Meisenheimer Rearrangement of Azetopyridoindoles. VIII.[1] Synthesis and Antiviral Activities of 12-Carbaeudistomin Analogs

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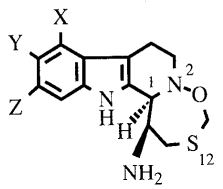
Eudistomins, isolated from the colonial tunicate *Eudistoma olivaceum*, have been a synthetic target due to their strong antiviral activity against *Herpes simplesx* virus (HSV-1) and activities against certain types of tumors *in vivo*. In order to examine the structure–activity relationship of eudistomins, 12-carbaeudistomin analogs were synthesized and their activities against influenza A and B virus, HSV-1, HSV-2 and human cytomegalovirus were investigated. Among them, racemic 6-methoxy-12-carbaeudistomin showed similar activity to (−)-debromoeudistomin K, synthesized as a control compound.

Key words eudistomin; 12-carbaeudistomin; antiviral activity; Meisenheimer rearrangement; structure–activity relationship; MNDO calculation

Eudistomins **1**, isolated from the colonial tunicate *Eudistoma olivaceum*,[3] have a unique 1,3,7-oxathiazepine ring system and have been a synthetic target due to their strong antiviral activity against *Herpes simplex* virus-1 (HSV-1) and activities against certain types of tumors *in vivo*.[4] Several 12-carbaeudistomins (**4**—**7**, **11**—**13**),[5] which have a carbon atom in place of the sulfur atom in the D-ring of tetracyclic eudistomins **1**, have been synthesized for investigation of the structure–activity relationship of **1**. It is interesting to note that compound **4** showed a significant activity specifically against influenza B virus. The most important structural requirements for activity of **1** are the 1,10-*cis* stereochemistry and the axial-NH_2 group.[6] Van Maarseveen *et al.* reported that 6-methoxydebromoeudistomin **3**[6] exhibited potent antiviral and antitumor activities. These results prompted us to design novel 12-carbaeudistomin analogs having an oxygen function at the C(6)-position and one-carbon homologs at the C(10)-position of **4**. We describe herein the synthesis of novel 12-carbaeudistomins (**8**—**10**, **14**, **15**) via the Meisenheimer rearrangement of azetopyridoindoles (**27**, **40**) and we report on their antiviral activities, including those of **4**—**7** and **11**—**13**, which we synthesized peviously.[5]

Chemistry

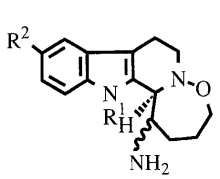
Synthesis of 6-Methoxy- and 6-Hydroxy-12-carbaeudistomins (8—10) Modified Pictet–Spengler cyclization of *N*-benzyltryptamine **17**, obtained from 5-methoxyindole,[7] gave *β*-carbolineacetate **18**, which was converted to the 9-benzenesulfonyl or 9-methyl derivative (**19** or **20**) in good yield. Catalytic debenzylation of **19** (**20**) gave the amine **21** (**22**), and the amino group was protected with a *tert*-butoxycarbonyl (Boc) group to yield the carbamate **23** (**24**). The product was converted into the key intermediate, 5-methoxyazetopyridoindole **27** (**28**) according to our established procedures.[5a)] Thus, the allyl alcohol **25** (**26**), prepared from **23** (**24**) by aldol condensation with acrolein, was subsequently treated with i) methanesulfonyl chloride (MsCl) and triethylamine (TEA), ii) dry hydrogen chloride, and iii) 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in dimethyl sulfoxide (DMSO) to give **27** (42% from **23**) or **28** (44% from **24**), respectively. The structures of these compounds (**27**, **28**) were readily confirmed by



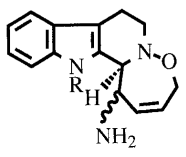
1: eudistomins
L: X=Z=H, Y=Br
K: X=Y=H, Z=Br
C: X=H, Y=OH, Z=Br
E: X=Br, Y=OH, Z=H

2: X=Y=Z=H
(debromoeudistomin K)

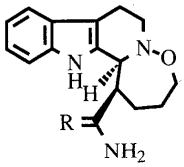
3: X=Z=H, Y=OMe
(synthesized eudistomin)



4: β-NH_2, R^1=R^2=H
5: α-NH_2, R^1=R^2=H
6: β-NH_2, R^1=Me, R^2=H
7: α-NH_2, R^1=Me, R^2=H
8: β-NH_2, R^1=H, R^2=OMe
9: β-NH_2, R^1=Me, R^2=OMe
10: β-NH_2, R^1=H, R^2=OH



11: β-NH_2, R=H
12: β-NH_2, R=Me
13: α-NH_2, R=Me



14: R=H_2
15: R=O

Fig. 1.
Eudistomin-type numbering is used for compounds **4**—**15**.

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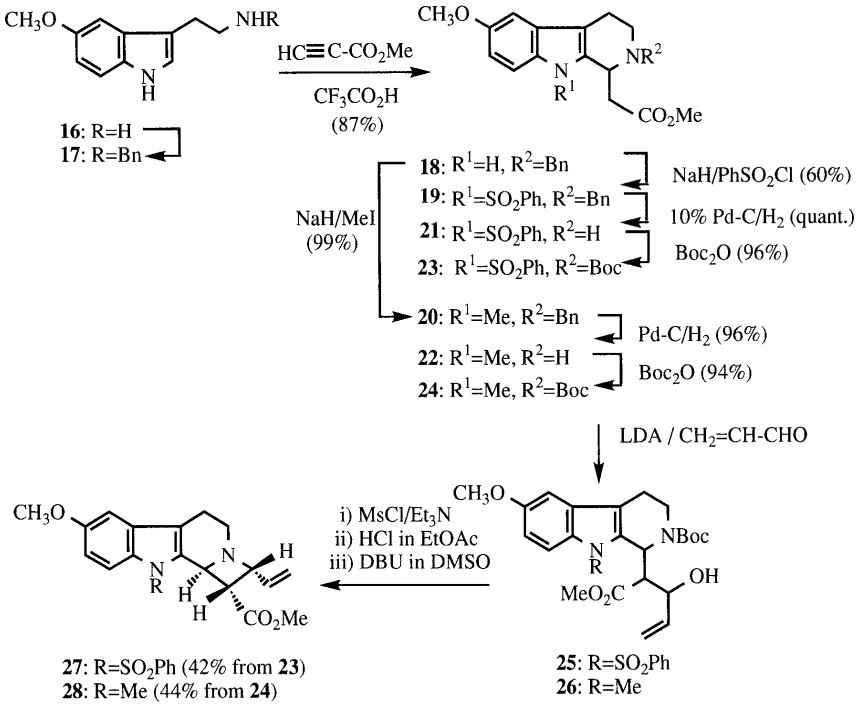

Chart 1

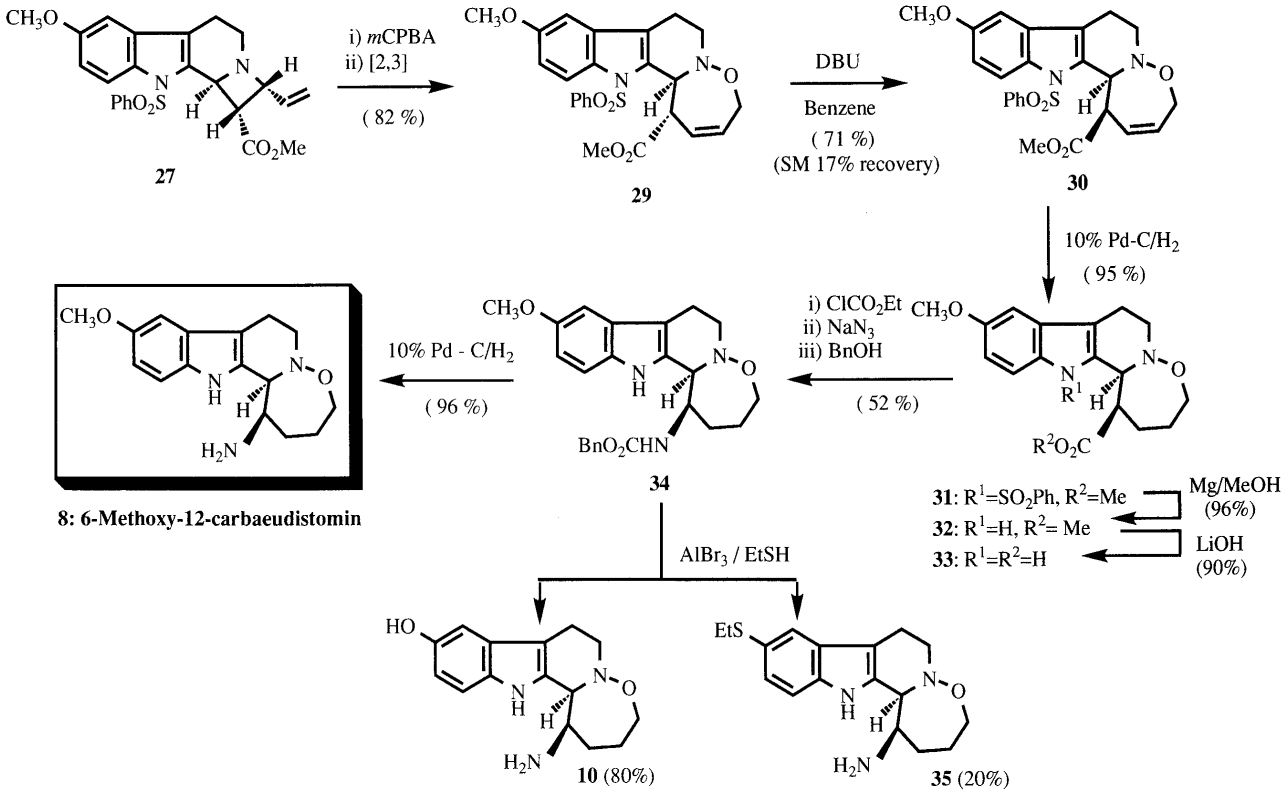

Chart 2

comparisons of their ^{1}H-NMR spectral data with those of the de-methoxy derivatives[5] (Chart 1).

Oxidation of the azetidine **27** with *m*-chloroperbenzoic acid (*m*CPBA) gave the oxazepine **29** *via* the [2,3]-Meisenheimer rearrangement of the corresponding N-oxide (Chart 2). The structural assignment of **29** was easily confirmed by comparison of the ^{1}H-NMR spectral data [δ 4.25 (dd, J=2.5, 9.0 Hz, 1-H), 5.18 (br s, 13b-H)] with those of the de-methoxy derivative.[5a] Isomerization of **29** with DBU in benzene at 40 °C gave an isomer **30** (71%), which was hydrogenated with 10% palladium on charcoal (Pd–C) to give the saturated ester **31** in 95% yield. Desulfonylation of **31** was effectively carried out by treatment with Mg in MeOH to give **32** in 96% yield. Although hydrolysis of **32** with KOH even in the presence of 18-crown-6 did not proceed, the carboxylic acid **33** was

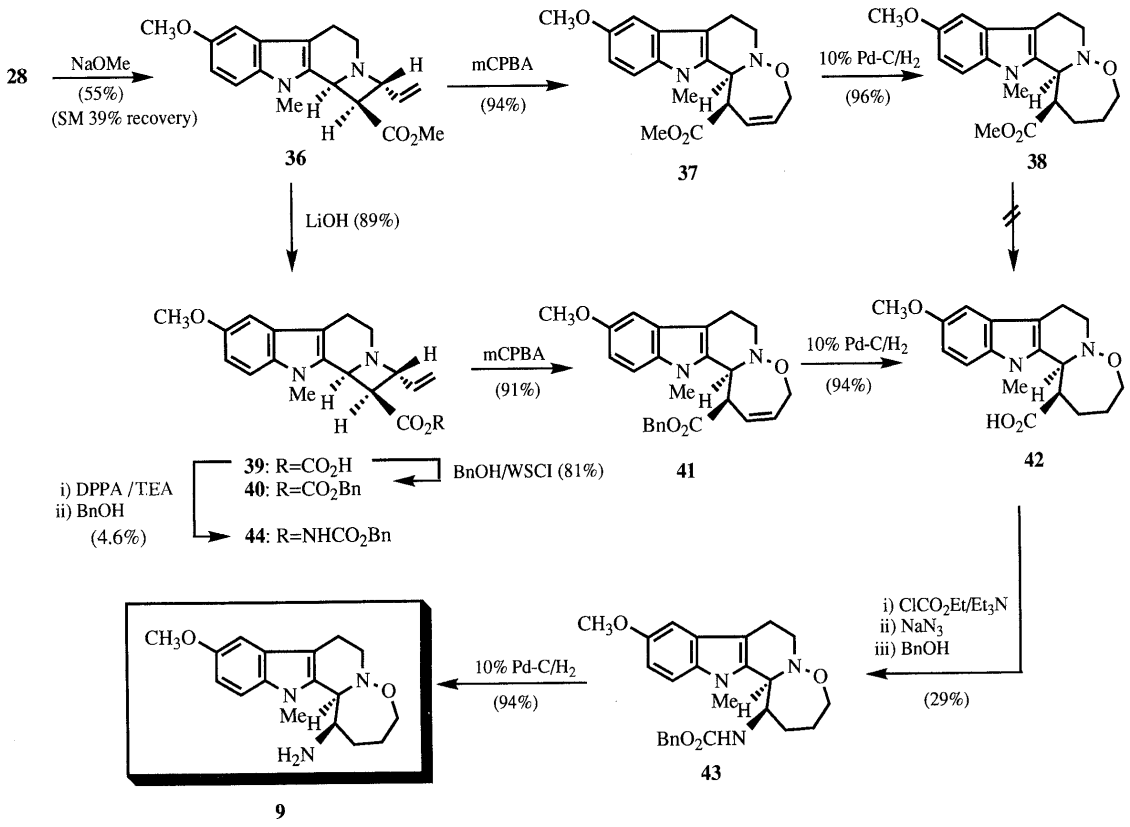

Chart 3

successfully obtained without isomerization at C(1)-position by treatment with lithium hydroxide (LiOH) in tetrahydrofuran (THF) at room temperature. Conversion of **33** to benzyl carbamate **34** was accomplished by means of the Curtius reaction [a mixed anhydride method using sodium azide (NaN_3)] in 52% yield. The desired amine **8** was obtained by catalytic debenzylation (10% Pd–C/H_2) of **34** in 96% yield. Treatment of **34** with a combination of aluminum tribromide ($AlBr_3$)–ethanethiol (EtSH)[8] gave a mixture of **10** (80%) with a hydroxyl group and **35** (20%) substituted by an ethylthio group on the indole ring. Compounds **8**, **10** and **35** thus obtained were subjected to antiviral assay.

Our attention was next focused on the synthesis of 6-methoxy-9-methyl-12-carbaeudistomin **9** (Chart 3). As done in the synthesis of 9-methyl-12-carbaeudistomin **6**[5b] from the corresponding 1,2-*cis*-azetizine, isomerization of 1,2-*trans*-azetidine **28** was carried out using NaOMe in MeOH to give the 1,2-*cis*-isomer **36** (55%) with recovery of **28** (39%). Oxidation of **36** with *m*CPBA gave an oxazepine **37** (94%), which was hydrogenated to afford the saturated ester **38** with 10% Pd–C/H_2. However, as hydrolysis of the ester group of **38** was not possible without some fission of the Me–O bond, the azetidine benzyl ester **40** was selected as a starting material. Hydrolysis (LiOH, 89%) of **36** followed by treatment of the resulting carboxylic acid **39** with benzyl alcohol in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSCI) gave the benzyl ester **40** in 81% yield. It was effectively converted into the saturated carboxylic acid **42** by catalytic hydrogenation of an unsaturated ester **41** prepared by *m*CPBA oxidation of **40**. Then, the Curtius reaction of **42** (a mixed anhydride method using NaN_3) followed by a catalytic debenzylation of **43** (29%) gave the amine **9** in 94% yield. Although another approach[5b] for the preparation of the intermediate **43** was attempted *via* the [2,3]-Meisenheimer rearrangement of the N-oxide of the azetidine carbamate **44**, the Curtius reaction of the carboxylic acid **39** using diphenylphosphoryl azide (DPPA) gave the carbamate **44** in only 4.6% yield.

Synthesis of Homo-12-carbaeudistomin Analogs (14, 15) Chart 4 shows the synthesis of homo-12-carbaeudistomins (**14**, **15**) which are one-carbon homologs at the C(10)-position. Reduction of the 1,13b-*cis*-ester **45**[5a] with diisobutylaluminum hydride (DIBAL) gave the alcohol **46** (95%), which was then oxidized with pyridinium dichromate (PDC) to give the aldehyde **47** (91%). The ^{1}H-NMR spectrum of **47** exhibited a singlet at δ 9.27 due to an aldehyde proton. On the other hand, the aldehyde **50**, prepared from the *trans*-ester **48**[5a] by the same procedures, showed an aldehyde proton signal at δ 9.98 as a singlet, indicating that no isomerization occurred at this stage. Reductive amination of **47** with benzylamine and sodium borohydride ($NaBH_4$) gave the *cis*-benzylamine **51** (85%), which was also obtained from the *trans*-aldehyde **50** in 54% yield *via* isomerization at the aldehyde position during reductive amination. This result indicated that the reductive amination of the *trans*-aldehyde was accompanied with isomerization. Removal of the benzenesulfonyl group ($LiAlH_4$ in THF) and benzyl group (10% Pd–C/H_2) provided the homo-12-carbaeudistomin **14** in 73% overall yield from **51**. The amide **15** was also prepared quantitatively under a mixed anhydride method ($ClCO_2Et$ and NH_3) from the carboxylic acid **53**.[5a]

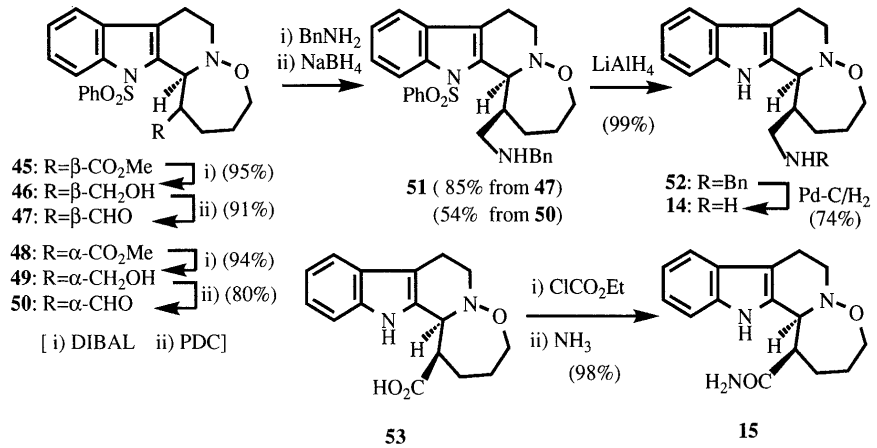

Chart 4

Antiviral Activities and Structure–Activity Relationships The activities of a group of 12-carbaeudistomins (**4**, **6**, **8**—**12**, **35**), α-isomers of these compounds (**5**, **7**, **13**), derivatives (**14**, **15**) substituted with other functional groups in place of C(1)-NH_2 and the β-carboline **23** were investigated against influenza A virus [A/PR/8/34 (H1N1) strain], influenza B virus (B/Gifu/2/73 strain), HSV-1 (VR-3 strain) and its thymidine kinase defective (TK^-) mutant ($VRTK^-$ strain), HSV-2 (UW-268 strain) and its TK^- mutant ($UWTK^-$ strain), and human cytomegalovirus (AD-169 strain). Ribavirin and (−)-debromoeudistomin K **2** were used as control compounds.

As shown in Tables 1 and 2, compounds **4** and **6** showed antiviral activities against influenza A and B viruses. In particular, **4** possessed a potent activity specifically against influenza B virus. Compound **6**, which has a methyl group in place of indole-NH of **4**, showed a high antiviral index of more than 10. On the other hand, no significant activity was observed with the corresponding α-isomers (**5**, **7**). Introduction of a substituent on the indole ring tends to increase the activity. The activity against influenza virus of methoxycarbaeudistomin **8**, which is a racemic modified derivative of carbaeudistomin **4**, was nearly equal to that of (−)-debromoeudistomin K **2**, namely 60 times greater against influenza A virus and 6 times greater against B virus than those of **4**, and an excellent antiviral index was observed. 11,12-Didehydro-12-carbaeudistomins (**11**—**13**), either α- or β-isomers, showed complete loss of the antiviral activity, suggesting that a change of the conformation of oxazepine ring induced by an introduction of a double bond may influence the activity of these compounds. Compounds **14** and **15** had no activity, indicating that the NH_2 group occupying the axial position at C(1) is essential for the anti-influenza virus activity. A group of compounds (**4**, **6**, **8**—**10**, **35**) showed antiviral activities against HSV-1, HSV-1 (TK^-), HSV-2, HSV-2 (TK^-) and cytomegalovirus. Among them, compound **8** also showed a high anti-herpes virus activity equivalent to that of **2**. The β-carboline **23** showed no anti-herpes virus activity, but had a weak activity against influenza virus. This phenomenon may suggest that **23** inhibits RNA synthesis of influenza virus, but not DNA synthesis of HSV-1 and HSV-2.

In summary, we reached the following conclusions. 1)

Table 1. Anti-influenza Virus Activity and Cytotoxicity of Synthetic 12-Carbaeudistomin Derivatives in MDCK Cell Cultures

Compound	ID_{50} (μg/ml)		ED_{50} (μg/ml) MDCK
	Influenza A virus (A/PR/8/34)	Influenza B virus (B/Gifu/2/73)	
4	4.0	0.7	2.0
5	>10	>10	12.5
6	4.5	4.5	50.5
7	>10	>10	N.T.
8	0.07	0.12	0.56
9	8.9	6.5	12.0
10	14.0	3.0	10.0
35	1.4	0.8	0.7
11	>10	>10	N.T.
12	>10	>10	10.0
13	>10	>10	14.0
14	>10	>10	12.5
15	>10	>10	17.8
23	7.1	>10	N.T.
2	0.05	0.06	0.8
Ribavirin	1.4	1.0	3.0

N.T.: Not tested.

Table 2. Anti-herpes Virus Activity and Cytotoxicity of Synthetic 12-Carbaeudistomin Derivatives in HEL Cell Cultures

Compd.	ID_{50} (μg/ml)					ED_{50} (μg/ml) HEL
	HSV-1 (VR-3)	HSV-1 ($VRTK^-$)	HSV-2 (UW-268)	HSV-2 ($UWTK^-$)	HCMV (AD-169)	
4	4.7	0.84	4.5	3.5	1—4	0.76
6	24.4	13.0	24.4	18.3	4—10	5.9
8	1.5	0.084	0.63	0.56	N.T.	<0.1
10	4.7	N.T.	1.4	N.T.	<1	N.T.
11	23.2	6.4	17.3	28.2	N.D.	1.4
35	1.7	N.T.	0.75	N.T.	N.D.	N.T.
23	>100	N.T.	>100	N.T.	>1	N.T.
2	0.5	0.17	0.63	0.52	N.T.	<0.1
Ribavirin	>100	>100	>100	>100	N.T.	4.0

N.T.: Not tested. N.D.: Not determined because of cell damage during prolonged incubation with test compounds.

The optimized structure of 12-carbaeudistomin **4** (Fig. 2) obtained by the modified neglect of differential overlap (MNDO)[9] calculation is essentially the same as the X-ray structure of natural eudistomin K (Fig. 2),[10] in which the

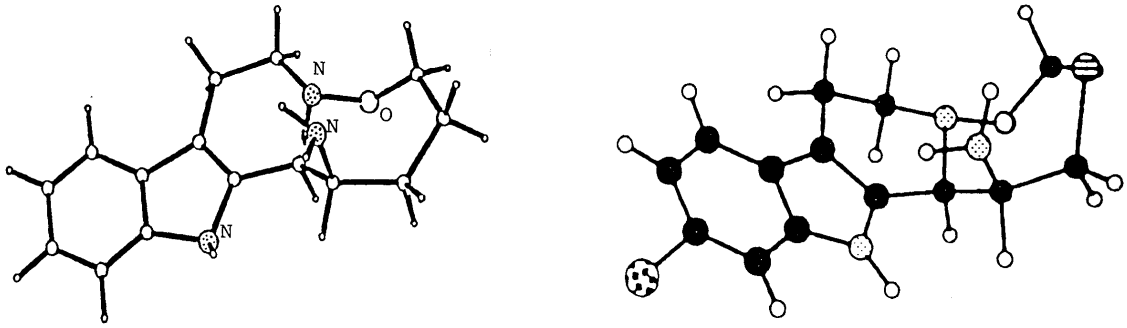

Fig. 2. MNDO-Optimized Structure of Synthesized 12-Carbaeudistomin **4** (Left) and X-Ray Structure of Natural Eudistomin K[6] (Right)

NH_2 group points in the same direction as the lone pair on N-2. 2) A group of 12-carbaeudistomins, having an NH_2 group at the axial position at the C(10)-position and the same conformation as found in the natural eudistomins, showed antiviral activities against influenza and/or herpes viruses. However, the α-isomer had no antiviral activity. 3) Antiviral activities are increased by the introduction of substituents at the C(6)-position on the indole ring. 4) These results clearly indicate that the oxazepine ring is equivalent to the oxathiazepine ring in the natural eudistomins for antiviral activity.

Experimental

Melting points were determined on a Yanagimoto apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-435 spectrometer. ^{1}H-NMR spectra were recorded with Varian XL-300 and Varian Gemini-200 spectrometers in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard and MS with Hitachi M-80 and M-4000H instruments. All reactions were carried out in a nitrogen atmosphere. For column chromatography, SiO_2 (Merck Art 9385) was used.

Methyl 2-Benzyl-6-methoxy-1,2,3,4-tetrahydro-β-carboline-1-acetate (18) A solution of **16** (11.76 g, 61.8 mmol) and benzaldehyde (6.89 g, 64.9 mmol) in MeOH (120 ml) was refluxed for 2 h. After cooling to 0 °C, $NaBH_4$ (2.39 g, 63.1 mmol) was added portionwise to the reaction mixture, and the whole was stirred at room temperature for 2 h. The solvent was removed by evaporation under reduced pressure, and the residue was dissolved in a mixture of EtOAc and water. The separated organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give *N*-benzyl-5-methoxytrypthamine **17**[11] as an oil. Then, methyl propiolate (5.71 g, 68.0 mmol) was added dropwise to a solution of the crude **17** obtained above in $CHCl_3$ (70 ml). The mixture was stirred at room temperature for 30 min, then trifluoroacetic acid (16.92 g, 148 mmol) was added. The whole was stirred for an additional 1 h, and poured into ice-water. The solution was made alkaline with 5 N NaOH solution, and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2) to give **18** (19.76 g, 87%) as an oil. IR (neat) cm^{-1}: 3390 (NH), 1720 (CO). ^{1}H-NMR δ: 2.47—3.20 (m, 6H, 3-H_2, 4-H_2, C$\underline{H}_2$CO$_2$Me), 3.70 (s, 3H, CO_2Me), 3.80 (s, 2H, CH_2Ar), 3.87 (s, 3H, OMe), 4.18 (m, 1H, 1-H), 6.80—7.40 (m, 8H, ArH), 8.35 (br s, 1H, NH). EI-MS *m/z*: 364 (M^+). HR-MS Calcd for $C_{22}H_{24}N_2O_3$: 364.1785. Found: 364.1782.

Methyl 9-Benzenesulfonyl-2-benzyl-6-methoxy-1,2,3,4-tetrahydro-β-carboline-1-acetate (19) A solution of **18** (10.68 g, 29.3 mmol) in dimethylformamide (DMF) (60 ml) was added dropwise to a suspension of 60% NaH (1.75 g, 43.9 mmol) in DMF (30 ml) with stirring at −40 to −50 °C. Stirring was continued for 3 h, then a solution of benzenesulfonyl chloride (9.30 g, 52.7 mmol) in DMF (10 ml) was added dropwise, and the mixture was stirred for an additional 1 h under ice-cooling. The reaction was quenched with water, the mixture was made alkaline with saturated $NaHCO_3$ solution, 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 residue was recrystallized from EtOH to give **19** (8.87 g, 60%), mp 175—176 °C. IR (KBr) cm^{-1}: 1740 (CO), 1365, 1155 (SO_2). ^{1}H-NMR δ: 2.40—3.23 (m, 5H, 3-H_2, 4-H_2, C$\underline{H}$HCO$_2$Me), 3.40 (dd, 1H, *J*=2.0, 15.0 Hz, CH$\underline{H}$CO$_2$Me), 3.60 (s, 2H, CH_2Ar), 3.75 (s, 3H, CO_2Me), 3.85 (s, 3H, OMe), 4.75 (dd, 1H, *J*=3.0, 10.5 Hz, 1-H), 6.80—7.60 (m, 10H, ArH), 7.68 (d, 2H, *J*=7.5 Hz, ArH), 8.20 (d, 1H, *J*=7.5 Hz, 8-H). *Anal.* Calcd for $C_{28}H_{28}N_2O_5S$: C, 66.64; H, 5.59; N, 5.55. Found: C, 66.69; H, 5.67; N, 5.63.

Methyl 9-Benzenesulfonyl-6-methoxy-1,2,3,4-tetrahydro-β-carboline-1-acetate (21) A solution of **19** (10.2 g, 20.2 mmol) in MeOH (600 ml) containing concentrated HCl (3.5 ml) was hydrogenated over 10% Pd–C (3.5 g) at an initial pressure of 5 kg/cm^2 for 24 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 **21** (8.42 g, 100%) as an oil. IR (neat) cm^{-1}: 3320 (NH), 1730 (CO), 1365, 1160 (SO_2). ^{1}H-NMR δ: 2.50—3.20 (m, 5H, 3-H_2, 4-H_2, C$\underline{H}$HCO$_2$Me), 3.27 (dd, 1H, *J*=2.0, 15.5 Hz, CH$\underline{H}$CO$_2$Me), 3.76 (s, 3H, CO_2Me), 3.82 (s, 3H, OMe), 4.95 (d, 1H, *J*=10.0 Hz, 1-H), 6.75—7.53 (m, 5H, ArH), 7.68 (d, 2H, *J*=7.5 Hz, ArH), 8.04 (d, 1H, *J*=7.5 Hz, 8-H). EI-MS *m/z*: 414 (M^+). HR-MS Calcd for $C_{21}H_{22}N_2O_5S$: 414.1248. Found: 414.1255.

Methyl 9-Benzenesulfonyl-2-*tert*-butoxycarbonyl-6-methoxy-1,2,3,4-tetrahydro-β-carboline-1-acetate (23) A solution of Boc_2O (5.22 g, 23.9 mmol) in THF (60 ml) was added to a solution of **21** (7.62 g, 18.4 mmol) in THF (40 ml), and the whole was stirred for 2 h, then concentrated *in vacuo* to give a solid. This was recrystallized from EtOH to give **23** (9.1 g, 96%), mp 139—140 °C. IR (KBr) cm^{-1}: 1740, 1690 (CO), 1365, 1160 (SO_2). ^{1}H-NMR δ: 1.53 (s, 9H, CO_2CMe_3), 2.47—3.46 (m, 5H, CH_2CO_2Me, 4-H_2, 3-H$\underline{H}$), 3.75 (s, 3H, CO_2Me), 3.80 (s, 3H, OMe), 4.08—4.51 (m, 1H, 3-H$\underline{H}$), 6.25—6.55 (m, 1H, 1-H), 6.70—7.95 (m, 7H, ArH), 8.05 (d, 1H, *J*=7.5 Hz, 8-H). *Anal.* Calcd for $C_{26}H_{30}N_2O_7S$: C, 60.68; H, 5.88; N, 5.45. Found: C, 60.83; H, 5.94; N, 5.37.

Methyl (1*S,2*R**,10b*S**)-10-Benzenesulfonyl-7-methoxy-2-vinyl-1,2,4,5,10,10b-hexahydroazeto[1′,2′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylate (27)** A solution of **23** (4.74 g, 9.2 mmol) in THF (25 ml) was added dropwise to a solution of lithium diisopropylamine (LDA) [prepared from diisopropylamine (1.55 ml, 11.1 mmol) and *n*-BuLi (15% hexane solution, 7.08 ml, 11.1 mmol)] at −78 °C, and the mixture was stirred at this temperature for 2 h. Then, acrolein (1.23 ml, 18.5 mmol) was added in one portion, 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 EtOAc, 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-6-methoxy-1,2,3,4-tetrahydro-β-carbolin-1-yl)-3-hydroxy-4-pentenoate (**25**) as an oil. Then, TEA (3.87 ml, 27.6 mmol) and MsCl (1.11 ml, 14.4 mmol) were added successively to a solution of the crude alcohol (**25**) obtained above in CH_2Cl_2 (12 ml) under ice-cooling, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with 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, without purification, dissolved in 2.3 N HCl in EtOAc (48 ml) and the solution was stirred at room temperature for 1.5 h. After removal of the solvent by evaporation *in vacuo*, the residue was dissolved in DMSO (9 ml) containing DBU (2.76 ml, 18.4 mmol). This solution was allowed to stand for 2.5 h, diluted with water, and extracted with EtOAc. The extract was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by column chromatography (30% EtOAc in hexane) to give **27** (1.73 g, 42%), which was recrystallized from EtOH to give crystals, mp 199—201 °C. IR (KBr) cm^{-1}: 1735 (CO),

1365, 1160 (SO_2). ^{1}H-NMR δ: 2.55—3.10 (m, 4H, 4-H_2, 5-H_2), 3.41 (dd, 1H, J=3.0, 9.0 Hz, 1-H), 3.82 (s, 3H, CO_2Me), 3.87 (s, 3H, OMe), 4.25 (dd, 1H, J=7.0, 9.0 Hz, 2-H), 5.21 (br s, 1H, 10b-H), 5.24 (d, 1H, J=10.0 Hz, *cis*-CH=CHH), 5.39 (d, 1H, J=17.0 Hz, *trans*-CH=CHH), 5.84 (ddd, 1H, J=7.0, 10.0, 17.0 Hz, =CH), 6.90—7.85 (m, 7H, ArH), 8.10 (d, 1H, J=7.5 Hz, 9-H). EI-MS m/z: 452 (M^+). *Anal.* Calcd for $C_{24}H_{24}N_2O_5S\cdot 1/5H_2O$: C, 63.20; H, 5.39; N, 6.14. Found: C, 63.28; H, 5.38; N, 6.24.

Methyl 2-Benzyl-6-methoxy-9-methyl-1,2,3,4-tetrahydro-β-carboline-1-acetate (20) The same procedure as described for the preparation of **19** provided a crude product from **18** (4.21 g, 11.5 mmol), 60% NaH (692 mg, 17.3 mmol) and MeI (3.27 g, 23.1 mmol), and this was purified by recrystallization from EtOH to give **20** (4.33 g, 99%), mp 104—105 °C. IR (KBr) cm^{-1}: 1750 (CO). ^{1}H-NMR δ: 2.42—3.35 (m, 6H, 3-H_2, 4-H_2, CH_2CO_2Me), 3.59 (s, 3H, NMe), 3.67 (s, 3H, CO_2Me), 3.37, 3.82 (each d, each 1H, J=13.2 Hz, CH_2Ar), 3.88 (s, 3H, OMe), 4.29 (dd, 1H, J=3.7, 10.6 Hz, 1-H), 6.84—7.40 (m, 8H, ArH). EI-MS m/z: 378 (M^+). *Anal.* Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.93; N, 7.40. Found: C, 73.06; H, 6.96; N, 7.57.

Methyl 6-Methoxy-9-methyl-1,2,3,4-tetrahydro-β-carboline-1-acetate (22) The same procedure as described for the preparation of **21** provided a crude product from **20** (3.71 g, 9.8 mmol) and 10% Pd–C (1.4 g), and this was purified by recrystallization from EtOH to give **22** (2.71, 96%), mp 109—110 °C. IR (KBr) cm^{-1}: 1725 (CO). ^{1}H-NMR δ: 2.60—3.30 (m, 6H, 3-H_2, 4-H_2, CH_2CO_2Me), 3.63 (s, 3H, NMe), 3.77 (s, 3H, CO_2Me), 3.85 (s, 3H, OMe), 4.59 (dd, 1H, J=3.7, 10.6 Hz, 1-H), 6.83—7.40 (m, 3H, ArH). EI-MS m/z: 288 (M^+). *Anal.* Calcd for $C_{16}H_{20}N_2O_3$: 66.64; H, 6.99; N, 9.72. Found: C, 66.79; H, 6.85; N, 9.69.

Methyl 2-*tert*-Butoxycarbonyl-6-methoxy-9-methyl-1,2,3,4-tetrahydro-β-carboline-1-acetate (24) The same procedure as described for the preparation of **23** provided a crude product from **22** (6.80 g, 23.6 mmol) and Boc_2O (6.70 g, 30.6 mmol), and this was purified by recrystallization from EtOH to give **24** (8.61 g, 94%), mp 109—110 °C. IR (KBr) cm^{-1}: 1735 and 1685 (CO). ^{1}H-NMR δ: 1.48 (s, 9H, CO_2CMe_3), 2.45—3.46 (m, 5H, CH_2CO_2Me, 4-H_2, 3-HH), 3.67 (s, 3H, NMe), 3.73 (s, 3H, CO_2Me), 3.86 (s, 3H, OMe), 4.20—4.55 (m, 1H, 3-HH), 5.60—5.87 (m, 1H, 1-H), 6.80—7.20 (m, 3H, ArH). EI-MS m/z: 388 (M^+). *Anal.* Calcd for $C_{21}H_{28}N_2O_5$: C, 64.93; H, 7.26; N, 7.21. Found: C, 65.03; H, 7.02; N, 7.34.

Methyl (1*S,2*R**,10b*S**)-7-Methoxy-10-methyl-2-vinyl-1,2,4,5,10,10b-hexahydroazeto[1′,2′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylate (28)** The same procedure as described for the preparation of **27** provided a crude product from **24** (1.50 g, 3.87 mmol) *via* **26**, and this was purified by column chromatography (30% EtOAc in hexane) to give **28** (555 mg, 44%), which was recrystallized from EtOH to give crystals, mp 117—118 °C. IR (KBr) cm^{-1}: 1730 (CO). ^{1}H-NMR δ: 2.65—3.12 (m, 4H, 4-H_2, 5-H_2), 3.15 (dd, 1H, J=2.5, 9.0 Hz, 1-H), 3.55 (s, 3H, NMe), 3.81 (s, 3H, CO_2Me), 3.89 (s, 3H, OMe), 4.32 (dd, 1H, J=7.0, 9.0 Hz, 2-H), 5.08 (br s, 1H, 10b-H), 5.24 (d, 1H, J=10.0 Hz, *cis*-CH=CHH), 5.39 (d, 1H, J=17.0 Hz, *trans*-CH=CHH), 5.93 (ddd, 1H, J=7.0, 10.0, 17.0 Hz, =CH), 6.87—7.25 (m, 3H, ArH). EI-MS m/z: 326 (M^+). *Anal.* Calcd for $C_{19}H_{22}N_2O_3$: C, 69.91; H, 6.80; N, 8.58. Found: C, 69.86; H, 7.03; N, 8.57.

Methyl (1*S,13b*S**)-13-Benzenesulfonyl-10-methoxy-1,4,7,8,13,13b-hexahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylate (29)** A solution of 80% *m*CPBA (255 mg, 1.18 mmol) in CH_2Cl_2 (30 ml) was added to a solution of **27** (446 mg, 0.99 mmol) in CH_2Cl_2 (10 ml) under ice-cooling. The reaction mixture was stirred at room temperature for 24 h, then diluted with CH_2Cl_2 (40 ml). The solution was washed with saturated $NaHCO_3$ solution, water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (50% EtOAc in hexane) to give **29** (378 mg, 82%), which was recrystallized from EtOH to give crystals, mp 158—159 °C. IR (KBr) cm^{-1}: 1735 (CO), 1370, 1165 (SO_2). ^{1}H-NMR δ: 2.40—3.10 (m, 3H, 7-HH, 8-H_2), 3.51 (m, 1H, 7-HH), 3.78 (s, 3H, CO_2Me), 3.82 (s, 3H, OMe), 4.25 (dd, 1H, J=2.5, 9.0 Hz, 1-H), 4.40 (m, 2H, 4-H_2), 5.18 (br s, 1H, 13b-H), 5.55—5.90 (m, 2H, 2-H, 3-H), 6.60—7.60 (m, 7H, ArH), 8.02 (d, 1H, J=7.5 Hz, 12-H). EI-MS m/z: 468 (M^+). *Anal.* Calcd for $C_{24}H_{24}N_2O_6$: C, 61.52; H, 5.16; N, 5.98. Found: C, 61.41; H, 5.39; N, 5.92.

Methyl (1*R,13b*S**)-13-Benzenesulfonyl-10-methoxy-1,4,7,8,13,13b-hexahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylate (30)** A solution of **29** (2.56 g, 5.47 mmol) containing DBU (1.29 g, 8.21 mmol) in benzene (100 ml) was allowed to stand at 40 °C for 24 h. The reaction mixture was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc in hexane) to give **30** (1.82 g, 71%) from the first fraction. This was recrystallized from EtOH to give crystals, mp 132—133 °C. IR (KBr) cm^{-1}: 1735 (CO), 1360, 1165 (SO_2). ^{1}H-NMR δ: 2.45—2.97 (m, 3H, 7-HH, 8-H_2), 3.32 (s, 3H, CO_2Me), 3.62 (m, 1H, 7-HH), 3.80 (s, 3H, OMe), 4.35 (dd, 1H, J=3.3, 16.0 Hz, 4-HH), 4.47 (q, 1H, J=3.3 Hz, 1-H), 4.67 (d, 1H, J=16.0 Hz, 4-HH), 4.88 (br d, 1H, J=3.3 Hz, 13b-H), 5.98 (m, 2H, 2-H, 3-H), 6.70—7.60 (m, 7H, ArH), 8.01 (d, 1H, J=7.5 Hz, 12-H). EI-MS m/z: 468 (M^+). *Anal.* Calcd for $C_{24}H_{24}N_2O_6S$: C, 61.52; H, 5.16; N, 5.98. Found: C, 61.32; H, 5.29; N, 5.98.

The second eluate (40% from EtOAc in hexane) gave the starting material (**29**) (452 mg, 17% recovery).

Methyl (1*R,13b*S**)-13-Benzenesulfonyl-10-methoxy-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylate (31)** A solution of **30** (2.54 g, 5.42 mmol) in a mixture of MeOH (10 ml) and EtOAc (150 ml) was hydrogenated with 10% Pd–C (1.0 g) under atmospheric pressure for 16 h. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated *in vacuo*. The residue was recrystallized from EtOH to give **31** (2.42 g, 95%), mp 158—160 °C. IR (KBr) cm^{-1}: 1740 (CO), 1365, 1165 (SO_2). ^{1}H-NMR δ: 1.70—2.95 (m, 7H, 2-H_2, 3-H_2, 7-HH, 8-H_2), 3.40 (s, 3H, CO_2Me), 3.52 (m, 1H, 7-HH), 3.75 (m, 1H, 4-HH), 3.78 (s, 3H, OMe), 3.97 (q, 1H, J=3.0 Hz, 1-H), 4.12 (m, 1H, 4-HH), 4.50 (br d, 1H, J=3.0 Hz, 13b-H), 6.64—7.60 (m, 7H, ArH), 7.95 (d, 1H, J=7.5 Hz, 12-H). EI-MS m/z: 470 (M^+). *Anal.* Calcd for $C_{24}H_{26}N_2O_6S$: C, 61.26; H, 5.57; N, 5.95. Found: C, 61.20; H, 5.52; N, 6.00.

Methyl (1*R,13b*S**)-10-Methoxy-1,2,3,4,7,8,13,13b-octahydro[1′,2′]-oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylate (32)** A catalytic amount of iodine was added to a stirred suspension of Mg (122 mg, 5.1 mmol) in MeOH (5 ml). A solution of **31** (160 mg, 0.34 mmol) in MeOH (5 ml) was added to this suspension and the whole was stirred at 40 °C for 3 h. 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 (30% EtOAc in hexane) to give **32** (108 mg, 96%), which was recrystallized from EtOH to give crystals, mp 198—199 °C. IR (KBr) cm^{-1}: 3400 (NH), 1735 (CO). ^{1}H-NMR δ: 1.63—1.85 (m, 1H, 3-HH), 2.0—2.23 (m, 3H, 3-HH, 2-H_2), 2.71 (m, 1H, 8-HH), 2.97—3.16 (m, 2H, 7-HH, 8-HH), 3.28 (td, 1H, J=3.8, 5.4 Hz, 1-H), 3.58 (s, 3H, CO_2Me), 3.64—3.73 (m, 1H, 7-HH), 3.85 (s, 3H, OMe), 3.88, 4.11 (each m, each 1H, 4-H_2), 4.37 (br d, 1H, J=3.8 Hz, 13b-H), 6.74—7.23 (m, 3H, ArH), 8.05 (br s, 1H, NH). EI-MS m/z: 330 (M^+). *Anal.* Calcd for $C_{18}H_{22}N_2O_4$: C, 65.43; H, 6.71; N, 8.48. Found: C, 65.36; H, 6.70; N, 8.48.

(1*R,13b*S**)-10-Methoxy-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylic Acid (33)** A solution of **32** (242 mg, 0.73 mmol) and LiOH (54 mg, 2.19 mmol) in a mixture of water (2.5 ml) and THF (20 ml) was stirred at room temperature for 16 h. After evaporation of the solvent, the residue was neutralized with 5% HCl, and extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was recrystallized from EtOH to give **33** (208 mg, 90%), mp 199—200 °C (dec.). IR (KBr) cm^{-1}: 3300 (NH and/or COOH), 1725 (CO). ^{1}H-NMR δ: 2.0—2.16 (m, 2H, 3-H_2), 2.20—2.35 (m, 2H, 2-H_2), 2.82—3.27 (m, 3H, 7-HH, 8-H_2), 3.46 (m, 1H, 1-H), 3.64—3.77 (m, 1H, 7-HH), 3.85 (s, 3H, OMe), 4.01, 4.28 (each m, each 1H, 4-H_2), 4.23 (d, 1H, J=5.4 Hz, 13b-H), 6.77—7.13 (m, 3H, ArH), 8.27 (br s, 1H, NH). EI-MS m/z: 316 (M^+). HR-MS Calcd for $C_{17}H_{20}N_2O_4$: 316.1421. Found: 316.1419. *Anal.* Calcd for $C_{17}H_{20}N_2O_4\cdot 1/10H_2O$: C, 64.18; H, 6.40; N, 8.81. Found: C, 63.94; H, 6.35; N, 8.70.

(1*R,13b*S**)-1-Benzyloxycarbonylamino-10-methoxy-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole (34)** Ethyl chloroformate (0.33 ml, 3.23 mmol) was added to a solution of **33** (787 mg, 2.49 mmol) and TEA (0.49 ml, 3.73 mmol) in THF (20 ml) under ice-cooling. The mixture was stirred for 10 min, NaN_3 (500 mg, 7.64 mmol) and MeCN (30 ml) were added, 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 partitioned between CH_2Cl_2 and water. The separated organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Benzyl alcohol

(5 ml) and anhydrous $MgSO_4$ (200 mg) were added to a solution of this residue in dry benzene (25 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 **34** (545 mg, 52%), which was recrystallized from EtOH to give crystals, mp 144—145 °C. IR (KBr) cm^{-1}: 3350 (NH), 1705 (CO). ^{1}H-NMR δ: 1.70—2.15 (m, 4H, 2-H_2, 3-H_2), 2.65—3.10 (m, 3H, 7-HH, 8-H_2), 3.52 (m, 1H, 7-HH), 3.74, 4.07 (each m, each 1H, 4-H_2), 3.85 (s, 3H, OMe), 4.14 (br s, 1H, 13b-H), 4.52 (m, 1H, 1-H), 4.85, 4.95 (each d, each 1H, J=11.0 Hz, CH_2Ar), 5.20 (d, 1H, J=10.0 Hz, NHCO), 6.77—7.45 (m, 8H, ArH), 8.07 (br s, 1H, NH). EI-MS *m/z*: 421 (M^+). *Anal.* Calcd for $C_{24}H_{27}N_3O_4$: C, 68.39; H, 6.46; N, 9.97. Found: C, 68.55; H, 6.54; N, 9.91.

(1*R,13b*S**)-1-Amino-10-methoxy-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole [6-Methoxy-12-carbaeudistomin] (8)** A solution of **34** (264 mg, 0.63 mmol) in a mixture of MeOH and EtOAc (1 : 1, 20 ml) was hydrogenated with 10% Pd–C (30 mg) under atmospheric pressure for 6 h. Work-up as described for the preparation of **31** gave a crude oil, which was purified by column chromatography (5% MeOH in $CHCl_3$) to give **8** (173 mg, 96%) as a crystalline solid. IR (KBr) cm^{-1}: 3400 (NH_2). ^{1}H-NMR δ: 1.60—2.20 (m, 4H, 2-H_2, 3-H_2), 2.55—3.0 (m, 3H, 7-HH, 8-H_2), 3.20—4.0 (m, 5H, 1-H, 4-H_2, 7-HH, 13b-H), 3.80 (s, 3H, OMe), 6.78—7.40 (m, 3H, ArH), 9.0 (br s, 1H, NH). EI-MS *m/z*: 287 (M^+). HR-MS Calcd for $C_{16}H_{21}N_3O_2$: 287.1633. Found: 287.1635. The perchlorate of **8** was recrystallized from EtOH–hexane to give an analytical sample, mp 214—215 °C (dec.). *Anal.* Calcd for $C_{16}H_{21}N_3O_2 \cdot HClO_4 \cdot 1/2H_2O$: C, 48.43; H, 5.84; N, 10.59. Found: C, 48.59; H, 5.81; N, 10.54.

(1*R,13b*S**)-1-Amino-10-hydroxy-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole [6-Hydroxy-12-carbaeudistomin] (10) and (1*R**,13b*S**)-1-Amino-10-ethylthio-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole (35)** A solution of **34** (100 mg, 0.24 mmol) in CH_2Cl_2 (2.5 ml) was added to a stirred suspension of $AlBr_3$ (380 mg, 1.4 mmol) in EtSH (2.5 ml) under ice-cooling. The reaction mixture was stirred at room temperature for 1 h, then the reaction was quenched with water (10 ml), and the whole 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 (10% MeOH in $CHCl_3$) to give **35** (15 mg, 20%) as an oil. IR (neat) cm^{-1}: 3400 (NH_2). ^{1}H-NMR δ: 1.10—1.42 (t, 3H, J=7.5 Hz, MeCH$_2$S), 1.69—2.50 (m, 4H, 2-H_2, 3-H_2), 2.65—3.12 (m, 5H, 7-HH, 8-H_2, SCH$_2$Me), 3.46—4.36 (m, 5H, 1-H, 4-H_2, 7-HH, 13b-H), 6.95—7.65 (m, 3H, ArH), 9.0 (br s, 1H, NH). EI-MS *m/z*: 317 (M^+). HR-MS Calcd for $C_{17}H_{23}N_3OS$: 317.1561. Found: 317.1561.

The aqueous layer was saturated with NaCl and extracted with a mixture of $CHCl_3$ and MeOH (2 : 1, 30 ml). The extract was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (10% MeOH in $CHCl_3$) to give **10** (52 mg, 80%) as an amorphous powder. IR (KBr) cm^{-1}: 2850—3470 (NH_2, OH). ^{1}H-NMR δ: 1.72—2.25 (m, 4H, 2-H_2, 3-H_2), 2.58—3.05 (m, 3H, 7-HH, 8-H_2), 3.42—3.81 (m, 2H, 1-H, 7-HH), 3.99—4.25 (m, 3H, 4-H_2, 13b-H), 7.22—7.61 (m, 3H, ArH), 9.0 (br s, 1H, indole-NH). EI-MS *m/z*: 273 (M^+). HR-MS Calcd for $C_{15}H_{19}N_3O_2$: 273.1476. Found: 273.1472.

Methyl (1*R,2*R**,10b*S**)-7-Methoxy-10-methyl-2-vinyl-1,2,4,5,10,10b-hexahydroazeto[1′,2′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylate (36)** A solution of **28** (1.21 g, 3.71 mmol) containing 95% NaOMe (408 mg, 7.42 mmol) in dry MeOH (30 ml) was refluxed for 2 h. After evaporation of the solvent, the residue was extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc in hexane) to recover **28** (468 mg, 39%) from the first fraction. The second eluate (50% EtOAc in hexane) gave **36** (660 mg, 55%), which was recrystallized from EtOH to give crystals, mp 134—135 °C. IR (KBr) cm^{-1}: 1725 (CO). ^{1}H-NMR δ: 2.50—3.14 (m, 4H, 4-H_2, 5-H_2), 3.46 (s, 3H, CO_2Me), 3.54 (s, 3H, NMe), 3.65 (t, 1H, J=8.0 Hz, 1-H), 3.88 (s, 3H, OMe), 4.36 (t, 1H, J=8.0 Hz, 2-H), 5.13 (d, 1H, J=8.0 Hz, 10b-H), 5.20 (d, 1H, J=10.0 Hz, *cis*-CH=CHH), 5.36 (d, 1H, J=17.0 Hz, *trans*-CH=CHH), 6.0 (ddd, 1H, J=7.0, 10.0, 17.0 Hz, =CH), 6.83—7.22 (m, 3H, ArH). EI-MS *m/z*: 326 (M^+). *Anal.* Calcd for $C_{19}H_{22}N_2O_3$: C, 69.91; H, 6.80; N, 8.58. Found: C, 69.66; H, 6.59; N, 8.54.

Methyl (1*R,13b*S**)-10-Methoxy-13-methyl-1,4,7,8,13,13b-hexahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylate (37)** The same procedure as described for the preparation of **29** provided a crude product from **36** (238 mg, 0.73 mmol) and 80% *m*CPBA (189 mg, 0.88 mmol), and this was purified by column chromatography (30% EtOAc in hexane) to give **37** (234 mg, 94%) as an amorphous powder. IR (KBr) cm^{-1}: 1735 (CO). ^{1}H-NMR δ: 2.65—3.10 (m, 3H, 7-HH, 8-H_2), 3.24 (s, 3H, CO_2Me), 3.63 (m, 1H, 7-HH), 3.68 (s, 3H, NMe), 3.84 (s, 3H, OMe), 3.93 (t, 1H, J=5.0 Hz, 1-H), 4.34 (dd, 1H, J=5.0, 17.5 Hz, 4-H), 4.64 (d, 1H, J=4.0 Hz, 13b-H), 4.74 (d, 1H, J=17.5 Hz, 4-H), 5.75 (m, 1H, 2-H), 5.96 (m, 1H, 3-H), 6.80—7.20 (m, 3H, ArH). EI-MS *m/z*: 342 (M^+). HR-MS Calcd for $C_{19}H_{22}N_2O_4$: 342.1578. Found: 342.1572.

Methyl (1*R,13b*S**)-10-Methoxy-13-methyl-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylate (38)** The same procedure as described for the preparation of **8** provided a crude product from **37** (228 mg, 0.67 mmol) and 10% Pd–C (50 mg), and this was purified by column chromatography (30% EtOAc in hexane) to give **38** (219 mg, 96%) as an amorphous powder. IR (KBr) cm^{-1}: 1740 (CO). ^{1}H-NMR δ: 1.68—1.88 (m, 1H, 3-HH), 2.05—2.40 (m, 3H, 2-H_2, 3-HH), 2.67—3.03 (m, 3H, 7-HH, 8-H_2), 3.24 (s, 3H, CO_2Me), 3.36 (d, 1H, J=5.5 Hz, 1-H), 3.53 (m, 1H, 7-HH), 3.64 (s, 3H, NMe), 3.70—3.80 (m, 1H, 4-HH), 3.84 (s, 3H, OMe), 4.11 (m, 1H, 4-HH), 4.37 (d, 1H, J=5.5 Hz, 13b-H), 6.78—7.27 (m, 3H, ArH). EI-MS *m/z*: 344 (M^+). HR-MS Calcd for $C_{19}H_{24}N_2O_4$: 344.1735. Found: 344.1739.

(1*R,2*R**,10b*S**)-7-Methoxy-10-methyl-2-vinyl-1,2,4,5,10,10b-hexahydroazeto[1′,2′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylic Acid (39)** The same procedure as described for the preparation of **33** provided a crude product from **36** (396 mg, 1.21 mmol) and LiOH (89 mg, 3.64 mmol), and this was purified by recrystallization from isopropanol to give **39** (338 mg, 89%), mp 201—203 °C. IR (KBr) cm^{-1}: 3500 (COOH), 1625 (CO). ^{1}H-NMR δ: 2.20—3.0 (m, 4H, 4-H_2, 5-H_2), 3.37 (s, 3H, NMe), 3.70 (t, 1H, J=8.0 Hz, 1-H), 3.80 (s, 3H, OMe), 4.62 (t, 1H, J=7.5 Hz, 2-H), 5.06 (d, 1H, J=10.0 Hz, *cis*-CH=CHH), 5.20—5.40 (m, 2H, 10b-H, *trans*-CH=CHH), 5.88 (m, 1H, =CH), 6.70—7.05 (m, 3H, ArH). EI-MS *m/z*: 312 (M^+). HR-MS Calcd for $C_{18}H_{20}N_2O_3$: 312.1473. Found: 312.1468. *Anal.* Calcd for $C_{18}H_{20}N_2O_3 \cdot 1/10H_2O$: C, 68.81; H, 6.48; N, 8.92. Found: C, 68.83; H, 6.45; N, 8.91.

Benzyl (1*R,2*R**,10b*S**)-7-Methoxy-10-methyl-2-vinyl-1,2,4,5,10,10b-hexahydroazeto[1′,2′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylate (40)** WSCI (149 mg, 0.78 mmol) was added to a solution of **39** (220 mg, 0.71 mmol), benzyl alcohol (78 mg, 1.06 mmol) and a catalytic amount of 4-dimethylaminopyridine (8.6 mg, 0.07 mmol) in CH_2Cl_2 (5 ml) under ice-cooling, and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with CH_2Cl_2, and the solution was washed with 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 **40** (230 mg, 81%), which was recrystallized from EtOH to give crystals, mp 141—142 °C. IR (KBr) cm^{-1}: 1725 (CO). ^{1}H-NMR δ: 2.46—3.14 (m, 4H, 4-H_2, 5-H_2), 3.32 (s, 3H, NMe), 3.70 (t, 1H, J=8.0 Hz, 1-H), 3.89 (s, 3H, OMe), 4.40 (t, 1H, J=8.0 Hz, 2-H), 4.48 (s, 2H, CH_2Ar), 5.13 (d, 1H, J=8.0 Hz, 10b-H), 5.20 (d, 1H, J=10.0 Hz, *cis*-CH=CHH), 5.36 (d, 1H, J=17.0 Hz, *trans*-CH=CHH), 6.0 (ddd, 1H, J=7.0, 10.0, 17.0 Hz, =CH), 6.84—7.31 (m, 8H, ArH). EI-MS *m/z*: 402 (M^+). *Anal.* Calcd for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96. Found: C, 74.40; H, 6.52; N, 7.10.

Benzyl (1*R,13b*S**)-10-Methoxy-13-methyl-1,4,7,8,13,13b-hexahydro-[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylate (41)** The same procedure as described for the preparation of **37** provided a crude product from **40** (465 mg, 1.16 mmol) and 80% mCPBA (299 mg, 1.39 mmol), and this was purified by column chromatography (30% EtOAc in hexane) to give **41** (441 mg, 91%), which was recrystallized from EtOH to give crystals, mp 112—113 °C. IR (KBr) cm^{-1}: 1735 (CO). ^{1}H-NMR δ: 2.61—3.10 (m, 3H, 7-HH, 8-H_2), 3.61 (s, 3H, NMe), 3.67 (m, 1H, 7-HH), 3.87 (s, 3H, OMe), 3.97 (t, 1H, J=5.0 Hz, 1-H), 4.36 (dd, 1H, J=5.0, 17.5 Hz, 4-H), 4.55, 4.75 (each d, each 1H, J=11.0 Hz, CH_2Ar), 4.64 (d, 1H, J=4.0 Hz, 13b-H), 4.76 (d, 1H, J=17.5 Hz, 4-H), 5.79 (m, 1H, 2-H), 6.01 (m, 1H, 3-H), 6.69—7.24 (m, 8H, ArH). EI-MS *m/z*: 418 (M^+). *Anal.* Calcd for $C_{25}H_{26}N_2O_4$: C, 71.75; H, 6.28; N, 6.69. Found: C, 71.80; H, 6.33; N, 6.77.

(1*R,13b*S**)-10-Methoxy-13-methyl-1,2,3,4,7,8,13,13b-octahydro-[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylic Acid (42)** The same procedure as described for the preparation of **31** provided a crude product from **41** (166 mg, 0.4 mmol) and 10% Pd–C (100 mg), and this was purified by column chromatography (EtOAc) to give **42** (124 mg, 94%), which was recrystallized from isopropanol, mp 201—203 °C. IR (KBr) cm^{-1}: 1740 (CO). ^{1}H-NMR δ: 1.96—2.20 (m, 2H, 3-H_2),

2.20—2.35 (m, 2H, 2-H_2), 2.71—3.26 (m, 3H, 7-HH, 8-H_2), 3.66 (m, 1H, 7-HH), 3.70 (s, 3H, NMe), 3.87 (s, 3H, OMe), 3.73—4.03, 4.21—4.32 (each m, each 1H, 4-H_2), 4.35 (br s, 1H, 13b-H), 6.86—7.22 (m, 3H, ArH). EI-MS *m/z*: 330 (M^+). *Anal.* Calcd for $C_{18}H_{20}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.25; H, 6.74; N, 8.35.

(1*R,13b*S**)-1-Benzyloxycarbonylamino-10-methoxy-13-methyl-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole (43)** The same procedure as described for the preparation of **34** provided a crude product from **42** (232 mg, 0.38 mmol), TEA (0.15 ml, 1.05 mmol), ethyl chloroformate (0.087 ml, 0.91 mmol), NaN_3 (137 mg, 1.30 mmol) and benzyl alcohol (2 ml), and this was purified by column chromatography (15% EtOAc in hexane) to give **43** (88 mg, 29%) as an oil. IR ($CHCl_3$) cm^{-1}: 3400 (NH), 1715 (CO). ^{1}H-NMR δ: 1.65—2.25 (m, 4H, 2-H_2, 3-H_2), 2.65—3.10 (m, 3H, 7-HH, 8-H_2), 3.43 (m, 1H, 7-HH), 3.73, 4.06 (each m, each 1H, 4-H_2), 3.70 (s, 3H, NMe), 3.87 (s, 3H, OMe), 4.24 (br s, 1H, 13b-H), 4.66 (m, 1H, 1-H), 4.83 (s, 2H, CH_2Ar), 5.13 (d, 1H, J=10.0 Hz, NHCO), 6.83—7.40 (m, 8H, ArH). EI-MS *m/z*: 435 (M^+). HR-MS Calcd for $C_{25}H_{29}N_3O_4$: 435.2156. Found: 435.2149.

(1*R,13b*S**)-Amino-10-methoxy-13-methyl-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole (9)** The same procedure as described for the preparation of **8** provided a crude product from **43** (80 mg, 0.18 mmol) and 10% Pd–C (25 mg), and this was purified by column chromatography (5% MeOH in $CHCl_3$) to give **9** (52 mg, 94%) as an oil. IR ($CHCl_3$) cm^{-1}: 3400 (NH_2). ^{1}H-NMR cm^{-1}: 1.60—2.20 (m, 4H, 2-H_2, 3-H_2), 2.65—3.08 (m, 3H, 7-HH, 8-H_2), 3.40—4.30 (m, 5H, 1-H, 4-H_2, 7-HH, 13b-H), 3.65 (s, 3H, NMe), 3.87 (s, 3H, OMe), 6.83—7.20 (m, 3H, ArH). EI-MS *m/z*: 301 (M^+). HR-MS Calcd for $C_{17}H_{23}N_3O_2$: 301.1788. Found: 301.1791.

(1*R*,2*R,10b*S**)-1-Benzyloxycarbonylamino-7-methoxy-10-methyl-2-vinyl-1,2,4,5,10,10b-hexahydroazeto[1′,2′ : 1,2]pyrido[3,4-*b*]indole (44)** A solution of **39** (146 mg, 0.47 mmol), TEA (52 mg, 0.52 mmol) and DPPA (135 mg, 0.49 mmol) in benzene (10 ml) was refluxed for 1 h. Benzyl alcohol (101 mg, 0.94 mmol) was added to the reaction mixture, and the whole was refluxed for an additional 24 h, then diluted with EtOAc. The reaction mixture was washed with 10% citric acid solution, water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (50% EtOAc in hexane) to give **44** (9.0 mg, 4.6%) as a solid. IR (KBr) cm^{-1}: 3400 (NH), 1725 (CO). ^{1}H-NMR δ: 2.58—3.15 (m, 4H, 4-H_2, 5-H_2), 3.33 (s, 3H, NMe), 3.65 (t, 1H, J=8.5 Hz, 1-H), 3.88 (s, 3H, OMe), 4.70 (m, 1H, 2-H), 5.05, 5.28 (each d, each 1H, J=11.0 Hz, CH_2Ar), 5.15 (d, 1H, J=8.0 Hz, 10b-H), 4.98 (m, 2H, $-CH=CH_2$), 6.02 (m, 1H, CH=), 6.85—7.39 (m, 8H, ArH). EI-MS *m/z*: 417 (M^+). HR-MS Calcd for $C_{25}H_{27}N_3O_3$: 417.2051. Found: 417.2053.

(1*R,13b*S**)-13-Benzenesulfonyl-1-hydroxymethyl-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole (46)** A 1.5 M solution of DIBAL in THF (5.8 ml, 8.7 mmol) was added to a solution of **45** (1.28 g, 2.9 mmol) in THF (12 ml) at −78 °C. The mixture was stirred at 0 °C for 40 min, then the reaction was quenched with cold water and the whole was extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc in hexane) to give **46** (1.14 g, 95%), which was recrystallized from a mixture of EtOH and hexane to give crystals, mp 154—157 °C. IR (KBr) cm^{-1}: 3420 (OH), 1370, 1170 (SO_2). ^{1}H-NMR δ: 1.87 (m, 1H, 3-H), 2.13 (m, 2H, 2-H_2), 2.28 (m, 1H, 3-H), 2.45—2.92 (m, 3H, 7-HH, 8-H_2), 3.01 (m, 1H, 1-H), 3.34 (dd, 1H, J=3.3, 11.1 Hz, CHHOH), 3.45 (m, 1H, 7-HH), 3.55 (dd, 1H, J=6.8, 11.1 Hz, CHHOH), 3.85 (m, 1H, 4-HH), 4.12 (m, 1H, 4-HH), 4.62 (br s, 1H, 13b-H), 7.20—7.50 (m, 6H, ArH), 7.60 (d, 2H, J=8.0 Hz, ArH), 8.12 (d, 1H, J=7.5 Hz, 12-H). EI-MS *m/z*: 412 (M^+). *Anal.* Calcd for $C_{22}H_{24}N_2O_4S$: C, 64.06; H, 5.86; N, 6.79. Found: C, 64.15; H, 5.88; N, 6.79.

(1*R,13b*S**)-13-Benzenesulfonyl-1,2,3,4,7,8,13,13b-octahydro[1′,2′]-oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole-1-carbaldehyde (47)** A solution of **46** (85 mg, 0.21 mmol) in CH_2Cl_2 (2 ml) was added to a solution of PDC (240 mg, 0.61 mmol) in CH_2Cl_2 (2 ml) at room temperature. The reaction mixture was stirred for 5 h, then filtered through a Celite pad. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography ($CHCl_3$) to give **47** (77 mg, 91%), which was recrystallized from a mixture of EtOH and hexane to give crystals, mp 164—167 °C. IR (KBr) cm^{-1}: 1720 (CO), 1370, 1170 (SO_2), ^{1}H-NMR δ: 1.77 (m, 1H, 3-HH), 2.05 (m, 2H, 2-HH, 3-HH), 2.43 (m, 1H, 2-HH), 2.63 (m, 1H, 8-HH), 2.82 (m, 1H, 8-HH), 2.94 (m, 1H, 7-HH), 3.52 (m, 1H, 7-HH), 3.64 (m, 1H, 1-H), 3.77 (m, 1H, 4-HH), 4.07 (m, 1H, 4-HH), 4.71 (br s, 1H, 13b-H), 7.20—7.50 (m, 6H, ArH), 7.60 (d, 2H, J=8.0 Hz, ArH), 8.12 (d, 1H, J=7.5 Hz, 12-H), 9.27 (s, 1H, CHO). EI-MS *m/z*: 410 (M^+). *Anal.* Calcd for $C_{22}H_{22}N_2O_4S$: C, 64.37; H, 5.40; N, 6.82. Found: C, 64.42; H, 5.46; N, 6.79.

(1*S,13b*S**)-13-Benzenesulfonyl-1-benzylaminomethyl-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole (51)** From **47**: A suspension of **47** (254 mg, 0.62 mmol) and benzylamine (66 mg, 0.62 mmol) in the presence of molecular sieves 4 Å (200 mg) in a mixture of EtOH and benzene (1 : 1, 10 ml) was stirred at room temperature for 24 h, then $NaBH_4$ (124 mg, 3.3 mmol) was added portionwise, and the whole was stirred for an additional 24 h. The molecular sieves was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was partitioned between EtOAc and water, and the separated organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (25% EtOAc in benzene) to give **51** (262 mg, 85%), which was recrystallized from EtOH to give crystals, mp 175—178 °C. IR (KBr) cm^{-1}: 3400 (NH), 1370, 1170 (SO_2). ^{1}H-NMR δ: 1.70 (m, 1H, 3-HH), 2.08 (m, 4H, 2-H_2, 3-HH, CHHNH), 2.56 (m, 3H, 8-H_2, CHHNH), 2.81 (dt, 1H, J=3.2, 9.7 Hz, 7-HH), 3.05 (br s, 1H, 1-H), 3.39 (m, 1H, 7-HH), 3.57 (dd, 2H, J=12.7, 18.8 Hz, CH_2Ar), 3.73 (m, 1H, 4-HH), 4.07 (m, 1H, 4-HH), 4.53 (br s, 1H, 13b-H), 7.05—7.45 (m, 11H, ArH), 7.60 (d, 2H, J=8.0 Hz, ArH), 8.12 (d, 1H, J=7.5 Hz, 12-H). EI-MS *m/z*: 501 (M^+). *Anal.* Calcd for $C_{29}H_{31}N_3O_3S$: C, 69.43; H, 6.23; N, 8.38. Found: C, 69.27; H, 6.25; N, 8.46.

From **50**: The same procedure as that starting from **47** provided a crude product from **50** (53 mg, 0.13 mmol), and this was purified by column chromatography to give **51** (35 mg, 54%). This was identical with **51** obtained from **47** based on comparison of their ^{1}H-NMR spectra.

(1*S,13b*S**)-1-Benzylaminomethyl-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole (52)** A solution of **51** (101 mg, 0.2 mmol) in THF (7 ml) was added to a suspension of $LiAlH_4$ (114 mg, 3.0 mmol) in THF (1 ml) under ice-cooling. The reaction mixture was stirred at 40 °C for 12 h, then quenched with cold water under ice-cooling and 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 (10% MeOH in $CHCl_3$) to give **52** (72 mg, 99%), which was recrystallized from EtOH to give crystals, mp 145—148 °C. IR (KBr) cm^{-1}: 3400 (NH). ^{1}H-NMR δ: 1.73 (m, 1H, 3-HH), 1.96 (m, 3H, 2-H_2, 3-HH), 2.50 (m, 2H, 1-H, CHHNH), 2.62—3.07 (m, 4H, 7-HH, 8-H_2, CHHNH), 3.53 (m, 1H, 7-HH), 3.63 (s, 2H, CH_2Ar), 3.83 (m, 1H, 4-HH), 4.03 (m, 1H, 4-HH), 4.17 (s, 1H, 13b-H), 7.07—7.54 (m, 9H, ArH). EI-MS *m/z*: 361 (M^+). *Anal.* Calcd for $C_{23}H_{27}N_3O$: C, 76.42; H, 7.53; N, 11.62. Found: C, 76.58; H, 7.58; N, 11.34.

(1*S,13b*S**)-1-Aminomethyl-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole [Homo-12-carbaeudistomin] (14)** A solution of **52** (360 mg, 1.0 mmol) in MeOH (24 ml) was hydrogenated over 10% Pd–C (300 mg) under the initial pressure of 4 kg/cm^2 for 24 h. The catalyst was removed through a Celite pad, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (15% MeOH in $CHCl_3$) to give **14** (201 mg, 74%), which was recrystallized from a mixture of EtOH and hexane to give crystals, mp 206—208 °C. IR (KBr) cm^{-1}: 3400 (NH_2). ^{1}H-NMR δ: 1.74 (m, 1H, 3-HH), 2.0 (m, 3H, 2-H_2, 3-HH), 2.30 (m, 1H, 1-H), 2.45 (dd, 1H, J=4.7, 13.3 Hz, CHHNH), 2.88 (m, 4H, 7-HH, 8-H_2, CHHNH), 3.53 (m, 1H, 7-HH), 3.81 (m, 1H, 4-HH), 4.12 (m, 2H, 4-HH, 13b-H), 7.05—7.50 (m, 4H, ArH), 8.88 (m, 4H, ArH). EI-MS *m/z*: 271 (M^+). *Anal.* Calcd for $C_{16}H_{21}N_3O$: C, 70.82; H, 7.80; N, 15.49. Found: C, 70.85; H, 7.88; N, 15.50.

(1*S,13b*S**)-13-Benzenesulfonyl-1-hydroxymethyl-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′ : 1,2]pyrido[3,4-*b*]indole (49)** The same procedure as described for the preparation of **46** provided a crude product from **48** (100 mg, 0.23 mmol) and DIBAL (2.05 ml, 2.05 mmol), and this was purified by column chromatography (30% EtOAc in $CHCl_3$) to give **49** (88 mg, 94%), which was recrystallized from EtOH to give crystals, mp 215—217 °C. IR (KBr) cm^{-1}: 3600 (OH), 1360, 1160 (SO_2). ^{1}H-NMR δ: 1.67 (m, 1H, 3-H), 1.80—2.50 (m, 5H, 2-H_2, 3-H_2, 8-HH), 2.75 (m, 1H, 1-H), 2.85 (m, 2H, 7-HH, 8-HH), 3.48 (m, 1H, 7-HH), 3.90 (m, 2H, 4-H_2), 4.15 (m, 3H, 13b-H, CH_2OH), 7.13—7.44 (m, 6H, ArH), 7.47 (d, 2H, J=8.0 Hz, ArH), 8.10 (d, 1H, J=7.5 Hz, 12-H). EI-MS *m/z*: 412 (M^+). *Anal.* Calcd for $C_{22}H_{24}N_2O_4S$: C, 64.06; H, 5.86; N, 6.79. Found: C, 64.05; H, 5.86; N, 6.73.

(1*S,13b*S**)-13-Benzenesulfonyl-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′:1,2]pyrido[3,4-*b*]indole-1-carbaldehyde (50)** The same procedure as described for the preparation of **47** provided a crude product from **49** (100 mg, 0.24 mmol) and PDC (365 mg, 0.97 mmol), and this was purified by column chromatography to give **50** (75 mg, 80%), which was recrystallized from EtOAc to afford crystals, mp 224—227 °C. IR (KBr) cm^{-1}: 1720 (CO), 1360, 1160 (SO_2). ^{1}H-NMR δ: 1.68 (m, 2H, 3-H_2), 2.22 (m, 2H, 2-H_2), 2.50 (m, 1H, 8-HH), 2.88 (m, 2H, 7-HH, 8-HH), 3.54 (m, 1H, 7-HH), 3.80 (m, 3H, 1-H, 4-H_2), 4.95 (br s, 1H, 13b-H), 7.20—7.50 (m, 6H, ArH), 7.55 (d, 2H, J=8.0 Hz, ArH), 8.12 (d, 1H, J=7.5 Hz, 12-H), 9.98 (s, 1H, CHO). EI-MS m/z: 410 (M^+). *Anal.* Calcd for $C_{22}H_{22}N_2O_4S$: C, 64.37; H, 5.40; N, 6.82. Found: C, 64.20; H, 5.49; N, 6.75.

(1*R,13b*S**)-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′:1,2]-pyrido[3,4-*b*]indole-1-carboxamide (15)** Ethyl chloroformate (0.1 ml, 1.3 mmol) was added to a solution of **53** (286 mg, 1.0 mmol) and TEA (0.2 ml, 1.5 mmol) in THF (10 ml) under ice-cooling. The mixture was stirred for 10 min, then gaseous NH_3 was bubbled into it, and the whole was stirred at room temperature for 30 min. The solvent was removed by evaporation under reduced pressure, and the residue was dissolved in $CHCl_3$ and water. The separated organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was recrystallized from EtOH to give **15** (279 mg, 98%) as crystals, mp 210—211 °C. IR (KBr) cm^{-1}: 3400 (NH_2), 1660 (CO). ^{1}H-NMR δ: 1.82—2.33 (m, 5H, 2-H_2, 3-H_2, 8-HH), 2.87—3.16 (m, 2H, 7-HH, 8-HH), 3.32 (br s, 1H, 1-H), 3.61 (m, 1H, 7-HH), 3.85 (m, 1H, 4-HH), 4.16 (m, 2H, 4-HH, 13b-H), 5.50 (br s, 2H, $CONH_2$), 7.04—7.52 (m, 4H, ArH), 9.10 (br s, 1H, NH). *Anal.* Calcd for $C_{16}H_{19}N_3O_2$: C, 67.35; H, 6.71; N, 14.73. Found: C, 67.15; H, 6.73; N, 14.61.

Determination of Antiviral and Anticellular Activity All compounds were dissolved in DMSO at 10 mg/ml, and stored at −20 °C. The A/PR/8/34 (H1N1) strain of influenza A virus and the B/Gifu/2/73 strain of influenza B virus were grown in 11-day-old embryonated eggs. The VR-3 and $VRTK^-$ strains of HSV-1, the UW-268 and $UWTK^-$ strains of HSV-2, and the AD-169 stain of human cytomegalovirus were grow in human embryonic lung (HEL) cells. The infectivity titer (plaque forming unit) was determined, and the viruses were stored in small aliquots at −80 °C. MDCK cells (strain cell of canine kidney cell) and HEL cells were cultivated in Eagle's minimum essential medium (MEM) supplemented with 10% calf serum.

Assay for antiviral activities of the test compounds towards influenza viruses was carried out by the 50% plaque reduction method as follows. Confluent monolayers of MDCK cells grown in a 24-well microplate were infected with about 50 PFU of the A/PR/8/34 strain or the B/Gifu/2/73 strain per well. After 1.5 h of incubation at 37 °C, the cell sheets were washed 3 times with MEM and overlaid with MEM containing 10 μg/ml trypsin, a 3-fold concentration of MEM–amino acids and vitamins, 0.8% agar and serially diluted test compound. The infected cells were incubated at 37 °C for 2 d, fixed with formalin and stained with crystal violet. The plaque counts were expressed as a percentage of the number obtained in controls wells and were plotted to give dose–response lines, from which the 50% plaque inhibition dose (ID_{50}) was calculated.

Antiviral activities of the test compounds against herpes viruses were also determined by the above method except that HEL cell monolayers in 24-well microplates were used and the infected cells were overlayed with MEM containing 2% calf serum, 0.5% methyl cellulose and serially diluted test compound. Incubation periods were 3 d for HSV-1 and HSV-2, and 2 to 3 weeks for cytomegalovirus.

Assay for inhibitory effect of the test compounds on cell growth was carried out as follows. The MDCK cells or the HEL cells were seeded in 24-well microplates at 2×10^4 cells/well. After 2 d, the cells were replenished with MEM–10% calf serum containing an appropriate amount of the test compound. After incubation for 2 d, cells were dispersed by treatment with trypsin, and the viable cell numbers were counted. The 50% effective dose for cell growth (ED_{50}) was determined graphically.

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