Pd-CATALYZED CROSS-COUPLING REACTION OF STERICALLY HINDERED VINYL IODIDES AND ORGANOZINC REAGENTS. SYNTHESIS OF VITAMIN D ANALOGUES WITH AN AROMATIC RING ATTACHED AT C-17

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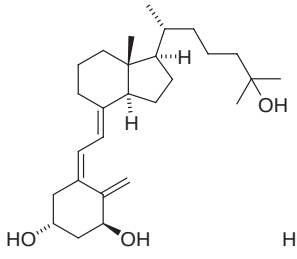
This paper is dedicated to the memory of Dr Václav Černý.

Palladium-catalyzed coupling of steroid 17-iodo-6β-methoxy-3α,5-cyclo-5α-androst-16-ene (**4**) 17-iodoandrosta-5,16-dien-3β-ol (**5**), and structurally similar (3a*S*,7*R*,7a*R*)-benzenesulfonyl-3-iodo-3a-methyl-3a,4,5,6,7,7a-hexahydro-1*H*-indene (**6**) with various arylzinc chlorides, which were generated from aryl bromides **8** [1-bromomethylbenzene (**8a**), *O*-(triethylsilyl-2-bromophenyl)propan-2-ol (**8b**), 2-(4-bromophenyl)propan-2-ol (**8c**), 4-bromobenzonitrile (**8d**), 4-bromobenzoic acid methyl ester (**8e**), 4-bromobenzoic acid *tert*-butyl ester (**8f**) and 3-bromopyridine (**8g**)] *via* aryllihium derivatives (the Negishi coupling) was examined. The respective cross-coupling products were obtained in good yields for all aryl bromides except of **8c** and **8e**. Building blocks for synthesis of certain vitamin D analogues have been prepared.

Keywords: Negishi cross-coupling; Organozinc reagents; Steroids; Vinyl iodides; Palladium; Vitamins.

17-Iodoandrost-16-ene and 17-iodoestr-16-ene derivatives, easily accessible from the corresponding 17-ones[1,2], have emerged as major intermediates in steroid synthesis due to progress in the transition-metal-mediated coupling reactions of vinyl iodides[3]. Thus, an approach to 17-pyridyl androstane derivatives utilizing diethyl(3-pyridyl)borane and the Suzuki coupling[4], Stille coupling involving a furane derivative[5], and carbonylation in the presence of organotin reagents[6] or hydroxamic acid derivatives[7,8] have been recently reported. The Heck reaction of 17-iodo-16-ene steroids with ethyl vinyl ethers has also been examined[9]. In certain cases enol triflates generated from 17-ones provide a plausible alternative to the iodides[10–13]; however, these intermediates are operationally less convenient and their preparation requires more expensive reagents.

In conjunction with the synthesis of analogues of 1α,25-dihydroxyvitamin D_3 (**1**) ongoing in our laboratory, we were interested in palladium-catalyzed coupling of 17-iodo-16-ene steroids with aromatic organozinc compounds (the Negishi coupling reaction[14]). This reaction was thought particularly suited for our purposes because organozinc reagents are easy to prepare, capable to accommodate functional groups useful for further elaborating of the coupling products (as the cyano group and, possibly, the alkoxycarbonyl group), and tolerant to unprotected hydroxy groups[15]. The effect of steric hindrance on the efficiency of the Negishi coupling could not be apprised. However, literature reports on the coupling of representative 17-iodo-16-ene steroids and trifluoroisopropenylzinc reagents[16] and on some experiments with attachment of 2- and 4-bromopyridine to the steroid ring system[11] were encouraging. Now, we present a scrutiny of reaction of vinyl iodides **4**, **5** and **6** with a variety of aryl bromides and the synthesis of key building blocks for construction of vitamin D analogues **2** and **3**[17].



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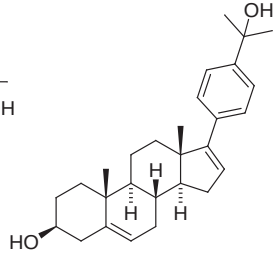

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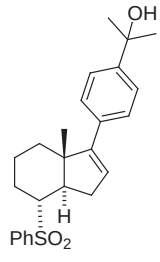

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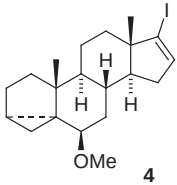

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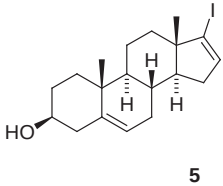

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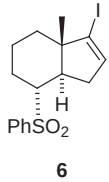

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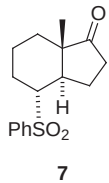

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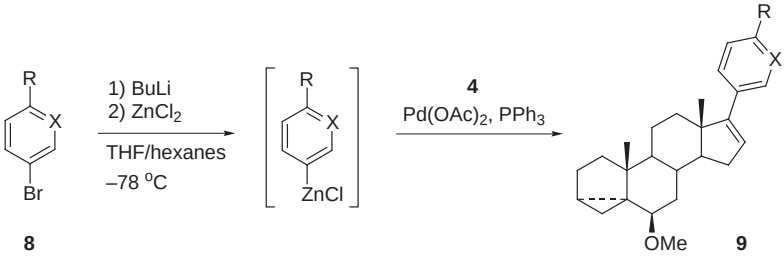
RESULTS AND DISCUSSION

Iodides **4** and **5**[1] were prepared from the corresponding ketones *via* hydrazones using the original Barton procedure[1]. Iodide **6** was obtained from ketone **7** which was synthesized in an analogous way as described earlier for its enantiomer[18].

4-Bromotoluene (**8a**) (Scheme 1), in THF at –78 °C, was treated with butyllithium (1.1 molar equivalent, in hexanes) and then with zinc chlo-

ride solution (1.5 molar equivalent, in THF). The obtained solution of tolylzinc chloride was allowed to react with a pre-formed mixture of iodide **4** and tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$], the latter being generated *in situ* from palladium(II) acetate, 10 mole %, and triphenylphosphine, 40 mole %. The tolyl derivative **9a** was obtained in 78% yield. TLC analysis of the crude product showed that **9a** was contaminated with only traces of a more mobile product which was identified as 6β-methoxy-3,5-cyclo-5α-androst-16-ene; no other side products could be detected. The reaction of the organozinc derivative generated from a bromide bearing the silyloxy group **8b** smoothly afforded product **9b**. Under analogous conditions, the respective free alcohol **8c** [19] failed to afford any product, presumably due to insolubility of the organometalic intermediate. Coupling of iodide **4** with 4-bromobenzonitrile (**8d**) gave **9d** in an excellent yield.



8 **9**

R	X	Aryl bromide	Product	Yield, %
Me	CH	**8a**	9a	78
CMe_2OSiEt_3	CH	**8b**	9b	88
CMe_2OH	CH	**8c**	9c	-
CN	CH	**8d**	9d	89
CO_2Me	CH	**8e**	9e	-
$CO_2C(CH_3)_3$	CH	**8f**	9f	59, 69[a]
H	N	**8g**	9g	78

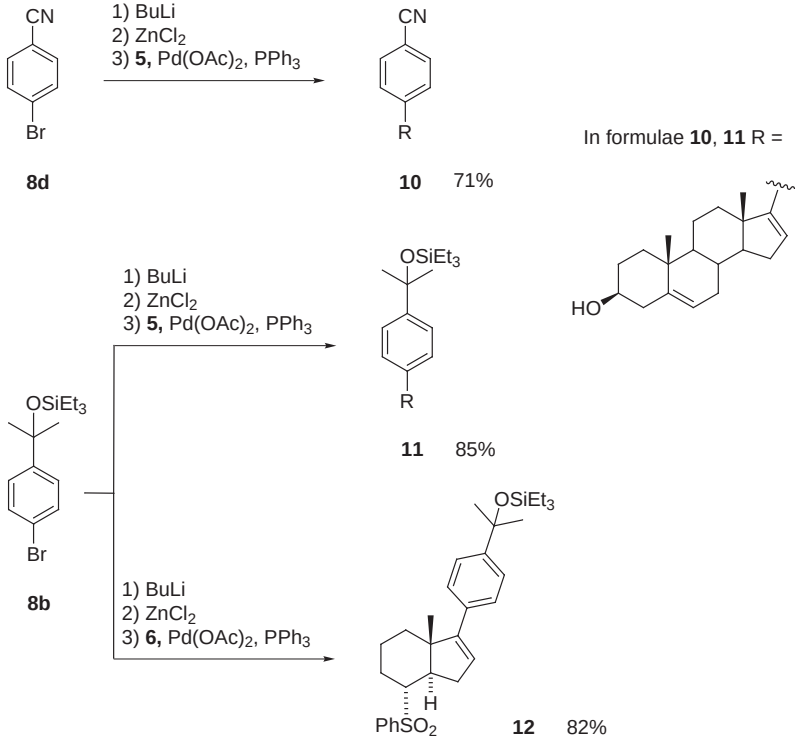
[a] The reaction was carried out at –96 °C.

SCHEME 1

The above discussed results and the reported application of ethyl 2- and 3-bromobenzoates in the zinc-mediated coupling with primary alkyl iodides[20], prompted us to examine also bromobenzoic acid derivatives. When methyl 4-bromobenzoate (**8e**) was used no coupling product could be obtained. However, *tert*-butyl 4-bromobenzoate[21] (**8f**) afforded the desired product **9f** in 59% yield under standard conditions (–78 °C) and in 69% yield when halogen–lithium and lithium–zinc exchange reactions were carried out at –96 °C.

It was of interest to examine, *en route*, the reaction of iodide **4** with a 3-pyridyl organozinc derivative which could lead to 17-(3-pyridyl)androstane derivatives that appear to have potential therapeutic value[22]. 3-Bromopyridine (**8g**) was transformed into the corresponding lithium and then zinc derivative which was used in the Negishi coupling reaction. Pyridylandrostane derivative **9g** was obtained in a 78% yield as, virtually, the only reaction product. The high yield of this preparation is noteworthy since analogous pyridylandrostane derivatives were obtained in only *ca* 10% yield by the reaction of 17-oxoandrostanes with 3-lithiompyridine, followed by dehydration[23,24] and since the afore mentioned Suzuki coupling employing the respective vinyl iodide and diethyl(3-pyridyl)borane[4] afforded the product contaminated with a steroid dimer, which required tedious purification[4,11].

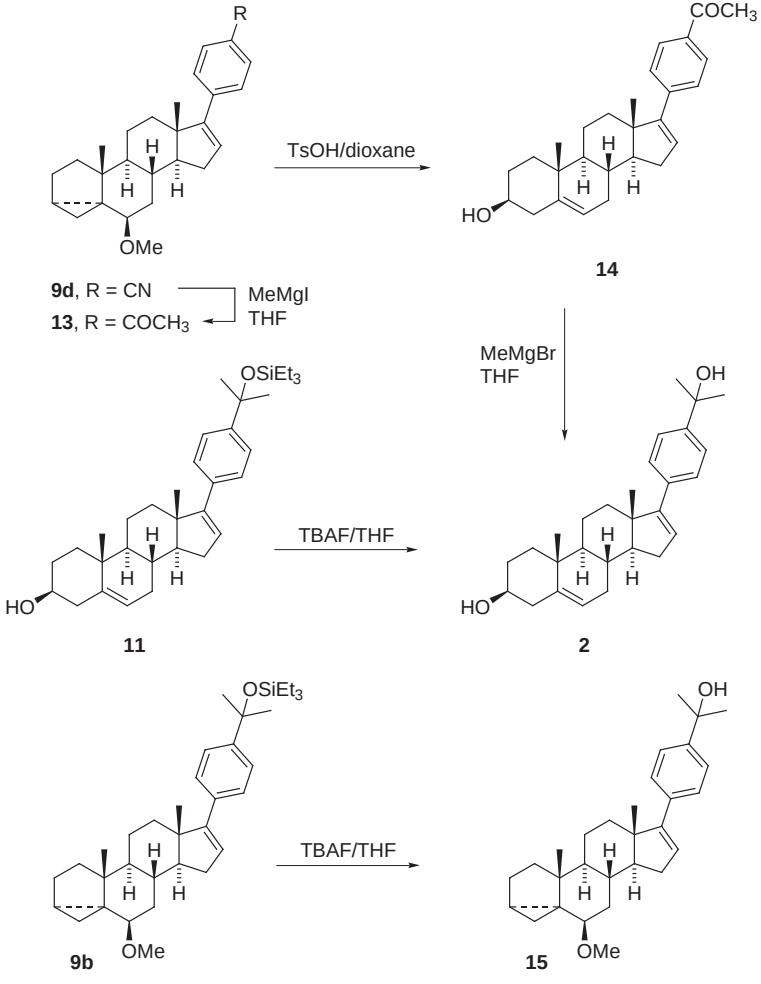
When vinyl iodide with an unprotected hydroxy group **5** was treated with an excess of organozinc reagent prepared from **8d**, in the presence of 10 mole % of $Pd(PPh_3)_4$, the cross-coupling product **10** (Scheme 2) was ob-



SCHEME 2

tained in 71% yield. Under the similar conditions, coupling of **5** with the silyloxy derivative **8b** gave **11** in 85% yield. Finally, iodide **6** with the phenylsulfonyl group and the adjacent acidic proton smoothly underwent coupling with silyloxy bromide **8b** to afford **12** in 82% yield.

The required cholesterol derivative **2** was generated by desilylation of **11** (Scheme 3). It could be also conveniently synthesized from nitrile **9d**. The reaction of **9d** with methylmagnesium iodide followed by hydrolysis afforded the acetophenone derivative **13**. At this stage the *i*-steroid protective system was cleaved and the resulting keto alcohol **14** was treated with ex-



SCHEME 3

cess of the Grignard reagent. The thus obtained acid-sensitive diol **2** was purified by chromatography and crystallization. Desilylation of **9b** afforded **15** which is another precursor of **2**.

In conclusion, it was shown that 17-iodo-16-ene steroids smoothly react with aromatic organozinc reagents in the presence of a palladium catalyst. Comparison of our results with those of other cross-coupling reactions reported in the literature indicates that the Negishi cross-coupling reaction is particularly well suited for the vinyl iodide moiety located in a sterically hindered environment.

EXPERIMENTAL

Melting points were determined on a hot-stage apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ solutions at 200 MHz with Varian Gemini instrument. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. IR spectra (wavenumbers in cm^{-1}) were recorded on Perkin–Elmer 1670 FT unit. Mass spectra (electron impact, 70 eV) were taken on AMD 604 (AMD Intectra GmbH, Germany). Reactions involving organometallic reagents were carried out in flame-dried glassware under analytical grade argon (containing less than 0.5 ppm of oxygen and less than 1.4 ppm of water). THF was dried over Na-K alloy and distilled under argon. Organic extracts were dried over anhydrous $MgSO_4$ and the solvents were removed on a rotary evaporator under reduced pressure. Merck silica gel, 230–400 mesh, was used for column chromatography. Butyllithium (2.0–2.3 M solution in hexanes), zinc chloride (0.5 M solution in THF) and palladium(II) acetate (99.98%), were purchased from Aldrich.

17-Iodo-6β-methoxy-3α,5-cyclo-5α-androst-16-ene (**4**)

To a solution of 6β-methoxy-3α,5-cyclo-5α-androstan-17-one (1.6 g, 5.3 mmol) in ethanol (98%, 45 ml) containing triethylamine (25 ml), hydrazine hydrate (50%, 22 ml) was added. The mixture was heated under reflux for 1.5 h, cooled and the bulk of the solvent was removed. The residue was diluted with chloroform, washed with water and dried. The solvent was evaporated and the crude hydrazone (2.3 g) was dissolved in THF (50 ml) and triethylamine (20 ml). To this solution, vigorously stirred and cooled with cold water, a solution of iodine (6.0 g, 23.6 mmol) in THF (15 ml) was added dropwise until brown color persisted. After consumption of the hydrazone (TLC), the mixture was extracted with toluene. The combined extracts were washed with water, dried and the solvent was evaporated. The residue (2.2 g) was chromatographed on silica gel (100 g, hexanes–ether 99.6:0.4) to give **4** as an oil (1.2 g, 55%). M.p. 72–73 °C (acetone–H_2O). ^{1}H NMR: 0.47 dd, 1 H, *J* = 8.0, 5.1 (H-4α); 0.68 t, 1 H, *J* = 4.5 (H-4β); 0.79 s, 3 H (3 × H-18); 1.06 s, 3 H (3 × H-19); 2.80 t, 1 H, *J* = 2.7 (H-6); 3.35 s, 3 H (OCH_3); 6.13 dd, *J* = 3.1, 1.8 (H-16). EI-MS, *m/z* (%): 412 (22) [M^+], 397 (57) [$M^+ - CH_3$], 380 (44) [$M^+ - H_3COH$], 357 (95) [$M^+ - C_4H_7$], 91 (100). For $C_{20}H_{29}IO$ (412.4) calculated: 58.26% C, 7.09% H; found: 58.29% C, 7.10% H.

(3a*S*,7*R*,7a*R*)-Benzenesulfonyl-3-iodo-3a-methyl-3a,4,5,6,7,7a-hexahydro-1*H*-indene (**6**)

This compound was prepared by the procedure described above, using the (3a*R*,4*R*,7a*S*)-4-benzenesulfonyl-7a-methyloctahydroinden-1-one[18] (**7**; 110 mg, 0.38 mmol), ethanol (8 ml), triethylamine (1.4 ml) and hydrazine hydrate (2.8 ml). The hydrazone was isolated with methylene chloride and the crude product in THF (7.5 ml) and triethylamine (0.75 ml) was treated with iodine (200 mg, 0.79 mmol) in THF (2 ml). The product was isolated with dichloromethane and purified by chromatography on silica gel (14 g, hexanes–acetone 95:5) to give iodide **6** as an oil (101 mg, 70%). M.p. (decomp.) 172–184 °C (acetone–hexane). ^{1}H NMR: 0.78 s, 3 H (3a-CH_3); 2.01 td, 1 H, J = 11.3, 6.6 (H-7a); 2.36 and 2.61 AB part of ABXY system, 2 H, $J_{1A,1B}$ = 15.7, $J_{2A,7a}$ = 11.0, $J_{1A,2}$ = 1.7, $J_{1B,7a}$ = 6.6, $J_{1B,2}$ = 3.3 (H-2); 3.22 td, 1 H, J = 11.6, 3.4 (H-7a); 6.18 dd, 1 H, J = 3.3, 1.6 (H-2); 7.52–7.72 m, 3 H (H-Ph); 7.84–7.92 m, 2H (H-Ph). EI-MS, *m/z* (%): 402 (14) [M^+], 261 (29) [$M^+ - SO_2Ph$], 134 (100) [$M^+ - SO_2Ph - I$]. For $C_{16}H_{19}IO_2S$ (402.3) calculated: 47.76% C, 4.77% H, 7.97% S; found: 47.81% C, 4.68% H, 8.05% S.

General Procedure for the Coupling Reaction

To a solution of aryl halide in THF, stirred at –78 °C, butyllithium (2.3 M solution in hexanes, 0.24 ml, 0.55 mmol) and then, after 7 min, zinc chloride (0.5 M solution in THF, 1.5 ml, 0.75 mmol) were added. The mixture was stirred for 10 min at the initial temperature, the cooling bath was removed and stirring was continued for 30–35 min (solution A). In parallel, palladium(II) acetate and triphenylphosphine were placed in a flask, dried and de-oxygenated by consecutive application of vacuum and argon, then dissolved in THF and stirred at room temperature for 1 h. The resulting clear bright-yellow solution was added by a syringe to the dried and de-oxygenated **4**, **5**, or **6** and the whole was immediately taken into the syringe and added to the solution A. The mixture was stirred for 18 h, aqueous ammonium chloride solution was added, and the mixture was diluted with dichloromethane. The organic layer was washed with water, dried and the solvent was evaporated.

6β-Methoxy-17-(4-methylphenyl)-3α,5-cyclo-5α-androst-16-ene (**9a**). *p*-Tolylbromide (**8a**; 86 mg, 0.50 mmol) in THF (0.7 ml), butyllithium (2.3 M solution, 0.24 ml, 0.55 mmol) zinc chloride (0.5 M solution, 1.5 ml, 0.75 mmol) and palladium(II) acetate (2.7 mg, 0.012 mmol) and triphenylphosphine (12.6 mg, 0.048 mmol) in THF, and iodide **4** (50 mg, 0.12 mmol). The residue (70 mg) was chromatographed on silica gel (7 g, hexanes–dichloromethane 8:2) to give **9a** as an oil (36 mg, 78%). ^{1}H NMR: 0.46 dd, 1 H, J = 8.0, 5.1 (H-4α); 0.67 t, 1 H, J = 4.4 (H-4β); 1.07 s, 6 H (3 × H-18 and 3 × H-19); 2.33 s, 3 H (Ar-CH_3); 2.82 t, 1 H, J = 2.6 (H-6); 3.37 s, 3 H (OCH_3); 5.85 dd, 1 H, J = 3.1, 1.8 (H-16); 7.15 and 7.27 AA′BB′ system, 4 H, J = 8.1 (4 × H-Ar). EI-MS, *m/z* (%): 376 (100) [M^+], 361 (20) [$M^+ - CH_3$], 329 (56) [$M^+ - CH_3 - H_3COH$], 321 (32) [$M^+ - C_4H_7$]. HR-MS: for $C_{27}H_{36}O$ calculated: 376.27662; found: 376.27643. TLC analysis of the crude reaction product showed that **9a** was contaminated by traces of a more mobile component to which structure of 6β-methoxy-3α,5-cyclo-5α-androst-16-ene was ascribed.

6β-Methoxy-17-(4-{2-[(triethylsilyl)oxy]propan-2-yl}phenyl)-3α,5-cyclo-5α-androst-16-ene (**9b**). *O*-Triethylsilyl 2-(4-bromophenyl)propen-2-ol (**8b**), prepared from **8c**[19] in the usual way (380 mg, 1.15 mmol) in THF (5 ml), butyllithium (2.0 M solution, 0.57 ml, 1.15 mmol), zinc chloride (0.5 M solution, 3 ml, 1.5 mmol) and palladium(II) acetate (5 mg, 0.022 mmol), triphenylphosphine (23.5 mg, 0.090 mmol), THF (2.5 ml), and iodide **4** (80 mg, 0.19 mmol). The crude product (397 mg) was chromatographed on silica gel (10 g, hexanes–ether

99.6:0.4) to give **9b** (92 mg, 88%) as an oil. ^{1}H NMR: 0.47 dd, 1 H, *J* = 8.1, 5.1 (H-4α); 0.52–0.72 m, 6 H (Si(C**H**$_2$CH$_3$)$_3$) and 1 H (H-4β); 0.95 t, 9 H, *J* = 7.8 (Si(CH$_2$C**H**$_3$)$_3$); 1.09 s, 6 H (3 × H-18 and 3 × H-19); 1.56 s, 6 H (Et$_3$SiOC(C**H**$_3$)$_2$); 2.82 t, 1 H, *J* = 2.6 (H-6); 3.37 s, 3 H (OCH$_3$); 5.90 dd, 1 H, *J* = 3.1, 1.8 (H-16); 7.32 and 7.37 ABq, 4 H, *J* = 8.6 (4 × H-Ar). EI-MS, *m/z* (%): 534 (18) [M$^+$], 519 (100) [M$^+$ – CH$_3$], 505 (18) [M$^+$ – CH$_2$CH$_3$], 403 (18) [M$^+$ – OSiEt$_3$]. HR-MS: for $C_{35}H_{54}O_2Si$ calculated: 534.38931; found: 534.39020.

*17-(4-Cyanophenyl)-6*β*-methoxy-3*α*,5-cyclo-5*α*-androst-16-ene* (**9d**). 4-Bromobenzonitrile (**8d**; 455 mg, 2.5 mmol) in THF (15 ml), butyllithium (2.3 M solution, 1.05 ml, 2.41 mmol), zinc chloride (0.5 M solution, 5.4 ml, 2.7 mmol) and palladium(II) acetate (13.5 mg, 0.060 mmol), triphenylphosphine (63 mg, 0.24 mmol) in THF (11 ml), and iodide **4** (259 mg, 0.63 mmol). The crude product (550 mg) was chromatographed on silica gel (11 g, hexanes–ether 99.5:0.5) to give **9d** as an oil (216 mg, 89%). IR: 2226 (CN). ^{1}H NMR: 0.48 dd, 1 H, *J* = 7.9, 5.4 (H-4α); 0.69 t, 1 H, *J* = 4.4 (H-4β); 1.08 and 1.10 2 s, 6 H (3 × H-18 and 3 × H-19); 2.83 t, 1 H, *J* = 2.9 (H-6); 3.37 s, 3 H (OCH$_3$); 6.07 dd, 1 H, *J* = 3.2, 1.8 (H-16); 7.57 and 7.45 ABq, 4 H, *J* = 8.6 (H-Ar). EI-MS, *m/z* (%): 387 (42) [M$^+$], 372 (65) [M$^+$ – CH$_3$], 355 (39) [M$^+$ – H$_3$COH], 340 (42) [M$^+$ – CH$_3$ – H$_3$COH], 332 (100) [M$^+$ – C$_4$H$_7$]. HR-MS: for $C_{27}H_{33}NO$ calculated: 387.25621; found: 387.25625.

*17-[4-(tert-Butoxycarbonyl)phenyl]-6*β*-methoxy-3*α*,5-cyclo-5*α*-androst-16-ene* (**9f**). The reaction was carried out as described above but at –96 °C, using *tert*-butyl 4-bromobenzoate[25] (**8f**; 167 mg, 0.65 mmol) in THF (2.7 ml), butyllithium (2.0 M solution, 0.33 ml, 0.66 mmol), zinc chloride (0.5 M solution, 1.7 ml, 0.85 mmol) and palladium(II) acetate (2.4 mg, 0.011 mmol), triphenylphosphine (11.2 mg, 0.042 mmol) in THF (1.3 ml), and iodide **4** (44 mg, 0.11 mmol). The crude product (145 mg) was chromatographed on silica gel (3.5 g, hexanes–ether 99.4:0.6) to give a mixture of **4** and 6β-methoxy-5α-androst-16-ene (8 mg), and then **9f** (34 mg, 69%). M.p. 152–157 °C (acetone). IR: 1709 (COO*t*-Bu). ^{1}H NMR: 0.47 dd, 1 H, *J* = 8.0, 5.0 (H-4α); 0.68 t, 1 H, *J* = 4.9 (H-4β); 1.08 and 1.10 2 s, 6 H (3 × H-18 and 3 × H-19); 1.59 s, 9 H (COOC(CH$_3$)$_3$); 2.83 t, 1 H, *J* = 2.7 (H-6); 3.37 s, 3 H (OCH$_3$); 6.01 dd, 1 H, *J* = 3.0, 1.8 (H-16); 7.40 and 7.90 ABq, 4 H, *J* = 8.2 (H-Ar). EI-MS, *m/z* (%): 462 (100) [M$^+$], 447 (36) [M$^+$ – CH$_3$], 415 (38) [M$^+$ – CH$_3$ – H$_3$COH], 407 (49) [M$^+$ – C$_4$H$_9$], 389 (25) [M$^+$ – *t*-BuO], 359 (32) [M$^+$ – HCOO*t*-Bu – H]. For $C_{31}H_{42}O_3$ (462.7) calculated: 80.48% C, 9.15% H; found: 80.43% C, 9.11% H. An analogous reaction carried out at –78 °C gave **9f** in a 59% yield.

*6*β*-Methoxy-17-(3-pyridyl)-3*α*,5-cyclo-5*α*-androst-16-ene* (**9g**). 3-Bromopyridine (**8g**; 100 mg, 0.63 mmol) in THF (2.2 ml), butyllithium (2.1 M solution, 0.30 ml, 0.63 mmol), zinc chloride (1.8 ml solution, 0.9 mmol), and palladium(II) acetate (2.7 mg, 0.012 mmol), triphenylphosphine (12.6 mg, 0.048 mmol) in THF (1.8 ml), and iodide **4** (52 mg, 0.126 mmol). The crude product was chromatographed on silica gel (3 g, hexanes–acetone 98:2) to give **9g** (36 mg, 78%). ^{1}H NMR: 0.47 dd, 1 H, *J* = 8.1, 5.1 (H-4α); 0.69 t, 1 H (H-4β); 1.08 s, 6 H (3 × H-18 and 3 × H-19); 2.83 t, 1 H, *J* = 2.7 (H-6); 3.37 s, 3 H (OCH$_3$); 5.98 dd, 1 H, *J* = 3.1, 1.8 (H-16); 7.21 dd, 1 H, *J* = 7.9, 4.8 (H-5′); 7.64 dt, 1 H, *J* = 7.9, 1.9 (H-4′); 8.45 d, 1 H, *J* = 4.5 (H-6′); 8.62 brs, 1 H (H-2′). EI-MS, *m/z* (%): 363 (92) [M$^+$], 348 (75) [M$^+$ – CH$_3$], 331 (42) [M$^+$ – H$_3$COH], 316 (79) [M$^+$ – CH$_3$ – H$_3$COH], 308 (100) [M$^+$ – C$_4$H$_7$]. For $C_{25}H_{33}NO$ (363.5) calculated: 82.60% C, 9.15% H, 3.85% N; found: 82.45% C, 9.16% H, 3.69% N.

*17(4-{2-[(Triethylsilyl)oxy]propan-2-yl}phenyl)androsta-5,16-dien-3*β*-ol* (**11**). Bromide **8b** (254 mg, 0.77 mmol), THF (3 ml), butyllithium (2.5 M solution, 310 μl, 0.77 mmol), zinc chloride (0.5 M solution, 1.8 ml, 0.9 mmol), palladium(II) acetate (3 mg, 0.013 mmol) and triphenylphosphine (15.3 mg, 0.058 mmol), THF (1.8 ml), iodide **5** (45 mg, 0.11 mmol). The

crude product was chromatographed on silica gel (7.5 g, hexanes–acetone 95:5) to give **11** as a crystalline mass (50 mg, 85%). ^{1}H NMR: 0.50–0.66 m, 6 H (Si(C**H**$_2$CH$_3$)$_3$); 0.95 t, 9 H, *J* = 8.2 (Si(CH$_2$C**H**$_3$)$_3$); 1.06 and 1.07 2 s, 6 H (3 × H-18 and 3 × H-19); 1.56 s, 6 H (Et$_3$SiO(C**H**$_3$)$_2$); 3.44–3.65 m, 1 H (H-3); 5.39 brd, 1 H, *J* = 4.8 (H-6); 5.91 dd, 1 H, *J* = 3.1, 1.8 (H-16); 7.31 and 7.37 ABq, 4 H, *J* = 8.7 (H-Ar). EI-MS, *m/z* (%): 520 (16) [M$^+$], 505 (100) [M$^+$ – CH$_3$], 491 (23) [M$^+$ – CH$_2$CH$_3$], 389 (27) [M$^+$ – OSiEt$_3$], 371 (13) [M$^+$ – OSiEt$_3$ – H$_2$O]. HR-LSIMS for $C_{34}H_{52}NaO_2Si$ calculated: 543.36343; found: 543.36593.

O-Triethylsilyl-(3aR,4R,7aS)-2-[4-(4-benzenesulfonyl-7a-methyl-3a,4,5,6,7,7a-hexahydro-3H-inden-1-yl)phenyl]propan-2-ol (**12**). Bromide **8b** (208 mg, 0.63 mmol), butyllithium (2.5 M solution, 255 μl, 0.64 mmol), zinc chloride (0.5 M solution, 1.6 ml, 0.8 mmol), palladium(II) acetate (2.7 mg, 0.012 mmol) and triphenylphosphine (12.6 mg, 0.048 mmol) in THF (1.8 ml), and iodide **6** (42 mg, 0.10 mmol). The crude product was chromatographed on silica gel (7 g, hexanes–acetone 95:5) to give **12** as an oil (45 mg, 82%). ^{1}H NMR: 0.51–0.66 m, 6 H, (Si(C**H**$_2$CH$_3$)$_3$); 0.94 t, 9 H, *J* = 7.8 (Si(CH$_2$C**H**$_3$)$_3$); 1.07 s, 3 H (7a-CH$_3$); 1.55 s, 6 H (Et$_3$SiOC(C**H**$_3$)$_2$); 2.39 and 2.65 AB part of ABXY system, 2 H, $J_{15A,15B}$ = 16.2, $J_{15A,14}$ = 11.1, $J_{15A,16}$ = 1.7, $J_{15B,14}$ = 6.6, $J_{15B,16}$ = 3.3 (H-3); 3.31 td, 1 H, *J* = 11.6, 3.2 (H-4); 5.88 dd, 1 H, *J* = 3.2, 1.8 (H-2); 7.25 and 7.37 ABq, 4 H, *J* = 8.6 (H-Ar); 7.57–7.71 m, 3 H (H-Ph); 7.85–7.95 m, 2 H (H-Ph). EI-MS, *m/z* (%): 524 (8) [M$^+$], 509 (76) [M$^+$ – CH$_3$], 495 (14) [M$^+$ – CH$_2$CH$_3$], 393 (23) [M$^+$ – OSiEt$_3$], 251 (100) [M$^+$ – OSiEt$_3$ – PhSO$_2$ – H]. HR-MS: for $C_{31}H_{44}O_3SSi$ calculated: 524.27805; found: 524.27505.

17-(4-Cyanophenyl)androsta-5,16-dien-3β-ol (**10**)

a) 4-Bromobenzonitrile (**8d**; 128 mg, 0.70 mmol) in THF (3 ml), butyllithium (2.1 M solution, 0.34 ml, 0.71 mmol), zinc chloride (0.5 M solution, 1.8 ml, 0.9 mmol) and palladium(II) acetate (3.7 mg, 0.016 mmol) and triphenylphosphine (16.9 mg, 0.064 mmol) in THF (2.5 ml), and iodide **5** (36 mg, 0.09 mmol). The crude product (107 mg) was chromatographed on silica gel (3.5 g, hexanes–acetone 95:5) to give **10** (24 mg, 71%). M.p. 197–199 °C (acetone). IR: 3616 (OH), 2221 (CN). ^{1}H NMR: 1.07 s, 6 H (3 × H-18 and 3 × H-19); 1.57 s (OH and H$_2$O); 3.43–3.65 m, 1 H (H-3); 5.39 brd, 1 H, *J* = 5.4 (H-6); 6.08 dd, 1 H, *J* = 3.3, 1.9 (H-16); 7.46 and 7.57 ABq, 4 H, *J* = 8.6 (H-Ar). EI-MS, *m/z* (%): 373 (96) [M$^+$], 358 (71) [M$^+$ – CH$_3$], 355 (37) [M$^+$ – H$_2$O], 340 (100) [M$^+$ – CH$_3$ – H$_2$O]. HR-MS: for $C_{26}H_{31}NO$ calculated: 373.24056; found: 373.24107.

b) *i*-Ether **9d** (87 mg, 0.22 mmol) was dissolved in dioxane (36 ml) containing water (1.2 ml) and 4-toluenesulfonic acid monohydrate (*ca* 7 mg, 0.037 mmol) and the mixture was stirred at 68 °C for 6 h. The product was isolated with dichloromethane and chromatographed on silica gel to give **10** (66 mg, 78%), identical with the sample described above.

17-(4-Acetylphenyl)-6β-methoxy-3α,5-cyclo-5α-androst-16-ene (**13**)

To a solution of nitrile **9d** (86 mg, 0.22 mmol) in THF (3.2 ml) methylmagnesium iodide (2.5 M solution in ether, 3.2 ml, 8 mmol) was added and the mixture was stirred at 50 °C for 2 h. After cooling, the mixture was diluted with toluene, the reaction was quenched by careful addition of water and then aqueous NH_4Cl was added. The organic layer was separated, washed with water and the solvent was removed. The residue was chromatographed on silica gel (3.5 g, hexanes–acetone 99.2:0.8) to give **13** as an oil (62 mg, 69%). IR: 1679 (conjugated COCH$_3$); 1601, 1554 (double bonds). ^{1}H NMR: 0.47 dd, 1 H, *J* = 7.9, 5.1 (H-4α); 0.69 t, 1 H, *J* = 4.4 (H-4β); 1.09 and 1.12 2 s, 6 H (3 × H-18 and 3 × H-19); 2.59 s, 3 H (CH$_3$CO);

2.80 t, 1 H, *J* = 2.7 (H-6); 3.38 s, 3 H (OCH_3); 6.06 dd, 1 H, *J* = 3.3, 2.0 (H-16); 7.46 and 7.89 ABq, 4 H, *J* = 8.6 (H-Ar). EI-MS, *m/z* (%): 404 (96) [M^+], 389 (81) [$M^+ - CH_3$], 372 (35) [$M^+ - H_3COH$], 357 (85) [$M^+ - CH_3 - H_3COH$], 349 (92) [$M^+ - C_4H_7$], 43 (100). For $C_{28}H_{36}O_2$ (404.6) calculated: 83.12% C, 8.97% H; found: 83.35% C, 8.89% H.

17-(4-Acetylphenyl)androsta-5,16-dien-3β-ol (**14**)

A solution of *i*-ether **13** (37 mg, 0.09 mmol) and 4-toluenesulfonic acid monohydrate (3 mg, 0.016 mmol) in dioxane (1.2 ml) containing water (0.4 ml) was stirred at 65 °C. After 5 h, the mixture was diluted with dichloromethane and washed with water. The solvent was evaporated and the residue was chromatographed on silica gel (1.5 g, hexanes–acetone 90:10). Alcohol **14** (24 mg, 67%) was obtained. M.p. 218–219 °C (acetone). IR: 3408, 1666 (conjugated $COCH_3$); 1601, 1553. ^{1}H NMR: 1.08 and 1.09 2 s, 6 H (3 × H-18 and 3 × H-19); 1.56 s (OH and H_2O); 2.59 s, 3 H ($COCH_3$); 3.43–3.65 m, 1 H (H-3); 5.40 brd, 1 H (H-6); 6.08 dd, 1 H, *J* = 3.3, 1.9 (H-16); 7.46 and 7.89 ABq, 4 H, *J* = 8.6 (H-Ar). EI-MS, *m/z* (%): 390 (68) [M^+], 375 (53) [$M^+ - CH_3$], 372 (11) [$M^+ - H_2O$], 357 (48) [$M^+ - H_2O - CH_3$]; 43 (100). For $C_{27}H_{34}O_2$ (390.5) calculated: 83.03% C, 8.77% H; found: 83.03% C, 8.59% H.

17-[4-(2-Hydroxypropan-2-yl)phenyl]androsta-5,16-dien-3β-ol (**2**)

a) To a solution of ketone **14** (15 mg, 0.04 mmol) in THF (1 ml), methylmagnesium iodide (2.5 Msolution in ether, 1 ml, 2.5 mmol) was added and the mixture was stirred at 60–65 °C for 1 h. After cooling, the mixture was diluted with dichloromethane and water, and aqueous NH_4Cl was added. The organic layer was separated, washed with water and evaporated to give a crystalline residue (14 mg). This product was chromatographed on silica gel (1.5 g, hexanes–acetone 90:10) to give **2** (6 mg, 38%) which was recrystallized from dichloromethane. M.p. 214–217 °C. ^{1}H NMR: 1.06 and 1.59 2 s, 6 H (3 × H-18 and 3 × H-19); 1.57 s (OH and H_2O); 1.59 s, 6 H ($ArC(CH_3)_2OH$); 3.42–3.65 m, 1 H (H-3); 5.39 brd, 1 H, *J* = 5.7 (H-6); 5.92 dd, 1 H, *J* = 3.2, 1.9 (H-16); 7.36 and 7.42 ABq, 4 H, *J* = 8.8 (H-Ar). EI-MS, *m/z* (%): 406 (100) [M^+], 391 (98) [$M^+ - CH_3$], 373 (26) [$M^+ - CH_3 - H_2O$], 355 (10) [$M^+ - CH_3 - H_2O - H_2O$]. For $C_{28}H_{38}O_2$ (406.6) calculated: 82.71% C, 9.42% H; found: 82.70% C, 9.39% H.

b) A solution of crude silyl ether **11** (44 mg, 0.085 mmol) and tetrabutylammonium fluoride trihydrate (110 mg, 0.35 mmol) in THF (3 ml) was stirred at room temperature for 4 h. The product was crystallized from dichloromethane to give **2** (26 mg, 76%) identical with the sample described above.

17-[4-(2-Hydroxypropan-2-yl)phenyl]-6β-methoxy-3α,5-cyclo-5α-androst-16-ene (**15**)

A solution of **8b** (51 mg, 0.095 mmol) and tetrabutylammonium fluoride trihydrate (104 mg, 0.33 mmol) in THF (3 ml) was set aside at room temperature for 3 days. The mixture was diluted with dichloromethane, washed with water and the solvent was evaporated. The crystalline residue (45 mg) was chromatographed on silica gel (6 g, hexanes–acetone 97:3) to give **15** (37 mg, 93%). M.p. 188–190 °C (acetone). ^{1}H NMR: 0.46 dd, 1 H, *J* = 7.9, 4.9 (H-4α); 0.68 t, 1 H, *J* = 4.5 (H-4β); 1.08 s, 6 H (3 × H-18 and 3 × H-19); 1.58 s, 6 H ($ArC(CH_3)_2OH$); 2.82 t, 1 H, *J* = 2.7 (H-6); 3.36 s, 3 H (OCH_3); 5.90 dd, 1 H, *J* = 3.1, 1.8 (H-16); 7.36 and 7.40 ABq, 4 H, *J* = 8.8 (H-Ar). EI-MS, *m/z* (%): 420 (100) [M^+], 405 (52)

$[M^+ - CH_3]$, 373 (33) $[M^+ - CH_3 - H_3COH]$, 365 (22) $[M^+ - C_4H_7]$. For $C_{29}H_{40}O_2$ (420.6) calculated: 82.81% C, 9.59% H; found: 82.76% C, 9.61% H.

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