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Total Syntheses of the Thiopeptides Amythiamicin C and D

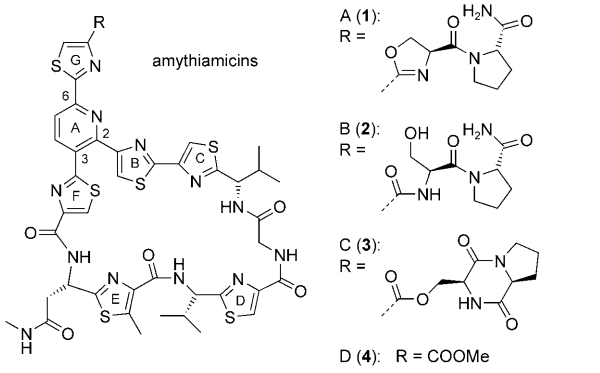
Carolin Ammer and Thorsten Bach*[a]

Abstract: The thiopeptides amythiamicin C and D were synthesized by employing amide bond formation, a Stille cross-coupling reaction, and two Negishi cross-coupling reactions as key transformations. The central 2,3,6-trisubstituted pyridine ring of the target compounds was introduced as a 2,6-dibromo-3-iodopyridine, which was selectively metalated at the 3-position and connected to the complete Southern fragment of the amythiamicins by a Negishi cross-coupling. For the synthesis of amythiamicin C, this step was followed by a Negishi cross-coupling at C-6 of the pyridine core. Subsequent attachment of the Eastern fragment was achieved by amide bond formation and macrolactam ring closure by a Stille cross-coupling at C-2. The Eastern bithiazole fragment of the amythiamins was constructed also by regioselective metalation and cross-coupling reactions. The pivotal step involved the diastereoselective addition of 4-bromothiazole-2-magnesium bromide to a chiral sulfinyl imine. For the synthesis of amythiamicin D, the order of cross-coupling at C-6, amide bond formation, and cross-coupling at C-2 was changed. The amide bond formation to the Eastern fragment was performed first and it was subsequently attempted to close the macrolactam by an intramolecular regioselective Stille cross-coupling at C-2. Despite the low regioselectivity of this reaction it paved the way to the immediate completion of the amythiamicin D synthesis when followed by a Negishi cross-coupling at C-6 with 2-zincated methyl thiazole-5-carboxylate.

Keywords: antibiotics · cross-coupling · macrocycles · natural products · total synthesis

Introduction

Amythiamicins A (**1**), B (**2**), C (**3**), and D (**4**) were isolated in 1994 by Takeuchi et al. from the fermentation broth of *Amycolatopsis* sp. MI481-42F4.[1] The microorganism was found in soil samples collected in Nerima-ku, Tokyo (Japan). The amythiamicins belong to an increasing class of complex naturally occurring, sulfur-containing macrocyclic peptides called thiopeptides or thiazolyl peptides.[2] The structure of the amythiamicins was elucidated by chemical degradation and NMR spectroscopic analysis. Degradation studies were performed by hydrolysis of the individual amythiamicins with 6 N HCl. Subsequent esterification and N-acetylation delivered the *N*-acetyl-*O*-methyl derivatives, which were studied by NMR and UV/Vis spectroscopy.[1] Structurally, all amythiamicins exhibit a trisubstituted pyridine core surrounded by six thiazole moieties, five of which form together with other amino acid fragments a macrolactam ring connecting positions C-2 and C-3 of the pyridine ring. The sixth thiazole ring G is bound by its carbon atom C-2 (thiazole numbering) to carbon atom C-6 of the pyridine (pyridine numbering). The amythiamicins differ in the substituents R at the latter thiazole ring. In amythiamicin D (**4**) the substituent is a plain methoxycarbonyl group. In amythiamicin B (**2**) the substituent is a serine-prolinamide dipeptide, the serine part of which is condensed to an oxazo-



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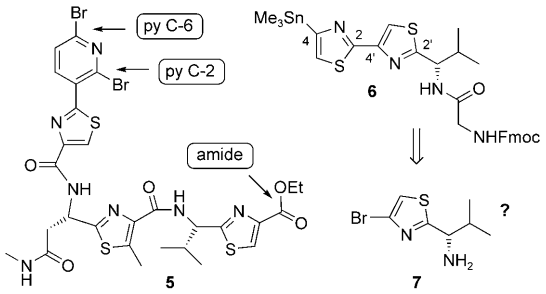
line in amythiamicin A (**1**). Amythiamycin C (**3**) carries the serine-prolinamide fragment as the serine ester with a diketopiperazine being formed between the proline and serine amino acid fragments.

Biological interest in the amythiamicins stems from their inhibition potential toward the bacterial elongation factor EF-Tu.[3] Proof for their antibacterial activity has been obtained already in 1997 by a paper disc diffusion assay.[4] In addition, it was found that the plastid of *P. falciparum*, the metabolism of which is closely related to a bacterium and which is essential for survival of the malaria parasite, is inhibited by amythiamicins, most notably by amythiamicin A ($IC_{50}=10$ nM).[5] Inhibition of EF-Tu is a likely pathway for the mode of action also in this case.

The first total synthesis of an amythiamicin, amythiamicin D (**4**), was achieved by Moody et al. in 2004.[6] The key step was a biomimetic hetero-Diels–Alder reaction of an enamide and an azadiene, which was used for the construction of the central pyridine ring. Nicolaou, Chen et al. reported in 2008 the total syntheses of amythiamicins A–C (**1**–**3**)[7] by employing a key step earlier established for the construction of the central pyridine core of thiostreptone[8] and GE 2270A.[9] In this case, a hetero-Diels–Alder reaction occurred as a 2-azadiene dimerization, which was induced by thermolysis of an appropriate precursor. The formation of the macrocylic ring was in both synthetic approaches to the amythiamicins achieved by macrolactamization, either at the amide bond connecting the glycine to thiazolecarboxylic acid D[6] or at the amide bond connecting the thiazole fragments E and F.[7] Other strategies and total syntheses of thiopeptide antibiotics have been reviewed extensively.[2,10,11] The most notable recent achievement has been the synthesis and stereochemical assignment of micrococcin P1 by Ciufolini and Lefranc, in which the central pyridine ring was constructed by a Hantzsch synthesis.[12]

Our own synthetic work in the area of thiopeptides was triggered by methodology studies concerning the regioselectivity of cross-coupling reactions[13] on certain heterocycles, specifically on pyridines and thiazoles. A strategy for the preparation of 2′,4-disubstituted 2,4′-bithiazoles[14] was implemented in the total synthesis of cystothiazole E and the formal syntheses of cystothiazoles A and C.[15] The regioselective assembly of 2,3,6-trisubstituted pyridines was first probed in the synthesis of a degradation product of GE 2270A, which served to establish the relative configuration of this thiopeptide,[16] and was later employed in its total synthesis.[17] In the latter synthesis, 2,6-dibromo-3-iodopyridine had served as a central ring template to which the individual parts of the thiopeptide were attached. Following this strategy it was anticipated that a similar bond construction was possible also for the synthesis of the amythiamicins (Scheme 1). With compound **5** as a key intermediate it was planned to conduct subsequent reactions at the indicated positions by cross-coupling at the pyridine core and by amide bond formation.

In the synthesis of GE 2270A[17] it was shown that macrolactam ring formation can be favorably achieved after cross-coupling at C-6 (py C-6) and amide bond (amide) formation by an intramolecular Stille cross-coupling (py C-2). Alternatively, one could consider the amide bond formation to be conducted first with a regioselective macrocyclization to follow. Either way, a stannylated fragment, such as **6**, would be required for the synthesis of the amythiamicins. It exhibits an amino-substituted stereogenic center, which would be possibly introduced through the previously unknown building block **7**.



Scheme 1. Key fragments **5**–**7** in the retrosynthetic analysis of amythiamicins C and D according to a regioselective cross-coupling protocol.

In this account we report on the total synthesis of amythiamicins C (**3**) and D (**4**). The synthesis of amythiamicin C (**3**) was accomplished by following the precedented bond-formation sequence (py C-6, amide, py C-2), whereas in the synthesis of amythiamicin D (**4**) the alternative sequence (amide, py C-2, py C-6) was probed. An access to enantiomerically pure compound **7** was established allowing its installation in the bithiazole core of compound **6**. An improved procedure for the preparation of 2,6-dibromo-3-iodopyridine was established and applied to the synthesis of the key intermediate **5**.

Results and Discussion

Preparation of the Southern fragment and cross-coupling to key intermediate 5: The Southern fragment of the amythiamicins consists of three thiazole-containing fragments that are connected by amide bonds. Bond disconnection at these positions leads retrosynthetically to the three fragments **8**, **11**, and **13** depicted in Scheme 2. 2-Iodothiazole **13** contains the iodine atom as a potential leaving group in the cross-coupling event and has been previously prepared.[17b] The syntheses of compounds **8**[18] and **11**[19] are also precedented and start from the respective amino acid derived building blocks **10** and **12**. Monobenzyl ester **10** is obtained in two steps from aspartic acid.[20] *N-tert*-Butoxycarbonyl (Boc)-protected valine (**12**) is commercially available or can be prepared from valine in one step.[21]

The synthesis of valine-based thiazole **11** with a Hantzsch thiazole reaction as a key step proceeded racemization-free as proven by chiral HPLC analysis. However, it was found in the Gabriel synthesis employed for the thiazole bond construction from intermediate **9** that racemization was not

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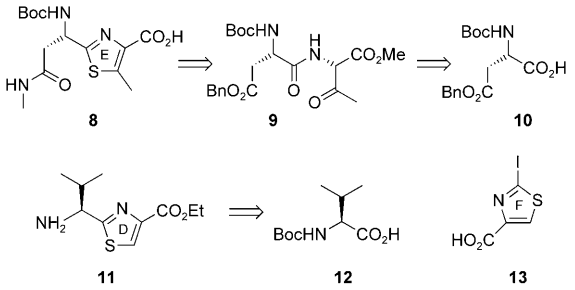
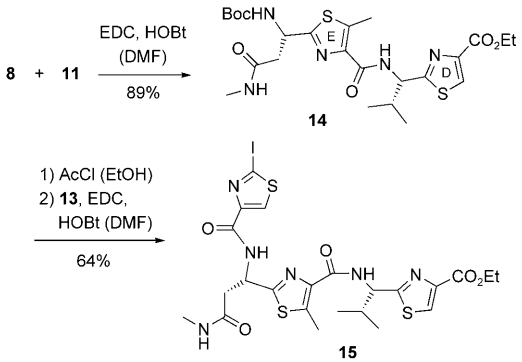


Scheme 2. The three building blocks **8**, **11**, and **13** required for the construction of the Southern fragment of the amythiamicins and their key precursors.

completely suppressed. A closer inspection of the reaction conditions revealed that the quality of the Lawesson reagent was critical to the success of the reaction. With commercially available reagent, which showed an acidic pH of 2, the product was obtained in only 66% *ee*. Recrystallization of the reagent from toluene increased the pH to 6 and the subsequent Gabriel reaction proceeded in 88% *ee*.[22]

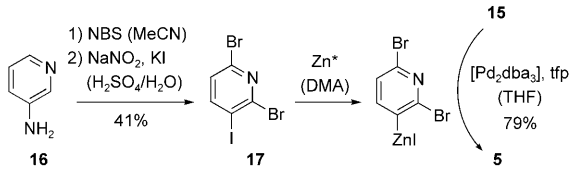
The assembly of the individual building blocks was performed under typical peptide coupling conditions by employing *N*-(3-dimethylaminopropyl)-*N*′-ethyl-carbodiimide hydrochloride (EDC) in the presence of 1-hydroxybenzotriazole (HOBt) as the reagent (Scheme 3).[23] The substrates and reagents were mixed at −10°C and the mixture was subsequently stirred at ambient temperature. Dipeptide **14** was deprotected at its N-terminus under acidic conditions and the coupling to thiazole carboxylic acid **13** proceeded smoothly under the conditions previously employed for the synthesis of **14**.[17] Due to the incomplete enantiomeric purity of asparagine-derived building block **8** (see above), the target compound **15** was contaminated with minor amounts of its epimer. A chromatographic separation of the diastereomers could be achieved at this stage. The yield given in Scheme 3 refers to diastereomerically pure product **15**.

A pivotal step of our synthetic strategy towards the amythiamicins was the connection of the complete Southern fragment **15** to the central pyridine core by a Negishi cross-



Scheme 3. Preparation of the trithiazole **15**, the Southern fragment required for cross-coupling with the pyridine core of the amythiamicins.

coupling. Earlier work had revealed that 2,6-dibromo-3-iodopyridine (**17**) is a superior precursor in the metalation step relative to 2,3,6-tribromopyridine.[17] Selective access to this compound is best achieved from 3-aminopyridine (**16**, Scheme 4).[24] We found the bromination with *N*-bromosuccinimide (NBS) to occur beneficially in acetonitrile relative to tetrachloromethane providing 3-amino-2,6-dibromopyridine in 58% yield. Subsequent iodo-de-amination turned out to proceed smoothly and delivered pyridine **17** in 71% yield (41% overall).



Scheme 4. Preparation of 2,6-dibromo-3-iodopyridine (**17**), its zincation, and cross-coupling to iodothiazole **15**.

Reductive metalation of 3-iodopyridine **17** was performed according to the Knochel protocol[25] in *N*,*N*-dimethyl acetamide (DMA). Zincated iodide underwent a clean Negishi cross-coupling[26] reaction with iodide **15** at 45°C in a solvent mixture of THF/DMA by using $[Pd_2(dba)_3]$/tfp (12 mol% Pd) as the catalyst (dba = dibenzylidenacetone, tfp = tri(2-furyl)phosphane). The effectivity of the Negishi cross-coupling reaction is undermined by the high yield achieved in this reaction. Nonetheless, the process turned out to be somewhat more capricious than previously conducted cross-coupling reactions because starting material **15** and product **5** could not be separated by TLC. The reaction had to be followed by analytical HPLC and the addition of zincated pyridine was required in some instances to make the conversion complete. Along the longest linear sequence starting from known building block **8** diastereomerically pure product **5** was obtained in four steps and an overall yield of 45%.

Preparation of thiazole 7 and the complete bithiazole fragment 6: Based on our previous experience with the generation of a 2-metalated thiazole **18** from 2,4-dibromothiazole (**19**)[27] and based on the plan to set up the 2,4′-connectivity in bithiazole building block **6** by regioselective cross-coupling[16] possible chiral imine equivalents were considered, which would give access to the enantiopure amine **7** (Scheme 5). Since Grignard reagent **18** had been shown to react nicely with nitriles[27] it was expected that it would equally well add to the more electrophilic imines. In a seminal report, oxime ether **20** was described by Moody et al. to react with a 2-lithiated thiazole diastereoselectively.[28] Despite the efficiency of this method, the reductive conditions required for cleavage of the chiral auxiliary (Zn, HOAc) were considered to be incompatible with the bromine atom in the 4-position. The addition of Grignard reagents to chiral sulfinyl imines as described by Ellman et al.[29] offered

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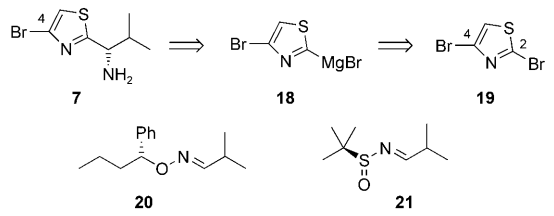
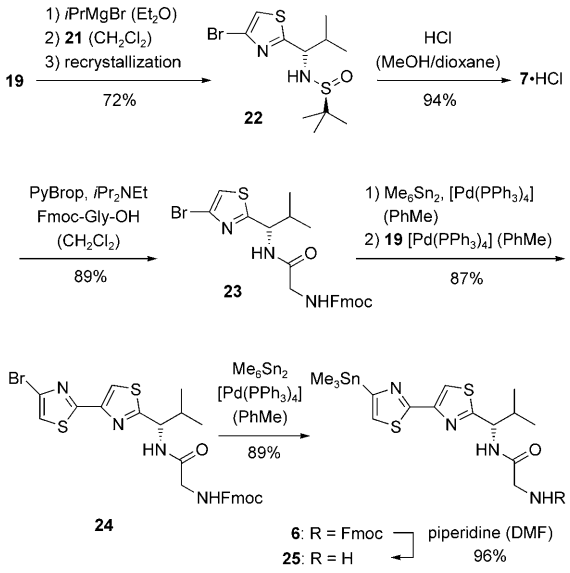


Scheme 5. Retrosynthetic consideration for the construction of product **7** and synthetic equivalents **19** and **20** for a chiral isobutyraldehyde imine.

a viable alternative approach. More specifically, it was envisioned to convert thiazole **19** into the respective Grignard reagent **18**, which would then react with imine **21** in a diastereoselective fashion. While our work was in progress a publication appeared[30] in which it was reported that a diastereoselecitive addition of this kind is possible for related selectively metalated heterocycles, but not referring to our earlier work on the preparation and addition reactions of reagent **18**.

Based on literature precedence, in which phenyl magnesium bromide was added to imine **21** yielding the (*S*)-enantiomeric amine predominantly (diastereomeric ratio d.r. 89:11),[29c] the (*S*)-configured sulfinyl amide was chosen as an auxiliary and condensed with isobutyric aldehyde to yield imine **21**. Grignard reagent **18** was generated from dibromothiazole **19** by regioselective bromine–magnesium exchange[27] and added to a solution of imine **21** in CH_2Cl_2 (Scheme 6). Initial experiments were disappointing delivering the desired addition product **22** with a d.r. slightly above 50:50 irrespective of whether the Grignard reagent was prepared in THF or diethyl ether. It turned out that it was crucial for a high selectivity to increase the concentration of the Grignard reagent in the etheral solvent to as high a level as possible and to maintain a large excess of CH_2Cl_2 in the



Scheme 6. Synthesis of the Eastern fragment **24** of the amythiamicins employing 2,4-dibromothiazole (**19**) as a key building block.

final solvent mixture. It is likely that the tight six-membered transition state responsible for successful chirality transfer[29] is disfavored in coordinating ethereal solvents. Employing a concentrated solution ($c = 2.5$ M) of the Grignard reagent in diethyl ether with an eventual ratio of CH_2Cl_2/diethyl ether 27.5:1 in the reaction mixture, a d.r. of 85:15 was achieved. Upon recrystallization from *tert*-butylmethyl ether and cyclohexane, the desired product **22** was obtained in a diastereomerically pure form (d.r. > 95:5). Cleavage of the auxiliary was achieved by treatment of sulfinyl amine **22** with HCl in a mixture of methanol/dioxane delivering the hydrochloride of amine **7**. The absolute configuration of the amine was proven by *N*-Boc protection and debromination. The resulting *N*-Boc protected (*S*)-configured amine is literature known and was reported to be levorotatory.[31] The compound we obtained was also levorotarory and showed a specific rotation in accord with the literature data. The result is in line with the earlier transition-state model for the addition to chiral sulfinyl imines, such as **21**.[29]

Amine **7** was coupled with 9-fluorenylmethyloxycarbonyl (Fmoc)-protected glycine (Fmoc-Gly-OH) by using bromotri(pyrrolidino)phosphonium hexafluorophosphate (PyBrop) as the coupling reagent.[32] For the further assembly of key intermediate **6**, a regioselective Stille reaction[33] with 2,4-dibromothiazole (**19**) was performed[14] upon converting 4-bromothiazole **23** to the respective stannane by a Pd-catalyzed stannyl-debromination with hexamethylditin.[34] For the stannylation, a high temperature (100 °C) and a short reaction time (1.5 h) proved to be beneficial. The brominated dithiazole[35] **24** was subjected to a second stannyl-debromination providing building block **6** in a N-protected form. The overall yield for the transformation of isobutyraldehyde to compound **6** was 47 % over six reaction steps.

Synthesis of amythiamicin D (4): After liberating the carboxylic acid of the Southern fragment **5** by saponification and after *N*-Fmoc deprotection of the amine protecting group in the Eastern fragment **6** (Scheme 6), the two fragments were coupled with diphenylphosphoryl azide (DPPA)[36] and Hünig's base in DMF (Scheme 7). By using a slight excess of amine **25**, the complete peptide backbone **26** of the amythiamicin macrolactam was assembled. Stille cross-coupling reactions were attempted to connect the stannylated bithiazole intramolecularly to the central dibromopyridine core. Cylization reactions were indeed observed, if the reaction was conducted under dilute conditions ($c =$ 1 mM) in toluene. For the separation of the two regioisomers **27** and **28**, the solvent system had to be carefully chosen and the solid phase had to be mixed with potassium fluoride (10 % w/w)[37] to remove any tin impurities.

The constitution assignment of the two regioisomers was based on earlier work,[16] in which we had seen that related 2,3-disubstituted 6-bromopyridines exhibit a strong ^{1}H NMR spectroscopic upfield shift for the protons at C-5 and C-4 relative to the competitively formed 3,6-disubstituted 2-bromopyridines (e.g. $\delta = 7.61$ vs. 8.33 ppm at C-5 and $\delta = 8.27$ vs. 8.54 ppm at C-4). In the present case, one regioisomer

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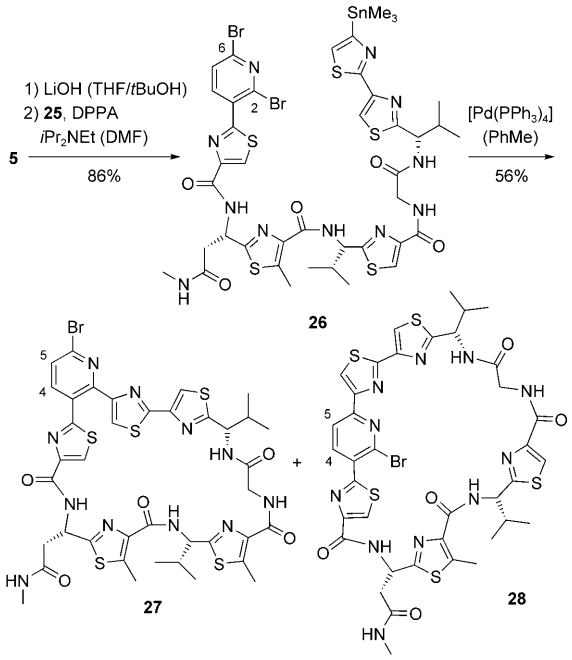
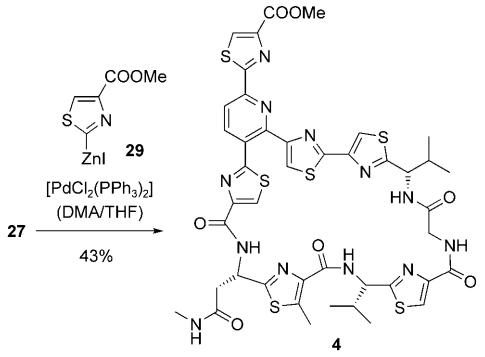


Scheme 7. Intramolecular Stille cross-coupling reaction employing 2,6-dibromopyridine **26** as the starting material.

showed ^{1}H NMR spectroscopic signals for these protons at $\delta = 7.56$ (C-5) and 7.82 ppm (C-4), whereas the other regioiosmer displayed resonances at $\delta = 8.03$ (C-5) and 8.55 ppm (C-4). Structure **28** was consequently assigned to the latter regioisomer and—in agreement with its further conversion into amythiamicin D (see below)—structure **27** to the former regiosiomer. A significant regioselectivity was unfortunately not detected. Both regioisomers formed in almost identical amounts but could be fully separated. The desired regioisomer **27** was so obtained in 28% yield with $[Pd(PPh_3)_4]$ as the catalyst at 85°C in toluene. Apparently, the ring closure at C-2 to the naturally occurring macrolactam, which was considered to be favorable by conformational factors and due to a templating effect by the metal, competes successfully with the sterically favored cross-coupling reaction at C-6. It is, however, not able to dominate the reaction course. Rather, both factors are perfectly balanced. A beneficial aspect of the chosen sequence was the fact that the last cross-coupling reaction proceeded smoothly providing the desired product amythiamicin D in 96% yield.

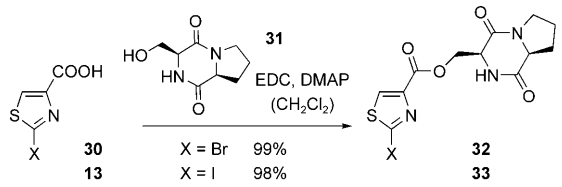
Insufficient separation of minor quantities of triphenylphosphane oxide by flash chromatography forced us to use semipreparative HPLC to obtain a pure sample of the natural product limiting the yield in the final step (Scheme 8) to 43%. Further optimization attempts to find an improved method for the impurity removal were not possible due to the limited material available.

Synthesis of amythiamicin C (3): Although the intramolecular cross-coupling reaction of dibromopyridine **26** was not regioselective, the access to key intermediate **27** was rapid (Scheme 7) and the results regarding the cross-coupling of



Scheme 8. Completion of the total synthesis of amythiamicin D (**4**).

the final thiazole to carbon atom C-6 of the pyridine core were promising (Scheme 8). It was therefore initially considered to attach the complete Northern fragment of amythiamicin C to bromopyridine **27** in a Negishi cross-coupling reaction. The requisite bromo- and iodothiazoles **32** and **33** were readily accessible from the corresponding carboxylic acids **30** and **13** by esterification with known alcohol **31**.[38] A mixture of EDC and *N*,*N*-dimethylaminopyridine (DMAP) turned out to be an excellent reagent combination to achieve this conversion in almost quantitative yields (Scheme 9). Despite extensive experimental effort it was,



Scheme 9. Preparation of the Northern fragments **32** and **33** of amythiamicin C.

however, not possible to convert bromide **32** or iodide **33** into the respective zinc reagent. Decomposition was observed under conditions of direct zincation and halogen–metal exchange. In some instances, the amino alcohol **31** was recovered. *N*-Boc protection of the acidic NH group in the diketopiperazine part of **32** and **33** did not improve the stability of the substrates in the zincation step.

The instability of the complete Northern fragment of amythiamicin C towards zincation made us return to a better precedented[17] strategy for its preparation (Scheme 10). To this end, dibromopyridine **5** was regioselectively coupled with the 2-zincated *tert*-butyl thiazole-5-carboxylate (**34**). It was expected that intermediate **35** would allow for the installation of the Eastern fragment **25** and ring closure as well as—after *tert*-butyl deprotection—for attachment of alcohol **31**.

Indeed, after saponification of ethyl ester **35** to the free carboxylic acid **36** the Eastern fragment **25** could be attached by peptide coupling with DPPA and Hünig's base in

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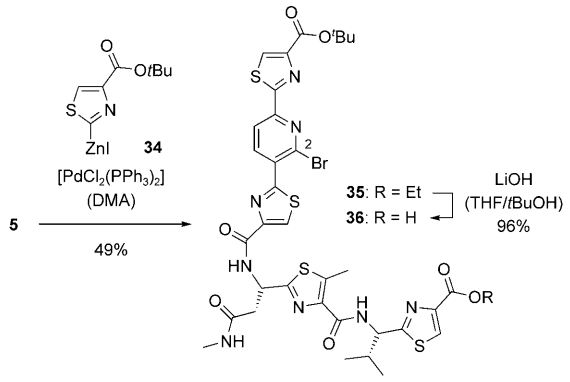
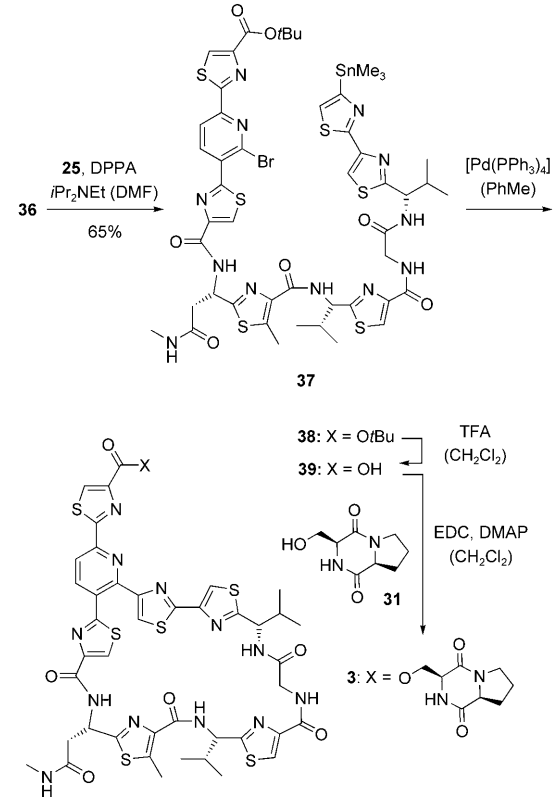


Scheme 10. Regioselective intermolecular Negishi cross-coupling of zinc reagent **34** and 2,6-dibromopyridine **5** and subsequent saponification of product **35**.

DMF. The macrolactam was formed by an intramolecular Stille cross-coupling reaction at the 2-position of pyridine **37** in 79% yield. Subsequent functional-group transformations included the hydrolysis of *tert*-butyl ester **38** and attachment of the diketopiperazine **31** to the free acid **39**. Whereas the ester hydrolysis proceeded uneventfully, the esterification of free acid **39** caused some purification problems (Scheme 11).

Alcohol **31** had to be used in excess (5 equiv) to achieve quantitative conversion to amythiamicin C (**3**), but could not be completely removed by column chromatography



Scheme 11. Completion of the total synthesis of amythiamicin C (**3**).

after work-up. In addition, some phosphane oxide impurities were visible, which had apparently remained from the cross-coupling step. For the sake of purity, we therefore decided to run the reaction without major purification by starting from intermediate **37** and attempted a purification step by HPLC at the end of the three-step sequence. In the purification procedure alcoholic solvents should be avoided because the ester group of amythiamicin C (**3**) is labile towards transesterification. Attempted HPLC purification on a reverse-phase column with $MeOH/H_2O$ as the eluent led to the isolation of amythiamicn D (**4**) but did not lead to any recovery of **3**. The fragility of product **3** did limit the yield, with which it was eventually obtained along the three-step procedure to 20%. Overall, however, the yield of amythiamicn C (**3**) by starting from imine **21** is relatively high with 5.8% over a total of eleven linear steps.

The spectral data of synthetic amythiamicins C (**3**) and D (**4**) matched the reported data perfectly (see the Experimental Section). The spectra of amythiamicin C (**3**) were recorded in $CDCl_3$ instead of the previously used [D_5]pyridine. The former solvent allowed us to re-isolate the material more readily and to employ it for biological tests. Assignments are based on previously reported studies and on the analogy of amythiamicins C (**3**) and D (**4**) in the macrolactam core.

Conclusion

In summary, two approaches were pursued for the synthesis of amythiamicins, both of which rely on regioselective cross-coupling reactions. In the first approach it was attempted to differentiate the 2- and 6-position of a 3-substituted 2,6-dibromopyridine (substrate **26**) by an intramolecular Stille cross-coupling reaction. The reaction turned out to be possible but there was no significant regioselectivity. Cross-coupling reactions were observed at both positions delivering the two regioisomeric products **27** and **28** in moderate yield (56%). Nonetheless, intermediate **27** served as a very useful intermediate for the synthesis of amythiamicin D (**4**) allowing for its total synthesis in only ten steps with 4.5% yield along the longest linear sequence. For amythiamicin C (**3**), a second approach was taken, in which an intermolecular Negishi cross-coupling served to differentiate the 2- and 6-position of a 3-substituted 2,6-dibromopyridine (substrate **5**). By this means the thiazole of the Northern fragment was selectively installed at the 6-position. Subsequent attachment of the Eastern fragment and an intramolecular Stille cross-coupling delivered the desired product, amythiamicin C (**3**), in a highly convergent fashion.

Experimental Section

General: All reactions involving water-sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under argon. THF, diethyl ether (Et_2O), and dichloromethane (CH_2Cl_2) were purified by using

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a SPS-800 solvent purification system (M. Braun). Diisopropylamine was distilled over calcium hydride. All other chemicals were either commercially available or prepared according to the cited references. TLC was performed on silica-coated glass plates (silica gel 60 F_{254}) with detection by UV (254 nm) or $KMnO_4$ (0.5% in water) with subsequent heating. Flash chromatography was performed on silica gel 60 (Merck, 230–400 mesh) with the indicated eluent. Common solvents for chromatography (pentane (P), ethyl acetate (EtOAc), diethyl ether (Et_2O), dichloromethane, methanol (MeOH)) were distilled prior to use. HPLC analyses were performed by using the stationary phases AD-RH Daicel, ODS-A YMC, OD Daicel Chiracell, or AD-H Daicel Chirapak (analytical: 250×4.6 mm, 5 μm; semi-preparative: 250×20 mm, 5 μm) employing *n*-hexane/*i*-propanol, methanol/water, or acetonitrile/water as eluents and UV-detection at 20°C. IR: JASCO IR-4100 (ATR). GCMS: Agilent 6890 instrument with Agilent N7873 mass detection, carrier gas: Helium (method: 60°C, 3 min; 60°C → 300°C, 16 min; 300°C, 5 min). MS/HRMS: Finnigan MAT 8200 (EI)/Finnigan MAT 95S (HR-EI)/Finnigan LCQ classic (ESI)/Thermo Finnigan LTQ FT (HRMS-ESI). ^{1}H and ^{13}C NMR spectra: Bruker AV-250, Bruker AV-360, Bruker AV-500, Bruker AV-600 recorded at 303 K. Chemical shifts are reported relative to tetramethylsilane. The multiplicities of the ^{13}C NMR signal were determined by DEPT experiments, assignments are based on COSY, HMBC, and HMQC experiments. ^{1}H or ^{13}C NMR spectroscopic signals are usually assigned by using significant short sections of the molecular formula. Heteroaromatic and aromatic signals are assigned by using the respective atom numbers according to IUPAC rules and the letters A–F as depicted in the schemes. The symbols $^{\#}$, *, §, and ˜ denote interconvertible assignments. Optical rotations were measured by using a Perkin–Elmer 241 MC Polarimeter. Elemental analyses were carried out on a Elementar Vario EL in the Department Chemie at the Technische Universität München.

Ethyl-(*S*,*S*)-2-{1-[(2-{1-[(2-(2,6-dibromopyridine-3-yl)thiazole-4-carbonyl)-amino]-2-methylcarbamoyl-ethyl}-5-methylthiazole-4-carbonyl)amino]-2-methylpropyl}thiazole-4-carboxylate (5)

Zincation: DMA (0.76 mL) and 1,2-dibromoethane (7.13 μL, 15 mg, 87.7 μmol) were added to a flame-dried flask charged with zinc dust (53 mg, 0.817 mmol). The zinc suspension was shortly heated with a heat gun until evolution of ethylene occurred and then allowed to reach ambient temperature. This procedure was repeated three times. TMSCl (23.8 μL, 20 mg, 0.186 mmol) was added neat and the reaction mixture was stirred for 5 min. 2,6-Dibromo-3-iodopyridine (**17**) (99 mg, 0.272 mmol) dissolved in THF (0.47 mL) was added. The stirring was continued for 30 min at 25°C, then the zinc dust was allowed to settle (30 min).

Negishi cross-coupling: The supernatant liquid containing the zincated dibromopyridine was added to a solution of trithiazole **15** (47 mg, 68.0 μmol), [Pd_2(dba)$_3$] (3.7 mg, 4.08 μmol, 6 mol%), and tfp (47 mg, 68.0 μmol, 12 mol%) in THF (0.51 mL). The reaction mixture was stirred at room temperature (12–24 h) until full conversion was achieved (monitored by HPLC). After quenching with saturated aq. NH_4Cl (4 mL), the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash chromatography (EtOAc) to yield the desired product **5** (43 mg, 53.8 μmol, 79%) as a grey solid. M.p. 113°C; R_f = 0.36 (EtOAc; UV); $[\alpha]_D^{20} = -22.1$ (c = 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 0.98 (d, ^3J = 6.5 Hz, 3H; D: CH(CH_3)$_2$), 1.01 (d, ^3J = 6.8 Hz, 3H; D: CH(CH_3)$_2$), 1.41 (t, ^3J = 7.2 Hz, 3H; D: OCH$_2$CH_3), 2.35–2.44 (m, 1H; D: CH(CH$_3$)$_2$), 2.60 (d, ^3J = 4.7 Hz, 3H; E: NHCH_3), 2.73 (s, 3H; E: C5-CH$_3$), 2.94 (dd, ^2J = 14.8, ^3J = 4.9 Hz, 1H; E: CHHCONHCH$_3$), 3.33 (dd, ^2J = 14.8, ^3J = 4.3 Hz, 1H; E: CHHCONHCH$_3$), 4.41 (q, ^3J = 7.2 Hz, 2H; D: OCH_2CH$_3$), 5.32 (dd, ^3J = 9.0, 8.6 Hz, 1H; D: CH), 5.82 (ddd, ^3J = 8.6, 4.9, 4.3 Hz, 1H; E: CH), 6.85 (q, ^3J = 4.7 Hz, 1H; E: NHCH$_3$), 7.60 (d, ^3J = 8.3 Hz, 1H; A: H-5), 8.11 (s, 1H; D: H-5), 8.36 (s, 1H; F: H-5), 8.52 (d, ^3J = 8.3 Hz, 1H; A: H-4), 8.58 (d, ^3J = 9.0 Hz, 1H; D: NH), 9.48 ppm (d, ^3J = 8.6 Hz, 1H; E: NH); ^{13}C NMR ($CDCl_3$, 90 MHz): δ = 12.5 (q; E: C5-CH_3), 14.3 (q; D: OCH$_2$CH_3), 18.1 (q; D: CH(CH_3)$_2$), 19.1 (q; D: CH(CH_3)$_2$), 26.1 (q; E: NHCH$_3$), 34.5 (d; D: CH(CH$_3$)$_2$), 38.5 (t; E: CH_2CONHCH$_3$), 48.5 (d; E: CH), 56.1 (d; D: CH), 61.6 (t; OCH_2CH$_3$), 126.2 (d; F: C-5), 127.4 (d; D: C-5), 127.7 (d; A: C-5), 130.1 (s; A: C-3), 138.8 (s; A: C-2)*, 141.1 (d; A: C-4), 141.3 (s; A: C-6)*, 141.9 (s; E: C-5)$^{\#}$, 142.1 (s; E: C-4)$^{\#}$, 146.3 (s; D: C-4), 149.6 (s; F: C-4), 160.4 (s; F: CO), 161.4 (s; D: COO), 161.8 (s; F: C-2), 162.1 (s; E: CO), 166.5 (s; E: C-2), 170.7 (s; D: C-2), 171.3 ppm (s; E: CONHCH$_3$); IR (ATR): $\tilde{\nu}$ = 3785 (w; NH), 2346 (m), 1712 (m; CO), 1650 (s; CONH), 1549 (m), 1486 (s; CH), 1367 (m), 1331 (m), 1215 (m), 1163 (m), 1020 (w), 755 cm^{-1} (w); HRMS (ESI): m/z: calcd for $C_{28}H_{30}Br_2N_7O_5S_3$: 797.9837 [$M$+H]$^+$; found: 797.9841.

(*S*)-*N*-[(*S*)-1-(4-Bromothiazole-2-yl)-2-methylpropyl]-2-methylpropan-2-sulfinamide (22)

Imine 21: A suspension of (*S*)-*tert*-butylsulfinamide (1.00 g, 8.25 mmol),[29] isobutyraldehyde (828 μL, 654 mg, 9.07 mmol), and anhydrous cesium carbonate (5.91 g, 18.1 mmol) in CH_2Cl_2 (16.5 mL) was stirred for 16 h at 45°C. The reaction mixture was filtered over a pad of Celite, the filter cake was washed with CH_2Cl_2 (2×5 mL), and the residue purified by flash chromatography (3×15 cm, CH_2Cl_2). The solvent was removed under reduced pressure (400 mbar) to give imine **21**, which was used directly in the diastereoselective addition reaction.

Diastereoselective addition: A solution of isopropylmagnesiumbromide (4.8 mL, 3.45 M in diethyl ether) was added slowly to a stirred solution of 2,4-dibromothiazole (**18**)[39] (4.01 g, 16.5 mmol) in diethyl ether (1.8 mL). After stirring for 30 min at 0°C, the Grignard reagent solution was added to a stirred solution of sulfinyl imine **21** (8.25 mmol) in CH_2Cl_2 (50 mL) at −48°C. After 2 h at −48°C, the reaction mixture was allowed to reach room temperature over a period of 12 h. The reaction was quenched by adding saturated NH_4Cl solution (50 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (2×50 mL) and the combined organic layers were dried with Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (P/EtOAc 1:1→1:2) to yield (2.50 g, 7.36 mmol, 89%, 70% *de*) *N*-[(1-(4-bromothiazole-2-yl)-2-methylpropyl]-2-methylpropan-2-sulfinamide as a mixture of two diastereoisomers. Single recrystallisation (*tert*-butyl methyl ether/cyclohexane) yielded 2.02 g (5.97 mmol, 72%, >95% *de*) of the major diastereoisomer **22**. M.p. 91°C; R_f = 0.24 (P/EtOAc 1:1; UV); $[\alpha]_D$ = +35.4 (c = 1.1 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 0.94 (d, ^3J = 8.3 Hz, 3H; CH(CH_3)$_2$), 0.96 (d, ^3J = 8.3 Hz, 3H; CH(CH_3)$_2$), 1.27 (s, 9H; C(CH$_3$)$_3$), 2.24–2.33 (m, 1H; CH(CH$_3$)$_2$), 4.16 (d, ^3J = 8.1 Hz, 1H; NH), 4.39 (dd, ^3J = 8.1, 5.8 Hz, 1H; CHNH), 7.16 ppm (s, 1H; H-5); ^{13}C NMR ($CDCl_3$, 90 MHz): δ = 17.9 (q; CH(CH_3)$_2$), 19.3 (q; CH(CH_3)$_2$), 22.8 (s; C(CH_3)$_3$), 35.0 (d; CH-(CH$_3$)$_2$), 56.7 (s; C(CH$_3$)$_3$), 63.5 (d; CHNH), 116.8 (d; C-5), 124.8 (s; C-4), 172.5 ppm (s; C-2); MS (EI, 70 eV): m/z: (%): 307 (1) [M−S]$^+$, 295 (1) [M−C$_2$H$_6$N]$^+$, 284 (24) [M−C$_4$H$_7$]$^+$, 221 (82), 206 (34), 191 (8), 57 (100) [C$_4$H$_9^+$], 41 (32) [C$_2$H$_3$N$^+$]; elemental analysis calcd (%) for $C_{11}H_{19}BrN_2OS_2$ (339.32): C 38.94, H 5.64, N 8.26; found: C 39.23, H 5.58, N 8.16.

2-[(1*S*)-1-({[2-(2,6-Dibromopyridine-3-yl)-thiazole-4-yl]carbonyl}amino)-3-(methylamino)-3-oxopropyl]-5-methyl-*N*-((1*S*)-2-methyl-1-{4-[4-({(1*S*)-2-methyl-1-[4-(trimethylstannyl)-2,4′-bithiazole-2′-yl]propyl}amino)-2-oxo-ethylamino]-thiazole-2-yl}propyl)thiazole-4-carboxamide (26)

Saponification: Aqueous lithium hydroxide solution (1 M; 0.5 mL, 0.500 mmol) was added to a solution of the ethyl ester **5** (40 mg, 50.0 μmol) in *t*BuOH (0.5 mL) and THF (0.5 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h, concentrated in vacuo, and the crude solid was dissolved in H_2O (3 mL). The aqueous layer was acidified with aq. HCl (2 M) to pH 1 and extracted with CH_2Cl_2 (2×4 mL) and EtOAc (2×4 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to yield the free carboxylic acid (36 mg, 46.7 μmol, 93%) as a colorless solid.

Peptide coupling: Free carboxylic acid (17 mg, 22.0 μmol) and amine **25** (13 mg, 28.3 μmol) were dissolved in DMF (2 mL) and cooled to 0°C. Diisopropylethylamine (13.5 μL, 10 mg, 81.5 μmol) and DPPA (8.6 μL, 11 mg, 39.7 μmol) were consecutively added to this mixture. The reaction mixture was allowed to reach room temperature over 16 h and was then partitioned between ethyl acetate (10 mL) and saturated aq. NH_4Cl (10 mL). The aqueous layer was extracted with ethyl acetate (2×10 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (EtOAc) gave product **26**

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(25 mg, 20.6 μmol, 93%) as a yellow oil. R_f=0.32 (EtOAc; UV); $[\alpha]_D^{20}$=−35.7 (c=0.45 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ=0.37 (s, 9H; $Sn(CH_3)_3$), 0.94–0.99 (m, 12H; D: $CH(CH_3)_2$, C: $CH(CH_3)_2$), 2.29–2.39 (m, 2H; D: $CH(CH_3)_2$, C: $CH(CH_3)_2$), 2.63 (d, ^3J=4.5 Hz, 3H; E: $NHCH_3$), 2.73 (s, 3H; E: C5-CH_3), 2.93 (dd, ^2J=16.0, ^3J=5.0 Hz, 1H; E: $CHHCONHCH_3$), 3.25 (dd, ^2J=16.0, ^3J=4.0 Hz, 1H; E: $CHHCONHCH_3$), 4.13 (dd, ^2J=16.5, ^3J=4.5 Hz, 1H; Gly: CH_2), 4.51 (dd, ^2J=16.5, ^3J=7.0 Hz, 1H; Gly: CH_2), 5.17 (dd, ^3J=8.2, 6.0 Hz, 1H; D: CH), 5.33 (dd, ^3J=9.0, 6.0 Hz, 1H; C: CH), 5.73–5.79 (m, 1H; E: CH), 6.83 (q, ^3J=4.5 Hz, 1H; E: $NHCH_3$), 7.31 (d, ^3J=8.2 Hz, 1H; D: NH), 7.35 (s, 1H; C: H-5), 7.61 (d, ^3J=8.2 Hz, 1H; A: H-5), 7.90 (s, 1H; B: H-5), 8.08 (s, 1H; D: H-5), 8.15 (br s, 1H; C: NH), 8.22–8.24 (m, 1H; Gly: NH), 8.34 (s, 1H; F: H-5), 8.52 (d, ^3J=8.2 Hz, 1H; A: H-4), 9.65 ppm (d, ^3J=9.0 Hz, 1H; E: NH); ^{13}C NMR ($CDCl_3$, 90 MHz): δ=−8.83 (q; $Sn(CH_3)_3$), 12.6 (q; E: C5-CH_3), 17.9 (q; C: $CH(CH_3)_2$), 18.1 (q; D: $CH(CH_3)_2$), 19.2 (q; D: $CH(CH_3)_2$), 19.2 (q; C: $CH(CH_3)_2$), 26.1 (q; E: $NHCH_3$), 33.6 (d; C: $CH(CH_3)_2$), 34.5 (d; D: $CH(CH_3)_2$), 38.3 (t; E: $CH_2CONHCH_3$), 43.2 (t; Gly: CH_2), 48.4 (d; E: CH), 55.6 (d; D: CH), 56.8 (d; C: CH), 115.3 (d; C: C-5), 123.6 (d; D: C-5), 126.1 (d; F: C-5), 126.3 (d; B: C-5), 127.8 (d; A: C-5), 129.0 (s; E: C-5), 130.1 (s; A: C-3), 138.8 (s; A: C-2), 141.2 (d; A: C-4), 141.2 (s; A: C-6), 142.1 (s; E: C-4), 148.9 (s; D: C-4), 149.7 (s; F: C-4), 149.8 (s; C: C-4), 160.5 (s; F: CO), 161.3 (s; B: C-2), 161.4 (s; D: CO)*, 161.9 (s; F: C-2), 162.1 (s; E: CO), 163.0 (s; B: C-4), 166.8 (s; E: C-2), 169.1 (s; Gly: CO)*, 169.9 (s; C: C-2), 170.5 (s; D: C-2), 171.3 ppm (s; E: $CONHCH_3$); IR (ATR): $\tilde{\nu}$=3297 (w; NH), 2961 (w; NH), 1654 (s; CONH), 1537 (s), 1490 (m; CH), 1406 (w; CH), 1070 (w), 773 cm^{-1} (w); HRMS (ESI): m/z: calcd for $C_{41}H_{48}Br_2N_{11}O_5S_5{}^{120}Sn$: 1211.9832 $[M+H]^+$; found: 1211.9817.

Regiosiomeric macrocycles 27 and 28 by an intramoleculaur Stille cross-coupling reaction: Stannane **26** (18 mg, 16.5 μmol) and tetrakis(triphenylphosphane)palladium(0) (4.2 mg, 3.63 μmol, 22 mol%) were dissolved in degassed toluene (16.5 mL) and stirred until full conversion (45 h) was achieved at 85°C. The reaction mixture was concentrated in vacuo. Flash chromatography (10% KF in silica, EtOAc→CH_2Cl_2/MeOH 98:2→96:4→94:6→92:8→90:10) yielded regioisomers **27** (4.0 mg, 4.13 μmol, 28%) and **28** (4.0 mg, 4.13 μmol, 28%).

Regioisomer 27: R_f=0.20 (CH_2Cl_2/MeOH 95:5; UV); ^{1}H NMR ($CDCl_3$, 360 MHz): δ=0.89 (d, ^3J=7.2 Hz, 3H; D: $CH(CH_3)_2$), 0.95 (d, ^3J=6.8 Hz, 3H; C: $CH(CH_3)_2$), 0.99 (d, ^3J=6.8 Hz, 3H; D: $CH(CH_3)_2$), 1.01–1.11 (m, 1H; E: $CHHCONHCH_3$), 1.13 (d, ^3J=6.8 Hz, 3H; C: $CH(CH_3)_2$), 2.07–2.13 (m, 1H; D: $CH(CH_3)_2$), 2.26–2.31 (m, 1H; C: $CH(CH_3)_2$), 2.63 (d, ^3J=4.9 Hz, 3H; E: $NHCH_3$), 2.67 (s, 3H; E: C5-CH_3), 2.68–2.74 (m, 1H; E: $CHHCONHCH_3$), 3.86 (dd, ^2J=17.3, ^3J=3.4 Hz, 1H; Gly: CHH), 4.94–5.23 (m, 2H; C: CH, Gly: CHH), 5.24 (dd, ^3J=8.1, ^3J=4.7 Hz, 1H; D: CH), 5.39–5.44 (m, 1H; E: CH), 6.20 (d, ^3J=6.1 Hz, 1H; C: NH), 6.73 (q, ^3J=4.9 Hz, 1H; E: $NHCH_3$), 7.17 (t, ^3J=3.4 Hz, 1H; Gly: NH), 7.20 (s, 1H; C: H-5), 7.56 (d, ^3J=8.0 Hz, 1H; A: H-5), 7.82 (d, ^3J=8.0 Hz, 1H; A: H-4), 8.11 (s, 1H; D: H-5), 8.16 (s, 1H; B: H-5), 8.35 (s, 1H; F: H-5), 8.78 (d, ^3J=8.1 Hz, 1H; D: NH), 8.93 ppm (d, ^3J=9.0 Hz, 1H; E: NH); HRMS (ESI): m/z: calcd for $C_{38}H_{38}BrN_{11}NaO_5S_5$: 990.0742 $[M+Na]^+$; found: 990.0747.

Regioisomer 28: R_f=0.18 (CH_2Cl_2/MeOH 95:5; UV); $[\alpha]_D^{20}$=−9.6 (c=0.44 in $CHCl_3$); IR (ATR): $\tilde{\nu}$=3675 (w; NH), 1652 (s; CONH), 1536 (s), 1495 (s, CH), 1347 (w), 1252 (w), 1074 (m), 734 (s), 693 cm^{-1} (w); ^{1}H NMR ($CDCl_3$, 360 MHz): δ=0.97 (d, ^3J=7.9 Hz, 3H; $CH(CH_3)_2$), 1.05 (d, ^3J=6.8 Hz, 3H; $CH(CH_3)_2$), 1.09 (d, ^3J=6.8 Hz, 3H; $CH(CH_3)_2$), 1.14 (d, ^3J=7.6 Hz, 3H; $CH(CH_3)_2$), 2.28–2.34 (m, 1H; D: $CH(CH_3)_2$), 2.61–2.67 (m, 1H; C: $CH(CH_3)_2$), 2.78–2.81 (m, 6H; E: $NHCH_3$, E: C5-CH_3), 3.00 (dd, ^2J=15.1, ^3J=7.9 Hz, 1H; E: $CHHCONHCH_3$), 3.06 (dd, ^2J=15.1, ^3J=5.4 Hz, 1H; E: $CHHCONHCH_3$), 3.97 (dd, ^2J=17.1, ^3J=5.0 Hz, 1H; Gly: CHH), 4.49 (dd, ^2J=17.1, ^3J=7.6 Hz, 1H; Gly: CHH), 5.28 (dd, ^3J=8.5, 7.2 Hz, 1H; D: CH), 5.40 (dd, ^3J=9.2, 8.6 Hz, 1H; C: CH), 5.91–5.95 (m, 1H; E: CH), 6.05 (q, ^3J=4.7 Hz, 1H; E: $NHCH_3$), 7.49 (d, ^3J=8.5 Hz, 1H; D: NH), 7.67 (s, 1H; C: H-5), 7.73–7.76 (m, 1H; Gly: NH), 7.97 (s, 1H; D: H-5), 8.03 (d, ^3J=8.3 Hz, 1H; A: H-5), 8.05 (d, ^3J=9.2 Hz, 1H; C: NH), 8.26 (s, 1H; B: H-5), 8.35 (s, 1H; F: H-5), 8.32 (d, ^3J=9.0 Hz, 1H; E: NH), 8.55 ppm (d, ^3J=8.3 Hz, 1H; A: H-4); ^{13}C NMR ($CDCl_3$, 90 MHz): δ=12.7 (q; E: C5-CH_3), 17.5 (q; C: $CH(CH_3)_2$), 18.6 (q; D: $CH(CH_3)_2$), 19.3 (q; D: $CH(CH_3)_2$), 19.6 (q; C: $CH(CH_3)_2$), 26.4 (q; E: $NHCH_3$), 33.2 (d; C: $CH(CH_3)_2$), 34.3 (d; D: $CH(CH_3)_2$), 42.1 (t; E: $CH_2CONHCH_3$), 43.6 (t; Gly: CH_2), 47.2 (d; E: CH), 56.1 (d; D: CH), 56.3 (d; C: CH), 119.0 (d; C: C-5), 119.9 (d; A: C-5), 120.4 (d; B: C-5), 122.8 (d; D: C-5), 126.1 (d; F: C-5), 129.4 (s; A: C-3), 139.8 (d; A: C-4), 140.0 (s; A: C-2)*, 141.8 (s; E: C-5)[#], 142.9 (s; E: C-4)[#], 148.9 (s; C: C-4), 149.3 (s; F: C-4), 150.0 (s; D: C-4), 153.3 (s; B: C-4), 153.9 (s; A: C-6)*, 160.1 (s; F: CO)′, 161.5 (s; Gly: CO)$^-$, 162.1 (s; C: C-2), 162.3 (s; B: C-2), 163.1 (s; F: C-2)′, 163.8 (s; E: C-2)[§], 168.6 (s; D: CO)$^-$, 169.4 (s; E: $CONHCH_3$)[§], 170.0 (s; E: CO), 174.2 ppm (s; D: C-2); HRMS (ESI): m/z: calcd for $C_{38}H_{38}BrN_{11}NaO_5S_5$: 990.0742 $[M+Na]^+$; found: 990.0747.

Ethyl-(*S,S*)-2-{1-[(2-{1-[(2-{2-bromo-6-(4-*tert*-butoxycarbonyl-thiazole-2-yl)pyridine-3-yl}thiazole-4-carbonyl)amino]-2-methylcarbamoyl-ethyl}-5-methylthiazole-4-carbonyl)amino]-2-methylpropyl}thiazole-4-carboxylate (35)

Zincation: DMA (0.61 mL) and 1,2-dibromoethane (6.1 μL, 15 mg, 80.8 μmol) were added to a flame-dried flask charged with zinc dust (41 mg, 0.625 mmol). The zinc suspension was shortly heated with a heat gun until evolution of ethylene occurred and was then allowed to reach 25°C. This procedure was repeated three times. TMSCl (16.7 μL, 14 mg, 0.131 mmol) was added neat and the reaction mixture was stirred for 5 min. *tert*-Butyl 2-iodothiazole-4-carboxylate (62 mg, 0.200 mmol) was added. Stirring was continued for 45 min at 25°C, then the zinc dust was allowed to settle (30 min).

Negishi cross-coupling: The supernatant liquid containing the zinc organyl **34** was transferred to a flask containing $[PdCl_2(PPh_3)_2]$ (5.3 mg, 7.50 μmol, 30 mol%). Pyridine **5** (19.7 mg, 25.0 μmol) and DMA (1.5 mL) were added to this mixture, which was then stirred at 45°C for 3.5 h. The reaction mixture was partitioned between saturated aq. NH_4Cl (6 mL) and EtOAc (3×6 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (P/EtOAc 1:1→0:1) afforded a yellow solid containing the desired pyridine **35** (11 mg, 12.2 μmol, 49%, yellow solid) together with triphenylphosphane oxide. Separation of the oxidated ligand from compound **35** was performed by reverse-phase HPLC (RP, ODS-A, MeCN/H_2O 10:90, 7 mL min^{-1}). M.p. 135°C; R_f=0.36 (EtOAc; UV); $[\alpha]_D^{20}$=−25.5 (c=0.45 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz): δ=0.98 (d, ^3J=6.8 Hz, 3H; D: $CH(CH_3)_2$), 1.01 (d, ^3J=6.8 Hz, 3H; D: $CH(CH_3)_2$), 1.41 (t, ^3J=7.2 Hz, 3H; D: OCH_2CH_3), 1.63 (s, 9H; G: $C(CH_3)_3$), 2.36–2.45 (m, 1H; D: $CH(CH_3)_2$), 2.64 (d, ^3J=4.7 Hz, 3H; E: $NHCH_3$), 2.74 (s, 3H; E: C5-CH_3), 3.02 (dd, ^2J=14.8, ^3J=5.8 Hz, 1H; E: $CHHCONHCH_3$), 3.31 (dd, ^2J=14.8, ^3J=4.3 Hz, 1H; E: $CHHCONHCH_3$), 4.42 (q, ^3J=7.2 Hz, 2H; D: OCH_2CH_3), 5.31 (dd, ^3J=8.6, 5.4 Hz, 1H; D: CH), 5.83–5.88 (m, 1H; E: CH), 6.82 (q, ^3J=4.7 Hz, 1H; E: $NHCH_3$), 8.13 (s, 1H; D: H-5), 8.20 (s, 1H; G: H-5), 8.38 (s, 1H; F: H-5), 8.39 (d, ^3J=8.3 Hz, 1H; A: H-5), 8.64 (d, ^3J=8.6 Hz, 1H; D: NH), 8.74 (d, ^3J=8.3 Hz, 1H; A: H-4), 9.39 ppm (d, ^3J=9.0 Hz, 1H; E: NH); ^{13}C NMR ($CDCl_3$, 90 MHz): δ=12.5 (q; E: C5-CH_3), 14.3 (q; D: OCH_2CH_3), 18.0 (q; D: $CH(CH_3)_2$), 19.1 (q; D: $CH(CH_3)_2$), 26.2 (q; E: $NHCH_3$), 28.2 (q; G: $C(CH_3)_3$), 34.5 (d; D: $CH(CH_3)_2$), 38.7 (t; E: $CH_2CONHCH_3$), 48.5 (d; E: CH), 56.3 (d; D: CH), 61.6 (t; OCH_2CH_3), 82.4 (s; G: $C(CH_3)_3$), 119.3 (d; A: C-5), 126.1 (d; F: C-5), 127.3 (d; D: C-5), 129.7 (d; G: C-5), 131.6 (s; A: C-3), 139.5 (s; A: C-2), 140.7 (d; A: C-4), 141.9 (s; A: C-6), 142.2 (s; E: C-5)[#], 146.4 (s; D: C-4), 149.8 (s; E: C-4)[#], 150.2 (s; F: C-4), 151.3 (s; G: C-4), 160.2 (s; G: COO), 160.5 (s; F: CO), 161.4 (s; D: COO), 162.1 (s; E: CO), 162.3 (s; F: C-2), 166.5 (s; G: C-2), 166.6 (s; E: C-2), 170.7 (s; D: C-2), 171.0 ppm (s; E: $CONHCH_3$); IR (ATR): $\tilde{\nu}$=2355 (m), 1719 (m; CO), 1668 (s; CONH), 1530 (s), 1476 (m; CH), 1338 (w), 1232 (m), 1159 (m), 1068 (w), 1020 (w), 749 cm^{-1} (w); HRMS (ESI): m/z: calcd for $C_{36}H_{39}BrN_8NaO_7S_4$: 925.0906 $[M+Na]^+$; found: 925.0914.

***tert*-Butyl-2-{2-bromo-3-[4-({[(1*S*)-3-(methylamino)-1-(5-methyl-4-{[((1*S*)-2-methyl-1-{4-[4-({(1*S*)-2-methyl-1-[4-(trimethylstannyl)-2,4′-bithiazole-2′-yl]propyl}amino)-2-oxo-ethylamino]thiazole-2-yl}propyl)amino]carbonyl}thiazole-2-yl)-3-oxopropyl]amino}carbonyl)thiazole-2-yl]pyridine-6-yl}thiazole-4-carboxylate (37)**

Saponification: Aqueous lithium hydroxide solution (1M, 99.6 μL, 99.6 μmol) was added to a solution of the ethyl ester **35** (9.0 mg,

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9.96 μmol) in *t*BuOH (199 μL) and THF (99.6 μL) at room temperature. The reaction mixture was stirred at room temperature for 1 h, concentrated in vacuo, and the crude solid was dissolved in H_2O (3 mL). The aqueous layer was acidified with aqueous citric acid (10%) to pH 3 and extracted with CH_2Cl_2 (2×4 mL) and EtOAc (2×4 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to yield the free carboxylic acid (8.5 mg, 9.70 μmol, 99%) as a yellow solid.

Peptide coupling: Free carboxylic acid (7.5 mg, 8.56 μmol) and amine **24** (5.0 mg, 10.9 μmol) were dissolved in DMF (1 mL) and cooled to 0°C. Diisopropylethylamine (6.1 μL, 4.7 mg, 36.7 μmol) and DPPA (3.9 μL, 4.9 mg, 17.9 μmol) were consecutively added to this mixture. The reaction mixture was allowed to reach room temperature over 16 h and then quenched with saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (EtOAc) gave the bromopyridine **37** (7.7 mg, 6.83 μmol, 65%) as a yellow oil. R_f=0.29 (EtOAc; UV); $[\alpha]_D^{20}=-34.0$ (c=0.60 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz): δ=0.37 (s, 9H; Sn(CH_3)$_3$), 0.94–1.00 (m, 12H; D: CH(CH_3)$_2$, C: CH(CH_3)$_2$), 1.63 (s, 9H; C(CH_3)$_3$), 2.31–2.39 (m, 2H; D: C*H*(CH_3)$_2$, C: C*H*(CH_3)$_2$), 2.67 (d, ^3J=4.7 Hz, 3H; E: NHC*H*$_3$), 2.74 (s, 3H; E: C5-CH_3), 2.99 (dd, ^2J=15.8, ^3J=5.0 Hz, 1H; E: CH*H*CONHCH$_3$), 3.26 (dd, ^2J=15.8, ^3J=4.3 Hz, 1H; E: C*H*HCONHCH$_3$), 4.15 (dd, ^2J=16.6, ^3J=4.3 Hz, 1H; Gly: CH_2), 4.53 (dd, ^2J=16.6, ^3J=6.5 Hz, 1H; Gly: CH_2), 5.19 (dd, ^3J=9.0, 8.6 Hz, 1H; D: CH), 5.32 (dd, ^3J=9.0, ^3J=6.1 Hz, 1H; C: CH), 5.75–5.79 (m, 1H; E: CH), 6.78 (q, ^3J=4.7 Hz, 1H; E: N*H*CH$_3$), 7.24 (d, 1H; NH), 7.36 (s, 1H; C: H-5), 7.90 (s, 1H; B: H-5), 8.08 (s, 1H; D: H-5), 8.08–8.13 (m, 1H; NH), 8.19–8.22 (m, 1H; Gly: NH), 8.21 (s, 1H; G: H-5), 8.35 (s, 1H; F: H-5), 8.38 (d, ^3J=7.9 Hz, 1H; A: H-5), 8.75 (d, ^3J=7.9 Hz, 1H; A: H-4), 9.62 ppm (d, ^3J=8.6 Hz, 1H; E: NH); ^{13}C NMR ($CDCl_3$, 90 MHz): δ=−8.80 (q; Sn(CH_3)$_3$), 12.7 (q; E: C5-*C*H$_3$), 17.9 (q; C: CH(*C*H$_3$)$_2$), 18.1 (q; D: CH(*C*H$_3$)$_2$), 19.2 (q; D: CH(*C*H$_3$)$_2$), 19.2 (q; C: CH(*C*H$_3$)$_2$), 26.1 (q; E: NHCH$_3$), 28.2 (q; G: C(*C*H$_3$)$_3$), 33.6 (d; C: *C*H(CH$_3$)$_2$), 34.4 (d; D: *C*H(CH$_3$)$_2$), 38.3 (t; E: *C*H$_2$CONHCH$_3$), 43.0 (t; Gly: CH_2), 48.3 (d; E: CH), 55.5 (d; D: CH), 56.8 (d; C: CH), 82.4 (s; G: *C*(CH$_3$)$_3$), 115.3 (d; C: C-5), 119.3 (d; A: C-5), 123.6 (d; D: C-5), 126.1 (d; F: C-5), 126.3 (d; B: C-5), 129.8 (d; G: C-5), 131.5 (s; A: C-3), 139.4 (s; A: C-2), 140.7 (d; A: C-4), 141.9 (s; A: C-6), 142.1 (s; E: C-5), 148.9 (s; D: C-4), 149.5 (s; C: C-4), 149.7 (s; E: C-4), 150.0 (s; F: C-4), 151.2 (s; G: C-4), 160.3 (s; G: CO), 160.5 (s; F: CO), 161.2 (s; B: C-2), 161.3 (s; D: CO)*, 162.0 (s; E: CO), 162.2 (s; F: C-2), 163.0 (s; B: C-4), 166.6 (s; G: C-2), 166.8 (s; E: C-2), 169.0 (s; Gly: CO)*, 169.9 (s; C: C-2), 170.4 (s; D: C-2), 171.1 ppm (s; E: *C*ONHCH$_3$); IR (ATR): $\tilde{\nu}$=3675 (w; NH), 2375 (s; NH), 2348 (s), 1825 (w), 1681 (m; CONH), 1668 (m; CONH), 1652 (m; CONH), 1540 (s), 1226 (w; C–O), 768 (m), 756 cm^{-1} (s); HRMS (ESI): m/z: calcd for $C_{49}H_{57}BrN_{12}NaO_7S_6{}^{120}Sn$: 1339.0900 $[M+Na]^+$; found: 1339.0902.

Amythiamicin C (3)

Stille macrocyclization: Stannane **37** (13 mg, 9.87 μmol) and $[Pd(PPh_3)_4]$ (2.5 mg, 2.17 μmol, 22 mol%) were dissolved in degassed toluene (9.9 mL) and stirred until full conversion (48 h) at 85°C. The reaction mixture was concentrated in vacuo. Flash chromatography (EtOAc→CH_2Cl_2/MeOH 98:2→90/10) yielded macrolide **38** (8.4 mg, 7.83 μmol, 79%) as a pale-yellow solid together with triphenylphosphane oxide.

Deprotection of* tert-*butyl ester 38: Trifluoroacetic acid (0.29 mL) was added at room temperature to a stirred solution of the macrocyle **38** (8.2 mg, 7.73 μmol) in CH_2Cl_2 (1.6 mL). After 8 h, the reaction mixture was concentrated in vacuo and then azetroped with toluene (2×5 mL) to give the corresponding acid **39** as a colorless solid. This material was used in the subsequent ester coupling without further purification.

Ester coupling: Acid **39**, diketopiperazine **31** (7.1 mg, 38.7 μmol), and DMAP (1.4 mg, 11.6 μmol) were dissolved in CH_2Cl_2 (0.8 mL) and stirred for 15 min. EDC (1.8 mg, 9.28 μmol) and CH_2Cl_2 (0.8 mL) were added and the reaction mixture was stirred for 24 h. Purification by flash chromatography (EtOAc/MeOH 100:0→2:1) yielded amythiamicin C (**3**) (15 mg) together with diketopiperazine **31**. Further purification by reverse-phase HPLC (RP, ODS-A, MeCN/H_2O 20:80→100:0, 50 min, 15 mL min^{-1}) gave amythiamicin C (**3**) (2.4 mg, 2.03 μmol, 20% over three steps) as a colorless solid. R_f=0.43 (EtOAc/MeOH 3:1); $[\alpha]_D^{20}=+114.0$ (c=0.18 in MeOH); ^{1}H NMR ($CDCl_3$, 600 MHz): δ=0.89 (d, ^3J=6.6 Hz, 3H; D: CH(C*H*$_3$)$_2$), 0.96 (d, ^3J=6.6 Hz, 3H; D: CH(C*H*$_3$)$_2$), 1.00 (d, ^3J=7.2 Hz, 3H; C: CH(C*H*$_3$)$_2$), 1.06–1.09 (m, 1H; E: C*H*HCONHCH$_3$), 1.15 (d, ^3J=6.6 Hz, 3H; C: CH(C*H*$_3$)$_2$), 1.91–1.98 (m, 1H; G: H_2-7′), 2.07–2.18 (m, 3H; C: C*H*(CH$_3$)$_2$, G: H_2-7′/H_2-8′), 2.28–2.31 (m, 1H; D: C*H*(CH$_3$)), 2.40–2.44 (m, 1H; G: H_2-8′), 2.65 (d, ^3J=4.8 Hz, 3H; E: NHC*H*$_3$), 2.66 (s, 3H; E: C5-CH_3), 2.72 (dd, ^2J=16.8, ^3J=3.0 Hz, 1H; E: C*H*HCONHCH$_3$), 3.58–3.62 (m, 1H; G: H_2-6′), 3.65–3.70 (m, 1H; G: H_2-6′), 3.89 (dd, ^2J=17.4, ^3J=3.0 Hz, 1H; Gly: C*H*H), 4.18 (t, ^3J=8.4 Hz, 1H; G: H-8a′), 4.55–4.61 (m, 2H; G: H-3′, G: CH_2OCO), 4.98–5.02 (m, 2H; Gly: CH*H*, C: CH), 5.19 (dd, ^2J=11.4, ^3J=2.4 Hz, 1H; G: CH_2OCO), 5.25 (dd, ^3J=10.2, 7.8 Hz, 1H; D: CH), 5.41–5.43 (m, 1H; E: CH), 6.31 (d, ^3J=6.0 Hz, 1H; C: NH), 6.55 (s, 1H; G: NH-2′), 6.78 (q, ^3J=4.8 Hz, 1H; E: N*H*CH$_3$), 7.26 (s, 1H; C: H-5), 7.78–7.90 (m, 1H; Gly: NH), 8.12 (d, ^3J=7.8 Hz, 1H; A: H-4), 8.12 (s, 1H; D: H-5), 8.24 (s, 1H; B: H-5), 8.35 (d, ^3J=7.8 Hz, 1H; A: H-5), 8.36 (s, 1H; G: H-5), 8.40 (s, 1H; F: H-5), 8.79 (d, ^3J=7.8 Hz, 1H; D: NH), 8.95 ppm (d, ^3J=9.0 Hz, 1H; E: NH); ^{13}C NMR ($CDCl_3$, 150 MHz): δ=12.3 (q; E: C5-*C*H$_3$), 18.1 (q; D: CH(*C*H$_3$)$_2$), 18.4 (q; D: CH(*C*H$_3$)$_2$), 19.2 (q; C: CH-(*C*H$_3$)$_2$), 19.2 (q; C: CH(*C*H$_3$)$_2$), 22.6 (t; G: C-7′), 26.3 (q; E: NHCH$_3$), 28.4 (t; G: C-8′), 33.4 (d; C: *C*H(CH$_3$)$_2$), 34.7 (d; D: *C*H(CH$_3$)$_2$), 38.4 (t; E: *C*H$_2$CONHCH$_3$), 41.5 (t; Gly: CH_2), 45.6 (t; G: C-6′), 48.3 (d; E: CH), 54.8 (d; G: C-3′), 56.2 (d; D: CH), 59.1 (d; G: C-8a′), 59.4 (d; C: CH), 64.3 (t; G: C-9′), 114.3 (d; C: C-5), 118.7 (d; A: C-5), 123.2 (d; B: C-5), 123.9 (d; D: C-5), 125.2 (d; F: C-5), 127.9 (s; A: C-3), 131.5 (s; G: C-5), 140.4 (d; A: C-4), 140.5 (d; E: C-5), 142.1 (s; E: C-4), 147.2 (s; G: C-4), 148.4 (s; D: C-4), 148.8 (s; C: C-4), 150.3 (s; A: C-2), 150.3 (s; F: C-4), 150.4 (s; A: C-6), 154.4 (s; B: C-4), 160.0 (s; B: C-2), 161.2 (s; F: CO), 161.3 (s; D: CO), 161.3 (s; G: CO), 162.0 (s; E: CO), 162.7 (s; G: C-4′), 164.8 (s; F: C-2), 167.6 (s; E: C-2), 168.6 (s; D: C-2), 169.1 (s; G: C-2), 169.3 (s; Gly: CO), 169.4 (s; G: C-1′), 169.6 (s; E: *C*ONHCH$_3$), 172.7 ppm (s, C: C-2); HRMS (ESI): m/z: calcd for $C_{50}H_{50}N_{14}NaO_9S_6$: 1205.2107 $[M+Na]^+$; found: 1205.2108.

Amythiamicin D (4)

Zincation: DMA (0.51 mL) and 1,2-dibromoethane (3.6 μL, 0.77 mg, 4.08 μmol) were added to a flame-dried flask charged with zinc dust (24 mg, 124 μmol). The zinc suspension was shortly heated with a heat gun until evolution of ethylene occurred and then allowed to reach 25°C. This procedure was repeated three times. TMSCl (10.2 μL, 8.7 mg, 79.8 μmol) was added neat and the reaction mixture was stirred for 5 min. Methyl 2-iodothiazole-4-carboxylate (33 mg, 124 μmol) was added. The stirring was continued for 1 h at 25°C, then the zinc dust was allowed to settle (30 min).

Negishi cross-coupling: The supernatant liquid (0.25 mL) containing the zinc organyl **29** was added to a flask containing $[PdCl_2(PPh_3)_2]$ (0.9 mg, 1.24 μmol, 30 mol%) and macrocycle **27** (3.9 mg, 4.02 μmol) in THF (0.14 mL). The reaction mixture was stirred at 45°C for 24 h. The reaction mixture was partitioned between H_2O (5 mL) and EtOAc (3×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (CH_2Cl_2/MeOH 100:0→94:6) afforded amythiamicin D (4) (4.0 mg, 3.88 μmol, 96%) together with triphenylphosphane oxide. Separation of the oxidated ligand from the natural product was performed by reverse-phase HPLC (RP, ODS-A, MeCN/H_2O 20:80→100:0, 50 min, 15 mL min^{-1}) yielding amythiamicin D (**4**) (1.7 mg, 1.65 μmol, 43%) as a colorless solid. R_f=0.30 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{20}=+170.0$ (c=0.15 in MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ=0.89 (d, ^3J=7.0 Hz, 3H; D: CH(C*H*$_3$)$_2$), 0.96 (d, ^3J=6.5 Hz, 3H; C: CH(C*H*$_3$)$_2$), 1.00 (d, ^3J=7.0 Hz, 3H; D: CH(C*H*$_3$)$_2$), 1.07 (m, 1H; E: C*H*HCONHCH$_3$), 1.14 (d, ^3J=6.5 Hz, 3H; C: CH-(C*H*$_3$)$_2$), 2.08–2.14 (m, 1H; C: C*H*(CH$_3$)$_2$), 2.25–2.33 (m, 1H; D: C*H*-(CH$_3$)$_2$), 2.65 (d, ^3J=4.5 Hz, 3H; E: NHC*H*$_3$), 2.66 (s, 3H; E: C5-CH_3), 2.73 (dd, ^2J=14.0, ^3J=3.5 Hz, 1H; E: CH*H*CONHCH$_3$), 3.89 (dd, ^2J=17.5, ^3J=3.0 Hz, 1H; Gly: C*H*H), 4.02 (s, 3H; G: OCH$_3$), 4.98–5.03 (m, 2H; Gly: CH*H*, C: CH), 5.25 (dd, ^3J=8.0, 4.5 Hz, 1H; D: CH), 5.41–5.43 (m, 1H; E: CH), 6.31 (d, ^3J=6.0 Hz, 1H; C: NH), 6.76 (q, ^3J=4.5 Hz, 1H; E: N*H*CH$_3$), 7.25 (s, 1H; C: H-5), 7.77 (dd, ^2J=9.5, ^3J=3.0 Hz, 1H; Gly: NH), 8.12 (s, 1H; D: H-5), 8.13 (d, ^3J=8.0 Hz, 1H; A: H-4), 8.24 (s,

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1H; B: H-5), 8.35 (s, 1H; G: H-5), 8.37 (s, 1H; F: H-5), 8.38 (d, ^3J= 8.0 Hz, 1H; A: H-5), 8.79 (d, ^3J=8.0 Hz, 1H; D: NH), 8.95 ppm (d, ^3J= 9.0 Hz, 1H; E: NH); ^{13}C NMR ($CDCl_3$, 150 MHz): δ=12.3 (q; E: C5-CH_3), 18.0 (q; D: CH(CH_3)$_2$), 18.3 (q; D: CH(CH_3)$_2$), 19.2 (q; C: CH-(CH_3)$_2$), 19.2 (q; C: CH(CH_3)$_2$), 26.2 (q; E: NHCH_3), 33.4 (d; C: *C*H-(CH_3)$_2$), 34.7 (d; D: *C*H(CH_3)$_2$), 38.4 (t; E: *C*H$_2$CONHCH_3), 41.4 (t; Gly: CH_2), 48.3 (d; E: CH), 52.6 (q; G: OCH_3), 56.2 (d; D: CH), 59.4 (d; C: CH), 114.3 (d; C: C-5), 118.6 (d; A: C-5), 123.2 (d; B: C-5), 123.9 (d; D: C-5), 125.2 (d; F: C-5), 127.7 (s; A: C-3), 130.4 (d; G: C-5), 140.3 (d; A: C-4), 140.5 (s; E: C-5), 142.1 (s; E: C-4), 148.2 (s; G: C-4), 148.3 (s; D: C-4), 148.8 (s; C: C-4), 150.3 (s; A: C-3), 150.3 (s; F: C-4), 150.5 (s; A: C-6), 154.5 (s; B: C-4), 160.0 (s; B: C-2), 161.2 (s; F: CO), 161.4 (s; D: CO), 161.8 (s; G: CO), 162.0 (s; E: CO), 164.9 (s; F: C-2), 167.6 (s; E: C-2), 168.6 (s; D: C-2), 169.1 (s; G: C-2), 169.1 (s; Gly: CO), 169.6 (s; E: *C*ONHCH$_3$), 172.7 ppm (s; C: C-2); HRMS (ESI): *m*/*z*: calcd for $C_{43}H_{42}N_{12}NaO_7S_6$: 1053.1521 $[M+Na]^+$; found: 1053.1523.

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