A Revised Mechanism for the Mitsunobu Reaction[1a]

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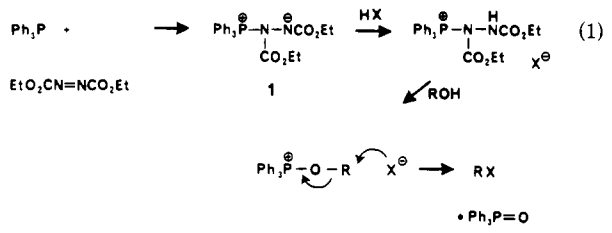
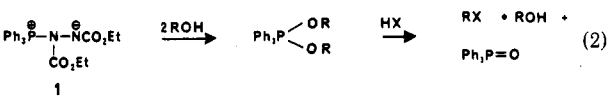
In contrast to previous studies, a ^{31}P NMR examination of the Mitsunobu reaction using a poorly nucleophilic acid (CF_3COOH) to retard intermediate reactions reveals a dual mechanism. Depending on the order of addition of the reactants, the reaction proceeds (a) exclusively by slow conversion of a protonated betaine to an alkoxyphosphonium salt or (b) by rapid conversion of a dialkoxyphosphorane to the same alkoxyphosphonium salt, with recycling of the liberated $^1/_2$ equiv of alcohol by pathway (a). Sodium benzoate dramatically accelerated the reaction, resulting in trifluoroacetate esters in high yields. This latter result provides the basis for an unusually mild procedure for the inversion of certain secondary alcohols.

The reaction of hydroxy compounds with acids (HX) ($pK_a \leq 11$) in the presence of triphenylphosphine and diethyl azodicarboxylate (Mitsunobu reaction) has become widely used for the functionalization of alcohols and related compounds.[2] Until the independent NMR studies of Grochowski and co-workers[3] and von Itzstein and Jenkins,[4] the mechanism was widely assumed to be as shown in eq 1 to account for the finding of inversion at carbon in asymmetric alcohols (ROH).[5]



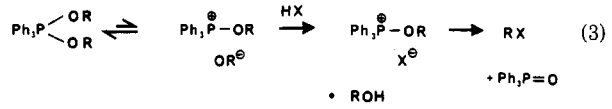
(1)

Both Grochowski[3] and Jenkins[4] concluded on the basis of ^{31}P NMR studies that the true intermediate is the dialkoxyphosphorane $Ph_3P(OR)_2$ (eq 2), which decomposes to products with recycling of the second molecule of ROH through the unreacted $^1/_2$ equiv of betaine 1.



(2)

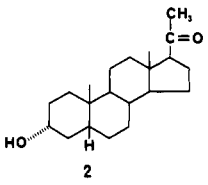
The nature of the (unobserved) intermediates between the dialkoxyphosphorane and the products was left open by Grochowski and considered to be alkoxyphosphonium salts by Jenkins (eq 3).



(3)

Both groups based their conclusions on experiments in which the reaction components were initially mixed *in the absence of the acid HX*, presumably due to the speed of the subsequent reaction with the nucleophile X^-. The experiments described below illustrate that the order of mixing can have a profound effect on the reaction pathway and demonstrate that the true mechanism of the Mitsunobu reaction is more complex than previous studies suggest.

As part of a synthetic program, we attempted to use the Mitsunobu reaction to prepare an alkoxyphosphonium salt containing a nonnucleophilic counterion for subsequent reaction with added nucleophiles. Indeed, when alcohol **2**, diethyl azodicarboxylate, and trifluoroacetic acid were mixed in THF, followed by the addition of triphenylphosphine, a polar TLC-visible intermediate gradually formed that was consistent with the expected phosphonium salt. This intermediate showed only partial conversion to the trifluoroacetate ester **3** over several hours.



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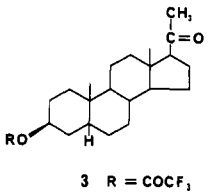

3 R = $COCF_3$
4 R = H

Addition of sodium benzoate to a fresh reaction mixture after 1 h caused rapid decomposition of this polar intermediate, resulting not in the anticipated benzoate ester but *in the formation of the trifluoroacetate ester* **3**, with inversion, in 90% isolated yield.[6] *It is remarkable that no significant amount of benzoate ester was formed in this reaction.*

It was previously shown by Loibner and Zbiral[7] that a trifluoroacetate could be prepared from 3β-cholestanol (**7**) in 44% yield by using a standard Mitsunobu reaction. In their procedure, the trifluoroacetic acid was added last and the reaction worked up after 4 h. Examination of the reaction of **2** following the procedure of Zbiral showed by TLC that, immediately after mixing the reagents, significant amounts of trifluoroacetate **3** were already present (in contrast to the above reaction), along with substantial amounts of the polar intermediate described above. Furthermore, addition of sodium benzoate to the reaction mixture at this point again led to the rapid disappearance of this intermediate with complete formation of the trifluoroacetate **3**. Apparently the presence or absence of the acid component during mixing of the other reactants is the key variable leading to the contrasting rates of product appearance, and we therefore examined these reactions by ^{31}P NMR in an attempt to understand the mechanistic implications.

When equimolar amounts of **2**, Ph_3P, and diethyl azodicarboxylate were mixed in THF (containing C_6D_6 as a

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(2) Mitsunobu, O. *Synthesis* **1981**, 1.

(3) Grochowski, E.; Hilton B. D.; Kupper, R. J.; Michejda, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 6876.

(4) Von Itzstein, M.; Jenkins, I. D. *Aust. J. Chem.* **1983**, *36*. 557.

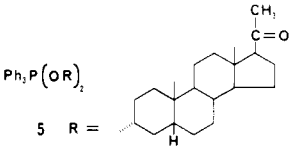
(5) Reference 2, and references therein.

(6) Sodium benzoate may be added after formation of the polar intermediate or immediately (5 min) after mixing the reactants. In either case, the reaction then proceeds rapidly to the trifluoroacetate ester. Catalytic amounts of sodium benzoate (e.g. 0.15–0.5 equiv) are also effective.

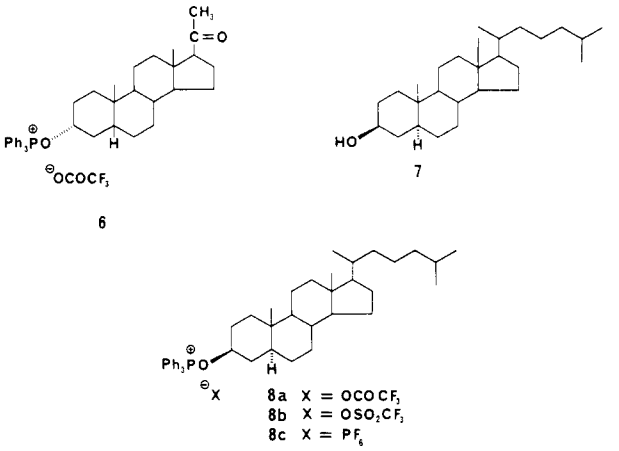
(7) Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, *59*, 2100.

0022-3263/87/1952-4235$01.50/0

lock signal) in the absence of CF_3COOH (Zbiral procedure), two approximately equal phosphorus signals were observed at +43.7 and −50.0 ppm, corresponding to the betaine **1** [lit.[8] +44.9 ppm (THF), +43.9 ppm (C_6H_6)] and dialkoxyphosphorane **5** [lit.[4] for $Ph_3P(O\text{-}i\text{-}Pr)_2$ −49.6 ppm



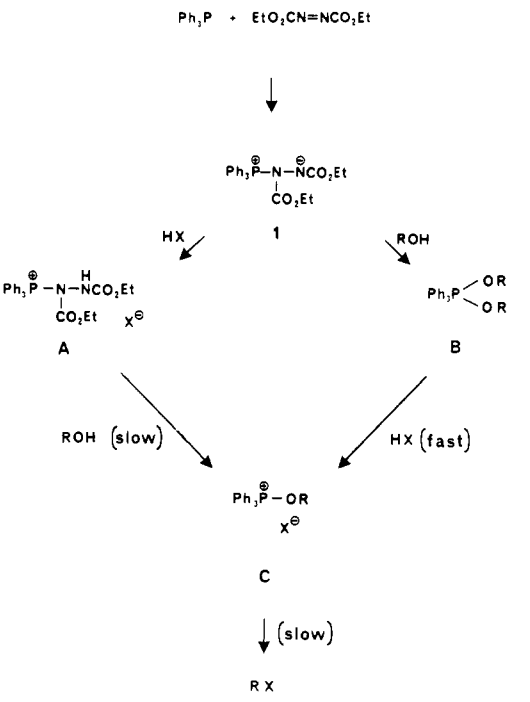
(THF)], respectively, in agreement with the studies of Grochowski[3] and Jenkins.[4] Addition of 1 equiv of trifluoroacetic acid at this point caused the immediate disappearance of both signals and the appearance of three new ones at approximately +26 ($Ph_3P{=}O$), +51.2, and +59.1 ppm. On the other hand, when trifluoroacetic acid was added to the betaine before the alcohol **2**, the +43-ppm resonance was replaced by one at +51.3 ppm. (This is the only resonance observed if acid is present during mixing of triphenylphosphine and diethyl azodicarboxylate.) On addition of alcohol **2**, the −50-ppm resonance is not observed; instead that at +51 ppm is gradually replaced by the previously observed signal at +59 ppm. This signal is in the region expected for a phosphonium salt and is consistent with the polar intermediate observed in the reaction at this point. A similar polar intermediate was observed by TLC in the reaction of 3β-cholestanol (**7**).



The identity of these intermediates as **6** and **8a** was confirmed by their isolation by rapid column chromatography to give unstable compounds that converted to the corresponding trifluoroacetate and Ph_3PO on handling or on standing over several hours. As found in the reaction mixture, decomposition of these intermediates as solutions in THF was accelerated by the addition of sodium benzoate, giving the trifluoroacetate, Ph_3PO, and some starting alcohol.

^1H NMR spectroscopy showed the intermediate **6** derived from **2** to have incorporated both the steroid and triphenylphosphine moieties in a 1:1 ratio, with no incorporation of diethyl azodicarboxylate derived fragments. The stereochemistry at the steroid carbinol carbon remained unchanged from that of the starting alcohol **2**, as shown by the half bandwidth of the 3β (axial) hydrogen (20–30 Hz); however, the 3 H resonance was shifted downfield to approximately 4.5 ppm, in agreement with the literature[9] value of 4.35 ppm for the corresponding proton in (cyclohexyloxy)triphenylphosphonium triflate.

Scheme I



Additional splitting of the 4.5-ppm resonance is consistent with coupling to phosphorus (expected $J_{POCH} \approx 7$ Hz).

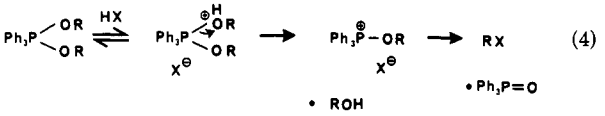
The corresponding intermediate isolated from the reaction of 3β-cholestanol (**7**) was shown to be a phosphonium salt by the ^{31}P NMR resonance at +59.2 ppm ($CDCl_3$), in good agreement with that observed in the above NMR studies. Further proof of the structure of **8a** was obtained by its independent synthesis (as the triflate salt **8b**) from Ph_3PO and triflic anhydride by the method of Hendrickson.[9,10] The phosphonium salt was isolated and characterized as the crystalline hexafluorophosphate **8c**, showing a ^{31}P NMR resonance at +59.1 ppm ($CDCl_3$) and a similar broad multiplet at 4.45 ppm in the ^1H NMR spectrum. We believe these observations are best represented by Scheme I.

There is no question that the betaine **1** (δ +43 ppm) is the initially formed intermediate.[3] However, when acid is present during the formation of **1**, or added subsequently, protonation occurs immediately to give the conjugate acid phosphonium salt A (δ +51 ppm) [lit.[8] for the BF_4^- salt +53.1 ppm (solvent not specified)]. On addition of alcohol, this salt undergoes slow conversion to the phosphonium salt C (δ +59 ppm). In the absence of acid, half of the betaine **1** reacts with alcohol, possibly as depicted by Jenkins,[4] to give the dialkoxyphosphorane B (δ −50 ppm). Addition of trifluoroacetic acid at this point protonates the remaining **1** to A (δ +51 ppm) and converts B instantaneously to C, leaving the liberated $^1/_2$ equiv of alcohol to recycle through (A) to the phosphonium salt C (δ +59 ppm).

Several important points emerge. Formation of the phosphonium salt C through the conjugate acid A is very slow relative to its instantaneous formation from B. This provides a ready explanation for the more rapid appearance of product when acid is added last (Zbiral procedure) than when acid is present earlier in the sequence. (Excess trifluoroacetic acid slows the formation of C even further.) The proposal[3,4] that the second molecule of alcohol lib-

(8) Guthrie, R. D.; Jenkins, I. D. *Aust. J. Chem.* **1982**, *35*, 767.
(9) Hendrickson, J. B.; Schwartzman, S. M. *Tetrahedron Lett.* **1975**, 277.
(10) The structure of the reactive species postulated to be triphenylphosphine ditriflate by Hendrickson (ref 9) has been reassigned. See: Aaberg, A.; Gramstad, T.; Husebye, S. *Tetrahedron Lett.* **1979**, 2263.

erated from the phosphorane B on treatment with acid (HX) is recycled via the unreacted betaine 1 is incorrect; the latter is converted to the conjugate acid A, and further consumption of unreacted alcohol necessarily takes place via A → C and not through B. Furthermore, the dialkoxyphosphorane B is only an intermediate in the Mitsunobu reaction in the special case where the acid is added last. Although the formation of some product directly from the dialkoxyphosphorane B cannot be ruled out, integration of the ^{31}P NMR spectrum shows that most if not all is converted to the phosphonium salt C. Dialkoxyphosphoranes analogous to B have been prepared previously by insertion of phosphines into peroxides and shown to react exothermically with benzoic acid to give benzoate esters.[11] Deliberate generation of B (=5) using 2 equiv of alcohol 2 followed by the addition of trifluoroacetic acid (1 equiv) again gave the immediate formation of C (=6) with only small amounts of 3 according to thin-layer chromatography. A possible mechanism may be as shown in eq 3 or 4.



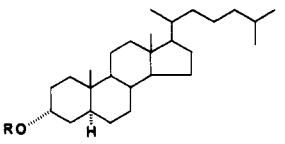
(4)

Interestingly, the conversion of a dialkoxyphosphorane to a phosphonium salt has previously been observed following treatment with fluoroboric acid;[8] however, the dialkoxyphosphorane[4] had been incorrectly assigned a different structure.

The formation of trifluoroacetate esters in the presence of sodium benzoate is intriguing. The inaccessibility of alkoxyphosphonium salts to external nucleophiles has been noted before,[12,13] and the precise nature of these intermediates and their mode of reaction have been the subject of much discussion.[12] Thus, Snyder and Weiss demonstrated the inability of cyanide to compete with chloride ion in the reaction of 2-phenylethanol with triphenylphosphine dichloride in DMSO[13] or in the pyrolysis of an isolated oxyphosphorane with sodium cyanide.[12] Pentacoordinate phosphoranes were commonly invoked[12-15] (possibly as precursors to ion pairs[12]) to explain this lack of accessibility to external nucleophiles. However, the proposal[15,16] that such species could give products with inversion through a symmetry-allowed $_{\sigma}2_s + _{\sigma}2_a$ pericyclic process seems to have been discounted.[17,18] No ^{31}P NMR data were provided to rule out the possibility that these intermediates are in fact phosphonium salts, as is clearly the case in the present work. The formulation of these intermediates as tight ion pairs[12] that collapse by backside attack also suffers from the untenable requirement that the counterion be located in a specific location.[17] More likely is the recent proposal,[17,18] supported by experimental data,[19] that clusters of ion pairs are involved. The dramatic rate increase on adding sodium benzoate to the reaction mixture may in part be explained by general base catalysis in the formation of C from A. However, the more rapid formation of products from C, both in the reaction mixture and as the isolated phosphonium salts 6 or 8a, is harder to explain. If C indeed exists as aggregates of tight ion pairs,[12] possibly the added salt disrupts these stable aggregates allowing attack of the closely held CF_3COO^- on a neighboring alkoxy group. Although the phosphonium salts 6 or 8a are not accessible to the external nucleophile, the reaction of alkoxyphosphonium salts having completely nonnucelophilic anions (e.g. BF_4^-, PF_6^-) with certain nucleophiles is well known.[20-24] However, treatment of the hexafluorophosphate salt 8c with sodium benzoate in THF resulted only in the formation of 3β-cholestanol (7) and elimination products (+Ph_3PO).

The insights into the mechanism of the Mitsunobu reaction described above were made possible by the fortunate choice of an acid of sufficiently low nucleophilicity to slow the formation and decomposition of the intermediate phosphonium salt. No doubt most synthetic procedures using this versatile reaction proceed rapidly to products regardless of the order of addition due to the more reactive nature of the nucleophiles commonly used. The Mitsunobu reaction therefore would appear to proceed by a combination of both phosphonium salt and phosphorane pathways or exclusively by a phosphonium salt as originally proposed, depending on the order of addition and possibly the pK_a of the acid.

The observations described above form the basis for a very mild method for the inversion of equatorial secondary alcohols.[25] Thus, alcohols 2 and 7 were converted to the trifluoroacetates 3 and 9 in 90.7% and 67% yield, respectively. Although these could readily be converted to



9 R = COCF3
10 R = H

the inverted alcohols 4 and 10 by methanolysis in 75% and 88% yields, isolation of the intermediate esters is inefficient and unnecessary. Reaction of 2 and 7 under the above conditions followed by refluxing with methanol gave the inverted alcohols 4 and 10 directly in 94% and 90% overall yield, respectively. We believe that trifluoroacetates may have advantages over more stable esters[2,26] for the inversion of suitable alcohols when base sensitivity dictates a particularly mild hydrolysis of the intermediate ester.

Experimental Section

^{31}P NMR spectra were measured on Bruker WM-300 or WH-90 instruments operating at 121.51 and 36.43 MHz, respectively.

(11) Denny, D. B.; Denny, D. Z.; Wilson, L. A. *Tetrahedron Lett.* **1968**, 85.
(12) Weiss, R. G.; Snyder, E. I. *J. Org. Chem.* **1970**, *35*, 1627.
(13) Weiss, R. G.; Snyder, E. I. *J. Org. Chem.* **1971**, *36*, 403.
(14) Aneja, R.; Davies, A. P.; Knaggs, J. A. *J. Chem. Soc., Chem. Commun.* **1973**, 110.
(15) Aneja, R.; Davies, A. P. *J. Chem. Soc., Perkin Trans. 1* **1974**, 141.
(16) Aneja, R.; Davies, A. P.; Knaggs, J. A. *Tetrahedron Lett.* **1974**, 67.
(17) Jones, L. A.; Sumner, C. E., Jr.; Franzus, B.; Huang, T. T.-S.; Snyder, E. I. *J. Org. Chem.* **1978**, *43*, 2821.
(18) Slagle, J. D.; Huang, T. T.-S.; Franzus, B. *J. Org. Chem.* **1981**, *46*, 3526.
(19) Ramos, S.; Rosen, W. *J. Org. Chem.* **1981**, *46*, 3530.
(20) Ohmori, H.; Nakai, S.; Sekiguchi, M.; Masui, M. *Chem. Pharm. Bull.* **1980**, *28*, 910.
(21) Colle, K. S.; Lewis, E. S. *J. Org. Chem.* **1978**, *43*, 571 and references therein.
(22) Lewis, E. S.; Colle, K. S. *J. Org. Chem.* **1981**, *46*, 4369.
(23) Lewis, E. S.; Walker, B. J.; Ziurys, L. M. *J. Chem. Soc., Chem. Commun.* **1978**, 424.
(24) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801.
(25) This method does not work well for more hindered alcohols, giving some trifluoroacetate with retention of configuration, particularly in the presence of sodium benzoate. This is attributed to the competing formation of trifluoroacetic anhydride when formation of alkoxyphosphonium salt is slow, followed by direct acylation of the starting alcohol (catalyzed by sodium benzoate) or by reaction through a (trifluoroacetoxy)phosphonium derivative with retention (at carbon).
(26) Bose, A. K.; Lal, B.; Hoffman, W. A., III; Manhas, M. S. *Tetrahedron Lett.* **1973**, 1619.

Phosphoric acid (85%) was used as an external standard, with downfield shifts being given positive values. Broadband noise-modulated decoupling was used to remove ^1H–^{31}P coupling, and flip angles were 30–40°. ^1H NMR spectra were measured on Bruker WM-300 and Varian HA-100 spectrometers operating at 300.133 and 100 MHz, respectively. Chemical shifts are reported relative to internal tetramethylsilane. Mass spectra were determined on a Varian MAT CH-4 low-resolution instrument. Melting points were measured in a Thomas-Hoover capillary melting point apparatus. Elemental analyses were determined by the Syntex Analytical Department.

(20-Oxo-5β-pregnanyl-3α-oxy)triphenylphosphonium Trifluoroacetate (6). Diethyl azodicarboxylate (174 mg, 1.00 mmol) and 3α-hydroxy-5β-pregnan-20-one (**2**) (238 mg, 0.75 mmol) in dry chloroform were treated with stirring with trifluoroacetic acid (0.077 mL, 1.00 mmol) followed by triphenylphosphine (262 mg, 1.00 mmol). After 5 min, sodium benzoate (144 mg, 1.00 mmol) was added. In this solvent, the reaction was very slow, and after 20 h a large polar intermediate was visible by TLC (7% MeOH in CH_2Cl_2 on silica gel). Evaporation of the solvent and rapid chromatography on silica gel, eluting with 10% MeOH in CH_2Cl_2, gave the desired unstable intermediate **6**: ^1H NMR ($CDCl_3$) δ 0.57 (3 H, s, 18-H), 0.86 (3 H, s, 19-H), 2.07 (3 H, s, 21-H), ca. 4.5 (1 H, br m, 3β-H), 7.3–8.0 (15 H, m, 3 Ph).

(3β-Cholestanyloxy)triphenylphosphonium Trifluoroacetate (8a). The above procedure was repeated with 3β-cholestanol (**7**) to give a labile gum, having ^{31}P NMR ($CDCl_3$) δ +59.2 (Ph_3P^+OR), and a minor impurity at +29.4 (Ph_3PO, increases on addition of authentic material).

(3β-Cholestanyloxy)triphenylphosphonium Hexafluorophosphate (8c). Triflic anhydride (trifluoromethanesulfonic anhydride) 1.5 mL, 0.009 mol) was added dropwise to a stirred solution of triphenylphosphine oxide (2.5 g, 0.009 mol) in dry dichloromethane (15 mL). After 10 min, solid 3β-cholestanol (**7**) (3.0 g, 0.008 mol) was added slowly, and 15 min later the solvent was evaporated rapidly in vacuo and a saturated solution of ammonium hexafluorophosphate added. The mixture was stored in the refrigerator for 3 h, by which time a solid had formed; filtration, washing with water, and drying in high vacuum gave **8c** (6.08 g, 97%): ^1H NMR ($CDCl_3$) δ 0.62 (3 H, s, 18-H), 0.81 (3 H, s, 19-H), ca. 4.45 (1 H, br m, 3α-H), 7.4–8.1 (15 H, m, 3 Ph); ^{31}P NMR ($CDCl_3$) δ +59.1 (Ph_3P^+OR), −144.2 (J = 716 Hz, PF_6^-). Anal. Calcd for $C_{45}H_{62}F_6OP_2$: C, 67.99; H, 7.86. Found: C, 68.12; H, 7.62.

3β-(Trifluoroacetoxy)-5β-pregnan-20-one (3). To a stirred solution of diethyl azodicarboxylate (628 mg, 3.61 mmol) and 3α-hydroxy-5β-pregnan-20-one (**2**) (1.00 g, 3.14 mmol) in dry THF (10 mL) was added trifluoroacetic acid (411 mg, 3.61 mmol), followed by solid triphenylphosphine (9.49 mg, 3.61 mmol). After 5 min, sodium benzoate (519 mg, 3.61 mmol) was added and the mixture stirred overnight. After evaporation of the solvent, the residue was partitioned between water and hexane and filtered to remove triphenylphosphine oxide, and the organic layer was dried ($MgSO_4$) and evaporated. Chromatography on silica gel, eluting with CH_2Cl_2, gave **3** (1.18 g, 90.7%). Recrystallization from hexane gave the analytical sample: mp 115–115.5 °C; ^1H NMR ($CDCl_3$) δ 0.60 (3 H, s, 18-H), 0.97 (3 H, s, 19-H), 2.07 (3 H, s, 21-H), 5.28 (1 H, m, 3α-H); mass spectrum, m/z 414 (M^+). Anal. Calcd for $C_{23}H_{33}F_3O_3$: C, 66.64; H, 8.02. Found: C, 66.70; H, 8.06.

3α-(Trifluoroacetoxy)cholestane (9). The above procedure was repeated with 3β-cholestanol (4.90 g) and 1.25 equiv of all other reagents in THF (24 mL) followed by chromatography on silica gel, eluting wiith hexane. (The silica gel was loaded using CH_2Cl_2, which was evaporated before adding the silica gel to the top of the column.) Recrystallization from MeOH gave **9** (67%): mp 71.5–73 °C (lit.[6] mp 68–72 °C); ^1H NMR ($CDCl_3$) δ 0.65 (3 H, s, 18-H), 0.80 (3 H, s, 19-H), 5.21 (1 H, m, 3β-H); mass spectrum, m/z 484 (M^+). Anal. Calcd for $C_{29}H_{47}F_3O_2$: C, 71.86; H, 9.78. Found: C, 71.98; H, 9.94.

Direct Preparation of 3β-Hydroxy-5β-pregnan-20-one (4). The trifluoroacetate was prepared in situ as above from **2** (3.18 g, 10 mmol) and 12.5 mmol of all other reagents in THF (20 mL). After 24 h, the solvent was evaporated, and the residue was treated with MeOH (20 mL) and heated under reflux with stirring overnight. After removal of the MeOH, the product was partitioned between CH_2Cl_2 and water, and the organic layer was washed twice with water, dried ($MgSO_4$), and evaporated. Chromatography on silica gel, eluting with EtOAc in hexane (2:8 to 1:1), and trituration of the pure fractions with hexane gave **4** (2.82 g, 94%) [mp 141–143 °C (lit.[27] mp 149 °C)] containing no detectable starting alcohol **2** by TLC (silica gel, CH_2Cl_2) or GC (3-ft 3% OV-225 column at 215 °C derivatized with BSTFA): ^1H NMR ($CDCl_3$) δ 0.59 (3 H, s, 18-H), 0.94 (3 H, s, 19-H), 2.07 (3 H, s, 21-H), 4.08 (1 H, m, 3α-H). Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.28; H, 10.98.

Direct Preparation of 3α-Cholestanol (10). Repeating the above procedure using 3β-cholestanol (**7**) (3.88 g, 10.0 mmol), followed by chromatography on silica gel, eluting with EtOAc in toluene (1:9), gave **10** containing no starting alcohol (TLC on silica gel, CH_2Cl_2). Recrystallization from ether–ethanol gave 3.50 g (90%): mp 184.5–185 °C (lit.[28] mp 185–186 °C, lit.[29] mp 182–184 °C); ^1H NMR ($CDCl_3$) δ 0.63 (3 H, s, 18-H), 0.76 (3 H, s, 19-H), 3.99 (1 H, m, 3β-H); mass spectrum, m/z 388 (M^+). Anal. Calcd for $C_{27}H_{48}O$: C, 83.43; H, 12.45. Found: C, 83.52; H, 12.45.

Preparation of 3β-Hydroxy-5β-pregnan-20-one (4) from 3. The trifluoroacetate **3** prepared as above (1.12 g, 2.70 mmol) and $NaHCO_3$ (227 mg, 2.70 mmol) in MeOH (10 mL) were heated under reflux until the formation of **4** was complete by TLC. Filtration, evaporation of the solvent, and chromatography on silica gel, eluting with 3% MeOH in CH_2Cl_2, followed by recrystallization from hexane gave **4** (650 mg, 75%) [mp 143–145.5 °C (lit.[27] mp 149 °C)] containing no starting alcohol detectable by TLC or GC (conditions as above). Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.16; H, 10.91.

Preparation of 3α-Cholestanol (10) from 7. The trifluoroacetate **9** from above (4.10 g, 8.46 mmol) and sodium benzoate (1.22 g, 8.46 mmol) in MeOH (25 mL) were heated under reflux for 4 h, and the solvent was removed. The product was partitioned between water and ether, and the organic layer was washed with water and dried ($MgSO_4$). Chromatography on silica gel as above and recrystallization from ether–MeOH gave 2.90 g (88%) of **10**: mp 182–185 °C (lit.[28] mp 185–186 °C). Anal. Calcd for $C_{27}H_{48}O$: C, 83.43; H, 12.45. Found: C, 83.54; H, 12.67.

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