Pergamon

Tetrahedron Letters, Vol. 35, No. 44, pp. 8119-8122, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01803-0

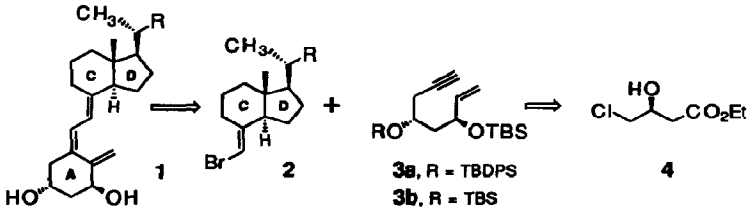
A Practical Asymmetric Synthesis of a 1,7-Enyne A-Ring Synthon En Route Toward the Total Synthesis of Vitamin D3 Analogues

Barry M. Trost and Paul R. Hanson*
Department of Chemistry
Stanford University
Stanford, CA 94305

Abstract: A concise synthesis of a key A-ring synthon of 1α,25-dihydroxyvitamin D3, **1**, has been achieved in 8 steps starting from readily available, inexpensive ethyl-4-chloroacetoacetate. This synthon serves as one of two main coupling partners in our previously developed Pd-catalyzed alkylative enyne cyclization leading toward the total synthesis of 1α,25-dihydroxyvitamin D3 and potentially useful analogues.

1α,25-Dihydroxyvitamin D3 [1α,25(OH)$_2$D$_3$, **1**], the physiologically active form of vitamin D (calciferol), plays a vital role in the immune system[1] and serves as a hormonal regulator (calcium homeostasis).[2] It has also been shown to suppress proliferation and induce differentiation of murine (M1) and human myeloid leukemia cells (HL-60) at nanomolar concentrations *in vitro*.[3] However, therapeutic dosages are known to induce a serious condition known as hypercalcemia.

Scheme 1



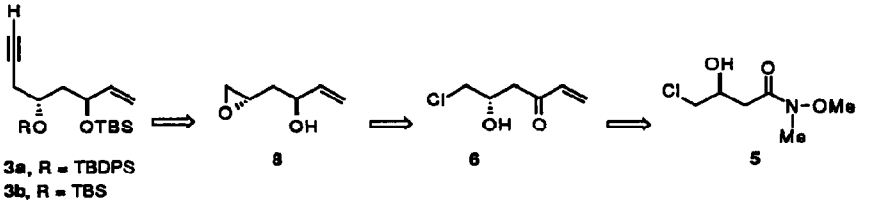
Efforts are therefore currently aimed at the development of more therapeutically useful analogues of 1α,25(OH)$_2$D$_3$ that can induce differentiation and inhibit proliferation of leukemic cells without inducing hypercalcemia.[4] Since attempts to correlate the differentiation ability and anticalcemic effects and structure are only in their infancy,[1,5] new methodologies[6,7] in this area play a pivotal role by allowing one to access new and diverse analogues of **1** which may prove to be useful antitumor agents.

We have recently reported on a new strategy for the total synthesis of 1α-hydroxyvitamin D derivatives which employs a Pd-catalyzed alkylative enyne cyclization[8] of the 1,7-enyne **3a** and the vinyl bromide **2** (derived from Grundmann's ketone) as outlined in Scheme 1. In continuation of our interest in synthetic routes

toward 1α-hydroxyvitamin D and closely related analogues, we herein report on an improved synthesis of our nonracemic diol **3b**.[9]

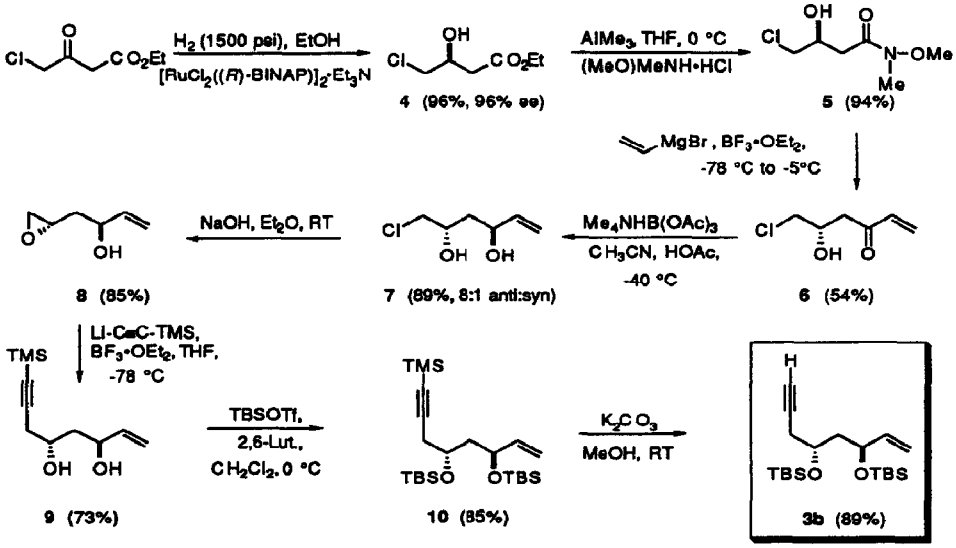
Our previous asymmetric synthesis of the 1,7-enyne **3a**,[8] although short, suffered from a nonselective vinyl-Grignard addition (~1.0:1.5 anti:syn) favoring the undesired isomer. The undesired isomer could be recycled using the Mitsunobu inversion, but ultimately this synthesis requires a Sharpless kinetic resolution to arrive at the nonracemic differentially protected *anti*-diol **3a**. Our new synthesis (Scheme 2) of the 1,7-enyne

Scheme 2



3b envisions a TMS-acetylide opening of epoxide **8**,[10] which is derived via selective anti-reduction using the Evan's protocol.[11] The β-hydroxy enone **6** can be derived from vinyl Grignard addition to the β-hydroxy amide **5** which, in turn, comes from the Noyori asymmetric hydrogenation[12] of the readily available, inexpensive ethyl-4-chloroacetoacetate, a procedure which then sets all the stereochemistry of the final target. Growing interest in this and related synthetic strategies leads us to communicate our results at this time.

Scheme 3



We began our route to the *anti*-diol **3b**[13] (Scheme 3) with the Noyori asymmetric hydrogenation[12] of

ethyl 4-chloroacetoacetate, a known reaction giving high enantiomeric selectivity (>95% ee).[14] This asymmetric reduction was conducted in a Parr bomb using 0.035% ruthenium catalyst [prepared from (cyclooctadienyl)ruthenium dichloride and (*R*)-BINAP] at hydrogen pressures of 1500 psi and temperatures exceeding 100 °C, giving the β-hydroxy ester **4** in 96% yield and 96% ee. Subsequent transamidation[15] gave the functionally laden 4-chloro-β-hydroxy-amide **5** (94% yield). Vinyl Grignard addition to the Weinreb amide **4** gave the β-hydroxy enone **6** in 54% yield, the more modest yield in this case deriving from the instability of enone **6**. This enone, prone to polymerization upon storage,[16] was immediately dissolved in CH_3CN and subjected to the Evan's reduction conditions[11] using 6.0 equivalents of $Me_4NBH(OAc)_3$ in CH_3CN with 16.0 equivalents of AcOH at -40 °C to give the *anti*-diol **7** in 89% yield and 8:1 diastereoselectivity (separable from the *syn* diastereomer using MPLC) with no 1,4-addition products seen. Base treatment (KOH, Et_2O, RT) effected smooth epoxide formation to give epoxide **8** in 85% yield. Addition of TMS-acetylene, following the Yamaguchi protocol,[10] gave enyne **9** in 73% yield as a low melting waxy solid. Final protection of the diol (TBSOTF, 2,6-lutidine, 85% yield) and cleavage of the terminal acetylenic TMS group (K_2CO_3, MeOH, RT, 89%) gave the desired nonracemic 1,7-enyne **3**, $[\alpha]_D^{25^\circ} = -9.11$ (c = 0.992, $CHCl_3$).

This new synthesis represents a short concise asymmetric route toward an important A-ring synthon. In all, our new route entails 8 steps, is amenable to large scale production of the 1,7-enyne **3b**, and represents one of the shortest syntheses of any A-ring synthon[9] to date. Furthermore it streamlines our continuing efforts toward an efficient asymmetric synthesis of Vitamin D_3 and potentially useful analogues. Additional efforts in this area will be reported in due course.

Acknowledgments: This investigation was supported by the National Institutes of Health, General Medical Sciences Institute. We thank Professor Scott Rychnovsky, Dacia Pickering, and Dr. Rebecca Hoye for helpful discussions, Dr. Steve King for the kind donation of (*R*)-BINAP and advice on the Noyori asymmetric reduction, and the NIH for postdoctoral fellowship support.

---

1 Reichel, H.; Koeffler H. P.; Norman, A. W. *New. Engl. J. Med.* **1989**, *320*, 980.

2 Norman, A. W.; Bouillon, R.; Thomasset, M. Vitamin D: Gene Regulation, Structure Function Analysis and Clinical Application; Walter de Gruyter and Co.: Berlin, **1991**.

3 Differentiation of Tumor Cells: Abe, E.; Miyaura, C.; Sakagami, H.; Takeda, M.; Konno, K.; Yamazaki, T.; Yoshiki, S.; Suda, T. *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 4990. b) Koeffler, H. P.; Amatruda, T.; Ikekawa, N.; Kobayashi, Y.; DeLuca, H. F. *Cancer Res.* **1984**, *44*, 5624.

4 a) Ikekawa, N. *Med. Res. Rev.* **1987**, *7*, 333. b) Zhou, J.-Y.; Norman, A. W.; Lübbert, M.; Collins, E. D.; Uskovic, M. R. Koeffler, H. P. *Blood* **1989**, *74*, 82. c) Figadare, B.; Norman, A. W.; Henry, H. L.; Koeffler, H. P.; Zhou, J.-Y.; Okamura, W.H. *J. Med. Chem.* **1991**, *34*, 2452. d) Perlman, K.; Kutner, A.; Prahl, J.; Smith, C.; Inaba, M.; Schnoes, H. K.; DeLuca, H. F. *Biochem.* **1990**, *29*, 190. e) Perlman, K. L.; DeLuca, H. F. *Tetrahedron Lett.* **1992**, *33*, 2937.

5 To date, many potentially useful analogues have been synthesized and tested by a number of elegant methodologies, with much of the effort being aimed at the sidechain which is known to be the site of metabolic activity. a) DeLuca, H. F.; Schnoes, H. K. *Ann. Rep. Med. Chem.* **1984**, *19*, 179.

6 Synthetic Sidechain Approaches to Vitamin D and its Analogues: a) Lythgoe, B. *Chem. Soc. Rev.* **1980**,*9*, 449. b) Craig, A. S.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1992**, *57*, 4374. c) Yamamoto, K.; Shimizu, M.; Yamada, S.; Iwata, S.; Hoshino, O. *J. Org. Chem.* **1992**, *57*, 33. d) Wilson, S. R.; Davey, A. E.; Guazzaroni, M. E. *J. Org. Chem.* **1992**, *57*, 2007. e) Yamamoto, K.; Takahashi, J.; Hamano, K.; Yamada, S.; Yamaguchi, K.; DeLuca, H. F. *J. Org. Chem.* **1993**, *58*, 2530. f) Sardino, F. J.; Mouriño, A.; Castedo, L. *J. Org. Chem.* **1986**, *51*, 1264. g) Mascareñas, J. L.; Mouriño, A.; Castedo, L. *J. Org. Chem.* **1986**, *51*, 1269. h) Partridge, J. J.; Toome, V.; Uskokovic´, M. R. *J. Am. Chem. Soc.* **1976**, *98*, 3739. i) Pérez-Sestelo, J.; Mascareñas, J. L; Castedo, L.; Mouriño, A. *Tetrahedron Lett.* **1994**, *35*, 275. j) Pérez-Sestelo, J.; Mascareñas, J. L.; Castedo, L. Mouriño, A. *J. Org. Chem.* **1993**, *58*, 118. k) Granja, J. R.; Castedo, L. Mouriño, A. *J. Org. Chem.* **1993**, *58*, 124. l) Fall, Y.; Torneiro, M. Castedo, L.; Mouriño, A. *Tetrahedron Lett.* **1992**, *33*, 6683.

7 Synthetic Approaches to C/D ring synthons: a) Dauben, W. G.; Ollmann, R. R. Jr.; Wu, S. C. *Tetrahedron Lett.* **1994**, *35*, 2149 and references cited therein. b) Marczak, S.; Wicha, J. *Tetrahedron Lett.* **1993**, *34*, 6627. c) Nagasawa, K.; Matsuda, N.; Noguchi, Y.; Yamanashi, M.; Zako, Y.; Shimizu, I. *J. Org. Chem.* **1993**, *58*, 1483. d) Clasby, M. C.; Craig, D.; Marsh, A. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1444. e) Fernández, B.; Pérez, J. A. M.; Granja, J. R.; Castedo, L; Mouriño, A. *J. Org. Chem.* **1992**, *57*, 3173. f) Brandes, E.; Grieco, P. A.; Garner, P. *J. C. S. Chem. Comm.* **1988**, 500. g) see also refs 8 and 9.

8 a) Trost, B. M.; Pfrengle, W.; Urabe, H.; Dumas J. *J. Am. Chem. Soc.* **1992**, *114*, 1923. b) Trost, B. M.; Dumas, J. *J. Am. Chem. Soc.* **1992**, *114*, 1924. c) Trost, B. M.; Dumas, J.; Villa, M. *J. Am. Chem. Soc.* **1992**, *114*, 9836. d) Trost, B. M.; Dumas, J. *Tetrahedron Lett.* **1993**, *34*, 19.

9 For recent related examples on the synthesis of A-ring synthons see: a) Takano, S.; Presented at the 114th Annual Meeting of the Pharmaceutical Society of Japan, April, 1994, paper 13-1. b) Nagasawa, K.; Ishihara, H.; Zako, Y.; Shimizu, I. *J. Org. Chem.* **1993**, *58*, 2523. c) Nuss, J. M.; Murphy, M. M.; Rennels, R. A. ; Heravi, M. H.; Mohr, B. J. *Tetrahedron Lett.* **1993**, *34*, 3079. d) Schrijver, J. D.; De Clercq, P. J. *Tetrahedron Lett.* **1993**, *34*, 4369. e) Chen, C.; Crich, D. *Tetrahedron* **1993**, *49*, 7943. f) Chen, C.; Crich, D. *Tetrahedron Lett.* **1992**, *33*, 1945. g) Mascareñas, J. L.; García, A. M.; Castedo, L.; Mouriño, A. *Tetrahedron Lett.* **1992**, *33*, 4365. h) Posner, G. H.; Carry, J. -C.; Anjeh, T. E. N.; French, A. N. *J. Org. Chem.* **1992**, *57*, 7012. i) Kabat, M. M.; Lange, M.; Wovkulich, P. M.; Uskokovic´, M. R. *Tetrahedron Lett.* **1992**, *33*, 7701.

10 a) Yamaguchi, M.; Waseda, T.; Hirao, I. *Chem. Lett.* **1983**, 35. b) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.

11 a) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560-3578. b) See also Anwar, S.; Davis, A. P. *J. Chem. Soc. Chem Commun.* **1986**, 831-832.

12 a) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856. b) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, Ohta, T.; Takaya, H.; S. Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629.

13 For a similar approach to a 1,3-*anti*-diol synthon that was reported subsequent to the initiation of our efforts see: Pickering, D. A.; Rychnovsky, S. D. Presented at the 207th National Meeting of the American Chemical Society, San Diego, CA, March **1994**; paper ORGN 209.

14 a) Kitamura, M.; Ohkuma, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 1555. b) Rychnovsky, S. D.; Griesegraber, G. *J. Org. Chem.* **1992**, *57*, 1559. c) King, S. A.; Thompson, A. S.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1992**, *57*, 6689.

15 a) Anwer, B.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171. b) Evans, D. A.; Rieger, D. L.; Jones, T. K.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 6260.

16 GC and NMR analysis of the crude isolated material was very clean showing no signs of epoxide formation. We are currently working on an in situ generation of enone **6** which can be directly subjected to the Evan's reduction conditions that lead to the *anti*-diol **7**.

(*Received in USA* 5 *August* 1994; *revised* 7 *September* 1994; *accepted* 8 *September* 1994)