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Synthesis of C-C Biaryl Segment of Complestatin and Chloropeptin: Approach to the Right Hand CEF-ring System of Complestatin

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Abstract: Studies toward C-C biaryl linkages between F-6 and E-3 of complestatin and F-7 and E-3 of chloropeptin involving Suzuki cross coupling reaction have been presented.
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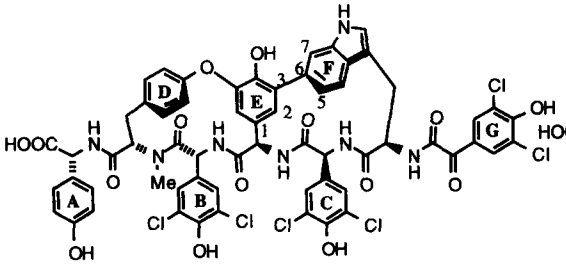
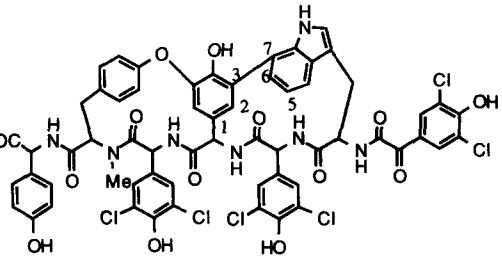
Complestatin (**1**) and chloropeptin (**2**) are unique glycopeptide antibiotics involved in modulation of cell-cell and cell-virion interactions. The inhibitory activity against GP-120 CD4-binding of **1** and **2** offered yet another category of new compounds with potential utility in AIDS-treatment. Complestatin **1** is a potent inhibitor with anticomplement activity such as flufenamic acid, leupeptin and K-76[1]. Compounds **1** and **2** are structurally related to glycopeptide antibiotics such as vancomycin. Although many structural differences exist between **1/2** and vancomycin[2], the dominant variations are (i) the presence of tryptophan residue instead of tyrosine in the E-ring and (ii) the existence of a unique aryl-ether-aryl-aryl (D-O-E-F) linkage instead of usual biaryl ether (C-O-D-O-E) linkages for vancomycin and other related glycopeptides. We envisaged that the C-C biaryl amino acid EF-ring segment is by far the most challenging endeavour of complestatin and chloropeptin synthesis. To our knowledge no synthetic study has yet been made on **1** and **2**. This communication examines for the first time : a) a general synthetic protocol for constructing C-C linkages between F-6 and E-3 of **1** and F-7 and E-3 of **2** by involving Suzuki cross coupling reaction[3], and b) an approach to the right hand CEF-ring system of complestatin (**1**).



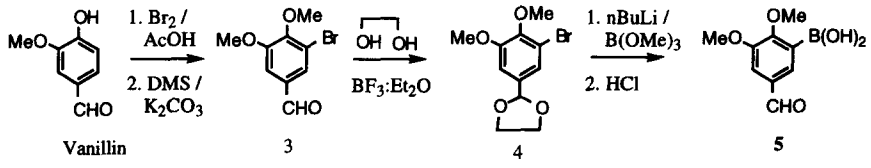
Complestatin (1)
(F-6, E-3 linkage)



Chloropeptin (2)
(F-7, E-3 linkage)

The route employed for the preparation of the boronic acid derivative (**5**) starting from vanillin is deleneated in scheme 1. Vanillin was successively brominated with Br_2-AcOH and methylated to afford **3** (80%). Subsequent protection of aldehyde group with $HOCH_2CH_2OH$-BF_3:OEt_2 (cat) gave **4** which on treatment with $B(OMe)_3$ in the presence of n-BuLi followed by acid work-up gave **5** (60%).

Scheme 1

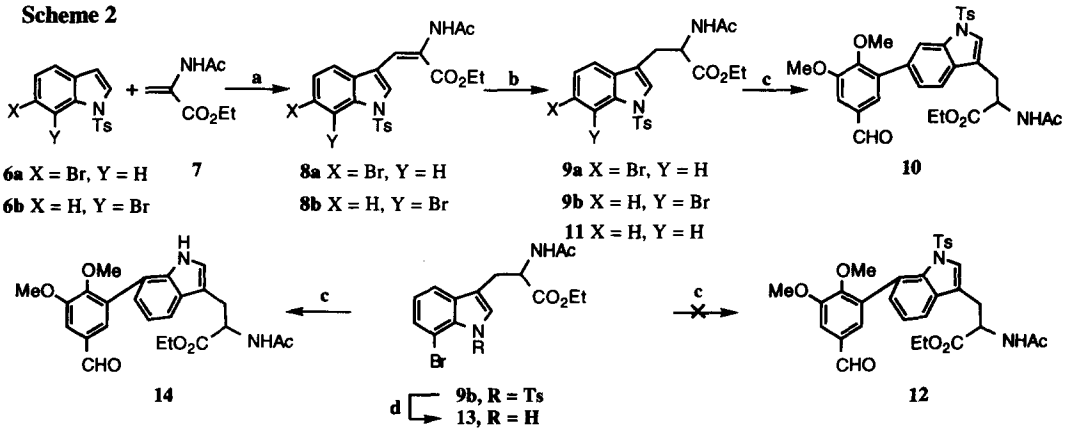


Vanillin 3 4 5

The requisite 6-bromo-tryptophan derivative (**9a**) was obtained by a modified procedure (Scheme 2). For example, 6-bromo-N-tosyl-indole[4] (**6a**) was coupled with the dehydroserine derivative (**7**) in the presence of $PdCl_2$-NaOAc in refluxing acetic acid to afford **8a** (50% yield). Subsequent reduction of C=C of **8a** at the expense of the bromo group was successfully achieved in the presence of Wilkinson catalyst at 60 psi in CH_2Cl_2:MeOH to afford **9a** (100% yield). The structure of **9a** was substantiated by the ^1H NMR and mass spectral data.

The next critical step of the sequence involved the Suzuki cross coupling reaction. After attempting many variations in Suzuki reaction to optimize the yields, we concluded that the coupling reaction could be conveniently carried out in the presence of $(PPh_3)_4Pd$ (0.03 eq.) and aqueous Na_2CO_3 (2 eq.) in DME-EtOH under reflux for 6 h which led to the formation of C-C biaryl derivative (**10**) in 67% yield. The ^1H NMR spectrum of **10** was amenable to first order analysis in which characteristic signals due to both the coupling partners were distinctly visible.

Scheme 2



6a X = Br, Y = H
6b X = H, Y = Br
7
8a X = Br, Y = H
8b X = H, Y = Br
9a X = Br, Y = H
9b X = H, Y = Br
11 X = H, Y = H
10
14
12

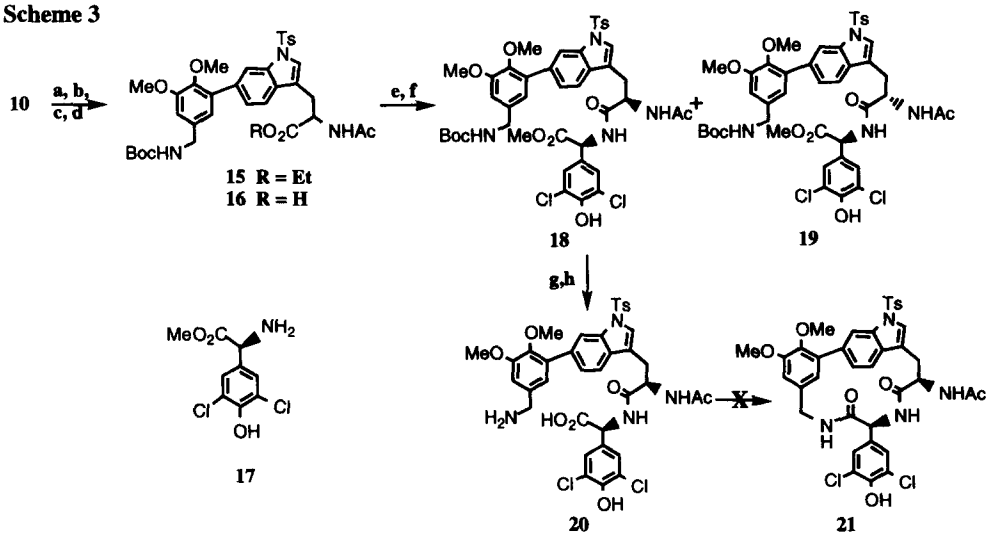
(a) $PdCl_2$, NaOAc, AcOH, reflux, 6 h, (b) $Rh(PPh_3)_3Cl$, CH_2Cl_2-MeOH, 60 psi, 18 h, (c) 5, $(PPh_3)_4Pd$, Na_2CO_3, DME-EtOH, reflux, 6 h, (d) Na, Naphthalene, DME, -78°C, 5 min.

Having developed a successful strategy to F-6 and E-3 linked biaryl compounds, we diverted our attention towards F-7 and E-3 linkage present in chloropeptin (**2**). The synthesis of 7-bromotryptophan derivative (**9b**) was accomplished from 7-bromoindole (**6b**)[5] via **8b** by the same strategy as reported for **9a**. However the Suzuki coupling reaction between **9b** and **5** under conditions described earlier was not successful. The reduced tryptophan derivative (**11**) was isolated. With considerable variations in conditions, still the formation of biaryl product (**12**) was preluded.

We compared structural parameters of 6-bromo-(**9a**) and 7-bromo-(**9b**) tryptophan derivatives and observed considerable steric hindrance existed in **9b** due to the presence of N-tosyl group. We felt that in the absence of the N-tosyl group, the new entity **13** may possibly undergo Suzuki reaction. With this contention, **9b** was detosylated[6] in the presence of Na-naphthalene in DME to give **13**, which on treatment with the boronic acid (**5**) in the presence of $(PPh_3)_4Pd$ and Na_2CO_3 afforded the biaryl derivative (**14**), albiet in 30% yield. The structure of **14** was confirmed by ^1H NMR and mass spectral analysis.

Having resolved the first part of our studies, we contemplated our investigations toward constructing the right hand CEF-ring system of complestatin (**1**). Conversion of **10** into the N-BOC derivative (**15**) was first accomplished and then the ester was saponified with LiOH in THF-MeOH-H_2O to afford the acid **16**. The intermolecular peptide bond formation between **16** and (S)-3,5-dichloro-4-hydroxy-phenylglycine methyl ester[7] (**17**) was promoted by DCC-HOBT in CH_2Cl_2-CH_3CN to give rise to a chromatographically separable diastereomeric mixture of **18** and **19** in good yield[8]. The methyl ester **18** was hydrolysed[9] under mild condition using LiOH in THF-MeOH-H_2O followed by deprotection of N-BOC with TFA-CH_2Cl_2. The resulting amino acid (**20**) was not purified but subjected to macrolactamisation in the presence of DCC-HOBT in CH_3CN, however no cyclisation was observed. Attempts to cyclise (**20**) with DPPA with Et_3N or iPr_2NEt was also met with failure[2,10].

Scheme 3



(a) $NaBH_4$, MeOH, RT, 30 min., (b) MsCl, CH_2Cl_2, Et_3N, RT, 6 h, (c) LiN_3, DMF, RT, 12 h, (d)(i) $SnCl_2$, Dioxane-H_2O, RT, 10 h, (ii) $NaHCO_3$, BOC_2O, RT, 3 h, (e) LiOH, THF-MeOH-H_2O, RT, 4 h, (f) 17, DCC, HOBt, CH_2Cl_2-CH_3CN, RT, 8 h, (g) LiOH, THF-MeOH-H_2O, RT, 2 h, (h) CH_2Cl_2, TFA, RT, 3 h.

Whether to attribute the above failure to inherent structural feature of the macrocyclization intermediate which could not attain the conformation required for peptide bond formation or to the steric hindrance due to the functional groups present in **20**, were not fully understood. However, based on reported failures[2] to synthesise C-O-D or D-O-E and AB ring systems[11] of vancomycin by a similar route involving

macrolactamisation, it could be pertinent to say that for CEF-segment of complestatin, one should plan the biomimetic approach of initial formation of linear tripeptide intermediate and then proceed for the macrocyclization by C-C biaryl coupling reaction. This work is under progress.

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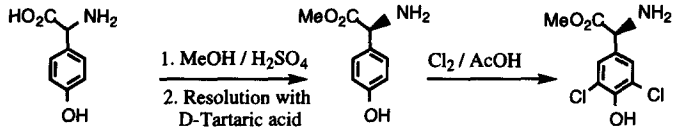
7. Compound **17** was prepared in an overall yield of 70% as follows:



17

8. All the new compounds were characterised by ^1H NMR, MS and HRMS analysis. The ^1H NMR (200 MHz, $CDCl_3$) spectral data of some selected compounds are described:
Compound **9a** : δ 1.15 (t, 3H, J = 8.0 Hz), 1.88 (s, 3H), 2.31 (s, 3H), 3.02 (dd, 1H, J = 5.0 Hz, 13.5 Hz), 3.2 (dd, 1H, J = 5.4 Hz, 13.5 Hz), 4.04 (m, 2H), 5.75 (dd, 1H), 6.0 (d, 1H, J = 7.1 Hz), 7.11 - 7.26 (m, 5H), 7.64 (d, 2H, J = 8.7 Hz), 8.02 (s, 1H). FABMS : 507 (M^++1).
Compound **10** : δ 1.21 (t, 3H, J = 8.0 Hz), 1.94 (s, 3H), 2.32 (s, 3H), 3.16 (dd, 1H, J = 5.0 Hz, 13.5 Hz), 3.27 (dd, 1H, J = 5.4 Hz, 13.5 Hz), 3.59 (s, 3H), 3.95 (s, 3H), 4.13 (m, 2H), 4.86 (dd, 1H), 6.05 (d, 1H, J = 6.7 Hz), 7.24 (d, 2H, J = 8.1 Hz), 7.3 - 7.6 (m, 5H), 7.72 (d, 2H, J = 8.1 Hz), 8.11 (s, 1H), 9.91 (s, 1H). FABMS : 593 (M^++1).
Compound **18** - $[\alpha]_D$ +26° (c 0.4, $CHCl_3$) : δ 1.43 (s, 9H), 1.92 (s, 3H), 2.25 (s, 3H), 3.06 (m, 2H), 3.44 (s, 3H), 3.65 (s, 3H), 3.86 (s, 3H), 4.24 (ABq, 2H), 4.88 (m, 2H), 5.23 (d, 1H, J = 6.6 Hz), 6.3 (m, 1H), 6.76 (s, 1H), 6.78 (s, 1H), 7.0 - 7.4 (m, 7H), 7.66 (d, 2H, J = 8.6 Hz), 8.05 (s, 1H). FABMS : 897 (M^++1).
9. 7-10% racemisation was observed during this step.
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