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Target-Directed Synthesis of Antibacterial Drug Candidate GSK966587

Eric A. Voight,*,†,‡ Hao Yin,† Susan V. Downing,† Stacie A. Calad,† Hayao Matsuhashi,† Ilaria Giordano,§ Alan J. Hennessy,§ Richard M. Goodman,† and Jeffery L. Wood†

GlaxoSmithKline, Synthetic Chemistry Department, 709 Swedeland Road, P.O. Box 1539, King of Prussia, Pennsylvania 19406, and Antibacterial DPU, Infectious Diseases CEDD, Gunnels Wood Road, Stevenage, SG1 2NY, U.K.

eric.a.voight@abbott.com

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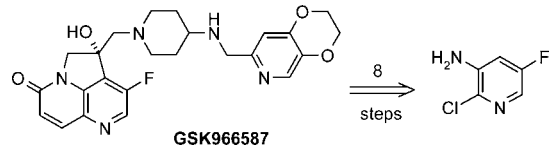
ABSTRACT



An efficient enantioselective total synthesis of the potent antibiotic GSK966587 was accomplished. Highlights of the synthesis include two innovative Heck reactions, a highly selective zincate base directed *ortho*-metalation, Sharpless asymmetric epoxidation, and a fully convergent final step fragment coupling.

In a study aiming to identify novel antimicrobial agents, GSK966587 (**1**, Figure 1) was chosen for further development due to its potent activity against Gram-positive and Gram-negative bacteria. The existing synthetic route to prepare compound **1** was lengthy and challenging to scale. An efficient and inexpensive catalytic asymmetric synthesis was needed to support material needs for a rapid project timeline. From a synthetic standpoint, the complex hexacyclic structure of GSK966587 presented ample opportunity for the discovery and development of novel organic reactions.

Our strategy to GSK966587 (**1**) is shown in Scheme 1. To maximize convergency, a disconnection that separated the fully elaborated side chain (**2**) from the tricyclic core spiro-epoxide (**3**) was chosen. The greater nucleophilicity of the piperidine nitrogen over the alkylamine would ideally circumvent the need for a protecting group. Diamine **2** would be derived from reductive amination of readily prepared aldehyde **5**[1] with commercially available 1-Boc-4-aminopiperidine (**4**). Spiro-epoxide **3** could be prepared from allylic alcohol **6** via Sharpless asymmetric epoxidation[2] followed by cyclization. We envisioned the preparation of alcohol **6** from a directed *ortho*-metalation reaction to install the C-8 substituent,[3] requiring 7-fluoro[1.5]naphthyridinone (**7**). Compound **7** could arise from an acrylate Heck reaction[4] of commercially available 2-chloro-5-fluoro-3-pyridinamine (**8**)[5] followed by cyclization.[6]

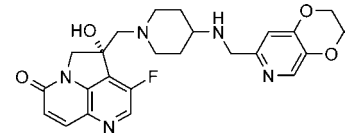


Figure 1. GSK966587 (**1**).

To begin the synthesis, the Heck reaction of chloropyridine **8** was investigated (Scheme 2). Although significant progress has been made regarding Heck reactions of aryl chlorides,[7] there are few examples with heteroaryl chloride substrates.[8] Initial screening of ligand, base, and solvent combinations

† Synthetic Chemistry Department, Chemical Development.
‡ Current Address: Abbott Laboratories.
§ Antibacterial Discovery Performance Unit, Infectious Diseases Center for Excellence in Drug Discovery.

(1) Cailleau, N.; Davies, D. T.; Hennessy, A. J.; Jones, G. E.; Miles, T. J.; Pearson, N. D. Patent WO 2007/071936 A1.

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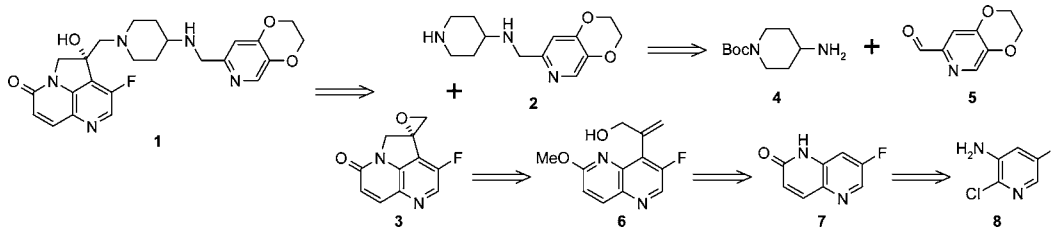
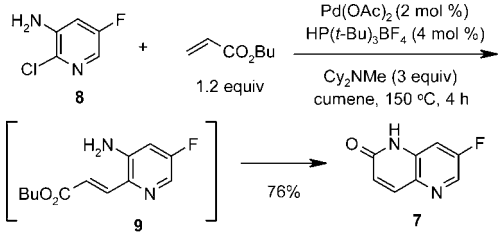
Scheme 1. Retrosynthetic Analysis



identified S-Phos[9] as an optimal ligand, affording Heck product **9** in 69% yield after chromatography. The coupling product could be treated with NaOEt in EtOH to produce the desired naphthyridinone **7** in 84% yield.[6a]

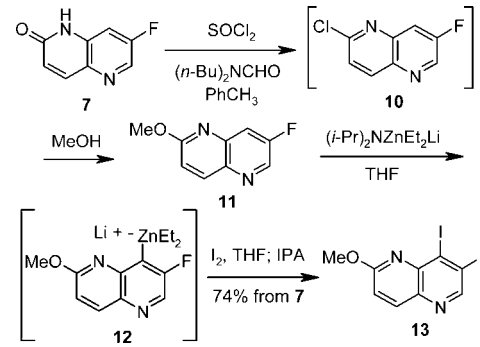
Scheme 2. One-Pot Heck/Cyclization Reaction of 2-Chloropyridine **8**



Although the two-step process was sufficient for supplying material for early development work, it was observed that desired naphthyridinone **7** was a major byproduct in reactions with tri-*tert*-butylphosphine as ligand in aromatic solvents.[10] Further optimization around the direct preparation of naphthyridinone **7** identified the current best conditions (Scheme 2) and afforded the product in 76% yield. The mechanism of the cyclization reaction remains unclear, but a palladium hydride addition/cyclization/elimination pathway seems to be the most likely rationale.[11]

With a reliable route to fluoronaphthyridinone **7** in hand, its conversion to methoxynaphthyridine **11** was investigated (Scheme 3). A vast array of direct methylation conditions gave primarily *N*-methylation, so an indirect path via chloronaphthyridine **10** was employed. Both $POCl_3$ and $SOCl_2$/DMF accomplished chlorination cleanly.[12] Basic conditions were originally used to convert chloronaphthyridine **10** to methoxynaphthyridine **11**, but competitive fluorine displacement was a persistent problem. As an alternative, the conversion of naphthyridinone **7** to chloronapthyridine **10** was followed by MeOH addition. The excess HCl that was generated promoted the transformation to methoxynaphthyridine **11**.[13] Demethylation back to naphthyridinone **7** was the major side reaction (6%), but this byproduct could be washed away efficiently with 4 N aqueous NaOH.

Scheme 3. Preparation of 7-Fluoro-8-iodo-2-methoxy[1.5]naphthyridine (**13**)

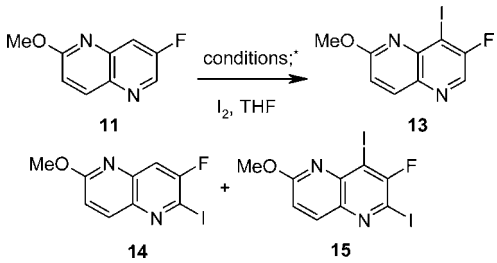


At this point in the synthesis, a regioselective directed *ortho*-metalation[3] of naphthyridine **11** was required (Table 1). Traditional alkyllithium or lithium amide bases gave poor

(2) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
(3) For related quinoline metalation strategies, see: (a) Bannacef, I.; Tymciu, S.; Dhilly, M.; Mongin, F.; Quéguiner, G.; Lasne, M.; Barré, L.; Perrio, C. *J. Org. Chem.* **2004**, *69*, 2622. (b) Lefebvre, O.; Marull, M.; Schlosser, M. *Eur. J. Org. Chem.* **2003**, 2115. (c) Marull, M.; Schlosser, M. *Eur. J. Org. Chem.* **2003**, 1576.
(4) Ziegler, C. B., Jr.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2941.
(5) 2-Chloro-5-fluoro-3-pyridinamine: $2295/kg from Archimica.
(6) For a similar strategy to a [1.5]naphthyridinone, see: (a) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1985**, *33*, 4764. (b) Li, J.; Zheng, L.; King, I.; Doyle, T. W.; Chen, S. *Curr. Med. Chem.* **2001**, *8*, 121.
(7) Littke, A. F.; Fu, G. C. *Org. Synth.* **2005**, *81*, 63, and references cited therein.
(8) (a) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989. (b) Basu, B.; Frejd, T. *Acta Chem. Scand.* **1996**, *50*, 316.
(9) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.
(10) A similar path to a [1,8]naphthyridinone has been reported in 42% yield: Singh, B.; Bacon, E. R.; Robinson, S.; Fritz, R. K.; Lesher, G. Y.; Kumar, V.; Dority, J. A.; Reuman, M.; Kuo, G.; Eissenstat, M. A.; Pagani, E. D.; Bode, D. C.; Bentley, R. G.; Connell, M. J.; Hamel, L. T.; Silver, P. J. *J. Med. Chem.* **1994**, *37*, 248.
(11) Intermediate **9** was observed by HPLC analysis during the one-step Heck cyclization, and exposure of isolated **9** to those reaction conditions provided cyclized product **7**. However, in the presence of only Cy_2NMe and xylene at 135 °C, the reaction from isolated **9** to napthyridinone **7** was very slow, suggesting that Pd catalyst is needed for the conversion.
(12) Dibutylformamide was later used in place of dimethylformamide to catalyze the $SOCl_2$ reaction in order to alleviate safety concerns around the potential formation of dimethylcarbamoyl chloride (DMCC), a known potent carcinogen. See: Levin, D. *Org. Process Res. Dev.* **1997**, *1*, 182.
(13) The mono-HCl salt of **10** did not react with MeOH; however, even a catalytic amount of HCl could convert the mono-HCl salt to **11**. Thanks to Huan Wang (GSK) for this suggestion.

results and required cryogenic conditions, since methoxynapthyridine **11** was prone to form dianions (entry 1) and/or suffered nucleophilic displacement of the C-7 fluorine. While LDA gave promising results under carefully controlled conditions (entry 2), we also became interested in zincate base methodology.[14] Uchiyama's zincate, TMPZn(*t*-Bu)$_2$Li, gave predominantly undesired monoiodide **14** (entry 3).[15] When (*i*-Pr)$_2$NZn(*t*-Bu)$_2$Li was used, monoiodide **13** was the major product, but the deprotonation was sluggish (entry 4). Since $ZnEt_2$ and LDA are both commercially available and inexpensive, we attempted to prepare and use (*i*-Pr)$_2$NZnEt$_2$Li.[16] This zincate reagent gave rapid deprotonation of naphthyridine **11** at −10 °C in THF, providing the desired monoiodide **13** with excellent selectivity after iodine quench (entry 5).[17] At least 3 equiv of iodine was needed, since EtI was also formed in the reaction. After addition of IPA, filtration, and a 1 N NaOH slurry, key intermediate **13** was isolated in 85% yield from naphthyridine **11**. In practice, the conversion of naphthyridinone **7** to iodide **13** was performed as a through process using a crude toluene stream of naphthyridine **11** (Scheme 3). This procedure gave isolated iodide **13** in 74% yield for the two steps. The novel heterocycle deprotonation demonstrated here complements the pioneering pyridine metalation techniques introduced by Schlosser and co-workers[18] and should be applicable to other challenging directed *ortho*-metalation reactions.

Table 1. Preparation of Iodide **13**[a]

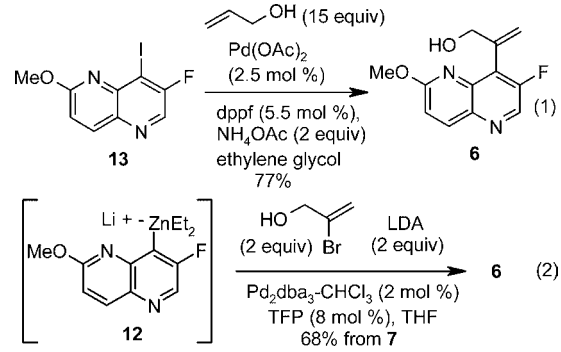


	base	equiv	time (min)	temp (°C)	**13/14/15** (area %)[b]
1	LDA	1.5	15	−70	42/8/40
2	LDA	1.1	5	−60	83/8/1.5
3	TMPZn(*t*-Bu)$_2$Li	1.1	30	23	26/34/23
4	(*i*-Pr)$_2$NZn(*t*-Bu)$_2$Li	1.0	120	23	45/5/0
5	(*i*-Pr)$_2$NZnEt$_2$Li[c]	1.2	30	−10	96/4/0

[a] All reactions in THF; quenched with excess I_2. [b] Area percentage by HPLC analysis. Remaining HPLC area was primarily starting material. [c] When this reaction was repeated in toluene, the ratio was 88/0/12.

After considerable experimentation with Negishi and Suzuki coupling approaches to prepare allylic alcohol **6**, the Heck reaction between iodonaphthyridine **13** and allyl alcohol was investigated (Scheme 4, eq 1). α-Regioselective allyl alcohol Heck reactions of aryl bromides are known to occur in ionic liquid solvents.[19] After extensive ligand and base screening, and optimization of temperature and reagent stoichiometry, a 71% yield of allylic alcohol **6** was obtained using [bmim][BF_4] as the solvent. While the ionic liquid conditions gave acceptable results, we also chose to explore traditional solvents. Ethylene glycol proved to perform as well as [bmim][BF_4], and after further optimization, a 77% yield of allyl alcohol **6** could be obtained following flash column chromatography.[20]

Scheme 4. Allyl Alcohol Coupling Reactions



As an alternative to the allyl alcohol Heck coupling, a Negishi coupling with zincate **12**, obtained from selective deprotonation with (*i*-Pr)$_2$NZnEt$_2$Li (Scheme 3), was also explored. The zincate base was added to naphthyridine **11** to form zincate **12**, and this solution was transferred to a preformed mixture of 2-bromopropen-3-ol, LDA, THF, Pd_2dba_3•$CHCl_3$, and trifurylphosphine. The process from naphthyridinone **7** to allyl alcohol **6** via Negishi coupling provided the product in 68% yield and only required a single purification (Scheme 4, eq 2). Compared to the Heck coupling strategy, this process is one step shorter since formation of iodide **13** is no longer necessary.

To introduce the single asymmetric center of GSK966587, a Sharpless asymmetric epoxidation of allylic alcohol **6** was used (Scheme 5).[2] This reaction took place at 0 °C with 10 mol % of Ti(O*i*-Pr)$_4$, 15 mol % of L-DIPT, 2.5 equiv of cumene hydroperoxide, and 100 wt % of 4 Å molecular sieves. Under these conditions, epoxy alcohol **16** could be isolated in 81% yield and 90% ee.

(14) For a review, see: Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem., Int. Ed.* **2007**, *47*, 3802.

(15) This regiochemical discrepancy has been observed in deprotonation of pyridines: Imahori, T.; Uchiyama, M.; Sakamoto, T.; Kondo, Y. *Chem. Commun.* **2001**, 2450. The regiochemistry of the undesired mono-iodide has not been confirmed.

(16) (*i*-Pr)$_2$NZnEt$_2$Li has not shown any propensity toward benzyne formation in our studies, even though (TMP)ZnMe$_2$Li is known to react with haloarenes to form benzynes: Uchiyama, M.; Miyoshi, T.; Kajihara, Y.; Sadamoto, T.; Otani, Y.; Ohwada, T.; Kondo, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8514.

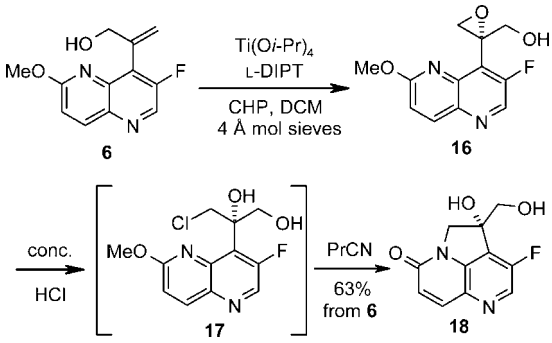
(17) A report of the unsuccessful use of this reagent in a screen of various zincate bases has appeared: Gauthier, D. R., Jr.; Limanto, J.; Devine, P. N.; Desmond, R. A.; Szumigala, R. H., Jr.; Foster, B. S.; Volante, R. P. *J. Org. Chem.* **2005**, *70*, 5938.

(18) (a) Marzi, E.; Bobbio, C.; Cottet, F.; Schlosser, M. *Eur. J. Org. Chem.* **2005**, 2116. (b) Schlosser, M.; Mongin, F. *Chem. Soc. Rev.* **2007**, *36*, 1161.

(19) Pei, W.; Mo, J.; Xiao, J. *J. Organomet. Chem.* **2005**, *690*, 3546.

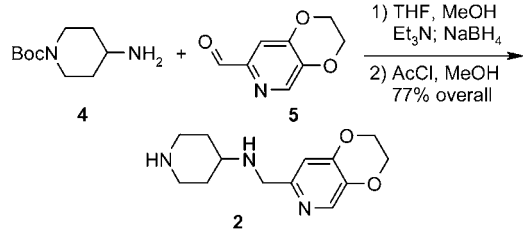
(20) A 65−70% yield was obtained via EtOAc/cyclohexane crystallization; however, this procedure remains in need of optimization.

Scheme 5. Preparation of Tricyclic Diol **18**



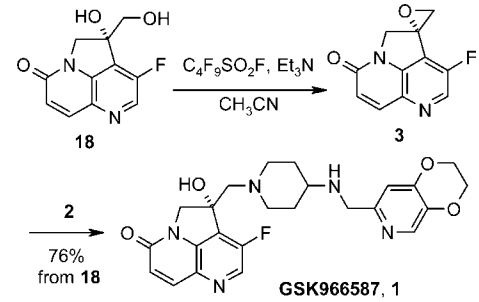
Encouraging results were obtained when epoxide **16** was opened with 4-Boc-aminopiperidine or fully elaborated side chain **2** (Scheme 1), but concerns about intramolecular fluorine displacement quickly led us to consider an alternative route (Scheme 5). When unpurified epoxy alcohol **16** was treated with concentrated HCl, chloro diol **17** was formed. After aqueous workup, the solution of chloro diol **17** in butyronitrile was heated to 100 °C for 1.5 h, causing cyclization and demethylation to occur in one pot.[21] Cooling to room temperature completed the crystallization of tricyclic diol **18** in 63% overall yield from allylic alcohol **6** with no deterioration of ee.[22] The high water solubility of tricyclic diol **18** precluded any reaction conditions requiring an aqueous workup, so this protocol was well-suited for efficient isolation.

Scheme 6. Preparation of Fully Elaborated Side Chain **2**



The preparation of fully elaborated side chain **2** is shown in Scheme 6. Commercially available *N*-Boc-4-aminopiperidine was condensed with aldehyde **5**,[1] followed by sodium borohydride addition to complete the reductive amination. Aqueous workup, concentration, and carbamate deprotection with AcCl/MeOH gave the tri-HCl salt of **2**, which was basified with aq NaOH and extracted with DCM. This procedure gave fully elaborated side chain **2** in 77% overall yield.

Scheme 7. Total Synthesis of GSK966587



To complete the synthesis of GSK966587 (Scheme 7), spiro-epoxide **3** was prepared for final fragment coupling. Diol **18** was first converted to spiro-epoxide **3** using Et_3N and perfluorobutanesulfonyl fluoride.[23] After 1 h at room temperature and filtration through silica gel, epoxide **3** (98% solution yield) was treated with side chain **2** (1.5 equiv) at room temperature for 14 h. GSK966587 precipitated directly from the reaction mixture in 76% isolated yield from **18** (98.7 HPLC area %, 98% ee).

An efficient new route to GSK966587 was developed, converting 2-chloro-5-fluoro-3-pyridinamine (**8**) to GSK966587 (**1**) in eight steps and 25% overall yield with three isolated intermediates. The route showcased two innovative Heck reactions, novel applications of zincate base methodology in regioselective heterocycle deprotonation and one-pot Negishi cross-coupling, a Sharpless asymmetric epoxidation, and a fully convergent final coupling without requiring protecting groups. Further development of this route could provide the foundation for a long-term manufacturing-scale supply of GSK966587.

Acknowledgment. Thanks to Carolyn Grady (GSK) for technical sourcing, Josephine Vega (GSK) for analytical support, and Kevin Leach (GSK) for NMR support.

Supporting Information Available: Experimental procedures and spectroscopic and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Chloromethane is generated in the conversion of **17** to **18** and safety precautions (proper ventilation) were taken.

(22) With the opposite enantiomers of **16**, **17**, and **18**, an overall yield of 71% was obtained when epoxy alcohol **17** was isolated.

(23) Klar, U.; Neef, G.; Vorbruggen, H. *Tetrahedron Lett.* **1996**, *37*, 7497.