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Indole Arylation Studies Directed Towards the Synthesis of Simplified Eastern Subunits of Chloropeptin and Kistamycin

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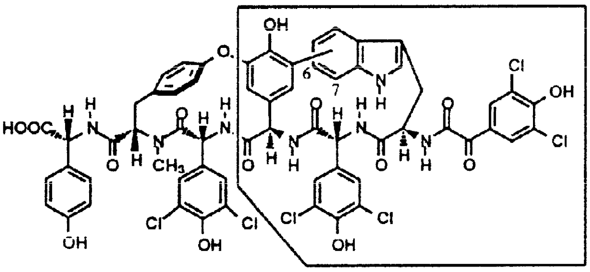
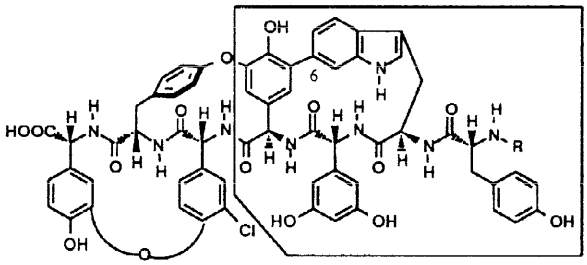
Abstract : Aryl indoles which are building blocks for the synthesis of simplified analogues of macropolypeptides containing an endo carbon-carbon bond are obtained by Suzuki Pd-catalyzed cross coupling reactions involving either haloindoles or indole boronic acids and properly meta *substituted phenyl components.* © 1998 Published by Elsevier Science Ltd. All rights reserved.

Chloropeptin I, II and Kistamycins are structurally complex natural macropolypeptides[1,2] made of two subunits. Models of the western part of both have been synthesized[3,4,5]. As far as the eastern part, characterized in both compounds by a carbon-carbon bond between position 6- or 7- of tryptophane and a central dihydroxyphenylglycine is concerned, attempts involving fully protected tryptophane were reported to be unsuccesful *via* macrolactamization[6]. Our own project in this field was aimed firstly at the synthesis of simplified subunits.

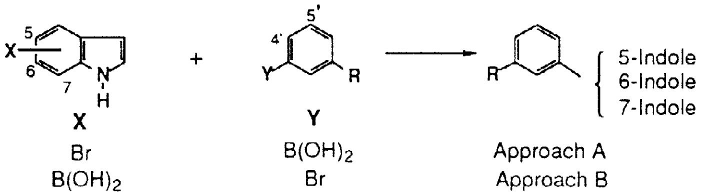


Chloropeptins I, II



Kistamicine

The access to functionalized aryl indole derivatives was central to our approach. A convenient method to obtain those compounds is the Suzuki Pd-mediated cross coupling reaction which for our present purpose could be performed with either haloindoles as electrophilic components (approach A) or indole boronic acids as nucleophiles (approach B), opposed to appropriately substituted phenyl components (Scheme 1). Few reactions of that type were reported in the literature[7a-f] and all but one[7a] proceeded *via* (A). Moreover, phenyl boronic acids employed as nucleophiles were often naked, or substituted (Me, OMe, F) at *para*, seldom at *ortho* and never, to the best of our knowledge at *meta* position.



Scheme 1

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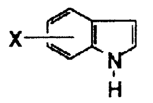
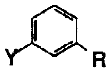
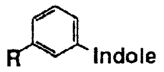
We were thus led to study both approaches for assessing the best one in terms of yield and feasibility, considering also that either should be compatible with the use of i) N-1 unprotected indoles, in order to avoid deprotection step at a later stage, ii) phenyl components carrying a *meta* substituent R stable under cross coupling reaction conditions, and thereafter efficiently converted to the CH_2NH_2 handle necessary for peptide coupling with aminoacid.

As a preliminary work[8] taking these prerequisites into account, we carried out cross-coupling reactions (A) between the commercially available 5-bromo indole **1a** and a large series of *meta* substituted phenyl boronic acids. The reactions between **1a** and **2a** or **2b** (entries 1, 2) gave 5-aryl indoles **3a** or **3b** in acceptable yields. The deactivated nucleophile **2c** was found not to react (entry 3) while **2d** which is less electron deficient than **2c** due to the two OMe groups, gave a very low yield of **3d** (entry 4). We then thought to use the 3-boronic acid benzylamine NHBoc **2e**, hitherto unknown as nucleophilic component in Suzuki reaction which reacted with **1a** (entry 5) to give a low yield of aryl indole **4**.

To perform Suzuki reaction *via* (B), 5-indole boronic acid **1b**[9] was reacted with the electrophiles **2f-j**. Thus, 5-aryl indoles **3a-e** were obtained from all reactions (entries 6-10) in yields significantly higher than those of the corresponding reactions *via* (A). Arylation of 5-indole boronic acid with **2j** to give **4** (entry 10) was encouraging in the context of the ensuing experiments.

With the results of this comparative study in hand, we turned to Suzuki cross-coupling reactions involving indole and aryl components selected for their interest regarding the synthesis of simplified analogues of the title natural products. 6-Bromo indole **5a** reacted much better than **1a** with **2c** (entry 11) to give 6-aryl indole **6a**; the same observation was made for reaction with **2d** (entry 12) whose yield was ten times higher than that of the corresponding experiment *via* (A) (entry 4). The reaction of N-Boc protected 3-boronic benzylamine acid **2e** with **5a** (entry 13) gave directly the aryl indole **6c** carrying the CH_2NHBoc handle.

Table 1

								
	Entry		X		Y	R	**5-Aryl Indole**	
(A)	1	**1a**	5- Br	2a	B(OH)$_2$;	Me	**3a**	45%
	2			2b		OMe	**3b**	60%
	3			2c		CHO	**3c**	0%
	4			2d		CHO; 4',5'-(OMe)$_2$	**3d**	4%
	5			2e		CH_2NHBoc	**4**	10%
(B)	6	**1b**	5- B(OH)2	2f	Br	Me	**3a**	51%
	7			2g		OMe	**3b**	35%
	8			2h		CHO	**3c**	34%
	9			2i		CHO;4,5-(OMe)$_2$	**3d**	45%
	10			2j		CH_2NHBoc	**4**	36%
							6-Aryl Indole	
(A)	11	**5a**	6- Br	2c	B(OH)$_2$;	CHO	**6a**	18%
	12			2d		CHO;4',5'-(OMe)$_2$	**6b**	40%
	13			2e		CH_2NHBoc	**6c**	18%
(B)	14	**5b**	6-B(OH)2	2h	Br	CHO	**6a**	49%
	15			2i		CHO;4',5'-(OMe)$_2$	**6b**	31%
	16			2j		CH_2NHBoc	**6c**	33%
							7-Aryl Indole	
(B)	17	**7a**	7-B(OH)2	2j	Br	CH_2NHBoc	**8**	41%

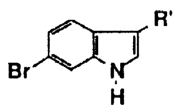
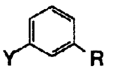
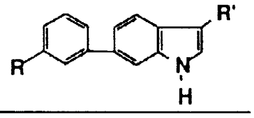
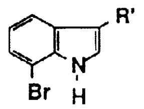
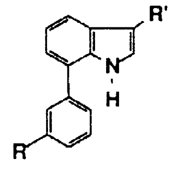
To obtain these same 6-aryl indole derivatives **6a-c** by Suzuki cross-coupling reaction *via* (B), the electrophilic phenyl components **2h-j** were treated with 6-boronic acid indole **5b**. As observed in the 5-aryl indole series, the yields of compounds **6a** (entry 14) and **6c** were higher than those provided by approach (A). Very interestingly the 6-aryl indole derivative **6c** was now obtained in useful yield for further steps towards the synthesis of analogues of Chloropeptin II and Kistamycin.

From all the above results, it became obvious that Suzuki reaction *via* (B) might provide a promising access also to the 7-aryl indole series and hence to analogues of Chloropeptin I. The cross-coupling reaction carried out between 7-boronic indole acid **7a**[9] and the properly functionalized N-Boc protected 3-boronic benzylamine acid **2j** gave indeed the product **8** (entry 17) in quite satisfactory yield.

In order to elaborate a convergent synthesis it was felt necessary to perform cross coupling reactions between 3-indole propionic derivatives and appropriately functionalized aromatic components. First, the 6-bromo-3-indole propionic acid glycine peptide **5c** was reacted with **2c** *via* (A) (entry 18) to give **6g** possessing the carbon skeleton of the analogue of Chloropeptin II or Kistamycin eastern subunit. The electrophile **5d** was found to react quite well with the nucleophile **2d** to give **6h** (entry 19) in 71 % optimized yield, providing thus a promising linear route to the target compounds, but more interestingly it reacted with **2e** (entry 20) in synthetically useful yield to give **6i** on which the missing amino acid could be introduced by standard procedure at either terminus.

The nucleophilic phenyl components **2d**, **2e** reacted also with the 7-bromoindole-3-propionic acid ethyl ester **7a**. Only trace amounts of **9a** (entry 21) and a low yield of **9b** (entry 22) were obtained. Since **2d**, **2e** reacted quite well with the isomeric 6-bromo compound **5d**, steric hindrance at C-7 was presumed to be partly at the origin of very poor yields, but the absence of hindrance at N-1 has most probably allowed this disappointing in terms of yield arylation to take place.

Table 2

								
	Entry		R'		Y	R		
(A)	18	5c	$(CH_2)_2CONHCH_2CO_2Et$	2c	$B(OH)_2$	CHO	6g	17%
	19	5d	$(CH_2)_2CO_2Et$	2d		CHO; 4,5-$(OMe)_2$	6h	42% (71%)
	20	5d		2e		CH_2NHBoc	6i	30%
								
			R'					
	21	7a	$(CH_2)_2CO_2Et$	2d	$B(OH)_2$	CHO; 4,5-$(OMe)_2$	9a	traces
	22	7a		2e		CH_2NHBoc	9b	8%

Conclusion

Thus, the Suzuki Pd-catalyzed indole arylation using the indole either as electrophile (approach A) or better, as nucleophile (approach B) gave 5-, 6-, or 7-aryl indole derivatives. Structurally more complexe derivatives belonging to the 3-indole propionic acid series were obtained only *via* (A).[10,11] This preliminary study provided experimental support to an access towards analogues of the eastern subunits of Chloropeptin I, II and Kistamycin based upon cyclisation *via* carbon-carbon bond formation of precursors bilt from **6c** or **8a** in addition to the more classical macrolactamization approach starting from derivatives of **6h** or **6i.**

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8. All reactions were carried out according to a procedure reported by Campi, E.M.; Jackson, W.R.; Marcuccio, S.M.; Naeslund, C.G.M. *J. Chem. Soc., Chem. Com.* **1994**, 2395. Typical conditions were as follows : A solution of bromo compound (1 mmol), boronic acid component (1.2 mmol) in degassed 95% aqueous ethanol (10 ml) is stirred under argon atmosphere in the presence of $Ba(OH)_2$ (3 mmol) and a catalytic amount of $Pd(OAc)_2$ (~ 0.02 mml) for 24 hours at room temperature. Filtration on a celite column and vacuum evaporation gave the crude product. It was observed (entry 19) that the yield can be increased by stepwise addition of an excess of boronic acid component (1 mmol) in the course of the reaction.
9. Indole boronic acids **1b**, **5b**, **7a** were prepared for the corresponding 5-bromo, 6-bromo, 7-bromo indoles treated with fresh t-butyllithium and $B(OH)_3$ *via* the N-1 potassio salt according to the method described by Moyer, P.; Shiurba, J.F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106-5110.
10. Our efforts to prepare the boronic acids from the corresponding 6- or 7-Br, 3-indole propionic acid derivatives have failed to give the needed compounds because of the sensitivity of the chain under the basic conditions so that, up to now, cross coupling reactions *via* B could not be explored.
11. Spectroscopic data (M.S.; ^{1}H NMR; ^{13}C NMR) of all new compounds are in accord with the structures.