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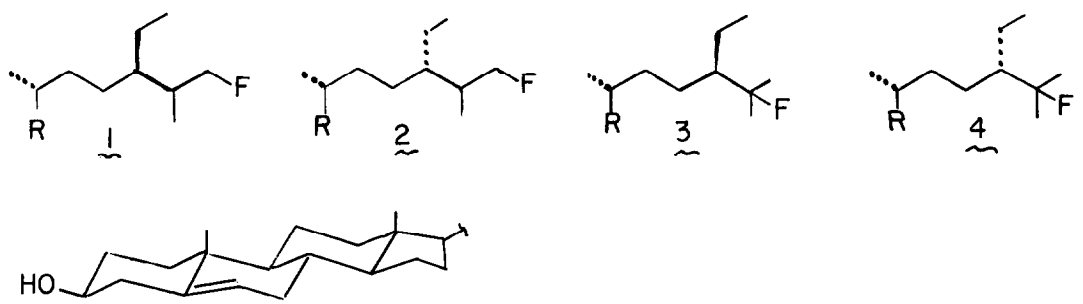
SIDE CHAIN MODIFIED STEROLS AS PROBES INTO INSECT MOLTING HORMONE METABOLISM. I: SYNTHESIS OF MONOFLUOROPHYTOSTEROLS

Toni B. Kline and Glenn D. Prestwich*
Department of Chemistry
State University of New York
Stony Brook, New York 11794

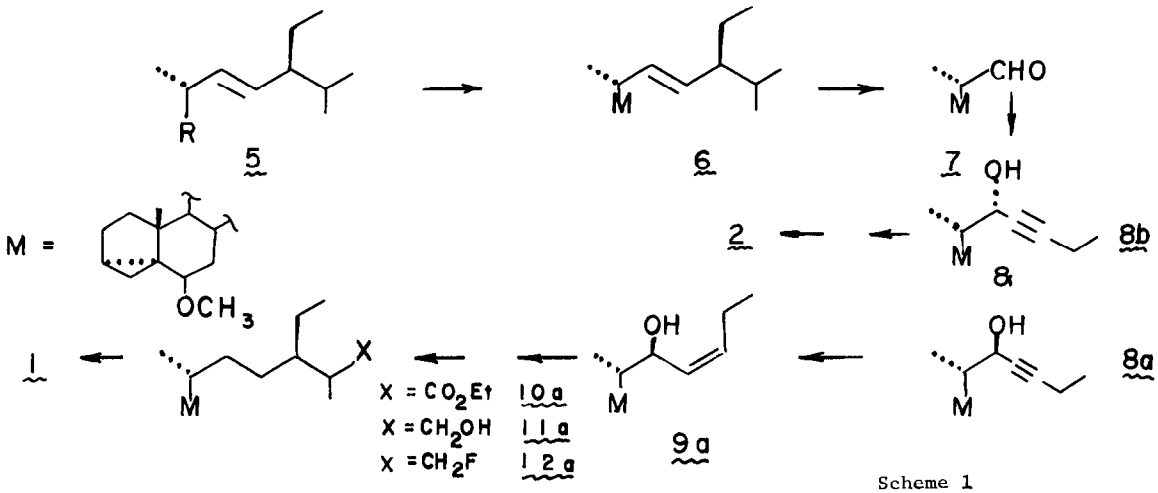
Summary: 25- and 26-monofluorophytosterols were synthesized from stigmasterol as potential arthropod-activated competitive inhibitors of side chain hydroxylations occurring in ecdysone biogenesis.

An attractive biosynthetic pathway for the design of arthropod-selective control agents is the conversion of dietary C_{28} and C_{29} sterols via cholesterol to the ecdysteroid molting hormones. This requires dealkylation at C-24, several oxidative steps in the sterol nucleus, and finally hydroxylation at C-20, 22, 25, and (in ovaries) 26 of the side chain.[1] We describe herein the synthesis of the monofluorophytosterols 1-4 designed to interfere with hydroxylation at C-25 and C-26.



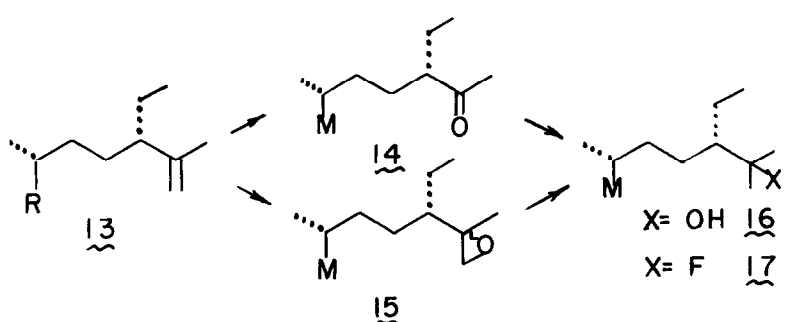
The preparation of 26-fluorositosterol (1, 24 R) and 26-fluoroclionosterol (2, 24 S) from stigmasterol (5) is shown in Scheme 1. Protection of the A/B ring as the iso-methyl

*Fellow of the Alfred P. Sloan Foundation (1981-1983) and Camille and Henry Dreyfus Teacher-Scholar (1981-1986). Address correspondence to this author.



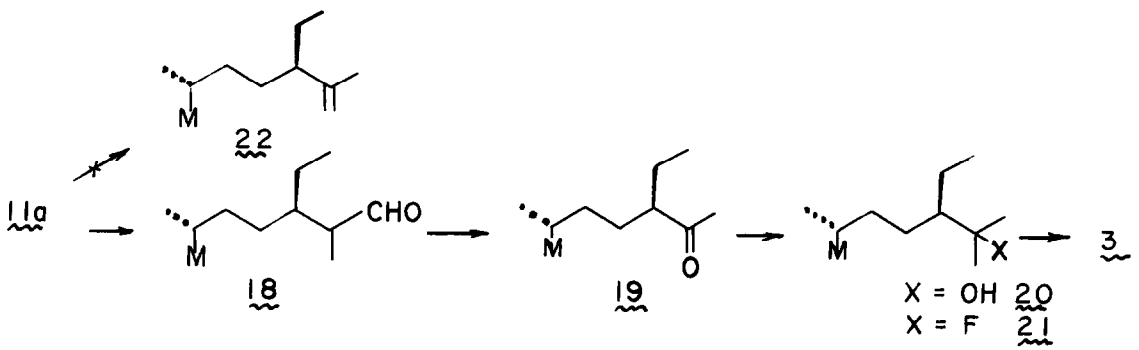
Scheme 1

ether 6 was followed by ozonolysis to aldehyde 7. Addition of the magnesium acetylide of 1-butyne gave a 1:1 mixture of propargylic alcohols 8a and 8b which were separated by flash chromatography (20% EtOAc-hexane). Each 8 was carried further as follows: Partial hydrogenation (H_2, Lindlar, EtOAc) of 8 and Claisen orthoester rearrangement of the resultant allylic alcohols 9 ($CH_3CH_2C(OEt)_3$, catalytic 2,4,6-trimethylbenzoic acid, xylene, 140°C) followed by hydrogenation of the resultant Δ^{22} esters (Pt, H_2, EtOAc) gave the C-26 esters 10 as an epimeric mixture at C-25. Reduction ($LiAlH_4$ in refluxing THF) of 10 followed by fluorination[4,5] (diethylaminodimethylaminosulfurdifluoride, CH_2Cl_2, -78°C) gave the 26-fluoro compounds[6] 12 in 42% yield (from 8). Regeneration of the steroid A/B ring was effected with pTsOH in 50% aqueous dioxane to give 1 and 2:[7] ^{1}H NMR of 1: δ5.4 (br d, 4 Hz, H-7), 4.3 (ddd, 48,8, 4 Hz, H-26), 3.5 (m, H-3), 2.0-0.5 (steroid envelope). ^{13}C (C_6D_6): δ141.3 (C-3), 126.7 (C-6), 86.7 (d, J_{C-F} = 170 Hz, C-26, 71.6 (C-3). EI-MS (70eV): m/z 432 (5.6%, M^+), 414 (M^+-HF), 107 (100% $C_8H_{11}^+$). HRMS: $C_{29}H_{49}OF$ requires 432.3768, found (1) 432.3795, (2) 432.3740. $[\alpha]_D$(1)= -32.8° (5.03%, $CHCl_3$).



Scheme 2

Clerosterol[8] (13) was elaborated to 25-fluoroclionosterol (4) according to Scheme II. Following A/B ring protection, two routes to the tertiary alcohol 16 were explored in anticipation of future biological tracer experiments: ozonolysis to 14 followed by Grignard reaction (10 equivalents of MeMgBr, THF, 4 h reflux) would permit introduction of ^{14}C; epoxidation (2 equivalents MCPBA/solid $NaHCO_3/CH_2Cl_2$, rt 3h) to 15 followed by hydride reduction ($LiAlH_4$ in refluxing Et_2O, 2h) would facilitate deuterium or tritium labelling. Overall yields from clerosterol iso-methylether to alcohol 16 were ca 50% for either pathway.[9] Fluorination with diethylaminosulfur trifluoride[4] (DAST, CH_2Cl_2, -78°C, 10 min, warm to rt) proceeds well on tertiary alcohols, and A/B ring deprotection completes the sequence to 4 in 65% yield from 16. ^1H NMR: δ5.25 (br s, H-6), 3.4 (m,H-3), 1.2 (d, 22 Hz, H-26,27). ^{13}C NMR (C_6D_6): δ141.2 (C-5), 121.5 (C-6), 97.19 (d, 170 Hz, C-25), 71.6 (C-3). EI-MS (70 eV): m/z 432 (4.2%, M^+), 412 (10%), M^+-HF), 55 (100%). HRMS: $C_{29}H_{49}OF$ requires 432.3768, found 432.3745.



Scheme 3

Attempts to epimerize ketone 14 in order to obtain 25-fluorositosterol (3) were unsuccessful, and our attention was turned to intermediate alcohol 11a as the starting material for the 24 epimer of 4. Alcohol 11a proved remarkably resistant to a variety of dehydration methods,[10] but was easily oxidized (1.1 equivalent PCC, CH_2Cl_2, rt, 3h) to aldehyde 18 as shown in Scheme III.[11] Degradation[12] of 18 (0.5 equivalent DABCO, 0.02 equivalent $Cu(OAc)_2$-bipyridyl complex, O_2, DMF at 45°C, 48 h) to ketone 19 was followed by a sequence analogous[13] to the conversion of 14 to 4 to afford 3 in 27% yield (from 19). Results of feeding compounds 1-4 to the tobacco hornworm Manduca sexta will be reported elsewhere.

Acknowledgments. We thank the NIH for financial support (Grant AI-17031-01 TMP to G.D.P.) and Upjohn for a generous gift of stigmasterol.

References and Notes

1. H.H. Rees, T.G. Davis, L.N. Dinan, W.J.S. Lockley, and T.W. Goodwin, In "Progress in Ecdysone Research". J. Hoffmann, ed. Elsevier North Holland Biomedical Press. Amsterdam, 1980.

2. J. Wiersig, N. Waespe-Sarcevic, and C. Djerassi, J. Org. Chem. 44, 3374 (1979).

3. All 80 MHz ^{1}H NMR and 20 MHz ^{13}C NMR were obtained on a Varian CFT-20, using $CDCl_3$ as solvent and reference unless otherwise indicated. Values are reported in ppm downfield from δ (TMS) = 0. IR spectra were recorded on a Perkin-Elmer 727 Spectrophotometer as neat oils on NaCl plates. Low resolution mass spectra were obtained on a Hewlett Packard Model 5908A interfaced to an HP5710A gas chromatograph. HRMS were obtained on a MS-30 instrument using a DS-50 data system. Diagnostic spectral data are reported here.

4. W. Middleton, J. Org. Chem. 45, 574 (1975). C. Poulter, P. Wiggins and T. Plummer, J. Org. Chem. 46, 1532 (1981).

5. Attempted fluorinations with KF/18-crown-6/DMF, fluoroalkylamine reagent, diethylaminosulfurtrifluoride, HF-pyridine/triphenylphosphine/DEAD, or by displacement of the mesylate of 11 met with failure.

6. 11: ^{1}H NMR: δ 3.4 (dd, 2,6 Hz, H-26). ^{13}C δ 66.3 (C-26). IR: 3350 cm^{-1}. HRMS: $C_{30}H_{52}O_2$ requires 444.3967, found 444.3961. 12: ^{1}H NMR: δ 4.3 (ddd, 48, 8,6 Hz, H-26). ^{13}C NMR (C_6D_6): δ 95.6 (d, 170 Hz, C-26). EI-MS: m/z 446 (0.3%, M^+), 414 (M^+-MeOH), 145 (100%, $C_9H_{18}F^+$).

7. Crystals of each compound were obtained from ethanol: 1, mp121-124°C; 2, mp120-123°C; 4, 123-125°C. Diastereomeric mixtures at C-25 for 1 and 2 were not resolvable by gas chromatography (1% SP-2100, 3% SP-2401, 25m OV-101), although the Claisen conditions employed would be expected [2] to produce roughly equal amounts of C-25 epimers.

8. Clerosterol was purified by flash chromatography (10% EtOAc-hexane on silica gel) from the non-saponifiable lipids of Codium fragile collected on Long Island. Isolation and characterization: I. Rubenstein and L.J. Goad, Phytochem. 13, 481, 1974.

9. 14: ^{1}H NMR: δ 2.6 (m, H-24), 2.1 (s, H-26). ^{13}C NMR: δ 176.3 (C=O), 48.1 (C-26). HRMS: $C_{29}H_{48}O_2$ requires 428.3654, found 428.3643. 15: ^{1}H NMR: δ 2.4 (s, H-26). 16: ^{1}H NMR: δ 1.1 (s, H 26,27). IR: 3400 cm^{-1} (OH). HRMS: $C_{30}H_{52}O_2$ requires 432.3967, found 432.3997.

10. Alcohol 11a proved refractory to dehydration with $POCl_3$/pyridine, $SOCl_2$/pyridine, reaction with phenylselenylcyanate/n-butylphosphine/pyridine, dimethylformamide dimethylacetal, conversion to a mesylate or chloride and attempted elimination. Pyrolysis (in vacuo, sealed tube, T >260°C) of an intermediate xanthate gave terminal olefin 22 in low and variable yield.

11. 18: ^{1}H NMR: δ 8.4 (d, 1 Hz, CHO), 2.4 (m, H-24), 1.0 (d, 8 Hz, H-26). IR: 1715 cm^{-1} (CHO). HRMS: $C_{30}H_{50}O_2$ requires 442.3811, found 442.3856.

12. Van Rheenen, V. Tetrahedron Lett. 985 (1969). 19: ^{1}H NMR: 2.4 (m, H-24), 2.1 (s, H-26). IR: 1705 cm^{-1} (C=O). HRMS: $C_{29}H_{48}O_2$ requires 428.3654, found 428.3606.

13. 20: HRMS: $C_{30}H_{52}O_2$ requires 444.3967, found 444.3997. 21: ^{1}H NMR: δ 1.3 (d, 22 Hz, H-26,27). EI-MS: m/z 426 (3.6%, M^+), 394 (10%, M^+-HF and -MeOH). $C_{30}H_{51}OF$ requires 446.3924, found 446.3936. 3: ^{1}H NMR: δ 5.3 (br d, 3 Hz, H-6), 3.4 (m, H-3), 1.3 (d, 22 Hz, H-26,27). EI-MS: m/z 412 (17%, M^+-HF). HRMS: $C_{29}H_{48}OF$ requires 432.3768, found 432.3745.

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