A New Metabolite of Paricalcitol: Stereoselective synthesis of (22Z)- isomer of 1α, 25-dihydroxy-19-norvitamin D2

Article *in* Tetrahedron Letters · February 2016

DOI: 10.1016/j.tetlet.2016.01.110

CITATION
1

READS
222

5 authors, including:

Ramakrishna Samala
GVK Bio
4 PUBLICATIONS **6** CITATIONS
SEE PROFILE

Somesh Sharma
GVK Bio
28 PUBLICATIONS **199** CITATIONS
SEE PROFILE

Mukkanti Khagga
Jawaharlal Nehru Technological University, Hyderabad
402 PUBLICATIONS **3,147** CITATIONS
SEE PROFILE

Tetrahedron Letters 57 (2016) 1309–1312

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A new metabolite of Paricalcitol: stereoselective synthesis of (22*Z*)-isomer of 1α,25-dihydroxy-19-norvitamin D_2

Ramakrishna Samala [a], Somesh Sharma [a,*], Manas K. Basu [a], K. Mukkanti [a], Frank Porstmann [b]

[a] *Chemistry Services, GVK Biosciences Pvt. Ltd, Plot No. 5C, IDA, Uppal, Hyderabad 500 039, AP, India*
[b] *API R&D, AZAD Pharmaceutical Ingredients AG, 8200 Schaffhausen, Switzerland*

ARTICLE INFO

Article history:
Received 28 December 2015
Revised 25 January 2016
Accepted 30 January 2016
Available online 13 February 2016

Keywords:
Paricalcitol
19-Nor-1,25-$(OH)_2$-vitamin D_2
Vitamin D_2 (Ergocalciferol)
D-(−)-Quinic acid
Julia–Lythgoe's olefination
Horner–Wadsworth–Emmons reaction

ABSTRACT

Stereoselective synthesis of (22*Z*)-isomer of Paricalcitol, an analog of 1,25-dihydroxyergocalciferol, an active form of vitamin D_2 (Ergocalciferol) has been described. The two key critical synthetic steps involved are Julia–Lythgoe's Wittig–Horner coupling of aldehyde functionality of CD-ring system with benzothiazolyl sulfone, and Horner–Wadsworth–Emmons reaction of phosphine oxide with a Windaus–Grundmann's ketone to build a diene motif between the A and CD-ring system of Paricalcitol.

Introduction

The natural hormones 1α,25-dihydroxyvitamin D_3 (**1**, Calcitriol), 1α,25-hydroxyvitamin D_3 (**2**, Alfacalcidol), 1α,25-hydroxyvitamin D_2 (**3**, Doxercalciferol) (Fig. 1), are members of steroid/thyroid/androgen nuclear receptor super-family, and act as endogenous ligands for the nuclear vitamin D receptor (VDR), and show significant biological activities.[1] Calcitriol (**1**) is well known as a primary regulator for calcium and phosphate homeostasis,[2,3] and plays a critical role in regulation of the proliferation of malignant cells.[4,5]

In recent times, the non-natural vitamin D_2 (**6**, Ergocalciferol) has been administrated to humans and domestic animals[6] in parallel to vitamin D to influence metabolism and biological activities. There is also a strong evidence on vitamin D_2 undergoing double hydroxylation[7,8] to produce 1α,25-dihydroxyvitamin D_2.

Further, most of analogs examined so far belong to natural vitamin D_3 series. In comparison to vitamin D_3 derivatives, vitamin D_2 derivatives are challenging to synthesize due to an additional chiral center at C-24 and a double bond (*E*-geometry) at C-22. Among these Paricalcitol (**4**) is being used to treat secondary hyperparathyroidism (SHPT) in patients with chronic kidney disease (CKD).[9] Several synthesis routes have been published for the synthesis of Paricalcitol.[10]

However, these synthetic approaches focus on the synthesis of the *E*-configuration at C-22. For verification of analytical methods for Paricalcitol it is necessary to provide reference material of the corresponding *Z*-isomer. This requirement will become even more important with the expected implementation of the new USP method specifying this compound specifically.[11]

Various structural modifications (Fig. 1) explored on 1α,25-dihydroxy 19-nor vitamin D are in side chain viz. reduced double bond or substituents around double bond, surprisingly researchers failed to evaluate the potential of isomerization at C-22, 23 position. Herein, we report the first total synthesis of *Z*-stereoisomer of Paricalcitol at C-22, 23 by maneuvering the coupling of A-ring system with a Windaus–Grundmann's keto-acetal under Wittig–Horner condition,[12–14] and subsequently Julia–Lythgoe[15] olefination on ACD-ring system. (Strategy II, Fig. 2.)

Results and discussion

As a part of our quest on the stereoselective synthesis of vitamin D_2 metabolites, we approached our scientific efforts in two ways: (i) synthesis of either precursor **7** (Strategy I) or **12** (Strategy II) (Fig. 2) and (ii) preparation of benzothiazolyl sulfone **8**, a key intermediate for bringing side chain under Julia–Lythgoe olefination condition.

Our studies began with the synthesis of intermediate **13**[16] from D-(−)-Quinic acid,[17] and its conversion to phosphine oxide **11** in 10

* Corresponding author. Tel.: +91 40 66281305; fax: +91 40 66929900.
E-mail address: somesh.sharma@gvkbio.com (S. Sharma).

http://dx.doi.org/10.1016/j.tetlet.2016.01.110
0040-4039/

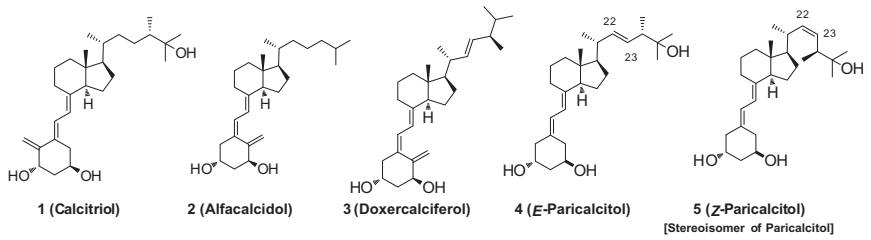


Figure 1. Structures of vitamin D receptor analogs.

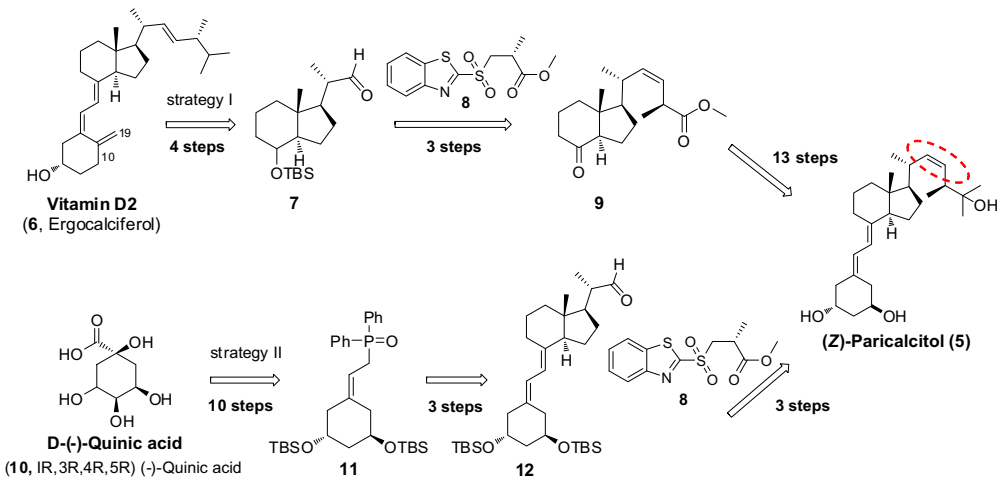
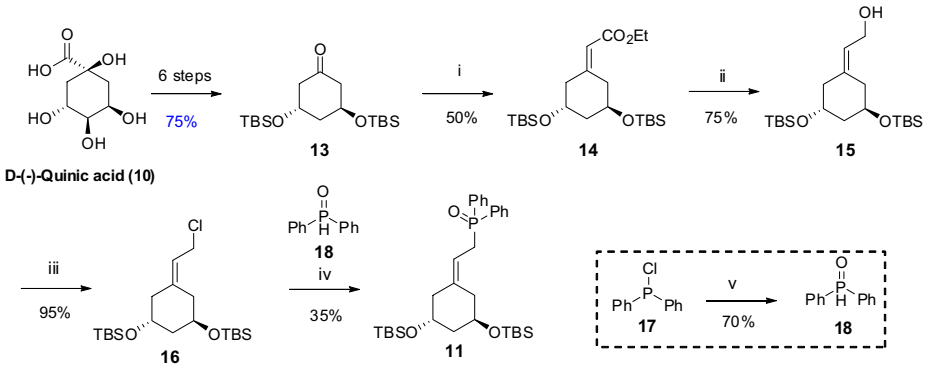


Figure 2. Retro synthetic approach of (*E*)-Paricalcitol and its stereoisomer (*Z*)-Paricalcitol.

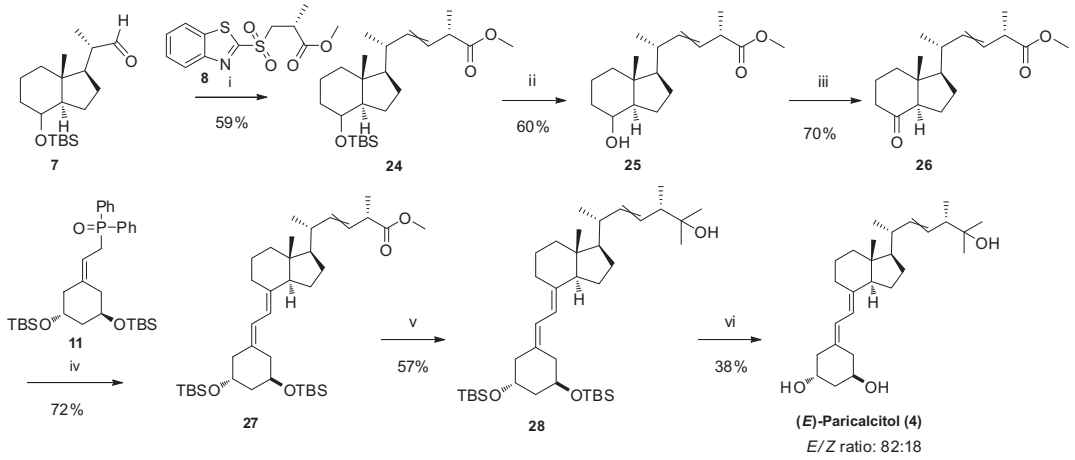
steps (Scheme 1). The preparation of **11** was critical for the success of this method, as this will participate in constructing A-ring system[18] in Paricalcitol (Fig. 2; Strategy II). Various attempts were made to convert **15** to **11**, either through the preparation of tosylate of **15** under standard condition[19] or chloride **16** with NCS as reported by Uskokovic group,[20] and subsequently their displacement with lithium phenylphosphine. The preparation of **16** was challenging in the above condition, thereof, we shifted our attention to triphosgene (in hexane) condition.[21] Intermediate **16** was displaced with diphenyl phosphine oxide to get **11**. The main advantage of this reaction condition was the preparation of air stable diphenylphosphine oxide from inexpensive chlorodiphenylphosphine **17** and its usage. Another crucial intermediate **7** was prepared from Ergocalciferol (**6**) in multiple steps (Scheme 2) as per literature report.[22]

Julia–Lythgoe olefination of **7** and sulfone **8** in the presence of NaHMDS/or LiHMDS in THF (−78 °C, 30 min) afforded prominently *trans*-olefin **24** (*E*/*Z*-isomer ratio 82:18) in 59% yield. We further explored the potential of other reagents like methyl 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]acetate and diphenoxy phosphonate to obtain the desired result but were unsuccessful. The intermediate **24** was taken forward to synthesize Paricalcitol, thinking to get separation of these isomers at some stage. However, our efforts were not encouraging and isomers (*E*- and *Z*-isomer) were separated only by preparative HPLC purification.

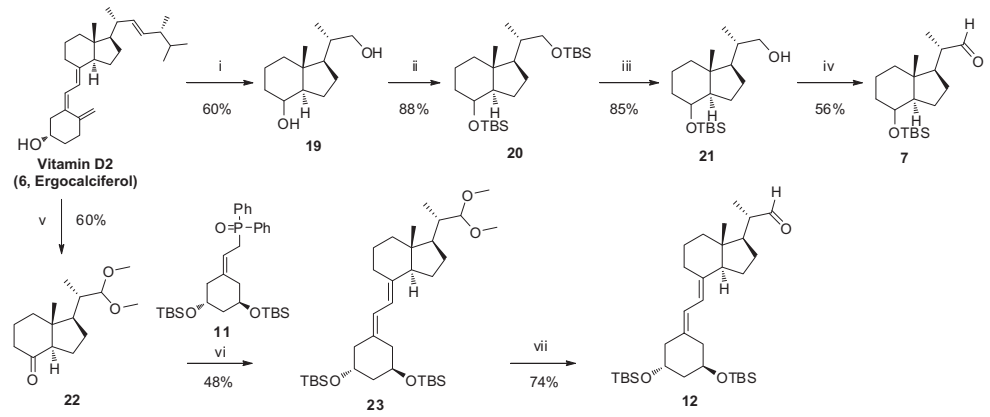
Unpromising results on first strategy (Scheme 2) impelled us to look for alternative plan to achieve the desired results. The critical intermediate **22** of CD-ring system was conveniently prepared by ozonolytic cleavage of vitamin D_2 (**6**) in methanol, using $CHCl_3$ as co-solvent (Scheme 3). The residual acid in $CHCl_3$ was sufficient



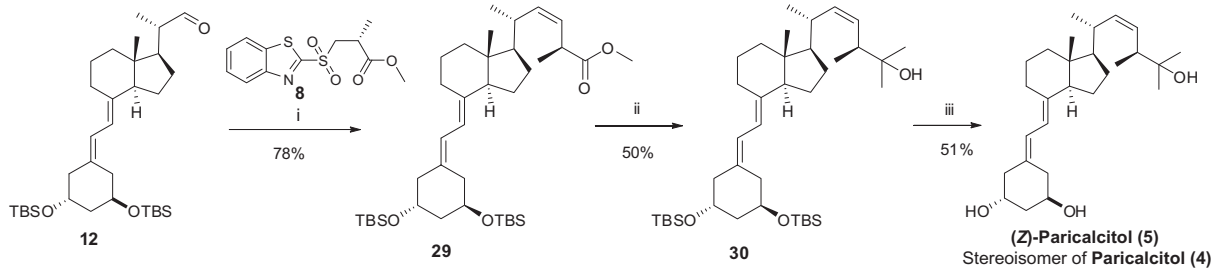
Scheme 1. Reagents and conditions: (i) $(TMS)CH_2CO_2Et$ (1.5 equiv), LiHMDS (1 M in THF, 1.5 equiv), THF, 0 °C–rt, 15 min; then cooled to −78 °C, add **13**, −78 °C, 3 h; (ii) DIBAL-H (2.5 equiv); toluene, −78 °C to rt, 3 h; (iii) Triphosgene (0.5 equiv), pyridine (2 equiv), hexane, 0 °C–rt, 30 min; (iv) **18** (1 equiv), NaH (1 equiv), DMF, 0 °C–rt, 30 min; then cooled to −60 °C, add **16** (1 equiv), −60 °C to 1 h; rt to 1 h; (v) 1 N aq HCl (2 vol), rt, 18 h.



Scheme 2. Reagents and conditions: (i) **8** (1.5 equiv), LiHMDS (1 M in THF; 1.5 equiv), THF, −78 °C to 15 min; then add **7** (1 equiv), −78 °C to rt, 5 h; (ii) TBAF (1 M in THF), THF, 80 °C, 24 h; (iii) PDC (2.5 equiv), 4 A MS, CH_2Cl_2; 0 °C, 4 h; (iv) **11** (1 equiv), NaHMDS (1 M in THF, 1.1 equiv), THF, −78 °C, 10 min; then add **26** (1 equiv), −78 °C, 1 h; (v) MeMgBr (3 M in Et_2O, 5 equiv), THF, 0 °C, 4 h; (vi) NH_4F (5 equiv), MeOH, reflux, 5 h.



Scheme 3. Reagents and conditions: (i) (a) O_3, $NaHCO_3$, MeOH, 8 h; (b) $NaBH_4$, rt, 18 h; (ii) TBSCl (3 equiv), Imidazole (4 equiv), DMAP (cat), DMF, rt, 18 h; (iii) TBAF (1 M in THF), THF, 0 °C–rt, 18 h; (iv) PCC (2.2 equiv), Celite, CH_2Cl_2, 0 °C–rt, 18 h; (v) (a) O_3, pyridine, MeOH, −78 °C, 8 h; Me_2S (6 equiv), −78 °C to 1 h; rt to 1 h; (vi) **11** (1 equiv), NaHMDS (1 M in THF), THF, −78 °C to 5 min, then add **22** (1 equiv), −78 °C to 15 min; (vii) $CHCl_3/H_2O$/TFA (4:2:1), 0 °C–rt, 1 h.



Scheme 4. Reagents and conditions: (i) **8** (1.1 equiv), LiHMDS (1 M in THF), THF, −78 °C to 15 min; then add **12** (1 equiv), −78 °C, 15 min; (ii) MeMgBr (3 M in Et_2O, 3 equiv), THF, 0 °C, 4 h; (iii) TBAF (1 M in THF, 5 equiv), THF, 60 °C, 2 h.

to catalyze acetalization of the aldehyde functionality to provide keto-acetal **22** during a reductive workup with dimethyl sulfide in 60% yield. Wittig–Horner coupling of keto-acetal **22** with phosphine oxide **11** (ring A synthon) afforded the diene keto-acetal **23**, which on deprotection provided aldehyde **12**.[23] However, Julia–Lythgoe olefination on **12** with sulfone **8** in the presence of LiHMDS in THF (−78 °C, 30 min) gave ester **29** in good yield (78%) with desired stereoselectivity, a *Z*-isomer. Grignard reaction on ester **29** with MeMgBr (3 M in Et_2O) in ether (0 °C, 4 h), followed by removal of silyl protecting group on **30** gave target *Z*-isomer of Paricalcitol **5** in 51% yield (Scheme 4). The overall yield of this sixteen step synthesis is 0.1% starting from Quinic acid (**10**).

The characteristic difference in *E* and *Z*-isomer of Paricalcitol was in chemical shift of protons on C-22 and C-23 atoms. These protons were observed as multiple peaks in the region 5.27–5.40 for *E*-isomer, however, in case of *Z*-isomers these protons were well distinguished at 5.162–5.216 (m, 1H), 5.33–5.33 (m, 1H) respectively by ^1H NMR (Fig. 3). The other protons are in

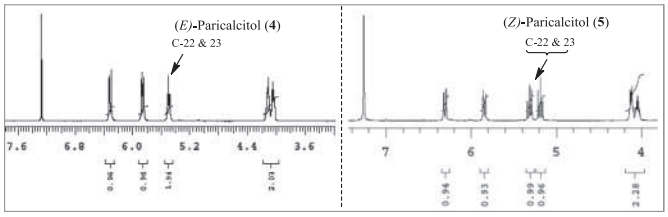


Figure 3. Characteristic protons of (*E*)-Paricalcitol (**4**) and its stereoisomer (*Z*)-Paricalcitol (**5**) in $CDCl_3$ solvent (400 MHz).

agreement with reported value[24] for *E*-isomer. These isomers are separable on HPLC.

The solution form of *Z*-isomer of Paricalcitol **5** was found to be stable under the thermal condition (60–180 °C) in various solvents (viz. EtOH, acetonitrile, Dowtherm).

Conclusion

In conclusion, we have succeeded in developing an efficient synthetic approach for the synthesis of *Z*-isomer of Paricalcitol from Quinic acid under Julia–Lythgoe's olefination condition. The key intermediates in this synthesis effort were phosphine oxide **11** and benzothiazolyl sulfone **8**.

Acknowledgments

We sincerely thank GVK Biosciences Private Limited for financial support and facility for accomplishing this research work. We are extremely thankful to Azad pharma for sharing research challenge with us and supporting in our pursuit.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.01.110.

References and notes

1. (a) Eelen, G.; Verlinden, L.; De Clercq, P.; Vandewalle, M.; Bouillon, R.; Verstuyf, A. *Anticancer Res.* **2006**, *26*, 2717–2721; (b) Beer, T. M.; Myrthue, A. *Mol. Cancer Ther.* **2004**, *3*, 373–381; (c) Trump, D.; Muindi, J.; Fakih, M.; Yu, W.; Johnson, C. *Anticancer Res.* **2006**, *26*, 2551–2556.
2. Bouillon, R.; Carmeliet, G.; Verlinden, L.; van Etten, E.; Verstuyf, A.; Luderer, H. F.; Lieben, L.; Mathieu, C.; Demay, M. *Endocr. Rev.* **2008**, *29*, 726–776.
3. Direct synthesis: Perlman, K. L.; Sicinski, R. R.; Schnoes, H. K.; DeLuca, H. F. *Tetrahedron Lett.* **1990**, *31*, 1823–1824.
4. (a) Reinhardt, T. A.; Ramberg, C. F.; Horst, R. L. *Arch. Biochem. Biophys.* **1989**, *273*, 64; (b) Morzycki, J. W.; Schnoes, H. K.; DeLuca, H. F. *J. Org. Chem.* **1984**, *49*, 2148; (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.
5. (a) Granja, J. R.; Castedo, L.; Mouriño, A. *J. Org. Chem.* **1993**, *58*, 124; (b) Torneiro, M.; Fall, Y.; Castedo, L.; Mouriño, A. *J. Org. Chem.* **1997**, *62*, 6344.
6. (a) Norman, A. W. *Vitamin D, The Calcium Homeostatic Steroid Hormone*; Academic Press: New York, 1979; (b) DeLuca, H. F. *Handb. Physiol.* **1978**, *7*, 265.
7. (a) Drescher, D.; DeLuca, H. F.; Imrie, H. H. *Arch. Biochem. Biophys.* **1969**, *130*, 657; (b) Norman, A. W.; Roth, J.; Orci, L. *Endocr. Rev.* **1982**, *3*, 331; (c) Sjoden, G.; Smith, C.; Lindgren, U.; DeLuca, H. F. *Proc. Soc. Exp. Biol. Med.* **1985**, *178*, 432; (d) Reddy, G. S. *Biochemistry* **1986**, *25*, 5328. and references therein.
8. (a) Koszewski, N. J.; Reinhardt, T. A.; Napoli, J. L.; Beitz, D. C.; Horst, R. L. *Biochemistry* **1988**, *27*, 5785; (b) Jones, G.; Schnoes, H. K.; DeLuca, H. F. *Biochemistry* **1975**, *14*, 1250.
9. (a) Perlman, Kato L.; Sicinski, Rafal R.; Schnoes, Heinrich K.; DeLuca, Hector F. *Tetrahedron Lett.* **1990**, *31*, 1823–1824; (b) Graul, A.; Leeson, P. A.; Castaner, J. *Drugs Future* **1998**, *23*, 602–606.
10. (a) Deluca, Hector F.; Schnoes, Heinrich K.; Perlman, Kato L.; Sicinski, Rafal R.; Prahl, Jean Martin. W.O. Patent 1,990,010,620, 1990; (b) Bader, Thomas; Stutz, Alfred; Bichsel, Hans-Ulrich; Fu, Changchun. W.O. Patent 2,010,009,879, 2010.
11. USP monograph for Paricalcitol PF 41, currently under review.
12. Indirect synthesis: (a) Perlman, K. L.; Swenson, R. E.; Paaren, H. E.; Schnoes, H. K.; DeLuca, H. F. *Tetrahedron Lett.* **1991**, *32*, 7663–7666.
13. (a) Sicinski, R. R.; Perlman, K. L.; DeLuca, H. F. *J. Med. Chem.* **1994**, *37*, 3730–3738; (b) Shimizu, M.; Iwasaki, Y.; Shibamoto, Y.; Sato, M.; DeLuca, H. F.; Yamada, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 809–812; (c) Shimizu, M.; Iwasaki, Y.; Shimazaki, M.; Amano, Y.; Yamamoto, K.; Reischl, W.; Yamada, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1451–1455; (d) Glebocka, A.; Sicinski, R. R.; Plum, L. A.; Deluca, H. F. *J. Med. Chem.* **2011**, *54*, 6832–6842.
14. (a) Ono, K.; Yoshida, A.; Saito, N.; Fujishima, T.; Honzawa, S.; Suhara, Y.; Kishimoto, S.; Sugiura, T.; Waku, K.; Takayama, H.; Kittaka, A. *J. Org. Chem.* **2003**, *68*, 7407–7415; (b) Snchez-Abella, L.; Fernndez, S.; Verstuyf, A.; Verlinden, L.; Gotor, V.; Ferrero, M. *J. Med. Chem.* **2009**, *52*, 6158–6162.
15. (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14*, 4833–4836; (b) Vedejs, E. *Stud. Nat. Prod. Chem.* **1991**, *8*, 205–218; (c) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175–1178.
16. Perlman, K. L.; Swenson, R. E.; Paaren, H. E.; Schnoes, H. K.; DeLuca, H. F. *Tetrahedron Lett.* **1991**, *32*, 7663–7666.
17. (a) Sicinski, R. R.; Prahl, J. M.; Smith, C. M.; DeLuca, H. F. *New J. Med. Chem.* **1998**, *41*, 4662–4674; (b) Desmaele, D.; Tanier, S. *Tetrahedron Lett.* **1985**, *26*, 4941.
18. Perlman, K. L.; Sicinski, R. R.; Schnoes, H. K.; DeLuca, H. F. *Tetrahedron Lett.* **1990**, *31*, 1823–1824.
19. Monneret, C. *Eur. J. Med. Chem.* **2005**, *40*, 1–13.
20. Bagiollini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovic, M. R. *J. Org. Chem.* **1986**, *51*, 3098–3108.
21. (a) Andrzej, R. D.; Lisa, M. G.; Stanley, D. H.; Marek, M. K. *J. Org. Chem.* **2002**, *67*, 1580–1587; (b) Andrzej, R. D.; Lisa, M. G.; Stanley, D. H. *Synth. Commun.* **2002**, *32*, 3031–3040.
22. (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; (c) Posner, G. H.; Li, Z.; White, M. C.; Vinader, V.; Takeuchi, K.; Guggino, S. E.; Kensler, T. W. *J. Med. Chem.* **1995**, *38*, 4529–4537.
23. McGILL University; Jim Gleason; Tan Quach; Mendoza Luz Elisa Tavera; John White. W.O. Patent 2,007,131,364 A1, 2007.
24. Toyoda, A.; Nagai, H.; Yamada, T.; Moriguchi, Y.; Abe, J.; Tsuchida, T.; Nagasawa, K. *Tetrahedron* **2009**, *65*, 10002–10008.