Tetrahedron Letters, Vol. 33, No. 12, pp. 1633-1636, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press Ltd

A Synthesis of A-Ring Synthons for Dihydrotachysterols

Rob Boer Rookhuizen[1*], Jaap C. Hanekamp[1,2], Hendrik J. T. Bos[2]

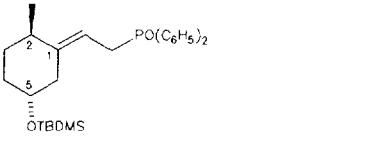
1) Research Group for Bone Metabolism, University Hospital Utrecht, Heidelberglaan 100, 3584 GA Utrecht, The Netherlands.

2) Department for Preparative Organic Chemistry, The Debye Institute, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands.

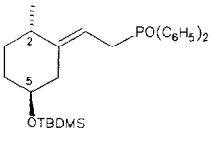
Abstract: *Phosphine oxides 1 and 2, enantiomeric synthons for the preparation of dihydrotachysterols, were synthesized from the appropriate dihydrocarvones*

25-Hydroxydihydrotachysterol$_2$ (25-OH-DHT$_2$, 3 figure 1) is one of the metabolites formed *in vivo* from dihydrotachysterol$_2$ (DHT$_2$, 4 figure 1) as shown by Bosch *et al.*,[1] after analysing serum from DHT$_2$ treated rats. Recently the synthesis of 25-OH-DHT$_2$, from 3-*O*-*tert*-butyldimethylsilyl-25-*O*-methoxymethylvitamin D$_2$, was reported and the results of Bosch *et al.* were confirmed.[2] However, a serious lack in the knowledge of its biological properties and metabolism still exists. Therefore we decided to develop a convergent

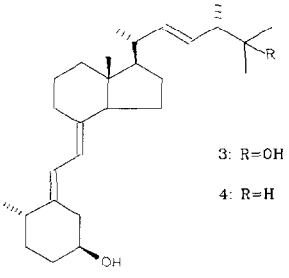
figure 1



1 (R,R')



2 (S,S')

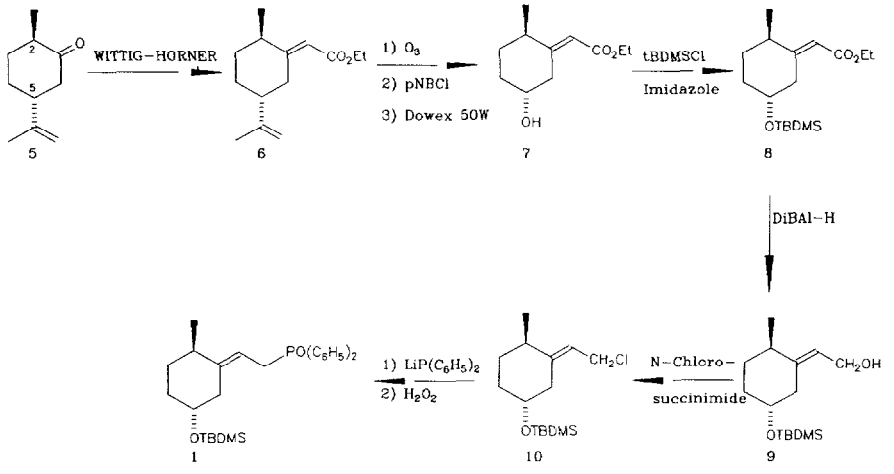


3: R=OH

4: R=H

synthesis for this metabolite based on the Lythgoe methodology,[3] which we consider to be more straightforeward compared to the procedure recently published by Solladie.[4] As a first result of our work in this field we reported a new synthesis of Grundmann's ketone.[5] We now report the synthesis of phosphine oxides **1** and **2** (figure 1), key intermediates in the synthesis of 25-hydroxylatedtachyssterol, and other dihydrovitamins.

scheme 1



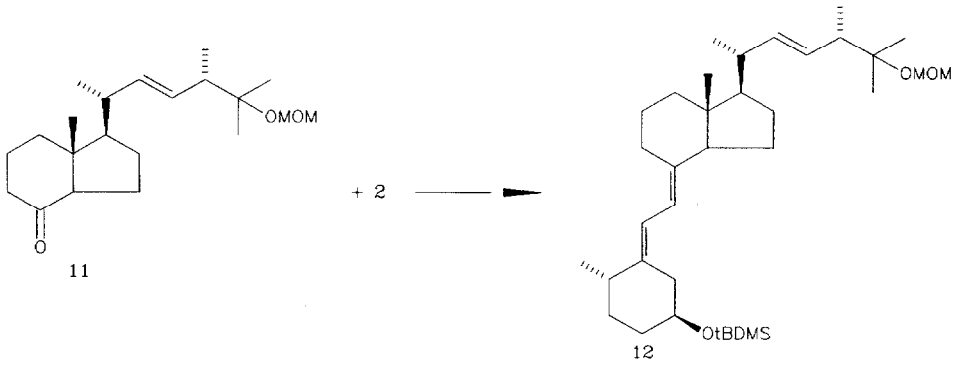
We started with (2R,5R)-dihydrocarvone **5**, obtained by chromatographic separation (silicagel, hexane/ethylacetaat 0-2%) of the commercially available mixture of (2S,5R)- and (2R,5R)- dihydrocarvone.[6] We planned to introduce the hydroxyl group by oxidative degradation (ozonolysis) of the isopropenyl sidechain.[7] However, in order to avoid a sequence of protection and deprotection of the carbonylgroup (needed in case of reduction of the intermediate ozonide to a carbonyl followed by a Bayer-Villiger oxidation; see eg. ref. 4), we decided to introduce the unsaturated ester moiety first, which can be used to generate the phosphine. Thus (2R,5R)-dihydrocarvone was subjected to a Wittig-Horner reaction with the sodium carbanion of ethyl(diethyloxyphosphinyl)acetate to yield the ester **6**, in an all *E* configuration, in a quantitative amount.[8,9] Next, the isopropenyl sidechain was subjected to a selective ozonolysis (MeOH, -78°C.). Acylation of the hydroxyperoxide with 4-nitrobenzoyl chloride (pNBCl), in situ Criegee rearrangement[7] (CH_2Cl_2, -60° - RT, 20 hr., 2 hr. reflux), and treatment with a H^+ cation exchange resin resulted in alcohol **7** in a good yield (65% after chromatographic purification). After protection of the hydroxyl group, the ester moiety was reduced with diisobutylaluminium hydride to give the allylic alcohol **9** (90% from **7**). The allylic alcohol **9** was converted to the corresponding phosphine oxide

1 by the known three step reaction sequence of chlorination (*N*-chlorosuccinimide/Me_2S),[10] treatment with lithium diphenylphosphide, and finally oxidation with hydrogen peroxide.[5,11,12] After chromatografic purification the phosphine oxide was obtained as an oil in a 80% yield. Crystallization was achieved from hexane at low temperatures.[13]

Lithiation of phosphine oxide **1** followed by reaction with cyclododecanone gave the desired diene in moderate yield, only the *E*-isomer was observed.

Phosphine oxide **2** was synthesized from (2S,5S)-dihydrocarvone following the described synthetic route. (2S,5S)-dihydrocarvone was obtained by reduction of S-(+)-carvone with lithiumbronze according to the procedure of Mueller,[14] and chromatographic separation of the isomeric mixture. This phosphine oxide[15] gave after lithiation and reaction with Grundmann's keton **11** the desired protected 25-OH-DHT_2 **12** in good yield (scheme 2).

scheme 2



Acknowledgments

Support for this research from Prof. Dr. S. A. Duursma (University Hospital Utrecht) is gratefully acknowledged. R. B. R. and J. C. H. thank Duphar (Weesp, The Netherlands) for financial support.

Notes and References:

1 Bosch, R.; Versluis, C.; Terlouw, J. K.; Thijssen, J. H. H.; Duursma, S. A. *J. Steroid Biochem.* **1985**, *23*, 223.

2 Boer Rookhuizen, R.; Bosch, R.; Castedo, L.; Cota, J. G.; Granja, J.;Maestro, M. A.; Martinez de Marigorta, E.; Mouriño, A. *Proc. 7th Workshop Vitamin D, Vitamin D: Mol. Cell. Clin. Endocrinol.* **1988**, *7*, 68.

3 Lythgoe, B.; Moran, T. A.; Nambudiry, M. E. N.; Tideswell, J.; Wright, P. W. *J. chem. soc. Perkin I* **1978**, 590.

4 Solladie, G.; Hutt, J. *J. Org. Chem.* **1987**, *52*, 3560.

5 Hanekamp, J. C.; Boer Rookhuizen, R.; Bos, H. J. T.; Brandsma, L. *Tetrahedron Lett.* **1991**, 5397.

6 The isomers are easily distinguished by their ^1H NMR signals of the methylene group belonging to the isopropenyl sidechain. A multiplet at 4.6 ppm for the (2R,5R) isomer and two broad singlets at 4.67 and 4.81 ppm for the (2S,5R) isomer.

7 Schreiber, S. L.; Liew, W. F. *Tetrahedron Lett.* **1983**, *24*, 2363.

8 All new compounds had statisfactory NMR- and Mass spectra.

9 Boutagy, J.; Thomas, R.; *Chem. Rev.* **1974**, *74*, 87.

10 Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, 4339.

11 Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovic, M. R. *J. Org. Chem.* **1986**, *51*, 3098.

12 Toh, H. T.; Okamura, W. H. *J. Org. Chem.* **1983**, *48*, 1414.

13 NMR data: ^1H (200 MHz, $CDCl_3$ as solvent and internal standard, J in Hz, δ in ppm downfield from Me_4Si) δ 7.62 (4H, m, H^{ar}ortho), 7.38 (6H, H^{ar}meta, para), 5.12 (1H, dd, J=7.5,$^2J_{HP}$=7.0, HC=), 3.2 (1H, m, HC^5), 3.04 (2H, dd, J=7.5, J=15.1, HCP), 2.44 (1H, dd, J=3.2, J=13.2, $H_{eq}C^6$), 1.9 - 1.1 (6H, m), 0.82 (3H, d, J=7, CH_3), 0.78 (9H, s, C_4H_9Si), - 0.05 (6H, s, CH_3Si).

^{13}C (50.5 MHz, $CDCl_3$, J in Hz, δ) 145.1 (C^1, $^3J_{CP}$=11.5), 132 (C^{ar}ipso, $^1J_{CP}$=90), 131 - 130 (C^{ar}meta, para), 128,1 (C^{ar}ortho, J_{CP}=11.1), 108.5 (C=CH, J_{CP}=8), 70.9 (C^5), 38.6 (C^3), 37.3 (C^2), 35,0 (C^4), 32.7 (C^6), 30.0 (CH_2P, $^1J_{CP}$=70), 25.5 (CH_3CSi), 17.8 ($(CH_3)_3CSi$), 17,4 (CH_3), -5.0 (CH_3Si).

^{31}P (80,9 MHz, ref. 85% H_3PO_4 external, $CDCl_3$) δ=31.3.

Rotatory power: α= + 1,36 (c: 0.01, CH_2Cl_2).

14 Mueller, R.; Sillick, J. G. *J. Org. Chem.* **1978**, *43*, 4647.

15 The NMR data of this compound are the same as reported for **1**.
Its rotatory power is opposite to that of **1**: α=- 1.24 (c: 0.01, CH_2Cl_2)

(Received in UK 13 December 1991)