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Total Synthesis of Chloropeptin II (Complestatin) and Chloropeptin I

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Complestatin (**1**, chloropeptin II) was first disclosed in 1980 as an inhibitor of the alternate pathway of human complement,[1] Figure 1. Nine years later, both its original isolation[2] from *Streptomyces lavendulae* at Sankyo and additional details of its complement activity were reported along with its structure elucidation by Seto[3] that defined its connectivity and partial stereochemistry. Shortly thereafter, the first report of its activity against HIV infectivity and its cytopathic effects were disclosed.[4] Five years later, Omura reported the isolation of both chloropeptin I (**2**) and chloropeptin II (**1**) from *Streptomyces* sp. WK-3419 as inhibitors of HIV gp120-CD4 binding, determined that chloropeptin II and complestatin are identical, and established their partial stereochemistry.[5] A more detailed analysis of their NMR data provided the full structural and stereochemical assignment for chloropeptin I (**2**) including the axial atropisomer chirality.[6] A remarkable acid-catalyzed rearrangement (TFA, 50 °C, >90%) of chloropeptin II (**1**, complestatin) to the less strained chloropeptin I (**2**) that proceeds with retention of the atropisomer stereochemistry subsequently established the full stereochemical assignments for **1**.[1c,7] These later studies were conducted in the course of the additional isolations of the natural products at Merck[8] and Schering-Plough,[9] with the latter establishing that chloropeptin I (**2**) is an authentic natural product and not an acid-catalyzed artifact derived from chloropeptin II (**1**).

As a result of the challenging structural features and complexity of **1** and **2**, rivaling that of the glycopeptide antibiotics (e.g., vancomycin), combined with their equally important HIV activity derived through a unique site of action, they have attracted considerable interest. Although structurally similar to the glycopeptide antibiotics, one of the characteristic biaryl ether linkages is replaced with a biaryl linkage to C6 or C7 of a (*R*)-tryptophan indole embedded in the macrocyclic core adopting a single atropisomer stereochemistry (*R*) that is not capable of thermal interconversion. Snapper and Hoveyda reported the first, and to date only, total synthesis of a member of this unique class of natural products, chloropeptin I (**2**), confirming the structural and stereochemical assignments.[10] Their approach, enlisting a late stage intramolecular biaryl Stille coupling for closure of the right-hand macrocyclic ring system (38−42%, three steps) provided exclusively the natural (*R*)-atropisomer of **2** as a single diastereomer when conducted on substrate containing the left-hand macrocycle. Remarkably, they later found that extending this approach to chloropeptin II (**1**), using an analogous late stage intramolecular biaryl Suzuki coupling, provided exclusively (63%) the unnatural (*S*)-atropisomer (isocomplestatin).[11]

Complementary to these and related ongoing efforts,[12] herein we report the first total synthesis of chloropeptin II (**1**, complestatin), the more strained and challenging of the natural products. Key to the approach is the use of an intramolecular Larock indole synthesis[13] for the initial macrocyclization, adopting conditions that permit utilization of a 2-bromoaniline[14] and incorporating a removable terminal alkyne substituent (−$SiEt_3$) that sterically dictates the indole cyclization regioselectivity,[13−15] Figure 1.

Not only did this key reaction provide the fully functionalized right-hand ring system of **1** in superb conversion (89%) and good

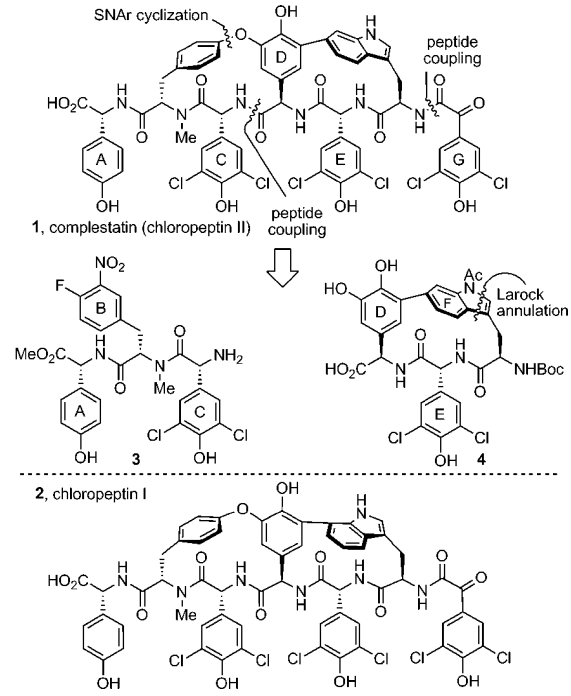

Figure 1. Natural products and key retrosynthetic disconnections.

atropdiastereoselectivity (4:1), but it also represents the first reported example of what may prove to be a useful Larock macrocyclization strategy. Subsequent introduction of the left-hand ring system by enlisting an aromatic nucleophilic substitution reaction for ring closure with biaryl ether formation completed the assemblage of the core bicyclic structure of **1** and represents a macrocyclization order complementary to that of Snapper and Hoveyda. Intrinsic in the design of the approach and by virtue of the single-step acid-catalyzed conversion of **1** to chloropeptin I (**2**), the route also provides a total synthesis of **2**.

Although **1** is composed of seven amino acid subunits, each is extensively modified, four are racemization prone phenylglycines, five are incorporated with the unnatural D-configuration, and one is incorporated as a *N*-methyl derivative. Four of these (A, C, E, and G) are readily accessible from commercially available precursors,[16] whereas the remaining three required more significant synthetic operations key to implementation of our approach. The B subunit **5**, substituted to accommodate its use in an intramolecular aromatic nucleophilic substitution reaction for macrocyclic biaryl ether formation, simply required *N*-methylation of the Boc derivative of (*S*)-4-fluoro-3-nitrophenylalanine prepared by a four-step synthesis previously utilized to access its enantiomer,[17] Scheme 1. The F subunit **6** bearing the TES-substituted alkyne required for the Larock indole annulation was accessed by diastereoselective alkylation (dr >99:1) of (*S*)-**8** with the propargylic diphenylphosphate **7**[15] following a protocol detailed

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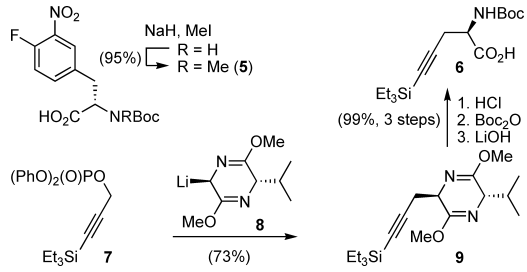
by Cook[15] in an approach where the inexpensive (*S*)-Schollkopf reagent derived from L-valine provides the (*R*)-amino acid derivative **6**, Scheme 1.

Scheme 1

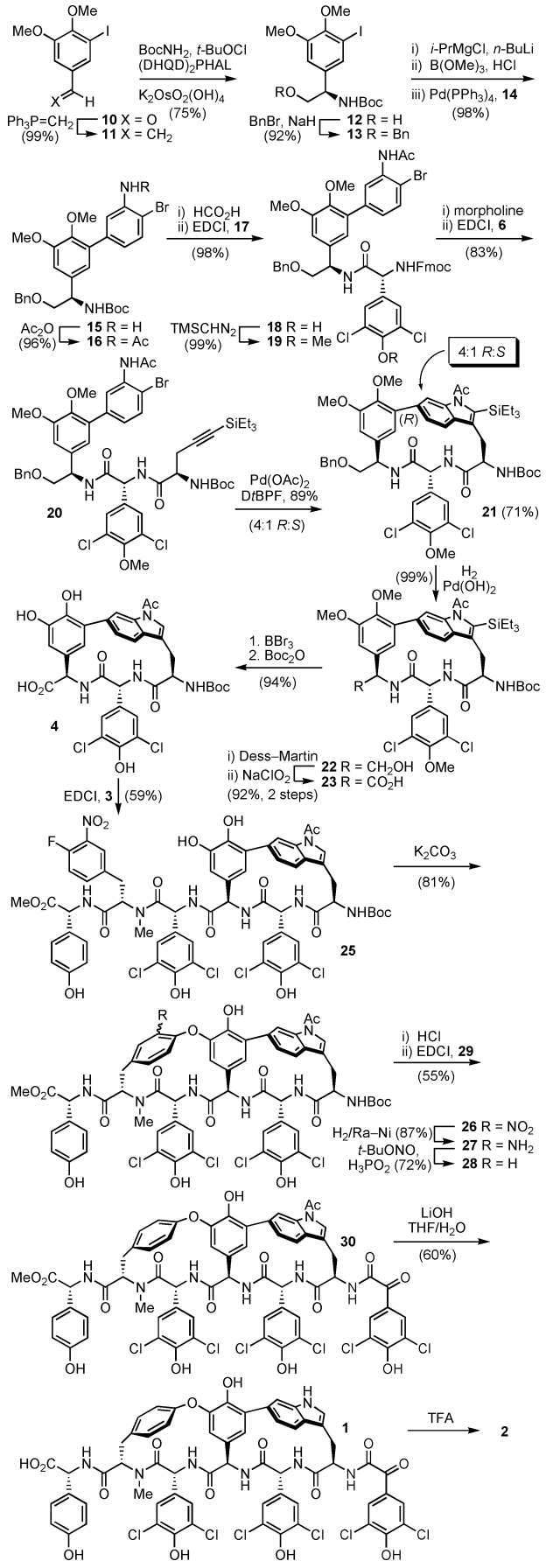


The D subunit central to the structure of **1** and **2** was prepared from commercially available 3-iodo-4,5-dimethoxybenzaldehyde (**10**), Scheme 2. Asymmetric aminohydroxylation of the corresponding styrene **11** in the presence of $(DHQD)_2PHAL$[18] produced **12** in good yield (75% **12**), regioselectivity (5:1), and enantioselectivity (>98% ee). The primary alcohol was protected as its benzyl ether **13** and carried through the sequence that provided **4** as a protected alcohol avoiding potential epimerization, but requiring a late stage oxidation. Conversion of the aryl iodide **13** to the corresponding aryl boronic acid, its selective Suzuki coupling[19] with 2-bromo-5-iodoaniline (**14**),[16] and acetylation of aniline **15** provided **16**.

Boc deprotection of **16** (HCO_2H, 23 °C) followed by coupling of the amine with (*R*)-FmocHN-3,5-Cl_2Hpg-OH[16] (**17**, EDCI, HOAt, DMF/CH_2Cl_2 1:6, −20 °C, 16 h, 98%, dr >99:1) and subsequent protection of the phenol **18** ($TMSCHN_2$, 99%) provided **19**. Fmoc deprotection of **19** (morpholine, DMF/CH_3CN 1:2, 23 °C, 16 h) followed by coupling with **6** (EDCI, HOAt, DMF, 23 °C, 18 h, 83%) provided the cyclization substrate **20**. Following extensive exploration of the Larock macrocyclization that entailed examination of not only **20** but also the free aniline, the trifluoroacetamide, and their corresponding iodides,[20] we found that treatment of **20** with $Pd(OAc)_2$ (1.1 equiv) in the presence of the bidentate ligand DtBPF (1.3 equiv) and the soluble base Et_3N (1.3 equiv) in refluxing toluene/CH_3CN (1:1, 1 mM, 110 °C, 1 h) cleanly provided **21** (71%) and its (*S*)-atropisomer (not shown) in a superb combined yield (89%) in a reaction that proceeds with complete cyclization regioselectivity and in good atropdiastereoselectivity (4:1 *R*:*S*) favoring the natural isomer. The substitution of a soluble base (Et_3N vs $NaHCO_3$ > KOAc > K_2CO_3) in the conditions reported by Farina and Senanayake, permitting the use of 2-bromoanilines (DtBPF),[14] eliminated competitive aryl chloride dehalogenation as well as a problematic epimerization observed with insoluble inorganic bases. The large TES alkyne substituent dictates the exclusive indole cyclization regioslectivity,[13−15] and the aniline acetamide not only serves to deactivate the strained indole toward subsequent electrophilic reagents but also favorably influences the cyclization atropdiastereoselectivity. At present, efforts to reduce the reaction to one that is catalytic in Pd have been modestly successful but provide less dependable conversions. Extensive NMR characterization of **21** and its unnatural (*S*)-atropisomer confirmed the stereochemical assignments.[16] As noted by Hoveyda,[11] the most recognizable diagnostic distinctions in the atropisomers are the chemical shifts, multiplicity, and NOEs for the Trp α-CH (acetone-d_6: δ 3.59 for *R* vs δ 5.05 for *S*) and diastereotopic Trp β-CH_2 (δ 3.12, d and 3.70, dd for *R* vs δ 3.32, dd and 3.51, dd for *S*).

Liberation of the C-terminus primary alcohol **22** by benzyl ether hydrogenolysis (H_2, $Pd(OH)_2$, THF, 23 °C, 99%) and two-step oxidation to the carboxylic acid **23** (92%), both of which benefit from the indole substitution, preceded global deprotection to provide **4** with BBr_3 (25 equiv, CH_2Cl_2, 23 °C, 17 h) removing the three aryl methyl ethers, the TES group, and the Boc group that was reinstalled upon

Scheme 2



treatment with Boc_2O providing **4**. Notably, the indole *N*-acetamide was unaffected by this treatment, and the intrinsically strained ring system did not undergo rearrangement to the more stable C7 (vs C6) biaryl indole linkage. The assigned structure and stereochemistry were reaffirmed, through a full spectroscopic characterization of **4**, not only with observation of key NOEs[16] and the diagnostic chemical shifts of the Trp α-CH (THF-d_8: δ 3.86, app t) and the diastereotopic Trp β-CH_2 (δ 2.82, d and 3.43, app t) as well as their multiplicity[11] but also simply through the indole coupling pattern where C7−H remains a singlet (δ 8.30, s) while C4−H and C5−H appear as coupled doublets in **4**.

This set the stage for introduction of the left-hand ring system. Coupling (EDCI, HOAt, DMF/CH_2Cl_2 1:3, −5 °C, 6 h, 59%) of **4** with the tripeptide **3**, prepared by the sequential couplings and N-terminus deprotections of (*R*)-H_2N-Hpg-OMe (**24**)[16] with **5** (PyBOP, 80%; 4 N HCl, dioxane) and (*R*)-FmocHN-3,5-Cl_2Hpg-OH[16] (**17**, DEPBT, $NaHCO_3$, THF, 0 °C, 24 h, 83%, 9:1 dr; Bu_4NF,[21] THF, 0−23 °C, <1 h),[16] provided **25**. Macrocyclization[22] of **25** to provide **26** as predominantly a single atropisomer of an inconsequential mixture of atropisomers was accomplished upon treatment with K_2CO_3 in THF (0.5 mM, 60 °C, 48−64 h) in the presence of 18-c-6 and 4 Å MS in conversions as high as 81%, provided rigorous anhydrous conditions were maintained to prevent competitive methyl ester hydrolysis. Two-step removal of the activating nitro group (H_2, Ra−Ni, MeOH, 0−23 °C, 6 h, 87%; *t*-BuONO, H_3PO_2, THF, 0 °C, 3 h, 72%)[23] afforded **28**. Boc deprotection (4 N HCl, dioxane, 23 °C, 1−3 h) and coupling of the amine with 2-(3,5-dichloro-4-hydroxyphenyl)-2-oxoacetic acid (**29**,[10,16] EDCI, HOAt, DMF/CH_2Cl_2 1:5, 0 °C, 2 h, 55%) provided the penultimate precursor **30**. Deprotection of **30** to provide **1** was accomplished with LiOH (THF/H_2O, 0 °C, 3 h, 60%) in a reaction where the indole *N*-acetyl group was removed faster (<30 min) than the methyl ester hydrolysis. Finally, and although we did not conduct the reaction on a preparative scale providing an isolated yield, the clean acid-catalyzed conversion of **1** to **2** was conducted on a small scale with both synthetic and authentic **1** and monitored by LCMS. The two samples behaved in the same manner providing only **2** and was most conveniently conducted with 50% TFA/H_2O at 50 °C progressing at a rate that is easily monitored (5 h, vs <5−15 min with neat TFA at 50 °C[7]).[24]

Continued efforts on the optimization and definition of the scope of the Larock macrocyclization reaction, the examination of the reverse macrocyclization order, and the extension of the approach to additional natural products and their key analogues are in progress and will be disclosed in due course.

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Supporting Information Available: Full experimental details are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Crowley, B. M.; Mori, Y.; McComas, C. C.; Tang, D.; Boger, D. L. *J. Am. Chem. Soc.* **2004**, *126*, 4310–4317.
(24) Abbreviations: DEPBT, 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4-one; DtBPT, 1,1′-bis(di-*tert*-butylphosphino)ferrocene; EDCI, 1-[3-(dimethyl-amino)propyl]-3-ethylcarbodiimide hydrochloride; HOAt, 1-hydroxy-7-azabenzotriazole; PyBOP, (benzotriazol-1-yl)tripyrrolidinophosphonium hexafluorophosphate.

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