in order to rapidly identify active compounds (Tables 2−5). ADT, which was previously identified as a lead compound,[22,23] was used as a reference. For compounds showing the best inhibitory activity, further

Table 1. Yields, Ratios, and Characteristic Data of 3α (**C**) and 3β (**D**) Alkylated Products and Identification of Compounds **C**−**F** Reported in Scheme 3

entry	R	starting material (**52**) (%)[a]	yield of **C** + **D** (%)[a]	ratio **C/D** (%)	identification of compounds and characteristic data[b]			
					C (R_f, δ of C3)	**D** (R_f, δ of C3)	**E**	**F**
1[c,d]	CH_3	18	60	35/65	**53** (0.26, 71.45)	**70** (0.75, 69.78)	**10**	**15**
2[c,d]	$CH_3(CH_2)_2$	13	65	31/69	**55** (0.38, 72.87)	**72** (0.60, 71.61)	**11**	**17**
3[c,d]	$CH_3(CH_2)_3$	5	71	30/70	**57** (0.50, 72.80)	**74** (0.72, 71.60)		**19**
4[c,f]	$CH_3CH_2(CH_3)CH$	20	60	44/56	**58** (0.54, 74.51)	**75** (0.73, 74.03)		**20**
5[f]	$(CH_3)_3C$	20	72	34/66	**59** (0.47, 71.33)	**76** (0.82, 75.45)		**21**
6[c,d]	$CH_3(CH_2)_5$	10	76	26/74	**60** (0.54, 72.80)	**77** (0.67, 71.56)		**22**
7[c,d]	$CH_3(CH_2)_7$	5	61	31/69	**65** (0.31, 72.80)	**82** (0.84, 71.62)		**27**
8[c,d]	$CH_3(CH_2)_{11}$	5	51	25/75	**69** (0.56, 72.82)	**86** (0.83, 71.56)		**31**
9[c,d]	cyclohexyl	0	76	18/82	**61** (0.54, 74.01)	**78** (0.76, 73.39)		**23**
10[c,e]	cyclohexyl-CH_2	8	37	13/87	**63** (0.54, 73.63)	**80** (0.73, 72.28)		**25**
11[g]	cyclohexyl-$(CH_2)_2$	0	89	36/64	**66** (0.52, 72.74)	**83** (0.73, 71.59)		**28**
12[g]	phenyl-$(CH_2)_2$	0	58	33/66	**67** (0.27, 72.77)	**84** (0.65, 71.48)		**29**
13[c,e]	phenyl-$(CH_2)_3$	25	52	31/69	**68** (0.41, 72.73)	**85** (0.61, 71.51)		**30**
14[d]	CH_2=CH	22	56	58/42	**54** (0.36, 72.54)	**71** (0.57, 72.07)		**16**
15[d]	CH_2=$CHCH_2$	10	66	58/42	**56** (0.45, 72.22)	**73** (0.66, 71.05)	**12**	**18**
16[d]	phenyl	0	88	57/43	**62** (0.41, 74.14)	**79** (0.65, 73.55)	**13**	**24**
17[d]	phenyl-CH_2	18	61	60/40	**64** (0.58, 72.42)	**81** (0.75, 71.22)	**14**	**26**

[a] Isolated yield after chromatography. [b] R_f values obtained on TLC and chemical shift (δ in ppm) of C3. [c] 10−20% of reduction products were also isolated. [d] Commercially available Grignard reagent. [e] Grignard reagent generated in situ. [f] Commercially available lithium reagent. [g] Lithium reagent generated in situ.

assays were carried out in order to determine their IC_{50} values (Tables 4 and 5).

ADT 3α-ether derivatives **1**−**9** showed only weak inhibitory activities (Table 2), those substituted with a methyl, an ethyl, or an allyl group being the best. In the linear alkyl series tested at 0.3 μM, the smaller was the substituent, the higher was the percentage of inhibition (83−45% for the 3α-methyl ether **1** to the 3α-*n*-hexyl ether **4**). For the same length of alkyl side chain, the inhibitory activity decreased when a polar group, such as alcohol (compounds **6** and **7**) or carboxylic acid (compound **8**), was present. The 3α-methyl ether **1** was the most potent inhibitor in this series of ADT derivatives **1**−**9**.

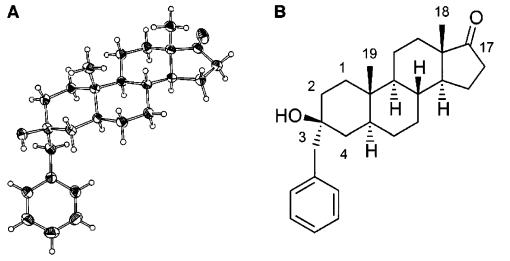
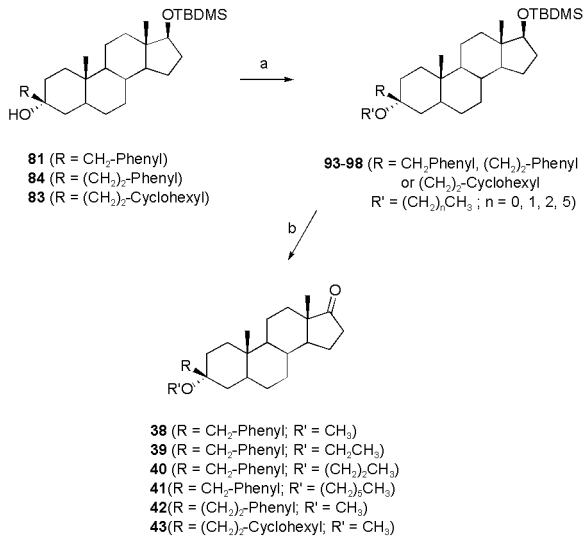


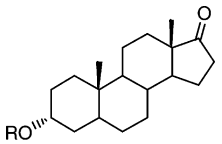
Figure 3. Crystal 3D structure (A) and corresponding 2D structure (B) of **14**. A few carbons are numbered in the structure in (B).

Scheme 5. Chemical Synthesis of ADT 3α-Ether-3β-Substituted Derivatives **38**−**43**[a]



[a] Reagents: (a) NaH, R′I(Br), THF, reflux; (b) (i) MeOH/HCl (2%), room temp; (ii) Jones' reagent (2.7 M), acetone, 0 °C.

Table 2. Inhibition of Type 3 17β-HSD by ADT 3α-Ether Derivatives **1**−**9**

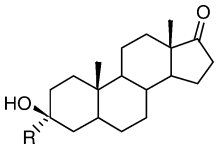


compd	R	inhibition of type 3 17β-HSD (%)[a]	
		0.3 μM	3 μM
ADT	H	50	88
1	CH_3	83	94
2	CH_3CH_2	69	95
3	$CH_3(CH_2)_2$	49	93
4	$CH_3(CH_2)_5$	45	92
5	CH_2=$CHCH_2$	73	95
6	$CH_3CH(OH)CH_2$	40	89
7	$HO(CH_2)_3$	38	86
8	$HOOC(CH_2)_2$	7	48
9	$Br(CH_2)_3$	56	93
Δ^4-dione[b]		24	78

[a] Compounds were tested at two concentrations (0.3 and 3 μM), and the error was ±10%. [b] Unlabeled 4-androstene-3,17-dione.

None of the *epi*-ADT derivatives, namely, 3α-alkylated derivatives **10**−**14**, **32**, and **36** and *epi*-ADT itself, showed inhibitory activities at 0.3 μM (Table 3). At 3 μM, they were less potent inhibitors than ADT or unlabeled Δ^4-dione used as inhibitor. The ADT 3β-alkylated derivatives **15**−**31**, **33**, **35**, and **37** were generally good inhibitors of type 3 17β-HSD; almost all showed an inhibitory activity higher than that of ADT (Table 4). As for the 3α-ether derivatives, a hydrophobic substituent has better inhibitory potency than a hydrophilic one, but a loss of inhibitory activity was observed when this 3β substituent became too large (only 50% inhibition at 0.3 μM for 3β-*n*-dodecyl-ADT (**31**)). In the

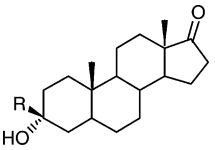
Table 3. Inhibition of Type 3 17β-HSD by *epi*-ADT 3α-Alkylated Derivatives **10**−**14**, **32**, and **36**



compd	R	inhibition of type 3 17β-HSD (%)[a] 0.3 μM	3 μM
ADT		50	88
epi-ADT	H	1	18
10	CH_3	9	16
11	$CH_3(CH_2)_2$	9	33
12	CH_2=$CHCH_2$	14	36
13	phenyl-CH_2	10	39
14	phenyl	7	39
32	$HO(CH_2)_3$	2	17
36	$(CH_2)_2CO$ (lactone, 3β-O)	9	53
Δ^4-dione[b]		24	78

[a] Compounds were tested at two concentrations (0.3 and 3 μM), and the error was ±10%. [b] Unlabeled 4-androstene-3,17-dione.

Table 4. Inhibition of Type 3 17β-HSD by ADT 3β-Alkylated Derivatives **15**−**31**, **33**, **35**, and **37**

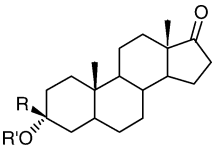


compd	R	inhibition of type 3 17β-HSD (%)[a] 0.3 μM	3 μM	IC_{50} (nM)
ADT	H	50	88	330 ± 60
15	CH_3	72	93	nd[b]
16	CH_2=CH	77	94	nd[b]
17	$CH_3(CH_2)_2$	89	94	67 ± 6
18	CH_2=$CHCH_2$	31	76	nd[b]
19	$CH_3(CH_2)_3$	88	92	116 ± 10
20	$CH_3CH_2(CH_3)CH$	85	90	73 ± 5
21	$(CH_3)_3C$	89	93	142 ± 4
22	$CH_3(CH_2)_5$	93	95	100 ± 10
23	cyclohexyl	88	95	97 ± 3
24	phenyl	88	95	81 ± 6
25	cyclohexyl-CH_2	93	95	87 ± 19
26	phenyl-CH_2	90	94	57 ± 5
27	$CH_3(CH_2)_7$	88	92	147 ± 29
28	cyclohexyl-$(CH_2)_2$	92	93	60 ± 16
29	phenyl-$(CH_2)_2$	93	93	99 ± 1
30	phenyl-$(CH_2)_3$	93	97	nd[b]
31	$CH_3(CH_2)_{11}$	50	77	nd[b]
33	$HO(CH_2)_3$	17	74	nd[b]
35	$(CH_2)_3O$ (cycloether)	3	94	nd[b]
37	$(CH_2)_2CO$ (lactone)	50	93	nd[b]
Δ^4-dione[c]		24	78	758 ± 139

[a] Compounds were tested at two concentrations (0.3 and 3 μM), and the error was ±10%. [b] Not determined. [c] Unlabeled 4-androstene-3,17-dione.

series of saturated linear alkyl groups, the inhibitory activity at 0.3 μM increased with the length of the chain and reached a maximum value for the 3β-*n*-hexyl-ADT (**22**) with 93% of inhibition. The activity then decreased to reach a minimum for 3β-*n*-dodecyl-ADT (**31**) with 50% (see **15**, **17**, **19**, **22**, **27**, and **31**). The 3β-(*n*, *s*, and *t*)-butyl-ADTs (**19**, **20**, and **21**, respectively) showed about the same activity, slightly higher for the 3β-*s*-butyl (**20**, IC_{50} = 73 nM). Switching from 3β-*n*-hexyl-ADT (**22**) to 3β-cyclohexyl-ADT (**23**) did not increase the inhibitory

Table 5. Inhibition of Type 3 17β-HSD by ADT 3α-Ether-3β-Alkylated Derivatives **38**−**43**



compd	R	R′	inhibition of type 3 17β-HSD (%)[a] 0.3 μM	3 μM	IC_{50} (nM)
ADT	H	H	50	88	330 ± 60
38	phenyl-CH_2	CH_3	91	93	154 ± 16
39	phenyl-CH_2	CH_3CH_2	80	92	352 ± 71
40	phenyl-CH_2	$CH_3(CH_2)_2$	60	87	nd[b]
41	phenyl-CH_2	$CH_3(CH_2)_5$	24	28	nd[b]
42	phenyl-$(CH_2)_2$	CH_3	61	95	73 ± 11
43	cyclohexyl-$(CH_2)_2$	CH_3	80	88	354 ± 116
Δ^4-dione[c]			24	78	758 ± 139

[a] Compounds were tested at two concentrations (0.3 and 3 μM), and the error was ±10%. [b] Not determined. [c] Unlabeled 4-androstene-3,17-dione.

activity (IC_{50} = 100 and 97 nM, respectively), but 3β-cyclohexylmethyl-ADT (**25**) and 3β-cyclohexylethyl-ADT (**28**) derivatives gave better results with IC_{50} values of 87 and 60 nM, respectively. On the other hand, 3β-cyclohexyl-ADT (**23**) and 3β-phenyl-ADT (**24**) gave almost the same inhibitory activity (IC_{50} = 97 and 81 nM, respectively). Replacing the phenyl group by a phenylmethyl resulted in a significant increase of inhibitory activity; an IC_{50} value of 57 nM being obtained for **26** compared to 81 nM for **24**. This activity, however, dropped when other methylene groups were added. Thus, for 3β-phenylethyl-ADT (**29**), an IC_{50} value of 99 nM was obtained. For two of our best 3β-alkylated ADT derivatives, the 3β-phenylmethyl-ADT (**26**), 3β-phenylethyl-ADT (**29**), the 17β-OH analogues were also tested, and as expected from previous studies,[19−21] a drastic drop of inhibitory activity was noted in both cases (results not shown).

In the last series of synthesized compounds, we explored the effect of a combination of 3α-ether and 3β-alkyl on an ADT nucleus. The results obtained are presented in Table 5. Generally, a loss of inhibitory activity was observed when compared to the corresponding 3β-alkylated derivatives. Indeed, the 3β-phenylmethyl-ADT (**26**) was 3-fold more potent than its 3α-methyl ether analogue **38** and 6-fold more potent than its 3α-ethyl ether analogue **39**. Since the 3α-*n*-propyl ether analogue **40** and the 3α-*n*-hexyl ether analogue **41** showed only 60% and 24% of inhibition at 0.3 μM, the IC_{50} value was not determined. In the same experiment, 3β-phenylethyl-ADT (**29**) gave an IC_{50} value of 99 nM. In the 3β-phenylmethyl-3α-ether series, the inhibitory activity decreased when the size of the ether increased (see compounds **38**−**41**). Indeed, the percentage of inhibition dropped from 91% for **38** to 24% for **41** at 0.3 μM. Moreover, the 3β-cyclohexylethyl-ADT (**28**) was 6-fold more potent than its 3α-methyl ether analogue **43**. A slight gain of inhibitory activity was, however, observed for the 3β-phenylethyl 3α-methyl ether ADT (**42**), which showed an IC_{50} value of 73 nM.

Conclusion

The design of ADT 3α-ether and/or 3β-substituted derivatives as inhibitors of type 3 17β-HSD was suc-

cessful. Indeed, the inhibitory activity of most of them is higher than that of Δ^4-dione, the natural substrate of the enzyme, and that of ADT, the lead compound previously identified. However, all *epi*-ADT derivatives (3β-OH) tested show a very poor inhibitory activity, even lower than that of ADT (3α-OH). Such data demonstrate the importance of a hydroxy group at position 3α for the inhibition of type 3 17β-HSD. Our most potent inhibitors of type 3 17β-HSD belong to the series of 3β-alkylated ADT derivatives; IC_{50} values of approximately 60 nM were obtained for 3β-*n*-propyl-ADT (**17**), 3β-phenylmethyl-ADT (**26**), and 3β-cyclohexylethyl-ADT (**28**). Blocking the ADT hydroxy group with an ether link in combination with a 3β-alkyl group did not bring a major increase of inhibitory activity. An exception in this series, 3β-phenylethyl 3α-methyl ether ADT (**42**) has an IC_{50} value of 73 nM, a value comparable to those of other good 3β-alkylated derivatives. In fact, this class of ADT derivatives might be more resistant to biological degradation than the ADT derivatives that are only 3β-alkylated.

The hydrophobicity of the group at position 3β seems to be an important requirement for inhibition of type 3 17β-HSD. However, this is not the only parameter to consider, as indicated by the drop of inhibitory potency observed with a longer 3β-alkyl side chain. Considering the series of alkyl groups tested in our SAR study, it is possible to estimate the size of the hydrophobic pocket that the 3β-oriented group occupies. Moreover, we previously reported the synthesis through parallel liquid-phase chemistry of ADT derivatives having diversified tertiary amide groups at position 3β. The results of this study[24] agree with the presence of a medium-size hydrophobic pocket located close to position 3β, although its exact topography is not known. It could be better defined by extending our SAR study to additional diversified analogues of our best inhibitors. Such a SAR study focusing on medium-sized alkyl groups could also lead to the design of a more potent inhibitor. Crystallizing a typical inhibitor with the enzyme would also yield precious information about the shape of this hydrophobic pocket. Unfortunately, the crystallization of a membrane enzyme such as type 3 17β-HSD remains a great challenge.

In conclusion, compounds **17**, **26**, and **28** are potent inhibitors and also constitute valuable lead compounds for pursuing the optimization of this new family of type 3 17β-HSD inhibitors. Although they likely inhibit the enzyme in a reversible fashion, further experiments have to be carried out in order for us to understand their mechanisms of action and to ascertain the type of inhibition. These results and the degree of selectivity of this new type 3 17β-HSD inhibitors among 17β-HSDs will be reported in due time.

Experimental Section

Chemical Synthesis. Chemical reagents and starting materials (androsterone and dihydrotestosterone) were purchased from Aldrich Chemical Co. (Milwaukee, WI), Sigma Chemical Company (St. Louis, MO), or Steraloids (Wilton, NH). Dichloromethane and diethyl ether, 99.8% anhydrous grade, were purchased from Aldrich Chemical Co. (Milwaukee, WI). THF, used in anhydrous conditions, was distilled from sodium benzophenone ketyl. Solvents for chromatography were obtained from BDH Chemicals (Montreal, Canada) or Fisher Chemicals (Montreal, Canada). Thin-layer chromatography (TLC) was performed on 0.20 mm silica gel 60 F_{254} plates (E. Merck, Darmstadt, GE), and 230−400 mesh ASTM silica gel 60 (E. Merck) was used for flash chromatography. Infrared spectra (IR) are expressed in cm^{-1} and were obtained on a Perkin-Elmer 1600 (FT-IR series) spectrophotometer. Nuclear magnetic resonance spectra (NMR) were obtained at 300 MHz for ^1H and at 75.5 MHz for ^{13}C with a Bruker AC/F 300 spectrometer. The chemical shifts (δ) are expressed in ppm and are referenced to residual chloroform (7.26 ppm for ^1H and 77.00 ppm for ^{13}C). For ^1H NMR, only specific signals were reported. For ^{13}C NMR, all signals were reported. Elemental analyses were performed by Robertson Microlit Laboratories (Madison, NJ). When necessary, complementary mass spectra (MS) and high-performance liquid chromatography (HPLC) analyses were carried out using an LCQ Finnigan apparatus (San Jose, CA) and a Waters Associates system (Milford, MA), respectively.

Synthesis of ADT 3α-Ether Derivatives 1−5 (Scheme 1). 17,17-Ethylenedioxy-3α-hydroxy-5α-androstane (44). Ethylene glycol (5.77 mL, 10 equiv) and *p*-toluenesulfonic acid (197 mg, 0.1 equiv) were added to a solution of androsterone (3.00 g, 10.34 mmol) in benzene (150 mL). The resulting mixture was refluxed overnight on a Dean−Stark apparatus. The reaction mixture was then cooled to room temperature, washed with water and brine and then dried over $MgSO_4$. The colorless oil obtained after concentration under reduced pressure was submitted to flash chromatography using a mixture of hexanes and EtOAc (9/1) containing 1% of triethylamine. The unreacted androsterone (10%) was removed, and ketal **44** was obtained as a white solid in 85% yield. $R_f = 0.35$ (hexanes/EtOAc, 7/3); IR (film) 3353 (OH, alcohol); ^1H NMR ($CDCl_3$) δ 0.77 (s, CH_3-19), 0.82 (s, CH_3-18), 3.81−3.94 (m, OCH_2CH_2O), 4.02 (t_{app}, $J = 2.6$ Hz, CH-3β); ^{13}C NMR ($CDCl_3$) δ 11.13, 14.37, 20.14, 22.59, 28.41, 28.96, 30.69, 31.23, 32.17, 34.15, 35.73, 35.87, 36.11, 39.08, 45.94, 50.32, 54.06, 64.50, 65.11, 66.46, 119.47.

General Procedure for the Synthesis of 3α-Ethers 45−49. Ketal **44** was dissolved in dry THF, and NaH (10 equiv) was added. The mixture was stirred under an argon atmosphere at refluxing temperature for 1 h. The appropriate iodide or bromide (8 equiv) was added: methyl iodide for **45**, ethyl iodide for **46**, propyl iodide for **47**, *n*-hexyl iodide for **48**, and allyl bromide for **49**. The reaction mixture was stirred at refluxing temperature overnight and then cooled to room temperature before addition of water and extraction with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated to dryness under reduced pressure. The yellow oil obtained was purified by flash chromatography, using a mixture of hexanes and EtOAc (9.5/0.5) containing 1% of triethylamine. The reaction was complete, and the pure ether was obtained with a yield generally above 95%. The chemical data of compounds **45**−**49** are reported in Supporting Information.

General Procedure for Hydrolysis of the Ketal Group (Synthesis of 1−5). A 5% aqueous H_2SO_4 solution was added to ketals **45**−**49** dissolved in 1,4-dioxane. The resulting mixture was stirred at room temperature, and the reaction, monitored by TLC, was generally completed after 2−3 h. The solution was then neutralized by addition of a saturated $NaHCO_3$ solution, and the extraction was done with EtOAc. The organic phase was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The concentrate obtained was purified by flash chromatography using a mixture of hexanes and EtOAc as eluent. All the hydrolyses proceeded quantitatively, and the pure ketones **1**−**5** were obtained as a white solid or white foam.

3α-Methoxy-5α-androstan-17-one (1). White solid; $R_f =$ 0.21 (hexanes/EtOAc, 9/1); IR (film) 1738 (C=O, ketone); ^1H NMR ($CDCl_3$) δ 0.80 (s, CH_3-19), 0.84 (s, CH_3-18), 2.42 (dd, $J_1 = 19.0$ Hz and $J_2 = 8.5$ Hz, CH-16β), 3.28 (s, CH_3O), 3.42 (t_{app}, $J = 2.5$ Hz, CH-3β); ^{13}C NMR ($CDCl_3$) δ 11.37, 13.80, 20.00, 21.71, 24.98, 28.27, 30.77, 31.54, 32.51, 32.78, 35.01, 35.84, 36.00, 39.47, 47.80, 51.46, 54.32, 55.64, 75.39, 221.52. Anal. ($C_{20}H_{32}O_2$) C, H.

3α-Ethoxy-5α-androstan-17-one (2). White solid; R_f = 0.26 (hexanes/EtOAc, 9/1); IR (film) 1741 (C=O, ketone); ^{1}H NMR ($CDCl_3$) δ 0.80 (s, CH_3-19), 0.85 (s, CH_3-18), 1.19 (t, J = 7.2 Hz, CH_3-2′), 2.43 (dd, J_1 = 19.0 Hz and J_2 = 8.7 Hz, CH-16β), 3.43 (q, J = 6.6 Hz, CH_2O), 3.53 (t_{app}, J = 2.4 Hz, CH-3β); ^{13}C NMR ($CDCl_3$) δ 11.43, 13.83, 15.73, 20.05, 21.76, 25.62, 28.31, 30.78, 31.59, 32.65, 33.33, 35.05, 35.86, 36.07, 39.52, 47.83, 51.53, 54.33, 62.92, 73.29, 221.51. Anal. ($C_{21}H_{34}O_2$) C, H.

3α-Propanoxy-5α-androstan-17-one (3). White solid; R_f = 0.39 (hexanes/EtOAc, 9/1); IR (film) 1741 (C=O, ketone); ^{1}H NMR ($CDCl_3$) δ 0.80 (s, CH_3-19), 0.85 (s, CH_3-18), 0.92 (t, J = 7.4 Hz, CH_3-3′), 2.42 (dd, J_1 = 19.0 Hz and J_2 = 8.7 Hz, CH-16β), 3.32 (t, J = 6.6 Hz, CH_2O), 3.51 (t_{app}, J = 2.6 Hz, CH-3β); ^{13}C NMR ($CDCl_3$) δ 10.75, 11.44, 13.83, 20.05, 21.76, 23.35, 25.62, 28.33, 30.82, 31.59, 32.68, 33.30, 35.07, 35.86, 36.05, 39.55, 47.83, 51.53, 54.37, 69.48, 73.39, 221.52. Anal. ($C_{22}H_{36}O_2$) C, H.

3α-Hexanoxy-5α-androstan-17-one (4). White foam; R_f = 0.35 (hexanes/EtOAc, 9/1); IR (film) 1742 (C=O, ketone); ^{1}H NMR ($CDCl_3$) δ 0.80 (s, CH_3-19), 0.85 (s, CH_3-18), 0.88 (t, J = 7.0 Hz, CH_3-6′), 2.43 (dd, J_1 = 19.0 Hz and J_2 = 8.8 Hz, CH-16β), 3.35 (t, J = 6.7 Hz, CH_2O), 3.50 (t_{app}, J = 2.5 Hz, CH-3β); ^{13}C NMR ($CDCl_3$) δ 11.44, 13.83, 14.06, 20.05, 21.76, 22.66, 25.68, 25.93, 28.32, 30.13, 30.82, 31.59, 31.71, 32.70, 33.27, 35.07, 35.86, 36.05, 39.55, 47.83, 51.53, 54.39, 67.86, 73.40, 221.50. Anal. ($C_{25}H_{42}O_2$) C, H.

3α-(Prop-2′-enoxy)-5α-androstan-17-one (5). White foam; R_f = 0.34 (hexanes/EtOAc, 9/1); IR (film) 1741 (C=O, ketone), 1651 (C=C, alkene); ^{1}H NMR ($CDCl_3$) δ 0.80 (s, CH_3-19), 0.84 (s, CH_3-18), 2.41 (dd, J_1 = 19.0 Hz and J_2 = 8.8 Hz, CH-16β), 3.57 (t_{app}, J = 2.5 Hz, CH-3β), 3.93 (m, CH_2-1′), 5.13 (d, J = 10.3 Hz, 1H of CH_2-3′), 5.26 (d, J = 17.2 Hz, 1H of CH_2-3′), 5.92 (m, CH-2′); ^{13}C NMR ($CDCl_3$) δ 11.37, 13.80, 20.00, 21.71, 25.51, 28.26, 30.75, 31.54, 32.61, 33.18, 35.01, 35.82, 36.02, 39.49, 47.79, 51.48, 54.29, 68.80, 73.11, 116.09, 135.74, 221.44. Anal. ($C_{22}H_{34}O_2$) C, H.

Synthesis of ADT 3α-Ether Derivatives 6−9 (Scheme 2). To a stirred solution of **49** (0.796 g, 2.13 mmol) in dry THF (80 mL) at 0 °C was added dropwise 16.7 mL (6.9 equiv) of a 1 M borane solution in THF. The mixture was allowed to react under an argon atmosphere for 3 h, then 3.5 mL of a 3 N NaOH solution and 1.5 mL of H_2O_2 (30% w/v) were added. The resulting mixture was stirred at room temperature for 1 h before addition of water and extraction with EtOAc. The organic phase was washed with water and brine and dried over $MgSO_4$. After evaporation under reduced pressure, the crude product was purified by flash chromatography using a mixture of hexanes and EtOAc (8/2) containing 1% of triethylamine. The two alcohols **50** and **51** were obtained, in a ratio of 1:3, with a 76% global yield. The chemical data of compounds **50** and **51** are reported in Supporting Information. The keto alcohols **6** and **7** were quantitatively obtained after hydrolysis of **50** and **51** with a 5% H_2SO_4 solution in 1,4-dioxane according to the procedure described above.

3α-(2′-Hydroxypropanoxy)-5α-androstan-17-one (6). White solid; R_f = 0.19 (hexanes/EtOAc, 7/3); IR (film) 3458 (OH, alcohol), 1740 (C=O, ketone); ^{1}H NMR ($CDCl_3$) δ 0.80 (s, CH_3-19), 0.85 (s, CH_3-18), 1.14 (d, J = 6.3 Hz, CH_3-3′), 2.42 (dd, J_1 = 19.0 Hz and J_2 = 8.7 Hz, CH-16β), 3.12 and 3.38 (2m, CH_2-1′), 3.55 (m, CH-3β), 3.92 (m, CH-2′); ^{13}C NMR ($CDCl_3$) δ 11.38, 13.80, 18.52, 20.00, 21.71, 25.54 (25.69), 28.22, 30.77, 31.50, 32.55 (32.64), 32.97 (33.06), 34.98, 35.84, 36.03, 39.53 (39.59), 47.80, 51.44, 54.32, 66.55 (66.61), 73.31 (73.40), 74.16 (74.30), 221.50. Anal. ($C_{22}H_{36}O_3$) C, H.

3α-(3′-Hydroxypropanoxy)-5α-androstan-17-one (7). White solid; R_f = 0.29 (hexanes/EtOAc, 7/3); IR (film) 3447 (OH, alcohol), 1739 (C=O, ketone); ^{1}H NMR ($CDCl_3$) δ 0.79 (s, CH_3-19), 0.83 (s, CH_3-18), 2.41 (dd, J_1 = 19.1 Hz and J_2 = 8.7 Hz, CH-16β), 3.53 (t_{app}, J = 2.2 Hz, CH-3β), 3.59 (m, CH_2-1′), 3.78 (t, J = 5.4 Hz, CH_2-3′); ^{13}C NMR ($CDCl_3$) δ 11.37, 13.77, 19.99, 21.70, 25.42, 28.23, 30.69, 31.44, 31.95, 32.61, 32.91, 34.97, 35.84, 35.99, 39.67, 47.79, 51.35, 54.18, 63.04, 68.07, 74.45, 221.55. Anal. ($C_{22}H_{36}O_3$) C, H.

3-(17′-Oxo-5′α-androstan-3′α-oxy)propanoic Acid (8). To a stirred solution of alcohol **51** (0.150 g, 0.38 mmol) in acetone (20 mL) at 0 °C was added dropwise a 2.7 M solution of Jones' reagent (1.5 mL). The reaction was monitored by TLC and was completed after 30 min, and then isopropyl alcohol was added dropwise until a persistent green color remained. Organic solvents were removed under reduced pressure. The resulting green concentrate was dissolved in water, and extraction was done with EtOAc. Combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification by flash chromatography using a mixture of hexanes and EtOAc (6/4) yielded the keto acid **8**. White solid; R_f = 0.10 (hexanes/EtOAc, 6/4); IR (film) 3447 broad (OH, acid), 1738 (C=O, ketone and acid); ^{1}H NMR ($CDCl_3$) δ 0.79 (s, CH_3-19′), 0.84 (s, CH_3-18′), 2.41 (dd, J_1 = 19.0 Hz and J_2 = 8.8 Hz, CH-16′β), 2.61 (t, J = 6.2 Hz, CH_2-2), 3.58 (m, CH-3′β), 3.65 (t, J = 6.5 Hz, CH_2-1); ^{13}C NMR ($CDCl_3$) δ 11.39, 13.79, 20.01, 21.73, 25.55, 28.20, 30.74, 31.52, 32.57, 32.86, 35.00, 35.06, 35.84, 36.00, 39.51, 47.81, 51.45, 54.26, 62.90, 74.51, 175.41, 221.51. Anal. ($C_{22}H_{34}O_4$) C, H.

3α-(3′-Bromopropanoxy)-5α-androstan-17-one (9). Alcohol **51** (0.142 g, 0.36 mmol), PPh_3 (0.19 g, 2 equiv), and CBr_4 (0.24 g, 2 equiv) in dry CH_2Cl_2 (50 mL) was stirred at 0 °C under an argon atmosphere. The reaction was completed after 2 h. The crude mixture was then adsorbed on silica gel and flash chromatography performed using a mixture of hexanes and EtOAc (9/1) as eluent to afford the bromide **9.** White solid (88% yield); R_f = 0.3 (hexanes/EtOAc, 9/1); IR (film) 1740 (C=O, ketone); ^{1}H NMR ($CDCl_3$) δ 0.80 (s, CH_3-19), 0.85 (s, CH_3-18), 2.43 (dd, J_1 = 19.0 Hz and J_2 = 8.7 Hz, CH-16β), 3.47−3.56 (m, CH-3β, CH_2-3′ and CH_2-1′); ^{13}C NMR ($CDCl_3$) δ 11.41, 13.81, 20.03, 21.74, 25.73, 28.27, 30.82, 31.28, 31.54, 32.70, 32.97, 33.13, 35.02, 35.86, 36.03, 39.57, 47.83, 51.46, 54.37, 64.79, 73.77, 221.59. Anal. ($C_{22}H_{35}O_2Br$) C, H.

Synthesis of *epi*-ADT and ADT Derivatives Substituted at Positions 3α and 3β (Compounds 10−31, Scheme 3). 17β-[(*tert*-Butyldimethylsilyl)oxy]-5α-androstan-3-one (52). To a solution of dihydrotestosterone (10.00 g, 34.48 mmol) in dry DMF (500 mL) were added 11.74 g (5 equiv) of imidazole (11.74 g, 5 equiv) and *tert*-butyldimethylsilyl chloride (TBDMS-Cl) (15.61 g, 3 equiv). The reaction mixture was stirred at room temperature overnight. The mixture was then poured onto ice and filtered. The resulting precipitate was washed with water and dried over phosphorus pentoxide under reduced pressure for 48 h. 17β-TBDMS-dihydrotestosterone (**52**) was obtained as a white solid (91% yield). R_f = 0.80 (hexanes/EtOAc, 8/2); IR (KBr) 1720 (C=O, ketone); ^{1}H NMR ($CDCl_3$) δ −0.001 and 0.005 (2s, $Si(CH_3)_2$), 0.71 (s, CH_3-18), 0.87 (s, $SiC(CH_3)_3$), 1.01 (s, CH_3-19), 3.54 (t, J = 8.2 Hz, CH-17α); ^{13}C NMR ($CDCl_3$) δ −4.81, −4.48, 11.40, 11.51, 18.10, 21.13, 23.55, 25.86 (3×), 28.88, 30.94, 31.35, 35.53, 35.77, 37.12, 38.20, 38.64, 43.35, 44.73, 46.83, 50.54, 54.14, 81.78, 212.02.

General Procedure for Alkylation of C3-Carbonyl. To a stirred solution of 17β-TBDMS-DHT (**52**) (0.500 g, 1.24 mmol) in dry THF (100 mL) at 0 °C were added dropwise 3 equiv of commercially available Grignard reagent in THF or diethyl ether. The mixture was allowed to stir at 0 °C for 3 h and left overnight at room temperature. A saturated solution of NH_4Cl was added, and the crude product was extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The two stereoisomers **C** (**53**−**69**) and **D** (**70**−**86**) were easily separated by flash chromatography using a mixture of hexanes and EtOAc as eluent. Ratios, global yields, and some characteristic data are given in Table 1. When the Grignard reagent was generated in situ (as for **63** and **80** or **68** and **85**), an amount of 5 equiv was prepared using a well-known procedure described by Smith,[28] and the alkylation was done in dry diethyl ether. Ketone **52** was then dissolved in dry diethyl ether and added dropwise to the solution of Grignard reagent generated in situ.

In some cases, the Grignard reagent was replaced by the corresponding lithium reagent (as for **58** and **75** or **59** and **76**). The commercially available lithium reagent (3 equiv) was

added to the ketone **52**, exactly as in the case of commercially available Grignard reagent. When the lithium reagent was generated in situ (as for **66** and **83** or **67** and **84**), an amount of 8 equiv was prepared in a mixture of *n*-pentane and diethyl ether (3/2, v/v) at −78 °C, using a well-known procedure described by Bailey and Punzalan.[29] Ketone **52** was then dissolved in diethyl ether and added dropwise at 0 °C to the freshly prepared lithium reagent (generated in situ).

The chemical data of compounds **53**−**86** are reported in Supporting Information.

General Procedure for Hydrolysis and Oxidation at Position 17. The silylated ethers **C** and **D** of Scheme 3 were dissolved in a methanolic solution of HCl (2%, v/v), and the resulting mixture was stirred at room temperature for 3 h. Water was added, MeOH was evaporated under reduced pressure, and the residue was extracted with EtOAc. The organic phase was washed with brine and dried over $MgSO_4$. The white concentrate obtained after evaporation under reduced pressure was directly oxidized with Jones' reagent according to the procedure described above for the preparation of compound **8**. Purification of the final products was performed by flash chromatography using a mixture of hexanes and EtOAc as eluent.

For **13** (3α-phenyl), **16** (3*β*-vinyl), and **24** (3*β*-phenyl), instead of the methanolic solution a TBAF solution was used for hydrolysis of the silylated ether, and PCC instead of Jones' reagent was used for the oxidation. Thus, to a solution of the silylated ether in dry THF was added 1.5 equiv of a 1 M TBAF solution, and the mixture was stirred at refluxing temperature for 6 h. The reaction mixture was then cooled to room temperature. A saturated $NaHCO_3$ solution was added, and the extraction was done with EtOAc. The combined organic phase was washed with brine, dried over $MgSO_4$, and evaporated to dryness under reduced pressure. The crude residue was dissolved in CH_2Cl_2 and added dropwise to a suspension of PCC (1.5 equiv), NaOAc (3 equiv), and 4 Å molecular sieves in CH_2Cl_2. The reaction mixture was stirred at room temperature under argon for 3 h. Filtration was performed on a silica gel column, using CH_2Cl_2 as eluent, and purification of the final product was done by flash chromatography using a mixture of hexanes and EtOAc as eluent.

3*β*-Hydroxy-3α-methyl-5α-androstan-17-one (10). White solid; 90% yield; R_f = 0.21 (hexanes/EtOAc, 7/3); IR (film) 3436 (OH, alcohol), 1738 (C=O, ketone); ^{1}H NMR ($CDCl_3$) *δ* 0.82 (s, CH_3-19), 0.84 (s, CH_3-18), 1.24 (s, CH_3-1′), 2.42 (dd, J_1 = 19.0 Hz and J_2 = 8.7 Hz, CH-16*β*); ^{13}C NMR ($CDCl_3$) *δ* 11.84, 13.79, 20.46, 21.74, 26.60, 28.34, 30.85, 31.55, 35.07, 35.79, 36.18, 36.33, 36.51, 43.19, 44.24, 47.78, 51.46, 54.57, 71.29, 221.21; MS calcd for $C_{20}H_{32}O_2$ 304.2, found 305.1 $[MH]^+$, 287.1 $[MH - H_2O]^+$, 269.2 $[MH - 2H_2O]^+$ *m/z*; HPLC purity 97.7% (t_R = 12.3 min, YMC-Pak C4, 4.6 mm × 250 mm, CH_3CN/H_2O/MeOH (30:40:30) at 1 mL/min flow rate).

3*β*-Hydroxy-3α-propyl-5α-androstan-17-one (11). White solid; 92% yield; R_f = 0.24 (hexanes/EtOAc, 8/2); IR (KBr) 3593 and 3450 (OH, alcohol), 1737 (C=O, ketone); ^{1}H NMR ($CDCl_3$) *δ* 0.83 (s, CH_3-18 and CH_3-19), 0.91 (t, J = 7.2 Hz, CH_3-3′), 2.41 (dd, J_1 = 19.0 Hz and J_2 = 8.7 Hz, CH-16*β*); ^{13}C NMR ($CDCl_3$) *δ* 12.05, 13.75, 14.62, 16.00, 20.42, 21.71, 28.32, 30.83, 31.51, 34.30, 35.02, 35.77, 36.04, 36.10, 39.74, 40.92, 43.67, 47.76, 51.42, 54.55, 72.65, 221.24. Anal. ($C_{22}H_{36}O_2$) C, H.

3*β*-Hydroxy-3α-(prop-2′-enyl)-5α-androstan-17-one (12). White solid; 92% yield; R_f = 0.41 (hexanes/EtOAc, 7/3); IR (film) 3452 (OH, alcohol), 1738 (C=O, ketone), 1628 (C=C, alkene); ^{1}H NMR ($CDCl_3$) *δ* 0.84 (s, CH_3-19 and CH_3-18), 2.32 (d, J = 7.4 Hz, CH_2-1′), 2.43 (dd, J_1 = 18.9 Hz and J_2 = 8.7 Hz, CH-16*β*), 5.11 (d_{app}, J = 16.8 Hz, 1H of CH_2-3′), 5.16 (d_{app}, J = 9.5 Hz, 1H of CH_2-3′), 5.86 (m, CH-2′); ^{13}C NMR ($CDCl_3$) *δ* 12.04, 13.76, 20.41, 21.71, 28.26, 30.83, 31.50, 33.87, 35.01, 35.77, 35.90, 36.02, 40.72, 41.81, 43.54, 47.75, 51.40, 54.56, 72.04, 118.82, 133.67, 221.22; MS calcd for $C_{22}H_{34}O_2$ 330.2, found 331.1 $[MH]^+$, 313.1 $[MH - H_2O]^+$, 296.3 $[MH - 2H_2O]^+$ *m/z*. Anal. ($C_{22}H_{34}O_2$) C. H: calcd, 79.95; found, 77.86.

3*β*-Hydroxy-3α-phenyl-5α-androstan-17-one (13). White solid; 88% yield; R_f = 0.30 (hexanes/EtOAc, 7/3); IR (film) 3428 (OH, alcohol), 1736 (C=O, ketone), 1601 and 1494 (C=C, aromatic ring); ^{1}H NMR ($CDCl_3$) *δ* 0.57 (m, 1H), 0.83 (s, CH_3-18), 0.94 (s, CH_3-19), 2.37 (m, 2H), 7.28 (t, J = 6.9 Hz, CH-4′), 7.36 (t, J = 7.5 Hz, CH-3′ and −5′), 7.53 (d, J = 7.3 Hz, CH-2′ and −6′); ^{13}C NMR ($CDCl_3$) *δ* 12.39, 13.74, 20.38, 21.69, 28.19, 30.61, 31.43, 33.92, 34.91, 35.74, 35.99, 36.68, 41.03, 43.55, 47.72, 51.30, 54.28, 73.73, 126.18 (2×), 127.41, 128.48 (2×), 144.68, 221.22. Anal. ($C_{25}H_{34}O_2$) C, H.

3*β*-Hydroxy-3α-phenylmethyl-5α-androstan-17-one (14). White solid; 93% yield; R_f = 0.38 (hexanes/EtOAc, 7/3); IR (film) 3461 (OH, alcohol), 1736 (C=O, ketone), 1602 and 1495 (C=C, aromatic ring); ^{1}H NMR ($CDCl_3$) *δ* 0.86 (2s, CH_3-18 and CH_3-19), 2.29 (m, 1H), 2.43 (dd, J_1 = 19.0 Hz and J_2 = 8.8 Hz, CH-16*β*), 2.84 (s, C*H*$_2$−Ph), 7.24 (m, 5H of Ph); ^{13}C NMR ($CDCl_3$) *δ* 12.20, 13.82, 20.50, 21.78, 28.20, 29.68, 30.99, 31.58, 33.60, 35.11, 35.83, 36.15, 40.52, 43.36, 43.83, 47.82, 51.51, 54.72, 72.32, 126.51, 128.31 (2×), 130.53 (2×), 137.30, 221.23. Anal. ($C_{26}H_{36}O_2$) C, H.

3α-Hydroxy-3*β*-methyl-5α-androstan-17-one (15). White solid; 91% yield; R_f = 0.22 (hexanes/EtOAc, 7/3); IR (film) 3448 (OH, alcohol), 1739 (C=O, ketone); ^{1}H NMR ($CDCl_3$) *δ* 0.75 (s, CH_3-19), 0.83 (s, CH_3-18), 1.17 (s, CH_3-3*β*), 2.40 (dd, J_1 = 19.0 Hz and J_2 = 8.6 Hz, CH-16*β*); ^{13}C NMR ($CDCl_3$) *δ* 11.15, 13.76, 20.20, 21.70, 28.11, 30.80, 31.55 (2×), 33.93, 34.84, 35.05, 35.66, 35.77, 41.01, 41.70, 47.73, 51.45, 54.29, 69.59, 221.26. Anal. ($C_{20}H_{32}O_2$) C, H.

3α-Hydroxy-3*β*-vinyl-5α-androstan-17-one (16). White solid; 91% yield; R_f = 0.30 (hexanes/EtOAc, 7/3); IR (film) 3452 (OH, alcohol), 1738 (C=O, ketone), 1664 (C=C, alkene); ^{1}H NMR ($CDCl_3$) *δ* 0.80 (s, CH_3-19), 0.86 (s, CH_3-18), 2.44 (dd, J_1 = 19.0 Hz and J_2 = 8.7 Hz, CH-16*β*), 5.00 (d, J = 10.5 Hz, CH-2′), 5.22 (d, J = 17.0 Hz, CH-2′), 5.92 (dd, J_1 = 17.3 Hz and J_2 = 10.6 Hz, CH-1′); ^{13}C NMR ($CDCl_3$) *δ* 11.24, 13.84, 20.24, 21.78, 28.12, 30.85, 31.58, 33.22, 33.58, 35.12, 35.75, 35.86, 39.95, 40.65, 47.81, 51.50, 54.29, 72.02, 110.96, 146.74, 221.35. Anal. ($C_{21}H_{32}O_2$) C, H.

3α-Hydroxy-3*β*-propyl-5α-androstan-17-one (17). White solid; 87% yield; R_f = 0.17 (hexanes/EtOAc, 8/2); IR (film) 3460 (OH, alcohol), 1737 (C=O, ketone); ^{1}H NMR ($CDCl_3$) *δ* 0.72 (s, CH_3-19), 0.81 (s, CH_3-18), 0.87 (t, J = 6.3 Hz, CH_3-3′), 2.39 (dd, J_1 = 19.0 Hz and J_2 = 8.7 Hz, CH-16*β*); ^{13}C NMR ($CDCl_3$) *δ* 11.09, 13.73, 14.65, 16.24, 20.14, 21.66, 28.17, 30.77, 31.49, 33.00, 33.71, 34.99, 35.74, 35.92, 39.72, 40.71, 46.86, 47.70, 51.40, 54.25, 71.36, 221.26. Anal. ($C_{22}H_{36}O_2$) C, H.

3α-Hydroxy-3*β*-(prop-2′-enyl)-5α-androstan-17-one (18). White solid; 90% yield; R_f = 0.39 (hexanes/EtOAc, 7/3); IR (film) 3462 (OH, alcohol), 1739 (C=O, ketone), 1638 (C=C, alkene); ^{1}H NMR ($CDCl_3$) *δ* 0.75 (s, CH_3-19), 0.84 (s, CH_3-18), 5.09 (d, J = 15.7 Hz, 1H of CH_2-3′), 5.13 (d, J = 8.1 Hz, 1H of CH_2-3′), 5.86 (m, CH-2′); ^{13}C NMR ($CDCl_3$) *δ* 11.16, 13.78, 20.21, 21.73, 28.18, 30.81, 31.54, 33.05, 33.72, 35.06, 35.79, 39.83, 40.73, 44.53, 46.57, 48.69, 51.45, 54.25, 70.89, 118.72, 133.60, 221.28; MS calcd for $C_{22}H_{34}O_2$ 330.3, found 313.1 $[MH - H_2O]^+$, 295.3 $[MH - 2H_2O]^+$ *m/z*.

3*β*-*n*-Butyl-3α-hydroxy-5α-androstan-17-one (19). White solid; 89% yield; R_f = 0.60 (hexanes/EtOAc, 8/2); IR (film) 3458 (OH, alcohol), 1734 (C=O, ketone); ^{1}H NMR ($CDCl_3$) *δ* 0.75 (s, CH_3-19), 0.84 (s, CH_3-18), 0.89 (t, J = 6.4 Hz, CH_3-4′), 2.41 (dd, J_1 = 19.0 Hz and J_2 = 8.6 Hz, CH-16*β*); ^{13}C NMR ($CDCl_3$) *δ* 11.15, 13.77, 14.08, 20.20, 21.72, 23.28, 25.25, 28.23, 30.81, 31.54, 33.06, 33.77, 35.04, 35.79, 35.97, 39.77, 40.80, 44.22, 47.76, 51.45, 54.29, 71.42, 221.33. Anal. ($C_{23}H_{38}O_2$) C, H.

3*β*-*s*-Butyl-3α-hydroxy-5α-androstan-17-one (20). White solid; 88% yield; R_f = 0.14 (hexanes/EtOAc, 8/2); IR (film) 3468 (OH, alcohol), 1738 (C=O, ketone); ^{1}H NMR ($CDCl_3$) *δ* 0.75 (s, CH_3-19), 0.85 (s, CH_3-18), 0.89 (d, J = 6.6 Hz, C*H*$_3$CH), 0.90 (t, J = 7.0 Hz, C*H*$_3$CH$_2$), 2.42 (dd, J_1 = 19.0 Hz and J_2 = 8.7 Hz, CH-16*β*); ^{13}C NMR ($CDCl_3$) *δ* 11.15, 13.82, 20.23, 21.75, 23.31, 23.37, 28.38, 29.81, 30.21, 30.86, 31.57, 33.82, 35.09, 35.84, 36.53, 37.00, 40.79, 46.28, 47.80, 51.48, 54.29, 73.92, 221.42. Anal. ($C_{23}H_{38}O_2$) C, H.

3*β*-*tert*-Butyl-3α-hydroxy-5α-androstan-17-one (21). White solid; 92% yield; R_f = 0.27 (hexanes/EtOAc, 8/2); IR (film) 3545 (OH, alcohol), 1729 (C=O, ketone); ^{1}H NMR

($CDCl_3$) δ 0.74 (s, CH_3-19), 0.85 (s, CH_3-18), 0.92 (s, $C(CH_3)_3$), 2.42 (dd, J_1 = 19.0 Hz and J_2 = 8.8 Hz, CH-16β); ^{13}C NMR ($CDCl_3$) δ 11.11, 13.82, 20.24, 21.75, 25.00 (3×), 26.99, 28.47, 30.88, 31.57, 33.91, 34.04, 35.09, 35.56, 35.84, 37.61, 40.96, 47.81, 51.46, 54.26, 75.37, 221.40. Anal. ($C_{23}H_{38}O_2$) C, H.

3β-*n*-Hexyl-3α-hydroxy-5α-androstan-17-one (22). White solid; 91% yield; R_f = 0.19 (hexanes/EtOAc, 8/2); IR (film) 3507 (OH, alcohol), 1739 (C=O, ketone); ^{1}H NMR ($CDCl_3$) δ 0.76 (s, CH_3-19), 0.85 (s, CH_3-18), 0.87 (t, J = 8.0 Hz, CH_3-6′), 2.42 (dd, J_1 = 19.0 Hz and J_2 = 8.6 Hz, CH-16β); ^{13}C NMR ($CDCl_3$) δ 11.18, 13.80, 14.05, 20.24, 21.75, 22.60, 23.02, 28.26, 29.90, 30.85, 31.59, 31.84, 33.11, 33.82, 35.10, 35.82, 36.03, 39.83, 40.86, 44.56, 47.79, 51.49, 54.35, 71.49, 221.30. Anal. ($C_{25}H_{42}O_2$) C, H.

3β-Cyclohexyl-3α-hydroxy-5α-androstan-17-one (23). White solid; 87% yield; R_f = 0.15 (hexanes/EtOAc, 8/2); IR (film) 3461 (OH, alcohol), 1736 (C=O, ketone); ^{1}H NMR ($CDCl_3$) δ 0.74 (s, CH_3-19), 0.85 (s, CH_3-18), 2.42 (dd, J_1 = 19.0 Hz and J_2 = 8.7 Hz, CH-16β); ^{13}C NMR ($CDCl_3$) δ 11.15, 13.82, 20.23, 21.75, 26.59 (2×), 26.79 (3×), 28.38, 30.31, 30.86, 31.57, 33.85, 35.08, 35.84, 35.97, 37.08, 40.78, 47.82, 49.34, 51.46, 54.29, 73.30, 221.45. Anal. ($C_{25}H_{40}O_2$) C, H.

3α-Hydroxy-3β-phenyl-5α-androstan-17-one (24). White solid; 86% yield; R_f = 0.31 (hexanes/EtOAc, 7/3); IR (film) 3442 (OH, alcohol), 1736 (C=O, ketone), 1591 and 1492 (C=C, aromatic ring); ^{1}H NMR ($CDCl_3$) δ 0.88 (s, CH_3-19), 0.91 (s, CH_3-18), 2.44 (dd, J_1 = 19.0 Hz and J_2 = 8.5 Hz, CH-16β), 7.25 (m, CH-4′), 7.35 (t_{app}, J = 7.5 Hz, CH-2′ and 6′), 7.50 (d, J = 7.6 Hz, CH-3′ and 5′); ^{13}C NMR ($CDCl_3$) δ 11.37, 13.85, 20.29, 21.76, 28.13, 30.84, 31.59, 34.14, 34.89, 35.13, 35.74, 35.85, 41.20, 41.89, 47.82, 51.50, 54.30, 73.49, 124.37 (2×), 126.74, 128.21 (2×), 149.38, 221.28. Anal. ($C_{25}H_{34}O_2$) C, H.

3β-Cyclohexylmethyl-3α-hydroxy-5α-androstan-17-one (25). White solid; 92% yield; R_f = 0.15 (hexanes/EtOAc, 8/2); IR (film) 3491 (OH, alcohol), 1726 (C=O, ketone); ^{1}H NMR ($CDCl_3$) δ 0.76 (s, CH_3-19), 0.85 (s, CH_3-18), 2.43 (dd, J_1 = 19.0 Hz and J_2 = 8.6 Hz, CH-16β); ^{13}C NMR ($CDCl_3$) δ 11.23, 13.81, 20.22, 21.75, 26.25, 26.47 (2×), 28.27, 30.86, 31.55, 32.97, 33.79 (2×), 35.07, 35.63 (2×), 35.84, 35.93, 40.35, 40.81, 47.79, 51.46, 52.11, 54.32, 72.19, 221.38. Anal. ($C_{26}H_{42}O_2$) C, H.

3α-Hydroxy-3β-phenylmethyl-5α-androstan-17-one (26). White solid; 92% yield; R_f = 0.31 (hexanes/EtOAc, 7/3); IR (KBr) 3408 (OH, alcohol), 1732 (C=O, ketone), 1604 and 1500 (C=C, aromatic ring); ^{1}H NMR ($CDCl_3$) δ 0.75 (s, CH_3-19), 0.84 (s, CH_3-18), 2.41 (dd, J_1 = 18.9 Hz and J_2 = 8.8 Hz, CH-16β), 2.70 (s, CH_2−Ph), 7.25 (m, 5H of Ph); ^{13}C NMR ($CDCl_3$) δ 11.18, 13.78, 20.20, 21.71, 28.16, 30.79, 31.52, 33.18, 33.70, 35.04, 35.79, 35.89, 39.94, 40.69, 47.75, 50.38, 51.41, 54.22, 71.12, 126.40, 128.09 (2×), 130.52 (2×), 136.92, 221.27. Anal. ($C_{26}H_{36}O_2$) C, H.

3α-Hydroxy-3β-octyl-5α-androstan-17-one (27). White solid; 89% yield; R_f = 0.22 (hexanes/EtOAc, 8/2); IR (film) 3460 (OH, alcohol), 1739 (C=O, ketone); ^{1}H NMR ($CDCl_3$) δ 0.74 (s, CH_3-19), 0.83 (s, CH_3-18), 0.85 (t, J = 6.4 Hz, CH_3-8′), 2.40 (dd, J_1 = 19.0 Hz and J_2 = 8.7 Hz, CH-16β); ^{13}C NMR ($CDCl_3$) δ 11.15, 13.76, 14.05, 20.20, 21.71, 22.60, 23.03, 28.22, 29.24, 29.58, 30.22, 30.81, 31.53, 31.83, 33.07, 33.77, 35.04, 35.78, 35.97, 39.77, 40.79, 44.53, 47.75, 51.44, 54.29, 71.42, 221.30. Anal. ($C_{27}H_{46}O_2$) C, H.

3β-Cyclohexylethyl-3α-hydroxy-5α-androstan-17-one (28). White solid; 88% yield; R_f = 0.35 (hexanes/EtOAc, 7/3); IR (film) 3462 (OH, alcohol), 1740 (C=O, ketone); ^{1}H NMR ($CDCl_3$) δ 0.76 (s, CH_3-19), 0.86 (s, CH_3-18), 2.43 (dd, J_1 = 19.0 Hz and J_2 = 8.8 Hz, CH-16β); ^{13}C NMR ($CDCl_3$) δ 11.22, 13.83, 20.25, 21.77, 26.40 (2×), 26.70, 28.27, 30.59, 30.87, 31.59, 33.15, 33.46 (2×), 33.83, 35.11, 35.86, 36.04, 38.22, 39.80, 40.88, 41.76, 47.83, 51.50, 54.33, 71.53, 221.43. Anal. ($C_{27}H_{44}O_2$) C, H.

3α-Hydroxy-3β-phenylethyl-5α-androstan-17-one (29). White solid; 91% yield; R_f = 0.14 (hexanes/EtOAc, 8/2); IR (film) 3486 (OH, alcohol), 1737 (C=O, ketone), 1605 and 1495 (C=C, aromatic ring); ^{1}H NMR ($CDCl_3$) δ 0.79 (s, CH_3-19), 0.86 (s, CH_3-18), 2.43 (dd, J_1 = 18.9 Hz and J_2 = 8.6 Hz, CH-16β), 2.71 (m, CH_2−Ph), 7.24 (m, 5H of Ph); ^{13}C NMR ($CDCl_3$) δ 11.22, 13.82, 20.26, 21.76, 28.26, 29.55, 30.87, 31.59, 33.27, 33.80, 35.10, 35.84, 36.07, 39.89, 40.89, 46.43, 47.80, 51.49, 54.35, 71.42, 125.69, 128.31 (2×), 128.39 (2×), 142.70, 221.31. Anal. ($C_{27}H_{38}O_2$) C, H.

3α-Hydroxy-3β-phenylpropyl-5α-androstan-17-one (30). White solid; 87% yield; R_f = 0.44 (hexanes/EtOAc, 8/2); IR (film) 3458 (OH, alcohol), 1736 (C=O, ketone), 1602 and 1496 (C=C, aromatic ring); ^{1}H NMR ($CDCl_3$) δ 0.75 (s, CH_3-19), 0.85 (s, CH_3-18), 2.43 (dd, J_1 = 19.0 Hz and J_2 = 8.7 Hz, CH-16β), 2.61 (t, J = 7.6 Hz, CH_2−Ph), 7.24 (m, 5H of Ph); ^{13}C NMR ($CDCl_3$) δ 11.19, 13.82, 20.23, 21.75, 25.05, 28.23, 30.83, 31.55, 33.11, 33.77, 35.07, 35.84, 36.01, 36.40, 39.78, 40.85, 44.09, 47.79, 51.46, 54.32, 71.43, 125.71, 128.28, 128.38 (2×), 142.44 (2×), 221.39. Anal. ($C_{28}H_{40}O_2$) C, H.

3β-Dodecyl-3α-hydroxy-5α-androstan-17-one (31). White solid; 89% yield; R_f = 0.47 (hexanes/EtOAc, 7/3); IR (film) 3545 and 3462 (OH, alcohol), 1735 (C=O, ketone); ^{1}H NMR ($CDCl_3$) δ 0.75 (s, CH_3-19), 0.84 (s, CH_3-18), 0.87 (t, J = 6.4 Hz, CH_3-12′), 2.42 (dd, J_1 = 19.0 Hz and J_2 = 8.7 Hz, CH-16β); ^{13}C NMR ($CDCl_3$) δ 11.18, 13.80, 14.08, 20.23, 21.75, 22.66, 23.06, 28.26, 29.32, 29.63 (5×), 30.25, 30.85, 31.58, 31.90, 33.11, 33.82, 35.10, 35.82, 36.03, 39.83, 40.85, 44.56, 47.79, 51.49, 54.35, 71.47, 221.29. Anal. ($C_{31}H_{54}O_2$) C, H.

Synthesis of Other *epi*-ADT and ADT Derivatives Substituted at Positions 3α and 3β (Compounds 32−37, Scheme 4). Formation of Ketals 87 and 88. The C17-carbonyl of compounds **12** and **18** were respectively protected as ketals **87** and **88**, using *p*-toluenesulfonic acid and ethylene glycol in CH_2Cl_2, according to the procedure described above.

17,17-Ethylenedioxy-3β-hydroxy-3α-(prop-2′-enyl)-5α-androstane (87). White solid; 62% yield; R_f = 0.54 (hexanes/EtOAc, 7/3); IR (film) 3423 (OH, alcohol), 1638 (C=C, alkene); ^{1}H NMR ($CDCl_3$) δ 0.81 (s, CH_3-18 and CH_3-19), 2.30 (d, J = 7.4 Hz, CH_2-1′), 3.86 (m, OCH_2CH_2O), 5.10 (d, J = 16.9 Hz, 1H of CH_2-3′), 5.14 (d, J = 10.0 Hz, 1H of CH_2-3′), 5.85 (m, CH-2′); ^{13}C NMR ($CDCl_3$) δ 12.06, 14.38, 20.59, 22.58, 28.46, 30.64, 31.31, 33.95, 34.11, 35.72, 35.93, 35.99, 40.86, 41.86, 43.57, 45.93, 50.28, 54.29, 64.47, 65.11, 72.12, 118.72, 119.41, 133.79.

17,17-Ethylenedioxy-3α-hydroxy-3β-(prop-2′-enyl)-5α-androstane (88). White solid; 75% yield; R_f = 0.55 (hexanes/EtOAc, 7/3); IR (film) 3494 (OH, alcohol), 1662 (C=C, alkene); ^{1}H NMR ($CDCl_3$) δ 0.73 (s, CH_3-18), 0.82 (s, CH_3-19), 2.16 (d, J = 7.5 Hz, CH_2-1′), 3.83 (m, OCH_2CH_2O), 5.06 (d, J = 19.1 Hz, 1H of CH_2-3′), 5.13 (d, J = 8.0 Hz, 1H of CH_2-3′), 5.87 (m, CH-2′); ^{13}C NMR ($CDCl_3$) δ 11.17, 14.40, 20.38, 22.62, 28.38, 29.68, 30.71, 31.24, 33.08, 33.82, 34.16, 35.78, 39.95, 40.76, 45.95, 48.72, 50.30, 53.92, 64.52, 65.14, 70.98, 118.62, 119.46, 133.73.

Oxidative Hydroboration of 87 and 88. Primary alcohols **89** and **90** were respectively obtained from alkenes **87** and **88** by an oxidative hydroboration with a 1 M borane solution, a 3 N NaOH solution, and H_2O_2 according to the procedure described above.

17,17-Ethylenedioxy-3β-hydroxy-3α-(3′-hydroxypropyl)-5α-androstane (89). White solid; 62% yield; R_f = 0.13 (hexanes/EtOAc, 4/6); IR (film) 3348 (OH, alcohol); ^{1}H NMR ($CDCl_3$) δ 0.82 (s, CH_3-18 and CH_3-19), 3.65 (t, J = 4.6 Hz, CH_2-3′), 3.86 (m, OCH_2CH_2O); ^{13}C NMR ($CDCl_3$) δ 12.10, 14.38, 20.61, 22.61, 26.27, 28.51, 30.66, 31.30, 34.06, 34.14, 34.56, 35.74, 35.98, 36.24, 41.09, 43.76, 45.98, 50.29, 54.29, 63.29, 64.49, 65.13, 72.50, 119.43.

17,17-Ethylenedioxy-3α-hydroxy-3β-(3′-hydroxypropyl)-5α-androstane (90). White solid; 72% yield; R_f = 0.11 (hexanes/EtOAc, 4/6); IR (film) 3356 (OH, alcohol); ^{1}H NMR ($CDCl_3$) δ 0.74 (s, CH_3-19), 0.83 (s, CH_3-18), 3.65 (t, J = 6.0 Hz, CH_2-3′), 3.86 (m, OCH_2CH_2O); ^{13}C NMR ($CDCl_3$) δ 11.19, 14.40, 20.39, 22.64, 26.37, 28.42, 30.72, 31.27, 33.24, 33.87, 34.19, 35.79, 35.93, 40.06, 40.94, 41.18, 45.97, 50.34, 54.03, 63.49, 64.53, 65.14, 71.16, 119.47.

Hydrolysis of Ketals 89 and 90. The deprotection of the carbonyl groups of **89** and **90** was done with a 5% H_2SO_4 solution in 1,4-dioxane according to the procedure described above, leading respectively to **32** and **33**.

3β-Hydroxy-3α-(3′-hydroxypropyl)-5α-androstan-17-one (32). White solid; 91% yield; R_f = 0.23 (hexanes/EtOAc, 2/8); IR (film) 3359 (OH, alcohol), 1735 (C=O, ketone); ^{1}H NMR ($CDCl_3$) δ 0.84 (s, CH_3-18 and CH_3-19), 2.43 (dd, J_1 = 19.1 Hz and J_2 = 8.7 Hz, CH-16β), 3.66 (t, J = 5.1 Hz, CH_2-3′); ^{13}C NMR ($CDCl_3$) δ 12.09, 13.80, 20.44, 21.74, 26.20, 28.32, 30.84, 31.53, 34.05, 34.47, 35.04, 35.80, 36.09, 36.14, 40.94, 43.73, 47.80, 51.45, 54.57, 63.26, 72.42, 221.35. Anal. ($C_{22}H_{36}O_3$) C, H.

3α-Hydroxy-3β-(3′-hydroxypropyl)-5α-androstan-17-one (33). White solid; 95% yield; R_f = 0.14 (hexanes/EtOAc, 5/5); IR (film) 3378 (OH, alcohol), 1738 (C=O, ketone); ^{1}H NMR ($CDCl_3$) δ 0.76 (s, CH_3-19), 0.85 (s, CH_3-18), 2.43 (dd, J_1 = 19.0 Hz and J_2 = 8.7 Hz, CH-16β), 3.65 (t, J = 5.9 Hz, CH_2-3′); ^{13}C NMR ($CDCl_3$) δ 11.19, 13.81, 20.24, 21.75, 26.31, 28.23, 30.84, 31.57, 33.24, 33.80, 35.08, 35.83, 36.03, 39.95, 40.89, 41.23, 47.79, 51.48, 54.35, 63.41, 71.05, 221.35. Anal. ($C_{22}H_{36}O_3$) C, H.

Bromination with Formation of Cycloethers 34 and 35. The bromination of **89** and **90** was performed, using PPh_3 and CBr_4 in CH_2Cl_2, according to the procedure described above. Hydrolysis of the C17-ketal and cyclization at C3 occurred during this reaction, leading to a mixture of the two C3 epimers. In both cases, the same result was observed on TLC. Flash chromatography afforded a 50/50 epimeric mixture of **34** and **35** in addition to a fraction of **35** alone. A 90% overall yield was thus obtained.

3α/3β-(Spirotetrahydrofuran-2-yl)-5α-androstan-17-one (34). White solid; IR (film) 1741 (C=O, ketone); ^{1}H NMR ($CDCl_3$) δ 0.79, 0.84 and 0.85 (s, CH_3-18 and CH_3-19), 2.43 (2m, CH-16β), 3.80 (2m, CH_2-3′); ^{13}C NMR ($CDCl_3$) δ 11.35, (11.76), 13.80, 20.21, (20.45), 21.74, 25.33, (25.95), 28.32 (28.54), 30.73, (30.90), 31.56, 32.43, (33.24), (34.68), 34.89, 35.03, 35.60, 35.84, (35.96), (36.92), 38.30, 39.65, (40.31), 42.00, (44.80), 47.80, 51.45, 54.21 (54.57), 66.28 (66.64), 81.60 (83.38), 221.44 (221.58). Anal. ($C_{22}H_{34}O_2$) C, H.

3α-*O*-(Spirotetrahydrofuran-2-yl)-5α-androstan-17-one (35). White solid; R_f = 0.45 (hexanes/EtOAc, 8/2); IR (film) 1741 (C=O, ketone); ^{1}H NMR ($CDCl_3$) δ 0.80 (s, CH_3-19), 0.85 (s, CH_3-18), 2.42 (dd, J_1 = 19.1 Hz and J_2= 8.5 Hz, CH-16β), 3.80 (t, J = 6.7 Hz, CH_2-3′); ^{13}C NMR ($CDCl_3$) δ 11.37, 13.83, 20.24, 21.77, 25.36, 28.36, 30.75, 31.60, 32.46, 34.92, 35.09, 35.63, 35.87, 38.34, 39.68, 42.02, 47.83, 51.51, 54.26, 66.65, 81.61, 221.52; MS calcd for $C_{22}H_{34}O_2$ 330.3, found 331.1 $[MH]^+$, 313.3 $[MH - H_2O]^+$ *m/z*.

Lactonization. Compounds **12** and **18** were respectively submitted to oxidative hydroboration conditions as described above for compound **49**. The obtained triols **91** and **92** were submitted to an excess of Jones' reagent, leading to the corresponding lactones **36** and **37**.

3α,3β-*O*-(1′-Oxo-1′,3′-propanediyloxy)-5α-androstan-17-one (36). White solid; 80% yield; R_f = 0.47 (hexanes/EtOAc, 6/4); IR (film) 1787 (C=O, lactone), 1738 (C=O, ketone); ^{1}H NMR ($CDCl_3$) δ 0.85 (s, CH_3-19), 0.86 (s, CH_3-18), 2.43 (dd, J_1 = 19.0 Hz and J_2 = 8.7 Hz, CH-16β), 2.56 (t, J = 8.2 Hz, CH_2-2′); ^{13}C NMR ($CDCl_3$) δ 11.71, 13.77, 20.44, 21.70, 28.18, 28.53, 30.72, 31.26, 31.47, 32.28, 34.94, 35.46, 35.66, 35.75, 39.26, 43.33, 47.72, 51.36, 54.34, 87.21, 176.45, 220.98. Anal. ($C_{22}H_{32}O_3$) C, H.

3β,3α-*O*-(1′-Oxo-1′,3′-propanediyloxy)-5α-androstan-17-one (37). White solid; 76% yield; R_f = 0.21 (hexanes/EtOAc, 6/4); IR (film) 1768 (C=O, lactone), 1736 (C=O, ketone); ^{1}H NMR ($CDCl_3$) δ 0.82 (s, CH_3-19), 0.85 (s, CH_3-18), 2.42 (dd, J_1 = 19.0 Hz and J_2 = 8.9 Hz, CH-16β), 2.57 (t, J = 8.4 Hz, CH_2-2′); ^{13}C NMR ($CDCl_3$) δ 11.42, 13.82, 20.23, 21.73, 27.93, 28.59, 30.57, 31.50, 33.21, 34.28 (2×), 35.03, 35.54, 35.81, 39.82, 41.29, 47.73, 51.35, 53.96, 86.13, 176.68, 221.09; HPLC purity: 99.8% (t_R = 10.0 min, Nova-Pak C18, 3.9 mm × 150 mm, CH_3CN/H_2O/MeOH (30/37/33) at 1 mL/min flow rate). Anal. ($C_{22}H_{32}O_3$) C. H: calcd, 76.70; found, 76.07.

Synthesis of ADT 3α-Ether 3β-Substituted Derivatives 38−43 (Scheme 5). Ether Formation. The 3α-ethers **38**−**43** were obtained from the corresponding alcohols **81**, **84**, and **83** according to the procedure described above for compounds **45**−**49**. The appropriate iodide was used in each case: methyl iodide for **93**, **97**, and **98**; ethyl iodide for **94**; propyl iodide for **95**; and *n*-hexyl iodide for **96**. In all cases, 20−30% of the starting material was recovered; the yields of compounds **93**−**98** (80−88%) have been corrected accordingly. Chemical data of these compounds are reported in Supporting Information.

Hydrolysis of TBDMS Group and Oxidation at Position 17 (Synthesis of 38−43). A methanolic solution of HCl (2%, v/v) was used for the hydrolysis of the silylated ether at position 17 and the resulting alcohol was oxidized with Jones' reagent, according to the procedure described above.

3α-Methoxy-3β-(phenylmethyl)-5α-androstan-17-one (38). White solid; 92% yield; R_f = 0.40 (hexanes/EtOAc, 8/2); IR (film) 1739 (C=O, ketone), 1602 and 1496 (C=C, aromatic ring); ^{1}H NMR ($CDCl_3$) δ 0.69 (s, CH_3-19), 0.84 (s, CH_3-18), 2.42 (dd, J_1 = 19.1 Hz and J_2 = 8.7 Hz, CH-16β), 2.63 and 2.77 (2d, J = 13.7 Hz, AB system, CH_2Ph), 3.29 (s, CH_3O), 7.22 (m, 5H of Ph); ^{13}C NMR ($CDCl_3$) δ 11.52, 13.82, 20.23, 21.73, 28.13, 28.95, 30.85, 31.56, 33.71, 35.07, 35.54, 35.84, 36.69, 40.39, 43.16, 47.80, 48.48, 51.47, 54.35, 75.82, 126.02, 127.91 (2×), 130.26 (2×), 137.72, 221.39. Anal. ($C_{27}H_{38}O_2$) C, H.

3α-Ethoxy-3β-(phenylmethyl)-5α-androstan-17-one (39). White solid; 88% yield; R_f = 0.57 (hexanes/EtOAc, 8/2); IR (film) 1739 (C=O, ketone), 1602 and 1496 (C=C, aromatic ring); ^{1}H NMR ($CDCl_3$) δ 0.69 (s, CH_3-19), 0.84 (s, CH_3-18), 1.23 (t, J = 7.0 Hz, CH_3CH_2O), 2.42 (dd, J_1 = 19.0 Hz and J_2 = 8.7 Hz, CH-16β), 2.63 and 2.77 (2d, J = 13.7 Hz, AB system, CH_2Ph), 3.48 (q, J = 7.0 Hz, CH_2O), 7.20 (m, 5H of Ph); ^{13}C NMR ($CDCl_3$) δ 11.58, 13.79, 15.69, 20.20, 21.71, 28.04, 29.52, 30.82, 31.52, 33.80, 35.04, 35.50, 35.81, 37.03, 40.38, 43.95, 47.78, 51.43, 54.38, 55.45, 75.66, 125.93, 127.83 (2×), 130.28 (2×), 137.84, 221.40; MS calcd for $C_{28}H_{40}O_2$ 408.3, found 363.1 $[MH - ethylOH]^+$, 345.1 $[MH - ethylOH - H_2O]^+$ *m/z*; HPLC purity: 99.9% (t_R = 10.2 min, Nova-Pak C18, 3.9 mm × 150 mm, CH_3CN/H_2O/MeOH (30/15/55) at 1 mL/min flow rate). Anal. ($C_{28}H_{40}O_2$) C. H: calcd, 82.30; found, 81.31.

3α-Propanoxy-3β-(phenylmethyl)-5α-androstan-17-one (40). White solid; 79% yield; R_f = 0.26 (hexanes/EtOAc, 9/1); IR (film) 1740 (C=O, ketone), 1601 and 1496 (C=C, aromatic ring); ^{1}H NMR ($CDCl_3$) δ 0.67 (s, CH_3-19), 0.84 (s, CH_3-18), 0.97 (t, J = 7.4 Hz, CH_3-3′), 2.42 (dd, J_1 = 19.0 Hz and J_2 = 9.0 Hz, CH-16β), 2.65 and 2.77 (2d, J = 13.8 Hz, AB system, CH_2Ph), 3.37 (t, J = 7.0 Hz, CH_2O), 7.22 (m, 5H of Ph); ^{13}C NMR ($CDCl_3$) δ 11.03, 11.61, 13.82, 20.24, 21.74, 23.50, 28.07, 29.47, 30.90, 31.56, 33.79, 35.07, 35.53, 35.85, 36.94, 40.39, 44.00, 47.82, 51.46, 54.48, 61.86, 75.45, 125.93, 127.85 (2×), 130.34 (2×), 138.00, 221.47. Anal. ($C_{29}H_{42}O_2$) C, H.

3α-Hexanoxy-3β-(phenylmethyl)-5α-androstan-17-one (41). White solid; 81% yield; R_f = 0.58 (hexanes/EtOAc, 8/2); IR (film) 1741 (C=O, ketone), 1605 and 1496 (C=C, aromatic ring); ^{1}H NMR ($CDCl_3$) δ 0.67 (s, CH_3-19), 0.84 (s, CH_3-18), 0.90 (t, J = 6.7 Hz, CH_3-6′), 2.42 (dd, J_1 = 19.1 Hz and J_2 = 8.7 Hz, CH-16β), 2.65 and 2.77 (2d, J = 13.7 Hz, AB system, CH_2Ph), 3.40 (t, J = 7.1 Hz, CH_2O), 7.21 (m, 5H of Ph); ^{13}C NMR ($CDCl_3$) δ 11.61, 13.83, 14.08, 20.24, 21.75, 22.73, 26.14, 28.08, 29.50, 30.28, 30.91, 31.56, 31.57, 33.80, 35.08, 35.53, 35.85, 36.94, 40.39, 43.97, 47.82, 51.49, 54.52, 60.15, 75.48, 125.93, 127.85 (2×), 130.34 (2×), 138.00, 221.48; MS calcd for $C_{32}H_{48}O_2$ 464.4, found 363.1 $[MH - hexylOH]^+$, 345.1 $[MH - hexylOH - H_2O]^+$ *m/z*; HPLC purity: 97.2% (t_R = 16.3 min, Nova-Pak C18, 3.9 mm × 150 mm, CH_3CN/H_2O/MeOH (35/10/55) at 1 mL/min flow rate). Anal. ($C_{32}H_{48}O_2$) C. H: calcd, 82.70; found, 81.60.

3α-Methoxy-3β-(2′-phenylethyl)-5α-androstan-17-one (42). White solid; 80% yield; R_f = 0.40 (hexanes/EtOAc, 8/2); IR (film) 1739 (C=O, ketone), 1605 and 1496 (C=C, aromatic ring); ^{1}H NMR ($CDCl_3$) δ 0.80 (s, CH_3-19), 0.86 (s, CH_3-18), 2.44 (dd, J_1 = 19.0 Hz and J_2 = 8.7 Hz, CH-16β), 2.61 (t, J = 8.6 Hz, CH_2Ph), 3.17 (s, CH_3O), 7.23 (m, 5H of Ph); ^{13}C NMR ($CDCl_3$) δ 11.59, 13.83, 20.26, 21.77, 28.23, 29.17, 30.87 (2×), 31.59, 33.68, 35.12, 35.86 (2×), 37.02, 39.61, 40.42, 47.83, 48.13, 51.50, 54.36, 74.92, 125.65, 128.24 (2×), 128.36 (2×), 143.01, 221.42. Anal. ($C_{28}H_{40}O_2$) C, H.

3β-(2′-Cyclohexylethyl)-3α-methoxy-5α-androstan-17-one (43). White solid; 92% yield; $R_f = 0.62$ (hexanes/EtOAc, 8/2); IR (film) 1741 (C═O, ketone); ^{1}H NMR ($CDCl_3$) δ 0.77 (s, CH_3-19), 0.85 (s, CH_3-18), 2.42 (dd, $J_1 = 19.0$ Hz and $J_2 = 8.6$ Hz, CH-16β), 3.07 (s, CH_3O); ^{13}C NMR ($CDCl_3$) δ 11.57, 13.82, 20.24, 21.76, 26.39 (2×), 26.70, 28.23, 29.10, 30.10, 30.87, 31.59, 33.47 (2×), 33.70, 34.64, 35.11, 35.85 (2×), 37.00, 38.21, 40.36, 47.83, 47.92, 51.50, 54.35, 75.01, 221.43. Anal. ($C_{28}H_{46}O_2$) C, H.

Inhibition of Type 3 17β-HSD. Preparation of the Enzyme Source. The expression vectors encoding type 3 17β-HSD were transfected into human embryonic kidney 293 (HEK-293) cells using a calcium phosphate procedure as reported previously.[31] Cells were then sonicated in 50 mM sodium phosphate buffer (pH 7.4) containing 20% glycerol and 1 mM ethylenediaminetetraacetic acid (EDTA) and centrifuged at 10000*g* for 1 h to remove the mitochondria, plasma membranes, and cells fragments. The supernatant was further centrifuged at 100000*g* to separate the microsomal fraction, which was used as a source of type 3 17β-HSD for the enzymatic assay.

Enzymatic Assay. The inhibition test was carried out at 37 °C in 1 mL of 50 mM sodium phosphate buffer, pH 7.4, containing 20% glycerol, 1 mM EDTA, and 2 mM of cofactor (NADPH) in the presence of 0.1 μM [^{14}C]-Δ^4-dione ([4-^{14}C]-4-androstene-3,17-dione (New England Nuclear, Boston, MA) and the indicated concentration of compound to be tested. The reaction was stopped after 1 h by adding 2 mL of diethyl ether containing 10 μM of unlabeled Δ^4-dione and T. The metabolites were extracted twice with 2 mL of diethyl ether, evaporated, and then dissolved in CH_2Cl_2 before being applied on silica gel 60 TLC plates. TLC was developed in a mixture of toluene and acetone (4/1). Substrate [^{14}C]-Δ^4-dione and metabolite [^{14}C]-T were identified by comparison with reference steroids and revealed by autoradiography, then quantified using the PhosphoImager system (Molecular Dynamics, Sunnyvale, CA). The percentage of transformation (% transf) and the percentage of inhibition were calculated from eqs 1 and 2, respectively:

$$\%\ \text{transf} = \frac{[^{14}\text{C}]\text{-T}}{[^{14}\text{C}]\text{-T} + [^{14}\text{C}]\text{-}\Delta^4\text{-dione}} \times 100 \qquad (1)$$

$$\%\ \text{inhibition} = \frac{(\%\ \text{transf without inhibitor}) - (\%\ \text{transf with inhibitor})}{\%\ \text{transf without inhibitor}} \times 100 \qquad (2)$$

When several concentrations of an inhibitor were used in the enzymatic assay, an inhibition curve was plotted using the percentage of transformation versus the concentration of inhibitor. From this inhibition curve, the IC_{50} value (the concentration of inhibitor that provokes 50% of enzyme inhibition) was calculated by computer (DE_{50} program, CHUL Research Center, Québec, Canada).

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Supporting Information Available: R_f, IR, ^{1}H NMR, and ^{13}C NMR data of intermediate compounds **45**−**51**, **53**−**86**, and **93**−**98**, elemental analysis results for final compounds, and Tables 1−8 listing crystallographic details for compound **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Labrie, F.; Luu-The, V.; Labrie, C.; Bélanger, A.; Simard, J.; Lin, S. X.; Pelletier, G. Endocrine and Intracrine Sources of Androgens in Women: Inhibition of Breast Cancer and Other Roles of Androgens and Their Precursor Dehydroepiandrosterone. *Endocr. Rev.* **2003**, *24*, 152−182.

(2) Vihko, P.; Harkonen, P.; Oduwole, O.; Torn, S.; Kurkela, R.; Porvari, K.; Pulkka, A.; Isomaa, V. 17β-Hydroxysteroid Dehydrogenases and Cancers. *J. Steroid Biochem. Mol. Biol*. **2003**, *83*, 119−122.

(3) Labrie, F.; Luu-The, V.; Lin, S. X.; Simard, J.; Labrie, C. Role of 17β-Hydroxysteroid Dehydrogenases in Sex Steroid Formation in Peripheral Intracrine Tissues. *Trends Endocrinol. Metab.* **2000**, *11*, 421−427.

(4) Sasano, H.; Suzuki, T.; Takeyama, J.; Utsunomiya, H.; Ito, K.; Ariga, N.; Moriya, T. 17-Beta-Hydroxysteroid Dehydrogenase in Human Breast and Endometrial Carcinoma. *Oncology* **2000**, *59* (Suppl. 1), 5−12.

(5) Moghrabi, N.; Andersson, S. 17β-Hydroxysteroid Dehydrogenases: Physiological Roles in Health and Disease. *Trends Endocrinol. Metab.* **1998**, *9*, 265−270.

(6) Labrie, F.; Luu-The, V.; Lin, S.-X.; Labrie, C.; Simard, J.; Breton, R. The Key Role of 17β-Hydroxysteroid Dehydrogenases in Sex Steroid Biology. *Steroids* **1997**, *62*, 148−158.

(7) Mindnich, R.; Moller, G.; Adamski, J. The Role of 17β-Hydroxysteroid Dehydrogenases. *Mol. Cell. Endocrinol*. **2004**, *218*, 7−20.

(8) Luu-The, V. Analysis and Characteristics of Multiple Types of Human 17β-Hydroxysteroid Dehydrogenase. *J. Steroid Biochem. Mol. Biol.* **2001**, *76*, 143−151.

(9) Adamski, J.; Jakob, F. J. A Guide to 17β-Hydroxysteroid Dehydrogenases. *Mol. Cell. Endocrinol.* **2001**, *171*, 1−4.

(10) Peltoketo, H.; Luu-The, V.; Simard, J.; Adamski, J. 17β-Hydroxysteroid Dehydrogenase (HSD)/17-Ketosteroid Reductase (KSR) Family; Nomenclature and Main Characteristics of the 17HSD/KSR Enzymes. *J. Mol. Endocrinol*. **1999**, *23*, 1−11.

(11) Poirier, D. Inhibitors of 17β-Hydroxysteroid Dehydrogenases. *Curr. Med. Chem.* **2003**, *10*, 453−477.

(12) Smith, H. J.; Nicholls, P. J.; Simons, C.; Le Lain, R. Inhibitors of Steroidogenesis as Agents for the Treatment of Hormone-Dependent Cancers. *Expert Opin. Ther. Pat.* **2001**, *11*, 789−824.

(13) Penning, T. M. 17β-Hydroxysteroid Dehydrogenase: Inhibitors and Inhibitor Design. *Endocr.-Relat. Cancer* **1996**, *3*, 41−56.

(14) Geissler, W. M.; Davis, D. L.; Wu, L.; Bradshaw, K. D.; Patel, S.; Mendonca, B. B.; Elliston, K. O.; Wilson, J. D.; Russell, D. W. Andersson, S. Male Pseudohermaphroditism Caused by Mutations of Testicular 17β-Hydroxysteroid Dehydrogenase 3. *Nat. Genet.* **1994**, *7*, 34−39.

(15) Andersson, S.; Geissler, W. M.; Patel, S.; Wu, L. The Molecular Biology of Androgenic 17β-Hydroxysteroid Dehydrogenases. *J. Steroid Biochem. Mol. Biol.* **1995**, *53*, 37−39.

(16) Le Lain, R.; Barrell, K. J.; Saeed, G. S.; Nicholls, P. J.; Simons, C.; Kirby, A.; Smith, H. J. Some Coumarins and Triphenylethene Derivatives as Inhibitors of Human Testes Microsomal 17β-Hydroxysteroid Dehydrogenase (17β-HSD Type 3): Further Studies with Tamoxifen on the Rat Testes Microsomal Enzyme. *J. Enzyme Inhib. Med. Chem.* **2002**, *17*, 93−100.

(17) Le Lain, R.; Nicholls, P. J.; Smith, H. J.; Maharlouie, F. H. Inhibitors of Human and Rat Testes Microsomal 17β-Hydroxysteroid Dehydrogenase (17β-HSD) as Potential Agents for Prostatic Cancer. *J. Enzyme Inhib*. **2001**, *16*, 35−45.

(18) Dufort, I.; Rheault, P.; Huang, X. F., Soucy, P.; Luu-The, V. Characteristics of a Highly Labile Human Type 5 17β-Hydroxysteroid Dehydrogenase. *Endocrinology* **1999**, *140*, 568−574.

(19) Luu-The, V.; Dufort, I.; Pelletier, G.; Labrie, F. Type 5 17β-Hydroxysteroid Dehydrogenase: Its Role in the Formation of Androgens in Women. *Mol. Cell. Endocrinol*. **2001**, *171*, 77−82.

(20) Verhoeven, G. Androgens and the testis. *Verh.−K. Acad. Geneeskd. Belg.* **1992**, *54*, 299−327.

(21) Pittaway, D. E. Inhibition of Testosterone Synthesis in the Canine Testis in Vitro. *Contraception* **1983**, *27*, 431−436.

(22) Poirier, D.; Labrie, F.; Luu-The, V. Inhibition de la 17β-Hydroxystéroïde Déshydrogénase de Type 3 par des Dérivés Stéroïdiens: Étude Exploratoire (Inhibition of Type 3 17β-Hydroxysteroid Dehydrogenase by Steroid Derivatives: Exploratory Study). *Médecine-Sciences* **1995**, *11* (Suppl. 2), 24.

(23) Tchédam Ngatcha, B.; Luu-The, V.; Poirier, D. Androsterone Derivatives Substituted at Position 16: Chemical Synthesis, Inhibition of Type 3 17β-Hydroxysteroid Dehydrogenase, Binding Affinity for Steroid Receptors, and Proliferative/Antiproliferative Activity on Shionogi (AR^+) Cells. *J. Enzyme Inhib. Med. Chem*. **2002**, *17*, 155−165.

(24) Maltais, R.; Luu-The, V.; Poirier, D. Synthesis and Optimization of a New Family of Type 3 17β-Hydroxysteroid Dehydrogenase Inhibitors by Parallel Liquid-Phase Chemistry. *J. Med. Chem.* **2002**, *45*, 640−653.

(25) Maltais, R.; Luu-The, V.; Poirier, D. Parallel Solid-Phase Synthesis of 3β-Peptido-3α-hydroxy-5α-androstane-17-one Derivatives for Inhibition of Type 3 17β-Hydroxysteroid Dehydrogenase. *Bioorg. Med. Chem.* **2001**, *9*, 3101−3111.

(26) Tchédam Ngatcha, B.; Luu-The, V.; Poirier, D. Androsterone 3β-Substituted Derivatives as Inhibitors of Type 3 17β-Hydroxysteroid Dehydrogenase. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2533−2536.

(27) Ward, D. E.; Rhee, C. K. A Simple Method for the Microscale Preparation of Mosher's Acid Chloride. *Tetrahedron Lett.* **1991**, *32*, 7165−7166.
(28) Smith, J. Higher Aliphatic Compounds. Part II. The Systems Hexadecyl Iodide−Octadecyl Iodide and Hexadecane−Octadecane. *J. Chem. Soc.* **1932**, 738−741.
(29) Bailey, W. F.; Punzalan, E. R. Convenient General Method for the Preparation of Primary Alkyllithium by Lithium−Iodine Exchange. *J. Org. Chem.* **1990**, *55*, 5404−5406.
(30) Tchédam Ngatcha, B.; Poirier, D. Diastereoselective Addition of Organomagnesium Reagents to 17β-TBDMS-dihydrotestosterone. *Synth. Commun.* **1999**, *29*, 1065−1074.
(31) Luu-The, V.; Zhang, Y.; Poirier, D.; Labrie, F. Characteristics of Human Types 1, 2 and 3 17β-Hydroxysteroid Dehydrogenase Activities: Oxidation/Reduction and Inhibition. *J. Steroid Biochem. Mol. Biol.* **1995**, *55*, 581−587.

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