A Facile Approach to the Synthesis of 3-(6-Chloro-thiazolo[5,4-*b*]pyridin-2-ylmethoxy)-2,6-difluoro-benzamide (PC190723)

Zi-Chun Ding,[a] Weicheng Zhou,[a] Xiang Ma*[a,b]

[a] State Key Lab of New Drug & Pharmaceutical Process, Shanghai Key Lab of Anti-Infectives, Shanghai Institute of Pharmaceutical Industry, State Institute of Pharmaceutical Industry, 1111 North Zhongshan No.1 Rd, Shanghai 200437, P. R. of China

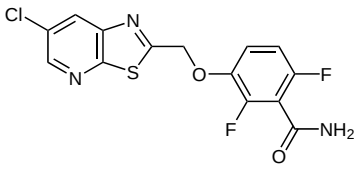
[b] School of Pharmacy, Tongji Medical College, Huazhong University of Science and Technology, 13 Hangkong Road, Wuhan 430030, Hubei, P. R. of China
Fax +86(27)83692750; E-mail: maxwellcn@yahoo.com

Received: 16.01.2012; Accepted after revision: 24.02.2012

Abstract: Practical synthesis of PC 190723, a bacterial cell division protein Ftsz inhibitor, has been achieved in a high overall yield of 45% in six steps from commercially available starting materials.

Key words: antibacterial agents, cell division inhibitors, thiazolo[5,4-*b*]pyridine, FtsZ

Antibiotic-resistant strains of pathogenic bacteria are increasingly prevalent in hospitals and the community.[1] Gram-positive infections caused by some antibiotic-resistant pathogens, such as the multidrug-resistant strains of *Staphylococcus aureus* in particular, are raising significant medical, economic, and public health concerns worldwide.[2] New antibiotics are needed to combat these bacterial pathogens, but progress in developing them are on the decline. Although over the past decades, more than 100 new antibacterial agents have been developed, most of these recently developed antimicrobial agents are new members of established antibiotic classes rather than novel drugs.[1a] There is therefore a great need to identify novel antibiotic targets and discover new antibiotic classes that will help to combat the rise of resistant pathogens.



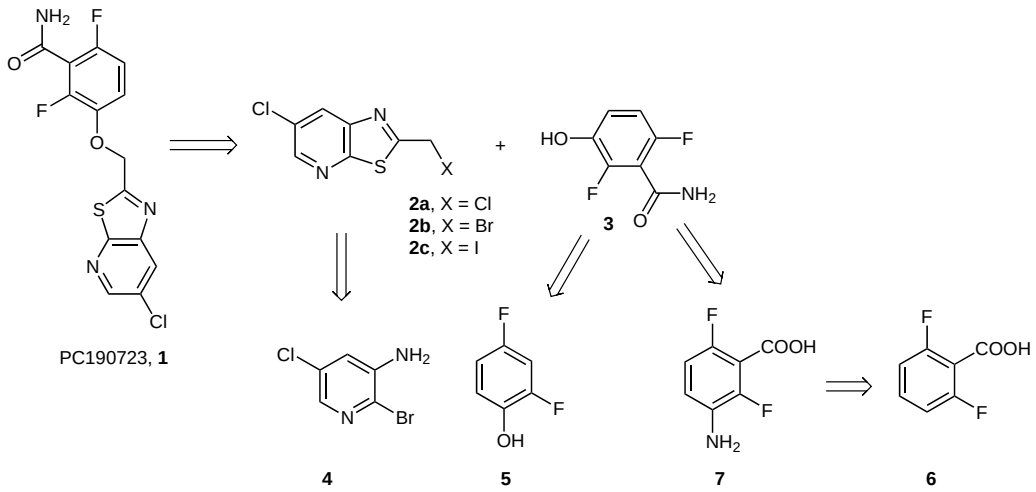
PC190723, **1**

Figure 1 Structure of PC 190723

In this context, bacterial cytoskeleton and cell division proteins, in particular FtsZ, have been recognized as unexploited and attractive targets in the search for new antibiotics with which to fight the widespread emergence of pathogens resistant to current antibiotics.[3] FtsZ is the key protein of bacterial cell division and undergoes guanosine 5′-triphosphate (GTP) dependent polymerization to form the Z ring at the mid-cell during cell division.[3a] Considerable progress has been made recently in the field of antibacterial small-molecule FtsZ inhibitors.[3a,4] PC190723 (**1**; Figure 1), a benzamide derivative with a thiazolo[5,4-*b*]pyridine fragment, is one such synthetic compound that is active on the GTPase of FtsZ.[5] This compound was discovered at Prolysis Inc, and operates through a new mechanism of action based on its interaction with FtsZ. It has potent and selective in vitro bactericidal activity against staphylococci, including methicillin- and multi-drug-resistant aureus and was efficacious in an in vivo model of infection, curing mice infected with a lethal dose of *S. aureus*.[5] There are a limited numbers of syntheses reported for PC190723, including recent publications by Haydon et al.[5a] and Sorto et al.[6] The synthesis of PC190723, which was initialized in medicinal chemistry research on a small scale by Haydon et al., started from expensive 2,6-difluoro-3-methoxybenzamide and used benzyloxyacetyl chloride as a protection strategy. Subsequently, Sorto et al. reported a five-step synthesis of PC190723 in a practical way by following a closely related route. Due to its promising biological properties, our group is interested in developing efficient syntheses of PC190723 with the long-term goal of discovering new antibiotic agents using PC190723 as a lead and understanding the mechanism by which these compounds act on this protein. We started the synthesis of PC190723 by examining the use of 6-chloro-2-(chloromethyl)thiazolo[5,4-*b*]pyridine, the synthesis of which we reported recently,[7] with the aim of developing a more versatile access to this class of compounds. We herein report an efficient synthetic route that is suitable for scaling up the production of PC190723.

The retrosynthetic analysis shown in Scheme 1 revealed the synthetic strategy used for the preparation of PC190723 (**1**), which involved the coupling reaction of halomethyl substituted thiazolo[5,4-*b*]pyridine **2** and 2,6-difluoro-3-hydroxybenzamide (**3**). The heterocycle **2** was prepared from 2-bromo-5-chloropyridin-3-ylamine (**4**) in a sequence of five steps. Benzamide **3** was readily synthesized from 2,4-difluorophenol (**5**) by regioselective lithiation and carboethoxylation followed by aminolysis. We also considered the alternative possibility of synthesizing **3** from 2,6-difluorobenzoic acid (**6**) by a reaction sequence based on the retrosynthetic analysis depicted in Scheme 1, involving the preparation and diazotization of

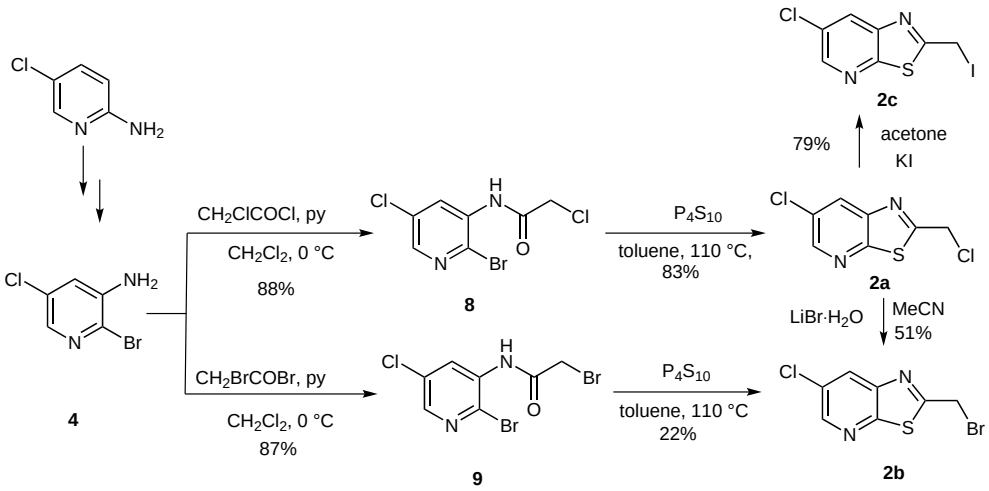
SYNLETT 2012, 23, 1039–1042
Advanced online publication: 05.04.2012
DOI: 10.1055/s-0031-1290777; Art ID: ST-2012-W0040-L



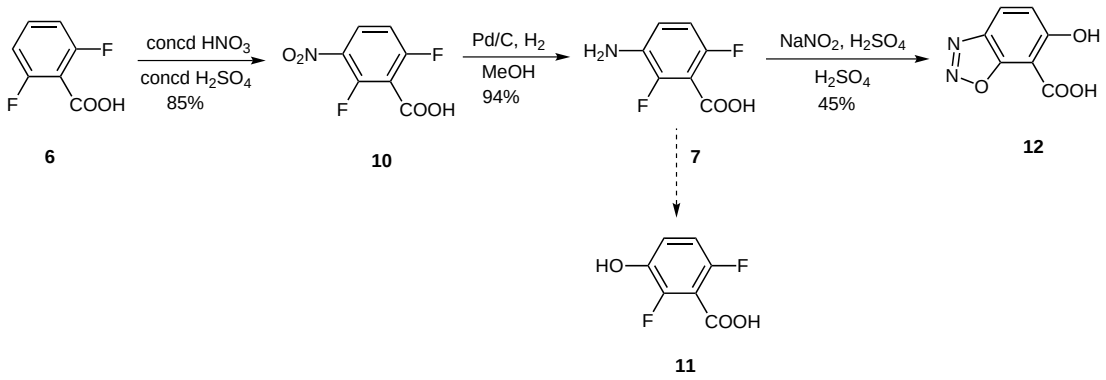
Scheme 1 Retrosynthetic route to PC190723 (**1**)

3-amino-2,6-difluoro-benzoic acid (**7**) to introduce the 3-hydroxy group on the phenyl ring.

The synthesis commenced with the known intermediate 2-bromo-5-chloropyridin-3-ylamine (**4**), which was prepared from 2-amino-5-chloropyridine after nitration,[8] diazotization–bromination[8] and reduction,[7] according to previously described procedures[7] (Scheme 2). The subsequent acylation of **4** with commercially available chloroacetyl chloride under the optimized conditions[7] allowed compound **8** to be efficiently prepared in 92% yield. In a similar manner, bromide **9** was synthesized in 87% yield by using bromoacetyl bromide as an acylation agent. Subsequent sulfurization and ring closure of **8** and **9** suffered some problems with dehalogenation byproduct formation using Lawesson's reagents either in toluene or *p*-xylene. The formation of unwanted dechlorinated byproduct was also observed when 2,5-dichloropyridin-3-ylamine was used to prepare **2a** under the same sulfurization conditions reported in the previous publication.[6] It was thought that 2-bromo-5-chloropyridin-3-ylamine derivative **8** may behave differently to the 2,5-dichloropyridin-3-ylamine reported in the previous study on the ring closure process. However, after many unsuccessful attempts using Lawesson's reagent, we solved the problem of dehalogenation by changing the sulfurization reagent into the more common reagent phosphorus decasulfide (P_4S_{10}). Optimal conditions were achieved when the sulfurization and ring closure were conducted in a P_4S_{10}/toluene system at 110 °C for only 30 minutes. The shorter reaction time may help minimize the formation of the unwanted dechlorinated byproducts and thus increase the yield. Compound **2a** was obtained in 83% yield with only a trace amount of dechlorinated byproduct being detected by TLC analysis. However, under the same conditions, the sulfurization and ring closure of **9** did not go well, with much larger amounts of unwanted debrominated byproduct being formed, and with only 22% yield of **2b**. Bromide **2b** was also prepared through a halogen exchange from **2a** in 51% yield. The synthesis of iodide **2c** required heating of compound **2a** with sodium iodide in acetone at room temperature for 20 hours, which ensured almost complete conversion while preventing decomposition of the product (79% yield).



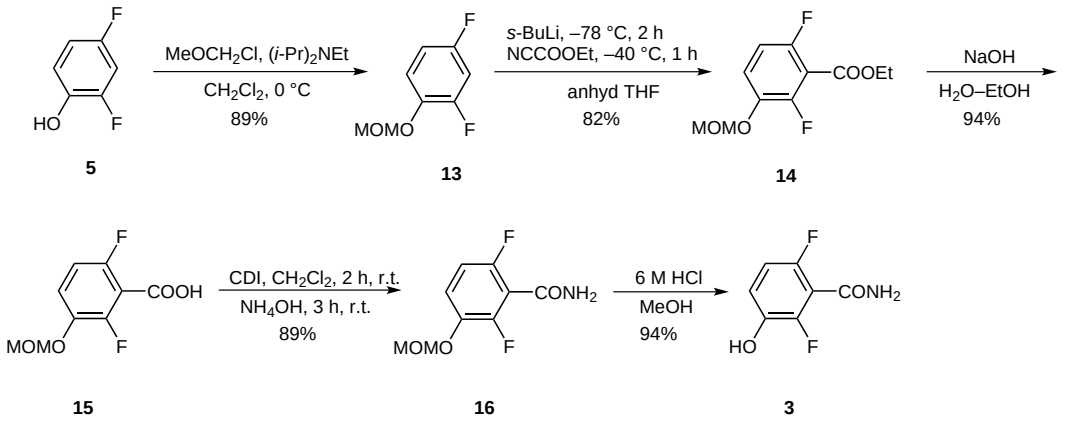
Scheme 2 Synthesis of 6-chloro-2-(chloromethyl)thiazolo[5,4-*b*]pyridine



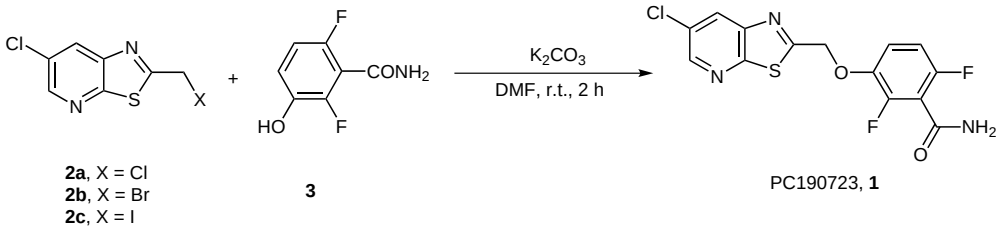
Scheme 3 Attempted synthesis of 2,6-difluoro-3-hydroxybenzoic acid (**11**) from 2,6-difluorobenzoic acid (**6**)

We initially attempted the synthesis of 2,6-difluoro-3-hydroxybenzoic acid (**11**) from inexpensive and readily available 2,6-difluorobenzoic acid (**6**), since the value of aniline as an efficient precursor of phenols is well recognized (Scheme 3). Nitration of **6** proceeded smoothly in concentrated HNO_3/H_2SO_4 to obtain **10** in 85% yield. Subsequent reduction of **10** was performed in 94% yield with H_2 over 10% Pd/C in methanol to give **7**. Diazotization of the latter to a diazonium ion seemed go very well, however, subsequent displacement of the diazonium group by a hydroxy group upon heating in water was unsuccessful. Attempts were made to solve the problem by reducing the reaction temperature and by using ethyl ester or amide forms of **7** as a starting material for the diazotization. However, all attempts failed and the starting material was converted into 6-hydroxy-1-oxa-2,3-diazaindene-7-carboxylic acid (**12**)[9] via the diazonium intermediate. Ultimately, we abandoned this route and instead chose to use commercially available 2,4-difluoro-phenol (**5**) as the starting material for the synthesis of fragment **3** (Scheme 4). Protection of phenol **5** as the methoxymethyl ether **13** was carried out over two hours in the presence of *N*,*N*-diisopropylethylamine (DIPEA) at 0 °C. The regioselective lithiation of **13** was conveniently carried out with *s*-BuLi in anhydrous tetrahydrofuran (THF). The following phenyl ring carboethoxylation was furnished using ethyl cyanoformate to give compound **14**. The use of ethyl cyanoformate has attracted attention because it allows for one step formation of the ester of carboxylic acids, and as we proposed that it could be easily converted into amide **16** during subsequent aminolysis. Unfortunately, amide **16** could not be prepared from the ester directly via aminolysis under a variety of conditions. The next step led, by efficient hydrolysis of the ester (94% yield), to acid **15**. Activation of carboxylic acid using *N*,*N*′-carbonyldiimidazole (CDI) successfully converted acid **15** into amide **16** in 89% yield. Deprotection of **16** completed the synthesis of **3** in 94% yield.

With fragments **2** and **3** in hand, we continued the synthesis of target compound **1** according to the strategy described in Scheme 5. Initial attempts to obtain **1** were discouraging; the coupling reaction of **2a** with **3** was very sluggish. When Cs_2CO_3 was used as the base in acetonitrile, as suggested in a report by Sorto et al.,[6] only approximately 10% of product **1** was obtained after stirring for 3 h at 65 °C, with many other byproducts being formed. The difficulties mainly arose from the moderate reactivity of chloride **2a** and its tendency to undergo dechlorination. We therefore chose to include NaI as a catalyst for the alkylation, which eventually led to the desired coupling product **1**, albeit in a very modest isolated yield of 10%. The alkylation reaction was then conducted at room temperature. However, even reaction times of longer than 24 hours did not result in a better yield of **1**. Alternatively, by



Scheme 4 Synthesis of 2,6-difluoro-3-hydroxybenzamide (**3**) from 2,4-difluorophenol (**5**)



2a, X = Cl
2b, X = Br
2c, X = I

3

PC190723, **1**

Scheme 5 The synthesis of PC190723

taking advantage of the higher reactivity of bromide **2b**, 0.2 equivalent of NaI was used in the reaction with **3** in a K_2CO_3/DMF system, which led to a marked improvement in the efficiency of the reaction (36% yield). The improvement prompted us to use **2c** in the same reaction system, which led to a further enhancement in the yield of **1** to 56%, although the preparation of **2c** was more expensive than those of **2a** and **2b**. Fortunately, in the course of the optimization of the reaction conditions, we observed that the yields improved when different base and solvent systems were used. By using K_2CO_3 as base in acetonitrile at room temperature, the reaction of **2a** and **3** catalyzed by 0.2 equivalent of NaI resulted in a marked improvement in the efficiency of this reaction, and **1** was obtained in 79% yield.[10]

In summary, we have disclosed a short and efficient approach to a practical synthesis of PC190723 starting from 2,4-difluorophenol and 2-bromo-5-chloropyridin-3-ylamine. Reaction conditions were generally mild and only a single protecting group was used during the process. We believe that this is a general approach towards the synthesis of this class of FtsZ inhibitors, which can be easily used in the context of the formation of other analogues in medicinal chemistry research. Although the synthesis of PC1970223 requires metalation of an intermediate with *s*-BuLi, it is easily scalable for the production of multigram quantities. A major contrast between this approach and the previously reported routes is the use of low-cost starting materials, specifically avoiding 2,6-difluoro-3-methoxybenzamide and benzyloxyacetyl chloride. Further development and use of this methodology for the synthesis of new inhibitors is in progress in our laboratory and will be reported shortly.

Acknowledgment

This work was financially supported by The National Basic Research Program (973 Program) (2010CB735601 and 2012CB724501).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) (a) Fischbach, M. A.; Walsh, C. T. *Science* **2009**, *325*, 1089. (b) Furtado, G. H.; Nicolau, D. P. *Expert Opin. Ther. Pat.* **2010**, *20*, 1273.

(2) Spellberg, B.; Guidos, R.; Gilbert, D.; Bradley, J.; Boucher, H. W.; Scheld, W. M.; Bartlett, J. G.; Edwards, J. Jr. *Clin. Infect. Dis.* **2008**, *46*, 155.

(3) (a) Lock, R. L.; Harry, E. J. *Nat. Rev. Drug Discovery* **2008**, *7*, 324. (b) Vollmer, W. *Appl. Microbiol. Biotechnol.* **2006**, *73*, 37.

(4) (a) Mathew, B.; Srivastava, S.; Ross, L. J.; Suling, W. J.; White, E. L.; Woolhiser, L. K.; Lenaerts, A. J.; Reynolds, R. C. *Bioorg. Med. Chem.* **2011**, *19*, 7120. (b) Czaplewski, L. G.; Collins, I.; Boyd, E. A.; Brown, D.; East, S. P.; Gardiner, M.; Fletcher, R.; Haydon, D. J.; Henstock, V.; Ingram, P.; Jones, C.; Noula, C.; Kennison, L.; Rockley, C.; Rose, V.; Thomaides-Brears, H. B.; Ure, R.; Whittaker, M.; Stokes, N. R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 524. (c) Margalit, D. N.; Romberg, L.; Mets, R. B.; Hebert, A. M.; Mitchison, T. J.; Kirschner, M. W.; RayChaudhuri, D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11821.

(5) (a) Haydon, D. J.; Bennett, J. M.; Brown, D.; Collins, I.; Galbraith, G.; Lancett, P.; Macdonald, R.; Stokes, N. R.; Chauhan, P. K.; Sutariya, J. K.; Nayal, N.; Srivastava, A.; Beanland, J.; Hall, R.; Henstock, V.; Noula, C.; Rockley, C.; Czaplewski, L. *J. Med. Chem.* **2010**, *53*, 3927. (b) Haydon, D. J.; Stokes, N. R.; Ure, R.; Galbraith, G.; Bennett, J. M.; Brown, D. R.; Baker, P. J.; Barynin, V. V.; Rice, D. W.; Sedelnikova, S. E.; Heal, J. R.; Sheridan, J. M.; Aiwale, S. T.; Chauhan, P. K.; Srivastava, A.; Taneja, A.; Collins, I.; Errington, J.; Czaplewski, L. G. *Science* **2008**, *321*, 1673.

(6) Sorto, N. A.; Olmstead, M. M.; Shaw, J. T. *J. Org. Chem.* **2010**, *75*, 7946.

(7) Ding, Z.; Ma, X.; Zhou, W. *Synth. Commun.* **2012**, DOI: 10.1080/00397911.2011.566408.

(8) Zhou, Z. L.; Navratil, J. M.; Cai, S. X.; Whittemore, E. R.; Espitia, S. A.; Hawkinson, J. E.; Tran, M.; Woodward, R. M.; Weber, E.; Keana, J. F. *Bioorg. Med. Chem.* **2001**, *9*, 2061.

(9) Analytical and spectral data: beige solid; mp 166–168 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.29 (d, *J* = 9.2 Hz, 1 H), 7.43 (d, *J* = 9.6 Hz, 1 H), 14.10 (s, 1 H), 15.00 (br s, 1 H); MS (ESI): *m*/*z* = 203.04 $[M + Na]^+$; HRMS (ESI): *m*/*z* $[M^+ + Na]^+$ calcd for $C_7H_4N_2O_4$: 203.0069; found: 203.0070.

(10) Analytical and spectral data: yellow solid; mp 220–222 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.72 (s, 2 H), 7.10 (td, *J* = 9.0, 2.0 Hz, 1 H), 7.41 (td, *J* = 9.2, 5.2 Hz, 1 H), 7.81 (br s, 1 H), 8.10 (br s, 1 H), 8.65 (d, *J* = 2.4 Hz, 1 H), 8.72 (d, *J* = 2.0 Hz, 1 H); MS (ESI): *m*/*z* = 378.04 $[M + Na]^+$, 394.02 $[M + K]^+$. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.85, 161.12, 155.67, 152.83 (dd, *J* = 240.35, 6.3 Hz), 148.33 (dd, *J* = 247.95, 9.6 Hz), 146.20, 145.95, 141.97 (dd, *J* = 11.2, 3.3 Hz), 129.92, 129.36, 117.16–116.71 (m), 111.32 (d, *J* = 4.2 Hz), 111.09 (d, *J* = 3.2 Hz), 69.29; ^{19}F NMR (500 MHz, DMSO-d_6): δ = –122.78 (dd, *J* = 10.0, 5.0 Hz, 6-F), –133.55 (d, *J* = 10.0 Hz, 2-F); MS (ESI): *m*/*z* = 378.04 $[M + Na]^+$, 394.02 $[M + K]^+$; HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_8ClF_2N_3O_2S$: 377.9892; found: 377.9895.

