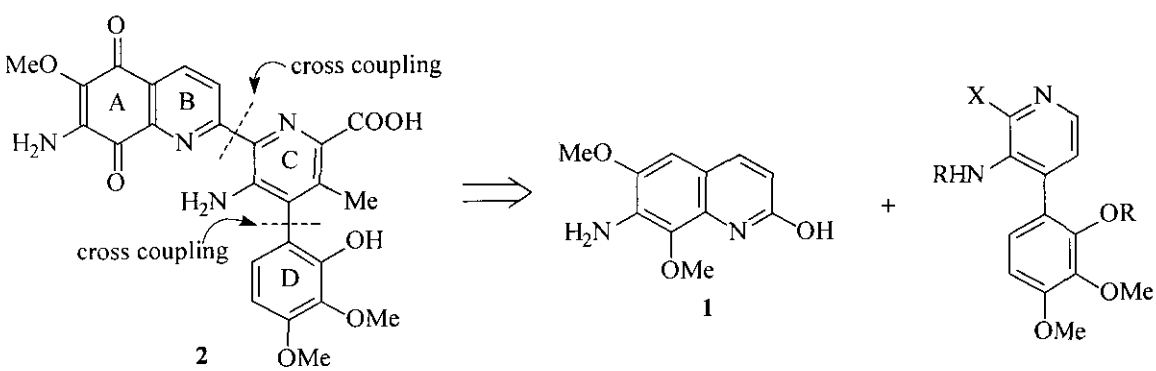
CROSS COUPLING STRATEGIES TOWARDS THE SYNTHESIS OF THE STREPTONIGRIN CD MOIETY

Renier Crous, Catherine Dwyer, and Cedric W. Holzapfel*

Department of Chemistry and Biochemistry, Rand Afrikaans University, P.O. Box 524, Auckland Park, 2006, South Africa

Abstract- An efficient route to an appropriate model of the streptonigrin 4-phenylpyridine CD moiety is reported. 4-Chloro-3-nitropyridine was found to be the key precursor and its reactivity in cross coupling reactions was further investigated.

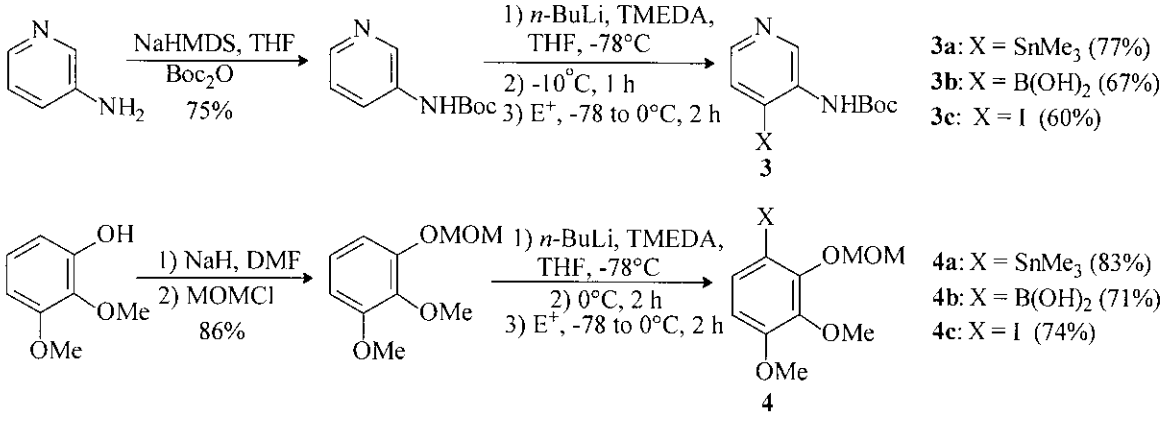
We recently reported a facile route to an AB ring equivalent (**1**) of streptonigrin (**2**), a potent anticancer compound.[1] Our overall strategy towards the total synthesis of streptonigrin involves the use of preformed and largely prefunctionalised rings, which are linked by palladium catalysed cross coupling reactions at the points indicated in the retrosynthesis (Scheme 1). We now wish to report the synthesis of a suitably functionalised model for the CD moiety from readily available substrates *via* both Stille and Suzuki cross coupling methodologies.



Scheme 1

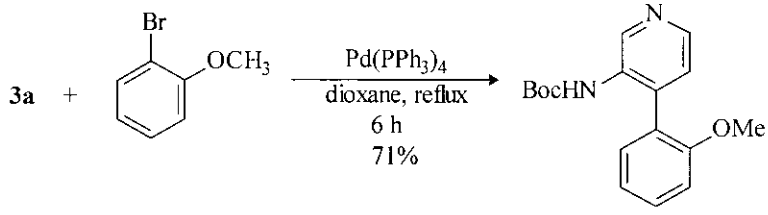
Starting from commercially available 3-aminopyridine and 2,3-dimethoxyphenol, the amino and hydroxy groups were converted to suitable directing metalation groups *via* standard methodology.[2] Metallation

with *n*-BuLi followed by quenching with Me_3SnCl, $B(OMe)_3$ or I_2 afforded substrates (**3a-c**) and (**4a-c**) in generally good yields (Scheme 2).[3]



Scheme 2

Initial cross coupling reactions of **3a** and **3b** with simple substrates indicated that the particularly stable pyridylstannane (**3a**)[4] afforded better yields than the corresponding boronic acid (**3b**) due to competetive hydrolytic deboronation in the case of the latter. As a result, the use of boronic acids was initially excluded in further work. The success of sterically demanding cross couplings of pyridylstannane (**3a**), such as that shown in Scheme 3, gave us great hope for success.



Scheme 3

However, the Stille coupling between substrates (**3a**) and (**4c**) proceeded poorly under a variety of conditions. Optimum yields of cross coupled product (**5**)[5] were only 20-30% using a $Pd_2dba_3/AsPh_3$ catalyst system in dioxane (Table 1). Changing of the catalyst [$Pd(PPh_3)_4$, $Pd_2dba_3/P(o\text{-tol})_3$, or 'ligandless' Pd_2dba_3], the solvent (DMF, NMP) or the temperature, as well as the use of copper additives, afforded no improvement. It was reasoned that placing the weakly nucleophilic trimethyltin group on the electron rich ring (**4a**) and the halogen on the electron deficient ring (**3c**) would provide optimum electronic assistance to the reaction. However, this also afforded only slightly improved yields of **5** despite similar attempts at optimisation (Table 1).

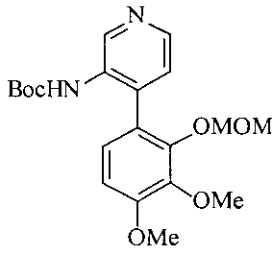
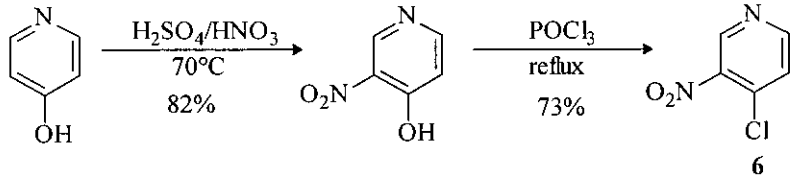
	Optimum conditions	Yield	Product
3a + 4c	$Pd_2dba_3.CHCl_3$ / $AsPh_3$, dioxane, reflux, 12 h	20%	 **5**
4a + 3c	$Pd_2dba_3.CHCl_3$ / $AsPh_3$, dioxane, reflux, 12 h	26%	

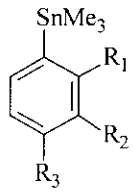
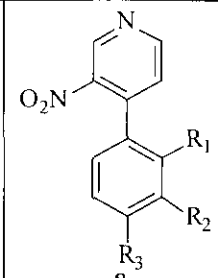
Table 1: Model C-D ring cross couplings

A change in strategy was required. We decided to continue with **4a** as our D-ring precursor due to electronic considerations and its ready preparation from 2,3-dimethoxyphenol, but to look for an alternative C-ring equivalent. The requirement was a pyridine ring substituted with an appropriate halogen in position 4, as well as an amine equivalent at position 3, which could be converted to a directing metalation group at a later stage. Nitration of commercially available 4-hydroxypyridine[6] followed by conversion to the chloride using $POCl_3$ provided access to 4-chloro-3-nitropyridine (**6**)[7] in good overall yield (Scheme 4). For most cross couplings, chloride is an unsatisfactory leaving group as the rate of palladium insertion is too slow. However, good results have been obtained using chlorides activated by very electron deficient systems, particularly pyridines.[8] In addition, our experience with cross couplings of *o*-nitrophenyltriflates[9] has confirmed the activating effect of an *ortho*-nitro substituent, so we were reasonably confident in our choice.



Scheme 4

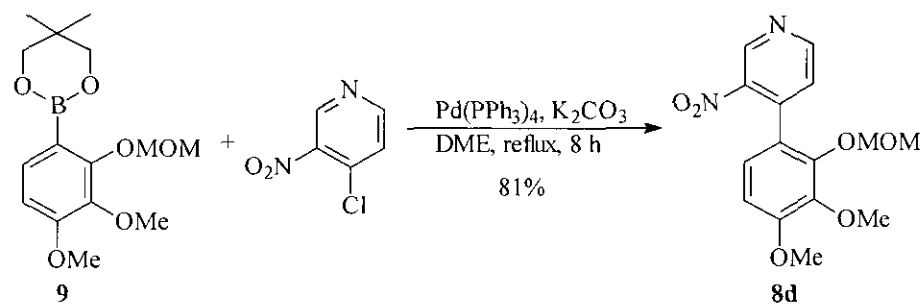
Some initial model cross coupling reactions were undertaken on simple substrates (**7a-c**) to gauge the potential of **6** as a viable substrate. As can be seen in Table 2, the cross couplings of **6** with a selection of simple arylstannanes proceeded very well using $Pd_2dba_3/P(o\text{-tol})_3$ as the catalyst. Under the same conditions, compound (**8d**) was prepared in a yield of 45%.[10] Comparable results were obtained when using $Pd_2dba_3/AsPh_3$. However, the addition of a catalytic amount of CuBr to the reaction mixture resulted in a dramatic improvement in yield to 83%. This co-catalytic effect of copper salts in Stille couplings has been extensively reported.[11]

Arylstannane	Yield (%)	Product
 **7a**: $R_1 = R_2 = R_3 = H$	79 [a]	
7b: $R_1 = R_2 = H$, $R_3 = OMe$	84 [a]	
7c: $R_1 = OMe$, $R_2 = R_3 = H$	80 [a]	
7d: $R_1 = OMOM$, $R_2 = R_3 = OMe$	45 [a] 83 [b]	
7		**8**

Conditions:
a) $Pd_2dba_3.CHCl_3$, P(*o*-tol)$_3$, dioxane, 90°C
b) $Pd_2dba_3.CHCl_3$, $AsPh_3$, CuBr, dioxane, 90°C

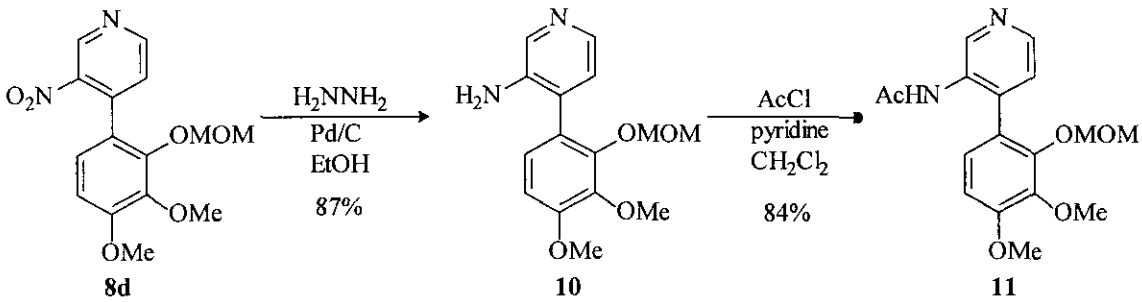
Table 2: Coupling reactions of 4-chloro-3-nitropyridine

The success of the 4-chloro-3-nitropyridine couplings led us to reinvestigate the use of boronic acids. Simple coupling of **6** with phenylboronic acid afforded the cross coupled product (**8a**) in a yield of 95% using $Pd(PPh_3)_4/K_2CO_3$/DME. The same coupling using KO^{t}Bu as the base did not afford any of the desired product, but gave side products.[12] Thus it appears that the correct choice of reaction conditions is crucial. The coupling of crude boronic acid (**4b**) with **6** to afford product (**8d**) proceeded well using the $Pd(PPh_3)_4/K_2CO_3$/DME system. However, due to incomplete metallation, some unreacted 2,3-dimethoxyphenol was carried through the coupling reaction, complicating isolation of the product. Conversion of the boronic acid to the 2,2-dimethylpropyl ester derivative (**9**)[13] appeared quantitative on TLC, and the compound was isolated in an overall yield of 71% over two steps (metalation and derivatisation). The ester was then subjected to the same cross coupling conditions and afforded the cross coupled product (**8d**) in a yield of 81% (Scheme 5). While the yields of this Suzuki coupling are comparable to those of the corresponding Stille reaction, the boronic acid route is obviously preferred due to the toxicity of organotin compounds and the added expense of copper salt additives.



Scheme 5

While initial attempts to reduce the nitro group of **8d** led to reduction of the pyridine ring, selective reduction to the amine was achieved in good yield when employing hydrazine and 10% Pd/C (Scheme 6). The reduced product (**10**) was characterised as its acetyl derivative (**11**).[14]



Scheme 6

Starting from simple precursors, the preparation of a suitable streptonigrin CD ring model has been successfully achieved using both Stille and Suzuki cross coupling methodologies. In addition, the use of catalytic quantities of copper(I) bromide was shown to greatly improve the Stille coupling. This route compares very favorably with those reported by Quéguiner and co-workers,[15] as all steps (including the sterically demanding cross coupling) are high yielding and involve simple and generally inexpensive starting materials and reagents. The introduction of the 4-chloro-3-nitropyridine to the cross coupling tactic clearly affords an easy entry into the streptonigrin CD ring structure.

ACKNOWLEDGEMENTS

We thank the FRD (South Africa), AECI and SASOL for funding.

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3. Representative physical data: **4a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.01 (1H, d, *J*=7.9 Hz), 6.69 (1H, d, *J*=7.9 Hz), 5.14 (2H, s), 3.84 (3H, s), 3.81 (3H, s), 3.52 (3H, s), 0.28 (9H, s); ^{13}C NMR (300 MHz, $CDCl_3$): δ 154.87, 154.74, 140.80, 130.82, 126.57, 108.20, 98.92, 60.59, 57.52, 56.00, -8.62); MS: *m/z* 362 [M^+ (Sn^{120}), 5%], 347 [M^+ (Sn^{120})-15, 100%].
4. R. Crous, C.W. Holzapfel, and G.J. Kruger, *Acta Cryst.*, 1998, **C54**, 760.

5. **5**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.02 (1H, s), 8.34 (1H, d, *J*=4.8 Hz), 7.15 (1H, d, *J*=4.8 Hz), 6.90 (1H, d, *J*=8.4 Hz), 6.79 (1H, d, *J*=8.4 Hz), 6.67 (1H, br s), 4.89 (2H, s), 3.88 (3H, s), 3.87 (3H, s), 2.89 (3H, s), 1.41 (9H, s); ^{13}C NMR (300 MHz, $CDCl_3$): δ 154.46, 153.11, 153.02, 147.80, 144.39, 143.97, 142.30, 138.09, 132.85, 125.14, 123.53, 108.71, 99.29, 80.63, 60.87, 56.68, 55.99, 28.08; MS: *m/z* 390 (M^+, 12%), 334 (M^+-56, 100%).
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9. C.W. Holzapfel and C.L. Dwyer, *Heterocycles*, 1998, **48**, 1513.
10. **8d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.13 (1H, s), 8.78 (1H, d, *J*=5.1 Hz), 7.40 (1H, d, *J*=5.1 Hz), 7.03 (1H, d, *J*=8.7 Hz), 6.81 (1H, d, *J*=8.7 Hz), 4.93 (2H, s), 3.91 (3H, s), 3.84 (3H, s), 2.93 (3H, s); ^{13}C NMR (300 MHz, $CDCl_3$): δ 155.41, 152.95, 148.27, 146.07, 145.20, 141.20, 132.21, 126.52, 123.63, 122.68, 108.28, 99.36, 61.03, 56.88, 56.07; MS: *m/z* 320 (M^+, 100%).
11. V. Farina, S. Kapadia, B. Krishnan, C. Wang, and L.S. Liebeskind, *J. Org. Chem.*, 1994, **59**, 5905.
12. Products obtained were 4-methoxy-3-nitropyridine (32%) and 3-nitro-4-phenoxypyridine (45%).
13. **9**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (1H, d, *J*=8.4 Hz), 6.65 (1H, d, *J*=8.4 Hz), 5.10 (2H, s), 3.83 (4H, s), 3.81 (3H, s), 3.73 (3H, s), 3.57 (3H, s), 0.99 (6H, s); ^{13}C NMR (300 MHz, $CDCl_3$): δ 155.63, 155.58, 141.77, 130.98, 107.39, 99.98, 72.29, 60.77, 57.15, 55.79, 31.67, 21.86; MS: *m/z* 294 (M^+, 32%).
14. **11**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.12 (1H, s), 8.40 (1H, d, *J*=5.1 Hz), 7.68 (1H, br s), 7.19 (1H, d, *J*=5.1 Hz), 6.92 (1H, d, *J*=8.4 Hz), 6.81 (1H, d, *J*=8.4 Hz), 4.95 (2H, s), 3.90 (3H, s), 3.89 (3H, s), 2.92 (3H, s), 2.03 (3H, s); ^{13}C NMR (300 MHz, $CDCl_3$): δ 168.58, 154.58, 147.52, 145.99, 145.78, 142.17, 138.85, 132.05, 125.40, 125.22, 123.58, 108.94, 99.66, 60.96, 56.92, 56.06, 24.06; MS: *m/z*: 332 (M^+, 100%).
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Received, 14th December, 1998