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Enantioselective Synthesis of A Key A-Ring Intermediate for the Preparation of 1α,25-Dihydroxyvitamin D_3

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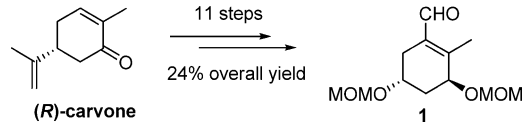
ABSTRACT



A novel approach to the key A-ring α, *β*-unsaturated aldehyde 1, an important intermediate for the preparation of 1α,25-dihydroxyvitamin D_3, 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 D_3 analogues bearing the modification at the C-2 position.

1α,25-Dihydroxyvitamin D_3 (calcitriol), the active form of vitamin D_3, 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 D_3 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 D_3 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 1α,25-dihydroxyvitamin D_3 in Julia's olefination approach[5] (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.; Mouriño, 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.; Prahl, 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) Sicinskil, 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.

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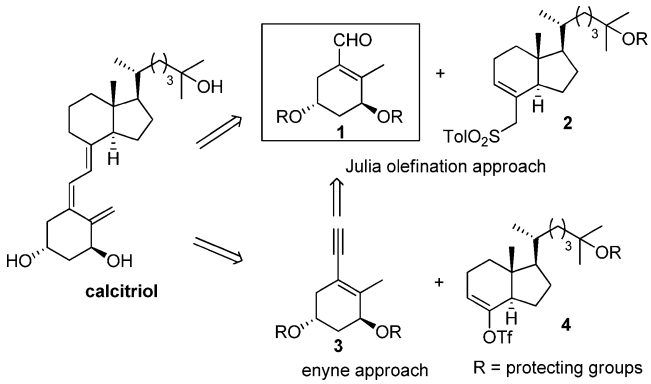


Figure 1. α,β-Unsaturated aldehyde **1** as a key intermediate to synthesize calcitriol.

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

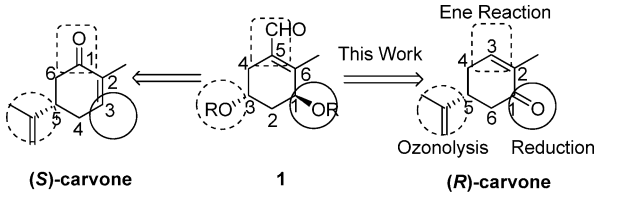
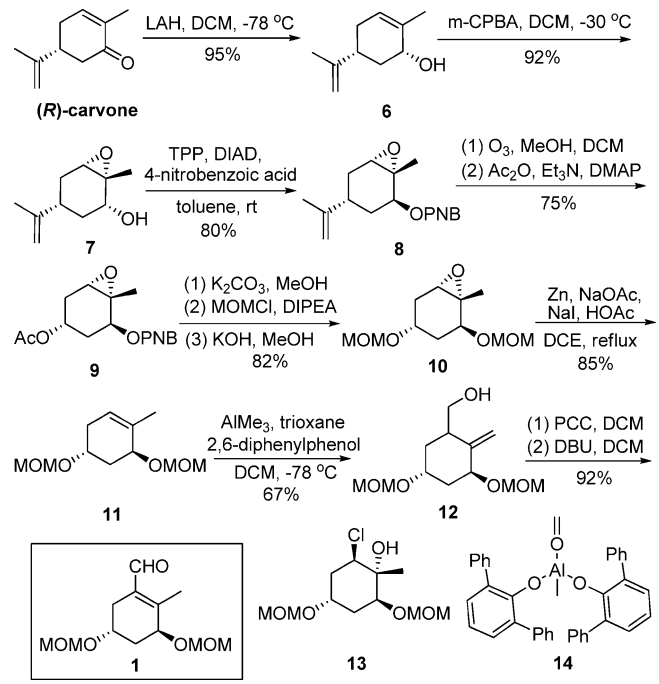


Figure 2. Comparison of the synthetic strategies to construct **1**.

previous methods, the alkoxyl 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 actived 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 °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 °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] Ozonolysis[12] of **8** at −78 °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 D_3 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 epoxide functionality

(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) Mascareiias, 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) Baggiolini, 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.; Mascareiias, 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.

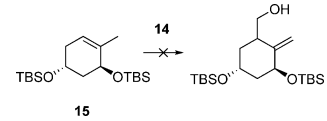
(10) Bourque, L. E.; Cleary, P. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 12602–12603.

(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.



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 Yamamoto[17] 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 $AlMe_3$, 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's[20] strategy, in which the A-ring part, 1,7-enyne **18**, was obtained from chiral monosaccharides (Figure 3). Therefore, our

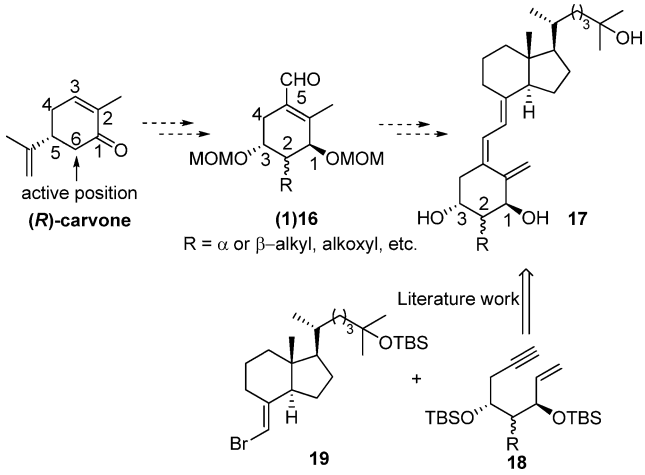
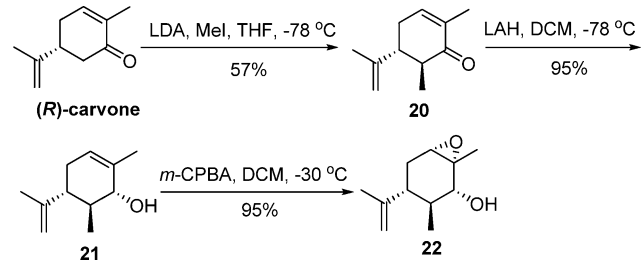


Figure 3. Significant feature of this strategy.

strategy opens new possibilities for the preparation of vitamin D_3 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 diisopropylamide (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 absolutely configurations were confirmed by X-ray crystal analysis, Figure 4) was obtained in 90% yield over

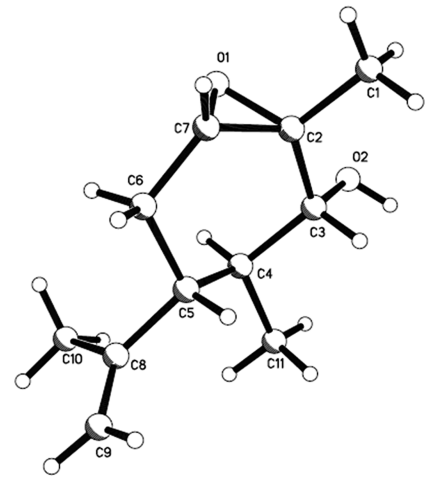


Figure 4. X-ray structure of **22**.

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 D_3 synthesis: (a) Riveiros, R.; Rumbo, A.; Sarandeses, L. A.; Mouriño, A. *J. Org. Chem.* **2007**, *72*, 5477–5485. (b) Reino, C. G.; Vitale, C.; Maestro, M.; Mouriño, A. *Org. Lett.* **2005**, *7*, 5885–5887. (c) Moriaty, 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.; Mouriño, 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) Suhara, 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 1α,25-dihydroxyvitamin D_3 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 D_3 analogues bearing the modification at the C-2 position. Further synthetic applications of this method are being investigated in our laboratories.

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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.

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

(21) Srikrishna, A.; Kumar, P. R. *Tetrahrdron 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.