

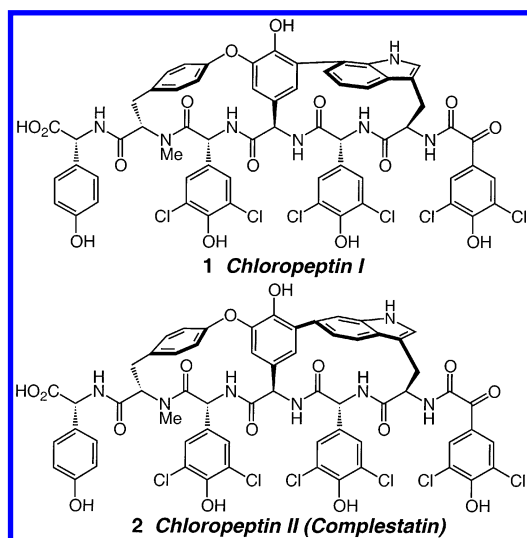
## Total Synthesis of Anti-HIV Agent Chloropeptin I

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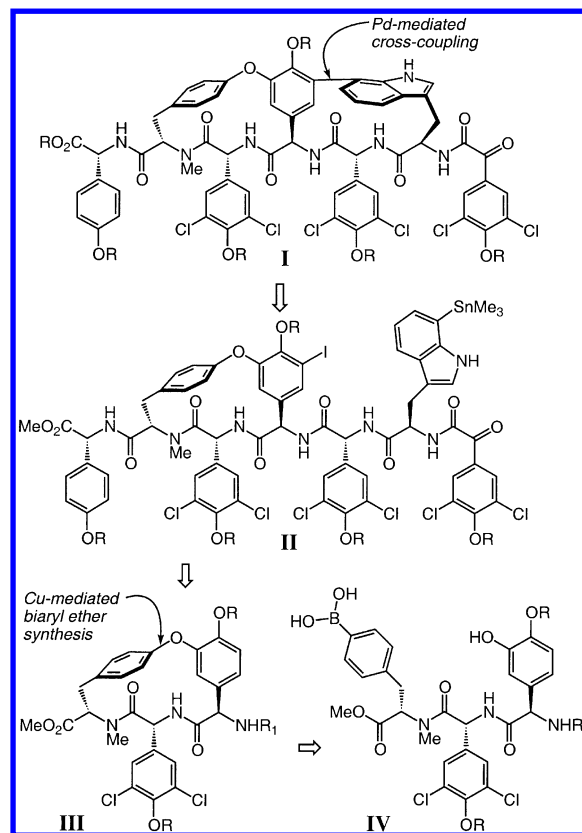
Chloropeptin I (**1**) was obtained from *Streptomyces* sp. WK-3419 in 1994, and its structure was elucidated through NMR spectroscopy.<sup>1</sup> Five years earlier, chloropeptin II (or complestatin) had been isolated from a fermentation broth of *Streptomyces lavendulae*.<sup>2</sup> Complestatin isomerizes to **1** under acidic conditions.<sup>3,4</sup> Both natural products exhibit notable activity against HIV-1-induced cytopathicity and syncytium formation in CD-4<sup>+</sup> lymphocytes.<sup>1,2</sup> They inhibit HIV replication by disruption of HIV gp-120 glycoprotein binding to the CD4 receptor of T-lymphocytes (IC<sub>50</sub> values of 2.0 and 3.3  $\mu$ M for **1** and **2**, respectively).<sup>1a,d</sup> More recently, researchers at Merck isolated two additional derivatives and an atropisomer of **2** (isocomplestatin), which demonstrate anti-HIV integrase property.<sup>5,6</sup> Structural complexity and potent biological activity of **1** and **2**, which carry racemization-prone electron-deficient chlorinated amino acids, and the requirement for stereo-selective biaryl macrocycle formation render these natural products important targets for total synthesis. The first stereoselective total synthesis of the more active member of this family, chloropeptin I (**1**), is reported herein.<sup>7</sup>



As indicated by the retrosynthesis plan in Scheme 1, the success of the proposed route depends on the availability of effective and stereoselective methods for biaryl ether formation (**IV**  $\rightarrow$  **III**) and biaryl cross coupling (**II**  $\rightarrow$  **I**) as well as efficient protocols for preparation of the required arylglycine units. Accordingly, our first objective became the selective synthesis of tripeptide **7** (Scheme 2) and the study of its conversion to biaryl ether **8**.

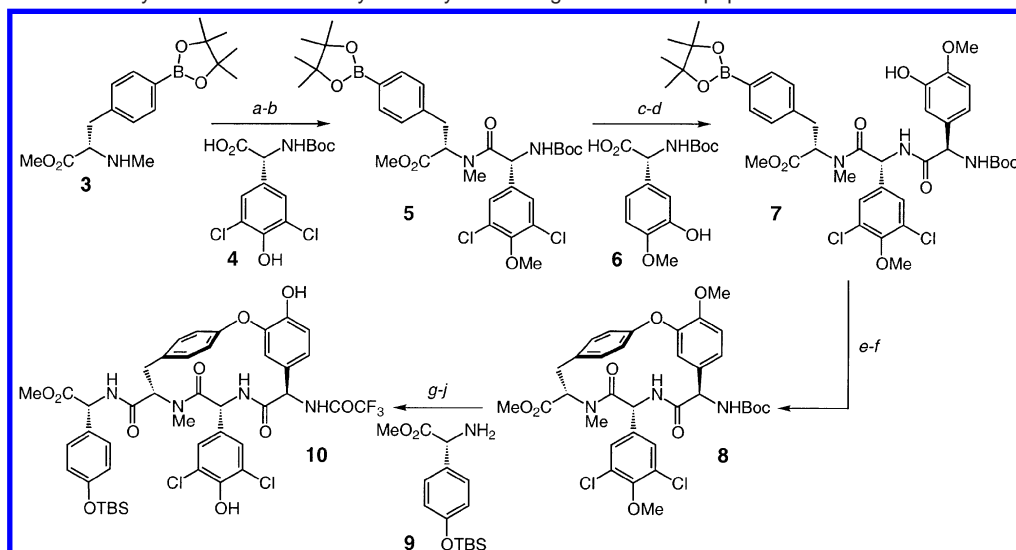
As depicted in Scheme 2, boronic ester **3**, prepared<sup>8</sup> in 90–95% yield from the corresponding Boc-protected amino acid,<sup>9</sup> was coupled with **4**<sup>10</sup> in the presence of DEPBT<sup>11,12</sup> and methylated with TMSCHN<sub>2</sub> to afford dipeptide **5** in 74% overall yield. A variety of protocols were investigated to identify the conditions shown in Scheme 2, such that peptide coupling could be effected in high yield with minimal epimerization at the sensitive site of the dichlorophenylglycine moiety.<sup>13</sup> Removal of the Boc group and union of the resulting amine salt (to avoid diketopiperazine

Scheme 1

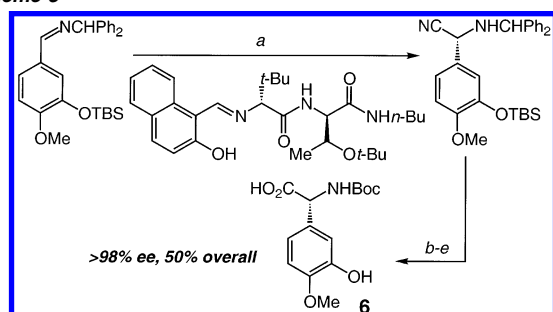


formation) with optically pure **6**, which can be prepared by Ti-catalyzed asymmetric cyanide addition (Scheme 3),<sup>14,15</sup> delivered **7** (86% overall). Treatment of **7** with a dilute solution (0.01 M) of NaIO<sub>4</sub><sup>16</sup> led to the derived boronic acid; higher concentrations gave rise to the formation of unidentified byproducts and a low yield of the desired compound.

The resulting boronic acid was subjected to conditions reported previously for Cu-mediated formation of biaryl ethers.<sup>17</sup> These procedures provide **8** but in low yields (15–20%), particularly when the reaction was carried out on gram scale. Extensive experimentation led us to determine that the presence of 10 equiv of MeOH (vs substrate) is crucial for efficient biaryl ether formation; reactions proved to be significantly more sluggish without MeOH (>24 h vs 3–6 h for >98% conv). The positive influence of MeOH may be linked to the in situ formation of the boron dimethyl ester or the increased solubility of the Cu salt.<sup>18</sup> We also determined that use of Et<sub>3</sub>N leads to notably more facile transformations (vs pyridine). As illustrated in Scheme 2, biaryl ether **8** was converted to tetrapeptide **10** in four steps (75% overall). It is noteworthy that installment of the phenylglycine terminus was performed after the two phenols were unmasked along with conversion of the methyl ester to the desired carboxylic acid (AlBr<sub>3</sub>, EtSH); thus, peptide coupling was effected with excellent site-selectivity without the need for hydroxyl group differentiation. It should also be noted

**Scheme 2.** Enantioselective Synthesis of the Macrocyclic Biaryl Ether Segment of Chloropeptins<sup>a</sup>

<sup>a</sup> (a) 1.5 equiv of **4**, 1.6 equiv of DEPBT, 1 equiv of NaHCO<sub>3</sub>, THF, 0 °C → 22 °C, 12 h; 74%. (b) 1.5 equiv of TMSCHN<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 22 °C, 1.5 h; >98%. (c) HCl (g), MeOH, −78 °C → 22 °C, 1 h. (d) 1.5 equiv of HOAt, 1.5 equiv of EDC, 1 equiv of **6**, THF/DMF, 0 °C → 22 °C, 12 h; 86% from **5**. (e) 3 equiv of NaIO<sub>4</sub>, 3 equiv of NH<sub>4</sub>OAc, acetone/water (0.01 M), 22 °C, 12 h. (f) 2 equiv of Cu(OAc)<sub>2</sub>, 10 equiv of Et<sub>3</sub>N, 4 Å MS, 10 equiv of MeOH, CH<sub>2</sub>Cl<sub>2</sub> (0.01 M), 22 °C, 5 h, 50% from **7**. (g) HCl (g), MeOH, −78 °C → 22 °C, 1.5 h; NaHCO<sub>3</sub>. (h) 1.5 equiv of TFAA, 3 equiv of 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C → 22 °C, 2 h; 94% for two steps. (i) 20 equiv of AlBr<sub>3</sub>, EtSH, 0 °C, 1.5 h. (j) 1.1 equiv of **9**, 1.5 equiv of HOAt, 1.5 equiv of EDC, 1.5 equiv of NaHCO<sub>3</sub>, THF, 0 °C → 22 °C, 12 h, 80% for two steps.

**Scheme 3**<sup>a</sup>

<sup>a</sup> (a) 10 mol % chiral ligand, 10 mol % Ti(O<sup>*i*</sup>-Pr)<sub>4</sub>, 2 equiv of TMSCHN<sub>2</sub>, 2 equiv of *i*-PrOH (over 12 h), toluene, 4 °C; 93% ee, >98%. (b) HCl (g), MeOH/HOAc, −78 °C (30 min) → 22 °C (2 h). (c) 10 equiv of Et<sub>3</sub>SiH, TFA, 72 °C, 2 h. (d) HCl (g), MeOH, −78 °C (10 min) → 65 °C (2 h). (e) 1 equiv of Boc<sub>2</sub>O, aqueous NaOH, dioxane, 22 °C, 1 h; >98% ee, 50% overall for four steps.

that, although **10** was isolated as a single conformational isomer, until amino acid unit **9**<sup>8</sup> was installed, all intermediates existed as a mixture of rotamers (ratios depending on solvent and substrate);<sup>13</sup> such observations are consistent with the results of previous degradation studies.<sup>5,6</sup>

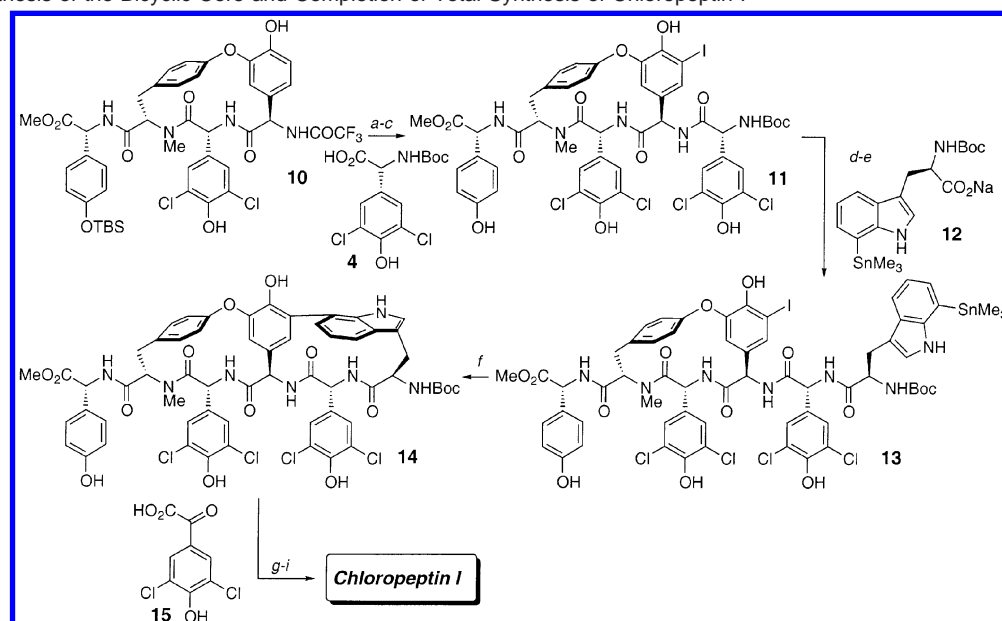
With tetrapeptide **10** in hand, we began to outfit this advanced intermediate in preparation for performing the second key macrocyclization. Toward this end, as outlined in Scheme 4, subjection of **10** to NIS led to selective formation of the desired *o*-iodide. Subsequent removal of the TBS and TFA protecting groups under meticulously controlled acidic conditions<sup>19</sup> and installment of the second dichlorophenylglycine module (**4**) afforded **11** in nearly 70% overall yield. Following the cleavage of the Boc group, the deprotected amine terminus derived from **11** was coupled with Na salt **12** to afford **13**, which was directly subjected to 1 equiv of Pd(P<sup>*t*</sup>-Bu)<sub>3</sub>, 5 equiv of CsF, and 10 equiv of collidine (dioxane, 50 °C, 5 h) to afford **14**, isolated as a single diastereomer (38–42% overall yield from **11**). Several issues regarding the sequence transforming from **10** to **14** are noteworthy: (1) Removal of the Boc and TFA groups had to be performed under <2 M acidic conditions; otherwise, significant decomposition would ensue due to cleavage of the terminal phenylglycine methyl ester. (2) Stannyl tryptophane **12**

was prepared<sup>20</sup> in the manner illustrated in eq 1 (Scheme 5). (3) Amino acid **12** was introduced as its Na salt, because the corresponding carboxylic acid proved to be unstable (labile C–Sn bond). (4) The biaryl coupling conditions are based on those reported previously.<sup>21</sup> However, after extensive studies, we established that this critical C–C bond forming reaction (**13** → **14**) is significantly more efficient in the presence of collidine. The positive effect of added base might be related to stabilization of the active Pd complex; in the absence of this additive, the reaction turns black (vs light brown), and no further conversion is detected after 30 min.<sup>13</sup>

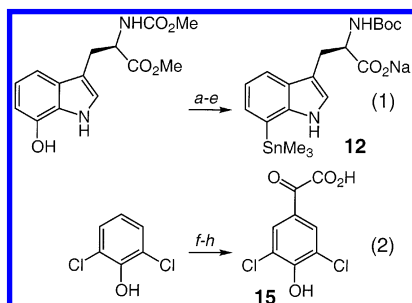
The total synthesis of chloropeptin I was completed from **14** in three steps. Removal of the Boc group of **14** under acidic conditions, coupling of the resulting amine terminus with α-ketoacid **15**, prepared as illustrated in eq 2 (Scheme 5), and conversion of the methyl ester to the desired carboxylic acid delivered **1** in 60% overall yield without complications due to epimerization or hydrate formation. The synthetic sample proved to be identical to authentic material by extensive <sup>1</sup>H NMR analysis, as well as by HRMS, analytical HPLC, and optical rotation.<sup>22</sup>

In summary, we have completed the first stereoselective total synthesis of anti-HIV agent chloropeptin I. Salient features of the total synthesis include the discovery of two critical positive effects exerted by additives: MeOH in the Cu-mediated biaryl ether formation and collidine in the Pd-mediated cross-coupling, resulting in efficient formation of the two macrocycles of the target molecule. Future studies include optimization and a detailed study of several key steps in the total synthesis, and application of the protocols outlined above to the synthesis of other members of this important class of natural products.

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**Scheme 4.** Synthesis of the Bicyclic Core and Completion of Total Synthesis of Chloropeptin I<sup>a</sup>

<sup>a</sup> (a) 1.5 equiv of NIS, MeCN, 22 °C, 1 h; 60% (82% based on recovered **10**). (b) HCl, MeOH, 45 °C, 4 h; NaHCO<sub>3</sub>. (c) 1.5 equiv of HATU, 3 equiv of collidine, 1.1 equiv of **4**, CH<sub>2</sub>Cl<sub>2</sub>/THF, 0 °C → 22 °C, 3 h; 85% for two steps. (d) HCl, MeOH, 22 °C, 3 h. (e) 1.1 equiv of HATU, 5 equiv of collidine, CH<sub>2</sub>Cl<sub>2</sub>/THF, 0 °C → 22 °C, 4 h. (f) 1 equiv of Pd(Pt-Bu<sub>3</sub>)<sub>2</sub>, 10 equiv of collidine, 5 equiv of CsF, dioxane (0.002 M), 50 °C, 5 h; ~40% from **11**. (g) HCl, MeOH, 22 °C, 1.5 h. (h) 1.5 equiv of **15**, 1.5 equiv of HOAt, 3 equiv of EDC, CH<sub>2</sub>Cl<sub>2</sub>/DMF, 0 °C → 22 °C, 3 h; 60% for two steps. (i) 10 equiv of LiOH, H<sub>2</sub>O/THF (1/5), 0 °C, 2 h; 98%.

**Scheme 5**<sup>a</sup>

<sup>a</sup> (1) 1.1 equiv of H<sub>2</sub>O, 1.2 equiv of Et<sub>3</sub>N, -78 °C, 2 h; >98%. (2) 3 equiv of TMSI, CHCl<sub>3</sub>, 65 °C, 3 h. (c) 1.1 equiv of (Boc)<sub>2</sub>O, THF, 22 °C, 12 h. (d) 1 equiv of (Me<sub>3</sub>Sn)<sub>2</sub>, 3 equiv of LiCl, 0.5 mol % BHT, 5 mol % Pd(PPh<sub>3</sub>)<sub>4</sub>, dioxane, 85 °C, 7 h; 80% for two steps. (e) aqueous NaOH, MeOH, 0 °C → 22 °C, 1 h; >98%. (f) 1.5 equiv of NIS, THF, 22 °C, 2 h. (g) 2.5 equiv of *n*-BuLi, 5 equiv of MeO(CO)<sub>2</sub>OMe, THF, -78 °C, 1 h; 47% for two steps. (h) 10 equiv of aqueous NaOH, MeOH, 0 °C → 22 °C, 1 h; >98%.

**Note Added after ASAP.** In the version posted ASAP on 7/2/03, the description of the synthesis of **12** shown in Scheme 5 was incorrect. The version posted 7/2/03 and the print version are correct.

**Supporting Information Available:** Experimental procedures and spectral and analytical data for select intermediates and **1** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (12) Abbreviations: DEPBT = 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one, EDC = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide, HATU = 2-(1-*H*-7-azabenzotriazol-1,1,3,3-methyluronium hexafluorophosphate, HOAt = 1-hydroxy-7-azabenzotriazole.
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- (22) In addition, the synthetic Me ester of **1** (prior to LiOH treatment) was determined to be identical to an authentic sample (prepared from **1**) by <sup>1</sup>H NMR (see the Supporting Information).

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