Tetrahedron Vol 47, No 36, pp 7615-7624, 1991
Printed in Great Britain

0040-4020/91 $3 00+00

The Second Generation Synthesis of a Tumor Promoter Pendolmycin

Kazuaki Okabe and Mitsutaka Natsume*

Research Foundation Itsuu Laboratory
2-28-10 Tamagawa, Setagaya-ku, Tokyo 158, Japan

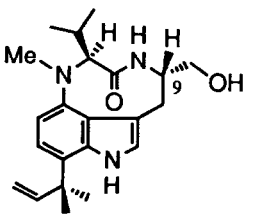
(*Received in Japan* 1 *July* 1991)

Key Words Pendolmycin, Indole alkaloid, Tumor promoter, Stereospecific synthesis, Thioamide indole cyclization

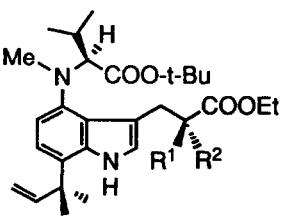
Abstract: *— Total synthesis of a tumor promoter pendolmycin (1) was accomplished in the stereospecific manner using a D-serine derivative 7 and an L-valine derivative 16 as chiral sources Methyl 2-(bromomethyl)benzoate was used for the critical step of the indole cyclization 25 →26 and 28*

Pendolmycin (**1**) is a metabolite of *Nocardiopsis* strain SA 1715 It was first isolated as an inhibitor of EGF (epidermal growth factor)-induced phosphatidylinositol turnover.[1] But the structural resemblance of **1** to teleocidins A suggested that **1** is one of the tumor promoters of the teleocidin class The tumor promoting activity of **1** has been shown to be moderate and its potency is somewhat between teleocidins A and (–)-indolactam V [2]

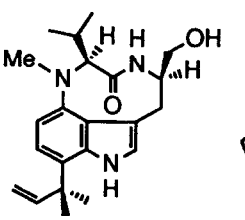
Synthesis of **1** was achieved by us only in thirteen steps starting from 1-[(4-methylphenyl)sulfonyl]-pyrrole.[3] But this had a drawback of *ca* 1 1 production of amino-diesters **3a** and **3b** in the reduction of the oxime group of **2** (Chart 1) Therefore formation of an unnecessary material, 9-epipendolmycin (**4**), was unavoidable in an equal amount along with the desired **1** at the final stage of the synthesis To improve this unfavorable fact and establish a stereospecific synthesis of the tumor promoters of the teleocidin family, we planned an alternative synthetic pathway for pendolmycin (**1**) by using a pyrrole derivative such as **5** for the key starting intermediate



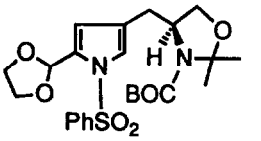
1 Pendolmycin



2 R^1, R^2 = NOH
3a $R^1 = NH_2$, R^2 = H
3b R^1 = H, $R^2 = NH_2$



4



5

Chart 1

Here compound **5** carries the requisite side chain of a chiral amino-alcohol grouping from the beginning and also a protected aldehyde group for anchoring various functionalities and building up the 7-alkyl-4-aminoindole portion later on.

The starting compound **6** was prepared from 4-bromo-2-formylpyrrole[4] by sulfonylation with benzenesulfonyl chloride in the presence of sodium hydride in tetrahydrofuran in 89% yield, followed by acetalization in the usual manner in 98.5% yield (Chart 2). Condensation of a chiral aldehyde[5] **7** with **6** was carried out by metallation of **6** with n-butyllithium in tetrahydrofuran and the subsequent addition of **7** at low temperature to afford **8** as an inseparable mixture of two diastereomers in 53 5% yield, accompanied by the formation of **9** and **10** in 6.5% and 26% yields A by-product **9** was formed by a prior metal-migration reaction from the C-3 to C-2 positions on the pyrrole ring[6] and **10** was a protonation product of 3-lithio pyrrole, by abstracting the acidic proton from **7** during the above condensation

The next step was taking off the hydroxy group in **8** to convert into **5**. However, this was unsuccessful at present, probably due to both steric hindrance and intramolecular participation of t-butoxycarbonyl group Thus the catalytic hydrogenolysis (H_2, Pd-C, MeOH), tosylation (TsCl, Et_3N, CH_2Cl_2), and chlorination (Ph_3P, CCl_4) ended up with the recovery of **8**[7] Mesylation of **8** afforded a chloro derivative **11** and a cyclic carbamate **12** in 38 5% and 57% yields, respectively, while the unstable **11** tended to be transformed spontaneously on standing to **12** The existence of the benzenesulfonyl group at the pyrrole nitrogen enabled the hydroxyl function to resist the reduction with sodium cyanoborohydride in an acidic medium So the removal of the hydroxy group was postponed to a later stage.

A mixture of acetates **13** derived from **8** in 97% yield was treated with a catalytic amount of *p*-toluenesulfonic acid in anhydrous acetone to give **14** in 86% yield Elongation of this aldehyde group to get the well-experienced 4-oxo-4-pyrrolylbutyramide side chain[3,8,9] as in **19** was carried out using an acetylene

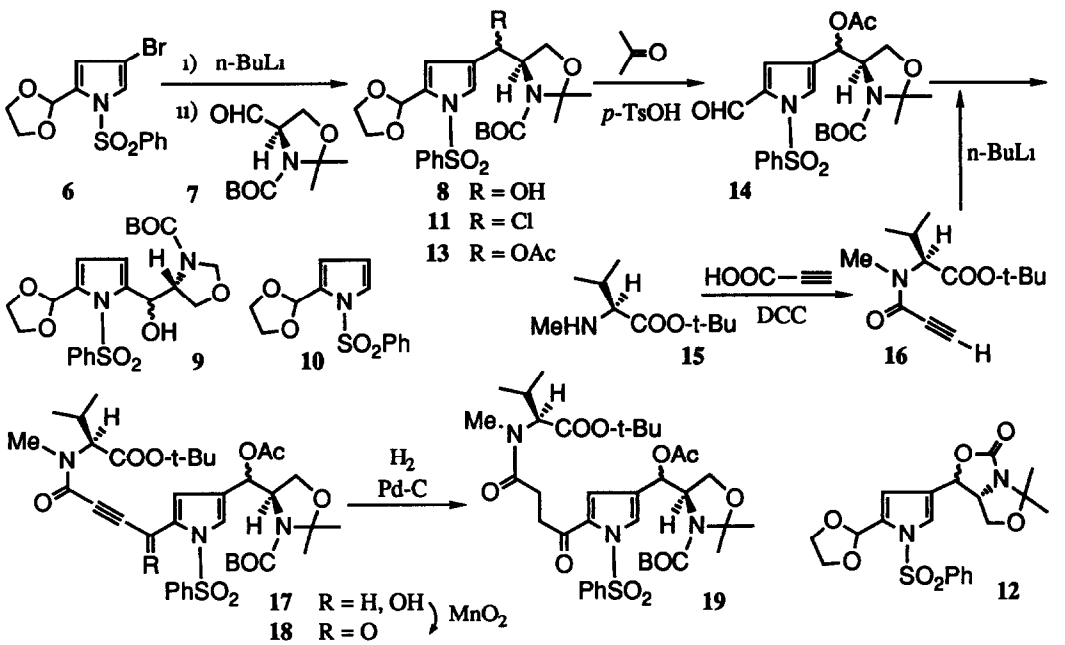


Chart 2

derivative **16** prepared from t-butyl *N*-methyl-L-valinate (**15**) and propionic acid with *N,N'*-dicyclohexylcarbodiimide in 79% yield. The reagent **16** was lithiated with n-butyllithium in tetrahydrofuran at *ca.* –80°C and the aldehyde **14** was coupled with this at the same temperature to afford **17** in 92.5% yield. The manganese dioxide oxidation of **17** in benzene, followed by catalytic hydrogenation of the unstable keto-ynamide derivative **18**, produced **19** in 91% yield.

Grignard reaction of **19** with 3-methyl-2-butenyl (prenyl) bromide in the presence of magnesium in tetrahydrofuran proceeded without trouble and the reaction mixture was directly treated with magnesium in methanol with the addition of ammonium chloride to make the reaction mixture a little acidic for the purpose of activation of the magnesium surface (Chart 3). The diol derivative **20** was obtained in 78% yield, where elimination of the secondary hydroxy group was tried using sodium cyanoborohydride The reaction required an acidic solution, but the usual combination of hydrochloric acid and methanol afforded the over-reduction product **22** in a considerable amount as exemplified by an experiment in which **20** was reduced with sodium cyanoborohydride (10 molar equivalent) in methanol containing a 3 6 molar equivalent of 3 5% aqueous hydrochloric acid to yield **21** (51%) and **22** (25%) The loss of the rest of the compounds might be ascribed to concomitant deprotection of the amino-alcohol moiety due to a strong acidic medium So the polarity of the

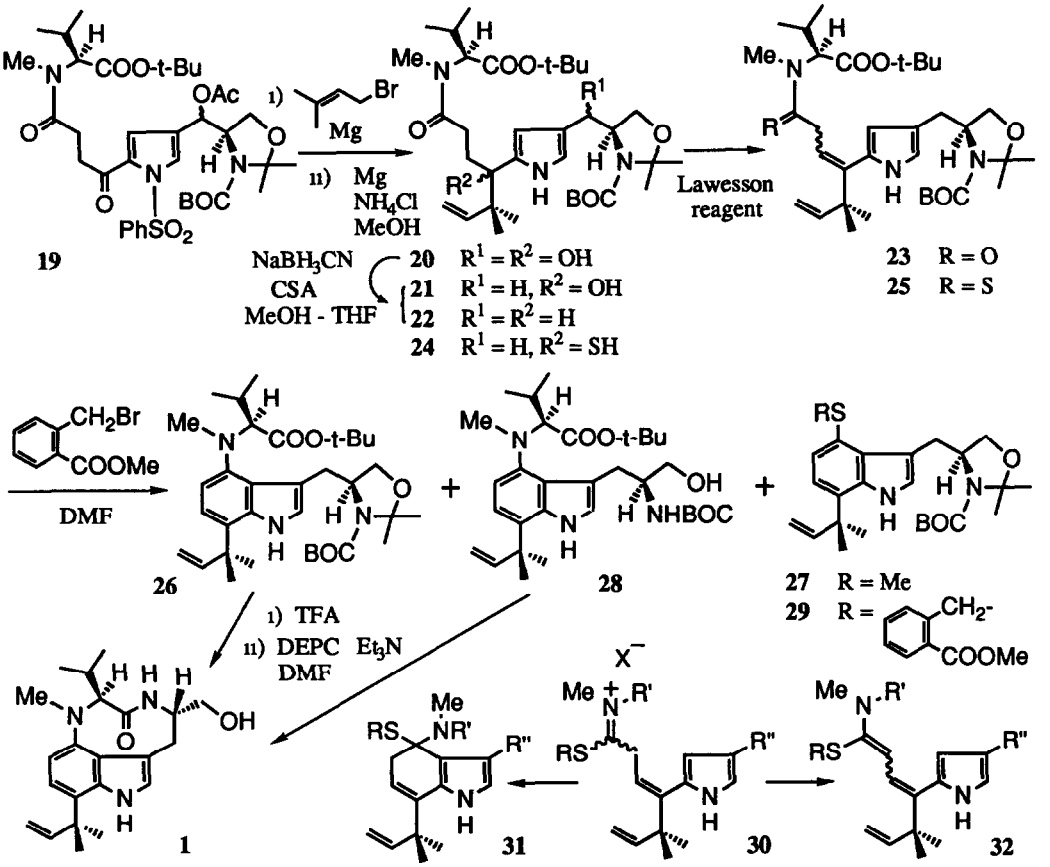


Chart 3

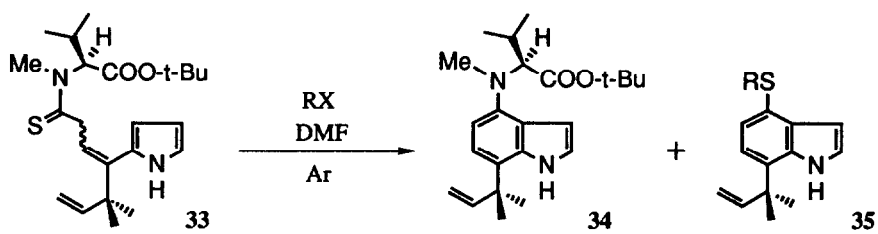
solvent was diminished using a 1.1 mixture of tetrahydrofuran and methanol, the mineral acid was changed to organic acids such as acetic acid and oxalic acid, and an acid was added portionwise to keep the solution slightly acidic. Using 10-camphorsulfonic acid (4.6 molar equivalent) with the same amount of the reducing agent as above gave the best formation of **21** in 76% yield, accompanied by **22** and the recovered **20** in 10% yield each.

The indole formation reactions from **21** are crucial steps in the present synthesis. At first a problem occurred at the dehydration step of the tertiary alcohol In the previous study this was only possible by reflux in benzene in the presence of *p*-toluenesulfonic acid.[8,9] But this procedure is not applicable to **21** owing to the ready loss of the protecting group. An effort to find an effective alternative method was pursued here and it was found that stirring **21** in benzene with the freshly prepared Lawesson reagent[10] at room temperature afforded **23** in 63% yield, accompanied by a by-product **24** in 22% yield. The amide **23** was converted to the thioamide **25** as usual using the Lawesson reagent in refluxing tetrahydrofuran, in 69% yield with the recovery of **23** in 5% yield.

The second and more serious problem was that the previous method for the formation of 7-alkyl-4-aminoindole derivatives, *i e* treatment of **25** with methyl iodide in dimethylformamide, afforded only a 19% yield of **26** Major products were a methyl sulfide **27** in 24.5% yield and the recovered material in the form of the amide **23** in 33% yield These results are clearly due to the effect of a spatially congested side chain (R") at the intermediate **30** The recovery of **23** may originate in a retarded cyclization from **30** to **31** as a consequence of steric repulsion between the R" and the reaction center This brought about migration of the double bond in part to the conjugated location as in **32**, whose work-up yielded **23** by hydrolysis Even if **31** was formed as an essential intermediate, the bulky side chain R" made it easy to eliminate another bulky valinate function and produce **27** in a considerable amount A solution for obtaining **26** as the major product is to look for such an appropriate alkylating agent RX to increase the leaving ability of RS group in **31**

So the reported step[3] **33** → **34** was studied again only to find a new alkylating agent, which afforded the

Table 1 Indole Cyclization Reaction of **33** with Alkylating Agent RX to Form **34**



RX (Mol Equiv)	React Temp	React Time	Yield of **34**	Yield of **35**
MeI (20 5)[3]	20°C	18 h	73%[3]	14%[3] (R=Me-)
$PhCH_2Br$ (15 5)	40°C	21 h	73%	7 5% ($R=PhCH_2$-)
$4\text{-}O_2NC_6H_4CH_2Br$ (15)	40°C	9 h	79%	7% ($R=4\text{-}O_2NC_6H_4CH_2$-)
$2\text{-}MeO_2CC_6H_4CH_2Br$ (10)	45-50°C	10 5 h	72%	5% ($R=2\text{-}MeO_2CC_6H_4CH_2$-)

minimum formation of the by-products **35** (Table 1) 4-Nitrobenzyl bromide and methyl 2-(bromomethyl)-benzoate seemed to be equally applicable, but the former compound was discarded as the alkylating agent because of its sparingly soluble nature in the solvent. So the indole cyclization reaction of **25** in question was tested using methyl 2-(bromomethyl)benzoate as an alkylating reagent in warming dimethylformamide. A considerable amount of the materials disappeared during the reaction, probably due to cleavage of the protecting groups sensitive to the acidic conditions Therefore 2-methyl-2-butene was added to trap hydrogen bromide and finally to produce the desired compounds **26** and **28** in 24 5% and 10% yields, together with the formation of **23** and **29** in 6% and 5% yields, respectively

The last step was the removal of the protecting groups from **26** and **28**, followed by the formation of the nine-membered lactam ring. Both **26** and **28** were stirred in trifluoroacetic acid at room temperature to cleave all of the protecting groups and the residue was treated with diethylphosphoryl cyanide (DEPC) as before to afford pendolmycin (**1**) in 58% and 57% yields, respectively. Thus the stereospecific synthesis of **1** was successful starting from the chiral compound **8**, where the requisite absolute stereochemistry of the amino group was maintained from the beginning The second chirality of the valine residue was introduced by the reaction of its acetylene derivative **16** with the aldehyde **14**, and the unnecessary epimeric secondary hydroxyl groups were effectively removed at the stage of the compound **20** Therefore we could achieve the initial objective with regard to the stereospecific synthesis, although we had to increase in some way the yield of the key reaction step to form indole derivative **26** or **28**

EXPERIMENTAL

General Method — Melting points were measured on a Yanagimoto micro-melting point apparatus and are not corrected. High resolution mass spectra (HRMS) and mass spectra (MS) were taken on Hitachi RMS-4 and M-80B mass spectrometers Liquid SIMS (LSIMS) were measured at Hitachi M-90 mass spectrometer IR spectra were determined on Hitachi 215 spectrophotometer ^{1}H NMR spectra were measured at Varian EM 390 spectrometer (90 MHz) and JEOL JNM-GX-400 (400 MHz) in $CDCl_3$ with TMS as an internal reference Column chromatography was conducted on silica gel Fuji Davison BW 200 and preparative thin-layer chromatography (PTLC) was carried out on glass plates (20 × 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, followed by evaporation of the solvents under reduced pressure

4-Bromo-2-(1,3-dioxolan-2-yl)-1-(phenylsulfonyl)pyrrole (6) — To a solution of 31 5 mg (0.18 mmol) of 4-bromo-2-formylpyrrole[4] in THF (2.5 ml) was added 18 mg (0.45 mmol) of 60% NaH at 0°C, and then 0 28 ml (0 22 mmol) of 10% v/v $PhSO_2Cl$-THF at the same temperature The mixture was stirred under Ar atmosphere at 0°C for 0 5 hr and at 20°C for 1 hr Quenching with sat NH_4Cl-H_2O, extraction with Et_2O, usual work-up and PTLC [hexane-EtOAc (5 1)] afforded 50 5 mg (89%) of 4-bromo-2-formyl-1-phenylsulfonylpyrrole as colorless prisms, mp 102-103 5°C (CH_2Cl_2-hexane) Anal Calcd for $C_{11}H_8BrNO_3S$ C, 42 06, H, 2 57, N, 4 46 Found C, 42 00, H, 2 59, N, 4 38 MS (*m/z*) 313 and 315 (M^+) IR (KBr) cm^{-1}· 1675 ^{1}H NMR (90 MHz) δ 7 08 (1H, d, J=1.5 Hz), 7 40-8 11 (6H, m), 9 92 (1H, s) A solution of 110 mg (0.35 mmol) of 4-bromo-2-formyl-1-phenylsulfonylpyrrole and ethylene glycol (0 5 ml) in benzene (16 ml) was refluxed with a catalytic amount (8 mg) of *p*-TsOH H_2O using a Dean-Stark apparatus for 1 hr After cooling at 0°C, sat $NaHCO_3$-H_2O was added and the mixture was extracted with CH_2Cl_2 Usual work-up and PTLC [hexane-EtOAc (9 2)] gave 123 5 mg (98 5%) of **6** as colorless needles, mp 83-84°C or colorless prisms, mp 114.5-115°C (CH_2Cl_2-hexane) Anal Calcd for $C_{13}H_{12}BrNO_4S$ C, 43 59, H, 3 38, N, 3 91 Found. C, 43 45, H, 3.51, N, 4 07 MS (*m/z*) 357 and 359 (M^+) ^{1}H NMR (90 MHz) δ 3 90 (4H, s), 6.34 (1H, s), 6 38 (1H, d, J=2 Hz), 7 24 (1H, d,

J=2 Hz), 7.29-8.13 (5H, m).

t-Butyl (*R*)-4-[5-(1,3-Dioxolan-2-yl)-1-(phenylsulfonyl)pyrrol-3-yl]hydroxymethyl-2,2-dimethyl-3-oxazolidinecarboxylate (8) — A solution of 108 mg (0.30 mmol) of **6** in THF (3 6 ml) was allowed to cool at -85°C for 6 min under Ar atmosphere and 0.39 ml (0.61 mmol) of 15% n-BuLi-hexane was added to this The mixture was stirred at -85 – -82°C for 5 min, and to this was added 153 mg (0.67 mmol) of t-butyl (*R*)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate[5] (**7**) in toluene (1.8 ml). After keeping this mixture under Ar atmosphere at -82 – -70°C for 25 min, the reaction was quenched with sat. NH_4Cl-H_2O Extraction with EtOAc, usual work-up and silica gel column chromatography [hexane-EtOAc (3:2)] afforded 51 mg of the crude **10**, 15 mg of the crude **9**, and 90 mg of the crude **8**. Purification of the crude **10** by PTLC [hexane-CH_2Cl_2 (1:2)] gave 22 mg (26%) of **10**, mp 55-56°C as colorless prisms (CH_2Cl_2-hexane). Anal. Calcd for $C_{13}H_{13}NO_4S$: C, 55.90; H, 4.69, N, 5 02. Found: C, 55.97; H, 4 70; N, 5.16. HRMS Calcd for $C_{13}H_{13}NO_4S$: 279.056 Found: 279.058 ^{1}H NMR (90 MHz) δ. 3.90 (4H, s), 6.17 (1H, dd, J=3.5, 3.5 Hz), 6.41 (1H, dd, J=3.5, 1.5 Hz), 7.23 (1H, dd, J=3 5, 1.5 Hz), 7.30-8.08 (5H, m). The crude **9** was purified by PTLC (2% MeOH-CH_2Cl_2) to give 10 mg (6.5%) of **9** as colorless syrup. HRMS Calcd for $C_{24}H_{32}N_2O_8S$: 508.188. Found: 508.187. IR ($CHCl_3$) cm^{-1}: 1694 ^{1}H NMR (90 MHz) δ: 1.44, 1.45 and 1.48 (15H, s each), 3.90 (4H, s), 5.45 (1H, dd, J=6, 2 Hz, changed to d, J=2 Hz with D_2O), 6 38 (1H, s), 7.28-7 67 (3H, m), 7 67-8.12 (2H, m). The crude **8** was purified by PTLC (2% MeOH-CH_2Cl_2) to give 82 mg (53.5%) of **8** as colorless syrup. HRMS Calcd for $C_{24}H_{32}N_2O_8S$: 508.188. Found: 508.190 IR ($CHCl_3$) cm^{-1}· 1692, 1680, 1655 ^{1}H NMR (90 MHz, 50°C) δ. 1.35, 1 37, 1.42, 1 43 , 1.46 and 1.48 (15H, s each), 4.56-4.99 (1H, m), 6 28-6.33 (1H, m), 6.35 and 6 43 (1H, d each, J=2 Hz), 7.14-7 23 (1H, m), 7 28-7.68 (3H, m), 7 73-8.04 (2H, m)

Mesylation of 8 to Form 11 and 12 — A solution of 26 5 mg (0.052 mmol) of **8** and 58 μl (0.42 mmol) of Et_3N in CH_2Cl_2 (2 5 ml) was treated with 16 μl (0.21 mmol) of MsCl under Ar atmosphere at 0°C for 5 min and at 20°C for 75 min. After cooling at 0°C, sat. $NaHCO_3$-H_2O was added and the mixture was extracted with CH_2Cl_2 The organic layer was washed with sat. $CuSO_4$-H_2O and worked up as usual. PTLC [hexane-EtOAc (3 2)] gave 10 5 mg (38.5%) of **11** and 10 mg (44%) of one diastereomer **12a** and 3.5 mg (13%) of the other diastereomer **12b**. **11**: Colorless syrup MS (*m/z*) 526 and 528 (M^+). IR ($CHCl_3$) cm^{-1}· 1695, 1680. ^{1}H NMR (90 MHz) δ 5.00-5.51 (1H, m), 6.27 and 6 34 (1H, s each), 6 36-6.54 (1H, m), 7 08-7 29 (1H, m), 7.29-7.70 (3H, m), 7.70-8.06 (2H, m) **12a**: Colorless syrup MS (*m/z*)· 434 (M^+) IR ($CHCl_3$) cm^{-1}: 1760. ^{1}H NMR (90 MHz) δ 1.42 (3H, s), 1.74 (3H, s), 3.91 (4H, s), 5.08 (1H, d, J=6 Hz), 6.34 (1H, s), 6.45 (1H, d, J=1 5 Hz), 7.32 (1H, d, J=1 5 Hz), 7.37-7.74 (3H, m), 7.79-8.07 (2H, m). **12b**: Colorless syrup. MS (*m/z*)· 434 (M^+) IR ($CHCl_3$) cm^{-1}. 1760. ^{1}H NMR (90 MHz) δ. 1.43 (3H, s), 1.68 (3H, s), 3.28 (1H, dd, J=9, 9 Hz), 3.68 (1H, dd, J=9, 6 Hz), 3 91 (4H, s), 4 45 (1H, ddd, J=9, 9, 6 Hz), 5.52 (1H, d, J=9 Hz), 6.28 (1H, d, J=2 Hz), 6 32 (1H, s), 7 25 (1H, d, J=2 Hz), 7 33-7.73 (3H, m), 7.73-8.04 (2H, m)

t-Butyl (*R*)-4-[5-(1,3-Dioxolan-2-yl)-1-(phenylsulfonyl)pyrrol-3-yl]acetoxymethyl-2,2-dimethyl-3-oxazolidinecarboxylate (13) — A solution of 102.5 mg (0.20 mmol) of **8** and Ac_2O (2 ml) in pyridine (5 ml) was stirred at 20°C for 3 hr Pyridine was evaporated *in vacuo*, sat. $NaHCO_3$-H_2O was added to the residue, and the mixture was extracted with CH_2Cl_2. Usual work-up and purification by PTLC [hexane-EtOAc (3:2)] gave 107 5 mg (97%) of **13** as colorless syrup HRMS Calcd for $C_{26}H_{34}N_2O_9S$· 550 198 Found 550.197 IR ($CHCl_3$) cm^{-1} 1745, 1695 ^{1}H NMR (90 MHz, 50°C) δ 1.37, 1.43, 1.47 and 1.50 (15H, s each), 2 00 and 2.11 (3H, s each), 6 26 and 6 31 (1H, s each), 7.02-7.28 (1H, m), 7 31-7 67 (3H, m), 7.76-8.04 (2H, m)

t-Butyl (*R*)-4-[5-Formyl-1-(phenylsulfonyl)pyrrol-3-yl]acetoxymethyl-2,2-dimethyl-3-oxazolidinecarboxylate (14) — A solution of 121.5 mg (0.221 mmol) of **13** and *p*-TsOH H_2O(21 mg) in anhydrous acetone (11 ml) was stirred under Ar atmosphere at 0°C for 6 5 hr Sat $NaHCO_3$-H_2O was added and the whole was extracted with CH_2Cl_2 Usual work-up and purification by PTLC [hexane-EtOAc (2·1)] afforded 96 mg (86%) of **14** as colorless syrup MS (*m/z*) 264 (M^+– $PhSO_2$ – t-BuOCO) IR ($CHCl_3$) cm^{-1}· 1728, 1694. ^{1}H NMR (90 MHz, 50°C) δ 1 41, 1 45, 1 50 and 1 52 (15H, s each), 2 04 and 2 11 (3H, s each), 3 75-4.36 (3H, m), 6 07-6.25

(1H, m), 6.96-7.14 (1H, m), 7.32-7 74 (4H, m), 7.77-8.04 (2H, m), 9.86 (1H, s).

Preparation of t-Butyl *N*-Methyl-*N*-propynoyl-L-valinate (16) — To a solution of 76.5 mg (1.09 mmol) of propiolic acid and 204 mg (1.09 mmol) of t-butyl *N*-methyl-L-valinate (**15**) in CH_2Cl_2 (4 ml) was added 225 5 mg (1 09 mmol) of DCC at 0°C and the mixture was stirred at 0°C for 0.5 hr It was filtered on a celite bed, the celite was washed with CH_2Cl_2, and the combined CH_2Cl_2 solution was evaporated *in vacuo*. The residue was purified by silica gel column chromatography [hexane-EtOAc (5:1)] to give 206 mg (79%) of **16** as colorless syrup MS (*m/z*): 239 (M^+). IR ($CHCl_3$) cm^{-1}: 2115, 1730, 1634. ^1H NMR (90 MHz) δ: 0.86, 0.90 and 1 02 (6H, d each, J=7 Hz), 1.48 (9H, s), 1.94-2.62 (1H, m), 2.91 and 3.18 (3H, s each), 3.13 and 3.18 (1H, s each. The chemical shift of this acetylenic proton varies depending upon concentration of the material.), 4 45 and 4 71 (1H, d each, J=10 5 Hz).

t-Butyl (*R*, *S*)-*N*-[4-[4-(3-t-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)acetoxymethyl-1-(phenylsulfonyl)pyrrol-2-yl]-4-hydroxy-2-butynoyl]-*N*-methylvalinate (17) — A solution of 880 mg (3.68 mmol) of **16** in THF (9 ml) was stirred under Ar atmosphere at -85 – -84°C for 8 min, 2 2 ml (3.44 mmol) of 15% n-BuLi-hexane was added to this, and the mixture was stirred at -84 – -82°C for 7 min A solution of 267 mg (0 53 mmol) of **14** in THF (6 ml) was added to the mixture and stirring was continued at -82 – -73°C for 16 min The reaction was stopped with sat NH_4Cl-H_2O, the whole was extracted with CH_2Cl_2, and the organic layer was worked up as usual. Separation of the residue by column chromatography over silica gel using hexane-EtOAc (4 1) and then EtOAc afforded 735.5 mg of the recovered **16** and 405 5 mg of a mixture of **17** and **14**. This mixture was further separated by PTLC [hexane-EtOAc (2.1)] to give 377 5 mg of the crude **17** and 21.5 mg of the crude starting material **14**. PTLC (2% MeOH-CH_2Cl_2) of the crude **17** gave 363.5 mg (92.5%) of **17** as colorless syrup. LSIMS (*m/z*)· 746 (MH^+) IR ($CHCl_3$) cm^{-1}· 1730, 1694, 1632 ^1H NMR (90 MHz, 50°C) δ 0 85, 0.87 and 1 03 (6H, d each, J=7 Hz), 1.45 and 1.49 (15H, s each), 2.01 and 2 09 (3H, s each), 2.92 and 3 16 (3H, s each), 3.60-4 33 (3H, m), 3 64 (1H, br s, OH), 4 45, 4 47 and 4 69 (1H, d each, J=10 5 Hz), 5 83-6 15 (1H, m), 6 40-6 66 (1H, m), 7 05-7 32 (1H, m), 7.32-7 72 (3H, m), 7 72-8 00 (2H, m) The crude **14** was purified by PTLC (0 5% MeOH-CH_2Cl_2), followed by PTLC [hexane-DME (7 2)] to give 11 mg (4%) of **14**

t-Butyl (*R*, *S*)-*N*-[4-[4-(3-t-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)acetoxymethyl-1-(phenylsulfonyl)pyrrol-2-yl]-4-oxobutanoyl]-*N*-methylvalinate (19) — A mixture of 363 5 mg (0 49 mmol) of **17** and 424 mg (4.88 mmol) of MnO_2 in benzene (35 ml) was stirred under Ar atmosphere at 21°C for 25 min It was filtered through a celite bed, the celite was washed with CH_2Cl_2, and the combined organic solution was evaporated *in vacuo* to afford 356 mg of the crude **18**, which was used without further purification due to its unstable nature The above material **18** in EtOAc (37 5 ml)was hydrogenated catalytically in the presence of 10% Pd-C (60 mg) at 21°C for 2 hr 45 min The catalyst was filtered off through a celite bed, the celite was washed with EtOAc, and the combined EtOAc solution was evaporated *in vacuo* Purification by silica gel column chromatography [hexane-EtOAc (3·2)] afforded 347 mg of the crude **19**, which was further purified by PTLC (0 8% MeOH-CH_2Cl_2) to give 331 5 mg (91%) of **19** as colorless syrup LSIMS (*m/z*) 748 (MH^+) IR ($CHCl_3$) cm^{-1} 1728, 1695, 1646. ^1H NMR (90 MHz) δ 0 78, 0 85, 0 97 and 0 99 (6H, d, each, J=7 Hz), 1 45, 1 48, 1 50 and 1 54 (15H, s each), 2.08 and 2 18 (3H, s each), 2 47-2 90 (2H, m), 2 80 and 2 99 (3H, s each), 2 90-3 25 (2H, m), 6 13 and 6 20-6 38 (1H, d, J=7 Hz and m), 6 92-7 24 (1H, m), 7 31-7 61 (3H, m), 7 61-7 81 (1H, m), 7.81-8 10 (1H, m)

t-Butyl (*R*, *S*)-*N*-[4-[4-(3-t-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)hydroxymethyl-1-phenylsulfonylpyrrol-2-yl]-5,5-dimethyl-4-hydroxy-6-heptenoyl]-*N*-methylvalinate (20) — To a solution of 115 mg (0 154 mmol) of **19** and 75 mg (3 09 mmol) of Mg in THF (4.5 ml) was added 0 28 ml (2 43 mmol) of 3-methyl-2-butenyl (prenyl) bromide at 0°C and the mixture was stirred under Ar atmosphere at 0°C for 40 min It was quenched with sat. NH_4Cl-H_2O and extracted with CH_2Cl_2. Usual work-up and PTLC (1 5% MeOH-CH_2Cl_2) afforded 100 mg of the *N*-phenylsulfonyl derivative of **20**. This was dissolved in MeOH (10 ml) and stirred vigorously with Mg (235 mg) and NH_4Cl (235 mg) at 20°C for 1 5 hr The reaction was stopped with sat

NH_4Cl-H_2O and the whole was extracted with CH_2Cl_2. Usual work-up and purification by PTLC (2% MeOH-CH_2Cl_2) afforded 76 mg (78%) of **20** as colorless syrup. MS (*m/z*): 617 ($M^+ - H_2O$). IR ($CHCl_3$) cm^{-1}: 1728, 1692, 1620. ^1H NMR (90 MHz) δ: 0.76 and 0.81 (3H, d each, J=7 Hz), 0.98 (6H, s), 1.38, 1.44 and 1.53 (15H, s each), 2.82 (3H, s), 3.45-4 40 (4H, m), 4 72 and 4.78 (1H, d each, J=10.5 Hz), 4.80 and 4.88 (1H, s each, tertiary OH) 5 66-5.89 (1H, m), 6 10 (1H, dd, J=17, 11 Hz), 6.50-6.70 (1H, m), 8.65 (1H, br s)

t-Butyl (*S*, *S*)-*N*-[4-[4-(3-t-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)methyl-1-(phenylsulfonyl)-pyrrol-2-yl]-5,5-dimethyl-4-hydroxy-6-heptenoyl]-*N*-methylvalinate (21) — To a solution of 71 mg (0 11 mmol) of **20** and 74 mg (1.12 mmol) of 95% $NaBH_3CN$ in THF (3.1 ml) and MeOH (3.1 ml) was added 64 μl (0 128 mmol) of 2*M* 10-camphorsulfonic acid (CSA) in MeOH at 20°C and the mixture was stirred under Ar atmosphere for 10 min. The same amount of CSA-MeOH solution was added three times at the interval of 10 min during stirring. After cooling at 0°C, the reaction was quenched with sat. $NaHCO_3$-H_2O and the whole was extracted with CH_2Cl_2. Usual work-up and separation by PTLC [hexane-EtOAc (7:2)] afforded 54 mg of the crude **21**, 7.5 mg of the crude **22** and 8 mg of the crude **20**. Purification of the crude **21** by PTLC (1.5% MeOH-CH_2Cl_2) gave 52 5 mg (76%) of **21** as colorless syrup MS (*m/z*): 601 ($M^+ - H_2O$) IR ($CHCl_3$) cm^{-1}: 1730, 1690, 1620. ^1H NMR (90 MHz, 50°C) δ: 0.66-0.88 (3H, m), 1.00 (6H, s), 1.44 and 1.53 (15H, s each), 2.55 (1H, dd, J=13 5, 10 Hz), 2 81 (3H, s), 2 97 (1H, br d, J=13.5 Hz), 3.67, 4.71 and 4.75 (1H, br d, d and d, J=10.5 Hz), 3.67-4 11 (3H, m), 4.56 (1H, br s, OH), 4 96 (1H, dd, J=18, 1 5 Hz), 5.01 (1H, dd, J=10.5, 1 5 Hz), 5.58-5.78 (1H, m), 6 07 (1H, dd, J=18, 10.5 Hz), 6 32-6.49 (1H, m), 8 45 (1H, br s). PTLC (1 5% MeOH-CH_2Cl_2) of the crude **22** afforded 6 5 mg (10%) of **t-butyl (*S*, *S*)-*N*-[4-[4-(3-t-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)methyl-1-(phenylsulfonyl)pyrrol-2-yl]-5,5-dimethyl-6-heptenoyl]-*N*-methylvalinate (22)** as colorless syrup. HRMS Calcd for $C_{34}H_{57}N_3O_6$: 603.425 Found: 603 427. IR ($CHCl_3$) cm^{-1}: 1728, 1692, 1632. ^1H NMR (90 MHz) δ. 0.92 and 0.95 (6H, s each), 1 42, 1.44 and 1.50 (15H, s each), 2.50 (1H, dd, J=13.5, 10.5 Hz), 2.73, 2.77 and 2.82 (3H, s each), 3 55, 3.59. 4 72 and 4 82 (1H, each, J=10 5 Hz), 3 69-4.25 (3H, m), 4.92 (1H, dd, J=17, 1.5 Hz), 4 97 (1H, dd, J=11, 1.5 Hz), 5.60-5 87 (1H, m), 5 86 (1H, dd, J=17, 11 Hz), 6 31-6 50 (1H, m), 7.92 and 8 08 (1H, br s each) The crude **20** was purified by PTLC [hexane-EtOAc (2:1)] to recover 7.5 mg (10%) of the starting material.

t-Butyl (*S*, *S*)-*N*-[4-[4-(3-t-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)methyl-1-(phenylsulfonyl)-pyrrol-2-yl]-5,5-dimethyl-3,6-heptadienoyl]-*N*-methylvalinate (23) — To a solution of 42.5 mg (0 069 mmol) of **21** in anhydrous benzene (4 ml) was added 22 mg (0 054 mmol) of the Lawesson reagent[10] and the mixture was stirred under Ar atmosphere at 18°C for 2.5 hr. Sat $NaHCO_3$-H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and PTLC [hexane-EtOAc (7 2)] afforded 27 mg of the crude **23** and 10 mg of the crude **24** PTLC (1 5% MeOH-CH_2Cl_2) of the crude **23** gave 26 mg (63%) of **23** as colorless syrup HRMS Calcd for $C_{34}H_{55}N_3O_6$: 601 409 Found 601 409 IR ($CHCl_3$) cm^{-1} 1730, 1692, 1628 ^1H NMR (90 MHz) δ 0 82, 0 84, 0 96 and 1 02 (6H, d each, J=7 Hz), 1.14 (6H, s), 1 44 and 1 50 (15H, s each), 2.90 and 2 96 (3H, s each), 3.06 and 3 13 (2H, d each, J=7.5 Hz), 5 00 (1H, dd, J=10 5, 1 Hz), 5.03 (1H, dd, J=18 1 Hz), 5 62 and 5 65 (1H, t each, J=7.5 Hz), 5.86-6.06 (1H, m), 5 94 (1H, dd, J=18, 10.5 Hz), 6.42-6 60 (1H, m), 9 22 and 9 42 (1H, br s each) PTLC (1.5% MeOH-CH_2Cl_2) of the crude **24** afforded 9 5 mg (22%) of **t-butyl (*S*, *S*)-*N*-[4-[4-(3-t-butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)methyl-1-(phenylsulfonyl)pyrrol-2-yl]-5,5-dimethyl-4-mercapto-6-heptenoyl]-*N*-methylvalinate (24)** as colorless syrup HRMS Calcd for $C_{34}H_{57}N_3O_6S$ 635 397 Found 635.397. IR ($CHCl_3$) cm^{-1} 1728, 1693, 1632 ^1H NMR (90 MHz) δ· 1.08 and 1 10 (6H, s each), 1 45 and 1 54 (15H, s each), 1.93 (1H, s, SH), 2.86 and 2 88 (3H, s each), 3 72-4 26 (3H, m), 4.99 (1H, dd, J=17, 1 5 Hz), 5 05 (1H, dd, J=10 5, 1 5 Hz), 5 82-6.03 (1H, m), 5 90 (1H, dd, J=17, 10 5 Hz), 6 35-6.55 (1H, m), 8 53 and 8 62 (1H, br s each)

t-Butyl (*S*, *S*)-*N*-[4-[4-(3-t-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)methyl-1-(phenylsulfonyl)-pyrrol-2-yl]-5,5-dimethyl-1-thioxo-3,6-heptadienyl]-*N*-methylvalinate (25) — A solution of 263.5 mg (0 44 mmol) of **23** in THF (23 ml) was heated at 70-75°C for 8 min To this heated solution was added 310 mg (0 77

mmol) of the Lawesson reagent and the mixture was stirred under Ar atmosphere at 70-75°C for 25 min. After cooling to 0°C, sat. $NaHCO_3$-H_2O was added and the whole was extracted with Et_2O. Usual work-up gave 321.5 mg of the crude reaction mixture, which was at first separated by silica gel chromatography [hexane-EtOAc (9 2) → hexane-EtOAc (1:1)] to afford 191 mg of the crude **25** and 40 mg of the crude starting material **23**. The former was further purified by silica gel chromatography [hexane-CH_2Cl_2 (1:4)] to give 185.5 mg (69%) of **25** as colorless syrup. HRMS Calcd for $C_{34}H_{55}N_3O_5S$ 617.386 Found 617.387. IR ($CHCl_3$) cm^{-1}. 1730, 1692 ^1H NMR (90 MHz) δ: 0.75, 0.89 and 1.02 (6H, d each, J=7 Hz), 1.14 (6H, s), 1.42, 1.45 and 1.51 (15H, s each), 2 11-2.44 (1H, m), 2.36-2.73 (1H, m), 2.73-3.17 (1H, m), 3:05 and 3.32 (3H, s each), 3.47 and 3 57 (2H, d each, J=7 5 Hz), 3.71-4.16 (3H, m), 4.16 and 6.13 (1H, d each, J=10.5 Hz), 5.00 (1H, dd, J=10.5, 1.5 Hz), 5.02 (1H, dd, J=18, 1.5 Hz), 5 65 (1H, t, J=7.5 Hz), 5.76-5 96 (1H, m), 5.93 (1H, dd, J=18, 10.5 Hz), 6.36-6.57 (1H, m), 8 63 and 8.82 (1H, br s each). PTLC [hexane-EtOAc (4:1)] of the crude **23** gave 13.5 mg (5%) of the recoverd starting material.

t-Butyl (*S*, *S*)-*N*-[3-[(3-t-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)methyl]-7-(2-methyl-3-buten-2-yl)-4-indolyl]-*N*-methylvalinate (26) and t-Butyl (*S*, *S*)-*N*-[3-(2-t-Butoxycarbonylamino-3-hydroxypropyl)-7-(2-methyl-3-buten-2-yl)-4-indolyl]-*N*-methylvalinate (28) — To a solution of 106 5 mg (0 17 mmol) of **25** in DMF (11.5 ml) was added 1.6715 g (7.30 mmol) of methyl 2-(bromomethyl)benzoate and 0 37 ml (3.50 mmol) of 2-methyl-2-butene. This solution was warmed at 45°C for 6 h 40 min under Ar atmosphere After cooling at 0°C, sat. $NaHCO_3$-H_2O was added to the reaction mixture and the whole was extracted with Et_2O Usual work-up gave 1.753 g of the residue, which was chromatographed over silica gel (40g) After removal of methyl 2-(bromomethyl)benzoate with hexane-EtOAc (24·1), the solvent was changed to hexane-EtOAc (7·3) to elute 117 mg of a crude mixture, which contained **26**, **29** and **23**. Further elution with 10% MeOH-CH_2Cl_2 gave 13 5 mg of the crude **28** The crude mixture (117 mg) was purified by PTLC [hexane-EtOAc (4 1)] to give a mixture (71 mg) of **26** and bis(2-methoxycarbonylbenzyl) sulfide, the crude **29** (5 5 mg) and the crude **23** (24 mg) The above mixture (71 mg) was separated by PTLC [hexane-CH_2Cl_2 (1 2)] to afford 32 mg of the impure sulfide and 25 mg (24 5%) of **26** as colorless syrup HRMS Calcd for $C_{34}H_{53}N_3O_5$ 583 398 Found. 583.398 IR ($CHCl_3$) cm^{-1} 1712, 1690 ^1H NMR (90 MHz, 50°C) δ· 0.96 (3H, d, J=7 Hz), 1.14 (3H, d, J=7 Hz), 1 23 (9H, s), 1.44 (9H, s), 1 51 (9H, s), 1 63 (3H, s), 2 00-2 48 (1H, m), 2 89 (3H, s), 3 25 (1H, br dd, =15, 3 Hz), 3 45 (1H, d, J=9 Hz), 3 54 (1H, dd, J=15, 9 Hz), 3 73-4.00 (2H, m), 4 00-4.34 (1H, m), 5 13 (1H, dd, J=10 5, 1 5 Hz), 5 21 (1H, dd, J=18, 1.5 Hz), 6.17 (1H, dd, J=18, 10 5 Hz), 6.70-6 85 (1H, m), 6 86 (1H, d, J=9 Hz), 6 96 (1H, d, J=9 Hz), 8 33 (1H, br s) The impure sulfide (32 mg) was purified by PTLC [hexane-DME (9 1)] to afford 25 5 mg (45%) of **bis(2-methoxycarbonylbenzyl) sulfide** as colorless syrup HRMS Calcd for $C_{18}H_{18}O_4S$: 330 093 Found 330 092 IR ($CHCl_3$) cm^1 1724 ^1H NMR (90 MHz) δ 3 81 (6H, s), 4 01 (4H, s), 7 07-7 50 (6H, m), 7 68-7 95 (2H, m) Purification of the crude **29** (5 5 mg) by PTLC [hexane-CH_2Cl_2 (1 2)] afforded 5 mg (5%) of **29** as colorless syrup HRMS Calcd for $C_{33}H_{42}N_2O_5S$. 578 281 Found 578 284 IR ($CHCl_3$) cm^{-1} 1720, 1683 ^1H NMR (90 MHz, 50°C) δ 1 28 (9H, s), 1 52 (9H, s), 1.62 (3H, s), 3 23 (1H, dd, J=15, 6 5 Hz), 3 48 (1H, dd, J=15, 7 Hz), 3 84 (3H, s), 4 15-4 44 (1H, m), 4 52 (2H, s), 5 15 (1H, dd, J=10 5, 1 5 Hz), 5 22 (1H, dd, J=18, 1 5 Hz), 6 16 (1H, dd, J=18, 10 5 Hz), 6 85 (1H, d, J=2 Hz), 7.05-7 37 (3H, m), 7 71-7 94 (1H, m), 8 41 (1H, br s) The crude **23** (24 mg) was purified by PTLC (1% MeOH-CH_2Cl_2) to give 6 5 mg (6%) of **23** as colorless syrup. The most polar fraction (13 5 mg) containing **28** was purified by PTLC [hexane-EtOAc (2 1)] and further by PTLC (1 5% MeOH-CH_2Cl_2) to give 9 mg (10%) of **28** as colorless syrup HRMS Calcd for $C_{31}H_{49}N_3O_5$: 543 367 Found· 543 366 IR ($CHCl_3$) cm^1 1714 ^1H NMR (90 MHz, 50°C) δ 0 99 (3H, d, J=7 Hz), 1 06 (3H, d, J=7 Hz), 1 22 (9H, s), 1 43 (9H, s), 1 48 (6H, s), 2.06-2 50 (1H, m), 2 93 (3H, s), 3 07 (1H, dd, J=15, 7 Hz), 3.37 (1H, dd, J=15, 7.5 Hz), 3.47-4 00 (1H, m), 3 54 (1H, d, J=9 Hz), 5 15 (1H, d, J=10 5 Hz), 5 20 (1H, d, J=18 Hz), 5 23-5 69 (1H, m, NHBOC), 6 15 (1H, dd, J=18, 10 5 Hz), 6 85 (1H, d, J=8 Hz), 6 87-6 99 (1H, m), 6 97 (1H, d, J=8), 8 42 (1H, br s) Usage of MeI as the alkylating agent afforded **26** (19%) and **27**, colorless syrup HRMS Calcd for $C_{25}H_{36}N_2O_3S$ 444.245 Found 444.246 IR ($CHCl_3$) cm^{-1}

1683. ^{1}H NMR (90 MHz, 50°C) δ: 1 31 (9H, s), 1 49 (9H, s), 1.63 (3H, s), 2.52 (3H, s), 3.22-3.50 (2H, m), 3.78-3 99 (2H, m), 4.12-4.53 (1H, m), 5.16 (1H, dd, J=10.5, 1.5 Hz), 5.25 (1H, dd, J=18, 1.5 Hz), 6.19 (1H, dd, J=18, 10.5 Hz), 6.86 (1H, d, J=3 Hz), 6.90 (1H, d, J=7.5 Hz), 7.07 (1H, d, J=7.5 Hz), 8.43 (1H, br s).

Pendolmycin (1) from t-Butyl (*S*, *S*)-*N*-[3-[(3-t-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-methyl]-7-(2-methyl-3-buten-2-yl)-4-indolyl]-*N*-methylvalinate (26) — A solution of 45 mg (0.077 mmol) of **26** in trifluoroacetic acid (TFA) (2.8 ml) was stirred under Ar atmosphere at 24°C for 17.5 h. After evaporation of TFA *in vacuo* at room temperature, four operations of CH_2Cl_2 (3 ml) addition followed by evaporation of CH_2Cl_2 were carried out for thorough removal of TFA. The resulting mixture was completely dried over P_2O_5 for 2 h, and to this was added DMF (2.5 ml), 1.1 ml (0.395 mmol) of 5% v/v Et_3N/DMF and 0.38 ml (0.12 mmol) of 5% w/v DEPC/DMF successively. The solution was stirred under Ar atmosphere at 24°C for 17.5 h. The reaction was quenched by addition of sat. $NaHCO_3$-H_2O and the whole was extracted with Et_2O Usual work-up and separation by PTLC [hexane-EtOAc (1·2)] gave 18 mg of the crude **1**, which was purified by PTLC (4% MeOH-CH_2Cl_2) to give 16.5 mg (58%) of **pendolmycin (1)** as colorless amorphous powder, whose spectral data [HRMS, $[\alpha]_D$, IR, ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz)] were identical with those in the previous paper [3]

Pendolmycin (1) from t-Butyl (*S*, *S*)-*N*-[3-(2-t-Butoxycarbonylamino-3-hydroxypropyl)-7-(2-methyl-3-buten-2-yl)-4-indolyl]-*N*-methylvalinate (28) — A solution of 28.5 mg (0.052 mmol) of **28** in TFA (2 ml) was stirred under Ar atmosphere at 24°C for 17.5 h. After the same treatment as above, the residue in DMF (1 7 ml) was stirred with 0.73 ml (0.26 mmol) of 5% v/v Et_3N/DMF and 0.26 ml (0.08 mmol) of 5% w/v DEPC/DMF under Ar atmosphere at 24°C for 21 h The same work-up as above afforded the residue (30 mg), which was separated by PTLC [hexane-EtOAc (1:2)] to give 12.5 mg of the crude **1**. This was purified by PTLC (4% MeOH-CH_2Cl_2) to afford 11 mg (57%) of **pendolmycin (1)** as colorless amorphous powder, which was identical with our previous synthetic pendolmycin in all respects.

ACKNOWLEDGMENT

Authors' thanks are due to Research Laboratories, Shionogi & Co. Ltd. for the measurement of elemental analysis This work was supported by a Grant-in-Aid from the Ministry of Education, Science and Culture, which is gratefully acknowledged.

REFERENCES AND NOTES

1. Yamashita, T ; Imoto, M., Isshiki, K ; Sawa, T., Naganawa, S ; Zhu, B -Q.; Umezawa, K *J Nat Prod* **1988**, *51*, 1184
2. Nishiwaki, S., Fujuki, H.; Yoshizawa, S , Suganuma, M ; Furuya-Suguri, H , Okabe, S ; Nakayasu, M , Okabe, K ; Muratake, H , Natsume, M , Umezawa, K., Sakai, S ;Sugimura, T *Jpn J Cancer Res* submitted for publication
3. Okabe, K ; Muratake, H , Natsume, M *Tetrahedron* **1990**, *46*, 5113.
4. Anderson, H. J ; Lee, S -F *Can J Chem* **1965**, *43*, 409
5. Garner, P., Park, J M *J Org Chem* **1987**, *52*, 2361
6. Metal migration from 3-lithio-1-(phenylsulfonyl)indole to 2-lithio derivative was well studied Saulnier, M. G , Gribble, G. W *J Org Chem* **1982**, *47*, 757.
7. Replacement with a sulfur group (PhSSPh, Bu_3P, DMF) and the formation of a dithiocarbonate (NaH, CS_2, MeI, THF) failed affording a complex mixture. Treatment of **8** with thiocarbonyldiimidazole in dichloroethane gave **8** (R=SH) in 48 5% yield Nakagawa, I , Hata, T. *Tetrahedron Lett* **1975**, 1409 Barton, D H R , McCombie, S W *J Chem Soc , Perkin Trans 1* **1975**, 1574.
8. Muratake, H , Natsume, M. *Tetrahedron Lett* **1987**, *28*, 2265
9. Muratake, H., Okabe, K , Natsume, M *Tetrahedron Lett* **1988**, *29*, 6267
10. Scheibye, S , Pederse, B S., Lawesson, S. O *Bull Soc Chim Belg* **1978**, *87*, 229