Tetrahedron Letters,Vol.28,No.19,pp 2099-2102,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

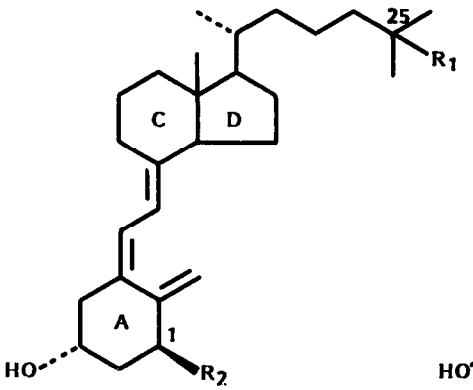
AN IMPROVED SYNTHESIS OF 1α,25-DIHYDROXYVITAMIN D A SYNTHONS[1]

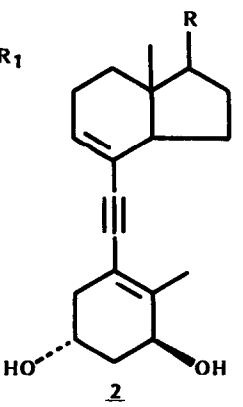
L. Castedo, J.L. Mascareñas and A. Mouriño

Departamento de Química Orgánica. facultad de Química y
Sección de Alcaloides del C.S.I.C. Santiago de Compostela. Spain.

Summary: A new improved preparation of key intermediates (9b, 11) for the synthesis of 1α,25-dihydroxyvitamin D is described.

1α,25-Dihydroxyvitamin D_3 (1b) is considered to be biologically the most important metabolite of vitamin D_3 (1a). This hormone stimulates intestinal calcium absorption (ICA) and bone-calcium mobilization (BCM), and recent studies indicate that it may also be involved in the regulation of cell differentiation and proliferation.[2] Lythgoe and coworkers, in an effort to circumvent the troublesome classical route to 1b, developed a convergent approach in which the intermdiates 2 and 3 are obtained by coupling of synthons containing ring A and rings CD. One major drawback of this promising approach is the low yield obtained in the synthesis of the required A-ring-containing fragments.[3]





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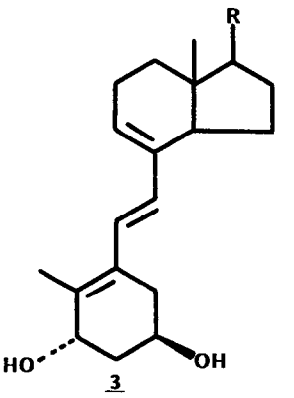

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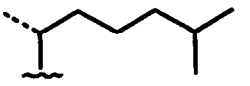
1a, $R_1=R_2=H$

1b, $R_1=R_2=OH$

R=



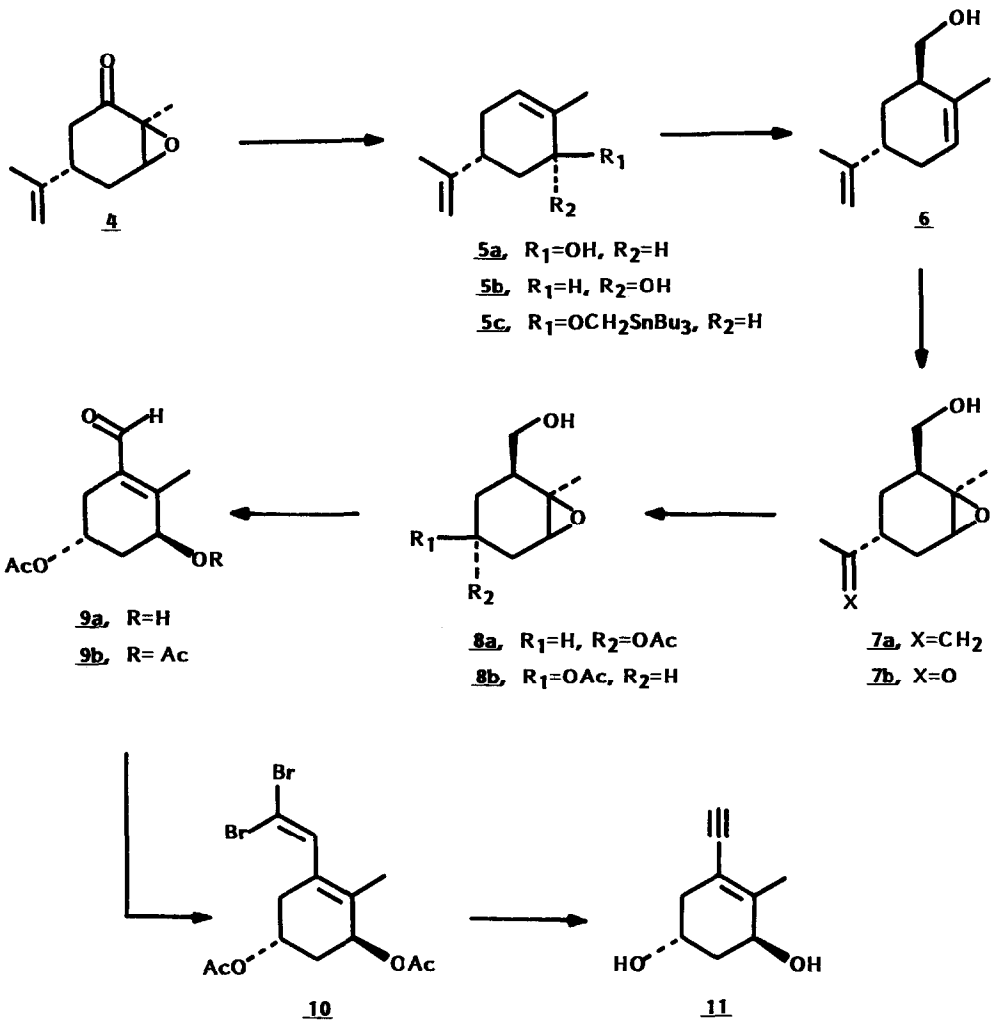
We here describe our initial efforts towards the synthesis of 1b, which have resulted in improved syntheses of aldehyde 9b and enyne 11.[4] These compounds should lead satisfactorily by known methods[3,5] to 25-hydroxylated 2 and 3, which in turn should afford the desired 1b.

The starting point for our synthesis is d-carvone ((S)-(+)-carvone) or l-carvone. Stereoselective epoxidation of d-carvone (30% H_2O_2, LiOH, MeOH, 0 ºC) provided the epoxide 4[6] in 95% yield after kugelrohr distillation. Conversion of 4 into allylic alcohol 5a[7] was accomplished in 60% yield by Wharton's reaction (4 equiv of $NH_2NH_2.H_2O$, $Me_2NCH_2CH_2OH$, RT, 24 h)[8] after conventional chromatography and kugelrohr distillation.[9] The allylic alcohol 5a was alternatively prepared in 72% overall yield[10] from l-carvone by the sequence: (1) reduction ($NaBH_4$-$CeCl_3$, MeOH)[11], (2) Mitsunobu inversion (3 equiv of diethyl azodicarboxylate, 3 equiv of Ph_3P, 3 equiv of $PhCO_2H$, THF, RT: 40 h)[12], and (3) benzoate saponification (2M KOH-MeOH, RT, 12 h).

Deprotonation of alcohol 5a (2 equiv of KH, THF, RT: 3 h) and alkylation (1.1 equiv of ICH_2SnBu_3[13], THF, 0 ºC: 15 min, RT: 12 h) gave, after flash chromatography, the allylic stannyl methyl ether 5c in 75% yield. This ether was then converted into the desired homoallylic alcohol 6 in 77% yield via (2,3)-sigmatropic rearrangement[14] (1.2 equiv of n-BuLi, THF, -78 ºC, RT: 20 min) and flash chromatography (10% EtOAc/hexanes).[15] Hydroxyl-directed epoxidation of 6 (catalytic $VO(acac)_2$, PhH, 50 ºC: 5 min; then 1.2 equiv of 3M TBHP in toluene, RT: 3 h) followed by flash chromatography (10% EtOAc/hexanes) afforded epoxyalcohol 7a in 86% yield. 7a was subjected to oxitative cleavage at the double bond (catalytic OsO_4, THF-H_2O/2.5:1, RT: 10 min; then 3 equiv of KIO_4, RT: 5 h)[16] to give, after flash chromatography (30% EtOAc/hexanes), pure methyl ketone 7b in 78% yield. Baeyer Villiger oxidation of 7b using aqueous pH 8 buffer (2.75 equiv of m-CPBA, $CHCl_3$, 12 h)[17] afforded the monoacetate 8a in 85% yield.

In order to check the purity of 7b and that no epimerization had taken place during the last steps, the enantiomer of 5b, prepared in 85% yield by reduction ($NaBH_4$-$CeCl_3$)[11] of d-carvone, was subjected to the same sequence of reactions. The synthesized epi-monoacetate 8b (30% overall yield) is clearly distinguished from 8a by 250 ^1H NMR.

Swern oxidation of 8a (1.2 equiv of oxalyl chloride, 2.2 equiv of DMSO, CH_2Cl_2, -60 ºC: 10 min; then 6.4 equiv of Et_3N, RT: 4 h) gave the aldehyde 9a which was acetylated (2 equiv of Ac_2O, Py, catalytic DMAP, CH_2Cl_2, RT: 6 h) to the known diacetate 9b[3b] in 70% yield (two steps) (15% overall yield from d-carvone, 9 steps). Chain extension[18] to the desired enyne 11 was accomplished in 72% yield by conversion to the vinyl dibromide 10 (6 equiv of Zn, 6 equiv of CBr_4, 6 equiv of Ph_3P, 12 equiv of Py, RT: 1 h, flash chromatography: 15% EtOAc/hexanes) and subsequent elimination with n-butyllithium (7 equiv, THF, -78 ºC: 30 min, RT: 1 h, flash chromatography: 30% EtOAc/hexanes). Enyne 11[3a] was thus finally obtained from d-carvone in 10% overall yield (11 steps).[19,20]



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4. These compounds were synthesized in less than 2% and 1% yield respectively.[3]

5. For a recent improved synthesis of 1-hydroxydienynes by palladium-catalyzed coupling of enol triflates with stannyl enynes, see: L. Castedo, A. Mouriño, and L.A. Sarandeses, **Tetrahedron Lett.**, 1986, **27**, 1523.

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9. GLC analysis showed slight contamination with the epimer 5b (approx. 3%).

10. 250 MHz ^{1}H NMR analysis showed 5% contamination with the epimer 5b after kugelrohr distillation. Although this method provides a higher overall yield of the desired allylic alcohol, it proved to be less satisfactory in multigram scales (> 1 g) due to chromatography problems found during purification.

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15 This sequence was also accomplished in slightly lower yield without isolating the stannyl ether derivative.

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19 All new compounds gave satisfactory ^{1}H NMR and high resolution mass spectra.

20. We gratefully acknowlegdge the financial support of the Comisión Asesora de Investigación Científica (CAICYT) and the courtesy of Hoffmann la Roche (Nutley) for sending their work for publication simultaneously with ours (see accompanying communication). We also thank Dr. B. Fraser-Reid for providing us with the detailed procedure for the chain extension. J.L.M. thanks the Ministerio de Educación y Ciencia for the grant of a fellowship.

(Received in UK 2 March 1987)