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First general methods toward aldehyde enolphosphates

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ABSTRACT

We herein report two innovative methods toward aldehyde enolphosphates and the first saccharidic aldehyde enolphosphates. Aldehyde enolphosphate function is worthwhile to be considered as a good phosphoenolpyruvate analogue.

1. Introduction

Enolphosphates derivatives are compounds of great interest in metal-catalysed cross-coupling reactions. They are key intermediates in the formation of C—C bonds via ring-closing metathesis or palladium-catalysed functionalisation of lactones, lactams, ketones and enones. Enolphosphates constitute a promising alternative to their analogous triflates, because they are more stable, easier to isolate and undergo effective Pd-catalysed coupling. The synthetic potential of the enolphosphates was demonstrated by its successful application to the construction of N- and O-heterocycles, complex polycyclic ethers and numerous natural products [1–9].

Moreover, enolphosphates could become of various interests in terms of biological applications, because they incorporate the structural part of phosphoenolpyruvate (PEP). This is biologically interesting as the PEP is involved in essential metabolic transformations of living organisms mainly as a phosphate donor and plays an important role in the metabolism of ulosonic acids like KDO, DAH or KDN [10]. Previous investigations about inhibitors of KDO 8-phosphate synthase and DAH 7-phosphate synthase suggest that enolphosphate group derived from aldehyde could be a good analogue of PEP [11–13].

However, the synthesis of aldehyde enolphosphates remains a challenging task in organic synthesis as suppression of the carboxylic acid moiety of PEP increases the fragility of the vinyl group structure. Moreover, only few syntheses of a vinylphosphate moiety have been reported. Most of them are based on the electrophilic phosphorylation of enolates which reacts at the *O*-position with phosphochloridate derivatives [2,14]. The method is subordinated to the preparation and stability of the enolates and is totally inadequate for enolphosphates derived from aldehyde enolates.

The second direct way to enolphosphates is the Perkow reaction involving trialkylphosphites and α-halogenoketones [15]. Its general use is first limited by the availability of the halogenated carbonyl compounds, but its main drawback is usually the competitive Michaelis–Arbuzov reaction leading to corresponding β-ketophosphonate [16]. Thus, the study of this reaction is restricted to haloketones bearing nonsensitive functionality [17].

2. Results and discussion

Based on recent findings with synthetic and biological results of enolphosphates derived from aldehydes [13], we report herein the full details of two complementary approaches to aldehyde enolphosphates: the first one is based on Perkow reaction, the second one on hydroalumination–phosphorylation tandem reaction.

2.1. Based on Perkow reaction

Previously, we reported a rapid and efficient synthesis of glucidic phosphoenolpyruvic acid derivatives based on a Perkow reaction using a suitable halogenated precursor, β-halogeno-α-ketoester or α-halogenoglycidic ester, and trimethylphosphite [18]. Prompted by these results, we decided to investigate the Perkow reaction between α-iodoaldehydes and trialkylphosphite in order to prepare the first functionalised aldehyde enolphosphates (Scheme 1).

We used a large variety of functions on our model compounds to test its compatibility with the synthesis' conditions: alkyl chain, free alcohol, pivaloyl or methyl ester, silyl ether, dialkylphosphate and isopropylidene acetal. While **1a** is commercial, the synthesis of

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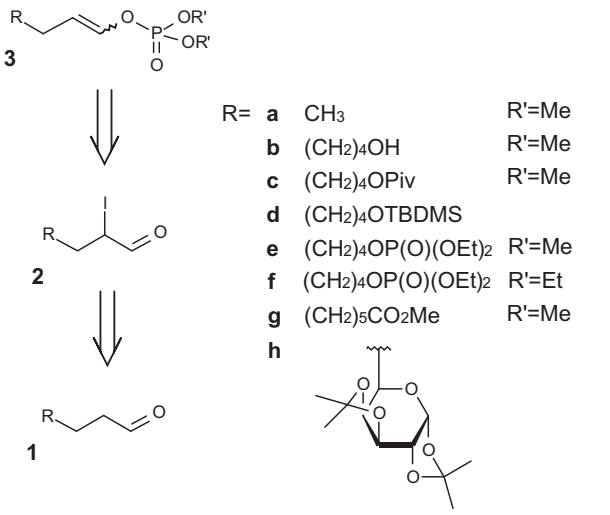
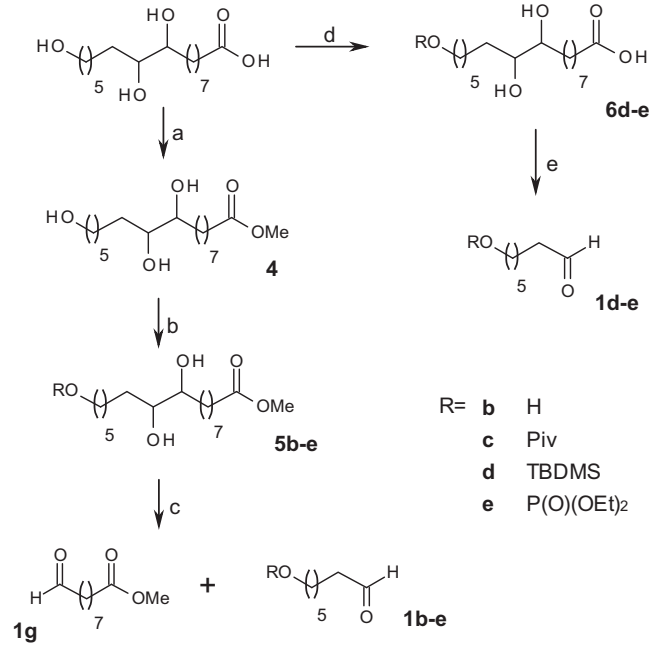


Scheme 1. Retrosynthetic scheme for the preparation of aldehyde enolphosphates using Perkow reaction.

required aldehydes **1b–g** is shown in Scheme 2 and aldose **1h** in Scheme 4.

Treatment of 9,10,16-trihydroxyhexadecanoic acid (commercially available) with MeOH, in the presence of catalytic $BF_3.Et_2O$, led to the formation of the corresponding methyl ester **4**. Although the synthesis can be carried out with the free primary alcohol (**5b**), we studied various protections as diethylphosphate (**5e**), pivaloyl (**5c**) or *tert*-butyldimethylsilyl (**5d**) functions. Selective protection of the primary 16-OH of triols, **4** or the commercial one, was obtained following conditions in Table 1.

Using periodate oxidation under Malaprade conditions on diols **5b–e** afforded the target aldehydes **1b–g** in good yields. In the case of the silylated protection, **1d**, yield was slightly lower for this step



Scheme 2. Synthesis of aldehydes **1b–g**. Reagents and conditions: (a) BF_3—Et_2O cat., MeOH, 15 h, 35 °C, 75%; (b) see Table 1; (c) 1.1 eq. $NaIO_4$, H_2O/MeOH 1:3, 18 h, 20 °C, **1b**: 60%–**1c**: 66%–**1d**: 53%–**1e**: 69%; (d) see Table 1; (e) 1.1 eq. $NaIO_4$, solid $NaHCO_3$ until pH 9, H_2O/MeOH 1:3, 18 h, 20 °C, **1d**: 35%–1e: 59%.

Table 1
Mono protection for terminal alcohol of triols.

Product	Conditions	Yields (%)
5c	PivCl (1 eq.), Pyridine, 0 °C, 2 h	89
5d	TBDMSCl (1.1 eq.), Et_3N (1.1 eq.), DMAP (0.5 eq.), 12 h, CH_2Cl_2	88
5e	$ClP(O)(OEt)_2$ (1 eq.), DMAP (0.5 eq.), 12 h, 0 °C, Pyridine	96
6d	TBDMSCl (2.1 eq.), Et_3N (2.1 eq.), DMAP (0.5 eq.), 72 h, CH_2Cl_2	80
6e	$ClP(O)(OEt)_2$ (1 eq.), DMAP (0.5 eq.), 12 h, 0 °C, Pyridine	97

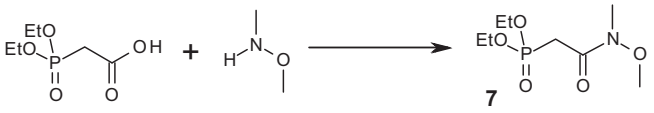
(even if global yield is good: 35% from commercial compound) due to partial cleavage of the protecting group leading to 12% of compound **1b**.

It's worth noting 9,10,16-trihydroxyhexadecanoic acid can be used instead of its methyl ester **4**. Selective phosphorylation or silylation, directly carried out on the carboxylic acid, followed by periodate oxidation (maintaining pH to 9 by direct addition of solid $NaHCO_3$) gave satisfactory yields of the corresponding aldehydes **1d–e**.

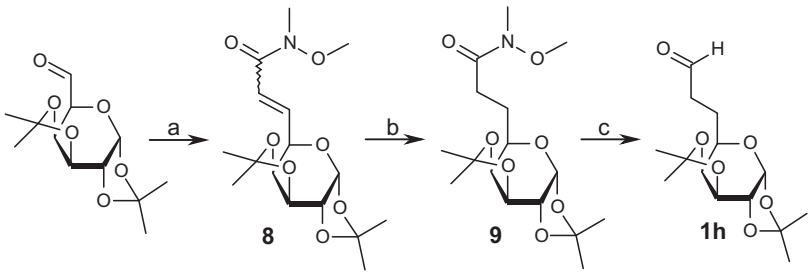
Dialdose **1h** has been prepared from easily accessible 1,2;3,4-di-*O*-isopropylidene-dialdo-α-D-galactopyranoside [19]. Homologation method used the Weinreb's phosphonoacetamide **7**, a Horner's reagent which is generally obtained by laborious Michaelis–Arbuzov reaction between triethylphosphite and chloroacetamide [20]. We re-investigated the preparation of Weinreb's phosphonoacetamide with the aim of shortening the reaction time and increasing the effectiveness of preparation. Following our previous work on the synthesis of *C*-phosphonopeptides [21], Weinreb's phosphonoacetamide was synthesised by the coupling of diethylphosphonoacetic acid with *N*,*O*-dimethylhydroxylamine in presence of BOP and triethylamine in dichloromethane. The phosphonoacetamide was obtained pure after an easy chromatographic purification in good yield (Scheme 3). This new synthesis allowed preparing large amounts of Weinreb's phosphonoacetamide **7** more readily than the known method.

Homologation has then been performed following Scheme 4. Horner reaction was achieved on 1,2;3,4-di-*O*-isopropylidene-dialdo-α-D-galactopyranoside using the Weinreb's phosphonoacetamide which was deprotonated by slow addition to LDA solution at −70 °C in THF. Dialdose was then added and reaction stirred 30 min at room temperature. Usual work-up and silica-gel chromatography gave acetamide **8** in good yield (76%). *E*/*Z* ratio of 73/27 has been determined by ^1H NMR [$\delta_{H\beta}$ is 6.12 ppm for (*Z*)-**8** and 6.93 ppm for (*E*)-**8**].

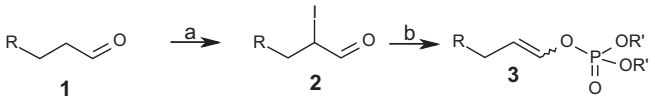
Two successive reductions allowed preparing dialdose **1h**. The first one, a quantitative catalytic hydrogenation of **8** with palladium on carbon led to carboxamide **9** after a simple filtration of catalytic material. The second one was much more complicated as the amide had to be reduced to its corresponding aldehyde. Reduction was achieved with lithium aluminium hydride with very good yield as long as temperature was kept between −3 and 5 °C. Likewise, no purification was required for this step as aldehyde was of high purity after standard workup.

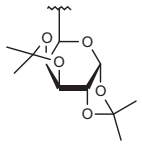


Scheme 3. Preparation of Weinreb's phosphonoacetamide. Reagents and conditions: 1 eq. BOP, 1 eq. Et_3N, CH_2Cl_2, 12 h, rt, 77%.



Scheme 4. Homologation of 1,2;3,4-di-*O*-isopropylidene-dialdo-α-D-galactopyranoside. Reagents and conditions: (a) 1 eq. LDA, 1 eq. Weinreb's reagent, THF, −70 °C then 30 min. rt, 76%; (b) H_2 (10 bars), Pd/C cat., MeOH, 12 h, rt, 100%; (c) 1 eq. $LiAlH_4$, N_2, THF, 0 °C, 30 min, 87%.



R=			Yield (%) **2**	Yield (%) **3**	E/Z ratio
a	CH_3	R'=Me	100	100	58/42
b	$(CH_2)_4OH$	R'=Me	97	100	28/72
c	$(CH_2)_4OPiv$	R'=Me	98	100	61/39
d	$(CH_2)_4OTBDMS$		0 (90% of **2b**)	/	/
e	$(CH_2)_4OP(O)(OEt)_2$	R'=Me	98	100	52/48
f	$(CH_2)_4OP(O)(OEt)_2$	R'=Et	98	100	48/52
g	$(CH_2)_5CO_2Me$	R'=Me	100	100	45/55
h			0	/	/

Scheme 5. α-Iodination of aldehydes 1 and Perkow reaction to 3. Reagents and conditions: (a) 1 eq. I_2, 0.5 eq. $HgCl_2$, CH_2Cl_2, rt, 4 h. (b) 1 eq. $(R'O)_3P$, rt, 12 h.

Aldehydes **1a–h** were submitted to direct iodination using the $HgCl_2/I_2$ system described by Barluenga with long chain aldehydes (Scheme 5) [22]. The mixture reaction was stirred vigorously for 4 h at room temperature. The solution was filtered and the filtrate washed with an aqueous sodium thiosulfate solution. After standard work up, **2a–c**,**e–g** were cleanly obtained in nearly quantitative yields without further purification. It should be noted the very good stability of the phosphate, methyl and pivaloyl ester functions in spite of iodination conditions' acidic medium. However **1d** submitted to iodination system gave a 90% of **2b** α-iodoaldehyde: silyl ether protection was totally cleaved leading to the alcohol compound. Regarding the carbohydrate **1h**, its isopropylidene acetals and its skeleton were completely degraded by the acidic medium.

The α-iodoaldehyde function being very fragile, compounds **2** must be engaged in the Perkow reaction quickly. Reaction of **2a–c**,**e–g** with trialkylphosphite, at room temperature, without solvent and stirring for 12 h, led to the clean and quantitative formation of diethyl and dimethylenolphosphates **3a–c**,**e–g** (Scheme 5). As clearly indicated, especially by the ^{31}P NMR spectra of the crude materials, the α-iodoaldehydes **2** were completely consumed and no by-product can be detected. α-Iodoaldehydes were found to be particularly suitable substrates for the reaction of Perkow. After a simple evaporation of residual trialkylphosphite's excess, the purity and yields of enolphosphates **3a-c,e-g** were excellent. Iodoaldehydes differ significantly from halogenoketones for whom the competitive formation of the Michaelis–Arbusov reaction product is difficult to avoid. ^1H NMR spectra showed mixtures of *E* (J_{1H-2H} = 11.8 Hz) and *Z* (J_{1H-2H} = 7.7 Hz) geometrical isomers. Due to deshielding by the ester phosphate group, the 2-H signal in *E*-isomer (δ 5.45) appeared at considerably lower field than the corresponding *Z*-enolphosphate's 2-H signal (δ 4.88). Interestingly, the examination of the ^{31}P NMR spectra showed the presence of both *E*- (δ_P −0.83) and *Z*- (δ_P −1.26) enolphosphates. It could be noted the significant δ_P values' difference between saturated (δ_P 0.40) and unsaturated phosphate moiety of **3e,f**.

This first synthesis of 1-alkenyldiphosphates is rapid, simple, efficient and can easily be scaled up. Chemical yields are excellent and the reaction's conditions allow preserving some of the functionalities and avoiding uneasy purifications of fragile products at each step. However, this method cannot be applied to compounds bearing acidic sensitive function, like isopropylidene or silylether protections. It is however compatible with free alcohol, pivaloyl or methylester and dialkylphosphate function.

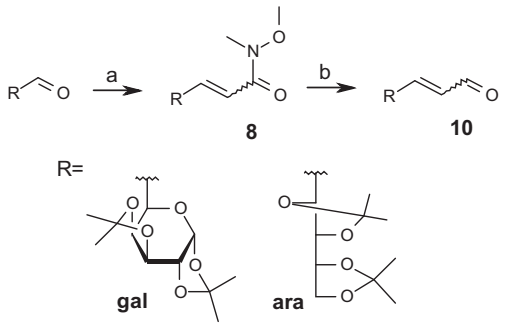
2.2. Hydroalumination–phosphorylation tandem reaction

This major inconvenient led us to develop another method for those highly sensitive compounds. Inspired by Tsuda and co. about the alkylation and silylation of the aluminium enolates generated by hydroalumination of α,β-unsaturated carbonyl compounds [23], we developed a second strategy, to the first enolphosphates in glucidic series: this method is based on the hydroalumination of α,β-unsaturated dialdose **10gal** or aldose **10ara**, leading to its respective aluminium enolates which could be activated as ate-complexes to be phosphorylated by dialkylchlorophosphate. α,β-Unsaturated aldoses **10gal**, **10ara** were prepared by homologation of 1,2;3,4-di-*O*-isopropylidene-dialdo-α-D-galactopyranoside and 2,3;4,5-di-*O*-isopropylidene-D-arabinose (obtained from D-arabinose according Zinner et al. procedure [24]) respectively (Scheme 6).

Horner reaction between aldoses and Weinreb's reagent was performed as exposed above (Schemes 3 and 4). Yield, which was good with galactose derivative, was excellent with arabinose derivative. As presented previously, the sensitive and selective reduction of carboxamides **8gal**, **8ara** by $AlLiH_4$ solution, leading to α,β-unsaturated aldehydes **10gal**, **10ara**, was realised in good yield as long as reaction's temperature was maintained between −3 and 5 °C. ^1H NMR allowed us to determine *E*/*Z* ratio of 91/9 for **10gal** and higher than 95/5 for **10ara**. Finally, it should be noted that we developed a very good pathway to (*E*)-α,β-unsaturated aldehydes using the Weinreb's phosphonoacetamide.

Synthesis of glucidic enolphosphates **11gal**, **11ara** is presented in Scheme 7.

Aluminium enolates were generated from α,β-ethylenic aldehydes **10gal**, **10ara** by selective conjugate addition of methyl copper with DIBAH–HMPA. Catalytic methyl copper was prepared in situ reacting CuI and MeLi in presence of HMPA. DIBAH was then added to release a "CuH" complex which can reduce selectively the conjugated double *C*—*C* bond of α,β-unsaturated aldehydes **10gal**, **10ara**. The aluminium enolates were then activated as lithium

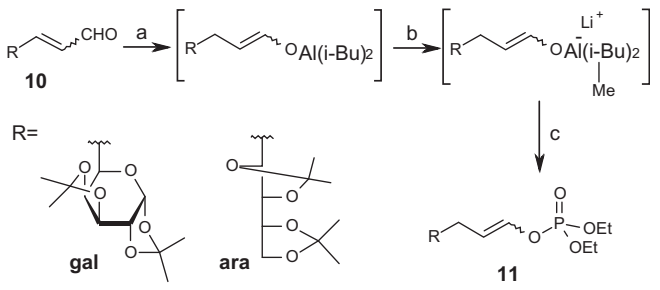


Scheme 6. Preparation of α,β-unsaturated aldoses. Reagents and conditions: (a) 1 eq. LDA, 1 eq. Weinreb's reagent, THF, −70 °C then rt 30 min, **8gal**: 76%–**8ara**: 98%; (b) 1 eq. $LiAlH_4$, N_2, THF, 0 °C, 30 min, **10gal**: 87%–**10ara**: 71%.

ate-complexes to increase their nucleophilicity. This activation was carried out by addition of methyl lithium to the reaction. Ate-complexes were finally reactive enough to be trapped by diethylchlorophosphate. Appropriate treatment of the reaction has been developed to obtain crude enolphosphates **11gal**, **11ara** which are extremely fragile: after evaporation of THF, diethylether was added to precipitate aluminium, copper and lithium salts. After centrifugation, supernatant was concentrated under high vacuum and flash chromatographed on silica-gel. It is important to note that a 1 h chromatography degraded the whole enolphosphates: chromatography must be very quick.

Finally, the first glucidic enolphosphates derived from aldehydes **11gal**, **11ara** are obtained in 35% overall yields from α,β-unsaturated aldehydes, with good purity (higher than 90%). Although this yield may seem modest, it results three successive reactions one pot. Moreover, the only by-products identified were corresponding saturated aldehydes. This observation reflects a good selectivity of the α,β-ethylenic aldehydes' reduction. Isopropylidene acetals were compatible with this strategy and were not degraded.

In conclusion, our needs to synthesise PEP analogues led us to develop two complementary methods to aldehyde enolphosphates. The first one is rapid, simple, efficient and leads to 1-alkenyldiphosphates with excellent chemical yields, avoiding uneasy purifications of fragile products at each step, provided that the compound does not contain acidic sensitive function. The second one is much more convenient for those highly sensitive compounds. We showed that use of Weinreb's phosphonoacetamide reagent is suitable to prepare α,β-unsaturated aldehydes which can be converted to enolphosphates by hydroalumination–phosphorylation tandem reaction. Yields are good considering the high sensitivity of our model compounds.



Scheme 7. Hydroalumination–activation–phosphorylation. Reagents and conditions: (a) 0.05 eq. CuI, 0.05 eq. MeLi (1.6 M in ether), 1.5 eq. HMPA, 1.1 eq. DIBAH (1.5 M in toluene), THF, N_2, −50 °C, 1 h; (b) 1.1 eq. MeLi (1.6 M in ether), −50 °C, 15 min; (c) 1.1 eq. $(EtO)_2P(O)Cl$, −50 °C, 2 h then rt overnight.

3. Experimental

3.1. General

Reactions were monitored by TLC (Merck – 5535 – Kieselgel 60-F_{254}), detection being carried out by UV, by iodine vapour or by spraying solution of H_2SO_4 15% in ethanol followed by heating.

NMR spectra were recorded on a Bruker DRX-250. Chemical shifts are expressed as parts per million downfield from the internal standard tetramethylsilane for ^1H and ^{13}C and from external standard phosphoric acid for ^{31}P. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broadened singlet). IR spectra were recorded on Nicolet 210 FTIR (film between NaCl pellets).

3.2. Protections of 9,10,16-trihydroxyhexadecanoic acid

3.2.1. Methyl 9,10,16-trihydroxyhexadecanoate *4*

$C_{17}H_{34}O_5$; MW = 318 g mol^{-1}; bp = 72–73 °C.

6 g of 9,10,16-Trihydroxyhexadecanoic acid (19.8 mmol – mp = 110 °C) is refluxed for 15 min under N_2 with 3 mL of $BF_3{\cdot}Et_2O$ in 100 mL of MeOH. Reaction is diluted in 80 mL of water and extracted three times with Et_2O. Organic layers are washed with saturated Na_2CO_3 aqueous solution and water. Crude product is diluted with toluene and distilled, under atmospheric pressure, to give 4.72 g of pure **4**, a pale yellow oil, with 75% yield.

RMN ^1H ($CDCl_3$, 250 MHz): 1.24–1.72 (22H, m, CH_2—CH_2), 2.31 (2H, t, $C\underline{H}_2$—CO_2Me, J_{H-H} = 4.75 Hz), 3.34–3.58 (4H, m, CH—O, CH_2—OH), 3.68 (3H, s, Me).

IR (NaCl): $\nu_{C=O}$ = 1738 cm^{-1}.

3.2.2. Methyl 16-[(pivaloyl)oxy]-9,10-dihydroxyhexadecanoate *5c*

$C_{22}H_{42}O_6$; MW = 403 g mol^{-1}; Rf = 0.5 – AcOEt/Hexane (1:1).

193 μL of pivaloyl chloride (1 eq.) is slowly added to a solution of 500 mg of **4** (1.57 mmol) in 3 mL of Pyridine at 0 °C. After 2 h at 0 °C, 3 drops of water are added to reaction before diluting with 30 mL of Et_2O. Organic layer is washed with an HCl aqueous solution (2 N), $NaHCO_3$ saturated solution and NH_4Cl saturated solution. After drying with Na_2SO_4, reaction is concentrated under vacuum to give 625 mg of **5c** (90% pure), a pale yellow oil, in 89% yield.

RMN ^1H ($CDCl_3$, 250 MHz): 1.20 (9H, s, tBu), 1.24–1.72 (22H, m, CH_2—CH_2), 2.32 (2H, t, $C\underline{H}_2$—CO_2Me, J_{H-H} = 4.75 Hz), 3.37–3.42 (2H, m, CH—O), 3.67 (3H, s, O—Me), 4.06 (2H, t, CH_2—O—Piv, J_{H-H} = 8.25 Hz).

IR (NaCl): $\nu_{C=O}$ = 1740 cm^{-1}.

3.2.3. Methyl 16-[(tert-butyldimethylsilyl)oxy]-9,10-dihydroxyhexadecanoate *5d*

$C_{23}H_{48}O_5Si$; MW = 433 g mol^{-1}.

1 g of **4** (3.15 mmol), 500 mg of *tert*-butyl(chloro)dimethylsilane (1.1 eq.), 50 mg of DMAP (cat.) and 0.5 mL of Et_3N (1.1 eq.) are reacted in 15 mL of CH_2Cl_2 for 12 h. Reaction is concentrated and diluted with 20 mL of Et_2O. Salts are filtered to give 1.20 g of crude **5d**, a pale yellow oil, with 88% yield. Product is purified after Malaprade oxidation.

RMN ^1H ($CDCl_3$, 250 MHz): 0.11 (6H, s, CH_3—Si), 0.91 (9H, s, tBu), 1.24–1.72 (22H, m, CH_2—CH_2), 1.39 (3H, s, Me), 2.31 (2H, t, $C\underline{H}_2$—CO_2Me, J_{H-H} = 4.75 Hz), 3.34–3.46 (2H, m, CH—O), 3.61 (2H, t, CH_2—O—Si, J_{H-H} = 6.35 Hz).

IR (NaCl): $\nu_{C=O}$ = 1738 cm^{-1}.

3.2.4. Methyl 16-[(diethoxyphosphoryl)oxy]-9,10-dihydroxyhexadecanoate *5e*

$C_{21}H_{43}O_8P$; MW = 456 g mol^{-1}.

1 g of **4** (3.15 mmol), 952 μL of diethylchlorophosphate (1 eq.) and 100 mg of DMAP (0.5 eq.) are stirred in 24 mL of Pyridine for

12 h. Reaction is concentrated, diluted with CH_2Cl_2 and washed by an HCl aqueous solution (1 M) down to pH 6. Organic layer is dried with $MgSO_4$ and concentrated under vacuum to give 2.01 g of crude **5e** (68% pure) and a 96% yield. Product, a pale yellow oil, is purified after Malaprade oxidation.

RMN ^{1}H ($CDCl_3$, 250 MHz): 1.24–1.72 (22H, m, CH_2—CH_2), 1.39 (3H, t, Me, J_{H-H} = 7.1 Hz), 2.32 (2H, t, C$\underline{H}_2$—CO_2Me, J_{H-H} = 4.75 Hz), 4.01–4.16 (4H, m, CH—O, CH_2—C$\underline{H}_2$—O—P), 4.22–4.31 (4H, m, CH_3—C$\underline{H}_2$—O—P).

RMN ^{31}P ($CDCl_3$, 101 MHz): 0.2 (s).

IR (NaCl): $\nu_{C=O}$ = 1739 cm^{-1}, $\nu_{P=O}$ = 1251 cm^{-1}.

3.2.5. 16-[(Tert-butyldimethylsilyl)oxy]-9,10-dihydroxyhexadecanoic acid **6d**

$C_{22}H_{46}O_5Si$; MW = 419 g mol^{-1}.

2 g of 9,10,16-Trihydroxyhexadecanoic acid (6.60 mmol), 1.98 g of *tert*-butyl(chloro)dimethylsilane (2 eq.), 800 mg of DMAP (0.5 eq.) and 2.0 mL of Et_3N (2.1 eq.) are reacted in 20 mL of CH_2Cl_2 for 72 h. Reaction is concentrated and diluted with 20 mL of hexane. Salts precipitate and are filtered to lead to 2.29 g of crude compound **6d**, a pale yellow oil, in 80% yield. Product is purified after Malaprade oxidation.

RMN ^{1}H ($CDCl_3$, 250 MHz): 0.11 (6H, s, CH_3—Si), 0.91 (9H, s, *t*Bu), 1.24–1.72 (22H, m, CH_2—CH_2), 2.31 (2H, t, C$\underline{H}_2$—CO_2H, J_{H-H} = 4.75 Hz), 3.34–3.46 (2H, m, CH—O), 3.61 (2H, t, CH_2—O—Si, J_{H-H} = 6.35 Hz).

3.2.6. 16-[(Diethoxyphosphoryl)oxy]-9,10-dihydroxyhexadecanoic acid **6e**

$C_{20}H_{41}O_8P$; MW = 441 g mol^{-1}.

5 g of 9,10,16-Trihydroxyhexadecanoic acid (16.50 mmol), 4.76 mL of diethylchlorophosphate (1 eq.) and 500 mg of DMAP (0.5 eq.) are reacted in 120 mL of Pyridine for 24 h. Reaction is concentrated, diluted with CH_2Cl_2 and washed by an HCl aqueous solution (1 M) down to pH 4. Organic layer is dried with $MgSO_4$ and concentrated under vacuum to give 7.51 g of crude **6e**, a pale yellow oil, in 97% yield.

RMN ^{1}H ($CDCl_3$, 250 MHz): 1.24–1.72 (22H, m, CH_2—CH_2), 1.32 (3H, t, Me, J_{H-H} = 7.0 Hz), 2.32 (2H, t, C$\underline{H}_2$—CO_2H, J_{H-H} = 4.75 Hz), 4.01–4.16 (4H, m, CH—O, CH_2—C$\underline{H}_2$—O—P), 4.22–4.31 (4H, m, CH_3—C$\underline{H}_2$—O—P).

RMN ^{31}P ($CDCl_3$, 101 MHz): 0.0 (s).

3.3. Malaprade oxidation

4 mmol of diol **5** or **6** in 10 mL of MeOH are agitated in a flask with $CaCl_2$ protection. In case of **6**, 2.5 g of $NaHCO_3$ powdered is added to pH 9. 1 eq. of $NaIO_4$ suspended in 3 mL of water is then slowly added. After 18 h, reaction is concentrated, diluted with CH_2Cl_2 and neutralised by an HCl·Et_2O solution. Precipitate is centrifuged, supernatant dried with Na_2SO_4 and evaporated. Aldehyde, a pale yellow oil, is purified by silicagel chromatography.

3.3.1. 7-Hydroxyheptanal **1b**

$C_7H_{14}O_2$; MW = 130 g mol^{-1}; Rf = 0.35 – AcOEt/Hexane – 5:1; Yield = 60%.

RMN ^{1}H ($CDCl_3$, 250 MHz): 1.22–1.71 (8H, m, CH_2—CH_2), 2.40 (2H, td, C$\underline{H}_2$—CHO, J_{H-H} = 1.8 Hz, J_{H-H} = 7.2 Hz), 3.63 (2H, t, CH_2—OH, J_{H-H} = 7.2 Hz), 9.74 (1H, t, CHO, J_{H-H} = 1.8 Hz).

IR (NaCl): ν_{OH} = 3360–3050 cm^{-1}; $\nu_{C=O}$ = 1718 cm^{-1}.

3.3.2. 7-[(Pivaloyl)oxy]-heptanal **1c**

$C_{12}H_{22}O_3$; MW = 214 g mol^{-1}; Rf = 0.50 – AcOEt/Hexane – 1:3; Yield = 66%.

RMN ^{1}H ($CDCl_3$, 250 MHz): 1.19 (9H, s, tBu), 1.22–1.71 (8H, m, CH_2—CH_2), 2.45 (2H, td, C$\underline{H}_2$—CHO, J_{H-H} = 1.8 Hz, J_{H-H} = 7.2 Hz), 4.05 (2H, t, CH_2—O—Piv, J_{H-H} = 8.3 Hz), 9.74 (1H, t, CHO, J_{H-H} = 1.8 Hz).

IR (NaCl): $\nu_{C=O}$ = 1741, 1718 cm^{-1}.

3.3.3. 7-[(Tert-butyldimethylsilyl)oxy]-heptanal **1d**

$C_{13}H_{28}O_2$; MW = 244 g mol^{-1}; Rf = 0.85 – AcOEt/Hexane – 5:1; Yield = 35% from **6d**–53% from **5d**.

RMN ^{1}H ($CDCl_3$, 250 MHz): 0.1 (6H, s, Me—Si), 0.91 (9H, s, *t*Bu), 1.21–1.74 (8H, m, CH_2—CH_2), 2.45 (2H, td, C$\underline{H}_2$—CHO, J_{H-H} = 1.8 Hz, J_{H-H} = 7.3 Hz), 3.62 (2H, t, CH_2—O—Si, J_{H-H} = 6.3 Hz), 9.79 (1H, t, CHO, J_{H-H} = 1.8 Hz).

IR (NaCl): $\nu_{C=O}$ = 1719 cm^{-1}.

3.3.4. 7-[(Diethoxyphosphoryl)oxy]-heptanal **1e**

$C_7H_{14}O_2$; MW = 130 g mol^{-1}; Rf = 0.35 – AcOEt/Hexane – 5:1; Yield = 59% from **6e**–69% from **5e**.

RMN ^{1}H ($CDCl_3$, 250 MHz): 1.34 (3H, t, CH_3, J_{H-H} = 7.1 Hz), 1.22–1.72 (8H, m, CH_2—CH_2), 2.44 (2H, td, C$\underline{H}_2$—CHO, J_{H-H} = 1.8 Hz, J_{H-H} = 7.25 Hz Hz), 4.03 (2H, m, CH_2—C$\underline{H}_2$—OH), 4.11 (4H, m, CH_3—CH_2—O), 9.76 (1H, t, CHO, J_{H-H} = 1.8 Hz).

RMN ^{31}P ($CDCl_3$, 101 MHz): 0.2 (s).

IR (NaCl): $\nu_{C=O}$ = 1719 cm^{-1}, $\nu_{P=O}$ = 1247 cm^{-1}.

3.4. Homologation of glucidic aldoses

3.4.1. Preparation of Weinreb's phosphonoacetamide **7**

$C_8H_{18}NO_5P$; MW = 239 g mol^{-1}; Rf = 0.35 – AcOEt/EtOH – 8:2.

1.28 mL of Et_3N (1 eq.) is added dropwise to 891 mg of *N*,*O*-dimethylhydroxylammonium chloride (1 eq.) in suspension in 40 mL of CH_2Cl_2. Check that pH is neutral. A solution of 1.8 g phosphonoacetic acid (9.2 mmol) in 60 mL of CH_2Cl_2 and then 4.1 g of BOP (1 eq.) in solution in 20 mL of CH_2Cl_2 are added to reaction. Finish by adding 1.28 mL of Et_3N (1 eq.) diluted in 20 mL of CH_2Cl_2. Check that pH is basic (pH $\geqslant$ 9). After stirring overnight at rt, reaction is diluted with 50 mL of CH_2Cl_2 and washed with aqueous solutions of H_2SO_4 (3 $\times$ 20 mL – 2 M), NaCl (10 mL – saturated), $NaHCO_3$ (3 $\times$ 20 mL – saturated) and NaCl (10 mL – saturated). Organic layers are dried with $MgSO_4$ and concentrated under vacuum. Crude product is purified by silicagel chromatography (AcOEt/EtOH – 8:2) to give 1.7 g of **7**, a pale yellow oil, in 77% yield.

RMN ^{1}H (250 MHz, $CDCl_3$): 1.37 (6H, t, C$\underline{H}_3$—CH_2, J_{H-H} = 4.8 Hz), 3.19 (2H, d, P—CH_2, $^2J_{H-P}$ = 22 Hz), 3.24 (3H, s, N—Me), 3.79 (3H, s, O—Me), 4.20 (4H, dq, CH_2—O—P, $^3J_{H-P}$ = J_{H-H} = 4.9 Hz).

RMN ^{31}P (101 MHz, CDCl3): 21.37 (s).

IR (NaCl): $\nu_{C=O}$ = 1660 cm^{-1}, $\nu_{P=O}$ = 1253 cm^{-1}.

3.4.2. Wittig–Horner reaction on aldoses

Under nitrogen, 1 eq. of diisopropylamine (MW = 101 g mol^{-1} – d = 0.7255 g L^{-1}) in solution in 30 mL of THF is slowly added to 3.0 mL of BuLi (1.4 M in Hexane – 1 eq.) in solution in 30 mL of THF at −50 °C. Reaction is allowed to warm to rt for 20 min, then cooled to −70 °C for the addition of a solution of 1 g of Weinreb's phosphonoacetamide **7** (4.18 mmol) in 30 mL of THF. Reaction is stirred for 15 min at −70 °C before being allowed to warm slowly to rt. 1 eq. of dialdogalactose in solution in 30 mL of THF are added to reaction. After 30 min at rt, 20 mL of NH_4Cl saturated solution are added to reaction. Mixture is extracted three times with 40 mL of CH_2Cl_2 and organic layers dried with $MgSO_4$. Concentration under vacuum lead to crude product being purified by silicagel chromatography (AcOEt/Hexane – 1:1) and give carboxamides **8gal** and **8ara**, pale yellow oils.

*3.4.2.1. Compound **8gal**.* $C_{16}H_{25}NO_7$; MW = 343 g mol^{-1}; Rf = 0.50 (*Z*)-**8gal** and 0.35 (*E*)-**8gal** – AcOEt/Hexane – 1:1.

240 mg of (*Z*)-**8gal** and 655 mg of (*E*)-**8gal** in a global 76% yield.

(Z)-***8gal***. RMN ^{1}H ($CDCl_3$, 400 MHz): 1.25 (3H, s, H isopropylidene), 1.26 (3H, s, H isopropylidene), 1.42 (3H, s, H isopropylidene), 1.50 (3H, s, H isopropylidene), 3.14 (3H, s, Me—N), 3.63 (3H, s, Me—O—N), 4.25 (1H, dd, H_2, J_{H-H} = 1.5 Hz, J_{H-H} = 3.1 Hz), 4.55 (2H, 2 dd, H_3, H_4, J_{H-H} = 1.5 Hz, J_{H-H} = 5.0 Hz, J_{H-H} = 1.25 Hz, J_{H-H} = 5.0 Hz), 5.41 (1H, m, H_5), 5.49 (1H, d, H_1, J_{H-H} = 3.1 Hz), 6.12 (1H, dd, H_6, J_{H-H} = 4.5 Hz, J_{H-H} = 9.8 Hz), 6.37 (1H, m, H_7).

RMN ^{13}C ($CDCl_3$, 101 MHz): 24.3; 25.1; 26.0; 26.1 (CH_3 isopropylidene), 32.6 (Me—N), 61.7 (Me—O—N), 65.7 (C_5), 70.3 (C_2), 71.0 (C_3), 73.5 (C_4), 96.4 (C_1), 108.8; 109.1 (C isopropylidene), 118.2 (C_7), 143.8 (C_6).

(E)-***8gal***. RMN ^{1}H ($CDCl_3$, 400 MHz): 1.25 (3H, s, H isopropylidene), 1.26 (3H, s, H isopropylidene), 1.42 (3H, s, H isopropylidene), 1.50 (3H, s, H isopropylidene), 3.10 (3H, s, Me—N), 3.65 (3H, s, Me—O—N), 4.31 (1H, dd, H_4, J_{H-H} = 1.25 Hz, J_{H-H} = 5.0 Hz), 4.36 (1H, dd, H_2, J_{H-H} = 1.5 Hz, J_{H-H} = 3.25 Hz), 4.51 (1H, m, H_5), 4.64 (1H, dd, H_3, J_{H-H} = 1.5 Hz, J_{H-H} = 5.0 Hz), 5.62 (1H, d, H_1, J_{H-H} = 3.25 Hz), 6.68–6.73 (1H, m, H_7), 6.93 (1H, dd, H_6, J_{H-H} = 2.25 Hz, J_{H-H} = 9.5 Hz);

RMN ^{13}C ($CDCl_3$, 101 MHz): 24.4; 24.9; 25.9; 26.1 (CH_3 isopropylidene), 32.3 (Me—N), 61.8 (Me—O—N), 67.6 (C_5), 70.5 (C_2), 70.9 (C_3), 72.7 (C_4), 96.4 (C_1), 108.7; 109.5 (C isopropylidene), 119.6 (C_7), 141.4 (C_6).

IR (NaCl): $\nu_{C=O}$ = 1668 cm^{-1}, $\nu_{C=C}$ = 1639 cm^{-1}.

3.4.2.2. Compound 8ara. $C_{15}H_{25}NO_6$; MW = 315 g mol^{-1}; Rf = 0.55 – AcOEt/Hexane – 6:4.

749 mg of *(Z)*-***8ara*** (17%) and *(E)*-***8ara*** (83%) mixture in a global 98% yield.

(Z)-***8ara***. RMN ^{1}H (250 MHz, $CDCl_3$): 1.37 (3H, s, H isopropylidene), 1.45 (3H, s, H isopropylidene), 1.44 (3H, s, H isopropylidene), 1.47 (3H, s, H isopropylidene), 3.23 (3H, s, Me—N), 3.69 (3H, s, Me—O—N), 3.90–4.38 (4H, m, H_5, H_6, H_7), 5.33 (1H, m, H_4), 6.07 (1H, dd, H_3, J_{H-H} = 9.2 Hz, J_{H-H} = 12.0 Hz), 6.44–6.53 (1H, m, H_2).

RMN ^{13}C (63 MHz, $CDCl_3$): 25.3; 26.7; 26.9; 27.0 (Me isopropylidene), 64.6 (C_7), 72.9 (C_6), 79.4 (C_5), 81.2 (C_4), 110.1 (C isopropylidene), 119.2 (d, C_2), 143.8 (C_3), 192.1 (C_1).

(E)-***8ara***. RMN ^{1}H (250 MHz, $CDCl_3$): 1.37 (3H, s, H isopropylidene), 1.45 (3H, s, H isopropylidene), 1.44 (3H, s, H isopropylidene), 1.47 (3H, s, H isopropylidene), 3.28 (3H, s, Me—N), 3.73 (3H, s, Me—O—N), 3.90–4.38 (4H, m, H_5, H_6, H_7), 4.62 (1H, m, H_4), 6.75 (1H, dd, H_2, J_{H-H} = 2.4 Hz, J_{H-H} = 15.8 Hz), 7.05 (1H, dd, H_3, J_{H-H} = 4.75 Hz, J_{H-H} = 15.8 Hz).

RMN ^{13}C (63 MHz, $CDCl_3$): 25.3; 26.7; 26.8; 27.0 (Me isopropylidene), 67.4 (C_7), 72.5 (C_6), 78.2 (C_5), 80.6 (C_4), 110.1 (C isopropylidene), 119.2 (d, C_2), 143.8 (C_3), 192.1 (C_1).

3.4.3. Catalytic hydrogenation of ***8gal***

$C_{16}H_{27}NO_7$; MW = 345 g mol^{-1}; Rf = 0.45 – AcOEt/Hexane – 1:1.

A 400 mg mixture of *(Z)*-***8gal*** and *(E)*-***8gal*** (1.16 mmol) in solution in 20 mL of MeOH and 50 mg of Palladium on carbon are stirred in a reactor under 10 bars of hydrogen overnight. Filtration on Celite and concentration under vacuum give 890 mg of pale yellow oil. Yield in compound **9gal** is quantitative.

RMN ^{1}H ($CDCl_3$, 400 MHz): 1.31 (3H, s, H isopropylidene), 1.35 (3H, s, H isopropylidene), 1.46 (3H, s, H isopropylidene), 1.48 (3H, s, H isopropylidene), 1.89–2.00 (2H, m, H_6), 2.46–2.76 (2H, m, H_7), 3.17 (3H, s, Me—N), 3.70 (3H, s, Me—O—N), 4.79–4.83 (1H, m, H_5), 4.17 (1H, d, H_4, J_{H-H} = 7.8 Hz), 4.28 (1H, dd, H_2, J_{H-H} = 1.8 Hz, J_{H-H} = 5.2 Hz), 4.58 (1H, dd, H_3, J_{H-H} = 1.8 Hz, J_{H-H} = 7.8 Hz), 5.52 (1H, d, H_1, J_{H-H} = 5.2 Hz);

RMN ^{13}C ($CDCl_3$, 101 MHz): 24.4; 25.0; 25.9; 26.0 (CH_3 isopropylidene), 24.9 (C_6), 27.0 (C_7), 32.3 (Me—N), 61.3 (Me—O—N), 66.5 (C_5), 70.7 (C_2), 70.9 (C_3), 73.0 (C_4), 96.5 (C_1), 108.4; 109.1 (C isopropylidene).

3.4.4. Reduction of ***9gal*** *to* ***1h***

$C_{14}H_{22}O_6$; MW = 286 g mol^{-1}; Rf = 0.45 – AcOEt/Hexane – 1:1.

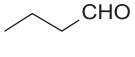
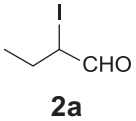
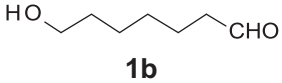
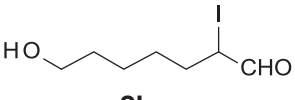
1.2 mL of $AlLiH_4$ (1 M in Et_2O – 1 eq.) is added on a solution of 405 mg of carboxamide **9gal** (1.17 mmol) in 10 mL of THF under nitrogen at 0 °C. Temperature must be controlled between −3 and +5 °C. After 30 min, a solution of 190 mg of $KHSO_4$ (1.40 mmol) in 1.5 mL of water is added to reaction. After concentration under vacuum, aqueous layer is extracted 3 times with CH_2Cl_2. Organic layers are washed with aqueous solutions of HCl (3 N), NaCl (sat.), $NaHCO_3$ (sat.) and NaCl (sat.) before being dried with Na_2SO_4 and concentrated under vacuum to give 292 mg of pure **1h**, a pale yellow oil, without further purification, in 87% yield.

RMN ^{1}H ($CDCl_3$, 400 MHz): 1.33 (3H, s, H isopropylidene), 1.36 (3H, s, H isopropylidene), 1.47 (3H, s, H isopropylidene), 1.50 (3H, s, H isopropylidene), 1.89–2.40 (2H, m, H_6), 2.54–2.72 (2H, m, H_7), 4.74–4.83 (1H, m, H_5), 4.17 (1H, dd, H_4, J_{H-H} = 1.6 Hz, J_{H-H} = 8.9 Hz), 4.31 (1H, dd, H_2, J_{H-H} = 2.4 Hz, J_{H-H} = 5.2 Hz), 4.60 (1H, dd, H_3, J_{H-H} = 2.4 Hz, J_{H-H} = 8.9 Hz), 5.52 (1H, d, H_1, J_{H-H} = 5.2 Hz), 9.64 (1H, t, H aldehyde, J_{H-H} = 1.2 Hz).

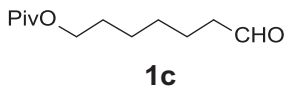
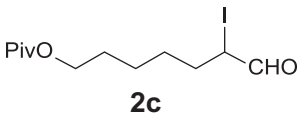
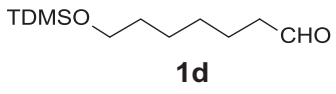
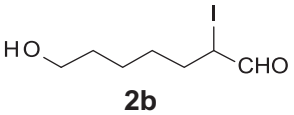
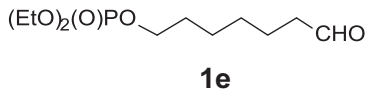
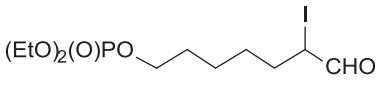
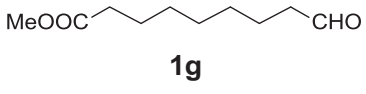
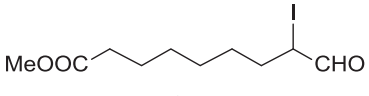
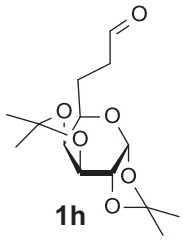
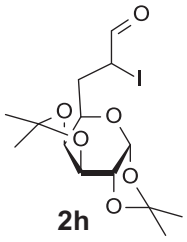
IR (NaCl): $\nu_{C=O}$ = 1718 cm^{-1}.

3.5. Iodation of aldehydes ***1a–h***

In a dark flask protected by $CaCl_2$, 3 mmol of aldehyde **1**, mercuric chloride and iodine are mixed in 10 mL of CH_2Cl_2 at rt. Suspension is agitated 2–4 h before being filtered. Filtrate is washed by an aqueous solution of $Na_2S_2O_3$ (0.1 N) recently prepared and KI (sat.). Organic layer is dried with Na_2SO_4 and concentrated under vacuum. Crude product **2** is used for the Perkow reaction.

Aldehyde substrate	Halogenation system	Product		Yield%
 **1a**	0.5 $HgCl_2$/1 I_2/2 h	 **2a**	C_4H_7IO MW = 198 g mol^{-1}	100
 **1b**	0.5 $HgCl_2$/1 I_2/4 h	 **2b**	$C_7H_{13}IO_2$ MW = 256 g mol^{-1}	97

(*continued on next page*)

Aldehyde substrate	Halogenation system	Product		Yield%
 **1c**	0.5 $HgCl_2$/1 I_2/4 h	 **2c**	$C_{12}H_{21}IO_3$ MW = 340 g mol^{-1}	98
 **1d**	0.5 $HgCl_2$/1 I_2/4 h	 **2b**	$C_7H_{13}IO_2$ MW = 256 g mol^{-1}	90
 **1e**	1.5 $HgCl_2$/1 I_2/4 h	 **1e**	$C_{11}H_{22}IO_5P$ MW = 392 g mol^{-1}	98
 **1g**	0.5 $HgCl_2$/1 I_2/4 h	 **2g**	$C_{10}H_{17}IO_3$ MW = 312 g mol^{-1}	90
 **1h**	0.5 $HgCl_2$/1 I_2/4 h	 **2h**	$C_{14}H_{21}IO_6$ MW = 412 g mol^{-1}	0

3.6. Preparation of enolphosphates **3a–g**

1 Eq. of trialkylphosphite is added on 1 mmol of α-iodoaldehydes **2a–g** at 0 °C. Reaction is allowed to warm to rt overnight. Mixture is concentrated under high vacuum and enolphosphates **3a–g** are obtained, as pale yellow oils, with great purity and quantitative yield.

3.6.1. **3a**

$C_6H_{13}O_4P$; MW = 180 g mol^{-1}; Ratio *E*/*Z*: 58/42; Yield: 100%.

RMN ^1H ($CDCl_3$, 250 MHz): 1.00 (3H, t, C<u>H</u>$_3$—CH_2, J_{H-H} = 7.1 Hz); 2.00 (0.84H, td, CH_3—C<u>H</u>$_2$, J_{H-H} = 7.1 Hz, J_{H-H} = Hz); 2.17 (1.16H, td, CH_3—C<u>H</u>$_2$, J_{H-H} = 7.1 Hz, J_{H-H} = Hz); 3.82 (6H, 2 d, CH_3—O—P, J_{H-P} = 11.25 Hz, stereoisomer *Z* and *E*); 4.89 (0.58H, tdd, CH_2—C<u>H</u>, stereoisomer *Z*, J_{H-H} = J_{Hvinyl} = 7.7 Hz, J_{H-P} = 2.3 Hz); 5.49 (0.42H, tdd, CH_2—C<u>H</u>, stereoisomer *E*, J_{H-H} = 7.7 Hz, J_{H-H} = 10.7 Hz, J_{H-P} = 1.3 Hz); 6.39 (1H, m, CH—O—P).

RMN ^{31}P ($CDCl_3$, 101 MHz): −0.88 (s, stereoisomer *Z*), −1.20 (s, stereoisomer *E*).

3.6.2. **3b**

$C_9H_{19}O_5P$; MW = 238 g mol^{-1}; Ratio *E*/*Z*: 28/72; Yield: 100%.

RMN ^1H ($CDCl_3$, 250 MHz): 1.25–2.23 (8H, m, CH_2); 2.36 (2H, t, C<u>H</u>$_2$—OH); 3.80 (6H, 2 d, CH_3—O—P, J_{H-P} = 11.78 Hz, stereosiomer *Z* and *E*); 4.82–5.03 (0.28H, m, CH_2—C<u>H</u>, stereoisomer *Z*); 5.17–5.52 (0.72H, m, CH_2—C<u>H</u>, stereoisomer *E*); 6.34–6.45 (1H, m, CH—O—P).

RMN ^{31}P ($CDCl_3$, 101 MHz): −1.23 (s, enolphosphate *E*); −0.81 (s, enolphosphate *Z*).

MS (FAB^+): *m*/*z* 239 ($[M+H]^+$, 21%); MS (FAB^-): *m*/*z* 237 ($[M-H]^-$, 18%).

IR (NaCl): ν_{P-O-C} = 1021 cm^{-1}, $\nu_{P=O}$ = 1279 cm^{-1}, $\nu_{C=C}$ = 1670 cm^{-1}, ν_{OH} = 3300 cm^{-1}.

3.6.3. **3c**

$C_{14}H_{27}O_6P$; MW = 322 g mol^{-1}; Ratio *E*/*Z*: 61/39; Yield: 100%.

RMN ^1H ($CDCl_3$, 250 MHz): 1.22 (9H, s, *t*Bu); 1.30–2.28 (8H, m, CH_2); 3.83 (6H, 2 d, CH_3—O—P, J_{H-P} = 11.25 Hz, stereoisomer *Z* and *E*); 4.89 (0.61H, tdd, CH_2—C<u>H</u>, stereoisomer *Z*, J_{H-H} = J_{Hvinyl} = 7.7 Hz, J_{H-P} = 2.3 Hz); 5.46 (0.39H, tdd, CH_2—C<u>H</u>, stereoisomer *E*, J_{H-H} = 7.7 Hz, J_{H-H} = 10.7 Hz, J_{H-P} = 1.3 Hz); 6.41 (1H, m, CH—O—P).

RMN ^{31}P ($CDCl_3$, 101 MHz): −1.23 (s, enolphosphate *E*); −0.80 (s, enolphosphate *Z*).

MS (FAB^+): *m*/*z* 323 ($[M+H]^+$, 100%).

IR (NaCl): ν_{P-O-C} = 1021 cm^{-1}, $\nu_{P=O}$ = 1279 cm^{-1}, $\nu_{C=C}$ = 1670 cm^{-1}, ν_{OH} = 3300 cm^{-1}.

3.6.4. **3e**

$C_{13}H_{28}O_8P_2$; MW = 374 g mol^{-1}; Ratio *E*/*Z*: 52/48; Yield: 100%.

RMN ^1H ($CDCl_3$, 250 MHz): 1.35 (6H, t, C<u>H</u>$_3$—CH_2, J_{H-H} = 7.0 Hz); 1.30–2.50 (8H, m, CH_2); 3.82 (6H, 2 d, CH_3—O—P, J_{H-P} = 11.25 Hz, stereosiomer *Z* and *E*); 4.03 (4H, m, CH_2—C<u>H</u>$_2$—O—P); 4.13 (4H, m, CH_3—C<u>H</u>$_2$—O—P); 4.88 (0.58H, tdd, CH_2—C<u>H</u>, stereoisomer *Z*, J_{H-H} = J_{Hvinyl} = 7.7 Hz, J_{H-P} = 2.3 Hz); 5.45 (0.42H, tdd, CH_2—C<u>H</u>, stereoisomer *E*, J_{H-H} = 7.7 Hz, J_{H-H} = 10.7 Hz, J_{H-P} = 1.3 Hz); 6.39 (1H, m, CH—O—P).

RMN ^{31}P ($CDCl_3$, 250 MHz): −1.26 (s, enolphosphate *Z*); −0.83 (s, enolphosphate *E*); 0.40 (s, phosphate).

RMN ^{13}C ($CDCl_3$, 63 MHz): 15.9 ($C\underline{H}_3$—CH_2); 23.0–30.1 (4 CH_2); 54.4 ($C\underline{H}_3$—O—P); 62.7 (CH_2—$C\underline{H}_2$—O—P); 67.3 (CH_3—$C\underline{H}_2$—O—P); 116.1 ($C\underline{H}$=CH—O); 134.8 (CH=$C\underline{H}$—O).

MS (FAB^+): *m/z* 375 ($[M+H]^+$, 100%).

IR (NaCl): ν_{P-O-C} = 1015 cm^{-1}, $\nu_{P=O}$ = 1271 cm^{-1}, $\nu_{C=C}$ = 1665 cm^{-1}.

3.6.5. ***3f***

$C_{15}H_{32}O_8P_2$; MW = 402 g mol^{-1}; Ratio *E*/*Z*: 48/52; Yield: 100%.

RMN ^1H ($CDCl_3$, 250 MHz): 1.35 (12H, t, $C\underline{H}_3$—CH_2, J_{H-H} = 7.0 Hz); 1.30–2.50 (8H, m, CH_2); 4.03 (4H, m, CH_2—$C\underline{H}_2$—O—P); 4.09–4.17 (8H, m, CH_3—$C\underline{H}_2$—O—P); 4.88 (0.58H, tdd, CH_2—$C\underline{H}$, stereoisomer *Z*, J_{H-H} = J_{Hvinyl} = 7.7 Hz, J_{H-P} = 2.3 Hz); 5.45 (0.42H, tdd, CH_2—$C\underline{H}$, stereoisomer *E*, J_{H-H} = 7.7 Hz, J_{H-H} = 10.7 Hz, J_{H-P} = 1.3 Hz); 6.39 (1H, m, CH—O—P).

RMN ^{31}P ($CDCl_3$, 250 MHz): −1.26 (s, enolphosphate *Z*); −0.83 (s, enolphosphate *E*); 0.40 (s, phosphate).

RMN ^{13}C ($CDCl_3$, 63 MHz): 15.9 ($C\underline{H}_3$—CH_2); 23.0–30.1 (4 CH_2); 62.7 (CH_2—$C\underline{H}_2$—O—P); 67.3 (CH_3—$C\underline{H}_2$—O—P); 116.1 ($C\underline{H}$=CH—O); 134.8 (CH=$C\underline{H}$—O).

MS (FAB^+): *m/z* 403 ($[M+H]^+$, 100%).

IR (NaCl): ν_{P-O-C} = 1015 cm^{-1}, $\nu_{P=O}$ = 1271 cm^{-1}, $\nu_{C=C}$ = 1665 cm^{-1}.

3.6.6. ***3g***

$C_{12}H_{23}O_6P$; MW = 294 g mol^{-1}; Ratio *E*/*Z*: 45/55; Yield: 100%.

RMN ^1H ($CDCl_3$, 250 MHz): 1.30–2.50 (10H, m, CH_2); 2.32 (2H, t, $C\underline{H}_2$—CO_2Me, J_{H-H} = 4.75 Hz); 3.68 (3H, s, CO_2Me); 3.82 (6H, 2 d, CH_3—O—P, J_{H-P} = 11.23 Hz, stereosiomer *Z* and *E*); 4.88 (0.45H, tdd, CH_2—$C\underline{H}$, stereoisomer *Z*, J_{H-H} = J_{Hvinyl} = 7.7 Hz, J_{H-P} = 2.3 Hz); 5.45 (0.55H, tdd, CH_2—$C\underline{H}$, stereoisomer *E*, J_{H-H} = 7.7 Hz, J_{H-H} = 10.7 Hz, J_{H-P} = 1.3 Hz); 6.39 (1H, m, CH—O—P).

RMN ^{31}P ($CDCl_3$, 101 MHz): −1.25 (s, enolphosphate *Z*); −0.83 (s, enolphosphate *E*).

MS (FAB^+): *m/z* 295 ($[M+H]^+$, 54%).

IR (NaCl): ν_{P-O-C} = 1015 cm^{-1}, $\nu_{P=O}$ = 1271 cm^{-1}, $\nu_{C=C}$ = 1736 cm^{-1}.

3.7. Preparation of α,β-unsaturated aldehydes ***10gal–ara***

1 eq. of $AlLiH_4$ (1 M in Et_2O) is added on a solution of 400 mg of carboxamide **8gal** (1.16 mmol) or **8ara** (1.27 mmol) in 20 mL of THF under nitrogen at 0 °C. Temperature must be controlled between −3 and +5 °C. After 30 min, a solution of 1.2 eq. of $KHSO_4$ in 3.0 mL of water is added to reaction. After concentration under vacuum, aqueous layer is extracted three times with CH_2Cl_2. Organic layers are washed with aqueous solutions of HCl (3 N), NaCl (sat.), $NaHCO_3$ (sat.) and NaCl (sat.) before being dried with Na_2SO_4 and concentrated under vacuum.

3.7.1. ***10gal***

$C_{14}H_{20}O_6$; MW = 284 g mol^{-1}; Rf = 0.40 – AcOEt/Hexane – 6:4 – pale yellow oil.

Pure **10gal** is obtained, without further purification, in 87% yield. (*E*)-stereoisomer is the major product (91%).

RMN ^1H ($CDCl_3$, 400 MHz): 1.31 (3H, s, H isopropylidène), 1.32 (3H, s, H isopropylidène), 1.39 (3H, s, H isopropylidène), 1.50 (3H, s, H isopropylidène), 4.32 (1H, dd, H_4, J_{H-H} = 4.8 Hz, J_{H-H} = 1.5 Hz), 4.35 (1H, dd, H_2, J_{H-H} = 3.1 Hz, J_{H-H} = 1.6 Hz), 4.54 (1H, m, H_5), 4.65 (1H, dd, H_3, J_{H-H} = 1.6 Hz, J_{H-H} = 4.8 Hz), 5.58 (1H, d, H_1, J_{H-H} = 3.1 Hz), 6.35 (1H, ddd, H_7, J_{H-H} = 1.25 Hz, J_{H-H} = 5.0 Hz, J_{H-H} = 9.8 Hz), 6.77 (1H, dd, H_6, J_{H-H} = 2.75 Hz, J_{H-H} = 9.8 Hz), 9.64 (1H, d, H aldehyde, J_{H-H} = 5 Hz).

IR (NaCl): $\nu_{C=O}$ = 1721 cm^{-1}, $\nu_{C=C}$ = 1690 cm^{-1}.

3.7.2. ***10ara***

$C_{13}H_{20}O_5$; MW = 256 g mol^{-1}; Rf = 0.40 – AcOEt/Hexane – 6:4 – pale yellow oil.

Pure **10ara** is obtained, without further purification, in 71% yield. (*E*)-stereoisomer is the major product (>95%).

RMN ^1H (250 MHz, $CDCl_3$): 1.38 (3H, s, H isopropylidene), 1.43 (3H, s, H isopropylidene), 1.44 (3H, s, H isopropylidene), 1.47 (3H, s, H isopropylidene), 3.62–4.23 (4H, m, H_5, H_6, H_7), 4.67 (1H, m, H_4), 6.46 (1H, ddd, H_2, J_{H-H} = 1.5 Hz, J_{H-H} = 7.75 Hz, J_{H-H} = 15.75 Hz), 6.92 (1H, dd, H_3, J_{H-H} = 4.0 Hz, J_{H-H} = 15.75 Hz), 9.62 (1H, d, H_1, J_{H-H} = 8.0 Hz).

IR (NaCl): $\nu_{C=O}$ = 1721 cm^{-1}, $\nu_{C=C}$ = 1690 cm^{-1}.

3.8. Hydroalumination–phosphorylation to ***11gal–ara***

0.05 Eq. (MW = 190 g mol^{-1}) of dried CuI are suspended in 4 mL of anhydrous THF at −50 °C in a dried flask, under nitrogen. 0.05 eq. of MeLi (1.6 M in Et_2O) is added dropwise followed by 1.5 eq. of HMPA (MW = 179 g mol^{-1} – *d* = 1.03 g.mL^{-1}) and then 1.1 eq. of DIBAL (1.5 M in Toluene). Reaction is stirred at −50 °C for 30 min before adding 1.5 mmol of α,β-unsaturated aldehyde ***10gal*** (426 mg) or ***10ara*** (384 mg) in solution in 4 mL of THF. Reaction is stirred one more hour at −50 °C before adding 1.1 eq. of MeLi (1.6 M in Et_2O). After 15 min at −50 °C, 1.1 eq. of diethylchlorophosphate (MW = 172 g mol^{-1} – d = 1.194) are added and reaction is kept 2 h at −50 °C. Reaction is finally stirred at rt overnight. THF is evaporated under vacuum and Et_2O is added to the obtained mixture. After centrifugation of precipitated salts, filtrate is concentrated, and taken up in 25 mL of CH_2Cl_2. Solution is rapidly washed with 5 mL of water, dried with Na_2SO_4 and concentrated under vacuum. A very fast silicagel chromatography on filter (AcOEt/Hexane – 6:4) is realised in less than 15 min to give 35% of expected product **11gal–ara** (60 % (*E*)/40% (*Z*)), as pale oils, with a great purity.

3.8.1. ***11gal***

$C_{18}H_{31}O_9P$; MW = 422 g mol^{-1}.

RMN ^1H (400 MHz, $CDCl_3$): 1.31 (3H, s, H isopropylidene), 1.32 (3H, s, H isopropylidene), 1.34 (6H, t, $C\underline{H}_3$—CH_2, J_{H-H} = 7.0 Hz), 1.39 (3H, s, H isopropylidene), 1.50 (3H, s, H isopropylidene), 2.04–2.12 (2H, m, H_6), 3.85–4.45 (8H, m, H_2, H_3, H_4, H_5, CH_3—$C\underline{H}_2$—O), 4.60–4.79 (1H, m, H_7), 5.60 (1H, d, H_1, J_{H-H} = 3.0 Hz), 5.68–6.03 (1H, m, H_8);

RMN ^{31}P (162 MHz, $CDCl_3$): −0.84 (s, enolphosphate (*E*)), −0.70 (s, enolphosphate (*Z*)).

RMN ^{13}C ($CDCl_3$, 101 MHz): 24.4; 24.9; 25.9; 26.1 (CH_3 isopropylidene), 29.6 (C_6), 67.6 (C_5), 70.5 (C_2), 70.9 (C_3), 72.7 (C_4), 96.4 (C_1), 108.7; 109.5 (C isopropylidene), 132.8 (C_7), 151.5 (C_8).

MS (FAB^+): *m/z* 423 ($[M+H]^+$, 68%).

3.8.2. 11ara

$C_{17}H_{31}O_8P$; MW = 394 g mol^{-1}.

RMN ^1H (400 MHz, $CDCl_3$): 1.27; 1.29; 1.31; 1.34 (18H, m, isopropylidene; $C\underline{H}_3$—CH_2), 2.16 (1H, m, H_3), 2.40 (1H, m, H'_3), 3.84–4.20 (9H, m, H_4, H_5, H_6, H_7, CH_3—$C\underline{H}_2$—O), 5.01 (0.4H, m, H_2(*Z*)), 5.46 (0.6H, ddt, H_2(*E*), $^3J_{H-P}$ = 0.75 Hz, J_{H-H} = 4.75 Hz, J_{H-H} = 7.6 Hz), 5.60–6.02 (0.4H, m, H_1(*Z*)), 6.41 (0.6H, dd, H_1(*E*), J_{H-H} = 3.5 Hz, J_{H-H} = 7.6 Hz);

RMN ^{31}P (162 MHz, $CDCl_3$): −4.60 (s);

RMN ^{13}C (101 MHz, $CDCl_3$): 16.1; 16.2 ($\underline{C}H_3$—CH_2), 25.2; 26.7; 27.0; 27.2 (isopropylidene), 30.6 (C_3), 64.3; 64.4 (CH_3—$\underline{C}H_2$), 67.8 (C_7), 77.1 (C_6), 79.8 (C_5), 80.2 (C_4), 110.2; 110.3 (C isopropylidene), 112.3; 112.4 (C_2), 137.7 (C_1).

MS (FAB^+): *m/z* 395 ($[M+H]^+$, 77%).

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