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Entry into the bi-aryl moiety of the TMC-95 proteasome inhibitors via the Stille protocol

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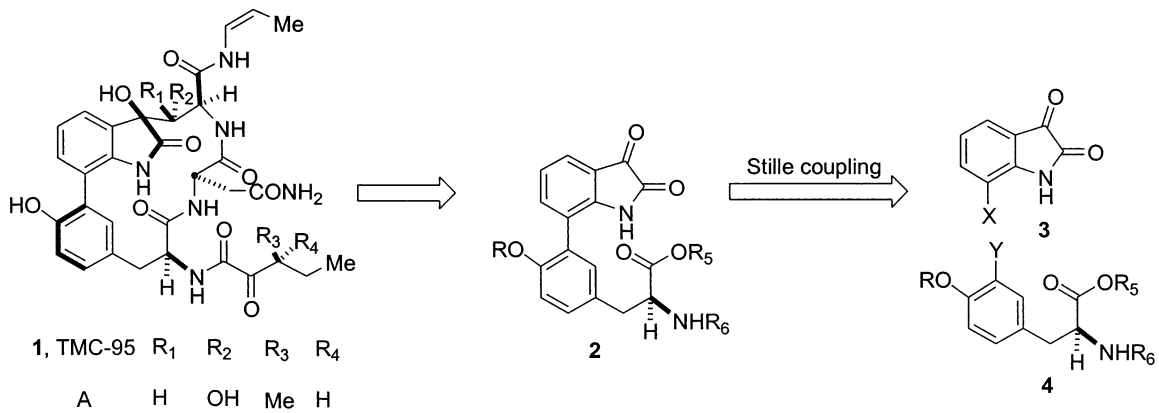
Abstract—The synthesis of the bi-aryl moiety of the TMC-95 natural products has been achieved via a palladium-catalyzed Stille cross-coupling reaction of an aryl stannane tyrosine derivative and 7-iodoisatin.

TMC-95 A–D are potent proteasome inhibitors isolated from the fermentation broth of *Apiosopora montagnei* Sacc. TC 1093 by Kohno and co-workers.[1] These natural products are unique cyclic peptides containing L-tyrosine, L-asparagine, a highly oxidized L-tryptophan-derived oxindole, (*Z*)-1-propenylamine, and 3-methyl-2-oxopentanoic acid units. It has been shown that these compounds are biologically active against chymotrypsin-like, trypsin-like, and peptidylglutamyl-peptide hydrolysing proteases.[1] Recently, proteasome inhibitors have received considerable attention due to the critical role they play in intracellular processes such as cell progression, antigen presentation, and cytokine-stimulated signal transduction.[2] The great interest emerging in the field of proteasome inhibition, the considerable biological activity, and the distinctive structures of the TMC-95s have provided motivation to contemplate a total synthesis of these compounds that would be readily adaptable to preparing analogs.

When contemplating the synthesis of the TMC-95s, it was envisioned that the biaryl moiety could best be constructed via a palladium-catalyzed cross-coupling reaction.[3] When considering coupling partners, we envi-



1, TMC-95	R_1	R_2	R_3	R_4
A	H	OH	Me	H
B	H	OH	H	Me
C	OH	H	Me	H
D	OH	H	H	Me

Figure 1.

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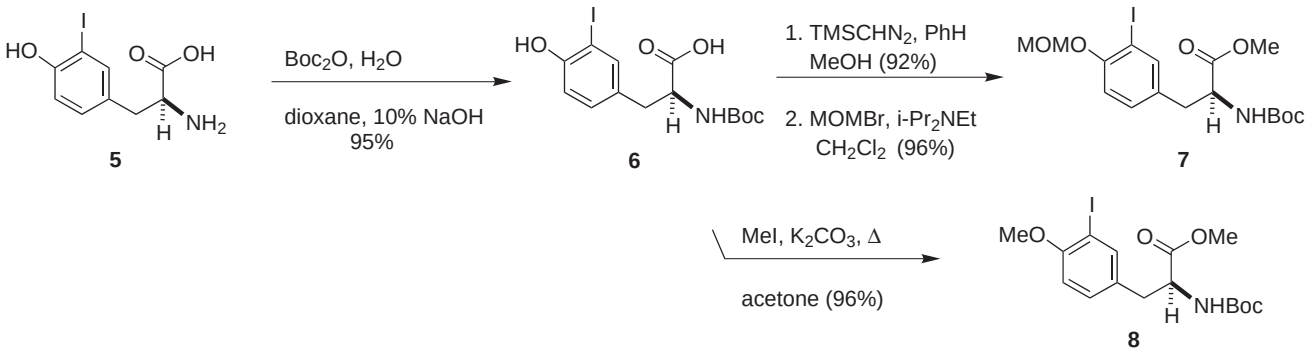
sioned coupling two readily available, chemically manipulative fragments such as 7-iodoisatin **3** (X = I) and a 3-stannyltyrosine derivative **4** (Y = SnR_3, Fig. 1). It is conceivable that any type of biaryl coupling[4] method could lead to the biaryl portion, but in our hands the Stille coupling protocol proved to be both compatible with other functionality and high yielding. Herein we report the entrance into the biaryl moiety of the TMC-95 natural products via a palladium-catalyzed Stille cross-coupling reaction.[5]

7-Iodoisatin was prepared from 2-iodoaniline via the Sandmeyer procedure.[6] In order to obtain the appropriate aryl stannane necessary for the Stille coupling, manipulations were made to commercially available 3-iodotyrosine **5**. The free amino acid was first protected to give the *N*-Boc amino acid **6**. Next, we decided to explore several protecting group alternatives to determine the effect of the blocking groups on the coupling yields. First, compound **6** was subjected to $TMSCHN_2$, followed by bromomethyl methyl ether and *i*-Pr_2NEt to furnish fully protected MOM-ether-3-iodotyrosine-O-Me ester **7**. Secondly, compound **6** was treated with 2.2 equiv. of MeI and 1.5 equiv. of K_2CO_3 in refluxing acetone to give the *O*-methyl ether of 3-iodotyrosine-O-Me ester **8** (Scheme 1).

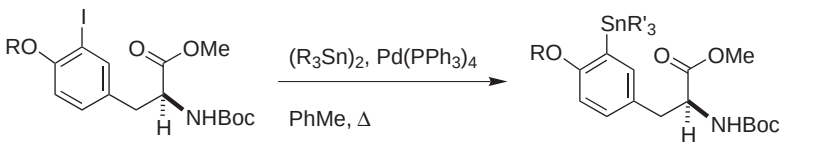
The aryl iodides were converted to the corresponding aryl stannane by treatment with either hexamethylditin or hexabutylditin and $Pd(PPh_3)_4$ in refluxing toluene (Scheme 2).[7]

With both coupling partners in hand, we focused our attention on optimising the Stille coupling conditions. Stille coupling of 7-iodoisatin and aryl stannane (Scheme 3) was attempted under several conditions, as summarized in Table 1.

We had initially envisioned using the aryl trimethylstannane derivatives due to the fact that access to these compounds was accompanied by very high yields. In the event, coupling experiments demonstrated that there was competitive methyl group transfer to 7-iodoisatin, especially in polar solvents such as DMF (Table 1, entries 1, 2, 5, and 6). It has been shown that aryl stannanes with *ortho*-substituents have significant



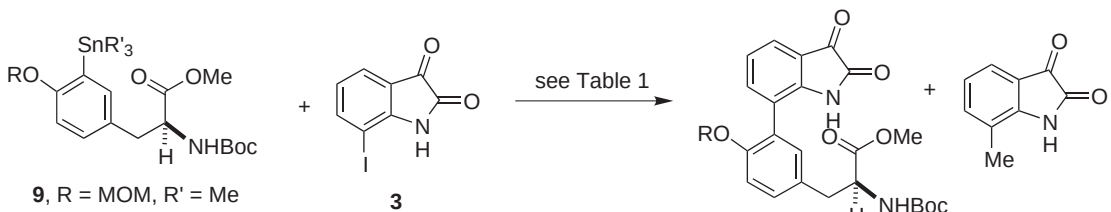
Scheme 1.



7, R = MOM
8, R = Me

9, R = MOM, R' = Me (92%)
10, R = MOM, R' = Bu (50%)
11, R = R' = Me (90%)
12, R = Me, R' = Bu (60%)

Scheme 2.



9, R = MOM, R' = Me
10, R = MOM, R' = Bu
11, R = R' = Me
12, R = Me, R' = Bu

3

13, R = MOM
14, R = Me

15

Scheme 3.

Table 1. Reaction conditions for the Stille coupling outlined in Scheme 3

Entry	R	R′	Conditions	Product, ratio	Yield (%)
1	MOM	Me	$Pd(PPh_3)_2Cl_2$,[a] DMF, LiCl, 100°, 20 h	**13**:**15**, 1:1	<5
2	MOM	Me	$Pd(dppf)Cl_2$,[a] DMF, LiCl, 100°, 5.5 h	**13**:**15**, 1:1	<5
3	MOM	Me	$Pd(PPh_3)_2Cl_2$,[a] THF, CuI, reflux, 24 h	No reaction	–
4	MOM	Me	$Pd(dppf)Cl_2$,[a] dioxane, CuI, reflux, 6 h	13	<2
5	MOM	Me	$Pd(PhCN)_2Cl_2$,[b] DMF, $AsPh_3$, CuI, 100°, 1 h	**13**:**15**, 1:1	18
6	Me	Me	$Pd(dppf)Cl_2$,[b] DMF, CuI, dppf, 100°, 10 h	**14**:**15**, 1:1	6
7	Me	Bu	$Pd(dppf)Cl_2$,[b] DMF, CuI, 100°, 2.5 h	14	15
8	Me	Bu	$Pd(PhCN)_2Cl_2$,[b] DMF, $AsPh_3$, CuI, 3 h	14	20
9	Me	Bu	$Pd(dppf)Cl_2$,[a] MeCN, CuBr, reflux, 7.5 h	14	80[d]
10	Me	Bu	$Pd(dppf)Cl_2$,[a] PhMe, CuI, reflux, 24 h	No reaction	–
11	MOM	Bu	$Pd(dppf)Cl_2$,[c] MeCN, CuBr, reflux, 24 h	13	68
12	MOM	Bu	$Pd(PPh_3)_2Cl_2$,[c] MeCN, CuBr, reflux, 48 h	13	57

[a] 5 mol% catalyst.
[b] 10 mol% catalyst.
[c] 7 mol% catalyst.
[d] Based on recovered starting material, 60% otherwise.

methyl group transfer, with phenyl transfer being only five times faster than methyl transfer.[8] These results made us turn our attention to preparing the tributylstannanes as potential coupling partners. We observed that, although the yields for incorporation of the tributylstannane are lower, the coupling reactions proceed much more smoothly, with no butyl transfer observed. It was also seen that solvents played an important role in the coupling with, MeCN being better than DMF, whereas THF, dioxane, and toluene displayed virtually no reaction at all. As expected, we were unable to observe any significant difference between the two phenolic protecting groups used.

In summary, we have found that a palladium-catalyzed Stille cross-coupling reaction between a tri-*n*-butylstannane derivative of tyrosine and 7-iodoisatin is an efficient method for the synthesis of the biaryl moiety of the TMC-95 class of natural products. Studies to apply this method for the construction of the TMC-95 proteasome inhibitors and select analogs is currently in progress in these laboratories.

Acknowledgements

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