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Facile Construction of the 7,8-Olefin Linkage in Vitamin D_3: A Practical Synthesis Benefiting the Vitamin D_3 Analog Study

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Abstract: A facile procedure for construction of the 7,8-olefin linkage in vitamin D_3 is described. Treatment of a mixture of A-ring phosphine oxide and CD-ring ketone in THF with lithium hexamethyldisilazide (LHMDS) at $-20^{\circ}C$ followed by gradual heating to $50^{\circ}C$ gives the key intermediate of vitamin D_3 analogs in excellent yield. This simplified procedure makes possible small-scale synthesis benefiting the vitamin D_3 analog study.

Keywords: Horner–Wittig olefination, vitamin D_3, vitamin D_3 analog

INTRODUCTION

The active form of vitamin D_3, 1α,25-dihydroxyvitamin D_3 [1α,25$(OH)_2D_3$, calcitriol] (**1**) has been identified as a highly potent and multifunctional hormone (Figure 1). Therapeutic potential of calcitriol (**1**) for various diseases, such as osteoporosis, cancer, secondary hyperparathyroidism, and psoriasis, have been reported.[1] However, because of its hypercalcemic effects, the use of calcitriol (**1**) in disease treatment is limited. In response to this issue, various analogs of calcitriol (**1**) with attenuated calcemic

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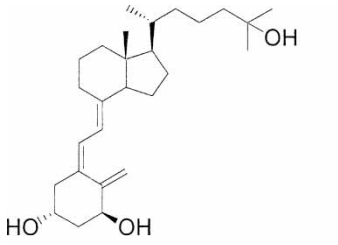
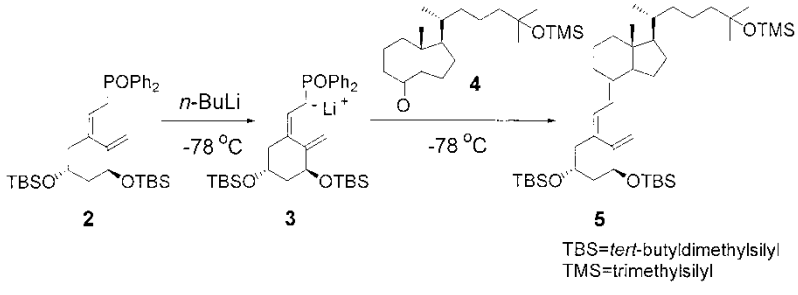


1: 1α,25(OH)$_2$D$_3$ (calcitriol)

Figure 1. Structure of active vitamin D_3.

effects and enforced desirable effects have been synthesized to obtain useful medical candidates.[2–5]

In the vitamin D_3 analog study, small-scale, micromolar synthesis is preferable and efficient. This is because only a few micrograms of sample are required for the preliminary biological assay.[6,7] Nevertheless, the small-scale synthesis is impractical in the most typical synthetic strategy, the Horner–Wittig olefination. The Horner–Wittig olefination constructs the 7,8-olefin linkage in vitamin D_3 as follows: A-ring phosphine oxide (**2**) is treated with *n*-BuLi at −78°C to produce a ylide (**3**); to the ylide, CD-ring ketone (**4**) is added at −78°C to form the *E*-olefin (**5**) stereoselectively in good yield (Scheme 1).[8,9] In this procedure, the reaction scale affects the yield significantly. It has been reported that with reactions using 80–100 mg or more of A-ring phosphine oxide, the yield is routinely excellent; on the other hand, small-scale reactions of 10–20 mg result in a very poor yield.[10] The reason for the low yield in the small-scale reactions could be water contamination from moisture, leading to disappearance of ylide. At the very low temperature of −78°C, the water contamination is inevitable, especially in small-scale reactions. Therefore, a practical and facile procedure for small-scale synthesis is desirable.

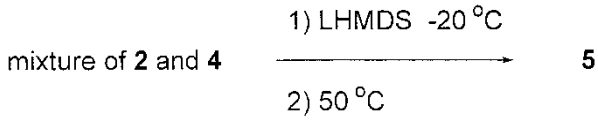


Scheme 1. Established procedure.

RESULTS AND DISCUSSION

Presuming that the low temperature in the established procedure is caused by the instability of the generated ylide and the prevention of the enolation of the base-sensitive CD-ring ketone,[8] we treated a mixture of the phosphine oxide (**2**) and the ketone (**4**) in THF with lithium hexamethyldisilazide (LHMDS) to react the ylide with the existing ketone as soon as possible after its generation from the phosphine oxide (Scheme 2). The reaction successfully occurred when a mixture of 1.1 equivalents of A-ring phosphine oxide (**2**) and 1.0 equivalent of CD-ring ketone (**4**) was treated with 1.1 equivalents of LHMDS in THF at $-20^{\circ}C$ followed by gradual heating to $50^{\circ}C$. The heating was required to complete the olefin formation with elimination of diphenylphosphinic acid. Neither the *Z*-olefin nor the epimer of the CD-ring was generated. Next, we were interested in utilization of this procedure for various analog syntheses. All the reactions were tested on a small scale using 13 mg (22 μmol) of A-ring phosphine oxide; the yields were satisfactory, as shown in Table 1. The higher reaction temperature of $-20^{\circ}C$ and the simpler addition procedure than the established procedure should prevent water contamination from moisture and make the small-scale reactions workable.

In conclusion, we developed a facile reaction procedure for the Horner–Wittig olefination, which constructs the 7,8-olefin linkage in vitamin D_3. The procedure made small-scale synthesis possible, benefiting vitamin D_3 analog study. The procedure would also be beneficial to industrial-scale synthesis of vitamin D_3 analog because the procedure is simpler than the established method and the low temperature of $-78^{\circ}C$ is not required.

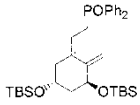
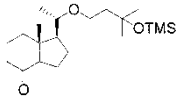
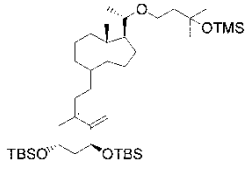
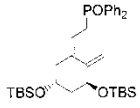
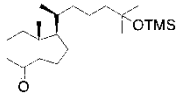
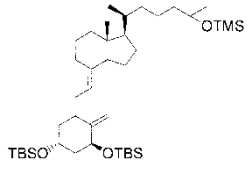
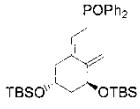
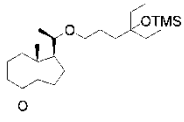
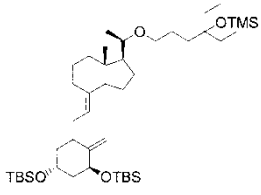
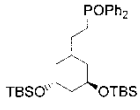
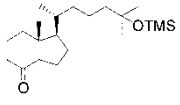
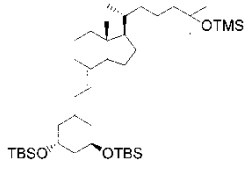
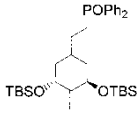
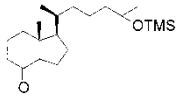
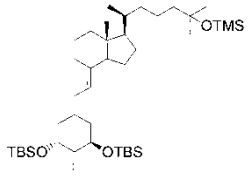


Scheme 2. Improved procedure.

EXPERIMENTAL

Benzene and THF were obtained from Kanto Chemical Co., Inc., as dehydrated solvents (water content: $<0.005\%$ for THF, $<0.003\%$ for benzene) and used without further purification. LHMDS (1 M in THF) was purchased from Aldrich. Silica-gel preparative TLC was purchased from Merck (silica gel 60 F_{254}, 0.5 mm). ^1H NMR spectra were recorded on a Jeol JNM-EX270 spectrometer using $CDCl_3$ as a solvent. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane.

Table 1. Wittig reaction using 13 mg (22 μmol) of phosphine oxide

Entry	Phosphine oxide	Ketone	Product	Yield (%)
1[11]				92
2[12]				87
3[12]				91
4[13]				62
5[7]				95

General Procedure

To a reaction vessel, 100 μl of 0.22 M solution of A-ring phosphine oxide (22 μmol) in benzene and 66.7 μl of 0.3 M solution of CD-ring ketone

(20 μmol) in benzene were added. The benzene was evaporated, and the mixture was dried by vacuum pump for 3 h. The reaction vessel was sealed with a septum and charged with dry nitrogen gas. The residue was dissolved or suspended in 200 μl of THF. The mixture was cooled to −20°C, and 2 μl of LHMDS (1 M in THF) were added 11 times in 1-s intervals (22 μl in total, 22 μmol), at −20°C; then the cooling bath was removed. The mixture was warmed to room temperature gradually for 10 min, then heated and kept at a temperature of 50°C for 16 h. The solvent was evaporated, and the residue was purified by silica-gel preparative TLC developed with hexane/ethyl acetate (20 : 1) to give the target product.

^{1}H NMR Spectral Data

3β-*tert*-Butyldimethylsilyl-1α-*tert*-butyldimethylsilyloxy-22-oxa-25-trimethylsilyloxyvitamin D_3 (product of entry 1): 0.03–0.17 (m, 21H), 0.52 (s, 3H), 0.82–0.93 (m, 18H), 1.16 (d, 3H, $J = 5.9$ Hz), 1.20 (s, 6H), 3.17–3.22 (m, 1H), 2.15–2.25 (m, 1H), 2.40–2.50 (m, 1H), 2.78–2.87 (m, 1H), 3.28–3.36 (m, 1H), 3.60–3.70 (m, 1H), 4.17–4.23 (m, 1H), 4.35–4.40 (m, 1H), 4.86 (s, 1H), 5.18 (s, 1H), 6.02 (d, 1H, $J = 11.3$ Hz), 6.22 (d, 1H, $J = 11.3$ Hz).

3β-*tert*-Butyldimethylsilyl-1α-*tert*-butyldimethylsilyloxy-25-trimethylsilyloxy(20*S*)-vitamin D_3 (product of entry 2): 0.03–0.17 (m, 21H), 0.55 (s, 3H), 0.82–0.93 (m, 21H), 1.20 (s, 6H), 2.18–2.25 (m, 1H), 2.40–2.50 (m, 1H), 2.78–2.88 (m, 1H), 4.17–4.22 (m, 1H), 4.37–4.42 (m, 1H), 4.84 (s, 1H), 5.19 (s, 1H), 6.00 (d, 1H, $J = 11.5$ Hz), 6.21 (d, 1H, $J = 11.5$ Hz).

3β-*tert*-Butyldimethylsilyl-1α-*tert*-butyldimethylsilyloxy-24,25,26-trihomo-22-oxa-25-trimethylsilyloxy-(20*S*)-vitamin D_3 (product of entry 3): 0.03–0.17 (m, 21H), 0.55 (s, 3H), 0.79–0.90 (m, 27H), 1.07 (d, 3H, $J = 5.8$ Hz), 1.43–1.50 (m, 4H), 1.96–2.03 (m, 1H), 2.17–2.25 (m, 2H), 2.42–2.50 (m, 1H), 2.80–2.88 (m, 1), 3.10–3.20 (m, 1H), 3.20–3.30 (m, 1H), 3.50–3.60 (m, 1H), 4.13–4.21 (m, 1H), 4.34–4.40 (m, 1H), 4.86 (s, 1H), 5.19 (m, 1H), 6.00 (d, 1H, $J = 11.0$ Hz), 6.24 (d, 1H, $J = 11.0$ Hz).

3β-*tert*-Butyldimethylsilyl-1α-*tert*-butyldimethylsilyloxy-25-trimethylsilyloxy-19-norvitamin D_3 (product of entry 4): 0.05 (s, 9H), 0.11 (s, 12H), 0.54 (s, 3H), 0.82–0.90 (m, 18H), 0.93 (d, 3H, $J = 6.1$ Hz), 1.20 (s, 6H), 2.88–3.83 (m, 1H), 4.01–4.10 (m, 2H), 5.80 (d, 1H, $J = 11.3$ Hz), 6.16 (d, 1H, $J = 11.3$ Hz).

3β-*tert*-Butyldimethylsilyl-1α-*tert*-butyldimethylsilyloxy-2-methylene-25-trimethylsilyloxy-19-nor-(20*S*)-vitamin D_3 (product of entry 5): 0.04–0.15 (m, 21H), 0.54 (s, 3H), 0.82–0.95 (m, 21H), 1.20 (s, 6H), 2.12–2.20 (m, 1H), 2.30–2.38 (m, 1H), 2.42–2.58 (m, 2H), 2.78–2.88 (m, 1H), 4.34–4.42 (m, 2H), 4.92 (s, 1H), 4.97 (s, 1H), 5.83 (s, 1H, $J = 11.2$ Hz), 6.21 (s, 1H, $J = 11.2$ Hz).

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