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AN ASYMMETRIC TOTAL SYNTHESIS OF VITAMIN D_3 (CHOLECALCIFEROL)

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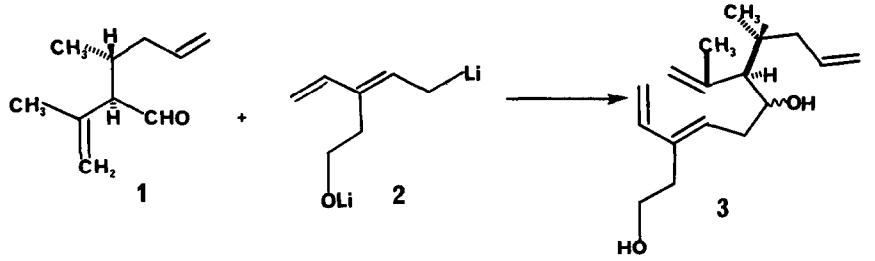
Summary - The total synthesis of cholecalciferol via an intramolecular Diels-Alder approach is described.

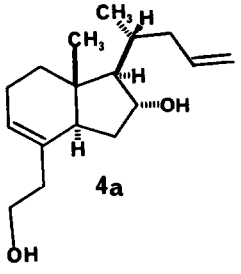
Synthetic efforts directed towards vitamin D_3 and its metabolites have been renewed since the discovery that specific hydroxylated derivatives are involved in a complex control of calcification processes. In contrast to the traditional passive characterization of vitamin D_3 as a vitamin, it is now known [1] that vitamin D_3 acts as other classical steroid hormones: that is, its active form is synthesized in the liver and kidney in response to various stimuli and is transported to its site of action by a specific carrier protein. Early synthetic work has been reviewed [2] and a recent synthesis by the Hoffmann-LaRoche group[3] has appeared.

Our own efforts have centered on developing an effective approach to these compounds based on the intramolecular Diels-Alder reaction[4]. We have recently reported [5] model studies which show that cyclization proceeds in suitably substituted cases to produce trans C/D synthons with a β-side chain. This technology has now been extended to the synthesis of vitamin D_3 itself.

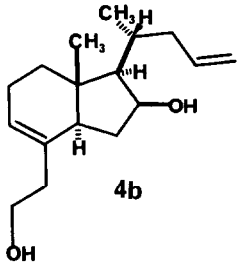
Our synthesis of aldehyde 1 (in 54% overall yield from crotonaldehyde) via the Homo-Claisen rearrangement[6] was described earlier [5] and produces a



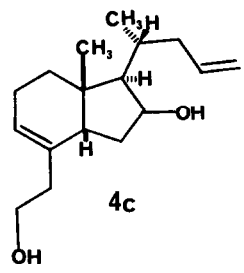
starting material possessing the correct relative configuration at the eventual C(17) and C(20) positions.[7] Reaction of 1 with dianion 2 (derived from metallation of 3-vinyl-4-penten-1-ol with 2 moles of n-butyl lithium) gave adduct 3[7] in 78% yield as a 3:1 mixture of epimers. Diels-Alder cyclization of this mixture followed by chromatography gave a 60/20/20 ratio of 4a-c in 89% yield[8]. Thus in a single step from acyclic precursers, all four asymmetric centers of vitamin D_3 and other steroids have been created in the correct relative configuration. Compounds 4a (mp 102-103°) and 4b (mp 88-89°) represent excellent functionalized starting materials for steroid total synthesis.



4a

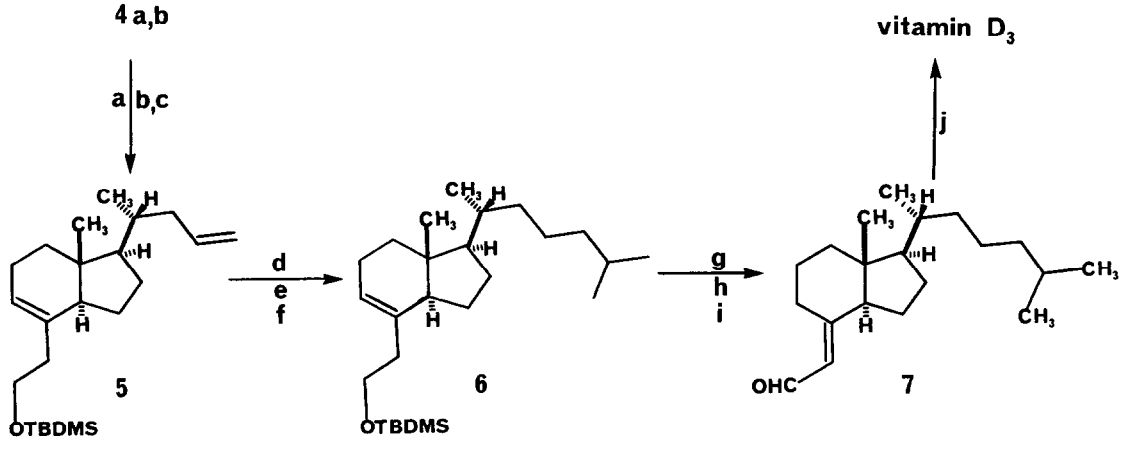


4b



4c

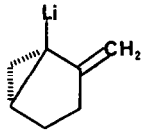
In the present instance, both 4a and 4b have been processed similarly. The primary hydroxyl was selectively protected and the C(16) hydroxyl removed by known methods[9] to yield 5.



5 6 7

legend: a. Cl-TBDMS,imidazole, DMF (90%).
b. n-Buli, Cl-PO(NMe_2)$_2$, THF, TMEDA (97%).
c. Li,NH_3, THF (92%).
d. diisoamylborane, THF,H_2O_2, NaOH (94%).
e. TsCl, pyridine (98%).
f. i-PrMgBr, Li_2CuCl_4, THF (95%).
g. (n-Bu)$_4$N+F-,THF (96%).
h. PCC,CH_2Cl_2 (71%).
i. KO-t-butoxide(cat),THF (52%).
j. compound 9,H^+ (45%).

Side chain elaboration involved hydroboration/oxidation, tosylation and subsequent coupling[10] with isopropylmagnesium bromide mediated by Li_2CuCl_4 to give 6. Deprotection and oxidation gave an aldehyde which was treated with KO-tButoxide (double bond conjugation) to produce aldehyde 7 (53% yield with no trace of Z-isomer). Synthetic 7 was identical in all respects with material obtained by degradation of vitamin D_3. While 7 has already been converted to vitamin D_3 by Inhoffen[2b], our approach involves addition to 7 of optically pure Ring A synthon 9, whose synthesis is described in the following paper.[11]



9

Solvolysis of the resulting cyclopropylcarbinols gives vitamin D_3 in 45% yield from 7.

Our new approach described in this communication is efficient, flexible and unique. We believe that many of the derivatives of vitamin D_3 will be readily accessible from these intermediates and are currently pursuing that goal. The accompanying paper[11] describes in more detail our new ring A reagents.

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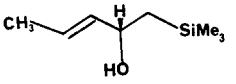
7. Although the synthesis of aldehyde 7 was carried out in the racemic series, our starting



i

material[6] i was efficiently resolved by the Sharpless[12] kinetic resolution.

8. The angular methyl signal serves as a convenient marker of cis (~0.9δ) vs trans (~0.7δ) ring fusion. Compound 4a showed: NMR: ($CDCl_3$/TMS): 5.98-5.76 (m, 1H), 5.39 (broad s, 1H), 5.12-5.02 (m, 2H), 4.14 (t, J=5 Hz, 1H), 3.68 (t, J=5 Hz, 2H), 2.38-2.62 (m, 2H), 1.66 (broad s, 3H), 1.12 (dd, J=11,6 Hz, 1H), 0.99 (d, J=7Hz, 3H), 0.71 (s, 3H) IR: 2.80, 3.30, 6.08 (w), 7.00, 7.32, 8.10, 9.68. MS: m/e (rel intensity): 264(1), 249(3), 246(7), 231(29), 215(11), 201(11), 178(20), 177(100), 161(12), 159(24), 145(17), 133(27), 131(21), 119(23), 107(21), 105(32), 93(28), 91(44), 79(33), 41(73).

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