Tetrahedron Letters,Vol.24,No.41,pp 4477-4480,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

STUDIES ON THE SYNTHESIS OF SIDE CHAIN HYDROXYLATED METABOLITES OF VITAMIN D. STEREOSPECIFIC SYNTHESES OF 25-HYDROXY-7,8-DIHYDRO-ERGOSTEROL AND ITS C-24 EPIMER[16]

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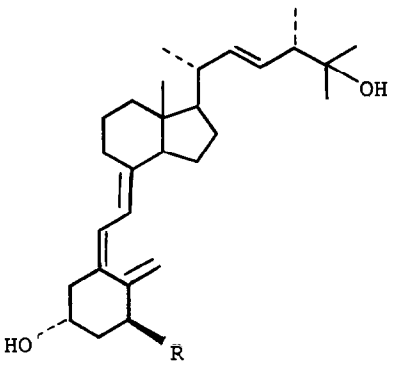
Abstract: An efficient, stereospecific synthesis of 25-hydroxy-7,8-dihydro-ergosterol, starting from the aldehyde 3 (7 steps, 30% overall) was developed. Key steps are the stereospecific displacement of an allylic carbamate by $Li_2Cu_3(CH_3)_5$ and the stereoselective reduction of a propargylic ketone by a chiral aluminum complex.

Biochemists engaged in vitamin D research often complain about the scarcity of synthetic metabolites of vitamin D_2, since this is the main reason for the current lack of detailed information about the biological significance of these compounds. The close structural and metabolic relationship between vitamin D_2 and vitamin D_3 (a well studied group)[1], further increases the interest in vitamin D_2 derivatives, specially in 25-hydroxylated metabolites such as 25-hydroxyvitamin D_2 (1) and 1α,25-dihydroxyvitamin D_2 (2)[2].

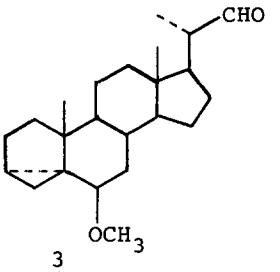
We wish to report the results of our efforts for developing a short, stereospecific synthesis of 25-hydroxylated vitamin D_2 metabolites. Our first goal is the construction of the 25-hydroxyergosterol side chain. This approach is based on the stereospecific S_N2' type displacement of allylic carboxylates by cuprates, which is known to take place in a syn fashion with carbamates and in an anti one with benzoates[3]. The required carboxylates (carbamates 6a,b and benzoates 7a,b), were readily obtained from the known aldehyde 3[4]. Thus, reaction of 3 with $LiC{\equiv}C(CH_3)_2OMOM$[5] yielded an easily separable mixture of propargylic alcohols 4a,b,[6a,b] (85% combined yield, 1:1 ratio). Oxydation of this mixture with PDC[7] and reduction of the resulting ketone 8[6a,b] (waxy solid, 92%), with $LiAlH_4$-N-methylephedrine,3,5-dimethylphenol system[8] comprised a simple method to improve the stereoselectivity of the preparation of 4a,b specially when l(-)-N-methylephedrine was used (4a:4b ratio: 13/1, 90%). The ratio 4a:4b obtained using the d-(+)-enantiomer was only 1:2.5 (70% conversion). Hydrogenation (H_2, 10% Pd-C,dioxane,$HNaCO_3$)[9] and acidic hydrolysis (pTsOH, dioxane,H_2O, 80%)[9] of 4a,b allowed the stereochemistry at C-22 to be established. Thus, 4a (mp 121.5°C, less polar epimer), and 4b (mp 80.5-81°C) gave (22S)-25-dihydroxycholesterol (mp 190 °C, lit[10] 186 - 187 °C) and (22R)-

25-dihydroxycholesterol (mp 250-252°C, lit.[10] 253-255°C), respectively. Semi-hydrogenation (5% Pd-$BaSO_4$-quinoline) of 4a,b afforded 5a,b[6a] (99%, 92%), which without further purification were allowed to react with PhNCO or PhCOCl (pyridine-DMAP) to yield 6a,b (foams) or 7a(syrup) and 7b (mp 111.5-112.5°C) in almost quantitative yield[6a,b]. Treatment of 6a with $Li_2Cu_3(CH_3)_5$[3] (48 h, RT), gave the bis protected form of the target compound, 9a[6a,11] (77%). Similarly 6b gave 9b[6a] in a much cleaner and faster reaction (4h, RT, 100%). The NMR data of the resulting compounds show that the reaction proceeds with complete stereospecificity[12,13].



1 R=H

2 R=OH



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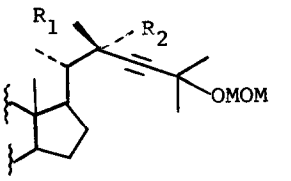
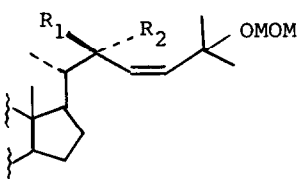


4a R_1=OH, R_2=H

4b R_1=H, R_2=OH



5a R_1=OH, R_2=H

5b R_1=H, R_2=OH

6a R_1=OCONHPh, R_2=H

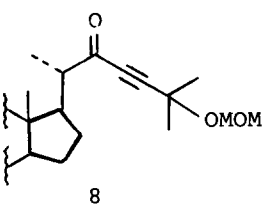
6b R_1=H, R_2=OCONHPh

7a R_1=OCOPh, R_2=H

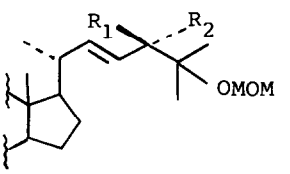
7b R_1=H, R_2=OCOPh

10a R_1=CH_3, R_2=H

10b R_1=H, R_2=CH_3

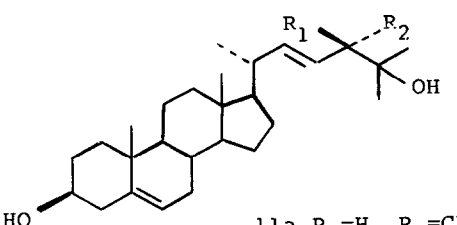


8



9a R_1=H, R_2=CH_3

9b R_1=CH_3, R_2=H



11a R_1=H, R_2=CH_3

11b R_1=CH_3, R_2=H

Displacement of the benzoates was less stereospecific since 7a afforded 9b (66%) along with a byproduct tentatively assigned as 10b[14a] (nmr ratio: 10/1), and 7b gave 9a and tentatively assigned 10a[14b] (nmr ratio: 1/1, 76% combined yield). In this case reaction of 7a was much faster than that of 7b (4h, 32h, respectively). Our stereochemical assignments are based on the proposed stereochemical course of cuprate displacement on carbamates (syn way) and benzoates (anti way).[3]

The target compound 11a (mp 168.5-169.5°C) and its C-24 epimer 11b (mp 183.5-184°C), were obtained by acidic hydrolysis from 9a,b (pTsOH, dioxane,H_2O, 80°C, 80%)[10]. The first stereospecific synthesis of 25-hydroxy-7,8-dihydro-ergosterol was achieved[4,15] in this way (24S side chain: 7 steps, 38% and 24R side chain: 7 steps 30%).

Work is in progress in this laboratory to further expand the scope of this approach to the synthesis of other side chain hydroxylated metabolites of vitamin D_2 and D_3, as well as to unravel the origin of the difference in reactivity of the epimeric pairs 6a:6b; 7a:7b with $Li_3Cu_2(CH_3)_5$.

ACKNOWLEDGEMENTS: We wish to thank the Comisión Asesora (Spain) for its financial support. We are grateful to Hoffmann La Roche for a gift of the aldehyde 3, and to Bruker for the 300 MHz nmr spectra of compounds 10a,b. J.S. thanks the Ministry of Education and Science for a fellowship.

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2. Its vitamin D_3 counterpart is the most active vitamin D_3 metabolite known with regard to ICA and BCM responses.

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4. W,G.Salmond and M.C.Sobala, Tetrahedron Lett., 1695, (1977).

5. The use of the THP derivatives gave less satisfactory results in part due to the elimination of the C-25 functionality during the cuprate displacement.

6. (a) NMR, IR, MS; (b) Elemental analysis.

7. E.J.Corey and G.Schmidt, Tetrahedron Lett., 399, (1979).

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10. B.M.Trost and Y.Matsumura, J.Org.Chem., 42, 2036, (1977).

11. Minor amounts of a less polar byproduct lacking the C-25 functionality were also isolated.

12. (a) 9a, 80MHz, δ: 5.38-5.31 (1H, dd, J=7.6, 15.3 Hz), 5.20-5.22 (1H, dd, J=7.6, 15.3 Hz), 5.31 (1H, br s), 0.96 (3H, d, J=6.9 Hz), 0.67 (3H, s); (b) 9b, δ: 5.35-5.27 (1H, dd, J=8.2, 15.3 Hz), 5.25-5.17 (1H, dd, J=8.2, 15.3 Hz), 3.50 (1H, m). The rest, same as for 9a.

13. The shape of the multiplets due to H-22 in the 80 MHz NMR spectra allowed complete differentiation between epimers 9a and 9b. The examination of the 300 MHz spectra of 10a,b confirmed the stereospecificity of these reactions.

14. (a) 10b, 80 MHz, δ: 5.55-5.44 (2H, m), 4.68 (2H, s); (b) 10a, δ: 5.44 (2H, m), 4.69 (2H, s).

15. For previous syntheses of this type of hydroxylated side chain steroids, see: Y.Mazur, D.Segev and G.Jones. "Vitamin D, Chemical, Biochemical, and Clinical Endocrinology of Calcium Metabolism". A.W.Norman, K.Schaefer, D.V.Herrath and H.G.Grigoleit. Eds. Walter de Gruyter & Co., Berlin, NY, 1101-1106, (1982).

16. Dedicated to Professor I.Ribas.

(Received in UK 18 July 1983)