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STEREOSPECIFIC SYNTHESIS OF HYDROXYLATED STEROID SIDE CHAINS. SYNTHESIS OF 25,28-DIHYDROXY-7,8-DIHYDROERGOSTEROL AND ITS C-24 EPIMER VIA [2,3] SIGMATROPIC REARRANGEMENT.

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Abstract: An efficient, stereospecific synthesis of hydroxylated ergosterol and C-24 epi-ergosterol side chains has been developed using a C-20 keto-steroid as starting material. The side chain is elaborated via stereoselective hydroboration, asymmetric reduction and a stereospecific [2,3] sigmatropic rearrangement.

During the past several years a variety of synthetic routes have been developed for control of stereochemistry at C-20 of steroid side chains.[1] The isolation and characterization of new vitamin D metabolites and marine steroids has stimulated interest in the synthesis of hydroxylated steroid side chains with control of stereochemistry beyond C-20.[2] Furthermore, the 28-hydroxymethyl group may be conveniently manipulated as shown in the synthesis of the marine sterol saringosterol.[2f] Herein we report a facile route to hydroxylated ergosterol side chains from C-20 ketone precursors. Such compounds may serve as models for potential vitamin D_2 metabolites. The process is outlined in Scheme I.

Our starting material is the readily available 20-ketosteroid pregnenolone (1). Protection of the 3β-hydroxy group and addition of triphenylphosphonium methylide gave the 20(22)-methylene steroid 2. Hydroboration of the 20(22)-methylene steroid with dicyclohexylborane provided the desired 20S configuration as the predominant product (26:1).[2f] Oxidation of the alcohol provided the 22-aldehyde 3 from which the minor 20R epimer could be removed by chromatography. This compound is commonly prepared via ozonolysis of stigmasterol.[3] However, the 5(6)-double bond must then be protected. Addition of

$LiC{\equiv}CC(CH_3)_2OTBDMS$ (t-butyldimethylsilyl) to the aldehyde gave two isomers (4 and 5) in a 1:1 ratio. At this point the two C-22 epimers were separated by chromatography in order to achieve the stereospecific synthesis of the two C-24 epimers. The less polar isomer was assigned as the (22R)-steroid 4.[2c,d] Compound 4 could be prepared more efficiently by asymmetric reduction of ketone 6 with Alpine-borane[4] ((+)-α-pinene, 92% e.e.). Compound 4 is obtained in a greater than 125:1 ratio by this process. The asymmetric reduction of 6 is reinforced by the neighboring chiral center.[5]

Catalytic reduction of acetylene 4 or 5 provided the (Z)-allylic alcohol. The alcohol was converted to the trimethyltin derivative 7 or 8 and subjected to [2,3] sigmatropic rearrangement according to Still's[6] procedure to provide the 25,28-dihydroxylated side chain of ergosterol, 9, or its 24 epimer, 10, respectively. The suprafaciality of related Wittig rearrangements has been demonstrated.[7] Both 9 and 10 exhibited very similar ^1H and ^{13}C NMR spectra with a slight difference in the C-28 ^1H NMR pattern. However the compounds were clearly different by melting point, rotation, and HPLC retention times. Analysis of the reaction mixtures for 9 and 10 by HPLC revealed that in both cases the chirality transfer of the [2,3] sigmatropic rearrangement was virtually complete (>120:1 epimeric purities).

This route represents a short and efficient stereospecific synthesis of hydroxylated steroid side chains from readily available 20-keto steroids. It also demonstrates the use of stereoselective hydroboration of an α-chiral olefin, reinforcement of asymmetric reduction of an α-chiral alkynyl ketone with anti-Cram selectivity and virtually complete chirality transfer in the parent [2,3] sigmatropic (Wittig) rearrangement.

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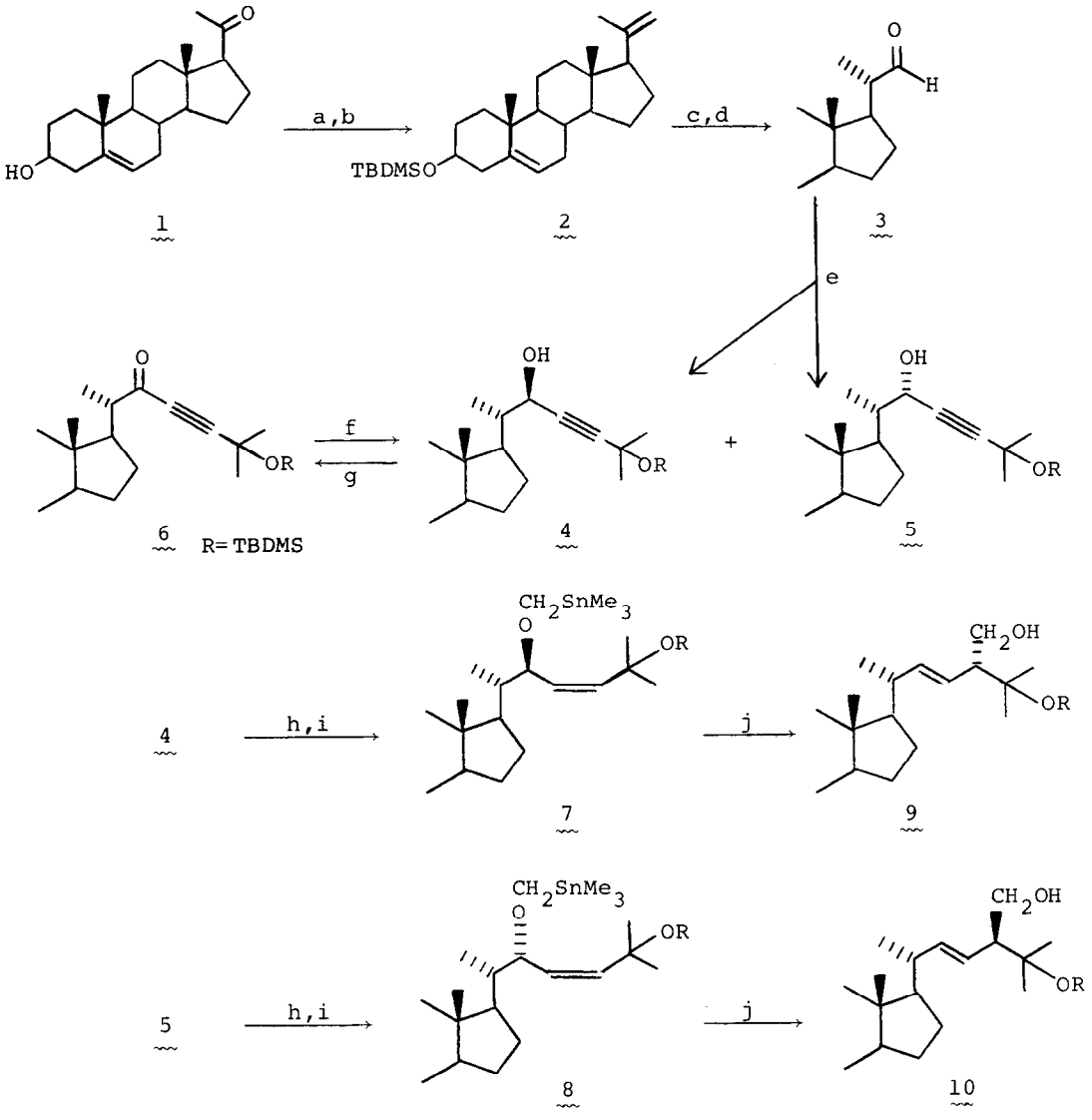
Scheme I



(a) 2 eq. TBDMSCl, 4 eq. imidazole, DMF, r.t. 17 h; (b) 6 eq. Ph_3PCH_3I, 6 eq. t-BuOK/t-BuOH, THF, reflux, 15h, 92% in two steps; (c) 1.6 eq. dicyclohexylborane, 0°C, 17h, $NaOH/H_2O_2$; (d) 1.6 eq. PCC, r.t. 18h, 85% in two steps; (e) $LiC{\equiv}CC(CH_3)_2OTBDMS$, -78°, 1h, RT, 12h, 98-100% yield; (f) 2.3 eq. 92% e.e. R-Alpine-borane, RT, 92h, 98% yield; (g) 1.6 eq. PCC, r.t. 18h, 86%; (h) H_2, Lindlar cat. or 5% Pd/C; (i) 2 eq. NaH, 2.2 eq. ICH_2SnMe_3, 60-63% yield; (j) 1.6 eq. n-BuLi, 82-84% yield.

REFERENCE AND NOTES

1. (a) Piatak, D.M.; Wicha J. Chem. Rev. **1978**, 78, 199; (b) Redpath, B.J.; Zeelen, F.J. Chem. Soc. Rev. **1983**, 12, 75; (c) Midland, M.M.; Kwon, Y.C. Tetrahedron Lett. **1982**, 23, 2077; (d) Schmuff, N.R.; Trost, B.M. J. Org. Chem. **1983**, 48, 1404 and references therein.

2. (a) Hayami, H.; Sato, M.; Kanemoto, S.; Morizawa, Y.; Oshima, K.; Nazaki, H. J. Am. Chem. Soc. **1983**, 105, 4491; (b) Koizumi, N.; Ishiguro, M.; Yasuda, M.; Ikekawa, N. J. Chem. Soc. Perkin Trans. I. **1983**, 1401; (c) Sardina, F.J.; Mourino, A.; Castedo, L. Tetrahedron Lett. **1983**, 24, 4477; (d) Hirano, Y.; Djerassi, C. J. Org. Chem. **1982**, 47, 2420; (e) Zielinski, J.; Li, H.; Djerassi, C. J. Org. Chem. **1982**, 47, 620; (f) Midland, M.M.; Kwon, Y.C. J. Am. Chem. Soc. **1983**, 105, 3725; (g) Catalan, C.A.N.; Kokke, W.C.M.C.; Duque, C.; Djerassi, C. J. Org. Chem. **1983**, 48, 5207.

3. Salmond, W.G.; Sobala, M.C. Tetrahedron Lett. **1977**, 1695.

4. Reduction of alkynyl ketones with R-Alpine-Borane (prepared from 91.3% (+)-α-pinene and 9-BBN) always gives R-propargyl alcohols. (a) Midland, M.M.; McDowell, D.C.; Hatch, R.L.; Tramontano, A. J. Am. Chem. Soc. **1980**, 102, 867; (b) Midland, M.M.; Graham, R.S. Org. Synth., **1984**, 63, 57; (c) Brown, H.C.; Pai, G.G. J. Org. Chem. **1985**, 50, 1384; (d) Midland, M.M.; Tramontano, A.; Kazubski, A.; Graham, R.S.; Tsai, D.J.-S.; Cardin, D.B. Tetrahedron, **1984**, 40, 1371.

5. Midland, M.M.; Kwon, Y.C. Tetrahedron Lett. **1984**, 25, 5981.

6. Still, W.C.; Mitra, A. J. Am. Chem. Soc. **1978**, 100, 1927. The tri-n-butyltin derivative was also prepared although in lower yield.

7. (a) Sayo, N.; Azuma, K.; Mikami, K.; Nakai, T. Tetrahedron Lett. **1984**, 25, 565. (b) Marshall, J.A.; Jenson, T.M. Ibid. **1984**, 49, 1707. (c) Midland, M.M.; Kwon, Y.C. Previous paper in this issue; also see: Midland, M.M.; Tsai, D.J.-S. J. Org. Chem. **1984**, 49, 1842.

8. Selected physical data are as follows: **9**: (R=TBDMS) mp, 183-184°C, $[\alpha]^{25}_D$ - 26.3° (c 4.0, $CHCl_3$), HPLC retention time 23.4 min (4% ethyl acetate/hexane, Whatman M-9 silica column, 10 mm x 50 cm, 2.5 ml/min flow rate), ^1H NMR (300 MHz, $CDCl_3$), δ5.41 (dd, J=8.58, 15.3 Hz), 5.23 (dd, J=9.46, 15.3 Hz), 3.82 (dd, J=5.6, 10.5 Hz), 3.56 (dd, J=7.5, 10.5 Hz). **10**: (R=TBDMS) mp, 149-150°C, $[\alpha]^{25}_D$-33.3° (c 4.0, $CHCl_3$), HPLC retention time 28.1 min, ^1H NMR (300 MHz, $CDCl_3$), δ5.41 (dd, J=8.5, 15.3 Hz), 5.24 (dd, J=9.3, 15.3 Hz), 3.82 (dd, J=5.7, 10.5 Hz), 3.57 (dd, J=7.1, 10.5 Hz).

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