A New and Productive Route to 1-Heteroarylcyclopropanols[‡]

Vladimir N. Belov,[a,b] Andrei I. Savchenko,[a] Viktor V. Sokolov,[a] Alexander Straub,[c][‡‡] and Armin de Meijere*[a,b]

Dedicated to Professor Henry Shine on the occasion of his 80th birthday

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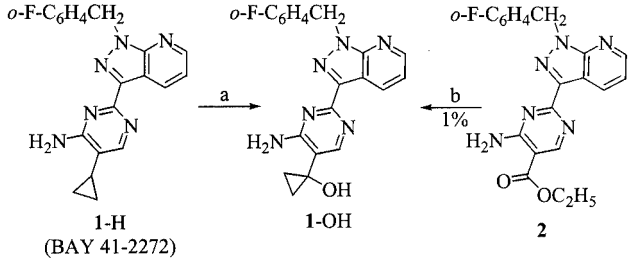
(*E*/*Z*)-2-(1-Allyloxycyclopropyl)-3-methoxyacrylonitrile (**4**-All) was designed and prepared in five steps (58% overall yield) from ethyl cyclopropylidenacetate as a valuable precursor to various 1-heteroarylcyclopropanols. Its condensation with amidines, guanidine, hydrazine, and methyl thioglycolate and subsequent removal of the allyl protecting group yields 1-heteroarylcyclopropanols such as **1**-OH (36% over 2 steps), a very potent NO-independent stimulator of soluble guanylate cyclase. Direct cleavage of the allyl ether protecting group [by palladium-catalyzed substitution with lithium *p*-toluenesulfinate in AcOH or treatment with *c*-HexMgBr/Ti(O*i*Pr)$_4$] gives highly functionalized, sterically congested 1-heteroarylcyclopropanols **29**, **30**, and **34** with intact amino and ester groups.

Introduction

The recent discovery that a particular 1-heteroarylcyclopropanol (**1**-OH) is a potent new NO-independent stimulator of the soluble guanylate cyclase (sGC) has triggered an interest in the development of a viable synthesis of this compound and of functionally substituted 1-heteroarylcyclopropanols in general, because of their potential physiological activities.[1] Compound **1**-OH was first isolated from rat hepatocyte suspensions after administration of the cyclopropyl-substituted 4-aminopyrimidine derivative **1**-H (BAY 41-2272), which had been developed as a most promising stimulator of sGC.[2] It was found that the long-lasting oral activity of BAY-2272 is partially due to its main metabolite **1**-OH, which displayed strong hypotensive activity in vivo (rats and dogs). Its first synthesis was achieved,[3] albeit in a poor yield of less than 1%, by reductive cyclopropanation of the ester **2** with the Kagan reagent (Sm/CH_2I_2), by application of Imamoto's procedure.[4]



Scheme 1. Isolation of 1-hetarylcyclopropanol **1**-OH, a main metabolite of BAY 41-2272 in rats and dogs;[1] reagents and conditions:[3] a) rat hepatocytes (in vivo); b) Sm/CH_2I_2, THF, 50 °C, 70 min; 1 M HCl; RP18 chromatography, 1%

In order to enable extensive biological tests to be conducted, it was essential to make this compound **1**-OH available in larger quantities by a productive total synthesis.

Results and Discussion

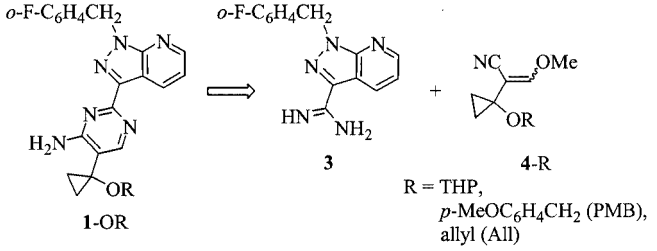
A survey of the literature found only three reports concerning the formation of 1-heteroarylcyclopropanols.[5] 2-

[‡] Cyclopropyl Building Blocks in Organic Synthesis, 84. Part 83: A. de Meijere, Andrei Leonov, Thomas Heiner, Mathias Noltemeyer, M. Teresa Bes, *Eur. J. Org. Chem.*, **2003**, in press. Part 82: T. Voigt, H. Winsel, A. de Meijere, *Synlett* **2002**, 1362–1364.

[a] Institut für Organische Chemie, Georg-August-Universität Göttingen,
Tammannstrasse 2, 37077 Göttingen, Germany
Fax: (internat.) + 49-(0)551/399475
E-mail: Armin.deMeijere@chemie.uni-goettingen.de
[b] KAdemCustomChem GmbH,
Brombeerweg 13, 37077 Göttingen, Germany
Fax: (internat.) + 49-(0)551/23423
[c] Institute of Medicinal Chemistry, Pharma Research Center, BAYER AG,
42096 Wuppertal, Germany
[‡‡] Current address: BAYER Cropscience, Bldg. 6550,
40789 Monheim, Germany
Fax: (internat.) + 49-(0)2173/384880
E-mail: alexander.straub.as@bayer-ag.de

Alkanoylpyridines and -pyrazines, 4-alkanoylpyrimidines, and 3-isopentanoylpyridazine undergo isomerization of their $ArCOCH_2CH_2R$ fragments upon irradiation, to give 1-arylcyclopropanol fragments through diradical intermediates. However, this did not appear to be a viable process for the preparation of reasonable quantities of pure 1-heteroarylcyclopropanols such as **1**-OH, especially since it is limited to 2-alkanoyl-substituted N-heterocycles. The Kulinkovich reaction, which constitutes an excellent route to 1-alkylcyclopropanols from aliphatic carboxylates,[6,7] failed to yield **1**-OH from the corresponding ethyl carboxylate **2**.

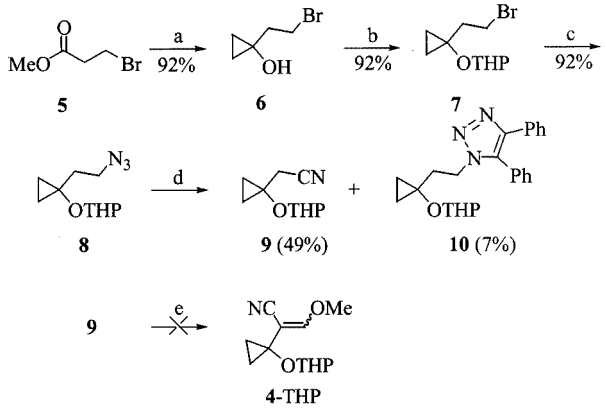
Another obvious synthetic strategy, designed on the basis of the known reactions between 3-methoxyacrylonitriles and 1,3-dinucleophiles,[8] requires the heteroamidine **3**[2,3] and an appropriately protected 2-(1-hydroxycyclopropyl)-3-methoxyacrylonitrile **4**-R as key intermediates. These should yield, through a condensation reaction, the protected cyclopropanol **1**-OR, and its subsequent deprotection should provide **1**-OH (Scheme 2).



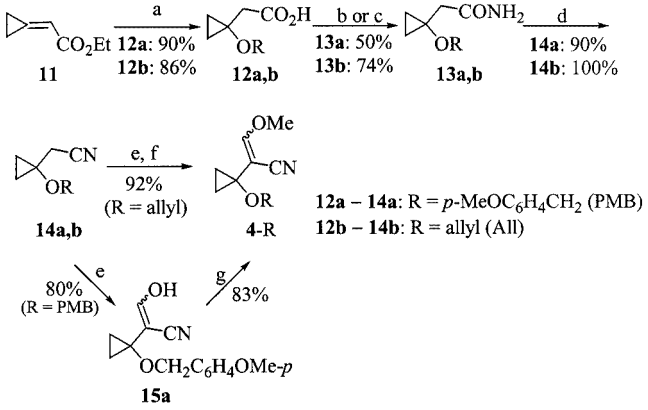
Scheme 2. Synthetic strategy for the construction of 1-hetarylcyclopropanol **1**-OH

Since cyclopropanols are reasonably stable towards acid,[9] the first choice of protecting group was the tetrahydropyranyl (THP) moiety. It was therefore attempted to prepare the building block **4**-THP from methyl 3-bromopropanoate (**5**, Scheme 3). Conversion of **5** into the cyclopropanol **6** was achieved in high yield by use of the EtMgBr/Ti(O*i*Pr)$_4$ reagent.[10] After protection of **6** with dihydropyran under standard conditions,[9d] the resulting substituted THP ether **7** was transformed into the azidoethyl derivative **8** in very high yield. By adoption of the known procedure[11] with some modifications, the latter could be converted into the nitrile **9**, albeit under drastic conditions and only in moderate yield. Separation of **9** from a small amount of the triazole by-product **10** was achieved by column chromatography. However, all attempts to transform the nitrile **9** into the desired methoxymethylene derivative **4**-THP failed, probably due to the large steric demand of the THP group. This approach is still important, as it may be used for the synthesis of other (1-alkoxycyclopropyl)acetonitriles **14a** and **14b** (Scheme 4) with sterically less demanding ether protecting groups, such as methoxymethyl, methylthiomethyl, 2-(trimethylsilyl)ethoxymethyl, benzyloxymethyl, introduced by treatment of the corresponding chlorides with the cyclopropanol **6**.

An alternative route to (1-alkoxycyclopropyl)acetonitriles **14a** and **14b** − with 4-methoxybenzyl and allyl protecting groups, respectively − was developed (Scheme 4). Michael



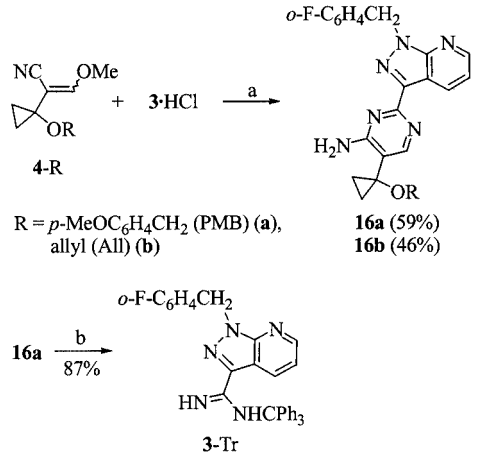
Scheme 3. Attempted synthesis of **4**-THP from methyl 3-bromopropionate: a) EtMgBr (2.2 equiv.), Ti(O*i*Pr)$_4$ (0.1 equiv.), Et_2O/THF, 20 °C, 4 h; b) 3,4-dihydro-2*H*-pyran, py·TsOH, CH_2Cl_2, 0 → 20 °C, 16 h; c) NaN_3, DMF, 75 °C, 4 h; d) diphenylacetylene, 10% Pd/C, *p*-xylene, reflux, 6 h; e) KH, HCO_2Me, THF, 0 → 20 °C; $(MeO)_2SO_2$, 18-crown-6, 20 → 50 °C



Scheme 4. Synthesis of the main building blocks **4**-R: a) ROH, NaH, 20 °C, 4 h; b) $SOCl_2$, CH_2Cl_2, reflux, 2 h; concd. aq. NH_3 (**13a**); c) *N*,*N*′-carbonyldiimidazole, THF, 25 °C, 2.5 h; NH_4OAc, 20 °C, 16 h (**13b**); d) TFAA/py, CH_2Cl_2, 0 → 20 °C, 16 h; e) KH, HCO_2Me, THF, 0 → 20 °C, 3 h; f) $(MeO)_2SO_2$, 18-crown-6, 0 → 50 °C; g) NaH, THF, room temp., 2 h, then $(MeO)_2SO_2$, 40 °C, 2 h

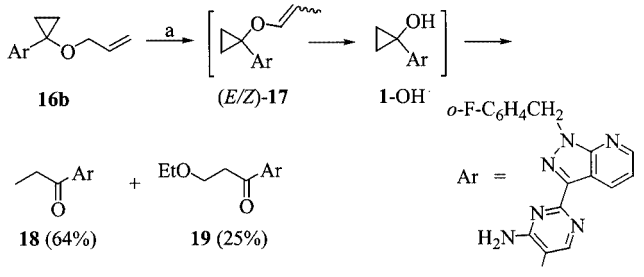
addition of 4-methoxybenzyl alcohol or allyl alcohol to ethyl cyclopropylideneacetate (**11**)[12] and hydrolysis of the ester group afforded the (1-alkoxycyclopropyl)acetic acids **12a** and **12b**. Their conversion into the amides **13a** and **13b** was accomplished by activation with *N*,*N*′-carbonyldiimidazole, followed by treatment with NH_4OAc. Conventional transformation of **12a** into the acyl chloride ($SOCl_2$) and subsequent treatment with NH_3 was found to give a significantly lower yield of **13a** when this reaction was carried out on a larger scale. Dehydration of the amides **13a** and **13b** to provide the nitriles **14a** and **14b** proceeded quantitatively under conditions described by Della et al.[13] The subsequent two-step sequence − condensation with methyl formate and KH, followed by methylation with dimethyl sulfate − also worked well and afforded the desired building blocks **4**-R. A one-pot operation without isolation of the enol **15b** was found to be superior, especially when the methylation was performed in the presence of 18-crown-6. *O*-Methylation of the enols **15** enhances the reactivity of

the α,β-unsaturated nitrile fragment towards nucleophiles. While the attempted direct condensation of the enol **15a** with the amidine **3** failed to yield any product, heating of **4**-PMB or **4**-All with **3** and sodium ethoxide in ketone-free ethanol furnished the desired (1-alkoxycyclopropyl)pyrimidines **16a** and **16b** in good yields (Scheme 5). To go to completion, these reactions required 1.4−1.8 equiv. of the amidine **3** and 36 h heating under reflux.



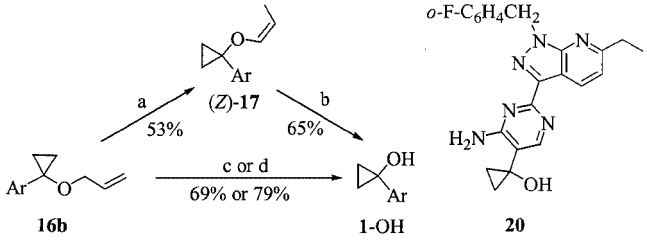
Scheme 5. Synthesis of the *O*-protected precursors **16a** and **16b** of the metabolite **1**-OH: a) EtOH, EtONa, reflux, 20 h; b) Ph_3CBF_4 (2 equiv.), CH_2Cl_2, room temp., 16 h; reflux, 5 h

All attempts to deprotect the *p*-methoxybenzyl ether **16a** and to obtain the metabolite **1**-OH failed. Oxidative deprotection either left the starting compound intact (DDQ, CH_2Cl_2/H_2O), or, when Ph_3CBF_4 was used as a reagent, destroyed the pyrimidine ring and yielded *N*-triphenylmethylated amidine **3**-Tr (Scheme 5). Attempted hydrogenolysis at ambient pressure in the presence of 34% Pd/C (10% Pd) in MeOH/THF left the starting compound **16a** intact. Isomerization of the allyl ether group in **16b** into the propenyl ether turned out to be difficult. Treatment with the Wilkinson catalyst $(Ph_3P)_3RhCl$ failed to give any product. The deprotection method of Scheffold et al. (Pd/C, EtOH, 1 M aq. HCl, reflux)[14] resulted in opening of the cyclopropane ring, and gave 1-arylpropanone **18** and 1-aryl-3-ethoxypropanone **19** (Scheme 6). The experiment thus gave indirect evidence that the cyclopropanol **1**-OH had been formed.



Scheme 6. Opening of the cyclopropanol ring during deprotection of the allyl ether **16b**: a) 10% Pd/C, EtOH, 1 M aq. HCl, reflux, 40 h

Eventually, the desired isomerization of **16b** to the propenyl ether (*Z*)-**17** was achieved by a classical method, by treatment with potassium *tert*-butoxide in DMSO at 85−95 °C (Scheme 7). In accordance with Warren et al.,[15] 2 equiv. of *t*BuOK per equivalent of the starting compound were necessary to bind the "active" H. The propenyl ether (*Z*)-**17** was isolated by chromatography on neutral Al_2O_3. Final deprotection was effected by gentle heating of **17** in dilute methanolic HCl, and so the desired metabolite **1**-OH was obtained in an overall yield of 34% over both steps. After considerable optimization, an even better yield (69%) was achieved by direct cleavage of the allyl ether **16b** with the $RMgBr/Ti(OiPr)_4$ reagent recently recommended by Cha et al. for the cleavage of allyl ethers under mild conditions.[16] The ethyl-substituted by-product **20** was formed when ethylmagnesium bromide was used in this deprotection. However, this alkylation did not occur with cyclohexylmagnesium bromide.

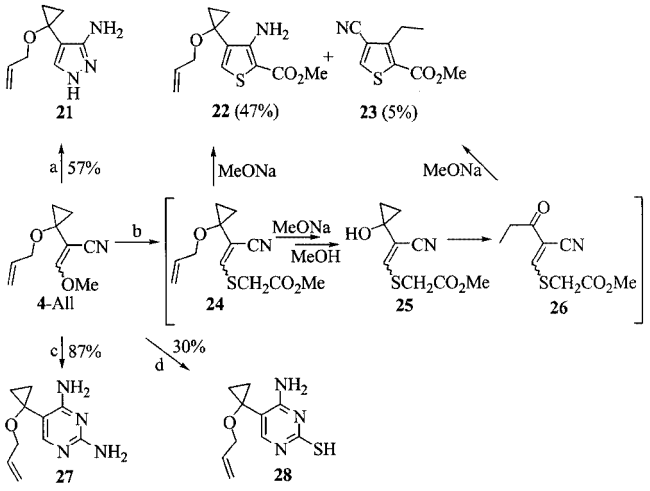


Scheme 7. Synthesis of the metabolite **1**-OH by deprotection of the allyl ether **16b**: a) *t*BuOK (2 equiv.), DMSO, 85−95 °C, 1.5 h; b) 0.5 M aq. HCl, MeOH, 55−60 °C, 1.5 h; c) THF/diethyl ether, *c*HexMgBr (1 equiv.), $Ti(OiPr)_4$ (1 equiv.), then *c*HexMgBr (4 equiv.), 10 → 20 °C, 3 h; d) $PdCl_2$ (1 equiv.), AcONa, AcOH, *p*-$MeC_6H_4SO_2Li$ (2.6 equiv.), $Pd(Ph_3P)_4$ (13 mol %), 50 °C, 90 min

The highest yield of the metabolite **1**-OH was obtained when the allyloxy group was removed in the presence of 100 mol % of $PdCl_2$ with sodium acetate and 13 mol % of $Pd(Ph_3P)_4$ in glacial acetic acid with lithium *p*-toluenesulfinate (as a scavenger for the allyl group) at 50 °C. The reaction was complete within 1.5 h, and no cyclopropyl ring-opening product was found. This combination of two known procedures was found to be efficient, while neither $PdCl_2$/AcONa in AcOH,[17] nor $Pd(Ph_3P)_4$ in AcOH with[18] or without[19] a stoichiometric amount of *p*-toluenesulfinic acid removed the allyl group in **16b** at 50 °C, and higher temperatures were found to cause opening of the cyclopropanol ring. The obvious disadvantage of this method − the high consumption of palladium − may be tolerated if the molecular weight of the starting allyl ether is high or the reaction is run on a small scale. However, an advantage is that acetic acid is used as a solvent. Unlike tetrahydrofuran or diethyl ether as used in Cha's procedure,[16] acetic acid easily dissolves most nitrogen heterocycles and thus facilitates the deprotection reaction.

Appropriate conditions for effective cleavage of the allyloxy group in the protected cyclopropanol **16b** having been found, further heterocyclization reactions of 3-methoxyacrylonitrile **4**-All aimed at the preparation of other 1-heteroarylcyclopropanols were studied. Well-known con-

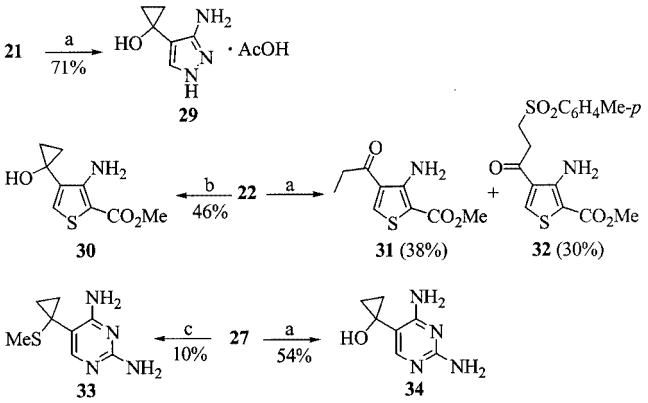
densations of 2-substituted 3-hydroxy-, 3-alkoxy-, or 3-tosyloxyacrylonitriles with 1,2-dinucleophiles (hydrazine,[20] hydroxylamine,[21] and methyl thioglycolate[22]) and 1,3-dinucleophiles (guanidine[8a−8c,8e−8h] and thiourea[8d]) afforded various five- and six-membered heterocycles, though in variable yields. In the case of **4**-All, treatment with a large excess of anhydrous hydrazine gave 3-aminopyrazole **21** in 57% yield (Scheme 8). Heating of **4**-All in the presence of 1 equiv. of hydroxylamine hydrochloride with sodium methoxide in methanol did not produce the expected isoxazole. Condensation of **4**-All with methyl thioglycolate gave the desired thiophene **22** as the main product, together with methyl 4-cyano-3-ethylthiophene-2-carboxylate (**23**). The formation of the two products **22** and **23** may be explained by assuming that the reaction proceeds via the intermediate **24**. A similar intermediate was isolated on treatment of methyl thioglycolate with 2-benzyl-3-tosyloxyacrylonitrile.[22f] The direct cyclization of this intermediate **24** yields aminothiophene **22** as the main product, while the allyloxy group may isomerize to some extent under the influence of sodium methoxide during the prolonged heating in methanol, giving the propenyl ether. Methanolysis of the latter should yield cyclopropanol **25**, which, under the basic conditions, undergoes ring-opening to the ketone **26**. An intramolecular aldol condensation of this ketone then provides the cyanothiophenecarboxylate **23** (Scheme 8).



Scheme 8. Condensation reactions of **4**-All, affording various *O*-allyl ethers of 1-heteroarylcyclopropanols: a) NH_2NH_2, MeOH, reflux, 16 h; b) $HSCH_2CO_2Me$, MeONa, MeOH, reflux, 16 h; c) guanidine·HCl, MeONa, MeOH, reflux, 24 h; d) thiourea, MeONa, MeOH, reflux, 24 h

Treatment of **4**-All with guanidine gave the 2,4-diaminopyrimidine **27** in a very high yield, while under similar conditions thiourea produced only 30% of 4-amino-2-mercaptopyrimidine **28**.

Thanks to the experience obtained during the deprotection of the allyl ether **16b**, cleavage of the allyloxy group in the 3-aminopyrazole derivative **21** was easily achieved, yielding 71% of the corresponding cyclopropanol **29**



Scheme 9. Deprotection of hetarylcyclopropyl allyl ethers: a) $PdCl_2$ (0.6−0.8 equiv.), AcONa, AcOH, $pMeC_6H_4SO_2Li$ (1.1−1.5 equiv.), $Pd(Ph_3P)_4$ (7 mol %), 40 °C, 30−90 min; b) $Ti(OiPr)_4$ (2 equiv.), *c*HexMgBr (6 equiv.), Et_2O, 20 °C, 16 h; c) *t*BuOK (4 equiv.), DMSO, 85−95 °C, 1.5 h

(Scheme 9). Under the same conditions [Pd^{II}/Pd^0, $pMeC_6H_4SO_2Li$ in AcOH at 40 °C), however, none of the expected cyclopropanol was isolated from the thiophene derivative **22**, the two ketones **31** and **32** being obtained instead (Scheme 9). The cyclopropanol **30** or its palladium cyclopropoxide precursor appear to be particularly prone to ring-opening by attack of acetic acid to yield the ketone **31**. The palladium-mediated ring-opening of 1-alkyl- and 1-alkenylcyclopropanols was recently reported by Cha to yield the corresponding α,β-unsaturated ketones.[23] Apparently, Michael addition of the *p*-toluenesulfinate anion, present in the mixture as a scavenger for the allyl group, across the double bond of the intermediately formed α,β-unsaturated ketone may easily explain the formation of the β-arylsulfonyl-substituted ketone **32**. An analogous reaction mode was observed when the allyl ether **16b** was heated in ethanol in the presence of palladium on charcoal and dilute aq. HCl (Scheme 6).

Eventually, the deprotection of the thiophene derivative **22** was successfully accomplished without rearrangement by gradual addition of an excess of cyclohexylmagnesium bromide in the presence of 2 equiv. of titanium tetraisopropoxide at ambient temperature in diethyl ether. The methyl ester group remained intact, even though it was exposed overnight to a sixfold excess of the Grignard reagent. The moderate yield of **30** (46%) may be due to losses of the highly polar product during the workup and chromatography. Probably, this new procedure, modified with respect to that of Cha et al.,[16] should also be usable to cleave any other allyl 1-arylcyclopropyl ethers containing one or more methyl ester group(s) attached to the heterocyclic fragment. However, the allyl 1-hetarylcyclopropyl ethers must be sufficiently soluble in diethyl ether or tetrahydrofuran. Otherwise (e.g., for the 2,4-diaminopyrimidine derivative **27**), the deprotection with cyclohexylmagnesium bromide and titanium tetraisopropoxide does not work.

An attempt to isomerize the allyloxy group in **27** to the propenyl ether by treatment with potassium *tert*-butoxide in DMSO at 85−95 °C was accompanied by decomposition

of the starting material, and only afforded a small isolated amount of 2,4-diamino-5-(1-methylthiocyclopropyl)pyrimidine (**33**), the mode of formation of which is unknown. Eventually, palladium-mediated deprotection of **27** gave the required 1-(2,4-diaminopyrimidin-5-yl)cyclopropanol (**34**) in acceptable yield (54%).

All attempts to deprotect the 1-(4-amino-2-mercaptopyrimidin-5-yl)cyclopropyl ether **28** by any of these procedures failed. The solubility of **28** in tetrahydrofuran is very low, and so the modified procedure similar to that of Cha[16] cannot be used.

Conclusion

Protection of alcohols as allyl ethers is quite common, and many new methods for their cleavage have been developed during the last two decades.[24] Most reported applications have been concerned with carbohydrates. This investigation has shown that 1-heteroarylcyclopropanols can most favorably be prepared through the allyl-protected intermediates. Two efficient cleavage procedures have been elaborated for a variety of allyl 1-hetarylcyclopropyl ethers prepared from (*E*/*Z*)-2-(1-allyloxycyclopropyl)-3-methoxyacrylonitrile (**4**-All).

Experimental Section

General Remarks: Melting points (uncorrected) were determined in capillaries with a Büchi 510 apparatus. NMR spectra were recorded with a Bruker AM 250 instrument at 250 (^{1}H) and 62.9 MHz (^{13}C and DEPT). All spectra were calibrated against tetramethylsilane as an internal standard (δ = 0) or the signals of the residual protons of deuterated solvents: δ = 7.26 for $CHCl_3$, δ = 2.50 for [D_5]DMSO, and δ = 3.30 for [D_3]MeOH. Multiplicities of signals are described as follows: s = singlet, d = doublet, t = triplet, q = quadruplet, quint = quintuplet, m_c = centrosymmetrical multiplet. Coupling constants (*J*) are given in Hz; *J* values in ^{13}C NMR spectra refer to ^{13}C-^{19}F couplings. EI-MS data were recorded with Finnigan MAT 95 and Varian CH 5 spectrometers (70 eV). HRMS data were acquired with a Micromass LCT (TOF MS, electrospray ionization, positive and negative modes). IR: Bruker IFS 66 (FT-IR) spectrophotometer, measured as KBr pellets or oils between KBr plates. Analytical TLC was performed on Macherey−Nagel ready-to-use plates (AluGram Sil G/UV_{254}). Detection was under a UV lamp at 254 nm, development with molybdatophosphoric acid solution (5% in EtOH) or 0.5% aq. $KMnO_4$. Column chromatography: Merck silica gel, grade 60, 230−400 mesh; neutral aluminum oxide (ICN), activity grade III. Elemental analyses were carried out at the Mikroanalytisches Laboratorium des Instituts für Organische Chemie der Georg-August-Universität Göttingen. Solvents were purified by standard procedures. Organic solutions were dried with $MgSO_4$, unless otherwise stated. PE = petroleum ether.

2-{[1-(2-Bromoethyl)cyclopropyl]oxy}tetrahydro-2*H*-pyran (7): Ester **5** (5.01 g, 30.0 mmol) was converted according to the published procedure[10] into cyclopropanol **6** (4.54 g, 92%), which was protected with dihydro-2*H*-pyran in CH_2Cl_2 as described[9d] to give the title compound (7.00 g, 92%) with b.p. 75−85 °C (0.01 Torr, Kugelrohr). ^{1}H NMR ($CDCl_3$): δ = 0.38−0.62 (m, 2 H), 0.68−0.86 (m, 1 H), 0.95−1.14 (m, 1 H), 1.39−1.82 (m, 6 H), 1.82−1.98 (m, 1 H), 2.30−2.52 (m, 1 H), 3.43−3.72 (m, 3 H), 3.78−3.97 (m, 1 H), 4.64−4.78 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.1 (CH_2), 12.5 (CH_2), 20.2 (CH_2), 25.2 (CH_2), 29.8 (CH_2), 31.7 (CH_2), 40.2 (CH_2), 61.1 (C), 63.5 (CH_2), 99.1 (CH) ppm.

2-{[1-(2-Azidoethyl)cyclopropyl]oxy}tetrahydro-2*H*-pyran (8): This compound was synthesized from **7** (7.00 g) in 92% yield (5.35 g) by a known procedure.[11] B.p. 105−108 °C (0.01 Torr, Kugelrohr). ^{1}H NMR ($CDCl_3$): δ = 0.40−0.52 (m, 2 H), 0.73−0.85 (m, 1 H), 0.95−1.06 (m, 1 H), 1.40−1.67 (m, 6 H), 1.70−1.82 (m, 1 H), 2.05−2.17 (m, 1 H), 3.39−3.59 (m, 3 H), 3.83−3.91 (m, 1 H), 4.68−4.71 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.2 (CH_2), 12.5 (CH_2), 20.5 (CH_2), 25.2 (CH_2), 31.8 (CH_2), 35.7 (CH_2), 48.2 (CH_2), 59.6 (C), 63.5 (CH_2), 99.2 (CH) ppm. IR (neat): $\tilde{\nu}$ = 3088 cm^{-1}, 2097. $C_{10}H_{17}N_3O_2$ (211.26): calcd. C 56.85, H 8.11, N 19.89; found C 57.11, H 8.29, N 19.76.

[1-(Tetrahydropyran-2-yloxy)cyclopropyl]acetonitrile (9) and 4,5-Diphenyl-1-(2-{1-[(tetrahydropyran-2-yl)oxy]cyclopropyl}ethyl)-1*H*-1,2,3-triazole (10): Pd/C (600 mg, 10% Pd in the oxidized form, Merck) in *p*-xylene (20 mL) was stirred under H_2 at ambient pressure for 1 h, and the suspension was then heated under reflux under N_2 for 1 h, in order to remove hydrogen adsorbed on the catalyst. A solution of the azide **8** (3.17 g, 15.0 mmol) and diphenylacetylene (3.20 g, 18.0 mmol) in *p*-xylene (4 mL) was then added dropwise to this suspension over 15 min. The mixture was heated under reflux for 6 h and then filtered through Celite®. After the solvent had been removed in vacuo, the oily residue (6.10 g) was purified by chromatography on silica gel (75 g). Elution with PE removed stilbene, and gradient elution with PE/EtOAc (10:1 → 5:1) afforded 1.35 g of the crude title compound, which was distilled (b.p. 100−110 °C at 0.01 Torr in a Kugelrohr) to give pure **9** (1.32 g, 49%). ^{1}H NMR ($CDCl_3$): δ = 0.67−0.77 (m, 2 H), 0.86−0.92 (m, 1 H), 1.08−1.13 (m, 1 H), 1.44−1.80 (m, 6 H), 2.56 (d, *J* = 17.1 Hz, 1 H), 3.12 (d, *J* = 17.1 Hz, 1 H), 3.50−3.60 (m, 1 H), 3.90−4.05 (m, 1 H), 4.77−4.82 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.6 (CH_2), 13.2 (CH_2), 19.5 (CH_2), 25.1 (CH_2), 26.0 (CH_2), 31.2 (CH_2), 58.1 (C), 62.9 (CH_2), 99.5 (CH), 117.9 (C) ppm. IR (neat): $\tilde{\nu}$ = 3089 cm^{-1}, 2247. $C_{10}H_{15}NO_2$ (181.24): calcd. C 66.27, H 8.34; found C 66.10, H 8.45. Elution with EtOAc gave **10** (0.41 g, 7%), which was recrystallized from PE to yield a colorless solid, m.p. 78−79 °C. ^{1}H NMR ($CDCl_3$): δ = 0.25−0.35 (m, 2 H), 0.66−0.76 (m, 1 H), 0.85−0.95 (m, 1 H), 1.20−1.30 (m, 1 H), 1.34−1.95 (m, 5 H), 1.95−2.10 (m, 1 H), 2.15−2.30 (m, 1 H), 3.30−3.40 (m, 1 H), 3.58−3.68 (m, 1 H), 4.40−4.55 (m, 2 H), 4.58−4.62 (m, 1 H), 7.15−7.30 (m, 3 H), 7.35−7.40 (m, 2 H), 7.45−7.60 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.9 (CH_2), 12.2 (CH_2), 19.9 (CH_2), 25.1 (CH_2), 31.5 (CH_2), 36.8 (CH_2), 45.6 (CH_2), 59.2 (C), 63.1 (CH_2), 98.6 (CH), 126.7 (CH), 127.5 (CH), 128.0 (C), 128.3 (CH), 129.1 (CH), 129.5 (CH), 130.1 (CH), 131.0 (C), 133.9 (C), 144.1 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3067, 3000, 2957, 2936, 1457, 1444, 1354, 1210, 1201, 1130, 1119, 1107, 1050, 1030, 998. MS (CI): *m*/*z* (%) = 390 (100) [M + H^+], 368 (12), 284 (14), 102 (18). $C_{24}H_{27}N_3O_2$ (389.50): calcd. C 74.01, H 6.99; found C 74.26, H 7.11.

2-[1-(4-Methoxybenzyloxy)cyclopropyl]acetic Acid (12a): NaH (450 mg of a 60% suspd. in mineral oil, 11.2 mmol) was washed three times with anhydrous pentane and dried in vacuo, and *p*-methoxybenzyl alcohol (19.0 mL, 21.1 g, 0.152 mol) was added dropwise with stirring. After the sodium hydride had dissolved, ethyl cyclopropylideneacetate (**11**,[12] 6.32 g, 50.1 mmol) was added dropwise with stirring and cooling with ice/water over 5 min. The reaction mixture was stirred at ambient temp. for 4 h and diluted

with EtOH (50 mL), and a solution of NaOH (4.0 g, 0.10 mol) in H_2O (20 mL) was added. After the mixture had been stirred for an additional 4 h at room temp., EtOH was evaporated in vacuo, and the residue was mixed with H_2O (50 mL) and extracted with diethyl ether (3 × 30 mL). The aqueous layer was carefully acidified with 1 M aq. HCl, and extracted with diethyl ether (3 × 30 mL). The combined organic solutions were washed with water (20 mL), dried, and concentrated in vacuo to yield the title compound as a yellowish oil, which soon crystallized to a solid with m.p. 71−74 °C. Yield 10.7 g (90%) of **12a**, which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ = 0.69 (m_c, 2 H), 1.01 (m_c, 2 H), 2.68 (s, 2 H), 3.78 (s, 3 H), 4.50 (s, 2 H), 6.85 (m, 2 H), 7.23 (m, 2 H), 10.6 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.5 (CH_2), 39.4 (CH_2), 55.1 (MeO), 58.8 (C−O), 69.1 (CH_2O), 113.2 (CH), 129.8 (C and CH), 159.0 (C), 176.8 (C) ppm. MS (EI): *m*/*z* (%) = 236 (0.4) [M^+], 210 (0.4) [$M^+ - C_2H_2$], 121 (100) [$C_8H_9O^+$].

2-[1-(4-Methoxybenzyloxy)cyclopropyl]acetamide (13a): A solution of the acid **12a** (2.50 g, 10.6 mmol) and $SOCl_2$ (2 mL) in CH_2Cl_2 (30 mL) was heated under reflux for 2 h. The solution was concentrated in vacuo, the yellow residue was dissolved in THF (5 mL), and this solution was added dropwise with ice-cooling and stirring to concd. aq. NH_3 (50 mL). After 30 min, the crude product was filtered off, washed with cold water, dried in air, and recrystallized from diethyl ether with a small amount of *i*PrOH to yield a colorless solid (1.24 g, 50%) with m.p. 118−120 °C. ^{1}H NMR ($CDCl_3$): δ = 0.63 (m_c, 2 H), 1.00 (m_c, 2 H), 2.57 (s, 2 H), 3.79 (s, 3 H), 4.46 (s, 2 H), 5.79 (br. s, 1 H), 6.86 (br. s, 1 H), 6.86 (m, 2 H), 7.24 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.8 (CH_2), 40.1 (CH_2), 55.1 (MeO), 58.5 (C−O), 68.8 (CH_2O), 113.8 (CH), 129.3 (C and CH), 159.2 (C), 173.6 (C) ppm. MS (EI): *m*/*z* (%) = 235 (0.1) [M^+], 121 (100) [$C_8H_9O^+$]. $C_{13}H_{17}NO_3$ (235.28): calcd. C 66.36, H 7.28, N 5.95; found C 65.98, H 7.29, N 5.73.

2-[1-(4-Methoxybenzyloxy)cyclopropyl]acetonitrile (14a): Trifluoroacetic anhydride (0.80 mL, 1.2 g, 5.7 mmol) was added dropwise with stirring over 3 min to a suspension of the amide **13a** (1.21 g, 5.14 mmol) in CH_2Cl_2 (8 mL) and pyridine (1.00 mL, 0. 978 g, 12.4 mmol). The clear solution was stirred overnight at ambient temp., diluted with pentane (50 mL), washed with water (20 mL), 1 M aq. HCl (10 mL), water (10 mL), satd. aq. $NaHCO_3$ (10 mL), and brine (10 mL), and then dried. Evaporation of the organic solvents in vacuo left the almost pure title compound (1.01 g, 90% yield) as an oil, which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ = 0.74 (m_c, 2 H), 1.06 (m_c, 2 H), 2.72 (s, 2 H), 3.80 (s, 3 H), 4.52 (s, 2 H), 6.88 (m, 2 H), 7.24 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.6 (CH_2), 23.9 (CH_2), 55.1 (MeO), 57.9 (C−O), 69.6 (CH_2O), 113.7 (CH), 117.4 (C), 129.1 (CH), 129.4 (C), 159.2 (C) ppm. MS (EI): *m*/*z* (%) = 217 (2) [M^+], 121 (100) [$C_8H_9O^+$].

(*E*/*Z*)-3-Hydroxy-2-[1-(4-methoxybenzyloxy)cyclopropyl]acrylonitrile (15a): Potassium hydride (1.40 g of a 35% susp. in mineral oil, 12.2 mmol) was washed three times with diethyl ether under N_2, and then suspended in THF (13 mL). This suspension was added in small portions, with stirring and cooling with ice, to a solution of methyl formate (3.0 mL, 2.9 g, 49 mmol) and the nitrile **14a** (1.00 g, 4.60 mmol) in THF (13 mL). The reaction mixture was stirred at ambient temperature for 3 h, and water (50 mL) was carefully added, followed by AcOH (ca. 1 mL) until the pH value was 4−5. The mixture was extracted with CH_2Cl_2 (5 × 60 mL), and the combined organic solutions were washed with H_2O (2 × 50 mL), dried, and concentrated in vacuo. The colorless solid was boiled with 20 mL of diethyl ether, pentane (40 mL) was then added, and the mixture was kept overnight at +4 °C. The product was removed by filtration, washed with pentane/diethyl ether (2:1, 5 mL) and dried in air to give a colorless solid (904 mg, 80%) with m.p. 135−137 °C (dec.). ^{1}H NMR ($CDCl_3$/[D_6]DMSO, 10:1; signals of the major isomer are marked with *): δ = 0.60−0.91 (m, 4 H), 3.60 (s, 3 H), 4.21*/4.27 (s, 2 H), 6.66 (d, *J* = 8.4 Hz, 2 H), 7.01−7.05 (m, 2 H), 7.13/7.14* (s, 1 H), 10.62 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$/[D_6]DMSO, 10:1; signals of the major isomer are marked with *): δ = 12.7*/13.6 (CH_2), 54.7 (OMe), 56.0/58.7* (C−O), 68.1*/68.9 (CH_2O), 88.0*/89.2 (CN), 113.0/113.1* (CH), 116.7*/119.8 (C), 128.7*/128.9 (CH), 129.4*/129.7 (C), 158.5 (C), 159.2/160.2* (CH) ppm. IR (KBr): $\tilde{\nu}$ = 3424, 3091, 3039, 2979, 2211, 1657, 1612, 1516, 1249, 1207, 1183, 1081, 1027. MS (EI): *m*/*z* (%) = 245 (1) [M^+], 121 (100) [$C_8H_9O^+$]. HRMS: calcd. for $C_{14}H_{14}NO_3$ [M^+ − H] 244.0974; found 244.0993.

(*E*/*Z*)-3-Methoxy-2-[1-(4-methoxybenzyloxy)cyclopropyl]acrylonitrile (4-PMB). Method A: Compound **15a** (100 mg, 0.408 mmol) in diethyl ether (2 mL) was methylated by addition of an excess of diazomethane in diethyl ether at 0 °C. When the spot corresponding to **15a** was no longer detectable on the TLC plate ($R_f \approx 0.1$, CH_2Cl_2), the solvent was evaporated, and the product was separated from an impurity with $R_f = 0$ by filtering through SiO_2 (1 g) and eluting with CH_2Cl_2. Yield 70 mg (66%) of **4**-PMB as a colorless oil. **Method B:** NaH (248 mg of a 60% susp. in mineral oil, 6.20 mmol) was added in small portions to **15a** (763 mg, 3.11 mmol) in THF (5 mL). The mixture was stirred at ambient temperature for 2 h, $(MeO)_2SO_2$ (0.50 mL, 0.65 g, 5.3 mmol) was added dropwise, and the suspension was heated at 40 °C for 2 h. The excess of NaH was quenched by careful addition of H_2O (0.5 mL), the solvent was evaporated in vacuo, and the residue was dissolved in diethyl ether (20 mL) and washed with water (5 mL). After the mixture had been dried, the solvent was evaporated and the product (667 mg, 83%) was isolated by chromatography on SiO_2 (20 g), eluting with hexane/EtOAc (3:1). ^{1}H NMR ($CDCl_3$, the signals of the major isomer are marked with *): δ = 0.84 (m, 2 H), 1.10 (m, 2 H), 3.78 (s, 3 H), 3.88*/3.89 (s, 3 H), 4.42*/4.44 (s, 2 H), 6.83−6.91 (m, 2 H), 6.94 (s, 1 H), 7.18−7.23 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, signals of the major isomer are marked with *): δ = 13.4*/14.2 (CH_2), 55.2 (OMe), 59.0 (C−O), 61.9*/62.5 (OMe), 69.2*/69.8 (CH_2O), 91.1 (CN), 113.6/113.8* (CH), 129.26*/129.33 (CH) 129.6 (C), 159.2 (C), 163.5 (CH).

2-[1-(Allyloxy)cyclopropyl]acetic Acid (12b): NaH (0.200 g of a 60% susp. in mineral oil, 5.00 mmol) was added in small portions at 0 °C with stirring to a solution of **11** (2.90 g, 23.0 mmol) in prop-2-en-1-ol (8.00 mL, 6.83 g, 118 mmol). Stirring was continued overnight at ambient temperature. The alcohol was evaporated in vacuo, the residue was dissolved in EtOH (15 mL), and aq. NaOH (30%, 3 mL) was added. After the mixture had been stirred at ambient temp. for 6 h, the volatiles were evaporated in vacuo, water (50 mL) was added, and the alkaline solution was extracted with diethyl ether (2 × 30 mL). The aqueous layer was acidified with 2 M aq. HCl and saturated with solid NaCl. The acid **12b** was extracted with diethyl ether (3 × 50 mL) to give a clear oil (3.10 g, 86%), which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ = 0.67 (m_c, 2 H), 0.93 (m_c, 2 H), 2.62 (s, 2 H), 4.03 (m, 2 H), 5.08−5.28 (m, 2 H), 5.81−5.93 (m, 1 H), 8.3 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.5 (CH_2), 39.5 (CH_2), 59.0 (C−O), 68.6 (CH_2O), 116.7 (CH_2), 134.6 (CH), 176.5 (C) ppm.

2-[1-(Allyloxy)cyclopropyl]acetamide (13b): *N*,*N*′-Carbonyldiimidazole (3.54 g, 21.9 mmol) was added in one portion to a stirred solution of **12b** (3.10 g, 19.9 mmol) in anhydrous THF (22 mL). A vig-

orous reaction with gas evolution was observed after several seconds. After the mixture had been stirred for 2.5 h at 25 °C, NH_4OAc (1.69 g, 22 mmol) was added, and the mixture was stirred overnight. The solvent was removed, and the residual oil was treated with ice/water (15 mL). Aq. HCl (3 M) was added to the slurry of imidazole and the product until the pH was 2. The clear solution, with traces of a solid, was saturated with NaCl at 0 °C. The precipitated product was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine (20 mL) and dried, and the solvents were evaporated. The semi-solid residue was triturated with diethyl ether and hexane, kept for 2 h at 0 °C, and the first crop of the product was filtered off (2.10 g, m.p. 89−90 °C). A second crop (0.17 g) was obtained after the mother liquor had been diluted with hexane and kept at −15 °C. Total yield 2.27 g (74%). ^{1}H NMR ($CDCl_3$): δ = 0.56 (m_c, 2 H), 0.92 (m_c, 2 H), 2.48 (s, 2 H), 3.99 (m, 2 H), 5.10, 5.14, 5.19 and 5.25 (4 m_c, 2 H), 5.77−5.90 (m, 1 H), 6.1 (br. s, 1 H), 6.8 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.6 (CH_2), 40.2 (CH_2), 58.6 (C−O), 67.9 (CH_2O), 116.9 (CH_2), 134.2 (CH), 173.8 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3349, 3174, 3094, 3014, 2856, 1668, 1634, 1460, 1414, 1302, 1262, 1175, 1137, 1117, 1048, 1026. $C_8H_{13}NO_2$ (155.19): calcd. C 61.91, H 8.44, N 9.02; found C 61.77, H 8.13, N 9.07.

2-[1-(Allyloxy)cyclopropyl]acetonitrile (14b): Compound **14b** was prepared from **13b** (2.00 g, 12.9 mmol) and trifluoroacetic anhydride (1.97 mL, 2.96 g, 14.2 mmol) as described for **14a**, in quantitative yield (1.80 g) and as an oil (R_f = 0.3 on SiO_2 with CH_2Cl_2 as eluent); it was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ = 0.72 (m_c, 2 H), 1.02 (m_c, 2 H), 2.74 (s, 2 H), 4.07 (m, 2 H), 5.14, 5.19, 5.25 and 5.32 (4 m_c, 2 H), 5.80−5.93 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.6 (CH_2), 24.0 (CH_2), 58.2 (C−O), 69.0 (CH_2O), 116.9 (CH_2), 117.4 (CN), 134.2 (CH) ppm.

(*E*/*Z*)-2-[1-(Allyloxy)cyclopropyl]-3-methoxyacrylonitrile (4-All): KH (3.98 g of a 35% susp. in mineral oil, 34.8 mmol) was washed with anhydrous benzene (3 ×) and suspended in THF. This suspension was added in small portions at 0 °C and under N_2 to a stirred solution of methyl formate (8.50 mL, 8.25 g, 0.138 mol) and **14b** (1.80 g, 13.1 mmol) in THF (30 mL). The mixture was stirred at ambient temperature until the evolution of H_2 ceased, and 18-crown-6 (0.3 g) was added, followed by $(MeO)_2SO_2$ (1.05 mL, 1.40 g, 11.1 mmol). The suspension was stirred at ambient temperature for an additional 1 h, and then at 40 °C for 2 h. It was then filtered, and the filtrate was concentrated in vacuo, diluted with diethyl ether (100 mL), washed with water (15 mL) and brine (20 mL), and dried. TLC (CH_2Cl_2/MeOH, 20:1) revealed only 2 UV-active, closely positioned spots, $R_f \approx 0.8$. Concentration left an oil (2.15 g, 92%), which according to the NMR spectra was the title compound with traces of 18-crown-6 (δ = 3.95 ppm) as an impurity. This substance was used in the condensation reactions without further purification. ^{1}H NMR ($CDCl_3$, the signals of a major isomer are marked with *): δ = 0.82 (m, 2 H), 1.06 (m, 2 H), 3.88*/3.89 (s, 3 H, MeO), 3.98*/4.00 (m_c, 2 H, CH_2O), 5.10−5.28 (m, 2 H, CH_2=), 5.80−5.96 (m, 1 H, CH=), 6.89/6.92* (s, 1 H, CH=) ppm. ^{13}C NMR ($CDCl_3$, the signals of a major isomer are marked with *): δ = 13.3*/14.1 (CH_2), 58.5*/58.9 (OMe), 61.9*/62.6 (C−O), 68.3*/69.0 (CH_2O), 91.1 (CN), 115.9/116.7* (C), 116.8 (CH_2), 134.2*/134.5 (CH), 162.8/163.3* (CH) ppm.

3-(4-Amino-5-{1-[(4-methoxybenzyl)oxy]cyclopropyl}pyrimidin-2-yl)-1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-b]pyridine (16a): A solution of EtONa (1.04 M, 4 mL) was added to a solution of **3**·HCl (1.28 g, 4.18 mmol) and **4**-PMB (0.585 g, 2.26 mmol) in anhydrous ketone-free EtOH (20 mL). The mixture was heated under reflux with stirring under N_2 for 20 h, and the solvent was evaporated in vacuo. The thick precipitate was suspended in water/diethyl ether (1:1, 15 mL), and aq. HCl (1 M) was added dropwise with stirring at 0 °C until the pH of the aqueous layer reached 7. The precipitate was removed, washed with cold water (10 mL), dried, and crystallized from anhydrous EtOH (40 mL). The first crop (0.45 g of the pure **16a**) had m.p. 191−193 °C. A second crop (0.21 g) contained a very small amount of **3**·HCl as an impurity. Total yield 0.66 g (59%). ^{1}H NMR ($CDCl_3$): δ = 0.97 (m_c, 2 H), 1.21 (m_c, 2 H), 3.74 (s, 3 H, OMe), 4.30 (s, 2 H, OCH_2), 5.93 (s, 2 H, CH_2N), 6.01 (br. s, 2 H, NH_2), 6.81 (d, *J* = 8.0 Hz, 2 H), 6.92−7.19 (m, 4 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 7.26 (dd, *J* = 4.5 and 7.5 Hz, 1 H, 5-H), 8.28 (s, 1 H, 6′-H), 8.58 (dd, *J* = 1.5 and 4.5 Hz, 1 H, 4-H), 8.94 (dd, *J* = 1.5 and 8.0 Hz, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.8 (CH_2), 44.7 (d, *J* = 5.2, NCH_2), 55.2 (OMe), 59.0 (C−O), 69.7 (CH_2O), 113.4 (C-3a), 113.8 (CH in PMB), 115.2 (C-5′′ in the pyrimidine ring), 115.2 (CH, d, *J* = 21.4, C-3′), 118.2 (CH, C-5), 124.1 (d, *J* = 14.5, C-1′), 124.1 (CH, d, *J* = 3.8, C-5′), 129.0 (CH, d, *J* = 4.4, C-4′ or C-6′), 129.1 (d, *J* = 8.8, C-6′ or C-4′), 129.4 (C in PMB), 129.8 (CH in PMB), 133.1 (CH, C-4), 141.7 (C-3), 149.2 (CH, C-6), 151.5 (C-7a), 154.0 (CH in the pyrimidine ring), 159.3 (C), 160.1 (C), 160.1 (d, *J* = 247, CF), 169.9 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3487, 3281, 3150, 1631, 1586, 1543, 1514, 1491, 1475, 1438, 1287, 1247, 1228, 1166, 1094, 1036. MS (ESI, positive ions): *m*/*z* (%) = 993 (12) [2 M + H^+], 519 (13) [M + Na^+], 497 (100) [M + H^+]. $C_{28}H_{25}FN_6O_2$ (496.55): calcd. C 67.73, H 5.07, N 16.92; found C 67.74, H 5.17, N 16.98.

3-{5-[1-(Allyloxy)cyclopropyl]-4-aminopyrimidin-2-yl}-1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridine (16b): Compound **16b** was prepared as described for **16a**, starting from **4**-All (2.10 g, 11.7 mmol) and **3**·HCl (5.12 g, 16.7 mmol) in anhydrous ketone-free EtOH (40 mL), to which EtONa (1.04 M, 16 mL) was added. Crystallization from anhydrous EtOH yielded the pure title compound (1.80 g) with m.p. 193−194 °C. A second crop (0.44 g) of **16b** was obtained after chromatographic purification of the residue from the mother liquor on Al_2O_3 (100 g), eluting with CH_2Cl_2. Total yield 2.24 g (46%). ^{1}H NMR ($CDCl_3$): δ = 0.96 (m_c, 2 H), 1.20 (m_c, 2 H), 3.89 (dt, *J* = 5.7 and 1.3 Hz, 2 H, OCH_2), 5.08, 5.13, 5.15 and 5.21 (4 m_c, 2 H, CH_2=), 5.74−5.89 (m, 3 H, NH_2, CH=), 5.96 (s, 2 H, NCH_2), 6.89−7.07 (m, 3 H), 7.14−7.21 (m, 1 H), 7.24 (dd, *J* = 4.5 and 8.1 Hz, 1 H, 5-H), 8.23 (s, 1 H, 6′-H), 8.58 (dd, *J* = 1.5 and 4.5 Hz, 1 H, 4-H), 8.94 (dd, *J* = 1.5 and 8.0 Hz, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.8 (CH_2), 44.7 (d, *J* = 5.1, NCH_2), 59.1 (C−O), 68.9 (CH_2O), 113.3 (C-3a), 115.23 (CH, d, *J* = 21.1, C-3′), 115.25 (C-5′′ in the pyrimidine ring), 117.3 (CH_2=), 118.2 (CH, C-5), 124.08 (CH, d, *J* = 3.6, C-5′), 124.13 (d, *J* = 14.5, C-1′), 128.9 (CH, d, *J* = 3.8, C-4′ or C-6′), 129.1 (d, *J* = 7.9, C-6′ or C-4′), 133.2 (CH, C-4), 134.1 (CH=), 141.7 (C-3), 149.2 (CH, C-6), 151.6 (C-7a), 154.0 (CH in the pyrimidine ring), 160.1 (C), 160.1 (d, *J* = 247, CF), 163.0 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3481, 3282, 3154, 3017, 1632, 1585, 1544, 1491, 1478, 1288, 1229. MS (EI): *m*/*z* (%) = 416 (39) [M^+], 387 (100) [M^+ − Et], 347 (32), 109 (82) [$C_7H_6F^+$]. $C_{23}H_{21}FN_6O$ (416.46): calcd. C 66.33, H 5.08, N 20.18; found C 65.82, H 5.04, N 20.12.

Treatment of 16a with Trityl Tetrafluoroborate To Yield Compound 3-Tr: A solution of the *p*-methoxybenzyl ether **16a** (115 mg, 0.232 mmol) and Ph_3CBF_4 (148 mg, 0.448 mmol) in anhydrous CH_2Cl_2 (15 mL) was stirred overnight at ambient temp., and then heated under reflux for 5 h. It was diluted with CH_2Cl_2 (25 mL), washed with sat. aq. $NaHCO_3$ (10 mL), dried, and concentrated, and the residue was placed on Al_2O_3 (20 g, activity grade II). Elution with CH_2Cl_2 gave **3**-Tr (R_f = 0.2, 102 mg, 87%) as a white

foam. Crystallization from EtOH/CH_2Cl_2 gave an analytical sample with m.p. 186 °C. ^{1}H NMR ($CDCl_3$, two isomers in a ratio of ca. 5:1, the signals of the major one are marked *): δ = 4.82 (br. s, 2 H, NH_2), 5.63*/5.66 (s, 2 H, NCH_2), 6.92−7.08 (m, 3 H), 7.13−7.28 (m, 12 H), 7.38−7.42 (m, 5 H), 8.47/8.51* (dd, *J* = 1.8 and 4.6 Hz, 1 H, 6′-H), 8.59/8.89* (br. d/dd, *J* = 8.0/1.8 and 8.0, 1 H) ppm. IR (KBr): ṽ = 3478, 3377, 3052, 3028, 1638, 1586, 1571, 1483, 1446, 1296, 1264, 1236, 1171, 1133, 1031, 1016. MS (EI): *m*/*z* (%) = 511 (100) [M^+], 497 (17), 418 (16), 258 (22), 243 (57) [Ph_3C^+], 182 (23), 165 (22), 109 (16). $C_{33}H_{26}FN_5$ (511.61): calcd. C 77.47, H 5.12, N 13.69; found C 77.74, H 5.26, N 13.44.

3-(4-Amino-5-propanoylpyrimidin-2-yl)-1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridine (18) and 3-[4-Amino-5-(3-ethoxypropanoyl)-pyrimidin-2-yl]-1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridine (19): Pd/C (30 mg, 10% Pd in the oxidized form, Merck) in EtOH (6 mL) was saturated with hydrogen by passing a slow stream of H_2 through the suspension for 2 h. The mixture was heated under reflux under Ar for 2 h, and **16b** (110 mg, 0.264 mmol) was then added, followed by aq. HCl (1 M, 0.5 mL), and heating was continued for 40 h. The catalyst was removed by filtration, washing with hot EtOH (30 mL), and the solvent was evaporated. The residue was separated on Al_2O_3 (50 g) eluting with CH_2Cl_2. The substance (75 mg) with the same R_f value as the starting material (0.8, CH_2Cl_2/MeOH, 60:1) turned out to be a 1:2 mixture (molar ratio) of **16b** and **18**. Crystallization from EtOH gave the pure compound **18** (45 mg) with m.p. 219−220 °C in 64% yield (based on converted **16b**). ^{1}H NMR ($CDCl_3$): δ = 1.24 (t, *J* = 7.2 Hz, 3 H), 3.00 (q, *J* = 7.2 Hz, 2 H), 5.97 (s, 2 H, NCH_2), 6.11 (br. s, 1 H, NH), 6.95−7.08 (m, 3 H), 7.15−7.30 (m, 2 H), 8.60 (dd, *J* = 1.5 and 4.5 Hz, 1 H, 4-H), 8.82 (br. s, 1 H, NH), 8.91 (dd, *J* = 1.5 and 8.0 Hz, 1 H, 6-H), 9.04 (s, 1 H, 6′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 8.3 (CH_3), 31.7 (CH_2), 45.0 (d, *J* = 2.6, NCH_2), 110.0 (C-3a), 115.3 (CH, d, *J* = 21.4, C-3′), 115.6 (C-5′′ in the pyrimidine ring), 118.7 (CH, C-5), 123.8 (C, d, *J* = 14.5, C-1′), 124.1 (d, *J* = 3.8, C-5′), 129.1 (CH, d, *J* = 3.8, C-4′ or C-6′), 129.2 (d, *J* = 6.9, C-6′ or C-4′), 133.1 (CH, C-4), 140.9 (C-3), 149.4 (CH, C-6), 151.6 (C-7a), 159.6 (CH in the pyrimidine ring), 160.1 (d, *J* = 247, CF), 162.4 (C), 200.9 (C) ppm. MS (EI): *m*/*z* (%) = 376 (100) [M^+], 347 (42) [M^+ − Et], 281 (9), 226 (10), 109 (38). The substance with the lower R_f value (0.7, CH_2Cl_2/MeOH, 60:1) was identified as **19** (21 mg), yield 25% (based on converted **16b**), m.p. 174 °C (dec., EtOH). ^{1}H NMR ($CDCl_3$): δ = 1.19 (t, *J* = 7.0 Hz, 3 H), 3.23 (t, *J* = 6.3 Hz, 2 H), 3.54 (q, *J* = 7.0 Hz, 2 H), 3.85 (t, *J* = 6.3 Hz, 2 H), 5.97 (s, 2 H, NCH_2), 6.13 (br. s, 1 H, NH), 6.92−7.08 (m, 3 H), 7.15−7.30 (m, 2 H), 8.59 (dd, *J* = 1.5 and 4.5 Hz, 1 H, 4-H), 8.80 (br. s, 1 H, NH), 8.92 (dd, *J* = 1.5 and 8.0 Hz, 1 H, 6-H), 9.06 (s, 1 H, 6′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.8 (CH_3), 38.7 (CH_2), 45.0 (d, *J* = 5.3, NCH_2), 65.5 (CH_2O), 66.6 (CH_2O), 110.4 (C-3a), 115.3 (CH, d, *J* = 19.5, C-3′), 115.7 (C-5′′ in the pyrimidine ring), 118.7 (CH, C-5), 123.8 (C, d, *J* = 14.5, C-1′), 124.1 (d, *J* = 3.8, C-5′), 129.1 (CH, d, *J* = 3.8, C-4′ or C-6′), 129.3 (d, *J* = 8.2, C-6′ or C-4′), 133.1 (CH, C-4), 140.8 (C-3), 149.4 (CH, C-6), 151.6 (C-7a), 160.1 (CH in the pyrimidine ring), 160.1 (d, *J* = 247, CF), 162.5 (C), 198.5 (C) ppm.

(*Z*)-3-(4-Amino-5-{1-[(1-propenyl)oxy]cyclopropyl}pyrimidin-2-yl)-1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridine [(*Z*)-17]: *t*BuOK (224 mg, 2.00 mmol) was added under N_2 at ambient temp. to a solution of **16b** (416 mg, 1.00 mmol) in anhydrous DMSO (4.5 mL), and the mixture was heated at 90 °C for 1.5 h. After cooling, it was diluted with ice/water (15 mL) and extracted with EtOAc (3 × 50 mL). The resulting brown solution was washed with water (10 mL) and brine (10 mL) and dried. Chromatography on Al_2O_3, eluting with CH_2Cl_2/MeOH (100:1), gave (*Z*)-**17** (220 mg, 53%) as a colorless solid, which was used in the last step without further purification. ^{1}H NMR ($CDCl_3$): δ = 1.03 (m_c, 2 H), 1.29 (m_c, 2 H), 1.51 (dd, *J* = 6.9 and 1.8 Hz, 3 H), 4.49 (quint, *J* = 6.7, 1 H, CH=), 5.79 (s, 2 H, NH_2), 5.96 (s, 2 H, NCH_2), 6.05 (dq, *J* = 6.3 and 1.7 Hz, 1 H, OCH=), 6.92−7.10 and 7.18−7.28 (2 m, 5 H, 5-H and 4 H in *o*-FC_6H_4), 8.26 (s, 1 H, 6′-H), 8.58 (dd, *J* = 1.6 and 4.5 Hz, 1 H, 4-H), 8.94 (dd, *J* = 1.6 and 8.0 Hz, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 9.2 (CH_3), 11.4 (CH_2), 44.7 (d, *J* = 5.1, NCH_2), 59.8 (C−O), 104.4 (CH=), 113.3 (C-3a), 115.20 (CH, d, *J* = 21.1, C-3′), 115.23 (C-5′′ in the pyrimidine ring), 118.2 (CH, C-5), 123.9 (d, *J* = 3.6, C-1′), 124.1 (CH, d, *J* = 3.8, C-5′), 128.9 (CH, d, *J* = 3.8, C-4′ or C-6′), 129.1 (d, *J* = 7.9, C-6′ or C-4′), 133.2 (CH, C-4), 134.1 (CH=), 141.6 (C-3), 142.0 (OCH=), 149.2 (CH, C-6), 151.5 (C-7a), 154.0 (CH in the pyrimidine ring), 160.1 (d, *J* = 247, CF), 160.2 (C) ppm. MS (EI): *m*/*z* (%) = 416 (19) [M^+], 414 (59), 362 (48), 347 (95), 321 (30), 251 (16), 226 (12), 109 (100).

(*Z*)-3-[4-Amino-5-(1-hydroxycyclopropyl)pyrimidin-2-yl]-1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridine (Metabolite 1-OH). Hydrolysis of the Propenyl Ether (*Z*)-17: Aq. HCl (0.5 M, 2.0 mL, 1.0 mmol) was added to a suspension of (*Z*)-**17** (220 mg, 0.529 mmol) in MeOH (2 mL), and the mixture was heated at 55 °C for 1.5 h. At first, (*Z*)-**17** dissolved, and the product **1**-OH then precipitated gradually. Most of the methanol was evaporated, the residue was neutralized with aq. NaOH (1 M), and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, Al_2O_3 (20 g) was added, and the solvent was evaporated. CH_2Cl_2 was added to the residue, and the suspension was concentrated to dryness once more. The residue was placed on a column prepacked with Al_2O_3 (100 g) and eluted with CH_2Cl_2/MeOH (50:1). The crude product was isolated as a colorless solid (170 mg). Recrystallization from MeOH gave the pure metabolite **1**-OH (130 mg, 65%), m.p. 208−213 °C. The product was in all respects identical to the material isolated from rat hepatocyte suspensions.[1] ^{1}H NMR ([D_4]MeOH): δ = 0.93 (m_c, 2 H), 1.07 (m_c, 2 H), 5.87 (s, 2 H, NCH_2), 7.03−7.13 (m, 3 H), 7.14−7.21 (m, 1 H), 7.24 (dd, *J* = 4.5 and 8.1 Hz, 1 H, 5-H), 8.14 (s, 1 H, H-6′), 8.56 (dd, *J* = 1.5 and 4.5 Hz, 1 H, 4-H), 9.04 (dd, *J* = 1.5 and 8.0 Hz, 1 H, 6-H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 12.8 (CH_2), 44.2 (d, *J* = 3.8, NCH_2), 51.6 (C−O), 114.8 (C-3a), 115.7 (CH, d, *J* = 20.7, C-3′), 117.1 (C-5′′ in the pyrimidine ring), 118.5 (CH, C-5), 124.2 (d, *J* = 14.5, C-1′), 124.8 (CH, d, *J* = 3.8, C-5′), 130.1 (CH, d, *J* = 7.5, C-4′ or C-6′), 130.3 (d, *J* = 4.4, C-6′ or C-4′), 133.5 (CH, C-4), 141.7 (C-3), 149.4 (CH, C-6), 151.0 (C-7a), 152.8 (CH in the pyrimidine ring), 158.9 (C), 160.1 (d, *J* = 247, CF), 163.0 (C) ppm. IR (KBr): ṽ = 3482, 3288, 3155, 3017, 1632, 1545, 1491, 1458, 1230. MS (EI): *m*/*z* (%) = 376 (100) [M^+], 347 (39) [M^+ − Et], 281 (10) [M^+ − C_5H_5NO], 226 (9), 109 (40) [$C_7H_6F^+$]. $C_{20}H_{17}FN_6O$ (376.40): calcd. C 63.82, H 4.55; found C 63.66, H 4.52.

Direct Cleavage of Allyl Ether 16b with Grignard Reagents in the Presence of Ti(O*i*Pr)$_4$: A solution of cyclohexylmagnesium bromide in diethyl ether (1.9 M, 0.58 mL, 1.1 mmol) was added at 10 °C to a solution of **16b** (434 mg, 1.04 mmol) in THF (25 mL), followed by Ti(O*i*Pr)$_4$ (304 mg, 1.07 mmol). The dropwise addition of cyclohexylmagnesium bromide was then continued at 10 °C until 2.32 mL (4.41 mmol) had been added over 1 h, and the mixture was then stirred for an additional 2 h. It was poured into a 1:1 mixture of brine and cold water (50 mL), the aqueous mixture was extracted with EtOAc (4 × 80 mL), and the combined organic layers were washed with brine and dried. After evaporation of the

solvent, the solid residue was treated successively with pentane (2 × 5 mL), pentane/diethyl ether (1:1, 5 mL), and diethyl ether (5 mL) in an ultrasound bath to get rid of dicyclohexyl as the main impurity. Crystallization from MeOH afforded **1**-OH [R_f = 0.14 (hexane/EtOAc) or 0.23 (hexane/EtOAc/EtOH, 4:1:0.5, 270 mg, 69%]. A lower yield of **1**-OH (44%) was observed in an analogous experiment with ethylmagnesium bromide in place of cyclohexylmagnesium bromide. Compound **20** was isolated as a by-product in 12% yield after chromatographic purification of the crude product. **20**: R_f = 0.31 (hexane/EtOAc/EtOH, 4:1:0.5), m.p. 168−171 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 0.85 (m$_c$, 2 H), 1.00 (m$_c$, 2 H), 1.29 (t, *J* = 7.5 Hz, 3 H), 2.92 (q, *J* = 7.5 Hz, 2 H), 5.77 (s, 2 H, NCH_2), 7.10−7.40 (m, 4 H), 7.26 (d, *J* = 7.4 Hz, 1 H, 5-H), 8.16 (s, 1 H, 6′-H), 8.82 (d, *J* = 7.4 Hz, 1 H, 6-H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 12.7 (CH_2), 13.8 (Me), 31.1 (CH_2), 44.0 (d, *J* = 3.8, NCH_2), 51.6 (C−O), 112.9 (C-3a), 115.7 (CH, d, *J* = 21.4, C-3′), 116.9 (C-5′′ in the pyrimidine ring), 117.9 (CH, C-5), 124.3 (d, *J* = 14.5, C-1′), 124.8 (CH, d, *J* = 3.1, C-5′), 130.1 (CH, d, *J* = 8.2, C-4′ or C-6′), 130.4 (d, *J* = 3.8, C-6′ or C-4′), 133.4 (CH, C-4), 141.5 (C-3), 151.1 (C-7a), 152.8 (CH in the pyrimidine ring), 160.0 (d, *J* = 247, CF), 162.1 (C), 162.8 (C), 163.4 (C) ppm. IR (KBr): ṽ = 3474, 3286, 3154, 1632, 1545, 1492, 1459, 1231.

Palladium-Promoted Cleavage of Allyl Ether 16b: [Pd(Ph$_3$P)$_4$] (8.0 mg, 0.0069 mmol) was added under N_2 to a suspension of **16b** (22.5 mg, 0.054 mmol), $PdCl_2$ (9.6 mg, 0.054 mmol), and NaOAc (10 mg, 0.12 mmol) in AcOH (0.25 mL), followed by lithium *p*-toluenesulfinate (22.4 mg, 0.138 mmol). The reaction mixture was heated with stirring at 50 °C for 1.5 h, EtOAc (5 mL) was added, and the suspension was passed through a fritted glass filter (No. 5). The insoluble residue was washed with EtOAc (3 × 5 mL), the combined filtrates were concentrated to dryness in vacuo, and the residue was subjected to chromatography on Al_2O_3 (20 g), eluting with CH_2Cl_2 to remove the yellow zone of by-products with higher retention indices (allyl *p*-toluenesulfinate and unidentified products); subsequent elution with CH_2Cl_2/MeOH (100:1) gave **1**-OH (16.0 mg, 79%).

4-[1-(Allyloxy)cyclopropyl]-3-amino-1*H*(2*H*)-pyrazole (21): A mixture of **4**-All (400 mg, 2.23 mmol) and anhydrous N_2H_4 (200 mg, 6.25 mmol) in MeOH (3 mL) was heated at 85 °C overnight. The solvent was evaporated, and the residue was subjected to chromatography on SiO_2 (25 g), eluting with CH_2Cl_2/MeOH (15:1), to yield **21** (230 mg, 57%) as a colorless oil, R_f = 0.35−0.40. ^{1}H NMR ($CDCl_3$): δ = 0.76 (m$_c$, 2 H), 1.08 (m$_c$, 2 H), 3.88 (dt, *J* = 5.6 and 1.4 Hz, 2 H, OCH_2), 5.06−5.24 (m, 2 H, CH_2=), 5.78−5.92 (m, 1 H, CH=), 7.16 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.7 (CH_2), 55.0 (C−O), 68.0 (CH_2O), 105.4 (C-4), 116.6 (CH_2=), 130.0 (CH), 134.8 (CH=), 152.8 (C-3) ppm. IR (neat): ṽ = 3429, 3314, 3211, 3089, 3012, 2959, 1611, 1585, 1505, 1408, 1225, 1044. MS (CI): *m*/*z* (%) = 359 (64) [2 M + H$^+$], 197 (38) [M + NH_4^+], 180 (100) [M + H$^+$]. HRMS: found 178.1014, calcd. for $C_9H_{12}N_3O$ [M$^+$ − H]: 178.0980.

Methyl 4-[1-(Allyloxy)cyclopropyl]-3-aminothiophene-2-carboxylate (22) and Methyl 4-Cyano-3-ethylthiophene-2-carboxylate (23): A solution of sodium methoxide (1.52 M, 3 mL, 4.56 mmol) in MeOH was added to a mixture of **4**-All (585 mg, 3.27 mmol) and methyl thioglycolate (0.460 mL, 543 mg, 5.12 mmol). The mixture was heated under reflux overnight. The blue-black reaction mixture was filtered through SiO_2 (2.5 g), the filter cake was washed with CH_2Cl_2 (25 mL), and the filtrate was concentrated in vacuo. The oily residue was subjected to chromatography on SiO_2 (25 g); elution with hexane/EtOAc (5:1) gave **22** (R_f = 0.45, 389 mg, 47%) as a colorless oil, which crystallized to a solid with m.p. 50 °C. ^{1}H NMR ($CDCl_3$): δ = 0.86 (m$_c$, 2 H), 1.12 (m$_c$, 2 H), 3.82 (s, 3 H, OMe), 3.85 (dt, *J* = 5.6 and 1.2 Hz, 2 H, OCH_2), 5.08−5.22 (m, 2 H, CH_2=), 5.78−5.92 (m, 1 H, CH=), 5.99 (br. s, 2 H, NH_2), 7.00 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.2 (CH_2), 51.2 (OMe), 58.6 (C−O), 68.7 (CH_2O), 116.9 (CH_2=), 128.0 (CH, C-5), 130.8 (C-4), 134.3 (CH=), 153.6 (C), 158.0 (C), 164.9 (C) ppm. IR (KBr): ṽ = 3453, 3339, 3077, 3017, 2924, 1675, 1607, 1553, 1476, 1448, 1295, 1217, 1027. MS (EI): *m*/*z* (%) = 253 (39) [M$^+$], 224 (12) [M$^+$ − Et], 184 (24), 180 (37), 170 (100), 152 (38). HRMS: calcd. for $C_{12}H_{15}NO_3S$ 253.0773; found 253.0773. **23**: R_f = 0.40, yield 32 mg (5%) of a colorless oil, which crystallized to a solid with m.p. 35 °C. ^{1}H NMR ($CDCl_3$): δ = 1.38 (t, *J* = 7.6 Hz, 3 H), 3.04 (q, *J* = 7.6 Hz, 2 H), 3.88 (s, 3 H, OMe), 7.76 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.3 (Me), 23.5 (CH_2), 52.5 (OMe), 108.6 (C-3), 113.8 (CN), 131.7 (C-4), 134.0 (CH, C-5), 161.1 (C), 164.8 (C) ppm. IR (KBr): ṽ = 3106, 3063, 2970, 2955, 2229, 1725, 1543, 1446, 1385, 1266, 1205, 1169, 1094, 1066. MS (EI): *m*/*z* (%) = 195 (50) [M$^+$], 180 (100), 164 (59). HRMS: calcd. for $C_9H_9NO_2S$ 195.0354; found 195.0354.

5-[1-(Allyloxy)cyclopropyl]-2,4-diaminopyrimidine (27): A solution of sodium methoxide in MeOH (1.52 M, 3 mL, 4.56 mmol) was added to a solution of **4**-All (460 mg, 2.57 mmol) and guanidine hydrochloride (382 mg, 4.00 mmol) in MeOH (3 mL), and the mixture was heated under reflux overnight. Water (5 mL) was added to the cooled reaction mixture, and the solvents were evaporated in vacuo. The solid residue was suspended in cold water (5 mL), filtered off, washed with cold water, and dried in air to give the title compound **27** (500 mg, 87%) as monohydrate with m.p. 128−129 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 0.71 (m$_c$, 2 H), 0.98 (m$_c$, 2 H), 3.76 (br. d, *J* = 5.3, 2 H, OCH_2), 5.01−5.20 (m, 2 H, CH_2=), 5.73−5.84 (m, 1 H, CH=), 5.98 (s, 2 H, NH_2), 6.1 (br. s, 2 H, NH_2), 7.62 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 11.8 (CH_2), 58.7 (C−O), 67.5 (CH_2O), 103.8 (C-5), 116.2 (CH_2=), 135.6 CH=), 156.3 (CH, C-6), 163.2 (C), 163.4 (C) ppm. IR (KBr): ṽ = 3479, 3440, 3319, 3153, 3017, 2908, 1651, 1633, 1598, 1557, 1465, 1330, 1273, 1218, 1106, 1036. MS (CI): *m*/*z* (%) = 413 (16) [2 M + H$^+$], 207 (100) [M + H$^+$]. $C_{10}H_{14}N_4O{\cdot}H_2O$ (224.26): calcd. C 53.56, H 7.19, N 24.98; found C 53.79, H 7.20, N 25.19.

5-[1-(Allyloxy)cyclopropyl]-4-amino-2-mercaptopyrimidine (28): Sodium methoxide (2.0 mL of a 1.9 M solution in MeOH, 3.8 mmol) was added to a solution of **4**-All (460 mg, 2.57 mmol) and thiourea (342 mg, 4.50 mmol) in MeOH (6 mL), and the mixture was heated under reflux for 24 h. After the mixture had been cooled in an ice bath, glacial acetic acid was added dropwise until the pH value was 5. A precipitate appeared, the suspension was kept at 0 °C for 16 h and filtered, and the crude product was washed with cold water (2 mL) and MeOH (1 mL). After crystallization from aq. EtOH, the title compound **28** (170 mg, 30%) was obtained as a light brown solid (decomp. without melting at > 250 °C). ^{1}H NMR ([D$_6$]DMSO): δ = 0.79 (m$_c$, 2 H), 1.02 (m$_c$, 2 H), 3.80 (br. d, *J* = 5.3, 2 H, OCH_2), 5.03−5.23 (m, 2 H, CH_2=), 5.71−5.86 (m, 1 H, CH=), 6.8 (br. s, 1 H, NH/SH), 7.36 (s, 1 H), 7.8 (br. s, 1 H, NH/SH), 8.0 (br. s, 1 H, NH/SH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 11.8 (CH_2), 58.0 (C−O), 68.1 (CH_2O), 106.1 (C-5), 116.2 (CH_2=), 135.1 (CH=), 141.7 (CH, C-6), 161.8 (C), 179.4 (C) ppm. IR (KBr): ṽ = 3407, 3347, 3093, 3043, 2974, 1659, 1567, 1547, 1296, 1234, 1202, 1171, 1040. MS (CI): *m*/*z* (%) = 224 (100) [M + H$^+$]. HRMS: calcd. for $C_{10}H_{12}N_3OS$ [M$^+$ − H] 222.0701; found 222.0756.

3-Amino-4-(1-hydroxycyclopropyl)-1*H*(2*H*)-pyrazole (29): [Pd(Ph$_3$P)$_4$] (66 mg, 0.057 mmol) and lithium *p*-toluenesulfinate (162 mg, 1.00 mmol) were added under N_2 to a suspension of the

allyl ether **21** (158 mg, 0.882 mmol), $PdCl_2$ (120 mg, 0.677 mmol), and sodium acetate (120 mg, 1.46 mmol) in glacial acetic acid (1 mL), and the mixture was heated with stirring at 40 °C for 40 min. After cooling, it was worked up as described for **1**-OH (Pd-assisted cleavage of **16b**). Chromatography on SiO_2 (20 g), eluting with CH_2Cl_2/MeOH (15:1 → 3:1), gave **29**·AcOH (125 mg, 71%) as an oil. ^1H NMR ([D$_4$]MeOH): δ = 0.78 (m_c, 2 H), 0.96 (m_c, 2 H), 1.96 (s, 3 H), 7.22 (s, 1 H) ppm. ^{13}C NMR ([D$_4$]MeOH): δ = 14.7 (CH_2), 21.6 (Me), 49.0 (C−O), 110.4 (C-4), 131.2 (CH), 155.8 (C-3), 178.9 (C) ppm. IR (KBr): ṽ = 3429, 3335, 3210, 2973, 2935, 1645, 1543, 1399, 1224, 1124, 1035, 1011. MS (EI): *m*/*z* (%) = 139 (36) [M^+], 110 (100) [M^+ − Et], 83 (15), 60 (12). HRMS: found 139.0746, calcd. for $C_9H_9N_3O$: 139.0746.

Methyl 3-Amino-4-propionylthiophene-2-carboxylate (31) and Methyl 3-Amino-4-{3-[(4-methylphenyl)sulfonyl]propanoyl}thiophene-2-carboxylate (32): [$Pd(Ph_3P)_4$] (47 mg, 0.041 mmol) and lithium *p*-toluenesulfinate (99 mg, 0.61 mmol) were added under N_2 to a suspension of **22** (105 mg, 0.415 mmol), $PdCl_2$ (29 mg, 0.16 mmol), and sodium acetate (31 mg, 0.38 mmol) in acetic acid (0.5 mL), and the mixture was heated at 48 °C with stirring. After 45 min, the starting material had not yet been consumed, and two new spots with lower R_f values had appeared on the TLC. After addition of more $PdCl_2$ (25 mg, 0.14 mmol) and sodium acetate (29 mg, 0.35 mmol), the reaction was complete within another 15 min. The mixture was worked up as described for **1**-OH (Pd-assisted cleavage of **16b**). Chromatography on SiO_2 (20 g), eluting with PE/EtOAc (4:1), first gave the ketone **31** (34 mg, 38%) as an oil that soon crystallized to a pale yellow solid, m.p. 100 °C (heptane). ^1H NMR ($CDCl_3$): δ = 1.19 (t, *J* = 7.7 Hz, 3 H), 2.86 (q, *J* = 7.7 Hz, 2 H), 3.83 (s, 3 H), 7.2 (br. s, 2 H, NH_2), 8.01 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 8.2 (Me), 32.7 (CH_2), 51.3 (MeO), 128.3 (C), 138.5 (CH), 154.1 (C), 158.1 (C), 164.4 (C), 196.8 (C) ppm. IR (KBr): ṽ = 3469, 3351, 3078, 2982, 2940, 1671, 1646, 1580, 1520, 1447, 1313, 1244, 1209, 1141, 1087, 1072. MS (EI): *m*/*z* (%) = 213 (96) [M^+], 184 (100) [M^+ − Et], 182 (12), 181 (15), 153 (18), 152 (42). HRMS: calcd. for $C_9H_{11}NO_3S$ 213.0460; found 213.0460. Further elution gave **32** (45 mg, 30%) as a solid with m.p. 175 °C (heptane). ^1H NMR ($CDCl_3$): δ = 2.44 (s, 3 H), 3.29−3.37 (m, 2 H), 3.44−3.52 (m, 2 H), 3.83 (s, 3 H), 7.0 (br. s, 2 H, NH_2), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 8.0 Hz, 2 H), 8.05 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.6 (Me), 32.1 (CH_2), 50.6 (CH_2), 51.4 (MeO), 127.5 (C), 128.0 (CH), 130.0 (CH), 135.8 (C), 139.1 (CH), 145.1 (C), 154.0 (C), 164.2 (C), 190.9 (C) ppm. IR (KBr): ṽ = 3465, 3351, 2950, 1692, 1651, 1597, 1527, 1448, 1301, 1259, 1222, 1148, 1124, 1084. HRMS: *m*/*z* (%) = 367 (100) [M^+], 262 (8), 213 (25), 184 (27), 180 (96), 152 (23). MS (HR-EI): calcd. for $C_{16}H_{17}NO_5S_2$ 367.0548; found 367.0548.

Methyl 3-Amino-4-(1-hydroxycyclopropyl)thiophene-2-carboxylate (30): $Ti(OiPr)_4$ (0.147 mL, 142 mg, 0.500 mmol) was added dropwise with stirring, at room temperature, to a solution of **22** (64 mg, 0.25 mmol) in anhydrous diethyl ether (5 mL). Cyclohexylmagnesium bromide (1.13 mL of 1.33 M solution in THF, 1.5 mmol) was then added very slowly (over ca. 4 h). The product spot was detectable by TLC after ca. 0.6 mL of the Grignard reagent had been added. The dark reaction mixture was stirred overnight at room temperature, satd. aq. NH_4Cl (2 mL) and EtOAc (10 mL) were then added, and the whole mixture was filtered through Celite® (2 mL). The filter cake was washed with EtOAc (3 × 5 mL), the organic layer was separated, and the solvents were evaporated in vacuo. The brown, oily residue was subjected to chromatography on SiO_2 (8 g), eluting with a hexane/EtOAc mixture (2:1), to yield cyclopropanol **30** (24.5 mg, 46%) as a colorless solid, m.p. 102−103 °C (heptane). ^1H NMR ($CDCl_3$): δ = 0.88 (m_c, 2 H), 1.10 (m_c, 2 H), 3.80 (s, 3 H), 5.95 (br. s, 2 H, NH_2), 7.00 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.3 (CH_2), 51.2 (MeO), 52.7 (C−O), 101.2 (C), 126.9 (CH), 134.4 (C), 153.6 (C), 165.0 (C) ppm. IR (KBr): ṽ = 3465, 3396, 3362, 3341, 3089, 2946, 1677, 1646, 1553, 1476, 1451, 1318, 1290, 1237, 1134, 1102, 1020. MS (EI): *m*/*z* (%) = 213 (37) [M^+], 184 (12) [M^+ − Et], 181 (23), 153 (100), 125 (29), 108 (9), 97 (36). HRMS: calcd. for $C_9H_{11}NO_3S$ 213.0460; found 213.0460.

2,4-Diamino-5-[1-(methylthio)cyclopropyl]pyrimidine (33): The allyl ether **27**·H_2O (125 mg, 0.56 mmol) was dried in vacuo at 110 °C for 30 min, until its mass was constant (116 mg). It was dissolved in anhydrous DMSO (2 mL), potassium *tert*-butoxide (252 mg, 2.24 mg) was added, and the solution was stirred at 80 °C under N_2 for 50 min, until the spot corresponding to **27** had disappeared. The reaction mixture was worked up as described above for (*Z*)-**17**. Sulfide **33** (11 mg, 10%) was isolated by column chromatography on SiO_2 (20 g), eluting with EtOAc/MeOH (20:1 → 10:1), m.p. 221 °C (*i*PrOH/heptane). ^1H NMR ([D$_6$]DMSO): δ = 0.92 (m_c, 2 H), 1.00 (m_c, 2 H), 1.93 (s, 3 H), 5.38 (br. s, 2 H, NH_2), 5.83 (br. s, 2 H, NH_2), 7.54 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 13.4 (Me), 14.0 (CH_2), 22.0 (C−S), 106.1 (C), 155.0 (CH), 161.0 (C), 161.3 (C) ppm. IR (KBr): ṽ = 3455, 3434, 3385, 3135, 3023, 2922, 1657, 1635, 1594, 1555, 1467, 1266, 1186, 1032. MS (EI): *m*/*z* (%) = 196 (24) [M^+], 195 (76), 181 (42) [M^+ − Me], 153 (22), 149 (100) [M^+ − MeS]. MS (ESI, positive ions): *m*/*z* (%) = 197 (100) [M + H^+]. HRMS: calcd. for $C_8H_{12}N_4S$ 196.0783; found 196.0783.

2,4-Diamino-5-(1-hydroxycyclopropyl)pyrimidine (34): Compound **27**·H_2O (95 mg, 0.42 mmol) was deprotected by treatment with $PdCl_2$ (43 mg, 0.24 mmol), sodium acetate (43 mg, 0.52 mmol), lithium *p*-toluenesulfinate (76 mg, 0.47 mmol), and $(Ph_3P)_4Pd$ (35 mg, 0.03 mmol) in acetic acid (0.60 mL) at 40 °C as described above for compound **29**. The reaction was complete within 35 min. MeOH (10 mL) was added with stirring to the reaction mixture, which had solidified into a light brown paste, the inorganic salts were removed by filtration, and the filter cake was washed with MeOH (2 × 5 mL). Concentration of the filtrate yielded a yellow solid, which was subjected to chromatography on Al_2O_3 (35 g). Elution with CH_2Cl_2/MeOH (3:1) gave 38 mg (54%) of **34** as a yellowish solid, m.p. 202−203 °C. ^1H NMR ([D$_6$]DMSO): δ = 0.66 (m_c, 2 H), 0.83 (m_c, 2 H), 5.52 (s, 1 H, OH), 5.82 (s, 2 H, NH_2), 6.1 (br. s, 2 H, NH_2), 7.59 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 12.8 (CH_2), 51.4 (C−O), 108.7 (C-5), 154.4 (CH), 162.8 (C), 163.4 (C) ppm. IR (KBr): ṽ = 3435, 3327, 3155, 3081, 3006, 1657, 1635, 1598, 1557, 1464, 1446, 1347, 1209, 1025. MS (EI): *m*/*z* (%) = 166 (23) [M^+], 165 (100), 137 (68) [M^+ − Et], 123 (8), 110 (100). HRMS: calcd. for $C_7H_{10}N_4O$ 166.0855; found 166.0855.

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[1] A. Straub, J. Benet-Buchholz, R. Fröde, A. Kern, C. Kohlsdorfer, P. Schmitt, T. Schwarz, H.-M. Siefert, J.-P. Stasch, *Bioorg. Med. Chem.* **2002**, *10*, 1711−1717.
[2] A. Straub, J.-P. Stasch, C. Alonso-Alija, J. Benet-Buchholz, B. Ducke, A. Feurer, C. Fürstner, *Bioorg. Med. Chem.* **2001**, *11*, 781−784.
[3] A. Straub, A. Feurer, C. Alonso-Alija, E. Stahl, J.-P. Stasch, E.

Perzborn, K. Dembowsky, A. Kern, WO 00/66582, **2000**; *Chem. Abstr.* **2000**, *133*, 350132.
[4] T. Imamoto, T. Hatajima, N. Takiyama, T. Takeyama, Y. Kamija, T. Yoshizawa, *J. Chem. Soc., Perkin Trans. 1* **1991**, 3127−3135.
[5] [5a] E. C. Alexander, R. J. Jackson, *J. Am. Chem. Soc.* **1976**, *98*, 1609−1610. [5b] M. A. Brumfield, W. C. Agosta, *J. Am. Chem. Soc.* **1988**, *110*, 6790−6794. [5c] S. Prathapan, K. E. Robinson, W. C. Agosta, *J. Am. Chem. Soc.* **1992**, *114*, 1838−1843.
[6] O. G. Kulinkovich, S. V. Sviridov, D. A. Vasilevski, *Synthesis* **1991**, 234.
[7] For reviews see: [7a] O. G. Kulinkovich, A. de Meijere, *Chem. Rev.* **2000**, *100*, 2789−2834. [7b] A. de Meijere, S. I. Kozhushkov, A. I. Savchenko, "Titanium-Mediated Syntheses of Cyclopropanols and Cyclopropylamines" in *Titanium and Zirconium in Organic Synthesis* (Ed.: I. Marek), Wiley, New York, **2002**, pp. 390−434.
[8] [8a] B. H. Chase, J. P. Thurston, J. Walker, *J. Chem. Soc.* **1951**, 3439−3446. [8b] P. B. Russel, *J. Am. Chem. Soc.* **1954**, 2951−2955. [8c] H. Takamizawa, *Chem. Pharm. Bull.* **1964**, *12*, 393−396. [8d] C. K. Chu, U. Reichman, K. A. Watanabe, J. J. Fox, *J. Org. Chem.* **1977**, *42*, 711−714. [8e] K.-D. Kampe, *Angew. Chem.* **1982**, *94*, 543−544; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 540−541. [8f] P. S. Manchand, P. Rosen, P. S. Belica, G. V. Oliva, A. V. Perrotta, H. S. Wong, *J. Org. Chem.* **1992**, *57*, 3531−3535. [8g] C. S. Lee, J. Du, C. K. Chu, *Nucleosides Nucleotides* **1996**, *15*, 1223−1236. [8h] G. Barlin, B. Kotecka, K. H. Rieckmann, *Austr. J. Chem.* **1996**, *49*, 647−650.
[9] [9a] U. Schöllkopf, J. Paust, *Chem. Ber.* **1966**, *99*, 777−783. [9b] J. Paust, U. Schöllkopf, *Angew. Chem.* **1965**, *77*, 262; *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 246. [9c] J. Ollivier, J. Salaün, *Tetrahedron Lett.* **1984**, *25*, 1269−1272. [9d] J. Salaün, Y. Almirantis, *Tetrahedron* **1983**, *39*, 2421−2428.
[10] S. V. Sviridov, D. A. Vasilevskii, O. G. Kulinkovich, *Zh. Org. Khim.* **1991**, *27*, 1431−1433; *J. Org. Chem. USSR (Engl. Transl.)* **1991**, *27*, 1251−1253.
[11] H. Hayashi, A. Ohno, S. Oka, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 506−509.
[12] D. Spitzner, H. Swoboda, *Tetrahedron Lett.* **1986**, *27*, 1281−1284.
[13] E. W. Della, H. Gangodawila, *Austr. J. Chem.* **1989**, *42*, 1485−1492.
[14] R. Boss, R. Scheffold, *Angew. Chem.* **1976**, *88*, 578−579; *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 558−559.
[15] J. Cunningham, R. Gigg, C. D. Warren, *Tetrahedron Lett.* **1964**, *5*, 1191−1196.
[16] J. Lee, J. K. Cha, *Tetrahedron Lett.* **1996**, *37*, 3663−3666.
[17] A. B. Smith, III, R. A. Rivero, K. J. Hale, H. A. Vaccaro, *J. Am. Chem. Soc.* **1991**, *113*, 2092−2112.
[18] M. Honda, H. Morita, I. Nakagura, *J. Org. Chem.* **1997**, *62*, 8932−8936.
[19] K. Nakayama, K. Uoto, K. Higashi, T. Soga, T. Kusama, *Chem. Pharm. Bull.* **1992**, *40*, 1718−1720.
[20] [20a] Robins, *J. Am. Chem. Soc.* **1956**, *78*, 784−790. [20b] E. L. Anderson, *J. Med. Chem.* **1964**, *7*, 259−268. [20c] H.-G. Müller, K. Hartke, *Arch. Pharm. (Weinheim, Ger.)* **1988**, *321*, 879−884. [20d] H.-J. Lankau, M. Menzer, A. Rostock, T. Arnold, C. Rundfeldt, K. Unverferth, *Arch. Pharm. (Weinheim, Ger.)* **1999**, *332*, 219−221.
[21] [21a] V. M. Neplyev, *Chem. Heterocycl. Compd. (Engl. Transl.)* **1978**, *14*, 782−784; *Khim. Geterotsikl. Soedin.* **1978**, *14*, 969−971. [21b] G. L'abbe, L. Dyall, K. Meersman, W. Dehaen, *J. Chem. Soc., Perkin Trans. 2* **1996**, 2111−2118.
[22] General approaches to 3-aminothiophenes according to Fiesselman and Gompper are described in: [22a] S. Gronowitz, *Thiophene and Its Derivatives*, Part 1 (Ed.: S. Gronowitz), John Wiley & Sons Inc., New York, **1985**, p. 66−126. 3-Aminothiophenes with electron-withdrawing groups at position 2 are numerous: [22b]K. Saito, S. Kambe, A. Sakurai, H. Midorikawa, *Synthesis* **1982**, 1056−1059. [22c] M. Augustin, R. Schmidt, W.-D. Rudorf, *Z. Chem.* **1977**, *17*, 289−290. [22d] O. Günther, K. Hartke, *Arch. Pharm. (Weinheim, Ger.)* **1975**, *308*, 693. [22e] G. Kirsch, D. Caqniat, P. Cagniat, *J. Heterocycl. Chem.* **1982**, *19*, 443−445. For recent syntheses of compounds with a methyl 3-amino-2-thiophenecarboxylate fragment starting from methyl thioglycolate see: [22f] P. E. Morris, A. J. Elliott, J. A. Montgomery, *J. Heterocycl. Chem.* **1999**, *36*, 423−427. [22g] C. E. Stephens, M. B. Price, W. J. Sowell, *J. Heterocycl. Chem.* **1999**, *36*, 659−666. [22h] F. Jourdan, D. Ladurée, M. Robba, *J. Heterocycl. Chem.* **1994**, *31*, 305−313.
[23] S.-B. Park, J. K. Cha, *Org. Lett.* **2000**, *2*, 147−149.
[24] T. W. Green, P. G. Wuts, *Protective Groups in Organic Synthesis*, 3rd ed., Wiley, New York, **1999**, p. 67−74.

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