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TOTAL SYNTHESIS OF INDOLE ALKALOID PENDOLMYCIN

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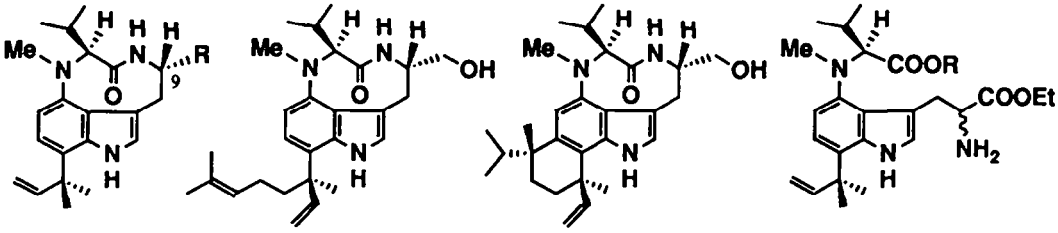
Abstract — The teleocidin class of an indole alkaloid, pendolmycin (**1**) was synthesized from 1-(4-methylphenylsulfonyl)pyrrole in thirteen steps by way of the indole derivative (**16**), the amino-diester compound (**6**), and the ethyl carboxylate (**5**).

Pendolmycin (**1**) is an indole alkaloid, isolated from *Nocardiopsis* strain SA1715 as an inhibitor of EGF (epidermal growth factor) - induced phosphatidylinositol turnover, and has the chemical structure of 7-(2-methyl-3-buten-2-yl)-(–)-indolactam V[1] (Chart 1). This means that pendolmycin belongs to a class of the teleocidin family whose representatives are lyngbyatoxin A (**2**)[2] and teleocidin B-4 (**3**).[3] So pendolmycin (**1**) has biological activities akin to these tumor promoters. It has been reported to inhibit cellular binding of EGF and 12*O*,13-dibutyrylphorbol, and activate arachidonic acid release and 2-deoxyglucose transport.[4]

We initiated the study of pendolmycin (**1**) synthesis at the request of biologists to supply ample amounts of it for specimens, because the above micro-organism does not produce pendolmycin any more. At the same time, we were asked to make our synthesis pathway compatible with the preparation of ^{3}H-labeled pendolmycin (**4**) at the carbinol methylene group being used in a biological study concerning the binding site of pendolmycin (**1**).



1 R = CH_2OH **2** **3** **6** R = t - Bu
4 R = $C[^3H]_2OH$ **7** R = H
5 R = COOEt

Chart 1

Having these demands in mind, we planned the synthesis of pendolmycin (**1**) by way of the carboxylate (**5**) at the final stage, since **5** would be readily reduced to **1** with sodium borohydride whose tritio derivative is commercially available. Another benefit of passing through **5** is that an unnecessary C-9 epimer of **5** could be isomerized to **5**, so that an efficient production of **1** could be achieved without being concerned about the stereochemistry at the C-9 position. This plan enabled us to provide as an essential precursor for **5** an amino-diester derivative (**6**) in which two carboxylic acids were differently esterified. In the compound (**6**), the tertiary butyl ester of the *N*-methylvalinate portion was selectively cleaved to give an amino acid (**7**), which was the required substrate for the formation of the nine-membered lactam ring to produce **5**. Preparation of **6** was carried out principally according to our synthesis of lyngbyatoxin A (**2**)[5] (Chart 2).

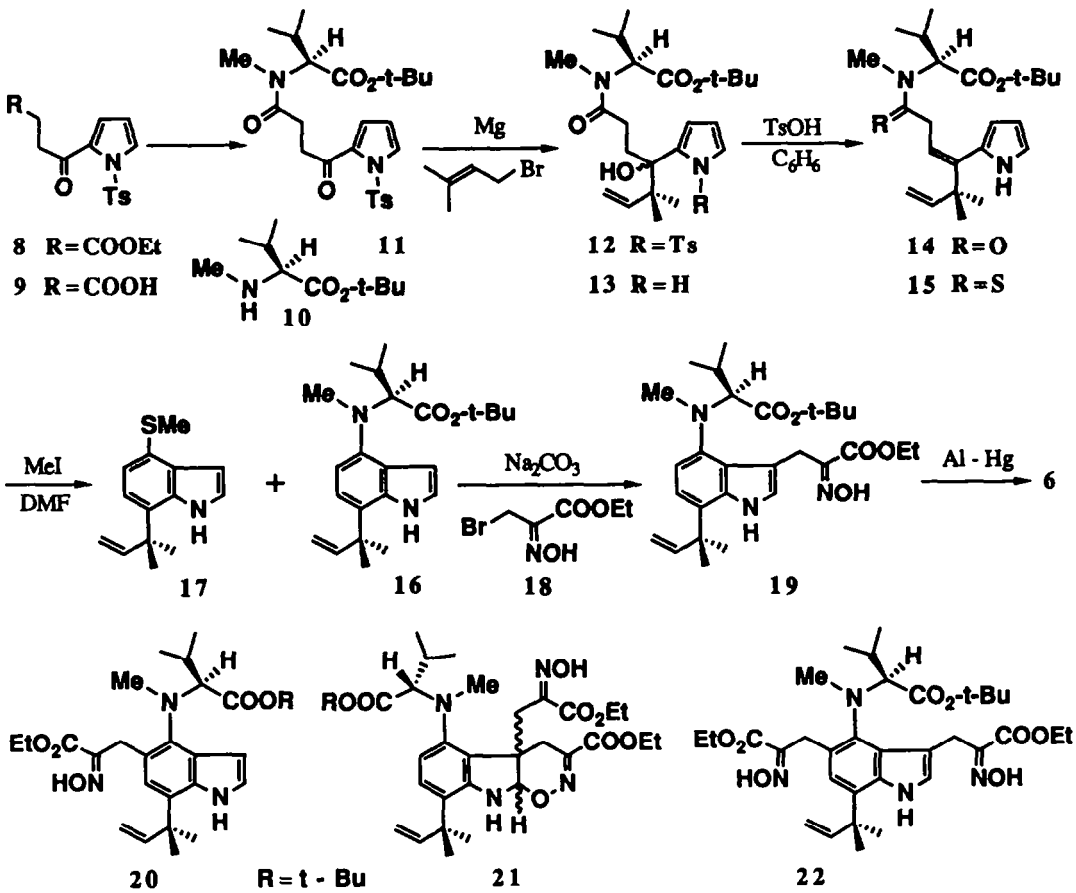


Chart 2

Ethyl 4-[1-(4-methylphenylsulfonyl)-2-pyrrolyl]-4-oxobutanoate (**8**), obtained from 1-(4-methylphenylsulfonyl)pyrrole by the borontrifluoride etherate-catalyzed Friedel-Crafts reaction using ethyl succinyl chloride,[6] was hydrolyzed to the carboxylic acid (**9**) with 2.5% potassium hydroxide in tetrahydrofurn-water (3:1) in 95% yield. This was converted to a mixed anhydride with ethyl chloroformate in the presence of triethylamine, followed by condensation with *t*-butyl L-*N*-methylvalinate (**10**)[7] in tetrahydrofuran to give the amide (**11**) in 89% yield. Introduction of the requisite terpenic side chain was achieved by treating **11** with the Grignard reagent prepared from 3-methyl-2-butenyl (prenyl) bromide at –20°C to afford a mixture of **12** and its detosylated compound (**13**). These were separated over silica gel and the tosyl group of **12** was removed by stirring with magnesium in methanol[8] at room temperature for 2.5 h. Thus the pyrrole derivative (**13**) was obtained in 80% yield calculated from **11** as a mixture of two diastereomers. Dehydration of **13** was carried out by refluxing in benzene with a catalytic amount of *p*-toluenesulfonic acid for 3 min to give **14** in 85% yield, and this was coverted into the thioamide derivative (**15**) in 78% yield using Lawesson reagent[9] in a tetrahydrofuran solution at reflux for 30 min.

Indole formation from **15** was effected by stirring with methyl iodide in dimethylformamide at room temperature for 18 h to afford *t*-butyl L-*N*-methyl-*N*-[7-(2-methyl-3-buten-2-yl)-4-indolyl]valinate (**16**), mp 105

– 106°C, $[\alpha]_D^{21.5}$ –212.5° (*c* 0.55, $CHCl_3$) in 73% yield, accompanied by the formation of **17**, mp 82.5-83°C, in 14% yield. The indole derivative (**16**) was treated with an equimolar amount of ethyl 3-bromo-2-hydroxyimino-propionate (**18**)[10] in the presence of sodium carbonate in dichloromethane at room temperature for 18 h. The desired compound (**19**) was obtained in 57% yield, along with the recovery of **16** in 12.5% yield and a variety of by-products (**20**, **21**, and **22**) in 21%, 3%, and 5% yields, respectively. Using an increased amount of the reagent (**18**) to avoid recovering the starting indole derivative (**16**) only caused the formation of the by-products in much higher yields. Reduction of the hydroxyimino group of **19** was carried out with aluminium amalgam in tetrahydrofuran-water (9:1) at 45 - 50°C for 2 h. No stereochemical control occured during the reduction, and the amino-diester derivative (**6**) was produced in 90% yield as *ca.* a 1:1 mixture of two diastereomers.

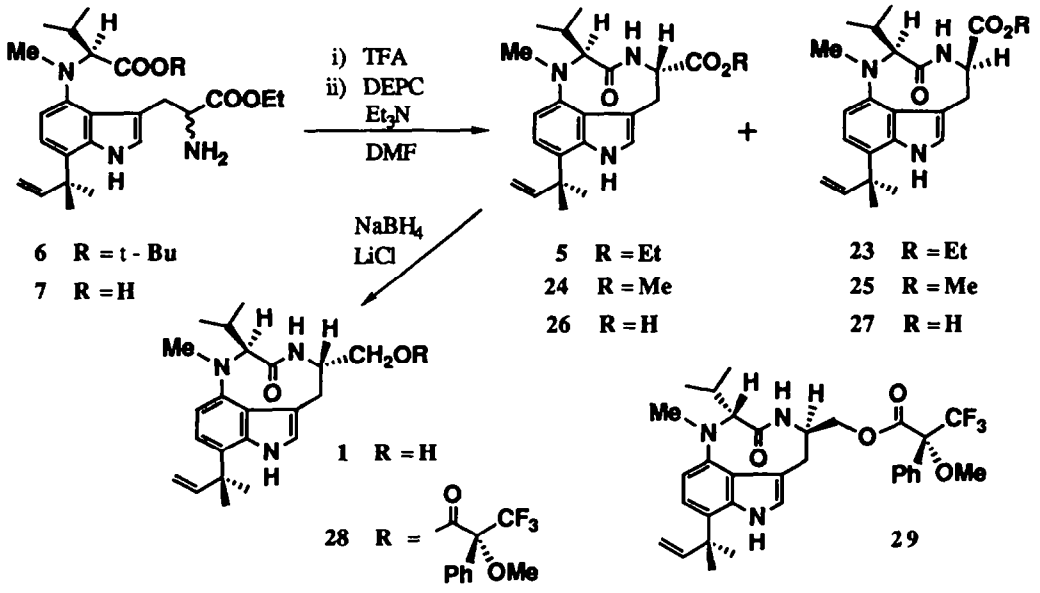


Chart 3

With the necessary compound (**6**) in hand, we studied cleavage of the tertiary butyl ester and the subsequent formation of the nine-membered lactam ring (Chart 3). Notwithstanding the presence of an acid-labile 4-aminoindole skeleton, treatment of **6** with neat trifluoroacetic acid proceeded without trouble for the removal of the tertiary butyl group. After stirring at room temperature (20°C) for 28 h, the reaction mixture was evaporated to dryness under reduced pressure. The residue was then dissolved in dimethylformamide and treated with diethylphosphoryl cyanide (DEPC)[11] in the presence of triethylamine at room temperature for 24 h to afford **5** and its C-9 epimer (**23**) in 47% and 40% yields respectively. Reduction of the ethyl carboxylate group was successful when the compound (**5**) was stirred with a mixture of sodium borohydride and lithium chloride[12] in ethanol and tetrahydrofuran (4:3) at room temperature for 10 h. Colorless amorphous powder, $[\alpha]_D^{25}$ -121° (*c* 0.16, MeOH), obtained in 97% yield, was identified as pendolmycin (**1**) by comparing our ^1H- and ^{13}C-NMR spectral data with those in the literature.[1] The optically pure state of the synthetic material (**1**) was confirmed by the HPLC analysis of its ester (**28**) with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(+)-MTPA]. A standard sample of **29** prepared from the enantiomer of **1**[13] had a different retention time .

Epimerization of the carboxylate group of **23** was next examined using the procedure reported by Nakatsuka *et al.* in their synthesis of (±)-indolactam V.[14] Treatment of **23** with $NaHCO_3$ in methanol at 40°C for 16 h

afforded a mixture of **24**, **25**, **26**, and **27**, so it was treated with diazomethane to give **24** and **25** in 44% yield each. The resulting compound (**24**) was reduced to **1** and further converted to **28** as above. The HPLC analysis showed that no racemization took place during the $NaHCO_3$ treatment of **23**.

Thus a total synthesis of pendolmycin (**1**) was accomplished in thirteen steps starting from 1-(4-methylphenylsulfonyl)pyrrole.

EXPERIMENTAL

General Methods — Melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. High resolution mass spectra (HRMS) were determined on JEOL JMS-DX-300 spectrometer. Optical rorations were measured on JASCO DIP-370 polarimeter. Mass spectra (MS) were taken on Hitachi RMS-4 spectrometer. IR spectra were determined on Hitachi 215 spectrophotometer. ^1H NMR spectra were measured at Varian EM 390 spectrometer (90 MHz) and JOEL JMN-GX-400 (400 MHz) in the solvent stated with tetramethylsilane as an internal reference. ^{13}C NMR spectra were measured on JEOL JMN-GX-400 (100 MHz) and chemical shifts were given in ppm related to the resonance of $CDCl_3$ (77.0 ppm). 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). HPLC was carried out with ODS YMC pack A-324, 10 × 300 mm on Varian 8500. Usual work-up refers to washing the organic layers with water or brine, drying on anhydrous sodium sulfate and evaporation of the solvents under reduced pressure.

4-[1-(4-methylphenylsulfonyl)-2-pyrrolyl]-4-oxobutanoic acid (9) — A solution of 78 mg (0.22 mmol) of the ester (**8**) in 2 ml of 2.5% KOH in THF-H_2O (3:1) was kept at 20°C for 3 h. The reaction mixture was acidified with 0.3 ml of 10% HCl-H_2O and extracted with Et_2O. Usual work-up and PTLC (10% MeOH-CH_2Cl_2) afforded **9** (68 mg, 95%) as colorless prisms, mp 177-178°C (CH_2Cl_2-MeOH). Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 56.06; H, 4.71; N, 4.36. Found: C, 55.96; H, 4.66; N, 4.27. MS *m/z*: 321 (M^+). IR (KBr) cm^{-1}: 1713, 1680. ^1H NMR [90 MHz, $CDCl_3$-CD_3OD (4:1)] δ: 2.41 (3H, s), 2.60 (2H, t, J=7 Hz), 3.04 (2H, t, J=7 Hz), 6.36 (1H, dd, J=3.5, 3.5 Hz), 7.17 (1H, dd, J=3.5, 1.5 Hz), 7.30 and 7.86 (A_2B_2, J=8.5 Hz), 7.77 (1H, dd, J=3.5, 1.5 Hz).

***t*-Butyl L-*N*-Methyl-*N*-[4-[1-(4-methylphenylsulfonyl)-2-pyrrolyl]-4-oxobutanoyl]valinate (11)** — To a solution of 830 mg (2.59 mmol) of **9** in 5 ml of THF and 0.4 ml (2.88 mmol) of Et_3N was added 5.26 ml (2.75 mmol) of 5% v/v $ClCO_2Et$-THF at –20°C and the reaction mixture was stirred for 15 min at that temperature. To this was added at –20°C a solution of 568 mg (3.04 mmol) of the L-valine derivative (**10**) in 3 ml of THF and the mixture was stirred at –20°C for 15 min and at 18°C for 1.5 h. After quenching with sat. $NaHCO_3$-H_2O, the mixture was extracted with CH_2Cl_2. The aqueous layer was made acidic with 30% AcOH-H_2O to pH 4-5 and extracted with CH_2Cl_2. The organic extracts were combined and worked up as usual. Column chromatography over silica gel using CH_2Cl_2 afforded 49 mg (6%) of the recovery of **9** and1.128 g (89%) of **11**,colorless needles, mp 115-116°C (CH_2Cl_2-hexane). Anal. Calcd for $C_{25}H_{34}N_2O_6S$: C, 61.20; H, 6.99; N, 5.71. Found: C, 61.11; H, 7.00; N, 5.82. $[\alpha]_D^{24}$ –62.5° (*c* 0.48, $CHCl_3$). MS *m/z*: 490 (M^+). IR (KBr) cm^{-1}:1731, 1681, 1640. ^1H NMR (90 MHz, $CDCl_3$) δ: 0.75 and 0.95 (3H, d each, J=7 Hz), 0.84 and 0.98 (3H, d each, J=7 Hz), 1.40 and 1.43 (9H, s each), 1.98-2.40 (1H, m), 2.40 (3H, s), 2.52-2.89 (2H, m), 2.89-3.27 (2H, m), 2.81 and 2.98 (3H, s each), 3.86 and 4.75 (1H, d each, J=11 Hz and J=10.5 Hz), 6.33 (1H, dd, J=3.5, 3.5 Hz), 7.18 (1H, dd, J=3.5, 2 Hz), 7.28 and 7.88 (A_2B_2, J=8.5 Hz), 7.77 (1H, dd, J=3.5, 2 Hz).

***t*-Butyl L-*N*-[5,5-Dimethyl-4-hydroxy-4-(2-pyrrolyl)-6-heptenoyl]-*N*-methylvalinate (13)** — To a solution of 209 mg (0.43 mmol) of **11** and 83 mg (3.42 mmol) of Mg in 6.5 ml of THF was added 0.20 ml (1.71 mmol) of 3-methyl-2-butenyl bromide at –20°C and the mixture was stirred under Ar atmosphere at that temperature for 2 h 15 min. Quenching with sat. NH_4Cl-H_2O, extraction with Et_2O, usual work-up and PTLC

[hexane-EtOAc (7:2)] afforded 152 mg of **12** and 31 mg of **13**. The former compound (**12**) was stirred with 165 mg (6.79 mmol) of Mg in 10 ml of MeOH at 20°C for 2.5 h. Addition of sat. NH_4Cl-H_2O, extraction with CH_2Cl_2, usual work-up, and PTLC [hexane-EtOAc (4:1)] afforded 108 mg of **13**. In total 139 mg (80%) of **13** was obtained as colorless syrup. MS *m/z*: 389 ($M^+ - \cdot OH$). IR ($CHCl_3$) cm^{-1}: 1728, 1620. ^1H NMR (90 MHz, $CDCl_3$) δ: 0.75 (d, J=7 Hz), 0.80 (d, J=7 Hz), 1.01 (6H, s), 1.34 and 1.42 (9H, s each), 2.82 and 2.83 (3H, s each), 3.65, 3.67, 4.77 (1H, d each, J=10.5 Hz), 4.77 (OH, s), 5.70-5.89 (1H, m), 6.02-6.21 (1H, m), 6.52-6.73 (1H, m), 8.80 (1H, br s).

***t*-Butyl L-*N*-[5,5-Dimethyl-4-(2-pyrrolyl)-3,6-heptadienoyl]-*N*-methylvalinate (14)** — To a solution of 37 mg (0.091 mmol) of **13** in 4 ml of benzene was added 4 mg of *p*-TsOH·H_2O and the mixture was heated at *ca.* 90°C for 3 min. 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 (5:1)] afforded 30 mg (85%) of **14** as colorless syrup. MS *m/z*: 388 (M^+). IR ($CHCl_3$) cm^{-1}: 1730, 1630. ^1H NMR (90 MHz, $CDCl_3$) δ: 0.82, 0.85, 0.97 and 1.03 (6H, d each, J=7 Hz), 1.21 (6H, s), 1.45 and 1.50 (9H, s each), 1.85-2.50 (1H, m), 2.90 and 2.94 (3H, s each), 3.06 and 3.12 (2H, d each, J=7.5 Hz), 3.75 and 4.78 (1H, d each, J=10.5 Hz), 5.00 (1H, dd, J=10.5, 1.5 Hz), 5.03 (1H, dd, J=18, 1.5 Hz), 5.65 and 5.68 (1H, t each, J=7.5 Hz), 5.95 (1H,dd, J=18, 10.5 Hz), 5.97-6.23 (2H, m), 6.51-6.80 (1H, m), 9.41 (1H, br s).

***t*-Butyl L-*N*-[5,5-Dimethyl-4-(2-pyrrolyl)-3,6-heptadienethioyl]-*N*-methylvalinate (15)** — A solution of 30 mg (0.077 mmol) of **14** in 3 ml of THF was preheated at 80°C for 4 min and 39.5 mg (0.098 mmol) of the Lawesson reagent was added to this. The reaction mixture was stirred under Ar atmosphere at 80°C for 30 min. 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 (6:1)] afforded 24.5 mg (78%) of **15** as colorless syrup. MS *m/z*: 404 (M^+). IR ($CHCl_3$) cm^{-1}: 1628. ^1H NMR (90 MHz, $CDCl_3$) δ: 0.76, 0.81, 0.94 and 1.07 (6H, d each, J=7 Hz), 1.15 (6H, s), 1.40 and 1.43 (9H, s each), 1.97-2.58 (1H, m), 3.03 and 3.30 (3H, s each), 3.47 and 3.57 (2H, d each, J=7.5 Hz), 4.14 and 6.11 (1H, d each, J=10.5 Hz), 4.99 (1H, d, J=10.5 Hz), 5.02 (1H, d, J=18 Hz), 5.68 and 5.69 (1H, t each, J=7.5 Hz), 5.86-6.25 (2H, m), 6.49-6.77 (1H, m), 8.85 (1H, br s).

***t*-Butyl L-*N*-Methyl-*N*-[7-(2-methyl-3-buten-2-yl)-4-indolyl]valinate (16)** — A solution of 95.5 mg (0.24 mmol) of **15** in 3 ml of DMF was stirred with 0.3 ml (4.82 mmol) of MeI under Ar atmosphere at room temperature (20°C) for 18 h. After evaporation of MeI, it was cooled at 0°C, sat. $NaHCO_3$-H_2O was added, and the mixture was extracted with Et_2O. Usual work-up and PTLC [hexane-CH_2Cl_2 (3:2)] gave 64 mg (73%) of the more polar compound (**16**) and 7.5 mg (14%) of the less polar compound (**17**). **16**: Colorless prisms, mp 105-106°C (MeOH-H_2O). Anal. Calcd for $C_{23}H_{34}N_2O_2$: C, 74.56; H, 9.25; N, 7.56. Found: C, 74.49; H, 9.26; N, 7.57. $[\alpha]_D^{21.5}$ −212.5° (*c* 0.55, $CHCl_3$). MS *m/z*: 370 (M^+). IR (KBr) cm^{-1}: 1705. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.95 (3H, d, J=7 Hz), 1.04 (3H, d, J=7 Hz), 1.38 (9H, s), 1.48 (3H, s), 1.50 (3H, s), 2.34 (1H, dqq, J=11, 7, 7 Hz), 3.01 (3H, s), 3.92 (1H, d, J=11 Hz), 5.20 (1H, dd, J=10.5, 1.5 Hz), 5.30 (1H, dd, J=18, 1.5 Hz), 6.21 (1H, dd, J=18, 10.5 Hz), 6.59 (1H, d, J=8 Hz), 6.75 (1H, dd, J=3, 2 Hz), 7.00 (1H, d, J=8 Hz), 7.07 (1H, dd, J=3, 3 Hz), 8.56 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$) ppm: 19.4 (q), 19.8 (q), 27.1 (q), 27.9 (d), 28.0 (q), 33.8 (q), 40.1 (s), 71.1 (d), 80.4 (s), 101.5 (d), 107.4 (d), 111.1 (t), 118.7 (d), 120.9 (s), 121.5 (d), 123.4 (s), 135.3 (s), 144.8 (s), 149.4 (d), 171.2 (s). **17**: 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, $CDCl_3$) 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).

The Compound (19) — To a solution of 112 mg (0.30 mmol) of **16** in 7 ml of CH_2Cl_2 was added 64 mg (0.60 mmol) of Na_2CO_3 and 64 mg (0.30 mmol) of ethyl 3-bromo-2-hydroxyiminopropionate (**18**), and the mixture was stirred under Ar atmosphere at room temperature (20°C) for 18 h. After cooling at 0°C, sat. NH_4Cl-H_2O was added and the mixture was shaken with CH_2Cl_2. Usual work-up and separation by column chromatography over silica gel [from hexane-EtOAc (4:1) to EtOAc] afforded 14 mg (12.5%) of the recovery of

16, 38.5 mg of the crude **20**, 108 mg of the crude **19**, and 27 mg of a crude mixture of **21** and **22**. PTLC (1% EtOH-CH_2Cl_2) of the crude **19** gave 85.5 mg (57%) of the pure **19** as colorless syrup. MS *m/z*: 499 (M^+). IR ($CHCl_3$) cm^{-1}: 1720. ^1H NMR (90 MHz, $CDCl_3$) δ: 1.00 (3H, d, J=7 Hz), 1.11 (3H, d, J=7 Hz), 1.23 (3H, t, J=7 Hz), 1.31 (9H, s), 1.48 (6H, s), 1.94-2.56 (1H, m), 2.88 (3H, s), 3.57 (1H, d, J=7.5 Hz), 4.22 (2H, q, J=7 Hz), 4.46 (2H, s), 5.13 (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), 6.68 (1H, d, J=1.5 Hz), 6.91 (1H, d, J=8 Hz), 7.00 (1H, d, J=8 Hz), 8.34 (1H, br s), 9.83 (1H, br s, OH). PTLC (0.5 % EtOH-CH_2Cl_2) of the crude **20** gave 32 mg (21%) of the pure **20** as colorless syrup. MS *m/z*: 499 (M^+). IR ($CHCl_3$) cm^{-1}: 1720. ^1H NMR (90 MHz, $CDCl_3$, 50°C) δ: 1.00 (3H, d, J=7 Hz), 1.11 (3H, d, J=7 Hz), 1.23 (9H, s), 1.23 (3H, t, J=7 Hz), 1.45 (6H, s), 2.19 (1H, dqq, J=7, 7, 7 Hz), 3.06 (3H, s), 3.56 (1H, br d, J=7 Hz), 4.21 (2H, q, J=7 Hz), 4.34 (1H, d, J=15 Hz), 5.14 (1H, dd, J=10.5, 1.5 Hz), 5.18 (1H, dd, J=18, 1.5 Hz), 6.14 (1H, dd, J=18, 10.5 Hz), 6.59 (1H, dd, J=3, 2 Hz), 6.87 (1H, s), 6.96 (1H, dd, J=3, 3 Hz), 8.38 (1H, br s), 9.50 (1H, br s, OH). PTLC [hexane-EtOAc (3:2)] of the crude mixture of **21** and **22** afforded 10 mg of the crude **21** and 15 mg of the crude **22**, which were separately purified by PTLC using 1% EtOH-CH_2Cl_2 and 2% EtOH-CH_2Cl_2 to give 6 mg (3%) of **21** and 9 mg (5%) of **22**, respectively. **21**: Colorless syrup. MS *m/z*: 628 (M^+). IR ($CHCl_3$) cm^{-1}: 1720. ^1H NMR (90 MHz, $CDCl_3$) δ: 0.97 (3H, d, J=7 Hz), 1.26 (3H, d, J=7 Hz), 1.30 (6H, t, J=7 Hz), 1.39 (15H, s), 2.67 and 2.82 (3H, s each), 4.19 and 4.27 (4H, q, J=7 Hz), 5.11-5.31 (1H, NH), 5.95 (1H, dd, J=18, 10.5 Hz), 6.69 (1H, d, J=8 Hz), 6.98 (1H, d, J=8 Hz), 8.70 (1H, br s, OH). **22**: Colorless syrup. MS *m/z*: 628 (M^+). IR ($CHCl_3$) cm^{-1}: 1728. ^1H NMR (90 MHz, $CDCl_3$) δ: 3.01 and 3.04 (3H, s each), 4.48, (1H, d, J=15 Hz), 4.78 (1H, d, J=15 Hz), 5.13 (1H, d, J= 10.5), 5.22 (1H, d, J=18 Hz), 6.12 (1H, dd, J=18, 10.5 Hz), 6.63 and 6.68 (1H, s each), 8.24 (1H, br s), 10.06 (2H, br s, OH).

The Compound (6) — A solution of 177 mg (0.355 mmol) of **19** in 13.5 ml of THF and 1.5 ml of H_2O was stirred with Al-Hg, prepared from 272 mg (10.1 mmol) of Al, under Ar atmosphere at 45-50°C for 2 h. The reaction mixture was passed through a celite bed, the celite was washed with CH_2Cl_2 and then with 10% EtOH-CH_2Cl_2, and the combined filtrates were worked up as usual. PTLC (3% EtOH-CH_2Cl_2) afforded 155.5 mg (90%) of **6** as colorless syrup. MS *m/z*: 485 (M^+). IR ($CHCl_3$) cm^{-1}: 1728. ^1H NMR (400 MHz, $CDCl_3$, 50°C) (*ca.* a 1:1 mixture of two diastereomers) δ: 1.00, 1.01, 1.11 and 1.12 (6H, d each, J=7 Hz), 1.18 and 1.23 (3H, t each, J=7 Hz), 1.20 and 1.21 (9H, s each), 1.47, 1.48, 1.48, 1.49 (6H, s each), 1.67 (2H, NH_2), 2.27 and 2.28 (1H, dqq each, J=7, 7, 7 Hz), 2.84 and 2.85 (3H, s each), 3.10 and 3.27 (1H, dd each, J=15, 9 Hz), 3.51 and 3.53 (1H, d each, J=7 Hz), 3.55 and 3.64 (1H, br dd and ddd, J=15, 5.5 Hz and J=15, 5, 1 Hz), 3.85 and 3.93 (1H, dd each, J=9, 5.5 Hz and J=9, 5 Hz), 4.13 and 4.16 (2H, q each, J=7 Hz), 5.19 and 5.20 (1H, dd each, J=11, 1 Hz), 5.27 (1H, dd, J=18, 1 Hz), 6.18 and 6.19 (1H, dd each, J=18, 11 Hz), 6.93 (1H, d, J=8 Hz), 6.96 and 6.98 (1H, d each, J=3 Hz), 6.99 (1H, d, J=8 Hz), 8.40 (1H, br s).

The Compound (5) and The Compound (23) — A solution of 50 mg (0.10 mmol) of **6** in 4.5 ml of trifluoroacetic acid (TFA) was stirred under Ar atmosphere at 20°C for 28 h. Evaporation of TFA at room temperature, followed by the two times operation of addition of 3 ml of CH_2Cl_2 and evaporation of the solvent afforded the carboxylic acid (**7**). After drying over P_2O_5 *in vacuo* at 20°C for 17 h, **7** was dissoved in 3.5 ml of DMF and treated with 1.43 ml (0.51 mmol) of 5% v/v Et_3N/DMF and 0.51 ml (0.16 mmol) of 5% w/v DEPC/DMF under Ar atmosphere at 20°C for 24 h. The reaction mixture was cooled at 0°C, quenched with sat. $NaHCO_3$-H_2O, and extracted with Et_2O. Usual work-up and PTLC [hexane-EtOAc (3:1)] afforded 21 mg of **5** and 18 mg of **23**. These were further purified by PTLC (0.5% EtOH-CH_2Cl_2) to give 20 mg (47%) of **5** and 17 mg (40%) of **23**. **5**: Colorless syrup. HRMS Calcd for $C_{24}H_{33}N_3O_3$: 411.252. Found: 411.253. $[\alpha]_D^{21.5}$ –85° (*c* 0.60, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 1737, 1670. ^1H NMR (400 MHz, $CDCl_3$) (*ca.* a 4:3 mixture of two conformers) δ: (major conformer) 0.93 (3H, d, J=7 Hz), 1.24 (3H, t, J=7 Hz), 1.25 (3H, d, J=7 Hz), 1.51 (6H, s), 2.38 (1H, dqq, J=11, 7, 7 Hz), 2.73 (3H, s), 3.03 (1H, d, J=11 Hz), 3.15 (1H, dd, J=14, 2 Hz), 3.20 (1H, dd, J=14, 5 Hz), 4.10 (1H, dq, J=11, 7 Hz), 4.16 (1H, dq, J=11, 7 Hz), 5.09 (1H, ddd, J=11, 5, 2 Hz), 5.22 (1H, d, J=11 Hz), 5.25 (1H, dd, J=11, 1.5 Hz), 5.34 (1H, dd, J=18, 1.5 Hz), 6.21 (1H, dd, J=18, 11 Hz),

6.84 (1H, d, J=2.5 Hz), 7.01 (1H, d, J=8 Hz), 7.11 (1H, d, J=8 Hz), 8.66 (1H, br s); (minor conformer) 0.67 (3H, d, J=7 Hz), 0.93 (3H, d, J=7 Hz), 1.23 (3H, t, J=7 Hz), 1.50 (3H, s), 1.52 (3H, s), 2.62 (1H, dqq, J=10, 7, 7 Hz), 2.90 (3H, s), 3.27 (1H, d, J=17 Hz), 3.60 (1H, d, J=17.5 Hz), 4.19 (1H, dq, J=11, 7 Hz), 4.23 (1H, d, J=10 Hz), 4.24 (1H, dq, J=11, 7 Hz), 5.03-5.08 (1H, m), 5.23 (1H, dd, J=11, 1.5 Hz), 5.35 (1H, dd, J=18, 1.5 Hz), 6.21 (1H, dd, J=18, 11 Hz), 6.53 (1H, d, J=8 Hz), 6.73 (1H, br d, J=2 Hz), 6.88-6.91 (1H, m), 7.02 (1H, d, J=8 Hz), 8.55 (1H, br s). **23**: Colorless syrup. HRMS Calcd for $C_{24}H_{33}N_3O_3$: 411.252. Found: 411.253. $[\alpha]_D^{21.5}$ −161° (*c* 0.62, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 1740, 1660. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.72 (3H, d, J=7 Hz), 0.75 (3H, d, J=7 Hz), 1.39 (3H, t, J=7 Hz), 1.48 (3H, s), 1.51 (3H, s), 2.66 (1H, dqq, J=10.5, 7, 7 Hz), 3.10 (3H, s), 3.26 (1H, dd, J=15, 4 Hz), 3.48 (1H, dd, J=15, 3 Hz), 3.74 (1H, d, J=10.5 Hz), 4.32 (1H, dq, J=11, 7 Hz), 4.38 (1H, dq, J=11, 7 Hz), 4.46 (1H, ddd, J=7, 4, 3 Hz), 5.21 (1H, dd, J=10.5, 1 Hz), 5.31 (1H, dd, J=18, 1 Hz), 6.19 (1H, dd, J=18, 10.5 Hz), 6.64 (1H, d, J=7 Hz), 6.76 (1H, d, J=8 Hz), 6.93 (1H, d, J=2.5 Hz), 6.99 (1H, d, J=8 Hz), 8.48 (1H, br s).

Pendolmycin (1) — To a solution of 19 mg (0.046 mmol) of **5** in 2 ml of EtOH and 1.5 ml of THF was added 39 mg of LiCl and 35 mg of $NaBH_4$. After stirring under Ar atmosphere at 20°C for 10 h, H_2O was added, the mixture was extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4. Evaporation of the solvent and PTLC[hexane-EtOAc (1:3)] gave 17.5 mg of **1**, which was further purified by PTLC (4% MeOH-CH_2Cl_2) to afford 16.5 mg (97%) of **1** as colorless amorphous powder. HRMS Calcd for $C_{22}H_{31}N_3O_2$: 369.242. Found: 369.242. $[\alpha]_D^{21.5}$ −121° (*c* 0.16, MeOH). *cf.* Lit.[1] $[\alpha]_D$ −154° (*c* 0.1, MeOH). IR ($CHCl_3$) cm^{-1}: 1660. ^1H NMR (400 MHz, $CDCl_3$-D_2O) (*ca.* a 5:1 mixture of two conformers) δ: (major conformer) 0.65 (3H, d, J=7 Hz), 0.92 (3H, d, J=7 Hz), 1.48 (3H, s), 1.51 (3H, s), 2.58 (1H, dqq, J=10, 7, 7 Hz), 2.90 (3H, s), 3.05 (1H, dd, J=17, 4 Hz), 3.15 (1H, d, J=17 Hz), 3.55 (1H, dd, J=12, 8 Hz), 3.73 (1H, dd, J=12, 4 Hz), 4.28-4.38 (1H, m), 4.34 (1H, d, J=10 Hz), 5.21 (1H, dd, J=11, 1 Hz), 5.32 (1H, dd, J=18, 1 Hz), 6.19 (1H, dd, J=18, 11 Hz), 6.48 (1H, d, J=8 Hz), 6.82-6.87 (1H, m), 7.00 (1H, d, J=8 Hz), 8.48 (1H, br s); (minor conformer) 0.93 (3H, d, J=7 Hz), 1.25 (3H, d, J=7 Hz), 1.52 (3H, s), 1.53 (3H, s), 2.38 (1H, dqq, J=11, 7, 7 Hz), 2.73 (3H, s), 2.81 (1H, dd, J=15, 2 Hz), 2.99 (1H, d, J=11 Hz), 3.38 (1H, dd, J=11, 7 Hz), 3.45 (1H, dd, J=11, 6.5 Hz), 4.39-4.48 (1H, m), 5.27 (1H, dd, J=11, 1 Hz), 5.36 (1H, dd, J=18, 1 Hz), 6.21 (1H, dd, J=18, 11 Hz), 6.97 (1H, d, J=2 Hz), 7.02 (1H, d, J=8 Hz), 7.12 (1H, d, J=8 Hz), 8.72 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$) ppm: (major conformer) 19.6 (q), 21.6 (q), 26.7 (q), 27.2 (q), 28.5 (d), 33.1 (q), 33.9 (t), 40.1 (s), 55.8 (d), 65.1 (t), 71.0 (d), 106.4 (d), 111.3 (t), 114.2 (s), 118.7 (s), 119.0 (d), 121.0 (d), 122.8 (s), 137.4 (s), 146.5 (s), 149.5 (d), 174.5 (s).

The MTPA Ester (28) — A solution of 2.5 mg of **1** in 0.4 ml of pyridine was treated with 51 mg of the acid chloride derived from (*R*)-(+)-MTPA at 20°C for 1 h 45 min. The reaction mixture was cooled at 0°C, quenched with sat. $NaHCO_3$-H_2O and extracted with CH_2Cl_2. Usual work-up and PTLC[hexane-EtOAc (4:1)] afforded 3.5 mg (88%) of **28** as colorless syrup. MS *m/z*: 585 (M^+). IR ($CHCl_3$) cm^{-1}: 1750, 1675. ^1H NMR (90 MHz, $CDCl_3$-D_2O) δ: 1.51 and 1.52 (6H, s each), 2.72 and 2.83 (3H, s each), 3.51 (3H, s), 8.48 and 8.68 (1H, br s each). Conditions for HPLC analysis of **28** were as follows; mobile phase: MeOH-H_2O (88:12); flow rate: 1.0 ml/min. The MTPA ester (**28**) showed one peak at 73.5 min of the retention time, while the compound (**29**)[13] at 76.4 min.

The Compound (24) and The Compound (25) — A solution of 17.5 mg (0.043 mmol) of **23** and 715 mg of $NaHCO_3$ in 3.5 ml of MeOH was stirred under Ar atmosphere at 40°C for 16 h. After cooling, H_2O was added and the mixture was extracted with EtOAc. The organic layer was worked up as usual to give 13.5 mg of a residue, which contained **24** as a major product and **25** as a minor product. The aqueous layer was acidified to *ca.* pH 3-4 with 1*N* HCl-H_2O at 0°C and extracted with EtOAc. Usual work-up gave a mixture of the carboxylic acids (**26** and **27**), whose MeOH solution (2.0 ml) was treated with CH_2N_2 in Et_2O at 0°C. It was quenched with AcOH, made alkaline by addition of sat. $NaHCO_3$-H_2O and extracted with EtOAc. Usual work-up gave 4 mg of the residue, in which **25** was predominant. This was combined with the above organic residue and purified by PTLC [hexane-EtOAc (5:2)] to give 8 mg each of **24** and **25**. Both were purified further by PTLC

(0.5% MeOH-CH_2Cl_2) to give 7.5 mg (44%) of **24** and 7.5 mg (44%) of **25**. **24**: Colorless syrup. HRMS Calcd for $C_{23}H_{31}N_3O_3$: 397.237. Found: 397.236. $[\alpha]_D^{21.5}$ –77° (*c* 0.36, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 1742, 1672. ^1H NMR (400 MHz, $CDCl_3$) (*ca.* a 4:3 mixture of two conformers) δ: (major conformer) 0.93 (3H, d, J=7 Hz), 1.25 (3H, d, J=7 Hz), 1.52 (6H, s), 2.38 (1H, dqq, J=11, 7, 7 Hz), 2.73 (3H, s), 3.02 (1H, d, J=11 Hz), 3.14 (1H, dd, J=15, 2 Hz), 3.20 (1H, dd, J=15, 5 Hz), 3.68 (3H, s), 5.12 (1H, ddd, J= 11, 5, 2 Hz), 5.22 (1H, d, J=11 Hz), 5.26 (1H, dd, J=11, 1 Hz), 5.35 (1H, dd, J=18, 1 Hz), 6.21 (1H, dd, J=18, 11 Hz), 6.84 (1H, d, J=2.5 Hz), 7.01 (1H, d, J=8 Hz), 7.11 (1H, d, J=8 Hz), 8.66 (1H, br s); (minor conformer) 0.66 (3H, d, J=7 Hz), 0.93 (3H, d, J=7 Hz), 1.49 (3H, s), 1.51 (3H, s), 2.62 (1H, dqq, J=10, 7, 7 Hz), 2.90 (3H, s), 3.27 (1H, d, J=17 Hz), 3.60 (1H, d, J=17, 5 Hz), 3.75 (3H, s), 4.22 (1H, d, J=10 Hz), 5.09-5.12 (1H, m), 5.23 (1H, dd, J=11, 1.5 Hz), 5.34 (1H, dd, J=18, 1.5 Hz), 6.20 (1H, dd, J=18, 11 Hz), 6.52 (1H, d, J=8 Hz), 6.73 (1H, br d, J=2 Hz), 6.89-6.92 (1H, m), 7.01 (1H, d, J=8 Hz), 8.54 (1H, br s). **25**: Colorless prisms, mp 226-227°C (MeOH-H_2O). Anal. Calcd for $C_{23}H_{31}N_3O_3$: C, 69.50; H, 7.86; N, 10.57. Found: C, 69.53; H, 7.65; N, 10.73. HRMS Calcd for $C_{23}H_{31}N_3O_3$: 397.237. Found: 397.236. $[\alpha]_D^{21.5}$ –206° (*c* 0.24, $CHCl_3$). MS *m/z*: 397 (M^+). IR (KBr) cm^{-1}: 1745, 1655. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.72 (3H, d, J=7 Hz), 0.75 (3H, d, J=7 Hz), 1.48 (3H, s), 1.51 (3H, s), 2.66 (1H, dqq, J=10.5, 7, 7 Hz), 3.10 (3H, s), 3.27 (1H, dd, J=15, 4 Hz), 3.48 (1H, dd, J=15, 3 Hz), 3.74 (1H, d, J=10.5 Hz), 3.91 (3H, s), 4.48 (1H, ddd, J=7, 4, 3 Hz), 5.22 (1H, dd, J=11, 1 Hz), 5.32 (1H, dd, J=18, 1 Hz), 6.19 (1H, dd, J=18, 11 Hz), 6.64 (1H, d, J=7 Hz), 6.76 (1H, d, J=8 Hz), 6.94 (1H, d, J=2.5 Hz), 6.99 (1H, d, J=8 Hz), 8.47 (1H, br s). The compound (**24**, 2 mg) was converted into the MTPA ester (**28**) (2 mg, 68%). HPLC analysis data of this MTPA ester showed a single peak using the same conditions as above.

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