1 PERKIN

Total synthesis of (−)-eudistomins with an oxathiazepine ring. Part 1. Formation of the oxathiazepine ring system

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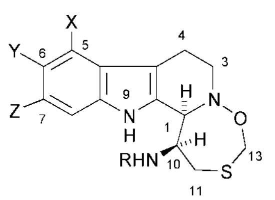
Formation of the oxathiazepine ring in eudistomins **1** was investigated. Thiazolidinyl-β-carboline **5** was successfully transformed into thiaindoloquinolizidine **7**, but attempted oxidative transformation of **7** to **1** was not successful. The oxidative cyclization of 1-substituted-2 hydroxy-β-carboline **24** with NCS or the acid-catalyzed cyclization of the corresponding *S*-oxide **26** with TsOH gave oxathiazepine **25**, which was readily converted to (+)-debromoeudistomin L (+)-**1f**. (−)-Debromoeudistomin L (−)-**1f** was prepared from *N*-hydroxytryptamine **11** and the D-cysteinal **30**.

In 1984, an unprecedented series of potent antiviral compounds, eudistomins **1**, were isolated from the Caribbean, tunicate *Eudistoma olivaceum* by Rinehart and co-workers.[1] Eudistomins L, K, C, E, and F, **1a**–**e**, are representative alkaloids that are characterized by a novel 2-hydroxy-β-carboline moiety fused with an unprecedented oxathiazepine ring system. Two related compounds in this family, debromoeudistomin L **1f** and eudistomin K sulfoxide, have since been isolated from the New Zealand ascidian *Ritterella sigillinoids* along with **1a**–**e**.[2] The original structure of this new class of alkaloids was first elucidated by Rinehart's group based on NMR and mass spectroscopic evidence.[1a] The stereochemistry at the 2-position was revised by a subsequent, extensive NMR spectroscopic study[3] and confirmed by an X-ray analysis of the *p*-bromobenzoyl derivative of eudistomin K.[4] All of these compounds were found to exhibit potent antiviral activity and to have significant antimicrobial properties.[1b,2b]

The unique structures of these indole alkaloids coupled with their interesting biological properties have inspired several ingenious synthetic endeavors.[5] We reported the first enantioselective total synthesis of (−)-debromoeudistomin L **1f**,[6] (−)-eudistomin L **1a**,[6] and (−)-eudistomin F **1e**,[7] and con-



	Eudistomins	X	Y	Z	R
1	**a**: Eudistomin L	H	Br	H	H
	b: Eudistomin K	H	H	Br	H
	c: Eudistomin C	H	OH	Br	H
	d: Eudistomin E	Br	OH	H	H
	e: Eudistomin F	H	OH	Br	COOMe

firmed their absolute configurations by synthetic methods. More recently, an alternative synthesis of (−)-debromoeudistomin L (−)-**1f** was reported by Hermkens and co-workers using the intramolecular cyclization of *N*-alkoxytryptamines.[8] In this two-part report, we provide the complete details of our progress in this area, which has culminated in the total synthesis of (−)-eudistomins L, K, C, E, F, and debromoeudistomin L in enantiomerically pure form.

There are two major problems to be solved in the total synthesis of these eudistomins. The first problem is how to construct the oxathiazepine ring, which has not been previously reported in either natural products or synthetic compounds.[9] The second problem is the introduction of substituents on the benzene ring, since the eudistomins that show strong bioactivity towards viruses are derivatives with a bromine and a hydroxy group on the benzene ring. In this report, we focus on construction of the oxathiazepine ring and the successful synthesis of natural debromoeudistomin L **1f**. The total synthesis of other natural eudistomins is reported in the following paper.

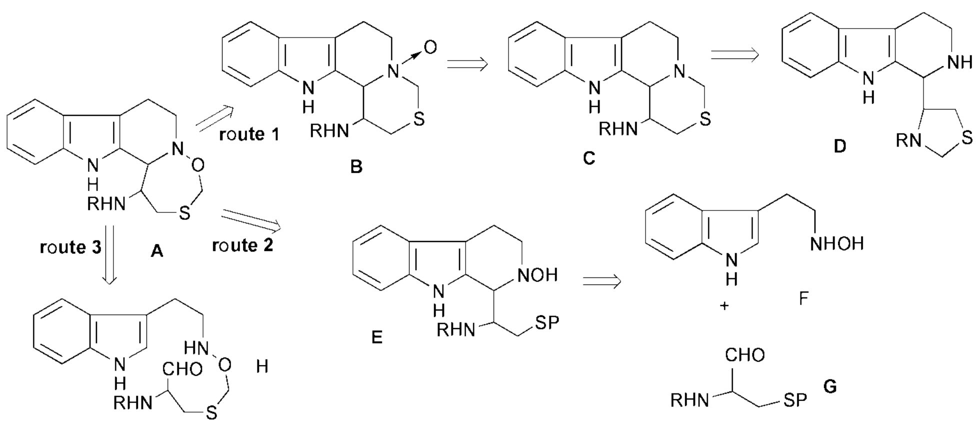
Our initial retrosynthetic analysis involved two routes to construct the oxathiazepine ring, as shown in Scheme 1. The first is successive ring transformations of a 1-thiazolidin-4-yltetrahydro-β-carboline (**D**) to form a thiaindoloquinolizidine (**C**), followed by Meisenheimer rearrangement of its *N*-oxide (**B**) to the desired oxathiazepine framework (**A**).

The second approach involves the direct formation of the oxathiazepine ring from a properly 1-substituted *N*-hydroxy-β-carboline (**E**) by reaction with a one carbon unit. The *N*-hydroxytetrahydro-β-carboline (**E**) can be obtained by the Pictet–Spengler reaction of *N*-hydroxytryptamine (**F**) and cysteinal (**G**). A third route, developed by Hermkens' group[8] and Kirkup's group,[5f] is the intramolecular Pictet–Spengler reaction of *N*-alkoxytryptamine (**H**) to form an oxathiazepine ring with the β-carboline in one step. Using D-cysteine derivatives as starting materials, this total synthesis should provide direct evidence for the absolute stereochemistry of eudistomins. We began by examining the first route.[5b]

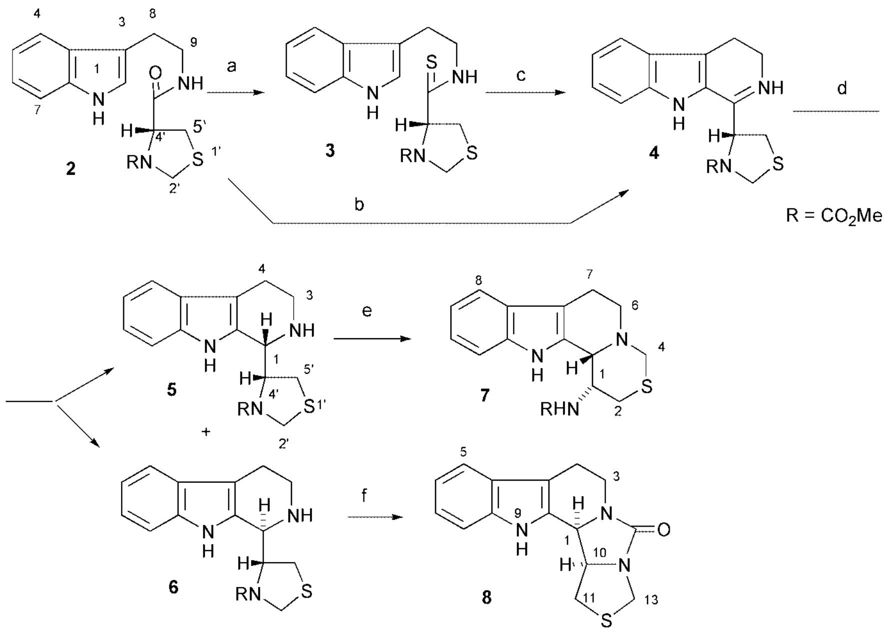
Results and discussion

Cyclization of tryptamine amide **2**, prepared from tryptamine and the L-thiazolidine carboxylic acid, with phosphoryl trichloride followed by reduction of the 3,4-dihydro-β-carboline **4** by sodium borohydride gave a mixture of 1-substituted tetrahydro-β-carbolines **5** and **6** in 83% yield (Scheme 2). The 1β-isomer **5** was obtained as the major isomer (63%), but both products were found to be racemic due to racemization during the Bischler–Napieralski reaction. Therefore, we carried out mild cyclization of the corresponding thioamide **3**, prepared from **2**, with benzyl bromide[10] to give **4**. Immediate reduction of **4** with sodium borohydride resulted in preferential formation of the optically active 1β-isomer (−)-**5**, as observed in the above case.

Ring transformations of the tetrahydro-β-carbolines **5** and **6** were initially examined for racemic compounds. Reflux of racemic 1β-isomer (±)-**5** in trifluoroacetic acid resulted in



Scheme 1



Scheme 2 *Reagents and conditions*: (a) Lawesson reagent, toluene, reflux, 1 h; (b) $POCl_3$; (c) $PhCH_2Br$, CH_2Cl_2, reflux, 46 h; (d) $NaBH_4$, MeOH–CH_2Cl_2; (e) 50% AcOH, reflux, 42 h; (f) 50% AcOH, reflux, 25 h.

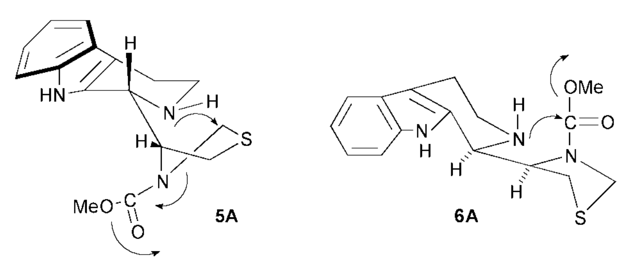
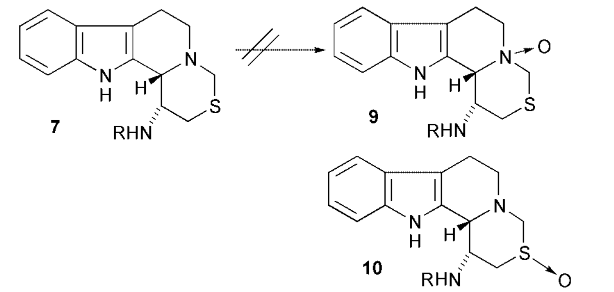


Fig. 1

epimerization to the 1α-isomer (±)-**6** (50%). Heating of the 1β-isomer (±)-**5** in TsOH–benzene (8 h) or in $BF_3 \cdot Et_2O$–CH_2Cl_2 (7 h) gave only recovered starting material. However, when (±)-**5** was refluxed in 50% AcOH for 42 h it rearranged to 1-(methoxycarbonylamino)thiaindoloquinolizidine (±)-**7** in 40% yield, accompanied by a small amount of the 1α-isomer (±)-(**6**). The structure and stereochemistry were determined by spectral data (Experimental section) as well as X-ray analysis.[5b] On the other hand, similar heating of the 1α-isomer (±)-(**6**) in 50% acetic acid for 25 h gave a new pentacyclic compound [(±)-**8**] in 33% yield. These characteristic reactivities may be explained by the conformation of both isomers, as shown in Fig. 1.

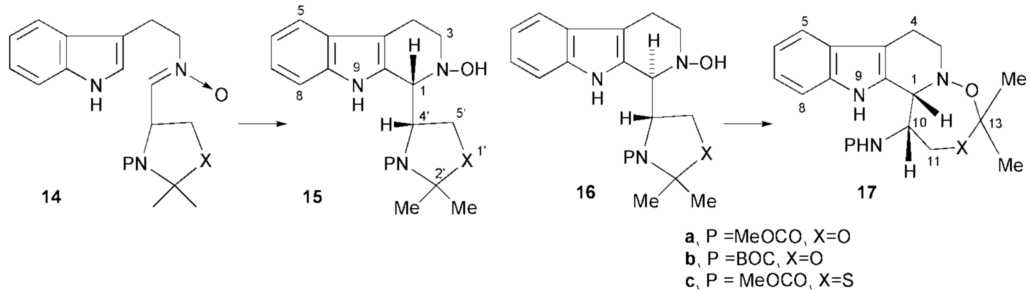
The conformation of the 1β isomer **5** can be drawn as **5A**, which converts to the thiaindoloquinolizidine **7**, while the conformer **6A**, corresponding to the 1α isomer **6**, converts to the pentacyclic compound **8**. Likewise, the ring transformation of optically active 1β-tetrahydro-β-carboline (−)-**5** in refluxing aq. acetic acid gave the optically active thiaindoloquinolizidine (+)-**7**, $[\alpha]_D$ +133, in 25% yield with high enantiomeric purity. Attempted selective oxidation of the thiaindoloquinolizidine **7** to the *N*-oxide **9** with *m*-chloroperbenzoic (MCPBA) acid failed, and gave only the corresponding *S*-oxide **10** as the sole product (Scheme 3). Therefore, we investigated another possibility for transformation to the oxathiazepine ring.



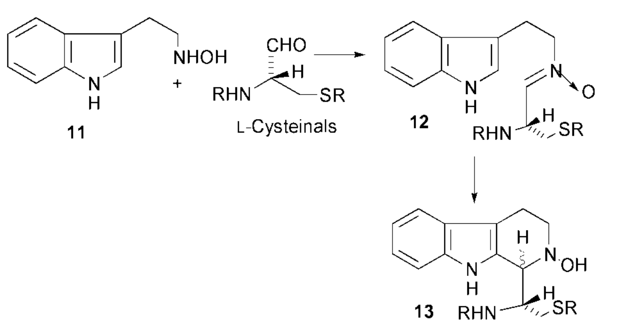
Scheme 3 *Reagents and conditions*: MCPBA, CH_2Cl_2, aq. K_2CO_3, rt.

Another candidate for transformation to the oxathiazepine ring is the 1-thiazolin-4-yl-*N*-hydroxytetrahydro-β-carboline **15c**, which is equivalent to an *N*-oxide of thiaindoloquinolizidine. We previously reported that the cyclization of nitrones prepared from *N*-hydroxytryptamine **11** and aldehydes gave

Table 1 Ring transformation of 1-oxazolidinyl- and thiazolidinyl-β-carbolines **15**, **16** to **17**



Run	Substrates	Conditions	Yield **17** (%)
1	**15a**	TsOH, DMP, benzene, rt 1 h	**17a** 44
2	**15a**	TFA, benzene, reflux, 3 h	**17a** 15
3	**16a**	TFA, benzene, reflux, 3 h	—
4	**15b** + **16b**	TFA, CH_2Cl_2, reflux, 5 h	**17b** 24
5	**15c**	TsOH, toluene, reflux, 1.5 h	**17c** 11

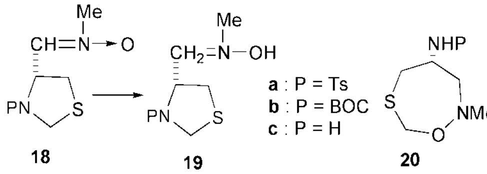


Scheme 4

the corresponding *N*-hydroxytetrahydro-β-carbolines,[11,12] and furthermore, nitrones **12** from cysteinals also gave *N*-hydroxy-tetrahydro-β-carbolines **13** (Scheme 4).[13,14] We applied the same protocol to obtain 1-thiazolidinyl-β-carboline derivatives and oxa-analogs **15** and **16** *via* nitrones **14** prepared from *N*-hydroxytryptamine **11** and thiazolidine- and oxazolidine-carbaldehydes, respectively. Ring transformation of these *N*-hydroxy-β-carbolines **15** and **16** was examined under various conditions.

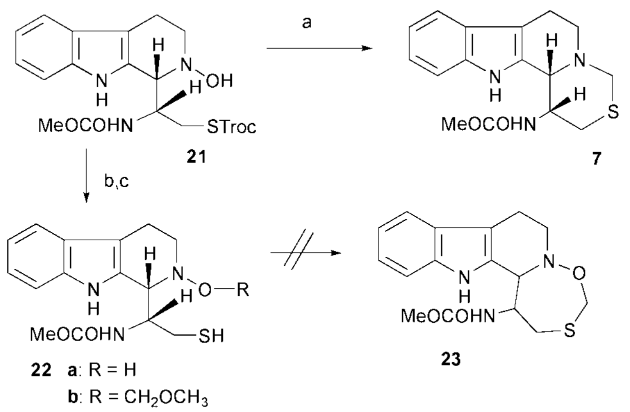
The results of this rearrangement to oxathiazepines and dioxazepines **17** are shown in Table 1. The 2′,2′-dimethyl-oxazolidinyl derivative (run 1) gave **17a** in 44% yield, but this was not satisfactory. Only 1β-tetrahydro-β-carbolines **15** gave the desired 1β-oxathiazepine or dioxazepine **17**, as above, although the oxygen analogs gave better results. It is clear that the dimethyl substitution at the 2′-position is essential for this transformation. The structures of the products (**17a**,**b** and **c**) were confirmed by their NMR spectra, in comparison with those of N-protected debromoeudistomin L (see below).

We further examined the possibility of ring transformation of thiazolidine derivatives to a monocyclic oxathiazepine. Nitrones **18** were prepared from thiazolidinecarbaldehydes and *N*-methylhydroxylamine. Nitrones **18** were reduced with $NaBH_4$ to thiazolidinylmethyl-*N*-methylhydroxylamines **19**. Rearrangement of these thiazolidines **19** to the corresponding oxathiazepine **20** under various conditions gave poor results (Scheme 5).



Scheme 5

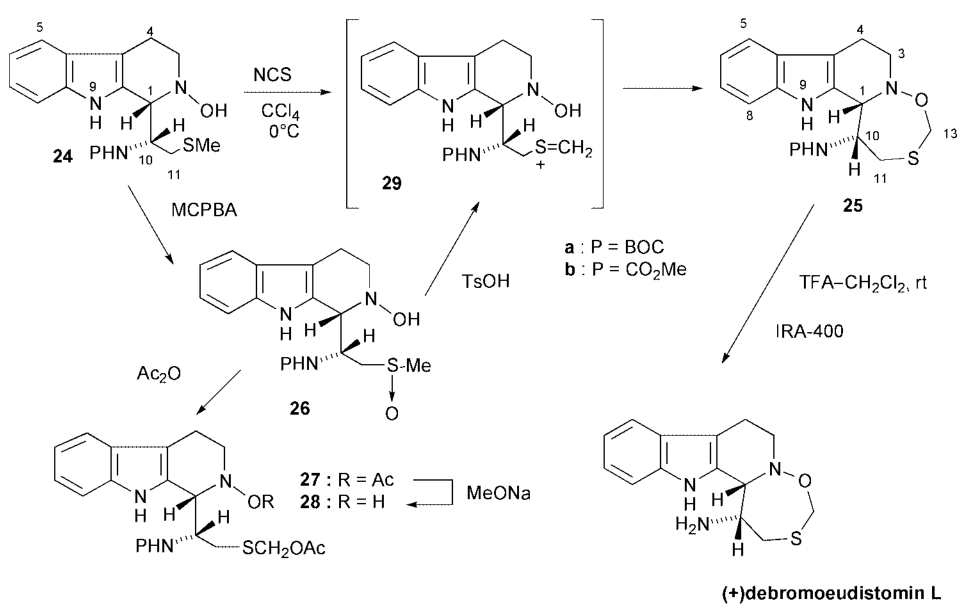
We now changed our focus to route 2, to form an oxathiazepine ring by insertion of a C_1 unit into 1-substituted β-carboline derivatives. The insertion of a C_1 unit was examined for the *N*-methoxycarbonyl-*S*-Troc-β-carboline **21**[13] † derived from an L-cysteine derivative. The β-carboline **21** was treated with Zn–acetic acid–formaldehyde–methanol in an attempt at sequential deprotection of the Troc group and simultaneous insertion of C_1 between the O and S atoms. However, reductive N-hydroxylation occurred to form the thiaindoloquinolizidine **7**. Although mild deprotection of the Troc group by Zn–MeOH smoothly gave the OH–SH derivative **22a**, attempted insertion of a C_1 unit in this compound was unsuccessful. Therefore, a C_1 unit was introduced onto the *N*-hydroxy group at an early stage in the synthesis. Thus, the methoxymethyl (MOM) derivative **22b** was obtained by methoxymethylation of the β-carboline **21** followed by deprotection of the Troc group. However, nucleophilic attack of the sulfur atom at the carbon between two oxygen atoms failed to give the oxathiazepine **23** under various conditions (Scheme 6).



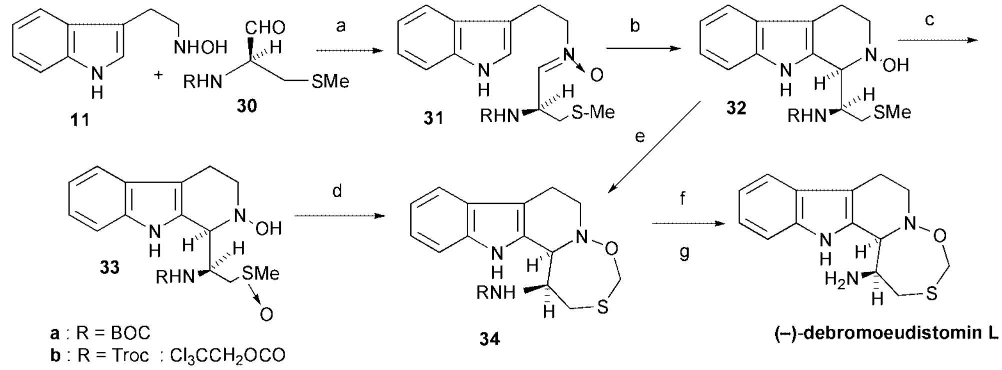
Scheme 6 *Reagents and conditions*: (a) Zn–AcOH–35% CH_2O–MeOH; (b) **22a**: Zn–Cu couple, MeOH, 1.5 h, reflux; (c) **22b**: (1) MOMCl, Pr^i_2NEt, CH_2Cl_2, 4 h, rt; (2) Zn–AcOH–MeOH.

To identify favourable conditions for the desired cyclization *via* a more reactive intermediate, we next carried out the intramolecular Pummerer-type cyclization of the *S*-methyl sulfide **24** derived from L-cysteine[13] by halogenation with various reagents (Scheme 7). After several attempts under various conditions, the first direct cyclization to the oxathiazepine ring was achieved when *N*-chlorosuccinimide (NCS) was used, although the yield was low. Thus, the reaction of **24a** with NCS (1.2

† Troc = 2,2,2-trichloroethoxycarbonyl.



Scheme 7



Scheme 8 *Reagents and conditions*: (a) CH_2Cl_2, rt, 2 h; (b) TFA (5 equiv.), −78 °C, CH_2Cl_2, 2 h; (c) MCPBA, CH_2Cl_2, 10 min, rt; (d) *p*-TsOH, PPTS, rt, overnight; (e) NCS, $CHCl_3$, 0 °C; 10 min; (f) (1) TFA, CH_2Cl_2, rt, 15 min then (2) IRA-400, 15 min, rt.

equiv.) in CCl_4 at 0 °C for 12 h gave the tetracycle **25** (4%) as crystals and the starting material was recovered (>50%); no by-products have as yet been identified. Since the use of NBS or *N*-iodosuccinimide (NIS) did not improve the yield of **25**, assignment of the oxathiazepine ring system in **25** was strongly supported by its ^{1}H NMR spectrum, which revealed the presence of two protons due to the newly formed methylene group between O and S as two doublets (*J* 9 Hz) at *δ* 4.94 and 4.81, respectively, consistent with those reported for natural eudistomins.[1,2] In addition, the SMe group had disappeared in the ^{1}H NMR spectrum of **25a**. Structural assignment for **25a** was subsequently confirmed by its conversion to (+)-debromoeudistomin L (+)-**1f**. Toward this end, deprotection of **25a** with 50% TFA–CH_2Cl_2 at room temperature for 15 min followed by treatment with Amberlite (CG-400, in OH-form) gave the enantiomeric (+)-debromoeudistomin L (+)-**1f**, the spectral data of which were identical with those of the natural product.[2]

To improve this oxidative cyclization, an acid-catalyzed Pummerer-type cyclization of the sulfoxides **26** was tried. Although the Pummerer reaction is well documented,[15] there are few examples of this reaction being used for cyclization. Generally, the Pummerer reaction of sulfoxides is carried out in the presence of trifluoroacetic anhydride (TFAA) or Ac_2O. Therefore, we first examined the Pummerer-type cyclization of **26** under general conditions. As shown in Scheme 7, the sequence began with MCPBA oxidation of the N^b-hydroxy-β-carboline **24**.[13] The reaction proceeded rapidly and gave the desired sulfoxides **26**; no indole-oxidized by-products were detected. Treatment of **26** with TFAA at −78 °C gave a complex mixture of decomposition products. On the other hand, with acetic anhydride, the reaction gave the diacetates **27** and the desired oxathiazepine derivative was not obtained. Conversion of the diacetate **27** to the corresponding monoacetates **28** was carried out in the presence of NaOMe (1 equiv.). However, **28** failed to cyclize to the corresponding oxathiazepine compounds **25**. We applied a modified Pummerer reaction with *p*-TsOH,[16] and the yields of **25** increased up to 23% (**25b**) and 10% (**25a**), respectively, when CO_2Me (**26b**) and CO_2Bu*t* (**26a**) were used as protecting groups. Both the NCS-catalyzed and TsOH-induced Pummerer-type reactions were presumed to proceed *via* a sulfonium intermediate such as **29** which undergoes intramolecular nucleophilic cyclization by the NOH group to give the oxathiazepine ring system. These results were applied to the total synthesis of other eudistomin congeners.

Starting with D-cysteine, (−)-debromoeudistomin L (−)-**1f** was readily synthesized (Scheme 8). Careful reduction[17] of *N*-Boc-*S*-methyl-D-cysteine methyl ester with diisobutylaluminium hydride (DIBAH) (2 equiv.) at −60 °C for 2 h gave the optically active cysteinal **30a** (≈60%) contaminated by the corresponding alcohol. The crude cysteinal **30a** was used in the next step without chromatographic purification to avoid possible racemization.[16] Coupling reaction of the crude (−)-cysteinal **30a** with N^b-hydroxytryptamine **11** in CH_2Cl_2 (rt, 2 h) gave the (−)-nitrone **31a** (90%), which cyclized in the presence of TFA (5 equiv.) at −78 °C to give the corresponding N^b-hydroxy-β-carboline **32a** (90%) and its 1β-isomer (4%). The major isomer, **32a**, which has the correct stereochemistry, was then treated with NCS in CCl_4 at 5–10 °C for 1.5 h to give the (−)-*N*-Boc-debromoeudistomin (−)-**34a** as colorless prisms, mp 197–198 °C, in 8% yield. The same compound (**34a**) was also obtained *via S*-oxide **33a** in 11% yield. After deprotection of **34a** with 50% TFA–CH_2Cl_2 followed by treatment with IRA 400 (Amberlite), (−)-debromoeudistomin L (−)-**1f** was obtained as a colorless, amorphous solid. Similar results were obtained with *N*-Troc-*S*-methyl-D-cysteine methyl ester **30b**. The synthetic product was consistent with the spectral data provided by Professor Munro, University of Canterbury, New Zealand.

A similar cyclization to racemic debromoeudistomin L in better yield has been reported.[18] A sila-Pummerer-type cyclization to the oxathiazepine ring was developed by Still and Strautmanis.[5e] Synthesis of (−)-debromoeudistomin L (−)-**1f** was reported by applying intramolecular Pictet–Spengler reactions.[8c,e] The cyclization proceeded smoothly, but the stereoselectivity has to be improved.[8] The biological activities of these oxathiazepines and analogs obtained by the intramolecular Pictet–Spengler reaction have been recently reported.[19]

Experimental

Mps were determined with Yamato MP-1 and Yanagimoto micro-melting point apparatuses and are uncorrected. IR spectra (ν in cm^{-1}) were recorded with a Hitachi 260-10 spectrophotometer. UV-visible spectra were taken with Hitachi 323 and 340 spectrometers. Mass spectra were recorded on a JEOL HX-110A spectrometer. NMR spectra were recorded on JEOL JNM-FX-270, JNM-GSX-400 or 500 spectrometers for solutions in $CDCl_3$, unless otherwise noted, and chemical shifts were recorded as δ-values (ppm) relative to Me_4Si. Optical rotations were recorded with a JASCO DIP 140 polarimeter; $[a]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. Extracts were dried over $MgSO_4$.

N-[*N*-(Methoxycarbonyl)thiazolidin-4-ylcarbonyl]tryptamine 2

A mixture of *N*-(methoxycarbonyl)thiazolidine-4-carboxylic acid (3.6 g, 18.8 mmol), prepared from L-cysteine, tryptamine (2.7 g, 16.9 mmol) and dicyclohexylcarbodiimide (DCC) (3.5 g, 16.9 mmol) in CH_2Cl_2 (200 ml) was kept for 16 h at rt and refluxed for 1 h. Insoluble materials were filtered off and the mixture was washed successively with 5% HCl and saturated aq. $NaHCO_3$, and dried. Evaporation of the solvent left a residue, which was purified through a silica gel column with hexane–AcOEt (1.5 : 1) to (1 : 2) to give the amide **2** (5.5 g, 98%) as an amorphous powder, $[a]_D^{17}$ −97 (*c* 0.38, MeOH); λ_{max} (EtOH)/nm 224, 276, 284, 292; ν_{max} (KBr)/cm^{-1}: 3310, 1690, 1650, 1530; ^{1}H NMR (270 MHz) δ 2.99 (2H, t, *J* 7 Hz, 8-H_2), 3.17 (1H, m, 5′-H), 3.40 (1H, m, 5′-H), 3.60 (2H, m, 9-H_2), 3.65 (3H, s, OMe), 4.16 (1H, d, *J* 9 Hz, 2′-H), 4.60 (1H, d, *J* = 9 Hz, 2′-H), 4.71 (1H, br, 4′-H), 6.32 (1H, br, CONH, exchangeable), 7.13 (1H, s, 2-H), 7.15–7.62 (4H, m, ArH), 8.10 (1H, br, NH, exchangeable); MS *m*/*z* (%) 333 (M^+, 21%), 143 (100), 130 (85).

(±)-Tetrahydro-β-carbolines 5 and 6 from 2

Phosphoryl trichloride (5 ml) was added to a boiling solution of the amide **2** (1.0 g, 3 mmol) in benzene (10 ml), and the mixture was heated for 20 min. Evaporation of the solvent under reduced pressure left a residue, which was dissolved in CH_2Cl_2. The solution was neutralized with aq. sodium hydroxide and washed with brine. Evaporation of the solvent gave a residue, which was purified through an alumina column to give crude dihydro-β-carboline **4** (860 mg, 91%).

To a solution of crude **4** (2.87 g, 9.1 mmol) in MeOH (2 ml) was gradually added $NaBH_4$ (860 mg, 2.5 mmol) at rt, and the mixture was stored for 10 min. Evaporation of the solvent left a residue, which was dissolved in CH_2Cl_2 and washed with brine. The solvent was evaporated under reduced pressure to give a residue, which was recrystallized from ethyl acetate to give (±)-**5** (830 mg). Further purification of the mother liquor through a silica gel column gave (±)-**5** (total 1.83 g, 63%) and (±)-**6** (580 mg, 20%).

(±)-**5**: *colorless prisms*; mp 182–182.5 °C (from AcOEt–hexane); λ_{max} (EtOH)/nm (ε) 226 (35 600), 275 (7600), 283 (8100), 291 (6600); ν_{max} (KBr)/cm^{-1} 3340, 1675; ^{1}H NMR (270 MHz) δ 1.82 (1H, br, NH, exchangeable), 2.66–2.85 (2H, m, 4-H_2), 2.92 (1H, dd, *J* 7, 12 Hz, 5′-H), 3.03 (1H, m, 5′-H), 3.27 (1H, m, 3-H), 3.37 (1H, dd, *J* 7, 12 Hz, 3-H), 3.65 (3H, s, OMe), 4.40 (1H, d, *J* 9 Hz, 2′-H), 4.51 (1H, br, 1-H), 4.70 (1H, m, 4′-H), 4.89 (1H, d, *J* 9 Hz, 2′-H), 7.06–7.49 (4H, m, ArH), 8.19 (1H, br, NH, exchangeable); MS *m*/*z* (%) 317 (M^+, 1), 318 (6), 171 (100) (Calc. for $C_{16}H_{19}N_3O_2S$: C, 60.55; H, 6.04; N, 13.24. Found: C, 60.46; H, 6.09; N, 13.04%).

(±)-**6**: *colorless needles*; mp 177–178 °C (from AcOEt–hexane); λ_{max} (EtOH)/nm (ε) 226 (35 000), 275 (7700), 282 (7900), 291 (6500). ν_{max} (KBr)/cm^{-1} 3340, 1690; ^{1}H NMR (270 MHz) δ 1.82 (1H, br, NH, exchangeable), 2.73–2.76 (2H, m, 4-H_2), 2.97 (1H, dd, *J* 6, 12 Hz, 5′-H), 3.05 (1H, m, 3-H), 3.23 (1H, dd, *J* 6, 12 Hz, 5′-H), 3.33 (1H, m, 3-H), 3.79 (3H, s, OMe), 4.28 (1H, d, *J* 10 Hz, 2′-H), 4.60 (2H, br, 1- and 4′-H), 5.00 (1H, d, *J* 10 Hz, 2′-H), 7.07–7.50 (4H, m, ArH), 8.02 (1H, br, NH, exchangeable); MS *m*/*z* (%): 317 (M^+, 1%), 318 (3), 171 (100) (Calc. for $C_{16}H_{19}N_3O_2S$: C, 60.55; H, 6.04; N, 13.24. Found: C, 60.64; H, 6.08; N, 13.17%).

Optically active β-carbolines: (−)-5 and (−)-6 from 2 *via* thioamide 3 and 4

(1) Thionamide 3. A mixture of the amide **2** (1.1 g, 3.3 mmol) and Lawesson reagent (0.76 g, 1.7 mmol) in toluene (40 ml) was refluxed for 1 h. The solvent was evaporated to give a residue, which was purified on a silica gel column with hexane–AcOEt (1.5 : 1) to (1 : 2). The thioamide **3** (1.0 g, 87%) was obtained as a white amorphous solid $[a]_D^{17}$ −140 (*c* 0.28, MeOH). λ_{max} (EtOH)/nm 223, 275, 292; ν_{max} (KBr)/cm^{-1} 1700, 1530; ^{1}H NMR (270 MHz) δ 3.14 (2H, t, *J* 7 Hz, 8-H_2), 3.34 (1H, m, 5′-H), 3.56 (1H, m, 5′-H), 3.84–4.01 (2H, m, 9-H_2), 4.05 (1H, d, *J* 9 Hz, 2′-H), 4.54 (1H, d, *J* 9 Hz, 2′-H), 5.03 (1H, m, 4′-H), 7.05 (1H, d, *J* 2 Hz, 2-H), 7.12–7.62 (4H, m, ArH), 7.91 (1H, br, NH, exchangeable), 8.15 (1H, br, NH, exchangeable); MS *m*/*z* (%) 349 (M^+, 11%), 143 (100), 130 (39).

(2) (−)-5 and (−)-6 from 3. Benzyl bromide (1.4 g, 8.2 mmol) was added to a solution of the thioamide **3** (1.0 g, 2.9 mmol) in CH_2Cl_2 (20 ml) under Ar. The mixture was refluxed for 46 h and the solvent was evaporated to give a residue (crude **4**), which was washed with diethyl ether to remove excess of reagents. To a solution of this crude dihydrocarboline **4** in MeOH–CH_2Cl_2 (10 ml each) was added $NaBH_4$ (110 mg, 2.9 mmol) in small portions, and the mixture was stirred for 10 min at rt. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (100 ml). Conventional work-up as above gave (−)-**5** (400 mg, 44%) and (−)-**6** (170 mg, 19%). (−)-**5**: amorphous, $[a]_D^{21}$ −134 (*c* 0.30, MeOH). (−)-**6**: $[a]_D^{21}$ −95 (*c* 0.32, MeOH). The spectral data of these compounds were identical with those of the racemic compounds.

Ring transformation of 5 to thiaindoloquinolizidine 7

(1) Racemic compounds. A solution of (±)-**5** (460 mg, 0.69 mmol) in 50% acetic acid (10 ml) was refluxed for 42 h under Ar. The mixture was poured into water, neutralized with K_2CO_3 and extracted with CH_2Cl_2. Usual work-up and purification by a silica gel column with hexane–AcOEt (3 : 1) gave the *thiaindoloquinolizidine* **7** (150 mg, 40%) as colorless prisms, mp 225 °C (decomp., from AcOEt–hexane); λ_{max} (EtOH)/nm (ε) 225 (37 600), 274 (7400), 282 (7800), 291 (6300); ν_{max} (KBr)/cm^{-1}: 3300, 1690, 1507; ^{1}H NMR (270 MHz) δ 2.63–2.79 (2H, m, 7-H), 2.89 (1H, dq, *J* 2.3, 14 Hz, 2-H), 2.92–3.12 (2H, m, 6-H_2), 3.18 (1H, dd, *J* 2, 14 Hz, 2-H), 3.51 (3H, s, OMe), 3.64 (1H, d, *J* 1 Hz, 12b-H), 3.73 (1H, dd, *J* 2, 12 Hz, 4-H), 3.86 (1H, d,

J 12 Hz, 4-H_2), 4.53 (1H, m, 1-H), 5.86 (1H, d, J 9 Hz, NH, exchangeable), 7.06–7.46 (4H, m, ArH), 8.33 (1H, br, NH, exchangeable); MS, m/z (%) 317 (M^+, 14%), 216 (100), 183 (53), 169 (50) (Calc. for $C_{16}H_{19}N_3O_2S$: C, 60.55; H, 6.04; N, 13.24. Found: C, 60.44; H, 6.03; N, 13.21%).

(2) Optically active compound (+)-7. A solution of (−)-**5** (0.5 g, 1.58 mmol) in 50% AcOH (10 ml) was refluxed for 37 h under Ar. Similar work-up as above gave (+)-**7** (126 mg, 25.2%) as colorless prisms, mp 204 °C (decomp., from AcOEt–hexane). Compounds **8** (9%), **5** (14%) and **6** (16%) were also isolated. (+)-**7**: $[\alpha]_D^{21}$ +133 (c 0.20, MeOH). The spectral data were identical with those of the racemic **7**. The NMR spectra of (−)-**5** and (+)-**7** using a derivative of the chiral reagent tris[3-(heptafluoropropylhydroxymethylene)-d-camporato]europium(III) showed the absence of the other enantiomer.

Transformation of (±)-6 to the pentacyclic compound 8

A solution of (±)-**6** (100 mg, 0.32 mmol) in aq. acetic acid (AcOH 2 ml and water 1 ml) was refluxed for 25 h under Ar. The solvent was removed to give a residue, which was dissolved in CH_2Cl_2. The solution was washed with saturated aq. $NaHCO_3$ and dried. Evaporation of the solvent gave a residue, which was purified through a silica gel column with hexane–AcOEt (1 : 3) to give (±)-**8** (30 mg, 33%) as colorless needles, mp 260–261 °C (from AcOEt–hexane); λ_{max} (EtOH)/nm 226, 275, 283, 291; ν_{max} (KBr)/cm^{-1} 3300, 1690; ^{1}H NMR (270 MHz) δ (non-systematic numbering scheme) 2.27 (1H, t, J 10 Hz, 11-H), 2.67 (1H, dd, J 6, 10 Hz, 11-H), 2.85 (2H, m, 4-H_2), 3.15 (1H, m, 3-H), 4.16 (1H, d, J 9 Hz, 13-H), 4.20 (1H, m, 10-H), 4.38 (1H, m, 3-H), 5.08 (1H, d, J 9 Hz, 13-H), 5.27 (1H, d, J 7 Hz, 1-H), 7.12–7.52 (4H, m, ArH), 7.24 (1H, br, N9-H, exchangeable); MS m/z (%) 285 (M^+, 100), 239 (49), 170 (89).

Oxidation of thiaindoloquinolizidine 7 with MCPBA

To a solution of (±)-thiaindoloquinolizidine **7** (200 mg, 0.63 mmol) in CH_2Cl_2 (10 ml) was added 10% aq. K_2CO_3 (4 ml) and MCPBA (192 mg, 0.95 mmol) in CH_2Cl_2 (10 ml) at rt. The mixture was then stirred for a few min and diluted with CH_2Cl_2. The organic layer was washed with brine and dried. Evaporation of the solvent gave a residue, which was triturated with hexane–AcOH to give S-oxide **10** (63 mg, 31%) as a colorless solid. Another isomer (20 mg, 10%) was also isolated, but could not be purified. S-oxide **10**; mp 217–218 °C (from AcOEt–hexane); λ_{max} (EtOH)/nm: 225, 275, 283, 291; ν_{max} (KBr)/cm^{-1}: 1700, 1515, 1015; ^{1}H NMR (270 MHz) δ 2.30–2.75 (2H, m, 7-H_2), 2.80 (1H, dd, J 3.0, 12.0 Hz, 2-H), 3.00 (1H, m, 6-H_2), 3.14 (1H, m, 6-H), 3.50 (3H, s, OMe), 3.57 (1H, d, J 11 Hz, 4-H), 3.99 (1H, br, 12b-H), 4.03 (1H, dt, J 3.4, 12 Hz, 2-H), 4.56 (1H, dd, J 3, 11 Hz, 4-H_2), 4.70 (1H, br, 1-H), 5.05 (1H, d, J 9 Hz, NH, exchangeable), 7.10–7.50 (4H, m, ArH), 8.27 (1H, br, NH, exchangeable); MS m/z (%) 333 (M^+, 2%), 202 (100), 169 (78).

Ring transformation of *N*-hydroxy-1-oxa(thia)zolidin-4-yltetrahydro-β-carbolines 15 and 16

1. Preparation of nitrones 14.

14a. The reaction of N-hydroxytryptamine **11** [2.69 g, prepared from 3-(nitroethyl)indole (2.70 g, 14.2 mmol)] and N-(methoxycarbonyl)oxazolidine-4-carbaldehyde (3.18 g, 17 mmol), prepared from the corresponding oxazolidinecarboxylate, gave **14a** (4.18 g, 86%), $[\alpha]_D^{14}$ −28.5 (c 1.23, EtOH); λ_{max} (EtOH)/nm 222, 237sh, 273, 281, 289; ν_{max} (KBr)/cm^{-1} 3350, 1700, 1600; ^{1}H NMR (500 MHz) δ 1.40 (3H, s, 2′-Me), 1.47 (3H, s, 2′-Me), 3.39 (2H, d, J 7.0 Hz, 8-H_2), 3.53 (3H, s, OMe), 4.06 (2H, d-like, 5′-H_2), 4.11 (2H, d, J 7.0 Hz, 9-H), 4.88 (1H, br, 12-H), 6.40 (1H, br, 11-H), 7.05 (1H, br, 2-H), 7.13 (1H, t, J 7.3 Hz, 5-H), 7.20 (1H, t, J 7.3 Hz, 6-H), 7.37 (1H, d, J 7.3 Hz, 7-H), 7.60 (1H, d, J 7.6 Hz, 4-H), 8.25 (1H, br, NH).

14b. (84% from **11**) A colorless amorphous solid, $[\alpha]_D$ −13.0 (c 1.00, MeOH); λ_{max} (EtOH)/nm 222, 242sh, 273, 282, 291; ν_{max} (KBr)/cm^{-1} 3250, 2950, 1670, 1590; ^{1}H NMR (500 MHz) δ 1.37 (6H, s, 2 × Me), 1.45 (9H, s, t-Bu), 3.31 (1H, m, 8-H), 3.45 (1H, m, 8-H), 4.00 (1H, q, J 7.2 Hz, 5′-H), 4.12 (1H, q, J 7.2 Hz, 5′-H), 4.91 (1H, br, 4′-H), 6.46 (1H, br, 11-H), 7.07 (1H, s, 2-H), 7.14 (1H, t-like, 5-H), 7.21 (1H, t-like, 6-H), 7.37 (1H, d, J 8.0 Hz, 4-H), 7.60 (1H, d, J 7.7 Hz, 7-H), 8.16 (1H, br, NH); EI-MS m/z (%) 387 (M^+, 0.19%), 370 (4), 187 (24), 144 (80), 143 (100), 130 (61) (Calc. for $C_{21}H_{29}N_3O_4$: M, 387.2155. Found: M^+, 387.2132).

14d. (70% from **11** and thiazolidinylcarbaldehyde) as a pale yellow amorphous solid, λ_{max} (EtOH)/nm 224, 275, 281, 290; ν_{max} (KBr)/cm^{-1} 3400, 3320, 1690, 1500; ^{1}H NMR (400 MHz) δ 3.00 (1H, br, 5′-H), 3.23 (1H, dd, J 6.7, 10 Hz, 5′-H), 3.31 (1H, dt, J 6.2, 14.8 Hz, 8-H), 3.43 (1H, dt, J 7.2, 14.8 Hz, 8-H), 3.65 (3H, s, OMe), 4.00 (2H, t-like, 9-H_2), 4.28 (1H, d, J 9.3 Hz, 2′-H), 4.51 (1H, br, 4′-H), 5.20 (1H, br, 4′-H), 6.46 (1H, d, J 5.3 Hz, 11-H), 7.06 (1H, d, J 1.0, 7.5 Hz, 2-H), 7.13 (1H, dt, J 1.0, 7.5 Hz, 5-H), 7.20 (1H, dt, J 1.1, 7.6 Hz, 6-H), 7.37 (1H, td, J 0.9, 8.0 Hz, 7-H), 7.60 (1H, d, J 7.7 Hz, 4-H), 8.21 (1H, s, NH).

14e. (80% from **11** and thiazolidinylcarbaldehyde) as a pale yellow amorphous solid; $[\alpha]_D^{18}$ −16.7 (c 1.14, EtOH); λ_{max} (EtOH)/nm 222, 275, 282, 290; ν_{max} (KBr)/cm^{-1}: 3300, 3200, 1690; ^{1}H NMR (500 MHz) δ 1.42 (9H, s, t-Bu), 2.95 (1H, br, 5′-H), 3.24 (1H, m, 8-H_2), 3.31 (1H, m, 8-H), 3.45 (1H, br, 5′-H), 4.00 (2H, t-like, 9-H_2), 4.24 (1H, d, J 9.1 Hz, 2′-H), 4.49 (1H, br, 2′-H), 5.18 (1H, br, 4′-H), 6.47 (1H, br, 11-H), 7.07 (1H, d, J 1.8 Hz, 2-H), 7.13 (1H, t, J 7.9, 5-H), 7.37 (1H, d, J 8.0 Hz, 7-H), 7.60 (1H, d, J 8.0 Hz, 4-H), 8.21 (1H, s, NH).

2. Cyclization of 14 to β-carbolines 15 and 16. *(1) **15a** and **16a**.* (i) At −78 °C. To a solution of **14a** (346 mg, 1.0 mmol) in CH_2Cl_2 (20 ml) was added CF_3CO_2H (0.40 ml, 5.0 mmol) at −78 °C over a period of 5 min. The mixture was stirred at this temperature for 1.5 h and neutralized with $NaHCO_3$. Usual work-up gave **16a** (113 mg, 33%) and **15a** (186 mg, 54%).

(ii) At room temperature. The similar reaction of **14a** (1.88 g, 5.44 mmol) and CF_3CO_2H (2.10 ml, 27.2 mmol) in CH_2Cl_2 (60 ml) at rt for 10 min gave **16a** (432 mg, 23%) and **15a** (1.12 g, 60%).

16a: $[\alpha]_D^{13}$ +5.66 (c 1.02, EtOH); λ_{max} (EtOH)/nm 226, 274sh, 283, 290; ν_{max} (KBr)/cm^{-1} 3360, 2930, 1680; ^{1}H NMR (400 MHz) δ 1.53 (3H, s, 2′-Me), 1.58 (3H, s, 2′-Me), 2.81 (1H, m, 4-H), 3.00 (1H, m, 4-H), 3.10 (1H, m, 3-H), 3.60 (1H, m, 3-H), 3.78 (3H, s, OMe), 4.08 (2H, d, J 2.0 Hz, 5′-H_2), 4.57 (1H, m, 1-H), 4.79 (1H, dd, J 1.3, 2.0 Hz, 4′-H), 7.00 (1H, br, OH), 7.08 (1H, t-like, 6-H), 7.15 (1H, t, J 7.0 Hz, 7-H), 7.31 (1H, d, J 8.1 Hz, 8-H), 7.46 (1H, d, J 7.3 Hz, 5-H), 9.19 (1H, br, NH) [Calc. for $C_{18}H_{24}N_3O_4$ (MH^+): 346.1767. Found: m/z, 346.1762].

15a: $[\alpha]_D^{13}$ −43.23 (c 1.064, EtOH); λ_{max} (EtOH)/nm 226, 274sh, 282, 290; ν_{max} (KBr)/cm^{-1} 3470, 3360, 2950, 1680; ^{1}H NMR (400 MHz) δ 1.52 (3H, s, 2′-Me), 1.80 (3H, s, 2′-Me), 2.82 (1H, d, J 15.4 Hz, 4-H), 3.01 (1H, m, 4-H), 3.17 (1H, td, J 10.9, 4.5 Hz, 3-H), 3.59 (1H, m, 3-H), 3.79 (3H, s, OMe), 3.91 (1H, dd, J 3.1, 9.9 Hz, 5′-H), 4.08 (1H, d, J 2.2 Hz, 5′-H), 4.60 (1H, s, 1-H), 4.66 (1H, t-like, 4′-H), 5.10–5.30 (1H, br, OH), 7.10 (1H, m, 6-H), 7.17 (1H, m, 7-H), 7.30 (1H, m, 8-H), 7.49 (1H, m, 5-H), 8.30–8.33 (1H, br, NH) [Calc. for $C_{18}H_{23}N_3O_4$ (M): 345.1689. Found: M^+, 345.1681].

*(2) A mixture of **15b** and **16b** was obtained (91%) by a similar reaction at rt from **14b**.* **15b** and **16b** (mixture) EI-MS m/z (%) 387 (M^+, 0.15%), 370 (3), 314 (2), 187 (62), 171 (100). The diastereomers (110 mg) were separated after hydrolysis to the dihydroxy derivatives with toluene-p-sulfonic acid (TsOH) to give α-isomer (9 mg) and β-isomer (23 mg).

3. Ring transformation of 15 and/or 16 (see Table 1). *(i) Ring transformation of **15a**.* A mixture of **15a** (50 mg, 0.145 mmol), TsOH (50 mg, 0.29 mmol), and 2,2-dimethoxypropane (DMP) (45 mg, 0.435 mmol) in CH_2Cl_2 (30 ml) was stirred for 1 h at rt. The mixture was neutralized with $NaHCO_3$ and conventional work-up gave the dioxazepine **17a** (22 mg, 44%) as a yellow amorphous solid, $[\alpha]_D^{18}$ +122.8 (*c* 1.123, EtOH); λ_{max} (EtOH)/nm 225, 274, 283, 290; ν_{max} (KBr)/cm^{-1} 3489, 3370, 1730, 1690; ^{1}H NMR (400 MHz) δ (non-systematic numbering) 1.33 (3H, s, 13-Me), 1.50 (3H, s, 13-Me), 2.78–2.83 (1H, m, 4-H), 2.93–3.14 (1H, m, 4-H), 3.08 (1H, ddd, *J* 4.2, 9.9, 11.8 Hz, 3-H), 3.46–3.50 (1H, m, 3-H), 3.47 (3H, s, OMe), 3.70 (1H, dd, *J* 3.5, 12.3 Hz, 11-H), 4.11 (1H, s, 1-H), 4.12 (1H, d, *J* 11.7 Hz, 11-H), 4.32 (1H, dt, *J* 3.1, 10.2 Hz, 10-H), 5.52 (1H, d, *J* 10.3 Hz, 10-NH), 7.08 (1H, t-like, 6-H), 7.13 (1H, t-like, 7-H), 7.31 (1H, d, *J* 7.9 Hz, 8-H), 7.44 (1H, d, *J* 7.7 Hz, 5-H), 8.46 (1H, s, NH, exchangeable) [HRMS-(FAB) Calc. for $C_{18}H_{24}N_3O_4$ (MH^+): 346.1767. Found: *m/z* 346.1772].

*(ii) Ring transformation of **15b** and **16b**.* A mixture of **15b** and **16b** (163 mg, 0.42 mmol) and TFA (0.04 ml, 0.52 mmol) in CH_2Cl_2 (15 ml) was refluxed for 5 h. The mixture was neutralized with $NaHCO_3$, washed with brine, and dried. Conventional work-up and silica gel column separation with AcOEt–hexane (1 : 5) to (1 : 3) gave the dioxazepine **17b** (38 mg, 24%) and recovered **15b** and **16b** (75 mg, 46%). **17b**: white solid. $[\alpha]_D^{20}$ +126.5 (*c* 0.27, $CHCl_3$); λ_{max} (EtOH)/nm 225, 273, 282, 291; ν_{max} (KBr)/cm^{-1} 3450, 3350, 1690, 1620; ^{1}H NMR (500 MHz) δ (non-systematic numbering) 1.20, 1.25 (9H, s, *t*-Bu), 1.33 (3H, s, 13-Me), 1.51 (3H, s, 13-Me), 2.81 (1H, dd, *J* 4.1, 14.8 Hz, 4-H), 3.00 (1H, td-like, 4-H), 3.09 (1H, td-like, 3-H), 3.49 (1H, dd, *J* 4.7, 9.6 Hz, 3-H), 3.69 (1H, dd, *J* 3.3, 12.1 Hz, 11-H), 4.10 (1H, s, 1-H), 4.14 (1H, d, *J* 12.4 Hz, 11-H), 4.30 (1H, dt, *J* 10.5, 3.3 Hz, 10-H), 5.37 (1H, d, *J* 10.5 Hz, 10-NH), 7.03–7.12 (2H, m, 6- and 7-H), 7.27 (1H, *J* 8.0 Hz, 5-H), 7.42 (1H, d, *J* 7.7 Hz, 8-H), 8.57 (1H, br, NH); ^{13}C NMR (100.4 MHz) δ 29.78 (C-4), 23.31 and 24.02 (13-Me), 28.13 (*t*-Bu), 50.73 (C-10), 54.82 (C-3), 63.71 (C-11), 68.69 (C-1), 79.91 (*C*Me$_3$), 103.63 (C-13), 109.22 (C-4a), 111.32 (C-8), 117.84 (C-5), 119.23 (C-6), 121.65 (C-7), 126.48 (C-4b), 131.24 (C-9a), 137.20 (C-8a), 156.49 (C=O) (Calc. for $C_{21}H_{29}N_3O_4$: *M*, 387.2156. Found: M^+, 387.2148).

*(iii) Ring transformation of **15c** and **16c**: oxathiazepine **17c**.* A mixture of **15c** and **16c** (100 mg, 0.29 mmol) and anhydrous TsOH [prepared from monohydrate (53 mg, 0.28 mmol)] in toluene (25 ml) was refluxed for 1.5 h. The mixture was diluted with AcOEt, neutralized with $NaHCO_3$, washed with brine, and dried. Evaporation of the solvent left a residue, which was purified through a silica gel column to give the oxathiazepine **17c** (11 mg, 11%) and recovered **15c** and **16c** (32 mg, 32%). **17c**: brown caramel, λ_{max} (EtOH)/nm 225, 275sh, 283, 291; ν_{max} (KBr)/cm^{-1} 3400, 3320, 1695, 1620; ^{1}H NMR (400 MHz) δ (non-systematic numbering) 1.59, 1.63 (6H, two s, 2 × Me), 2.76 (1H, dd, *J* 5.7, 14.5 Hz, 11-H), 2.77 (1H, m, 4-H), 2.94 (1H, m, 4-H), 3.18 (1H, ddd, *J* 4.0, 10.1, 11.9 Hz, 3-H), 3.23 (1H, dd, *J* 1.1, 14.7 Hz, 11-H), 3.45 (3H, s, OMe), 3.50 (1H, ddd, *J* 1.6, 5.0, 10.1 Hz, 3-H), 4.20 (1H, s, 1-H), 4.62 (1H, m, 10-H), 5.87 (1H, d, *J* 10.5 Hz, 10-NH), 7.09 (1H, t, *J* 7.9 Hz, 6-H), 7.13 (1H, t, *J* 7.9 Hz, 7-H), 7.30 (1H, td, *J* 0.9, 7.9 Hz, 8-H), 7.44 (1H, d, *J* 7.7 Hz, 5-H), 8.41 (1H, s, NH) [Calc. for $C_{18}H_{24}N_3O_3S$ (M + H): 362.1538. Found: *m/z*, 362.1524].

Preparation of nitrones 18a and b

To a solution of *N*-methylhydroxyamine, prepared from its hydrochloride (9.8 g, 117 mmol), in CH_2Cl_2 (150 ml) was added *N*-Boc-L-thiazolidine-4-carbaldehyde (5.11 g, 23.5 mol, prepared from the corresponding ester by reduction with DIBAL-H) in CH_2Cl_2 (100 ml) at rt under N_2. The mixture was stirred overnight and worked up as usual. Nitrone **18b** (5.09 g, 88%) was obtained as a pale yellow caramel, $[\alpha]_D^{22}$ −22.6 (*c* 0.935, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1680, 1380, 1160; ^{1}H NMR (270 MHz) δ 1.46 (9H, s, *t*-Bu), 3.26 (1H, m, 5-H), 3.36 (1H, dd-like, 5-H), 3.70 (3H, s, NMe), 4.44 (1H, d, *J* 9.5 Hz, 2-H), 4.56 (1H, br, 2-H), 5.21 (1H, m, 4-H), 6.81 (1H, d, *J* 5.5 Hz, 6-H); MS *m/z* (%) 247 (M^+ + 1, 0.34%), 190 (M^+ + 1 − *t*-Bu, 30.82), 144 (77.1), 57 (100).

In a similar manner, *N*-Ts-nitrone **18a** (731 mg, 74%) was obtained from the corresponding aldehyde (0.99 g) as pale brown crystals, mp 103–104 °C (from AcOEt–hexane), IR (KBr)/cm^{-1}: 1600, 1340, 1150; ^{1}H NMR (270 MHz) δ 2.45 (3H, s, Ar*Me*), 3.07 (2H, d-like, 5-H), 3.71 (3H, s, NMe), 4.50 (2H, br, 2-H$_2$), 4.97 (1H, m, 4-H), 6.97 (1H, d, *J* 5.2 Hz, 6-H), 7.35 (2H, m, ArH), 7.75 (2H, m, ArH); MS, *m/z* (%) 301 (M^+ + 1, 0.4%), 155 (24), 139 (43), 91 (100).

***N*-Methyl-*N*-(thiazolidin-4-ylmethyl)hydroxylamines 19**

Sodium borohydride (2.27 g, 60.0 mmol) was added to a solution of *N*-Ts nitrone **18a** (1.80 g, 5.99 mmol) in MeOH (70 ml) at room temperature. The mixture was stirred for 10 min and worked up as usual to give the *N-Ts hydroxylamine* **19a** (1.55 g, 86%) as colorless cotton-like needles, mp 112.5–113.5 °C (from AcOEt–hexane); $[\alpha]_D^{24}$ −4.3 (*c* 0.563, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3450, 1340, 1150; ^{1}H NMR (270 MHz) δ 2.44 (3H, s, Ar*Me*), 2.49 (1H, dd, *J* 6.72, 11.29 Hz, 6-H), 2.61 (1H, dd, *J* 5.80, 12.82 Hz, 5-H), 2.69 (4H, s + dd, *J* 2.14, 11.29 Hz, NMe + 6-H), 2.84 (1H, dd, *J* 8.55, 12.82 Hz, 5-H), 4.34 (1H, d, *J* 10.38 Hz, 2-H), 4.57 (1H, m, 4-H), 4.73 (1H, d, *J* 10.38 Hz, 2-H), 5.70 (1H, br, NOH, exchangeable), 7.32 (2H, m, ArH), 7.76 (2H, m, ArH); *m/z* (%) 303 (M^+ + 1, 0.56%), 287 (M^+ − Me, 0.94), 149 (18), 91 (33), 44 (100) (Calc. for $C_{12}H_{18}N_2O_3S$: C, 47.66; H, 6.00; N, 9.26. Found: C, 47.57; H, 5.96; N, 9.31%). In a similar manner, *N-Boc-hydroxylamine* **19b** (85%) was obtained from **18b** as colorless rods, mp 87.0–88.0 °C (from AcOEt–hexane); $[\alpha]_D^{14}$ −8.3 (*c* 1.301, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3300–3200, 1680, 1390, 1160; ^{1}H NMR (270 MHz) δ 1.49 (9H, s, *t*-Bu), 2.6–2.7 (5H, s + m, NMe + CH_2), 2.85 (1H, m, OH), 3.17 (1H, dd, *J* 6.72, 11.29 Hz, 6-H), 4.21 (1H, d, *J* 8.9 Hz, 2-H), 4.59 (1H, d, *J* 8.6 Hz, 2-H), 4.72 (1H, m, 4-H), 7.07 (1H, br, OH, exchangeable); *m/z* (%) 249 (M^+ + 1, 0.49%), 192 (41), 59 (100) (Calc. for $C_{10}H_{20}N_2O_3S$: C, 48.37; H, 8.12; N, 11.28. Found: C, 48.45; H, 8.06; N, 11.31%).

Hydrolysis of *N*-Boc hydroxylamine **19b** (1.18 g, 4.76 mmol) with conc. HCl (6 ml) in AcOEt (30 ml) at rt for 50 min gave the *deprotected hydroxylamine* **19c** (497 mg, 71%) as colorless crystals, mp 99–99.5 °C (from AcOEt–hexane); $[\alpha]_D^{25}$ −16.6 (*c* 0.337, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3250, 3200, 1460; ^{1}H NMR (270 MHz) δ 2.0 (1H, br, NH, exchangeable), 2.61 (1H, dd, *J* 7.0, 10.4 Hz, 5-H), 2.67 (3H, s, NMe), 2.73 (1H, dd, *J* 4.88, 8.24, 6-H), 2.84 (1H, dd, *J* 4.88, 13.12 Hz, 6-H), 3.04 (1H, dd, *J* 6.4, 10.4 Hz, 5-H), 3.62 (1H, m, 4-H), 4.13 (1H, d, *J* 9.77 Hz, 2-H), 4.24 (1H, d, *J* 9.77 Hz, 2-H), 7.3 (1H, br, OH, exchangeable); EI-MS *m/z* (%) 148 (M^+, 23%), 131 (M^+ − OH, 10), 88 (95), 44 (100); CI-MS *m/z* (%) 149 (MH^+, 100) (Calc. for $C_5H_{12}N_2OS$: C, 40.52; H, 8.16; N, 18.90; S, 21.63. Found: C, 40.45; H, 8.21; N, 19.08; S, 21.47%).

Insertion of C-1 between O and S atoms

1. Attempted cyclization of 21: Formation of 7. To a solution of (±)-*N*-methoxycarbonyl-*S*-Troc-carboline **13** (**21**, a mixture of 1α and 1β isomers, 50 mg, 0.1 mmol) in MeOH (1 ml)–AcOH (0.2 ml) were added 35% formalin (0.5 ml) and Zn powder (240 mg), and the mixture was stirred for 12 h at rt under Ar. The mixture was diluted with CH_2Cl_2, and filtered to remove insoluble materials. The solvent was evaporated to leave a residue, which was purified by preparative TLC with hexane–AcOEt (1 : 2) to give the thiaindoloquinolizidine **7** (18 mg, 57%). The spectral data were identical with those of the compound obtained above.

2. Preparation of 22a. To a mixture of (±)-β-carboline **21** (1α : 1β = 1 : 6; 110 mg, 0.22 mmol) in MeOH (20 ml) was added Zn–Cu (440 mg) and the mixture was refluxed for 1.5 h under

Ar. The mixture was filtered through Celite and evaporated. The residue was dissolved in CH_2Cl_2, and the solution was washed with brine and dried. Evaporation of the solvent gave a mixture of diastereomers **22a** (1α and β, 55 mg, 77%). The diastereomers could not be separated, but the NMR spectra showed that the ratio was the same as that of the starting material. Selected ^{1}H NMR (500 MHz) δ 1.69 (1H, br, SH), 3.57 (3 × 6/7H, s, MeO), 3.71 (3 × 1/7H, MeO), 4.23 (1/7H, br, 1-H), 4.37 (6/7H, br, 1-H), 8.56 (6/7H, br, 9–H), 8.69 (1/7H, br, 9-H); FAB MS [Calc. for $C_{15}H_{20}N_3O_3S$ (MH^+): 322.1225. Found: *m*/*z* 322.1228].

3. Preparation of 22b. To a solution of (±)-**21** (1α : 1β = 1 : 8, 994 mg, 2 mmol) in CH_2Cl_2 (20 ml) were added methoxymethyl chloride (194 mg, 2.4 mmol) and $Pr^i{}_2NEt$ (310 mg, 2.4 mmol) at rt under Ar. The mixture was stirred for 4 h at room temperature. Usual work-up and purification on a silica gel column gave the *O*-MOM derivative (470 mg, 43%) as an amorphous solid. ^{1}H NMR (270 MHz) δ 2.81–2.87 (2H, m, 4-H_2), 3.19–3.29 (2H, m, 11-H_2), 3.47 (3H, s, OMe), 3.50 (1H, m, 3-H), 3.60 (1H, m, 3-H), 3.66 (3H, s, OMe), 4.44 (2H, 10- and 1-H), 4.79 (1H, d, *J* 12 Hz, $CHCCl_3$), 4.83 (1H, d, *J* 8 Hz, OCHO), 4.93 (1H, d, *J* 8 Hz, OCHO), 4.94 (1H, m d, *J* 12 Hz, $CHCCl_3$), 5.76 (1H, *J* 8 Hz, CONH), 7.07–7.48 (4H, m, ArH), 8.57 (1H, br, NH); *m*/*z* (%) 509 (M^+ − MeOH, 0.2%), 478, 480 (1, 1), 231 (100), 170 (59).

This S-Troc derivative (450 mg, 0.83 mmol) was treated with Zn (1.38 g)–MeOH (15 ml)–AcOH (0.5 ml) for 45 min at room temperature to give the O-MOM-SH compound **22b**, (330 mg, quant.) as an amorphous solid, λ_{max} (EtOH)/nm 226, 274, 283, 291; ν_{max} (KBr)/cm^{-1} 3350, 2550, 1700, 1515; ^{1}H NMR (270 MHz) δ 1.59 (1H, dd, *J* 8 and 9 Hz, SH), 2.76 (1H, m, 11-H), 2.88 (2H, m, 4-H_2), 3.16 (1H, m; +D_2O changed to dd, *J* 6 and 14 Hz, 11-H), 3.28 (1H, m, 3-H), 3.47 (3H, s, OMe), 3.48–3.70 (1H, m, 3-H), 3.65 (3H, s, OMe), 4.16 (1H, br, 10-H), 4.58 (1H, d-like, *J* 7 Hz, CONH), 7.06–7.48 (4H, m, ArH), 8.38 (1H, br, NH); *m*/*z* (%) 365 (0.7%), 231 (100), 202 (36), 170 (65).

Synthesis of *ent*-(+)-debromoeudistomin L (±)-1f

1. Oxidative cyclization of 24. *(i) Cyclization by NCS oxidation.* NCS (67 mg, 0.5 mmol) was added to a solution of **24a**[13] (189 mg, 0.5 mmol) in CCl_4 (10 ml) at 0 °C. The mixture was stirred for 12 h at the same temperature and then filtered. The filtrate was diluted with CH_2Cl_2, washed successively with water and brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by preparative TLC (SiO_2; 40 g, developer hexane–AcOEt 1 : 4) to give (+)-*N*-Boc-debromoeudistomin **25a** (7 mg, 4%) as a white solid.

(ii) Cyclization through sulfoxide **26a**. A solution of MCPBA (0.56 g, 2.6 mmol) in CH_2Cl_2 (20 ml) was added to a solution of **24a** (0.97 g, 2.6 mmol) in CH_2Cl_2 (20 ml) over a period of 5 min at rt. The mixture was diluted with CH_2Cl_2 and quenched with saturated $NaHCO_3$. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed to give crude sulfoxide **26a** as a yellowish amorphous solid (926 mg, 92%).

To a solution of sulfoxide **26a** (790 mg, 2.0 mmol) in dry CH_2Cl_2 (20 ml) was added dry TsOH (696 mg, 4.0 mmol) and pyridinium toluene-*p*-sulfonate (PPTS) (506 mg, 2.0 mmol). The mixture was stirred at rt for 16 h and evaporated *in vacuo*. The residue was chromatographed over SiO_2 with AcOEt–hexane (2 : 1) to AcOEt to give **25a** as a white solid (75 mg, 10%). Recrystallization from AcOEt–hexane gave colorless prisms, mp 197–198 °C (lit.,[8c] 214–216 °C); $[\alpha]_D^{21}$ +105.8 (*c* 0.19, MeOH) {lit.,[8c] $[\alpha]_D^{27}$ +93.8 (*c* 1.6, MeOH)}; ν_{max} (KBr)/cm^{-1} 3390, 1690, 1500; *m*/*z* 375 (M^+), 186 (100); ^{1}H NMR (500 MHz) δ (non-systematic numbering) 1.34 (9H, br, *t*-Bu), 2.76–2.83 (2H, m, 4- and 11-H), 2.93 (1H, m, 4-H), 3.13 (1H, m, 3-H), 3.33 (1H, m, 11-H), 360 (1H, m, 3-H), 4.15 (1H, br s, 1-H), 4.65 (1H, m, 10-H), 4.81 (1H, d, *J* 9.1 Hz, 13-H), 4.94 (1H, d, *J* 9.1 Hz, 13-H), 5.68 (1H, d, *J* 10.5 Hz, NH, exchangeable), 7.00 (1H, ddd, *J* 8.0, 7.0, 1.1 Hz, 6-H), 7.09 (1H, ddd, *J* 8.0, 7.2, 1.1 Hz, 7-H), 7.27 (1H, d, *J* 7.7 Hz, 5-H), 7.42 (1H, d, *J* 7.7 Hz, 8-H), 8.52 (1H, br s, exchangeable, 9-H) (Calc. for $C_{19}H_{25}N_3O_3S$: C, 60.78; H, 6.71; N, 11.19; S, 8.54. Found: C, 60.68; H, 6.63; N, 11.00; S, 8.82%).

A similar cyclization of *N*-methoxycarbonyl sulfoxide **26b** with TsOH 2 equiv. in refluxing CH_2Cl_2 for 6 h gave the methoxycarbonyloxathiazepine **25b** (23%), $[\alpha]_D^{23}$ +87.3 (*c* 0.51, MeOH); λ_{max} (EtOH)/nm 226, 275, 283, 291; ν_{max} (KBr)/cm^{-1} 3350, 3300, 1685, 1505; ^{1}H NMR (500 MHz) δ (non-systematic numbering) 2.83 (2H, br, 4- and 11-H), 2.98 (1H, br, 4-H), 3.16 (1H, m, 3-H), 3.29 (1H, d, *J* 14.3 Hz, 11-H), 3.60 (4H, br, OMe, 3-H), 4.17 (1H, br, 1-H), 4.80 (1H, br, 10-H), 4.83 (1H, d, *J* 9.1 Hz, 13-H), 4.95 (1H, d, *J* 9.1 Hz, 13-H), 5.92 (1H, br, NH), 7.09, 7.14 (each 1H, t-like, ArH), 7.29, 7.47 (each 1H, d, *J* 7.7 Hz, ArH), 8.51 (1H, br, NH).

2. (+)-*ent*-Debromoeudistomin L (+)-1f. To a solution of **25a** (26 mg, 0.069 mmol) in dry CH_2Cl_2 (2 ml) was added TFA (2 ml) by injection at rt under Ar. The mixture was stirred for 15 min and then evaporated. The residue was dissolved in MeOH (5 ml), and Amberlite (CG-400, in OH^- form, 500 m) was added. After being stirred for another 15 min, the mixture was filtered and the filtrate was evaporated *in vacuo* to give crude *ent*-debromoeudistomin L, which was flash chromatographed over SiO_2 with AcOEt. (+)-Debromoeudistomin L (+)-**1f** was obtained as a white amorphous solid (19 mg, quantitative): $[\alpha]_D^{21}$ +105.8 (*c* 0.19, MeOH), {lit.,[8c] $[\alpha]_D^{22}$ +114.4 (*c* 2.1, MeOH)}. The spectral data, except for the sign of the specific rotation, were identical with those reported for the natural product.[2]

Synthesis of natural (−)-debromoeudistomin L (−)-1f

1. *N*-Troc-*S*-methyl-D-cysteine methyl ester. *N*-Troc-D-cysteine methyl ester (10.05 g, 32.36 mmol), prepared from the corresponding cystine, was S-methylated with MeI (20 ml, 321 mmol) and $Pr^i{}_2NEt$ (11.3 ml, 65 mmol) in CH_2Cl_2 (89 ml) at rt to give the *S*-methyl derivative (9.72 g, 93%), as a colorless oil, $[\alpha]_D^{22}$ +29.5 (*c* 1.36, MeOH); ^{1}H NMR (500 MHz) δ 2.14 (3H, s, SMe), 3.00 (2H, m, CH_2), 3.80 (3H, s, OMe), 4.64 (1H, m, CH), 4.72 (1H, d, *J* 12 Hz, Troc CH), 4.78 (1H, d, *J* 12 Hz, Troc CH), 5.84 (1H, br d, *J* 7.7 Hz, NH) (Calc. for $C_8H_{12}Cl_3NO_4S$: *M*, 322.955. Found: M^+, 322.955).

N-Boc-*S*-methyl-D-cysteine methyl ester was prepared similarly in 95% yield. $[\alpha]_D^{23}$ +30.8 (*c* 0.38, MeOH).

2. Nitrone 31. *(i) N-Boc derivative.* To a solution of *N*-Boc-*S*-methyl-D-cysteine methyl ester (8.2 g, 32.9 mmol) in dry toluene was added DIBAL-H (1 M in toluene solution; 66 ml, 66.0 mmol) by injection over a period of 20 min at −78 °C under argon. After stirring of the mixture for 2 h at the same temperature, excess of DIBAL-H was quenched by 10% HCl and the organic layer was separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to give the crude aldehyde **30a** (8.05 g). N^b-Hydroxytryptamine **11** (2.11 g, 12 mmol) was added in one portion to a solution of the crude aldehyde **30a** (4.38 g, 20 mmol) in dry CH_2Cl_2 at rt. After being stirred for 2 h, the reaction mixture was evaporated *in vacuo* and the residue was chromatographed over SiO_2 with AcOEt–hexane (3 : 1) to AcOEt to give the nitrone **31a** (4.09 g, 90%); $[\alpha]_D^{23}$ −68.6 (*c* 0.5, MeOH). The spectral data were identical with those of the corresponding enantiomer.[11]

(ii) N-Troc derivative. Similar reaction of the crude *N*-hydroxytryptamine **11**, (3.0 g, 17.0 mmol) and *N*-Troc-*S*-methyl-D-cysteinal **30b** (8.43 g, 28.3 mmol) gave the *N*-Troc-*S*-

methyl nitrone **31b** (6.17 g, 80% from hydroxytryptamine) as a pale yellow caramel, $[\alpha]_D^{22}$ −32.2 (*c* 1.458, MeOH). The spectral data were identical with those of the corresponding (+)-isomer.[11]

3. Cyclization of 31 to β-carboline 32. *(i) N-Boc-β-carboline 32a.* To a solution of **31a** (1.51 g, 4.0 mmol) in CH_2Cl_2 (50 ml) was added TFA (2.28 g, 20.0 mmol) by injection during 5 min at −78 °C under Ar. After being stirred for 2 h at −78 °C, the reaction mixture was quenched with saturated aq. $NaHCO_3$ and diluted with CH_2Cl_2. Usual work-up gave a crude mixture of **32a** (1α and β), which was separated on a silica gel column with hexane–AcOEt (5:1) to (4:1) to give **32a** (1α-isomer, 1.35 g, 90%) $[\alpha]_D^{23}$ +15.4 (*c* 0.52, MeOH) and its 1β-isomer (62 mg, 4%). **32a** (1β-isomer) showed mp 170 °C (from AcOEt–hexane); $[\alpha]_D^{23}$ +22.5 (*c* 0.44, MeOH) (Calc. for $C_{19}H_{27}N_3O_3S$: C, 60.45; H, 7.21; N, 11.13. Found: C, 60.37; H, 7.34; N, 11.06%).

The spectral data of these compounds were identical with those of the corresponding enantiomers.[11]

(ii) N-Troc-β-carboline 32b. The nitrone **31b** (460 mg, 1.02 mmol) as a solution in CH_2Cl_2 (15 ml) was treated with TFA (0.4 ml, 5.2 mmol) at −80 °C as above to give β-carboline **32b** (381 mg, 83%), and the corresponding 1β-isomer (26 mg, 6%). **32b** showed $[\alpha]_D^{23}$ +16.9 (*c* 0.417, MeOH) [Calc. for $C_{16}H_{17}N_3O_3C_{13}$ (M^+ − SMe): 404.634/406.03. Found: *m*/*z*, 404.034/406.03].

For 1β-isomer of **32b**: $[\alpha]_D^{20}$ −9.0 (*c* 0.466, MeOH).

Other spectral data were identical with those of the corresponding (+)-isomer.[11]

4. *N*-Protected debromoeudistomin L 34. *(1) N-Boc derivative 34a.* (i) Cyclization of **32a** by NCS oxidation. NCS (160 mg, 1.2 mmol) was added to a solution of the β-carboline **32a** (377 mg, 1.0 mmol) in CCl_4 (10 ml) at 5–10 °C. The mixture was stirred for 1.5 h at the same temperature. The reaction mixture was filtered and the filtrate was diluted with CH_2Cl_2, washed successively with water and brine, and dried over $MgSO_4$. The solvent was removed *in vacuo* to give a residue, which was purified by silica gel column chromatography with AcOEt–hexane (9:1) to AcOEt–MeOH (50:1) to (20:1). The *N*-Boc-debromoeudistomin L **34a** was obtained as a white solid (25 mg, 7%, or 8% based on the recovery of **32a**).

(ii) Cyclization of **32a** through sulfoxide **33a**. A solution of MCPBA (80%; 0.65 g, 3.0 mmol) in CH_2Cl_2 (30 ml) was added to a solution of **32a** (1.13 g, 3.0 mmol) in CH_2Cl_2 (30 ml) over a period of 10 min at rt. The reaction mixture was diluted with CH_2Cl_2 (100 ml) and quenched with saturated aq. $NaHCO_3$. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed to give the crude sulfoxide **33a**, which was purified by flash silica gel chromatography with AcOEt–hexane (1:3) to CH_2Cl_2–MeOH (2:1). The sulfoxide **33a** was obtained as a yellowish amorphous solid (1.11 g, 94%).

To a solution of the sulfoxide **33a** (393 mg, 1.0 mmol) in CH_2Cl_2 (10 ml) were added dry TsOH (348 mg, 2.0 mmol) and PPTS (253 mg, 1.0 mmol). The reaction mixture was stirred at rt overnight. The solvent was removed and the residue was purified by silica gel flash chromatography to give the *N*-Boc-debromoeudistomin **34a** as a white solid (41.5 mg, 11%, or 17% based on the recovery of the sulfoxide of **33a**). Recrystallization from AcOEt–hexane gave colorless prisms of compound **34a**, mp 197–198 °C (lit.,[8c] 214–216 °C); $[\alpha]_D^{22}$ −99.0 (*c* 0.1, MeOH). {lit.,[8c] $[\alpha]_D^{22}$ −94.2 (*c* 3.8, MeOH)}; λ_{max} (EtOH)/nm 225.5, 274, 284, 291; ν_{max} (KBr)/cm^{-1} 3390, 1690, 1500; ^{1}H NMR (500 MHz) δ (non-systematic numbering) 1.34 (9H, br s, *t*-Bu), 2.76–2.83 (2H, m, 4- and 11-H), 2.93 (1H, m, 4-H), 3.13 (1H, m, 3-H), 3.33 (1H, m, 11-H), 3.60 (1H, m, 3-H), 4.15 (1H, br, 1-H), 4.65 (1H, m, 10-H), 4.81 (1H, d, *J* 9.1 Hz, 13-H), 4.94 (1H, d, *J* 9.1 Hz, 13-H), 5.68 (1H, d, *J* 10.5 Hz, NH), 7.00 (1H, ddd, *J* 8.0, 7.0, 1.0 Hz, 6-H), 7.09 (1H, ddd, *J* 8.0, 7.2, 1.1 Hz, 7-H), 7.27 (1H, d, *J* 7.7 Hz, 5-H), 7.42 (1H, d, *J* 7.7 Hz, 8-H) (Calc. for $C_{19}H_{25}N_3O_3S$: C, 60.78; H, 6.71; N, 11.19; S, 8.54. Found: C, 60.68; H, 6.63; N, 11.00; S, 8.82%). The spectral data were identical with those of the enantiomer described above.

(iii) *N*-Troc-debromoeudistomin L: **34b**. To a solution of the above compound **32b** (101 mg, 0.22 mmol) in $CHCl_3$ (3 ml) was added NCS (33 mg, 0.26 mmol) at 0 °C under Ar. The mixture was stirred for 10 min at 0 °C and diluted with CH_2Cl_2. The mixture was washed with aq. $NaHCO_3$ and dried. Evaporation of the solvent left a residue, which was purified by preparative TLC to give *N-Troc-debromoeudistomin L* **34b** (5 mg, 5%); $[\alpha]_D^{22}$ −50.6 (*c* 0.350, MeOH); λ_{max} (EtOH)/nm 224, 274, 281, 290; ν_{max} (KBr)/cm^{-1} 3350, 1710; ^{1}H NMR (500 MHz) δ 2.84 (2H, m, 4- and 11-H), 2.95 (1H, m, 4-H), 3.15 (1H, m, 3-H), 3.36 (1H, d, *J* 14.3 Hz, 11-H), 3.60 (1H, dd, *J* 4.7, 9.4 Hz, 3-H), 4.20 (1H, br, 1-H), 4.35 (1H, d, *J* 12.1 Hz, Troc-CH), 4.71 (2H, d + m, *J* 12.1 Hz, Troc-CH + 10-H), 4.84 (1H, d, *J* 8.8 Hz, 13-H), 4.96 (1H, d, *J* 8.8 Hz, 13-H), 6.13 (1H, d, *J* 10.2 Hz, NH-Troc, exchangeable), 7.06 (1H, t-like, 6- or 7-H), 7.12 (1H, t-like, 6- or 7-H), 7.26 (1H, d, *J* 7.2 Hz, 5- or 8-H), 7.41 (1H, d, *J* 7.7 Hz, 8- or 5-H), 8.16 (1H, br, NH, exchangeable) (Calc. for $C_{17}H_{18}Cl_3N_3O_3S$: *M*, 449.014/451.010. Found: M^+, 449.014/451.010).

5. Synthesis of (−)-debromoeudistomin L (−)-1f. To a solution of **34a** (12 mg, 0.032 mmol) in CH_2Cl_2 (1 ml) was added TFA (1 ml) by injection at rt under Ar. After stirring for 15 min, the solution was removed and the residue was dissolved in MeOH (5 ml). Amberlite (IRA-400, 240 mg) was added and the mixture was stirred at rt for 15 min. The mixture was filtered and the filtrate was evaporated *in vacuo* to give a residue, which was purified by preparative TLC with CH_2Cl_2–MeOH (10:1) to give (−)-debromoeudistomin L **1f** (8 mg, 94% from **34a**) as a yellowish amorphous solid $[\alpha]_D^{23}$ −96.3 (*c* 0.08, MeOH) {lit.,[2] $[\alpha]_D$ −58.3 (*c* 0.06, MeOH); lit.,[8c] $[\alpha]_D^{22}$ −115.3 (*c* 3.0, MeOH)}.

(−)-Debromoeudistomin L (−)-**1f** (15 mg, 72%) was also obtained from *N*-Troc derivative **34b** (34 mg, 0.075 mmol) with Zn (0.5 g) in THF and acetate buffer at rt; λ_{max} (EtOH)/nm 224, 274, 283, 291; *m*/*z* (FABMS) 276 (M^+ + 1); ^{1}H NMR (500 MHz, CD_3OD) δ (non-systematic numbering) 2.81–2.84 (2H, m, C_{11}, 4- and 11-H), 2.97 (1H, m, 4-H), 3.15 (1H, m, 3-H), 3.32 (1H, d, *J* 14.3 Hz, 11-H), 3.58 (1H, m, 3-H), 3.62 (1H, m, 10-H), 4.12 (1H, br, 1-H), 4.92 (1H, d, *J* 9.1 Hz, 13-H), 7.00 (1H, ddd, *J* 8.0, 7.0, 1.1 Hz, 6-H), 7.09 (1H, ddd, *J* 8.0, 7.2, 1.1 Hz, 7-H), 7.31 (1H, d, *J* 8.3 Hz, 5-H), 7.40 (1H, d, *J* 8.0 Hz, 8-H); ^{1}H NMR (500 MHz) δ (non systematic numbering) 2.14 (2H, br, 10-NH), 2.8–2.9 (2H, m, 4- + 11-H), 2.94 (1H, m, 4-H), 3.14 (1H, m, 3-H), 3.32 (1H, d, *J* 14.3 Hz, 11-H), 3.55 (1H, br, 10-H), 3.58 (1H, ddd, *J* 9.9, 5.0, 1.7 Hz, 3-H), 4.10 (1H, br, 1-H), 4.81 (1H, d, *J* 9.1 Hz, 13-H), 4.93 (1H, d, *J* 9.1 Hz, 13-H), 7.12 (1H, t-like, 6-H), 7.18 (1H, t-like, 7-H), 7.33 (1H, d-like, 5-H), 7.47 (1H, d, *J* 7.7 Hz, 8-H), 8.21 (1H, br, N H).

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