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The thioacetate approach to vitamin D analogues. Part 2: Synthesis of (25*S*)-23-thia-1α,25,26-trihydroxyvitamin D_3

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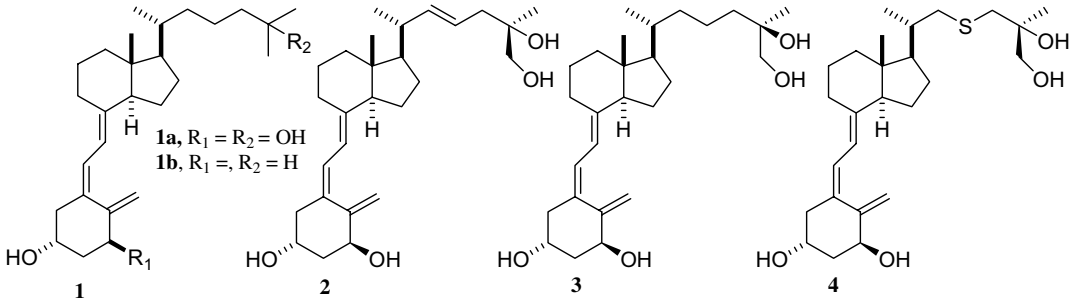
Abstract—(25*S*)-23-Thia-1α,25,26-trihydroxyvitamin D_3 (**4**) was prepared from alcohol **5** in 56% overall yield (five steps) using our previously developed methodology. Alcohol **5** was synthesized from commercially available vitamin D_2.

It has long been known that 1α,25-dihydroxyvitamin D_3 (**1a**, calcitriol; see Fig. 1) is the hormonally active form of vitamin D_3 (**1b**). Besides regulating calcium homeostasis, it is also involved in other cellular processes, including cell differentiation, immune system regulation and gene transcription.[1] This has led to speculation that **1a** might be an effective drug for the treatment of diseases such as leukaemia and psoriasis. However, its therapeutic utility is limited because effective doses have calcaemic side effects. Much research has accordingly been devoted to searching for analogues with high antiproliferation activity and low calcaemic activity, and several antiproliferative analogues with little or no calcaemic activity have already been prepared.[2]

We recently started a research programme directed towards the synthesis of thia analogues of calcitriol,[3] which have been reported to be less calcaemic than calcitriol itself.[4] In particular, we were interested in 23-thia analogue **4** (Fig. 1), the similarly 26-hydroxylated analogues **2** and **3** having been, respectively, reported to have antiosteoporotic potential[5] and to inhibit the biosynthesis of calcitriol.[6] Scheme 1 indicates our approach to **4** from commercially available vitamin D_2 (**7**) and the protected chiral epoxide **6**. Vitamin D_2 was used to prepare alcohol **5** by the procedure described by Calverley,[7] as modified by Choudhry et al.[8] Compound **6** was obtained by the protection of commercially available (*S*)-2-methylglycidol.



Keywords: Vitamin D; Calcitriol; Vitamin D thia analogues; Thioacetate; Vitamin D_2.
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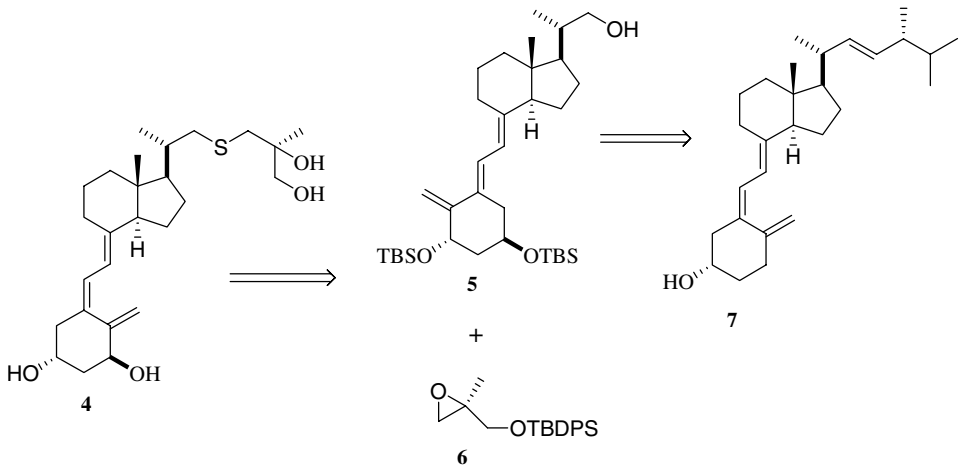
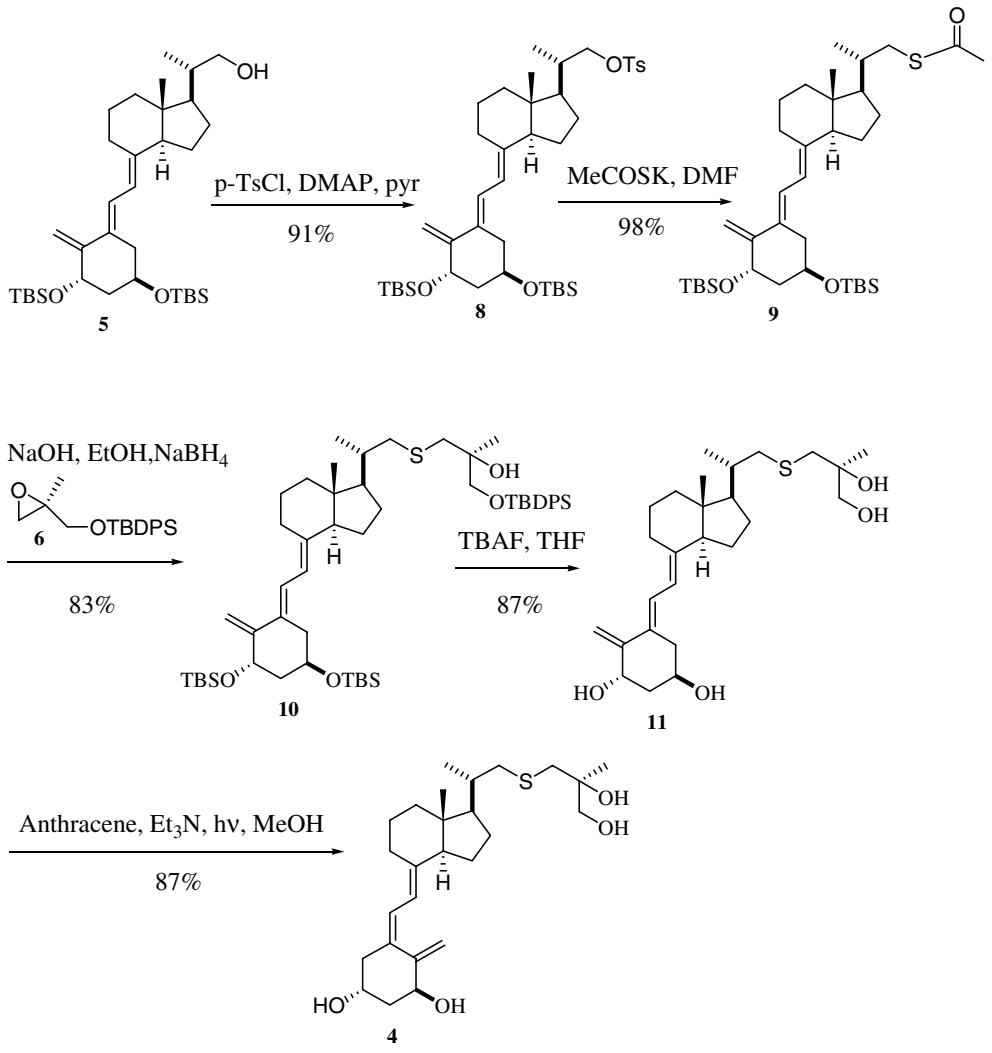


Scheme 1. Retrosynthetic analysis for **4**.

Tosylation of alcohol **5**, followed by the displacement of the tosylate group by potassium thioacetate, afforded thioacetate **9** in excellent yield (Scheme 2). Reaction of **9** with chiral epoxide **6** using our previously described methodology[3] gave alcohol **10** in 83% yield, and removal of the silyl groups of **10** gave **11**.[9] Finally, photosensitized isomerization of **11** using anthracene as triplet sensitizer afforded target compound **4**[10] in 56% overall yield from alcohol **5**.



Scheme 2. Synthesis of (25*S*)-23-thia-1α,25,26-trihydroxyvitamin D_3 (**4**).

In conclusion, (25*S*)-23-thia-1α,25,26-trihydroxyvitamin D_3 (**4**) can be synthesized straightforwardly from commercially available vitamin D_2 and (*S*)-2-methylglycidol. Further results on the synthesis of novel thia analogues of vitamin D will be reported in due course.

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References and notes

1. For general reviews of the chemistry and/or biochemistry of vitamin D, see: (a) *Vitamin D: Chemistry, Biology and Clinical Applications of the Steroid Hormone*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; Vitamin D Workshop: Riverside, CA, 1997; (b) Feldman, D.; Glorieux, F. H.; Pike, J. W. *Vitamin D*; Academic Press: San Diego, 1997; (c) Pardo, R.; Santelli, M. *Bull. Soc. Chim. Fr.* **1985**, 98–114; (d) Dai, H.; Posner, G. H. *Synthesis* **1994**, 1383–1398; (e) Zhu, G.-D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877–1952; (f) Posner, G. H.; Kahraman, M. *Eur. J. Org. Chem.* **2003**, 3889–3895.
2. (a) Binderup, L.; Bramm, E. *Biochem. Pharmacol.* **1988**, *37*, 889–895; (b) Abe, J.; Takita, Y.; Nakano, T.; Miyaura, C.; Suda, T.; Nishii, Y. *Endocrinology* **1989**, *124*, 2645–2647; (c) Oikawa, T.; Yoshida, Y.; Shimamura, M.; Ashino-Fuse, H.; Iwaguchi, T.; Tominaga, T. *Anticancer Drugs* **1991**, *2*, 475–480; (d) Abe, J.; Nakano, T.; Nishii, Y.; Matsumoto, T.; Ogata, E.; Ikeda, K. *Endocrinology* **1991**, *129*, 832–837; (e) Abe-Hashimoto, J.; Kikuchi, T.; Matsumoto, T.; Nishi, Y.; Ogata, E.; Ikeda, K. *Cancer Res.* **1993**, *53*, 2534–2537; (f) Chen, T. C.; Parsons, K.; Uskokovic, M. R.; Horst, R. L.; Holick, M. F. *J. Nutr. Biochem.* **1993**, *4*, 49–57; (g) Posner, G. H.; Lee, J. K.; Wang, S.; Peleg, S.; Burke, M.; Brem, H.; Dolan, P.; Kensler, T. W. *J. Med. Chem.* **1998**, *41*, 3008–3014; (h) Steinmeyer, A.; Schwarz, K.; Haberey, M.; Langer, G.; Wiesing, H. *Steroids* **2001**, *66*, 257–266; (i) Peleg, S.; Posner, G. H. *Curr. Top. Med. Chem.* **2003**, *3*, 1555–1572; (j) Posner, G. H.; Jeon, H. B.; Sarjeant, A.; Riccio, E. S.; Doppalapudi, R. S.; Kapetanovic, I. M.; Saha, U.; Dolan, P.; Kensler, T. W. *Steroids* **2004**, *69*, 757–762.
3. Fall, Y.; Diouf, O.; Gómez, G.; Bolaño, T. *Tetrahedron Lett.* **2003**, *44*, 6069–6072.
4. (a) Hesse, R. Eur. Pat. Appl. EP 78704, 1983; 75 pp; (b) Kubodera, N.; Miyamoto, K.; Akiyama, M.; Matsumoto, M.; Mori, T. *Chem. Pharm. Bull.* **1991**, *39*, 3221–3224; (c) Calverley, M. J.; Grue-Soerensen, G.; Binderup, E. T. PCT Int. Appl. WO 9115475, 1991; 64 pp; (d) Allewaert, K.; Van Baelen, H.; Bouillon, R.; Zhao, X. Y.; De Clercq, P.; Vandewalle, M. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1859–1862; (e) Grue-Sorensen, G.; Pedersen, H.; Binderup, E. T.; Tranholm, M. PCT Int. Appl. WO 0156981, 2001; 50 pp.
5. (a) Drezner, M. K.; Nesbitt, T. *Metabolism* **1990**, *39*, 18–23; (b) Drezner, M. K.; Nesbitt, T.; Quarles, L. D. In *Vitamin D: Gene Regulation, Structure–Function Analysis and Clinical Application*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1991; pp 816–822; (c) Okabe, M.; Sun, R.-C. *Tetrahedron Lett.* **1993**, *34*, 6533–6536.
6. Wovkulich, P. M.; Barcelos, F.; Batcho, A. D.; Sereno, J. F.; Baggiolini, E. G.; Hennessy, B. M.; Uskokovic, M. R. *Tetrahedron* **1984**, *40*, 2283–2296.
7. Calverley, M. J. *Tetrahedron* **1987**, *43*, 4609–4619.
8. Choudhry, S. C.; Belica, P. S.; Coffen, D. L.; Focella, A.; Maehr, H.; Manchand, P. S.; Serico, L.; Tang, R. T. *J. Org. Chem.* **1993**, *58*, 1496–1500.
9. Data for compound **11**. White solid, mp 56–59 °C, $R_f = 0.45$ (10% MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.55 (1H, d, $J = 11.5$ Hz, H-6), 5.87 (1H, d, $J = 11.5$ Hz, H-7), 5.11 (1H, s, H-19), 4.96 (1H, s, H-19), 4.88 (1H, m, H-1), 4.22 (1H, m, H-3), 3.55 (1H, s), 3.45 (1H, s), 2.87 (2H, m), 2.75 (2H, m), 2.55 (2H, m), 2.35 (3H, m), 1.55 (11H, m), 1.21 (3H, s, H-26), 1.08 (3H, d, $J = 6.5$ Hz, H-21), 0.56 (3H, s, H-18). ^{13}C NMR ($CDCl_3$), δ: 151.69 (C-10), 144.84 (C-8), 132.90 (C-5), 123.28 (CH-6), 116.09 (CH-7), 109.71 (CH_2-19), 72.50 (C-25), 71.13 (CH-1), 68.98 (CH_2-27), 65.95 (CH-3), 56.34 (CH-14), 55.58 (CH-17), 46.08 (C-13), 42.80 (CH_2), 42.24 (CH_2), 41.99 (CH_2), 37.33 (CH-21), 36.78 (CH_2), 29.01 (CH_2), 27.62 (CH_2), 23.86 (CH_3-26), 23.46 (CH_2), 22.27 (CH_2), 18.82 (CH_3-18), 12.20 (CH_3-21). MS (*m*/*z*, %): 451.29 [$(M+1)^+$, (25)], 450.27 [M^+, (32)], 362.23 (35), 309.07 (25), 284.23 (30), 190.17 (34), 185.12 (100). HRMS: calcd for $C_{26}H_{42}O_4S$, 450.2863; found, 450.2859.
10. Data for compound **4**. Colourless oil, $R_f = 0.45$ (10% MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.30 (1H, d, $J = 10.9$ Hz, H-6), 5.94 (1H, d, $J = 11.3$ Hz, H-7), 5.25 (1H, s, H-19), 4.93 (1H, s, H-19), 4.36 (1H, m, H-1), 4.16 (1H, m, H-3), 3.65 (1H, s), 3.45 (2H, s), 2.65 (6H, m), 2.25 (1H, m), 1.85 (6H, m), 1.35 (8H, m), 1.25 (3H, m), 1,15 (3H, s, H-26), 1.02 (3H, d, $J = 6.5$ Hz, H-21), 0.48 (3H, s, H-18). ^{13}C NMR ($CDCl_3$), δ: 147.63 (C-10), 142.73 (C-8), 133.11 (C-5), 124.88 (CH-6), 117.20 (CH-7), 111.76 (CH_2-19), 72.48 (C-25), 70.79 (CH-1), 68.96 (CH_2-27), 66.86 (CH-3), 56.17 (CH-14), 55.54 (CH-17), 45.24 (CH_2), 42.85 (CH_2), 42.76 (CH_2), 40.26 (CH_2), 37.35 (CH-20), 29.70 (CH_2), 29.00 (CH_2), 27.62 (CH_2), 23.85 (CH-26), 23.49 (CH_2), 22.26 (CH_2), 18.81 (CH_3-18), 12.07 (CH_3-21). HRMS: calcd for $C_{26}H_{42}O_4S$, 450.2863; found, 450.2859.