Studies towards the Synthesis of Alkyl *N*-(4-Nitrophenyl)-3/2-oxomorpholine-2/3-carboxylates

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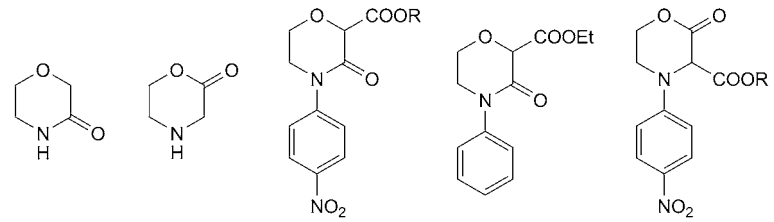
The syntheses of methyl 4-(4-nitrophenyl)-3-oxomorpholine-2-carboxylate (**3a**) and ethyl 4-(4-nitrophenyl)-2-oxomorpholine-3-carboxylate (**5b**), important building blocks for the synthesis of factor Xa inhibitor rivaroxaban analogs with potential dual antithrombotic activity, *via* $Rh_2(OAc)_4$-catalyzed O–H and N–H carbene insertion reactions are described.

1. Introduction. – Development of efficient synthetic methodologies is frequently driven by the need of novel key intermediates for the synthesis of bioactive compounds of pharmaceutical interest. The morpholin-3-one (**1**) and morpholin-2-one (**2**) skeletons, and their derivatives are important synthons for the design of bioactive compounds and reagents [1]. In the course of our medicinal-chemistry program aimed at discovering dual antithrombotic compounds with highly overlapping factor Xa inhibitor and fibrinogen receptor antagonist pharmacophores [2], protected 4-(4-nitrophenyl)-3-oxomorpholine-2-carboxylates and 4-(4-nitrophenyl)-2-oxomorpholine-3-carboxylates, **3** and **5**, respectively, were required in order to functionalize the parent oxomorpholin moiety of the lead compound with a negatively charged carboxylate group.

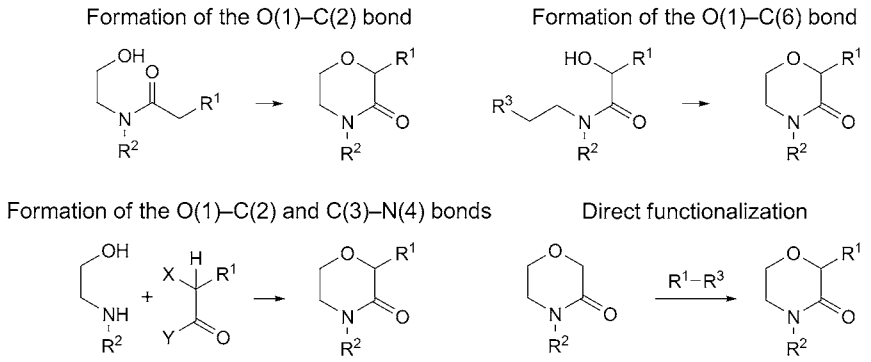


1 **2** **3a** R = Me **3b** R = Et **4** **5a** R = Me **5b** R = Et

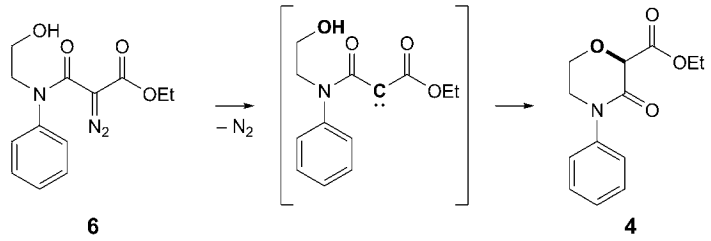
2,4-Disubstituted morpholin-3-ones had previously been prepared by either one- or two-bond cyclization reactions (formation of O(1)–C(2) bond, formation of O(1)–C(6) bond, or concurrent formation of O(1)–C(2) and C(3)–N(4) bonds) [1][3–7] or by direct functionalization of 4-substituted morpholin-3-ones at C(2), using strong bases and various electrophilic reagents [8–13] (*Scheme 1*). Ethyl 3-oxo-4-phenylmorpho-

line-2-carboxylate (**4**) [14] is the only known 4-phenylmorpholin-3-one derivative bearing a protected carboxylate group that closely resembles our target compounds **3**. Although **3b** and **4** differ solely in the *p*-NO_2 substituent on a Ph ring, a direct transfer of the methodology for synthesizing **4**, comprising O(1)–C(2) bond-formation by intramolecular insertion of a carbene generated from α-diazo ester **6** into the O–H bond of the 4-(2-hydroxyethyl) moiety [14] (*Scheme 2*), proved to be useless for preparing **3b**. We, therefore, explored alternative methods for the synthesis of this key intermediate and isomeric 2-oxomorpholine-3-carboxylates **5**. This finally resulted in a four-step $Rh_2(OAc)_4$-catalyzed synthesis of the hitherto unknown methyl 4-(4-nitrophenyl)-3-oxomorpholine-2-carboxylate (**3a**) and in a simple $Rh_2(OAc)_4$-promoted preparation of ethyl 4-(4-nitrophenyl)-2-oxomorpholine-3-carboxylate (**5b**), the latter being the first 4-arylmorpholin-2-one bearing a protected 3-carboxylate group. A synthesis of closely related ethyl 4-[(benzyloxy)carbonyl]-2-oxomorpholine-3-carboxylate by $Rh_2(OAc)_4$-catalyzed N–H insertion has previously been unsuccessful [15].

Scheme 1



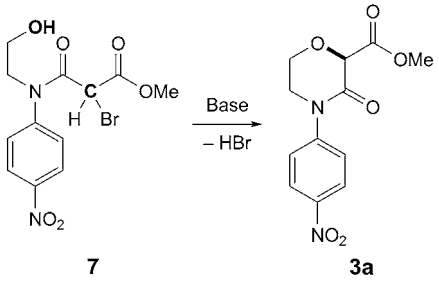
Scheme 2. *$Rh_2(OAc)_4$-Catalyzed Cyclization* [14]



6 **4**

2. Results and Discussion. – We initially planned to synthesize **3a** by exploiting the strategy of O(1)–C(2) bond-formation by intramolecular nucleophilic substitution of Br in **7** (*cf. Scheme 3*). To this end, to prepare methyl 2-bromo-3-[(2-hydroxyethyl)(4-nitrophenyl)amino]-3-oxopropanoate (**7**), 2-[(4-nitrophenyl)amino]ethanol (**8**) [16] was reacted, in the presence of Et_3N in CH_2Cl_2, with either methyl 2-bromo-3-chloro-3-

Scheme 3. *Planned Synthesis of* **3a** *by Intramolecular Nucleophilic Substitution*



7 **3a**

oxopropanoate (**9**)[1]) or methyl 3-chloro-3-oxopropanoate (**10**; *Scheme 4*). Compound **9** was prepared by treating **10** with Br_2 in a mixture of CH_2Cl_2 and CCl_4 and these reaction conditions were also intended to be used in the synthesis of **7** from intermediate **11**. However, after reacting **8** with **9** or **10**, analysis of the reaction products revealed that the negative inductive and mesomeric effects of the *p*-NO_2 group in **8** decreased the nucleophilicity of the secondary amine N-atom to such an extent that *O*-acylation predominated over *N*-acylation, resulting in *O*-acylated compounds **12** and **13**, and *N*,*O*-diacylated products **12a** and **13a**. *N*-Acylated products **7** and **11** were not detected in the mixtures (*Scheme 4*). In the attempt to obtain **12** from **13**, bromination took place preferentially on the Ph ring to give products **14** and **14a** (*Scheme 5*) in which the Br-atom entered into the position *meta*[2]) to the NO_2 group.

The unexpected access to 1-methyl 3-{2-[(4-nitrophenyl)amino]ethyl} 2-bromomalonate (**12**) offered us the opportunity to prepare, by its cyclization, methyl 4-(4-nitrophenyl)-2-oxo-morpholine-3-carboxylate (**5a**). To obtain **5a**, compound **12** was refluxed with a base in THF, but intramolecular substitution of the Br-atom with the secondary amine did not take place.

In our next attempt to obtain ethyl 4-(4-nitrophenyl)-2-oxomorpholine-3-carboxylate (**5b**), we combined our earlier observation that *O*-acylation of 2-[(4-nitrophenyl)amino]ethanol (**8**) is preferred over *N*-acylation in the Rh^{II}-catalyzed approach for preparation of ethyl 3-oxo-4-phenylmorpholine-2-carboxylate (**4**) [14]. To our satisfaction, *O*-acylation of **8** with ethyl 3-chloro-2-diazo-3-oxopropanoate (**15**) [14] in the presence of Et_3N afforded 1-ethyl 3-{2-[(4-nitrophenyl)amino]ethyl}-2-diazomalonate (**16**) which, *via* subsequent $Rh_2(OAc)_4$-catalyzed intramolecular N–H carbene insertion, afforded **5b** [17] (*Scheme 6*).

Our attempts to prepare the isomeric alkyl 3-oxomorpholin-2-carboxylates **3** first relied on synthetic strategies of direct functionalization of *N*-substituted morpholin-3-one derivatives. This appeared feasible because of the acidic character of the H-atoms at C(2) in the morpholin-3-one ring [4][8][9]. Preparation of 4-(4-nitrophenyl)mor-

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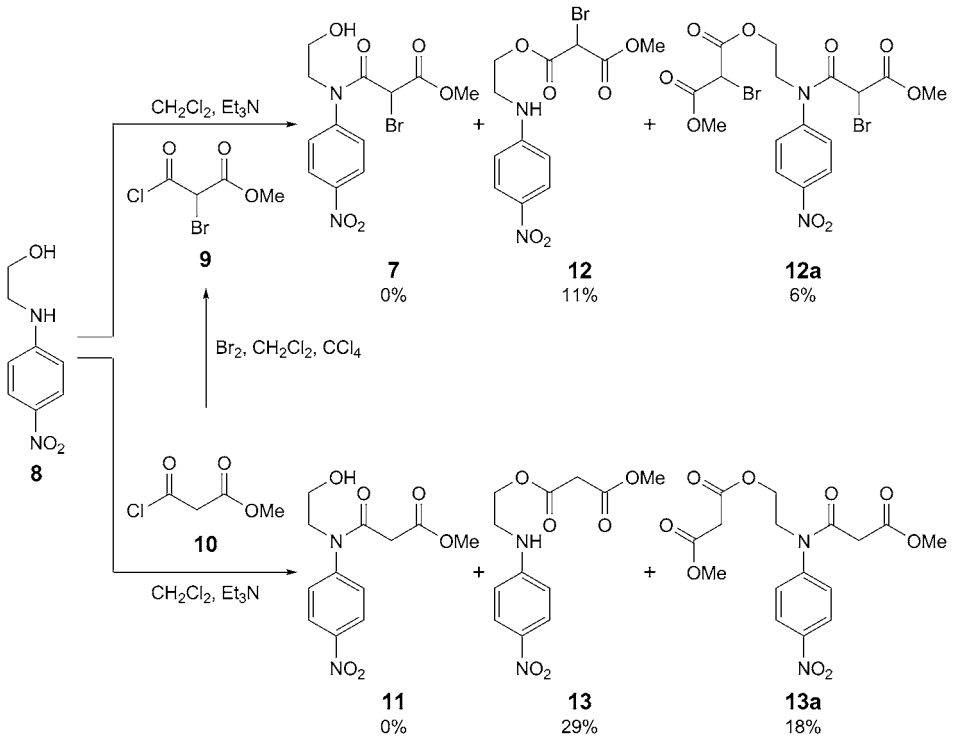
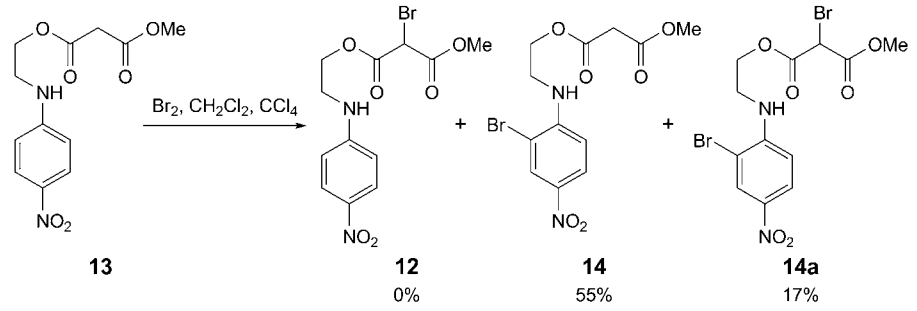
1) According to ^{1}H-NMR analysis, crude **9** could be a mixture of 2-bromo-3-chloro-3-oxopropanoate and 2-bromo-3-bromo-3-oxopropanoate, and was used without purification.

2) The position of the Br-atom *meta* to the NO_2 group on Ph of compounds **14** and **14a** was confirmed by ^{1}H,^{13}C-HMBC analysis.

Scheme 4

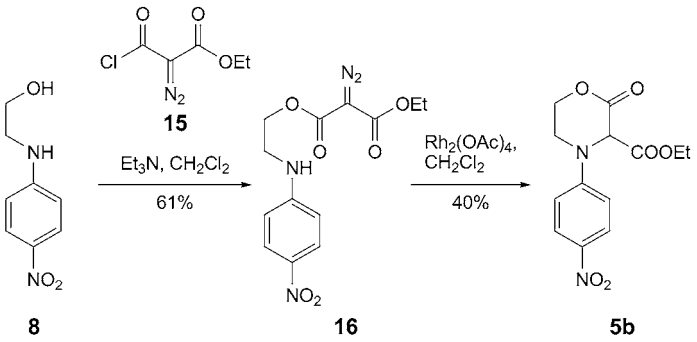


Scheme 5



pholin-3-one (**20**) from **17** *via* **19** [18] was thus targeted by several attempts, in which reagents, bases, solvents, and reaction temperatures were varied, to introduce the ethoxycarbonyl moiety at C(2) of the morpholin-3-one moiety (*Scheme 7* and *Table*). Although the *N*-Me analog of **3b** has been synthesized in this way, using ClHCOOEt and lithium diisopropylamide (LDA) as a base [8], our attempts to synthesize **3b** under these conditions were not successful.

Scheme 6



Scheme 7

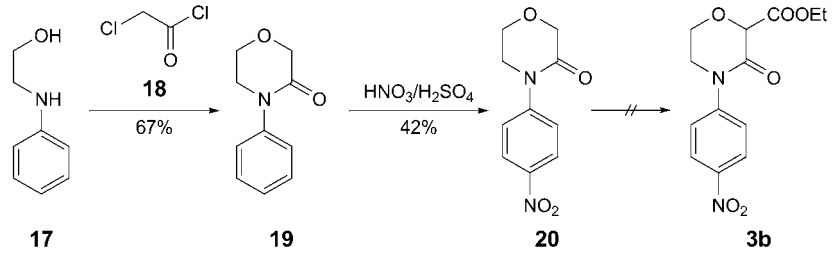
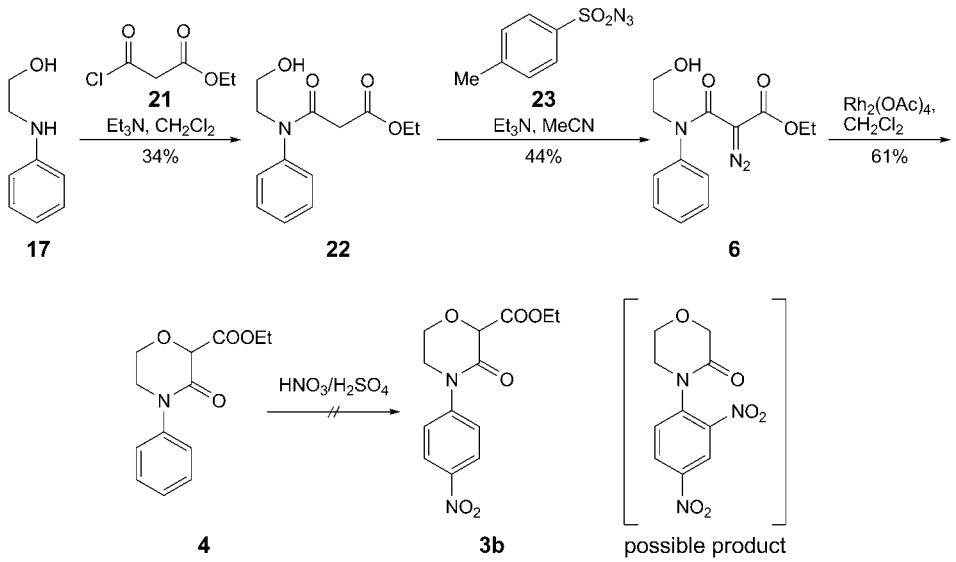


Table. *Reaction Conditions Applied in Attempted Synthesis of* **3b** *from* **20**

Reagent	Base	Solvent	Temp. [°]
ClCOOEt	LDA	THF	– 80 – 20
ClCOOEt	NaH	THF/DMF	Reflux
$(EtO)_2CO$	NaH	THF	Reflux
$(EtO)_2CO$	NaOEt	EtOH	Reflux

The failure in synthesizing **7** (*Scheme 4*) and in attempts to introduce the 2-ethoxycarbonyl group to morpholin-3-one **20** (*Scheme 7*), coupled with the successful preparation of **5b**, stimulated us to consider the $Rh_2(OAc)_4$-catalyzed carbene insertion reaction also for preparing alkyl 4-(4-nitrophenyl)-3-oxomorpholine-2-carboxylates **3**. In our first attempt to exploit the $Rh_2(OAc)_4$-catalyzed intramolecular O–H insertion reaction, we planned to prepare **3b** by nitration of the known ethyl 3-oxo-4-phenylmorpholine-2-carboxylate (**4**) [14] obtained from ethyl 2-diazo-3-[(2-hydroxyethyl)(phenyl)amino]-3-oxopropanoate (**6**; *Scheme 8*). Although the synthesis of **4** has been described and could be repeated in low yields, we developed another synthetic pathway for its preparation. 2-(Phenylamino)ethanol (**17**) was *N*-acylated with ethyl 3-chloro-3-oxopropanoate (**21**) to afford ethyl 3-[(2-hydroxyethyl)(phenyl)amino]-3-oxopropanoate (**22**). In this case, stimulated by the NO_2 group, *N*-acylation took place rather than the *O*-acylation in case of the substrate **8**. In the next step, TsN_3 (**23**) was

Scheme 8



used as a reagent to introduce the diazo group[3]) at C(2) of **22** to give **6**, which was cyclized to compound **4** using $Rh_2(OAc)_4$ catalysis. Compound **4** was then nitrated in HNO_3/H_2SO_4, but ^{1}H-NMR analysis of the crude product indicated nitration of the Ph ring in the *ortho*- and *para*-positions[4]), and absence of the COOEt group, rendering this last step unpromising for the synthesis of **3b**. Methyl 2-diazo-3-[(2-hydroxyethyl)(4-nitrophenyl)amino]-3-oxopropanoate (**28**), a *p*-NO_2 derivative of **6**, was, therefore, prepared (*Scheme 9*), and synthesis of the desired methyl 4-(4-nitrophenyl)-3-oxomorpholine-2-carboxylate (**3a**) attempted by analogy to the synthesis of **4** [14] (*cf. Scheme 2*).

To this end, 4-nitroaniline (**24**) was first *N*-acylated with **10**, and the resulting methyl 3-[(4-nitrophenyl)amino]-3-oxopropanoate (**25**) was subjected to diazotization with TsN_3 (**23**). The product was isolated from Et_2O as the Et_3NH^+ salt **26**, which, due to the increased nucleophilicity of its amide N-atom, reacted smoothly in the nucleophilic substitution of 2-bromoethanol (**27**) to afford **28**. However, when **28** was treated with $Rh_2(OAc)_4$ in CH_2Cl_2 at room temperature, followed by refluxing in CH_2Cl_2, benzene, THF, or H_2O, intramolecular carbene insertion into the O–H bond did not take place, and **3a** could not be obtained by this strategy. To explore whether failure of cyclization was due to an unfavorable distance of the OH to the N_2 group of **28**, methyl 2-diazo-3-[(3-hydroxypropyl)(4-nitrophenyl)amino]-3-oxopropanoate (**31**) and methyl 2-diazo-

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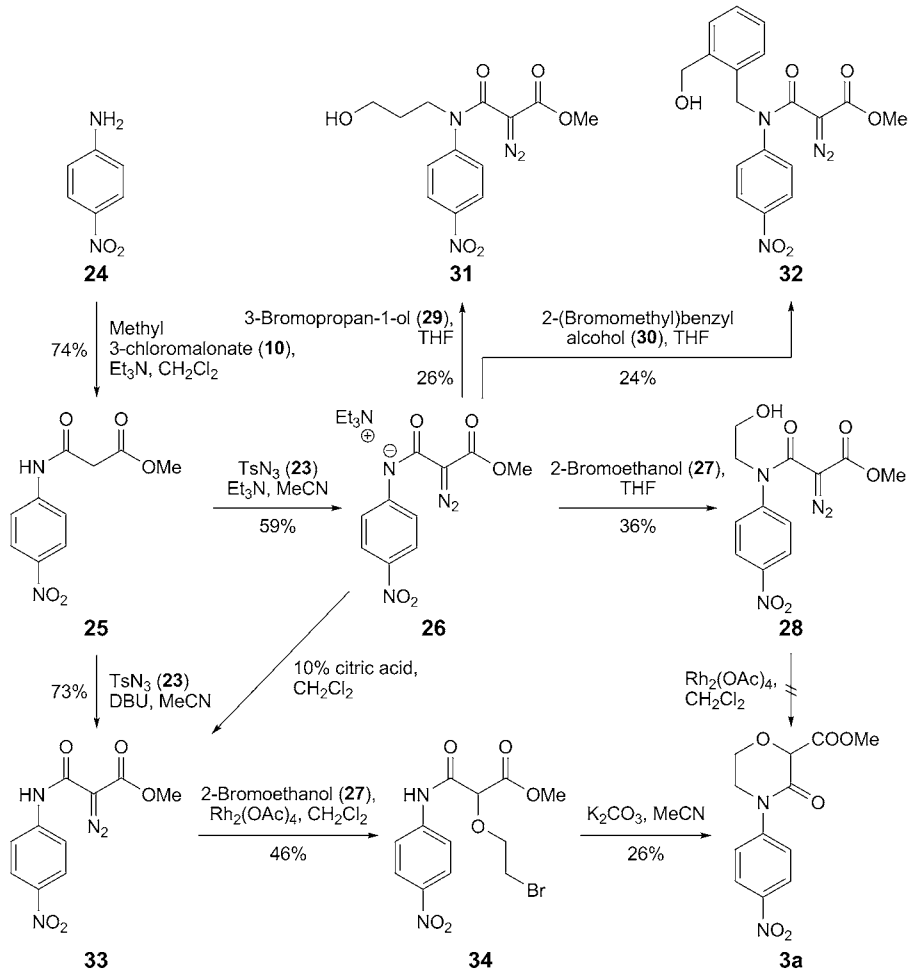
[3]) Acylation of CH_2N_2 by the reaction of CH_2N_2 with acyl halides or anhydrides, and diazo transfer of an azide reagent to the C-atom adjacent to a C=O group are two basic methods for preparation of α-diazocarbonyl compounds.

[4]) Chemical shifts and coupling constants of three aromatic H-atoms in the ^{1}H-NMR spectrum of the product: 8.86 (*d*, $J_m = 2.5$), 8.57 (*dd*, $J_o = 8.7$, $J_m = 2.5$), 7.70 (*d*, $J_o = 8.7$).

Scheme 9



3-{[2-(hydroxymethyl)benzyl](4-nitrophenyl)amino}-3-oxopropanoate (**32**) were prepared from **26** (*Scheme 9*). They also could not be cyclized in the presence of $Rh_2(OAc)_4$, indicating that the synthetic pathway used to prepare **4** [14] is not generally applicable. Since synthesis of ethyl 4-(4-nitrophenyl)-2-oxomorpholine-3-carboxylate (**5b**; *Scheme 6*) was accomplished despite the presence of the NO_2 group, we concluded that the latter does not affect the activity of $Rh_2(OAc)_4$ as catalyst. Instead of an in-depth analysis to explain these unsuccessful attempts at cyclization, we explored an alternative synthetic pathway for the construction of the 3-oxomorpholine skeleton. Methyl 3-[(4-nitrophenyl)amino]-3-oxopropanoate (**25**) was subjected to diazotization with TsN_3 (**23**) in the presence of 1,8-diazabicycloundec-7-ene (DBU) to give methyl 2-diazo-3-[(4-nitrophenyl)amino]-3-oxopropanoate (**33**), which could also be obtained by treating a CH_2Cl_2 solution of **26** with 10% citric acid. Compound **33** and 2-

bromoethanol (**27**), in the presence of $Rh_2(OAc)_4$, afforded methyl 2-(2-bromoethoxy)-3-[(4-nitrophenyl)amino]-3-oxopropanoate (**34**), which finally gave **3a**[5]) [17] by intramolecular nucleophilic substitution (*Scheme 9*).

3. Conclusions. – As a result of in-depth studies of several feasible approaches towards the synthesis of alkyl *N*-(4-nitrophenyl)-3/2-oxomorpholine-2/3-carboxylates, we have developed successful strategies for $Rh_2(OAc)_4$-catalyzed preparation of methyl 4-(4-nitrophenyl)-3-oxomorpholine-2-carboxylate (**3a**) starting from 4-nitroaniline, and of ethyl 4-(4-nitrophenyl)-2-oxomorpholine-3-carboxylate (**5b**) starting from 2-[(4-nitrophenyl)amino]ethanol. Both compounds are important intermediates in the synthesis of compounds with potential cardiovascular activities and, in general, versatile building blocks for the synthesis of bioactive compounds of pharmaceutical interest.

Experimental Part

General. Chemicals obtained from *Aldrich Chemical Co.*, *Acros*, and *Alfa Aesar* were used without purification. Anal. TLC: *Merck* silica gel (*60* F_{254}) plates (0.25 mm); visualization with UV light and ninhydrin. Column chromatography (CC): silica gel *60* (SiO_2; particle size 240–400 mesh; *Merck*). M.p.: *Reichert* hot-stage microscope; uncorrected. IR Spectra: *Perkin–Elmer* FT-IR *System Spectrum BX* or *Nicolet Nexus 470* FT-IR spectrometer. ^{1}H- and ^{13}C-NMR spectra: at 300 (400) and 75 (100) MHz, resp., on a *Bruker AVANCE DPX300* or a *Bruker AVANCE III* spectrometer in (D_6)DMSO or $CDCl_3$ at 295K; spectra assigned by using gradient COSY, HSQC, and HMBC experiments. MS: *VG Analytical Autospec Q* mass spectrometer. Microanalyses: *Perkin-Elmer C,H,N analyzer 240 C*. All reported yields refer to purified products.

2-[(4-Nitrophenyl)amino]ethanol (**8**) [16]. 2-Aminoethanol (3.02 ml, 50 mmol) and 1-fluoro-4-nitrobenzene (7.76 g, 55 mmol) were dissolved in DMSO (75 ml). After addition of anh. K_2CO_3 (10.37 g, 75 mmol), the mixture was stirred for 15 h at 55°. The mixture was then poured into cold H_2O (500 ml) and extracted with AcOEt (3 × 100 ml), which was further dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was recrystallized from MeOH to yield **8** (7.32 g, 80%). M.p.108–111° ([16]: 108°). ^{1}H-NMR (300 MHz, $CDCl_3$): 8.12 (*d*, *J* = 9.2, H–C(3), H–C(5)); 6.60 (*d*, *J* = 9.2, H–C(2), H–C(6)); 4.87 (*s*, NH); 3.93 (*q*, *J* = 5.3, CH_2OH); 3.42 (*q*, *J* = 5.3, $NHCH_2$); 1.61 (*t*, *J* = 5.1, OH).

Methyl 2-[(4-Nitrophenyl)amino]ethyl 2-Bromopropanedioate (**12**) *and 2-[(2-Bromo-3-methoxy-3-oxopropanoyl)(4-nitrophenyl)amino]ethyl Methyl 2-Bromopropanedioate* (**12a**). A soln. of Br_2 (0.80 g, 5 mmol) in anh. CCl_4 (2.5 ml) was added dropwise to a stirred boiling soln. of methyl 3-chloro-3-oxopropanoate (0.68 g, 5 mmol) in the same solvent (10 ml). The mixture was then stirred for 15 h at r.t., and the solvent was removed under reduced pressure. Half of the crude product, which was according to the ^{1}H-NMR spectrum identified as a mixture [18] of *methyl 2-bromo-3-chloro-3-oxopropanoate* (**9**) and methyl 2,3-dibromo-3-oxopropanoate, was dissolved in THF (3 ml) and added to the soln. of **8** (0.45 g, 2.5 mmol) and K_2CO_3 (0.52 g, 3.75 mmol) in THF (10 ml) at 0°. The mixture was, after 2 h at 0°, poured into H_2O (15 ml) and extracted with AcOEt (3 × 15 ml). The org. phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash CC (FCC; CH_2Cl_2/MeOH; 99:1) to afford **12** and **12a**.

Data of **12**. Yield: 11%. Yellow oil. IR (neat): 3398, 2975, 1741, 1605, 1480, 1311, 1205, 1145, 1113, 1035, 911, 839, 753, 662, 628, 569, 492. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.12 (*d*, *J* = 9.2, H–C(3), H–C(5));

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[5]) Methyl 2-[(4-nitrophenyl)carbamoyl]oxetane-2-carboxylate was isolated as a by-product resulting from undesired intramolecular nucleophilic substitution of the Br-atom with the carbanion resulting from H-atom abstraction from malonic intermediate **34**.

6.61 (*d*, *J* = 9.2, H–C(2), H–C(6)); 4.90 (*s*, CHBr); 4.85 (*t*, *J* = 9.1, NH); 4.47–4.53 (*m*, CH_2O); 3.85 (*s*, Me); 3.59 (*dd*, *J* = 5.9, CH_2N). ^{13}C-NMR (75 MHz, $CDCl_3$): 41.3 (BrCH); 41.9 ($NHCH_2$); 54.2 (Me); 64.9 (CH_2O); 111.4 (C(2), C(6)); 126.5 (C(3), C(5)); 138.5 (C(4)); 152.8 (C(1)); 164.6 (CH_2OCO); 165.4 (COOMe). ESI-MS: 362 (6, $[M+H]^+$ for ^{81}Br), 360 (6, $[M+H]^+$ for ^{79}Br), 151 (100). HR-ESI-MS: 359.9963 ($[M+H]^+$, $C_{12}H_{13}BrN_2O_6^+$; calc. 359.9956). Anal. calc. for $C_{12}H_{13}N_2O_6Br$ (361.15): C 39.91, H 3.63, N 7.76; found: C 39.94, H 3.81, N 7.59.

Data of **12a**. Yield: 6%. Yellow oil. IR (neat): 2958, 1744, 1676, 1594, 1525, 1436, 1348, 1310, 1151, 1014, 856, 756, 700. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.38 (*d*, *J* = 8.9, H–C(3), H–C(5)); 7.62 (*d*, *J* = 8.9, H–C(2), H–C(6)); 4.81 (*s*, BrCH); 4.73 (*s*, BrCH); 4.45 (*t*, *J* = 4.8, CH_2O); 4.10 (*t*, *J* = 4.8, CH_2N); 3.84 (*s*, Me); 3.82 (*d*, *J* = 2.3, Me). ESI-MS: 542 (0.15, $[M+H]^+$ for ^{81}Br), 540 (0.3, $[M+H]^+$ for ^{81}Br/^{79}Br), 538 (0.15, $[M+H]^+$ for ^{79}Br), 151 (100). HR-ESI-MS: 537.9238 ($[M+H]^+$, $C_{16}H_{16}Br_2N_2O_9^+$; calc. 537.9222).

Methyl 2-[(4-Nitrophenyl)amino]ethyl Propanedioate (**13**) *and 2-[(3-Methoxy-3-oxopropanoyl)(4-nitrophenyl)amino]ethyl Methyl Propanedioate* (**13a**). Compound **10** (1.37 g, 10 mmol) was diluted with THF (5 ml) and added to the soln. of **8** (1.81 g, 10 mmol) and K_2CO_3 (1.86 g, 13.5 mmol) in THF (15 ml) at 0°. The mixture was, after 2 h at 0°, poured into H_2O (25 ml) and extracted with AcOEt (3 × 25 ml). The org. phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Residue was purified by FCC (CH_2Cl_2/MeOH, 49:1) to furnish **13** and **13a**.

Data of **13**. Yield: 29%. Yellow oil. IR (neat): 3349, 1758, 1604, 1551, 1472, 1436, 1286, 1036, 905, 833, 753, 697, 680, 573. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.08 (*d*, *J* = 9.2, H–C(3), H–C(5)); 6.59 (*d*, *J* = 9.2, H–C(2), H–C(6)); 4.73 (*s*, NH); 4.41 (*t*, *J* = 5.4, CH_2O); 3.75 (*s*, Me); 3.54 (*t*, *J* = 5.4, CH_2N); 3.43 (*s*, $COCH_2CO$). ^{13}C-NMR (75 MHz, $CDCl_3$): 41.2 ($COCH_2CO$); 42.1 ($NHCH_2$); 52.8 (Me); 63.3 (CH_2O); 111.3 (C(2), C(6)); 126.4 (C(3), C(5)); 138.4 (C(4)); 152.9 (C(1)); 166.5 (CH_2OCOCH_2); 167.3 (COOMe). ESI-MS: 283 (18, $[M+H]^+$), 165 (100). HR-ESI-MS: 283.0930 ($[M+H]^+$, $C_{12}H_{15}N_2O_6^+$; calc. 283.0930). Anal. calc. for $C_{12}H_{14}N_2O_6$ (282.09): C 51.06, H 5.00, N 9.93; found: C 51.28, H 4.92, N 9.89.

Data of **13a**. Yield: 18%. Yellow oil. IR (neat): 2956, 1740, 1670, 1594, 1347, 1155, 1015, 856, 757, 702. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.32 (*d*, *J* = 9.0, H–C(3), H–C(5)); 7.52 (*d*, *J* = 9.0, H–C(2), H–C(6)); 4.34 (*t*, *J* = 5.3, CH_2O); 4.07 (*t*, *J* = 5.3, CH_2N); 3.74 (*s*, Me); 3.69 (*s*, Me); 3.33 (*s*, $COCH_2CO$); 3.26 (*s*, $COCH_2CO$). ESI-MS: 383 (5, $[M+H]^+$), 265 (100). HR-ESI-MS: 383.1086 ($[M+H]^+$, $C_{16}H_{19}N_2O_9^+$; calc. 383.1091). Anal. calc. for $C_{16}H_{18}N_2O_9$ (382.10): C 50.26, H 4.75, N 7.33; found: C 50.44, H 4.90, N 7.41.

2-[(2-Bromo-4-nitrophenyl)amino]ethyl Methyl Propanedioate (**14**) *and 2-[(2-Bromo-4-nitrophenyl)amino]ethyl Methyl 2-Bromopropanedioate* (**14a**). A soln. of Br_2 (1.36 g, 8.5 mmol) in anh. CCl_4 (5 ml) was added dropwise to a stirred boiling soln. of **13** (1.74 g, 6.17 mmol) in CH_2Cl_2/CCl_4 (15 ml). The mixture was then stirred for 15 h at r.t., and the solvent was removed under reduced pressure. The residue was purified by FCC (CH_2Cl_2/MeOH (99:1) to give **14** and **14a**.

Data of **14**. Yield: 55%. Yellow oil. IR (neat): 3383, 2956, 1736, 1593, 1502, 1327, 1154, 1119, 1031, 897, 747, 689. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.39 (*d*, *J* = 2.6, H–C(3)); 8.13 (*dd*, *J* = 9.1, 2.5, H–C(5)); 6.66 (*d*, *J* = 9.1, H–C(6)); 5.41 (*t*, NH); 4.45 (*t*, *J* = 5.5, CH_2O); 3.76 (*s*, Me); 3.62 (*dd*, *J* = 11.0, 5.6, CH_2N); 3.45 (*s*, $COCH_2CO$). ESI-MS: 363 (10, $[M+H]^+$ for ^{81}Br), 361 (10, $[M+H]^+$ for ^{79}Br), 243 (100), 245 (100). HR-ESI-MS: 361.0036 ($[M+H]^+$, $C_{12}H_{14}BrN_2O_6^+$; calc. 361.0035). Anal. calc. for $C_{12}H_{13}BrN_2O_6$ (360.00): C 39.91, H 3.63, N 7.76; found: C 40.18, H 3.48, N 7.76.

Data of **14a**. Yield: 17%. Yellow oil. IR (neat): 3390, 3087, 2957, 2641, 2443, 2229, 1744, 1593, 1501, 1450, 1394, 1324, 1155, 1120, 1029, 897, 814, 746, 647. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.34 (*d*, *J* = 2.5, H–C(3)); 8.09 (*dd*, *J* = 9.1, 2.5, H–C(5)); 6.66 (*d*, *J* = 9.1, H–C(6)); 5.39 (*t*, *J* = 5.3, NH); 4.91 (*s*, BrCH); 3.82 (*s*, Me); 4.50 (*m*, CH_2O); 3.65 (*dd*, *J* = 11.1, 5.7, CH_2N). ESI-MS: 443 (22, $[M+H]^+$) for ^{81}Br, 441 (45, $[M+H]^+$ for ^{81}Br/^{79}Br), 439 (22, $[M+H]^+$ for ^{79}Br), 243 (100). HR-ESI-MS: 438.1330 ($[M+H]^+$, $C_{12}H_{13}Br_2N_2O_6^+$; calc. 438.9140).

Ethyl 3-Chloro-2-diazo-3-oxopropanoate (**15**) [14]. To a stirred soln. of triphosgene (6.50 g, 21.9 mmol) in anh. benzene (30 ml) at 0°, anh. pyridine (200 µl) was added causing the formation of a white precipitate. To this suspension, diazoacetate (5.70 ml, 54.3 mmol) was added at such a rate that the temp. of the mixture did not rise above 10°. After 20 h at r.t., the soln. was filtered through *Celite* and concentrated under reduced pressure. Bulb-to-bulb distillation of residue provided **15** (3.05 g, 79%).

Yellow oil. B.p. 90–95° (<1 mbar). ^{1}H-NMR (300 MHz, $CDCl_3$): 4.30 (*q*, *J* = 7.2, CH_2); 1.29 (*t*, *J* = 7.2, Me).

Ethyl 2-[(4-Nitrophenyl)amino]ethyl 2-Diazopropanedioate (**16**). A soln. of **15** (353 mg, 2 mmol) in CH_2Cl_2 (3 ml) was added dropwise to a stirred soln. of **8** (364 mg, 2 mmol) and Et_3N (306 µl, 2.2 mmol) in CH_2Cl_2 (10 ml) at 0°. After 20 h at r.t., the solvent was evaporated under reduced pressure. The residue was purified by FCC (AcOEt/hexane, 2:1) to afford **16** (390 mg, 61%). Yellow crystals. M.p. 105–108°. IR (ATR): 3358, 2961, 2136, 1746, 1593, 1531, 1463, 1337, 1295, 1184, 1146, 1072, 834, 750, 698, 599. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.09 (*d*, *J* = 9.2, H–C(3), H–C(5)); 6.60 (*d*, *J* = 9.2, H–C(2), H–C(6)); 5.08 (*s*, NH); 4.50 (*t*, *J* = 5.4, CH_2O); 4.32 (*q*, *J* = 7.1, Me*C*H_2); 3.57 (*dd*, *J* = 11.0, 5.6, $NHCH_2$); 1.33 (*t*, *J* = 7.1, Me). ^{1}H-NMR (300 MHz, (D_6)DMSO): 8.00 (*d*, *J* = 9.3, H–C(3), H–C(5)); 7.35 (*t*, *J* = 5.9, NH); 6.70 (*d*, *J* = 9.3, H–C(2), H–C(6)); 4.31 (*t*, *J* = 5.5, CH_2O); 4.20 (*q*, *J* = 7.2, Me*C*H_2); 3.50 (*dd*, *J* = 11.1, 5.6, $NHCH_2$); 1.21 (*t*, *J* = 7.1, Me). ^{13}C-NMR (75 MHz, (D_6)DMSO): 14.1 (Me); 41.0 (CH_2N); 61.1 (Me*C*H_2); 63.3 (CH_2O); 64.8 (CN_2); 110.9 (C(2), C(6)); 126.2 (C(3), C(5)); 135.9 (C(4)); 154.4 (C(1)); 156.0 (CH_2CH_2OCO); 160.2 (COO). ESI-MS: 323.1 (58, $[M+H]^+$), 165.1 (100). HR-ESI-MS: 323.0991 ($[M+H]^+$, $C_{13}H_{15}N_4O_6^+$; calc. 323.0992).

Ethyl 4-(4-Nitrophenyl)-2-oxomorpholine-3-carboxylate (**5b**). To a stirred soln. of **16** (0.97 g, 3 mmol) in CH_2Cl_2 (30 ml), $Rh_2(OAc)_4$ (7 mol-%) was added, and the mixture was stirred for 4 d at r.t. The solvent was evaporated under reduced pressure, and residue was purified by FCC (AcOEt/hexane; 2:1) to furnish **5b** (354 mg, 40%). Yellow oil. IR (ATR): 3380, 2922, 1751, 1594, 1497, 1465, 1376, 1322, 1277, 1227, 1194, 1110, 1065, 1015, 980, 944, 831, 752, 712, 693, 655, 629, 579. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.20 (*d*, *J* = 9.5, H–C(3), H–C(5)); 6.73 (*d*, *J* = 9.4, H–C(2), H–C(6)); 5.19 (*s*, CH); 4.59–4.77 (*m*, CH_2O); 4.36 (*ddd*, *J* = 14.3, 7.1, 2.1, Me*C*H_2); 3.75–3.80 (*m*, CH_2N); 1.36 (*t*, *J* = 7.2, Me). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.0 (Me); 42.8 (CH_2N); 62.3 (CH); 63.6 (Me*C*H_2); 65.1 (CH_2O); 111.2 (C(2), C(6)); 126.1 (C(3), C(5)); 139.6 (C(4)); 151.0 (C(1)); 163.0 (CH_2CH_2OCO); 166.6 (COO). ESI-MS: 295.1 (100, $[M+H]^+$). HR-ESI-MS: 295.0941 ($[M+H]^+$, $C_{13}H_{15}N_2O_6^+$; calc. 295.0930).

4-Phenylmorpholin-3-one (**19**) [18]. To a stirred soln. of **17** (12.54 ml, 100 mmol) in EtOH (12.75 ml) and H_2O (38.25 ml), **18** (23.88 ml, 300 mmol) and 45% soln. of NaOH (6.2 equiv.) were added concurrently at such a rate that the temp. remained between 35° and 45°, and pH between 12 and 12.5. After 1 h at r.t., the mixture was stirred on an ice bath for 30 min. The precipitate was filtered off, washed with H_2O, and dried to constant mass at 50° to yield **19** (11.87 g, 67%). White crystals. M.p. 113–115° ([18]: 114°). ^{1}H-NMR (300 MHz, (D_6)DMSO): 7.38–7.40 (*m*, H–C(2), H–C(3), H–C(5), H–C(6)); 7.26–7.30 (*m*, H–C(4)); 4.21 (*s*, CH_2CO); 3.98 (*t*, *J* = 5.1, CH_2O); 3.74 (*t*, *J* = 5.1, CH_2N).

4-(4-Nitrophenyl)morpholin-3-one (**20**) [18]. Conc. HNO_3 (4 ml) was added dropwise to a stirred soln. of **19** (10 g, 56.5 mmol) in conc. H_2SO_4 (24 ml) at −5° over 1 h. The mixture was stirred at −5° for another h and then diluted with brine (75 ml). The obtained soln. was neutralized with 25% NH_3 soln., diluted with acetone (150 ml), and heated to 40°. The org. phase was separated in separatory funnel, concentrated to *ca.* 25% of its volume under reduced pressure and cooled to 5–10°. The precipitate was filtered off, washed with cold acetone, and dried to afford **20** (5.25 g, 42%). Light-brown crystals. M.p. 148–151° ([18]: 152°). ^{1}H-NMR (300 MHz, $CDCl_3$): 8.27 (*d*, *J* = 9.2, H–C(3), H–C(5)); 7.77 (*d*, *J* = 9.2, H–C(2), H–C(6)); 4.28 (*s*, CH_2CO); 4.00–4.03 (*m*, CH_2O); 3.84–3.88 (*m*, CH_2N).

Ethyl 3-[(2-Hydroxyethyl)(phenyl)amino]-3-oxopropanoate (**22**). A soln. of **21** (5.79 ml, 45 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a stirred soln. of **17** (5.01 ml, 40 mmol) and Et_3N (6.68 ml, 48 mmol) in CH_2Cl_2 (80 ml) at 0°. After 24 h at r.t., the mixture was washed successively with 1M HCl (2 × 50 ml) and brine (1 × 50 ml). The org. phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by FCC (AcOEt/hexane; 3:1) to yield **22** (3.41 g, 34%). Colorless oil. IR (ATR): 3397, 2983, 1735, 1643, 1593, 1494, 1401, 1368, 1321, 1242, 1154, 1074, 1052, 1027, 946, 849, 771, 701, 663, 558. ^{1}H-NMR (400 MHz, (D_6)DMSO): 7.34–7.48 (*m*, H–C(2), H–C(3), H–C(4), H–C(5), H–C(6)); 4.73 (*t*, *J* = 5.6, OH); 3.98 (*q*, *J* = 7.1, Me*C*H_2); 3.69 (*t*, *J* = 6.5, CH_2N); 3.46 (*q*, *J* = 6.2, *C*H_2OH); 3.12 (*s*, $COCH_2CO$); 1.11 (*t*, *J* = 7.1, Me). ^{13}C-NMR (100 MHz, (D_6)DMSO): 13.9 (Me); 41.8 ($COCH_2CO$); 51.1 (CH_2N); 57.7 (CH_2OH); 60.4 (Me*C*H_2); 128.0 (C(4)); 128.3 (C(2), C(6)); 129.6 (C(3), C(5)); 142.1 (C(1)); 165.3 (NCO); 167.3 (COO). ESI-MS: 252.1 (100, $[M+H]^+$). HR-ESI-MS: 252.1232 ($[M+H]^+$, $C_{13}H_{18}NO_4^+$; calc. 252.1236).

Ethyl 2-Diazo-3-[(2-hydroxyethyl)(phenyl)amino]-3-oxopropanoate (**6**). To a soln. of **22** (2.84 g, 11.3 mmol) and Et_3N (1.57 ml, 11.3 mmol) in MeCN (30 ml) TsN_3 (**23** [19]; 2.40 g, 11.3 mmol) was added dropwise, and the mixture was stirred for 15 h at r.t. The solvent was evaporated under reduced pressure. The residue was purified by FCC (AcOEt/hexane; 2:1) to, yield **6** (1.38 g, 44%). Yellow oil. IR (ATR): 3434, 2982, 2115, 1717, 1628, 1591, 1493, 1436, 1387, 1287, 1171, 1115, 1075, 1033, 896, 845, 748, 698, 680, 618, 595, 574, 528. ^{1}H-NMR (400 MHz, (D_6)DMSO): 7.37–7.42 (*m*, H–C(2), H–C(3), H–C(5), H–C(6)); 7.25–7.29 (*m*, H–C(4)); 4.79 (*t*, $J = 5.6$, OH); 3.92 (*q*, $J = 7.1$, MeCH_2); 3.78 (*t*, $J = 6.4$, CH_2N); 3.51 (*q*, $J = 6.2$, CH_2OH); 1.03 (*t*, $J = 7.1$, Me). ^{13}C-NMR (100 MHz, (D_6)DMSO): 14.0 (CH_2*Me*); 52.6 (CH_2N); 57.8 (CH_2OH); 60.9 (Me*C*H_2); 65.4 (CN_2); 126.5 (C(2), C(6)); 126.6 (C(4)); 129.1 (C(3), C(5)); 142.6 (C(1)); 159.4 (NCO); 161.4 (COO). ESI-MS: 278.1 (100, $[M+H]^+$). HR-ESI-MS: 278.1136 ($[M+H]^+$, $C_{13}H_{16}N_3O_4^+$; calc. 278.1141).

Ethyl 3-Oxo-4-phenylmorpholine-2-carboxylate (**4**) [14]. Compound **6** (985 mg, 3.55 mmol) was dissolved in CH_2Cl_2 (35 ml). $Rh_2(OAc)_4$ (12 mol-%) was added, and the mixture was stirred for 48 h at r.t. The residue obtained after solvent removal was purified by FCC (CH_2Cl_2/MeOH; 49:1) to furnish **4** (541 mg, 61%). Colorless oil. IR (ATR): 2982, 1740, 1663, 1595, 1494, 1470, 1427, 1376, 1316, 1257, 1191, 1150, 1123, 1098, 1025, 949, 852, 761, 695, 609, 561. ^{1}H-NMR (400 MHz, (D_6)DMSO): 7.38–7.46 (*m*, H–C(2), H–C(3), H–C(5), H–C(6)); 7.28–7.32 (*m*, H–C(4)); 4.94 (*s*, CH); 4.17–4.25 (*m*, MeCH_2, 1 H of CH_2N); 4.06 (*td*, $J = 12.0$, 5.1, 1 H of CH_2N); 3.81 (*t*, $J = 5.1$, CH_2O); 1.23 (*t*, $J = 7.1$, Me). ^{13}C-NMR (100 MHz, (D_6)DMSO): 13.9 (CH2 *Me*); 48.9 (CH_2O); 61.3 (*C*H2 Me); 62.1 (CH_2N); 76.7 (CH); 125.3 (C(2), C(6)); 126.7 (C(4)); 128.9 (C(3), C(5)); 141.3 (C(1)); 162.6 (NCO); 167.3 (COO). ESI-MS: 250.1 (100, $[M+H]^+$). HR-ESI-MS: 250.1071 ($[M+H]^+$, $C_{13}H_{16}NO_4^+$; calc. 250.1079).

Methyl 3-[(4-Nitrophenyl)amino]-3-oxopropanoate (**25**). A soln. of **10** (3.22 ml, 30 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a stirred soln. of **24** (4.14 g, 30 mmol) and Et_3N (5.01 ml, 36 mmol) in CH_2Cl_2 (80 ml) at 0°. After 24 h at r.t., the mixture was washed successively with 1M HCl (2 × 30 ml) and brine (2 × 30 ml). The org. phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was taken up in 100 ml of Et_2O and filtered to afford **25** (5.28 g, 74%). Beige crystals. M.p. 147–150°. IR (ATR): 3314, 3094, 1721, 1665, 1618, 1596, 1570, 1507, 1426, 1337, 1246, 1197, 1171, 1112, 1000, 971, 906, 857, 826, 790, 751, 692, 614, 583, 533. ^{1}H-NMR (400 MHz, (D_6)DMSO): 10.79 (*s*, NH); 8.23 (*d*, $J = 9.2$, H–C(3), H–C(5)); 7.82 (*d*, $J = 9.2$, H–C(2), H–C(6)); 3.68 (*s*, Me); 3.57 (*s*, $COCH_2CO$). ^{13}C-NMR (100 MHz, (D_6)DMSO): 43.6 (CH_2); 52.1 (Me); 118.8 (C(2), C(6)); 125.0 (C(3), C(5)); 142.4, 144.8 (C(1), C(4)); 165.0 (NCO); 167.7 (COO). ESI-MS: 239.1 (92, $[M+H]^+$), 139.0 (100). HR-ESI-MS: 239.0664 ($[M+H]^+$, $C_{10}H_{11}N_2O_5^+$; calc. 239.0668).

N,N-*Diethylethanaminium (2-Diazo-3-methoxy-3-oxopropanoyl)(4-nitrophenyl)azanide* (**26**). To a soln. of **25** (5.24 g, 22 mmol) and Et_3N (3.06 ml, 22 mmol) in MeCN (50 ml), **23** [19] (4.69 g, 22 mmol) was added dropwise, and the mixture was stirred for 15 h at r.t. The mixture was concentrated under reduced pressure. The crude product was recrystallized from MeOH/Et_2O to give **26** (4.74 g, (59%). Yellow crystals. M.p. 115–117°. IR (ATR): 2993, 2952, 2601, 2440, 2361, 1693, 1604, 1514, 1498, 1452, 1404, 1337, 1307, 1287, 1181, 1111, 1059, 975, 941, 901, 854, 837, 817, 783, 763, 750, 726, 690. ^{1}H-NMR (400 MHz, (D_6)DMSO): 9.00 (*s*, $(MeCH_2)_3NH^+$); 8.42 (*d*, $J = 9.4$, H–C(3), H–C(5)); 8.30 (*d*, $J = 9.4$, H–C(2), H–C(6)); 3.64 (*s*, Me); 3.11 (*q*, $J = 7.3$, $(MeCH_2)_3NH^+$); 1.17 (*t*, $J = 7.3$, $(MeCH_2)_3NH^+$). ^{13}C-NMR (100 MHz, (D_6)DMSO): 8.6 (Me); 45.7 (CH_2); 49.5 (Me); 116.6 (CN_2); 117.2 (C(3), C(5)); 124.9 (C(2), C(6)); 143.1 (C(1)); 143.4 (C(4)); 159.7 ($^-$NCO); 162.7 (COO). ESI-MS: 265.1 (100, $[M+H]^+$). ESI-MS (neg.): 263.0 (100, $[M-H]^-$). HR-ESI-MS: 265.0581 ($[M+H]^+$, $C_{10}H_9N_4O_5$; calc. 265.0573). HR-ESI-MS (neg.): 263.0409 ($[M-H]^-$, $C_{10}H_7N_4O_5^-$; calc. 263.0416).

General Procedure for the Preparation of Compounds **28**, **31**, *and* **32**. To a soln. of **26** in THF (0.1M), the corresponding alcohol (5 equiv. of **27** or 1.5 equiv. of **29**, or 1.25 equiv. of **30**) was added. The mixture was stirred for 2–3 d at 66°, and then the solvent was evaporated under reduced pressure. The residue was purified by FCC (CH_2Cl_2/MeOH, 49:1) to afford **28** and **31**, or, recrystallized from MeOH, **32**.

Methyl 2-Diazo-3-[(2-hydroxyethyl)(4-nitrophenyl)amino]-3-oxopropanoate (**28**). Yield: 734 mg (36%). Pale-yellow crystals. M.p. 173–177°. IR (ATR): 3449, 3115, 3079, 1703, 1671, 1594, 1523, 1476, 1434, 1384, 1345, 1264, 1234, 1200, 1146, 1117, 1072, 1051, 963, 934, 884, 855, 808, 772, 749, 728, 694, 626, 604, 544. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.45 (*d*, $J = 9.2$, H–C(3), H–C(5)); 8.27 (*d*, $J = 9.2$, H–C(2), H–C(6)); 5.01 (*t*, $J = 6.2$, OH); 4.76 (*t*, $J = 5.2$, CH_2N); 3.88 (*dd*, $J = 10.7$, 5.8, CH_2OH); 3.82 (*s*, Me).

^{13}C-NMR (100 MHz, (D_6)DMSO): 51.5 (Me); 57.5 (CH_2N); 58.9 (CH_2OH); 108.6 (CN_2); 120.9 (C(2), C(6)); 125.2 (C(3), C(5)); 139.8 and 146.0 (C(1), C(4)); 155.3 (NCO); 158.8 (COO). ESI-MS: 309.1 (100, $[M+H]^+$). HR-ESI-MS: 309.0831 ($[M+H]^+$, $C_{12}H_{13}N_4O_6^+$; calc. 309.0835).

Methyl 2-Diazo-3-[(3-hydroxypropyl)(4-nitrophenyl)amino]-3-oxopropanoate (**31**). Yield: 420 mg (26%). Pale-orange crystals. M.p. 158–161°. IR (ATR): 3418, 3117, 2953, 2872, 1676, 1590, 1517, 1477, 1453, 1383, 1338, 1314, 1296, 1223, 1189, 1152, 1114, 1057, 1006, 924, 897, 859, 813, 770, 749, 683. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.45 (*d*, *J* = 9.3, H–C(3), H–C(5)); 8.28 (*d*, *J* = 9.3, H–C(2), H–C(6)); 4.76 (*t*, *J* = 7.1, CH_2N); 4.71 (*s*, OH); 3.83 (*s*, Me); 3.53 (*t*, *J* = 5.7, CH_2OH); 2.02–2.11 (*m*, $CH_2CH_2CH_2$). ^{13}C-NMR (100 MHz, (D_6)DMSO): 31.6 ($CH_2CH_2CH_2$); 51.5 (Me); 52.5 (CH_2N); 57.5 (CH_2OH); 108.6 (CN_2); 120.9 (C(2), C(6)); 125.1 (C(3), C(5)); 139.9, 146.0 (C(1), C(4)); 155.2 (NCO); 158.7 (COO). ESI-MS: 323.1 (100, $[M+H]^+$). HR-ESI-MS: 323.1000 ($[M+H]^+$, $C_{13}H_{15}N_4O_6^+$; calc. 323.0992).

Methyl 2-Diazo-3-{[2-(hydroxymethyl)benzyl](4-nitrophenyl)amino}-3-oxopropanoate (**32**). Yield: 184 mg (24%). Pale-yellow crystals. M.p. 215–217°. IR (ATR): 3374, 3051, 2957, 2879, 1704, 1666, 1593, 1512, 1469, 1383, 1345, 1204, 1147, 1109, 1061, 1016, 939, 856, 748, 690, 620, 582. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.45 (*d*, *J* = 9.3, H–C(3), H–C(5)); 8.25 (*d*, *J* = 9.3, H–C(2), H–C(6)); 7.46 (*d*, *J* = 7.5, H–C(3′)); 7.35 (*dt*, *J* = 7.5, 1.5, 1 H of H–C(4′)/H–C(5′)); 7.27 (*dt*, *J* = 7.4, 1.4, 1 H of H–C(4′)/H–C(5′)); 7.10 (*d*, *J* = 7.6, H–C(6′)); 6.02 (*s*, CH_2N); 5.29 (*t*, *J* = 5.4, OH); 4.68 (*d*, *J* = 5.3, CH_2OH); 3.76 (*s*, Me). ^{13}C-NMR (100 MHz, (D_6)DMSO): 51.6 (Me); 54.7 (CH_2N); 61.0 (CH_2OH); 109.0 (CN_2); 121.0 (C(2), C(6)); 125.1 (C(3), C(5)); 126.9, 127.5, 127.8, 128.1 (C(3′), C(4′), C(5′), C(6′)); 131.5, 139.8 (C(1′), C(2′)); 139.9 (C(1)); 146.0 (C(4)); 155.1 (NCO); 158.6 (COO). ESI-MS: 385.1 (100, $[M+H]^+$). HR-ESI-MS: 385.1138 ($[M+H]^+$, $C_{18}H_{17}N_4O_6^+$; calc. 385.1148).

Methyl 2-Diazo-3-[(4-nitrophenyl)amino]-3-oxopropanoate (**33**). To a soln. of **25** (2.38 g, 10 mmol) and **23** [19] (2.13 g, 10 mmol) in MeCN (50 ml), DBU (2.25 ml, 15 mmol) was added dropwise, and the mixture was stirred for 15 h at r.t. The solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (75 ml) and washed with 10% citric acid soln. (3 × 50 ml). The org. phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was recrystallized from MeOH to afford **33** (1.92, 73%). Pale-yellow crystals (stored in closed container at 2–8°!). M.p. 178–180°. IR (ATR): 3274, 3220, 3087, 2963, 2144, 1683, 1655, 1608, 1601, 1553, 1503, 1440, 1410, 1329, 1278, 1247, 1200, 1172, 1110, 949, 854, 819, 783, 751, 726, 685, 535. ^{1}H-NMR (400 MHz, (D_6)DMSO): 9.98 (*s*, NH); 8.24 (*d*, *J* = 9.2, H–C(3), H–C(5)); 7.88 (*d*, *J* = 9.3, H–C(2), H–C(6)); 3.87 (*s*, Me). ^{13}C-NMR (100 MHz, (D_6)DMSO): 52.9 (Me); 68.7 (CN_2); 119.5 (C(2), C(6)); 125.0 (C(3), C(5)); 142.7 and 143.8 (C(1), C(4)); 159.0 (NCO); 163.7 (COO). ESI-MS: 265.1 (68, $[M+H]^+$). HR-ESI-MS: 265.0566 ($[M+H]^+$, $C_{10}H_9N_4O_5^+$; calc. 265.0573).

Methyl 2-(2-Bromoethoxy)-3-[(4-nitrophenyl)amino]-3-oxopropanoate (**34**). Compound **33** and *2-bromoethanol* (**27**; 1 equiv.) were dissolved in CH_2Cl_2 (0.065M). $Rh_2(OAc)_4$ (7 mol-%) was added, and the mixture was stirred for 15 h at r.t. After removal of undissolved $Rh_2(OAc)_4$, which was dried and successfully reused, the solvent was evaporated under reduced pressure. The residue was purified by FCC (AcOEt/hexane; 1:2) to afford **34** (1.05 g, 46%). Pale-yellow crystals. M.p. 128–133°. IR (ATR): 3295, 3108, 1744, 1696, 1618, 1596, 1559, 1507, 1437, 1410, 1377, 1344, 1293, 1255, 1231, 1169, 1109, 1065, 978, 941, 918, 857, 841, 774, 749, 688, 628, 610, 567. ^{1}H-NMR (400 MHz, (D_6)DMSO): 10.73 (*s*, NH); 8.25 (*d*, *J* = 9.3, H–C(3), H–C(5)); 7.92 (*d*, *J* = 9.3, H–C(2), H–C(6)); 4.90 (*s*, CH); 3.97 (*t*, *J* = 5.8, CH_2O); 3.74 (*s*, Me); 3.68 (*t*, *J* = 5.8, $BrCH_2$). ^{13}C-NMR (100 MHz, (D_6)DMSO): 31.4 (CH_2Br); 52.5 (Me); 70.5 (CH_2O); 79.7 (CH); 119.7 (C(2), C(6)); 124.9 (C(3), C(5)); 142.9, 144.1 (C(1), C(4)); 165.0 (NCO); 167.3 (COO). ESI-MS: 363.0 (92, $[M+H]^+$ for ^{81}Br), 361.0 (100, $[M+H]^+$ for ^{79}Br). HR-ESI-MS: 361.0045 ($[M+H]^+$, $C_{12}H_{14}BrN_2O_6^+$; calc. 361.0035).

Methyl 4-(4-Nitrophenyl)-3-oxomorpholine-2-carboxylate (**3a**). To a soln. of **34** (964 mg, 2.67 mmol) in MeCN (30 ml), K_2CO_3 (368 mg, 2.67 mmol) was added, and the resulting suspension was heated at 82° for 2 h. After solvent removal, the residue was dissolved in CH_2Cl_2 (60 ml) and washed with H_2O (2 × 30 ml). The org. phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by FCC (CH_2Cl_2/AcOEt; 19:1) to yield **3a** and a side-product[5]). Prolongation of reaction time did not give **3a**. Yield: 195 mg (26%). Yellow crystals. M.p. 132–135°. IR (ATR): 3111, 2957, 1743, 1660, 1607, 1590, 1513, 1490, 1472, 1432, 1377, 1343, 1319, 1291, 1255, 1225, 1201, 1151, 1126, 1103, 1032, 984, 968, 938, 856, 815, 752, 700, 606, 534. ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.30 (*d*, *J* = 9.2,

H–C(3), H–C(5)); 7.75 (*d*, *J* = 9.2, H–C(2), H–C(6)); 5.07 (*s*, CH); 4.21 – 4.26 (*m*, CH_2N); 4.08 – 4.13 (*m*, CH_2N); 3.92 – 3.95 (*m*, CH_2O); 3.75 (*s*, Me). ^{13}C-NMR (100 MHz, (D_6)DMSO): 48.2 (CH_2O); 52.6 (Me); 62.0 (CH_2N); 76.6 (CH); 124.2 (C(3), C(5)); 125.3 (C(2), C(6)); 144.8, 146.8 (C(1), C(4)); 163.1 (NCO); 167.6 (COO). ESI-MS: 281.1 (100, $[M+H]^+$). HR-ESI-MS: 281.0775 ($[M+H]^+$, $C_{12}H_{13}N_2O_6^+$; calc. 281.0774).

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