Tetrahedron 65 (2009) 7794–7800

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Development of a one-pot method for the homologation of aldehydes to carboxylic acids

James McNulty *, Priyabrata Das

Department of Chemistry, McMaster University, 1280 Main Street West, Hamilton, Ontario L8S 4M1, Canada

ARTICLE INFO

Article history:
Received 29 April 2009
Received in revised form 2 July 2009
Accepted 10 July 2009
Available online 16 July 2009

ABSTRACT

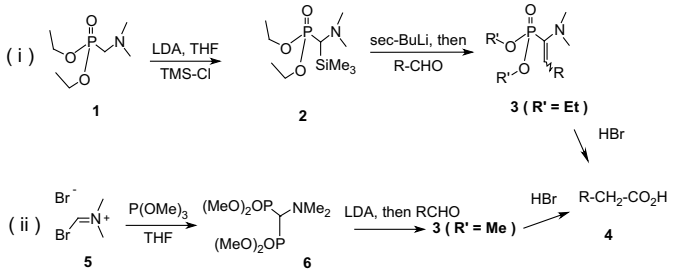
A highly efficient method is described for the one-carbon homologation of aldehydes to carboxylic acid derivatives employing the reaction of a 1,1-bis-dimethylphosphonate derivative with the aldehyde and controlled acid hydrolysis of the derived α-phosphonoenamine intermediate.

1. Introduction

Carbonyl-containing compounds occupy a central role in organic synthesis by virtue of their participation in a large repertoire of predictable and controllable chemistry. Carbonyl homologation strategies are of great importance in the synthesis of reactants and conversion of the products of reactions (aldol adducts, alkylkation or Michael addition products) to an expansive array of useful intermediates. As a particular example, phenylacetic acid derivatives are of great interest in view of the wide range of biological activity displayed by many[1] as well as their use as synthetic intermediates.[2] Currently, industrial production of such derivatives requires the synthesis of a benzyl chloride, which is converted to the nitrile and subsequently hydrolyzed. The method requires several steps and is noted to suffer from considerable drawbacks.[3] Direct methods for the synthesis of phenylacetic acids through the homologation of readily available aromatic aldehydes is thus an area of great interest. The conversion of aliphatic aldehydes to their one-carbon homologated acids is also of interest and has proven to be more challenging.

Several methods have been developed to achieve the aldehyde to homologated carboxylic acid transformation, usually requiring two or three steps.[4] The most efficient method to date is the benzotriazole method of Katritzky et al. employing a Peterson reaction that allowed for the one-pot interconversion of a range of aldehydes to homologated carboxylic acids in 45–57% yield.[4f] Most other methods are multistep, employ reagents that are not readily available or suffer from harsh conditions[4] and resulting in poor to moderate overall yields (typically 35–60%). As a result, there is still a need to develop an operationally simple and efficient synthetic procedure using readily available reagents for this desirable transformation, ideally in a single step.

Gross and Costisella[4b] and Degenhardt[6a] reported methods involving the intermediacy of α-phosphonoenamines **3** as a route for this homologation reaction using the anion derived from the bis-diethylphosphonate ester of **6**, Scheme 1. We recently reported[4o] an improved method that utilized a Peterson reaction of the α-trimethylsilyl derivative **2** in accord with previous studies by Dufrechou et al.[6b] (Scheme 1, path i). The major obstacle toward application of this biphosphonate route to carbonyl homologation is the lack of an efficient method for the generation of phosphonoenamines **3** from aldehydes. While the electronic effect demonstrated in the silicon-directed route allows for better efficiency (70–87% yield[4o] vs 8–69%[6b]) in the conversion to the phosphonoenamine intermediates, overall these results appear to indicate that steric factors are detrimental to the aldehyde addition step. In this paper we report our complete study on the α-silyl-aminophosphonate homologation route (Scheme 1, path i) as well as a new very efficient one-pot method involving the use of a lithiated bis-dimethylphosphonate formed by deprotonation of **6** (Scheme 1, path ii).



Scheme 1. Aldehyde to carboxylic acid homologation strategies via phosphonoenamine intermediates **3**.

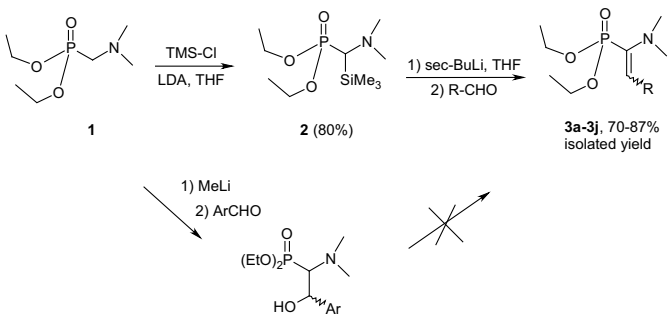
* Corresponding author. Tel.: +1 905 525 9140x27393; fax: +1 905 522 2509.
E-mail address: jmcnult@mcmaster.ca (J. McNulty).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.07.032

2. Results and discussion

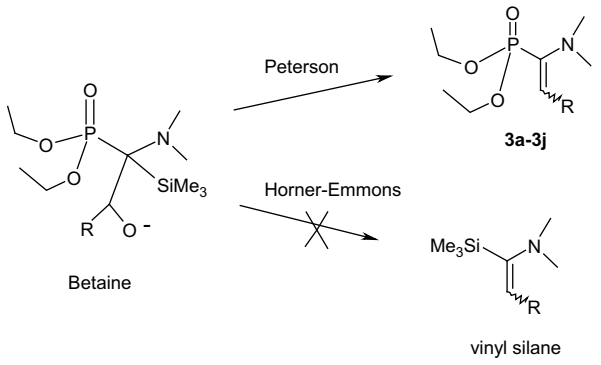
In our hands, the direct aldolization of various enolate derivatives of **1** with aromatic aldehydes or ketones to yield the expected α-phosphonoenamines **3** proved problematic. For example, reaction of the anion of **1** (formed with MeLi, THF, −78 °C) with 4-chlorobenzaldehyde or acetone gave the corresponding β-hydroxyl-α-aminophosphonate adducts in moderate yields of 67% (two diastereomers) and 60%, respectively. Attempts to dehydrate these intermediates to the α-phosphonoenamines were not fruitful giving complex mixtures and resulting in poor yields of **3**.

The failure to selectively dehydrate these intermediates prompted us to attempt a Peterson variant of the reaction using a functionalized α-silyl carbanion.[7a] To this end, we prepared the α-trimethylsilyl derivative **2** (Scheme 2) employing a silylation strategy first described by Padwa et al. in the silylation of cyanoamines.[7b] Silylation of **1** with chlorotrimethylsilane proved to be rapid and gave the *N*-trimethylsilyl ammonium chloride salt. Deprotonation with LDA promoted the desired N to C migration of the trimethylsilyl group most likely via a nitrogen ylide intermediate. The trimethylsilyl intermediate **2** proved to be stable to silica gel and could be stored under argon for several days without decomposition. The intermediate was however readily hydrolyzed back to the starting aminophosphonate **1** when treated with aqueous acid.



Scheme 2. Direct and silicon-assisted routes to aminophosphonates **3**.

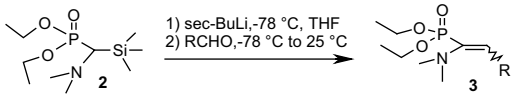
Formation of the α-silyl carbanion from the above intermediate **2** using *s*-BuLi in THF (−78 °C) and addition of piperonal, as outlined in Scheme 1, to our delight led to the formation of the corresponding phosphonoenamine **3a** with 95% conversion and 87% isolated yield.[8] Although the precise mechanism of the Peterson reaction is still unclear (so-called betaine versus oxasiletanide intermediates)[7a] the present intermediate, shown as the betaine (Scheme 3), selected the Peterson elimination pathway over the Horner–Emmons route. Vinylsilanes are also possible products from this reaction and this 'challenge' unambiguously demonstrates the prominence of the Peterson pathway,[6b] reactivity also observed with simple α-silylphosphonates.[7a]

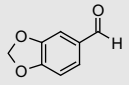
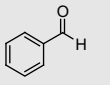
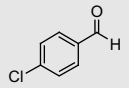
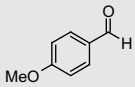
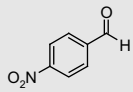
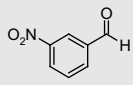
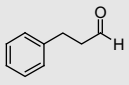
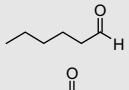
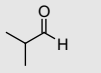
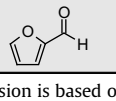


Scheme 3. Possible pathways for elimination from the α-silylated 'betaine-type' intermediate.

The scope of the reaction was investigated with a range of aromatic and aliphatic aldehydes the results of which are summarized in Table 1. Conversions are high in all cases with isolated yields being only slightly lower. Under these conditions of kinetic control, aromatic aldehydes provided a mixture of (*E*)/(*Z*) olefins that rapidly isomerize to give exclusively the thermodynamically more stable (*E*)-isomers. No significant electronic effect was observed with both electron rich and electron poor derivatives reacting equally well (entries 16). In the case of aliphatic aldehydes, dihydro-cinnamaldehyde (entry 7) provided a single (*E*)-adduct, most likely as the kinetic product, while other aliphatic aldehydes gave (*E*)/(*Z*) mixtures (entries 8 and 9). These isomers could be separated and proved to be configurationally stable. The heteroaryl aldehyde 2-furfural also yielded its corresponding adduct efficiently (entry 10).

Table 1
Peterson reaction of α-trimethylsilyl-α-dimethylaminophosphonate with aldehydes



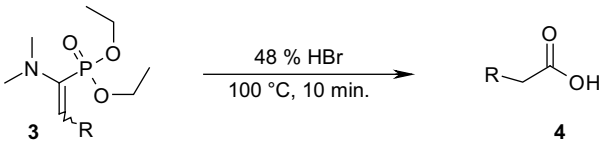
Entry	RCHO		Conversion[a] (%) **3**	Isolated yield of **3**[b] (%)	*E*/*Z*[c]
1		(**2a**)	>95 **3a**	87	100:0
2		(**2b**)	>90 **3b**	67	100:0
3		(**2c**)	>94 **3c**	80	100:0
4		(**2d**)	>95 **3d**	85	100:0
5		(**2e**)	>95 **3e**	82	100:0
6		(**2f**)	>95 **3f**	80	100:0
7		(**2g**)	>90 **3g**	75	100:0
8		(**2h**)	>90 **3h**	70	60:40
9		(**2i**)	>90 **3i**	70	65:35
10		(**2j**)	>95 **3j**	75	100:0

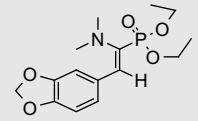
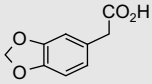
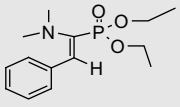
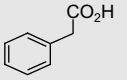
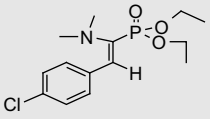
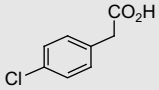
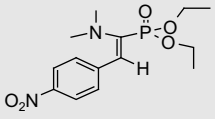
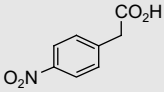
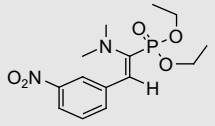
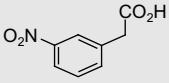
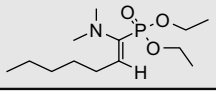
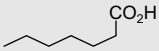
[a] Conversion is based on the recovered aldehyde partner.
[b] Isolated yield of the phosphonoeneamine **3** after chromatographic purification.
[c] The (*Z*)- isomer derived from aromatic aldehydes fully converts to the (*E*)-isomer, see text. Configurational isomers derived from aliphatic aldehydes were readily separated.

In the previous report on phosphonoenamine hydrolysis, boiling hydrochloric acid was used in the conversion to the carboxylic acids. Three examples of this homologation were reported by Gross and Costisella[4b] and the route appears to have been applied only once.[6a] The hydrolysis mechanism likely involves initial enamine hydrolysis and cleavage of the derived α-ketophosphonate

intermediate.[4b] This overall homologation protocol is perhaps underutilized due to the difficulties in accessing intermediates **3** and the need for optimization of the conditions for enamine hydrolysis, which also produces ketophosphonate intermediates and also results in decarboxylation with β-aryl acids.[6a] We investigated the hydrolysis of the adduct **3a** under various conditions and determined that heating with hydrobromic acid for a short period of time was superior to the use of hydrochloric acid. Nonetheless, high yields of the homologated acid could be obtained only under a tightly held set of conditions. Treatment of the piperonal-derived adduct **3a** with 48% hydrobromic acid and warming to 100 °C with a heat-gun led to rapid hydrolysis and isolation of the homologous acid in 90% yield (Table 2, entry 1). Longer heating time gives very poor yield of the homologated acid, presumably due to rapid decarboxylation, whereas with shorter heating time the α-ketophosphonate was detected. The optimal heating time appeared to be between 5 and 10 min. The use of HBr under these reaction conditions proved to be general for both electron rich and electron deficient aryl derivatives (Table 2, entries 2–5) with high yields of carboxylic acid being obtained in all cases. Lastly, the hexanal derived α-phosphonoenamine **3f** was readily hydrolyzed to heptanoic acid (Table 2, entry 6) extending the scope to aliphatic derivatives also.

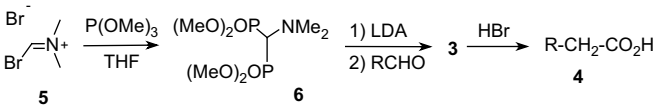
Table 2
Hydrolysis of α-phosphonoenamines to provide the corresponding homologous carboxylic acids



Entry	Phosphonoenamine		**4** Isolated yield (%)	
1		(**3a**)		(**4a**) 90%
2		(**3b**)		(**4b**) 93%
3		(**3c**)		(**4c**) 95%
4		(**3d**)		(**4d**) 98%
5		(**3e**)		(**4e**) 97%
6		(**3f**)		(**4f**) 90%

In terms of the overall homologation method (Scheme 1, **1**→**2**→**3**→**4**), the intermediate phosphonoenamines **3** were obtained in 70–87% isolated yield after silica gel chromatography. Purification was necessary to remove traces of unreacted aldehyde. The HBr-mediated hydrolysis gave the homologated acid cleanly in 90–98% isolated yield. Although the overall yields of this two-step route to homologated acids are in the 75% range, the overall process is less efficient than desired. It appears that the aldehyde addition step is sluggish, perhaps due to steric constraints using the hindered anion derived from **2**.

These considerations prompted us to consider an alternative approach toward the synthesis of the phosphonoenamine (Scheme 1, path ii) intermediate **3** via the diphosphonate **6** (Scheme 4). Degenhardt previously employed the tetraethyl ester corresponding to **6** as an alternative route to phosphonoenamines,[6a] and also reported their hydrolysis using concentrated hydrochloric acid. This route provided homologated acids in low yields, typically 35%. As an extension of this method, we generated the less sterically demanding 1,1-bis-dimethylphosphonate intermediate of structural type **6** (Scheme 4). The isolatable intermediate **6** was prepared by the reaction of commercially available (bromomethylene)-dimethyliminium bromide[5] **5** with 2 equiv of trimethylphosphite. Sequential treatment of **6** with 1.1 equiv of LDA in THF at −78 °C followed by addition of 1 equiv of 4-nitrobenzaldehyde yielded the phosphonoenamine derivative **3** (Scheme 1, R′=Me, R=4-(NO_2)C_6H_4–).



Scheme 4. Diphosphonate route toward aminophosphonates **3**.

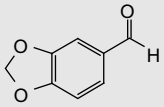
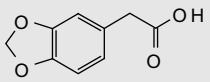
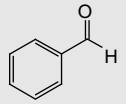
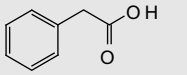
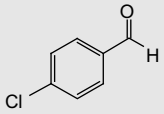
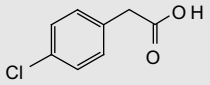
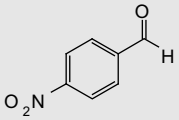
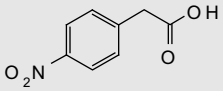
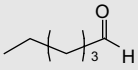
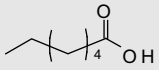
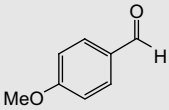
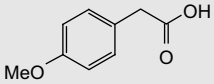
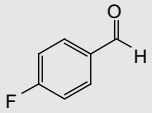
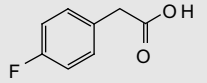
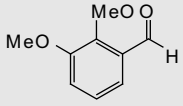
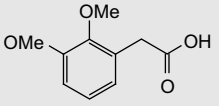
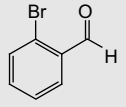
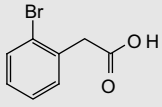
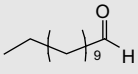
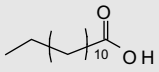
To our surprise, conversion of the aldehyde was complete and the phosphonoenamine **3** could be isolated in 92–93% yield. Steric factors appear to play a critical role in the overall efficiency of the carbonyl-addition step to yield the phosphonoenamine. Acidic hydrolysis of **3** employing 48% HBr yielded the homologated 4-nitrophenylacetic acid **4d** in >98% isolated yield.

We next developed a protocol that allowed for all of the chemistry described to be conducted efficiently in one flask. A vacuum strip of solvent was introduced after formation of the bisphosphonate **6** to remove traces of bromomethane due to its potential reactivity with the enamine. Sequential addition of base followed by aldehyde led to the formation of **3**. While the direct introduction of aqueous HBr after the Horner-type reaction (conversion of **6** to **3**) and conventional heating (100 °C, 10 min) completed the hydrolysis effectively,[4o] we also determined that microwave irradiation at 100 °C for a short period (3 min) effects rapid hydrolysis. The homologated acids were isolated efficiently without the need for chromatographic purification employing a simple base extraction, separation, and re-acidification work-up protocol.

The scope of this one-pot interconversion was investigated with a range of aromatic and aliphatic aldehydes the results of which are presented in Table 3. No major electronic effect was observed as electron rich and electron deficient aldehydes all yielded the corresponding phenylacetic acid derivatives in high isolated yield, although yields appear to be slightly higher with more reactive aldehydes. In addition, hindered *ortho*-substituted aldehydes could be employed (entries 8 and 9) effectively. We also demonstrated that enolizable aliphatic aldehydes (entries 5 and 10) could be converted to the homologated acids in good isolated yield following the same reaction and work-up protocol.

The overall results are consistent with lower aldol-type reactivity of non-activated aromatic aldehydes, hindered aldehydes, and enolizable aldehydes, and are evidence that the carbonyl-addition step is still sluggish. Nonetheless, the sterically less demanding bis-dimethylphosphonate allows for a very efficient general synthesis of α-phosphonoenamines in comparison to its ethyl ester analog,[6a] and shows that high yields of phosphonoenamines can be attained without recourse to α-silylation.[4o,6]

Table 3
One-pot homologation of aldehydes to carboxylic acids

Entry	RCHO	RCH_2CO_2H		Yield (%)
1			(**4a**)	82
2			(**4b**)	83
3			(**4c**)	80
4			(**4d**)	90
5			(**4f**)	75
6			(**4g**)	80
7			(**4h**)	85
8			(**4i**)	79
9			(**4j**)	90
10			(**4k**)	77

Significant results reported in Table 3 include the direct conversion of piperonal (entry 1) to its high-value phenylacetate derivative in 82% yield as well as the conversion of 4-chlorobenzaldehyde (entry 3) to 4-chlorophenylacetic acid (4-CPA). Chiral auxiliaries derived from both of these phenylacetate derivatives have found extensive use in asymmetric synthesis.[2] Additionally, 4-CPA has recently been shown to inhibit estrogen-induced mammary tumor formation directly,[1e] while other phenylacetate derivatives are currently employed or are under investigation in cancer chemotherapy. The direct, general synthesis of phenylacetic acids, suitable for further elaboration, from readily available aromatic aldehydes is thus highly significant and should allow rapid access to a wide range of structural analogs for further biological investigation.

3. Conclusion

In conclusion, we have demonstrated that the commercially available salt (bromomethylene)-dimethyliminium bromide **5** reacts with trimethylphosphite providing the 1,1-bisphosphonate derivative **6** and that the anion derived from **6** undergoes a Horner-type reaction with aldehydes, yielding phosphonoenamines **3**. These same phosphonoenamines can be generated from the Peterson reaction of the anion derived of α-silylated-*N*,*N*-dimethylaminophosphonate **2** with aldehydes. The controlled hydrolysis of these phosphonoenamine intermediates using hydrobromic acid provides entry to the homologated carboxylic acid derivatives in high yield. Overall, the dimethyl-bisphosphonate route is more efficient than the Peterson route and previous routes using diethylphosphonates[6a] most likely due to steric effects. A general, one-pot procedure was developed successfully for the aldehyde-homologated carboxylic acid conversion employing both aromatic and enolizable aliphatic aldehydes. This new method allows for the achievement of this desirable interconversion in the highest yields reported to date, similar to a recently reported two-step method employing trichloromethyl carbinols.[4p] Further developments of the methodology and synthetic applications are currently under investigation in our laboratories.

4. Experimental section

4.1. General

Reactions were carried out under argon in oven-dried glassware. Diethyl-2-*N*,*N*-dimethylaminomethano phosphonate was obtained from Cytec, all other fine chemicals were obtained from Aldrich. *S*-Butyl lithium was obtained from Aldrich as a 1.4 M solution in cyclohexane. THF was distilled from sodium with benzophenone indicator. CIMS were run on a Micromass Quattro Ultima spectrometer fitted with a direct injection probe (DIP) with ionization energy set at 70 eV and HRMS (EI) were performed with a Micromass Q-Tof Ultima spectrometer. ^{1}H, ^{13}C spectra were recorded on a Bruker 200 and AV 600 spectrometer in $CDCl_3$ with TMS as internal standard, chemical shifts (δ) are reported in parts per million downfield of TMS and coupling constants (J) are expressed in Hertz. The (*E*) to (*Z*) ratios were determined from the relative integration of the ^{1}H spectra for the olefinic protons. Microwave reactions were performed in crimp-capped vials using a Biotage Initiator 2.5 reactor. Thin layer chromatography was performed on Macherey-Nagel SIL-G/UV_{254} plates and column chromatography performed over Merck 70–230 mesh silica gel.

4.2. Synthesis of diethyl-2-trimethylsilyl-2-*N*,*N*-dimethylaminomethanophosphonate 2

Into a 20 mL flame-dried round bottom flask, containing a magnetic stirring bar, was added diethyl-2-*N*,*N*-dimethylaminomethanophosphonate **1** (500 μL, 4.13 mmol) under argon. To this was added dry THF (8.26 mL). The contents were cooled to −78 °C and stirred for 15 min. whereupon TMS-Cl (550 μL, 4.35 mmol) was added to the reaction flask over 5 min. Upon stirring for 30 min, a solution of LDA (2.5 mL, 5.0 mmol, 2 M, THF) was added slowly to the reaction flask maintained at −78 °C. The flask was kept at −78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 6 h. The resulting mixture was concentrated to remove solvent. Water was added (10 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3×15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product, R_f 0.32 (EtOAc, pink-red to ninhydrin), was purified by silica gel column chromatography (EtOAc). The silica gel was neutralized by adding five drops of triethylamine into the initial silica gel slurry. The title compound **2**, 882.2 mg (80%), was isolated as a brown oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.14 (s, 9H), 1.33 (t, J_{HH}=6.4 Hz, 6H), 2.38 (d, J_{PH}=22.2 Hz, 1H), 2.47 (s, 6H), 4.07 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ −0.6 (d, J=2.5 Hz), 16.5 (dd, J=6.30, 2.5 Hz), 45.5 (d,

J=3.8 Hz), 55.3 (d, J=112.5 Hz), 60.7 (t, J=7.8 Hz); ^{31}P NMR (80 MHz, $CDCl_3$): δ 30.8; HRMS $(M)^+$ calculated for $C_{10}H_{26}N_1O_3SiP$: 267.1421, found: 267.1420.

4.3. Experimental procedure for the synthesis of aminophosphonates, Table 1

4.3.1. Synthesis of *3a*

Into a flame-dried flask containing a magnetic stirring bar was weighed the α-silylphosphonate **2** (74 mg, 0.278 mmol). The flask was sealed under argon whereupon dry THF (556 μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at −78 °C at which time *s*-BuLi (239 μL, 1.4 M stock solution) was added slowly. After 40 min, a 0.5 M solution (in THF) of piperonal (50 mg, 0.33 mmol) was added slowly to the reaction flask at −78 °C. The flask was kept at −78 °C for 2 h and then slowly warmed to room temperature. At the end of the reaction two spots were visible on TLC (UV–visible and pink-red with ninhydrin). The product was separated using column chromatography (ethyl acetate as eluant) to give **3a**, 87% (79.1 mg). R_f (AcOEt): 0.36. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35 (t, J_{HH}=7.0 Hz, 6H), 2.65 (d, J_{PH}=2.0 Hz, 6H), 4.13 (m, 4H), 5.94 (s, 2H), 6.67 (d, J_{PH}=14.9 Hz, 1H), 6.75 (d, J_{HH}=7.8 Hz, 1H), 7.45 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.4 (d, J=6.8 Hz), 43.1 (d, J=2.3 Hz), 61.6 (d, J=5.6 Hz), 101.1, 107.9, 109.3, 125.0, 129.4 (d, J=15.7 Hz), 130.9 (d, J=31.8 Hz), 137.8 (d, J=182.1 Hz), 147.3, 147.5; ^{31}P NMR (80 MHz, $CDCl_3$): δ 18.0; HRMS $(M)^+$ calculated for $C_{15}H_{22}N_1O_5P_1$ 327.1237, found 327.1236.

4.3.2. Synthesis of *3b*

Into a flame-dried flask containing a magnetic stirring bar was weighed the α-silylphosphonate **2** (109.5 mg, 0.41 mmol). The flask was sealed under argon whereupon dry THF (820 μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at −78 °C. *s*-BuLi (352 μL, 1.4 M) stock solution was added to the reaction flask slowly. After 40 min, a 0.5 M solution (in THF) of benzaldehyde (52 mg, 0.49 mmol) was added slowly to the reaction flask at −78 °C. The flask was kept at −78 °C for 2 h and then slowly warmed to room temperature .At the end of the reaction two new spots were seen (UV–visible and pink-red with ninhydrin). The product was separated using column chromatography (ethyl acetate as eluant) to give **3b**, 67% (77.7 mg). R_f (AcOEt): 0.42. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37 (t, J_{HH}=7.4 Hz, 6H), 2.69 (d, J_{PH}=1.7 Hz, 6H), 4.15 (m, 4H), 6.7 (d, J_{PH}=15.4 Hz, 1H), 7.29 (m, 3H), 7.57 (d, J_{HH}=8.9 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.4 (d, J=6.4 Hz), 43.1, 61.8 (d, J=5.5 Hz), 127.4 (d, J=32.1 Hz), 127.6, 129.7, 135.3 (d, J=14.2 Hz), 139.2 (d, J=181.6 Hz); ^{31}P NMR (80 MHz, $CDCl_3$): δ 17.5; HRMS $(M)^+$ calculated for $C_{14}H_{22}N_1O_3P_1$: 283.1324, found 283.1337.

4.3.3. Synthesis of *3c*

Into a flame-dried flask containing a magnetic stirring bar was weighed the α-silylphosphonate **2** (38 mg, 0.14 mmol). The flask was sealed under argon whereupon dry THF (300 μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at −78 °C. *s*-BuLi (150 μL, 1.4 M stock) solution was added to the reaction flask slowly. After 40 min, a 0.5 M solution (in THF) of 4-chlorobenzaldehyde (24 mg, 0.17 mmol) was added slowly to the reaction flask at −78 °C. The flask was kept at −78 °C for 2 h and then slowly warmed to room temperature. At the end of the reaction two new spots were seen (UV–visible and pink-red with ninhydrin). The product was separated using column chromatography (ethyl acetate as eluant) to give **3c**, 80% (36.1 mg). R_f (AcOEt): 0.34. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35 (t, J_{HH}=7.3 Hz, 6H), 2.67 (d, J_{PH}=0.9 Hz, 6H), 4.14 (m, 4H), 6.61 (d, J_{PH}=14.5 Hz, 1H), 7.27 (d, J_{HH}=13.2 Hz, 2H), 7.5 (d, J_{HH}=13.2 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.4 (d, J=5.7 Hz), 43.2, 61.9 (d, J=5.5 Hz), 126.2 (d, J=35.7 Hz), 128.3, 130.8, 133.1, 134.1 (d, J=19.7 Hz), 140.1 (d, J=178.6 Hz); ^{31}P NMR (80 MHz, $CDCl_3$): δ 17.2; HRMS $(M)^+$ calculated for $C_{14}H_{21}N_1O_3C_{l1}P_1$: 317.0948, found 317.0953.

4.3.4. Synthesis of *3d*

Into a flame-dried flask containing a magnetic stirring bar was weighed the α-silylphosphonate **2** (91.6 mg, 0.34 mmol). The flask was sealed under argon whereupon dry THF (686 μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at −78 °C. *s*-BuLi (294 μL, 1.4 M) stock solution was added to the reaction flask slowly. After 40 min, a 0.5 M solution (in THF) of 4-methoxybenzaldehyde (50 μL, 0.41 mmol) was added slowly to the reaction flask at −78 °C. The flask was kept at −78 °C for 2 h and then slowly warmed to room temperature. At the end of the reaction two new spots were seen (UV–visible and pink-red with ninhydrin). The product was separated using column chromatography (ethyl acetate as eluant) to give **3d**, 85%. R_f (AcOEt): 0.36. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.36 (t, J_{HH}=7.2 Hz, 6H), 2.7 (d, J_{PH}=1.2 Hz, 6H), 3.72 (s, 3H), 4.14 (m, 4H), 6.72 (d, J_{PH}=14.2 Hz, 1H), 6.86 (d, J_{HH}=9.1 Hz, 2H), 7.65 (d, J_{HH}=8.7 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.5 (d, J=5.6 Hz), 43.1, 55.2, 61.6 (d, J=5.5 Hz), 113.6, 128.1 (d, J=18.2 Hz), 130.3 (d, J=34.2 Hz), 131.5, 137.3 (d, J=179.1 Hz), 159.3; ^{31}P NMR (80 MHz, $CDCl_3$): δ 18.3; HRMS $(M)^+$ calculated for $C_{15}H_{25}N_1O_4P_1$: 314.1513, found 314.1521.

4.3.5. Synthesis of *3e*

Into a flame-dried flask containing a magnetic stirring bar was weighed the α-silylphosphonate **2** (74 mg, 0.28 mmol). The flask was sealed under argon whereupon dry THF (555 μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at −78 °C. *s*-BuLi (238 μL, 1.4 M) stock solution was added to the reaction flask slowly. After 40 min, a 0.5 M solution (in THF) of 4-nitrobenzaldehyde (50 mg, 0.33 mmol) was added slowly to the reaction flask at −78 °C. The flask was kept at −78 °C for 2 h and then slowly warmed to room temperature. At the end of the reaction two new spots were seen (UV–visible and pink-red with ninhydrin). The product was separated using column chromatography (ethyl acetate as eluant) to give **3e**, 82% (74.8 mg). R_f (AcOEt): 0.29. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37 (t, J_{HH}=7.7 Hz, 6H), 2.75 (s, 6H), 4.14 (m, 4H), 6.52 (d, J_{PH}=14.9 Hz, 1H), 7.49 (d, J_{HH}=9.3 Hz, 2H), 8.15 (d, J_{HH}=9.3 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.4 (d, J=5.4 Hz), 43.6, 62.3 (d, J=5.5 Hz), 119.1 (d, J=34.6 Hz), 123.4, 129.3, 142.7 (d, J=18.5 Hz), 144.3 (d, J=178.1 Hz), 147.6; ^{31}P NMR (80 MHz, $CDCl_3$): δ 15.0; HRMS (M^+) calculated for $C_{14}H_{21}N_2O_5P_1$: 328.1188, found 328.1188.

4.3.6. Synthesis of *3f*

Into a flame-dried flask containing a magnetic stirring bar was weighed the α-silylphosphonate **2** (91.6 mg, 0.34 mmol). The flask was sealed under argon whereupon dry THF (686 μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at −78 °C. *s*-BuLi (238 μL, 1.4 M) stock solution was added to the reaction flask slowly. After 40 min, a 0.5 M solution (in THF) of 3-nitrobenzaldehyde (50 mg, 0.33 mmol) was added slowly to the reaction flask at −78 °C. The flask was kept at −78 °C for 2 h and then slowly warmed to room temperature .At the end of the reaction two new spots were seen (UV–visible and pink-red with ninhydrin). The product was separated using column chromatography (ethyl acetate as eluant) to give **3f**, 80% (73 mg). R_f (AcOEt): 0.28. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37 (t, J_{HH}=7.2 Hz, 6H), 2.73 (d, J_{PH}=1.6 Hz, 6H), 4.17 (m, 4H), 6.61 (d, J_{PH}=14.9 Hz, 1H), 7.46 (t, J_{HH}=8.5 Hz, 1H), 7.72 (d, J_{HH}=6.7 Hz, 1H), 8.03 (d, J_{HH}=6.7 Hz, 1H), 8.73 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.5 (d, J=5.5 Hz), 43.4, 62.2 (d, J=5.4 Hz), 120.2, 121.4 (d, J=33.2 Hz), 123.5, 128.9, 137.4 (d, J=17.2 Hz), 139.2 (d, J=179.4 Hz), 148.4; ^{31}P NMR (80 MHz, $CDCl_3$): δ 15.9 Hz; HRMS $(M)^+$ calculated for $C_{14}H_{22}N_2O_5P_1$: 329.1266, found 314.1266.

4.3.7. Synthesis of ***3g***

Into a flame-dried flask containing a magnetic stirring bar was weighed the α-silylphosphonate **2** (85 mg, 0.32 mmol). The flask was sealed under argon whereupon dry THF (636 μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at −78 °C. *s*-BuLi (273 μL, 1.4 M) stock solution was added to the reaction flask slowly. After 40 min, a 0.5 M solution (in THF) of hydrocinnamaldehyde (50 μL, 0.38 mmol) was added slowly to the reaction flask at −78 °C. The flask was kept at −78 °C for 2 h and then slowly warmed to room temperature .At the end of the reaction two new spots were seen (UV–visible and pink-red with ninhydrin). The product was separated using column chromatography (ethyl acetate as eluant). The yield of the new product was 75% (74 mg). R_f (AcOEt): 0.4. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, J_{HH}=6.7 Hz, 6H), 2.55 (d, J_{PH}=2.1 Hz, 6H), 2.67 (m, 4H), 4.02 (m, 4H), 6.12 (dt, J_{PH}=14.9 Hz, J_{HH}=7.3 Hz, 1H), 7.22 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.4 (d, *J*=6.6 Hz), 29.3 (d, *J*=14.8 Hz), 34.8, 43.8, 61.5 (d, *J*=7.0 Hz), 126.0, 128.4, 138.6 (d, *J*=31.1 Hz), 140.1 (d, *J*=179 Hz), 141.5; ^{31}P NMR (80 MHz, $CDCl_3$): δ 17.3 Hz; HRMS $(M)^+$ calculated for $C_{16}H_{27}N_1O_3P_1$: 312.1718, found 312.1729.

4.3.8. Synthesis of ***3h***

Into a flame-dried flask containing a magnetic stirring bar was weighed the α-silylphosphonate **2** (90.5 mg, 0.34 mmol). The flask was sealed under argon whereupon dry THF (678 μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at −78 °C. *s*-BuLi (290 μL, 1.4 M) stock solution was added to the reaction flask slowly. After 40 min, a 0.5 M solution (in THF) of hexanal (50 μL, 0.41 mmol) was added slowly to the reaction flask at −78 °C. The flask was kept at −78 °C for 2 h and then slowly warmed to room temperature. At the end of the reaction two new spots were seen (UV–visible and pink-red with ninhydrin). The two products were separated using column chromatography (ethyl acetate as eluting solvent). The total yield was 70% (66 mg). Isolated yield of the (*Z*)-isomer was 40% (26.3 mg) and that of the (*E*)-isomer was 60% (39.7 mg). (*Z*)-Isomer: R_f (AcOEt): 0.48. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, J_{HH}=4.5 Hz, 3H), 1.30 (m, 12H), 2.38 (m, 2H), 2.57 (s, 6H), 4.09 (m, 4H), 5.45 (dt, J_{PH}=41.8 Hz, J_{HH}=9.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 16.3 (d, *J*=6.0 Hz), 22.2, 28.2, 29.5, 31.5, 43.7 (d, *J*=5.2 Hz), 61.6 (d, *J*=5.0 Hz), 128.7 (d, *J*=28.4 Hz), 141.0 (d, *J*=190 Hz); ^{31}P NMR (80 MHz, $CDCl_3$): δ 16.0; HRMS $(M)^+$ calculated for $C_{13}H_{29}N_1O_3P_1$: 278.1885, found 278.1891. (*E*)-isomer: R_f (AcOEt): 0.52. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85 (t, J_{HH}=6.4 Hz, 3H), 1.30 (m, 12H), 2.23 (m, 2H), 2.58 (s, 6H), 4.06 (m, 4H), 6.11 (dt, J_{PH}=13.4 Hz, J_{HH}=6.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 16.4 (d, *J*=6.7 Hz), 22.4, 27.5 (d, *J*=14.6 Hz), 28.3 (d, *J*=2.0 Hz), 31.6, 43.8 (d, *J*=2.3 Hz), 61.4 (d, *J*=5.8 Hz), 139.7 (d, *J*=182.4 Hz), 140.4 (d, J=29.4 Hz); ^{31}P NMR (80 MHz, $CDCl_3$): δ 17.7; HRMS $(M)^+$ calculated for $C_{13}H_{29}N_1O_3P_1$: 278.1885, found 278.1891.

4.3.9. Synthesis of ***3i***

Into a flame-dried flask containing a magnetic stirring bar was weighed the α-silylphosphonate **2** (134.5 mg, 0.50 mmol). The flask was sealed under argon whereupon dry THF (1 mL) was added to make a 0.5 M solution. The flask was stirred for 15 min at −78 °C. *s*-BuLi (429 μL, 1.4 M) stock solution was added to the reaction flask slowly. After 40 min, a 0.5 M solution (in THF) of furfuraldehyde (50 μL, 0.60 mmol) was added slowly to the reaction flask at −78 °C. The flask was kept at −78 °C for 2 h and then slowly warmed to room temperature. At the end of the reaction two new spots were seen (UV–visible and pink-red with ninhydrin). The two products were separated using column chromatography (ethyl acetate as eluant). The total yield was 70% (80 mg). Isolated yield of the (*Z*)-isomer was 35% (28 mg) and that of the (*E*)-isomer was 65% (52 mg). (*Z*)-isomer: R_f (AcOEt): 0.42. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95 (t, J_{HH}=6.5 Hz, 6H), 1.30 (t, J_{HH}=7.1 Hz, 6H), 2.56 (s, 6H), 3.1 (m, 1H), 4.09 (m, 4H), 5.22 (dd, J_{PH}=42.2 Hz, J_{HH}=10.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.4 (d, *J*=6.3 Hz), 23.4, 27.4, 43.8 (d, *J*=6.9 Hz), 61.6 (d, *J*=6.3 Hz), 136.0 (d, *J*=24.7 Hz), 147.2 (d, *J*=180.5 Hz); ^{31}P NMR (80 MHz, $CDCl_3$) δ 16.2; HRMS $(M)^+$ calculated for $C_{11}H_{25}N_1O_3P_1$ 250.1565, found 250.1572. (*E*)-isomer: R_f (AcOEt): 0.47. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.99 (t, J_{HH}=7.6 Hz, 6H), 1.33 (t, J_{HH}=6.9 Hz, 6H), 2.60 (d, J_{PH}=2.2 Hz, 6H), 2.98 (m, 1H), 4.08 (m, 4H), 6.0 (dd, J_{PH}=14.2 Hz, J_{HH}=10.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.5 (d, *J*=6.25 Hz), 22.3, 26.8 (d, *J*=16.3 Hz), 44.4, 61.7 (d, *J*=7.3 Hz), 138.0 (d, *J*=181.5 Hz), 148.3 (d, *J*=28.9 Hz); ^{31}P NMR (80 MHz, $CDCl_3$): δ 17.7; HRMS $(M)^+$ calculated for $C_{11}H_{25}N_1O_3P_1$: 250.1565, found 250.1572.

4.3.10. Synthesis of ***3j***

Into a flame-dried flask containing a magnetic stirring bar was weighed the α-silylphosphonate **2** (134.5 mg, 0.50 mmol). The flask was sealed under argon whereupon dry THF (1 mL) was added to make a 0.5 M solution. The flask was stirred for 15 min at −78 °C. *s*-BuLi (290 μL, 1.4 M) stock solution was added to the reaction flask slowly. After 40 min, a 0.5 M solution (in THF) of hexanal (50 μL, 0.41 mmol) was added slowly to the reaction flask at −78 °C. The flask was kept at −78 °C for 2 h and then slowly warmed to room temperature. At the end of the reaction two new spots were seen (UV–visible and pink-red with ninhydrin). The product was separated using column chromatography (ethyl acetate as eluant) to give **3j**, 75% (103 mg). R_f (AcOEt): 0.37. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (t, J_{HH}=7.2 Hz, 6H), 2.72 (d, J_{PH}=2.0 Hz, 6H), 4.13 (m, 4H), 6.45 (m, 1H), 6.73 (m, 2H), 7.41(s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.5 (d, *J*=6.9 Hz), 43.2, 61.9 (d, *J*=5.8 Hz), 112.0 (d, *J*=15.1 Hz), 112.4, 118.7 (d, *J*=33.2 Hz), 142.4 (d, *J*=187.2 Hz), 145.7, 151.0; ^{31}P NMR (80 MHz, $CDCl_3$): δ 17.7; HRMS $(M)^+$ calculated for $C_{12}H_{21}N_1O_4P_1$: 274.1194, found 274.1208.

4.4. General experimental procedure for phosphonoenamine hydrolysis Table 2

4.4.1. Synthesis of 3′,4′-(methylenedioxy)phenylacetic acid ***4a***

Into a flame-dried flask was weighed phosphonoenamine **3a** (50 mg, 0.158 mmol) and 3.0 mL of 48% HBr was added to the flask. The flask was heated with a heat-gun for 10 min. The flask was cooled immediately. Deposits were seen in the reaction flask, which was extracted with diethyl ether (3×15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield **4a**, 26.8 mg, (95%); off-white solid, mp 125–127 °C; CAS registry number [2861-28-1].[9e]

4.5. Experimental procedure for the one-pot synthesis of homologated carboxylic acid Table 3

4.5.1. Synthesis of 4-nitrophenylacetic acid ***4d***

Into a flame-dried microwave vial, containing a magnetic stirring bar, was weighed (bromomethylene)-dimethyliminium bromide (216.9 mg, 1.0 mmol) under Ar and dry THF (2 mL) added. The flask was septa-sealed and stirred for 15 min under Ar at room temperature whereupon $P(OMe)_3$ (236 μL, 2.0 mmol) was added slowly. After 40 min the solvent was removed under argon flow and the concentrate vacuum dried for 20 min giving **6**. THF (2 mL) was added and the vial cooled to −78 °C under Ar for 15 min whereupon LDA (550 μL, 1.1 mmol, 2.0 M stock, heptane/THF/ethylbenzene) was added slowly. After 40 min a 0.5 M solution (in THF) of 4-nitrobenzaldehyde (159 mg, 1.05 mmol) was added slowly to the reaction flask maintained at −78 °C. The flask was kept at −78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The THF was removed under Ar and 3 mL of 48% HBr was added to the residue. The vial was now crimp-capped and

irradiated in the microwave at 100 °C for 3 min. The resulting mixture was extracted with diethylether (3×15 mL). The combined organic layers were partitioned with 10 mL of (10% w/v) aqueous NaOH allowing clean phase separation (15 min). The ether was extracted with water (2×10 mL). The combined aqueous layers were carefully acidified (10% w/v aqueous HCl) and the resulting mixture was extracted with diethyl ether (3×15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to yield **4d**, 159.4 mg, (88%) as a yellow solid. Mp 149–150 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.79 (s, 2H), 7.47 (d, J_{HH}=8.0 Hz, 2H), 8.20 (d, J_{HH}=8.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 40.7, 123.9, 130.5, 140.4, 147.4, 176.1. CAS registry number [104-03-0].[9d]

4.5.2. 3,4-(Methylenedioxy)phenylacetic acid (*4a*)[9e]

Mp 125–127 °C (lit.[4o] 125–127 °C); yield 82%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.57 (s, 2H), 5.91 (s, 2H), 6.71–6.81 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 41.4, 107.8, 109.3, 123.2, 127.7, 146.8, 147.9, 177.6.

4.5.3. Phenylacetic acid (*4b*)[9a]

Mp 75–77 °C (lit.[4n] 76–78 °C); yield 83%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.61 (s, 3H), 7.18–7.39 (m, 5H); ^{13}C NMR (50 MHz): δ 41.4, 127.0, 128.5, 129.5, 133.0, 177.9.

4.5.4. 4-Chlorophenylacetic acid (*4c*)[9c]

Mp 104–105 °C (lit.[4n] 104–106 °C); yield 80%. ^{1}H NMR (200 MHz, $CDCl_3$): 3.61 (s, 3H), 7.24–7.30 (m, 4H); ^{13}C NMR (50 MHz): δ 40.4, 128.9, 130.8, 131.7, 133.5, 177.3.

4.5.5. 3-Nitrophenylacetic acid (*4e*)

Mp 117–118 °C (lit.[4n] 118–120 °C); yield 80%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.51 (s, 2H), 7.43 (m, 2H), 7.98 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 47.1, 119.7, 125.1, 130.3, 135.6, 140.0, 148.6, 176.9.

4.5.6. Heptanoic acid (*4f*)[9g]

Yield 75%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (m, 3H), 1.20–1.40 (m, 6H), 1.63 (m, 2H), 2.34 (t, J_{HH}=7.4 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.7, 24.7, 28.7, 31.4, 34.3, 180.5.

4.5.7. 4-Methoxyphenylacetic acid (*4g*)[9f]

Mp 84–86 °C (lit.[4n] 85–87 °C); yield 80%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.63 (s, 2H), 3.77 (s, 3H), 6.83 (d, J_{HH}=7.7 Hz, 2H), 7.22 (d, J_{HH}=7.7 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 40.1, 56.2, 114.5, 125.6, 130.4, 159.0, 178.2.

4.5.8. 4-Fluorophenylacetic acid (*4h*)[9c]

Mp 83–84 °C (lit.[4n] 82–85 °C); yield 85%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.61 (s, 2H), 7.03–7.23 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 40.1, 115.6, 128.7, 130.9, 160.9, 177.5.

4.5.9. 2,3-Dimethoxyphenylacetic acid (*4i*)

Mp 82–83 °C (lit.[9h] 84 °C); yield 79%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.81 (s, 2H), 3.87 (s, 3H), 4.0 (s, 3H), 7.12 (d, J_{HH}=7.5 Hz, 2H), 7.57 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 35.6, 56.7, 60.6, 117.4, 122.6, 123.5, 124.8, 152.5, 167.1, 177.6; HRCI MS $(M)^+$ calculated for $C_{10}H_{12}O_4$: 196.0736, found: 196.0745.

4.5.10. 2-Bromophenylacetic acid (*4j*)[9b]

Mp 103–105 °C (lit. [9b] 103–105 °C); yield 90%. ^{1}H NMR (200 MHz, $CDCl_3$): 3.81 (s, 3H), 7.12 (m, 2H), 7.29 (d, J_{HH}=7.8 Hz, 1H), 7.58 (d, J_{HH}=7.8 Hz, 1H); ^{13}C NMR (50 MHz): δ 41.8, 124.1, 127.8, 129.0, 131.8, 132.6, 132.7, 177.7.

4.5.11. Tridecanoic acid (*4k*)

Yield 77%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (m, 3H); 1.20–1.40 (m, 18H), 1.63 (m, 2H), 2.36 (t, J_{HH}=7.3 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 22.7, 24.8, 29.3, 29.6, 31.9, 34.1, 177.2; HRCI MS $(M)^+$ calculated for $C_{13}H_{26}O_2$: 214.1933, found: 214.1929.

Acknowledgements

We thank NSERC, Cytec Canada Inc. and McMaster University for financial support of this work.

References and notes

1. Over 20 marketed pharmaceuticals are phenylacetic acid derivatives including diclofenac (anti-arthritic), ibufenac (anti-inflammatory), ritalin (anti-ADHD), homovanillic acid (schizophrenia), propanidid (anesthetic) guanfacine (antihypertensive), and 4-chlorophenylacetic acid (anti-neoplastic). For a selection of examples see: (a) Failli, A. A.; Kreft, A. F.; Musser, J. H. U.S. Patent 5,021,576, 1991; (b) Nahar, L.; Russel, W. R.; Middleton, M.; Shoeb, M.; Sarker, S. D. *Acta Pharm.* **2005**, *55*, 187–193; (c) Santini, C.; Berger, G. D.; Han, W.; Mosley, R.; MacNaul, K.; Berger, J.; Doebber, T.; Wu, M.; Moller, D. E.; Tolman, R. L.; Sahoo, S. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1277–1280; (d) Rakowitz, D.; Gmeiner, A.; Schroder, N.; Matuszczak, B. *Eur. J. Pharm. Sci.* **2006**, *27*, 188–193; (e) Sidell, N.; Kirma, N.; Morgan, E. T.; Nair, H.; Tekmal, R. R. *Cancer Lett.* **2007**, *251*, 302–310.
2. For a selection of synthetic applications see: (a) Gore, M. P.; Vederas, J. C. *J. Org. Chem.* **1986**, *51*, 3700–3704; (b) Prashad, M.; Kim, H. Y.; Har, D.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **1998**, *39*, 9369–9372; (c) Wittenberger, S. J.; McLaughlin, M. A. *Tetrahedron Lett.* **1999**, *40*, 7175–7178; (d) Bull, S. D.; Davies, S. G.; Key, M. S.; Nicholson, R. L.; Savory, E. D. *Chem. Commun.* **2000**, 1721–1722; (e) McNulty, J.; Nair, J. J.; Sliwinski, M.; Harrington, L. E.; Pandey, S. *Eur. J. Org. Chem.* **2007**, 5669–5673; (f) McNulty, J.; Nair, J. J.; Pandey, S.; Griffin, C. *J. Nat. Prod.* **2008**, *71*, 357–363.
3. (a) Kohlpaintner, C. W.; Beller, M. *J. Mol. Catal. A: Chem.* **1997**, *116*, 259–267; (b) Adams, R.; Thal, A. F. *Org. Synth.* **1922**, *2*, 9–11; (c) Adams, R.; Thal, A. F. *Org. Synth.* **1922**, *2*, 27–28.
4. (a) Corey, E. J.; Markl, G. *Tetrahedron Lett.* **1967**, *33*, 3201–3204; (b) Gross, H.; Costisella, B. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 391–392; (c) Schollkopf, U.; Schroder, R. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 311–312; (d) Jones, P. F.; Lappert, M. F. *J. Chem. Soc., Chem. Commun.* **1972**, 526; (e) White, D. R.; Wu, D. K. *J. Chem. Soc., Chem. Commun.* **1974**, 988–989; (f) Dinizo, S. E.; Freerksen, R. W.; Papst, W. E.; Watt, D. S. *J. Am. Chem. Soc.* **1977**, *99*, 182–186; (g) Gross, H.; Costisella, B. *Tetrahedron* **1982**, *38*, 139–145; (h) Takahashi, K.; Shibasaki, K.; Ogura, K.; Iida, H. *J. Org. Chem.* **1983**, *48*, 3566–3569; (i) Takahashi, K.; Msuda, T.; Ogura, K.; Iida, H. *Synthesis* **1983**, 1043–1045; (j) Hiyama, T.; Inoue, M.; Saito, K. *Synthesis* **1986**, 645–647; (k) Katritzky, A. R.; Dorin, T.; Linghong, X. *Synthesis* **1996**, 1425–1427; (l) Satoh, T.; Nakamura, A.; Iriuchijima, A.; Hayashi, Y.; Kubota, K. *Tetrahedron* **2001**, *57*, 9689–9696; (m) Huh, D. K.; Jeong, J. S.; Lee, H. B.; Ryu, H.; Kim, G. *Tetrahedron* **2002**, *58*, 9925–9932; (n) Zhou, G. B.; Zhang, P. F.; Pan, Y. J. *Tetrahedron* **2005**, *61*, 5671–5677; (o) McNulty, J.; Das, P.; Gosciniak, D. *Tetrahedron Lett.* **2008**, *49*, 281–285; (p) Cafiero, L. R.; Snowden, T. S. *Org. Lett.* **2008**, *10*, 3853–3856.
5. This reagent is available from the Aldrich Chemical Company.
6. (a) Degenhardt, C. R. *Synth. Commun.* **1982**, *12*, 415–421; (b) Dufrechou, S.; Combret, J. C.; Malhiac, C.; Collignon, N. *Phosphorus Sulfur Silicon Relat. Elem.* **1997**, *127*, 1–14.
7. (a) van Staden, L. F.; Gravestock, D.; Ager, D. J. *Chem. Soc. Rev.* **2002**, *31*, 195–200; (b) Padwa, A.; Eisenbarth, P.; Venkataramana, M. K.; Wong, G. S. K. *J. Org. Chem.* **1987**, *52*, 2427–2432.
8. Zumstein, F; Klingseisen, F. Ger. Offen DE 4029444 A1, 1990.
9. (a) Zhou, G. B.; Zhang, P. F.; Pan, Y. J. *Tetrahedron* **2005**, *61*, 5671–5677; (b) Adamczyk, M.; Watt, D. S. *J. Org. Chem.* **1984**, *49*, 4226–4237; (c) Milne, J. E.; Murry, J. A.; King, A.; Larsen, R. D. *J. Org. Chem.* **2009**, *74*, 445–447; (d) Ando, A.; Miki, T.; Kumadaki, I. *J. Org. Chem.* **1988**, *53*, 3637–3639; (e) Moreira, D. R. M.; Lima-Leite, A. C.; Pinheiro-Ferreira, P. M.; da Costa, P, M.; Costa-Lotufo, L. V.; de Moraes, M. O.; Brondani, D. J.; Pessoca, C. O. *Eur. J. Med. Chem.* **2007**, *42*, 351–357; (f) Li, P.; Alper, H. *J. Org. Chem.* **1986**, *51*, 4354–4356; (g) Niu, D. F.; Xiao, N. L. P.; Zhang, A. J.; Zhang, G. R.; Tan, Q. Y.; Lu, J. X. *Tetrahedron* **2008**, *64*, 10517–10520; (h) Chakravarti, S.; Swaminathan, M. *Indian J. Chem.* **1934**, *11*, 107–113.