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Efficient and Practical Synthesis of syn- and anti-β,γ-Dihydroxyphosphonates Derived from (S)-Mandelic Acid

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Abstract: A new efficient and practical synthesis of syn- and anti-β,γ-dihydroxyphosphonates 1 and 2 was developed in high diastereoselectivity via reduction of β-ketophosphonates readily obtained from (S)-mandelic acid. An example of “diastereoselective 1,2-induction” is showed and a mechanistic model to explain the stereochimical outcome is proposed. Assignment of the configuration at the new stereogenic centers was achieved by 1H NMR spectral data of their corresponding acetonides.

Key words: Diastereoselective 1,2-induction, diastereoselective reduction, β,γ-dihydroxyphosphonates, β-ketophosphonates, (S)-mandelic acid.

Introduction

Molecules with phosphonate functionalities are known to have significant importance in organic synthesis because of their anion stabilizing ability and their use in the construction of double bonds via the Horner-Wadsworth-Emmons reaction [1,2]. Additionally, the phosphonates display a broad spectrum of activities [3] including enzyme inhibitors [4] such as the synthase [5], HIV protease [6], renmin [7], phosphatasa [8], and PTPases [9]; they also are antibacterial [10], antiviral [11], antifungal agents [12], and antitumor agents [13], herbicides [14], plant regulators, potent antibiotics [15], and in the antibody generation [16]. Within this class of compounds the hydroxyphosphonates display interesting biological activities [17].

Synthesis of chiral hydroxyphosphonates includes opening reaction of epoxides with the anion of dialkylphosphites [18], nucleophilic addition of dialkylphosphites to aldehydes [19], enzymatic resolution of hydroxyphosphonates [20] and stereoselective reduction of ketophosphonates [21]. β,γ-Hydroxyphosphonates of type 1 and 2 have been mainly prepared by asymmetric dihydroxylation (AD) of the corresponding (E)- and (Z)-olefins [22], with the major disadvantage that AD reaction of (Z)-olefins proceeds with low enantioselectivities [23]. Highly diastereoselective reduction of γ-amino-β-ketophosphonates has been recently applied in our laboratories for the synthesis of phosphogabob (GABOB) [24] and phosphos-

Scheme 1.

Results and discussion

In our first attempt, the β-ketophosphonate (S)-4 was prepared in two steps from (S)-mandelic acid as is showed in the Scheme 1. Treatment of (S)-mandelic acid with iodo methane and silver oxide according to the literature procedure [26], afforded the methyl O-methylmandelate (S)-3 in 80% yield [27], which by subsequent addition of the lithium salt of dimethyl methylphosphonate gave the β-ketophosphonate (S)-4 in 93% yield (Scheme 1).

Article


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Having efficiently prepared the β-ketophosphonate (S)-4, initially we carried out its reduction using NaBH₄, LiBH₄, Zn(BH₄)₂, DIBAL-H and catecholborane (CB) as reducing agents, in order to obtain the syn-5 and anti-b,g-hydroxyphosphonate 6 in high diastereoselectivity. Conditions, yields and diastereoisomeric ratio are summarized in the Table 1.

As shown in Table 1, reduction of b-ketophosphonate (S)-4 with NaBH₄ in methanol at 0 °C afforded the corresponding β-hydroxyphosphonates syn-5 and anti-6 in excellent yield, but with only low diastereoselectivity (40:60) in favor of diastereoisomer anti-6 (Table 1, entry 1). Identical results were obtained when the reduction of (S)-4 was carried out with NaBH₄ and NaBH₄/LiClO₄ in methanol (Table 1, entries 2-3). A better diastereoselectivity in favor of anti-6 was observed when the reduction of (S)-4 was achieved using LiBH₄ as reducing agent (Table 1, entry 4); but the addition of LiClO₄ or TiCl₄ did not modify the diastereoselectivity (Table 1, entries 5-6). However, the reduction of (S)-4 with LiBH₄ in the presence of ZnCl₂ afforded the β-hydroxyphosphonates syn-5 and anti-6 in quantitative yield and high diastereoselectivity (9:91) in favor of diastereoisomer anti-6 (Table 1, entry 7). Contrary to what was expected, reduction of (S)-4 with Zn(BH₄)₂ resulted in a low diastereoselectivity (Table 1, entry 8). On the other hand, a reversal diastereoselectivity was observed when the reduction of (S)-4 was carried out with DIBAL-H and catecholborane, in both cases the diastereoisomeric ratio was 78:22 in favor of syn-6 (Table 1, entries 9-10). The configuration of syn-5 and anti-6 was tentatively assigned by comparison of the ³¹P NMR signals for the b-hydroxy-phosphonates syn-10 and anti-11 described below and some others reported in the literature [28].

In order to have the β,γ-dihydroxyphosphonate 2, the next step was the cleavage of methyl ether in anti-6 with BCl₃ in dichloromethane. However, under these conditions only decomposition of the starting material was observed.

Due to the difficulties in the cleavage of methyl ether in anti-6, we considered other protecting group which could induce both a high diastereoselectivity and an easier cleavage. In this context, the tert-butylidemethylsilyl moiety was incorporated into the β-ketophosphonate (S)-9. Thus, (S)-mandelic acid was treated with thionyl chloride in methanol according to the literature procedure [29], obtaining the methyl ester (S)-7 in 96% yield, which by reaction with tert-butylidemethysilyl chloride and imidazol in DMF gave the silyl derivative (S)-7 in 88% yield [30]. Finally, treatment of (S)-7 with the lithiated anion of dimethyl methylphosphonate at -78 °C afforded the b-ketophosphonate (S)-9 in 92% yield (Scheme 2).

![Scheme 2.](image_url)

**Table 1.** Diastereoselective reduction of (S)-4 with several reducing agents.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydride</th>
<th>Lewis acid</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>syn-5 : anti-6*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBH₄</td>
<td>—</td>
<td>MeOH, 0 °C</td>
<td>94</td>
<td>40 : 60</td>
</tr>
<tr>
<td>2</td>
<td>NaBH₄</td>
<td>—</td>
<td>MeOH, -78 °C</td>
<td>99</td>
<td>33 : 67</td>
</tr>
<tr>
<td>3</td>
<td>NaBH₄</td>
<td>LiClO₄</td>
<td>MeOH, 0 °C</td>
<td>99</td>
<td>36 : 64</td>
</tr>
<tr>
<td>4</td>
<td>LiBH₄</td>
<td>—</td>
<td>THF, -78 °C</td>
<td>80</td>
<td>18 : 82</td>
</tr>
<tr>
<td>5</td>
<td>LiBH₄</td>
<td>LiClO₄</td>
<td>THF, -78 °C</td>
<td>95</td>
<td>27 : 73</td>
</tr>
<tr>
<td>6</td>
<td>LiBH₄</td>
<td>TiCl₄</td>
<td>THF, -78 °C</td>
<td>99</td>
<td>17 : 83</td>
</tr>
<tr>
<td>7</td>
<td>LiBH₄</td>
<td>ZnCl₂</td>
<td>THF, -78 °C</td>
<td>98</td>
<td>90 : 91</td>
</tr>
<tr>
<td>8</td>
<td>Zn(BH₄)₂</td>
<td>—</td>
<td>THF, -78 °C</td>
<td>93</td>
<td>29 : 71</td>
</tr>
<tr>
<td>9</td>
<td>DIBAL-H</td>
<td>—</td>
<td>THF, -78 °C</td>
<td>92</td>
<td>78 : 22</td>
</tr>
<tr>
<td>10</td>
<td>CBb</td>
<td>—</td>
<td>THF, -78 °C</td>
<td>66</td>
<td>78 : 22</td>
</tr>
</tbody>
</table>

* Determined by ³¹P NMR at 81 MHz. b Catecholborane.
Once again the reduction of (S)-9 was performed with various reducing agents and reaction conditions, the results are summarized in the Table 2.

Reduction of (S)-9 with NaBH₄ at 0 °C resulted in a preferential production of anti-11 with a moderate diastereoselectivity (33:67), which was increased to (10:90) when the reduction was carried out at -78 °C (Table 2, entries 1-3). However, when the reduction of (S)-9 was carried out using NaBH₄ at 0 °C in the presence of LiClO₄, a reversal diastereoselectivity was observed (82:18) now in favor of syn-10 (Table 2, entry 3). With this result it was expected that reduction with LiBH₄ would afford the diastereoisomer syn-10 as the major product. Effectively, reduction of (S)-9 with LiBH₄, LiBH₄/LiClO₄, and LiBH₄/ZnCl₂ afforded the diastereoisomer syn-10 as principal product (Table 2, entries 4-6), but a lost of the diastereoselectivity was observed when (S)-9 was reduced with LiBH₄ in the presence of TiCl₄ (Table 2, entry 7). On the other hand, when the reduction of (S)-9 was carried out with Zn(BH₄)₂, the diastereoisomer syn-10 was obtained with excellent yield and good diastereoselectivity (90:10) in favor of syn-10 (Table 2, entry 8). When DIBAL-H and DIBAL-H/LiClO₄ were used as reducing agent, the corresponding β-hydroxyphosphonates syn-10 and anti-11 were obtained in moderate yield and diastereoselectivity, in favor of syn-10 (Table 2, entries 9 and 10), but a low diastereoselectivity was observed when DIBAL-H/ZnCl₂ and DIBAL-H/TiCl₄ were used (Table 2, entries 11-12). Reduction of (S)-9 with CB, CB/LiClO₄ and CB/TiCl₄ gave the β-hydroxyphosphonates syn-10 and anti-11 in only moderated diastereoselectivity (Table 2, entries 13-15); however, reduction of (S)-9 with CB in the presence of ZnCl₂ provided the β-hydroxyphosphonates syn-10 and anti-11 in moderated yield and excellent diastereoselectivity (93:7) in favor of syn-10 (Table 2, entry 16). At this point we had found the best conditions for the reduction of b-ketophosphonate (S)-9, obtaining syn-10 or anti-11 with excellent diastereoselectivity depending of reducing agent used.

The next step was the cleavage of the silyl protecting group in order to obtain the target molecules syn-1 and anti-2. In this context, the standard literature procedures to remove the silyl group were attempted with unfavorable results, since the reaction of syn-10 or anti-11 with n-tetrahydroammonium fluoride or cesium fluoride led to decomposition of the starting β-hydroxyphosphonates, and under acid conditions (HCO₂H or AcOH) just did not proceed. An alternative methodology developed in our laboratory to cleavage the silyl ether in syn-10 was their treatment with 2,2-dimethoxypropane in the presence of p-toluene sulphonic acid prior to the addition of cesium fluoride, obtaining the expected β-hydroxyphosphonate syn-1.

Table 2. Diastereoselective reduction of (S)-9 with several reducing agents.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydride</th>
<th>Lewis acid</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>syn-10 : anti-11</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBH₄</td>
<td>—</td>
<td>MeOH, 0 °C</td>
<td>94</td>
<td>33 : 67</td>
</tr>
<tr>
<td>2</td>
<td>NaBH₄</td>
<td>—</td>
<td>MeOH, -78 °C</td>
<td>96</td>
<td>10 : 90</td>
</tr>
<tr>
<td>3</td>
<td>NaBH₄</td>
<td>LiClO₄</td>
<td>MeOH, 0 °C</td>
<td>95</td>
<td>82 : 18</td>
</tr>
<tr>
<td>4</td>
<td>LiBH₄</td>
<td>—</td>
<td>THF, -78 °C</td>
<td>93</td>
<td>80 : 20</td>
</tr>
<tr>
<td>5</td>
<td>LiBH₄</td>
<td>LiClO₄</td>
<td>THF, -78 °C</td>
<td>97</td>
<td>86 : 14</td>
</tr>
<tr>
<td>6</td>
<td>LiBH₄</td>
<td>ZnCl₂</td>
<td>THF, -78 °C</td>
<td>93</td>
<td>81 : 19</td>
</tr>
<tr>
<td>7</td>
<td>LiBH₄</td>
<td>TiCl₄</td>
<td>THF, -78 °C</td>
<td>74</td>
<td>49 : 51</td>
</tr>
<tr>
<td>8</td>
<td>Zn(BH₄)₂</td>
<td>—</td>
<td>THF, -78 °C</td>
<td>98</td>
<td>90 : 10</td>
</tr>
<tr>
<td>9</td>
<td>DIBAL-H</td>
<td>—</td>
<td>THF, -78 °C</td>
<td>88</td>
<td>83 : 17</td>
</tr>
<tr>
<td>10</td>
<td>DIBAL-H</td>
<td>LiClO₄</td>
<td>THF, -78 °C</td>
<td>50</td>
<td>81 : 19</td>
</tr>
<tr>
<td>11</td>
<td>DIBAL-H</td>
<td>ZnCl₂</td>
<td>THF, -78 °C</td>
<td>33</td>
<td>42 : 58</td>
</tr>
<tr>
<td>12</td>
<td>DIBAL-H</td>
<td>TiCl₄</td>
<td>THF, -78 °C</td>
<td>53</td>
<td>61 : 39</td>
</tr>
<tr>
<td>13</td>
<td>CB</td>
<td>—</td>
<td>THF, -78 °C</td>
<td>95</td>
<td>70 : 30</td>
</tr>
<tr>
<td>14</td>
<td>CB</td>
<td>LiClO₄</td>
<td>THF, -78 °C</td>
<td>65</td>
<td>78 : 22</td>
</tr>
<tr>
<td>15</td>
<td>CB</td>
<td>TiCl₄</td>
<td>THF, -78 °C</td>
<td>68</td>
<td>64 : 36</td>
</tr>
<tr>
<td>16</td>
<td>CB</td>
<td>ZnCl₂</td>
<td>THF, -78 °C</td>
<td>65</td>
<td>93 : 07</td>
</tr>
</tbody>
</table>

*aDetermined by ³¹P NMR at 81 MHz. bCatecholborane
in 50% yield and its corresponding cyclic acetonide 12 in 33% yield, whereas anti-11 gave the β-hydroxyphosphonate anti-2 in 20% yield and the cyclic acetonide 13 in 46% yield (Scheme 3).

\[
\text{Scheme 3.}
\]

\( ^1H \) NMR analysis of acetonides 12 and 13 was used for the absolute configuration assignment in C-9. Thus, the coupling constant values for adjacent protons H\(_1\) and H\(_2\) at the stereogenic centers in acetonides 12 and 13 are \( J = 8.4 \) Hz and \( J = 6.1 \) Hz, respectively, which by comparison of these coupling constants values reported in the literature [31], particularly with those reported for phosphine oxide acetonides [32], where the coupling constant values are \( J = 8.0 \) Hz and \( J = 6.4 \) Hz, respectively. An additional coupling constant \( J = 1.8 \) Hz for H\(_2\) in acetonide 13 was observed (Figure 1). When the \( ^1H \) NMR spectrum decoupled to \( ^3P \) was carried out, the H\(_2\) signal changed from double of doublets \( J = 6.1, 1.8 \) Hz to doublet \( J = 6.1 \) Hz. From these values follows that H\(_2\) is coupled to phosphorus with a typical W coupling value (1.8 Hz). These data correlate with a structure depicted for diastereoisomer 13, confirming the relative configuration.

\[
\text{Figure 1. Vicinal coupling constant for acetonides 12 and 13.}
\]

Therefore, we propose that the reduction of (S)-9 with NaBH\(_4\) took place under non-chelation control or the Felkin-Ahn model [33], where the conformer leading to the major product will be that one where the bulky OTBS group is perpendicular to the carbonyl plane and the smallest group (hydrogen) is almost eclipsed to it [34], in this model, the bulkiness of the OTBS group is sufficient to simultaneously limit the rotamer populations around the hinge bounds adjacent to the carbonyl group blocking the si face of the carbonyl group and, thereby allowing the addition of hydride take place from the re face leading to diastereoisomer anti-11 (Figure 2a). On the other hand, when the reduction of (S)-9 was carried out in the presence of Lewis acid or hydrides possessing metal ions with coordinating ability (such as lithium, zinc, aluminum and boron), a Cram’s model is proposed [35], where the carbonyl, phosphoryl and OTBS groups are coordinated to the metal ion in a chair-like transition state A or B showed in Figure 2b. Because of the steric interactions between the phenyl group and the equatorial hydrogen in A, it is assumed that transition state B is favored, and the addition of hydride take place by the si face leading to syn-10 as the principal product (Figure 2b).

\[
\text{Figure 2. Reduction of (S)-9: (a) with NaBH}_4\text{, (b) in the presence of M}^{\text{III}}\text{.}
\]

**Conclusions**

In summary, we have found an alternative and practical methodology for the synthesis of β,γ-dihydroxy-phosphonates syn-1 and anti-2 in high diastereoselectivity via the reduction of b-ketophosphonate (S)-9 readily obtained from (S)-mandelic acid. Additionally, the conditions described in this paper show an example of highly diastereoselective 1,2-induction.

**Experimental**

Optical rotations were taken on a Perkin-Elmer 241 polarimeter in an 1 dm tube; concentrations are given in g/100 mL. For the flash chromatography, silica gel 60 (230-400 mesh ASTM) was used. \( ^1H \) NMR spectra were registered on a Varian Mercury 200 (200 MHz) and INOVA 400 (400 MHz); and \( ^13C \) NMR on a Varian Mercury 200 (50 MHz) and INOVA 400 (100 MHz), and \( ^3P \) NMR on a Varian Mercury 200 (81 MHz). The spectra were recorded in CDCl\(_3\), DMSO-d\(_6\), and CDOD solution, using TMS as internal reference. HRMS spectra were recorded on a JEOL JMS-700. Microanalyses were registered on an Elemental VARIO EL III. Flasks, stirrings bars, and hypodermic needles used for the generation of organometallic compounds were dried for ca. 12 h at 120 °C and allowed to cool in a desiccators over anhydrous calcium sulfate. Anhydrous solvents (ethers) were obtained by distillation from benzophenone ketyl.
Methyl (S)-O-methylmandelate (S)-3. Methyl ester (S)-3 was obtained according to the literature procedure [26].

Methyl (S)-mandelic acid (S)-7. Methyl ester (S)-7 was obtained according to the literature procedure [29].

Methyl 1-[tert-butyldimethylsilyloxy]-1-phenylacetate (S)-8. Methyl ester (S)-8 was obtained according to the literature procedure [30].

Dimethyl (S)-3-methoxy-3-phenyl 2-oxo-propylphosphonate (S)-4. A solution of dimethyl methylphosphonate 1.38 g (11.1 mmol) in anhydrous THF (80 mL) was cooled at -78 °C before the slow addition of 750 mg, 4.86 mL (11.7 mmol) of n-BuLi 2.4 M in hexanes. The resulting solution was stirred at -78 °C for 1.0 h, which was slowly added to a solution containing (S)-3 1.0 g (5.6 mmol) in THF (80 mL) at -78 °C. The reaction mixture was stirred for 3.0 h, quenched with aqueous NH₄Cl solution, and extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were dried over Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate-hexane 1:1) to afford 1.41 g (93%) of (S)-4 as a colorless oil. [α]D = +25.5 (c = 3.5, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 3.11 (dd, J = 22.0, 14.5 Hz, 1H, CH₂), 3.21 (dd, J = 22.0, 14.5 Hz, 1H, CH₂), 3.40 (s, 3H, CH₃O), 3.74 (d, J = 11.2, 3H, ((CH₂)₃Si), 3.75 (d, J = 11.2, 3H, ((CH₂)₃O)P), 4.88 (s, 1H, CHPh), 7.34-7.39 (m, 5H, Harom); ¹³C NMR (100 MHz, CDCl₃): δ 24.4. HRMS (FAB⁺) calc. for C₁₁H₁₀O₃PSi (MH⁺) 273.1600; found 273.1597

General procedure for the reduction of (S)-4 and (S)-9 with NaBH₄. To a solution of β-ketophosphonate (S)-4 or (S)-9 (1.0 equiv) in methanol (40 mL) was added NaBH₄ (4.0 equiv) at room temperature, 0 and -78 °C. After 5.0 h, the solvent was evaporated and the residue was diluted with H₂O and extracted with ethyl acetate (3 × 30 mL). The organic layer was dried over Na₂SO₄ and evaporated in vacuum. The crude was analyzed by ¹H and ¹³P NMR and purified by column chromatography.

General procedure for the reduction of (S)-4 and (S)-9 with NaBH₄/LiClO₄. To a solution of β-ketophosphonate (S)-4 or (S)-9 (1.0 equiv) in methanol (40 mL) was added LiClO₄ (1.0 equiv) at room temperature. After 1.0 h, NaBH₄ (4.0 equiv) was slowly added at 0 °C, and the reaction mixture was stirred for 5.0 h at 0 °C. The solvent was evaporated and the residue was diluted with H₂O and extracted with ethyl acetate (3 × 30 mL). The organic layer was dried over Na₂SO₄ and evaporated in vacuum. The crude was analyzed by ¹H and ¹³P NMR and purified by column chromatography.

General procedure for the reduction of (S)-4 and (S)-9 with LiBH₄/Zn(BH₄)₂ DIBAL-H and Catecholborane (CB). To a solution of β-ketophosphonate (S)-4 or (S)-9 (1.0 equiv) in anhydrous THF (50 mL) was added (2.0 equiv) of the reducing agent at -78 °C. The reaction mixture was stirred for 5.0 h at -78 °C. The reaction was quenched with aqueous NH₄Cl solution, and extracted with ethyl acetate (3 × 40 mL). The organic layer was dried over Na₂SO₄ and evaporated under reduced pressure. The crude was analyzed by ¹H and ¹³P NMR and purified by column chromatography.

General procedure for the reduction of (S)-4 and (S)-9 with LiBH₄ Dibal-H and CB in the presence of Lewis acid. To a solution of β-ketophosphonate (S)-4 or (S)-9 (1.0 equiv) and Lewis acid (1.0 equiv) in anhydrous THF (50 mL) was stirred for 1.0 h. After the reducing agent was added (2.0 equiv) at -78 °C, and stirred for 5.0 h. The reaction was quenched with aqueous NH₄Cl solution and extracted with ethyl acetate (3 × 40 mL). The organic layers were dried over Na₂SO₄ and evaporated under reduced pressure. The crude was analyzed by ¹H and ¹³P NMR and purified by column chromatography.

Dimethyl (S)-3-[tert-butyldimethylsilyloxy]-3-phenyl-2-oxo-propylphosphonate (S)-9. A solution of dimethyl methylphosphonate 1.3 g (10.7 mmol) in anhydrous THF (70 mL) was cooled at -78 °C before the slow addition of 710 mg, 4.42 mL (11.0 mmol) of n-BuLi 2.5 M in hexanes. The resulting solution was stirred at -78 °C for 1.0 h, which was slowly added to a solution containing (S)-8 1.0 g (3.6 mmol) in THF (80 mL) at -78 °C. The reaction mixture was stirred for 6.0 h, quenched with aqueous NH₄Cl solution, and extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were dried over Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate-hexane 1:1) to afford 1.22 g (92%) of (S)-9 as a colorless oil. [α]D = -5.15 (c = 4.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.05 (s, 3H, (CH₃)₂Si), 0.11 (s, 3H, (CH₃)₂Si), 0.9 (s, 9H, (CH₃)₂Si), 3.16 (dd, J = 10.6, 7.8 Hz, 1H, CH₂), 3.26 (dd, J = 10.6, 7.8 Hz, 1H, CH₂), 3.66 (d, J = 12.0 Hz, 3H, (CH₂)₂O), 3.69 (d, J = 12.0 Hz, 3H, (CH₂)₂O), 5.19 (s, 1H, CHPh), 7.29-7.43 (m, 5H, Harom); ¹³C NMR (100 MHz, CDCl₃): δ -4.9 (CH₃, Si), 4.8 (CH₃, Si), 18.4 ((CH₂)₂Si), 25.8 ((CH₂)₂Si), 34.2 (d, J = 136.3 Hz, CH₂), 52.9 (d, J = 7.6 Hz, (CH₂)₂O), 81.1 (d, J = 4.5 Hz, CHPh), 126.5, 126.8, 128.8, 137.7, 201.6 (d, J = 7.6 Hz, CO). ¹³P NMR (81 MHz, CDCl₃): δ 24.40. HRMS (FAB⁺) calc. for C₁₂H₁₀O₄PSi (MH⁺) 373.1600; found 373.1597
Cleavage of TBS ether in anti-11. The procedure is similar as for syn-10, using anti-11 as starting material. The reaction gave 115 mg (20%) of anti-2 as a colorless oil and 295 mg (46%) of 13 as a white solid.

**References**

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28. 31 P NMR signal for \( \text{syn-12} \) appears at higher field than signal for \( \text{anti-13} \). For other examples, see: ref. 25.


34. This mechanism had been proposed to explain the reduction of \( \text{b-ketodiphenylphosphine oxide analogue of (S)-9} \). For an extensive account about the mechanism, see: reference 32.