

Target-Directed Synthesis of
Antibacterial Drug Candidate GSK966587

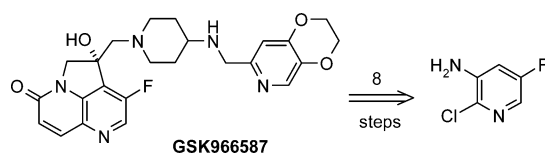
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ABSTRACT



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-aminopi-

peridine (**4**). Spiro-epoxide **3** could be prepared from allylic alcohol **6** via Sharpless asymmetric epoxidation² 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 reaction⁴ of commercially available 2-chloro-5-fluoro-3-pyridinamine (**8**)⁵ followed by cyclization.⁶

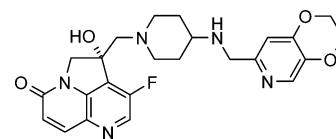


Figure 1. GSK966587 (**1**).

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

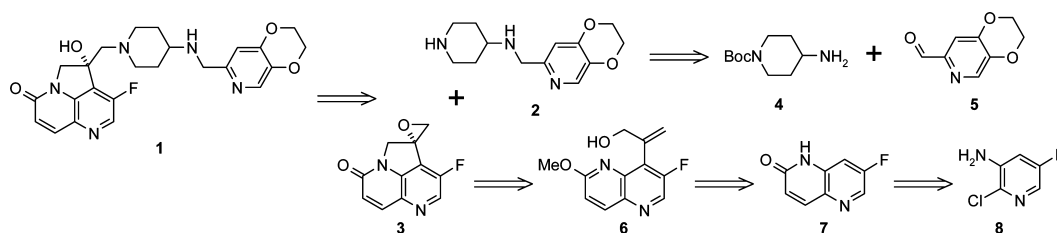
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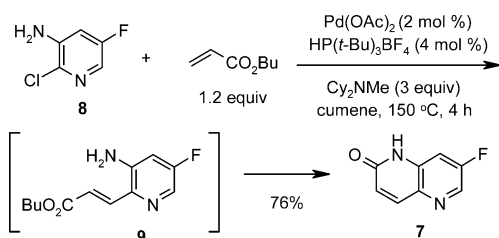
(1) Cailleau, N.; Davies, D. T.; Hennessy, A. J.; Jones, G. E.; Miles, T. J.; Pearson, N. D. Patent WO 2007/071936 A1.

Scheme 1. Retrosynthetic Analysis



identified S-Phos⁹ 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**

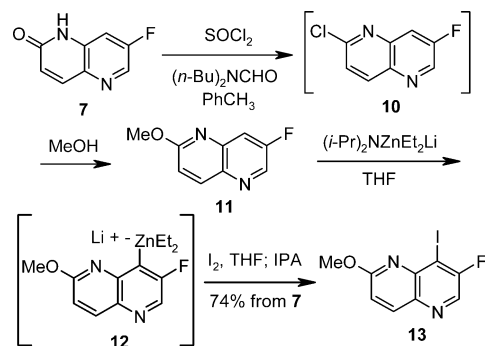


Although the two-step process was sufficient for supplying material for early development work, it was observed that desired naphthyridinone **7** was a major byproduct in reactions with tri-*tert*-butylphosphine as ligand in aromatic solvents.¹⁰ Further optimization around the direct preparation of 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

- (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.; Leshner, 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.

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 POCl₃ and SOCl₂/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 chloronaphthyridine **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*-metalation³ of naphthyridine **11** was required (Table 1). Traditional alkyllithium or lithium amide bases gave poor

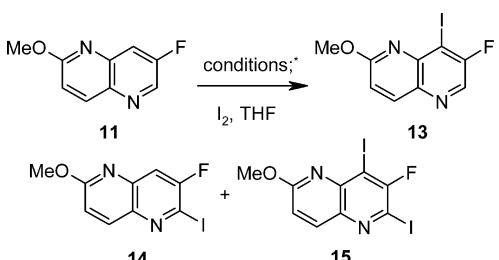
(11) Intermediate **9** was observed by HPLC analysis during the one-step Heck cyclization, and exposure of isolated **9** to those reaction conditions provided cyclized product **7**. However, in the presence of only Cy₂NMe and xylene at 135 °C, the reaction from isolated **9** to naphthyridinone **7** was very slow, suggesting that Pd catalyst is needed for the conversion.

(12) Dibutylformamide was later used in place of dimethylformamide to catalyze the SOCl₂ 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 methoxynaphthyridine **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, $\text{TMPZn}(t\text{-Bu})_2\text{Li}$, gave predominantly undesired monoiodide **14** (entry 3).¹⁵ When $(i\text{-Pr})_2\text{NZn}(t\text{-Bu})_2\text{Li}$ 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 $(i\text{-Pr})_2\text{NZnEt}_2\text{Li}$.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-workers¹⁸ and should be applicable to other challenging directed *ortho*-metalation reactions.

Table 1. Preparation of Iodide **13**^a



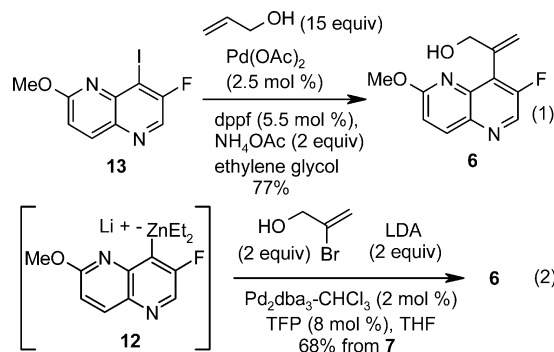
	base	equiv	time (min)	temp ($^\circ\text{C}$)	13/14/15 (area %) ^b
1	LDA	1.5	15	-70	42/8/40
2	LDA	1.1	5	-60	83/8/1.5
3	$\text{TMPZn}(t\text{-Bu})_2\text{Li}$	1.1	30	23	26/34/23
4	$(i\text{-Pr})_2\text{NZn}(t\text{-Bu})_2\text{Li}$	1.0	120	23	45/5/0
5	$(i\text{-Pr})_2\text{NZnEt}_2\text{Li}^c$	1.2	30	-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 $[\text{bmim}][\text{BF}_4]$ 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 $[\text{bmim}][\text{BF}_4]$, 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 $(i\text{-Pr})_2\text{NZnEt}_2\text{Li}$ (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, $\text{Pd}_2\text{dba}_3\cdot\text{CHCl}_3$, 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 $\text{Ti}(\text{O}i\text{-Pr})_4$, 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.

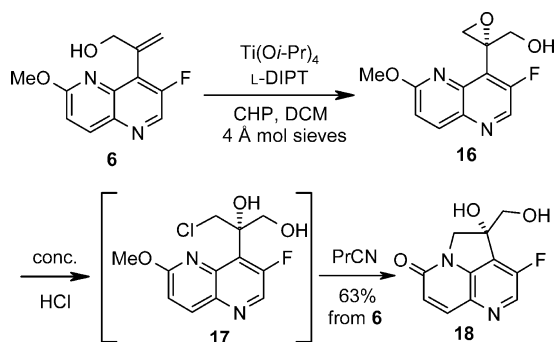
(16) $(i\text{-Pr})_2\text{NZnEt}_2\text{Li}$ has not shown any propensity toward benzyne formation in our studies, even though $(\text{TMP})\text{ZnMe}_2\text{Li}$ is known to react with haloarenes to form benzyne: Uchiyama, M.; Miyoshi, T.; Kajihara, Y.; Sadamoto, T.; Otani, Y.; Ohwada, T.; Kondo, 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.

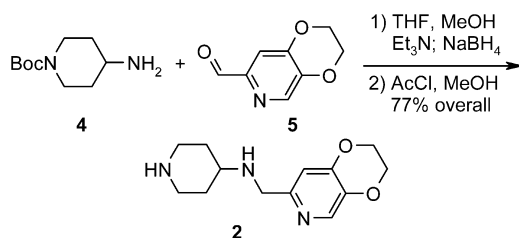
(18) (a) Marzi, E.; Bobbio, C.; Cottet, F.; Schlosser, M. *Eur. J. Org. Chem.* **2005**, 2116. (b) Schlosser, M.; Mongin, F. *Chem. Soc. Rev.* **2007**, *36*, 1161.

(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.

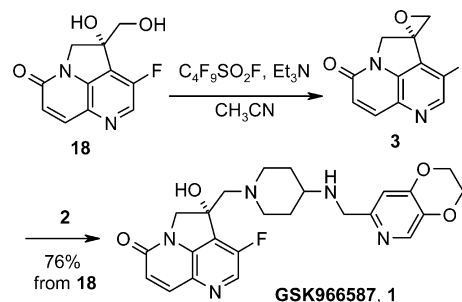
Scheme 6. Preparation of Fully Elaborated Side Chain **2**

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.

(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.

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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