N-Bromosuccinimide-Promoted Cyclization of β-Carboxymethyl Enamino Esters; Synthesis of Functionalized 4-Amino-2(5*H*)-Furanones

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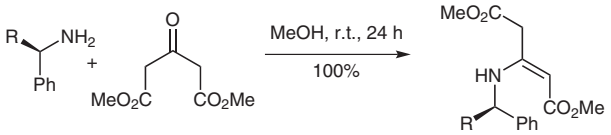
Abstract: An easy, two-step approach to various 5-carboxymethyl-2(5*H*)-furanones is described. A detailed study of the reaction of β-carboxymethyl enamino esters with *N*-bromosuccinimide is presented.

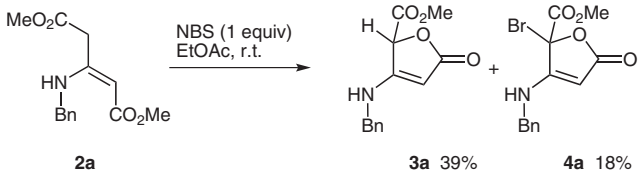
Key words: tetronamides, 4-amino-2(5*H*)-furanones, bromocyclization, alkylation, decarboxylation

4-Amino-2(5*H*)-furanones, which are commonly named tetronamides, are important intermediates in the synthesis of natural products,[1] and are also an interesting class of pharmaceutical and agrochemical compounds.[2] Many methods have been reported for the preparation of tetronamides. Most generally, the sequence of amino-addition to acetylenecarboxylates followed by intramolecular cyclization affords 5-unsubstituted primary or secondary 4-amino-2(5*H*)-furanones.[3] A sequence involving condensation between primary or secondary amines with tetronic acids followed by alkylation or aldolization using, most generally, *tert*-butyllithium as a base furnished 5-substituted tetronamides.[4] Nucleophilic halogen substitution on 4-bromofuranones is described as a method for the introduction of an alkylamino-group.[5] Tetronamides have been also used in aza-annulation processes with acrolein derivatives, and have even been used in asymmetric organocatalytic approaches for the synthesis of chiral piperidines.[6] Other synthetic routes involve the [2,3]-Wittig rearrangement of γ-allyloxy-β-enamino esters leading to γ-hydroxy-β-enamino esters, which can subsequently be lactonized to 5-substituted tetronamides.[7] Here, we would like to report an easy route to various 5-carboxymethyl substituted tetronamides **3**–**6** starting from enamino esters **2**, using *N*-bromosuccinimide (NBS) as reagent. The condensation of acetonedimethyldicarboxylate with different primary amines **1** allowed the formation of the two *Z*- and *E*-enamino esters **2** with the *Z*-diastereoisomers predominating (Scheme 1).[8] We observed that the chemical shift of the NH proton for the major *Z* stereoisomers was found downfield (δ = 8.5–9 ppm) from those of the *E* stereoisomers (δ = 5–5.5 ppm). Starting from the secondary amine, pyrrolidine compound **2d** was formed in quantitative yield solely as the *E*-diastereoisomer (see Scheme 3 below).

The crude mixture of *Z*- and *E*-enamino esters **2a** was used in an oxidative step using one equivalent of *N*-bromosuccinimide (NBS) in ethyl acetate. After 24 hours, evaporation of the solvent followed by chromatography on silica gel furnished the tetronamides **3a** and **4a**, respectively, in 39 and 18% yields (entry 1, Table 1) along with starting material **2a** (Scheme 2). The desired products could be isolated by chromatography without aqueous workup. In contrast, when the reaction was quenched with an aqueous solution of sodium sulfite, compound **4a** was reduced to **3a** and the latter compound was isolated after chromatography in 66% yield (Table 1, entry 2). Various reaction conditions were investigated to optimize the reaction; the results are listed in Table 1.



Scheme 1



Scheme 2

Solvents such as deuterochloroform and tetrahydrofuran were tested but they had no significant effect on the reaction outcome (entries 3 and 4). We also tried the reaction with more than one equivalent of *N*-bromosuccinimide in ethyl acetate. We expected to observe an enhancement in the yield of product **4a**, however, using 1.5 equivalents of *N*-bromosuccinimide led to the formation of compound **4a** in 44% yield (entry 5). Furthermore **3a** was obtained in good yield by quenching the reaction with an aqueous solution of sodium sulfite (entry 6). When three equivalents of *N*-bromosuccinimide were used, product **5a** was exclu-

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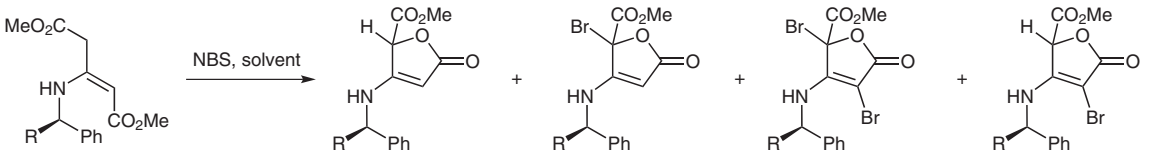
Table 1 Optimization of the Reaction



2 **3** **4** **5** **6**

Entry	2	R	NBS (equiv)	Solvent	Yield (%)[a]			
					3	**4**	**5**	**6**
1	**2a**	H	1	EtOAc	39	18	–	–
2	**2a**	H	1[b]	EtOAc	66	–	–	–
3	**2a**	H	1	$CDCl_3$	54[c]	46[c]	–	–
4	**2a**	H	1	THF	64[c]	36[c]	–	–
5	**2a**	H	1.5	EtOAc	29	44	–	–
6	**2a**	H	1.5[b]	EtOAc	69	–	–	–
7	**2a**	H	3	EtOAc	–	–	40	–
8	**2a**	H	3[b]	EtOAc	–	–	–	35
9	**2a**	H	2 × 1.5[b]	EtOAc	–	–	–	71
10	**2b**	Me	1	EtOAc	43	22	–	–
11	**2c**	CH_2OTBS	1	EtOAc	33	20	–	–

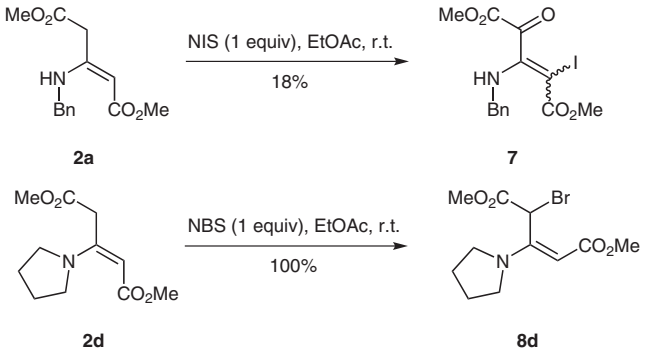
[a] Yield of isolated compound.
[b] The reactions were quenched with an aqueous solution of Na_2SO_3.
[c] Ratio determined by ^1H NMR analysis of the crude reaction mixture.

sively formed (entry 7), and when the reaction was followed by an aqueous sodium sulfite workup, tetronamide **6a** was isolated in 35% yield (entry 8). By slightly modifying the procedure (addition of 1.5 equiv of NBS 12 h after the first addition, entry 9), the yield of compound **6a** reached 71%. To our knowledge, the synthesis of 4-amino-5-halogeno-2(*5H*)-furanones such as **4a** and **5a**, has seldom been described.[9] Previously, the halogenation of 4-amino-2(*5H*)-furanones with *N*-bromosuccinimide,[10] bromine,[11] iodine,[12] or $I(py)_2BF_4$[13] were reported to give 3-halogenated products. Both substrates **2b** and **2c** gave the desired tetronamides **3b**, **4b**, **3c**, and **4c**, respectively, as a 50:50 mixture of diastereoisomers (entries 10–11).

N-Chlorosuccinimide furnished the expected product **3a** only in trace amounts after 24 hours, and gave a complex mixture of inseparable mono- and di-chloroenamino esters. *N*-Iodosuccinimide did not give the desired tetronamide **3a**, and only α-keto ester **7** could be isolated in 18% yield (Scheme 3).

It is noteworthy that the enamino ester **2d**, derived from the secondary amine pyrrolidine, gave the (*E*)-bromoenamino ester **8d**, which was unreactive under the given conditions (Scheme 3).

We then turned our attention to the mechanism of this transformation. To this end, we monitored the reaction by ^1H NMR spectroscopy in deuterochloroform using **2a** as starting material;[14] the results are presented in Table 2. Five minutes after addition of 1.5 equivalents of *N*-bromosuccinimide, the ^1H NMR spectrum showed that 8% of the starting material was still present in the medium and that no *N*-bromosuccinimide remained. We also observed the formation of enamino ester **8a** (36%) and dibrominated enamino ester **9a** (56%). Compounds **8a** and **9a**, which were too unstable to be isolated, were characterized by ^1H NMR analysis. We observed that the chemical shift of the allylic proton for the major *Z* stereoisomers resonated downfield in compound **8a** (δ = 4.95 ppm) from those of the starting product **2a** (δ = 3.11 ppm), and was absent in **9a**. It is likely that these signals arose from a brominated



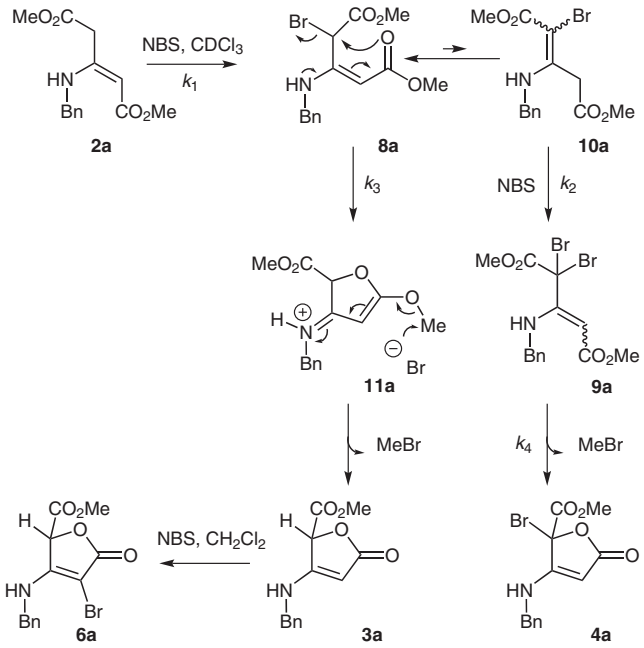
Scheme 3

iminium species. This latter may then afford the isomeric vinylic bromide **10a** through deprotonation of the most acidic proton, which is alpha to the bromine atom. After 3.5 hours, the percentage of the brominated enamino esters **8a** and **9a** fell, while those of tetronamides **3a** and **4a**, respectively, increased. After seven hours, only traces of uncyclized enamines **8a** and **9a** remained, and the amount of **3a** had increased. Finally, after 24 hours, equilibrium was reached and the tetronamides **3a** and **4a** were formed in almost the same proportions.

An examination of the frontier orbital interactions indicated that the vinylic bromide **10a**, which is in equilibrium with **8a**, has a HOMO much higher (–8.844 eV) than that of the allylic bromine **8a** (–9.128 eV), explaining the high level of formation of **9a**. The *gem*-dibromination should also be kinetically favored because the HOMO of **2a** is even lower (–8.868 eV), explaining why k_2 is higher than k_1 (Scheme 4).[15]

The mechanism of the cyclization from either **8a** or **9a** involves intramolecular nucleophilic substitution of bromine by the ester function. Further attack of a bromide anion on the methyl of iminium **11a** gives rise to the tetronamide **3a** and methyl bromide. Such a mechanism has already been outlined in the case of β-chloroenamino esters.[16] In respect to the cyclization, the *gem*-dibromoenamino ester **9a** is more reactive than the bromoenamino ester **8a**. Indeed the LUMO (σ* of the breaking C–Br bond) of **9a** is lower (–0.853 eV) than the LUMO of **8a** (–0.646 eV), which is consistent with the observation that k_4 is higher than k_3.

All attempts to isolate and purify intermediates **8a** and **9a** by chromatography on silica gel were unsuccessful. It is also noteworthy that bromination of purified **3a** with *N*-bromosuccinimide led to the formation of **6a**, suggesting that **4a** arises from **9a** (Scheme 4).

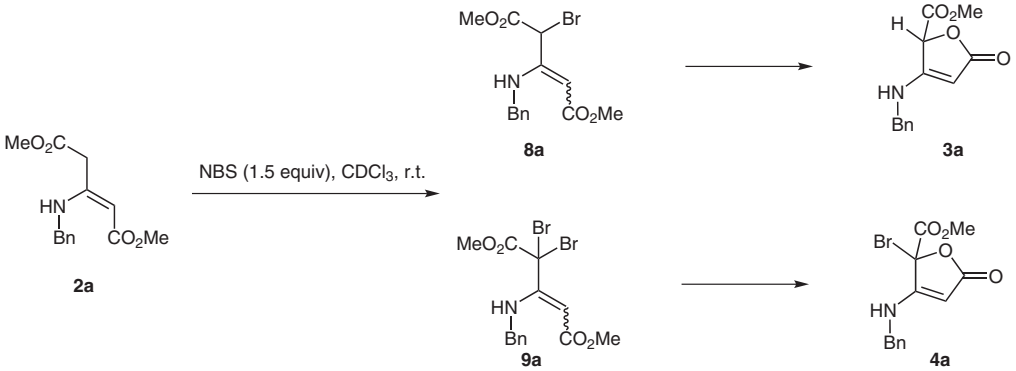


Scheme 4

Because compounds **3**–**6** are expected to be very useful synthons, we studied the regio- and stereoselective introduction of substituents at C-5. For example, product **3a** was regioselectively alkylated using lithium hexamethyldisilazide, sodium hexamethyldisilazide, or potassium carbonate as bases; the results are presented in Table 3.

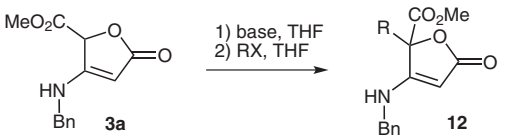
The first reaction was performed with potassium carbonate as base and benzyl bromide as electrophile in dichloromethane. After 48 hours, the reaction mixture was filtered and evaporated to furnish the expected regioisomer **12a** in 65% yield (entry 1). The yield of **12a** was enhanced by using the more basic lithium hexamethyldisilazide at room temperature (entry 2). Similar results

Table 2 Analysis of Product Formation over Time



Time	**2a** (%)	**8a** (%)	**9a** (%)	**3a** (%)	**4a** (%)
5 min	8	36	56	0	0
3.5 h	13	16	8	21	42
7 h	16	5	2	32	45
24 h	16	0	0	41	43

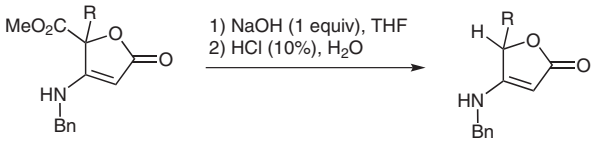
Table 3 Regio- and Stereoselective Introduction of Substituents at C-5



Entry	RX	Base (equiv)	Product	Yield (%)
1	BnBr	K_2CO_3 (2.5)[a]	**12a**	65
2	BnBr	LiHMDS (1)	**12a**	96
3	allyl bromide	K_2CO_3 (2.5)[a]	**12b**	84
4	allyl bromide	LiHMDS (1)	**12b**	98
5	MeI	K_2CO_3 (2.5)[a]	**12c**	24
6	MeI	LiHMDS (1)	**12c**	97
7	methyl bromoacetate	NaHMDS (1)	**12d**	95
8	bromoacetonitrile	NaHMDS (1)	**12e**	89

[a] K_2CO_3 in CH_2Cl_2.

were obtained when allyl bromide (entries 3 and 4) or methyl iodide (entries 5 and 6) were used as electrophiles to give compounds **12b** and **12c**, respectively. α-Bromo ester and α-bromo nitrile were also found to be successful reagents for this reaction (entries 7 and 8). We then turned our attention to the decarboxylation of compounds **3a** and **12** (Scheme 5). The reactions were performed by adding one equivalent of aqueous sodium hydroxide to a solution of esters **3a** and **12c–e** in tetrahydrofuran at reflux. After 30 minutes, the reaction was quenched with 10% aqueous hydrochloric acid solution. The results are summarized in Scheme 5.



3a R = H
12c R = Bn
12d R = CH_2CO_2Me
12e R = CH_2CN

13 65%
13c 74%
13d 99%
13e 22%

Scheme 5

In all cases, product **13** was formed as the major product. It is noteworthy that the second ester function in compound **12d** was stable under these conditions. This result would indicate that the high reactivity of the ester in compounds **3a** and **12c–e** towards saponification is due to concomitant decarboxylation.

In summary, the bromocyclization–regioselective alkylation sequence, in some cases followed by decarboxylation, gives easy access to 5-substituted tetronamides, which are important intermediates in the synthesis of many natural products. Applications of this methodology for the synthesis of 5-methylidene substituted tetronamides are in progress.

IR spectra were recorded with samples dissolved in chloroform. ^{1}H NMR spectra were measured at 250 MHz, in $CDCl_3$ or DMSO, using TMS as internal standard. ^{13}C NMR spectra were measured at 62.5 MHz in $CDCl_3$. The chemical shifts of ^{13}C NMR signals were recorded relative to the central resonance of $CDCl_3$ (δ = 77.3 ppm). HRMS were measured with a LTQ-Orbitrap instrument, using electrospray ionization.

Dimethyl 3-Benzylaminopent-2-enedioate (2a)

To a solution of 1,3-dimethyl acetonedicarboxylate (6.6 mL, 45.7 mmol) in MeOH (40 mL), was added benzylamine (5.0 mL, 45.8 mmol) and the reaction mixture was stirred at r.t. for 24 h. The mixture was evaporated to afford compound **2a** (quantitative) as a mixture of two diastereoisomers (65:35), which was used in the next step without purification.

***Z*-Isomer**

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.11 (s, 2 H, CCH_2), 3.50 (s, 3 H, CH_3), 3.53 (s, 3 H, CH_3), 4.32 (d, *J* = 6.4 Hz, 2 H, NCH_2), 4.54 (s, 1 H, CH), 7.09–7.26 (m, 5 H, PhH), 8.86 (t, *J* = 6.4 Hz, 1 H, NH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 38.0, 46.5, 49.7, 51.9, 84.6, 126.4, 127.1, 128.3, 138.0, 156.6, 168.7, 170.3.

***E*-Isomer**

IR (NaCl): 3322, 1739, 1674 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.45 (s, 3 H, CH_3), 3.57 (s, 3 H, CH_3), 3.80 (s, 2 H, CCH_2), 4.11 (d, *J* = 5.3 Hz, 2 H, NCH_2), 4.66 (s, 1 H, CH), 5.64 (t, *J* = 5.3 Hz, 1 H, NH), 7.09–7.26 (m, 5 H, PhH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 36.9, 47.0, 49.7, 51.6, 84.2, 126.4, 127.1, 128.4, 136.7, 154.4, 168.6, 170.2.

Dimethyl 3-[(1*R*)-Phenylethylamino]pent-2-enedioate (2b)

To a solution of 1,3-dimethyl acetonedicarboxylate (3.0 mL, 23.3 mmol) in MeOH (20 mL), was added (1*R*)-phenylmethylamine (3.36 mL, 23.3 mmol) and the reaction mixture was stirred at r.t. for 24 h. The mixture was evaporated to afford compound **2b** (quantitative) as a mixture of *Z* and *E* diastereoisomers (80:20), which was used in the next step without purification.

***Z*-Isomer**

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.72 (d, *J* = 6.8 Hz, 3 H, CH_3), 3.27 (d, *J* = 15.7 Hz, 1 H, CCH_2), 3.14 (d, *J* = 15.7 Hz, 1 H, CCH_2), 3.67 (s, 3 H, CH_3), 3.76 (s, 3 H, CH_3), 4.69 (s, 1 H,CH), 4.71–4.85 (br s, 1 H, NCH), 7.31–7.48 (m, 5 H, PhH), 9.21 (d, *J* = 8.0 Hz, 1 H, NH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 24.8, 38.4, 49.9, 52.0, 52.7, 84.9, 125.2, 127.0, 128.6, 144.3, 156.2, 168.8, 170.6.

***E*-Isomer**

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.67 (d, *J* = 6.8 Hz, 3 H, CH_3), 3.60 (s, 3 H, CH_3), 3.81 (s, 3 H, CH_3), 4.06 (d, *J* = 16.6 Hz, 1 H, CC*H*H), 4.22 (d, *J* = 16.6 Hz, 1 H, CCH*H*), 4.51–4.60 (m, 1 H, NCH), 4.66 (s, 1 H, CH), 5.74 (d, *J* = 5.9 Hz, 1 H, NH), 7.31–7.48 (m, 5 H, PhH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 23.5, 36.8, 49.9, 52.0, 52.7, 85.8, 125.4, 127.0, 128.2, 142.7, 153.2, 168.8, 170.6.

Dimethyl 3-[2-(*tert*-Butyldimethylsilanyloxy)-(1*S*)-phenylethylamino]pent-2-enedioate (2c)

1,3-Dimethyl acetonedicarboxylate (1.15 mL, 8.0 mmol) was added to a solution of 2-(*tert*-butyldimethylsilanyloxy)-(1*S*)-phenylethylamine (2 g, 8.0 mmol) in toluene (40 mL), and the reaction mixture was stirred at r.t. for 48 h. The solvent was evaporated to afford compound **2c** (quantitative) as a mixture of two diastereoisomers (74:26), which was used in the next step without purification.

***Z*-Isomer**

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.09 (s, 6 H, OTBS), 1.01 (s, 9 H, OTBS), 3.22 (d, *J* = 15.5 Hz, 1 H, C*H*HC), 3.38 (d, *J* = 15.5 Hz, 1 H, CH*H*C), 3.72 (s, 3 H, CH_3), 3.82 (s, 3 H, CH_3), 3.86–3.93 (m, 1 H, C*H*HO), 4.00–4.06 (m, 1 H, CH*H*O), 4.74 (s, 1 H, CH), 4.78–4.82 (m, 1 H, CHPh), 7.39–7.53 (m, 5 H, PhH), 9.34 (d, *J* = 8.8 Hz, 1 H, NH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –5.6, 18.3, 25.9, 39.3, 50.3–52.4, 59.2, 68.0, 85.4, 126.8–127.7–128.7, 140.1, 156.5, 169.3, 170.6.

Dimethyl 3-Pyrrolidin-1-yl-pent-2-enedioate (2d)

A solution containing 1,3-dimethyl acetonedicarboxylate (5.0 mL, 34.7 mmol) and pyrrolidine (2.9 mL, 34.7 mmol) in MeOH (30 mL) was stirred at r.t. overnight. Evaporation of the solvent afforded compound **2d** (quantitative) as a single diastereoisomer.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.75–1.82 (m, 4 H, 2 × CH_2), 3.02–3.23 (m, 4 H, 2 × NCH_2), 3.39 (s, 3 H, CH_3), 3.53 (s, 3 H, CH_3), 3.96 (s, 2 H, CH_2), 4.39 (s, 1 H, CH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 24.8, 35.2, 47.7, 49.7, 51.8, 84.5, 154.3, 168.9, 169.8.

Methyl 3-Benzylamino-5-oxo-2,5-dihydrofuran-2-carboxylate (3a)

To a solution of **2a** (1.06 g; 4.0 mmol) in EtOAc (40 mL), was added NBS (1.07 g, 6.0 mmol) and the mixture was stirred at r.t. for 24 h. A saturated aqueous solution of Na_2SO_3 (100 mL) was added and, 5 min later, the solution was extracted with EtOAc (3 × 100 mL). The organic layer was washed with H_2O (100 mL), dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by chromatography (Et_2O–PE, 70:30) to afford **3a**.

Yield: 69%.

IR (NaCl): 3355, 1761, 1732, 1623 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, CH_3), 4.31 (d, *J* = 5.5 Hz, 2 H, CH_2), 4.71 (s, 1 H, CH), 5.25 (s, 1 H, OCH), 5.73–5.80 (br s, 1 H, NH), 7.22–7.42 (m, 5 H, PhH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 49.2, 53.4, 75.5, 81.5, 127.3, 128.1, 128.8, 136.1, 164.2, 167.4, 173.7.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{13}NO_4$: 270.0742; found: 270.0737.

Methyl 5-Oxo-3-[(1*R*)-phenylethylamino]-2,5-dihydrofuran-2-carboxylate (3b) and Methyl 2-Bromo-5-oxo-3-[(1*R*)-phenylethylamino]-2,5-dihydrofuran-2-carboxylate (4b)

To a solution of **2b** (0.81 g, 2.9 mmol) in EtOAc (30 mL), was added NBS (0.52 g, 2.9 mmol) and the mixture was stirred for 24 h. The solution was extracted with EtOAc (3 × 100 mL) and the organic layer was washed with H_2O (100 mL), dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by chromatography (Et_2O–PE, 60:40) to afford **3b** (43% yield) as a mixture of two diastereoisomers (50:50) and **4b** (22% yield) as a mixture of two diastereoisomers (50:50).

First Diastereoisomer 3b

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.49 (d, *J* = 3.3 Hz, 3 H, CH_3), 3.74 (s, 3 H, CH_3), 4.28–4.41 (m, 1 H, NCH), 4.43 (s, 1 H, CH), 5.27 (s, 1 H, OCH), 6.11–6.16 (br s, 1 H, NH), 7.14–7.32 (m, 5 H, PhH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 23.1, 53.2, 55.3, 75.5, 82.3, 125.5, 127.7, 128.8, 141.9, 163.2, 167.4, 173.6.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{15}NO_4$: 284.0899; found: 284.0893.

Second Diastereoisomer 3b

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.52 (d, *J* = 3.0 Hz, 3 H, CH_3), 3.79 (s, 3 H, CH_3), 4.28–4.41 (m, 1 H, NCH), 4.43 (s, 1 H, CH), 5.22 (s, OCH, H-2), 6.11–6.16 (m, 1 H, NH), 7.14–7.32 (m, 5 H, PhH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 23.1, 53.3, 55.5, 75.4, 82.3, 125.8, 127.8, 128.8, 141.7, 163.1, 167.5, 173.6.

First Diastereoisomer 4b

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.62 (d, *J* = 6.6 Hz, 3 H, CH_3), 3.94 (s, 3 H, CH_3), 4.41–4.51 (m, 1 H, NCH), 4.53 (s, 1 H, CH), 5.95–6.03 (m, 1 H, NH), 7.20–7.42 (m, 5 H, PhH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 23.7, 54.6, 55.5, 79.3, 82.6, 125.8, 128.2, 129.2, 141.1, 165.4, 165.9, 168.1.

Second Diastereoisomer 4b

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.62 (d, *J* = 6.6 Hz, 3 H, CH_3), 3.93 (s, 3 H, CH_3), 4.41–4.51 (m, 1 H, NCH), 4.59 (s, 1 H, CH), 5.95–6.03 (m, 1 H, NH), 7.20–7.42 (m, 5 H, PhH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 23.4, 54.6, 55.9, 79.5, 82.5, 125.7, 128.2, 129.2, 141.4, 165.5, 165.9, 168.1.

Methyl 3-[2-(*tert*-Butyldimethylsilanyloxy)-(1*S*)-phenylethylamino]-5-oxo-2,5-dihydrofuran-2-carboxylate (3c) and Methyl 2-Bromo-3-[2-(*tert*-butyldimethylsilanyloxy)-(1*S*)-phenylethylamino]-5-oxo-2,5-dihydrofuran-2-carboxylate (4c)

To a solution of **2c** (0.58 g, 1.4 mmol) in EtOAc (13 mL), was added NBS (0.25 g, 1.4 mmol) and the mixture was stirred for 24 h. The solution was extracted with EtOAc (3 × 50 mL) and the organic layer was washed with H_2O (50 mL), dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by chromatography (Et_2O–PE, 50:50) to afford **3c** (33% yield) as a mixture of two diastereoisomers (50:50) and **4c** (20% yield) as a mixture of two diastereoisomers (50:50).

First Diastereoisomer 3c

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.03 (s, 3 H, OTBS), 0.05 (s, 3 H, OTBS), 0.90 (s, 9 H, OTBS), 3.68–3.78 (m, 1 H, C*H*HO), 3.86 (s, 3 H, CH_3), 4.00 (dd, *J* = 4.1, 10.5 Hz, 1 H, CH*H*O), 4.30–4.40 (br s, 1 H, NCH), 4.36 (s, 1 H, CH), 5.30 (s, 1 H, OCH), 6.32–6.37 (m, 1 H, NH), 7.14–7.38 (m, 5 H, PhH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –5.5, 18.1, 25.7, 53.3, 61.4, 66.6, 75.4, 83.5, 126.8, 128.3, 128.8, 137.1, 163.2, 167.5, 173.3.

Second Diastereoisomer 3c

^{1}H NMR (250 MHz, $CDCl_3$): δ = –0.08 (s, 3 H, OTBS), –0.01 (s, 3 H, OTBS), 0.88 (s, 9 H, OTBS), 3.68–3.78 (m, 2 H, CH_2O), 3.88 (s, 3 H, CH_3), 4.30–4.40 (m, 1 H, NCH), 4.40 (s, 1 H, CH), 5.30 (s, 1 H, OCH), 6.32–6.37 (m, 1 H, NH), 7.14–7.38 (m, 5 H, PhH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –5.5, 18.1, 25.7, 53.3, 60.6, 66.4, 75.5, 83.1, 126.5, 128.1, 128.6, 137.7, 162.9, 167.4, 173.3.

First Diastereoisomer 4c

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.04 (s, 3 H, OTBS), 0.06 (s, 3 H, OTBS), 0.91 (s, 9 H, OTBS), 3.68–3.78 (m, 1 H, CH*H*O), 3.93 (s, 3 H, CH_3), 3.97–4.04 (m, 1 H, C*H*HO), 4.37 (s, 1 H, CH), 4.37–4.44 (m, 1 H, NCH), 6.68–6.70 (br s, 1 H, NH), 7.19–7.38 (m, 5 H, PhH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –5.5, 18.2, 25.8, 54.5, 61.0, 66.7, 79.4, 83.0, 126.9, 128.5, 129.2, 136.7, 165.5, 165.8, 168.1.

Second Diastereoisomer 4c

^{1}H NMR (250 MHz, $CDCl_3$): δ = –0.02 (s, 3 H, OTBS), 0.00 (s, 3 H, OTBS), 0.91 (s, 9 H, OTBS), 3.68–3.78 (m, 1 H, CH*H*O), 3.95 (s, 3 H, CH_3), 3.97–4.04 (m, 1 H, C*H*HO), 4.37–4.44 (br s, 1 H, NCH), 4.44 (s, 1 H, CH), 6.52–6.54 (m, 1 H, NH), 7.19–7.38 (m, 5 H, PhH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –5.5, 18.2, 25.8, 54.5, 61.3, 66.4, 79.8, 82.6, 126.9, 128.5, 129.2, 137.2, 165.4, 165.7, 168.2.

Methyl 3-Benzylamino-2-bromo-5-oxo-2,5-dihydrofuran-2-carboxylate (4a)

To a solution of **2a** (9.7 mmol) in EtOAc (60 mL), was added NBS (2.60 g, 14.6 mmol) and the mixture was stirred at r.t. for 24 h. The solution was washed with H_2O (100 mL), extracted with EtOAc (3 × 100 mL), and the organic layer was washed with H_2O (100 mL), dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by chromatography (Et_2O–PE, 10:90) to afford **3a** (29% yield) as described above, and the bromo derivative **4a** as a mixture of two diastereoisomers (50:50).

Yield: 44%.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.93 (s, 3 H, CH_3), 4.42 (d, *J* = 5.7 Hz, 2 H, NCH_2), 4.80 (s, 1 H, CH), 6.05–6.12 (m, 1 H, NH), 7.30–7.43 (m, 5 H, PhH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 49.1, 54.5, 79.4, 81.1, 127.2, 128.1, 129.0, 135.6, 165.3, 166.6, 168.3.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{12}BrNO_4$: 347.9847 and 349.9827; found: 347.9842 and 349.9822

Methyl 3-Benzylamino-2,4-dibromo-5-oxo-2,5-dihydrofuran-2-carboxylate (5a)

To a solution of **2a** (0.50 g, 1.9 mmol) in EtOAc (18 mL), was added NBS (0.51 g, 2.8 mmol) and the mixture was stirred at r.t. for 24 h. Further NBS (0.51 g, 2.8 mmol) was added and, 15 min later, the solution was washed with H_2O (50 mL) and extracted with EtOAc (3 × 50 mL). The organic layer was dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (Et_2O–PE, 10:90) to afford the dibromo derivative **5a**.

Yield: 40%.

IR (NaCl): 3363, 1773, 1743, 1705, 1636 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.91 (s, 3 H, CH_3), 4.95 (dd, *J* = 15.1, 6.3 Hz, 2 H, NCH_2), 4.98 (dd, *J* = 15.1, 6.4 Hz, 2 H, NCH_2), 5.90–5.96 (br s, 1 H, NH), 7.32–7.45 (m, 5 H, PhH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 47.4, 54.9, 72.1, 80.0, 127.2, 128.2, 129.0, 136.9, 159.0, 164.7, 164.9.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{11}Br_2NO_4$: 425.8952, 427.8932, 429.8912; found: 425.8947, 427.8927, 429.8906.

Methyl 3-Benzylamino-4-bromo-5-oxo-2,5-dihydrofuran-2-carboxylate (6a)

To a solution of **2a** (0.43 g, 1.6 mmol) in EtOAc (16 mL), was added NBS (0.44 g, 2.4 mmol) and the mixture was stirred at r.t. for 12 h. Further NBS (0.44 g, 2.4 mmol) was added and, 15 min later, saturated aq Na_2SO_3 (50 mL) was added. After 5 min, the solution was extracted with EtOAc (3 × 50 mL) and the organic layer was washed with H_2O (50 mL), dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by chromatography on silica gel (Et_2O–PE, 50:50) to afford **6a**.

Yield: 71%.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.70 (s, 3 H, CH_3), 4.76 (d, *J* = 6.2 Hz, 2 H, NCH_2), 5.25 (s, 1 H, OCH), 5.45–5.55 (br s, 1 H, NH), 7.26–7.43 (m, 5 H, PhH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 47.4, 53.5, 75.5, 93.5, 127.1, 128.0, 128.9, 137.1, 158.0, 166.3, 169.3.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{12}BrNO_4$: 347.9847, 349.9827; found: 347.9842, 349.9822.

Dimethyl 3-Benzylamino-2-iodo-4-oxopent-2-enedioate (7)

To a solution of **2a** (0.30 g, 1.15 mmol) in EtOAc (10 mL), was added NIS (0.26 g, 1.15 mmol) and the mixture was stirred for 24 h. The mixture was concentrated and the residue was purified by silica gel column chromatography (Et_2O–PE, 20:80) to afford the iodo derivative **7**

Yield: 18%.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.67 (s, 3 H, CH_3), 3.77 (s, 3 H, CH_3), 4.31 (d, *J* = 5.9 Hz, 2 H, NCH_2), 5.66–5.71 (br s, 1 H, NH), 7.25–7.37 (m, 5 H, PhH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 48.6, 53.4, 53.6, 55.2, 128.1, 128.2, 128.9, 136.5, 158.5, 159.1, 166.9, 180.4.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{14}INO_5$: 425.9814; found: 425.9809.

Dimethyl 4-Bromo-3-pyrrolidin-1-ylpent-2-enedioate (8d)

To a solution of **2d** (0.09 g, 0.40 mmol) in CH_2Cl_2 (4 mL), was added NBS (0.07 g, 0.40 mmol) and the mixture was stirred for 24 h. The mixture was washed with H_2O (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated to afford **8d**.

Yield: 55%.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.80–1.91 (m, 4 H, 2 × CH_2), 2.95–3.10 (m, 2 H, NCH_2), 3.40–3.55 (m, 2 H, NCH_2), 3.60 (s, 3 H, CH_3), 3.75 (s, 3 H, CH_3), 4.52 (s, 1 H, CH), 7.90 (s, 1 H, CHBr).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 25.2, 39.6, 48.5, 50.7, 54.0, 85.7, 154.4, 167.6, 169.1.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{16}BrNO_4$: 328.0160, 330.0140; found: 328.0155, 330.0135.

Alkylation of 3a; General Procedure

To a solution of **3a** (0.36 g, 1.5 mmol) in THF (15 mL), was added LiHMDS (1 M in THF, 1.60 mL, 1.7 mmol) at 0 °C, and the mixture was stirred at r.t. for 30 min. The electrophile (benzyl bromide, allyl bromide, or methyl iodide; 1.5 mmol) was added and the solution was allowed to reach r.t. and stirred for 24 h. The solution was poured into saturated aq NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was dried over anhydrous $MgSO_4$ and evaporated to afford the corresponding alkylated compound.

Methyl 2-Benzyl-3-benzylamino-5-oxo-2,5-dihydrofuran-2-carboxylate (12a)

Yield: 96%.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.25 (d, *J* = 14.1 Hz, 1 H, CH*H*-Ph), 3.47 (d, *J* = 14.1 Hz, 1 H, C*H*HPh), 3.73 (s, 3 H, CH_3), 4.27 (d, *J* = 5.6 Hz, 2 H, NCH_2), 4.56 (s, 1 H, CH), 6.25 (t, *J* = 5.6 Hz, 1 H, NH), 7.24–7.45 (m, 5 H, PhH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 42.6, 49.2, 53.3, 83.0, 84.7, 127.6, 128.0, 128.3, 128.8, 128.9, 130.3, 132.7, 136.2, 166.1, 169.7, 172.4.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{19}NO_4$: 360.1212; found: 360.1206.

Methyl 2-Allyl-3-benzylamino-5-oxo-2,5-dihydrofuran-2-carboxylate (12b)

Yield: 98%.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.60 (dd, *J* = 14.3, 6.7 Hz, 1 H, C*H*H), 2.80 (dd, *J* = 14.3, 7.4 Hz, 1 H, CH*H*), 3.70 (s, 3 H, CH_3), 4.22 (d, *J* = 5.6 Hz, 2 H, NCH_2), 4.58 (s, 1 H, CH), 5.10 (m, 2 H, $=CH_2$), 5.60 (ddt, *J* = 16.7, 9.7, 7.1 Hz, 1 H, =CH), 5.92 (t, *J* = 5.6 Hz, 1 H, NH), 7.16–7.31 (m, 5 H, PhH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 41.0, 49.2, 53.4, 82.6, 84.2, 121.0, 127.4, 128.1, 128.9, 129.1, 136.2, 166.4, 169.6, 172.6.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{17}NO_4$: 310.1055; found: 310.1050.

Methyl 3-Benzylamino-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylate (12c)
Yield: 97%.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.72 (s, 3 H, CH_3), 3.75 (s, 3 H, CH_3), 4.29 (d, *J* = 5.7 Hz, 2 H, CH_a), 4.59 (s, 1 H, CH), 6.01–6.05 (br s, 1 H, NH), 7.20–7.36 (m, 5 H, PhH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 23.5, 49.1, 53.4, 81.4, 82.0, 127.2, 128.0, 128.9, 136.2, 168.3, 170.0, 172.8.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{15}NO_4$: 284.0899; found: 284.0893.

Methyl 3-Benzylamino-2-methoxycarbonylmethyl-5-oxo-2,5-dihydrofuran-2-carboxylate (12d)
NaHMDS (1 M in THF, 6.10 mL, 6.08 mmol) was added to a solution of **3a** (1.50 g, 6.08 mmol) in THF (60 mL) at 0 °C. After 30 min, methyl bromoacetate (0.60 mL, 6.08 mmol) was added and the mixture was stirred for 2 h. The mixture was poured into saturated aq NH_4Cl (150 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated to afford **12d**.

Yield: 95%.

IR (NaCl): 3331, 1735, 1627 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.86 (d, *J* = 16.7 Hz, 1 H, CH*H*), 3.11 (d, *J* = 16.7 Hz, 1 H, C*H*H), 3.57 (s, 3 H, CH_3), 3.69 (s, 3 H, CH_3), 4.17 (d, *J* = 5.6 Hz, 2 H, NCH_2), 4.54 (s, 1 H, CH), 6.13 (t, *J* = 5.6 Hz, 1 H, NH), 7.08–7.25 (m, 5 H, PhH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 41.5, 49.2, 52.6, 53.8, 81.6, 82.3, 127.3, 128.1, 129.0, 136.0, 166.6, 168.9, 169.7, 172.1.

Methyl 3-Benzylamino-2-cyanomethyl-5-oxo-2,5-dihydrofuran-2-carboxylate (12e)
NaHMDS (1 M in THF, 7.62 mL, 7.60 mmol) was added to a solution of **3a** (1.88 g; 7.60 mmol) in THF (70 mL) at 0 °C. After 30 min, bromoacetonitrile (0.48 mL, 6.84 mmol) was added and the mixture was stirred for 2 h. The mixture was poured into saturated aq NH_4Cl (150 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated to afford **12e**.

Yield: 89%.

IR (NaCl): 3305, 2228, 1721, 1607 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.16 (s, 2 H, CH_2), 3.88 (s, 3 H, CH_3), 4.34 (d, *J* = 5.4 Hz, 2 H, CH_2Ph), 4.86 (s, 1 H, CH), 5.50–5.54 (br s, 1 H, NH), 7.26–7.39 (m, 5 H, PhH).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{14}N_2O_4$: 309.0851; found: 309.0846.

Decarboxylation of 3a and 12c–e; General Procedure
A solution of **3a** (or **12c–e**; 1.22 mmol) in THF (12 mL) was heated at reflux and a solution of NaOH (0.05 g, 1.22 mmol) in H_2O (3 mL) was added. The mixture was stirred at reflux for 30 min, then allowed to reach r.t. and 10% HCl (2 mL) was added. The mixture was stirred under reflux for 1 h, then allowed to reach r.t. before being extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated to afford the corresponding decarboxylated compound after chromatography.

4-Benzylamino-5*H*-furan-2-one (13)
Yield: 65%.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.19 (d, *J* = 4.5 Hz, 2 H, NCH_2), 4.59 (br s, 3 H, OCH_2 and CH), 5.99 (br s, 1 H, NH), 7.17–7.29 (m, 5 H, PhH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 49.3, 68.1, 81.8, 127.7, 128.2, 129.1, 136.4, 168.7, 177.3.

5-Benzyl-4-benzylamino-5*H*-furan-2-one (13c)
Yield: 74%.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.00 (dd, *J* = 14.1, 6.8 Hz, 1 H, CH*H*Ph), 3.20 (dd, *J* = 14.1, 6.1 Hz, 1 H, C*H*HPh), 4.17 (d, *J* = 5.3 Hz, 2 H, NCH_2), 4.58–4.62 (m, 1 H, NH), 4.65 (s, 1 H, CH), 4.98 (t, *J* = 6.5 Hz, 1 H, OCH), 7.15–7.35 (m, 5 H, PhH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 39.7, 49.4, 78.4, 83.0, 127.5, 127.7, 128.2, 128.9, 129.0, 129.7, 134.8, 136.3, 169.4, 174.4.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{17}NO_2$: 302.1157; found: 302.1152.

Methyl (3-Benzylamino-5-oxo-2,5-dihydrofuran-2-yl)acetate (13d)
Yield: 99%.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.75 (dd, *J* = 18.1, 9.7 Hz, 1 H, CH*H*), 3.16 (dd, *J* = 18.1, 3.7 Hz, 1 H, C*H*H), 3.74 (s, 3 H, CH_3), 4.29 (d, *J* = 5.4 Hz, 2 H, NCH_2), 4.67 (s, 1 H, CH), 5.12 (dd, *J* = 9.7, 3.7 Hz, 1 H, OCH), 6.45–6.50 (br s, 1 H, NH), 7.24–7.40 (m, 5 H, PhH).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 38.1, 48.8, 52.2, 74.3, 80.8, 127.2, 127.7, 128.7, 136.4, 170.4, 171.0, 175.0.

(3-Benzylamino-5-oxo-2,5-dihydrofuran-2-yl)acetonitrile (13e)
Yield: 22%.

IR (NaCl): 3222, 2259, 1705, 1599 cm^{-1}.

^{1}H NMR (250 MHz, DMSO): δ = 3.12 (dd, *J* = 17.4, 5.1 Hz, 1 H, C*H*H), 3.34 (dd, *J* = 17.4, 4.0 Hz, 1 H, CH*H*), 4.32 (d, *J* = 5.7 Hz, 2 H, NCH_2), 4.74 (s, 1 H, CH), 5.12 (t, *J* = 4.5 Hz, 1 H, OCH), 7.27–7.41 (m, 5 H, PhH), 7.98 (t, *J* = 5.7 Hz, 1 H, NH).

^{13}C NMR (62.5 MHz, DMSO): δ = 21.9, 48.0, 72.3, 80.5, 116.4, 127.4, 127.5, 128.5, 137.4, 168.3, 172.6.

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