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Stereocontrolled Synthesis of Arylomycin-Based Gram-Negative Antibiotic GDC-5338

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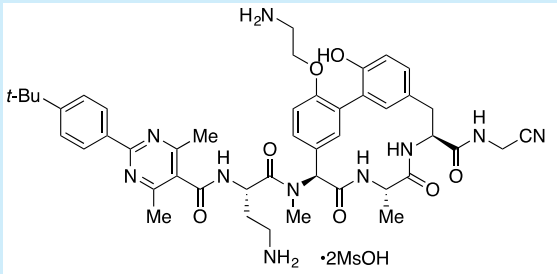
Supporting Information



GDC-5338 (1)

- 17 steps longest linear sequence, 15% overall yield
- High yielding Suzuki-Miyaura macrocyclization in 88% yield
- High stereochemical integrity (>99:1 dr)
- High overall purity >99 A % HPLC

ABSTRACT: We report herein an efficient, stereocontrolled, and chromatography-free synthesis of the novel broad spectrum antibiotic **GDC-5338**. The route features the construction of a functionalized tripeptide backbone, a high-yielding macrocyclization via a Pd-catalyzed Suzuki−Miyaura reaction, and the late-stage elaboration of key amide bonds with minimal stereochemical erosion. Through extensive reaction development and analytical understanding, these key advancements allowed the preparation of **GDC-5338** in 17 steps, 15% overall yield, >99 A % HPLC, and >99:1 dr.

The emerging resistance of bacteria to our existing antibiotic arsenal looms as a serious threat to the global human healthcare system. In spite of extensive research and development efforts, no new classes of antibiotics have been approved for the treatment of Gram-negative bacterial infections in the last 50 years.[1] Arylomycin analogues have been shown to represent a promising new class of inhibitors of bacterial type I signal peptidase (SPase), an enzyme essential for bacterial viability and growth.[2] The unique mechanism of action has thus attracted a broad interest in developing new antibiotics based on the arylomycin core, resulting in multiple syntheses reported by both the academic community[3] and the pharmaceutical industry.[4] These syntheses share a common strategy for macrocyclization centered on the construction of the biaryl bond via either a catalytic Suzuki−Miyaura reaction[3,4] or a stoichiometric Cu-mediated oxidative coupling[3e] from the corresponding linear tripeptide precursors. Despite recent advancements, the absence of preparatively useful chemistry to access suitable amounts of the arylomycin macrocyclic core has likely thwarted progress toward advancing new antibiotics to clinical development. The drawbacks of previously reported syntheses lie in poor to moderate overall yields, a lack of analytical characterization and understanding of stereochemical integrity and chemical purity, or the use of stoichiometric amounts of transition metals, which make them unsuitable for pharmaceutical research and development. Thus, there is a need to develop a reliable and robust synthetic route to enable both SAR studies of novel arylomycin analogues and their clinical evaluation. Our laboratories have recently described potential drug candidates based on the arylomycin core that exhibit broad spectrum antibiotic activity.[5] Further SAR studies led to the identification of **GDC-5338** (**1**) as one of the best candidates in this series. Herein, we report our development of a preparatively useful synthesis of **GDC-5338** (**1**) featuring a high-yielding and robust Suzuki−Miyaura coupling reaction to construct the macrocyclic arylomycin core that is complementary to our previously disclosed macrolactamization approach.[6]

Our retrosynthetic analysis of **1** is shown in Figure 1. We envisioned the amidoacetonitrile warhead could be installed last following the amide bond formation steps; coupling the macrocycle **2** with diamino acid **3** and pyrimidine acid **4**. Macrocycle **2** could be obtained through a Suzuki−Miyaura macrocyclization to forge the biaryl linkage from the corresponding linear tripeptide **6** assembled from derivatized amino acid building blocks. A judicious selection of orthogonal protecting groups would allow the flexible functionalization of

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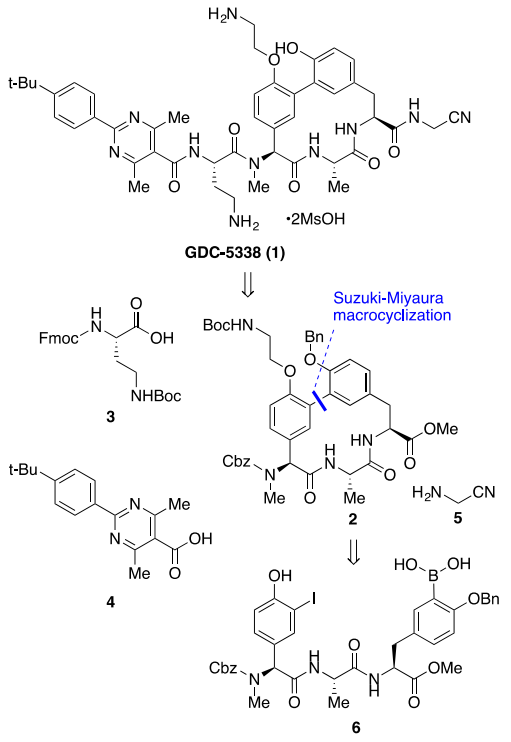
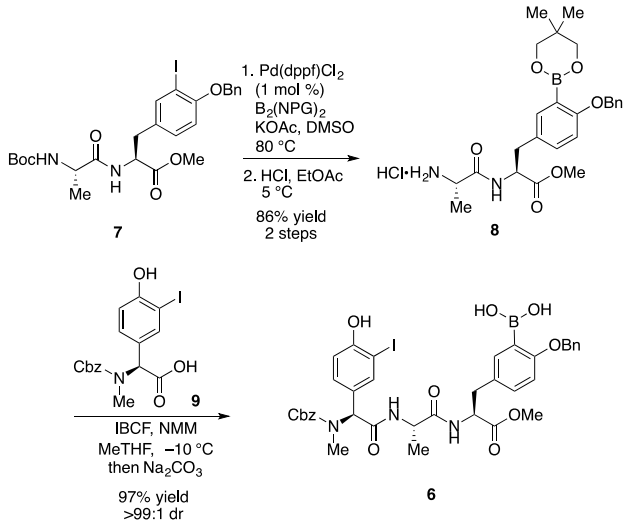


Figure 1. Retrosynthesis of **GDC-5338** (**1**).

the aromatic rings, appending appropriate side chains for SAR purposes and the elaboration of the delicate architecture found in **1**.

Our initial strategy to assemble the linear tripeptide **6** followed literature precedent[3a,d] employing an *N*- to *C*-terminus peptide coupling sequence (Scheme 1). However, we observed >20% epimerization at the alanine stereocenter in the coupling of Hpg-Ala dipeptide acid with the functionalized Tyr amine. We envisioned that the alternative *C*- to *N*-terminus coupling approach could minimize undesired stereochemical erosion.[3c] Thus, our synthetic route to tripeptide **6** commenced with functionalized dipeptide **7**, obtained from L-tyrosine over four steps in 45% yield and high stereochemical purity (>99:1 dr)[7] using a modified literature procedure (see the SI for details).[8] Subsequent Miyaura borylation[9] followed by Boc removal with HCl in EtOAc provided advanced intermediate **8** as an HCl salt in 86% yield over two steps. It is noteworthy that bis(neopentylglycolato)diboron ($B_2(NPG)_2$)[10] was found to be the optimal organoboron species, requiring a lower catalyst loading compared to bis(pinacolato)diboron (B_2Pin_2) (1 mol % vs 7.5 mol %) and resulting in faster hydrolysis to the corresponding boronic acid in the next step of the synthesis.[11,12] Coupling dipeptide **8** with functionalized Hpg **9** followed by hydrolysis of the boronate ester and crystallization from EtOH/*n*-heptane provided **6** in 97% yield without detectable stereochemical erosion (>99:1 dr).[13]

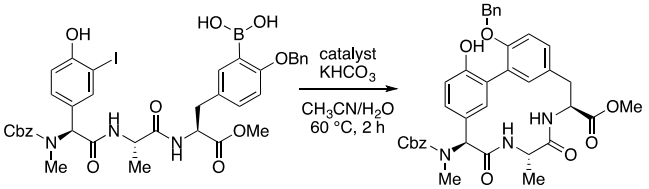
Scheme 1. Synthesis of Suzuki Macrocyclization Precursor 6



We next studied the key Suzuki−Miyaura macrocyclization of the linear tripeptide **6**. There were several challenges that remain unaddressed by past approaches on related substrates: (1) low to moderate yields (10−48%) for substrates with unprotected phenol on the Hpg residue;[3a,d] (2) high Pd catalyst loadings (5−20 mol %) requiring tedious purification by silica gel column chromatography; (3) lack of demonstration on preparative scale as the sole example reported above gram scale afforded less than 20% yield;[4] and (4) insufficient analytical evidence for chemical purity and stereochemical integrity of the desired product for pharmaceutical development.

Cognizant of these challenges, we decided to leverage our microscale high-throughput experimentation (HTE) platform to quickly evaluate reaction parameters such as catalyst, base, and solvent to identify leads. The combination of $KHCO_3$ as base and CH_3CN/H_2O (1:1) as solvent was found to be superior to others. Under these conditions, the three best performing catalysts (AmPhos Pd G3, cataCXium A Pd G3, and [(*t*-Bu_3P)Pd(crotyl)]Cl) were further validated at 20 mol % catalyst loading on mmol scale and [(*t*-Bu_3P)Pd(crotyl)]Cl[14] and gave the cleanest reaction profile (Table 1, entries 1−3). Gratifyingly, the reaction reached full conversion using 2 mol % catalyst loading (cf. entries 3 and 4). Comparison with a previously disclosed catalyst for the Suzuki−Miyaura macrocyclization, (t-$Bu_3P)_2Pd$, confirmed the superiority of [(*t*-Bu_3P)Pd(crotyl)]Cl presumably due to its improved oxygen and moisture tolerance (entry 5).

Table 1. Catalysts for Macrocyclization of 6[a]



entry	catalyst	loading (mol %)	**10** (HPLC A %)
1	AmPhos Pd G3	20	83
2	cataCXium A Pd G3	20	71
3	[(*t*-Bu_3P)Pd(crotyl)]Cl	20	89
4	[(*t*-Bu_3P)Pd(crotyl)]Cl	2	88
5	(t-$Bu_3P)_2Pd$	2	68

[a]All reactions were run by heating the mixture of tripeptide **6** (80.0 mg, 97.0 μmol) and $KHCO_3$ (10.2 mg, 1.05 equiv) in CH_3CN/H_2O (4 mL; 1:1, v/v) at 60 °C for 2 h.

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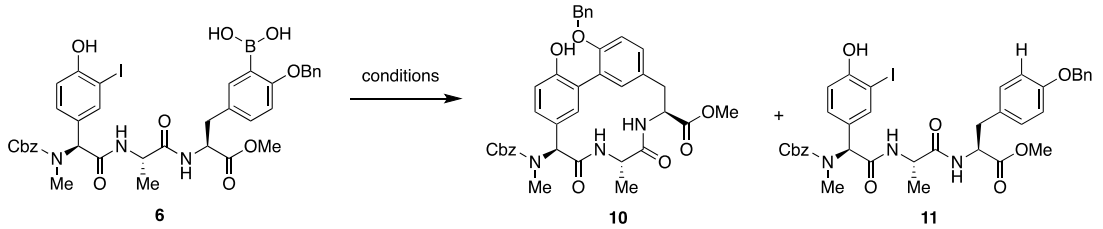
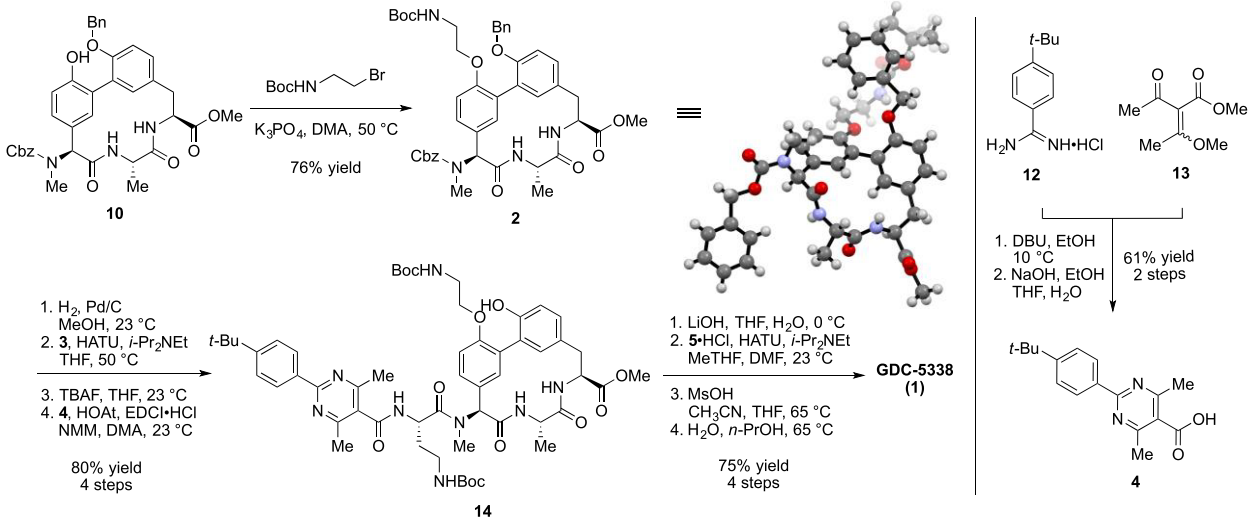
Table 2. Optimization of the Suzuki–Miyaura Macrocyclization



entry	conditions[a]	O_2 level headspace[b] (%)	[6][c] (mL/g)	11[d] (A %)	cyclic oligomers[d,g] (A %)	linear oligomers[d,e] (A %)	10[d] (A %)	assay yield (10)[f] (%)
1	A	<0.01	12	0	11	0	68	30
2	A	<0.01	500	0	2	0	95	78
3	B	<0.01	12	0	2	0	91	70
4	B	0.5–1[h]	12	6	2	6	66	37
5	B	5[h]	12	10	2	14	53	28
6	B	10[h]	12	15	2	14	48	21
7	B	21[h]	12	25	1	10	44	16
8	B	<0.01	50	0	2	0	95	88

[a]Conditions A: To a solution of **6** (12 mmol, 1.0 equiv) in CH_3CN (8 mL/g)/ H_2O (4 mL/g) was added catalyst (2 mol %) and the mixture was heated to 60 °C for 1 h. Conditions B: **6** (9.0 mmol, 0.75 equiv) of in CH_3CN (4 mL/g) was added to the solution of the catalyst (2 mol %) and **6** (3.0 mmol, 0.25 equiv) in CH_3CN/H_2O (8 mL/g; 1:1, v/v) over 1 h at 60 °C. [b]Headspace O_2 levels were monitored employing a headspace oxygen probe sensitive to a 0.01% limit. [c]Concentration is expressed as mL of solvent (CH_3CN/H_2O) per gram of **6**. [d]Results reported as HPLC A % in the crude reaction mixture. [e]Observed linear oligomers did not contain boron moieties. [f]Assay yields determined by HPLC analysis of the crude mixture. [g]The amount of cyclic oligomers represents only dimers and trimers; higher order oligomers were omitted for simplicity. [h]O_2 level was controlled by an initial sparge with N_2 to achieve levels below 0.01% followed by backfilling with O_2.

Scheme 2. End-Game Chemistry to GDC-5338 (1)



However, even under the optimized conditions using [(*t*-Bu_3P)Pd(crotyl)]Cl as precatalyst, a significant discrepancy was observed between the isolated yields of **10** and the clean reaction profile observed by HPLC analysis. Further HPLC method development indicated that the missing mass balance was associated with a late eluting mixture of linear and cyclic oligomers of the tripeptide precursor **6**, as elucidated by mass spectrometric (MS) analysis.[15]

To suppress the undesired cyclic oligomers, we first examined the effect of concentration (Table 2). Not surprisingly, when the substrate concentration was lowered, the amount of the undesired cyclic oligomer was minimized (cf. entries 1 and 2). To mimic these high dilution conditions but maintain practical reaction volumes, the linear precursor **6** was introduced as a solution in CH_3CN over 2 h to a solution of catalyst and base, which afforded a clean reaction profile with 70% assay yield as determined by quantitative HPLC analysis (entry 3).

To further improve the yield, we aimed to suppress the formation of linear oligomers. Interestingly, we only observed the protodeborylated linear peptide **11** and its corresponding oligomers via mass spectrometric analysis of the crude reaction mixtures but no detectable level of uncyclized oligomers containing the boronates. This observation led us to hypothesize that the linear precursor underwent protodeborylation before the intramolecular coupling and that the oxygen level in the reaction could be one of the critical process parameters.[16] Indeed, when the reaction was run at 0.5–1.0%

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O_2, both the reaction conversions and assay yields were diminished, with a concomitant formation of **11** as well as the linear oligomer side products (entry 4). Additional increase of the headspace O_2 level led to even higher amounts of the undesired side products (cf. entries 5−7). Thus, a very strict degassing protocol was implemented to ensure consistent reaction performance. Finally, running a reaction at higher overall dilution (50 mL/g) accompanied by a slow addition of **6** led to further improvement in isolated yield (entry 8). Consequently, this represents >60% increase in yield compared to the sole example of this type of the Suzuki−Miyaura macrocyclization previously described on decagram scale.[4]

After successful execution of the very challenging Suzuki−Miyaura macrocyclization, we proceeded to complete the synthesis of **1** (Scheme 2). Alkylation of macrocycle **10** with *tert*-butyl *N*-bromoethyl carbamate[17] led to functionalized macrocycle **2**[18] in a 76% yield after crystallization. The absolute stereochemistry of **2** was unambiguously assigned by single-crystal X-ray diffraction.

The Cbz group on macrocycle **2** was removed via Pd/C hydrogenolysis in DMA. Initial evaluation of typical amide coupling conditions for the attachment of diaminobutyric acid (Dab) **3** to the macrocycle led to 18% epimerization at the Dab stereocenter. After careful examination, the combination of HATU[19] and *i*-Pr_2NEt was identified as the optimal conditions to minimize the level of epimer (<0.05%), affording the desired product in 99 A % purity by HPLC analysis after crystallization from CH_3CN/THF.

Fmoc deprotection using TBAF[20] allowed for a simple aqueous workup to purge the corresponding byproduct. Biaryl acid **4**, obtained through a condensation of amidine **12** and ketoester **13** followed by ester hydrolysis in 61% yield over two steps (Scheme 2),[21] was then introduced through an EDCI/HOAt coupling to give the desired functionalized macrocycle **14** in 80% yield over four steps after precipitation from *i*-PrOAc/*n*-heptane from compound **2**.

Initial investigations of the ester hydrolysis in **14** proved to be challenging due to competing epimerization at the Hpg stereocenter (2.6−4.0 A % HPLC). Ultimately, we found that using 2.5 equiv of LiOH in THF/H_2O at 0 °C afforded the corresponding acid with >98.5:1.5 dr as ascertained by HPLC analysis. The resulting acid was then activated with HATU in MeTHF and coupled with aminoacetonitrile hydrochloride in the presence of *i*-Pr_2NEt as base in DMF. Subsequent crystallization from DMF/H_2O afforded the complete framework of **1**.

Identifying suitable conditions for the global deprotection and salt formation of the penultimate macrocycle proved especially difficult due to the inherent reactivity of the nitrile warhead in the presence of the nucleophilic free amine side chains. Various acids and solvents combinations were evaluated; however, due to high aqueous solubility of the ammonium salts, significant loss upon aqueous workup was observed. Attempts to obtain free base **1** by neutralization of the ammonium salts resulted in competing hydrolysis of the nitrile warhead. The combination of MsOH in THF and CH_3CN at 70 °C led to the formation of crude **1** as the corresponding bis-methanesulfonate salt, which readily crystallized from the solution and thus avoided an aqueous workup. A subsequent recrystallization from *n*-PrOH/H_2O was essential to ensure high purity API and remove several impurities including amide hydrolysis, nitrile hydrolysis, partial Boc deprotection, dimer, and Ritter reaction side products. **GDC-5338** was isolated in 75% yield over four steps as the bis-mesylate salt from ester **15**, with high chemical (>99 A % HPLC) and stereochemical (>99:1 dr) purity.

In conclusion, we have developed an efficient, practical, and stereocontrolled synthesis of **GDC-5338** that proceeds in 17 steps and 15% overall yield. Central to our approach was the strategic *C*- to *N*-terminus assembly of the linear tripeptide backbone as well as the in-depth reaction understanding that resulted in a high-yielding Suzuki−Miyaura macrocyclization,[22] leading to a >4-fold yield improvement (from 20% to 88%) compared to the sole previously described approach on decagram scale.[4] The final chemoselective deprotection and salt formation afforded a stable, crystalline, pharmaceutical grade **GDC-5338**, with high stereochemical integrity (>99:1 dr). We are confident that this practical entry into the arylomycin core and synthetic analogues will accelerate further development of new Gram-negative antibiotics.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03481.

Experimental details and spectroscopic data (PDF)

Accession Codes

CCDC 1959253 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(11) The corresponding BF_3K salt resulted in inconsistent performance in the Suzuki−Miyaura macrocyclization.

(12) Although upon isolation a 70:30 ratio of boronate ester and boronic acid was obtained, the mixture was inconsequential to downstream chemistry, as the boronate ester was fully converted to the boronic acid in the next chemical step.

(13) Synthesis of fragment **9** was previously described in our earlier work (ref 6).

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(17) Other alkylating agents were also explored: *tert*-butyl aziridine-1-carboxylate (12% assay yield), *tert*-butyl 1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (28% assay yield), *tert*-butyl (2-iodoethyl) carbamate (37% assay yield), *tert*-butyl (2-chloroethyl)carbamate (58% assay yield), and 2-((*tert*-butoxycarbonyl)amino)ethyl 4-methylbenzenesulfonate (74% assay yield).

(18) Atropisomers were only observed for disubstituted phenol **2**.

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(21) See the Supporting Information for the synthesis of pyrimidine acid **4**.

(22) We have demonstrated the Suzuki−Miyaura macrocyclization on > 100 kg scale and the overall synthesis has produced > 5 kg of API.

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