

Regioselective Passerini and Passerini–Knoevenagel Reactions with vic-Diketo Amides

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The Passerini reaction of *vic*-diketo amides with a variety of isocyanides and carboxylic acids has been examined. α -Acyloxy β -keto carboxamides were formed regioselectively as the major products. For the Passerini reactions with elec-

Introduction

Multicomponent reactions^[1] are useful tools for medicinal chemistry^[2,3] and diversity-oriented synthesis (DOS).^[4–6] Their discovery dates back to the mid-19th century. Chronologically, the Strecker reaction (1837,^[7] 1850^[8]) was followed by Hantzsch dihydropyridine synthesis (1882),^[9] Biginelli reaction (1891),^[10] and Mannich reaction (1903,^[11] 1912^[12]). The first isocyanide-based multicomponent reaction (IMCR) was discovered by Passerini in 1921.^[13] The reaction of an aldehyde **1**, a carboxylic acid **2**, and an isocyanide **3** to give an α -acyloxycarboxamide **4** is called the Passerini three-component reaction (P-3CR) (Scheme 1). Ugi expanded this reaction by the addition of an amine to give a four component reaction leading to α -acylaminocarboxamides.^[14] The development of IMCRs has had a strong impact on combinatorial chemistry.^[15]



Scheme 1. The use of aldehydes and *vic*-dicarbonyl compounds in the Passerini reaction.

As well as ketones and aldehydes, the Passerini reaction has been applied to *vic*-dicarbonyl compounds, i.e., α -keto

tron-withdrawing-group-substituted acetic acids, a one-pot Passerini–Knoevenagel reaction was accomplished by the addition of triethylamine.

aldehydes, $^{[16-20]}$ 2-oxoacetates and 2-oxoacetamides, $^{[21]}$ $\alpha \text{-}$ keto esters,^[22,23] trifluoro-2-oxopropanoates,^[24] and 2-oxo- β -lactams.^[25] In these examples, reactivity is a question of chemoselectivity. Of the α -diketones 5, only symmetrical starting materials have been used, i.e., benzil,^[26-28] butanedione,^[28] and 1,4-dibromobutanedione.^[29] The reaction of a symmetrical diketone 5 with an acid 2 and an isocvanide 3 leads to an α -acyloxycarboxamide 6. To the best of our knowledge, the regioselectivity of the Passerini reaction involving α -dicarbonyl compounds has not been investigated. The symmetrical indan-1,2,3-trione is the only example of a vic-tricarbonyl compound that has been used in a Passerini reaction.^[30] The potential of a-dicarbonyl Passerini reactions extends to the formation of heterocycles, i.e., oxazoles,^[17] pyrrolidine-2,4-diones,^[29] and butenolides. Cyclization of butenolides has been achieved by Knoevenagel condensation,^[18] Aldol condensation,^[19,28] Dieckmann condensation,^[23] or Horner-Wadsworth-Emmons (HWE) olefination.^[20]

Vicinal tricarbonyl compounds offer the chance for multifunctionalization, and if a regioselective functionalization can be achieved, they would have considerable potential as synthetic building blocks. The addition of nucleophiles to unsymmetrical acyclic vic-tricarbonyl compounds has, to date, been limited to O- and N-nucleophiles.^[31,32] Stereoselective additions of C-nucleophiles have only been investigated with symmetrical vic-tricarbonyl compounds, in particular diethyl ketomalonate^[33-37] or for an intramolecular aldol reaction.^[38] Recently, we showed that the regio- and diastereoselective alkylation of diketo amides and diketo esters is possible by using crotylboration reactions.^[39] The reaction of a diketo amide 7 with (E)-crotylboronate 8 resulted in an attack of the nucleophile at the β keto group, and the diastereoselective formation of homoallylic alcohol 9 (Scheme 2). A Passerini reaction of a diketo amide 7 could lead to two regioisometric α -acylamino-carboxamides. An attack at the α -keto group would result in the

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formation of compound **10**, while attack at the β -keto group would produce compound **11**. In this paper we present the results of a study on the Passerini reaction of *vic*-tricarbonyl compounds of type **7**.



Scheme 2. *vic*-Diketo amides as starting materials for the Passerini reaction.

Table 1. Passerini three-component reaction of *vic*-diketo amides 7 with aliphatic carboxylic acids and *tert*-butyl isocyanide.



[a] Isolated yield of α -Passerini product 14. [b] Determined from the ¹H NMR spectrum of the crude material. [c] 96% of an isomeric mixture of 14a and 15a; 85:15 ratio. [d] 95% of an isomeric mixture of 14a and 15a; 89:11 ratio. [e] 98% of an isomeric mixture of 14a and 15b; 91:9 ratio. [f] 99% of an isomeric mixture of 14c and 15c; 92:8 ratio. [g] 99% of an isomeric mixture of 14f and 15f; 95:5 ratio.

Results and Discussion

The synthesis of the *vic*-diketo amides ideally starts from the corresponding β -keto amide (i.e., **12**; Scheme 3).^[30,31] Reliable procedures for the conversion of the keto amide into the tricarbonyl compound include the oxidative cleavage of α -methylene derivatives,^[40] direct oxidation,^[41,42] and the use of α -diazo β -dicarbonyl compounds.^[43] In our hands, this last method gave the best results. For diketo amides **12**, Regitz diazo transfer using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) gave α -diazo β -keto amides **13**. Subsequent treatment with *tert*-butyl hypochlorite in formic acid led, after distillation, to the desired tricarbonyl compounds (i.e., **7**).



Scheme 3. Synthesis of vic-diketo amides 7.

Treatment of *vic*-diketo amides 7 with different aliphatic carboxylic acids and *tert*-butyl isocyanide yielded Passerini products 14 and 15 with a high regioselectivity in favour of compound 14; compound 14 results from an α -addition to the α -keto group (Table 1). The structural assignment of Passerini product 14a was done using an X-ray structure (Figure 1).^[46]



Figure 1. X-ray structure of Passerini product 14a.

When *vic*-diketo amides are used in a Passerini reaction, the remaining unreacted keto group may undergo further subsequent transformations. For carboxylic acids bearing an electron-withdrawing group (EWG), an aldol condensation of the Knoevenagel type could lead to butenolides as final products (Scheme 4). In an α -selective Passerini reaction of a *vic*-diketo amide 7, the initial product (i.e., **16**) could undergo a subsequent aldol condensation to give but-



Scheme 4. Passerini reaction and subsequent aldol condensation.

Entry

Table 2. Passerini reaction of *vic*-diketo amides with α -EWG-substituted acetic acid derivatives and *tert*-butyl isocyanide.



1	7a	CO_2Me	toluene	0.25	18a, 86 ^[c]	98:2
2	7a	CO_2Me	CH_2Cl_2	0.5	18a, 89 ^[d]	98:2
3	7a	Ts	toluene	1.5	18b, 97	99:1
4	7a	Ts	CH_2Cl_2	1.8	18b, 99	99:1
5	7a	$PO(OEt)_2$	CH_2Cl_2	17	18c, 75	n.d.
6	7a	Cl	CH_2Cl_2	17	18d, 85 ^[e]	86:14
7	7a	Br	CH_2Cl_2	18	18e, 87 ^[f]	87:13
8	7b	Ts	toluene	0.7	18f, 64 ^[g]	88:12
9	7b	Ts	CH_2Cl_2	0.8	18f, 84	89:11
10	7b	CO_2Me	toluene	0.3	18g, 60 ^[h]	90:10
11	7b	CO_2Me	CH_2Cl_2	0.5	18g, 82 ^[i]	91:9
12	7b	$PO(OEt)_2$	CH_2Cl_2	17	18h, 88 ^[j]	93:7

[a] Isolated yield of α -Passerini product **18**. [b] Determined from the ¹H NMR spectrum of the crude material. [c] 97% of a mixture of **18a** and **20a**; 89:11 ratio. [d] 98% of a mixture of **18a** and **20a**; 91:9 ratio. [e] 99% of an isomeric mixture of **18d** and **19d**; 86:14 ratio. [f] 99% of an isomeric mixture of **18e** and **19e**; 87:13 ratio. [g] 88% of a mixture of **18f** and **20f**; 73:27 ratio. [h] 87% of a mixture of **18g** and **20g**; 69:31 ratio. [i] 89% of a mixture of **18g** and **20g**; 91:9 ratio. [j] Compound **19h** was also formed in 4.5% yield. n.d.: not determined.

enolide 17. The Passerini product resulting from attack at the β -position could also lead to a related aldol condensation product.

Different EWG-substituted acetic acids were examined in Passerini reactions using *tert*-butyl isocyanide and various *vic*-diketo amides (Table 2). For EWG = CO₂Me and *p*-TolSO₂ (Ts), Passerini products **18a** and **18b** were isolated in very good yields and with excellent α -selectivities when diketodimethylamide **7a** was used (Table 2, entries 1–4). The structural assignment of Passerini product **18g** was done using an X-ray structure (see Supporting Information).^[46] Lower α -selectivities were obtained for the morpholino diketo amide **7b** (Table 2, entries 8–11). With halo-substituted acetic acids, isomeric mixtures were observed (Table 2, entries 6 and 7). Only minor amounts of Knoevenagel-type aldol condensation products 20 and 21 were formed under these conditions.

For chloroacetic acid (Table 2, entry 6), the initial Passerini product (i.e., **18d**) could be isolated, and this compound was subjected to a separate aldol reaction (Scheme 5). Using LiHMDS (lithium hexamethyldisilazide) as base, chlorohydrin **22** was obtained in an intramolecular aldol addition. X-ray-structural analysis of compound **22** revealed the *cis* configuration of the chlorohydrin (see Supporting Information).^[46] Attempts to obtain epoxides from the haloacetic-acid-derived Passerini products in a Darzenstype reaction were unsuccessful, probably due to the *cis* configuration of the halohydrins.



Scheme 5. Intramolecular aldol addition of Passerini product **18d** to give **22**.

To promote the formation of the Knoevenagel-type aldol condensation products, the addition of base in a one-pot fashion was examined. Triethylamine was found to promote the aldol condensation to form butenolides **20** and **21** directly (Table 3). α -Knoevenagel products **20** were obtained as the major products when EWG = CO₂Me, Ts, and PO(OEt)₂ (Table 3, entries 3–7 and 10–12). The structural assignment of the Passerini–Knoevenagel product **20f** was done using an X-ray structure (Figure 2).^[46] For cyanoacetic acid, the addition of a base was not necessary for the formation of the aldol condensation product (Table 3, entries 1, 2, 8, and 9).

The isocyanide component was varied using several commercially available isocyanides. Keto isocyanide **24** was synthesized by dehydration of amide **23** (Scheme 6).

For vic-diketo amide **7b** and acetic acid as the carboxylic acid, Passerini products **26** were formed with various isocyanides in very good yields and with very good α -selectivities (Table 4). No by-products were observed with the more acidic isocyanides (Table 4, entries 2–4). Aryl isocyanides gave results comparable to those obtained with alkyl isocyanides.

The successful use of keto isocyanide **24** in a Passerini reaction is noteworthy. The short 1,4-distance between the ketone and the isocyanide group prevents an intramolecular α -addition. Only the intermolecular Passerini product (i.e., **26f**) was formed in excellent yield.

Passerini–Knoevenagel products 27 were formed in a three-component reaction of various isocyanides with *vic*-diketo amide 7b and cyanoacetic acid (Table 5). Lower yields were seen with more acidic isocyanides (Table 5, entries 2 and 3), but the formation of by-products was not observed.



Figure 2. X-ray structure of Passerini-Knoevenagel product 20f.

Table 3. The base-promoted Passerini–Knoevenagel reaction of *vic*-diketo amides with α -EWG-substituted acetic acid derivatives.



Entry	7	EWG	Solvent	Time [h]	20 , yield [%] ^[a]	20/21 ^[b]
1 ^[c]	7a	CN	toluene	2	20a , 82 ^[d]	92:8
2 ^[c]	7a	CN	CH_2Cl_2	2	20a , 66 ^[e]	91:9
3	7a	CO ₂ Me	toluene	1	20b , 75 ^[f]	75:25
4	7a	CO ₂ Me	CH_2Cl_2	1.2	20b , 82 ^[g]	88:12
5	7a	Ts	toluene	2	20c , 58 ^[h]	72:28
6	7a	Ts	CH_2Cl_2	2.2	20c , 55 ^[i]	72:28
7	7a	$PO(OEt)_2$	CH_2Cl_2	24	20d , 37 ^[j]	86:14 ^[k]
8[c]	7b	CN	toluene	1.2	20e , 87	99:1
9 ^[c]	7b	CN	CH_2Cl_2	0.9	20e , 86	99:1
10	7b	CO_2Me	CH_2Cl_2	2	20f , 81	90:10
11	7b	Ts	CH_2Cl_2	3.83	20g , 31 ^[1]	78:22
12	7b	$PO(OEt)_2$	CH_2Cl_2	24	20h , 18 ^[m]	81:19 ^[k]

[a] Isolated yield of α -Passerini–Knoevenagel product **20**. [b] Determined from the ¹H NMR spectrum of the crude material. [c] With cyanoacetic acid, no base was added. [d] 90% of an isomeric mixture of **20a** and **21a**; 91:9 ratio. [e] 72% of an isomeric mixture of **20a** and **21a**; 92:8 ratio. [f] Compound **21b** was also formed in 17% yield. [g] Compound **21b** was also formed in 12% yield. [h] 78% of an isomeric mixture of **20c** and **21c**; 74:26 ratio. [i] 74% of an isomeric mixture of **20c** and **21c**; 74:26 ratio. [j] β -Passerini–HWE product **28a** was also formed in 6% yield. [k] Based on isolated yields. [I] 36% of the isomeric mixture of **20g/21g** 87:13. [m] β -Passerini–HWE product **28b** (6%) and α -Passerini–HWE product **29** (7%) were also formed.



Scheme 6. Synthesis of keto isocyanide 24.

with acetic acid and various isocyanides.



Table 4. Passerini three-component reaction of vic-diketo amide 7b

Entry	K	Reaction time	Product, isolated yield
		[h]	[%]
1	tBu	0.5	14d, 92
2	CH ₂ Ts	24	26a , 92
3	CH ₂ CO ₂ Me	20	26b , 87
4	$CH_2PO(OEt)_2$	24	26c , 100
5	2-naphthyl	21.5	26d , 97
6	$4-MeO-C_6H_4$	21	26e , 100
7	(CH ₂) ₂ COMe	16	26f , 99

Table 5. Passerini–Knoevenagel reaction of *vic*-diketo amide **7b** with cyanoacetic acid and various isocyanides.



Entry	R	Reaction time [h]	Product, isolated yield [%]
1	tBu	0.9	20e , 86
2	CH ₂ Ts	24	27a , 57
3	CH ₂ CO ₂ Me	23	27b , 64
4	$CH_2PO(OEt)_2$	24	27c , 82
5	2-naphthyl	23	27d , 66
6	4-MeO-C ₆ H ₄	23	27e , 75
7	(CH ₂) ₂ COMe	16	27f , 80

Conclusions

In summary, the Passerini reaction of *vic*-diketo amides with a variety of isocyanides and carboxylic acids leads to α -acyloxy- β -keto-carboxamides with high α -regioselectively. A one-pot Passerini–Knoevenagel reaction is possible if EWG-substituted acetic acids are used as substrates. For cyanoacetic acid, the aldol condensation occurs spontaneously, while for other EWG-substituted acetic acids, the presence of a base such as triethylamine is necessary. The α -acyloxy- β -keto-carboxamides and butenolides obtained by this new method could be used as intermediates in the synthesis of complex target molecules. Besides *vic*-diketo amides, other *vic*-tricarbonyl compounds should be good substrates for this type of multicomponent reaction.

Experimental Section

General Remarks: All non-aqueous reactions were carried out using flame-dried glassware under an argon atmosphere. All solvents were distilled by rotary evaporation prior to use. Solvents for nonaqueous reactions were dried as follows before use: dichloromethane was distilled from CaH₂ under an argon atmosphere. Toluene was distilled from sodium under an argon atmosphere. HPLCgrade acetonitrile was used as supplied. All commercially available reagents and reactants were used without purification unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) using Merck Silica Gel 60 F₂₄₅ plates, which were visualized by fluorescence quenching under UV light. In addition, TLC plates were stained using cerium sulfate/phosphomolybdic acid or potassium permanganate stains. Chromatographic purification of products was carried out on Machery-Nagel Silica 60 M (230–400 mesh) unless otherwise noted, using a forced flow of eluent. Concentration under reduced pressure was carried out by rotary evaporation at 40 °C and appropriate pressure, and by exposing to high vacuum at room temperature if necessary. IR spectra were recorded with a Bruker Alpha FTIR interferometer. The absorption bands are given in wavenumbers (cm⁻¹), and intensities are reported as follows: s = strong, m = medium, w = weak, br. = broad band. NMR spectra were recorded with Bruker DPX-250, AV-300, DRX-400, DRX-500, AV-500, and AV-600 spectrometers at ambient temperature. Chemical shifts are reported in ppm, and the solvent resonance was used as an internal standard ($C^{1}HCl_{3}$: δ = 7.26 ppm; $C^{I}HD_{2}COCD_{3}$: δ = 2.05 ppm; $^{I3}CDCl_{3}$: δ = 77.16 ppm; $(CD_3)_2{}^{13}CO: \delta = 206.26$ ppm; $CD_3{}^{13}CN: \delta =$ 118.26 ppm). Data are reported as follows: s = singlet, d = doublet, t = triplet, sept = septet, m = multiplet. Mass spectra were recorded with a Finnigan LTQ-FT or a QStar-Pulsar i instrument (both operated by the mass spectroscopy service of the Philipps University of Marburg). Melting points were determined by using a capillary with a Stuart SMP10 device.

Preparation of 2-Diazo-3-oxobutanamides 13a and 13b. General Procedure A: β-Keto amide (1.00 equiv.) and 4-acetamidobenzenesulfonyl azide (1.00 equiv.) were dissolved in acetonitrile (1 mL/ 0.3 mmol), and triethylamine (1.10 equiv.) was added. The mixture was stirred at ambient temperature for 16 h, then the solution was filtered through a layered pad of sodium sulfate on silica gel, eluting with ethyl acetate. The solvent was removed under reduced pressure, and the crude product was suspended in dichloromethane. The suspension was filtered through a layered pad of sodium sulfate on silica gel, eluting with dichloromethane. The solvent was removed under reduced pressure to give the diazo compound.

2-Diazo-*N*,*N***-dimethyl-3-oxobutanamide (13a):** Following general procedure A on a 38.7 mmol scale, **13a** (6.01 g, 38.7 mmol, quant.) was obtained as a yellow liquid. TLC (pentane/ethyl acetate, 1:1): $R_{\rm f} = 0.24$. ¹H NMR (300 MHz, CDCl₃): $\delta = 3.01$ [s, 6 H, N(CH₃) 2], 2.35 (s, 3 H, 4-H₃) ppm. ¹³C NMR (62.9 MHz, CD₃CN): $\delta =$



190.7 (C-3), 161.9 (C-1), 73.4 (C-2), 37.5 [2 C, N(CH_3)₂], 27.4 (C-4) ppm. FTIR (neat): $\tilde{v} = 2930$ (w), 2099 (s), 1623 (s), 1492 (m), 1442 (m), 1385 (s), 1361 (s), 1260 (s), 1227 (s), 1140 (m), 1049 (m), 963 (m), 892 (w), 847 (w), 733 (m), 685 (w), 634 (m), 607 (m), 546 (w), 517 (m), 471 (w), 440 (w) cm⁻¹. HRMS (ESI): calcd. for C₆H₉N₃O₂Na [M + Na]⁺ 178.0587; found 178.0588.

2-Diazo-1-morpholinobutane-1,3-dione (13b): Following general procedure A on a 29.2 mmol scale, **13b** (5.76 g, 29.2 mmol, quant.) was obtained as a yellow liquid. TLC (pentane/ethyl acetate, 1:1): $R_{\rm f} = 0.31$. ¹H NMR (300 MHz, CDCl₃): $\delta = 3.76-3.70$ [m, 4 H, O(CH₂)₂], 3.54–3.47 [m, 4 H, N(CH₂)₂], 2.33 (s, 3 H, 4-H₃) ppm. ¹³C NMR (62.9 MHz, CD₃CN): $\delta = 189.7$ (C-3), 161.1 (C-1), 74.2 (C-2), 67.2 [2 C, O(CH₂)₂], 46.5 [2 C, N(CH₂)₂], 27.3 (C-4) ppm. FTIR (neat): $\tilde{v} = 2968$ (w), 2923 (w), 2858 (w), 2105 (s), 1620 (s), 1419 (s), 1361 (m), 1247 (s), 1192 (m), 1111 (s), 1068 (m), 1015 (m), 961 (m), 925 (w), 878 (m), 836 (m), 752 (m), 670 (w), 626 (m), 582 (m), 549 (w), 518 (m), 445 (w) cm⁻¹. HRMS (ESI): calcd. for C₈H₁₁N₃O₃Na [M + Na]⁺ 220.0693; found 220.0694.

Preparation of 2,3-Dioxobutanamides 7a and 7b. General Procedure B: *tert*-Butyl hypochlorite (1.10 equiv.) was added by syringe to a solution of the diazo compound (1.00 equiv.) in formic acid (1 mL/ 0.3 mmol) at 0 °C. After the bubbling had ceased, the mixture was allowed to warm to ambient temperature, and the solvent was evaporated under reduced pressure. The crude product was purified by bulb-to-bulb distillation.

N,*N*-Dimethyl-2,3-dioxobutanamide (7a): Following general procedure B on a 3.22 mmol scale, **7a** (461 mg, 3.22 mmol, quant.) was obtained as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ = 3.03 (s, 3 H, NCH₃), 2.95 (s, 3 H, NCH₃), 2.46 (s, 3 H, 4-H₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 197.6 (C-3), 184.9 (C-2), 165.6 (C-1), 36.7 (NC_aH₃), 34.2 (NC_bH₃), 24.6 (C-4) ppm. FTIR (neat): \tilde{v} = 2939 (w), 1715 (s), 1645 (s), 1506 (w), 1448 (w), 1405 (m), 1357 (m), 1271 (w), 1164 (w), 1035 (m), 954 (w), 868 (m), 767 (w), 735 (w), 692 (w), 657 (w), 631 (w), 591 (m), 501 (m), 436 (w) cm⁻¹. HRMS (ESI): calcd. for C₆H₁₀NO₃ [M + H]⁺ 144.0655; found 144.0656.

1-Morpholinobutane-1,2,3-trione (7b): Following general procedure B on a 2.53 mmol scale, **7b** (469 mg, 2.53 mmol, quant.) was obtained as a yellow solid. TLC (pentane/ethyl acetate, 1:1): $R_{\rm f} = 0.43$. ¹H NMR (500 MHz, CDCl₃): $\delta = 3.76-3.73$ (m, 2 H, OCH₂), 3.71-3.65 (m, 4 H, OCH₂, NCH₂), 3.37-3.33 (m, 2 H, NCH₂), 2.46 (s, 3 H, 4-H₃) ppm. ¹³C NMR (75 MHz, CDCl₃): $\delta = 197.5$ (C-3), 184.6 (C-2), 164.2 (C-1), 66.7 (OCH₂), 66.5 (OCH₂), 46.1 (NCH₂), 42.0 (NCH₂), 24.5 (C-4) ppm. FTIR (neat): $\tilde{v} = 2972$ (w), 2923 (w), 2860 (w), 1716 (m), 1640 (s), 1442 (m), 1358 (m), 1272 (m), 1231 (w), 1193 (w), 1164 (w), 1111 (s), 1071 (m), 1012 (m), 954 (m), 923 (w), 834 (m), 733 (m), 582 (m), 502 (m), 474 (w), 437 (w) cm⁻¹. HRMS (ESI): calcd. for C₈H₁₁NO₄Na [M + Na]⁺ 208.0580; found 208.0578.

General Procedure C, Passerini Reaction: Diketo amide 7a or 7b (1.00 equiv.) was dissolved in dichloromethane or toluene (final concentration of 7a/7b: 0.30 M) at room temperature. The carboxylic acid (1.20 equiv.) was added, followed by the isocyanide (1.20 equiv.). The reaction mixture was stirred at room temperature for the indicated time, then it was diluted with dichloromethane (20 mL), and the mixture was washed with sodium hydrogen carbonate solution (saturated aq.; 20 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were dried with sodium sulfate, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (eluent indicated in each case).

1-(tert-Butylamino)-2-(dimethylcarbamoyl)-1,3-dioxobutan-2-yl Acetate (14a): Following general procedure C in toluene or dichloromethane on a 0.80 mmol scale using 7a, after a reaction time of 2 h, and using pentane/ethyl acetate, 2:1 as eluent, 14a was isolated as a mixture of 14a and 15a (in toluene: 220 mg, 0.76 mmol, 96%, 85:15 14a/15a; in dichloromethane: 217 mg, 0.76 mmol, 95%, 89:11 14a/15a) as a colourless solid. TLC (pentane/ethyl acetate, 3:1): $R_{\rm f}$ = 0.12; m.p. 105 °C (ethyl acetate). ¹H NMR (400 MHz, CDCl₃): δ = 7.56 (s, 1 H, NH), 3.04 (s, 3 H, NCH₃), 2.96 (s, 3 H, NCH₃), 2.30 (s, 3 H, 4- H_3), 2.28 (s, 3 H, C H_3 CO₂), 1.35 [s, 9 H, C(C H_3)₃] ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 197.9 (C-3), 168.8 (CO₂), 164.8 (2-CONMe₂), 161.2 (C-1), 88.3 (C-2), 52.3 [C(CH₃)₃], 37.6 (NCH₃), 37.4 (NCH₃), 28.6 [3 C, C(CH₃)₃], 25.9 (C-4), 20.8 (CH_3CO_2) ppm. FTIR (neat): $\tilde{v} = 3363$ (w), 2969 (w), 2934 (w), 1759 (m), 1732 (m), 1692 (s), 1644 (s), 1527 (m), 1456 (m), 1394 (m), 1365 (m), 1218 (s), 1100 (m), 1062 (w), 1029 (w), 991 (w), 897 (w), 847 (w), 823 (w), 753 (s), 666 (w), 603 (w), 574 (w), 531 (m), 461 (w), 430 (w), 405 (w) cm⁻¹. HRMS (ESI): calcd. for $C_{13}H_{22}N_2O_5Na [M + Na]^+ 309.1421$; found 309.1422.

1-(tert-Butylamino)-2-(dimethylcarbamoyl)-1,3-dioxobutan-2-yl Isobutyrate (14b): Following general procedure C in dichloromethane on a 0.73 mmol scale using 7a, after a reaction time of 16.2 h, and using chloroform as eluent, 14b was isolated as a mixture of 14b and 15b (226 mg, 0.72 mmol, 98%, 91:9 14b/15b) as a colourless liquid. TLC (pentane/ethyl acetate, 2:1): $R_f = 0.31$. ¹H NMR (300 MHz, CDCl₃): δ = 7.53 (s, 1 H, NH), 3.02 (s, 3 H, NCH₃), 2.93 (s, 3 H, NCH₃), 2.76 (sept, J = 7.0 Hz, 1 H, CHCO₂), 2.25 (s, 3 H, 4- H_3), 1.32 [s, 9 H, C(C H_3)₃], 1.27 [d, J = 7.0 Hz, 6 H, CH(CH₃)₂] ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 198.0 (C-3), 174.6 (CO₂), 164.9 (2-CONMe₂), 161.2 (C-1), 87.8 (C-2), 52.1 [C(CH₃)₃], 37.6 (NCH₃), 37.3 (NCH₃), 34.0 (CHCO₂), 28.5 [3 C, C(CH₃)₃], 25.8 (C-4), 18.9 (CHCH₃), 18.8 (CHCH₃) ppm. FTIR (neat): $\tilde{v} = 3384$ (w), 2973 (w), 2935 (w), 2879 (w), 2114 (w), 1732 (s), 1695 (s), 1644 (s), 1530 (s), 1460 (m), 1392 (m), 1360 (m), 1253 (m), 1222 (m), 1184 (s), 1132 (s), 1097 (s), 1056 (m), 989 (w), 915 (w), 883 (w), 854 (w), 820 (w), 737 (w), 681 (w), 651 (w), 581 (w), 538 (m), 461 (w), 415 (w) cm⁻¹. HRMS (APCI): calcd. for $C_{15}H_{26}N_2O_5Na [M + Na]^+$ 337.1734; found 337.1725.

1-(tert-Butylamino)-2-(dimethylcarbamoyl)-1,3-dioxobutan-2-yl Pivalate (14c): Following general procedure C in dichloromethane on a 0.73 mmol scale using 7a, after a reaction time of 16.7 h, and using chloroform as eluent, 14c was isolated as a mixture of 14c and 15c (239 mg, 0.73 mmol, 99%, 92:8 14c/15c) as a colourless solid. TLC (pentane/ethyl acetate, 3:1): $R_f = 0.31$; m.p. 54 °C (chloroform). ¹H NMR (300 MHz, CDCl₃): δ = 7.54 (s, 1 H, N*H*), 3.02 (s, 3 H, NCH₃), 2.93 (s, 3 H, NCH₃), 2.24 (s, 3 H, 4-H₃), 1.31 [s, 9 H, NHC(CH₃)₃], 1.31 [s, 9 H, (CH₃)₃CCO₂] ppm. ¹³C NMR $(75 \text{ MHz}, \text{CDCl}_3): \delta = 198.0 \text{ (C-3)}, 176.0 \text{ (CO}_2), 165.0 \text{ (2-}$ CONMe₂), 161.2 (C-1), 87.6 (C-2), 52.0 [NHC(CH₃)₃], 39.0 [(CH₃)₃CCO₂], 37.6 (NCH₃), 37.2 (NCH₃), 28.5 [3 C, NHC- $(CH_3)_3$, 27.2 [3 C, $(CH_3)_3$ CCO₂], 25.8 (C-4) ppm. FTIR (neat): $\tilde{v} =$ 2971 (w), 2934 (w), 2876 (w), 1737 (m), 1695 (s), 1645 (s), 1532 (m), 1484 (w), 1457 (m), 1394 (m), 1362 (m), 1277 (w), 1222 (w), 1174 (m), 1126 (s), 1062 (w), 1029 (w), 988 (w), 897 (w), 837 (w), 799 (w), 766 (w), 733 (w), 688 (w), 650 (w), 583 (w), 539 (w), 452 (w), 403 (w) cm⁻¹. HRMS (APCI): calcd. for C₁₆H₂₈N₂O₅Na $[M + Na]^+$ 351.1890; found 351.1881.

1-(*tert***-Butylamino)-2-(morpholinocarbonyl)-1,3-dioxobutan-2-yl Acetate (14d):** Following general procedure C in toluene on a 0.63 mmol scale, or in dichloromethane on a 0.54 mmol scale, using **7b**, after a reaction time of 55 min (toluene) or 30 min (dichloromethane), and using pentane/ethyl acetate, 2:1 as eluent, **14d** (toluene: 191 mg, 0.58 mmol, 92%; dichloromethane: 163 mg, 0.50 mmol, 92%) was isolated as a colourless solid. TLC (pentane/ ethyl acetate, 2:1): $R_f = 0.18$; m.p. 136 °C (pentane). ¹H NMR $(500 \text{ MHz}, \text{CDCl}_3): \delta = 7.46 \text{ (s, 1 H, NH)}, 4.00-3.32 \text{ [m, 8 H,}$ N(C₂H₄)₂O], 2.31 (s, 3 H, 4-H₃), 2.30 (s, 3 H, CH₃CO₂), 1.40 [s, 9 H, C(CH₃)₃] ppm. ¹³C NMR (150 MHz, CDCl₃): δ = 197.7 (C-3), 168.8 (CO₂), 163.1 [2-CON(C₂H₄)₂O], 161.1 (C-1), 87.9 (C-2), 66.8 (OCH₂), 66.6 (OCH₂), 52.3 [C(CH₃)₃], 46.9 (NCH₂), 43.8 (NCH₂), 28.5 [3 C, C(CH₃)₃], 25.9 (C-4), 20.8 (CH₃CO₂) ppm. FTIR (neat): $\tilde{v} = 3358$ (w), 3328 (w), 2976 (w), 2856 (w), 1772 (w), 1712 (m), 1687 (s), 1657 (s), 1586 (w), 1516 (m), 1480 (m), 1430 (m), 1367 (m), 1298 (m), 1272 (m), 1241 (s), 1202 (s), 1108 (s), 1044 (m), 986 (m), 929 (w), 895 (m), 869 (w), 822 (m), 783 (w), 758 (w), 729 (w), 667 (w), 609 (s), 589 (m), 532 (m), 461 (m) cm⁻¹. HRMS (ESI): calcd. for $C_{15}H_{24}N_2O_6Na [M + Na]^+$ 351.1527; found 351.1524.

1-(tert-Butylamino)-2-(morpholinocarbonyl)-1,3-dioxobutan-2-yl Isobutyrate (14e): Following general procedure C in dichloromethane on a 0.57 mmol scale using 7b, after a reaction time of 3.5 h, and using pentane/ethyl acetate, 2:1 as eluent, 14e (163 mg, 0.46 mmol, 81%) was isolated as a colourless solid. TLC (pentane/ ethyl acetate, 2:1): $R_{\rm f} = 0.27$; m.p. 68 °C. ¹H NMR (300 MHz, CDCl₃): δ = 7.38 (s, 1 H, NH), 3.99–3.20 [m, 8 H, N(C₂H₄)₂O], 2.71 (sept, J = 7.0 Hz, 1 H, CHCO₂), 2.17 (s, 3 H, 4-H₃), 1.29 [s, 9 H, C(CH₃)₃], 1.23 [d, J = 7.0 Hz, 6 H, CH(CH₃)₂] ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 197.7 (C-3), 174.5 (CO₂), 163.1 [2-CON(C₂H₄)₂O], 161.1 (C-1), 87.3 (C-2), 66.6 [2 C, O(CH₂)₂], 52.1 [C(CH₃)₃], 46.8 (NCH₂), 43.7 (NCH₂), 33.9 (CHCO₂), 28.4 [3 C, C(CH₃)₃], 25.7 (C-4), 18.7 (CH₃CH), 18.7 (CH₃CH) ppm. FTIR (neat): $\tilde{v} = 3346$ (w), 2972 (w), 2929 (w), 2862 (w), 1732 (m), 1693 (s), 1642 (s), 1532 (m), 1436 (m), 1392 (w), 1360 (m), 1300 (w), 1272 (m), 1244 (m), 1192 (m), 1111 (s), 1022 (w), 977 (w), 915 (w), 848 (w), 805 (w), 733 (m), 646 (w), 586 (m), 538 (w), 458 (w), 419 (w) cm⁻¹. HRMS (APCI): calcd. for $C_{17}H_{28}N_2O_6Na$ [M + Na]⁺ 379.1840; found 379.1832.

1-(tert-Butylamino)-2-(morpholinocarbonyl)-1,3-dioxobutan-2-yl Pivalate (14f): Following general procedure C in dichloromethane on a 0.59 mmol scale using 7b, after a reaction time of 100 min, and using pentane/ethyl acetate, 3:1 as eluent, 14f was isolated as a mixture of 14f and 15f (218 mg, 0.59 mmol, 99%, 95:5 14f/15f) as a colourless liquid. TLC (pentane/ethyl acetate, 3:1): $R_{\rm f} = 0.28$. ¹H NMR (300 MHz, CDCl₃): δ = 7.40 (s, 1 H, N*H*), 3.95–3.25 [m, 8 H, N(C₂ H_4)₂O], 2.14 (s, 3 H, 4- H_3), 1.28 [s, 9 H, NHC(C H_3)₃], 1.25 [s, 9 H, $(CH_3)_3CCO_2$] ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 197.7 (C-3), 176.0 (CO₂), 163.1 [2-CON(C₂H₄)₂O], 161.0 (C-1), 87.1 (C-2), 66.6 [2 C, O(CH₂)₂], 52.0 [NHC(CH₃)₃], 46.8 (NCH₂), 43.7 (NCH₂), 38.8 [(CH₃)₃CCO₂], 28.4 [3 C, NHC(CH₃)₃], 27.0 [3 C, $(CH_3)_3CCO_2$], 25.6 (C-4) ppm. FTIR (neat): $\tilde{v} = 2970$ (w), 2926 (w), 2862 (w), 1738 (m), 1694 (m), 1643 (s), 1534 (m), 1436 (m), 1396 (w), 1362 (m), 1275 (m), 1243 (m), 1193 (w), 1115 (s), 1023 (w), 976 (w), 930 (w), 885 (w), 854 (w), 767 (w), 733 (m), 692 (w), 648 (w), 589 (m), 541 (w), 452 (w) cm⁻¹. HRMS (ESI): calcd. for $C_{18}H_{30}N_2O_6Na [M + Na]^+$ 393.1996; found 393.1994.

1-(*tert*-Butylamino)-2-(dimethylcarbamoyl)-1,3-dioxobutan-2-yl Methyl Malonate (18a): Following general procedure C in toluene on a 0.68 mmol scale, or in dichloromethane on a 0.65 mmol scale, using 7a, after a reaction time of 15 min (toluene) or 30 min (dichloromethane), and using pentane/ethyl acetate, 1:1 as eluent, 18a was isolated as a mixture of 18a and 20a (toluene: 225 mg, 0.66 mmol, 97%, 89:11 18a/20a; dichloromethane: 218 mg, 0.64 mmol, 98%, 91:9 18a/20a) as a colourless liquid. TLC (pentane/ethyl acetate, 1:1): $R_{\rm f} = 0.28$. ¹H NMR (300 MHz, CDCl₃): δ = 7.46 (s, 1 H, NH), 3.78 (s, 3 H, OCH₃), 3.63 (s, 2 H, CH₂), 3.01 (s, 3 H, NCH₃), 2.97 (s, 3 H, NCH₃), 2.35 (s, 3 H, 4-H₃), 1.35 [s, 9 H, C(CH₃)₃] ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 197.2 (C-3), 166.5 (CO₂), 164.2 (CO₂), 163.9 (2-CONMe₂), 160.8 (C-1), 89.2 (C-2), 52.8 (OCH₃), 52.3 [C(CH₃)₃], 41.2 (CH₂CO₂), 37.4 (NCH₃), 37.3 (NCH₃), 28.5 [3 C, C(CH₃)₃], 26.0 (C-4) ppm. FTIR (neat): \tilde{v} = 3358 (w), 2967 (w), 1776 (m), 1734 (s), 1690 (s), 1648 (s), 1526 (s), 1447 (m), 1397 (m), 1358 (m), 1261 (m), 1213 (s), 1176 (s), 1139 (s), 1096 (s), 1015 (m), 903 (w), 840 (w), 797 (w), 755 (s), 676 (m), 582 (m), 531 (m), 460 (m), 402 (m) cm⁻¹. HRMS (ESI): calcd. for C₁₅H₂₅N₂O₇ [M + H]⁺ 345.1656; found 345.1654.

1-(tert-Butylamino)-2-(dimethylcarbamoyl)-1,3-dioxobutan-2-yl 2-Tosylacetate (18b): Following general procedure C in toluene on a 0.61 mmol scale, or in dichloromethane on a 0.68 mmol scale, using 7a, after a reaction time of 90 min (toluene) or 110 min (dichloromethane), and using pentane/ethyl acetate, 2:1 as eluent, 18b (toluene: 260 mg, 0.59 mmol, 97 %; dichloromethane: 296 mg, 0.67 mmol, 99%) was isolated as a colourless solid. TLC (pentane/ ethyl acetate, 1:1): $R_{\rm f}$ = 0.51; m.p. 58 °C (chloroform). ¹H NMR (300 MHz, CDCl₃): δ = 7.82 (d, J = 8.3 Hz, 2 H, 2 H_{ortho}), 7.38 (d, br. s, J = 8.0 Hz, 2 H, 1 H, 2 H_{meta} , NH), 4.34 (d, J = 14.5 Hz, 1 H, CH_2CO_2), 4.20 (d, J = 14.5 Hz, 1 H, CH_2CO_2), 2.99 (s, 3 H, NCH₃), 2.95 (s, 3 H, NCH₃), 2.45 (s, 3 H, CH₃Ar), 2.41 (s, 3 H, 4-*H*₃), 1.35 [s, 9 H, C(C*H*₃)₃] ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 196.4 (C-3), 163.9 (CO₂), 160.8 (2-CONMe₂), 159.5 (C-1), 146.0 (Cipso), 136.0 (Cpara), 130.3 (2 C, 2 Cmeta), 128.3 (2 C, 2 Cortho), 90.4 (C-2), 60.7 (CH₂CO₂), 52.5 [C(CH₃)₃], 37.4 (NCH₃), 36.9 (NCH₃), 28.4 [3 C, C(CH₃)₃], 26.3 (CH₃Ar), 21.8 (C-4) ppm. FTIR (neat): $\tilde{v} = 3364$ (w), 2972 (w), 2932 (w), 1769 (m), 1732 (m), 1689 (s), 1652 (s), 1598 (w), 1526 (m), 1455 (m), 1397 (m), 1364 (m), 1325 (s), 1153 (s), 1081 (s), 1024 (w), 995 (w), 919 (w), 893 (w), 814 (m), 751 (m), 699 (w), 654 (m), 585 (m), 515 (s), 461 (m) cm⁻¹. HRMS (ESI): calcd. for $C_{20}H_{29}N_2O_7S [M + H]^+$ 441.1690; found 441.1697.

1-(tert-Butylamino)-2-(dimethylcarbamoyl)-1,3-dioxobutan-2-yl 2-(Diethoxyphosphoryl)acetate (18c): Following general procedure C in dichloromethane on a 0.61 mmol scale using 7a, after a reaction time of 17 h, and using ethyl acetate as eluent, 18c (194 mg, 0.46 mmol, 75%) was isolated as a colourless liquid.^[44] TLC (ethyl acetate): $R_{\rm f} = 0.32$. ¹H NMR (300 MHz, CDCl₃): $\delta = 7.48$ (s, 1 H, NH), 4.17–4.00 [m, 4 H, P(OCH₂)₂], 3.11 (d, J = 6.0 Hz, 1 H, CH_2CO_2), 3.04 (d, J = 6.0 Hz, 1 H, CH_2CO_2), 2.92 (s, 3 H, NCH_3), 2.86 (s, 3 H, NCH₃), 2.30 (s, 3 H, 4-H₃), 1.32–1.21 [m, 6 H, P(OCH₂CH₃)₂], 1.26 [s, 9 H, C(CH₃)₃] ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 196.6 (C-3), 164.1 (2-CONMe₂), 162.8 (d, J = 5.9 Hz, CO_2), 161.1 (C-1), 89.5 (C-2), 63.0 (d, J = 6.4 Hz, PO CH_2), 62.6 $(d, J = 6.5 \text{ Hz}, \text{PO}CH_2), 52.1 [C(CH_3)_3], 37.1 (NCH_3), 36.8$ (NCH_3) , 33.8 (d, J = 135.6 Hz, CH_2CO_2), 28.2 [3 C, $C(CH_3)_3$], 26.0 (C-4), 16.3 (POCH₂CH₃), 16.2 (POCH₂CH₃) ppm. ³¹P NMR (101 MHz, CDCl₃): δ = 19.4 ppm. FTIR (neat): \tilde{v} = 3287 (w), 2977 (w), 2934 (w), 1765 (w), 1733 (m), 1657 (m), 1531 (m), 1454 (w), 1395 (m), 1364 (w), 1252 (s), 1178 (m), 1103 (m), 1021 (s), 968 (s), 864 (w), 787 (w), 733 (m), 699 (w), 637 (w), 591 (w), 533 (w), 466 (w), 401 (w) cm^{-1} . HRMS (ESI): calcd. for $C_{17}H_{31}N_2O_8PNa [M + Na]^+ 445.1710$; found 445.1717.

1-(*tert*-Butylamino)-2-(dimethylcarbamoyl)-1,3-dioxobutan-2-yl 2-Chloroacetate (18d): Following general procedure C in dichloromethane on a 0.85 mmol scale using 7a, after a reaction time of 17 h, and using chloroform as eluent, 18d was isolated as a mixture of 18d and 19d (272 mg, 0.85 mmol, 99%, 86:14 18d/19d) as a colourless solid. TLC (pentane/ethyl acetate, 2:1): $R_f = 0.16$; m.p.



112 °C (pentane). ¹H NMR (600 MHz, CDCl₃): δ = 7.45 (s, 1 H, NH), 4.29 (d, J = 14.8 Hz, 1 H, CH₂CO₂), 4.26 (d, J = 14.8 Hz, 1 H, CH₂CO₂), 3.01 (s, 3 H, NCH₃), 2.97 (s, 3 H, NCH₃), 2.35 (s, 3 H, 4-H₃), 1.35 [s, 9 H, C(CH₃)₃] ppm. ¹³C NMR (150 MHz, CDCl₃): δ = 197.0 (C-3), 165.1 (CO₂), 164.2 (2-CONMe₂), 160.5 (C-1), 89.3 (C-2), 52.5 [C(CH₃)₃], 40.5 (CH₂CO₂), 37.6 (NCH₃), 37.4 (NCH₃), 28.5 [3 C, C(CH₃)₃], 26.0 (C-4) ppm. FTIR (neat): \tilde{v} = 3354 (w), 2969 (w), 1778 (m), 1736 (m), 1685 (s), 1639 (s), 1528 (m), 1495 (w), 1455 (w), 1401 (m), 1362 (m), 1321 (w), 1267 (w), 1218 (m), 1152 (s), 1095 (m), 1064 (w), 1027 (w), 990 (w), 922 (w), 839 (w), 802 (w), 758 (w), 692 (w), 625 (w), 602 (m), 580 (m), 555 (m), 524 (w), 462 (w), 435 (w), 400 (w) cm⁻¹. HRMS (ESI): calcd. for C₁₃H₂₁ClN₂O₅Na [M + Na]⁺ 343.1031; found 343.1034.

1-(tert-Butylamino)-2-(dimethylcarbamoyl)-1,3-dioxobutan-2-yl 2-Bromoacetate (18e): Following general procedure C in dichloromethane on a 0.80 mmol scale using 7a, after a reaction time of 18 h, and using chloroform as eluent, 18e was isolated as a mixture of 18e and 19e (289 mg, 0.79 mmol, 99%, 87:13 18e/19e) as a colourless solid. TLC (pentane/ethyl acetate, 2:1): $R_{\rm f} = 0.33$; m.p. 82 °C (pentane). ¹H NMR (600 MHz, CDCl₃): δ = 7.45 (s, 1 H, NH), 4.04 (s, 2 H, CH₂CO₂), 3.03 (s, 3 H, NCH₃), 2.97 (s, 3 H, NCH₃), 2.35 (s, 3 H, 4-H₃), 1.35 [s, 9 H, C(CH₃)₃] ppm. ¹³C NMR (150 MHz, CDCl₃): δ = 197.1 (C-3), 164.9 (CO₂), 164.2 (2-CONMe₂), 160.6 (C-1), 89.3 (C-2), 52.4 [C(CH₃)₃], 37.7 (NCH₃), 37.3 (NCH₃), 28.5 [3 C, C(CH₃)₃], 26.0 (C-4), 24.9 (CH₂CO₂) ppm. FTIR (neat): $\tilde{v} = 3403$ (w), 2969 (w), 1732 (m), 1693 (s), 1646 (s), 1523 (s), 1456 (m), 1395 (m), 1363 (m), 1264 (s), 1220 (m), 1177 (s), 1097 (s), 1026 (w), 991 (w), 915 (w), 888 (w), 826 (w), 754 (m), 714 (w), 672 (w), 644 (w), 581 (m), 552 (m), 459 (w), 402 (w) cm⁻¹. HRMS (ESI): calcd. for $C_{13}H_{21}BrN_2O_5Na [M + Na]^+$ 387.0526; found 387.0528.

1-(tert-Butylamino)-2-(morpholinocarbonyl)-1,3-dioxobutan-2-yl 2-Tosylacetate (18f): Following general procedure C in toluene or in dichloromethane on a 0.54 mmol scale using 7b, after a reaction time of 40 min (toluene) or 50 min (dichloromethane), and using pentane/ethyl acetate, 2:1 as eluent, 18f was isolated as a mixture of 18f and 20f (toluene: 227 mg, 0.47 mmol, 88%, 73:27 18f/20f) or as pure 18f (dichloromethane: 219 mg, 0.45 mmol, 84%) as a colourless solid. TLC (pentane/ethyl acetate, 2:1): $R_{\rm f} = 0.10$. ¹H NMR (300 MHz, CDCl₃): δ = 7.84 (d, J = 8.3 Hz, 2 H, 2 H_{ortho}), 7.40 (d, J = 8.1 Hz, 2 H, 2 H_{meta}), 7.29 (s, 1 H, NH), 4.35 (d, J =14.6 Hz, 1 H, CH₂CO₂), 4.17 (d, J = 14.6 Hz, 1 H, CH₂CO₂), 3.99-3.26 [m, 8 H, N(C₂H₄)₂O], 2.47 (s, 3 H, CH₃Ar), 2.43 (s, 3 H, 4-*H*₃), 1.36 [s, 9 H, C(C*H*₃)₃] ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 196.0 (C-3), 162.4 (CO₂), 160.8 [2-CON(C₂H₄)₂O], 168.5 (C-1), 146.1 (Cipso), 135.9 (Cpara), 130.3 (2 C, 2 Cmeta), 128.2 (2 C, 2 Cortho), 90.2 (C-2), 66.6 (OCH₂), 66.3 (OCH₂), 60.5 (CH₂CO₂), 52.5 [C(CH₃)₃], 46.5 (NCH₂), 43.4 (NCH₂), 28.3 [3 C, C(CH₃)₃], 26.2 (CH_3Ar) , 21.8 (C-4) ppm. FTIR (neat): $\tilde{v} = 3365$ (w), 2971 (w), 2926 (w), 2864 (w), 1769 (m), 1732 (m), 1688 (s), 1651 (s), 1598 (w), 1526 (m), 1443 (m), 1395 (w), 1363 (m), 1325 (m), 1224 (s), 1154 (s), 1112 (s), 1079 (s), 1018 (w), 981 (m), 913 (m), 815 (m), 766 (w), 731 (s), 652 (m), 587 (s), 541 (m), 514 (s), 460 (m) cm⁻¹. HRMS (ESI): calcd. for C₂₂H₃₁N₂O₈S [M + H]⁺ 483.1796; found 483.1791.

1-(*tert*-Butylamino)-2-(morpholinocarbonyl)-1,3-dioxobutan-2-yl Methyl Malonate (18g): Following general procedure C in toluene on a 0.58 mmol scale, or in dichloromethane on a 0.59 mmol scale, using 7b, after a reaction time of 20 min (toluene) or 30 min (dichloromethane), and using pentane/ethyl acetate, 2:1 as eluent, 18g was isolated as a mixture of 18g and 20g (toluene: 192 mg,

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0.50 mmol, 87%, 69:31 18g/20g; dichloromethane: 204 mg, 0.53 mmol, 89%, 91:9 18g/20g) as a colourless solid. TLC (pentane/ ethyl acetate, 1:1): $R_f = 0.28$; m.p. 84 °C (chloroform). ¹H NMR $(300 \text{ MHz}, \text{CDCl}_3): \delta = 7.27 \text{ (s, 1 H, NH)}, 3.82-3.33 \text{ [m, 8 H,}$ N(C₂H₄)₂O], 3.77 (s, 3 H, OCH₃), 3.59 (s, 2 H, CH₂CO₂), 2.30 (s, 3 H, 4-H₃), 1.33 [s, 9 H, C(CH₃)₃] ppm. ¹³C NMR (75 MHz, $CDCl_3$): $\delta = 197.1$ (C-3), 166.4 (CO₂), 164.0 (CO₂), 162.7 [2-CON(C₂H₄)₂O], 160.8 (C-1), 88.9 (C-2), 66.7 [2 C, O(CH₂)₂], 52.9 (OCH₃), 52.5 [C(CH₃)₃], 46.8 (NCH₂), 43.8 (NCH₂), 41.2 (CH_2CO_2) , 28.5 [3 C, C $(CH_3)_3$], 26.0 (C-4) ppm. FTIR (neat): $\tilde{v} =$ 3324 (w), 2966 (w), 2860 (w), 1792 (m), 1769 (m), 1737 (s), 1686 (m), 1637 (s), 1541 (m), 1441 (m), 1340 (m), 1278 (m), 1248 (m), 1195 (m), 1145 (s), 1106 (s), 1067 (m), 1008 (m), 951 (w), 909 (w), 854 (w), 830 (w), 795 (w), 731 (w), 685 (w), 656 (w), 588 (m), 526 (w), 458 (m), 396 (w) cm⁻¹. HRMS (ESI): calcd. for $C_{17}H_{27}N_2O_8 [M + H]^+$ 387.1762; found 387.1760.

1-(tert-Butylamino)-2-(morpholinocarbonyl)-1,3-dioxobutan-2-yl 2-(Diethoxyphosphoryl)acetate (18h): Following general procedure C in dichloromethane on a 0.49 mmol scale using 7b, after a reaction time of 17 h, and using ethyl acetate as eluent, 18h was isolated as a mixture of 18h and 19h (206 mg, 0.44 mmol, 91%, 97:3 18h/19h) as a colourless liquid.^[44] TLC (ethyl acetate): $R_f = 0.34$. ¹H NMR $(300 \text{ MHz}, \text{CDCl}_3): \delta = 7.44 \text{ (s, 1 H, NH)}, 4.22-4.06 \text{ [m, 4 H,}$ $P(OCH_2)_2$], 3.80–3.35 [m, 8 H, $N(C_2H_4)_2O$], 3.15 (dd, J = 20.8, J= 15.0 Hz, 1 H, CH_2CO_2), 3.07 (dd, J = 21.1, J = 15.0 Hz, 1 H, CH₂CO₂), 2.34 (s, 3 H, 4-H₃), 1.38–1.27 [m, 6 H, P(OCH₂CH₃)₂], 1.32 [s, 9 H, C(CH₃)₃] ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 196.9 (C-3), 163.1 (d, J = 5.9 Hz, CO_2), 162.7 [2- $CON(C_2H_4)_2O$], 161.2 (C-1), 88.4 (C-2), 66.6 (OCH₂), 66.4 (OCH₂), 63.2 (d, J = 6.5 Hz, $POCH_2$), 62.8 (d, J = 6.6 Hz, $POCH_2$), 52.3 [$C(CH_3)_3$], 46.6 (NCH_2) , 43.5 (NCH_2) , 34.0 $(d, J = 135.5 Hz, CH_2CO_2)$, 28.4 [3 C, C(CH₃)₃], 26.2 (C-4), 16.4 (POCH₂CH₃), 16.4 (POCH₂CH₃) ppm. ³¹P NMR (101 MHz, CDCl₃): δ = 19.2 ppm. FTIR (neat): \tilde{v} = 3287 (w), 2975 (w), 2923 (w), 2864 (w), 1766 (m), 1733 (m), 1686 (m), 1657 (m), 1531 (m), 1441 (m), 1395 (w), 1363 (w), 1249 (s), 1111 (m), 1020 (s), 971 (s), 861 (w), 819 (w), 787 (w), 754 (w), 677 (w), 591 (m), 531 (w), 462 (m) cm⁻¹. HRMS (ESI): calcd. for C₁₉H₃₃N₂O₉PNa [M + Na]⁺ 487.1816; found 487.1814.

1-(tert-Butylamino)-2-methyl-4-morpholino-1,3,4-trioxobutan-2-yl 2-(Diethoxyphosphoryl)acetate (19h): From the reaction described above, a small amount of pure 19h (10 mg, 0.02 mmol, 4.5%) was isolated as a colourless liquid. TLC (ethyl acetate): $R_{\rm f} = 0.40$. ¹H NMR (500 MHz, CDCl₃): δ = 7.04 (s, 1 H, NH), 4.26–4.19 [m, 4 H, P(OCH₂)₂], 3.77–3.68 [m, 5 H, O(CH₂)₂, NCH₂], 3.60–3.53 (m, 2 H, NCH₂, NCH₂), 3.47 (dt, J = 13.6, J = 4.7 Hz, 1 H, NCH₂), 3.11 (dd, J = 21.5, J = 14.6 Hz, 1 H, CH_2CO_2), 3.05 (dd, J = 20.8, J = 14.5 Hz, 1 H, CH_2CO_2), 1.89 (s, 3 H, 2- CH_3), 1.42–1.38 [m, 6 H, P(OCH₂CH₃)₂], 1.41 [s, 9 H, C(CH₃)₃] ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 192.2 (C-3), 165.7 (C-1), 164.8 (d, J = 6.4 Hz, CO₂), 163.3 (C-4), 86.3 (C-2), 66.7 (OCH₂), 66.5 (OCH₂), 63.2 (d, J = 6.3 Hz, POCH₂), 63.1 (d, J = 6.4 Hz, POCH₂), 51.9 $[C(CH_3)_3], 46.3 (NCH_2), 42.1 (NCH_2), 34.4 (d, J = 133.2 Hz,$ CH₂CO₂), 28.6 [3 C, C(CH₃)₃], 22.4 (2-CH₃), 16.5 (d, J = 3.7 Hz, POCH₂CH₃), 16.5 (d, J = 3.7 Hz, POCH₂CH₃) ppm. ³¹P NMR (101 MHz, CDCl₃): δ = 19.5 ppm. FTIR (neat): \tilde{v} = 3333 (w), 2973 (w), 2927 (w), 2864 (w), 1737 (m), 1679 (m), 1646 (s), 1530 (m), 1448 (m), 1394 (w), 1366 (w), 1264 (s), 1160 (w), 1112 (m), 1021 (s), 969 (s), 819 (w), 788 (w), 654 (w), 624 (w), 584 (w), 550 (w), 488 (w) cm⁻¹. HRMS (ESI): calcd. for $C_{19}H_{33}N_2O_9PNa [M + Na]^+ 487.1816$; found 487.1816.

General Procedure D, Passerini-Knoevenagel Reaction: Diketo amide 7a or 7b (1.00 equiv.) was dissolved in dichloromethane or toluene (final concentration of **7a/7b**: 0.30 M) at room temperature. The carboxylic acid (1.20 equiv.) was added, followed by the isocyanide (1.20 equiv.). The reaction mixture was stirred at room temperature for the indicated time, then triethylamine (2.50 equiv.) was added. The reaction mixture was stirred at room temperature for the indicated time, then it was diluted with dichloromethane (20 mL), and the mixture was washed with ammonium chloride solution (saturated aq.; 20 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were dried with sodium sulfate, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (eluent indicated in each case).

N-tert-Butyl-4-cyano-N,N,3-trimethyl-5-oxofuran-2,2(5H)-dicarboxamide (20a): Following general procedure C in toluene on a 0.76 mmol scale, or in dichloromethane on a 0.71 mmol scale, using 7a, after a reaction time of 2 h, and using pentane/ethyl acetate, 2:1 as eluent, 20a was isolated as a mixture of 20a and 21a (toluene: 202 mg, 0.69 mmol, 90%, 91:9 20a/21a; dichloromethane: 150 mg, 0.51 mmol, 72%, 92:8 20a/21a) as a colourless solid. TLC (pentane/ ethyl acetate, 1:1): $R_f = 0.46$; m.p. 169 °C (pentane). ¹H NMR $(500 \text{ MHz}, \text{ CDCl}_3): \delta = 6.29 \text{ (s, 1 H, NH)}, 3.05 \text{ (s, 3 H, NCH}_3),$ 2.97 (s, 3 H, NCH₃), 2.59 (s, 3 H, 3-CH₃), 1.35 [s, 9 H, C(CH₃)₃] ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 181.5 (C-3), 165.5 (C-5), 162.5 (2-CONMe₂), 161.1 (2-CONHtBu), 109.9 (4-CN), 104.8 (C-4), 91.3 (C-2), 53.3 [C(CH₃)₃], 37.2 (NCH₃), 36.9 (NCH₃), 28.4 [3 C, C(CH₃)₃], 16.9 (3-CH₃) ppm. FTIR (neat): $\tilde{v} = 3369$ (m), 2969 (w), 2938 (w), 2243 (w), 1777 (s), 1691 (s), 1663 (s), 1527 (s), 1454 (m), 1401 (m), 1370 (m), 1315 (w), 1281 (m), 1215 (m), 1172 (m), 1055 (s), 1014 (m), 939 (w), 907 (w), 841 (w), 756 (m), 698 (w), 649 (m), 624 (w), 565 (m), 493 (m), 469 (w), 433 (w), 403 (w) cm⁻¹. HRMS (ESI): calcd. for $C_{14}H_{19}N_3O_4Na [M + Na]^+$ 316.1268; found 316.1266.

Methyl 5-(tert-Butylcarbamoyl)-5-(dimethylcarbamoyl)-4-methyl-2oxo-2,5-dihydrofuran-3-carboxylate (20b): Following general procedure D in toluene on a 0.66 mmol scale, or in dichloromethane on a 0.59 mmol scale, using 7a, after a reaction time of 30 min, triethylamine was added, and the mixture was stirred for a further 30 min (toluene) or 40 min (dichloromethane). Pentane/ethyl acetate, 1:1 was used as eluent. Compound 20b (toluene: 161 mg, 0.49 mmol, 75%; dichloromethane: 159 mg, 0.49 mmol, 82%) was isolated as a colourless colourless solid. TLC (pentane/ethyl acetate, 1:1): $R_f = 0.42$; m.p. 184 °C. ¹H NMR (300 MHz, CDCl₃): $\delta =$ 6.45 (s, 1 H, NH), 3.85 (s, 3 H, OCH₃), 3.04 (s, 3 H, NCH₃), 2.93 (s, 3 H, NCH₃), 2.60 (s, 3 H, 4-CH₃), 1.35 [s, 9 H, C(CH₃)₃] ppm. ¹³C NMR (150 MHz, CDCl₃): δ = 178.0 (C-4), 166.9 (C-2), 163.2 (5-CONMe₂), 162.3 (5-CONHtBu), 161.1 (3-CO₂Me), 117.7 (C-3), 89.2 (C-5), 52.7 (OCH₃), 52.4 [C(CH₃)₃], 37.1 (NCH₃), 36.7 (NCH₃), 28.3 [3 C, C(CH₃)₃], 16.2 (4-CH₃) ppm. FTIR (neat): $\tilde{v} =$ 3347 (m), 2975 (w), 1785 (s), 1720 (m), 1675 (s), 1651 (s), 1533 (m), 1439 (m), 1353 (s), 1286 (m), 1220 (s), 1166 (m), 1108 (m), 1044 (s), 1015 (s), 939 (w), 904 (w), 836 (w), 798 (m), 759 (w), 694 (w), 659 (w), 582 (m), 529 (w), 503 (w), 460 (w), 410 (w) cm⁻¹. HRMS (ESI): calcd. for $C_{15}H_{23}N_2O_6$ [M + H]⁺ 327.1551; found 327.1553.

Methyl 5-(*tert*-Butylcarbamoyl)-4-(dimethylcarbamoyl)-5-methyl-2oxo-2,5-dihydrofuran-3-carboxylate (21b): From the reaction described above, 21b (toluene: 36 mg, 0.11 mmol, 17%; dichloromethane: 24 mg, 0.07 mmol, 12%) was isolated as a colourless liquid. TLC (pentane/ethyl acetate, 1:1): $R_f = 0.17$. ¹H NMR (500 MHz, CDCl₃): $\delta = 6.32$ (s, 1 H, NH), 3.83 (s, 3 H, OCH₃), 3.06 (s, 3 H, NCH₃), 2.76 (s, 3 H, NCH₃), 1.84 (s, 3 H, 5-CH₃), 1.31 [s, 9 H, C(CH₃)₃] ppm. ¹³C NMR (125 MHz, CDCl₃): $\delta = 169.5$ (C-4), 165.2 (C-2), 165.1 (5-CONH*t*Bu), 161.5 (4-CONMe₂), 159.8 (3-CO₂Me), 118.0 (C-3), 87.3 (C-5), 53.0 (OCH₃), 52.2 [C(CH₃)₃], 37.7 (NCH₃), 34.3 (NCH₃), 28.4 [3 C, C(CH₃)₃], 24.6 (5-CH₃) ppm. HRMS (ESI): calcd. for C₁₅H₂₃N₂O₆ [M + H]⁺ 327.1551; found 327.1554.

N-tert-Butyl-N,N,3-trimethyl-5-oxo-4-tosylfuran-2,2(5H)-dicarboxamide (20c): Following general procedure D in toluene or dichloromethane on a 0.59 mmol scale using 7a, after a reaction time of 60 min, triethylamine was added, and the mixture was stirred for a further 60 min (toluene) or 70 min (dichloromethane). Pentane/ ethyl acetate, 1:1 was used as eluent. Compound 20c was isolated as a mixture of 20c and 21c (toluene: 196 mg, 0.46 mmol, 78%, 74:26 20c/21c; dichloromethane: 186 mg, 0.44 mmol, 74%, 74:26 **20c/21c**) as a colourless solid. TLC (pentane/ethyl acetate, 1:1): $R_{\rm f}$ = 0.51; m.p. 156 °C (pentane). ¹H NMR (500 MHz, CDCl₃): δ = 7.92 (d, J = 8.4 Hz, 2 H, 2 H_{ortho}), 7.35 (d, J = 8.1 Hz, 2 H, 2 H_{meta}), 5.97 (s, 1 H, NH), 2.97 (s, 3 H, NCH₃), 2.89 (s, 3 H, NCH₃), 2.76 (s, 3 H, 3-CH₃), 2.43 (s, 3 H, CH₃Ar), 1.34 [s, 9 H, C(CH₃)₃] ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 176.1 (C-3), 164.7 (C-5), 162.8 (2-CONMe₂), 161.7 (2-CONHtBu), 146.0 (C_{ipso}), 136.3 (C_{para}), 130.1 (2 C, 2 C_{meta}), 128.6 (2 C, 2 C_{ortho}), 126.8 (C-4), 89.5 (C-2), 53.1 [C(CH₃)₃], 37.1 (NCH₃), 36.8 (NCH₃), 28.4 [3 C, $C(CH_3)_3$], 21.9 (CH₃Ar), 15.6 (3-CH₃) ppm. FTIR (neat): $\tilde{v} =$ 3350 (w), 2976 (w), 2933 (w), 1775 (m), 1684 (m), 1655 (m), 1618 (m), 1517 (m), 1455 (w), 1395 (m), 1362 (m), 1331 (m), 1260 (m), 1207 (m), 1156 (s), 1108 (m), 1051 (m), 987 (m), 901 (w), 814 (w), 756 (m), 704 (w), 660 (s), 609 (m), 558 (s), 516 (m), 492 (m) cm⁻¹. HRMS (ESI): calcd. for $C_{20}H_{27}N_2O_6S [M + H]^+ 423.1584$; found 423.1576.

Diethyl 5-(tert-Butylcarbamoyl)-5-(dimethylcarbamoyl)-4-methyl-2oxo-2,5-dihydrofuran-3-ylphosphonate (20d): Following general procedure D in dichloromethane on a 0.63 mmol scale using 7a, after a reaction time of 16.5 h, triethylamine was added, and the mixture was stirred for a further 7 h. tert-Butyl methyl ether was used as eluent. Compound 20d (96 mg, 0.24 mmol, 37%) was isolated as a colourless solid. TLC (ethyl acetate): $R_{\rm f} = 0.49$; m.p. 175 °C (pentane). ¹H NMR (500 MHz, CDCl₃): δ = 6.07 (s, 1 H, NH), 4.34– 4.15 [m, 4 H, P(OCH₂)₂], 3.07 (s, 3 H, NCH₃), 2.99 (s, 3 H, NCH₃), 2.66 (d, J = 2.8 Hz, 3 H, 3-CH₃), 1.42–1.37 [m, 6 H, P(OCH₂-CH₃)₂], 1.38 [s, 9 H, C(CH₃)₃] ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 181.6 (d, J = 13.2 Hz, C-4), 168.9 (d, J = 20.9 Hz, C-2), 163.4 $(5-CONMe_2)$, 162.6 (5-CONHtBu), 117.0 (d, J = 204.4 Hz, C-3), 90.8 (d, J = 17.2 Hz, C-5), 63.5 (d, J = 6.0 Hz, POCH₂), 63.2 (d, J $= 5.7 \text{ Hz}, \text{ POCH}_2$), 52.8 [C(CH₃)₃], 37.2 (NCH₃), 36.9 (NCH₃), 28.5 [3 C, C(CH₃)₃], 16.5 (d, J = 6.0 Hz, POCH₂CH₃), 16.4 (d, J= 6.4 Hz, POCH₂CH₃), 16.9 (d, J = 1.5 Hz, 4-CH₃) ppm. ³¹P NMR (202 MHz, CDCl₃): δ = 6.81 ppm. FTIR (neat): \tilde{v} = 3313 (w), 2971 (w), 2932 (w), 1769 (s), 1653 (s), 1620 (m), 1533 (m), 1452 (w), 1397 (m), 1367 (m), 1259 (s), 1220 (m), 1165 (m), 1103 (w), 1011 (s), 965 (s), 817 (w), 763 (m), 694 (w), 654 (w), 614 (m), 545 (m), 489 (m) cm⁻¹. HRMS (ESI): calcd. for $C_{17}H_{29}N_2O_7PNa$ $[M + Na]^+$ 427.1605; found 427.1606.

*N*²-*tert*-**Butyl**-*N*³,*N*³,2-*trimethyl*-5-oxo-2,5-*dihydrofuran*-2,3-*di*carboxamide (28a): From the reaction described above, 28a (10 mg, 0.04 mmol, 6%) was isolated as a colourless solid. TLC (ethyl acetate): $R_{\rm f} = 0.55$; m.p. 134 °C (pentane). ¹H NMR (400 MHz, CDCl₃): $\delta = 6.25$ (s, 1 H, N*H*), 5.92 (s, 1 H, 4-*H*), 3.05 (s, 3 H, NC*H*₃), 2.86 (s, 3 H, NC*H*₃), 1.87 (s, 3 H, 2-C*H*₃), 1.33 [s, 9 H, C(C*H*₃)₃] ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 169.8$ (C-5), 166.7 (2-CONH*t*Bu), 163.8 (C-3), 163.0 (3-CONMe₂), 116.4 (C-4), 89.7 (C-2), 51.9 [*C*(CH₃)₃], 38.4 (NC*H*₃), 34.6 (NC*H*₃), 28.6 [3 C, C(C*H*₃)₃], 24.5 (2-C*H*₃) ppm. FTIR (neat): $\tilde{v} = 3371$ (w), 3098 (w),



2970 (w), 2933 (w), 1772 (s), 1668 (s), 1630 (s), 1452 (m), 1404 (m), 1363 (m), 1283 (m), 1226 (s), 1160 (m), 1108 (m), 1060 (w), 1026 (m), 962 (m), 907 (m), 861 (m), 814 (w), 787 (w), 758 (w), 721 (w), 680 (w), 644 (w), 596 (m), 535 (w), 460 (w) cm⁻¹. HRMS (ESI): calcd. for $C_{13}H_{20}N_2O_4Na \ [M + Na]^+$ 291.1315; found 291.1315.

N-tert-Butyl-4-cyano-3-methyl-2-(morpholinocarbonyl)-5-oxo-2,5-dihydrofuran-2-carboxamide (20e): Following general procedure C in toluene on a 0.55 mmol scale, or in dichloromethane on a 0.54 mmol scale, using **7b**, after a reaction time of 70 min (toluene) or 40 min (dichloromethane), and using pentane/ethyl acetate, 2:1 as eluent, 20e (toluene: 160 mg, 0.48 mmol, 87%; dichloromethane: 156 mg, 0.47 mmol, 86%) was isolated as a colourless solid. TLC (pentane/ethyl acetate, 2:1): $R_{\rm f} = 0.46$; m.p. 148 °C (pentane). ¹H NMR (500 MHz, CDCl₃): δ = 6.30 (s, 1 H, NH), 3.79–3.39 [m, 8 H, N(C₂H₄)₂O], 2.60 (s, 3 H, 3-CH₃), 1.37 [s, 9 H, C(CH₃)₃] ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 181.2 (C-3), 165.9 (C-5), 161.3 [2-CON(C₂H₄)₂O], 161.0 (2-CONHtBu), 110.0 (4-CN), 104.9 (C-4), 91.4 (C-2), 66.5 (OCH₂), 66.2 (OCH₂), 53.4 [C(CH₃)₃], 46.5 (NCH₂), 43.4 (NCH₂), 28.3 [3 C, C(CH₃)₃], 16.9 (3-CH₃) ppm. FTIR (neat): $\tilde{v} = 3368$ (w), 2973 (w), 2927 (w), 2864 (w), 2243 (w), 1786 (s), 1690 (s), 1656 (s), 1520 (s), 1437 (m), 1368 (m), 1274 (s), 1249 (m), 1215 (s), 1114 (s), 1070 (m), 1017 (s), 936 (w), 909 (w), 885 (w), 850 (w), 823 (m), 754 (m), 696 (w), 665 (w), 823 (m), 754 (m), 696 (w), 665 (w), 588 (m), 541 (m), 490 (m), 449 (w) cm⁻¹. HRMS (APCI): calcd. for $C_{16}H_{22}N_3O_5 [M + H]^+$ 336.1554; found 336.1551.

Methyl 5-(tert-Butylcarbamoyl)-4-methyl-5-(morpholinocarbonyl)-2oxo-2,5-dihydrofuran-3-carboxylate (20f): Following general procedure D in dichloromethane on a 0.59 mmol scale using 7b, after a reaction time of 95 min, triethylamine was added, and the mixture was stirred for a further 20 min. Pentane/ethyl acetate, 2:1 was used as eluent. Compound 20f (178 mg, 0.48 mmol, 81%) was isolated as a colourless solid. TLC (pentane/ethyl acetate, 2:1): $R_{\rm f}$ = 0.30; m.p. 190 °C. ¹H NMR (500 MHz, CDCl₃): $\delta = 6.17$ (s, 1 H, NH), 3.88 (s, 3 H, OCH₃), 3.79-3.38 [m, 8 H, N(C₂H₄)₂O], 2.62 (s, 3 H, 4-CH₃), 1.34 [s, 9 H, C(CH₃)₃] ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 177.6 (C-4), 166.8 [5-CON(C₂H₄)₂O], 162.4 (C-2), 162.2 (5-CONHtBu), 161.1 (3-CO₂Me), 118.0 (C-3), 89.2 (C-5), 66.6 (OCH₂), 66.2 (OCH₂), 52.9 [C(CH₃)₃], 52.6 (OCH₃), 46.5 (NCH₂), 43.3 (NCH₂), 28.4 [3 C, C(CH₃)₃], 16.3 (4-CH₃) ppm. FTIR (neat): $\tilde{v} = 3341$ (m), 2970 (w), 2864 (w), 1784 (s), 1722 (m), 1680 (s), 1648 (s), 1529 (m), 1443 (m), 1360 (m), 1336 (m), 1277 (m), 1237 (m), 1209 (s), 1110 (m), 1059 (m), 1020 (s), 933 (w), 884 (w), 845 (w), 797 (m), 761 (w), 683 (w), 655 (w), 589 (m), 526 (w), 503 (w), 456 (w) cm⁻¹. HRMS (ESI): calcd. for $C_{17}H_{25}N_2O_7 [M + H]^+$ 369.1656; found 369.1660.

N-tert-Butyl-3-methyl-2-(morpholinocarbonyl)-5-oxo-4-tosyl-2,5dihydrofuran-2-carboxamide (20g): Following general procedure D in dichloromethane on a 0.54 mmol scale using 7b, after a reaction time of 3.2 h, triethylamine was added, and the mixture was stirred for a further 40 min. Diethyl ether was used as eluent. Compound 20g was isolated as a mixture of 20g and 21g (90 mg, 0.20 mmol, 36%, 87:13 20g/21g) as a colourless solid. TLC (pentane/ethyl acetate, 2:1): $R_f = 0.47$; m.p. 192 °C (pentane). ¹H NMR (500 MHz, CDCl₃): $\delta = 7.97$ (d, J = 8.4 Hz, 2 H, 2 H_{ortho}), 7.40 (d, J = 8.1 Hz, 2 H, 2 H_{meta}), 5.92 (s, 1 H, NH), 3.93–3.36 [m, 8 H, N(C₂H₄)₂O], 2.80 (s, 3 H, 3-CH₃), 2.47 (s, 3 H, CH₃Ar), 1.38 [s, 9 H, C(CH₃)₃] ppm. ¹³C NMR (125 MHz, CDCl₃): $\delta = 175.7$ (C-3), 164.5 (C-5), 161.7 [2-CON(C₂H₄)₂O], 161.6 (2-CONH*t*Bu), 146.1 (C_{ipso}), 136.2 (C_{para}), 130.2 (2 C, 2 C_{meta}), 128.7 (2 C, 2 C_{ortho}), 127.0 (C-4), 89.3 (C-2), 66.6 (OCH₂), 66.1 (OCH₂), 53.2 [C(CH₃)₃], 46.4 (NCH₂), 43.3 (N*C*H₂), 28.4 [3 C, C(*C*H₃)₃], 21.9 (*C*H₃Ar), 15.5 (3-*C*H₃) ppm. FTIR (neat): $\tilde{\nu}$ = 3424 (w), 2975 (w), 2928 (w), 2865 (w), 1795 (s), 1685 (m), 1647 (s), 1600 (w), 1515 (m), 1452 (m), 1397 (w), 1364 (w), 1325 (m), 1301 (w), 1274 (m), 1222 (s), 1149 (s), 1110 (m), 1065 (w), 1003 (s), 956 (w), 927 (w), 884 (w), 857 (w), 815 (m), 791 (w), 755 (m), 732 (w), 703 (w), 660 (s), 588 (s), 522 (s), 485 (w), 459 (w), 409 (w) cm⁻¹. HRMS (ESI): calcd. for C₂₂H₂₈N₂O₇SNa [M + Na]⁺ 487.1509; found 487.1505.

Diethyl 5-(tert-Butylcarbamoyl)-4-methyl-5-(morpholinocarbonyl)-2oxo-2,5-dihydrofuran-3-ylphosphonate (20h): Following general procedure D in dichloromethane on a 0.51 mmol scale using 7b, after a reaction time of 16.5 h, triethylamine was added, and the mixture was stirred for a further 7 h. tert-Butyl methyl ether/ethyl acetate was used as eluent. Compound 20h (41 mg, 0.09 mmol, 18%) was isolated as a colourless solid. TLC (ethyl acetate): $R_{\rm f} = 0.47$; m.p. 166 °C (CDCl₃). ¹H NMR (500 MHz, CDCl₃): δ = 5.96 (s, 1 H, NH), 4.31-4.12 [m, 4 H, P(OCH₂)₂], 3.80-3.36 [m, 8 H, $N(C_2H_4)_2O$], 2.62 (d, J = 2.8 Hz, 3 H, 3- CH_3), 1.36 (d, J = 7.1 Hz, 3 H, POCH₂CH₃), 1.36 (d, J = 7.1 Hz, 3 H, POCH₂CH₃), 1.34 [s, 9 H, C(CH₃)₃] ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 181.0 (d, J = 13.3 Hz, C-4), 168.7 (d, J = 20.8 Hz, C-2), 162.5 (5-CONHtBu), 162.2 [5-CON(C₂H₄)₂O], 117.3 (d, J = 204.8 Hz, C-3), 90.6 (d, J = 17.4 Hz, C-5), 66.6 (OCH₂), 66.2 (OCH₂), 63.6 (d, J = 5.9 Hz, $POCH_2$), 63.2 (d, J = 5.8 Hz, $POCH_2$), 52.8 [$C(CH_3)_3$], 46.5 (NCH_2) , 43.3 (NCH_2) , 28.4 [3 C, $C(CH_3)_3$], 16.5 (d, J = 6.0 Hz, POCH₂*C*H₃), 16.4 (d, *J* = 6.4 Hz, POCH₂*C*H₃), 16.9 (d, *J* = 1.8 Hz, 4-*C*H₃) ppm. ³¹P NMR (202 MHz, CDCl₃): δ = 6.70 ppm. FTIR (neat): $\tilde{v} = 3285$ (w), 2984 (w), 2914 (w), 2862 (w), 1775 (s), 1677 (m), 1655 (s), 1623 (m), 1539 (m), 1444 (m), 1391 (w), 1366 (m), 1265 (s), 1221 (m), 1196 (m), 1111 (m), 1063 (w), 1006 (s), 970 (s), 848 (w), 821 (w), 768 (m), 689 (w), 656 (w), 618 (m), 589 (m), 548 (m), 501 (w), 461 (w), 433 (w) cm⁻¹. HRMS (ESI): calcd. for $C_{19}H_{31}N_2O_8PNa [M + Na]^+$ 469.1710; found 469.1717.

N-tert-Butyl-2-methyl-3-(morpholinocarbonyl)-5-oxo-2,5-dihydrofuran-2-carboxamide (28b): From the reaction described above, 28b (9 mg, 0.03 mmol, 6%) was isolated as a colourless solid. TLC (ethyl acetate): $R_{\rm f} = 0.60$; m.p. 144 °C (CDCl₃). ¹H NMR $(500 \text{ MHz}, \text{CDCl}_3): \delta = 6.23 \text{ (s, 1 H, NH)}, 5.91 \text{ (s, 1 H, 4-H)}, 3.93$ $(dt, J = 13.4, J = 4.1 Hz, 1 H, NCH_2), 3.77-3.73 (m, 2 H, 2 OCH_2),$ $3.72-3.66 \text{ (m, 1 H, OC}H_2), 3.59 \text{ (ddd, } J = 11.5, J = 5.5, J = 3.3 \text{ Hz},$ 1 H, OC H_2), 3.53 (ddd, J = 13.4, J = 6.5, J = 4.6 Hz, 1 H, NC H_2), 3.30 (ddd, J = 13.2, J = 7.5, J = 3.2 Hz, 1 H, NCH₂), 3.20 (ddd, J $= 13.3, J = 4.8, J = 3.1 \text{ Hz}, 1 \text{ H}, \text{NC}H_2$, 1.88 (s, 3 H, 2-CH₃), 1.32 [s, 9 H, C(CH₃)₃] ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 169.4 (C-5), 166.6 (2-CONHtBu), 162.9 (C-3), 161.7 [3-CON(C₂H₄)₂O], 116.7 (C-4), 89.7 (C-2), 66.6 (OCH₂), 66.5 (OCH₂), 52.0 [C(CH₃)₃], 47.3 (NCH₂), 41.9 (NCH₂), 28.6 [3 C, C(CH₃)₃], 24.5 $(2-CH_3)$ ppm. FTIR (neat): $\tilde{v} = 3355$ (m), 3111 (w), 2974 (w), 2918 (w), 2864 (w), 1762 (s), 1667 (s), 1643 (s), 1617 (s), 1523 (s), 1549 (m), 1435 (s), 1397 (w), 1366 (m), 1300 (m), 1227 (s), 1143 (m), 1107 (s), 1063 (m), 999 (m), 962 (m), 912 (m), 872 (m), 837 (m), 807 (w), 773 (w), 737 (w), 624 (m), 589 (m), 555 (w), 520 (w), 457 (w), 410 (w) cm⁻¹. HRMS (ESI): calcd. for $C_{15}H_{22}N_2O_5Na [M + Na]^+ 333.1421$; found 333.1419.

N-tert-Butyl-3-methyl-2-(morpholinocarbonyl)-5-oxo-2,5-dihydrofuran-2-carboxamide (29): From the reaction described above, 29 (11 mg, 0.04 mmol, 7%) was isolated as a colourless liquid. TLC (ethyl acetate): $R_f = 0.74$. ¹H NMR (500 MHz, CDCl₃): $\delta = 5.99$ (s, 1 H, NH), 5.86 (q, J = 1.5 Hz, 1 H, 4-H), 3.78–3.40 [m, 8 H, N(C₂H₄)₂O], 2.34 (d, J = 1.5 Hz, 3 H, 3-CH₃), 1.34 [s, 9 H, C(CH₃)₃] ppm. ¹³C NMR (125 MHz, CDCl₃): $\delta = 171.1$ (C-5), 170.5 (C-3), 163.6 (2-CONH*t*Bu), 162.7 [3-CON(C₂H₄)₂O], 115.9 (C-4), 90.5 (C-2), 66.7 (OCH₂), 66.3 (OCH₂), 52.5 [*C*(CH₃)₃], 46.5 (NCH₂), 43.3 (NCH₂), 28.5 [3 C, C(CH₃)₃], 15.7 (3-CH₃) ppm. FTIR (neat): $\tilde{v} = 3341$ (w), 2971 (w), 2925 (w), 2862 (w), 1767 (s), 1653 (s), 1522 (m), 1439 (m), 1367 (m), 1275 (m), 1248 (m), 1200 (m), 1110 (s), 1072 (w), 1030 (m), 995 (m), 911 (m), 849 (m), 753 (m), 656 (w), 588 (m), 509 (w), 454 (w) cm⁻¹. HRMS (ESI): calcd. for C₁₅H₂₃N₂O₅ [M + H]⁺ 311.1601; found 311.1610.

(2R*,3S*,4S*)-N-tert-Butyl-4-chloro-3-hydroxy-N,N,3-trimethyl-5-oxodihydrofuran-2,2(3H)-dicarboxamide (22): Chloroacetate 18d (50 mg, 0.16 mmol) was dissolved in tetrahydrofuran (2 mL), and the solution was cooled to -78 °C. Lithium hexamethyldisilazide (1 M in tert-butyl methyl ether; 0.17 mL, 0.17 mmol) was added, and the reaction mixture was stirred for 6 h at -78 °C. Then, the reaction mixture was poured into ammonium chloride solution (saturated aq.; 20 mL), and the mixture was extracted with dichloromethane (3×20 mL). The combined organic extracts were dried with sodium sulfate, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica (pentane/ethyl acetate, 2:1). Aldol addition product 22 (10.5 mg, 0.033 mmol, 21%) was obtained as a colourless solid. TLC (pentane/ethyl acetate, 2:1): $R_{\rm f} = 0.32$; m.p. 144 °C (chloroform). ¹H NMR (500 MHz, CDCl₃): δ = 6.50 (s, 1 H, NH), 4.73 (s, 1 H, 4-H), 3.99 (s, 1 H, OH), 3.13 (s, 3 H, NCH₃), 3.05 (s, 3 H, NCH₃), 1.64 (s, 3 H, 3-CH₃), 1.37 [s, 9 H, C(CH₃)₃] ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 169.1 (C-5), 167.5 (2-CONMe₂), 163.3 (2-CONHtBu), 89.6 (C-2), 80.4 (C-3), 59.7 (C-4), 52.9 [C(CH₃)₃], 38.6 (NCH₃), 37.8 (NCH₃), 28.5 [3 C, $C(CH_3)_3$], 22.2 (3-CH₃) ppm. FTIR (neat): $\tilde{v} = 3478$ (w), 3389 (w), 2961 (w), 2921 (m), 2852 (w), 1804 (s), 1737 (w), 1683 (m), 1636 (s), 1517 (m), 1456 (m), 1375 (m), 1262 (m), 1207 (m), 1174 (s), 1116 (m), 1062 (m), 1028 (m), 1000 (w), 956 (s), 894 (w), 834 (w), 793 (w), 732 (w), 673 (m), 649 (w), 529 (s), 483 (m), 405 (m) cm⁻¹. HRMS (ESI): calcd. for $C_{13}H_{21}ClN_2O_5Na [M + Na]^+ 343.1031$; found 343.1032.

4-Isocyanobutan-2-one (24): In a flame-dried flask under an inert gas atmosphere, dichloromethane (123 mL) was cooled to 0 °C, and triethylamine (18.1 mL, 130 mmol) was added. N-(3-Oxobutyl)formamide 23 (5.0 g, 43.4 mmol; prepared according to Brederek et al.^[45]) was added in one portion, and then phosphoryl chloride (4.0 mL, 43.4 mmol) was added dropwise by syringe. The reaction mixture was stirred for 40 min at 0 °C. The reaction mixture was allowed to warm to room temperature, then it was stirred for 30 min at room temperature. The reaction mixture was poured into ammonium chloride solution (saturated aq.; 150 mL), and the phases were separated. The aqueous phase was extracted with dichloromethane (3×150 mL), and the combined organic extracts were dried with sodium sulfate. The solvent was evaporated under reduced pressure with the temperature kept below 18 °C. Vacuum distillation (45 °C, 1.3 mbar) gave keto-isocyanide 24 (2.16 g, 22.3 mmol, 51%) as a colourless liquid. TLC (pentane/ethyl acetate, 2:1): $R_{\rm f} = 0.38$. b.p. 45 °C (1.3 mbar). ¹H NMR (300 MHz, CDCl₃): δ = 3.63 (tt, J = 6.8, J = 2.0 Hz, 2 H, 4-H₂), 2.86 (tt, J = 6.7, J = 1.8 Hz, 2 H, 3-H₂), 2.20 (s, 3 H, 1-H₃) ppm. ¹³C NMR $(75 \text{ MHz}, \text{CDCl}_3)$: $\delta = 203.7 \text{ (C-2)}, 157.1 \text{ (t, } J = 5.2 \text{ Hz}, \text{ NC}), 42.6$ (C-3), 36.1 (t, J = 7.2 Hz, C-4), 30.1 (C-1) ppm. FTIR (neat): $\tilde{v} =$ 2958 (w), 2153 (m), 1716 (s), 1440 (w), 1412 (w), 1369 (m), 1270 (w), 1169 (m), 1075 (w), 1036 (w), 993 (w), 952 (w), 792 (w), 748 (w), 583 (w), 493 (m) cm^{-1} . HRMS (ESI): calcd. for $C_5H_7NONa [M + Na]^+ 120.0420$; found 120.0421.

2-(Morpholinocarbonyl)-1,3-dioxo-1-(tosylmethylamino)butan-2-yl Acetate (26a): Following general procedure C in dichloromethane on a 0.54 mmol scale using **7b**, after a reaction time of 24 h, and using *tert*-butyl methyl ether as eluent, **26a** (219 mg, 0.50 mmol, 92%) was isolated as a colourless solid. TLC (tert-butyl methyl ether): $R_{\rm f} = 0.18$; m.p. 75 °C (chloroform). ¹H NMR (400 MHz, CDCl₃): δ = 8.58 (br. s, 1 H, N*H*), 7.73 (d, *J* = 8.3 Hz, 2 H, 2 H_{ortho}), 7.35 (d, J = 8.2 Hz, 2 H, 2 H_{meta}), 4.75 (dd, J = 14.1, J = 14.17.0 Hz, 1 H, NHC H_2), 4.62 (dd, J = 14.1, J = 6.6 Hz, 1 H, NHCH₂), 3.82–3.39 [m, 8 H, N(C₂H₄)₂O], 2.44 (s, 3 H, CH₃Ar), 2.24 (s, 3 H, CH₃CO₂), 2.19 (s, 3 H, 4-H₃) ppm. ¹³C NMR $(75 \text{ MHz}, \text{CDCl}_3)$: $\delta = 197.1 (\text{C-3}), 168.6 (CO_2), 163.1 (\text{C-1}), 162.3$ [2-CON(C₂H₄)₂O], 145.5 (C_{ipso}), 134.3 (C_{para}), 130.2 (2 C, 2 C_{meta}), 128.9 (2 C, 2 Cortho), 87.3 (C-2), 66.5 (2 C, 2 OCH2), 60.6 (NHCH2), 47.1 (NCH₂), 44.2 (NCH₂), 25.5 (C-4), 21.8 (CH₃Ar), 20.6 (CH_3CO_2) ppm. FTIR (neat): $\tilde{v} = 3336$ (w), 3935 (w), 3858 (w), 2120 (w), 1759 (m), 1733 (m), 1699 (s), 1643 (s), 1598 (w), 1516 (m), 1435 (m), 1365 (w), 1321 (m), 1294 (m), 1215 (s), 1141 (s), 1113 (s), 1083 (m), 1020 (w), 975 (m), 933 (w), 886 (w), 857 (w), 817 (m), 752 (m), 668 (w), 565 (s), 511 (s), 455 (m), 411 (w) cm⁻¹. HRMS (ESI): calcd. for $C_{19}H_{24}N_2O_8SNa [M + Na]^+ 463.1146$; found 463.1147.

Methyl 2-[2-Acetoxy-2-(morpholinocarbonyl)-3-oxobutanamido]acetate (26b): Following general procedure C in dichloromethane on a 0.54 mmol scale using 7b, after a reaction time of 20 h, and using tert-butyl methyl ether as eluent, 26b (162 mg, 0.47 mmol, 87%) was isolated as a colourless solid. TLC (ethyl acetate): $R_{\rm f}$ = 0.51; m.p. 105 °C. ¹H NMR (400 MHz, CDCl₃): δ = 8.02 (br. s, 1 H, NH), 4.10 (dd, J = 17.9, J = 5.6 Hz, 1 H, NHCH₂), 4.04 $(dd, J = 18.0, J = 5.7 Hz, 1 H, NHCH_2), 3.92-3.40 [m, 8 H,$ N(C₂H₄)₂O], 3.75 (s, 3 H, OCH₃), 2.31 (s, 3 H, 4-H₃), 2.28 (s, 3 H, CH_3CO_2) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 196.8 (C-3), 169.2 (CO₂Me), 168.8 (CH₃CO₂), 163.2 (C-1), 162.6 [2-CON(C₂H₄)₂O], 87.9 (C-2), 66.7 (2 C, 2 OCH₂), 52.6 (OCH₃), 47.0 (NCH₂), 44.0 (NCH₂), 41.8 (NHCH₂), 25.9 (C-4), 20.7 (CH₃CO₂) ppm. FTIR (neat): $\tilde{v} = 3304$ (w), 2926 (w), 2863 (w), 1742 (s), 1678 (m), 1645 (s), 1511 (m), 1438 (m), 1367 (m), 1304 (w), 1258 (m), 1204 (s), 1170 (s), 1108 (s), 1066 (w), 1019 (w), 978 (m), 933 (w), 892 (w), 865 (w), 804 (w), 713 (m), 687 (w), 657 (w), 588 (m), 528 (m), 467 (m) cm⁻¹. HRMS (ESI): calcd. for $C_{14}H_{20}N_2O_8Na [M + Na]^+$ 367.1112; found 367.1112.

1-[(Diethoxyphosphoryl)methylamino]-2-(morpholinocarbonyl)-1,3-dioxobutan-2-yl Acetate (26c): Following general procedure C in dichloromethane on a 0.54 mmol scale using 7b, after a reaction time of 24 h, and using chloroform/methanol, 20:1 as eluent, 26c (228 mg, 0.54 mmol, 100%) was isolated as a colourless liquid. TLC (chloroform/methanol, 20:1): $R_f = 0.36$. ¹H NMR (300 MHz, CDCl₃): δ = 8.06 (br. s, 1 H, N*H*), 4.15 (ddd, *J* = 8.1, *J* = 7.0, *J* = 6.0 Hz, 2 H, POCH₂), 4.11 (ddd, J = 8.1, J = 7.1, J = 5.9 Hz, 2 H, $POCH_2$), 3.79 (ddd, J = 15.8, J = 12.4, J = 6.3 Hz, 1 H, NHC H_2), 3.69 (ddd, J = 15.8, J = 12.2, J = 5.8 Hz, 1 H, NHCH₂), 3.71–3.44 [m, 8 H, N(C₂H₄)₂O], 2.28 (s, 3 H, 4-H₃), 2.27 (s, 3 H, CH₃CO₂) 1.32 [dt, J = 6.9, J = 5.8 Hz, 6 H, P(OCH₂CH₃)₂] ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 196.9 (C-3), 168.7 (CH₃CO₂), 162.8 (d, J = 5.9 Hz, C-1), 162.8 [2-CON(C₂H₄)₂O], 87.6 (C-2), 66.6 (2 C, 2 OCH_2), 62.8 [d, J = 6.5 Hz, 2 C, $P(OCH_2)_2$], 47.0 (NCH₂), 44.0 (NCH_2) , 35.7 (d, J = 156.8 Hz, $NHCH_2$), 25.7 (C-4), 20.7 $(CH_{3}CO_{2})$, 16.5 (d, J = 5.1 Hz, POCH₂CH₃), 16.5 (d, J = 5.0 Hz, POCH₂*C*H₃) ppm. ³¹P NMR (202 MHz, CDCl₃): δ = 21.5 ppm. FTIR (neat): $\tilde{v} = 3547$ (w), 2984 (w), 2927 (w), 2862 (w), 2152 (w), 1765 (w), 1734 (m), 1689 (m), 1648 (m), 1526 (w), 1437 (m), 1369 (w), 1367 (w), 1302 (w), 1215 (s), 1111 (m), 1018 (s), 970 (s), 857 (w), 823 (w), 791 (w), 702 (w), 658 (w), 599 (w), 533 (m), 453 (w) cm⁻¹. HRMS (ESI): calcd. for $C_{16}H_{27}N_2O_9PNa$ [M + Na]⁺ 445.1346; found 445.1347.



2-(Morpholinocarbonyl)-1-(naphthalen-2-ylamino)-1,3-dioxobutan-2-yl Acetate (26d): Following general procedure C in dichloromethane on a 0.54 mmol scale using 7b, after a reaction time of 21.5 h, and using diethyl ether as eluent, 26d (209 mg, 0.52 mmol, 97%) was isolated as a pale yellow solid. TLC (diethyl ether): $R_{\rm f} = 0.31$; m.p. 74 °C (chloroform). ¹H NMR (500 MHz, CDCl₃): $\delta = 10.14$ (s, 1 H, N*H*), 8.21 (d, J = 2.0 Hz, 1 H, 1'-*H*), 7.82–7.76 (m, 3 H, 4'-H, 5'-H, 8'-H), 7.49 (dd, J = 8.8, J = 2.2 Hz, 1 H, 3'-H), 7.46 (ddd, J = 7.8, J = 7.1, J = 1.5 Hz, 1 H, 7'-H), 7.42 (ddd, J = 7.9, J) $J = 7.0, J = 1.6 \text{ Hz}, 1 \text{ H}, 6'-H), 3.99-3.49 \text{ [m, 8 H, N(C_2H_4)_2O]},$ 2.37 (s, 3 H, 4-H₃), 2.34 (s, 3 H, CH₃CO₂) ppm. ¹³C NMR $(75 \text{ MHz}, \text{CDCl}_3)$: $\delta = 198.0 (C-3), 168.9 (CH_3CO_2), 163.1 [2-$ CON(C₂H₄)₂O], 160.5 (C-1), 134.6 (C-2'), 133.9 (C-8a'), 131.2 (C-4a'), 129.0, 127.9, 127.7, 126.8 (C-7'), 125.5 (C-6'), 120.3 (C-3'), 117.5 (C-1'), 87.5 (C-2), 66.8 (2 C, 2 OCH2), 47.2 (NCH2), 44.2 (NCH_2) , 25.8 (C-4), 20.7 (CH_3CO_2) ppm. FTIR (neat): $\tilde{v} =$ 3316 (w), 3054 (w), 2966 (w), 2922 (w), 2856 (w), 1759 (m), 1731 (m), 1694 (s), 1640 (s), 1594 (m), 1543 (s), 1502 (m), 1431 (s), 1359 (s), 1299 (w), 1216 (s), 1109 (s), 1019 (m), 973 (m), 933 (w), 888 (m), 854 (m), 813 (m), 749 (m), 703 (w), 662 (w), 594 (m), 521 (w), 474 (m), 427 (w) cm⁻¹. HRMS (ESI): calcd. for $C_{21}H_{22}N_2O_6Na \ [M + Na]^+ 421.1370;$ found 421.1372.

1-(4-Methoxyphenylamino)-2-(morpholinocarbonyl)-1,3-dioxobutan-2-yl Acetate (26e): Following general procedure C in dichloromethane on a 0.54 mmol scale using 7b, after a reaction time of 21 h, and using tert-butyl methyl ether as eluent, 26e (205 mg, 0.54 mmol, 100%) was isolated as an orange solid. TLC (tert-butyl methyl ether): $R_f = 0.29$; m.p. 154 °C (chloroform). ¹H NMR $(500 \text{ MHz}, \text{ CDCl}_3)$: $\delta = 9.73$ (s, 1 H, NH), 7.46–7.41 (m, 2 H, 2 Hortho), 6.88-6.84 (m, 2 H, 2 H_{meta}), 3.96-3.44 [m, 8 H, N(C₂H₄) ₂O], 3.79 (s, 3 H, OCH₃), 2.33 (s, 3 H, 4-H₃), 2.31 (s, 3 H, CH₃CO₂) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 198.1 (C-3), 169.0 (CH₃CO₂), 163.0 [2-CON(C₂H₄)₂O], 160.1 (C-1), 157.1 (C_{para}), 130.3 (Cipso), 122.1 (2 C, 2 Cortho), 114.3 (2 C, 2 Cmeta), 87.4 (C-2), 66.7 (2 C, 2 OCH₂), 55.6 (OCH₃), 47.2 (NCH₂), 44.2 (NCH₂), 25.9 (C-4), 20.7 (CH₃CO₂) ppm. FTIR (neat): $\tilde{v} = 3318$ (w), 2926 (w), 2855 (w), 1760 (m), 1731 (m), 1690 (s), 1643 (s), 1600 (m), 1512 (s), 1437 (m), 1363 (m), 1302 (w), 1219 (s), 1177 (s), 1108 (s), 1026 (s), 976 (m), 935 (w), 900 (w), 828 (s), 753 (m), 664 (w), 596 (m), 517 (m), 452 (m) cm⁻¹. HRMS (ESI): calcd. for $C_{18}H_{23}N_2O_7$ [M + H]⁺ 379.1500; found 379.1505.

2-(Morpholinocarbonyl)-1,3-dioxo-1-(3-oxobutylamino)butan-2-yl Acetate (26f): Following general procedure C in dichloromethane on a 0.62 mmol scale using 7b, after a reaction time of 16 h, and using ethyl acetate as eluent, 26f (210 mg, 0.61 mmol, 99%) was isolated as a colourless liquid. TLC (ethyl acetate): $R_{\rm f} = 0.29$. ¹H NMR (400 MHz, CDCl₃): δ = 7.82 (br. s, 1 H, N*H*), 3.78–3.45 [m, 10 H, N(C₂ H_4)₂O, 1'- H_2], 2.69 (dt, J = 6.2, J = 3.2 Hz, 2 H, 2'-H₂), 2.27 (s, 3 H, 4-H₃), 2.26 (s, 3 H, CH₃CO₂), 2.15 (s, 3 H, 4'- H_3) ppm. ¹³C NMR (75 MHz, CDCl₃): $\delta = 207.0$ (C-3'), 197.2 (C-3), 168.8 (CH₃CO₂), 162.9 [2-CON(C₂H₄)₂O], 162.8 (C-1), 87.8 (C-2), 66.7 (2 C, 2 OCH₂), 46.9 (NCH₂), 44.0 (NCH₂), 42.6 (C-2'), 35.2 (C-1'), 30.2 (C-4'), 25.9 (C-4), 20.8 (CH₃CO₂) ppm. FTIR (neat): $\tilde{v} = 3599$ (w), 3348 (w), 2926 (w), 2860 (w), 1761 (m), 1683 (s), 1644 (s), 1522 (m), 1433 (m), 1363 (m), 1302 (w), 1215 (s), 1174 (s), 1111 (s), 1020 (m), 976 (m), 932 (w), 891 (w), 858 (w), 833 (w), 803 (w), 754 (w), 662 (w), 598 (m), 523 (m), 453 (m), 410 (w) cm⁻¹. HRMS (ESI): calcd. for $C_{15}H_{22}N_2O_7Na [M + Na]^+$ 365.1319; found 365.1318.

4-Cyano-3-methyl-2-(morpholinocarbonyl)-5-oxo-*N*-(tosylmethyl)-**2,5-dihydrofuran-2-carboxamide (27a):** Following general procedure C in dichloromethane on a 0.54 mmol scale using **7b**, after a reac-

tion time of 24 h, and using diethyl ether as eluent, 27a (139 mg, 0.31 mmol, 27%) was isolated as a colourless solid. TLC (tert-butyl methyl ether): $R_{\rm f} = 0.36$; m.p. 180 °C (chloroform, decomp.). ¹H NMR (500 MHz, CDCl₃): δ = 7.75 (d, J = 8.3 Hz, 2 H, 2 H_{ortho}), 7.43 (d, J = 8.0 Hz, 2 H, 2 H_{meta}), 7.39 (t, J = 6.5 Hz, 1 H, NH), 4.67 (dd, J = 14.2, J = 6.7 Hz, 1 H, NHC H_2), 4.64 (dd, J = 14.5, J = 6.8 Hz, 1 H, NHC H_2), 3.78–3.31 [m, 8 H, N(C₂ H_4)₂O], 2.49 (s, 3 H, CH₃Ar), 2.39 (s, 3 H, 3-CH₃) ppm. ¹³C NMR (125 MHz, $CDCl_3$): $\delta = 180.0 (C-3), 164.3 (C-5), 162.7 [2-CON(C_2H_4)_2O],$ 160.3 (2-CONH), 146.6 (Cipso), 133.6 (Cpara), 130.6 (2 C, 2 Cmeta), 128.7 (2 C, 2 Cortho), 109.4 (4-CN), 105.5 (C-4), 90.3 (C-2), 66.5 (2 C, 2 OCH₂), 59.9 (NHCH₂), 46.7 (NCH₂), 43.6 (NCH₂), 21.9 (CH_3Ar) , 16.8 (3- CH_3) ppm. FTIR (neat): $\tilde{v} = 3298$ (w), 2925 (w), 2868 (w), 2238 (w), 1795 (s), 1695 (s), 1653 (s), 1597 (w), 1534 (m), 1509 (m), 1438 (m), 1398 (w), 1374 (w), 1315 (m), 1266 (m), 1216 (m), 1112 (s), 1077 (s), 1029 (s), 927 (m), 873 (w), 844 (w), 812 (m), 751 (m), 713 (w), 658 (m), 597 (s), 559 (m), 506 (s), 436 (m), 408 (w) cm⁻¹. HRMS (ESI): calcd. for C₂₀H₂₁N₃O₇SNa $[M + Na]^+$ 470.0992; found 470.0997.

Methyl 2-[4-Cyano-3-methyl-2-(morpholinocarbonyl)-5-oxo-2,5-dihydrofuran-2-carboxamido]acetate (27b): Following general procedure C in dichloromethane on a 0.59 mmol scale using 7b, after a reaction time of 19 h, and using chloroform/tert-butyl methyl ether as eluent, 27b (133 mg, 0.38 mmol, 64%) was isolated as a colourless solid. TLC (pentane/ethyl acetate, 1:1): $R_{\rm f} = 0.31$; m.p. 206 °C (acetone). ¹H NMR [500 MHz, (CD₃)₂CO]: δ = 8.56 (br. s, 1 H, NH), 4.14 (dd, J = 17.4, J = 6.6 Hz, 1 H, CH₂NH), 3.93 (dd, J = 17.4, J = 5.6 Hz, 1 H, CH₂NH), 3.71 (s, 3 H, OCH₃), 3.69-3.41 [m, 8 H, N(C₂ H_4)₂O], 2.56 (s, 3 H, 3-C H_3) ppm. ¹³C NMR $[125 \text{ MHz}, (\text{CD}_3)_2\text{CO}]: \delta = 180.9 \text{ (C-3)}, 170.3 \text{ (CO}_2\text{Me)}, 165.7 \text{ (C-}$ 5), 164.1 (2-CONH), 162.0 [2-CON(C₂H₄)₂O], 111.0 (4-CN), 105.8 (C-4), 91.9 (C-2), 67.1 (OCH₂), 67.0 (OCH₂), 52.7 (OCH₃), 47.6 (NCH₂), 44.0 (NCH₂), 41.8 (NHCH₂), 16.9 (3-CH₃) ppm. FTIR (neat): $\tilde{v} = 3506$ (w), 3353 (w), 2926 (w), 2861 (w), 2235 (w), 1799 (s), 1751 (w), 1691 (s), 1656 (s), 1531 (w), 1439 (m), 1370 (m), 1251 (m), 1212 (s), 1142 (m), 1115 (m), 1015 (s), 932 (w), 877 (w), 848 (w), 817 (w), 760 (w), 703 (w), 668 (w), 591 (m), 548 (w), 502 (w), 436 (w) cm⁻¹. HRMS (ESI): calcd. for $C_{15}H_{17}N_3O_7Na$ [M + Na]⁺ 374.0959; found 374–0967.

Diethyl [4-Cyano-3-methyl-2-(morpholinocarbonyl)-5-oxo-2,5-dihydrofuran-2-carboxamido|methylphosphonate (27c): Following general procedure C in dichloromethane on a 0.54 mmol scale using 7b, after a reaction time of 24 h, and using ethyl acetate as eluent, 27c (190 mg, 0.44 mmol, 82%) was isolated as a colourless solid. TLC (ethyl acetate): $R_{\rm f} = 0.22$; m.p. 180 °C (chloroform). ¹H NMR $(500 \text{ MHz}, \text{ CDCl}_3)$: $\delta = 7.42$ (t, J = 5.4 Hz, 1 H, NH), 4.19-4.10[m, 4 H, $P(OCH_2)_2$], 3.81 (ddd, J = 15.7, J = 12.5, J = 6.7 Hz, 1 H, NHC H_2), 3.77–3.35 [m, 8 H, N(C₂ H_4)₂O], 3.55 (ddd, J = 13.5, J = 5.8, J = 3.9 Hz, 1 H, NHCH₂), 2.59 (s, 3 H, 3-CH₃), 1.35 [dt, J = 7.1, J = 3.2 Hz, 6 H, P(OCH₂CH₃)₂] ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 179.9 (C-3), 164.7 (C-5), 162.4 (d, J = 3.8 Hz, 2-CONH), 161.0 [2-CON(C₂H₄)₂O], 109.7 (4-CN), 105.5 (C-4), 90.7 (C-2), 66.6 (OCH₂), 66.4 (OCH₂), 63.3 (d, J = 6.5 Hz, POCH₂), 63.2 (d, J = 6.6 Hz, POCH₂), 46.7 (NCH₂), 43.5 (NCH₂), 35.5 (d, J = 157.3 Hz, NHCH₂), 16.9 (3-CH₃), 16.6 [d, J = 5.6 Hz, 2 C, $P(OCH_2CH_3)_2$] ppm. FTIR (neat): $\tilde{v} = 3207$ (w), 3045 (w), 2983 (w), 2928 (w), 2872 (w), 2239 (w), 1788 (m), 1688 (m), 1653 (s), 1543 (w), 1438 (m), 1397 (w), 1372 (w), 1308 (w), 1267 (m), 1205 (s), 971 (m), 909 (m), 870 (w), 843 (w), 813 (w), 753 (m), 659 (w), 600 (m), 543 (w), 486 (m), 411 (w) cm⁻¹. HRMS (ESI): calcd. for $C_{17}H_{24}N_3O_8PNa [M + Na]^+ 452.1193$; found 452.1194.

4-Cyano-3-methyl-2-(morpholinocarbonyl)-N-(naphthalen-2-yl)-5oxo-2,5-dihydrofuran-2-carboxamide (27d): Following general procedure C in dichloromethane on a 0.54 mmol scale using 7b, after a reaction time of 19 h, and using pentane/ethyl acetate, 3:1 as eluent, 27d (145 mg, 0.36 mmol, 66%) was isolated as a brown oil. TLC (pentane/ethyl acetate, 3:1): $R_f = 0.20$. ¹H NMR (500 MHz, $CDCl_3$): $\delta = 8.54$ (s, 1 H, NH), 8.25 (d, J = 2.1 Hz, 1 H, 1'-H), 7.90-7.80 (m, 3 H, 4'-H, 5'-H, 8'-H), 7.57-7.45 (m, 3 H, 3'-H, 6'-H, 7'-H), 3.90–3.47 [m, 8 H, N(C₂H₄)₂O], 2.72 (s, 3 H, 3-CH₃) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 181.0 (C-3), 165.7 (C-5), 161.0 [2-CON(C₂H₄)₂O], 169.9 (2-CONH), 133.6 (C-2'), 133.1 (C-8a'), 131.6 (C-4a'), 129.6, 128.0, 127.9, 127.3 (C-7'), 126.3 (C-6'), 119.4 (C-3'), 118.0 (C-1'), 109.7 (4-CN), 105.5 (C-4), 91.2 (C-2), 66.6 (OCH₂), 66.2 (OCH₂), 46.6 (NCH₂), 43.7 (NCH₂), 17.2 (3- CH_3) ppm. FTIR (neat): $\tilde{v} = 3341$ (w), 3059 (w), 2970 (w), 2924 (w), 2861 (w), 2249 (w), 1793 (m), 1692 (m), 1651 (s), 1597 (w), 1541 (m), 1502 (m), 1434 (m), 1361 (m), 1310 (w), 1268 (m), 1242 (m), 1113 (m), 1056 (w), 1020 (m), 961 (w), 909 (m), 856 (w), 814 (m), 728 (s), 646 (m), 590 (m), 501 (w), 473 (m), 429 (w) cm⁻¹. HRMS (ESI): calcd. for $C_{22}H_{19}N_3O_5Na [M + Na]^+$ 428.1217; found 428.1222.

4-Cyano-N-(4-methoxyphenyl)-3-methyl-2-(morpholinocarbonyl)-5oxo-2,5-dihydrofuran-2-carboxamide (27e): Following general procedure C in dichloromethane on a 0.54 mmol scale using 7b, after a reaction time of 19 h, and using pentane/ethyl acetate, 2:1 as eluent, 27e (156 mg, 0.41 mmol, 75%) was isolated as an off-white solid. TLC (pentane/ethyl acetate, 2:1): $R_{\rm f} = 0.25$; m.p. 84 °C (CDCl₃). ¹H NMR (500 MHz, CDCl₃): δ = 8.36 (s, 1 H, NH), 7.51-7.45 (m, 2 H, 2 Hortho), 6.93-6.88 (m, 2 H, 2 Hmeta), 3.81 (s, 3 H, OCH₃), 3.78–3.46 [m, 8 H, N(C₂H₄)₂O], 2.67 (s, 3 H, 3-CH₃) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 181.2 (C-3), 165.9 (C-5), 161.0 [2-CON(C₂H₄)₂O], 159.4 (2-CONH), 157.9 (C_{para}), 128.7 (Cipso), 122.1 (2 C, 2 Cortho), 114.7 (2 C, 2 Cmeta), 109.7 (4-CN), 105.3 (C-4), 91.2 (C-2), 66.5 (OCH2), 66.2 (OCH2), 55.7 (OCH3), 46.6 (NCH₂), 43.6 (NCH₂), 17.2 (3-CH₃) ppm. FTIR (neat): $\tilde{v} =$ 3312 (w), 2966 (w), 2925 (w), 2860 (w), 2245 (w), 1795 (s), 1688 (s), 1647 (s), 1605 (w), 1512 (s), 1439 (m), 1368 (w), 1305 (w), 1241 (s), 1178 (w), 1112 (s), 1060 (m), 1023 (s), 901 (w), 824 (m), 761 (w), 731 (m), 689 (w), 644 (w), 589 (m), 526 (m), 482 (w), 441 (w) cm⁻¹. HRMS (ESI): calcd. for $C_{19}H_{19}N_3O_6Na [M + Na]^+ 408.1166$; found 408.1169.

4-Cyano-3-methyl-2-(morpholinocarbonyl)-5-oxo-N-(3-oxobutyl)-2,5-dihydrofuran-2-carboxamide (27f): Following general procedure C in dichloromethane on a 0.54 mmol scale using 7b, after a reaction time of 16 h, and using ethyl acetate as eluent, 27f (150 mg, 0.43 mmol, 80%) was isolated as a colourless solid. TLC (ethyl acetate): $R_f = 0.45$; m.p. 114 °C (chloroform). ¹H NMR (500 MHz, CDCl₃): δ = 6.98 (t, J = 5.6 Hz, 1 H, NH), 3.85–3.19 [m, 10 H, 1'- H_2 , N(C₂ H_4)₂O], 2.75 (ddd, J = 18.6, J = 7.0, J = 4.8 Hz, 1 H, 2'- H_2), 2.68 (ddd, J = 18.6, J = 7.0, J = 4.9 Hz, 1 H, 2'- H_2), 2.60 (s, 3 H, 3-CH₃), 2.18 (s, 3 H, 4'-H₃) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 207.3 (C-3'), 180.6 (C-3), 164.8 (C-5), 162.1 (2-CONH), 161.0 [2-CON(C₂H₄)₂O], 109.7 (4-CN), 105.2 (C-4), 90.7 (C-2), 66.6 (OCH₂), 66.2 (OCH₂), 46.5 (NCH₂), 43.5 (NCH₂), 41.8 (C-2'), 35.2 (C-1'), 30.2 (C-4'), 17.1 (3-*C*H₃) ppm. FTIR (neat): $\tilde{v} =$ 3343 (w), 2925 (w), 2862 (w), 2244 (w), 1793 (s), 1683 (s), 1649 (s), 1525 (m), 1437 (m), 1368 (m), 1309 (w), 1269 (m), 1249 (m), 1218 (m), 1170 (w), 1112 (m), 1070 (m), 1020 (m), 880 (w), 849 (w), 817 (w), 754 (s), 696 (w), 667 (w), 588 (m), 484 (w), 441 (w), 408 (w) cm⁻¹. HRMS (ESI): calcd. for $C_{16}H_{19}N_3O_6Na [M + Na]^+$ 372.1166; found 372.1168.

1-(*tert*-Butylamino)-3-(dimethylamino)-1,3-dioxopropan-2-yl 2-(Diethoxyphosphoryl)acetate (30a): After an undocumented time standing in CDCl₃, a small amount of **30a** was isolated as a colourless liquid. TLC (ethyl acetate): $R_{\rm f} = 0.20$. ¹H NMR (500 MHz, CDCl₃): $\delta = 6.99$ (s, 1 H, NH), 5.78 (s, 1 H, 2-H), 4.26–4.08 [m, 4 H, $P(OCH_2)_2$, 3.25 (s, 3 H, NCH₃), 3.17 (dd, J = 21.9, J = 14.7 Hz, 1 H, CH_2CO_2), 2.98 (s, 3 H, NCH_3), 2.98 (dd, J = 20.0, J =14.7 Hz, 1 H, CH₂CO₂), 1.38–1.32 [m, 6 H, P(OCH₂CH₃)₂], 1.36 [s, 9 H, C(CH₃)₃] ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 165.1 (C-3), 164.0 (d, J = 6.1 Hz, CO_2), 163.8 (C-1), 71.0 (C-2), 63.2 (d, J = 6.4 Hz, POCH₂), 63.0 (d, J = 6.4 Hz, POCH₂), 52.0 [C(CH₃) 3], 37.9 (NCH₃), 36.4 (NCH₃), 34.1 (d, J = 133.7 Hz, CH_2CO_2), 28.7 [3 C, C(CH₃)₃], 16.5 [d, J = 6.0 Hz, 2 C, P(OCH₂CH₃)₂] ppm. ³¹P NMR (101 MHz, CDCl₃): δ = 19.7 ppm. FTIR (neat): \tilde{v} = 3315 (w), 2975 (w), 2934 (w), 1749 (m), 1659 (s), 1536 (w), 1454 (w), 1398 (w), 1366 (w), 1251 (s), 1156 (w), 1112 (w), 1018 (s), 969 (s), 866 (w), 817 (w), 786 (w), 714 (w), 624 (w), 575 (w), 529 (w), 473 (m) cm⁻¹. HRMS (ESI): calcd. for C₁₅H₂₉N₂O₇PNa [M + Na]⁺ 403.1605; found 403.1603.

1-(tert-Butylamino)-3-morpholino-1,3-dioxopropan-2-yl 2-(Diethoxyphosphoryl)acetate (30b): After an undocumented time standing in CDCl₃, a small amount of 30b was isolated as a colourless liquid. TLC (ethyl acetate): $R_f = 0.22$. ¹H NMR (500 MHz, CDCl₃): δ = 6.99 (s, 1 H, N*H*), 5.74 (s, 1 H, 2-*H*), 4.27–4.08 [m, 4 H, $P(OCH_2)_2$], 3.91 (ddd, J = 13.1, J = 4.2, J = 4.2 Hz, 1 H, NCH_2), 3.79 (ddd, J = 13.3, J = 5.4, J = 3.1 Hz, 1 H, NCH_2), 3.77-3.74 (m, 2 H, 2 OCH₂), 3.71 (ddd, J = 11.5, J = 5.5, J = 5.53.4 Hz, 1 H, OCH₂), 3.67–3.60 (m, 2 H, NCH₂, OCH₂), 3.51 (ddd, J = 13.2, J = 7.4, J = 3.2 Hz, 1 H, NCH₂), 3.18 (dd, J = 21.9, J =14.7 Hz, 1 H, CH_2CO_2), 3.00 (dd, J = 20.1, J = 14.7 Hz, 1 H, CH_2CO_2 , 1.39–1.32 [m, 6 H, P(OCH_2CH_3)_2], 1.37 [s, 9 H, $C(CH_3)_3$] ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 163.9 (d, J = 6.0 Hz, CO₂), 163.5 (C-3), 163.5 (C-1), 71.0 (C-2), 66.8 (OCH₂), 66.8 (OCH₂), 63.3 (d, J = 6.4 Hz, POCH₂), 63.1 (d, J = 6.5 Hz, POCH₂), 52.1 [C(CH₃)₃], 47.0 (NCH₂), 43.2 (NCH₂), 34.1 (d, J = 133.7 Hz, CH₂CO₂), 28.7 [3 C, C(CH₃)₃], 16.5 [d, J = 6.0 Hz, 2 C, P(OCH₂*C*H₃)₂] ppm. ³¹P NMR (101 MHz, CDCl₃): δ = 19.6 ppm. FTIR (neat): $\tilde{v} = 3315$ (w), 2974 (w), 2926 (w), 2864 (w), 2244 (w), 1750 (m), 1659 (s), 1536 (w), 1450 (m), 1395 (w), 1365 (w), 1251 (s), 1162 (w), 1112 (m), 1019 (s), 968 (s), 866 (w), 836 (w), 786 (w), 731 (m), 567 (w), 531 (w), 480 (m), 428 (w) cm^{-1} . HRMS (ESI): calcd. for C₁₇H₃₁N₂O₈PNa [M + Na]⁺ 445.1710; found 445.1706.

Supporting Information (see footnote on the first page of this article): Copies of the ¹H, ¹³C, and ³¹P NMR spectra for all compounds; X-ray structures of compounds **18g** and **22**.

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[44] Eventually, Passerini products **18c** and **18h** underwent deacylation in chloroform to give deacylated products **30a** and **30b**.



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