A New Candidate for a Properly Substituted CD Ring Component of Vitamin D_3 via Intramolecular Asymmetric Olefination of a 1,3-Cyclopentanedione Derivative

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Summary: A highly diastereoselective synthesis of hydrindenone derivative **5** (98% de) was achieved via diastereotopic differentiation of 1,3-cyclopentanedione derivative **4** by intramolecular Horner–Emmons olefination. In addition, the compound **5** was converted to ketone **2**, a new building block for 1α,25-dihydroxyvitamin D_3 (**1**).

The recent growing interest in the biological activities of 1α,25-dihydroxyvitamin D_3 (**1**) and its analogs have provided considerable impetus for the development of practical synthetic methods for their preparation.[1] According to the retrosynthesis depicted in Figure 1, the molecule **1** is divided into three fragments as indicated by dotted lines a and b. The acetyl group in **2** is accepted as a versatile substituent to introduce various side chains by Pd-catalyzed reactions[2] as well as others.[3] In addition, the hydroxymethyl appendage in **2** could be modified for connection to an A-ring unit such as **3**. In this sense, **2**, which possesses both the proper functionalities and the desired absolute configuration, appeared to be a very promising and novel intermediate for the synthesis of **1**. Hence, we were strongly motivated to elaborate an efficient route to **2** and describe our results herein.

On the basis of this strategy, we have envisioned an asymmetric cyclization by intramolecular Horner–Emmons olefination of 1,3-cyclopentanedione derivative **4** as shown in Scheme 1. Among the reactions with chiral phosphonoacetates,[4] two remarkable methods have been reported involving asymmetrization of meso dicarbonyl compounds such as *meso* dialdehydes[4c] or *meso* 1,2-diketones.[4d] However, little is known about intramolecular asymmetrization of a symmetric cyclic 1,3-dicarbonyl system.[5]

The phosphono ester **4** was prepared according to the procedure illustrated in Scheme 2. Highly C-selective allylation of 2-methyl-1,3-cyclopentanedione was uneventfully achieved by the palladium-catalyzed reaction of allyl methyl carbonate to afford the diketone **6** (88%) avoiding formation of O-allylated product.[6] Diketalization[7] of **6** followed by consecutive treatment of **7** with BH_3, oxidative workup, MsCl/Py, and NaI gave iodide **8**. Alkylation of **9**[4a–c,e] with **8** and deprotection produced the chiral phosphono ester **4**.

Initially, the reaction of a chiral phosphono ester having (−)-menthol as a chiral auxiliary in place of 8-phenylmenthol in **4** was examined using various bases such as n-BuLi in the presence or absence of HMPA, NaH, and ^{t}BuOK in THF at the range of −70 °C to room

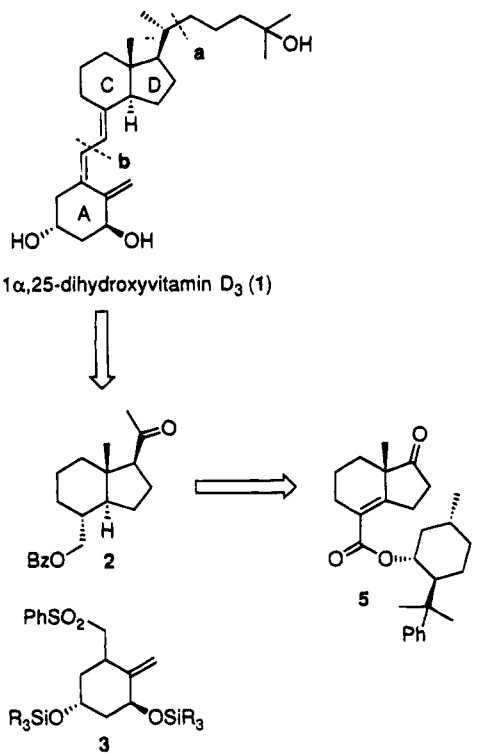
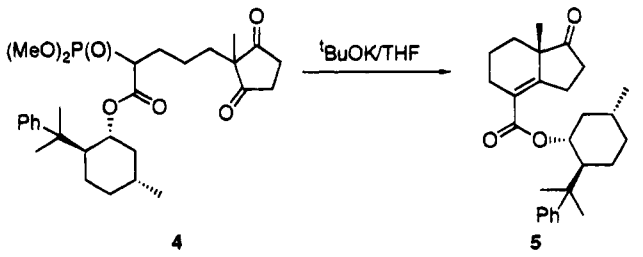


Figure 1.

Scheme 1



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(1) Semisynthesis: (a) Sardina, F. J.; Mourino, A.; Castedo, L. *J. Org. Chem.* **1986**, *51*, 1264. (b) Castedo, L.; Mascarenas, J. L.; Mourino, A.; Sarandeses, L. A. *Tetrahedron Lett.* **1988**, *29*, 1203. (c) Mascarenas, J. L.; Sestelo, J. P.; Castedo, L. Mourino, A. *Tetrahedron Lett.* **1991**, *32*, 2813. (d) Hatakeyama, S.; Sugawara, K.; Numata, H.; Takano, S. *J. Org. Chem.* **1991**, *56*, 461. (e) Torneiro, M.; Fall, Y.; Castedo, L.; Mourino, A. *Tetrahedron Lett.* **1992**, *33*, 105. (f) Sarandeses, L. A.; Mascarenas, J. L.; Castedo, L.; Mourino, A. *Tetrahedron Lett.* **1992**, *33*, 5445. Total synthesis: (g) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Uskokovic, M. *J. Am. Chem. Soc.* **1982**, *104*, 2945. (h) Wovkulich, P. M.; Barcelos, F.; Batcho, A. D.; Sereno, J. F.; Baggiolini, E. G. *Tetrahedron* **1984**, *40*, 2283. (i) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovic, M. R. *J. Org. Chem.* **1986**, *51*, 3098. (j) Nemoto, H.; Kurobe, H.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1986**, *51*, 5311.

(2) (a) Mandai, T.; Matsumoto, T.; Tsuji, J. *J. Org. Chem.* **1992**, *57*, 6090. (b) Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *Tetrahedron* **1994**, *50*, 475.

(3) Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199.

(4) (a) Gais, H. J.; Schmiedl, G.; Ball, W. A. *Tetrahedron Lett.* **1988**, *29*, 1773. (b) Rehwinkel, H.; Skupsch, J.; Vorbruggen, H. *Tetrahedron Lett.* **1988**, *29*, 1775. (c) Kann, N.; Rein, T. *J. Org. Chem.* **1993**, *58*, 3802. (d) Tanaka, K.; Ohta, Y.; Fuji, K. *Tetrahedron Lett.* **1993**, *34*, 4071. (e) Rein, T.; Kann, N.; Kreuder, R.; Gangloff, B.; Reiser, O. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 556.

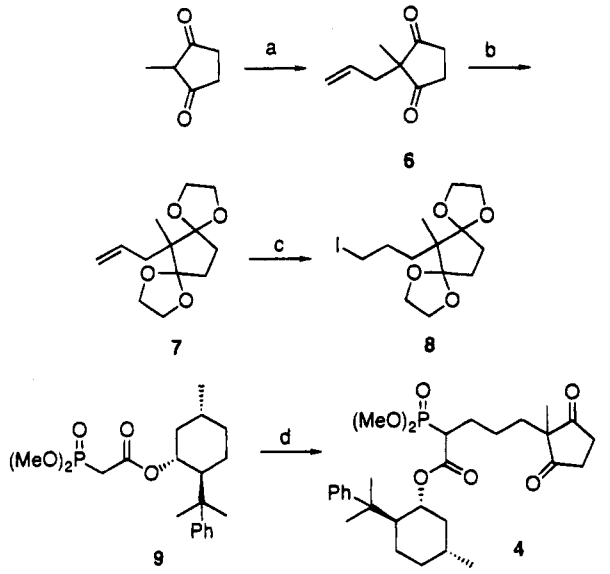
(5) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1980**, *102*, 5699.

(6) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523.

(7) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357. The reaction in CH_2Cl_2 as the solvent under the same reaction conditions resulted in monoacetalization.

0022-3263/94/1959-5847$04.50/0

Scheme 2



[a] Key: (a) $Pd(OAc)_2/PPh_3$ (1.8 mol %/5.4 mol %)/THF, CH_2=C-HCH_2OCO_2Me, rt, 6 h, 88%; (b) $(CH_2OTMS)_2$/TMSOTf (5 mol %), −2−0 °C, 10 h, 95%; (c) (i) BH_3/Me_2S/THF, 0 °C to rt, 4 h, H_2O_2/3 N NaOH, rt, 14 h, (ii) MsCl/Et_3N, CH_2Cl_2, 0 °C, 10 min, (iii) NaI/$NaHCO_3$/acetone, reflux, 2.5 h, 56%; (d) (i) **8**, NaH/DMF, rt, 13 h, 70%, (ii) cat. Amberlyst-15/acetone, rt, 14 h, 95%.

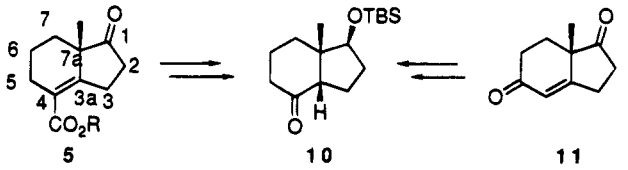
temperature. Among the bases employed, ^{t}BuOK in THF (60% de) was superior to the other bases. The moderate diastereoselectivities (30−60% de) encouraged us to use a more effective auxiliary, i.e., (−)-8-phenylmenthol.[8] The reaction of **4** proceeded smoothly to realize an excellent diastereoselectivity, and the results are summarized in Table 1. The best results (80%, 98.0% de) were obtained at −50 °C with respect to both chemical yield and diastereoselectivity (entry 3).

The optically active cyclized product **5**[9] thus obtained was revealed to have the desired *S* configuration at the 7a-position. The absolute stereochemistry of **5** was confirmed by the comparison of the sign of the specific rotation of cis-fused ketone **10**[10] ($[\alpha]_D$ = +67.9 (*c* 0.50, $CHCl_3$)) with that ($[\alpha]_D$ = +50.9 (*c* 0.49, $CHCl_3$)) of an authentic sample derived from the well-established compound **11** (73.3% ee).[11]

Table 1. Intramolecular Horner−Emmons Reactions of 4[a]

entry	temp (°C)	time (h)	yield[b] (%) **5**	% de[c] **5**
1	−50	24	80	97.5
2	−80	20	64	98.0
	−60	30		
3	−80	0.5	80	98.0
	−50	24		
4	−50	15	86	97.5
	−50 to −20	2		
5	25	0.5	80	90.9

[a] A solution of ^{t}BuOK in THF (2.3 mL, 1.15 mmol) was added to a solution of **4** (534 mg, 1.0 mmol) in THF (6 mL) at the indicated temperature. [b] Isolated by column chromatography. [c] Determined by HPLC (MeOH/H_2O = 10:1).

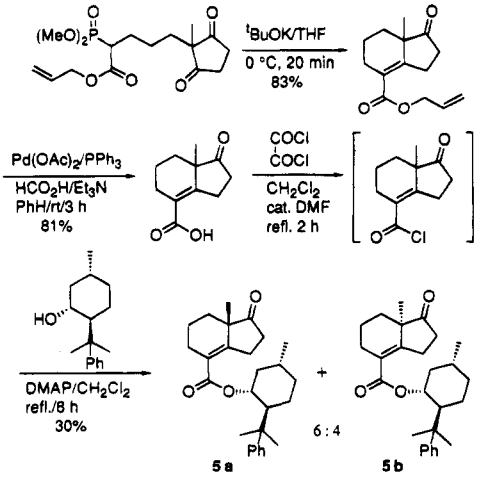


The successful preparation of the chiral keto ester **5** in a highly diastereoselective manner allowed us to proceed with the conversion to the versatile intermediate **2** (Scheme 3). Initial attempts focused on the conversion of the C-1 keto group into an acetyl moiety by a sequence of reactions including Pd-catalyzed hydrogenolysis as a key step. The keto ester **5** (98% de) was treated with 2-lithiopropene to give allylic alcohol **12a** (56%) with an α-oriented isopropenyl group as the sole product together with recovered starting material **5** (38%), presumably resulting from competing enolization. The allylic alcohol **12a** was carbonated by reaction with ^{t}BuLi and methyl chloroformate to provide methyl carbonate **12b** (95%). Next a stereoselective Pd-catalyzed hydrogenolysis of **12b** was achieved by the previously developed method:[12] the reaction of HCO_2H/Et_3N (5 equiv each) and a catalyst of $Pd(acac)_2/PBu_3$ (1/1). Although the hydrogenolysis was highly regioselective, the stereoselectivity was somewhat lower than previously observed.[12] Thus, an inseparable mixture of olefins **13a** and **13b** (93%) was obtained in a 10:1 ratio. The mixture of **13a** and **13b** was then converted to ketone **14** by sequential treatment with OsO_4 and $NaIO_4$. The keto ester **14** thus obtained was found to be contaminated with the α-isomer (10%) derived from **13b**. Fortunately, the optically pure **14**[13] was easily isolated (45%) by simple recrystallization from MeOH.

The next challenge was the generation of a trans ring junction from **14**. Thus, acetal **15** derived from **14** was

(8) (a) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908. (b) Ort, O. *Org. Synth.* **1987**, *65*, 203.

(9) The diastereomeric ratio of **5** was determined by comparison with ^{1}H NMR and HPLC analytical data of both isomers of **5** prepared as follows.



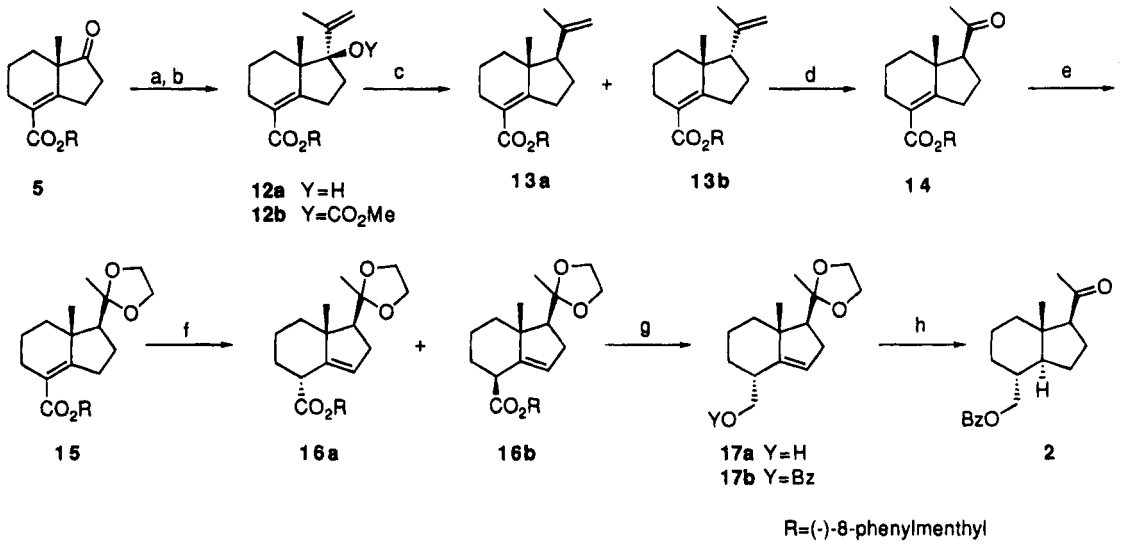
(10) Synthesis of cis-fused ketone **10** in a racemic form has been reported; Fernandez, B.; Martinez, J. A.; Granja, J. R.; Castedo, L.; Mourino, A. *J. Org. Chem.* **1992**, *57*, 3173. Details of our synthetic procedure are provided in the supplementary material.

(11) For the *S* isomer: (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Hajos, Z. G.; Parrish, D. R. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 363. For the *R* isomer: (c) Ohloff, G.; Maurer, B.; Winter, B.; Giersch, W. *Helv. Chim. Acta* **1983**, *66*, 192.

(12) (a) Mandai, T.; Suzuki, S.; Murakami, T.; Fujita, M.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1992**, *33*, 2987. (b) Mandai, T.; Matsumoto, T.; Tsuji, J. *Tetrahedron Lett.* **1993**, *34*, 2513.

(13) **14**: mp 146−146.5 °C; $[\alpha]_D$ +81.7 (*c* 0.933, PhH); ^{1}H NMR δ 0.85 (s, 3H, CH_3), 0.86 (d, J = 6.96 Hz, 3H, CH_3), 0.85−2.15 (m, 16H, CH_2 and CH), 1.20 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.44 (dd, J = 11.9 and 7.0 Hz, 1H, CHCO), 2.55−2.72 (m, 2H, CH_2), 4.96 (dt, J = 10.6 and 4.4 Hz, 1H, CO_2CH), 7.05−7.28 (m, 5H, aromatic); ^{13}C NMR δ 18.1, 19.6, 21.8, 23.6, 23.63, 24.4, 26.6, 28.4, 28.7, 31.3, 31.5, 34.5, 34.8, 39.6, 42.3, 45.6, 50.5, 62.1, 73.1, 120.7, 124.7, 125.3, 127.7, 151.9, 161.4, 166.7, 209.1. Anal. Calcd for $C_{29}H_{40}O_3$: C, 79.77; H, 9.24. Found: C, 79.57; H, 9.50.

Scheme 3



[a] Key: (a) CH_2=CH(Li)CH_3/Et_2O, −80 °C, 56%; (b) ^{t}BuLi/THF/$ClCO_2Me$, −80 °C to rt, 14 h, 95%; (c) Pd(acac)$_2$/Bu_3P (1:1), HCO_2H/Et_3N (5 equiv each), PhH, rt, 3 h, 93%; (d) (i) OsO_4/dioxane/H_2O, rt, 2 h, 61%, (ii) $NaIO_4$/acetone, rt, 3 h, 85%; (e) $(CH_2OTMS)_2$/cat. TMSOTf/CH_2Cl_2, −25 °C, 3 h, 95%; (f) (i) LDA/THF/−50 °C, (ii) MeOH/AcCl, −80 °C, 10 min, 56%; (g) (i) $LiAlH_4$/Et_2O, (ii) BzCl/Py, 82%; (h) (i) H_2 (1 atm), Pd/C/$NaHCO_3$, rt, 14 h, (ii) cat. *p*-TsOH/acetone, rt, 10 min, 95%.

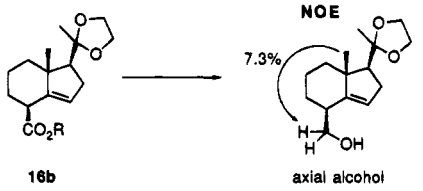
successively treated with LDA and HCl, giving a mixture of equatorial β,γ-unsaturated ester **16a** (56%), axial ester **16b**[14] (5.5%), and the starting ester **15** (36.6%). Fortunately, the desired **16a** was easily separated by flash column chromatography. Reduction of **16a** with $LiAlH_4$ and protection by BzCl/Py gave benzoate **17b**[15] (82%). Catalytic hydrogenation of **17b** followed by deacetalization provided **2**[16] (95%) as white crystals whose ^{1}H, ^{13}C NMR, and NOE experiments confirmed that the hydrogenation took place with complete trans stereoselectivity.

In summary, we have successfully achieved a highly enantioselective synthesis of CD ring component **2** via keto ester **5**. Incorporation of both a proper side chain and A ring **3** is currently under investigation and will be reported in due course.

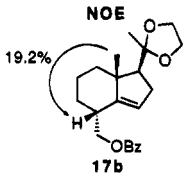
Acknowledgment. This work was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

Supplementary Material Available: Experimental procedures for the main steps and physical data including copies of NMR spectra for the important compounds (29 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) The stereochemistry was corroborated by NOE experiments after convertion to an allylic alcohol.



(15) The stereochemistry was determined by NOE experiments.



(16) **2**: mp 72.5–73.5 °C; $[\alpha]_D$ +55.0 (*c* 0.34, PhH); ^{1}H NMR δ 0.66 (s, 3H, CH_3), 0.98–2.22 (m, 12H, CH_2, CH), 2.13 (s, 3H, CH_3), 2.56 (t, *J* = 9.3 Hz, 1H, CHCO), 4.11 (dd, *J* = 10.6 and 6.60 Hz, 1H, CH_2OBz), 4.23 (dd, *J* = 10.6 and 4.8 Hz, 1H, CH_2OBz), 7.40–7.48 (m, 2H, aromatic), 7.52–7.58 (m, 1H, aromatic), 7.99–8.06 (m, 2H, aromatic); ^{13}C NMR δ 13.1, 21.5, 22.6, 24.8, 29.7, 31.6, 36.2, 38.9, 44.6, 52.7, 63.4, 68.7, 128.3, 129.5, 130.3, 132.9, 166.6, 209.3. Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.35; H, 8.53.