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A Unified Strategy for the Syntheses of the Isoquinolinium Alkaloids Berberine, Coptisine, and Jatrorrhizine

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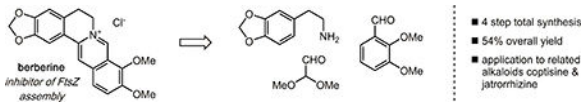
Abstract

Total syntheses of the antibacterial alkaloids berberine, coptisine, and jatrorrhizine have been achieved in four steps through a unified route. The key step of this strategy is an efficient intramolecular Friedel–Crafts alkoxyalkylation which, following oxidation, establishes the isoquinolinium core of these natural products. Herein, the design and development of this synthetic strategy, which has enabled the shortest and most efficient syntheses of these alkaloids reported to date, is described.

Graphical Abstract



Antibacterial resistance constitutes an ever-increasing public health threat around the world.[1] Contrary to the global need to access new treatment options, very few antibiotics have been developed over the past couple of decades[2] and the current development pipeline is very limited.[3] Therefore, there is a growing urgency[4] for the development of new treatment regimes. This has spurred efforts to discover and identify new antibiotic classes that operate through novel modes of action.

Filamenting temperature-sensitive mutant Z (FtsZ) is a prokaryotic tubulin homologue that is necessary for bacterial cell division and is conserved among all bacteria,[5] making it a potential antibacterial target.[6] Berberine (**1a**, Figure 1),[7] an alkaloid isolated from plant tissues with a long history of use in Chinese folk medicine and a wide range of interesting biological activities (e.g., antifungal, antimalarial, antidiabetic, and anticancer activities),[8] has been shown to exhibit moderate antibacterial activity by inhibiting FtsZ assembly.[9] Semisynthetic berberine analogues that show improved binding affinity for FtsZ display a corresponding increase in antibacterial potency.[10] However, structure–activity relationship

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ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and ^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF)

(SAR) studies have thus far been limited to derivatives accessible by modification of natural berberine.[11,12] To facilitate the study of as-of-yet unknown SAR studies, our laboratory has devised a short and efficient total synthesis of berberine that will enable the preparation of a wide range of fully synthetic berberine analogues for biological testing. Additionally, we have demonstrated that this synthetic strategy enables the preparation of the structurally related congeners coptisine and jatrorrhizine, both of which have antibacterial activity of unknown origin.[13]

Pictet and Gams published the first purported synthesis of berberine in 1911;[14] however, Buck and Davis later contested this report by demonstrating that the key annulation utilized in Pictet's synthesis delivered an isomeric alkaloid as opposed to berberine.[15] Successful total syntheses of berberine have been reported by Kametani,[16] Donohoe,[17] Anand,[18] and Tong[19] (Scheme 1). Kametani completed the first total synthesis of berberine in 1969, which required more than six steps and proceeded with low overall efficiency.[16] In 2014, Donohoe developed a more efficient synthetic route to berberine that featured a carefully designed, palladium-catalyzed enolate arylation.[17] This route required seven total steps (five steps longest linear sequence) and provided berberine in an impressive 50% overall yield. Anand and Tong also devised synthetic routes to berberine; however, these strategies proceeded with modest overall efficiency (24% and 19% yield, respectively).[18,19] Common to these previous approaches has been the need to access prefunctionalized precursors (e.g., aryl bromides and aryl acetylenes) in order to execute the key step of the synthesis.

As part of our efforts to develop new antibacterials that target FtsZ, herein we report a new synthetic route to berberine, coptisine, and jatrorrhizine that features classical synthetic transformations that proceed without the use of transition-metal catalysts or prefunctionalized synthetic intermediates. This approach provides berberine in only four steps with a 53% overall yield and, therefore, constitutes the most concise and efficient total synthesis of berberine to date. Our synthetic approach has also been applied to the preparation of coptisine (four steps, 39% yield) and jatrorrhizine (four steps, 20% yield), highlighting the versatility and efficiency of our strategy. It is worth noting that Song reported a related strategy that facilitated the construction of several berberine analogues;[20] this strategy enabled the construction of the isoquinolinium core of the natural product in five steps with overall yields ranging from 12% to 34%, depending on the substitution pattern of the analogue in question. Unfortunately, this route was never used to construct berberine itself and therefore cannot be directly compared to the work reported in this manuscript. We anticipate that this route will be useful for the future preparation of fully synthetic analogues of these alkaloids, which could be used for SAR studies directed toward identifying new inhibitors of FtsZ assembly as potential antibacterials.

Our retrosynthetic analysis involved disconnection of the isoquinolinium core of these natural products, which revealed three simple building blocks, phenethylamine **2**, acetal **3**, and benzaldehyde derivative **4**, as potential precursors (Scheme 2). We planned to construct tetrahydroisoquinoline **5**, using a Pictet—Spengler reaction. We recognized that there were several possible annulation strategies that would likely enable the assembly of tetrahydroisoquinoline **5** and aldehyde **4**, including direct union via the Pomeranz–Fritsch reaction.[21] More importantly, this strategy would divide the target into two fragments of

roughly equal complexity (e.g., **2** and **4**) that could then be united using 2,2-dimethoxyacetaldehyde (**3**) as a linchpin. Such a strategy would likely be valuable when employed as a method to enable the synthesis of novel natural product analogs for biological testing.

Our total synthesis of berberine began with the preparation of tetrahydroisoquinoline **5ab** (Scheme 3). A Pictet–Spengler reaction between commercially available 3,4-(methylenedioxy)phenethylamine (**2ab**) and 2,2-dimethoxyacetaldehyde (**3**) in the presence of trifluoroacetic acid afforded tetrahydroisoquinoline **5ab** in 69% yield. Unfortunately, efforts to convert **5ab** directly into berberine by way of Pomeranz–Fritsch reaction with 2,3-dimethoxybenzaldehyde (**4ac**) failed. This result is consistent with the absence of literature reports that utilize the Pomeranz–Fritsch protocol to access isoquinoliniums from acetals bearing secondary amines; to the best of our knowledge, all reports detailing the application of this annulation involve the conversion of primary amine derivatives into neutral isoquinolines.

To solve this issue, an alternative annulation tactic was pursued (Scheme 4). Toward this end, a reductive amination was carried out using tetrahydroisoquinoline **5ab** and 2,3-dimethoxybenzaldehyde (**4ac**), which provided tertiary amine **6** in 79% yield. This intermediate was then treated with triflic acid to promote a Friedel–Crafts alkoxyalkylation that presumably delivers intermediate **7**, which undergoes subsequent E1 elimination of methanol to afford lambertine (**8**).[22] This intermediate was characterized by NMR analysis of the crude reaction mixture and subsequently isolated as the corresponding iminium triflate (55%, not shown). Oxidation of lambertine using iodine in the presence of potassium acetate produced berberine (**1a**) in almost quantitative yield. This concise and highly efficient synthesis of berberine proceeded in 54% overall yield and required only four synthetic operations.

To demonstrate the versatility of our synthetic strategy, we applied it in the syntheses of two berberine congeners: coptisine (**1b**, Scheme 5) and jatrorrhizine (**1c**, Scheme 6). Coptisine was prepared via reductive amination of **5ab** using 2,3-(methylenedioxy)benzaldehyde (**4b**) to deliver tertiary amine 9 in 57% yield. Triflic acid promoted Friedel–Crafts cyclization followed by oxidation with iodine afforded coptisine (**1b**) in quantitative yield, thereby completing a four step total synthesis that proceeded in 39% overall yield. Our synthesis compares favorably with the most efficient total synthesis of coptisine previously reported (four steps, 43% overall yield).[23]

To access jatrorrhizine, phenethylamine **2c** and 2,2-dimethoxyacetaldehyde (**3**) were engaged in a Pictet–Spengler reaction to provide tetrahydroisoquinoline **5c** in 82% yield as a mixture of regioisomeric products (rr = 1.0:6.7). This inseparable mixture of regioisomers was utilized in a reductive amination with 2,3-dimethoxybenzaldehyde (4ac) to afford tertiary amine **10** in 60% yield (also as a mixture of isomers, 3.3:1.0 ratio in favor of the isomer shown). Friedel–Crafts cyclization and subsequent oxidation delivered isomerically pure jatrorrhizine (**1c**) in 41% yield. This rapid synthesis of jatrorrhizine required just four steps and proceeded in 20% overall yield. To the best of our knowledge, this is first total synthesis of this alkaloid.

In conclusion, we have developed a unified synthetic route that provides rapid and efficient access to the isoquinolinium alkaloids berberine, coptisine, and jatrorrhizine. Our strategy features an initial Pictet–Spengler reaction, followed by a two-step annulation protocol involving reductive amination and subsequent Friedel–Crafts alkoxyalkylation, which ultimately forges the key isoquinolinium ring of each natural product. Subsequent oxidation delivers the targeted natural products. We are currently utilizing this synthetic strategy to target fully synthetic analogues of berberine, coptisine, and jatrorrhizine for biological study as potential antibacterial agents that operate by inhibition of FtsZ assembly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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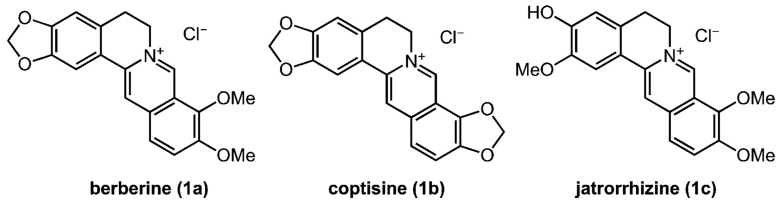
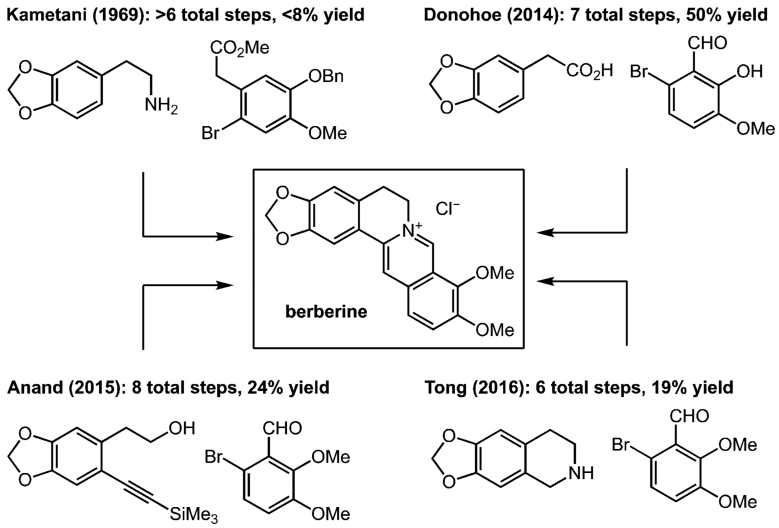
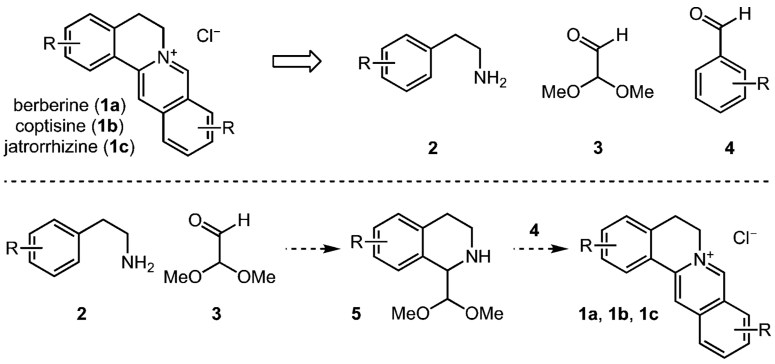


Figure 1.
Antibacterial isoquinolinium alkaloids of interest.

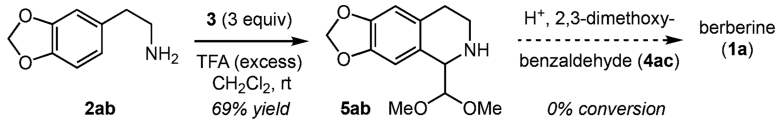


Scheme 1.
Previous Total Syntheses of Berberine



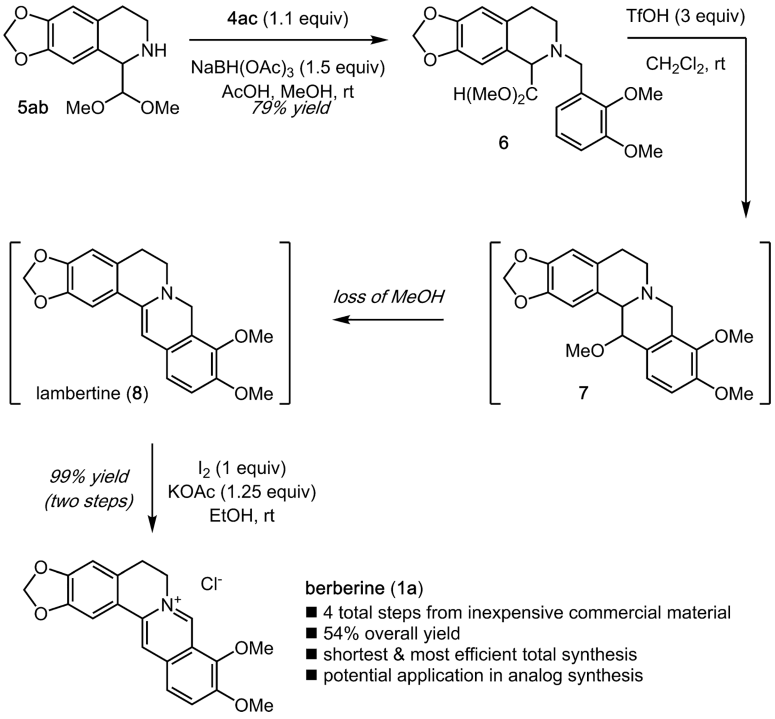
Scheme 2.

A Unified Synthetic Approach to the Berberine Family of Alkaloids



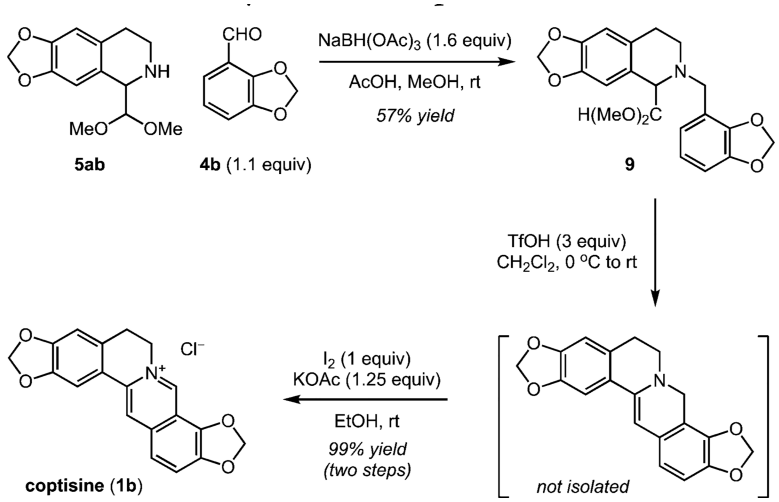
Scheme 3.

Synthesis of Tetrahydroisoquinoline 5ab and Unsuccessful Pomeranz–Fritsch Annulation

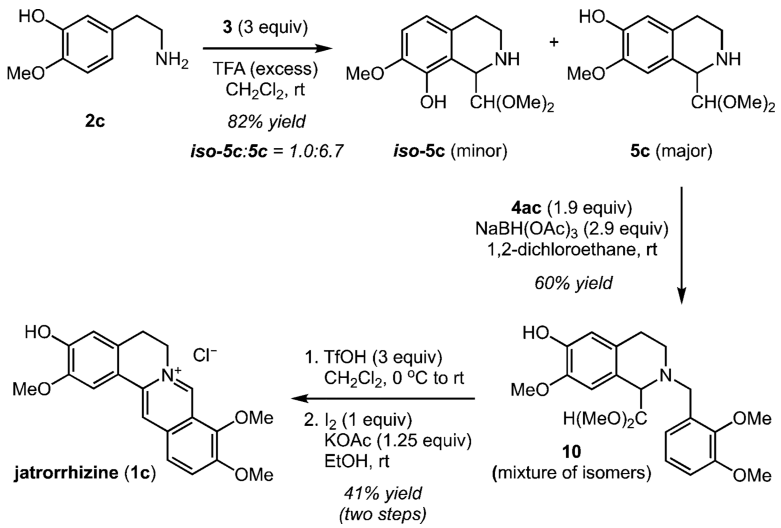


Scheme 4.

Completion of the Total Synthesis of Berberine



Scheme 5.
Total Synthesis of Coptisine



Scheme 6.
Total Synthesis of Jatrorrhizine