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

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Complestatin $(1)^{[1]}$ and chloropeptin I (2),^[2] isolated from *Streptomyces lavendulae* and *Streptomyces* sp. WK-3419,



respectively, display potent activities against HIV-1-induced cytopathicity and syncyctium formation in CD-4 lymphocytes and inhibit HIV replication by inhibition of gp120–CD-4 binding at a low-micromolar level (IC₅₀=3.3 and 2.0 μ M, respectively).^[3] The absolute configurations of the amino acid constituents of **1**^[4] and **2**^[5] were elucidated through detailed NMR, computational, and degradation studies. Complestatin

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- Supporting information for this article (including experimental procedures, product characterization, and the ¹H and ¹³C NMR spectra) is available on the WWW under http://www.angewand-te.org or from the author.

and chloropeptin differ only in the position of the phenylindole ring junction, and it has been demonstrated that the former is readily isomerized to the latter under mildly acidic conditions.^[6] These compounds belong to a growing family of vancomycin-type polymacrocyclopeptides with unusual endo aryl-aryl ether and endo biaryl linkages.^[7] 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,^[8] only the group of Snapper and Hoveyda has accomplished the total synthesis of chloropeptin I (2)^[9] and an atropisomer of complestatin named isocomplestatin (3; Scheme 1).^[10] 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^[11,12] and have recently reported an atropselective synthesis of the DEFG ring of complestatin by way of an intramolecular Suzuki-Miyaura reaction.^[13] 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^[14] and Suzuki-Miyaura^[15] 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**)^[16] with (*R*)-*N*-Boc-3,5-dichloro-4-hydroxyphenylglycine (**8**)^[17] 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, NaHCO₃, 0°C to room temperature), the dipeptide (**9**) was isolated in 54% yield, together with its C_{C2} epimer (18%). Fortuitously, the desired dipeptide **9** can be purified from a mixture of diastereomers by crystallization in a solution of CH₂Cl₂/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, CH₂Cl₂) afforded the TFA salt of the amine, which was coupled directly with (*R*)-*N*-Boc-3-iodo-4,5-dihydroxyphenylglycine



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Scheme 1. Diastereomers of complestatin and chloropeptin I.

(10)^[13] 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.^[18] 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, NaHCO₃, THF, 0°C \rightarrow RT, 12 h, 54%; b) 1. TFA, CH₂Cl₂; 2. (R)-**10**, HATU, NaHCO₃, THF/DMF (3:1), 71%; c) K₂CO₃, DMSO, RT, 36 h, 72%. Boc: *tert*-butoxycarbonyl; DEPBT: 3-(diethyloxyphosphoryloxy)-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_NAr 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/H₂O) 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.^[19] Coupling of 14 with (*R*)-4-hydroxyphenyl-glycine 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,



Scheme 3. Elaboration of the BCD ring into the ABCDE fragment. a) $SnCl_2 \cdot 2H_2O$, EtOH, $60^{\circ}C$; b) H_3PO_2 , $NaNO_2$, THF/H_2O (3:1), 80%; c) Me_3SnOH , 1,2-DCE, 80°C; d) **15**, EDC, HOAt, $NaHCO_3$, THF, 59% for **16**; 70% for **21**; e) 7% conc. HCl in MeCN; f) (*R*)-**8**, HATU, lutidine, THF/CH₂Cl₂ 3:1, 73% for **17**; 90% for **22**; g) TBSCl, imidazole, DMF. 1,2-DCE = 1,2-dichloroethane; EDC = *N*-(3-dimethylaminopropyl)-*N*'- ethylcarbodiimide hydrochloride; HOAt = 1-hydroxy-7-azabenzotriazole; TBS = *tert*-butyldimethylsilyl; P = protecting group.

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

Since we have previously shown that the protection of the phenol group can influence the atropselectivity of the intramolecular Suzuki–Miyaura reaction,^[13] 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, CH₂ClCH₂Cl, 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*)-12 d. 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_{B2}/H_{C2}). However, that of 24 adopted a *trans* conformation, as evidenced by the characteristic NOE crosspeaks between the NMe and H_{C2} signals. The downfield shift of the H_{B2} 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 macrocyle 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^[20] 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.^[10] 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.^[10] The same atropselectivity has also been observed in our synthesis of RP-66453, a structurally related bismacrocyclic natural product.^[21] Attempted thermal atropisomerization of 3 failed to provide the natural atropisomer.

Smith and co-workers^[8e] 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.^[22] To verify this hypothesis, we synthesized hexapep-

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Scheme 4. Synthesis of isocomplestatin methyl ester 3. a) HATU, lutidine (1 equiv), THF, 0°C to room temperature, 5 h, 84%; b) [PdCl₂- (dppf)]·CH₂Cl₂ (1 equiv), 1,4-dioxane/H₂O (50:3), K₂CO₃ (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 bismacrocycle **4**, the axial chirality of which was determined



4 epi-AA-C_{C2}-complestatin methyl ester

Scheme 5. Synthesis of *epi*-AA-C_{C2}-complestatin methyl ester **4**. a) HATU, lutidine (6 equiv), THF/CH₂Cl₂ (1:1), 5 °C, overnight, 69%; b) [PdCl₂(dppf)]·CH₂Cl₂ (1 equiv), 1,4-dioxane/H₂O (50:3), K₂CO₃ (10 equiv), 90 °C, 1 h, 48%.

to be a*R*, in accord with that of the natural product. The characteristic NOE correlations of NMe/H_{C2}, H_{C2}/H_{D2}, H_{D6}/H_{F6}, H_{D6}/H_{F5}, H_{E2}/H_{F5}, H_{F5}/H_{F3}, H_{F2}/H_{F3}, and H_{F2}/H_{F3} were indicative of the stereochemistry of **4**. The chemical shift of the H_{F2} signal in compounds **3** and **4** ($\delta = 5.58$ ppm for **3**, $\delta = 4.42$ ppm for **4**; CD₃CN) is also supportive of the assigned atropisomerism. Molecular models showed that the H_{F2} signal for a*R* atropisomer **4** was located underneath that of the indole ring, whereas that for a*S* atropisomer **3** was in the deshield zone of the indole ring.

To verify whether the terminal α -ketoamide unit can alter the atopselectivity of the aryl-aryl bond-forming process,^[23] compound **31a** was synthesized by coupling of **23** with tryptophan derivative **30a** (Scheme 6). Cyclization of **31a** proceeded smoothly to afford the desired bismacrocycle. However, the a*S* 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 isochloropeptin **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 chloropeptin atropspecifically,^[24] the isochloropeptin **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

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Scheme 6. Synthesis of isochloropeptin I methyl ester **5**. a) **23**, HATU, lutidine (2.5 equiv), THF, 5 h, 90%; b) [PdCl₂(dppf)]·CH₂Cl₂ (1 equiv), 1,4-dioxane/H₂O (50:3), K₂CO₃ (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/CH₂Cl₂ (1:5), 3 h, 83% (over 2 steps).

 α -ketoacid **35** then furnished the desired isochloropeptin **5** in 83% yield. In this case, the signal for the F_{H2} proton in isochloropeptin appeared in the ¹H NMR spectrum at a higher field (δ = 4.46 ppm) than the equivalent signal in chloropeptin (δ = 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 aSselective. 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_NAr 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_{C2}-isochloropeptin methyl ester **6**. a) HATU, lutidine, 67%; b) $[PdCl_2(dppf)]\cdot CH_2Cl_2$ (1 equiv), 1,4-dioxane/ H₂O (50:3), K₂CO₃ (10 equiv), 90°C, 1 h, 42%.

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

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