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A Concise Enantioselective Synthesis of a Key A-Ring Synthon for 1α-Hydroxyvitamin D_3 Compounds

Hiroko Hiyamizu, Hidenori Ooi, Yoko Inomoto, Tomoyuki Esumi, Yoshiharu Iwabuchi, and Susumi Hatakeyama*

Faculty of Pharmaceutical Sciences, Nagasaki University, Nagasaki 852, Japan

susumi@net.nagasaki-u.ac.jp

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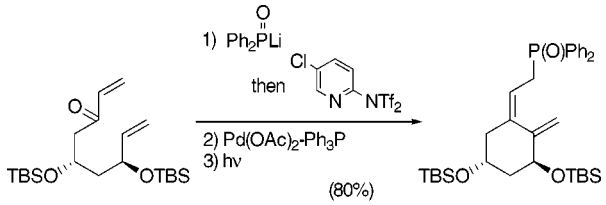
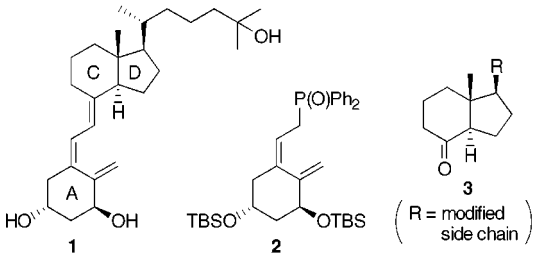
ABSTRACT



This report describes a concise enantioselective synthesis of the A-ring synthon for the synthesis of 1α-hydroxyvitamin D_3 compounds. The synthesis involves two notable transformations: (i) stereoselective construction of the enol triflate from the vinyl ketone by Michael addition of $Ph_2P(O)Li$ followed by in situ triflation of the resulting enolate and (ii) palladium-catalyzed Heck type cyclization of the enol triflate.

1α,25-Dihydroxyvitamin D_3 (**1**), the hormonally active form of vitamin D_3, plays an important role in the modulation of cell proliferation and cell differentiation as well as in the maintenance of calcium homeostasis via regulation of gene transcription. In view of its intriguing biological function and growing potential therapeutic applications, current research has focused on the synthesis of analogues having separated and specific biological activities for developing drugs for osteoporosis, cancer, psoriasis, and so on.[1] For the synthesis of analogues bearing a modified C/D-ring part, one of the most useful approaches is the Hoffmann La Roche route[2] via coupling of A-ring synthon **2** and the corresponding C/D-ring ketone **3**, based on Lythgoe's methodology.[3] We now wish to report a short and efficient synthesis[4] of



A-ring synthon **2** based on a new strategy, which centers around an unprecedented palladium-catalyzed intramolecular Heck reaction[5,6] of triflate **7**.

We envisaged that Michael addition of metalated diphenylphosphine oxide **5** to vinyl ketone **4**, followed by triflation, would allow stereoselective formation of enol triflate **7** via chelated intermediate **6**. It was anticipated that palladium-

(1) (a) *Vitamin D*; Feldman, D., Glorieux, F. H., Pike, J. W., Eds.; Academic Press: New York, 1997. (b) Bouillon, R.; Okamura, W. H.; Norman, A. W. *Endocr. Rev.* **1995**, *16*, 200.

(2) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2945.

(3) For a review, see: Zhu, G. D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877.

(4) For recent reports, see: (a) Koiwa, M.; Hareau, G. P. J.; Sato, F. *Tetrahedron Lett.* **2000**, *41*, 2389. (b) Hareau, G. P. J.; Koiwa, M.; Sato, F. *Tetrahedron Lett.* **2000**, *41*, 2385. (c) Anné, S.; Yong, W.; Vandewalle, M. *Synlett* **1999**, 1435. (d) Mouriño, A.; Torneiro, M.; Vitale, C.; Fernandez, S.; Pèrez-Sestlo, J.; Anné, S.; Gregorio, C. *Tetrahedron, Lett.* **1997**, *38*, 4713. (e) Yokoyama, H.; Miyamoto, K.; Hirai, Y.; Takahashi, T. *Synlett* **1997**, 187. (f) Achmatowicz, B.; Jankowski, P.; Wicha, J. *Tetrahedron Lett.* **1996**, *37*, 5589. (g) Vrielyneck, S.; Vandewalle, M.; Garcia, A. Mascareñas, J.; Mouriño, A. *Tetrahedron Lett.* **1995**, *36*, 9023.

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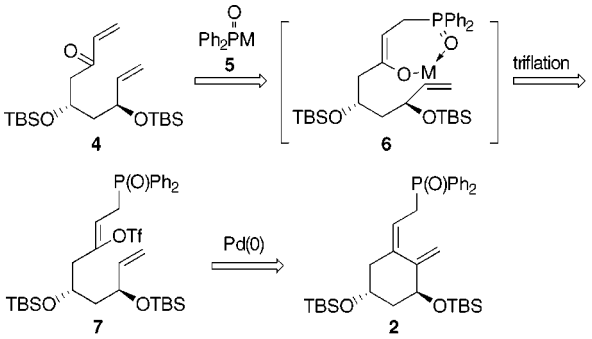
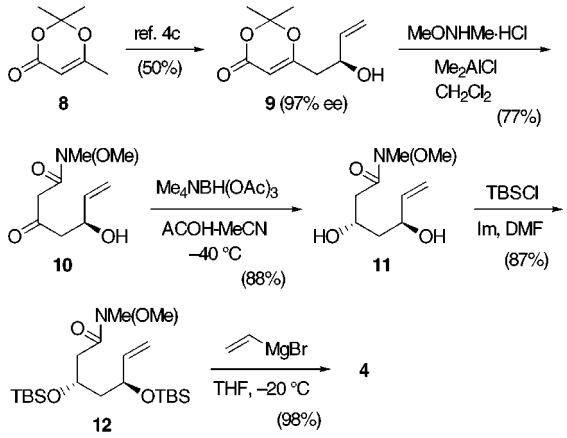
catalyzed Heck type cyclization of **7** would produce A-ring synthon **2** stereoselectively (Scheme 1).

Scheme 1



The required vinyl ketone **4** was prepared from known *S*-dioxinone **9** (97% ee), easily available[4c,7] from 2,2,6-trimethyl-4*H*-1,3-dioxi-4-one (**8**), as depicted in Scheme 2.

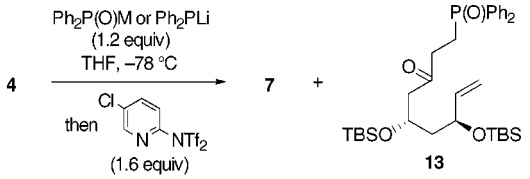
Scheme 2



Reaction of **9** with $Cl_2Al[N(OMe)Me]$,[8,9] followed by reduction of the resulting **10** with $Me_4NB(OAc)_3$,[10] gave *anti*-diol **11** in 94:6 diasteroselectivity. Diol **11** was then subjected to silylation and Grignard reaction[8] using vinylmagnesium bromide to afford vinyl ketone **4** in 75% overall yield.

The Michael addition−triflation process was surveyed using $Ph_2P(O)Li$,[11] $Ph_2P(O)Na$, and $Ph_2P(O)K$ as a metalated diphenylphosphine oxide and 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine[12] as a triflating agent. The results are summarized in Table 1. To our delight, we found

Table 1. Preparation of Enol Triflate **7** from Vinyl Ketone **4**[a]



		isolated yield (%)	
entry	phosphorus reagent[b]	**7** (*E*:*Z*)[c]	**13**
1	$Ph_2P(O)Li$	89 (0:100)	7
2	$Ph_2P(O)Li$ (HMPA)[d]	71 (0:100)	12
3	$Ph_2P(O)Na$	7 (0:100)	13
4	$Ph_2P(O)K$	3 (8:92)	13
5	Ph_2PLi	64 (0:100)	28

[a] After reaction of **4** and $Ph_2P(O)M$ or Ph_2PLi (1.2 equiv) in THF at −78 °C for 30 min, the reaction mixture was treated with the triflating reagent (1.6 equiv) and stirred at −78 °C for 20 h. [b] Prepared from $Ph_2P(O)H$ or Ph_2PH (1.2 equiv) using *n*-BuLi, NaH, or KH (1.2 equiv) as a base in THF at 0 °C for 1 h. [c] Determined by ^1H NMR analysis. [d] HMPA (1.2 equiv) was added with the triflating reagent.

that this process was realized very effectively using $Ph_2P(O)Li$ under the conditions listed in entry 1. Thus, upon successive treatment with $Ph_2P(O)Li$ and the triflating agent in THF at −78 °C, vinyl ketone **4** underwent stereoselective Michael addition−triflation reaction to give enol triflate **7** in 89% yield together with untriflated ketone **13** (7% yield). The corresponding *E*-isomer of **7** was not produced in this case. This result strongly suggests the participation of chelated intermediate **6** (M = Li) in this process as we expected. Addition of HMPA appeared to interfere with triflation of the resulting lithium enolate to decrease the yield of **7** although the combined yield of **7** and **13** was almost same as that of entry 1 (entry 2). Both $Ph_2P(O)Na$ and $Ph_2P(O)K$ are ineffective in this transformation, producing **7** and **13** in poor combined yield in each case (entries 3 and 4). Furthermore, it was also found that Michel addition of Ph_2PLi[13] to **4**, followed by in situ triflation of the resulting enolate, gave **7** in 64% yield along with **13** (28% yield) after oxidative workup with aqueous H_2O_2 (entry 5). This process again proceeded with complete *Z*-selectivity, suggesting participation of enolate **14** stabilized by chelation. It is important to note that ketone **13** could be converted to **7** in 60% yield by deprotonation with *n*-BuLi, followed by triflation at −78 °C in THF. The perfect regio- and stereoselectivity of this process can be explained by assuming preferential deprotonation of Ha rather than Hb via chelation

(6) For relevant intramolecular Heck reactions, see: refs 4d−g and (a) Codesido, E. M.; Cid, M. M.; Castedo, L.; Mouriño, Granja, J. R. *Tetrahedron Lett*. **2000**, *41*, 5861. (b) Higashi, T.; Miura, K.; Kikuchi, R.; Shimada, K.; Hiyamizu, H.; Ooi, H.; Iwabuchi, Y.; Hatakeyama, S.; Kubodera, N. *Steroids* **2000**, *65*, 281. (c) Hatakeyama, S.; Ikeda, T.; Maeyama, J.; Esumi, T.; Iwabuchi, Y.; Irie, H.; Kawase, A.; Kubodera, N. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2871. (d) Yokoyama, H.; Takahashi, T. *Tetrahedron Lett*. **1997**, *38*, 595. (e) Hatakeyama, S.; Irie, H.; Shintani, T.; Noguchi, Y. Yamada, H. Nishizawa, M. *Tetrahedron* **1994**, *50*, 13369. (f) Takahashi, T.; Nakazawa, M. *Synlett* **1993**, 37. (g) Mascareñas, J. L.; García, A. M.; Castedo, L.; Mouriño, A. *Tetrahedron Lett.* **1992**, *33*, 4365.

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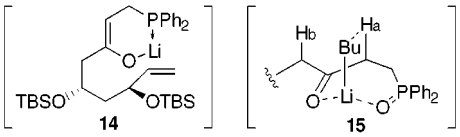
(13) Vedejs, E.; Fuch, P. L. *J. Am. Chem. Soc*. **1973**, *95*. 822.

generating **6** (M = Li) as depicted in **15**. Interestingly, LDA was not an effective base in this particular case.



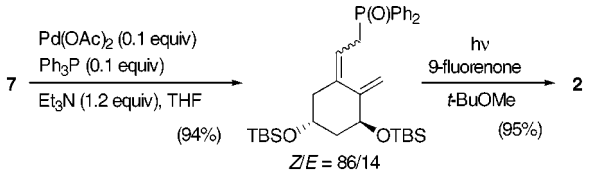
With enol triflate **7** in hand, we then examined palladium-catalyzed cyclization of **7** under various conditions (Table 2). As a result, $Pd(OAc)_2-Ph_3P$ was eventually found to be the catalyst of choice although some *Z*/*E*-isomerization always occurred.[14] Thus, upon treatment of **7** with a catalytic amount of $Pd(OAc)_2-Ph_3P$ (10 mol %) and Et_3N in THF at room temperature, cyclization took place very cleanly to give an inseparable 86:14 mixture of **2** and its *E*-isomer in 94% yield. Finally, we also found that photochemical isomerization[15] of the cyclization product in the presence of 9-fluorenone using a medium-pressure mercury arc lamp resulted in exclusive formation of the *Z*-isomer to furnish A-ring synthon **2** in 95% yield (Scheme 3).

Table 2. Palladium Catalyzed Cyclization of Enol Triflate **7**[a]

entry	catalyst (10 mol %)	solvent	time (h)	yield (%)[b] (*E*:*Z*)[c]
1	$Pd(OAc)_2-Ph_3P$	THF	20	94 (14:86)
2	$Pd(OAc)_2-Ph_3P$	MeCN	16	79 (17:83)
3	$Pd(OAc)_2-Ph_3P$	DMSO	21	20 (43:57)
4	$(Ph_3P)_4Pd$	THF	13	34 (29:71)
5	$Pd_2(dba)_2{\cdot}CHCl_3$	THF	8	55 (13:87)
6	$PdCl_2(CN)_2$	THF	17	0[c]
7	$PdCl_2(PhCN)_2$	THF	20	0[d]

[a] Reactions were carried out using Et_3N (1.2 equiv) as a base at room temperature. [b] **7** could not be recovered unless otherwise noted. [c] Determined by ^1H NMR analysis. [d] **7** was recovered in 83% yield. [e] **7** was recovered in 87% yield.

Scheme 3



In conclusion, A-ring fragment **2** for the synthesis of 1α-hydroxyvitamin D_3 analogues was successfully synthesized in nine steps from commercially available **8** in 23% overall yield. The present work illustrates a new methodology of potential value for the stereoselective preparation of various functionalized allylphosphine oxides.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via Internet at http://pubs.acs.org.

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(14) Compound **2** did not isomerize to the *E*-isomer at all under the cyclization conditions.

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