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STEREOSPECIFIC SYNTHESIS OF THE LYTHGOE'S RING A ALDEHYDE FOR THE PREPARATION OF 1α-HYDROXYLATED TACHYSTEROLS AND CALCIFEROLS

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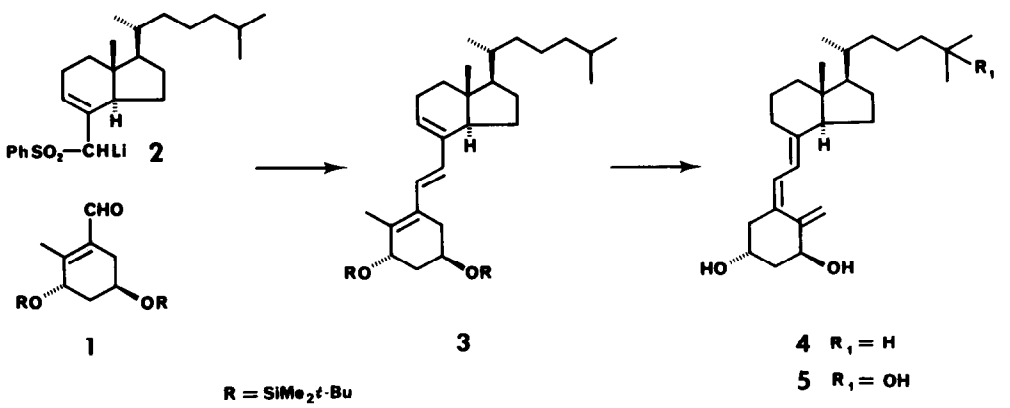
Summary: The dihydroxyaldehyde 1, an important intermediate for the synthesis of 1α-hydroxylated vitamin D derivatives via the corresponding tachysterol precursors, was prepared from (S)-(+)-carvone (6). The sequence involves as central step, the decarboxylation and rearrangement of the epoxyglycidic acid 15, prepared from carvone oxide 7.

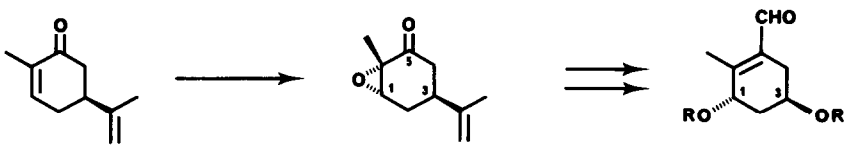
It is now well established that Vitamin D_3 (Cholecalciferol) must first undergo a variety of metabolic hydroxylations in order to become biologically active[1]. Of the known metabolites, the central role is played by 1α,25-dihydroxycholecalciferol (5), which is believed to be the hormonally active form of the vitamin and which has been the object of considerable synthetic endeavour since its discovery[2].



As part of a pioneering program designed to synthesize the calciferols via convergent strategies[3], Lythgoe and co-workers effected[4] an efficient preparation of the clinically important 1α-hydroxycholecalciferol (4) by using the Julia's reductive

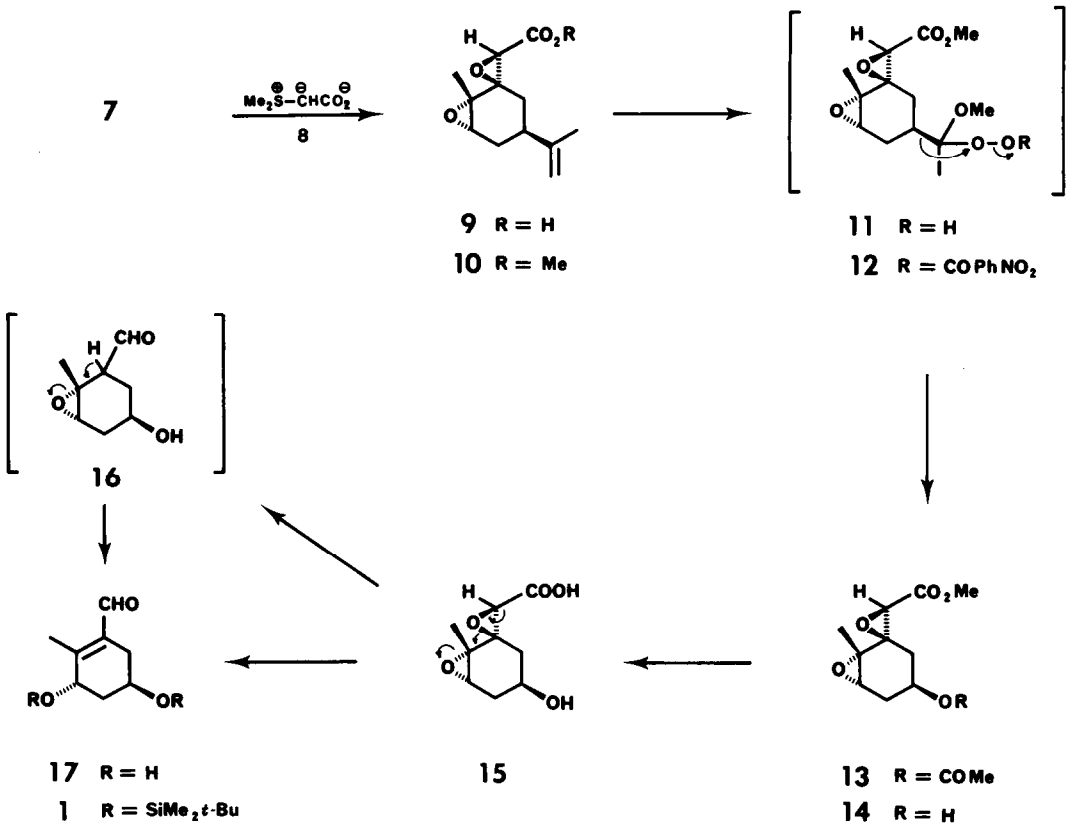
elimination of the β-hydroxysulphones obtained from the condensation of the carbaldehyde 1 with the lithium carbanion 2. The so-obtained tachysterol$_3$ intermediate 3 was finally converted to the desired 4 via triplet sensitized photoisomerization followed by thermal rearrangement.

The dihydroxyaldehyde 1, which is also a key intermediate for the synthesis of 5[5] and of a variety of 1α-hydroxylated vitamin D derivatives using this route, was originally prepared from 5-methoxy-2-methylbenzoic acid[4b,6] and more recently from quinic acid[7]. We report here a stereospecific synthesis of 1 starting from (S)-(+)-carvone (6).



6 7 1

This monoterpene is known to undergo regio- and stereospecific oxidation with alkaline hydrogen peroxide to give the epoxyketone 7. Our synthetic strategy was to oxidatively degrade the isopropenyl side chain of 7 at C-3[8] with retention of configuration, to take advantage of the epoxide moiety in order to form the desired allylic alcohol of 1 and to convert the keto group at C-5 into a one carbon homologous aldehyde. To effect the latter transformation, we investigated the use of a Darzens condensation[9]. However, reaction of 7 with a number of α-haloesters and using a variety of bases and reaction conditions, gave only poor yields of the desired glycidic ester. Better results were on the other hand obtained by using the dimethylthetin anion 8[10], prepared from dimethyl(carboxymethylene) sulfonium bromide[11] and sodium amide (liq. NH_3/THF, -78°C then r.t.) which gave the glycidic acid 9[12] in good yield (88%). Its structure was confirmed by X-ray single crystal analysis. After conversion to the corresponding methyl ester 10[13] (NaOH, MeI, HMPA, r.t., 95% yield), the oxidative degradation of the isopropenyl side chain was attempted by ozonolysis (to give the corresponding methyl ketone) followed by Bayer-Villiger oxidation. Unexpected difficulties were, however, encountered in carrying out the latter transformation, apparently because of the sensitivity of the diepoxide system to the peracids used. These difficulties were overcome by using instead the sequence of transformations described by Criegee[14]. To this end, 10 was ozonized in the presence of methanol ($MeOH/CH_2Cl_2$, -78°C) and the so-obtained methoxyhydroperoxide 11, acylated with p-nitrobenzoylchloride (CH_2Cl_2, Py, 0°C) to give the corresponding peroxyester (12), which underwent rearrangement to 13 in the same reaction medium (r.t. then 40°C). To facilitate the purification, the crude product was deacetylated to 14[15] (NaOMe, MeOH, 93% overall yield from 9). Saponification (NaOH, H_2O/THF, quant.yield) gave the hydroxy acid 15[16] which underwent smooth decarboxylation over copper chromite[17] in pyridine (100°C, 90% yield) to solely give the dihydroxyaldehyde 17[18]. This transformation can conceivably



occur via the epoxyaldehyde 16 which suffers base catalyzed isomerization to 17. On the other hand, a concerted process in which the decarboxylation takes place with simultaneous opening of both epoxides cannot be ruled out. No epimerization at C-1 was detected. Silylation [(t-Bu)(Me_2)SiCl, imidazole, CH_2Cl_2, r.t., 86% yield] gave the desired product 1[19].

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References and Notes

1) (a) A.W. Norman, *Vitamin D, The Calcium Homeostatic Hormone, Academic:New York*, **1979**. (b) H.F. DeLuca, H.K. Schnoes, *Annu.Rev.Biochem.*, **1983**, *52*, 411. (c) H.F. DeLuca, H.K. Schnoes, *Annu.Rep.Med.Chem.*, **1984**, *19*, 179.

2) (a) E.J. Semmler, M.F. Holick, H.K. Schnoes, H.F. DeLuca, *Tetrahedron Lett.*, **1972**, 4147. (b) D.H.R. Barton, R.H. Hesse, M.M. Pechet, E.J. Rizzardo, *J.Chem.Soc.,Chem.-Commun.* **1974**, 203. (c) Z. Cohen, E. Keinan, Y. Mazur, A. Ulmann, *J.Org.Chem.*, **1976**,

41, 2651. (d) L. Vanmaele, P.J. DeClerq, M. Vandewalle, *Tetrahedron*, **1985**, *41*, 141. (e) E.G. Baggiolini, J.A. Iacobelli, B.M. Hennessy, A.D. Batcho, J.F. Sereno, M.R. Uskokovic, *J.Org.Chem.*, **1986**, *51*, 3098.

3) (a) B. Lythgoe, *Chem.Soc.Rev.*, **1981**, 449. (b) R. Pardo, M. Santelli, *Bull.Soc.Chim.Fr.*, **1984**, 98.

4) (a) P.J. Kocienski, B. Lythgoe, I. Waterhouse, *Tetrahedron Lett.*, **1979**, 4419. (b) P.J. Kocienski, B. Lythgoe, *J.Chem.Soc.*, **1980**, 1400.

5) A total synthesis of 1α,25-dihydroxycholecalciferol (5) using this approach was completed and will be reported later.

6) (a) R.G. Harrison, B. Lythgoe, P.W. Wright, *J.Chem.Soc.*, **1974**, 2654. (b) R.G. Harrison, B. Lythgoe, P.W. Wright, *Tetrahedron Lett.*, **1973**, 3649.

7) D. Desmaele, S. Tanier, *Tetrahedron Lett.*, **1985**, *26*, 4941.

8) Steroidal numbering is used.

9) S.F. Martin, *Synthesis*, **1979**, 633.

10) J.Adam, L. Hoffman, Jr., B.M. Trost, *J.Org.Chem.*, **1970**, *35*, 1600.

11) Prepared in 75% yield by stirring a solution of equimolar amounts of bromoacetic acid and dimethylsulfide in toluene at room temperature for two weeks. The crystalline precipitate formed was filtered and washed with toluene.

12) 9: mp 123-124°C, $[\alpha]^{25}D$ -38.4° (c 0.2, EtOH); ^1H NMR (100 MHz, $CDCl_3$) δ 1.16 (s, 3H), 1.67 (br s, 3H), 3.26 (m, 1H), 3.69 (s, 1H), 4.67 (br s, 1H), 4.72 (br s, 1H), 7.95 (very br s, 1H) ppm.

13) 10: mp 46-47°C, $[\alpha]^{25}D$ -46.5° (c 0.5, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 3H), 1.67 (s, 3H), 3.28 (br s, 1H), 3.69 (s, 1H), 3.83 (s, 3H), 4.70 (br s, 1H), 4.75 (br s, 1H) ppm.

14) (a) R. Criegee, R. Kaspar, *Justus Liebigs Ann.Chem.*, **1948**, *77*, 127. (b) S.L. Schreiber, W.-F. Liew, *Tetrahedron Lett.*, **1983**, *24*, 2363.

15) 14: mp 69-70°C, $[\alpha]^{25}D$ -42.2 (c 0.3, EtOH): ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 3H), 3.19 (br s, 1H), 3.68 (s, 1H), 3.82 (s, 3H), 3.99 (br s, 1H) ppm.

16) 15: mp 141-142°C, $[\alpha]^{25}D$ -40.1° (c 0.5, EtOH); ^1H NMR (100 MHz, CD_3OD) δ 1.10 (s, 3H), 3.20 (m, 1H), 3.63 (s, 1H), 3.73 (m, 1H) ppm.

17) The copper chromite used (Lazier catalyst) was a free sample from the Harshaw Chemical Co., Cleveland, Ohio 44106. For its preparation see: W.A. Lazier, H.R. Arnold, *Org.Synth.Coll.Vol. 2*, 142.

18) 17: $[\alpha]^{25}D$ -188.5° (c 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 4.16 (br s, 1H), 4.40 (br s, 1H), 10.17 (s, 1H) ppm.

19) 1: $[\alpha]^{25}D$ -91.1° (c 0.3, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.09 (s, 3H), 0.15 (s, 3H), 0.17 (s, 3H), 0.89 (s, 9H), 0.94 (s, 9H), 1.82 (apparent t, 2H), 2.05 (br d, J = 16.4 Hz, 1H), 2.19 (br s, 3H), 2.53 (br d, J = 16.4 Hz, 1H), 4.12 (m, 1H), 4.36 (br s, 1H), 10.15 (s, 1H) ppm.

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