Meisenheimer Rearrangement of Azetopyridoindoles. VI.[1] Synthesis of 12-Carbaeudistomin and Related Compounds

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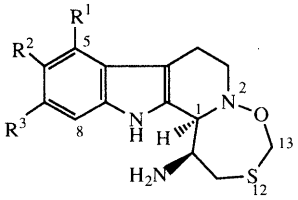
For structure–activity relationship investigation of eudistomins 1, 12-carbaeudistomin 3, its 1,10-*trans* isomer 4, and 11,12-didehydro-12-carbaeudistomin 5 have been synthesized. The [2,3]-Meisenheimer rearrangement of the corresponding N-oxide of the 2-vinylazetopyridoindole 12a bearing a benzenesulfonyl group as a protective group of the indole nitrogen atom afforded the oxazepino ester 14, which was easily isomerized to 20a. Compounds 3 and 4 were synthesized from 14 and 20a, respectively, according to the following reaction sequences [hydrogenation of the double bond (Pd–C/H_2), desulfonylation (Mg in MeOH), hydrolysis ($AlBr_3$–EtSH), and Curtius rearrangement (a mixed anhydride method using NaN_3), followed by debenzylation (Pd–C/H_2)]. The Curtius reaction of the carboxylic acid 27 using DPPA gave the carbamate 29, which was subjected to debenzylation ($AlBr_3$–EtSH) followed by desulfonylation ($LiAlH_4$) to afford 5. Evaluation of anti-influenza virus activities of the amino compounds 3, 4, and 5 revealed that 12-carbaeudistomin 3 possesses a specific activity against influenza virus B.

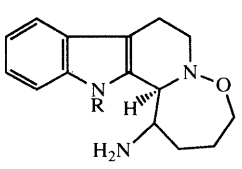
Keywords 12-carbaeudistomin; 11,12-didehydro-12-carbaeudistomin; Meisenheimer rearrangement; azetopyridoindole; Curtius reaction; antivirus activity

Previously, we reported[1] the synthesis of 9-methyl-12-carbaeudistomin (**2**) and some related compounds in order to cast light on the structure–activity relationship of eudistomins **1**[3] which had been shown to possess a strong antiviral activity against *Herpes simplex* virus-1 (HSV-1). Some of the synthesized compounds exhibited slight antiviral activity. Being encouraged by this result, we synthesized 12-carbaeudistomin **3**[4] and its 1,10-*trans* isomer **4** as well as 11,12-didehydro-12-carbaeudistomin (**5**) through a ring expansion of azetopyridoindole **12**, *via* the [2,3]-Meisenheimer rearrangement of the corresponding N-oxide as a key reaction. This paper describes these results.

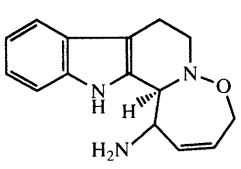
We first explored preparation of the azetopyridoindole **12a**, having a benzenesulfonyl group as a protective group of the indole nitrogen, as a key intermediate for the synthesis of target compounds (**3**—**6**) (Chart 1). Treatment of the tetrahydro-β-carbolineacetate **7** with benzenesulfonyl chloride and sodium hydride (NaH) in dimethyl formamide (DMF) followed by catalytic debenzylation (10% Pd–C/H_2) of the resulting sulfonate **8** gave the ester **9** in 65% overall yield. Reaction of **9** with di-*tert*-butyl dicarbonate (Boc_2O) gave the carbamate **10** in 91% yield. Aldol condensation of **10** with acrolein in the presence of lithium diisopropylamide (LDA) at −78 °C in tetrahydrofuran (THF) gave the allyl alcohol **11** as an oily mixture of diastereomers in good yield. This product was then treated with methanesulfonyl chloride (MsCl) and triethylamine (TEA) in methylene dichloride (CH_2Cl_2) at room temperature followed by the de-Boc group with dry hydrogen chloride in ethyl acetate (EtOAc). The resulting crude oil, without purification, was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dimethyl sulfoxide (DMSO) to give a mixture of the azetidine **12a** (43%) [MS *m/z*: 422 (M^+)] and the oxazinone **13** (9%) [MS *m/z*: 466 (M^+)], after purification by column chromatography. The stereochemistry of the four-membered unit in **12a** was established through a comparison of the ^{1}H-NMR spectral data [δ 3.38 (dd, J=3.0, 9.0 Hz, 1-H), 4.22 (dd, J=7.0, 9.0 Hz, 2-H), and 5.23 (br s, 10b-H)] with those of the 10-methylazetidine **12b**[5] [δ 3.13 (dd, J=3.0, 8.0 Hz, 1-H), 4.33 (t, J=8.0 Hz, 2-H), and 5.10 (br s, 10b-H)]. The second product **13** was assigned as the indolopyrido[1,3]oxazine on the basis of the spectral data



1 eudistomins
L: R^1=R^3=H, R^2=Br
K: R^1=R^2=H, R^3=Br
C: R^1=H, R^2=OH, R^3=Br
E: R^1=Br, R^2=OH, R^3=H



2: R=Me, β-NH_2 (9-methyl-12-carbaeudistomin)[a]
3: R=H, β-NH_2 (12-carbaeudistomin)
4: R=H, α-NH_2



5: β-NH_2 (11,12-didehydro-12-carbaeudistomin)
6: α-NH_2

a) eudistomin-type numbering is used for compounds **2**–**5**

Fig. 1

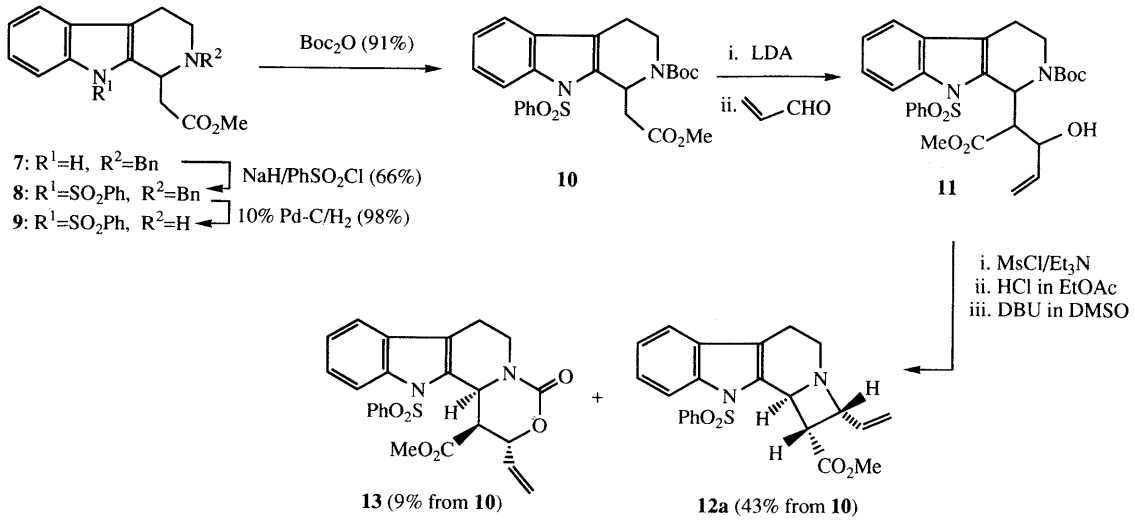


Chart 1

and elemental analysis (see Experimental). The stereochemistry was determined, based on a comparison of the ^{1}H-NMR data with those of the corresponding 12-methyl derivative.[5]

Oxidation of **12a** with *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2[6] afforded a new substance, to which we assigned the oxazepine structure **14** (80%) [MS *m/z*: 438 (M^+)] formed by the [2,3]-Meisenheimer rearrangement of the corresponding N-oxide of **12a**. Catalytic hydrogenation (5% Pd–C/H_2) of **14** in MeOH gave the dihydro derivative **15** quantitatively. Desulfonylation of **15** was most effectively carried out by reduction with Mg in MeOH[7] at 40 °C to yield **16**. The conversion of the ester group to the amino group was principally performed according to our previous method.[1] Thus, treatment of **16** with the aluminum tribromide ($AlBr_3$)–ethanethiol (EtSH)[8] gave the carboxylic acid **18** in quantitative yield. Reaction of **18** with ethyl chloroformate in the presence of TEA followed by the addition of sodium azide (NaN_3) gave the acyl azide. Without purification, this product was heated with benzyl alcohol in benzene at 65 °C to give the benzyl carbamate **19** by Curtius rearrangement in 54% overall yield. The desired amine **4** was obtained by catalytic debenzylation (10% Pd–C/H_2) of **19** in 90% yield. We next investigated the synthesis of the β-amino derivative (12-carbaeudistomin, **3**). Upon treatment of **14** with DBU in benzene at room temperature for 24 h, isomerization at the 1-position was observed to give **20a** in 73% yield with recovery of **14** in 14% yield. This result indicates that the β-isomer **20a** is more stable than the α-isomer **14**. Definitive information was not provided by the ^{1}H-NMR data, since the signal of 13b-H in **20a**, observed as a broad singlet at δ 4.89, was very similar to that of **14**. However, formation of the conjugate ester **17** from **14** and **20a** by treatment with 1 N NaOH strongly suggested the structure **20a**. In the preceding paper,[1] we reported the synthesis of **20b** by the [2,3]-Meisenheimer rearrangement of the N-oxide of **21b**, which was obtained by treatment of **12b** with NaOMe. However, reaction of **12a** with NaOMe gave none of the isomerized product **21a** with only the starting material being recovered. Catalytic hydrogenation (5% Pd–C/H_2) of **20a** gave the dihydro derivative **22**, which could not be obtained by isomerization of **15** under basic conditions. Indeed, treatment of **17** or **14** with Mg in MeOH selectively gave **16** in 77% or 94% yield, respectively. It is known that α,β-unsaturated esters containing an isolated double bond are reduced by Mg in MeOH to give saturated esters with retention of the isolated double bond.[9] Thus, it may be concluded that **14** was reduced to **16** *via* **17**. Compound **22** was then subjected to the same sequence as that used for the preparation of **4** to obtain the target compound **3** [namely; i) desufonylation (91%) of **22** with Mg–MeOH, ii) hydrolysis (100%) of **23** with $AlBr_3$–EtSH, iii) Curtius reaction (58%) of **24** by a mixed anhydride method, iv) catalytic debenzylation (86%) of **25**].

Our attention was next turned to the synthesis of 11,12-didehydro-12-carbaeudistomin (**5**) and its isomer **6** (Fig. 1 and Chart 3). As previously reported,[1] hydrolysis of the unsaturated esters **14** and **20a** was successfully carried out by treatment with $AlBr_3$–EtSH to give the carboxylic acids **26** and **27** without migration of the double bond. While application of the Curtius rearrangement to the carboxylic acids by the mixed anhydride method did not give good results, the benzyl carbamate **29** was obtained in 41% yield by treatment of **27** with diphenylphosphoryl azide (DPPA)[10] in the presence of benzyl alcohol in benzene. However, we could not obtain the α-isomer **28** from **26**. Recently, it has been reported[11] that 1,8-bis(dimethylamino)naphthalene (Proton Sponge™) is superior to TEA in the Curtius rearrangement using DPPA. The Proton Sponge did not, however, improve the yield of the carbamate **29**. Treatment of **29** with $AlBr_3$–EtSH gave the amine **30** in moderate yield. Finally, reductive desulfonylation of **30** was successfully performed by $LiAlH_4$ to afford 11,12-didehydro-12-carbaeudistomin (**5**) in 62% yield, although reaction with Mg–MeOH failed to give the desired compound.

Anti-influenza virus activity of the amino derivatives **3**, **4**, and **5** synthesized here was investigated. It is very interesting to note that 12-carbaeudistomin (**3**), which has the same stereochemistry at both C-1 and C-10 as the natural eudistomins **1**, possessed significant activity

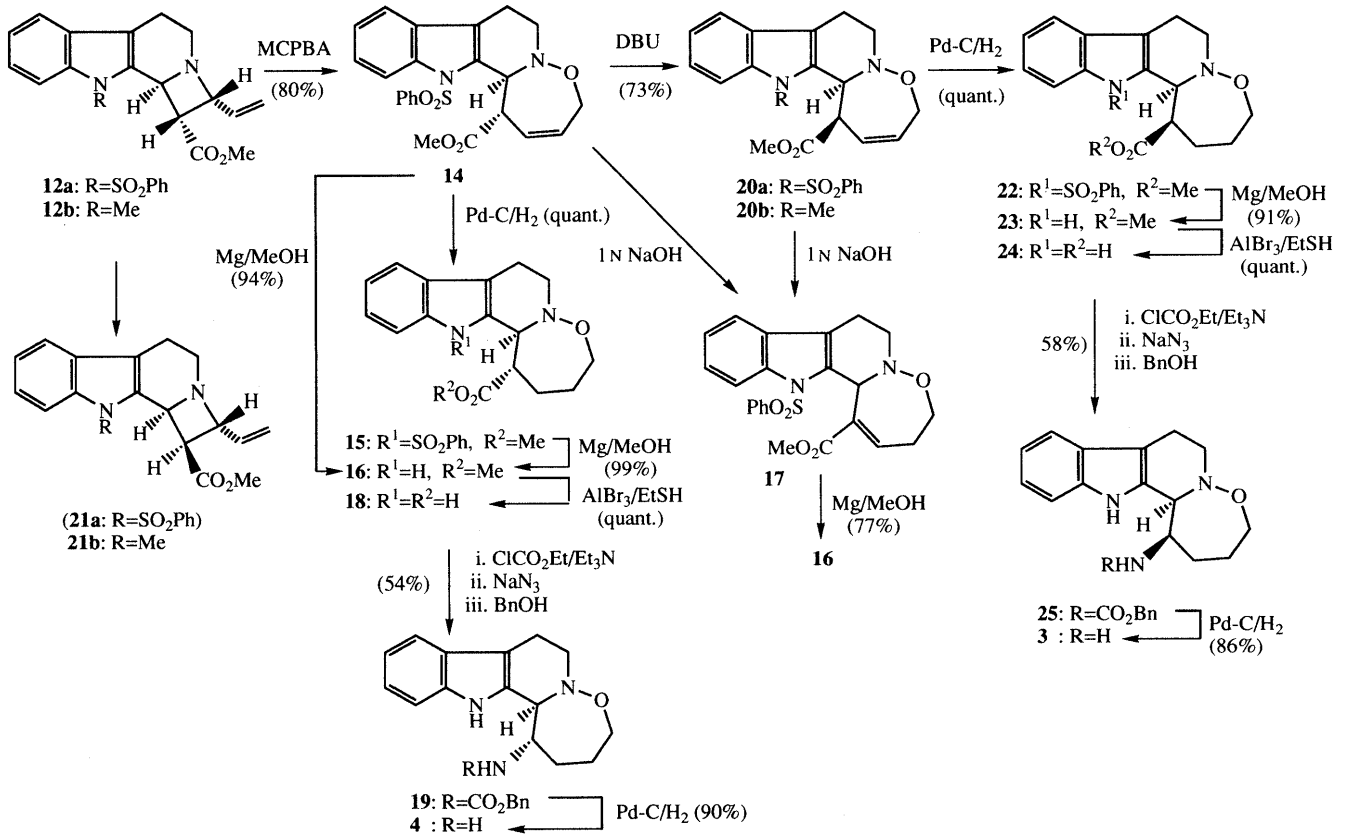


Chart 2

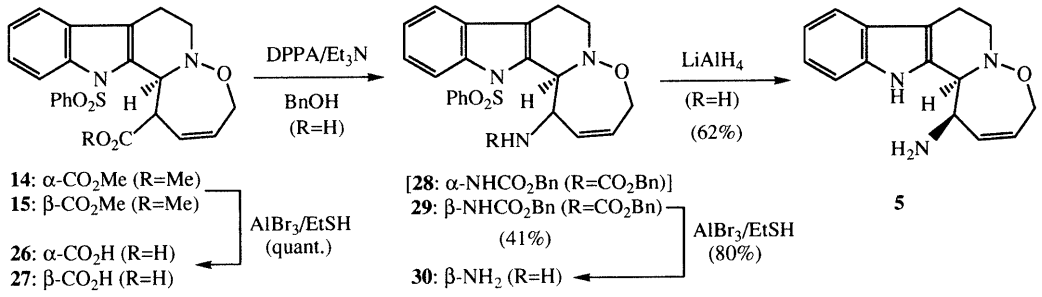


Chart 3

specifically against influenza virus B (MIC, $<1\,\mu g/ml$), whereas no significant anti-influenza virus A activity (4—5 $\mu g/ml$) was found. Details of these results will be reported in the near future.

Experimental

Melting points were determined on a Yanagimoto apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-435 spectrophotometer. ^{1}H-NMR spectra were determined with a Varian Gemini-200 spectrometer in $CDCl_3$, and MS with a Hitachi M-80 instrument. All reactions were carried out under a nitrogen atmosphere. For column chromatography, SiO_2 (Merck Art 9385) was used.

Methyl 9-Benzenesulfonyl-2-benzyl-1,2,3,4-tetrahydro-β-carboline-1-acetate (8) A solution of **7**[12] (3.01 g, 9 mmol) in DMF (5 ml) was added to a suspension of 60% NaH (432 mg, 10.8 mmol) in DMF (2 ml) with stirring at 10—15 °C. Stirring was continued for 1 h, then a solution of benzenesulfonyl chloride (3.19 g, 18 mmol) in DMF (3 ml) was added dropwise with external cooling with ice-water, and the mixture was stirred for an additional 20 min at room temperature. The reaction was quenched with water, and the mixture was made alkaline with saturated $NaHCO_3$ solution to decompose excess benzenesulfonyl chloride, and the solution was extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual solid was recrystallized from EtOH to give **8** (2.81 g, 66%), mp 172—173 °C. IR (Nujol): 1730 (CO), 1370 and 1160 (SO_2) cm^{-1}. ^{1}H-NMR δ: 2.38—3.20 (5H, m, 3-H_2, 4-H_2, C<u>H</u>HCOOCH$_3$), 3.30 (1H, dd, J=2.0, 15.0 Hz, C<u>H</u>H<u>H</u>COOCH$_3$), 3.61 (2H, s, CH_2Ar), 3.71 (3H, s, COOCH$_3$), 4.76 (1H, dd, J=3.0, 10.5 Hz, 1-H), 7.14—7.60 (11H, m, ArH), 7.69 (2H, d, J=7.5 Hz, ArH), 8.20 (1H, d, J=7.5 Hz, 8-H). MS *m/z*: 474 (M$^+$). *Anal.* Calcd for $C_{27}H_{26}N_2O_4S$: C, 68.33; H, 5.52; N, 5.90. Found: C, 68.19; H, 5.53; N, 5.91.

Methyl 9-Benzenesulfonyl-1,2,3,4-tetrahydro-β-carboline-1-acetate (9) A solution of **8** (11 g, 23 mmol) in MeOH (500 ml) containing concentrated HCl (3 ml) was hydrogenated using a Skita apparatus under an initial pressure of 5 kg/cm^2 with 10% Pd–C (2.2 g) for 18 h. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated *in vacuo*. The residue was neutralized with saturated $NaHCO_3$ solution and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was recrystallized from EtOH to give **9** (8.69 g, 98%), mp 142—143 °C. IR (KBr): 3400 (NH), 1720 (CO), 1340 and 1160 (SO_2) cm^{-1}. ^{1}H-NMR δ: 2.62—3.20 (5H, m, 3-H_2, 4-H_2, C<u>H</u>HCOOCH$_3$), 3.27 (1H, dd, J=2.0, 15.5 Hz, CH<u>H</u>COOCH$_3$), 3.75 (3H, s, CO_2CH_3), 5.0 (1H, d, J=10.0 Hz, 1-H), 7.14—7.55 (6H, m, ArH), 7.68 (2H, d, J=7.5 Hz, ArH), 8.13 (1H, d, J=7.5 Hz, 8-H). *Anal.* Calcd for $C_{20}H_{20}N_2O_4S$: C, 62.48; H, 5.24;

N, 7.29. Found: C, 62.44; H, 5.24; N, 7.22.

Methyl 9-Benzenesulfonyl-2-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-β-carboline-1-acetate (10) A solution of Boc_2O (6.5 g, 30 mmol) in THF (10 ml) was added to a solution of **9** (10.4 g, 27 mmol) and 4-dimethylaminopyridine (33 mg, 0.27 mmol) in THF (50 ml), and the whole was stirred for 30 min, then concentrated to give a solid. This was recrystallized from EtOH to give **10** (11.9 g, 91%), mp 120—121 °C. IR (Nujol): 1720 and 1680 (CO), 1360 and 1160 (SO_2) cm^{-1}. ^{1}H-NMR δ: 1.50 [9H, s, $COOC(CH_3)_3$], 2.48—3.46 (5H, m, CH_2COOCH_3, 4-H_2, 3-HH), 3.71 (3H, s, $COOCH_3$), 4.08—4.51 (1H, m, 3-HH), 6.27—6.55 (1H, m, 1-H), 7.10—7.52 (6H, m, ArH), 7.55—7.94 (2H, d, J=7.5 Hz, ArH), 8.10 (1H, d, J=7.5 Hz, 8-H). MS m/z: 484 (M^+). *Anal.* Calcd for $C_{25}H_{28}N_2O_6S$: C, 61.97; H, 5.83; N, 5.78. Found: C, 62.02; H, 5.84; N, 5.78.

Methyl 10-Benzenesulfonyl-2-vinyl-1,2,4,5,10,10b-hexahydroazeto-[1′,2′:1,2]pyrido[3,4-*b*]indole-1-carboxylate (12a) and Methyl 12-Benzenesulfonyl-4-oxo-2-vinyl-1,6,7,12b-tetrahydro-2*H*,4*H*-indolo-[2,3-*c*]pyrido[1,2-*c*][1,3]oxazine-1-carboxylate (13) A solution of **10** (3.0 g, 6.2 mmol) in THF (15 ml) was added dropwise to a solution of LDA [prepared from diisopropylamine (1.04 ml, 7.4 mmol) and *n*-BuLi (15% hexane solution, 4.76 ml, 7.4 mmol)] in THF (10 ml) at −78 °C, and the mixture was stirred at this temperature for 30 min. Then, 90% acrolein (0.92 ml, 12 mmol) was added in one portion to this solution, and the whole was stirred at −78 °C for 30 min. The reaction was quenched with water, and THF was removed by evaporation. The residue was extracted with CH_2Cl_2, and the extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give methyl 2-(9-benzenesulfonyl-2-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-β-carbolin-1-yl)-3-hydroxy-4-pentenoate (**11**) as an oil in a quantitative yield [MS m/z: 540 (M^+)]. Then, TEA (2.6 ml, 18.6 mmol) and MsCl (0.72 ml, 9.3 mmol) were added successively to a solution of the crude alcohol **11** obtained above in CH_2Cl_2 (20 ml) under ice-cooling, and the mixture was stirred at room temperature for 1.5 h. The reaction was quenched with water, and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was, without purification, dissolved in 2.3 N HCl in EtOAc (35 ml) and the solution was stirred for 3 h. After removal of the solvent by evaporation *in vacuo*, the residue was dissolved in DMSO (9 ml) containing DBU (1.86 ml, 12.4 mmol). This solution was allowed to stand for 1.5 h, diluted with water (150 ml), and then extracted with EtOAc. The extract was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to column chromatography (50% EtOAc in hexane) to give **12a** (1.14 g, 43% overall yield from **10**), which was recrystallized from EtOH to give crystals, mp 159—161 °C. IR (KBr): 1720 (CO), 1360 and 1160 (SO_2) cm^{-1}. ^{1}H-NMR δ: 2.65—3.05 (4H, m, 4-H_2, 5-H_2), 3.38 (1H, dd, J=3.0, 9.0 Hz, 1-H), 3.80 (3H, s, $COOCH_3$), 4.22 (1H, dd, J=7.0, 9.0 Hz, 2-H), 5.20 (1H, d, J=10.0 Hz, *cis*-CH=CHH), 5.23 (1H, br s, 10b-H), 5.37 (1H, d, J=17.0 Hz, *trans*-CH=CHH), 5.83 (1H, ddd, J=7.0, 10.0, 17.0 Hz, CH=), 7.20—7.58 (6H, m, ArH), 7.82 (2H, d, J=7.5 Hz, ArH), 8.18 (1H, d, J=7.5 Hz, 9-H). MS m/z: 422 (M^+). *Anal.* Calcd for $C_{23}H_{22}N_2O_4S$: C, 65.38; H, 5.25; N, 6.63. Found: C, 65.32; H, 5.32; N, 6.54.

The second eluate (EtOAc) gave **13** (200 mg, 9%), which was recrystallized from a mixture of $CHCl_3$ and MeOH to give crystals, mp 220 °C (dec.). IR ($CHCl_3$): 1720 and 1680 (CO), 1360 and 1160 (SO_2) cm^{-1}. ^{1}H-NMR δ: 2.50—2.90 (3H, m, 6-HH, 7-H_2), 3.38 (3H, s, $COOCH_3$), 4.06 (1H, dd, J=2.0, 3.0 Hz, 1-H), 4.78 (1H, m, 6-HH), 5.26 (1H, br s, 2-H), 5.33 (1H, br s, 12b-H), 5.51 (1H, br d, J=10.5 Hz, *cis*-CH=CHH), 5.60 (1H, br d, J=17.0 Hz, *trans*-CH=CHH), 6.09 (1H, ddd, J=3.0, 10.5, 17.0 Hz, CH=), 7.20—7.50 (8H, m, ArH), 8.08 (1H, d, J=8.0 Hz, 11-H). MS m/z: 466 (M^+). *Anal.* Calcd for $C_{24}H_{22}N_2O_6S \cdot 1/2H_2O$: C, 60.62; H, 4.88; N, 5.89. Found: C, 60.74; H, 4.62; N, 5.92.

Methyl (1,13b-*trans*)-13-Benzenesulfonyl-1,4,7,8,13,13b-hexahydro-[1′,2′]oxazepino[2′,3′:1,2]pyrido[3,4-*b*]indole-1-carboxylate (14) A solution of 80% MCPBA (595 mg, 2.76 mmol) in CH_2Cl_2 (15 ml) was added to a solution of **12a** (972 mg, 2.3 mmol) in CH_2Cl_2 (15 ml) at room temperature. After being stirred for 30 min, the reaction mixture was washed with 5% Na_2CO_3 solution and water, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (50% EtOAc in hexane) to give **14** (807 mg, 80%). Recrystallization from a mixture of EtOH and benzene gave crystals, mp 170—172 °C. IR (Nujol): 1740 (CO), 1360 and 1150 (SO_2) cm^{-1}. ^{1}H-NMR δ: 2.40—3.20 (3H, m, 7-HH, 8-H_2), 3.51 (1H, m, 7-HH), 3.78 (3H, s, $COOCH_3$), 4.20 (1H, dd, J=2.5, 9.0 Hz, 1-H), 4.32 and 4.44 (each 1H, each d, J=18.0 Hz, 4-H_2), 5.18 (1H, br s, 13b-H), 5.54 (1H, d, J=12.0 Hz, 3-H), 5.76 (1H, dd, J=9.0, 12.0 Hz, 2-H), 7.10—7.42 (6H, m, ArH), 7.52 (2H, d, J=7.5 Hz, ArH), 8.10 (1H, d, J=7.5 Hz, 12-H). MS m/z: 438 (M^+). *Anal.* Calcd for $C_{23}H_{22}N_2O_5S$: C, 63.00; H, 5.06; N, 6.39. Found: C, 63.01; H, 5.10; N, 6.22.

Methyl (1,13b-*trans*)-13-Benzenesulfonyl-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′:1,2]pyrido[3,4-*b*]indole-1-carboxylate (15) A solution of **14** (300 mg, 0.68 mmol) in EtOAc (30 ml) was hydrogenated with 5% Pd–C (120 mg) under atmospheric pressure for 4 h. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated *in vacuo*. The residue was recrystallized from MeOH to give **15** (301 mg, 100%), mp 206—208 °C. IR ($CHCl_3$): 1730 (CO), 1370 and 1160 (SO_2) cm^{-1}. ^{1}H-NMR δ: 1.50—1.67 (2H, m, 3-H_2), 1.97—2.33 (2H, m, 2-H_2), 2.41 (1H, m, 8-HH), 2.68—2.99 (2H, m, 7-HH, 8-HH), 3.47 (1H, m, 7-HH), 3.64—3.97 (3H, m, 1-H, 4-H_2), 3.83 (3H, s, $COOCH_3$), 4.95 (1H, br s, 13b-H), 7.15—7.42 (6H, m, ArH), 7.53 (2H, d, J=7.5 Hz, ArH), 8.11 (1H, d, J=7.5 Hz, 12-H). MS m/z: 440 (M^+). *Anal.* Calcd for $C_{23}H_{24}N_2O_5S$: C, 62.71; H, 5.49; N, 6.36. Found: C, 62.71; H, 5.54; N, 6.33.

Preparation of Methyl (1,13b-*trans*)-1,2,3,4,7,8,13,13b-Octahydro-[1′,2′]oxazepino[2′,3′:1,2]pyrido[3,4-*b*]indole-1-carboxylate (16) From **15**: A catalytic amount of iodine was added to a stirred suspension of Mg (215 mg, 9 mg-atom) in MeOH (8 ml). A solution of **15** (263 mg, 0.6 mmol) in THF (8 ml) was added to this suspension and the whole was stirred at 40 °C for 16 h during which Mg disappeared. The reaction was quenched with saturated NH_4Cl solution, and the solvent was removed by evaporation *in vacuo*. The residue was extracted with $CHCl_3$ and the extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc in hexane) to give **16** (177 mg, 99%), which was recrystallized from EtOH to give crystals, mp 105—107 °C. IR (Nujol): 3400 (NH), 1710 (CO) cm^{-1}. ^{1}H-NMR δ: 1.78—2.45 (4H, m, 2-H_2, 3-H_2), 2.63—3.16 (4H, m, 7-HH, 8-H_2, 1-H), 3.56—3.85 (2H, m, 7-HH, 4-HH), 3.87 (3H, s, $COOCH_3$), 3.98 (1H, m, 4-HH), 4.46 (1H, br d, J=9.0 Hz, 13b-H), 7.03—7.50 (4H, m, ArH), 8.40 (1H, br s, NH). MS m/z: 300 (M^+). *Anal.* Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.91; H, 6.74; N, 9.34.

From **14**: The same procedure as that from **15** provided a crude product from **14** (1.86 g, 4.2 mmol) with Mg (1.5 g, 63.5 mg-atom), and this was purified by column chromatography to give **16** (1.20 g, 94%). This product was identical with the sample of **16** obtained by method A, based on comparison of their IR and ^{1}H-NMR spectra.

From **17**: The same procedure as that from **15** provided a crude product from **17** (35 mg, 0.08 mmol) with Mg (41 mg, 1.7 mg-atom), and this was purified by column chromatography to give **16** (18 mg, 77%). This product was identical with the sample of **16** obtained by method A, based on comparison of their IR and ^{1}H-NMR spectra.

Methyl 13-Benzenesulfonyl-3,4,7,8,13,13b-hexahydro[1′,2′]oxazepino[2′,3′:1,2]pyrido[3,4-*b*]indole-1-carboxylate (17) An aqueous NaOH (1 N, 0.8 ml, 0.8 mmol) was added to a solution of **14** (22 mg, 0.05 mmol) in a mixture of MeOH–THF (1 : 1) and the whole was stirred at room temperature for 6 h. After evaporation of the solvent, the residue was dissolved in EtOAc, and the organic solution was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (3% EtOAc in CH_2Cl_2) to recover **14** (8 mg, 36%) from the first fraction. The second fraction gave **17** (14 mg, 64%), which was recrystallized from EtOH to give crystals, mp 206—208 °C. IR ($CHCl_3$): 1710 (CO), 1360 and 1160 (SO_2) cm^{-1}. ^{1}H-NMR δ: 2.40 (1H, m, 3-HH), 2.57—3.10 (4H, m, 3-HH, 7-HH, 8-H_2), 3.45 (3H, s, $COOCH_3$), 3.48—3.55 (1H, m, 7-HH), 4.08 (2H, m, 4-H_2), 5.73 (1H, br s, 13b-H), 7.08 (1H, dd, J=5.2, 8.0 Hz, 2-H), 7.15—7.50 (6H, m, ArH), 7.63 (2H, d, J=7.5 Hz, ArH), 8.02 (1H, d, J=7.5 Hz, 12-H). MS m/z: 438 (M^+). *Anal.* Calcd for $C_{23}H_{22}N_2O_5S$: C, 63.00; H, 5.06; N, 6.39. Found: C, 62.78; H, 5.08; N, 6.26.

(1,13b-*trans*)-1,2,3,4,7,8,13,13b-Octahydro[1′,2′]oxazepino[2′,3′:1,2]pyrido[3,4-*b*]indole-1-carboxylic Acid (18) A solution of **16** (381 mg, 1.27 mmol) in CH_2Cl_2 (8 ml) was added to a stirred, ice-cooled suspension of $AlBr_3$ (3.34 g, 12.7 mmol) in EtSH (8 ml). After being stirred at room temperature for 30 min, the reaction mixture was quenched with cold water, and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give **18** (363 mg, 100%) as an amorphous powder, which showed a single spot on TLC. This product was used for the following reaction without purification. IR (KBr): 3400 (NH), 1700 (CO) cm^{-1}. ^{1}H-NMR δ: 1.88

(2H, m, 3-H_2), 2.10—2.50 (2H, m, 2-H_2), 2.69 (1H, m, 8-HH), 2.86—3.22 (3H, m, 1-H, 7-HH, 8-HH), 3.51—4.11 (3H, m, 4-H_2, 7-HH), 4.49 (1H, d, J=9.5 Hz, 13b-H), 6.99—7.37 (4H, m, ArH), 7.48 (1H, d, J=8.0 Hz, 12-H), 8.40 (1H, br s, NH) (the signal of COOH was not detected). MS m/z: 286 (M^+). HRMS Calcd for $C_{16}H_{18}N_2O_3$: 286.1316. Found: 286.1318.

(1,13b-*trans*)-1-Benzyloxycarbonylamino-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole (19) Ethyl chloroformate (0.49 ml, 5 mmol) was added to a suspension of **18** (1.10 g, 3.86 mmol) and TEA (0.82 ml, 5.8 mmol) in THF (20 ml) under ice-cooling. After being stirred for 15 min, NaN_3 (774 mg, 11.6 mmol) and CH_3CN (20 ml) were added to the reaction mixture, and the whole was stirred at room temperature for 6 h. The solvent was removed by evaporation under reduced pressure below 30 °C, and the residue was dissolved in CH_2Cl_2 and water. The separated organic solution was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Benzyl alcohol (5 ml) and anhydrous $MgSO_4$ (200 mg) was added to a solution of the residue in dry benzene (5 ml), and the mixture was stirred at 65 °C for 10 h, then diluted with $CHCl_3$. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc in hexane) to give **19** (814 mg, 54%). This was recrystallized from a mixture of benzene and hexane to give crystals, mp 169—170 °C. IR (KBr): 3300 (NH), 1680 (CO) cm^{-1}. ^{1}H-NMR δ: 1.69—1.88 (4H, m, 2-H_2, 3-H_2), 2.62—3.10 (3H, m, 7-HH, 8-H_2), 3.60 (1H, m, 7-HH), 3.95 (3H, m, 4-H_2, 13b-H), 4.33 (1H, br s, 1-H), 5.22 (2H, s, CH_2Ar), 5.44 (1H, m, CONH), 7.02—7.59 (9H, m, ArH), 9.50 (1H, br s, NH). MS m/z: 391 (M^+). *Anal.* Calcd for $C_{23}H_{25}N_3O_3$: C, 70.57; H, 6.44; N, 10.73. Found: C, 70.47; H, 6.74; N, 10.85.

(1,13b-*trans*)-1-Amino-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole [(1,10-*trans*)-12-Carbaeudistomin] (4) A solution of **19** (568 mg, 1.45 mmol) in a mixture of EtOAc–MeOH (1 : 1), (50 ml) was hydrogenated with 10% Pd–C (170 mg) under atmospheric pressure for 6 h. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc in hexane) to give **4** (337 mg, 90%), which was recrystallized from EtOH to give crystals, mp 182—183 °C. IR (KBr): 3300 (NH_2) cm^{-1}. ^{1}H-NMR δ: 1.50—2.20 (4H, m, 2-H_2, 3-H_2), 2.70—3.10 (4H, m, 1-H, 7-HH, 8-H_2), 3.41—3.80 (3H, 4-HH, 7-HH, 13b-H), 4.11 (1H, m, 4-HH), 6.97—7.38 (3H, m, ArH), 7.48 (1H, d, J=7.5 Hz, 12-H), 10.40 (1H, br s, indole-NH) (the signals of NH_2 were not detected). MS m/z: 257 (M^+). *Anal.* Calcd for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 69.92; H, 7.43; N, 16.31.

Methyl (1,13b-*cis*)-13-Benzenesulfonyl-1,4,7,8,13,13b-hexahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylate (20a) A solution of **14** (796 mg, 1.8 mmol) and DBU (342 mg, 2.18 mmol) in benzene (15 ml) was allowed to stand at room temperature for 24 h. After evaporation of benzene *in vacuo*, the residue was diluted with CH_2Cl_2. The solution was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to column chromatography. The first fraction eluted by 20% EtOAc in hexane gave **20a** (579 mg, 73%), which was recrystallized from EtOH to give crystals, mp 153—155 °C. IR ($CHCl_3$): 1720 (CO), 1360 and 1160 (SO_2) cm^{-1}. ^{1}H-NMR δ: 2.45—2.97 (3H, m, 7-HH, 8-H_2), 3.27 (3H, s, $COOCH_3$), 3.50 (1H, m, 7-HH), 4.33 (1H, dd, J=3.3, 16.0 Hz, 4-HH), 4.45 (1H, q, J=3.3 Hz, 1-H), 4.65 (1H, d, J=16.0 Hz, 4-HH), 4.89 (1H, br d, J=3.3 Hz, 13b-H), 5.97 (2H, m, 2-H, 3-H), 7.10—7.50 (6H, m, ArH), 7.58 (2H, d, J=7.5 Hz, ArH), 8.10 (1H, d, J=7.5 Hz, 12-H). MS m/z: 438 (M^+). *Anal.* Calcd for $C_{23}H_{22}N_2O_5S$: C, 63.00; H, 5.06; N, 6.39. Found: C, 62.70; H, 5.00; N, 6.35. [This was treated with 1 N NaOH by the same procedure as that described for the preparation of **17** from **14**. The crude product was purified by column chromatography to give **17** (23%), which was identical with the sample of **17** obtained from **14**, with recovery of **20a** (73%)]. The second fraction eluted by EtOAc gave the starting material **14** (115 mg, 14%).

Methyl (1,13b-*cis*)-13-Benzenesulfonyl-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylate (22) The same procedure as described for the preparation of **15** provided a crude product from **20a** (400 mg, 0.91 mmol) with 5% Pd–C (340 mg), and this was recrystallized from MeOH to give **22** (399 mg, 100%), mp 150—152 °C. IR ($CHCl_3$): 1720 (CO), 1360 and 1160 (SO_2) cm^{-1}. ^{1}H-NMR δ: 1.66—2.43 (4H, m, 2-H_2, 3-H_2), 2.43—2.96 (3H, m, 7-HH, 8-H_2), 3.33 (3H, s, $COOCH_3$), 3.50 (1H, m, 7-HH), 3.73 (1H, m, 4-HH), 3.95 (1H, q, J=3.0 Hz, 1-H), 4.10 (1H, m, 4-HH), 4.53 (1H, br d, J=3.0 Hz, 13b-H), 7.05—7.45 (6H, m, ArH), 7.54 (2H, d, J=7.5 Hz, ArH), 8.02 (1H, d, J=7.5 Hz, 12-H). MS m/z: 440 (M^+). *Anal.* Calcd for $C_{23}H_{24}N_2O_5S$: C, 62.71; H, 5.49; N, 6.36. Found: C, 62.59; H, 5.45; N, 6.39.

Methyl (1,13b-*cis*)-1,2,3,4,7,8,13,13b-Octahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylate (23) The same procedure as described for the preparation of **16** (method A) provided a crude product from **22** (870 mg, 2 mmol) with Mg (711 mg, 30 mg-atom), and this was purified by column chromatography (20% EtOAc in hexane) to give **23** (537 mg, 91%), mp 168—170 °C (from EtOH). IR ($CHCl_3$): 3450 (NH), 1710 (CO) cm^{-1}. ^{1}H-NMR δ: 1.62—1.84 (1H, m, 3-HH), 2.00—2.23 (3H, m, 3-HH, 2-H_2), 2.71 (1H, m, 8-HH), 2.96—3.17 (2H, m, 7-HH, 8-HH), 3.28 (1H, td, J=3.8, 5.4 Hz, 1-H), 3.55 (3H, s $COOCH_3$), 3.64—3.72 (1H, m, 7-HH), 3.85 and 4.11 (each 1H, each m, 4-H_2), 4.34 (1H, br d, J=3.8 Hz, 13b-H), 7.00—7.50 (4H, m, ArH), 8.17 (1H, br s, NH). MS m/z: 300 (M^+). *Anal.* Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.97; H, 6.75; N, 9.32.

(1,13b-*cis*)-1,2,3,4,7,8,13,13b-Octahydro[1′,2′]oxazepino[2′,3′ : 1,2]-pyrido[3,4-*b*]indole-1-carboxylic Acid (24) The same procedure as described for the preparation of **18** provided a crude product from **23** (96 mg, 0.32 mmol), $AlBr_3$ (835 mg, 3.2 mmol) and EtSH (2 ml), and this was purified by recrystallization to give **24** (92 mg, 100%), mp 188—190 °C (from EtOH). IR (KBr): 3350 (NH), 1720 (CO) cm^{-1}. ^{1}H-NMR δ: 1.95—2.40 (4H, m, 2-, 3-H_2), 2.82—3.29 (3H, m, 7-HH, 8-H_2), 3.48 (1H, m, 1-H), 3.69 (1H, m, 7-HH), 3.99 (1H, m, 4-HH), 4.18—4.37 (2H, m, 4-HH, 13b-H), 7.01—7.49 (4H, m, ArH), 8.51 (1H, br s, NH) (the signal of COOH was not detected). MS m/z: 286 (M^+). *Anal.* Calcd for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.34; N, 9.79. Found: C, 66.94; H, 6.43; N, 9.68.

(1,13b-*cis*)-1-Benzyloxycarbonylamino-1,2,3,4,7,8,13,13b-octahydro-[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole (25) The same procedure as described for the preparation of **19** provided a crude product from **24** (536 mg, 1.88 mmol), ethyl chloroformate (0.24 ml, 2.4 mmol), NaN_3 (376 mg, 5.6 mmol) and benzyl alcohol (3 ml), and this was purified by column chromatography (20% EtOAc in hexane) to give **25** (428 mg, 58%), mp 190—191 °C (from a mixture of benzene–hexane). IR (KBr): 3300 (NH), 1690 (CO) cm^{-1}. ^{1}H-NMR δ: 1.60—2.15 (4H, m, 2-H_2, 3-H_2), 2.30—3.10 (3H, m, 7-HH, 8-H_2), 3.51 (1H, m, 7-HH), 3.65 and 4.08 (each 1H, each m, 4-H_2), 4.17 (1H, br s, 13b-H), 4.54 (1H, m, 1-H), 4.85 and 4.95 (each 1H, each d, J=11.0 Hz, CH_2Ar), 5.21 (1H, d, J=10.0 Hz, NHCO), 6.90—7.50 (9H, m, ArH), 8.20 (1H, br s, NH). MS m/z: 391 (M^+). *Anal.* Calcd for $C_{23}H_{25}N_3O_3$: C, 70.57; H, 6.44; N, 10.73. Found : C, 70.47; H, 6.74; N, 10.85.

(1,13b-*cis*)-1-Amino-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole (12-Carbaeudistomin) (3) The same procedure as described for the preparation of **4** provided a crude product from **25** (326 mg, 0.83 mmol) with 10% Pd–C (100 mg), and this was purified by column chromatography (10% MeOH in $CHCl_3$) to give **3** (184 mg, 86%), mp 184—185 °C (from benzene). IR (KBr): 3400 (NH_2) cm^{-1}. ^{1}H-NMR δ: 1.60—2.15 (4H, m, 2-H_2, 3-H_2), 2.70—3.10 (3H, m, 7-HH, 8-H_2), 3.43 (1H, br q, J=3.0 Hz, 1-H), 3.53 (1H, m, 7-HH), 3.73 (1H, m, 4-HH), 4.08 (2H, m, 4-HH, 13b-H), 7.05—7.55 (4H, m, ArH), 8.14 (1H, br s, indole-NH) (the signals of NH_2 were not detected). MS m/z: 257 (M^+). *Anal.* Calcd for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 69.94; H, 7.37; N, 16.30.

(1,13b-*trans*)- and (1,13b-*cis*)-13-Benzenesulfonyl-1,4,7,8,13,13b-hexahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylic Acids (26 and 27) The same procedure as described for the preparation of **18** provided a crude product from **14** (or **20a**) (88 mg, 0.2 mmol), $AlBr_3$ (543 mg, 2.0 mmol) and EtSH (2 ml), and this was purified by recrystallization to give **26** (or **27**) quantitatively.

26 had mp 207—208 °C (dec.) (from MeOH). IR (KBr): 1710 (CO), 1360 and 1170 (SO_2) cm^{-1}. ^{1}H-NMR ($CDCl_3$ + a drop of DMSO-d_6) δ: 2.40—3.10 (3H, m, 7-HH, 8-H_2), 3.51 (1H, m, 7-HH), 4.23 (1H, br d, J=9.0 Hz, 1-H), 4.38 (2H, m, 4-H_2), 5.19 (1H, br s, 13b-H), 5.55 (1H, d, J=12.0 Hz, 3-H), 5.85 (1H, t, J=12.0 Hz, 2-H), 7.15—7.45 (6H, m, ArH), 7.53 (2H, d, J=7.5 Hz, ArH), 8.10 (1H, d, J=7.5 Hz, 12-H) (the signal of COOH was not detected). MS m/z: 424 (M^+). *Anal.* Calcd for $C_{22}H_{20}N_2O_5S$: C, 62.25; H, 4.75; N, 6.60. Found: C, 62.18; H, 4.71; N, 6.59.

27 had mp 199—200 °C (dec.) (from EtOH). IR (KBr): 1725 (CO), 1370, 1170 (SO_2) cm^{-1}. ^{1}H-NMR δ: 2.60—3.20 (3H, m, 7-HH, 8-H_2), 3.75 (1H, m, 7-HH), 4.50 (2H, m, 1-H, 4-HH), 4.80 (1H, d,

J=16.0 Hz, 4-HH), 4.94 (1H, br s, 13b-H), 6.05 (2H, m, 2-, 3-H), 7.20—7.50 (6H, m, ArH), 7.60 (2H, d, J=7.5 Hz, ArH), 8.09 (1H, d, J=7.5 Hz, 12-H) (the signal of COOH was not detected). MS m/z: 424 (M^+). *Anal.* Calcd for $C_{22}H_{20}N_2O_5S$: C, 62.25; H, 4.75; N, 6.60. Found: C, 62.15; H, 4.76; N, 6.57.

(1,13b-*cis*)-13-Benzenesulfonyl-1-benzyloxycarbonylamino-1,4,7,8,13,-13b-hexahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole (29) A solution of **27** (165 mg, 0.39 mmol), TEA (43 mg, 0.427 mmol) and DPPA (112 mg, 0.41 mmol) in benzene (4 ml) was refluxed for 1 h. Benzyl alcohol (84 mg, 0.78 mmol) was then added to the reaction mixture, and the whole was refluxed for additional 24 h, then diluted with EtOAc. The mixture was washed with 10% aqueous citric acid, water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc in hexane) to give **29** (83 mg, 41%) as an amorphous powder. IR (KBr): 1720 (CO), 1370 and 1170 (SO_2) cm^{-1}. ^{1}H-NMR δ: 2.50—3.00 (3H, m, 7-HH, 8-H_2), 3.62 (1H, m, 7-HH), 4.30—5.60 (7H, m, 1-H, 4-H_2, 13b-H, CH_2Ar, NH), 5.83 and 6.14 (each 1H, each m, 3-, 2-H), 7.20—7.50 (11H, m, ArH), 7.60 (2H, d, J=7.5 Hz, ArH), 8.12 (1H, d, J=7.5 Hz, 12-H). MS m/z: 529 (M^+). HRMS Calcd for $C_{29}H_{27}N_3O_5S$: 529.1669. Found: 529.1666.

(1,13b-*cis*)-1-Amino-13-benzenesulfonyl-1,4,7,8,13,13b-hexahydro-[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole (30) The same procedure as described for the preparation of **18** provided a crude product from **29** (70 mg, 0.13 mmol), $AlBr_3$ (353 mg, 1.32 mmol) and EtSH (2 ml), and this was purified by column chromatography (4% MeOH in $CHCl_3$) to give **30** (42 mg, 80%) as an oil. IR (neat): 3330 (NH_2) cm^{-1}. ^{1}H-NMR δ: 2.50—3.00 (3H, m, 7-HH, 8-H_2), 3.61 (1H, m, 7-HH), 4.32 (2H, m, 1-H, 4-HH), 4.59 (1H, d, J=16.0 Hz, 4-HH), 4.88 (1H, br s, 13b-H), 5.70 and 6.07 (each 1H, each m, 3-, 2-H), 7.20—7.50 (6H, m, ArH), 7.61 (2H, d, J=7.5 Hz, ArH), 8.15 (1H, d, J=7.5 Hz, 12-H). MS m/z: 396 (M^++1). HRMS Calcd for $C_{21}H_{22}N_3O_3S$: 396.1380 (M^++1). Found: 396.1377.

(1,13-*cis*)-1-Amino-1,4,7,8,13,13b-hexahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole (11,12-Didehydro-12-carbaeudistomin) (5) A solution of **30** (48 mg, 0.12 mmol) in THF (0.5 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (42 mg, 1.10 mmol) in dry THF (2 ml) at room temperature, and the reaction mixture was refluxed for 8 h. The reaction was quenched with ice-water, and the mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (4% MeOH in $CHCl_3$) to give **5** (19 mg, 62%), which was recrystallized from a mixture of $CHCl_3$–hexane to give crystals, mp 146—148 °C. IR (KBr): 3400 (NH_2) cm^{-1}. ^{1}H-NMR δ: 2.70—3.20 (3H, m, 7-HH, 8-H_2), 3.68 (1H, m, 7-HH), 3.80 (1H, br s, 1-H), 4.33 (1H, dd, J=5.0, 16.0 Hz, 4-HH), 4.42 (1H, br s, 13b-H), 4.57 (1H, d, J=16.0 Hz, 4-HH), 5.29 and 6.00 (each 1H, each m, 3-, 2-H), 7.15—7.50 (4H, m, ArH), 8.19 (1H, br s, indole-NH) (the signals of NH_2 were not detected). MS m/z: 255 (M^+). HRMS Calcd for $C_{15}H_{17}N_3O$: 255.1369. Found: 255.1360. *Anal.* Calcd for $C_{15}H_{17}N_3O \cdot 1/5H_2O$: C, 69.59; H, 6.77; N, 16.23. Found: C, 69.70; H, 6.72; N, 15.93.

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References and Notes

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