

Enantioselective Synthesis of A Key A-Ring Intermediate for the Preparation of 1 α ,25-Dihydroxyvitamin D₃

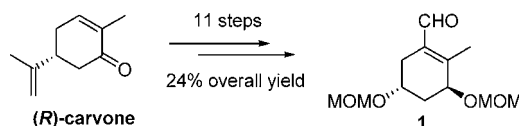
Yan Chen* and Tong Ju

Tianjin Key Laboratory for Modern Drug Delivery & High-Efficiency, School of Pharmaceutical Science and Technology, Tianjin University, Tianjin 300072, China

cylcy2005@yahoo.com.cn

Received October 27, 2010

ABSTRACT



A novel approach to the key A-ring α , β -unsaturated aldehyde **1**, an important intermediate for the preparation of 1 α ,25-dihydroxyvitamin D₃, has been developed. The strategy started from the inexpensive starting material (*R*)-carvone with an ene reaction serving as the key step toward the potential synthesis of vitamin D₃ analogues bearing the modification at the C-2 position.

1 α ,25-Dihydroxyvitamin D₃ (calcitriol), the active form of vitamin D₃, is a multifunctional steroidal hormone that regulates cell differentiation, cell proliferation, and the immune system, in addition to its classical function in calcium and phosphate metabolism.¹ However, therapeutic utility of calcitriol in the treatment of cancer and psoriasis is limited by its potent calcemic effects.² Thus, the research for noncalcemic therapeutic agents and for convenient methods of synthesizing modified calcitriol has been greatly stimulated by medical needs. It is not surprising that more than 3000 vitamin D₃ analogues have been synthesized over the past few decades.³ However, most of these synthetic studies involved side-chain modification and the decoration of the A-ring is not intensively reported.⁴ Therefore, the construction of building blocks that could lead to vitamin

D₃ analogues bearing the modification on the A-ring is of important significance.

The α , β -unsaturated aldehyde **1** is an essential building block for the synthesis of 1 α ,25-dihydroxyvitamin D₃ in Julia's olefination approach⁵ (Figure 1). And in the enyne approach,⁶ **1** is a key intermediate which could furnish the A-ring **3** by Corey–Fuchs homologation.⁷ Although the majority of the syntheses of **1** utilized (*S*)-carvone as the starting material,⁸ application of (*R*)-carvone remains unexploited despite the obvious cost advantage over its enanti-

(1) (a) Feldman, D.; Pike, J. W.; Glorieux, F. H., Eds. *Vitamin D*, 2nd ed.; Elsevier Academic Press: New York, 2005. (b) DeLuca, H. F. *Nutr. Rev.* **2008**, *66*, s73–s87. (c) Adorini, L.; Penna, G. *Nat. Clin. Pract. Rheumatol.* **2008**, *4*, 404–412. (d) White, P.; Cooke, N. *Trends Endocrinol. Metab.* **2000**, *11*, 320–327. (e) Hammes, S. R. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 21680–21700. (f) Holick, M. F., Eds. *Vitamin D*; Humana Press: Totowa, NJ, 1999.

(2) (a) Bouillon, R.; Okamura, W. H.; Norman, A. W. *Endocr. Rev.* **1995**, *16*, 200–257. (b) Carlberg, C.; Mourifio, A. *Expert Opin. Ther. Patents* **2003**, *13*, 761–772. (c) DeLuca, H. F. *J. Bone Miner. Metab.* **1990**, *8*, 1–9. (d) Bexkman, M. J.; DeLuca, H. F. *Prog. Med. Chem.* **1998**, *35*, 1–56. (e) Stein, M. S.; Wark, J. D. *Expert Opin. Investig. Drugs* **2003**, *12*, 825–840.

(3) (a) Zhu, G. D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877–1952. (b) Dai, H.; Posner, G. H. *Synthesis* **1994**, 1383–1398. (c) Mathieu, C.; Adorini, L. *Trends Mol. Med.* **2002**, *8*, 174–179. (d) Nagpal, S.; Na, S.; Rathnachalam, R. *Endocr. Rev.* **2005**, *26*, 662–687. (e) Laverny, G.; Penna, G.; Uskokvic, M.; Marczak, S.; Maehr, H.; Jankowski, P.; Ceailles, C.; Vouros, P.; Smith, B.; Robinson, M.; Reddy, G. S.; Adorini, L. *J. Med. Chem.* **2009**, *52*, 2204–2213. (f) Nakabayashi, M.; Yamada, S.; Yoshimoto, N.; Tanaka, T.; Igarashi, M.; Ikura, T.; Ito, N.; Makishima, M.; Tokiwa, H.; DeLuca, H. F.; Shimizu, M. *J. Med. Chem.* **2008**, *51*, 5320–5329.

(4) (a) Norman, A. W.; Ishizuka, S.; Okamura, W. H. *J. Steroid. Biochem. Mol. Biol.* **2001**, *76*, 49–59. (b) Sicinski, R. R.; Rotkiewicz, P.; Kolinski, A.; Sicinska, W.; Prah, J. M. *J. Med. Chem.* **2002**, *45*, 3366–3380. (c) Saito, N.; Suhara, Y.; Kurihara, M.; Fijishima, T.; Honzawa, S.; Takayanagi, H.; Kozono, T.; Matsumoto, M.; Ohmori, M.; Miyata, N.; Takayama, H.; Kittaka, A. *J. Org. Chem.* **2004**, *69*, 7463–7471. (d) Glebocka, A.; Sicinski, R.; Plum, L. L.; Clagett-Dame, M.; DeLuca, H. F. *J. Med. Chem.* **2006**, *49*, 2909–2920. (e) Sicinski, R. R.; Glebocka, A.; Plum, L. A.; DeLuca, H. F. *J. Med. Chem.* **2007**, *50*, 6154–6164.

(5) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1400–1404.

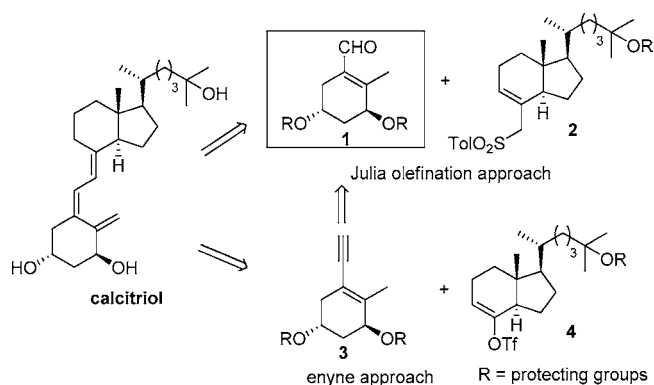


Figure 1. α,β -Unsaturated aldehyde **1** as a key intermediate to synthesize calcitriol.

omer.⁹ We wish to report herein an efficient enantioselective synthesis of the α,β -unsaturated aldehyde **1** from (*R*)-carvone.

Compared with Okamura's^{8b} and Mouriño's^{8c} approach, our strategy is conceptually different (Figure 2): In the

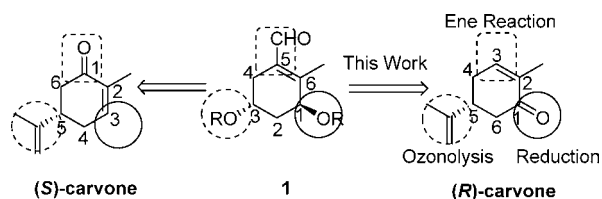
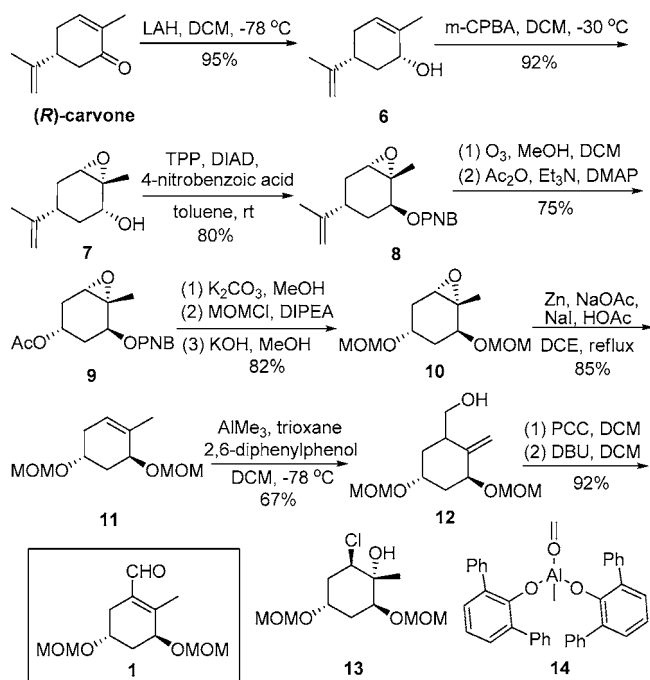


Figure 2. Comparison of the synthetic strategies to construct **1**.

previous methods, the alkoxy group at the C-1 position in **1** was introduced at the C-3 position of (*S*)-carvone by epoxidation and subsequent ring-opening. In comparison, we envisaged the installation of this group through a diastereoselective reduction of the ketone in (*R*)-carvone, and the formyl group at the C-5 position in compound **1** was assembled from (*R*)-carvone through an ene reaction with activated formaldehyde followed by oxidation.

Our pathway synthesis of **1** is outlined in Scheme 1. Diastereoselective reduction of (*R*)-carvone with LAH in DCM at $-78\text{ }^\circ\text{C}$ afforded the sole isomer *cis*-carveol **6** in

Scheme 1. Enantioselective Synthesis of α,β -Unsaturated Aldehyde **1** from (*R*)-Carvone



95% yield.¹⁰ Regioselective *syn*-epoxidation of the allylic double bond of **6** was achieved with *m*-CPBA in DCM at $-30\text{ }^\circ\text{C}$ producing the desired epoxide **7** in 92% yield. Mitsunobu reaction of this epoxy alcohol occurred with complete inversion of the configuration at C-1 of **7** affording nitrobenzoate **8**.¹¹ Ozonolysis¹² of **8** at $-78\text{ }^\circ\text{C}$ in the presence of methanol and in situ acylation of the resulting hydroperoxide intermediate gave the acetate product **9** predominantly.¹³ After saponification of the ester, the intermediate diol was protected with a MOM group which is among the most used protecting groups in the area of vitamin D₃ synthesis.^{14,15} It was found that the undesired epoxy ring-opened compound **13** was obtained as the major product in this reaction. Fortunately, the conversion of **13** to the desired product **10** took place smoothly under basic conditions. Thus, MOM ether **10** was achieved in a three-step sequence in high yield from **9**. The epoxy functionality

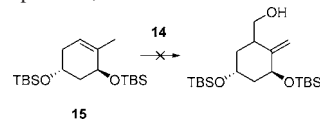
(10) Bourque, L. E.; Cleary, P. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 12602–12603.

(11) Barbier, P.; Mohr, P.; Muler, M.; Masciadri, R. *J. Org. Chem.* **1998**, *63*, 6984–6989.

(12) Daniewski, A. R.; Garofalo, L. M.; Hutchings, S. D.; Kabat, M. M.; Liu, W.; Okabe, M.; Radiov, R.; Yiannikouros, G. P. *J. Org. Chem.* **2002**, *67*, 1580–1587.

(13) The absolute configuration of ester groups at C-1 and C-3 of **9** was confirmed by X-ray crystal analysis (see Supporting Information).

(14) TBS was chosen as the protective group first, but it was found that the TBS ether **15** had no reaction when treated with the active form of formaldehyde **14**. Considering if the steric hindrance of the TBS group might be the initial problem, we turned our attention to the MOM group.



(6) (a) Harrison, R. G.; Lythgoe, B.; Wright, P. W. *Tetrahedron Lett.* **1973**, *14*, 3649–3652. (b) Okamura, W. H. *Acc. Chem. Res.* **1983**, *16*, 81–88. (c) Mascareñas, J. L.; Sarandeses, L. A.; Castedo, L.; Mouriño, A. *Tetrahedron* **1991**, *47*, 3485–3498. (d) Oves, D.; Ferrero, M.; Fernandez, S.; Gotor, V. *J. Org. Chem.* **2003**, *68*, 1154–1157. (e) Rodriguez, R.; Ollivier, C.; Stantelli, M. *Tetrahedron Lett.* **2004**, *45*, 2289–2292.

(7) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769–3772.

(8) (a) Baggolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D. *J. Org. Chem.* **1986**, *51*, 3098–3108. (b) Okamura, W. H.; Aurrecoechea, J. M.; Gibbs, R. A.; Norman, A. W. *J. Org. Chem.* **1989**, *54*, 4072–4083. (c) Castedo, L.; Mascareñas, J. L.; Mouriño, A. *Tetrahedron Lett.* **1987**, *28*, 2099–2102.

(9) Hatakeyama, S.; Numata, H.; Osanai, K.; Takano, S. *J. Org. Chem.* **1989**, *54*, 3515–3517.

in compound **10** was removed by Zn powder and NaI to reinstall the C=C bond to give product **11** in good yield.¹⁶ With the olefin **11** in hand, we studied the ene reaction following the protocol of Yamamoto¹⁷ and were delighted to isolate the single isomer **12**¹⁸ in moderate yield from the reaction of **11** with the active form of formaldehyde **14** which was prepared by use of AlMe₃, 2,6-diphenylphenol, and trioxane. Without purification, primary alcohol **12** was further subjected to oxidation and isomerization, and the final α,β -unsaturated aldehyde **1** was successfully achieved in 92% yield and 24% overall yield from (*R*)-carvone.

A significant feature of this new strategy was that the C-2 in product **1** maps onto the enolizable position of C-6 of (*R*)-carvone and is thus amenable to functionalization with a variety of electrophiles. Furthermore, it was found that some functionalization of the C-2 position on the A-ring increased the binding affinity for vitamin D receptor (VDR) with potent agonistic activity. According to literature,¹⁹ nearly all of the analogues of **17** were prepared by Trost's²⁰ strategy, in which the A-ring part, 1,7-enyne **18**, was obtained from chiral monosaccharides (Figure 3). Therefore, our

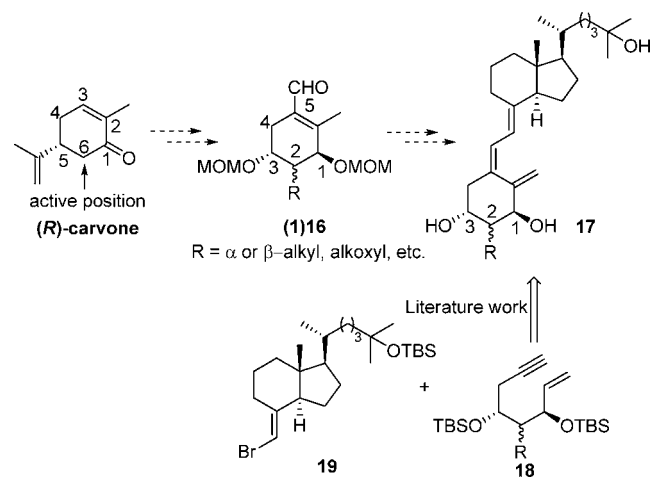


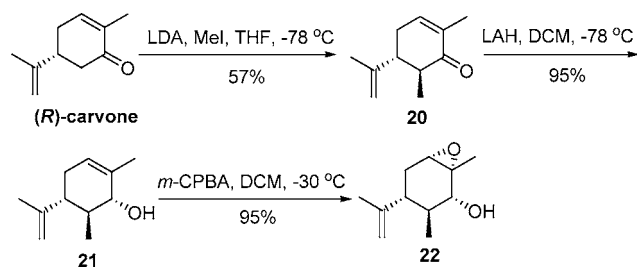
Figure 3. Significant feature of this strategy.

strategy opens new possibilities for the preparation of vitamin D₃ analogues of therapeutic potential, particularly with modifications at the C-2 position.

Our preliminary investigation of this potential was directed to preparation of the C-2 methylated analogue of calcitriol. Kinetic methylation of (*R*)-carvone using lithium diisopro-

pylamide (LDA) and methyl iodide furnished a 3:2 diastereomeric mixture of 6-methylcarvone, which upon low temperature crystallization provided the major *trans*-6-methylcarvone **20** in stereochemically pure form (Scheme 2).²¹ In the following reduction and epoxidation, it was found

Scheme 2. Modification of C-2 Position with Methyl Group



that the methyl group had no effect on the yield and the diastereoselectivity of these reactions, and the sole isomer **22** (the absolute configurations were confirmed by X-ray crystal analysis, Figure 4) was obtained in 90% yield over

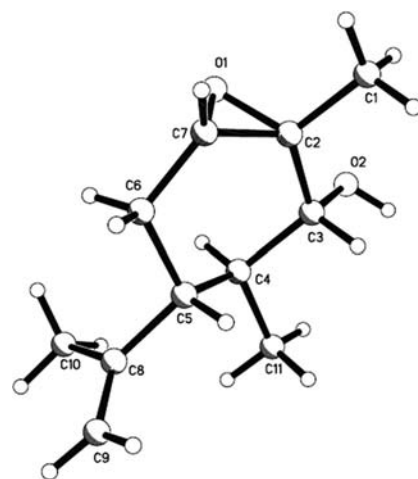


Figure 4. X-ray structure of **22**.

two steps. Subjecting **22**, in which the key stereocenters have been established, to our synthetic route in Scheme 1 and the

(15) Examples of the application of the MOM group in vitamin D₃ synthesis: (a) Riveiros, R.; Rumbo, A.; Sarandeses, L. A.; Mourinho, A. *J. Org. Chem.* **2007**, *72*, 5477–5485. (b) Reino, C. G.; Vitale, C.; Maestro, M.; Mourinho, A. *Org. Lett.* **2005**, *7*, 5885–5887. (c) Moriarty, R. M.; Kim, J.; Brumer, H. *Tetrahedron Lett.* **1995**, *36*, 51–54. (d) Nemoto, H.; Wu, X.; Kurobe, H.; Ihara, M.; Fukumoto, K.; Kametani, T. *Tetrahedron Lett.* **1983**, *24*, 4257–4260. (e) Castedo, L.; Granja, J.; Maestro, M. A.; Mourinho, A. *Tetrahedron Lett.* **1987**, *28*, 4589–4590.

(16) Li, Y.; Feng, J.; Wang, W.; Chen, J.; Cao, X. *J. Org. Chem.* **2007**, *72*, 2344–2350.

(17) Maruoka, K.; Conception, A. B.; Murase, N.; Oishi, M.; Hirayama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 3943–3949.

(18) The configuration of the new chiral center was not determined.

(19) (a) Sahara, Y.; Nihei, K.; Kurihara, M.; Kittaka, A.; Yamaguchi, K.; Fujishima, T.; Konno, K.; Miyata, N.; Takayama, H. *J. Org. Chem.* **2001**, *66*, 8760–8771. (b) Takahashi, T.; Doi, T.; Hijikuro, I. *J. Am. Chem. Soc.* **2001**, *123*, 3716–3722. (c) Saito, N.; Saito, H.; Anzai, M.; Yoshida, A.; Fujishima, T.; Takenouchi, K.; Miura, D.; Ishizuka, S.; Takayama, H.; Kittaka, A. *Org. Lett.* **2003**, *5*, 4859–4862. (d) Saito, N.; Matsunaga, T.; Saito, H.; Anzai, M.; Takenouchi, K.; Miura, D.; Namekawa, J.; Ishizuka, S.; Kittaka, A. *J. Med. Chem.* **2006**, *49*, 7063–7075. (e) Posner, G. H.; Woodard, B. T.; Grawford, K. R.; Peleg, S.; Brown, A. J.; Dolan, P.; Kensler, T. W. *Bioorg. Med. Chem.* **2002**, *10*, 2353–2365. (f) Posner, G. H.; Cho, C. G.; Anjeh, T. E. N.; Johnson, N.; Horst, R. L.; Kobayashi, T.; Okano, T.; Tsugawa, N. *J. Org. Chem.* **1995**, *60*, 4617–4628. (g) Posner, G. H.; Johnson, N. *J. Org. Chem.* **1994**, *59*, 7855–7861.

following literature work should lead to the C-2 methylated analogue **17** (R = α -Me).²²

In summary, we have developed a novel efficient enantiospecific synthesis of the key A-ring synthon for the preparation of $1\alpha,25$ -dihydroxyvitamin D₃ starting from inexpensive (*R*)-carvone, in 11 steps and 24% overall yield, with the ene reaction as the key step. The method has the potential to be applied to the synthesis of vitamin D₃ analogues bearing the modification at the C-2 position.

(20) Trost, B. M.; Dumas, J.; Villa, M. *J. Am. Chem. Soc.* **1992**, *114*, 9836–9845.

(21) Srikrishna, A.; Kumar, P. R. *Tetrahedron Lett.* **2002**, *43*, 1109–1111.

(22) The approach from **22** to analogue **17** (R = α -Me) is continued in our lab. Herein, we wish to report this potential application of our new strategy.

Further synthetic applications of this method are being investigated in our laboratories.

Acknowledgment. We acknowledge the National Cultivation Foundation (B) for New Faculty of Tianjin University (TJU-YFF-08B68) for financial support. We also thank Dr. Emile J. Velthuisen, GlaxoSmithKline, R.T.P., North Carolina, for revising our English text.

Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds (PDF) and X-ray structural data of **9** and **22** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL102586W