New Leads for the Treatment of Multidrug Resistant 
*Mycobacterium tuberculosis*

Approximately one-fourth of the world’s population are infected with *Mycobacterium tuberculosis* (Mtb), the pathogen responsible for tuberculosis (TB), and an estimated 10 million people fall ill with TB each year, resulting in over a million deaths annually.1 The efficacy of existing front-line drugs such as rifampicin is diminishing, and approximately 3% and 18% of new and recurring cases of TB, respectively, arise from multidrug-resistant (MDR) Mtb. While TB is relatively rare in the United States and other developed countries, it is prevalent in southeast Asian and African communities, which account for approximately 70% of new TB cases. Thus, the demand for additional TB therapeutics is increasing, but because of these geographical disparities the field is not as heavily resourced as it needs to be.

In this issue of *ACS Central Science*, Lei and co-workers describe the discovery, synthesis, and in vitro evaluation of novel agents active against TB, including MDR-TB, based on the glycosylated polyketide natural product chrysomycin A (1, Figure 1).2 This report is notable for several reasons. First, while chrysomycin A (1) was first discovered nearly 70 years ago, its anti-Mtb properties were only recently recognized, in independent studies by the Lei and Kumar3 laboratories. Chrysomycin A (1) is selective for Mtb and is essentially nontoxic to eukaryotic cells at effective doses.3 Second, while first-in-class syntheses of related natural products have been reported,4 the work of Lei and co-workers stands out for its brevity and flexibility. As outlined below, the synthetic pathway uses strategic C–H activation reactions to quickly assemble the polycyclic aromatic carbon framework, which ultimately allowed the authors to prepare over 30 analogues of the natural product. Finally, the manuscript deserves praise because it traverses the pathway from synthesis of the target, analogue production, and in vitro evaluation in a single report, culminating in the identification of synthetic analogues with potencies exceeding that of the natural product in cell culture.

The researchers’ route to chrysomycin A (1) began with the commercial reagent 1,8-naphthalene diol (not shown), which was converted to the aryl bromide (2) in two steps and 96% yield (Figure 1). A highly practical, site-selective iridium-catalyzed C–H borylation5 then provided the arylboronate 3. It is notable that this transformation could be conducted on >20 g scales using only 3 mol % of iridium as a catalyst. The carboxylic acid 4 was obtained in two steps, and 78% yield by palladium-catalyzed reduction of the bromide function in 4 and Suzuki coupling with a hindered aryl bromide (not shown). A silver-catalyzed C–H oxidation6 was used to convert the carboxylic acid 4 directly to the lactone 5 in 84% yield and on a multigram scale. The lactone 5 contains the central tetracyclic ring system of the target. Two aspects of the sequence are highlighted here. First, the pathway to 5 proceeds in six steps and 47% overall yield from 1,8-naphthalene diol. This level of efficiency is critical if one seeks to synthesize natural product derivatives, as the authors clearly accomplished (vide infra). Second, the tetracyclic polyaromatic skeleton found in 5 is derived biosynthetically from acetate and propionate building blocks, and this type...
The strategic use of C–H oxidation reactions enables rapid entry into the polyketide skeleton from an inexpensive and symmetric starting material.

The ethylene residue in the target was installed by a single-flask multistep sequence comprising hydrogenolysis of the O-benzyl substituent, triflation of the resulting phenol, and Suzuki coupling with potassium vinyltrifluoroborate (84%). In the second phase of the synthesis, the authors probed introduction of the β-D-virenose residue in the target. While most carbohydrates are linked through oxygen, the virenose fragment in chrysomycin A (1) is linked through carbon. These so-called C-glycosides are well-known; nonetheless, an issue of site-selectivity challenges the transformation here, as the acceptor may react with the carbohydrate donor at two positions (C2 and C4, see 5). After some experimentation, the authors discovered that treatment with an acetate donor, tin tetrachloride, and molecular sieves provided the desired C4 glycosylated product with 50% yield and complete site- and stereoselectivity. In developing this reaction, the authors found that the O-isopropyl substituent was labile under the reaction conditions, and its premature removal led to glycosylation at C2 exclusively. Thus, it was hypothesized that this substituent directs glycosylation to the desired C4 position through nonbonded interactions with the donor. Finally, removal of the carbohydrate protecting groups (sulfuric acid, methanol) provided chrysomycin A (1, 27% from 5).

This synthetic sequence establishes a foundation to produce derivatives of the natural product, and in this report the authors disclose the synthesis and evaluation of over 30 structurally distinct analogues. Significantly, C2 glycosylated derivatives were less potent than chrysomycin A (1), underscoring the necessity to control site-selectivity in the glycosylation. The most potent derivative, 6 (Figure 1), is highlighted here. This compound possesses an L-fucosyl residue in place of the D-virenose found in chrysomycin A (1). The derivative 6 was synthesized by a parallel pathway involving site-selective glycosylation using an L-fucosyl donor. It possessed a minimum inhibitory concentration in the range of 0.08–0.32 μg/mL against five rifampicin-resistant clinical isolates and was up to 5-fold more potent than chrysomycin A (1) against one of these strains. It is interesting to consider that the carbohydrate residues in 1 and 6 are pseudoenantiomeric, and further understanding of the mode of action of this class of molecules may reveal the basis for the increased potency of 6. Finally, it is worth noting that compounds such as 6 would be difficult to access via a semisynthetic approach as methods for cleavage of the carbon–carbon bond linking the glycoside would need to be developed.

Overall, this single report provides a strong foundation to further pursue this class of targets as novel TB agents. It is the full package: identification of a useful biological phenotype, effective implementation of a state-of-the-art synthetic strategy,
and preliminary studies to develop structure−activity relationships, all of which are needed to advance the class further. The efficiency of the authors’ synthetic strategy, coupled with the validated synthesis of dozens of analogues, underscores the robustness of the approach and sets the stage for development of this exciting new class of anti-TB agents.

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Notes

The author declares no competing financial interest.

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