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Synthesis of Teleocidins A, B and Their Congeners. Part 2.[1] Synthesis of Lyngbyatoxin A (Teleocidin A-1), Teleocidin A-2, Pendolmycin, and (*R*, *E*)- and (*S*, *E*)-7-(3,7,11-Trimethyl-1,6,10-dodecatrien-3-yl)-(–)-indolactams V

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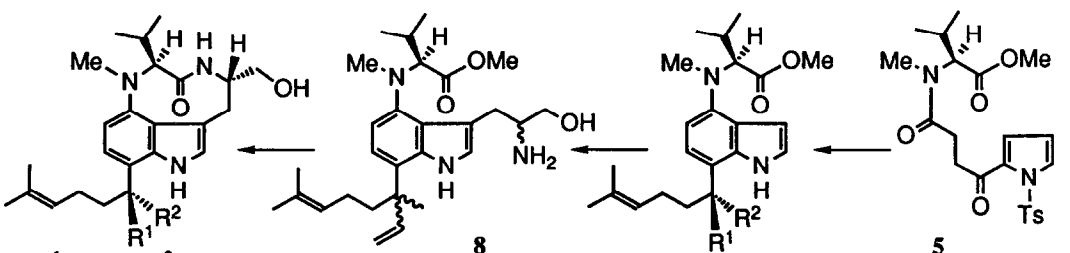
Abstract *— Details of the synthesis method of the tumor promoters, lyngbyatoxin A (= teleocidin A-1) (1) and teleocidin A-2 (2) from (R)- and (S)-methyl N-[7-(3,7-dimethyl-1,6-octadien-3-yl)-4-indolyl]-N-methyl-L-valinate (3* and *4) are presented Other titled compounds, 6, 7a, and 7b, were prepared analogously*

In the previous paper we reported the details of preparation of (*R*)- and (*S*)-methyl *N*-[7-(3,7-dimethyl-1,6-octadien-3-yl)-4-indolyl]-*N*-methyl-L-valinates (**3** and **4**) starting from the readily available methyl *N*-methyl-L-valinate derivative **5** Here we describe continuation of our synthesis to obtain lyngbyatoxin A (= teleocidin A-1) (**1**) and teleocidin A-2 (**2**) This synthesis pathway was also applied to the preparation of pendolmycin (**6**) and (*R*, *E*)- and (*S*, *E*)-7-(3,7,11-trimethyl-1,6,10-dodecatrien-3-yl)-(–)-indolactams V (**7a** and **7b**) to send them for biological evaluation

With the essential intermediates **3** and **4** in hand, the next task was to introduce the amino propanol side chain at the C-3 position of the indole moiety to form **8** and to set the stage to make the nine-membered lactam ring to complete the natural product synthesis This was first tried by applying conventionally either the Vilsmeier reagent or the gramine formation (Chart 1) Reaction of **9a** with the Vilsmeier reagent gave the expected product **10a** in 65% yield, but the formation of a position isomer **11a** was unavoidable, in 22% yield On the other hand, treating **9a**, **9b**, and an inseparable mixture[1] of **9c** and **9d** (**9c** + **9d**) with *N*, *N*-dimethyl(methylene)ammonium chloride[2] in dichloromethane at room temperature afforded only the expected compounds **12a**, **12b**, and **12c** + **12d** in 97%, 95%, and 88% yields, respectively And the gramine compounds

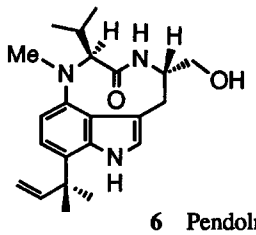


1 R^1 = vinyl R^2 = Me Lyngbyatoxin A (= Teleocidin A-1)
2 R^1 = Me R^2 = vinyl Teleocidin A-2

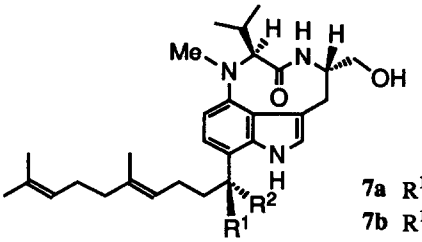
8

3 R^1 = vinyl R^2 = Me
4 R^1 = Me R^2 = vinyl

5



6 Pendolmycin

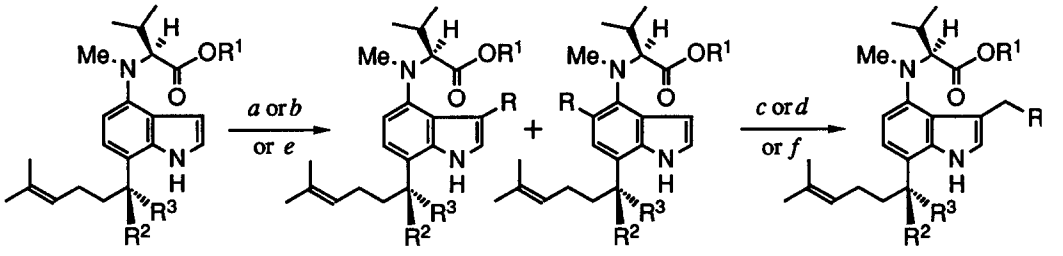


7a R^1 = vinyl R^2 = Me
7b R^1 = Me R^2 = vinyl

12b and **12c** + **12d** were transformed into a nitrodiester **13b** and acetamide triesters **14c** + **14d** in 91% and 49% yields, respectively, by a reaction with methyl nitroacetate[3] and diethyl acetamidomalonate with the aid of tributylphosphine [4] However, modest yield of **14c** + **14d** precluded subsequent experiments for trying decarboxylation Reduction of the nitro group of **13b** with aluminium-amalgam[5] or the cobaltous chloride – sodium borohydride reagent[6] was unsuccessful

A satisfactory result was obtained using ethyl 3-bromo-2-hydroxyiminopropanoate.[7] The respective reaction with **9a** and **9b** was effected in the presence of sodium carbonate in dichloromethane at room temperature to afford **15a** and **15b** in 59% and 65% yields, accompanied by the formation of regioisomers **16a** and **16b** in 20% and 15% yields Reduction of the oxime function to the primary amine group was readily carried out by treatment of **15a** and **15b** with aluminium – amalgam in aqueous tetrahydrofuran[8] to furnish **17a** and **17b** in 92% and 89% yields Judging from their proton NMR spectra, each was composed of a 1 1 mixture of diastereomers with respect to the amino group configuration, and therefore no stereochemical control was unfortunately operated during the reduction The chemical reactivity of the newly formed amino ester group was different from the *N*-methylvalinate ester, probably due to difference in the environmental situation Thus the reduction of **17a** and **17b** using sodium borohydride in refluxing ethanol[9] afforded **18a** and **18b** in 51% and 53% yields

The final step, the formation of a nine-membered lactam ring, was performed as reported by Ley and co-workers for indolactam V synthesis [10] The amino ester **18a** was hydrolyzed at reflux for 22 h with 10% potassium hydroxide in a 4 1 mixture of methanol and water (Chart 2) The potassium salt of the amino acid was



9 **10** R = CHO **11** R = CHO **13** R = $O_2NCHCOOMe$
12 R = CH_2NMe_2 **14** R = $AcHNC(COOEt)_2$
15 R = CH_2–C(=NOH)–COOEt **16** R = CH_2–C(=NOH)–COOEt **17** R = $H_2NCHCOOEt$
18 R = H_2NCHCH_2OH

	R^1	R^2	R^3
a	Me	vinyl	Me
b	Me	Me	vinyl
c	t-Bu	vinyl	Me
d	t-Bu	Me	vinyl

a Vilsmeier reagent *b* $Me_2\overset{+}{N}=CH_2\ Cl^-$ *c* O_2NCH_2COOMe
d $AcHNCH(COOEt)_2$, Bu_3P *e* $BrCH_2$–C(=NOH)–COOEt, Na_2CO_3
f Al-Hg, $THF\text{-}H_2O$ *g* $NaBH_4$, EtOH

Chart 1

neutralized with triethylamine hydrochloride, and after removing the solvent and thoroughly drying the remaining solid, the residue was treated with diphenylphosphoryl azide (DPPA)[11] and triethylamine in dimethylformamide at room temperature for 17 h. The reaction products were separated and purified by the usual silica gel chromatography and subsequent HPLC to afford lyngbyatoxin A (= teleocidin A-1) (**1**), the unnatural enantiomer of teleocidin A-2 (ent-**2**), and an inseparable mixture of 9-epilyngbyatoxin A (9-epi-**1**) and 9-epi-ent-**2** in 23%, *ca* 4%, and 27% yields, respectively The same series of treatments of **18b** afforded analogously teleocidin A-2 (**2**), the enantiomer of lyngbyatoxin A (ent-**1**), and an inseparable mixture of 9-epiteleocidin A-2 (9-epi-**2**) and 9-epi-ent-**1** in 21%, *ca* 4%, and 25% yields, respectively The two final compounds **1** and **2** as well as two by-products ent-**1** and ent-**2** obtained here were converted to the (+)-MTPA [(+)-α-methoxy-α-trifluoromethylphenylacetic acid] esters and their pure states were confirmed by HPLC analysis. The synthetic compounds **1** and **2** were identified as lyngbyatoxin A (= teleocidin A-1) and teleocidin A-2 by comparing their MS, ^{1}H and ^{13}C NMR, and CD spectra, and the mobility on HPLC They also exhibited the same order of biological activities as the natural products on the tests of mouse ear irritation, induction of ornithine decarboxylase, inhibition of specific ^{3}H-TPA binding, and activation of protein kinase C

The structures of ent-**1** and ent-**2** were supported by the antipodal CD curves, together with the identical MS, ^{1}H NMR spectra, and the mobility on HPLC, compared with those of **1** and **2** The origin of these enantiomers ent-**1** and ent-**2** as well as their C-9 epimers 9-epi-ent-**1** and 9-epi-ent-**2** was attributable to a rather drastic treatment with alkali during hydrolysis of the methyl ester group in **18a** and **18b** Partial racemization took place at the L-valine portion and the combination of this inversion (12*S* → 12*R*) with other chiralities at the C-9 and C-14 positions, for instance (9*S*, 14*R*), generated the compound 9-epi-ent-**2** This phenomenon was inevitable when the methyl valine ester was used, since it resisted the other mild hydrolysis conditions

Thus the first synthesis of lyngbyatoxin A (teleocidin A-1) (**1**) and teleocidin A-2 (**2**) was achieved in

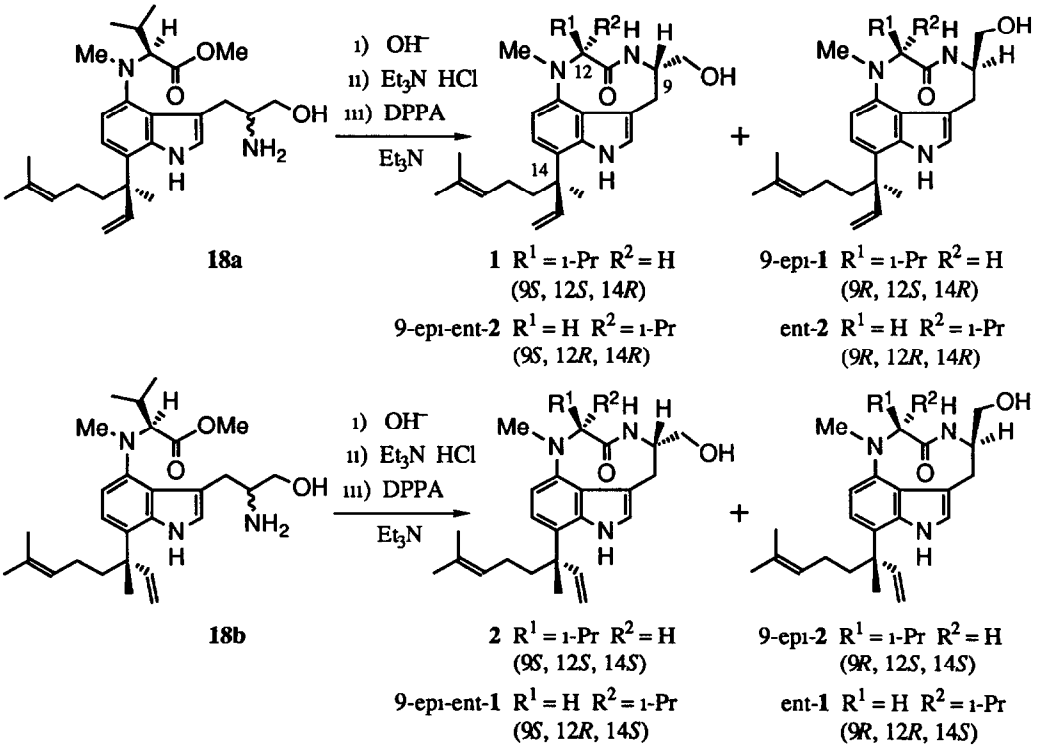


Chart 2

eleven steps from 1-[(4-methylphenyl)sulfonyl]pyrrole The success of this straightforward and relatively short synthesis was due to the pertinent selection of the starting intermediate **5**, which made it possible to introduce the linalyl side chain in a single step and to efficiently produce the 7-alkyl-4-aminoindole derivatives **3** and **4** Introduction of the aminopropanol side chain was readily achieved and subsequent formation of the nine-membered ring afforded the final compounds, although some unwanted by-products were unavoidably produced

This synthesis pathway is widely applicable to other teleocidins and related compounds So next we attempted to synthesize pendolmycin (**6**), a metabolite of *Nocardiopsis* strain SA 1715, and (*R*, *E*)- and (*S*, *E*)-7-(3,7,11-trimethyl-1,6,10-dodecatrien-3-yl)-(–)-indolactams V (**7a** and **7b**), unnatural analogues of lyngbyatoxin A (**1**) (Chart 3). The common starting intermediate was the ketoamide[1] **5** and the Grignard reaction of **5** with 3-methyl-2-butenyl (prenyl) bromide or (*E*, *E*)-3,7,11-trimethyl-2,6,10-dodecatrienyl (farnesyl) bromide[12] in the presence of magnesium afforded mixtures of **19a** and **20a**, and **19b** and **20b** These were separated and the *N*-tosyl group was reductively cleaved from **19a** and **19b** with magnesium in methanol Combined pyrrole derivatives **20a** and **20b** were obtained in 84% and 66% yields, respectively Both were dehydrated without trouble in 93% and 91% yields to afford **21a** and **21b**, whose amide function was changed to the thioamide group with Lawesson's reagent giving **22a** and **22b** in 74% and 77% yields The indole cyclization was carried out as before by treating these thioamides with iodomethane in dimethylformamide to yield **23a** (66%), **23b** (46 5%), and **24b** (25%), accompanied by the formation of by-products **25a** (19%) and **25b** (23%)

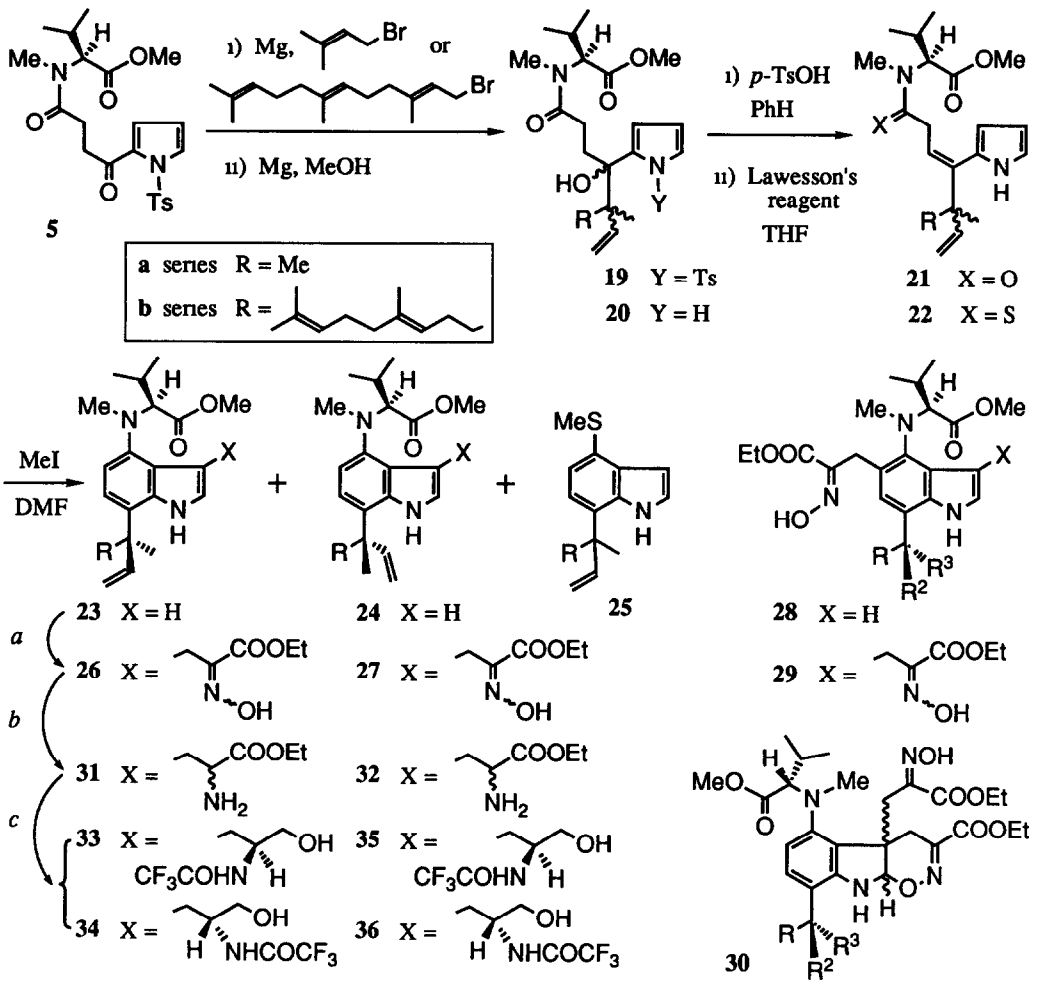
The carbon side chain was introduced into the C-3 position of the indole derivatives **23a**, **23b** and **24b** as usual by reacting ethyl 3-bromo-2-hydroxyiminopropanoate. The desired compounds **26a**, **26b** and **27b** were produced in 53%, 51% and 61% yields together with by-products **28a** (R^2 = Me, R^3= vinyl) (21%), **28b** (R^2 = vinyl, R^3= Me) (20%), **28b** (R^2 = Me, R^3= vinyl) (14%), **29a** (R^2 = Me, R^3= vinyl) (4%), **29b** (R^2 = vinyl, R^3= Me) (4%), **29b** (R^2 = Me, R^3= vinyl) (3%), and diastereoisomeric mixtures of **30a** (R^2 = Me, R^3= vinyl) (4%), **30b** (R^2 = vinyl, R^3= Me) (2 5%), and **30b** (R^2 = Me, R^3= vinyl) (3%) The oxime group in **26a**, **26b** and **27b** was reduced with aluminium-amalgam to give aminodiester compounds **31a**, **31b** and **32b** in 92%, 95% and 94% yields and their unhindered ester group was reduced with sodium borohydride in the presence of lithium chloride,[13] followed by conversion to the trifluoroacetates Diastereoisomers related to the amino group stereochemistry were separated here, affording sets of epimers **33a** (40%) and **34a** (37 5%), **33b** (40%) and **34b** (33%), as well as **35b** (38 5%) and **36b** (33%) Among them, the compounds produced in the better yields, *i e* **33a**, **33b** and **35b**, afforded the required products, pendolmycin (**37a** = **6**), and (*R*,*E*)- and (*S*,*E*)-7-(3,7,11-trimethyl-1,6,10-dodecatrien-3-yl)-(–)-indolactams V (**37b** = **7a** and **39b** = **7b**) in 54%, 56% and 47% yields by a series of operations i) alkaline hydrolysis of the methyl valinate part, ii) neutralization of the alkaline medium, iii) complete dryness of the reaction residue, and iv) treatment with diethylphosphoryl cyanide (DEPC)[14] (see Part 3, the following paper) and triethylamine in dimethylformamide Partial racemization during the alkaline hydrolysis gave rise to the formation of **38a**, **38b** and **40b** in 9%, 12% and 9% yields

The tumor promoting activities of pendolmycin (**6**) and 7-[(*R*,*E*)-3,7,11-trimethyl-1,6,10-dodecatrien-3-yl]-(–)-indolactam V (**7a**) were studied using our specimens and it was shown that the activity of **7a** was as potent as that of teleocidins A, whereas **6** was moderately active and its potency was somewhere between teleocidins A and (–)-indolactam V [15]

EXPERIMENTAL

General Procedures — Mass spectra (MS) were recorded on Hitachi RMS-4 and Hitachi M-80B spectrometers High resolution mass spectra (HRMS) were measured on JEOL JMS-DX-300 and Hitachi M-80B spectrometers Circular dichroism spectra (CD) were taken on JASCO J-500A Proton magnetic resonance (^{1}H NMR) spectra were recorded on Varian EM 390 (90 MHz), JEOL FX-200A (270 MHz) and JEOL JNM-GX-400 (400 MHz) spectrometers in $CDCl_3$ with TMS as an internal reference Preparative thin-layer chromatography over Al_2O_3 (Al_2O_3 PTLC) was carried out on glass plates (20 × 20 cm) coated with Merck aluminum oxide 60 PF_{254} (type E) (1 mm thick) Other General Methods were described in the Part 1 [1]

Vilsmeier Reaction on 9a to Form 10a and 11a — Vilsmeier-Haak reagent (0 5 ml, 0 098 mmol),



a , Na_2CO_3, CH_2Cl_2 *b* Al-Hg, THF-H_2O *c* i) $NaBH_4$, LiCl, EtOH-THF
ii) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2

Chart 3

prepared from $POCl_3$ (60 mg, 0 391 mmol) and DMF (2 ml) with stirring at 0°C for 5 min, was added to a solution of **9a** (13 mg, 0 033 mmol) in Et_2O (1 ml), and the mixture was stirred at 0°C for 30 min Sat $NaHCO_3$-H_2O (4 ml) was added to this and the whole was stirred vigorously at room temperature for 20 min Extraction with Et_2O, usual work-up and PTLC [hexane-EtOAc (4 1)] gave **10a** (9 mg, 65%) and **11a** (3 mg, 22%) **Methyl *N*-[3-Formyl-7-[(*R*)-3,7-dimethyl-1,6-octadien-3-yl]-4-indolyl]-*N*-methyl-L-valinate (10a)** Colorless syrup MS m/z 424 (M^+) IR ($CHCl_3$) cm^{-1} 1728, 1653 ^1H NMR (90 MHz) δ. 0 90 (3H, d, J=6 5 Hz), 1 09 (3H , d, J=6 5 Hz), 1 41 (3H, s), 1 47 (3H, s), 1 61 (3H, s), 2 92 (3H, s), 3 55 (3H, s), 3 66 (1H, d, J= 9 Hz), 4 89-5 16 (1H, m), 5 29 (1H, dd, J=18, 1 5 Hz), 5 32 (1H, dd, J=10 5, 1 5 Hz), 6 24 (1H, dd, J=18, 10 5 Hz), 7.08 (2H, s), 7 91 (1H, d, J=3 Hz, changed to s with D_2O), 9 25 (1H, br s, NH), 10 60 (1H, s) **Methyl *N*-[5-Formyl-7-[(*R*)-3,7-dimethyl-1,6-octadien-3-yl]-4-indolyl]-*N*-methyl-L-valinate (11a)** Colorless syrup MS m/z 424 (M^+) IR ($CHCl_3$) cm^{-1} 1723, 1658 ^1H NMR (90 MHz) δ 0 90 (3H, d, J=6 5 Hz), 1 18 (3H, d, J=6 5 Hz), 1 41 (3H, s), 1 50 (3H, s), 1 61 (3H, s), 3 22 (3H, s), 3 44 (3H, s), 3 59 (1H, d, J= 9 5 Hz), 4 88-5 14 (1H, m), 5 25 (1H, dd, J=18, 1 5 Hz), 5 27 (1H, dd, J=10, 1 5 Hz), 6 19 (1H, dd, J=18, 10 Hz), 6 65 (1H, dd, J=3, 2 Hz), 7 09 (1H, dd, J=3, 2 5 Hz), 7 64 (1H, s), 8 78 (1H, br s, NH), 10 50 (1H, s)

Reaction of 9a, 9b and 9c + 9d with *N*,*N*-Dimethyl(methylene)ammonium Chloride to Form Gramine Derivatives 12a, 12b and 12c + 12d — Preparation of **12a** is typical A solution of **9a** (37 mg, 0 093 mmol) in CH_2Cl_2 (2 ml) was stirred with *N*,*N*-dimethyl(methylene)ammonium chloride (25 mg, 0 267 mmol) at room temperature for 1 h 20 min Sat $NaHCO_3$-H_2O was added, the whole was extracted with CH_2Cl_2, and the extract was worked up as usual Purification by Al_2O_3 PTLC [hexane-EtOAc (3 2)] afforded **methyl *N*-[3-(dimethylamino)methyl-7-[(*R*)-3,7-dimethyl-1,6-octadien-3-yl]-4-indolyl]-*N*-methyl-L-valinate (12a)** (41 mg, 97%) as colorless syrup MS m/z 453 (M^+) IR ($CHCl_3$) cm^{-1} 1727, 1630 ^1H NMR (90 MHz) δ 0 90 (3H, d, J=6 5 Hz), 1 13 (3H, d, J=6 5 Hz), 1 38 (3H, s), 1 44 (3H, s), 1 60 (3H, s), 2 34 (6H, s), 2 86 (3H, s), 3 47 (3H, s), 3 58 (1H, d, J=8 5 Hz), 3 85 (1H, d, J=13 5 Hz), 4 12 (1H, d, J=13 5 Hz), 4 90-5 18 (1H, m), 5 23 (1H, dd, J=10 5, 1 5 Hz), 5 24 (1H, dd, J=18, 1 5 Hz), 6 21 (1H, dd, J=18, 10 5 Hz), 6 80 (1H, d, J=8 Hz), 6 95 (1H, d, J=8 Hz), 7 08 (1H, d, J=2 5 Hz, changed to s with D_2O), 8 53 (1, br s, NH) **Methyl *N*-[3-(Dimethylamino)methyl-7-[(*S*)-3,7-dimethyl-1,6-octadien-3-yl]-4-indolyl]-*N*-methyl-L-valinate (12b)** Colorless syrup MS m/z 453 (M^+) IR ($CHCl_3$) cm^{-1} 1727, 1628 ^1H NMR (90 MHz) δ 0 90 (3H, d, J=6 5 Hz), 1 10 (3H, d, J=6 5 Hz), 1 38 (3H, s), 1 43 (3H, s), 1 60 (3H, s), 2 30 (6H, s), 2 83 (3H, s), 3 52 (3H, s), 3 60 (1H, d, J=8 5 Hz), 3 83 (1H, d, 13 5 Hz), 4 09 (1H, d, J=13 5 Hz), 4 89-5 19 (1H, m), 5 22 (1H, dd, J=10 5, 1 5 Hz), 5 23 (1H, dd, J=18, 1 5 Hz), 6 20 (1H, dd, J=18, 10 5 Hz), 6 80 (1H, d, J=8 Hz), 6 95 (1H, d, J=8 Hz), 7 06 (1H, d, J=2 Hz, changed to s with D_2O), 8 50 (1, br s, NH) **t-Butyl *N*-[3-(Dimethylamino)methyl-7-(3,7-dimethyl-1,6-octadien-3-yl)-4-indolyl]-*N*-methyl-L-valinate (12c + 12d)** Colorless amorphous compound MS m/z 495 (M^+) IR ($CHCl_3$) cm^{-1} 1715 ^1H NMR (90 MHz) of two diastereomers δ 1 24 (9H, s), 1 43 (6H, s), 1 62 (3H, br s), 2 36 (6H, s), 2 83 and 2 80 (3H, s each), 3 51 and 3 54 (1H, d each, J=10 5 Hz), 3 94 (1H, d, 14 Hz), 4 13 (1H, d, J=14 Hz), 4 94-5 18 (1H, m), 5 24 (1H, dd, J=10 5, 2 5 Hz), 5 26 (1H, dd, J=18, 2 5 Hz), 6 21 (1H, dd, J=18, 10 5 Hz), 6 89 (1H, d, J=8 Hz), 6 99 (1H, d, J=8 Hz), 7 12 (1H, br d, J=2 Hz, changed to s with D_2O), 8 53 (1, br s, NH)

Methyl *N*-[7-[(*S*)-3,7-Dimethyl-1,6-octadien-3-yl]-3-(2-methoxycarbonyl-2-nitro)ethyl-4-indolyl]-*N*-methyl-L-valinate (13b) — A solution of **12b** (18 mg, 0 040 mmol) and methyl nitroacetate (40 mg, 0 336 mmol) in toluene (2 ml) was refluxed for 3 h under Ar atmosphere After evaporation to dryness, the residue was purified by PTLC [hexane-EtOAc (4 1)] to afford **13b** (19 mg, 91%), colorless syrup MS m/z 527 (M^+) IR ($CHCl_3$) cm^{-1} 1752, 1730, 1630, 1559, 1373 ^1H NMR (90 MHz) of major and minor diastereomers (*ca.* 3 2) δ 0 91 and 0 88 (3H, d each, J=6 5 Hz), 1 04 and 0 99 (3H, d each, J=6 5 Hz), 1 33 and 1 38 (3H, s each), 1 42 (3H, s), 1 60 (3H, s), 2 73 and 2 76 (3H, s each), 3 41 and 3 48 (3H, s each), 3 79 and 3 67 (3H, s each), 4 88-5 17 (1H, m), *ca* 5 90-6 32 (1H, m), 6 18 (1H, dd, J=18, 10 5 Hz), 8 49 (1H, br s, NH)

t-Butyl *N*-[3-(2-Acetamido-2,2-diethoxycarbonyl)ethyl-7-(3,7-dimethyl-1,6-octadien-3-yl)-4-indolyl]-*N*-methyl-L-valinate (14c + 14d) — A solution of **12c + 12d** (6 mg, 0.012 mmol), diethyl acetamidomaloate (8 mg, 0 037 mmol) and 95% n-Bu_3P (5 mg, 0 024 mmol) in CH_3CN (2 ml) was refluxed under N_2 atmosphere for 1 5 h, After evaporation to dryness, the residue was purified by PTLC (3% MeOH-CH_2Cl_2) to give a crude mixture (10 mg), which was further purified by PTLC [benzene-EtOAc (5·1)] to furnish **14c + 14d** (4 mg, 49%), colorless syrup MS m/z 667 (M^+) IR ($CHCl_3$) cm^{-1} 1730, 1680 ^1H NMR (90 MHz, 60°C) δ 1 21 (9H, s), 1 41 (6H, s), 1 61 (3H, s), 1 88 (3H, s), 2 07-2 49 (1H, m), 2 90 (3H, s), 3 49 (1H, d, J=8 Hz), 3 86-4 34 (6H, m), 4 92-5 12 (1H, m), 6 17 (1H, dd, J=18, 10 5 Hz), 6 83-7 04 (4H, m), 8 40 (1H, br s, NH)

Reaction of 9a and 9b with Ethyl 3-Bromo-2-hydroxyiminopropanoate to Form 15a, 16a, 15b and

16b — Preparation of **15a** and **16a** is typical. To a solution of **9a** (124 mg, 0 313 mmol) in CH_2Cl_2 (6 ml) were added successively Na_2CO_3 (66 mg, 0.623 mmol) and ethyl 3-bromo-2-hydroxyiminopropanoate (66 mg, 0 314 mmol) under Ar atmosphere and the mixture was stirred at 15°C for 15 h The mixture was filtered through a celite bed and the celite was linsed with CH_2Cl_2 The combined organic layer was washed with sat NH_4Cl-H_2O and worked up as usual Purification by PTLC (0 5% EtOH-CH_2Cl_2) afforded the recovered **9a** (10 mg, 8%), **16a** (33 mg, 20%) and the crude **15a** (99 mg) in the order of increasing polarity The crude **15a** was purified by PTLC [hexane-EtOAc (3·1)] to give **ethyl 7-[(*R*)-3,7-dimethyl-1,6-octadien-3-yl]-α-(hydroxyimino)-4-[[(*S*)-1-(methoxycarbonyl)-2-methylpropyl]methylamino]indole-3-propanoate (15a)** (97 mg, 59%) as colorless syrup HRMS Calcd for $C_{30}H_{43}N_3O_5$ 525 3202 Found· 525 3222 IR ($CHCl_3$) cm^{-1} 1722, 1628 ^{1}H NMR (90 MHz) δ 0 91 (3H, d, J=6 5 Hz), 1 11 (3H each, d, J=6 5 Hz), 1 18 (3H, t, J=7 Hz), 1 40 (6H, s), 1 60 (3H, s), 2 91 (3H, s), 3.51 (3H, s), 3 66 (1H, d, J=9 Hz), 4 21 (2H, q, J=7 Hz), 4 36 (1H, d, 15 5 Hz), 4 56 (1H, d, J=15 5 Hz), 4 89-5 20 (1H, m), 5 20 (1H, dd, J=10 5, 1 5 Hz), 5 22 (1H, dd, J=18, 1 5 Hz), 6.18 (1H, dd, J=18, 10 5 Hz), 6 70 (1H, d, J=2 Hz), 6 84 (1H, d, J=8 Hz), 6 97 (1H, d, J=8 Hz), 8 42 (1H, d, J=2 Hz, NH), 10 14 (1H, br s, OH) **Ethyl 7-[(*R*)-3,7-Dimethyl-1,6-octadien-3-yl]-α-(hydroxyimino)-4-[[(*S*)-1-(methoxycarbonyl)-2-methylpropyl]methylamino]indole-5-propanoate (16a)** Colorless syrup HRMS Calcd for $C_{30}H_{43}N_3O_5$ 525 3202 Found 525 3220 IR ($CHCl_3$) cm^{-1} 1720, 1630 ^{1}H NMR (90 MHz, 60°C) δ 0 90 (3H, d, J=6 5 Hz), 1 16 (3H each, d, J=6 5 Hz), 1 18 (3H, t, J=7 Hz), 1 36 (3H, s), 1 39 (3H, s), 1 57 (3H, s), 2 28 (1H, dqq, J=9, 6 5, 6 5 Hz), 3 05 (3H, s), 3 43 (3H, s), 3 48 (1H, d, J=9 Hz), 4 12 (1H, d, J=14 5 Hz), 4 17 (2H, q, J=7 Hz), 4 37 (1H, d, J=14 5 Hz), 4 87-5 11 (1H, m), 5 17 (1H, dd, J=18, 1 5 Hz), 5 19 (1H, dd, J=10, 1 5 Hz), 6 20 (1H, dd, J=18, 10 Hz), 6 47 (1H, dd, J=3 5, 2 Hz), 6 82 (1H, s), 6 97 (1H, dd, J=3 5, 3 Hz), 8 24-9 25 (1H, m, OH), 8 43 (1H, br s, NH) Similarly **15b** (65%) and **16b** (15%) were prepared from **9b** along with a 9% yield recovery of **9b** **Ethyl 7-[(*S*)-3,7-Dimethyl-1,6-octadien-3-yl]-α-(hydroxyimino)-4-[[(*S*)-1-(methoxycarbonyl)-2-methylpropyl]-methylamino]indole-3-propanoate (15b)** Colorless syrup HRMS Calcd for $C_{30}H_{43}N_3O_5$ 525 3202 Found 525 3196 IR ($CHCl_3$) cm^{-1} 1723, 1628 ^{1}H NMR (90 MHz) δ· 0 94 (3H, d, J=6 5 Hz), 1 10 (3H, d, J=6 5 Hz), 1 19 (3H, t, J=7 Hz), 1 41 (6H, s), 1 61 (3H, s), 2 89 (3H, s), 3 57 (3H, s), 3 69 (1H, d, J=9 Hz), 4 21 (2H, q, J=7 Hz), 4 38 (1H, d, J=16 5 Hz), 4 56 (1H, d, J=16 5 Hz), 4 86-5 19 (1H, m), 5 19 (1H, dd, J=10, 1 Hz), 5 22 (1H, dd, J=18, 1 Hz), 6 18 (1H, dd, J=18, 10 Hz), 6 70 (1H, d, J=2 Hz), 6 86 (1H, d, J=8 Hz), 6 98 (1H, d, J=8 Hz), 8 42 (1H, d, J=2 Hz, NH), 10 40 (1H, br s, OH) **Ethyl 7-[(*S*)-3,7-Dimethyl-1,6-octadien-3-yl]-α-(hydroxy-imino)-4-[[(*S*)-1-(methoxycarbonyl)-2-methylpropyl]methylamino]indole-5-propanoate (16b)** Colorless syrup HRMS Calcd for $C_{30}H_{43}N_3O_5$ 525 3202 Found 525 3203 IR ($CHCl_3$) cm^{-1} 1720, 1629 ^{1}H NMR (90 MHz, 60°C) δ 0 90 (3H, d, J=6 5 Hz), 1 18 (3H , d, J=6 5 Hz), 1 21 (3H, t, J=7 Hz), 1 37 (3H, s), 1 42 (3H, s), 1 60 (3H, s), 3 07 (3H, s), 3 42 (3H, s), 4 12 (1H, d, J=15 Hz), 4 39 (1H, d, J=15 Hz), 4 20 (2H, q, J=7 Hz), *ca* 4 89-5 15 (1H, m), 5 18 (1H, dd, J=18, 1 5 Hz), 5 20 (1H, dd, J=10 5, 1 5 Hz), 6 20 (1H, dd, J=18, 10 5 Hz), 6 48 (1H, dd, J=3, 2 Hz), 6 83 (1H, s), 6 98 (1H, dd, J=3, 3 Hz), 8 42 (1H, br s, NH), 8 78 (1H, br s, OH)

Aluminium-Amalgam Reduction to Form 17a and 17b — Preparation of **17a** is typical To a solution of **15a** (86 mg, 0 164 mmol) in THF-H_2O (9 1) (8 ml) was added Al-Hg prepared from Al (176 mg), and the mixture was stirred at 18°C for 4 h The whole was passed through a celite bed and the celite was washed with CH_2Cl_2 Usual work-up of the combined filtrate and purification by PTLC (3% EtOH-CH_2Cl_2) afforded **ethyl 7-[(*R*)-3,7-dimethyl-1,6-octadien-3-yl]-4-[[(*S*)-1-(methoxycarbonyl)-2-methylpropyl]methylamino]tryptophanate (17a)** (77 mg, 92%), colorless syrup HRMS Calcd for $C_{30}H_{45}N_3O_4$ 511 3409 Found 511 3401 IR ($CHCl_3$) cm^{-1} 1723, 1628 ^{1}H NMR (90 MHz) of two diastereomers (*ca* 1 1) δ 1 37 (3H, s), 1 40 (3H, s), 1 58 (3H, s), 1 71 (2H, s, NH_2), 2 85 (3H, s), 3.40 (3H, s), 4 07 and 4 15 (2H, q each, J=7 Hz), 4 90-5 19 (1H, m), 5 09-5 41 (2H, m), 6 21 (1H, dd, J=18, 10 5 Hz), 6 83 (1H, d, J=8 Hz), 6 97 (1H, d, J=8 Hz), 6 90-7 00 (1H, m), 8 56 (1H, br s, indole NH) **Ethyl 7-[(*S*)-3,7-Dimethyl-1,6-octadien-3-yl]-4-[[(*S*)-1-(methoxycarbonyl)-2-methylpropyl]methylamino]tryptophanate (17b)** Colorless syrup HRMS Calcd for $C_{30}H_{45}N_3O_4$ 511 3409 Found 511 3391 IR ($CHCl_3$) cm^{-1} 1723, 1628 ^{1}H NMR (90 MHz) of two diastereomers (*ca* 1 1) δ 0 94, 0 96, 1 10 and 1 12 (6H, d each, J=6 5 Hz), 1 21 (3H, t, J=7 Hz), 1 40 (3H, s), 1 44 (3H, s), 1 61 (3H, s), 1 75 (2H, s, NH_2), 2 85 (3H, s), 3 45 (3H, s), 4 09 and 4 16 (2H, q each, J=7 Hz), 4 87-5 23 (1H, m), 5 23 (1H, dd, J=18, 1 5 Hz), 5 23 (1H, dd, J=10 5, 1 5 Hz), 6 19 (1H, dd, J=18, 10 5 Hz), 6 83 (1H, d, J=8 Hz), 6 91-7 01 (1H, m), 6 97 (1H, d, J=8 Hz), 8 55 (1H, br s, indole NH)

Amino Alcohols 18a and 18b — Reduction of **17a** is typical A mixture of **17a** (28 mg, 0 055 mmol) and $NaBH_4$ (17 mg, 0 447 mmol) in EtOH was refluxed with stirring under Ar atmosphere for 20 h After cooling, brine was added and the whole was extracted thoroughly with CH_2Cl_2 Usual work-up and Al_2O_3 PTLC (4%

MeOH-CH_2Cl_2) gave **methyl *N*-[3-(2-amino-3-hydroxypropyl)-7-[(*R*)-3,7-dimethyl-1,6-octadien-3-yl]-4-indolyl]-*N*-methyl-L-valinate (18a)** (13 mg, 51%), colorless film HRMS Calcd for $C_{28}H_{43}N_3O_3$. 469.3304 Found 469 3303. IR ($CHCl_3$) cm^{-1} 1727, 1628. ^1H NMR (90 MHz) of two diastereomers (*ca* 1 1) δ. 0 90 (3H, d, J=6 5 Hz), 1 11 and 1.15 (3H, d each, J=6 5 Hz), 1 40 (3H, s), 1 45 (3H, s), 1.63 (3H, s), *ca* 2 64-3 03 [6H, m, changed to 2.82 and 2 84 (3H, s each) with D_2O], 3 40 and 3 44 (3H, s each), 4 90-5 19 (1H, m), 5.24 (1H, dd, J=10 5, 1 Hz), 5.26 (1H, dd, J=18, 1 Hz), 6 22 (1H, dd, J=18, 10 5 Hz), 6 80 (1H, d, J=8 Hz), 6.90-7.01 (1H, m), 6 98 (1H, d, J=8 Hz), 8 56 (1H, br s, indole NH) **Methyl *N*-[3-(2-Amino-3-hydroxypropyl)-7-[(*S*)-3,7-dimethyl-1,6-octadien-3-yl]-4-indolyl]-*N*-methyl-L-valinate (18b)**. Colorless film HRMS Calcd for $C_{28}H_{43}N_3O_3$· 469.3304. Found 469.3287 IR ($CHCl_3$) cm^{-1} 1728, 1630 ^1H NMR (90 MHz) of two diastereomers (*ca* 1.1) δ 0 93 (3H, d, J=6 5 Hz), 1 07 and 1 11 (3H, d each, J=6 5 Hz), 1 41 (3H, s), 1 43 (3H, s), 1 62 (3H, s), 2 80 (3H, s), 3 30 (3H, br s, NH_2 and OH), 3 45 and 3 47 (3H, s each), 4.92-5 21 (1H, m), 5 10-5 40 (2H, m), 6 20 (1H, dd, J=18, 10 5 Hz), 6 80 (1H, d, J=8 Hz), 6 92-7 04 [1H, m, changed to 6 97 (1H, s) with D_2O], 6 98 (1H, d, J=8 Hz), 8 56 (1H, br s, indole NH)

Lyngbyatoxin A (Teleocidin A-1) (1) — A solution of **18a** (14 mg, 0 030 mmol) in 10% KOH in MeOH-H_2O (4 1) (1 5 ml, 2 68 mmol) was refluxed with stirring under Ar atmosphere for 22 h After cooling at 0°C, Et_3N HCl (363 mg, 2.64 mmol) was added and the mixture was stirred at 0°C for 1 min and then at 20°C for 10 min The reaction mixture was concentrated *in vacuo* at room temperature and the residue was dried over P_2O_5 in reduced pressure for 1 h It was suspended in DMF (3 ml) and to this was added successively 5% w/v DPPA/DMF (0 20 ml, 0 036 mmol) and 8% v/v Et_3N/DMF (0 10 ml, 0 058 mmol) at 0°C The mixture was stirred at 0°C for 1 h and at room temperature for 17 h The reaction was quenched with sat $NaHCO_3$-H_2O, the whole was extracted with Et_2O and worked up as usual PTLC [hexane-EtOAc (2.3)] afforded a crude mixture of **1** and ent-**2** (4 5 mg) as a less polar fraction and a crude mixture of 9-epi-**1** and 9-epi-ent-**2** (4 mg) as a more polar fraction Both were purified respectively by PTLC (5% MeOH-CH_2Cl_2) to give a mixture of **1** and ent-**2** (3 5 mg) and a mixture of 9-epi-**1** and 9-epi-ent-**2** (3 5 mg, 27%) The former was separated by HPLC [column YMC A-024, SIL, S-5, 10 × 300 mm, mobile phase hexane-CH_2Cl_2-2-propanol (85 10 5), flow rate 4 ml/min] to afford lyngbyatoxin A (teleocidin A-1) (**1**) (3 mg, 23%, retention time 16 8 min) and (+)-teleocidin A-2 (ent-**2**) (0 5 mg, ca 4%, retention time 18 5 min) **The synthetic 1** Colorless film HRMS Calcd for $C_{27}H_{39}N_3O_2$. 437 3042 Found 437 3028 CD (c 1 67 × 10^{-4}, MeOH, 21°C) $[\theta]_{333}$ 0, $[\theta]_{313}$ +4600, $[\theta]_{298}$ 0, $[\theta]_{257}$ −17700, $[\theta]_{237\,5}$ 0, $[\theta]_{234}$ +7200, $[\theta]_{229\,5}$ 0, $[\theta]_{221\,5}$ −9300, $[\theta]_{215}$ 0 IR ($CHCl_3$) cm^{-1} 1657 ^1H NMR (400 MHz, $CDCl_3$-D_2O) δ (major conformer) 0 64 (3H, d, J=6 5 Hz), 0 92 (3H, d, J=6 5 Hz), 1 47 (3H, s), 1 51 (3H, s), 1 66 (3H, s), 1 67-2 06 (4H including minor conformer, m), 2 58 (1H, dqq, J=10 5, 6 5, 6 5 Hz), 2 90 (3H, s), 3 15 (1H, br d, J=17 Hz), 3 56 (1H, dd, =11, 8 5 Hz), 3 73 (1H, dd, J=11, 3 5 Hz), 4 29-4 36 (1H, m), 4 34 (1H, d, J=10 5 Hz), 5 02-5 11 (1H, m), 5 28 (1H, d, J=11 Hz), 5 30 (1H, d, J=18 Hz), 6 17 (1H, dd, J=18, 11 Hz), 6,47 (1H, d, J=8 Hz), 6 83 (1H, s), 6 97 (1H, d, J=8 Hz), 8 52 (1H, s, indole NH), (minor conformer) 0 93 (3H, d, J=6 5 Hz), 1 25 (3H, d, J=6 5 Hz), 1 45 (3H, s), 1 49 (3H, s), 1 64 (3H, s), 2 38 (1H, dqq, J=11, 6 5, 6 5 Hz), 2 73 (3H, s), 2 80 (1H, dd, J=14 5, 1 5 Hz), 3 39 (1H, dd, J=11, 7 Hz), 3 46 (1H, dd, =11, 6 5 Hz), 4 40-4 47 (1H, m), 5 02-5 11 (1H, m), 5 33 (1H, d, J=11 Hz), 5 35 (1H, d, J=18 Hz), 6 22 (1H, dd, J=18, 11 Hz), 6 96 (1H, s), 7 01 (1H, d, J=8 Hz), 7 09 (1H, d, J=8 Hz), 8 76 (1H, s, indole NH) ^{13}C NMR (100 MHz, $CDCl_3$-D_2O) δ 17 5, 19 6, 21 6, 23 1, 24 2, 25 7, 28 5, 33 1, 33 9, 38 6, 43 3, 55 7, 65 0, 71 0, 106 5, 112 4, 114 0, 118 7, 120 0, 120 9, 121 6, 124 6, 131 5, 137 6, 146 4, 148 4, 174 4 **(+)-Teleocidin A-2 (ent-2)** Colorless film HRMS Calcd for $C_{27}H_{39}N_3O_2$ 437 3042 Found 437 3041 CD (c 1 05 × 10^{-4}, MeOH, 22°C) $[\theta]_{329}$ 0, $[\theta]_{314}$ −3200, $[\theta]_{302}$ 0, $[\theta]_{252\,5}$ +14800, $[\theta]_{249\,5}$ +14300, $[\theta]_{227}$ +50500, $[\theta]_{212\,5}$ 0 ^1H NMR spectrum (270 MHz) was identical with that of teleocidin A-2 (**2**) described below **9-Epi-1 and 9-epi-ent-2** Colorless film Retention time of HPLC [TSK Silica 60, hexane-$CHCl_3$-2-propanol (85 10 5), 1 ml/min] 20 8 min HRMS Calcd for $C_{27}H_{39}N_3O_2$ 437 3042 Found 437 3041 IR ($CHCl_3$) cm^{-1} 1654 ^1H NMR (270 MHz, $CDCl_3$-D_2O) of major conformer δ 1 47 (3H, s), 1 49 (3H, s), 1 64 (3H, s), 3 09 (3H, br s), 5 02-5 11 (1H, m), 6 17 (1H, dd, J=18, 11 Hz), 6 81 (1H, s), 8 42 (1H, br s, indole NH)

Teleocidin A-2 (2) — The same treatment of **18b** (13 mg, 0 028 mmol) as above afforded teleocidin A-2 (**2**) (2 5 mg, 21%), (+)-teleocidin A-1 (ent-**1**) (0 5 mg, *ca* 4%), and a mixture of 9-epi-**2** and 9-epi-ent-**1** (3 mg, 25%) **Synthetic teleocidin A-2 (2)**. Colorless film HRMS Calcd for $C_{27}H_{39}N_3O_2$ 437 3042. Found. 437.3017. CD (c 2 72 × 10^{-4}, MeOH, 23°C) $[\theta]_{336}$ 0, $[\theta]_{314}$ +3900, $[\theta]_{302}$ 0, $[\theta]_{256}$ −17500, $[\theta]_{250\,5}$ −17000, $[\theta]_{227}$ −58000, $[\theta]_{212}$ 0 IR ($CHCl_3$) cm^{-1} 1658 ^1H NMR (400 MHz, $CDCl_3$-D_2O) δ (major conformer) 0 60 (3H, d, J=6 5 Hz), 0 91 (3H, d, J=6 5 Hz), 1 38 (3H, s), 1 45 (3H, s), 1 63 (3H, s), 1 76-2 04 (4H including minor conformer, m), 2 58 (1H, dqq, J=10 5, 6 5, 6 5 Hz), 2 90 (3H, s), 3 03 (1H, dd, J=17, 3 5 Hz), 3 15 (1H, br d, J=17 Hz), 3 54 (1H,

dd, J=11 5, 8 5 Hz), 3 72 (1H, dd, J=11.5, 3 5 Hz), 4 30-4 37 (1H, m), 4 34 (1H, d, J=10 5 Hz), 5.07 (1H of major and minor conformers, br dd, J=6 5, 6 5 Hz), 5 26 (1H, d, J=11 Hz), 5.30 (1H, d, J=18 Hz), 6 20 (1H of major and minor conformers, dd, J=18, 11 Hz), 6,47 (1H, d, J=8 Hz), 6.82 (1H, br s), 6 97 (1H d, J=8 Hz), 8.53 (1H, br s, indole NH), (minor conformer) 0 94 (3H, d, J=6 5 Hz), 1 25 (3H, d, J=6.5 Hz), 1.48 (3H, s), 1 65 (3H, s), 2 39 (1H, dqq, J=11, 6 5, 6 5 Hz), 2 74 (3H, s), 2 80 (1H, dd, J=15, 1.5 Hz), 3.38 (1H, dd, J=11, 7 Hz), 3.46 (1H, dd, J=11, 6 Hz), 4.40-4.46 (1H, m), 5 33 (1H, d, J=11 Hz), 5 34 (1H, d, J=18 Hz), 7.01 (1H, d, J=8 Hz), 7 10 (1H d, J=8 Hz), 8 76 (1H, br s, indole NH) ^{13}C NMR (100 MHz, $CDCl_3$-D_2O) δ: 17 3, 19 4, 21 6, 23 1, 24.8, 25 6, 28 5, 33 0, 34.0, 38.0, 43 3, 55.5, 65 0, 71.0, 106 0, 112.1, 114 0, 118 5, 120 3, 120.9, 121 1, 124 6, 131 4, 137 5, 146 5, 149.0, 174.2 **(+)-Teleocidin A-1 (ent-1).** Colorless film HRMS Calcd for $C_{27}H_{39}N_3O_2$ 437 3042 Found 437 3018. CD (c 1.37 × 10^{-4}, MeOH, 21°C) $[\theta]_{333}$ 0, $[\theta]_{312}$ −4600, $[\theta]_{298}$ 0, $[\theta]_{258}$ +17500, $[\theta]_{238}$ 0, $[\theta]_{233}$ −9100, $[\theta]_{228.5}$ 0, $[\theta]_{222}$ +8800. ^{1}H NMR spectrum (270 MHz) was identical with that of teleocidin A-1 (**1**) described above **9-Epi-2 and 9-epi-ent-1** Colorless film HRMS Calcd for $C_{27}H_{39}N_3O_2$ 437 3042 Found 437 3052 IR ($CHCl_3$) cm^{-1} 1655 ^{1}H NMR (270 MHz) δ 0 67 (3H, d, J=6 5 Hz), 0 74 (3H, d, J=6 5 Hz), 1 40 (3H, s), 1 44 (3H, s), 1 63 (3H, s), 2 89 (1H, br d, J=15 5 Hz), 3 09 (3H, s), 3 28 (1H, br d, J=15 5 Hz), 5 02-5 12 (1H, m), 5 26 (1H, dd, J=11, 1 5 Hz), 5 28 (1H, dd, J=18, 1 5 Hz), 6 21 (1H, dd, J=18, 11 Hz), 6 73 (1H, d, J=8 Hz), 6 80 (1H, s), 6 95 (1H, d, J=8 Hz), 7 32 (1H, br s, CONH), 8 44 (1H, br s, indole NH)

(+)-MTPA Esters of Teleocidin A-1 (1), Teleocidin A-2 (2), (+)-Teleocidin A-1 (ent-1) and (+)-Teleocidin A-2 (ent-2) — Preparation of (+)-MTPA ester of teleocidin A-2 (**2**) is typical A solution of **2** (3 5 mg, 0 008 mmol) in pyridine (0 2 ml) and CH_2Cl_2 (0 2 ml) was stirred with the acid chloride (24 mg, 0 095 mmol) derived from (*R*)-(+)-MTPA at 0°C for 1 h Sat $NaHCO_3$-H_2O was added, the mixture was extracted with Et_2O and the extract was worked up as usual Purification by PTLC[hexane-EtOAc (6 1)] afforded a crude product (5 mg), which was further purified by PTLC [hexane-CH_2Cl_2 (2 3)] to give the (+)-MTPA ester of **2** (4 5 mg, 86%), colorless film MS m/z 653 (M^+) IR ($CHCl_3$) cm^{-1} 1752, 1667 ^{1}H NMR (90 MHz) of two conformers δ 2 71 and 2.83 (3H, s each), 3 51 (3H, s), 6 79 (1H, br s), 6.96 (1H, d, J=7 5 Hz), 7 10 (1H, d, J=7 5 Hz), 8 53 and 8 71 (1H, br s each, indole NH) **The (+)-MTPA ester of 1** Colorless film MS m/z 653 (M^+) IR ($CHCl_3$) cm^{-1} 1750, 1670 ^{1}H NMR (90 MHz) of major and minor conformers δ 2 69 and 2 83 (3H, s each), 3 51 (3H, s), 6 79 (1H, br s), 6 97 (1H, d, J=7 5 Hz), 7 09 (1H, d, J=7 5 Hz), 8 76 and 8 53 (1H, br s each, indole NH) In the same manner as above, ent-**1** (*ca* 0 3 mg) and ent-**2** (*ca* 0 5 mg) were converted to their (+)-MTPA esters (*ca* 0 3 mg and *ca* 0 5 mg)

HPLC Analysis of the Four (+)-MTPA Esters — Column YMC A-314 (ODS, 6 × 300 mm), mobile phase MeOH-H_2O (88 12), flow rate 3 ml/min Retention time of (+)-MTPA esters of **1**, **2**, ent-**1** and ent-**2** 39 1 min, 36 4 min, 40 3 min and 37 6 min

Methyl *N*-[5,5-Dimethyl-4-hydroxy-4-(2-pyrrolyl)-6-heptenoyl]-*N*-methyl-L-valinate (20a) and Methyl *N*-[(*E*)-4-Hydroxy-4-(2-pyrrolyl)-5,9,13-trimethyl-5-vinyl-8,12-tetradecadienoyl]-*N*-methyl-L-valinate (20b) — Grignard reaction of **5** with 3-methyl-2-butenyl (prenyl) bromide or (*E*, *E*)-3,7,11-trimethyl-2,6,10-dodecatrienyl (farnesyl) bromide was carried out in the same manner as in the previous report[16] at -20°C for **20a** or 0°C for **20b** **20a** Colorless syrup MS m/z 347 (M^+ – OH) IR ($CHCl_3$) cm^{-1} 1740, 1635 (sh), 1620 ^{1}H NMR (90 MHz) of two diastereomers δ 0 70-0 92 (3H, m), 0 73 (3H, d, J=7 Hz), 0 98 (6H, s), 2 78 and 2 81 (3H, s each), 3.56-3 71and 4 74 (1H, m and d, J=10 Hz), 3 66 (3H, s), 4 62 (1H, s, OH), 5 71-5 90 (1H, m), 6 04-6 22 (1H, m), 6 57-6 73 (1H, m), 8.87 (1H, br s, NH) **20b** Colorless syrup MS m/z 482 (M^+ – H_2O) IR ($CHCl_3$) cm^{-1} 1738, 1620 ^{1}H NMR (90 MHz) δ 0 75, 0 80 and 0 96 (6H, d each, J=7 Hz), 1 01 (3H, s), 1 52 (3H, s), 1 60 (3H, s), 1 67 (3H, s), 2 78 and 2 81 (3H, s each), 3 58 and 3 66 (3H, s each), 3 77 and 4 87 (1H, d each, J=10 5 Hz), 4 12-4 35 (1H, m, OH), 5 70-5 88 (1H, m), 6 05-6 21 (1H, m), 6 54-6 71 (1H, m), 8 73 (1H, br s, NH)

Methyl *N*-[5,5-Dimethyl-4-(2-pyrrolyl)-3,6-heptadienoyl]-*N*-methyl-L-valinate (21a) and Methyl *N*-Methyl-*N*-[(3ξ, 8*E*)-4-(2-pyrrolyl)-5,9,13-trimethyl-5-vinyl-3,8,12-tetradecatrienoyl]-L-valinate (21b) — In the same manner as in the previous paper,[16] **20a** and **20b** were dehydrated with a catalytic amount of p-TsOH to yield **21a** and **21b** **21a** Colorless syrup MS m/z 346 (M^+) IR ($CHCl_3$) cm^{-1} 1740, 1635 ^{1}H NMR (90 MHz) of major and minor rotamers δ 0 85 and 0 83 (3H, d each, J=7 Hz), 1 00 and 0 94 (3H, d each, J=7 Hz), 1 18 (6H, s), 1 92-2 05 (1H, m), 2 92 and 2 87 (3H, s each), 3 07 and 3 13 (3H, d each, J=7 5 Hz), 3 70 (3H, s), 4 91 and 3 90 (1H, d each, J=10 5 Hz), 4 93-5 21 (2H, m), 5 80-6 23 (3H, m), 6 63-6 75 (1H, m), 9 28 (1H, br s, NH) **21b** Colorless syrup MS m/z 482 (M^+) IR ($CHCl_3$) cm^{-1} 1738, 1632 ^{1}H NMR (90 MHz) δ 0 81, 0 85 and 1 00 (6H, d each, J=7 Hz), 1 20 (3H, s), 1 51 (3H, s), 1 58 (3H, s), 1 66 (3H, s), 2 86 and 2 91 (3H, s each),

3 06, 3 07 and 3 12 (2H, d each, J=7 5 Hz), 3 69 (3H, s), 5 86 (1H, t, J=7 5 Hz), 6 57-6.77 (1H, m), 9 31 (1H, br s, NH)

Methyl *N*-[5,5-Dimethyl-4-(2-pyrrolyl)-3,6-heptadienthioyl]-*N*-methyl-L-valinate (22a) and Methyl *N*-Methyl-*N*-[(3ξ, 8*E*)-4-(2-pyrrolyl)-5,9,13-trimethyl-5-vinyl-3,8,12-tetradecatrienthioyl]-L-valinate (22b) — Thioamides **22a** and **22b** were prepared by the reaction of **21a** and **21b** with Lawesson's reagent as in the previous paper.[16] **22a** Colorless syrup MS m/z· 362 (M^+). IR ($CHCl_3$) cm^{-1}. 1740. ^1H NMR (90 MHz) of two rotamers δ 0.76, 0.91, 0 93 and 1 10 (6H, d each, J=7 Hz), 1 16 (6H, s), 2 31 (1H, dqq, J=10 5, 7, 7 Hz), 3 04 and 3 30 (3H, s each), 3 49 and 3 56 (2H, d each, J=7 5 Hz), 4 27 and 5 87 (1H, d each, J=10.5 Hz), 5 03 (1H, d, J=12 Hz), 5.05 (1H, d, J=17 5 Hz), 5.73 and 5.76 (1H, t each, J=7.5 Hz), 5 92-6.07 (1H, m), 6.07-6 22 (1H, m), 6 70-6 77 (1H, m), 8 80 (1H, br s, NH) **22b** Colorless syrup. MS m/z: 498 (M^+) IR ($CHCl_3$) cm^{-1} 1737 ^1H NMR (90 MHz) of two rotamers δ 0 77, 0 90, 0 91 and 1 08 (6H, d each, J=7 Hz), 1 21 (3H, s), 1 55 (3H, s), 1 59 (3H, s), 1 67 (3H, s), 3 05 and 3 31 (3H, s each), 3 71 (3H, s), 4.27 and 6.31 (1H, d each, J=10 5 Hz), 5 70 and 5 73 (1H, t each, J=7 5 Hz), 5 86-6 23 (2H, m), 6 56-6 78 (1H, m), 8 81 (1H, br s, NH)

Indole Cyclization with MeI — In a similar manner as in the preceding paper,[1] **22a** and **22b** were cyclized to indole derivatives **23a, 23b** and **24b** with MeI in DMF **Methyl *N*-[7-(1,1-Dimethyl-2-propenyl)-4-indolyl]-*N*-methyl-L-valinate (23a)**· Colorless needles, mp 100-103°C or colorless prisms, mp 106-107°C (MeOH-H_2O) Anal Calcd for $C_{20}H_{28}N_2O_2$ C, 73 14, H, 8 59, N, 8 53 Found. C, 73.00, H, 8 55, N, 8 38 $[\alpha]_D^{23}$ -44 1° (c 0 503, $CHCl_3$) MS m/z 328 (M^+) IR (KBr) cm^{-1} 1720 ^1H NMR (90 MHz) δ 0 94 (3H, d, J=7 Hz), 1 07 (3H, d, J=7 Hz), 1 50 (6H, s), 2 37 (1H, dqq, J=11, 7, 7 Hz), 3 04 (3H, s), 3.66 (3H, s), 4.08 (1H, d, J=11 Hz), 5 20 (1H, dd, J=10 5, 1 5 Hz), 5.29 (1H, dd, J=18, 1 5 Hz), 6 25 (1H, dd, J=18, 10.5 Hz), 6 60 (1H, d, J=8 Hz), 6 71 (1H, dd, J=3, 2 Hz), 7 03 (1H, d, J=8 Hz), 7 07 (1H, dd, J=3, 3 Hz), 8 60 (1H, br s, NH) **7-(1,1-Dimethyl-2-propenyl)-4-(methylthio)indole (25a)** Colorless needles, mp 82 5-83°C (MeOH-H_2O) Anal Calcd for $C_{14}H_{17}NS$ C, 72 68, H, 7 41, N, 6 05 Found C, 72 46, H, 7 54, N, 6 10 MS m/z 231 (M^+) IR (KBr) cm^{-1} 1630 ^1H NMR (90 MHz) δ 1 50 (6H, s), 2 54 (3H, s), 5 18 (1H, dd, J=10 5, 1 5 Hz), 5 27 (1H, dd, J=18, 1 5 Hz), 6 21 (1H, dd, J=18, 10 5 Hz), 6 62 (1H, dd, J=3, 2 Hz), 6 96 (1H, d, J=8 Hz), 7 05-7 20 (1H, m), 7 11 (1H, d, J=8 Hz), 8 63 (1H, br s, NH) **Methyl *N*-Methyl-*N*-[7-[(*R*, *E*)-3,7,11-trimethyl-1,6,10-dodecatrien-3-yl]-4-indolyl]-L-valinate (23b)** Colorless syrup HRMS Calcd for $C_{30}H_{44}N_2O_2$ 464 3403. Found. 464 3384 IR ($CHCl_3$) cm^{-1} 1725 ^1H NMR (400 MHz) δ. 0 94 (3H, d, J=7 Hz), 1 10 (3H, d, J=7 Hz), 1 43 (3H, s), 1 46 (3H, s), 1 59 (3H, s), 1 67 (3H, s), 2 38 (1H, dqq, J=11, 7, 7 Hz), 2 99 (3H, s), 3 59 (3H, s), 4.07 (1H, d, J=11 Hz), 5 00-5 14 (2H, m), 5 26 (1H, dd, J=11, 1 Hz), 5 29 (1H, dd, J=18, 1 Hz), 6 22 (1H, dd, H=18, 11 Hz), 6 57 (1H, d, J=8 Hz), 6 68 (1H, dd, J=3, 2 Hz), 6 98 (1H, d, J=8 Hz), 7 07 (1H, dd, J=3, 3 Hz), 8 62 (1H, br s, NH) **Methyl *N*-Methyl-*N*-[7-[(*S*, *E*)-3,7,11-trimethyl-1,6,10-dodecatrien-3-yl]-4-indolyl]-L-valinate (24b)** Colorless syrup HRMS Calcd for $C_{30}H_{44}N_2O_2$ 464 3403 Found 464 3401 IR ($CHCl_3$) cm^{-1} 1725 ^1H NMR (400 MHz) δ 0 93 (3H, d, J=7 Hz), 1 04 (3H, d, J=7 Hz), 1 44 (3H, s), 1 46 (3H, s), 1 58 (3H, s), 1 67 (3H, s), 2 38 (1H, dqq, J=11, 7, 7 Hz), 3 02 (3H, s), 3 66 (3H, s), 4 08 (1H, d, J=11 Hz), 5 02-5 13 (2H, m), 5 26 (1H, dd, J=11, 1 5 Hz), 5 28 (1H, dd, J=18, 1 5 Hz), 6 22 (1H, dd, H=18, 11 Hz), 6 57 (1H, d, J=8 Hz), 6 71 (1H, dd, J=3, 2 Hz), 6 97 (1H, d, J=8 Hz), 7 06 (1H, dd, J=3, 3 Hz), 8 61 (1H, br s, NH) **4-(Methylthio)-7-[(E)-3,7,11-trimethyl-1,6,10-dodecatrien-3-yl]indole (25b)** Colorless syrup HRMS Calcd for $C_{24}H_{33}NS$ 367 2334 Found 367 2315 ^1H NMR (400 MHz) δ 1 45 (3H, s), 1 48 (3H, s), 1 59 (3H, s), 1 67 (3H, d, J=1 Hz), 2 56 (3H, s), 5 02-5 13 (2H, m), 5 29 (1H, dd, J=11, 1 5 Hz), 5 30 (1H, dd, J=18, 1 5 Hz), 6 22 (1H, dd, H=18, 11 Hz), 6 62 (1H, dd, J=3, 2 Hz), 6 98 (1H, d, J=8 Hz), 7 09 (1H, d, J=8 Hz), 7 14 (1H, dd, J=3, 3 Hz), 8 66 (1H, br s, NH)

Reaction of 23a, 23b and 24b with Ethyl 3-Bromo-2-hydroxyiminopropanoate — According to the reported procedure,[1] **26a, 26b** and **27b** were prepared together with some by-products **Ethyl 7-(1,1-Dimethyl-2-propenyl)-α-(hydroxyimino)-4-[[(*S*)-1-(methoxycarbonyl)-2-methylpropyl]methylamino]indole-3-propanoate (26a)** Colorless syrup MS m/z 457 (M^+) IR ($CHCl_3$) cm^{-1} 1725 ^1H NMR (90 MHz) δ. 0 94 (3H, d, J=7 Hz), 1 13 (3H, d, J=7 Hz), 1 22 (3H, t, J=7 Hz), 1 47 (6H, s), 2 00-2 53 (1H, m), 2 92 (3H, s), 3 60 (3H, s), 3 68 (1H, d, J=9 Hz), 4 22 (2H, q, J=7 Hz), 4 37 (1H, d, J=15 Hz), 4 55 (1H, d, J=15 Hz), 5 12 (1H, dd, J=10 5, 1 5 Hz), 5 23 (1H, dd, J=18, 1 5 Hz), 6 16 (1H, dd, J=18, 10 5 Hz), 6 70 (1H, d, J=2 Hz), 6 85 (1H, d, J=8 Hz), 7 00 (1H, d, J=8 Hz), 8 38 (1H, br s, NH), 10 14 (1H, br s, OH) **Ethyl 7-(1,1-Dimethyl-2-propenyl)-α-(hydroxyimino)-4-[[(*S*)-1-(methoxycarbonyl)-2-methylpropyl]methylamino]indole-5-propanoate (28a)** Colorless syrup MS m/z 457 (M^+) IR ($CHCl_3$) cm^{-1} 1722 ^1H NMR (90 MHz) δ 0 92 (3H, d, J=7 Hz), 1 23 (3H, d, J=7 Hz), 1 25 (3H, t, J=7 Hz), 1 46 (6H, s), 2.07-2 56 (1H, m), 3 10 (3H, s), 3 45 (3H, s), 4 12 (1H, d, J=15 Hz), 4 24 (2H, q, J=7 Hz), 4 43 (1H, d, J=15 Hz), 5 16 (1H, dd, J=10 5, 1 5 Hz), 5 24 (1H, dd, J=18, 1 5 Hz), 6 18

(1H, dd, J=18, 10 5 Hz), 6 46 (1H, dd, J=3, 2 Hz), 6 87 (1H, s), 7 00 (1H, dd, J=3, 3 Hz), 8 46 (1H, br s, NH), 9 65 (1H, br s, OH). **Diethyl 7-(1,1-Dimethyl-2-propenyl)-α,α'-bis(hydroxyimino)-4-[[(*S*)-1-(methoxycarbonyl)-2-methylpropyl]methylamino]indole-3,5-bispropanoate (29a)**· Colorless film MS m/z. 586 (M^+) IR ($CHCl_3$) cm^{-1} 1728. ^1H NMR (90 MHz) δ 0 74 (3H, d, J=7 Hz), 0 97 (3H, d, J=7 Hz), 1.24 (3H, t, J=7 Hz), 1 25 (3H, t, J=7 Hz), 1.42 (6H, s), 1 65-2 30 (1H, m), 2 97 and 3 01 (3H, s each), 3 54 and 3.77 (3H, s each), 5 13 (1H, d, J=10.5 Hz), 5.22 (1H, d, J=18 Hz), 6 13 (1H, dd, J=18, 10 5 Hz), 6 53-6.77 (1H, m), 6.63 and 6 77 (1H, s each), 8 24 (1H, br s, NH), 9.24 (2H, br s, OH) **Ethyl 9,9a-Dihydro-8-(1,1-dimethyl-2-propenyl)-3-(ethoxycarbonyl)-α-hydroxyimino-5-[[(*S*)-1-(methoxycarbonyl)-2-methylpropyl]methylamino]-1,2-oxazino[6,5-b]indole-4a(4*H*)-propanoate (30a)**. Colorless film MS m/z 586 (M^+). IR ($CHCl_3$) cm^{-1} 1723 ^1H NMR (90 MHz) δ 0 93 (3H, d, J=7 Hz), 2 68 (3H, s), 3 60 and 3 63 (3H, s each), 5 97 (1H, dd, J=18, 10 5 Hz), 6 51 and 6 54 (1H, d each, J=9 Hz), 6 98 (1H, d, J=9 Hz), 8.71 (1H, br s, OH) **Ethyl α-(Hydroxyimino)-4-[[(*S*)-1-(methoxycarbonyl)-2-methylpropyl]methylamino]-7-[(*R*, *E*)-3,7,11-trimethyl-1,6,10-dodecatrien-3-yl]indole-3-propanoate (26b)**. Colorless syrup. MS m/z 593 (M^+). IR ($CHCl_3$) cm^{-1} 1730 ^1H NMR (90 MHz) δ 0 92 (3H, d, J=7 Hz), 1 13 (3H, d, J=7 Hz), 1 22 (3H, t, J=7 Hz), 1 45 (6H, s), 1 59 (3H, s), 1 68 (3H, s), 2 94 (3H, s), 3 53 (3H, s), 3 68 (1H, d, J=9 Hz), 4 23 (2H, q, J=7 Hz), 4 58 (1H, d, J=16 Hz), 4 89-5 23 (2H, m), 5 21 (1H, d, J=10 5 Hz), 5 23 (1H, d, J=18 Hz), 6 19 (1H, dd, J=18, 10 5 Hz), 6 71 (1H, d, J=2 Hz), 6 85 (1H, d, J=8 Hz), 6 98 (1H, d, J=8 Hz), 8 41 (1H, br s, NH), 10 09 (1H, br s, OH) **Ethyl α-(Hydroxyimino)-4-[[(*S*)-1-(methoxycarbonyl)-2-methylpropyl]methylamino]-7-[(*R*, *E*)-3,7,11-trimethyl-1,6,10-dodecatrien-3-yl]indole-5-propanoate (28b; R^2=vinyl, R^3=Me)** Colorless syrup MS m/z 593 (M^+) IR ($CHCl_3$) cm^{-1} 1720 ^1H NMR (90 MHz) δ· 0 91 (3H, d, J=7 Hz), 1 22 (3H, d, J=7 Hz), 1 22 (3H, t, J=7 Hz), 1 38 (3H, s), 1 42 (3H, s), 1 57 (3H, s), 1 65 (3H, s), 3 08 (3H, s), 3 23-3 56 (1H, m), 3 43 (3H s), 4 17 (2H, q, J=7 Hz), 4 39 (1H, d, J=15 Hz), 4 86-5 21 (2H, m), 5 19 (1H, dd, J=18, 1 5 Hz), 5 20 (1H, dd, J=10 5, 1 5 Hz), 6 19 (1H, dd, J=18, 10 5 Hz), 6 43 (1H, dd, J=3, 2 Hz), 6.80 (1H, s), 6 96 (1H, dd, J=3, 3 Hz), 8 46 (1H, br s, NH), 9 56 (1H, br s, OH) **Diethyl α,α'-Bis(hydroxyimino)-4-[[(*S*)-1-(methoxycarbonyl)-2-methylpropyl]methylamino]-7-[(*R*, *E*)-3,7,11-trimethyl-1,6,10-dodecatrien-3-yl]indole-3,5-bispropanoate (29b; R^2=vinyl, R^3=Me)** Colorless film MS m/z 722 (M^+) IR ($CHCl_3$) cm^{-1} 1722 ^1H NMR (90 MHz) δ: 0 71 (3H, d, J=7 Hz), 0 96 (3H, d, J=7 Hz), 1 26 (6H, t, J=7 Hz), 1.34 (3H, s), 1 40 (3H, s), 1 60 (3H, s), 1 69 (3H, s), 2 98 (3H, s), 3 78 (3H, s), 4 22 (2H, q, J=7 Hz), 4 24 (2H, q, J=7 Hz), 5 19 (1H, d, J=10 5 Hz), 5 21 (1H, d, J=18 Hz), 6 16 (1H, dd, J=18, 10 5 Hz), 6 51-6 76 (1H, m), 6 61 (1H, s), 8 28 (1H, br s, NH), 9 50 (2H, br s, OH) **Ethyl 9,9a-Dihydro-3-(ethoxycarbonyl)-α-hydroxyimino-5-[[(*S*)-1-(methoxycarbonyl)-2-methylpropyl]methylamino]-8-[(*R*, *E*)-3,7,11-trimethyl-1,6,10-dodecatrien-3-yl]-1,2-oxazino[6,5-b]indole-4a(4*H*)-propanoate (30b; R^2=vinyl, R^3=Me)** Colorless film MS m/z 722 (M^+) IR ($CHCl_3$) cm^{-1} 1725 ^1H NMR (90 MHz) δ 0 93 (6H, d, J=7 Hz), 1 33 (3H, s), 1 51 (3H, s), 1 61 (3H, s), 1 67 (3H, s), 2 69 and 2 82 (3H, s each), 3 54 and 3 57 (3H, s each), 4 25 (4H, q, J=7 Hz), 5 97 (1H, dd, J=18, 10 5 Hz), 6 49 and 6.52 (1H, d each, J=8 Hz), 6 93 (1H, d, J=8 Hz), 8 78 (1H, br s, OH) **Ethyl α-(Hydroxyimino)-4-[[(*S*)-1-(methoxycarbonyl)-2-methylpropyl]methylamino]-7-[(*S*, *E*)-3,7,11-trimethyl-1,6,10-dodecatrien-3-yl]indole-3-propanoate (27b)** Colorless syrup MS m/z 593 (M^+) IR ($CHCl_3$) cm^{-1} 1725 ^1H NMR (90 MHz) δ 0 93 (3H, d, J=7 Hz), 1 11 (3H, d, J=7 Hz), 1 20 (3H, t, J=7 Hz), 1 44 (6H, s), 1 58 (3H, s), 1 65 (3H, s), 2 91 (3H, s), 3 57 (3H, s), 3 66 (1H, d, J=8 Hz), 4 20 (2H, q, J=7 Hz), 4 53 (1H, d, J=15 Hz), 4 86-5 20 (2H, m), 5 20 (1H, d, J=18 Hz), 5 20 (1H, d, J=10 5 Hz), 6 16 (1H, dd, J=18, 10 5 Hz), 6 62 (1H, d, J=2 Hz), 6 83 (1H, d, J=8 Hz), 6.95 (1H, d, J=8 Hz), 8 38 (1H, br s, NH), 10 06 (1H, br s, OH) **Ethyl α-(Hydroxyimino)-4-[[(*S*)-1-(methoxycarbonyl)-2-methylpropyl]methylamino]-7-[(*S*, *E*)-3,7,11-trimethyl-1,6,10-dodecatrien-3-yl]indole-5-propanoate (28b; R^2=Me, R^3=vinyl)** Colorless syrup MS m/z 593 (M^+) IR ($CHCl_3$) cm^{-1} 1720 ^1H NMR (90 MHz) δ 0 89 (3H, d, J=7 Hz), 1 23 (3H, d, J=7 Hz), 1 24 (3H, t, J=7 Hz), 1 37 (3H, s), 1 42 (3H, s), 1 58 (3H, s), 1 65 (3H, s), 3 08 (3H, s), 3 24-3 56 (1H, m), 3 40 (3H s), 4 08 (1H, d, J=15 Hz), 4 18 (2H, q, J=7 Hz), 4 42 (1H, d, J=15 Hz), 4 87-5 21 (2H, m), 5 19 (1H, d, 10 5 Hz), 5 21 (1H, d, J=18 Hz), 6 17 (1H, dd, J=18, 10 5 Hz), 6 45 (1H, dd, J=3, 2 Hz), 6 80 (1H, s), 6 97 (1H, dd, J=3, 3 Hz), 8 45 (1H, br s, NH), 9 57 (1H, br s, OH) **Diethyl α,α'-Bis(hydroxyimino)-4-[[(*S*)-1-(methoxycarbonyl)-2-methylpropyl]methylamino]-7-[(*S*, *E*)-3,7,11-trimethyl-1,6,10-dodecatrien-3-yl]indole-3,5-bispropanoate (29b; R^2=Me, R^3=vinyl)** Colorless film MS m/z 722 (M^+) IR ($CHCl_3$) cm^{-1} 1725 ^1H NMR (90 MHz) δ 0 74 (3H, d, J=7 Hz), 0 96 (3H, d, J=7 Hz), 1 21 (3H, t, J=7 Hz), 1 25 (3H, t, J=7 Hz), 1 39 (6H, s), 1 56 (3H, s), 1 65 (3H, s), 2 94 and 3 00 (3H, s each), 3 52 and 3 76 (3H, s each), 5 18 (1H, d, J=10 5 Hz), 5 20 (1H, d, J=18 Hz), 6 15 (1H, dd, J=18, 10 5 Hz), 6 50-6 76 (1H, m), 6 57 (1H, s), 8 26 (1H, br s, NH), 9 15 (2H, br s, OH) **Ethyl 9,9a-Dihydro-3-(ethoxycarbonyl)-α-**

hydroxyimino-5-[[(*S*)-1-(methoxycarbonyl)-2-methylpropyl]methylamino]-8-[(*S*, *E*)-3,7,11-trimethyl-1,6,10-dodecatrien-3-yl]-1,2-oxazino[6,5-b]indole-4a(4*H*)-propanoate (30b; R²=Me R³=vinyl): Colorless film MS m/z 722 (M^+) IR ($CHCl_3$) cm^{-1} 1722 ^1H NMR (90 MHz) δ· 0.94 (3H, d, J=7 Hz), 1 32, 1.61 and 1 70 (12H, s each), , 2.68 and 2.78 (3H, s each), 3 58 and 3 63 (3H, s each), 4 27 (4H, q, J=7 Hz), 5 91 and 5.96 (1H, dd each, J=18, 10 5 Hz), 6.48 and 6 51 (1H, d each, J=8 Hz), 6 94 (1H, d, J=8 Hz), 8 61 and 9.03 (1H, br s each, OH)

Aluminium-Amalgam Reduction to Form Aminodiesters 31a, 31b and 32b — Reduction of **26a, 26b** and **27b** were carried out as above with 20-30 equivalents of Al-Hg at 45°C for 1 h **Ethyl 7-(1,1-Dimethyl-2-propenyl)-4-[[(*S*)-1-(methoxycarbonyl)-2-methylpropyl]methylamino]tryptophanate (31a)**: Colorless syrup MS m/z 443 (M^+) IR ($CHCl_3$) cm^1 1728 ^1H NMR (90 MHz) of two diastereomers (*ca.* 1 1) δ 0.94 (3H, d, J=7 Hz), 1 12 (3H, d, J=7 Hz), 1 22 (3H, t, J=7 Hz), 1 48 (6H, s), 1 66 (2H, s, NH_2), 2 04-2.55 (1H, m), 2 85 (3H, s), 3 48 (3H, s), 4 08 and 4 15 (2H, q each, J=7 Hz), 5 16 (1H, d, J=10 5 Hz), 5 23 (1H, d, J=18 Hz), 6 17 (1H, dd, J=18, 10.5 Hz), 6 81 (1H, d, J=8 Hz), 6 90-7 00 (1H, m), 6 98 (1H, d, J=8 Hz), 8 45 (1H, br s, indole NH) **Ethyl 4-[[(*S*)-1-(Methoxycarbonyl)-2-methylpropyl]methylamino]-7-[(*R*, *E*)-3,7,11-trimethyl-1,6,10-dodecatrien-3-yl]tryptophanate (31b)**: Colorless syrup MS m/z 579 (M^+) IR ($CHCl_3$) cm^1 1725 ^1H NMR (90 MHz) of two diastereomers δ 0 93 (3H, d, J=7 Hz), 1 12 and 1 23 (3H, t each, J=7 Hz), 1.17 (3H, d, J=7 Hz), 1 42 (3H, s), 1 48 (3H, s), 1 60 (3H, s), 1 68 (5H, s, changed to 3H, s with D_2O), 2 89 (3H, s), 3.42 (3H, s), 4 06 and 4 15 (2H, q each, J=7 Hz), 4 86-5 23 (2H, m), 5 22 (1H, d, J=10 5 Hz), 5 23 (1H, d, J=18 Hz), 6 20 (1H, dd, J=18, 10 5 Hz), 6 81 (1H, d, J=8 Hz), 6 81-7 06 (1H, m), 6 95 (1H, d, J=8 Hz), 8.53 (1H, br s, indole NH) **Ethyl 4-[[(*S*)-1-(Methoxycarbonyl)-2-methylpropyl]methylamino]-7-[(*S*, *E*)-3,7,11-trimethyl-1,6,10-dodecatrien-3-yl]tryptophanate (32b)**: Colorless syrup MS m/z 579 (M^+) IR ($CHCl_3$) cm^{-1} 1725 ^1H NMR (90 MHz) of two diastereomers δ 0 95 (3H, d, J=7 Hz), 1 11 (3H, d, J=7 Hz), 1 13 and 1 21 (3H, t each, J=7 Hz), 1 43 (6H, s), 1 56 (3H, s), 1 64 (3H, s), 1 78 (2H, br s, NH_2), 2 85 (3H, s), 3 45 (3H, s), 4.08 and 4.15 (2H, q each, J=7 Hz), 4 85-5 24 (2H, m), 5 22 (1H, d, J=18 Hz), 5 22 (1H, d, J=10 5 Hz), 6 18 (1H, dd, J=18, 10 5 Hz), 6 82 (1H, d, J=8 Hz), 6 82-7 05 (1H, m), 6 96 (1H, d, J=8 Hz), 8 52 (1H, br s, indole NH)

Preparation of Trifluoroacetamides 33 – 36 — A procedure for **33a** and **34a** is typical To a solution of **31a** (126 mg, 0 284 mmol) in THF (3 6 ml) and EtOH (4 8 ml) were added LiCl (241 mg, 5 67 mmol) and $NaBH_4$ (215 mg, 5 66 mmol) at room temperature under Ar atmosphere The mixture was stirred at that temperature for 21 5 h Water was added at 0°C, it was saturated with NaCl, and the whole was extracted with CH_2Cl_2 Usual work-up afforded a residue (114 5 mg), and to its solution in CH_2Cl_2 (12 ml) was added successively at -78°C Et_3N (1 20 ml, 8 63 mmol) and trifluoroacetic anhydride (0 40 ml, 2 83 mmol) After this solution was stirred at -78°C for 15 min, sat $NaHCO_3$-H_2O was added and the mixture was extracted with CH_2Cl_2 Usual work-up and separation by PTLC (1 5% MeOH-CH_2Cl_2) gave crude **33a** (61.5 mg) and **34a** (63 mg) Both were purified separately by PTLC [hexane-DME (5.2)] to afford **33a** (57 mg, 40%) and **34a** (53 mg, 37 5%) **Methyl *N*-[7-(1,1-Dimethyl-2-propenyl)-3-[(*S*)-3-hydroxy-2-(trifluoroacetamido)propyl]-4-indolyl]-*N*-methyl-L-valinate (33a)** Colorless film MS m/z 497 (M^+) IR ($CHCl_3$) cm^1 1720 ^1H NMR (90 MHz) δ 0 95 (3H, d, J=7 Hz), 1 15 (3H, d, J=7 Hz), 1 49 (6H, s), 2 06-2 70 (1H, m), 2 88 (3H, s), 3 19 (1H, dd, J=15, 7 Hz), 3 44 (3H, s), 3 90-4 36 (1H, m), 5 18 (1H, dd, J=10 5, 1 Hz), 5 24 (1H, dd, 18, 1 Hz), 6 16 (1H, dd, J=18, 10 5 Hz), 6 80 (1H, d, J=8 Hz), 6 98-7 12 (1H, m), 7 00 (1H, d, J=8 Hz), 8 62 (1H, br s, indole NH) **Methyl *N*-[7-(1,1-Dimethyl-2-propenyl)-3-[(*R*)-3-hydroxy-2-(trifluoroacetamido)propyl]-4-indolyl]-*N*-methyl-L-valinate (34a)** Colorless film MS m/z 497 (M^+) IR ($CHCl_3$) cm^{-1} 1720 ^1H NMR (90 MHz) δ 0 96 (3H, d, J=7 Hz), 1 08 (3H, d, J=7 Hz), 1 50 (6H, s), 2 04-2 58 (1H, m), 2 85 (3H, s), 3 17 (1H, dd, J=15, 7 Hz), 3 55 (3H, s), 4 06-4 51 (1H, m), 5 16 (1H, dd, J=10 5, 1 Hz), 5 23 (1H, dd, J=18, 1 Hz), 6 17 (1H, dd, J=18, 10 5 Hz), 6 83 (1H, d, J=7 5 Hz), 6 92-7 03 (1H, m), 7 01 (1H, d, J=7 5 Hz), 7 34 (1H, br d, J=7 5 Hz, $NHCOCF_3$), 8 55 (1H, br s, indole NH) **Methyl *N*-[3-[(*S*)-3-Hydroxy-2-(trifluoroacetamido)propyl]-7-[(*R*)-3,7,11-trimethyl-1,6,10-dodecatrien-3-yl]-4-indolyl]-*N*-methyl-L-valinate (33b)** Colorless film MS m/z 633 (M^+) IR ($CHCl_3$) cm^{-1} 1720 ^1H NMR (90 MHz) δ 0 92 (3H, d, J=7 Hz), 1 17 (3H, d, J=7 Hz), 1 38 (3H, s), 1 46 (3H, s), 1 56 (3H, s), 1 65 (3H, s), 2 89 (3H, s), 3 34 (3H, s), 3 85-4 25 (1H, m), 4 25-4 74 (1H, m, OH), 4 80-5 22 (2H, m), 5 22 (1H, d, J=18 Hz), 5 24 (1H, d, J=10 5 Hz), 6 18 (1H, dd, J=18, 10 5 Hz), 6 79 (1H, d, J=8 Hz), 6 96 (1H, d, J=8 Hz), 8 62 (1H, br s, indole NH) **Methyl *N*-[3-[(*R*)-3-Hydroxy-2-(trifluoroacetamido)-propyl]-7-[(*R*)-3,7,11-trimethyl-1,6,10-dodecatrien-3-yl]-4-indolyl]-*N*-methyl-L-valinate (34b)** Colorless syrup MS m/z 633 (M^+) IR ($CHCl_3$) cm^1 1727 ^1H NMR (90 MHz) δ 0 93 (3H, d, J=7 Hz), 1 08 (3H, d, J=7 Hz), 1 38 (3H, s), 1 45 (3H, s), 1 57 (3H, s), 1 66 (3H, s), 2 86 (3H, s), 3 45 (3H, s), 4 00-4 45 (1H, m), 4 87-5 24

(2H, m), 5 20 (1H, d, J=18 Hz), 5 22 (1H, d, J=10.5 Hz), 6 18 (1H, dd, J=18, 10 5 Hz), 6.81 (1H, d, J=8 Hz), 6 90-7 00 (1H, m), 6 96 (1H, d, J=8 Hz), 8 56 (1H, br s, indole NH). **Methyl *N*-[3-[(*S*)-3-Hydroxy-2-(trifluoroacetamido)propyl]-7-[(*S*)-3,7,11-trimethyl-1,6,10-dodecatrien-3-yl]-4-indolyl]-*N*-methyl-L-valinate (35b)**: Colorless syrup MS m/z· 633 (M^+) IR ($CHCl_3$) cm^{-1} 1720 ^1H NMR (90 MHz) δ 0 95 (3H, d, J=7 Hz), 1 15 (3H, d, J=7 Hz), 1 36 (3H, s), 1 44 (3H, s), 1.58 (3H, s), 1.66 (3H, s), 2.88 (3H, s), 3 38 (3H, s), 3 89-4 77 (1H, m, OH), 4.85-5 25 (2H, m), 5 22 (1H, dd, J=18, 1.5 Hz), 5.25 (1H, dd, J=10 5, 1 5 Hz), 6 19 (1H, dd, J=18, 10 5 Hz), 6 79 (1H, d, J=8 Hz), 6 97 (1H, d, J=8 Hz), 8 60 (1H, br s, indole NH). **Methyl *N*-[3-[(*R*)-3-Hydroxy-2-(trifluoroacetamido)propyl]-7-[(*S*)-3,7,11-trimethyl-1,6,10-dodecatrien-3-yl]-4-indolyl]-*N*-methyl-L-valinate (36b)**. Colorless syrup MS m/z 633 (M^+). IR ($CHCl_3$) cm^{-1}· 1720 ^1H NMR (90 MHz) δ· 0 98 (3H, d, J=7 Hz), 1 06 (3H, d, J=7 Hz), 1 39 (3H, s), 1 45 (3H, s), 1 59 (3H, s), 1 67 (3H, s), 2 87 (3H, s), 3 13 (1H, dd, J=14, 7 Hz), 3 47 (3H, s), 3 98-4 50 (1H, m), 4 86-5 24 (2H, m), 5 22 (1H, dd, J=18, 1 5 Hz), 5 24 (1H, dd, J=10, 1 5 Hz), 6 18 (1H, dd, J=18, 10 Hz), 6 82 (1H, d, J=8 Hz), 6 90-7 01 (1H, m), 6 98 (1H, d, J=8 Hz), 8 56 (1H, br s, indole NH).

Pendolmycin (37a=6) and 12-Epipendolmycin (38a) — A solution of **33a** (56 mg, 0 113 mmol) and KOH (180 mg, 3 21 mmol) in MeOH (1 3 ml) and H_2O (0 5 ml) was refluxed with stirring under Ar atmosphere for 22 h After cooling in an ice bath, Et_3N HCl (426.5 mg, 3 10 mmol) was added and the mixture was stirred at 0°C for 1 min and then at 20°C for 10 min The mixture was concentrated *in vacuo* and the residue was dried thoroughly over P_2O_5 *in vacuo* for 10 h The resulting solid was suspended in DMF (3 ml) and to this was added successively 5% w/v DEPC/DMF (0 44 ml, 0 135 mmol) and 5% v/v Et_3N/DMF (0 63 ml, 0 226 mmol) The whole was stirred at 20°C for 45 5 h under Ar atmosphere The reaction was quenched with sat $NaHCO_3$-H_2O at 0°C and the mixture was extracted with Et_2O Usual work-up and separation by PTLC [hexane-EtOAc (1 2)] furnished crude **6** (=**37a**) (23 5 mg) and **38a** (7 mg) in the order of increasing polarity Both were separately purified by PTLC (4% MeOH-CH_2Cl_2) to give pendolmycin (**6**) (22 5 mg, 54%) as colorless amorphous powder, whose spectral data have been already reported[16] and **38a** (3 8 mg, 9%), colorless needles, mp 198-200°C (MeOH-H_2O) HRMS Calcd for $C_{22}H_{31}N_3O_2$ 369 2416 Found 369 2407 IR (KBr) cm^{-1} 1640 ^1H NMR (400 MHz, $CDCl_3$-D_2O) δ (major conformer) 0 73 (3H, d, J=7 Hz), 0 75 (3H, d, J=7 Hz), 1 47 (3H, s), 1 51 (3H, s), 2 63 (1H, dqq, J=10 5, 7, 7 Hz), 2 91 (1H, dd, J=15, 2 5 Hz), 3 10 (3H, s), 3 28 (1H, dd, J=15, 2 5 Hz), 3 77-3 98 (3H containing minor conformer, m), 3 90 (1H, d, J=10 5 Hz), 5 21 (1H, dd, J=10 5, 1 Hz), 5 31 (1H, dd, J=18, 1 Hz), 6 18 (1H, dd, J=18, 10.5 Hz), 6 75 (1H, d, J=8 Hz), 6 83 (1H, d, J=2 Hz), 6 98 (1H, d, J=8 Hz), 8 40 (1H, br s, indole NH), (minor conformer) 0 94 (3H, d, J=7 Hz), 1 26 (3H, d, J=7 Hz), 1 53 (6H, s), 2 37 (1H, dqq, J=11, 7, 7 Hz), 2 73 (3H, s), 2 78 (1H, d, J=14 Hz), 3 03 (1H, d, J=11 Hz), 3 05 (1H, d, J=14 Hz), 5 27 (1H, d, J=10 5 Hz), 5 38 (1H, d, J=18 Hz), 6 22 (1H, dd, J=18, 10 5 Hz), 7 01 (1H, d, J=8 Hz), 7 02 (1H, d, J=2 Hz), 7 13 (1H, d, J=8 Hz), 8 68 (1H, br s, indole NH)

Preparation of 7-[(*R*, *E*)-3,7,11-Trimethyl-1,6,10-dodecatrien-3-yl]-(–)-indolactam V(37b=7a) and 38b — Similarly **33b** (48 mg, 0 076 mmol) was converted to **7a** (=**37b**) (21 5 mg, 56%) and **38b** (4 5 mg, 12%) **7a=37b** Colorless film HRMS Calcd for $C_{32}H_{47}N_3O_2$ 505 3668 Found 505 3661 $[\alpha]_D^{24}$ -147 2° (c 0 67, $CHCl_3$) IR ($CHCl_3$) cm^{-1} 1655 ^1H NMR (400 MHz, $CDCl_3$-D_2O) δ (major conformer) 0 65 (3H, d, J=7 Hz), 0 92 (3H, d, J=7 Hz), 1 47 (3H, s), 1 50 (3H, s), 1 59 (3H, s), 1 68 (3H, s), 2 58 (1H, dqq, J=10, 7, 7 Hz), 2 90 (3H, s), 3 05 (1H, dd, J=18, 3 Hz), 3 15 (1H, d, J=18 Hz), 3 56 (1H, dd, J=12, 8 Hz), 3 73 (1H, dd, J=12, 4 Hz), 4 27-4 39 (1H, m), 4 34 (1H, d, J=10 Hz), 5 01-5 15 (2H containing minor conformer, m), 5 28 (1H, d, J=11 Hz), 5 30 (1H, d, J=18 Hz), 6 17 (1H, dd, J=18, 11 Hz), 6 47 (1H, d, J=8 Hz), 6 83 (1H, s), 6 97 (1H, d, J=8 Hz), 8 51 (1H, br s, indole NH), (minor conformer) 0 93 (3H, d, J=7 Hz), 1 25 (3H, d, J=7 Hz), 1 44 (3H, s), 1 58 (3H, s), 2 38 (1H, dqq, J=11, 7, 7 Hz), 2 73 (3H, s), 2 81 (1H, dd, J=15, 2 Hz), 3 00 (1H, d, J=11 Hz), 3 06 (1H, d, J=15 Hz), 3 38 (1H, dd, J=11, 7 Hz), 3 46 (1H, dd, J=11, 6 Hz), 4 39-4 48 (1H, m), 5 33 (1H, d, J=11 Hz), 5 35 (1H, d, J=18 Hz), 6 22 (1H, dd, J=18, 11 Hz), 7 01 (1H, d, J=8 Hz), 7.09 (1H, d, J=8 Hz), 8 77 (1H, br s, indole NH). **7-[(*R*, *E*)-3,7,11-Trimethyl-1,6,10-dodecatrien-3-yl]-12epi-(–)-indolactam V(38b)** Colorless prisms, mp 148-149°C (MeOH-H_2O) HRMS Calcd for $C_{32}H_{47}N_3O_2$ 505 3668 Found 505 3661 IR ($CHCl_3$) cm^{-1} 1658 ^1H NMR (400 MHz, $CDCl_3$-D_2O) δ (major conformer) 0 67 (3H, d, J=7 Hz), 0 74 (3H, d, J=7 Hz), 1 40 (3H, s), 1 45 (3H, s), 1 58 (3H, s), 1 67 (3H, s), 2 61 (1H, dqq, J=10, 7, 7 Hz), 2,89 (1H, d, J=16 Hz), 3 10 (3H, s), 3 28 (1H, d, J=16 Hz), 3 91(1H, d, J=10 Hz), 5 01-5 15 (2H containing minor conformer, m), 5 27 (1H, dd, J=11, 1 Hz), 5 30 (1H, dd, J=18, 1 Hz), 6 21 (1H, dd, J=18, 11 Hz), 6 73 (1H, d, J=8 Hz), 6 81 (1H, d, J=2 Hz), 6 95 (1H, d, J=8 Hz), 8 46 (1H, br s, indole NH), (minor conformer) 0 95 (3H, d, J=7 Hz), 2 37 (1H, dqq, J=11, 7, 7 Hz), 2 72 (3H, s), 2 78 (1H, d, J=14 Hz), 3 03 (1H, d, J=11 Hz), 5 34 (1H, d, J=11 Hz), 5 36 (1H, d, J=18 Hz), 7 00

(1H, d, J=8 Hz), 7.01 (1H, d, J=3 Hz), 7.10 (1H, d, J=8 Hz), 8 73 (1H, br s, indole NH).

Preparation of 7-[(*S*, *E*)-3,7,11-Trimethyl-1,6,10-dodecatrien-3-yl]-(–)-indolactam V(39b=7b) and 40b — Similarly **35b** (47 mg, 0 074 mmol) was converted to **7b** (=**39b**) (17.5 mg, 47%) and **40b** (3 5 mg, 9%) **7b=39b** Colorless film. HRMS Calcd for $C_{32}H_{47}N_3O_2$ 505 3668. Found· 505 3668 $[\alpha]_D^{24}$ -206.4° (c 0 49, $CHCl_3$) IR ($CHCl_3$) cm^{-1} 1655 ^1H NMR (400 MHz, $CDCl_3$-D_2O) δ (major conformer) 0.60 (3H, d, J=7 Hz), 0 91 (3H, d, J=7 Hz), 1 39 (3H, s), 1 45 (3H, s), 1 58 (3H, s), 1 67 (3H, s), 2 57 (1H, dqq, J=10, 7, 7 Hz), 2 90 (3H, s), 3 05 (1H, dd, J=18, 3 Hz), 3 14 (1H, d, J=18 Hz), 3 56 (1H, dd, J=12, 8 Hz), 3 73 (1H, dd, J=12, 3 Hz), 4 28-4 40 (1H, m), 4 35 (1H, d, J=10 Hz), 5 01-5 15 (2H containing minor conformer, m), 5 26 (1H, dd, J=11, 1 Hz), 5 30 (1H, dd, J=18, 1 Hz), 6 21 (1H, dd, J=18, 11 Hz), 6 47 (1H, d, J=8 Hz), 6.83 (1H, s), 6 97 (1H, d, J=8 Hz), 8 53 (1H, br s, indole NH), (minor conformer) 0 94 (3H, d, J=7 Hz), 1 25 (3H, d, J=7 Hz), 1 49 (3H, s), 1.59 (3H, s), 2 38 (1H, dqq, J=11, 7, 7 Hz), 2 73 (3H, s), 2 80 (1H, dd, J=15, 1 5 Hz), 2 99 (1H, d, J=11 Hz), 3.37 (1H, dd, J=11, 7 Hz), 3.45 (1H, dd, J=11, 6 Hz), 4.40-4.48 (1H, m), 7.01 (1H, d, J=8 Hz), 7 10 (1H, d, J=8 Hz), 8 76 (1H, br s, indole NH) **7-[(*S*, *E*)-3,7,11-Trimethyl-1,6,10-dodecatrien-3-yl]-12epi-(–)-indolactam V(40b)** Colorless film HRMS Calcd for $C_{32}H_{47}N_3O_2$· 505 3668 Found. 505 3696 IR ($CHCl_3$) cm^{-1}. 1655 ^1H NMR (400 MHz, $CDCl_3$-D_2O) δ (major conformer) 0 72 (3H, d, J=7 Hz), 0 75 (3H, d, J=7 Hz), 1 47 (3H, s), 1 49 (3H, s), 1 59 (3H, s), 1 68 (3H, s), 2 63 (1H, dqq, J=10 5, 7, 7 Hz), 2 91 (1H, d, J=15 Hz), 3 10 (3H, s), 3 27 (1H, d, J=15 Hz), 3.90 (1H, d, J=10 5 Hz), 5 02-5 14 (2H containing minor conformer, m), 5 28 (1H, d, J=11 Hz), 5 30 (1H, d, J=18 Hz), 6 17 (1H, dd, J=18, 11 Hz), 6 74 (1H, d, J=8 Hz), 6 81 (1H, s), 6 96 (1H, d, J=8 Hz), 8 43 (1H, br s, indole NH), (minor conformer) 0 95 (3H, d, J=7 Hz), 1 26 (3H, d, J=7 Hz), 1 45 (3H, s), 1 50 (3H, s), 2 37 (1H, dqq, J=11, 7, 7 Hz), 2 72 (3H, s), 2 78 (1H, d, J=14 Hz), 3 04 (1H, d, J=11 Hz), 6 23 (1H, dd, J=18, 11 Hz), 7 01 (1H, d, J=8 Hz), 7 01 (1H, s), 7 10 (1H, d, J=8 Hz), 8 73 (1H, br s, indole NH)

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