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A general synthesis of 2- or 3-alkyl substituted 5-hydroxymethyl-δ-valerolactones, precursors of 5-formyl-δ-valerolactones, via lithiated *N*-allyl(bisdimethylamino)-*N*-methylphosphoramide carbanions

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Abstract

A convenient strategy is reported for the synthesis of 2- or 3-alkylsubstituted 5-hydroxymethyl and 5-formyl-δ-valerolactones, which are very useful starting blocks for the total synthesis of leukotrienes and lactonic pheromones. It has been found that lithiated enephosphoramide ambident anions reacted exclusively in the γ position with 2,3-*O*-isopropylidene glycerol triflate to give corresponding alkylated enephosphoramides by a C3–C3 backbone connection. Enephosphoramide group was further selectively hydrolyzed in the presence of isopropylidene function in mild acidic conditions and led to expected aldehydes in high yields. Oxidation of these aldehydes using silver oxide or potassium permanganate afforded corresponding acids. Further hydrolysis of the isopropylidene group led to unstable dihydroxyacids which directly lactonized. The latter were converted to 5-formyl-δ-valerolactones using PDC oxidant. © 1999 Elsevier Science S.A. All rights reserved.

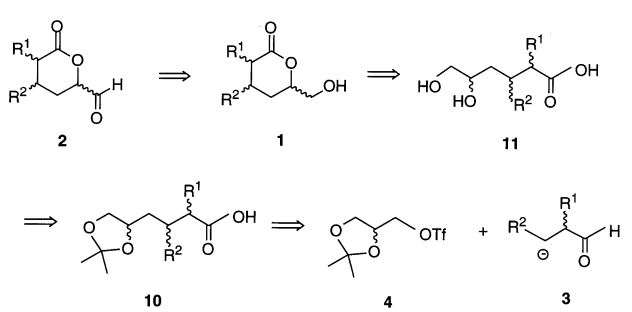
Keywords: Enephosphoramide; 2,3-*O*-Isopropylidene glycerol; Lithium reagents; δ-Valerolactone

1. Introduction

Many chiral functionalized γ- or δ-lactones are biologically active compounds [1]. They are also important synthetic building blocks used in natural product synthesis. 5-hydroxymethyl δ-valerolactone **1a**, ($R^1 = R^2 =$ H) for example, has been prepared by various methods in racemic and enantiomerically pure form [2], and has been used as a key synthon for leukotriene LTB_5 synthesis. This compound is also potentially useful for the preparation of a range of insect pheromones. However, availability of this enantiomerically pure δ-lactone **1a** and its oxidation product, 5-formyl δ-valerolactone **2a** ($R^1 = R^2 = H$) is rather difficult [2]. Moreover the access to 2- or 3-alkyl-substituted ring derivatives **1b**–**d** or **2b**–**d** is limited [2b,e,i]. It follows that the synthesis of such a molecule represents an interesting target.

Conceptually, a simple retrosynthetic pathway involves the addition of a homoenolate anion **3** to the suitable 2,3-*O*-isopropylidene glycerol derivative **4** to build the required γ-lactone **1** via a C3–C3 backbone connection (Scheme 1).

In earlier work we reported the suitability of lithiated *N*-alkenyl-*N*-methyl-(bisdimethylamino) phosphoramide anions (**6**) as an effective source of homoenolate



Scheme 1.

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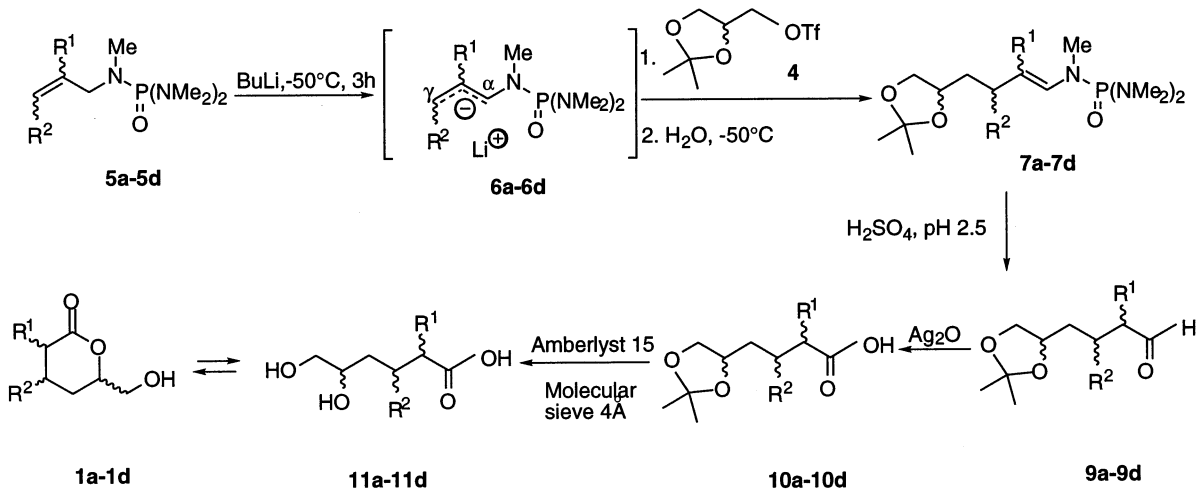


Scheme 2.

synthetic equivalents for the preparation of various aldehydes [3] or γ-lactols [4], and for the stereocontrolled synthesis of the sole 5-formyl-δ-valerolactone (**1a**) [5]. The synthetic value of this strategy is based on: (i) the remarkable capacity of these lithiated allylphosphoramide ambident anions to react exclusively at the γ position with alkylhalides; and (ii) on the nature of the conjugate enephosphoramide moiety present in **7** which is stable to bases, but liberates the aldehydic group under mild acid conditions.

Since 2,3-*O*-isopropylidene glycerol triflate **4** is easily available, we have considered that its reaction with the lithiated anions **6** would provide, after a series of suitable transformations, a general and versatile approach to the synthesis of other diastereomeric substituted γ-lactones **1** and **2** (Scheme 2). This paper describes the details of this approach.

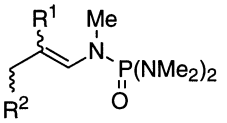
2. Results and discussion

*2.1. Reaction between lithiated anions **6** and 2,3-O-isopropylidene glycerol triflate **4***

The lithiated anions **6** were prepared from the corresponding enephosphoramides **5** by deprotonation with *n*-BuLi at −50°C in THF as previously described [3]. As with alkyl halides, these ambident carbanions only reacted at the γ position [3] with triflate **4** to afford after neutral hydrolysis the expected conjugate enephosphoramides **7** but also recovered starting materials **5** and their transposed forms **8**, resulting from the α and γ protonation of unreacted carbanions **6** during hydrolysis (Schemes 2 and 3).

A series of experiments was performed in order to determine alkylation factors as shown in Table 1. The highest yields were obtained with lithiated anion **6a** derived from allylphosphoramide **5a**. In all other cases (**5b**–**d**), the presence of substituents in the β or γ position increased the hindrance of the corresponding lithiated anions **6b**–**d** and decreased their reactivity. The effect of the stoichiometry was studied in these cases. Using 2 equivalents of lithiated anions led to conjugate enephosphoramides **7b** and **7c** with improved yields (compare entries 3–5; 6–7). In contrast, the addition of HMPT was quite ineffective under the same conditions. No significant improvement in yields was observed with increased reaction time beyond 1 h. In the case of phosphoramide **5d**, no further improvement in yields was obtained by employing various reaction conditions (entries 8–11).

The enephosphoramides **7a**–**d** were obtained as a mixture of diastereomers (two *Z* and *E* stereomers were possible for **7a** and **7d** and four diastereomers were possible for **7b** and **7c** which combined the different *R*, *S* chiral centers and the *Z*,*E* carbon–carbon double bonds). As a result the ^{1}H-NMR spectra of the crude product mixtures were complex and difficult to assign. Moreover, the crude product evolved slowly, which did not facilitate its analysis: after hydrolysis of the reaction mixture, the conjugate enephosphoramides **7** and **8** presented notable amounts of *Z* stereomers supposed to be the result of an internal chelation of lithium with the



8a-8d

Scheme 3.

Table 1
Formation of conjugate enephosphoramides **7** by alkylation of lithiated anions **6** with triflate **4**

Entry	**5**	R^1	R^2	**5** (equivalent)[a]	Time (h)	**5** [c]	**8** [c]	**7** [c]	**7**	(%) [d]	(*E*/*Z*) [e]
1	**5a**	H	H	1.15	1	2	13	85	**7a**	98	(78/22)
2	**5a**	H	H	1.15 [b]	1	2	12	86	**7a**	99	(80/20)
3	**5b**	H	Me	1.15	1	28	14	58	**7b**	65	(70/30) [f]
4	**5b**	H	Me	1.15 [b]	1	21	19	60	**7b**	69	(72/28)
5	**5b**	H	Me	2	1	38	18	44	**7b**	88	(69/31)
6	**5c**	H	Ph	1.15	1	25	18	57	**7c**	65	(32/68) [g]
7	**5c**	H	Ph	2	1	44	18	38	**7c**	76	(35/65)
8	**5d**	Me	H	1.15	1	30	26	44	**7d**	50	(93/7)
9	**5d**	Me	H	1.15 [b]	1	37	18	44	**7d**	51	–
10	**5d**	Me	H	1.15	4	17	37	46	**7d**	52	–
11	**5d**	Me	H	2	4	27	47	27	**7d**	53	–

[a] Equivalents relative to the triflate **4**.
[b] Reactions were run in THF with one equivalent of HMPT/lithiated anion.
[c] Percentage of each phosphoramide in the crude mixture after hydrolysis.
[d] Percentage was determined by NMR measurements and based on the conversion of the starting substrate **4**.
[e] Estimated ratio based on ^{31}P-NMR spectrum of the crude mixture carried out after 15 h at room temperature.
[f] The *E* stereomer was itself a mixture of two *E* diastereomers (55/45), idem for the *Z* stereomer (ratio not determined).
[g] The *E* stereomer was itself a mixture of two *E* diastereomers (60/40), idem for the *Z* stereomer (70/30).

free nitrogen orbital, in the carbanionic precursors **6** [3] (see Fig. 1).[1]

After 12 h at room temperature (r.t.) the enephosphoramides **7** *Z* or **8** *Z* turned into more stable *E* isomers [3,6] except in the case of **7c**. As a result, accurate NMR assignments became possible for all stereomers **7** *E*.

The *trans* relationship of the hydrogens linked to the double bond was assigned on the basis of the greatest ^{1}H-NMR coupling constant $^3J_{trans} = 14$ Hz observed for **7a**–**c** *E* compared with $^3J_{cis} = 10$ Hz observed for **7c** *Z*. The *E* stereomers also presented a ^{31}P-NMR downfield chemical shift of 23.0–24.4 ppm, whereas *Z* stereomers were characterized by a chemical shift to higher fields of 25.1–25.4 ppm. In all cases **7a**–**d**, only the stereomers that differed in the ethylenic configuration presented a different chemical shift in ^{31}P-NMR. It was also noteworthy that ^{31}P-NMR data allowed the identification of **7d** *Z* and **7d** *E* by analogy with the ^{31}P-NMR chemical shifts of corresponding **7a**–**c** stereomers, since in the case of **7d**, a *cis*/*trans* relationship based on the coupling constant values of two vicinal hydrogens on a carbon–carbon double bond was naturally impossible.

For the reasons mentioned above about the complexity of the NMR spectra of the crude product just after hydrolysis, a possible diastereoselectivity of the nucleophilic substitution of the enephosphoramide anion **6b** on the chiral triflate **4** has only been estimated after the complete conversion of the crude mixture **7b** *E*/*Z* into **7b** *E*. The enephosphoramide **7b** *E* was revealed to be a mixture of two diastereomers *E* (55/45). In the case of the reaction between **6c** and the chiral triflate **4**, the obtained enephosphoramide **7c** (*Z*/*E* = 68/32) did not evolve with time, the ^{1}H-NMR signals were well separated and allowed the identification of two diastereomers for **7c** *Z* (70/30) and two diastereomers for **7c** *E* (60/40). From these two examples, it resulted that the diastereoselectivity of the reaction between **6b**–**c** and the chiral triflate **4** slightly increased with the steric hindrance of R^2.

It was been otherwise noted that satisfactory conditions for separation of the different enephosphoramides **7a**–**d** from the crude mixture were not found. As a result, yields were estimated from NMR data on the crude products obtained after neutral hydrolysis. Further acid hydrolysis was then carried out on **7a**–**d**.

2.2. Acid hydrolysis of the conjugate enephosphoramides 7

The sensitivity of **7a**–**d** towards acids can be compared with enamines for the enephosphoramide function and with acetals for the dioxolane protective group. With a 2 N aqueous solution of hydrochloric or sulfuric acid [3], both dioxolane and enephosphoramide functionalities of **7a** were hydrolyzed involving a direct

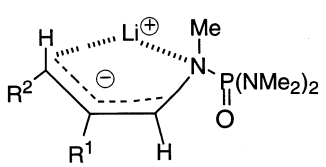
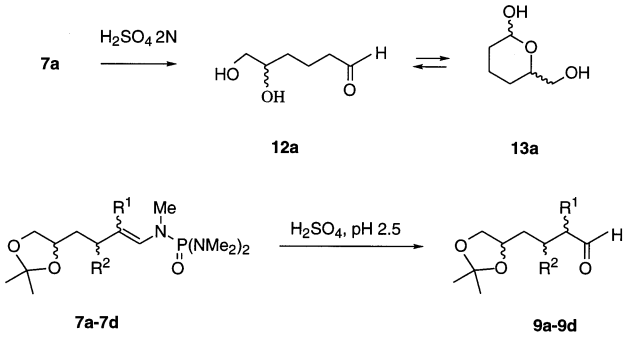


Fig. 1.

[1] However it was only possible to assign the ^{1}H-NMR signals to the *Z* stereomer of **7c** and not in the cases of **7a**, **7b** and **7d** as a consequence of a partial or total recovery with the signals of corresponding *E* stereomers and with the signals of the recovered starting product **5**.



Scheme 4.

cyclization of the intermediate dihydroxyaldehyde **12a** into the lactol **13a** (Scheme 4). An accurate study of the hydrolysis of **7a**–**d** determined the optimal conditions for the chemoselective cleavage of the nitrogen–carbon bond for each enephosphoramide **7a**–**d** with sulfuric acid at pH 2.5 and led to the corresponding aldehydes **9a**–**d** in good yield (Table 2).

2.3. Oxidation of aldehydes *9*

The acetal group present in the aldehydes **9** limited the choice of oxidants. Acetals are stable only in neutral or basic conditions. Two types of oxidant were tested: potassium permanganate [7], the most popular reagent which can be used in neutral, acid or basic media, and silver oxide [8]. Both oxidations were run in basic media. The carboxylate was then protonated using a solution of oxalic acid until pH 3.2 (Scheme 5, Table 3).

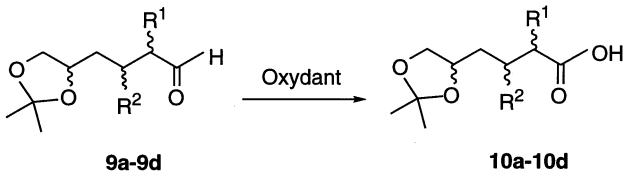
The reaction of **9a** with potassium permanganate was rapid and complete within 1 h (entry 1) whereas the reaction of **9b** was sluggish and required more forcing conditions to give a product (entry 3). Reactions of **9c**, **9d** with permanganate failed. The result for **9c** can be explained by the presence of a phenyl substituent which by its hindrance and its hydrophobic character limited the reaction in aqueous media. In all cases, the pure acid was obtained in fairly good yields when silver oxide was used under very mild conditions.

The results clearly indicate that silver nitrate is a fairly specific oxidizing agent for aldehydes **9a**–**d** and does not readily attack the isopropylidene ketal group.

Table 2
Chemoselective hydrolysis of enephosphoramides **7** into aldehydes **9**

Entry	7	R^1	R^2	Time (min)	9	Yield (%) [a]
1	**7a**	H	H	40	**9a**	77
2	**7a**	H	H	90	**9a**	87
3	**7b**	H	Me	240	**9b**	82
4	**7c**	H	Ph	210	**9c**	93
5	**7d**	Me	H	240	**9d**	68

[a] Yields of pure products after chromatography.



Scheme 5.

2.4. Deprotecting step: hydrolysis of ketals *10*

Hydrolysis of ketals **10** led directly to lactones **1**, which are very sensitive and unstable compounds. Their purification either by column chromatography or distillation could not be achieved without substantial loss of material. Several groups reported their rapid polymerization in the presence of water or impurities. Besides, lactones are often prepared at the last step of a multistep synthetic sequence and, as a result, are obtained in relatively small amounts, which increases the difficulty in obtaining a sufficient amount of pure product [9].

The hydrolysis of compound **10a** ($R^1 = R^2 = H$), chosen as a model substrate, was examined by using a variety of conditions. Direct conversion of **10a** to lactone **1a** using either acetic acid 80% or sulfuric acid under reflux failed and decomposition of lactone **1a** occurred.

Satisfying results were obtained, either with HCl (g) in the presence of a trace amount of water, or with cationic resins as described previously for the production of **1a** from **10a** (entry 2) [10]. The results of Table 4 proved that formation of substituted lactones **1b**–**d** was preferentially accomplished by stirring ketals **9b**–**d** in the presence of etheral HCl (g). On the other hand, **10a**, the most sensitive to acidic conditions, afforded preferentially **1a** using amberlyst 15 and molecular sieves. In all cases it was never possible to isolate the intermediate dihydroxyacid **11**.

2.5. Oxidation of 5-hydroxymethyl-δ-valerolactones *1* into 5-formyl-δ-valerolactones *2*

During the course of the first total synthesis of leukotriene B_4, Corey used the couple PDC-activated

Table 3
Oxidation of aldehydes **9** into acids **10**

Entry	9	R^1	R^2	Oxidant	10	Yield (%) [a]
1	**9a**	H	H	$KMnO_4$	**10a**	61
2	**9a**	H	H	Ag_2O	**10a**	70
3	**9b**	H	Me	$KMnO_4$	**10b**	49
4	**9b**	H	Me	Ag_2O	**10b**	97
5	**9c**	H	Ph	$KMnO_4$	**10c**	–
6	**9c**	H	Ph	Ag_2O	**10c**	92
7	**9d**	Me	H	$KMnO_4$	**10d**	–
8	**9d**	Me	H	Ag_2O	**10d**	75

[a] Yields of pure products after chromatography.

Table 4
Lactonization of acids **10** into **1**

Entry	10	R^1	R^2	Resins acid [a]	Molecular sieves (Å)	Time (h)	1	Yield (%)
1	**10a**	H	H	HCl	–	1	**1a**	54
2	**10a**	H	H	200 [b]	3	15	**1a**	70
3	**10a**	H	H	200 [b]	4	12	**1a**	72
4	**10a**	H	H	15 [a]	4	6	**1a**	75
5	**10b**	H	Me	15 [c]	4	17	**1b**	93
6	**10b**	H	Me	HCl	–	1	**1b**	96
7	**10c**	H	Ph	15 [c]	4	70	**1c**	87
8	**10c**	H	Ph	HCl	–	1	**1c**	98
9	**10d**	Me	H	15 [c]	4	4	**1d**	75
10	**10d**	Me	H	HCl	–	1	**1d**	73

[a] Resins were used in presence of molecular sieves.
[b] Amberlite 200.
[c] Amberlyst 15.

powdered molecular sieve in suspension in dichloromethane in order to oxidize the enantiomerically pure 5-hydroxymethyl-δ-valerolactone (**1a**) to 5-formyl-δ-valerolactone (**2a**) [2a]. Application of this procedure to 5-hydroxymethyl-δ-valerolactones (**1a**–**d**) gave satisfying yields of crude products **2a**–**d** in consideration of their high sensitivity. Yields were determined by ^{1}H-NMR measurements based on percentage conversion of **1a**–**d** (**2a**, 58%; **2b**, 75%; **2c**, 67%; **2d**, 67%) (Scheme 6).[2]

3. Conclusions

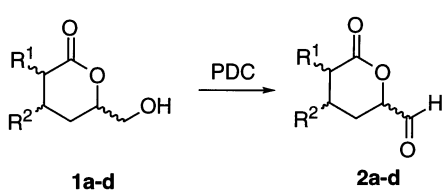
A convenient route to 2- or 3-alkyl substituted 5-hydroxymethyl-δ-valerolactones **1** diastereomers, precursors of 5-formyl-δ-valerolactones **2** diastereomers, was proposed based on the reaction between lithiated *N*-alkenyl-*N*-methyl-(bisdimethylamino) phosphoramide anions (**6**) and 2,3-*O*-isopropylideneglycerol triflate. Although it was not possible to determine the stereoselectivity of the different steps involved in this approach, nevertheless, the formation of pure diastereomers **1** was possible after chromatographic separation but with a substantial loss of material. On the other hand, the great fragility of 2- or 3-alkyl substituted 5-formyl-δ-valerolactones (**2**) prevented any attempt of diastereomeric purification on the crude mixture resulting from the oxidation of **1**. These aldehydes had to be used immediately for further synthetic purpose. As a consequence, the formation of each diastereomer of **2** was only possible from pure diastereomer **1** obtained after column chromatography. It should also be noted that this method could led to an enantioselective synthesis of **1a** and **2a** when the (*R*)-(−) or (*S*)-(+)-2,3-*O*-isopropylidene glycerol is used as the starting compound [5].

[2] We noted that this step was very sensitive to reaction conditions. Oxidation was optimal for amounts of starting compound **1** up to 100 mg . In these conditions no more than 40 mg of crude aldehyde **2** could be obtain with about 90% purity estimated from the ^{1}H-NMR data. Moreover, these aldehydes rapidly degraded and had to be used immediately [5].

4. Experimental

4.1. General methods

IR spectra were obtained using a Nicolet 205 spectrometer and are given in cm^{-1}. ^{1}H-NMR spectra were recorded using a Bruker AM400 or AC250 and ^{31}P-NMR/^{13}C-NMR spectra were recorded using a Bruker AC250. Data for ^{1}H-NMR spectra are reported in δ units downfield from internal Me_4Si or from the $CHCl_3$ solvent peak at 7.26 ppm relative to Me_4Si. Orthophosphoric acid (85%) was used as an external standard for ^{31}P-NMR. ^{13}C-NMR spectra were referenced to the $CDCl_3$ peak at 77.2 ppm relative to Me_4Si. Multiplicities are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Mass spectra were obtained with a TRIO 1000 FISONS spectrometer. Analytical chromatography was performed on silica gel 60 F254 plates. Products were revealed by spraying sulfuric acid followed by calcination, or by iodine. Preparative chromatographic separations were carried out on Merck silica gel 60 (230–400 mesh). Et_2O was distilled over P_2O_5 and stored over Na. THF was freshly distilled from Na/naphtalene prior to use. HMPA was distilled



1a-d **2a-d**

Scheme 6.

from CaH_2 at reduced pressure and stored over molecular sieves (3 Å). Hexane was distilled over Na and dried over molecular sieves (3 Å). *n*-Butyllithium was purchased from Aldrich and was titrated using the Watson and Eastham procedure [11].

4.2. General procedure for the preparation of enephosphoramides 7

To a stirred solution of enephosphoramide **5** (10.0 mmol) [3] in THF (60 ml) at −50°C was added 7.2 ml (11.5 mmol) of a 1.6 M *n*-butyllithium in hexane. After stirring for 3 h under nitrogen at −50°C, 2.4 g (9 mmol) of triflate [12] **4** in THF (5 ml) at −50°C was added slowly. The mixture was stirred for 1 h at the same temperature and then hydrolyzed with water (30 ml). The aqueous solution was extracted with methylene chloride (3 × 20 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude enephosphoramides (**7**) were obtained as pale yellow oils and were stored under nitrogen at −20°C.

4.2.1. [4-(2,2-dimethyl-1,3-dioxolan-4-yl)-1-butenyl]-pentamethyl phosphoric triamide 7a

IR (neat) cm^{-1}: 1655 (C=C), 1375, 1365 (CH_3). **7a** (*E*) (78%). ^{31}P-NMR (170 MHz, $CDCl_3$), δ: 24.3. ^{1}H-NMR: (400 MHz, $CDCl_3$), δ: 6.32 (H^1, dd, 1H, $^3J(H^1–H^2) = 14.0$ Hz, $^3J(H^1 - P) = 6.0$ Hz), 4.45 (H^2, dt, 1H, $^3J(H^2–H^1) = 14.0$ Hz, $^3J(H^2–H^3) = 7.0$ Hz), 4.10–3.90 (H^6, $H^{6'}$, m, 2H), 3.50–3.40 (H^5, m, 1H), 2.65 (CH_3–N–P, d, 3H, $^3J(CH_3–N–P) = 8.0$ Hz), 2.56 (CH_3–N–P, d, 12H, $^3J(CH_3–N–P) = 9.0$ Hz), 2.15–1.40 (H^3, H^4, m, 4H), 1.34 (CH_3, s, 3H), 1.28 (CH_3, s, 3H). **7a** (*Z*) (22%). ^{31}P-NMR (170 MHz, $CDCl_3$), δ: 25.4.

4.2.2. [3-methyl-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-1-butenyl] pentamethyl phosphoric triamide 7b

IR (neat) cm^{-1}: 1650 (C=C), 1375, 1365 (CH_3). **7b** (*E*) (70%). ^{31}P-NMR (170 MHz, $CDCl_3$), δ: 24.4. First diastereomer (55%). ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 6.31 (H^1, ddd, 1H, $^3J(H^1–H^2) = 14.0$ Hz, $^3J(H^1–P) = 6$ Hz, $^4J(H^1–H^3) = 0.5$ Hz), 4.26 (H^2, dd, 1H, $^3J(H^2–H^1) = 14.0$ Hz, $^3J(H^2–H^3) = 9.0$ Hz), 4.15–3.90 (H^6, $H^{6'}$, 2H), 3.60–3.32 (H^5, 1H), 2.69 (CH_3–N–P, d, 3H, $^3J(CH_3–N–P) = 8.5$ Hz), 2.57 (CH_3–N–P, d, 12H, $^3J(CH_3–N–P) = 9$ Hz), 2.40–1.38 (H^4, H^3, m, 3H), 1.33 (CH_3, s, 3H), 1.25 (CH_3, s, 3H), 3H), 0.97 (CH_3–CH^3, d, 3H, $^3J(CH_3–H^3) = 6.5$ Hz). Second diastereomer (45%). ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 6.27 (H^1, ddd, 1H, $^3J(H^1–H^2) = 14.0$ Hz, $^3J(H^1–P) = 6$ Hz, $^4J(H^1–H^3) = 0.5$ Hz), 4.36 (H_2, dd, 1H, $^3J(H^2–H^1) = 14.0$ Hz, $^3J(H^2–H^3) = 9.0$ Hz), 4.15–3.90 (H^6, $H^{6'}$, 2H), 3.60–3.32 (H^5, 1H), 2.68 (CH_3–N–P, d, 3H, $^3J(CH_3–N–P) = 8.5$ Hz), 2.59 (CH_3–N–P, d, 12H, $^3J(CH_3–N–P) = 9$ Hz), 2.40–1.38 (H^4, H^3, m, 3H), 1.34 (CH_3, s, 3H), 1.27 (CH_3, s, 3H), 0.96 (CH_3–CH^3, d, 3H, $^3J(CH_3–H^3) = 6.5$ Hz). **7b** (*Z*) (30%). ^{31}P-NMR (170 MHz, $CDCl_3$), δ: 25.3.

4.2.3. [3-phenyl-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-1-butenyl] pentamethylphosphoric triamide 7c

IR (neat) cm^{-1}: 1650 (C=C), 1380, 1370 (CH_3). **7c** (*Z*) (68%). ^{31}P-NMR (170 MHz, $CDCl_3$), δ: 25.1. First diastereomer (70%). ^{1}H-NMR: (400 MHz, $CDCl_3$), δ: 7.40–7.20 (C_6H_5, m, 5H), 6.10 (H^1, dd, 1H, $^3J(H^1–H^2) = 10$ Hz, $^3J(H^1–P) = 6$ Hz), 4.56 (H^2, dt, 1H, $^3J(H^2–H^1) = {}^3J(H^2–H^3) = 10$ Hz, $^3J(H^2–P) = 2$ Hz), 4.03 (H^6, $H^{6'}$, dd, 2H, $^2J(H^6–H^{6'}) = 8$ Hz, $^3J(H^6–H^5) =$ 6 Hz), 3.60–3.24 (H^5, H^3, m, 2H), 3.05 (CH_3–N–P, d, 3H, $^3J(CH_3–N–P) = 9$ Hz), 2.60 (CH_3–N–*P*, d, 6H, $^3J(CH_3–N–P) = 9$ Hz), 2.58 (CH_3–N–P, d, 6H, $^3J(CH_3–N–P) = 9$ Hz), 2.05–1.65 (H^4, m, 2H), 1.42 (CH_3, s, 3H), 1.30 (CH_3, s, 3H). Second diastereomer (30%). ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 7.40–7.20 (C_6H_5, m, 5H), 5.97 (H^1, dd, 1H, $^3J(H^1–H^2) = 10$ Hz, $^3J(H^1–P) = 6$ Hz), 4.80 (H^2, dt, 1H, $^3J(H^2–H^1) =$ $^3J(H^2–H^3) = 10$ Hz, $^3J(H^2–P) = 2$ Hz), 3.80 (H^6, $H^{6'}$, dd, 2H, $^2J(H^6–H^6) = 8$ Hz, $^3J(H^6–H^5) = 6$ Hz), 3.60–3.24 (H^5, H^3, m, 2H), 2.65 (CH_3–N–P, d, 3H, $^3J(CH_3–N–P) = 9$ Hz), 2.59 (CH_3–N–P, d, 6H, $^3J(CH_3–N–P) = 9$ Hz), 2.57 (CH_3–N–P, d, 6H, $^3J(CH_3–N–P) = 9$ Hz), 2.05–1.65 (H^4, m, 2H), 1.36 (CH_3, s, 3H), 1.28 (CH_3, s, 3H). **7c** (*E*) (32%). ^{31}P-NMR (170 MHz, $CDCl_3$), δ: 23.3. First diastereomer (60%). ^{1}H-NMR: ($CDCl_3$, 400 MHz), δ: 7.15–7.45 (C_6H_5, m, 5H), 6.30 (H^1, dd, 1H, $^3J(H^1–H^2) = 14$ Hz, $^3J(H^1–P) = 6.5$ Hz), 4.73 (H^2, dd, 1H, $^3J(H^2–H^1) = 14$ Hz, $^3J(H^2–H^3) = 7.0$ Hz). Second diastereomer (40%). ^{1}H-NMR ($CDCl_3$, 250 MHz), δ: 7.15–7.45 (C_6H_5, m, 5H), 6.36 (H^1, dd, 1H, $^3J(H^1–H^2) = 13{,}5$ Hz, $^3J(H^1–P) = 6.5$ Hz), 4.70 (H^2, dd, 1H, $^3J(H^2–H^1) = 13{,}5$ Hz, $^3J(H^2–H^3) = 6.0$ Hz).

4.2.4. [2-methyl-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-1-butenyl] pentamethyl phosphoric triamide 7d

IR (neat) cm^{-1} 1660, 1375, 1365 (CH_3). **7d** (*E*) (93%). ^{31}P-NMR (170 MHz, $CDCl_3$), δ: 23.0. ^{1}H-NMR: (400 MHz, $CDCl_3$), δ: 5.79 (H^1, m, 1H), 4.20–4.00 (H^6, $H^{6'}$, m, 2H), 3.70–3.40 (H^5, m, 1H), 2.79 (CH_3–N–P, d, 3H, $^3J(CH_3–N–P) = 9$ Hz), 2.68 (CH_3–N–*P*, d, 12H, $^3J(CH_3–N–P) = 9$ Hz), 2.20–1.45 (H^3, H^4, m, 4H), 1.74 (CH_3–C^2, s, 3H), 1.41 (CH_3, s, 3H), 1.35 (CH_3, s, 3H). **7d** (*Z*) (7%). ^{31}P-NMR (170 MHz, $CDCl_3$), δ: 25.3.

4.3. General procedure for the preparation of adehydes 9

Enephosphoramide **7** (2.00 mmol) was dissolved in Et_2O (25 ml) and a 2 N aqueous solution of sulfuric

acid was added up to pH 2.5. Then, the mixture was stirred for the time indicated in Table 2, according to the nature of the enephosphoramide **7**. The pH of the aqueous layer was readjusted every hour to its initial value by addition of a 2 N aqueous solution of H_2SO_4. The course of the reaction was monitored by IR. Once the IR aldehydic absorption stabilized, the aqueous layer was extracted with Et_2O (3×15 ml). The ether layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column (1:1 Et_2O–hexane) to give the aldehyde **9** as a yellow clear oil.

4.3.1. 4-(2,2-dimethyl-1,3-dioxolan-4-yl)butanal **9a**

R_f: 0.68 (1:1 ethyl acetate–hexane). IR: 2720 (CHO), 1720 (C=O), 1384, 1375 (CH_3). ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 9,71 (H^1, t, 1H, $^3J(H^1–H^2) = 1.5$ Hz), 4.20–4.00 (H^6, H^5, m, 2 H), 3.45 ($H^{6'}$, dd with the appearance of a triplet, 1H, $^3J(H^5–H^6) = {}^2J(H^{6'}–H^6) = 7$ Hz), 2.43 (H^2, dt, 2H, $^3J(H^2–H^3) = 7$ Hz, $^3J(H^2–H^1) = 1.5$ Hz), 1.78–1.45 (H^3, H^4, m, 4H), 1.38 (CH_3, s, 3H), 1.32 (CH_3, s, 3H). ^{13}C-NMR (62 MHz, $CDCl_3$): C^1 201.9; $C(CH_3)_2$ 108.7; C^5 75.5; C^6 69.1; C^2, C^4 43.5, 32.8; CH_3: 26.8, 25.5; C^3 18.3. Anal. Calc. for $C_9H_{16}O_3$: C% 62.77; H% 9.36. Found: C% 62.50; H% 9.40.

4.3.2. 3-methyl-4-(2,2-dimethyl-1,3-dioxolan-4-yl)butanal **9b**

R_f: 0.79 (1:1 EtOAc–Ep). IR: 2720 (CHO), 1720 (C=O), 1384, 1380 (CH_3). First diastereomer (70%). ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 9.87 (H^1, t, 1H, $^3J(H^1–H^2) = 2$ Hz), 4.12–4.02 (H^6, m, 1H), 3.98 (H^5, m, 1H), 3.43 ($H^{6'}$, dd, 1H, $^2J(H^{6'}–H^6) = {}^2J(H^6–H^5) = 7.5$ Hz), 2.45 (H^2, ddd, 1H, $^2J(H^2–H^{2'}) = 16.0$ Hz, $^3J(H^2–H^3) = 5.5$ Hz, $^3J(H^2–H^1) = 2$ Hz), 2.21 ($H^{2'}$, ddd, 1H, $^2J(H^{2'}–H^2) = 16.0$ Hz, $^3J(H^{2'}–H^3) = 7.5$ Hz, $^3J(H^{2'}–H^1) = 2$Hz), 2.28–2.10 (H^3, m, 1H), 1.55 (H^4, ddd, 2H, $^2J(H^4–H^{4'}) = 14.0$ Hz, $^3J(H^4–H^5) = 7.5$ Hz, $^3J(H^4–H^3) = 6.5$ Hz, 1.43 ($H^{4'}$, ddd, 1H, $^2J(H^{4'}–H^4) = 14.0$ Hz, $^3J(H^{4'}–H^5) = 7.5$ Hz, $^3J(H^{4'}–H^3) = 6.5$ Hz), 1,32 (CH_3–C, s, 3H), 1,27 (CH_3–C, s, 3H), 0.96 (CH_3–CH^3, d, 3H, $^3J(CH_3–CH^3) = 6.5$ Hz). ^{13}C-NMR (62 MHz, $CDCl_3$), δ: C^1 201.6; $C(CH_3)_2$ 96.2; C^5 73.9; C^6 69.7; C^2, C^4 50.6, 40.3; $(CH_3)_2$–C 27.1, 25.8; CH_3–CH 20.6. Second diastereomer (30%). ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 9.87 (H^1, t, 1H, $^3J(H^1–H^2) = 1.5$ Hz), 4.20–4.08 (H^6, H^5, m, 2H), 3.62–3.53 ($H^{6'}$, m, 1H), 2.45 (H^2, dd, 2H, $^3J(H^2–H^1) = 1.5$ Hz, $^3J(H^2–H^3) = 7$ Hz), 2.19–1.55 (H^3, H^4, m, 3H), 1.40 (CH_3–C, s, 3H), 1.30 (CH_3–C, s, 3H), 0.97 (CH_3–CH^3, d, 3H, $^3J(CH_3–CH^3) = 7$Hz). ^{13}C-NMR (62 MHz,$CDCl_3$), δ: C^1 201.55; $C(CH_3)_2$ 108.9; C^5 74.1; C^6 69.8; C^2, C^4 50.6, 40.8; $(CH_3)_2$–C 27.1, 25.6; CH_3–CH 20.2. Anal. Calc. for $C_{10}H_{18}O_3$: C% 64.49; H% 9.74. Found: C% 64.10; H% 9.52.

4.3.3. 3-phenyl-4-(2,2-dimethyl-1,3-dioxolan-4-yl)butanal **9c**

R_f: 0.72 (1:1 EtOAc–Ep). IR: 2720 (CHO), 1720 (C=O), 1380, 1370 (CH_3). First diastereomer (77%). ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 9.59 (H^1, t, 1H, $^3J(H^1–H^2) = 2$ Hz), 7.50–7.10 (C_6H_5, m, 5H), 3.94 (H^6, dd, 1H, $^2J(H^6–H^{6'}) = 8$ Hz, $^3J(H^6–H^5) = 6$ Hz), 3.84 (H^5, q, 1H, $^3J(H^6–H^5) = {}^3J(H^{6'}–H^5) = {}^3J(H^5–H^4) = {}^3J(H^5–H^{4'}) = 6$ Hz), 3.80–3.72 (H^3, m, 1H), 3.66 ($H^{6'}$, dd, 1H, $^2J(H^{6'}–H^6) = 8$ Hz, $^3J(H^{6'}–H^5) = 6$ Hz), 2.80–2.63 (H^2, $H^{2'}$, m, 2H), 1.99 (H^4, ddd, 1H, $^2J(H^4–H^{4'}) = 13$ Hz, $^3J(H^4–H^5) = 6$ Hz, $^3J(H^4–H^3) = 8.5$ Hz), 1.80–1.64 ($H^{4'}$, m, 1H), 1.31 (CH_3, s, 3H), 1.21 (CH_3, s, 3H). ^{13}C-NMR (62 MHz, $CDCl_3$), δ: C^1 201.5; C_6H_5 142.8, 128.8, 127.5, 127.2; $C(CH_3)_2$ 108.6; C^5 73.9; C^6 69.3; C^2, C^4 50.5, 40.8; C^3 37.2; $(CH_3)_2$–C 27.0, 25.6. Second diastereomer (23%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.58 (H^1, t, 1H, $^3J(H^1–H^2) = 1.5$ Hz), 7.50–7.10 (C_6H_5, m, 5H), 3.50 (H^6, dd, 1H, $^2J(H^6–H^{6'}) = {}^3J(H^6–H^5) = 7.5$ Hz), 3.42–3.32 (H^3, m, 1H), 3.24 ($H^{6'}$, dd, 1H, $^2J(H^{6'}–H^6) = {}^3J(H^{6'}–H^5) = 7.5$ Hz), 3.20 (H^5, q, 1H, $^3J(H^5–H^{6'}) = {}^3J(H^5–H^{6'}) = {}^3J(H^5–H^4) = {}^3J(H^5–H^{4'}) = 7.5$ Hz), 2.80–2.63 (H^2, $H^{2'}$, m, 2H), 1.87 (H^4, ddd, 1H, $^2J(H^4–H^{4'}) = 13$ Hz, $^3J(H^4–H^5) = {}^3J(H^4–H^3) = 8$ Hz) 1.80–1.64 ($H^{4'}$, m, 1H), 1.33 (CH_3, s, 3H), 1.21 (CH_3, s, 3H). ^{13}C-NMR (62 MHz, $CDCl_3$), δ: C^1 201.45; C_6H_5 142.9, 128.7, 127.5, 126.9; $C(CH_3)_2$ 108.7; C^5 73.4; C^6 69.2; C^2, C^4 49.9, 40.1; C^3 36.6; $(CH_3)_2$–C 26.9, 25.6. Anal. Calc. for $C_{15}H_{20}O_3$: C% 72.55; H% 8.12. Found: C% 72.63; H% 7.98.

4.3.4. 2-methyl-4-(2,2-dimethyl-1,3-dioxolan-4-yl)butanal **9d**

R_f: 0.71 (1:1 EtOAc–Ep). IR: 2720 (CHO), 1720 (C=O), 1384, 1370 (CH_3). First diastereomer (60%). ^{1}H-NMR (250 MHz, $CDCl_3$), δ: 9.63 (H^1, d, 1H, $^3J(H^1–H^2) = 2$ Hz), 4.15–4.10 (H^6, m, 2H), 4.10–4.00 (H^5, m, 1H), 3.52 ($H^{6'}$, m, 1H), 2.30 (H^2, m, 1H), 2.00–1.45 (H^3, H^4, m, 4H), 1.40 (CH_3–C, s, 3H), 1.35 (CH_3–C, s, 3H), 1.12 (CH_3–CH^2, d, 3H, $^3J(CH_3–CH^2) = 7$ Hz). Second diastereomer (40%), δ: 9.62 (H^1, d, 1H, $^3J(H^1–H^2) = 2$ Hz), 4.15–4.10 (H^6, m, 1H), 4.10–4.00 (H^5, m, 1H), 3.63 ($H^{6'}$, m, 1H), 2.30 (H^2, m, 1H), 2.00–1.45 (H^3, H^4, m, 4H), 1.40 (CH_3–C, s, 3H), 1.35 (CH_3–C, s, 3H), 1.125 (CH_3–CH^2, d, 3H, $^3J(CH_3–CH^2) = 7$ Hz). Anal. Calc. for $C_{10}H_{18}O_3$: C% 64.49; H% 9.74. Found: C% 64.20; H% 9.58.

4.4. General procedure for the preparation of acids **10**

With silver nitrate: silver nitrate powder (3.954 g, 23 mmol) was added slowly at 5°C to a cold stirred solution of sodium hydroxide (1.86 g, 46 mmol) in distilled water (14 ml). After stirring for 10 min, aldehyde **9** (11.63 mmol) was added dropwise with a syringe. The mixture was stirred for 1 h and filtered. The

filtrate was acidified to pH 3.75 with a saturated solution of oxalic acid. The aqueous solution was extracted with ethyl acetate (3 × 25 ml), dried and concentrated. The residue was purified by column chromatography (SiO_2, ethyl acetate).

With potassium permanganate: $KMnO_4$ (0.754g, 4.77 mmol) was added in small portions at 5°C to a stirred and ice-cooled mixture of aldehydes **9** (5.8 mmol) and KOH (0.512 g, 9.12 mmol) in H_2O (20 ml). After the completion of addition, the reaction mixture was stirred at r.t. until all the permanganate was completely consumed. The precipitated MnO_2 was removed by filtration through celite and the solution was neutralized with 1 M H_2SO_4 using phenolphthalein as indicator. The total aqueous solution was evaporated to dryness in vacuo. After addition of CH_2Cl_2, the inorganic salt precipitated and was filtered; the filtrate was dried over anhydrous magnesium sulfate. The potassium salt of **10** was obtained as a white pasty solid after vacuum evaporation. This solid was dissolved in the mixture CH_2Cl_2 (50 ml)/Et_2O (30 ml). The addition of HCl (g) in Et_2O (6 ml) led to the acid **10** after centrifugation and evaporation under vacuum. The crude acid was purified by column chromatography (SiO_2, ethyl acetate).

4.4.1. 4-(2,2-dimethyl-1,3-dioxolan-4-yl) butanoic acid ***10a***

R_f: 0.73 (EtOAc). IR: 3700–2400 (OH), 1750 (C=O), 1720 (C=O), 1384, 1377 (CH_3). ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 9.5 (OH, s, 1H), 4.14–4.03 (H^6, H^5, m, 2H), 3.55–3.49 ($H^{6'}$, dd with the appearance of a triplet, 1H, $^2J(H^{6'}–H^6) = {}^3J(H^{6'}–H^5) = 7.0$ Hz, 1H), 2.41 (H^2, t, 2H, $^3J(H^2–H^3) = 7$ Hz), 1.80 − 1.50 (H^3, H^4, m, 4H), 1.41 (CH_3, s, 3H), 1.36 (CH_3, s, 3H). ^{13}C-NMR (62 MHz, $CDCl_3$), δ: C^1 178.8; $(CH_3)_2C$ 108.5; C^5 75.6; C^6 69.1; C^2, C^4 33.7, 32.7; $(CH_3)_2C$ 26.8, 25.5; C^3 20.9. Anal. Calc. for $C_9H_{16}O_4$: C% 57.43; H% 8.57. Found: C% 57.61; H% 8.39.

4.4.2. 3-methyl-4-(2,2-dimethyl-1,3-dioxolan-4-yl)butanoic acid ***10b***

R_f: 0.74 (EtOAc). IR: 3700–2300 (OH), 1740 (C=O), 1720 (C=O), 1384, 1377 (CH_3). First diastereomer (64%). ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 8.06–9.26 (OH, s, 1H), 4.23–4.14 (H^6, m, 1H), 4.11–4.03 (H^5, m, 1H), 3.58–3.47 ($H^{6'}$, m, 1H), 2.43 (H^2, dd, 1H, $^2J(H^2–H^{2'}) = 15$ Hz, $^3J(H^2–H^3) = 6$ Hz), 2.24 ($H^{2'}$, dd, 1H, $^2J(H^{2'}–H^2) = 15$ Hz, $^3J(H^{2'}–H^3) = 7.5$ Hz), 1.70–1.52 (H^4, m, 2H), 1.41 (CH_3–C, s, 3H), 1.36 (CH_3–C, s, 3H), 1.05 (CH_3–CH^3, d, 3H, $^3J(CH_3–CH^3 = 6.5$ Hz). ^{13}C-NMR (62 MHz, $CDCl_3$), δ: C^1 178.2; $(CH_3)_2$–C 108.8; C^5 74.0; C^6 69.5; C^2, C^4 41.0, 39.9; $(CH_3)_2$–C 26.9, 26.3; CH_3–CH^3 21.0. Second diastereomer (36%). ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 8.06–9.26 (OH, s, 1H), 4.23–4.14 (H^6, m, 1H), 4.11–4.03 (H^5, m, 1H), 3.58–3.47 ($H^{6'}$, m, 1H), 2.46 (H^2, dd, 1H, $^2J(H^2–H^{2'}) = 15$Hz, $^3J(H^2–H^3) = 6$Hz), 2.22 ($H^{2'}$, dd, 1H, $^2J(H^{2'}–H^2) = 15$ Hz, $^3J(H^{2'}–H^3) = 7.5$ Hz), 1.80–1.52 (H^4, m, 2H), 1.41 (CH_3–C, s, 3H), 1.35 (CH_3–C, s, 3H), 1.02 (CH_3–CH^3, d, 3H, $^3J(CH_3–CH^3 = 6.5$ Hz). ^{13}C-NMR (62 MHz, $CDCl_3$), δ: C^1 178,3; $(CH_3)_2$–C 109.0; C^5 74.1; C^6 69.6; C^2, C^4 41.6, 40.3; $(CH_3)_2$–C 27.6, 26.3; CH_3–CH^3 20.7. Anal. Calc. for $C_{10}H_{18}O_4$: C% 59.39; H% 8.97. Found: C% 59.69; H% 8.39.

4.4.3. 3-phenyl-4-(2,2-dimethyl-1,3-dioxolan-4-yl)butanoic acid ***10c***

R_f: 0.73 (EtOAc). IR: 3700–2400 (OH), 1750 (C=O), 1720 (C=O), 1384, 1377 (CH_3). First diastereomer. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 9.00 (OH, s, 1H), 7.35–7.15 (C_6H_5, m, 5H), 3.99 (H^6, dd, 1H, $^2J(H^6–H^{6'}) = 7.5$ Hz, $^3J(H^5–H^6) = 6$ Hz), 3.90–3.70 (H^5, m, 1H), 3.56 ($H^{6'}$, dd with the appearance of a triplet, 1H, $^2J(H^{6'}–H^6) = {}^3J(H^{6'}–H^5) = 7.5$ Hz), 3.14–3.05 (H^3, m, 1H), 2.77–2.59 (H^2, $H^{2'}$, m, 2H), 2.08 (H^4, ddd, 1H, $^2J(H^4–H^{4'}) = 13$ Hz, $^3J(H^4–H^3) = 6$ Hz, $^3J(H^4–H^5) = 9$ Hz), 1.83 ($H^{4'}$, ddd, 1H, $^2J(H^4–H^{4'}) = 13$ Hz, $^3J(H^{4'}–H^3) = 6$ Hz, $^3J(H^{4'}–H^5) = 9$ Hz), 1.38 (CH_3, s, 3H), 1.26 (CH_3, s, 3H). ^{13}C-NMR (62 MHz, $CDCl_3$), δ: C^1 177.0; C_6H_5 142.6, 128.5, 128.4, 127.0; $(CH_3)_2$–C 108.6; C^5 73.4; C^6 68.8; C^2, C^4 40.8, 39.5; C^3 38.4; $(CH_3)_2$–C 26.6, 25.4. Second diastereomer. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 9.00 (OH, s, 1H), 7.35–7.15 (C_6H_5, m, 5H), 4.10 (H^6, dd, 1H, $^2J(H^6–H^{6'}) = 7.5$ Hz, $^3J(H^5–H^6) = 6$ Hz, 1H), 3.90–3.70 (H^5, m, 1H), 3.68 ($H^{6'}$, dd, 1H, $^2J(H^{6'}–H^6) = 7.5$ Hz, $^3J(H^{6'}–H^5) = 6$ Hz), 3.37–3.30 (H^3, m, 1H), 2.77–2.59 (H^2, $H^{2'}$, m, 2H), 1.91 (H^4, ddd, 1H, $^2J(H^4–H^{4'}) = 13.5$ Hz, $^3J(H^4–H^5) = 8.5$ Hz, $^3J(H^4–H^3) = 5$ Hz), 1.82 ($H^{4'}$, ddd, 1H, $^2J(H^{4'}–H^4) = 13.5$ Hz, $^3J(H^{4'}–H^5) = 8.5$ Hz, $^3J(H^{4'}–H^3) = 5$ Hz), 1.38 (CH_3, s, 3H), 1.26 (CH_3, s, 3H). ^{13}C-NMR (62 MHz, $CDCl_3$), δ: C^1 177.2; C_6H_5 142.8, 128.4, 127.3, 126.7; $(CH_3)_2$–C 108.5; C^5 74.0; C^6 69.1; C^2, C^4 41.2, 40.2; C^3 38.9; $(CH_3)_2$–C 26.8, 25.4. Anal. Calc. for $C_{15}H_{20}O_4$: C% 68.16; H% 7.63. Found: C% 68.34; H% 7.52.

4.4.4. 2-methyl-4-(2,2-dimethyl-1,3-dioxolan-4-yl)butanoic acid ***10d***

R_f: 0.73 (EtOAc). IR: 3750–2400 (OH), 1740 (C=O), 1725 (C=O), 1384, 1377 (CH_3). First diastereomer. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 9.50 (OH, s, 1H), 4.15–4.00 (H^6, H^5, m, 2H), 3.55–3.48 ($H^{6'}$, m, 1H), 2.55–2.40(H^2, m, 1H), 1.92–1.53 (H^3, H^4, m, 4H), 1.40 (CH_3–C, s, 3H), 1.34 (CH_3–C, s, 3H), 1.20 (CH_3–CH^2, d, 3H, $^3J(CH_3–CH^2) = 7$ Hz). ^{13}C-NMR (62 MHz, $CDCl_3$), δ: C^1 181.70; $(CH_3)_2$–C 108.78; C^5 75.65; C^6 69.1; C^2 39.3; C^4 36.75; $(CH_3)_2$–C 31.2, 29.7; CH_3–CH^2 26.8. Second diastereomer. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 9.50 (OH, s, 1H), 4.15–4.00 (H^6, H^5, m,

2H), 3.55–3.48 ($H^{6'}$, m, 1H), 2.70–2.55(H^2, m, 1H), 1.92–1.53 (H^3, H^4, m, 4H), 1.40 (CH_3–C, s, 3H), 1.34 (CH_3–C s, 3H), 1.19 (CH_3–CH^2, d, 3H, $^3J(CH_3$–$CH^2) = 7$ Hz). ^{13}C-NMR (62 MHz, $CDCl_3$), δ: C^1 181.73; $(CH_3)_2$–*C* 108.80; C^5 75.59; C^6 69.2; C^2 39.0; C^4 36.68; $(CH_3)_2$–C 30.9, 29.3; *C*H_3–CH^2 25.6. Anal. Calc. for $C_{10}H_{18}O_4$: C% 59.39; H% 8.97. Found: C% 59.54; H% 9.22.

4.5. General procedure for the preparation of hydroxymethyl δ-valerolactones **1**

Activated 4 Å molecular sieves (120 mg), Amberlyst 15 H^+ resin (120 mg) were added to a solution of acid **10** (100 mg) in acetonitrile (10 ml). The mixture was stirred vigorously at room temperature. The reaction was monitored by TLC. The mixture was then filtered and evaporated under reduced pressure. The residue was chromatographed on silica gel (eluting with AcOEt) to give the pure lactone.

4.5.1. 5–Hydroxymethyl-δ-valerolactone **1a**

R_f: 0.29 (EtOAc). IR: 3445 (OH), 1720 (C=O). ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 4.50–4.35 (H^5, m, 1H), 3.85–3.60 (H^6, m, 2H), 3.20 (OH, s, 1H), 2.70–2.35 (H^2, m, 2H), 2.05–1.60 (H^4, H^3, m, 4H). MS *m*/*z* 130 (M^+). Anal. Calc. for $C_6H_{10}O_3$: C% 55.37; H% 7.74. Found: C% 55.85; H% 8.02 (see Ref. [2a, 5]).

4.5.2. 5–Hydroxymethyl-3-methyl-δ-valerolactone **1b**

R_f: 0.32 (EtOAc). IR: 3400 (OH), 1730 (C=O). First diastereomer (60%). ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 4.50–4.40 (H^5, m, 1H), 3.85 (H^6, dd, 1H, $^2J(H^6$–$H^{6'}) =$ 13 Hz, $^3J(H^6$–$H^5) = 3$ Hz), 3.62 ($H^{6'}$, dd, 1H, $^2J(H^{6'}$–$H^6) = 13$ Hz, $^3J(H^{6'}$–$H^5) = 3$ Hz), 3.30–2.90 (OH, s, 1H), 2.78–2.70 (H^2, m, 1H), 2.52 ($H^{2'}$, dd,1H, $^2J(H^{2'}$–$H^2) = 15$ Hz, $^3J(H^{2'}$–$H^3) = 5$ Hz), 2.20–1.45 (H^3, H^4, m, 3H), 1.05 (CH_3, d, 3H, $^3J(CH_3$– $CH^3) = 6.5$ Hz). ^{13}C-NMR (62 MHz, $CDCl_3$), δ: C^1 172.2; C^5 77.8; C^6 64.8; C^2 37.5; C^3 30.7; C^4 24.0; *C*H_3–CH^3 21.05. Second diastereomer (40%). ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 4.57–4.50 (H^5, m, 1H), 3.80 (H^6, dd, 1H, $^2J(H^6$–$H^{6'}) =$ 13 Hz, $^3J(H^6$–$H^5) = 3$ Hz), 3.58 ($H^{6'}$, dd, 1H, $^2J(H^{6'}$–$H^6) = 13$ Hz, $^3J(H^{6'}$–$H^5) = 3$ Hz), 3.30–2.90 (OH, s, 1H), 2.80–2.40 (H^2, $H^{2'}$, m, 2H), 2.20–1.45 (H^3, H^4, m, 3H), 0.99 (CH_3, d, 3H, $^3J(CH_3$–$H^3) = 6.5$ Hz). ^{13}C-NMR (62 MHz, $CDCl_3$), δ: C^1 171.2, C^5 81.1, C^6 64.8; C^2 38.2 C^3 32.4 C^4 26.4 *C*H_3^- CH^3 21.5. MS *m*/*z* 144 (M^+). Anal. Calc. for $C_7H_{12}O_3$: C% 58.32; H% 8.39. Found: C% 57.90; H% 8.15.

4.5.3. 5–Hydroxymethyl-3-phenyl-δ-valerolactone **1c**

R_f: 0.38 (EtOAc). IR: 3416 (OH), 1729 (C=O). First diastereomer (60%). ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 7.38–7.10 (C_6H_5, m, 5H) 4.50–4.43 (H^5, m, 1H), 3.78 (H^6, dd, 1H, $^2J(H^6$–$H^{6'}) = 12.5$ Hz, $^3J(H^6$–$H^5) = 3.5$ Hz), 3.69 ($H^{6'}$, dd, 1H, $^2J(H^{6'}$–$H^6) = 12.5$ Hz, $^3J(H^{6'}$–$H^5) = 5$ Hz), 3.46–3.34 (H^3, m, 1H), 2.77 (H^2, $H^{2'}$, dd, 2H, $^2J(H^{2'}$–$H^2) = 17.5$ Hz, $^3J(H^{2,2'}$–$H^3) = 5.5$ Hz), 2.23 (H^4, ddd, 1H, $^2J(H^{4'}$–$H^4) = 14.0$ Hz, $^3J(H^4$–$H^3) = 8.5$ Hz, $^3J(H^4$–$H^5) = 6$Hz), 2.12–1.90 ($H^{4'}$, m, 1H). ^{13}C-NMR (62 MHz, $CDCl_3$), δ: C^1 171.9; C_6H_5 142.5, 128.8, 127.0, 126.5; C^5 77.9, C^6 64.2; C^2 36.9; C^3 34.4; C^4 30.9. Second diastereomer (40%). ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 7.38–7.10 (C_6H_5, m, 5H), 4.58–4.50 (H^5, m, 1H), 3.85 (H^6, dd, 1H, $^2J(H^6$–$H^{6'}) = 12.5$ Hz, $^3J(H^6$–$H^5) = 3.0$ Hz), 3.69 ($H^{6'}$, dd, 1H, $^2J(H^{6'}$–$H^6) = 12.5$ Hz, $^3J(H^{6'}$–$H^5) = 5$ Hz), 3.26–3.15 (H^3, m, 1H), 2.90 (H^2, dd, 1H, $^2J(H^{2'}$–$H^2) = 17.5$ Hz, $^3J(H^2$–$H^3) = 5.5$ Hz), 2.55 ($H^{2'}$, dd, 1H, $^2J(H^{2'}$–$H^2) =$ 17.5 Hz, $^3J(H^{2'}$–$H^3) = 5.5$ Hz), 2.12–1.90 ($H^{4'}$, m, 2H). ^{13}C-NMR (62 MHz, $CDCl_3$), δ: C^1 171.1; C_6H_5 142.4, 128.8, 127.1, 126.3; C^5 81.0, C^6 64.4; C^2 37.4; C^3 35.6; C^4 31.4. MS *m*/*z* 206 (M^+). Anal. Calc. for $C_{12}H_{14}O_3$: C% 69.89; H% 6.84. Found: C% 70.08; H% 6.7.

4.5.4. 5–Hydroxymethyl-2-methyl-δ-valerolactone **1d**

R_f: 0.33 (EtOAc). IR: 3416 (OH), 1727 (C=O). First diastereomer (60%): ^{1}H (400 MHz, $CDCl_3$), δ: 4.48–4.39 (H^5, m, 1H), 3.69 (H^6, dd, 1H, $^2J(H^6$–$H^{6'}) = 14$Hz, $^3J(H^6$–$H^5) = 6$ Hz), 3.65 ($H^{6'}$, dd, 1H, $^2J(H^6$–$H^{6'}) = 14$ Hz, $^3J(H^6$–$H^5) = 6$ Hz), 2.68–2.57 (H^2, m, 1H), 2.15–1.50 (H^3, H^4, m, 4H), 1.31 (CH_3–, d, 3H, $^3J(CH_3$–$CH^2) = 7$ Hz). Second diastereomer (40%). ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 4.48–4.39 (H^5, m, 1H), 3.79 (H^6, dd, 1H, $^2J(H^6$–$H^{6'}) = 8$Hz, $^3J(H^6$–$H^5) =$ 3.5Hz), 3.77 ($H^{6'}$, dd, 1H, $^2J(H^6$–$H^{6'}) = 8$Hz, $^3J(H^6$–$H^5) = =$ 3.5 Hz), 2.68–2.57 (H^2, m, 1H), 2.15–1.50 (H^3, H^4, m, 4H), 1.27 (CH_3–, d, 3H, $^3J(CH_3$–$CH^2) = 7$ Hz). MS *m*/*z* 144 (M^+). Anal. Calc. for $C_7H_{12}O_3$: C% 58.32; H% 8.39. Found: C% 58.11; H% 8.48.

4.6. Typical procedure for the preparation of 5-formyl-δ-valerolactone **2**

Freshly activated 4 Å molecular sieves (800 mg) and anhydrous PDC (1.808 g) were added slowly to a solution of lactone **1** (100 mg) in methylene chloride (5 ml) at 23°C. The mixture was stirred vigorously at room temperature. The reaction was followed by TLC. The mixture was then dissolved in Et_2O, filtered under nitrogen and concentrated to give the crude lactone **2**. Due to its inherent instability and difficulties in purification, the crude lactone **2** has to be used immediately [5].

4.6.1. 5-formyl-δ-valerolactone **2a**

IR (neat) cm^{-1}: 1729 (C=O). ^{1}H-NMR (250 MHz, $CDCl_3$), δ: 9.70 (H^6, s, 1H), 5.20–4.80 (H^5, m, 1H), 2.70–2.20 (H^2, m, 2H), 2.00–1.50 (H^3, H^4, m, 4H). ^{13}C-NMR ($CDCl_3$, 62 MHz): δ: C^6 190.3; C^1 170.6; C^5 80.2; C^2 32.6; C^3 29.6; C^4 23.7

4.6.2. 5-formyl-3-methyl-δ-valerolactone **2b**

IR (neat) cm^{-1}: 1728 (C=O), 1718 (C=O). First diastereomer (72%), ^{1}H-NMR (250 MHz, $CDCl_3$), δ: 9.72 (H^6, s, 1H), 4.88 (H^5, dd with the appearance of a triplet, 1H, $^3J(H^5–H^4) = {}^3J(H^5–H^{4'}) = 5.5$Hz, 2.75–2.45 ($H^2$,$H^{2'}$, m, 2H), 2.20–1.40 ($H^4$, $H^{4'}$, H^3, m, 3H), 1.00 (CH_3–, d, 3H, $^3J(CH_3–CH^{3'}) = 6.0$Hz). ^{13}C-NMR (62 MHz, $CDCl_3$), δ: C^6 198.4; C^1 169.3; C^5 81.1; C^2 37.7; C^3 29.6; C^2 23.8; CH_3–20.7. Second diastereomer (28%), ^{1}H-NMR (250 MHz, $CDCl_3$), δ: 9.60 (H^6, s, 1H), 5.07 (H^5, dd, 1H, $^3J(H^5–H^4) = 2.5$ Hz, $^3J(H^5–H^{4'}) = 5.5$ Hz), 0.95 (CH_3–, d, 3H, $^3J(CH_3–CH^{3'}) = 6.0$ Hz). ^{13}C-NMR (62 MHz, $CDCl_3$), δ: C^6 197.5, C^1 170.1, C^5 82.3, C^2 37.6, C^3 29.4, C^4 23.5, CH_3– 21.0.

4.6.3. 5-formyl-3-phenyl-δ-valerolactone **2c**

IR (neat) cm^{-1}: 1735 (C=O), 1725 (C=O). First diastereomer (71%). ^{1}H-NMR (250 MHz, $CDCl_3$), δ: 9.75 (H^6, s, 1H), 7.35–7.05 (C_6H_5, m, 5H), 5.10–4.50 (H^5, m, 1H), 3.30–3.05 (H^3, m, 1H), 2.95–2.50 (H^2, $H^{2'}$, m, 2H), 2.50–1.75 (H^4, $H^{4'}$, m, 2H). ^{13}C-NMR (62 MHz, $CDCl_3$), δ: 197.8, 172.4. Second diastereomer (29%). ^{1}H-NMR (250 MHz, $CDCl_3$): δ: 9.65 (H^6, s, 1H). ^{13}C-NMR (62 MHz, $CDCl_3$), δ: 197.0, 172.1.

4.6.4. 5-formyl-2-methyl-δ-valerolactone **2d**

IR (neat) cm^{-1}: 1730 (C=O), 1725 (C=O). First diastereomer (65%). ^{1}H-NMR (250 MHz, $CDCl_3$), δ: 9.75 (H^6, s, 1H), 5.02–4.80 (H^5, m, 1H), 2.70–2.52 (H^2, m, 1H), 2.20–1.40 (H^3, H^4, m, 4H), 1.28 (CH_3–, d, 3H, $^3J(CH_3–CH^2) = 6.5$Hz). ^{13}C-NMR (62 MHz, $CDCl_3$), δ: 198.6, 172.5. Second diastereomer (35%). ^{1}H-NMR (250 MHz, $CDCl_3$), δ: 9.70 (H^6, s, 1H), 1.25 (CH_3–, d, 3H, $^3J(CH_3–CH^2) = 6.5$Hz). ^{13}C-NMR (62 MHz, $CDCl_3$), δ: 197.4, 171.2.

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