Total synthesis of clostrubin

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Clostrubin is a potent antibiotic against methicillin- and vancomycin-resistant bacteria that was isolated from a strictly anaerobic bacterium Clostridium beijerinckii in 2014. This polyphenol possesses a fully substituted arene moiety on its pentacyclic scaffold, which poses a considerable challenge for chemical synthesis. Here we report the first total synthesis of clostrubin in nine steps (the longest linear sequence). A desymmetrization strategy is exploited based on the inherent structural feature of the natural product. Barton–Kellogg olefination forges the two segments together to form a tetrasubstituted alkene. A photoinduced 6π electrocyclization followed by spontaneous aromatization constructs the hexasubstituted B ring at a late stage. In total, 200 mg of clostrubin are delivered through this approach.

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The discovery of effective antibiotic agents is an urgent global demand for combating drug-resistant pathogenic bacteria strains. Secondary metabolites that are produced by microbes as chemical defence have proven to be the most important source of such agents. In May 2014, Hertweck and co-workers reported the isolation of clostrubin (1, Fig. 1) from the strictly anaerobic bacterium C. beierrinchii. This compound exhibits remarkable potency against methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci, with minimum inhibitory concentrations of 0.12 and 0.97 μM, respectively. From a structural perspective, clostrubin (1) poses considerable synthetic challenge owing to the fused aromatic ring system and multisubstitution pattern. The potential of 1 as a lead compound for antibiotic development and its limited supply from natural sources stimulated us to launch a chemical synthesis programme immediately.

In this paper, we report the first total synthesis of clostrubin (1) from commercially available starting materials. This concise synthesis (nine-step for the longest linear sequence) benefits from the inherent structural symmetry of 1. A Barton–Kellogg olefination would be used for assembling a sterically hindered symmetrical, tetrasubstituted olefin 2 such strategy is rare in natural product synthesis. Preparing the symmetrical, tetrasubstituted olefin 2 is indeed of significant challenge with the conventional olefination methods, and Barton–Kellogg reaction is envisioned as a suitable solution. Interestingly, this olefination method has found remarkable applications in material science rather than natural product synthesis in recent years.

The inherent structural symmetry of the molecule inspires a desymmetrization strategy. A Barton–Kellogg olefination was constructed through Barton–Kellogg olefination, and a 6π electrocyclization promoted by ultraviolet light assembled the fully substituted B ring.

**Results**

**Retro-synthetic analysis.** We undertook a retro-synthetic analysis of clostrubin (1) taking advantage of the inherent symmetry of its molecular architecture, as illustrated in Fig. 1. The initial disassembly of the fully substituted B ring leads to a precursor 2; the recombination of the sterically hindered C8–C9 biaryl bond could rely on a 6π electrocyclization reaction. Electrocyclization has emerged as a powerful tool for the construction of fused ring systems since Nicolaou’s pioneering synthesis of endiandric acids. In particular, the strategy of 6π electrocyclization/aromatization has demonstrated a significant advantage in the synthesis of mult subsituted arenes. Recently, we exploited such a strategy in the total syntheses of a series of natural products, such as tubingensin A, daphenylline, xiamycin and oridamycin families, and rubrifodilactone A. It should be mentioned that the construction of hexa subst ituted arenes using such strategy is rare in natural product synthesis. Preparing the symmetrical, tetrasubstituted olefin 2 is indeed of significant challenge with the conventional olefination methods, and Barton–Kellogg reaction is envisioned as a suitable solution.

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**Figure 1 | Retrosynthetic analysis of clostrubin.** The inherent structural symmetry of the molecule inspires a desymmetrization strategy. A Barton–Kellogg olefination would be used for assembling a sterically hindered tetrasubstituted olefin. A 6π electrocyclization/aromatization sequence is envisioned as the key step for the construction of the hexa substituted aromatic B ring.

**Figure 2 | Synthesis of the anthraquinone segment.** Reagents and conditions: (a) tetrahydrofuran (THF), –78°C, 6 h; then silica gel, 22°C, 2 h. (b) K2CO3 (3.0 eq), Mel (2.5 eq), N,N-dimethylformamide (DMF), 22°C, 18 h, 45% (two steps). (c) SnCl2•H2O (6.0 eq), aqueous HCl (37 wt%), AcOH, 22°C, 30 min. (d) DBU (3.0 eq), TsN2 (1.1 eq), methylene chloride (CH2Cl2), 22°C, 20 h, 89% (two steps). TMS, trimethylsilyl.
silica gel may accelerate the hydrolysis of the silyl ether and thus led to a rapid aromatization along with release of HBr. Notably, when a single equivalent of 8 was used for the D–A reaction, a bromonaphthoquinone was readily prepared, presumably with the intermediacy of a mono cycloadduct\(^\text{61}\). The crude 9 was treated with \(\text{K}_2\text{CO}_3\) and \(\text{MeI}\) to give compound 11 (45% overall yield from 8). 11 underwent Clemmensen-type reduction in the presence of \(\text{SnCl}_2\) and \(\text{HCl}\) to give the corresponding monoketone\(^\text{62}\), which instantaneously tautomerized to anthranol. Exposure of crude 12 to \(1,8\text{-diazabicyclo}[5.4.0\text{]}\text{undec-7-ene}\) (DBU) and TsN\(_3\) furnished diazoketone \(^\text{13}\). Exposure of crude 12 to \(\text{SnCl}_2\) and \(\text{HCl}\) gave \(\text{CS}_2\) and \(\text{HCl}\) to give the corresponding monoketone\(^\text{62}\), which instantaneously tautomerized to anthranol. 12. Exposure of crude 12 to \(1,8\text{-diazabicyclo}[5.4.0\text{]}\text{undec-7-ene}\) (DBU) and TsN\(_3\) furnished diazoketone 3 in 89% overall yield.

We observed unexpected reactivity of anthraquinone 11 (Fig. 3) during the above studies, which influenced the overall strategy of the synthesis. In theory, the C9 carbonyl of 11 should be sterically more hindered for nucleophilic attack due to two neighbouring methoxy groups. From an electronic perspective, this upper ketone could be considered as an equivalent of a double vinylogous carbonate than is also rather unreactive as an electrophile. To our surprise, we obtained hydrazone 13 in 61% yield when treating 11 with TsNHNH\(_2\); the anticipated regioisomer was not detected. The structure of 13 was determined by X-ray crystallographic analysis. This observation interrupted our initial plan of exploiting the C10 tosylhydrazone of 11 as the potential precursor for the Barton–Kellogg olefination. We further examined other types of nucleophiles such as benzylic Grignard reagent for the addition reaction with 11. In this case, two regioisomeric alcohols 14 and 15 were isolated in 32% and 40% yields, respectively. Both structures were confirmed by nuclear Overhauser effect (NOE) studies. The enhanced reactivity of the C9 carbonyl may be attributable to inductive effects from the \(\text{OCH}_3\) substituents or relief of 1,3-allylic strain that occurs on nucleophilic additions. Thus, the strategy involving direct olefination of C10 carbonyl of anthraquinone 11 (for example, with functionalized benzylic metal species or phosphonate carbanion) had to be abandoned due to the poor regioselectivity.

We then focused on the synthesis of the thioester segment as the electron donor in the devised Barton–Kellogg olefination, as shown in Fig. 4. Aldehyde 16 was prepared in one step from commercially available 2-iodophenol\(^\text{63}\). Treatment with \(\text{K}_2\text{CO}_3\) and \(\text{MeI}\) gave methyl ether 17 (99% yield), which underwent MeMgBr addition followed by silylation to provide compound 18 (94% yield) in one pot. Hexamethyldisilazane (HMPA) was found to be crucial to enhance the nucleophilicity of the magnesium alkoxide. 18 was subjected to the magnesium–halogen exchange conditions (EtMgBr) to generate a functionalized Grignard reagent\(^\text{43,47,64–66}\), which was quenched by \(\text{CS}_2\) and \(\text{MeI}\) to give dithioester 19. It is noteworthy that lithiation–halogen exchange did not lead to a satisfactory result. The desilylation took place spontaneously during acid workup to deliver alcohol 20 in 67% yield from 18. Oxidation of 20 with Dess–Martin periodinane (DMP) afforded ketone 21 (83% yield) without destroying the sulfur-containing functionalities, and the subsequent methanolysis furnished thioester 4 in 66% yield.

**Completion of the synthesis.** With both fragments in hand, we directed our attention to the construction of the aromatic B ring, as depicted in Fig. 5. It is well documented in the literature of Barton–Kellogg olefination that thioketones readily react with diazo compounds without promoters or catalysts\(^\text{53–57}\). After examination of the conventional conditions, we realized that the stabilized dithioester 3 needed to be activated by \(\text{Rh}_2\text{(OAc)}_4\) to form the metal–carbenoid intermediate\(^\text{52,54,67–70}\), which was further trapped by relatively unreactive thioester 4. The

![Figure 3 | Unusual reactivity of the anthraquinone intermediate.](image)

**Figure 3 | Unusual reactivity of the anthraquinone intermediate.**

Reagents and conditions: (a) TsNHNH\(_2\) (1.0 eq), \(\text{TsOH}\cdot\text{HOCl}\) (10 mol%), \(\text{EtOH}\), 60°C, 2 h, 61%. (b) \(\text{BnMgBr}\) (1.0 eq), tetrahydrofuran (THF), 22°C, 15 min, 32% for 14 and 40% for 15. ORTEP, Oak Ridge Thermal Ellipsoid Plot.

![Figure 4 | Synthesis of the thioester segment.](image)

**Figure 4 | Synthesis of the thioester segment.** Reagents and conditions: (a) \(\text{K}_2\text{CO}_3\) (1.5 eq), \(\text{Mel}\) (1.5 eq), \(N,N\text{-dimethylformamide}\) (DMF), 22°C, 20 h, 99%. (b) \(\text{MeMgBr}\) (1.05 eq), 0°C, 10 min; then HMPA (2.0 eq), triethylamine (Et\(_3\)N; 1.5 eq), chlorotrimethylsilane (TMSCl; 1.5 eq), tetrahydrofuran (THF), 22°C, 10 min, 94%. (c) EtMgBr (1.5 eq), THF, 50°C, 1 h; then \(\text{CS}_2\) (30 eq), 70°C, 3 h; then \(\text{MeI}\) (4.0 eq), 22°C, 8 h, 67%. (d) DMP (1.2 eq), methylene chloride (CH\(_2\)Cl\(_2\)), 22°C, 1 min, 83%. (e) MeONa (10.0 eq), methanol (MeOH), 50°C, 4 h, 66%.
postulated episulfide intermediate 22 was reduced by Cu powder in situ to afford tetrasubstituted olefin 2 in 85% overall yield. We examined a series of conditions such as heating or FeCl₃, to promote the last C–C bond formation but only observed decomposition. Inspired by our synthesis of daphenylline, we irradiated 2 with ultraviolet light (λ = 365 nm). To our delight, this symmetrical olefin underwent a 6π electrolyzation, presumably to provide pentacyclic intermediate 23, which was spontaneously oxidized under an air atmosphere during workup to furnish tetramethyl clostrubin 24 (55% yield from 2). Global deprotection of the methyl groups with aqueous HBr (48 wt%) gave clostrubin (1) with excellent efficiency. The spectra and physical properties of the synthetic 1 are consistent with those reported for the natural product. In total, 200 mg of 1 were obtained through the synthesis.

**Discussion**

In summary, we have accomplished the first total synthesis of clostrubin. The concise and efficient route took advantage of the 6π electrolyzation strategy as well as the inherent structural symmetry of the molecule. The synthesis provides a practical means to obtain this potent antibiotic for further investigations, considering the limited supply and difficult isolation of the naturally occurring sample.

**Methods**

**General.** All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran was distilled immediately before use from sodium-benzophenone ketyl. Methylene chloride, N,N-dimethylformamide, triethylamine, N,N-diisopropylethylamine and chlorotrimethylsilane were distilled from calcium hydride and stored under an argon atmosphere. Methanol was distilled from magnesium and stored under an argon atmosphere. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Solvents for chromatography were used as supplied by Titan Chemical. Reactions were monitored by thin-layer chromatography carried out on S-2 0.25 mm E. Merck silica gel plates (60F-254) using ultraviolet light as visualizing agent and aqueous ammonium cerium nitrate/ammonium molybdate or basic aqueous potassium permanganate as visualizing agent. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). Nuclear magnetic resonance (NMR) spectra were recorded on Bruker AV-400 or Agilent 500/54/ASP instrument and calibrated by using residual undeuterated chloroform (δ_NH = 7.26 p.p.m.) and CDCl₃ (δ_NH = 77.16 p.p.m.) or undeuterated dimethylsulfoxide (δ_S = 39.52 p.p.m.), as internal references. Infrared spectra were recorded on a Thermo Scientific Nicolet 380 FT-IR spectrometer. Melting points are uncorrected and were recorded on a Shanghai Jingke SGE X-4 apparatus. High-resolution mass spectra were recorded on a Bruker APEXIII 7.0 Tesla ESI-FT or a Waters Micromass GCT Premier EI mass spectrometer. For ¹H and ¹³C NMR spectra of compounds, see Supplementary Figs 1–26. For heteronuclear multiple quantum correlation spectroscopy (HMQC) and heteronuclear multiple-bond correlation spectroscopy (HMBC) spectra of compound 13, see Supplementary Figs 27 and 28. For nuclear Overhauser effect spectroscopy (NOESY) spectra of compound 14 and 15, see Supplementary Figs 29 and 30. For the comparisons of ¹H and ¹³C NMR spectra of the natural and synthetic clostrubin, see Supplementary Figs 31 and 32. For the comparisons of ¹H and ¹³C NMR spectroscopic data of the natural and synthetic clostrubin, see Supplementary Tables 1 and 2. For the experimental procedures and spectroscopic and physical data of compounds and the crystallographic data of compound 13, see Supplementary Methods.

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Author contributions

A.L., M.Y. and J.L. conceived the synthetic route; A.L. directed the project; M.Y. and J.L. conducted the work; A.L., M.Y. and J.L. analysed the results; and A.L. wrote the manuscript.

Additional information

Accession codes: The X-ray crystallographic coordinates for structure (13) reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition number CCDC 1028256. These data can be obtained free of charge.
