Facile Synthesis of 5α-Fluorocholestan-3-one from 4-Cholesten-3-one *via* Molecular Fluorine Addition and Reductive Defluorination

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A facile synthesis of 5α-fluorocholestan-3-one from 4-cholesten-3-one has been accomplished. Direct fluorination of the enone by molecular fluorine gave the *cis*-vicinal difluoride. Treatment of this adduct with triphenyltin hydride in the presence of azobisisobutyronitrile afforded the title compound.

Keywords fluorination; molecular fluorine; 5α-fluorocholestan-3-one; reductive defluorination; triphenyltin hydride

The use of molecular fluorine as a fluorinating agent has been steadily increasing in the last decade.[1] This halogen has come into use as a common reagent for organic chemists since: 1) it was realized that fluorine diluted with inert gases (N_2 or Ar) undergoes controllable and selective reactions in both addition to carbon–carbon double bonds in alkenes[2] and substitution of C–H functions in alkanes[3] and 2) a diluted solution has become available commercially.[1] Though the addition of fluorine to alkenes is categorized as an electrophilic process,[4] the fluorination of α,β-unsaturated ketones has often been used for the preparation of the corresponding difluorides. In the steroid field, Merritt and Stevens reported the selective formation of the 4α,5α-difluoride from 4-cholesten-3-one[5] and Barton *et al.* obtained the 16α,17α-difluorides as the major products from steroidal 16-en-20-ones.[6]

While there are many ways to introduce a fluorine atom at the α-position of a ketone function,[7] there is none for introducing a fluorine atom at the β-position by using the fluorine molecule as the fluorination reagent.[8] For example, in the synthesis of 1α-fluorovitamin D_3, introduction of a fluorine atom at the 1-position of 3-oxosteroids from the corresponding Δ^4-steroids has only been achieved by epoxidation of 3-oxo-Δ^1-steroids followed by hydrofluoride-mediated epoxide ring opening reaction.[9] Hence, we became interested in examining the route shown in Chart 1. Such a route would provide a method with fewer steps than the above-mentioned route and has ample precedents for the synthesis of the other halogen derivatives (Cl, Br, or I), but none for fluorinated ones. The only difficulty is to find suitable reducing reagents capable of eliminating the fluorine atom from α-fluoroketones.

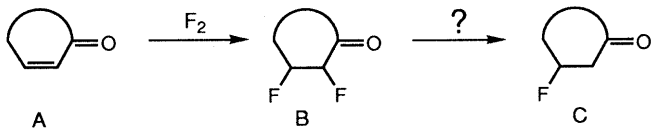

Chart 1. Synthetic Plan of β-Fluoroketones from α,β-Unsaturated Ketones

In order to obtain the α,β-difluorinated ketone, we repeated the addition reaction of molecular fluorine to 4-cholesten-3-one (**1**) under comparable conditions to those reported by Merritt and Stevens,[5] who claimed to have obtained the *cis*-difluoride (**2**) in *ca.* 70% yield as the sole isolable product. In our hands, however, in addition to the *cis*-difluoride (**2**) in 23% yield,[10] two by-products (**3** and **4**) were obtained in 9% and 18% yields, respectively.

The structural assignment of these two by-products (**3** and **4**) was based on physical and spectroscopic data (see Experimental). Both compounds were formulated as $C_{27}H_{42}FO$ on the basis of their microanalyses and were thus isomeric with each other. The absence of a conjugated enone chromophore was evident from the UV spectrum of each compound. We favour the process outlined in Chart 3, in which the initially formed α-face tight ion-pair (D) can either collapse to give the normal addition product (**2**) or undergo a series of carbocation rearrangements *via* the carbocation species (E). Strong presumptive evidence against the proposal that the products (**3** and **4**) arose from the adduct (**2**), under the reaction conditions employed, was provided by the observation that all products appeared in the early stages of the reaction, and could be isolated together even before

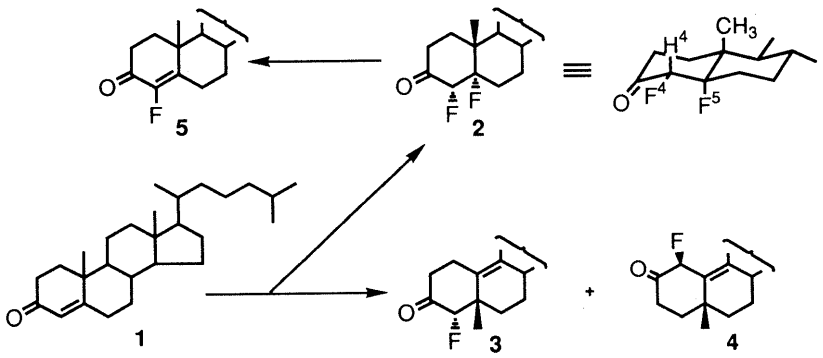

Chart 2

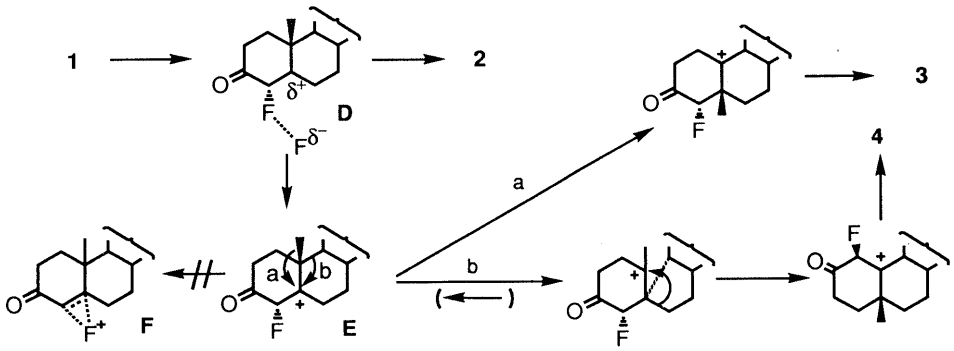

Chart 3

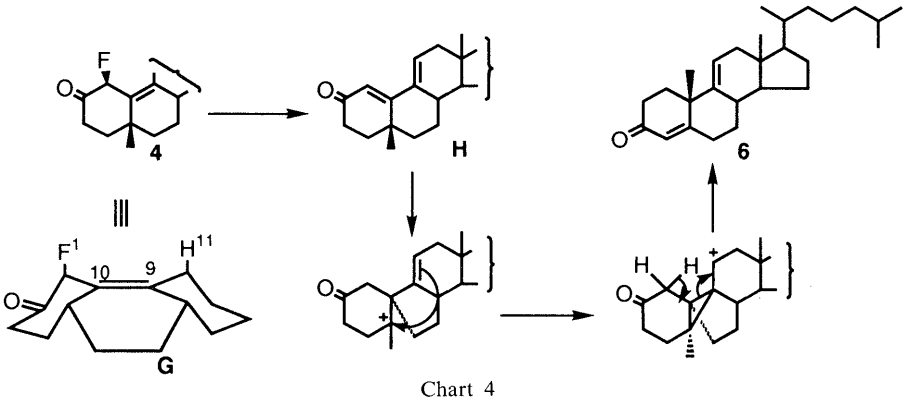

Chart 4

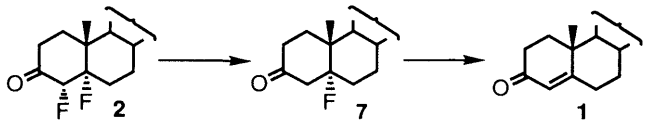

Chart 5

completion of the reaction. It should be noted that the use of more protic solvent systems (*e.g.* $CFCl_3 : CHCl_3 : EtOH = 5 : 4 : 1$, $CHCl_3 : EtOH = 1 : 1$) led to the same three products (**2**, **3**, and **4**) in comparable ratios to those obtained under the aforementioned conditions ($CFCl_3$).

It should be noted that product **4** could be quantitatively dehydrofluorinated to the known cholesta-4,9-dien-3-one (**6**),[11] simply by adsorbing it on a silica gel TLC plate. The easy elimination of HF from **4** is due to the favorable arrangement of the fluorine and one of the H_{11} atoms, which permits concerted noncyclic *cis*-1,4-elimination.[12] This arrangement is effective only if the fluorine atom in **4** has quasi-axial conformation and hence, the fluorine atom in the starting material (**4**) should have β-configuration.

Next, we examined the reductive defluorination reaction of **2**, whose structure was confirmed as the 4α,5α-difluoride by dehydrofluorination with DBU in CH_2Cl_2 to afford 4-fluoro-4-cholesten-3-one (**5**).[13,14] Many reducing reagents (*e.g.* Zn–AcOH, Zn–HCl, or Ph_3P–MeOH–C_6H_6) were examined without success, but finally triphenyltin hydride was found to be the reagent of choice.[15] Thus, when **2** was refluxed in benzene containing triphenyltin hydride and AIBN, 5α-fluorocholestan-3-one (**7**) was obtained in 90% yield. Treatment of **7** with DBU at room temperature gave 4-cholesten-3-one (**1**) in quantitative yield. 5α-Fluorocholestan-3-one (**7**) was previously synthesized from cholesteryl acetate by addition of hydrogen fluoride, hydrolysis to the cholestanol and subsequent oxidation with chromium trioxide in acetic acid.[16]

The result obtained in the present study may open a new general route for the introduction of fluorine at the β-position of a carbonyl group. We are currently investigating the generality of this reductive defluorination reaction utilizing 2-fluoro-4-*tert*-butylcyclohexanones as the substrates and our preliminary results indicate that, though both isomers could be defluorinated, the ease of the reactions depends on the fluorine configuration. The details of these experiments will be reported separately. It should be noted that the fluorination of **1** by molecular fluorine is not as selective a reaction as claimed by Merritt and Stevens[5] and gave appreciable amounts of by-products obviously formed through carbocation rearrangements. Since the addition of bromine or chlorine to **1** gave the normal addition products as the sole products,[17,18] the result of the present study strongly indicates that the β-fluorocarbocation has much higher reactivity than the corresponding higher halogen derivatives. We presume that the latter carbocations are stabilized by halonium ion formation (*cf.* F in Chart 3), while the former is not. The formation of two by-products (one is the angular methyl-shifted and the other is 9-methylene-shifted) clearly shows the unmasked nature of the β-fluorocarbocation (*cf.* E in Chart 3). Utilization of the β-fluorocarbocation generated by addition of F_2 to carbon–carbon double bonds, which in the present case provides the shortest route to **4** and hence **6**, seems to have considerable promise.

Experimental

All melting points were determined on a Yanagimoto micro-hot stage and are uncorrected. Optical rotations were measured with a JASCO

DIP-340 digital polarimeter, and $[\alpha]_D$ values are given in 10^{-1} deg $cm^2 g^{-1}$. IR spectra were recorded on a JASCO A-102 spectrometer. ^{1}H-NMR spectra were recorded with a JEOL JNM-PMX 60 or Hitachi R-300 spectrometer with tetramethylsilane (TMS) as an internal standard. Low-resolution mass spectra (MS) were obtained on a JEOL JMS-DX303 mass spectrometer. Silica gel used for column chromatography was Wakogel C-200. Merck Kieselgel 60 F-254 was employed for thin-layer chromatography (TLC). The ratios of mixtures of solvents for chromatography are shown as v/v.

Fluorination of Cholest-4-en-3-one (1) A solution of **1** (1.92 g, 5.0 mmol) in $CFCl_3$ (200 ml) was cooled to −78 °C and 5% F_2/N_2 was passed into the solution until 7.5 mmol of F_2 had passed through the flowmeter (*ca.* 36 min). The reaction mixture was washed with aqueous $NaHCO_3$ solution and then water. The organic layer was dried over $MgSO_4$, and the solvent was evaporated *in vacuo*. The residue was chromatographed over silica gel [hexane–AcOEt (20 : 1)] to give recovered **1** (557 mg, 29%), **2** (359 mg, 17%), **3** (141 mg, 7%), and **4** (261 mg, 13%). **2**: mp 186—189 °C (from MeOH) (lit.[16] mp 187—188 °C). IR ($CHCl_3$): 1749 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 5.0 (1H, dd, J=47, 32 Hz, 4-H). MS *m/z*: 422 (M^+). **3**: mp 137—139 °C (from MeOH), $[\alpha]_D^{20}$ +12.5° (c=0.86, $CHCl_3$). IR ($CHCl_3$): 2960, 1736 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.63 (3H, s, 18-H_3), 1.20 (3H, s, 5-CH_3), 4.82 (1H, d, J=50 Hz, 4-H). MS *m/z*: 402 (M^+). *Anal.* Calcd for $C_{27}H_{43}FO$: C, 80.54; H, 10.76. Found: C, 80.49; H, 10.78. **4**: mp 157—159 °C (from MeOH), $[\alpha]_D^{26}$ −48.6° (c=0.2, $CHCl_3$). IR ($CHCl_3$): 2970, 1740 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.65 (3H, s, 18-H_3), 1.26 (3H, s, 5-CH_3), 5.13 (1H, d, J=49 Hz, 1-H). MS *m/z*: 402 (M^+). *Anal.* Calcd for $C_{27}H_{43}FO$: C, 80.54; H, 10.76. Found: C, 80.50; H, 10.93.

Dehydrofluorination of 4α,5α-Difluorocholestan-4-one (2) to 4-Fluorocholest-4-en-3-one (5) A mixture of **2** (21 mg, 0.05 mmol) and DBU (1 drop) in CH_2Cl_2 (1 ml) was stirred for 10 min at room temperature. The solvent was evaporated *in vacuo*, and the residue was purified by preparative TLC [hexane–AcOEt (10 : 1)] to give **5** (18.5 mg, 92%) as a colorless solid. **5**: mp 102—103 °C (lit.[16] mp 102—103 °C). IR ($CHCl_3$): 1685 cm^{-1} (lit.[16] 1686 cm^{-1}).

Reductive Defluorination of 2 to 5α-Fluorocholestan-3-one (7) A mixture of **2** (83 mg, 0.2 mmol), Ph_3SnH (70 mg, 0.2 mmol) and AIBN (1.3 mg) in dry benzene (4 ml) was refluxed for 40 min under an Ar atmosphere. The solvent was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography [benzene–AcOEt (20 : 1)] to give **7** (72.2 mg, 90%) as colorless needles. **7**: mp 148—149 °C (lit.[16] mp 150—151 °C). IR ($CHCl_3$) 1720 cm^{-1}. MS *m/z*: 404 (M^+). *Anal.* Calcd for $C_{27}H_{45}FO$: C, 80.14; H, 11.21. Found: C, 80.04; H, 11.24.

Conversion of 1β-Fluoro-5β-methyl-19-norcholest-9(10)-en-2-one (4) to Cholest-4,9(11)-dien-3-one (6) Compound **4** (6 mg, 0.015 mmol) was dissolved in chloroform (1 ml) and the solution was adsorbed on a TLC plate. The plate was kept standing at room temperature for 24 h, then the sample was developed with benzene–ethyl acetate (10 : 1) to give **6** (3 mg, 52%) as colorless needles. **6**: mp 115—116 °C (from MeOH) (lit.[11a] mp 116—116.5 °C), $[\alpha]_D^{22}$ +84.6° (c=0.3, $CHCl_3$) [lit.[11a] $[\alpha]_D^{25}$ +81° (c=1.84, $CHCl_3$)]. IR ($CHCl_3$): 2960, 1662 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.46 (1H, d, J=5.9 Hz, 11-H), 5.74 (1H, d, J=1.8 Hz, 4-H). MS *m/z*: 382 (M^+).

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10) Yields were calculated based on the consumed starting materials.
11) The synthesis of **6** has been accomplished by two groups. The first group[11a] used degradation of the A ring followed by recyclization and the second one[11b] utilized Breslow's remote chlorination method[19] for the introduction of the 9-ene function. *a*) J. T. Edward, N. E. Lawson, *J. Org. Chem.*, **35**, 1426 (1970); *b*) B. Lythgoe, D. A. Roberts, *J. Chem. Soc., Perkin Trans. 1*, **1980**, 892.
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14) The dehydrofluorination of **2** was carried out originally by Merritt and Stevens by using sodium methoxide in methanol.[5] The fact that DBU or even Et_3N in CH_2Cl_2 at room temperature provided **5** indicates that 4-H and 5-F are in a *trans* diaxial relation.
15) Since the initial report of their reducing ability,[15a] organotin hydrides have enjoyed considerable vogue as reagents for reductive replacement of halogen in organic halides. Although iodides and bromides usually react spontaneously with tin hydrides, chlorides react with difficulty and fluorides are practically unreactive.[15b] To our knowledge, formation of acetophenone from α-fluoroacetophene by reaction with triphenyltin hydride, reported by Tanner *et al.*,[15c] is the only known example of fluorine abstraction. *a*) J. G. Noltes, G. J. M. Van der Kerk, *Chem. Ind.* (London), **1959**, 294; *b*) M. Pereyre, J-P. Quintard, A. Rahm, "Tin in Organic Synthesis," Butterworths & Co., Ltd., London, 1987, pp. 35—68; *c*) D. D. Tanner, G. E. Diaz, A. Potter, *J. Org. Chem.*, **50**, 2149 (1985).
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17) Chlorine and bromine add onto the carbon–carbon double bond of some α,β-unsaturated ketones, especially Δ^4- and Δ^1-3-ketones. The products have the usual *trans*-diaxial configuration of halogens and hence the addition should be electrophilic in nature. *a*) Bromine addition: D. N. Kirk, D. K. Patel, V. Petrow, *J. Chem. Soc.*, **1956**, 627; *b*) Chlorine addition: D. N. Kirk, D. K. Patel, V. Petrow, *J. Chem. Soc.*, **1956**, 1184. See also, D. N. Kirk, V. Petrow, *J. Chem. Soc.*, **1958**, 1334.
18) The additions of halogens (Cl_2, Br_2, and I_2) are stepwise reactions; that is, they proceed through intermediates (the corresponding halonium ions) in which only one of the two halogen atoms has become attached to the olefin. In classical examples, both the sodium salts of dimethylmaleic and fumaric acids gave, in addition to the α,β-dibromo acids, the monobrominated 4-membered lactone.[18a] Since the α,β-dibromo acids do not cyclize to the lactone under these conditions, it is evident that the addition involves cationic intermediates and hence is electrophilic in nature, even if electron-deficient olefins are used as the substrates. Further evidence for electrophilic halogen additions to electron-deficient olefins is provided in reference.[18b] *a*) P. D. Bartlett, D. S. Tarbell, *J. Am. Chem. Soc.*, **58**, 466 (1936); *b*) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry-Holt and Company, Inc., 1960, pp. 520—527.
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