Introduction of Substituents on the 2-Oxo-piperazine Skeleton by [3+2] Cycloaddition and Subsequent Transformation*

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The 3,4-substituted 2-oxo-piperazines **5 – 9** are obtained by [3+2] cycloaddition from nitrone **1** and a variety of alkenes. Subsequent functionalization of the bicyclic adducts involves reductive N-O bond cleavage. A route towards libraries of immobilized 1,3-aminoalcohols with a 3,4-substituted 2-oxo-piperazine scaffold is briefly discussed for adducts derived from *N*-substituted maleic imides.

Key words: 2-Oxo-piperazine, Scaffold, [3+2] Cycloaddition, Nitrone, N-O Bond Cleavage

Introduction

In medicinal and agricultural chemistry heterocycles are among the target molecules for synthesizing libraries of compounds for finding lead structures. This is also the case for 2-oxo-piperazines and derivatives, which are privileged biologically active scaffolds and promising pharmaceutical target molecules [1]. From a medicinal standpoint the fields of applications are numerous, *e. g.* 2-oxo-piperazines were successfully investigated as farnesyl-protein transferase inhibitors, fXa inhibitors or non-peptide GPII antagonists [2]. Members of this class of compounds were investigated as nucleoside analogs [3]. They were found to display antiviral activity against a mammalian retrovirus [4]. Furthermore, 2-oxo-piperazines are promising scaffolds in the treatment of asthma and bronchitis [5].

Recently, we have reported [3+2] cycloaddition reactions of a polymer-bound 2-oxo-piperazine-derived nitrone with alkenes and alkynes furnishing libraries of 3,4-disubstituted and 3,4,5-trisubstituted 2-oxo-piperazines [1, 6]. The bicyclic (2-oxo-piperazine)-based isoxazolidines and isoxazolines are well suited for additional functionalization steps starting with N-O bond cleavage furnishing versatile libraries of 2-oxo-piperazines.

In this paper we describe exemplarily details for the preparation of 3,4-disubstituted 2-oxo-piperazines in solution. In addition, we present key steps for the preparation of libraries of functionalized 1,3-aminoalcohols from maleic imide-based cycloadducts by reductive N-O bond cleavage on solid support using $Mo(CO)_6$.

Results and Discussion

For the [3+2] cycloadditions in solution described here the nitrone **1** was synthesized starting from 2-oxo-piperazine **2** by alkylation of the amide with bromoacetic acid methyl ester followed by deprotection of the Boc-protecting group using trifluoroacetic acid in anisole. The secondary amine was generated prior to oxidation by adjusting a pH-value of 7.5 using triethylamine. Subsequent treatment with 30% aqueous H_2O_2 (2.2 equiv.) using $Na_2WO_4 \times 2H_2O$ in methanol as catalyst gave nitrone **1** in 73% isolated yield (Scheme 1) [7]. This proved to be the method of choice, since oxidation with Davis' Reagent [7] (2.0 equiv.) in either CH_2Cl_2 or $CHCl_3$ yielded nitrone **1** only in 32 and 34% yield, respectively.

Starting from 5*H*-furan-2-one and crotonic acid methyl ester the expected cycloadducts **5** and **6** (Scheme 2) were isolated in thermal reactions in good yields, although long reaction times were required (**5**: 56 h, **6**: 42 h). Notably, $Yb(OTf)_3 \times H_2O$-catalyzed reactions (20 mol%) could be successfully applied to

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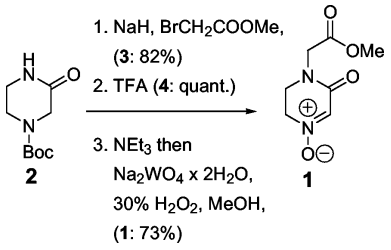
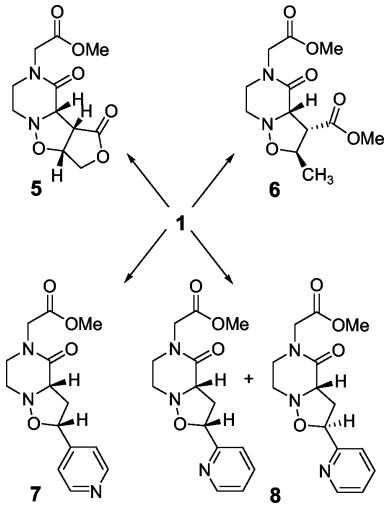


Scheme 1. Synthesis of the nitrone **1**.

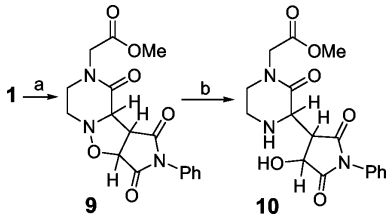


Scheme 2. [3+2] Cycloadditions of nitrone **1** with alkenes.

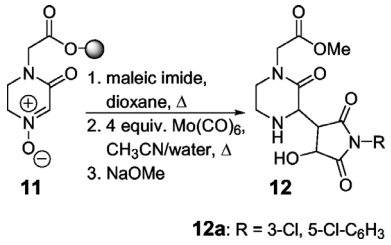
shorten the reaction times (**5**: 4 h, **6**: 14 h). The *endo*-adducts were obtained regioselectively, as confirmed by NOE experiments.

The *endo*-preference is also very high for [3+2] cycloaddition reactions using 2-vinylpyridine and 4-vinylpyridine (Scheme 2). Only a small amount of *exo*-**8** was detected and structurally assigned. In test reactions we also examined *N*-phenylmaleic imide as dipolarophile (Scheme 3). The reaction proceeded regioselectively, the resulting adduct **9** was isolated in 66% yield and was treated with $Mo(CO)_6$ for cleavage of the N-O bond to obtain the 1,3-aminoalcohol **10** (Scheme 3).

Usually Pd/C, $Pd(OH)_2$/C or Raney nickel in the presence of H_2, or zinc in acetic acid are used for N-O bond cleavage in solution phase studies [8]. However, for the preparation of libraries of compounds on solid support using polystyrene resins these methods are not suitable, because of the heterogeneous reaction conditions or insufficient swelling of the resins. For automated solid phase synthesis we also needed to avoid reaction conditions under pressure. Therefore, we turned our attention to a $Mo(CO)_6$-mediated (0.7 – 6 equiv.) reductive cleavage of the N-O bond in wet acetonitrile at 85 °C [9]. The aminoalcohol **10** was obtained in 38% yield (Scheme 3). Unfortunately, the purification proceeded sluggishly. Generally, only after several manipulations, including separation of the impurities derived from $Mo(CO)_6$ by hyflow® filtrations, precipitation with ether and a flash-column chromatography prior to a preparative RP-HPLC, pure product was isolated [1, 9]. However, solid phase synthesis can result in an easier purification of intermediates, by removing the excess of reagents applied by simple washing procedures prior to cleavage from the solid. Consequently, we turned our attention next to automated solid phase synthesis without further optimization of solution phase studies.



Scheme 3. Conditions: (a) *N*-Phenylmaleic imide (3 equiv.), THF, 65 °C, (b) $Mo(CO)_6$ (3 equiv.), $MeCN/H_2O$, 85 °C.



Scheme 4. Automated synthesis of 1,3-aminoalcohols **12**: R = Me (56%), Et (62%), Pr (75%), C_6H_{11} (81%), $CH_2C_6H_5$ (70%), C_6H_5 (65%), **12a:** 3-Cl,5-Cl-C_6H_3 (90%).

The polymer-bound nitrone **11** was prepared as previously described [1]. The compound immobilized on Wang resin is stable at r. t. and can be stored on the bench for several months without decomposition. For the synthesis of a library we employed seven *N*-substituted maleic imides. The reactions were carried out in a myriad core system (Mettler Toledo) in dioxane at 65 °C. All cycloadditions proceeded smoothly, as well as the subsequent reductive N-O bond cleavage with 4 equivalents of $Mo(CO)_6$ followed by cleavage of the 1,3-aminoalcohols from Wang resin using NaOMe.

The products were isolated in good to excellent yields (Scheme 4) compared with solution phase studies. During workup we observed the elimination of

water by treatment with NaOMe in MeOH/THF and subsequent evaporation of the solvent with a speed vac concentrator at 60 °C. Thus, we obtained the corresponding unsaturated maleic imides as the only byproducts in minor amounts (analytical RP-HPLC/MS). Byproduct formation can be avoided by evaporation of the solvent at lower temperature (20 °C). Pure aminoalcohols were isolated after cleavage from the resin by a single purification step using preparative RP-HPLC.

In conclusion, we have demonstrated a preparatively useful access to 3,4-disubstituted 2-oxo-piperazine templates and successfully proven the use of $Mo(CO)_6$ for N-O bond cleavage in automated solid phase synthesis. This route has already been developed further beneficially as a starting point for more complex transformations for library generation [1, 6].

Experimental Section

General information

Solvents for the automated synthesis on solid support were used in p. a. quality without further purification. All products were characterized with RP-HPLC/LC-MS after cleavage from the resin. NMR spectra were measured on Bruker spectrometers AC200, AC400, AM400 and DRX500 at 200, 400 and 500 MHz for ^{1}H and 50.3, 100.6 and 125.7 MHz for ^{13}C at room temperature. Starting materials, reagents and compound **10** were prepared by following the literature procedure [1], and products were purified and analyzed by RP-HPLC as previously described by us.

1-Methoxycarbonylmethyl-4-tert-butyloxycarbonyl-2-oxo-piperazine (**3**)*:* Sodium hydride (1.73 g, 73.0 mmol, 1.15 equiv.) was added in one portion at 0 °C to a stirred solution of **2** (12.70 g, 63.0 mmol, 1.0 equiv.) in 280 ml of DMF. The reaction mixture was maintained at this temperature for 1 h until bromoacetic acid methylester (6.60 ml, 69.0 mmol, 1.10 equiv.) was added. After 20 min at 0 °C the solution was allowed to warm to r. t. and stirring was continued (18 h, TLC monitoring). Then methanol (10 ml), water (10 ml) and brine (180 ml) were added. The organic layer was separated and the aqueous layer was extracted with diethyl ether (1×250 ml, 3×140 ml). The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica (pentane/acetone $4:1 \rightarrow 2:1$) afforded **3** (14.16 g, 82%, 52.0 mmol) as a white solid. – M. p. 57 °C. – $R_f = 0.60$ (pentane/acetone 1:1). – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.15$ (s, 2H; NCH_2COOCH$_3$), 4.11 (s, 2H; O=C-CH$_2$-N), 3.72 (s, 3H; CH$_3$), 3.69 – 3.66 (t, 2H, $^3J = 5.5$ Hz; CH$_2$), 3.42 – 3.39 (t, 2H, $^3J = 5.5$ Hz; CH$_2$), 1.44 (s, 9H; CH$_3$). – ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 169.0$ (C=O), 166.3 (C=O), 153.7 (C=O), 80.8 (C(CH$_3$)$_3$), 52.2 (C=O-OCH$_3$), 48.0 (CH$_2$), 47.5 (CH$_2$), 40.0 (br, CH$_2$), 28.2 (C(CH$_3$)$_3$). – IR (KBr): $\nu = 2988$, 2954, 2874, 1758 (C=O, ester), 1692 (C=O, Boc), 1654 (C=O, 2-oxo-piperazine), 1493, 1480, 1422, 1367, 1337, 1322, 1293, 1239, 1133, 1099, 1073, 1011, 990, 979, 965, 868, 771 cm^{-1}. – MS (EI, 90 °C): *m/z* (%) = 272 (1) [M$^+$], 216 (12), 172 (20), 157 (8), 113 (16), 85 (8), 57 (100). – HR-MS (EI): calcd. 272.1372; found 272.1377. – $C_{12}H_{20}N_2O_5$ (272.3): calcd. C 52.93, H 7.40, N 10.29; found C 52.90, H 7.34, N 10.15.

Compound **4**: Trifluoroacetic acid (48.2 ml, 0.626 mol, 16.50 equiv.) was added to a stirred solution of **3** (10.42 g, 38 mmol, 1.0 equiv.) in anisole (86 ml). After 90 min (TLC monitoring) toluene (85 ml) was added and the solvent was removed *in vacuo*. The crude product **4** was used in the next step without further purification (14.77 g, quant.), pale yellow solid. – M. p. 112 °C. – $R_f = 0.01$ (methanol). – ^{1}H NMR (200 MHz, CD_3CN): $\delta = 4.12$ (s, 2H; NCH_2COOCH$_3$), 3.81 (s, 2H; O=C-CH$_2$-N), 3.68 (s, 3H; CH$_3$), 3.63 – 3.58 (m, 2H; CH$_2$), 3.48 – 3.43 (m, 2H; CH$_2$). – ^{13}C NMR (50.3 MHz, CD_3CN): $\delta = 169.9$ (C=O), 163.1 (C=O), 161.3 (q, $^2J = 36.1$ Hz; F$_3$CCOO$^-$), 52.9 (C=O-OCH$_3$), 48.7, 45.6, 45.1, 41.6 (CH$_2$). The signals of the C-atom of the CF$_3$-group are not detectable. – IR (KBr): $\nu = 3017$, 2965, 2828, 2767, 2676, 2594, 2491, 1752 (C=O, ester), 1672 (F$_3$CC=O), 1659 (C=O, 2-oxo-piperazine), 1504, 1483, 1472, 1428, 1402, 1354, 1296, 1261, 1230, 1203, 1193, 1169, 1143, 1080, 1021, 837, 799, 723, 685, 515 cm^{-1}. – MS (EI, 120 °C): *m/z* (%) = 172 (92) [M$^+$-F$_3$CCOOH], 113 (12) [F$_3$CCOO$^-$], 102 (40), 85 (100), 69 (40), 56 (88), 57 (32), 51 (24). – HR-MS (EI): calcd. for $C_7H_{12}N_2O_3$ 172.0847; found 172.0844.

Nitrone **1**: Triethylamine (5.37 ml, 14.20 mmol, 1.1 equiv.) was added dropwise to a suspension of **4** (5.0 g, 12.95 mmol, 1.0 equiv.) in methanol (50 ml), until pH 7.5 was adjusted. Then the reaction mixture was stirred at r. t. (1 h) before $Na_2WO_4 \times 2\ H_2O$ (0.29 g, 0.65 mmol, 0.05 equiv.) was added in one portion. After cooling the reaction mixture to 0 °C, 30% aqueous H_2O_2 (3.92 ml, 28.50 mmol, 2.2 equiv.) was added (10 min). The reaction mixture was stirred at 0 °C (15 min) and after warming to r. t. stirring was continued until TLC monitoring indicated complete consumption of the starting material (2 h 45 min). The solvent was removed *in vacuo* and the remaining residue was dissolved in dichloromethane (40 ml). The organic layer was washed with brine (2×40 ml) and then the aqueous layer extracted with dichloromethane. The combined organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo* yielding 5.78 g of **1** as a pale yellow oil. Purification by flash chromatography on silica (ethyl acetate/methanol 80 : 1) afforded **1** (1.76 g, 73%, 9.45 mmol) as a white solid. – M. p. 78 °C. – $R_f = 0.68$ (methanol). – ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.17$ (s, 1H; N=CH), 4.23 (s, 2H; CH$_2$), 4.19 – 4.13 (t, 2H, $^3J = 6.35$ Hz; CH$_2$), 3.78 – 3.72 (t, 2H, $^3J = 6.35$ Hz; CH$_2$),

3.75 (s, 3H; CH_3). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 168.6 (C=O), 159.3 (C=O), 128.4 (C=N), 58.7 (CH_2), 52.3 (CH_3), 46.9, 43.8 (CH_2). – IR (KBr): ν = 3059, 2991, 1758 (C=O, ester), 1652 (C=O, 2-oxo-piperazine), 1574 (C=N), 1488, 1457, 1432, 1399, 1365, 1349, 1339, 1305, 1282, 1250, 1214, 1171, 1131, 1085, 1023, 986, 970, 932, 884, 845, 722, 694 cm^{-1}. – MS (EI, 60 °C): *m/z* (%) = 186 (78) [M$^+$], 127 (100) [M$^+$-CO_2CH_3], 116 (14), 69 (86), 56 (40), 51 (42). – HR-MS (EI): calcd. 186.0640; found 186.0639. – $C_7H_{10}N_2O_4$ (186.17): calcd. C 45.16, H 5.41, N 15.04; found C 45.09, H 5.48, N 15.17.

[3+2] Cycloaddition reactions of nitrone **1** *with alkenes in solution*

General procedure: Nitrone **1** was dissolved in THF and the alkene (3.0 equiv.) was added. Then the reaction mixture was heated to reflux until TLC monitoring indicated complete consumption of the starting material. The solvent was removed *in vacuo* and the resulting crude product was purified by flash chromatography on silica or by preparative RP-HPLC.

Cycloadduct (**5**): yellow solid. – M. p. 160 °C. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.97 – 4.89 (dddd, 1H, ^3J = 7.28 Hz, ^3J = 5.5 Hz, ^3J = 1.9 Hz, ^4J = 1.2 Hz; 8-H), 4.53 – 4.39 (m, 2H, ^3J = 5.5 Hz, ^3J = 1.9 Hz; 9-H, 9'-H), 4.29 (d, 1H, ^2J = 17.08 Hz; N*C*H$_2$COOCH$_3$), 4.25 (d, 1H, ^3J = 2.44 Hz; 3-H), 4.07 – 3.93 (m, 2H; 6-H, 7-H), 3.96 (d, 1H, ^2J = 17.08 Hz; NC*H*$_2$COOCH$_3$), 3.73 (s, 3H; CH_3), 3.52 – 3.43 (m, 2H; 5-H, 5'-H), 3.16 – 3.07 (ddd, 1H, J = 1.96, 4.40, 5.36 Hz; 6'-H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 175.5 (C=O; C-11), 168.5 (C=O; NCH$_2$*C*OOCH$_3$), 166.7 (C=O; C-2), 75.4 (C-8), 74.2 (C-9), 66.6 (C-3), 52.2 (CH_3), 51.6 (C-7), 48.5 (N*C*H$_2$COOCH$_3$), 46.2 (C-5), 43.3 (C-6). For the signal assignments ^{1}H,^{1}H-COSY, HMBC, NOE and HMQC spectra were recorded. – IR (KBr): ν = 2982, 2969, 2949, 1774 (C=O, C-11), 1742 (C=O, ester), 1652 (C=O, 2-oxo-piperazine), 1502, 1461, 1399, 1389, 1380, 1359, 1338, 1295, 1219, 1207, 1189, 1149, 1075, 1054, 987, 944, 934, 902, 836, 731, 724, 575, 530, 491 cm^{-1}. – MS (EI, 120 °C): *m/z* (%) = 270 (60) [M$^+$ + 1], 211 (100) [M$^+$-COOCH$_3$], 183 (24), 158 (44), 125 (20), 123 (16), 56 (66), 55 (26). – HR-MS (EI): calcd. 270.0851; found 270.0853. – $C_{11}H_{14}N_2O_6$ (270.24): calcd. C 48.89, H 5.22, N 10.36; found C 48.70, H 5.43, N 9.92.

Cycloadduct **6**: yellow oil, 98%. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.54 – 4.52 (m, 1H; 8-H), 4.39 (d, 1H, ^3J = 10.05 Hz; 3-H), 4.22 (d, 1H, ^2J = 17.30 Hz; NC*H*$_2$COOCH$_3$), 3.97 (d, 1H, ^2J = 17.30 Hz; NC*H*$_2$ COOCH$_3$) 3.69 (s, 3H; COOCH$_3$), 3.65 (s, 3H; COOCH$_3$), 3.63 – 3.58 (m, 1H; 6-H), 3.56 – 3.53 (m, 1H; 5-H), 3.38 – 3.35 (m, 1H; 5'-H), 3.32 (d, 1H, ^3J = 10.05 Hz; 7-H), 3.21 – 3.18 (m, 1H; 6'-H), 1.34 (d, 3H, ^3J = 6.00 Hz; 9-H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 171.5 (C=O), 168.5 (C=O), 166.2 (C=O), 76.7 (C-8), 67.6 (C-3), 58.5 (C-7), 52.2 (COO*C*H$_3$), 52.0 (COO*C*H$_3$), 47.6 (N*C*H$_2$COOCH$_3$), 47.1 (C-6), 44.9 (C-5), 18.4 (C-9). For the signal assignments ^{1}H, ^{1}H-COSY and HMQC spectra were recorded. – IR (ATR): ν = 2955, 1735 (C=O), 1655 (C=O), 1640 (C=O), 1491, 1436, 1404, 1373, 1344, 1292, 1277, 1201, 1179, 1103, 1078, 1037, 998, 974, 938 cm^{-1}. – MS (EI, 120 °C): *m/z* (%) = 286 (24) [M$^+$], 255 (20) [M$^+$-OCH_3], 211 (58), 199 (26), 183 (50), 158 (100), 127 (16), 123 (30), 69 (30), 56 (66). – HR-MS (EI): calcd. for $C_{12}H_{18}N_2O_6$ 286.1164; found 286.1165.

Cycloadduct **7**: By following the general procedure, nitrone **1** (200 mg, 1.07 mmol) dissolved in THF (5.0 ml) was treated with 4-vinylpyridine (0.35 ml, 3.22 mmol, 3.0 equiv.) for 22 h. Purification by flash column chromatography (pentane/acetone 4:1) afforded *endo*-**7** [(3*S*, 8*R*) and (3*R*, 8*S*)], (233 mg, 75%, 0.80 mmol) as a yellow oil. – R_f = 0.24 (acetone). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.79 – 8.76 (dd, 2H, ^3J = 6.82 Hz, ^4J = 1.54 Hz; *ortho*-H), 7.79 (d, 2H, ^3J = 6.82 Hz; *meta*-H), 5.41 – 5.33 (dd, 1H, ^3J = 5.86 Hz, ^3J = 4.40 Hz; 8-H), 4.36 (d, 1H, ^2J = 17.56 Hz; NC*H*$_2$COOCH$_3$), 4.16 – 4.10 (dd, 1H, ^3J = 2.92 Hz, ^3J = 8.30 Hz; 3-H), 4.05 – 3.93 (m, 1H; 5-H), 4.04 – 3.95 (d, 1H, ^2J = 17.56 Hz; NC*H*$_2$COOCH$_3$), 3.76 (s, 3H; CH_3), 3.67 – 3.46 (m, 2H; 6-H, 6'-H), 3.35 – 3.21 (m, 2H; 7-H, 5'-H), 2.66 – 2.52 (ddd, 1H, ^3J = 5.86 Hz, ^3J = 8.30 Hz, ^2J = 14.10 Hz; 7'-H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.9 (C=O; NCH$_2$*C*OOCH$_3$), 168.6 (C=O; C-2), 160.5 (C-quart), 143.3 (*ortho*-C), 123.0 (*meta*-C), 75.8 (C-8), 63.1 (C-3), 52.4 (COO*C*H$_3$), 48.5 (N*C*H$_2$COOCH$_3$), 47.4 (C-6), 43.6 (C-5), 41.8 (C-7). For the signal assignments ^{1}H, ^{1}H-COSY, HMBC, NOE and HMQC spectra were recorded. – IR (ATR): ν = 2954, 2855, 1748 (C=O, ester), 1655 (C=O, 2-oxo-piperazine), 1600, 1560, 1491, 1438, 1412, 1364, 1345, 1290, 1214, 1182, 1067, 994, 815 cm^{-1}. – MS (EI, 120 °C): *m/z* (%) = 292 (12) [M$^+$+1], 291 (100) [M$^+$], 274 (44), 204 (28), 158 (68), 125 (76), 106 (40), 69 (44), 56 (92). – HR-MS(EI): calcd. 291.1219; found 291.1221. – $C_{14}H_{17}N_3O_4$ (291.31): calcd. C 57.72, H 5.88, N 14.42; found C 57.81, H 6.01, N 14.25.

Cycloadduct **8**: By following the general procedure, nitrone **1** (250 mg, 1.34 mmol) dissolved in THF (5.0 ml) was treated with 2-vinylpyridine (0.43 ml, 4.03 mmol, 3.0 equiv.) for 23 h. Purification by flash column chromatography (pentane/acetone 4 : 1 → acetone) afforded *endo*-**8** [(3*S*, 8*R*) and (3*R*, 8*S*)], and *exo*-**8** [(3*R*, 8*R*) and (3*S*, 8*S*)]: *endo*-**8** (285 mg, 73%, 0.98 mmol), yellow oil. – R_f = 0.57 (acetone). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.53 (d, 1H, ^3J = 4.88 Hz; *ortho*-H), 7.73 – 7.64 (m, 1H; *para*-H), 7.48 (d, 1H, ^3J = 7.80 Hz; *meta*-H), 7.23 – 7.16 (m, 1H; *meta*-H), 5.21 – 5.12 (m, 1H, ^3J = 8.30 Hz; 8-H), 4.28 (d, 1H, ^2J = 17.56 Hz; NC*H*$_2$COOCH$_3$), 4.26 – 4.18 (dd, 1H, ^3J = 6.34 Hz, ^3J = 6.80 Hz; 3-H), 4.01 (d, 1H, ^2J =

17.56 Hz; NCH_2COOCH$_3$), 3.90 – 3.78 (m, 1H; 5-H), 3.71 (s, 3H; COOCH$_3$), 3.60 – 3.39 (m, 2H; 6-H, 6'-H), 3.35 – 3.09 (m, 2H; 7-H, 5'-H), 2.76 – 2.62 (ddd, 1H, ^3J = 6.80 Hz, ^3J = 8.30 Hz, ^2J = 13.3 Hz; 7'-H). – ^{13}C NMR (125 MHz, CDCl$_3$): δ = 169.3 (C=O, NCH$_2$*C*OOCH$_3$), 169.0 (C=O, 2-oxo-piperazine), 159.1 (q; C-aromat), 149.1 (*ortho*-C), 137.0 (*para*-C), 122.9 (*meta*-C), 121.2 (*meta*-C), 80.6 (C-8), 63.9 (C-3), 52.3 (COO*C*H$_3$), 48.6 (N*C*H$_2$COOCH$_3$), 48.2 (C-6), 44.2 (C-5), 40.4 (C-7). – IR (ATR): ν = 2955, 1746 (C=O, ester), 1646 (C=O, 2-oxo-piperazine), 1592, 1489, 1437, 1405, 1345, 1210, 1182, 994, 947, 779, 750 cm^{-1}. – MS (EI, 130 °C): *m/z* (%) = 291 (18) [M$^+$], 184 (28), 170 (20), 125 (24), 122 (56), 108 (100), 97 (28), 69 (24), 56 (56). – HR-MS (EI): calcd. 291.1219; found 291.1221. – $C_{14}H_{17}N_3O_4$ (291.31): calcd. C 57.72, H 5.88, N 14.42; found C 57.93, H 6.07, N 14.09; *exo*-**8** (54 mg, 14%, 0.19 mmol), yellow oil. – R_f = 0.27 (acetone). – ^{1}H NMR (200 MHz, CDCl$_3$): δ = 8.44 (d, 1H, ^3J = 4.88 Hz; *ortho*-H), 7.63 – 7.54 (dd, 1H, ^3J = 7.80 Hz, ^3J = 7.82 Hz; *para*-H), 7.39 (d, 1H, ^3J = 7.82 Hz; *meta*-H), 7.12 – 7.05 (m, 1H; *meta*-H), 5.27 – 5.20 (m, 1H, ^3J = 4.88 Hz; 8-H), 4.23 (d, 1H, ^2J = 17.56 Hz; NCH_2COOCH$_3$), 4.21 – 4.14 (m, 1H; 3-H), 4.13 (d, 1H, ^2J = 17.56 Hz; NCH_2COOCH$_3$), 3.83 – 3.72 (m, 1H; 5-H), 3.75 (s, 3H; COOCH$_3$), 3.52 – 3.33 (m, 3H; 5'-H, 6-H, 6'-H), 3.21 – 3.07 (m, 1H; 7-H), 2.98 – 2.85 (m, 1H; 7'-H). – ^{13}C NMR (125 MHz, CDCl$_3$): δ = 169.0 (C=O, NCH$_2$*C*OOCH$_3$), 168.8 (C=O, 2-oxo-piperazine), 160.3 (q; C-aromat), 147.7 (*ortho*-C), 138.5 (*para*-C), 123.1 (*meta*-C), 121.1 (*meta*-C), 77.8 (C-8), 63.4 (C-3), 52.4 (COO*C*H$_3$), 48.2 (N*C*H$_2$COOCH$_3$), 48.1 (C-6), 44.2 (C-5), 40.5 (C-7). – IR (ATR): ν = 2954, 1747 (C=O, ester), 1654 (C=O, 2-oxo-piperazine), 1591, 1570, 1491, 1473, 1437, 1404, 1364, 1344, 1291, 1213, 1182, 1152, 1046, 994, 835, 780, 751 cm^{-1}. – MS (EI, 140 °C): *m/z* (%) = 292 (8) [M$^+$ + 1], 291 (24) [M$^+$], 274 (12), 273 (20), 260 (12), 185 (92), 184 (56), 125 (30), 117 (32), 108 (100), 56 (26). – HR-MS (EI): calcd. for $C_{14}H_{17}N_3O_4$: 291.1219; found 291.1223.

Cycloadduct **9**: By following the general procedure, nitrone **1** (250 mg, 1.34 mmol) dissolved in THF (4.0 ml) was treated with *N*-phenylmaleic imide (0.70 g, 4.02 mmol, 3.0 equiv.) dissolved in THF (1 ml) for 2 h. Purification by flash chromatography (pentane/ethyl acetate 2 : 1 → 1 : 1) afforded **9** (320 mg, 66%, 0.89 mmol) as a yellow amorphous solid. – M. p. 85 °C. – R_f = 0.54 (ethyl acetate). – ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.49 – 7.46 (m, 2H; H-aromat), 7.42 – 7.39 (m, 1H; H-aromat), 7.31 (d, 2H, ^3J = 7.5 Hz; H-aromat), 4.95 (d, 1H, ^3J = 7.5 Hz; 8-H), 4.35 (br d, 1H; 3-H), 4.26 (d, 1H, ^3J = 7.5 Hz; 7-H), 4.19 (d, 1H, ^2J = 17.3 Hz; NCH_2COOCH$_3$), 4.13 (d, 1H, ^2J = 17.3 Hz; NCH_2COOCH$_3$), 4.10 – 4.04 (ddd, 1H, ^2J = 11.7 Hz, ^3J = 4.0 Hz, ^3J = 4.9 Hz; 5-H), 3.75 (s, 3H; COOCH$_3$), 3.67 – 3.64 (dd, 1H, ^2J = 11.3 Hz, ^3J = 4.0 Hz; 6-H), 3.51 – 3.45 (ddd, 1H, ^2J = 11.3 Hz, ^3J = 4.9 Hz, ^3J = 4.7 Hz; 6'-H), 3.18 – 3.15 (dd, 1H, ^2J = 11.7 Hz, ^3J = 4.7 Hz; 5'-H). – ^{13}C NMR (125 MHz, CDCl$_3$): δ = 174.0 (C=O), 173.6 (C=O), 168.8 (C=O, NCH$_2$*C*OOCH$_3$), 166.7 (C=O, 2-oxo-piperazine), 131.2 (q; C-aromat), 129.3 (*ortho*-C), 129.1 (*para*-C), 126.4 (*meta*-C), 75.2 (C-8), 66.3 (C-3), 52.6 (COO*C*H$_3$), 52.1 (C-7), 48.7 (N*C*H$_2$COOCH$_3$), 46.1 (C-6), 43.2 (C-5). For the signal assignments ^{1}H, ^{1}H-COSY and HMQC spectra were recorded. – IR (KBr): ν = 2953, 1721 (br, C=O, ester, imide), 1656 (C=O, 2-oxo-piperazine), 1597, 1495, 1438, 1389, 1350, 1250, 1206, 1069, 1024, 939, 869, 769, 733, 710, 693, 602 cm^{-1}. – MS (EI, 180 °C): *m/z* (%) = 360 (20) [M$^+$ + 1], 359 (100) [M$^+$], 300 (16), 272 (12), 211 (50), 184 (17), 173 (29), 158 (44), 125 (32), 119 (26), 56 (38). – HR-MS (EI): calcd. 359.1116; found 359.1118. – $C_{17}H_{17}N_3O_6$ (359.34): calcd. C 56.82, H 4.77, N 11.60; found C 57.01, H 4.61, N 11.43.

General procedure for automated solid phase synthesis according to Scheme 4: Resin **11** (200 mg, 0.16 mmol, 0.78 mmol/g) was swollen in dioxane (3 ml, 1 min, 1×), the solvent removed *in vacuo* and the resin dried (0.5 min). After the addition of dioxane (1.0 ml), a 0.85 M solution of the *N*-substituted maleic imide in dioxane (2.75 ml, 2.34 mmol, 15.0 equiv.) was added. The reaction mixture has heated to 65 °C for 2 h. Then the solvent was removed *in vacuo* and dried *in vacuo* (0.5 min), washed twice with THF (3 ml, 1 min, 1×) and dried (0.33 min). For reductive N-O bond cleavage the resins were swollen in acetonitrile (3 ml, 1 min, 1×). Then the solvent was removed *in vacuo* and the resin was dried (0.5 min). After the addition of acetonitrile (3.30 ml), water (0.20 ml) and Mo(CO)$_6$ (164 mg, 0.62 mmol, 4.0 equiv.) the reaction mixture was heated to 85 °C for 3 h. Afterwards the solvent was removed *in vacuo*, and the resin was dried (1.0 min) prior to three times washing with acetonitrile (3 ml, 1 min, 2×) and drying (0.5 min), followed by washing with THF (3 ml, 1 min, 2×) and drying (0.5 min) and washing with methanol (3 ml, 1 min, 2×) and drying (0.5 min).

For the cleavage of the 1,3-aminoalcohols the resins (50 mg, 0.03 – 0.04 mmol, 0.65 – 0.72 mmol/g) were swollen in 4 ml of THF and 0.5 ml of methanol (5 min). After the addition of neat NaOMe (6.3 mg, 0.12 mmol, 3.33 – 3.64 equiv.) the reaction mixture was stirred at room temperature for 22 h. Afterwards the solvent was removed *in vacuo* and the resin was washed with methanol (1.0 ml, 4 min, 1×). The combined filtrates were dried in a speed vac concentrator. The crude products were analyzed by analytical RP-HPLC/MS eluting with acetonitrile/water 5 : 95 + 0.1% TFA → acetonitrile/water 100 : 0 + 0.1% TFA within 5 min.

Spectroscopic data of compound **12a**: yellow oil. – R_f = 0.13 (ethyl acetate). – ^{1}H NMR (200 MHz, CDCl$_3$): δ = 7.57 (d, 2H, ^4J = 1.96 Hz; H-aromat), 7.09 (m, 1H; H-aromat), 4.98 (d, 1H, ^3J = 8.78 Hz; CH), 4.30 (d, 1H, ^3J = 8.78 Hz;

CH), 4.22 (br m, 3H; CH, CH_2), 3.81 (s, 3H; CH_3), 3.77 – 3.61 (m, 3H; CH_2), 3.47 – 3.24 (m, 1H, CH_2). The signals of the secondary amine and the hydroxy group were not detectable. – IR (ATR): $\nu = 3455$ (OH), 3315 (NH), 3185, 3082, 2954, 1747 (C=O, ester), 1690 (br, 2 C=O, imide), 1652 (C=O, 2-oxo-piperazine), 1588, 1544, 1487, 1443, 1412, 1366, 1306, 1209, 1182, 1136, 1114, 994, 985, 927, 844, 801, 763, 723, 670 cm^{-1}. – MS (EI, 230 °C) *m/z* (%) = 433 (10) $[M^+ + 4]$, 431 (64) $[M^+ + 2]$, 430 (20) $[M^+ + 1]$, 429 (96) $[M^+]$, 415 (14), 413 (38), 251 (56), 240 (28), 223 (66), 211 (26), 180 (32), 163 (62), 161 (100), 125 (24), 83 (26), 71 (32), 57 (56). – HR-MS (EI): calcd. for $C_{17}H_{17}N_3O_6Cl_2$: 429.0494; found 429.0491.

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[1] F. Wierschem, K. Rück-Braun, Eur. J. Org. Chem. 2321 (2004) and references cited therein. For details, see the supporting information.

[2] S. Maignan, J. P. Guilloteau, Y. M. Choi-Sledeski, M. R. Becker, W. R. Ewing, H. W. Pauls, A. P. Spada, V. Mikol, J. Med. Chem. **46**, 685 (2003); S. Kitamura, H. Fukushi, T. Miyawaki, M. Kawamura, Z. Terashita, H. Sugihara, T. Naka, Chem. Pharm. Bull. **9**, 258 (2001).

[3] A. Benjahad, R. Benhaddou, R. Granet, M. Kaouadji, P. Krausz, S. Piekarski, F. Thomasson, C. Bosgiraud, S. Delebasssée, Tetrahedron Lett. **35**, 9545 (1994).

[4] C. J. Dinsmore, J. H. Hutchinson, T. M. Williams PCT Int. Appl. WO 99 09, 985 (Cl. A61 K31/495) (1999), GB Appl. 98/975 (1998); B. Baudoin, N. Dereu, Y. El-Ahmad, P. Jimonet, A. Le Brun PCT Int. Appl. WO 99 41, 242 (Cl. C07D241/08) (1999), U.S. Appl. PV 81, 602 (1998).

[5] T. P. Burkholder, M. E. Kudlacz, Le Tieu-Binh PTC Int. Appl. WO 96 28,441 (Cl. C07 D403/06) (1996); U. S. Appl. 404, 788 (1995); M. Matsuo, D. Hagiwara, H. Miyake PTC Int. Appl. WO 96 37,488 (Cl. C07 D403/06) (1996); GB Appl.95/10, 600 (1995).

[6] K. Rück-Braun, T. H. E. Freysoldt, F. Wierschem, Chem. Soc. Rev. **34**, 507 (2005).

[7] S. I. Murahashi, H. Mitsui, T. Shiota, T. Tsuda, S. Watanabe, J. Org. Chem. **95**, 1736 (1990); F. A. Davis, S. Chattopadhyay, J. C. Towson, S. Lal, T. Reddy, J. Org. Chem. **53**, 2087 (1988).

[8] O. Tamura, K. Gotanda, J. Yoshino, Y. Morita, R. Terashima, M. Kikushi, T. Miyawaki, N. Mita, M. Yamashita, H. Ishibashi, M. Sakamoto, J. Org. Chem. **65**, 8544 (2000); J. Marcus, J. Brussee, A. V. D. Gen, Eur. J. Org. Chem. 2513 (1998).

[9] S. Cicchi, A. Goti, A. Brandi, A. Guarna, F. De Sarlo, Tetrahedron Lett. **31**, 3351 (1990); B. M. Trost, L. S. Chupak, T. Lübbers, J. Am. Chem. Soc. **120**, 1732 (1998); J. W. Bode, E. M. Carreira, J. Org. Chem. **66**, 6410 (2001).