Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 877–884
Tetrahedron

Synthesis of new α or γ-functionalized hydroxymethylphosphinic acid derivatives

Henri-Jean Cristau,* Agnès Hervé and David Virieux*

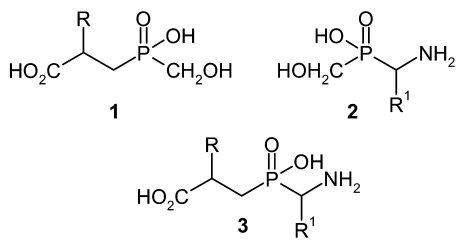
Laboratoire de Chimie Organique, UMR 5076, Ecole Nationale Supérieure de Chimie de Montpellier 8, Rue de l'Ecole Normale, 34296 Montpellier cedex 5, France

Received 14 July 2003; revised 1 October 2003; accepted 18 November 2003

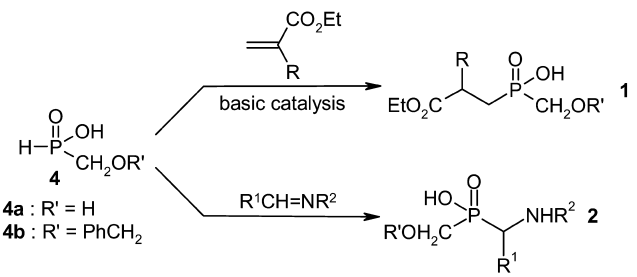
Abstract—The syntheses of new γ-ethoxycarbonyl- and α-amino-alkyl hydroxymethylphosphinic acid derivatives are described. These compounds were conveniently prepared by Michael addition or Kabachnik–Fields reaction of an original precursor, ethyl benzyloxymethyl hydrogenophosphinate, respectively to α,β-unsaturated esters using a basic activation or to imines. Selective deprotection of the alcohol function was achieved by hydrogenolysis on Pd/C, whereas lithium bromide was used to selectively cleave the phosphinate ester group. Acidic hydrolysis readily gave the free hydroxymethylphosphinic acids.

1. Introduction

The phosphonic group [$-P(O)(OH)_2$] belongs to a wide range of biologically active compounds.[1–4] But, its high ionic character limits the transmembranar transport and consequently some phosphonic acids derivatives show a very low bioavailability.[5] Searching for new biologically active phosphorus compounds, we investigated the possibility to use the hydroxymethylphosphinic group [$-P(O)(OH)(CH_2OH)$] as a substitute for the phosphonic one. This substitution should modify the physical and chemical properties of the substrates,[6] particularly their ionic character, and consequently improve their biological activity. To evaluate the potential of such replacement, we decided to synthesize new functionalized phosphinic acids of structure **1** and **2**, which can be considered as analogs of valuable inhibitors of various proteases,[7] the phosphinic pseudo-dipeptides **3**.



Currently, in the syntheses of hydroxymethylphosphinic derivatives, the hydroxymethyl group is introduced in the last step. There are only few publications dealing with the synthesis of a general precursor which could react with various functional electrophiles.[8] Herein, we describe the synthesis of compounds **1**–**2**, using a common precursor, phosphinate **4b** which is consequently added to α,β-unsaturated esters or to imines (Scheme 1).



Scheme 1.

2. Results and discussion

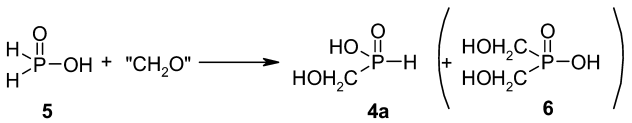
2.1. Synthesis of hydroxymethylphosphinic acid 4a

We first chose to prepare hydroxymethylphosphinic acid **4a**, as common precursor of the target compounds. Dihydrogenophosphinic acid, H_3PO_2 **5** and formaldehyde were selected as starting material.[9] Reactions were performed in various conditions using acidic activation (see Section 4). Unfortunately, reaction mixtures were generally composed by the unreacted H_3PO_2 **5**, the targeted hydroxymethylphosphinic acid **4a** and often with the di-addition product, bis(hydroxymethyl)phosphinic acid **6** as a consequence of the lack of selectivity of the reaction (Scheme 2).[9b]

In the best conditions, the use of 50% aqueous H_3PO_2 **5** with

Keywords: Phosphinic acid; Kabachnik–Fields reaction; Ester group.
* Corresponding authors. Tel.: +33-4-67-14-43-14; fax: +33-4-67-14-43-19; e-mail address: virieux@cit.enscm.fr

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.11.045



Scheme 2.

an excess (1.5 equiv.) of paraformadehyde in the presence of hydrochloric acid (1.5 equiv.) in refluxing ethanol, after 12 h, afforded the mono-adduct **4a** in 76% yield with only starting H_3PO_2 **5** as side-product. Unfortunately, all attempts to separate **4a** from **5** either by selective precipitation or by separation after chemical modification failed.

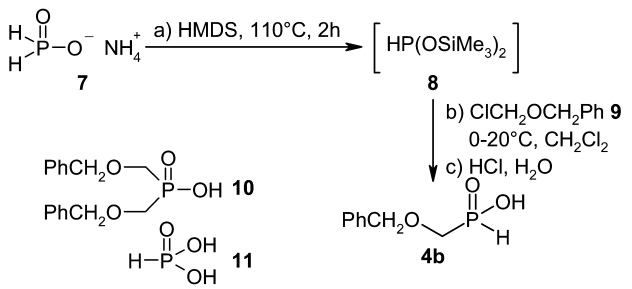
2.2. Synthesis of ethyl benzyloxymethylphosphinate 12 as precursor

Then, we turned to the synthesis of another precursor: ethyl benzyloxymethylphosphinate **12**, in which the acidic function is protected by an ester group and the hydroxymethyl substituent is protected as benzyloxymethyl group, allowing an easier purification step and avoiding retroformylation reaction which can occur in basic media.[10]

Preparation of compound **12** was achieved in two steps: synthesis of benzyloxymethylphosphinic acid **4b**, followed by its esterification.

2.3. Synthesis of benzyloxymethylphosphinic acid 4b

Phosphinic acid **4b** was prepared by a silyl-Arbuzov reaction using benzyloxymethylchloride **9** and in situ generated bis(trimethylsilyl)phosphonite **8**, formed accordingly to the literature (Scheme 3).[11] Unfortunately, besides the desired phosphinic acid **4b**, the symmetric phosphinic acid **10** was obtained as the result of a double silyl-Arbuzov reaction of **9** with phosphonite **8**.

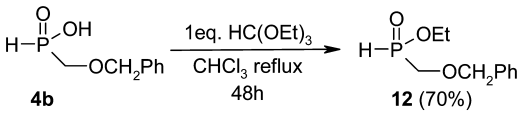


Scheme 3.

The lack of selectivity may probably be attributed to the high reactivity of the benzyloxymethyl chloride **9**. A similar observation was pointed out by Coward and Grobelny for the reaction of the phosphonite **8** with 1 equiv. of *N*-(bromomethyl)phthalimide.[12] Dihydrogenophosphinic acid **5** (10%) and hydrogenophosphonic acid **11** (9%) were also formed as by-products. The latter probably resulted from the oxidation of **8** known to be a very sensitive and pyrophoric compound.[11] Dilution of the reagent **9** in dry dichloromethane and subsequent dropwise addition to the phosphonite **8** solution did not improve the yield of **4b** with a **4b/10** ratio of 82:18. But, the use of a fourfold excess of compound **8** led to a **4b/10** ratio of 96:4, thus allowing the purification by a two-step extraction procedure. Compound **4b** was isolated in 65% yield.

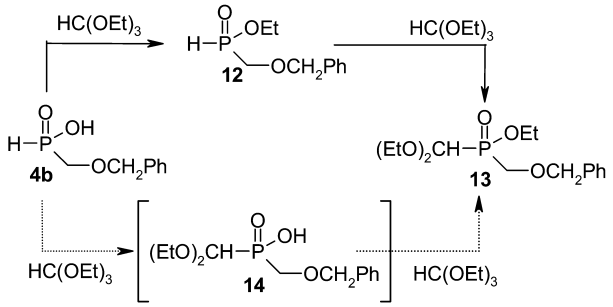
2.4. Synthesis of ethyl benzyloxymethylphosphinate 12

As a final step for the preparation of compound **12**, the esterification of acid **4b** was first accomplished with triethyl orthoformate. Indeed, trialkyl orthoformates have been extensively used to form phosphonates and phosphinates from the corresponding acids.[13] Esterification of **4b** was performed in refluxing chloroform. Thus, reaction of **4b** with 1 equiv. of triethyl orthoformate afforded after 48 h, the ester **12**, isolated in 70% yield after purification by extraction (Scheme 4).



Scheme 4.

The use of an excess of triethyl orthoformate did not improve the yield of compound **12** but lead to the formation of a major by-product exhibiting a ^{31}P signal at δ 38.37 ppm. This compound was identified by its ^{31}P, ^{1}H, ^{13}C, IR and mass spectra as ethyl (diethoxymethyl) phosphinate **13**. Its formation can be rationalized by a S_N reaction of the tricoordinated phosphorus atom of compound **12** to the central atom of triethyl orthoformate as reported by Gallagher et al.[13a] and Schwabacher et al.[13b] for the formation of methyl dimethoxymethylphosphinate in the esterification reaction of bis(hydrogeno)phosphinic acid with trimethylorthoformate. Phosphinate **13** could also be the result of the P-alkylation reaction of acid **4b** with triethyl orthoformate followed by the esterification of the intermediate acid **14**. But no trace of **14** was detected by ^{31}P NMR analysis (Scheme 5).



Scheme 5.

Kinetic monitoring of the reaction, by ^{31}P NMR was performed to determine the best conditions for the formation of phosphinate **12**. Concentrations of **4b**, **12** and **13** are plotted versus time in Figure 1. Indeed, after 16 h, the phosphinate **12** is the only detected product even with an excess of esterification reagent.

Another attempt to improve the formation of phosphinate **12** using another esterification reagent was successfully

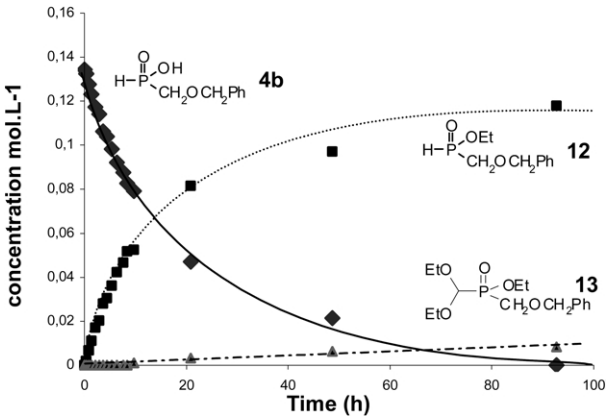
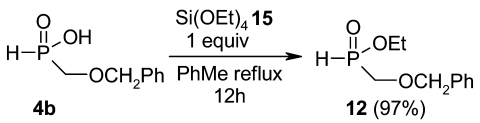


Figure 1.

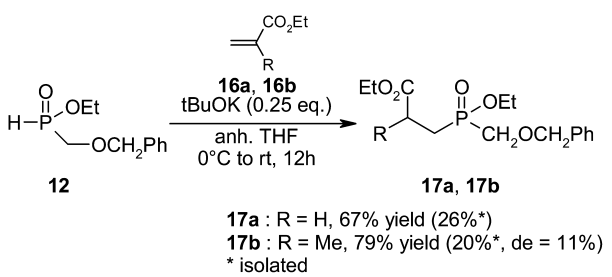
accomplished using tetraethyl orthosilicate **15**, recently employed to esterify phosphinic acids.[14] Acid **4b** was thus treated with 1 equiv. of tetraethyl orthosilicate **15** in refluxing toluene for 12 h to quantitatively afford ester **12**, isolated in 97% yield. (Scheme 6). As reported by Montchamp,[14] simple partioning of the crude product between acetonitrile and hexane is sufficient to provide almost pure phosphinate by elimination of the non-polar silicon derived impurities.



Scheme 6. Ethyl benzyloxymethylphosphinate **12** has thus been prepared in two steps and isolated in 63% overall yield (Schemes 3 and 6).

2.5. Michael addition of phosphinate 12 to α,β-unsaturated esters

Michael addition of phosphinate **12** to α,β-unsaturated esters was performed according to a method previously developed in our laboratory,[4] using a catalytic *tertio* butoxide activation (Scheme 7). Compound **12** was reacted with 1 equiv. of ethyl acrylate **16a** or ethyl methacrylate **16b** in dry THF in the presence of 0.25 equiv. of potassium *tertio*butoxide to afford the corresponding Michael products **17a** and **17b** in 69 and 79% yields, respectively. Phosphinate **17b** was formed as a mixture of two diastereoisomers resulting from the two chiral centers. Diastereoselectivity is poor, with a 11% diastereoisomeric excess. Compounds **17a** and **17b** were purified by column chromatography on silica gel and isolated, respectively in 26 and 20% yields. These low isolated yields result from the



Scheme 7.

presence in the reaction mixture of four unidentified compounds ($^{31P}\delta$=44.36, 49.48, 49.85 and 52.91 ppm in the reaction with **16a** and δ=46.60, 48.52, 48.88 and 48.91 ppm in the reaction with **16b**) which are difficult to separate from the desired Michael adducts.

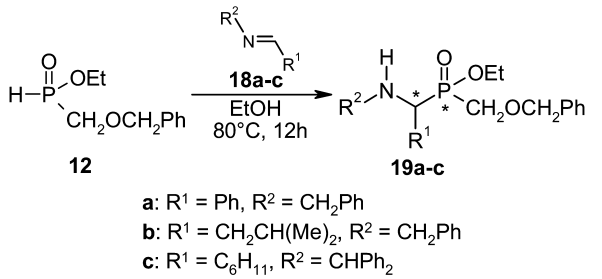
We found that the selectivity of the formation of adducts depended on the quantity of potassium *tertio*butoxide used, as shown in the reaction of **12** with ethyl methacrylate **16b** (Table 1). The use of 0.20 equiv. of potassium *tertio* butoxide afforded phosphinate **17b** as a diastereoisomeric mixture (ed=18%) in 91% yield. No side-product was detected in the reaction mixture and after neutralization, compound **17b** was isolated in 69% yield by column chromatography. However, higher amounts of *t*BuOK induce a notable decrease of the yield (Table 1).

Table 1. Influence of *t*BuOK amount on the Michael addition of phosphinate **12** to **16b**

*t*BuOK (equiv.)	Conversion (**12**) (%)	^{31}P NMR yield (**17b**) (%)	Isolated yield (**17b**) (%)	de (**17b**) (%)
0.20	100	91	69	18
0.25	100	79	20	11
0.30	100	36	—	5

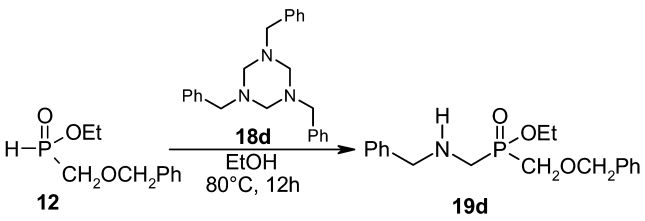
2.6. Aminoalkylation of phosphinate 12 with imines

N-Protected ethyl α-aminoalkyl-benzyloxymethyl-phosphinates **19a–c** were prepared by a Kabachnik–Fields reaction involving the addition of phosphinate **12** to the corresponding aldimines **18a–c** or to the 1,3,5-*N*-benzyl-1,3,5-hexahydrotriazine **18d**. The reaction of phosphinate **12** with 1 equiv. of imines **18a** and **18b** in refluxing ethanol afforded the expected phosphinates **19a** and **19b**, respectively in 81 and 56% yields as an equimolar mixtures of two diastereoisomers resulting from the chirality of the phosphinate group and the α-amino carbon atom (Scheme 8).



Scheme 8.

The ^{31}P NMR analysis of the crude reaction mixture showed the presence of benzyloxymethylphosphinic acid **4b** as side-product (respectively 12% and 29%). A possible explanation for the formation of the acid **4b** is a dealkylation reaction of ethyl phosphinate **12** by nucleophiles present in the reaction mixture such as amines.[15] Theses amines could thus react with phosphinate **12** by a nucleophilic attack of the nitrogen atom on the ethyl ester phosphinic group, leading to the formation of acid **4b** (Scheme 9). This hypothesis is supported by the fact that, in a control experiment, the reaction of phosphinate **12** with



Scheme 9.

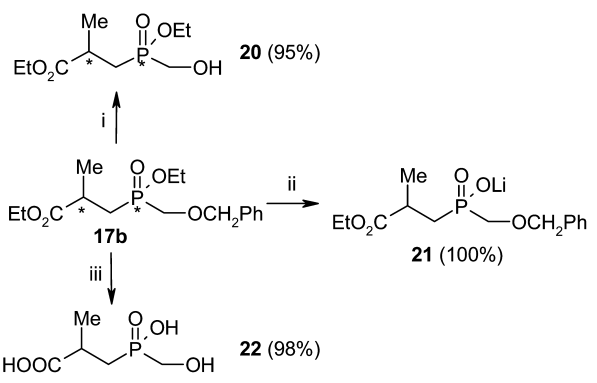
dibenzylamine resulted in the quantitative transformation of ester **12** into acid **4b**.

Consequently, the addition of a slight excess (1.2 equiv.) of imine **18a** afforded the corresponding phosphinate **19a** in 96% yield and **4b** in only 4%. This result implies that the addition reaction of phosphinate **12** to the aldimine is faster than the dealkylation reaction. Phosphinate **19a** was then purified on silica gel by column chromatography and isolated in 70% yield as a mixture of two diastereoisomers. Similar results were obtained with imines **18b** and **18c** which led to the corresponding phosphinates **19b** and **19c** which were isolated after column chromatography in 84 and 69% yields, respectively. Phosphinate **19a** constitutes a precursor of the analog of phosphonoleucine which is known to inhibit leucine aminopeptidase.[16]

Then, we applied the reaction to the 1,3,5-*N*-benzyl-1,3,5-hexahydrotriazine **18d** in order to prepare the analog of phosphonoglycine (Scheme 9).[17] Ethylphosphinate **12** was first treated with 1 equiv. of the triazine **18d** in refluxing ethanol. In contrast to aldimines **18a–c**, total disappearance of **12** in this case needed 48 h. The resulting phosphinate **19d** was formed in 50% yield, but isolated after column chromatography in only 8% yield. This low yield is due to the formation in the reaction mixture of four side-products at δ 49.20 and 49.30 ppm (23%) and at δ 48.84 and 48.94 ppm (5%). In the other hand, **4b** was formed in only 4% yield. Unfortunately, these side-products were very difficult to separate from the targeted phosphinate **19d**. Use of a 1.5 excess of triazine **18d** increased the yield to 60%, and the phosphinate **19d** was isolated in 33% yield.

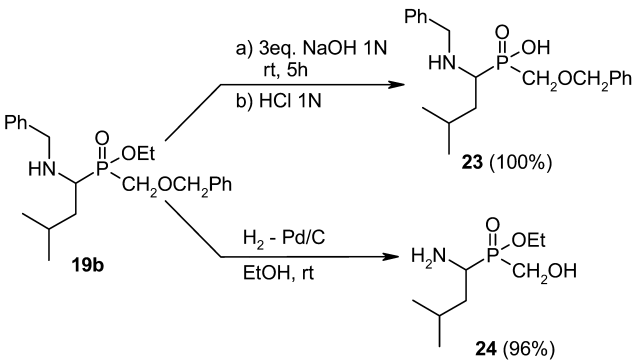
2.7. Total or selective deprotections

Total or selective deprotections have been performed on compound **17b** (Scheme 10). The benzylic group was removed by hydrogenolysis on Pd/C[18] to give the corresponding phosphinate **20** in 95% yield. Selective cleavage of the ester group was achieved by using a two fold excess of lithium bromide in refluxing acetonitrile for 5 days.[19] The corresponding salt **21** was isolated after concentration in 100% yield. Finally, compound **17b** was totally deprotected by an excess of 35% hydrochloric acid at 80 °C for 3 h, affording the phosphinic acid **22** in 98% yield.[6]



Scheme 10. *Conditions and reagents*: (i) H_2-Pd/C, EtOH, Patm, rt; (ii) LiBr (2 equiv.), MeCN, reflux, 3 days; (iii) excess 35% HCl, 80 °C, 3 h.

The same deprotection methodology can be performed on α-aminoalkylphosphinic acid (Scheme 11). The phosphinic acid function of **19b** was selectively deprotected in the presence of an excess of sodium hydroxide to afford the phosphinic acid **23** isolated in quantitative yield (Scheme 11) while total deprotection of both hydroxy and amino groups was achieved by hydrogenolysis on Pd/C leading to the phosphinate **24** isolated in 96% yield.



Scheme 11.

3. Conclusion

A new versatile and stable precursor for the introduction of hydroxymethylphosphinic group, ethyl benzyloxymethyl phosphinate **12**, has been synthesized in two steps and isolated in 65% overall yield. Subsequent reaction with various electrophiles such as α,β-unsaturated esters in the presence of catalytic amount of potassium *tertio*butoxide and imines or triazine afforded the corresponding γ-carboxy- or α-aminoalkylphosphinates. Total or selective deprotections can be performed demonstrating the compatibility and the complementarity of the various protecting groups. The synthetic sequence, described here, affords a reliable and general access to this particular class of functionalized phosphinic acids. Using the same precursor, several aryl or heteroaryl hydroxymethylphosphinic acid derivatives were prepared by palladium (0) catalyzed arylation.[20]

4. Experimental

4.1. General remarks

All reactions involving air or moisture sensitive reagents or intermediates were carried out under dry nitrogen in flame-dried glassware. Reagents and solvents were purified before use and stored under nitrogen atmosphere. All reactions were monitored by TLC (Merk, SIL, G/UV_{254}) or ^{31}P NMR. Merck silica gel (70–200 μm) was used for column

chromatography. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker Ac 200 (^{1}H at 200.13 MHz, ^{13}C at 50.32 MHz and ^{31}P at 81.01 MHz) and on a Brucker AC 250 spectrometers (^{1}H at 250.13 MHz, ^{13}C at 62.89 MHz and ^{31}P at 101.25 MHz). Chemical shifts are expressed in ppm and coupling constants in Hz. IR spectra were obtained with Perkin–Elmer 377 and Nicolet FT-IR 210 spectrometers. Mass spectra were measured with a Jeol JMS DX-300 spectrometer (positive FAB ionisation and High Resolution using glycerol-thioglycerol or *p*-nitrobenzyl alcohol matrix).

4.2. Hydroxymethylphosphinic acid 4a

Reactions conditions for the direct synthesis of hydroxymethylphosphinic acid **4a** using H_3PO_2 **5** or its ammonium salt and the different forms of formaldehyde are listed in Table 2. The best result is observed for entry 9 where **4a** is selectively obtained in 76% yield (Table 2).

4.3. Preparation of ammonium phosphinate 7

Commercially available 50% aqueous phosphinic acid (40 g, 301 mmol) was slowly added to 25% aqueous ammonia (46.6 mL, 301 mmol) at 0 °C. The mixture was allowed to reach room temperature and stirred over a period of 5 h. Removal of water was achieved under reduced pressure and followed by rigorous drying over P_2O_5 under vacuum to obtain ammonium phosphinate **7** as a white solid in 93% yield (23.3 g, 280 mmol).

4.3.1. Benzyloxymethyl-hydrogeno-phosphinic acid 4b. Ammonium phosphinate **7** (10 g, 120.4 mmol) and hexamethyldisilazane (25.6 mL, 120.4 mmol) were heated together under nitrogen at 100–110 °C until all the ammonia by-product has evolved (ca. 2 h) The mixture was then cooled to 0 °C before the addition of dry dichloromethane (100 mL). After 15 min stirring at 0 °C, a solution of benzyloxymethylchloride (4.17 mL, 30.1 mmol) in 50 mL of dry dichloromethane was added dropwise over 15 min. The resulting mixture was allowed to warm to room temperature and stirred for 12 h. Then, 18% HCl (5 mL) was slowly added and the mixture stirred for additional 15 min. The mixture was filtered and the solution was extracted with water (3×5 mL). The organic layer was dried over $MgSO_4$ before the solvent was removed under reduced pressure to afford a colourless oil (4.06 g). This oil was dissolved in water (100 mL) and extracted with ethyl acetate (3×5 mL). The aqueous layer was then continuously extracted with dichloromethane for 5 h. The resulting organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to afford benzyloxymethyl-phosphinic acid **4b** as a colourless oil in 65% yield (3.63 g, 19.52 mmol).

^{31}P NMR ($CDCl_3$): 29.40 (dt, $^{1}J_{PH}$=566.0 Hz, $^{2}J_{PH}$=7.4 Hz). ^{1}H NMR ($CDCl_3$): 3.71–3.78 (2dd, ABX system, δ_{HA}=3.73, δ_{HB}=3.77, $^{2}J_{HAHB}$=13.4 Hz, $^{2}J_{PHA}$=2.2 Hz, $^{2}J_{PHB}$=2.2 Hz, 2H, PCH_2), 4.62 (s, 2H, $PhCH_2$), 4.92 (bs, OH), 7.08 (d, $^{1}J_{PH}$=566.0 Hz, $^{3}J_{HH}$=2.2 Hz, 1H, P-H), 7.34–7.39 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): 66.51 (d, $^{1}J_{PC}$=115.4 Hz, PCH_2), 75.23 (d, $^{3}J_{PC}$=11.9 Hz, $PhCH_2$), 128.15 (s, 2CH), 128.22 (s, CH), 128.58 (s, 2CH), 136,70 (s, C). MS FAB+(NBA) *m/z*=187 (17%) $[M+H]^+$, 91 (100%) $C_7H_7^+$. HRMS calcd for $C_8H_{12}O_3P$: 187.0534, found: 187.0531.

4.3.2. Ethyl benzyloxymethyl-hydrogeno-phosphinate 12 (method 1). Triethyl orthoformate (2.2 mL, 13.20 mmol) was added to a solution of benzyloxymethylphosphinic acid **4b** (2.5 g, 13.20 mmol) in 70 mL of anhydrous chloroform. The reaction mixture was refluxed for 48 h. The conversion yield determined by ^{31}P NMR was 77 whereas, 33% of acid **4b** remained unchanged. As no evolution has been observed after additional 3 h of stirring, the reaction mixture was cooled to room temperature before addition of aqueous $KHCO_3/K_2CO_3$ (1 M). The biphasic mixture was stirred at room temperature for additional 15 min before partition of the organic and aqueous layers. The organic layer was dried over $MgSO_4$ before the solvent was removed under reduced pressure to afford the phosphinate **12** as a colourless oil in 70% yield (2.15 g, 9.30 mmol).

4.3.3. Ethyl benzyloxymethyl-hydrogeno-phosphinate 12 (method 2). Tetraethyl orthosilicate (1.8 mL, 8.26 mmol) was added to a solution of benzyloxymethylphosphinic acid **4b** (1.5 g, 8.26 mmol) in 15 mL of dry toluene. The reaction mixture was refluxed for 12 h. At this time, the ^{31}P NMR

Table 2. Synthesis of hydroxymethylphosphinic acid **4a**

Entry	Formaldehyde source	Phosphorus reagent	Conditions	Reaction mixture (%)		
				6	**4b**	**7**
1	Trioxymethylene (1 equiv.)	aq. H_3PO_2	MeOH, 7d, 20 °C, HCl (1 equiv.)	100	—	—
2	Trioxymethylene (1 equiv.)	aq. H_3PO_2	H_2O, 7d, 20 °C, HCl (1 equiv.)	98	2	—
3	Trioxymethylene (1 equiv.)	aq. H_3PO_2	MeOH, 7d, 60 °C, HCl (1 equiv.)	99	1	
4	Trioxymethylene (1 equiv.)	aq. H_3PO_2	H_2O, 7d, 60 °C, HCl (1 equiv.)	31	66	3
5	37% aq. Formaldehyde (1 equiv.)	aq. H_3PO_2	MeOH, 2.5 days, 20 °C, NH_4Cl (1 equiv.)	73	27	—
6	37% aq. Formaldehyde (1 equiv.)	aq. H_3PO_2	H_2O, 2.5 days, 20 °C, NH_4Cl (1 equiv.)	28	54	18
7	37% aq. Formaldehyde (1 equiv.)	aq. H_3PO_2	MeOH, 2.5 days, 60 °C, NH_4Cl (1 equiv.)	66	34	—
8	Paraformaldehyde (1 equiv.)	aq. H_3PO_2	EtOH, 7 days, 80 °C, HCl (1 equiv.)	46	54	—
9	Paraformaldehyde (1.5 equiv.)	aq. H_3PO_2	EtOH, 7 days, 80 °C, HCl (1.5 equiv.)	24	76	—
10	Paraformaldehyde (1 equiv.)	aq. H_3PO_2	H_2O, 7 days, 80 °C, HCl (1 equiv.)	6	77	17
11	Gazeous Formaldehyde	anh. H_3PO_2	EtOH, 7 h, 80 °C, PTSA (2 equiv.)	46	54	—
12	Paraformaldehyde (1 equiv.)[a]	aq. H_3PO_2	EtOH, 2 days, 110 °C, HCl (1 equiv.)	15	71	14
13	Paraformaldehyde (1.2 equiv.)[a]	aq. H_3PO_2	EtOH, 2 days, 110 °C, HCl (1.2 equiv.)	12	83	5
14	Paraformaldehyde (1.5 equiv.)[a]	aq. H_3PO_2	EtOH, 2 days, 110 °C, HCl (1.5 equiv.)	5	83	12

[a] Reactions were performed in a caped thick-wall tube.

analysis showed that all the acid **4b** had quantitatively been transformed to the phosphinate **12**. The mixture was then allowed to cool to room temperature and the solvent was removed under reduced pressure. According to Montchamp procedure, the oily residue was purified by partition between CH_3CN and hexane. The hexane layer contained the non-polar silicon-derived by-products, while the polar phosphinate remained in the CH_3CN layer. This latter was concentrated under reduced pressure to afford phosphinate **12** as a colourless oil in 97% yield (1.72 g, 8.03 mmol). Further purification can be accomplished using chromatography on silica gel with dichloromeyhane as eluent.

^{31}P NMR ($CDCl_3$): 32.22 (dquint., $^1J_{PH}$=552.5 Hz, $^2J_{PH}$=8.7 Hz). ^1H NMR ($CDCl_3$): 1.33 (t, $^3J_{H-H}$=7.1 Hz, 3H CH_3), 3.73–3.81 (2 dd, ABX system, δ_{HA}=3.76, δ_{HB}=3.80, $^2J_{HAHB}$=−13.8 Hz, $^2J_{PHA}$=4.2 Hz, $^2J_{PHB}$=10.1 Hz, 2H, PCH_2), 4.08–4.19 (m, 2H, $POCH_2$), 4.58 (s, 2H, $PhCH_2$), 7.08 (d, $^1J_{PH}$=552.5 Hz, $^3J_{HH}$=2.3 Hz, 1H, PH), 7.30–7.34 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): 16.32 (d, $^3J_{PC}$= 6.0 Hz, CH_3), 62.83 (d, $^2J_{PC}$=7.0 Hz, $POCH_2$), 65.82 (d, $^1J_{PC}$=114.2 Hz, PCH_2), 75.28 (d, $^3J_{PC}$=11.9 Hz, $PhCH_2$), 128.13 (s, 2CH), 128.28 (s, CH), 128.57 (s, 2CH), 136.56 (s, C). IR (NaCl): 1200 (PO); 1125 (COC); 1100, 1050 (POC). MS FAB+(NBA) *m*/*z*=215 (21%) $[M+H]^+$; 91 (100%) $C_7H_7^+$. HRMS calcd for $C_{10}H_{16}O_3P$: 251.0837, found: 215.0815.

4.4. General procedure for preparation of phosphinates 17. Synthesis of 17b

A solution of phosphinate **12** (1 g, 4.67 mmol) in 8 mL of anhydrous THF was added dropwise to precooled (0 °C, ice bath) suspension of potassium *tertio*butoxide (105 mg, 0.93 mmol) in 10 mL of anhydrous THF. The resulting mixture was stirred at 0 °C for 15 min. After this time, ethyl methacrylate (0.57 mL, 4.67 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred under nitrogen for 12 h. At this time, ^{31}P NMR analysis of the mixture showed that all the phosphinate **12** had reacted and that phosphinate **17b** had been formed as a mixture of two diastereoisomers in 91% yield. The reaction mixture was then neutralized by addition of aqueous HCl (1N)and diluted with 20 mL of water. The solution was extracted with ethyl acetate (3×30 mL). The organic layer was first washed with brine and then dried over $MgSO_4$. Evaporation of the solvent afforded the crude phosphinate **17b** as a yellow oil which was purified by flash chromatography on silica gel (gradient for elution: from petroleum ether/ethyl acetate, 80:20 to ethyl acetate 100%) to afford the pure phosphinate **17b** as a mixture of two diastereoisomers (59:41) in 69% yield (yellow oil, 1.05 mg, 3.22 mmol).

4.4.1. Ethyl (2-ethoxycarbonyl-1-ethyl)-(benzyloxymethyl)-phosphinate 17a. ^{31}P NMR ($CDCl_3$): 49.88. ^1H NMR ($CDCl_3$): 1.20 (t, $^3J_{HH}$=6.3, 3H, CH_3), 1.27 (t, $^3J_{HH}$= 7.0, 3H, CH_3), 1.24–1.30 (m, 1H, CH_2), 2.02–2.15 (m, 1H, CH_2), 3.67–3.70 (m, 2H, CH_2), 3.91–4.55 (m, 6H, $3CH_2$), 4.55 (s, 2H, CH_2), 7.25–7.33 (m, 5H, CH). ^{13}C NMR ($CDCl_3$): 14.13 (s, CH_3), 16.53 (d, $^3J_{PC}$=5.9 Hz, CH_3), 21.73 (d, $^1J_{PC}$=95.3 Hz, CH_2), 26.,32 (d, $^3J_{PC}$=2.6 Hz, CH_2), 60.86 (s, CH_2), 60.91 (d, $^2J_{PC}$=4.8 Hz, $POCH_2$), 64.92 (d, $^1J_{PC}$=110.2 Hz, PCH_2O), 75.17 (d, $^3J_{PC}$=12.6 Hz, CH_2), 128.05 (CH), 128.,11 (s, CH), 128.51 (s, CH), 136.,67 (s, C), 172.15 (d, $^3J_{PC}$=16.4 Hz, CO). IR (NaCl): 1745 (C═O), 1220 (PO); 1100, 1080, 1040 (O–C). MS FAB+ (NBA) *m*/*z*=315 (100%) $[M+H]^+$, 91 (86%) $C_7H_7^+$.

4.4.2. Ethyl (2-ethoxycarbonyl-1-propyl)-(benzyloxymethyl)-phosphinate 17b. ^{31}P NMR ($CDCl_3$): 48.82 (59%) and 49.87(41%). ^1H NMR ($CDCl_3$): 1.04–1.16 (m, 9H, CH_3, $2CH_3$), 1.68–1.71 (m, 1H, CH), 2.14–2.23 (m, 1H, CH), 2.73–2. 75 (m, 1H, H), 3.54–3.59 (m, 2H, CH_2), 3.84–4.00 (m, 4H, $2CH_2$), 4.42–4.45 (m, 2H, CH_2), 7.11–7.28 (5H, CH). ^{13}C NMR ($CDCl_3$): 16.47 (s, CH_3), 18,90 (d, $^3J_{PC}$=6.0 Hz, CH_3), 21.02 (d, $^3J_{PC}$=6.0 Hz, CH_3), 21.46 (d, $^3J_{PC}$=6.0 Hz, CH_3), 32.13 (d, $^1J_{PC}$=93.8 Hz, CH_2), 32.,22 (d, $^1J_{PC}$=93.8 Hz, CH_2), 35.93 (d, $^2J_{PC}$=3.3 Hz, CH), 35.96 (d, $^2J_{PC}$=2.7 Hz, CH), 63.11 (s, CH_2), 63.,24 (d, $^2J_{PC}$=4.9 Hz, CH_2), 67.65 (d, $^1J_{PC}$=109.8 Hz, CH_2), 67,85 (d, $^1J_{PC}$=109.4 Hz, CH_2), 77.44 (d, $^3J_{PC}$=12.6 Hz, CH_2), 77.48 (d, $^3J_{PC}$=12.6 Hz, CH_2), 130.41, 130.47, 130.49, 130.86: 6-CH, 139.21, 139.29, 177.63, 177.46 (4C). IR (NaCl): 1740 (C═O); 1220 (PO); 1100, 1040 (OC). MS FAB+(NBA) *m*/*z*=329 (100%) $[M+H]^+$, 91 (93%) $C_7H_7^+$.

4.5. General procedure for preparation of phosphinates 19a–d

In a typical procedure, a solution of imine or hexahydrotriazine **18a–d** (1.2 equiv., 1 mol L^{-1}) in anhydrous ethanol is added dropwise to a solution of phosphinate **12** (1 equiv., 0.2 mol L^{-1}) in anhydrous ethanol. The mixture is refluxed under nitrogen until the complete consumption of starting material **12** (generally in 12 h; excepted for **19d**; 48 h were needed). The reaction mixture is then concentrated and chromatographied on silica gel (gradient of elution: from petroleum ether/ethyl acetate, 90:10 to ethyl acetate 100%) to afford the phosphinate **19a–d**.

4.5.1. Ethyl (*N*-benzylamino-phenyl-methyl)-benzyloxymethyl phosphinate 19a. ^{31}P NMR ($CDCl_3$): 45.42 (s, 47%), 46.10 (s, 53%). ^1H NMR ($CDCl_3$): 1.08, 1.31 (2 t, $^3J_{PH}$=7.0, 7.0 Hz, 3H, CH_3), 3.20 (bs, NH), 3.42–4.21 (m, 7H, CH_2, CH_2, CH, CH_2), 4.45, 4.57 (2s, 2H, PCH_2), 7.26–7.40 (m, 15H, Ph). ^{13}C NMR ($CDCl_3$): 16.40, 16.73 (2d, $^3J_{PC}$=5.2, 5.6 Hz, CH_3), 51.17, 51.31 (2d, $^3J_{PC}$=14.9, 16.7 Hz, CH_2), 58.43, 59.99 (2d, $^1J_{PC}$=104.2, 100.1 Hz, CH), 61.70, 62.31 (2d, $^2J_{PC}$=7.1, 7.4 Hz, CH_2), 63.94, 64.15 (2d, $^1J_{PC}$=111.3, 111.0 Hz, CH_2), 74.92, 75.34 (2d, $^3J_{PC}$= 15.1, 15.2 Hz, CH_2), 127–128,93 (Ph), 135,13, 135,20 (2d, $^2J_{PC}$=8.2, 8.6 Hz, C), 136.84, 137.02 (2s, C), 139.30, 139.34 (2s, C). MS FAB+(NBA) *m*/*z*=410 (5%) $[M+H]^+$, 196 (16%) $[(PhCH_2N(H)(Ph)CH]^+$, 91 (100%) $C_7H_7^+$. IR (NaCl): 1220 (PO), 1110 (POC). HRMS calcd for $C_{24}H_{29}O_3$: 410.1885, found: 410.1870.

4.5.2. Ethyl 1-(1-*N*-benzylamino-3-methyl-butyl)-benzyloxy-methyl phosphinate 19b. ^{31}P NMR ($CDCl_3$): 51.29 (s, 52%), 51.56 (s, 48%). ^1H NMR ($CDCl_3$): 0.77–0.95 (m, 3H, CH_3), 1.32–1.37 (m, 3H, CH_3), 2.00–2.04 (m, 2H, CH_2), 3.15 (bs, NH), 3.85–4.15 (m, 8H, $3CH_2$, 2CH), 5.26–5.30 (m, 2H, CH_2), 7.25–7.63 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$): 16.66, 16.76 (2d, $^3J_{PC}$=5.6, 5.2 Hz, CH_3), 21.47 (d, $^3J_{PC}$= 23.1 Hz, CH), 23.43 (d, $^4J_{PC}$=10.4 Hz, CH_3), 24.43, 24.68

(2d, $^4J_{PC}$=11.2, 10.0 Hz, CH_3), 37.68, 38.15 (2d, $^2J_{PC}$=2.2, 4.1 Hz, CH_2), 51.87 (d, $^1J_{PC}$=105.7 Hz, ^{11}CH), 52.39, 52.47 (2d, $^3J_{PC}$=6.6, 3.7 Hz, CH_2), 52.60 (d, $^1J_{PC}$=99.4 Hz, CH), 61.16, 61.19 (2d, $^2J_{PC}$=7.4, 7.8 Hz, CH_2), 63.49, 64.06 (2d, $^1J_{PC}$=104.2, 100.9 Hz, CH_2), 75.25, 75.31 (d, $^3J_{PC}$= 12.3, 12.3 Hz, CH_2), 127.16, 127.19, 127.22, 127.44, 127.69, 128.00, 128.06, 127.06, 127.08, 128.13, 128.15, 128.19, 128.30, 128.38, 128.45, 128.50 (CH_{Ar}), 136.81, 136.85 (2s, C), 140.06, 140.14 (2s, C). MS FAB+(NBA) *m/z*=390 (18%) $[M+H]^+$, 178 (100%) $[(PhCH_2N(H))(Me_2CHCH_2)]CH^+$, 91 (100%) $C_7H_7^+$, 77 (10%) Ph^+. IR (NaCl): 2990, 1240, 1220 (PO), 1110 (POC). HRMS calcd for $C_{22}H_{33}O_3NP$: 390.2207, found 390.2198.

4.5.3. Ethyl benzyloxymethyl-1-(*N*-diphenylmethyl-amino)-1-cyclohexyl-methyl phosphinate 19c. ^{31}P NMR ($CDCl_3$): 50.72 (s, 49%), 51.42 (s, 51%). ^1H NMR ($CDCl_3$): 1.17–1.42 (m, 10H), 1.33–1.40 (2t, $^3J_{HH}$=7.1, 7.2 Hz, 3H, CH_3), 2.23 (bs, 1H, CH), 2.89, 2.93 ppm (2 bs, 1H, NH), 3.78–3.82 (m, 2H, CH_2), 4.00–4.66 (m, 4H, $2CH_2$), 5.20, 5.28 (2 bs, 1H, CH), 7.20–7.40 (m, 15H, Ph). ^{13}C NMR ($CDCl_3$): 16.66, 16.89 (2d, $^3J_{PC}$=5.2, 5.2 Hz, CH_3), 26.18, 26.28, 26.50, 26.67, 26.86, 26.93, 28.11, 28.89, 28.93, 31.37, 31.57, 31.62 ($5CH_2$), 38.39, 38.73 (2d, $^2J_{PC}$=6.3, 6.7 Hz, CH), 56.81, 57.07 (2d, $^1J_{PC}$=99.5, 91.5 Hz, CH), 60.63, 60.78 (2d, $^2J_{PC}$=6.1, 6.3 Hz, CH_2), 65.05, 65.08 (2d, $^1J_{PC}$=101.9, 97.1 Hz, CH_2), 65.44, 65.74 (2d, $^3J_{PC}$=8.2, 11.9 Hz, CH), 75.17, 75.26 (2d, $^3J_{PC}$=11.9, 12.6 Hz, CH_2), 127.16, 127.19, 127.22, 127.44, 127.69, 128.00, 128.06, 128.12, 128.29, 128.34, 128.44, 128.50 (CH_{Ar}), 136.81, 136.88 (2s, C), 143.26, 143.49 (2s, C), 143.59, 143.83 (C). MS FAB+(NBA) *m/z*=492 (5%) $[M+H]^+$, 278 (33%) $[(Ph_2CHN(H))(Cy)]CH^+$, 167 (100%) $C_7H_7^+$. IR (NaCl): 2950, 2870, 1220 (PO); 1105 (POC). MS HR (NBA): HRMS calcd for $C_{24}H_{29}NO_3P$: 410.0385, found 410.0368.

4.5.4. Ethyl 1-(*N*-benzylaminomethyl)-benzyloxymethyl phosphinate 19d. ^{31}P NMR ($CDCl_3$): 48.40 (s). ^1H NMR ($CDCl_3$): 1.34 (t, $^3J_{HH}$=7.0 Hz, 3H, CH_3), 2.15 (bs, NH), 3.61–3.67 (dd, 2H, PCH_2N), 3.76–3.93 (m, 4H, PCH_2, $PhCH_2N$), 4.07–4,66 (m, 2H, $POCH_2$), 4.61 (s, 2H, $PhCH_2O$), 7.27–7.37 (m, 10H, 2Ph). ^{13}C NMR ($CDCl_3$): 16.64 (d, $^3J_{PC}$=5.2 Hz, CH_3), 44.32 (d, $^1J_{PC}$=105.7 Hz, PCH_2N), 54.97 (d, $^3J_{PC}$=15.3 Hz, $PhCH_2N$), 63.99 (d, $^1J_{PC}$=109.8 Hz, PCH_2O), 61.33 (d, $^2J_{PC}$=7.1 Hz, $POCH_2$), 75.25 (d, $^3J_{PC}$=12.3 Hz, $PhCH_2O$), 127.25 (s, CH), 128.08 (s, CH), 128.15 (s, CH), 128.28 (s, CH), 128.45 (s, CH), 136.87 (s, C), 139.13 (s, C). MS FAB+(NBA) *m/z*= 334 (5%) $[M+H]^+$, 120 (30%) $PhCH_2N(H)CH_2^+$,91 (100%) $C_7H_7^+$. MS HR (NBA): HRMS calcd for $C_{18}H_{25}NO_3P$: 334.1572, found 334.1563.

4.5.5. Ethyl (2-ethoxycarbonyl-1-propyl)-(hydroxy-methyl)-phosphinate 20, hygrogenolysis of 17b. Pd/C 10% (212 mg, 0.20 mmol) was added to a solution of phosphinate **17b** (330 mg, 1 mmol) in 10 mL of absolute ethanol. The mixture was placed under hydrogen at atmospheric pressure and room temperature. After consumption of the required volume of nitrogen, the mixture was filtered on celite and the filtrate was concentrated under reduced pressure to afford phosphinate **20** as a yellow oil in 95% yield (227 mg, 0.95 mmol).

^{31}P NMR ($CDCl_3$): 52.22 (59%), 52.85 (41%). ^1H NMR ($CDCl_3$): 1.15–1.25 (m, 9H, $3CH_3$), 1.67–1.89 and 2.15–2.37 (m, 2H, CH_2), 2.80–2.86 (m, 2H, CH), 3.77–3.78 (m, 2H, CH_2), 4.01–4.11 (m, 4H, $2CH_2$), 4.79 (bs, OH). ^{13}C NMR ($CDCl_3$): 14.02 (s, CH_3), 16.47 (d, $^3J_{PC}$=5.6 Hz, CH_3), 19.02, 19.13 (2d, $^3J_{PC}$=8.9, 9.3 Hz, CH_3), 29.15, 29.20 (2d, $^1J_{PC}$=89.7, 89.9 Hz, CH_2), 33.68 (d, $^2J_{PC}$= 3.3 Hz, CH), 58.65, 59.14 (2d, $^1J_{PC}$=106.1, 106.1 Hz, CH_2), 60.80 (s, CH_2), 61.01, 61.14 (2d, $^2J_{PC}$=13.0, 13.0 Hz, CH_2), 175.38, 175.51 (2d, $^3J_{PC}$=8.9, 8.9 Hz, C). IR (NaCl): 3390 (OH); 1730 (C=O); 1210, 1180 (PO); 1030 (OC). MS FAB+(NBA) *m/z*=239 (100%), $[M+H]^+$; 211 (8%), $[M+H-Et]^+$.

4.5.6. Lithium (2-ethoxycarbonyl-1-propyl)-(benzyloxy-methyl)-phosphinate 21. Lithium bromide (81 mg, 0.92 mmol) was added to a solution of phosphinate **17b** (150 mg, 0.46 mmol) in 5 mL of CH_3CN. The reaction mixture was refluxed for 5 days and the solvent is evaporated to quantitatively afford compound **21** (141 mg, 0.46 mmol) as a yellow oil.

^{31}P NMR (D_2O): 51.61. ^{13}C NMR (D_2O): 13.7 (s, C), 19.05 (d, $^3J_{PC}$=8.1 Hz, CH_3), 32.31 (d, $^1J_{PC}$=91.3 Hz, CH_2), 34.89 (d, $^2J_{PC}$=23.0 Hz, CH), 62.34 (s, CH_2), 68.38 (d, $^1J_{PC}$=109.7 Hz, CH_2), 75.13 (d, $^3J_{PC}$=11.5 Hz, CH_2), 128.72, 128.93, 129.10 (s, 5CH), 137.57 (s, C), 185.35 (d, $^4J_{PC}$=9.8 Hz, C). IR (NaCl): 3300 (OH); 1750 (C=O); 1225 (PO); 1105 (OC).

4.5.7. (2-Carboxy-1-propyl)-(hydroxymethyl)-phosphinic acid 22. Phosphinate **17b** (160 mg, 0.49 mmol) was stirred with 35% aqueous HCl (0.5 mL, 15 equiv.) at 80 °C for 5 h. Neutralisation with 2N aqueous NaOH followed by evaporation of the solvent and drying over P_4O_{10} afforded acid **22** in 98% yield (87 mg, 0.48 mmol).

^{31}P NMR (D_2O): 40.88. ^1H NMR (D_2O): 1.61 (br s, 3H, CH_3), 1.85–2.08 (m, 1H, CH), 2.29–2.48 (m, H, CH), 2.85–3.42 (m, 1H, CH), 4.00 (br s, OH), 10.16 (bs, OH). ^{13}C NMR (D_2O): 21.21 (d, $^3J_{PC}$=7.4 Hz, CH_3), 38.44 (d, J_{PC}=3.2 Hz, CH), 47.61 (d, $^1J_{PC}$=91.91 Hz, CH_2), 48.68 (d, $^1J_{PC}$=94.5 Hz, CH_2), 182.33 (d, $^3J_{PC}$=7.8 Hz, C). IR (NaCl): 3350 (OH); 1710 (C=O); 1225 (PO). MS FAB+ (NBA) *m/z*=183 (100%) $[M+H]^+$.

4.5.8. 1-(1-*N*-Benzylamino-3-methyl-butyl)-benzyloxy-methyl phosphinic acid 23. Same procedure as described for 17b. ^{31}P NMR (D_2O): 39.06 (s). ^1H NMR (D_2O): 1.01–1.35 (m, 6H, CH_3), 1.63–1.97 (m, 2H, CH_2), 3.21 (bs, NH), 3.82–4.12 (m, 5H, CH, $2CH_2$), 4.61 (s, 2H, CH_2) 7.26–7.38 (10H, Ph), 8.2 (bs, OH). ^{13}C NMR (D_2O): 21.41 (s, CH_3), 22.15 (s, CH_3), 24.78 (d, $^3J_{PC}$=7.1 Hz, CH), 35.53 (s, CH_2), 49.76 (d, $^1J_{PC}$=92.6 Hz, CH_2), 50.27 (s, CH_2), 65.72 (d, $^1J_{PC}$=118.0 Hz, CH_2), 75.48 (d, $^3J_{PC}$=13.4 Hz, CH_2), 128.18, 128.36, 128.47, 129.04, 129.49, 130.89 (s, CH_{Ar}), 130.03 (s, ^3C), 136.35 (s, ^{19}C). MS FAB+(NBA) *m/z*=362 (21%) $[M+H]^+$, 178 (100%) $PhCH_2N(Me_2CH CH_2)CH^+$, 91 (100%) $C_7H_7^+$, 77 (5%) Ph^+. IR (NaCl) 3320 (OH), 1225 (PO), 1105 (POC). MS HR (NBA); HRMS calcd for $C_{20}H_{28}O_3NP$: 362.1513, found 362.1542.

4.5.9. Ethyl 1-(1-amino-3-methyl-butyl)-hydroxymethyl phosphinate 24. A solution of **19** (140 mg, 0,36 mmol, 1 equiv.) in 5 mL of ethanol was added to a solution of sodium hydroxide (1 N, 3 equiv.). The reaction mixture was stirred 5 h at room temperature and was neutralized by the addition of 1 N hydrochloric acid. After filtration and concentration, 130 mg of a yellowish oil were recovered (100% yield, 0.36 mmol).

^{31}P NMR ($CDCl_3$): 47.94 (s, 51%), 49.30 (s, 49%). ^{1}H NMR ($CDCl_3$): 0.83–0.91 (m, 6H, $2CH_3$), 1.23–1.30 (m, 3H, CH_3), 1.29 (bs, NH_2), 1.92–1.98 (m, 2H, CH_2), 3.29–3.51 (m, 1H, CH) 3.85–4.26 (m, 5H, $2CH_2$, CH), 5.52 (bs, OH). ^{13}C NMR ($CDCl_3$): 16.50 (d, $^{3}J_{PC}$=4.8 Hz, CH_3), 21.09 (d, $^{4}J_{PC}$=6.3 Hz, CH_3), 23.17 (d, $^{4}J_{PC}$=3.72 Hz, CH_3), 24.09 ppm (d, $^{3}J_{PC}$=9.3 Hz, CH), 37.27 (2d, $^{2}J_{PC}$=1.9, 2.2 Hz, CH_2), 45.73, 47.61 (2d, $^{1}J_{PC}$=97.9, 90.8 Hz), 56.61, 56.99 (d, $^{1}J_{PC}$=103.8, 101.4 Hz, CH_2), 62.18 (d, $^{2}J_{PC}$= 117.0 Hz, CH_2). MS FAB+(NBA) m/z=210 (51%) $[M+H]^+$, 86 (100%) $H_2N(Me_2CHCH_2)CH^+$. IR (NaCl) 3310 (OH), 1230 (PO), 1115 (POC). HRMS calcd for $C_8H_{21}O_3NP$ 210.1263, found 210,1259.

References and notes

1. Fields, S. C. *Tetrahedron* **1999**, *55*, 12237–12273.
2. Kafarski, P.; Lejczak, B.; Masterlerz, P. *Phosphonopeptides—synthesis and biological activity Beitr, Wirkstofforsch*, 1985; Vol. 2.
3. Kukhar, V. P.; Hudson, H. R. *Aminophosphonic and aminophosphinic acids: chemistry and biological*; Wiley: New York, 2000.
4. Cristau, H.-J.; Coulombeau, A.; Genevois-Borella, A.; Sanchez, F.; Pirat, J.-L. *J. Organomet. Chem.* **2002**, *643–645*, 381–457.
5. Sietsema, W. K.; Ebetino, F. H. *Exp. Opin. Invest. Drugs* **1994**, *3*, 1255–1276.
6. Cristau, H.-J.; Brahic, C.; Pirat, J.-L. *Tetrahedron* **2001**, *57*, 9149–9156.
7. (a) Baylis, K.; Campbell, C. D.; Dingwall, J. D. *J. Chem. Soc., Perkin Trans 1* **1984**, 2845–2853. (b) Morgan, B. P.; Scholtz, M. C.; Ballinger, M. D.; Zipkin, I. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1991**, *113*, 297–307. (c) Parson, W. H.; Patchett, A. A.; Bull, H. G.; Schoen, W. R.; Taub, D.; Davidson, J.; Combs, P. L.; Springer, J. P.; Gadebusch, H.; Weissberger, B.; Valiant, M. E.; Mellin, T. N.; Busch, R. D. *J. Med. Chem.* **1988**, *31*, 1772–1778. (d) Grobelny, D.; Wrondak, E. W.; Galardy, R. E.; Oroszlan, S. *Biochem. Biophys. Res. Commun.* **1990**, *169*, 1111–1116.
8. (a) Rosenthal, A. F.; Gringauz, A.; Vargas, L. A. *J. Chem. Soc. Chem. Commun.* **1976**, 384–385. (b) Kapura, A.; Shermergorn, I. M. *J. Gen. Chem. USSR* **1989**, *59*, 1137–1142. (c) Maier, L. *Phosphorus Sulfur* **1981**, *11*, 139–148. (d) Prishchenko, A. A.; Livantsov, M. V.; Boganova, N. V.; Lutsenko, I. F. *J. Gen. Chem. USSR* **1989**, *59*, 2133–2134. (e) Froestl, W.; Mickel, S. J.; Hall, R. G.; Sprecher, G.; von, G.; Strub, D.; et al. *J. Med. Chem.* **1995**, *38*, 3297–3312. (f) Reck, F.; Marmor, S.; Fisher, S.; Wuonola, M. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1451–1454.
9. (a) Ville, M. *J. Ann. Chim. (Paris, Fr.)* **1891**, *23*, 289–362. (b) Mollier, H.; Vincens, M.; Vidal, M.; Pasqualini, R.; Duet, M. *Bull. Soc. Chim. Fr.* **1991**, 787–795. (c) Nazarov, Yu. V.; Muslinkin, A. A. *Russ. J. Appl. Chem.* **2000**, *73*, 1043–1047.
10. (a) Baylis, E. K. *Tetrahedron Lett.* **1995**, *36*, 9389–9392. (b) Cristau, H.-J.; Virieux, D. *Tetrahedron Lett.* **1999**, *40*, 703–706.
11. (a) Boyd, A. C.; Regan, *Tetrahedron Lett.* **1992**, *33*, 813–816. (b) Boyd, E. A.; Regan, A. C.; James, K. *Tetrahedron Lett.* **1994**, *34*, 4223–4226. (c) Chen, S.; Cowards, J. K. *J. Org. Chem.* **1998**, *63*, 502–509.
12. Chen, S.; Coward, J. K. J. *Org. Chem.* **1998**, *63*, 502–509.
13. (a) Fitch, S. J. *J. Am. Chem. Soc.* **1967**, *86*, 61–64. (b) Gallagher, M. J.; Honegger, H. *Aust. J. Chem.* **1980**, *33*, 287–294. (c) Schwabacher, W.; Stefanescu, A. D. *Tetrahedron Lett.* **1996**, *37*, 425–428.
14. (a) Montchamp, J.-L.; Dumond, Y. R. *J. Am. Chem. Soc.* **2001**, *123*, 510–511. (b) Dumond, Y. R.; Baker, R. L.; Montchamp, J.-L. *Org. Lett.* **2000**, *2*, 3341–3344.
15. (a) Maier, L. *Phosphorus, Sulfur Silicon* **1991**, *62*, 29–34. (b) Fields, E. K. *J. Am. Chem. Soc.* **1952**, *74*, 1528–1531.
16. (a) Giannousis, P.; Bartlett, P. A. *J. Med. Chem.* **1987**, *30*, 1603–1615. (b) Lejczak, B.; Karfarski, P.; Zymunt, J. *Biochemistry* **1989**, *28*, 3549.
17. Franz, J. E. Ger. Offen, 2 152826, 1972, *Chem. Abstr.*, **1972**, *77*, 165059k..
18. (a) Hartung, W. H.; Simonoff, R.; Rorer, W. R. *Organic reactions*; Wiley: London, 1953; Vol. VII. pp 263–326.

(b) Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746–1757.

19. Breuer, E.; Mahajna, M. *Heteroat. Chem.* **1992**, *3*, 251.
20. Cristau, H. J.; Hervé, A.; Virieux, D. *Synthesis* **2003**, in press.