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SUPPORTING INFORMATION

Title: 2-Oxopiperazine Scaffolds by [3+2] Cycloaddition Reaction with a Polymer-Supported Cyclic Nitrone
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Ref. No.: O040150

Contents:

1. General Experimental Part

Manual synthesis on solid support

Solvents for the manual synthesis on solid support were used in p. a. quality and dried as follows: Tetrahydrofuran over potassium/benzophenone, dichloromethane over calcium hydride and chloroform over phosphorous pentoxide. Dimethylformamide was bought from Fluka over molecular sieve in p. a. quality closed with a septum and transferred *via cannula* under argon atmosphere. Acetonitrile and methanol were used in "HPLC-grade" quality from Fisher scientific without further purification. Solvents for work-up procedures and chromatography were used in technical quality and purified as followed: Pentane and dichloromethane over phosphorous pentoxide, ethyl acetate over potassium carbonate and diethylether over sodiumhydroxide/copper(I)chloride. Methanol and acetone were distilled. For RP-HPLC chromatography acetonitrile and water in "HPLC-grade" quality were used from Fisher scientific. Trifluoroacetic acid was used in "spectrophotometric grade" quality and was bought from Aldrich.

Wang resins (p-Benzyloxybenzyl Alcohol resin, 100-200 mesh, 1% DVB) with loadings 0.4 mmol/g, 0.78 mmol/g, 0.8 mmol/g and 0.9 mmol/g were bought from Advanced ChemTech.

For all reactions on solid support silanized glass vessels were used. The vessels were silanized by treatment with 20% dichlorodimethylsilane/dichloromethane for 15 min, methanol for 15 min, followed by oven heating at 120 °C for at least 2 h.

For large scale reactions (up to 7.0 g Wang resin), as for example the immobilization or the cleavage of the Fmoc-protecting group, a silanized reaction vessel was used as shown in Figure 1.

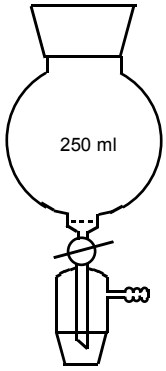


Figure 1. Vessel for large scale solid-phase synthesis.

Medium-scale (e.g. nitrone synthesis: up to 6.5 g; [3+2] cycloaddition: up to 1.6 g; reductive N-O-cleavage: up to 1.9 g) and small-scale reactions (e.g. all cleavages: 250 mg) on solid phase were floatingly stirred in silanized vessels comparable to cell culture vessels to reduce the mechanical stress as shown in Figure 2.

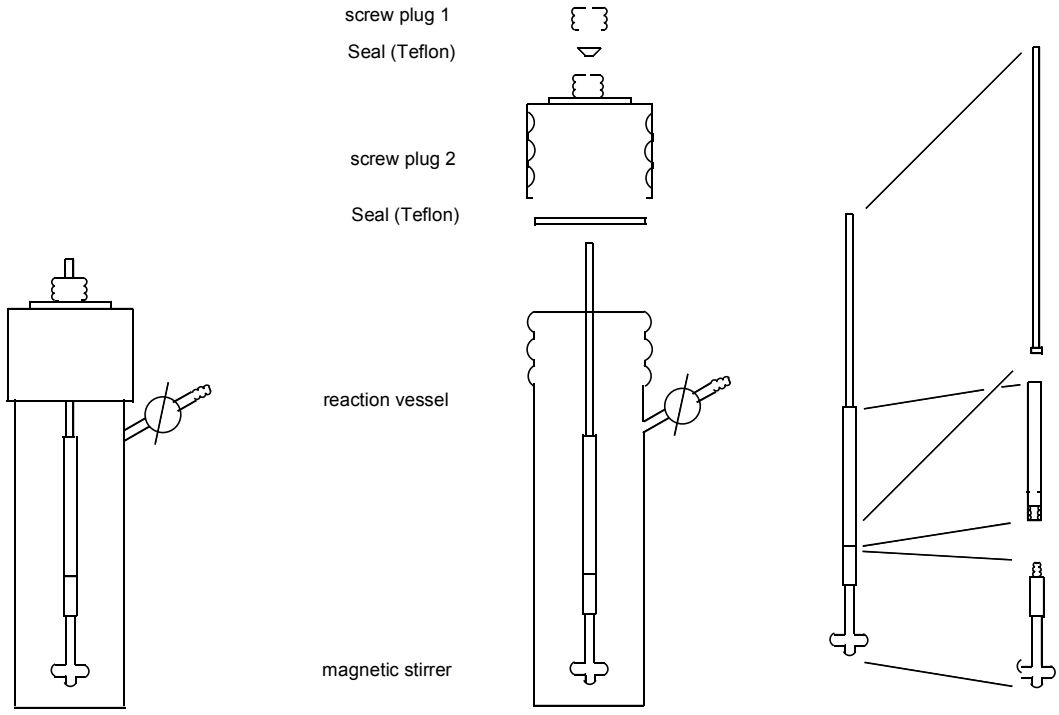


Figure 2. Vessels for solid-phase synthesis.

All reactions on solid support were monitored by IR-spectroscopy (KBr-pellets). Resin attachment was determined by the disappearance of the distinct IR absorption of Wang resin at about 3576 cm^{-1}. The immobilization process was investigated and quantified by elemental analysis of the nitrogen content of the immobilized Fmoc-protected nitrone precursor. Yields are calculated over all steps on solid support according to the loading of the commercially available Wang resins.

Analytical RP-HPLC was performed with a Bio-Tek System 525 pump, a diode array detector 545 V of the company Bio Tek and an auto sampler 565 of the company Kontron, using a Luna 5µ RP C18(2) column (250x4.6 mm) of the company Phenomenex®. The time of retention is abbreviated with R_t.

For purification preparative RP-HPLC was done with a L-6200 Intelligent Pump and a L-4200 UV-detector of Merck-Hitachi. Chromatographies were performed with a LUNA 10µ-Prep RP C18(2) column (250x50 mm) of Phenomenex®. The time of retention is abbreviated with R_T.

All reactions described were performed under argon atmosphere.

Automated synthesis on solid support

Solvents used in the automated synthesis on solid support were used in p. a. quality without further purification. The synthesis (small-scale: 250 mg resin) were performed in a myriad core system of the company Mettler Toledo. Reactions were not monitored by IR-spectroscopy and not carried out under inert gas atmosphere. All crude products obtained by automated syntheses were characterized with RP-HPLC/LC-MS after cleavage from the resin. Percent conversions and purities were determined by analytical RP-HPLC at 210 nm based

on the sum of the peak areas of the starting materials and all isomeric products.

Analytical RP-HPLC was performed with an Agiland Series 1100 of the company Agiland in combination with the mass detector 1100 MSD of the company Agiland using a Chromolith Speed ROD RP-18e 50x4.6 mm-column of the company Merck. The time of retention is abbreviated with R_t.

Preparative RP-HPLC was done with a Thermo Finnigan Aqua of the company Finnigan in combination with a mass detector. Chromatographies were performed with a Purospher® STAR RP-18 endcapped (3 μm) column (85x10 mm) of the company Merck. The time of retention is abbreviated with R_T.

Product Analysis

Reactions in solution were monitored by analytical thin-layer chromatography (silica gel, Merk 60 F_{254} plates). For visualization UV light (254 nm), basic potassium permanganate solution or acidic cerium(II)sulfate was used. For flash chromatography silica gel (32-63 μm, 60Å) of the company *ICN Biomedicals GmbH* was used.

Deuterated solvents for NMR-spectroscopy were bought from the company *Deutero GmbH*. For the removal of traces of acid, deutero chloroform was filtrated over neutral aluminum oxide (MN-aluminum oxide, neutral, *Machery-Nagel*) and immediately used for the measurements of the isoxazolines.

^{1}H NMR spectra were measured on *Bruker* spectrometers AC200, AC400, AM400 and DRX500 at 200 MHz, 400 MHz or 500 MHz at room temperature. Solvents used are mentioned for the particular substances. The chemical shifts are quoted as dimensionless δ–values in ppm, residual solvent protons were used as internal standards. Chemical shifts are given in ppm relative to

tetramethylsilane and coupling constants are given in Hz. The number of protons was determined by integration of the signals. The multiplicity of the signals were abbreviated as followed: s = singlet, d = doublet, t = triplet, m = multiplet.

^{13}C NMR spectra were recorded on *Bruker* spectrometers AC200, AC400, AM400 and DRX500 at 50.3, 100.6 and 125.7 MHz. Solvents are mentioned for the particular substances. The chemical shifts are quoted as dimensionless δ-values in ppm.

^{1}H,^{1}H-COSY, HMQC, HMBC spectra were recorded at room temperature on *Bruker* DRX500.

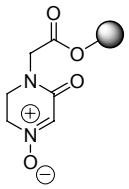
IR spetra were measured with a *Perkin Elmer* spectrometer 881 as attenuated total reflectance (ATR) or as KBr-pellets with a *Perkin Elmer* FT-IR spectrometer 1760X or with the *Nicolet* FT-IR spectrometer Magna 750. The peaks are listed as wave number in cm^{-1}.

MS- and **HR-MS** spectra were recorded on a *Varian* CH 7A, MAT 311A, MAT 711 or on a *Finnigan* MAT 95 SQ. The samples were ionized at an ionization potential of 70 eV (EI).

Melting points were measured with a *Büchi* melting point determination apparatus according to *Dr. Tottoli* and remained uncorrected.

Elemental analyses were performed with a *Heraeus* CHN-apparatus Vario El or with a Elementar Vario El of the company Analytik Jena.

2.1 Synthesis of the Polymer-supported Nitrone 1



1

In 30 ml THF and 33 ml methanol the resin **3** (6.50 g, 5.27 mmol, 0.81 mmol/g) was swollen in a solid phase reactor for 20 min. After addition of sodium wolframate (0.16 g, 0.26 mmol, 0.05 eq) the reaction mixture was cooled to 0 °C and stirred for 1 h. Afterwards a 30% aqueous hydrogen peroxide solution (1.15 ml, 22.88 mmol, 4.40 eq) was added with a syringe within 5 min. The reaction mixture was stirred for 15 min at 0 °C and for 20 h at room temperature. Afterwards, the resin was transferred into a frit (5.5 cm diameter) and rinsed in membrane pump vacuum with water (20 ml, 30 x), methanol (20 ml, 40 x), water (20 ml, 10 x), methanol (20 ml, 10 x) and THF (20 ml, 20 x) and was dried for 3 h (membrane pump vacuum). The characteristic IR-absorption of the amine functionality at 3338 cm^{-1} disappeared completely and the new absorption of the C=N functionality at 1563 cm cm^{-1} appeared. The reaction was repeated analogously, except that the reaction mixture was stirred 12 h yielding the colourless resin **1** (6.60 g). IR (KBr): 3082, 3059, 3025, 2920, 2850, 1944, 1872, 1804, 1743 (COO-linkage), 1662 (C=O, piperazin-2-one), 1600, 1583, 1563 (C=N), 1513, 1492, 1451, 1402, 1353, 1305, 1220, 1171, 1113, 1065, 1027, 964, 905, 824, 747, 697, 535; EA: calculated (loading of the Wang resin 0.8 mmol/g) for N: 1.99, found N: 1.88. The data from elemental analysis confirm within the accuracy of the measurements the efficient resin attachment, which was also investigated directly after the immobilization of the Fmoc-protected nitrone precursor (95% conversion). The reaction was also performed with resins having different loadings (0.4 mmol/g, 078 mmol/g and 0.8 mmol/g) giving the same IR-spectroscopic data.

2.2 Synthesis of Isoxazolidines 6 by [3+2] Cycloaddition Reactions with Alkenes on Solid Support

2.2.1 General Procedure

The resin **1** (up to 1.60 g, max. loading 0.80 mmol/g) was swollen in 10 ml THF in a solid phase reactor for 15 min. After addition of the alkene (21.10 mmol, 16.50 eq) the reaction mixture was heated to reflux. The reaction was monitored by IR-spectroscopy: 5 mg resin were transferred into a syringe (Isolute SPE column from Separtis, size C, 6 ml with 20 μm frit) rinsed in membrane pump vacuum with THF (2 ml, 5 x), dichloromethane (2 ml, 3 x) and dried for 15 min. Afterwards a KBr-pellet was prepared. When the characteristic IR-absorption of the C=N functionality of the nitrone at 1563 cm^{-1} disappeared completely, the resin was transferred into a frit (5.5 cm diameter) or a syringe (Isolute SPE column from Separtis, size D, 15 ml with 20 μm frit, or Isolute SPE column from Separtis, size C, 6 ml with 20 μm frit) and rinsed in membrane pump vacuum. Afterwards the resin was dried 1.5-6 h in membrane pump vacuum.

For cleavage, the resin (250 mg) was swollen in 4 ml THF and 1 ml methanol in a solid phase reactor for 15 min ($V_{THF}/V_{methanol}$ = 4:1). After addition of neat NaOMe (Merck), the reaction mixture was stirred at room temperature for 23-25 h. Afterwards the resin was transferred into a syringe (Isolute SPE column from Separtis, size C, 6 ml with 20 μm frit) and rinsed in membrane pump vacuum. The filtrate was concentrated in vacuo. The residue was dissolved in 8 ml saturated sodium chloride solution and 10 ml dichloromethane and extracted with dichloromethane (10 ml, 6 x). The combined organic layers were dried ($MgSO_4$) and the solvent was concentrated in vacuo. The crude product was purified by preparative RP-HPLC. The completeness of the cleavage was examined by IR-spectroscopy

of the remaining resin by the disappearance of the characteristic IR-absorption of the amide functionality at 1660 cm^{-1} and the ester functionality at 1742 cm^{-1}.

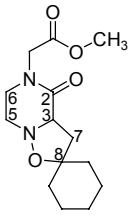
2.2.2 Characteristic Data of New Compounds

Synthesis of the Polymer-bound Isoxazolidine 5b

Method A:
In analogy to the general procedure resin **1** (1.50 g, 1.07 mmol, 0.71 mmol/g) was swollen in 7.5 ml THF. After addition of methylencyclohexane (1.50 ml, 17.64 mmol, 16.50 eq) the reaction mixture was heated to reflux for 17.5 h. The resin was transferred into a frit and rinsed in membrane pump vacuum with water (5 ml, 40 x), THF (5 ml, 30 x) and dichloromethane (5 ml, 60 x) and was dried for 5 h yielding 1.60 g of an orange resin **5b**; IR (KBr): 3083, 3059, 3024, 2931, 2911, 2848, 1944, 1873, 1804, 1746 (COO-linkage), 1656 (C=O, piperazin-2-one), 1601, 1583, 1513, 1492, 1452, 1345, 1265, 1169, 1113, 1068, 1027, 965, 905, 825, 757, 735, 696, 535.

Method B:
In analogy to method A resin **1** (0.50 g, 0.36 mmol, 0.71 mmol/g) was swollen in 2.5 ml THF. After addition of methylencyclohexane (2.5 ml, 20.80 mmol, 58.60 eq) the reaction mixture was heated to reflux. After 8.5 h IR-spectroscopy showed complete conversion. The resin was rinsed and dried as described in method A yielding 536 mg of an orange resin **5b**.
The reaction was also performed with resins having different loadings (0.69 mmol/g and 0.80 mmol/g) giving the same IR-spectroscopic data.

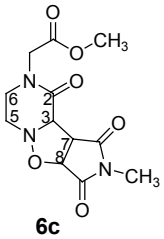
Spectroscopic Data of the Isoxazolidine 6b



6b

According to the general procedures 43 mg (82%, 0.15 mmol) **6b** were obtained by manual synthesis starting from 400 mg resin (0.67 mmol/g) obtained from [3+2] cycloaddition on solid support by cleavage with neat NaOMe in MeOH/THF, work-up, purification and preparative RP-HPLC. Yellow oil; TLC: R_f = 0.62 (methanol); R_t = 9.08 min (MeCN/H_2O 30:70 + 0.1% TFA); R_T = 69 min (MeCN/H_2O 40:60 + 0.1% TFA); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.70 (br m, 1H, H-3), 4.56 (d, 1H, ^2J = 17.4 Hz, NC$\underline{H}_2$COOCH$_3$), 4.03-3.99 (m, 1H, H-6), 3.86 (d, 1H, ^2J = 17.4 Hz, NC$\underline{H}_2$COOCH$_3$), 3.80-3.76 (m, 1H, H-5), 3.76 (s, 3H, COOCH$_3$), 3.66-3.63 (m, 1H, H-5`), 3.45-3.42 (m, 1H, H-6`), 2.70-2.66 (dd, 1H, ^2J = 13.1 Hz, ^3J = 8.2 Hz, H-7), 2.63-2.60 (dd, 1H, ^2J = 13.1 Hz, ^3J = 3.5 Hz, H-7`), 1.78-1.75 (m, 2H, CH$_2$-cyclohexyl), 1.70-1.64 (m, 4H, CH$_2$-cyclohexyl), 1.45-1.42 (m, 4H, CH$_2$-cyclohexyl); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 168.1 (C=O, ester), 165.6 (C=O, piperazin-2-one), 87.7 (C-8), 62.0 (C-3), 52.4 (COO$\underline{C}$H$_3$), 48.4 (N$\underline{C}$H$_2$COOCH$_3$), 47.2 (C-6), 42.0 (C-5), 36.1, 35.9, 24.5, 23.6 (C-7, CH$_2$-cyclohexyl). For the signal assignments ^{1}H,^{1}H-COSY- and HMQC-spectra were measured; IR (ATR): 2937, 2860, 1750 (C=O, ester), 1669 (C=O, piperazin-2-one), 1489, 1450, 1408, 1348, 1291, 1185, 1140, 996, 826, 720; MS (FD) m/z (%): 282 (12) [M^+], 187 (46), 95 (12), 69 (100), 56 (20), 51 (68); MS (EI, 100 °C) m/z (%): 282 (22) [M^+], 188(6), 187 (100), 171 (4), 158 (4), 125 (4), 56 (10); HR-MS calculated 282.1579, found: 282.1581; EA: calculated for $C_{14}H_{22}N_2O_4$ (282.3) C 59.56, H 7.85, N 9.92, found: C 59.59, H 7.81, N 9.83.

Synthesis of the Isoxazolidine 6c



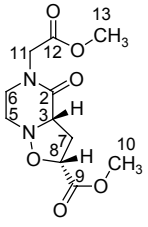
6c

As described in the general procedure for [3+2] cycloaddition reaction by manual synthesis on solid support resin **1** (1.60 g, 1.28 mmol, 0.80 mmol/g) was swollen in 10.0 ml THF. After addition of *N*-methyl maleic imide (2.35 g, 21.12 mmol, 16.50 eq) the reaction mixture was heated for 1 h (IR-monitoring) and then cooled to room temperature. The resin was transferred into a 15 ml syringe and rinsed in membrane pump vacuum with THF (2 ml, 60 x) and dried for 2 h yielding 1.88 g of the yellow resin **5c**. IR (KBr): 3082, 3059, 3025, 2974, 2846, 1944, 1874, 1804, 1747 (COO-linkage), 1717 (br, C=O, imide), 1663 (C=O, piperazin-2-one), 1601, 1583, 1513, 1493, 1452, 1381, 1349, 1287, 1170, 1065, 1028, 965, 907, 822, 757, 697, 536.

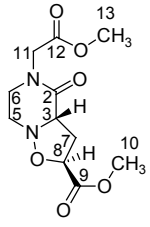
For cleavage in analogy to the general procedure resin **5c** (250 mg, 0.16 mmol, 0.66 mmol/g) was swollen in 4 ml THF and 1 ml methanol. After addition of NaOMe (13.0 mg, 0.24 mmol, 1.45 eq) the resin was stirred for 24 h. Afterwards, the resin was transferred into a 6 ml syringe and rinsed in membrane pump vacuum with THF (2 ml, 5 x), methanol (2 ml, 5 x), THF (2 ml, 10 x), methanol (2 ml, 5 x) and THF (2 ml, 10 x). The filtrate was concentrated in vacuo. The residue was dissolved in 8 ml saturated sodium chloride solution and 10 ml dichloromethane and extracted with dichloromethane (7 ml, 6 x). The combined organic layers were dried over $MgSO_4$ and the solvent was concentrated in vacuo. The crude product (24 mg yellow oil, 50%, purity 92%, R_t = 6.25 min (MeCN/H_2O 30:70)) was purified by preparative RP-HPLC chromatography yielding 13.5 mg (28%) **6c** as a colourless oil; TLC: R_f = 0.44 (ethyl acetate); R_T = 52 min (MeCN/H_2O 30:70); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.80 (d, 1H, ^3J = 7.5 Hz, H-8), 4.21 (br s, 1H, H-3), 4.16 (d, 1H, ^2J = 17.3 Hz, NC$\underline{H}_2$COOCH$_3$), 4.12 (d, 1H, ^2J = 17.3 Hz, NC$\underline{H}_2$COOCH$_3$), 4.09 (d, 1H, ^3J = 7.5 Hz, H-7), 4.06-4.00 (dt, 1H, ^2J = 11.8 Hz, ^3J =

4.0 Hz, H-6), 3.73 (s, 3H, $COO\underline{C}H_3$), 3.61-3.57 (dd, 1H, ^2J = 14.7 Hz, ^3J = 4.0 Hz, H-5), 3.45-3.39 (dt, 1H, ^2J = 14.7 Hz, ^3J = 4.9 Hz, H-5`), 3.14-3.11 (dd, 1H, $^2J$ = 11.8 Hz, $^3J$ = 4.9 Hz, H-6`), 3.04 (s, 3H, $N\text{-}CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.7 (C=O), 174.4 (C=O), 168.7 (C=O), 166.7 (C=O), 75.2 (C-8), 65.9 (C-3), 52.4 ($COO\underline{C}H_3$), 52.1 (C-7), 48.6 ($N\underline{C}H_2COOCH_3$), 46.1 (C-6), 43.2 (C-5), 25.3 ($N\text{-}CH_3$); IR (KBr): 3013, 2989, 2982, 2957, 2932, 2880, 1751 (C=O, ester), 1703 (br, 2 C=O), 1659 (C=O, piperazin-2-one), 1487, 1438, 1413, 1385, 1366, 1360, 1347, 1330, 1318, 1289, 1282, 1267, 1246, 1215, 1180, 1148, 1136, 1082, 1059, 1034, 1001, 976, 967, 943, 935, 890, 796, 772, 738, 725, 697, 609, 574, 516, 496, 464; IR (ATR): 2955, 1746 (C=O, ester), 1704 (br, 2 C=O), 1655 (C=O, piperazin-2-one), 1491, 1436, 1405, 1385, 1365, 1349, 1291, 1214, 1183, 1136, 1085, 1064, 1037, 998, 967, 875, 777, 724; MS (EI, 150 °C) m/z (%): 298 (10) [M^++1], 297 (64) [M^+], 238 (52), 210 (30), 158 (42), 123 (30), 84 (38), 69 (54), 56 (100); HR-MS calculated 297.0960, found: 297.0961; EA: calculated for $C_{12}H_{15}N_3O_6$ (297.3) C 48.49, H 5.09, N 14.14, found: C 48.37, H 5.14, N 14.05.

Characteristic Data of Compound 6e



endo-**6e**

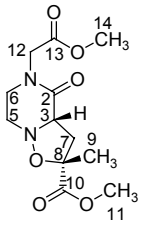


exo-**6e**

Compound **6e**: 57% *endo*-**6e** and 43% *exo*-**6e** [*endo*: (3*S*, 7*R*) and (3*R*, 7*S*); *exo*:(3*S*, 7*S*) and (3*R*,7*R*)], colourless oil; TLC: R_f = 0.69 (methanol); R_T = 46 min ($MeCN/H_2O$ 30:70); ^1H NMR (500 MHz, $CDCl_3$): δ = 4.67-4.65 (t, 1H, ^3J = 6.9 Hz, H-8), 4.61-4.56 (dd, 1H, ^3J = 9.0 Hz, ^3J = 7.9 Hz, H-8), 4.24-4.19 (m, 2H, H-11, both isomers), 4.13-4.03 (m, 4H, H-11`, both isomers, H-3, both isomers), 3.87-3.82 (ddd, 1H, $^3J$ = 3.2 Hz, $^3J$ = 3.9 Hz, $^2J$ = 15.6 Hz, H-5), 3.78 (s, 3H, H-10), 3.76 (s, 3H, H-10), 3.74 (s, 6H, H-13, both isomers), 3.69-3.63 (m, 1H, H-5), 3.53-3.48 (m, 2H, H-6, both isomers), 3.45-3.41 (m, 3H, H-5`, H-6`, H-

6`), 3.26-3.22 (m, 1H, H-5), 3.04-3.01 (m, 1H, H-7), 2.93-2.90 (m, 2H, H-7`, both isomers), 2.72-2.68 (m, 1H, H-7); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.9, 171.6 (C=O, C-9, both isomers), 168.9 (C=O, C-12, both isomers), 168.8, 167.9 (C=O, C-2, both isomers), 75.8, 74.3 (C-8, both isomers), 63.6, 62.5 (C-3, both isomers), 52.6, 52.4 (C-10, C-13, both isomers), 48.6, 48.2 (C-6, both isomers), 47.8, 47.7 (C-11, both isomers), 44.4, 43.6 (C-5, both isomers), 37.5, 37.3 (C-7, both isomers). For the signal assignments ^{1}H,^{1}H-COSY- and HMQC-spectra were measured; IR (ATR): 2955, 2852, 1743 (br, C=O, ester), 1653 (br, C=O, piperazin-2-one), 1490, 1438, 1405, 1365, 1345, 1290, 1269, 1211, 1181, 1107, 1010; MS (EI, 90 °C) m/z (%): 272 (44) [M^+], 213 (26) [M^+-$COOCH_3$], 185 (44), 158 (68), 125 (100), 84 (26), 70 (30), 56 (100); HR-MS calculated: 272.1008, found: 272.1009; EA: calculated for $C_{11}H_{16}N_2O_6$ (272.3) C 48.53, H 5.92, N 10.29, found: C 48.31, H 5.75, N 10.37.

Spectroscopic Data of the Isoxazolidine 6f



***endo*-6f**

Compound **6f** [*endo*: (3*S*, 7*R*) and (3*R*, 7*S*)]: colourless oil; TLC: R_f = 0.33 (ethyl acetate), 0.69 (methanol), R_T = 56 min (MeCN/H_2O 30:70); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.20 (d, 1H, ^{2}J = 17.6 Hz, $NC\underline{H}_2COOCH_3$), 4.21-4.13 (dd, 1H, ^{3}J = 7.3 Hz, ^{3}J = 8.3 Hz, H-3), 4.05 (d, 1H, ^{2}J = 17.6 Hz, $NC\underline{H}_2COOCH_3$), 3.76 (s, 3H, $COOCH_3$), 3.74 (s, 3H, $COOCH_3$), 3.60-3.43 (m, 2H, H-5, H-5`), 3.37-3.31 (m, 2H, H-6, H-6`), 3.07-2.96 (dd, 1H, ^{3}J = 7.3 Hz, ^{2}J = 13.2 Hz, H-7), 2.66-2.55 (dd, 1H, ^{3}J = 8.3 Hz, ^{2}J = 13.2 Hz, H-7`), 1.54 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.5 (C=O, C-10), 168.8 (C=O, C-13), 167.6 (C=O, C-2), 83.2 (C-8), 64.0 (C-3), 52.8 (C-14), 52.4 (C-11), 48.4 (C-6), 47.7 (C-12), 44.4 (C-5), 43.1 (C-7), 24.8 (C-9). For the signal assignments ^{1}H,^{1}H-COSY-, HMBC-, NOE- and HMQC-spectra were measured; IR (ATR): 3459, 2955, 1745 (C=O, ester), 1662 (C=O, C-10), 1640 (C=O,

piperazin-2-one), 1486, 1437, 1406, 1368, 1344, 1290, 1255, 1212, 1181, 1116, 989, 898, 841, 795, 755; MS (EI, 120 °C) m/z (%): 286 (38) [M^+], 227 (42), 185 (100), 184 (46), 158 (46), 125 (60), 97 (38), 56 (97); HR-MS calculated 286.1164, found: 286.1166.

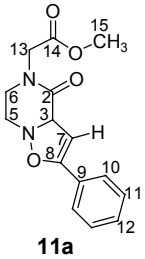
2.3 Synthesis of Isoxazolines 11 by Manual Solid Phase Synthesis

2.3.1 General Procedure

The resin **1** (270 mg, 0.19 mmol, 0.69 mmol/g) was swollen in 2.5 ml THF in a solid phase reactor for 15 min. After addition of 2.50 ml (22.80 mmol, 122 eq) alkyne the reaction mixture was heated to 60 °C. For IR-monitoring 5 mg resin were transferred into a syringe (Isolute SPE column from Separtis, size C, 6 ml with 20 μm frit) rinsed in membrane pump vacuum with THF (2 ml, 10 x), dichloromethane (2 ml, 5 x) and dried for 15 min before a KBr-pellet was prepared. When the characteristic IR-absorption of the C=N functionality of the nitrone at 1563 cm^{-1} disappeared completely, the resin was transferred into a syringe (Isolute SPE column from Separtis, size C, 6 ml with 20 μm frit, or Isolute SPE column from Separtis, size C, 6 ml with 20 μm frit), rinsed and dried (3 h) in membrane pump vacuum.

2.3.2 Characteristic Data of New Compounds

Spectroscopic Data of the Isoxazoline 11a

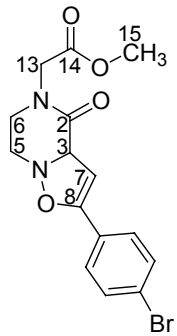


11a

Compound **11a**: yellow oil; TLC: R_f = 0.46 (ethyl acetate); R_t = 10.0 min (MeCN/H_2O 40:60); R_T = 71 min (MeCN/H_2O 50:50); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.53-7.51 (dd, 2H, ^3J = 4.3 Hz, ^3J = 1.9 Hz, *meta*-H), 7.36

(d, 1H, ^{3}J = 1.9 Hz, *para*-H), 7.34 (d, 2H, ^{3}J = 4.3 Hz, *ortho*-H), 5.34 (d, 1H, ^{3}J = 2.2 Hz, H-7), 5.15 (d, 1H, ^{3}J = 2.2 Hz, H-3), 4.25 (d, 1H, ^{2}J = 17.5 Hz, H-13), 4.09 (d, 1H, ^{2}J = 17.5 Hz, H-13`), 3.74 (s, 3H, H-15), 3.59-3.56 (m, 1H, H-5), 3.55-3.53 (m, 1H, H-6), 3.52-3.50 (m, 1H, H-6`), 3,49-3.46 (m, 1H, H-5`); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.9 (C=O, C-14), 167.0 (C=O, C-2), 154.0 (C-8), 129.5 (*para*-C), 128.5 (*ortho*-C), 127.9 (C-9), 125.7 (*meta*-C), 93.6 (C-7), 69.5 (C-3), 52.4 (C-15), 50.2 (C-6), 48.0 (C-13), 43.7 (C-5). For the signal assignments $^{1}H,^{1}H$-COSY- and HMQC-spectra were measured; IR (ATR): 2951, 2855, 1748 (C=O, ester), 1660 (C=O, piperazin-2-one), 1487, 1447, 1404, 1339, 1322, 1291, 1212, 1181, 1020, 771, 719, 692; MS (FD) m/z (%): 289.7 (17.0) [M^{+}+1], 288.6 (100) [M^{+}]; MS (EI, 70 °C) m/z (%): 288 (10) [M^{+}], 260 (12), 215 (14), 201 (100), 183 (24), 159 (14), 145 (20), 131 (12), 105 (36), 69 (14), 56 (52); HR-MS calculated 288.1110, found: 288.1112; EA: calculated for $C_{15}H_{16}N_2O_4$ (288.3) C 62.49, H 5.59, N 9.72, found: C 62.53, H 5.61, N 9.60.

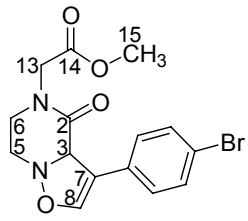
Characteristic Data of Compound 11b



11b

5-substituted Isoxazoline: orange oil; TLC: R_f = 0.44 (ethyl acetate); R_t = 4.99 min (MeCN/H_2O 70:30); R_T = 67 min (MeCN/H_2O 60:40); ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.48 (d, 2H, ^{3}J = 8.80 Hz, H-aromat), 7.36 (d, 2H, ^{3}J = 8.8 Hz, H-aromat), 5.44 (d, 1H, $^{3}J_{H-7,\ H-3}$ = 2.44 Hz, H-7), 5.12 (d, 1H, $^{3}J_{H-3,\ H-7}$ = 2.44 Hz, H-3), 4.24 (d, 1H, $^{2}J_{H-13,\ H-13`}$ = 17.56 Hz, H-13), 4.09 (d, 1H, $^{2}J_{H-13`,\ H-13}$ = 17.56 Hz, H-13`), 3.73 (s, 3H, H-15), 3.53-3.43 (m, 4H, CH_2-CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.9 (C=O, C-14), 166.8 (C=O, C-2), 153.1 (C-8), 131.9 (C-aromat), 131.7 (C-aromat), 129.8 (C-aromat), 127.8 (C-aromat), 126.8 (C-9), 123.6 (C-aromat-Br), 94.4 (C-

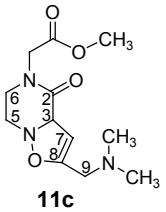
7), 69.5 (C-3), 52.4 (C-15), 50.2 (C-6), 48.0 (C-13), 43.6 (C-5). IR (ATR): 2953, 2854, 1749 (C=O, ester), 1658 (C=O, piperazin-2-one), 1587, 1487, 1438, 1400, 1341, 1288, 1212, 1180, 1071, 1008, 820; MS (EI, 170 °C) m/z (%): 370 (17), 369 (99), 368 (18), 367 (100, M^++1), 365 (24), 340 (48), 338 (48), 281 (48), 279 (48), 187 (22), 185 (96), 183 (100), 157 (20), 155 (20), 56 (68); HR-MS calculated for $C_{15}H_{16}N_2O_4Br$: 367.0292, found: 367.0291.



11b

4-substituted Isoxazoline: yellow oil; TLC: R_f = 0.47 (ethyl acetate); R_t = 4.77 min (MeCN/H_2O 70:30); R_T = 64 min (MeCN/H_2O 60:40); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.84 (d, 2H, ^3J = 8.35 Hz, H-aromat), 7.59 (d, 2H, ^3J = 8.35 Hz, H-aromat), 7.49 (s, 1H, H-8), 7.25 (s, 1H, H-3), 4.30 (d, 1H, $^2J_{CH2,\ CH2`}$ = 17.56 Hz, H-13), 4.00 (d, 1H, $^2J_{CH2,\ CH2}$ = 17.56 Hz, H-13`), 3.79-3.75 (m, 4H, H-5, H-15), 3.54-3.51 (m, 2H, H-6, H-6`), 3.37-3.34 (m, 1H, H-5`); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.0 (C=O), 167.7 (C=O), 140.1 (C-7), 135.2 (q, C-aromat),132.0 (C-aromat), 129.8 (C-aromat), 128.7 (C-8), 127.4 (C-aromat-Br), 78.2 (C-3), 52.4 (C-15), 52.2 (C-6), 47.9 (C-13), 40.5 (C-5); For the signal assignments ^1H,^1H-COSY- and HMQC-spectra were measured; IR (ATR): 2952, 2924, 2852, 1749 (C=O, ester), 1653 (C=O, piperazin-2-one), 1585, 1488, 1437, 1399, 1345, 1284, 1209, 1181, 1135, 1071, 1008, 999, 833; MS (EI, 170 °C) m/z (%): 370 (12), 369 (48), 368 (18), 367 (48, M^+ +1), 187 (32), 185 (98), 183 (100), 91 (68), 56 (22); HR-MS calculated for $C_{15}H_{15}N_2O_4Br$: 367.0292, found: 367.0293

Characteristic Data of Compound 11c



11c

Compound **11c**: yellow oil; TLC: R_f = 0.78 (ethyl acetate); R_t = 3.89 min (MeCN/H_2O 30:70); R_T = 47 min (MeCN/H_2O 30:70); ^1H NMR (500 MHz, $CDCl_3$): δ = 4.99 (br s, 1H, H-7), 4.96 (br s, 1H, H-3), 4.19 (d, 1H, ^2J = 17.3 Hz, NCH_2COOCH_3), 4.12 (d, 1H, ^2J = 17.3 Hz, NCH_2COOCH_3), 3.74 (s, 3H, $COOCH_3$), 3.65-3.61 (m, 1H, H-5), 3.53-3.48 (m, 1H, H-6), 3.46-3.42 (m, 1H, H-6`), 3.39-3.35 (m, 1H, H-5`), 3.17 (d, 1H, ^2J = 14.1 Hz, H-9), 3.12 (d, 1H, ^2J = 14.1 Hz, H-9`), 2.34 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 168.7 (C=O), 166.8 (C=O), 152.4 (C-8), 97.6 (C-7), 68.2 (C-3), 53.6 (C-9), 52.1 ($COOCH_3$), 50.0 (C-6), 47.9 (NCH_2COOCH_3), 44.7 ($N(CH_3)_2$), 43.3 (C-5). For the signal assignments $^1H,^1H$-COSY-, HMBC-, NOE- and HMQC-spectra were measured; IR (ATR): 2953, 2856, 2782, 1745 (C=O, ester), 1644 (C=O, piperazin-2-one), 1487, 1439, 1405, 1363, 1342, 1293, 1211, 1179, 1138, 1079, 995, 946, 848, 800, 753, 720; MS (EI, 110 °C) m/z (%): 269 (2) [M^+], 241 (2), 211 (8), 182 (14), 137 (2), 81 (6), 69 (10), 58 (100), 55 (4); HR-MS calculated for $C_{12}H_{19}N_3O_4$ 269.1375, found: 269.1377.

2.4 Synthesis of 1,3-Amino Alcohols 8 and Lactams 10 by Reductive N-O-Bond Cleavage

2.4.1 General Procedure for N-O-bond Cleavage by Manual Synthesis on Solid Support

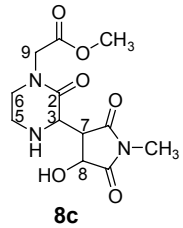
In a vessel for solid-phase synthesis (Figure 2) up to 1.90 g (1.39 mmol) resin (max. loading 0.73 mmol/g) was swollen in 19.50 ml acetonitrile and 1.30 ml water ($V_{acetonitrile}/V_{water}$ 15:1) for 15 min. After addition of 2.68 g (10.15 mmol, 7.40 eq) $Mo(CO)_6$ the reaction mixture was heated to reflux (85 °C) for 5 h up to 29 h. Afterwards the resin was transferred into a

syringe (Isolute SPE column from Separtis, size D, 15 ml with 20 μm frit), rinsed with acetonitrile (4 ml, 25 x), THF (4 ml, 25 x), methanol (4 ml, 25 x), THF (4 ml, 15 x), methanol (4 ml, 15 x), acetonitrile (4 ml, 15 x), THF (4 ml, 25 x), methanol (4 ml, 25 x), THF (4 ml, 15 x), methanol (4 ml, 15 x), acetonitrile (4 ml, 15 x), THF (4 ml, 20 x) and dried (3 h) in membrane pump vacuum.

For the cleavage of the polymer-supported 1,3-amino alcohols 240 mg (0.16 mmol) resin (0.65 mmol/g) were swollen in 4 ml THF for 15 min in a solid phase reactor. Afterwards 1 ml methanol was added and the resin was swollen for further 10 min ($V_{THF}/V_{methanol}$ 4:1). After addition of 22.9 mg (0.42 mmol, 2.70 eq) neat NaOMe the reaction mixture was stirred at room temperature for 24 h. Afterwards the resin was transferred into a syringe (Isolute SPE column from Separtis, size C, 6 ml with a 20 μm frit) and rinsed in membrane pump vacuum. The filtrate was concentrated in vacuo. The residue was dissolved in 15 ml dichloromethane and 4 ml saturated sodium chloride solution and extracted with dichloromethane (6 x). The combined organic layers were dried ($MgSO_4$) and the solvent was concentrated in vacuo. The crude product was purified by preparative RP-HPLC (λ = 210 nm).

2.4.2 Characteristic Data of New Compounds

Spectroscopic Data of the 1,3-Amino alcohol 8c

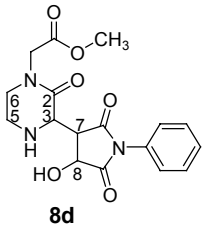


8c

Compound **8c**: slightly soiled yellow oil; R_t = 2.97 min (MeCN/H_2O 30:70); R_T = 39 min (MeCN/H_2O 30:70); ^1H NMR (200 MHz, CD_3CN): δ = 6.23 and 5.54 (br s, 2H, OH, NH), 4.73-4.59 (br m, 1H, H-3), 4.47-4.35 (br m, 1H, H-7), 4.28 (d, 1H, ^2J = 17.6 Hz, H-9), 4.12 (d, 1H, ^2J =

17.6 Hz, H-9`), 4.10-3.96 (m, 1H, H-5), 3.80 (s, 3H, $COOCH_3$), 3.78 (br m, 1H, H-8), 3.64-3.50 (br m, 2H, H6, H6`), 3.45-3.35 (br m, 1H, H5`), 2.99 (s, 3H, $N-CH_3$); ^{13}C NMR (125 MHz, CD_3CN): δ = 173.3 (C=O), 171.5 (C=O), 170.1 (C=O), 169.6 (C=O), 73.0 (C-3), 56.2 (C-7), 52.3 ($COO\underline{C}H_3$), 51.8 (C-8), 48.8 (C-9), 47.6 (C-6), 37.8 (C-5), 22.5 ($N-CH_3$); IR (ATR): 3457 (OH), 3324 (NH), 2925, 1747 (C=O, ester), 1707 (C=O, imide), 1674 (C=O, imide), 1653 (C=O, piperazin-2-one), 1492, 1439, 1411, 1383, 1364, 1283, 1216, 1182, 1044; MS (EI, 150 °C) m/z (%): 299 (14) [M^+], 211 (14), 137 (18), 95 (20), 81 (48), 69 (100), 57 (24); HR-MS calculated for $C_{12}H_{17}N_3O_6$ 299.1117, found: 299.1112.

Spectroscopic Data of Compound 8d

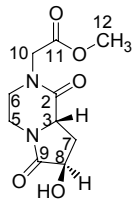


8d

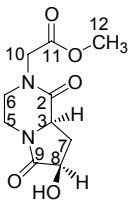
Compound **8d**: colourless oil; TLC: R_f = 0.40 (ethyl acetate); R_t = 6.05 min (MeCN/H_2O 30:70); R_T = 63 min (MeCN/H_2O 30:70); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.59 (d, 2H, ^3J = 7.5 Hz, H-aromat), 7.46-7.29 (m, 2H, H-aromat), 7.11-7.08 (m, 1H, H-aromat), 4.99 (br m, 1H, H-3), 4.33 (m, 1H, H-7), 4.21 (br m, 3H, NH, $NC\underline{H}_2COOCH_3$), 3.79 (s, 3H, $COOC\underline{H}_3$), 3.69 (br m, 2H, H-5, H-8), 3.44-3.42 (m, 1H, H-6), 3.32 (m, 2H, H-5`, H-6`), the OH-signal is not detectable in the ^1H NMR spectra; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.7 (C=O), 169.1 (C=O), 168.4 (C=O), 166.7 (C=O), 138.0 (C_{quart}), 129.0, 124.4, 119.8 (all C-aromat), 71.0 (C-3), 55.5 (C-7), 52.7 ($COO\underline{C}H_3$), 51.6 (C-8), 48.7 ($NC\underline{H}_2COOCH_3$), 47.4 (C-6), 36.7 (C-5). For the signal assignments $^1H,^1H$-COSY- and HMQC-spectra were measured; IR (ATR): 3490 (OH), 3308 (NH), 3140, 3085, 2955, 2928, 1744, (C=O, ester), 1712 (br, 2 C=O, imide), 1666 (C=O, piperazin-2-one), 1599, 1550, 1495, 1444, 1364, 1342, 1304, 1256, 1213, 1179, 1136, 1107, 1081, 1028, 985, 953, 910, 870, 842, 808, 760, 694, 666; MS (EI, 190 °C) m/z (%): 362 (12) [M^++1], 361 (62) [M^+], 320 (100), 233 (28),

158 (68), 125 (64), 93 (38), 77 (42), 56 (78); HR-MS calculated 361.1273, found: 361.1272; EA: calculated for $C_{17}H_{19}N_3O_6$ (361.4) C 56.51, H 5.30, N 11.63, found: C 56.22, H 5.41, N 11.84.

Spectroscopic Data of Compound 10a



***exo*-derivative 10a**

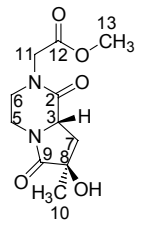


***endo*-derivative 10a**

Compound **10a**: mixture of the *exo*- and *endo*-derivatives [*exo*: (3*S*, 7*R*) and (3*R*, 7*S*); *endo*: (3*R*, 7*R*) and (3*S*, 7*S*)] in a ratio of 57:43, colourless oil; R_t = 4.61 min (MeCN/H_2O 30:70); R_T = 36 min (MeCN/H_2O 30:70); TLC: R_f = 0.84 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.40-4.35 (m, 2H, H-3, *exo*, H-8, *exo*), 4.37-4.35 (t, 1H, ^3J = 7.9 Hz, H-8, *endo*), 4.19 (d, 1H, ^2J = 17.5 Hz, H-10, *exo*), 4.17 (d, 1H, ^2J = 17.5 Hz, H-10, *endo*), 4.15-4.07 (m, 3H, H-3, *endo*, H-5, *endo*, H-5`, *endo*), 4.11 (d, 1H, $^2J$ = 17.5 Hz, H-10`, *endo*), 4.07 (d, 1H, ^2J = 17.5 Hz, H-10`, *exo*), 3.73 (s, 3H, COOC$\underline{H}_3$, *exo*), 3.73 (s, 3H, COOC$\underline{H}_3$, *endo*), 3.63-3.53 (m, 2H, H-6, *endo*, H-6, *exo*), 3.43-3.27 (m, 4H, H-5, *exo*, H-5`, *exo*, H-6`, *endo*, H-6`, *exo*), 2.95-2.89 (m, 1H, H-7, *endo*), 2.48-2.44 (m, 1H, H-7, *exo*), 2.41-2.39 (m, 1H, H-7`, *exo*), 2.05-1.95 (m, 1H, H-7`, *endo*), the OH-signals are not detectable; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.4 (C=O, C-9, *endo*), 173.3 (C=O, C-9, *exo*), 169.0 (C=O, C-11, *exo*), 168.9 (C=O, C-2, C-11, *endo*), 168.1 (C=O, C-2, *exo*), 69.9 (C-8, *exo*), 69.5 (C-8, *endo*), 55.9 (C-3, *exo*), 53.8 (C-3, *endo*), 52.5 (C-12, *exo*), 52.4 (C-12, *endo*), 48.3 (C-10, *endo*), 48.2 (C-10, *exo*), 47.2 (C-6, *endo*, C-6, *exo*), 37.2 (C-5, *exo*), 36.9 (C-5, *endo*), 32.8 (C-7, *endo*), 31.0 (C-7, *exo*). For the signal assignments ^{1}H,^{1}H-COSY- and HMQC-spectra were measured; IR (ATR): 3345, 2951, 1742 (C=O, ester), 1652 (br, C=O, lactame, piperazin-2-one), 1490, 1434, 1406, 1364, 1340, 1274, 1210, 1178, 1108, 1081, 981, 916; MS (EI, 130 °C) m/z (%): 243 (12) [M^++1], 242 (70) [M^+], 224 (36) [M^+-H_2O], 214 (54), 185 (52), 155 (100), 127 (34), 125 (34), 83 (32), 56 (68); HR-MS calculated

242.0902, found: 242.0905; EA: calculated for $C_{10}H_{14}N_2O_5$ (242.2) C 49.58, H 5.83, N 11.57, found: C 49.47, H 5.87, N 11.54.

Spectroscopic Data of Compound 10b



***exo*-derivative 10b**

Compound **10b** [*exo*: (3*S*, 7*R*) and (3*R*, 7*S*)]: colourless oil; TLC: R_f = 0.70 (ethyl acetate), R_T = 37 min (MeCN/H_2O 30:70); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.37-4.34 (dd, 1H, ^3J = 7.9 Hz, ^3J = 6.9 Hz, H-3), 4.32-4.29 (d, 1H, ^2J = 17.6 Hz, H-11), 4.16-4.11 (ddd, 1H, ^3J = 2.6 Hz, ^3J = 3.4 Hz, ^2J = 13.3 Hz, H-5), 4.03-4.00 (d, 1H, ^2J = 17.6 Hz, H-11`), 3.75 (s, 3H, H-13), 3.64-3.58 (ddd, 1H, ^3J = 2.4 Hz, ^3J = 3.4

Hz, ^2J = 12.8 Hz, H-6), 3.44-3.38 (m, 2H, H-5`, H-6`), 2.62-2.57 (dd, 1H, ^3J = 7.9 Hz, ^2J = 13.9 Hz, H-7), 2.21-2.17 (dd, 1H, ^3J = 6.9 Hz, ^2J = 13.9 Hz, H-7`), 1.46 (s, 3H, H-10), the OH-signal is not detectable; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.6 (C-9), 168.9 (C-12), 168,8 (C-2), 75.0 (C-8), 54.8 (C-3), 52.5 (C-13), 48.3 (C-11), 47.3 (C-6), 37.4 (C-7), 37.3 (C-5), 24.3 (C-10). For the signal assignments ^{1}H,^{1}H-COSY-, HMBC-, NOE- and HMQC-spectra were measured; IR (ATR): 2956, 2930, 1740 (C=O, ester), 1675 (C=O, lactame), 1655 (C=O, piperazin-2-one), 1488, 1436, 1365, 1340, 1275, 1209, 1180, 1113, 1076, 1004, 988, 953; MS (EI, 170 °C) m/z (%): 256 (32) [M^+], 228 (100), 185 (68), 169 (38), 125 (22), 99 (23), 83 (24), 56 (48); HR-MS calculated for $C_{11}H_{16}N_2O_5$: 256.1059, found: 256.1051.

2.5 Automated Amine Acylations of Polymer-bound 1,3-Amino Alcohols 7

2.5.1 General Procedure and Table of Compounds

For automated acylation 200 mg (0.13 mmol – 0.14 mmol) resin (0.67 mmol/g – 0.71 mmol/g) were swollen in DMF (2 ml, 1 min, 1 x). After removal of the solvent in vacuo the resin was dried (0.5 min). Afterwards 1.30 ml DMF, 0.56 ml (0.28 mmol, 2.0 – 2.10 eq) carboxylic acid (0.50 M solution in DMF), 0.56 ml (0.28 mmol, 2.0 – 2.10 eq) TBTU (0.50 M solution in DMF) and 0.80 ml (0.56 mmol, 3.90 – 4.20 eq) DIPEA (0.70 M solution in DMF) were added and the reaction mixture was stirred at room temperature for 16 h. Afterwards the solvent was removed in vacuo. The resin was dried (0.5 min), rinsed with DMF (3 ml, 1 min, 2 x), dried (0.5 min), rinsed with THF (3 ml, 1 min, 2 x), dried (0.5 min), rinsed with methanol (3 ml, 1 min, 2 x), dried (0.5 min), rinsed with methanol (3 ml, 1 min, 2 x), dried (0.5 min), rinsed with dichloromethane (3 ml, 2 min, 2 x) and dried (0.5 min).

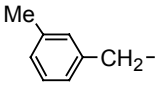
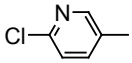
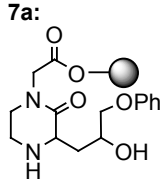
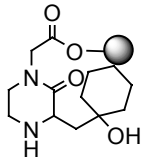
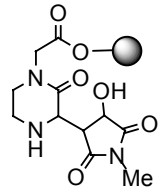
For cleavage the resin was swollen in 2.0 ml THF and 0.5 ml methanol for 5 min. After addition of 26.1 mg (0.48 mmol, 3.40 - 3.60 eq) neat NaOMe the reaction mixture was stirred at room temperature for 20 h. Afterwards the solvent was removed in vacuo and the resin was rinsed with methanol (1.0 ml, 5 min, 1 x). The combined filtrates were concentrated in a speed vac Beta-RCV of the company Christ at 60 °C. The residue was dissolved in 2 ml saturated sodium chloride solution and 3 ml dichloromethane, mixed (2 x) and extracted using a Myriad Allex robot (3 x). The solvent of the combined organic layers was concentrated in a speed vac at 60 °C.

The crude products were analysed by analytical RP-HPLC in combination with a mass detector using a Chromolith Speed ROD RP-18e-column and MeCN/H_2O 5:95 + 0.1% TFA → MeCN/H_2O 100:0 + 0.1% TFA within 5 min.

The crude products were purified by preparative RP-HPLC in combination with a mass detector using MeCN/H_2O + 0.1% TFA as solvent: 0 min: 80% water → 3 min: 50% water → 10 min: 20% water → 13 min to 16 min: 0% water. The purities of the crude

products were calculated for each derivative from the amount of the mentioned isomeric products (parent acid and ester) and the starting material in comparison to all peaks in the analytical RP-HPLC-MS-spectra.
After acylation the OH-signals of the products were not detectable in the ^{1}H NMR spectra.

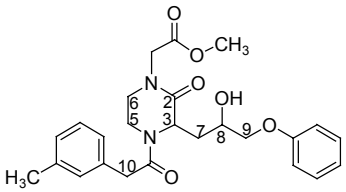
Table 1. Library of piperazin-2-ones derived from polymer-supported 1,3-amino alcohols **7** by automated amine acylation

7 \ R^4 =	**12** $CH_3CH(CH_3)CH_2CH_2$-	**13** 	**14** 	**15** 
7a: 	**16a**[a,b] {77} [72] 5	**16b**[a,b] {75} [92] 5	**16c**[a] {67} [58] 3	**16d**[a,b] {74} [74] 11
7b: 	**17a**[a,b] {91} [31] 8	**17b**[a] {66} [41] 4	**17c**[a] {62} [43] 7	**17d**[a] {70} [43] 9
7c: 	**18a**[a] {88} [75] 7	**18b**[a] {100} [80] 8	**18c**[a] {75} [35] 3	**18d**[a] {59} [86] 3

[a] {Percent conversion, %} [purity, RP-HPLC/LC-MS, %] isolated yield, preparative RP-HPLC, %. [b] After cleavage from the resin the parent acid besides the ester determined by RP-HPLC/LC-MS.

2.5.2 Characteristic Data of New Compounds

Characteristic Data of Compound 16b

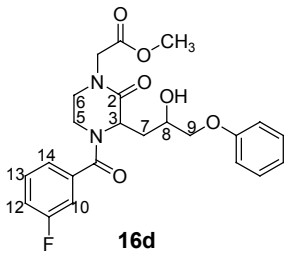


16b

Crude product: ratio of ester:acid:1,3-amino alcohol = 62.5% : 12.5% : 25%; purity 92%; R_t ester = 3.10 min; R_t acid = 2.76 min; R_t 1,3-amino alcohol= 1.92 min.

Yield of ester **16b** after preparative RP-HPLC: 3 mg (5%, 0.01 mmol), pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29-7.20 (m, 3H, H-aromat), 7.10-7.03 (m, 3H, H-aromat), 6.99-6.88 (m, 3H, ^3J = 7.3 Hz, ^3J = 7.9 Hz, H-aromat), 4.23 (d, 1H, ^2J = 17.3 Hz, $NC\underline{H}_2COOCH_3$), 4.08-4.06 (dd, 1H, ^2J = 8.6 Hz, ^3J = 4.9 Hz, H-9), 3.97-3.82 (m, 4H, $NC\underline{H}_2COOCH_3$, H-5, H-8, H-9`), 3.80 (s, 1H, H-10), 3.79 (s, 1H, H-10`), 3.72 (s, 3H, $COOCH_3$), 3.64-3.50 (m, 2H, H-3, H-5`), 3.22-3.16 (m, 2H, H-6, H-6`), 2.34 (s, 3H, CH_3), 2.27-2.22 (m, 1H, H-7), 2.07-2.02 (m, 1H, H-7`); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.2 (C=O), 168.9 (C=O), 168.7 (C=O), 158.6, 139.1, 133.6 (all C_{quart}), 129.6, 129.5, 129.17, 129.10, 128.3, 125.4, 121.0, 114.6, 114.5 (all C-aromat), 71.1 (C-9), 66.2 (C-8), 53.4 (C-3), 52.5 ($COO\underline{C}H_3$), 48.2 ($N\underline{C}H_2COOCH_3$), 47.4 (C-6), 41.2 (C-10), 40.4 (C-5), 36.0 (C-7), 21.4 (C-aromat-$\underline{C}H_3$). For the signal assignments HMQC-spectra were measured; IR (ATR): 2953, 2925, 2871, 1747 (C=O, ester), 1652 (br, C=O, piperazin-2-one, the C=O signal of the amide is overlapped by an adjacent signal), 1600, 1588, 1492, 1449, 1365, 1342, 1291, 1245, 1214, 1181, 1106, 1093, 1042, 966, 827, 758, 693; MS (EI, 190 °C) m/z (%): 454 (6) [M^+], 436 (20), 347 (70), 316 (30), 275 (20), 211 (18), 171 (100), 121 (54), 105 (82), 85 (34), 71 (42), 57 (70); HR-MS calculated for $C_{25}H_{30}N_2O_6$: 454.2103, found 454.2100.

Characteristic Data of Compound 16d



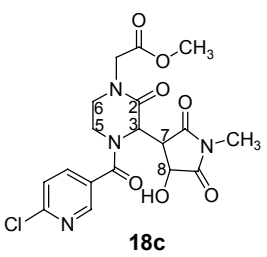
16d

Compound **16d**: crude product: ratio of ester : acid : 1,3-amino alcohol = 70% : 4% : 26%;

purity 74%; R_t ester = 2.88 min; R_t acid = 2.63 min; R_t 1,3-amino alcohol = 1.92 min.

Yield of ester **16d** after preparative RP-HPLC: 7 mg (11%, 0.02 mmol), orange oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (br m, 1H, H-aromat), 7.30-7.26 (m, 3H, ^3J = 7.9 Hz, H-aromat), 7.20-7.14 (m, 2H, ^3J = 7.6 Hz, H-aromat), 6.99-6.91 (m, 3H, ^3J = 7.3 Hz, ^3J = 7.9 Hz, H-aromat), 4.26 (d, 1H, ^2J = 17.5 Hz, $NC\underline{H}_2COOCH_3$), 4.12 (m, 2H, ^2J = 17.5 Hz, $NC\underline{H}_2COOCH_3$, H-8), 4.05-3.92 (m, 2H, H-9, H-9`), 3.84 (br m, 1H, H-5), 3.77 (s, 3H, $COOCH_3$), 3.76-3.72 (m, 1H, H-3), 3.70 (br m, 2H, H-5, H-6), 3.25 (br m, 1H, H-6`), 2.35 (br m, 1H, H-7), 2.25-2.20 (m, 1H, H-7`); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.8 (C=O), 168.7 (br, 2 C=O), 162.7 ($^1J_{C,F}$ = 245 Hz, F-C-aromat), 158.5 (C_{quart}), 136.0 ($^3J_{C,F}$ = 6.9 Hz, (C=O)-$\underline{C}$-aromat), 130.9 ($^3J_{C,F}$ = 7.8 Hz, C-13), 129.6 ($^2J_{C,F}$ = 16.2 Hz, C-10), 129.5 (C-aromat), 122.5 ($^4J_{C,F}$ = 2.8 Hz, C-14), 121.1 (C-aromat), 117.8 ($^2J_{C,F}$ = 21.3 Hz, C-12), 114.6 (C-aromat), 71.0 (C-9), 66.6 (C-8), 53.9 (C-3), 52.6 ($COO\underline{C}H_3$), 48.4 ($N\underline{C}H_2COOCH_3$), 48.1 (C-6), 41.4 (C-5), 35.4 (C-7). For the signal assignments ^{1}H,^{1}H-COSY- and HMQC-spectra were measured; IR (ATR): 3411 (OH), 2953, 2929, 2874, 1748 (C=O, ester), 1653 (br, C=O, piperazin-2-one, the C=O signal of the amide is overlapped by an adjacent signal), 1599, 1586, 1492, 1446, 1424, 1368, 1339, 1291, 1269, 1246, 1215, 1183, 1136, 1079, 1045, 965, 882, 801, 756, 693; MS (EI, 220 °C) m/z (%): 445 (28) [M^++1], 427 (22) [M^+-18], 337 (44), 293 (24), 171 (14), 123 (100), 95 (18); HR-MS calculated for $C_{23}H_{26}N_2O_6F$ [M^++1]: 445.1774, found: 445.1771.

Characteristic Data of Compound 18c



18c

Compound **18c**: crude product: ratio of ester : acid : 1,3-amino alcohol = 75% : 0% : 25%;

purity 35%; R_t ester = 1.78 min, 1.88 min; R_t 1,3-amino alcohol = 1.18 min.

Yield of ester **18c** after preparative RP-HPLC: mixture of rotamers in a ratio of 60:40, 2 mg (3%, 0.005 mmol), slightly soiled pale red oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.54 (d, 1H, ^4J = 1.9 Hz, H-aromat), 7.85-7.77 (m, 1H, H-aromat), 7.45 (d, 1H, ^3J = 8.3 Hz, H-aromat), 4.73-4.70 (d, 1H, ^3J = 5.8 Hz, H-3), 4.52-4.19 (m, 2H, H-7, $NC\underline{H}_2COOCH_3$), 3.94-3.63 (m, 5H, H-5, H-5`, H-6, H-8, $NC\underline{H}_2COOCH_3$), 3.76 (s, 3H, $COOCH_3$), 3.30-3.24 (m, 1H, H-6`), 3.01 (s, 3H, N-CH_3); IR (ATR): 3455 (OH), 2955, 2925, 2870, 2854, 1744 (C=O, ester), 1707 (br, 2 C=O, imide), 1646 (br C=O, piperazin-2-one, the C=O signal of the amide is overlapped by an adjacent signal), 1585, 1494, 1436, 1378, 1363, 1285, 1211, 1186, 1138, 1106, 1081, 965, 895, 801, 760; MS (EI, 205 °C) m/z (%): 438 (4) [M^+], 420 (6) [M^+-18], 311 (10), 298 (12), 280 (42), 266 (10), 238 (4), 192 (4), 171 (10), 142 (32) 140 (100), 122 (10), 115 (22), 112 (32), 56 (32); HR-MS calculated for $C_{18}H_{19}N_4O_7Cl$: 438.0942, found: 438.0954.

2.6 Automated Mitsunobu-reactions of Polymer-bound Lactams 9

2.6.1 General Procedure and Table of Compounds

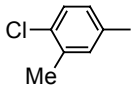
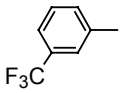
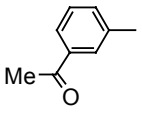
For automated Mitsunobu-reactions on solid support 250 mg resin (max. loading 0.74 mmol/g) was swollen in THF (2 ml, 5 min, 1 x). After removal of the solvent in vacuo the resin was dried (0.5 min). Afterwards 0.20 ml THF, 0.93 ml (1.40 mmol, 7.65 eq) phenol (1.50 M solution in THF) and 1.40 ml (0.70 mmol, 3.83 eq) $P(Ph)_3$ (0.5 M solution in THF) were added. The reaction mixture was stirred for 15 min. After addition of 1.17 ml (1.40 mmol, 7.65 eq) DIAD (1.20 M solution in THF) the reaction mixture was stirred at room temperature for 24 h. Afterwards the solvent was removed in vacuo. The resin was

dried (0.5 min) and rinsed with DMF (3 ml, 3 min, 1 x), dried (0.5 min), rinsed with DMF (3 ml, 3 min, 2 x), dried (0.5 min), rinsed with THF (3 ml, 3 min, 3 x), dried (0.5 min), rinsed with methanol, dichloromethane and methanol (3 ml, 3 min, 1 x), dried (0.5 min), rinsed with dichloromethane, methanol and dichloromethane (3 ml, 3 min, 1 x), dried (0.5 min), rinsed with dichloromethane (3 ml, 3 min, 2 x) and dried (0.5 min).

For cleavage, the resin was swollen in 2.0 ml THF and 0.5 ml methanol for 15 min. After addition of 24.9 mg (0.46 mmol, 2.50 eq) neat NaOMe the reaction mixture was stirred at room temperature for 22 h. Afterwards the solvent was concentrated in vacuo and the resin was rinsed with methanol (2.0 ml, 5 min, 1 x). The combined filtrates were concentrated in a speed vac at 60 °C. The crude products were analyzed by analytical RP-HPLC in combination with a mass detector using a Chromolith Speed ROD RP-18e-column and MeCN/H_2O 5:95 + 0.1% TFA → MeCN/H_2O 100:0 + 0.1% TFA within 5 min as solvent.

The crude products were purified by preparative RP-HPLC in combination with a mass detector using MeCN/H_2O + 0.1% TFA as solvent: 0 min: 80% water → 3 min: 50% water → 10 min: 20% water → 13 min to 16 min: 0% water. The purities of the crude products were calculated for each derivative from the amount of the mentioned isomeric products (parent acid and ester), in comparison to all peaks in the analytical RP-HPLC-MS-spectra.

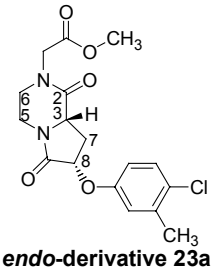
Table 2. Automated Mitsunobu-reactions of polymer-bound isoxazolidine-derived lactams **9**

9: \ R =	19 	20 	21 	22 
9a: R^1 = H, R^3 = H	**23a:** 18%[a,b]	**23b:** 16%[a,b]	**23c:** 16%[a,b]	**23d:** 20%[a,b]
9b: R^1 = Me, R^3 = H	**24a:** 5%[a,b]	**24b:** 16%[a,b]	**24c:** 0%[a,b]	**24d:** 9%[a,b]

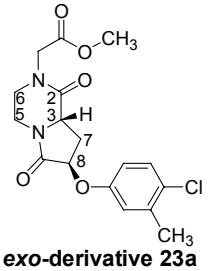
[a] Isolated yield after purification by preparative RP-HPLC. [b] After cleavage from the resin the parent acid besides the ester determined by RP-HPLC/LC-MS (ratio of ester:acid = 67:33 up to 100:0).

2.6.2 Characteristic Data of New Compounds

Spectroscopic Data of Compound 23a



***endo*-derivative 23a**



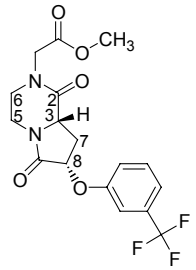
***exo*-derivative 23a**

Compound **23a**: crude product: ratio of ester : acid = 72% : 28%; purity 96%; R_t ester = 2.75 min, 2.83 min; R_t acid = 2.50 min, 2.59 min.

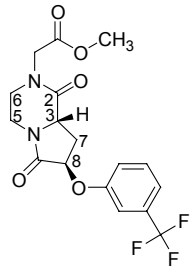
Yield of ester **23a** after preparative RP-HPLC: 12 mg (18%, 0.03 mmol) as a 57:43 mixture of the *endo*- and *exo*-derivatives [*endo*: (3*S*, 7*S*) and (3*R*, 7*R*); *exo*: (3*S*, 7*R*) and (3*R*, 7*S*)], pale yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.24 (br s, H-aromat), 7.20 (br s, H-aromat), 6.89-6.87 (m, H-aromat), 6.82-6.74 (m, H-aromat of both isomers), 5.01-4.92 (t, 1H, ^3J = 8.8 Hz), 4.86-4.81 (dd, 1H, ^3J = 6.3 Hz, ^3J = 6.8 Hz, H-8, both isomers), 4.52-4.45 (t, 1H, ^3J = 7.7 Hz), 4.32-4.11 (m, 3H, H-5, both isomers, H-3, both isomers), 4.26 (d, 1H, ^2J = 17.1 Hz, $NC\underline{H}_2COOCH_3$), 4.23 (d, 1H, ^2J = 17.1 Hz, $NC\underline{H}_2COOCH_3$), 4.08 (d,

1H, ^{2}J = 17.1 Hz, NC<u>H</u>$_2$COOCH$_3$), 4.02 (d, 1H, ^{2}J = 17.1 Hz, NC<u>H</u>$_2$COOCH$_3$), 3.76 (s, 6H, COOC<u>H</u>$_3$, both isomers), 3.70-3.57 (m, 2H, H-6, both isomers), 3.50-3.30 (m, 4H, H-5`, H-6`, both isomers), 3.15-2.95 (m, 1H, H-7), 2.69-2.45 (m, 2H, H-7, H-7`), 2.29 (s, 6H, CH$_3$, both isomers), 2.24-2.13 (m, 1H, H-7`); ^{13}C NMR (50.3 MHz, CDCl$_3$): δ = 169.9 (C=O), 169.5 (C=O), 168.6 (C=O), 168.4 (C=O), 168.3 (C=O), 168.0 (C=O), 155.8, 155.6 (C$_{quart}$, O-C-aromat, both isomers), 137.1 (C$_{quart}$, <u>C</u>-aromat-CH$_3$, both isomers), 129.5 (C$_{quart}$, C-aromat-Cl, both isomers), 127.4, 127.2, 118.4, 118.2, 114.5, 114.3 (all C-aromat), 75.5, 75.0 (C-8, both isomers), 55.6, 53.8 (C-3, both isomers), 52.4 (NCH$_2$COO<u>C</u>H$_3$, both isomers), 48.2 (N<u>C</u>H$_2$COOCH$_3$, both isomers), 47.1 (C-6, both isomers), 37.1, 36.9 (C-5, both isomers), 30.9, 30.1 (C-7, both isomers), 20.1 (CH$_3$, both isomers). For the signal assignments HMQC-spectra were measured; IR (ATR): 2951, 2929, 1748 (C=O, ester), 1708 (C=O, lactame), 1664 (C=O, piperazin-2-one), 1481, 1437, 1405, 1364, 1341, 1284, 1242, 1213, 1173, 1044; MS (EI, 200 °C) m/z (%): 368 (35) [M$^+$+2], 367 (20) [M$^+$+1], 366 (100) [M$^+$], 277 (14), 225 (20), 197 (32), 165 (26), 137 (16), 56 (14); HR-MS calculated for $C_{17}H_{19}N_2O_5Cl$ 366.0982, found: 366.0987.

Spectroscopic Data of Compound 23c



***endo*-derivative 23c**



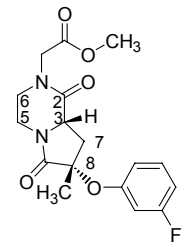
***exo*-derivative 23c**

Compound **23c**: crude product: ratio of ester : acid = 80% : 20%; purity 96%; R$_t$ ester = 2.74 min, 2.81 min; R$_t$ acid = 2.48 min, 2.57 min.

Yield of ester **23c** after preparative RP-HPLC: 11 mg (16%, 0.03 mmol) as a 57:43 mixture of the *endo*- and *exo*-derivatives [*endo*: (3*S*, 7*S*) and (3*R*, 7*R*); *exo*: (3*S*, 7*R*) and (3*R*, 7*S*)], pale yellow oil; ^{1}H NMR (200 MHz, CDCl$_3$): δ = 7.41 (br s, H-aromat), 7.37 (br s, H-

aromat), 7.27-7.21 (m, H-aromat of both isomers), 5.12-5.03 (dd, 1H, ^{3}J = 8.3 Hz, ^{3}J = 8.8 Hz), 4.97-4.92 (dd, 1H, ^{3}J = 6.3 Hz, ^{3}J = 6.8 Hz, H-8, both isomers), 4.56-4.48 (dd, 1H, ^{3}J = 7.3 Hz, ^{3}J = 7.8 Hz), 4.36-3.97 (m, 3H, H-3, both isomers, H-5, both isomers), 4.28 (d, 1H, ^{2}J = 17.6 Hz, $NC\underline{H}_2COOCH_3$), 4.26 (d, 1H, ^{2}J = 17.6 Hz, $NC\underline{H}_2COOCH_3$), 4.15 (d, 1H, ^{2}J = 17.6 Hz, $NC\underline{H}_2COOCH_3$), 4.09 (d, 1H, ^{2}J = 17.6 Hz, $NC\underline{H}_2COOCH_3$), 3.76 (s, 6H, $COOC\underline{H}_3$, both isomers), 3.76-3.57 (m, 2H, H-6, both isomers), 3.51-3.35 (m, 4H, H-5`, H-6`, both isomers), 3.20-3.05 (m, 1H, H-7), 2.66-2.57 (m, 2H, H-7, H-7`), 2.34-2.18 (m, 1H, H-7`); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 169.6 (C=O), 169.2 (C=O), 168.6 (C=O), 168.4 (C=O), 168.3 (C=O), 167.9 (C=O), 157.3, 157.2 (C_{quart}, O-C-aromat, both isomers), 130.0 (2C), 120.8, 119.0, 118.7, 118.6, 112.8, 112.6 (all C-aromat of both isomers), 75.4, 74.8 (C-8, both isomers), 55.5, 53.8 (C-3, both isomers), 52.4 ($COO\underline{C}H_3$, both isomers), 48.2 ($N\underline{C}H_2COOCH_3$, both isomers), 47.1, 47.0 (C-6, both isomers), 37.1, 37.0 (C-5, both isomers), 30.7, 30.1 (C-7, both isomers). The carbons $\underline{C}$-aromat-CF_3 and $\underline{C}F_3$ are not detectable due to the low signal intensity. For the signal assignments HMQC-spectra were measured; IR (ATR): 2955, 2868, 1748 (C=O, ester), 1709 (C=O, lactame), 1664 (C=O, piperazin-2-one), 1593, 1492, 1449, 1438, 1365, 1329, 1284, 1217, 1169, 1124, 1065, 999, 986, 928, 888, 797, 793, 737, 724, 699, 659; MS (EI, 160 °C) m/z (%): 387 (20) [M^++1], 386 (100) [M^+], 299 (48), 224 (22), 197 (82), 56 (30); HR-MS calculated for $C_{17}H_{17}N_2O_5F_3$: 386.1089, found: 386.1090.

Characteristic Data of Compound 24b

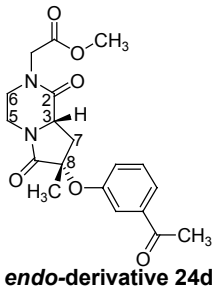


***endo*-derivative 24b**

Compound **24b**: crude product: ratio of ester:acid = 97% : 3%; purity 10%; R_t ester: 2.31 min; R_t acid = 2.01 min.

Yield of ester **24b** [*endo*: (3*S*, 7*S*) and (3*R*, 7*R*)] after preparative RP-HPLC: 10 mg (16%, 0.03 mmol), soiled orange oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.84-6.57 (m, 4H, H-aromat), 4.34-4.06 (m, 4H, $NC\underline{H}_2COOCH_3$, H-3, H-5), 3.71 (s, 3H, $COOCH_3$), 3.67-3.57 (m, 1H, H-6), 3.44-3.22 (m, 2H, H-5`, H-6`), 2.96-2.89 (m, 1H, H-7), 2.26-2.15 (m, 1H, H-7`), 1.58 (s, 3H, CH_3); IR (ATR): 2982, 2934, 1743 (C=O, ester), 1709 (C=O, lactame), 1665 (C=O, piperazin-2-one), 1592, 1486, 1446, 1375, 1340, 1321, 1262, 1214, 1181, 1133, 1106, 1034, 1010, 988, 967, 913, 760; MS (EI, 200 °C) m/z (%): 350 (2) [M^+], 239 (42), 238 (54), 237 (100), 223 (6), 209 (20), 178 (16), 151 (28), 112 (14), 82 (10), 71 (12), 57 (26), 56 (36), 55 (20); HR-MS calculated for $C_{17}H_{19}N_2O_5F$: 350.1277, found: 350.1270.

Spectroscopic Data of Compound 24d



***endo*-derivative 24d**

Compound **24d**: crude product: ratio of ester:acid = 71% : 29%; purity 20%; R_t ester = 2.11 min; R_t acid = 1.85 min.

Yield of ester **24d** [*endo*: (3*S*, 7*S*) and (3*R*, 7*R*)] after preparative RP-HPLC: 6 mg (9%, 0.02 mmol), slightly soiled pale yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.69-7.56 (m, 1H, H-aromat), 7.52-7.28 (m, 2H, H-aromat), 7.21-7.02 (m, 1H, H-aromat), 4.41 (d, 1H, ^2J = 17.6 Hz, $NC\underline{H}_2COOCH_3$), 4.35-4.13 (m, 2H, H-3, H-5), 4.01 (d, 1H, ^2J = 17.6 Hz, $NC\underline{H}_2COOCH_3$), 3.92-3.83 (m, 1H, H-6), 3.73 (s, 3H, $COOC\underline{H}_3$), 3.51-3.32 (m, 2H, H-5`, H-6`), 2.65-2.58 (m, 2H, H-7, H-7`), 2.56 (s, 3H, $COC\underline{H}_3$), 1.56 (s, 3H, $N(CO)C(C\underline{H}_3)$); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 197.8 ($(\underline{C}{=}O)CH_3$), 172.2 (C=O), 168.5

(C=O), 168.0 (C=O), 154.6 (C_{quart}, O-C-aromat), 137.9 (C_{quart}), 129.7, 125.3, 123.0, 116.9 (all C-aromat), 81.2 (C-8), 53.6 (C-3), 52.3 (COO$\underline{C}H_3$), 48.1 (N$\underline{C}H_2COOCH_3$), 47.0 (C-6), 37.0 (C-5), 33.9 (C-7), 26.4 (CO-$\underline{C}H_3$), 21.7 (CH_3). For the signal assignments HMQC-spectra were measured; IR (ATR): 2982, 2955, 2935, 2879, 1745 (C=O, ester), 1709 (C=O, lactame), 1683 (br, C=O, piperazin-2-one, one C=O signal is overlapped by an adjacent signal), 1596, 1583, 1484, 1437, 1375, 1363, 1341, 1269, 1214, 1182, 1145, 1107, 1081, 1010, 991, 967, 920, 799, 692; MS (EI, 220 °C) m/z (%): 375 (4) [M^++1], 374 (8) [M^+], 239 (100), 223 (30), 211 (12), 151 (28), 121 (20), 57 (12).

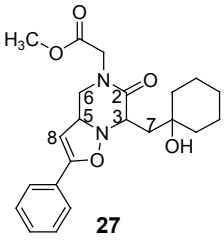
2.7 Synthesis of Compound 27

In 5.0 ml dichloromethane 260 mg (0.17 mmol) resin **5b** (0.67 mmol/g) was swollen in a solid phase reactor for 20 min. After cooling to –78 °C, 0.45 g (15.0 eq) MCPBA in 5 ml dichloromethane were added. The reaction mixture was stirred for 20 min, until the resin was transferred into a syringe (Isolute SPE column from Separtis, size C, 6 ml with 20 µm frit), rinsed in membrane pump vacuum with dichloromethane (2 ml, 30 x), THF (2 ml, 30 x), dichloromethane (2 ml, 40 x), water (2 ml, 20 x), dichloromethane (2 ml, 50 x) and THF (2 ml, 50 x) and was dried for 6 h.

For acylation 160 mg (0.11 mmol) resin (0.66 mmol/g) was transferred into a syringe (Isolute SPE column from Separtis, size C, 6 ml with 20 µm frit). After addition of 4 ml pyridine/Ac_2O 3:1 ([v]/[v]) the reaction mixture was shaken for 45 min. Afterwards the resin was rinsed in membrane pump vacuum with THF (2 ml, 20 x), dichloromethane (2 ml, 20 x), water (2 ml, 10 x), dichloromethane (2 ml, 10 x), water (2 ml, 10 x), dichloromethane (2 ml, 15 x), water (2 ml, 15 x), dichloromethane (2 ml, 10 x), THF (2 ml, 10 x), dichloro-methane (2 ml, 10 x), THF (2 ml, 10 x), dichloromethane (2 ml, 20 x), THF (2 ml, 20 x) and was dried for 3 h. The reaction was repeated a second time analogously by shaking the reaction mixture 20 min.

In analogy to the general procedure of the synthesis of polymer-bound isoxazolines 160 mg (0.10 mmol) resin (0.65 mmol/g) was swollen in 2.5 ml THF for 25 min. After addition of phenyl acetylene (2.5 ml, 22.8 mmol, 220 eq) the reaction mixture was heated to 60 °C for 1 h. Afterwards the resin was transferred into a frit and rinsed in membrane pump vacuum with THF (2 ml, 30 x), water (2 ml, 10 x), THF (2 ml, 30 x), dichloromethane (2 ml, 30 x), THF (2 ml, 25 x), dichloro-methane (2 ml, 25 x) and THF (2 ml, 30 x) and was dried for 3 h.

For cleavage, the resin (165 mg, 0.10 mmol, 0.62 mmol/g) was swollen in 4 ml THF and 1 ml methanol in a solid phase reactor for 15 min ($V_{THF}/V_{methanol}$ = 4:1). After addition of 18.5 mg (0.34 mmol, 3.35 eq) neat NaOMe, the reaction mixture was stirred at room temperature for 23 h. Afterwards the resin was transferred into a syringe (Isolute SPE column from Separtis, size C, 6 ml with 20 μm frit) and rinsed in membrane pump vacuum with THF (2 ml, 15 x), methanol (2 ml, 15 x) and THF (2 ml, 10 x). The filtrate was concentrated in vacuo. The residue was dissolved in 4 ml saturated sodium chloride solution and 4 ml dichloromethane and extracted with dichloro-methane (4 ml, 7 x). The combined organic layer was dried ($MgSO_4$) and the solvent was concentrated in vacuo. The crude product was purified by preparative RP-HPLC.



27

Compound **27**: slightly soiled yellow oil; TLC: R_f = 0.58 (ethyl acetate), 0.92 (methanol); R_T = 53 min; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.77-7.36 (m, 3H, H-aromat), 7.14-7.10 (m, 2H, H-aromat), 4.37 (br m, 2H, H-8, $NC\underline{H}_2COOCH_3$), 4.19 (br m, 2H, H-3, $NC\underline{H}_2COOCH_3$), 3.85-3.74 (m, 1H, CH_2-CH-piperazin-2-one), 3.80 (s, 3H, $COOCH_3$), 2.96-2.83 (m, 2H, CH_2-CH-piperazin-2-one), 2.30 (br m, 2H, H-7, H-7`), 1.66-1.44 (m, 10H, H-cyclohexyl); IR (ATR): 2931, 2857, 1747 (C=O, ester), 1675 (C=O, piperazin-2-one), 1545, 1514, 1449, 1440, 1407, 1368, 1314, 1299, 1204, 1183, 1068, 1034, 989, 819, 657; MS (EI, 170 °C) m/z (%): 401 (8) [M^++1], 384 (10), 295 (6), 277 (10), 178 (52), 177 (10), 149 (16), 120 (28), 102 (100), 91 (34), 81 (50), 55 (100), 51 (28); HR-MS calculated for $C_{22}H_{29}N_2O_5$ [M^++1]: 401.2076, found: 401.2087.