Total Synthesis of Clerocidin via a Novel, Enantioselective Homoallenylboration Methodology

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Clerocidin (**1**),[1] terpentecin (**2**),[2] and UCT4B (**3**)[3] (Figure 1) are recently isolated diterpenoid antibiotics that exhibit very promising antitumor activities in vitro and in vivo.[4] 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] In addition to their remarkable biological profile, these compounds possess a challenging molecular architecture, beckoning the development of synthetic methodology.[6] Their common structural motif consists of a highly functionalized side-chain (C11−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**).

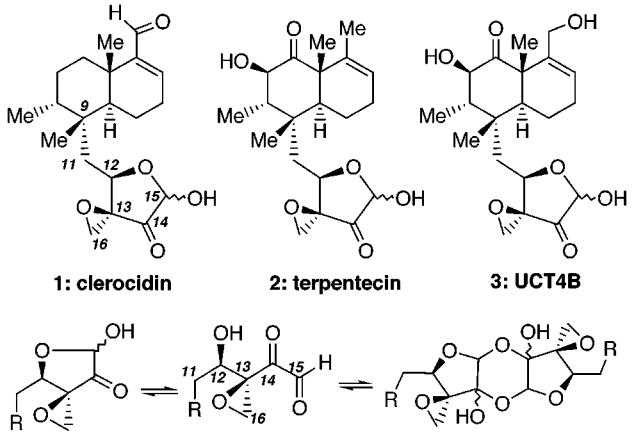

Figure 1. Structures of clerocidin (**1**), terpentecin (**2**), and UCT4B (**3**).

Herein, we disclose a chemical synthesis of **1** employing a key asymmetric homoallenylboration 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 homoallenylboration reaction, in total synthesis.[7]

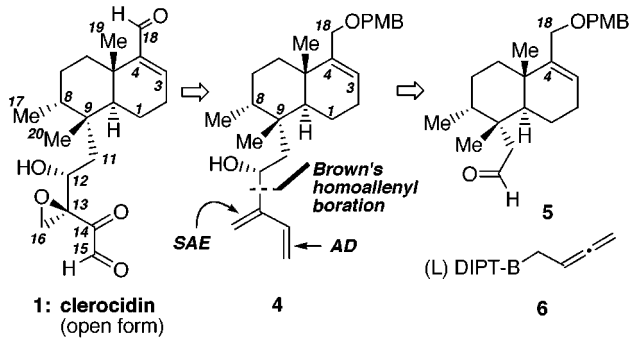

Figure 2. Strategic bond disconnections of clerocidin (**1**).

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 homoallenylboration 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 homoallenylboronate 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 epoxidation[10] and dihydroxylation[11] methodologies (Figure 2). Application of this plan to the synthesis of clerocidin (**1**) is shown in Scheme 1.

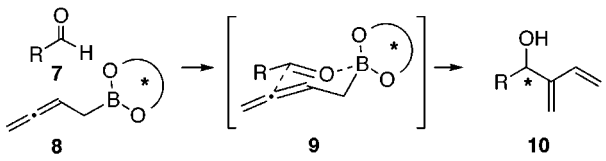

Figure 3. Brown's asymmetric homoallenylboration.

The synthesis of clerocidin (**1**) commenced with the optically active alcohol **11**, which is readily available by a

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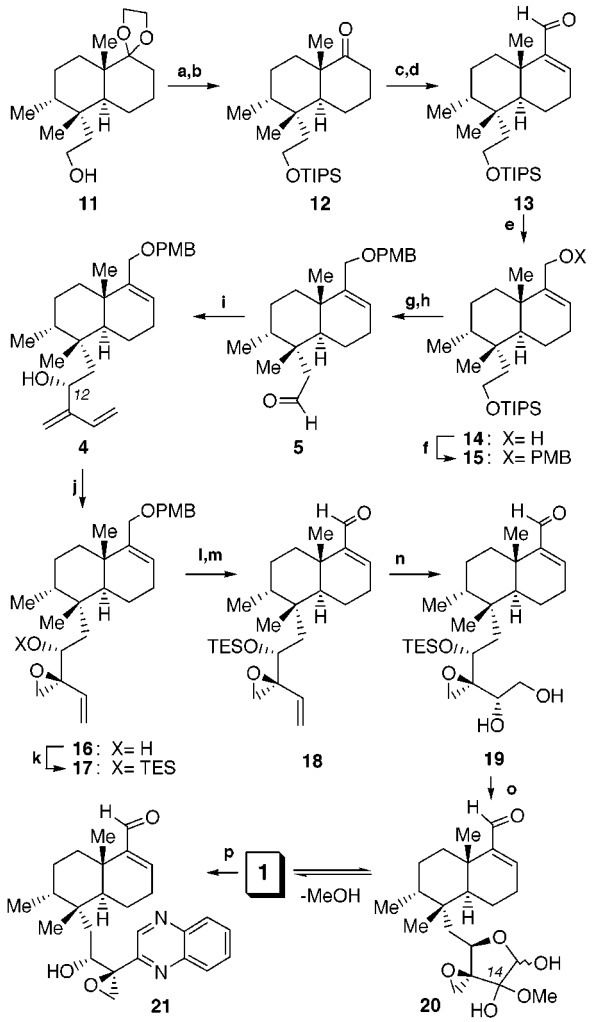
Scheme 1. Total Synthesis of Clerocidin (1)[a]



[a] Reagents and conditions: (a) 1 N HCl, THF, 25 °C, 2 h, 98%; (b) 1.1 equiv TIPSCl, 2.0 equiv imid, CH_2Cl_2, 25 °C, 2 h, 91%; (c) 1.5 equiv NaHMDS, 2.0 equiv $PhNTf_2$, THF, −78 °C, 1 h, 100%; (d) 10% $Pd(PPh_3)_4$, CO, 3.0 equiv LiCl, 1.1 equiv Bu_3SnH, THF, 50 °C, 4 h, 88%; (e) 1.05 equiv 9-BBN, THF, 0 °C, 2 h; MeOH, 10 equiv NaOH, 10 equiv H_2O_2, 89%; (f) 1.5 equiv NaH, 1.5 equiv PMBCl, 0.2 equiv of $(Bu_4N)^+I^-$, DMF, 25 °C, 6 h, 83%; (g) 1.5 equiv TBAF·THF 25 °C, 2 h, 98%; (h) 1.5 equiv PCC/Celite, CH_2Cl_2, 25 °C, 1.5 h, 91%; (i) 2.0 equiv **6**, toluene, MS, −78 °C, 72 h, 83% (71% de); (j) 0.25 equiv D-(−)-DET, 0.22 equiv $Ti(^iPrO)_4$, 2.0 equiv tBuOOH, MS, CH_2Cl_2, −20 °C, 88% (86% de); (k) 1.1 equiv TESOTf, 2.0 equiv 2,6-lutid, CH_2Cl_2, 25 °C, 0.5 h, 97%; (l) 1.5 equiv DDQ, wet CH_2Cl_2, 25 °C, 3 h, 95%; (m) 1.3 equiv Dess−Martin periodinane, 3.0 equiv pyrid, CH_2Cl_2, 25 °C, 4 h, 98%; (n) 0.01 equiv $(DHQD)_2PHAL$, 0.01 equiv $K_2OsO_2(OH)_4$, 3.0 equiv $K_3Fe(CN)_6$, 3.0 equiv K_2CO_3, tBuOH, H_2O, 0 °C, 7 h, 72% (50% de); (o) 5.0 equiv $(COCl)_2$, 8.0 equiv DMSO, CH_2Cl_2, −78 °C then 16 equiv Et_3N, 2 h, −78 °C to 25 °C then 1.5 equiv TBAF·THF, MeOH, 25 °C, 1 h, 76%; (p) 2.0 equiv 1,2-phenylenediamine, CH_3CN/H_2O, 25 °C, 1 h, 73%.

modification of the reported procedure.[12] Acid-induced deprotection of the C4 acetal, followed by silylation of the C12 primary alcohol afforded **12** in 89% yield. Ketone **12** was then converted to the corresponding enol triflate, which upon treatment with tributyltin hydride under CO atmosphere and Pd(0) catalysis[13] gave rise to the α,β unsaturated aldehyde **13** (88% yield). 9-BBN-mediated reduction[14] of the C18 aldehyde afforded allylic alcohol **14**, which was protected as the corresponding *p*-methoxybenzyl ether **15** (two steps, 74%). Fluoride-induced desilylation of **15**, followed by PCC oxidation of the resulting alcohol, yielded the desired aldehyde **5** (two steps, 89% yield) (Scheme 1).

The stage was now set for the construction of alcohol **4**. Thus, reaction of (L)-diisopropyl tartrate (DIPT) boronate **6** with aldehyde **5** (toluene, molecular sieves (4 Å MS), −78 °C, 72 h) afforded **4** in 83% yield and 6:1 ratio at C12 in favor of the desired diastereomer.[8,15] Sharpless asymmetric epoxidation[10] of the C13−C16 double bond, using (−) diethyl tartrate (DET) as the chiral ligand, followed by silylation of the C12 hydroxyl group gave rise to **17** via alcohol **16** (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% $(DHQD)_2PHAL$)[11] 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 desilylation of the C12 silyl ether, gave rise to synthetic clerocidin, which was isolated as 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 homoallenylboration[8] for the assembly of the clerocidin's 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** (28 pages).

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