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STEREOSELECTIVE SYNTHESIS OF 25-HYDROXYVITAMIN D_2 SIDE CHAIN VIA THE ACETAL TEMPLATE ROUTE

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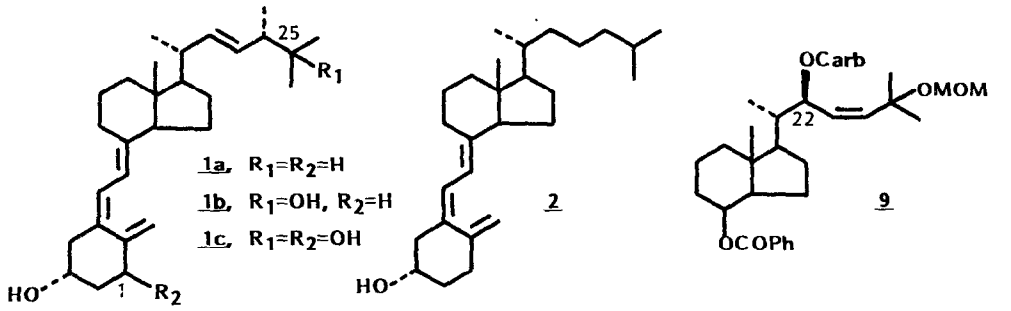
Summary: A highly stereoselective synthesis of the side chain of 25-hydroxyvitamin D_2 and 1α,25-dihydroxyvitamin D_2 is described.

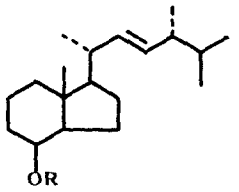
Before exerting its physiological action, the unnatural vitamin D_2 (**1a**), like the natural vitamin D_3 (**2**), must be hydroxylated to first 25-hydroxyvitamin D_2 (**1b**) and then 1α,25-dihydroxyvitamin D_2 (**1c**).[1] Despite the close relationship between these two vitamins, the biological activity of vitamin D_2 metabolites remains largely unknown due to the scarcity of synthetic material.[2]



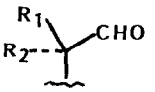
We have recently reported a stereocontrolled synthesis of the side chain of the principal metabolites of vitamin D_2, **1b** and **1c**, from the carbamate **9**. This synthesis was based on an efficient S_N2' syn displacement of the carbamate group by methyl cuprates.[2c,e] We now report a significantly improved synthesis of the key intermediate **9** based on asymmetric opening of chiral acetals.

The starting point for our synthesis was the alcohol **3a**.[3] Protection of **3a** (PhCOCl, py-DMAP), and ozonolysis of the resulting benzoate **3b**[4] (O_3, MeOH-CH_2Cl_2-py, -80 ºC; $P(OEt)_3$, afforded the aldehyde **4a**[2e] in 93% overall yield.[5] Next, the acetals **5a,b**[4] were prepared in 97% yield by reaction of **4a** with the appropriate diol ($BF_3.OEt_2$, THF, 0 ºC, 16 h). The absence of epimerization at C-20 (steroidal numbering) during acetalization was verified by comparison of the above acetals with those obtained under the same reaction conditions from the aldehyde epimer **4b**.[6] Reaction of the individual acetals **5a,b** with $TMSC{\equiv}CCMe_2OTMS$ in the presence of several Lewis acids[7] in CH_2Cl_2 followed by quenching of the reaction mixture with methanol, afforded starting material or the corresponding dimethoxy acetal. In view of these unsuccessful reactions, we turned our attention to the recent results obtained by Yamamoto and coworkers by reaction of similar acetals with simple stannylacetylenes.[8] Treatment at -70 ºC of a solution of **5a** and $Bu_3SnC{\equiv}CCMe_2OTMS$[9] (molar ratio 1:3) in CH_2Cl_2 with a solution of $TiCl_4$ in CH_2Cl_2 (1.75 equiv) gave, after stirring for 5 min, quenching with methanol, conventional work-up and column chromatography, the diol **6a** and its C-22 epimer (ratio 2:1) in 85% yield.[10] Under similar conditions, the acetal template **5b** gave the diol **6b**[4] and its C-22 isomer in 130:1 ratio[10] (94%).

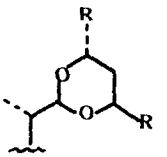
Oxidation of **6b** (PCC, CH_2Cl_2, 0 ºC, 8 h) and protection of the resulting ketoalcohol **7a** (ClMOM, $EtN(i\text{-}Pr)_2$-DMAP, CH_2Cl_2, 0 ºC, 18 h, RT) gave **7b**[4] in 95% overall yield (two steps). This compound was transformed in 98% yield into the desired alcohol **8**[2e] by elimination with K_2CO_3 in MeOH (3 h, RT) (79% overall yield from the starting alcohol **3a**).[11] Finally, **8** was converted to the desired key carbamate **9** by published procedures.[2e,12]



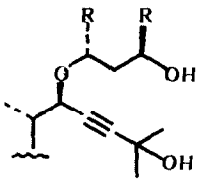
3a, R=H
3b, R=COPh



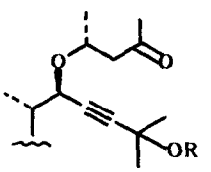
4a, R_1=H, R_2=CH_3
4b, R_1=CH_3, R_2=H



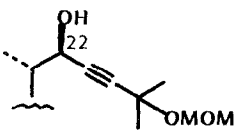
5a, R=H
5b, R=CH_3



6a, R=H
6b, R=CH_3



7a, R=H
7b, R=MOM



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REFERENCES AND NOTES

1. (a) T. Suda, H.F. DeLuca, H.K. Schnoes and J.W. Blunt, **Biochemistry**, **8**, 3515 (1969); (b) G. Jones, H.K. Schnoes and H.F. DeLuca, **J. Biol. Chem.**, **251**, 24 (1976); (c) G. Jones, H.K. Schnoes and H.F. DeLuca, **Biochemistry**, **14**, 1250 (1975).
2. To date, only a few syntheses of 25-hydroxyvitamin D_2 side-chain have been reported: (a) W.C. Salmond, M.C. Sobala, **Tetrahedron Lett.**, 1695 (1977); (b) Y. Mazur, D. Segev, G. Jones, "Vitamin D. Chemical, Biochemical and Clinical Endocrinology of Calcium Metabolism", Walter de Gruyter. Berlin-New York. 1102 (1982); (c) F.J. Sardina, A. Mouriño, L. Castedo, **Tetrahedron Lett.**, **24**, 4477 (1983); (d) S. Yamada, M. Shiraishi, M. Ohmori, H. Takayama, **Tetrahedron Lett.**, **25**, 3347 (1984); (e) F.J. Sardina, A. Mouriño, L. Castedo, **J. Org. Chem.**, **51**, 1264 (1986).
3. J.L. Mascareñas, A. Mouriño, L. Castedo, **J. Org. Chem.**, **51**, 1269 (1986).
4. Satisfactory microanalyses or exact mass spectra were obtained for all new compounds.
5. This sequence is an excellent method for multigram scale preparation of **4a**.
6. A sample of the epimer **4b** was obtained by equilibration of **4a** with syn-collidine in xylene.
7. (a) P.A. Bartlett, W.S. Johnson, J.D. Elliott, **J. Am. Chem. Soc.**, **105**, 2088 (1983); (b) W.S. Johnson, J.D. Elliott, G.J. Hauson, **J. Am. Chem. Soc.**, **106**, 1138 (1984); (c) W.S. Johnson, M.F. Chan, **J. Org. Chem.**, **50**, 2598 (1985).
8. Y. Yamamoto, S. Nishii, J. Yamada, **J. Am. Chem. Soc.**, **108**, 7116 (1986).
9. Prepared by reaction of $LiC{\equiv}CCMe_2OTMS$ with $ClSnBu_3$.
10. (a) This low diastereoselectivity was unexpected in view of the results obtained by Yamamoto[8]; (b) The epimeric ratios were determined by ^1H-NMR integration of the 22-H at the alcohol **8** stage.
11. This route is experimentally simpler and more economical than that previously reported in which the A-ring of the starting vitamin D_2 is destroyed.[2e,3]

12. We are grateful to the Comisión Asesora de Investigación (CAICYT) for financial support of this work. We thank Hoffmann la Roche (Basel) for the generous gift of vitamin D_2. J.G. thanks the Ministerio de Educación y Ciencia for a research grant.

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