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Efficient and Versatile Synthesis of A-Ring Precursors of 1α,25-Dihydroxy-vitamin D_3 and Analogues. Application to the Synthesis of Lythgoe-Roche Phosphine Oxide.§

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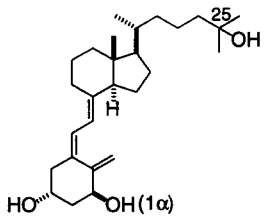
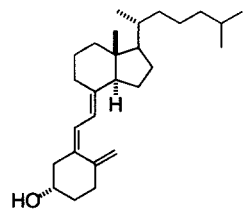
Abstract: An efficient, versatile synthesis of Lythgoe-Phosphine Oxide has been developed starting from *l*-carvone. The key steps are rupture of protected epoxide **7** to give dicarbonyl compound **8**, preparation of vinylic triflate **2**, and palladium-catalysed cyclization-carbonylation of vinylic triflate **2**.

Chemical and pharmacological research in the vitamin D field has greatly intensified since the discovery that 1α,25-dihydroxy-vitamin D_3 [calcitriol; **1a**, 1α,25-$(OH)_2$-D_3] - the hormonally active form of vitamin D_3[1] - can promote cell-differentiation and inhibit cell-proliferation.[2] Already, calcitriol and several of its analogues have been used or are being tested as drugs for the treatment of a wide range of human diseases, including rickets, osteoporosis, cancer, AIDS, psoriasis and Alzheimer's disease.[3]

Figure 1



1a [1α,25-$(OH)_2$-D_3]

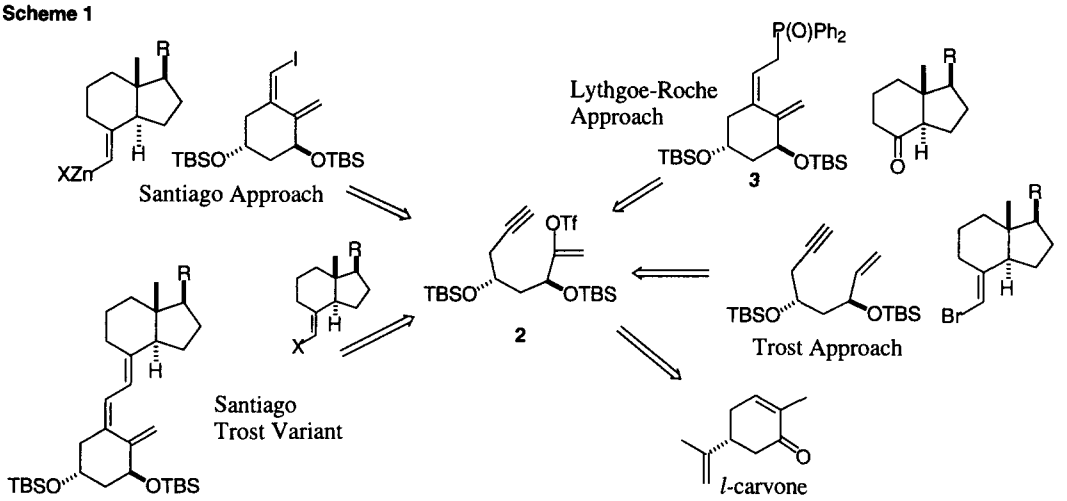


1b (vitamin D_3)

Analogues of 1α,25-$(OH)_2$-D_3 that have strong cell-differentiating activity and weak or negligible calcemic effects are of potential therapeutic utility. To obtain these analogues, several research groups are currently working on the development of new synthetic routes to the vitamin D skeleton, and on the improvement of existing convergent routes.[4] Among the most useful routes is the convergent approach developed by Lythgoe and co-workers and later improved by Hoffmann-La Roche.[4,5] In this strategy the vitamin D triene system is prepared directly by coupling the ylide derived from phosphine oxide **3** with ketones bearing the C,D-ring and

side-chain moieties (Scheme 1). Proof of the importance of this route is the large number of synthetic approaches to **3** that have been reported.[5c,6] In the present work, we report the synthesis of **3** *via* vinylic triflate **2** from *l*-carvone. Compound **2** is also a potentially useful A-ring precursor for use in other synthetic approaches to 1α,25-$(OH)_2$-D_3 and analogues (Scheme 1).

Scheme 1



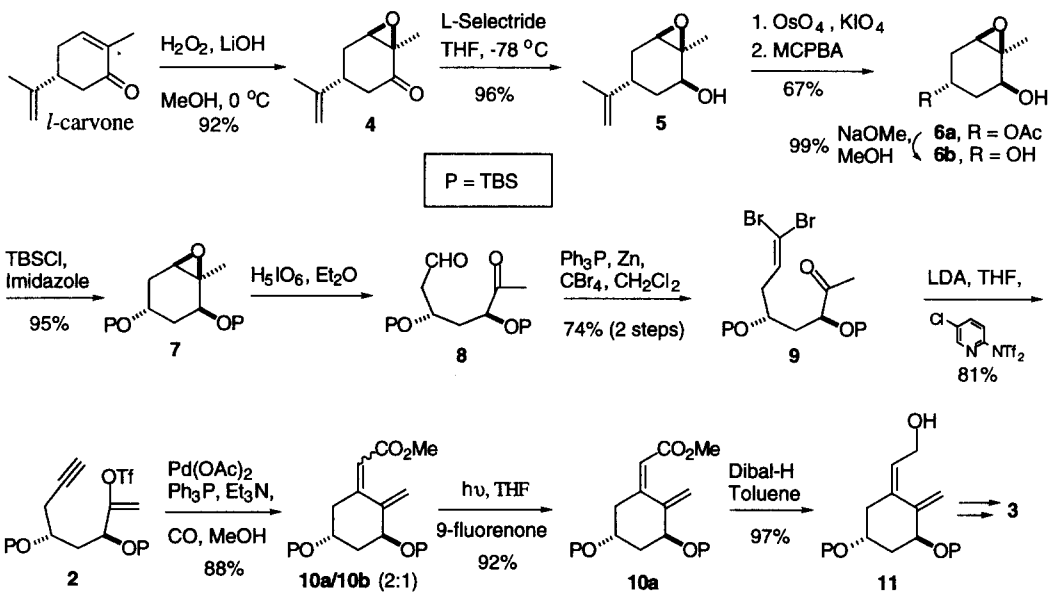
Scheme 2 details the synthesis of vinylic triflate **2** and its subsequent conversion into phosphine oxide **3**. The key steps are cleavage of protected epoxide **7** to give the dicarbonyl compound **8**, and palladium-catalysed stereoselective cyclization-carbonylation of vinylic triflate **2**.[7]

Protected epoxide **7** was prepared by modification of Takano's procedure.[6b] Stereoselective epoxidation[8] of *l*-carvone gave, after purification by flash chromatography and bulb-to-bulb distillation, epoxide **4**[9] in 92% yield. Stereoselective reduction of **4** with L-Selectride®, gave alcohol **5**[6b] in 96% yield. Compound **5** was converted to **6a** in 67% yield by oxidative cleavage of the double bond with a catalytic amount of osmium tetroxide and potassium periodate, followed by Baeyer-Villiger oxidation (MCPBA, Na_2HPO_4-KH_2PO_4, pH 7.6). The acetate **6a** was hydrolysed to afford the desired dihydroxy epoxide **6b** [mp 106-8 °C(EtOAc); $[\alpha]_D^{20}$ = -35 (c = 4.9 MeOH), 99% yield], which was protected using *tert*-butyldimethylsilyl chloride in the presence of imidazole to give the known silylated compound **7**[6b] in 95% yield.

The next step was the crucial oxidative cleavage of the epoxide. Reaction of protected epoxide **7** with periodic acid (1.5 equiv) in diethyl ether[10] gave aldehyde **8**, which was immediately subjected to Wittig reaction using modified Corey-Fuchs conditions[11] (1.5 equiv CBr_4, 1.5 equiv Ph_3P, 1.5 equiv Zn, CH_2Cl_2-py, 0 °C, 1 h), to afford, after flash chromatography, vinylic dibromide **9** (74% yield for the two steps).[12] After several experiments, we were delighted to find that **9** could be converted into the desired vinylic triflate **2** in one simple operation by treatment with LDA (3.5 equiv, -78 °C) in THF, followed by *N*-(5-chloro-2-pyridyl)triflimide[13] (2 equiv) (81% yield from **9**). Cyclization followed by carbonylation of vinylic triflate **2** was performed under

CO (balloon pressure) in methanol, using $Pd(OAc)_2$ as catalyst, which afforded a 2:1 mixture of the *Z*- and *E*-esters **10a** and **10b**, respectively, in 88% combined yield. Photoisomerization of this mixture using the Hoffmann-La Roche method[5c] gave the known ester **10a**[6c,i] (92%). Reduction of **10a** gave alcohol **11**[5c,6b,c,m] {$[\alpha]_D^{25}$ = + 8.7 (0.4, EtOH), lit[5c] $[\alpha]_D^{25}$ = + 7.9 (c 0.4, EtOH)}. Transformation of alcohol **11** into the target phosphine oxide **3** can be achieved using known methods.[5c,6]

Scheme 2



In conclusion, an efficient, versatile 12-step sequence has been developed for the conversion of *l*-carvone into alcohol **11** in 26% overall yield. Alcohol **11** can be transformed into Lythgoe-Roche **3** by known procedures. Further investigations on the synthesis of vitamin D analogues using compounds **8** and **2** are being pursued in our laboratories.

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References and Notes

§ This paper is dedicated to the memory of Prof. William Dauben.

‡ Erasmus student on leave from the University of Gent, (Belgium).

1. (a) Vitamin D, The Calcium Homeostatic Steroid Hormone; Norman, A. W., Ed.; Academic Press: New York, **1979**. (b) For a leading review on the classical actions of 1,25-$(OH)_2$-D_3, see: DeLuca, H. F.; Burmester, J.; Darwish, H.; Krisinger, J. Molecular Mechanism of the Action of 1,25-Dihydroxyvitamin D_3. In *Comprehensive Medicinal Chemistry*; Hansch, C., Sammes, P. C.; Taylor, J. B., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, 1129-1143.

2. a) Uskokovic', M. R. Recent Advances in Vitamin D Chemistry and Pharmacological Activity. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1783-1896. (b) Norman, A. W., Bouillon, R., Thomasset, M., Eds. Vitamin D, A Pluripotent Steroid Hormone: Structural Studies, Molecular Endocrinology and Clinical Applications; Walter de Gruyter: Berlin, 1994.
3. (a) Calverley, M. J.; Jones, G. "Vitamin D" in Antitumor Steroids; Blickenstaff, R. T., Ed.; Academic Press: San Diego, **1992**; 193-27. (b) Bouillon, R.; Okamura, W. H.; Norman, A. W. Structure-Function Relationships in the Vitamin D Endocrine System. *Endocr. Rev.* **1995**, *16*, 200-257 and references therein.
4. a) Dai, H.; Posner, G. H. Synthetic Approaches to Vitamin D. *Synthesis* **1994**, 1383-1398. (b) Zhu, G-D.; Okamura, W. H. Synthesis of Vitamin D (Calciferol). *Chem. Rev.* **1995**, *95*, 1877-1952.
5. (a) Kocienski, P. J.; Lythgoe, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1440. (b) Lythgoe, B. *Chem. Soc. Rev.* **1981**, 449. (c) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovic´, M. R. *J. Org. Chem.* **1986**, *51*, 3098.
6. (a) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Uskokovic´, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2945. (b) Hatakeyama, S.; Numata, H.; Osanai, K.; Takano, S. *J. Org. Chem.* **1989**, *54*, 3515. (c) Kobayashi, S.; Shibata, J.; Shimada, M.; Ohno, M. *Tetrahedron Lett.* **1990**, *31*, 1577. (d) Posner, G. H.; Kinter, C. M. *J. Org. Chem.* **1990**, *55*, 3967. (e) Posner, G. H.; Carry, J.-C.; Anjeh, T. E. N.; French, A. N. *J. Org. Chem.* **1992**, *57*, 7012. (f) Stork, G.; Hutchinson, D.; Okabe, M.; Parker, D.; Ra, C.; Ribéreau, F.; Suzuki, T.; Zebovitz, T. *Pure & Appl. Chem.* **1992**, *64*, 1809. (g) Kabat, M. M.; Lange, M.; Wovkulich, P. M.; Uskokovic', M. R. *Tetrahedron Lett.* **1992**, *33*, 7701. (h) De Schrijver, J.; De Clerq, P.J. *Tetrahedron Lett.* **1993**, *34*, 4369. (i) Nagasawa, K.; Ishihara, H.; Zako, Y., Shimizu, I. *J. Org, Chem.* **1993**, *58*, 2523. (j) Chen, C.; Crich, D. *Tetrahedron* **1993**, *49*, 7943. (k) Torneiro, M.; Vrielynck, S.; García, A. M.; Mascareñas, J. L.; Castedo, L.; Mouriño, A. In Vitamin D, A . Pluripotent Steroid Hormone: Structural Studies, Molecular Endocrinology and Clinical Applications; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; Walter de Gruyter: Berlin 1994, 39. (l) Tazumi. K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1994**, 1903. (m) Hatakeyama, S.; Irie, H.; Shintani, T.; Noguchi, Y.; Yamada, H.; Nishizawa, M. *Tetrahedron* **1994**, *50*, 13369. (n) Vrielynck, S.; Vandewalle, M.; Garcia, A.; Mascareñas, J. L.; Mouriño, A. *Tetrahedron Lett.* **1995**, *36*, 9023.
7. Palladium-catalysed cyclization-carbonylation has been successfully carried out on simpler substrates such as vinylic bromides lacking a hydroxyl group at C-1 (steroidal numbering), See: Nuss, J. M.; Murphy, M. M.; Rennels, R. A.; Heravi, M. H.; Mohr, B. J. *Tetrahedron Lett.* **1993**, *34*, 3079.
8. Mascareñas, J. L.; Sarandeses, L. A.; Castedo, L.; Mouriño, A. *Tetrahedron* **1991**, *47*, 3485.
9. Klein, E.; Ohloff, G. *Tetrahedron* **1963**, *19*, 1091.
10. Ohloff, G.; Paulak, M. *Helv. Chim. Acta.* **1973**, *56*, 1176.
11. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1992**, 3769.
12. No epimerization at C-1 (steroidal numbering) was detected by ^{1}H or ^{13}C NMR.
13. Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

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