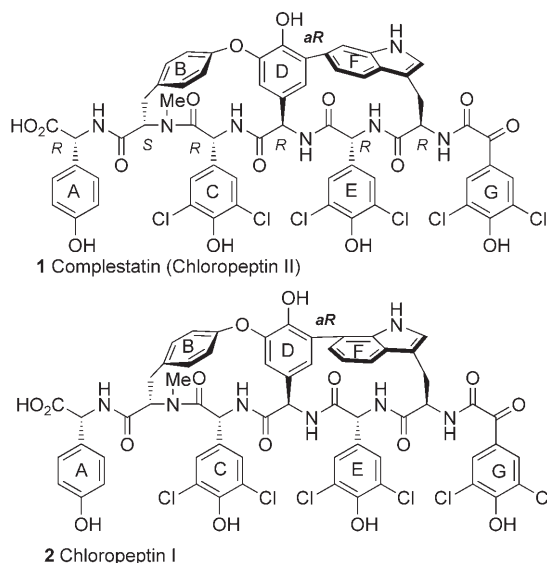


# Synthesis of Diastereomers of Complestatin and Chloropeptin I: Substrate-Dependent Atroposelectivity of the Intramolecular Suzuki–Miyaura Reaction\*\*

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Complestatin (**1**)<sup>[1]</sup> and chloropeptin I (**2**)<sup>[2]</sup> isolated from *Streptomyces lavendulae* and *Streptomyces* sp. WK-3419,



respectively, display potent activities against HIV-1-induced cytopathicity and syncytium formation in CD-4 lymphocytes and inhibit HIV replication by inhibition of gp120–CD-4 binding at a low-micromolar level ( $IC_{50}$  = 3.3 and 2.0  $\mu$ M, respectively).<sup>[3]</sup> The absolute configurations of the amino acid constituents of **1**<sup>[4]</sup> and **2**<sup>[5]</sup> were elucidated through detailed NMR, computational, and degradation studies. Complestatin

and chloropeptin differ only in the position of the phenyl-indole ring junction, and it has been demonstrated that the former is readily isomerized to the latter under mildly acidic conditions.<sup>[6]</sup> These compounds belong to a growing family of vancomycin-type polymacrocyclopeptides with unusual *endo* aryl–aryl ether and *endo* biaryl linkages.<sup>[7]</sup> The presence of racemization-prone chlorinated arylglycines and the inherent difficulties associated with the construction of strained macrocycles made the synthesis of these natural products highly challenging. Although a number of groups have been involved in the total-synthesis exercises,<sup>[8]</sup> only the group of Snapper and Hoveyda has accomplished the total synthesis of chloropeptin I (**2**)<sup>[9]</sup> and an atropisomer of complestatin named isocomplestatin (**3**; Scheme 1).<sup>[10]</sup> These total syntheses have also allowed Snapper, Hoveyda, and co-workers to assign the *aR* configuration to the axial chirality of natural products **1** and **2**.

We have been interested in this type of natural product<sup>[11,12]</sup> and have recently reported an atropselective synthesis of the DEFG ring of complestatin by way of an intramolecular Suzuki–Miyaura reaction.<sup>[13]</sup> As a continuation of this work, we describe herein the syntheses of two atropisomers of the natural products, isocomplestatin (**3**) and isochloropeptin (**5**), as well as two other  $C_{C2}$  epimers, **4** and **6** (Scheme 1). The intramolecular  $S_NAr$ <sup>[14]</sup> and Suzuki–Miyaura<sup>[15]</sup> reactions are the two key steps used for the construction of macrocycles BCD and DEF, respectively. We observe that the atropselectivity in the formation of the DEF ring is highly sensitive to both the aryl–aryl bond connectivity and the stereogenicity of the amino acid constituents. A change in the absolute configuration of amino acid C invariably switches the sense of atropselectivity of the subsequent biaryl-forming process.

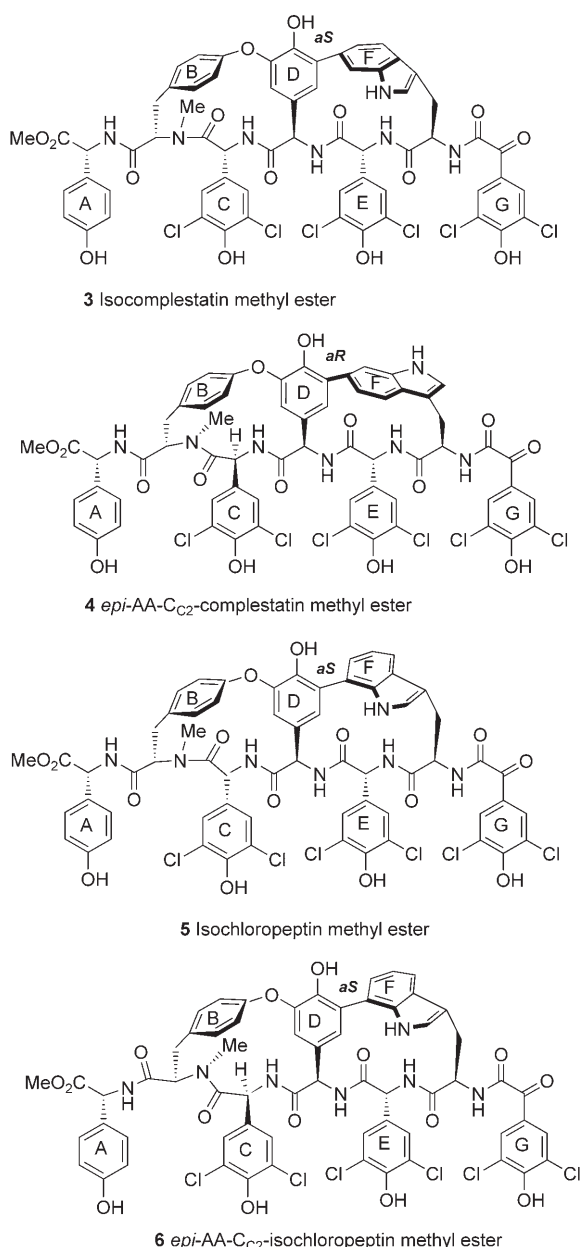
The synthesis of the BCD ring is summarized in Scheme 2. Coupling of (*S*)-*N*-methyl-4-fluoro-3-nitrophenylalanine methyl ester (**7**)<sup>[16]</sup> with (*R*)-*N*-Boc-3,5-dichloro-4-hydroxyphenylglycine (**8**)<sup>[17]</sup> turned out to be particularly challenging due to the low nucleophilicity of **7** and the high sensitivity of **8** towards epimerization. Under optimized conditions (DEPBT,  $NaHCO_3$ , 0 °C to room temperature), the dipeptide (**9**) was isolated in 54 % yield, together with its  $C_{C2}$  epimer (18 %). Fortunately, the desired dipeptide **9** can be purified from a mixture of diastereomers by crystallization in a solution of  $CH_2Cl_2$ /heptane, and the stereochemical integrity of the product was confirmed by X-ray analysis (see the Supporting Information). Removal of the *N*-Boc function (TFA,  $CH_2Cl_2$ ) afforded the TFA salt of the amine, which was coupled directly with (*R*)-*N*-Boc-3-iodo-4,5-dihydroxyphenylglycine

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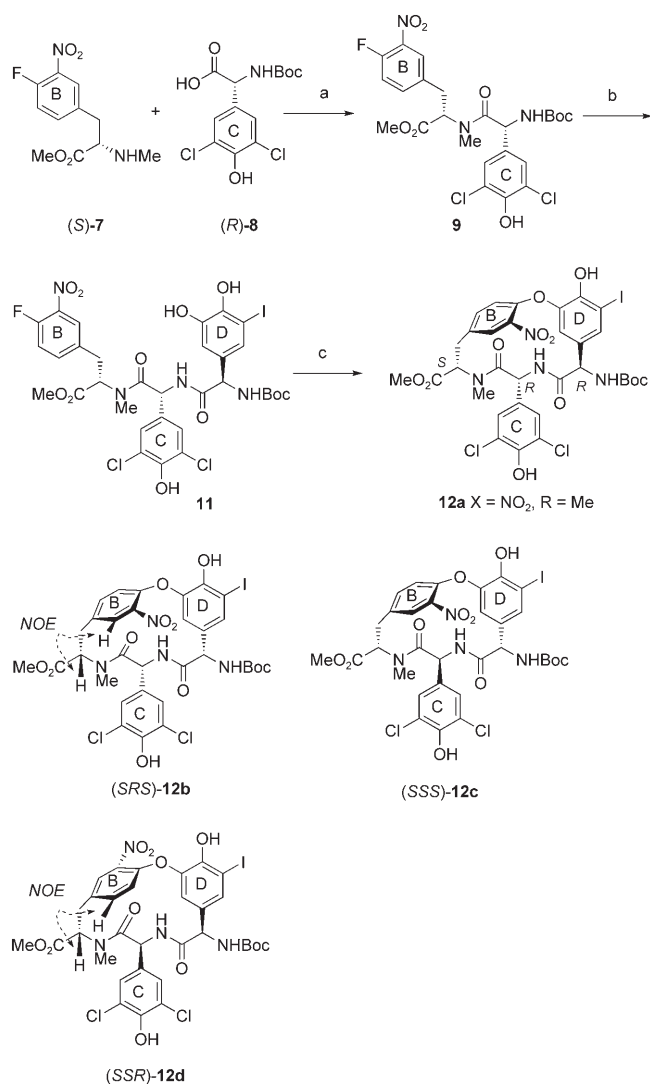
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Supporting information for this article (including experimental procedures, product characterization, and the  $^1H$  and  $^{13}C$  NMR spectra) is available on the WWW under <http://www.angewandte.org> or from the author.



**Scheme 1.** Diastereomers of complestatin and chloropeptin I.

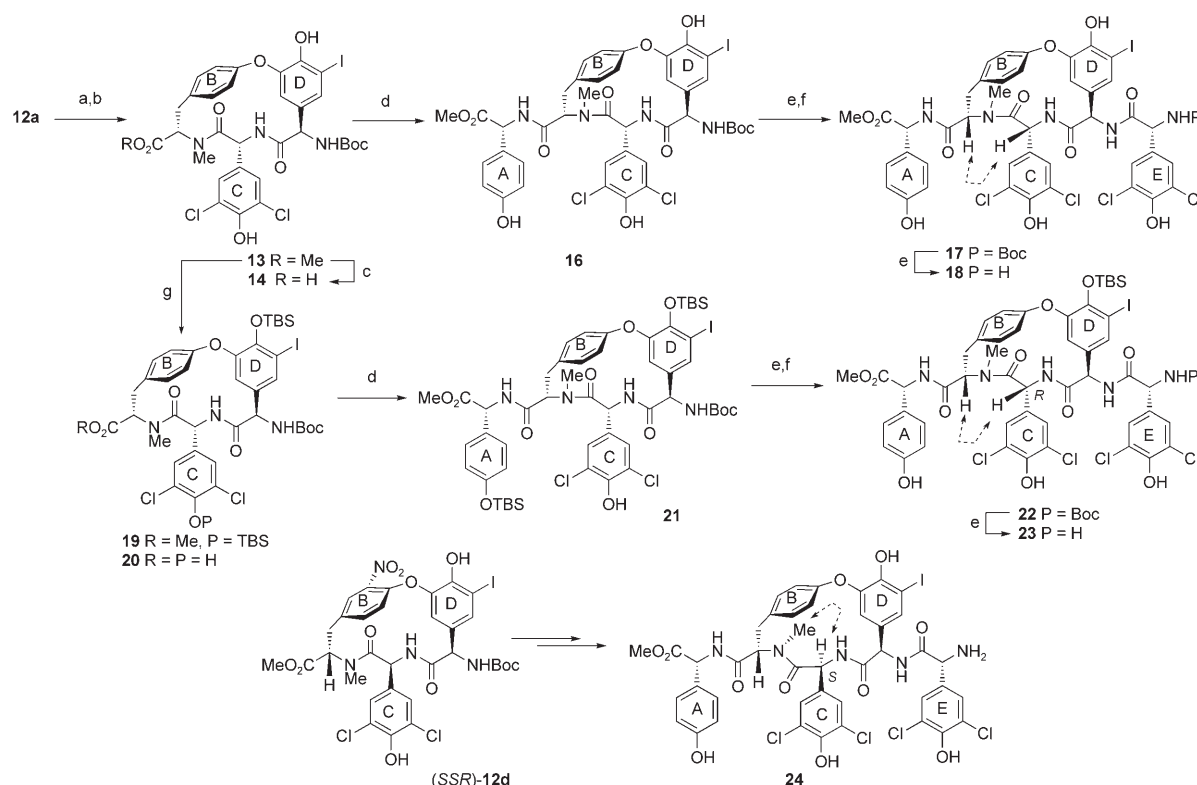
(10)<sup>[13]</sup> to afford the tripeptide **11** in 71% yield. The key cyclization was realized in a degassed DMSO solution of **11** ( $c = 0.003$  M, room temperature) in the presence of potassium carbonate and 4 Å molecular sieves to provide the desired 16-membered *meta,para*-cyclophane **12a** (72%) as a single atropisomer. The cyclization is regioselective since the alternative 17-membered and 14-membered *para,para*-cyclophanes, resulting from nucleophilic attack of the other two hydroxy groups on the fluoro nitro aromatic system, were not observed.<sup>[18]</sup> By following the same synthetic route as that indicated for (*SRR*)-**12a**, the diastereomeric macrocycles (*SRS*)-**12b**, (*SSS*)-**12c**, and (*SSR*)-**12d** were synthesized individually by using (*S*)-**8** and/or (*S*)-**10** as coupling partners of (*S*)-**7**. Analysis of the cyclization products indicated conclusively that no epimerization occurred during the intra-



**Scheme 2.** Synthesis of the BCD ring and its epimers. a) DEPBT, NaHCO<sub>3</sub>, THF, 0 °C → RT, 12 h, 54%; b) 1. TFA, CH<sub>2</sub>Cl<sub>2</sub>; 2. (*R*)-**10**, HATU, NaHCO<sub>3</sub>, THF/DMF (3:1), 71%; c) K<sub>2</sub>CO<sub>3</sub>, DMSO, RT, 36 h, 72%. Boc: *tert*-butoxycarbonyl; DEPBT: 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one; DMF: *N,N*-dimethylformamide; DMSO: dimethylsulfoxide; HATU: *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate; TFA: trifluoroacetic acid; THF: tetrahydrofuran.

molecular S<sub>N</sub>Ar reaction. Although of no consequence, the planar chirality of **12a–12c** was determined to be *pS*, while that of **12d** was assigned as *pR* on the basis of NOE studies.

Reductive removal of the nitro group from **12a** via the aniline and then diazonium intermediates provided compound **13** in 80% overall yield (Scheme 3). Hydrolysis of the methyl ester of **13** under basic conditions (LiOH, THF/H<sub>2</sub>O) caused extensive epimerization. However, prolonged heating (3 days) of a 1,2-dichloroethane solution of **13** in the presence of trimethyltin hydroxide (TMTH) afforded the desired carboxylic acid **14** in essentially quantitative yield without epimerization.<sup>[19]</sup> Coupling of **14** with (*R*)-4-hydroxyphenylglycine methyl ester (**15**) furnished the tetrapeptide **16**. Removal of the *N*-Boc group followed by coupling of the resulting amine with (*R*)-**8** provided the pentapeptide **17**,



which after N-deprotection afforded the free amine **18**, the spectral data for which are in accord with those described in the literature.<sup>[9]</sup>

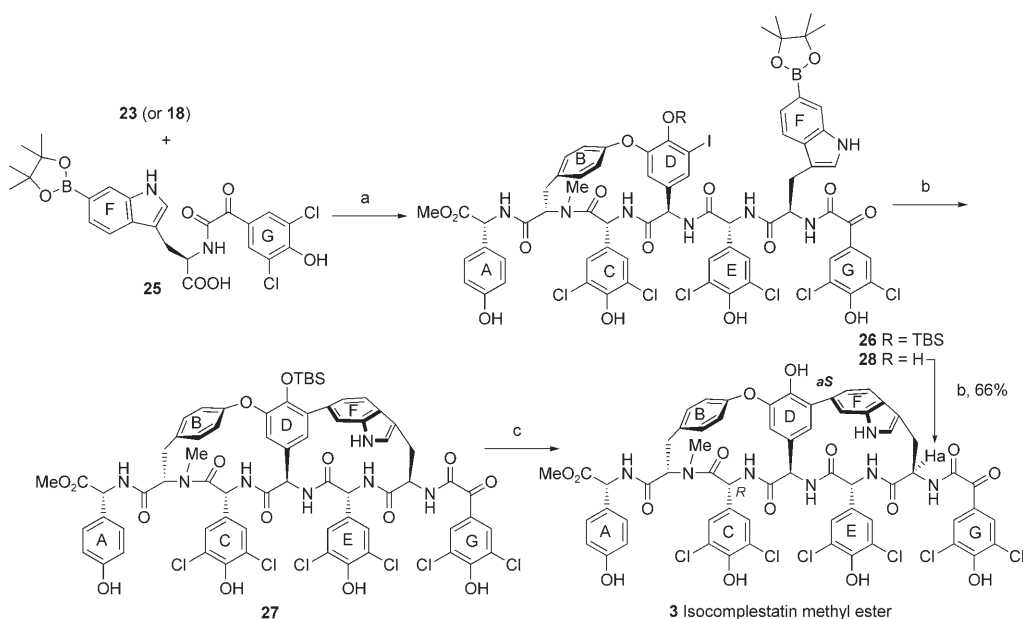
Since we have previously shown that the protection of the phenol group can influence the atropselectivity of the intramolecular Suzuki–Miyaura reaction,<sup>[13]</sup> we decided to introduce a TBS group onto the phenol rings; this was realized under standard conditions. Hydrolysis of **19** took place rapidly to afford compound **20** in 89 % yield (TMTH, CH<sub>2</sub>ClCH<sub>2</sub>Cl, 80 °C, 12 h). The TBS ether of amino acid C was concurrently removed, whereas that of ring D survived under these conditions. Compound **20** was converted into pentapeptide **23** by the same sequence of reactions as that described for the preparation of **18**.

By applying the same synthetic sequence, the pentapeptide (*RSSRR*)-**24** was also synthesized from macrocycle (*SSR*)-**12d**. It is worth noting that compounds **18**, **23**, and **24** have different conformational preferences in solution. The *N*-methyl amide bond between amino acids B and C of **18** and **23** adopted the *cis* conformation, as found in the natural product (NOE: H<sub>B2</sub>/H<sub>C2</sub>). However, that of **24** adopted a *trans* conformation, as evidenced by the characteristic NOE cross-peaks between the NMe and H<sub>C2</sub> signals. The downfield shift of the H<sub>B2</sub> signal for compound **24** ( $\delta = 5.64$  versus 4.91 ppm for **23**) is also in accord with the proposed rotamer structure. As observed previously, the attachment of amino acid A locked the conformation of macrocycle BCD, and a single

conformer was detected on the NMR timescale for compounds **16–18** and **21–24**.

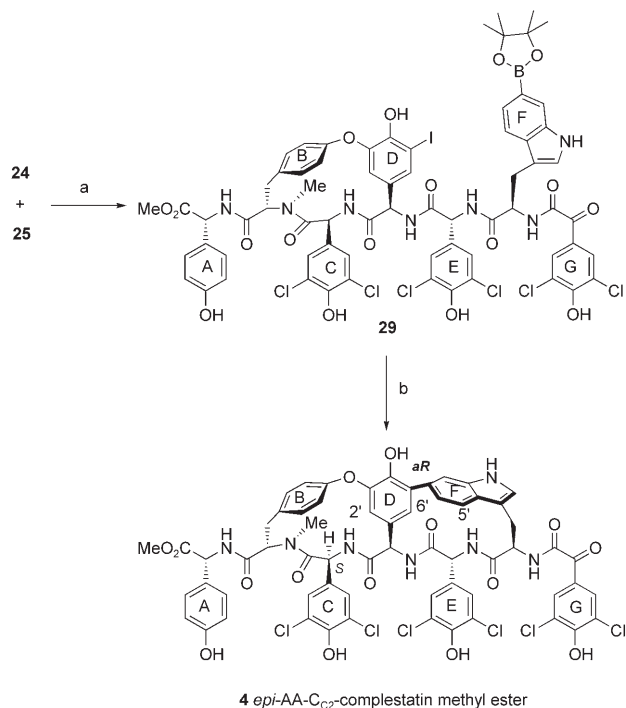
The completion of the synthesis of bismacrocycle **3** is depicted in Scheme 4. A HATU-mediated coupling of **23** with tryptophan derivative **25**<sup>[20]</sup> afforded hexapeptide **26**, which underwent a palladium-promoted intramolecular Suzuki–Miyaura coupling to furnish the bismacrocycle **27** in 52 % yield. Removal of the TBS protective group then afforded a compound for which the spectral data were identical in all respects with those described for isocomplestatin methyl ester **3**.<sup>[10]</sup> Alternatively, cyclization of free phenol **28**, obtained by coupling of **18** with **25**, directly furnished macrocycle **3** in 66 % yield. Thus, the Suzuki–Miyaura cyclization afforded the *aS* atropisomer regardless the phenol-protecting groups. The preferential formation of the nonnatural atropisomer in the Suzuki–Miyaura reaction is in accord with the observations of Snapper, Hoveyda, and co-workers.<sup>[10]</sup> The same atropselectivity has also been observed in our synthesis of RP-66453, a structurally related bismacrocylic natural product.<sup>[21]</sup> Attempted thermal atropisomerization of **3** failed to provide the natural atropisomer.

Smith and co-workers<sup>[8c]</sup> have demonstrated that the stereogenicities of amino acids C and D influenced the conformational preference of the BCD macrocycle. We surmised that such conformational change should, in turn, influence the atropselectivity of the subsequent macrocyclization.<sup>[22]</sup> To verify this hypothesis, we synthesized hexapep-



**Scheme 4.** Synthesis of isocomplestatin methyl ester **3**. a) HATU, lutidine (1 equiv), THF, 0°C to room temperature, 5 h, 84%; b) [PdCl<sub>2</sub>-(dppf)]·CH<sub>2</sub>Cl<sub>2</sub> (1 equiv), 1,4-dioxane/H<sub>2</sub>O (50:3), K<sub>2</sub>CO<sub>3</sub> (10 equiv), 90°C, 1 h, 52%; c) KF, HBr in DMF, 1 h, 90%. dppf: 1,1'-bis(diphenylphosphino)ferrocene.

tide **29** wherein the *R* amino acid C of the natural product was replaced by its *S* antipode. As shown in Scheme 5, the intramolecular Suzuki–Miyaura reaction of **29** afforded bismacrocyclic **4**, the axial chirality of which was determined

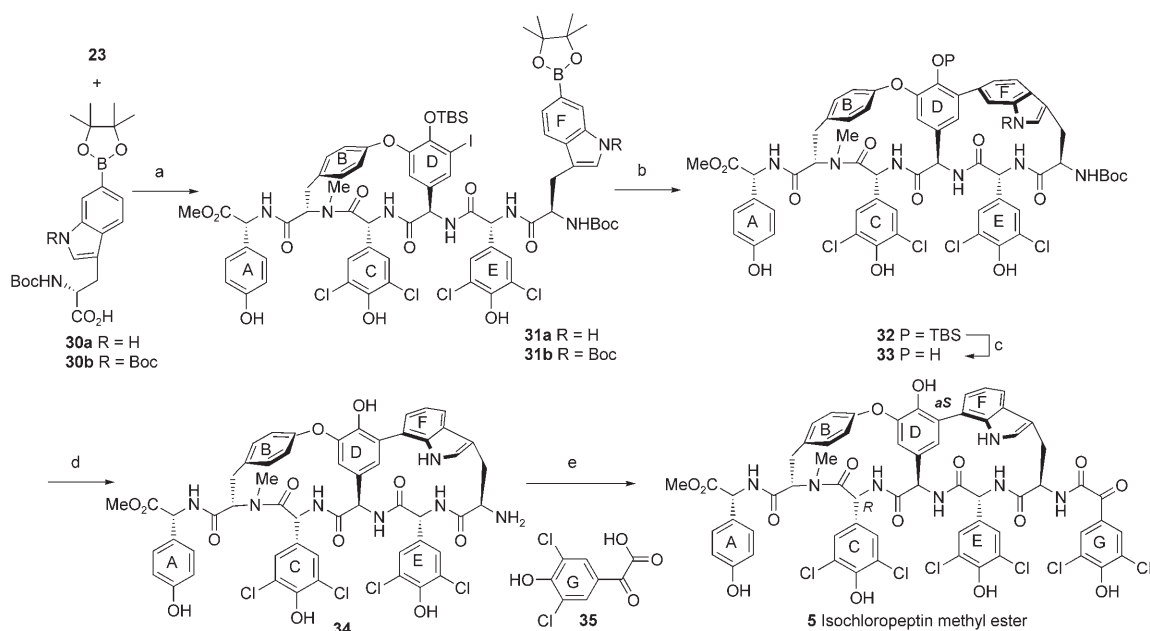


**Scheme 5.** Synthesis of *epi*-AA-C<sub>2'</sub>-complestatin methyl ester **4**. a) HATU, lutidine (6 equiv), THF/CH<sub>2</sub>Cl<sub>2</sub> (1:1), 5°C, overnight, 69%; b) [PdCl<sub>2</sub>(dppf)]·CH<sub>2</sub>Cl<sub>2</sub> (1 equiv), 1,4-dioxane/H<sub>2</sub>O (50:3), K<sub>2</sub>CO<sub>3</sub> (10 equiv), 90°C, 1 h, 48%.

to be *aR*, in accord with that of the natural product. The characteristic NOE correlations of NMe/H<sub>C2</sub>, H<sub>C2</sub>/H<sub>D2'</sub>, H<sub>D6'</sub>/H<sub>E2</sub>, H<sub>D6'</sub>/H<sub>F6'</sub>, H<sub>D6'</sub>/H<sub>F5'</sub>, H<sub>E2</sub>/H<sub>F5'</sub>, H<sub>F5'</sub>/H<sub>F3β</sub>, H<sub>F2</sub>/H<sub>F3α</sub>, and H<sub>F2</sub>/H<sub>F3α</sub> were indicative of the stereochemistry of **4**. The chemical shift of the H<sub>F2</sub> signal in compounds **3** and **4** (δ = 5.58 ppm for **3**, δ = 4.42 ppm for **4**; CD<sub>3</sub>CN) is also supportive of the assigned atropisomerism. Molecular models showed that the H<sub>F2</sub> signal for *aR* atropisomer **4** was located underneath that of the indole ring, whereas that for *aS* atropisomer **3** was in the deshield zone of the indole ring.

To verify whether the terminal α-ketoamide unit can alter the atropselectivity of the aryl–aryl bond-forming process,<sup>[23]</sup> compound **31a** was synthesized by coupling of **23** with tryptophan derivative **30a** (Scheme 6). Cyclization of **31a** proceeded smoothly to afford the desired bismacrocyclic. However, the *aS* atropisomer was once again the only isolable atropisomer. On the other hand, cyclization of **31b**, wherein the indolyl nitrogen atom was protected as an *N*-Boc group, failed to produce the cyclic product.

It has been reported that attempts to convert isocomplestatin **3** into isochloropectin **5** under acidic conditions met with failure, due probably to the higher ring strain in isocomplestatin **3** than in complestatin **1**. Since intramolecular Stille coupling afforded the chloropectin atropselectively,<sup>[24]</sup> the isochloropectin **5** is currently inaccessible synthetically. On the basis that the absence of the terminal α-ketoamide unit in **33** might render it conformationally more flexible than isocomplestatin, the acid-promoted isomerization of **33** was carried out. Fortuitously, heating of a TFA solution of **33**, obtained by removal of the TBS protective group from **32**, to 50°C for 15 min removed the terminal *N*-Boc function and triggered a bond reorganization to afford the rearranged product **34** in quantitative yield. Coupling of **34** with



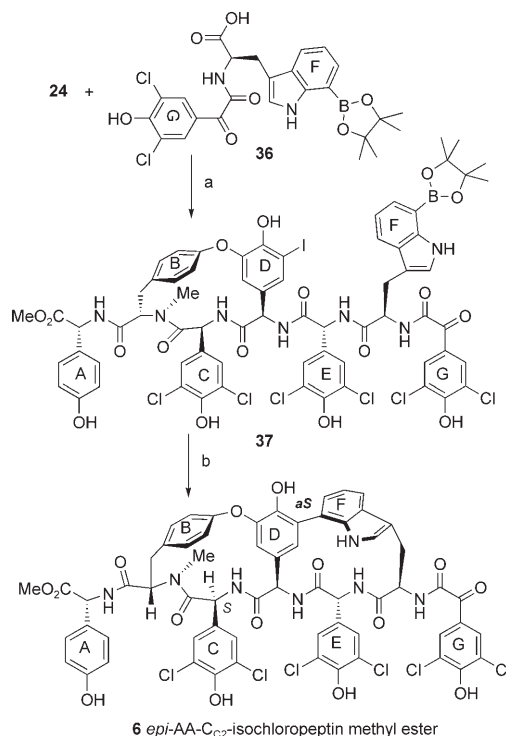
**Scheme 6.** Synthesis of isochloropeptin I methyl ester **5**. a) **23**, HATU, lutidine (2.5 equiv), THF, 5 h, 90%; b) [PdCl<sub>2</sub>(dppf)]·CH<sub>2</sub>Cl<sub>2</sub> (1 equiv), 1,4-dioxane/H<sub>2</sub>O (50:3), K<sub>2</sub>CO<sub>3</sub> (10 equiv), 90°C, 1 h, 55%; c) KF, HBr in DMF, 0.03 M, room temperature, 83%; d) TFA, 50°C, 15 min; e) EDC (2.0 equiv), HOAt (1 equiv), DMF/CH<sub>2</sub>Cl<sub>2</sub> (1:5), 3 h, 83% (over 2 steps).

$\alpha$ -ketoacid **35** then furnished the desired isochloropeptin **5** in 83% yield. In this case, the signal for the F<sub>H2</sub> proton in isochloropeptin appeared in the <sup>1</sup>H NMR spectrum at a higher field ( $\delta$  = 4.46 ppm) than the equivalent signal in chloropeptin ( $\delta$  = 5.08 ppm).

In Snapper, Hoveyda, and co-workers' synthesis of chloropeptin, the natural *R* atropisomer was obtained by an intramolecular Stille coupling. Since we had demonstrated that the stereochemistry of amino acid C changed the atropselectivity of the ring-closure reaction in the complestatin series (see the syntheses of **3** and **4**), we set out to examine the cyclization of hexapeptide **37**, which should afford the macrocycle with the phenyl-indole connectivity found in chloropeptin (Scheme 7). Coupling of **24** with amide **36** proceeded without event to furnish the cyclization precursor **37**. The intramolecular Suzuki–Miyaura coupling of **37** worked smoothly to provide bismacrocycle **6**, the axial chirality of which was determined to be *aS*, in 42% yield. Thus, the atropselectivity switched once again from *aR* to *aS* selective. These results indicated that the absolute configuration of amino acid C has a dramatic effect on the atropselectivity of the DEF-ring-forming reaction regardless the biaryl ring connectivity.

In conclusion, we have developed a unified strategy for the synthesis of analogues of complestatin and chloropeptin by employing intramolecular S<sub>N</sub>Ar and Suzuki–Miyaura reactions for the closure of the two macrocycles. While Suzuki–Miyaura reaction was highly atropstereoselective, the absolute configuration of the axial chirality was found to be extremely sensitive to both the stereogenicity of the linear peptide and the aryl–aryl bond connectivity. It is noteworthy that changing the absolute configuration of amino acid C

reverses the atropselectivity of the subsequent macrocyclization in both the complestatin and chloropeptin series. We believe that ready accessibility of stereoisomers, including



**Scheme 7.** Synthesis of *epi*-AA-C<sub>22</sub>-isochloropeptin methyl ester **6**. a) HATU, lutidine, 67%; b) [PdCl<sub>2</sub>(dppf)]·CH<sub>2</sub>Cl<sub>2</sub> (1 equiv), 1,4-dioxane/H<sub>2</sub>O (50:3), K<sub>2</sub>CO<sub>3</sub> (10 equiv), 90°C, 1 h, 42%.

atropisomers, of the natural products should help to define the structure–activity relationship of these biologically important macrocycles.<sup>[25]</sup>

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