A Convenient Preparation of Difficultly Accessible *sec*-Alkylmethylphosphinates Using Sequential Pudovik/Abramov–Barton/McCombie Reactions

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Abstract: A one-pot procedure for the syntheses of (1-hydroxy-*sec*-alkyl)methylphosphinates from ketones, hexamethyldisilazane and ethyl methylphosphinate was developed. The hydroxy group could be removed by a modified Barton/McCombie radical deoxygenation procedure. The *sec*-alkylmethylphosphinates can be dealkylated/hydrolyzed by treatment with trimethylsilyl bromide or refluxing in hydrochloric acid. This is a convenient route to a variety of *sec*-alkylmethylphosphinates, which are difficult to prepare by other methods.

Key words: methylphosphinates, methylphosphinic acids, Barton deoxygenation, Pudovik addition, Abramov addition

The phosphinic acid group and methylphosphinic acid group (Figure 1) continue to attract considerable interest as bioisosteric replacements for carboxylic acid groups,[1,2] being potential regulators, mediators or inhibitors of metabolic processes.[3] Several methylphosphinic acids act as potent agonists or antagonists at carboxylic acid receptors, e.g. the cholecystokinin receptor,[4] the β-adrenergic receptor,[5] and their analogs act at the receptors for the inhibitory neurotransmitter γ-aminobutyric acid (GABA)[6–8] and the excitatory neurotransmitter glutamate.[9,10] Furthermore, many phosphinic and methylphosphinic acids are inhibitors of metabolic enzymes, e.g. inhibitors of aminoacyl-t-RNA synthetase,[3] creatine kinase,[11] ornithine decarboxylase,[12] nitric oxide synthase,[13] matrix metalloproteinases,[14,15] and glutamine synthetase[16–19] including many herbicides like the widely used phosphinothricin.[20] A large number of phosphinic acids have also been prepared as transition state mimics for studies or inhibition of enzymes which have carboxylic acid derivatives as substrates.[21–24] Although the phosphinic acids often show similar biological profiles as methylphosphinic acids, recent animal experiments indicate that the methylphosphinic acid moiety is considerably more metabolically stable than the phosphinic acid moiety.[7]

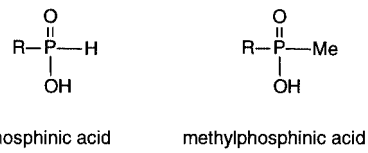
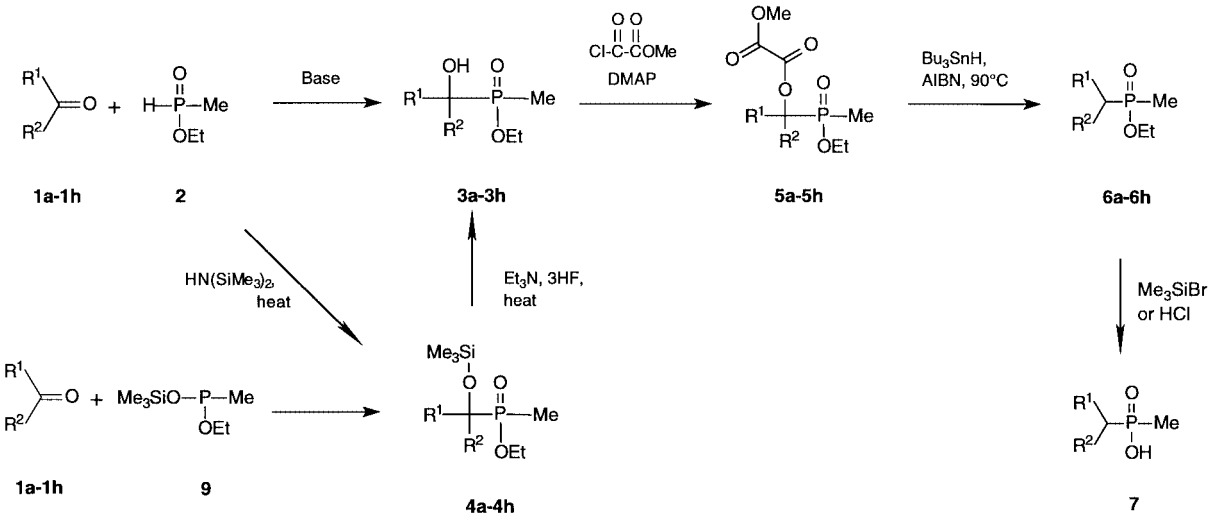


Figure 1 The phosphinic acid and methylphosphinic acid groups

Classical routes to the esters of alkylmethylphosphinic acids are: 1) alkylation of dialkyl alkylphosphonites (the Michaelis–Arbuzov reaction),[10,25–27] 2) alcoholysis of dialkylchlorophosphines,[28–33] 3) reaction of alkylphosphonohalides with Grignard reagents,[34-40] and 4) cleavage of dialkylphenylphosphine oxides with NaOH.[41–43] Newer routes include: 5) stepwise silylation and alkylation of phosphinates (the silyl-Arbuzov reaction),[6,7,44–46] 6) Michael addition of alkyl methylphosphinates to α,β-unsaturated substrates,[2,44,47,48] 7) radical addition of alkyl alkylphosphinates to alkenes, and 8) alkylation of the anion of alkyl alkylphosphinates (the Michaelis–Becker reaction).[6,49,50] These routes all have some drawbacks involving either reactive trivalent phosphorus compounds or poisonous compounds as intermediates, or rather harsh conditions. Furthermore, the most popular routes (the Arbuzov and Michaelis–Becker reactions) generally give very low or no yield when alkylation with non-activated halides or with *sec*-alkyl halides are required.[26,45,49] As a consequence of these difficulties, only very few *sec*-alkylmethylphosphinates have been reported in the literature: A literature search (February 1999) for alkylmethylphosphinates in the Beilstein Crossfire database gave 470 hits and of these only 17 hits were *sec*-alkylmethylphosphinates.

We report here a simple route to *sec*-alkylmethylphosphinates from ketones and the easily obtainable ethyl methylphosphinate **(2)**[50,51] using sequential Pudovik/Abramov–Barton/McCombie reactions. This route circumvents the drawbacks of previous procedures. The steps involved are addition of **2** to representative ketones to give the ethyl (1-hydroxy-*sec*-alkyl)methylphosphinates **3** (Scheme) and subsequent removal of the hydroxy group with tributyltin hydride after activation with methyl oxalyl chloride to give the *sec*-alkylmethylphosphinates **6**. These esters can be easily cleaved by, e.g. treatment with trimethylsilyl bromide (the McKenna reaction[52]) or refluxing in hydrochloric acid[53] to give the *sec*-alkylmethylphosphinic acids **7**.

The first step, the addition of **2** to the ketone, was first attempted under Pudovik conditions,[54] i.e. heating under base-catalyzed conditions typically with alkoxides or tertiary amines. However, whereas the Pudovik reaction gives high yield for the amine-catalyzed addition of H-phosphonates to both aldehydes and ketones,[54] we found



Scheme

that under these conditions **2** only adds to aldehydes[50] and reactive ketones like cyclohexanone and piperidinones (Table 1). Acyclic ketones were unreactive under these conditions and even under forcing conditions like refluxing for 5 days. The use of stronger bases gave higher yields of **3**, albeit, still not satisfactory. Thus, using potassium *tert*-butoxide as base only 40% of **3d** was formed according to ^{31}P NMR spectroscopy. This was independent of the relative stoichiometry of **1d** and **2** which indicate competing side reactions, e.g. aldol condensation. The use of 1 equivalent of lithium diisopropylamide (LDA) at –78 °C gave quantitative yields of **3a–e,g** according to ^{31}P NMR, however, isolated yields were typically only 20–50%, which we ascribe to decomposition during the aqueous acidic workup of the reactions. Under the strong alkaline conditions even small amounts of water cause the hydroxyphosphinates **3** to decompose to the starting materials **1** and **2**. For the addition to benzophenone, yet another side reaction was observed, which we on the basis of ^{31}P NMR tentatively ascribe to phosphinate-phosphonate rearrangement[25] of the oxyanion of **3h** to the phosphonate **8h** (Figure 2). This side reaction could be partially suppressed by acidic quenching at low temperature, but still occurred to an extent of 30% at –20 °C and only 15% of **3h** was isolated.

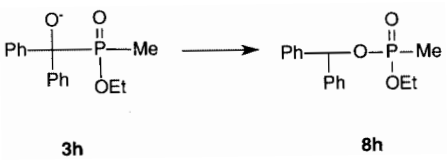
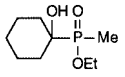
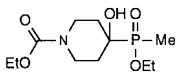
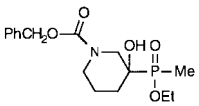
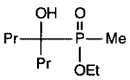
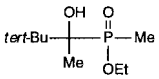
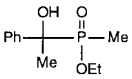
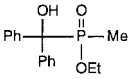
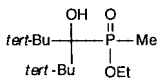


Figure 2 Proposed phosphinate-phosphonate rearrangement of **3h** to **8h**

Encountering these problems, we looked for another way of performing the addition reaction. A known way of activating H-phosphonates[55] and H-phosphinates[44–46] is to convert them into their trimethylsilyloxy derivatives,[56] like the ethyl trimethylsilyl methylphosphonite **9** (Scheme). This approach (the silyl-Abramov reaction[56]) was successful. Refluxing **9** with ketones **1** gave the α-trimethylsilyloxyphosphinates **4** in near quantitative yields as 1:1 diastereomeric mixtures according to ^{31}P NMR. The silylphosphonite **9** can be prepared by the reaction of **2** with an equivalent amount of anhydrous triethylamine and trimethylsilyl chloride but this procedure is tedious when filtration of the hydrolysis sensitive **9** is required. A more convenient preparation is the in situ formation of **9** by refluxing **2** with neat hexamethyldisilazane (HMDS). Quantitative formation of **9**, however, takes up to 2 days with 1.5–2 equivalents of HMDS. Interestingly, we found that the addition of **2** to ketones can conveniently be performed as a one-pot reaction via **9** by simply heating a mixture of equivalent amounts of ketone, HMDS and **2**. Although HMDS is a known reagent for conversion of ketones into silyl enol ethers, the competing silyl-Abramov reaction apparently is a faster reaction. Subsequent removal of the trimethylsilyl (TMS) group was surprisingly difficult. The TMS-group survived chromatography on silica gel eluting with $MeOH/CH_2Cl_2$ (1:9) and even treatment with methanolic acetic acid, and short-lived 1 M hydrochloric acid in MeCN.

Difficulties in removing TMS-groups even from secondary hydroxy methylphosphinates have been observed by others.[19] The TMS-groups were accordingly removed by treatment with fluoride ions. However, the choice of the F^--source was crucial. Alkaline sources like tetrabutylammonium fluoride (TBAF) readily cleaved the TMS-groups but the resulting methylphosphino oxyanions are unstable and break down to **1** and **2**. A convenient source of mild acidic F^- is the liquid complex triethylamine trishydrofluoride, excess of which is easily removed again by aqueous extraction. The α-trimethylsilyloxyphosphinates **4** were silyl-deprotected in high yields by heating with 1.5–2 equivalents of $Et_3N{\bullet}3HF$ forming the α-hy-

Table 1 Compounds **3a–e, g, h** and **4f** Prepared

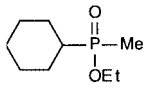
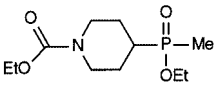
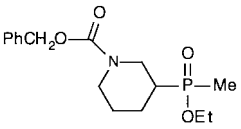
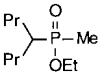
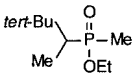
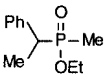
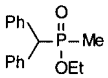
Product[a]		Yield[b] (%)	mp (°C)	^{1}H NMR[c] δ, *J* (Hz)	^{13}C NMR[c] δ, *J* (Hz)	^{31}P NMR[c] δ	FAB-MS $(M+H)^+$ (calcd.)
	**3a**	80[d]	96–99	4.04 (2 H, m), 3.26 (1 H, br s), 1.82–1.49 (10 H, m), 1.37 (3 H, d, $^2J_{PH}$ = 13), 1.25 (3 H, t, *J* = 7)	71.4 (d, $^1J_{PC}$ = 114), 60.9, 30.4 (d, $^2J_{PC}$ = 79), 25.3, 19.9, 16.6, 8.7 (d, $^1J_{PC}$ = 85)	55.2	207.1 (207.1)
	**3b**	75[d]		–[e]	–[e]	–[e]	–[e]
	**3c**	60[d]	oil	7.25 (5 H, m), 5.05 (2 H, s), 4.00 (4 H, m), 3.45 (1 H, br s), 3.25 (1 H, m), 2.80 (1 H, m), 1.90–1.55 (4 H, m), 1.45 (3 H, d, $^2J_{PH}$ = 13), 1.25 (3 H, t, *J* = 7)	158.0, 136.5, 128.3, 127.8, 127.6, 67.1, 61.3 (d, $^2J_{PC}$ = 8), 61.2 (d, $^2J_{PC}$ = 9), 48.2 (d, $^2J_{PC}$ = 12), 44.0, 29.0 (br s), 19.5 (br s), 16.5, 9.3 (d, $^1J_{PC}$ = 87), 8.8 (d, $^1J_{PC}$ = 87)	54.05, 53.08	342.0 (342.0)
	**3d**	72[f]	73–76	4.13–3.99 (2 H, m), 3.20 (1 H, s), 1.70–1.49 (4 H, m), 1.44 (3 H, d, $^2J_{PH}$ = 13), 1.39 (4 H, m), 1.27 (3 H, t, *J* = 7), 0.88 (6 H, t, *J* = 7)	–[g]	55.1	223.1 (223.1)
	**3e**	54[f]	oil	4.08–3.84 (2 H, m), 2.79 (1 H, br s), 1.39 (3 H, 2 s, dia), $^2J_{PH}$ = 13.1), 1.27–1.15 (6 H, m), 0.97 (9 H, 2 s, dia)	–[g]	58.8, 57.4	209.1 (209.1)
	**3g**	68[f]	85–90	7.55–7.49 (2 H, m), 7.33–7.18 (3 H, m), 4.08–3.87 (2 H, m), 3.75 (1 H, br s), 1.74 (3 H, d, $^2J_{PH}$ = 13.5), 1.22 (3 H, 2 s), 1.18 (3 H, t, *J* = 6.7)	141.4, 128.0, 127.9, 127.2, 127.1, 125.7, 125.6, 73.9 (d, $^1J_{PC}$ = 109), 61.4 and 61.3 (dia), 24.7 and 24.6 (dia), 16.5 and 16.4 (dia), 9.2 (d, $^1J_{PC}$ = 90)	54.0, 53.5	229.2 (229.1)
	**3h**	72[f]	138–141	7.74–7.16 (10 H, m), 4.01–3.73 (2 H, m), 3.67 (1 H, br s), 1.30 (3 H, d, $^2J_{PH}$ = 13.8), 1.10 (3 H, t, *J* = 7.1)	141.2, 140.6, 132.3, 129.9, 128.2, 127.6, 126.8, 126.7, 78.2 (d,$^1J_{PC}$ = 106), 61.9, 16.4, 10.8 (d,$^1J_{PC}$ = 94)	53.0	291.1 (291.1)
	**4f**	1[f,h]	–[g]	–[g]	–[g]	–[g]	–[g]

[a] Satisfactory microanalyses obtained: C ± 0.39, H ± 0.22, N ± 0.10.
[b] Yield of isolated, purified products.
[c] Recorded at 400 MHz in $CDCl_3$/TMS. For ^{31}P NMR $CDCl_3/H_3PO_4$ (ext). dia = diastereoisomers.
[d] Et_3N-catalyzed Pudovik addition.
[e] The spectral data are reported in Ref. 53.
[f] HMDS-catalyzed silyl-Abramov addition.
[g] Not determined.
[h] Yield of **4f** was estimated from ^{31}P NMR spectroscopy.

droxyphosphinates **3** as 1:1 diastereomeric mixtures (Table 1). The addition step is somewhat sensitive to sterically demanding groups as seen from the yields of **3e** (addition to *tert*-butyl methyl ketone, 54%) reaching the limit with addition to the very hindered di-*tert*-butyl ketone giving only 1% **4f**.

The next step, removal of the tertiary hydroxy group, was first attempted by ionic hydrogenation.[57,58] However, **3a** and **3b** which were tried for reduction in this way, were completely resistant to this procedure and were isolated again in quantitative yield after treatment with TFA and Et_3SiH. This is most likely a consequence of the electron-withdrawing effect of the neighboring phosphinate group possessing an electronegativity comparable to the CF_3-group.[59] The phosphorus moiety is also a well known α-anion stabilizing group[60] and is known to destabilize α-cations.[61] We then turned our attention to the radical deoxygenation procedure of Barton et al.,[62–64] as phosphorus is also known to stabilize α-radicals.[65,66] However, the Barton procedure requires activation of the hydroxy group by conversion into a thionocarbonate or dithiocarbonate derivative and we found that **3a** and **3b** were unreactive towards treatment with a chlorothionoformate and 4-

Table 2 Compounds **6a–e, g, h** Prepared

Product[a]		Yield[b] (%)	^{1}H NMR[c] δ, *J* (Hz)	^{31}P NMR[c] δ	FAB-MS $(M+H)^+$ (calcd.)
	**6a**	68	4.02–3.94 (2 H, m), 1.89 (2 H, m), 1.76 (2 H, m), 1.67–1.56 (2 H, m), 1.31 (3 H, d, $^2J_{PH}$ = 13), 1.24 (3 H, t, *J* = 7), 1.30–1.15 (5 H, m)	56.3	191.1 (191.1)
	**6b**	90	–[d]	–[d]	–[d]
	**6c**	58	7.25 (5 H, m), 5.05 (2 H, s), 4.30 (1 H, m), 4.00 (3 H, m), 2.95–2.65 (2 H, m), 2.05 (1 H, m), 1.85–1.65 (3 H, m), 1.60–1.45 (2 H, m), 1.30 (3 H, m), 0.95 (3 H, t, *J* = 7)	52.07, 51.99	326.1 (326.1)
	**6d**	71	4.16–4.02 (2 H, m), 1.66 (1 H, m,), 1.54–1.24 (4 H, m), 1.40 (3 H, d, $^2J_{PH}$ = 12.9), 1.31 (3 H, t, *J* = 7.0), 0.93 (3 H, t, *J* = 6.9)	59.6	207.2 (207.2)
	**6e**	35	4.14–3.96 (2 H, m), 1.68 (1 H, m), 1.44 and 1.43 [3 H, 2 d (dia), $^2J_{PH}$ = 12.5], 1.31 (3 H, t, *J* = 7.0), 1.19 [3 H, 2 d (dia), *J* = 7.5], 1.11 and 1.10 [9 H, 2 s (dia)]	59.8, 58.3	193.2 (193.2)
	**6g**	53	7.33–7.26 (5 H, m), 4.15–3.81 (2 H, m), 3.13 (1 H, m), 1.59 and 1.58 [3 H, 2 d (dia), $^2J_{PH}$ = 16.2], 1.35–1.20 (6 H, m)	55.0, 54.5	213.2 (213.2)
	**6h**	28	7.49–7.41 and 7.24–7.10 (10 H, m), 4.17 (1 H, d, $^2J_{PH}$ = 16.8), 3.78 and 3.54 (2 H, 2 m), 1.24 (3 H, d, $^2J_{PH}$ = 13.7), 0.98 (3 H, t, *J* = 7.0)	50.6	275.0 (275.0)

[a] Satisfactory microanalyses obtained: C ± 0.39, H ± 0.22, H ± 0.10.
[b] Yield of isolated, purified products.
[c] Recorded at 400 MHz in $CDCl_3$/TMS. For ^{31}P NMR $CDCl_3/H_3PO_4$ (ext). dia = diastereoisomers.
[d] Spectral data are given in Ref. 53.

dimethylaminopyridine (DMAP). This is most likely due to the sterically hindered nature of the tertiary alcohol, known to be a problem in the Barton deoxygenation.[67] Furthermore, the alcohol has a low nucleophilicity because of the neighboring electron-withdrawing phosphinate group. Illustratively, even a secondary α-hydroxy phosphine oxide was recently reduced in only 28% yield by the thionocarbonate method.[68]

The Barton deoxygenation of secondary and tertiary alcohols was improved by Dolan and MacMillan[67] by using methyl oxalate ester activation instead of thionocarbonate activation. The α-hydroxyphosphinates **3** were readily converted in quantitative yields to their methyl oxalate esters **5** by treatment with commercially available methyl oxalyl chloride and DMAP and subsequently reduced by tributyltin hydride in hot toluene forming deoxygenated phosphinates **6** as 1:1 diastereomeric mixtures (Table 2). Again, the reduction step is somewhat sensitive to sterically demanding groups as seen from the yield of **6e** (35%). Also, groups capable of stabilizing radicals (e.g. phenyl) lowers the yield of the deoxygenated product **6** as seen for **6h**. By ^{31}P NMR we observed an increased amount of P–C bond cleavage when reducing **5h**. An attempt to increase the yield of the deoxygenation step by using milder reduction conditions by running the reaction at room temperature with triethylborane as radical initiator instead of AIBN was unsuccessful. Prolonged heating with excess Bu_3SnH resulted in decomposition of the phosphinates **6**. An attempt to use the recently developed catalytic Barton reduction[69] of **5a** with an catalytic amount of Bu_3SnH and polymethylhydrosiloxane was unsuccessful, as only hydroxyphosphinate **3a** was isolated most likely due to alcoholysis of the methyl oxalate ester **5a** by the butan-1-ol required in the catalytic reduction method.

In conclusion, we have developed a one-pot procedure for the syntheses of (1-hydroxy-*sec*-alkyl)methylphosphinates from ketones, hexamethyldisilazane and ethyl methylphosphinate. The hydroxy group could be removed by a modified Barton radical deoxygenation procedure and the

sec-alkylmethylphosphinates dealkylated by trimethylsilyl bromide or refluxing in hydrochloric acid. This is a convenient route to a variety of *sec*-alkylmethylphosphinates, which are difficult to prepare by other methods. This method for the syntheses of *sec*-alkylmethylphosphinates seems to be quite general and can also be used for the syntheses of other phosphinic acids and phosphonic acids in good yields.[53] In addition, the developed reaction conditions are rather mild and many different functional groups can be tolerated without compromising yields.

Ketones, Et_3N, tributyltin hydride, methyl oxalyl chloride, azoisobutyronitrile (AIBN) and lithium diisopropylamide (2 M in THF) were from Fluka. Methyldichlorophosphine was from Hoechst. All other reagents were from Aldrich. Ethyl methylphosphinate **(2)**[50] was prepared by a known literature method.[51] Solvents were HPLC grade from LAB-SCAN and were dried over molecular sieves (4 Å). Column chromatography was run on Merck 9385 silica gel 60 (0.040–0.063 mm). ^{31}P NMR spectra were recorded on a Varian Unity 300 MHz spectrometer, ^1H NMR and ^{13}C NMR spectra on a Varian Unity 400 MHz spectrometer, FAB MS data were obtained using a JEOL HX 110/110 Mass Spectrometer.

Ethyl (*N*-Ethoxycarbonyl-4-hydroxypiperidin-4-yl)methylphosphinate (3b); Typical Procedure for Pudovik Addition

Amine-Catalyzed: *N*-Ethoxycarbonylpiperid-4-one (8.6 g, 50 mmol), ethyl methylphosphinate (**2**; 9.8 g, 50 mmol) and anhyd Et_3N (7.0 mL, 50 mmol) were heated under N_2 to 100°C for 2 h. The mixture was cooled to 30 °C and anhyd Et_2O (40 mL) was added with stirring. The mixture was cooled to 0°C. The colorless crystals formed were filtered, washed with anhyd Et_2O (2 x 6 mL) and dried in vacuo (Table 1).

LDA-Promoted: Ethyl methylphosphinate (**2**; 9.8 g, 50 mmol) was dissolved in anhyd THF (50 mL) under N_2 and cooled to –78°C. LDA (2 M in THF; 25 mL, 50 mmol) was added under N_2 during 15 min. The mixture was stirred 5 min at –78 °C, the ketone added in one portion and the mixture allowed to warm to r.t. The mixture was quenched by addition of sat. aq NH_4Cl solution (50 mL), the THF evaporated in vacuo and the mixture extracted with CH_2Cl_2 (2 × 50 mL). The organic phase was dried (Na_2SO_4) evaporated in vacuo and the crystallized product washed with cold Et_2O (2 × 15 mL) (Table 1).

Ethyl (1-Hydroxy-1-phenylethyl)methylphosphinate (3g); Typical Procedure for Silyl-Abramov Reaction

Ethyl methylphosphinate (**2**; 1.08 g, 10 mmol), acetophenone (1.20 g, 10 mmol) and hexamethyldisilazane were mixed under N_2 and heated to 90 °C until analysis by ^{31}P NMR spectroscopy showed complete conversion to the TMS-protected product (27 h). After cooling to r.t., MeCN (10 mL) and Et_3N•3HF (0.53 g, 4.0 mmol) were added and heated to 40 °C. After 24 h CH_2Cl_2 (100 mL) was added, the mixture washed with satd aq $NaHCO_3$ solution (30 mL), 0.1 M HCl (30 mL), and brine (50 mL). Each aqueous phase was back-extracted with CH_2Cl_2 (50 mL), and the combined organic phases were evaporated in vacuo to give **3g** as white crystals (1.54 g, 68%) (Table 1).

Ethyl (1-Propylbutyl)methylphosphinate (6d); Typical Procedure for Barton–McCombie Reaction

Ethyl (1-hydroxy-1-propylbutyl)methylphosphinate (**3d**; 1.40 g, 6.3 mmol) and 4-(dimethylamino)pyridine (1.40 g, 11.4 mmol) were dissolved in anhyd MeCN (10 mL) under N_2 and cooled to 0 °C. Methyl oxalyl chloride (1.15 g, 9.4 mmol) was added and the mixture allowed to warm to 23 °C for 2.5 h. After addition of EtOAc (120 mL) the mixture was filtered, the EtOAc phase washed with sat. aq $NaHCO_3$ solution (30 mL) and brine (30 mL), dried (Na_2SO_4) and evaporated in vacuo to give a colorless oil (1.94 g, ~100%). The oil (1.94 g, 6.3 mmol), AIBN (0.29 g, 1.6 mmol), and Bu_4SnH (1.68 g, 9.5 mmol) were dissolved in anhyd toluene (40 mL) under N_2 and heated to 90°C for 5.5 h. The solution was evaporated in vacuo, and the product was purified by flash chromatography using 8% MeOH in CH_2Cl_2 as eluent to give the pure **6d** as a colorless oil (0.81 g, 72%) (Table 2).

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