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The First Synthesis of Simplified 16- and 17-Membered Ring Macropolypeptides Containing The Phenyl-indole System of Kistamycin and Chloropeptin I, II

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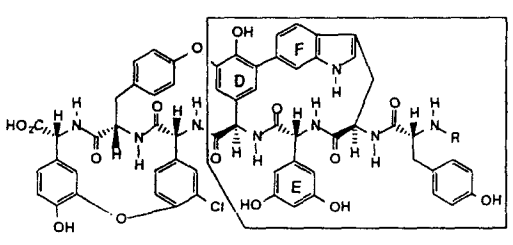
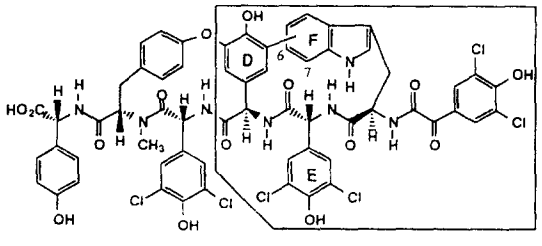
Abstract : The synthesis of simplified 16- and 17-membered ring macropolypeptides was achieved by Ni^{o} mediated carbon-carbon ring closure of properly substituted linear precursors.

Kistamycin[1] and Chloropeptin I, II[2] are polycyclic macropolypeptides whose eastern substructure bears close analogy. Indeed, they comprise a tryptophane **F** connected at C-6 or at C-7 to a central dihydroxyphenyl glycine **D** by an *endo* C-C bond and a variously substituted phenylglycine **E** forming a characteristic 16-or 17-membered ring macrocycle. The recently reported unsuccessful macrolactamisation approach[3] prompts us to publish the results of our own investigations which led to the first synthesis of simplified 16- and 17-membered ring macrocycles *via* C-C ring closure as models of the eastern part of the title compounds.



Kistamycin



Chloropeptin I (C-7)
Chloropeptin II (C-6)

To perform the key C-C ring closure step, we devised an approach based on the intramolecular version of the Suzuki-Pd mediated arylation of indole at C-6 and C-7 which in preliminary work had been shown to give moderate, but useful yields of cross coupled products[4]. Intramolecular reactions mediated by low order cuprates[5] and Ni^{o}[6] were also considered.[7]

Starting from 6- or 7-bromo indole, standard methods[8,9] gave the key components **5** and **6** from which the four precursors bearing appropriate function on the terminal rings were prepared. Coupling of **5** or **6** with 3-benzylamine boronic acid gave **7** and **10** ready for intramolecular Suzuki Pd-catalyzed reactions while coupling with 3-bromo benzylamine gave **8** and **11**, ready for testing low order cuprate and Ni^{o} mediated intramolecular reactions.

The approach based on intramolecular Suzuki Pd-catalyzed reactions was performed on **7** and **10** and failed to give the target compounds **12** and **13**. Only the reduction compound **9** was isolated and identified from these reactions. The cuprate mediated cyclisation attempted on **8** and **11** led to **9** as the major product along with several unidentified compounds. In contrast, the intramolecular version of the Ni^{o} based coupling reaction led to a mixture from which was isolated and characterized, besides the

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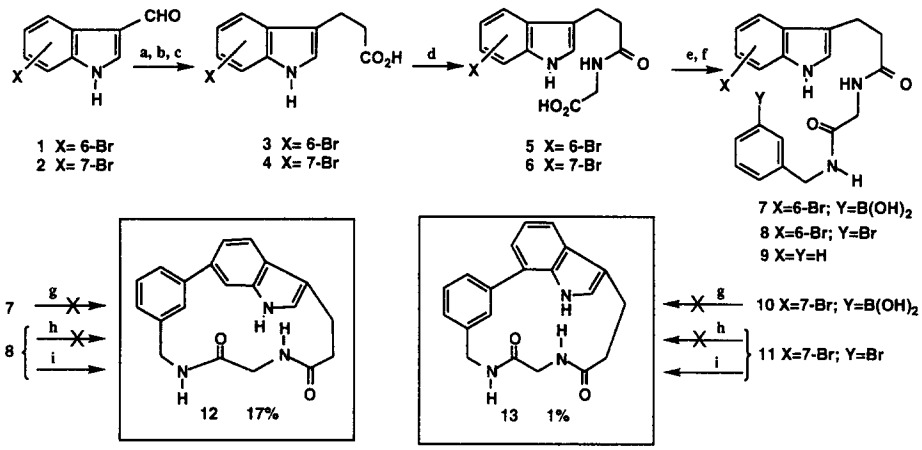
reduction product **9**, the 17-membered ring macrocycle **12**[10] resulting from C-C bond formation at C-6. The yield was moderate but reproducible. The 16-membered ring compound **13**[10] was similarly obtained from **11** by coupling at C-7. It is likely that steric hindrance at this position and additional factors pertaining to the intramolecular Ni° mediated reaction (which remains to investigate further) rendered this cyclisation less efficient than that which had led to **12**.



Reagents and conditions. a: $CO_2HCH_2CO_2Et$/pyridine, piperidine 50°C, (Ref. 8); b: $NaBH_4$, $BiCl_3$/ETOH 0°C, (Ref. 9); c: NaOH/MeOH/H_2O; d: glycine methyl ester hydrochloride, NEt_3, HOBt, EDC/DMF; e: 3-Boronic benzylamine acid/ CH_2Cl_2; f: 3-Bromobenzylamine hydrochloride, NEt_3, HOBt, EDC/DMF g: **7**, **10** 0.01M, $(AcO)_2Pd$, $Ba(OH)_2$/EtOH/DME, (Ref. 4); h: **8**, **11** 0.01M, KH, t-BuLi/THF - 78 °C, CuCN, 0.01M in THF -78°C, O_2 - 40°C, (Ref. 5); i: **8**, **11** 0.01M, $Ni(Ph_3P)_2Cl_2$, Zn, Ph_3P, DMF, (Ref. 6).

The simplified 17-membered ring macrocycle **12** is the model compound of the eastern substructure of Kistamycin and Chloropeptin II while the 16-membered ring macrocycle **13** is the corresponding model of Chloropeptin I. Further work is in progress.

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10. Compound **12** was fully characterised by ^1H NMR, ^{13}C NMR, NOESY, MS and HRMS while compound **13** was characterised by ^1H NMR and HRMS.