Tetrahedron Letters,Vol.28,No.42,pp 4947-4950,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A SHORT, ENANTIOSPECIFIC SYNTHESIS OF THE 1α-HYDROXYVITAMIN D ENYNE A-RING SYNTHON

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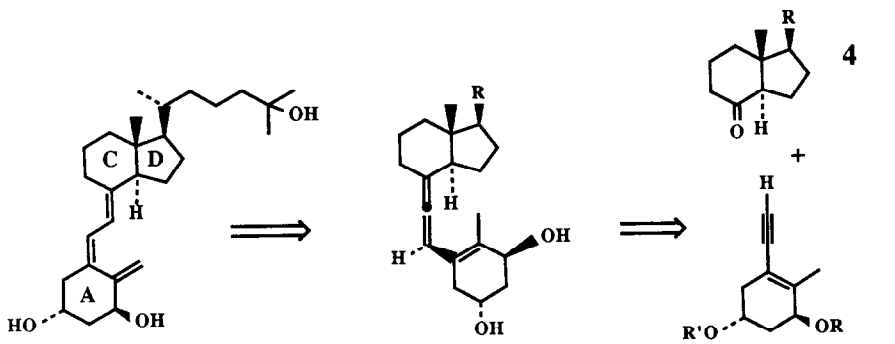
Abstract: The vitamin D A-ring synthon, the enyne **3b**, was synthesized in 5 steps (37% overall yield) from (S)-(+)-carvone (5). The key step was the SmI_2-Pd^0 mediated transformation of epoxypropargyl ester 6 to **3b**.

It has been recently established that 1α,25-dihydroxyvitamin D_3 [1α,25-$(OH)_2D_3$] (1), the hormonal form of vitamin D_3, is able to suppress proliferation and induce differentiation in human myeloid leukemia cells.[1] More classically, this hormone is considered to be the most potent stimulator of calcitropic effects known.[2] These findings have stimulated efforts towards the search for analogues of 1α,25-$(OH)_2D_3$ that, while retaining potent cell differentiating and anti-proliferative activity, do not cause the toxic hypercalcemia associated with the normal calcitropic effects of 1α,25-$(OH)_2D_3$.



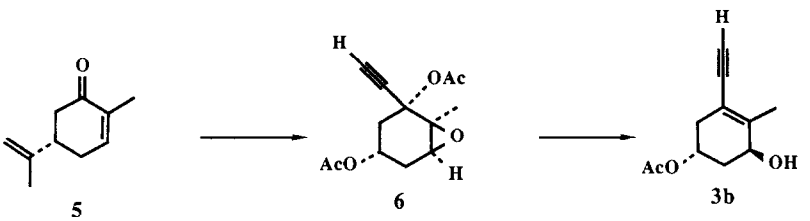
3 **a** R = R' = H
b R = H, R' = Ac

Lythgoe's convergent approach to the synthesis of vitamin D derivatives makes use of the coupling of an A-ring enyne with an appropriate CD-ring fragment.[3] Ongoing investigations in our laboratories have led to the utilization of a [1,5]-sigmatropic H-shift of vinylallenes of the type 2 to generate the triene portion of vitamin D.[4] The hydroxyenyne 3 should be a suitable A-ring fragment for the generation of such vinylallene systems[5] derived from the

coupling of a suitably protected form of 3 and a CD-ring fragment 4.

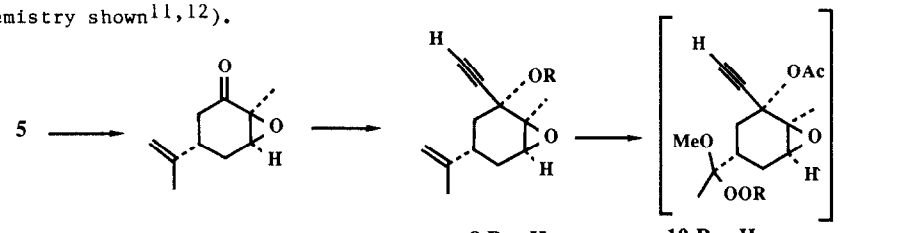
This A-ring synthon 3 was first prepared in 12 steps and 3% overall yield by Lythgoe who used it in a synthesis of $1\alpha,25\text{-}(OH)_2D_3$.[6] More recently, Castedo et al have reported[7a] a more efficient synthesis (11 steps, 10% overall yield) of 3 and the synthesis of a closely related substance has been independently reported by the Hoffmann-La Roche group[7b] and by Desmaele and Tanier[7c].

We now report an expeditious, enantiospecific synthesis of 3 starting from S-(+)-carvone 5, a starting material also utilized by Castedo et al[7a] and the Roche group.[7b] The key step in the synthesis is a novel SmI_2-promoted reductive elimination of the epoxypropargyl acetate 6 with concomitant ring opening of the epoxide moiety to afford the enynol 3b.

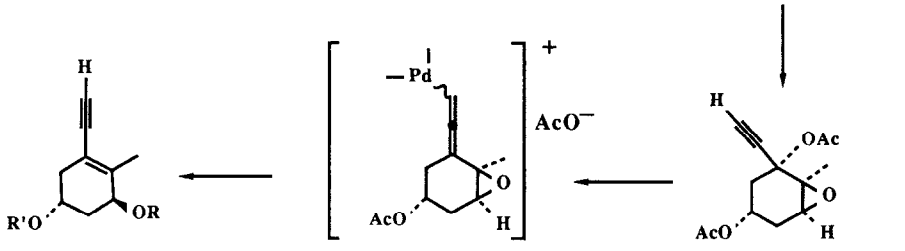


5 6 3b

Our synthesis makes use of the known stereoselective epoxidation of S-(+)-carvone to give cis-carvone epoxide 7 (89%).[8] Addition of lithium acetylide[9] (THF, -78 °C) to 7 proceeded highly stereoselectively to afford the propargyl alcohol 8[10] (81%) (tentatively assigned the stereochemistry shown[11,12]).



7 **8 R = H**
9 R = Ac
10 R = H
11 R = p-$NO_2C_6H_4CO$



3 a R = R' = H
b R = H, R' = Ac
c R = R' = TMS

12 **6**

After acetylation of the hydroxyl group (acetic anhydride, Et_3N, DMAP, 25 °C, 87%) to give 9,[13] ozonolysis (O_3, CH_2Cl_2, MeOH, -78 °C) of the isopropenyl side chain followed by direct acylation of 10 (p-nitrobenzoyl chloride, CH_2Cl_2, pyridine, 0 °C) and in situ Criegee rearrangement[14] (40 °C) of the resulting methoxyperoxyester 11 afforded the key diacetate 6,[15] in 70% overall yield from the monoacetate 9.

The crucial reductive elimination of 6 to 3b was effected using the method recently developed by Inanaga for the conversion of propargyl acetates into allenes.[5b] Under slightly modified conditions [2 eq SmI_2, $Pd(PPh_3)_4$, THF, 25 °C, absence of a proton source[16]) the presumed palladium complex intermediate 12 underwent not only reduction but also epoxide ring opening to cleanly afford the hydroxyenyne 3b[17] in 83% yield [five steps, 37% overall yield from (S)-(+)-carvone].

The use of the A-ring synthon 3 in the synthesis of $1\alpha,25\text{-}(OH)_2D_3$ analogues suitable for biological assay as well as the development of further uses in this context of the new reductive elimination-epoxide ring opening process are presently in progress.

Acknowledgements. The National Institutes of Health (USPHS Grant CA-43277) provided the support for this investigation. We are grateful to A. Mouriño and L. Castedo (Universidad de Santiago de Compostela, Spain) and E.G. Baggiolini (Hoffmann-LaRoche, Nutley, New Jersey) for informing us of their results prior to publication.

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(10) Data for **8**: mp 55-56°C; $[\alpha]_D^{25}$ 0° (c 2.0, $CHC\ell_3$); ^1H NMR (200 MHz, $CDC\ell_3$) δ1.5-1.8 (2H, m), 1.60 (3H, s), 1.71 (3H, s), 2.0-2.3 (3H, m), 2.58 (1H, s), 2.97 (1H, s), 3.36 (1H, m), 4.72 (1H, br s), 4.77 (1H, m). All new compounds exhibited satisfactory spectral and mass spectral analytical data. Additional selected spectroscopic data are presented in footnotes 13, 15 and 17.

(11) The assignment was made on the basis of preferential attack at the less hindered face of the epoxyketone, i.e. opposite to the 10β-methyl[12] group. For a discussion on the stereochemistry of hydride attack on α-ketoepoxides, see Chautemps, P.; Pierre, J.L. Tetrahedron, 1976, 32, 549.

(12) The steroidal numbering system is used wherein the methyl group corresponds to C_{19} and is attached to C_{10}.

(13) Data for **9**: bp (Kugelrohr) 110°C/1.4 mm Hg; $[\alpha]_D^{25}$ + 0.8° (c 1.8, $CHC\ell_3$); ^1H NMR (200 MHz, $CDC\ell_3$) δ1.5-1.7 (2H, m), 1.66 (3H, s), 1.67 (3H, s), 2.03 (3H, s), 2.1-2.3 (3H, m), 3.0 (1H, m), 4.66 (1H, br s), 4.70 (1H, br s).

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(15) Data for **6**: mp 115-116°C; $[\alpha]_D^{25}$ - 19.0° (c 0.5, $CHC\ell_3$); ^1H NMR (200 MHz, $CDC\ell_3$) δ1.61 (3H, s), 1.94 (1H, dd, J = 14.2, 3.4 Hz), 2.03 (3H, s), 2.10 (3H, s), 1.9-2.1 (1H, m), 2.35 (1H, dd, J = 15.8, 6.1 Hz), 2.70 (1H, s), 2.83 (1H, ddd, J = 14.2, 5.4, 1.0 Hz), 3.15 (1H, d, J = 3.4 Hz), 4.97 (1H, m).

(16) Studies on the model system **13** showed that in addition to the desired enyne **14**, unidentified side-products were obtained if, following Inanaga's conditions, a proton source was used.

13 **14**

(17) Data for **3b**: oil; $[\alpha]_D^{25}$ - 101.3° (c 3.0, $CHC\ell_3$); ^1H NMR (200 MHz, $CDC\ell_3$) δ1.8-2.0 (8H, m), 2.1 (1H, m), 2.5 (1H, m), 3.06 (1H, s), 3.3 (1H, br), 4.1 (1H, br), 5.05 (1H, m). Further characterized as the bis(trimethylsilyl)ether **3c**, previously reported by Lythgoe.[6] Data for **3c**: oil, $[\alpha]_D^{25}$ -102.5° (c 0.4, $CHC\ell_3$) [lit.[6] $[\alpha]_D^{22}$ ($CHC\ell_3$) - 90°]; ^1H NMR[6] (200 MHz, $CDC\ell_3$) δ 0.13 (9H, s), 0.17 (9H, s), 1.6-1.9 (2H, m), 1.92 (3H, br s), 2.1 (1H, m), 2.4 (1H, dd, J = 16.6, 4.9 Hz), 3.05 (1H, s), 4.0-4.2 (2H, m).

(Received in USA 23 June 1987)