New Double-Chain and Aromatic (α-Hydroxyalkyl)phosphorus Amphiphiles

Alice Brun,*[1] Guita Etemad-Moghadam[2]

Laboratoire des IMRCP, UMR CNRS 5623, Université Paul Sabatier, 118, route de Narbonne, Bât. 2R1, 31062 Toulouse Cedex 04, France
Fax +33(5)61558155; E-mail: alice.brun@mpikg.golm.mpg.de

Received 5 March 2002; revised 5 April 2002

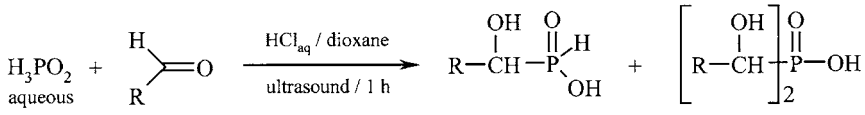
Abstract: New double-chain bis-(α-hydroxyalkyl)phosphinic acids **1** are synthesized from $NaH_2PO_2 \cdot H_2O$ and aliphatic aldehydes. Direct and quantitative one-pot synthesis of new 4-alkoxybenzaldehydes **2** is realized from 1-bromoalkanes and 4-hydroxybenzaldehyde. Addition of $NaH_2PO_2 \cdot H_2O$ to aldehydes **2** leads to the formation of the bis-adducts and also to the cleavage of the ether bond. New [α-hydroxy-(4-alkoxybenzyl)]phosphinic acids **3** are prepared by addition of aldehydes **2** to aqueous hypophosphorous acid.

Key words: aldehydes, surfactants, phosphorylations, phosphinic acids, benzaldehydes, addition reactions

(α-Hydroxyalkyl)phosphoryl derivatives (phosphinic and phosphonic acids, esters and salts) have potential biological activities such as enzyme and metalloenzyme inhibitors,[3] bone resorption inhibitors,[4] anti-viral, anti-tumoral and anti-bacterial agents, or fungicides.[5] These compounds may also be used as precursors for the synthesis of organophosphorus polymers possessing flame-resistant, corrosion-resistant and ion-exchange properties.[6] Indeed, (α-hydroxyalkyl)phosphinic and -phosphonic acids are also used as extractants for the recovery or separation of some metal ions.[6,7] The presence of a hydrophobic moiety must then widen their application field, biological and coordinating properties being enhanced by the coexistence of hydrophobic and hydrophilic groups in the molecule. Furthermore, synthetic long-chain phosphinate and phosphonate esters, which can be considered as analogs of phospholipids (the main components of biological membranes), have applications as models of natural membranes,[8] enhancers of the transdermal penetration of drugs,[9] or for the vectorisation of anti-cancerous drugs.[10] In the laboratory, new single-chain (α-hydroxyalkyl)phosphinic and -phosphonic acid amphiphiles of different head-group polarity have been synthesized.[11,12] These surfactants self-organize in aqueous media in micelles and lyotropic liquid crystals and are able to form stable and compact monolayers at the air/water interface only when they possess a sufficiently long alkyl chain.[12] To the best of our knowledge, no other (α-hydroxyalkyl)phosphinic acid amphiphiles have been described since then. With a view to study the influence of hydrophobicity on the molecular aggregation properties of this new class of surfactants, we decided to prepare new double-chain and aromatic (α-hydroxyalkyl)phosphorus amphiphiles.

Our previous work on the synthesis of (α-hydroxyalkyl)phosphinic acids from 50% aqueous hypophosphorous acid and various aldehydes showed that the monoadduct is usually obtained as the main product accompanied by 5% of the bis-adduct in the case of aliphatic aldehydes and 15% to 25% of the bis-adduct in the case of aromatic aldehydes (Scheme 1).[11,13]

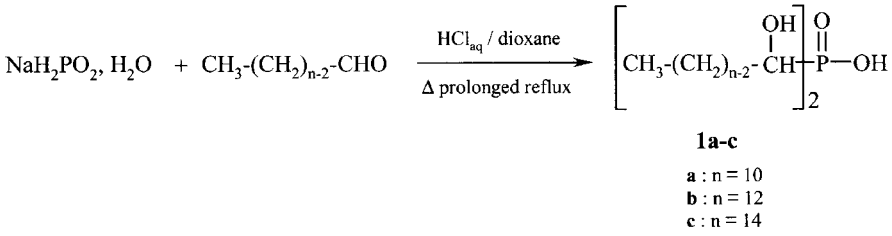
To prepare phosphorus double-chain amphiphiles, the double addition of long chain aldehydes was realized on sodium hypophosphite, a crystalline commercial compound which allows reaction in more concentrated media compared to 50% aqueous hypophosphorous acid previously used for the synthesis of the corresponding single-chain analogs (Scheme 1). Reaction of monohydrated sodium hypophosphite, $NaH_2PO_2 \cdot H_2O$ with 2.5 equivalents of long chain aldehyde in the presence of 2 equivalents of hydrochloric acid in dioxane under reflux leads after 24 hours to bis-(α-hydroxyalkyl)phosphinic acids **1a**–**c** bearing two alkyl chains (Schemes 2 and 3).



Scheme 1 Synthesis of (α-hydroxyalkyl)phosphinic acids from hypophosphorous acid and aliphatic or aromatic aldehydes.

Synthesis 2002, No. 10, 30 07 2002. Article Identifier:
1437-210X,E;2002,0,10,1385,1390,ftx,en;Z04402SS.pdf.
© Georg Thieme Verlag Stuttgart · New York
ISSN 0039-7881

Downloaded by: University of Arizona Library. Copyrighted material.



Scheme 2 Synthesis of bis-(α-hydroxyalkyl)phosphinic acids **1** from sodium hypophosphite and aliphatic aldehydes.

Compounds **1a**–**c** were obtained with 40% yield. Actually, prolonged heating leads also to the competitive oxidation of the intermediate phosphinic acid P–H bond, to give the corresponding phosphonic acid (Scheme 3). The synthesis of (α-hydroxyalkyl)phosphonic acids was described elsewhere.[11]

The ^{31}P NMR spectrum of the crude reaction mixture shows two signals for bis-(α-hydroxyalkyl)phosphinic acids **1a**–**c**. Due to the presence of two stereogenic carbons bonded to the phosphorus atom, and the phosphorus atom being itself a pseudo-asymmetric center,[14] these compounds exist in 3 diastereomeric forms: 2 meso and 1 racemic pair. However, the ^{31}P NMR spectra of compounds **1a**–**c** exhibit degeneracies due to the rapid prototropic transfer of the acidic proton between phosphoryl (P=O) and acidic (P–OH) sites and only two signals are observed around 40 ppm, corresponding to the racemic form *R,R*/*S,S* and the meso *R,S*.[11,13] After purification, one signal only may be observed (Table 1), probably due to a too small magnetic difference or a too small chemical shift difference between isomers to be detectable by NMR analysis.

In all cases, the presence of the two diastereomers in the final product was confirmed by ^{13}C NMR analysis of bis-(α-hydroxyalkyl)phosphinic acids **1a**–**c** and the presence of two doublets $\Delta\delta$ = 0.05–0.2 ppm (δ ^{13}C ~ 68, $^{1}J_{CP}$ ~ 100 Hz).

Following the idea of preparing new (α-hydroxyalkyl)phosphorus amphiphiles of enhanced hydrophobicity, bearing one or two alkyl chains, we decided to prepare a new series of long chain aromatic aldehydes which could be further used to prepare phosphorus amphiphiles using the phosphorylation reactions described previously (vide supra).

Table 1 Yields and NMR Parameters of Bis-(α-hydroxyalkyl)phosphinic Acids **1**

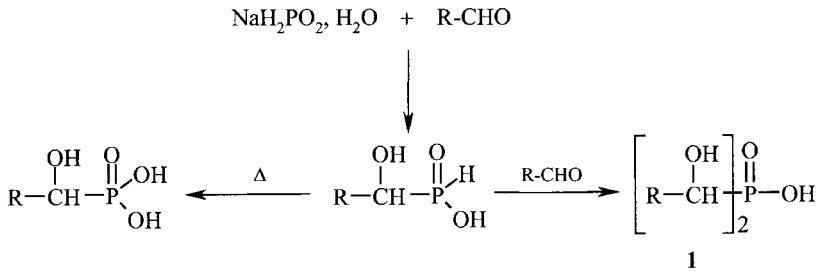
Compnd No.	δ (^{31}P)[a]	δ (^{13}C) ($^{1}J_{CP}$)[b]	δ (^{1}H)[b]	Yield (%)[c]
1a	40.4	68.77 (101.8) 68.64 (102.5)	3.77	41
1b	43.0 42.3	68.59 (101.6) 68.39 (103.1)	3.83	44
1c	41.8	68.75 (98.7) 68.70 (102.3)	3.77	40

[a] ^{31}P NMR chemical shifts in $CDCl_3$ + 2 drops of CD_3COOD.
[b] ^{13}C and ^{1}H NMR chemical shifts of the methyne protons in $CDCl_3$ + 2 drops of CD_3COOD, *J* in Hz.
[c] Isolated yields.

Long chain aromatic aldehydes **2** were prepared from 4-hydroxybenzaldehyde and 1-bromoalkanes following the method described by Lindsey et al.[15] The one-pot addition of 4-hydroxybenzaldehyde to alkylbromide bearing various chain lengths (10 to 18 carbons), in the presence of excess anhydrous potassium carbonate, in DMF, leads after 1.5 hour at 80 °C to aromatic aldehydes **2** (Scheme 4).

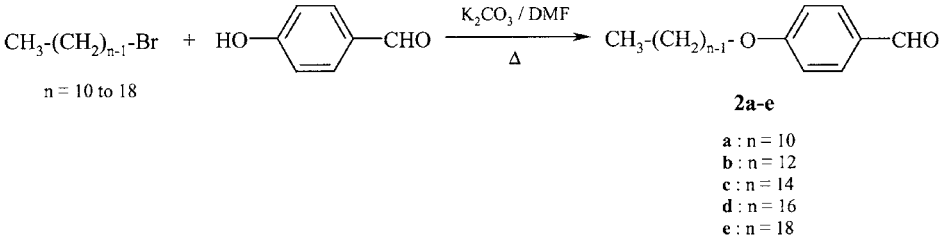
The compounds **2a**–**e** are obtained in quantitative yields, without any previous protection of the aldehyde moiety. Results are shown in Table 2. The presence of the ether group (O–CH_2) is confirmed by ^{1}H NMR (δ ^{1}H ~ 4.00, $^{3}J_{HH}$ = 6.5 Hz) and ^{13}C NMR (δ ^{13}C ~ 68) analysis. The signals at δ ^{1}H ~ 9.8 and δ ^{13}C ~ 190 are consistent with the presence of the aldehyde moiety.

For the synthesis of bis-[α-hydroxy-(4-alkoxybenzyl)]phosphinic acids, under the same reaction conditions as for aliphatic aldehydes (cf Table 1), monohydrated so-



Scheme 3 Competitive reactions in the case of addition of sodium hypophosphite to aliphatic aldehydes.

Downloaded by: University of Arizona Library. Copyrighted material.



Scheme 4 Synthesis of 4-alkoxybenzaldehydes **2** from 1-bromoalkanes and 4-hydroxy-benzaldehyde.

Table 2 Yields and NMR Parameters of 4-Alkoxybenzaldehydes **2**

Compnd No.	δ (^{1}H) ($^3J_{HH}$)[a]	δ (^{13}C)[a]	δ (^{1}H)[b]	δ (^{13}C)[b]	Yield (%)[c]
2a	3.81 (6.4)	68.2	9.86	190.2	91
2b	4.02 (6.5)	68.4	9.86	190.8	90
2c	4.00 (6.5)	68.4	9.85	190.8	96
2d	4.01 (6.4)	68.4	9.85	190.7	88
2e	4.02 (6.5)	68.5	9.87	190.8	81

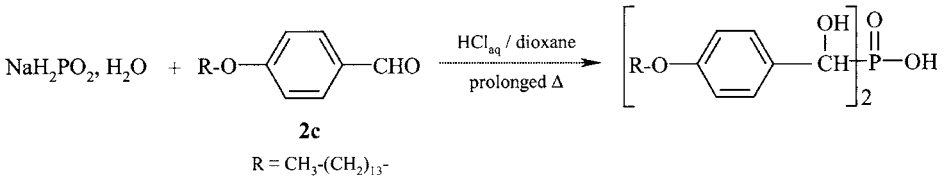
[a] ^{1}H and ^{13}C NMR chemical shifts of the O–CH_2 moiety in $CDCl_3$, *J* in Hz.
[b] ^{1}H and ^{13}C NMR chemical shifts of the aldehyde group in $CDCl_3$.
[c] Isolated yields.

dium hypophosphite was added to 2.5 equivalents of 4-tetradecyloxybenzaldehyde **2c** and heated under reflux (Scheme 5).

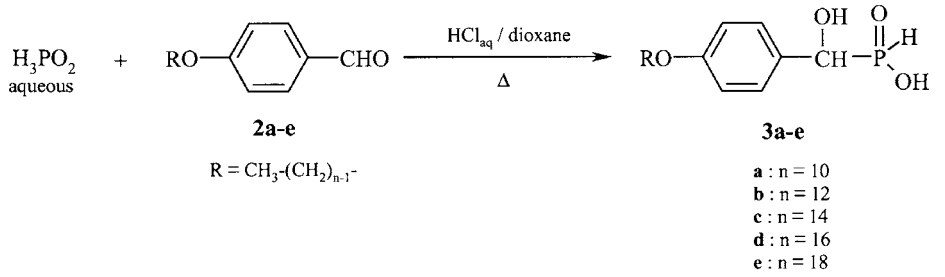
$^{31}P\{^1H\}$ NMR analysis of the reaction mixture shows two signals at δ ^{31}P = 38.3 and 36.9 corresponding to the two bis-[α-hydroxy-(4-tetradecyloxybenzyl)]phosphinic acid diastereomers (cf. II). However, formation of mono-substituted [α-hydroxy-(4-hydroxybenzyl)]phosphinic acid (δ ^{31}P = 26.3, $^1J_{PH}$ = 582 Hz) and bis-substituted bis-[α-hydroxy-(4-hydroxybenzyl)]phosphinic acids (δ ^{31}P = 32.6 and 31.7) also occurs at the same time, these compounds being the main products. Long heating under reflux induced the cleavage of the ether group and consequently the loss of the long alkyl chain(s). Actually, it was shown previously that cleavage of ethers could be achieved with aqueous hydrochloric acid in the presence of surfactants, leading to the corresponding alkyl chlorides.[16] This type of micellar-catalyzed reaction can be transposed to our case with respect to the amphiphilic nature of our reactants and adducts. Our attempts to catalyze the addition of sodium hypophosphite on 4-alkoxybenzaldehydes by another acid such as sulfuric acid remained unsuccessful.

We finally used the 4-alkoxybenzaldehydes **2a**–**e** to prepare single-chain α-hydroxy-(4-alkoxybenzyl)]phosphinic acid amphiphiles of enhanced hydrophobicity compared to (α-hydroxyalkyl)phosphinic and -phosphonic acids previously prepared in the laboratory.[11,12] We used the same protocol as for aliphatic aldehydes: 50% aqueous hypophosphorous acid was added to aromatic aldehydes **2a**–**e** (Scheme 6).

The reaction was carried out under heating but for a limited time of 2 hours due to the possibility of cleavage of the ether bond in the presence of hydrochloric acid (vide supra). New [α-hydroxy-(4-alkoxybenzyl)]phosphinic acids



Scheme 5 Synthesis of bis-[α-hydroxy-(4-tetradecyloxybenzyl)]phosphinic acid from sodium hypophosphite and 4-tetradecyloxybenzaldehyde.



Scheme 6 Synthesis of [α-hydroxy-(4-alkoxybenzyl)]phosphinic acids **3** from hypophosphorous acid and 4-alkoxybenzaldehydes **2**.

Downloaded by: University of Arizona Library. Copyrighted material.

3a–e were consequently obtained in moderate yields (30% to 50%). Results are reported in Table 3.

In the ^{31}P NMR spectra of compounds **3a–e** we observe a doublet at $\delta\ ^{31}P \sim 29.7$ ($^1J_{PH} \sim 525$ Hz) consistent with the presence of a phosphinic acid moiety. The ether moiety ($O–CH_2$) resonates at $\delta\ ^{13}C \sim 67$ and $\delta\ ^1H \sim 3.95$, confirming the conservation of the long alkyl chain.

New double-chain bis-(α-hydroxyalkyl)phosphinic acids were prepared from aliphatic aldehydes and sodium hypophosphite $NaH_2PO_2{\cdot}H_2O$ under prolonged heating. The same reaction carried out with new 4-alkoxybenzaldehydes, quantitatively prepared by an one-pot reaction, also leads to the bis-adducts but in very poor yields due to the cleavage of the ether bond in hydrochloric acid and micellar media. Finally, a new series of [α-hydroxy-(4-alkoxybenzyl)]phosphinic acids bearing a 10 to 18 carbon single chain was synthesized from 4-alkoxybenzaldehydes and 50% aqueous hypophosphorous acid under limited heating.

The study of the molecular aggregation of these new double-chain bis-(α-hydroxyalkyl)phosphinic acids and single-chain [α-hydroxy-(4-alkoxybenzyl)]phosphinic acids is currently in progress. After studying the properties of the (α-hydroxyalkyl)phosphinic and -phosphonic acids,[12] we wish to compare the influence of an enhanced hydrophobicity, brought about either by an additional alkyl chain or the introduction of an aromatic moiety, on the formation of stable monolayers at the air/water interface or on the formation of micelles, vesicles and lyotropic liquid crystals in aqueous media.

Spectra were recorded using the following instruments: IR spectra, Perkin-Elmer 225 or Perkin-Elmer IR-FT 1600; ^1H, ^{13}C and ^{31}P NMR spectra, Bruker AC80, AC200 or 250WM; mass spectra by chemical ionization (DCI/NH_3), Nermag R10-10H.

Melting points were measured in open glass capillaries with a Leitz Biomed apparatus or by differential scanning calorimetry (DSC) using a Perkin-Elmer Pyris 1 calorimeter.

Elemental analyses were performed by the Microanalytical Service Laboratory of the 'Laboratoire de Chimie de Coordination' of Toulouse.

1-Bromoalkanes C_{10} (Acros), C_{12}, C_{14} (Aldrich) and C_{16}, C_{18} (Lancaster), 4-hydroxybenzaldehyde (Aldrich), 50% aq hypophosphorous acid (Aldrich), aliphatic aldehydes (C_{10}–C_{14}) (Aldrich) and monohydrated sodium hypophosphite (Aldrich) were used as received without further purification. DMF was maintained over 4 Å molecular sieves and stored in dark bottles protected from moisture. K_2CO_3 was dried at 80 °C over night before use.

The purity of materials was assessed by elemental microanalysis, ^1H, ^{13}C and ^{31}P NMR, IR and mass spectroscopy. Yields indicated correspond to pure products.

Bis-(α-hydroxyalkyl)phosphinic acids 1; General procedure

To a solution of $NaH_2PO_2{\cdot}H_2O$ (0.5 g, 4.71 mmol) in dioxane (7 mL) was added long chain aldehyde (2.5 equiv) and aq HCl (37%) (2 equiv). The mixture was heated under reflux for 24 hours, leading to a brown solution which was then rotary evaporated. The obtained residue was washed with H_2O, THF and acetone to give a white powder (after removing solvents), and finally recrystallized from dioxane.

Bis-(α-hydroxydecyl)phosphonic Acid (1a)

Yield: 41%; mp 198 °C (from dioxane – decomposition temperature observed by DSC).

IR (KBr): 1141.5 and 1123.8 (P=O), 958.3 (POH) cm^{-1}.

^1H NMR (250.13 MHz, $CDCl_3$ + 2 drops of CD_3COOD): δ = 3.77 (d, $^2J_{HP}$ = 10.0 Hz, 2 H), 1.48–1.16 (m, 32 H), 0.76 (t, $^3J_{HH}$ = 6.8 Hz, 6H).

^{13}C NMR (100.61 MHz, $CDCl_3$ + 2 drops of CD_3COOD): δ = 68.8 (d, $^1J_{CP}$ = 102 Hz), 68.6 (d, $^1J_{CP}$ = 103 Hz), 31.9–22.6 (m), 13.9 (s).

^{31}P NMR (81.01 MHz, $CDCl_3$ + 2 drops of CD_3COOD): δ = 40.4 (m).

MS (DCI/NH_3): m/z = 379 $(M + H)^+$, 396 $(M + NH_4)^+$.

Anal. Calcd for $C_{20}H_{43}O_4P$: C, 63.46; H, 11.45. Found: C, 62.51; H, 11.10.

Bis-(α-hydroxydodecyl)phosphonic Acid (1b)

Yield: 44%; mp 143 °C (from hexane, observed by DSC).

IR (KBr): 1142.4 (P=O), 963.0 (POH) cm^{-1}.

^1H NMR (200.13 MHz, $CDCl_3$ + 2 drops of CD_3COOD): δ = 3.83 (m, 2 H), 1.49–1.15 (m, 40 H), 0.76 (t, $^3J_{HH}$ = 6.6 Hz, 6 H).

^{13}C NMR (50.32 MHz, $CDCl_3$ + 2 drops of CD_3COOD): δ = 68.6 (d, $^1J_{CP}$ = 102 Hz), 68.4 (d, $^1J_{CP}$ = 103 Hz), 31.8–22.5 (m), 13.8 (s).

^{31}P NMR (81.01 MHz, $CDCl_3$ + 2 drops of CD_3COOD): δ = 43.0 and 42.3 (m).

Table 3 Yields and NMR Parameters of [α-Hydroxy-(4-alkoxybenzyl)]phosphinic Acids **3**

Compd No.	δ (^{31}P) ($^1J_{PH}$)[a]	δ (^{13}C) ($^1J_{CP}$)[b]	δ (^1H) ($^2J_{HP}$)[b]	δ (^{13}C)[c]	δ (^1H)[c]	Yield (%)[d]
3a	29.7 (526)	71.0 (110.4)	4.66 (8.2)	67.3	3.94	46
3b	29.6 (526)	71.0 (110.5)	4.65 (8.2)	67.3	3.94	30
3c	29.7 (525)	71.1 (109.0)	4.66 (8.1)	67.4	3.96	30
3d	29.7 (525)	71.0 (109.0)	4.65 (7.7)	67.3	3.93	45
3e	29.7 (525)	71.4 (109.0)	4.65 (8.1)	67.6	3.95	40

[a] ^{31}P NMR chemical shifts in DMSO-d_6, J in Hz.
[b] ^{13}C and ^1H NMR chemical shifts of the methyne proton in DMSO-d_6, J in Hz.
[c] ^{13}C and ^1H NMR chemical shifts of ($O–CH_2$) moiety in DMSO-d_6.
[d] Isolated yields.

Downloaded by: University of Arizona Library. Copyrighted material.

MS (DCI/NH_3): *m*/*z* = 435 $(M + H)^+$, 452 $(M + NH_4)^+$.

Anal. Calcd for $C_{24}H_{51}O_4P$: C, 66.32; H, 11.83. Found: C, 66.02; H, 12.38.

Bis-(α-hydroxytetradecyl)phosphonic Acid (1c)
Yield 40%; mp 136 °C (from hexane, observed by DSC).

IR (KBr): 1141.3 and 1071.2 (P=O), 958.3 (POH) cm^{-1}.

^1H NMR (200.13 MHz, $CDCl_3$ + 2 drops of CD_3COOD): δ = 3.77 (d, $^2J_{HP}$ = 11.8 Hz, 2 H), 1.55–1.21 (m, 48 H), 0.83 (m, 6 H).

^{13}C NMR (62.89 MHz, $CDCl_3$ + 2 drops of CD_3COOD): δ = 68.8 (d, $^1J_{CP}$ = 99 Hz), 68.7 (d, $^1J_{CP}$ = 102 Hz), 31.8–22.6 (m), 13.9 (s).

^{31}P NMR (81.01 MHz, $CDCl_3$ + 2 drops of CD_3COOD): δ = 41.8 (m).

MS (DCI/NH_3): *m*/*z* = 491 $(M + H)^+$, 508 $(M + NH_4)^+$.

Anal. Calcd for $C_{28}H_{59}O_4P$: C, 68.53; H, 12.12. Found: C, 68.59; H, 12.27.

4-Alkoxybenzaldehydes 2; General Procedure
The reaction was carried out under an argon atmosphere. To a stirred mixture of 4-hydroxybenzaldehyde (1.22 g, 1 equiv) and anhyd K_2CO_3 (7 g, 5 equiv) in anhyd DMF (30 mL) was added 1-bromoalkane (1 equiv). The mixture was stirred at 80 °C for 90 min, allowed to cool to r.t. and then diluted with H_2O (75 mL). After extraction with EtOAc (4 × 30 mL), the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and rotary evaporated. The resulting oily residue was finally purified on chromatographic silica column eluted with CH_2Cl_2 leading to a yellow waxy solid.

4-Decyloxybenzaldehyde (2a)
Yield: 91%; R_f (CH_2Cl_2) 0.48.

IR (KBr): 1693.3 (C=O), 1601.2 (C=C) cm^{-1}.

^1H NMR (200.13 MHz, $CDCl_3$): δ = 9.86 (s, 1 H), 7.62 (m, 2 H), 6.79 (m, 2 H), 3.81 (t, $^3J_{HH}$ = 6.4 Hz, 2 H), 1.62 (m, 2 H), 1.11 (m, 14 H), 0.73 (t, $^3J_{HH}$ = 7.1 Hz, 3 H).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 190.2 (s), 164.1 (s), 131.7 (s), 114.6 (s), 129.7 (s), 68.2 (s), 31.9–22.6 (m), 14.0 (s).

MS (DCI/NH_3): *m*/*z* = 263 $(M + H)^+$, 280 $(M + NH_4)^+$.

4-Dodecyloxybenzaldehyde (2b)
Yield: 90%; mp 25–28 °C (from CH_2Cl_2); R_f (CH_2Cl_2) 0.53.

IR (KBr): 1694.8 (C=O), 1601.4 (C=C) cm^{-1}.

^1H NMR (200.13 MHz, $CDCl_3$): δ = 9.86 (s, 1 H), 7.81 (m, 2 H), 6.97 (m, 2 H), 4.02 (t, $^3J_{HH}$ = 6.5 Hz, 2 H), 1.80 (m, 2 H), 1.25 (m, 18 H), 0.86 (t, $^3J_{HH}$ = 6.2 Hz, 3 H).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 190.8 (s), 164.3 (s), 132.0 (s), 114.8 (s), 129.8 (s), 68.4 (s), 31.9–22.7 (m), 14.1 (s).

MS (DCI/NH_3): *m*/*z* = 291 $(M + H)^+$, 308 $(M + NH_4)^+$.

4-Tetradecyloxybenzaldehyde (2c)
Yield: 96%; mp 39–40 °C (from CH_2Cl_2); R_f (CH_2Cl_2) 0.57.

IR (KBr): 1692.1 (C=O), 1601.5 (C=C) cm^{-1}.

^1H NMR (200.13 MHz, $CDCl_3$): δ = 9.85 (s, 1 H), 7.79 (m, 2 H), 6.96 (m, 2 H), 4.00 (t, $^3J_{HH}$ = 6.5 Hz, 2 H), 1.79 (m, 2 H), 1.24 (m, 22 H), 0.86 (t, $^3J_{HH}$ = 6.6 Hz, 3 H).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 190.8 (s), 164.3 (s), 132.0 (s), 114.8 (s), 129.8 (s), 68.4 (s), 32.0–22.7 (m), 14.2 (s).

MS (DCI/NH_3): *m*/*z* = 319 $(M + H)^+$, 336 $(M + NH_4)^+$.

4-Hexadecyloxybenzaldehyde (2d)
Yield: 88%; mp 49–50 °C (from CH_2Cl_2); R_f (CH_2Cl_2) 0.56.

IR (KBr): 1690.2 (C=O), 1602.0 (C=C) cm^{-1}.

^1H NMR (200.13 MHz, $CDCl_3$): δ = 9.85 (s, 1 H), 7.80 (m, 2 H), 6.96 (m, 2 H), 4.01 (t, $^3J_{HH}$ = 6.4 Hz, 2 H), 1.79 (m, 2 H), 1.24 (m, 26 H), 0.86 (t, $^3J_{HH}$ = 6.5 Hz, 3 H).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 190.7 (s), 164.3 (s), 132.0 (s), 114.7 (s), 129.8 (s), 68.4 (s), 32.0–22.7 (m), 14.1 (s).

MS (DCI/NH_3): *m*/*z* = 347 $(M + H)^+$, 364 $(M + NH_4)^+$.

4-Octadecyloxybenzaldehyde (2e)
Yield 81%; mp 52–54 °C (from CH_2Cl_2); R_f (CH_2Cl_2) 0.61.

IR (KBr): 1691.7 (C=O), 1601.6 (C=C) cm^{-1}.

^1H NMR (200.13 MHz, $CDCl_3$): δ = 9.87 (s, 1 H), 7.81 (m, 2 H), 6.97 (m, 2 H), 4.02 (t, $^3J_{HH}$ = 6.5 Hz, 2 H), 1.80 (m, 2 H), 1.25 (m, 30 H), 0.87 (t, $^3J_{HH}$ = 6.2 Hz, 3 H).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 190.8 (s), 164.3 (s), 132.0 (s), 114.8 (s), 129.8 (s), 68.5 (s), 32.0–22.7 (m), 14.2 (s).

MS (DCI/NH_3): *m*/*z* = 375 $(M + H)^+$, 392 $(M + NH_4)^+$.

[α-Hydroxy-(4-alkoxybenzyl)]phosphinic Acids 3; General Procedure
A heterogeneous mixture of hypophosphorous acid (50% aq) (6.8 mmol), aldehyde (1 equiv) and aq HCl (37%) (0.05 mL) in dioxane (6 mL) was stirred at 80 °C for 2 h. Solvents were rotary evaporated and the residue was washed with distilled H_2O, *n*-hexane, 2-propanol and finally recrystallized from dioxane. The given white solid was then filtered off and dried under vacuum.

[α-Hydroxy-(4-decyloxybenzyl)]phosphinic Acid (3a)
Yield: 46%; mp 107–117 °C (from dioxane).

IR (KBr): 2407.1 (PH), 1609.9 (C=C), 1156.3 and 1103.7 (P=O), 960.2 (POH) cm^{-1}.

^1H NMR (200.13 MHz, DMSO-d_6): δ = 7.27 (m, 2 H), 6.89 (m, 2 H), 6.71 (d, $^1J_{HP}$ = 526 Hz, 1 H), 4.66 (d, $^2J_{HP}$ = 8.2 Hz, 1 H), 3.94 (t, $^3J_{HH}$ = 6.2 Hz, 2 H), 1.70 (m, 2 H), 1.26 (m, 14 H), 0.87 (t, $^3J_{HH}$ = 6.4 Hz, 3 H).

^{13}C NMR (50.32 MHz, DMSO-d_6): δ = 158.0 (s), 129.1 (s), 128.2 (s), 113.8 (s), 71.0 (d, $^1J_{CP}$ = 110 Hz), 67.3 (s), 31.2–22.0 (m), 13.9 (s).

^{31}P NMR (81.01 MHz, DMSO-d_6): δ = 29.7 (d, $^1J_{PH}$ = 526 Hz).

MS (DCI/NH_3): *m*/*z* = 330 $(MH_2)^+$, 346 $(M + NH_4)^+$.

Anal. Calcd for $C_{17}H_{29}O_4P$: C, 62.18; H, 8.90. Found: C, 62.29; H, 8.73.

[α-Hydroxy-(4-dodecyloxybenzyl)]phosphinic Acid (3b)
Yield: 30%; mp 109–119 °C (from dioxane).

IR (KBr): 2409.1 (PH), 1609.4 (C=C), 1156.3 and 1103.0 (P=O), 960.1 (POH) cm^{-1}.

^1H NMR (200.13 MHz, DMSO-d_6): δ = 7.27 (m, 2 H), 6.89 (m, 2 H), 6.72 (d, $^1J_{HP}$ = 526 Hz, 1 H), 4.65 (d, $^2J_{HP}$ = 8.2 Hz, 1 H), 3.94 (t, $^3J_{HH}$ = 6.2 Hz, 2 H), 1.70 (m, 2 H), 1.26 (m, 18 H), 0.87 (t, $^3J_{HH}$ = 6.4 Hz, 3 H).

^{13}C NMR (50.32 MHz, DMSO-d_6): δ = 158.0 (s), 129.1 (s), 128.2 (s), 113.8 (s), 71.0 (d, $^1J_{CP}$ = 111 Hz), 67.3 (s), 31.2–22.0 (m), 13.9 (s).

^{31}P NMR (81.01 MHz, DMSO-d_6): δ = 29.6 (d, $^1J_{PH}$ = 526 Hz).

MS (DCI/NH_3): *m*/*z* = 358 $(MH_2)^+$, 374 $(M + NH_4)^+$.

Anal. Calcd for $C_{19}H_{33}O_4P$: C, 64.02; H, 9.33. Found: C, 64.05; H, 9.21.

Downloaded by: University of Arizona Library. Copyrighted material.

[α-Hydroxy-(4-tetradecyloxybenzyl)]phosphinic Acid (3c)
Yield: 30%; mp 108–116 °C (from dioxane).

IR (KBr): 2428.6 (PH), 1608.4 (C=C), 1173.9 (P=O), 1002.7 and 939.8 (POH) cm^{-1}.

^{31}P NMR (81.01 MHz, DMSO-d_6): δ = 29.7 (d, $^1J_{PH}$ = 525 Hz).

^1H NMR (200.13 MHz, DMSO-d_6): δ = 7.29 (m, 2 H), 6.89 (m, 2 H), 6.71 (d, $^1J_{HP}$ = 526 Hz, 1 H), 4.66 (d, $^2J_{HP}$ = 8.1 Hz, 1 H), 3.96 (t, $^3J_{HH}$ = 6.4 Hz, 2 H), 1.71 (m, 2 H), 1.27 (m, 22 H), 0.87 (m, 3 H).

^{13}C NMR (50.32 MHz, DMSO-d_6): δ = 158.1 (s), 129.2 (s), 128.2 (s), 113.8 (s), 71.1 (d, $^1J_{CP}$ = 109 Hz), 67.4 (s), 31.2–21.9 (m), 13.8 (s).

MS (DCI/NH_3): *m*/*z* = 386 $(MH_2)^+$, 402 $(M + NH_4)^+$.

Anal. Calcd for $C_{21}H_{37}O_4P$: C, 65.60; H, 9.70. Found: C, 65.52; H, 10.10.

[α-Hydroxy-(4-hexadecyloxybenzyl)]phosphinic Acid (3d)
Yield: 45%; mp 110–113 °C (from acetone).

IR (KBr): 2434.5 (PH), 1608.5 (C=C), 1174.0 (P=O), 1004.0 (POH) cm^{-1}.

^{31}P NMR (81.01 MHz, DMSO-d_6): δ = 29.7 (d, $^1J_{PH}$ = 525 Hz).

^1H NMR (200.13 MHz, DMSO-d_6): δ = 7.26 (m, 2 H), 6.88 (m, 2 H), 6.70 (d, $^1J_{HP}$ = 525 Hz, 1 H), 4.65 (d, $^2J_{HP}$ = 7.7 Hz, 1 H), 3.93 (t, $^3J_{HH}$ = 5.6 Hz, 2 H), 1.69 (m, 2 H), 1.24 (m, 26 H), 0.85 (m, 3 H).

^{13}C NMR (50.32 MHz, DMSO-d_6): δ = 158.0 (s), 129.2 (s), 128.3 (s), 113.8 (s), 71.0 (d, $^1J_{CP}$ = 109 Hz), 67.3 (s), 31.2-22.0 (m), 13.9 (s).

MS (DCI/NH_3): *m*/*z* = 414 $(MH_2)^+$, 430 $(M + NH_4)^+$.

Anal. Calcd for $C_{23}H_{41}O_4P$: C, 66.96; H, 10.01. Found: C, 66.95; H, 10.01.

[α-Hydroxy-(4-octadecyloxybenzyl)]phosphinic Acid (3e)
Yield: 40%; mp 108-120 °C (from dioxane).

IR (KBr): 2363.4 (PH), 1610.6 (C=C), 1156.6 and 1101.9 (P=O), 961.6 (POH) cm^{-1}.

^1H NMR (200.13 MHz, DMSO-d_6): δ = 7.29 (m, 2 H), 6.87 (m, 2 H), 6.74 (d, $^1J_{HP}$ = 526 Hz, 1 H), 4.65 (d, $^2J_{HP}$ = 8.1 Hz, 1 H), 3.95 (t, $^3J_{HH}$ = 6.4 Hz, 2 H), 1.70 (m, 2 H), 1.20 (m, 30 H), 0.87 (t, $^3J_{HH}$ = 6.2 Hz, 3 H).

^{13}C NMR (50.32 MHz, DMSO-d_6): δ = 158.1 (s), 129.4 (s), 128.1 (s), 113.9 (s), 71.4 (d, $^1J_{CP}$ = 109 Hz), 67.6 (s), 31.2–21.9 (m), 13.6 (s).

^{31}P NMR (81.01 MHz, DMSO-d_6): δ = 29.7 (d, $^1J_{PH}$ = 525 Hz).

MS (DCI/NH_3): *m*/*z* = 442 $(MH_2)^+$, 458 $(M + NH_4)^+$.

Anal. Calcd for $C_{25}H_{45}O_4P$: C, 68.15; H, 10.29. Found: C, 68.62; H, 9.94.

References

(1) New address: Alice Brun, Max-Planck-Institute of Colloids and Interfaces, 14424 Potsdam, Germany; fax +49(331)5679202; e-mail alice.brun@mpikg-golm.mpg.de
(2) Deceased 07.03.2002.
(3) (a) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5587. (b) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5591. (c) Stowasser, B.; Budt, K. H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 1625. (d) Peyman, A.; Budt, K. H.; Spanig, J.; Ruppert, D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1720. (e) Black, R. M.; Harrison, J. M. *The Chemistry of Organophosphorus Compounds*, Vol. 4; Hartley, F. R., Ed.; Wiley: New York, **1996**, 781; and references cited therein.
(4) (a) Ruel, R.; Bouvier, J.-P.; Young, R. N. *J. Org. Chem.* **1995**, *60*, 5209. (b) Page, P. C. B.; Moore, J. P. G.; Mansfield, I.; McKenzie, M. J.; Bowler, W. B.; Gallagher, J. A. *Tetrahedron* **2001**, *57*, 1837.
(5) (a) Einhäuser, Th. J.; Galanski, M.; Vogel, E.; Keppler, B. K. *Inorg. Chim. Acta* **1997**, *257*, 265. (b) Kalir, A.; Kalir, H. H. *The Chemistry of Organophosphorus Compounds*, Vol. 4; Hartley, F. R., Ed.; Wiley: New York, **1996**, 767; and references cited therein. (c) Fields, S. C. *Tetrahedron* **1999**, *55*, 12237; and references cited therein. (d) Baylis, E. K. Eur. Pat. Appl. EP 614900, **1994**. (e) Budavari, S. *Merck Index*, 11th Ed.; Merck Rahway: NJ, **1989**, 665; (no. 4169). (f) Hidaka, T.; Iwakura, H.; Imai, S.; Soto, H. *J. Antibiot.* **1992**, *45*, 1008. (g) Shiraki, K.; Okuno, T.; Yamanishi, K.; Takahashi, M. *Antiviral Res.* **1989**, *12*, 311. (h) Hudson, H. R.; Ismail, F.; Pianka, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2001**, *173*, 143.
(6) (a) Petrov, K. A.; Parshina, V. A. *Russ. Chem. Rev.* **1968**, *37*, 532; and references cited therein. (b) Kerr, E. A.; Rideout, J. Eur. Pat. Appl. EP 516,346, **1992**. (c) Telegdi, J.; Shaglouf, M. M.; Shaban, A.; Karman, F. H.; Betroti, I.; Mohai, M.; Kalman, E. *Electrochim. Acta* **2001**, *46*, 3791.
(7) (a) Herranz, C. *Tenside Detergents* **1981**, *18*, 190. (b) Herranz, C.; Martinez, M. J. *J. Disp. Sci. Technol.* **1988**, *9*, 209. (c) Martinez, M.; Herranz, C.; Miralles, N.; Sastre, A. *J. Disp. Sci. Technol.* **1995**, *16*, 221. (d) Martinez, M.; Miralles, N.; Sastre, A.; Herranz, C. *Hydrometallurgy* **1993**, *33*, 95.
(8) (a) Kunitake, T.; Okahata, Y. *Bull. Chem. Soc. Jpn.* **1978**, *51(6)*, 1877. (b) Wagenaar, A.; Rupert, L. A. M.; Engberts, J. B. F. N.; Hoekstra, D. *J. Org. Chem.* **1989**, *54*, 2638. (c) Walde, P.; Wessicken, M.; Rädler, U.; Berclaz, N.; Conde-Frieboes, K.; Luisi, P. L. *J. Phys. Chem. B* **1997**, *101*, 7390.
(9) Aoyagi, T.; Yamamura, M.; Matsui, K.; Nagase, Y. *Drug Des. Discov.* **1991**, *8*, 47.
(10) Einhäuser, Th. J.; Galanski, M.; Vogel, E.; Keppler, B. K. *Inorg. Chim. Acta* **1997**, *257*, 265.
(11) Albouy, D.; Brun, A.; Munoz, A.; Etemad-Moghadam, G. *J. Org. Chem.* **1998**, *63*, 7223.
(12) Brun, A.; Albouy, D.; Perez, E.; Rico-Lattes, I.; Etemad-Moghadam, G. *Langmuir* **2001**, *17*, 5208.
(13) Albouy, D.; Etemad-Moghadam, G.; Koenig, M. *Eur. J. Org. Chem.* **1999**, 861.
(14) (a) Majewski, P. *Synthesis* **1987**, 555. (b) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, **1994**, 67. (c) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, **1994**, 123. (d) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, **1994**, 230.
(15) Wagner, R. W.; Lindsey, J. S.; Turowska-Tyrk, I.; Scheidt, W. R. *Tetrahedron* **1994**, *50*, 11097.
(16) Jursic, J. *J. Chem. Res., Synop.* **1989**, 284.

Downloaded by: University of Arizona Library. Copyrighted material.