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STEREOCONTROLLED SYNTHESIS OF STEROID SIDE CHAIN; STEREOSELECTIVE SYNTHESES OF CHOLESTEROL AND 25-HYDROXYCHOLESTEROL

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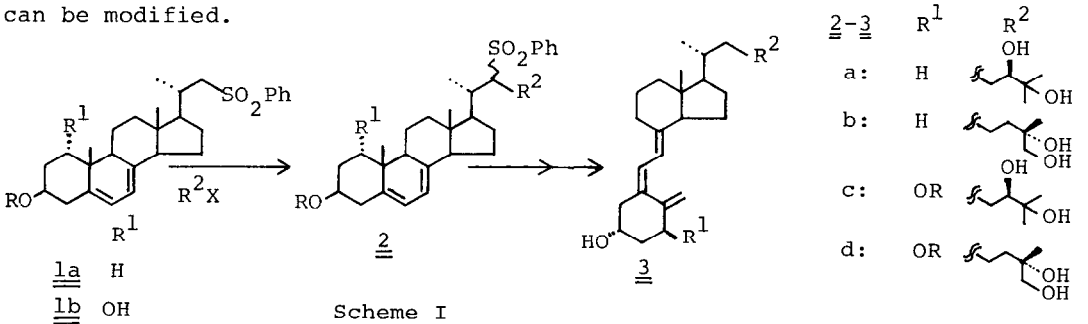
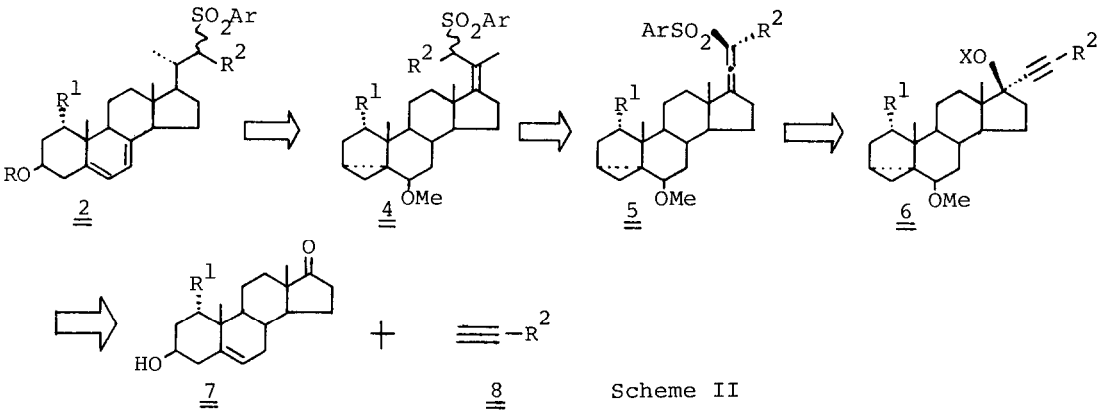
Summary: Novel stereoselective method to introduce side chain onto 17-oxosteroids has been deviced, and using the method cholesterol and 25-hydroxycholesterol are synthesized.

Stereocontrolled introduction of the side chain onto the tetracyclic steroid skeleton has been the subject of recent investigation[1] in connection with the synthetic studies on the biologically important new steroidal natural products possessing modified cholesterol side chain.[2] As a part of our studies on the stereoselective synthesis of vitamin D metabolites[3] possessing chiral center on the side chain using chiral template, we have synthesized 24R,25-dihydroxyvitamin D_3 (3a)[3a] and 25S,26-dihydroxyvitamin D_3 (3b).[3b] In the syntheses the target molecules were constructed from C(22)-steroid sulfone (1a) and the chiral synthons (R^2X) to constitute the C(23)-C(27) part of the side chain (Scheme I). The sulfone (1a) is a versatile activated C(22)-steroid synthon which can be combined with a wide variety of electrophiles making it possible to introduce desirable structures to the C(23)-C(27) part of the side chain. We planned to extend the method to the synthesis of 1α-hydroxylated analogues (3c and 3d) of the metabolites. Dehydroepiandrosterone hydroxylated at the 1α-position (7, R^1=OH) was attractive as the starting material for the synthesis because of its potential availability by microbiological oxidation of C(19)-steroids[4] and ease with which it can be modified.



Scheme I

Our strategy for the synthesis is outlined in Scheme II. In the method, sulfonyl allene (5)[5] which is easily obtained from α-hydroxyacetylene (6, X=H) via sulfinate ester rearrangement is used as the key intermediate. The 21-methyl group may be introduced to the sulfonyl allene (5) with the desired stereochemistry by conjugate addition of methyl copper reagent from the less hindered side of the allenic bond. Both natural stereochemistries at C(17) and C(20) may be attained by catalytic hydrogenation of the allyl sulfone (4). The desirable side chain structure at C(23)-C(27) (R^2) can be introduced either to the starting acetylene molecule or to the any synthetic intermediates (2 and 4-6). Here we wish to report the stereoselective syntheses of cholesterol (14a) and 25-hydroxycholesterol (14b) using our novel method to introduce steroid side chain.

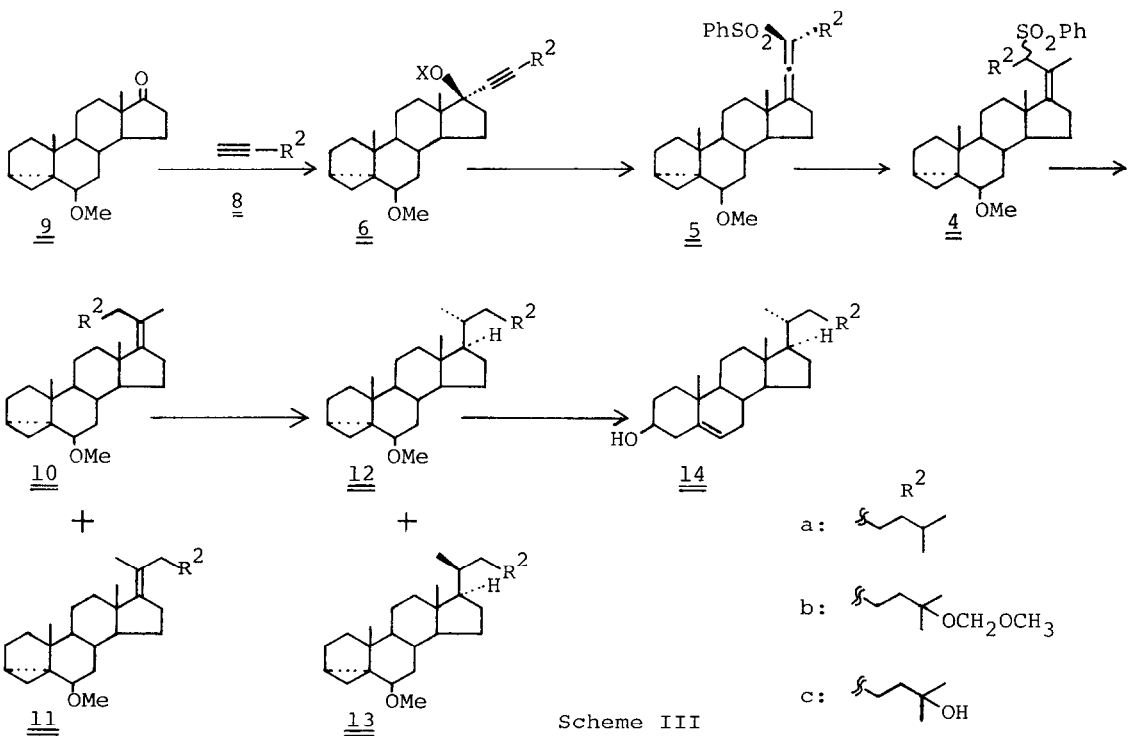


Scheme II

Of the several approaches, we first examined the introduction of acetylene derivatives possessing the desired side chain structure to the 17-oxosteroid (Scheme III). Lithium salt of acetylene (8a) which includes the cholesterol side chain structure was reacted with 17-oxosteroid (9) (LDA, THF, 0°C) to afford α-hydroxyacetylene (6a, X=H) (75%). The sulfinate ester (6a, X=SOPh) obtained (PhSOCl, pyridine; 85% yield) from the alcohol (6a, X=H) was subjected to thermal [2,3]-sigmatropic rearrangement (chlorobenzene, Li_2CO_3, reflux) to yield sulfonyl allene (5a) [IR ($CHCl_3$) 1960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (3H, s, H-18), 0.85 (6H, d, J=6 Hz, H-26,27), 1.03 (3H, s, H-19), 2.77 (1H, t, J=3 Hz, H-6)] in almost quantitative yield. The reaction of the allene (5a) with Me_2CuLi (THF, 0°C) proceeded stereoselectively to afford only the (Z)-allyl sulfone (4a) as a mixture of the epimers at C(22) (ca. 1.4:1 ratio) [major (less polar isomer) : mp 127-128°C; ^1H NMR ($CDCl_3$) δ 0.82 (3H, s, H-18), 1.71 (3H, s, H-21), minor (more polar isomer) : mp 166-167°C; ^1H NMR ($CDCl_3$) δ 0.53 (3H, s, H-18), 1.69 (3H, s, H-21)] (85%). The stereochemistry of the 17(20)-double bond in 4a was deduced based on the stereochemical course of the reaction and

finally confirmed by the transformation into cholesterol as described below. Reductive desulfonylation of the allyl sulfone (4a) under ordinary conditions (Na-Hg, $Na_2H\ PO_4$, MeOH) was accompanied by the isomerization of the 17(20)-double bond giving rise to 10a and 11a[6] in 2:1 ratio in 57% total yield. The isomerization was minimized and the total yield was raised (90%) by carring out the reduction with Li in ethylamine at -75°C, the (Z)-isomer (10a) being obtained in 90% selectivity. Catalytic hydrogenation of the 17(20)-double bond in 10a proceeded smoothly but the selectivity was not exclusive.[7] Thus, hydrogenation using 10% Pd/C (AcOEt. 0°C-room temp.) afforded dihydroderivatives 12a and 13a in 3:1 ratio in 90% total yield. The desired isomer (12a) with natural stereochemistry was obtained in slightly higher selectivity (80%) by the reduction using PtO_2 (AcOEt-AcOH) as the catalyst but the total yield was lower (70%). The i-ether (12a) was transformed (TsOH, aq. dioxane; quantitative) into cholesterol (14a) which was identical in all respect with the authentic sample.

Stereoselective synthesis of 25-hydroxycholesterol (14c) was performed using the same methodology. Starting with the i-ether (9) and acetylene (8b), allyl sulfone (4b) [^{1}H NMR ($CDCl_3$) δ 0.55 and 0.85 (3H, s, H-18), 1.16 and 1.20 (6H, s, H-26,27), 1.73 (3H, s, H-21)] was obtained in 44% overall yield. Reductive desulfonylation followed by catalytic hydrogenation (Pd/C, AcOEt) afforded the i-ether (12b) [^{1}H NMR ($CDCl_3$) δ 0.72 (3H, s, H-18), 0.93 (3H,d, J=5 Hz, H-21), 1.03 (3H, s, H-19), 1.21 (6H, s, H-26,27), 2.79(1H, t, J=3 Hz, H-6)] in 42% over-



Scheme III

all yield. The i-ether (12b) was transformed (TsOH, aq. dioxane, 80°C, quantitative) into 25-hydroxycholesterol (14c), the structure of which was confirmed by the spectral data as well as by mixed melting point determination with the authentic sample.[8]

Further studies along this line are progressing in our laboratory.

References and Notes

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