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Synthesis of Teleocidins A, B and Their Congeners. Part 1.[1] An Efficient Synthesis Method of *N*-(7-Alkyl-4-indolyl)-*N*-methyl-L-valine Esters, Essential Intermediates for Teleocidin Synthesis

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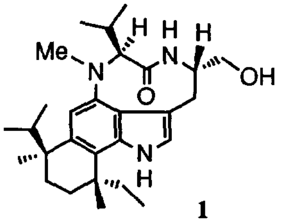
Abstract *— Details of the synthesis method of N-[7-(3,7-dimethyl-1,6-octadien-3-yl)-4-indolyl]-N-methyl-L-valine esters **19** and **20**, essential precursors for the tumor promoters lyngbyatoxin A (= teleocidin A-1) (**2**) and teleocidin A-2 (**3**) are presented Key reaction steps are i) introduction of the linalyl side chain into **12** to form **18** and ii) successive indole cyclization of **21** by way of thioamide derivatives **22***

Teleocidin A was first isolated from the mycelia of *Streptomyces mediocidicus* as a strong skin irritant and a fish poison by Takashima and Sakai in 1960[2] Two years later, they obtained an extremely toxic substance, teleocidin B having a partial structure similar to the above from another strain of *Streptomyces* and characterized its chemical behavior by securing crystalline dihydroteleocidin B[3] In 1966 Hirata and co-workers studied the structure of teleocidin B and proposed a structure **1** for dihydroteleocidin B by chemical and X-ray crystallography[4,9] Independently in Hawaii, Moore and co-workers studied ingredients of the blue-green alga *Lyngbya majuscula* Gomont to find the origin of a severe dermatitis known as swimmers' itch, and isolated a highly inflammatory and vesicatory compound, lyngbyatoxin A in 1979 They proposed its structure to be **2** with an unknown absolute configuration at the chiral center C-14[5]

Meanwhile Fujiki *et al* found that the above sample of dihydroteleocidin B had a strong tumor promoter activity in the screening system of the tests on irritation of the mouse ear, induction of ornithine decarboxylase in mouse skin, and adhesion of human promyelocytic leukemia cells[6] So the Takashima and Sakai's teleocidins A and B were reinvestigated extensively using high performance liquid chromatography (HPLC) for efficient and complete separation of the natural products and it is now firmly established that the above teleocidin A is actually composed of two compounds teleocidins A-1 (**2**) and A-2 (**3**),[7] and teleocidin B has been separated into four stereoisomers, teleocidins B-1 (**4**), B-2 (**5**), B-3 (**6**), and B-4 (**7**)[8] One of these substances, teleocidin A-1 is identical with lyngbyatoxin A and the previous dihydroteleocidin B is now termed dihydroteleocidin B-4[9]



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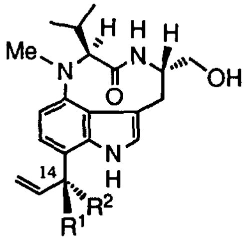
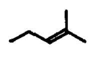
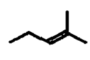
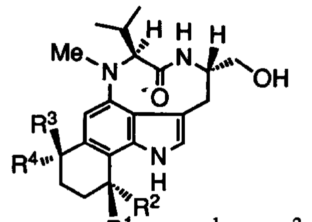


		R^1	R^2
2	Lyngbyatoxin A = Teleocidin A-1	Me	
3	Teleocidin A-2		Me
8	Pendolmycin	Me	Me

Recently pendolmycin (**8**) was isolated from *Nocardiopsis* strain SA 1715, collected in the river near Shanghai.[10] All these teleocidins are proved to be potent tumor promoters [11 12]

In regard to the synthesis of this class of natural products, only one report on (±)-teleocidins B-3 and B-4 has appeared[13] except our papers concerning teleocidins A-1, A-2, B-3, and B-4 in short communications[1 14] and pendolmycin [15] In the series of papers starting from this report, we describe the details of our syntheses of all of these natural products as well as their congeners



	R^1	R^2	R^3	R^4
4 Teleocidin B-1	vinyl	Me	i-Pr	Me
5 Teleocidin B-2	Me	vinyl	Me	i-Pr
6 Teleocidin B-3	Me	vinyl	i-Pr	Me
7 Teleocidin B-4	vinyl	Me	Me	i-Pr

The idea of the synthesis came from the previous finding[16] that the Grignard reaction of 2-[3-(1,3-dioxolan-2-yl)-1-oxopropyl]-1-[(4-methylphenyl)sulfonyl]pyrrole (**9**) with the reagent generated *in situ* from magnesium and (*E*)-3,7-dimethyl-2,6-octadienyl (geranyl) bromide in tetrahydrofuran afforded regioselectively the allylic reaction product **10** in good yield (Chart 1). This produced readily 7-(3,7-dimethyl-1,6-octadien-3-yl)indole (**11**) by removal of the nitrogen protecting group, followed by treatment with a catalytic amount of *p*-toluenesulfonic acid in boiling benzene So a suitable starting compound leading to the natural products was selected to be either the methyl or the t-butyl ester of *N*-methyl-*N*-[4-[1-[(4-methylphenyl)sulfonyl]-2-pyrrolyl]-4-oxobutanoyl]-L-valine (**12a**, **12b**) After introducing necessary terpenoid side chains as above to get **13**, we aimed at the indole cyclization reaction to form *N*-(7-alkyl-4-indolyl)-L-valine derivatives **14** In this report, we describe the initial studies in which we established the synthetic pathway for these essential intermediates **14**, which served not only as precursors for the lyngyatoxin A (teleocidin A-1) (**2**) and teleocidin A-2 (**3**) but also as useful compounds for the other teleocidin synthesis With this knowledge, we have now achieved a straightforward synthesis of pendolmycin (**8**) starting from the key intermediate **12b** [15]

Preparation of 4-[1-[(4-methylphenyl)sulfonyl]-2-pyrrolyl]-4-oxobutyric acid (**17**) from 1-[(4-methylphenyl)sulfonyl]pyrrole[17] by way of the Friedel-Crafts reaction product **16** was described previously [18] It was coupled with methyl[19] or t-butyl[20] *N*-methyl-L-valinate and methyl or t-butyl L-valinate,[21] using the mixed anhydride method[22] to obtain **12a**, **12b**, **12c**, and **12d** in 87%, 90%, 92%, and 90% yields [23] Grignard reaction on **12a** – **12d** was carried out by stirring with (*E*)-3,7-dimethyl-2,6-octadienyl (geranyl) bromide and magnesium in tetrahydrofuran at 0°C for 1 – 3 5 h The tosyl group was eliminated during the reaction, and **18a**, **18b**, **18c**, and

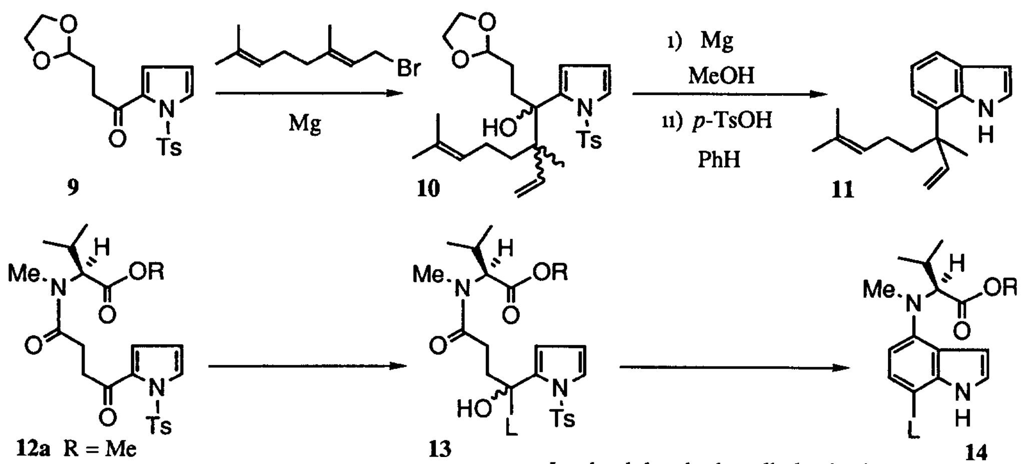


Chart 1

18d were produced in 80%, 80%, 49%, and 46% yields, respectively.

In search of the cyclization procedure from these amides **18** to the indole derivatives **14**, we tried first the conventional Bischler-Napieralski reaction using phosphorus oxychloride[24] on the t-butyl esters **18b** and **18d**. The results were quite disappointing in that **18b** afforded merely an 8% yield of an inseparable mixture of **19b** and **20b** except for **21b** in 30% yield, and **18d** gave only a trace of **19d** + **20d** when refluxed with phosphorus oxychloride in diethyl ether or dichloromethane for long time. Adding pyridine made the yield of **19b** + **20b** a little better, but it was only 19% yield at best in acetonitrile at 40°C. Other reagents, phosphorus pentoxide, trichloromethyl chloroformate, polyphosphate ester (PPE),[25] triphenylphosphine ditriflate,[26] and trimethylsilyl polyphosphate[27] afforded none of the desired products.

So we turned our attention to the synthesizing of 7-alkyl-4-aminoindole derivatives **19** and **20** by detouring the corresponding thioamides[28] instead of the direct and shortest step from the amides **18** (Chart 3). For that purpose, **18a** – **18c** were dehydrated by refluxing in benzene in the presence of *p*-toluenesulfonic acid for a short period to afford **21a**, **21b**, and **21c** in 88%, 91% and 86% yields, respectively. These were then treated with Lawesson's reagent[29] in refluxing tetrahydrofuran and thioamide derivatives **22a**, **22b**, and **22c** were obtained in 65%, 65%, and 90% yields with an uncertain geometry around the double bond conjugated with the pyrrole ring. The indole formation from **22a** – **22c** was examined in those conditions using a variety of the alkylating agents (iodomethane, iodoethane, 2-iodopropane, allyl bromide, methyl methanesulfonate, ethyl *p*-toluenesulfonate) and a metal reagent (silver tetrafluoroborate) in various solvents (dichloromethane, diethyl ether, tetrahydrofuran, t-butanol, acetonitrile, dimethylformamide). Some of the experimental results were summarized in Table 1. The reaction from thioamide **22c** was unsatisfactory (Entries 1 – 3). Using iodomethane and allyl bromide as alkylating agents, the major products were alkyl 4-indolyl sulfides **23** (A = methyl and allyl) and the compound **24**. Presumably an intermediate **25** arose during the reaction course. Either the sulfur or the nitrogen substituent from **25** was liberated to afford the indole derivatives **19** and **20** or the sulfide **23**. In the above two cases, the latter path predominated over the desired former step. Compound **24** was formed directly from **22** by catalysis of hydrogen iodide, which was generated from **22** to **25** during the reactions.

For the next trial, the substrate was changed to thioamide **22b**, and the reaction was tested by using a variety of alkylating agents and solvents (Entries 4 – 10). Iodomethane afforded the best yield of the requisite products **19b** + **20b** (Entries 4 – 6) but a longer reaction time was required for the completion in t-butanol and tetrahydrofuran compared to acetonitrile. Other alkyl halides were inferior to iodomethane in demanding elevated reaction temperature and nevertheless providing poor yields of the products (Entries 7 and 8). Using the sulfonate ester and the metal reagent was not encouraging, because the reaction did not occur in clean states and the yields had to be only moderate (Entries 9 and 10). The sulfide **23** was not detected in all cases of **22b**

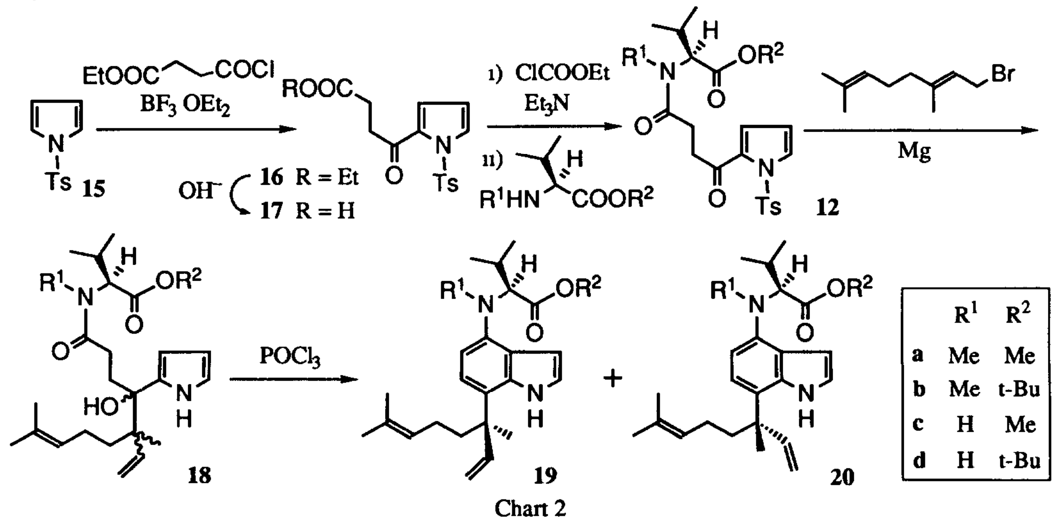


Chart 2

Judgıng from the result of Entry 4, thıs combınatıon of the substrate, alkylatıng agent, and solvent looked acceptable, but dısadvantage of the use of **22b** consısted ın that the reactıon product **19b** + **20b** were hardly separable A small amount of only **19b** was obtaıned ın the pure form by chromatography on a Lobar column

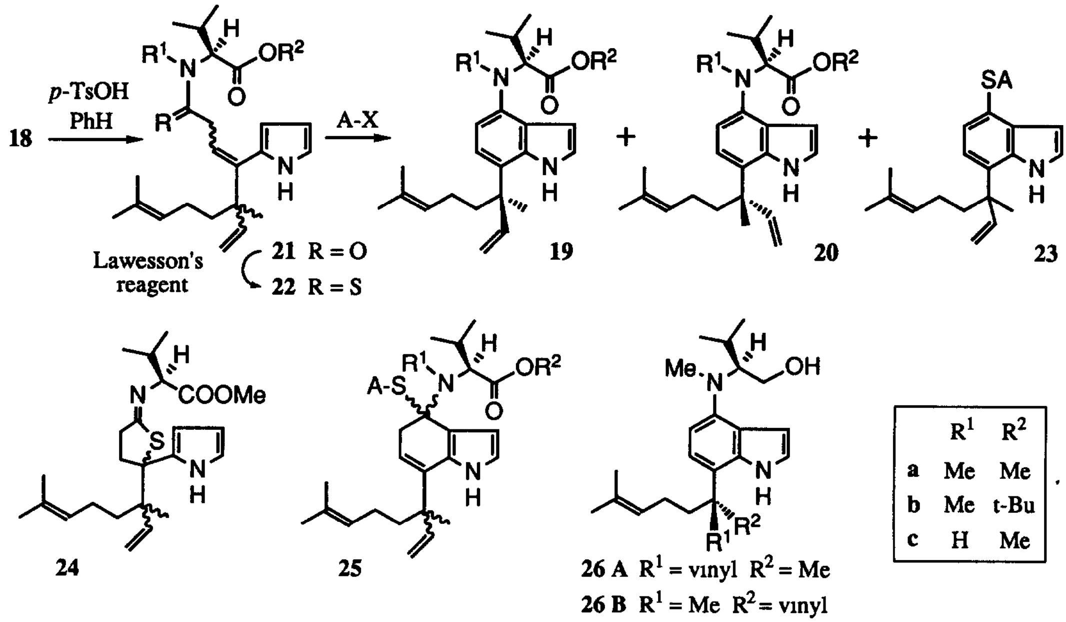
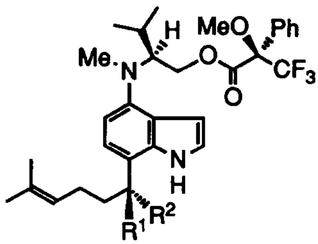


Chart 3

Table 1 Reactıon of the Thıoamıde **22** wıth the Alkylatıng Agent to Form Indole Derıvatıves **19** and **20**

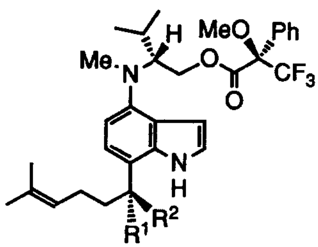
<table>
<tr><th>Entry</th><th>Thıo-amıde</th><th>Alkylatıng agent A-X</th><th>Solvent</th><th>Temp °C</th><th>Tıme h</th><th>Product 19 Yıeld %</th><th>Product 20 Yıeld %</th><th>Sulfide 23 Yıeld %</th></tr>
<tr><td>1</td><td>22c</td><td>MeI</td><td>MeCN</td><td>28</td><td>6</td><td>19</td><td>12</td><td>36, 24 26</td></tr>
<tr><td>2</td><td>22c</td><td>allyl bromıde</td><td>MeCN</td><td>18</td><td>24</td><td>12</td><td>7</td><td>30, 24 37</td></tr>
<tr><td>3</td><td>22c</td><td>$AgBF_4$</td><td>CH_2Cl_2</td><td>27</td><td>1 5</td><td>19</td><td>13</td><td></td></tr>
<tr><td>4</td><td>22b</td><td>MeI</td><td>MeCN</td><td>26</td><td>2 5</td><td colspan="2">62</td><td></td></tr>
<tr><td>5</td><td>22b</td><td>MeI</td><td>t-BuOH</td><td>22</td><td>7</td><td colspan="2">62</td><td></td></tr>
<tr><td>6</td><td>22b</td><td>MeI</td><td>THF</td><td>24</td><td>20</td><td colspan="2">59</td><td></td></tr>
<tr><td>7</td><td>22b</td><td>EtI</td><td>t-BuOH</td><td>50-55</td><td>8</td><td colspan="2">39</td><td></td></tr>
<tr><td>8</td><td>22b</td><td>Me_2CHI</td><td>THF</td><td>reflux</td><td>9</td><td colspan="2">8</td><td></td></tr>
<tr><td>9</td><td>22b</td><td>MsOMe</td><td>$ClCH_2CH_2Cl$</td><td>reflux</td><td>1 75</td><td colspan="2">46</td><td></td></tr>
<tr><td>10</td><td>22b</td><td>$AgBF_4$</td><td>CH_2Cl_2</td><td>27</td><td>3</td><td colspan="2">44</td><td></td></tr>
<tr><td>11</td><td>22a</td><td>MeI</td><td>DMF</td><td>24</td><td>3</td><td>37</td><td>25</td><td>27</td></tr>
<tr><td>12</td><td>22a</td><td>MeI</td><td>MeCN</td><td>27</td><td>3 5</td><td>32</td><td>20</td><td>4</td></tr>
<tr><td>13</td><td>22a</td><td>MeI</td><td>t-BuOH</td><td>25</td><td>6</td><td>27</td><td>18</td><td>11</td></tr>
</table>

which was not applicable to the preparation of **19b** in a large scale.



27 A R^1 = vinyl R^2 = Me

27 B R^1 = Me R^2 = vinyl



28 A R^1 = vinyl R^2 = Me

28 B R^1 = Me R^2 = vinyl

So we examined the reaction with **22a** by selecting iodomethane as the alkylating agent and tried to find a suitable solvent (Entry 11-13) The reaction condition of Entry 11 gave a satisfactory result, although the methyl 4-indolyl sulfide was produced in 27% yield. The resulting 7-alkyl-4-aminoindole derivatives were readily separated by the usual silica gel chromatography to produce **19a** and **20a** as crystalline substances in 37% and 25% yields These crystals contained about 4 – 6% of the double bond isomers having a 3,7-dimethyl-1,7-octadien-3-yl side chain, which were formed during the dehydration process of **18a** with *p*-toluenesulfonic acid [16,30] Repeated recrystallization afforded the pure **19a** and **20a** in 27% and 19% yields, respectively The product **20c** was correlated with **20a** by methylation with iodomethane in the presence of sodium bicarbonate in 78% yield [31] The indole derivative **19b** was also correlated with **19a** by reducing both with lithium aluminum hydride to give the same alcohol **26 A** in 60% and 78% yields The analogous reduction of **20a** afforded **26 B** in 75% yield The configuration of the linalyl side chain of **19a** and **20a** was uncertain at this stage, and completion of the natural product synthesis revealed the chirality as shown

The compounds **26 A** and **26 B** are good substrates for examining optical purity There was a little possibility of partial racemization of the L-valinate chirality at the stage of the Grignard reaction So the amino alcohols **26 A** and **26 B** were converted to their esters **27 A** and **27 B** with (+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) and tested for purity by HPLC For comparison, enantiomers of **26 A** and **26 B** (ent-**26 A** and ent-**26 B**) were prepared from methyl *N*-methyl-D-valinate by tracing all of the reaction steps (**17** → **12a** → **18a** → **22a** → **19a** and **20a**) now established, and transformed them into their (+)-MTPA esters **28 A** and **28 B** Good separation of HPLC peaks was secured among all of **27 A**, **27 B**, **28 A** and **28 B**, and comparison of their charts revealved that either **27 A** or **27 B** did not contain any trace of **28 A** or **28 B**, and vice versa Therefore no racemization had occurred during the processes to synthesize the amino-alcohols **26 A** and **26 B** Thus the requisite *N*-(7-alkyl-4-indolyl)-L-valine esters **19** and **20** were obtained in four steps from the readily available compound **12** Completion of the natural product synthesis is reported in the next paper [32]

EXPERIMENTAL

General Procedures — Melting points (mp) were determined on a Yanagimoto micro-melting point apparatus and are not corrected Optical rotations were measured on Perkin-Elmer 241and JASCO DIP-370 polarimeters Mass spectra (MS) were taken on a Hitachi RMS-4 spectrometer High resolution mass spectra (HRMS) were measured on a JEOL JMS-DX-300 spectrometer Infrared spectra (IR) were determined on a Hitachi 215 spectrophotometer Proton magnetic resonance (^{1}H NMR) spectra were recorded on a Varian EM 390 (90 MHz) spectrometer in $CDCl_3$ with TMS as an internal reference unless otherwise specified Column chromatography was conducted on silica gel Fuji Davison BW 200 and preparative thin-layer chromatography (PTLC) was carried out on glass plates (20 x 20 cm) coated with Merck silica gel 60 PF_{254} (1 mm thick). "Usual work-up" refers to washing the organic layers with water or brine, drying over anhydrous sodium sulfate and evaporating the solvents under reduced pressure

Methyl *N*-Methyl-*N*-[4-[1-[(4-methylphenyl)sulfonyl]-2-pyrrolyl]-4-oxobutanoyl]-L-valinate (12a), Methyl and t-Butyl *N*-[4-[1-[(4-Methylphenyl)sulfonyl]-2-pyrrolyl]-4-oxobutanoyl]-L-valinates (12c and 12d) — Preparation of **12a** is typical A solution of **17** (128 mg, 0 399 mmol) in THF (5 ml) and Et_3N (0 13 ml, 0 934 mmol) was cooled at -20°C, and to this was added 5% v/v ClCOOEt-THF (0 82 ml, 0 43 mmol) After stirring at -20°C for 10 min, methyl *N*-methyl-L-valinate hydrobromide[19] (108 mg, 0 478 mmol) was added and the mixture was stirred at that temperature for 10 min and then at room temperature for 45 min Quenching the reaction with sat $NaHCO_3$-H_2O, extraction with CH_2Cl_2, usual-work-up and PTLC [hexane-EtOAc (3 2)] afforded **12a** (155 mg, 87%), colorless needles, mp 132-133°C (CH_2Cl_2-hexane). Anal Calcd for $C_{22}H_{28}N_2O_6S$ C, 58 91, H, 6 29, N, 6 25 Found C, 58 81, H, 6.20; N, 6 17 $[\alpha]_D^{22}$ -69 4° (c 1 01, CH_2Cl_2). MS m/z. 448 (M^+). IR (KBr) cm^{-1} 1739, 1672, 1625. ^1H NMR of major and minor rotamers δ 0 77 and 0 84 (3H, d each, J=6 5 Hz), 0 93 and 0 96 (3H, d each, J=6.5 Hz), *ca* 1 94-2 37 (1H, m), 2 37 (3H, s), 2.95 and 2 80 (3H, s each), 3 64 and 3 68 (3H, s each), 4 82 and 3 99 (1H, d each, J=10 5 Hz), 6 29 (1H, dd, J=3 5, 3.5 Hz), 7 13 (1H, dd, J=3.5, 2 Hz), 7 25 and 7 84 (A_2B_2, J=8.5 Hz), 7 74 (1H, dd, J=3 5, 2 Hz) Acidification of the $NaHCO_3$-H_2O layer to pH 5 with 30% HOAc-H_2O, followed by extraction with CH_2Cl_2, usual work-up and PTLC (10% MeOH-CH_2Cl_2) recovered **17** (8 mg, 6%) **12c** Colorless prisms, mp 94-95°C (Et_2O) Anal Calcd for $C_{21}H_{26}N_2O_6S$. C, 58 05, H, 6 03, N, 6 45 Found. C, 57 91, H, 5 94, N, 6 36 $[\alpha]_D^{22}$ -1 3° (c 0 91, CH_2Cl_2) MS m/z 434 (M^+). IR ($CHCl_3$) cm^{-1} 1738, 1674. ^1H NMR δ 0 83 (3H, d, J=7 Hz), 0.86 (3H, d, J=7 Hz), 2.08 (1H, dqq, J=5, 7, 7 Hz), 2 31-2 79 (2H, m), 2.40 (3H, s), 2.79-3 39 (2H, m), 3 69 (3H, s), 4 46 (1H, dd, J=8 5, 5 Hz), 6 24 (1H, br d, J=8 5 Hz, NH), 6 31 (1H, dd, J=3 5, 3 5 Hz), 7 11 (1H, dd, J=3 5, 2 Hz), 7 28 and 7 88 (A_2B_2, J=8 5 Hz), 7 78 (1H, dd, J=3 5, 2 Hz) The compound **12d** was prepared in the same way as in the previous report [15a] **12d**· Colorless prisms, mp 100-101°C (Et_2O). Anal Calcd for $C_{24}H_{32}N_2O_6S$ C, 60 48, H, 6 77, N, 5 88 Found C, 60 25, H, 6 70, N, 5 75 $[\alpha]_D^{22}$ +4 6° (c 0 96, $CHCl_3$) MS m/z 476 (M^+) IR ($CHCl_3$) cm^{-1} 1728, 1675 ^1H NMR δ: 0.84 (6H, d, J=7 Hz), 1 44 (9H, s), 1 79-2 28 (1H, m), *ca* 2 28-2 78 (2H, m), 2 38 (3H, s), 2 78-3 40 (2H, m), 4 36 (1H, dd, J=8 5, 4 5 Hz), 6 17 (1H, br d, J=8 5 Hz, NH), 6 28 (1H, dd, J=3 5, 3 5 Hz), 7 09 (1H, dd, J=3 5, 1 5 Hz), 7 26 and 7 86 (A_2B_2, J=8 5 Hz), 7 75 (1H, dd, J=3 5, 1 5 Hz)

Grignard Reaction on 12a-12d — In a similar manner as in the previous report,[15a] **18a-18d** were prepared by the Grignard reaction of **12a-12d** with (*E*)-3,7-dimethyl-2,6-octadienyl (geranyl) bromide in the presence of Mg at 0°C **Methyl *N*-[5,9-Dimethyl-4-hydroxy-4-(2-pyrrolyl)-5-vinyl-8-decenoyl]-*N*-methyl-L-valinate (18a)** Colorless syrup HRMS Calcd for $C_{25}H_{40}N_2O_4$. 432 2988 Found 432 2965 IR ($CHCl_3$) cm^{-1} 1733, 1622 ^1H NMR δ 0 97 (3H, s), 1 49 (3H, s), 1 60 (3H, s), 2.77 and 2 79 (3H, s each), 3 64 (3H, s), 5 70-5 86 (1H, m), 6 04-6 19 (1H, m), 6 55-6 69 (1H, m), 8 80 (1H, br s, NH) **t-Butyl *N*-[5,9-Dimethyl-4-hydroxy-4-(2-pyrrolyl)-5-vinyl-8-decenoyl]-*N*-methyl-L-valinate (18b)** Colorless syrup MS m/z 474 (M^+) IR ($CHCl_3$) cm^{-1} 1729, 1620 ^1H NMR δ 0 65, 0 76 and 0 84 (3H, d each, J=7 Hz), 0 69, 0 80 and 0 87 (3H, d each, J=7 Hz), 1 01 (3H, s), 1.34 and 1 44 (9H, s each), 1 52 (3H, s), 1 63 (3H, s), 2 80 and 2 83 (3H, s each), 3 65, 3 68, 4 75 and 4 79 (1H, d each, J=10 5, 10 5, 10 and 10 Hz, respectively), 4 30, 4 36, 4 40 and 4 50 (1H, s each, OH), 5 74-5 90 (1H, m), 6 07-6 23 (1H, m), 6 57-6 73 (1H, m), 8 73 (1H, br s, NH) **Methyl *N*-[5,9-Dimethyl-4-hydroxy-4-(2-pyrrolyl)-5-vinyl-8-decenoyl]-L-valinate (18c)** Colorless syrup MS m/z 400 (M^+-H_2O) IR ($CHCl_3$) cm^{-1} 1734, 1652 ^1H NMR δ 1 49 (3H, s), 1 61 (6H, br s), 3 67 (3H, s), 3 91, 4 18 and 4 79 (1H, s each, OH), 4 45 and 4 46 (1H, dd each, J=8 5, 5 Hz), 5 70-5 86 (1H, m), 6 06-6 19 (1H, m), 6 22-6 50 (1H, m, CONH), 6 58-6 71 (1H, m), 8 90 (1H, br s, pyrrole NH) The following by-product was obtained in 13% yield along with **19c** Methyl *N*-[4-oxo-4-(2-pyrrolyl)-butanoyl]-L-valinate Colorless scales, mp 95-96°C (Et_2O) Anal Calcd for $C_{14}H_{20}N_2O_4$ C, 59 98, H, 7 19; N, 10 00 Found C, 59 82, H, 7 17, N, 9 99 MS m/z 280 (M^+) IR (KBr) cm^{-1} 1740, 1635 ^1H NMR δ 0 87 (3H, d, J=6 5 Hz), 0 89 (3H, d, J=6 5 Hz), 1 84-2 43 (1H, m), 2 47-2 94 (2H, m), 3 15 (2H, dd, J=7, 7 Hz), 4 55 (1H, dd, J=9, 5 5 Hz), 6 23 (1H, ddd, J= 4, 2 5, 2 5 Hz), 6 72 (1H, br d, J=9 Hz, CONH), 6 88-7 08 (2H, m), 9 83 (1H, br s, pyrrole NH) **t-Butyl *N*-[5,9-Dimethyl-4-hydroxy-4-(2-pyrrolyl)-5-vinyl-8-decenoyl]-L-valinate (18d)** Colorless syrup MS m/z 460 (M^+) IR ($CHCl_3$) cm^{-1} 1722, 1653 ^1H NMR δ 1 43 (9H, s), 1 49 (3H, s), 1 62 (6H, br s), 4 39 (1H, dd, J=8 5, 4 5 Hz), 4 83-5 30 (1H, m), 5 71-5 87 (1H, m), 6 08-6 22 (1H, m), 6 59-6 72 (1H, m), 8 88 (1H, br s, pyrrole NH) The following by-product was obtained in 29% yield along with **19d** t-Butyl *N*-[4-oxo-4-(2-pyrrolyl)-butanoyl]-L-valinate Colorless syrup MS m/z 322 (M^+) IR ($CHCl_3$) cm^{-1} 1722, 1668, 1641 ^1H NMR δ 0 90 (3H, d, J=7 Hz), 0 92 (3H, d, J=7 Hz), 1 48 (9H, s), 1 92-2.37 (1H, m), 2 43-3 04 (2H, m), 3 19 (2H, dd, J=7, 7 Hz), 4 53 (1H, dd, J=9, 4 5 Hz), 6 18-6 34 (1H, m), 6 90-7 11 (2H, m), 7 07 (1H, br d, J=9 Hz, CONH), 10 22 (1H, br s, pyrrole NH)

Indole Cyclization of 18b under Bischler-Napieralski Condition. t-Butyl *N*-[7-(3,7-Dimethyl-1,6-octadien-3-yl)-4-indolyl]-*N*-methyl-L-valinate (19b + 20b) — A solution of **18b** (29 mg, 0 06 mmol), $POCl_3$

(0 10 ml, 1.08 mmol) and pyridine (0 3 ml) in CH_3CN (3 ml) was heated at 40°C under N_2 atmosphere for 14 h The reaction was quenched with sat. $NaHCO_3$-H_2O at 0°C and the mixture was extracted with CH_2Cl_2 Usual work-up and PTLC [hexane-benzene (1.2)] yielded *ca.* 3:2 mixture of **19b** and **20b** (5 mg, 19%) as colorless syrup MS m/z. 438 (M^+). IR ($CHCl_3$) cm^{-1}. 1714, 1630 ^{1}H NMR (300 MHz) of **19b** and **20b** δ 0.96 and 0 94 (3H, d each, J=6.5 Hz), 1 08 and 1 01 (3H, d each, J=6.5 Hz), 1 35 and 1 38 (9H, s each), 1.64 (3H, br s), 2 98 and 3 01 (3H, s each), 3 93 and 3 94 (1H, d each, J=11 Hz), 5 01-5 11 (1H, m), 5 21-5 32 (2H, m), 6 20 and 6 21 (1H, dd each, J=17.5, 11 Hz), 6.58 and 6 60 (1H, d each, J=8 and 7.5 Hz), 6 70 and 6 75 (1H, dd each, J=3, 2 Hz), 6 97 (1H, d, J=8 Hz), 7 03-7.09 (1H, m), 8.58 (1H, br s, NH)

Dehydration of 18a – 18c — In the same manner as in the previous report,[15a] **21a** – **21c** were prepared from **18a** – **18c**. **Methyl *N*-[5,9-Dimethyl-4-(2-pyrrolyl)-5-vinyl-3,8-decadienoyl]-*N*-methyl-L-valinate (21a)** Colorless syrup HRMS Calcd for $C_{25}H_{38}N_2O_3$ 414 2882. Found 414 2873 IR ($CHCl_3$) cm^{-1} 1740, 1632 ^{1}H NMR δ: 1.15 (3H, s), 1 49 (3H, s), 1 60 (3H, s), 2 84 and 2.88 (3H, s each), 2 96-3 21 (2H, m), 3 67 (3H, s), 5 65 (1H, t, J=7 5 Hz), 6 59-6 74 (1H, m), 9 28 (1H, br s, NH). **t-Butyl *N*-[5,9-Dimethyl-4-(2-pyrrolyl)-5-vinyl-3,8-decadienoyl]-*N*-methyl-L-valinate (21b)** Colorless syrup MS m/z 456 (M^+) IR ($CHCl_3$) cm^{-1} 1730, 1628 ^{1}H NMR of major and minor rotamers δ 0 83 and 0 80 (3H, d each, H=7 Hz), 1 00 and 0 95 (3H, d each, J=7 Hz), 1 18 (3H, s), 1 46 and 1 43 (9H, s each), 1 51 (3H, s), 1 63 (3H, s), 2 91 and 2 87 (3H, s each), 3.06 and 3 13 (2H, d each, J=7 5 Hz), 4 78 and 3 76 (1H, d each, J=10 5 Hz), 6 57-6 75 (1H, m), 9 53 (1H, br s, NH). **Methyl *N*-[5,9-Dimethyl-4-(2-pyrrolyl)-5-vinyl-3,8-decadienoyl]-L-valinate (21c)** Colorless syrup MS m/z 400 (M^+). IR ($CHCl_3$) cm^{-1} 1733, 1660 ^{1}H NMR δ 0 86 (3H, d, J=7 Hz), 0 91 (3H, d, J=7 Hz), 1 17 (3H, s), 1 48 (3H, s), 1 61 (3H, s), 2 16 (1H, dqq, J=5 5, 7, 7 Hz), 2 89 (2H, d, J=8 Hz), 3 72 (3H, s), 4 53 (1H, dd, J=9, 5 5 Hz), *ca* 4.87-5 19 (1H, m), 5 03 (1H, dd, J=18, 1 5 Hz), 5 07 (1H, dd, J=11, 1 5 Hz), 5 71 (1H, t, J=8 Hz), 5 88-6 33 (4H, m), 6 64-6 77 (1H, m), 9 44 (1H, br s, NH)

Thioamidation of 21a – 21c — In the same way as in the previous report,[15a] **22a** – **22c** were obtained by the reaction of **21a** – **21c** with Lawesson's reagent **Methyl *N*-[5,9-Dimethyl-4-(2-pyrrolyl)-5-vinyl-3,8-decadienthioyl]-*N*-methyl-L-valinate (22a)** Colorless syrup HRMS Calcd for $C_{25}H_{38}N_2O_2S$ 430 2654 Found 430 2654 IR ($CHCl_3$) cm^{-1} 1736, 1630 ^{1}H NMR of major and minor rotamers δ 0 87 and 0 74 (3H, d each, J=6 5 Hz), 1 06 and 0 90 (3H, d each, J=6 5 Hz), 1 18 (3H, s), 1 50 (3H, s), 1 61 (3H, s), 2 29 (1H, dqq, J=10 5, 6 5, 6 5 Hz), 3 01 and 3.27 (3H, s each), 3 69 (3H, s), 6 29 and 4 26 (1H, d each, J=10 5 Hz), ca 4 85-5 11 (1H, m), 5 04 (1H, dd, J=17, 1 5 Hz), 5 07 (1H, dd, J=11, 1 5 Hz), 5 68 and 5 73 (1H, t each, J=7 Hz), 6 57-6 73 (1H, m), 8 85 (1H, br s, NH) **t-Butyl *N*-[5,9-Dimethyl-4-(2-pyrrolyl)-5-vinyl-3,8-decadienthioyl]-*N*-methyl-L-valinate (22b)**: Colorless syrup MS m/z 472 (M^+) IR ($CHCl_3$) cm^{-1} 1731 ^{1}H NMR of two rotamers δ· 1 16 (3H, s), 1 51 (3H, s), 1 61 (3H, s), 3 03 and 3 30 (3H, s each), 3 47 and 3 57 (2H, d each, J=7 5 Hz), 5 67 and 5 69 (1H, t each, J=7 5 Hz), 6 59-6 75 (1H, m), 8 97 (1H, br s, NH) **Methyl *N*-[5,9-Dimethyl-4-(2-pyrrolyl)-5-vinyl-3,8-decadienthioyl]-L-valinate (22c)** Colorless syrup MS m/z 416 (M^+) ^{1}H NMR δ 0 92 (3H, d, J=7 Hz), 0 97 (3H, d, J=7 Hz), 1 19 (3H, s), 1 52 (3H, s), 1 63 (3H, s), 2 33 (1H, dqq, J=5, 7, 7 Hz), 3 38 (2H, d, J=8 Hz), 3 77 (3H, s), 4 87-5 26 (4H, m), *ca* 5 64-6 07 (2H, m), 5 94-6 09 (1H, m), 6 07-6 24 (1H, m), 6 70 (1H, ddd, J=2 5, 2 5, 1 5 Hz), 7 69 (1H, br d, J=8 5 Hz, valine NH), 8 92 (1H, br s, pyrrole NH)

Indole Cyclization of 22c to Form 19c, 20c, 23 and 24 — The procedure with MeI is a representative A solution of **22c** (23 mg, 0.055 mmol) in CH_3CN (1 ml) was stirred with MeI (0 50 ml, 8 03 mmol) at room temperature for 6 h. After evaporation to dryness, sat $NaHCO_3$-H_2O was added and the mixture was extracted with CH_2Cl_2 Usual work-up and PTLC [hexane-EtOAc (9 1)] afforded **23** (6 mg, 36%), **20c** (2 5 mg, 12%), **19c** (4 mg, 19%) and **24** (6 mg, 26%) in the order of increasing polarity **Methyl *N*-[7-[(*R*)-3,7-Dimethyl-1,6-octadien-3-yl]-4-indolyl]-L-valinate (19c)** Colorless syrup HRMS Calcd for $C_{24}H_{34}N_2O_2$ 382 2620 Found 382 2623 IR ($CHCl_3$) cm^{-1} 1734 ^{1}H NMR δ 1 04 (3H, d, J=6 5 Hz), 1 08 (, d, J=6 5 Hz), 1 41 (3H, s), 1 45 (3H, s), 1 62 (3H, s), 2 19 (1H, dqq, J=6 5, 6 5, 6 5 Hz), 3 69 (3H, s), 4 03 (1H, d, J=6 5 Hz), 4 12-4 66 (1H, br s, valine NH), *ca* 4 90-5.21 (1H, m), 5 21 (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 20 (1H, d, J=8 Hz), 6 47 (1H, dd, J=3, 2 5 Hz), 6 93 (1H, d, J=8 Hz), 7 02 (1H, dd, J=3, 3 Hz), 8 57 (1H, br s, indole NH) **Methyl *N*-[7-(*S*)-[3,7-Dimethyl-1,6-octadien-3-yl]-4-indolyl]-L-valinate (20c)** Colorless syrup HRMS Calcd for $C_{24}H_{34}N_2O_2$ 382 2620 Found 382 2632 IR ($CHCl_3$) cm^{-1} 1732 ^{1}H NMR δ 1 02 (3H, d, J=6 5 Hz), 1 08 (3H, d, J=6 5 Hz), 1 41 (3H, s), 1 43 (3H, s), 1 61 (3H, s), 2 19 (1H, dqq, J=6 5, 6 5, 6 5 Hz), 3 69 (3H, s), 4 01 (1H, d, J=6 5 Hz), 4 37 (1H, br s, valine NH), 4 92-5 19 (1H, m), 5 22 (1H, dd, J=10 5, 1 5 Hz), 5 23 (1H, dd, J=18, 1 5 Hz), 6 19 (1H, d, J=8 Hz), 6 20 (1H, dd, J=18, 10 5 Hz), 6 46 (1H, dd, J=3, 2 Hz), 6 93 (1H, d, J=8 Hz), 7.02 (1H, dd, J=3, 3 Hz), 8 57 (1H, br s, indole NH) **7-(3,7-Dimethyl-1,6-octadien-3-yl)-4-(methylthio)indole (23, A=Me)** Colorless syrup HRMS Calcd for $C_{19}H_{25}NS$: 299 1707 Found 299 1690 IR ($CHCl_3$) cm^{-1}: 1628 ^1H NMR δ 1 43 (3H, s), 1.45 (3H, s), 1 60 (3H, s), 2 53 (3H, s), 4 88-5 17 (1H, m), 5 24 (1H, dd, J=10 5, 1 5 Hz), 5 25 (1H, dd, J=18, 1 5 Hz), 6.21 (1H, dd, J=18, 10 5 Hz), 6.60 (1H, dd, J=3, 2 5 Hz), 6.95 (1H, d, J=7.5 Hz), 7 08 (1H , d, J=7 5 Hz), 7 11 (1H, dd, J=3, 3 Hz), 8 64 (1H, br s, NH) **Methyl *N*-[5-(3,7-Dimethyl-1,6-octadien-3-yl)-5-(2-pyrrolyl)-2-tetrahydrothiophenylidene]-L-valinate (24)** Colorless syrup MS m/z 416 (M^+) IR ($CHCl_3$) cm^{-1} 1733, 1635. ^1H NMR δ 1 11 (3H, s), 1 50 (3H, s), 1 63 (3H, s), 3 69 and 3 72 (3H, s each), 6 56-6.73 (1H, m), 8 34 (1H, br s NH). By use of allyl bromide was obtained **7-(3,7-dimethyl-1,6-octadien-3-yl)-4-(2-propen-1-ylthio)indole (23, A=allyl)**: Colorless syrup MS m/z 325 (M^+) ^1H NMR δ: 1 42 (3H, s), 1 47 (3H, s), 1 62 (3H, s), 3 60 (2H, d, J=7 Hz), 4 87-5 20 (3H, m), 5 12-5 41 (2H, m), 5.93 (1H, ddt, J=17, 10, 7 Hz), 6 23 (1H, dd, J=18, 10 5 Hz), 6 67 (1H, dd, J=3, 2 Hz), 7.04 (1H, d, J=8 Hz), 7 12 (1H, d, J=8 Hz), 7 13 (1H, dd, J=3, 3 Hz), 8 67 (1H, br s, NH)

Indole Cyclization of 22a to Form 19a, 20a and 23 — According to the reported procedure,[15a] **22a** (740 mg, 1 72 mmol) in DMF (6 ml) was stirred with MeI (3 0 ml, 48 mmol) at 18°C for 4 h After workig up as before, column chromatography over silica gel (35 g) [hexane-EtOAc (49 1)] afforded **23** (A=Me) (141 mg, 27%), the crude **19a** (252 mg, 37%) and the crude **20a** (170 mg, 25%) in the order of increasing polarity The crude **19a** was recrystallized from MeOH-H_2O to give **methyl *N*-[7-[(*R*)-3,7-dimethyl-1,6-octadien-3-yl]-4-indolyl]-*N*-methyl-L-valinate (19a)** (183 mg, 27%) Colorless needles, mp 58-59 5°C. Anal Calcd for $C_{25}H_{36}N_2O_2$ C, 75 71, H, 9 15, N, 7 07 Found C, 75 69, H, 9 30, N, 6 98 $[\alpha]_D^{22}$ -157 7° (c 0 995, CH_2Cl_2) MS m/z 396 (M^+) IR (KBr) cm^{-1} 1727, 1627 ^1H NMR δ 0 92 (3H, d, J=6 5 Hz), 1 09 (3H, d, J=6 5 Hz), 1.41 (3H, s), 1 45 (3H, s), 1.62 (3H, s), 2 37 (1H, dqq, J=11, 6 5, 6 5 Hz), 2 98 (3H, s), 3 57 (3H, s), 4 04 (1H, d, J=11 Hz), 4 88-5 17 (1H, m), 5 21 (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 54 (1H, d, J=8 Hz), 6 65 (1H, dd, J=3, 2 5 Hz), 6 94 (1H, d, J=8 Hz), 7 02 (1H, dd, J=3, 3 Hz), 8 57 (1H, br s, NH) Similarly recrystallization of the crude **20a** from MeOH-H_2O afforded 129 mg (19%) of **methyl *N*-[7-[(*S*)-3,7-dimethyl-1,6-octadien-3-yl]-4-indolyl]-*N*-methyl-L-valinate (20a)** Colorless scales, mp 75-77°C Anal Calcd for $C_{25}H_{36}N_2O_2$ C, 75 71, H, 9 15, N, 7 07 Found C, 75 71, H, 9 21, N, 6 91 $[\alpha]_D^{22}$ -191 1° (c 1 005, CH_2Cl_2) MS m/z 396 (M^+) IR (KBr) cm^{-1} 1725, 1628 ^1H NMR δ 0 92 (3H, d, J=6 5 Hz), 1 02 (3H, d, J=6 5 Hz), 1 43 (3H, s), 1 44 (3H, s), 1 61 (3H, s), 2 37 (1H, dqq, J=11, 6 5, 6 5 Hz), 2 99 (3H, s), 3 63 (3H, s), 4 05 (1H, d, J=11 Hz), 4 91-5.19 (1H, m), 5 21 (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 54 (1H, d, J=8 Hz), 6 67 (1H, dd, J=3, 2 5 Hz), 6 94 (1H, d, J=8 Hz), 7 02 (1H, dd, J=3, 3 Hz), 8 57 (1H, br s, NH)

Transformation of 20c to 20a — To a solution of **20c** (16 mg, 0.042 mmol) in MeOH (2 ml) were added MeI (2 0 ml, 32 mmol) and $NaHCO_3$ (35 mg, 0 42 mmol), and the mixture was refluxed for 48 h under Ar atmosphere After evaporation to dryness, H_2O was added and the whole was extracted with CH_2Cl_2 Usual work-up and PTLC [hexane-EtOAc (19 1)] afforded **20a** (13 mg, 78%)

Reduction of 19b to Form 7-[(*R*)-3,7-Dimethyl-1,6-octadien-3-yl)-4-[*N*-[(*S*)-1-hydroxy-3-methylbut-2-yl]-*N*-methyl]aminoindole (26 A) — A mixture of **19b** (10 mg, 0 023 mmol) and $LiAlH_4$ (16 mg, 0.42 mmol) in THF (3 ml) was refluxed for 1 h After cooling, sat Rochelle salt-H_2O was added and the resulting mixture was extracted with Et_2O Usual work-up and PTLC [hexane-EtOAc (9·1)] gave **26 A** (5 mg, 60%), colorless syrup HRMS Calcd for $C_{24}H_{36}N_2O$ 368 2827 Found 368 2832 IR ($CHCl_3$) cm^{-1} 1633 ^1H NMR δ: 0 75 (3H, d, J=6 5 Hz), 0 83 (3H, d, J=6 5 Hz), 1 44 (6H, s), 1 61 (3H, s), 2 70-3 09 (1H, m, OH), 2 86 (3H, s), 3 60 (1H, dd, J=12, 12 Hz), 3 66-4 07 (2H, m), 4 93-5 19 (1H, m), 5 22 (1H, dd, J=10 5, 1 5 Hz), 5 25 (1H, dd, J=18, 1 5 Hz), 6 20 (1H, dd, J=18, 10 5 Hz), 6 57 (1H, d, J=8 Hz), 6 81 (1H, dd, J=3, 2 5 Hz), 6 97 (1H, d, J=8 Hz), 7 01 (1H, dd, J=3, 3 Hz), 8.61 (1H, br s, NH)

Reduction of 19a — Reaction of **19a** (18 mg, 0 045 mmol) with $LiAlH_4$ (10 mg, 0 263 mmol) in THF (3 ml) was carried out at 18°C for 30 min to give **26 A** (13 mg, 78%)

7-[(*S*)-3,7-Dimethyl-1,6-octadien-3-yl]-4-[*N*-[(*S*)-1-hydroxy-3-methylbut-2-yl]-*N*-methyl]amino-indole (26 B) — The ester **20a** (10 mg, 0.025 mmol) was reduced with $LiAlH_4$ (6 mg, 0.158 mmol) as above to give **26 B** (7 mg, 75%), colorless syrup HRMS Calcd for $C_{24}H_{36}N_2O$: 368 2827. Found 368 2806. IR ($CHCl_3$) cm^{-1} 1627 ^{1}H NMR δ: 0.69 (3H, d, J=6 5 Hz), 0 80 (3H, d, J=6 5 Hz), 1.37 (3H, s), 1 42 (3H, s), 1.60 (3H, s), 2 68-3 16 (1H, m, OH), 2.85 (3H, s), 3 60 (1H, dd, J=12, 12 Hz), *ca* 3 66-4 11 (2H, m), 4 96-5 23 (1H, m), 5 23 (1H, dd, J=10.5, 1.5 Hz), 5 26 (1H, dd, J=18, 1.5 Hz), 6 23 (1H, dd, J=18, 10.5 Hz), 6.58 (1H, d, J=8 Hz), 6 83 (1H, dd, J=3, 2 Hz), 6.98 (1H, d, J=8 Hz), 6 98-7 13 (1H, m), 8 65 (1H, br s, NH)

The MTPA Ester 27 A — A solution of **26 A** (7 mg, 0.019 mmol) in pyridine (0 3 ml) and CH_2Cl_2 (0 3 ml) was stirred with the acid chloride (20 mg, 0 079 mmol) derived from (*R*)-(+)-MTPA at 0°C – room temperature for 1 h The reaction was quenched with sat $NaHCO_3$-H_2O and the mixture was extracted with Et_2O Usual work-up and PTLC [hexane-EtOAc (12 1)] afforded **27 A** (11 mg, 99%), colorless syrup HRMS Calcd for $C_{34}H_{43}F_3N_2O_3$ 584 3225 Found: 584 3237 IR ($CHCl_3$) cm^{-1} 1747 ^{1}H NMR δ 0 93 (3H, d, J=6 5 Hz), 1 04 (3H, d, J=6 5 Hz), 1.44 (6H, s), 1 63 (3H, s), 2 79 (3H, s), 3 36 (3H, s), 3 71-3 99 (1H, m), 4 36 (1H, dd, J=11 5, 2 5 Hz), 4.64 (1H, dd, J=11 5, 6 Hz), 4.96-5 20 (1H, m), 5 12-5 40 (2H, m), 6 20 (1H, dd, J=18, 10 5 Hz), 6 40 (1H, d, J=8 Hz), 6.47 (1H, dd, J=3, 2 Hz), 6 92 (1H, d, J=8 Hz), 6 98 (1H, dd, J=3, 3 Hz), *ca* 7 28-7 59 (5H, m), 8 58 (1H, br s, NH)

The MTPA Ester 27 B — The same treatment of **26 B** (6 mg, 0 016 mmol) as above gave **27 B** (9 mg, 95%), colorless syrup HRMS Calcd for $C_{34}H_{43}F_3N_2O_3$ 584 3225 Found 584 3241 IR ($CHCl_3$) cm^{-1} 1743, 1626 ^{1}H NMR δ. 0 94 (3H, d, J=7 Hz), 1 02 (3H, d, J=7 Hz), 1 44 (6H, s), 1 63 (3H, s), 2 80 (3H, s), 3 33 (3H, s), 3 74-4 02 (1H, m), 4 38 (1H, dd, J=11 5, 3 Hz), 4 67 (1H, dd, J=11 5, 6 Hz), 4 93-5 19 (1H, m), 5 22 (1H, dd, J=10 5, 1 5 Hz), 5 24 (1H, dd, J=18, 1 5 Hz), 6 19 (1H, dd, J=18, 10 5 Hz), 6 39 (1H, d, J=8 Hz), 6 47 (1H, dd, J=3, 2 Hz), 6.89 (1H, d, J=8 Hz), 6 97 (1H, dd, J=3, 3 Hz), 7 20-7 59 (5H, m), 8 56 (1H, br s, NH)

Methyl *N*-Methyl-D-valinate Hydrobromide — This was prepared from D-valine according to the literature [19] mp 133 5-134 5°C (MeOH-Et_2O), colorless needles Anal Calcd for $C_7H_{16}BrNO_2$ C, 37 18, H, 7 13, N, 6 20 Found C, 37 13, H, 7 06, N, 6 09 $[\alpha]_D^{23}$ -19 7° (c 2 005, DMF)

Ent-12 — Colorless needles, mp 132-133°C (CH_2Cl_2-hexane) Anal Calcd for $C_{22}H_{28}N_2O_6S$ C, 58 91, H, 6 29, N, 6 25 Found C, 58 92, H, 6 27, N, 6 22 $[\alpha]_D^{23}$ +68 3° (c 1 010, CH_2Cl_2)

Ent-19a — Colorless needles, mp 62 5-64°C (MeOH-H_2O) Anal Calcd for $C_{25}H_{36}N_2O_2$ C, 75 71, H, 9 15, N, 7 07 Found C, 75 82, H, 9 03, N, 7 07 $[\alpha]_D^{23}$ +155 2° (c 1 000, CH_2Cl_2)

Ent-20a — Colorless scales, mp 76-78°C (MeOH-H_2O) Anal Calcd for $C_{25}H_{36}N_2O_2$ C, 75 71, H, 9 15, N, 7 07 Found C, 75 86, H, 9 16, N, 7 15 $[\alpha]_D^{23}$ +199 0° (c 1 012, CH_2Cl_2)

The MTPA Ester 28 A Derived from Ent-19a — Colorless syrup MS m/z 584 (M^+) IR ($CHCl_3$) cm^{-1} 1745, 1628 ^{1}H NMR δ 0 96 (3H, d, J=6 5 Hz), 1 03 (3H, d, J=6 5 Hz), 1 44 (6H, s), 1 62 (3H, s), 2 73 (3H, s), 3 39 (3H, s), 3 69-4 01 (1H, m), 4 33 (1H, dd, J=11 5, 3 Hz), 4 65 (1H, dd, J=11 5, 6 Hz), 4 93-5 20 (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 43 (1H, d, J=8 Hz), *ca* 6 43-6 56 (1H, m), *ca* 6 86-7 04 (1H, m), 6 94 (1H, d, J=8 Hz), 7 12-7 61 (5H, m), 8 57 (1H, br s, NH)

The MTPA Ester 28 B Derived from Ent-20a — Colorless syrup MS m/z 584 (M^+) IR ($CHCl_3$) cm^{-1} 1747, 1630 ^{1}H NMR δ 0 95 (3H, d, J=6 5 Hz), 1 02 (3H, d, J=6 5 Hz), 1 42 (6H, s), 1 61 (3H, s), 2 75 (3H, s), 3 39 (3H, s), 3 72-4 02 (1H, m), 4 34 (1H, dd, J=11 5, 3 Hz), 4 67 (1H, dd, J=11 5, 6 Hz), 4 91-5 23 (1H, m), 5 23 (1H, dd, J=10 5, 1 5 Hz), 5 24 (1H, dd, J=18, 1 5 Hz), 6 20 (1H, dd, J=18, 10 5 Hz), 6 44 (1H, d, J=8 Hz), *ca* 6 44-6 57 (1H, m), *ca* 6 87-7 03 (1H, m), 6 94 (1H, d, J=8 Hz), 7 20-7 62 (5H, m), 8 58 (1H, br s, NH)

HPLC Analysis of the Four MTPA Esters 27 A, 27 B, 28 A and 28 B — Column TSK Silica 60, 4 6 × 250 mm, mobile phase hexane – benzene – 2-propanol (95 4 9 0 1), flow rate 0 25 ml/min Retention time of **27 A, 27 B, 28 A and 28 B** 30 2 min, 38 2 min, 29 4 min and 35 5 min

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