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Intramolecular Suzuki–Miyaura Reaction for the Total Synthesis of Signal Peptidase Inhibitors, Arylomycins A_2 and B_2

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In Memory of Professor Keith Fagnou

Abstract: Development of the total syntheses of arylomycins A_1 and B_2 is detailed. Key features of our approach include 1) formation of 14-membered *meta*,*meta*-cyclophane by an intramolecular Suzuki–Miyaura reaction; 2) incorporation of *N*-Me-4-hydroxyphenylglycine into the cyclization precursor, which avoids the late-stage low-yielding *N*-methylation step; 3) segment coupling of a fully elaborated peptide side chain to the macrocycle, which makes the synthesis highly convergent. Overall, arylomycin A_2 was obtained in 13 steps from L-Tyr for the longest linear sequence, in 13% overall yield. Arylomycin B_2 was synthesized in 10 steps from L-3-nitro-Tyr, in 10% overall yield.

Keywords: antibiotics · biaryls · cross-coupling · macrocycles · natural products

Introduction

The need for the discovery of new families of antibiotics with novel mechanisms of action[1] has been growing because of the constant emergence of multi-drug-resistant bacteria. Recently, efforts have focused back on finding new antibiotics from bacterial natural products.[2] In this context, secondary metabolites arylomycins were isolated in 2002 from *Streptomyces* strain *Tü 6075* by Fiedler, Jung and coworkers.[3] Independently, several related lipohexapeptides and glycopeptides of this family were isolated in 2004 by Kulanthaivel and collaborators.[4] Initial studies have shown that arylomycins displayed activities against a series of Gram-positive aerobic soil bacteria. Moreover, some members of the family were found to be as potent as the currently prescribed antibiotics against *Staphylococcus epidermis*, a Gram-positive human pathogen.[5] Based on the X-ray co-crystal structure with a catalytic fragment of an *Escherichia coli* enzyme,[6] it was concluded that these natural products act as potent signal peptidase I (SPase I) inhibitors.[7,8] The SPase I is a transmembrane serine protease that cleaves the amino-terminal signal peptide from pre-proteins to release secretary and membrane proteins. Arylomycins are competitive inhibitors of SPase I with K_i values ranging from 50 to 158 nM[4] and, consequently, are capable of blocking bacterial protein secretion in vivo, which leads to bacterial death. SPase I represents a very attractive target in the search for new antibiotics for several reasons: 1) it is essential for bacterial viability and growth; 2) its active site, located on the periplasmic surface of the cytoplasmic membrane, is particularly accessible for a potential drug in cases when permeability may be an issue; 3) it is strongly expressed in bacteria; 4) it presents an unique Ser–Lys catalytic dyad that is not affected by standard serine protease inhibitors. This last point offers an opportunity to selectively inhibit the bacterial SPase I without threat to human proteases. Therefore, as inhibitors of SPase I, arylomycins could be considered as ideal leads for the development of a new generation of antibiotics that are less likely to suffer from cross resistance.

Structurally, arylomycins are lipohexapeptides (D-Me-Ser-D-Ala-Gly-L-Me-Hpg-L-Ala-L-Tyr; Hpg = 4-hydroxyphenylglycine) that can be divided into two series, A and B. Arylomycins B differ from the A series by the presence of a nitro substituent on the tyrosine aromatic ring, which is responsible for their characteristic yellow color. Both series have a saturated C11 to C15 *n*, *iso*, or *anteiso* fatty acid residue attached to the N-terminal amino acid, serine. The aromatic rings of Hpg and Tyr are cross linked by an aryl–aryl bond, which forms a 14-membered *meta*,*meta*-cyclophane. Two of

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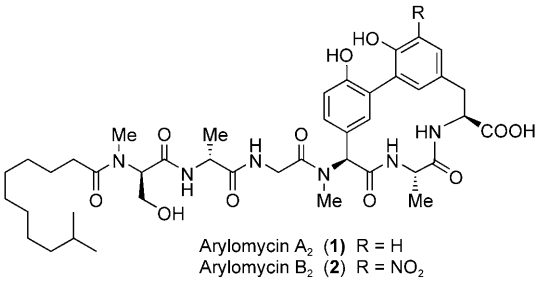
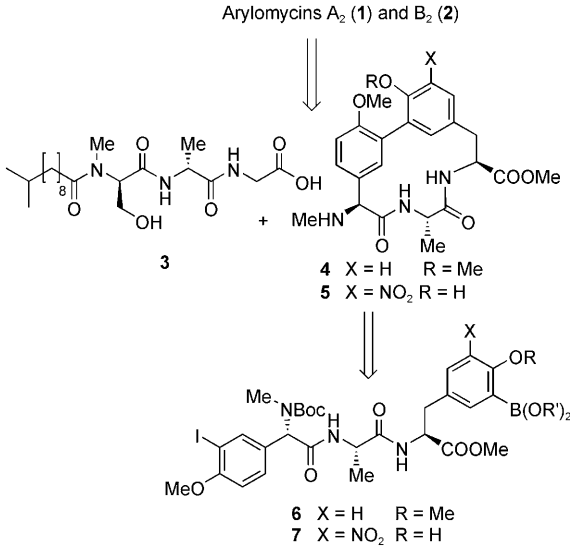
the hexapeptide amide nitrogen atoms are *N*-methylated and the first two residues are non-proteinogenic amino acids with D stereochemistry. The related glycopeptides, isolated by Kulanthaivel et al.,[4] differ from other members by the degree of glycosylation and hydroxylation of the Hpg residue. Due to the ring strain associated with this macrocycle, arylomycins can exist as a mixture of two atropisomers at room temperature. Interestingly, the X-ray crystal structure of SPase I–arylomycin A_2 complex indicated that only the *aS*-configured atropisomer of the arylomycin was bound to the SPase.[6]



Structurally, the arylomycins belong to a growing family of complex macrocycles, which includes biphenomycin (an antibacterial agent),[9] the family of TMC-95 (proteasome inhibitors),[10] RP-66453 (a neurotensine receptor antagonist),[11] and vancomycin-type glycopeptide antibiotics.[12] The presence of strained macrocycles with an *endo* aryl–aryl bond is a characteristic structural feature of these medicinally relevant natural products.[13] The complex molecular architecture and important bioactivities have made these macrocycles attractive, yet challenging, synthetic targets. Indeed, these molecules have provided impetus for the development of numerous new synthetic methodologies.

Different strategies can be considered for the closure of the strained macrocycles found in these cyclopeptides. Among them, construction of the biaryl unit followed by macrolactamization has been successfully used in the synthesis of the AB ring of vancomycin,[14] biphenomycin B,[15] and TMC-95 A and B,[16] to name just a few. On the other hand, macrocyclization by formation of an aryl–aryl bond is particularly attractive because of its inherent convergence and has indeed proved to be a powerful alternative when macrolactamization is inefficient.[5,17] Reactions such as nickel(0)-promoted reductive coupling of aryl halides,[18] redox-neutral photochemical cyclization,[19] and oxidative coupling of cyanocuprates[20] and electron-rich arenes[21] have been used for this purpose. Realizing that these cyclizations were generally low yielding and/or not compatible with peptidic structures, our group has been working on the intramolecular Suzuki–Miyaura reaction[22] for macrocycle formation and has accomplished total syntheses of a number of natural products with an *endo* aryl–aryl bond.[23]

Recently, Romesberg et al.[5] and our group[24] independently reported total syntheses of arylomycin A_2 (**1**) with similar strategies. As a continuation of this research program, we became interested in the synthesis of arylomycins B because they display greater antibacterial activity than the A series.[3] Our general synthetic strategy, applicable to both the A and B series, is depicted in Scheme 1. In a forward



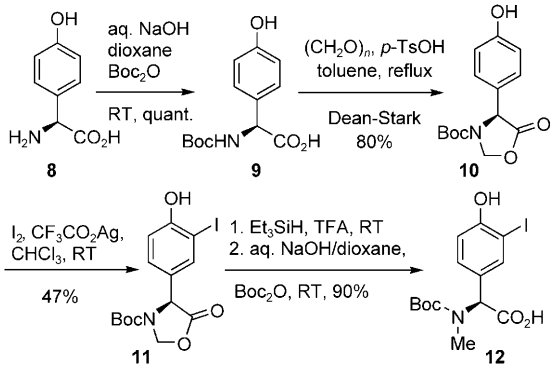
Scheme 1. Retrosynthetic analysis of arylomycins A_2 (**1**) and B_2 (**2**).

sense, intramolecular Suzuki–Miyaura reaction of linear peptides **6** and **7** would afford cyclophanes **4** and **5**, respectively. Coupling of the fully elaborated peptidic side chain **3** with cyclophanes **4** and **5** would provide, after deprotection, the natural products **1** and arylomycin B_2 (**2**), respectively. Herein, we report in full detail our total synthesis of **1** and the first total synthesis of **2**. We also document some unexpected observations in the arylomycin B_2 series. Indeed, an alternative route for the synthesis of the cyclization precursor of **2** needed to be developed due to the presence of the nitro group.

Results and Discussion

Preparation of *N*-methylated building blocks: *N*-Methyl amino acids are found in a large number of peptidic natural products. They have also found broad application in medicinal chemistry because they are known to increase membrane permeability and conformational rigidity. A range of methods have been developed, which include direct alkylation and reductive aminoalkylation of the parent amino acids.[25,26] However, to the best of our knowledge, biocatalytic kinetic resolution of the *N*-Me-Hpg amide developed by Wang and co-workers was the only reported method for the synthesis of enantiomerically enriched *N*-Me-Hpg.[27]

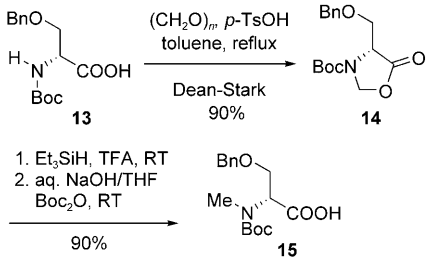
Our synthesis of 3-iodo-4-hydroxy-*N*-methyl arylglycine (**12**) is shown in Scheme 2. Reduction of oxazolidinone **11** under acidic conditions, as disclosed by Freidinger et al.,[28] is the key step for the introduction of the *N*-methyl func-



Scheme 2. Preparation of L-*N*-Me-*N*-Boc-3-iodo-Hpg (**12**).

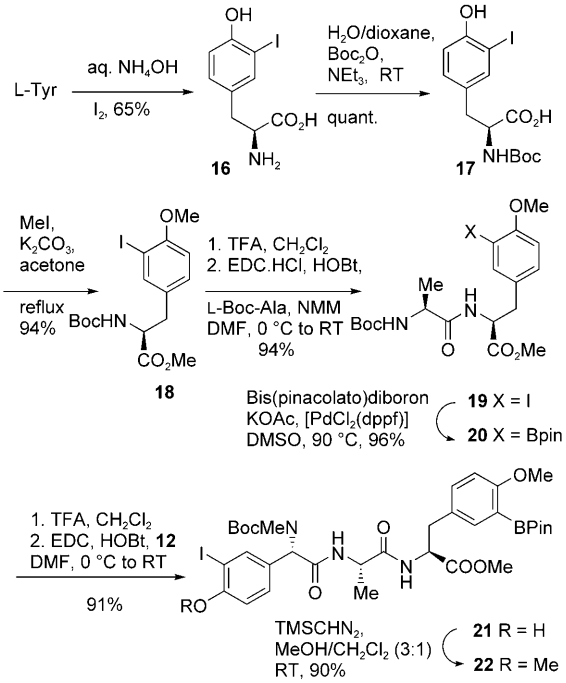
tion.[24,29] Reasoning that the formation of the phenoxide could render the α-CH of Hpg less prone to deprotonation, thus reducing the likelihood of racemization, we decided to leave the phenol group of Hpg unprotected during the synthesis. L-Hydroxyphenylglycine (**8**) was first quantitatively *N*-*tert*-butoxycarbonyl (Boc) protected (Boc_2O, aqueous NaOH, dioxane, RT) to give **9**, which was subsequently converted into oxazolidinone **10** (paraformaldehyde, toluene sulfonic acid (*p*-TsOH), reflux). Iodination of **10** with trifluoroacetyl hypoiodite, generated in situ from iodine and silver trifluoroacetate,[30] afforded the desired 3-iodo-derivative **11**, which was readily separated from the bis-iodinated side product, in 47% yield. Finally, reduction of **11** by Et_3SiH in trifluoroacetic acid (TFA) followed by reinstallation of the *N*-Boc function afforded the desired *N*-methyl amino acid **12** in 90% yield. To reveal the *N*-methyl function, several other reduction conditions were investigated, which included $NaBH_3CN/Me_3SiCl$[31] and $Et_3SiH/AlCl_3$.[32] Whereas the former led to the recovery of starting material, the latter provided only the hydrolyzed product.

N-Me-D-Ser (**15**) was prepared by the same oxazolidinone reduction strategy, depicted in Scheme 3. Reaction of commercially available *N*-Boc(OBn)Ser (**13**, Bn = benzyl) with paraformaldehyde in the presence of *p*-TsOH afforded oxazolidinone **14**, which was subsequently transformed to **15** in 90% yield, over two conventional steps.



Scheme 3. Preparation of D-*N*-Me-*N*-Boc(OBn)-Ser (**15**).

Preparation of the macrocycle of arylomycin A_2: The synthesis of linear tripeptides **21** and **22** is shown in Scheme 4.

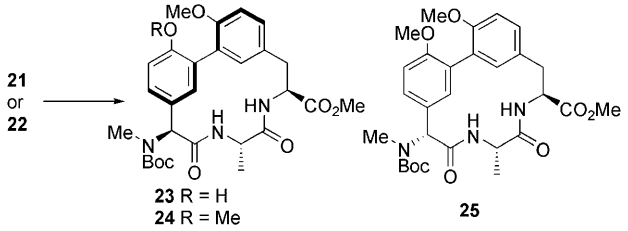


Scheme 4. Preparation of linear tripeptides **21** and **22**.

Methyl-L-*N*-Boc-3-iodo-4-methoxyphenyl alanate (**18**) was prepared from L-Tyr in three steps. Selective monoiodination of L-Tyr in basic aqueous solution by Joullié's procedure[33] afforded compound **16**, which was further *N*-Boc-protected to give carbamate **17**. A solution of **17** in acetone was heated to reflux in the presence of an excess of iodomethane and potassium carbonate to provide **18** in excellent yield. Removal of the *N*-Boc group from **18** followed by coupling of the resulting TFA salt with L-Boc-alanine proceeded smoothly to afford dipeptide **19** in 94% yield (EDC,[34] HOBt,[34] NMM,[34] DMF). Installation of the boron functional group was achieved with Miyaura's palladium-catalyzed borylation procedure[35] to provide aryl boronate **20** with an excellent yield. N-Deprotection followed by peptide coupling with L-*N*-Me-*N*-Boc-Hpg (**12**) (EDC, HOBt, DMF) gave the tripeptide **21** in 91% isolated yield. Finally, methylation of phenol **21** with trimethylsilyldiazomethane ($TMSCHN_2$) in a mixture of MeOH and CH_2Cl_2 afforded compound **22** in 90% yield.[36]

With the properly functionalized tripeptides **21** and **22** in hand, we set out to examine the desired macrocyclization by intramolecular Suzuki–Miyaura reaction (Table 1).[22,23,37] The inherent need for a base in such cross-coupling reactions poses an epimerization problem.[38] It was assumed that the presence of the unprotected phenol could minimize the epimerization of **21**. Treatment of a solution of **21** in DMSO ($c = 0.02$ M, 90 °C) in the presence of $[PdCl_2(dppf)]$[34] (0.05 equiv) and K_2CO_3 (7 equiv) afforded macrocycle **23** in an encouraging 29% yield (Table 1, entry 1). Both the solvent and the palladium source were shown to influence the reaction outcome. DMSO or toluene/H_2O (30:1) were better solvents than acetonitrile for this reaction (Table 1,

Table 1. Survey of reaction conditions[a] of palladium-catalyzed intramolecular cyclization of linear tripeptides **21** and **22**.



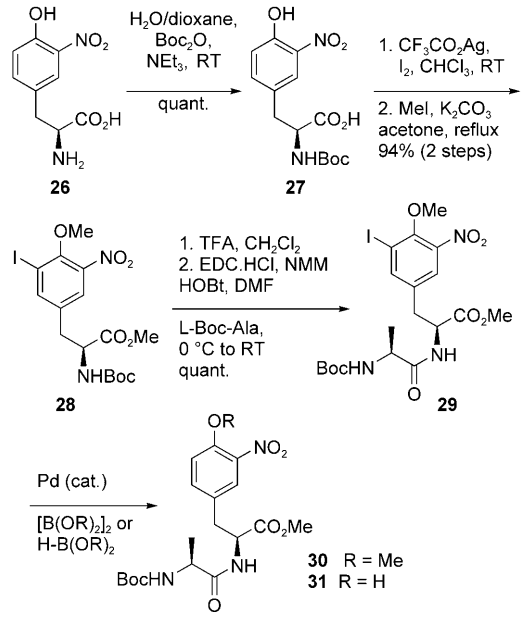
Entry	Substrate	Solvent	Catalyst	T [°C], t [h]	Yield [%][b]
1	**21**	DMSO	[$PdCl_2$(dppf)]	90, 2	29
2	**21**	CH_3CN	[$PdCl_2$(dppf)]	80, 2	9
3	**21**	Tol/H_2O (30:1)	[$PdCl_2$(dppf)]	90, 2	23
4	**21**	Tol/H_2O (30:1)	[$Pd(dba)_2$]+(*R*)-MOP	90, 2	13
5	**21**	Tol/H_2O (30:1)	[$Pd(dba)_2$]+SPhos	90, 2	28
6[c]	**21**	Tol/H_2O (30:1)	[$Pd(dba)_2$]+SPhos	90, 2	27
7	**21**	Tol/H_2O (30:1)	[$PdCl_2$(SPhos)$_2$]	90, 2	35
8	**21**	DMSO	[$PdCl_2$(SPhos)$_2$]	90, 2	37
9[d]	**21**	Tol/H_2O (5:1)	[$PdCl_2$(SPhos)$_2$]	90, 2	0
10	**21**	Tol/H_2O (30:1)	[$PdCl_2$(SPhos)$_2$]	90(MW),[g] 1	39
11	**21**	Tol/H_2O (30:1)	[$PdCl_2$(SPhos)$_2$]	110(MW),[g] 0.5	38
12	**22**	Tol/H_2O (30:1)	[$PdCl_2$(SPhos)$_2$]	90(MW),[g] 1	40 (20)[e]
13	**22**	Tol/H_2O (30:1)	[$PdCl_2$(SPhos)$_2$]	90, 2	39 (17)[e]
14	**22**	DMSO	[$PdCl_2$(dppf)]	90, 2	12
15	**22**	EtCN	[$PdCl_2$(SPhos)$_2$]	90, 18	28 (9)[e]
16[f]	**22**	Tol/H_2O (30:1)	[$PdCl_2$(SPhos)$_2$]	90, 2	54 (9)[e]

[a] Pd cat. (5 mol%), K_2CO_3 (7 equiv), $c = 0.02$ M. [b] Isolated yield of macrocycle **23** (from **21**) or **24** (from **22**). [c] Concentration = 0.002 M. [d] In the presence of $(n\text{Bu})_4\text{NBr}$. [e] Yield in parentheses refers to minor isomer **25**. [f] $NaHCO_3$ used instead of K_2CO_3. [g] Reaction heated by microwave irradiation, see reference [40]).

entries 1 and 3 versus 2). The best ligand appeared to be SPhos,[34] which was more efficient than dppf or (*R*)-MOP[34] (Table 1, entry 5 versus 3 and 4). Finally, the use of the preformed catalyst [$PdCl_2$(SPhos)$_2$], described by Buchwald et al.,[39] afforded the macrocycle with better yields in both DMSO and 30:1 toluene/H_2O (Table 1, entries 7 and 8). Addition of phase-transfer reagent $(n\text{-Bu})_4\text{NBr}$ was detrimental to the cyclization (Table 1, entry 9). Microwave irradiation[40,41] shortened the reaction time, but did not improve the yield (Table 1, entries 10 and 11 versus 7). Performing the cyclization under high-dilution conditions had no significant impact on the yield of **23**, an indication that tripeptide **21** may be conformationally biased for the intramolecular reaction (Table 1, entry 6).[42]

Cyclization of compound **22** was next investigated. When compound **22** was placed under the optimal conditions found for phenol **21** (K_2CO_3, toluene/H_2O (30:1), [$PdCl_2$(SPhos)$_2$]), two cyclized products were isolated (Table 1, entries 12 and 13). The major compound was identical to a sample prepared by methylation of the phenol-containing macrocycle **23** ($TMSCHN_2$, MeOH/CH_2Cl_2). We therefore assumed that the major product was the desired macrocycle **24** and the minor one, **25**, was an epimer of **24** produced by epimerization of the arylglycine unit. Interestingly, NOE spectroscopic analysis of macrocycle **24** showed that the *aS* atropisomer was formed exclusively (Scheme 13, see below). A mixture of toluene and H_2O (30:1) was found to be a better reaction media than DMSO (Table 1, entries 13 versus 14). Use of propionitrile as a solvent slowed the reaction without improvement to the macrocyclization yield (Table 1, entry 15). Fortunately, when the reaction was conducted in the presence of a weaker base ($NaHCO_3$), the extent of epimerization was reduced significantly. Under optimized conditions ([$PdCl_2$(SPhos)$_2$], $c =$ 0.02 M in toluene/H_2O (30:1), $NaHCO_3$ (7 equiv), 90 °C, 2 h), cyclization of **22** afforded the macrocycle **24** in 54% yield (Table 1, entry 16). It is notable that the intramolecular Suzuki–Miyaura reaction is, for the moment, the only way to build the cyclophane unit of the arylomycins; macrolactamization was reported to be inefficient.[5]

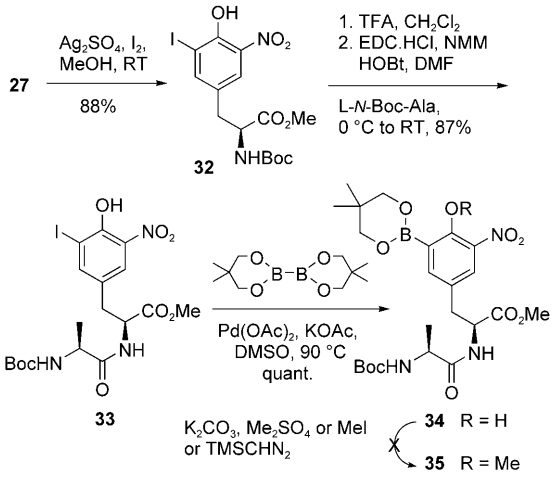
Preparation of the macrocycle of arylomycin B_2: With this efficient and convergent synthesis of macrocycles **23** and **24** in hand, we turned our attention to the synthesis of the macrocycle of **2**, which differs from **23** and **24** only by the presence of a nitro group on the tyrosine unit. To build this macrocycle, we initially followed a similar strategy to that designed for **1**. Thus, commercially available L-3-NO_2-Tyr (**26**) was quantitatively *N*-Boc-protected (Scheme 5). Iodination of the deactivated aromatic ring with a combination of iodine and silver trifluoroacetate afforded, after methylation of both the acid and phenol functions, compound **28** with an excellent yield of 94%, over two steps. N-Deprotection of **28** then coupling with L-*N*-Boc-alanine under standard conditions (EDC, HOBt, DMF) proceeded smoothly to afford dipeptide **29** quantitatively. Surprisingly, palladium-catalyzed borylation of dipeptide **29** with bis(pinacolato)diboron[35] did not afford the expected boronate; instead, a mixture of reduced compounds **30** and **31** was produced (Scheme 5). The *O*-demethylation of the methyl ether in **29** was quite surprising in view of the successful preparation of **20** under similar conditions. We think that a Pd^{II} salt may act as a Lewis acid, coordinate to the phenoxy group and, thus, activate the nucleophilic attack of either acetate or iodide on the methyl group. The fact that nitrophenol is a good leaving group may facilitate this C–O bond cleavage.[43] Related Pd^{II}-catalyzed debenzylation of benzyl ether has been observed by Balme and coworkers.[44] Although reduction of aryl iodides to arenes is a common side reaction encountered in the palladium-catalyzed process, the hydride source under the present reaction



Scheme 5. Attempted preparation of the borylated dipeptide fragment.

conditions was unclear. We also briefly investigated other borylation reagents, such as bis(neopentylglycolato)diboron[45] and pinacolborane,[46] however, none of these conditions afforded the desired aryl boronate.

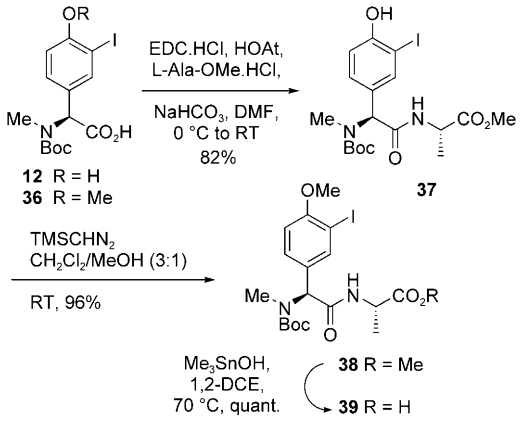
To check if protection of the phenol as a methyl ether was indeed detrimental to the borylation of dipeptide **29** the borylation of dipeptide **33**, with a free nitrophenol function, was evaluated. N-Protected tyrosine **27** was simultaneously iodinated and esterified[47] with a mixture of iodine and silver sulfate in methanol (Scheme 6). Removal of the *N*-Boc carbamate from tyrosine **32** under mild acidic conditions (TFA, CH_2Cl_2) followed by standard peptide coupling with *N*-Boc-Ala afforded dipeptide **33** in 87% yield. The palladium-catalyzed borylation of iodophenol **33** with bis(pinacolato)diboron afforded the expected aryl boronate **34**,



Scheme 6. Preparation of borylated dipeptide **34**.

together with hydrolyzed aryl boronic acid. The aryl boronate was stable upon aqueous workup and filtration through a short pad of Celite, but readily decomposed during flash-column chromatography. Bis(neopentylglycolato)diboron was found to be more efficient as a borylation agent under otherwise identical conditions and provided **34** quantitatively. The catalyst $Pd(OAc)_2$[48] was as efficient as [$PdCl_2$(dppf)] in this reaction but advantageously turned to Pd "black" at the end of the reaction and, therefore, could be easily removed by filtration. Methylation of phenol **34** failed to provide methyl ether **35** on treatment with several reagents (MeI, Me_2SO_4, $TMSCHN_2$) under a variety of conditions.

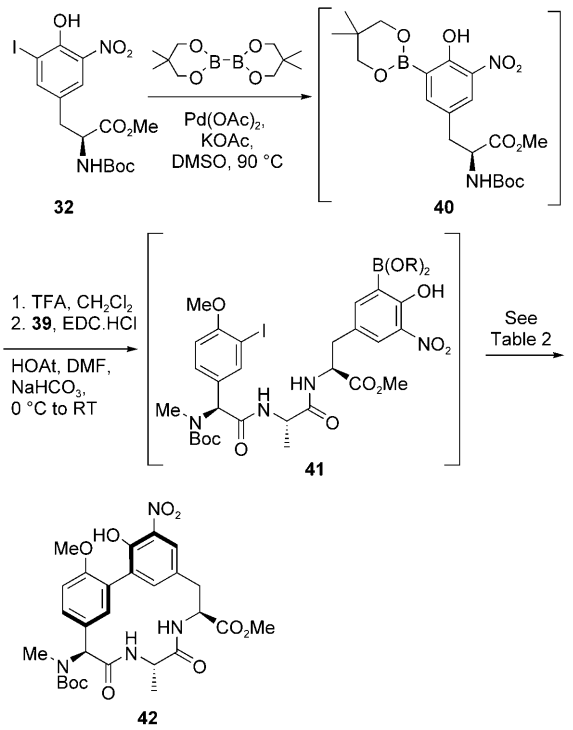
In light of these results, the late methylation of the Hpg unit adopted en route to **1** (conversion of **21** to **22**, Scheme 4) was deemed inappropriate. Therefore, we prepared *O*-methylated arylglycine **36** in 3 steps from compound **10** ($TMSCHN_2$; I_2, Ag_2SO_4; TFA/Et_3SiH then Boc_2O; see the Supporting Information) to couple with dipeptide **34**. However, extensive epimerization observed during the attempted coupling of acid **36** with L-Ala-OMe prompted us to modify this sequence.[49] Thus, coupling of arylglycine **12** with L-Ala-OMe in the presence of HOAt[34] and EDC·HCl afforded dipeptide **37** in 82% yield without epimerization (Scheme 7). Methylation of **37** by action of $TMSCHN_2$ in a



Scheme 7. Preparation of dipeptide **39**.

3:1 mixture of CH_2Cl_2/MeOH afforded **38** in 96% yield. Hydrolysis of methyl ester **38** was realized in the presence of Me_3SnOH[50] and gave acid **39** quantitatively, without epimerization. This sequence allowed us to prepare dipeptide **39** efficiently, ready to be coupled with a tyrosine–boronic ester unit.

Since purification of a substrate with a boronic ester *ortho* to a nitrophenol function proved to be difficult, we decided to carry out four consecutive steps to reach the cyclophane **42** from tyrosine derivative **32**, with filtration or extraction as the only purification methods (Scheme 8). Borylation of compound **32** with bis(neopentylglycolato)diboron provided aryl boronate **40** after a filtration through Celite. The exclusive formation of the latter was confirmed by NMR spectroscopy. Amino ester **40** was then N-deprotected in acidic



Scheme 8. Synthesis of macrocycle **42**.

media and the resultant amino ester was coupled directly with dipeptide **39** to afford the crude tripeptide **41**, which was used directly in the macrocyclization step. The conditions investigated for the intramolecular Suzuki–Miyaura reaction are summarized in Table 2. The yield of macrocycle **42** indicated is calculated over four steps from **32** (borylation, N-deprotection, peptide coupling, and macrocyclization).

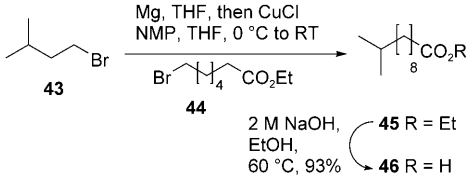
Table 2. Survey of reaction conditions[a] of palladium-catalyzed intramolecular cyclization of crude linear tripeptide **41**.

Entry	Base	Solvent	Catalyst	T [°C], t [h]	Yield of **42** [%][b]
1	K_2CO_3	Tol/H_2O (30:1)	$[PdCl_2(SPhos)_2]$	90, 2	0
2	K_2CO_3	DMSO	$[PdCl_2(SPhos)_2]$	90, 1.5	0
3	K_2CO_3	DMSO	$Pd(OAc)_2$	90, 1.5	11
4	K_2CO_3	DMSO	$[\{Pd(allyl)Cl\}_2]$	90, 1.5	13
5	KOAc	DMSO	$[\{Pd(allyl)Cl\}_2]$	90, 1.5	19
6	KOAc	DMSO	$[\{Pd(allyl)Cl\}_2]$	110, 1.5	17

[a] Pd (5 mol%), base (7 equiv), $c = 0.02$ M. [b] Isolated yield of macrocycle **42** over 4 steps from **32**.

When compound **41** was placed under the optimal conditions found for the macrocyclization of **22** (Table 2, entry 1; K_2CO_3, toluene/H_2O (30:1), $[PdCl_2(SPhos)_2]$), extensive degradation was observed without formation of the desired macrocycle **42**. This result is probably due to deprotonation of the nitrophenol, which would make the precursor **41** highly soluble in the concentrated basic aqueous layer. The nature of the catalyst proved to be important. Indeed, when the reaction was performed in DMSO, $[PdCl_2(SPhos)_2]$ was a completely inefficient catalyst (Table 2, entry 2), whereas $Pd(OAc)_2$ and $[\{Pd(allyl)Cl\}_2]$ were both active catalysts (Table 2, entries 3 and 4). Changing the base from K_2CO_3 to potassium acetate (KOAc) slightly improved the yield of the reaction (Table 2, entry 4 versus 5). Heating the reaction mixture at 110 °C instead of 90 °C did not improve the yield (Table 2, entry 5 versus 6). The best overall yield of **42** was 19% over four steps from tyrosine **32**, obtained under the following conditions: $[\{Pd(allyl)Cl\}_2]$ (5 mol%), KOAc (7 equiv), DMSO (0.02 M), 90 °C, 1.5 h. Notably, this result meant that the average yield for each of the four steps, including the macrocyclization, was higher than 66%.

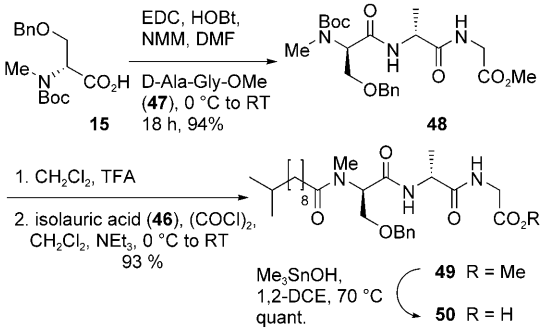
Preparation of the peptidic side chain: Though isolauric acid (**46**) is commercially available, its prohibitive price prompted us to develop a scalable synthesis. Our approach features a key copper-catalyzed coupling reaction between a Grignard reagent and an alkyl bromide and is shown in Scheme 9. Grignard reagent, freshly prepared in situ from 1-



Scheme 9. Preparation of isolauric acid (**46**).

bromo-3-methylbutane (**43**) and magnesium, coupled smoothly with ethyl-7-bromoheptanoate (**44**) in the presence of a catalytic amount of CuCl and excess of NMP[34] to afford the ethyl ester **45** in 72% yield. This reaction, developed by Cahiez et al.,[51] was highly chemoselective and could easily be performed on a multigram scale. Hydrolysis of **45** under standard conditions (2 N NaOH, EtOH) provided **46** in 93% yield.

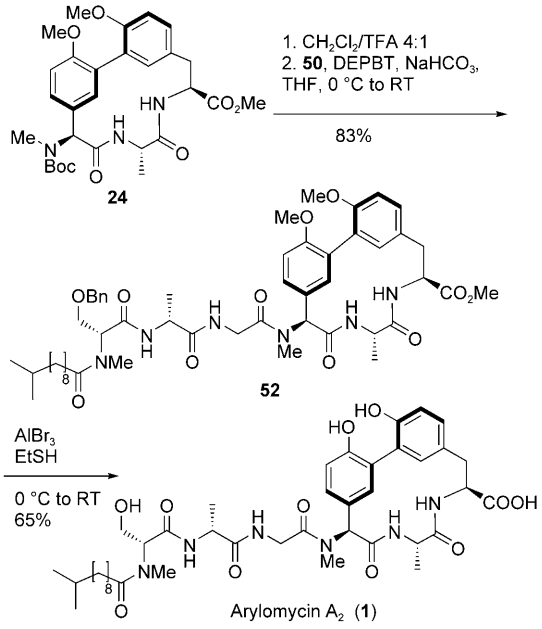
The synthesis of the fully elaborated side chain of the arylomycins is depicted in Scheme 10. Coupling of D-*N*-Boc-(OBn)Ser (**15**) with dipeptide D-Ala–Gly-OMe (**47**) afforded tripeptide **48** in 94% yield. Removal of the *N*-Boc func-



Scheme 10. Preparation of the peptidic side chain **50**.

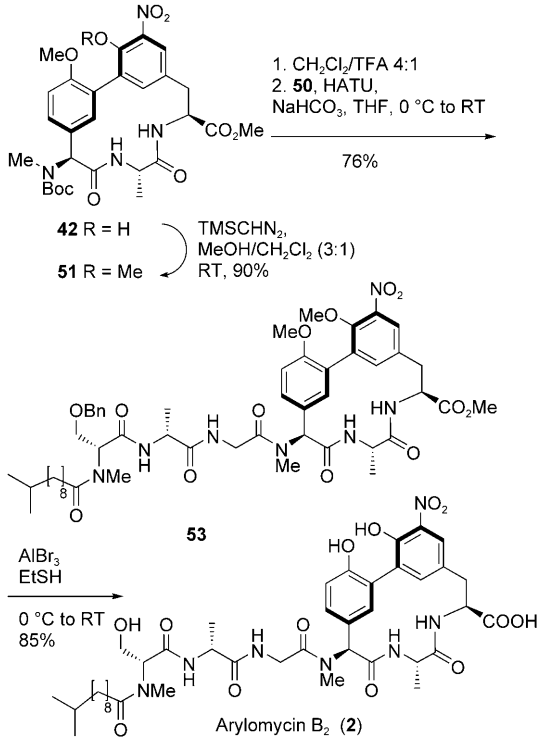
tion (TFA, CH_2Cl_2) followed by acylation with isolauric acyl chloride, generated in situ from **46** and oxalyl chloride in CH_2Cl_2, provided amide **49** in 93% yield. Hydrolysis of methyl ester **49** under standard conditions (2 M LiOH, 1:1 dioxane/H_2O) gave acid **50** in low yield. A close examination of the reaction mixture revealed the presence of benzyl alcohol in the reaction mixture, most probably generated through β-elimination of the serine side chain. Fortunately, performing the hydrolysis in the presence of non-basic Me_3SnOH effectively avoided this side reaction and led to tripeptidic acid **50** in essentially quantitative yield.[50]

Total synthesis of arylomycins A_2 and B_2: Attachment of the side chain **50** to the macrocyclic core and global O-deprotection are the last steps in our syntheses of **1** and **2**. Segment coupling of a sterically hindered secondary amine with a peptide is known to be problematic. One common practice consists of stepwise elongation of the secondary amine by coupling with individual amino acids[52] and this was the strategy employed by Romesberg et al. in their synthesis of **1**.[5] However, we thought that coupling with the whole peptidic side chain **50** could be possible in the present case because the first amino acid residue, Gly, had no encumbering side chain and, consequently, no epimerization problem. Removal of *N*-Boc (TFA, CH_2Cl_2), followed by DEPBT[34]-mediated coupling[53] of the free amine with tripeptide **50** provided hexapeptide **52** in 83% yield (Scheme 11). One-step global deprotection of **52** was realized with an excess of Lewis acid $AlBr_3$ (1 M in CH_2Br_2) in ethanethiol[54] to provide **1** in 65% isolated yield. In this reaction, two methyl ethers, one benzyl ether, and one methyl ester were successfully removed under these push–pull conditions.



Scheme 11. Completion of the total synthesis of arylomycin A_2 (**1**).

By following the same synthetic scheme, the total synthesis of **2** was accomplished as shown in Scheme 12. Coupling performed on the N-deprotected macrocycle **42**, with a free



Scheme 12. Completion of the total synthesis of arylomycin B_2 (**2**).

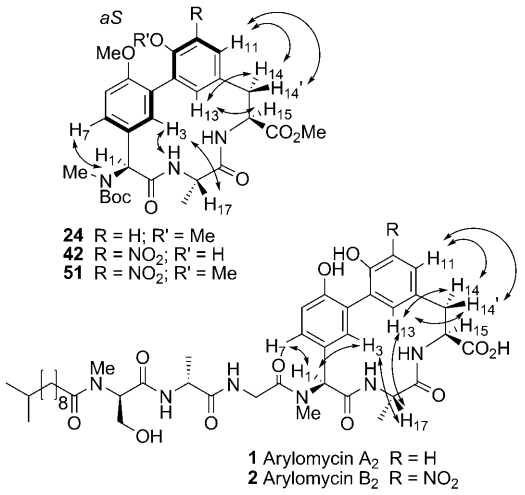
phenol group, proved to be extremely sluggish. Changing the coupling reagent from DEPBT to HATU[34,55] led to a cleaner reaction, but esterification of the phenol took place concurrently. To avoid this undesired side reaction, the free phenol of macrocycle **42** was protected as its methyl ether by reaction with $TMSCHN_2$ to afford **51**. This high-yielding reaction represents an additional step in the synthesis, but ensures a better yield of peptide coupling with the side-chain **50**. Removal of the *N*-Boc group from **51** followed by HATU-mediated segment coupling between the resultant amine and tripeptide **50** afforded the hexapeptide **53** in 76% yield. Global O-deprotection of **53** ($AlBr_3$, EtSH) gave **2** in 85% yield.

The spectroscopic data (^{1}H NMR, ^{13}C NMR, HRMS) of synthetic arylomycins **1** and **2** were identical to those reported for the natural products.[3]

Atropisomerism and conformational studies: Arylomycins **1** and **2** were reported to exist in a conformational equilibrium in solution and up to four sets of signals have been observed in their NMR spectra. Two major sets of signals were assigned to the *cis–trans* isomerization around the tertiary amide that links *N*-Me-Ser to the fatty acid. The presence of

a second tertiary amide (*N*-Me-Hpg) could be responsible for the two other sets of signals, however, due to restricted rotation of the biaryl bond across the 14-membered macrocycle, atropisomerism may also be anticipated. In the solid state, compound **1**, when bound to its target, was found to present the *aS* configuration at the biaryl axis.

Macrocycles **24**, **42**, and **51** (Scheme 13) displayed two distinguishable sets of signals in a 2:1 ratio in their ^{1}H NMR spectra in $CDCl_3$. The alpha protons of the arylglycine resi-



Scheme 13. NOE effects in macrocycles **24**, **42**, and **51** and arylomycins A_2 (**1**) and B_2 (**2**).

dues were especially affected; they appeared at $\delta = 5.93$ and 5.61 ppm for compound **24** and $\delta = 5.94$ and 5.61 ppm for compound **42**. To understand the nature of these two isomers, NOESY spectra were recorded and selected cross peaks are indicated in Scheme 13. It is interesting to note that NOE cross peaks between H7 and H1 and between H13 and H15, characteristic of the *aS* configuration at the biaryl axis, were observed for both pairs. Therefore, we concluded that all three compounds existed in solution as a single atropisomer and that the two sets of signals observed in the ^{1}H NMR spectra were due to the presence of rotamers of the external tertiary carbamate.

NOESY spectra were also recorded for **1** and **2**. It was found that both H7 and H3 strongly correlated with H1. In addition, equally intense cross peaks between H13 or H11 and the two H14 protons were also present. Such NOEs were inconsistent with the presence of a single atropisomer and it was concluded that the arylomycins existed in solution as a mixture of two rapidly interconverting atropisomers.

Conclusion

We have accomplished the total syntheses of arylomycins A_2 (**1**) and B_2 (**2**), two members of a new and promising family of antibiotics that are potent SPase I inhibitors. Arylomycin **1** was obtained in 13 steps for the longest linear sequence from L-Tyr in 13% overall yield, whereas **2** was synthesized in 10 steps from L-3-NO_2-Tyr with 10% overall yield. An intramolecular Suzuki–Miyaura reaction was employed as a key step for the construction of the strained 14-membered *meta,meta*-cyclophanes. Other key features of our approach are 1) the incorporation of *N*-Me-Hpg into the macrocyclization precursor, which avoids the low-yielding *N*-methylation of the macrocycle; 2) the convergent segment coupling of a fully elaborated peptidic side chain to the macrocycle. The finding that cyclophanes **24**, **42**, and **51** existed in solution as single *aS* atropisomers, the bioactive conformer of the natural products, provided useful direction for the future development of simpler and more effective SPase I inhibitors based on this family of natural products.

Experimental Section

General information: ^{1}H NMR spectra were recorded at 300 or 500 MHz on Bruker AC-300 or AC-500 spectrometers, respectively. ^{13}C NMR spectra were similarly recorded at 75 or 125 MHz (broadband-decoupled mode) with the multiplicities obtained by using a JMOD or DEPT sequence. ^{1}H and ^{13}C NMR chemical shifts (δ) are reported in parts per million (ppm) relative to residual proton signals in $CDCl_3$ ($\delta = 7.26$, 77.16 ppm), CD_3OD ($\delta = 3.31$, 49.00 ppm), or [D_6]DMSO ($\delta = 2.50$, 39.52 ppm). Coupling constants (J) are reported in Hertz (Hz) and refer to apparent multiplicities. The following abbreviations are used for the multiplicities: singlet (s), doublet (d), triplet (t), quartet (q), quintet (qu), multiplet (m), broad (br). Melting points (m.p.) were recorded on a Büchi B-540 melting-point apparatus. Optical rotations were measured on a Jasco P-1010 polarimeter in 10 cm cells at the sodium-D line (589 nm), in the solvent and at the concentration and temperature indicated. Infrared spectra were recorded on a Perkin–Elmer Spectrum BX FT-IR spectrometer. Mass spectra were recorded on an AEI MS-9 by positive or negative electrospray ionization (ES^+ or ES^-); HRMS were obtained by MALDI-TOF. Elemental analyses were performed on a CHN 2400 Perkin–Elmer analyzer (carbon, hydrogen, nitrogen). Flash chromatography was performed with SDS silica gel 60 (35–70 μm). TLC was carried out on 5×20 cm plates with a layer thickness of 0.25 mm (SDS Silica gel 60 F254). Preparative TLC was carried out on 20×20 cm glass support plates with a layer thickness of 0.25 or 0.5 mm (SDS Silica gel 60 F_{254}). All reagents were obtained from commercial suppliers unless otherwise stated. When necessary, organic solvents were dried and/or distilled prior to use. When needed, solvents were degassed by freeze-drying. All reactions requiring anhydrous conditions were performed in flame- or oven-dried apparatus under an argon atmosphere.

Compound 24: Under argon, $NaHCO_3$ (43.6 mg, 518.7 μmol, 7 equiv) and [$PdCl_2$(SPhos)$_2$] (3.7 mg, 3.7 μmol, 5 mol%) were added successively to a degassed solution of **22** (60.0 mg, 74.1 μmol) in toluene (3.60 mL) and water (0.12 mL). The reaction was heated to 90°C and stirred for 2 h. The reaction mixture was cooled, diluted with aqueous saturated NH_4Cl solution, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was filtered by a short flash-column chromatography (Al_2O_3, 2:1 EtOAc/heptane). Final purification by preparative TLC (SiO_2, 20:1 CH_2Cl_2/MeOH) afforded the title compound **24** as a white solid (22.2 mg, 54%) and **25** as a colorless foam (3.7 mg, 9%). R_f = 0.48 (2:1 EtOAc/heptane); m.p. 146–148°C; $[\alpha]_D^{26} = +44$ ($c = 1.1$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 2:1 mixture of rotamers): δ = 7.20–7.25 (m, 1H), 6.98 (d, $J = 8.4$ Hz, 1H), 6.94 and 6.93 (d, $J = 8.5$ Hz, 1H), 6.85 (d, $J = 8.4$ Hz, 1H), 6.78 and 6.73 (s, 1H), 6.75 and 6.68 (s, 1H), 6.34–6.27 (m, 1H), 6.26 and 6.21 (d, $J = 8.5$ Hz, 1H), 5.93 and 5.61 (s, 1H), 4.95–

4.87 (m, 1H), 4.77–4.67 (m, 1H), 3.83 (s, 3H), 3.82 and 3.81 (s, 6H), 3.58–3.47 (m, 1H), 3.05 and 3.04 (dd, $J=15.9$, 6.9 Hz, 1H), 2.71 and 2.70 (s, 3H), 1.51 and 1.49 (brs, 9H), 1.42–1.37 ppm (m, 3H); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 1:1 mixture of rotamers): $\delta=9.06$–9.01 (m, 1H), 8.37 and 8.31 (d, $J=8.3$ Hz, 1H), 7.24–7.11 (m, 2H), 7.10–7.05 (m, 1H), 7.00 (d, $J=8.5$ Hz, 1H), 6.70–6.60 (m, 2H), 5.92 and 5.74 (s, 1H), 4.91–4.79 (m, 1H), 4.78–4.65 (m, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.70 (s, 3H), 3.33–3.27 (m, 1H, overlaps with solvent), 3.07–2.96 (m, 1H), 2.53 (s, 3H, overlaps with solvent), 1.44 and 1.41 (s, 9H), 1.18 ppm (d, $J=6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers): $\delta=172.2$, 171.8, 171.0, 158.6, 156.8 and 156.7 (1C), 155.9, 134.8, 134.3, 129.7, 128.7, 128.6, 128.4, 127.1, 126.5, 111.8, 111.6, 80.0, 62.6 and 61.2 (1C), 55.9 (2C), 52.8, 52.6, 49.6 and 49.5 (1C), 34.3, 31.8, 28.5 and 28.3 (3C), 19.6 ppm; IR (neat) $\tilde{\nu}=3280$, 2361, 1745, 1694, 1649, 1509, 1440, 1367, 1272, 1254, 1148 cm^{-1}; HRMS (ES$^+$): m/z: calcd for $C_{29}H_{37}N_3O_8Na$: 578.2478 $[M+Na]^+$; found: 578.2490.

Compound 52: At 0°C, TFA (0.1 mL) was slowly added to a solution of **24** (25.0 mg, 45.0 μmol) in CH_2Cl_2 (0.4 mL). The solution was allowed to warm to RT and stirred for 2 h. The solvent was evaporated and the residue was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ solution, and concentrated under reduced pressure to yield the free amine, which was used in the next step without purification. At 0°C, acid **50** (35.1 mg, 67.5 μmol, 1.5 equiv), DEPBT (21.6 mg, 72.2 μmol, 1.6 equiv), and $NaHCO_3$ (3.8 mg, 45.0 μmol, 1.0 equiv) were successively added to a solution of the amine in THF (0.3 mL). The resulting mixture was allowed to warm to RT and stirred for 18 h. The reaction was concentrated under reduced pressure and the residue was dissolved in EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash-column chromatography (SiO_2, 28:1 CH_2Cl_2/MeOH) afforded **52** as a white solid (36.0 mg, 83%). $R_f=0.39$ (28:1 CH_2Cl_2/MeOH); m.p. 181–184°C; $[\alpha]_D^{24}=+106$ ($c=1.0$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.36$–7.26 (m, 5H), 7.17 (brs, 1H), 7.12 (d, $J=8.7$ Hz, 1H), 7.09 (d, $J=7.4$ Hz, 1H), 6.99 (d, $J=8.4$ Hz, 1H), 6.93 (d, $J=8.7$ Hz, 1H), 6.85 (d, $J=8.4$ Hz, 1H), 6.81 (brs, 1H), 6.73 (brs, 1H), 6.61 (d, $J=8.1$ Hz, 1H), 6.43 (d, $J=6.8$ Hz, 1H), 6.31 (s, 1H), 5.29 (t, $J=6.6$ Hz, 1H), 4.99–4.91 (m, 1H), 4.76–4.67 (m, 1H), 4.60 (d, $J=11.8$ Hz, 1H), 4.57–4.51 (m, 1H), 4.48 (d, $J=11.8$ Hz, 1H), 4.17 (dd, $J=17.8$, 3.7 Hz, 1H), 4.09 (dd, $J=17.8$, 3.7 Hz, 1H), 3.73 (dd, $J=10.3$, 6.6 Hz, 1H), 3.84–3.78 (m, 1H), 3.84 (s, 3H), 3.81 (brs, 6H), 3.55 (dd, $J=15.9$, 3.8 Hz, 1H), 3.05 (dd, $J=15.9$, 7.6 Hz, 1H), 2.97 (s, 3H), 2.81–2.79 (brs, 3H), 2.39–2.31 (m, 2H), 1.67–1.58 (m, 2H), 1.51 (septet, $J=6.6$ Hz, 1H), 1.37 (d, $J=6.8$ Hz, 3H), 1.32 (d, $J=7.0$ Hz, 3H), 1.34–1.20 (m, 10H), 1.18–1.11 (m, 2H), 0.86 ppm (d, $J=6.6$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=174.6$, 172.1, 171.9, 171.8, 170.0, 169.2, 169.1, 157.1, 156.0, 137.6, 135.1, 134.1, 129.6, 128.9, 128.8, 128.4, 128.2, 127.8, 127.8, 127.1, 125.7, 112.0, 111.6, 73.1, 67.2, 60.1, 56.3, 55.9 (2C), 52.8, 52.5, 49.7, 48.7, 41.8, 39.0, 34.3, 33.7, 32.5, 31.7, 29.9, 29.7, 29.6, 29.4, 28.0, 27.4, 25.0, 22.7, 19.5, 18.4 ppm; IR (neat): $\tilde{\nu}=3296$, 2926, 1747, 1634, 1509, 1410, 1271, 1134, 1031, 803 cm^{-1}; HRMS (ES$^+$): m/z: calcd for $C_{52}H_{72}N_6O_{11}Na$: 979.5157 $[M+Na]^+$; found: 979.5164.

Arylomycin A_2 (1): Under argon, at 0°C, $AlBr_3$ (1M in CH_2Br_2, 271.6 μL, 271.6 μmol, 20 equiv) was added slowly to a solution of **52** (13.0 mg, 13.6 μmol) in EtSH (0.7 mL). The solution was allowed to warm to RT and stirred for 6 h. The volatile components were evaporated under reduced pressure and the residue was taken up in a minimum of CH_2Cl_2 and quenched by a few drops of MeOH at 0°C. Purification by preparative TLC (SiO_2, 9:2.5:1 EtOAc/MeOH/H_2O) and preparative reverse-phase HPLC (SunFire C_{18}, 19×150 mm, H_2O+0.1% TFA/CH_3CN+0.1% TFA 60:40, 28 mL min^{-1}; retention time (t_R)=14 min) afforded **1** as a white solid (7.3 mg, 65%). $R_f=0.40$ (9:2.5:1 EtOAc/MeOH/H_2O); m.p. > 200°C, decomposition; $[\alpha]_D^{24}=+29$ ($c=0.3$, MeOH); ^{1}H NMR (500 MHz, MeOD, 1:6.4 mixture of isomers, hydrogen atoms of the amides were partially exchanged): $\delta=8.91$ (d, $J=8.0$ Hz, 1H), 8.61 (d, $J=8.1$ Hz, 1H), 8.17–8.05 (m, 2H), 7.23 and 8.13 (d, $J=8.3$ Hz, 1H), 7.11 (d, $J=8.3$ Hz, 1H), 7.03 (brs, 1H), 7.00 (brs, 1H), 6.96 (d, $J=8.4$ Hz, 1H), 6.87 (d, $J=8.4$ Hz, 1H), 6.35 and 5.87 (s, 1H), 4.99–4.94 (m, 1H), 4.57–4.51 (m, 2H, overlaps with solvent), 4.56–4.46 (m, 1H), 4.25 (d, $J=17.1$ Hz, 1H), 4.08–4.00 (m, 2H), 3.95–3.85 (m, 1H), 3.46–3.36 (m, 1H), 3.16–3.07 (m, 1H), 3.11 and 2.89 (s, 3H), 2.80 and 2.76 (s, 3H), 2.57–2.42 (m, 2H), 1.67–1.58 (m, 2H), 1.52 (septet, $J=6.6$ Hz, 1H), 1.41 (d, $J=7.0$ Hz, 3H), 1.35 (d, $J=6.6$ Hz, 3H), 1.42–1.26 (m, 10H), 1.21–1.15 (m, 2H), 0.88 ppm (d, $J=6.6$ Hz, 6H); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 1:3.1 mixture of isomers): $\delta=12.81$ (brs, 1H), 9.69 (brs, 2H), 9.07–8.95 and 8.35–8.27 (m, 1H), 8.62–8.54 (m, 1H), 8.03–7.87 (m, 2H), 7.14 and 7.10 (d, $J=7.8$ Hz, 1H), 6.98 (d, $J=8.5$ Hz, 1H), 6.95 and 6.93 (brs, 1H), 6.91–6.80 (m, 3H), 6.29 and 5.85 (s, 1H), 5.03–4.98 and 4.91–4.84 (m, 1H), 4.97 and 3.44 (dd, $J=8.2$, 5.8 Hz, 1H), 4.83–4.73 (m, 1H), 4.69–4.61 (m, 1H), 4.41–4.30 (m, 1H), 4.20 and 4.02 (d, $J=17.3$ Hz, 1H), 3.96 (dd, $J=17.3$, 4.4 Hz, 1H), 4.85–4.74 (m, 1H), 3.71–3.62 (m, 1H), 3.28–3.20 (m, 1H), 3.16–3.07 (dd, $J=16.7$, 12.1 Hz, 1H), 2.93 and 2.76 (s, 3H), 2.69 and 2.63 (s, 3H), 2.39–2.27 (m, 2H), 1.56–1.45 (m, 3H), 1.25 (d, $J=7.3$ Hz, 3H), 1.32–1.20 (m, 10H), 1.18 (d, $J=6.7$ Hz, 3H), 1.18–1.11 (m, 2H), 0.85 ppm (d, $J=6.6$ Hz, 6H); ^{13}C NMR (125 MHz, [D$_6$]DMSO, mixture of isomers): $\delta=173.1$, 173.0, 171.9, 171.4, 169.7, 168.9, 168.6, 152.9, 151.8, 133.7, 130.2, 129.1 and 129.0 (1C), 128.7, 127.8, 127.1, 126.0, 125.6, 116.9 and 116.8 (1C), 116.4 and 116.2 (1C), 59.1, 59.0, 58.1, 50.8, 48.0 and 48.1 (1C), 47.4, 40.8, 38.5, 32.9 and 32.8 (1C), 32.4, 31.7 and 31.5 (1C), 31.2, 29.3, 29.0 and 28.9 (1C), 28.8, 28.7 and 28.6 (1C), 27.3, 26.8, 24.8, 22.5, 19.1 and 19.0 (1C), 18.2 and 18.1 ppm (1C); IR (neat): $\tilde{\nu}=3278$, 2926, 1644, 1658, 1506, 1454, 1413 1200, 1140, 799, 723 cm^{-1}; HRMS (ES$^-$): m/z: calcd for $C_{42}H_{59}N_6O_{11}$: 823.4242 $[M-H]^-$; found: 823.4269; HPLC (SunFire C_{18}, 5 μm, 3×150 mm, H_2O+0.1% TFA/CH_3CN+0.1% TFA 60:40, 0.7 mL min^{-1}): $t_R=17.7$ min.

Compound 42: Under argon, KOAc (34.9 mg, 355.6 μmol, 7.0 equiv), bis(neopentylglycolato)diboron (23.0 mg, 101.6 μmol, 2.0 equiv), and Pd(OAc)$_2$ (0.6 mg, 2.5 μmol, 5 mol%) were added to a solution of **32** (24.0 mg, 50.8 μmol) in degassed DMSO (1.0 mL). The resulting mixture was heated at 90°C for 2 h, then allowed to cool to RT and poured into water (5 mL). The aqueous layer was carefully acidified to pH 2–3 by addition of aqueous HCl (0.1M) then extracted with EtOAc. The combined organic layers were washed with a saturated aqueous NH_4Cl solution, brine, and water, then dried over Na_2SO_4 and concentrated under reduced pressure. Filtration through Celite afforded the boronic ester **46** as a brown residue (23 mg), which was used in the next step without further purification.

At 0°C, TFA (0.1 mL) was added slowly to a solution of the crude boronic ester **46** in CH_2Cl_2 (0.4 mL). The solution was allowed to warm to RT and stirred for 2 h. The solvent was evaporated under reduced pressure. At 0°C, EDC·HCl (14.6 mg, 76.2 μmol, 1.5 equiv), HOAt (10.4 mg, 76.2 μmol, 1.5 equiv), acid **39** (25 mg, 50.8 μmol, 1.0 equiv), and $NaHCO_3$ (5.1 mg, 61.0 μmol, 1.2 equiv) were added successively to a solution of the residue in DMF (0.5 mL). The resulting mixture was allowed to warm to RT and stirred for 18 h. The aqueous layer was carefully acidified to pH 3–4 by addition of aqueous HCl (0.1M) and extracted with EtOAc. The combined organic layers were washed with aqueous HCl (0.1M), saturated aqueous NH_4Cl solution, and brine, then dried and concentrated under reduced pressure to afford a crude brown oil (43.0 mg), which was used without purification in the next step.

Under argon, KOAc (34.9 mg, 355.6 μmol, 7.0 equiv) and [{Pd(allyl)Cl}$_2$] (0.9 mg, 2.5 μmol, 5 mol%) were added successively to a solution of the previous crude product in degassed DMSO (2.8 mL). The flask was purged with argon, heated to 90°C, and stirred at this temperature for 2 h. The reaction mixture was cooled and partitioned between EtOAc and water. The aqueous layer was carefully acidified to pH 2–3 by addition of aqueous HCl (0.1M) and extracted with EtOAc. The combined organic layers were washed with a saturated aqueous NH_4Cl solution, water, and brine, then dried and concentrated under reduced pressure. Purification by preparative TLC (SiO_2, 2:1 EtOAc/heptane) afforded **42** as a yellow solid (5.6 mg, 19% over 4 steps). $R_f=0.42$ (2:1 EtOAc/heptane); m.p. 236–237°C; $[\alpha]_D^{25}=+94$ ($c=0.5$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 1:2.3 mixture of rotamers): $\delta=10.77$ and 10.75 (s, 1H), 7.81 (s, 1H), 7.31 (dd, $J=8.5$, 1.9 Hz, 1H), 7.12 and 7.06 (s, 1H), 6.99 and 7.00 (d, $J=8.5$ Hz, 1H), 6.76 and 6.73 (d, $J=1.9$ Hz, 1H), 6.48 and 6.43 (d, $J=6.2$ Hz, 1H), 6.27 and 6.23 (d, $J=8.5$ Hz, 1H), 5.94 and 5.61 (s, 1H), 4.89–4.81 (m, 1H), 4.83–4.75 (m, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.61 and 3.57 (dd, $J=15.2$, 4.3 Hz, 1H), 3.09 (dd, $J=15.2$, 6.6 Hz, 1H), 2.71 (s,

3H), 1.51 and 1.49 (brs, 9H), 1.41 and 1.40 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers): $\delta=172.7$, 171.1 and 171.0 (1C), 170.8, 156.8, 156.7, 151.8, 142.4 and 142.2 (1C), 134.5 and 134.2 (1C), 133.9, 131.1, 130.8, 127.5, 126.8, 125.8, 124.0, 112.1, 80.4 and 80.3 (1C), 62.5 and 61.0 (1C), 56.3, 53.2, 52.9 and 52.8 (1C), 49.4 and 49.3 (1C), 34.3 and 34.2 (1C), 31.8 and 31.7 (1C), 28.4, 19.7 and 19.5 ppm (1C); IR (neat): $\tilde{\nu}=3276$, 2975, 1692, 1644, 1538, 1510, 1316, 1273, 1147, 1029 cm^{-1}; HRMS (ES$^+$): m/z: calcd for $C_{28}H_{34}N_4O_{10}Na$: 609.2173 $[M+Na]^+$; found: 609.2173.

Compound 51: Under argon, at RT, $TMSCHN_2$ (2 M in hexanes, 31 μL, 61.3 μmol, 2 equiv) was added slowly to a solution of phenol **42** (18.0 mg, 30.7 μmol) in 3:1 CH_2Cl_2/MeOH (80 μL). After stirring for 2 h, the solvents were evaporated under reduced pressure. Purification by flash-column chromatography (SiO_2, 1:1 EtOAc/heptane) afforded **51** as a white solid (17.8 mg, 97%). $R_f=0.42$ (2:1 EtOAc/heptane); m.p. 210°C; $[\alpha]_D^{26}=+96$ ($c=1.5$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 1:1.9 mixture of rotamers): $\delta=7.46$ (s, 1H), 7.32 (br d, $J=8.1$ Hz, 1H), 7.00–6.89 (m, 2H), 6.75 (brs, 1H), 6.40 and 6.35 (d, $J=5.9$ Hz, 1H), 6.26 and 6.21 (d, $J=8.4$ Hz, 1H), 5.94 and 5.60 (s, 1H), 4.96–4.88 (m, 1H), 4.81–4.70 (m, 1H), 3.85 (brs, 6H), 3.68 and 3.67 (s, 3H), 3.70–3.56 (m, 1H), 3.10 (dd, $J=14.8$, 5.8 Hz, 1H), 2.68 (s, 3H), 1.51 and 1.49 (brs, 9H), 1.41 and 1.40 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers): $\delta=172.6$ and 172.5 (1C), 171.1 and 171.0 (1C), 170.7, 156.7, 156.4 and 155.7 (1C), 150.1, 143.8, 139.1 and 138.8 (1C), 134.8 and 134.7 (1C), 134.4 and 134.1 (1C), 131.2 and 131.1 (1C), 130.3 and 130.2 (1C), 127.5 and 127.0 (1C), 126.8 and 126.6 (1C), 124.3, 111.8, 80.4 and 80.3 (1C), 62.5 and 61.0 (1C), 61.6, 55.9, 53.2, 52.3 and 52.2 (1C), 49.5 and 49.4 (1C), 34.3 and 34.2 (1C), 31.5 and 31.4 (1C), 28.5, 19.7 and 19.6 ppm (1C); IR (neat): $\tilde{\nu}=3287$, 2976, 1743, 1692, 1535, 1509, 1367, 1255 cm^{-1}; HRMS (ES$^+$): m/z: calcd for $C_{29}H_{36}N_4O_{10}Na$: 623.2329 $[M+Na]^+$; found: 623.2322.

Compound 53: At 0°C, TFA (50.0 μL) was slowly added to a solution of **51** (12.0 mg, 20.0 μmol) in CH_2Cl_2 (150 μL). The solution was allowed to warm to RT and stirred for 2 h before the solvent was evaporated under reduced pressure. At 0°C, acid **50** (15.6 mg, 30.0 μmol, 1.5 equiv), HATU (15.2 mg, 40.0 μmol, 2.0 equiv), and $NaHCO_3$ (8.4 mg, 100.0 μmol, 5.0 equiv) were successively added to a solution of the residue in THF (200 μL). The resulting mixture was allowed to warm to RT and stirred for 18 h. The solvent was removed under reduced pressure and the residue was taken up in EtOAc. The organic layer was washed with saturated $NaHCO_3$ aqueous solution, aqueous HCl (0.5 M), and brine, then dried over Na_2SO_4 and concentrated under reduced pressure. Purification by preparative TLC (SiO_2, 15:1 CH_2Cl_2/MeOH) afforded **53** as a white solid (15.3 mg, 76%). $R_f=0.18$ (20:1 CH_2Cl_2/MeOH); m.p. 138–140°C; $[\alpha]_D^{21}=+94$ ($c=1.2$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.46$ (s, 1H), 7.36–7.26 (m, 6H), 7.19 (d, $J=7.9$ Hz, 1H), 7.13 (d, $J=6.6$ Hz, 1H; NH), 6.97 (s, 1H), 6.96 (d, $J=7.9$ Hz, 1H), 6.87 (brs, 1H; NH), 6.79 (brs, 1H), 6.63 (brs, 1H; NH), 6.35 (s, 1H), 5.31–5.26 (m, 1H), 5.00–4.95 (m, 1H), 4.81–4.72 (m, 1H), 4.63–4.58 (m, 1H), 4.59 (d, $J=11.7$ Hz, 1H), 4.47 (d, $J=11.7$ Hz, 1H), 4.18–4.13 (m, 2H), 3.91–3.79 (m, 2H), 3.86 (s, 3H), 3.83 (brs, 3H), 3.69 (s, 3H), 3.64 (dd, $J=15.7$, 3.3 Hz, 1H), 3.11 (dd, $J=15.7$, 7.2 Hz, 1H), 2.97 (s, 3H), 2.82 (s, 3H), 2.39–2.32 (m, 2H), 1.65–1.60 (m, 2H), 1.51 (septet, $J=6.6$ Hz, 1H), 1.36 (d, $J=6.8$ Hz, 3H), 1.36–1.22 (m, 13H), 1.18–1.12 (m, 2H), 0.86 ppm (d, $J=6.6$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=174.6$, 172.6, 172.1, 171.2, 170.0, 169.3, 169.2, 156.7, 150.0, 143.8, 138.8, 137.6, 134.7, 137.6, 130.8, 130.6, 128.4, 127.8, 127.8, 127.0, 127.0, 124.5, 112.0, 73.1, 67.3, 61.6, 59.8, 56.3, 55.9, 53.2, 52.2, 49.4, 48.6, 41.9, 39.0, 34.1, 33.7, 32.5, 31.6, 29.9, 29.6, 29.4, 28.0, 27.4, 25.0, 22.7, 19.5, 18.5 ppm; IR (neat): $\tilde{\nu}=3290$, 2925, 1745, 1636, 1537, 1512, 1411, 1262 cm^{-1}; HRMS (ES$^+$): m/z: calcd for $C_{52}H_{71}N_7O_{13}Na$: 1024.5008 $[M+Na]^+$; found: 1024.5054.

Arylomycin B_2 (2): Under argon, at 0°C, a freshly prepared solution of $AlBr_3$ (1 M in CH_2Br_2, 239.5 μL, 239.5 μmol, 20 equiv) was slowly added to a solution of **53** (12.0 mg, 12.0 μmol) in EtSH (0.6 mL). The solution was allowed to warm to RT and stirred for 6 h. The volatile components were evaporated under reduced pressure and the residue was taken up in a minimum of CH_2Cl_2 and quenched by a few drops of MeOH at 0°C. Purification by preparative TLC (SiO_2, 10:2:1 EtOAc/MeOH/H_2O) and preparative reverse-phase HPLC (SunFire C_{18}, 19×150 mm, H_2O+0.1% TFA/CH_3CN+0.1% TFA 60:40, 28 mL min^{-1}; $t_R=24$ min) afforded **2** as an orange solid (8.6 mg, 83%). $R_f=0.22$ (10:2:1 EtOAc/MeOH/H_2O); m.p. 239–240°C; $[\alpha]_D^{24}=+27$ ($c=0.6$, MeOH); ^{1}H NMR (500 MHz, CD_3OD, 1:8.6 mixture of isomers, acidic protons were exchanged with solvent): $\delta=7.68$ (d, $J=2.0$ Hz, 1H), 7.27 (d, $J=2.0$ Hz, 1H), 7.15 (s, 1H), 7.10 and 7.03 (d, $J=8.3$ Hz, 1H), 6.85 and 6.83 (d, $J=8.3$ Hz, 1H), 6.33 and 5.81 (s, 1H), 4.98–4.93 (m, 1H), 4.92 (q, $J=6.7$ Hz, 1H), 4.56–4.44 (m, 1H), 4.50–4.44 (m, 1H), 4.26 (d, $J=17.0$ Hz, 1H), 4.09–4.00 (m, 1H), 4.05 (d, $J=17.0$ Hz, 1H), 3.92 and 3.88 (dd, $J=11.7$, 8.0 Hz, 1H), 3.38–3.32 (m, 1H), 3.11 and 2.90 (s, 3H), 3.06 (dd, 1H, $J=15.3$, 7.5 Hz, 1H), 2.82 and 2.78 (s, 3H), 2.52–2.47 and 2.47–2.42 (m, 2H), 1.66–1.58 (m, 2H), 1.52 (septet, $J=6.6$ Hz, 1H), 1.44–1.25 (m, 10H), 1.41 (d, $J=7.2$ Hz, 3H), 1.35 (d, $J=6.7$ Hz, 3H), 1.21–1.14 (m, 2H), 0.88 ppm (d, $J=6.6$ Hz, 6H); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 1:3.7 mixture of isomers): $\delta=8.65$ and 8.62 (d, $J=9.2$ Hz, 1H; NH), 8.33 and 8.29 (d, $J=9.2$ Hz, 1H; NH), 7.99–7.87 (m, 2H; NH), 7.44 (brs, 1H), 7.12 and 7.07 (s, 1H), 6.91 and 6.87 (s, 1H), 6.81 (d, $J=8.2$ Hz, 1H), 6.67 and 6.65 (d, $J=8.2$ Hz, 1H), 6.23 and 5.78 (s, 1H), 4.98–4.85 (m, 1H), 4.85–4.75 (m, 1H), 4.54–4.48 (m, 1H), 4.40–4.30 (m, 1H), 4.07–3.92 (m, 2H), 4.84–4.72 (m, 1H), 3.70–3.62 (m, 1H), 3.18–3.12 (m, 1H), 2.95–2.88 (m, 1H), 2.92 and 2.76 (s, 3H), 2.69 and 2.64 (s, 3H), 2.37–2.28 (m, 2H), 1.54–1.44 (m, 3H), 1.32–1.19 (m, 10H), 1.24 (d, $J=6.6$ Hz, 3H), 1.17 (d, $J=6.7$ Hz, 3H), 1.17–1.10 (m, 2H), 0.85 ppm (d, $J=6.6$ Hz, 6H), NH were partially exchanged, OH and COOH were exchanged with solvent; ^{13}C NMR (125 MHz, [D$_6$]DMSO, mixture of isomers): $\delta=173.2$, 173.1, 172.2, 171.2, 169.7, 168.9, 168.6, 161.3, 158.0, 138.5, 134.3, 134.2, 131.9, 127.9, 127.3, 124.6, 124.4, 120.4, 118.1 and 118.0 (1C), 60.9, 60.8 and 59.4 (1C), 59.0, 58.1, 48.6 and 48.1 (1C), 48.1 and 47.7 (1C), 40.8, 38.4, 32.4, 32.5, 31.8, 31.5, 29.3 and 29.0 (1C), 28.9, 28.8, 28.7 and 28.6 (1C), 27.3, 26.7, 24.5, 22.5, 19.0 and 18.8 (1C), 18.2 and 18.0 ppm (1C); IR (neat): $\tilde{\nu}=3384$, 2922, 1644, 1513, 1399, 1261, 1169, 1113, 1033 cm^{-1}; HRMS (ES$^-$): m/z: calcd for $C_{42}H_{58}N_7O_{13}$: 826.4093 $[M-H]^-$; found: 868.4107; HPLC (SunFire C_{18}, 5 μm, 3×150 mm, H_2O+0.1% TFA/CH_3CN+0.1% TFA 60:40, 0.7 mL min^{-1}): $t_R=21.7$ min.

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