Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 6069–6072

TETRAHEDRON LETTERS

The thioacetate approach to the synthesis of the side chain of vitamin D metabolites and analogues

Yagamare Fall,[a,*] Ousmane Diouf,[b] Generosa Gómez[a] and Tamara Bolaño[a]

[a]*Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Vigo, 36200 Vigo, Spain*
[b]*Laboratoire de Chimie Inorganique, Departement de Chimie, Faculté des Sciences et Techniques, Université Cheikh Anta Diop de Dakar, Senegal*

Received 12 May 2003; revised 11 June 2003; accepted 12 June 2003

Abstract—We describe an efficient synthesis of thia analogues of the vitamin D side chain that is based on the in situ generation of a thiolate anion and its alkylation with electrophiles.

1α,25-Dihydroxyvitamin D_3 [**1**, 1α,25-$(OH)_2$-D_3, calcitriol], the hormonally active form of vitamin D_3 (**2**, cholecalciferol), promotes cell differentiation,[1] inhibits cell proliferation,[1] regulates phosphorus metabolism, intestinal calcium absorption and bone calcium mobilization,[1] and has certain indirect effects on the immunological system.[2] Since its hypercalcaemic effects limit its clinical utility for treatment of cancers and skin disorders, there is much interest in the design and synthesis of analogues of **1** with more selective (or even different) biological effects,[2] and several antiproliferative analogues with little or no calcaemic activity have already been prepared.[3] One is the oxa derivative OCT[3c–f] (**3**), a broad range of analogues of which (including compounds with modifications at C25, C21 and ring D) is currently being synthesized in our laboratories for biological evaluation and SAR studies.[4]

A rapid search of the literature shows that very little has been done on the synthesis of thia analogues of vitamin D,[5] in spite of the 23-thia analogue of calcitriol having been reported to be less calcaemic than calcitriol.[5d] We describe here an efficient method for synthesis of the side chains of analogues **4** and **5** (Fig. 1); our approach has been inspired by the earlier work of Schmittberger and Uguen[6] on the synthesis of side chains of sterols (Scheme 1).

We started from the Inhoffen–Lythgoe diol (**11**), which is easily obtained by degradation of vitamin D_2[7] (Scheme 2). Selective tosylation of its primary alcohol gave tosylate **12** in 93% yield, and protection of the secondary alcohol of **12** (99%), followed by displacement of the tosylate group by potassium thioacetate, afforded an 89% yield of thioacetate **14**.[8] However, all attempts to reduce thioacetate **14** to thiol **15** failed, the product obtained being disulphide **18**[8] (in 82% yield using LAH and nearly 100% using $NaBH_4$); and although experimental details kindly supplied by Professor Uguen suggest that this thiol might be formed if perfect degasing of the reaction mixture is ensured by connecting the reaction vessels to vacuum and argon lines, the high yield of disulphide **18** encouraged us to pursue our objective by reduction and in situ alkylation of this latter intermediate, following the procedure described by Braga and co-workers.[9] Gratifyingly, upon reaction with sodium borohydride and alkylation with bromide **16**,[10] **18** cleanly afforded thioether **17**[8] in 78% yield. Furthermore, we found that under the same experimental conditions reduction and alkylation of thioacetate **14** itself afforded thioether **17** in one step in even better yield, 93%,[11] a significant improvement with respect to the two-step procedure employed by Uguen to obtain an 82% overall yield of **10** from **7** (Scheme 1). In any case the relative stability of thiol **8** towards autooxidation as compared to targeted thiol **15** might be explained by the fact that solid thiols are less prone to autooxidation than liquid thiols.

To explore the scope and limitations of direct reduction/alkylation of **14**, we carried out the reaction using a number of different electrophiles, with all but one of which yields greater than 90% were obtained (Table 1;

* Corresponding author. Fax: +34-986-812262; e-mail: yagamare@uvigo.es

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01462-X

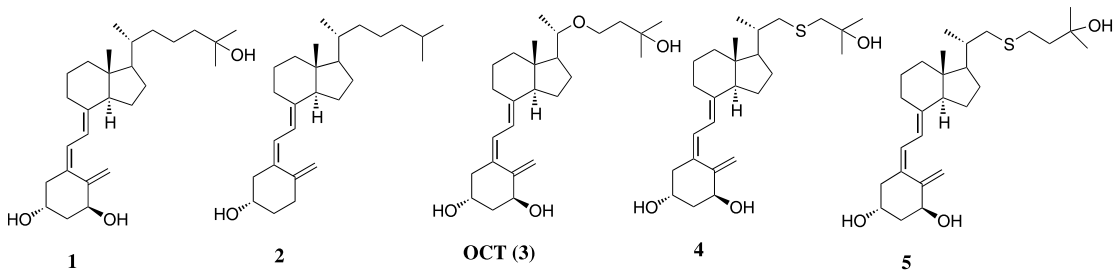
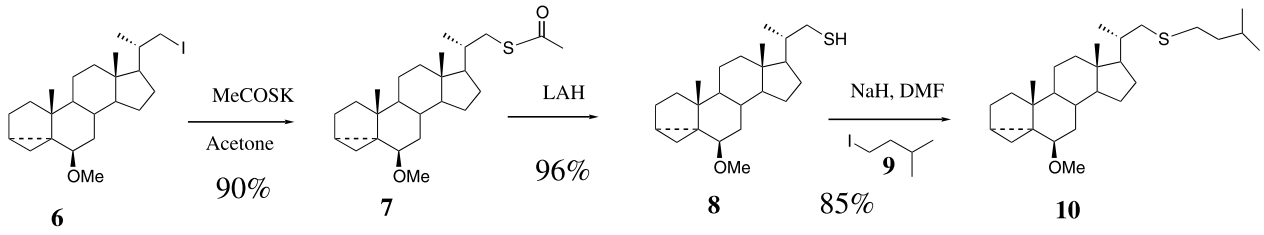
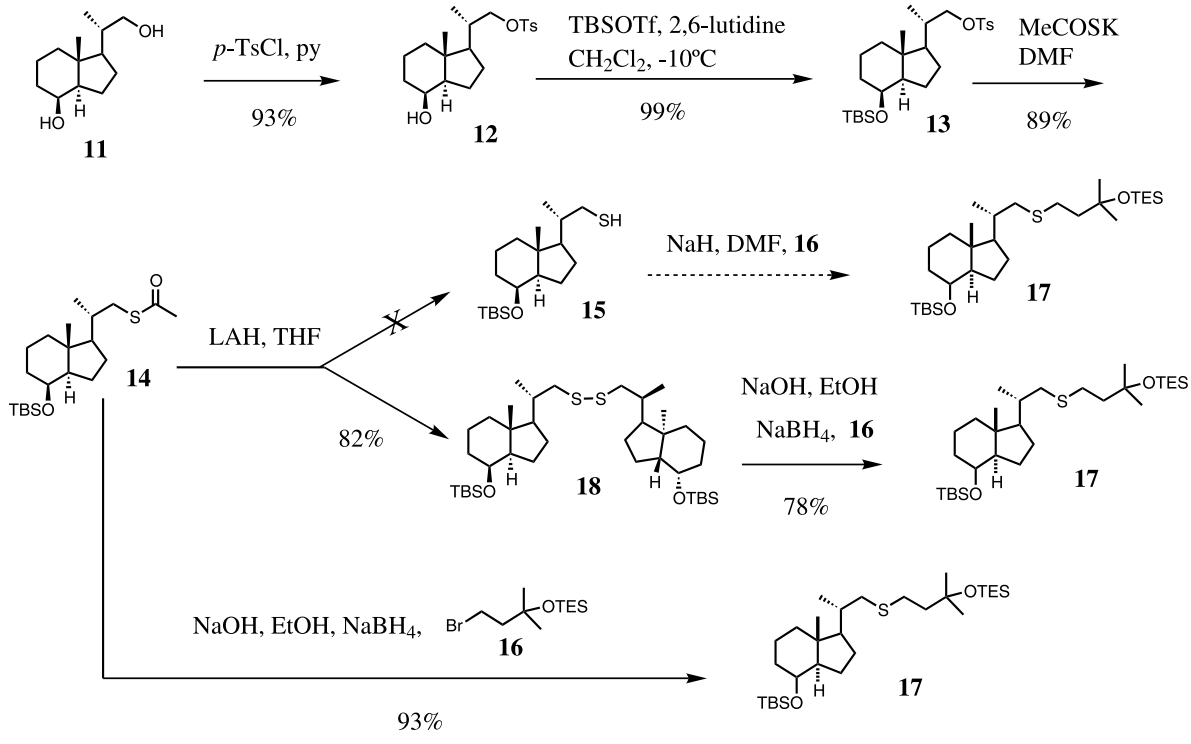


Figure 1.



Scheme 1. Uguen's approach.

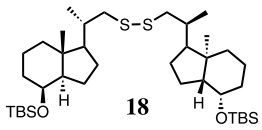
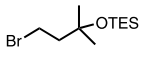
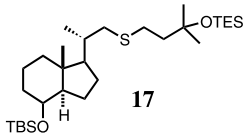
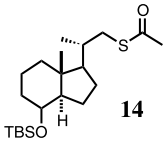
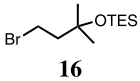
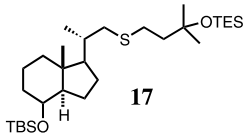
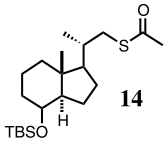
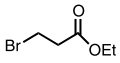
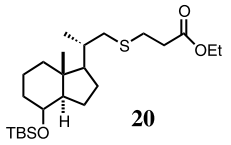
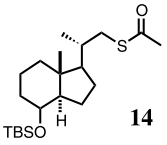
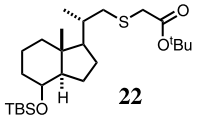
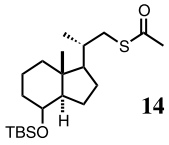
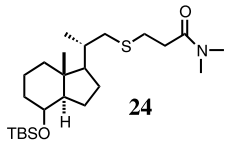
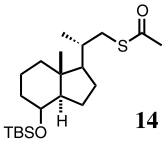
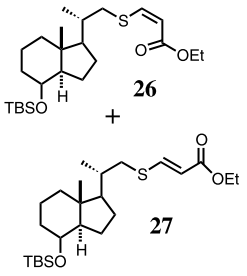
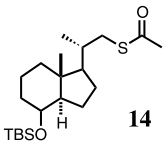
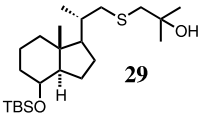


Scheme 2. Our approach.

the acetylene **25** afforded a 68% combined yield of isomers **26** and **27**). Ester groups were not affected by the reaction conditions (entries 3 and 4), the Michael acceptors dimethylacrylamide and ethyl propiolate underwent sulphur addition (entries 5 and 6), and epoxide **28** was efficiently opened. These results enlarge Braga's procedure since various electrophilic species could be used (only alkyl halides were used in the aforementioned procedure). Compounds **29** and **17** are direct precursors of vitamin D_3 analogues **4** and **5**, and compounds **20**, **22** and **24** can lead not only to **4** and **5** but also to C25-modified analogues. Furthermore, it would be possible to use the sulphur atom at C23 to introduce a double bond with *trans* configuration through a Ramberg–Bäcklund rearrangement.[6,12] Thus compound **14** is a very flexible intermediate for the synthesis of vitamin D side chain analogues.

In conclusion, we have found an excellent (and practically odourless) method for the synthesis of thia ana-

Table 1. Formation of the 23-thia side chains

Entry	Substrate	Electrophile	Product	Yield (%)
1	 **18**	 **16**	 **17**	78
2	 **14**	 **16**	 **17**	93
3	 **14**	 **19**	 **20**	93
4	 **14**	 **21**	 **22**	92
5	 **14**	 **23**	 **24**	94
6	 **14**	**25**	 **26** + **27**	68
7	 **14**	 **28**	 **29**	92

logues of the vitamin D side chain. Work is in progress on the synthesis of the corresponding vitamin D's and their modification by means of the Ramberg–Bäcklund rearrangement.

Acknowledgements

This work was supported by grants from the Xunta de Galicia (PGIDT01PXI30105PR) and the Vicerectorate for Research of the University of Vigo, and by a grant to O.D. by the Spanish Ministry of Foreign Affairs (MAE). We also thank Professor D. Uguen of the University of Strasbourg for supplying us with useful unpublished experimental details; Solvay Pharmaceuticals (Weesp, The Netherlands) for the gift of starting materials; and the NMR service of the CACTI, University of Vigo, for NMR studies.

References

1. Bouillon, R.; Okamura, W. H.; Norman, A. W. *Endocr. Rev.* **1995**, *16*, 200–257.
2. For general reviews of vitamin D chemistry and biology, see: (a) *Vitamin D: Chemistry, Biology and Clinical Applications of the Steroid Hormone*; Norman, A. W.; Bouillon, R.; Thomasset, M., Eds.; Vitamin D Workshop, Inc.: Riverside, CA, 1997; (b) Feldman, D.; Glorieux, F. H.; Pike, J. W. *Vitamin D*; Academic Press: San Diego, 1997; (c) Dai, H.; Posner, G. H. *Synthesis* **1994**, 1383–1398; (d) Zhu, G.-D.; Okamura. W. H. *Chem. Rev.* **1995**, 95, 1877–1952.
3. (a) Binderup, L.; Bramm, E. *Biochem. Pharmacol.* **1988**, *37*, 889–895; (b) Chen, T. C.; Parsons, K.; Uskokovic, M. R.; Horst, R. L.; Holick, M. F. *J. Nutr. Biochem.* **1993**, *4*, 49–57; (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) Abe, J.; Takita, Y.; Nakano, T.; Miyaura, C.; Suda, T.; Nishii, Y. *Endocrinology* **1989**, *124*, 2645–2647.
4. (a) Fall, Y. *Tetrahedron Lett.* **1997**, *38*, 4909–4912; (b) Fall, Y.; González, V.; Vidal, B.; Mouriño, A. *Tetrahedron Lett.* **2002**, *43*, 427–429; (c) Fall, Y.; Bolaño, T.; Fernández, C.; Gómez, G.; Momán, E., manuscript in preparation.
5. (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) Calverly, 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.
6. Schmittberger, T.; Uguen, D. *Tetrahedron Lett.* **1996**, *37*, 29–32.
7. (a) Leyes, G. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6099–6105; (b) Sardina, F. J.; Mouriño, A.; Castedo, L. *J. Org. Chem.* **1986**, *51*, 1264–1269.
8. All new compounds exhibited satisfactory ^{1}H and ^{13}C NMR, analytical, and/or high-resolution mass spectral data.
9. Braga, A. L.; Appelt, H. R.; Schneider, P. H.; Silveira, C. C.; Wessjohann, L. A. *Tetrahedron: Asymmetry* **1999**, *10*, 1733–1738. For other reducing conditions, see: (b) Barluenga, J.; Rubiera, C.; Fernandez, J. R.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1987**, *6*, 425–426; (c) Ramon, D. J.; Yus, M. *Tetrahedron Lett.* **1990**, *31*, 3763–3766; (d) Fujii, T.; Ohba, M.; Hatakeyama, H. *Chem. Pharm. Bull.* **1985**, *33*, 2355–2359.
10. Andrews, D. R.; Barton, D. H. R.; Hesse, R. H.; Pechet, M. M. *J. Org. Chem.* **1986**, *51*, 4819–4828.
11. Reduction and in situ alkylation of thioacetate **14**, typical procedure (entry 4): To a solution of **14** (200 mg, 0.52 mmol) and sodium hydroxide (41 mg, 1.04 mmol, 2 equiv.) in dry ethanol (5 mL) under an argon atmosphere (baloon), solid sodium borohydride (42.28 mg, 1.12 mmol, 2.15 equiv.) was added in one portion, by quickly opening the septum and the mixture was stirred for 30 min at room temperature. *tert*-Butyl bromoacetate **21** (154 μl, 1.04 mmol, 2 equiv.) was added neat by injection via syringe through the rubber septum and the resulting mixture was stirred at room temperature for 1 h. The ethanol was rotatory evaporated and the residue dissolved in dichloromethane (15 mL), washed with water (2×10 ml), and dried over sodium sulphate. Filtration and solvent evaporation afforded a residue which was purified by column chromatography on silicagel (EtOAc/hexane, 10:80) to give **22** in 92% yield as an oil. Selected analytical data for **22**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.01 (1H, br s, CH-8), 3.10 (1H, d, $J=14.3$, CH-24a), 3.03 (1H, d, $J=14.3$, CH-24b), 2.81 (1H, dd, $J=12.3$, 2.7, CH-22a), 2.34 (1H, dd, $J=12.3$, 8.8, CH-22b), 1.48 (9H, s, O*t*Bu), 1.05 (3H, d, $J=6.5$, CH_3-21), 0.92 (3H, s, CH_3-18), 0.89 (9H, s, *t*BuSi), 0.01 (3H, s, MeSi), 0.00 (3H, s, MeSi); ^{13}C NMR ($CDCl_3$): δ 170.21 (C), 81.56 (C), 69.73 (C-8), 56.38, 53.29, 42.71 (C), 40.80 (CH_2), 40.47 (CH_2), 36.15, 35.96 (CH_2), 34.75 (CH_2), 28.36 (O*t*Bu), 27.57 (CH_2), 26.18 (*t*BuSi), 23.40 (CH_2), 19.05, 18.37 (C), 17.98 (CH_2), 14.15, −4.42 (MeSi), −4.79 (MeSi); MS (*m*/*e*): 456 (M+, 9%), 401 (49%), 399 (16%), 355 (9%), 343 (14%), 309 (12%), 269 (42%), 267 (18%), 209 (14%), 177 (100%).
12. (a) Paquette, L. *Org. React.* **1970**, *25*, 1–71; (b) Chan, T.-L.; Fong, S.; Li, Y.; Man, T.-O.; Poon, C.-D. *J. Chem. Soc., Chem. Commun.* **1994**, 1771–1772; (c) Vanda, C.; Giuseppe, M.; Francesca, P.; Salvatore, P.; Alfredo, R. *Tetrahedron* **2000**, *56*, 1225–1231; (d) Schmittberger, T.; Uguen, D. *Tetrahedron Lett.* **1997**, *38*, 2837–2840.