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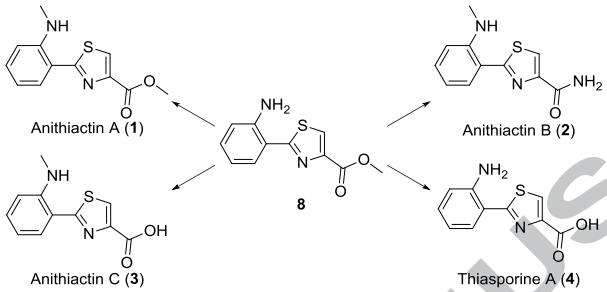

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Total synthesis of anithiactins A-C and thiasporine A

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ABSTRACT

The total syntheses of anithiactins A-C (**1**-**3**) and thiasporine A (**4**) have been achieved in good overall yields. The key reaction in the synthetic sequence was the Suzuki-Miyaura cross-coupling between 2-aminophenylboronic acid hydrochloride and methyl 2-bromothiazole-4-carboxylate forming the common intermediate methyl 2-(2-aminophenyl)thiazole-4-carboxylate (**8**), which could be further transformed by hydrolysis, alkylation, and aminolysis to give the four title natural products. This work represents the first total synthesis of anithiactin B (**2**) and C (**3**).

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1. Introduction

Anithiactins A-C (**1**-**3**) (Fig. 1) was first reported by Kim and co-workers isolated from *Streptomyces sp*. 10A085 samples collected from mudflat sediment on the southern coast of the Korean peninsula.[1] Shortly thereafter Fu and MacMillan reported the isolation of anithiactin A (**1**) and C (**3**) from *Actionomycetospora sp*. SNC-032 collected from a mangrove swamp in Vava'u, Tonga,[2,3] together with thiasporine A (**4**).[4,5] Compounds **1**-**3** showed moderate acetylcholinesterase inhibitory activity, and anithiactin A (**1**) acted as a competitive inhibitor of monoamine oxidase A (K_i = 1.84 μM).[1,6] Thiasporine A (**4**) displayed cytotoxicity against the non-small-cell lung cancer cell line H2122 (IC_{50} = 5.4 μM),[2] while compounds **1**-**3** showed no significant cytotoxicity.[1] Anithiactin A (**1**) has been prepared synthetically by Kim and co-workers as part of their structure elucidation work,[1] and by the group of Hawkins.[7] The syntheses, which were three and four steps long, respectively, gave the desired compound in 24% and 8% overall yield, respectively. As part of the structure revision of thiasporine A (**4**),[5] the natural product was prepared in a one-pot sequence from 2-aminobenzonitrile in 37% yield.[4] Herein, we report our total syntheses of natural products **1**-**4**, which also represents the first total synthesis of anithiactin B (**2**) and anithiactin C (**3**).

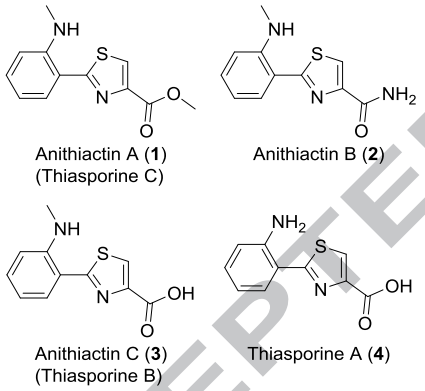


Figure 1. Structures of anithiactin A-C (**1**-**3**) and thiasporine A (**4**).

2. Results and Discussion

Our synthesis was based on the preparation of the common intermediate methyl 2-(2-aminophenyl)thiazole-4-carboxylate (**8**) that could be further converted to all four products by either conducting an alkylation, alkylation-hydrolysis or -aminolysis sequence. Biaryl **8** was envisioned as being prepared by a Suzuki-Miyaura cross-coupling[8] between 2-aminophenylboronic acid hydrochloride (**5**) or the corresponding boronate **6** (see ESI) and methyl 2-bromothiazole-4-carboxylate (**7**). The preparation of compound **8** turned out to be quite challenging, at least partly due to sulfur being a catalyst poison.[9] Therefore, laborious optimization studies of the Suzuki-Miyaura cross-coupling conditions were conducted, details of which can be found in Table 1 and Table S1 in the ESI.

Utilizing palladium-tetrakis(triphenylphosphine) as catalyst and potassium carbonate as base in toluene/water (3:1) heated in a microwave (MW) oven gave 14-15% of the desired cross-coupling product (Table 1, entries 1 and 2). Further attempts to improve this yield were unsuccessful. Switching the catalyst to palladium(II) acetylacetonate and changing the reaction conditions, which also included addition of XPhos, improved matters slightly resulting in the formation of compound **8** in 26% yield (Table 1, entry 3). However, turning to tris(dibenzylideneacetone)dipalladium(0) as the catalyst and utilizing XPhos as the ligand finally solved the problem (Table 1, entries 4-9). 1,4-Dioxane (Table 1, entries 6-9) was found to be a better solvent for the reaction than a mixture of ethanol and water (Table 1, entries 4 and 5).

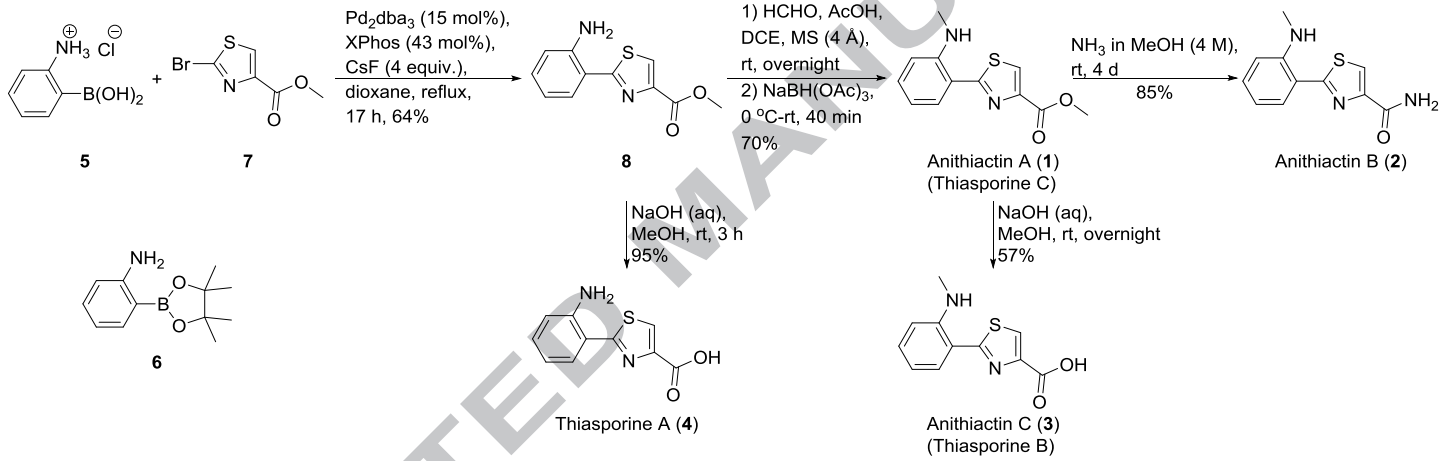
In our hands the highest yield of the desired cross-coupling product was obtained when treating boronic acid **5** and bromothiazole **7** with Pd_2dba_3 and XPhos using CsF as base in 1,4-dioxane at reflux[10] resulting in a 64% isolated yield of ester **8** (Table 1, entry 8). An attempt to increase the reaction time did not result in an increased yield most likely due to decomposition of the product over time (Table 1, entry 9). In order to further improve the yield of compound **8** boronate **6** was used instead of boronic acid **5** (Table 1, entry 10), however, to our disappointment the yield dropped.

Table 1. Optimization of the Suzuki-Miyaura cross-coupling of boronic acid **5** and 2-bromothiazole-4-carboxylate (**7**).

Entry	Catalyst	Ligand	Base	Solvent	Temp./condition	Time	Yield
1[a]	$Pd(PPh_3)_4$ (20 mol%)	-	K_2CO_3 (4 equiv.)	Toluene/H_2O (3:1)	110 °C, MW	0.5 h	14%
2[b]	$Pd(PPh_3)_4$ (20 mol%)	-	K_2CO_3 (4 equiv.)	Toluene/H_2O (3:1)	110 °C, MW	1.5 h	15%
3[a]	$Pd(acac)_2$ (10 mol%)	XPhos (20 mol%)	CsF (3.5 equiv.)	Dioxane	150 °C, MW	0.75 h	26%
4	$Pd_2(dba)_3$ (15 mol%)	XPhos (5 mol%)	KOAc (3 equiv.)	EtOH/H_2O (9:1)	130 °C, MW	1 h	23%
5[c]	$Pd_2(dba)_3$ (10 mol%)	XPhos (20 mol%)	KOAc (3.5 equiv.)	EtOH/H_2O (9:1)	130 °C, MW	1 h	54%
6[b]	$Pd_2(dba)_3$ (10 mol%)	XPhos (43 mol%)	CsF (3.5 equiv.)	Dioxane	150 °C, MW	0.5 h	51%
7[b]	$Pd_2(dba)_3$ (10 mol%)	XPhos (1 equiv.)	CsF (3.5 equiv.)	Dioxane	150 °C, MW	1.5 h	35%
8[a]	$Pd_2(dba)_3$ (10 mol%)	XPhos (43 mol%)	CsF (4 equiv.)	Dioxane	Reflux	17 h	64%
9[a,d]	$Pd_2(dba)_3$ (15 mol%)	XPhos (43 mol%)	CsF (4 equiv.)	Dioxane	Reflux	20 h	53%
10[e]	$Pd_2(dba)_3$ (15 mol%)	XPhos (43 mol%)	CsF (4 equiv.)	Dioxane	Reflux	17 h	29%

[a]2 equiv. of boronic acid **5** was used; [b]1.5 equiv. of boronic acid **5** was used; [c]1.1 equiv. of boronic acid **5** was used; [d]0.1 equiv. of 18-crown-6 was added; [e]1.05 equiv. of boronate **6** was used.

Scheme 1. Synthesis of anithiactin A-C (**1**-**3**) and thiasporine A (**4**).



With the optimized cross-coupling conditions in hand, focus then shifted towards the next challenge in the synthesis, namely the alkylation of substrate **8**. The monomethylation of compound **8** to give anithiactin A (**1**) has been proved to be non-trivial as can be seen from the rather low yield obtained by Kim and co-workers for this transformation (43%).[1] Initially we treated substrate **8** with formaldehyde (37% w in water) in ethanol under a hydrogen atmosphere over Pd/C according to our previously

reported method.[11] Unfortunately, this only resulted in the formation of anithiactin A (**1**) in 30% yield. However, by modifying the reductive amination conditions reported by Kim and co-workers[1] by using sodium triacetoxyborohydride as the reducing agent in the presence of 4 Å molecular sieves (MS) in 1,2-dichloroethane (DCE) provided anithiactin A (**1**) in 70% isolated yield (Scheme 1), thus resulting in the formation of anithiactin A (**1**) in 45% yield over the two steps.

Subjecting anithiactin A (**1**) to aminolysis using 4 M NH_3 in methanol utilizing a modified procedure reported in a patent by Billedeau and co-workers[12] gave anithiactin B (**2**) in 85% yield after a reaction time of 4 days (Scheme 1). This transformation could also be conducted by using 2 M NH_3 in methanol, however, the reaction was more sluggish and did not reach completion over the course of 5 days. Under the latter conditions, the target product was isolated in 71% yield in addition to recovery of the starting material. Hydrolysis of natural product **1** upon treatment with aqueous sodium hydroxide in methanol at room temperature gave anithiactin C (**3**) in 57% yield. Finally, subjecting ester **8** to similar hydrolysis conditions as used for compound **1** gave the final natural product, viz. thiasporine A (**4**), in 95% yield. The spectroscopic data obtained for anithiactins A-C (**1**-**3**) and thiasporine A (**4**) are in agreement with the data reported for the isolated compounds (see ESI, Table S2 for details).

3. Conclusion

We have successfully prepared anithiactins A-C (**1**-**3**) and thiasporine A (**4**) using a Suzuki-Miyaura cross-coupling reaction as the key step forming methyl 2-(2-aminophenyl)thiazole-4-carboxylate (**8**). Compound **8** was further elaborated giving the four natural products **1**-**4** in good overall yield. This work represents the first total synthesis of anithiactin B (**2**) and C (**3**).

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Supplementary Material

Supplementary material including ^{1}H and ^{13}C NMR charts of compounds **1**-**4** and **8** can be found in the online version at doi:…..

Highlight

An efficient total synthesis of the natural products anithiactin A-C and thiasporine A.