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FUNCTIONALIZATION OF VITAMIN D METABOLITES AT C-18 AND APPLICATION TO THE SYNTHESIS OF 1α,18,25-TRIHYDROXYVITAMIN D_3 AND 18,25-DIHYDROXYVITAMIN D_3.[1]

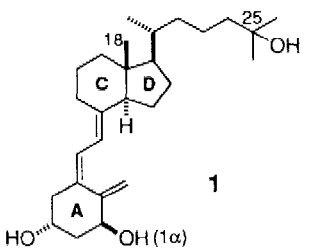
María José Vallés, Luis Castedo, and Antonio Mouriño*

Departamento de Química Orgánica. Facultad de Química y Sección de Alcaloides del C.S.I.C., 15706 Santiago de Compostela. Spain.

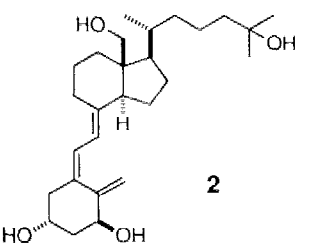
Key Words: 1α,25-Dihydroxyvitamin D_3; Analogues at C-18; 1α,18,25-Trihydroxyvitamin D_3; 18,25-Dihydroxyvitamin D_3; Synthesis; Dienyne route; Wittig-Horner approach.

Abstract: A general procedure for the introduction of a hydroxyl group at C-18 in several intermediates derived from the Inhoffen-Lythgoe diol is described for the first time. As an application, the syntheses of 1α,18,25-trihydroxyvitamin D_3 (**2**, dienyne route) and 18,25-dihydroxyvitamin D_3 (**3**, Wittig-Horner approach) are described. The synthetic strategy allows further functionalization of the hormone 1α,25-dihydroxyvitamin D_3 at C-18.

It is now known that 1α,25-dihydroxyvitamin D_3 [**1**, 1α,25-$(OH)_2$-D_3, calcitriol], in addition to its important role in calcium homeostasis,[2] promotes cell differentiation and inhibits cell proliferation.[3] However, the use of this hormone in the treatment of certain cancers and skin disorders has been limited in part due to its potent calcemic effects.[4] As a consequence, a considerable amount of attention has been focussed on the synthesis of structurally modified analogues of **1** and, to date, a few D-ring and side-chain-modified analogues have already been chosen for clinical studies with promising results.[4,5] The fact that vitamin D analogues functionalized at C-18 have not been reported, led us to undertake studies directed toward the synthesis and biological evaluation of analogues of **1** and other vitamin D metabolites.



1



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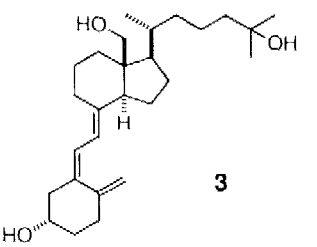
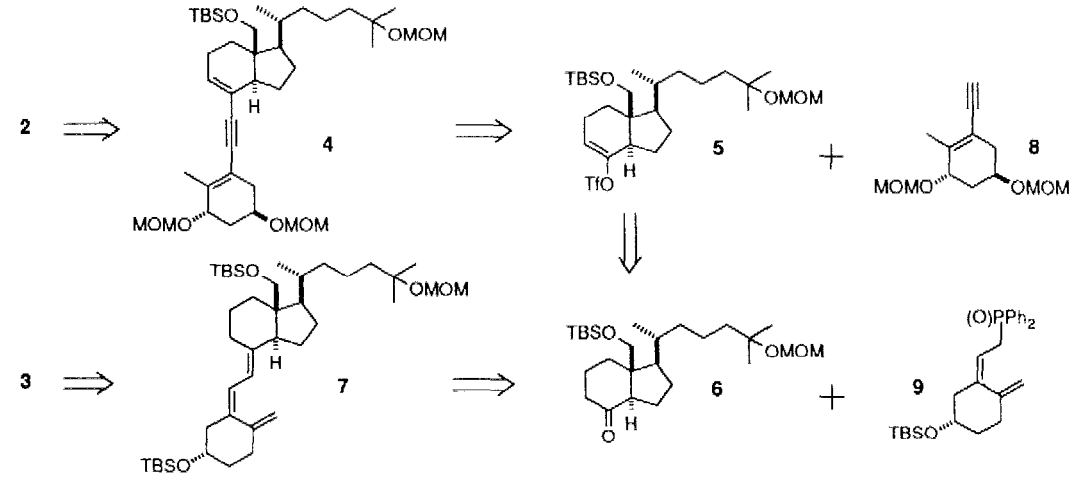


3

We describe here our initial results which have led to functionalization of vitamin D metabolites at C-18 and to the synthesis of 1α,18,25-trihydroxyvitamin D_3 (**2**) and 18,25-dihydroxyvitamin D_3 (**3**). For the synthesis of **2**, we selected the recently improved dienyne route[6,7] due to the easy preparation of the A-ring fragment **8** from the commercially available (*S*)-(+)-carvone[8] (Scheme 1). In this strategy, the C-18 hydroxyl group is protected as its silyl ether in order to be able to selectively deprotect it in the final steps of the synthesis. This synthetic route could lead to potentially useful photoaffinity labels to study the active site of the receptor of **1**. The approach selected for the synthesis of **3** relied on a Lythgoe type Wittig-Horner coupling[9] between the anion

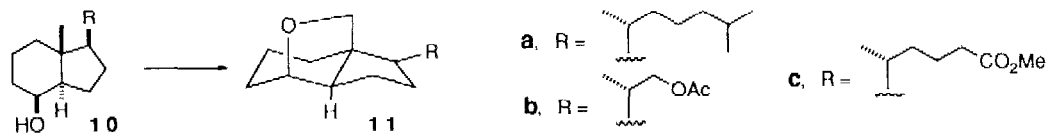
of the phosphine oxide **9**, which is easily prepared by degradation of vitamin D_2,[10] and the key ketone **6**.

Scheme 1



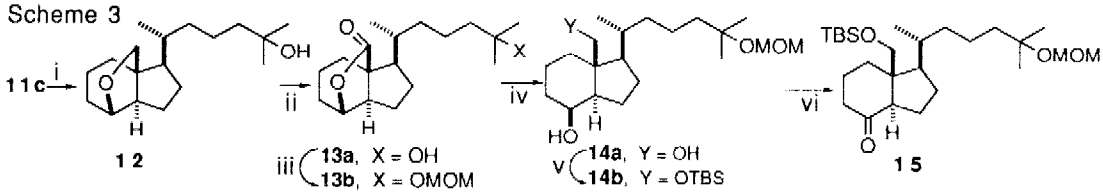
The key feature of both syntheses is the intramolecular functionalization of the C-18 position, present in all known vitamin D metabolites. This functionalization was first examined on the simple known alcohol **10a**[7] (Scheme 2). After some experimentation, we found that treatment of **10a** with lead tetraacetate gave the desired cyclic ether **11a** in 60 % yield.[11] Extension of this method to the functionalization of the intermediates **10b**[12] and **10c**[13] provided the key cyclic ethers **11b** and **11c** in 67 and 62 % yield respectively.[14,15]

Scheme 2



As part of our program directed toward the synthesis of vitamin D analogues functionalized at C-18 from the above cyclic ethers, we first focussed our attention on the synthesis of the target compounds **2** and **3**. For this purpose, we used the ether **11c**, which was converted to the alcohol **12** in 95 % yield by treatment with methyllithium (Scheme 3). Oxidation of **12** at C-18 was accomplished with a catalytic amount of ruthenium tetroxide in the presence of sodium periodate to give the lactone **13a** in 56 % yield. Protection of the hydroxyl group of **13a** with chloromethyl methyl ether and subsequent reduction of the lactone functionality with diisobutylaluminum hydride (DIBAL-H) afforded the 18-hydroxylated compound **14a** (98 % yield over the two steps). Selective protection of the C-18 hydroxyl group of **14a** with *tert*-butyldimethylsilyl chloride followed by oxidation of the resulting silyl ether **14b** with pyridinium dichromate gave the required ketone **15** (66 % yield over the two steps), which serves as a common intermediate for the synthesis of both vitamin D analogues **2** and **3**.

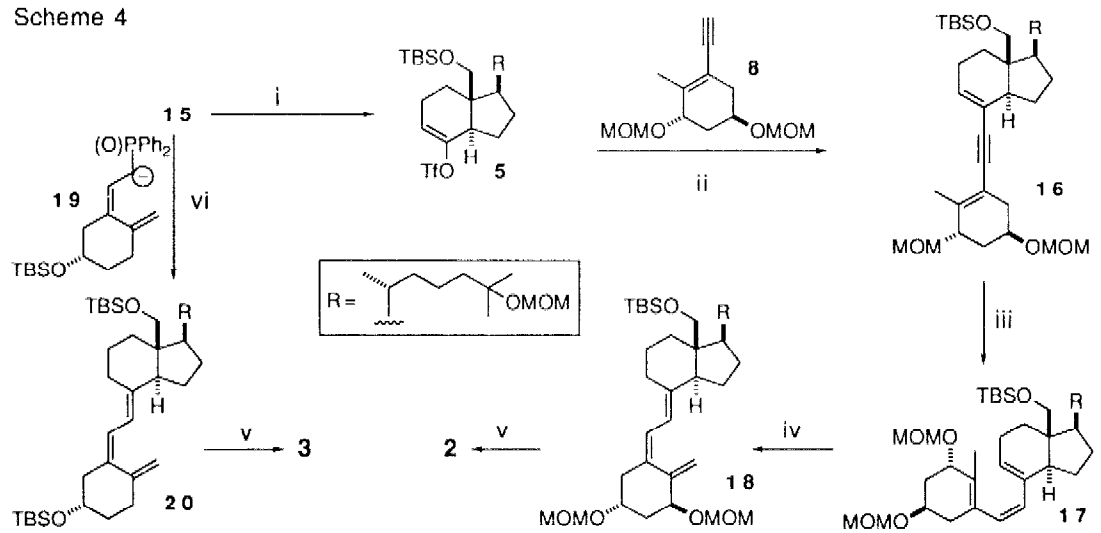
Scheme 3



(i) -78 °C, MeLi (2.2 equiv), Et_2O, -78 °C → r.t. (95 %). (ii) $CCl_4/H_2O/CH_3CN$ (1:1.5:1), $NaIO_4$ (4.1 equiv), $RuO_4 \cdot H_2O$ (0.07 equiv), r.t., 15 days (56 %). (iii) CH_2Cl_2, 0 °C, ClMOM (4.4 equiv), *i*-Pr_2NH (4.4 equiv), DMAP (0.3 equiv), 6h; r.t., 12 h (98 %). (iv) THF/toluene (1.5:1), -78 °C, DIBAL-H (3.5 equiv), 15 min; -78 °C → r.t., (99%). (v) DMF, TBSCl (1.1 equiv), imidazole (1.8 equiv), **14a** in CH_2Cl_2, r.t., 1 h (76 %). (vi) CH_2Cl_2, 0 °C, PDC (2.7 equiv), PPTS (trace), 1h; r.t., 4 h (87 %).

The vinyl triflate **5** (upper fragment) was prepared in 82 % yield by treatment of **15** with LDA and trapping of the resulting kinetic enolate with N-phenyltriflimide (Scheme 4). The A-ring-containing fragment **8** was obtained in 68% yield from the corresponding *tert*-butyldimethylsilyl-protected enyne[8] by deprotection (*n*-Bu_4NF, THF) and reprotection (MOMCl, *i*-Pr_2NEt). Palladium-catalyzed assembly of both fragments **5** and **8** afforded the dienyne **16** (75 % yield), which was converted to the previtamin **17** by partial hydrogenation in the presence of Lindlar catalyst (93 %). The previtamin **17** was thermally equilibrated to a mixture of **18** and **17** (85:15), which was subsequently subjected to deprotection with AG 50W-X4 cation-exchange resin in methanol to provide, after chromatography, the desired vitamin D analogue **2** (41 % over the two steps). On the other hand, reaction of **15** with the phosphine oxide anion **19**[10] afforded the protected vitamin D **20** (87 %), which upon deprotection as above gave the desired vitamin D analogue **3** (47 %).16

Scheme 4



(i) LDA (1.6 equiv), THF, -78 °C, **15** in THF, $PhNTf_2$ (2 equiv) in THF, 2h, -78 °C → r.t. (slowly) (82 %), plus **15** (14 %). (ii) DMF, Et_3N (3 equiv), **8** (1 equiv), $(Ph_3P)_2PdCl_2$ (0.04 equiv), 70-75 °C, 75 min (74 %). (iii) Hexane, Lindlar, quinoline, H_2 (balloon), r.t., 15 min (93 %). (iv) Isooctane, 100 °C, 5 h, ratio **18**:**17** (85:15) (82 %). (v) AG 50W-X4, MeOH, r.t., 6 days in the dark (51 %). (vi) **19** (3 equiv), THF, -78 °C, **15** in THF, 1 h; -78 °C → r.t. (87 %).

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References and Notes

1. This work is dedicated to the memory of Enrico Baggiolini.

2. (a) Norman, A.W. "Vitamin D, the Calcium Homeostatic Steroid Hormone"; Academic Press: NY, 1979. (b) Jones, G. *Steroids* **1987**, *49*, 1. (c) Ikekawa, N. *Med. Res. Rev.* **1987**, *7*, 333. (d) Dickon, I. *Nature* **1987**, *325*, 18.

3. (a) Provvedini, D.M.; Tsoukas, C.D.; Deftos, L.J.; Manolagas, S.C. *Science (Washington D.C.)* **1983**, *221*, 1181. (b) For a review, see: Ostream, V.K.; DeLuca, H.F. *Steroids* **1987**, *49*, 73.

4. For leading references, see: Figadère, B.; Norman, A.W.; Henry, H.L.; Koeffler, H.P.; Zhou, J.-Y.; Okamura, W.H. *J. Med. Chem.* **1991**, *34*, 2452.

5. Proceedings of the Eighth Workshop on Vitamin D, Paris, France, July 1991. Norman, A.W.; Schaefer, K.; Grigoleit, H.G.; Herrath, D.v. Eds.; Walter de Gruyter: Berlin, in press.

6. (a) Castedo, L.; Mouriño, A.; Sarandeses, L.A. *Tetrahedron Lett.* **1986**, *27*, 1523. (b) Mascareñas, J.L.; Sarandeses, L.A.; Castedo, L.; Mouriño, A. *Tetrahedron* **1991**, *40*, 3485.

7. For reviews on the synthesis of vitamin D metabolites and analogues, see: Quinkert, G. Ed.; *Synform* **1985**, **1986**, **1986**, *3*, *4*, *5*.

8. Okamura, W.H.; Aurrecoechea, J.M.; Gibbs, R.A.; Norman, A.W. *J. Org. Chem.* **1989**, *54*, 4072.

9. For a review, see: Lythgoe, B. *Chem. Soc. Rev.* **1980**, 449.

10. Mascareñas, J.L.; Mouriño, A.; Castedo, L. *J. Org. Chem.* **1986**, *51*, 1269 and ref. therein.

11. The use of $Pb(OAc)_4$, AcOH/ RuO_4, $NaIO_4$ or $Pb(OAc)_4$, I_2/CrO_3, H_2SO_4 gave the corresponding lactone at C-18 (57-60 %)

12. **10b** was easily prepared (87 %) by selective esterification (1 equiv Ac_2O, py, 0 °C, 24 h) of the Lythgoe-Inhoffen dio[6b].

13. Mascareñas, J.L.; Pérez-Sestelo, J.; Castedo, L.; Mouriño, A. *Tetrahedron Lett.* **1991**, *32*, 2813.

14. Substantial amounts of the corresponding ketones (30 %) were obtained as byproducts. These materials were recycled to the starting alcohols **10b** and **10c** by reduction with $NaBH_4$.

15. General procedure: A mixture of starting alcohol (1 equiv), $Pb(OAc)_4$ (2 equiv) in dry benzene (30 mL/mmol of alcohol) was refluxed under argon for 12 h. An additional amount of $Pb(OAc)_4$ (0.6 equiv) was added and the reflux was continued for 10 h. Conventional work up gave a residue which was purified by medium pressure column chromatography (Meyers, A.I.; Slade, J.; Smith, R.K.; Mihelich, E.P.; Herhenson, F.M.; Liang, C.O. *J. Org. Chem.* **1979**, *44*, 2247.

16. All new compounds exhibited satisfactory ^1H and ^{13}C NMR, analytical, and /or high resolution mass spectral data. The synthesis of other analogues functionalized at C-18 is in progress.

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