Tetrahedron Letters,Vol.29,No.10,pp 1203-1206,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

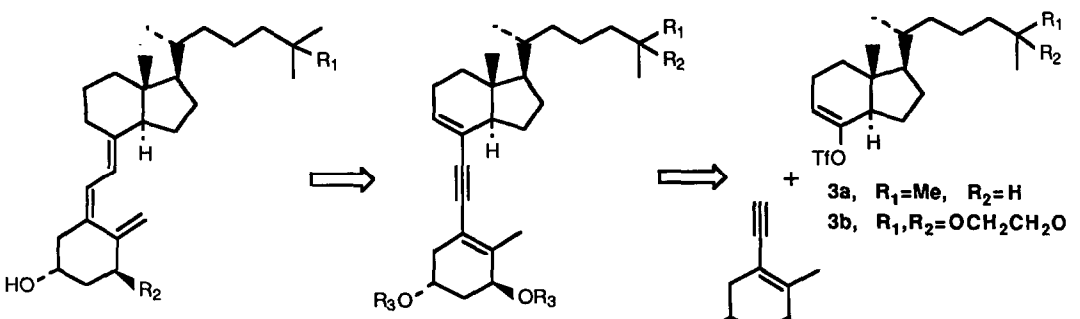
PALLADIUM-CATALYZED SYNTHESIS OF DIENYNES RELATED TO 1α,25-DIHYDROXYVITAMIN D_3

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

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

Summary: This note describes an efficient synthesis of a 25-functionalized dienyne precursor of the natural hormone 1α,25-dihydroxyvitamin D_3 which allows easy labelling on the side chain.

1α,25-Dihydroxyvitamin D_3 (**1b**) is considered the most potent known metabolite of vitamin D_3 (**1a**). This metabolite, which acts like the classical steroidal hormones, stimulates the physiological functions attributed in the past to vitamin D_3, such as intestinal calcium absorption and bone calcium mobilization,[1] and recent studies indicate that it is also involved in regulating the differentiation and proliferation of several types of leukemia cells.[2] In previous communications we reported an efficient method for the construction of dienyne precursors of the vitamin D_3 triene system by palladium-catalyzed coupling of 1-hydroxylated A-ring stannyl enynes and A-ring-containing enynones with enol triflates.[3] More recently we reported the synthesis of the Lythgoe A-ring enyne corresponding to 1α,25-dihydroxyvitamin D_3, **4a**.[4] In this communication we report an efficient method for the preparation of dienyne **2c**, the precursor of the natural hormone **1b**.



1a, $R_1=R_2=H$
1b, $R_1=R_2=OH$

2a, R_1=Me, $R_2=R_3=H$
2b, R_1=Me, R_2=H, $R_3=SiMe_2t$-Bu
2c, $R_1,R_2=OCH_2CH_2O$, $R_3=SiMe_2t$-Bu

3a, R_1=Me, R_2=H
3b, $R_1,R_2=OCH_2CH_2O$

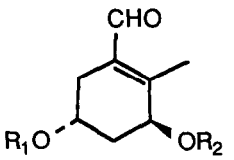
4a, R=H
4b, $R=SiMe_2t$-Bu

We have found that treatment of enynol **4a**[4] with the enol triflate **3a**[3] gives the dienyne **2a** in only 55 % yield under the conditions previously reported for the construction of the triene system of vitamin D_3 from enynones and enol triflates (catalyst: $Pd(PPh_3)_2Cl_2$, NEt_3, DMF).[3] In view of this moderate yield we decided to prepare the protected A-ring enyne **4b** and to study its coupling reaction with enol triflate **3a**. Saponification of **5a**[4] (2.8 equiv of NaOMe in MeOH, RT, 4h) and protection of the resulting diol **5b**[5] ($ClSiMe_2t$-Bu, imidazole, CH_2Cl_2) afforded the protected aldehyde **5c** in 82 % overall yield. Chain extension[6,4] to the desired protected enyne **4b** was accomplished in 75 % yield by conversion to the vinyl dibromide **6** (6 equiv of Zn, 6 equiv of PPh_3, 6 equiv of CBr_4, RT, 12 equiv of py, 20 min, flash chromatography: hexanes) and subsequent elimination with n-butyllithyum (2.1 equiv, THF, -70 °C, 15 min, flash chromatography: hexanes). Coupling the protected enyne **4b** with enol triflate **3a** under the same catalytic conditions as before afforded the dienyne **2b** in 90 % yield. This result encouraged us to prepare the 25-functionalized enol triflate **3b**, which would allow easy labelling in the final steps of the synthesis of **1b**.

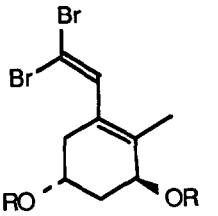
The Inhoffen diol **7a**[7] was transformed into the iodide **7b** in 93 % yield by the sequence (p-TsCl, py; NaI, acetone). Construction of the side chain was carried out by using the zinc-copper-mediated conjugated addition of iodides to α,β-unsaturated ketones in aqueous media recently developed by Luche an coworkers.[8] Sonication of an oxygen-free mixture of purified CuI (1 equiv), Zn (4 equiv), iodide **7b** and methyl vinyl ketone (1.3 equiv) in $EtOH:H_2O$ (7:3) for 20 min and further sonication for 30 min after the addition of more CuI (0.5 equiv) and Zn (2 equiv) at RT afforded the ketoalcohol **8a**[9] in 78 % yield after work-up (filtration, washing with Et_2O, brine, extraction with Et_2O) and flash chromatography (5 % EtOAc/hexanes). Ketalization of **8a** ($HOCH_2CH_2OH$, p-TsOH) gave the protected alcohol **8b**[9] (96 %), which in turn was oxidized to the ketone **8c**[9] (3 equiv of PDC, trace of PPTS, CH_2Cl_2) in 94 % yield (65 % overall yield from **7a**, 5 steps).[10] Kinetic enolate formation on **8c** (1.1 equiv of LDA, THF, -80 °C: 15 min, RT: 2h, -80 °C) followed by the addition of N-phenyltrifluoromethanesulphonimide ($PhNTf_2$, 1.1 equiv) in THF and stirring for 12 h at 0 °C afforded the triflate **3b** in 92 % yield after flash chromatography (5-10 % EtOAc/hexanes).

Finally, coupling reaction between enol triflate **3b** and enyne **4b** (3 % equiv of $Pd(PPh_3)_2Cl_2$, 3 equiv of NEt_3, DMF, 70 °C)[11] afforded the desired dienyne **2c**[12] in 93 % yield after work-up and flash chromatography (2 % EtOAc/hexanes).[13]

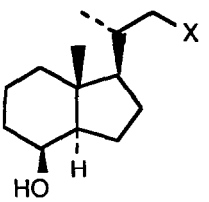
The key intermediate **2c** can be used for the preparation, by known procedures,[14] of the natural hormone 1α,25-dihydroxyvitamin D_3 including labelled analogs in the side chain.



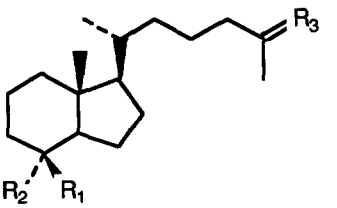
5a, R_1=Ac, R_2=H
5b, R_1=R_2=H
5c, R_1=R_2=SiMe$_2$t-Bu



6, R=SiMe$_2$t-Bu



7a, X=OH
7b, X=I



8a, R_1=OH, R_2=H, R_3=O
8b, R_1=OH, R_2=H, R_3=OCH$_2$CH$_2$O
8c, R_1=R_2=O, R_3=OCH$_2$CH$_2$O

Acknowledgements: We gratefully acknowledge the financial support of the Comisión Asesora de Investigación Científica (CAICYT). We thank Hoffmann La Roche (Basel) for the generous gift of vitamin D_2 used for the preparation of **7a**. J.L.M. thanks the Ministerio de Educación y Ciencia for the grant of a fellowship.

REFERENCES AND NOTES

1. (a) A.W. Norman, "Vitamin D, the Calcium Homeostatic Steroid Hormone"; Academic Press: New York, 1979; (b) H.F. DeLuca, H.E. Paaren, H.K. Schnoes, *Top. Curr. Chem.*, **83**, 1 (1979).

2. (a) "Vitamin D: Chemical, Biochemical and Clinical Update", Ed.: A.W. Norman, K. Schaefer, H.-G. Grigoleit, D.v. Herrath, Walter de Gruyter & Co. Berlin-New York. 1985 and ref. therein; (b) J.A. MacLaughlin, W. Gange, D. Taylor, E. Smith, M.F. Holick, *Proc. Natl. Acad. Sci. USA*, **82**, 5409 (1985).

3. L. Castedo, A. Mouriño, and L.A. Sarandeses, *Tetrahedron Lett.*, **27**, 1523 (1986).

4. L. Castedo, J.L. Mascareñas, and A. Mouriño, *Tetrahedron Lett.*, **28**, 2099 (1987).

5. E.G. Baggiolini, B.M. Hennessy, J.A. Iacobelli, and M.R. Uskokovic, *Tetrahedron Lett.*, **28**, 2095 (1987).

6. E.J. Corey and P.L. Fuch, *Tetrahedron Lett.*, 3769 (1972).

7. F.J. Sardina, A. Mouriño, and L. Castedo, *J. Org. Chem.*, **51**, 1264 (1986), and ref. therein.

8. C. Petrier, C. Dupuy, and J.L. Luche, *Tetrahedron Lett.*, **27**, 3149 (1986).

9. J.L. Mascareñas, A. Mouriño, and L. Castedo, *J. Org. Chem.*, **51**, 1269 (1986).

10. This easy route is an improvement on previous methods[9] for functionalization of the side chain of 1α,25-dihydroxyvitamin D_3 at C-25.

11. Previously, a different palladium catalyst and 1-hydroxylated A-ring stannyl derivatives were used for the construction of the triene system.

12. 250 MHz ^{1}H-NMR (δ, $CDCl_3$, TMS, **2c**): 0.07 (6H, s), 0.10 (6H, s), 0.69 (3H, s), 0.88 (9H, s), 0.89 (9H, s), 0.94 (3H, d), 1.32 (3H, s), 1.90 (3H, br s), 3.94 (4H, m), 4.13 (1H, m), 4.20 (1H, m), 5.97 (1H, d).

13. All new compounds gave satisfactory microanalysis or high resolution mass spectra results.

14. (a) R.G. Harrison, B. Lythgoe, and P.W. Wright, *J.C.S. Perkin I*, 2654 (1974); (b) T.M. Dawson, J. Dixon, P.S. Littlewood, B. Lythgoe, and A.K. Saksena, *J. Chem. Soc. (C)*, 2960 (1971).

(Received in UK 29 December 1987)