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# Diastereoselective multicomponent phosphoramidate-aldehyde-dienophile (PAD) process for the synthesis of polysubstituted cyclohex-2-enyl-amine derivatives

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## ABSTRACT

The reaction of diethyl phosphoramidate, conjugated aldehydes and maleimides takes place in a multicomponent sequence named phosphoramidate-aldehyde-dienophile (PAD). The reaction affords a series of *N*-substituted phosphoramidates in good yields with  $\alpha,\beta$ -unsaturated aldehydes bearing hydrogens at the  $\gamma$ -position. The reaction is diastereoselective and the effect of chiral information in the maleimide is evaluated. A mechanism is also postulated and the feasible hydrolysis of the phosphoramidate functional group is achieved although the final allylic amine is difficult to isolate.

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## 1. Introduction

Phosphoramidates are not very common structures either in Nature or in synthetic biologically active compounds [1–3]. However, the reported compounds exhibit interesting effects in humans [2]. For example, phosphoramidates are known anticancer agents [–6,2,4,5] and antiviral products [7] effective against hepatitis B or C viruses [8–10]. Roles as covalent intermediates in phosphoryl group transfer reactions have also been reported during the study of the behaviour of several hydrolases [11]. There are three groups of phosphoramidates depending on the substitution of heteroatoms (Fig. 1), with the type III group being the most interesting from a biochemical point of view.

The preparation of phosphoramidates can be achieved by the sequential addition of amines to phosphorochloridate and treatment with alcohols or phenols [12], the addition of amines onto phosphonic acids in the presence of dehydrating-coupling reagents

[13], the amination of phosphoryl azide [14,15], starting from phosphorus oxychloride [16], and employing diethyl phosphite with amines in the presence of iodine [17]. The *in situ* generation of alkyl azides, followed by reaction with triethylphosphite [18], the *O*-phosphorylation with *L*-ethoxyalaninyl phosphorochloridate derivatives [19], and the Atherton–Todd reaction between a trialkyl phosphite and a primary amine in the presence of carbon tetrachloride [20] (or its photochemical version) [21] constitute alternative approaches to the synthesis of these compounds.

Focusing our attention on the Amide-Aldehyde-Dienophile (AAD) reaction, reported by Beller and co-workers in 2001 (Scheme 1a) [22], we envisaged that diethyl phosphoramidate can be an appropriate component to replace the amine/amide in this process to generate type III phosphoramidates. The same group expanded the scope of this multicomponent AAD reaction using different dienophiles, several substituted  $\alpha,\beta$ -unsaturated aldehydes and different linear or cyclic amides (or sulfonamides), obtaining in all cases only the *endo*-approach of the Diels-Alder reaction to produce compounds **1** (Scheme 1a) [23]. Also, they performed the chiral version using a stereocenter in the amide moiety [24]. In addition, we were able to optimize the multicomponent reaction of benzyl or 4-methoxybenzylamine, maleimides

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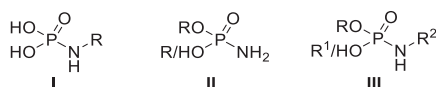
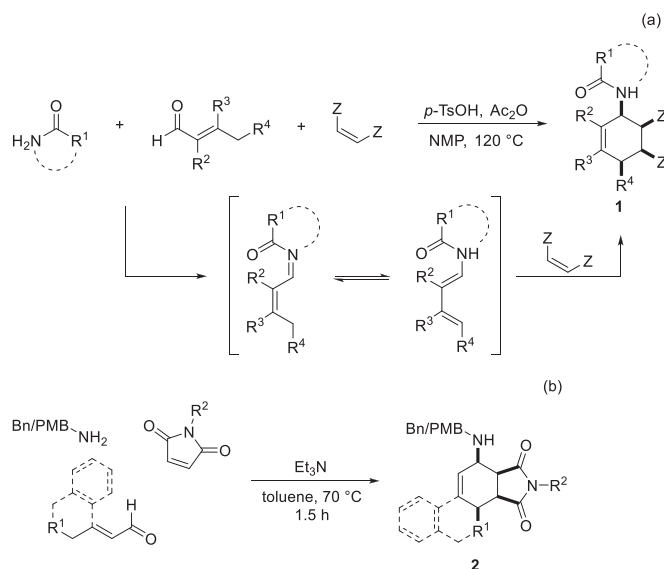


Fig. 1. Classification of phosphoramidates.



Scheme 1. General multicomponent Amine/Amide-Aldehyde-Dienophile (AAD) reaction.

and a conjugated aldehyde containing hydrogen atoms at  $\gamma$ -position to obtain polycyclic compounds **2** (Scheme 1b) [25,26].

In this work, we have optimized the original Phosphoramidate-Aldehyde-Dienophile (PAD) sequence and studied the most appropriate aldehydes and dipolarophiles to achieve access to novel polyfunctionalized phosphoramidates.

## 2. Results and discussion

The model reaction used for the optimization of this multicomponent PAD involved diethyl phosphoramidate, crotonaldehyde and *N*-methylmaleimide (NMM) as the dienophile (Scheme 2). We took advantage of the results obtained in our previous contribution [25] to optimize the process. Thus, toluene was selected as the solvent and the reaction needed to be heated for 8 h in order to observe a noticeable conversion/yield of cycloadduct **3a** (Table 1, compare entries 1–4). The presence of additives such as acetic anhydride and *p*-toluenesulfonic acid (TsOH) were crucial for the reactions of amides or sulfonamides [23], so we analyzed their effects in the multicomponent PAD synthesis. Separately, the presence of acetic anhydride is more important than the presence of TsOH in terms of the isolated yield (Table 1, entries 5 and 6). The highest yield for **3a** was achieved employing only 5 mol% of acetic anhydride and 5 mol% of TsOH (Table 1, entry 7; compare entries 7–10). The crude product **3a** was very pure and could be used for

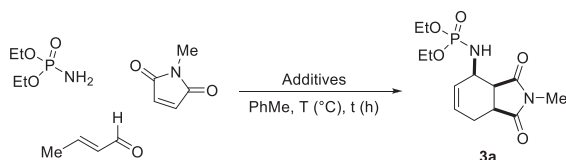
Scheme 2. Multicomponent PAD synthesis of product **3a**.

Table 1

Optimization of the reaction conditions to synthesize *N*-cyclohex-2-en-1-yl phosphoramidate **3a** via the PAD reaction.<sup>a</sup>

Entry	Ac <sub>2</sub> O (mol%)	TsOH (mol%)	T (°C)	t (h)	Yield <b>3a</b> (%) <sup>b</sup>
1	—	—	25	24	—
2	—	—	110	4	64
3	—	—	110	8	62
4	—	—	110	24	60
5	(5)	—	110	8	65
6	—	(5)	110	8	56
7	(5)	(5)	110	16	88
8	(50)	(5)	110	16	87
9	(100)	(5)	110	16	86
10	(100)	(10)	110	16	88
11	(100)	(10) <sup>c</sup>	70	16	29
12	(100)	(10) <sup>c</sup>	110	16	33

<sup>a</sup> Reagents and conditions: diethyl phosphoramidate (1 mmol), crotonaldehyde (1 mmol), additive (0.05 mmol), NMM (1 mmol), toluene (1 mL), temperature, time. \

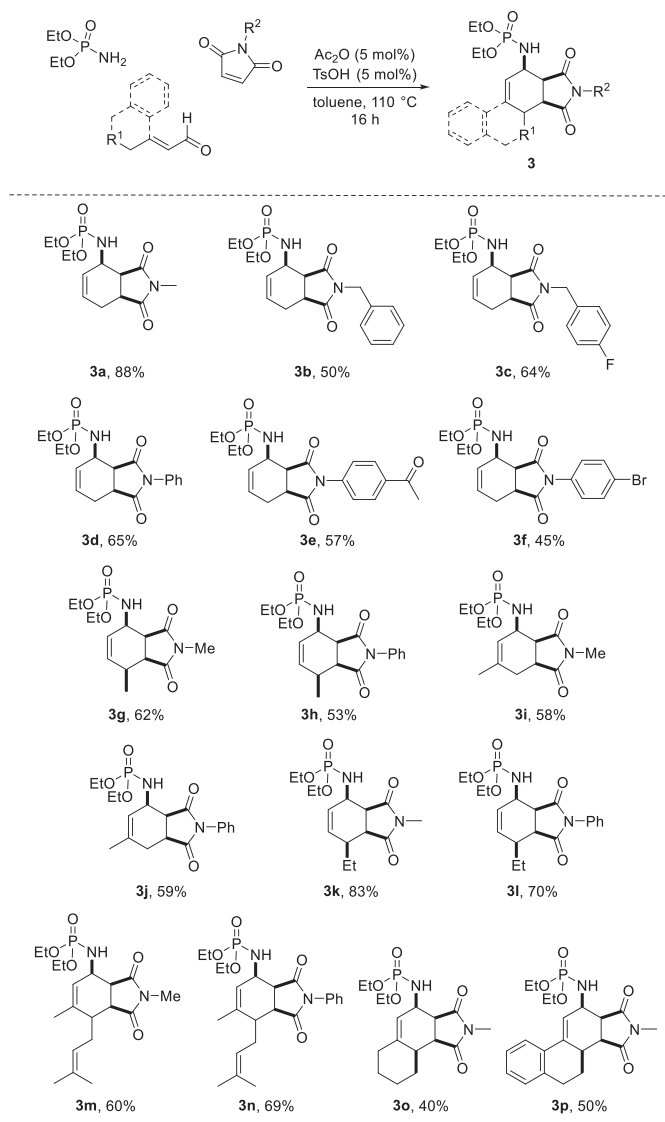
<sup>b</sup> Isolated yield after flash chromatography.

<sup>c</sup> Reaction performed in chloroform.

the synthesis of the free allylic amine after hydrolysis of the diethyl phosphoryl group (see below). The reaction with chloroform took place in very low yields (Table 1, entries 11 and 12). Interestingly, the *N*-cyclohex-2-en-1-amide scaffold **3** is present in somatostatin analogues and the Kessler group conveniently applied this reaction to achieve the desired product [27]. Beller's group also applied this reaction to synthesize corollosporine analogues to test their antimicrobial activity [28].

Using the optimal conditions shown in Entry 7 of Table 1, the effects of the structure of both aldehyde and maleimide components were analyzed (Scheme 3). Crotonaldehyde and diethyl phosphoramidate reacted in the presence of *N*-alkyl, *N*-benzyl, and *N*-arylmaleimides to give compounds **3a–f** in good yields (Scheme 3). It is notable that fluorinated maleimide [29] afforded the corresponding compound **3c** in 64% yield, which can offer a potential biological activity. (*E*)-2-Pentenal was assayed with both NMM and *N*-phenylmaleimide (NPM) yielding products **3g** and **3h** in 62% and 53% yield, respectively (Scheme 3). Similar behaviour was observed when 3-methylcrotonaldehyde was employed in reactions with both maleimides, affording the expected bicyclic skeletons **3i** and **3j** in similar yields (58% and 59%). Hex-2-enal and diethyl phosphoramidate afforded high yields of products **3k** and **3l** in the reactions with NMM and NPM, respectively (Scheme 3). Geranial possesses two different types of hydrogens at the  $\gamma$ -position. This aldehyde failed in our previous amine/aldehyde/dienophile process [25], but in this PAD multicomponent reaction the mechanism preferred the abstraction of one of the two  $\gamma$ -methylenic hydrogens to generate *in situ* the most substituted 1-aminodiene intermediate. Thus, compound **3m** was obtained in 60% yield and a ratio of 85:15 (determined by <sup>1</sup>H NMR), whilst **3n** was isolated in higher yield (69%) with a 90:10 ratio (determined by <sup>13</sup>C NMR) (Scheme 3). Interestingly, tricyclic product **3o** and the pseudo-steroidal tetracyclic scaffold **3p** were isolated from the corresponding cyclic acrylic aldehydes [30] in 40% and 50% yield, respectively (see Scheme 3).

The relative configuration of all compounds **3** was confirmed by nOe experiments and by comparison of chemical shifts (<sup>1</sup>H NMR) with the corresponding analogous amines previously obtained by our group [25]. Despite the temperature, all compounds were isolated as single diastereoisomers except the already described examples using geranial (see above). As well as in our precedent AAD sequential reaction, PAD transformations with fumarates, maleic anhydride, acrylates, vinylic sulfones, chalcone derivatives and nitroalkenes completely failed. In some examples, complex crude reaction mixtures were obtained and the expected products

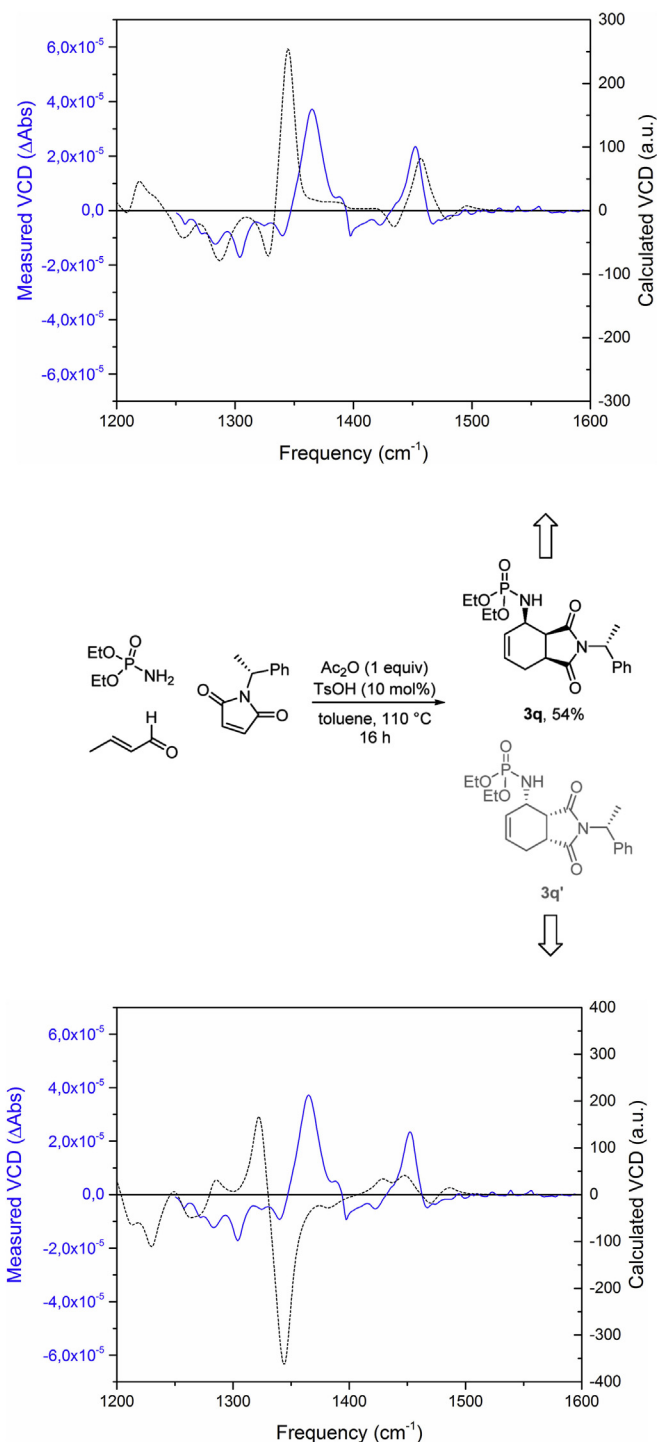


**Scheme 3.** Synthesis of *N*-cyclohex-2-enyl phosphoramidates **3** via the PAD reaction.

were isolated in very low yields.

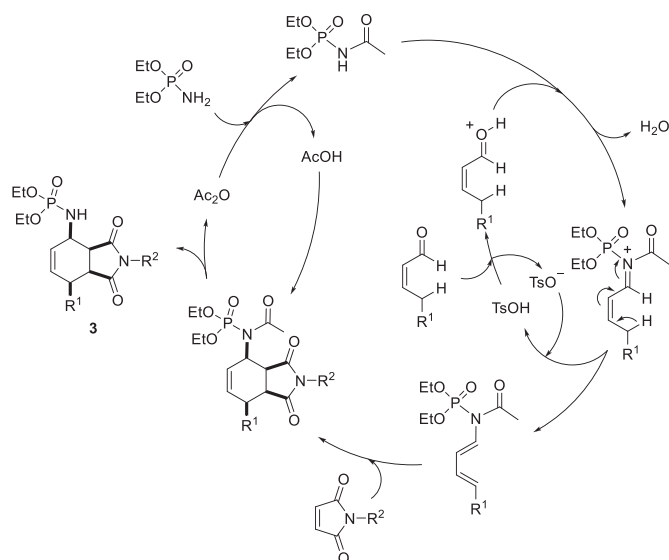
The diastereoselective version of this AAD transformation was also examined employing (*R*)-*N*-(1-phenylethyl)maleimide (**Fig. 2**). The reaction proceeded with high diastereoselectivity despite the temperature employed (82:18 from  $^1\text{H}$  NMR of the crude product). After purification by flash chromatography only the major stereoisomer **3q** could be isolated. The proposed absolute configuration was assigned on the basis of VCD analysis (**Fig. 2**). Both diastereoisomers **3q** and **3q'** exhibited opposite theoretical VCD patterns, which was more relevant in the fingerprint absorption area. The theoretical VCD (black dots plot) and the measured spectra for diastereoisomer **3q** matched almost perfectly (**Fig. 2**). The observed displacement between the theoretical and experimental plots for **3q** can be due to the formation of intramolecular hydrogen bonds between the NH and the closer carbonyl group [31]. This interaction was also supported by the *all-cis* relative configuration of this fused ring such as that which occurred in the analogous AAD reaction [25].

The crucial presence of acetic anhydride and TsOH allowed us to propose a mechanism where both the diethyl phosphoramidate and the aldehyde are independently activated. The reaction



**Fig. 2.** VCD analysis of product **3q** and its enantiomeric form **3q'**. The blue line corresponds to experimentally measured VCD, whilst the dashed black plot is the VCD calculated with a B3LYP/6-311G+(2d,2p) level for configuration **3q**.

operated with substoichiometric amounts of acetic anhydride and so deacetylation of the intermediate *N*-acylphosphoramidate occurred prior to the formation of the final product **3** (see **Scheme 4**). The partial generation of the intermediate diethyl *N*-acetylphosphoramidate was observed after heating the reaction mixture containing all reagents except the maleimide (see ESI). To the resulting mixture the maleimide was added and the expected reaction took place.

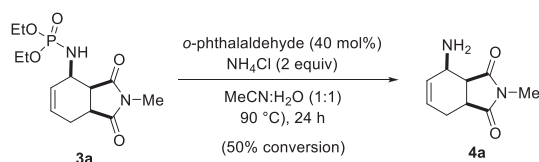


**Scheme 4.** Proposed mechanism for the synthesis of cycloadducts **3**.

The publication of a family of antibacterial agents containing a 3-aminocyclohexene core [32] encouraged us to study the hydrolysis of the phosphoramidate moiety. A convenient method was reported in the literature based on the hydrolysis of various organophosphorus compounds bearing P(O)–NH subunits catalyzed by *o*-phthalaldehyde [33]. Following this procedure compound **3a** was submitted to several test reactions using ammonium *p*-toluenesulfonate or ammonium chloride, at reflux in THF or MeCN. With  $\text{NH}_4\text{OTs}$  the reaction did not work, however,  $\text{NH}_4\text{Cl}$  (2 equiv.) offered the best conversion. Thus,  $\text{NH}_4\text{Cl}$  (2 equiv.), *o*-phthalaldehyde (40 mol%), MeCN/ $\text{H}_2\text{O}$  (90 °C, 24 h) were the most appropriate conditions to obtain a 50% conversion (from the crude  $^1\text{H}$  NMR) (Scheme 5). Primary amine **4a** could be identified (see ESI) but its isolation was not possible either by flash chromatography or precipitation/crystallization by adding 1 equiv. of  $\text{HCl}/\text{Et}_2\text{O}$ . In all these cases equimolar mixtures of **3a** and **4a** were detected (see ESI). We unsuccessfully tried to introduce Boc, benzoyl or acetyl protecting groups in order to aid isolation [34].

### 3. Conclusion

A novel approach for the preparation of polysubstituted phosphoramidates, derived from cyclohex-2-enamines, based on a multicomponent diethyl phosphoramidate-aldehyde-dienophile (PAD) process has been optimized. Maleimides and conjugated aldehydes incorporating a  $\gamma$ -hydrogen are appropriate components to run this reaction in high yields. The high diastereoselectivity achieved is a notable aspect of this transformation generating an *all-cis* relative configuration in the resulting final products. The introduction of chiral information at the *N*-substituent of the maleimide gave an enantiomerically enriched cycloadduct whose absolute configuration was determined by VCD spectroscopy. These



**Scheme 5.** Hydrolysis of cycloadduct **3a**.

final phosphoramidates are potentially bioactive compounds and it was also demonstrated that their hydrolysis is feasible yielding interesting cyclohex-2-enamine building blocks for general organic synthesis.

## 4. Experimental section

### 4.1. General

All commercially available reagents and solvents were used without further purification, only aldehydes were also distilled prior to use. Only the aldehyde precursor of compound **6i** was prepared according to the literature [27]. Analytical TLC was performed on Schleicher & Schuell F1400/LS 254 silica gel plates, and the spots were visualized under UV light ( $\lambda = 254$  nm). Flash chromatography was carried out on handpacked columns of Merck silica gel 60 (0.040–0.063 mm). Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. The structurally most important peaks of the IR spectra (recorded using a Nicolet 510 P-FT) are listed and wave numbers are given in  $\text{cm}^{-1}$ . NMR spectra were obtained using a Bruker AC-300 or AC-400 and were recorded at 300 MHz for  $^1\text{H}$  NMR, 75 or 100 MHz for  $^{13}\text{C}$  NMR, and 121 MHz for  $^{31}\text{P}$  NMR.  $^1\text{H}$  NMR were recorded using  $\text{CDCl}_3$  as solvent and TMS as internal standard (0.00 ppm). The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved and br s = broad signal. All coupling constants (*J*) are given in Hz and chemical shifts in ppm.  $^{13}\text{C}$  NMR spectra were referenced in  $\text{CDCl}_3$  at 77.16 ppm. DEPT-135 experiments were performed to assign  $\text{CH}$ ,  $\text{CH}_2$  and  $\text{CH}_3$ .  $^{19}\text{F}$  NMR were recorded at 282 MHz using  $\text{CDCl}_3$  as solvent.  $^{31}\text{P}$  NMR were performed in  $\text{CDCl}_3$  and referenced at 0.00 ppm (aqueous phosphoric acid). Low-resolution electron impact (EI) mass spectra were obtained at 70 eV using a Shimadzu QP-5000 by injection or DIP; fragment ions in *m/z* are given with relative intensities (%) in parentheses. High-resolution mass spectra (HRMS) were measured on an instrument using a quadrupole time-of-flight mass spectrometer (QTOF) and also through the electron impact mode (EI) at 70 eV using a Finnigan VG Platform or a Finnigan MAT 95S. VCD analysis was recorded in a Jasco FVS-6000.

### 4.2. General procedure for the synthesis of products **6**

To a stirred solution of diethyl phosphoramidate (154 mg, 1 mmol), TsOH (8.6 mg, 0.05 mmol), acetic anhydride (4.8  $\mu\text{L}$ , 0.05 mmol) in 3 mL of toluene was added the aldehyde (1 mmol), the maleimide (1 mmol). The solution was stirred under reflux for 24 h, and then the solvent was removed under vacuum. The crude of the reaction was purified with flash chromatography to give the desired compound.

#### 4.2.1. Diethyl [(3*aSR*,4*RS*,7*aSR*)-2-methyl-1,3-dioxo-2,3,3*a*,4,7,7*a*-hexahydro-1*H*-isoindol-4-yl]phosphoramidate (**3a**)

Pale brown sticky oil, (278 mg, 88% yield). IR (neat)  $\nu_{\text{max}}$ : 1687, 1436, 1023,  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR  $\delta$ : 1.34 (td, *J* = 7.0, 3.2 Hz, 6H,  $2\times\text{CH}_3\text{CH}_2\text{O}$ ), 2.02–2.27 (m, 2H,  $\text{CHCH}_2\text{CH}$ ), 2.67 (dd, *J* = 15.7, 6.6 Hz, 1H,  $\text{CH}_2\text{CHC}=\text{O}$ ), 2.94 (s, 3H,  $\text{NCH}_3$ ), 3.15–3.20 (m, 1H,  $\text{CHCHC}=\text{O}$ ), 3.28 (t, *J* = 7.1 Hz, 1H,  $\text{NHCHCH}$ ), 3.98 (br s, 1H,  $\text{NHCH}$ ), 4.12 (m, 4H,  $2\times\text{CH}_2\text{CH}_3$ ), 4.53 (br s, 1H,  $\text{NCHCH}=\text{O}$ ), 5.72–5.91 (m, 2H,  $\text{CH}=\text{CH}$ ).  $^{13}\text{C}$  NMR  $\delta$ : 16.2, 16.4 (d,  $2\times\text{CH}_3$ ), 24.1 ( $\text{CH}_3$ ), 25 ( $\text{CHCH}_2\text{CH}$ ), 39.1 ( $\text{CH}_2\text{CHC}=\text{O}$ ), 44.3 (NHCH), 48.2 ( $\text{NCHCHC}=\text{O}$ ), 62.9 ( $2\times\text{OCH}_2$ ), 127, 135 ( $\text{C}=\text{C}$ ), 179.1, 179.5 ( $2\times\text{C}=\text{O}$ ).  $^{31}\text{P}$  NMR  $\delta$ : 5.66 ppm. MS (EI) *m/z*: 316 ( $\text{M}^+$ , 37%), 287 (10), 205 (98), 179 (100), 148 (28), 94 (20), 81 (12), 68 (60); HRMS calculated for



C<sub>13</sub>H<sub>21</sub>N<sub>2</sub>O<sub>5</sub>P: 316.1188, found: 316.1192.

#### 4.2.2. Diethyl [(3aSR,4RS,7aSR)-2-benzyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3b**)

Pale brown sticky oil, (196 mg, 50% yield). IR (neat)  $\nu_{\max}$ : 1693, 1399, 1239, 1024 cm<sup>-1</sup>. <sup>1</sup>H NMR  $\delta$ : 1.33 (t, *J* = 7.0 Hz, 6H, 2xCH<sub>3</sub>CH<sub>2</sub>O), 2.07–2.20 (m, 1H, CHCH<sub>2</sub>CH), 2.63–2.71 (m, 1H, CHCH<sub>2</sub>CH), 3.14–3.19 (m, 1H, CH<sub>2</sub>CHC=O), 3.27 (dd, *J* = 8.9, 5.8 Hz, 1H, NCHCHC=O), 3.96 (br s, 1H, CHNH), 4.04–4.14 (m, 4H, 2xCH<sub>2</sub>CH<sub>3</sub>), 4.44–4.57 (m, 1H, NCHCH = ), 4.59 (s, 2H, NCH<sub>2</sub>), 5.77–5.87 (m, 2H, CH=CH), 7.22–7.33 (m, 5H, ArH). <sup>13</sup>C NMR  $\delta$ : 16.2 (2xCH<sub>3</sub>CH<sub>2</sub>), 24.3 (=CHCH<sub>2</sub>CH), 39.1 (CH<sub>2</sub>CHC=O), 42.5 (NHCH), 44.3 (O=CNCH<sub>2</sub>Ar), 48.2 (NCHCHC=O), 62.7 (d, 2xOCH<sub>2</sub>), 126.8, 127.9, 128.3, 128.6, 135.0, 135.5 (ArC and C=C), 178.7, 179.0 (2xC=O). <sup>31</sup>P NMR  $\delta$ : 6.09 ppm. MS (EI) *m/z*: 392 (M<sup>+</sup>, 40%), 256 (15), 255 (52), 205 (100), 176 (18), 174 (10), 148 (20), 138 (12), 94 (16), 91 (60), 81 (11), 79 (10), 77 (13), 68 (50), 65 (14). HRMS calculated for C<sub>19</sub>H<sub>25</sub>N<sub>2</sub>O<sub>5</sub>P: 392.1501; found: 392.1509.

#### 4.2.3. Diethyl [(3aS,4R,7aS)-2-(4-fluorobenzyl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3c**)

Pale brown sticky oil, (262 mg, 64% yield). IR (neat)  $\nu_{\max}$ : 1698, 1510, 1510, 1025 cm<sup>-1</sup>. <sup>1</sup>H NMR  $\delta$ : 1.33 (t, *J* = 7.1 Hz, 6H, 2xCH<sub>3</sub>CH<sub>2</sub>O), 2.04–2.21 (m, 1H, CHCH<sub>2</sub>CH), 2.66 (dd, *J* = 15.6, 7.0 Hz 1H, CHCH<sub>2</sub>CH), 3.17 (td, *J* = 9.0, 8.5 Hz, 1H, CH<sub>2</sub>CHC=O), 3.27 (dd, *J* = 8.8, 5.9 Hz, 1H, NCHCHC=O), 3.95 (br s, 1H, CHNH), 4.07–4.14 (m, 2xCH<sub>2</sub>CH<sub>3</sub>), 4.5 (br s, 1H, NCHCH = ), 4.55 (s, 2H, NCH<sub>2</sub>), 5.71–5.88 (m, 2H, CH=CH), 6.94–7.0 (m, 2H, ArH), 7.24–7.29 (m, 2H, ArH). <sup>13</sup>C NMR  $\delta$ : 16.3 (dd, 2xCH<sub>3</sub>CH<sub>2</sub>), 24.3 (d, =CHCH<sub>2</sub>CH), 39.2 (CH<sub>2</sub>CHC=O), 41.8 (d, NHCH), 44.3 (d, O=CNCH<sub>2</sub>Ar), 48.2 (NCHCHC=O), 62.9 (d, 2xOCH<sub>2</sub>), 115.6 (d, <sup>2</sup>*J*<sub>C-F</sub> = 21.7 Hz, CHCF), 126.8, (C=C), 130.4 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.1 Hz, CHCHCF), 135 (C=C), 160.8 (CCHCHCF), 164.1 (CF), 178.7, 179.0 (2xC=O). <sup>19</sup>F NMR  $\delta$ : -114.1. <sup>31</sup>P NMR  $\delta$ : 5.55 ppm. MS (EI) *m/z*: 410 (M<sup>+</sup>, 39%), 274 (12), 273 (51), 205 (100), 177 (11), 176 (20), 174 (10), 148 (25), 138 (14), 110 (10), 109 (84), 94 (16), 83 (11), 81 (13), 79 (12), 77 (10), 68 (56), 67 (11). HRMS calculated for C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub>P: 410.1407; found: 410.1428.

#### 4.2.4. Diethyl [(3aSR,4RS,7aSR)-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3d**)

Pale brown sticky oil (246 mg, 65% yield). IR (neat)  $\nu_{\max}$ : 1700, 1498, 1384 cm<sup>-1</sup>. <sup>1</sup>H NMR  $\delta$ : 1.34 (t, *J* = 7.1 Hz, 6H, 2xCH<sub>3</sub>), 2.20–2.31 (ddd, *J* = 15.6, 8.0, 2.5 Hz, 1H, CHCH<sub>2</sub>CH), 2.77 (dd, *J* = 15.7, 6.6 Hz, 1H, CHCH<sub>2</sub>CH), 3.33 (dd, *J* = 9.0, 8.0 Hz, 1H, CH<sub>2</sub>CHC=O), 3.45 (dd, *J* = 9.1, 5.9 Hz, 1H, NCHCHC=O), 4.04–4.10 (m, 4H, 2xCH<sub>2</sub>CH<sub>3</sub>), 4.53 (br s, 1H, NCHCH = ), 5.89–6.01 (m, 2H, CH=CH), 7.18–7.21 (m, 2H, ArH), 7.39–7.48 (m, 3H, ArH). <sup>13</sup>C NMR  $\delta$ : 16.3, 16.4 (d, 2xCH<sub>3</sub>), 24.6 (CHCH<sub>2</sub>CH), 39.3 (CH<sub>2</sub>CHC=O), 44.5 (d, NHCH), 48.4 (d, NCHCHC=O), 62.9, 63.0 (2xOCH<sub>2</sub>), 126.5, 127.0, 129.0, 129.3, 131.6, 135.1, 135.2 (ArC and C=C), 178.2, 178.5 (2xC=O). <sup>31</sup>P NMR  $\delta$ : 5.78 ppm. MS (EI) *m/z*: 378 (M<sup>+</sup>, 54%), 241 (47), 205 (100), 176 (15), 148 (16), 94 (12), 68 (31). HRMS calculated for C<sub>18</sub>H<sub>23</sub>N<sub>2</sub>O<sub>5</sub>P: 378.1345; found: 378.1355.

#### 4.2.5. Diethyl [(3aSR,4RS,7aSR)-2-(4-acetylphenyl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3e**)

Pale brown sticky oil, (239 mg, 57% yield). IR (neat)  $\nu_{\max}$ : 1704, 1379, 1237, 1024, cm<sup>-1</sup>. <sup>1</sup>H NMR  $\delta$ : 1.35 (t, *J* = 7.0 Hz, 6H, 2xCH<sub>3</sub>CH<sub>2</sub>O), 2.22–2.33 (m, 1H, CHCH<sub>2</sub>CH), 2.61 (s, 3H, CH<sub>3</sub>), 2.78 (dd, *J* = 15.7, 6.4 Hz 1H, CHCH<sub>2</sub>CH), 3.37 (t, *J* = 8.4 Hz, 1H, CH<sub>2</sub>CHC=O), 3.47–3.50 (m, 1H, NCHCHC=O), 4.05–4.16 (m, 4H, 2xCH<sub>2</sub>CH<sub>3</sub>), 4.47 (br s, NCHCH = ), 5.91–6.01 (m, 2H, CH=CH), 7.36 (d, *J* = 8.6 Hz, 2H, ArH), 8.03 (d, *J* = 8.6 Hz 2H, ArH). <sup>13</sup>C NMR  $\delta$ : 16.2 (2xCH<sub>3</sub>CH<sub>2</sub>), 24.4 (COCH<sub>3</sub>), 26.6 (=CHCH<sub>2</sub>CH), 39.2 (CH<sub>2</sub>CHC=O),

44.4 (NHCH), 48.2 (NCHCHC=O), 62.7 (2xOCH<sub>2</sub>), 126.4, 126.9, 129.0, 134.9, 135.5, 136.8 (ArC and C=C), 177.6, 178.0, 196.9 (3xC=O). <sup>31</sup>P NMR  $\delta$ : 5.48 ppm. MS (EI) *m/z*: 420 (M<sup>+</sup>, 13%), 283 (29), 205 (100), 200 (13), 176 (13), 154 (12), 148 (15), 94 (12), 68 (40), 43 (12). HRMS calculated for C<sub>20</sub>H<sub>25</sub>N<sub>2</sub>O<sub>6</sub>P: 420.1450; found: 420.1444.

#### 4.2.6. Diethyl [(3aSR,4RS,7aSR)-2-(4-bromophenyl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3f**)

Pale brown sticky oil, (205 mg, 45% yield). IR (neat)  $\nu_{\max}$ : 2341, 1702, 1385, 1189, 1024 cm<sup>-1</sup>. <sup>1</sup>H NMR  $\delta$ : 1.34 (t, *J* = 7.1 Hz, 6H, 2xCH<sub>3</sub>CH<sub>2</sub>O), 2.22–2.32 (m, 1H, CHCH<sub>2</sub>CH), 2.77 (dd, *J* = 15.7, 6.5 Hz 1H, CHCH<sub>2</sub>CH), 3.31–3.37 (m, 1H, CH<sub>2</sub>CHC=O), 3.46 (dd, *J* = 9.1, 5.9 Hz, 1H, NCHCHC=O), 4.05–4.17 (m, 4H, 2xCH<sub>2</sub>CH<sub>3</sub>), 4.47 (br s, NCHCH = ), 5.92–5.99 (m, 2H, CH=CH), 7.11 (d, *J* = 8.8 Hz 2H, ArH), 7.58 (d, *J* = 8.8 Hz, 2H, ArH). <sup>13</sup>C NMR  $\delta$ : 16.4 (2xCH<sub>3</sub>CH<sub>2</sub>), 24.6 (=CHCH<sub>2</sub>CH), 39.3 (CH<sub>2</sub>CHC=O), 44.5 (NHCH), 48.4 (NCHCHC=O), 62.9 (2xOCH<sub>2</sub>), 122.8, 127.0, 128.0, 130.5, 132.5, 135.2 (ArC and C=C), 177.9, 178.2 (2xC=O). <sup>31</sup>P NMR  $\delta$ : 5.86 ppm. MS (EI) *m/z*: 456 (M<sup>+</sup>, 7%), 321 (14), 319 (15), 205 (100), 176 (14), 154 (22), 148 (16), 94 (13), 68 (43). HRMS calculated for C<sub>18</sub>H<sub>22</sub>BrN<sub>2</sub>O<sub>5</sub>P: 456.0450; found: 456.0446.

#### 4.2.7. Diethyl [(3aSR,4RS,7aSR)-2,7-dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3g**)

Brown sticky oil, (204 mg, 62% yield). IR (neat)  $\nu_{\max}$ : 1690, 1434, 1383, cm<sup>-1</sup>. <sup>1</sup>H NMR  $\delta$ : 1.29 (t, *J* = 7.1 Hz, 6H, 2xCH<sub>3</sub>CH<sub>2</sub>O), 1.34 (d, *J* = 7.4 Hz, 3H, CHCH<sub>3</sub>), 2.39 (br s, 1H, CHCH<sub>3</sub>), 2.85 (s, 3H, NCH<sub>3</sub>), 2.98–3.03 (m, 1H, NCHCHC=O), 3.18–3.23 (m, 1H, CHCHC=O), 3.88 (br s, 1H, CHNH), 3.99–4.11 (m, 4H, 2xCH<sub>3</sub>CH<sub>2</sub>O), 4.59 (t, *J* = 11.0, Hz, 1H, NCHCH), 5.52–5.58 (m, 1H, NCHCH=C), 5.76–5.81 (m, 1H, NCHCH=C). <sup>13</sup>C NMR  $\delta$ : 16.1, 16.3 (2xCH<sub>3</sub>), 16.6 (CHCH<sub>3</sub>), 24.6 (NCH<sub>3</sub>), 30.5 (CHCH<sub>3</sub>), 43.9 (NHCH), 45.2, 45.3 (2xNHCHC=O), 48.5 (CHCHC=O), 62.6, 62.7 (2xOCH<sub>2</sub>), 133.4, 134 (C=C), 176.7, 179 (2xC=O). <sup>31</sup>P NMR  $\delta$ : 5.92 ppm. MS (EI) *m/z*: 330 (M<sup>+</sup>, 9%), 219 (100), 193 (25), 162 (11), 82 (19); HRMS calculated for C<sub>14</sub>H<sub>23</sub>N<sub>2</sub>O<sub>5</sub>P: 330.1345, found: 330.1347.

#### 4.2.8. Diethyl [(3aSR,4RS,7SR,7aSR)-7-methyl-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3h**)

Pale brown sticky oil (207 mg, 53% yield). IR (neat)  $\nu_{\max}$ : 1700, 1498, 1382 cm<sup>-1</sup>. <sup>1</sup>H NMR  $\delta$ : 1.34 (t, *J* = 7.1 Hz, 6H, 2xCH<sub>3</sub>CH<sub>2</sub>), 1.43 (d, *J* = 7.4 Hz, 3H, CH<sub>3</sub>CH), 2.55 (br s, 1H, CH<sub>3</sub>CH), 3.21 (t, *J* = 8.1 Hz, 1H, CH<sub>3</sub>CHCHC=O), 3.44 (dd, *J* = 8.7, 5.8 Hz, 1H, NCHCHC=O), 4.07–4.16 (m, 4H, 2xCH<sub>2</sub>CH<sub>3</sub>), 4.64 (br s, 1H, NCHCH = ), 5.71 (dt, *J* = 9.3, 3.3 Hz, 1H, NCHCH=CH), 5.94 (dt, *J* = 9.3, 3.0 Hz, 1H, NCHCH=CH), 7.16–7.19 (m, 2H, ArH), 7.36–7.48 (m, 3H, ArH). <sup>13</sup>C NMR  $\delta$ : 16.3, 16.4 (d, 2xCH<sub>3</sub>CH<sub>2</sub>), 16.8 (CH<sub>3</sub>CH), 30.8 (CH<sub>3</sub>CH), 44.1 (CH<sub>3</sub>CHCHC=O), 45.6 (NCHCHC=O), 48.9 (NHCH), 62.9, 63.0 (2xOCH<sub>2</sub>), 126.6, 128.9, 129.2, 131.5, 133.5, 134.2, 134.3 (ArC and C=C), 175.7, 178.2 (2xC=O). <sup>31</sup>P NMR  $\delta$ : 5.53 ppm. MS (EI) *m/z*: 392 (M<sup>+</sup>, 5%), 219 (100), 82 (15). HRMS calculated for C<sub>19</sub>H<sub>25</sub>N<sub>2</sub>O<sub>5</sub>P: 392.1501; found: 392.1499.

#### 4.2.9. Diethyl [(3aSR,4RS,7aSR)-2,6-dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3i**)

Brown sticky oil, (191 mg, 58% yield). IR (neat)  $\nu_{\max}$ : 1696, 1437, 1385 cm<sup>-1</sup>. <sup>1</sup>H NMR  $\delta$ : 1.27 (t, *J* = 7.1 Hz, 6H, 2xCH<sub>3</sub>CH<sub>2</sub>), 1.65 (s, 3H, CH<sub>3</sub>C=CH), 2.03–2.20 (m, 1H, CCH<sub>2</sub>CH), 2.45 (d, *J* = 15.3, 1.3 Hz, 1H, CCH<sub>2</sub>CH), 2.88 (s, 1H, NCH<sub>3</sub>), 3.04–3.21 (m, 2H, CH<sub>2</sub>CHC=O, NCHCHC=O), 3.84 (br s, 1H, CH=NH), 3.99–4.09 (m, 4H, 2xCH<sub>2</sub>CH<sub>3</sub>), 4.27 (br s, 1H, NCHCH = ), 5.45 (s, 1H, NCHCH=C). <sup>13</sup>C NMR  $\delta$ : 16.1, 16.3 (t, 2xCH<sub>3</sub>), 23 (CH<sub>3</sub>), 25 (NCH<sub>3</sub>), 29.2 (CCH<sub>2</sub>CH), 39.2 (CH<sub>2</sub>CHC=O), 44.0, 44.1 (d, NCH), 48.5 (CHCHC=O), 62.6, 62.8 (2xOCH<sub>2</sub>), 127.0, 127.1 (d, CH=C), 136.1 (Cq), 179.0, 179.4 (2xC=O).

$^{31}\text{P}$  NMR  $\delta$ : 6.08 ppm. MS (EI)  $m/z$ : 330 ( $\text{M}^+$ , 20%), 301 (11), 219 (21), 193 (100), 179 (10), 154 (21), 108 (12), 82 (42); HRMS calculated for  $\text{C}_{14}\text{H}_{23}\text{N}_2\text{O}_5\text{P}$ : 330.1345, found: 330.1349.

#### 4.2.10. Diethyl [(3aSR,4RS,7aSR)-6-methyl-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3j**)

Pale brown sticky oil (231 mg, 59% yield). IR (neat)  $\nu_{\text{max}}$ : 1702, 1498, 1384,  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR  $\delta$ : 1.33 (t,  $J = 7.1$  Hz, 6H,  $2\times\text{CH}_3\text{CH}_2\text{O}$ ), 1.78 (s, 3H,  $\text{CH}_3\text{C}=\text{CH}$ ), 2.27–2.37 (m, 1H,  $\text{CCH}_2\text{CH}$ ), 2.61 (d,  $J = 15.3$ , 1.3 Hz, 1H,  $\text{CCH}_2\text{CH}$ ), 3.31 (ddd,  $J = 9.0, 7.5, 1.6$  Hz, 1H,  $\text{CH}_2\text{CHC}=\text{O}$ ), 3.41 (dd,  $J = 8.9, 6.0$  Hz, 1H,  $\text{NCHCHC}=\text{O}$ ), 3.66 (s, 1H,  $\text{CH}-\text{NH}$ ), 4.06–4.17 (m, 4H,  $2\times\text{CH}_2\text{CH}_3$ ), 4.42 (br s, 1H,  $\text{NCHCH}=\text{C}$ ), 5.61 (s, 1H,  $\text{NCHCH}=\text{C}$ ), 7.15–7.19 (m, 2H, ArH), 7.39–7.49 (m, 3H, ArH).  $^{13}\text{C}$  NMR  $\delta$ : 16.3, 16.4 ( $2\times\text{CH}_3\text{CH}_2\text{O}$ ), 23.0 ( $\text{CH}_3\text{C}=\text{CH}$ ), 29.7 ( $\text{CCH}_2\text{CH}$ ), 39.4 ( $\text{CH}_2\text{CHC}=\text{O}$ ), 44.4 ( $\text{NCHCHC}=\text{O}$ ), 48.8 (NHCH), 62.8, 62.9 ( $2\times\text{OCH}_2$ ), 126.5, 127.3, 127.4, 128.9, 129.3, 131.6, 136.3 (ArC and  $\text{C}=\text{C}$ ), 178.3, 178.5 ( $2\times\text{C}=\text{O}$ ).  $^{31}\text{P}$  NMR  $\delta$ : 5.99 ppm. MS (EI)  $m/z$ : 392 ( $\text{M}^+$ , 34%), 255 (100), 239 (15), 219 (46), 190 (15), 154 (29), 108 (18), 82 (60). HRMS calculated for  $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_5\text{P}$ : 392.1501; found: 392.1494.

#### 4.2.11. Diethyl [(3aS,4R,7S,7aS)-7-ethyl-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3k**)

Pale brown sticky oil, (286 mg, 83% yield). IR (neat)  $\nu_{\text{max}}$ : 1693, 1429, 1224, 1026  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR  $\delta$ : 0.99 (t,  $J = 7.3$  Hz, 3H,  $\text{CH}_3\text{CH}_2\text{CH}$ ), 1.27 (t,  $J = 7.1$  Hz, 6H,  $2\times\text{CH}_3\text{CH}_2\text{O}$ ), 1.65 (m, 1H,  $\text{CH}_3\text{CH}_2\text{CH}$ ), 1.84 (m, 1H,  $\text{CH}_3\text{CH}_2\text{CH}$ ), 2.08 (br s, 1H,  $\text{CH}_3\text{CH}_2\text{CH}$ ), 2.82 (s, 3H,  $\text{NCH}_3$ ), 3.07–3.11 (m, 1H,  $\text{EtCHCHC}=\text{O}$ ), 3.18 (dd,  $J = 8.6, 5.9$  Hz, 1H,  $\text{NCHCHC}=\text{O}$ ), 3.86 (br s, 1H,  $\text{CHNH}$ ), 4.04 (m, 4H,  $2\times\text{CH}_3\text{CH}_2\text{O}$ ), 4.55 (t,  $J = 10.9$  Hz, 1H,  $\text{NHCH}$ ), 5.58 (dt,  $J = 9.3, 3.4$  Hz, 1H,  $\text{NCHCH}=\text{CH}$ ), 5.78 (dt,  $J = 9.9, 3.1$  Hz, 1H,  $\text{NCHCH}=\text{CH}$ ).  $^{13}\text{C}$  NMR  $\delta$ : 12.5 ( $\text{CH}_3\text{CH}_2\text{CH}$ ), 16.2, 16.3 (dd,  $2\times\text{CH}_3\text{CH}_2\text{O}$ ), 23.9 ( $\text{CH}_3\text{CH}_2\text{CH}$ ), 24.6 ( $\text{NCH}_3$ ), 38.0 ( $\text{EtCHCHC}=\text{O}$ ), 42.3 ( $\text{EtCHCHC}=\text{O}$ ), 45.1 (d,  $\text{NCHCHC}=\text{O}$ ), 48.6 (NHCH), 62.6, 62.7 (d,  $2\times\text{OCH}_2$ ), 176.6, 178.7 ( $2\times\text{C}=\text{O}$ ).  $^{31}\text{P}$  NMR  $\delta$ : 5.91 ppm. MS (EI)  $m/z$ : 344 ( $\text{M}^+$ , 10%), 234 (12), 233 (100), 207 (21), 204 (12), 176 (13), 96 (11). HRMS calculated for  $\text{C}_{15}\text{H}_{25}\text{N}_2\text{O}_5\text{P}$ : 344.1501; found: 344.1500.

#### 4.2.12. Diethyl [(3aSR,4RS,7SR,7aSR)-7-ethyl-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3l**)

Pale brown sticky oil, (284 mg, 70% yield). IR (neat)  $\nu_{\text{max}}$ : 1700, 1498, 1382  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR  $\delta$ : 1.09 (t,  $J = 7.3$  Hz, 3H,  $\text{CH}_3\text{CH}_2\text{CH}$ ), 1.34 (t,  $J = 7.1$  Hz, 6H,  $2\times\text{CH}_3\text{CH}_2\text{O}$ ), 1.76 (ddd,  $J = 13.6, 8.5, 7.0$  Hz, 1H,  $\text{CH}_3\text{CH}_2\text{CH}$ ), 1.96 (dt,  $J = 14.2, 7.0$  Hz, 1H,  $\text{CH}_3\text{CH}_2\text{CH}$ ), 2.26 (br s, 1H,  $\text{CH}_3\text{CH}_2\text{CH}$ ), 3.32 (dd,  $J = 8.7, 7.0$  Hz, 1H,  $\text{EtCHCHC}=\text{O}$ ), 3.44 (dd,  $J = 8.7, 5.7$  Hz, 1H,  $\text{NCHCHC}=\text{O}$ ), 4.05–4.16 (m, 4H,  $2\times\text{CH}_3\text{CH}_2\text{O}$ ), 4.19–4.28 (m, 1H,  $\text{NHCH}$ ), 5.77 (dt,  $J = 9.3, 3.3$  Hz, 1H,  $\text{NCHCH}=\text{CH}$ ), 5.96 (dt,  $J = 9.3, 3.0$  Hz, 1H,  $\text{NCHCH}=\text{CH}$ ), 7.15–7.19 (d,  $J = 7.0, 2\text{H}$ , ArH), 7.37–7.47 (m, 3H, ArH).  $^{13}\text{C}$  NMR  $\delta$ : 12.8 ( $\text{CH}_3\text{CH}_2\text{CH}$ ), 16.3, 16.4 ( $2\times\text{CH}_3\text{CH}_2\text{O}$ ), 24.1 ( $\text{CH}_3\text{CH}_2\text{CH}$ ), 38.4 ( $\text{EtCHCHC}=\text{O}$ ), 42.5 ( $\text{EtCHCHC}=\text{O}$ ), 45.4 ( $\text{NCHCHC}=\text{O}$ ), 49.0 (NHCH), 62.9, 63.0 ( $2\times\text{OCH}_2$ ), 126.6, 128.9, 129.2, 131.6, 132.4, 134.4, 134.5 (ArC and  $\text{C}=\text{C}$ ), 175.7, 178.1 ( $2\times\text{C}=\text{O}$ ).  $^{31}\text{P}$  NMR  $\delta$ : 6.01 ppm. MS (EI)  $m/z$ : 406 ( $\text{M}^+$ , 4%), 269 (10), 233 (100), 176 (11). HRMS calculated for  $\text{C}_{20}\text{H}_{27}\text{N}_2\text{O}_5\text{P}$ : 406.1658; found: 406.1654.

#### 4.2.13. Diethyl [(3aSR,4RS,7aSR)-2-methyl-6-(4-methylpent-3-en-1-yl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3m**)

Yellow sticky oil, (240 mg, 60% yield). IR (neat)  $\nu_{\text{max}}$ : 1700, 1500, 1382,  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR  $\delta$ : 1.34 (t,  $J = 7.1$  Hz, 6H,  $2\times\text{CH}_3\text{CH}_2\text{O}$ ), 1.70 (s, 3H,  $\text{CCH}_3$ ), 1.71 [s, 3H,  $\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2$ ], 1.73 [s, 3H,  $\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2$ ], 2.28 (br s, 1H,  $\text{CH}_2\text{CHCHC}=\text{O}$ ), 2.44–2.53 (m, 1H,  $\text{CH}_2\text{CHCHC}=\text{O}$ ), 2.70–2.80 (m, 1H,  $\text{CH}_2\text{CHCHC}=\text{O}$ ), 2.89 (s, 3H,

$\text{NCH}_3$ ), 3.15–3.17 (m, 2H,  $\text{CH}_2\text{CHCHC}=\text{O}$ ,  $\text{NHCHCHC}=\text{O}$ ), 3.88 (br s, 1H,  $\text{NHCH}$ ), 4.04–4.18 (m, 4H,  $2\times\text{CH}_3\text{CH}_2\text{O}$ ), 4.73–4.45 (m, 1H,  $\text{NCHCH}=\text{C}$ ), 5.22 (ddt,  $J = 7.8, 6.4, 1.4$  Hz, 1H,  $\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2$ ), 5.52 (br s, 1H,  $\text{NCHCH}=\text{C}$ ).  $^{13}\text{C}$  NMR  $\delta$ : 16.1, 16.3 ( $2\times\text{CH}_3\text{CH}_2\text{O}$ ), 18.0 [ $\text{C}(\text{CH}_3)_2$ ], 18.9 ( $\text{CH}_3\text{C}=\text{CCH}$ ), 24.6 [ $\text{C}(\text{CH}_3)_2$ ], 25.9 ( $\text{NCH}_3$ ), 26.3 [ $\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2$ ], 39.9 (NCH), 41.9 ( $\text{CCH}_2\text{CH}_2\text{CH}$ ), 44.8, 44.9 ( $2\times\text{CHCHC}=\text{O}$ ), 48.7 ( $\text{NCHCHC}=\text{O}$ ), 62.5, 62.6 ( $2\times\text{OCH}_2$ ), 122.4, 127.4, 134.1, 139.4 ( $\text{C}=\text{C}$ ), 177.3, 178.8 ( $2\times\text{C}=\text{O}$ ).  $^{31}\text{P}$  NMR  $\delta$ : 5.87 ppm. MS (EI)  $m/z$ : 398 ( $\text{M}^+$ , 10%), 329 (28), 261 (10), 245 (15), 230 (12), 207 (29), 193 (37), 154 (100), 126 (19), 98 (16), 81 (13), 41 (12); HRMS calculated for  $\text{C}_{19}\text{H}_{31}\text{N}_2\text{O}_5\text{P}$ : 398.1971, found: 398.1991.

#### 4.2.14. Diethyl [(3aSR,4RS,7aSR)-6-(4-methylpent-3-en-1-yl)-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl]phosphoramidate (**3n**)

Pale brown sticky oil, (317 mg, 69% yield). IR (neat)  $\nu_{\text{max}}$ : 1700, 1500, 1382,  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR  $\delta$ : 1.34 (t,  $J = 7.1$  Hz, 6H,  $2\times\text{CH}_3\text{CH}_2\text{O}$ ), 1.70 (s, 3H,  $\text{CCH}_3$ ), 1.74 [s, 3H,  $\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2$ ], 1.78 [s, 3H,  $\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2$ ], 2.39 (br s, 1H,  $\text{CH}_2\text{CHCHC}=\text{O}$ ), 2.51 (dt,  $J = 14.0, 6.4$  Hz, 1H,  $\text{CH}_2\text{CH}=\text{C}$ ), 2.80 (dt,  $J = 15.0, 8.7$  Hz, 1H,  $\text{CH}_2\text{CH}=\text{C}$ ), 3.32–3.36 (m, 2H,  $\text{CH}_2\text{CHCHC}=\text{O}$ ,  $\text{NHCHCHC}=\text{O}$ ), 4.04–4.18 (m, 4H,  $2\times\text{CH}_3\text{CH}_2\text{O}$ ), 4.41 (br s, 1H,  $\text{NCHCH}=\text{C}$ ), 5.24 [ddt,  $J = 7.8, 6.4, 1.4$  Hz, 1H,  $\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2$ ], 5.64 (br s, 1H,  $\text{NCHCH}=\text{C}$ ), 7.11–7.16 (m, 2H, ArH), 7.37–7.47 (m, 3H, ArH).  $^{13}\text{C}$  NMR  $\delta$ : 16.3, 16.4 ( $2\times\text{CH}_3\text{CH}_2\text{O}$ ), 18.2, 19.1 [ $\text{C}(\text{CH}_3)_2$ ], 26.0 ( $\text{CH}_3\text{C}=\text{CCH}$ ), 26.3 [ $\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2$ ], 40.3 ( $\text{CH}_2\text{CHCHC}=\text{O}$ ), 42.0 ( $\text{CH}_2\text{CHCHC}=\text{O}$ ), 45.3 ( $\text{NCHCHC}=\text{O}$ ), 49.1 (NHCH), 62.8, 62.9 ( $2\times\text{OCH}_2$ ), 122.4, 126.6, 127.7, 128.9, 129.3, 131.6, 134.4, 139.7 (ArC and  $\text{C}=\text{C}$ ), 176.3, 178.0 ( $2\times\text{C}=\text{O}$ ).  $^{31}\text{P}$  NMR  $\delta$ : 5.88 ppm. MS (EI)  $m/z$ : 460 ( $\text{M}^+$ , 7%), 391 (18), 307 (15), 207 (40), 154 (100), 134 (15), 119 (18), 98 (15). HRMS calculated for  $\text{C}_{24}\text{H}_{33}\text{N}_2\text{O}_5\text{P}$ : 460.2127; found: 460.2124.

#### 4.2.15. Diethyl [(3aSR,4RS,9bSR)-2-methyl-1,3-dioxo-2,3,3a,4,6,7,8,9,9a,9b-decahydro-1H-benzo[e]isoindol-4-yl]phosphoramidate (**3o**)

Pale brown sticky oil, (148 mg, 40% yield). IR (neat)  $\nu_{\text{max}}$ : 1692, 1433, 1283  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR  $\delta$ : 1.34 (t,  $J = 6.9$  Hz, 6H,  $2\times\text{CH}_3\text{CH}_2\text{O}$ ), 1.49–1.59 (m, 1H,  $\text{CHCH}_2\text{CH}$ ), 2.63–2.71 (m, 2H,  $\text{CHCH}_2\text{CH}_2\text{CH}_2$ ), 1.76–1.86 (m, 2H,  $\text{CHCH}_2\text{CH}_2\text{CH}_2$ ), 2.21–2.37 (m, 1H,  $\text{CHCH}_2\text{CH}_2\text{CH}_2$ ), 2.90 (s, 3H,  $\text{CH}_3$ ), 2.91–3.01 (m, 2H,  $\text{CH}=\text{CCH}_2\text{CH}_2$ ), 3.09–3.15 (m, 1H,  $\text{NCHCHC}=\text{O}$ ), 3.19–3.24 (m, 1H,  $\text{CHCHC}=\text{O}$ ), 3.94 (br s, 1H,  $\text{NHCH}$ ), 4.05–4.17 (m,  $2\times\text{CH}_2\text{CH}_3$ ), 5.51 (s, 1H,  $\text{NCHCH}=\text{C}$ ).  $^{13}\text{C}$  NMR  $\delta$ : 16.3 ( $2\times\text{CH}_3\text{CH}_2\text{O}$ ), 21.5 ( $\text{CHCH}_2\text{CH}$ ), 22.1 ( $\text{CH}_3$ ), 24.4 ( $\text{CHCH}_2\text{CH}_2\text{CH}_2$ ), 24.7 ( $\text{CHCH}_2\text{CH}_2\text{CH}_2$ ), 29.1 ( $\text{CHCH}_2\text{CH}_2\text{CH}_2$ ), 36.26 (NHCH), 43.4 ( $\text{CHCH}_2\text{CH}_2\text{CH}_2$ ), 45.1 ( $\text{CHCHC}=\text{O}$ ), 48.1 ( $\text{NCHCHC}=\text{O}$ ), 62.8 ( $2\times\text{OCH}_2$ ), 124.9 ( $\text{CH}=\text{CCH}_2\text{CH}_2$ ), 141.5 ( $\text{CH}=\text{CCH}_2\text{CH}_2$ ), 177.3, 179.1 ( $2\times\text{C}=\text{O}$ ).  $^{31}\text{P}$  NMR  $\delta$ : 5.89 ppm. MS (EI)  $m/z$ : 370 ( $\text{M}^+$ , 21%), 341 (10), 259 (41), 258 (21), 234 (15), 233 (100), 230 (26), 202 (11), 154 (16), 122 (14), 98 (11), 91 (19), 81 (11), 43 (11). HRMS calculated for  $\text{C}_{17}\text{H}_{27}\text{N}_2\text{O}_5\text{P}$ : 370.1658; found: 392.1656.

#### 4.2.16. Diethyl [(3aSR,11RS,11aSR)-2-methyl-1,3-dioxo-2,3,3a,3b,4,5,11,11a-octahydro-1H-naphtho[2,1-e]isoindol-11-yl]phosphoramidate (**3p**)

Pale brown sticky oil, (209 mg, 50% yield). IR (neat)  $\nu_{\text{max}}$ : 1691, 1435, 1239  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR  $\delta$ : 1.35 (t,  $J = 7.1$  Hz, 6H,  $2\times\text{CH}_3\text{CH}_2\text{O}$ ), 2.12–2.21 (m, 2H,  $\text{CHCH}_2\text{CH}_2$ ), 2.57–2.64 (m, 1H,  $\text{CHCH}_2\text{CH}_2$ ), 2.64–2.73 (m, 2H,  $\text{NCHCHC}=\text{O}$ ), 2.76–2.82 (m, 2H,  $\text{CHCH}_2\text{CH}_2$ ), 2.85 (s, 3H,  $\text{CH}_3$ ), 3.23–3.27 (m, 1H, 1H,  $\text{NHCH}$ ), 3.34–3.38 (m, 1H,  $\text{CHCHC}=\text{O}$ ), 4.07–4.17 (m, 4H,  $2\times\text{CH}_2\text{CH}_3$ ), 4.71 (br s, 1H,  $\text{CHNH}$ ), 7.09–7.11 (m, 1H, ArH), 7.14–7.17 (m, 1H, ArH), 7.26 (s, 1H, ArH), 7.40–7.42 (m, 1H, ArH).  $^{13}\text{C}$  NMR  $\delta$ : 16.4 ( $2\times\text{CH}_3\text{CH}_2\text{O}$ ), 24.4 ( $\text{CH}_3$ ),

24.9 (CCH<sub>2</sub>CH<sub>2</sub>CH), 30.0 (CCH<sub>2</sub>CH<sub>2</sub>CH), 36.5 (CCH<sub>2</sub>CH<sub>2</sub>CH), 43.2 (NHCH), 45.8 (CHCHC=O), 49.2 (NCHCHC=O), 62.9 (2xOCH<sub>2</sub>), 123.7, 126.7, 127.9, 128.4, 132.9, 136.9, 138.3 (ArC and C=C), 176.8, 179.0 (2xC=O). <sup>31</sup>P NMR δ: 6.05 ppm. MS (EI) *m/z*: 418 (M<sup>+</sup>, 44%), 389 (42), 282 (20), 281 (100), 196 (15), 179 (11), 168 (12), 154 (25), 153 (23), 152 (10). HRMS calculated for C<sub>21</sub>H<sub>27</sub>N<sub>2</sub>O<sub>5</sub>P: 418.1658; found: 418.1663.

#### 4.2.17. Diethyl {(3*a*S,4*R*,7*a*S)-1,3-dioxo-2-[(*R*)-1-phenylethyl]-2,3,3*a*,4,7,7*a*-hexahydro-1*H*-isoindol-4-yl}phosphoramidate (**3q**)

Pale brown sticky oil, (82.4 mg, 51.72% yield), [α]<sub>D</sub><sup>24</sup> = +41.26 (c 0.6, CHCl<sub>3</sub>). IR (neat) ν<sub>max</sub>: 1690, 1392, 1226, 1024 cm<sup>-1</sup>. <sup>1</sup>H NMR δ: 1.25 (t, *J* = 7.1 Hz, 6H, 2xCH<sub>3</sub>CH<sub>2</sub>O), 1.65 (d, *J* = 7.3 Hz, 3H, CHCH<sub>3</sub>), 1.95–2.12 (m, 1H, CHCH<sub>2</sub>CH), 2.49–2.63 (m, 1H, CHCH<sub>2</sub>CH), 3.02 (m, 1H, CH<sub>2</sub>CHC=O), 3.12 (dt, *J* = 8.9, 5.5 Hz, 1H, NCHCHC=O), 3.86 (br s, 1H, CHNH), 4.01 (m, 4H, 2xCH<sub>2</sub>CH<sub>3</sub>), 4.49 (dt, *J* = 8.5, 10.9 Hz, 1H, NCHCHC=O), 5.28 (q, *J* = 7.3 Hz, 1H, NCHCH<sub>3</sub>) 5.62–6.86 (m, 2H, CH=CH), 7.18–7.20 (m, 2H, ArH), 7.21–7.26 (m, 3H, ArH). <sup>13</sup>C NMR δ: 16.2, 16.3 (2xCH<sub>3</sub>CH<sub>2</sub>), 16.6 (CH<sub>3</sub>CH), 24.4 (CHCH<sub>2</sub>CH), 38.9 (CH<sub>2</sub>CHC=O), 43.8 (NHCH), 48.3 (NCHCHC=O), 50.2 (CH<sub>3</sub>CH), 62.7, 62.8 (2xOCH<sub>2</sub>), 126.6, 127.1, 127.7, 128.3, 135.0, 139.0, 139.2 (ArC and C=C), 178.8, 179.1 (2xC=O). <sup>31</sup>P NMR δ: 5.84 ppm. MS (EI) *m/z*: 406 (M<sup>+</sup>, 35%), 269 (17), 206 (10), 205 (100), 176 (17), 174 (14), 165 (20), 154 (12), 148 (19), 138 (12), 105 (47), 103 (11), 94 (11), 79 (16), 77 (23), 68 (45). HRMS calculated for C<sub>20</sub>H<sub>27</sub>N<sub>2</sub>O<sub>5</sub>P: 406.1658; found: 406.1660.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tet.2019.130801>.

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