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# De novo synthesis of teleocidin B analogs

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ABSTRACT

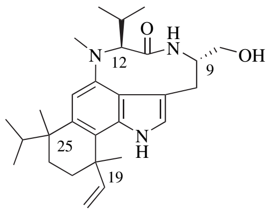
Teleocidin B analogs have been synthesized in 24 steps and 1.9% overall yield. The key steps include aromatic Claisen rearrangement, intramolecular Heck reaction of a tetra-substituted alkene, and ruthenium (II) catalyzed indole cyclization. Teleocidin and the new analogs promote cell spreading on fibroblast cells that were treated with amino-Nogo, an inhibitor of cell spreading.

## 1. Introduction

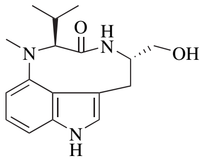
Teleocidins B **1**–**4** (**1a**–**d**), natural products that were isolated from the Mycelia of *Streptomyces mediocidicus*,[1] are potent tumor promoters.[2] They belong to a family of tumor promoters, represented by 12-*O*-teteadecanoylphorbol 13 acetate (TPA), that bind to and activate a group of kinase receptors, including protein kinase C and D (PKC and PKD).[3] Recently, we have found that teleocidin B and TPA reverse the inhibitory cell spreading effect of the myelin-associated inhibitor, NogoA, and do so through activation of PKD.[4] Additionally, teleocidin B stimulates neurite outgrowth of cerebellar neurons that were treated with Nogo. The newly discovered biological activities of teleocidin B sparked our interest in the synthesis of teleocidin B analogs.

Teleocidin B is a mixture of four stereoisomers, teleocidin B-1 (**1a**), teleocidin B-2 (**1b**), teleocidin B-3 (**1c**), and teleocidin B-4 (**1d**) (Fig. 1).[5] It is an indolactam-based alkaloid that possesses the nine-membered ring lactam, (−)-indolactam V (IL-V, **2**) fused to a six-membered cyclic monoterpenoid with quaternary carbon centers at positions C-25 and C-19.

Several groups have pursued the synthesis of teleocidin B.[6] Total syntheses of (±)-teleocidins B-3 and B-4 have been accomplished by Nakatsuka et al. in 1987[6d] and Okabe et al. in 1991.[6j] A key reaction that was used in both of these syntheses is an acid-mediated Friedel–Crafts type of cyclization to form the C-25 quaternary center of the six-membered ring. However, the strong acidic conditions caused undesired side reactions and low yields. Alternatively, Tanner et al.[7] envisioned the utilization of an intramolecular Heck reaction (IHR) to form the C-25 quaternary carbon. However,

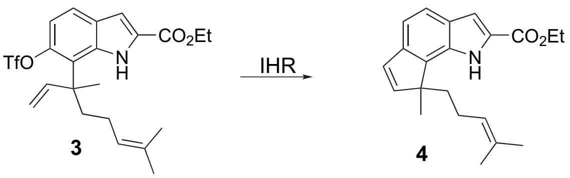


**1a** teleocidin B-1 (19 R, 25 S)
**1b** teleocidin B-2 (19 S, 25 R)
**1c** teleocidin B-3 (19 S, 25 S)
**1d** teleocidin B-4 (19 R, 25 R)



**2** indolactam V (IL-V)

**Figure 1.** Structures of teleocidins B (**1**–**4**) and indolactam V (IL-V).



**Scheme 1.** Tanner's model study of intramolecular Heck reaction (IHR).

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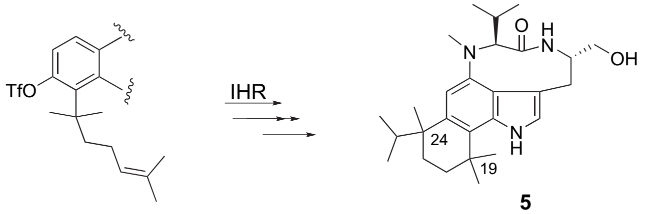
in the model study, it was found that cyclization with triflate **3** provided cyclopentadieno-indole **4** (Scheme 1), the result of the reaction proceeding in a 5-*endo-trig* manner with the less sterically hindered terminal alkene.

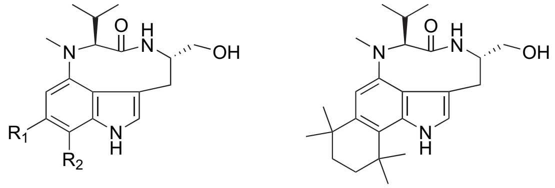
We rationalized that the intramolecular Heck reaction would provide the desired six-membered ring product by replacement of the terminal alkene with a methyl group. Such a change in functionality would lead, eventually, to dimethyl teleocidin analog **5** (Fig. 2).



**5**

**Figure 2.** Structure of target teleocidin B analog **5**.

We predicted that analog **5** would possess similar biological activity to teleocidin B based on the activities of reported analogs.[8] In particular, tetramethyl **8**,[9] a teleocidin analog without the terminal alkene has been shown to possess comparable PKC binding activity to teleocidin B. The core structure, IL-V (**2**) is essential for PKC binding and alkyl substituents at either the C-6 (**6**) or C-7 (**7**) positions of the indole nucleus have increased potency compared to the unsubstituted IL-V (**2**) (Fig. 3).



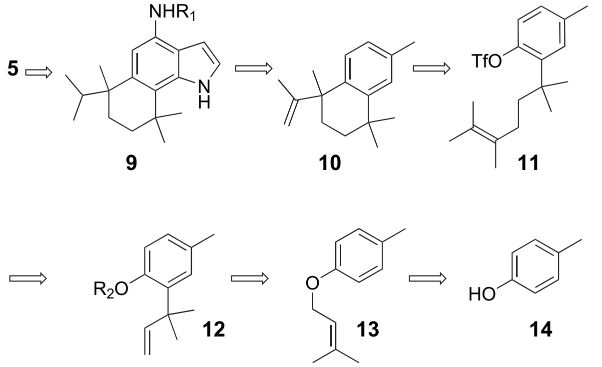
**6** $R_1$ = alkyl, $R_2$ = H
**7** $R_1$ = H, $R_2$ = alkyl

**8**

**Figure 3.** Structures of teleocidin B analogs **6**, **7**, and **8**.

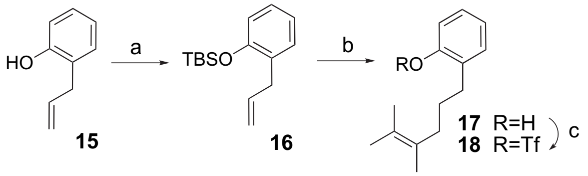
## 2. Chemistry

We envisioned a synthetic route to make analog **5** that utilizes tricyclic indole intermediate **9** whereby, the transformation to the teleocidin scaffold can be prepared by methods described in the literature.[6,8] The 4-amino indole **9** could be synthesized from dihydronaphthalene **10** in an analogous manner to that which was used by Webb et al.[9] Intermediate **10** could be made by the intramolecular Heck reaction (IHR)[10] from tetra-substituted alkene **11**. Compound **11** could be made with a hydroboration–Suzuki protocol[11] from **12**, which, in turn could be prepared from an aromatic Claisen rearrangement of ether **13**[12] (Scheme 2).



**Scheme 2.** Retrosynthetic analysis of teleocidin B analog **5**.

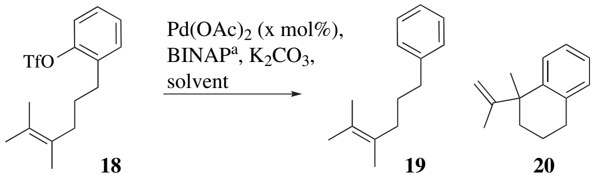
Since there are few examples of an intramolecular Heck reaction with a highly sterically hindered tetra-substituted alkene,[13] a model study was initiated to explore and optimize cyclization conditions. In this regard, compound **18** was prepared as a simplified cyclization substrate compared to intermediate **11**. Thus, treatment of commercially available 2-allylphenol (**15**) with *tert*-butyldimethylsilyl chloride (TBSCl) afforded compound **16** in good yield (Scheme 3). A hydroboration–Suzuki protocol[11] provided side chain extension and desilylation to give phenol **17**, which was subsequently converted to triflate **18** in excellent yield.



**Scheme 3.** Reagents and conditions: (a) TBSCl, imidazole, $CH_2Cl_2$, rt, 16 h, 90%. (b) i. 9-BBN, THF, 0 °C to rt, 4 h. ii. $PdCl_2(dppf)_2$, 3 M NaOH (3 equiv), 2-bromo-3-methyl-but-2-ene, 60 °C, 16 h, 70% for two steps. (c) $Tf_2O$, triethylamine, $CH_2Cl_2$, 0 °C to rt, 2 h, 90%.

We then examined the IHR cyclization to convert triflate **18** to tetrahydronaphthalene **20** (Table 1). In our first attempt at the cyclization, substrate **18**, with 10% $Pd(OAc)_2$, 20% *rac*-BINAP, and $K_2CO_3$ was heated in THF at 70 °C. However, no reaction took place (entry 1). It was realized that a higher temperature may be required to initiate the reaction. Therefore, the solvent was changed to DMF and the reaction was heated to 90 °C. In this case, compound **19**, the product of reduction of the triflate, was isolated as the single product in 72% yield (entry 2). Fortunately, when *N*,*N*-dimethylacetamide (DMA) was used as the solvent and the reaction mixture was heated to 120 °C, cyclization product **20** was obtained in 82% yield (entry 3). These results demonstrate that solvent and temperature play a pivotal role in the cyclization reaction. Next, the reaction conditions were optimized by lowering catalyst loading from 10% to 5% $Pd(OAc)_2$ (entry 4), which gave comparable yields.

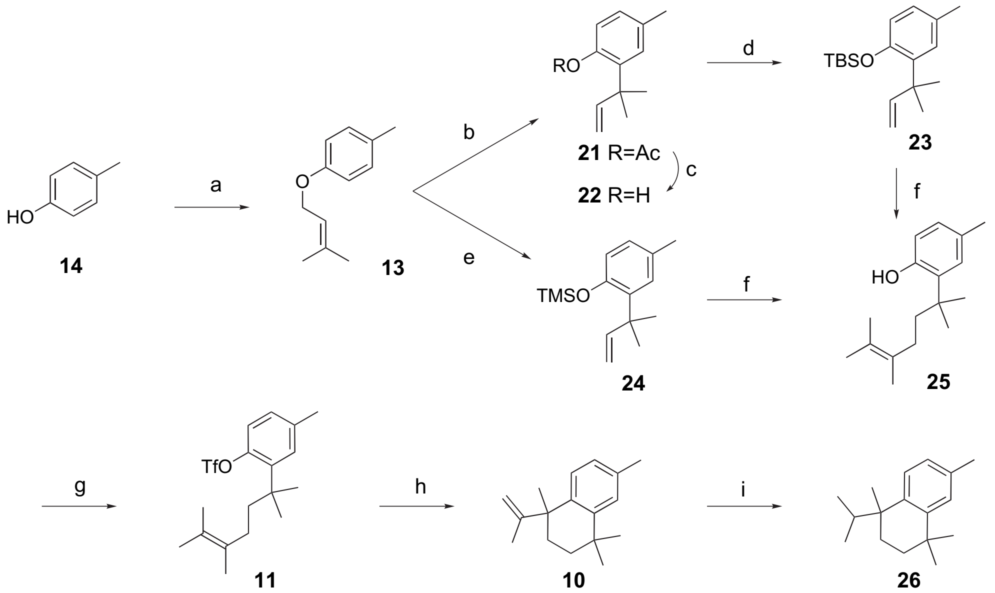
**Table 1**
Reaction conditions for intramolecular Heck reaction of compound **18**



| Entry | $x^a$ | Solvent | $T$ (°C) | Results[b] |
|---|---|---|---|---|
| 1 | 10 | THF | 70 | No reaction |
| 2 | 10 | DMF | 90 | **19** (72%)[c] |
| 3 | 10 | DMA | 120 | **20** (82%)[c] |
| 4 | 5 | DMA | 120 | **20** (80%)[c] |

[a] $Pd(OAc)_2$/*rac*-BINAP, 1:2.
[b] Isolated yield.
[c] Only product detected.

With confidence that the integral IHR step will be successful, the synthesis of analog **5** was initiated, starting with the preparation of intermediate **26**. Alkylation of 4-methylphenol (**14**) with 1-bromo-3-methyl-but-2-ene afforded compound **13**[14] in excellent yield (Scheme 4). Compound **13** underwent an aromatic Claisen rearrangement[15] in *N*,*N*-dimethylaniline in the presence of acetic anhydride at 200 °C, and crude acetate **21** was converted to phenol **22** by basic hydrolysis in 30–40% yield for two steps. Protection of phenol **22** as the *tert*-butyldimethylsilyl (TBS) ether gave compound **23**. Alternatively, the thermally stable 1,1,1,3,3,3-hexamethyl-disilazane (HMDS)[16] was used as the trapping reagent in

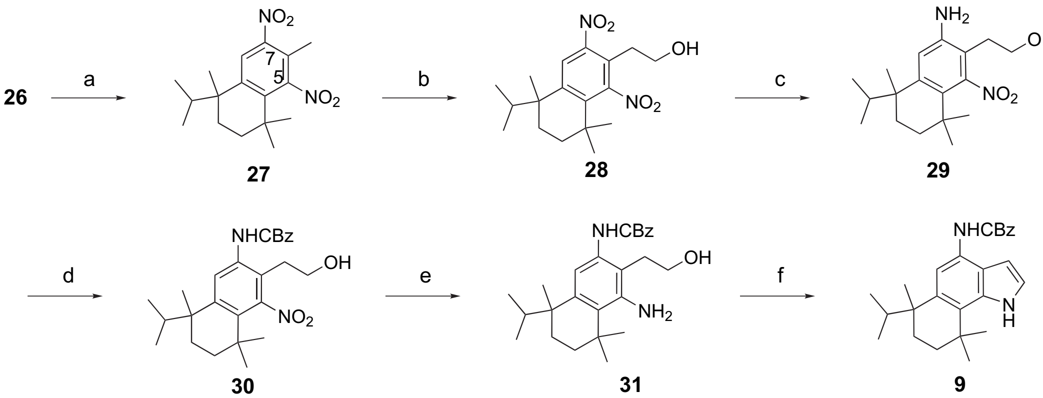


**Scheme 4.** Reagents and conditions: (a) 1-bromo-3-methyl-but-2-ene, $K_2CO_3$, acetone, 60 °C, 16 h, 90%. (b) $Ac_2O$, *N*,*N*-dimethylaniline, 200 °C, 24 h. (c) KOH/MeOH, 40 °C, 2 h; 30–40% for two steps. (d) TBSCl, imidazole, $CH_2Cl_2$, rt, 16 h, 66%. (e) HMDS, *N*,*N*-dimethylaniline, 200 °C, 24 h, 78%. (f) i. 9-BBN, THF, 0 °C to rt, 4 h; ii. 2-bromo-3-methyl-but-2-ene, $PdCl_2(dppf)_2$ (5 mol %), 3 M NaOH, 60 °C, 16 h, 88% for two steps. (g) NaH, $PhN(Tf)_2$, 0 °C to rt, 2 h, 87%. (h) $Pd(OAc)_2$ (5 mol %), BINAP, *N*,*N*-dimethylacetamide, $K_2CO_3$, 120 °C, 16 h, 85%. (i) $H_2$ (1 atm), Pd/C (10%), EtOH, 16 h, 90%.

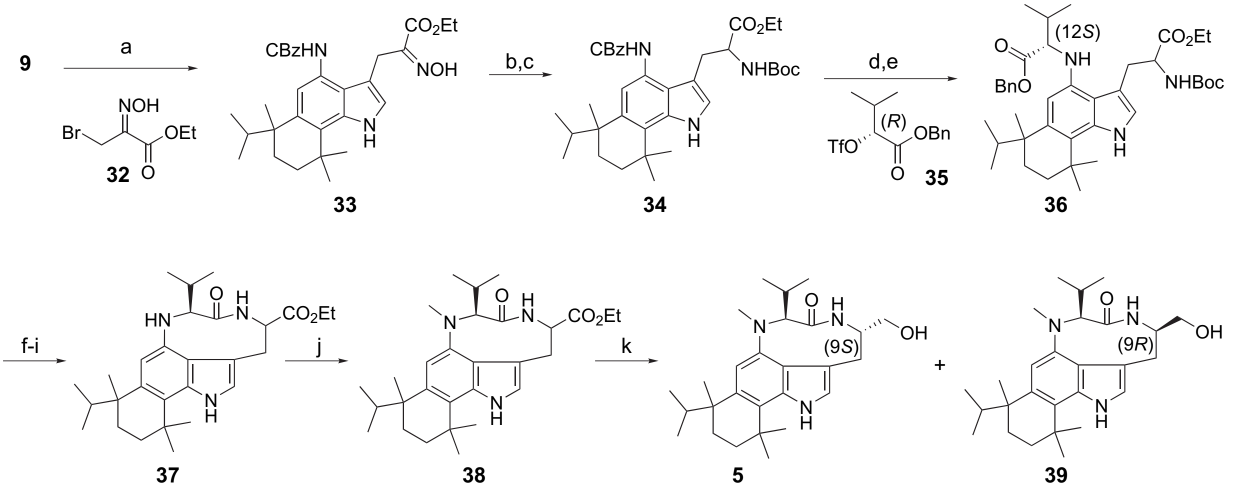
the Claisen rearrangement instead of the thermally unstable acetic anhydride. In this case, silyl ether **24** was obtained in one-step from alkene **13** in 78% yield. Hydroboration of compounds **23** and **24** with 9-BBN followed by Suzuki coupling with 2-bromo-3-methyl-but-2-ene afforded tetra-substituted alkene **25**, whereby the silyl group was also removed. Compound **25** was converted to triflate **11** in good yield. Cyclization of intermediate **11**, under the optimized intramolecular Heck reaction conditions, afforded tetrahydronaphthalene **10** as a single product in 90% yield. Catalytic hydrogenation of alkene **10** provided intermediate **26** in good yield.

With key intermediate **26** in hand, a strategy analogous to that which was developed by Webb et al.[9] was used to convert this compound to 4-amino indole **9**. Thus, nitro groups were introduced at the C-5 and C-7 positions of **26** by treatment with concentrated nitric acid and sulfuric acid to provide dinitro **27** in excellent yield (Scheme 5). Compound **27** was then treated with Triton-B and paraformaldehyde to give 2-arylethanol **28** in 90% yield. The less sterically hindered C-7 nitro group of **28** was reduced by transfer hydrogenation[17] (10% Pd/C, cyclohexene/ethanol, reflux) to provide amine **29** in quantitative yield. Protection of **29** with benzyl carbamate (CBz) afforded compound **30**. The C-5 nitro group was then reduced to amine **31** with iron in acetic acid/ethanol[18] in 95% yield. Cyclization of intermediate **31** with a catalytic amount of tris (triphenylphosphine) ruthenium (II) dichloride[9,19] in refluxing toluene furnished indole **9** in 90% yield.

The remaining steps of the synthesis required formation of the lactam ring. Thus, reaction of indole **9** with ethyl (3-bromo-2-oximido)pyruvate (**32**; Gilchrist's reagent[20]) gave oxime **33** in quantitative yield (Scheme 6). Reduction of oxime **33** with aluminum amalgam in wet THF afforded an amine intermediate, which was subsequently protected with Boc anhydride to provide compound **34**. Removal of the CBz group in **34** by hydrogenation followed by treatment of the resulting 4-aminoindole with triflate **35**, a reagent that was synthesized from D-valine in three steps,[6i] provided (*S*)-*N*-valylindole **36**. The *S*-configuration at the C-12 stereocenter is presumed due to the $S_N2$ mechanism of the reaction with triflate **35**, which would lead to inversion of stereochemistry. Following removal of the benzyl group, the resulting carboxylic acid was converted to the succinimide.[21] Removal of the Boc group with TFA followed by cyclization formed the nine-membered lactam intermediate **37**, which was then *N*-methylated by reductive amination to afford compound **38** (21% yield in five steps). Reduction of ester **38** with $LiBH_4$ in THF provided the corresponding alcohol. Flash chromatographic separation of diastereomers at this step



**Scheme 5.** Reagents and conditions: (a) $HNO_3$, $H_2SO_4$, 1,2-dichloroethane, 0 °C, 3 h, 92%. (b) Triton-B, HCHO, DMSO, rt, 16 h, 90%. (c) $H_2$, Pd/C, cyclohexene, EtOH, 80 °C, 4 h, 99%. (d) CBzCl, aqueous $NaHCO_3$, THF, rt, 16 h, 90%. (e) Fe/AcOH, EtOH, 80 °C, 3 h, 95%. (f) $RuCl_2(PPh_3)_2$ (5 mol %), toluene, 120 °C, 16 h, 90%.



**Scheme 6.** Reagents and conditions: (a) **32**, $Na_2CO_3$, $CH_2Cl_2$, rt, 1 h, 97%. (b) Al(Hg), THF/$H_2O$, rt, 16 h. (c) $(Boc)_2O$, aqueous $NaHCO_3$, THF, 16 h, 81% for two steps. (d) $H_2$ (45 psi), Pd/C (10%), EtOH, 4 h. (e) **35**, 2,6-lutidine, 1,2-dichloroethane, 83 °C, 12 h, 85% for two steps. (f) $H_2$ (45 psi), Pd/C (10%), EtOH, 2 h. (g) HOSu, DCC, MeCN, 0 °C to rt, 2 h. (h) TFA, $CH_2Cl_2$, 0 °C to rt, 2 h. (i) aqueous $NaHCO_3$, EtOAc, 70 °C, 3 h. (j) HCHO, $NaBH(OAc)_3$, AcOH, 1,2-dichloroethane, rt, 12 h, 21% for five steps. (k) $LiBH_4$, THF, 0 °C to rt, 4 h, 56%.

gave two fractions in equal amount. We tentatively assigned one fraction as compound **5**, which possesses natural 9*S* stereocenter and the other fraction as compound **39** with the epimeric 9*R* stereocenter. Further separation of compound **5** by HPLC gave compounds **40** and **41** in a ratio of 1:1.

Elucidation of the C-9 stereochemistry by NMR analysis proved to be inconclusive. Therefore, our assignment of stereochemistry at the C-9 position is made by comparison to literature examples. The $^1$H NMR spectra of diastereomers **40** and **41** indicate the presence of two conformers in a 3:1 ratio, a feature typical of teleocidin systems with 9*S*, 12*S* stereochemistry. It has been reported that the conformers are due to the *cis* (twist) and *trans* (sofa) configurations of the amide, with the *cis*-amide being the predominant form.[6a,9,22] In NOESY experiments with compounds **5**, **40**, and **41**, a correlation between the predominant H-8 and the predominant H-12 is observed, a typical feature found in teleocidin systems. Alternatively, the $^1$H NMR of compound **39** and its diastereomeic components (data not shown) indicates a single conformer. A similar observation was made by Webb et al. with a 9*R*,12*S* analog of teleocidin. From these observations, we postulated the stereochemical assignments of **5** and **39**.[9]

The assignment of the stereochemistry at C-24 was postulated from the NOE interaction between isopropyls at the C-12 and C-24 positions in compound **40**, a correlation that clearly demonstrates their *syn* relationship. Thus, the configuration at position 24 in **40** was defined as 24*R* and the configuration in **41** was determined to be 24*S* (Fig. 4).

## 3. Biological activity

In a previous study, it was found that teleocidin B promotes cell spreading on NIH/3T3 fibroblast cells that were treated with the

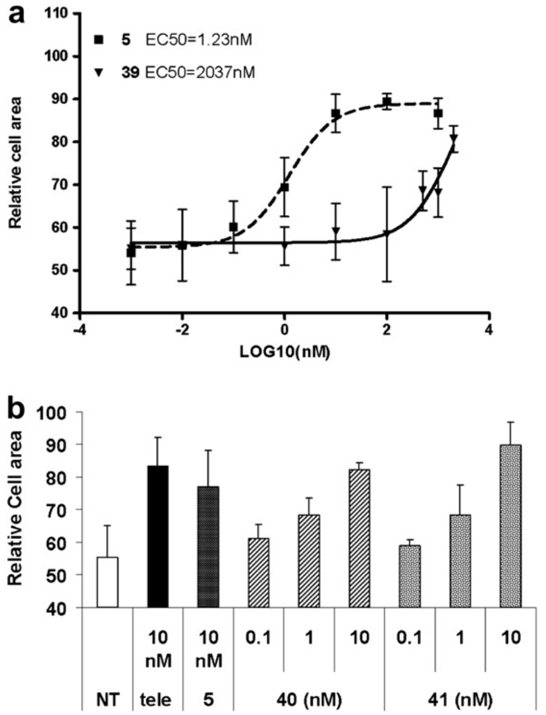


**Figure 5.** Cell spreading activity of compounds **5**, **39**, **40**, and **41**. NIH/3T3 cells were seeded on Nogo substrate. (A) Fibroblast spreading assay was performed on Nogo substrate with different concentrations of compounds 5 and 39; (B) fibroblast spreading was performed on Nogo substrate without treatment (NT, white bar), with teleocidin (tele, black bar), compound 5 (trellis bar), and three concentrations of compounds 40 (striped bars) and 41 (confetti bars). Cells were fixed and stained for F-actin. Cell area of each Hoechst positive cell was measured. Triplicate wells per treatment in each experiment. Relative mean cell area combined from at least three independent experiments is shown.

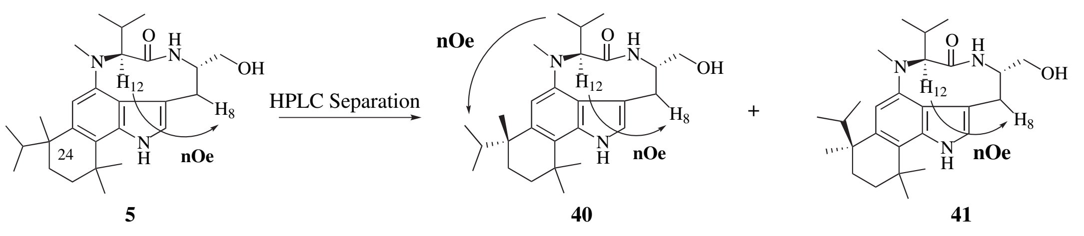


**Figure 4.** Isolation and characterization of compounds **40** and **41**.

cell spreading inhibitor, Nogo.[4] The $EC_{50}$ value of this effect is 4.3 nM. Compound **5** demonstrated comparable cell spreading activity, with an $EC_{50}$ value of 1.2 nM, whereas, diastereomer **39** was much less potent ($EC_{50}$=2037 nM) (Fig. 5a). The activity of compounds **40** and **41** is similar to their parent compound **5** and teleocidin B extract (Fig. 5b). These results are in accordance with literature reports that demonstrate that the 9*S* and 12*S* configurations are crucial for the biological activity of teleocidin B (**1a–d**) and its derivatives.[8] Similarly, our analogs with 9*S* and 12*S* configuration, mixture **5**, and its components **40** and **41**, are active, while compound **39** with 9*R*, 12*S* stereocenters, shows significantly reduced activity. Additionally, it was found that the stereochemistry at C-24 is irrelevant to its biological activity as is evident by the similar activities of **40** and **41**.

## 4. Conclusions

In summary, teleocidin B analogs have been synthesized in 24 linear steps with an overall yield of 1.9%. The key steps include an aromatic Claisen rearrangement, an intramolecular Heck reaction of a tetra-substituted alkene, and a tris(triphenylphosphine) ruthenium (II) dichloride catalyzed indole cyclization of an *ortho*-amino arylethanol. Analogs with 9*S* and 12*S* stereochemistry (diastereomeric mixture **5** and its components **40** and **41**) demonstrated comparable cell spreading activity with teleocidin B.

## 5. Experimental section

### 5.1. General

All reagents and solvents were purchased from commercial sources and used as received. $^1H$ and $^{13}C$ NMR spectra were determined on a 400 MHz Varian Unity Plus, using $Me_4Si$ as the internal standard. Chemical shifts are reported in parts per million downfield from zero and coupling constants are reported in hertz (Hz). Mass spectra were recorded on a Micromass LCT mass spectrometer. HRMS were recorded in FAB mode on an Agilent mass spectrometer. Optical rotation was recorded with a Jasco P-1020 polarimeter with a 30 mm cell. Melting points were taken on a Mel-Temp 3.0 capillary melting point apparatus and were uncorrected.

Cell spreading assay-NIH/3T3 cells were obtained from ATCC (CRL-1658). Cells were grown in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% bovine calf serum (BCS) (Invitrogen), 100 U/mL penicillin/streptomycin (Invitrogen), and 200 mM L-glutamine in an incubator maintained at 37 °C with 5% $CO_2$. NIH/3T3 cells were cultured to 70–80% confluence before trypsinized and plated at a sub-confluent density ($2.67\times10^4/cm^2$) 24 h before the cell spreading assay. Nogo (2–4 μg/mL in $H_2O$, 50 μL/well) or control (50 μL $H_2O$) was air-dried on poly-D-lysine coated 96-well plate overnight in a tissue culture hood. Cells were removed by 0.05% trypsin/EDTA (Invitrogen). The reaction was neutralized with DMEM/10% BCS. Then, NIH/3T3 cells were added to wells at 2500 cell/well and grow for 1 h at 37 °C in a 5% $CO_2$ incubator. Cells were fixed with 4% paraformaldehyde, permeablized with 0.3% Triton X-100 in PBS for 5 min and then stained with Hoechst 33342 (Invitrogen) and AlexaFluor 488 conjugated phalloidin (Invitrogen) in PBS for 20 min. Cell images were scanned and cell spreading was quantified by MetaXpress cell scoring module (Molecular Device). All data is presented as percentage mean cell area compared with cell area on control substrate ±SEM.

### 5.2. 2-(4,5-Dimethylhex-4-enyl)phenol 17

To a solution of (2-allylphenoxy)(*tert*-butyl)dimethylsilane **16** (3.0 g, 12.0 mmol) in anhydrous THF (40 mL) at 0 °C under $N_2$ was added a solution of 9-BBN (0.5 M in THF, 31.2 mL, 15.6 mmol) dropwise. The mixture was stirred at 0 °C for 30 min. The ice-water bath was removed and the mixture was stirred at room temperature for 5 h. Aqueous NaOH solution (3 M, 12.0 mL, 36.0 mmol) was then added dropwise followed by addition of 2-bromo-3-methyl-but-2-ene (2.2 mL, 18.0 mmol) and $PdCl_2$ $(dppf)_2$ (0.47 g, 0.6 mmol). The mixture was stirred at 60 °C under $N_2$ for 16 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (100 mL), and washed with water (100 mL). The aqueous layer was extracted with ethyl acetate (2×80 mL). The combined organic layers were washed with brine (60 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with ethyl acetate/hexane (0–20%) to provide compound **17** (1.7 g, 90%) as a colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.12 (d, $J$=7.5 Hz, 1H), 7.08 (t, $J$=7.7 Hz, 1H), 6.87 (t, $J$=7.4 Hz, 1H), 6.74 (d, J=7.4 Hz, 1H), 4.69 (s, 1H), 2.58 (t, $J$=7.8 Hz, 2H), 2.12 (t, $J$=7.5 Hz, 2H), 1.70 (m, 2H), 1.65 (s, 9H). $^{13}C$ NMR $\delta$ 153.3, 130.1, 130.0, 128.4, 127.4, 127.0, 124.4, 120.8, 115.2, 34.2, 29.7, 28.2, 20.6, 20.2, 18.2. MS: (+ESI) $(M+H)^+$ $m/z$ 205.2. HRMS: calcd 204.1515 for $C_{14}H_{20}O$, found 204.1515.

### 5.3. 2-(4,5-Dimethylhex-4-enyl)phenyl trifluoromethanesulfonate 18

To a solution of compound **17** (1.6 g, 7.9 mmol) in anhydrous methylene chloride (20 mL) under $N_2$ at 0 °C were added triethylamine (3.3 mL, 23.4 mmol) and triflic anhydride (2.0 mL, 11.9 mmol) dropwise. The mixture was then stirred at room temperature for 2 h. The reaction was quenched with water (30 mL) and diluted with methylene chloride (50 mL). The mixture was separated and the aqueous layer was extracted with methylene chloride (3×50 mL). The combined organic layers were washed with satd aqueous $NaHCO_3$ (50 mL) and brine (50 mL), then dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with ethyl acetate/hexane (0–20%) to provide compound **18** (2.4 g, 90%) as a colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.36–7.34 (m, 4H), 2.70 (t, $J$=7.9 Hz, 2H), 2.14 (t, $J$=7.5 Hz, 2H), 1.76–1.70 (m, 2H), 1.66 (s, 9H). $^{13}C$ NMR $\delta$ 148.1, 135.4, 131.1, 128.3, 127.6, 126.8, 124.8, 121.2, 117.6, 34.1, 29.8, 28.4, 20.5, 20.0, 18.2. MS: (+ESI) $(M+H)^+$ $m/z$ 337.1.

### 5.4. 1-Methyl-1-(prop-1-en-2-yl)-1,2,3,4-tetrahydronaphthalene 20

To a solution of compound **18** (1.0 g, 3.0 mmol) in anhydrous *N*,*N*-dimethylacetamide (10 mL) were added potassium carbonate (1.3 g, 8.9 mmol) and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (0.065 g, 0.3 mmol). The mixture was degassed with $N_2$ for 15 min. Palladium acetate (0.042 g, 0.15 mmol) was added and the mixture was degassed with $N_2$ for an additional 15 min. The mixture was heated in an oil bath at 120 °C under $N_2$ for 16 h. The dark solution was cooled to room temperature and the solvent was removed under reduced pressure. The mixture was diluted with ethyl acetate (50 mL) and washed with water (20 mL). The aqueous layer was extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with ethyl acetate/hexane (0–10%) to provide compound **20** (0.44 g, 80%) as a colorless oil. $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.07–7.01 (m, 4H), 4.87 (d, $J$=1.3 Hz, 1H), 4.62 (d, $J$=1.3 Hz, 1H), 2.70 (t, $J$=6.4 Hz, 2H), 1.92 (m, 1H), 1.71 (m, 2H), 1.55 (s, 3H), 1.45 (m, 1H), 1.34 (s, 3H). $^{13}C$

NMR $\delta$ 152.2, 142.5, 136.2, 128.7, 127.6, 125.6, 125.4, 112.0, 43.3, 34.9, 29.6, 28.6, 19.1. MS: (+ESI) $(M+H)^+$ *m*/*z* 187.2.

### 5.5. 4-Methyl-2-(2-methyl-but-3-en-2-yl) phenol 22

A solution of 1-methyl-4-(3-methyl-but-2-enyloxy) benzene **13**[14] (0.60 g, 3.41 mmol), acetic anhydride (10 mL), and *N*,*N*-dimethylaniline (10 mL) was added to a thick-walled tube (125 mL). The solution was purged with $N_2$ for 5 min. The sealed tube was then inserted into an oil bath at 200 °C. The mixture was stirred for 24 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (60 mL). The mixture was washed with 3 M aqueous HCl (3×30 mL). The organic layer was further washed with satd aqueous $NaHCO_3$ (1×100 mL) and brine (30 mL), then dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The obtained crude dark oil **21** (1.0 g) was dissolved in anhydrous MeOH (10 mL). KOH (0.50 g, 9.2 mmol) was added. The dark solution was stirred at 40 °C until TLC indicated completion of reaction. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (2×60 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with ethyl acetate/hexane (20%) to provide compound **22** (0.18 g, 30% yield for two steps) as a colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.03 (d, *J*=2.0 Hz, 1H), 6.94 (m, 1H), 6.71 (d, *J*=8.1 Hz, 1H), 6.16 (dd, *J*=10.7, 17.6 Hz, 1H), 5.55 (br, 1H) 5.25 (m, 2H), 2.27 (s, 3H), 1.42 (s, 6H). $^{13}C$ NMR $\delta$ 152.4, 147.9, 131.7, 129.7, 128.6, 126.8, 117.5,113.4, 40.2, 26.9, 20.2. MS: (+ESI) $(M+H)^+$ *m*/*z* 177.9.

### 5.6. *tert*-Butyldimethyl(4-methyl-2-(2-methyl-but-3-en-2-yl)phenoxy)silane 23

To a solution of compound **22** (0.55 g, 3.12 mmol) in anhydrous methylene chloride (5 mL) was added imidazole (0.64 g, 9.40 mmol) and TBSCl (0.72 g, 4.71 mmol). The mixture was stirred at room temperature under $N_2$ atmosphere overnight. The reaction mixture was diluted with methylene chloride (50 mL) and washed with water (30 mL). The organic layer was washed with brine (50 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with ethyl acetate/hexane (10%) to provide compound **23** (0.60 g, 66% yield) as a colorless oil. $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 6.96 (d, *J*=2.2 Hz, 1H), 6.84 (m, 1H), 6.68 (d, *J*=8.1 Hz, 1H), 6.11 (dd, *J*=10.7, 17.4 Hz, 1H), 4.83 (m, 2H), 2.16 (s, 3H), 1.35 (s, 6H), 0.93 (s, 9H), 0.21 (s, 6H). $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 152.0, 148.7, 131.1, 129.4, 128.8, 128.1, 118.8,110.8, 40.6, 28.0, 26.8, 21.1, 18.9, −3.2. MS: (+ESI) $(M+H)^+$ *m*/*z* 291.4.

### 5.7. Trimethyl(4-methyl-2-(2-methyl-but-3-en-2-yl) phenoxy)silane 24

1-Methyl-4-(3-methyl-but-2-enyloxy) benzene **13** (10.0 g, 55.8 mmol) was dissolved in a solution of *N*,*N*-dimethylaniline (50 mL), and 1,1,1,3,3,3-hexamethyl-disilazane (HMDS, 50 mL) in a thick-walled flask (350 mL). The solution was purged with $N_2$ for 5 min. The sealed flask was then inserted into an oil bath at 200 °C. The mixture was stirred for 16 h. The mixture was cooled to room temperature and diluted with ethyl acetate (300 mL). The mixture was extracted with aqueous HCl (3 M, 3×100 mL). The organic layer was further washed with satd aqueous $NaHCO_3$ (2×100 mL) and brine (100 mL), then dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with ethyl acetate/hexane (0–20%) to provide compound **24** (12.1 g, 78%) as a colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.10 (d, *J*=1.9 Hz, 1H), 6.92 (m, 1H), 6.68 (d, *J*=8.2 Hz, 1H), 6.17 (dd, *J*=10.1, 17.8 Hz, 1H), 4.95 (m, 2H), 2.30 (s, 3H), 1.46 (s, 6H), 0.32 (s, 9H). $^{13}C$ NMR $\delta$ 151.7, 148.2, 137.5, 129.4, 128.2, 127.4, 118.3, 109.8, 40.3, 27.2, 20.8, 0.7. MS: $(M+H)^+$ *m*/*z* 249.4. HRMS: calcd 249.1666 for $C_{15}H_{24}OSi$, found 249.1667.

### 5.8. 4-Methyl-2-(2,5,6-trimethylhept-5-en-2-yl) phenol 25

To a solution of **24** (2.5 g, 10.3 mmol) in anhydrous THF (60 mL) at 0 °C under $N_2$ was added a solution of 9-BBN (0.5 M in THF, 27.8 mL, 13.4 mmol) dropwise. The mixture was stirred at 0 °C for 30 min. The ice-water bath was removed and the mixture was stirred at room temperature for 5 h. Aqueous NaOH solution (3 M, 11.0 mL, 32.0 mmol) was added dropwise followed by addition of 2-bromo-3-methyl-but-2-ene (1.9 mL, 16.0 mmol) and $PdCl_2$ $(dppf)_2$ (0.39 g, 0.5 mmol). The mixture was stirred at 60 °C under $N_2$ for 16 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (100 mL), and washed with water (100 mL). The aqueous layer was extracted with ethyl acetate (2×80 mL). The combined organic layers were washed with brine (60 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with ethyl acetate/hexane (0–20%) to provide compound **25** (2.4 g, 90%) as a colorless oil. $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.96 (s, 1H), 6.85 (s, 1H), 6.76 (d, *J*=8.1 Hz, 1H), 6.63 (d, *J*=8.1 Hz, 1H), 2.16 (s, 3H), 1.81 (m, 2H), 1.62 (m, 2H), 1.53 (s, 3H), 1.51 (s, 3H), 1.48 (s, 3H), 1.28 (s, 6H). $^{13}C$ NMR (DMSO-$d_6$) 153.4, 132.9, 128.0, 127.9, 126.9, 126.5, 122.2, 115.6, 38.3, 37.4, 30.1, 27.8, 20.4, 20.3, 19.5, 18.3. MS $(M-H)^-$ *m*/*z* 245.1. HRMS [M−H]: calcd 245.1911 for $C_{17}H_{26}O$, found 245.1910.

### 5.9. 4-Methyl-2-(2,5,6-trimethylhept-5-en-2-yl)phenyl trifluoromethanesulfonate 11

To a solution of compound **25** (3.0 g, 12.2 mmol) in anhydrous THF (40 mL) was added sodium hydride (0.73 g, 18.3 mmol, 60% in mineral oil) in three portions at 0 °C under $N_2$. The mixture was stirred at 0 °C for 1 h. *N*-phenyltrifluoromethane sulfonamide (6.5 g, 18.3 mmol) was added. The mixture was stirred at room temperature for 1 h. The reaction mixture was quenched by slow addition of water (60 mL) and extracted with ethyl acetate (3×80 mL). The combined organic layers were washed with brine (60 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with ethyl acetate/hexane (5–20%) to provide compound **11** (4.0 g, 87%) as a colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.16 (m, 2H), 7.02 (m, 1H), 2.33 (s, 3H), 1.73 (m, 2H), 1.68 (m, 2H), 1.56 (s, 3H), 1.54 (s, 3H), 1.50 (s, 3H), 1.39 (s, 6H). $^{13}C$ NMR $\delta$ 147.3, 139.6, 137.5, 130.5, 128.4, 127.6, 123.9, 120.9, 120.2, 40.3, 38.3, 30.4, 29.0, 21.3, 20.7, 19.9, 18.4. MS: $(M+H)^+$ *m*/*z* 378.9.

### 5.10. 1,4,4,6-Tetramethyl-1-(prop-1-en-2-yl)-1,2,3,4-tetrahydronaphthalene 10

To a solution of compound **11** (3.9 g, 10.3 mmol) in anhydrous *N*,*N*-dimethylacetamide (40 mL) was added potassium carbonate (4.3 g, 30.9 mmol) and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (0.65 g, 1.03 mmol). The mixture was degassed with $N_2$ for 15 min. Palladium acetate (0.16 g, 0.57 mmol) was added and the mixture was degassed with $N_2$ for an additional 15 min. The mixture was heated in an oil bath at 120 °C under $N_2$ for 16 h. The dark solution was cooled to room temperature and the solvent was removed under reduced pressure. The mixture was diluted with ethyl acetate (100 mL) and washed with water (100 mL). The aqueous layer was extracted with ethyl acetate (2×100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with ethyl acetate/hexane (0–10%) to provide compound **10** (2.0 g, 85%) as a colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.12 (s, 1H), 6.99 (d, $J$=8.0 Hz, 1H), 6.92 (m, 1H), 4.90 (s, 1H), 4.64 (d, $J$=0.4 Hz, 1H), 2.31 (s, 3H), 2.03 (m, 1H), 1.73 (m, 1H), 1.64 (s, 3H), 1.62 (m, 1H), 1.47 (m, 1H), 1.42 (s, 3H), 1.29 (s, 3H), 1.23 (s, 3H). $^{13}C$ NMR $\delta$ 152.9, 145.2, 139.0, 135.0, 128.0, 126.8, 126.4, 112.1, 44.1, 35.1, 33.9, 31.9, 31.7, 31.4, 28.8, 21.2, 19.9. MS: $(M+H)^+$ $m/z$ 229.2.

### 5.11. 1-Isopropyl-1,4,4,6-tetramethyl-1,2,3,4-tetrahydronaphthalene 26

To a solution of compound **10** (2.7 g, 11.7 mmol) in ethanol (98%, 30 mL) under $N_2$ was added 10% Pd/C (0.2 g). The system was vacuumed and purged with $H_2$ three times. The mixture was stirred under $H_2$ atmosphere (1 atm) overnight. The solution was filtered through a pad of Celite and the pad was washed with ethyl acetate (100 mL). The solvent was removed under reduced pressure. The crude product was purified by flash chromatography eluting with ethyl acetate/hexane (0–10%) to provide compound **26** (2.4 g, 90%) as colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.22 (m, 2H), 7.01 (m, 1H), 2.39 (s, 3H), 2.26 (m, 1H), 1.87 (m, 2H), 1.61 (m, 2H), 1.39 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H), 1.08 (d, $J$=6.8 Hz, 3H), 0.71 (d, $J$=6.8 Hz, 3H). $^{13}C$ NMR $\delta$ 145.0, 140.6, 133.8, 126.1, 125.9, 39.1, 36.6, 34.4, 33.2, 31.5, 30.8, 28.6, 25.2, 20.7, 17.9, 16.6. MS: (EI) $(M+H)^+$ $m/z$ 231.2.

### 5.12. 1-Isopropyl-1,4,4,6-tetramethyl-5,7-dinitro-1,2,3,4-tetrahydronaphthalene 27

To a stirred solution of fuming nitric acid (98%, 15 mL) and concentrated sulfuric acid (95–98%, 20 mL) in anhydrous dichloroethane (15 mL) at 0 °C under $N_2$ was added a solution of compound **26** (2.3 g, 1.0 mmol) in anhydrous dichloroethane (10 mL) dropwise through a dropping funnel over 15 min. After completion of addition, the reaction mixture was stirred at 0 °C for 3 h. The mixture was slowly poured into ice-water (approximately 200 mL). The mixture was extracted with methylene chloride (3×100 mL). The combined organic layers were washed with water (1×100 mL), satd aqueous $NaHCO_3$ (2×100 mL) and brine (60 mL), then dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with ethyl acetate/hexane (10–20%) to provide compound **27** (2.9 g, 92%) as pale yellow solid. Mp 124–127 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.92 (s, 1H), 2.32 (s, 3H), 2.18 (m, 1H), 1.95 (m, 1H), 1.84 (m, 1H), 1.56 (m, 1H), 1.53 (s, 3H), 1.41 (m, 1H), 1.35 (s, 3H), 1.30 (s, 3H), 1.02 (d, $J$=6.6 Hz, 3H), 0.65 (d, $J$=6.8 Hz, 3H). $^{13}C$ NMR $\delta$ 152.7, 148.2, 147.4, 141.6, 124.4, 122.4, 41.5, 37.9, 37.5, 34.8, 30.4, 28.7, 28.3, 24.3, 18.3, 16.7, 13.9. MS: (EI) $(M+H)^+$ $m/z$ 321.1.

### 5.13. 2-(5-Isopropyl-5,8,8-trimethyl-1,3-dinitro-5,6,7,8-tetrahydronaphthalen-2-yl)ethanol 28

To a solution of compound **27** (3.1 g, 9.7 mmol) in anhydrous DMSO (20 mL) were added paraformaldehyde (0.43 g, 14.5 mmol) and a Triton-B solution (40% in methanol, 0.5 mL) at room temperature. The resulting purple solution was stirred at room temperature overnight. The solvent was removed under reduced pressure. The mixture was diluted with ethyl acetate (100 mL) and washed with water (100 mL). The aqueous layer was extracted with ethyl acetate (2×60 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with ethyl acetate/hexane (10–20%) to provide compound **28** (3.0 g, 90%) as white solid. Mp 110–112 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.89 (s, 1H), 3.79 (m, 2H), 3.16 (m, 1H), 2.77 (m, 1H), 2.13 (m, 1H), 1.85 (m, 2H), 1.64 (m, 1H, OH), 1.53 (m, 1H), 1.38 (m, 1H), 1.31 (s, 3H), 1.29 (s, 3H), 1.27 (s, 3H), 0.99 (d, $J$=6.7 Hz, 3H), 0.62 (d, $J$=6.8 Hz, 3H). $^{13}C$ NMR $\delta$ 152.1, 148.2, 147.9, 141.3, 124.5, 122.4, 61.9, 41.2, 37.5, 37.1, 34.4, 30.2, 29.9, 28.2, 27.8, 23.8, 17.9, 16.2. MS: (+ESI) $(M+Na)^+$ $m/z$ 373.1. HRMS [M+NH4]: calcd 368.2180 for $C_{18}H_{26}N_2O_5$,, found 368.2197.

### 5.14. Benzyl 3-(2-hydroxyethyl)-8-isopropyl-5,5,8-trimethyl-4-nitro-5,6,7,8-tetrahydronaphthalen-2-ylcarbamate 30

To a stirred solution of compound **28** (8.3 g, 24.7 mmol) in ethanol (100 mL) under $N_2$ at room temperature were added cyclohexene (3.5 mL, 34.2 mmol) and 10% Pd/C (0.9 g). The mixture was heated at 83 °C under $N_2$ overnight. The mixture was cooled to room temperature and was filtered through a pad of Celite. The pad was washed with ethyl acetate (200 mL). The filtrate was concentrated under reduced pressure to afford the crude amine intermediate **29** (7.4 g, 99%) as a yellow oil, which was used in the next step without further purification.

To a solution of the crude amine **29** in THF (100 mL) were added satd aqueous $NaHCO_3$ (30 mL) and benzyl chloroformate (6.6 mL, 46.2 mmol) at 0 °C. The mixture was stirred at room temperature overnight. The mixture was diluted with water (100 mL) and extracted with ethyl acetate (2×100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with methylene chloride/ethyl acetate (0–20%) to provide compound **30** (10.3 g, 92% for two steps) as yellow solid. Mp 167–169 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.52 (br s, 1H, ArH), 7.95 (br, 1H, $ArNHCO_2$), 7.41–7.33 (m, 5H, Ph), 5.20 (m, 2H, $PhCH_2$), 3.96–3.91 (m, 2H, $OCH_2$), 2.85 (m, 1H), 2.41 (m, 1H), 2.23 (br, 1H, OH), 1.94 (m, 2H), 1.81 (m, 1H), 1.48 (m, 1H), 1.36 (m, 1H), 1.32 (s, 3H), 1.28 (s, 3H), 1.25 (s, 3H), 0.98 (d, $J$=5.0 Hz, 3H), 0.64 (br, 3H). $^{13}C$ NMR $\delta$ 149.6, 147.5, 142.1, 131.6, 131.5, 127.3, 124.0, 123.7, 118.9, 115.8, 62.4, 59.7, 36.6, 33.5, 33.3, 29.4, 25.7, 25.2, 25.1, 24.4, 24.0, 20.1, 13.7, 12.2. MS: (ESI) $(M-H)^-$ $m/z$ 453.2. HRMS: calcd 454.2468 for $C_{26}H_{34}N_2O_5$, found 454.2469.

### 5.15. Benzyl 6-isopropyl-6,9,9-trimethyl-6,7,8,9-tetrahydro-1*H*-benzo[g]indol-4-ylcarbamate 9

To a solution of compound **30** (10.3 g, 22.7 mmol) in ethanol (100 mL) were added iron powder (12.9 g, 0.27 mol) and acetic acid (30 mL). The mixture was stirred at 80 °C for 3 h and was cooled to room temperature. The solution was filtered through a pad of Celite and the pad was washed with ethyl acetate. The filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (200 mL) and washed with satd aqueous $NaHCO_3$ (2×200 mL). The organic layer was washed with brine (100 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The crude product was dissolved in anhydrous toluene (100 mL) and the solvent was removed under reduced pressure. The crude amine intermediate was placed under high vacuum pump for 2 h. The amine intermediate **31** (9.5 g) was dissolved in anhydrous toluene (150 mL) and the solution was degassed with $N_2$ for 15 min. After addition of tris(triphenylphosphine)ruthenium dichloride (2.2 g, 2.3 mmol), the mixture was stirred at 120 °C under $N_2$ overnight. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography eluting with ethyl acetate/hexane (10–30%) to provide compound **9** (7.9 g, 86% for two steps) as yellow solid. Mp 107–109 °C. $^1H$ NMR (DMSO-$d_6$) $\delta$ 9.20 (br s, 1H), 7.44–7.31 (m, 6H), 7.08

(t, *J*=2.9 Hz, 1H), 6.6 (d, *J*=1.0 Hz, 1H), 5.14 (s, 2H, $PhCH_2$), 2.05 (m, 1H, $CH(CH_3)_2$), 1.72 (m, 2H, $CH_2CH_2$), 1.58 (m, 1H, $CH_2$), 1.39 (s, 3H), 1.35 (s, 3H), 1.28 (m, 1H, $CH_2$), 1.22 (s, 3H), 0.90 (d, *J*=6.7 Hz, 3H), 0.42 (d, *J*=6.6 Hz, 3H). $^{13}$C NMR $\delta$ 153.9, 136.9, 136.8, 133.6, 128.4, 128.2, 128.0, 127.9, 124.3, 123.1, 119.2, 98.6, 65.5, 54.9, 37.1, 36.9, 32.6, 29.9, 28.6, 26.9, 25.0, 18.0, 17.1. MS: (ESI) $(M-H)^-$ *m/z* 403.2. HRMS: calcd 404.2464 for $C_{26}H_{32}N_2O_2$, found 404.2465.

### 5.16. Ethyl 3-(4-(benzyloxycarbonylamino)-6-isopropyl-6,9,9-trimethyl-6,7,8,9-tetrahydro-1*H*-benzo[g]indol-3-yl)-2-(hydroxyimino)propanoate 33

To a solution of compound **9** (7.4 g, 18.3 mmol) in anhydrous methylene chloride (100 mL) were added sodium carbonate (3.0 g, 36.5 mmol) and ethyl 4-bromo-2-(hydroxyimino)butanoate **32** (3.8 g, 18.3 mmol) at room temperature under $N_2$. The reaction mixture was stirred overnight. The mixture was filtered through a pad of Celite and the pad was washed with ethyl acetate. The filtrate was concentrated and the crude product was purified by flash chromatography eluting with ethyl acetate/hexane (30–80%) to provide compound **33** (9.4 g, 97% yield) as yellow solid. Mp 118.2–120.8 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 12.35 (br s, 1H, NOH), 10.23 (s, 1H), 9.0 (br s, 1H), 7.37–7.26 (m, 5H), 6.83 (br s, 1H), 6.58 (m, 1H), 5.12 (s, 2H), 4.18 (q, *J*=7.1 Hz, 2H), 3.98 (s, 2H), 2.08 (m, 1H), 1.78 (m, 2H), 1.61 (9m, 1H), 1.39 (s, 3H), 1.36 (s, 3H), 1.31 (m, 1H), 1.22 (s, 3H), 1.17 (t, *J*=7.1 Hz, 3H), 0.91 (d, *J*=6.8 Hz, 3H), 0.41 (d, *J*=6.7 Hz, 3H). $^{13}$C NMR $\delta$ 164.6, 164.2, 155.0, 150.5, 150.3, 137.1, 137.0, 134.5, 128.3, 127.8, 127.7, 127.6, 126.3, 121.6, 121.5, 120.5, 107.2, 65.4, 60.9, 52.2, 36.9, 32.7, 29.6, 24.9, 21.3, 21.2, 17.9, 17.1, 14.0. MS: (ESI) $(M-H)^-$ *m/z* 533.2. HRMS: calcd 533.2897 for $C_{31}H_{39}N_3O_5$, found 533.2892.

### 5.17. Ethyl 3-(4-(benzyloxycarbonylamino)-6-isopropyl-6,9,9-trimethyl-6,7,8,9-tetrahydro-1*H*-benzo[g]indol-3-yl)-2-(*tert*-butoxycarbonylamino)propanoate 34

To a solution of compound **33** (9.4 g, 18.3 mmol) in THF/$H_2O$ (100 mL/10 mL) were added mercury chloride solution (2% $HgCl_2$ in $H_2O$ solution, 10 mL) and aluminum foil (5.0 g, 0.18 mol, which has been cut into small pieces). The green solution was stirred at room temperature overnight. The mixture was filtered through a pad of Celite and the pad was washed with ethyl acetate (100 mL). The filtrate was diluted with water (60 mL) and extracted with ethyl acetate (3×80 mL). The combined organic layers were washed with brine (60 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated to afford the amine intermediate (9.0 g, 94% yield), which was used in the next step without further purification.

To a solution of the crude amine (9.0 g, 17.3 mmol) in THF (100 mL) was added satd aqueous $NaHCO_3$ (20 mL) and di-*tert*-butyl dicarbonate (7.6 g, 34.6 mmol). The mixture was stirred at room temperature overnight. The reaction mixture was extracted with ethyl acetate (3×80 mL). The combined organic layers were washed with brine (60 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The crude product was purified by flash chromatography eluting with ethyl acetate/hexane (30–50%) to give compound **34** (8.7 g, 81% for two steps) as yellow solid. Mp 91–95 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 10.43 (br s, 1H), 8.83 (br s, 1H), 7.42–7.24 (m, 5H), 7.16 (m, 1H), 7.01 (m, 1H), 6.76 (br s, 1H), 5.03 (s, 2H), 4.19 (m, 1H), 4.06–3.97 (m, 2H), 3.21 (m, 1H), 2.98 (m, 1H), 2.02 (m, 1H), 1.71 (m, 2H), 1.58 (m, 1H), 1.41–1.39 (m, 4H), 1.33 (two sets of singlet, 3H from $CH_3$), 1.30 (s, 9H), 1.22 (s, 3H), 1.06 (m, 3H), 0.91 (m, 3H), 0.42 (m, 3H). $^{13}$C NMR $\delta$ (mixture of diastereomers) 172.8, 155.5, 155.5, 155.3, 137.0, 136.6, 134.6, 134.6, 128.3, 128.2, 127.7, 127.6, 127.6, 127.5, 126.6, 123.5, 121.4, 108.9, 78.0, 78.0, 65.6, 60.1, 55.1, 54.9, 37.0, 36.9, 36.8, 32.7, 29.6, 28.5, 28.5, 28.1, 28.1, 27.8, 27.3, 27.2, 26.7, 26.6, 25.0, 25.0, 18.0, 17.1, 17.1, 14.0, 14.0. MS: (ESI) $(M+H)^+$ *m/z* 620.4. HRMS: calcd 619.3621 for $C_{36}H_{49}N_3O_6$, found 619.3624.

### 5.18. (2*S*)-Benzyl 2-(3-(2-(*tert*-butoxycarbonylamino)-3-ethoxy-3-oxopropyl)-6-isopropyl-6,9,9-trimethyl-6,7,8,9-tetrahydro-1*H*-benzo[g]indol-4-ylamino)-3-methylbutanoate 36

A mixture of compound **34** (5.20 g, 8.4 mmol) and 10% Pd/C (0.5 g) in methanol (100 mL) was hydrogenated at 45 psi on a Parr shaker apparatus. After 4 h, the suspension was filtered through a pad of Celite and the pad was washed with methanol. The filtrate was concentrated under reduced pressure to afford the crude amine intermediate (4.2 g) as a green solid, which was used in the next step without further purification.

To a solution of the amine (4.2 g, 8.4 mmol) in anhydrous 1,2-dichloroethane (100 mL) was added 2,4-lutidine (1.5 mL, 12.6 mmol) and (*S*)-benzyl 4-methyl-2-(trifluoromethylsulfonyloxy)pentanoate **35** (3.87 g, 10.9 mmol). The mixture was stirred under $N_2$ at 83 °C for 12 h. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography eluting with ethyl acetate/hexane (10–30%) to give compound **36** (4.8 g, 82% for two steps) as a brown solid. Mp 82–85 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 10.10 (br s, 1H, NH), 7.33–7.31 (m, 5H, Ph), 6.92 (m, 1H), 6.03 (m, 1H, Ph-H), 5.13–4.97 (m, 2H, $OCH_2Ph$), 4.55–4.52 (m, 1H, PhNH), 4.24 (m, 1H, $CHCO_2Et$), 4.19–4.01 (m, 2H, $OCH_2$), 3.28–3.22 (m, 1H, 1H of $CH_2$), 3.14–3.11 (m, 1H, 1H of $CH_2$), 2.18–2.16 (m, 1H, $NCHCO_2Et$), 2.13–1.99 (m, 1H, PhNH–CH), 1.72–1.63 (m, 2H), 1.56–1.51 (m, 1H), 1.41–1.26 (m, 12H, $C(CH_3)_3$ and $CH_3$), 1.22–1.16 (m, 6H, $CH_3$), 1.11 (m, 1H, CH), 1.09–1.01 (m, 6H, $CH_3$), 0.92 (m, 3H, $CH_3$), 0.89–0.77 (two sets of doublets, 3H, $CH_3$), 0.48–0.32 (m, 3H, $CH_3$). $^{13}$C NMR $\delta$ (mixture of diastereomers) 173.9, 173.8, 172.5, 155.5, 155.4, 138.8, 137.2, 135.6, 128.3, 128.2, 128.1, 128.0, 127.9, 122.4, 120.1, 120.0, 119.8, 114.8, 108.3, 78.2, 78.1, 78.1, 65.9, 65.8, 62.2, 60.4, 60.2, 56.2, 56.0, 37.3, 37.2, 36.9, 36.8, 36.8, 32.2, 31.2, 31.1, 31.0, 30.0, 29.9, 29.9, 29.8, 28.4, 28.4, 28.1, 27.7, 27.6, 27.0, 26.8, 26.7, 24.9, 19.4, 19.3, 19.2, 19.1, 19.1, 19.0, 18.9, 18.2, 18.0, 17.9, 17.8, 17.1, 17.0, 16.9, 14.0, 13.9, 13.9. MS: (+ESI) $(M+H)^+$ *m/z* 676.3. HRMS: calcd 675.4247 for $C_{40}H_{57}N_3O_6$, found 675.4250.

### 5.19. (7*S*)-Ethyl 7,10-diisopropyl-8,10,13,13-tetramethyl-6-oxo-3,4,5,6,7,8,10,11,12,13-decahydro-1*H*-benzo[*g*][1,4]diazonino-[7,6,5-*cd*]indole-4-carboxylate 38

A mixture of 10% Pd/C (0.1 g) and compound **36** (0.62 g, 0.92 mmol) in methanol (20 mL) was hydrogenated at 45 psi on a Parr shaker apparatus. After 2 h, the reaction was complete as determined by TLC. The suspension was filtered through a pad of Celite and the pad was washed with methanol. The filtrate was concentrated under reduced pressure to afford the crude acid intermediate (0.54 g) as a green solid, which was used in the next step without further purification.

To a solution of the crude acid (0.54 g, 0.92 mmol) in anhydrous acetonitrile (10 mL) at 0 °C was added *N*,*N*′-dicyclohexylcarbodiimide (0.31 g, 1.47 mmol) and *N*-hydroxysuccinimide (0.21 g, 1.79 mmol). The mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. The solvent was removed under reduced pressure. The solid was dissolved in ethyl ether and filtered through a pad of Celite. The pad was washed with ethyl ether. The filtrate was concentrated. The crude product was purified by flash chromatography eluting with ethyl acetate/hexane (50–80%) to give the activated ester intermediate (0.57 g) as white solid.

To a solution of the activated ester (0.57 g, 0.83 mmol) in anhydrous methylene chloride (5 mL) at 0 °C under $N_2$ was added trifluoroacetic acid (5 mL) dropwise. The mixture was then stirred at room temperature for 2 h. The solvent was removed under reduced pressure (the temperature should be kept under 30 °C).

To a solution of the crude amine in ethyl acetate (10 mL) was added satd aqueous $NaHCO_3$ (6 mL). The mixture was stirred at 70 °C for 16 h. The mixture was cooled to room temperature, diluted with ethyl acetate (50 mL), and washed with water (50 mL). The aqueous layer was extracted with ethyl acetate (2×50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The crude product was purified by flash chromatography eluting with ethyl acetate/hexane (10–50%) to give lactam **37** (0.18 g, 41% yield over four steps) as a mixture of diastereomers.

To a solution of lactam **37** (0.18 g, 0.39 mmol) in anhydrous methylene chloride (10 mL) was added paraformaldehyde (0.058 g, 1.93 mmol) and acetic acid (0.11 mL, 1.93 mmol). The mixture was stirred at room temperature for 1 h. Sodium triacetoxyborohydride (0.36 g, 1.93 mmol) was added in one portion. The mixture was stirred at room temperature under $N_2$ for 16 h. The reaction was quenched by addition of water (20 mL). The mixture was diluted with methylene chloride (50 mL) and the layers were separated. The aqueous layer was extracted with methylene chloride (2×30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The crude product was purified by flash chromatography eluting with ethyl acetate/hexane (0–30%) to give lactam **38** (0.16 g, 21% yield over five steps) as a mixture of diastereomers. Mp 102–106 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ (mixture of four diastereomers) 8.25 (br s, 1H), 7.01 (s, 1H), 6.99 (s, 1H), 5.12 (m, 1H), 4.22 (m, 3H), 3.58 (m, 1H), 3.18 (m, 1H), 2.75 (s, 3H), 2.61 (m, 1H), 2.39 (m, 1H), 1.85 (m, 2H), 1.66 (m, 2H), 1.47 (m, 3H), 1.39 (m, 3H), 1.26 (m, 6H, 3H each overlapping), 0.99 (m, 3H), 0.92 (m, 3H), 0.58 (m, 6H). $^{13}$C NMR $\delta$ (mixture of four diastereomers) 172.2, 172.1, 171.9, 171.2, 171.1, 171.0, 170.9, 145.3, 145.1, 142.7, 139.6, 139.5, 139.3, 139.2, 137.2, 136.9, 127.3, 126.8, 126.2, 126.1, 123.1, 123.0, 122.8, 122.3, 121.8, 121.5, 120.8, 120.2, 117.4, 117.1, 113.9, 113.7, 107.6, 107.5, 107.3, 71.2, 71.2, 62.0, 61.8, 61.0, 58.0, 57.8, 55.6, 55.6, 40.2, 39.8, 39.7, 38.0, 37.6, 37.5, 37.4, 37.3, 37.1, 36.1, 35.9,35.9, 35.4, 33.2, 33.1, 33.1, 32.9, 31.1, 31.0, 30.8, 30.0, 29.9, 29.7, 29.0, 28.6, 28.5, 28.4, 28.4, 27.8, 27.7, 27.6, 27.5, 25.6, 25.5, 24.5, 24.4, 21.9, 21.8, 20.4, 19.8, 19.7, 19.5, 19.4, 19.3, 18.3, 18.2, 18.1, 17.3, 17.2, 17.1, 17.1, 14.4, 14.3, 14.2, 14.1. MS: (ESI) $(M+H)^+$ *m*/*z* 482.3. HRMS: calcd 481.3304 for $C_{29}H_{43}N_3O_3$, found 481.3308.

## 5.20. Teleocidin B analogs 5 and 39

To a solution of ester **38** (0.15 g, 0.31 mmol) in anhydrous THF (5 mL) at 0 °C under $N_2$ was added a solution of $LiBH_4$ (0.93 mL, 0.93 mmol, 1 M solution in THF) dropwise. The mixture was stirred at 0 °C for 3 h until TLC revealed completion of reaction. The mixture was quenched with $H_2O$ (10 mL). The mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated to provide a white solid. The crude product was purified by flash chromatography eluting with ethyl acetate/hexane (80–100%) to give alcohol **5** (43 mg, 29% yield) as the first fraction and alcohol **39** (38 mg, 27% yield) as the second fraction.

Teleocidin B analog **5** (mixture of two diastereomers): mp 165–169 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.32 (br, 1H, NH), 8.12 (br, 1H, NH), 8.06 (br, 1H, NH), 7.01 (m, 1H), 6.82 (m, 1H), 6.57 (s, 1H), 6.44 (s, 1H), 4.42 (m, 1H), 4.38 (br, 1H), 4.31 (d, $J$=12 Hz, 1H), 4.28 (d, $J$=12 Hz, 1H), 3.74 (m, 2H), 3.56 (m, 2H), 3.18 (m, 2H), 3.06 (m, 1H), 2.98 (m, 1H), 2.89 (two sets of singlets, 3H, N–$CH_3$), 2.72 (two sets of singlets, 3H, N–$CH_3$), 2.62 (m, 2H), 2.18 (m, 2H), 1.83 (m, 4H), 1.62 (m, 4H), 1.49 (m, 3H), 1.47 (s, 3H), 1.42 (m, 3H), 1.41 (m, 3H), 1.32 (m, 3H), 1.31 (m, 3H), 1.01 (m, 6H), 0.96 (m, 6H), 0.72 (m, 3H), 0.62 (m, 3H), 0.56 (m, 3H), 0.51 (m, 3H). $^{13}$C NMR $\delta$ 174.6, 174.3, 173.6, 145.7, 145.3, 139.2, 138.8, 137.3, 137.2, 125.3, 123.6, 121.1, 120.6, 120.1, 117.2, 116.6, 113.7, 113.6, 106.9, 106.8, 70.9, 70.8, 64.8, 64.7, 63.1, 55.8, 55.7, 54.3, 40.1, 39.9, 38.2, 37.9, 37.8, 37.7, 33.9, 33.8, 33.5, 31.0, 29.7, 28.9, 28.5, 27.8, 27.8, 25.7, 25.6, 21.9, 19.7, 19.2, 18.2, 18.1, 17.2, 17.1. MS: (ESI) $(M+H)^+$ *m*/*z* 440.3. HRMS: calcd 439.3201 for $C_{27}H_{41}N_3O_2$, found 439.3197.

Teleocidin B analog **39** (mixture of two diastereomers): mp 137–141 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.06 (br, 1H, NH), 7.99 (br, 1H, NH), 6.86 (s, 1H), 6.83 (s, 1H), 6.80 (s, 1H), 6.73 (s, 1H), 3.84 (m, 5H, H-9, H-12, H-14 and H-19), 3.26 (m, 1H, H-8), 3.09–3.06 (two sets of singlets, 6H, N–$CH_3$), 2.89 (m, 1H, H-8), 2.62 (m, 1H, H-15), 2.19 (m, 1H), 1.86 (m, 2H), 1.62 (m, 2H), 1.49 (m, 3H), 1.45 (s, 3H), 1.36 (s, 3H), 1.29 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 1.01 (m, 3H), 0.96 (m, 3H), 0.83 (m, 6H), 0.74 (m, 6H), 0.58 (m, 3H), 0.52 (m, 3H). $^{13}$C NMR $\delta$ 174.9, 174.8, 145.8, 145.6, 138.8, 138.6, 136.4, 136.4, 122.8, 121.3, 120.6, 118.8, 118.7, 113.6, 110.1, 110.0, 68.5, 65.4, 57.6, 57.5, 40.3, 39.9, 38.2, 37.6, 37.2, 37.1, 33.1, 32.8, 32.5, 32.3, 31.1, 30.8, 29.7, 29.3, 29.0, 28.2, 28.1, 27.8, 27.3, 25.3, 20.5, 20.4, 20.3, 19.7, 18.8, 18.2, 17.2, 17.1. MS: (ESI) $(M+H)^+$ *m*/*z* 440.3. HRMS: calcd 439.3201 for $C_{27}H_{41}N_3O_2$, found 439.3271.

## 5.21. Teleocidin B analogs 40 and 41

*HPLC separation of alcohol* **5**: chiralcel AD-H column, 2×25 cm; detection at 280 nm; temperature: 25 °C; sample was dissolved in EtOH, sample concentration: 0.035 g/mL; mobile phase: 5% isopropanol in hexane; flow rate: 20 mL/min.; injection volume: 5 µL in EtOH.

*Teleocidin B analog* **40**: 18 mg, white solid: mp 197–199 °C. $[\alpha]_D^{25}$ −353.8 (c, 0.5, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.13 (br s, 1H, NH), 6.88 (s, 1H), 6.52 (s, 1H), 4.36 (br, 1H), 4.32 (d, $J$=12 Hz, 1H, H-12), 3.72 (m, 1H), 3.56 (m, 2H), 3.18 (q, J=15 Hz, 1H, H-8), 3.05 (qd, J=4, 15 Hz, 1H, H-8), 2.91 (s, 3H), 2.86 (br s, 1H, OH), 2.62 (m, 1H), 2.18 (m, 1H), 1.82 (m, 2H), 1.64 (m, 2H), 1.48 (s, 3H), 1.41 (s, 3H), 1.31 (s, 3H), 1.01 (d, $J$=9.0 Hz, 3H), 0.96 (d, $J$=6.8 Hz, 3H), 0.72 (d, $J$=6.7 Hz, 3H), 0.51 (d, $J$=9.0 Hz, 3H). $^{13}$C NMR $\delta$ 174.3, 145.3, 139.2, 137.3, 121.1, 120.6, 117.2, 113.9, 106.9, 70.9, 65.1, 55.8, 40.2, 38.0, 37.6, 33.8, 33.1, 32.9, 31.0, 29.7, 28.5, 27.8, 25.7, 21.7, 19.7, 18.1, 17.2. MS: (ESI) $(M+H)^+$ *m*/*z* 440.3. HRMS: calcd 439.3201 for $C_{27}H_{41}N_3O_2$, found 439.3201.

*Teleocidin B analog* **41**: 13 mg, white solid: mp 173–175 °C. $[\alpha]_D^{25}$ −153.8 (c, 0.5, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.08 (br s, 1H, NH), 6.81 (s, 1H), 6.42 (s, 1H), 4.38 (br s, 1H), 4.30 (d, $J$=12 Hz, 1H, H-12), 3.76 (m, 1H), 3.59 (m, 1H), 3.53 (br, 1H, OH), 3.16 (q, J=15 Hz, 1H, H-8), 3.06 (qd, $J$=4.2, 15 Hz, 1H, H-8), 2.88 (s, 3H), 2.58 (m, 1H), 2.17 (m, 1H), 1.86 (m, 2H), 1.66 (m, 2H), 1.49 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H), 0.98 (d, $J$=9.1 Hz, 3H), 0.91 (d, $J$=6.8 Hz, 3H), 0.62 (d, $J$=6.8 Hz, 3H), 0.56 (d, $J$=9.1 Hz, 3H). $^{13}$C NMR $\delta$ 174.6, 145.7, 138.8, 137.2, 121.1, 120.6, 116.6, 113.6, 106.8, 70.8, 65.6, 55.7, 39.8, 37.8, 37.7, 33.9, 33.2, 32.6, 31.2, 28.9, 28.4, 27.7, 25.6, 21.9, 19.2, 18.1, 17.1. MS: (ESI) $(M+H)^+$ *m*/*z* 440.3. HRMS: calcd 439.3201 for $C_{27}H_{41}N_3O_2$, found 439.3109.

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