Total synthesis of (−)-eudistomins with an oxathiazepine ring. Part 2. Synthesis of (−)-eudistomins C, E, F, K, and L

Jin-Jun Liu, Tohru Hino, Akihiko Tsuruoka, Naoki Harada and Masako Nakagawa *

Faculty of Pharmaceutical Sciences, Chiba University, Yayoi-cho, Chiba-shi, 263-8522, Japan

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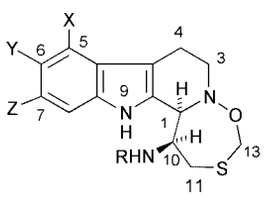
Eudistomins L, K, C, E (**30**) and F (**33**) were synthesized from the corresponding *N*-hydroxytryptamine **21** and the D-cysteinal **23**. A bromine of eudistomin L was biomimetically introduced onto the pyrroloindolic intermediate **8**. Other eudistomins were prepared from substituted indoles **17**. A modified Pummerer reaction was used to obtain the oxathiazepine ring.

In our previous paper[1] we reported the formation of the oxathiazepine ring system, which is an essential framework of the antiviral marine alkaloids known as eudistomins.[2] This method was successfully applied to the total synthesis of (−)-debromoeudistomin L, although the yield of the cyclization was not satisfactory. We now investigate a synthetic method for introducing substituents on the benzene ring of eudistomins, which are found in natural products. We previously reported the total synthesis of L-, debromo-L,[3] and F-eudistomins.[4] Racemic *N*-acetyleudistomin L has been obtained by a sila-Pummerer reaction,[5] (−)-debromoeudistomin L has been obtained by the intramolecular Pictet–Spengler reaction,[6] and racemic debromoeudistomin L,[7] and related compounds[8] have also been synthesized. These compounds have been reported to have various biological activities, such as antiviral and antibacterial activities.[2,9] To develop the synthetic utility of tetracyclic compounds such as **4**, we report here the details for introducing substituents on the benzene ring and for the synthesis of eudistomins C, E, F, K, and L.



Eudistomins	X	Y	Z	R
Eudistomin L	H	Br	H	H
Eudistomin K	H	H	Br	H
Eudistomin C	H	OH	Br	H
Eudistomin E	Br	OH	H	H
Eudistomin F	H	OH	Br	COOMe

Most bioactive eudistomins contain a bromine and a hydroxy group at the 5, 6, or 7 position (non-systematic numbering). These eudistomins may be derived from tryptophan and D-cysteine. The introduction of substituents may occur late in their biosynthesis.

During our studies[10–13] on the Pictet–Spengler reaction of *N*-hydroxytryptamine **1** and L-cysteinals **2**, it became clear that tetracyclic compounds **4** were obtained as major products from the intermediate nitrones **3** at room temperature, while tetrahydro-β-carbolines **5** with the correct stereochemistry for eudistomins were obtained as major products at low temperature together with **6** (Scheme 1).

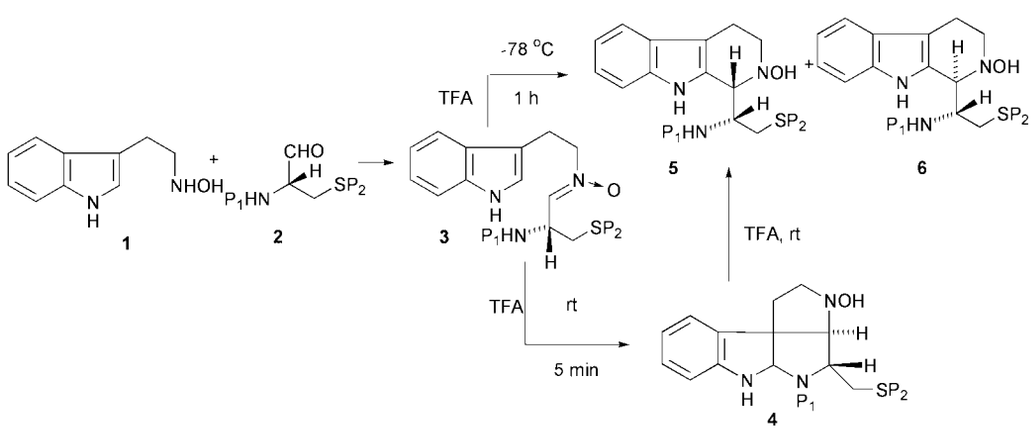
Furthermore, we found that the tetracycle **4** could be converted to the 1β-substituted β-carboline **5** as the major product under acidic conditions, and we discussed the possible mechanism of the Pictet–Spengler reaction.[12,13] We examined the electrophilic substitution of tetracyclic compound **4** to develop a method for introducing a substituent on the benzene ring, which is necessary for the synthesis of substituted eudistomins.

Tetracycle **4** is an aniline derivative and not an indolic compound, as in the case of the cyclic tautomers of tryptophan.[14] Therefore, we expected that a bromine atom or a hydroxy group could be introduced at the 10-position (non-systematic numbering scheme as shown) of tetracycles **4** by electrophilic substitutions, when D-cysteine derivatives were used as starting materials.

Results and discussion

Synthesis of (−)-eudistomin L

The nitrone **7** prepared from *N*-hydroxytryptamine and *N*-*tert*-butoxycarbonyl(Boc)-*S*-methyl-D-cysteinal[1] was treated with trifluoroacetic acid (TFA) at room temperature to give the



Scheme 1

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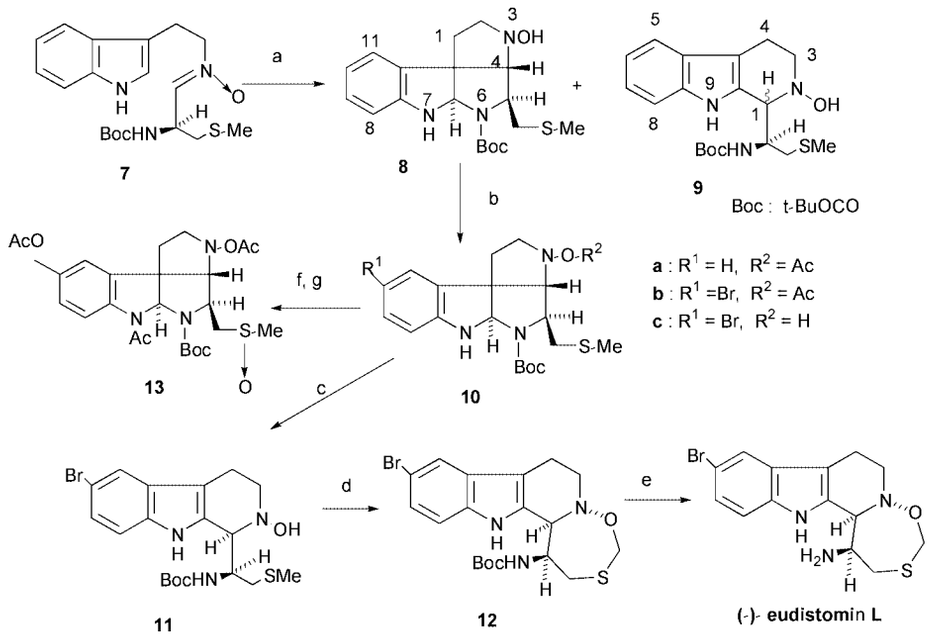
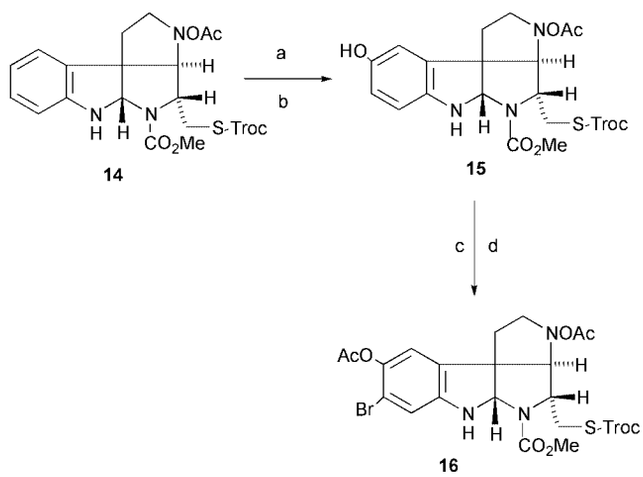


Scheme 2 *Reagents and conditions*: (a) TFA, CH_2CH_2, rt, 5 min; (b) NBS, AcOH, 0 °C, 15 min; (c) TFA, CH_2Cl_2, rt, 40 h; (d) NCS, CCl_4, 8–12 °C, 1.5 h; (e) TFA, CH_2Cl_2; (f) $Pb(OAc)_4$, TFA, CH_2Cl_2, 30 min, then Zn, 20 min; (g) Ac_2O, pyridine.

corresponding tetracycle **8** along with the tetrahydro-β-carboline **9**. Direct bromination of **8** with *N*-bromosuccinimide (NBS) gave a complex result. However, bromination of the *O*-acylated compound **10a** with NBS in AcOH[15a] proceeded regioselectively to give the corresponding bromo derivative **10b**, which gave the desired bromo derivative **10c** in 76% yield (3 steps) from the tetracyclic compound **8**. Like the unsubstituted tetracyclic compound **4**, **10c** rearranged to the 6-bromo-N^b-hydroxy-β-carboline **11** (33%), which has the same stereochemistry as the natural product, together with the 1β-isomer (7%), when treated with TFA. The major isomer **11** has the opposite configuration at C-1 compared with the C-4 position of **10c**, demonstrating that **10c** rearranged to **11** *via* the nitrone **7** formed by reversion, as reported previously (Scheme 2).[12,13]

As discussed previously,[1] cyclization of **11** with *N*-chlorosuccinimide (NCS) to an oxathiazepine ring provided the optically active *N*-Boc-eudistomin L **12** (7%). Final deprotection of **12** with TFA and purification by Amberlite CG 400 gave (−)-eudistomin L (76%) as a yellowish amorphous semisolid $[\alpha]_D^{22}$ −58.3.[2]

On the other hand, the oxidation of **10a** with lead tetraacetate in TFA–CH_2Cl_2 gave only the *S*-oxide **13**, and not the desired hydroxy derivative. Therefore, we changed the protective groups in **8** to *N*-methoxycarbonyl-*S*-(2,2,2-trichloroethoxycarbonyl) (Troc) groups. Similar hydroxylation of tetracyclic compound (**14**) with lead tetraacetate in TFA–CH_2Cl_2, followed by reduction with Zn for 15 min in a single-pot operation,[15b] gave the desired hydroxylated product **15** (44%). Further bromination of **15** with NBS in CH_2Cl_2 followed by acetylation provided the acetoxy bromide **16** in 80% yield, which has substituents at the correct positions for the synthesis of eudistomins C and F (Scheme 3). These results suggest the possibility of a biosynthetic pathway. However, many steps are required for the complete synthesis of natural eudistomin C or F from this compound by changing the protective groups to those suitable for further manipulation. Therefore, we turned our attention to introducing the substituent functionality into the benzene ring earlier in the synthesis, Accordingly, we planned to synthesize substituted *N*-hydroxytryptamines by conventional methods, as shown below (structures **17**–**20**).



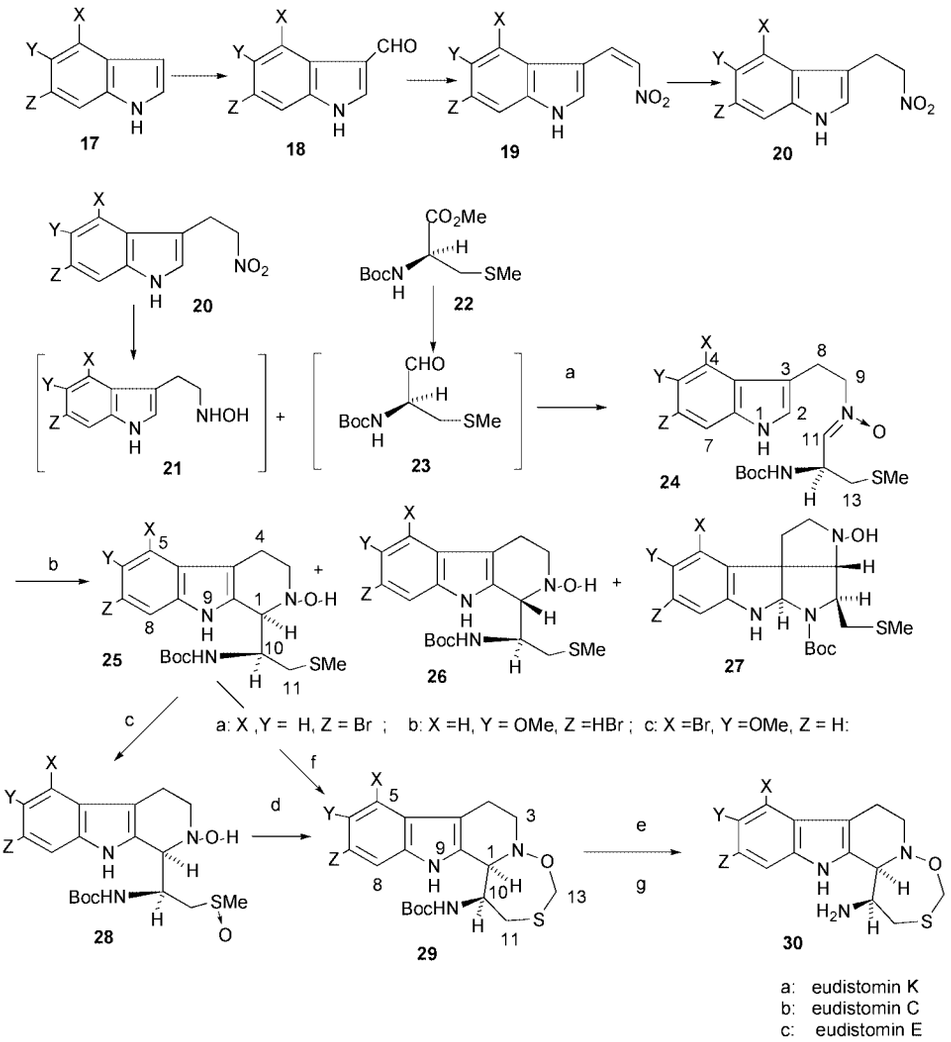
Scheme 3 *Reagents and conditions*: (a) $Pb(OAc)_4$, TFA, CH_2Cl_2, 30 min; (b) Zn, 10 min; (c) NBS, CH_2Cl_2, rt; (d) Ac_2O, pyridine.

Synthesis of (−)-eudistomins K, C and E

These eudistomins contain a bromine atom at the β-carboline 7-position (K), and a methoxy group and a bromine atom at C-6 and C-7 (C), or at C-6 and C-5 (E), respectively. The total syntheses of these eudistomins began with the corresponding substituted 3-(2-nitroethyl)indole and *N*-Boc-*S*-methylcysteine methyl ester, as shown in Scheme 4.

Substituted 3-(2-nitroethyl)indoles **20** were prepared from corresponding indoles **17**. The Vilsmeier formylation of indoles, then condensation with nitromethane, followed by reduction with sodium borohydride, as reported previously gave the corresponding nitroethylindole **20**.[12,16] The *N*-hydroxytryptamine **21** obtained by reduction of the 3-(2-nitroethyl)-indole **20** with Al amalgam or Zn–ammonium chloride was used immediately for the next reaction.[12,13,16] *N*-Boc-*S*-methyl-D-cysteine methyl ester **22** was prepared from *N*-Boc-D-cystine methyl ester by reduction of the disulfide bond followed by methylation of the free thiol.[12] The corresponding D-cysteinal **23** was freshly prepared by diisobutylaluminium hydride (DIBAL-H) reduction of the ester at −78 °C.

6-Bromoindole **17a** for the synthesis of eudistomin K was prepared by the cyclization of ethyl β-azido-*p*-bromocinnamate[17] followed by decarboxylation.[18,19] The formylation of 6-bromoindole[20] and sequential established reactions gave 6-bromo-3-(2-nitroethyl)indole **20a**.[12,16] The reaction of freshly prepared 6-bromo-N^b-hydroxytryptamine **21a** and the



Scheme 4 *Reagents and conditions*: (a) CH_2Cl_2, rt, 2 h; (b) TFA, CH_2Cl_2, −78 °C, 2 h; (c) MCPBA, CH_2Cl_2, rt, 5 min; (d) *p*-TsOH, PPTS, CH_2Cl_2, rt, 15 h; (e) TFA, CH_2Cl_2; (f) NCS, CCl_4, 2.5 h; (g) BBr_3, CH_2Cl_2, −78 °C, rt, 2 h. For eudistomin K: (a) (b) (c) (d) (e); for eudistomin C: (a) (b) (f) (g); for eudistomin E: (a) (b) (c) (d) (g).

D-cysteinal **23**, gave the nitrone **24a** in 80% yield.[12,13] The Pictet–Spengler reaction of the nitrone **24a** with TFA at −78 °C gave 1α*H*-tetrahydro-β-carboline **25a** (90%) and the 1β*H*-isomer **26a** (7%), as in previous results on an L-cysteinal series.[1,12] The cyclization of 1α*H*-β-carboline *S*-oxide **28a**, obtained by (*m*-chloroperbenzoic acid) (MCPBA) oxidation of the β-carboline **25a**, with TsOH–pyridinium toluene-*p*-sulfonate (PPTS) in dichloromethane[1] gave the desired *N*-Boc-eudistomin K **29a**, mp 211–211.5 °C; $[\alpha]_D$ −102,† in 11% yield along with recovered *S*-oxide **28a** (36%). The *tert*-butoxycarbonyl group was removed by TFA[1] at rt to give crystalline (−)-eudistomin K **30a**, mp 166.5–168 °C, in excellent yield. The spectral data including the specific optical rotation values are consistent with those previously reported, although the natural product was reported to be an oil.[2]

Eudistomin C was synthesized from the nitrone **24b**[13] prepared from 6-bromo-5-methoxy-3-(2-nitroethyl)indole **20b** and the D-cysteinal **23** as above. The Pictet–Spengler reaction of **24b** with TFA at low temperature gave 1α*H*-β-carboline **25b** (94%), and trace amounts of the 1β*H*-isomer **26b** and tetracycle **27b**. The cyclization of 1α*H*-β-carboline **25b** to *N*-Boc-*O*-methyleudistomin C **29b** on the other hand, was carried out not only with NCS on **25b** but also with TsOH–PPTS on the *S*-oxide **28b** although the yields are not satisfactory with either method. *N*-Boc-*O*-methyleudistomin C **29b** was treated with BBr_3 in dichloromethane to give (−)-eudistomin C **30b**, mp 170–173 °C; $[\alpha]_D$ −67.9. The spectral data agree with those of the natural product.[2]

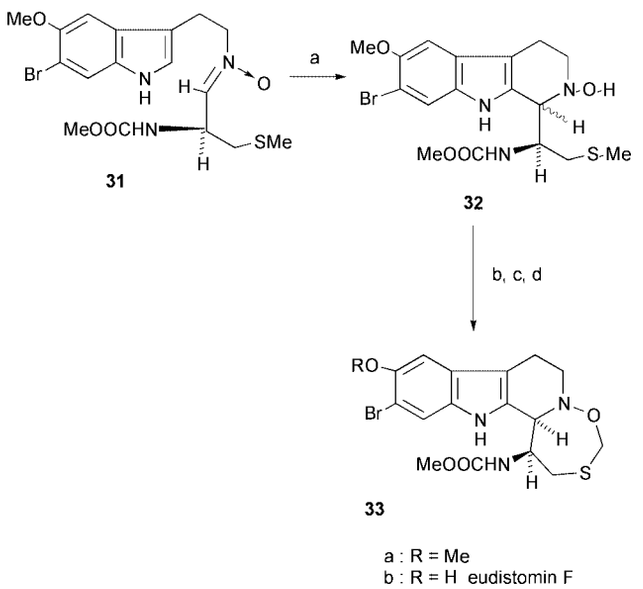
In a similar way, eudistomin E **30c** was synthesized from 4-bromo-5-methoxyindole **17c**, which was prepared from its 2-carboxylate[16] on decarboxylation.[19] In this series, Pictet–Spengler reaction of the nitrone **24c** gave 1α*H*-β-carboline **25c** and the tetracycle **27c** in comparable yields (46 and 42%) even at −78 °C. Cyclization of the *S*-oxide **28c** with TsOH–PPTS gave *N*-Boc-*O*-methyleudistomin E **29c** (8%), which provided (−)-eudistomin E **30c** upon treatment with BBr_3.

Synthesis of (−)-eudistomin F

Since the amino group in natural eudistomin F **33b** is protected by the methoxycarbonyl group, a different approach was required for its total synthesis. The nitrone **31** was prepared by reaction of 6-bromo-5-methoxy-3-(2-nitroethyl)indole **20b** and *N*-methoxycarbonyl-*S*-methyl-D-cysteine methyl ester as above (Scheme 5). The Pictet–Spengler reaction of the nitrone **31** gave 1α,β-carboline **32** in excellent yield. Cyclization of its *S*-oxide with TsOH in dichloromethane gave *O*-methyl-eudistomin F **33a** (21%), mp 234–236 °C. Demethylation of *O*-methyleudistomin F **33a** with BBr_3 in dichloromethane at −78 °C gave (−)-eudistomin F **33b**, $[\alpha]_D$ −67.5. The spectral data agree with those of the natural product.[2]

Thus, all of the natural eudistomins containing an oxathiazepine ring, except eudistomin K *S*-oxide, have been

† $[\alpha]_D$-Values are givein in units of 10^{-1} deg cm^2 g^{-1}.



Scheme 5 *Reagents and conditions*: (a) TFA, CH_2Cl_2, −78 °C; (b) MCPBA, CH_2Cl_2; (c) TsOH, CH_2Cl_2, rt, 20 h; (d) BBr_3, CH_2Cl_2, −78 °C, 5 min; then rt, 2 h.

synthesized and identified. These results chemically confirmed the absolute stereochemistry of the natural products derived from D-cysteine. However, the method used to form the oxathiazepine ring needs to be improved.

Experimental

General

See Part 1.[1]

8 from nitrone 7

To a solution of nitrone **7**[1] (1.89 g, 5.0 mmol) in dry CH_2Cl_2 (50 ml) was added TFA (0.57 g, 5.0 mmol) by injection at rt. The mixture was stirred for 5 min and then quenched with saturated aq. $NaHCO_3$, and diluted with CH_2Cl_2 (100 ml). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Separation of the residue by flash chromatography gave **8** (1.31 g, 70%) as a white solid. In addition, β-carboline **9** (0.54 g, 29%) were isolated. Recrystallization of **8** from hexane–AcOEt gave colorless prisms, mp 169.5–171 °C; $[\alpha]_D^{22}$ +138.3 (*c* 0.47, MeOH). Other spectral data were identical with those previously reported[12] (Calc. for $C_{19}H_{27}N_3O_3S$: C, 60.45; H, 7.21; N, 11.13. Found: C, 60.47; H, 7.23; N, 11.11%).

Bromination of 8: formation of 10c *via* 10a and 10b

A mixture of **8** (1.0 g, 2.65 mmol) and Ac_2O–pyridine (0.27 ml–2 ml) was stirred at room temperature for 20 min. The solvent was removed *in vacuo* and the residue was purified by flash chromatography to give **10a** (1.26 g) as a pale yellow caramel which was dissolved in AcOH (10 ml). NBS (0.47 g, 2.65 mmol) was added at 0 °C over a period of 5 min. The mixture was stirred at rt for another 15 min. Usual work-up gave the bromide **10b** (1.42 g), which was again dissolved in MeOH (20 ml), and NaOMe (143 mg, 2.65 mmol) was added. After 20 min, the mixture was concentrated *in vacuo*. The residue was diluted with CH_2Cl_2, washed successively with water and brine, and dried over $MgSO_4$. Removal of the solvent gave crude bromide **10c**, which was purified by flash chromatography over SiO_2 to give **10c** (0.92 g, 76% from **8**) as a pale yellow semisolid; $[\alpha]_D^{23}$ +171.3 (*c* 0.40, MeOH); λ_{max} (EtOH) 252.5, 316 nm; *m*/*z* 455, 457 (M^+); ^{1}H NMR (500 MHz) δ (non-systematic numbering) 1.50 (9H, s, *t*-Bu), 1.90 (1H, dd, *J* 13.2, 12.4 Hz, 12-H), 2.08 (3H, s, SMe), 2.22 (2H, m, 1-H), 2.64, 2.72 (1H, dd, *J* 13.2, 3.1 Hz, 12-H), 3.20 (1H, m, 2-H), 3.42 (1H, m, 2-H), 3.61 (1H, s, 4-H), 4.09, 4.23 (1H, dd, *J* 12.4, 3.1 Hz, 5-H), 4.58, 4.97 (1H, 2 × br s, exchangeable, 7H), 5.28, 5.41 (1H, 2 × br s, 6a-H), 5.53 (1H, br, exchangeable, OH), 6.43 (1H, d, *J* 8.3 Hz, 8-H), 7.23 (1H, m, 9-H), 7.26 (1H, d, *J* 0.8 Hz, 11-H) (Calc. for $C_{19}H_{27}BrO_3N_3S$: *M*H 456.0958. Found: MH^+ 456.0949%).

Rearrangement of 10c to β-carboline 11

A mixture of **10c** (0.65 g, 1.4 mmol) and TFA (0.49 g, 4.2 mmol) in dry CH_2Cl_2 (40 ml) was stirred at rt for 40 h. The mixture was diluted with CH_2Cl_2 (150 ml) and quenched with saturated aq. $NaHCO_3$. Usual work-up gave a residue, which was separated by flash chromatography with AcOEt–hexane (1 : 4) to (1 : 1). The β-carboline **11** (0.13 g, 20%, or 33% based on the recovery of **10c**) was obtained as a white semisolid. In addition, recovered **10c** (252 mg, 39%) and the 1β*H*-β-carboline {isomer of **11,** 27 mg (4, or 6% based on the recovery of **10c**), $[\alpha]_D^{24}$ +4.4 (*c* 0.27, MeOH)}, were isolated. **11**: $[\alpha]_D^{24}$ +31.3 (*c* 0.40, MeOH); λ_{max} (EtOH)/nm 230.5, 237sh, 284, 293, 301; *m*/*z* (FAB MS) 456 and 458 (M^+ + 1); ν_{max} (KBr) 3370, 1690, 1500 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.34 (9H, s, *t*-Bu), 2.20 (3H, s, SMe), 2.71–2.78 (2H, m, 11- and 4-H), 3.07 (2H, m, 3- and 4-H), 3.21 (1H, m, 11-H), 3.64 (1H, br, 3-H), 4.48 (1H, br, 10-H), 4.54 (1H, br s, 1-H), 4.80 (1H, br, OH, exchangeable), 5.36 (1H, br, NH, exchangeable), 7.15 (1H, d, *J* 8.5 Hz, 8-H), 7.21 (1H, dd, *J* 8.5, 1.4 Hz, 7-H), 7.60 (1H, d, *J* 1.4 Hz, 5-H), 8.75 (1H, br s, 9-H, exchangeable).

Preparation of (−)-eudistomin L

1. (−)-*N*-Boc-eudistomin L 12 from 11. To a solution of **11** (377 mg, 0.83 mmol) in dry CCl_4 (8 ml) was added NCS (132 mg, 1.2 eq.) at 8–12 °C. The mixture was stirred at the same temperature for 1.5 h. Usual work-up gave a residue, which was purified by flash chromatography. (−)-*N*-Boc-eudistomin L **12** was obtained as a pale yellow semisolid (25 mg, 7%, or 13% based on the recovery of **11**); $[\alpha]_D^{24}$ −24.0 (*c* 0.10, MeOH); λ_{max} (EtOH) 230.5, 237sh, 284, 293, 301 nm; ν_{max} (KBr)/cm^{-1} 3320, 1685, 1495; *m*/*z* 453 and 455 (M^+), 264, 266 (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), 3.59 (1H, m, 3-H), 4.13 (1H, br s, 1-H), 4.64 (1H, m, 10-H), 4.80 (1H, d, *J* 9.3 Hz, 13-H), 4.94 (1H, d, *J* 9.0 Hz, 13-H), 5.71 (1H, d, *J* 10.7 Hz, NH, exchangeable), 7.14 (1H, d, *J* 8.8 Hz, 7-H), 7.19 (1H, d, *J* 8.5 Hz, 8-H), 7.55 (1H, d-like, 5-H), 8.66 (1H, br s, 9-H, exchangeable).

2. (−)-Eudistomin L. The *N*-Boc derivative **12** (11 mg, 0.24 mmol) was deprotected[1] with TFA (1.5 ml) in CH_2Cl_2 (1.5 ml) and the crude product was treated with Amberlite CG 400 and further purified by preparative TLC with CH_2Cl_2–MeOH (15 : 1) to give (−)-eudistomin L (6.5 mg, 76%) as a yellowish semisolid; $[\alpha]_D^{22}$ −58.3 (*c* 0.06, MeOH) [lit.,[2b] −77 (*c* 0.2, MeOH)]; λ_{max} (EtOH)/nm 230.5, 237sh, 284, 293, 301; *m*/*z* (FAB MS) 354 and 356 (M^+ + 1); ^{1}H NMR (400 MHz; CD_3CN) δ (non-systematic numbering) 2.73–2.79 (3H, m, 4-H_2 and 11-H), 3.04 (1H, m, 3-H), 3.27 (1H, d, *J* 14.5 Hz, 11-H), 3.54–3.57 (2H, m, 10- and 3-H), 4.06 (1H, br s, 1-H), 4.76 (1H, d, *J* 9.2 Hz, 13-H), 4.89 (1H, d, *J* 9.2 Hz, 13-H), 7.19 (1H, dd, *J* 8.6, 1.8 Hz, 7-H), 7.26 (1H, d, *J* 8.6 Hz, 8-H), 7.58 (1H, d, *J* 1.8 Hz, 5-H), 9.21 (1H, br s, 9-H).

Oxidation of tetracyclic compounds

1. Oxidation of 10a with $Pb(OAc)_4$. To a solution of **10a** (284 mg, 0.676 mmol) in CH_2Cl_2 (25 ml) was added a mixture of $Pb(OAc)_4$ (450 mg, 1.02 mmol) in TFA (4 ml) under ice-cooling in Ar. The mixture was stirred for 30 min and for an additional 20 min after the addition of Zn (0.5 g) under ice-cooling. The mixture was diluted with CH_2Cl_2 and decanted to remove Zn. The solution was washed with saturated aq. $NaHCO_3$ and

dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was acetylated with Ac_2O (2 ml)–pyridine (10 ml) to give the crude *S*-oxide **13** (115 mg, 36%) as a colorless caramel, ν_{max}(KBr)/cm^{-1} 1760, 1700, 1660, 1480, 1390, 1360, 1040; ^{1}H NMR (500 MHz) δ (non-systematic numbering) 1.53 (9H, s-like × 2, *t*-Bu), 2.09 (3H, s-like × 2, OAc), 2.2–2.5 ($9\frac{1}{3}$H, s-like, SMe + NAc + 1-H_2, 12-H), 2.62 ($\frac{2}{3}$H, dd, *J* 6.3, 13.2 Hz, 12-H), 3.27 (1H, dd-like × 2, *J* 9.1, 18.4 Hz, 2-H), 3.63 ($\frac{4}{3}$H, m, 2- and 4-H), 3.74 ($\frac{2}{3}$H, s-like, 4-H), 4.91 (1H, m, 5-H), 6.26, 6.29 (1H, s-like, 6a-H), 7.14 (1H, m, ArH), 7.27 (2H, m, ArH), 8.14 (1H, m, 8-H); *m*/*z* (%) 477 (M^+, 2.9%), 417 (M^+ − OAc + 1, 7.4), 335 (24.5), 272 (100), 144 (79).

2. Oxidation of tetracyclic 14 (D-cysteine series). *(1) Formation of* ***15****.* Tetracyclic acetate **14** (563 mg, 1.04 mmol), prepared by acetylation of **4** (P^1 = CO_2Me, P^2 = Troc),[12] in TFA (5 ml) was added to an ice-cold solution of $Pb(OAc)_4$ (930 mg, 2.1 mmol) in CH_2Cl_2 (4 ml), and the mixture was stirred for 30 min. Zn powder (1 g) was added to the mixture, which was stirred for 10 min before being diluted with CH_2Cl_2, and insoluble materials were removed by filtration. The organic layer was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by flash column chromatography with AcOEt–hexane (2:1) to give **15** (256 mg, 44%), as a pale brown amorphous solid, λ_{max} (EtOH)/nm 243, 318 (EtOH + OH^-) 246, 328; ν_{max} (KBr)/cm^{-1} 3350–3400, 1750, 1695–1710; ^{1}H NMR (500 MHz) δ (non-systematic numbering) 2.08 (3H, s, Ac), 2.3 (2H, m, 1-, 12-H), 2.52 (1H, m, 1-H), 3.1–3.3 (2H, m, 12-, 2-H), 3.61 (1H, m, 2-H), 3.71 (1H, s, 4-H), 3.76, 3.77 (3H, s, OMe), 4.36 (1H, dd, *J* 4.1, 9.6 Hz, 5-H), 4.7–4.9 (4H, d × 2 + br, *J* 12, Troc + NH + OH), 5.43, 5.54 (1H, s, 6a-H), 6.49 (1H, d, *J* 8.0 Hz, 8-H), 6.63 (1H, d-like, *J* 8.0, 9-H), 6.72 (1H, d, *J* 2.2 Hz, 11-H).

(2) Bromination of ***15****.* NBS (17 mg, 0.095 mmol) was added to the above compound **15** (51 mg, 0.092 mmol) in CH_2Cl_2 (5 ml) at rt in Ar, and the mixture was stirred for 10 min. Evaporation of the solvent gave a residue, which was purified by preparative TLC to give a bromide (19 mg, 23%). This bromide (12 mg, 0.014 mmol) was dissolved in a mixture of pyridine (3 ml) and Ac_2O (0.5 ml), and the mixture was stirred for 3 h at rt. Evaporation of the solvent under reduced pressure gave a residue, which was purified by preparative TLC with AcOEt–hexane (2:1) to give **16** (8.4 mg, 80%), ν_{max}(KBr)/cm^{-1} 3150, 3080, 1770, 1700, 1370, 1200, 1120; ^{1}H NMR (500 MHz) δ (non-systematic numbering) 2.07 (3H, s, Ac), 2.27 (3H, s, Ac), 2.33 (2H, m, 1-, 12-H), 2.6 (1H, m, 1-H), 3.2–3.3 (2H, m, 2-, 12-H), 3.6 (1H, m, 2-H), 3.73 (1H, s, 4-H), 3.79 (3H, s, OMe), 4.40 (1H, dd, *J* 4.4, 9.6 Hz, 5-H), 4.76 (1H, d, *J* 11.8 Hz, Troc), 4.86 (1H, d, *J* 11.8 Hz, Troc), 5.12 (1H, s, NH), 5.54, 5.65 (1H, s, 6a-H), 6.86 (1H, s, 8-H), 7.05 (1H, s, 11-H) [Calc. for $C_{22}H_{24}N_3O_8BrCl_3S$: (*M* + H), 675.9503. Found: *m*/*z*, 675.9473].

Synthesis of (−)-eudistomin K 30a

1. 6-Bromo-3-(2-nitroethyl)indole 20a. A solution of 6-bromo-3-formylindole **18a**[17,20] (1.78 g, 7.94 mmol) and $AcONH_4$ (0.61 g, 7.94 mmol) in nitromethane (20 ml) was refluxed for 1.5 h. Upon cooling, the separated solid was collected and recrystallized from hexane–AcOEt to give 6-bromo-3-(2-nitrovinyl)indole **19a** (1.93 g, 91%), ν_{max}(KBr)/cm^{-1} 3250, 1620, 1520, 1470, 1420, 1300, 1240, 1230, 1120, 1060, 900, 850, 820, 800, 730.

A solution of the nitrovinylindole **19a** (561 m, 2.10 mmol) in MeOH (100 ml) was reduced with $NaBH_4$ (120 mg, 3.17 mmol) at rt to give 6-bromo-3-(2-nitroethyl)indole **20a** (466 mg, 83%) as a yellow solid, ν_{max} (KBr)/cm^{-1} 3430, 3100, 2900, 1720, 1610, 1550, 1450, 1430, 1380, 1340, 1240, 1100, 1050, 895, 850, 800, 710.

2. Preparation of the nitrone 24a. To a solution of **20a** (1.0 g, 3.7 mmol) in THF–water (150 ml–15 ml) was added freshly prepared Al(Hg) (from 4 g of Al) at 0 °C with vigorous stirring. After being stirred for 10 min, the reaction mixture was filtered through a Büchner funnel and then a Celite filter. The filtrate was evaporated and the residue was diluted with CH_2Cl_2 and washed successively with water and brine. Drying over $MgSO_4$ and removal of the solvent gave crude 6-bromo-N^b-hydroxytryptamine **21a** (0.90 g, 95%) as a white solid which was used in the next step without purification by chromatography.

To a solution of crude **21a** (0.88 g, 3.5 mmol) in dry CH_2Cl_2 (50 ml) was added *N*-Boc-*S*-methylcysteinal **23**[1] (1.51 g, 6.89 mmol) at rt. After being stirred for 2 h, the reaction mixture was evaporated *in vacuo* and the residue was flash chromatographed over SiO_2 with AcOEt–hexane (2:1) to AcOEt to give the nitrone **24a** (1.25 g, 80%) as a white amorphous solid, $[\alpha]_D^{17}$ −55.4 (*c* 0.26, MeOH); λ_{max} (EtOH) 228.5, 279.5, 287, 296 nm; ν_{max} (KBr)/cm^{-1} 3280, 2950, 1695, 1160; ^{1}H NMR (500 MHz) δ 1.43 (9H, s, *t*-Bu), 2.07 (3H, s, SMe), 2.70 (1H, dd-like, 13-H), 2.89 (1H, dd, *J* 13.8, 6.9 Hz, 13-H), 3.33 (2H, t, *J* 6.6 Hz, 8-H), 3.98 (2H, t, *J* 6.6 Hz, 9-H), 4.55 (1H, m, 12-H), 5.92 (1H, br, exchangeable, 10-H), 6.57 (1H, br s, N=CH), 7.04 (1H, d, *J* 2.2 Hz, 2-H), 7.23 (1H, dd, *J* 8.5, 1.7 Hz, 5-H), 7.45 (1H, d, *J* 8.5 Hz, 4-H), 7.52 (1H, d, *J* 1.7 Hz, 7-H), 8.18 (1H, br s, exchangeable, 1-H) (Calc. for $C_{19}H_{27}BrN_3O_3S$: *M* + H, 456.0957/458.0936. Found: *m*/*z*, 456.0955/458.0947).

3. Cyclization of 24a: 7-bromo-β-carbolines 25a and 26a. A solution of the nitrone **24a** (1.10 g, 2.4 mmol) in dry CH_2Cl_2 (50 ml) was cooled to −78 °C, and TFA (1.38 g, 12.1 mmol) was added by injection over a period of 5 min under Ar. After being stirred for 2 h at the same temperature, the reaction mixture was quenched carefully with saturated aq. $NaHCO_3$ at −78 °C, diluted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was flash chromatographed over SiO_2 with AcOEt–hexane (1:4) to give **25a** (990 mg, 90%), along with **26a** (75 mg, 7%), as a white amorphous mixture: **25a**: $[\alpha]_D^{17}$ −23.9 (*c* 0.23, MeOH); ν_{max} (KBr)/cm^{-1} 3350, 2592, 1680, 1500, 1365, 1160; *m*/*z* 439, 437 (M^+ − H_2O, 0.1, 0.1%), 249, 251 (100, 90%); ^{1}H NMR (500 MHz) δ 1.36 (9H, s, *t*-Bu), 2.20 (3H, s, SMe), 2.72 (1H, m, 11-H), 2.78 (1H, m, 4-H), 3.07 (2H, m, 3-, 4-H), 3.22 (1H, m, 11-H), 3.63 (1H, br, 3-H), 4.52 (2H, br s, 1-, 10-H), 4.90 (1H, br, OH, exchangeable), 5.35 (1H, br, NH, exchangeable), 7.19 (1H, dd, *J* 8.3, 1.6 Hz, 6-H), 7.34 (1H, d, *J* 8.3 Hz, 5-H), 7.44 (1H, d, *J* 1.4 Hz, 8-H), 8.71 (1H, br s, NH, exchangeable) (Calc. for. $C_{19}H_{27}BrN_3O_3S$: *M* + H, 456.0957/458.1017. Found: *m*/*z*, 456.0942/458.0993).

4. (−)-*N*-Boc-eudistomin K 29a. To a solution of the major isomer **25a** (0.92 g, 2.02 mmol) in dry CH_2Cl_2 (40 ml) was added MCPBA (80%; 0.43 g, 2.02 mmol) as a solution in dry CH_2Cl_2 (10 ml) by injection over a period of 5 min at rt. After the addition, the reaction mixture was quenched with saturated aq. $NaHCO_3$, diluted with CH_2Cl_2, and washed successively with water and brine. Drying over $MgSO_4$ and removal of the solvent gave the corresponding *S*-oxide **28a** (0.95 g) which was used in the next step without purification.

To a solution of the crude **28a** (0.90 g, 1.9 mmol) in dry CH_2Cl_2 (50 ml) were added dry *p*-TsOH (0.71 g, 4.1 mmol) and dry PPTS (0.51 g, 2.0 mmol) at rt under Ar. The reaction mixture was stirred for 15 h and then quenched with saturated aq. $NaHCO_3$, and diluted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed over SiO_2 with AcOEt–hexane (1:2), AcOEt and AcOEt–MeOH (20:1) to give (−)-*N-Boc-eudistomin K* **29a** (96 mg, 11% in two steps) and recovered **28a** (0.32 g, 36%); **29a**: mp 211–211.5 °C (from AcOEt–hexane); $[\alpha]_D^{17}$ −102.0 (*c* 0.15, MeOH); λ_{max} (EtOH)/nm 222.5, 274, 284, 291; ν_{max} (KBr)/cm^{-1} 3320, 1680, 1490, 1155; *m*/*z* (%) 455, 453 (M^+, 3, 3%), 312, 310 (13, 14), 266, 264 (99, 100); ^{1}H NMR (500 MHz) δ (non-systematic numbering) 1.19 (9H, br, *t*-Bu), 2.80 (2H, m, 4-, 11-H), 2.92 (1H, m, 4-H), 3.14 (1H, m, 3-H), 3.32 (1H, d, *J* 14.6

Hz, 11-H), 3.59 (1H, m, 3-H), 4.11 (1H, br s, 1-H), 4.62 (1H, m, 10-H), 4.80 (1H, d, *J* 8.8 Hz, 13-H), 4.94 (1H, d, *J* 9.1 Hz, 13-H), 5.71 (1H, d, *J* 10.5 Hz, NH, exchangeable), 7.15 (1H, dd, *J* 8.3, 1.7 Hz, 6-H), 7.27 (1H, d, *J* 8.2 Hz, 5-H), 7.43 (1H, s, 8-H), 8.63 (1H, br s, NH, exchangeable) (Calc. for $C_{19}H_{24}BrN_3O_3S$: C, 50.22; H, 5.32; N, 9.25. Found: C, 50.26; H, 5.32; N, 9.22%).

5. (−)-Eudistomin K 30a. To a solution of **29a** (32 mg, 0.07 mmol) in dry CH_2Cl_2 (50 ml) was added TFA (5 ml) by injection at rt under Ar. The solution was stirred for 15 min and then was evaporated *in vacuo* to give a residue, which was dissolved in MeOH (5 ml) and treated with CG-400 (1 g) at rt for 1 min. The reaction mixture was filtered, and evaporated *in vacuo* to give a yellowish solid, which was purified by a short SiO_2 column to give (−)-eudistomin K **30a** (23 mg, 93%); mp 166.5–168 °C (from CH_2Cl_2); $[a]_D^{19}$ −152.6 (*c* 0.23, MeOH) {lit.,[2b] $[a]_D^{25}$ −102 (*c* 0.2, MeOH); lit.,[2d] −131}; λ_{max} (EtOH)/nm 231.5, 285, 295; ν_{max} (KBr)/cm^{-1} 3400, 1615, 1575, 1025; *m*/*z* (FAB MS) 354, 356 (M^+) [Calc. for $C_{14}H_{16}BrN_3OS$ (*M*), 354.0276/356.0255. Found: M^+, 354.0291/356.0270]; ^{1}H NMR (500 MHz; CD_3CN) δ (non-systematic numbering) 2.73 (1H, m, 11-H), 2.77 (1 H, m, 4-H), 2.83 (1H, ddd, *J* 15.5, 4.7, 2.2 Hz, 4-H), 3.04 (1H, ddd, *J* 10.0, 11.3, 4.7 Hz, 3-H), 3.28 (1H, d, *J* 14.3 Hz, 11-H), 3.51 (1H, br, 10-H), 3.55 (1H, ddd, *J* 9.9, 4.7, 2.2 Hz, 3-H), 4.03 (1H, br s, 1-H), 4.81 (1H, d, *J* 9.1 Hz, 13-H), 4.89 (1H, d, *J* 9.1 Hz, 13-H), 7.14 (1H, dd, *J* 8.4, 1.7 Hz, 6-H), 7.33 (1H, d, *J* 8.3 Hz, 5-H), 7.49 (1H dd, *J* 1.7, 0.6 Hz, 8-H), 9.20 (1H, br s, NH, exchangeable) (Calc. for $C_{14}H_{16}BrN_3OS{\cdot}0.4CH_2Cl_2$: C, 44.50; H, 4.36; N, 10.81. Found: C, 44.54; H, 4.60; N, 10.85%). These spectral data agree with those of natural eudistomin K.[2]

Synthesis of (−)-eudistomin C 30b

1. Cyclization of the nitrone 24b: formation of 25b and 26b. A solution of the nitrone **24b**[13] (784.7 mg, 1.61 mmol) in CH_2Cl_2 (60 ml) was cooled to −78 °C under Ar and TFA (0.62 ml, 8.07 mmol) was added. The mixture was stirred for 2 h at −78 °C, quenched with saturated aq. $NaHCO_3$ at −78 °C, and extracted with CH_2Cl_2. The extracts were then washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a residue (872 mg). Flash chromatography, with AcOEt–hexane (1:4) as eluent, gave **26b** (12 mg, 2%) and **25b** (733 mg, 94%) as colorless amorphous solids. The tetracyclic compound **27b** (10 mg, 1%) was also isolated as a colorless amorphous solid. **25b**: $[a]_D^{23}$ −1.3 (*c* 0.60, MeOH); λ_{max} (EtOH)/nm 230.5, 291sh, 302.5, 313sh; ν_{max} (KBr)/cm^{-1} 3370, 1690, 1500; ^{1}H NMR (500 MHz) δ 1.36 (9H, s, *t*-Bu), 2.20 (3H, s, SMe), 2.70 (1H, m, 11-H), 2.78 (1H, m, 4-H), 3.07 (2H, m, 3-, 4-H), 3.22 (1H, m, 11-H), 3.65 (1H, br, 3-H), 3.92 (3H, s, OMe), 4.51 (2H, br s, 1-, 10-H), 4.80 (1H, br, OH, exchangeable), 5.34 (1H, br, NH, exchangeable), 6.95 (1H, s, 5-H), 7.49 (1H, s, 8-H), 8.57 (1H, br s, NH, exchangeable) (Calc. for $C_{20}H_{24}BrN_3O_4S$: M^+, 486.1062. Found: M^+, 486.1062).

26b: mp 192–194 °C; $[a]_D^{24}$ +23.7 (*c* 0.19, MeOH); λ_{max} (EtOH)/nm 230.5, 291sh, 302.5, 313sh; ν_{max} (KBr)/cm^{-1} 3370, 1690, 1500; *m*/*z* 469, 467 ($M^+ - H_2O$; 1, 2%), 281, 279 (99%). ^{1}H NMR (500 MHz) δ 1.45 (9H, s, *t*-Bu), 2.15 (3H, s, SMe), 2.76 (2H, m, 4-H_2), 2.87 (2H, m, 3-, 11-H), 3.18 (1H, m, 11-H), 3.49 (1H, m, 3-H), 3.94 (3H, s, OMe), 4.15 (1H, d, *J* 1.7 Hz, 1-H), 4.40 (1H, br s, 10-H), 5.30 (1H, br, NH, exchangeable), 5.82 (1H, br, OH, exchangeable), 6.93 (1H, s, 5-H), 7.50 (1H, s, 8-H), 8.37 (1H, br s, 9-H, exchangeable).

27b: λ_{max} (EtOH)/nm 225sh, 247sh, 303sh, 313, 326, *m*/*z* (%) 487 ($M^+ + 2$, 8%), 485 (M^+, 10), 471 ($M^+ + 2 - O$, 22), 469 ($M^+ - O$, 26), 253, 251 (100); ^{1}H NMR (500 MHz) δ (non-systematic numbering) 1.49 (9H, s, *t*-Bu), 1.80, 1.87 (1H, t-like, 12-H), 2.08, 2.10 (3H, s, SMe), 2.22 (2H, m, 1-H_2), 2.65, 2.73 (1H, dd-like, 12-H), 3.21 (1H, m, 2-H), 3.42 (1H, m, 2-H), 3.64 (1H, s, 4-H), 3.84 (3H, s, OMe), 4.09, 4.23 (1H, dd-like, 5-H), 4.41, 4.78 (1H, br s, NH), 5.27, 5.40 (1H, br s, 6a-H), 5.72 (1H, br, OH), 6.77 (1H, s, 8-H), 6.78, 6.82 (1H, s, 11-H).

2. *N*-Boc-*O*-methyleudistomin C 29b. *(1) with NCS.* To a solution of **25b** (350 mg, 0.72 mmol) in CCl_4 (15 ml) was added NCS (116 mg, 1.2 eq.) at 5 °C, and the mixture was stirred for 2.5 h under Ar. Usual work-up followed by flash chromatography with AcOEt–hexane (gradient, 1:2 to 1:1) gave **29b** (29 mg, 8%).

*(2) via sulfoxide **28b**.* Oxidation of β-carboline **25b** (749 mg, 1.54 mmol) with MCPBA as above gave the sulfoxide **28b** (719 mg, 96%) (Calc. for $C_{20}H_{29}BrN_3O_5S$: *M*, 502.1011. Found: M^+, 502.1040).

The sulfoxide **28b** (711 mg, 1.41 mmol) was treated with TsOH and PPTS as above to give *N*-Boc-eudistomin C **29b** (6%) and **28b** (207 mg recovered). **29b**: $[a]_D^{22}$ −19.6 (*c* 0.25, MeOH); λ_{max}(EtOH)/nm 222.5, 274, 284, 291; ν_{max}(KBr)/cm^{-1} 3350, 1690, 1500; ^{1}H NMR (500 MHz) δ (non-systematic numbering) 1.19 (9H, br, *t*-Bu), 2.79 (2H, m, 4-, 11-H), 2.94 (1H, m, 4-H), 3.14 (1H, m, 3-H), 3.31 (1H, d, *J* 14.3 Hz, 11-H), 3.60 (1H, m, 3-H), 3.91 (3H, s, OCH_3), 4.10 (1H, br s, 1-H), 4.62 (1H, m, 10-H), 4.80 (1H, d, *J* 9.1 Hz, 13-H), 4.94 (1H, d, *J* 9.1 Hz, 13-H), 5.70 (1H, d, *J* 10 Hz, NH), 6.89 (1H, s, 5-H), 7.48 (1H, s, 8-H), 8.48 (1H, br s, 9-H) [Calc. for $C_{20}H_{26}BrN_3O_4S$: (M + 2), 485.0809; *M*, 483.0829. Found: (M^+ + 2), 485.0804; M^+, 483.0827].

3. (−)-Eudistomin C 30b. A solution of **29b** (27 mg, 0.056 mmol) in CH_2Cl_2 (5 ml) was cooled to −78 °C and BBr_3 (0.2 ml) was added slowly. After 30 min of stirring at −78 °C, the mixture was warmed to rt and stirred for 2 h. The solution was recooled to −78 °C, quenched with water (7 ml), and diluted with CH_2Cl_2. The CH_2Cl_2 layer was washed successively with 5% aq. Na_2CO_3 and brine, dried over $MgSO_4$, and evaporated to give eudistomin C **30b** (19.9 mg, 97%) as a pale yellow solid, mp 170–173 °C; $[a]_D^{18}$ −67.9 (*c* 0.196, MeOH) {lit.,[2b] $[a]_D^{25}$ −52 (*c* 0.4, MeOH)}; λ_{max} (EtOH)/nm 228, 285, 305, 315; (EtOH + OH^-) 231sh, 282, 337; ν_{max} (KBr)/cm^{-1} 3350, 2920, 2850, 1450, 1260, 1140, 1040; ^{1}H NMR (500 MHz; CD_3CN) δ 2.66–2.79 (3H, m, 4-H_2, 11-H), 3.02 (1H, m, 3-H), 3.25 (1H, d, *J* 14.3 Hz, 11-H), 3.54 (2H, m, 3-, 10-H), 4.00 (1H, br, 1-H), 4.75 (1H, d, *J* 9.1 Hz, 13-H), 4.87 (1H, d, *J* 9.1 Hz, 13-H), 6.93 (1H, s, 5-H), 7.46 (1H, s, 8-H), 8.94 (1H, br, NH) [Calc. for $C_{14}H_{17}BrN_3O_2S$: (M + H), 370.0225. Found: *m*/*z*, 370.0202]. The spectral data agree with those of natural eudistomin C.[2a,b]

Synthesis of eudistomin E 30c

1. 4-Bromo-5-methoxy-3-(2-nitroethyl)indole 20c. 4-Bromo-5-methoxy-3-(2-nitrovinylindole **19c** (565 mg, 1.91 mmol), prepared from the corresponding indole-2-carboxylate[16] according to the method for the 6-bromo-5-methoxy derivative **19b**, was reduced with $NaBH_4$ (1.29 g, excess) in MeOH (250 ml) to give **20c** (465 mg, 82%) as a *white solid* (Calc. for $C_{11}H_{11}BrN_2O_3$: *M*, 297.9953. Found: M^+, 297.9951).

2. Nitrone 24c. The reaction was carried out as described above, using 4-bromo-5-methoxy-3-(2-nitroethyl)indole **20c** (640 mg, 2.14 mmol) and the D-cysteinal **23** (777 mg, 3.54 mmol) to give **24c** (531 mg, 61%) as a *colorless powder*, $[a]_D^{19}$ −63.1 (*c* 0.42, MeOH); λ_{max} (EtOH)/nm 225, 282.5, 302, 315sh; ν_{max} (KBr)/cm^{-1} 3370, 1685, 1510; [Calc. for $C_{20}H_{29}BrN_3O_4S$: (M + H), 486.1064. Found: *m*/*z*, 486.1059]; ^{1}H NMR (500 MHz) δ 1.43 (9H, s, *t*-Bu), 2.08 (3H, s, SMe), 2.74 (1H, dd, *J* 6.6, 13.5 Hz, 13-H), 2.93 (1H, dd, *J* 7.2, 13.5 Hz, 13-H), 3.58 (2H, t, *J* 6.5 Hz, 8-H), 3.93 (3H, s, OMe), 4.09 (2H, t-like, 9-H), 4.54 (1H, m, 12-H), 6.02 (1H, br, NH), 6.58 (1H, d, *J* 5.9 Hz, 11-H), 6.91 (1H, d, *J* 8.8 Hz, 6-H), 7.11 (1H, d, *J* 2.4 Hz, 2-H), 7.26 (1H, d, *J* 8.8 Hz, 7-H), 8.09 (1H, br, NH) (Calc. for $C_{20}H_{28}BrN_3O_4S$: C, 49.38; H, 5.80; N, 8.64. Found: C, 49.50; H, 5.78; N, 8.60%).

3. Cyclization of 24c to 25c, 26c, and 27c. TFA (690 mg, 6.1 mmol) was added to a chilled solution of **24c** (590 mg, 1.21 mmol) in CH_2Cl_2 (120 ml) at −78 °C. The mixture was stirred at the same temperature for 2 h and worked up as above. Compounds **25c** (320 mg, 46%), **26c** (trace), and **27c** (250 mg, 42%) were obtained. **25c**: $[\alpha]_D^{19}$ +36.5 (*c* 0.51, MeOH); λ_{max} (EtOH)/nm 227, 284, 300sh, 314sh; ν_{max} (KBr)/cm^{-1} 3350, 2970, 2920, 1680, 1500, 1425, 1155, 780.

27c: colorless amorphous solid. ^{1}H NMR (500 MHz) δ (non-systematic numbering) 1.49 (9H, s, *t*-Bu), 1.71 (1H, dd-like, 12-H), 2.08, 2.11 (3H, s, SMe), 2.23 (1H, m, 1-H), 2.37 (1H, m, 1-H), 2.57, 2.64 (1H, dd, *J* 3.6, 13.5 Hz, 12-H), 3.53 (2H, m, 2-H), 3.82 (3H, s, OMe), 4.09, 4.11 (1H, m, 5-H), 4.37, 4.39 (1H, m, 4-H), 4.88, 5.18 (1H, s, NH), 5.47, 5.78 (1H, br, 6a-H), 6.53 (1H, m, 8-H), 6.69 (1H, m, 9-H).

4. *N*-Boc-eudistomin E 29c. The reaction was carried out as above, using **25c** (290 mg, 0.60 mmol) in CH_2Cl_2 (15 ml) and MCPBA (129 mg, 0.60 mmol), to give the sulfoxide **28c** (320 mg), which was treated with TsOH (210 mg, 2 equiv.) and PPTS (150 mg, 1 equiv.) in CH_2Cl_2 (5 ml) for 15 h at rt. Work-up followed by flash chromatography with AcOEt–hexane (2:1) gave **29c** (22.3 mg, 8% from **24c**) as a pale yellow amorphous solid along with recovered **28c** (47%). **29c**: colorless solid, $[\alpha]_D^{19}$ −2.7 (*c* 0.22, MeOH); λ_{max} (EtOH)/nm 229.5, 287, 304, 315; ν_{max} (KBr)/cm^{-1} 3300, 1675, 1495, 1420; ^{1}H NMR (400 MHz) δ (non-systematic numbering) 2.80 (1H, dd, *J* 5.5, 14.5 Hz, 11-H), 3.13 (1H, m, 4-H), 3.21 (1H, m, 3-H), 3.31 (1H, d, *J* 14.3 Hz, 11-H), 3.40 (1H, m, 4-H), 3.59 (1H, dd, *J* 4.5, 9.9 Hz, 3-H), 3.89 (3H, s, OMe), 4.10 (1H, br s, 1-H), 4.62 (1H, m, 10-H), 4.81 (1H, d, *J* 9.2 Hz, 13-H), 4.94 (1H, d, *J* 9.0 Hz, 13-H), 5.73 (1H, d, *J* 11.4 Hz, NH), 6.80 (1H, d, *J* 8.6 Hz, 7-H), 7.14 (1H, d, *J* 8.8 Hz, 8-H), 8.60 (1H, br, 9-H) [Calc. for $C_{20}H_{27}BrN_3O_4S$: (*M* + H), 484.0908. Found: *m*/*z*, 484.0922].

5. (−)-Eudistomin E 30c. Deprotection of the Boc group and demethylation of **29c** (9.2 mg, 0.019 mmol) by BBr_3 (0.07 ml) was carried out according to the method described above to give (−)-eudistomin E **30c** (6 mg, 85%) as a pale yellow solid, λ_{max} (EtOH)/nm 225sh, 280, 300, 313sh; (EtOH + OH$^-$) 231, 280, 315, 336 [Calc. for $C_{14}H_{17}BrN_3O_2S$: (*M* + H), 370.0225. Found: *m*/*z*, 370.0211].

Synthesis of eudistomin F

1. Preparation of the nitrone 31. *(1) Preparation of N-methoxycarbonyl-S-methyl-D-cysteine methyl ester.*[21] A mixture of *N*-methoxycarbonyl-D-cysteine methyl ester (9.50 g, 49.2 mmol), CH_3I (13.98 g, 98.4 mmol), and Pr^i_2NEt (6.3 g, 50.0 mmol) in CH_2Cl_2 (30 ml) was stirred for 1 h at rt. The mixture was evaporated to leave a residue, which was dissolved in AcOEt, washed with water, and dried over $MgSO_4$. Evaporation of the solvent gave a residue (9.22 g), which was purified by flash column chromatography with AcOEt–hexane (3:1) to AcOEt–MeOH (20:1) to give the title *S*-methyl-D-cysteine methyl ester (8.70 g, 85%) as an oil, $[\alpha]_D^{18}$ +32.3 (*c* 0.31, MeOH); ν_{max} (neat)/cm^{-1} 3300, 1750, 1720, 1530; ^{1}H NMR (270 MHz) δ 2.20 (3H, s, SMe), 2.95 (2H, d, *J* 6 Hz, CH_2S), 3.70 (3H, s, NCO_2Me), 3.76 (3H, s, OMe), 4.60 (1H, m, CH), 5.60 (1H, br, NH).

(2). The nitrone **31** was prepared from 6-bromo-5-methoxy-3-(2-nitroethyl)indole **20b**[4] and *N*-methoxycarbonyl-5-methyl-D-cysteinal[4,22] as in the case of **24b**. Nitrone **31** (51% from **20b**): $[\alpha]_D^{19}$ −41.0 (*c* 0.30, MeOH); λ_{max} (EtOH)/nm 227, 285sh, 291.5, 303, 314sh; ν_{max} (KBr)/cm^{-1} 3300, 1700, 1530, 1470, 1235, 1040; ^{1}H NMR (500 MHz) δ 2.07 (3H, s, SMe), 2.71 (1H, dd, *J* 6.9, 13.5 Hz, 13-H), 2.87 (1H, dd, *J* 6.9, 13.5 Hz, 13-H), 3.32 (2H, m, 8-H_2), 3.65 (3H, s, OMe), 3.94 (3H, OMe), 3.99 (2H, t, *J* 6.7 Hz, 9-H_2), 4.57 (1H, m, 12-H), 6.13 (1H, br s, NH), 6.61 (1H, br s, 11-H), 7.03 (1H, d, *J* 2.5 Hz, 2-H), 7.06 (1H, s, ArH), 7.56 (1H, s, ArH), 8.04 (1H, br s, NH).

2. Cyclization of nitrone 31. Cyclization of the nitrone (250 mg, 0.56 mmol) with TFA (320 mg, 2.82 mmol) in CH_2Cl_2 at −78 °C gave a mixture of the 1α and 1β isomers of the β-carboline **32** (240 mg, 96%, the 1αH isomer was the major product); $[\alpha]_D^{18}$ +12.6 (*c* 0.321, MeOH).

3. *O*-Methyleudistomin F (−)-33a. A mixture of the β-carboline **32** (850 mg, 1.91 mmol) was oxidized with MCPBA (410 mg, 1.91 mmol) to give *S*-oxide (910 mg). The crude *S*-oxide (600 mg, 1.3 mmol) was cyclized with TsOH (450 mg, 2.6 mmol) in dry CH_2Cl_2 (50 ml) for 20 h at rt. Work-up as above gave the *oxathiazepine derivative* **33a** (120 mg, 21%), mp 234–236 °C (from MeOH), and recovered *S*-oxide (390 mg, 65% recovery). Compound **33a**: $[\alpha]_D^{19}$ −70.8 (*c* 0.12, MeOH) [Calc. for $C_{17}H_{21}BrN_3O_4S$: (*M* + H), 442.0436. Found: *m*/*z*, 442.0456. Calc. for $C_{17}H_{20}BrN_3O_4S$: C, 46.16; H, 4.56; N, 9.50. Found: C, 46.45; H, 4.58; N, 9.47%].

5. (−)-Eudistomin F (−)-33b. *O*-Methyleudistomin F **33a** (88 mg, 0.20 mmol) was dissolved in CH_2Cl_2 (20 ml) and BBr_3 (1.0 ml, 10.5 mmol) was added to the chilled solution at −78 °C. After 5 min, the mixture was allowed to warm to rt for 2 h. The mixture was quenched with water (20 ml) at −78 °C and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to give a residue (61 mg), which was purified by flash column chromatography with AcOEt–hexane (1:2.5) and preparative TLC to obtain eudistomin F **33b** (26 mg, 30%) as an amorphous solid, $[\alpha]_D^{20}$ −67.5 (*c* 0.11, MeOH).

The specific optical rotation of the natural product has not been reported.[2] λ_{max}(EtOH)/nm 229, 283, 287, 305, 317; (EtOH + OH$^-$) 231, 285, 338 nm; ν_{max}(KBr)/cm^{-1} 3350, 1695, 1510, 1450; *m*/*z* (%) 429/427 (M^+, 6/6%), 360 (36), 358 (19), 282/280 (99/100); ^{1}H NMR (500 MHz; CD_3CN) δ (non-systematic numbering) 2.70 (1H, m, 4-H), 2.80 (1H, m, 11-H), 2.88 (1H, m, 4-H), 3.03 (1H, m, 3-H), 3.27 (1H, d, *J* 14.3 Hz, 11-H), 3.28 (1H, s, CO_2Me), 3.41 (2H, s, CO_2Me), 3.54 (1H, br, 3-H), 4.41 (1H, s, 1-H), 4.52 (1H, br, 10-H), 4.79 (1H, d, *J* 9.1 Hz, 13-H), 4.91 (1H, d, *J* 9.1 Hz at 50 °C, 13-H), 5.59 (1H, d, *J* 9.5 Hz, 10-NH), 6.64 (1H, br, 6-OH), 6.95 (1H, s, 5-H), 7.45 (1H, s, 8-H), 8.80 (1H, br, 9-NH).

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