Total Synthesis of Clerocidin via a Novel, Enantioselective Homoallenylboration Methodology

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Clerocidin (1), terpentecin (2), and UCT4B (3) (Figure 1) are recently isolated diterpenoid antibiotics that exhibit very promising antitumor activities in vitro and in vivo. It has been postulated that their antitumor properties arise through interference with topoisomerase II, a nuclear enzyme implicated in DNA metabolism and cell proliferation.5 Their common structural motif consists of a highly functionalized side-chain (C11–trans C16) attached at the C9 carbon of a trans-decalin core. Undoubtedly, this side chain is the most provocative part of the molecule, both from a structural and biological standpoint. Structurally, its high degree of oxygenation and strong electrophilic nature give rise to several forms in equilibrium (Figure 1) and present a formidable synthetic endeavor. Biologically, this side chain is believed to be responsible for the observed “topoisomerase II poison” activity.5 Our interest in these aspects of this class of compounds led us to undertake the total synthesis of clerocidin (1). Herein, we disclose a chemical synthesis of employing a key asymmetric homoenallenylation reaction for the construction of clerocidin’s carbon framework (Figure 2). This reaction sequence constitutes the first total synthesis of any of these natural products, proves the absolute stereochemistry of 1, and provides the first demonstration of the versatility of the asymmetric homoenallenylation reaction, in total synthesis.7

Our synthetic strategy was designed to target the keto aldehyde form (open form) of clerocidin (1), which exists in equilibrium with its hemiacetal form. This retrosynthetic analysis reveals that the entire carbon skeleton of 1 can be constructed by an asymmetric addition of a 1,3-butadienyl unit on the carbonyl carbon of 5 (Figure 2). To this end, application of the novel homoenallenylation methodology, recently developed by Brown and co-workers, appeared to be the best reaction candidate.8 Conceptually, this reaction involves treatment of an aldehyde 7 with a chiral homoenalenyboronate ester 8 to furnish alcohol 10.9 The stereochemical outcome at the C* center (ultimately C12 in clerocidin) is dictated by the chirality of the boronate ester 8 and transferred to the product via a putative six-membered transition state 9 (Figure 3). Use of this method was expected to produce alcohol 4, which could then be transformed to clerocidin (1) via the use of Sharpless’s asymmetric epoxidation10 and dihydroxylation11 methodologies (Figure 2). Application of this plan to the synthesis of clerocidin (1) is shown in Scheme 1. The synthesis of clerocidin (1) commenced with the optically active alcohol 11, which is readily available by a

Figure 1. Structures of clerocidin (1), terpentecin (2), and UCT4B (3).

Figure 2. Strategic bond disconnections of clerocidin (1).

Figure 3. Brown’s asymmetric homoenallenylation.

*S Supporting Information is available on the Web at http://pubs.acs.org.

(1) Andersen, N. R.; Lorck, H. O. B.; Rasmussen, P. R. J. Antibiot. 1983, 36, 753.
was then converted to the corresponding enol triflate, which deprotection of the C4 acetal, followed by silylation of the 1990 Parkowitz, A. D. J. Org. Chem.

1.1 equiv TIPSCl, 2.0 equiv imid, CH2Cl2, 25 °C, 2 h, 91%; (c) 1.5 equiv 1 h, 76%; (p) 2.0 equiv 1,2-phenylenediamine, CH3CN/H2O, 25 °C, 1

98%; (h) 1.5 equiv PCC/Celite, CH2Cl2, 25 °C, 1.5 h, 91%; (i) 2.0 equiv (Bu4N) 88%; (e) 1.05 equiv 9-BBN, THF, 0 °C, 2 h; MeOH, 10 equiv NaOH, 10 equiv H2O2, 89%; (f) 1.5 equiv NaH, 1.5 equiv PMBCl, 0.2 equiv of 85% yield. Conversion of 16 to the corresponding (S)- and (R)-Mosher esters and subsequent 1H NMR analysis confirmed the correct R-stereochemistry of the C12 hydroxyl group.16

Our attention was then focused on the dihydroxylation of the terminal olefin of 17. This was accomplished by first converting 17 to the α,β unsaturated aldehyde 18, which upon dihydroxylation (1%) afforded diol 19 in 67% yield over three steps (3:1 ratio at C14, in favor of the indicated isomer). Swern oxidation of 19,17 followed by in situ deprotection of the C12 silyl ether, gave rise to its C14 methanol adduct (20) upon methanolic workup (76% yield). Synthetic 20 exhibited identical spectroscopic and analytical data with the natural compound. Compound 20 is known to exist in equilibrium with 1,1 and its complete conversion to 1 was accomplished by dissolving 20 in methylene chloride and evaporating the solvent. Further evidence confirming the structure of synthetic 1 was obtained by treating 1 with o-phenylenediamine to produce the phthalazine adduct 21, which also exhibited identical spectroscopic data to the one derived from natural clerocidin.

In summary, the first total synthesis of clerocidin (1) has been designed and executed in an enantioselective fashion. The cornerstone of our strategy involves the use of asymmetric homoallylation8 for the assembly of the clerocidin framework. Our strategy provides the first synthetic application of this method and clearly demonstrates its utility for the construction of complex 1,3-butadienyl-2-carbinols. In addition, our synthesis proves unambiguously the absolute stereochemistry of clerocidin (1) and should allow access to a variety of potentially bioactive analogues.

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Supporting Information Available: Selected experimental procedures and spectral data for compounds 1, 4, 5, and 11–21 (20 pages).

(15) Use of chiral substituents on the boron was indispensable for the observed asymmetric reactivity, since use of the isopropyl boronate yielded alcohol 4 with complete scrambling of the stereochemistry at the C12 center, while use of the (D)-DIPT boronate afforded preferentially 4 with the unwanted stereoisomer at C12.