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TETRAHEDRON

Steroid Phosphate Esters

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Abstract: Four phosphorylation procedures were used in the preparation and characterization of sundry steroid phosphate and phosphonate esters, as well as some P^1,P^2-disteroid pyrophosphates. An attempt to prepare cholest-3,5-dien-3-yl dialkyl phosphate by a vinylogous Perkow reaction from 6-bromocholest-4-en-3-one yielded only dienenones. As a model for P^1,P^2-disteroid pyrophosphate (and steroid phosphate) behavior in solution, the neutral crystalline complex 2,2'-bipyridine zinc P^1,P^2-bis(1-*n*-dodecyl)pyrophosphate was prepared and characterized.

We report herein on a number of steroid phosphate and phosphonate esters (Figures 1 and 2) which we had occasion to synthesize and characterize in the course of work in our laboratories, and whose availability may be of interest to researchers working *inter alia* on lipid membranes, vesicles, ion association and transport in these,[1] and of course, on steroidal hormones. As already noted by Ramirez,[2] the preparation of such pure compounds in good yield has frequently proved not as trivial as might be presumed.

The observation which engendered one of our projects was that a well-defined crystalline ternary complex was obtained from the interaction of P^1,P^2-bis(1-dodecyl)pyrophosphate with Zn^{++} ion and 2,2'-bipyridine. NMR spectroscopy showed that when the last mentioned was replaced by 4-iodo-2,2'-bipyridine[3] a similar complex was formed, though it was not isolated in crystalline form. It had previously been demonstrated that in an appropriately constructed system an iodine substituent on an aromatic ring could act as a 'relay station', loosely binding a chlorine atom originating in the photochemical decomposition of phenyliodine dichloride ($PhICl_2$) and selectively directing the intramolecular free radical abstraction of a specific proximate hydrogen by that chlorine atom. The carbon radical thus produced continues a chain reaction by abstracting a chlorine atom from $PhICl_2$. Specific tertiary hydrogens (on C-9; or C-14, or C-17, or C-20) were thus selectively replaced by chlorine in various steroid molecules to which a judiciously chosen iodoaryl 'template' had been covalently attached in a sterically advantageous position in each case.[4,5,6,7,8,9,10] A further finding had been that the phenomenon of ion-pairing in organic solvent could also be harnessed to direct chlorine atom bearing iodoaryl

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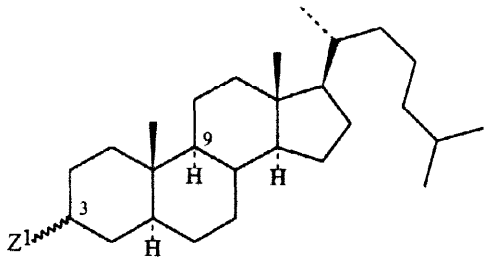
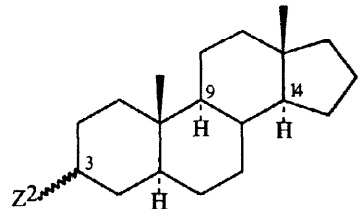
'templates' to the desired targets, though be it at the expense of yield and relative selectivity.[11,12] The question therefore arose as to the effectiveness of a system in which the 'template' (specifically in this case, the heteroaryl 4-iodo-2,2'-bipyridine) and a substrate steroid molecule are held in mutual proximity by metal ion coordination. To this end, and with the above mentioned ternary complex in mind as analogue, we synthesized a number of the steroid phosphate derivatives shown in Figures 1 and 2. The selective C-9 chlorination of 3β-esters **2**, **4**, **12**, **16** (*vide infra*) and C-14 chlorination of 3α-esters **7**, **9**, **14** (*vide infra*) observed when their anions were reacted in solution in the presence of equimolar quantities of 4-iodo-2,2'-bipyridine and zinc ion (plus acetate in the case of the monoanions) with $PhICl_2$, indicated that both the steroid pyrophosphates and the simple steroid phosphate monoanions assembled to geometrically defined complexes with the bipyridine chelated zinc ions.[13] This phenomenon could be useful in other contexts. Thus the hydrophobic steroid moiety of such ionophoric complexes could serve to anchor them to membranes, etc.[1]



1. $Z^1 = 3\beta\text{–}OP(O)(OCH_3)_2$
2. $Z^1 = 3\beta\text{–}OP(O)(OCH_3)OH$
3. $Z^1 = 3\beta\text{–}OP(O)(C_6H_5)OCH_3$
4. $Z^1 = 3\beta\text{–}OP(O)(C_6H_5)OH$



5. $Z^2 = 3\alpha\text{–}OP(O)(OCH_2C_6H_5)_2$
6. $Z^2 = 3\alpha\text{–}OP(O)(OCH_2C_6H_5)OH$
7. $Z^2 = 3\alpha\text{–}OP(O)(OH)_2$
8. $Z^2 = 3\alpha\text{–}OP(O)(C_6H_5)OCH_3$
9. $Z^2 = 3\alpha\text{–}OP(O)(C_6H_5)OH$
10. $Z^2 = 3\beta\text{–}OP(O)(OCH_2C_6H_5)_2$
11. $Z^2 = 3\beta\text{–}OP(O)(OCH_2C_6H_5)OH$
12. $Z^2 = 3\beta\text{–}OP(O)(OH)_2$

Figure 1

Others of the steroidal esters shown in Figures 1 and 2 were synthesized for biological screening after it was found that some steroid phosphate esters significantly augmented lymphocyte response to phytohemmaglutinin, and enhanced the production of interleukin-2, interleukin-3-like activity, interferon and tumor necrosis factor by human mononuclear cells *in vitro*. In *in vivo* experiments these same steroid derivatives were found to induce a rise in blood glucose and an increase in leucocytes when injected into mice.[14] This stimulation of immune system factors is in contrast to the immune system depression often caused by corticosteroids.

The literature of 25-35 years ago contains a number of reports of the phosphorylation of the C(21)-hydroxyl groups of hormonally active steroids.[15,16,17,18,19,20,21] The goals were the water soluble phosphate salts of the

steroid mono-esters, and these were the subject of numerous patents. Some of the preparations proceeded via phosphate triesters, whereas others did not. Surprisingly however, there are relatively few reports of the preparation and characterization of phosphate esters of sparsely functionalized steroids.[22] The earliest of these

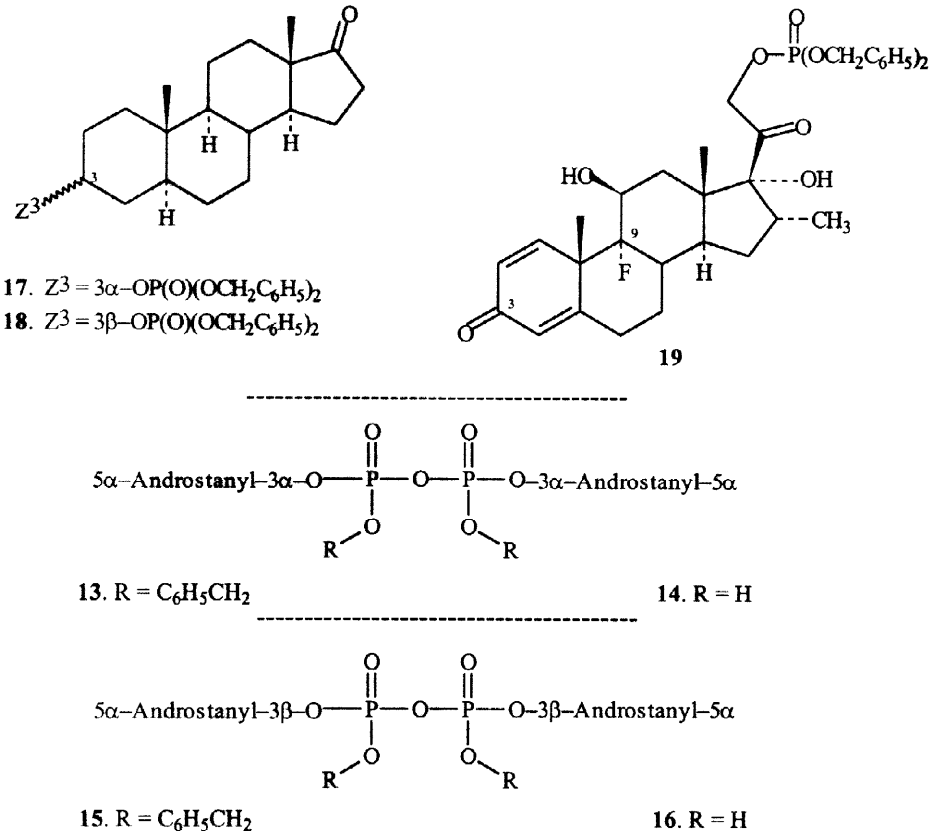


Figure 2

refer to the phosphorylation of cholesterol with $POCl_3$,[23] but lacking sufficiently effective techniques for purification and characterization, the investigators of yore, and even some more recent ones, were unaware of side reactions and of impurity of products.[24,25,26,27,28] This became clear again in our preparation of pure dimethyl 3β-cholestanyl phosphate, **1** (see Experimental Section). The latter was converted to methyl hydrogen 3β-cholestanyl phosphate, **2**, following monodemethylation by NaI in refluxing acetone. Using phenylphosphonyl dichloride, we prepared methyl 3β-cholestanyl phenylphosphonate, **3**, and from it, hydrogen 3β-cholestanyl phenylphosphonate, **4**. In the androstane series the $Cl_2P(O)OP(O)Cl_2$ method[19,26,27] was used to prepare 5α-androstan-3β-yl dihydrogen phosphate, **12**. The simplicity of this method is enticing, but the crude product is difficult to purify, and in our hands the yield (40%, crude) was not attractive.[26] A much more satisfactory route, which was used to prepare both 5α-androstan-3β-yl dihydrogen phosphate, **12**, and its 3α isomer, **7**, involved the low temperature reaction of the respective lithium 3-androstanolates with tetrabenzyl

pyrophosphate. The resulting dibenzyl 5α-androstan-3-yl phosphates (**10**, **5**) were readily purified by chromatography, and catalytically bis-debenzylated by hydrogenolysis over a Pt catalyst in overall yields of 86-91% based on unrecovered 3-androstanols. Furthermore, mono-debenzylation was accomplished in both cases, yielding **11** and **6** respectively, by treatment with NaI in refluxing acetone, though the 3β isomer reacted more slowly than the 3α isomer. Reaction with dicyclohexyl carbodiimide converted the benzyl hydrogen 5α-androstan-3α-yl phosphate, **6**, to P^1,P^2-bis(benzyl 5α-androstan-3α-yl)pyrophosphate, **13**, which was catalytically hydrogenolysed to P^1,P^2-bis(hydrogen 5α-androstan-3α-yl)pyrophosphate, **14**. A similar series of reactions was carried out in the 3β series, yielding **15** and **16**, but characterization in that series was limited to ^{1}H NMR. Methyl 5α-androstan-3α-yl phenylphosphonate, **8**, was prepared with the aid of phenylphosphonyl dichloride, and it was demethylated to give hydrogen 5α-androstan-3α-yl phenylphosphonate, **9**.

Though tetrabenzyl pyrophosphate has proved the reagent of choice for the phosphorylation of the simple steroid alcoholates, it was inappropriate for the phosphorylation of steroids bearing additional functional groups sensative to strong base. For these compounds we resorted to phosphitylation with N,N-diisopropyl dibenzyl phosphoramidite, followed by oxidation to the phosphate esters with *m*-chloroperbenzoic acid.[29] In this manner we prepared both dibenzyl androsteron-3-yl phosphate,[30] **17**, and dibenzyl epiandrosteron-3-yl phosphate,[31] **18**, as well as 21-*O*-(dibenzyloxyphosphoryl)dexamethasone,[32] **19**. The preparation of the latter from the 21-iodide has been reported in the old patent literature,[33] but of course its spectral properties have not. Deserving of note are the significantly different chemical shifts of the two diastereotopic benzyl groups of **19** (^{1}H $\Delta\delta$ = 0.16; ^{13}C $\Delta\delta$ = 0.18), a phenomenon of magnitude not observed for the other dibenzyl phosphate esters reported herein, and which is presumably to be ascribed to a larger paramagnetic effect of the nearby (C-20) carbonyl on one of the benzyl groups.

The Perkow reaction is one in which the action of a trialkyl phosphite on an α-halo carbonyl compound yields an enol phosphate.[34] The mechanism of this reaction has been extensively studied, and it appears that, depending on the identity of the particular reactants, it may proceed by different pathways.[34] The literature also records the successful execution of a vinylogous Perkow reaction, leading from the γ-halo-α,β-unsaturated ketone, 1-phenyl-4,4,4-trichlorobut-2-enone, plus triethyl phosphite to the dienol phosphate, diethyl 1-phenyl-4,4-dichloro-1,3-butadienyl phosphate.[35] To investigate the applicability of this approach to the synthesis of a steroidal 3,5-dien-3-yl dialkyl phosphate we prepared both pure 6β-bromocholest-4-en-3-one (**20**β) and an equilibrium mixture (~1:1), (**20**α+β), of the 6α- (**20**α) and the 6β-isomers.[36,37,38,39,40] Both of these were subjected to reaction with trimethyl phosphite under a variety of conditions. In no case was any phosphorus containing steroid obtained - not even a steroidal phosphonate. Under conditions found necessary to induce reaction, only products of elimination, cholest-4,6-dien-3-one (**21**) and its isomer cholest-1,4-dien-3-one (**22**), were obtained. (For details see Experimental Section). The paths leading to this outcome were not researched, but it is it is possible that HBr elimination is auto-catalytic, and that this acid further catalyzes the

isomerization of one of the isomers of **20** in the reaction mixture to the other. The formation of **22** may proceed via the 2-enol of **20**,[41] but the possibility of an acid catalyzed isomerization of **21** to **22** has not been excluded (Figure 3). Though it is tempting to speculate on the mechanistic significance, if any, of the failure of this attempted vinylogous Perkow reaction, prudence dictates restraint.

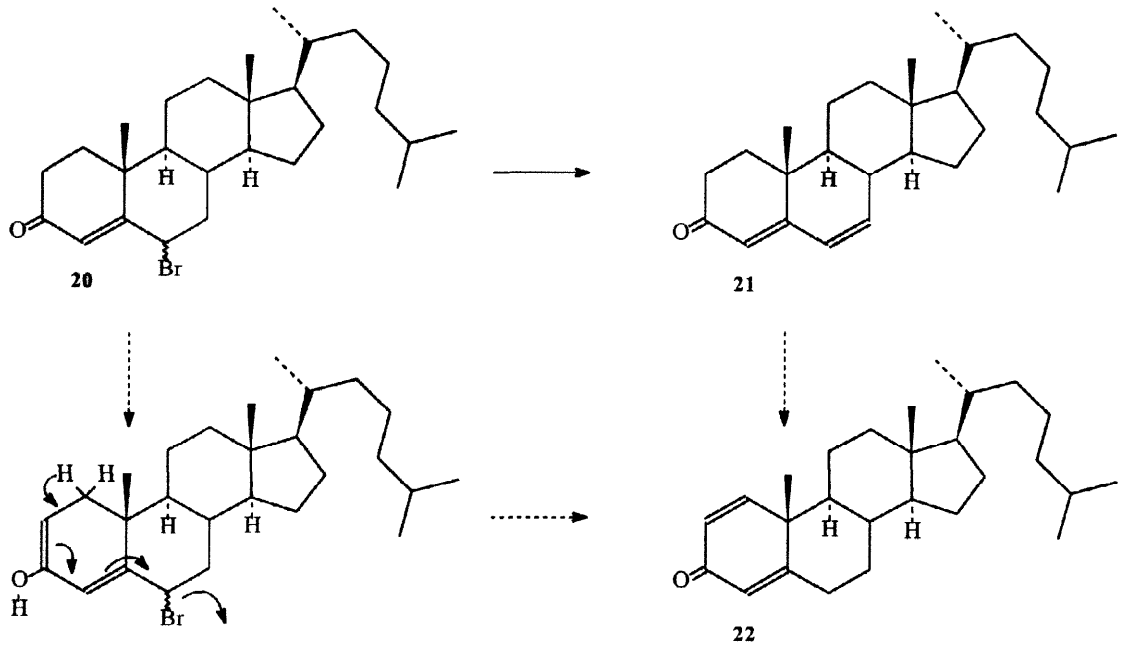


Figure 3

EXPERIMENTAL SECTION

Melting points were determined on a Melt-Temp or Fisher-Johns (heated metal block) apparatus, or in a capillary melting point apparatus (Thomas-Hoover), and are uncorrected. Infra-red (IR) spectra were determined on a Perkin-Elmer 1420 spectrometer or a Nicolet FT-IR 60 SXB spectrometer in KBr pellets. Only peaks of strong (s) or medium (m) intensity in the 1800 - 600 cm^{-1} region are listed. Ultra-violet (UV) spectra were recorded on a Varian DMS 100S instrument; values of λ_{max} in nm (ε in $M^{-1}cm^{-1}$). Mass spectra (MS; ionization potential 60-70 eV) were determined on a Finnigan 4021 mass spectrometer or a Nermag R-10-10 quadrupole instrument. MS-FAB spectra were determined on a V6 Analytical 7070EQ instrument. NMR spectra were determined on Varian series VXR or Brucker AM-200 or AM-300 instruments. Chemical shift values, (for ^{1}H and ^{13}C, ppm downfield from TMS) were determined using the following values for residual solvent proton (or ^{13}C) resonances as references: $C\underline{H}Cl_3$ δ 7.26; $C\underline{H}_3OH$ δ 3.31; $C\underline{H}_2Cl_2$ δ 5.30; $^{13}\underline{C}HCl_3$ δ 77.16.[42] Coupling constants (J) are in Hertz (Hz). Thin layer chomatography (TLC) was performed on precoated silica plates (from EM science) containing fluorescent indicator, or, in some cases, on Merck Aluminum foils 60 F 254. UV

active compounds were visualized under UV lighting. Other compounds were detected by dipping in a phosphomolybdic acid solution (6% in ethanol) followed by heating. Flash (column) chromatography was performed using Merck Silica Gel 6 (60-230 mesh) or Merck Silica Gel 60 (320-400 mesh). Chemicals and reagents were purchased from Aldrich and purified when necessary. Solvents were purified (when necessary), thoroughly dried by standard methods and distilled shortly before use. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, N.Y., U.S.A.; by Alfred Bernhardt Analytical Laboratory, Germany; and by the Microanalytical Laboratory, Hebrew University, Jerusalem, Israel.

2,2'-Bipyridine zinc P^1,P^2-bis(1-*n*-dodecyl)pyrophosphate: 1-*n*-Dodecyl phosphate (532 mg; 2mmol), 2,2'-bipyridine (157 mg, 1 mmol) and dicyclohexyl carbodiimide (208 mg, 1 mmol) were dissolved in dry CH_2Cl_2 (~35 mL) and kept at ambient temperature with exclusion of moisture for 40 h. The solvent was then evaporated, the residue treated with cyclohexane (~35 mL), the dicyclohexylurea filtered off, and the filtrate treated with an equal volume of methanol containing zinc acetate dihydrate (220 mg, 1 mmol). Within a few minutes a heavy white crystalline precipitate of the desired ternary complex appeared. It was collected, dried under vacuum, and purified by solution in CH_2Cl_2, centrifugation to permit separation from a little insoluble impurity, and slow crystallization by gradual addition of excess methanol. The white crystals were dried at 55 °C under vacuum (454 mg, 62%); mp 260-262 °C. UV λ_{max} (nm): 307.5 (ε 12,700), 296 (ε 12,800), 246 (ε 8,900). IR (KBr) ν (cm^{-1}): 1605 (m), 1595 (m), 1467 (m), 1440 (m), 1312 (m), 1287 (s), 1250 (s), 1228 (s), 1167 (m), 1141 (s), 1121 (s), 1093 (sh), 1025 (m), 1017 (m), 957 (s), 850 (m), 775 (m), 735 (m), 729 (m). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86 (t, *J*=6.5 Hz, 6H, CH_3), 1.15, 1.22 (m, 36H, -$(CH_2)_n$-), 1.52 (m, 4H, -CH_2-CH_2-O-), 3.90 (m, 4H, -CH_2-OP), 7.57 (3 peak m, 2H, bipyridine 5-CH), 8.02 (3 peak m, 2H, bipyridine 4-CH), 8.16 (2 peak m, 2H, bipyridine 3-CH), 9.22 (m, 2H, bipyridine 6-CH). MS-FAB *m/z*: 733 [M^+], 734 [M+1]$^+$, 735 [M+2]$^+$, 736 [M+3]$^+$, 737 [M+4]$^+$ (Isotopic peaks). *m/z* 733 ion intensity itself is ~24% of the base peak at *m/z* 157 [$C_{10}H_9N_2$]$^+$. Anal. calcd. for $C_{34}H_{58}N_2O_7P_2Zn$: C, 55.62%, H, 7.96%, P, 8.44%, N, 3.82%, Zn, 8.91%. Found: C, 55.55%, H, 8.06%, P, 8.79%, N, 3.67%, Zn, 8.76%.

4-Iodo-2,2'bipyridine zinc P^1,P^2-bis(1-*n*-dodecyl pyrophosphate): This ternary complex (45 mg, 0.052 mmol) was prepared in a manner similar to the preparation of the unsubstituted analog, by the use of 4-iodo-2,2'-bipyridine[3] in place of 2,2'-bipyridine. (Though not crystallized, its NMR spectrum was that of a pure compound). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, *J* = 6.8 Hz, 6H, CH_3), 1.14, 1.21 (2 peak m, 36H, -$(CH_2)_n$ -), 1.52 (3 peak m, 4H, CH_2-CH_2-O-), 3.89 (m, 4H, CH_2-O-P), 7.53 (pseudo-t, 1H, 5'-CH), 7.98 (pseudo-d, 1H, 5-CH), 8.07 (pseudo-t, 1H, 4'-CH), 8.15 (pseudo-d, 1H, 3'-CH), 8.49 (s, 1H, 3-CH), 9.18 (pseudo d, 1H, 6'-CH).

Dimethyl 5α-cholestan-3β-yl phosphate (1): This triester was prepared by esterification of α-cholestan-3β-yl dihydrogen phosphate[43] (2.43 g, 5.18 mmol) with diazomethane in THF-ether solution. It was purified by flash chromatography on silica using cyclohexane-ethyl acetate (1/1, $^{v}/_{v}$) to yield the *title compound* **1** (2.23 g, 4.5 mmol, 86%) and recrystallized from hexane (80% recovery); white solid, mp 99.8-101 °C.[44] $[\alpha]_D^{26.5}$ +16.4°, $[\alpha]_{577}^{28}$ +17.2°, $[\alpha]_{546}^{28}$ +19.3°, $[\alpha]_{435}^{28}$ +32.3°, $[\alpha]_{365}^{28}$ +49.9° (c 0.035, $CHCl_3$). IR (KBr) ν (cm^{-1}): 1478 (m), 1465 (m), 1456 (m), 1388 (m), 1235 (broad, m), 1202 (broad, m), 1178 (m), 1140 (s), 1130 (s), 1115 (s), 1097 (s), 1087 (s), 1023 (vs), 991 (m), 976 (m). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.60 (s, 3H, 18-C**H**$_3$), 0.77 (s, 3H, 19-C**H**$_3$), 0.82 (d, *J*=6.8 Hz, 6H, 25-CH(C**H**$_3$)$_2$), 0.86 (d, *J*=6.6 Hz, 3H, 20-CHC**H**$_3$), 3.70 (d, J_{PH}=11.2 Hz, 6H, P(OC**H**$_3$)$_2$), 4.25 (bm 8 peaks, 1H, 3-C**H**$_\alpha$). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 12.25 (C-18), 12.40 (C-19), 18.85 (C-21), 21.42 (C-11), 22.72 (C-27), 22.96 (C-26), 24.02 (C-23), 24.38 (C-15), 28.18 (C-25), 28.40 (C-16), 28.74 (C-6), 29.54 (d, J_{PC}=4.4 Hz, C-2), 32.16 (C-7), 35.47 (C-10), 35.69 (C-8), 35.96 (C-20), 36.00 (d, J_{PC}≈5 Hz, C-4), 36.36 (C-22), 36.96 (C-1), 39.70 (C-24), 40.16 (C-12), 42.78 (C-13), 44.88 (C-5), 54.18 (d, J_{PC}=5.6 Hz, O**C**H$_3$), 54.38 (C-9), 56.49 (C-17), 56.58 (C-14), 78.66 (d, J_{PC}=6.0 Hz, C-3). MS (CI, NH_3) ***m/z***: 497 $[M+1]^+$ and isotopic peaks, 498, 499. Anal. calcd. for $C_{29}H_{53}O_4P$: C, 70.13%; H, 10.75%; P, 6.24%. Found: C, 70.42%; H, 10.81%; P, 5.99%.

Methyl hydrogen 5α-cholestan-3β-yl phosphate (2): A solution of **1** (1.54 g, 3.1 mmol) and dry NaI (10 g, 66.7 mmol) in dry acetone (200 mL) were refluxed with stirring for 18 h, during which time a copious precipitate appeared. The solvent was removed by rotary evaporation, and the residue triturated with dry ether (650 mL). The solid was collected by filtration and dissolved in a mixture of 3 M hydrochloric (100 mL) and CH_2Cl_2 (300 mL). The aqueous layer was extracted with an additional portion of CH_2Cl_2 (150 mL). The combined CH_2Cl_2 solutions were washed successively with acidified 8% aqueous $NaHSO_3$ solution (30 mL) and water (30 mL), dried and rotary evaporated. The residue, after vacuum drying (1.49 g), was dissolved in methanol (125 mL) and the solution filtered to remove insoluble material and then taken to dryness. The residue was triturated with acetone to give the *title compound* **2** (1.38 g, 92%) as a white solid, mp 165-167 °C; recrystallized from cyclohexane, mp 166-167.2 °C (Lit.[45] mp 164-166 °C). $[\alpha]_D^{29}$ +16.8°, $[\alpha]_{577}^{29}$ +17.4°, $[\alpha]_{546}^{29}$ +19.6°, $[\alpha]_{435}^{29}$ +32.5°, $[\alpha]_{365}^{29}$ +50.1° (c 0.033, $CHCl_3$). (Lit.[45] $[\alpha]_D$ +16° ($CHCl_3$)). IR (KBr) ν (cm^{-1}): 1469 (m), 1450 (m), 1383 (m), 1269 (m), 1246 (bm), 1023 (vs), 910 (m), 886 (m), 782 (m). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.64 (s, 3H, 18-C**H**$_3$), 0.81 (s, 3H, 19-C**H**$_3$), 0.86 (d, *J*=6.4 Hz, 6H, 25-CH(C**H**$_3$)$_2$), 0.89 (d, *J*=6.6 Hz, 3H, 20-CHC**H**$_3$), 3.74 (d, J_{PH}=11.4 Hz, 3H, POC**H**$_3$), 4.23 (bm 8 peaks, 1H, 3-C**H**$_\alpha$). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 12.21 (C-18), 12.37 (C-19), 18.83 (C-21), 21.39 (C-11), 22.71 (C-27), 22.97 (aC-26), 23.96 (C-23), 24.36 (C-15), 28.16 (C-25), 28.40 (C-16), 28.72 (C-6), 29.39 (d, J_{PC}=4.1 Hz, C-2), 32.16 (C-7), 35.45 (C-10), 35.59 (C-8), 35.97 (C-20), 35.88 (d, J_{PC}=3.8 Hz, C-4), 36.33 (C-22), 36.95 (C-1), 39.66 (C-24),

40.13 (C-12), 42.74 (C-13), 44.88 (C-5), 53.9 (d, J_{PC}≈5 Hz, OCH_3), 54.37 (C-9), 56.47 (C-17), 56.58 (C-14), 78.66 (d, J_{PC}=5.6 Hz, C-3).

Methyl 5α-cholestan-3β-yl phenylphosphonate (3): A dry ether solution of cholestanol (1g, 2.58 mmol) was added dropwise under a dry argon atmosphere to a well stirred ice-bath cooled solution of phenylphosphonyl dichloride (5 mL, 35 mmol) and triethylamine (2.1 mL, 15 mmol) in dry ether (15 mL). After completion of the addition, cooling was discontinued and the reaction mixture was maintained at rt overnight. Dry methanol (20 mL) was added, and following a further 24 h at rt the mixture diluted with a large volume of CH_2Cl_2. The CH_2Cl_2 solution was extracted repeatedly with 3 N hydrochloric acid, then with water and with saturated NaCl solution. After drying over $MgSO_4$ and evaporation of the solvent, the residue was flash-chromatographed on a column of silica (3 x 17 cm) using ethyl acetate-hexane (7/3) as eluent to yield the *title compound* **3** (1.8 g, 84.5%) crystallized from hexane; white solid, mp 93-95 °C; $[\alpha]_D^{25}$ +14.2° (c 1.00, $CHCl_3$). Since the phosphorous atom has become a center of chirality, the product is, as evidenced by its NMR spectra, a mixture of two diastereoisomers. IR (KBr) ν (cm^{-1}): 1470 (m), 1435 (m), 1372 (m), 1245 (s), 1125 (s), 1041 (s), 998 (br s), 974 (sh), 942 (m), 902 (m), 879 (m), 794 (s), 746 (m), 698 (m), 682 (m). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.63 (s, 3H, 18-C**H**$_3$), 0.80 (s, 3H, 19-C**H**$_3$), 0.856 (d, *J*=6.4 Hz, 3H, 27-C**H**$_3$), 0.860 (d, *J*=6.4 Hz, 3H, 26-C**H**$_3$), 0.89 (d, *J*=6.4 Hz, 3H, 21-C**H**$_3$), 3.71 (bd, J_{PH}=11 Hz, 3H, POC**H**$_3$), 4.25-4.49 (m, 1H, 3-C**H**$_\alpha$), 7.38-7.61 (m, 3H, arom), 7.72-7.88 (m, 2H, arom). ^{13}C-NMR (75 MHz, $CDCl_3$): two diastereomers, δ 12.07 (C-18), 12.23 (C-19), 18.68 (C-21), 21.22 (C-11), 22.55 (C-27), 22.80 (C-26), 23.84 (C-23), 24.20 (C-15), 28.00 (C-25), 28.22 (C-16), 28.52 and 28.56 (C-6), 29.62 and 29.84 (two d, J_{PC}=4.3 Hz and 3.5 Hz, C-2), 31.96 and 31.99 (C-7), 35.29 (C-10), 35.48 (C-8), 35.78 (C-20), 36.18 (C-22), 36.14 and 36.34 (two d, J_{PC}=6.6 Hz and 2.6 Hz, C-4), 36.81 and 36.86 (C-1), 39.52 (C-24), 39.98 (C-12), 42.60 (C-13), 44.72 and 44.76 (C-5), 52.33 (d, J_{CP}=5.3 Hz, POCH_3), 54.20 (C-9), 56.29 (C-17), 56.40 (C-14), 76.94 and 76.97 (two d, J_{PC}=6.5 Hz and 6 Hz, C-3), 128.36 (d, J_{PC}=15 Hz, arom C-*m*), 128.61 (d, J_{PC}=189 Hz, arom C-*ipso)*, 131.72 and 131.74 (two d, J_{PC}=10 Hz and 10 Hz, arom C-*o*), 132.23 (d, J_{PC}=2.6 Hz, arom C-*p*). MS (CI, isobutane) *m/z*: 543 (MH^+, 100%), 173 ($[C_7H_{10}PO_3]^+$, 68%). Anal. calcd. for $C_{34}H_{55}O_3P$: C, 75.24%, H, 10.21%, P, 5.71%. Found: C, 75.25%, H, 10.14%, P, 5.81%.

Hydrogen 5α-cholestan-3β-yl phenylphosphonate (4): A mixture of dry NaI (14.94 g, .01 mol), the methyl ester **3** (2.44 g, 4.5 mmol) and dry acetone (300 mL) was vigorously stirred and refluxed under a dry nitrogen atmosphere for 48 h. The cooled mixture was diluted with ether, and the solid collected by filtration was taken up in a mixture of CH_2Cl_2 and aqueous 3 N HCl. The aqueous phase was thoroughly extracted with a number of portions of CH_2Cl_2 and the combined organic solutions were washed with 8% aqueous $NaHSO_3$ and with water, and dried ($MgSO_4$). Evaporation of solvent and crystallization of the residue from CH_2Cl_2-CH_3OH yielded the

title compound **4** (1.73 g, 73%), as a white solid, mp 220-221 °C; $[\alpha]_D^{25}$ +13.66° (c 1.03, $CHCl_3$). IR (KBr) ν (cm^{-1}): 1467 (m), 1439 (m), 1382 (m), 1193 (bm), 1139 (m), 1035 (sh), 1021 (s), 1009 (s), 998 (s), 749 (m), 721 (m), 693 (m). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.64 (s, 3H, 18-CH_3), 0.79 (s, 3H, 19-CH_3), 0.857 (d, J=6.6 Hz, 3H, 27-CH_3), 0.860 (d, J=6.6 Hz, 3H, 26-CH_3), 0.893 (d, J=6.4 Hz, 3H, 21-CH_3), 4.47-4.22 (m, 1H, 3-CH_α), 7.36-7.58 (m, 3H, arom), 7.75-7.85 (m, 2H, arom). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 12.08 (C-18), 12.23 (C-19), 18.71 (C-21), 21.25 (C-11), 22.56 (C-27), 22.81 (C-26), 23.97 (C-23), 24.23 (C-15), 28.03 (C-25), 28.27 (C-16), 28.58 (C-6), 29.68 (d, J_{PC}=4.3 Hz, C-2), 32.04 (C-7), 35.33 (C-10), 35.49 (C-8), 35.85 (C-20), 36.18 (d, J_{PC}=5 Hz, C-4), 36.22 (C-22), 36.90 (C-1), 39.53 (C-24), 40.04 (C-12), 42.63 (C-13), 44.84 (C-5), 54.25 (C-9), 56.39 (C-17), 56.48 (C-14), 76.81 (d, J_{PC}=6.4 Hz, C-3), 128.23 (d, J_{PC}=15 Hz, arom C-*m*), 129.56 (d, J_{PC}=195 Hz, arom C-*ipso*), 131.19 (d, J_{PC}=9.9 Hz, arom C-*o*), 132.06 (d, $J_{PC}\approx$2 Hz, arom C-*p*). MS (CI, NH_3) *m/z*: 529 (MH^+). Anal. calcd. for $C_{33}H_{53}O_3P$: C, 74.96%, H, 10.10%, P, 5.86%. Found: C, 75.24%, H, 10.15%, P, 5.70%.

Dibenzyl 5α-androstan-3α-yl phosphate (5): A nominally 1.5 M hexane solution of lithium diisopropylamide (Aldrich) (6 mL) was added under argon to a cold (-78 °C) stirred solution of 5α-androstan-3α-ol (2 g, 7.24 mmol) and tetrabenzyl pyrophosphate (4.62 g, 8.6 mmol) in dry THF (140 mL). Following 1 h at -78 °C the mixture was allowed to warm to ambient temperature and stirring was continued for 24 h, at which time TLC (silica, ether/hexane: 8/2; R_f of androstanol, 0.45; of product, 0.26) indicated little unreacted androstanol. It was then poured into aqueous 8% $NaHCO_3$ solution (450 mL) and extracted with two 700 mL portions of ether. The combined ether extract was washed successively with water, 0.5 N HCl, water and brine, and rotary evaporated. The residual oil was dried in a vacuum dessicator and flash-chromatographed on silica using ether/hexane (8/2, $^v/_v$) eluent. Unreacted 3α-androstanol (318 mg, 16%) was recovered. Fractions of analytically pure *title compound* **5** (2.83 g, 73%) were obtained as an oil which crystallized to a white solid on standing; mp 57.5-58.5 °C. $[\alpha]_D^{22.5}$ −2.0°, $[\alpha]_{577}^{22.5}$ −2.0°, $[\alpha]_{546}^{22.5}$ −2.2°, $[\alpha]_{435}^{22.5}$ −4.54°, $[\alpha]_{365}^{22.5}$ −7.96° (c 0.036, $CHCl_3$). IR (KBr) ν (cm^{-1}): 1454 (m), 1443 (m), 1380 (m), 1273 (s), 1259 (s), 1244 (m), 1220 (m), 1047 (m), 1020 (vs.), 1010 (vs), 999 (vs), 975 (s), 965 (s), 952 (m), 923 (m), 877 (m), 789 (m), 753 (m), 740 (m), 699 (s). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.67 (s, 3H, 18-CH_3), 0.74 (s, 3H, 19-CH_3), 4.66 (m, 1H, 3-CH_β), 5.033 (d, J_{PH}=8 Hz, 2H, PhCH_2), 5.043 (d, J_{PH}=8 Hz, 2H, PhCH_2), 7.35 (m, 10H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.53 (C-19), 17.65 (C-18), 20.61 (C-16), 20.87 (C-11), 25.59 (C-15), 27.71 (d, J_{PC}=4.5 Hz, C-2), 28.33 (C-6), 32.36 (C-1, C-7), 34.37 (d, J_{PC}=4.4 Hz, C-4), 35.90 (C-8, C-10), 38.99, 39.25 (C-12, C-5), 40.54 (C-17), 40.94 (C-13), 54.37, 54.69 (C-14, C-9), 69.07 (d, J_{PC}=5.6 Hz, Ph**C**), 75.87 (d, J_{PC}=5.8 Hz, C-3), 127.85, 127.89, 128.48, 128.63 (arom **C**), 136.29 (d, J_{PC}=6.9 Hz, arom *ipso* **C**). MS (CI, NH_3) *m/z* 538 $[M+2]^+$, 539 $[M+3]^+$. Strongest peak *m/z* 279, 280 indicating facile elimination of axial dibenzyl phosphate group. Anal. calcd. for $C_{33}H_{45}O_4P$: C, 73.85%, H, 8.45%; P, 5.77%. Found: C, 73.70%; H, 8.29%; P, 5.38%.

Benzyl hydrogen 5α-androstan-3α-yl phosphate (6): A solution of the dibenzyl ester **5** (1.36 g, 2.53 mmol) and dry sodium iodide (4 g, 26.7 mmol) in dry acetone (80 mL) was refluxed under argon for 7 h, during which time a copious gel separated. Rotary evaporation of the acetone and vigorous stirring of the residue with dry ether (250 mL) yielded a fine precipitate of sodium salts which was collected by filtration and dissolved in a $CHCl_3$-CH_3OH mixture (2/1, $^{v}/_{v}$; 240 mL). This solution was shaken with aqueous 2 M hydrochloric acid-methanol (1/1, $^{v}/_{v}$; 50 mL) and the two phases separated. Following extraction of the aqueous (upper) layer with $CHCl_3$-CH_3OH (2/1; 150 mL), the combined $CHCl_3$-CH_3OH phases were washed with H_2O-CH_3OH (1/1) and rotary evaporated. A CH_2Cl_2 solution of the residue was shaken with an 8% aqueous $NaHSO_3$ solution to remove traces of iodine, washed with water, dried (Na_2SO_4) and rotary evaporated. The *title compound* **6**, a white solid (0.82 g, 73%), was recrystallized from cyclohexane; mp 128-129 °C. $[\alpha]_D^{28}$ −1.40°, $[\alpha]_{577}^{27}$ −1.47°, $[\alpha]_{546}^{27}$ −1.55°, $[\alpha]_{435}^{27}$ −3.86°, $[\alpha]_{365}^{27}$ −7.68° (c 0.02, $CHCl_3$). IR (KBr) ν (cm^{-1}): 1467 (m), 1451 (m), 1379 (m), 1254 (s), 1240 (s), 1220 (s), 1183 (m), 1170 (m), 1162 (m), 1151 (m), 1135 (m), 1015 (broad & vs), 950 (m), 921 (m), 890 (m), 876 (m), 860 (m), 746 (m), 698 (m). ^{1}H NMR (200 MHz, $CDCl_3$): 0.68 (s, 3H, 18-CH_3); 0.75 (s, 3H, 19-CH_3); 4.64 (m, 1H, 3-**CH**), 5.05 (d, J_{PH}=7.8 Hz, 2H, PhCH_2), 7.35 (m, 5H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.48 (C-19), 17.62 (C-18), 20.57 (C-16), 20.83 (C-11), 25.53 (C-15), 27.54 (d, J_{PC}=4.1 Hz, C-2), 28.29 (C-6), 32.28 (C-1, C-7), 34.24 (d, J_{PC}=5.2 Hz, C-4), 35.83 (C-8, C-10), 38.92, 39.05 (C-12, C-5), 40.48 (C-17), 40.85 (C-13), 54.24, 54.58 (C-14, C-9), 68.76 (d, J_{PC}=5.3 Hz, Ph**C**), 75.65 (d, J_{PC}=5.8 Hz, C-3), 127.68, 128.30, 128.51, 128.55 (arom **C**), 136.24 (d, J_{PC}=7 Hz, arom *ipso* **C**). MS (CI, NH_3) *m/z*: 547 $[M+1]^+$, 548 $[M+2]^+$ - both very weak. Very strong *m/z* 258, 259, indicating facile elimination of axial benzyl phosphate group. Anal. calcd. for $C_{26}H_{39}O_4P$: C, 69.93%; H, 8.80%; P, 6.94%. Found: C, 70.39%, H, 8.98%; P, 6.78%.

5α-Androstan-3α-yl dihydrogen phosphate (7): Hydrogenolysis of the dibenzyl ester **5** (0.84 g; 1.56 mmol) in dry THF solution (40 mL) using PtO_2 catalyst (200 mg) proceeded rapidly and quantitatively at ambient temperature and atmospheric pressure. Removal of Pt by filtration and of solvent by rotary evaporation followed by oil-pump evacuation, yielded the *title compound* **7** (0.56 g, 100%) as a white solid; mp 180.5-182 °C. The product may be crystallized from THF solution by slow addition of CH_2Cl_2. $[\alpha]_D^{22.5}$ +2.37°, $[\alpha]_{577}^{22.5}$ +3.13°, $[\alpha]_{546}^{22.5}$ +3.16°, $[\alpha]_{435}^{22.5}$ +4.61°, $[\alpha]_{365}^{22.5}$ +6.48° (c 0.024, $CHCl_3$-CH_3OH (2/1, $^{v}/_{v}$)). IR (KBr) ν (cm^{-1}): 1445 (m), 1385 (m), 1375 (m), 1364 (m), 1292 (s), 1227 (s), 1180 (m), 1155 (m), 1131 (m), 1109 (m), 1084 (m), 1030 (broad & vs), 973 (s), 950 (m), 937 (m), 808 (m), 788 (m). MS (CI, NH_3) *m/z*: 374 $[M+NH_4]^+$, no $[M+1]^+$. Strong *m/z* 257, 258, 259 and 276 - all indicating facile elimination of axial phosphate function. ^{1}H NMR (200 MHz, CD_3OD): δ 0.73 (s, 3H, 18-CH_3), 0.84 (s, 3H, 19-CH_3), 4.54 (m, 1H, 3-CH_β). Anal. calcd. for $C_{19}H_{33}O_4P$; C, 64.02%; H, 9.33%; P, 8.69%. Found: C, 64.00%; H, 9.63%; P, 8.41%.

Methyl 5α-androstan-3α-yl phenylphosphonate (8): The procedure described for the preparation of methyl 5α-cholestan-3β-yl phenylphosphonate, **3**, was applied to 5α-androstan-3α-ol (0.92 g, 3.3 mmol) and yielded the *title compound* **8** (0.783 g, 55%) as a white solid crystallized from hexane; mp 90-92 °C; $[\alpha]_D^{25}$ -1.99° (c 1.01, $CHCl_3$). Since the phosphorous atom has become a center of chirality, the product is, as evidenced by its NMR spectra, a mixture of two diastereoisomers. IR (KBr) ν (cm^{-1}): 1453 (m), 1440 (m), 1375 (m), 1248 (s), 1129 (m), 1048 (m), 1000(sh), 991 (vs), 980 (vs), 823 (m), 811 (m), 752 (m), 688 (m). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.68 (s, 3H, 18-C**H**$_3$), 0.76 (s, 3H, 19-C**H**$_3$), 3.71 and 3.72 (two d, J_{PH}=11 Hz and 11 Hz, 3H, POC**H**$_3$), 4.69-4.83 (m, 1H, 3-C**H**$_\beta$), 7.40-7.61 (m, 3H, arom), 7.73-7.89 (m, 2H, arom). ^{13}C-NMR (75 MHz, $CDCl_3$): two diastereomers, δ 11.45 (C-19), 17.56 (C-18), 20.51 (C-16), 20.82 (C-11), 25.49 (C-15), 27.83 and 28.09 (two d, J_{PC}=4.4 Hz and 3.5 Hz, C-2), 28.22 and 28.38 (C-6), 32.29 and 32.34 (C-1), 32.42 and 32.55 (C-7), 34.42 and 34.81 (two d, J_{PC}=4 Hz and 3.2 Hz, C-4), 35.84 (C-8), 35.95 (C-10), 38.91 (C-12), 39.33 and 39.45 (C-5), 40.45 (C-17), 40.83 (C-13), 52.34 and 52.39 (two d, J_{CP}=5 Hz and 5 Hz, $POCH_3$), 54.45 (C-14), 54.61 (C-9), 73.76 and 73.82 (two d, J_{PC}=4.7 Hz and 4.8 Hz, C-3), 128.38 (d, J_{PC}=15 Hz, arom C-*m*), 128.68 (d, J_{PC}=190 Hz, arom C-*ipso)*, 131.71 and 131.76 (two d, J_{PC}=9.9 Hz and 9.6 Hz, arom C-*o*), 132.20 (broad, arom C-*p*). MS (CI, isobutane), *m/z*: 431 (MH^+, 100%), 173 ($[C_7H_{10}PO_3]^+$, 27%). Anal. calcd. for $C_{26}H_{39}O_3P$: C, 72.54%, H, 9.06%, P, 7.19%. Found: C, 72.38%, H, 9.31%, P, 6.89%.

Hydrogen 5α-androstan-3α-yl phenylphosphonate (9): The procedure described for the preparation of hydrogen 5α-cholestan-3β-yl phenylphosphonate, **4**, was applied to the methyl ester **8** (0.42 g, 0.98 mmol) and yielded 0.36 g (88%) of compound **9**, crystallized from CH_2Cl_2-CH_3OH; white solid, mp 154-156 °C; $[\alpha]_D^{25}$ +1.38° (c 1.02, $CHCl_3$). IR (KBr) ν (cm^{-1}): 1439 (m), 1376 (m), 1220 (bm), 1135 (m), 1004 (vs), 994 (vs), 819 (m), 749 (m), 719 (m), 695 (m). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.68 (s, 3H, 18-C**H**$_3$), 0.75 (s, 3H, 19-C**H**$_3$), 4.61-4.73 (m, 1H, 3-C**H**$_\beta$), 7.36-7.58 (m, 3H, arom), 7.73-7.88 (m, 2H, arom). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 11.46 (C-19), 17.57 (C-18), 20.52 (C-16), 20.83 (C-11), 25.50 (C-15), 27.86 (d, J_{PC}=3.8 Hz, C-2), 28.30 (C-6), 32.26 (C-1), 32.38 (C-7), 34.53 (d, J_{PC}=4 Hz, C-4), 35.86 (C-8, C-10), 38.91 (C-12), 39.16 (C-5), 40.46 (C-17), 40.83 (C-13), 54.32 (C-14), 54.59 (C-9), 73.70 (d, J_{PC}=6 Hz, C-3), 128.21 (d, J_{PC}=15 Hz, arom C-*m*), 129.9 (d, J_{PC}=194 Hz, arom C-*ipso)*, 131.20 (d, J_{PC}=10 Hz, arom C-*o*), 131.90 (d, J_{PC}=3 Hz arom C-*p*). MS (CI, isobutane) *m/z*: 417 (MH^+, 100%), 259 ($[M\text{-}C_6H_5PO_3H]^+$, 10.3%). Anal. calcd. for $C_{25}H_{37}O_3P$: C, 72.09%, H, 8.88%, P, 7.44%. Found: C, 71.98%, H, 8.81%, P, 7.27%.

Dibenzyl 5α-androstan-3β-yl phosphate (10): This compound was prepared from 5α-androstan-3β-ol in 74-78% yield in a manner similar to the preparation of its isomer, dibenzyl 5α-androstan-3α-yl phosphate, **5**, except that the THF solution of the androstanol and lithium diisopropylamide were stirred at -78 °C for *ca.* 1 h before tetrabenzyl pyrophosphate addition. Separation of product from unreacted starting material was

accomplished by flash chromatography on silica using an ethyl acetate-cyclohexane-pentane (7/7/6, $^{v}/_{v}$) mixture. The product can be recrystallized from hexane or cyclohexane to give the *title compound* **10** as a white solid, mp 88.5-89.5 °C. $[\alpha]_D^{27}$ −3.40°, $[\alpha]_{577}^{26}$ −3.63°, $[\alpha]_{546}^{26}$ −4.30°, $[\alpha]_{435}^{26}$ −7.14°, $[\alpha]_{365}^{26}$ − 11.1° (c 0.03, $CHCl_3$). IR (KBr) ν (cm^{-1}): 1493 (m), 1465 (m), 1453 (m), 1378 (m), 1290 (s), 1265 (m), 1217 (m), 1098 (m), 1080 (m), 1048 (s), 1036 (vs), 1018 (vs), 980 (m), 912 (m), 899 (m), 893 (m), 886 (s), 740 (s), 727 (s), 694 (s). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.68 (s, 3H,18-C**H**$_3$). 0.79 (s, 3H, 19-C**H**$_3$), 4.27 (bm 8 peaks, 1H, 3-C**H**$_\alpha$), 5.02 (d, J_{PH}=8.2 Hz, 4H, PhC**H**$_2$), 7.34 (s, 10H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.36 (C-19), 17.64 (C-18), 20.61 (C-16), 21.34 (C-11), 25.61 (C-15), 28.63 (C-6), 29.43 (d, J_{PC}=4.5 Hz, C-2), 32.43 (C-7), 35.50 (C-10), 35.87 (d, J_{PC}=4.3 Hz, C-4), 35.90 (C-8), 36.93 (C-1), 38.93 (C-12), 40.52 (C-5), 40.94 (C-13), 44.77 (C-17), 54.55 (C-9, C-14), 69.10 (d, J_{PC}=5.4 Hz, Ph**C**), 78.79 (d, J_{PC}=6.1 Hz, C-3), 127.97, 128.02, 128.50, 128.56, 128.62 (arom **C**), 136.21 (d, J_{PC}=6.9 Hz, arom *ipso* **C**). MS (CI, NH_3) *m/z*: 537 $[M+1]^+$ and isotopic peaks 538, 539, 540. 554 $[M+NH_4]^+$, and isotopic peaks 555, 556. Anal. calcd. for $C_{33}H_{45}O_4P$: C, 73.85%; H, 8.45%; P, 5.77%. Found: C, 74.06%; H, 8.51%; P, 5.69%.

Benzyl hydrogen 5α-androstan-3β-yl phosphate (11): This compound was prepared from **10** in 96% yield in a manner similar to that used for the preparation of its isomer, benzyl hydrogen 5α-androstan-3α-yl phosphate, **6**. However, the reaction time necessary was up to 18 h. The product may be triturated with acetone with little loss, and recrystallized from toluene-cyclohexane to give the *title compound* **11**, mp 164-165 °C. $[\alpha]_D^{22.5}$ −4.83°, $[\alpha]_{577}^{22.5}$ −5.08°, $[\alpha]_{546}^{22.5}$ -5.80°, $[\alpha]_{435}^{22.5}$ −10.0°, $[\alpha]_{365}^{22.5}$ −15.6° (c 0.023, $CHCl_3$). IR (KBr) ν (cm^{-1}): 1453 (m), 1383 (m), 1246 (s), 1227 (s), 1213 (s), 1193 (m), 1170 (m), 1102 (m), 1080 (s), 1063 (vs), 1025 (broad & vs), 1006 (s), 983 (m), 923 (m), 915 (m), 905 (m), 896 (m), 731 (s), 695 (m), 606 (m). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.68 (s, 3H, 18-C**H**$_3$), 0.79 (s, 3H, 19-C**H**$_3$), 4.24 (bm 8 peaks, 1H, 3-C**H**$_\alpha$), 5.04 (d, J_{PH}=7.2 Hz, 2H, PhC**H**$_2$), 7.35 (s, 5H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.42 (C-19), 17.71 (C-18), 20.68 (C-16), 21.43 (C-11), 25.68 (C-15), 28.74 (C-6), 29.44 (d, J_{PC}=3.8 Hz, C-2), 32.53 (C-7), 35.59 (C-10), 35.90 (d, J_{PC}=3.5 Hz, C-4), 35.99 (C-8), 37.05 (C-1), 38.04 (C-12), 40.60 (C-5), 41.01 (C-13), 44.92 (C-17), 54.67 (C-9, C-14), 68.99 (d, J_{PC}=4.9 Hz, Ph**C**), 78.82 (d, J_{PC}=5.8 Hz, C-3), 127.85, 128.44, 128.62 (arom **C**), 136.18 (d, J_{PC}=7.4 Hz, arom *ipso* **C**). MS (CI, NH_3) *m/z*: 447 $[M+1]^+$ and isotopic peaks 448, 449. 464 $[M+NH_4]^+$ and isotopic peaks 465, 466. Anal. calcd. for $C_{26}H_{39}O_4P$: C, 69.93%; H, 8.80%; P, 6.94%. Found: C, 70.24%; H, 8.99%; P, 6.75%.

5α-Androstan-3β-yl dihydrogen phosphate (12): Method (a).[19] A solution of 100 mg 5α-androstan-3β-ol in 0.5 mL pyrophosphoryl chloride was kept at 0 °C for 40 min. Ice water was then added and the mixture was stirred vigorously until a filterable solid separated. The latter was triturated with ether and then with hot

cyclohexane. The residual product, 49 mg (40%), was crystallized from ethyl acetate and dried *in vacuo* at 55 °C; mp 174-175 °C.

Method (b). A purer product was obtained in essentially quantitative yield by the hydrogenolysis of **10** as described for the 3α epimer **7**. The 5α-androstan-3β-yl dihydrogen phosphate (**12**) isolated from THF tends to retain some of the solvent. It may be recrystallized from hot ethyl acetate, or by solution in a minimum of THF and the slow addition of CH_2Cl_2. In either case it must be well dried in vacuum at 55 °C to remove residual solvent. It is a white solid; mp 178-179 °C. $[\alpha]_D^{22.5}$ −3.37°, $[\alpha]_{577}^{22.5}$ −3.38°, $[\alpha]_{546}^{22.5}$ −3.88°, $[\alpha]_{435}^{27}$ −7.31°, $[\alpha]_{365}^{22.5}$ −11.8° (c 0.025, $CHCl_3$-CH_3OH; 2/1, $^v/_v$). IR (KBr) ν (cm^{-1}): 1465 (m), 1450 (m), 1385 (m), 1376 (m), 1261 (m), 1225 (s), 1200 (broad, s), 1133 (broad, vs) 1121 (vs), 1100 (vs), 1085 (vs), 1075 (vs), 1025 (broad, vs), 1000 (vs), 983 (s), 970 (s), 955 (m), 802 (m). ^1H NMR (200 MHz, $CDCl_3$): δ 0.69 (s, 3H, 18-CH_3), 0.81 (s, 3H, 19-CH_3), 4.23 (bm, 1H, 3-CH_α). (200 MHz, CD_3OD): δ 0.73 (s, 1H, 18-CH_3), 0.86 (s, 3H, 19-CH_3), 4.16 (bm, 1H, 3-CH_α). MS (CI, NH_3) *m/z* 374 $[M+NH_4]^+$and isotopic peak 375; no $[M+1]^+$ peak. Strong *m/z* 276, 277 indicating elimination of phosphate group. Anal. calcd. for $C_{19}H_{33}O_4P$: C, 64.02%; H, 9.33%; P, 8.69%. Found: C, 64.04%; H, 9.74%; P, 8.59 %.

P^1,P^2-Bis(benzyl 5 -androstan-3 -yl)pyrophosphate (13) and P^1,P^2-Bis(5α-androstan-3α-yl hydrogen) pyrophosphate (14): Benzyl hydrogen 5α-androstanyl phosphate (523 mg; 1.17 mmol) were thoroughly dried by solution in 65 mL dry benzene, distillation of 45 mL of the solvent (Dean-Stark trap) and treatment of the residual solution with activated 4Å molecular sieves overnight. Dicyclohexyl carbodiimide (126 mg, 0.6 mmol) was added, and the reaction allowed to proceed at ambient temperature. After 24 h the precipitated dicyclohexyl urea was removed by filtration, the solvent evaporated, and P^1,P^2-bis(benzyl 5α-androstan-3α-yl)pyrophosphate **13** was obtained as a glassy froth. ^1H NMR (200 MHz $CDCl_3$): δ 0.67 (s, 18-CH_3), 0.74 (s, 19-CH_3), 4.78 (m, 3-CH_β), 5.17 (m, PhCH_2), 7.37 (m, aromatic H).

The above 'froth' was dissolved in 20 mL dry THF and hydrogenolyzed at ambient temperature and atmospheric pressure using 75 mg PtO_2. The product, which is only very sparingly soluble in THF, precipitated during hydrogenolysis and had to be redissolved by the addition of a 100 mL methanol to permit removal by filtration of the Pt catalyst. The solvent was removed by rotary evaporation at ambient temperature, and the residue thoroughly triturated with 25 mL methanol to selectively remove residual androstanyl dihydrogen phosphate. The insoluble product, P^1,P^2-bis(5α-androstan-3α-yl hydrogen) pyrophosphate, **14** (346 mg; 85%), was dried under vacuum at 80 °C for 3 h; white solid, mp 129-130.5 °C. IR (KBr) ν 950-963 cm^{-1} (broad, vs; P-O-P). ^1H NMR (200 MHz, $CDCl_3$): δ 0.67 (s, 18-CH_3), 0.76 (s, 19-CH_3), 4.74 (m, 3-CH_β). (300 MHz; CD_3OD): δ 0.73 (s, 18-CH_3), 0.84 (s, 19-CH_3), 4.69 (m, 3-CH_β). (200 MHz; CH_2Cl_2): δ 0.68 (s, 18-CH_3), 0.78 (s, 19-CH_3), 4.74 (m, 3-$CH\beta$). In all the above solvents the product was only very sparingly soluble. It was satisfactorily soluble

in a $CDCl_3$-CD_3OD (~2/1) mixture. ^1H NMR (300 MHz, $CDCl_3$-CD_3OD (~2/1; $^v/_v$)a): δ 0.71 (s, 18-CH_3), 0.82 (s, 19-CH_3), 4.74 (m, 3-CH_β). MS-FAD *m/z* 717 $[M+Na]^+$ - strong peak. Anal. calcd. for $C_{38}H_{64}O_7P_2$: C, 65.68%; H, 9.28%; P, 8.92%. Found: C, 65.03%; H, 9.58%, P, 8.59 %.

P^1,P^2-Bis (benzyl 5α-androstan-3β-yl)pyrophosphate (15): It was prepared from **11** in a manner analogous to its 3α isomer, **13**. ^1H NMR (200 MHz, $CDCl_3$): δ 0.68 (s, 18-CH_3), 0.78 (s, 19-CH_3). 4.38 (m, 3-CH_α), 5.15 (m, PhCH_2), 7.37 (m, aromatic).

P^1,P^2-Bis(5α-androstan-3β-yl hydrogen)pyrophosphate (16): It was prepared by hydrogenolysis of its P^1,P^2-dibenzyl ester, **15**, in a manner analogous to its 3α isomer, **14**. ^1H NMR (300 MHz, $CDCl_3$): δ 0.68 (s, 18-CH_3), 0.81 (s, 19-CH_3), 4.34 (bm, 3-CH_α).

Dibenzyl androsteron-3-yl phosphate (17):[30] To a well stirred solution of dibenzyl N,N-diisopropylphoshoramidite (1.029 g, 2.98 mmol) in dry chloroform under a dry argon atmosphere were added 3α-hydroxy-5α-androstan-17-one (0.514 g, 1.77 mmol) and 1H-tetrazole (0.245 g, 3.50 mmol). Dissolution occurred upon heating and reflux was continued for 23 h. Following cooling to 0 °C and addition of of *m*-CPBA (1.028 g, 2.98 mmol; 50% in benzoic acid), the reaction mixture was allowed to warm to rt. The chloroform olution was then vigorously shaken in succession with two 5 mL portions of 1 M HCl saturated with ferrous sulfate, two 5 mL portions of 1 M $NaHCO_3$ solution, 5 mL H_2O, 5 mL saturated NaCl solution, dried over Na_2SO_4 and evaporated to dryness. The residual yellow oil was flash-chromatographed on a silica column (3 x 20 cm) using ethyl acetate-hexane (7/3) as eluant, to yield 0.700 g (72%) of the *title compound* **17** as a colorless oil (TLC R_f = 0.23, ethyl acetate- hexane, 1/1). The latter was taken up in hot hexane and allowed to crystallize slowly over the course of a week to white needles, mp 91 °C. $[\alpha]_D^{21}$ +50.91° (c 0.031, $CHCl_3$). IR (KBr) ν (cm^{-1}): 1734 (s), 1498 (m), 1456 (s), 1430 (m), 1373 (m), 1276 (s), 1236 (m), 1218 (m), 1166 (m), 1056 (s), 1038 (s), 1024 (s), 993 (s), 926 (m), 917 (m), 892 (s), 877 (m), 852 (m), 737 (s), 698 (s). ^1H-NMR (300 MHz, $CDCl_3$): δ 0.76 (s, 3H, 19-CH_3), 0.85 (s, 3H, 18-CH_3), 2.08 (dt, *J*=19 Hz, 9 Hz, 1H), 4.62-4.72 (m, 1H, 3-CH_β), 5.022 and 5.042 (dABq, *J*=12 Hz, 8 Hz, 2H, PhCH_2), 5.040 and 5.050 (dABq, *J*=12 Hz, 8 Hz, 2H, PhCH_2), 7.34 (m, 10 H, arom). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 11.35 (C-19), 13.80 (C-18), 20.01 (C-11), 21.71 (C-15), 27.49 (d, J_{PC}=3.7 Hz, C-2), 27.84 (C-6), 30.68 (C-7), 31.58 (C-12), 32.14 (C-1), 34.15 (d, J_{PC}=3.9 Hz, C-4), 34.98 (C-8), 35.77 (C-10, 16 ?), 39.14 (C-5 ?), 47.72 (C-13), 51.50 (C-14), 54.12 (C-9), 68.97 (d, J_{PC}=4.8 Hz, CPh) 75.44 (d, J_{PC}=5.6 Hz, C-3), 127.68 (arom C-*p*), 128.31 and 128.45 (arom C-*o*, C-*m*), 136.12 (d, J_{PC}=6 Hz, arom C-*ipso*), 220.67 (C-17). ^{31}P-NMR (81 MHz, $CDCl_3$) δ (*vs* ext. 85% H_3PO_4) -0.83. MS (CI, isobutane) *m/z* 551 (MH^+, 48.3%), 279 ($[(C_6H_5CH_2O)_2P(OH)_2]^+$,100%). Anal. calcd. for $C_{33}H_{43}O_5P$: C, 72.0%, H, 7.9%. Found: C, 72.2%, H, 7.8%.

Dibenzyl epiandrosteron-3-yl phosphate (18):[31] The procedure described for the dibenzyl phosphorylation of 3α-hydroxy-5α-androstan-17-one was applied to 0.502 g (1.73 mmol) of its 3β isomer, and yielded 0.621 g (65%) of the *title compound* **18** as white needles (TLC R_f = 0.27, ethyl acetate- hexane, 1/1); mp 72 °C. $[\alpha]_D^{22}$ +43.43° (c 0.033, $CHCl_3$). IR (KBr) ν (cm^{-1}): 1743 (s), 1498 (m), 1454 (s), 1377 (m), 1289 (s), 1216 (m), 1103 (m), 1020 (broad vs), 912 (s), 887 (s), 824 (m), 739 (s), 728 (s), 694 (s). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.81 (s, 3H, 19-C**H**$_3$), 0.85 (s, 3H, 18-C**H**$_3$), [peak of t or dd with *J*=9 Hz visible above skeletal absorption at 2.16], 2.43 (dd, *J*=19 Hz, 9 Hz, 1H), 4.12-4.40 (m, 1H, 3-C**H**$_\alpha$), 5.01 and 5.03 (dABq, *J*=12 Hz, 8 Hz, 4H, PhC**H**$_2$), 7.34 (bs, 10 H, arom). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 12.17 (C-19), 13.78 (C-18), 20.46 (C-11), 21.73 (C-15), 28.14 (C-6), 29.19 (d, J_{PC}=4.3 Hz, C-2), 30.75 (C-7), 31.53 (C-12), 34.99 (C-8), 35.41 (C-10), 35.64 (d, J_{PC}=3.5 Hz, C-4), 35.75 (C- 16), 36.68 (C-1), 44.63 (C-5 ?), 47.68 (C-13), 51.33 (C-14), 54.24 (C-9), 69.00 (d, J_{PC}=5.4 Hz, CPh) 78.32 (d, J_{PC}=6 Hz, C-3), 127.78 (arom C-*p*), 128.31 and 128.43 (arom C-*o*, C-*m*), 136.03 (d, J_{PC}=6.7 Hz, arom C-*ipso*), 220.67 (C-17). ^{31}P-NMR (81 MHz, $CDCl_3$) δ (*vs* ext. 85% H_3PO_4) -1.11. MS (CI, isobutane) *m/z*: 551 (MH^+, 31%), 279 ($[(C_6H_5CH_2O)_2P(OH)_2]^+$, 23.9%), 263 (100%). Anal. calcd. for $C_{33}H_{43}O_5P$: C, 72.0%, H, 7.9%. Found: C, 71.7%, H, 7.7%.

21-*O*-(Dibenzyloxyphosphoryl)dexamethasone (19):[32] Dibenzyl N,N-diisopropyl-phoshoramidite (0.169 g, 0.49 mmol), dexamethasone (0.078 g, 0.2 mmol) and 1H-tetrazole (0.053 g, 0.76 mmol) were dissolved, in the order stated and under a dry argon atmosphere, in THF (5 mL) freshly distilled from sodium. After stirring 21 h at rt the reaction mixture was cooled in an acetone-dry ice bath and a solution of *m*-CPBA (0.228 g, 0.66 mmol; 50% in benzoic acid) in CH_2Cl_2 (1 mL) was added. The cooling bath was removed, the mixture allowed to reach rt, and the solvent was evaporated. The residue was taken up in CH_2Cl_2 (5 mL) and the vigorously shaken in succession with 3 mL 1 M HCl saturated with ferrous sulfate, three 3 mL portions of 1 M $NaHCO_3$ solution, 3 mL H_2O and 3 mL saturated NaCl solution, and dried over Na_2SO_4. The residue obtained upon evaporation of the solvent was flash-chromatographed on a silica column (3 x 18 cm) using ethyl acetate-hexane as eluent. The oil obtained (0.086 g, 65%) was crystallized from hot methanol; white solid, mp 88 °C. $[\alpha]_D^{20}$ +60.51° (c 0.029, $CHCl_3$). IR (KBr) ν (cm^{-1}): 1724 (m), 1654 (s), 1618 (m), 1604 (m), 1442 (m), 1260 (m), 1245 (m), 1224 (m), 1172 (m), 1097 (m), 1062 (s), 1027 (s), 1013 (s), 949 (m), 910 (m), 886 (s), 724 (m), 682 (m). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.90 (d, *J*=7.3 Hz, 3H, 22-C**H**$_3$), 1.05 (s, 3H, 18-C**H**$_3$), 1.53 (s, 3H, 19-C**H**$_3$), 2.21-2.47 (bm, 2H), 2.54-2.69 (bm, 1H), 3.04-3.21 (bm, 1H), 4.32 (bd, one *J*=9.4 Hz, 1H, 11-C**H**$_\alpha$), 4.65-5.00 (ABm, 2H, conc dependent, 21-C**H**$_2$), 5.02 and 5.06 (dABq, *J*=12 Hz, 8 Hz, 2H, PhC**H**$_2$), 5.16 and 5.24 (dABq, *J*=12 Hz, 8 Hz, 2H, PhC**H**$_2$), 6.10 (bs, 1H, 4-C**H**), 6.33 (dd, *J*=10 Hz, 2 Hz, 1H, 2-C**H**), 7.22 (d, *J*=10 Hz, 1H, 1-C**H**), 7.30-7.45 (m, 10H, arom). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.74 (C-22), 16.72 (C-18), 22.91 (d, J_{FC}=5.5 Hz, C-19), 27.41 (C-7 ?), 31.05 (C-6), 32.28 (C-15 ?), 34.27 (d, J_{FC}=19.5 Hz, C-8), 35.85 (C-16), 36.33 (C-12), 43.99 (C-14), 48.36 (d, J_{CF}=23 Hz, C-10), 48.43 (C-13), 69.64 (d, J_{PC}=5.6 Hz, **C**Ph), 69.86 (d, J_{PC}=5.6 Hz, **C**Ph), 71.17 (d,

J_{PC}=4.9 Hz, C-21), 71.85 (d, J_{FC}=38.4 Hz, C-11), 91.25 (C-17), 100.29 (d, J_{FC}=176 Hz, C-9), 124.96 (C-4), 127.93, 128.03, 128.54, 128.57, 128.60 (arom C-*p*, *m*, *o*), 129.58 (C-2), 135.52 (d, J_{PC}=6.3 Hz, arom C-*ipso*), 135.69 (d, J_{PC}=7.5 Hz, arom C-*ipso*), 152.53 (C-1), 166.44 (br, C-5), 186.69 (C-3), 204.64 (d, J_{PC}=2.5 Hz, C-20). ^{31}P-NMR (81 MHz, $CDCl_3$) δ (*vs* ext. 85% H_3PO_4) -0.49. UV (MeOH, 3 x 10^{-5} M) λ_{max} 237 nm (ε 13800). MS (CI, isobutane) *m/z*: 653 (MH^+, 1.1%), 375 ($[M-(C_6H_5CH_2O)_2PO_2]^+$, 71.5%), 369 (100%), 279 ($[(C_6H_5CH_2O)_2P(OH)_2]^+$, 32.1%). Anal. calcd. for $C_{36}H_{42}FO_8P$: C, 66.3%, H, 6.5%. Found: C, 66.8%, H, 6.2%.

6β-Bromocholest-4-en-3-one and **6α-Bromocholest-4-en-3-one:** The 6β isomer was obtained as described in the literature by bromination of 3β-cholesterol to give 5α,6β-dibromocholestan-3β-ol,[36] the kinetic product; oxidation to 5α,6β-dibromocholestan-3-one;[36] and dehydrobromination.[37] In order to prepare the 6α isomer, 5α,6β-dibromocholestan-3β-ol was isomerized to the thermodynamically more stable 5β,6α-dibromocholestan-3β-ol,[39] and the latter was oxidized to the 3-ketone. However, in our hands, and in contrast to the report of Barton and Miller,[39] dichromate oxidations as well as oxidation with Jones reagent were always accompanied by dehydrobromination and epimerization, yielding an equilibrium mixture (~1:1) of 6α and 6β-bromocholest-4-en-3-one. The same mixture was obtained by the hydrogen chloride catalyzed isomerization of the 6β isomer.[40] We were unsuccessful in our attempts to repeat the chromatographic separation of the two isomers reported by de la Mare.[40]

Reactions of 20 with $P(OCH_3)_3$: No reaction was detected at room temperature between $P(OCH_3)_3$ and **20**β in methanol solution for 14 days, or with **20**α+β in acetic acid solution for 6 days. In refluxing methanol in the presence of ~60 fold excess of $P(OCH_3)_3$ a slow reaction yielding **21** was followed over the course of 8 days. Heating a 1 M solution of **20**β in 1,4-dioxane with 1.4 eq of $P(OCH_3)_3$ at 100 °C for 24 h lead to a mixture of **20**α, **20**β, **21**, **22** in the ratio of 1:1:8:5. Heating a mixture of **20**α+β and 1.2 eq $P(OCH_3)_3$ at 120 °C for 7.5 h produced **21** and **22** in the ratio of 1.7:1. Irradiation (250 nm) of a 0.04 M solution of **20**α+β in acetonitrile containing 5 eq of $P(OCH_3)_3$ converted all of the steroid to **21**. The reactions were followed by UV and NMR spectroscopy, by TLC, and by isolation of products **21** and **22**.

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