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SYNTHESIS OF *(25R S)*-26-FLUORO-5-CHOLESTEN-3β 25-DIOL 3-ACETATE AND ITS 27-ALKYL C_1-C_3 HOMOLOGUES FROM METHYL 3β-HYDROXY-5-CHOLENOATE INVOLVING ALLENE OXIDE FOR INTRODUCTION OF FLUORINE

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SUMMARY

(25R S)-26-Fluoro-25-hydroxy cholesterol 1a *and its 27-alkyl homologues* 1b-d *were synthesized from methyl 3β-hydroxy-5-cholenoate* 2 *Fluorine was introduced at the C-26 position of the side-chain via the reaction of allene oxide* 7 *with tetrabutylammonium fluoride trihydrate Addition of alkyl magnesium halides to the C-25 carbonyl group of fluoroketone* 8 *yielded (25R S)-25-hydroxy-26-fluoro-27-alkyl derivatives* 10-14

INTRODUCTION

Cholesterol derivatives are suitable precursors for the synthesis of vitamin D_3 analogues *via* a conventional route 5-ene → 5 6-diene → previtamin D_3 → vitamin [1] Owing to recent interest in vitamins D_2 and D_3 which induce differentiation of leukemic cells [2] much effort has been directed [3] towards synthesizing new analogues for possible therapeutic application In a search for a compound having a strong effect on leukemic cell differentiation but without the typical vitamin D activity (*i e* elevation of serum levels of calcium and phosphorus for bone formation) deactivation

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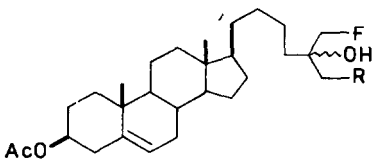
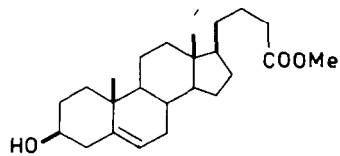
of the biologically active forms [2a 4] of vitamins D by introducing fluorine atoms into the molecule has been proposed Fluorination of side-chains has led [5] to various vitamin D_2 and D_3 analogues and is an effective tool for vitamin D activity modification

Bearing this in mind in our laboratory studies were initiated to modify vitamin D_3 by introduction of a fluorine atom(s) into these positions in the side-chain which are involved in D_3 biological activity This paper presents a novel mild method for the synthesis of *(25R S)*-26-fluoro-5-cholesten-3ß 25-diol 3-acetate 1a and its versatile 27-alkyl homologues 1b-d as cholesterol-type precursors of 25-hydroxy-26-fluoro vitamin D_3 and its 27-alkyl analogues from methyl 3ß-hydroxy-5-cholenoate 2 (scheme 1)



1 a) R=H b) R=Me
c) R=Et d) R=n-Pr



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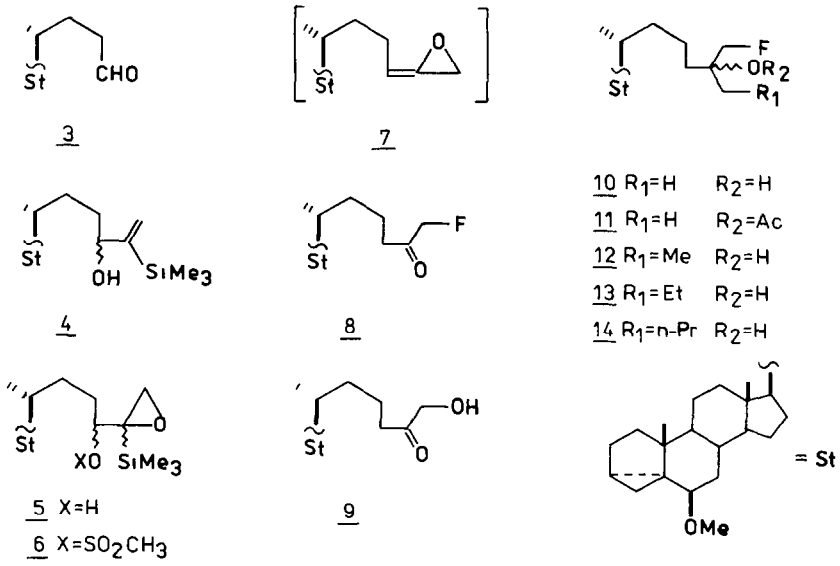
SCHEME 1

RESULTS

Treatment of 6ß-methoxy-3α 5-cyclo-cholan-24-al 3 [6] (scheme 2) (obtained from commercially available [7] methyl 3ß-hydroxy-5-cholenoate 2) with 1-lithium-1-(trimethylsilyl) ethylene [8] in a tetrahydrofuran (THF) solution at -25 °C according to Chan s procedure [9] afforded allylic alcohols 4 (83% yield) as a mixture of epimers at C-24 in a 1 1 ratio The presence of epimers in adduct 4 was confirmed by its ^{1}H NMR spectrum in which signals of the angular methyl group (C-18) and of the methoxy group at C-6 appeared as two pairs of singlets at δ 0 715 & 0 721 and 3 321 & 3 322 ppm



SCHEME 2

respectively The lack of stereoselectivity in this reaction was not surprising because of the absence of a stereocontrolling centre in the vicinity of the carbonyl group (C-24) This was of no importance as the epimeric centre at C-24 was eliminated in the next steps It is worth noting that the yield of vinyl silane addition to the aldehyde 3 was high in the presence [10] of boron trifluoride etherate (BF_3 Et_2O) in the reaction mixture In the absence of Lewis acid a mixture of products was obtained together with the decomposed carbonyl compound Oxidation [11] of the C(25-26) double bond of adduct 4 with tert-butyl hydroperoxide (t-BuOOH) and vanadyl acetylacetonate catalyst in benzene afforded diastereomeric epoxides 5 (94%) In the ^1H NMR spectrum of compound 5 protons of the C(25-26) epoxide appeared at δ 2 927 ppm /one proton, doublet, J(H-H) gem=4 98 Hz/ and at δ 2 574 & 2 576 ppm /one proton two doublets, each with J(H-H)gem=4 98 Hz/

For introduction of fluorine at C-26 our new method [12] involving the synthesis of α-fluoromethyl ketones *via* allene oxides was used For this purpose the conversion of the hydroxyl group in the C-24 position of compound 5 into a good leaving group was required Accordingly alcohol 5 was treated with methanesulphonyl chloride (MsCl) in a dichloromethane solution yielding mesylates 6 in a nearly quantitative yield Compound 6 was used to obtain unstable allene oxide 7 whereupon fluoroketone 8 was formed The synthesis of 8 from 6 required at least 2 moles of fluoride *per* 1 mol of 6 Treatment of compound 6 (1 mol) with tetrabutylammonium fluoride trihydrate (2 5 moles) in THF at room temperature afforded fluoroketone 8 in a 75% yield The product of this reaction 6β-methoxy-26-fluoro-27-nor-3α 5-cyclo-5α-cholestan-25-one 8 showed in the IR spectrum characteristic absorption of the C=O group (1730 cm^{-1}), and in its ^1H NMR spectrum - a doublet of two C-26 protons at δ 4 79 ppm with geminal coupling constant J(H-F)=47 72 Hz A by-product hydroxyketone 9 (6%) [IR 3500 and 1730 cm^{-1} ^1H NMR 4 23 /2H d J(H-H)= 4 47 Hz, C-26/ 2 51 (2H m C-24)] formed by the reaction of water (from TBAF $3H_2O$) with allene oxide 7 was isolated from the reaction mixture

The above synthesis of fluoroketone 8 from 6 was the key step in the preparation of the title compounds Addition of an appropriate alkylmagnesium halide to the C-25 carbonyl group of 8 completed the syntheses of 26-fluoro-25-hydroxy cholesterol 10 and its homologues 12-14 hovewer because of the non-stereospecificity of the method for introduction of C-27 alkyl substituents the products were obtained as a mixture of epimers at C-25

Treatment of fluoroketone 8 with methylmagnesium iodide (MeMgI) in Et_2O at room temperature gave *(25R S)*-6β-methoxy-26-fluoro-3α 5-cyclo-5α-cholestan-25-ol 10 in a 89% yield For additional characterization compound 10 was acetylated with acetic anhydride (Ac_2O) in pyridine (Py) and using a 4-dimethyl aminopyridine (DMAP) catalyst during 3 days at room temperature to give acetate 11 In the ^1H NMR spectrum of 11 singlets at δ 0 717 1 022 2 020 and 3 323 ppm corresponded to the signals of the C-18 and C-19 angular methyl groups and acetoxy (C-25)

and methoxy (C-6) groups respectively but the C-27 methyl group signal appeared as two singlets at δ 1 441 and 1 445 ppm in a 1 1 ratio indicating the presence of an epimeric centre In the next step the cyclo-compound 10 was converted into the title *(25R S)*-26-fluoro-5-cholesten-3ß 25-diol 3-acetate 1a by treatment with acetic acid and BF_3 Et_2O in anhydrous Et_2O according to the procedure [13] of Hosoda *et al*

The Grignard reaction of fluoroketone 8 with other alkyl magnesium reagents ethylmagnesium bromide (EtMgBr), n-propylmagnesium bromide (n-PrMgBr) and n-butylmagnesium iodide (n-BuMgI) also gave high yields of *(25R S)*-27-alkyl-(methyl ethyl and propyl)-25-hydroxy cholesterol homologues 12 13 and 14 After regeneration of the C(5-6) double bond 3ß-acetoxy-$\Delta^{5\ 6}$-derivatives 1b-d were obtained

Summing up the presented method allowed for transformation with a high yield of methyl 3ß-hydroxy-5-cholenoate 2 into *(25R S)*-25-hydroxy cholesterol derivatives 1a-d with the fluorine atom located at C-26 of the side-chain Thus the synthesized cholesterol derivatives may serve as precursors of new analogues of 25-hydroxy-26-fluoro vitamin D_3 which can be expected to be potent factors regulating the calcium and phosphorus metabolism and/or anti-leukemic activity

EXPERIMENTAL

Melting points were recorded on Kofler hot-stage apparatus and are uncorrected The spectra were recorded using the following units IR spectra - Beckman 4240 or Unicam SP 200 ^1H NMR spectra - Bruker AM 500 (in a $CDCl_3$ solution) mass spectra (high resolution and at 70 eV ionisation potential) - Finnigan MAT 8200 Chemical shifts were reported in δ units (ppm) downfield shift from Me_4Si, they are denoted as s - singlet d - doublet t - triplet m - multiplet brs - broad singlet dd - double doublet Column chromatography was performed on Kieselgel 60 (70-230 mesh) Merck and TLC - on aluminium sheets Kieselgel 60 - Merck Organic solutions were

dried over anhydrous $MgSO_4$ and solvents were evaporated under reduced pressure on a rotary evaporator Yields refer to homogeneous products (TLC) Elementary analyses were performed in our anlytical laboratory

(24R,S)-6ß-methoxy-25-trimethylsilyl-27-nor-3α,5-cyclo-5α-cholest-25-en-24-ol 4

To a solution of 1-lithium-1-(trimethylsilyl)ethylene in THF (20 ml) which was prepared under argon from 1-bromovinyl-trimethylsilane (1 49 g, 8 33 mmol) and n-BuLi (5 2 ml of a 1 6 M solution in hexane 8 33 mmol) at -20 °C a solution of 6ß-methoxy-3α 5-cyclo-5α-cholan-24-al 3 (1 5 g, 4 17 mmol) and BF_3 Et_2O (592 mg 4 17 mmol) in THF (8 ml) was added The reaction mixture was stirred at -25 °C for 1 h whereupon the temperature was slowly (*ca* 1 h) raised to 25 °C The product was extracted with Et_2O (50 ml) the ether solution was washed successively with saturated $NaHCO_3$ and water and then it was dried After evaporation of solvent the residue was chromatographed on a silica gel column (30 g) with hexane-Et_2O - (93 7) as eluate to afford vinyl alcohol 4 (1 63 g 83%), m p =65-74 °C (hexane-Et_2O)

IR ($CHCl_3$) 3450 (OH) 1250 ($SiMe_3$) cm^{-1}

^1H NMR δ 0 142 /9H s $Si(CH_3)_3$/ 0 429 /1H dd J_1(H-H)= 5 10 Hz J_2(H-H)=7 99 Hz cyclopropyl-H/ 0 645 /1H dd J_1(H-H)=4 74 Hz J_2(H-H)=4 65 Hz cyclopropyl-H/ 0 715 and 0 721 (3H 2s 18-H) 0 928 (3H d J=6 57 Hz 21-H) 1 021 (3H s 19-H) 2 77 (1H t J=2 72 Hz 6-H) 3 321 and 3 322 (3H 2s OCH_3) 4 21 (1H brs 24-H) 5 41 and 5 77 (2H 2m, 26-H)

m/e 472 (M^+ 68%) 457 (M-15 53%) 440 (M-32 60%) 417 (M-55 83%) 73 (100%)

High resolution for $C_{30}H_{52}O_2Si$ calculated - 472 3736
found - 472 3736

Elemental analysis for $C_{30}H_{52}O_2Si$ calc C-76 21% H-11 09%
found C-76 48% H-11 26%

(24R,S),(25R,S)-6ß-methoxy-25-trimethylsilyl-25,26-epoxy-27-nor-3α,5-cyclo-5α-cholestan-24-ol 5

A solution containing vinyl alcohol 4 (1.23 g, 2.61 mmol), t-BuOOH (1.3 ml of 3.0 M solution in toluene, 3.91 mmol), vanadyl acetylacetonate (10 mg), and benzene (15 ml) was stirred at room temperature for 1 h. Then the solvent was evaporated *in vacuo* and the residue was chromatographed on a silica gel column (30 g) with hexane-Et_2O (93:7) as eluate, to give epoxide 5 as an oil (1.2 g, 94%).
IR (film): 3500 (OH), 1250 ($SiMe_3$) cm^{-1};
^1H NMR, δ: 0.097 /9H, s, $Si(CH_3)_3$/, 0.430 /1H, dd, J_1(H-H)= 5.09 Hz, J_2(H-H)=7.98 Hz, cyclopropyl-H/, 0.645 /1H, dd, J_1(H-H)=4.83 Hz, J_2(H-H)=4.68 Hz, cyclopropyl-H/, 0.718 and 0.728 (3H, 2s, 18-H), 0.929 and 0.931 (3H, 2d, J=6.59 Hz, 21-H), 1.022 (3H, s, 19-H), 2.574 and 2.576 (1H, 2d, J=4.98 Hz, 26-H), 2.77 (1H, t, J=2.77 Hz, 6-H), 2.927 (1H, d, J=4.98 Hz, 26-H), 3.320 and 3.323 (3H, 2s, OCH_3), 3.809 (1H, t, J=10.48 Hz, 24-H);
m/e: 488 (M^+, 34%), 437 (M-15, 29%), 456 (M-32, 19%), 433 (M-55, 51%), 253 (80%), 73 (100%);
High resolution: for $C_{30}H_{52}O_3Si$ calculated - 488.3685
found - 488.3685

(24R,S),(25R,S)-6ß-methoxy-25-trimethylsilyl-25,26-epoxy-27-nor-3α,5-cyclo-5α-cholestan-24-ol methanesulphonyl ester 6

To a cold (-10 °C) solution containing alcohol 5 (1.1 g, 2.25 mmol) and Et_3N (376 µl, 2.7 mmol) in anhydrous CH_2Cl_2 (10 ml), methanesulphonyl chloride (209 µl, 2.7 mmol) was slowly added. The reaction mixture was stirred for 1 h, whereupon water was added and the product was extracted with CH_2Cl_2. The organic layer was washed successively with water, 5% HCl and saturated $NaHCO_3$, and then it was dried. After evaporation of solvent, the residue was chromatographed on a silica gel column (30 g) with hexane-Et_2O (92:8) as eluate, to afford mesylate 6 (1.22 g, 96%) as an oil.
IR ($CHCl_3$): 1250 ($SiMe_3$) cm^{-1};

^{1}H NMR, δ: 0.139 and 0.144 /9H, 2s, $Si(CH_3)_3$/, 0.430 /1H, dd, J_1(H-H)=5.15 Hz, J_2(H-H)=7.80 Hz, cyclopropyl-H/, 0.646 /1H, dd, J_1(H-H)=4.23 Hz, J_2(H-H)=4.35 Hz, cyclopropyl-H), 0.717 and 0.722 (3H, 2s, 18-H), 0.930 and 0.935 (3H, 2d, each J=6.57 Hz, 21-H), 1.020 (3H, s, 19-H), 2.646 and 2.648 (1H, 2d, each J=4.95 Hz, 26-H), 2.77 (1H, m, 6-H), 2.903 (1H, d, J=4.98 Hz, 26-H), 3.030 (3H, 2s, OSO_2CH_3), 3.320 and 3.321 (3H, 2s, OCH_3), 4.450 (1H, dd, J_1=2.97 Hz, J_2=8.88 Hz, 24-H);
m/e: 566 (M^+, 87%), 551 (M-15, 46%), 533 (M-33, 73%), 511 (M-55, 69%), 253 (96%), 73 (100%);
High resolution: for $C_{31}H_{54}O_5SSi$ calculated - 566.3461
found - 566.3461

6β-methoxy-26-fluoro-27-nor-3α,5-cyclo-5α-cholestan-25-one 8, and
6β-methoxy-26-hydroxy-27-nor-3α,5-cyclo-5α-cholestan-25-one 9

To a solution of compound 6 (920 mg, 1.63 mmol) in THF (30 ml), a solution of TBAF·$3H_2O$ (1.28 g, 4.06 mmol) in THF (5 ml) was added as one portion. The reaction mixture was stirred at room temperature for 15 min., whereupon water was added and solution was extracted with Et_2O. The ether layer was washed 4 times with water and dried. After evaporation of solvent, the residue was chromatographed on a silica gel (30 g) column, with:

a) hexane-Et_2O (94:6), to give fluoroketone 8 (509 mg, 75%) as a glass;
IR ($CHCl_3$): 1730 cm^{-1};
^{1}H NMR, δ: 0.430 (1H, dd, J_1=5.04 Hz, J_2=6.62 Hz, cyclopropyl-H), 0.646 (1H, dd, J_1=4.79 Hz, J_2=4.65 Hz, cyclopropyl-H), 0.715 (3H, s, 18-H), 0.935 (3H, d, J=6.58 Hz, 21-H), 1.021 (3H, s, 19-H), 2.51 (2H, m, 24-H), 2.77 (1H, t, J=2.79 Hz, 6-H), 3.323 (3H, s, OCH_3), 4.791 (2H, d, J(H-F)=47.72 Hz, 26-H);
m/e: 418 (M^+, 74%), 403 (M-15, 58%), 386 (M-32, 95%), 363 (M-55, 100%);
High resolution: for $C_{27}H_{43}O_2F$ calculated - 418.3247
found - 418.3247

Elemental analysis for $C_{27}H_{43}O_2F$ calc C-77 47% H-10 35%
found C-77 36% H-10 51%

b) hexane-Et_2O to give 9 (41 mg 6%) as an oil
IR ($CHCl_3$) 3500 (OH) 1730 (C=O) cm^{-1}
^1H NMR δ 0 431 /1H dd J_1(H-H)=5 11 Hz J_2(H-H)=7 95 Hz cyclopropyl-H/ 0 647 /1H dd J_1(H-H)=4 91 Hz J_2(H-H)=4 85 Hz cyclopropyl-H/ 0 713 (3H s 18-H) 0 930 (3H d J=6 58 Hz 21-H) 1 021 (3H s 19-H) 2 37 (2H m 24-H) 2 76 (1H t J=2 78 Hz 6-H) 3 323 (3H s OCH_3) 4 238 (2H d J=4 47 Hz 26-H)
m/e 416 (M^+ 73%) 401 (M-15 64%) 384 (M-32 100%) 361 (M-55 98%)
High resolution for $C_{27}H_{44}O_3$ calculated - 416 3290
found - 416 3290
Elemental analysis for $C_{27}H_{44}O_3$ calc C-77 84% H-10 65%
found C-77 68% H-10 71%

General procedure for the Grignard reaction of fluoroketone 6 with alkylmagnesium halides

Typically to a solution of alkylmagnesium halide prepared from magnesium (3 6 mg 0 15 mmol) and alkyl halide (0 15 mmol) in Et_2O (1 ml) a solution of fluoroketone 8 (42 mg 0 1 mmol) in Et_2O (1 ml) was added at room temperature The reaction mixture was stirred at room temperature for 30 min , whereupon a saturated solution of ammonium chloride was added and the product was extracted with Et_2O The organic layer was washed with water and dried The following compounds were obtained by the above procedure

a) with methyl magnesium iodide
(25R,S)-6ß-methoxy-26-fluoro-3α,5-cyclo-5α-cholestan-25-ol 10
(86% yield) m p =155-159 °C (hexane-Et_2O)
IR (KBr) 3450 (OH) cm^{-1}
^1H NMR, δ 0 430 /1H, dd J_1(H-H)=5 17 Hz J_2(H-H)=7 92 Hz cyclopropyl-H/ 0 648 /1H dd J_1(H-H)=4 11 Hz J_2(H-H)=4 54 Hz cyclopropyl-H/ 0 717 (3H s 18-H) 0 932 (3H d J=6 56 Hz 21-H) 1 022 (3H s 19-H) 2 77 (1H t J=2 51 Hz 6-H) 3 323 (3H s, OCH_3) 4 214 and 4 232 /dd J(H-H)=19 13 Hz, J(H-F)=47 78 Hz 26-H of one epimer/, 4 212 and 4 230 /dd

J(H-H)=16 27 Hz J(H-F)=47 76 Hz 26-H of the second epimer integration of both epimers = 2H/,
m/e 434 (M^+ 92%) 419 (M-15 62%) 402 (M-32 100%), 379 (M-55 96%)
High resolution for $C_{28}H_{47}O_2F$ calculated - 434 3560
found - 434 3560
Elemental analysis for $C_{28}H_{47}O_2F$ calc C-77 37% H-10 90%
found C-77 43% H-11 04%

b) with ethylmagnesium bromide
(25R,S)-6ß-methoxy-26-fluoro-27-methyl-3∝ 5-cyclo-5∝-cholestan 25-ol 12
(82% yield) m p =133-137 °C (hexane-Et_2O),
IR (Nujol) 3500 (OH) cm^{-1}
^1H NMR δ 0 430 /1H dd J_1(H-H)=5 05 Hz J_2(H-H)=7 98 Hz cyclopropyl-H/ 0 647 /1H dd J_1(H-H)=4 63 Hz J_2(H-H)=4 52 Hz cyclopropyl-H/ 0 715 (3H s 18-H) 1 022 (3H s 19-H) 2 77 (1H t J=2 75 Hz, 6-H) 3 323 (3H s OCH_3) 4 267 /2H d J(H-F)=47 73 Hz 26-H/,
m/e 448 (M^+, 97%), 433 (M-15 61%) 416 (M-32, 100%) 393 (M-55 94%)
High resolution for $C_{29}H_{49}O_2F$ calculated - 448 3717
found - 448 3717
Elemental analysis for $C_{29}H_{49}O_2F$ calc C-77 63% H-11 01%
found C-77 89% H-10 95%

c) with n-propylmagnesium bromide
(25R,S)-6ß-methoxy-26-fluoro-27-ethyl-3∝,5-cyclo-5∝-cholestan-25-ol 13
(80% yield), m p =124-129 °C (hexane-Et_2O),
IR ($CHCl_3$) 3600 (OH) cm^{-1}
^1H NMR δ 0 430 /1H dd J_1(H-H)=4 92 Hz, J_2(H-H)=7 98 Hz cyclopropyl-H/ 0 646 /1H dd J_1(H-H)=4 72 Hz J_2(H-H)=4 65 Hz cyclopropyl-H/ 0 715 (3H, s 18-H) 1 022 (3H s 19-H) 2 77 (1H t J=2 73 Hz 6-H) 3 323 (3H s OCH_3) 4 255 and 4 258 /2H 2d each J(H-F)=47 76 Hz 26-H/
m/e 462 (M^+ 19%) 447 (M-15 10%) 430 (M-32 18%) 215 (41%) 57 (100%)
High resolution for $C_{30}H_{51}O_2F$ calculated - 462 3872
found - 462 3872
Elemental analysis for $C_{30}H_{51}O_2F$ calc C-77 87%, H-11 11%
found C-77 92% H-11 04%

d) with n-butylmagnesium iodide

(25R S)-6ß-methoxy-26-fluoro-27-propyl-3∝,5-cyclo-5∝-cholestan 25-ol 14

(76% yield) m p =68-73 °C (hexane)
IR (Nujol) 3450 (OH) cm^{-1}
^1H NMR δ 0 430 /1H dd J_1(H-H)=5 01 Hz J_2(H-H)=7 88 Hz cyclopropyl-H/ 0 646 /1H dd J_1(H-H)=4 08 Hz J_2(H-H)=4 32 Hz cyclopropyl-H/ 0 716 (3H, s 18-H) 1 022 (3H s 19-H) 2 77 (1H m 6-H) 3 323 (3H, s OCH_3) 4 257 and 4 260 /2H, 2d each J(H-F)=47 75 Hz 26-H/
m/e 476 (M^+ 43%) 461 (M-15 30%) 444 (M-32 47%) 421 (M-55 44%) 57 (100%)
High resolution for $C_{31}H_{53}O_2F$ calculated - 476 4030
found - 476 4030
Elemental analysis for $C_{31}H_{52}O_2F$ calc C-78 10% H-11 21%
found C-77 92% H-11 28%

(25R,S)-6ß-methoxy-26-fluoro-3∝,5-cyclo-5∝-cholestan-25-ol 25-acetate 11

Alcohol 10 (8 mg 0 02 mmol) was acetylated with Ac_2O (1 ml) in pyridine (2 ml) at room temperature, in the presence of DMAP (1 mg) during 3 days Standard work-up afforded acetate 11 (8 mg 88%) as an oil
IR ($CHCl_3$) 1740 (C=O) cm^{-1}
^1H NMR δ 0 430 /1H, dd J_1(H-H)=5 07 Hz J_2(H-H)=7 95 Hz cyclopropyl-H/ 0 646 /1H dd J_1(H-H)=4 83 Hz, J_2(H-H)=4 72 Hz cyclopropyl-H/ 0 717 (3H s 18-H) 0 914 (3H d J=6 56 Hz 21-H) 1 022 (3H, s 19-H) 1 441 and 1 445 (3H 2s 27-H) 2 020 (3H, s, $OCOCH_3$) 2 77 (1H t J=2 73 Hz, 6-H), 3 323 and 3 327 (3H 2s OCH_3) 4 522 and 4 542 /dd, J(H-H)=13 05 Hz J(H-F)=47 39 Hz 26-H of one epimer/ 4 521 and 4 540 /dd J(H-H)=11 56 Hz, J(H-F)=47 38 Hz 26-H of the second epimer, integration of both isomers = 2H/,
m/e 476 (M^+ 82%) 461 (M-15, 53%) 444 (M-32 71%) 421 (M-55 83%) 384 (35%) 55 (94%) 43 (100%)
High resolution for $C_{30}H_{49}O_3F$ calculated - 476 3666
found - 476 3666
Elemental analysis for $C_{30}H_{49}O_3F$ calc C-75 59%, H-10 36%
found C-75 67% H-11 41%

Typical procedure for regeneration of the C(5-6) double bond in 3α 5-cyclo-6ß-methoxy derivatives

Typically a solution containing the cyclo-compound (0 05 mmol) BF_3 Et_2O (0 3 ml) and AcOH (0 3 ml) in anhydrous Et_2O (2ml) was stirred at room temperature for 30 min whereupon water was added and the product was extracted with Et_2O The ether layer was washed successively with water and saturated $NaHCO_3$ whereupon it was dried After evaporation of solvent the residue was purified by column chromatography on a silica gel column (5 g) with hexane-Et_2O as eluent The following compounds were obtained by the above procedure

a) *(25R,S)-26-fluoro-5-cholesten-3ß,25-diol* 3-acetate 1a

(79% yield) m p =123-128 °C (hexane-Et_2O) eluent hexane-Et_2O (93 7)

IR (Nujol) 3450 (OH) 1730 (C=O) cm^{-1}

^1H NMR δ 0 678 (3H s 18-H) 0 931 (3H d J=6 57 Hz 21-H) 1 019 (3H s 19-H) 2 031 (3H s $OCOCH_3$) 4 214 and 4 232 /dd J(H-H)=18 77 Hz J(H-F)=47 77 Hz 26-H of one epimer/ 4 212 and 4 230 /dd J(H-H)=16 88 Hz J(H-F)=47 79 Hz 26-H of the second epimer/, 4 61 (1H m 3-H) 5 37 (1H m 6-H)

m/e 462 (M^+ 1%) 402 (M-60 100%) 378 (M-75 10%)

High resolution for $C_{29}H_{47}O_3F$ calculated - 462 3509
found - 462 3509

Elemental analysis for $C_{29}H_{47}O_3F$ calc C-75 28% H-10 24%
found C-75 39% H-10 27%

b) *(25R,S)-26-fluoro-27-methyl-5-cholesten-3ß 25-diol* 3-acetate 1b

(81% yield) m p =96-99 °C (hexane-Et_2O) eluent hexane-Et_2O (95 5)

IR ($CHCl_3$) 3600 (OH) 1730 (C=O) cm^{-1},

^1H NMR δ 0 677 (3H s 18-H) 1 019 (3H s 19-H) 2 031 (3H s $OCOCH_3$) 4 265 /2H d J(H-F)=47 72 Hz 26-H/ 4 61 (1H m 3-H) 5 37 (1H m 6-H)

m/e 416 (M-AcOH 100%), 401 (M-75 11%) 57 (60%)

High resolution for $C_{28}H_{45}OF$ (M-AcOH) calculated - 416 3454
found - 416 3454

Elemental analysis for $C_{30}H_{49}O_3F$ calc C-75 59% H-10 36%
found C-75 33% H-10 42%

c) *(25R S)*-26-fluoro-27-ethyl-5-cholesten-3ß,25-diol 3-acetate 1c

(76% yield) an oil eluent hexane-Et_2O (95 5)
IR ($CHCl_3$) 3600 (OH) 1735 (C=O) cm^{-1}
^1H NMR δ 0 678 (3H s 18-H) 1 019 (3H s 19-H) 2 031 (3H s $OCOCH_3$) 4 257 and 4 259 /2H 2d each J(H-F)=47 74 Hz 26-H/ 4 61 (1H, m 3-H) 5 37 (1H m 6-H)
m/e 430 (M-AcOH 31%) 57 (100%)
High resolution for $C_{29}H_{47}OF$ (M-AcOH) calculated - 430 3611
found - 430 3611
Elemental analysis for $C_{31}H_{51}O_3F$ calc C-75 88% H-10 48%
found C-75 76%, H-10 55%

d) *(25R,S)*-26-fluoro-27-propyl-5-cholesten-3ß,25-diol 3-acetate 1d

(73% yield) an oil eluent hexane-Et_2O (93 7)
IR ($CHCl_3$) 3600 (OH) 1735 (C=O) cm^{-1}
^1H NMR, δ 0 678 (3H s 18-H) 1 019 (3H s 19-H) 2 032 (3H s $OCOCH_3$) 4 260 /2H d J(H-F)=47 75 Hz 26-H/ 4 61 (1H m 3-H) 5 37 (1H m 6-H)
m/e 504 (M^+ 0 6%) 444 (M-AcOH 100%) 57 (91%), 43 (94%)
High resolution for $C_{30}H_{49}OF$ (M-AcOH) calculated - 444 3767
found - 444 3767
Elemental analysis for $C_{32}H_{53}O_3F$ calc C-76 15% H-10 58%
found C-75 88% H-10 72%

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