ORGANIC LETTERS

2007
Vol. 9, No. 12
2401−2404

Synthesis of DEFG Ring of Complestatin and Chloropeptin I: Highly Atropdiastereoselective Macrocyclization by Intramolecular Suzuki-Miyaura Reaction

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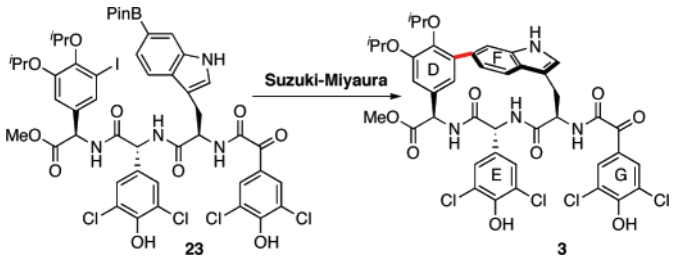
Received April 17, 2007

ABSTRACT



Palladium-catalyzed intramolecular Suzuki-Miyaura reaction of linear tripeptide (23) afforded the 16-membered DEFG ring of complestatin (3) in good yield with an excellent atropdiastereoselectivity. Acidic treatment of 3 triggers a stereospecific rearrangement leading to the corresponding DEFG ring 4 of chloropeptin I.

A number of biologically important natural products contain strained macrocycle(s) with a specific atropisomeric configuration(s). The vancomycin family of glycopeptide antibiotics that contain both planary and axially chiral cyclophane subunits are notable examples.[1] Recent additions to this class of compounds include chloropeptin (**1**)[2] and complestatin (**2**),[3] isolated from *Streptomyces sp*. WK-3419 and *Streptomyces lavendulae*, respectively. Both bicyclic natural cyclophanes display potent activities against HIV-1 induced cytopathicity and syncytium formation in CD-4 lymphocytes and inhibit HIV replication by inhibition of gp 120-CD4 binding at a low-micromolar level (IC_{50} = 2.0 and 3.3 μM, respectively).[4] The absolute configurations of the amino acid constituents of **1**[5] and **2**[6] were elucidated through detailed NMR, computational, as well as degradation studies. Complestatin is readily isomerized to chloropeptin I under mild acidic conditions.[7] The presence of highly racemization-prone

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10.1021/ol070889p CCC: $37.00
Published on Web 05/12/2007

chlorinated arylglycines and inherent difficulties associated with the construction of strained macrocycles with defined atropisomerism 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 Snapper and Hoveyda group accomplished the total syntheses of chloropeptin I (**1**)[9] and an atropisomer of complestatin (**2**) (Figure 1).[10] These total syntheses have also allowed them

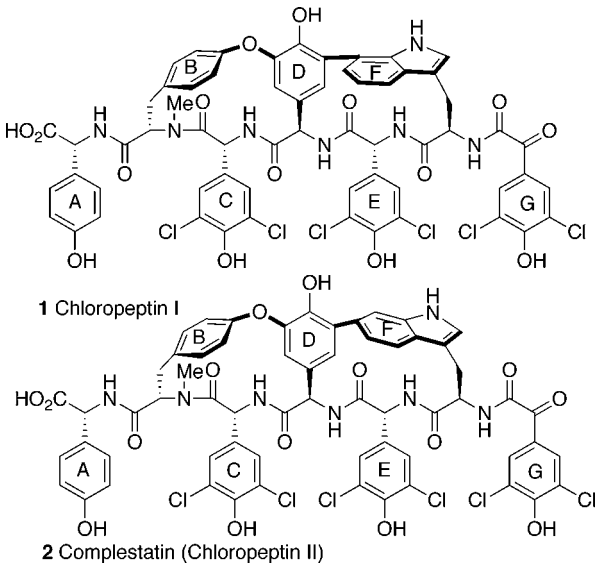

Figure 1. Structures of chloropeptin I (**1**) and complestatin (**2**).

to assign the (*R*)-configuration to the axial chirality of both natural products and highlighted the dependence of atropselectivity on the structure of the linear precursor. Indeed, they documented that cyclization of a model peptidic precursor is non-atropselective leading to two atropisomers in a 1/1 ratio.

We have a long interest in the synthesis of this type of macrocyclic natural products[11,12] and have recently accomplished the first total synthesis of an atropstereomer of RP-66453,[13] structurally related to **1** and **2**. As a continuation of this research program, we report herein the first completely atropdiastereoselective synthesis of fully functionalized DEFG ring (**3**) and (**4**) of complestatin and chloropeptin I, respectively (Figure 2). The syntheses feature a key atrop-

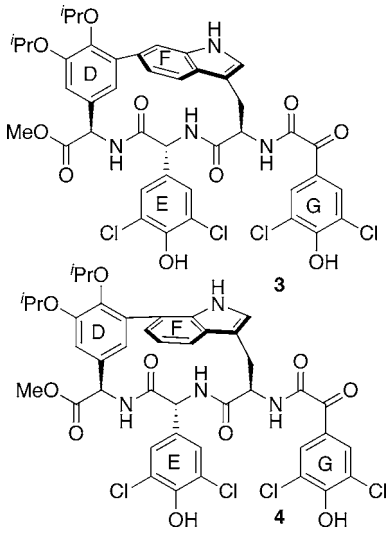

Figure 2. DEFG fragments of chloropeptin I and complestatin.

diastereoselective intramolecular Suzuki-Miyaura reaction. We document also that the presence of free-hydroxy group is not required for the stereospecific isomerization of **3** to **4** under acidic conditions.

To begin our synthesis, the tryptophane derivative **13** is prepared as summarized in Scheme 1. Palladium-catalyzed annulation of 2-iodo-5-nitroaniline **5** with (*R*)-2-*N*,*N*-di-*tert*-butoxycarbonyl-5-oxopentane **6** according to our recently developed conditions afforded the protected 6-nitro tryptophane **7**[14−16] that was subsequently converted to the 6-amino derivative (**8**) under standard conditions. Diazotization of aniline followed by iodination provided iodo derivative **9**, which underwent palladium-catalyzed cross coupling with bis(pinacolato) diboron under Miyaura's conditions to provide the corresponding arylboronate (**10**).[17,18] Removal of *N*-Boc protective groups under mild conditions

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(15) The annulation reaction has been independantly developed by the group of Baran, see: (a) Baran, P. S.; Guerrero, C. A.; Ambhaikar, N. B.; Hafensteiner, B. D. *Angew. Chem., Int. Ed*. **2005**, *44*, 606−609. (b) Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc*. **2006**, *128*, 8678−8693.

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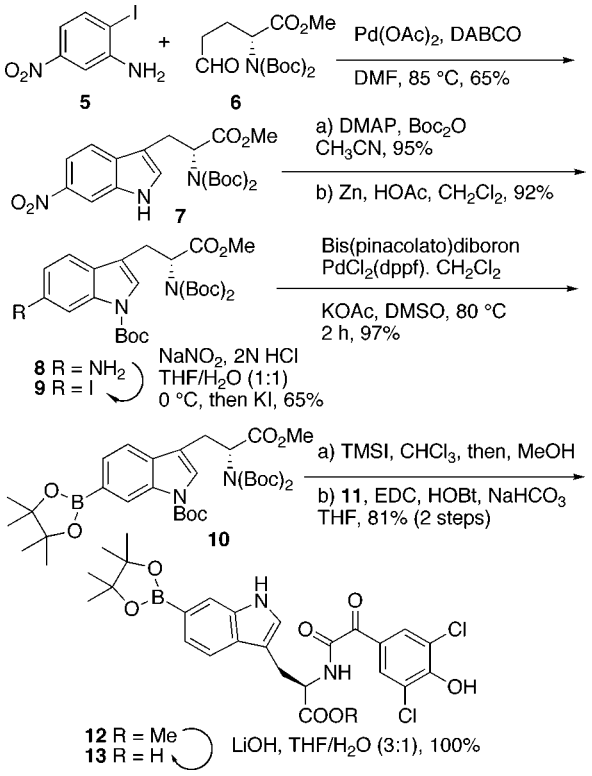
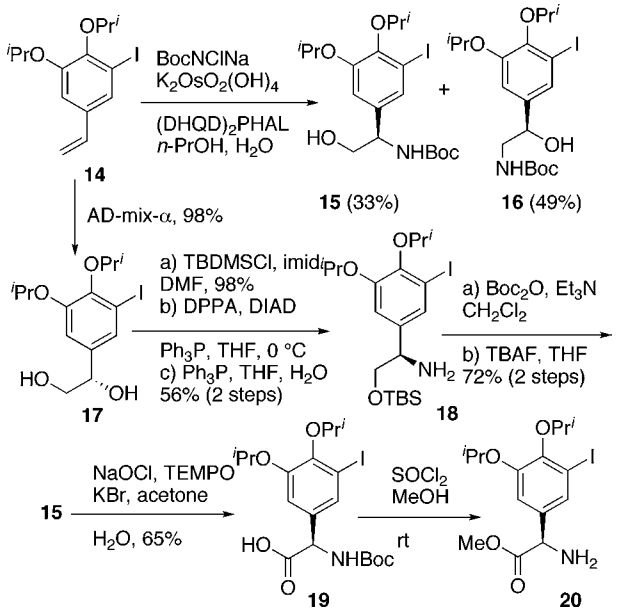
(18) This substituted tryptophane has been synthesized independently by the group of J. M. Campagne, private communication.

Scheme 1. Synthesis of Tryptophane Derivative **13**



Scheme 2. Synthesis of *N*-Boc-D-3-iodo-4,5-diisopropyloxyphenyl Glycine Methyl Ester **20**



(TMSI, $CHCl_3$, then MeOH) followed by coupling with 2-(3,5-dichloro-4-hydroxyphenyl)-2-oxoethanoic acid (**11**)[10] furnished the keto amide (**12**), which was hydrolyzed to the corresponding acid **13** under mild basic conditions.

Synthesis of D-3-iodo-4,5-diisopropyloxyphenyl glycine methyl ester **20** is summarized in Scheme 2. Sharpless aminohydroxylation of styrene **14**[19] under a variety of conditions afforded the desired amino alcohol (**15**) in only 33% yield (76% *ee*), together with the wrong regioisomer (**16**).[20] The low-regioselectivity and moderate enantioselectivity of this transformation prompted us to examine an alternative, albeit longer reaction sequence using Sharpless asymmetric dihydroxylation as a key step.[21] Treatment of **14** with AD-mix-α afforded the desired (*S*)-diol (**17**) in an excellent yield and enantiomerical purity (95% *ee*). The so-obtained diol was converted to amino alcohol **18** via a conventional three-step sequence involving (a) selective protection of the primary alcohol; (b) Mitsunobu reaction; and (c) reduction of azide under Staudinger conditions. Protecting group manipulation of **18** afforded **15**, which was oxidized to the acid **19** without event. The *N*-Boc deprotection and esterification of carboxylic acid of **19** was realized in methanol in the presence of thionyl chloride to afford directly the amino ester **20**.[22] The Sharpless AA of styrene **14** with (DHQ)PHAL afforded (*S*)-**15** in 33% yield (88% ee). Chiral HPLC analysis indicated that the enantiomeric excess (*ee*) of the (*R*)-**15** synthesized by the Sharpless AD method is higher than 92%.

The synthesis of linear tripeptide and subsequent macrocyclization via formation of the *endo* aryl−aryl bond is depicted in Scheme 3. Coupling of the amino ester **20** with D-*N*-Boc-3,5-dichloro-4-hydroxyphenyl glycine **21** afforded the dipeptide **22** in 80% yield. Removal of *N*-Boc group from **22** (TFA, CH_2Cl_2) followed by coupling with tryptophane derivative **13** (HATU, 2,5-lutidine) afforded the tripeptide **23** in 78% overall yield.

The macrocyclization via intramolecular Suzuki-Miyaura reaction turned out to be extremely difficult to realize.[12,23] After extensive optimization of reaction conditions varying the palladium sources, the ligands, the solvents, and the reaction temperatures, the best conditions found consist of performing the reaction in dioxane-H_2O in the presence of 1 equiv of $PdCl_2$(dppf) and 10 equiv of K_2CO_3. Under these conditions, cyclization of **23** afforded cyclophane **3** in 66% yield as a single atropdiastereomer. The distinguishing feature of the cyclic structure is the upfield shift of proton Ha from $\delta = 7.3$ ppm in **23** to $\delta = 5.7$ ppm in **3**, presumably due to the anisotropic effect of indole ring. The axial chirality of **3** was determined to be *R* by the observation of the characteristic NOE correlations as shown in Scheme 3. The chemical shift of the proton Hb ($\delta = 4.10$ ppm) is also in accord with Snapper and Hoveyda's assignment.[10]

It is interesting to note that cyclization of model tripeptide **24** lacking an OH group in the amino acid residue D gave

(19) Synthesized from known 3,4-dihydroxy-5-iodobenzaldehyde in two steps: (a) *i*-PrBr, K_2CO_3, DMF, 55°C, 91%; (b) Ph_3PCH_3Br, *n*-BuLi, THF, −20−0 °C, 84%.

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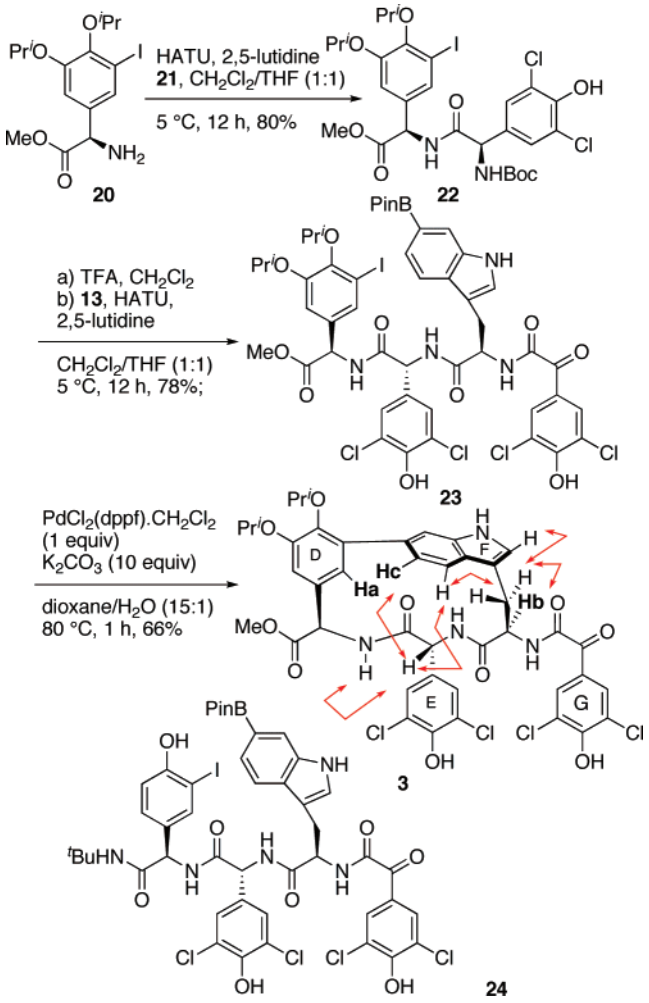
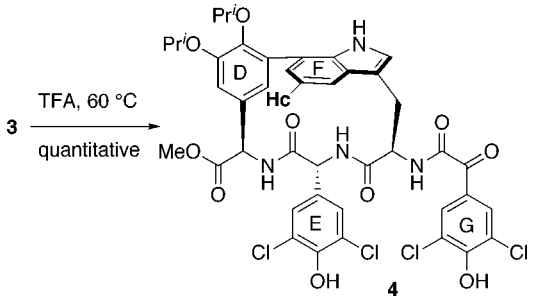
Scheme 3. Synthesis of Macrocycle **3**



the two atropstereoisomers in a one to one ratio under similar reaction conditions.[10] The atropstereoselectivity of this intramolecular Suzuki-Miyaura reaction is thus highly substrate-dependent.[24]

Stereospecific rearrangement of complestatin to chloropeptin I has been reported that involved the participation of free hydroxy group.[7] We found that upon heating a TFA solution of **3** to 60 °C for 30 min, a smooth isomerization occurred to give the corresponding DEFG ring (**4**) of chloropeptin I. The proton Hc appeared as a doublet in **3** became a triplet (J = 8.0 Hz) in cyclophane **4** that is indicative of the ring connectivity. This experiment showed that the presence of a free hydroxy group is not a prerequisite to this type of rearrangement. However, it is reasonable to assume that the same mechanism might be operating in the isomerization of **3** to **4** (Scheme 4).

Scheme 4. Isomerization of **3** to **4**



In summary, we have developed an efficient synthesis of strained DEFG ring **3** of complestatin featuring a key atropdiastereoselective intramolecular Suzuki-Miyaura reaction. The palladium-catalyzed heteroannulation and the Sharpless asymmetric dihydroxylation have been used as key steps for the syntheses of non-proteinogenic amino acids **10** and **20**, respectively. We also documented that the presence of free phenol group is not compulsory for the stereospecific rearrangement of **3** to the corresponding chloropeptin I subunits **4**. We are exploiting these results for the atropstereoselective total syntheses of both complestatin and chloropeptin I.

Acknowledgment. The financial supports from CNRS and the Institut de Chimie des Substances Naturelles are gratefully acknowledged.

Supporting Information Available: Experimental details, physical data for compounds **5**−**10**, **12**−**19**, **22**, **23**, **3**, **4**, and copies of ^{1}H NMR specrtra. This material is available free of charge via the Internet at http://pubs.acs.org.

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