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Biphenomycin B and Derivatives: Total Synthesis and Translation Inhibition

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Abstract: A full account on the synthesis of the antibiotic natural product biphenomycin B and several derivatives is reported, which employs a Suzuki coupling reaction of a free carboxylic acid and macrolactam formation as key transformations. Liberal exchange of the central amino acid was demonstrated. This procedure gave derivatives to study the influence of the polar side chain of the central amino acids on translation inhibition.

Keywords: antibiotics · cross couplings · natural products · peptides · synthesis design

Introduction

In many biologically active natural products, key structural elements often account for a particular biological activity and hence may be regarded as "privileged".[1] To identify such privileged elements, the screening of compound libraries has proven to be increasingly useful.[2] The biaryl subunit is found in many biologically active molecules as an important privileged motif.[3] The structurally related biarylcyclopeptide biphenomycin (**1**–**3**)[4] and arylomycin natural products (**4**)[5] represent interesting case studies for chemical syntheses and integrated biological studies. Both of them display a biaryl amino acid embedded in a small peptide macrocycle. Whilst the 15-membered ring biphenomycins **1** and **2** were reported to inhibit bacterial protein biosynthesis,[6] the 14-membered ring arylomycins **4** bind to a bacterial signal peptidase.[7]

The biphenomycin biarylcyclopeptides[8] **1**–**3** are peptide alkaloid antibiotics isolated from *Streptomyces filipinensis*[9] and *S. griseorubiginosus*[10] by Ezaki et al.[11] The 15-membered ring compounds **1**–**3** carry two distinct structural features: a biaryl moiety and a cyclic peptide with a hydroxyl ated ornithine side chain.[12] Within the biphenomycin family, biphenomycin A (**1**) has been most intensively studied. It shows antibacterial activity against Gram-positive bacteria in vitro and in vivo. However, during in vitro testing biphenomycin A was found to have quite a complex spectrum of activity, which seemed to be dependent on experimental conditions as well. For example, biphenomycin A was found to be highly active against *Cornybacterium xerosis*, but no activity could be observed with *Staphylococcus aureus* and *Streptococcus pyogenes* in agar-diffusion tests at 200 $\mu g\,mL^{-1}$. This notwithstanding, biphenomycin A was surprisingly effective in vivo in a mouse sepsis model.[9]

The nonhydroxylated congener biphenomycin B (**1**) occurs together with biphenomycin A. Both molecules have comparable activity in vitro.[13] Biphenomycin C (**3**) carries an elongated peptide tag, which extends the C-terminus of the peptide chain. This compound was shown to be a biosynthetic precursor of biophenomycin A,[10b] thereby suggesting a common predecessor peptide to be the starting material for all the biphenomycins.

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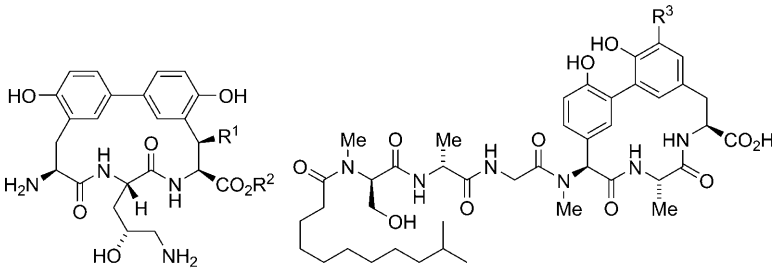


1 (R^1, R^2 = H)
2 (R^1 = OH, R^2 = H)
3 (R^1 = OH, R^2 = Arg-Ser-OH)

4a (R^3 = H)
4b (R^3 = NO_2)

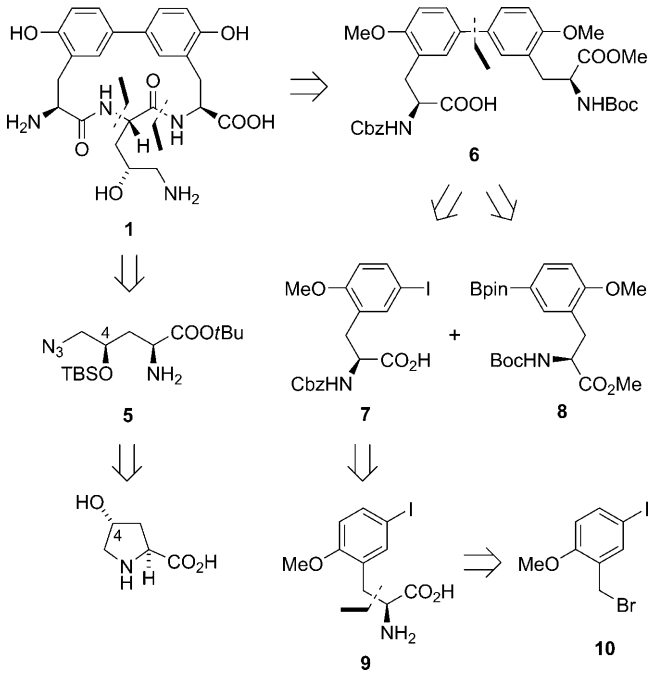
The molecular mode of action of the biphenomycin antibiotics currently remains unclear. In the patent literature it was claimed that protein biosynthesis should be involved.[14] However, full details were not given, and independent studies on this topic have not appeared. To prepare for investigations of the mode of action of these compounds and to explore the bioactive biaryl scaffold, we developed a flexible synthetic route to biphenomycin B.[15] For the synthesis, we intended to concentrate on biphenomycin B (**1**) as a target for the reasons of equal bioactivity, higher chemical stability, and absence of the synthetically inconvenient benzylic hydroxy group.

Total syntheses of biphenomycins were reported previously by Schmidt[16] and later on by Zhu.[17] Studies on the syntheses of a considerable number of biphenomycin derivatives which extend the Schmidt precedent were described in patents from the Bayer research laboratories,[14,18] aiming at acquiring SAR information and antibiotics development.[6] In terms of synthetic strategy, the Schmidt synthesis employed enantioselective hydrogenations to furnish a biaryl diamino diacid building block with homochiral termini, differentiated by protecting groups. The Zhu laboratory has alternatively shown that macrocyclization can be effectively executed by an intramolecular Suzuki coupling of a peptide-chain precursor. In our approach, we opted for biaryl formation by the Suzuki coupling, but with ring closure by macrolactam formation,[15] to enable liberal variation of the scaffold. Here, we give a full account on our biphenomycin B synthesis, detailed syntheses of a first set of derivatives, and report biological tests for translation inhibition by these compounds.

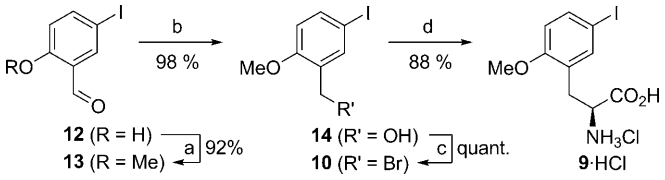
Results

Retrosynthetically, we planned to disconnect biphenomycin B (**1**) into amino acid **5** and the biaryl amino acid **6** (Scheme 1). Ornithine derivative **5** could be obtained from *trans*-4-hyroxyproline.[19] The biaryl building block **6** could be assembled from the *o*-tyrosine derivatives **7** and **8** by a transition-metal-mediated coupling reaction. Both coupling partners might be efficiently derived from the same amino acid **9** by divergent protection and functionalization. To obtain **9** in enantiopure form, a chiral amino acid synthesis was planned from benzyl bromide **10**. In the forward sense, building blocks **5**, **7**, and **8** could be individually varied later, if so desired.

To put this planning into synthetic practice, 2-hydroxy-5-iodobenzaldehyde **12**[20] was alkylated to provide methyl ether **13** (92% yield, Scheme 2) and subsequently reduced with diisobutylaluminum hydride (DIBAL-H) to give benzyl alcohol **14** in 98% yield. Next, alcohol **14** was transformed into benzyl bromide **10** by using phosphorus tribromide in quantitative yield. We found bromide **10** to be rather unstable on storage, hence **10** was immediately used for the next transformation. Amino acid **9** was prepared from benzyl bromide **10** by using Corey's asymmetric glycine enolate alkylation method, which utilizes benzophenone imines for temporary protection.[21]



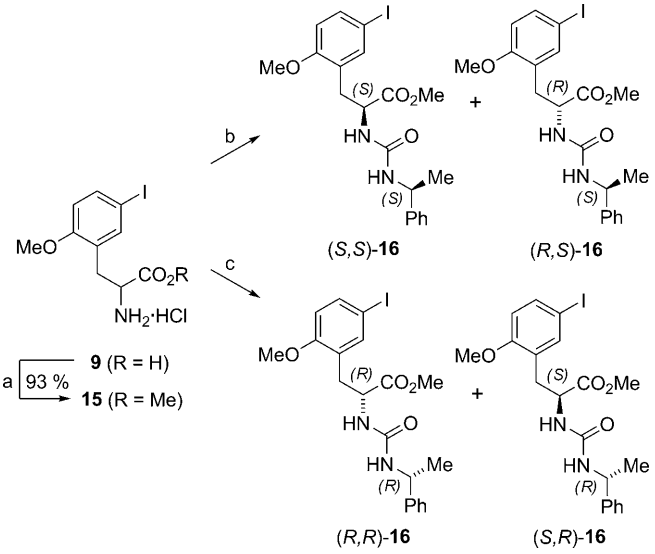
Scheme 1. Retrosynthetic disconnection of biphenomycin B (**1**) into amino acid building blocks. Bpin = 2,2,4,4-tetramethyl-1,3,2-dioxaborolan-2-yl, Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl, TBS = *tert*-butyldimethylsilyl.



Scheme 2. Synthesis of amino acid **9** (as its hydrochloride). Reagents and conditions: a) MeI (1.5 equiv), K_2CO_3 (1.5 equiv), acetone, reflux, 16 h, 92%; b) DIBAl-H (1.2 equiv), CH_2Cl_2, 0 °C, 2 h, 98%; c) PBr_3 (0.34 equiv), toluene, 100 °C, 50 min. quant.; d) $Ph_2C{=}GlyO$*t*Bu (**11**), *O*-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide (10 mol%), CsOH (10 equiv), CH_2Cl_2, −50 °C, 24 h; then 4 M HCl in dioxane, RT, 16 h, 88%, >96% *ee* (HPLC).

In our first experiments, the reactivity seemed to be quite low at −78 °C, and the enantiomeric excess (*ee*) of product **9** varied from batch to batch. It was speculated that larger amounts of product were only formed upon warming the reaction mixture before workup. Therefore, a temperature screen was conducted (−78 °C to 0 °C), which indicated an optimal reaction temperature of −50 °C. By using these conditions, both the yield and enantiomeric excess for amino acid **9** were excellent, and the transformation could be reliably conducted on a multi-gram scale.

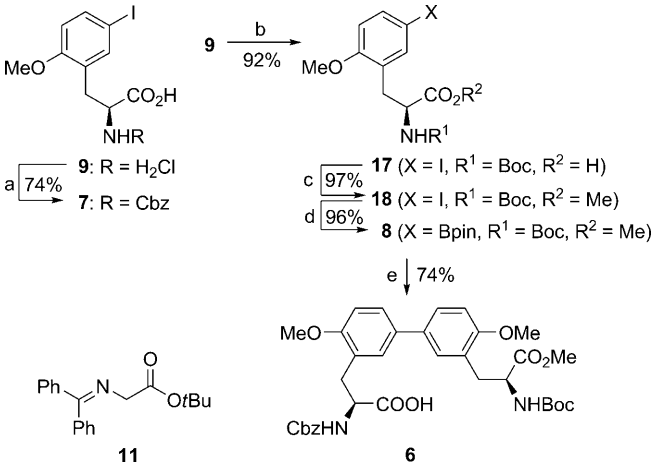
To determine the enantiomeric excess of compound **9**, it was converted into its corresponding methyl ester **15** (Scheme 3) and independently derivatized with (*R*)-(+)- and



Scheme 3. Synthesis of diastereomeric derivatives (*S*,*S*)-**16** and (*S*,*R*)-**16**. Reagents and conditions: a) $SOCl_2$ (1.1 equiv), MeOH, reflux, 8 h, 93 %; b) (*S*)-(−)-1-phenylethyl isocyanate (3.0 equiv), pyridine (5.0 equiv), CH_2Cl_2, RT, 16 h, 78 %; c) (*R*)-(+)-1-phenylethyl isocyanate (3.0 equiv), pyridine (5.0 equiv), CH_2Cl_2, RT, 16 h, 81 %.

(*S*)-(−)-1-phenylethylisocyanate on analytical scale, to give the two enantiomeric pairs (*S*,*S*)-**16**/(*R*,*R*)-**16** and (*S*,*R*)-**16**/(*R*,*S*)-**16**.[22] These diastereomers could be separated by HPLC. An *ee* of 96–98 % was routinely determined from the baseline separated isomers (see the Supporting Information). All peak assignments were confirmed by HPLC-MS.

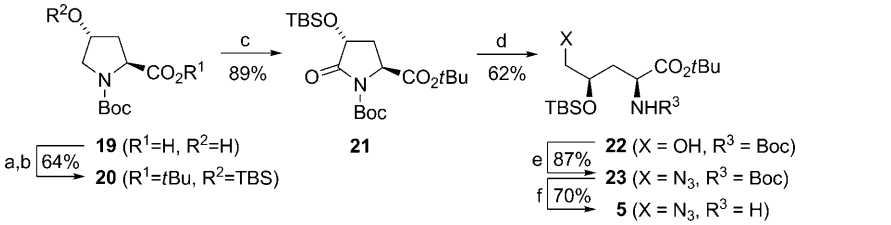
Three orthogonal protecting groups (Cbz, Boc, methyl ester) were then installed on two building blocks starting from the same compound **9** (Scheme 4). Cbz-protection of amine hydrochloride **9** provided iodide **7**. Boronate **8** was obtained in excellent yield after



Scheme 4. Suzuki coupling with a free carboxylic acid **6**. Reagents and conditions: a) CbzCl (1.2 equiv), $NaHCO_3$ (1.0 equiv), 1,4-dioxane/H_2O (1:1), 16 h, 74 %; b) Boc_2O (1.5 equiv), 2 M NaOH (2 equiv), dioxane/H_2O (1:1), 16 h, 92 %; c) MeI (1.5 equiv), K_2CO_3 (2 equiv), acetone, reflux, 16 h, 97 %; d) $(Bpin)_2$ (1.2 equiv), [$PdCl_2$(dppf)] (5 mol %), KOAc (3 equiv), DMSO, 80 °C, 16 h, 96 %; e) **7** (1.0 equiv), **8** (1.2 equiv), $Pd(OAc)_2$ (20 mol %), P(*o*-tolyl)$_3$ (40 mol %), Cs_2CO_3 (3 equiv), 1,4-dioxane/H_2O (9:1), 80 °C, 16 h, 74 %. dppf = bis(diphenylphosphino)ferrocene.

introduction of a Boc-group, methylester formation, and Pd^0-mediated borylation.[23] Biaryl acid **6** was produced in 74 % yield by a Suzuki coupling reaction of iodide **7** with boronate **8** using $Pd(OAc)_2$ as a catalyst, tri(*o*-tolyl)phosphine as a ligand, and Cs_2CO_3 as a base in dioxane/water 9:1 at 80 °C. This Suzuki coupling with a free carboxylic acid saved not only a protecting group and two reaction steps, but also afforded a simplified and flexible synthesis route.

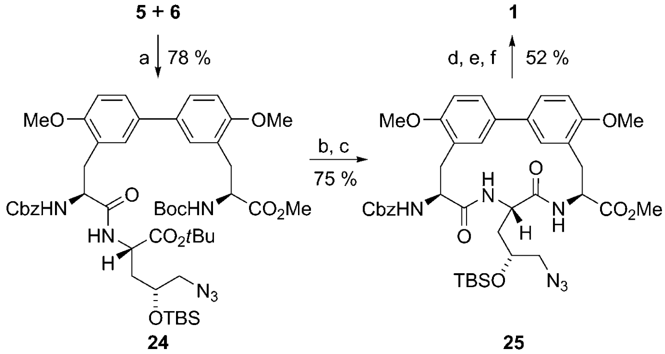
The central hydroxyornithine amino acid was elaborated from *N*-Boc-*trans*-4-hydroxyproline **19** (Scheme 5). Acid **19** was converted into its *tert*-butyl ester by using *O*-*tert*-butyl isourea[24] and silylated to provide the *tert*-butyldimethylsilyl (TBS) ether **20** in 64 % yield. To enable functionalization, pyrrolidine **20** was subjected to a regioselective α-oxidation with a catalytic amount of RuO_4,[25] which smoothly provided pyroglutamate **21** in 89 % yield.[26] The activated amide **21** could be regioselectivity reduced with $NaBH_4$ to give al-



Scheme 5. Synthesis of protected hydroxyornithine **5**. Reagents and conditions: a) *O*-*tert*-butyl *N*,*N*-diisopropylisourea (2 equiv), THF, 60 °C, 16 h, 68 %; b) TBSCl (1.2 equiv), DMAP (0.1 equiv), imidazole (2.6 equiv), 16 h, 94 %; c) RuO_2·*n*H_2O (25 mol %), $NaIO_4$ (3 equiv), EtOAc/H_2O (1:2), 16 h, 89 %; d) $NaBH_4$ (5 equiv), MeOH/NaP_i buffer (1:1, pH 7.0), 0 °C→RT, 8 h, 62 %; e) PPh_3 (3 equiv), DIAD (3 equiv), HN_3 (5 equiv), 4 h, 87 %; f) TBSOTf (1.5 equiv), 2,6-lutidine (2 equiv), CH_2Cl_2, 15 min, then TBAF (1 equiv), THF/H_2O (10:1), 70 %.

cohol **22** in 62% yield. The key for success was careful control of temperature and pH. Otherwise, deoxygenation and/or over reduction led to formation of several side products. Alcohol **22** was converted into the azide **23** by using a Mitsunobu displacement reaction with hydrazoic acid[27] in 87% yield. In a last step, amine **5** was liberated by selective Boc-group cleavage with TBSOTf[28] in 70% yield.

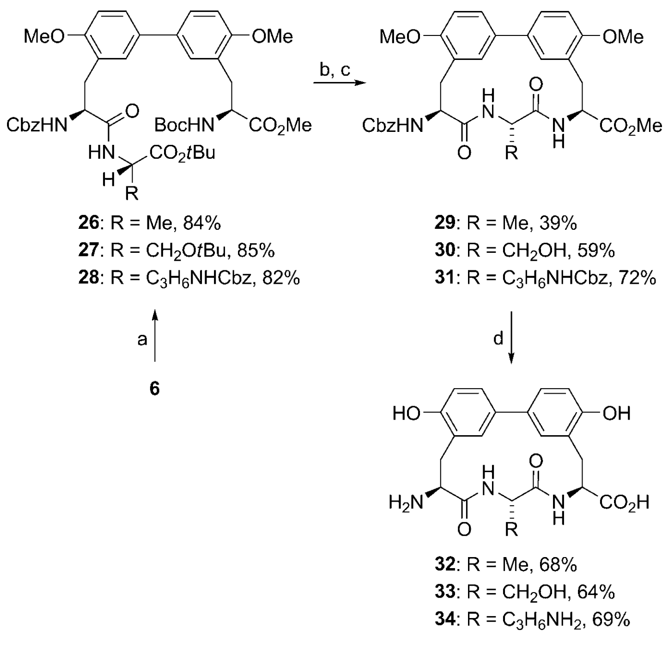
Biaryl acid **6** was then coupled with amine **5** using *N*-ethyl-*N*-dimethylaminopropyl carbodiimide (EDC)·HCl, 1-hydroxybenzotriazole (HOBt), and diisopropylethylamine (DIPEA) in 78% yield (Scheme 6), and the resulting dipeptide **24** was then simultaneously Boc- and *t*Bu-deprotected with TESOTf[29] in quantitative yield, which retained the TBS group. Other silyl triflates were either too reactive (TMSOTf) or led to incomplete conversion (TBSOTf). Ring closure was achieved by activation with HATU/HOAt[30] in dry dichloromethane using a syringe pump to obtain macrocycle **25** in 75% yield. In our initial plan, we intended to keep the azide intact as a potential diversification element until the very last step. However, during deprotection experiments we witnessed that strong Lewis acidic conditions would induce unexpected decomposition reactions of the 2-hydroxy azide side chain.



Scheme 6. Completion of the total synthesis of biphenomycin B (**1**). Reagents and conditions: a) EDC·HCl (1.5 equiv), HOBt (1.5 equiv), EtN(iPr)$_2$ (2.2 equiv), CH_2Cl_2, RT, 16 h, 78%; b) TESOTf (20 equiv), 2,6-lutidine (40 equiv), CH_2Cl_2, RT, 6 h, quant.; c) slow addition to HATU (1.5 equiv), HOAt (1.5 equiv), EtN(iPr)$_2$ (2.2 equiv), CH_2Cl_2, RT, 30 h, 75%; d) PMe_3 (9 equiv, 1 M in toluene), THF/0.1 M NaOH (9:1), RT, 8 h, quant.; e) 1 M HCl, RT, 16 h, quant.; f) BBr_3 (1 M in CH_2Cl_2, 20 equiv), RT, 24 h, 52% (prep. HPLC). EDC=*N*-Ethyl-*N*-dimethylaminopropyl carbodiimide, HOBt = 1-hydroxybenzotriazole, HATU = 7-aza-1-hydroxybenzotriazoluronium hexafluorophosphate, HOAt = 7-aza-1-hydroxybenzotriazole, TESOTf = triethylsilyl trifluoromethanesulfonate.

Therefore, the azide functional group was reduced first to the amine by using PMe_3 and aqueous hydroxide in quantitative yield. These conditions unmasked the carboxy terminus as well. Aqueous HCl was subsequently used for clean removal of the TBS group, because it was found that the secondary TBS ether was prone to S_N2-type displacement with bromide when treated with BBr_3.[31] The 2-amino alcohol obtained could be treated with excess BBr_3, which cleanly cleaved the Cbz and OMe groups. Biphenomycin B (**1**) was finally obtained in 52% yield after purification and desalting by preparative HPLC. The NMR spectral data, as well as the HRMS, IR, and optical rotation data were fully consistent with those reported for natural biphenomycin B. Additionally, we recorded a CD spectrum of the synthetic material (see the Supporting Information). While no original CD data for biphenomycin B (**1**) is available in the literature, the features found were similar to the ones reported for biphenomycin A (**2**)[32] and a derivative of **1**.[33] Notably, the strong positive ellipticity around 220 nm indicated a negative dihedral angle of the biaryl linkage, that is, *M*- (or *R*-) configuration. While there is no reason to believe in the existence of separable atropisomers for the biphenomycin scaffold due to the absence of potentially locking *o*,*o*-disubstitution, the minimum conformation of the cyclopeptide array still seems to program an *M*-configured axis for the biaryl motif in solution.[34] Such a conformation had been independently deduced earlier on for biphephenomycin A by a combination of 2D NMR spectroscopy and molecular modeling experiments.[32]

To study the influence of the side chain on the bioactivity of biphenomycin B in some detail, the successful total synthesis scheme was adapted to prepare three analogs with different side chains (Scheme 7). For this purpose, the biaryl acid **6** was independently extended with *t*Bu-protected L-alanine-, serine-, and ornithine-*t*Bu-ester using HOBt/EDC, to give the biarylpeptides **26**–**28** in 82–85% yield. To prepare for macrocycle formation, the *t*Bu-based protecting groups were removed by using 4 N HCl in 1,4-dioxane. Macrocycli-



Scheme 7. Synthesis of derivatves **32**, **33**, and **34** with different side chains. Reagents and conditions: a) L-H-alanine-O*t*Bu·HCl or L-H-serine-O*t*Bu·HCl or L-H-Orn(*Z*)-O*t*Bu·HCl (1.2 equiv), EDC·HCl (1.2 equiv), HOBt (1.2 equiv), EtN(iPr)$_2$ (2.2 equiv), CH_2Cl_2, RT, 16 h; b) 3 M HCl, 1,4-dioxane/water, RT, 4 h, then 4 M HCl, 1,4-dioxane/water, RT, 2 h; c) slow addition to HATU (1.5 equiv), HOAt (1.5 equiv), EtN(iPr)$_2$ (2.2 equiv), CH_2Cl_2, RT, 30 h; d) I_2 (32 equiv), Al (40 equiv), nBu$_4$N$^+$I$^-$ (10 mol%), benzene, 10°C, 1 h, then 60°C, 15 min, then prep. HPLC.

zation was executed as before and delivered the corresponding biaryl cyclopeptides **29**–**31** in 39–72% yield. Interestingly, the efficiency of ring closure seemed to be affected by the type of side chain present at the central amino acid. Increasing its steric bulk was apparently supporting ring closure, as the yield of derivative **29** was significantly lower than in the case of the bulky side chains **30**, **31**, and **25**. During studies which aimed at the final deprotection of the molecule, we sometimes observed sluggish reactivity of BBr_3. After some screening of stronger Lewis acids, we found that freshly prepared AlI_3[35] efficiently provided the fully deprotected biphenomycin derivatives. Despite the higher activity of the reagent, no byproducts or epimerization were observed when reaction times were kept short (15 min). In this way, the target compounds **32**–**34** were obtained in 64–69% yield after preparative HPLC purification.

Biological Tests

Synthetic biphenomycin B (**1**) and the derivatives **32**–**34** were then tested for bacterial growth inhibition. In line with previous reports,[6,8–13] we found it quite difficult to acquire reliable growth inhibition data in liquid cell culture.[36] Hence, we resorted to testing for bacterial translation inhibition, as the biphenomycins had been reported to inhibit protein biosynthesis.[14] We employed a coupled in vitro transcription/translation assay, which measures protein biosynthesis from the generation of fluorescence of a green fluorescent protein (GFP)-encoding vector through *E. coli* ribosome translation.[37] In this target-based assay (Table 1), we found synthetic biphenomycin B only moderately active (38 μM) when compared to typical ribosomal inhibitors of the large subunit (50S: chloramphenicol), the small subunit (30S: kanamycin), or elongation factors (EF-TU: kirromycin). Interestingly, the polar side chain seemed to have some influence on the activity of the compound, although its influence could not be firmly assessed. When the amino group was not present, activity was markedly reduced. Omission of the hydroxy group or all of the functionality rendered the compound completely inactive.

Table 1. Translation inhibition by biphenomycin B and analogs in comparison with ribosomal inhibitors.

Compound	IC_{50} value
kirromycin	0.38 μM ± 0.01 μM
kanamycin	0.18 μM ± 0.01 μM
chloramphenicol	3.0 μM ± 0.5 μM
biphenomycin B (**1**)	38 μM ± 7.9 μM
32	> 300 μM
33	approx. 200 μM
34	> 300 μM

These data support the hypothesis that the biphenomycins do inhibit protein biosynthesis in bacterial cells. The rather modest activity suggests that **1** binds to one of the components of the translational machinery in bacteria, but with moderate affinity. In principle, such modest translation inhibition as observed here could correlate with the weak effects that biphenomycin has on the growth of many bacterial strains in rich culture media in vitro. Nonetheless, such a standard mode of action and the weak activity consequently ensuing from it cannot easily account for the documented activity of biphenomycin B in vivo. In fact, all antibiotics tested here or elsewhere[37] with clearly assigned inhibition activity at the ribosome's key components also gave strong inhibition data in the test system used here. Therefore, it might be hypothesized that biphenomycin could have additional activities, which are not picked up well in this target-focused assay in vitro. To fully explain the context-dependent activity of the biphenomycins, other regulatory or conditional metabolic factors might contribute to the mode of action. At least, our results cannot exclude that alternative targets beyond the protein biosynthesis machinery could be involved under certain experimental conditions or in vivo.

Conclusions

We have achieved a total synthesis of biphenomycin B from three independent amino acid building blocks. The synthesis is short (14 steps, 15% total yield) and flexible, as demonstrated by the successful synthesis of three derivatives. Initial biological testing suggested that the biphenomycins influence translation, and clarified the influence of the side chain, but a more complex interaction pattern or target is likely. This observation is convergent with the efficacy of the biphenomycins mostly developing in vivo, but much less in vitro. Notably, the synthetic work developed herein will provide tool compounds for clarifying this point in the future.

Experimental Section

All reactions were carried out under an inert atmosphere of argon. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury 400 or a Bruker DRX 400 (400.13 MHz and 100.61 MHz respectively; 500.13 MHz and 125.61 MHz respectively), with chemical shifts (δ) reported in ppm relative to the solvent residual signals and coupling constants reported in Hz. High resolution mass spectra (HRMS) were measured on a Thermo Orbitrap coupled to a Thermo Accela HPLC system, electrospray ionization (ESI), and fast atom bombardment (FAB). Analytical HPLC-MS data were recorded on an Agilent HPLC (1100 series) with a C18 column (CC125/4 NUCLEODUR C18 Gravity 5μ) coupled to a Finnigan LCQ ESI spectrometer, detection: 280 nm; flow rate: 1.0 mL min^{-1}; time: 15 min; solvents A: 0.1% HCOOH in H_2O, B: 0.1% HCOOH in MeCN, 1 min 10% B, in 10 min to 100% B. Analytical GC MS data were recorded on a HP 6890 GC-MS system based on electron impact detection (EI) using an high resolution gas chromatography column (length: 25 m, I.D.: 0.2 mm, Film: 0.33 μm) and a heating profile of ambient temperature to 100 °C for 1 min, then for 5 min at 300 °C, and then constant at 300 °C for 5 min. Pre parative HPLC was performed on an Agilent HPLC (1100 series) and Waters HPLC 2767 by using a 125/21 NUCLEODUR C18 Gravity 5 μ column (Macherey & Nagel). For IR spectroscopy, a Bruker Tensor 27 FT equipped with an ATR and the OPUS software was used. Chromato-

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graphic purification refers to flash chromatography using the indicated solvents and Merck silica gel 60. Thin layer chromatography (TLC) was performed using silica (Merck silica gel 60 F254 on aluminum foil). Compounds on TLC were visualized by UV detection or staining with $KMnO_4$ solution. Melting points were determined using a Büchi B-540 device and are uncorrected. Anhydrous solvents were purchased from Fluka or Acros except for dichloromethane, which was distilled from calcium hydride. All other solvents were used as supplied (analytical or HPLC grade), without prior purification. Reagents were purchased from Aldrich or Acros and used as supplied.

*5-Iodo-2-methoxybenzaldehyde (**13**)*

A mixture of 2-hydroxy-5-iodbenzaldehyde **12** (80.0 g, 0.32 mol, 1.0 equiv), iodomethane (92.9 g, 40.7 mL, 0.48 mol, 1.5 equiv), and potassium carbonate (66.9 g, 0.48 mol, 1.5 equiv) in acetone (500 mL) was heated to reflux for 16 h. After removal of the solvent, water (300 mL) was added and the mixture was extracted with ethyl acetate (3×300 mL). The combined organic layers were washed with brine (200 mL), dried with $MgSO_4$, and concentrated. The residue was dried in vacuo to furnish **13** (75.9 g, 0.29 mol, 92%) as a colorless solid. R_f=0.78 (cyclohexane/ethyl acetate 2:1); m.p. 136–138°C. GC-MS (DB_50_S): t_R=6.66 min, *m/z* (relative intensity [%])=216 (9), 244 (18), 262 (100) $[M]^+$. IR: $\tilde{\nu}$=3231 (m), 2876 (m), 1665 (s), 1604 (s), 1463 (s), 1307 (s), 1271 (s), 1153 (s), 885 (s), 826 (s), 765 (s), 688 (m), 612 cm^{-1} (s). ^1H NMR (400 MHz, $CDCl_3$): δ=3.91 (s, 3H), 6.78 (d, J=8.8 Hz, 1H), 7.80 (dd, J=8.8 Hz, 2.32 Hz, 1H), 8.08 (d, J=2.4 Hz, 1H), 9.82 ppm (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.5, 83.6, 114.8, 127.2, 137.8, 144.8, 162.1, 188.9 ppm. HR-MS (FAB): calcd for $C_8H_8IO_2$: 262.9569 $[M+H]^+$; found: 262.9593.

*2-Methoxy-5-iodobenzyl alcohol (**14**)*

Aldehyde **13** (4.0 g, 15.0 mmol, 1.0 equiv) was dissolved in abs. dichloromethane (40 mL) and cooled to 0°C. A solution of diisobutylaluminum hydride (1 M in toluene, 18 mL, 18.0 mmol, 1.2 equiv) in toluene was added dropwise over 1 h and the mixture was stirred for 2 h. Saturated aqueous potassium sodium tartrate was added (30 mL) and the mixture was stirred for 5 h. The reaction mixture was warmed to room temperature and extracted with dichloromethane (3×30 mL). The combined organic layers were washed with brine (40 mL), dried with $MgSO_4$, and concentrated. The residue was dried in vacuo to furnish alcohol **14** as a colorless solid. Yield: 3.88 g, 14.7 mmol, 98%. R_f=0.34 (cyclohexane/ethyl acetate 3:1); m.p. 92–93°C. GC-MS (DB_50_S): t_R=4.52 min; *m/z* (relative intensity [%])=264 (100), $[M]^+$. IR: $\tilde{\nu}$=3286 (m), 2957 (m), 2835 (m), 1480 (s), 1439 (s), 1365 (s), 1239 (s), 1171 (s), 1126 (m), 1029 (s), 877 (s), 880 (m), 798 (s), 612 cm^{-1} (s). ^1H NMR (400 MHz, $CDCl_3$): δ=2.06 (s, 1H), 3.83 (s, 3H), 4.62 (s, 2H), 6.65 (d, J=8.4 Hz, 1H), 7.55 (dd, J=8.4 Hz, 2.12 Hz, 1H), 7.59 ppm (d, J=2.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=55.8, 61.5, 83.2, 112.9, 132.0, 137.4, 137.8, 157.5 ppm. HR-MS (FAB): calcd for $C_8H_9IO_2$: 263.9647 $[M]^+$; found: 263.9640.

*2-Methoxy-5-iodobenzyl bromide (**10**)*

Alcohol **14** (3.36 g, 12.8 mol, 1.0 equiv) was dissolved in toluene (50 mL) and heated to 40°C for 20 min. Phosphorus tribromide (0.41 mL, 4.36 mmol, 0.34 equiv) was added dropwise and the mixture was stirred at 100°C for 50 min. After cooling to room temperature, the mixture was washed with water (2×20 mL) and brine (20 mL). The organic layer was dried with magnesium sulphate and filtered to obtain 2-methoxy-5-iodobenzyl bromide as a solution in toluene. The product **10** could only be stored in a toluene solution, as it quickly decomposed after concentration. Yield: quantitative (GC-MS). R_f=0.76 (cyclohexane/ethyl acetate 3:1). GC-MS (DB_100_S): t_R=4.96 min; *m/z* (relative intensity [%])=217(27), 247 (100), 326 (12) $[M]^+$. IR: $\tilde{\nu}$=2938 (w), 2838 (w), 1624 (m), 1484 (s), 1433 (m), 1298 (m), 1249 (s), 1209 (s), 1149 (s), 1121 (s), 882 (m), 862 (m), 802 (s), 737 (m), 611 cm^{-1} (s). ^1H NMR (400 MHz, $CDCl_3$): δ=3.87 (s, 3H), 4.45 (s, 2H), 6.65 (d, J=8.8 Hz, 1H), 7.57 (dd, J=8.56, 2.12 Hz, 1H), 7.61 ppm (d, J=2.16 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=27.7, 56.1, 82.7, 113.6, 129.0, 139.1, 139.6, 157.7 ppm.

*(S)-2-Amino-3-(5′-iodo-2′-methoxyphenyl)-propionic acid hydrochloride (**9**)*

A mixture of diphenylmethyleneglycine *tert*-butyl ester (200 mg, 0.67 mmol, 1.0 equiv), cesium hydroxide monohydrate (1.2 g, 6.78 mmol, 10 equiv), and Corey's cinchonidine catalyst[21] (41.1 mg, 0.067 mmol, 0.1 equiv) in dichloromethane (50 mL) was cooled to −50°C. A solution of benzyl bromide **10** (443 mg, 1.35 mmol, 2.0 equiv) in toluene (30 mL) was added dropwise over 1 h and the mixture was stirred at −50°C for 16 h. After warming to room temperature, water (30 mL) was added and the mixture was extracted with diethyl ether (3×30 mL). The combined organic layers were washed with brine (30 mL), dried with $MgSO_4$, concentrated, and purified by flash chromatography (silica gel, cyclohexane/ethyl acetate/tri
ethylamine 95:5:1). The resulting product (R_f=0.32 in cyclohexane/ethyl acetate 3:1) was dissolved in 1,4-dioxane (20 mL). A saturated aqueous solution of HCl (10 mL) was added dropwise. After stirring at room temperature for 16 h, ethyl acetate (30 mL) was added and the mixture was extracted with water (3×25 mL). The aqueous extracts were concentrated and dried in vacuo to furnish the product **9** as a colorless solid. Yield: 314 mg, 0.59 mol, 88%; m.p.>228°C (decomp.); *ee*> 96%; $[\alpha]_D^{20}$=+8.9 (MeOH, C=0.5). HPLC-ESI: t_R=6.68 min; *m/z*=322.01 $[M-Cl^-]^+$. IR: $\tilde{\nu}$=3596 (m), 3276 (m), 2889 (s), 2640 (w), 1735 (s), 1569 (m), 1521 (s), 1484 (s), 1251 (s), 1204 (s), 1120 (s), 1027 (s), 880 (m), 806 (s), 614 cm^{-1} (m). ^1H NMR (400 MHz, CD_3OD): δ=3.07 (dd, J=3.8, 7.12 Hz, 1H), 3.35 (dd, J=2.74, 6.5 Hz, 1H), 3.89 (s, 3H), 4.25 (dd, J=7.64, 7.60 Hz, 1H), 6.87 (d, J=8.60 Hz, 1H), 7.55 (d, J=2.32 Hz, 1H), 7.65 ppm (dd, J=2.00 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ=32.9, 54.6, 56.7, 83.9, 115.1, 127.2, 140.1, 141.5, 159.9, 171.8 ppm. HR-MS (FAB): calcd for $C_{10}H_{13}INO_3^+$: 321.9935 $[M-Cl^-]^+$; found: 321.9927.

*(S)-2-(tert-Butyloxycarbonylamino)-3-(5′-iodo-2′-methoxyphenyl)-propionic acid (**17**)*

A mixture of amino acid hydrochloride **9** (2.00 g, 5.59 mmol, 1.0 equiv) and aqueous sodium hydroxide (2 M, 5.6 mL, 11.2 mmol, 2.0 equiv) in 1,4-dioxane/water 1:1 (50 mL, v/v) was cooled to 0°C. A solution of di-*tert*-butyl dicarbonate (1.83 g, 8.39 mmol, 1.5 equiv) in dioxane (2 mL) was added dropwise over 10 min. After the addition, the reaction mixture was stirred for 16 h at room temperature. Subsequently, the pH of the reaction mixture was adjusted to pH 2 with 1N hydrochloric acid. The mixture was extracted with ethyl acetate (3×25 mL). The combined organic layers were washed with brine (30 mL), dried with $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (silica gel, dichloromethane/MeOH 7:1) to give Boc-protected amine **17** as a colorless solid. Yield: 2.16 g, 5.13 mmol, 92%. R_f=0.46 (dichloromethane/MeOH 7:1); m.p. 121–124°C. $[\alpha]_D^{20}$=+13.3 (MeOH, c=1.0). HPLC-ESI: t_R=10.21 min. IR: $\tilde{\nu}$=3277 (m), 2921 (m), 1734 (s), 1568 (m), 1521 (s), 1484 (s), 1250 (s), 1203 (s), 1120 (s), 1027 (s), 880 (m), 805 cm^{-1} (s). ^1H NMR (400 MHz, CD_3OD): δ=1.39 (s. 9H, 3×CH_3), 2.76 (dd, J=3.72, 6.41 Hz, 1H), 3.16–3.21 (dd, J=4.88 6.74 Hz, 1H), 3.86 (s, 3H), 4.42 (dd, J=4.88, 4.78 Hz, 1H), 6.77 (dd, J=8.60 Hz, 1H), 7.46 (d, J=2.16 Hz, 1H), 7.53 ppm (dd, J=8.56, 2.12 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ=29.6, 34.6, 56.8, 81.3, 83.5, 138.9, 138.9, 141.6, 160.1, 166.8 ppm. HR-MS (FAB): calcd for $C_{15}H_{20}INO_5$: 421.0386 $[M]$; found: 421.0416.

*(S)-2-tert-Butyloxycarbonylamino-3-(2′-methoxy-5′-iodphenly)propionic acid methyl ester (**18**)*

Tyrosine derivative **17** (2.11 g, 5.0 mmol, 1.0 equiv), potassium carbonate (1.38 g, 10.0 mmol, 2.0 equiv), and iodomethane (0.47 mL, 7.5 mmol, 1.5 equiv) were suspended in acetone (40 mL) and heated to reflux for 20 h. After cooling to room temperature, the solvent was removed, the residue was treated with water (30 mL), and extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with brine (30 mL), dried with $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 3:1) to give methyl ester **18** as a yellow solid. Yield: 2.1 g, 4.8 mmol, 97%. R_f=0.49 (cyclohexane/ethyl acetate 3:1). HPLC-ESI: t_R= 10.21 min; m.p. 174–176°C. $[\alpha]_D^{20}$=+12.9 (MeOH, c=1.5). IR: $\tilde{\nu}$=3367

(w), 2975 (w), 1708 (s), 1489 (s), 1364 (m), 1251 (s), 1159 (s), 1048 (s), 1016 (s), 861 (w), 811 cm^{-1} (m). ^1H NMR (400 MHz, CD_3OD): $\delta = 1.39$ (s, 9H), 2.77 (dd, $J = 4.68$, 6.64 Hz, 1H), 3.17–3.21 (dd, $J = 6.64$, 2.74 Hz, 1H), 3.71 (s, 3H), 3.86 (s, 3H), 4.44 (dd, $J = 5.68$, 5.44 Hz, 1H), 6.77 (dd, $J = 8.60$ Hz, 1H), 7.43 (s, 1H), 7.53 ppm (dd, $J = 8.6$, 2.16 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD): $\delta = 29.5$, 34.6, 53.4, 55.3, 56.9, 81.4, 83.8, 114.8, 130.2, 139.1, 141.6, 158.5, 160.0, 175.1 ppm. HR-MS (FAB): calcd for $C_{16}H_{22}INO_5^+$: 435.0543 $[M]^+$; found: 435.0513.

*(S)-2-tert-*Butyloxycarbonylamino-3-[2′methoxy-5′-(4″,4″,5″,5″-tetramethyl 1″,3″,2″-dioxaborolane-2″-yl)phenyl]-propionic acid methyl ester (**8**8)

Iodide **18** (1.00 g, 2.3 mmol, 1.0 equiv) was dissolved in abs. DMSO (20 mL). After addition of potassium acetate (0.68 g, 6.9 mmol, 3.0 equiv), the suspension was purged with argon for 30 min. Bis(pinacolato)diboron (0.70 g, 2.76 mmol, 1.2 equiv) and $[PdCl_2(dppf)]\cdot CH_2Cl_2$ (84.1 mg, 0.12 mmol, 0.05 equiv) was added and the reaction mixture was heated to 80 °C for 4 h. After cooling to room temperature, water was added (20 mL) and the mixture was extracted with ethyl acetate (3× 30 mL). The combined organic layers were washed with brine (30 mL), dried with $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 1:1) to give boronate **8** as a yellow liqiud. Yield: 961 mg, 2.21 mmol, 96%. HPLC-ESI: $t_R = 10.49$ min; $m/z = 336.00$ $[M+H\text{-Boc}]^+$. $[\alpha]_D^{20} = +1.8$ ($CHCl_3$, $c = 1.0$). IR: $\tilde{\nu} = 2964$ (w), 2874 (w), 1665 (s), 1585 (s), 1473 (s), 1389 (m), 1266 (s), 1243 (s), 1176 (s), 1121 (s), 1018 (s), 881 (s), 817 (s), 643 (s), 610 cm^{-1} (s). ^1H NMR (400 MHz, CD_3OD): $\delta = 1.35$ (s, 12H), 1.37 (s. 9H), 2.88 (dd, $J = 6.54$, 8.76 Hz, 1H), 3.18 (dd, $J = 6.74$, 6.64 Hz, 1H), 3.69 (s, 3H), 3.90 (s, 3H), 4.44 (dd, $J = 5.88$, 5.76 Hz, 1H), 6.96 (d, $J = 8.20$ Hz, 1H), 7.51 (s, 1H), 7.66 ppm (dd, $J = 8.20$ Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD): $\delta = 25.8$, 29.3, 34.6, 53.2, 55.5, 56.5, 81.1, 111.5, 126.3, 137.4, 139.6, 162.5, 175.1 ppm. HR-MS: calcd for $C_{22}H_{34}BNO_7^+$: 435.2428 $[M]^+$; found: 435.2413.

*(S)-2-(Benzyloxycarbonylamino)-3-(5-iodo-2-methoxyphenyl)-propionic acid (**7**)*

Amino acid hydrochloride **9**·HCl (2.0 g, 5.59 mmol, 1.0 equiv) and sodium bicarbonate (0.59 g, 5.59 mmol, 1.0 equiv) were dissolved in water/1,4-dioxane 1:1 (50 mL) and cooled to 0 °C. A solution of benzyl chloroformate (0.94 mL, 6.70 mmol, 1.2 equiv) in dioxane (3 mL) was added dropwise over 10 min. The reaction mixture was warmed to room temperature and stirred for 16 h. Subsequently, the pH of the reaction mixture was adjusted to pH 1 with 1N HCl and the mixture was extracted with ethyl acetate (3×25 mL). The combined organic layers were washed with brine (30 mL), dried with $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (silica gel, dichloromethane/MeOH 7:1) to give acid **7** as a yellow liquid. Yield: 1.88 g, 4.14 mol, 74%. $[\alpha]_D^{20} = +8.3$ (MeOH, $c = 0.73$). HPLC-ESI: $t_R = 9.21$ min. IR: $\tilde{\nu} = 3304$ (s), 3032 (m), 2940 (m), 1688 (s), 1587 (s), 1537 (s), 1430 (s), 1343 (m), 1246 (s), 1125 (s), 1055 (s), 1026 (s), 880 (m), 738 (m), 695 cm^{-1} (s). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.93$–2.97 (dd, $^3J = 6.74$, 6.84 Hz, 1H), 3.27 (dd, $^3J = 6.64$, 6.94 Hz, 1H), 3.83 (s, 3H) 4.52 (dd, $J = 5.08$ Hz, 1H), 5.03 (m, 2H), 6.67 (d, $J = 8.60$ Hz, 1H), 7.33 (m, 5H), 7.48 (d, $J = 2.16$ Hz, 1-H), 7.55 ppm (dd, $J = 8.60$, 2.16 Hz, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2OD$): $\delta = 34.4$, 56.8, 66.1, 68.3, 83.8, 114.8, 128.8, 129.1, 129.4, 129.7, 130.2, 130.3, 139.0, 141.6, 143.6, 159.2, 160.9, 181.0 ppm. HR-MS: calcd for $C_{18}H_{18}INO_5$: 455.0229 $[M+H]^+$; found: 455.0260.

*(2S,2‴S)-2-(Benzyloxcarbonylamino)-3-(4′,4″-bis-methoxy-3″-[tert-butyloxy-carbonylamino-2‴-methoxycarbonylethyl]-biphenyl-3′-yl)-propionic acid (**6**)*

Iodide **7** (218 mg, 0.48 mmol, 1.0 equiv) and boronate **8** (250 mg, 0.57 mmol, 1.2 equiv) were dissolved in 1,4-dioxane/water (10 mL, 9:1). Cesium carbonate (469 mg, 1.44 mmol, 3.0 equiv) was added and the solution was purged with argon for 30 min. Palladium(II) acetate (21.6 mg, 0.10 mmol, 0.2 equiv) and tri(*o*-tolyl) phosphine (57.8 mg, 0.19 mmol, 0.4 equiv) were added and the reaction mixture was heated to 80 °C for 8 h. After cooling to room temperature, the mixture was diluted with water (10 mL), and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (30 mL), dried with $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (silica gel, dichloromethane/MeOH 7:1) to give biaryl acid **3** as a colorless solid. Yield: 226 mg, 0.36 mmol, 74%. $R_f = 0.56$ (dichloromethane/MeOH 7:1); m.p. 113–115 °C. $[\alpha]_D^{20} = +20.1$ (MeOH, $c = 1.2$). HPLC-ESI: $t_R = 9.79$ min; $m/z = 659.15$ $[M+Na]^+$. IR: $\tilde{\nu} = 3340$ (w), 2939 (w), 1709 (s), 1069 (m), 1492 (s), 1437 (m), 1243 (s), 1162 (m), 1024 (s), 853 (m), 738 (m), 697 cm^{-1} (m). ^1H NMR (400 MHz, CD_3OD): $\delta = 1.35$ (s, 9H), 2.87–3.36 (m, 4H), 3.68 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 4.48 (m, 1H), 4.54 (m, 1H), 5.02 (m, 2H), 6.98 (m, 2H), 7.24 (m, 4H), 7.44 ppm (m, 5H). ^{13}C NMR (100 MHz, CD_3OD): $\delta = 25.9$, 29.3, 56.8, 56.9, 68.3, 76.7, 112.6, 129.4, 129.6, 129.7, 130.3, 131.4, 138.9, 162.5, 168.9, 175.1 ppm. HR-MS (FAB): calcd for $C_{34}H_{40}N_2O_{10}Na^+$: 659.2575 $[M+Na]^+$; found: 659.2550.

*(2S,4R)-N-tert-butoxycarbonyl-4-(tert-butyldimethylsilyloxy)pyrrolidine-2-carboxylic acid tert-butylester (**20**)*

trans-N-Boc-4-hydroxyproline **19** (10.6 g, 46 mmol, 1.0 equiv) was dissolved in THF (20 mL), and *O-tert*-butyl isourea[24] (9.2 g, 46 mmol, 1.0 equiv) was added dropwise. The mixture was heated to 60 °C for 4 h. A second equivalent of *O-tert*-butyl isourea (9.2 g, 46 mmol, 1.0 equiv) was added at 60 °C and stirring was continued for 16 h. After cooling to room temperature, the mixture was filtered and the solvent was removed in vacuo. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 9:1→5:1). The *tert*-butylester was dissolved in dimethylformamide (85 mL), and 4-dimethylaminopyridine (DMAP; 0.54 g, 4.6 mmol, 0.1 equiv), imidazole (8.2 g, 120 mmol, 2.6 equiv), and TBSCl (8.4 g, 55 mmol, 1.2 equiv) were added at 0 °C. The mixture was stirred at room temperature for 16 h, diluted with water (250 mL), and extracted with ethyl acetate (3×500 mL). The combined organic layers were washed with brine (200 mL), dried with $MgSO_4$, and concentrated. After removal of the solvent, the crude product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 7:1) to give the TBS-protected proline derivative **20** as a colorless liquid. Yield: 11.9 g, 29.4 mmol, 64%. $R_f = 0.40$ (cyclohexane/ethyl acetate 5:1); m.p. 51.2–52.1 °C. $[\alpha]_D^{20} = -51.6$ (MeOH, $c = 1$). IR: $\tilde{\nu} = 2976$ (m), 2930 (m), 1719 (s), 1684 (m), 1472 (w), 1410 (s), 1366 (s), 1309 (s), 1157 (s), 1088 (s), 833 (s), 807 (s), 774 cm^{-1} (s). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.04$ (s, 6H), 0.85 (s, 9H), 1.42 (s. 9H), 1.44 (s. 9H), 1.94–2.00 (m, 1H), 2.07–2.19 (m, 1H), 2.23–3.36 (m, 1H), 3.52–3.60 (m, 1H), 4.16–4.27 (m, 1H), 4.38 ppm (t, $J = 9.4$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.9$, 17.9, 25.7, 27.9, 28.3, 38.8, 39.7, 54.2, 54.6, 58.5, 58.7, 69.5, 70.3, 79.8, 80.9, 154.0, 172.2 ppm. HR-MS (FAB): calcd for $C_{20}H_{40}NO_5Si^+$: 402.2670 $[M+H]^+$; found: 402.2645.

*(2S,4R)-N-tert-butoxycarbonyl-4-(tert-butyldimethylsilyloxy)-5-oxopyrrolidine-2-carboxylic acid tert-butylester (**21**)*

$RuO_2\cdot xH_2O$ (40 mg, 0.3 mmol, 0.27 equiv) was added to a solution of $NaIO_4$ (836 mg, 3.9 mmol, 3.5 equiv) in distilled water (12 mL). The yellow solution was stirred under an argon atmosphere at room temperature for 5 min and a solution of pyrrolidine **20** (451 mg, 1.12 mmol, 1.0 equiv) in ethyl acetate (9 mL) was added. Stirring was continued for 20 h at room temperature. The mixture was diluted with ethyl acetate (30 mL) and filtered through a pad of celite. The organic layer was washed with saturated aqueous $NaHSO_3$ solution (10 mL), brine (10 mL), and dried with $MgSO_4$. After removal of the solvent, the crude product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 9:1→7:1) to give pyrrolidine **21** as a colorless solid. Yield: 413 mg, 1.00 mmol, 89%; m.p. 65.0–65.5 °C. $R_f = 0.39$ (cyclohexane/ethyl acetate 5:1). $[\alpha]_D^{20} = +13.1$ (MeOH, $c = 1$). IR: $\tilde{\nu} = 2929$ (w), 2856 (w), 1797 (m), 1759 (s), 1723 (s), 1461 (m), 1392 (s), 1368 (s), 1308 (s), 1228 (s), 1138 (s), 970 (s), 882 (s), 777 cm^{-1} (s). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.12$ (s, 3H), 0.16 (s, 3H), 0.89 (s, 9H), 1.47 (s, 9H), 1.50 (s, 9H), 2.11–2.19 (m, 1H), 2.27–2.33 (m, 1H), 4.38–4.43 ppm (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.35$, −4.49, 18.2, 25.7, 27.9, 32.1, 55.8, 69.7, 82.4, 83.5, 149.4, 170.3, 172.1 ppm. HR-MS (FAB): calcd for $C_{20}H_{38}NO_6Si^+$: 416.2463 $[M+H]^+$; found: 416.2461.

*(2S,4R)-2-(tert-butoxycarbonylamino)-4-(tert-butyldimethylsilyloxy)-5-hydroxy-pentanoic acid (**22**)*

A solution of pyrrolidine **21** (3.5 g, 8.42 mmol, 1 equiv) in ethanol (250 mL) was cooled to 0 °C. A buffer solution ($NaHPO_4/NaH_2PO_4$, 80 mL, pH 7) and $NaBH_4$ (1.6 g, 42.1 mmol, 5.0 equiv) were added and the mixture was stirred at 0 °C for 2 h. More buffer was added (160 mL) and stirring was continued at room temperature for 4 h. Subsequently, the pH value was adjusted to pH 7 with NaH_2PO_4 and the mixture was stirred for 16 h. Ethanol was removed in vacuo at room temperature, and the aqueous layer was extracted with ethyl acetate (3×250 mL). The combined organic layers were washed with brine (100 mL), dried with $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 9:1→5:1) to give alcohol **22** as a colorless solid. Yield: 2.19 g, 5.22 mmol, 62 %. R_f = 0.33 (cyclohexane/ethyl acetate 4:1); m.p. 65.5–68.2 °C. $[\alpha]_D^{20}$ = +13.1 (MeOH, c = 1). IR: $\tilde{\nu}$ = 3433 (m), 2977 (w), 2930 (m), 2858 (m), 1714 (m), 1500 (m), 1391 (s), 1366 (s), 1252 (s), 1152 (s), 1060 (s), 835 (s), 776 (s), 668 cm^{-1} (s). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.07 (s, 6H), 0.90 (s, 9H), 1.43 (s, 9H), 1.46 (s, 9H), 1.45 (s, 9H), 1.80 (m, 1H), 1.95–1.98 (m, 1H), 3.47–3.50 (m, 1H), 3.59–3.62 (m, 1H), 3.78–3.79 (m, 1H), 4.21 (d, J = 5.4 Hz, 1H), 5.39 ppm (d, J = 5.45 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = −5.2, 18.5, 26.1, 28.3, 28.6, 33.9, 52.1, 61.0, 66.9, 80.2, 82.4, 155.7, 171.8 ppm. HR-MS (FAB): calcd for $C_{20}H_{42}NO_6Si^+$: 420.2776 $[M+H]^+$; found: 420.2769.

*(2S,4R)-5-azido-2-(tert-butoxycarbonylamino)-4-(tert-butyldimethylsilyloxy)pentanoic acid tert-butyl ester (**23**)*

Preparation of a HN_3 solution: NaN_3 (6.5 g, 100 mmol), H_2O (6.5 mL), and toluene (40 mL) were combined in a flask under an argon atmosphere. The mixture was cooled to 0 °C and stirred vigorously, then concentrated H_2SO_4 (98 %, 2.7 mL) was added dropwise. The mixture was stirred at 0 °C for 15 min and dried by adding excess $MgSO_4$. The concentration of the supernatant HN_3 solution in toluene was determined by titration of an aliquot against phenolphtaleine, with typical results between 1.2 and 1.6 M. **Caution**: HN_3 is a highly toxic, volatile, and an explosive reagent, which should be freshly prepared and handled with extreme care! To avoid potential hazards, the concentration of HN_3 in toluene should be kept lower than 2 M, and excess HN_3 should be immediately destroyed by neutralizing with NaOH. **Storing HN_3 solutions for longer than the duration of the experiment is strongly discouraged!**

Mitsunobu Displacement

Alcohol **22** (2.11 g, 5.0 mmol, 1.0 equiv) and triphenylphosphine (3.93 g, 15.0 mmol, 3.0 equiv) were dissolved in toluene (80 mL). A solution of HN_3 in toluene (1.3 M, 19.0 mL, 25.0 mmol, 4.0 equiv) and diisopropylazodicarboxylate (DIAD; 3.19 g, 15.0 mmol, 3.0 equiv) was added dropwise with protection under an argon atmosphere and stirred for 4 h. NaOH solution was added (1 M, 30 mL) and the aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (30 mL), dried with $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 9:1→5:1 (v/v)) to give azide **23** as a colorless oil. Yield: 1.93 g, 4.35 mmol, 87 %. R_f = 0.50 (cyclohexane/ethyl acetate 4:1). $[\alpha]_D^{20}$ = −31.8 (MeOH, c = 1). IR: $\tilde{\nu}$ = 3347 (m), 2978 (w), 2931 (w), 2859 (w), 2120 (s), 1714 (s), 1501 (s), 1366 (s), 1251 (s), 1150 (s), 1119 (s), 836 (s), 776 (s), 667 cm^{-1} (w). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 6H), 0.90 (s, 9H), 1.44 (s, 9H), 1.45 (s, 9H), 1.64–1.72 (m, 1H), 1.75–1.82 (m, 1H), 3.45–3.52 (m, 1H), 3.61–3.65 (m, 1H), 3.69–3.73 (m, 1H), 4.31 (m, 1H), 5.13 ppm (dd, J = 6.88 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.6, 18.2, 25.7, 27.9, 28.3, 33.6, 51.8, 60.6, 66.5, 79.8, 82.1, 155.4, 171.4 ppm. HR-MS (FAB): calcd for $C_{20}H_{41}N_4O_5^+$: 445.2841 $[M+H]^+$; found: 445.2832.

*(2S,4R)-tert-butyl-2-amino-5-azido-4-(tert-butyldimethylsilyloxy)pentanoate (**5**)*

Azide **23** (1.66 g, 3.7 mmol, 1.0 equiv) and 2,6-lutidine (0.8 g, 7.5 mmol, 2.0 equiv) were dissolved in dichloromethane (10 mL). TBSOTf (1.47 g, 5.5 mmol, 1.4 equiv) was added dropwise at room temperature and the mixture was stirred for 15 min. After addition of a saturated NH_4Cl solution, the reaction mixture was extracted with dichloromethane (2× 10 mL). After removal of the solvent, the residue was redissolved in THF/H_2O (10 mL/10:1). *tetra-n*-butylammonium fluoride (TBAF; 1 M, 3.7 mL, 3.7 mmol, 1.0 equiv) was added to the solution and the mixture was stirred for 1 h. Saturated NH_4Cl solution was added (5 mL) and the aqueous layer was extracted with diethylether (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 9:1→5:1) to give amine **23** as a colorless oil. Yield: 0.89 g, 2.6 mmol, 70 %. R_f = 0.40 (cyclohexane/ethyl acetate 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.08 (s, 6H), 0.90 (m, 9H), 1.39–1.45 (m, 12H), 1.62 (s, 2H), 1.78 (m, 1H), 3.46 (q, J = 4.69 Hz, 1H), 3.62–3.77 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.1, 18.5, 26.1, 28.3, 35.7, 42.3, 52.5, 60.1, 67.1, 81.6, 175.5. GC-MS: t_R = 5.30 min, m/z = 345. $[\alpha]_D^{20}$ = −73 ($CHCl_3$, c = 1.0). IR: $\tilde{\nu}$ = 1158, 1254, 1741, 2121, 2859, 2931 cm^{-1}. HR-MS (FAB): calcd for $C_{15}H_{33}N_4O_3Si^+$: 345.2316 $[M+H]^+$; found 345.2316.

*(2S,5R,2′S,2‴S)-2′-(Benzyloxcarbonylamino)-3′-{4″,4‴-bis-methoxy-3‴-[2‴-tert-butyloxy-carbonylamino-2‴-methoxycarbonylethyl]-biphenyl-3″-yl}-propanoylamino)-5-azido-4-(tert-butyldimethylsilyloxy) pentanoic acid tert-butyl ester (**24**)*

Biaryl acid **6** (162 mg, 0.25 mmol, 1.0 equiv), amine **5** (93.9 mg, 0.37 mol, 1.5 equiv), and HOBt (50.0 mg, 0.37 mmol, 1.5 equiv) were dissolved in abs. dichloromethane (15 mL). *N,N*-Diisopropylethylamine (90.9 μL, 0.55 mmol, 2.2 equiv) was added, the mixture was cooled to 0 °C and EDC·HCl (70.9 mg, 0.37 mmol, 1.5 equiv) was added. After stirring at room temperature for 16 h, 0.5 N aqueous H_2SO_4 (10 mL) was added and the reaction mixture was extracted with dichloromethane (3×10 mL). The combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 1:1) to give dipeptide **24** as a colorless solid. Yield: 191 mg, 0.2 mmol, 78 %. R_f = 0.63 (cyclohexane/ethyl acetate 1:1); m.p. 134–138 °C. $[\alpha]_D^{20}$ = +12.6 (MeOH, c = 0.5). HPLC-ESI: t_R = 12.89 min; m/z = 985.25 $[M+Na]^+$. IR: $\tilde{\nu}$ = 3344 (m), 2978 (w), 2123 (s), 1732 (m), 1688 (m), 1652 (s), 1523 (s), 1495 (s), 1439 (s), 1245 (s), 1167 (s), 1167 (s), 1136 (s), 1025 (w), 805 (s), 742 cm^{-1} (s). ^1H NMR (400 MHz, CD_3OD): δ = 0.12 (s, 6H), 0.94 (s, 9H), 1.35 (s, 9H), 1.35 (s, 9H), 1.45 (s, 9H), 1.70–1.89 (m, 2H), 2.89–3.00 (m, 2H), 3.19–3.25 (m, 2H), 3.44–3.47 (m, 1H), 3.60 (dd, J = 5.18, 5.28 Hz, 1H), 3.69 (s, 3H), 3.78 (dd, J = 5.26 Hz, 1H), 3.92 (s, 6H), 4.46–4.53 (m, 1H), 5.01 (q, J = 10.68 Hz, 2H), 7.01 (d, J = 8.36 Hz, 2H), 7.26 (m, 5H), 7.36–7.47 ppm (m, 4H). ^{13}C NMR (100 MHz, CD_3OD): δ = −4.8, 19.7, 26.9, 28.3, 28.8, 29.3, 33.9, 34.9, 52.6, 53.2, 56.7, 62.5, 68.3, 81.8, 83.7, 112.4, 112.5, 127.5, 129.4, 129.6, 130.1, 131.1, 138.7, 158.4, 158.9, 172.7, 175.1 ppm. HR-MS (ESI): calcd for $C_{49}H_{70}N_6O_{12}Si^+$: 963.4894 $[M+H]^+$; found: 963.4894.

*(4S,7S,10S,2′R)-10-Benzyoxycarbonylamino-1′,2′-bis-methoxy-7-[3′-azido-2′-(tert-butyldimethyl-silyloxy)propyl]-5,8-diaza-6,9-dioxo-1,2(4,2)-dibenzenacycloundecaphane-4-methyl carboxylate (**25**).*

Compound **24** (107.4 mg, 0.11 mmol, 1.0 equiv) and 2,6-lutidine (202.0 μL, 471.6 mg, 4.4 mol, 40 equiv) were dissolved in abs. dichloromethane (20 mL) and cooled to 0 °C. Triethylsilyl trifluoromethanesulfonate (501 μL, 582 mg, 2.20 mol, 20 equiv) was added dropwise and the mixture was stirred at room temperature for 16 h. Subsequently, a saturated NH_4Cl solution (15 mL) was added and the mixture was stirred vigorously for 4 h. The mixture was extracted with dichloromethane (3×5 mL). The combined organic layers were washed with brine (5 mL), dried with $MgSO_4$, and concentrated. The residue was purified by flash chromatography (silica gel, R_f = 0.54 in dichloromethane/MeOH 10:1). The amino acid obtained was dissolved in abs. dichloromethane (5 mL) and the solution was added dropwise at room temperature under vigorous stirring over a period of 30 h by a syringe pump (flow rate 0.8 mL/h) to a solution of HATU (62.7 mg, 0.16 mmol, 1.5 equiv), HOAt (22.4 mg, 0.16 mmol, 1.5 equiv), and $EtN(iPr)_2$ (37.8 μL, 29.6 mg, 0.24 mmol, 2.2 equiv) in abs. dichloromethane (500 mL). After the addition was complete, the reaction mixture was stirred for 8 h. The volatiles were removed and the residue was dissolved in dichloromethane (40 mL),

washed with aqueous 0.5 N H_2SO_4 (10 mL), aqueous 1 N $NaHCO_3$ (10 mL), brine (10 mL), dried with $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (silica gel, dichloromethane/MeOH 13:1) to give cyclopeptide **25** as a colorless solid. Yield: 65.1 mg, 0.83 mmol, 75 %. R_f = 0.58 (dichloromethane/MeOH 13:1); m.p. >210 °C. (decomp.). $[\alpha]_D^{20}$ = +20.1 (DMSO, c = 1.0). HPLC-ESI: t_R = 10.69 min; m/z = 767.1 $[M+H]^+$. IR: $\tilde{\nu}$ = 3266 (m), 2929 (m), 2857 (w), 2121 (s), 1643 (s), 1495 (s), 1244 (s), 1026 (w), 827 cm^{-1} (s). ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 0.11 (s, 6H), 0.91 (s, 9H), 1.27 (m, 2H), 1.65–1.72 (m, 2H), 2.81–2.88 (m, 2H), 3.55–3.66 (m, 2H), 3.73 (s, 3H), 3.75 (s, 3H), 3.85 (s, 3H), 4.51 (t, J = 5.96 Hz, 1H), 4.76–4.85 (m, 2H), 5.04–5.11 (q, J = 10.08 Hz, 2H), 6.47 (d, J = 7.24 Hz, 1H), 6.98–7.08 (m, 3H), 7.35–7.38 (m, 5H), 8.68 (d, J = 9.04 Hz, 1H), 9.19 ppm (d, J = 9.04 Hz, 1H). ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = −4.7, 18.7, 26.5, 34.3, 50.1, 51.8, 53.2, 55.0, 56.4, 61.1, 66.3, 67.1, 111.5, 122.4, 125.3, 127.0, 128.5, 128.6, 129.2, 130.5, 132.4, 132.6, 137.8, 156.5, 157.4, 170.8, 172.2, 172.7 ppm. HR-MS (ESI): calcd for $C_{40}H_{53}N_6O_9Si^+$: 789.3638 $[M+H]^+$; found: 789.3640.

*Biphenomycin B (**1**)*

Azide **25** (75 mg, 0.095 mmol, 1.0 equiv) was dissolved in THF/water (10 mL, 9:1). A solution of trimethylphosphine in THF (380 µL, 1 M in THF, 0.38 mmol, 4.0 equiv) and 0.1 N sodium hydroxide (2.8 mL, 0.28 mmol, 3 equiv) was added and the mixture was stirred for 6 h. The volatiles were removed under reduced pressure and the residue was suspended in 1 M aqueous HCl. After stirring for 8 h, the mixture was concentrated and dried in vacuo. The residue was suspended in abs. dichloromethane (20 mL) and cooled to 0 °C. A solution of boron tribromide (1 M in dichoromethane, 1.9 mL, 1.9 mmol, 20 equiv) was added dropwise over 10 min and the reaction mixture was stirred at room temperature for 6 h. Subsequently, the reaction mixture was cooled to 0 °C and abs. MeOH (1 mL) and 0.1 M aqueous lithium hydroxide (0.5 mL) were added. The mixture was stirred for 5 min. After removal of the solvent, the crude product was purified by preparative HPLC to give biphenomycin B as a colorless solid. Yield: 23.4 mg, 0.05 mmol, 52 %; m.p. >215 °C. (decomp.). $[\alpha]_D^{20}$ = +4.45 (1 M HCl, c = 0.375). HPLC-ESI: t_R = 2.25 min; m/z = 473.1 $[M+H]^+$. IR: $\tilde{\nu}$ = 3270 (m), 3078 (m), 2928 (w), 1637 (s), 1390 (s), 1242 (s), 848 cm^{-1} (s). ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 1.78–1.79 (m, 1H), 1.95–1.98 (m, 1H), 2.73–2.78 (m, 1H), 2.94 (m, 1H), 3.03 (m, 1H), 3.31 (m, 1H), 3.57 (m, 3H), 3.88 (d, J = 6.5 Hz, 1H), 4.13–4.35 (m, 1H), 4.79–4.80 (m, 1H), 6.80 (d, J = 8.0 Hz, 2H), 6.95 (s, 1H), 7.21 (s, 3H), 8.72 ppm (s, 2H). ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 29.5, 33.1, 35.3, 51.3, 51.6, 54.5, 55.0, 63.2, 116.2, 116.4, 124.4, 125.0, 125.1, 127.2, 128.0, 128.7, 131.7, 132.0, 154.8, 155.3, 170.6, 172.3, 176.7 ppm. ^1H NMR (400 MHz, D_2O): δ = 2.17–2.22 (m, 2H), 2.92 (dd, J = 5.60, 8.32 Hz, 1H), 3.05 (dd, J = 7.62, 3.12 Hz, 1H), 3.42–3.46 (m, 1H), 3.58–3.60 (m, 1H), 3.74–3.79 (m, 1H), 3.90–3.93 (m, 1H), 4.54 (m, 1H), 4.75 (m, 1H), 4.85 (m, 1H), 6.91 (s, 1H), 6.95 6.98–6.99 (m, 2H), 7.16 (s, 1H), 7.44 (d, J = 8.40 Hz, 1H), 7.52 ppm (m, J = 8.40 Hz, 1H). HR-MS (ESI): calcd for $C_{23}H_{29}N_4O_7^+$: 473.2031 $[M+H]^+$; found: 473.2026.

General Procedure 1: Biaryl Peptide Extension

Carboxylic acid (1.0 equiv), amino acid-*tert*-butylester hydrochloride (1.2 equiv), and HOBt (1.2 equiv) were dissolved in abs. dichloromethane (20 mM, 1 × vol). After addition of *N*,*N*-diisopropylethylamine (2.2 equiv), the mixture was cooled to 0 °C and EDC·HCl (1.2 equiv) was added. After stirring at room temperature for 16 h, 1 M aqueous HCl (1 × vol) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × vol). The combined organic layers were washed with brine (1 × vol), dried with $MgSO_4$, and concentrated.

*(2S,2′S,2‴′S)-tert-Butyl-2′-(benzyloxcarbonylamino)-3′-{4″,4‴-bis-methoxy-3‴-[2‴″-tert-butyloxycarbonylamino-2‴″-methoxycarbonylethyl]-biphenyl-3″-yl}-propanoylamino)-2-methylpropanoate (**26**)*

Dipeptide **26** was prepared from biaryl acid **6** (105 mg, 0.16 mmol) and L-alanine-*tert*-butylester hydrochloride (35.9 mg, 0.19 mol) according to general procedure 1, and obtained as a colorless solid after flash chromatography (silica gel, cyclohexane/ethyl acetate 1:1). Yield: 105 mg, 0.14 mmol, 84 %. R_f = 0.49 (cyclohexane/ethyl acetate 1:1); m.p. 122–125 °C. $[\alpha]_D^{20}$ = +6.4 (MeOH, c = 0.5). HPLC-ESI: t_R = 11.21 min; m/z = 786.2 $[M+Na]^+$. IR: $\tilde{\nu}$ = 3307 (w), 2926 (w), 1709 (m), 1656 (m), 1493 (s), 1452 (m), 1243 (s), 1130 (m), 1026 (s), 808 (s), 772 (w), 738 (m), 697 (m), 637 cm^{-1} (m). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (d, J = 6.40 Hz), 1.34 (s. 9H), 1.40 (s. 9H), 3.06–3.17 (m, 4H), 3.68 (s, 3H), 3.82 (s, 6H), 4.35 (t, J = 7.0 Hz, 1H), 4.51 (m, 1H), 4.53 (m, 1H), 5.01 (m, 2H), 5.26 (d, J = 7.60 Hz, 1H), 5.81 (m, 1H), 6.70 (m, 1H), 6.84 (t, J = 7.4 Hz), 7.23–7.25 (m, 6H), 7.31–7.35 ppm (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.8, 27.1, 28.2, 28.5, 33.3, 48.9, 52.3, 54.4, 55.7, 55.8, 56.5, 67.0, 79.8, 82.1, 110.7, 111.1, 125.3, 125.7, 126.7, 126.8, 128.1, 128.2, 128.7, 129.7, 129.9, 133.2, 133.6, 136.6, 155.5, 156.5, 156.7, 157.1, 170.9, 172.0, 173.1 ppm. HR-MS (ESI): calcd for $C_{41}H_{54}N_3O_{11}^+$: 764.3753 $[M+H]^+$; found: 764.3753.

*(2S,2′S,2‴′S)-tert-Butyl-2′-(Benzyloxcarbonylamino)-3′-{4″,4‴-bis-methoxy-3‴-[2‴″-tert-butoxycarbonylamino-2‴″-methoxycarbonylethyl]-biphenyl-3″-yl}-propanoylamino)-butyloxy-propanoate (**27**)*

Dipeptide **27** was prepared from biaryl acid **6** (100 mg, 0.16 mmol) and L-serine-*tert*-butylester hydrochloride (47.8 mg, 0.19 mol) according to general procedure 1, and was obtained as a colorless solid after flash chromatography (silica gel, cyclohexane/ethyl acetate 1:1). Yield: 114 mg, 0.14 mmol, 85 %. R_f = 0.48 (cyclohexane/ethyl acetate 1:1); m.p. >125–127 °C (decomp.). $[\alpha]_D^{20}$ = +27.9 (MeOH, c = 0.5). HPLC-ESI: t_R = 11.86 min; m/z = 858.32 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.06 (s, 9H), 1.31 (s, 9H), 1.40 (s, 9H), 2.95–3.08 (m, 3H), 3.17–3.22 (m, 1H), 3.45 (d, J = 6.4 Hz, 1H), 3.64 (s, 3H), 3.68–3.71 (m, 1H), 3.79 (s, 6H), 4.50–4.52 (m, 3H), 4.96 (s, 2H), 5.28 (d, J = 7.6 Hz), 5.76 (m, 1H), 6.79–6.84 (m, 3H), 7.20–7.22 (m, 5H), 7.31–7.33 ppm (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.4, 28.1, 28.4, 33.2, 33.9, 52.1, 53.4, 54.2, 55.6, 55.7, 56.1, 62.3, 66.7, 73.1, 77.4, 79.6, 81.9, 110.8, 110.9, 125.1, 125.8, 126.5, 126.7, 127.9, 128.0, 128.5, 129.6, 133.2, 133.3, 136.5, 155.4, 156.2, 156.7, 156.9, 169.2, 171.3, 172.9 ppm. HR-MS (ESI): calcd for $C_{45}H_{62}N_3O_{12}^+$: 836.4328 $[M+H]^+$; found: 836.4328.

*(2S,2′S,2‴′S)-tert-Butyl-2′-(Benzyloxcarbonylamino)-3′-{4″,4‴-bis-methoxy-3‴-[2‴″-tert-butyloxycarbonylamino-2‴″-methoxycarbonylethyl]-biphenyl-3″-yl}-propanoylamino)-2-benzyloxcarbonylamino-pentanoate (**28**)*

Dipeptide **28** was prepared from biaryl acid **6** (200 mg, 0.32 mmol) and L-H-Orn(*Z*)-O*t*Bu·HCl (135 mg, 0.38 mol) according to general procedure 1, and obtained as a colorless solid after flash chromatography (silica gel, cyclohexane/ethyl acetate 1:1). Yield: 242 mg, 0.26 mmol, 82 %; m.p. 141–143 °C. R_f = 0.53 (cyclohexane/ethyl acetate 1:1). $[\alpha]_D^{20}$ = +13.6 (MeOH, c = 0.5). HPLC-ESI: t_R = 11.01 min; m/z = 940.7 $[M+H]^+$. IR: $\tilde{\nu}$ = 3330 (w), 2936 (w), 1735 (m), 1692 (s), 1650 (s), 1520 (s), 1494 (m), 1390 (w), 1244 (s), 1160 (m), 1023 (s), 820 cm^{-1} (w). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 11H), 1.35 (s, 9H), 1.55 (m, 1H), 1.70 (m, 1H), 2.98–3.07 (m, 6H), 3.64 (s, 3H), 3.78 (s, 3H), 3.80 (s, 3H), 4.33–4.36 (m, 2H), 4.47 (d, J = 6.0 Hz, 1H), 4.96 (s, 2H), 5.00 (m, 2H), 5.20 (d, J = 7.2 Hz, 1H), 5.77 (d, J = 4.4 Hz, 1H), 6.60 (d, J = 6.8 Hz, 1H), 6.79–6.83 (m, 2H), 7.19–7.32 ppm (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.5, 28.3, 28.6, 30.1, 33.4, 40.8, 52.4, 52.6, 54.5, 54.5, 55.9, 55.9, 56.9, 66.9, 67.2, 79.9, 82.6, 111.1, 125.5, 126.8, 126.8, 128.2, 128.4, 128.4, 128.8, 128.8, 129.8, 130.2, 133.7, 136.7, 137.0, 155.6, 156.9, 157.3, 171.2, 171.3, 173.2 ppm. HR-MS (ESI): calcd for $C_{51}H_{65}N_4O_{13}^+$: 941.4543 $[M+H]^+$; found: 941.4545.

General Procedure 2: Deprotection and Macrolactam Formation

The protected precursor was dissolved in 1,4-dioxane/conc. HCl (3:1, 20 mM) and stirred for 3 h. More concentrated hydrochloric acid was added (12.5 vol %→4 M) and the mixture was stirred for 1 h. The solvent was removed and the residue was dissolved in anhydrous dichloromethane (5 mM = 1 vol). This solution was added dropwise to a previously prepared solution of HATU (1.5 equiv), HOAt (1.5 equiv), and Et*N*(*i*Pr)$_2$ (2.2 equiv) in anhydrous dichloromethane (0.2 mM) with vigorous stirring during 24 h by a syringe pump (flow rate 0.8 mL/h). After the addition was complete, the mixture was stirred for 4 h and concentrated. The residue was taken up in dichloromethane (1 × vol), washed with 1 M HCl (1 ×

vol), aqueous sodium bicarbonate (5 wt%, 1×vol), brine (1×vol), dried with $MgSO_4$, and concentrated.

*(4S,7S,10S)-10-Benzyloxycarbonylamino-1¹,2¹-bis-methoxy-7-methyl-5,8-diaza-6,9-dioxo-1,2(4,2)-dibenzenaycloundecaphane-4-methyl carboxylate (**29**)*

Cyclopeptide **29** was prepared from peptide **26** (76.3 mg, 0.10 mmol) according to general procedure 2, and obtained as a colorless solid after flash chromatography (silica gel, dichloromethane/MeOH 10:1). Yield: 22.9 mg, 0.04 mmol, 39%. R_f=0.37 (dichloromethane/MeOH 19:1); m.p. >241°C (decomp.). $[\alpha]_D^{20}$=+21.7 (DMSO, c=0.33). HPLC-ESI: t_R= 9.93 min; m/z=590.15 $[M+H]^+$. IR: $\tilde{\nu}$=3269 (s), 2925 (m), 2851 (w), 1745 (s), 1688 (s), 1634 (s), 1539 (s), 1494 (s), 1280 (m), 1246 (s), 1143 (m), 1028 (m), 800 (m), 697 cm^{-1} (s). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.28 (d, J=6.44 Hz, 3H), 2.83 (m, 2H), 3.35 (s, 3H), 3.42 (m, 2H), 3.75 (s, 3H), 3.84 (s, 3H), 4.51 (q, J=4.62 Hz, 1H), 4.72 (t, J=4.5 Hz, 1H), 4.85 (t, J=8.98 Hz, 1H), 5.08 (d, J=2.36 Hz, 2H), 6.23 (t, J= 7.6 Hz, 1H), 6.96–7.11 (m, 3H), 7.38 (m, 5H), 7.47–7.50 (m, 2H), 8.73 (d, J=8.96 Hz, 1H), 8.95 ppm (d, J=8.80 Hz, 1H). ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=19.7, 27.5, 29.6, 53.3, 56.4, 66.3, 111.5, 128.5, 128.7, 129.2, 132.1, 132.4, 156.6, 157.4, 169.9 ppm. HR-MS (ESI): calcd for $C_{32}H_{36}N_3O_8^+$: 590.2497 $[M+H]^+$; found: 590.2495.

*(4S,7S,10S)-10-Benzyloxycarbonylamino-1¹,2¹-bis-methoxy-7-hydroxymethyl-5,8-diaza-6,9-dioxo-1,2(4,2)-dibenzenaycloundecaphan-4-methyl carboxylate (**30**)*

Cyclopeptide **30** was prepared from peptide **27** (80.1 mg, 0.10 mmol) according to general procedure 2 and obtained as a colorless solid after flash chromatography (silica gel, dichloromethane/MeOH 10:1). Yield: 45.7 mg, 0.076 mmol, 59%. R_f=0.43 (dichloromethane/MeOH 10:1). m.p. >221°C (decomp.). $[\alpha]_D^{20}$=+28.4 (DMSO, c=0.5). HPLC-ESI: t_R= 9.35 min; m/z=606.13 $[M+H]^+$. IR: $\tilde{\nu}$=3418 (m), 2914 (m), 2360 (s), 1731 (s), 1639 (s), 1496 (m), 1241 (s), 1171 (m), 1020 (s), 801 (m), 696 (m), 668 cm^{-1} (m). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.89 (m, 2H), 3.29–3.41 (m, 2H), 3.55 (q, J=5.27 Hz, 1H), 3.62 (q, J=5.40 Hz, 1H), 3.73 (s, 6H), 3.84 (s, 3H), 4.56 (t, J=4.81, 2.76 Hz, 1H), 4.70 (t, J= 7.35 Hz, 1H), 4.82 (t, J=6.19 Hz, 1H), 4.91 (t, J=3.64 Hz, 1H), 5.10 (d, J=2.38 Hz, 2H), 6.35 (d, J=7.44 Hz, 1H), 6.97–7.13 (m, 3H), 7.34–7.48 (m, 8H), 8.45 (d, J=8.96 Hz, 1H), 8.98 ppm (d, J=8.60 Hz, 1H). ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=29.1, 31.3, 51.8, 53.2, 54.9, 55.5, 56.5, 62.9, 66.3, 111.6, 125.4, 125.8, 126.8, 126.9, 128.5, 128.7, 129.3, 132.2, 132.5, 137.9, 155.8, 156.6, 157.4, 170.7, 171.9 ppm. HR-MS (ESI): calcd for $C_{32}H_{36}N_3O_9^+$: 606.2446 $[M+H]^+$; found: 606.2444.

*(4S,7S,10S)-10-Benzyolxycarbonylamino-1¹,2¹-bis-methoxy-7-(3′-(benzyloxy-carbonylamino)-propyl)-5,8-diaza-6,9-dioxo-1,2(4,2)-dibenzenaycloundecaphan-4-methyl carboxylate (**31**)*

Carboxylate **31** was prepared from peptide **28** (103 mg, 0.13 mmol) according to general procedure 2 and obtained as a colorless solid after flash chromatography (silica gel, dichloromethane/MeOH 10:1 v/v). Yield: 72.3 mg, 0.09 mmol, 72%. R_f=0.48 (dichloromethane/MeOH 9:1). m.p. >220°C (decomp.). $[\alpha]_D^{20}$=+20.1 (DMSO, c=1). HPLC-ESI: t_R= 10.69 min; m/z=767.1 $[M+H]^+$. IR: $\tilde{\nu}$=3273 (m), 2928 (w), 1740 (w), 1689 (s), 1638 (s), 1537 (s), 1494 (s), 1242 (s), 1131 (m), 1026 (m), 802 (m), 695 cm^{-1} (s). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.44 (m, 2H), 1.62 (m, 1H), 1.94–2.01 (m, 1H), 2.75–2.81 (m, 2H), 2.97–2.99 (m, 2H), 3.35–3.40 (m, 1H), 3.66 (s, 6H), 3.78 (s, 3H), 4.48 (t, J=5.6 Hz, 1H), 4.57 (t, J=7.7 Hz, 1H), 4.78 (t, J=9.4 Hz, 1H), 4.98 (s, 2H), 5.02 (s, 2H) 6.18 (d, J=7.6 Hz, 1H), 6.90–6.96 (m, 2H), 7.04 (s, 1H), 7.23–7.42 (m, 13H), 8.61 (d, J=9.2 Hz, 1H), 8.93 ppm (d, J=8.8 Hz, 1H). ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=26.8, 28.9, 29.6, 31.3, 36.0, 51.5, 52.4, 53.2, 54.9, 56.4, 56.5, 66.1, 66.3, 111.6, 111.9, 125.2, 125.2, 125.3, 125.3, 125.7, 126.5, 126.5, 126.9, 128.6, 129.2, 129.6, 130.6, 132.1, 132.4, 137.9, 138.2, 155.8, 156.6, 157.0, 157.5, 170.3, 172.7, 172.8 ppm. HR-MS (ESI): calcd for $C_{42}H_{47}N_4O_{10}^+$: 767.3287 $[M+H]^+$; found: 767.3287.

General Procedure 3: Global Deprotection

The compound was dissolved in THF (50 mM, 1 vol), and 0.1 N aqueous NaOH (8 equiv) was added. After stirring at room temperature for 8 h, the solvent was removed. The residue was dried in vacuo, taken up in benzene (4 mM, 1×vol), added to a fresh solution of AlI_3 (prepared from aluminum gratings (40 equiv) and iodine (32 equiv) refluxed for 30 min in anhydrous benzene (2 mL mmol of iodine)) and nBu$_4$NI (0.1 equiv) at 10°C, and stirred for 30 min at 10°C. 2 M HCl (50 vol%) was added at 10°C, followed by EtOAc (3×vol). The layers were separated and the organic layer was extracted with water (3×2 vol). The aqueous extracts were combined and concentrated.

*(4S,7S,10S)-10-Amino-1¹,2¹-bis-hydroxy-7-methyl-5,8-diaza-6,9-dioxo-1,2(4,2) dibenzenacycloundecaphan-4-carboxylic acid (**32**)*

Cyclopeptide **29** (25.95 mg, 44 μmol) was deprotected according to general procedure 3 and the crude product was purified by preparative HPLC to yield product **32** as a colorless solid. Yield: 12.3 mg, 0.03 mmol, 68%; m.p. >258°C (decomp.). $[\alpha]_D^{20}$=−24 (DMSO, c=0.2). HPLC-ESI: t_R= 5.38 min; m/z=414.16 $[M+H]^+$. IR: $\tilde{\nu}$=3258 (m), 3079 (m), 2926 (m), 1678 (m), 1636 (s), 1438 (s), 1201 (s), 1134 (s), 873 (s), 722 cm^{-1} (m). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.31 (d, J=7.04 Hz, 3H), 2.70–2.77 (m, 2H), 3.01–3.06 (m, 2H), 4.10 (m, 1H), 4.72–4.81 (m, 2H), 6.82–6.86 (m, 2H), 7.23 (m, 2H), 7.32 (m, 2H), 7.96 (m, 2H), 8.97 (d, J=8.6 Hz, 1H), 9.07 (d, J=9.36 Hz, 1H), 9.53 ppm (s, 2H). ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=24.7, 31.4, 35.1, 67.2, 68.2, 117.5, 129.0, 130.7, 159.1, 165.8, 170.2 ppm. HR-MS (ESI): calcd for $C_{22}H_{24}N_3O_6^+$: 414.1660 $[M+H]^+$; found: 414.1655.

*(4S,7S,10S)-10-Amino-1¹,2¹-bis-hydroxy-7-hydroxymethyl-5,8-diaza-6,9-dioxo-1,2(4,2)-dibenzenacycloundecaphan-4-carboxylic acid (**33**)*

Cyclopeptide **30** (10.2 mg, 16.87 μmol) was deprotected according to general procedure 3 and the crude product was purified by preparative HPLC to yield product **33** as a colorless solid. Yield: 4.67 mg, 10.8 μmol, 64%; m.p. >248°C (decomp.). $[\alpha]_D^{20}$=−19.8 (DMSO, c=0.33). HPLC-ESI: t_R=5.05 min; m/z=429.9 $[M+H]^+$. IR: $\tilde{\nu}$=3270 (m), 2932 (m), 1670 (s), 1639 (s), 1441 (s), 1198 (s), 1134 (s), 981 (m), 826 (s), 798 (m), 721 cm^{-1} (m). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.74 (dd, J=9.5 Hz, 1H), 3.05–3.09 (m, 1H), 3.24–3.30 (m, 2H), 3.54–3.65 (m, 2H), 4.15 (s, 1H), 4.69–4.79 (m, 2H), 5.03 (s, 1H), 6.81–6.87 (m, 2H), 7.00 (s, 1H), 7.19–7.30 (m, 3H), 8.01 (s, 2H), 8.96–9.02 (m, 2H), 9.55 (s. 1H), 9.76 ppm (s. 1H). ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=29.1, 29.9, 51.7, 53.7, 55.3, 55.5, 62.9, 115.4, 115.9, 121.3, 124.7, 125.6, 126.3, 129.7, 130.5, 130.5, 131.8, 154.3, 155.1, 168.1, 170.3, 173.9 ppm. HR-MS (ESI): calcd for $C_{21}H_{34}N_3O_7^+$: 430.1609 $[M+H]^+$; found: 430.1608.

*(4S,7S,10S)-10-Amino-1¹,2¹-bis-hydroxy-7-(3′-aminopropyl)-5,8-diaza-6,9-dioxo-1,2(4,2)-dibenzenacycloundecaphan-4-carboxylic acid (**34**)*

Cyclopeptide **31** (26 mg, 34.0 μmol) was deprotected according to general procedure 3 and the crude product was purified by preparative HPLC to yield product **34** as a colorless solid. Yield: 10.7 mg, 23.4 μmol, 69%; m.p. >237°C (decomp.). $[\alpha]_D^{20}$=−16.1 (DMSO, c=0.2). HPLC-ESI: t_R= 4.30 min; m/z=457.1 $[M+H]^+$. IR: $\tilde{\nu}$=3021 (m), 2927 (m), 1721 (s), 1661 (m), 1550 (m), 1440 (s), 1262 (s), 987 (s), 823 (s), 763 cm^{-1} (m). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.70 (m, 4H), 2.76–2.79 (m, 4H), 2.99–3.02 (m, 2H), 4.14 (s, 1H), 4.67–4.68 (m, 2H), 6.81–6.92 (m, 3H), 7.17–7.25 (m, 3H), 8.14 (s, 6H), 9.02 ppm (m, 2H). ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=29.1, 29.8, 38.3, 40.1, 120.0, 125.2, 128.9, 130.2, 131.6, 154.8, 168.6, 171.0 ppm. HR-MS (ESI): calcd for $C_{23}H_{29}N_4O_6^+$: 457.2081 $[M+H]^+$; found: 457.2079.

Translation Inhibition Testing

The in vitro transcription/translation inhibition assay was performed in 384 well plates (Optiplate-384 F, PerkinElmer) using the RTS 100 *E. coli* HY Kit (Roche Diagnostics) as described.[37] In brief, the plasmid DNA template containing the GFP gene under the control of a T7 promoter was used as provided. 6 μL of buffer I (20 mM Tris-HCl, 10 mM $MgSO_4$, 20 mM NaCl, 5% trifluoroethanol (TFE; pH 7.4) were introduced per

well, and serial dilutions (6 μL) of the compounds were prepared in triplicates. The final concentration of TFE was 5% in each well.

2 μL of the reaction cocktail (containing no DNA template) were added to each well. To start transcription, 2 μL of the diluted plasmid (20:1) were added to each well to reach a total volume of 10 μL. The plates were sealed and incubated for 90 min at 30°C and then stored at 4°C overnight. Fluorescence per well was then analyzed by using a TECAN infinite M200 plate reader at 395 nm excitation and an emission wavelength of 504 nm (25 reads/well, optimal gain, 22°C). The data were normalized (I/I_{max}) and plotted against the compound concentration. Sigmoidal curves were fitted using Hill's equation to yield IC_{50} values by means of Origin 7.5 (OriginLab Corporation). Reactions with no inhibitor and with no DNA template were included as controls.

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