Meisenheimer Rearrangement of Azetopyridoindoles. V.[1] Synthesis of 9-Methyl-12-carbaeudistomin and Related Compounds

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9-Methyl-12-carbaeudistomin (1,13b-*cis*-1-amino-13-methyl-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino-[2′,3′: 1,2]pyrido[3,4-*b*]indole) (2), which has a carbon atom instead of the sulfur atom in the D-ring of tetracyclic eudistomins (1), its 1,10-*trans* isomer (3), and their 11,12-didehydro derivatives (4 and 5) were synthesized from 2-vinylazetopyridoindoles (8 and 17) *via* the [2,3]-Meisenheimer rearrangement of the corresponding *N*-oxides, for structure–activity relationship study of eudistomins (1). Similarly, 5-amino-3,6-epoxyhexahydroazocino[5,4-*b*]-indoles (6 and 7) were synthesized from 2-ethylazetopyridoindole (33) *via* the [1,2]-Meisenheimer rearrangement of the corresponding *N*-oxide.

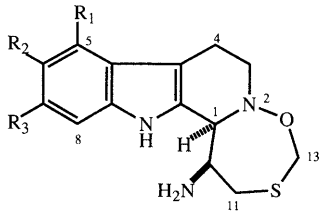
Keywords Meisenheimer rearrangement; 9-methyl-12-carbaeudistomin; azetopyridoindole; oxazepinopyridoindole; epoxyazocinoindole; Curtius rearrangement

Eudistomins (**1**) containing a unique 1,3,7-oxathiazepine ring system were isolated by Rinehart and co-workers from the colonial tunicate *Eudistoma olivaceum* in 1984,[3] and they have been a synthetic target[4] in a number of laboratories due to their strong antiviral activity against the *Herpes simplex* virus (HSV-1), certain types of *in vivo* antitumor activity, and calmodulin antagonist activity.[5] The most striking structural feature of **1** is the 7-membered oxathiazepine D-ring bearing the NH_2 substituent, and the most important requirements for activity are the 1,10-*cis*-stereochemistry and the axial-NH_2 group.[6]

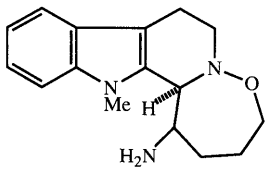
Recently, we reported a novel ring expansion of 2-vinylhexahydroazetopyridoindole (**8**) to the oxazepinopyridoindole (**9**) *via* the [2,3]-Meisenheimer rearrangement of the corresponding *N*-oxides.[7] Further, 2-ethylhexahydroazetopyridoindole (**33**) afforded 3,6-epoxyhexahydroazocinoindole (**34**) *via* the [1,2]-Meisenheimer rearrangement of the corresponding *N*-oxide.[8] The framework of **9** corresponds to that of a 12-carba-analog of eudistomins (**1**).[9] In order to study the structure–activity relationship of eudistomins (**1**), we have synthesized 9-methyl-12-carbaeudistomins (**2** and **3**), 9-methyl-11,12-didehydro-12-carbaeudistomins (**4** and **5**), as well as 5-amino-3,6-epoxyhexahydroazocinoindoles (**6** and **7**).

Synthesis of 9-Methyl-12-carbaeudistomin Derivatives We first explored synthesis of 1,13b-*trans* and 1,13b-*cis*-octahydrooxazepinopyridoindole-1-carboxylic acids (**11** and **16**) (Chart 1). Catalytic hydrogenation of oxazepine (**9**), prepared by oxidation of **8**[10] with *m*-chloroperbenzoic acid (MCPBA) in methylene dichloride (CH_2Cl_2), with 10% palladium on charcoal (Pd–C) in MeOH gave the dihydro derivative (**10**) (96%). Although alkaline hydrolysis of **10** even in refluxing MeOH did not proceed, the 1,13b-*trans*-carboxylic acid (**11**) was successfully obtained by treatment with powdered KOH/18-crown-6 in benzene at room temperature or with the aluminum tribromide/ethanethiol ($AlBr_3$/EtSH) system[11] in almost quantitative yield, respectively. However, the former reaction took too long to go to complete, so the latter was preferred. On the other hand, when the ester (**10**) was exposed to a cleavage condition, such as potassium *tert*-butoxide in dimethyl sulfoxide (DMSO), a crystalline product (**12**) was isolated in 60% yield. The IR spectrum showed characteristic absorption bands (3200 and 1620 cm^{-1}) due to the secondary vinylogous urethane moiety. The ^{1}H-NMR spectrum indicated the absence of methoxy protons. On the basis of these results, the structure of **12** was determined to be 9-methyl-1-(tetrahydro-2-pyron-3-ylidene)-1,2,3,4-tetrahydro-β-carboline. The mechanism of the formation of **12** from **10**, involving an initial formation of isoxazolidinone followed by dehydration of hydroxylamine, is proposed to be as shown in Chart 2.

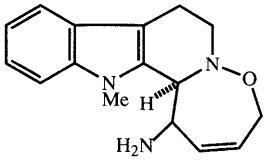
Efforts were next directed to the synthesis of the 1,13b-*cis*-carboxylic acid (**16**). Catalytic hydrogenation of the α,β-unsaturated ester (**13**)[11] over 5% rhodium (Rh) on alumina under an initial pressure of 3 kg/cm^2 gave the 1,13b-*cis*-ester (**19**) as a sole product in 38% yield. On the other hand, reduction of **13** with magnesium (Mg) in



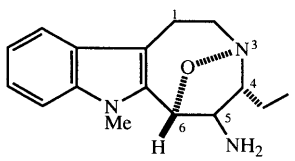
eudistomins (**1**)



2: β-NH_2 (9-methyl-12-carba-eudistomin)[a]
3: α-NH_2



4: β-NH_2 (9-methyl-11,12-didehydro-12-carbaeudistomin)[a]
5: α-NH_2



6: β-NH_2
7: α-NH_2

Fig. 1

a) Eudistomin-type numbering is used for compounds **2**—**5**.

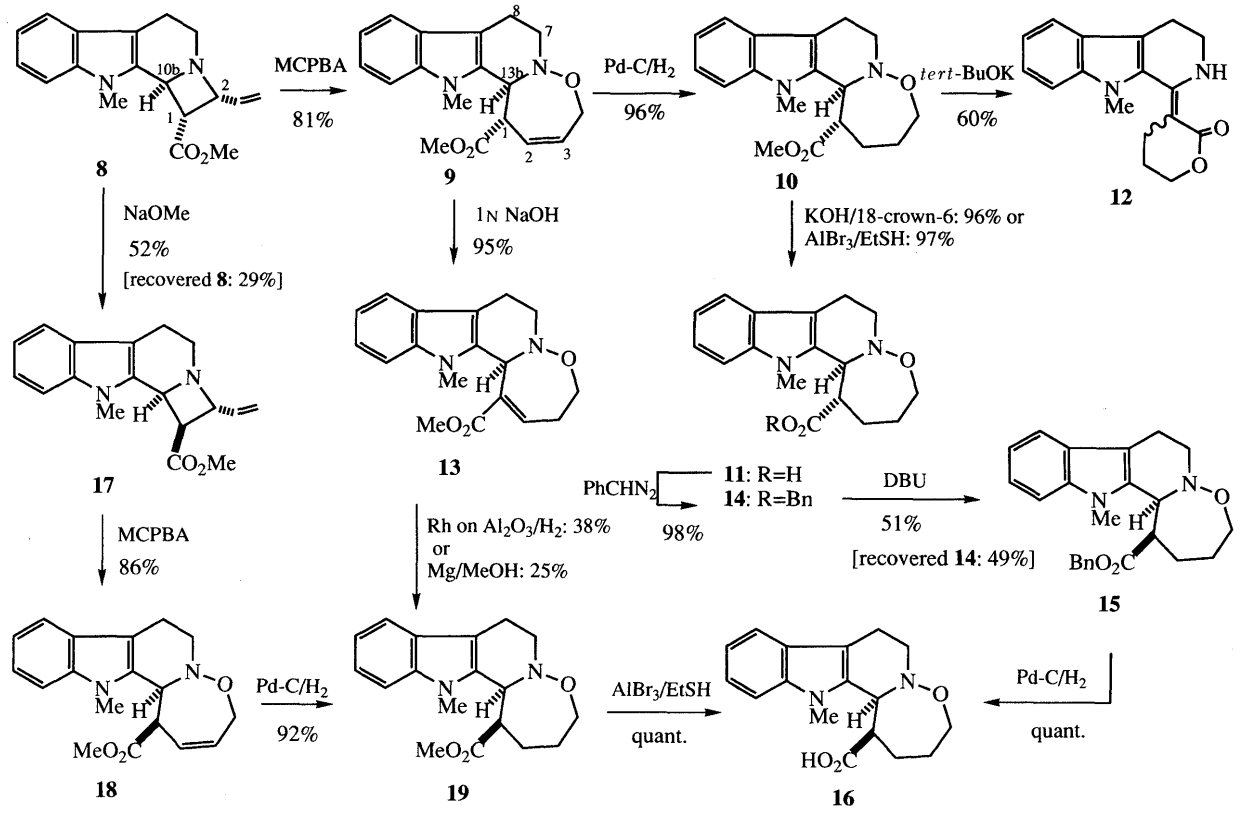


Chart 1

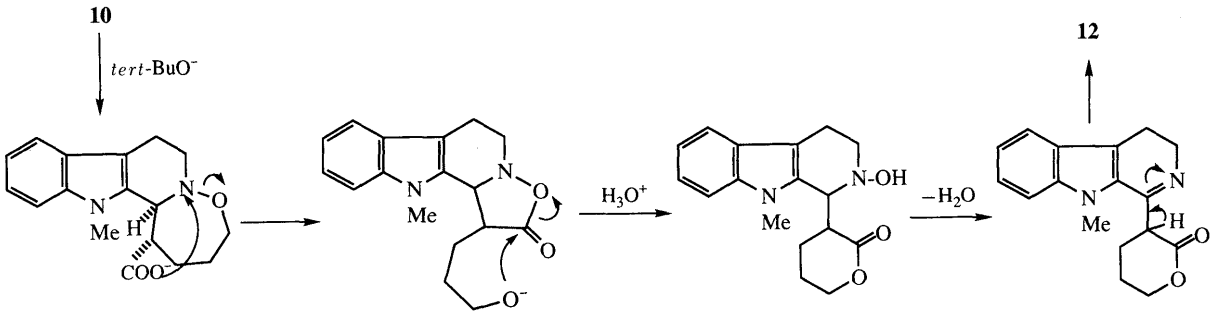


Chart 2

MeOH[12] resulted in a mixture of **19** (lower *Rf*) (25%) and **10** (upper *Rf*) (42%). In a previous paper,[1] we reported the preparation of the 1,13b-*cis*-ester (**18**) (86%) *via* the [2,3]-Meisenheimer rearrangement of the azetidine (**17**),[13] which was obtained from **8** in 52% yield by treatment with NaOMe as an equilibrium mixture with **8**. Catalytic hydrogenation (10% Pd–C) of **18** also afforded **19** in an excellent yield. Treatment of **19** with $AlBr_3$/EtSH gave the desired 1,13b-*cis*-carboxylic acid (**16**) quantitatively.

Another approach for synthesizing the 1,13b-*cis*-carboxylic acid (**16**) was investigated. Treatment of the 1,13b-*trans*-carboxylic acid (**11**) with phenyldiazomethane gave the benzyl ester (**14**) (98%), which was then warmed with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) in acetonitrile at 150 °C in a sealed tube to yield a 1 : 1 mixture of **14** and **15** in quantitative yield. The isolated 1,13b-*cis*-ester (**15**) was hydrogenolyzed with 10% Pd–C under a hydrogen atmosphere to give **16** in quantitative yield (Chart 1).

Conversion of the carboxylic acids (**11** and **16**) into the 9-methyl-12-carbaeudistomins (**3** and **2**) could be accomplished by the Curtius rearrangement (Chart 3). Treatment of the acids (**11** and **16**) with ethyl chloroformate in the presence of triethylamine (TEA), followed by the addition of sodium azide gave the acyl azides, which were, without isolation, heated in the presence of an excess of benzyl alcohol in benzene at 65 °C to give the benzyl carbamates [**20** (higher *Rf*) and **21** (lower *Rf*)] in 31 and 36% yields with recovery of the starting materials (**11** and **16**) in 22 and 38% yields, respectively. The desired amines [**3** (upper *Rf*) and **2** (lower *Rf*)] were successfully obtained by catalytic reduction of **20** and **21** over 10% Pd–C in 86 and 77% yields, respectively. The structures of these amines (**2** and **3**) were determined from the spectroscopic data (see Experimental) and on the basis of the

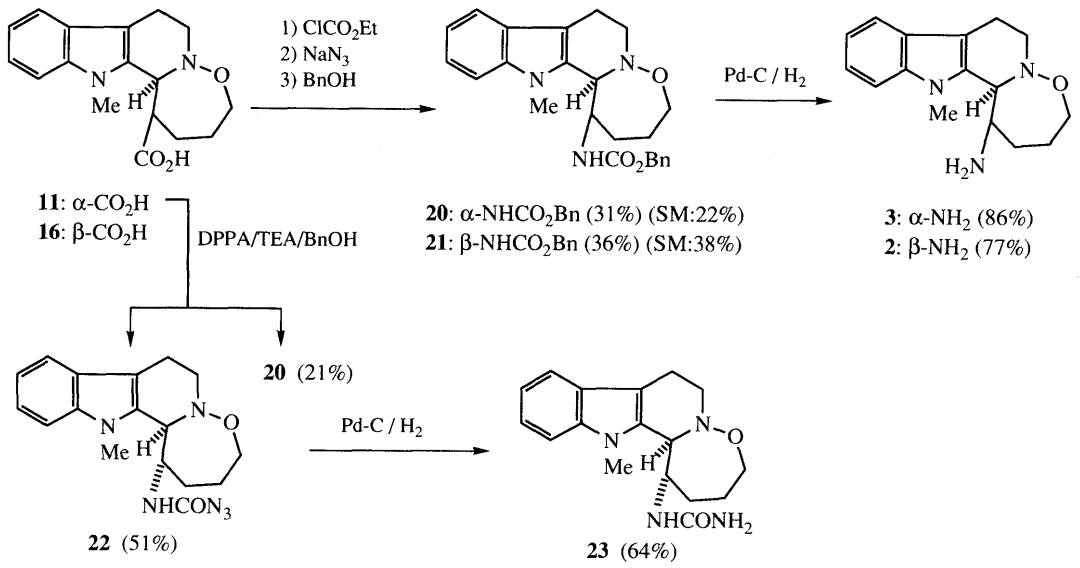


Chart 3

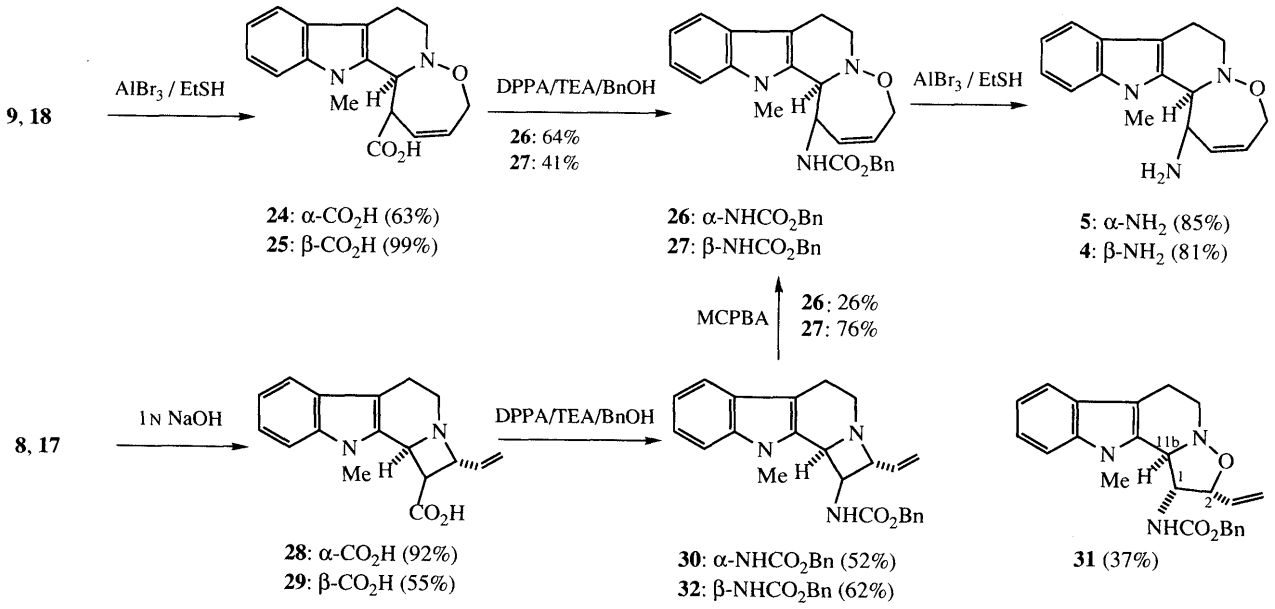


Chart 4

feature that configurations of the migrating group are completely retained.[14] Treatment of **11** with diphenylphosphoryl azide (DPPA)[15] and TEA in benzyl alcohol did not improve the yield and gave **20** (21%) along with a carbamoyl azide (**22**) (51%), which was converted into a crystalline urea derivative (**23**) in 64% yield by catalytic hydrogenation.

Synthesis of 9-Methyl-11,12-didehydro-12-carbaeudistomin Derivatives Chart 4 shows the synthesis of 9-methyl-12-carbaeudistomins (**5** and **4**) which have a double bond at C_{11}. Deprotections of the unsaturated ester groups of **9**[1] and **18** were performed by treatment with $AlBr_3$/EtSH, without any migration of the double bond, to afford the corresponding carboxylic acids (**24** and **25**) in 63 and 99% yields, respectively. Application of the Curtius rearrangement by a mixed anhydride method to **24** or **25** gave a complex mixture, from which the desired product (**26** or **27**) could not be obtained. However, the problem was overcome by use of the DPPA method, which gave the carbamates [**26** (64%) and **27** (41%)]. Cleavage of the benzyloxycarbonyl group in **26** and **27** was also successfully achieved by using the $AlBr_3$/EtSH system to give the amines [**5** (higher *Rf*) (85%) and **4** (lower *Rf*) (81%)], whose ^{1}H-NMR spectra exhibited the C_{13b}-H signal at δ 4.59 as a broad singlet and at δ 4.33 as a doublet (J = 5.0 Hz), respectively.

Alternatively, the carbamates (**26** and **27**) were prepared directly by the Meisenheimer rearrangement of the azetidines (**30** and **32**) having a benzyloxycarbamoyl group at C_1. Thus, hydrolysis of **8** (**17**) with 1 N NaOH solution at room temperature gave the carboxylic acid [**28**[1] (**29**)] in 92% (55%) yield, which was then converted into the carbamate [**30** (**32**)] by the DPPA method in 52% (62%) yield. Oxidation of **30** with MCPBA in CH_2Cl_2 at room

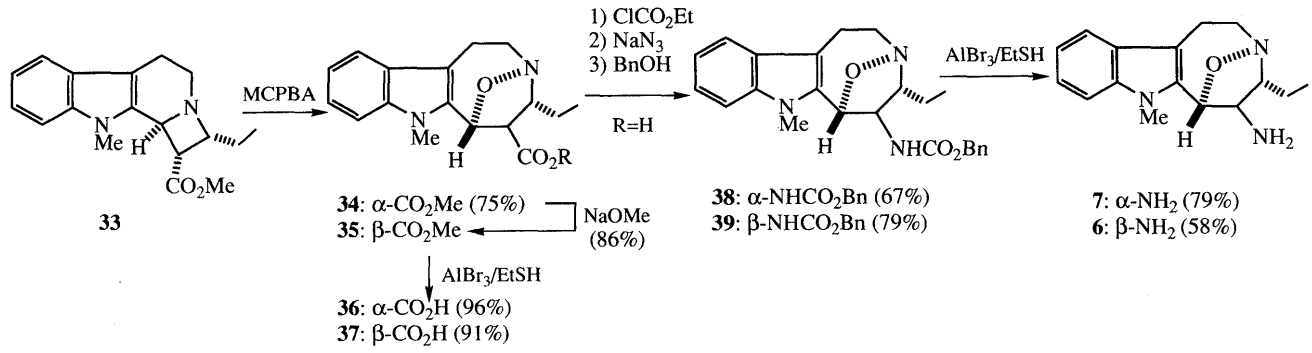


Chart 5

temperature gave a mixture of the [2,3]-Meisenheimer product (**26**) (26%) and the [1,2]-Meisenheimer product (**31**) (37%), of which the former was identical with **26** prepared from **24**. The stereochemical assignment of **31** was established through a positive nuclear Overhauser effect (NOE) at a vinyl proton ($-CH=CH_2$) and C_{11b}-H upon irradiation of the NH proton of the carbamate group. This result was very similar to that with azetopyridoindole bearing a hydroxymethyl group instead of an ester function at the C_1-position.[1] On the other hand, oxidation of **32** with MCPBA gave only the [2,3]-Meisenheimer product (**27**) in 76% yield.

Synthesis of 5-Amino-3,6-epoxyazocinoindole Derivatives In a previous paper,[8] we reported the [1,2]-Meisenheimer rearrangement of the corresponding *N*-oxide of the 1,10b-*trans*-2-ethylazetidine (**33**) to give the 5,6-*cis*-3,6-epoxyazocinoindole (**34**) (75%), which was readily isomerized to the 5,6-*trans*-3,6-epoxyazocinoindole (**35**) by treatment with NaOMe. The conversion of the esters (**34** and **35**) into amines (**6** and **7**) was accomplished through an analogous sequence to that described for the preparation of **2** and **3**. The reagents and yields of intermediates are shown in Chart 5.

According to recent results[16] of antiviral assay of compounds **2** and **3**, only compound **2** bearing a β-NH_2 group exhibited slight activity. Further biological assays of the synthesized compounds are in progress. The synthesis of indole nitrogen unsubstituted derivatives is also under investigation, for examination of their biological 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 a Varian Gemini-200 spectrometer in $CDCl_3$, unless otherwise stated, and MS with a Hitachi M-80 instrument. All reactions were carried out in a nitrogen atmosphere. For column chromatography, SiO_2 (Merck Art 9385) was used.

Methyl (1*S,13b*S**)-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 (10)** A solution of **9** (2.0 g, 6.4 mmol) in MeOH (100 ml) was hydrogenated under atmospheric pressure with 10% Pd–C (500 mg) for 4 h. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was recrystallized from EtOH to give **10** (1.94 g, 96%), mp 122—123 °C. IR (KBr): 1720 (CO) cm^{-1}. ^{1}H-NMR δ: 1.60—1.80 (2H, m, 3-H_2), 2.10—2.27, 2.34—2.53 (each 1H, each m, 2-H_2), 2.67—3.14 (3H, m, 7-H, 8-H_2), 3.29 (1H, q, J=4.5 Hz, 1-H), 3.47—3.67 (1H, m, 7-H), 3.54 (3H, s, NCH_3), 3.80—3.95 (2H, m, 4-H_2), 3.83 (3H, s, CO_2CH_3), 4.95 (1H, d, J=4.5 Hz, 13b-H), 7.05—7.28 (3H, m, ArH), 7.47 (1H, d, J=7.5 Hz, 12-H). MS *m/z*: 314 (M^+). *Anal.* Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.87; H, 7.01; N, 8.91.

(1*S,13b*S**)-13-Methyl-1,2,3,4,7,8,13,13*b*-octahydro[1′,2′]oxazepino-[2′,3′: 1,2]pyrido[3,4-*b*]indole-1-carboxylic Acid (11)** Method A: Powdered KOH (563 mg, 8.5 mmol) and 18-crown-6 (171 mg, 0.6 mmol) were added to a solution of **10** (669 mg, 2.1 mmol) in benzene (15 ml) and the mixture was vigorously stirred for 45 h. The reaction mixture was neutralized by the addition of 10% HCl and extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was recrystallized from MeOH to give **11** (613 mg, 96%), mp 208—210 °C. IR (KBr): 3420, 1700 (CO_2H) cm^{-1}. ^{1}H-NMR δ ($CDCl_3$ + a drop of DMSO-d_6): 1.50—1.80 (2H, m, 3-H_2), 2.10, 2.30 (each 1H, each m, 2-H_2), 2.45—3.00 (3H, m, 7-H, 8-H_2), 3.15 (1H, m, 1-H), 3.30—3.50 (1H, m, 7-H), 3.47 (3H, s, NCH_3), 3.75 (2H, m, 4-H_2), 4.80 (1H, d, J=4.0 Hz, 13b-H), 6.90—7.20 (3H, m, ArH), 7.33 (1H, d, J=7.5 Hz, 12-H). 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, 67.81; H, 6.68; N, 9.36.

Method B: A solution of **10** (36 mg, 0.11 mmol) in CH_2Cl_2 (2 ml) was added to a stirred, ice-cooled suspension of $AlBr_3$ (306 mg, 1.15 mmol) in EtSH (2 ml). After being stirred for 1 h at room temperature, the reaction mixture was quenched by the addition of cold H_2O, and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was recrystallized from MeOH to give **11** (33 mg, 97%), which was identical with **11**, prepared by method A, based on comparison of their IR and ^{1}H-NMR spectra.

9-Methyl-1-(tetrahydro-2-pyron-3-ylidene)-1,2,3,4-tetrahydro-β-carboline (12) A solution of **10** (314 mg, 1 mmol) in DMSO (4 ml) was treated with *tert*-BuOK (187 mg, 1.5 mmol) at room temperature. The mixture was stirred for 0.5 h, then the reaction was quenched by the addition of cold H_2O, and the whole was extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was recrystallized from EtOH to give **12** (170 mg, 60%), mp 226—228 °C. IR ($CHCl_3$): 3200 (NH), 1620 (CO) cm^{-1}. ^{1}H-NMR δ: 1.80 (2H, m, 5′-H_2), 2.64 (2H, br s, 4′-H_2), 2.78—2.97 (2H, m, 3-H_2), 3.35 (2H, br s, 4-H_2), 3.67 (3H, s, NCH_3), 4.31 (2H, m, 6′-H_2), 7.10—7.40 (3H, m, ArH), 7.59 (1H, d, J=7.5 Hz, 8-H). MS *m/z*: 282 (M^+). HR-MS Calcd for $C_{17}H_{18}N_2O_2$: 282.1366. Found: 282.1366. *Anal.* Calcd for $C_{17}H_{18}N_2O_2 \cdot 1/10H_2O$: C, 71.86; H, 6.46; N, 9.86. Found: C, 71.59; H, 6.46; N, 9.65.

Methyl (1*R,13b*S**)-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 (19)** Method A: A solution of **18** (246 mg, 0.8 mmol) in a mixture of EtOAc–MeOH (9 : 1, 10 ml) was hydrogenated under atmospheric pressure over 10% Pd–C (120 mg) for 6 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (elution with 15% EtOAc in hexane) to give **19** (228 mg, 92%). IR (neat): 1720 (CO) cm^{-1}. ^{1}H-NMR δ: 1.65—1.88 (1H, m, 3-H), 2.03—2.40 (3H, m, 2-H_2, 3-H), 2.67—3.10 (3H, m, 7-H, 8-H_2), 3.21 (3H, s, CO_2CH_3), 3.37 (1H, q, J=5.5 Hz, 1-H), 3.52 (1H, m, 7-H), 3.65 (3H, s, NCH_3), 3.65—3.85 (1H, m, 4-H), 4.11 (1H, m, 4-H), 4.37 (1H, d, J=5.5 Hz, 13b-H), 7.00—7.25 (3H, m, ArH), 7.43 (1H, d, J=7.5 Hz, 12-H). MS *m/z*: 314 (M^+). HR-MS Calcd for $C_{18}H_{22}N_2O_3$: 314.1619. Found: 314.1618.

Method B: A catalytic amount of iodine was added to a stirred suspension of Mg (122 mg, 4.7 mmol) in MeOH (2 ml). A solution of **13** (97 mg, 0.31 mmol) in tetrahydrofuran (THF) (3 ml) was added to the mixture and the whole was stirred at 40 °C for 4 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the solution

was evaporated under reduced pressure below 40 °C. The residue was extracted with EtOAc and the extract was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residual oil was subjected to column chromatography (elution with 15% EtOAc in hexane) to give **10** (41 mg, 42%) from the first fraction and **19** (24 mg, 25%) from the second fraction, both of which were identical with respective authentic samples, based on comparison of their IR and ^{1}H-NMR spectra.

Method C: A solution of **13** (30 mg, 0.096 mmol) in MeOH (10 ml) was hydrogenated using a Skita apparatus under an initial pressure of 3 kg/cm^2 for 16 h. An ordinary work-up gave an oil, which was purified by column chromatography (elution with 15% EtOAc in hexane) to give **19** (11 mg, 38%), which was identical with **19** obtained by method A.

Benzyl (1*S,13b*S**)-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 (14)** A solution of phenyldiazomethane in petroleum ether was added to an ice-cooled suspension of **11** (600 mg, 2 mmol) in CH_2Cl_2 (20 ml) until a red color persisted. The mixture was stirred for 1.5 h, then the reaction was quenched by the addition of acetic acid, and the whole was evaporated under reduced pressure. The residue was neutralized with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (elution with 15% EtOAc in hexane) to give **14** (762 mg, 98%), which was recrystallized from EtOH to give crystals, mp 114—115 °C. IR (KBr): 1730 (CO) cm^{-1}. ^{1}H-NMR δ: 1.47—1.73 (2H, m, 3-H$_2$), 2.18, 2.40 (each 1H, each m, 2-H$_2$), 2.61—3.10 (3H, m, 7-H, 8-H$_2$), 3.27 (1H, q, J=4.0 Hz, 1-H), 3.39 (3H, s, NCH_3), 3.53 (1H, m, 7-H), 3.82 (2H, m, 4-H$_2$), 4.92 (1H, br d, J=4.0 Hz, 13b-H), 5.26 (2H, s, CH_2Ar), 7.00—7.50 (9H, m, ArH). *Anal.* Calcd for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71; N, 7.18. Found: C, 73.87; H, 6.86; N, 7.04.

Benzyl (1*R,13b*S**)-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 (15)** A solution of **14** (1.98 g, 5 mmol) and DBU (1.12 g, 7.1 mmol) in CH_3CN (70 ml) was heated in a sealed tube at 150 °C for 18 h. After evaporation of the solvent, the residue was dissolved in $CHCl_3$ and the organic solution was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was subjected to column chromatography (elution with 15% EtOAc in hexane) to give the starting material (**14**) (971 mg, 49% recovery) from the first fraction. The second eluate (30% EtOAc in hexane) gave **15** (1009 mg, 51%), which was recrystallized from EtOH to give crystals, mp 95—96 °C. IR (KBr): 1735 (CO) cm^{-1}. ^{1}H-NMR δ: 1.64—1.83 (1H, m, 3-H), 2.30—2.47 (3H, m, 2-H$_2$, 3-H), 2.62—3.00 (3H, m, 7-H, 8-H$_2$), 3.42 (1H, q, J=4.0 Hz, 1-H), 3.47—3.58 (1H, m, 7-H), 3.58 (3H, s, NCH_3), 3.73, 4.10 (each 1H, each m, 4-H$_2$), 4.37 (1H, d, J=4.0 Hz, 13b-H), 4.57, 4.69 (each 1H, each d, J=12.5 Hz, CH_2Ar), 6.81—7.24 (8H, m, ArH), 7.43 (1H, d, J=7.5 Hz, 12-H). *Anal.* Calcd for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71; N, 7.18. Found: C, 73.92; H, 6.78; N, 7.17.

(1*R,13b*S**)-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 (16)** Method A: A solution of **19** (60 mg, 0.19 mmol) in CH_2Cl_2 (2 ml) was added to a stirred, ice-cooled suspension of $AlBr_3$ (505 mg, 1.9 mmol) in EtSH (2 ml). The mixture was stirred for 30 min at room temperature, then the reaction was quenched by the addition of cold H_2O, and the whole was extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and concentrated to give **16** (57 mg, 100%) as an amorphous powder, which showed a single-spot on TLC. IR ($CHCl_3$): 1730 (CO) cm^{-1}. ^{1}H-NMR δ: 1.90—2.34 (4H, m, 2-H$_2$, 3-H$_2$), 2.70—3.17 (3H, m, 7-H, 8-H$_2$), 3.48—3.63 (2H, m, 1-H, 7-H), 3.64 (3H, s, NCH_3), 3.73—3.96 (1H, m, 4-H), 4.12—4.26 (2H, m, 4-H, 13b-H), 6.98—7.23 (3H, m, ArH), 7.39 (1H, d, J=7.5 Hz, 12-H). MS m/z: 300 (M^+). HR-MS Calcd for $C_{17}H_{20}N_2O_3$: 300.1472. Found: 300.1466.

Method B: A solution of **15** (468 mg, 1.2 mmol) in a mixture of EtOAc–MeOH (1 : 1) (50 ml) was hydrogenated under atmospheric pressure with 10% Pd–C (144 mg) for 7 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give **16** (360 mg, 100%) as an amorphous powder. This was identical with an authentic sample, prepared by method A, based on comparison of their IR and ^{1}H-NMR spectra.

(1*S,13*S**)-1-Benzyloxycarbonylamino-13-methyl-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′: 1,2]pyrido[3,4-*b*]indole (20)** Ethyl chloroformate (0.18 ml, 1.9 mmol) was added to a suspension of **11** (445 mg, 1.5 mmol) and TEA (0.31 ml, 2.2 mmol) in THF (10 ml) under ice cooling. The mixture was stirred for 10 min, then powdered NaN_3 (298 mg, 4.4 mmol) and CH_3CN (10 ml) were added, and the whole was stirred for 6 h at room temperature. The solvent was removed by evaporation under reduced pressure below 35 °C, and the residue was dissolved in CH_2Cl_2 and H_2O. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Benzyl alcohol (2.5 ml) and anhydrous $MgSO_4$ (200 mg) were added to a solution of the residue in benzene (2.5 ml), and the mixture was stirred at 65 °C for 6 h, then diluted with $CHCl_3$. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography to give **20** (184 mg, 31%), mp 145—146 °C (from EtOH), from the first fraction eluted with 15% EtOAc in hexane. IR (KBr) 3330 (NH), 1680 (CO) cm^{-1}. ^{1}H-NMR δ: 1.60 (2H, m, 3-H$_2$), 1.80—2.30 (3H, m, 2-H$_2$, 8-H), 2.68—3.00 (2H, m, 7-H, 8-H), 3.50 (1H, br s, 7-H), 3.69 (3H, s, NCH_3), 3.90 (3H, m, 4-H$_2$, 13b-H), 4.69 (1H, br t, J=7.5 Hz, 1-H), 5.15 (2H, s, CH_2Ar), 5.43 (1H, d, J=10 Hz, NH), 7.40—7.46 (9H, m, ArH). MS m/z: 405 (M^+). *Anal.* Calcd for $C_{24}H_{27}N_3O_3$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.90; H, 6.80; N, 10.30.

The second eluate (EtOAc) gave the starting material (**11**) (96 mg, 22% recovery).

(1*R,13b*S**)-1-Benzyloxycarbonylamino-13-methyl-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′: 1,2]pyrido[3,4-*b*]indole (21)** The same procedure as described for the preparation of **20** provided a crude product from **16** (664 mg, 2.2 mmol), TEA (0.46 ml, 3.3 mmol), ethyl chloroformate (0.27 ml, 2.8 mmol), NaN_3 (445 mg, 6.8 mmol), and benzyl alcohol (8 ml), and this was purified by column chromatography to give **21** (320 mg, 36%) as an oil from the first fraction eluted with 15% EtOAc in hexane. IR ($CHCl_3$): 3410 (NH), 1700 (CO) cm^{-1}. ^{1}H-NMR δ: 1.50—2.30 (4H, m, 2-H$_2$, 3-H$_2$), 2.62—3.03 (3H, m, 7-H, 8-H$_2$), 3.42 (1H, m, 7-H), 3.65 (1H, m, 4-H), 3.70 (3H, s, NCH_3), 4.04 (1H, dd, J=11.0, 8.0 Hz, 4-H), 4.25 (1H, br s, 13b-H), 4.69 (1H, m, 1-H), 4.82 (2H, s, CH_2Ar), 5.11 (1H, d, J=9.5 Hz, NH), 6.85—7.38 (8H, m, ArH), 7.46 (1H, d, J=7.5 Hz, 12-H). MS m/z: 405 (M^+). HR-MS Calcd for $C_{24}H_{27}N_3O_3$: 405.2051. Found: 405.2064.

The second eluate (EtOAc) gave the starting material (**16**) (250 mg, 38% recovery).

(1*S,13b*S**)-1-Amino-13-methyl-1,2,3,4,7,8,13,13b-octahydro[1′,2′]-oxazepino[2′,3′: 1, 2]pyrido[3,4-*b*]indole [(1,10-*trans*)-9-Methyl-12-carbaeudistomin)] (3)** A solution of **20** (520 mg, 1.28 mmol) in a mixture of EtOAc–MeOH (1 : 1) (35 ml) was hydrogenated under atmospheric pressure with 10% Pd–C (140 mg) for 5.5 h. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was purified by column chromatography (elution with 5% MeOH in $CHCl_3$) to give **3** (298 mg, 86%) as an oil. IR (neat): 3100—3200 (NH_2) cm^{-1}. ^{1}H-NMR δ: 1.70 (4H, m, NH_2, 3-H$_2$), 2.00—2.45 (2H, m, 2-H$_2$), 2.70—3.05 (3H, m, 7-H, 8-H$_2$), 3.53 (1H, m, 7-H), 3.65 (1H, m, 4-H), 3.90—4.10 (3H, m, 4-H, 1-H, 13b-H), 3.93 (3H, s, NCH_3), 7.09—7.33 (3H, m, ArH), 7.49 (1H, d, J=7.5 Hz, 12-H). MS m/z: 271 (M^+). HR-MS Calcd for $C_{16}H_{21}N_3O$: 271.1683. Found: 271.1683. The perchlorate of **3** was recrystallized from EtOH to give crystals, mp 227—231 °C. *Anal.* Calcd for $C_{16}H_{22}ClN_3O_5 \cdot 1/2\ H_2O$: C, 50.46; H, 6.09; N, 11.03. Found: C, 50.45; H, 5.99; N, 11.32.

(1*R,13b*S**)-1-Amino-13-methyl-1,2,3,4,7,8,13,13b-octahydro[1′,2′]-oxazepino[2′,3′: 1,2]pyrido[3,4-*b*]indole (9-Methyl-12-carbaeudistomin) (2)** The same procedure as described for the preparation of **3** provided a crude product from **21** (281 mg, 0.69 mmol) with 10% Pd–C (90 mg), and this was purified by column chromatography (elution with 5% MeOH in $CHCl_3$) to give **2** (145 mg, 77%). Recrystallization from benzene gave crystals, mp 155—156 °C. IR (KBr): 3450 (NH_2) cm^{-1}. ^{1}H-NMR δ: 1.60—2.30 (4H, m, 2-H$_2$, 3-H$_2$), 2.70—3.05 (3H, m, 7-H, 8-H$_2$), 3.47 (1H, m, 7-H), 3.55 (1H, m, 1-H), 3.66 (1H, m, 4-H), 3.69 (3H, s, NCH_3), 4.08 (1H, m, 4-H), 4.20 (1H, br s, 13b-H), 7.02—7.32 (3H, m, ArH), 7.45 (1H, d, J=7.5 Hz, 12-H). MS m/z: 271 (M^+). HR-MS Calcd for $C_{16}H_{21}N_3O$: 271.1683. Found: 271.1684. *Anal.* Calcd for $C_{16}H_{21}N_3O$: C, 70.82; H, 7.80; N, 15.49. Found: C, 70.81; H, 7.85; N, 15.37.

Reaction of 11 with DPPA A suspension of **11** (113 mg, 0.38 mmol), TEA (0.06 ml, 0.45 mmol) and DPPA (0.1 ml, 0.46 mmol) in benzene (15 ml) was refluxed for 1 h. Benzyl alcohol (49 mg, 0.45 mmol) was added to the mixture, and the whole was refluxed for an additional 20 h, then diluted with EtOAc. The organic layer was washed with 10% aqueous citric acid, water and brine, dried (Na_2SO_4), and then concentrated under reduced pressure. The residue was subjected to column chromatography (elution with 15% EtOAc in hexane) to give **20** (32 mg, 21%), which was identical with an authentic sample, based on comparison of their IR and ^{1}H-NMR spectra. The second eluate (5% MeOH in $CHCl_3$)

gave (1*S**,13b*S**)-13-methyl-1,2,3,4,7,8,13,13b-octahydro[1′,2′]oxazepino[2′,3′: 1,2]pyrido[3,4-*b*]indole-1-carbamoyl azide (**22**) (66 mg, 51%) as an oil, which solidified by the addition of a drop of MeOH. It could not be recrystallized, because of thermal instability. IR ($CHCl_3$): 3400 (NH), 2150 (N_3), 1690 (CO) cm^{-1}. ^{1}H-NMR δ: 1.55—2.32 (4H, m, 2-H_2, 3-H_2), 2.67—3.00 (3H, m, 7-H, 8-H_2), 3.50 (1H, m, 7-H), 3.70 (3H, s, NCH_3), 3.91 (3H, br s, 4-H_2, 13b-H), 4.78 (1H, m, 1-H), 5.74 (1H, d, J=10 Hz, NH), 7.03—7.45 (4H, m, ArH). MS *m/z*: 340 (M^+). HR-MS Calcd for $C_{17}H_{20}N_6O_2$: 340.1654. Found: 340.1646.

(1*S,13b*S**)-13-Methyl-1-ureido-1,2,3,4,7,8,13,13b-octahydro[1′,2′]-oxazepino[2′,3′: 1,2]pyrido[3,4-*b*]indole (23)** A solution of **22** (76 mg, 0.22 mmol) in a mixture of EtOAc–MeOH (1 : 1) (10 ml) was hydrogenated under atmospheric pressure with 10% Pd–C (30 mg) for 6.5 h. The catalyst was removed by filtration, and the filtrate was concentrated *in varuo*. The residual solid was recrystallized from MeOH to give **23** (45 mg, 64%), mp 253—256 °C. IR (Nujol): 3200—3450 (NH), 1650 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$ + a drop of CD_3OD) δ: 1.50—2.20 (4H, m, 2-H_2, 3-H_2), 2.60—2.94 (3H, m, 7-H, 8-H_2), 3.45 (1H, br s, 7-H), 3.65 (3H, s, NCH_3), 3.84 (3H, m, 4-H_2, 13b-H), 4.59 (1H, br s, 1-H), 6.14 (1H, m, NH), 6.95—7.25 (3H, m, ArH), 7.45 (1H, d, J=7.5 Hz, 12-H). MS *m/z*: 314 (M^+). *Anal.* Calcd for $C_{17}H_{22}N_4O_2$: C, 64.94; H. 7.05; N, 17.82. Found: C, 64.87; H, 7.06; N, 17.61.

(1*R,13b*S**)-13-Methyl-1,4,7,8,13,13b-hexahydro[1′,2′]oxazepino-[2′,3′: 1,2]pyrido[3,4-*b*]indole-1-carboxylic Acid (25)** The same procedure as described for the preparation of **16** (method A) using the ester (**18**) (200 mg, 0.64 mmol), $AlBr_3$ (1.71 g, 6.4 mmol) and EtSH (4 ml) gave almost pure **25** (188 mg, 99%). This was used for the following reaction without purification. IR (KBr): 1700 (CO) cm^{-1}. ^{1}H-NMR δ: 2.80—3.30 (3H, m, 7-H, 8-H_2), 3.72 (3H, s, NCH_3), 3.75 (1H, m, 7-H), 4.01 (1H, br s, 1-H), 4.49 (1H, dd, J=16.0, 3.0 Hz, 4-H), 4.65 (1H, br s, 13b-H), 4.80 (1H, d, J=16.0 Hz, 4-H), 6.02 (2H, m, 2-H, 3-H), 7.05—7.30 (3H, m, ArH), 7.48 (1H, d, J=7.5 Hz, 12-H). MS *m/z*: 298 (M^+). HR-MS Calcd for $C_{17}H_{18}N_2O_3$: 298.1316. Found: 298.1317.

(1*S,13b*S**)-1-Benzyloxycarbonylamino-13-methyl-1,4,7,8,13,13b-hexahydro[1′,2′]oxazepino[2′,3′: 1,2]pyrido[3,4-*b*]indole (26)** Method A: The same procedure as described for the reaction of **11** with DPPA provided a crude product from **24**[1] (149 mg, 0.5 mmol), TEA (56 mg, 0.55 mmol), DPPA (145 mg, 0.53 mmol), and benzyl alcohol (108 mg, 1 mmol), and this was purified by column chromatography (elution with 20% EtOAc in hexane) to give **26** (129 mg, 64%). Recrystallization from EtOH gave crystals, mp 170—172 °C. IR (KBr): 3320 (NH), 1685 (CO) cm^{-1}. ^{1}H-NMR δ: 2.70—3.18 (3H, m, 7-H, 8-H_2), 3.60 (1H, m, 7-H), 3.77 (3H, s, NCH_3), 4.37 (1H, s, 13b-H), 4.39, 4.56 (each 1H, each d, J=15.5 Hz, 4-H), 5.01 (1H, m, 1-H), 5.13 (2H, s, CH_2Ar), 5.45 (1H, d, J=12.0 Hz, NH), 5.64 (1H, d, J=13.0 Hz, 3-H), 5.88 (1H, m, 2-H), 7.07—7.58 (9H, m, ArH). MS *m/z*: 403 (M^+). *Anal.* Calcd for $C_{24}H_{25}N_3O_3$: C, 71.44; H, 6.25; N, 10.42. Found: C, 71.39; H, 6.26; N, 10.35.

Method B: A solution of MCPBA (80% purity, 134 mg, 0.62 mmol) in CH_2Cl_2 (5 ml) was added to a solution of **30** (200 mg, 0.52 mmol) in CH_2Cl_2 (10 ml) at room temperature. After being stirred for 1 h, the reaction mixture was diluted with CH_2Cl_2. The solution was washed with 5% aqueous Na_2CO_3, and H_2O, dried (Na_2SO_4), and then concentrated under reduced pressure. The residue was purified by column chromatography (elution with 20% EtOAc in hexane) to give **26** (54 mg, 26%), which was identical with an authentic sample obtained by method A. The second eluate with the same solvent gave (1*R**,2*R**,11b*S**)-1-benzyloxycarbonylamino-11-methyl-2-vinyl-1,2,5,6,11,11b-hexahydroisoxazolo[2′,3′: 1,2]pyrido[3,4-*b*]indole (**31**) (76 mg, 37%), which was recrystallized from EtOH to give crystals, mp 159—161 °C. IR (KBr): 3300 (NH), 1675 (CO) cm^{-1}. ^{1}H-NMR δ: 2.73 (1H, m, 5-H), 3.04 (2H, m, 5-H, 6-H), 3.78 (1H, m, 6-H), 3.86 (3H, s, NCH_3), 4.52 (1H, t, J=4.0 Hz, 2-H), 4.68 (1H, dd, J=9.0, 4.0 Hz, 1-H), 4.82 (1H, s, 11b-H), 5.17 (2H, s, CH_2Ar), 5.32 [1H, br d, J=10.0 Hz, CH=C<u>H</u>H (*cis*)], 5.44 [1H, br d, J=17.0 Hz, CH=CH<u>H</u> (*trans*)], 5.76 (1H, ddd, J=17.0, 10.0, 5.5 Hz, CH=), 6.08 (1H, br d, J=9.0 Hz, NH), 7.16—7.55 (8H, m, ArH), 7.63 (1H, d, J=7.5 Hz, ArH). MS *m/z*: 403 (M^+). *Anal.* Calcd for $C_{24}H_{25}N_3O_3$: C, 71.44; H, 6.25; N, 10.42. Found: C, 71.55; H, 6.25; N, 10.46.

(1*R,13b*S**)-1-Benzyloxycarbonylamino-13-methyl-1,4,7,8,13,13b-hexahydro[1′,2′]oxazepino[2′,3′: 1,2]pyrido[3,4-*b*]indole (27)** Method A: The same procedure as described for the reaction of **11** with DPPA provided a crude product from **25** (144 mg, 0.48 mmol), TEA (54 mg, 0.53 mmol), DPPA (140 mg, 0.5 mmol), and benzyl alcohol (104 mg, 0.96 mmol), and this was purified by column chromatography (elution with 20% EtOAc in hexane) to give **27** (79 mg, 41%). Recrystallization from EtOH gave crystals, mp 97—98 °C. IR ($CHCl_3$): 3420 (NH), 1700 (CO) cm^{-1}. ^{1}H-NMR δ: 2.68—3.04 (3H, m, 7-H, 8-H_2), 3.62 (1H, br d, J=6.7 Hz, 7-H), 3.74 (3H, s, NCH_3), 4.25—5.05 (6H, m, 1-H, 4-H_2, 13b-H, CH_2Ar), 5.76—6.03 (2H, m, 2-H, 3-H), 6.48 (1H, br s, NH), 6.80—7.30 (8H, m, ArH), 7.47 (1H, d, J=7.5 Hz, ArH). MS *m/z*: 403 (M^+). *Anal.* Calcd for $C_{24}H_{25}N_3O_3$: C, 71.44; H, 6.25; N, 10.42. Found: C, 71.39; H, 6.19; N, 10.39.

Method B: The same procedure as described for the preparation of **26** (method B) provided a crude product from **32** (180 mg, 0.47 mmol) and MCPBA (80% purity, 120 mg, 0.56 mmol), and this was purified by column chromatography (elution with 20% EtOAc in hexane) to give **27** (142 mg, 76%), which was identical with an authentic sample obtained by method A.

(1*R,13b*S**)-1-Amino-13-methyl-1,4,7,8,13,13b-hexahydro[1′,2′]-oxazepino[2′,3′: 1,2]pyrido[3,4-*b*]indole (9-Methyl-11,12-didehydro-12-carbaeudistomin) (4)** The same procedure as described for the preparation of **16** (method A) provided a crude product from **27** (78 mg, 0.19 mmol), $AlBr_3$ (513 mg, 1.9 mmol), and EtSH (2 ml), and this was purified by column chromatography (elution with 5% MeOH in $CHCl_3$) to give **4** (42 mg, 81%) as an oil. IR ($CHCl_3$): 3350 (NH_2) cm^{-1}. ^{1}H-NMR δ: 1.45 (2H, br s, NH_2), 2.73—3.14 (3H, m, 7-H, 8-H_2), 3.65 (1H, m, 7-H), 3.69 (3H, s, NCH_3), 3.83 (1H, br s, 1-H), 4.42 (1H, dd, J=16.0, 5.0 Hz, 4-H), 4.59 (1H, br s, 13b-H), 4.60 (1H, d, J=16.0 Hz, 4-H), 5.74 (1H, ddd, J=13.0, 5.0, 1.5 Hz, 3-H), 6.02 (1H, m, 2-H), 7.08—7.35 (3H, m, ArH), 7.52 (1H, d, J=7.5 Hz, 12-H). MS *m/z*: 269 (M^+). HR-MS Calcd for $C_{16}H_{19}N_3O$: 269.1527. Found: 269.1530.

(1*S,13b*S**)-1-Amino-13-methyl-1,4,7,8,13,13b-hexahydro[1′,2′]-oxazepino[2′,3′: 1,2]pyrido[3,4-*b*]indole [(1,10-*trans*)-9-Methyl-11,12-didehydro-12-carbaeudistomin)] (5)** The same procedure as described for the preparation of **16** (method A) provided a crude product from **26** (179 mg, 0.44 mmol), $AlBr_3$ (1190 mg, 4.5 mmol), and EtSH (5 ml), and this was purified by column chromatography (elution with 5% MeOH in $CHCl_3$) to give **5** (102 mg, 85%) as an oil. IR (neat): 3300 (NH_2) cm^{-1}. ^{1}H-NMR δ: 1.60 (2H, br s, NH_2), 2.72—3.15 (3H, m, 7-H, 8-H_2), 3.56 (1H, m, 7-H), 3.89 (3H, s, NCH_3), 3.91 (1H, m, 1-H), 4.33 (1H, d, J=5.0 Hz, 13b-H), 4.38 (1H, d, J=16.5 Hz, 4-H), 4.57 (1H, br d, J=16.5 Hz, 4-H), 5.56 (1H, br d, J=12.0 Hz, 3-H), 5.76 (1H, m, 2-H), 7.05—7.35 (3H, m, ArH), 7.48 (1H, d, J=7.5 Hz, 12-H). MS *m/z*: 269 (M^+). HR-MS (Calcd for $C_{16}H_{19}N_3O$: 269.1527. Found: 269.1533.

(1*R,2*R**,10b*S**)-10-Methyl-2-vinyl-1,2,4,5,10,10b-hexahydroazeto-[1′,2′: 1,2]pyrido[3,4-*b*]indole-1-carboxylic Acid (29)** Aqueous NaOH (1 N, 0.53 ml, 0.53 mmol) was added to a solution of **17** (111 mg, 0.38 mmol) in MeOH (15 ml). After being stirred for 60 h, the solution was concentrated under reduced pressure. The residue was neutralized by the addition of 10% aqueous HCl and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and concentrated. The residual solid was recrystallized from EtOH to give **29** (58 mg, 55%), mp 231—232 °C. IR (KBr): 3350, 1610 (COOH) cm^{-1}. ^{1}H-NMR δ: 2.24—3.32 (4H, m, 4-H_2, 5-H_2), 3.42 (3H, s, NCH_3), 3.67 (1H, t, J=8.7 Hz, 1-H), 4.52 (1H, t, J=8.7 Hz, 2-H), 4.96 [1H, d, J=10.0 Hz, CH=C<u>H</u>H (*cis*)], 5.24 (1H, d, J=8.7 Hz, 10b-H), 5.27 [1H, d, J=16.2 Hz, CH=CH<u>H</u> (*trans*)], 5.78 (1H, m, CH=), 6.95—7.11 (3H, m, ArH), 7.44 (1H, d, J=7.5 Hz, 9-H). MS *m/z*: 282 (M^+). HR-MS Calcd for $C_{17}H_{18}N_2O_2$: 282.1367. Found: 282.1367. *Anal.* Calcd for $C_{17}H_{18}N_2O_2 \cdot 1/10\ H_2O$: C, 71.86; H, 6.46; N, 9.86. Found: C, 71.97; H, 6.36; N, 9.90.

(1*S,2*R**,10b*S**)-1-Benzyloxycarbonylamino-10-methyl-2-vinyl-1,2,4,5,10,10b-hexahydroazeto[1′,2′: 1,2]pyrido[3,4-*b*]indole (30)** The same procedure as described for the reaction of **11** with DPPA provided a crude product from **28** (141 mg, 0.5 mmol), TEA (0.08 ml, 0.55 mmol), DPPA (145 mg, 0.53 mmol), and benzyl alcohol (108 mg, 1 mmol), and this was purified by column chromatography (elution with 30% EtOAc in hexane) to give **30** (100 mg, 52%). Recrystallization from EtOH gave crystals, mp 135—137 °C. IR. (KBr): 3300 (NH), 1680 (CO) cm^{-1}. ^{1}H-NMR δ: 2.64—3.12 (4H, m, 4-H_2, 5-H_2), 3.84 (3H, s, NCH_3), 4.12 (1H, t, J=7.5 Hz, 1-H), 4.41 (1H, m, 2-H), 4.60 (1H, s, 10b-H), 5.19 (2H, s, CH_2Ar), 5.49 [1H, br d, J=9.7 Hz, CH=C<u>H</u>H (*cis*)], 5.60—5.93 [3H, m, C<u>H</u>=CH<u>H</u> (*trans*), NH], 7.08—7.46 (8H, m, ArH), 7.58 (1H, d, J=7.5 Hz, 9-H). MS *m/z*: 387 (M^+). *Anal.* Calcd for $C_{24}H_{25}N_3O_2$: C, 74.39; H, 6.50; N, 10.85. Found: C, 74.27; H, 6.49; N, 10.76.

(1*R,2*R**,10b*S**)-1-Benzyloxycarbonylamino-10-methyl-2-vinyl-1,2,4,5,10,10b-hexahydroazeto[1′,2′: 1,2]pyrido[3,4-*b*]indole (32)** The

same procedure as described for the reaction of **11** with DPPA provided a crude product from **29** (240 mg, 0.85 mmol), TEA (0.13 ml, 0.94 mmol), DPPA (0.19 ml, 0.89 mmol), and benzyl alcohol (0.18 ml, 1.7 mmol), and this was purified by column chromatography (elution with 20% EtOAc in hexane) to give **32** (203 mg, 62%). Recrystallization from EtOH gave crystals, mp 134—135 °C. IR (KBr): 3170 (NH), 1715 (CO) cm^{-1}. ^{1}H-NMR δ: 2.57—2.95 (3H, m, 4-H, 5-H_2), 3.09 (1H, dd, J=13.0, 4.5 Hz, 4-H), 3.37 (3H, s, NCH_3), 3.67 (1H, t, J=7.3 Hz, 2-H), 4.64 (1H, d, J=10.7 Hz, 10b-H), 4.78 (1H, dt, J=10.7, 7.3 Hz, 1-H), 4.97, 5.13 (each 1H, each d, J=12.0 Hz, CH_2Ar), 5.02 (1H, d, J=7.3 Hz, NH), 5.21 [1H, d, J=10.0 Hz, CH=C<u>H</u>H (*cis*)], 5.29 [1H, d, J=17.5 Hz, CH=C<u>H</u>H (*trans*)], 6.03 (1H, ddd, J=17.5, 10.0, 7.3 Hz, CH=), 7.10—7.42 (8H, m, ArH), 7.58 (1H, d, J=7.5 Hz, 9-H). MS *m/z*: 387 (M^+). *Anal.* Calcd for $C_{24}H_{25}N_3O_2$: C, 74.39; H, 6.50; N, 10.85. Found: C, 74.45; H, 6.46; N, 10.88.

(4*R,5*S**,6*S**)-3,6-Epoxy-4-ethyl-7-methyl-1,2,3,4,5,6-hexahydroazocino[5,4-*b*]indole-5-carboxylic Acid (36)** The same procedure as described for the preparation of **16** (method A) provided a crude product from **34** (291 mg, 0.93 mmol), $AlBr_3$ (2.47 g, 9.3 mmol), and EtSH (6 ml), and this was recrystallized from CH_3CN to give **36** (267 mg, 96%), mp 185—187 °C. IR (KBr): 1710 (CO) cm^{-1}. ^{1}H-NMR δ: 1.08 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.47—1.85 (2H, m, $C\underline{H}_2CH_3$), 2.98—3.21 (3H, m, 1-H_2, 2-H), 3.64—3.97 (3H, m, 2-H, 4-H, 5-H), 3.72 (3H, s, NCH_3), 5.85 (1H, d, J=3.5 Hz, 6-H), 7.06—7.32 (3H, m, ArH), 7.50 (1H, d, J=7.5 Hz, 8-H). MS *m/z*: 300 (M^+). HR-MS Calcd for $C_{17}H_{20}N_2O_3$: 300.1474. Found: 300.1473. *Anal.* Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.73; H, 6.71; N, 9.55.

(4*R,5*R**,6*S**)-3,6-Epoxy-4-ethyl-7-methyl-1,2,3,4,5,6-hexahydroazocino[5,4-*b*]indole-5-carboxylic Acid (37)** The same procedure as described for the preparation of **16** (method A) provided a crude product from **35** (1.43 g, 4.55 mmol), $AlBr_3$ (6.07 g, 22.8 mmol), and EtSH (15 ml), and this was recrystallized from a mixture of CH_3CN–MeOH to give **37** (1.24 g, 91%), mp 278—279 °C. IR (KBr) 1710 (CO) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.97 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 1.60 (2H, m, $C\underline{H}_2CH_3$), 2.81 (1H, br d, J=16.5 Hz, 1-H), 3.08—3.86 (5H, m, 1-H, 2-H_2, 4-H, 5-H), 3.72 (3H, s, NCH_3), 5.74 (1H, d, J=8.0 Hz, 6-H), 6.96—7.20 (2H, m, ArH), 7.35—7.50 (2H, m, ArH), 11.87 (1H, br s, COOH). MS *m/z*: 300 (M^+). HR-MS Calcd for $C_{17}H_{20}N_2O_3$: 300.1472. Found: 300.1474. *Anal.* Calcd for $C_{17}H_{20}N_2O_3 \cdot 1/5H_2O$: C, 67.17; H, 6.77; N, 9.22. Found: C, 67.18; H, 6.68; N, 9.26.

(4*R,5*S**,6*S**)-5-Benzyloxycarbonylamino-3,6-epoxy-4-ethyl-7-methyl-1,2,3,4,5,6-hexahydroazocino[5,4-*b*]indole (38)** The same procedure as described for the preparation of **20** provided a crude product from **36** (80 mg, 0.27 mmol), TEA (0.06 ml, 0.41 mmol), $ClCO_2Et$ (0.03 ml, 0.35 mmol), NaN_3 (54 mg, 0.81 mmol), and benzyl alcohol (1.5 ml), and this was purified by column chromatography (elution with 20% EtOAc in hexane) to give **38** (73 mg, 67%). Recrystallization from EtOH gave crystals, mp 149—150 °C. IR (KBr): 3310 (NH), 1700 (CO) cm^{-1}. ^{1}H-NMR δ: 0.91 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.60 (2H, m, $C\underline{H}_2CH_3$), 3.12 (2H, m, 1-H_2), 3.40 (2H, m, 4-H, 2-H), 3.75 (3H, s, NCH_3), 3.95 (1H, m, 2-H), 4.61 (1H, dd, J=9.0, 6.5 Hz, 5-H), 5.15 (2H, s, CH_2Ar), 5.26 (1H, br s, 6-H), 5.62 (1H, d, J=9.0 Hz, NH), 7.05—7.43 (8H, m, ArH), 7.49 (1H, d, J=7.5 Hz, 8-H). MS *m/z*: 405 (M^+). *Anal.* Calcd for $C_{24}H_{27}N_3O_3$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.85; H, 6.73; N, 10.29.

(4*R,5*R**,6*S**)-5-Benzyloxycarbonylamino-3,6-epoxy-4-ethyl-7-methyl-1,2,3,4,5,6-hexahydroazocino[5,4-*b*]indole (39)** The same procedure as described for the preparation of **20** provided a crude product from **37** (300 mg, 1 mmol), TEA (0.21 ml, 1.5 mmol), $ClCO_2Et$ (0.13 ml, 1.3 mmol), NaN_3 (195 mg, 3 mmol), and benzyl alcohol (1.5 ml), and this was purified by column chromatography (elution with 30% EtOAc in hexane) to give **39** (318 mg, 79%). Recrystallization from EtOH gave crystals, mp 154—155 °C. IR (KBr): 3180 (NH), 1705 (CO) cm^{-1}. ^{1}H-NMR δ: 1.04 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.82 (2H, m, $C\underline{H}_2CH_3$), 2.93 (1H, m, 4-H), 3.13 (2H, m, 1-H_2), 3.40 (1H, m, 2-H), 3.49 (3H, s, NCH_3), 3.87 (1H, m, 2-H), 4.54 (1H, d, J=8.5 Hz, NH), 4.80 (1H, m, 5-H), 4.96, 5.09 (each 1H, each d, J=11.5 Hz, CH_2Ar), 5.43 (1H, d, J=7.5 Hz, 6-H), 7.09—7.45 (8H, m, ArH), 7.52 (1H, d, J=7.5 Hz, 8-H). MS *m/z*: 405 (M^+). *Anal.* Calcd for $C_{24}H_{27}N_3O_3$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.93; H, 6.74; N, 10.42.

(4*R,5*S**,6*S**)-5-Amino-3,6-epoxy-4-ethyl-7-methyl-1,2,3,4,5,6-hexahydroazocino[5,4-*b*]indole (7)** The same procedure as described for the preparation of **16** (method A) provided a crude product from **38** (277 mg, 0.68 mmol), $AlBr_3$ (907 mg, 3.4 mmol), and EtSH (2 ml), and this was purified by column chromatography (elution with 5% MeOH in $CHCl_3$) to give **7** (146 mg, 79%) as an oil. IR (neat): 3380 and 3290 (NH_2) cm^{-1}. ^{1}H-NMR δ: 0.96 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.66 (2H, m, $C\underline{H}_2CH_3$), 3.05—3.50 (4H, m, 1-H_2, 2-H, 4-H), 3.71 (3H, s, NCH_3), 3.77 (1H, m, 5-H), 3.91 (1H, m, 2-H), 5.20 (1H, br s, 6-H), 7.06—7.32 (3H, m, ArH), 7.50 (1H, d, J=7.5 Hz, 8-H). MS *m/z*: 271 (M^+). HR-MS Calcd for $C_{16}H_{21}N_3O$: 271.1683. Found: 271.1679.

(4*R,5*R**,6*S**)-5-Amino-3,6-epoxy-4-ethyl-7-methyl-1,2,3,4,5,6-hexahydroazocino[5,4-*b*]indole (6)** The same procedure as described for the preparation of **16** (method A) provided a crude product from **39** (585 mg, 1.4 mmol), $AlBr_3$ (1.90 g, 7 mmol), and EtSH (4 ml), and this was purified by column chromatography (elution with 5% MeOH in $CHCl_3$) to give **6** (225 mg, 58%). Recrystallization from EtOH gave crystals, mp 134—135 °C. IR (KBr) cm^{-1}: 3360 (NH_2). ^{1}H-NMR δ: 1.07 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.78 (2H, m, $C\underline{H}_2CH_3$), 2.75 (1H, m, 4-H), 2.96—3.50 (3H, m, 1-H_2, 2-H), 3.71 (3H, s, NCH_3), 3.78—3.98 (2H, m, 2-H, 5-H), 5.26 (1H, d, J=7.5 Hz, 6-H), 7.08—7.39 (3H, m, ArH), 7.54 (1H, d, J=7.5 Hz, 8-H). MS *m/z*: 271 (M^+). HR-MS Calcd for $C_{16}H_{21}N_3O$: 271.1683. Found: 271.1687. *Anal.* Calcd for $C_{16}H_{21}N_3O$: C, 70.82; H, 7.80; N, 15.49. Found: C, 70.91; H, 7.85; N, 15.46.

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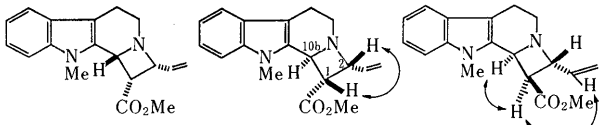
13) In a previous paper,[1] we reported an erroneous stereostructure (**17A**) for compound **17** ($J_{1\text{-H},2\text{-H}}=J_{1\text{-H},10b\text{-H}}=8.0$ Hz), based on the general rule that the vicinal coupling constants of the azetidines $^3J_{(H,H)cis}$ (7—8 Hz) are larger than $^3J_{(H,H)trans}$ (2—3 Hz)[17] in the ^{1}H-NMR spectra. However, the structure **17A**, in which the three neighboring methine protons on azetidine ring are all *cis*, seemed questionable. Thus, ^{1}H-NOE experiments on compound **8** and its isomer **17** were carried out. A positive NOE was observed between 1-H and 2-H in **8**, while two positive NOEs were observed between 1-H and 10b-H as well as 1-H and the vinyl proton (–C<u>H</u>=CH_2) in **17**. Therefore, the structure of **17A** should be revised to structure **17**. Thus, care is necessary in determining azetidine ring

stereochemistry from ^{1}H-NMR spectral data.



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