Syntheses of 11β-fluorocholestan-3-one derivatives

Tej Vir Singh*, Jatinder Kapur, Keshav Rai Agnihotri† & Paloth Venugopalan

Department of Chemistry, Panjab University,
Chandigarh 160014, India

†University Science Instrumentation Centre, Panjab University,
Chandigarh 160014

Received 29 January 2002; accepted (revised) 5 June 2002

The stereoselective syntheses of 11β-fluorocholestan-3-one 4 are described starting from enone 1. During this process, hitherto unreported fluoro derivatives 5, 6 of cholestan-3-one have been synthesized. The enones 1, 2 and 3 on treatment with ‘FBr’ generated in situ from poly(pyridinium)hydrogenfluoride (PPHF) and N-bromosuccinimide (NBS) followed by tri-n-butyltinhydride give 11β-fluorocholestan-3-one derivatives 5, 6 and 4, respectively. The survival of C-F bond during hydrogenation of 6 in the presence of Wilkinson’s catalyst is a significant advantage of this methodology.

Fluorinated analogues of cholesterol are biologically active compounds that can act as mechanistic probes for the metabolism of cholesterol1. They are also potential synthons for a variety of fluorovitamin D3 derivatives2. Attention has already been paid to the synthesis of various fluorinated vitamin D3 derivatives3. However, 11β-fluorovitamin D3 and its precursors such as 11β-fluorocholesterol or 11β-fluorocholest-4-ene-3-one 4 have not yet been synthesised. The stereoselective placement of fluorne at the 11β-position makes the molecule unique and quite important, as the fluorne lies geometrically in the middle of the steroidal/secosteroidal skeleton and can act as an efficient probe for the entire molecule. Since C-F bond does not cleave during metabolic processes, the role of one or more of the rings A, B, C and D in 11β-fluorocholesterol and rings C and D of fluorovitamin D3 can precisely be studied to determine biological activities4.

The seminal problem in using these compounds as selective probes, however, stems from the difficulty in their synthesis. This arises mainly on two grounds, namely, (a) substitution of a C-11 hydroxy group with fluorine results in elimination5 leading to the formation of Δ9(11) ene; (b) though, steroids such as pregn-4,9(11)-dien-3,20-dione can selectively be fluorinated at C-116, it undergoes elimination of hydrogen fluoride7 during the elaboration of the required side chain to obtain analogues of cholesterol and vitamin D3. Besides this, the generation of a C4-C5 double bond8 selectively in a cis-fused A, B rings (5β series) of the steroid is a facile single step process, while it involves multiple steps in a trans-fused A, B rings (5α series) of natural steroids. This communication presents a synthetic methodology to overcome the above mentioned difficulties and describes a new synthesis of cholest-4-9(11)-dien-3-one 9 as well as the regio- and stereo-selective introduction of fluorne at C-11 position to obtain 11β-fluorocholestan-3-one derivatives 4-6 as potential synthons for 11β-fluorocholesterol and 11β-fluorovitamin D3.

The synthesis of cholest-4,9(11)-dien-3-one 3 from 5α-cholest-9(11)-en-3-one10 is outlined in Scheme I. The dehydrogenation of 1 (1 mmole) with 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ, 3 mmole) in 1,4-dioxane gave choles-ta-1,4,9(11)-trien-3-one 2 in 60% yield. Its 1H NMR spectrum exhibited three multiplets at δ 5.46 (1H), 6.0(2H) and 7.1(1H) corresponding to C1-H, C1-H, C2-H and C4-H respectively. The mass spectrum displayed the molecular ion peak at m/z 380 (M+, base peak). A solution of 2 in dry benzene (0.04 M) under slightly positive pressure of hydrogen gas in the presence of tris(triphenylphosphine)chlororhodium (0.29 mole equivalent)11 gave 3 in 83% yield. The structure formula of 3 was confirmed by spectral data and melting point. Of all the published procedures9, our process is the most direct and provides the highest yield for 3 and is the only process which proceeds without protection and deprotection of functional group(s) starting from 5α-cholestan-3β-ol.

The dienone 3 (3.8 mmole) was allowed to react with NBS (7.6 mmole) and PPHF (12 mL)12 in THF at 0°C for 4 hr. The reaction mixture was treated with ice-cold liquor ammonia and extracted with ether to afford 9α-bromo-11β-fluoroenoene. This on reduction with tri-n-butyltin hydride (1.1 equiv.) in refluxing THF containing AIBN gave 11β-fluorocholest-4-en-3-one 4 in 79% yield.

The stereochemistry of fluorne was confirmed by X-ray crystallography11 (Figure 1). The addition of
Scheme I. Synthesis of 3 and 1β-fluorocholestan-3-one derivatives. Reagents and conditions: (a) PPHF/NBS in THF at 0-5 °C, 4-8 hr; n-Bu3SnH, AIBN in THF, reflux 4-7 hr; (b) DDQ in 1,4 dioxane, reflux 20-27 hr; (c) H2 (1 atm.), (PPh3)RhCl in benzene, 4-6 hr.

The sequence of steps is not strict for the general transformations depicted in Scheme I. The hydrogenation at Δ1,2 C-C double bond in the presence of Wilkinson’s catalyst can be carried out with or without the introduction of fluorine. Very mild conditions (slight positive pressure of hydrogen) suffice for the

Figure 1—A perspective view of 4 (thermal ellipsoids are at 50% probability level) with atom numbering scheme.
reduction of C-C double bond. The C-F bond is not attacked under these conditions and this selectivity (6 to 4) obviates the need of introduction of fluorine after C-C bond reduction.

In summary, we report a convenient and effective synthesis of 11β-fluorocholestan-3-one 4, a key synthone for 11β-fluoro-vitamin D₃ besides fluorosteroids 5 and 6. By this strategy, stereoselective introduction of fluorine at C-11 of a steroidal skeleton is achieved in fairly good yield and once transformed to the synthetic analogues of vitamin-D₃, novel and interesting binding properties and biological activities can be investigated.

Acknowledgement

Authors are grateful to the CSIR, New Delhi for financial support of this work.

References and Notes

(b) Ringold H J, & Turner A B Chem Ind (London), 1962, 211.
9 (a) Schneider J J, Tetrahedron, 28, 1972, 2717.
10 Cholest-9(11)ene-3-one 1 can be readily obtained in overall yield of 52% from 5α-cholestan-3-ol using Breslow’s procedure of remote functionalization followed by Jones oxidation (Breslow R, Corcoran R J, Snider B B, Doll R J, Khanna P L & Kaleya R, J Am Chem Soc, 99, 1977, 905).
13 Crystal data for 4: C₃₀H₃₆OF, M,=402.61, Orthorhombic, P2₁2₁2₁, a=6.2341(1), b=15.0702(2), c=26.1923(3)Å, V=2460.6(6) Å³, Z=4, MoKα, λ=0.71073Å, µ=0.068 mm⁻¹, F(000)=888, ρcal=1.087Mg/m³, T=293(1) K, R=0.0647, wR=0.1703 for 1311 reflections [F>4(J(F))].
14 Selected physical data for 4: white solid (recrystallized from methanol) mp 100-101.5°C, ¹H NMR (CDCl₃,300MHz): δ 0.86 (d, 3H, 18-Me, J₈=6.2 Hz), 1.36 (d, 3H, 19-Me, J₈=3.7 Hz), 5.04 (dd, 1H, 11-H; J₈=48.6 Hz, J₉=2.3Hz), 5.76 (s, 1H, 4-H); ¹³C NMR (CDCl₃, 90MHz): δ =-177 ppm; exact mass calculated for C₃₀H₃₆OF m/z 402.329, found 402.332, 5: mp 129-30.5°C; ¹H NMR (CDCl₃): δ 0.91 (d, 3H, 18-Me, J₈=6.4 Hz), 1.18 (d, 3H, 19-Me, J₈=3.4 Hz), 5.02 (dd, 1H, 11-H; J₈=48 Hz, J₉=2.7 Hz); ¹³C NMR (CDCl₃): δ=-176.35 ppm, exact mass calculated for C₃₀H₃₆OF m/z 404.3454, found 404.3458, 6: mp 152-154°C; ¹H NMR (CDCl₃): δ 0.91 (d, 3H, 18-Me, J₈=6.3 Hz), 1.37 (d, 3H, 19-Me, J₈=3.05 Hz), 5.07 (dd, 1H, 11-H; J₈=48 Hz, J₉=2.6 Hz), 6.04 (s, 1H, 4-H), 6.28 (d, 1H, 2-H, J₈=10 Hz), 7.19 (d, 1H, 1-H, J₈=10 Hz); ¹³C NMR (CDCl₃): δ=-177 ppm, exact mass calculated for C₂₇H₄₁OF m/z 400.3141, found 404.3141.