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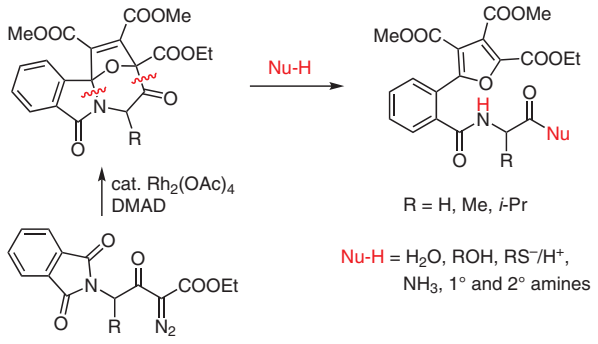
Tetrasubstituted Furans by Nucleophile-Induced Cleavage of Carbonyl Ylide–DMAD Cycloadducts

Matthias Dobesch[1]
Julian Greiner
Gerhard Maas*

Institute of Organic Chemistry I, Ulm University, Albert-Einstein-Allee 11, 89081 Ulm, Germany
gerhard.maas@uni-ulm.de



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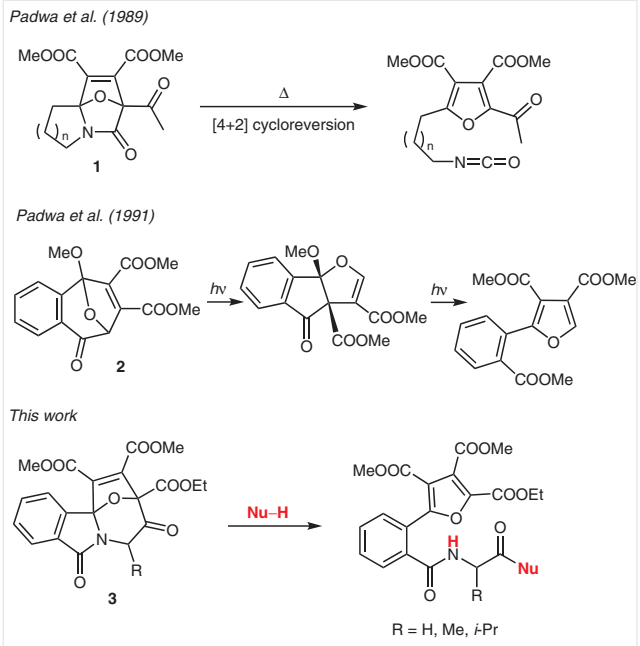
Abstract Compounds incorporating a 4-aza-8-oxabicyclo[3.2.1]oct-6-en-2-one moiety, which were prepared by a tandem carbenoid carbonyl ylide cyclization/[3+2]-cycloaddition reaction from ethyl 2-diazo-3-oxo-4-phthalimidobutanoates, undergo a nucleophile-induced two-bond ring cleavage when treated with protic heteronucleophiles. In this manner, tetrasubstituted furantricarboxylates, tethered with α-amino acids, esters, thioesters, and amides by a 2-carbonylphenyl moiety, are obtained.

Key words diazo compounds, carbonyl ylides, carboxamides, cycloaddition, furan

The tandem carbonyl ylide formation/[3+2] cycloaddition reaction is an interesting strategy for the fast construction of molecular complexity from structurally simple precursors. Carbonyl ylides are reactive 1,3-dipoles, which are usually generated and trapped in situ by inter- or intramolecular [3+2] cycloaddition with suitable alkenes, alkynes, and other π-bond systems.[1–3] In this manner, cyclic carbonyl ylides allow the preparation of bicyclic structures incorporating an oxygen bridge, which in turn provide an access to a wide range of (poly)cyclic natural and non-natural products.[1,4–7] While carbonyl ylides are most often generated from diazocarbonyl compounds,[1–3,7] other approaches also exist,[1,4] including the recently reported Rh(II)-catalyzed dediazotization of 1-sulfonyl-1,2,3-triazoles (bearing a carbonyl-containing substituent at C-4) followed by metallocarbenoid intramolecular carbonyl ylide formation and 1,3-dipolar cycloaddition.[8]

Quite a number of carbonyl ylides, which were generated from α-diazocarbonyl compounds, have been trapped with acetylenic dipolarophiles, such as dimethyl acetylenedicarboxylate (DMAD), alkyl propynoates, and arylacetylenes.[9–15] Since the resulting bi- or polycyclic cycloadducts contain a 2,5-dihydrofuran moiety, we saw opportunities to convert the latter into a non-bridged furan ring.

In fact, it has been reported that the carbonyl ylide–DMAD adduct **1** undergoes an easy thermal [4+2] cycloreversion into a furan and an isocyanate moiety (Scheme 1); this reactivity appears not to be induced by ring strain, since an analogous reaction occurs when no cycloalkane annulation is present.[10a] In another study, the 8-oxabicyclo[3.2.1]oct-6-en-2-one derivative **2** could be converted into a 2-arylfuran-3,4-dicarboxylate in two photochemical steps.[16]

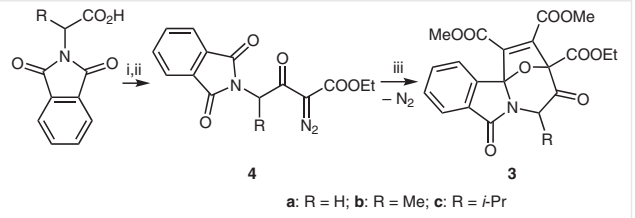


Scheme 1 Furan synthesis from carbonyl ylide–DMAD cycloadducts

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Herein we report on the two-bond cleavage of the oxabicyclooctene substructure of **3** using protic heteronucleophiles (Scheme 1); this transformation generates highly functionalized 5-(*ortho*-substituted aryl)furan-2,3,4-tricarboxylates. The interest in the synthesis of multiply substituted furans is ongoing. Classical approaches, such as cyclocondensation, cycloisomerization, and ring substitution, and novel modifications thereof[17] have recently been complemented in particular by novel transition-metal-catalyzed strategies.[18,19] Moreover, several new, metal-free approaches to tetrasubstituted furan-3,4-dicarboxylates have been published in recent years.[20,21]

This study was carried out with the carbonyl ylide–DMAD cycloaddition products **3a–c**, which were prepared from 2-diazo-3-oxo-4-phthalimidobutanoic esters **4** as outlined in Scheme 2. Syntheses of **3b**[14a] and of the carbonyl ylide precursor of **3a**[10b] along these lines have already been published. While the methyl derivative **3b** was obtained as a mixture of diastereomers (*exo*-Me/*endo*-Me 2:1), only the *exo*-isopropyl isomer of **3c** was obtained, as was confirmed by an XRD structure determination (Figure 1). In the course of our work, it turned out that the carbonyl reactivity of **3a–c** markedly depended on the steric demand of the adjacent substituent R.



Scheme 2 Preparation of 4-aza-8-oxabicyclo[3.2.1]octen-2-ones **3** used in this study. *Reagents and conditions*: (i) 1. phthalic anhydride, α-amino acid, NEt_3, toluene; 2. CDI, then $CH_2(COOEt)COOH$, NEt_3, anhyd $MgCl_2$; (ii) imidazole-1-sulfonyl azide·HCl, NEt_3; (iii) $Rh_2(OAc)_4$ (3 mol%), DMAD, benzene, 80 °C (yield: 53–76%). CDI = 1,1′-carbonyldiimidazole.

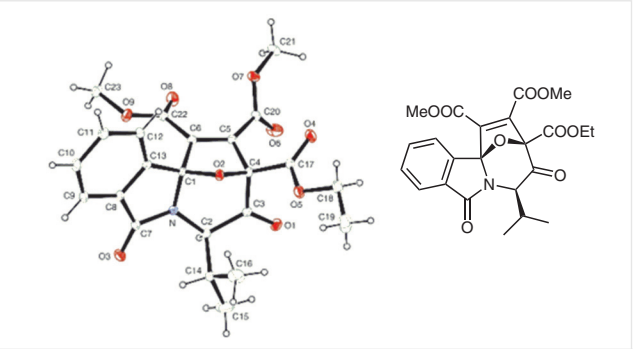
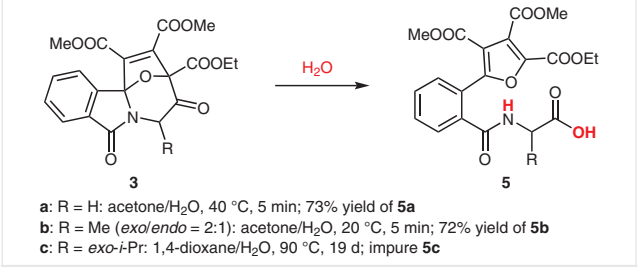


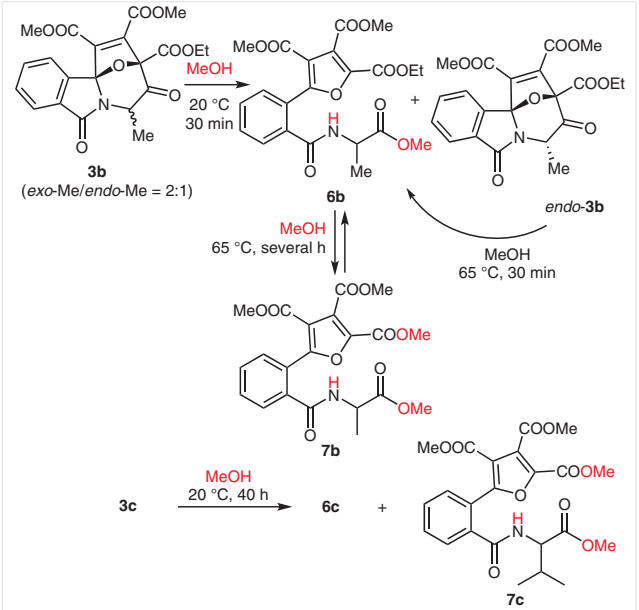
Figure 1 Solid-state molecular structure of *exo*-isopropyl-**3c** (ORTEP plot)

We have observed earlier, that the keto group of a carbonyl ylide–*N*-phenylmaleimide cycloadduct, structurally analogous to **3**, is easily hydrated and a keto/*gem*-diol equilibrium was detected in wet DMSO solution.[14a] In contrast, **3a** and **3b** in an acetone/water solution readily undergo a two-bond cleavage leading to carboxylic acids **5a** and **5b**, respectively (Scheme 3). The higher reaction temperature for **3a** compared to **3b** was chosen to achieve complete solubility of **3a** in aqueous acetone. On the other hand, isopropyl-substituted **3c** reacted with water only sluggishly; in refluxing aqueous acetone, a low conversion was observed even after 64 h (NMR control) and full conversion accompanied by extensive formation of undefined byproducts in aqueous 1,4-dioxane at 90 °C after 19 days. In contrast to the clean hydrolysis at neutral pH, exposure of **3b** to an equimolar amount of aqueous NaOH or $NaHCO_3$ led to unspecific decomposition.



Scheme 3 Reaction of **3a–c** with water

Encouraged by the smooth hydrolytic cleavage of **3a**,**b**, we became interested in analogous transformations using other protic heteronucleophiles. Scope and limitations of the reaction of **3a–c** with aliphatic alcohols can be seen in Table 1. As for the hydrolysis reaction, the success of the reaction with alcohols obviously depends very much on steric factors. Thus, the reactivity toward methanol, as the simplest alcohol, clearly decreases in the order **3a** > **3b** > **3c** (en-



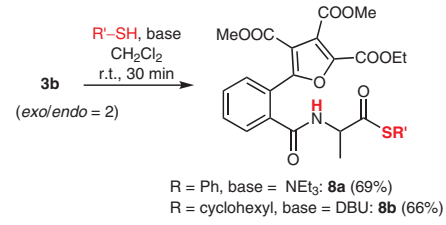
Scheme 4 Reaction of **3b** with methanol

tries 1–4). Moreover, a closer inspection of the methanolysis of alanine-derived **3b** revealed that *exo*-**3b** reacted faster than *endo*-**3b** at room temperature (Scheme 4). The latter diastereomer (clearly identified by an XRD diffraction analysis[14a]), as well as the diastereomeric mixture of **3b**, were readily and completely converted into **6b** in refluxing methanol. Prolonged heating of **6b** in methanol led to a transesterification equilibrium mixture of **6b** and tetramethyl tetracarboxylate **7b**. In a very slow reaction, valine-derived **3c** reacted with methanol at room temperature to give a mixture of **6c** and transesterification product **7c**, which, however, could not be separated. Extended heating of this mixture in hot methanol converted **6c** into **7c** accompanied by decomposition products, which could not be removed.

Higher primary aliphatic alcohols, benzyl and allyl alcohol also reacted in good yields with **3a** and **3b** (Table 1, entries 5–7, 11–14), but again the retarding effect of substituent R could be noted (entries 5/6 and 11/12). The limit was reached when α-branched aliphatic alcohols were applied: when glycine-derived **3a** was exposed to *i*-PrOH, the nucleophilic ring cleavage reaction was still achieved in fair yield (albeit with thermal activation, entry 8), but no reaction occurred in the case of alanine-derived **3b** (entry 9).

By the way, the latter fact allowed to recrystallize **3b** and **3c** from *i*-PrOH in the preparation procedure. Finally, even the sterically least biased tetracycle **3a** did not react with *t*-BuOH (entry 10).

In contrast to aliphatic alcohols, neutral SH compounds did not react with tetracycles **3**. In the presence of an appropriate base, however, **3b** reacted smoothly with thiophenolate or cyclohexanethiolate to afford thioesters **8a**,**b** (Scheme 5).



Scheme 5 Ring cleavage of **3b** with thiolates

We were pleased to find that the nucleophilic ring cleavage of tetracycles **3a–c** could also be achieved with a wide range of amines (ammonia, primary and secondary al-

Table 1 Reaction of **3a–c** with Alcohols[a]

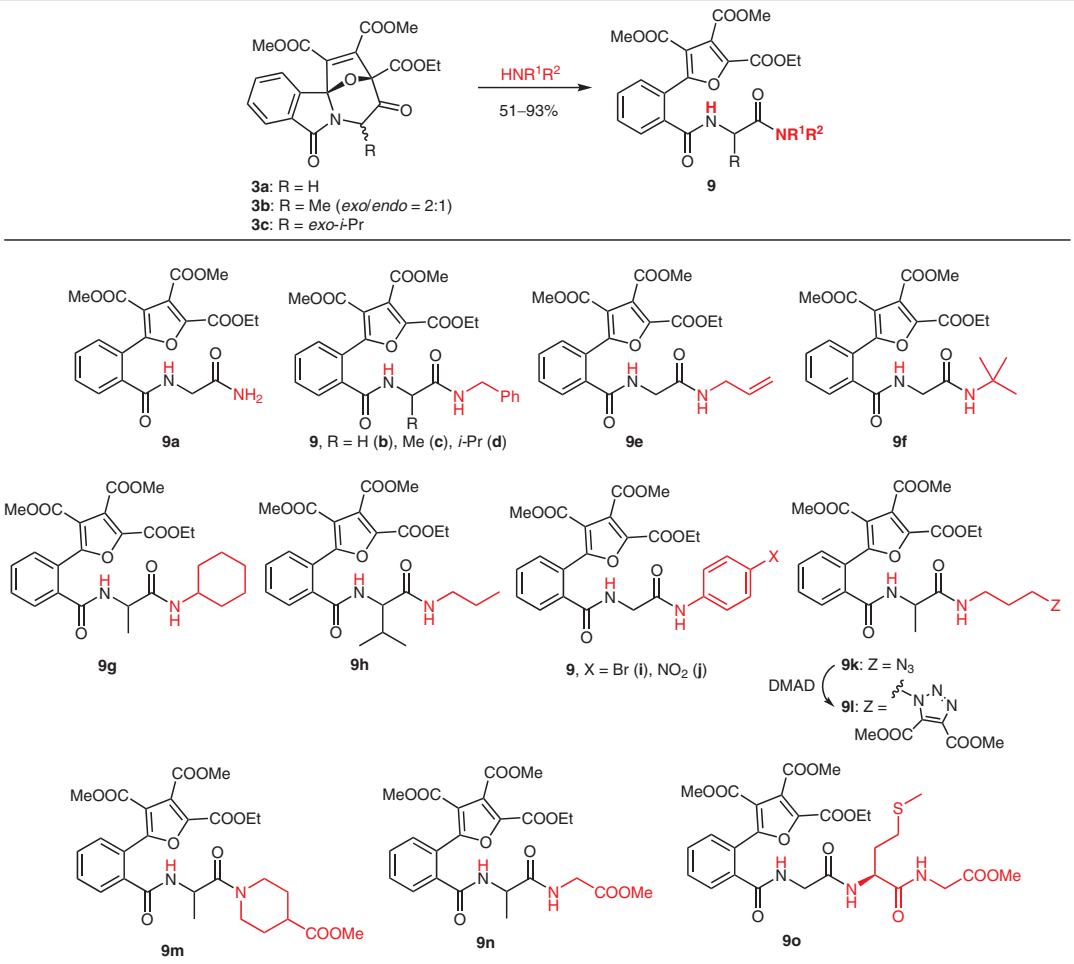
Entry	Substrate	R	Solvent/R'OH	T (°C)	Time	Product	Yield (%)
1	**3a**	H	CH_2Cl_2/MeOH	20	0.5 h	**6a**	72
2	**3b**	Me	CH_2Cl_2/MeOH	20	0.5 h	**6b** *endo*-**3b**	48 38
3	**3b**	Me	MeOH	65	0.5 h	**6b**	79
4	**3c**	*i*-Pr	MeOH	20	40 h	**6c** and **7c**[b]	
5	**3b**	Me	EtOH	78	6 h	**6d**	76
6	**3c**	*i*-Pr	EtOH	70	230 h	**6e**[c]	
7	**3b**	Me	PrOH	90	6 h	**6f**	80
8	**3a**	H	*i*-PrOH	82	8 h	**6g**	69
9	**3b**	Me	*i*-PrOH	82	20 h	no reaction	
10	**3a**	H	*t*-BuOH	reflux	20 h	no reaction	
11	**3a**	H	BnOH	65	6 h	**6h**	68
12	**3b**	Me	BnOH	100	12 h	**6i**	62
13	**3a**	H	hex-5-en-1-ol	95	6 h	**6j**	71
14	**3a**	H	CH_2=$CHCH_2OH$	85	6 h	**6k**	67

[a] Cycloadduct **3b** (R = Me) was used as a diastereomeric mixture (*exo*/*endo* 2:1), **3c** (R = *i*-Pr) as the *exo* isomer.
[b] Complete conversion into a 3:1 mixture of **6c** and **7c**; subsequent heating at 65 °C for 112 h afforded transesterification product **7c** and unidentified decomposition products.
[c] Unidentified decomposition products could not be removed.

iphatic amines, anilines) (Scheme 6) and furnished tetrasubstituted furans **9** tethered with α-amino acid amide moieties. The majority of the reactions were completed within 5–10 minutes, including those with sterically more demanding α-branched amines (*tert*-butylamine, cyclohexylamine, methyl piperidine-4-carboxylate, and H_2N-Met-Gly-OMe) and the less nucleophilic 4-bromoaniline. The reactions leading to **9d** (CH_2Cl_2, 40 °C, 16 h, 51% yield), **9h** (EtOAc, 20 °C, 40 h, 57%) and **9j** (CH_2Cl_2, 20 °C, 40 h, 70%) proceeded more reluctantly. In the first two cases, this can be attributed to the steric influence exerted by the isopropyl substituent of **3c**, in the third case to the low nucleophilicity of 4-nitroaniline.

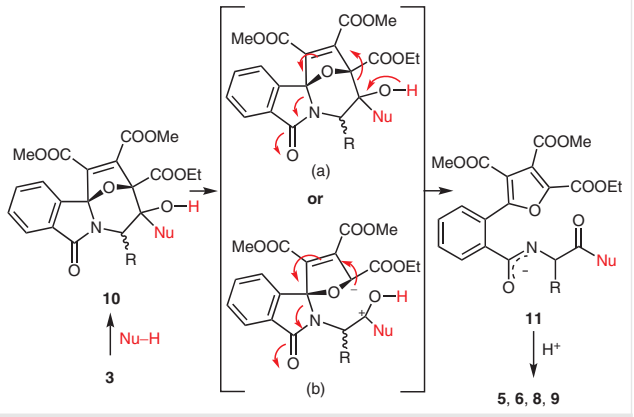
Gratifyingly, amines carrying additional functional groups can also be applied, allowing the preparation of multiply functionalized molecular structures. One such example is the *N*-(3-azidopropyl)carboxamide **9k**, which was further transformed into 1,2,3-triazole **9l** by a [3+2] cycloaddition reaction with DMAD (83% yield). The successful preparation of **9n** (from Gly-OMe) and **9o** (from NH_2-Met-Gly-OMe) suggests, that other amino acid and peptide derivatives decorated with these tetrasubstituted furan moieties can also be prepared.

A mechanistic proposal for the reported nucleophilic two-bond cleavage reactions of tetracycles **3** is outlined in Scheme 7. The transformation very likely begins with an addition of the protic nucleophile (or the thiolate anion in the case of RSH/base) to the keto group of the β-keto ester moiety of **3**. In contrast to the *N*-phenylmaleimide cycloadduct analogous to **3**, for which we have observed an equilibrium between the keto and the *gem*-diol form,[14a] tetrahedral carbonyl addition products **10** appear to undergo a spontaneous fragmentation, which can be considered as a variation of the retroaldol reaction of β-hydroxycarbonyl compounds.[22,23] Thus, **10** could undergo OH deprotonation followed by cleavage of the adjacent C–C bond and extended bond reorganization with delocalization of the negative charge as shown by intermediate structure (a). However,



Scheme 6 Ring cleavage of tetracycles **3a–c** with amines, and products **9**. *Reagents and conditions*: tetracycle **3** (~0.2–0.5 mmol), amine (moderate excess), CH_2Cl_2, r.t., 5–10 min; see text for exceptions.

the retroaldol reaction is in general base-catalyzed, which cannot apply to the cases where tetracycles **3** were exposed to water or alcohols. Therefore we propose that the first step of the fragmentation of **10** is a heterolytic bond fission resulting in a resonance-stabilized carbocation and relief of steric strain [see intermediate structure (b)]. In the second step, the 2,5-elimination at the dihydrofuran ring is completed as shown.



Scheme 7 Proposed mechanism for the nucleophilic two-bond cleavage of tetracycles **3**

A certain analogy of the 2,5-elimination is given by the conversion of a 5-methoxy-2,5-dihydrofuran-2-carboxylic ester into a furan devoid of the two substituents upon treatment with methanolic KOH. In this instance, a nucleophilic attack at the ester group initiates the fragmentation process.[24]

In conclusion, we have found that the 4-aza-8-oxabicyclo[3.2.0]hept-6-en-2-one substructure, which is part of the tetracyclic carbonyl ylide–DMAD cycloadducts **3**, can undergo a two-bond cleavage induced by protic heteronucleophiles. While this transformation results in the breakdown of the tetracyclic framework, it generates densely functionalized products, namely tetrasubstituted furans that are tethered with α-amino acids (or their esters and amides) by a carbonylphenyl moiety. In particular, primary and secondary amines are versatile reagents for this transformation, because their nucleophilicity can vary over a broad range, steric factors appear to be less important than in the case of alcohols, and functionalized amines can be used to introduce additional functional groups.

Solvents were dried by established procedures and stored over molecular sieves (4 Å; 3 Å for MeOH). Melting points were determined in open capillaries with a Büchi B-540 instrument at a heating rate of 2 °C/min. NMR spectra were recorded on a Bruker DRX 400 spectrometer (^{1}H: 400.13 MHz; ^{13}C: 100.61 MHz) and on a Bruker Avance 500 spectrometer (^{1}H: 500.16 MHz; ^{13}C: 125.76 MHz) and were calibrated based on the residual solvent signal: δ($CDCl_3$) = 7.26 and 77.00 (^{1}H and ^{13}C), δ(DMSO-d_6) = 2.50 and 39.52, δ(CD_2Cl_2) = 5.32 and 54.00. ^{13}C signals were assigned by means of APT, HMBC and HSQC experiments. IR spectra of solids were recorded on a Bruker Vector 22 FT-IR instrument (solids: KBr pellets or in the ATR mode; oils between NaCl plates); wavenumbers and relative intensities of selected absorptions are reported. Mass spectra were recorded with the following instruments: Finnigan MAT SSQ-7000 (CI, 100 eV), Bruker Daltonics Reflex III (MALDI-TOF), and Bruker solariX (HRMS). Elemental analyses were carried out with a Heraeus Vario EL or an elementar Hanau vario MICRO cube analyzer. Column chromatography was performed on silica gel (63–200 mesh). Differental Scanning Calorimetry (DSC) measurements were performed on a Perkin Elmer DSC 7 instrument (N_2 atmosphere, heating and cooling rates 10 °C min^{-1}); glass transition temperatures (T_g) were taken from the second heating cycle. PE = petroleum ether (bp 40–65 °C).

Syntheses of diazo ester **4a**[10b] (here prepared with imidazole-1-sulfonyl azide as diazo transfer reagent) and **4b**,[14a] as well as cycloadduct **3b**,[14a] have been published.

Ethyl 5-Methyl-3-oxo-4-phthalimidohexanoate

See Scheme 2. To a solution of *N*-phthaloyl-DL-valine (20.4 g, 83 mmol) in anhyd THF (200 mL) was added CDI (17.5 g, 108 mmol) in portions and the mixture was stirred at r.t. for 10 h. In the meantime, a second round-bottom flask was placed in an ice-water bath, purged with argon and charged with anhyd THF (120 mL). Hydrogen ethyl malonate (13.0 mL, 110 mmol), anhyd $MgCl_2$ (8.1 g, 84 mmol), and dry NEt_3 (17.0 mL, 123 mmol) were added. The suspension was stirred for 2 h at 0 °C, then the two preparations were combined and allowed to react at 20 °C for 15 h. The solution was concentrated to about 10% of its original volume and Et_2O was added. After extraction with water (3 ×) and re-extraction of the aqueous phases with Et_2O, all organic phases were combined and dried (Na_2SO_4) and the volatiles were evaporated. The residual yellow oil (27.8 g) could not be purified completely.

IR (NaCl): 1614 (w), 1720 cm^{-1} (s).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.78 (d, ^3J = 6.8 Hz, 3 H, CH*Me*), 1.02 (d, ^3J = 6.6 Hz, 3 H, CH*Me*), 1.11 (t, ^3J = 7.1 Hz, 3 H, OCH_2Me), 2.69–2.75 (m, 1 H, C*H*Me_2), 3.33 and 3.45 (AB d, ^2J = 15.7 Hz, 2 H, $COCH_2CO$), 3.99–4.06 (m, 2 H, OCH_2Me), 4.56 (d, ^3J = 8.1 Hz, 1 H, NCH), 7.73–7.77 (m, 2 H, H_{Ar}), 7.84–7.88 (m, 2 H, H_{Ar}); signals of the enol tautomer (8–9% by integration): δ = 5.32 (s, HO–C=C*H*), 12.09 (s, C–OH).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 13.81 (OCH_2Me), 18.79 and 20.68 ($CHMe_2$), 27.13 (*C*HMe_2), 46.73 ($COCH_2CO$), 61.41 (OCH_2Me), 63.48 (NCH), 123.65 (CH_{Ar}), 131.31 (C_q), 134.46 (CH_{Ar}), 166.46 (*C*OOEt), 167.70 (NC=O), 196.65 (*C*HC=O).

MS (CI): [M] calcd for $C_{17}H_{19}NO_5$: 317.34; *m*/*z* = 318 [M + H]$^+$, 272 [M – OEt]$^+$, 202 [M – $COCH_2COOEt$]$^+$.

Ethyl 2-Diazo-5-methyl-3-oxo-4-phthalimidohexanoate (4c)

Imidazole-1-sulfonyl azide hydrochloride (4.8 g, 23 mmol) and anhyd NEt_3 (11.0 mL, 79 mmol) were added to a solution of crude ethyl 5-methyl-3-oxo-4-phthalimidohexanoate (5.1 g, 16.0 mmol) in anhyd CH_2Cl_2 (250 mL), and the mixture was heated with stirring at reflux during 14 h. After cooling, the red solution was extracted with dilute 1 M aq HCl (2 ×), then with water. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated. Purification by column chromatography (silica gel, cyclohexane/Et_2O, 1:1) afforded **4c** (3.1 g, 56%) as a yellow oil.

IR (NaCl): 2144 (w), 1725 (s), 1266 cm^{-1} (vs).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.92 (d, ^3J = 6.9 Hz, 3 H, CH*Me*), 1.06 (d, ^3J = 6.7 Hz, 3 H, CH*Me*), 1.18 (t, ^3J = 7.1 Hz, 3 H, OCH_2*Me*), 2.81–2.95 (m, 1 H, C*H*Me_2), 4.09–4.23 (m, 2 H, OCH_2Me), 5.21 (d, ^3J = 8.6 Hz, 1 H, NCH), 7.67–7.75 (m, 2 H, H_{Ar}), 7.79–7.88 (m, 2 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 14.14 (OCH_2*Me*), 19.14 and 20.13 (CH*Me*$_2$), 28.00 (*C*HMe_2), 60.71 (NCH), 61.62 (OCH_2Me), 123.41 (CH_{Ar}), 131.47 (C_q), 134.05 (CH_{Ar}), 160.53 (*C*OOEt), 167.74 (NC=O), 187.06 (CH*C*=O); the diazo carbon signal was not observed.

MS (CI): *m*/*z* = 344 $[M + H]^+$, 316 $[M + H - N_2]^+$, 202 $[M - COCN_2COOEt]^+$.

Anal. Calcd for $C_{17}H_{17}N_3O_5$ (343.34): C, 59.47; H, 4.99; N, 12.24 (no correct elemental analysis obtained).

A preparation of diazo ester **4a** from **1a** according to this procedure afforded a pale orange-colored solid in 80% yield; mp 147–148 °C (Lit.[10b] 149–150 °C].

Carbonyl Ylide Cycloaddition Products 3

9-Ethyl 10,11-Dimethyl (9*RS*,11a*SR*)-9,11a-Epoxy-5,8-dioxo-7,8,9,11a-tetrahydro-5*H*-azepino[2,1-*a*]isoindole-9,10,11-tricarboxylate (3a)

To a solution of diazo ester **4a** (900 mg, 3.0 mmol) in dry benzene (14 mL) was added DMAD (0.4 mL, 3.3 mmol) dissolved in benzene (20 mL) and $Rh_2(OAc)_4$ (40 mg, 3 mol%). The magnetically stirred mixture was heated at reflux for 6 h, then at r.t. until formation of a green-colored precipitate had ceased. It was filtered off and, in order to remove the green rhodium catalyst, it was triturated with 1 M hydroxylamine hydrochloride[25] under ultrasonication. The green-colored water phase was decanted off and this procedure was repeated, until the remaining solid product was colorless. It was washed with water (2 × 10 mL) and dried (50 °C/10^{-3} mbar) to afford **3a** (869 mg, 70%) as a colorless solid; mp 198–200 °C.

IR (ATR): 1182 (m), 1230 (m), 1282 (m), 1643 (w), 1718 (s), 3278 cm^{-1} (br, w).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.33 (t, ^3J = 7.2 Hz, 3 H, OCH_2*Me*), 3.61 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), 4.29–4.45 (m, 3 H, N*CH*^{A}H^B, OCH_2Me), 4.87 (d, ^2J = 19.6 Hz, 1 H, NCH^A*H*^{B}), 7.60–7.72 (m, 3 H, H_{Ar}), 7.85–7.92 (m, 1 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 13.90 (OCH_2*Me*), 48.64 (NCH_2), 52.97 and 53.35 (OMe), 63.39 (OCH_2Me), 92.30 ($CH_2COC_{bridgehead}$), 97.64 ($NC_{bridgehead}$), 124.05, 124.18, 131.47 (CH_{Ar}), 132.29 (C_q), 132.88 (CH_{Ar}), 134.63, 138.90, 143.85 (C_q), 159.49 (COOMe), 161.58 (*C*OOEt), 162.06 (*C*OOMe), 165.63 (NC=O), 186.96 (CH_2*C*=O).

MS (CI): *m*/*z* = 416 $[M + H]^+$, 356 $[M - COOCH_3]^+$.

Anal. Calcd for $C_{20}H_{17}NO_9$ (415.35): C, 57.84; H, 4.13; N, 3.37. Found: C, 57.61; H, 4.14; N, 3.29.

9-Ethyl 10,11-Dimethyl (7*SR*,9*SR*,11a*RS*)-9,11a-Epoxy-7-*exo*-isopropyl-5,8-dioxo-7,8,9,11a-tetrahydro-5*H*-azepino[2,1-*a*]isoindole-9,10,11-tricarboxylate (3c)

To a solution of diazo ester **4c** (1.80 g, 5.2 mmol) in dry benzene (20 mL) was added DMAD (0.7 mL, 5.7 mmol) dissolved in benzene (40 mL) and $Rh_2(OAc)_4$ (77 mg, 3 mol%). The magnetically stirred mixture was heated at reflux for 6 h, then cooled to 20 °C. The solution was passed through a syringe filter to remove the catalyst, the resulting clear yellow solution was evaporated to dryness, and the remaining solid was recrystallized (*i*-PrOH). Drying (50 °C/10^{-3} mbar) gave **3c** (1.27 g, 53%) as a colorless solid; mp 167–170 °C.

IR (KBr): 1007 (m), 1276 (s), 1322 (s), 1374 (s), 1707 (s), 1725 (m), 1760 (s), 3435 cm^{-1} (br).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.91 (d, ^3J = 7.0 Hz, 3 H, CH_3CH*Me*), 1.21 (d, ^3J = 7.1 Hz, 3 H, *CH*$_3$CHMe), 1.34 (t, ^3J = 7.1 Hz, 3 H, OCH_2*Me*), 3.44–3.56 (m, 4 H, CH_3*CH*Me, OMe), 3.92 (s, 3 H, OMe), 4.27–4.47 (m, 2 H, OCH_2Me), 4.83 (d, ^3J = 3.4 Hz, 1 H, NCH), 7.59–7.70 (m, 3 H, H_{Ar}), 7.83–7.90 (m, 1 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.07 (OCH_2*Me*), 16.86 and 19.93 (CH*Me*$_2$), 28.72 (*C*HMe_2), 52.95 and 53.37 (OMe), 63.39 (OCH_2Me), 68.99 (NCH), 93.19 ($CHCOC_{bridgehead}$), 97.66 ($NC_{bridgehead}$), 123.53, 123.73, 131.43, 132.72 (CH_{Ar}), 133.87, 137.49, 139.02, 143.09 (C_q), 159.81 (*C*OOMe), 161.66 (*C*OOCH$_2$Me), 161.94 (*C*OOMe), 164.85 (NC=O), 188.94 (CH*C*=O).

MS (CI): *m*/*z* = 458 $[M + H]^+$, 426 $[M - OMe]^+$, 398 $[M - COOMe]^+$.

Anal. Calcd for $C_{23}H_{23}NO_9$ (457.44): C, 60.39; H, 5.07; N, 3.06. Found: C, 60.16; H, 5.05; N, 3.12.

Reactions of Tetracycles 3 with Water

N-{2-[5-(Ethoxycarbonyl)-3,4-bis(methoxycarbonyl)furan-2-yl]benzoyl}glycine (5a)

Tetracycle **3a** (160 mg, 0.38 mmol) was suspended in a mixture of acetone (5 mL) and water (2 mL). On warming to 40 °C, a clear solution resulted, which was stirred for 5 min. The solvents were removed in vacuo and the residue was triturated with Et_2O (10 mL) in an ultrasonic bath. The colorless solid was isolated and dried (50 °C/10^{-3} mbar) to furnish pure **5a** (122 mg, 73%); mp 171–172 °C.

IR (KBr): 1184 (s), 1239 (s), 1663 (m), 1729 (s), 3391 cm^{-1} (br, m).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (t, ^3J = 7.1 Hz, 3 H, $COOCH_2$*Me*), 3.71 (s, 3 H, OMe), 3.96 (s, 3 H, OMe), 4.13 (d, ^3J = 5.3 Hz, 2 H, NCH_2), 4.34 (q, ^3J = 7.1 Hz, 2 H, OCH_2Me), 6.53 (t, ^3J = 5.1 Hz, 1 H, NH), 7.55–7.61 (m, 3 H, H_{Ar}), 7.67–7.73 (m, 1 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.03 (OCH_2*Me*), 41.74 (NCH_2), 52.24 and 53.06 (OMe), 61.93 (OCH_2Me), 115.36, 126.03, 126.93 (C_q), 127.76, 130.34, 130.82, 131.64 (CH_{Ar}), 136.10, 140.56 (C_q), 157.21 (*C*OOEt), 158.79 (C_q), 161.55 and 163.59 (*C*OOMe), 168.20 (NC=O), 172.13 (COOH).

MS (CI): *m*/*z* = 434 $[M + H]^+$, 416 $[M - OH]^+$, 402 $[M - OCH_3]^+$, 359 $[M - NHCH_2COOH]^+$.

Anal. Calcd for $C_{20}H_{19}NO_{10}$ (433.37): C, 55.43; H, 4.42; N, 3.23. Found: C, 55.41; H, 4.64; N, 3.17.

N-{2-[5-(Ethoxycarbonyl)-3,4-bis(methoxycarbonyl)furan-2-yl]benzoyl}alanine (5b)

The solution of **3b** (300 mg, 0.70 mmol) in acetone/water (8 mL/3 mL) was stirred for 5 min at 20 °C. After evaporation of the volatiles in vacuo, the crude product was purified by column chromatography (silica gel, acetone) to give **5b** (227 mg, 72%) as a colorless solid; mp 179 °C.

IR (ATR): 1176 (s), 1230 (s), 1647 (m), 1718 (s), 3350 cm^{-1} (br, w).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.31 (t, ^3J = 7.1 Hz, 3 H, OCH_2*Me*), 1.40 (d, ^3J = 7.2 Hz, 3 H, CH*CH*$_3$), 3.68 (s, 3 H, OMe), 3.93 (s, 3 H, OMe), 4.32 (q, ^3J = 7.2 Hz, 2 H, OCH_2Me), 4.59 (m_c, 1 H, *CH*Me), 6.71 (d, ^3J = 7.3 Hz, 1 H, NH), 7.49–7.60 (m, 3 H, H_{Ar}), 7.62–7.71 (m, 1 H, H_{Ar}), 9.43 (br s, 1 H, COOH).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 13.99 (OCH_2*Me*), 17.77 (CH*Me*), 48.49 (*C*HMe), 52.21 (O*Me*), 53.02 (O*Me*), 61.87 (OCH_2Me), 115.24, 126.11, 126.78 (C_q), 127.75, 130.24, 130.78, 131.57 (CH_{Ar}), 136.25, 140.42 (C_q), 157.10 (*C*OOEt), 158.85 (C_q), 161.44 and 163.45 (*C*OOMe), 167.57 (NC=O), 175.83 (COOH).

HRMS (ESI): *m*/*z* [2 M + K]$^+$ calcd: 933.19625; found: 933.19634; *m*/*z* calcd [M + K]$^+$: 486.07970; found: 486.07993; *m*/*z* calcd [M + Na]$^+$: 470.10577; found: 470.10602.

N-{2-[5-(Ethoxycarbonyl)-3,4-bis(methoxycarbonyl)furan-2-yl]benzoyl}valine (5c)

In a thick-walled closed Schlenk tube, a solution of **3c** (155 mg, 0.33 mmol) in 1,4-dioxane/water (20 mL/3 mL) was heated at 90 °C for 19 d. After cooling, the precipitate was filtered off and discarded. The filtered solution was concentrated to leave a yellow oil, which contained the desired product beside unidentified impurities. Isolation and purification of **5c** was not possible, but its presence was indicated by the expected NMR signals and a molecular ion peak in a mass spectrum.

HRMS (MALDI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{26}NO_{10}$: 476.15512; found: 476.15539.

Reactions of Tetracycles 3 with Alcohols

2-Ethyl 3,4-Dimethyl 5-{2-[(2-Methoxy-2-oxoethyl)carbamoyl]phenyl}furan-2,3,4-tricarboxylate (6a)

The yellow solution of tetracycle **3a** (350 mg, 0.84 mmol) in anhyd CH_2Cl_2 (5 mL) and anhyd MeOH (3 mL) was stirred at r.t. for 30 min. The volatiles were evaporated in vacuo and the residue was subjected to column chromatography (silica gel, EtOAc/Et_2O, 1:1). The isolated product was dried (50 °C/10^{-3} mbar) to furnish **6a** (271 mg, 72%) as a colorless solid; mp 113–114 °C.

IR (ATR): 1178 (s), 1227 (s), 1532 (m), 1640 (m), 1719 (s), 3293 cm^{-1} (w).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (t, ^3J = 7.1 Hz, 3 H, OCH_2*Me*), 3.70, 3.76, 3.96 (3 s, each 3 H, 3 OMe), 4.11 (d, ^3J = 5.0 Hz, 2 H, NHCH_2), 4.34 (q, ^3J = 7.1 Hz, 2 H, OCH_2Me), 6.45 (t, ^3J = 4.9 Hz, 1 H, NH), 7.51–7.64 (m, 3 H, H_{Ar}), 7.66–7.72 (m, 1 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.07 (OCH_2CH_3), 41.72 (CH_2COOMe), 52.14 (OMe), 52.41 (OMe), 52.92 (OMe), 61.75 (OCH_2Me), 115.32, 126.13, 126.93 (C_q), 127.61, 130.19, 130.75, 131.67 (CH_{Ar}), 136.42, 140.56 (C_q), 157.10 (*C*OOEt), 158.73 (C_q), 161.46 and 163.35 (*C*OOMe), 167.62 (s, NC=O), 169.95 (s, CH_2*C*OOMe).

HRMS (MALDI): *m*/*z* [2 M + Na]$^+$ calcd: 917.22231; found: 917.22082, *m*/*z* [M + Na]$^+$ calcd: 470.10577; found: 470.10490.

Anal. Calcd for $C_{21}H_{21}NO_{10}$ (447.39): C, 56.38; H, 4.73; N, 3.13. Found: 56.26; H, 4.78; N, 3.21.

2-Ethyl 3,4-Dimethyl 5-{2-[(1-Methoxy-1-oxopropan-2-yl)carbamoyl]phenyl}furan-2,3,4-tricarboxylate (6b)

A solution of tetracycle **3b** (300 mg, 0.70 mmol, *exo*-Me/*endo*-Me 2:1) in MeOH (8 mL) was stirred at 20 °C for 30 min. The solvent was evaporated at 35 °C in vacuo and the resulting foam was treated with PE/*i*-PrOH. Crystals of *endo*-**3b** (115 mg, 38%) were obtained. The mother liquor was concentrated and the residue was purified by column chromatography (acetone) to obtain pure **6b** (155 mg, 48% based on **3b**) as a pale yellow solid; mp 134–136 °C.

IR (KBr): 1226 (s), 1636 (m), 1729 (s), 1752 (s), 3287 (m), 3427 cm^{-1} (br, s).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (t, ^3J = 7.1 Hz, 3 H, OCH_2*Me*), 1.40 (d, ^3J = 7.2 Hz, 3 H, CH*Me*), 3.71, 3.75, 3.96 (3 s, each 3 H, 3 OMe), 4.35 (q, ^3J = 7.2 Hz, 2 H, OCH_2Me), 4.64 (m_c, 1 H, *C*HMe), 6.48 (d, ^3J = 7.4 Hz, 1 H, NH), 7.52–7.61 (m, 3 H, H_{Ar}), 7.65–7.72 (m, 1 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.08 (OCH_2*Me*), 18.42 (CH*Me*), 48.48 (*C*HMe), 52.15, 52.53, 52.95 (3 OMe), 61.78 (OCH_2Me), 115.37, 126.23, 126.85 (C_q), 127.69, 130.11, 130.78, 131.61 (CH_{Ar}), 136.80, 140.55 (C_q), 157.08 (*C*OOEt), 158.87 (C_q), 161.42, 163.33 (*C*OOMe), 166.90 (NC=O), 173.11 (CH*C*OOMe).

HRMS (MALDI): *m*/*z* [2 M + Na]$^+$ calcd: 945.25361; found: 945.25182; *m*/*z* [M + K]$^+$ calcd: 500.09535; found: 500.09442; *m*/*z* [M + Na]$^+$ calcd: 484.12142; found: 484.12051.

Anal. Calcd for $C_{22}H_{23}NO_{10}$ (461.42): C, 57.27; H, 5.02; N, 3.04. Found: C, 56.95; H, 5.10; N, 2.94.

2,3,4-Trimethyl 5-{2-[(1-Methoxy-1-oxopropan-2-yl)carbamoyl]phenyl}furan-2,3,4-tricarboxylate (7b)

A suspension of tetracycle **3b** (300 mg, 0.70 mmol) in MeOH (8 mL) was heated at reflux for 2 h, then the volatiles (MeOH, EtOH) were evaporated, fresh MeOH was added and heating was continued for 2 h. This procedure was repeated four times. Workup as described for **6b** yielded **7b** (~65% yield) as a colorless solid, which was characterized by ^{1}H NMR only.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.33 (d, ^3J = 7.1 Hz, 3 H, CH*Me*), 3.64, 3.68, 3.81, 3.90 (4s, each 3 H, 4 OMe), 4.57 (m_c, 1 H, *C*HMe), 6.47 (d, ^3J = 7.8 Hz, 1 H, NH), 7.45–7.56 (m, 3 H, H_{Ar}), 7.62 (m, 1 H, H_{Ar}).

Trimethyl 5-{2-[(1-Methoxy-3-methyl-1-oxobutan-2-yl)carbamoyl]phenyl}furan-2,3,4-tricarboxylate (7c)

A solution of tetracycle **3c** (156 mg, 0.34 mmol) in anhyd MeOH (30 mL) was stirred at 20 °C for 40 h, then heated at reflux during 56 h. The solution was cooled and concentrated, fresh MeOH (30 mL) was added, and heating at reflux was continued for 56 h. After cooling to r.t., the solvent was removed in vacuo and the residue was dissolved in hot *i*-PrOH/cyclohexane (1:1). Petroleum ether (40–65 °C) was added until the solution became turbid. When the mixture was stored in a freezer at –30 °C, product **7c** (ca. 130 mg) separated as a colorless solid, together with unidentified components which could not be removed.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.87–0.94 (m, 6 H, CHMe_2), 2.10–2.21 (m, 1 H, *C*HMe_2), 3.70, 3.74, 3.87, 3.96 (4 s, each 3 H, 4 OMe), 4.59 (dd ^3J = 4.8, 8.6 Hz, 1 H, NCH), 6.43 (d, ^3J = 8.6 Hz, 1 H, NH), 7.53–7.60 (m, 3 H, H_{Ar}), 7.67–7.72 (m, 1 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 17.83, 18.76 (CHMe_2), 31.47 (*C*HMe_2), 52.16, 52.19, 52.47, 53.02 (OMe), 57.55 (s, NCH), 115.45, 126.39, 126.82 (C_q), 127.69, 130.13, 130.81, 131.65 (CH_{Ar}), 136.90, 140.35 (C_q), 157.50 (*C*OOMe), 159.02 (C_q), 161.39, 163.22 (*C*OOMe), 167.39 (NC=O), 172.12 (CH*C*OOMe).

MS (MALDI): [M] calcd for $C_{23}H_{25}NO_{10}$ (475.45); *m*/*z* = 514 [M + K]$^+$, 498 [M + Na]$^+$, 476 [M + H]$^+$.

2-Ethyl 3,4-Dimethyl 5-{2-[(1-Ethoxy-1-oxopropan-2-yl)carbamoyl]phenyl}furan-2,3,4-tricarboxylate (6d)

A suspension of tetracycle **3b** (215 mg, 0.50 mmol) in anhyd EtOH (8 mL) was heated at reflux during 6 h. The clear solution was cooled, the solvent was evaporated in vacuo, and the residue was subjected to column chromatography (silica gel, CH_2Cl_2/Et_2O, 8:2). The product

fraction furnished a yellow oil, which was triturated with Et_2O (10 mL) in an ultrasonic bath to give **6d** (181 mg, 76%) as a colorless solid; mp 144–145 °C.

IR (ATR): 1141 (m), 1170 (m), 1222 (s), 1321 (m), 1532 (m), 1634 (m), 1723 (s), 1746 (m), 3271 cm^{-1} (br, w).

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.28 (t, ^3J = 7.1 Hz, 3 H, OCH_2Me), 1.34 (t, ^3J = 7.1 Hz, 3 H, OCH_2Me), 1.40 (d, ^3J = 7.1 Hz, 3 H, $CHMe$), 3.71 (s, 3 H, OMe), 3.96 (s, 3 H, OMe), 4.20 (q, ^3J = 7.1 Hz, 2 H, OCH_2Me), 4.34 (q, ^3J = 7.1 Hz, 2 H, OCH_2Me), 4.61 (m_c, 1 H, $CHMe$), 6.51 (d, ^3J = 7.3 Hz, 1 H, NH), 7.51–7.62 (m, 3 H, H_{Ar}), 7.65–7.72 (m, 1 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.08 (OCH_2Me), 18.46 ($CHMe$), 48.56 ($CHMe$), 52.14 and 52.93 (OMe), 61.60 (OCH_2Me), 61.75 (OCH_2Me), 115.33, 126.26, 126.89 (s, C_q), 127.64, 130.07, 130.76, 131.61 (CH_{Ar}), 136.86, 140.52 (C_q), 157.09 (COOEt), 158.91 (C_q), 161.41 and 163.34 (COOMe), 166.87 (NC=O), 172.70 ($CHCOOEt$).

HRMS (MALDI): *m*/*z* [2 M + Na]$^+$ calcd: 973.28491; found: 973.28377; *m*/*z* [M + K]$^+$ calcd: 514.11100; found: 514.11059; *m*/*z* [M + Na]$^+$ calcd: 498.13707; found: 498.13665; *m*/*z* [M + H]$^+$ calcd: 476.15512; found: 476.15480.

Anal. Calcd for $C_{23}H_{25}NO_{10}$ (475.45): C, 58.10; H, 5.30; N, 2.95. Found: C, 58.34; H, 5.25; N, 2.92.

2-Ethyl 3,4-Dimethyl 5-{2-[(1-Ethoxy-3-methyl-1-oxobutan-2-yl)carbamoyl]phenyl}furan-2,3,4-tricarboxylate (6e)

In a thick-walled Schlenk tube, a solution of **3c** (0.30 mmol) in anhyd EtOH was heated at 70 °C during 232 h. After cooling, the solid precipitate was filtered off and the filtrate was concentrated to afford a brown oil, which contained **6c** beside a considerable amount of unidentified material. Isolation and purification of **6e** was not possible, but its presence was indicated by the expected NMR and MS data.

HRMS (MALDI): *m*/*z* [M + K]$^+$ calcd: 542.14230; found: 542.14296; *m*/*z* [M + Na]$^+$ calcd: 526.16837; found: 526.16902.

2-Ethyl 3,4-Dimethyl 5-{2-[(1-Oxo-1-propoxypropan-2-yl)carbamoyl]phenyl}furan-2,3,4-tricarboxylate (6f)

Prepared from tetracycle **3b** (200 mg, 0.47 mmol) in anhyd PrOH (8 mL) at 90 °C for 6 h as described for **6a**. Column chromatography (Et_2O) gave **6f** (182 mg, 80%) as a colorless solid; mp 99–101 °C.

IR (KBr): 1220 (s), 1638 (s), 1725 (s), 1752 (s), 3301 (m), 3425 cm^{-1} (br, m).

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.94 (t, ^3J = 7.4 Hz, 3 H, OCH_2CH_2Me), 1.33 (t, ^3J = 7.2 Hz, 3 H, OCH_2Me), 1.40 (d, ^3J = 7.1 Hz, 3 H, $CHMe$), 1.61–1.72 (m, 2 H, CH_2Me), 3.70 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), 4.05–4.16 (m, 2 H, OCH_2CH_2), 4.34 (q, ^3J = 7.1 Hz, 2 H, OCH_2Me), 4.63 (m_c, 1 H, $CHMe$), 6.53 (d, ^3J = 7.2 Hz, 1 H, NH), 7.51–7.62 (m, 3 H, H_{Ar}), 7.64–7.72 (m, 1 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 10.15 (CH_2CH_2Me), 13.98 (OCH_2Me), 18.35 ($CHMe$), 21.78 (OCH_2CH_2), 48.47 ($CHMe$), 52.04 and 52.84 (OMe), 61.65 (OCH_2Me), 67.02 (OCH_2CH_2), 115.20, 126.18, 126.80 (C_q), 127.54, 129.98, 130.67, 131.51 (CH_{Ar}), 136.73, 140.39 (C_q), 156.98 (COOEt), 158.85 (C_q), 161.30 and 163.25 (COOMe), 166.81 (NC=O), 172.68 ($COOC_3H_7$).

HRMS (MALDI): *m*/*z* [2 M + Na]$^+$ calcd: 1001.31621; found: 1001.31658; *m*/*z* [M + K]$^+$ calcd: 528.12665; found: 528.12646; *m*/*z* [M + Na]$^+$ calcd: 512.15272; found: 512.15252; *m*/*z* [M + H]$^+$ calcd: 490.17077; found: 490.17076.

Anal. Calcd for $C_{24}H_{27}NO_{10}$ (489.48): C, 58.89; H, 5.56; N, 2.86. Found: C, 59.10; H, 5.65; N, 2.77.

2-Ethyl 3,4-Dimethyl 5-{2-[(2-Isopropoxy-2-oxoethyl)carbamoyl]phenyl}furan-2,3,4-tricarboxylate (6g)

Prepared from tetracycle **3a** (250 mg, 0.60 mmol) in anhyd *i*-PrOH (8 mL) at reflux for 8 h. The reaction solution was brought to r.t., the solvent was evaporated in vacuo, and the residue was recrystallized (*i*-PrOH/cyclohexane, crystallization was completed at 7 °C during 20 h) to give **6g** (197 mg, 69%) as a colorless solid; mp 128–129 °C.

IR (KBr): 1177 (s), 1230 (s), 1666 (s), 1729 (s), 1760 (m), 3345 cm^{-1} (m).

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.27 (d, ^3J = 6.3 Hz, 6 H, $CHMe_2$), 1.34 (t, ^3J = 7.2 Hz, 3 H, OCH_2Me), 3.71 (s, 3 H, OMe), 3.96 (s, 3 H, OMe), 4.07 (d, ^3J = 5.0 Hz, 2 H, NCH_2), 4.34 (q, ^3J = 7.2 Hz, 2 H, OCH_2Me), 5.08 (m_c, ^3J = 6.3 Hz, 1 H, $CHMe_2$), 6.44 (t, ^3J = 4.7 Hz, 1 H, NH), 7.52–7.64 (m, 3 H, H_{Ar}), 7.66–7.73 (m, 1 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.07 (OCH_2Me), 21.70 ($CHMe_2$), 42.05 (NCH_2), 52.11 and 52.89 (OCH_3), 61.71 (OCH_2Me), 69.46 ($CHMe_2$), 115.27, 126.15, 126.98 (C_q), 127.54, 130.13, 130.72, 131.67 (CH_{Ar}), 136.52, 140.52 (C_q), 157.11 (COOEt), 158.78 (C_q), 161.45, 163.38 (COOMe), 167.55 (NC=O), 169.09 ($COOC_3H_7$).

HRMS (MALDI): *m*/*z* [2 M + Na]$^+$ calcd: 973.28491; found: 973.28394; *m*/*z* [M + K]$^+$ calcd: 514.11100; found: 514.11094; *m*/*z* [M + Na]$^+$ calcd: 498.13707; found: 498.13694; *m*/*z* [M + H]$^+$ calcd: 476.15512; found: 476.15505.

Anal. Calcd for $C_{23}H_{25}NO_{10}$ (475.45): C, 58.10; H, 5.30; N, 2.95. Found: C, 57.97; H, 5.35; N, 3.12.

2-Ethyl 3,4-Dimethyl 5-(2-{[2-(Benzyloxy)-2-oxoethyl]carbamoyl}phenyl)furan-2,3,4-tricarboxylate (6h)

Tetracycle **3a** (150 mg, 0.36 mmol) was suspended in benzyl alcohol (4 mL) and heated at 65 °C for 6 h. Evaporation of excess alcohol at 130 °C/10^{-3} mbar followed by column chromatography (Et_2O) gave **6h** (129 mg, 68%) as a colorless solid; DSC: T_g = 32 °C.

IR (ATR): 1175 (s), 1231 (s), 1663 (m), 1720 cm^{-1} (s).

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.32 (t, ^3J = 7.1 Hz, 3 H, OCH_2Me), 3.69 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), 4.14 (d, ^3J = 5.1 Hz, 2 H, NCH_2), 4.32 (q, ^3J = 7.1 Hz, 2 H, OCH_2Me), 5.19 (s, 2 H, $PhCH_2$), 6.50 (m_c, 1 H, NH), 7.30–7.40 (m, 5 H, H_{Ar}), 7.48–7.73 (m, 4 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.04 (OCH_2Me), 41.81 (NCH_2), 52.11 (OMe), 52.91 (OMe), 61.71 (OCH_2Me), 67.22 (CH_2Ph), 115.24, 126.12, 126.93 (C_q), 127.54, 128.35, 128.49, 128.59, 130.15, 130.71, 131.66 (CH_{Ar}), 135.10, 136.37, 140.50 (C_q), 157.08 (COOEt), 158.74 (C_q), 161.44 and 163.36 (COOMe), 167.64 (NC=O), 169.44 ($COOCH_2Ph$).

HRMS (MALDI): *m*/*z* [2 M + Na]$^+$ calcd: 1069.28491; found: 1069.28222; *m*/*z* [M + K]$^+$ calcd: 562.11100; found: 562.11078; *m*/*z* [M + Na]$^+$ calcd: 546.13707; found: 546.13669; *m*/*z* [M + H]$^+$ calcd: 524.15512; found 524.15475.

Anal. Calcd for $C_{27}H_{25}NO_{10}$ (523.49): C, 61.95; H, 4.81; N, 2.68. Found: C, 61.94; H, 4.75; N, 2.62.

2-Ethyl 3,4-Dimethyl 5-(2-{[1-(Benzyloxy)-1-oxopropan-2-yl]carbamoyl}phenyl)furan-2,3,4-tricarboxylate (6i)

Prepared as described above for **6h** from tetracycle **3b** (125 mg, 0.29 mmol) in benzyl alcohol (3 mL) at 100 °C for 12 h to give **6i** (97 mg, 62%) as an amorphous yellow solid; DSC: T_g = 36 °C.

IR (ATR): 1160 (s), 1229 (s), 1663 (m), 1722 (s), 3366 cm^{-1} (br, w).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.33 (t, ^3J = 7.1 Hz, 3 H, OCH_2Me), 1.41 (d, ^3J = 7.1 Hz, 3 H, $CHMe$), 3.69 (s, 3 H, OMe), 3.96 (s, 3 H, OMe), 4.33 (q, ^3J = 7.1 Hz, 2 H, OCH_2Me), 4.69 (m_c, 1 H, $CHMe$), 5.14–5.23 (AB system, 2 H, OCH_2Ph), 6.51 (d, ^3J = 7.3 Hz, 1 H, NH), 7.29–7.72 (m, 9 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.09 (OCH_2Me), 18.42 ($CHMe$), 48.56 ($CHMe$), 52.18 (OMe), 52.99 (OMe), 61.78 (OCH_2Me), 67.25 (OCH_2Ph), 115.29, 126.24, 126.85 (C_q), 127.62, 128.16, 128.46, 128.62, 130.12, 130.77, 131.65 (CH_{Ar}), 135.25, 136.75, 140.49 (C_q), 157.08 (COOEt), 158.90 (C_q), 161.42 and 163.39 (COOMe), 166.94 (NC=O), 172.58 ($CHCOOCH_2$).

HRMS (MALDI): m/z [2 M + Na]$^+$ calcd: 1097.31621; found: 1097.31224; m/z [M + K]$^+$ calcd: 576.12665; found: 576.12610; m/z [M + Na]$^+$ calcd: 560.15272; found: 560.15220.

Anal. Calcd for $C_{28}H_{27}NO_{10}$ (537.52): C, 62.57; H, 5.06; N, 2.61. Found: C, 62.41; H, 5.15; N, 2.49.

2-Ethyl 3,4-Dimethyl 5-(2-{[2-(Hex-5-enyloxy)-2-oxoethyl]carbamoyl}phenyl)furan-2,3,4-tricarboxylate (6j)

Tetracycle **3a** (322 mg, 0.78 mmol) was suspended in anhyd hex-5-en-1-ol (6 mL) and heated at 95 °C for 6 h. Evaporation of excess alcohol at 100 °C/10^{-3} mbar followed by column chromatography (Et_2O) furnished **6j** (284 mg, 71%) as a colorless viscous oil.

IR (NaCl): 1239 (br, s), 1309 (s), 1411 (s), 1450 (s), 1534 (s), 1666 (s), 1747 (s), 3379 cm^{-1} (br, m).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (t, ^3J = 7.1 Hz, 3 H, OCH_2Me), 1.40–1.50 (m, 2 H, $OCH_2CH_2CH_2$), 1.57–1.74 (m, 2 H, $OCH_2CH_2CH_2$), 2.00–2.16 (m, 2 H, H_2C=$CHCH_2$), 3.70 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), 4.10 (d, ^3J = 5.0 Hz, 2 H, NCH_2), 4.16 (t, ^3J = 6.7 Hz, 2 H, $OCH_2CH_2CH_2$), 4.34 (q, ^3J = 7.1 Hz, 2 H, OCH_2Me), 4.90–5.07 (m, 2 H, H_2C=$CHCH_2$), 5.70–5.86 (m, 1 H, H_2C=$CHCH_2$), 6.46 (br t, 1 H, NH), 7.50–7.73 (m, 4 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.07 (OCH_2Me), 25.02 ($O(CH_2)_2CH_2$), 27.87 (OCH_2CH_2), 33.16 (H_2C=$CHCH_2$), 41.80 (NCH_2), 52.14, 52.93 (OMe), 61.73 (OCH_2Me), 65.51 (OCH_2CH_2), 114.95 (H_2C=$CHCH_2$), 115.24 (C_q), 126.14 (C_q), 126.96 (C_q), 127.52, 130.16, 130.73, 131.70 (CH_{Ar}), 136.43 (C_q), 138.12 (H_2C=$CHCH_2$), 140.50 (C_q), 157.10 (COOEt), 158.79 (C_q), 161.45 and 163.39 and 167.60 (NC=O), 169.64 (NCH_2CO).

HRMS (MALDI): m/z [2 M + Na]$^+$ calcd: 1053.34751; found: 1053.34394; m/z [M + Na]$^+$ calcd: 538.16837; found: 538.16789.

Anal. Calcd for $C_{26}H_{29}NO_{10}$ (515.52): C, 60.58; H, 5.67; N, 2.72. Found: C, 60.32; H, 5.69; N, 2.79.

2-Ethyl 3,4-Dimethyl 5-(2-{[2-(Allyloxy)-2-oxoethyl]carbamoyl}phenyl)furan-2,3,4-tricarboxylate (6k)

Prepared as described for **6j** from tetracycle **3a** (200 mg, 0.48 mmol) and allyl alcohol (4 mL) at 85 °C for 6 h to give **6k** (153 mg, 67%) as a colorless oil.

IR (NaCl): 1186 (s), 1236 (s), 1531 (m), 1669 (s), 1750 (s), 3384 cm^{-1} (br, m).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.33 (t, ^3J = 7.1 Hz, 3 H, OCH_2Me), 3.70 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), 4.13 (d, ^3J = 5.1 Hz, 2 H, NCH_2), 4.33 (q, ^3J = 7.1 Hz, 2 H, OCH_2Me), 4.65 (d, ^3J = 5.8 Hz, 2 H, H_2C=$CHCH_2$), 5.20–5.37 (m, 2 H, H_2C=$CHCH_2$), 5.84–5.96 (m, 1 H, H_2C=$CHCH_2$), 6.48 (br t, 1 H, NH), 7.49–7.63 (m, 3 H, H_{Ar}), 7.66–7.71 (m, 1 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.06 (OCH_2Me), 41.75 (NCH_2), 52.15 and 52.93 (OMe), 61.73 (OCH_2Me), 66.08 (H_2C=$CHCH_2$), 115.21 (C_q), 119.01 (H_2C=$CHCH_2$), 126.10, 126.92 (C_q), 127.53, 130.18, 130.73 (CH_{Ar}), 131.36 (H_2C=$CHCH_2$), 131.67 (CH_{Ar}), 136.34 (C_q), 140.47 (C_q), 157.08 (COOEt), 158.76 (C_q), 161.44 and 163.38 (COOMe), 167.62 (NC=O), 169.25 (NCH_2C=O).

HRMS (MALDI): m/z [M + K]$^+$ calcd: 512.09535; found: 512.09520; m/z [M + Na]$^+$ calcd: 496.12142; found: 496.12120; m/z [M + H]$^+$ calcd: 474.13947; found: 474.13931.

Anal. Calcd for $C_{23}H_{23}NO_{10}$ (473.43): C, 58.35; H, 4.90; N, 2.96. Found: C, 58.29; H, 5.14; N, 2.82.

Reaction of Tetracycle 3b with Thiolates

2-Ethyl 3,4-Dimethyl 5-(2-{[1-Oxo-1-(phenylthio)propan-2-yl]carbamoyl}phenyl)furan-2,3,4-tricarboxylate (8a)

To a solution of tetracycle **3b** (200 mg, 0.46 mmol) in anhyd CH_2Cl_2 (5 mL) was added benzenethiol (57 µL, 0.56 mmol) and dry NEt_3 (97 µL, 0.70 mmol). The deep-yellow solution was stirred for 30 min, then the volatiles were evaporated. The resulting brown foam was purified by column chromatography (silica gel, Et_2O) to afford **8a** (174 mg, 69%) as an amorphous colorless solid; DSC: T_g = 36 °C.

IR (KBr): 1179 (m), 1237 (m), 1656 (m), 1727 (s), 3427 cm^{-1} (vs).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.32 (t, ^3J = 7.1 Hz, 3 H, OCH_2Me), 1.49 (d, ^3J = 7.1 Hz, 3 H, $CHMe$), 3.71 (s, 3 H, OMe), 3.94 (s, 3 H, OMe), 4.31 (q, ^3J = 7.1 Hz, 2 H, OCH_2Me), 4.90 (m_c, 1 H, $CHMe$), 6.46 (d, ^3J = 7.9 Hz, 1 H, NH), 7.38–7.44 (m, 5 H, H_{Ar}), 7.54–7.62 (m, 3 H, H_{Ar}), 7.72–7.77 (m, 1 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.07 (OCH_2Me), 18.79 ($CHMe$), 52.24 and 52.97 (OMe), 55.33 ($CHMe$), 61.83 (OCH_2Me), 115.38, 126.14, 126.60, 126.89 (C_q), 127.60, 129.24, 129.60, 130.31, 130.86, 131.73, 134.68 (CH_{Ar}), 136.55, 140.57 (C_q), 157.06 (COOEt), 158.87 (C_q), 161.51 (COOMe), 163.34 (COOMe), 167.15 (NC=O), 198.61 (SC=O).

HRMS (MALDI): m/z [M + K]$^+$ calcd: 578.08816; found: 578.08769; m/z [M + Na]$^+$ calcd: 562.11422; found: 562.11378; m/z [M + H]$^+$ calcd: 540.13228; found: 540.13189.

Anal. Calcd for $C_{27}H_{25}NO_9S$ (539.56): C, 60.10; H, 4.67; N, 2.60; S, 5.94. Found: C, 59.90; H, 4.80; N, 2.44; S, 5.70.

2-Ethyl 3,4-Dimethyl 5-(2-{[1-(Cyclohexylthio)-1-oxopropan-2-yl]carbamoyl}phenyl)furan-2,3,4-tricarboxylate (8b)

A solution of cyclohexanethiol (112 µL, 0.92 mmol) and DBU (112 µL, 0.75 mmol) in anhyd CH_2Cl_2 (5 mL) was added dropwise to a solution of tetracycle **3b** (320 mg, 0.75 mmol) in anhyd CH_2Cl_2 (5 mL). The deep-red solution was stirred for 30 min, then concentrated. Column chromatography (silica gel, cyclohexane/EtOAc, 2:8) furnished **8b** (269 mg, 66%) as an amorphous yellow solid; DSC: T_g = 32 °C.

IR (KBr): 1178 (m), 1234 (m), 1673 (m), 1729 (s), 3424 cm^{-1} (br, m).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.17–1.50 (m, 11 H, OCH_2Me, $CHMe$, 5 $CH_{c\text{-}hex}$), 1.54–1.77 (m, 3 H, $CH_{c\text{-}hex}$), 1.84–1.98 (m, 2 H, $CH_{c\text{-}hex}$), 3.44–3.55 (m, 1 H, SCH), 3.71 (s, 3 H, OMe), 3.96 (s, 3 H, OMe), 4.34 (q, ^3J = 7.1 Hz, 2 H, OCH_2Me), 4.73 (m_c, 1 H, $CHMe$), 6.46 (d, ^3J = 7.9 Hz, 1 H, NH), 7.52–7.62 (m, 3 H, H_{Ar}), 7.68–7.75 (m, 1 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.10 (OCH_2Me), 19.15 ($CHMe$), 25.46 (C-$4_{c\text{-}hex}$), 25.93 (C-$3_{c\text{-}hex}$), 32.88 (C-$2_{c\text{-}hex}$), 42.56 (SCH), 52.20 and 52.96 (OMe), 55.43 ($CHMe$), 61.80 (OCH_2Me), 115.30, 126.19, 126.83 (C_q), 127.62, 130.16, 130.81, 131.68 (CH_{Ar}), 136.70, 140.49 (C_q), 157.06 (COOEt), 158.91 (C_q), 161.46 and 163.34 (COOMe), 166.87 (NC=O), 200.03 (SC=O).

HRMS (MALDI): *m*/*z* [2 M + Na]$^+$ calcd: 1113.33313; found: 1113.33489; *m*/*z* [M + K]$^+$ calcd: 584.13586; found: 584.13511; *m*/*z* [M + Na]$^+$ calcd: 568.16117; found 568.16190.

Anal. Calcd for $C_{27}H_{31}NO_9S$ (545.60): C, 59.44; H, 5.73; N, 2.57; S, 5.88. Found: C, 59.30; H, 5.78; N, 2.71; S, 5.90.

Reactions of Tetracycles 3 with NH-Nucleophiles; General Procedure

Liquid amines (benzylamine, cyclohexylamine, allylamine, and *tert*-butylamine) were dried over powdered KOH and distilled. A solution of a tetracycle **3** (~0.2–0.7 mmol) in anhyd CH_2Cl_2 (4–5 mL) was treated with a moderate excess of a primary or secondary amine (for reaction conditions see individual compounds). The resulting yellow clear solution was diluted with CH_2Cl_2 (10 mL) and transferred to a separatory funnel. After extraction with 2 M aq HCl (3 × 10 mL) and water (2 × 10 mL), the organic phase was separated, dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The crude product was recrystallized (EtOAc/PE) and dried (50 °C/10^{-3} mbar).

2-Ethyl 3,4-Dimethyl 5-{2-[(2-Amino-2-oxoethyl)carbamoyl]phenyl}furan-2,3,4-tricarboxylate (9a)

*(a) From tetracycle **3a***: A solution of **3a** (96 mg, 0.23 mmol) in anhyd CH_2Cl_2 (3 mL) was combined with 0.5 M ammonia in 1,4-dioxane solution. After stirring at r.t. for 5 min, more CH_2Cl_2 (10 mL) was added and the solution was transferred to a separatory funnel. After extraction with water (10 mL) the organic layer was separated, dried (Na_2SO_4), and filtered and the volatiles were evaporated in vacuo. The residue was dried (50 °C/10^{-3} mbar) to give **9a** (92 mg, 92%) as a colorless solid.

*(b) From N-tert-butyl carboxamide **9f***: A solution of **9f** (123 mg, 0.25 mmol) in TFA (3 mL) was kept at 65 °C for 10 h. The volatiles were evaporated and the residue was purified by column chromatography (acetone). The desired product was isolated and dried (50 °C/10^{-3} mbar) to give **9a** (82 mg, 75%) as a colorless solid; mp 184–185 °C.

IR (ATR): 1170 (s), 1227 (m), 1648 (s), 1684 (m), 1701 (m), 1728 (s), 3372 (w), 3439 cm^{-1} (w).

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.26 (t, ^3J = 7.1 Hz, 3 H, OCH$_2$*Me*), 3.61 (s, 3 H, OMe), 3.68 (d, ^3J = 5.8 Hz, 2 H, C*H*$_2$NH), 3.86 (s, 3 H, OMe), 4.29 (q, ^3J = 7.1 Hz, 2 H, OC*H*$_2$Me), 7.09 (s, 1 H, CONH), 7.25 (s, 1 H, CONH), 7.60–7.70 (m, 3 H, H$_{Ar}$), 7.83–7.88 (m, 1 H, H$_{Ar}$), 8.74 (t, ^3J = 5.8 Hz, 1 H, CH$_2$N*H*).

^{13}C NMR (DMSO-d_6, 126 MHz): δ = 13.93 (OCH$_2$*Me*), 42.37 (CH$_2$NH), 52.08 and 52.87 (OMe), 61.62 (COO*C*H$_2$Me), 113.93, 126.06, 126.95 (C$_q$), 128.03, 130.08, 130.64, 131.42 (CH$_{Ar}$), 136.40 (C$_q$), 139.05 (C$_q$), 156.54 (COOEt), 159.92 (C$_q$), 160.85 and 162.71 (*C*OOMe), 166.96 (CONH), 170.60 (CONH$_2$).

HRMS (MALDI): *m*/*z* [2 M + Na]$^+$ calcd: 887.22298; found: 887.22244; *m*/*z* [M + K]$^+$ calcd: 471.08004; found: 471.07992; *m*/*z* [M + Na]$^+$ calcd: 455.10610; found: 455.10597.

Anal. Calcd for $C_{20}H_{20}N_2O_9$ (432.39): C, 55.56; H, 4.66; N, 6.48. Found: C, 55.60; H, 4.64; N, 6.40.

2-Ethyl 3,4-Dimethyl 5-(2-{[2-(Benzylamino)-2-oxoethyl]carbamoyl}phenyl)furan-2,3,4-tricarboxylate (9b)

Prepared from **3a** (150 mg, 0.36 mmol) and benzylamine (51 µL, 0.47 mmol) at 20 °C for 5 min to give **9b** (157 mg, 83%) as a colorless solid; mp 116–117 °C.

IR (ATR): 1177 (s), 1228 (s), 1543 (m), 1638 (m), 1726 (s), 3226 cm^{-1} (br, w).

^{1}H NMR (CD$_2$Cl$_2$, 500 MHz): δ = 1.29 (t, ^3J = 7.1 Hz, 3 H, OCH$_2$*Me*), 3.62 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 3.99 (d, ^3J = 5.2 Hz, 2 H, CH$_2$C=O), 4.27 (q, ^3J = 7.1 Hz, 2 H, OC*H*$_2$Me), 4.41 (d, ^3J = 5.9 Hz, 2 H, C*H*$_2$Ph), 6.53 (br t, 1 H, PhCH$_2$N*H*), 6.88 (br t, 1 H, N*H*CH$_2$C=O), 7.19–7.34 (m, 5 H, H$_{Ar}$), 7.52–7.61 (m, 3 H, H$_{Ar}$), 7.64–7.71 (m, 1 H, H$_{Ar}$).

^{13}C NMR (CD$_2$Cl$_2$, 126 MHz): δ = 14.40 (OCH$_2$*Me*), 43.81 (PhCH$_2$), 44.22 (NHCH$_2$C=O), 52.60 (OMe), 53.43 (OMe), 62.39 (OCH$_2$Me), 115.41 (C$_q$), 126.53 (C$_q$), 127.84, 127.90, 127.96, 129.11, 130.91, 131.35, 132.26 (CH$_{Ar}$), 136.84, 138.86, 140.87 (C$_q$), 157.63 (*C*OOEt), 159.83 (C$_q$), 162.01 (*C*OOMe), 163.76 (*C*OOMe), 168.36 (NCH$_2$NH*C*=O), 168.90 (PhCH$_2$NH*C*=O).

MS (MALDI): *m*/*z* = 561 [M + K]$^+$, 545 [M + Na]$^+$, 523 [M + H]$^+$.

Anal. Calcd for $C_{27}H_{26}N_2O_9$ (522.51): C, 62.07; H, 5.02; N, 5.36. Found: C, 62.14; H, 5.02; N, 5.28.

2-Ethyl 3,4-Dimethyl 5-(2-{[1-(Benzylamino)-1-oxopropan-2-yl]carbamoyl}phenyl)furan-2,3,4-tricarboxylate (9c)

Prepared from **3b** (140 mg, 0.33 mmol) and benzylamine (47 µL, 0.43 mmol) at 20 °C for 5 min to give **9c** (159 mg, 91%) as a colorless solid; mp 162–163 °C.

IR (ATR): 1234 (s), 1555 (s), 1633 (m), 1714 (m), 1730 (m), 1748 (m), 3205 (br, w), 3283 cm^{-1} (br, w).

^{1}H NMR (CD$_2$Cl$_2$, 400 MHz): δ = 1.31 (t, ^3J = 7.1 Hz, 3 H, OCH$_2$*Me*), 1.38 (d, ^3J = 6.9 Hz, 3 H, CH*Me*), 3.65 (s, 3 H, OMe), 3.92 (s, 3 H, OMe), 4.24–4.57 (m, 5 H, *CH*Me, C*H*$_2$NH, OC*H*$_2$Me), 6.52 (br t, 1 H, CH$_2$N*H*), 6.69 (d, ^3J = 7.4 Hz, 1 H, CHN*H*), 7.19–7.38 (m, 5 H, H$_{Ar}$), 7.54–7.70 (m, 4 H, H$_{Ar}$).

^{13}C NMR (CDCl$_3$, 101 MHz): δ = 14.06 (OCH$_2$*Me*), 18.11 (CH*Me*), 43.41 (CH$_2$NH), 49.28 (*C*HMe), 52.19 (OMe), 52.98 (OMe), 61.82 (OCH$_2$Me), 115.04, 126.18, 126.96 (C$_q$), 127.38, 127.40, 127.53, 128.62, 130.22, 130.76, 131.69 (CH$_{Ar}$), 136.53, 137.94, 140.38 (C$_q$), 157.07 (*C*OOEt), 159.11 (C$_q$), 161.42 and 163.34 (*C*OOMe), 167.51 (CHNH*C*=O), 171.57 (CH$_2$NH*C*=O).

MS (MALDI): *m*/*z* = 575 [M + K]$^+$, 559 [M + Na]$^+$.

Anal. Calcd for $C_{28}H_{28}N_2O_9$ (536.54): C, 62.68; H, 5.26; N, 5.22. Found: C, 62.51; H, 5.20; N, 5.27.

2-Ethyl 3,4-Dimethyl 5-(2-{[1-(Benzylamino)-3-methyl-1-oxobutan-2-yl]carbamoyl}phenyl)furan-2,3,4-tricarboxylate (9d)

Prepared from tetracycle **3c** (100 mg, 0.22 mmol) and benzylamine (60 µL, 0.55 mmol) at reflux for 16 h. The crude product was triturated with Et$_2$O in an ultrasonic bath for 5 min. Filtration and drying (80 °C/10^{-3} mbar) gave **9d** (63 mg, 51%) as a colorless solid; mp 190–191 °C.

IR (KBr): 1231 (m), 1635 (s), 1731 (s), 3273 cm^{-1} (m).

^{1}H NMR (500 MHz, CD$_2$Cl$_2$): δ = 0.88–0.98 (m, 6 H, CH*Me*$_2$), 1.31 (t, ^3J = 7.1 Hz, 3 H, OCH$_2$*Me*), 2.08–2.19 (m, 1 H, *CH*Me$_2$), 3.63 (s, 3 H, OMe), 3.92 (s, 3 H, OMe), 4.23–4.33 (m, 3 H, OC*H*$_2$Me, NHC*H*), 4.33–4.50 (AB part of ABX spin system, ^2J = 14.9 Hz, ^3J = 6.1 Hz, 2 H, NC*H*^{A}*H*^{B}), 6.31 (br t, 1 H, N*H*CH$_2$), 6.68 (d, ^3J = 8.2 Hz, 1 H, N*H*CH), 7.20–7.36 (m, 5 H, H$_{Ar}$), 7.53–7.62 (m, 3 H, H$_{Ar}$), 7.64–7.72 (m, 1 H, H$_{Ar}$).

^{13}C NMR (126 MHz, CD$_2$Cl$_2$): δ = 14.43 (OCH$_2$*Me*), 18.44 and 19.62 (CH*Me*$_2$), 31.87 (*C*HMe$_2$), 43.91 (NCH$_2$), 52.60 and 53.40 (OMe), 59.52 (NCH), 62.35 (OCH$_2$Me), 115.56, 126.59 (C$_q$), 127.87, 127.91, 128.10, 129.14, 130.79, 131.32, 132.25 (CH$_{Ar}$), 137.40, 138.90, 140.93 (C$_q$), 157.59 (*C*OOEt), 160.02 (C$_q$), 161.93 and 163.76 (*C*OOMe), 167.92 (C$_q$*C*=O), 171.00 (CH*C*=O).

MS (CI): *m*/*z* = 565 [M + H]$^+$, 458 [M – $NHCH_2Ph$]$^+$, 430 [M – $CONHCH_2Ph$]$^+$, 357 [M – $CONHCH_2Ph$ – COOEt]$^+$, 341 [M + H – $NHCH_2Ph$ – 2 COOMe]$^+$.

Anal. Calcd for $C_{30}H_{32}N_2O_9$ (564.59): C, 63.82; H, 5.71; N, 4.96. Found: C, 63.65; H, 5.66; N, 5.02.

2-Ethyl 3,4-Dimethyl 5-(2-{[2-(Allylamino)-2-oxoethyl]carbamoyl}phenyl)furan-2,3,4-tricarboxylate (9e)

Prepared from tetracycle **3a** (178 mg, 0.43 mmol) and allylamine (48 mL, 0.64 mmol) at r.t. for 5 min. After evaporation of the solvent, a yellow foam resulted, which was redissolved in acetone and subjected to flash chromatography (silica gel, acetone). The isolated product was dried (50 °C/10^{-3} mbar) to give **9e** (186 mg, 92%) as an amorphous yellow solid; DSC: T_g = 44 °C.

IR (ATR): 1241 (s), 1624 (s), 1690 (m), 1717 (s), 1746 (m), 3290 cm^{-1} (m).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (t, ^3J = 7.1 Hz, 3 H, OCH_2*Me*), 3.69 (s, 3 H, OMe), 3.85–3.91 (m_c, 2 H, $NHCH_2CH$=), 3.96 (s, 3 H, OMe), 4.01 (d, ^3J = 5.3 Hz, 2 H, $NHCH_2C$=O), 4.34 (q, ^3J = 7.1 Hz, 2 H, OCH_2Me), 5.05–5.21 (m, 2 H, =CH_2), 5.72–5.87 (m, 1 H, $NHCH_2CH$=), 6.30 (br t, 1 H, $NHCH_2CH$=), 6.80 (br t, 1 H, $NHCH_2C$=O), 7.52–7.70 (m, 4 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.06 (OCH_2*Me*), 41.83 ($NHCH_2CH$=), 43.87 ($NHCH_2C$=O), 52.16 and 52.93 (OMe), 61.81 (OCH_2Me), 114.96 (C_q), 116.35 ($CH_{2,olefin}$), 126.09, 127.26 (C_q), 127.38, 130.33, 130.74, 131.79 (CH_{Ar}), 133.64 (CH_{olefin}), 136.19 (C_q), 140.39 (C_q), 157.12 (*C*OOEt), 159.21 (C_q), 161.53 and 163.34 (*C*OOMe), 168.09 and 168.42 ($C{=}O_{amide}$).

HRMS (MALDI): *m*/*z* [2 M + Na]$^+$ calcd: 967.28558; found: 967.28463; *m*/*z* [M + K]$^+$ calcd: 511.11134; found: 511.11105; *m*/*z* [M + Na]$^+$ calcd: 495.13740; found: 495.13708.

Anal. Calcd for $C_{23}H_{24}N_2O_9$ (472.45): C, 58.47; H, 5.12; N, 5.93. Found: C, 58.68; H, 5.16; N, 5.87.

2-Ethyl 3,4-Dimethyl 5-(2-{[2-(*tert*-Butylamino)-2-oxoethyl]carbamoyl}phenyl)furan-2,3,4-tricarboxylate (9f)

Prepared from tetracycle **3a** (350 mg, 0.84 mmol) and *tert*-butylamine (132 mL, 1.26 mmol) at r.t. for 10 min to give **9f** (384 mg, 93%) as a yellow solid; mp 61–62 °C.

IR (ATR): 1177 (m), 1227 (s), 1647 (m), 1724 (s), 3319 cm^{-1} (br, w).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.29–1.39 (m, 12 H, OCH_2*Me*, $NHCMe_3$), 3.69 (s, 3 H, OMe), 3.89 (d, ^3J = 4.8 Hz, 2 H, CH_2NH), 3.95 (s, 3 H, OMe), 4.34 (q, ^3J = 7.1 Hz, 2 H, OCH_2Me), 5.74 (br, 1 H, $NHCMe_3$), 6.80 (br t, 1 H, CH_2NH), 7.50–7.63 (m, 3 H, H_{Ar}), 7.64–7.72 (m, 1 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.08 (OCH_2*Me*), 28.58 (CMe_3), 44.11 (CH_2NH), 51.52 (CMe_3), 52.09 and 52.91 (OMe), 61.72 (OCH_2Me), 115.03, 126.22, 127.20 (C_q), 127.42, 130.19, 130.67, 131.69 (CH_{Ar}), 136.32 (C_q), 140.31 (C_q), 157.12 (*C*OOEt), 159.14 (C_q), 161.43 and 163.41 (*C*OOMe), 167.29 ($CONHCMe_3$), 167.74 ($CONHCH_2$).

HRMS (MALDI): *m*/*z* [M + Na]$^+$ calcd: 511.16870; found: 511.16799; *m*/*z* [M + H]$^+$ calcd: 489.18676; found: 489.18615.

Anal. Calcd for $C_{24}H_{28}N_2O_9$ (488.49): C, 59.01; H, 5.78; N, 5.73. Found: C, 58.80; H, 5.85; N, 5.72.

2-Ethyl 3,4-Dimethyl 5-(2-{[1-(Cyclohexylamino)-1-oxopropan-2-yl]carbamoyl}phenyl)furan-2,3,4-tricarboxylate (9g)

Prepared from tetracycle **3b** (150 mg, 0.35 mmol) and cyclohexylamine (52 µL, 0.46 mmol) at r.t. for 5 min. The product obtained after workup was recrystallized (*i*-Pr_2O) to give **9g** (126 mg, 68%) as a colorless solid; mp 179–181 °C.

IR (ATR): 1235 (s), 1555 (m), 1632 (m), 1724 (m), 3194 (br, w), 3285 cm^{-1} (br, w).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.02–1.22 (m, 3 H), 1.25–1.41 (m, 8 H, OCH_2*Me*, CH*Me*, 2 $H_{c\text{-}hex}$), 1.53–1.77 (m, 3 H), 1.78–1.91 (m, 2 H), 3.64–3.77 (m, 4 H, OMe, $NCHCH_2$), 3.96 (s, 3 H, OMe), 4.34 (q, ^3J = 7.1 Hz, 2 H, OCH_2Me), 4.43 (m_c, ^3J = 6.9 Hz, 1 H, *C*HMe), 6.00 (d, ^3J = 8.2 Hz, 1 H, $NHCHCH_2$), 6.70 (d, ^3J = 7.4 Hz, 1 H, *NH*CHMe), 7.50–7.67 (m, 4 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 14.10 (s, OCH_2*Me*), 18.47 (CH*Me*), 24.74 (CH_2), 25.40 (CH_2), 32.82 and 32.85 ($NCHCH_2$), 48.41 ($NCHCH_2$), 49.39 (*C*HMe), 52.21 and 52.98 (OMe), 61.80 (OCH_2Me), 115.12, 126.24, 126.98 (C_q), 127.44, 130.15, 130.77, 131.71 (CH_{Ar}), 136.68 (C_q), 140.39 (C_q), 157.08 (*C*OOEt), 159.10 (C_q), 161.42 and 163.37 (*C*OOMe), 167.29 (CH_3CHNHC=O), 170.67 (CH_3CHC=O).

MS (CI): *m*/*z* = 529 [M + H]$^+$, 528 [M]$^+$, 430 [M – NH-cyclohexyl]$^+$, 359 [M – $NHCHR_2$]$^+$.

Anal. Calcd for $C_{27}H_{32}N_2O_9$ (528.56): C, 61.36; H, 6.10; N, 5.30. Found: C, 61.24; H, 6.05; N, 5.25.

2-Ethyl 3,4-Dimethyl 5-(2-{[3-Methyl-1-oxo-1-(propylamino)butan-2-yl]carbamoyl}phenyl)furan-2,3,4-tricarboxylate (9h)

Prepared from **3c** (110 mg, 0.24 mmol) and propylamine (30 µL, 0.37 mmol) in anhyd EtOAc (25 mL) at 20 °C for 40 h. The crude product was triturated with Et_2O in an ultrasonic bath for 5 min. After filtration, the product was recrystallized (*i*-PrOH/PE) to give **9h** (71 mg, 57%) as a colorless solid; mp 183–184 °C.

IR (KBr): 1248 (s), 1639 (s), 1732 (s), 3239 (m), 3334 cm^{-1} (m).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.85–0.96 (m, 9 H, NCH_2CH_2*Me*, $CHMe_2$), 1.33 (t, ^3J = 7.1 Hz, 3 H, OCH_2*Me*), 1.42–1.55 (m_c, 2 H, NCH_2CH_2), 2.05–2.15 (m_c, 1 H, *C*HMe_2), 3.06–3.18 and 3.20–3.32 (2 m, 2 H, $NCH^AH^BC_2H_5$), 3.68 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), 4.22 (dd, ^3J = 7.0 and 8.7 Hz, 1 H, NHC*H*), 4.33 (q, ^3J = 7.2 Hz, 2 H, OCH_2Me), 6.07 (m_c, 1 H, $NHCH_2$), 6.70 (d, ^3J = 8.7 Hz, 1 H, *NH*CH), 7.52–7.58 (m, 3 H, H_{Ar}), 7.61–7.70 (m, 1 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 11.31 (NCH_2CH_2*Me*), 14.08 (OCH_2*Me*), 18.24 and 19.16 ($CHMe_2$), 22.70 (NCH_2CH_2Me), 31.25 (*C*HMe_2), 41.20 ($NCH_2C_2H_5$), 52.11 and 52.89 (OMe), 59.13 (NCH), 61.71 (OCH_2Me), 115.11, 126.20, 127.29 (C_q), 127.34, 130.17, 130.71, 131.82 (s, CH_{Ar}), 136.80, 140.45 (C_q), 157.08 (*C*OOEt), 159.39 (C_q), 161.41 and 163.36 (*C*OOMe), 167.47 (C_qC=O), 170.52 (CH*C*=O).

HRMS (MALDI): *m*/*z* [M + H]$^+$ calcd: 517.21806; found: 517.21857; *m*/*z* [M – $NHCH_2CH_2CH_3$]$^+$ calcd: 458.14511; found: 458.14515.

Anal. Calcd for $C_{26}H_{32}N_2O_9$ (516.55): C, 60.46; H, 6.24; N, 5.42. Found: C, 60.41; H, 6.47; N, 5.23.

2-Ethyl 3,4-Dimethyl 5-[2-({2-[(4-Bromophenyl)amino]-2-oxoethyl}carbamoyl)phenyl]furan-2,3,4-tricarboxylate (9i)

Prepared from **3a** (150 mg, 0.36 mmol) and 4-bromoaniline (76 mg, 0.44 mmol). The crude yellow oil was purified by flash chromatography (silica gel, EtOAc), then recrystallized (*i*-PrOH) to give **9i** (142 mg, 67%) as a colorless solid; mp 177–178 °C.

IR (ATR): 1183 (s), 1232 (s), 1534 (s), 1646 (m), 1711 (s), 3270 (br, w), 3397 cm^{-1} (br, w).

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.29 (t, ^3J = 7.1 Hz, 3 H, OCH_2Me), 3.60 (s, 3 H, OMe), 3.94 (s, 3 H, OMe), 4.16 (d, ^3J = 5.5 Hz, 2 H, CH_2NH), 4.22 (q, ^3J = 7.1 Hz, 2 H, OCH_2Me), 6.88 (t, ^3J = 5.4 Hz, 1 H, CH_2NH), 7.34–7.44 (m, 4 H, H_{Ar}), 7.55–7.72 (m, 4 H, H_{Ar}), 8.68 (br, 1 H, CH_2CONH).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 13.97 (OCH_2Me), 45.14 (CH_2NH), 52.19 and 53.00 (OMe), 61.89 (OCH_2Me), 114.94 (C_q), 116.62 (C_q), 121.21 (CH_{Ar}), 126.06 (C_q), 127.29 (C_q), 127.42, 130.73, 130.88, 131.77, 131.95 (CH_{Ar}), 135.77, 136.93 (C_q), 140.42 (C_q), 156.87 (COOEt), 158.89 (C_q), 161.45 and 163.22 (COOMe), 166.70 (CH_2NHC=O), 168.91 (CH_2CONH).

HRMS (MALDI): *m*/*z* [M(^{81}Br, $^{13}C_1$) + H]$^+$ calcd: 590.06729; found: 590.06734; *m*/*z* [M(^{81}Br) + H]$^+$ calcd: 589.06409; found: 589.06399; *m*/*z* [M(^{79}Br, $^{13}C_1$) + H]$^+$ calcd: 588.06931; found: 588.06941; *m*/*z* [M(^{79}Br) + H]$^+$ calcd: 587.06597; found: 587.06601.

Anal. Calcd for $C_{26}H_{23}BrN_2O_9$ (587.38): C, 53.17; H, 3.95; N, 4.77. Found: C, 52.99; H, 3.98; N, 4.78.

2-Ethyl 3,4-Dimethyl 5-[2-({2-[(4-Nitrophenyl)amino]-2-oxoethyl}carbamoyl)phenyl]furan-2,3,4-tricarboxylate (9j)

Prepared from **3a** (100 mg, 0.24 mmol) and 4-nitroaniline (50 mg, 0.36 mmol) at r.t. for 40 h. A solution of the crude product in CH_2Cl_2 was passed over a short column filled with silica gel to remove excess 4-nitroaniline, then the product was eluted with acetone, isolated and recrystallized (*i*-PrOH) to give **9j** (93 mg, 70%) as a yellow solid; mp 189–191 °C.

IR (ATR): 1174 (s), 1231 (s), 1301 (s), 1333 (s), 1506 (s), 1717 (s), 3297 cm^{-1} (br, w).

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.23 (t, ^3J = 7.1 Hz, 3 H, OCH_2Me), 3.61 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 4.15 (q, ^3J = 7.1 Hz, 2 H, OCH_2Me), 4.26 (d, ^3J = 5.0 Hz, 2 H, CH_2NH), 7.17 (m_c, ^3J = 4.9 Hz, 1 H, CH_2NH), 7.53–7.79 (m, 6 H, H_{Ar}), 8.10 (d, ^3J = 9.1 Hz, 2 H, *o*-H_{Ar}), 9.61 (s, 1 H, CH_2CONH).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 13.90 (OCH_2Me), 45.18 (CH_2NH), 52.25 and 53.09 (OMe), 61.93 (OCH_2Me), 114.95 (C_q), 119.05 (*m*-CH_{Ar}), 124.86 (*o*-CH_{Ar}), 126.06 (C_q), 127.14 (C_q), 127.43, 130.97, 131.03, 132.04 (CH_{Ar}), 135.48, 140.36, 143.32, 143.70 (C_q), 156.80 (COOEt), 158.78 (C_q), 161.39 and 163.14 (COOMe), 167.14 (CH_2CONH), 169.26 (CH_2NHC=O).

HRMS (MALDI): *m*/*z* [M + Na]$^+$ calcd: 576.12247; found: 576.12197.

Anal. Calcd for $C_{26}H_{23}N_3O_{11}$ (553.48): C, 56.42; H, 4.19; N, 7.59. Found: C, 56.36; H, 4.29; N, 7.54.

2-Ethyl 3,4-Dimethyl 5-[2-({1-[(3-Azidopropyl)amino]-1-oxopropan-2-yl}carbamoyl)phenyl]furan-2,3,4-tricarboxylate (9k)

Prepared from **3b** (100 mg, 0.23 mmol) and 2-azidopropan-1-amine (25 μL, 0.25 mmol) at r.t. for 5 min. The yellow oil obtained after workup was triturated with Et_2O (5 mL) in an ultrasonic bath for 5 min to give **9k** (90 mg, 73%) as a colorless solid; mp 127–128 °C.

IR (KBr): 1233 (s), 1637 (s), 1665 (s), 1722 (s), 1739 (s), 2103 (m), 3214 (br, m), 3326 cm^{-1} (br, m).

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.30–1.40 (m, 6 H, OCH_2Me, CH*Me*), 1.74 (m_c, ^3J = 6.6 Hz, 2 H, $CH_2CH_2N_3$), 3.21–3.38 (m, 4 H, $NHCH_2$, $CH_2CH_2N_3$), 3.70 (s, 3 H, OMe), 3.96 (s, 3 H, OMe), 4.35 (q, ^3J = 7.1 Hz, 2 H, OCH_2Me), 4.48 (m_c, ^3J = 6.9 Hz, 1 H, C*H*Me), 6.62 (t, ^3J = 5.7 Hz, 1 H, CH_2NH), 6.67 (d, ^3J = 7.4 Hz, 1 H, CHN*H*), 7.50–7.68 (m, 4 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.07 (OCH_2Me), 18.03 (CH*Me*), 28.66 ($CH_2CH_2N_3$), 37.08 ($NHCH_2$), 49.20 ($CH_2CH_2N_3$), 49.35 (*C*HMe), 52.21 and 52.98 (OMe), 61.87 (OCH_2Me), 115.09, 126.18, 127.00 (C_q), 127.37, 130.29, 130.82, 131.74 (CH_{Ar}), 136.55 (C_q), 140.43 (C_q), 157.09 (*C*OOEt), 159.12 (C_q), 161.42 and 163.28 (*C*OOMe), 167.63 (CHN-*HC*=O), 171.79 (CH_2NHC=O).

MS (MALDI): *m*/*z* = 568 [M + K]$^+$, 552 [M + Na]$^+$, 530 [M + H]$^+$.

Anal. Calcd for $C_{24}H_{27}N_5O_9$ (529.51): C, 54.44; H, 5.14; N, 13.23. Found: C, 54.40; H, 5.24; N, 13.18.

2-Ethyl 3,4-Dimethyl 5-(2-{[1-({3-[4,5-Bis(methoxycarbonyl)-1*H*-1,2,3-triazol-1-yl]propyl}amino)-1-oxopropan-2-yl]carbamoyl}phenyl)furan-2,3,4-tricarboxylate (9l)

A solution of *N*-(2-azidopropyl)carboxamide **9k** (40 mg, 0.076 mmol) and DMAD (18 μL, 0.15 mmol) in dry $CHCl_3$ was heated at reflux temperature during 6 h. After cooling, the solvent was evaporated and the residue was triturated with *i*-Pr_2O accompanied by ultrasonication for 15 min. The resulting white solid was isolated by filtration and recrystallized ($CHCl_3$/PE) to give **9l** (42 mg, 83%) as a colorless solid; mp 138–139 °C.

IR (ATR): 1183 (s), 1224 (s), 1285 (m), 1635 (s), 1720 (s), 3304 cm^{-1} (m).

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.34 (t, ^3J = 7.1 Hz, 3 H, OCH_2Me), 1.39 (d, ^3J = 6.9 Hz, 3 H, CH*Me*), 2.15 (m_c, ^3J = 6.3 Hz, 2 H, NCH_2CH_2), 3.16–3.32 (m, 2 H, CH_2NH), 3.70 (s, 3 H, OMe), 3.89–4.00 (m, 9 H, OMe), 4.33 (q, ^3J = 7.1 Hz, 2 H, OCH_2Me), 4.50 (m_c, ^3J = 7.3 Hz, 1 H, C*H*Me), 4.61 (t, ^3J = 6.9 Hz, 2 H, $NHCH_2CH_2CH_2$), 6.61 (d, ^3J = 7.2 Hz, 1 H, CHN*H*), 6.69 (m_c, ^3J = 5.8 Hz, 1 H, CH_2NH), 7.51–7.63 (m, 3 H, H_{Ar}), 7.65–7.71 (m, 1 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.08 (OCH_2Me), 18.13 (CH*Me*), 29.79 ($NHCH_2CH_2$), 36.11 ($NHCH_2$), 47.92 ($NHCH_2CH_2CH_2$), 49.48 (*C*HMe), 52.28, 52.77, 53.02, 53.64 (OMe), 61.90 (OCH_2Me), 115.02, 126.14, 126.97 (C_q), 127.47 (CH_{Ar}), 129.88 (C_q), 130.27, 130.83, 131.72 (CH_{Ar}), 136.54, 139.96, 140.36 (C_q), 157.11 (*C*OOEt), 159.12, 159.14 (C_q, *C*OOMe), 160.43, 161.43, 163.30 (*C*OOMe), 167.64 (CHNH*C*=O), 172.03 (CH_2NHC=O).

HRMS (MALDI): *m*/*z* [M + Na]$^+$ calcd: 694.19671; found: 694.19648; *m*/*z* [M + H]$^+$ calcd: 672.21476; found: 672.21472.

Anal. Calcd $C_{30}H_{33}N_5O_{13}$ (671.62): C, 53.65; H, 4.95; N, 10.43. Found: C, 53.56; H, 4.93; N, 10.37.

2-Ethyl 3,4-Dimethyl 5-[2-({1-[4-(Methoxycarbonyl)piperidin-1-yl]-1-oxopropan-2-yl}carbamoyl)phenyl]furan-2,3,4-tricarboxylate (9m)

A suspension of **3b** (200 mg, 0.47 mmol) and methyl piperidine-4-carboxylate hydrochloride (93 mg, 0.52 mmol) in anhyd CH_2Cl_2 (5 mL) was treated with dry NEt_3 (76 μL, 0.55 mmol). After stirring at r.t. for 5 min, the clear yellow solution was worked up and the product was recrystallized (*i*-PrOH/Et_2O) to give **9m** (176 mg, 66%) as a colorless solid; mp 137–139 °C.

IR (KBr): 1178 (m), 1237 (s), 1625 (s), 1733 (vs), 3441 (v br, m).

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.25–1.38 (m, 6 H, CH*Me*, OCH_2Me), 1.57–1.83 (m, 2 H), 1.89–2.05 (m, 2 H), 2.50–2.64 (m, 1 H, *C*HCOOMe), 2.80–3.00 (m, 1 H), 3.07–3.24 (m, 1 H), 3.64 and 3.65 (2 s, each 3 H, 2 OMe), 3.75–3.91 (m, 1 H), 3.95 (s, 3 H, COOMe), 4.23–4.43 (m, 3 H, $COOCH_2Me$, NC_xH), 4.84–4.96 (m, 1 H, C*H*Me), 7.02 and 7.12 (2 d, ^3J = 7.2 Hz, 2×0.5 H, NH), 7.49–7.62 (m, 3 H, H_{Ar}), 7.62–7.71 (m, 1 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.09 (OCH_2*Me*), 18.72 and 19.08 (CH*Me*), 27.63, 27.67, 28.23, 28.33 (NCH_2CH_2), 40.49 and 40.75 (*C*H-COOMe), 41.30, 41.56, 44.42, 44.66 (NCH_2), 45.64 and 45.74 (*C*HMe), 51.88, 51.92, 52.09 (CHCOO*Me*, COO*Me*), 52.90 (COO*Me*), 61.67 ($COOCH_2$Me), 115.13, 126.31, 127.02, 127.06 (C_q), 127.39, 127.43, 129.95, 130.67, 131.62 (CH_{Ar}), 136.91, 140.34 (C_q), 157.11 (*C*OOEt), 159.14, 159.16 (C_q), 161.37 and 163.41 (*C*OOMe), 166.43 (s, NH*C*=O), 170.13, 170.29 (CH_3CHCO), 174.17, 174.35 (CH*C*OOMe).

HRMS (MALDI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{33}N_2O_{11}$: 573.20789; found: 573.20806.

Anal. Calcd for $C_{28}H_{32}N_2O_{11}$ (572.57): C, 58.74; H, 5.63; N, 4.89. Found: C, 58.61; H, 5.62; N, 4.89.

2-Ethyl 3,4-Dimethyl 5-[2-({1-[(2-Methoxy-2-oxoethyl)amino]-1-oxopropan-2-yl}carbamoyl)phenyl]furan-2,3,4-tricarboxylate (9n)

A suspension of **3b** (150 mg, 0.35 mmol) and methyl glycinate hydrochloride (48 mg, 0.38 mmol) in anhyd CH_2Cl_2 (5 mL) was treated with dry NEt_3 (55 μL, 0.40 mmol). After stirring at r.t. for 5 min, the clear yellow solution was worked up according to the general procedure, and the product was recrystallized (CH_2Cl_2/Et_2O) to give **9n** (123 mg, 68%) as a colorless solid; mp 155–156 °C.

IR (KBr): 1242 (s), 1543 (s), 1632 (s), 1650 (s), 1728 (s), 1753 (s), 3268 cm^{-1} (s).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.34 (t, ^3J = 7.1 Hz, 3 H, OCH_2*Me*), 1.39 (d, ^3J = 7.0 Hz, 3 H, CHMe), 3.70 (s, 3 H, OMe), 3.72 (s, 3 H, OMe), 3.95 (s, 3 H, OCH_3), 4.01 (d, ^3J = 5.4 Hz, 2 H, NH*C*H_2), 4.34 (q, ^3J = 7.1 Hz, 2 H, O*C*H_2Me), 4.59 (m_c, ^3J = 7.0 Hz, 1 H, *C*HMe), 6.63 (d, ^3J = 7.4 Hz, 1 H, N*H*CH), 6.78 (br t, 1 H, N*H*CH_2), 7.51–7.61 (m, 3 H, H_{Ar}), 7.63–7.69 (m, 1 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.06 (OCH_2*Me*), 17.81 (CH*Me*), 41.14 (CH_2NH), 49.06 (*C*HMe), 52.22 and 52.31 (OMe), 52.97 (OMe), 61.85 (O*C*H_2Me), 115.10, 126.13, 126.94 (C_q), 127.48, 130.23, 130.80, 131.66 (CH_{Ar}), 136.57 (C_q), 140.42 (C_q), 157.10 (*C*OOEt), 159.06 (C_q), 161.43 and 163.32 (*C*OOMe), 167.64 (CHNH*C*=O), 170.01 (CH_2*C*OOMe), 172.03 (CH*C*=O).

MS (CI): *m*/*z* = 519 [M + H]$^+$, 518 [M]$^+$, 430 [M – $NHCH_2COOCH_3$]$^+$, 359 [M – $NHCHR_2$]$^+$.

Anal. Calcd for $C_{24}H_{26}N_2O_{11}$ (518.48): C, 55.60; H, 5.05; N, 5.40. Found: C, 55.79; H, 4.99; N, 5.40.

2-Ethyl 3,4-Dimethyl 5-(2-{[2-({1-[(2-Methoxy-2-oxoethyl)amino]-4-(methylthio)-1-oxobutan-2-yl}amino)-2-oxoethyl]carbamoyl}phenyl)furan-2,3,4-tricarboxylate (9o)

N-[(*tert*-Butoxycarbonyl)-L-methionyl]glycine Methyl Ester (Boc-L-Met-Gly-OMe)

Syntheses by peptide coupling of Boc-L-Met-OH and Gly-OMe using DCC[26] or isobutyl chloroformate[27] as activating reagents have been published. The use of CDI as coupling reagent is described herein.

A solution of *N*-(*tert*-butoxycarbonyl)-L-methionine (5.00 g, 20 mmol) in dry CH_2Cl_2 (200 mL) was cooled at 0 °C, CDI (4.40 g, 27 mmol) was added in portions, and the mixture was stirred overnight. Methyl glycinate hydrochloride (2.60 g, 21 mmol) followed by NEt_3 (3 mL, 22 mmol) was added. The solution was stirred for 8 h, then diluted with CH_2Cl_2 (100 mL). After extraction with dilute 1 M aq HCl (100 mL) and water (2 × 100 mL), the organic layer was separated, dried (Na_2SO_4), and the solvent was evaporated. The residue was recrystallized (cyclohexane) to furnish Boc-L-Met-Gly-OMe (5.2 g, 81%) as a colorless solid; mp 86–87 °C (Lit.[27] 84–86 °C).

IR (KBr): 1173 (m), 1208 (m), 1545 (m), 1660 (s), 1758 (m), 3288 (br, m), 3425 cm^{-1} (br, m).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.43 (s, 9 H, CMe_3), 1.88–1.99 (m, 1 H, NCHC*H*^{A}H^B), 2.04–2.16 (m, 4 H, SMe, NCHCH^A*H*^{B}), 2.58 (m_c, 2 H, C*H*$_2$SMe), 3.74 (s, 3 H, OMe), 3.94–4.13 (m, 2 H, NCH_2), 4.30–4.40 (m, 1 H, NHC*H*), 5.18–5.41 (m, 1 H, N*H*CH), 6.89 (br s, 1 H, CH_2N*H*).

^{13}C NMR (DMSO-d_6, 101 MHz): δ = 14.78 (SMe), 28.38 (C*Me*$_3$), 29.71 (CH_2CH_2SMe), 31.85 (*C*H_2CH$_2$SMe), 40.77 (NCH_2), 51.94 (OMe), 53.50 (NCH), 78.46 (*C*Me$_3$), 155.58 (*C*OOCMe$_3$), 170.48 (*C*OOMe), 172.64 (CH*C*=O).

Anal. Calcd for $C_{13}H_{24}N_2O_5S$ (320.40): C, 48.73; H, 7.55; N, 8.74; S, 10.01. Found: C, 48.77; H, 7.49; N, 8.76; S, 9.93.

2-Ethyl 3,4-Dimethyl 5-(2-{[2-({1-[(2-Methoxy-2-oxoethyl)amino]-4-(methylthio)-1-oxobutan-2-yl}amino)-2-oxoethyl]carbamoyl}phenyl)furan-2,3,4-tricarboxylate (9o)

N-Boc-L-Met-Gly-OMe was kept in TFA at 65 °C for 12 h to obtain methyl (L-methionyl)glycine. A solution of tetracycle **3a** (287 mg, 0.69 mmol) in anhyd CH_2Cl_2 (5 mL) was combined with a solution of L-Met-Gly-OMe (152 mg, 0.69 mmol) in CH_2Cl_2 (5 mL). After stirring at r.t. for 10 min, the solvent was evaporated, and the remaining beige foam was suspended in *i*-Pr_2O (5 mL). The suspension was heated at reflux and EtOAc was added dropwise. In this manner, byproducts and impurities could be dissolved, whereas most of the desired product remained as a colorless solid. It was isolated by filtration of the hot suspension. An additional amount of the product was obtained by evaporation of the mother liquor and repetition of the preceding workup. The combined products were dried (50 °C/10^{-3} mbar) to furnish pure **9o** (307 mg, 70%) as a colorless solid; mp 147–149 °C.

IR (ATR): 1183 (s), 1231 (s), 1633 (s), 1716 (s), 3317 cm^{-1} (br, w).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (t, ^3J = 7.1 Hz, 3 H, OCH_2*Me*), 1.96–2.18 (m, 5 H, *C*H_2CH$_2$*S*Me), 2.52–2.66 (m, 2 H, CH_2*C*H_2SMe), 3.68–3.73 (m, 6 H, CH_2COO*Me*, COOMe), 3.96 (s, 3 H, OMe), 3.97–4.05 (m, 4 H, NCH_2), 4.34 (q, ^3J = 7.1 Hz, 2 H, O*C*H_2Me), 4.63–4.72 (m, 1 H, NHC*H*), 6.82–6.89 (m, 1 H, C_qCONH), 6.93–7.02 (m, 2 H, N*H*CHCON*H*), 7.52–7.65 (m, 3 H, H_{Ar}), 7.67–7.73 (m, 1 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.07 (OCH_2*Me*), 15.16 (SMe), 30.10 (CH_2CH_2SMe), 30.67 (*C*H_2CH$_2$SMe), 41.12 (*C*H_2COOMe), 43.74 (*C*H_2CONH), 52.22 (NHCH), 52.28 (COO*Me*, CH_2COO*Me*), 52.96 (COO*Me*), 61.87 ($COOCH_2$Me), 115.15, 126.11, 127.08 (C_q), 127.62, 130.29, 130.74, 131.73 (CH_{Ar}), 136.17, 140.40 (C_q), 157.16 (*C*OOEt), 158.95 (C_q), 161.52 and 163.38 (*C*OOMe), 168.22 (C_qCONH), 168.77 (CH_2*C*ONH), 170.03 (s, CH_2*C*OOMe), 171.19 (s, CH*C*=O).

HRMS (MALDI): *m*/*z* [M + K]$^+$ calcd for $C_{28}H_{33}N_3O_{12}SK$: 674.14165; found: 674.14168; *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{33}N_3O_{12}SNa$: 658.16772; found: 658.16672; *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{34}N_3O_{12}S$: 636.18577; found: 636.18543.

Anal. Calcd for $C_{28}H_{33}N_3O_{12}S$ (635.64): C, 52.91; H, 5.23; N, 6.61; S, 5.04. Found: C, 52.90; H, 5.18; N, 6.60; S, 5.04.

X-ray Structure Determination of *exo*-3c

Suitable crystals were obtained by crystallization (CH_2Cl_2/pentane) by the vapor diffusion method. Data collection was performed with an Oxford Diffraction instrument (SuperNova, Dual Source, Atlas CCD, Cu Kα radiation). Software for structure solution and refinement: SHELXS97[28a] and SHELXL-2014.[28b] Molecule plot: ORTEP.[29] CCDC-

1987125 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

Selected crystallographic data: $C_{23}H_{23}NO_9$ (457.42); monoclinic space group $P2_1/c$, a = 12.2649(2), b = 19.0631(2), c = 9.6849(1) Å, β = 104.817(1)°; V = 2189.10(4) Å^3; Z = 4, ρ_{calcd} = 1.388 g cm^{-3}, μ = 0.91 mm^{-1}. R = 0.0417 (3483 reflections with $I > 2\sigma(I)$), $wR2$ = 0.1112 (all 3864 data).

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707897.

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