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Total Synthesis of Complestatin: Development of a Pd(0)-Mediated Indole Annulation for Macrocyclization

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Abstract: Full details of the initial development and continued examination of a powerful intramolecular palladium(0)-mediated indole annulation for macrocyclization closure of the strained 16-membered biaryl ring system found in complestatin (**1**, chloropeptin II) and the definition of factors impacting its intrinsic atropodiastereoselectivity are described. Its examination and use in an alternative, second-generation total synthesis of complestatin are detailed in which the order of the macrocyclization reactions was reversed from our first-generation total synthesis. In this approach and with the ABCD biaryl ether ring system in place, the key Larock cyclization was conducted with substrate **36** (containing four phenols, five secondary amides, one carbamate, and four labile aryl chlorides) and provided the product **37** (56%) exclusively as a single atropisomer (>20:1, detection limits) possessing the natural (*R*)-configuration. In this instance, the complexity of the substrate and the reverse macrocyclization order did not diminish the atropodiastereoselectivity; rather, it provided an improvement over the 4:1 selectivity that was observed with the analogous substrate used to provide the isolated DEF ring system in our first-generation approach. Just as significant, the atroposelectivity represents a complete reversal of the diasteroselectivity observed with analogous macrocyclizations conducted using a Suzuki biaryl coupling.

Introduction

Complestatin (**1**, chloropeptin II) was first disclosed as an inhibitor of the alternate pathway of human complement in 1980,[1] although it was 9 years later that its original isolation[2] from *Streptomyces lavendulae* was reported along with its partial structure elucidation (connectivity and partial stereochemistry) by Seto (Figure 1).[3] Shortly thereafter, the first report of its activity against HIV infectivity and its cytopathic effects was disclosed.[4] Later in 1994, Omura reported the isolation of chloropeptin I (**2**) and chloropeptin II (**1**) from *Streptomyces* sp. WK-3419 as inhibitors of HIV gp120-CD4 binding, established that chloropeptin II and complestatin are identical, and determined their partial stereochemistry.[5] A subsequent detailed NMR analysis provided the full structural and stereochemical assignment for chloropeptin I (**2**) including that of the axial atropisomer chirality.[6] Additional isolations of the natural products have been reported at Merck[8] and Schering-Plough[9] that have not only described related members of the family but have also defined further insights into their biological properties including their additional ability to inhibit HIV-1 integrase. In

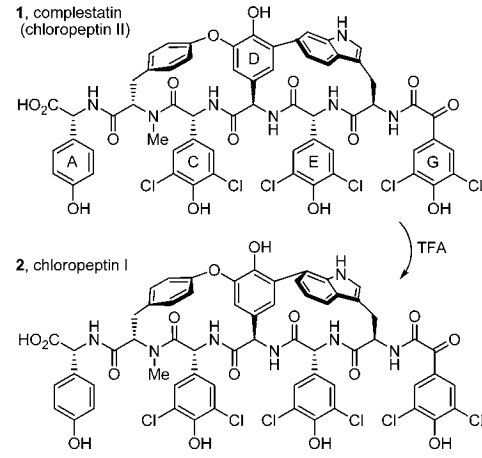

Figure 1. Natural products.

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10.1021/ja102304p

these studies, an acid-catalyzed rearrangement (TFA, 50 °C, >90%) of chloropeptin II (**1**, complestatin) to the less strained chloropeptin I (**2**) was discovered[1c] and shown to proceed with retention of the atropisomer stereochemistry, establishing the full stereochemical assignments for **1**.[7]

The chloropeptins have attracted considerable interest as a result of their structural complexity and their equally important HIV activity mediated through two complementary and unique sites of action. In addition to the importance of their effects at the two individual biological targets themselves, the fact that they act at two sites suggests viral resistance to the agents would be more difficult to emerge. 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 the indole of a (*R*)-tryptophan embedded in the macrocyclic core adopting a single atropisomer stereochemistry (*R*) that is not capable of thermal interconversion. Snapper and Hoveyda reported the first total synthesis of a member of this class of natural products, chloropeptin I (**2**), confirming the structural and stereochemical assignments.[10] Their approach enlisted a late stage intramolecular biaryl Stille coupling for closure of the right-hand macrocyclic ring system (38−42%, three steps) and provided exclusively the natural (*R*)-atropisomer of **2** when conducted on substrate containing the intact left-hand macrocycle.[10] Remarkably, it was 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] whereas closure of the isolated ring system proceeded in a non-atroposelective manner (52%, 1:1 *R*:*S*). Repeating this work, Zhu confirmed these observations again 3 years later and suggested that the atropodiastereoselectivity of the biaryl ring closure was dependent on the stereochemistry found in the preformed left-hand ring system.[12a] Complementary to these and related ongoing efforts,[12,13] we recently reported the first total synthesis of chloropeptin II (**1**, complestatin), the more strained and challenging of the natural products.[14] Intrinsic in the design

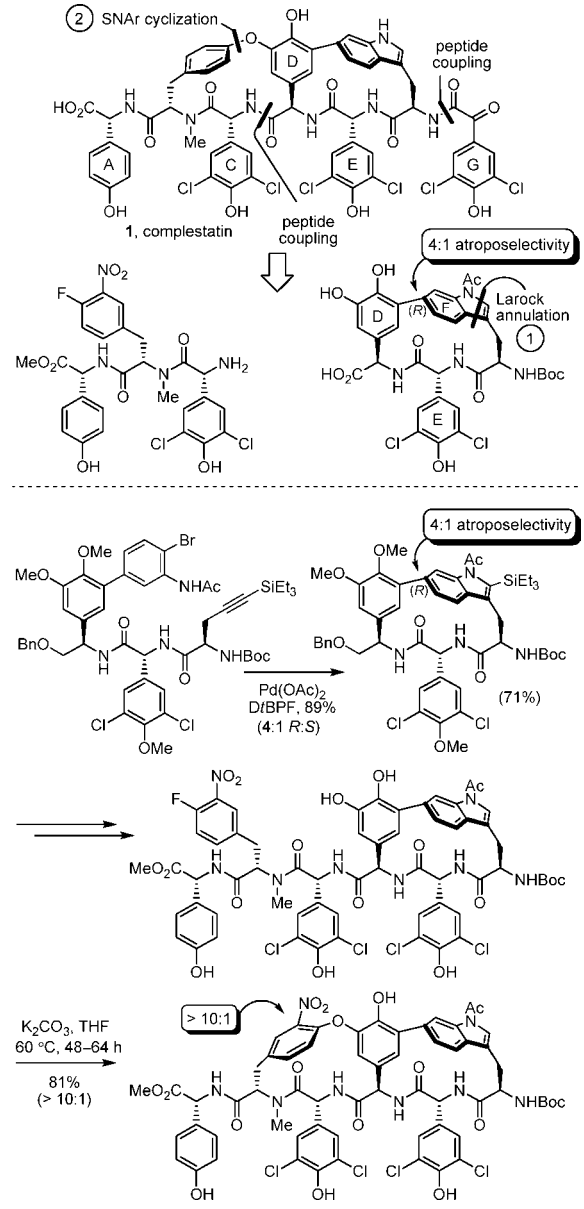

Figure 2. First-generation approach and key macrocyclization reactions.[14]

of the approach and by virtue of the single-step acid-catalyzed conversion of **1** to chloropeptin I (**2**), the route also provided a total synthesis of **2**. Key to the approach was the development of an intramolecular Larock indole synthesis[15] for the initial macrocyclization, adopting conditions that permit the use of a 2-bromoaniline[16] and incorporating a large removable terminal alkyne substituent (−$SiEt_3$) to sterically dictate the indole cyclization regioselectivity,[15−17] Figure 2. Not only did this cyclization provide the fully functionalized right-hand ring system of **1** in excellent conversion (89%) and good atropodiastereoselectivity (4:1), but it also represented the first reported

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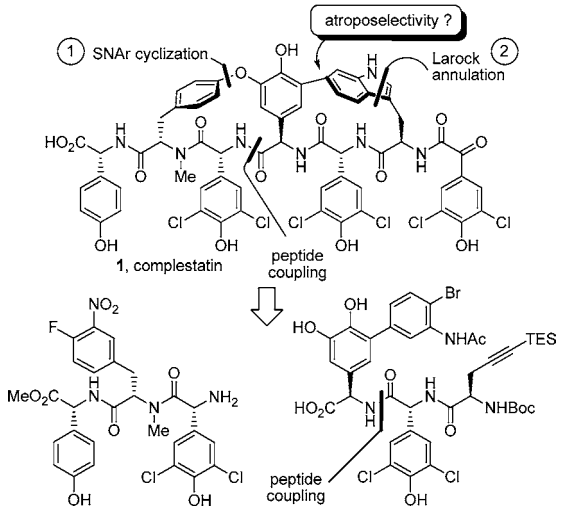


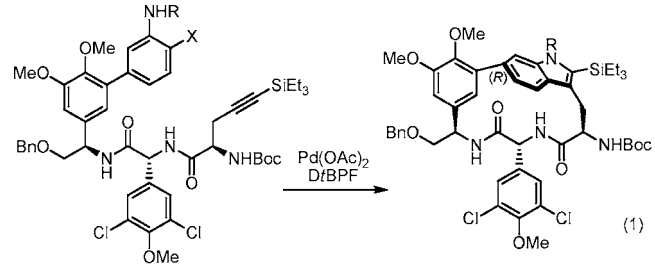
Figure 3. Alternative approach.

example of what will be a useful Larock macrocyclization strategy. Subsequent introduction of the left-hand ring system, enlisting an aromatic nucleophilic substitution reaction for ring closure with biaryl ether formation completed the assemblage of the bicyclic structure of **1**, and represented a macrocyclization order complementary to that used by Snapper and Hoveyda.[10,11]

The success with the Larock macrocyclization reaction for assemblage of the right-hand ring system of **1** and its tailored atropodiastereoselectivity for generation of the natural atropisomer raised the question of whether its utilization might overcome or even reverse the unnatural atropodiastereoselectivity observed with a Suzuki macrocyclization when applied to the reversed macrocyclization order (Figure 3). Herein, we report the results of the implementation of this second, alternative total synthesis of complestatin (**1**, chloropeptin II), establishing the ramifications of reversing the order of the macrocyclizations, and key details of the development of the Larock macrocyclization reaction.

Results and Discussion

Larock Macrocyclization. Early in our efforts and because of the strain in the right-hand ring systems, we explored approaches that would assemble the five-membered ring of the indole during or following macrocyclization. Because complestatin (**1**, chloropeptin II) can be directly converted to chloropeptin I (**2**), we focused our efforts on the synthesis of **1** even though the strain in its right-hand ring system is greater. A number of approaches were examined that included free radical or Heck alkene addition reactions as well as lactamizations for macrocyclization with derigidified substrates, none of which led to productive approaches.[18] In the course of these exploratory studies, we found that an intramolecular Larock indole synthesis was capable of both providing the macrocyclization and forming the five-membered ring of the indole simultaneously, albeit in initial modest conversions. Early studies revealed that the aryl bromides **3** and **5**, containing from the onset a large triethylsilyl group at the alkyne terminus to sterically dictate the cyclization regioselectivity,[15] participated in the intramolecular Larock cyclization promoted by $Pd(OAc)_2$. The reaction benefited from the use of the electron-rich bidentate phosphine ligand 1,1′-bis(di-*tert*-butylphosphino)ferrocene (Dt-BPF) and was conducted under conditions developed by Farina and Senanayake that permit the use of 2-bromoanilines.[16] In these early studies, we found that the low mass recovery of material, problematic substrate epimerization, and competitive reduction of the aryl chlorides observed when using the recommended inorganic base additives ($NaHCO_3$ > KOAc > K_2CO_3, Na_2CO_3)[16] could be minimized or eliminated with the use of organic base additives of which Et_3N (or *i*-Pr_2NEt) proved satisfactory. Still, at this early stage, the conversions were low, and there was a slight preference for formation of the unnatural (*S*)-atropisomer. Substantial improvements in the conversions were observed by enlisting microwave heating to achieve higher reaction temperatures (130 vs 110 °C, NMP). The free aniline **5** was found to participate more effectively than the corresponding trifluoroacetamide **3** that underwent hydrolysis under the reaction conditions, and the use of a 2-bromoaniline proved better than the corresponding 2-iodoaniline (e.g., **3** vs **4**). This latter observation was and remains especially interesting in light of the original Larock cyclization disclosures where only the latter, but not the former, substrates participate.[15] As we proceeded to advance the product **6** in the first-generation total synthesis, we found that the unprotected and strained indole in **6** often displayed a competitive reactivity that could be masked by acetylation. Consequently, we examined the use of the acetamide **7** directly in the macrocyclization reaction and found that it displayed an improved atropodiastereoselectivity, but suffered from lower conversions than observed with the free aniline **5**. Progressive reoptimization of the reaction conditions for the acetamide substrate **7** revealed that the use of increasingly less polar solvents (toluene/MeCN (1:1) > MeCN > DMF > NMP) incrementally improved the conversions, allowed the use of lower reaction temperatures, enhanced the atropodiastereoselectivity, and permitted a switch back to conventional thermal versus microwave reaction conditions. This latter development substantially impacted the progress in the total synthesis of **1** that had become scale limited by the microwave vessel volumes and the dilute reaction concentrations (1−4 mM) used to promote macrocyclization. Representative major observations chronicling some these improvements, which transpired over a period of years, are summarized in eq 1.



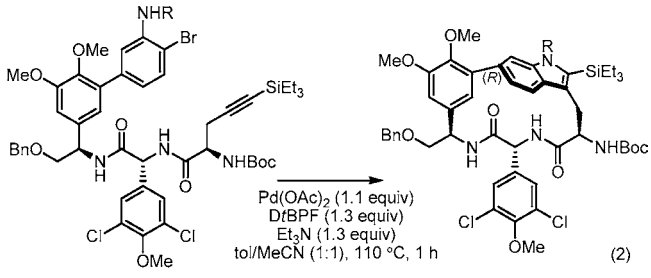
Substrate	Conditions	Product
3, X = Br, R = $COCF_3$	no ligand, NMP, 110 °C	00%, **6**, R = H[b]
3, X = Br, R = $COCF_3$	Et_3N, NMP, 110 °C, 6 h	50% (1:1.6 *R*:*S*); **6**, R = H[b]
3, X = Br, R = $COCF_3$	Et_3N, NMP, 130 °C[a], 25 min	61% (1:1.1 *R*:*S*); **6**, R = H[b]
4, X = I, R = $COCF_3$	Et_3N, NMP, 130 °C[a], 25 min	53% (1:1.1 *R*:*S*); **6**, R = H[b]
5, X = Br, R = H	Et_3N, NMP, 130 °C[a], 25 min	82% (1.2:1 *R*:*S*); **6**, R = H
7, X = Br, R = Ac	Et_3N, NMP, 130 °C[a], 25 min	25% (4:1 *R*:*S*); **8**, R = Ac
7, X = Br, R = Ac	Et_3N, DMF, 130 °C[a], 25 min[c]	33% (4:1 *R*:*S*); **8**, R = Ac
7, X = Br, R = Ac	Et_3N, DMF, 120 °C[a], 2 h	40% (3:1 *R*:*S*); **8**, R = Ac
7, X = Br, R = Ac	Et_3N, CH_3CN, 120 °C, 30 min	68% (3:1 *R*:*S*); **8**, R = Ac
7, X = Br, R = Ac	Et_3N, tol/CH_3CN, 110 °C, 1 h	89% (4:1 *R*:*S*); **8**, R = Ac

[a]Microwave conditions. [b]Trifluoroacetamide hydrolysis. [c]$(Ph_3P)_4Pd$ (4 eq), LiCl (1 eq).

In the interim since the completion of our first-generation total synthesis,[14] the impact of the aniline substituent on the

(18) Trzupek, J. D. Ph.D. Dissertation, 2006.

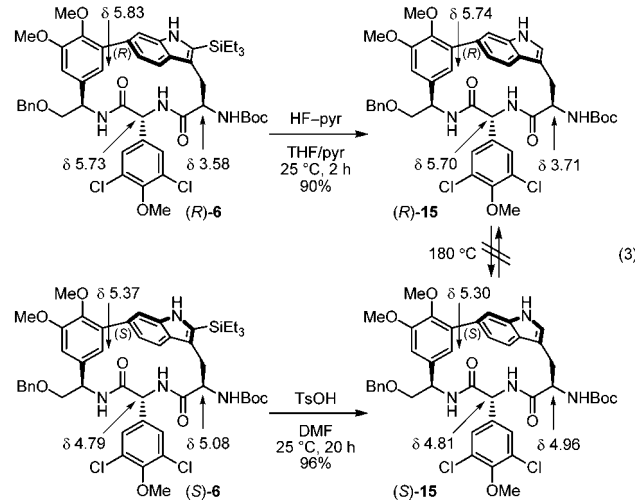
atropodiastereoselectivty of the macrocyclization reaction has been further investigated by enlisting a series of substrates prepared by single-step acylation of **5** (eq 2). Without optimization of the individual reactions, a smooth trend of increasing atropodiastereoselectivity is observed with both the nature of the acyl group (COR > CO_2R) and most notably as the size of the aniline acyl group increases with the reactions proceeding in conversions that approach those optimized for **7**. Significantly, the macrocyclization reactions of **11** (6.5:1 *R*:*S*) and especially that of **13** (>20:1 *R*:*S*, detection limits) proceed with atroposelectivities that exceed what we reported with **7** (4:1 *R*:*S*)[14] indicating that improvements in our first-generation total synthesis of **1** are possible. Although speculative and based only on the simple examination of molecular models, the aniline amine and its attached acyl substituent appear to be directed toward and lie over the peptide chain linking the reacting partners in intermediates leading to the unnatural (*S*)-atropisomer, whereas they are distal and directed away from the linking peptide chain in intermediates leading to the natural (*R*)-atropisomer. Thus, in retrospect it may not be surprising that the atroposelectivity of the macrocyclization increases with the steric size of the aniline substituent. The stereochemical assignments were confirmed by extensive NMR analysis and, as first defined by Hoveyda,[10] the most recognizable and diagnostic distinctions in the atropisomers that can be used confidently to assign the steroechemistry are the NMR chemical shifts, multiplicity, and NOE's for Trp α-CH ($CDCl_3$ or acetone-d_6: δ 3.54−3.71, t for *R* vs δ 5.01−5.07, m for *S*) and the diastereotopic Trp β-CH_2 (δ 2.96−3.14, d and 3.59−3.71, dd for *R* vs δ 3.22−3.31, dd and 3.31−3.55, dd for *S*), both of which are altered considerably relative to the starting precursors (δ 4.19−4.31, m and 2.65−2.28, m, respectively). Similarly, the E-ring α-CH ($CDCl_3$: δ 5.25−5.29, d for *R* vs δ 4.57−4.80, d for *S*) and the D-ring aryl CH that lies on the internal face of the macrocycle ($CDCl_3$: δ 5.43−5.57, s for *R* vs δ 5.13−5.20, s for *S*) exhibit chemical shifts that are diagnostic of the atropisomer stereochemistry.



(2)

Substrate	Product
5, R = H	67% (1:1 *R*:*S*) **6**, R = H
9, R = CO_2Me	78% (2.2:1 *R*:*S*) **10**, R = CO_2Me
7, R = $COCH_3$	89% (4:1 *R*:*S*) **8**, R = $COCH_3$[14]
11, R = CO_2Bn	74% (6.5:1 *R*:*S*) **12**, R = CO_2Bn
13, R = COPh	70% (>20:1 *R*:*S*) **14**, R = COPh

Reactivity and Rearrangement of the DEF Ring System. In initial studies, significant differences in the reactivity of the two atropisomers of **6**, bearing the free indole, were observed indicating that work with the unnatural (*S*)-isomer might not translate into analogous successful reactions with the natural (*R*)-isomer. For example, acid-catalyzed removal of the TES substituent with (*S*)-**6** proved straightforward (5 equiv of TsOH, DMF, 25 °C, 20 h) providing (*S*)-**15** (96%) without event or optimization (eq 3), whereas the analogous treatment of (*R*)-**6** provided only minor amounts of (*R*)-**15** along with a number of additional products. Clean protodesilylation of (*R*)-**6** was accomplished (eq 3), but required more controlled reaction conditions (HF-pyr, THF-pyr, 25 °C, 2 h) for the clean generation of (*R*)-**15** (90%). As a consequence, work progressing forward in our first-generation total synthesis, as well as herein, was only conducted with intermediates bearing the natural (*R*)-atropisomer stereochemistry. Additionally, and with the two atropisomers (*R*)- and (*S*)-**15** in hand, we were able to further confirm the stereochemical assignments and establish for ourselves that, as previously reported,[11] they are not capable of thermal interconversion.



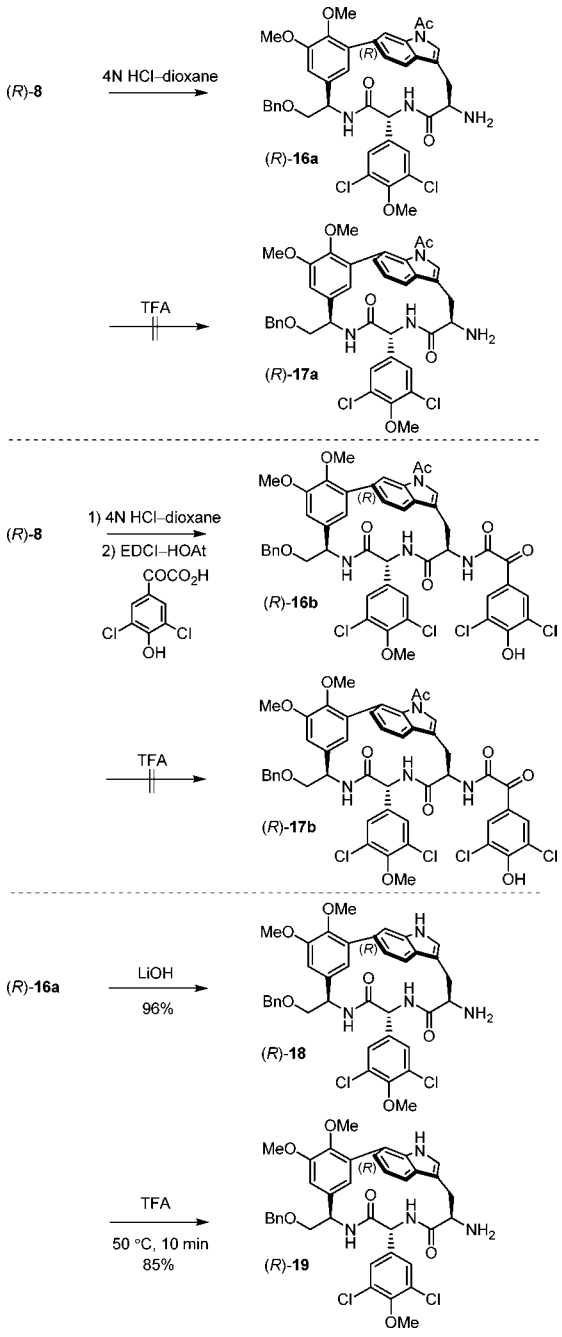
(3)

Analogous to complestatin itself,[7] the isolated DEFG ring system of complestatin containing the free indole undergoes the strain-releasing TFA-catalyzed rearrangement (50 °C, 15 min, >98%) providing the C7 versus C6 indole biaryl link characteristic of chloropeptin I, and this occurs with retention of the atropisomer stereochemistry.[11] Thus, it was of interest to establish the behavior of the corresponding indole acetamide derivatives **16a** and**16b** toward this same rearrangement (Scheme 1). In the course of our work, we came to appreciate and exploited the fact that acetylation of the indole tamed its electrophilic reactivity providing intermediates that exhibited a robust stability. Consistent with these observations but not investigated in detail, we found that exposure of either **16a** or**16b** to TFA at room temperature had no effect on **16** (24 h), that no rearrangement of either **16a** or**16b** was observed at 50 °C over 2.5−5 h, and that longer exposures of **16a** or**16b** to TFA at 50 °C (24 h) led to their slow consumption (decomposition) without evidence of rearrangement (Scheme 1). By comparison, the corresponding free indole **18**, resulting from deacylation of **16a** with LiOH (96%), underwent rearrangement to **19** within 10 min at 50 °C in TFA (85%, Scheme 1). Thus, indole *N*-acylation has a pronounced impact on the strained indole reactivity, and its importance should not be underestimated.

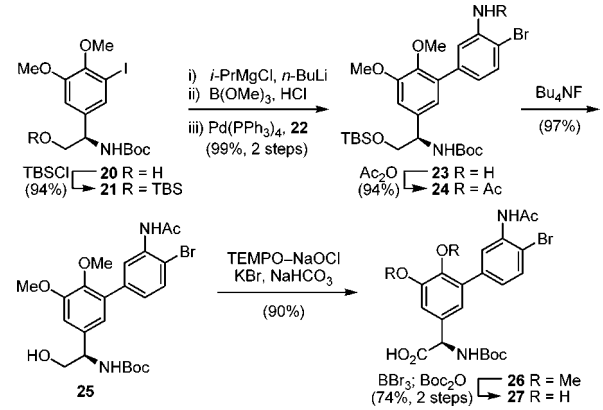
Second-Generation Total Synthesis of Complestatin. The central D subunit was prepared following small modifications in the approach previously detailed,[14] allowing for its global deprotection prior to incorporation into the route. Thus, asymmetric aminohydroxylation [$(DHQD)_2PHAL$][19] of the styrene derived from 3-iodo-4,5-dimethoxybenzaldehyde ($Ph_3P{=}CH_2$, 99%) produced the aminoalcohol **20** in good yield (75%),

(19) Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207–1217.

Scheme 1



Scheme 2



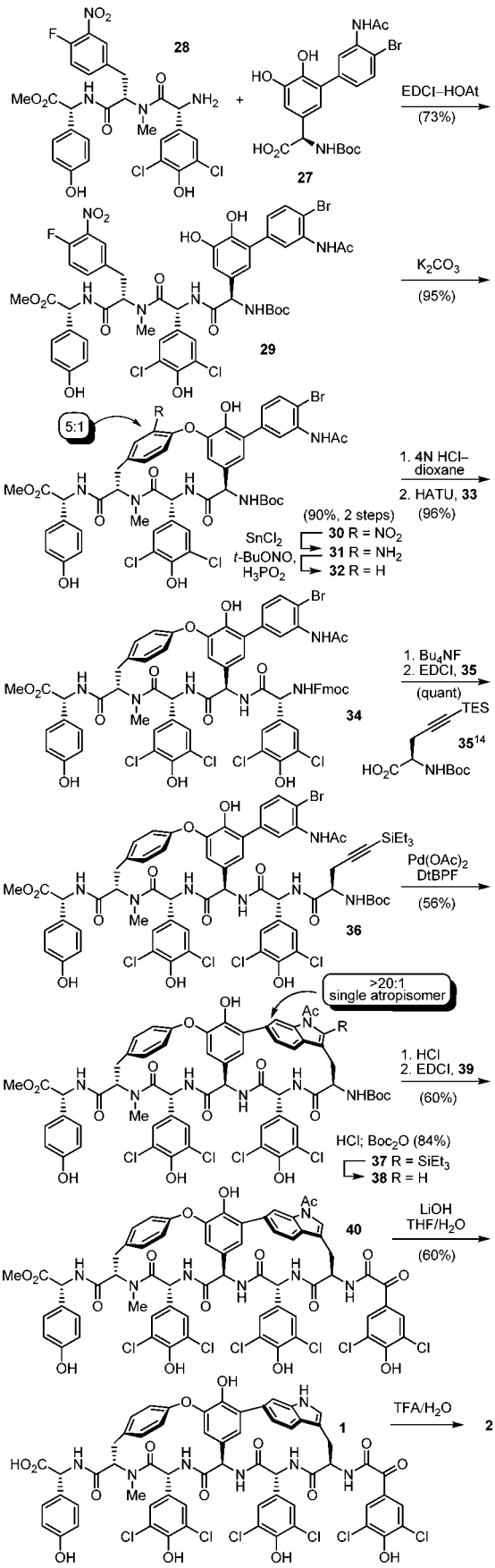
regioselectivity (5:1), and enantioslectivity (>98% ee) (Scheme 2).[14] Protection of the primary alcohol as its TBS ether **21** (94%) followed by conversion of the aryl iodide to the corresponding aryl boronic acid and its Suzuki coupling with 2-bromo-5-iodoaniline[14] (**22**, 99%, two steps) provided **23**. Aniline acetylation (97%), deprotection of **24** to provide the primary alcohol **25** (Bu_4NF, 97%), and its single-step oxidation (TEMPO/NaOCl) to the carboxylic acid provided **26** (90%). Deprotection of the aryl methyl ethers (BBr_3) under conditions that also remove the Boc group was followed by its reinstallation (Boc_2O) providing **27** (74%).

Coupling (EDCI/HOAt, THF, 0 °C) of **27** with the tripeptide **28**[14] provided **29** in good yield (73%). Although not essential for the progression of the work, we also took this opportunity to improve the synthesis (scalability) of the (*S*)-*N*-methyl-4-fluoro-3-nitrophenylalanine subunit central to the tripeptide **28**.[20] This set the stage for the first key macrocyclization reaction[21] for formation of the 16-membered biaryl ether (Scheme 3). Treatment of **29** with K_2CO_3 (10 equiv) in anhydrous THF (1 mM, 60 °C, 12 h) in the presence of 4 Å molecular sieves and 18-crown-6 proceeded exceptionally well, providing **30** in yields as high as 95% as an inconsequential 5:1 mixture of atropisomers. This represents an improvement over our first-generation approach (81%, essentially a single atropisomer)[14] where the ABCD ring closure was conducted on a substrate containing the intact DEF ring system. A trace of a separable product, constituting the epimer at the terminal 4-hydroxyphenylglycine, was detected, isolated (<5%), and characterized and represents the only indication of competitive epimerization of the substrate or product under these reaction conditions. Likely contributing to this lack of epimerization at the C-terminus methyl ester is the conduct of the cyclization with the A-ring free phenol that is deprotonated under the reaction conditions. The use of DMSO as solvent (1 mM, 25 °C, 36 h), while permitting the reaction to proceed at room temperature (71% yield) and providing an analogous 5:1 mixture of atropisomers, led to more significant epimerization at this center (>10%). Moreover and like observations made in our first-generation approach, no products were detected resulting from competitive participation of the additional three unprotected phenols in nucleophilic substitution reactions with the *o*-fluoronitroaromatic that would provide either the more strained or more hindered 14-membered or 17-membered biaryl ethers.

(20) Enzymatic hydrolysis (resolution) of readily available racemic *N*-acetyl-4-fluoro-3-nitrophenylalanine using *Aspergillus* acylase I following a procedure detailed for its isomer *N*-acetyl-3-fluoro-4-nitrophenylalanine provided (*S*)-4-fluoro-3-nitrophenylalanine (>40%, >95−99% ee, >3 g scale). See: Groll, M.; Gotz, M.; Kaiser, M.; Weyher, E.; Moroder, L. *Chem. Biol* **2006**, *13*, 607–614. Details are provided in the Supporting Information.

(21) (a) Boger, D. L. *Med. Res. Rev.* **2001**, *21*, 356–381. (b) Crowley, B. M.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 2885–2892. (c) Boger, D. L.; Kim, S. H.; Mori, Y.; Weng, J.-H.; Rogel, O.; Castle, S. L.; McAtee, J. J. *J. Am. Chem. Soc.* **2001**, *123*, 1862–1871. (d) Boger, D. L.; Kim, S. H.; Miyazaki, S.; Strittmatter, H.; Weng, J.-H.; Mori, Y.; Rogel, O.; Castle, S. L.; McAtee, J. J. *J. Am. Chem. Soc.* **2000**, *122*, 7416–7417. (e) Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Loiseleur, O.; Castle, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 3226–3227. (f) Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 10004–10011. (g) Boger, D. L.; Castle, S. L.; Miyazaki, S.; Wu, J. H.; Beresis, R. T.; Loiseleur, O. *J. Org. Chem.* **1999**, *64*, 70–80. (h) Boger, D. L.; Borzilleri, R. M.; Nukui, S.; Beresis, R. T. *J. Org. Chem.* **1997**, *62*, 4721–4736. (i) Boger, D. L.; Borzilleri, R. M.; Nukui, S. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 3091–3096. (j) Boger, D. L.; Borzilleri, R. M. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1187–1190. (k) Boger, D. L.; Nomoto, Y.; Teegarden, B. R. *J. Org. Chem.* **1993**, *58*, 1425–1433.

Scheme 3



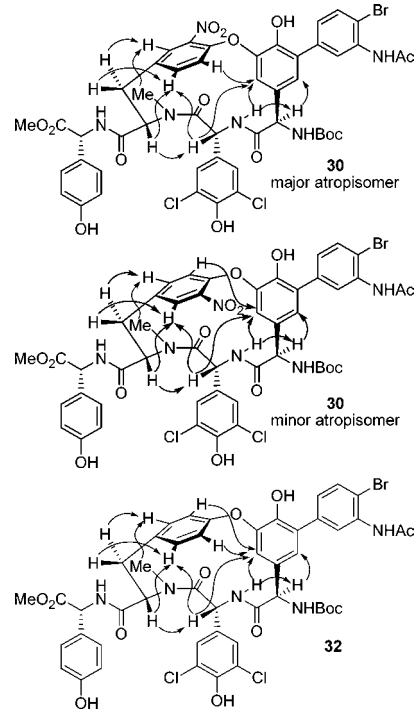


Figure 4. Diagnostic spectroscopic NOE's.

Extensive NMR analysis of each atropisomer of **30** indicate that both adopt a conformation containing a cis *N*-methyl amide at the site linking the B- and C-residues, and that the major product constitutes the (*M*)-atropisomer, whereas the minor isomer possesses the (*P*)-configuration (Figure 4). Given the ease and conversion for the cyclization of **29** relative to related isolated 16-membered biaryl ethers that we have examined,[21] it appears that the N-methyl amide facilitates ring closure perhaps by promoting the adoption of more compact versus extended conformations conducive to cyclization. In this regard, it is interesting to note that the ABCD ring system lacking the terminal 4-hydroxyphenylglycine residue (A ring) does not adopt this cis *N*-methyl amide conformation and the corresponding acyclic precursor would not be expected to cyclize with such ease.[12a] Individually or as the atropisomer mixture, **30** was subjected to a two-step procedure[22] for removal of the nitro group ($SnCl_2$; *t*-BuONO, H_3PO_2, THF), providing **32** in excellent conversions (90%, two steps, Scheme 3). Like **30**, the fully functionalized ABCD ring system **32** common to both complestatin I and II was found by NMR to adopt a conformation bearing a cis *N*-methyl amide linking the B- and C-residues (Figure 4).

With **32** in hand, this set the stage for examination of the key Larock macrocyclization reaction. *N*-Boc deprotection (4 N HCl in dioxane) and coupling (HATU, 2,6-lutidine, CH_2Cl_2/THF) of the crude amine with (*R*)-FmocHN-3,5-Cl_2-Hpg[14] (**33**) provided **34** in good yield (96%) under conditions devised to completely suppress epimerization (Scheme 3). Fmoc deprotection (Bu_4NF)[23] followed by coupling of the liberated amine with the alkyne bearing amino acid **35**[14,17] provided the required

(22) Crowley, B. M.; Mori, Y.; McComas, C. C.; Tang, D.; Boger, D. L. *J. Am. Chem. Soc.* **2004**, *126*, 4310–4317.

(23) (a) Jiang, W.; Wanner, J.; Lee, R. J.; Bounaud, P.-Y.; Boger, D. L. *J. Am. Chem. Soc.* **2002**, *124*, 5288–5290. (b) Jiang, W.; Wanner, J.; Lee, R. J.; Bounaud, P.-Y.; Boger, D. L. *J. Am. Chem. Soc.* **2003**, *125*, 1877–1887.

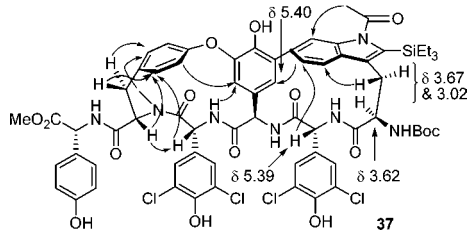


Figure 5. Key spectroscopic NOE's (THF-d_8).

substrate **36** in quantitative yield. Unlike our first-generation approach or the examples reported in eq 2, the macrocyclization of **36** is conducted with a substrate now containing four unprotected phenols (two of which are especially acidic), five secondary amides, one carbamate, and four labile aryl chlorides. Without optimization, exposure of **36**, bearing the aniline acetamide, to the conditions developed for conducting the intramolecular Larock cyclization (1.3 equiv of $Pd(OAc)_2$, 1.3 equiv of DtBPF, 5.0 equiv of Et_3N, 1 mM in toluene/MeCN 1:1, 110 °C, 2 h) provided **37** (56%) exclusively as a single atropisomer (>20:1, detection limits) possessing the natural (*R*)-configuration. Thus, the complexity of the substrate and the reverse macrocyclization order did not diminish the atropodiastereoselectivity, rather it provided an improvement over the 4:1 selectivity that we observed with the analogous acetamide substrate **7** providing the isolated DEF ring system.[14] More impressively, it represents a complete reversal of the atropodiasteroselectivity observed with the Suzuki coupling first described by Snapper and Hoveyda[11] and later confirmed by Zhu.[12a] Although limited efforts have been made to reduce this reaction to one that is catalytic in palladium, which have been only modestly successful providing reactions that proceed in less dependable conversions, we note that even the efforts enlisting a Stille or Suzuki coupling for macrocyclization of the DEF ring systems have also employed stoichiometric palladium to avoid substrate or product (peptide) sequestration of the reagent.[10,11,13] Extensive NMR characterization of **37** confirmed the atropisomer configuration exhibiting the characteristic chemical shifts, multiplicity, and NOE's for Trp α-CH (THF-d_8: δ 3.62, t), the diastereotopic Trp β-CH_2 (δ 3.02, d and 3.67, dd), the E-ring α-CH (δ 5.39, d) and the D-ring aryl CH that lies on the internal face of the macrocycle oriented toward the indole (δ 5.40, s) that are diagnostic of the atropisomer stereochemistry (Figure 5). Acid-catalyzed removal of the indole C2-triethylsilyl substituent (2 N HCl-dioxane/THF, 0 °C, 5 min) under conditions that were found to also partially deprotect the N-terminus Boc group (~30%), followed by its reinstallation (Boc_2O) provided **38** (84% overall) identical in all respects to the material prepared in our first-generation total synthesis.[14] Subsequent deprotection of **38** or more direct deprotection of **37** (4 N HCl in dioxane, 25 °C, 1 h), followed by acylation of the N-terminus free amine with 2-(3,5-dichloro-4-hydroxyphenyl)-2-oxoacetic acid (**39**, EDCI/HOAt, 0 °C, 2 h) provided our prior penultimate precursor **40**[14] (60%) to complestatin. As detailed earlier,[14] deprotection of **40** was accomplished with LiOH (THF/H_2O, 0 °C, 3 h, 60%) in a reaction where the indole *N*-acetyl group is removed faster (<30 min) than the methyl ester and provided complestatin (**1**, chloropeptin II), and its subsequent acid-catalyzed (50% TFA/H_2O, 50 °C, 5 h) rearrangement provided chloropeptin 1 (**2**).[24]

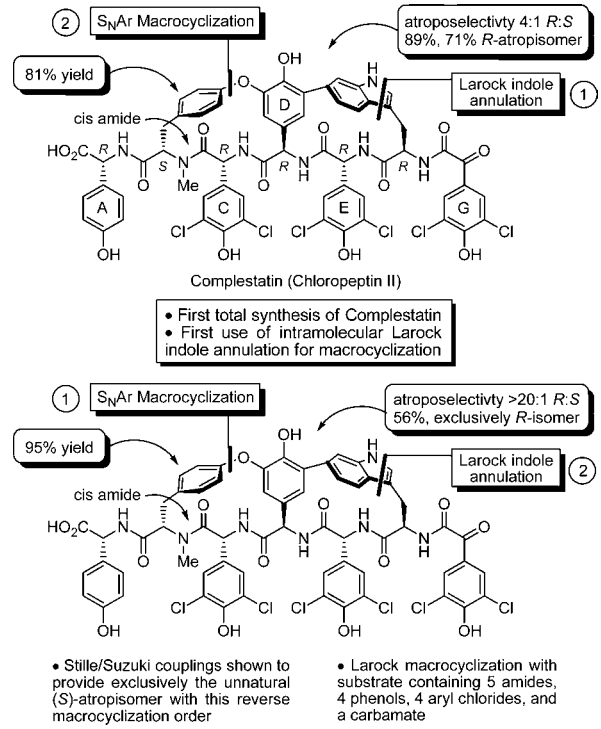


Figure 6. Key elements of the first- and second-generation total syntheses of complestatin.

Conclusions

Herein, we disclose full details of the development of a powerful intramolecular Larock indole annulation for macrocyclization closure of the strained 16-membered biaryl ring system found in complestatin (**1**, chloropeptin II),[25] the definition of factors impacting its intrinsic atroposelectivity, and its examination in a second-generation, alternative total synthesis of complestatin. The examination of this alternative approach, in which the order of the macrocyclization reactions is reversed and the Larock cyclization is conducted with a substrate (**36**) containing four unprotected phenols, five secondary amides, one carbamate, and four labile aryl chlorides, provided the product **37** (56%) exclusively as a single atropisomer (>20:1, detection limits) possessing the natural (*R*)-configuration. Thus, the complexity of this substrate or the reverse macrocyclization order not only did not diminish the atropodiastereoselectivity, but it also provided an improvement over the 4:1 selectivity that we observed with the acetamide substrate **7** used to provide the DEF ring system in our first-generation approach (Figure 6).[14] More impressively, it represents a complete reversal of

(24) Abbreviations: DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; DtBPF, 1,1′-bis(di-*tert*-butylphosphino)ferrocene; EDCI, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride; HATU, *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; HOAt, 1-hydroxy-7-azabenzotriazole; NMP, *N*-methylpyrrolidinone; TBS, *tert*-butyldimethylsilyl; TES, triethylsilyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran.

(25) For complementary palladium-catalyzed reactions introduced in the course of our natural products total synthesis efforts, see: (a) Boger, D. L.; Panek, J. S. *Tetrahedron Lett.* **1984**, *25*, 3175–3178. (b) Boger, D. L.; Panek, J. S.; Duff, S. R.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5782–5789, and 5790−5795. (c) Boger, D. L.; Patel, M. *Tetrahedron Lett.* **1987**, *28*, 2499–2502. (d) Boger, D. L.; Patel, M. *J. Org. Chem.* **1988**, *53*, 1405–1415.

the atropodiasteroselectivity observed with analogous macrocyclizations conducted using a Suzuki coupling.[11,12a] Extensions of these studies to natural products related to the chloropeptins, the preparation of key analogues, and further studies on the Larock macrocyclization are in progress and will be disclosed in due course.

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

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