Organic Process Research & Development **2010**, *14*, 168–173

Improved Synthesis of the Selective Rho-Kinase Inhibitor 6-Chloro-*N*4-{3,5-difluoro-4-[(3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)oxy]phenyl}pyrimidin-2,4-diamine

Hartmut Schirok,*,† Holger Paulsen,† Walter Kroh,† Gang Chen,‡ and Ping Gao‡

Bayer Schering Pharma AG, Medicinal Chemistry Wuppertal, 42096 Wuppertal, Germany, and Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, 200032 Shanghai, China

Abstract:

A highly potent and selective Rho-kinase inhibitor containing a 7-azaindole moiety has been developed at Bayer Schering Pharma. Herein we disclose details of a significantly improved synthesis of the compound in 8.2% overall yield. Key aspects include cost and safety considerations and the uncommon use of a trifluoromethyl group with controllable reactivity as a masked methyl group.

Introduction

The Rho-associated coiled-coil containing protein kinase (ROCK) is a serine/threonine kinase and belongs to the AGC kinase family. There are two isoenzymes known, ROCK-1 (ROKβ) and ROCK-2 (ROKα), that share ~90% homology in the kinase domain.[1] ROCK is an effector of the small GTP-binding protein RhoA,[2] and is implicated in a multitude of fundamental cellular processes[3] including smooth muscle contraction, cell growth and migration,[4] endothelial barrier maintenance,[5] and apoptosis.[6] Increased ROCK activity contributes to several cardiovascular diseases.[7] Moreover, ROCK plays a critical role in the induction of neurite retraction and growth cone collapse, and therefore small-molecule inhibitors might be therapeutically effective in the promotion of axonal regeneration after spinal cord and other nerve injuries.[8] Possible applications to inflammatory disorders such as asthma, chronic obstructive pulmonary disease (COPD), and multiple sclerosis (MS) have been reviewed.[9] The observation that a ROCK inhibitor diminishes the dissociation-induced apoptosis of embryonic stem cells was celebrated as a breakthrough in stem cell research.[10]

The pivotal role of ROCK in vascular smooth muscle contraction has been intensely examined; ROCK mediates the phosphorylation of the regulatory myosin-binding subunit (MBS) of myosin light chain (MLC) phosphatase. Phosphorylated MBS inhibits the phosphatase activity, causing an increase in the level of phosphorylated MLC and thus enhances the contractile tone of the vascular smooth muscle apparatus independently of any change in intracellular Ca^{2+} concentration, a phenomenon which is known as "calcium sensitization".[11] The central function of ROCK in the control of smooth muscle contraction makes it a suitable target for broadly efficacious antihypertensive agents and the treatment of other cardiovascular diseases.[12] Different physiological roles of the two ROCK isoforms are still matters of controversial debate. It has been suggested that ROCK-1 is primarily responsible for maintaining vascular tone.[13] In contrast, ROCK-2 exclusively binds directly to MBS, and it was hypothesized that ROCK-2 is the predominant regulator of smooth muscle cell contractility.[14]

* Corresponding author. E-mail: hartmut.schirok@bayerhealthcare.com.
† Bayer Schering Pharma AG.
‡ Shanghai Institute of Organic Chemistry.

(1) (a) Ishizaki, T.; Maekawa, M.; Fujisawa, K.; Okawa, K.; Iwamatsu, A.; Fujita, A.; Watanabe, N.; Saito, Y.; Kakizuka, A.; Morii, N.; Narumiya, S. *EMBO J.* **1996**, *15*, 1885. (b) Matsui, T.; Amano, M.; Yamamoto, T.; Chihara, K.; Nakafuku, M.; Ito, M.; Nakano, T.; Okawa, K.; Iwamatsu, A.; Kaibuchi, K. *EMBO J.* **1996**, *15*, 2208.
(2) Buchsbaum, R. J. *J. Cell Sci.* **2007**, *120*, 1149.
(3) (a) Riento, K.; Ridley, A. J. *Nat. Rev. Mol. Cell Biol.* **2003**, *4*, 446. (b) Loirand, G.; Guérin, P.; Pacaud, P. *Circ. Res.* **2006**, *98*, 322. (c) Calò, L. A.; Pessina, A. C. *J. Hypertens.* **2007**, *25*, 259.
(4) (a) Fritz, G.; Kaina, B. *Curr. Cancer Drug Targets* **2006**, *6*, 1. (b) Narumiya, S.; Yasuda, S. *Curr. Opin. Cell Biol.* **2006**, *18*, 199. (c) Lane, J.; Martin, T. A.; Watkins, G.; Mansel, R. E.; Jiang, W. G. *Intl. J. Onc.* **2008**, *33*, 585. (d) Wong, C. C.-L.; Wong, C.-M.; Tung, E. K.-K.; Man, K.; Ng, I. O.-L. *Hepatology* **2009**, *49*, 1583.
(5) (a) Sun, H.; Breslin, J. W.; Zhu, J.; Yuan, S. Y.; Wu, M. H. *Microcirculation* **2006**, *13*, 237. (b) van Nieuw Amerongen, G. P.; Beckers, C. M. L.; Achekar, I. D.; Zeeman, S.; Musters, R. J. P.; van Hinsbergh, V. W. M. *Arterioscler. Thromb. Vasc. Biol.* **2007**, 2332.
(6) (a) Rattan, R.; Giri, S.; Singh, A. K.; Singh, I. *J. Neurosci. Res.* **2006**, *83*, 243. (b) Shi, J.; Wei, L. *Arch. Immunol. Ther. Exp.* **2007**, *55*, 61.
(7) On the first direct evidence for ROCK activation in patients with PAH: Zhulanqiqige, D.; Fukumoto, Y.; Takaki, A.; Tawara, S.; Ohashi, J.; Nakano, M.; Tada, T.; Saji, K.; Sugimura, K.; Fujita, H.; Hoshikawa, Y.; Nawata, J.; Kondo, T.; Shimokawa, H. *Circ. J.* **2009**, *73*, 1731.
(8) (a) Mueller, B. K.; Mack, H.; Teusch, N. *Nat. Rev. Drug. Discovery* **2005**, *4*, 387. (b) Kubo, T.; Yamashita, T. *Recent Pat. CNS Drug Discovery* **2007**, *2*, 173. (c) Endo, M.; Yamashita, T. *Cent. Nerv. Syst. Agents Med. Chem.* **2007**, *7*, 241. (d) Kubo, T.; Yamaguchi, A.; Iwata, N.; Yamashita, T. *Ther. Clin. Risk Manage.* **2008**, *4*, 605.
(9) LoGrasso, P. V.; Feng, Y. *Curr. Top. Med. Chem.* **2009**, *9*, 704.
(10) (a) Watanabe, K.; Ueno, M.; Kamiya, D.; Nishiyama, A.; Matsumura, M.; Wataya, T.; Takahashi, J. B.; Nishikawa, S.; Nishikawa, S.-i.; Muguruma, K.; Sasai, Y. *Nat. Biotechnol.* **2007**, *25*, 681. (b) Li, X.; Meng, G.; Krawetz, R.; Liu, S.; Rancourt, D. E. *Stem Cells Dev.* **2008**, *17*, 1079. (c) Claassen, D. A.; Desler, M. M.; Rizzino, A. *Mol. Reprod. Dev.* **2009**, *76*, 722. (d) Li, X.; Krawetz, R.; Liu, S.; Meng, G.; Rancourt, D. E. *Hum. Reprod.* **2009**, *24*, 580.
(11) (a) Swärd, K.; Mita, M.; Wilson, D. P.; Deng, J. T.; Susnjar, M.; Walsh, M. P. *Curr. Hypertens. Rep.* **2003**, *5*, 66. (b) Somlyo, A. P.; Somlyo, A. V. *Physiol. Rev.* **2003**, *83*, 1325. (c) Christ, G.; Wingard, C. *Curr. Opin. Invest. Drugs* **2005**, *9*, 920. (d) Hirano, K. *J. Pharmacol. Sci.* **2007**, *104*, 109.
(12) (a) Shimokawa, H.; Takeshita, A. *Arterioscler. Thromb. Vasc. Biol.* **2005**, *25*, 1767. (b) Budzyn, K.; Marley, P. D.; Sobey, C. G. *Trends Pharmacol. Sci.* **2006**, *27*, 97. (c) Xing, X.-q.; Gan, Y.; Wu, S.-J.; Chen, P.; Zhou, R.; Xiang, X.-d. *Drug News Perspect.* **2006**, *19*, 517. (d) Noma, K.; Oyama, N.; Liao, J. K. *Am. J. Physiol. Cell Physiol.* **2006**, *290*, C661. (e) Liao, J. K.; Seto, M.; Noma, K. *J. Cardiovasc. Pharmacol.* **2007**, *50*, 17. (f) Shimokawa, H.; Rashid, M. *Trends Pharmacol. Sci.* **2007**, *28*, 296. (g) Fukumoto, Y.; Tawara, S.; Shimokawa, H. *Tohoku J. Exp. Med.* **2007**, *211*, 309. (h) Budzyn, K.; Sobey, C. G. *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 590. (i) Olson, M. F. *Curr. Opin. Cell Biol.* **2008**, *20*, 242. (j) Barman, S. A.; Zhu, S.; White, R. E. *Vasc. Health Risk Manage.* **2009**, *5*, 663.
(13) (a) Hu, E.; Lee, D. *Expert Opin. Ther. Targets* **2005**, *9*, 715. (b) Stavenger, R. A. *Annu. Rep. Med. Chem.* **2008**, *43*, 87.
(14) Wang, Y.; Zheng, X. R.; Riddick, N.; Bryden, M.; Baur, W.; Zhang, X.; Surks, H. K. *Circ. Res.* **2009**, *104*, 531.

10.1021/op900260k
Published on Web 12/11/2009

Fasudil (HA-1077)[15] is the only marketed inhibitor of ROCK and is used in Japan for the treatment of life-threatening cerebral vasospasm[16] after subarachnoidal bleeding.[17] Other ROCK inhibitors reported by different inventors did not reach late clinical phases.[13b,18−23]

In our own research program we developed azaindole **16** as potent and selective ROCK-1/-2 inhibitor. We recently reported on the design and synthesis[24] of **16** and on its pharmacological characterization[25] as a highly potent, selective, and orally available antihypertensive agent. The medicinal chemistry synthesis was designed to facilitate late-stage incorporation of structural diversity on the azaindole hinge-binding motif. For the preparation of **16** on multigram scale an improved synthetic route was required. Herein, we are describing the development of an alternative route with 10-fold improved yield and reduced cost of goods.

Results and Discussion

Depicted in Scheme 1 is the original synthesis of azaindole **16**, including the preparation of 7-azaindole (**3**)[26] from 2-aminopicoline (**1**) and its transformation into the literature-known 4-nitro *N*-oxide **5**.[27] One major challenge was the formation of the phenyl ether bond. We found that the 6-chloro atom in compound **6** leads to increased reactivity of the building block and can be easily removed later in the synthesis. Furthermore, the N1-protection in **7** was crucial to avoid N-deprotonation and subsequent rearrangement reactions.[28] Despite considerable improvements, the total yield over 15 steps was only 0.84%.

The depicted synthetic route was designed to allow for late-stage variation of the 3-position by bromine substitution for SAR investigations. However, with the 3-methyl group identified as the most desirable substituent, its multistep introduction renders the synthesis inefficient. A second major disadvantage of the synthesis as depicted in Scheme 1 is the low yield of the nitration step leading to compound **5**. Reports in the literature on the regioselectivity of the nitration of 7-azaindole *N*-oxide (**4**) are contradictory.[27] We observed the predominant formation of the unwanted 3-nitro isomer and isolated a maximum 30% yield of the 4-nitro analogue **5**. As a second limitation, the maximal scale of the reaction was 20−30 g for safety reasons.

The introduction of the methyl group on the azaindole moiety early in the synthesis which would solve both these problems failed. Several attempts to run a sequence starting with 3-methyl 7-azaindole were unsuccessful, and we were unable to get the 3-methylated pendant of intermediate **6**.

In parallel, we developed the large-scale synthesis of 3-trifluoromethyl 7-azaindole (**20**) starting from 2-fluoropyridine (**17**) (Scheme 2).[29] In analogy to the former synthesis, ether **25** can be obtained from compound **20** in good yield. Notably, the nitration step affording **22** works in 78% yield since the trifluoromethyl group blocks the 3-position from competing regioisomer formation.

We were intrigued by the notion of introducing the 3-methyl group in **16** masked as a perfluorinated carbon. This would require subsequent hydrodefluorination of the CF_3 group in the presence of a difluoroarene moiety.

Whilst the hydrodefluorination (HDF) of nonactivated aliphatic fluorocarbons remains challenging due to the strength of C_{sp3}−F bonds,[30] trifluoromethyl groups in conjugation with

(15) (a) Asano, T.; Ikegaki, I.; Satoh, S.; Suzuki, Y.; Shibuya, M.; Takayasu, M.; Hidaka, H. *J. Pharmacol. Exp. Ther.* **1987**, *241*, 1033. (b) Tamura, M.; Nakao, H.; Yoshizaki, H.; Shiratsuchi, M.; Shigyo, H.; Yamada, H.; Ozawa, T.; Totsuka, J.; Hidaka, H. *Biochim. Biophys. Acta* **2005**, *1754*, 245.

(16) Kolias, A. G.; Sen, J.; Belli, A. *J. Neurosci. Res.* **2009**, *87*, 1.

(17) (a) Suzuki, Y.; Shibuya, M.; Satoh, S.-i.; Sugimoto, Y.; Takakura, K. *Surg. Neurol.* **2007**, *68*, 126. (b) Suzuki, Y.; Shibuya, M.; Satoh, S.-I.; Sugiyama, H.; Seto, M.; Takakura, K. *Neurol. Med. Chir.* **2008**, *48*, 241.

(18) (a) Uehata, M.; Ishizaki, T.; Satoh, H.; Ono, T.; Kawahara, T.; Morishita, T.; Tamakawa, H.; Yamagami, K.; Inui, J.; Maekawa, M.; Narumiya, S. *Nature* **1997**, *389*, 990. (b) Gingras, K.; Avedissian, H.; Thouin, E.; Boulanger, V.; Essagian, C.; McKerracher, L.; Lubell, W. D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4931.

(19) (a) Doe, C.; Bentley, R.; Behm, D. J.; Lafferty, R.; Stavenger, R.; Jung, D.; Bamford, M.; Panchal, T.; Grygielko, E.; Wright, L. L.; Smith, G. K.; Chen, Z.; Webb, C.; Khandekar, S.; Yi, T.; Kirkpatrick, R.; Dul, E.; Jolivette, L.; Marino, J. P.; Willette, R.; Lee, D.; Hu, E. *J. Pharmacol. Exp. Ther.* **2006**, *320*, 89. (b) Stavenger, R. A.; Cui, H.; Dowdell, S. E.; Franz, R. G.; Gaitanopoulos, D. E.; Goodman, K. B.; Hilfiker, M. A.; Ivy, R. L.; Leber, J. D.; Marino, J. P., Jr.; Oh, H.-J.; Viet, A. Q.; Xu, W.; Ye, G.; Zhang, D.; Zhao, Y.; Jolivette, L. J.; Head, M. S.; Semus, S. F.; Elkins, P. A.; Kirkpatrick, R. B.; Dul, E.; Khandekar, S. S.; Yi, T.; Jung, D. K.; Wright, L. L.; Smith, G. K.; Behm, D. J.; Doe, C. P.; Bentley, R.; Chen, Z. X.; Hu, E.; Lee, D. *J. Med. Chem.* **2007**, *50*, 2.

(20) Goodman, K. B.; Cui, H.; Dowdell, S. E.; Gaitanopoulos, D. E.; Ivy, R. L.; Sehon, C. A.; Stavenger, R. A.; Wang, G. Z.; Viet, A. Q.; Xu, W.; Ye, G.; Semus, S. F.; Evans, C.; Fries, H. E.; Jolivette, L. J.; Kirkpatrick, R. B.; Dul, E.; Khandekar, S. S.; Yi, T.; Jung, D. K.; Wright, L. L.; Smith, G. K.; Behm, D. J.; Bentley, R.; Doe, C. P.; Hu, E.; Lee, D. *J. Med. Chem.* **2007**, *50*, 6.

(21) Sehon, C. A.; Wang, G. Z.; Viet, A. Q.; Goodman, K. B.; Dowdell, S. E.; Elkins, P. A.; Semus, S. F.; Evans, C.; Jolivette, L. J.; Kirkpatrick, R. B.; Dul, E.; Khandekar, S. S.; Yi, T.; Wright, L. L.; Smith, G. K.; Behm, D. J.; Bentley, R.; Doe, C. P.; Hu, E.; Lee, D. *J. Med. Chem.* **2008**, *51*, 6631.

(22) (a) Feng, Y.; Yin, Y.; Weiser, A.; Griffin, E.; Cameron, M. D.; Lin, L.; Ruiz, C.; Schürer, S. C.; Inoue, T.; Rao, P. V.; Schröter, T.; LoGrasso, P. *J. Med. Chem.* **2008**, *51*, 6642. (b) Sessions, E. H.; Yin, Y.; Bannister, T. D.; Weiser, A.; Griffin, E.; Pocas, J.; Cameron, M. D.; Ruiz, C.; Lin, L.; Schürer, S. C.; Schröter, T.; LoGrasso, P.; Feng, Y. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6390. (c) Chen, Y. T.; Bannister, T. D.; Weiser, A.; Griffin, E.; Lin, L.; Ruiz, C.; Cameron, M. D.; Schürer, S.; Duckett, D.; Schröter, T.; LoGrasso, P.; Feng, Y. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6406.

(23) Löhn, M.; Plettenburg, O.; Ivashchenko, Y.; Kannt, A.; Hofmeister, A.; Kadereit, D.; Schaefer, M.; Linz, W.; Kohlmann, M.; Herbert, J.-M.; Janiak, P; O'Connor, S. E.; Ruetten, H. *Hypertension* **2009**, *54*, 676.

(24) Schirok, H.; Kast, R.; Figueroa-Pérez, S.; Bennabi, S.; Gnoth, M. J.; Feurer, A.; Heckroth, H.; Thutewohl, M.; Paulsen, H.; Knorr, A.; Hütter, J.; Lobell, M.; Münter, K.; Geiss, V.; Ehmke, H.; Lang, D.; Radtke, M.; Mittendorf, J.; Stasch, J.-P. *ChemMedChem* **2008**, *3*, 1893.

(25) (a) Kast, R.; Schirok, H.; Figueroa-Pérez, S.; Mittendorf, J.; Gnoth, M. J.; Apeler, H.; Lenz, J.; Franz, J. K.; Knorr, A.; Hütter, J.; Lobell, M.; Zimmermann, K.; Münter, K.; Augstein, K. H.; Ehmke, H.; Stasch, J.-P. *Br. J. Pharmacol.* **2007**, *152*, 1070. (b) Dahal, B. K.; Kosanovic, D.; Lai, Y.-J.; Pamarthi, P. K.; Kast, R.; Schirok, H.; Stasch, J.-P.; Ghofrani, H. A.; Weissmann, N.; Grimminger, F.; Seeger, W.; Schermuly, R. T. *Eur. Respir. J.*,submitted.

(26) Hands, D.; Bishop, B.; Cameron, M.; Edwards, J. S.; Cottrell, I. F.; Wright, S. H. B. *Synthesis* **1996**, 877.

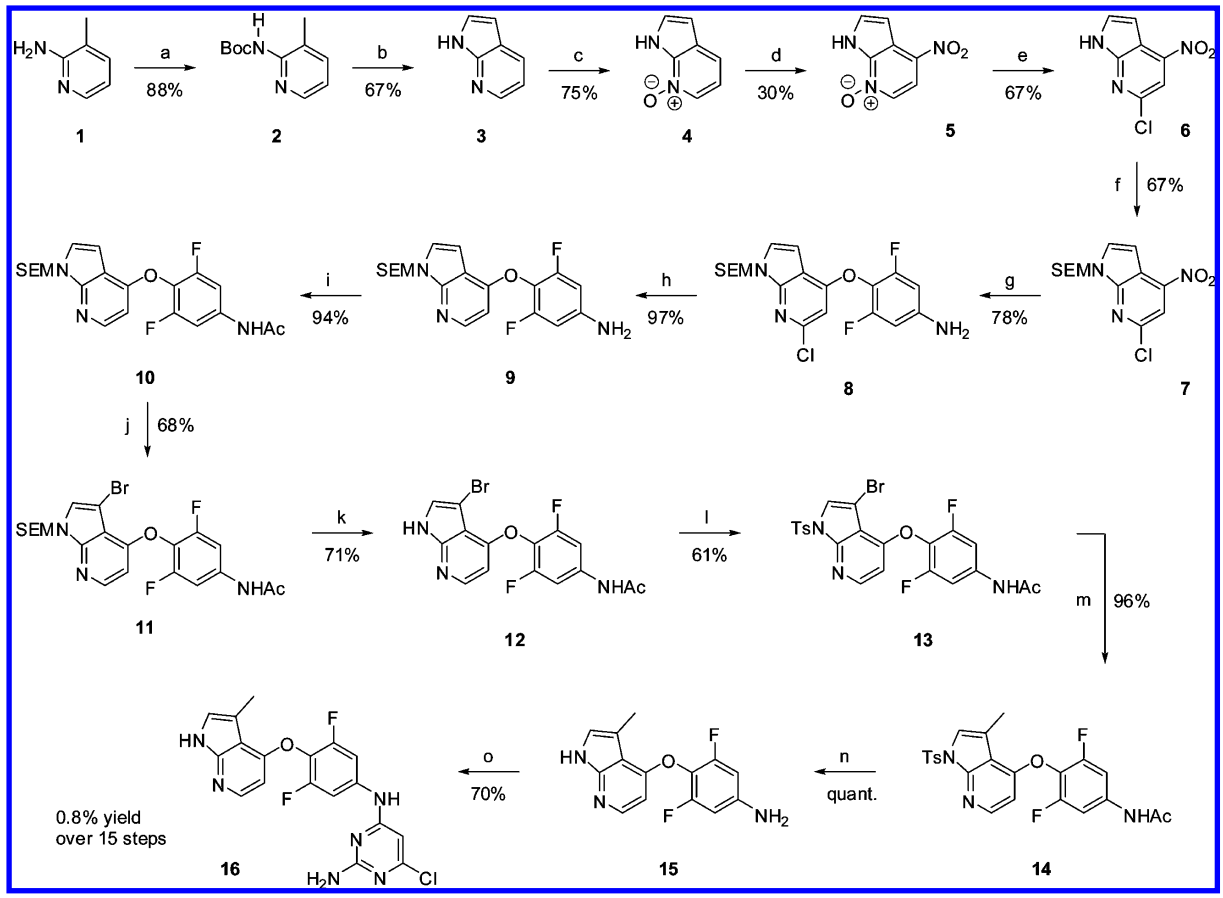
(27) (a) Schneller, S. W.; Luo, J.-K. *J. Org. Chem.* **1980**, *45*, 4045. (b) Antonini, I.; Claudi, F.; Cristalli, G.; Franchetti, P.; Grifantini, M.; Martelli, S. *J. Med. Chem.* **1982**, *25*, 1258.

(28) Figueroa-Pérez, S.; Bennabi, S.; Schirok, H.; Thutewohl, M. *Tetrahedron Lett.* **2006**, *47*, 2069.

(29) Schirok, H.; Figueroa-Pérez, S.; Thutewohl, M.; Paulsen, H.; Kroh, W.; Klewer, D. *Synthesis* **2007**, 251.

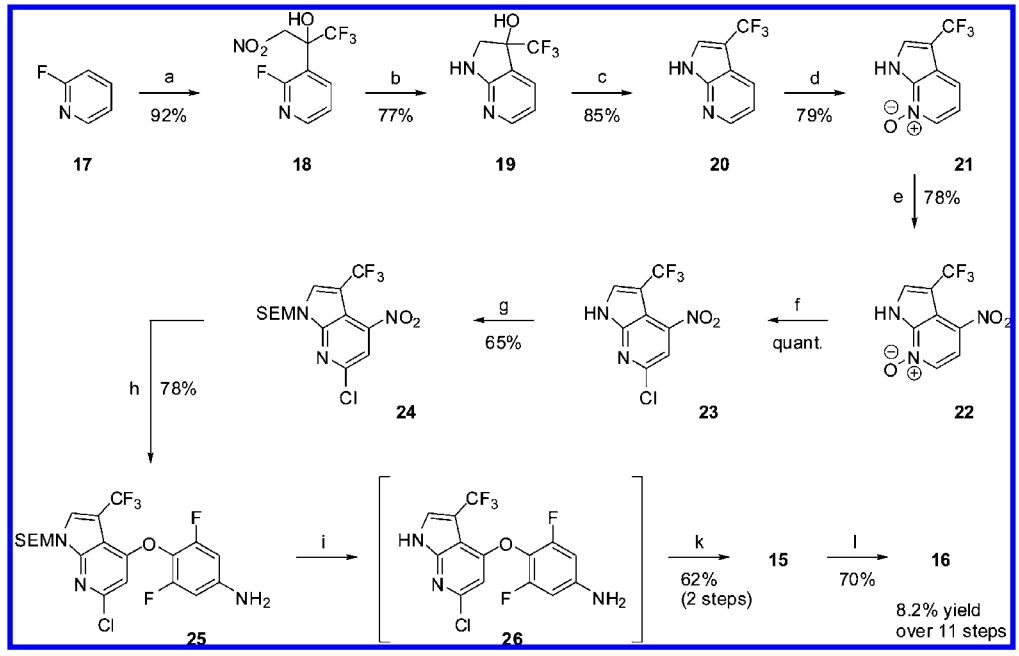
(30) (a) Review: Kiplinger, J. L.; Richmond, T. G.; Osterberg, C. E. *Chem. Rev.* **1994**, *94*, 373. (b) Kraft, B. M.; Lachicotte, R. J.; Jones, W. D. *J. Am. Chem. Soc.* **2001**, *123*, 10973. (c) Fuchibe, K.; Ohshima, Y.; Mitomi, K.; Akiyama, T. *J. Fluorine Chem.* **2007**, *128*, 1158. (d) Klahn, M.; Fischer, C.; Spannenberg, A.; Rosenthal, U.; Krossing, I. *Tetrahedron Lett.* **2007**, *48*, 8900. (e) Douvris, C.; Ozerov, O. V. *Science* **2008**, *321*, 1188. (f) Meier, G.; Braun, T. *Angew. Chem.* **2009**, *121*, 1575. *Angew. Chem., Int. Ed.* **2009**, *48*, 1546.

Scheme 1. **Synthesis of azaindole 16**[a]



[a] Reagents and conditions: (a) Boc_2O, *n*-heptane/EE, 55 °C, 88%. (b) *n*-BuLi, THF, −10 °C → 0 °C; DMF, 0 °C → 15 °C; aq HCl, −5 °C → 5 °C, 67%. (c) *m*-CPBA, CH_2Cl_2, 10 °C → 25 °C, 75%. (d) HNO_3 (65%), TFA, rt, 30%. (e) HMDS, $ClCO_2Me$, THF, rt, 67%. (f) NaH, DMF, 10 °C → rt; SEMCl, rt, 67%. (g) 4-amino-2,6-difluorophenol, K_2CO_3, DMSO, 120 °C, 78%. (h) Pd/C, H_2, TEA, EtOH, rt, 97%. (i) AcCl, TEA, CH_2Cl_2, rt, 94%. (j) Br_2, CH_2Cl_2, 0 °C, 68%. (k) 4 N HCl in dioxane, rt; aq LiOH, THF, rt (71%). (l) *n*-BuLi, TsCl, THF, −70 °C → rt, 61%. (m) Me_2Zn, $Pd(dppf)Cl_2 \times CH_2Cl_2$ (cat.), dioxane, 100 °C, 96%. (n) NaOH, H_2O, EtOH, rt, quant. (o) 4,6-dichloropyrimidine-2-amine, water, HCl, reflux, 70%.

Scheme 2. **Improved synthesis of azaindole 16**[a]



[a] Reagents and conditions: (a) LDA, THF, −75 °C; CF_3CO_2Et, −78 °C → rt; CH_3NO_2, rt, 92%. (b) H_2 (1 atm), PtO_2, EtOH, rt; filtration, reflux, 77%. (c) $SOCl_2$, Pyr, CH_2Cl_2, rt, 85%. (d) *m*-CPBA, EtOAc, 0 °C, 79%. (e) HNO_3, TFA, 70 °C, 78%. (f) Cl_3CCOCl, HMDS, THF, 0 °C; quant. (g) SEMCl, NaH, DMF, rt, 65%. (h) K_2CO_3, DMSO, 120 °C, 78%. (i) TFA, CH_2Cl_2, rt. (k) $LiAlH_4$, THF, reflux, 62%. (l) 4,6-Dichloropyrimidine-2-amine, water, aq HCl, reflux, 70%.

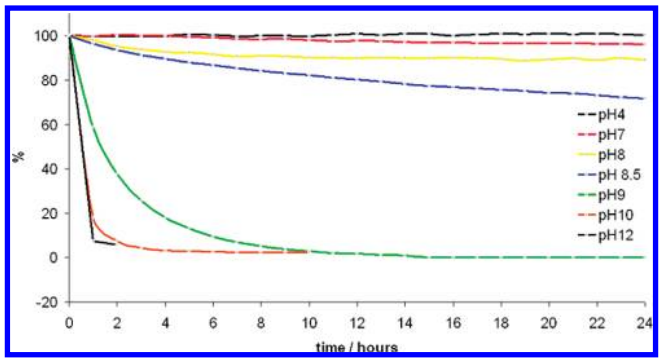


Figure 1. **pH-dependent aqueous stability of compound 20.**

an acidic NH group are highly reactive. This has been as reported for heterocycles such as pyrroles,[31] indoles,[32] imidazoles,[33] and pyrazoles.[34] Under basic conditions, such CF_3 groups are transformed into the carboxylic acid or ester.[35] We ourselves examined the hydrolysis of 3-trifluoromethyl 7-azaindol (**20**) in buffer solutions with different pHs at 37 °C (Figure 1) and discovered its high reactivity at pH >8.5. In addition, we accomplished the aminolysis of substrates such as **26** resulting in the transformation of the trifluoromethyl into a carbonitrile group.[24] These observations encouraged us to investigate the feasibility of a reductive defluorination despite little precedence.[36] The simultaneous dechlorination would further reduce the number of linear steps.

When we heated compound **25** in a THF solution of lithium aluminiumhydride, we detected the clean loss of chlorine with the SEM protecting group perfectly stable and the trifluoromethyl group left intact. In contrast, treatment of **25** with trifluoroacetic acid in dichloromethane led to cleavage of the SEM group. Subsequent heating with excess lithium aluminiumhydride resulted in reduction of the trifluoromethyl group and simultaneous (though somewhat slower) removal of the chloro atom to compound **15** in 62% overall yield.[37] The final reaction with 4,6-dichloropyrimidine-2-amine accomplished the synthesis of **16**.

This way, the length of the synthesis could be reduced from 15 to 11 linear steps. Only three intermediate products need chromatographic purification (compounds **24**, **25**, and **15**), and two mother liquors may be chromatographed to achieve optimal yields (compounds **19** and **16**). The major advantage of the new route consists in the very much improved overall yield of 8.2% compared to 0.8% in the former pathway.

Conclusion

Azaindole **16** is a representative of a new class of highly potent and selective ROCK inhibitors, which could be used for the treatment of diseases caused by smooth muscle hypercontraction or vascular atherosclerotic alterations. We presented an up-scaled synthesis consisting of 11 linear steps and 8.2% overall yield capable of providing multigram amounts of the target compound.

Experimental Section

General Methods and Materials. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 at rt on Bruker Avance spectrometers operating at 300, 400, and 500 MHz for ^{1}H NMR, and at 125 MHz for ^{13}C NMR. Flash chromatography was performed on silica gel 60 (0.063−0.200 mm) purchased from Merck KGaA (Germany). Preparative HPLC chromatography was performed on a 250 mm × 30 mm column packed with YMC gel ODS-AQ S-5/15 mm, with CH_3CN/H_2O as the eluent and UV detection. Solvents for extraction and chromatography were reagent grade and used as received. Commercial reagents were used without purification. Petroleum ether (PE) refers to the fraction boiling in the range 40−60 °C.

1,1,1-Trifluoro-2-(2-fluoropyridin-3-yl)-3-nitropropan-2-ol (18). To a solution of freshly prepared LDA (1.48 mol) in THF (3.2 L) at −75 °C was added 2-fluoropyridine (120 g, 1.24 mol), and the mixture was stirred for 4 h at this temperature. To the resulting suspension, ethyl trifluoroacetate (246 g, 1.73 mol) was added, during which the internal temperature should not rise above −45 °C. The reaction was warmed to rt. Nitromethane (134 mL, 2.47 mol) was added, and the reaction was stirred overnight. The solution was poured into HCl (aq 2 N, 17 L), and the mixture was extracted with EtOAc (2 × 8 L). (*Remark:* The retro-nitro-aldol reaction takes place under basic conditions. Therefore, the reaction mixture must be poured into an acidic medium.) The combined organic layers were washed with brine (5 L), dried (Na_2SO_4), and the solvent was evaporated. The crystalline residue was triturated with PE, and the product was collected by suction filtration to yield 290 g (92%) of the title compound. (*Remark:* The DTA analysis of **18** revealed a strongly exothermic decomposition beginning at 140 °C with 2300 kJ/kg.) ^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.10−5.16 (m, 1H), 5.68 (d, J = 13.2 Hz, 1H), 7.25 (ddd, J = 7.7, 4.8, 2.3 Hz, 1H), 8.27 (ddd, J = 10.0, 7.7, 1.9 Hz, 1H), 8.33−8.38 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 73.8 (dq, $^2J_{C,F}$ = 30.0 Hz, $^3J_{C,F}$ = 6.9 Hz), 77.1 (d, $^4J_{C,F}$ = 8.3 Hz), 116.7 (d, $^2J_{C,F}$ = 27.8 Hz), 122.6 (d, $^4J_{C,F}$ = 4.2 Hz), 123.8 (q, $^1J_{C,F}$ = 286 Hz), 141.6 (d, $^3J_{C,F}$ = 3.2 Hz), 148.9 (d, $^3J_{C,F}$ = 15.7 Hz), 159.0 (d, $^1J_{C,F}$ = 236 Hz). HRMS calcd for $C_8H_6F_4N_2O_3$: 254.0315; found: 254.0321.

3-(Trifluoromethyl)-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-3-ol (19). Compound **18** (100 g, 393 mmol) was dissolved in EtOH (1.5 L) and stirred under H_2 (1 atm) with PtO_2 (2.23

(31) Jones, R. A.; Rustidge, D. C.; Cushman, S. M. *Synth. Commun.* **1984**, *14*, 575.
(32) Kobayashi, Y.; Kumadaki, I.; Hirose, Y.; Hanzawa, Y. *J. Org. Chem.* **1974**, *39*, 1836.
(33) (a) Matthews, D. P.; McCarthy, J. R.; Whitten, J. P.; Kastner, P. R.; Barney, C. L.; Marshall, F. N.; Ertel, M. A.; Burkhard, T.; Shea, P. J.; Kariya, T. *J. Med. Chem.* **1990**, *33*, 317. (b) Hayakawa, Y.; Kimoto, H.; Cohen, L. A.; Kirk, K. L. *J. Org. Chem.* **1998**, *63*, 9448. (c) Choi, K.; Hamilton, A. *J. Am. Chem. Soc.* **2003**, *125*, 10241.
(34) Kobayashi, Y.; Yamashita, T.; Takahashi, K.; Kuroda, H.; Kumadaki, I. *Chem. Pharm. Bull.* **1984**, *32*, 4402.
(35) Similar reactions are also known from trifluoromethyl-substituted anilines via a quinone methide intermediate: Kiselyov, A. S.; Piatnitski, E. L.; Doody, J. *Org. Lett.* **2004**, *6*, 4061.
(36) Few reports exist in the literature on the hydrodefluorination of trifluoromethyl groups in conjugation with NH functions, amongst them 3-trifluoromethyl-substituted pyrroles and trifluoromethyl-substituted aminothiazoles: (a) Jones, R. A.; Rustidge, D. C.; Cushman, S. M. *Synth. Commun.* **1984**, *14*, 575. (b) Burger, K.; Höss, E.; Geith, K. *Synthesis* **1990**, 357. (c) Burger, K.; Höss, E.; Hennig, L.; Beyer, L. *Rev. Soc. Quím. Perú* **2005**, *71*, 12. (d) Yu, Y.-H.; Shen, Z.; Xu, H.-Y.; Wang, Y.-W.; Okujima, T.; Ono, N.; Li, Y.-Z.; You, X.-Z. *J. Mol. Struct.* **2007**, *827*, 130.
(37) The addition of transition metal salts such as $NiCl_2$, $NbCl_5$, and $PdCl_2$ did not further improve the yield: (a) Ashby, E. C.; Lin, J. J. *J. Org. Chem.* **1978**, *43*, 1263. (b) Henegar, K. E.; Ashford, S. W.; Baughman, T. A.; Sih, J. C.; Gu, R.-L. *J. Org. Chem.* **1997**, *62*, 6588.

g, 7.87 mmol) as catalyst. After the consumption of the theoretical amount of H_2, the solution was filtered, and the filtrate was refluxed overnight. Subsequently, the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (1 L) and washed with aq sat. $NaHCO_3$ solution (0.8 L). The aqueous phase was extracted with EtOAc (0.5 L), and the organic layer was dried (Na_2SO_4). The solvent was removed under reduced pressure, and the oily residue was triturated with CH_2Cl_2 (0.3 L). The crystalline product was collected by suction filtration and washed with CH_2Cl_2 (150 mL) to yield 57.2 g (71%) of the title compound. An additional 4.5 g (6%) was obtained after chromatographic purification on silica gel (1.0 kg, eluent: CH_2Cl_2/MeOH, 30:1 to 10:1) of the mother liquor. (*Remark:* Fluoride is liberated during the reaction and etches the glassware.) ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.45 (d, J = 11.7 Hz, 1H), 3.71 (d, J = 11.7 Hz, 1H), 6.59 (dd, J = 7.3, 5.1 Hz, 1H), 6.84 (s, 1H), 6.97 (s, 1H), 7.53 (d, J = 7.3 Hz, 1H), 7.97 (dd, J = 5.1, 1.2 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 52.2, 77.7 (q, $^2J_{C,F}$ = 29.9 Hz), 112.4, 117.7, 125.3 (q, $^1J_{C,F}$ = 284 Hz), 132.9, 149.9, 163.4. HRMS calcd for $C_8H_7F_3N_2O$: 204.0510; found: 204.0515.

3-(Trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (20). Compound **19** (211 g, 1.03 mol) was dissolved in CH_2Cl_2 (3.2 L). Pyridine (164 g, 2.07 mmol) and thionyl chloride (246 g, 2.07 mmol) were added, and the reaction was stirred for 2 h. Then ice was added, and the reaction was neutralized to pH 5.7 with aq NaOH solution. The solution was extracted with CH_2Cl_2 (2 × 1.5 L), and the combined organic layers were washed with water (1.5 L) and dried (Na_2SO_4). The solvent was removed in vacuo to yield tan crystals. The crude product was triturated with PE (600 mL) for 15 min, and the crystals were collected by suction filtration to yield 164 g (85%) of the title compound. (*Remark:* The DTA analysis of **20** showed a strongly exothermic decomposition beginning at >160 °C with ~850 kJ/kg.) ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.26 (dd, J = 7.9, 4.7 Hz, 1H), 8.05 (d, J = 7.9 Hz, 1H), 8.16 (s, 1H), 8.39 (dd, J = 4.7, 1.3 Hz, 1H), 12.51 (br s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 102.8 (q, $^2J_{C,F}$ = 36.8 Hz), 115.3, 117.2, 124.2 (q, $^1J_{C,F}$ = 266 Hz), 126.9, 127.2 (q, $^3J_{C,F}$ = 5.0 Hz), 144.5, 148.0. HRMS calcd for $C_8H_5F_3N_2$: 186.0405; found: 186.0407.

3-(Trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine 7-Oxide (21). A solution of *m*-chloroperbenzoic acid (335 g, 1.45 mol) in EtOAc (3 L) was dried (Na_2SO_4) and cooled to 0 °C. Compound **20** (180 g, 969 mmol) was added in portions. The mixture was stirred for 1 h during which time white crystals precipitated. They were collected by suction filtration and washed with EtOAc (600 mL) to yield 155 g (79%) of the desired *N*-oxide. (*Remark:* The DTA analysis revealed a weakly exothermic reaction of the mixture.) ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.25 (dd, J = 8.0, 6.2 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 8.16 (s, 1H), 8.31 (d, J = 6.2 Hz, 1H), 13.40 (br s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 105.4 (q, $^1J_{C,F}$ = 37.4 Hz), 117.5 118.5, 119.5 (q, $^3J_{C,F}$ = 2.2 Hz), 123.5 (q, $^1J_{C,F}$ = 266 Hz), 127.5 (q, $^1J_{C,F}$ = 5.0 Hz), 132.7, 138.5. HRMS calcd for $C_8H_5F_3N_2O$: 202.0354; found: 202.0348.

4-Nitro-3-(trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine 7-Oxide (22). A solution of compound **21** (162 g, 801 mmol) in trifluoroacetic acid (1.9 L) was heated to 70 °C. HNO_3 (65%, 111 mL, 1.60 mol) was added within 10 min. (*Remark:* The reaction was slightly exothermic, and the heating bath was removed for 30 min upon HNO_3 addition during which time the internal temperature was 65−75 °C.) The reaction was heated to 70 °C for 2 h. Then it was poured into an ice/water mixture (5.4 L). The precipitate was collected by suction filtration and washed with water (1.8 L). The product was dried in vacuum to yield 156 g (78%) of the title compound. (*Remark:* The DTA analysis of the nitration mixture resulted in a maximal tolerable internal temperature of 30 °C and a recommended maximal reaction volume of 2 L. The DTA analysis of **22** showed a strongly exothermic decomposition beginning at >105 °C with >2900 kJ/kg. However, the compound was not sensitive to impact or friction.) ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 8.09 (d, J = 6.9 Hz, 1H), 8.46 (s, 1H), 8.49 (d, J = 6.9 Hz, 1H), 14.2 (br s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 105.5 (q, $^2J_{C,F}$ = 37.9 Hz), 110.7, 115.4, 122.6 (q, $^1J_{C,F}$ = 266 Hz), 132.4, 132.7 (q, $^3J_{C,F}$ = 6.5 Hz), 137.0, 141.3. HRMS calcd for $C_8H_4F_3N_3O_3$: 247.0205; found: 247.0209.

6-Chloro-4-nitro-3-(trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (23). Compound **22** (152 g, 615 mmol) was dissolved in THF (2.6 L). Hexamethyldisilazane (130 mL, 615 mmol) was added, and the mixture was cooled to 0 °C. An orange precipitate was formed. Trichloroacetyl chloride (279 g, 1.54 mol) was added dropwise during which the precipitate dissolved, and the color changed to yellow. The mixture was subsequently warmed to rt. The mixture was stirred for 2 h and then poured into water (13 L) and extracted with EtOAc (2 × 5.3 L). The combined organic layers were washed with brine (2.6 L) and dried (Na_2SO_4). The solvent was evaporated, and the residue was triturated with PE. The product was collected by suction filtration to give the desired compound in quantitative yield (200 g). ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 8.08 (s, 1H), 8.63 (s, 1H), 13.62 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 102.5 (q, $^2J_{C,F}$ = 38.2 Hz), 105.2 (q, $^3J_{C,F}$ = 1.8 Hz), 111.6, 129.9 (q, $^1J_{C,F}$ = 266 Hz), 133.6 (q, $^3J_{C,F}$ = 5.7 Hz), 144.3, 148.5, 149.9. HRMS calcd for $C_8H_3ClF_3N_3O_2$: 264.9866; found: 264.9872.

6-Chloro-4-nitro-3-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-pyrrolo[2,3-*b*]pyridine (24). To compound**23** (204 g, 634 mmol) and [2-(chloromethoxy)ethyl](trimethyl)silane (116 g, 697 mmol) in DMF (2.5 L) was added NaH (60% suspension in mineral oil, 25.4 g, 634 mmol) in portions, and the mixture was stirred at rt for 45 min. The mixture was poured into brine and extracted with EtOAc (2 × 4 L). The combined organic layers were washed with brine (2 L), dried (Na_2SO_4), and evaporated. The crude product was purified by column chromatography on silica gel (6.0 kg, eluent: PE/EtOAc, 95:5) to yield 162 g (65%) of the title compound. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = −0.10 (s, 9H), 0.84 (dd, J = 8.1, 8.0 Hz, 2H), 3.58 (dd, J = 8.1, 8.0 Hz 2H), 5.70 (s, 2H), 8.16 (s, 1H), 8.83 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = −1.51, 17.0, 66.4, 73.9, 102.7 (q, $^2J_{C,F}$ = 38.6 Hz), 105.8 (q, $^3J_{C,F}$ = 1.9 Hz), 112.8, 122.7 (q, $^1J_{C,F}$ = 266 Hz), 136.1 (q, $^3J_{C,F}$ = 6.0 Hz), 145.1, 148.8,

148.9. HRMS calcd for $C_{14}H_{17}ClF_3N_3O_3Si$ + $[H^+]$: 396.0753; found: 396.0753.

4-[(6-Chloro-3-(trifluoromethyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-pyrrolo[2,3-*b*]-pyridin-4-yl)oxy]-3,5-difluoroaniline (25). Compound **24** (71.6 g, 181 mmol) was dissolved in DMSO (0.7 L) under argon. K_2CO_3 (75.0 g, 543 mmol) and 4-amino-2,6-difluorophenol (39.4 g, 271 mmol) were added, and the mixture was heated to 120 °C for 3 h. The mixture was poured into water (3.5 L) and extracted with EtOAc (2 × 1.5 L). The combined organic layers were washed with brine (1 L) and dried (Na_2SO_4), and the solvent was evaporated. The crude product was purified by column chromatography on silica gel (4.0 kg, eluent: PE/EtOAc, 4:1) to yield 72.5 g (96% pure, 78% yield) of the desired product. ^{1}H NMR (DMSO-d_6, 500 MHz): $\delta = -0.09$ (s, 9H), 0.84 (dd, $J = 8.1$, 8.0 Hz, 2H), 3.58 (dd, $J = 8.1$, 8.0 Hz, 2H), 5.62 (s, 2H), 5.90 (s, 2H), 6.40 (d, $J = 11.0$ Hz, 2H), 6.53 (s, 1H), 8.39 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = -1.50$, 17.0, 66.1, 73.4, 96.9 (dd, $^2J_{C,F} = 23.1$ Hz, $^3J_{C,F} = 4.0$ Hz), 101.3, 102.9 (q, $^2J_{C,F} = 38.8$ Hz), 104.7 (q, $^3J_{C,F} = 1.6$ Hz), 117.0 (t, $^2J_{C,F} = 16.4$ Hz), 123.1 (q, $^1J_{C,F} = 266$ Hz), 130.2 (q, $^3J_{C,F} = 5.6$ Hz), 146.7, 148.3, 148.7 (t, $^3J_{C,F} = 13.4$ Hz), 155.2 (dd, $^1J_{C,F} = 244$ Hz, $^3J_{C,F} = 6.9$ Hz), 159.2. HRMS calcd for $C_{20}H_{21}ClF_5N_3O_2Si$ + $[H^+]$: 494.1085; found: 494.1086.

3,5-Difluoro-4-[(3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)oxy]aniline (15). Compound **25** (20.0 g, 40.5 mmol) was dissolved in CH_2Cl_2 (200 mL) and trifluoroacetic acid (200 mL) was added. The mixture was stirred at rt for 1.5 h and then concentrated in vacuo. The residue was diluted with EtOAc (400 mL), and the solution was washed with brine (300 mL), dried (Na_2SO_4), and the solvent was evaporated. To the residue was added toluene (100 mL), and the mixture was concentrated again. This procedure was repeated three times to give the SEM-deprotected compound. The crude product (14.7 g, 40.4 mmol) was dissolved in THF (200 mL) under nitrogen and slowly treated with $LiAlH_4$ (2.4 M in THF, 170 mL, 408 mmol). The reaction was heated to reflux for 10 h. Then a second portion of $LiAlH_4$ (2.4 M in THF, 170 mL, 408 mmol) was added, and the mixture was heated to reflux for additional 14 h. Excess of $LiAlH_4$ was then hydrolyzed by the addition of aq 10% NaOH solution (100 mL). The solid was removed by filtration, and the filtrate was concentrated in vacuo to leave an aqueous solution which was extracted with EtOAc (2 × 200 mL). The combined organic layers were dried (Na_2SO_4), the solvent was evaporated, and the residue was purified by column chromatography on silica gel (500 g, eluent: ethyl acetate/petroleum ether, 1:2) to give the title compound (7.00 g, 62% over two steps). (*Remark:* Fluoride is liberated during the reaction and etches the glassware.) ^{1}H NMR (500 MHz, DMSO-d_6): $\delta =$ 2.42 (s, 3H), 5.77 (s, 2H), 6.17 (d, $J = 5.4$ Hz, 1H), 6.40 (d, $J = 10.7$ Hz, 2H), 7.13 (s, 1H), 7.98 (d, $J = 5.4$ Hz, 1H), 11.36 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 12.2$, 97.1 (dd, $^2J_{C,F} = 19.3$ Hz, $^4J_{C,F} = 4.6$ Hz), 98.5, 108.0, 109.2, 118.2 (t, $^2J_{C,F} = 16.4$ Hz), 122.2, 144.4, 148.0 (t, $^3J_{C,F} = 13.2$ Hz), 151.1, 155.9 (dd, $^1J_{C,F} = 243$ Hz, $^3J_{C,F} = 7.3$ Hz), 159.3. HRMS calcd for $C_{14}H_{11}F_2N_3O$ + $[H^+]$: 276.0943; found: 276.0948.

6-Chloro-N^4-{3,5-difluoro-4-[(3-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)oxy]phenyl}pyrimidin-2,4-diamine (16). Compound **15** (6.00 g, 21.8 mmol) and 4,6-dichloropyrimidine-2-amine (3.93 g, 24.0 mmol) were suspended in water (80 mL). HCl (4 N aq, 11 mL) was added, and the mixture was heated to reflux for 20 h. Subsequently, the mixture was basified with conc. aq NaOH solution. Some dmf was added, and the aqueous phase was extracted with EtOAc. The organic layer was washed with water and dried (Na_2SO_4), and the solvent was evaporated. The crude product was triturated with a small volume of ice-cold methanol. The precipitate was collected by suction filtration and washed with CH_2Cl_2 to yield 4.50 g (51%) of the title compound. The mother liquor was concentrated and purified by column chromatography on silica gel (200 g, eluent: CH_2Cl_2/MeOH, 100:4 with increasing proportion of MeOH) to yield further 1.70 g (19%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta =$ 2.44 (s, 3H), 6.04 (s, 1H), 6.21 (d, $J = 5.4$ Hz, 1H), 6.99 (br s, 2H), 7.16 (s, 1H), 7.74 (d, $J = 10.6$ Hz, 2H), 7.99 (d, $J = 5.4$ Hz, 1H), 9.77 (s, 1H), 11.43 (br s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta =$ 12.0, 94.3, 98.3, 103.1 (dd, $^2J_{C,F} = 21.3$ Hz, $^4J_{C,F} = 4.8$ Hz), 107.7, 108.9, 122.3, 123.0 (t, $^2J_{C,F} = 16.1$ Hz), 138.6 (t, $^3J_{C,F} = 13.0$ Hz), 144.1, 151.1, 154.9 (dd, $^1J_{C,F} = 245$ Hz, $^3J_{C,F} = 6.8$ Hz), 158.3, 158.4, 161.3, 162.6. HRMS calcd for $C_{18}H_{13}ClF_2N_6O$ + $[H^+]$: 403.0881; found: 403.0865.

Acknowledgment

We thank Dr. P. Schmitt, C. Streich, and D. Bauer for recording NMR spectra and helpful discussions. In addition we are grateful to M. Stoltefuss, G. Wiefel-Hübschmann, and S. Brauner for HRMS measurements. We thank Dr. D. Heitkamp, G. Berg, and F. Kleinrensing for several DTA analyses.

Supporting Information Available

^{1}H- and ^{13}C NMR spectra and HPLC chromatograms of compounds **15**−**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review October 6, 2009.

OP900260K