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Two Syntheses of the 16- and 17-Membered DEF Ring Systems of Chloropeptin and Complestatin

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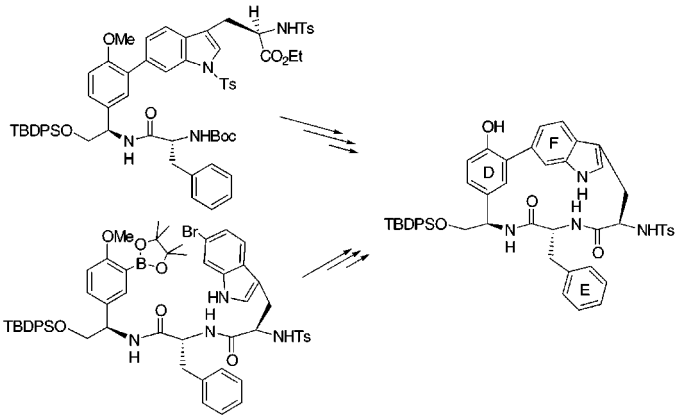
ABSTRACT



Two syntheses of a model system of the DEF ring system of complestatin and chloropeptin are described. The key step in both of these syntheses involves the formation of the biaryl linkage using a palladium-catalyzed Suzuki cross-coupling reaction and a catalytic enantioselective ene reaction to form the 6-bromo-D-tryptophan. Additionally, ring contraction of the 17-membered DEF ring system of complestatin generates the 16-membered DEF ring system of chloropeptin in a biomimetic fashion.

Chloropeptin and complestatin are two biologically active macrocyclic polypeptides isolated from *Streptomyces* sp. WK-3419 (Figure 1).[1] The phenyl−indole ring junction present in these natural products is rare in microbial metabolites but is found in natural products such as diazonamide A and the kistamicins. However, complestatin and chloropeptin show activities not seen in other molecules of similar structure, e.g. inhibition of gp120-CD4 binding (IC_{50} = 2.0 and 3.3 μM)[2] as well as inhibition of the alternative pathway of complement (IC_{50} = 2.0 and 0.5 μM).[3] Recently, chloropeptin has also shown activity against HIV-1 integrase ((IC_{50} = 0.3−0.5 μM).[4]

The presence of the biaryl junction makes synthesis of these natural products a challenge. To date, only Roussi and co-workers have disclosed the successful synthesis of a model DEF ring system of complestatin and chloropeptin.[5] The key step in their synthesis involved an intramolecular

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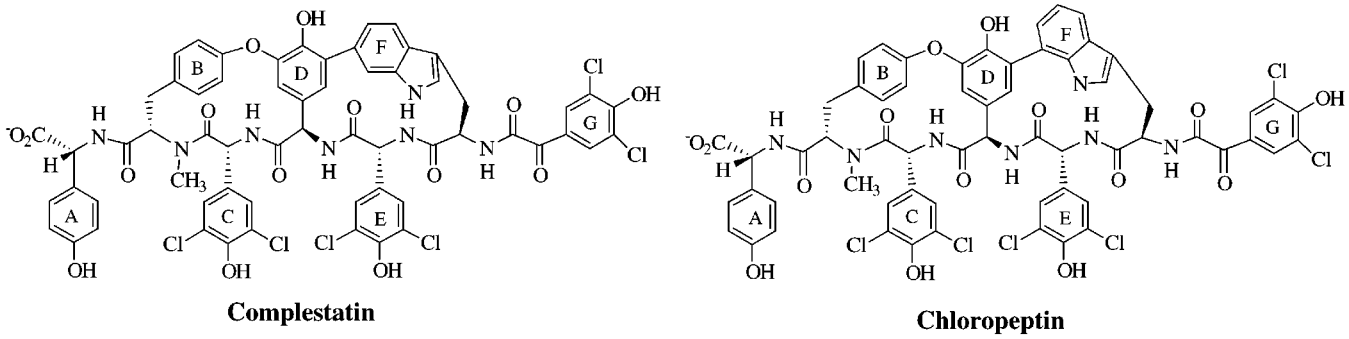


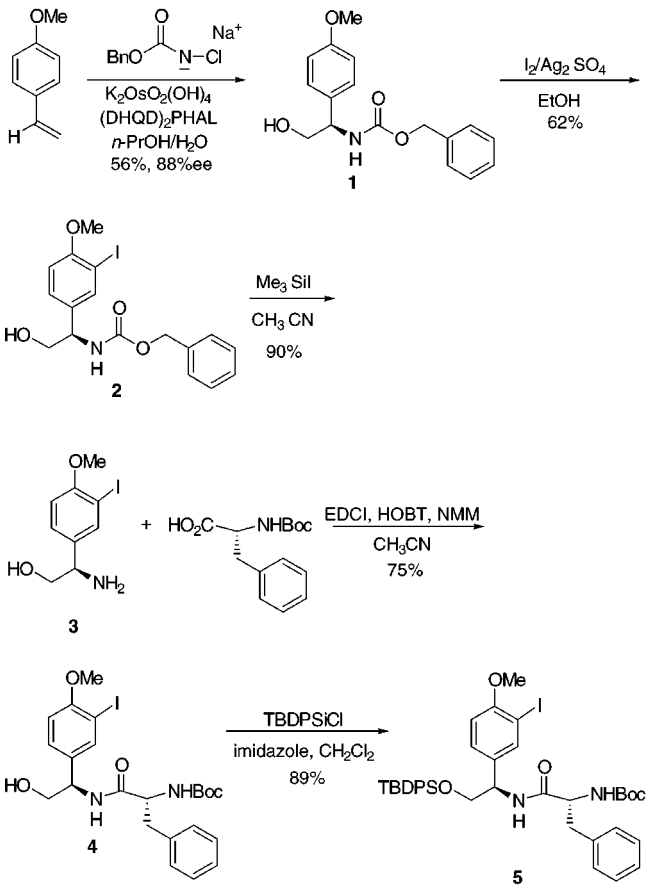
Figure 1.

Ni^0-mediated ring-closing reaction as the last step, yielding only 17% and 1% of the 17- and 16-membered ring systems, respectively. Here we report two different routes to the DEF ring system of complestatin. One utilizes a macrolactamization as the last step of the synthesis, while the more efficient route utilizes an intramolecular palladium-catalyzed ring closure to the 17-membered ring system of complestatin. Both routes afford access to the 16-membered ring system of chloropeptin by ring contraction of the 17-membered DEF ring system of complestatin.

The DEF ring system allows disconnection at two sites: the biaryl linkage or a peptide bond. Disconnection at a peptide bond allows formation of the biaryl linkage by a Suzuki reaction followed by macrolactamization to give the 17-membered DEF ring system. However, a potentially more versatile route involves formation of the peptide backbone prior to the intramolecular Pd-catalyzed Sukuzi reaction.

Synthesis of the phenylglycinol dipeptide unit **5** started with 4-methoxystyrene as the substrate for the Sharpless aminohydroxylation[6] (Scheme 1). Using $(DHQD)_2PHAL$ as the ligand, the correct regioisomer was obtained in 56% yield with an 88% ee (determined by formation of the Mosher ester). Compound **1** was selectively iodinated at the 3-position *ortho* to the methoxy group using Ag_2SO_4/I_2.[7] Removal of the Cbz group required harsher conditions than anticipated. Hydrogenation using H_2/Pd on carbon or transfer hydrogenation using Pd/C with 1,4-cyclohexadiene were unsuccessful. The use of bromocatecholborane yielded only 20% of the desired amine, but cleavage of the Cbz group with Me_3SiI[8] in acetonitrile gave the amine **3** (90% yield), which was coupled with Boc-D-phenylalanine, using EDCI and HOBt with NMM in acetonitrile. The phenylglycinol unit was converted to the *tert*-butyldiphenylsilyl ether **5**, which served as the precursor to the aryl boronate.

Scheme 1



The second component, 6-bromo-D-tryptophan, was synthesized by an enantioselective ene reaction (Schemes 2 and 3). 2,5-Dibromoaniline was reacted with *p*-toluenesulfonyl chloride and pyridine to produce the sulfonamide, which was further reacted with allyl bromide and K_2CO_3 at 80 °C to yield *N*-allyl-2,5-dibromo-*N*-(tolylsulfonyl)aniline (**7**). Compound **7** was then reacted with $Pd(OAc)_2$, PPh_3, and Ag_2CO_3[9] in an intramolecular Heck reaction in acetonitrile to

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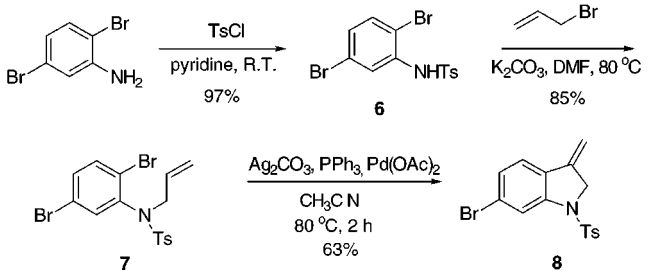
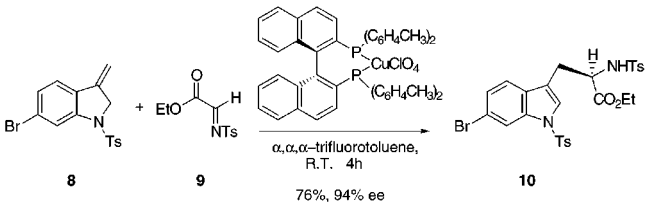
Scheme 2



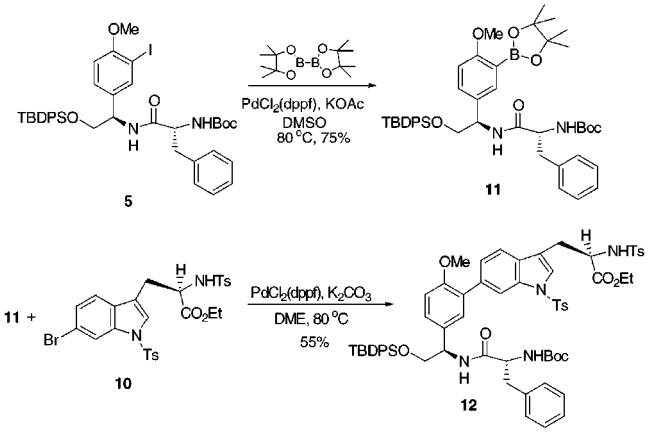
Scheme 3



give the 3-methyleneindoline derivative **8**. However, some 6-bromo-3-methylindole was also formed by isomerization at the higher temperature needed to effect reaction with the bromide. By moderating the temperature and solvent, indoline **8** was obtained in 63% yield and then used in a catalytic ene reaction to form the 6-bromo-D-tryptophan. Reaction of the α-imino ester **9** with indoline **8** in the presence of (*S*)-Tol-BINAP−$CuClO_4$·$2CH_3CN$[10] and benzotrifluoride gave the fully protected 6-bromo-D-tryptophan **10** in 94% ee. The enantiopurity was determined by converting the ester into the corresponding alcohol derivative and analyzing the Mosher ester.

Components **10** and **11** were joined via a Suzuki cross-coupling reaction (Scheme 4). Iodide **5** was converted into

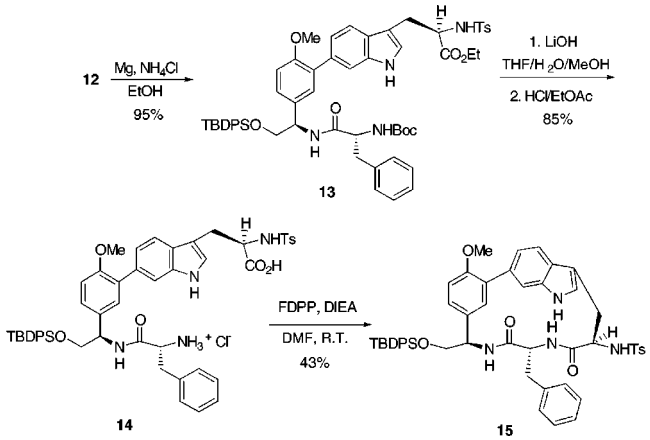
Scheme 4



the aryl boronate using Miyaura's conditions (bis(pinacolato)-diboron, $PdCl_2$(dppf), and KOAc in DMSO[11] for 40 h at 80 °C) to give **11** in 75% yield. KOAc and DMSO were critical for formation of the pinacol boronate. Suzuki coupling was then used to form the key biaryl linkage. Varying the reaction conditions (solvent, base, catalyst, and temperature) identified optimal conditions. Reaction of aryl halide **10** with pinacol boronate **11** and $PdCl_2$(dppf) with K_2CO_3 in the presence of DME at 80 °C gave **12** in 55% yield.

The biaryl system **12** was further elaborated into the cyclized model DEF ring system **15** (Scheme 5). The indole

Scheme 5



tosyl group was removed using magnesium[12] and ethanol with ammonium chloride to activate the metal. The ethyl ester was saponified with LiOH in THF with MeOH/H_2O without racemization. The Boc protecting group was selectively removed without loss of the *tert*-butyldiphenylsilyl ether by using HCl-saturated ethyl acetate to give the free amine as the HCl salt. Cyclization with pentafluorophenyl diphenylphosphinate (FDPP) and DIEA[13] in DMF gave the best results, while DPPA with Na_2CO_3[14] in DMF gave only a moderate yield under high-dilution conditions (5.0×10^{-3} mol/L). EDCI/HOBt and DCC/HOBt did not give cyclic product, and the cyclization failed with all reagents when the tosyl-protecting group was left on the indole ring nitrogen, as was found by Gurjar and Tripathy[15] in their attempts to synthesize the right-hand portion of complestatin.

Cyclization of the preformed tripeptides via an intramolecular coupling reaction proved to be the more effective route to the DEF ring system (Scheme 6). Synthesis of the tripeptide started with the boronate **11**, which was selectively converted to the free amine without loss of the *tert*-butyldiphenylsilyl ether and boronate using HCl-saturated

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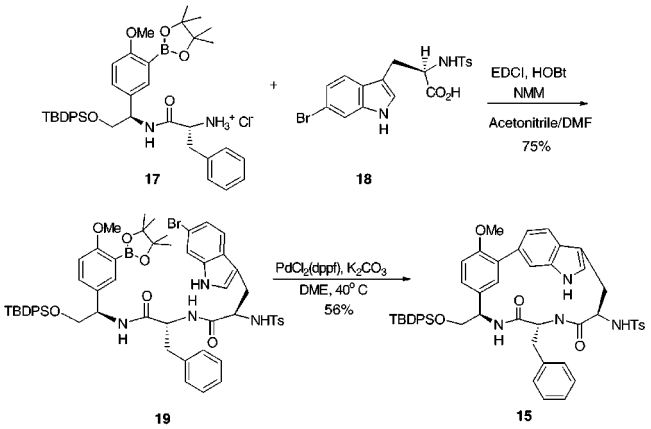
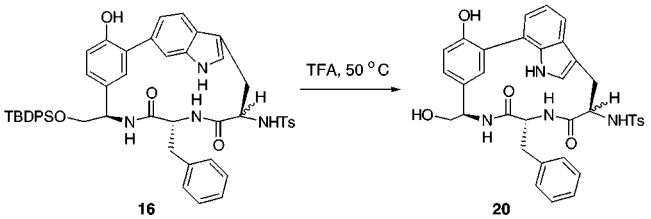
Scheme 6



ethyl acetate. Peptide coupling with EDCI, HOBt, and NMM in acetonitrile and DMF gave tripeptide **19**. A Suzuki reaction was used to effect the final cyclization to **15.** Remarkably, the intramolecular Suzuki reaction required a much lower temperature and shorter reaction time (5 h at 40 °C) than the corresponding bimolecular coupling (24 h at 80 °C). This difference in reactivity suggests that preorganization of the aryl rings in the tripeptide facilitates cyclization.

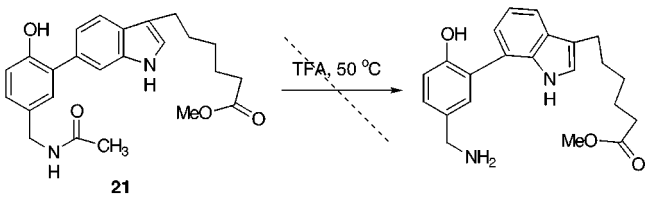
Conversion to the Chloropeptin Ring System (Scheme 7). The 16-membered DEF ring system of chloropeptin was

Scheme 7



synthesized by an acid-catalyzed ring contraction of the 17-membered DEF ring system of complestatin previously observed in the natural products.[16] A related ring contraction occurs with the myricanol glycosides,[17] where $BF_3{\cdot}OEt_2$ isomerized the 13-membered ring system in myricanone to the 12-membered ring system in isomyricanone. The 17-membered ring system of complestatin **16** (and its α-epimer at tryptophan) was contracted to the 16-membered ring system **20** by reaction with TFA at 50 °C. This reaction is very clean, and interestingly, both diastereomers undergo the migration. For comparison, a linear system was synthesized to see if migration from C6 to C7 occurred in an acyclic system (Scheme 8). However, no migration from the 6-posi-

Scheme 8



tion to the 7-position was observed, which indicates that additional factors such as ring strain or preorganization of reacting orbitals are needed to drive phenyl migration.

In summary, two efficient routes to the DEF ring systems found in complestatin and chloropeptin have been developed. The complestatin 17-member DEF ring system can be synthesized either by macrolactamization of the peptide backbone under high dilution conditions or by forming the final C−C bond in the 6-phenylindole moiety, the latter reaction appearing to be much faster. Both routes provide the 16-membered DEF ring system in chloropeptin by acid-catalyzed contraction of the complestatin DEF ring system. Characterization of the chemical and biological properties of these ring systems will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization for compounds **4**, **5**, **10**−**15**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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