

# Asymmetric Intramolecular Diels-Alder Cycloadditions of 2-Pyrone-3-Carboxylates and Synthesis of Vitamin D<sub>3</sub> A Ring Phosphine Oxide

Cheon-Gyu Cho\* and Gary H. Posner†\*

Department of Chemistry, Hanyang University, Seoul 133-791, Korea

†Department of Chemistry, The Johns Hopkins University, Baltimore, MD, USA 21218

Received April 25, 1998

Intramolecular Diels-Alder cycloadditions of 2-pyrone-3-carboxylates with *trans*-vinyl silaketal groups tethered *via* a chiral, non-racemic 1,3-butanediol auxiliary proceeded in unexpected stepwise cycloadditions through ionic intermediates to provide *cis*-disubstituted bicyclic lactones. The ratio of two isomers, *exo* and *endo*, was 5 to 1, and each isomer was found to be diastereomerically pure (>99% de). Their relative and absolute stereochemistries were determined by <sup>1</sup>H NMR spectroscopy and confirmed by X-ray crystallography of minor, *endo*-adduct **9**. The major *exo*-adduct was successfully transformed to (–)-2-butyl substituted A-ring phosphine oxide **16**, a key element for the synthesis of 2-butyl vitamin D<sub>3</sub>.

## Introduction

As a part of the research program involving synthesis of new calcitriol analogs as anticarcinogenic reagents and for chemotherapy of osteoporosis, we were interested in 2-alkyl substituted vitamin D<sub>3</sub> compounds.<sup>1</sup> A simple expansion of our methodology which utilizes intermolecular Diels-Alder cycloadditions of 2-pyrones with silyl enol ethers was not applicable mainly because the reactivity of 2-pyrones is not sufficient to tolerate any substituent groups on the silyl enol ether.<sup>2</sup> High pressure can be used, but from which no asymmetry can be expected.<sup>1b</sup> For both enhancement of chemical reactivity and introduction of chirality,<sup>3</sup> we connected 2-pyrone-3-carboxylates to dienophiles through chiral tether groups for the cycloadditions to occur intramolecularly.<sup>4</sup> Among the systems studied, a vinyl silaketal linked *via* a chiral, non-racemic 1,3-diol gave the best results in both chemical yield and asymmetric induction. We herein report intramolecular cycloadditions of such systems, and propose an explanation for the high diastereoselectivity (>99% de) we observed, as well as the subsequent transformations of the *exo*-cycloadduct **8** into (–)-2-butyl A ring phosphine oxide **16**.

## Results and Discussion

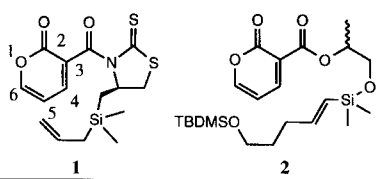
System **1** (Table 1) represents a pyrone carboxylate and allylic silane that were connected through a chiral thiazolidinethione.<sup>5</sup> Both thermal (120 °C up to 7 days) and high pressure (140 kpsi up to 7 days) conditions failed to provide the corresponding cycloadducts. Low reactivity of the dienophile, allylic silane, could account for the failures. Cycloadditions of system **2** (Table 1), linked with vinyl silane through 1,2-diol as a tether, also failed under the same conditions. The possible reasons for these failures, however, could be two-fold: 1) the reactivity of the vinyl silane might still be insufficient, and/or 2) the vinyl silane did not match the pyrone electronically.<sup>6</sup> From our earlier study, we learned that the carbon 6 in 2-pyrone-3-carboxylate carries the most positive partial charge.<sup>7</sup> Thus the

carbons 6 and 3 in the pyrone would have to line-up to the α-carbon and to the β-carbon next to the silicon, respectively. This alignment would exert too severe distortions, particularly in the portion of the tether group, for a cycloaddition to occur.

The systems in Table 2 were prepared, and this time vinyl silaketals were used as dienophile partners to be consistent with the above electronic factors.<sup>8</sup> The tether groups are chiral 1,2-propanediol for system **3** and chiral 2,3-butanediol for system **4**.

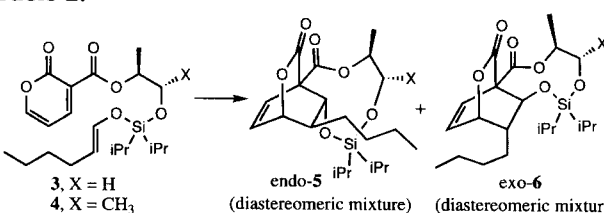
Attempted thermal cycloaddition reactions led only to the decomposition of the labile vinyl silaketal group. When they were pressurized, systems **3** and **4** underwent the desired cycloadditions to provide a mixture of *endo*-**5** and

Table 1.



Condition	Result
RT → Δ (up to 7 days)	no reaction
14 kpsi (up to 70 days)	no reaction

Table 2.



Condition	Total yield ( <b>5+6</b> )
RT → Δ	decomposition
140 kpsi	50%
	50%

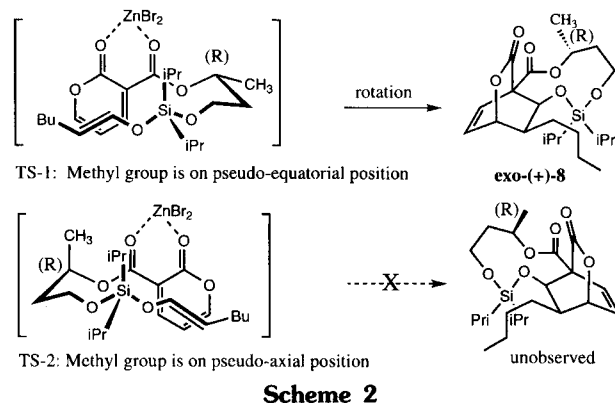
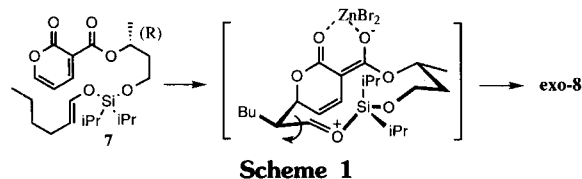
*exo*-6, each of which consisted of two diastereomers, in 50% total yield. The 2,3-butanediol tethered system **4** gave the similar results,<sup>9</sup> although it seemed to somewhat increase the rate of the reaction to reach 50% conversion through a buttressing effect. We then increased the length of the tether group to reduce the torsional strain that might exist in the transition state during the intramolecular cycloadditions. System **7** (Table 3)<sup>10</sup> was thus prepared and subjected to the cycloaddition reactions. Thermal reaction conditions resulted in similar breakage of the vinyl silaketal group as was observed in systems **3** and **4**. Upon being pressurized at 140 kpsi for 7 days in toluene, system **7** provided a mixture of the isomeric cycloadducts in 56% total yield.<sup>9</sup> Although we were pleased with these first examples of the intramolecular cycloadditions of the 2-pyrone-3-carboxylates, we decided to run the reactions in the presence of Lewis acids. After 4 days at  $-30\text{ }^{\circ}\text{C}$  in toluene and ethyl ether, the system **7** underwent a cycloaddition in the presence of  $\text{ZnBr}_2$  to provide a mixture of *exo*-**8** and *endo*-**9** in 90% total yield with a ratio of 5:1. Other Lewis acids  $\text{MgBr}_2$  and  $\text{Et}_2\text{AlCl}$  gave similar results. The stereochemical assignments of the two isomers were made mainly based on  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy, which were further confirmed by single crystal X-ray crystallography of the minor product, *endo*-**9**.<sup>11</sup>

Under the influence of Lewis acid, the cycloaddition proceeded in a stepwise fashion<sup>12</sup> rather than concerted to give rise to *cis*-disubstituted cycloadducts. As outlined in Scheme 1, a zwitterionic species was formed initially via 1,6 conjugate addition of the silyl enol ether to C6 on the pyrone system. This intermediate survived long enough to allow a rotation of the siloxy group to relieve the torsional strain in the linker. Upon final cyclization, *cis* adducts were formed. The possible retro-Aldol mechanism was excluded as a possible cause for the formation of *cis*-adducts because the *exo-trans* adduct, prepared earlier, was stable under the same reaction conditions used here. Lewis acid promoted *E-Z* isomerization of *E*-silyl enol ether was not observed under the reaction condition. The preferable formation of the *cis-exo* cycloadduct from the system **7** is believed to be due to the more stable *endo* transition state (secondary orbital interaction, *endo* TS led to *exo*-**8** because of the bond rotation).

More impressive was that both isolated *exo* and *endo* adducts were diastereomerically pure (>99%), not a mixture, based on NMR spectroscopy and their optical rotations. Apparently, the chiral methyl group in the tether served a

Table 3.

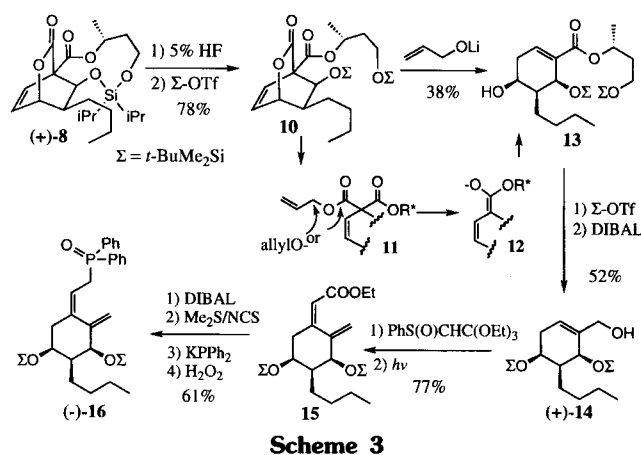
Conditions (4 days)	Total yield <b>8:9</b>	%de
$\text{ZnBr}_2$ / $-30\text{ }^{\circ}\text{C}$ /toluene	67%	2:1 not measured
$\text{MgBr}_2$ / $-30\text{ }^{\circ}\text{C}$ /toluene	65%	2:1 not measured
$\text{ZnBr}_2$ / $-30\text{ }^{\circ}\text{C}$ /toluene-ether (2:1)	90%	5:1 >99



critical role in this high and almost complete chiral induction. In the formation of the *exo*-adduct, there are two possible transition states, TS-1 and TS-2, which differ in the direction of the approaching vinyl silaketal group with respect to the face of the pyrone (Scheme 2).

TS-1, where the methyl group is in the pseudo-equatorial position, would be at lower energy state than TS-2, where the methyl group is in the pseudo-axial position. This energy difference in the transition state could be large enough at  $-30\text{ }^{\circ}\text{C}$ , leading to the dominant formation of the single diastereomer whose absolute stereochemistry, assigned spectroscopically and by comparison with similar systems,<sup>11</sup> is as drawn. The same argument can be applied to the exclusive formation of single diastereomeric *endo*-adduct **9** whose absolute stereochemistry is confirmed by X-ray crystallography to be as shown in Table 3.

Diastereomerically pure *exo*-(+)-**8**, the major adduct, was then carried through for the synthesis of optically active, 2-butyl substituted A-ring phosphine oxide **16** (Scheme 3). Upon silaketal ring opening with 5% HF and subsequent protection of the resulting diols with TBDMS (*t*-butyldimethylsilyl) triflate, the O-silylated cycloadduct **10** was obtained. Lactone ring opening with excess lithium allyl-



oxide provided unexpected tetrasubstituted cyclohexene **13**, presumably *via* formation of mixed allyl methyl malonate **11**, followed by concomitant deallyloxyacylation,<sup>13</sup> resulting from the attack of allyloxy in either direction of the arrows, and double bond conjugation as depicted in Scheme 3. O-silylation and reduction of the conjugated enoate **13** provided allylic alcohol (+)-**14**, which was converted to *Z* dienoate **15** using our sulfinylated orthoester protocol.<sup>14</sup> In this one-flask reaction, the enoate **13** underwent two-carbon homologation *via* a Claisen rearrangement followed by a spontaneous thermal sulfoxide elimination to give *E* and *Z* mixture of dienoate. The undesired *E* dienoate was photochemically isomerized to *Z* dienoate **15** that was subsequently transformed to optically active, A-ring phosphine oxide (-)-**16** after a few more reactions involving reduction, chlorination, displacement, followed by oxidation.

The phosphine oxide (-)-**16** can be readily converted to 2 $\beta$ -butyl-1 $\beta$ ,25-dihydroxyvitamin D<sub>3</sub> through Lythgoe coupling reaction with CD ring.<sup>15</sup> This highly diastereospecific intramolecular cycloaddition methodology was also successfully applied to construct a new calcitriol analog 2 $\beta$ -(3'-fluoropropyl)-1 $\beta$ ,25-dihydroxyvitamin D<sub>3</sub>.<sup>1a</sup> Conclusively, 2-pyrone-3-carboxylates with  $\beta$ -substituted vinyl silaketal, connected through 1,3-butanediol linker, underwent smooth intramolecular Diels-Alder cycloadditions with high asymmetric induction. This strategy using chiral, non-racemic 1,3-butanediol as a tether could be further applied to intramolecular cycloadditions of not only pyrone systems, but also other dienes for efficient and high asymmetric control.

## Experimental Section

**Cycloadducts (+)-8 and (-)-9.** To a flame dried 50 mL flask charged with 0.310 g (7.3 mmol) of the pyrone enol ether **7**, 3 mL of anhydrous ether and 6 mL of anhydrous toluene was added 0.160 g (7.3 mmol) of ZnBr<sub>2</sub>. Upon addition, the reaction mixture was cooled to -30 °C and stirred for 4 days. The reaction mixture was then concentrated by rotary evaporator and directly purified by column chromatography (97/3 hexane/EtOAc) to afford 0.233 g of the *exo*-cycloadduct **8** in 75% yield along with 0.045 g (15% yield) of the crystalline *endo*-cycloadduct **9**. For (+)-**8**: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  6.77 (dt, *J*=8.0, 1.2 Hz, 1H), 6.59 (dd, *J*=8.0, 5.2 Hz, 1H), 5.54-5.46 (m, 1H), 4.98 (dt, *J*=5.2, 1.6 Hz, 1H), 4.38 (s, 1H), 3.89-3.77 (m, 2H), 1.88-1.28 (m, 8H), 1.34 (d, *J*=6.4 Hz, 3H), 1.25-1.16 (m, 1H), 1.03 (d, *J*=3.2 Hz, 3H), 1.01 (d, *J*=3.6 Hz, 3H), 0.92-0.87 (m, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  168.5, 167.0, 130.8, 129.3, 76.4, 75.4, 70.3, 62.6, 59.8, 49.2, 37.7, 30.1, 29.3, 22.4, 20.6, 17.6, 17.4, 17.3, 17.2, 13.8, 12.7, 10.5; FT-IR (CHCl<sub>3</sub>) 2945, 2868, 1769, 1724, 1464, 1364, 1291 cm<sup>-1</sup>; HRMS, *m/e* (M<sup>+</sup>-*i*Pr) calc. for C<sub>19</sub>H<sub>31</sub>O<sub>6</sub>Si 381.1733, found 381.1740; [ $\alpha$ ]<sub>D</sub><sup>24</sup> +17.5 (c=22 mg/mL, CH<sub>2</sub>Cl<sub>2</sub>). For (-)-**9**: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  6.83 (dt, *J*=8.0, 1.2 Hz, 1H), 6.51 (dd, *J*=8.0, 5.0 Hz, 1H), 5.60-5.56 (m, 1H), 5.06 (m, 1H), 4.94 (d, *J*=7.6 Hz, 1H), 3.95 (m, 1H), 3.84 (m, 1H), 2.41 (m, 2H), 1.85 (m, 2H), 1.50-1.20 (m, 9H), 1.40 (d, *J*=6.4 Hz, 3H); HRMS, *m/e* (M<sup>+</sup>-*i*Pr) calc. for C<sub>19</sub>H<sub>31</sub>O<sub>6</sub>Si 381.1733, found 381.1739; [ $\alpha$ ]<sub>D</sub><sup>24</sup> -1.8 (c=35 mg/mL, CH<sub>2</sub>Cl<sub>2</sub>). Single crystal X-ray

analysis showed the absolute stereochemistry of (-)-**9** to be as shown in Table 3.

**Bis-Silyl Ether 12.** To a 100 mL round bottomed flask charged with 0.270 g (6.4 mmol) of (+)-**8** was added 27 mL of 5% HF in acetonitrile at RT. After 20 min, the reaction mixture was neutralized with aq. NaHCO<sub>3</sub> and extracted with CHCl<sub>3</sub> (2 $\times$ 50 mL). The combined solution was dried over MgSO<sub>4</sub>, concentrated by rotary evaporator and dissolved in 10 mL of DMF. To this solution were added 0.61 mL (2.6 mmol) of *t*-butyldimethylsilyl trifluoromethane sulfonate (TBDMS-OTf) and 0.30 mL (0.26 mmol) of 2,6-lutidine at RT. After 2 hours at RT, the reaction mixture was dumped into 50 mL of H<sub>2</sub>O and extracted with ether (2 $\times$ 25 mL). The combined ethereal solution was dried over MgSO<sub>4</sub>, concentrated and purified by column chromatography (90/10 hexane/ether) to give 0.270 g of the bis-silyl ether **10** as a light green oil in 79% yield from the *exo*-cycloadduct **8**. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  6.69 (dt, *J*=7.6, 1.2 Hz, 1H), 6.55 (dd, *J*=7.6, 5.2 Hz, 1H), 5.20-5.12 (m, 1H), 5.02 (dt, *J*=5.2, 1.2 Hz, 1H), 4.16 (bs, 1H), 3.72 (ddd, *J*=7.2, 7.2, 0.8 Hz, 2H), 2.01-1.93 (m, 1H), 1.82-1.73 (m, 1H), 1.65-1.57 (m, 2H), 1.55-1.42 (m, 1H), 1.36 (d, *J*=6.4 Hz, 3H), 1.37-1.27 (m, 4H, overlapped), 0.92 (t, *J*=7.2 Hz, 3H), 0.88 (s, 9H), 0.78 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  167.0, 166.7, 130.4, 130.1, 75.9, 73.6, 71.1, 63.0, 59.6, 49.4, 39.0, 30.0, 29.5, 25.9, 25.5, 22.6, 20.1, 18.2, 17.8, 13.9, -4.3, -5.2, -5.4, -5.4; FT-IR (CHCl<sub>3</sub>) 2957, 2931, 2858, 1760, 1733, 1472, 1464, 1362, 1288, 1258, 1094 cm<sup>-1</sup>; HRMS, *m/e* (M<sup>+</sup>-*t*Bu) calc. for C<sub>24</sub>H<sub>43</sub>O<sub>6</sub>Si<sub>2</sub> 483.2598, found 483.2594.

**Enoate 13.** To a 50 mL flame dried round bottomed flask charged with 37.0 mg (mmol) of the bis-silyl ether **10** was cannulated at 0 °C 2 mL of lithium allylic oxide in allylic alcohol (0.7 M), prepared from 4 mL of *n*BuLi (1.4 M in hexane) and 4 mL of freshly distilled allylic alcohol at 0 °C. After 30 min. at 0 °C, the reaction mixture was warmed to RT and stirred for 10 hours. Upon quenching with sat NH<sub>4</sub>Cl, the product mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 $\times$ 10 mL), dried over MgSO<sub>4</sub>, concentrated by rotary evaporator and chromatographed (10% EtOAc/hexane) to give 12.3 mg of the enoate **13** in 38% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  6.87 (dd, *J*=5.2, 2.4 Hz, 1H), 5.10-5.02 (m, 1H), 4.64 (d, *J*=2.4 Hz, 1H), 4.37 (ddd, *J*=10.8, 6.0, 4.0 Hz, 1H), 3.65 (ddd, *J*=8.4, 6.0, 2.0, 2H), 2.49 (dt, *J*=19.2, 5.6 Hz, 1H), 2.09 (ddd, *J*=19.6, 10.4, 2.8, 1H), 1.95-1.83 (m, 2H), 1.78-1.70 (m, 1H), 1.60-1.23 (m, 7H, overlapped), 1.28 (d, *J*=6.4 Hz, 3H), 0.88 (t, 3H, overlapped), 0.87 (s, 9H), 0.85 (s, 9H), 0.15 (s, 3H), 0.07 (s, 3H), 0.02 (s, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  166.0, 139.1, 131.4, 68.7, 67.7, 65.0, 59.5, 47.2, 39.1, 31.2, 30.4, 25.83, 25.80, 23.1, 22.6, 20.1, 18.2, 17.9, 14.0, 4.5, -4.9, -5.4, -5.5; FT-IR (CHCl<sub>3</sub>) 3613, 3020, 2957, 2930, 2858, 1704, 1472, 1253 cm<sup>-1</sup>; HRMS, *m/e* (M<sup>+</sup>-*t*Bu) calc. for C<sub>23</sub>H<sub>45</sub>O<sub>5</sub>Si<sub>2</sub> 457.2806, found 457.2809.

**O-Silyl Allylic Alcohol (+)-14.** To flask charged with 15.8 mg (0.03 mmol) of the enoate **13** in 0.3 mL of DMF were added 0.014 mL of TBDMS-OTf (0.06 mmol, 2 eq.) and 0.006 mL of 2,6-lutidine at RT. After 4 hours at RT, the product mixture was diluted with ether, washed with H<sub>2</sub>O and brine, concentrated by rotary evaporator and chromatographed (10% EtOAc/hexane) to give 30.0 mg of crude O-silylated product contaminated with some high

running material. To this crude product in 1.5 mL of anhydrous toluene was added 0.4 mL (0.4 mmol) of DIBAL-H at  $-78^{\circ}\text{C}$ . After 40 min. at  $-78^{\circ}\text{C}$ , the reaction mixture was treated with 1 mL of sodium potassium tartrate (2 M in  $\text{H}_2\text{O}$  and EtOH), and the resulting solution was warmed to RT. After 10 min, the organic layer was decanted, and the aqueous layer was further extracted with 10 mL of  $\text{CH}_2\text{Cl}_2$ . The combined organic solution was dried over  $\text{MgSO}_4$ , filtered through a plug of Celite, concentrated by rotary evaporator and chromatographed (10% EtOAc/hexane) to give 7.0 mg of the allylic alcohol (+)-**14** and 3.5 mg of the monoprotected chiral diol in 52% and 54% overall yield, respectively.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.67-5.65 (m, 1H), 4.21 (ddd,  $J=9.6$ , 5.6, 4.0, 1H), 4.14 (d,  $J=2.0$  Hz, 1H), 4.06 (d,  $J=1.2$  Hz, 2H), 2.14 (dt,  $J=17.2$ , 5.6 Hz, 2H), 2.03-1.96 (m, 1H), 1.76-1.71 (m, 1H), 1.43-1.22 (m, 7H), 0.91 (t, 3H, overlapped), 0.90 (s, 9H), 0.88 (s, 9H), 0.123 (s, 3H), 0.119 (s, 3H), 0.04 (s, 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  137.0, 125.2, 70.4, 66.1, 65.4, 47.5, 31.2, 30.1, 25.8, 23.1, 18.02, 17.93, 14.05, -4.2, -4.6, -4.7, -4.8; FT-IR ( $\text{CHCl}_3$ ) 3606, 3015, 2957, 2930, 2858, 1472, 1463, 1256  $\text{cm}^{-1}$ ;  $[\alpha]_{\text{D}}^{23}$   $\text{C}+32$  ( $c=0.016$ ,  $\text{CH}_2\text{Cl}_2$ ); HRMS,  $m/e$  ( $\text{M}^+t\text{Bu}$ ) calc. for  $\text{C}_{19}\text{H}_{39}\text{O}_3\text{Si}_2$  371.2438, found 371.2443.

**Z-Dienoate 15.** To a 5 mL hydrolysis tube were charged 26 mg (0.06 mmol) of the allylic alcohol (+)-**14**, 100 mg of 1-(phenylsufinyl)-2,2,2-triethoxyethane, 2 mg of 2,4,6-trimethylbenzoic acid and 1.5 mL of  $\text{CH}_2\text{Cl}_2$ . The tube was then sealed and heated at  $150^{\circ}\text{C}$  for 12 hr. The product mixture was cooled, filtered through a plug of silica gel with ether, concentrated by rotary evaporator and chromatographed (100% hexane  $\rightarrow$  5% EtOAc/hexane) to give 30 mg of product as a mixture of E and Z-dienoate. A 5 mL borosilicate test tube was charged with the product mixture, 2 mg (0.01 mmol, 0.2 eq) of 9-fluorenone and 2 mL of *tert*-butyl methyl ether. The test tube was then placed in a 2 M aq. solution of sodium orthovanadate ( $\text{Na}_3\text{VO}_4$ ) and irradiated with a medium pressure mercury arc lamp for 12 hours. This product mixture was purified by prep TLC (25% EtOAc/hexane) to afford 23 mg of the Z-dienoate **15** in 77% overall yield.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  5.60 (t,  $J=1.2$  Hz, 1H), 5.16 (dd,  $J=2.0$ , 1.6 Hz, 1H), 5.04 (dd,  $J=2.0$ , 1.2 Hz, 1H), 4.24-4.21 (m, 2H), 4.16-4.06 (m, 2H), 2.35 (ddd,  $J=13.2$ , 6.4, 1.2 Hz, 1H), 2.30-2.26 (m, 1H), 1.61-1.55 (m, 2H), 1.46-1.39 (m, 2H), 1.32-1.20 (m, 6H), 1.23 (t,  $J=7.2$ , 3H, overlapped), 0.92 (s, 9H), 0.87 (s, 9H), 0.071 (s, 3H), 0.068 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  165.9, 153.5, 117.3, 111.9, 76.3, 74.4, 68.4, 59.7, 50.9, 44.4, 29.7, 25.83, 25.77, 25.5, 23.0, 18.2, 18.1, 14.2, 14.0, -4.2, -4.6, -5.01, -5.03; FT-IR ( $\text{CHCl}_3$ ) 2943, 2857, 1719, 1472  $\text{cm}^{-1}$ ; HRMS,  $m/e$  ( $\text{M}^+$ ) calc. for  $\text{C}_{27}\text{H}_{52}\text{O}_4\text{Si}_2$  496.3404, found 496.3410. ( $\text{M}^+t\text{Bu}$ ) calc. 439.2700, found 439.2699.

**Phosphine Oxide (-)-16.** To a 25 mL flame dried round bottomed flask charged with 38.0 mg (0.1 mmol) of the Z-dienoate **15** and 2 mL of anhydrous toluene was added 0.33 mL (0.3 mmol, 3 eq.) of DIBAL-H (1.0 M in toluene) at  $-78^{\circ}\text{C}$ . After 55 min. at  $-78^{\circ}\text{C}$ , the reaction mixture was treated with 3 mL of sodium potassium tartrate (2 M in  $\text{H}_2\text{O}$  and EtOH) at  $-78^{\circ}\text{C}$ . The product mixture was then warmed to RT, stirred for 10 min and diluted with

$\text{H}_2\text{O}$ . The solution was extracted with 20 mL of  $\text{CH}_2\text{Cl}_2$  and 20 mL of  $\text{CHCl}_3$ . The combined organic solution was dried over  $\text{MgSO}_4$  and concentrated in vacuo to give 35 mg of the crude product allylic alcohol as a tan oil. To a separate 25 mL flame dried round bottomed flask charged with 78.0 mg (0.06 mmol) of NCS (N-chloro succinimide) and 2 mL of  $\text{CH}_2\text{Cl}_2$  was added 0.05 mL (0.06 mmol) of DMS (dimethylsulfide) at  $0^{\circ}\text{C}$  (reaction mixture immediately turned to white turbid solution). After 10 min at  $0^{\circ}\text{C}$ , the reaction mixture was cooled to  $-20^{\circ}\text{C}$  with dry ice-ethylene glycol bath. To this solution was added the crude allylic alcohol dissolved in 1.5 mL of  $\text{CH}_2\text{Cl}_2$  at  $-20^{\circ}\text{C}$ . After 2 hours, the product mixture was diluted with  $\text{H}_2\text{O}$  and extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 20$  mL). The combined organic solution was dried over  $\text{MgSO}_4$ , concentrated by rotary evaporator and filtered through a plug of florisil with 20% EtOAc/hexane and concentrated *in vacuo* to give the crude allylic chloride as a tan oil. This crude allylic chloride was then placed in 10 mL flame dried round bottomed flask with 1 mL of THF. To this solution was added of potassium diphenylphosphine (1 M solution in THF) until the red color persisted (about 10 mL was added) at  $-78^{\circ}\text{C}$ . After 1 hour at  $-78^{\circ}\text{C}$ , the reaction mixture was quenched with 2 mL of  $\text{H}_2\text{O}$ , extracted with twice with 10 mL of  $\text{CH}_2\text{Cl}_2$ . The combined solution was dried over  $\text{MgSO}_4$  and concentrated to reduced volume. To this solution was added 7 to 8 drops of 30%  $\text{H}_2\text{O}_2$  at RT. After 20 min at RT, the reaction mixture was partitioned into  $\text{H}_2\text{O}$  and  $\text{CH}_2\text{Cl}_2$ . The organic layer was decanted, and the aqueous layer was extracted with 10 mL of  $\text{CH}_2\text{Cl}_2$ . The combined solution was then dried over  $\text{MgSO}_4$ , concentrated by rotary evaporator and purified by prep TLC (70% EtOAc/hexane) to afford 30 mg of the phosphine oxide (-)-**16** as a white, viscous oil in 61% overall yield from the Z-dienoate **15**.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.74-7.69 (m, 4H), 7.55-7.44 (m, 6H), 5.30 (ddt,  $J=14.0$ , 7.2, 0.8 Hz, 1H), 5.09 (s, 1H), 4.75 (d,  $J=1.6$  Hz, 1H), 4.12 (dt,  $J=6.8$ , 3.6 Hz, 1H), 4.09 (d,  $J=7.2$  Hz, 1H), 3.34 (ddd,  $J=22.8$ , 14.8, 8.4 Hz, 1H), 3.18 (ddd,  $J=22.8$ , 15.2, 7.2 Hz, 1H), 2.30-2.24 (m, 1H), 2.22-2.17 (m, 1H), 1.57-1.52 (m, 1H), 1.47-1.15 (m, 6H), 0.91 (s, 9H), 0.88 (t,  $J=7.6$  Hz, 3H, overlapped), 0.82 (s, 9H), 0.05 (s, 3H), 0.006 (s, 3H), -0.001 (s, 3H), -0.032 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  146.7 (t,  $J=4.4$  Hz), 141.4 (d,  $J=45.6$  Hz), 133.3 (d,  $J=15.2$  Hz), 132.4 (d,  $J=18.4$  Hz), 131.74 (d,  $J=9.2$  Hz), 131.71 (d,  $J=9.2$  Hz), 131.1 (d,  $J=27.6$  Hz), 131.0 (d,  $J=27.6$  Hz), 128.6 (d,  $J=18.4$  Hz), 128.5 (d,  $J=18.0$  Hz), 114.3 (d,  $J=30.4$  Hz), 111.6-111.4 (m), 74.5 (d,  $J=9.2$  Hz), 68.4, 50.9, 43.5, 31.2 (d,  $J=28.2$  Hz), 29.7, 25.8, 22.9, 18.2, 18.1, 14.0, -4.3, -4.4, -4.9, -5.0; FT-IR ( $\text{CHCl}_3$ ) 3018, 2957, 2930, 2857, 1472, 1438  $\text{cm}^{-1}$ ;  $[\alpha]_{\text{D}}^{23}$   $\text{C}-5$  (0.007,  $\text{CH}_2\text{Cl}_2$ ); HRMS,  $m/e$  ( $\text{M}^+$ ) calc. for  $\text{C}_{37}\text{H}_{50}\text{O}_3\text{Si}_2\text{P}$  638.3743, found 638.3751.

**Acknowledgment.** Work at the Johns Hopkins University was supported by N.I.H grant CA 44530.

## References

- (a) Posner, G. H.; Cho, C.-G.; Tizah, E.; Johnson, N.; Horst, R. L.; Kobayashi, T.; Okano, T.; Tsugawa, N. *J. Org. Chem.* **1995**, *60*, 4617. (b) Posner, G. H.; Johnson, N. *J. Org. Chem.* **1994**, *59*, 7855. For biological

- activities of vitamin D<sub>3</sub> compounds, see: (c) Norman, A. W.; Nemere, I.; Muralidharan, K. R.; Okamura, W. H. *Biochem. Biophys. Res. Comm.* **1992**, *189*, 1450. (d) Nishi, Y.; Abe, S.; Kobayashi, T.; Okano, T.; Tsugawa, N.; Slatopolsky, E.; Brown, A. J.; Dusso, A.; Raisz, L. G. In *Vitamin D: Gene Regulation, Structure-Function Analysis, and Clinical Applications*; Norman, A. W., Bouillion, R., Thomsasset, R., Eds.; W. de Gruyter: New York, 1991; p 294.
- For reviews, see: (a) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111. (b) Krivta, V.; Fischer, W. *Chimia* **1993**, *47*, 3. (c) Posner, G. H. In *Stereocontrolled Organic Synthesis-Chemistry for the 21st Century*; Trost, B. M.; Beletskaya, I. P., Eds.; Blackwell Scientific Publications: Oxford, U.K., 1994; p 177. (d) Marko, I. E. *Organometallic Reagents in Organic Synthesis*; Academic Press: New York, 1994; Chapter 2, p 44.
  - For some of the recent examples on asymmetric cycloadditions, see: (a) Kozman, S.; Rawal, V. *J. Am. Chem. Soc.* **1997**, *119*, 7165. (b) Gilbertson, S. R.; Lopez, O. D. *J. Am. Chem. Soc.* **1997**, *119*, 3399. (c) Murakami, M.; Itami, K.; Ito, Y. *J. Am. Chem. Soc.* **1997**, *119*, 2950.
  - For general review on intramolecular cycloadditions, see: (a) Roush, W. R. In *Advances in Cycloadditions*; Curran, D. P., Ed.; JAI: Greenwich, CT, 1990; Vol. 2, pp 91-146. (b) Marwoka, K.; Yamamoto, H. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH publishers: 1994; Chapter 9, p 413. (c) Taber, D. F. *Intramolecular Diels-Alder and Alder Ene Reactions*, Springer-Verlag: New York, 1984. (d) Taschner, M. *Organic Synthesis: Theory and Application*, JAI Press, 1989, vol 1, p 1. (e) Caruthers, W. *Cycloaddition reactions in Organic Synthesis*; Pergamon: New York, 1990. (i) Enders, D.; Meyer, O. *Liebigs Ann.* **1996**, 1023.
  - Use of chiral thiazolidinethione for asymmetric cycloaddition: (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *Tetrahedron Lett.* **1984**, *25*, 4071. (b) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 2169.
  - Vinyl silane for IMDA: (a) Sieburth, S. M.; Fensterbank, L. *J. Org. Chem.* **1992**, *57*, 5279-5281. (b) Righi, P.; Marotta, E.; Landuzzi, A.; Rosini, G. *J. Am. Chem. Soc.* **1996**, *118*, 9446.
  - Posner, G. H.; Nelson, T. D.; Kinter, C. M.; Johnson, N. *J. Org. Chem.* **1992**, *57*, 4083.
  - For use of silaketals as tethered dienophiles for IMDA, see: (a) Shea, K. J.; Gauthier, D. R., Jr. *Tetrahedron Lett.* **1994**, *35*, 7311. (b) Garner, P. P.; Cox, P. B.; Klippenstein, S. J.; Young, W. J.; McConville, D. B. *J. Org. Chem.* **1994**, *59*, 6510. (c) Colombier, C.; Skrydstrup, T.; Beau, J.-M. *Tetrahedron Lett.* **1994**, *35*, 8167. (d) Fairbanks, A.; Perrin, E.; Sinay, P. *Synlett* **1996**, 679.
  - The high pressure Diels-Alder cycloadditions of systems **3**, **4**, **7** proceeded in a concerted manner to provide different stereochemical outcomes. Details will be published elsewhere.
  - For the synthesis of the system **7**, see: ref 1(a).
  - For the detailed stereochemical assignments, see: ref 1(a).
  - Some of the recent examples: (a) Storer, J. W.; raimondi, L.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 96753. (b) Linkert, F.; Laschat, S.; Kotila, S.; Fox, T. *Tetrahedron* **1996**, *52*, 955. (c) Leung, S.-W.; Singleton, D. *J. Org. Chem.* **1997**, *62*, 1955.
  - Mandai, T.; Imaji, M.; Takada, H.; Kawata, M.; Nokami, J.; Tsuji, J. *J. Org. Chem.* **1989**, *54*, 5395.
  - Posner, G. H.; Crouch, R. D.; Kinter, C. M.; Carry, J.-C. *J. Org. Chem.* **1991**, *56*, 6981.
  - Lythgoe, B.; Moran, T. A.; Nambudiry, M. E. N.; Tideswell, J.; Wright, P. W. *J. Chem. Soc. Perkin Trans. I* **1978**, 590.