Synthesis of Spirocyclopropanated Analogues of Iprodione[‡]

Farina Brackmann,[a] Mazen Es-Sayed,[b] and Armin de Meijere*[a]

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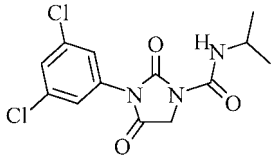
Methyl 1-(*tert*-butoxycarbonylamino)cyclopropanecarboxylate (**9**) was converted into the spirocyclopropanated five-membered ring analogue **7a** of Iprodione (**1**) in five steps with an overall yield of 28%. The spirocyclopropanated five-membered ring analogue **8a** was prepared from *tert*-butyl *N*-[1-(hydroxymethyl)cyclopropyl]carbamate (**10**) in five steps with an overall yield of 19%. En route to the spirocyclopropanated six-membered ring analogues of Iprodione (**1**), the oxalic acid diamides **5b** and **6b** could be obtained starting from **9** or **10** in 33 or 19% yield, respectively.

Introduction

For the last few decades substantial efforts of synthetically working scientists have been devoted to cyclopropane analogues of biologically active compounds,[1] because the incorporation of a cyclopropyl moiety in many cases had proved to have a beneficial influence on the biological activity.[2a] Introduction of a rigid three-membered ring into a molecule can e. g. enforce a certain orientation of the substituents along the chain of a molecule.[2b] Numerous examples of biologically active naturally occurring[3] as well as non-natural compounds rigidified by cyclopropane moieties are known. Among the latter are the antidepressant Tranylcypromin,[4] the antiinfectants Ciprofloxacin[5] and the once successful antiinfective Trovafloxacin.[6] Naturally occurring and synthetic pyrethroids are the best known cyclopropane derivatives with a pesticide activity.[3b,7]

Fungicides become more and more important because modern intensive agricultural procedures facilitate infestation of crops with fungi. The contact fungicide Iprodione (**1**), which was developed in 1970 by Rhône–Poulenc, and used to control a variety of fungal diseases by inhibiting the germination of spores and the growth of fungal mat,[8] has found a widespread application throughout the world. As we recently realized, biologically active motifs, like the one found in the neonicotinergic acetylcholine receptor agonists Imidacloprid[9] and Thiacloprid, may be modified by incorporation of spiroannelated cyclopropane rings,[10] with retention of the activity, but a change in the overall metabolic pathway. Encouraged by these results, we also set out to modify Iprodione (**1**) by introducing a 1,1-disubstituted three-membered ring to obtain the regioisomeric spirocyclopropanated five-membered analogues **7a** and **8a** as well as the six-membered analogues **7b** and **8b**. It was especially of interest to see, whether the substitution of the amide carbonyl group by a spiro-annelated cyclopropane ring, which is known for its alkene-like properties,[11] causes any effect upon fungicidal activity.



Iprodione **1**

Several synthetic sequences have been tried out without isolating and characterizing the intermediate products in an effort to develop a protocol for combinatorial approaches to libraries of such small molecules. Here we present our successful endeavours.

Results and Discussion

The envisaged synthetic route was designed to allow access to both the spirocyclopropanated five- as well as the six-membered ring analogues **7** and **8** of Iprodione (**1**) regioselectively from the same precursor of type **2**, which should be equipped in such a way as to permit selective substitution on each amino group to form the arylamines **3** and **4**, respectively. The latter then would be cyclized with an appropriate carbonyl-group containing component to afford the heterocycles **5** and **6**, respectively, which, in turn, would be converted into the biurets **7** and **8** (Scheme 1).

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[a] Institut für Organische und Biomolekulare Chemie der Georg-August-Universität Göttingen,
Tammannstrasse 2, 37077 Göttingen, Germany
Fax: +49-551-399475
E-mail: Armin.deMeijere@chemie.uni-goettingen.de
[b] Bayer CropScience AG,
Alfred-Nobel-Strasse 50, 40789 Monheim, Germany

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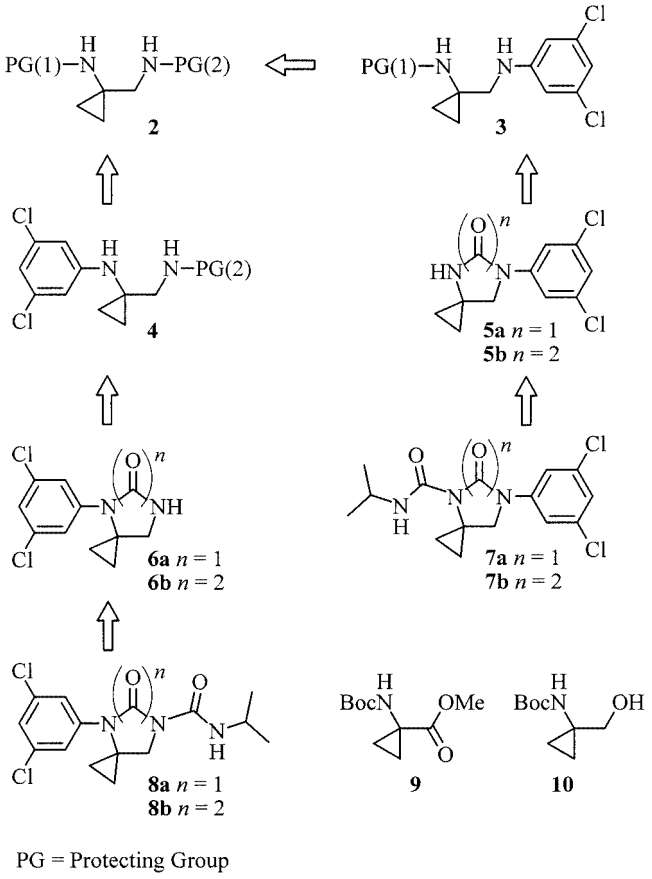
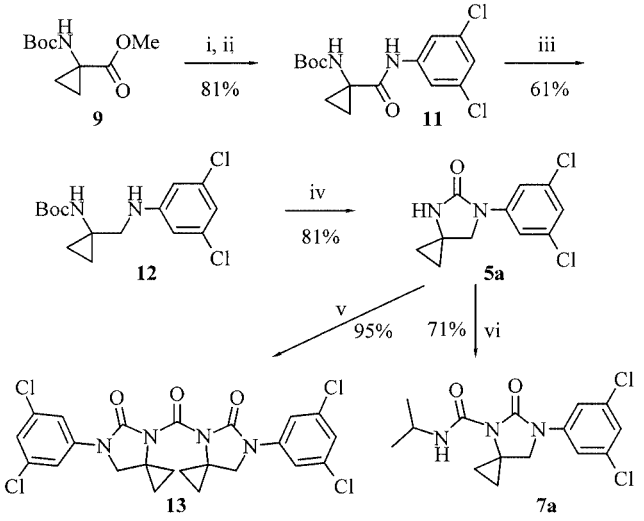


Scheme 1. Retrosynthetic considerations of the spirocyclopropanated analogues **7** and **8** of Iprodione (**1**).

The starting material chosen was methyl 1-(*tert*-butoxycarbonylamino)cyclopropanecarboxylate (**9**), which can be prepared in 57% yield by monohydrolysis[12a] followed by Curtius degradation[12b,12c] of the commercially available dimethyl cyclopropane-1,1-dicarboxylate. Reduction of **9** with lithium borohydride furnished *tert*-butyl *N*-[1-(hydroxymethyl)cyclopropyl]carbamate (**10**) in up to virtually quantitative yield.[12d,12e]

Spirocyclopropanated Analogues of Iprodione (1) with a Five-Membered Ring

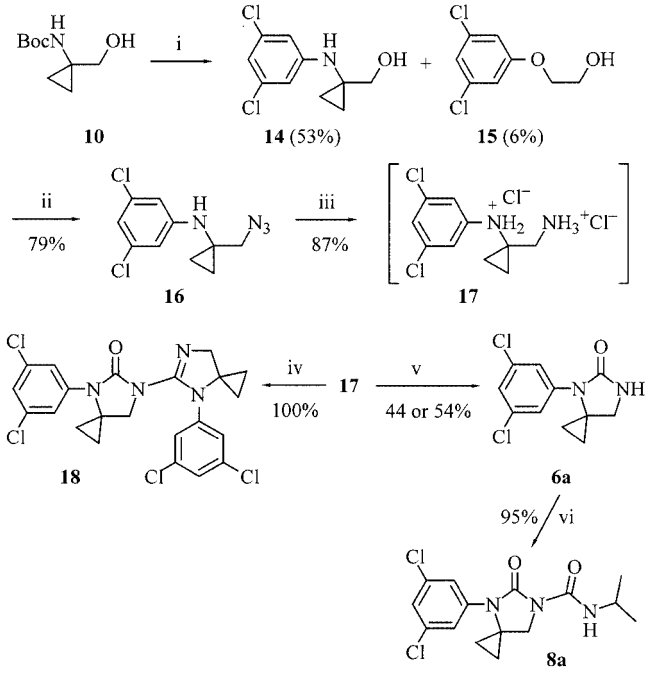
Mild hydrolysis of the *N*-Boc-protected amino ester **9,** followed by peptide coupling of the intermediate 1-(*tert*-butoxycarbonylamino)cyclopropanecarboxylic acid with 3,5-dichloroaniline mediated by dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) adopting a published procedure,[13] gave the amide **11** in 81% yield. While reduction of the latter with borane–THF complex (cf.[14]) furnished the corresponding amine **12** in less than 20% yield, careful reduction by slow addition of $LiAlH_4$ as an ethereal solution furnished **12** in 61% yield after column chromatography. The Boc protective group, under these conditions, is affected to a minimal extent only. Deprotection of the cyclopropylamino moiety in **12** with trifluoroacetic acid followed by treatment with hydrogen chloride in 2-propanol and subsequent cocyclization with phosgene, applied as a solution in toluene according to a published protocol,[15] provided the urea derivative **5a** (Scheme 2). This, after deprotonation with NaH, was treated again with an excess of the phosgene solution and then with isopropylamine. However, in contrast to published analogous reactions,[16] none of the desired product **7a** was formed, but exclusively the oligourea **13** arising by twofold substitution on phosgene with **5a**. This indicates that the intermediately formed carbamoyl chloride reacts more rapidly with the deprotonated **5a** than with isopropylamine. The spirocyclic urea **5a** did not react with isopropyl isocyanate in the presence of 10 mol% of NEt_3 (cf.[17]). Fortunately, the deprotonation of **5a** with an ethereal solution of ethylmagnesium bromide followed by treatment with a small excess of isopropyl isocyanate furnished the five-membered ring analogue **7a** (71% yield) of **1** along with some starting material **5a** (Scheme 2).



Scheme 2. Synthesis of the spirocyclopropanated five-membered ring analogue **7a** of Iprodione (**1**). Reagents and conditions: i) LiOH, $THF/H_2O/MeOH$, 0 to 20 °C, 20 h, then citric acid to pH ≈ 4; ii) 3,5-dichloroaniline, DCC, HOBt, THF, 0 to 20 °C, 19 h; iii) $LiAlH_4$ (inverse addition of a solution in Et_2O at 0 °C over 1 h), Et_2O, 0 °C, 4 h then 20 °C, 19 h; iv) TFA, 0 °C, 0.5 h, then HCl (5 M solution in *i*PrOH), then $COCl_2$ (20% solution in toluene), NEt_3, 0 to 20 °C, 2 h; v) NaH, THF, 20 °C, 10 min, then $COCl_2$ (20% solution in toluene), 20 °C, 1.5 h, then $iPrNH_2$, THF, 20 °C, 19 h; vi) EtMgBr, THF/Et_2O, 0 °C, 15 min, then *i*PrN=C=O, 20 °C, 24 h.

Deprotection of the *N*-Boc-protected aminoalcohol **10** as described above for compound **11** followed by a copper(I) iodide catalyzed Buchwald coupling[18] of the free base (obtained from the hydrochloride by treatment with sodium isopropanolate) with 3,5-dichloroiodobenzene[19] using ethylene glycol as a ligand and K_3PO_4 as a base, afforded the *N*-arylated aminoalcohol **14** (Scheme 3). The yield of this coupling went down upon scaling up the reaction, being 65% on a 2 mmol scale and only 53% on a 15–25 mmol scale.[20] The obtained product **14** was contaminated with up to 11 mol%[20] of 2-(3,5-dichlorophenoxy)ethanol (**15**) which resulted from the *O*-arylation of ethylene glycol and

could not be removed by column chromatography. Such an *O*-arylation has previously been reported only when Cs_2CO_3 was used as a base.[19a] The impure **14** was subjected to a Mitsunobu reaction[21] using hydrazoic acid[22] as the nucleophile, and after purification by column chromatography, the pure azide **16** was obtained in 79% yield. Reduction of the latter with 1,3-propanedithiol[23] furnished crude (1-aminomethylcyclopropyl)-(3,5-dichlorophenyl)amine which was isolated as its dihydrochloride **17** and further converted without purification (Scheme 3).



Scheme 3. Synthesis of the spirocyclopropanated five-membered ring analogue **8a** of Iprodione (**1**). Reagents and conditions: i) TFA, 0 °C, 0.5 h, then HCl (5 M solution in *i*PrOH), then *i*PrONa, then 3,5-dichloroiodobenzene, CuI, K_3PO_4, $HOCH_2CH_2OH$, *i*PrOH, 80 °C, 22 h; ii) PPh_3, DIAD, HN_3 (solution in benzene), THF, –78 to 20 °C, 22 h; iii) $HS(CH_2)_3SH$, NEt_3, MeOH, 20 °C, 1 d, then HCl (satd. solution in Et_2O), 0 °C; iv) $COCl_2$ (20% solution in toluene), NEt_3, THF, 0 to 20 °C, 2.5 h; v) NaOH, then Boc_2O, CH_2Cl_2, DMAP, 20 °C, 0.5 h (variant A, 44%) or CDA, CH_2Cl_2, 0 to 20 °C, 1 d (variant B, 54%); vi) EtMgBr, THF/Et_2O, 0 °C, 15 min, then *i*PrN=C=O, 20 °C, 3 h.

Surprisingly, contrary to the successful cocyclization of deprotected **12** with phosgene in toluene solution (see above), the attempted cocyclization of **17** under the same conditions resulted in the quantitative formation of the imidazolidinylimidazoline derivative **18**. Presumably, the initially formed desired product **6a**, under these conditions, reacts with excess phosgene to give a 2-chloroimidazoline derivative which can undergo formal nucleophilic substitution with a second molecule of **6a**. Alternatively, therefore, **17** was cocyclized with di-*tert*-butyl pyrocarbonate[24] under 4-(dimethylamino)pyridine (DMAP) mediation or with carbonyldiimidazole (CDA), respectively, to afford the spirocyclopropanated heterocycle **6a**, albeit in moderate yields (54 and 44%, respectively). Finally, the spirocyclopropanated five-membered ring analogue **8a** of Iprodione (**1**) was prepared by treatment of **6a** with an ethereal solution of ethylmagnesium bromide followed by addition of an excess of isopropyl isocyanate in full analogy to the synthesis of **7a** (Scheme 3).

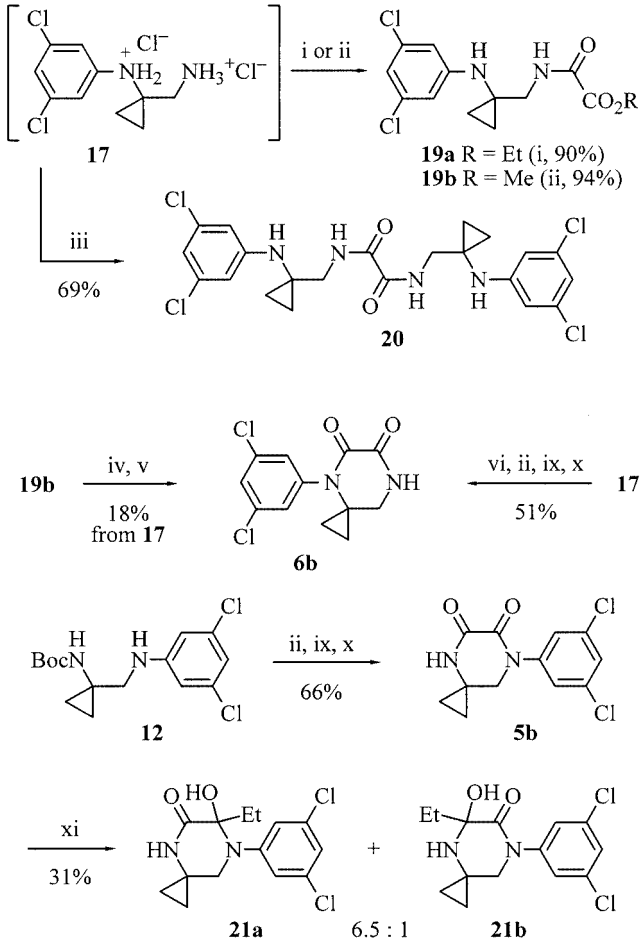
Approach to Spirocyclopropanated Analogues of Iprodione (1) with a Six-Membered Ring

Just as the attempted "shotgun" cocyclizations of the diamine **17** did not furnish any detectable quantity of the heterocycle **6a**, treatment of **17** with diethyl oxalate only led to the monoamide **19a** by attack of the primary amino group on the diester (90% yield), while the secondary arylamino function remained as such, even after prolonged heating in ethanol (cf.[25]) (Scheme 4). The analogous methyl ester **19b** was obtained from **17** upon treatment with methyl oxalyl chloride (oxalic acid chloride mono methyl ester), and it could not be cyclized even by prolonged heating in toluene in the presence of molecular sieves 4 Å. The more reactive oxalyl chloride[26] afforded the *N*,*N*′-disubstituted oxamide **20** in 69% yield as the sole product. However, a stepwise proceeding turned out to be successful. Thus, mild hydrolysis of the methyl ester function in **19b** with lithium hydroxide followed by conversion of the carboxylic acid moiety into the acid chloride with thionyl chloride, and finally treatment with imidazole gave the desired six-membered ring product **6b**, albeit in an overall yield from the dihydrochloride **17** of only 18%.

With the intention in mind to acylate the less reactive secondary arylamino group with the dicarbonyl building block first, the free base of **17** was treated with di-*tert*-butyl pyrocarbonate (Boc_2O) to protect the primary amino group, and the resulting Boc-protected diamine was allowed to react with methyl oxalyl chloride in the presence of NEt_3. The obtained intermediate was directly treated with TFA to remove the Boc group, and the resulting primary amine was converted into its hydrochloride with hydrogen chloride in 2-propanol, and finally this in turn treated with sodium methoxide in methanol at ambient temperature to provide the desired pure product **6b** in 51% overall yield starting from the dihydrochloride **17** without any purification of the intermediate products (Scheme 4).

This approach turned out to be successful also for the precursor **5b** of an Iprodione analogue with a six-membered ring. Applying exactly the same sequence of operations to the *N*-Boc-protected arylcyclopropyldiamine **12** – treatment with methyl oxalyl chloride in the presence of NEt_3, Boc-removal with TFA, conversion to the hydrochloride and final treatment with NaOMe – gave the ring-closed product **5b** in 66% overall yield from **12** (Scheme 4).

Surprisingly, the attempted deprotonation of **5b** and **6b** with ethylmagnesium bromide in order to add the amide anion to isopropyl isocyanate, the sequence which had proved successful in the preparation of the spirocyclopropanated Iprodione analogues **7a** and **8a** with a five-membered ring, failed and formed the products of Grignard addition to either one of the carbonyl functions, **21a** and **21b**



Scheme 4. Synthesis of the spirocyclopropanated heterocycles **5b**, **6b** and en route to the spirocyclopropanated six-membered ring analogues **7b** and **8b**. Reagents and conditions: i) NaOH, then $(CO_2Et)_2$, EtOH, 78 °C, 21 h; ii) NEt_3, then $ClCOCO_2Me$, THF, 0 to 20 °C, 2.5 h; iii) NEt_3, then $(COCl)_2$, THF, 0 to 20 °C, 2 h; iv) LiOH, THF/H_2O, 0 to 20 °C, 1.5 h; v) $SOCl_2$, DMF (cat.), CH_2Cl_2, 20 to 40 °C, then imidazole, MeCN, 20 to 80 °C, 20 h; vi) NaOH, then Boc_2O, CH_2Cl_2, 20 °C, 15 h; ix) TFA, 0 °C, 0.5 h, then HCl (5 M solution in *i*PrOH); x) NaOMe, MeOH, 20 °C, 1 d; xi) EtMgBr, THF/Et_2O, 0 °C, 15 min, then *i*PrN=C=O, 20 °C, 2 h.

in a ratio of 6.5: 1[27] in 31% yield (Scheme 4, the regiochemistry is attributed arbitrarily). Any further attempts to introduce the isopropylamide functionality into **5b**, e. g. by deprotonation with NaH or KF/aluminum oxide[28] and subsequent treatment with isopropyl isocyanate, failed as well.

Conclusions

An efficient route to novel Iprodione (**1**) analogues has been developed in which a spiroannelated cyclopropane ring occupies in position 4 or 5, respectively, of the cyclic urea. In addition, precursors to the six-membered spirocyclopropanated Iprodione analogues have been synthesized, containing an additional carbonyl group in the heterocycle. Unfortunately the introduction of the isopropyl urea side chain failed so far. The evaluation of the biological activity of these analogues is currently in progress.

Experimental Section

General Remarks: NMR spectra were recorded with a Varian UNITY-200 (200 MHz for ^1H and 50.2 MHz for ^{13}C NMR), a Bruker AM 250 (250 MHz for ^1H and 62.9 MHz for ^{13}C NMR) or a Varian UNITY-300 (300 MHz for ^1H and 75.5 MHz for ^{13}C NMR) instrument. Proton chemical shifts are reported in ppm relative to residual peaks of deuterated solvents. Multiplicities were determined by DEPT (Distortionless Enhancement by Polarisation Transfer), APT (Attached Proton Test) measurements or HMQC (Heteronuclear Multiple Quantum Coherence). Chemical shifts refer to $\delta_{TMS} = 0.00$ ppm according to the chemical shifts of residual solvent signals. IR: Bruker IFS 66 (FT-IR) spectrophotometer, measured as KBr pellets or oils between KBr plates. MS (EI at 70 eV or DCI with NH_3): Finnigan MAT 95 spectrometer. MS (HR-EI): pre-selected ion peak matching at $R >> 10000$ to be within ±2 ppm of the exact masses. Melting points: Büchi 510 capillary melting point apparatus, values are uncorrected. TLC: Macherey–Nagel precoated sheets, 0.25 mm Sil G/UV_{254}. Column chromatography: Merck silica gel, grade 60, 230–400 mesh. Elemental analyses: Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie, Universität Göttingen. Starting materials: Methyl (1-*tert*-butoxycarbonylamino)cyclopropane carboxylate (**9**),[11a–11c] *tert*-butyl (1-hydroxymethylcyclopropyl)carbamate (**10**)[11d,11e] and hydrazoic acid[21] were prepared according to published procedures. Anhydrous THF was obtained by distillation from sodium benzophenone ketyl, CH_2Cl_2 and MeCN from P_4O_{10}, MeOH from Mg, NEt_3 from CaH_2. All other chemicals were used as commercially available. All operations in anhydrous solvents were performed under nitrogen in flame-dried glassware. Organic extracts were dried with $MgSO_4$.

***tert*-Butyl [1-(3,5-Dichlorophenylcarbamoyl)cyclopropyl]carbamate (11):** To a solution of the *N*-Boc-amino ester **9** (7.43 g, 34.5 mmol) in a mixture of THF/H_2O/MeOH (30 mL/15 mL/15 mL) was added at 0 °C LiOH (4.14 g, 173 mmol) in one portion, and the resulting mixture was stirred at this temp. for 5 h and at ambient temp. for an additional 15 h. After evaporation of the volatile components, the residue was taken up with H_2O (15 mL) and brought to pH 4 with a 10% aq. citric acid solution. The aqueous phase was extracted with Et_2O (3 × 80 mL). The combined organic phases were dried and evaporated under reduced pressure. The resulting crude 1-(*tert*-butoxycarbonylamino)cyclopropanecarboxylic acid[29] (6.03 g, 30.0 mmol) was dissolved in THF (120 mL) and the solution cooled to 0 °C. 3,5-Dichloroaniline (4.86 g, 30.0 mmol), 1-hydroxybenzotriazol (4.54 g, 30.0 mmol, cont. 12% H_2O) and dicyclohexylcarbodiimide (6.50 g, 31.5 mmol) were added in this order, each in one portion. The reaction mixture was warmed to ambient temp. and stirred for an additional 19 h. The suspension was filtered through a pad of Celite and the filtrate was evaporated under reduced pressure. The residue was taken up in EtOAc (120 mL), and the organic layer was washed with satd. aq. $NaHCO_3$ solution (2 × 50 mL), aq. 0.2 N HCl solution (2 × 50 mL) and H_2O (50 mL), dried and concentrated under reduced pressure. Recrystallization of the residue from EtOAc yielded **11** (9.60 g, 81%) as a colorless voluminous solid, m.p. 150–153 °C. IR (KBr): $\tilde{\nu} = 3335\ cm^{-1}$ (N–H), 3298 (N–H), 3084 (C–H) 2986 (C–H), 2976 (C–H), 2930 (C–H), 1688 (C=O), 1583, 1168 (O*t*Bu), 848, 670. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.06–1.15 (m, 2 H, Cpr-H), 1.46 [s, 9 H, $C(CH_3)_3$], 1.59–1.67 (m, 2 H, Cpr-H), 5.43 (br. s, 1 H, CprNH), 7.02–7.08

(m, 1 H, Ar-H), 7.42–7.50 (m, 2 H, Ar-H), 8.68 (br. s, 1 H, ArNH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ = 18.2 (–, Cpr-C), 28.2 [+, C(CH_3)$_3$], 36.5 (–, Cpr-C), 81.6 [–, C(CH_3)$_3$], 117.9 (+, Ar-C), 124.1 (+, Ar-C), 135.1 (–, Ar-C), 139.7 (–, Ar-C), 156.2 (–, CprNCO), 170.6 (–, CprCON) ppm. MS (EI): *m*/*z* (%) = 348/346/344 (<1:5:8) [M^+], 292/290/288 (3:19:28) [$M^+ - C_4H_8$], 275/273/271 (<1:4:7) [M^+ – O*t*Bu], 248/246/244 (<1:5:9) [$M^+ - CO_2t$Bu + H], 231/229/227 (<1:<1:2) [$M^+ - H_2NCO_2t$Bu], 199 (4), [$M^+ - Cl_2Ar$], 165/163/161 (<1:4:8) [$Cl_2ArNH_2^+$], 149/147/145 (<1:<1:1) [Cl_2Ar^+], 127 (5) [$H_2NCOC_3H_4NHCO^+$], 100 (3) [$H_2NCOC_3H_4NH_2^+$, CO_2tBu$^+$ – H], 57 (100) [$C_4H_9^+$], 41 (8) [$C_3H_5^+$]. HRMS (EI) calcd. for $C_{15}H_{18}Cl_2N_2O_3$ [M^+] 344.0694, correct mass. $C_{15}H_{18}Cl_2N_2O_3$ (345.22): calcd. C 52.19, H 5.26, N 8.11; found C 52.45, H 5.18, N 7.86.

***tert*-Butyl [1-(3,5-Dichlorophenylaminomethyl)cyclopropyl]carbamate (12):** $LiAlH_4$ (8.52 mmol, 5.68 mL of a 1.50 M solution in Et_2O) was added to a stirred solution of **11** (1.96 g, 5.68 mmol) in anhydrous Et_2O (100 mL) at 0 °C over a period of 1 h. The reaction mixture was stirred at 0 °C for 4 h, warmed to ambient temp. and stirred at this temp. for an additional 19 h. A second portion of $LiAlH_4$ (2.65 mL, 3.98 mmol, 1.50 M in Et_2O) was added dropwise at 0 °C, and the reaction mixture was warmed up to ambient temp., stirred at this temp. for an additional 4 h and cooled to 0 °C again. An aq. satd. Na_2SO_4 solution (3 mL) was added carefully at 0 °C, and the resulting suspension was stirred for 13 h while warming up to ambient temp., then filtered through a pad of Celite. The filtrate was dried and evaporated under reduced pressure. Column chromatography of the residue (105 g of silica gel, 4×25 cm column, $CHCl_3$) yielded **12** (1.15 g, 61%) as a colorless voluminous solid, m.p. 79–81 °C, R_f = 0.48. IR (KBr): $\tilde{\nu}$ = 3365 cm^{-1} (N–H), 3057 (C–H), 2995 (C–H), 2972 (C–H), 2922 (C–H), 1676 (C=O), 1596, 1576, 1506, 1368, 1270, 1256, 1161, 1081. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.79–0.95 (m, 4 H, Cpr-H), 1.43 [s, 9 H, C(CH_3)$_3$], 3.11 (d, ^3J = 4.5 Hz, 2 H, CH_2N), 5.01 (br. s, 1 H, NH), 5.24 (br. s, 1 H, NH), 6.35–6.43 (m, 2 H, Ar-H), 6.55–6.67 (m, 1 H, Ar-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 13.5 (–, Cpr-C), 28.3 [+, C(CH_3)$_3$], 32.3 (C_{quat}, Cpr-C), 52.4 (–, CH_2N), 80.2 [C_{quat}, C(CH_3)$_3$], 110.3 (+, Ar-C), 116.2 (+, Ar-C), 135.3 (C_{quat}, Ar-C), 150.1 (C_{quat}, Ar-C), 156.6 (C_{quat}, NCO) ppm. MS (EI): *m*/*z* (%) = 334/332/330 (1:9:14) [M^+], 278/276/274 (1:10:15) [$M^+ - C_4H_8$], 178/176/174 (3:12:19) [$M^+ - C_3H_4NHCO_2t$Bu], 57 (100) [$C_4H_9^+$], 41 (15) [$C_3H_5^+$]. HRMS (EI) calcd. for $C_{15}H_{20}Cl_2N_2O_2$ [M^+] 330.0902, correct mass. $C_{15}H_{20}Cl_2N_2O_2$ (331.24): calcd. C 54.39, H 6.09, Cl 21.41, N 8.46; found C 54.21, H 5.87, Cl 21.61, N 8.31.

Deprotection of *N*-Boc-protected Amines. General Procedure 1 (GP, 1): The indicated quantity of the respective carbamate was stirred with TFA (5 mL) at 0 °C for 30 min. All volatile components of the reaction mixture were removed under reduced pressure. To the residue was added a solution of HCl (5 mL of a 5 M solution in *i*PrOH), and the reaction mixture was concentrated. This operation was repeated three times. The residual hydrochloride was used without further purification.

6-(3,5-Dichlorophenyl)-4,6-diazaspiro[2.4]heptan-5-one (5a): The hydrochloride obtained from the carbamate **12** (1.28 g, 3.85 mmol) according to GP1 was dissolved in anhydrous THF (50 mL), the solution cooled to 0 °C, treated with NEt_3 (2.19 mL, 15.8 mmol) and stirred for an additional 10 min. A 20% solution of phosgene in toluene (5.78 mmol, 3.06 mL) was added dropwise at 0 °C over a period of 30 min, the resulting mixture was warmed to ambient temp. and stirred for an additional 2 h. Water (1 mL) was added, and all volatile compounds were evaporated under reduced pressure. The residue was again treated with water (20 mL), and the mixture filtered. Column chromatography of the residue (85 g of silica gel, 4×20 cm column, $CHCl_3$/MeOH, 35:1) yielded **5a** (797 mg, 81%) as a colorless solid, m.p. 183–184 °C, R_f = 0.40. IR (KBr): $\tilde{\nu}$ = 3295 cm^{-1} (N–H), 1724, 1708 (C=O), 1561, 1460, 1394. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.78–0.90 (m, 2 H, Cpr-H), 0.90–1.02 (m, 2 H, Cpr-H), 3.87 (s, 2 H, CH_2N), 5.24 (br. s, 1 H, NH), 6.99–7.05 (m, 1 H, Ar-H), 7.45–7.50 (m, 2 H, Ar-H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ = 11.8 (–, Cpr-C), 34.5 (–, Cpr-C), 52.6 (–, CH_2N), 115.5 (+, Ar-C), 122.3 (+, Ar-C), 135.1 (–, Ar-C), 141.8 (–, Ar-C), 158.1 (–, CO) ppm. MS (EI): *m*/*z* (%) = 260/258/256 (8:63:100) [M^+], 245/243/241 (8:56:95), 232/230/228 (4:30:45) [M^+ – CO], 178 (23), 174 (36), 149/147/145 (3:19:29) [Cl_2Ar^+], 41 (62) [$C_3H_5^+$]. HRMS (EI) calcd. for $C_{11}H_{10}Cl_2N_2O$ [M^+] 256.0170, (correct HRMS) $C_{11}H_{10}Cl_2N_2O$ (257.12): calcd. C 51.39, H 3.91, Cl 27.58, N 10.90; found C 51.40, H 3.78, Cl 27.41, N 10.78.

Bis[6-(3,5-dichlorophenyl)-4,6-diaza-5-oxospiro[2.4]hept-4-yl]methanone (13): A solution of **5a** (321 mg, 1.25 mmol) in anhydrous THF (10 mL) was added dropwise to a suspension of NaH (80.0 mg, 2.00 mmol, 60% suspension in mineral oil) in anhydrous THF (10 mL), and the mixture stirred for 10 min at ambient temp. Phosgene (4.00 mmol, 2.12 mL of a 20% solution in toluene) was added, and the reaction mixture was stirred at the same temp. for an additional 1.5 h. The suspension was filtered through a pad of Celite, and the filtrate was evaporated under reduced pressure. The residue was dissolved in anhydrous THF (20 mL), treated with isopropylamine (266 μL, 4.00 mmol) and stirred at ambient temp. for an additional 19 h. The volatile compounds were evaporated under reduced pressure. The residue was treated with water (30 mL), and the mixture extracted with CH_2Cl_2 (4×30 mL). The combined organic phases were dried and evaporated under reduced pressure. Recrystallization of the residue from $CHCl_3$/Et_2O yielded **13** (321 mg, 95%) as a colorless solid, m.p. >250 °C. IR (KBr): $\tilde{\nu}$ = 3088 cm^{-1} (C–H), 3004 (C–H), 2867 (C–H), 1722 (C=O), 1700 (C=O), 1593, 1556, 1461, 1437, 1336, 1305, 1211. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.66–0.86 (m, 4 H, Cpr-H), 1.72–1.90 (m, 4 H, Cpr-H), 3.50 (d, ^2J = 8.2 Hz, 2 H, CH_2N), 4.21 (^2J = 8.2 Hz, 2 H, CH_2N), 7.07–7.15 (m, 2 H, Ar-H), 7.40–7.50 (m, 4 H, Ar-H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ = 5.5 (–, Cpr-C), 13.7 (–, Cpr-C), 39.0 (–, Cpr-C), 52.1 (–, CH_2N), 117.1 (+, Ar-C), 124.0 (+, Ar-C), 135.3 (–, Ar-C), 140.6 (–, Ar-C), 147.1 (–, CO), 152.2 (–, CO) ppm. MS (EI): *m*/*z* (%) = 546/544/542/540/538 (<1:1:6:14:11) [M^+], 287/285/283 (2:16:29) [$Cl_2ArNCH_2C_3H_4NCOCO^+$], 260/258/256 (9:59:100) [$Cl_2ArNCH_2C_3H_4NHCO^+$], 245/243/241 (2:17:25), 96 (53) [$C_3H_4CH_2NCO^+$], 68 (10), 53 (44), 41 (14) [$C_3H_5^+$]. $C_{23}H_{18}Cl_4N_4O_3$ (540.23): calcd. C 51.14, H 3.36, Cl 26.25, N 10.37; found C 50.84, H 3.43, Cl 26.70, N 10.15.

Reactions with Isopropyl Isocyanate. General Procedure 2 (GP, 2): A solution of the respective heterocycle (1.00 mmol) in anhydrous THF (15 mL) was treated with an ethereal solution of ethylmagesium bromide (1.00 mmol) at 0 °C, and the resulting mixture was stirred for an additional 15 min. Isopropyl isocyanate (1.10 mmol) was added at the same temp., the resulting mixture was warmed up to ambient temp. and stirred at this temp. for the indicated time. The reaction was quenched with an aq. satd. NH_4Cl solution (20 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (2×20 mL), the combined organic phases were dried and evaporated under reduced pressure. The product was purified by column chromatography on silica gel.

6-(3,5-Dichlorophenyl)-*N*-isopropyl-5-oxo-4,6-diazaspiro[2.4]heptane-4-carboxamide (7a): Column chromatography (25 g of silica

gel, 2×25 cm column, $CHCl_3$) of the residue obtained from **5a** (257 mg, 1.00 mmol), EtMgBr (1.00 mmol, 370 μL of a 2.70 M solution in Et_2O) and isopropyl isocyanate (108 μL, 1.10 mmol) according to GP2 (24 h stirring) yielded **7a** (243 mg, 71%) and some starting material **5a** (44 mg, 17%). An analytical sample of **7a** was obtained by recrystallization from hexane/CH_2Cl_2. **7a:** Colorless solid, m.p. 122–123 °C, R_f = 0.60. IR (KBr): $\tilde{\nu}$ = 3301 cm^{-1} (N–H), 3118 (C–H), 3064 (C–H), 2993 (C–H), 2970 (C–H), 2930 (C–H) 2885 (C–H), 1718 (C=O), 1684 (C=O), 1590, 1560, 1547 (NC=O), 1449, 1389, 1363, 1213, 1176, 671. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.59–0.67 (m, 2 H, Cpr-H), 1.18 [d, ^3J = 6.6 Hz, 6 H, $CH(CH_3)_2$], 2.03–2.17 (m, 2 H, Cpr-H), 3.74 (s, 2 H, CH_2N), 3.94 [sept, ^3J = 6.6 Hz, 1 H, $CH(CH_3)_2$], 7.06–7.13 (m, 1 H, Ar-H), 7.42–7.48 (m, 2 H, Ar-H), 8.21 (br. d, ^3J = 7.0 Hz, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 10.9 (–, Cpr-C), 22.8 [+, $CH(CH_3)_2$], 38.8 [+, $CH(CH_3)_2$], 41.7 (C_{quat}, Cpr-C), 51.9 (–, CH_2N), 116.7 (+, Ar-C), 123.8 (+, Ar-C), 135.3 (C_{quat}, Ar-C), 140.5 (C_{quat}, Ar-C), 151.6 (C_{quat}, CO), 155.3 (C_{quat}, CO) ppm. MS (EI): *m*/*z* (%) = 345/343/341 (<1:1:2) [M^+], 260/258/256 (8:67:100) [M^+ – *i*PrNHCO + H], 245/243/241 (5:29:59). HRMS (EI) calcd. for $C_{15}H_{17}Cl_2N_3O_2$ [M^+] 341.0698, correct mass. $C_{15}H_{17}Cl_2N_3O_2$ (342.22): calcd. C 52.65, H 5.01, Cl 20.72, N 12.78; found C 52.68, H 4.74, Cl 20.81, N 12.06.

[1-(3,5-Dichlorophenylamino)cyclopropyl]methanol (14): The residue obtained from *tert*-butyl (1-hydroxymethylcyclopropyl)carbamate (**10**) (3.09 g, 16.5 mmol) according to GP1 was added in small portions to a solution of NaO*i*Pr in *i*PrOH [freshly prepared by dissolving Na (380 mg, 16.5 mmol) in anhydrous *i*PrOH (40 mL)], and the resulting mixture stirred for 15 min at ambient temp. Then K_3PO_4 (6.37 g, 30.0 mmol), ethylene glycol (1.67 mL, 30.0 mmol), 3,5-dichloroiodobenzene (4.09 g, 15.0 mmol) and CuI (143 mg, 750 μmol) were added, and the resulting suspension was stirred at 80 °C for 22 h. After cooling to ambient temp., the reaction mixture was diluted with water (40 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (3×50 mL), the combined organic layers were dried and evaporated under reduced pressure. Column chromatography of the residue (150 g of silica gel, 4×25 cm column, $CHCl_3$) yielded **14** (1.85 g, calculated yield 53%) as a brown, viscous oil which was contaminated with 2-(3,5-dichlorophenoxy)ethanol (**15**) (180 mg, calculated yield 6%), R_f = 0.15. IR (KBr): $\tilde{\nu}$ = 3409 cm^{-1} (O–H, N–H), 2936 (C–H), 1592, 1572, 1450, 1036, 838, 802. **14**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.78–0.88 (m, 4 H, Cpr-H), 1.64 (br. s, 1 H, OH), 3.61 (s, 2 H, CH_2O), 4.52 (br. s, 1 H, NH), 6.53–6.60 (m, 2 H, Ar-H), 6.65–6.70 (m, 1 H, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, APT): δ = 12.7 (–, Cpr-C), 36.3 (–, Cpr-C), 65.4 (–, CH_2OH), 111.8 (+, Ar-C), 117.5 (+, Ar-C), 135.35 (–, Ar-C), 148.5 (–, Ar-C) ppm. **15:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56 (br. s, 1 H, OH), 3.90–3.98 (s, 2 H, CH_2O), 4.02–4.08 (s, 2 H, CH_2O), 4.52 (br. s, 1 H, NH), 6.78–6.82 (m, 2 H, Ar-H), 6.92–6.98 (m, 1 H, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, APT): δ = 61.1 (–, CH_2OH), 69.8 (–, CH_2OAr), 113.6 (+, Ar-C), 121.4 (+, Ar-C), 135.40 (–, Ar-C), 159.6 (–, Ar-C) ppm. **14 and 15:** MS (EI): *m*/*z* (%) = 235/233/231 (3:14:22) [M_1^+], 219/208/206 (2:13:22) [M_2^+], 204/202/200 (18:33:45) [M_1^+ – CH_2OH], 166/164/162 (12:68:100) [$Cl_2ArNH_3^+$], 149/147:145 (2:12:18) [Cl_2Ar^+], 109 (13), 99 (17), 75 (11), 63 (16), 45 (22), 41 (4) [$C_3H_5^+$]. This mixture was used in the next step without separation.

(1-Azidomethylcyclopropyl)-(3,5-dichlorophenyl)amine (16): Diisopropyl azodicarboxylate (2.98 mL, 15.4 mmol) and hydrazoic acid (15.2 mmol, 15.2 mL of a 1.0 M solution in benzene) were added one after the other to a stirred solution of PPh_3 (4.14 g, 15.8 mmol) in a mixture of the amino alcohol **14** and the hydroxy ether **15** [prepared as described above and containing **14** (2.71 g, 11.7 mmol) as well as **15** (309 mg, 1.50 mmol) according to its ^{1}H NMR spectrum] in anhydrous THF (100 mL) at –78 °C. The reaction mixture was warmed to ambient temp., stirred at this temp. for an additional 22 h and concentrated under reduced pressure. The residue was filtered through a pad of silica gel (200 g) eluting with chloroform, the solution concentrated under reduced pressure and the residue then purified by column chromatography (100 g of silica gel, 3×40 cm column, hexane/Et_2O, 30:1) to yield **16** (2.40 g, 9.33 mmol, 79%) as a pale yellow oil which crystallized while kept at –26 °C overnight, m.p. 49–50 °C, R_f = 0.16. IR (KBr): $\tilde{\nu}$ = 3347 cm^{-1} (N–H), 3094 (C–H), 3008 (C–H), 2924 (C–H), 2858 (C–H), 2100 (N_3), 1590, 1572, 1451, 1338, 1236, 821, 674. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.87–0.91 (m, 4 H, Cpr-H), 3.38 (s, 2 H, CH_2N), 4.50 (br. s, 1 H, NH), 6.56–6.60 (m, 2 H, Ar-H), 6.71–6.75 (m, 1 H, Ar-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 13.3 (–, Cpr-C), 34.5 (C_{quat}, Cpr-C), 55.3 (–, CH_2N), 111.6 (+, Ar-C), 117.8 (+, Ar-C), 135.41 (C_{quat}, Ar-C), 147.7 (C_{quat}, Ar-C) ppm. MS (EI): *m*/*z* (%) = 260/258/256 (2:10:14) [M^+], 218/216/214 (10:66:100) [$M^+ – N_3$], 204/202/200 (10:38:49) [$M^+ – CH_2N_3$], 181/179 (19:66) [$M^+ – N_3$ – Cl], 164 (41), 145 (25), 130 (13), 111 (14), 109 (20), 75 (22), 56 (22) [$CH_2N_3^+$], 41 (14) [$C_3H_5^+$]. HRMS (EI) calcd. for $C_{10}H_{10}Cl_2N_4$ [M^+] 256.0283, (correct HRMS). $C_{10}H_{10}Cl_2N_4$ (257.12): calcd. C 46.71, H 3.92, N 21.79; found C 46.61, H 3.63, N 21.74.

4,4′-Bis(3,5-dichlorophenyl)-5,6′-bi[4,6-diazaspiro[2.4]heptyl]-5-en-5′-one (18): A solution of the azide **16** (573 mg, 2.23 mmol) in MeOH (10 mL) was treated with NEt_3 (773 μL, 5.58 mmol) and 1,3-propanedithiol (560 μL, 5.58 mmol), and the mixture stirred for 1 d. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was taken up in Et_2O (2.5 mL), and a satd. HCl solution in Et_2O (2.5 mL) was added. The volatile compounds were evaporated in vacuo, and the residue was washed with Et_2O to yield crude (1-aminomethylcyclopropyl)-(3,5-dichlorophenyl)amine dihydrochloride (**17**) (587 mg, 1.93 mmol, 87%), slow decomp. >205 °C, m.p. 215–220 °C. ^{1}H NMR (300 MHz, D_2O): δ = 0.96–1.03 (m, 2 H, Cpr-H), 1.03–1.12 (m, 2 H, Cpr-H), 3.20 (s, 2 H, CH_2N), 6.76–6.83 (m, 2 H, Ar-H), 6.86–6.90 (m, 1 H, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, APT): δ = 14.3 (–, Cpr-C), 32.7 (–, Cpr-C), 51.5 (–, CH_2N), 112.6 (+, Ar-C), 118.1 (+, Ar-C), 136.1 (–, Ar-C), 149.2 (–, Ar-C) ppm. The crude **17** was dissolved in THF (20 mL), treated with NEt_3 (1.10 mL, 7.91 mmol) at 0 °C and stirred for 10 min. Phosgene (2.90 mmol, 1.53 mL of a 20% solution in toluene) was added over a period of 45 min at 0 °C. The resulting mixture was warmed to ambient temp. and stirred for an additional 2.5 h. Water (15 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were dried and concentrated under reduced pressure. Column chromatography of the residue (30 g of silica gel, 1×20 cm column, $CHCl_3$/MeOH, 35:1) yielded **18** (478 mg, 963 μmol, 100%) as a colorless solid, R_f = 0.35. An analytical sample was obtained by recrystallization from CH_2Cl_2/Et_2O and had m.p. 186–190 °C. IR (KBr): $\tilde{\nu}$ = 3085 cm^{-1} (C–H), 2859 (C–H), 1737 (C=O), 1612, 1585, 1572, 1402, 1376. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.51–0.67 (m, 2 H, Cpr-H), 0.67–0.82 (m, 4 H, Cpr-H), 0.82–0.94 (m, 2 H, Cpr-H), 3.94 (s, 2 H, CH_2N), 4.03 (s, 2 H, CH_2N), 6.78–6.88 (m, 2 H, Ar-H), 6.88–6.95 (m, 2 H, Ar-H), 7.18–7.25 (m, 1 H, Ar-H), 7.25–7.31 (m, 1 H, Ar-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 8.4 (–, Cpr-C), 10.9 (–, Cpr-C), 41.2 (C_{quat}, Cpr-C), 48.9 (C_{quat}, Cpr-C), 51.7 (–, CH_2N), 60.4 (–, CH_2N), 124.9 (+, Ar-C), 126.6 (+, Ar-C), 127.7 (+, Ar-C), 128.4 (+, Ar-C), 135.0 (C_{quat}, Ar-C), 135.3 (C_{quat}, Ar-C), 135.7 (C_{quat}, Ar-C), 142.8 (C_{quat}, Ar-C), 153.4 (C_{quat}, CO), 154.8 (C_{quat}, NNCN) ppm. MS (EI): *m*/*z* (%) = 502/

500/498/496/494 (<1:2:9:21:15) [M+], 339/337/335 (7:44:70) [M+ – Cl_2ArN], 311/309/307 (9:59:92) [M+ – Cl_2ArN – CO], 217/215/213 (13:62:100) [$Cl_2ArNC_3H_4CH_2^+$], 180/178 (27:89) [$ClArNC_3H_4CH_2^+$]. $C_{22}H_{18}Cl_4N_4O$ (496.22): calcd. C 53.25, H 3.66, Cl 28.58, N 11.29; found C 53.11, H 3.87, Cl 28.82, N 11.12.

4-(3,5-Dichlorophenyl)-4,6-diazaspiro[2.4]heptan-5-one (6a). Variant A: The crude **17** [152 mg, 500 μmol; obtained from **16** (148 mg, 575 mmol) as indicated above] was dissolved in a solution of NaOH (3.5 mL of aq. 1 M solution), and the mixture extracted with CH_2Cl_2 (5×3 mL). The combined organic layers were dried, concentrated under reduced pressure, and the residue taken up with anhydrous CH_2Cl_2 (2.5 mL). In a second flask, a solution of Boc_2O (120 mg, 550 μmol) in anhydrous CH_2Cl_2 (1.5 mL) was treated with DMAP (61.1 mg, 500 μmol) and stirred for 10 min at ambient temp. before the solution of the free base from **17** was added. The reaction mixture was stirred at ambient temp. for an additional 30 min, and the volatile components were evaporated under reduced pressure. Column chromatography of the residue (20 g of silica gel, 1×15 cm column, $CHCl_3$/MeOH, 40:1) yielded **6a** (57 mg, 222 μmol, 44%) as a colorless solid, R_f = 0.37. IR (KBr): $\tilde{\nu}$ = 3239 cm^{-1} (N–H), 3113 (C–H), 2863 (C–H), 1696 (C=O), 1584, 1443, 1232, 854, 685. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.60–0.68 (m, 2 H, Cpr-H), 1.69–1.79 (m, 2 H, Cpr-H), 3.57 (s, 2 H, CH_2N), 5.95 (br. s, 1 H, NH), 7.04–7.08 (m, 2 H, Ar-H), 7.26–7.30 (m, 1 H, Ar-H) ppm. ^{13}C NMR (50.2 MHz, $CDCl_3$, APT): δ = 8.6 (–, Cpr-C), 43.6 (–, Cpr-C), 47.7 (–, CH_2N), 127.9 (+, Ar-C), 127.9 (+, Ar-C), 135.2 (–, Ar-C), 136.8 (–, Ar-C), 160.9 (–, CO) ppm. MS (EI): *m*/*z* (%) = 260/258/256 (3:23:40) [M+], 216/214/212 (2:9:14), 180/178 (9:34) [$ClArNC_3H_4CH_2^+$], 149/147/145 (2:12:21) [Cl_2Ar^+], 97 (71) [$C_3H_4CH_2NHCO^+$], 84 (100) [$HNCH_2C_3H_4NH^+$]. $C_{11}H_{10}Cl_2N_2O$ (257.12): calcd. C 51.39, H 3.92, Cl 27.58, N 10.90; found C 51.23, H 3.74, Cl 27.33, N 10.77. **Variant B:** The crude dihydrochloride **17** [152 mg, 500 μmol; obtained from **16** (148 mg, 575 mmol) as indicated above] was dissolved in anhydrous CH_2Cl_2 (50 mL), treated with NEt_3 (281 μL, 2.03 mmol) at 0 °C and stirred for an additional 15 min. Carbonyldiimidazole (81.1 mg, 500 μmol) was added at 0 °C, the resulting mixture was stirred at this temp. for an additional 20 min, warmed to ambient temp. and stirred for an additional 1 d. The reaction mixture was washed with H_2O (30 mL), dried and concentrated in vacuo. Column chromatography of the residue (20 g of silica gel, 1×15 cm column, $CHCl_3$/MeOH, 45:1) yielded **6a** (69 mg, 268 μmol, 54%) as a colorless solid, m.p. 196–198 °C, R_f = 0.33.

4-(3,5-Dichlorophenyl)-*N*-isopropyl-5-oxo-4,6-diazaspiro-[2.4]heptane-6-carboxamide (8a): Column chromatography (25 g of silica gel, 2×25 cm column, hexane/$CHCl_3$, 1:3) of the residue obtained from **6a** (210 mg, 817 μmol), EtMgBr (817 μmol, 303 μL of a 2.70 M solution in Et_2O) and isopropyl isocyanate (100 μL, 1.02 mmol) according to GP2 (3 h stirring) yielded **8a** (267 mg, 780 μmol, 95%) as a colorless solid, m.p. 131–134 °C, R_f = 0.19. An analytical sample was obtained by recrystallization from hexane/CH_2Cl_2. IR (KBr): $\tilde{\nu}$ = 3312 cm^{-1} (N–H), 3063 (C–H), 2976 (C–H), 2895 (C–H), 1702 (C=O), 1672 (C=O), 1569, 1543 (N–CO), 1396 (*i*Pr) ppm. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.52–0.60 (m, 4 H, Cpr-H), 1.17 [d, ^3J = 6.0 Hz, 6 H, $CH(CH_3)_2$], 3.97 (s, 2 H, CH_2N), 4.02 [sept, ^3J = 6.0 Hz, 1 H, $CH(CH_3)_2$], 7.03–7.10 (m, 2 H, Ar-H), 7.31–7.38 (m, 1 H, Ar-H), 7.88 (br. d, ^3J = 7.0 Hz, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, DEPT): δ = 8.8 (–, Cpr-C), 22.9 [+, $CH(CH_3)_2$], 40.5 (C_{quat}, Cpr-C), 42.1 [+, $CH(CH_3)_2$], 48.7 (–, CH_2N), 128.0 (+, Ar-C), 128.9 (+, Ar-C), 135.1 (C_{quat}, Ar-C), 135.5 (C_{quat}, Ar-C), 152.1 (C_{quat}, CO), 156.0 (C_{quat}, CO) ppm. MS (EI): *m*/*z* (%) = 345/343/341 (2:9:13) [M+], 260/258/256 (9:62:100) [M+ – *i*PrNHCO + H], 232/230/228 (9:58:92) [$Cl_2ArNCH_2C_3H_4NH^+$], 97 (94) [$C_3H_4CH_2NHCO^+$], 84 (42) [$HNC_3H_4CH_2NH^+$], 43 (58). $C_{15}H_{17}Cl_2N_3O_2$ (342.22): calcd. C 52.65, H 5.01, Cl 20.72, N 12.28; found C 52.54, H 4.88, Cl 20.90, N 12.08.

***N*,*N*′-Bis[1-(3,5-dichlorophenylamino)cyclopropylmethyl]oxalamide (20):** The crude dihydrochloride **17** [304 mg, 1.00 mmol; obtained from **16** (296 mg, 1.15 mmol) as indicated above] was dissolved in anhydrous THF (10 mL), the solution treated with NEt_3 (380 μL, 2.73 mmol) at 0 °C and the mixture stirred for 15 min. A solution of oxalyl chloride (116 μL, 1.35 mmol) in THF (10 mL) was added at 0 °C over a period of 1 h, the resulting mixture was warmed to ambient temp. and stirred for an additional 2 h. Water (1 mL) was added, and the volatile components were evaporated in vacuo. The residue was triturated with H_2O (8 mL), filtered off and washed successively with water (5 mL), EtOH (5 mL) and Et_2O (5 mL) to yield **20** (179 mg, 347 μmol, 69%) as a pale grey solid, m.p. 245–250 °C (decomp.). IR (KBr): $\tilde{\nu}$ = 3412 cm^{-1} (N–H), 3305 (N–H), 1648 (C=O), 1592 (C=O), 1569, 1518, 1449. ^1H NMR (300 MHz, [D6]DMSO): δ = 0.52–0.63 (m, 4 H, Cpr-H), 0.80–0.93 (m, 4 H, Cpr-H), 3.32 (d, ^3J = 6.2 Hz, 4 H, CH_2N), 6.61 (s, 2 H, NH), 6.62–6.69 (m, 4 H, Ar-H), 6.75–6.85 (m, 2 H, Ar-H), 8.74 (t, ^3J = 6.2 Hz, 2 H, CONH) ppm. ^{13}C NMR (75.5 MHz, [D6]DMSO, APT): δ = 11.7 (–, Cpr-C), 33.2 (–, Cpr-C), 41.7 (–, CH_2N), 110.7 (+, Ar-C), 114.5 (+, Ar-C), 134.0 (–, Ar-C), 149.9 (–, Ar-C), 160.1 (–, CO) ppm. MS (EI): *m*/*z* (%) = 522/520/518/516/514 (<1:2:14:27:18) [M+], 306/304/302 (<1:6:13) [$Cl_2ArNHC_3H_4CH_2NHCOCONH_3^+$], 304/302/300 (6:13:10) [$Cl_2ArNHC_3H_4CH_2NHCOCONH^+$], 261/259/257 (2:9:16) [$Cl_2ArNHC_3H_4CH_2NHCO^+$], 219/217/215 (4:29:100) [$Cl_2ArNHC_3H_4CH_3^+$], 217/215/213 (29:100:100) [$Cl_2ArNC_3H_4CH_2^+$], 204/202/200 (6:45:71) [$Cl_2ArNHC_3H_4^+$], 180/178 (14:35) [$ClArNC_3H_4CH_2^+$], 166/164 (8:16) [$ClArNC_3H_4^+$].

4-(3,5-Dichlorophenyl)-4,7-diazaspiro[2.5]octane-5,6-dione (6b). Variant A: The crude dihydrochloride **17** [152 mg, 500 μmol; obtained from **16** (148 mg, 575 μmol) as indicated above] was dissolved in anhydrous THF (10 mL), treated at 0 °C first with NEt_3 (146 μL, 1.05 μmol) and then with methyl oxalyl chloride (46 μL, 500 μmol). The resulting mixture was stirred at 0 °C for 45 min, warmed to ambient temp. and stirred for an additional 2.5 h. Water (0.5 mL) was added, and all volatile components were evaporated under reduced pressure. The residue was filtered through a pad of silica gel (8 g, eluent $CHCl_3$/MeOH, 50:1), and the filtrate was concentrated in vacuo to yield crude **19b** (149 mg, 470 μmol) as a yellow oil. This oxalic acid ester was dissolved in THF/H_2O (4 mL/2 mL) and the mixture cooled to 0 °C. LiOH (56 mg, 2.35 mmol) was added in one portion, and the resulting mixture was stirred at 0 °C for 15 min, warmed to ambient temp. and stirred for an additional 1 h. The volatile components were evaporated under reduced pressure, the residue was dissolved in H_2O (10 mL), and the pH was brought to 1–2 using an aq 2 M HCl solution. The aqueous phase was extracted with Et_2O (3×20 mL), the combined organic phases were dried and concentrated under reduced pressure to yield the crude *N*-[1-(3,5-dichlorophenylamino)cyclopropylmethyl]oxalamic acid (121 mg, 399 μmol). This acid was dissolved in anhydrous CH_2Cl_2 (20 mL), treated with $SOCl_2$ (35 μL, 479 μmol) and DMF (1 drop). The reaction mixture was heated under reflux for 2.5 h, cooled to ambient temp. and concentrated in vacuo. The residual crude {[1-(3,5-dichlorophenylamino)cyclopropylmethyl]-amino}oxoacetyl chloride was taken up with anhydrous MeCN (20 mL), the mixture treated with imidazole (68 mg, 998 μmol) and stirred at ambient temp. for 2 h and at 80 °C for an additional 16 h. The reaction mixture was cooled to ambient temp., treated with H_2O (0.1 mL) and concentrated under reduced pressure. Column chromatography of the residue (20 g of silica gel, 1×20 column,

$CHCl_3$/MeOH, 20:1) yielded **6b** (25 mg, 87.7 μmol, 18%) as a yellow oil. **Variant B:** The crude dihydrochloride **17** [304 mg, 1.00 mmol; obtained from **16** (296 mg, 1.15 mmol) as indicated above] was suspended in CH_2Cl_2 (5 mL), the mixture treated with an aq. 1 M NaOH solution (3.5 mL) and stirred vigorously for 5 min. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic phases were dried and concentrated to a volume of 5 mL. Boc_2O (218 mg, 1.00 mmol) was added in one portion, and the reaction mixture was stirred for 15 h. All volatile components were removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (8 mL), the solution cooled to 0 °C and treated first with NEt_3 (146 μL, 1.05 mmol) and then with methyl oxalyl chloride (93 μL, 1.00 mmol). The reaction mixture was warmed to ambient temp. and stirred for 2 h. Water (0.1 mL) was added, and all volatile components were removed under reduced pressure. The residue was filtered through a pad of silica gel (5 g, eluent $CHCl_3$/MeOH, 50:1), the filtrate was concentrated under reduced pressure, and the residue was taken up with CH_2Cl_2 (2 mL). TFA (0.2 mL) was added, and the resulting mixture was stirred for 45 min at ambient temp. All volatile compounds were evaporated in vacuo. A solution of HCl (5 M solution of HCl in *i*PrOH) (2 mL) was added and the reaction mixture was evaporated under reduced pressure. This operation was repeated three times. The residue was dissolved in anhydrous MeOH (10 mL), the mixture treated with NaOMe (54 mg, 1.00 mmol) and stirred for 1 d. The reaction mixture was concentrated in vacuo, and the residue purified by column chromatography (30 g of silica gel, 1.5 × 30 cm column, $CHCl_3$/MeOH, 20:1) to yield **6b** (145 mg, 509 μmol, 51%) as a pale grey solid, m.p. 222–224 °C, R_f = 0.25. IR (KBr): $\tilde{\nu}$ = 3447 cm^{-1} (N–H), 3215 (C–H), 3113 (C–H), 1689 (C=O), 1585, 1571, 1439, 1336, 1317. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.76–0.92 (m, 2 H, Cpr-H), 0.92–1.05 (m, 2 H, Cpr-H), 3.57 (s, 2 H, CH_2N), 7.00–7.10 (m, 2 H, Ar-H), 7.32–7.40 (m, 1 H, Ar-H), 8.20 (br. s, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ = 11.2 (–, Cpr-C), 40.8 (–, Cpr-C), 48.1 (–, CH_2N), 126.9 (+, Ar-C), 128.8 (+, Ar-C), 135.6 (–, Ar-C), 137.8 (–, Ar-C), 158.77 (–, CO), 158.84 (–, CO) ppm. MS (EI): *m*/*z* (%) = 288/286/284 (2:19:27) [M^+], 260/258/256 (1:14:18) [M^+ – CO], 245/243/241 (1:12:20) [M^+ – CONH], 217/215/213 (3:22:37) [$Cl_2ArNC_3H_4CH_2^+$], 180/178 (26:100) [$ClArNC_3H_4CH_2^+$], 163/161/159 (17:40:56) [Cl_2ArN^+], 149/147/145 (4:27:44) [Cl_2Ar^+], 112 (30) [$HNC_3H_4CH_2NHCO^+$], 111/109 (13:34), 97 (39) [$C_3H_4CH_2NHCO^+$], 84 (54) [$HNC_3H_4CH_2NH^+$].

7-(3,5-Dichlorophenyl)-4,7-diazaspiro[2.5]octane-5,6-dione (5b): To a solution of compound **12** (1.32 g, 4.00 mmol) in CH_2Cl_2 (8 mL), kept at 0 °C was added first NEt_3 (582 μL, 4.20 mmol) and then methyl oxalyl chloride (368 μL, 4.00 mmol). The reaction mixture was warmed to ambient temp. and stirred for 2 h. H_2O (0.2 mL) was added and all volatile compounds were evaporated in vacuo. The residue was filtered through silica gel (15 g, 2 × 15 cm, $CHCl_3$/MeOH, 50:1), and the filtrate was concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 (5 mL), the mixture cooled to 0 °C, then treated with TFA (1 mL) and HCl (2 mL each portion) according to GP1. The residue was dissolved in anhydrous MeOH (40 mL), treated with NaOMe (432 mg, 8.00 mmol) and the mixture stirred at ambient temp. for 1 d. After evaporation of all volatile components, H_2O (15 mL) and CH_2Cl_2 (15 mL) were added. The resulting two-phase suspension was stirred for 10 min, filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 mL), the mixture cooled to 0 °C and filtered again. The combined precipitates were dried with P_4O_{10} in vacuo overnight to furnish **5b** (758 mg, 2.66 mmol, 66%) as a colorless solid, m.p. 244–246 °C. IR (KBr): $\tilde{\nu}$ = 3260 cm^{-1} (N–H), 3065 (C–H), 1707 (C=O), 1669 (C=O), 1583, 1575, 1452, 1339, 1128, 845, 674. ^1H NMR (200 MHz, [D_6]DMSO): δ = 0.60–1.00 (m, 4 H, Cpr-H), 3.82 (s, 2 H, CH_2N), 7.42–7.60 (m, 3 H, Ar-H), 9.00 (br. s, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz, [D_6]DMSO, APT): δ = 10.6 (–, Cpr-C), 32.5 (–, Cpr-C), 54.4 (–, CH_2N), 123.5 (+, Ar-C), 125.9 (+, Ar-C), 133.8 (–, Ar-C), 143.0 (–, Ar-C), 157.2 (–, CO), 157.8 (–, CO) ppm. MS (EI): *m*/*z* (%) = 288/286/284 (10:65:100) [M^+], 260/258/256 (3:23:37) [M^+ – CO], 245/243/241 (5:39:66) [M^+ – CONH], 232/230/228 (2:17:28) [M^+ – 2CO], 149/147/145 (2:14:22) [Cl_2Ar^+], 41 (72) [$C_3H_5^+$]. $C_{12}H_{10}Cl_2N_2O_2$ (285.13): calcd. C 50.55, H 3.53, N 9.82; found C 50.26, H 3.76, N 9.77.

7-(3,5-Dichlorophenyl)-6-ethyl-6-hydroxy-4,7-diazaspiro[2.5]octan-5-one (21a) and 7-(3,5-Dichlorophenyl)-5-ethyl-5-hydroxy-4,7-diazaspiro[2.5]octan-6-one (21b): Column chromatography (15 g of silica gel, 1 × 15 cm column, $CHCl_3$) of the residue obtained from 5b (285 mg, 1.00 mmol), EtMgBr (1.00 mmol, 370 μL of a 2.7 M solution in Et_2O) and isopropyl isocyanate (122 μL, 1.25 mmol) according to GP2 (2 h stirring) yielded a mixture of **21a** and **21b** (97 mg, 308 μmol, 31%) in a ratio of 6.5:1[27] as the only product. **21a and 21b:** Colorless solid, R_f = 0.47. IR (KBr): $\tilde{\nu}$ = 3376 cm^{-1} (N–H, O–H), 3353 (N–H, O–H), 3083 (C–H), 2979 (C–H), 2936 (C–H), 2876 (C–H), 1676 (C=O), 1579, 1522. ^1H NMR (300 MHz, $CDCl_3$, major isomer): δ = 0.85–0.98 (m, 4 H, Cpr-H), 1.07 (t, ^3J = 7.5 Hz, 3 H, CH_3), 2.92 (q, ^3J = 7.5 Hz, 2 H, CH_2CH_3), 3.18 (s, 2 H, CH_2N), 4.50 (br. s, 1 H, OH), 6.35–6.46 (m, 2 H, Ar-H), 6.70–6.75 (m, 1 H, Ar-H), 7.39 (br. s, 1 H, NH) ppm. ^1H NMR (300 MHz, $CDCl_3$, minor isomer): δ = 0.68–0.78 (m, 4 H, Cpr-H), 1.00–1.13 (m, 3 H, CH_3), 2.85–2,95 (m, 2 H, CH_2CH_3), 3.65 (s, 2 H, CH_2N), 6.58–6.64 (m, 2 H, Ar-H), 6.78–6.84 (m, 1 H, Ar-H) ppm. The signal of the OH proton could not be assigned. ^{13}C NMR (75.5 MHz, $CDCl_3$, APT, HSQC, major isomer): δ = 7.0 (+, CH_2CH_3), 12.8 (–, Cpr-C), 30.1 (–, CH_2CH_3), 32.1 (–, Cpr-C), 51.4 (–, CH_2N), 110.6 (+, Ar-C), 116.9 (+, Ar-C), 135.4 (–, Ar-C), 149.5 (–, Ar-C), 161.7 (–, COH), 199.4 (–, CO) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, APT, HMQC, minor isomer): δ = 7.0 (+, CH_2CH_3), 11.1 (–, Cpr-C), 30.1 (–, CH_2CH_3), 34.6 (–, Cpr-C), 55.3 (–, CH_2N), 116.1 (+, Ar-C), 120.0 (+, Ar-C), 135.5 (–, Ar-C), 148.9 (–, Ar-C), 161.7 (–, COH), 199.4 (–, CO) ppm. MS (EI): *m*/*z* (%) = 318/316/314 (7:61:100) [M^+], 261/259/257 (8:50:77) [M^+ – C_3H_5O], 233/231/229 (1:14:22) [M^+ – CO – C_3H_5O], 178/176/174 (10:18:33) [$Cl_2ArNCH_3^+$], 96 (33), 57 (35) [$C_3H_5O^+$].

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[1] a) The Chemistry of the Cyclopropyl Group (Ed.: Z. Rappoport), Wiley, Chichester, **1987**; b) Carbocyclic Three-Membered Ring Compounds, Methods of Organic Chemistry (Houben-Weyl), vol. E17a–c (Ed.: A. de Meijere), Thieme, Stuttgart, **1997**.

[2] a) C. J. Suckling, *Angew. Chem.* **1988**, *100*, 555–570; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 537–552; b) S. Abele, P. Seiler, D. Seebach, *Helv. Chim. Acta* **1999**, *82*, 1559–1571; See also: c) J.-F. Tocanne, *Tetrahedron* **1972**, *28*, 389–416; d) M. Pelissier, A. Serafini, J. Devanneaux, J.-F. Labarre, J.-F. Tocanne, *Tetrahedron* **1971**, *27*, 3271–3284.

[3] Reviews: a) J. Salaün, M. S. Baird, *Curr. Med. Chem.* **1995**, *2*, 511–542; b) J. Salaün, *Top. Curr. Chem.* **2000**, *207*, 1–67; c) J. Pietruszka, *Chem. Rev.* **2003**, *103*, 1051–1070; d) L. A. Wessjohann, W. Brandt, T. Thiemann, *Chem. Rev.* **2003**, *103*, 1625–1647.
[4] T. Fujita, *J. Med. Chem.* **1973**, *16*, 923–930.
[5] a) D. M. Campoli-Richards, J. P. Monk, A. Price, P. Benfield, P. A. Todd, A. Ward, *Drugs* **1988**, *35*, 373–447; b) R. Wise, J. M. Andrews, L. J. Edwards, *Antimicrob. Chemoter.* **1983**, *23*, 559–564.
[6] a) K. E. Brighty, WO Patent 91/02526, **1991**; EU Patent 413,455, **1991**, *Chem. Abstr.* **1991**, *115*, 232216; b) K. E. Brighty, US Patent 5,164,402, 1992, *Chem. Abstr.* **1993**, *119*, 117227; c) K. E. Brighty, M. J. Castaldi, *Synlett* **1996**, 1097–1099; d) E. Vilsmaier, T. Goerz, *Synthesis* **1998**, 739–744.
[7] *Recent Advances in the Chemistry of Insect Control* (Ed.: N. F. Janes), Royal Society of Chemistry, London, **1985**.
[8] a) M. Sauli (Rhône–Poulenc S. A.), Ger. Offen 2,149,923, **1972**, *Chem. Abstr.* **1972**, *77*, 19647; b) Rhône–Poulenc S. A., FR Patent 2,148,868, **1973**, *Chem. Abstr.* **1973**, *79*, 78805; c) L. Lacroix, M. Laurent, M. Buys in *Anal. Methods Pestic. Plant Growth Regul.* (Ed.: G. Zweig), Academic Press **1980**, *11*, 247–261.
[9] P. Jeschke, K. Moriya, R. Lantzsch, H. Seifert, W. Lindner, K. Jelich, A. Göhrt, M. E. Beck, W. Etzel, *Pflanzenschutz-Nachrichten Bayer* **2001**, *54*, 147–160.
[10] F. Brackmann, D. S. Yufit, J. A. K. Howard, M. Es-Sayed, A. de Meijere, *Eur. J. Org. Chem.* **2004**, 600–609.
[11] a) A. de Meijere, *Angew. Chem.* **1979**, *91*, 867–884; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 809–826; b) *Methods of Organic Chemistry (Houben-Weyl), vol. E 17c* (Ed.: A. de Meijere), Thieme, Stuttgart, **1997**.
[12] a) Z. Hell, Z. Finta, W. Dmowski, F. Faigl, Yu. M. Pustovit, L. Toke, V. Harmat, *J. Fluorine Chem.* **2000**, *104*, 297–302; b) Y. Kimura, S. Atarashi, M. Takahashi, I. Hayakawa, *Chem. Pharm. Bull.* **1994**, *42*, 1442–1454; c) T. N. Wheeler, J. A. Ray, *Synth. Commun.* **1988**, *18*, 141–150; d) M. P. Wentland, R. B. Perni, P. H. Dorff, J. B. Rake, *J. Med. Chem.* **1988**, *31*, 1694–1697; e) J. S. Kiely, M. C. Schroeder, J. C. Sesnie, *J. Med. Chem.* **1988**, *31*, 2004–2008.
[13] C. Pérollier, J. Pécaut, R. Ramasseul, J.-C. Marchon, *Bull. Soc. Chim. Fr.* **1997**, *134*, 517–523.
[14] K. Kawakami, H. Takahashi, H. Ohki, K. Kimura, S. Miyauchi, R. Miyauchi, M. Takemura, *Chem. Pharm. Bull.* **2000**, *48*, 1667–1672.
[15] A. B. Reitz, M. G. Goodman, B. L. Pope, D. C. Argentieri, S. C. Bell, L. E. Burr, E. Chourmouzis, J. Come, J. H. Goodman, D. H. Klaubert, B. E. Maryanoff, M. E. Mc Donnell, M. S. Pampulla, M. R. Schott, R. Chen, *J. Med. Chem.* **1994**, *37*, 3561–3578.
[16] a) U. Valcavi, A. Brandt, G. B. Corsi, S. Innocenti, F. Minoja, G. Pascucci, *Il Farmaco* **1980**, *35*, 563–572; b) I. Tapia, L. Alonso-Cires, P. L. López-Tudanca, R. Mosquera, L. Labeaga, A. Innerárity, A. Orjales, *J. Med. Chem.* **1999**, *42*, 2870–2880; c) W. H. Pirkle, K. A. Simmons, *J. Org. Chem.* **1983**, *48*, 2520–2527.
[17] M. Shi, Y.-M. Shen, *Heteroatom Chem.* **2001**, *12*, 610–616.
[18] a) F. Y. Kwong, A. Klapars, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 581–584; b) M. Wolter, G. Nordmann, G. E. Job, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 973–976.
[19] a) R. Bolton, C. Moore, J. P. B. Sandall, *J. Chem. Soc. Perkin Trans. 2* **1982**, 1593–1598; b) A. Ohno, A. Tsutsumi, N. Yamazaki, M. Okamura, Y. Mikata, M. Fujii, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1679–1685.
[20] The composition of this mixture was estimated by integrating the signals in the ^{1}H-NMR spectrum.
[21] Reviews: a) O. Mitsunobu, *Synthesis* **1981**, 1–28; b) D. L. Hughes, *Org. React.* **1992**, *42*, 335–656; c) D. L. Hughes, *Org. Prep. Proced. Int.* **1996**, *28*, 127–164.
[22] H. Wolff, *Org. React.* **1947**, *3*, 307–336.
[23] H. Bayley, D. N. Standring, J. R. Knowles, *Tetrahedron Lett.* **1978**, 3633–3634.
[24] a) H.-J. Knölker, T. Braxmeier, G. Schlechtingen, *Angew. Chem.* **1995**, *107*, 2746–2749; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2497–2500; b) H.-J. Knölker, T. Braxmeier, *Tetrahedron Lett.* **1998**, *39*, 9407–9410.
[25] a) G. Hervé, H. Bernard, L. Toupet, H. Handel, *Eur. J. Org. Chem.* **2000**, 33–36; b) F. Bellouard, F. Chuburu, N. Kervarec, L. Toupet, S. Triki, Y. Le Mest, H. Handel, *J. Chem. Soc. Perkin Trans. 1* **1999**, 3499–3506; c) U. T. Mueller-Westerhoff, M. Zhou, *J. Org. Chem.* **1994**, *59*, 4988–4992.
[26] E. E. Korshin, L. I. Sabirova, T. A. Ziablikova, I. E. Isamaev, Y. A. Levin, *Russ. Chem. Bull.* **1994**, *43*, 439–444.
[27] The assignment of the regioisomers is uncertain.
[28] a) B. E. Blass, M. Drowns, C. L. Harris, S. Liu, D. E. Portlock, *Tetrahedron Lett.* **1999**, *40*, 6545–6547; b) J. Yamawaki, T. Ando, *Chem. Lett.* **1979**, 755–758.
[29] For other preparations of this acid see ref. [11c] and also: a) M. Suzuki, E. E. Gooch, C. H. Stammer, *Tetrahedron Lett.* **1983**, *24*, 3839–3840; b) P. Aufranc, J. Ollivier, A. Stolle, C. Bremer, M. Es-Sayed, A. de Meijere, J. Salaün, *Tetrahedron Lett.* **1993**, *34*, 4193–4196; c) M. C. Pirrung, J. Cao, J. Chen, *J. Org. Chem.* **1995**, *60*, 5790–5794; d) M. Kordes, H. Winsel, A. de Meijere, *Eur. J. Org. Chem.* **2000**, 3235–3245.

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