GM25459) and for a loan of $IrCl_3 \cdot 3H_2O$ from the Johnson Matthey Co.

Supplementary Material Available: Spectroscopic and analytical data for complexes **1–6**, details of the structure determination for complexes **1** and **4**, including experimental description and ORTEP drawings showing full atomic numbering and packing in the crystal, and tables of crystal and data collection parameters, general temperature factor expressions (B's), positional parameters and their estimated standard deviations, and intramolecular distances and angles (29 pages); tables of observed and calculated structure factors for **1** and **4** (14 pages). Ordering information is given on any current masthead page.

Total Synthesis of (−)-Eudistomin L and (−)-Debromoeudistomin L

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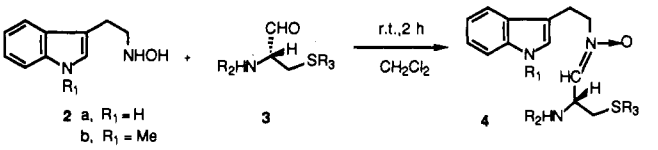
Received September 19, 1988

In 1984, Rinehart and Kobayashi reported the isolation of the first naturally occurring tetrahydro-β-carbolines incorporating an oxathiazepine ring, the eudistomins **1a–d** (Scheme III) from the colonial tunicate *Eudistoma olivaceum*.[1] More recently, the sulfoxide of eudistomin K[2] and the unsubstituted eudistomin **1e**[3] were isolated from *Ritterella sigillinoids*. These compounds display potent activity against *Herpes simplex* virus, type 1 (HSV-1). This fact, coupled with the unusual structural features, has attracted interest in **1** as a synthetic target and several groups have reported preliminary results.[4]

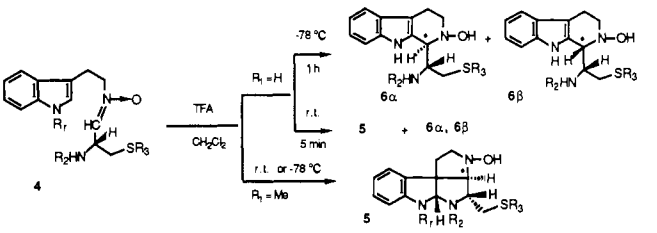
We wish to report the first total synthesis of (−)-eudistomin L (**1a**) and (−)-debromoeudistomin L (**1e**) in an optically pure form possessing the natural configuration. We have recently reported preliminary results on the Pictet–Spengler (PS) reaction of N_b-hydroxytryptamines **2** with the cysteinals **3**.[4e] Further investigations disclosed that the optically active nitrones **4**[5] can be isolated as the first intermediates of the PS reaction when **2** is reacted with L-cysteinal **3** (CH_2Cl_2, room temperature) (Scheme I, Table I).

When **4** (R_1 = H) was treated with trifluoroacetic acid (TFA, room temperature), the corresponding tetracyclic compounds **5** were obtained together with the normal PS reaction product, tetrahydro-β-carbolines **6** (Scheme II, Table II, entries 8–11), whereas at low temperature, **6** were the only products isolated, and, none of 5 was detected (Table II, entries 1–7). The compounds **5** were obtained as a single isomers, while **6** were obtained as a mixture of two diastereoisomers **6α** and **6β** with high diastereoselectivity for **6β**. On the other hand, **4** (R_1 = Me) gave

Scheme I



Scheme II



Scheme III

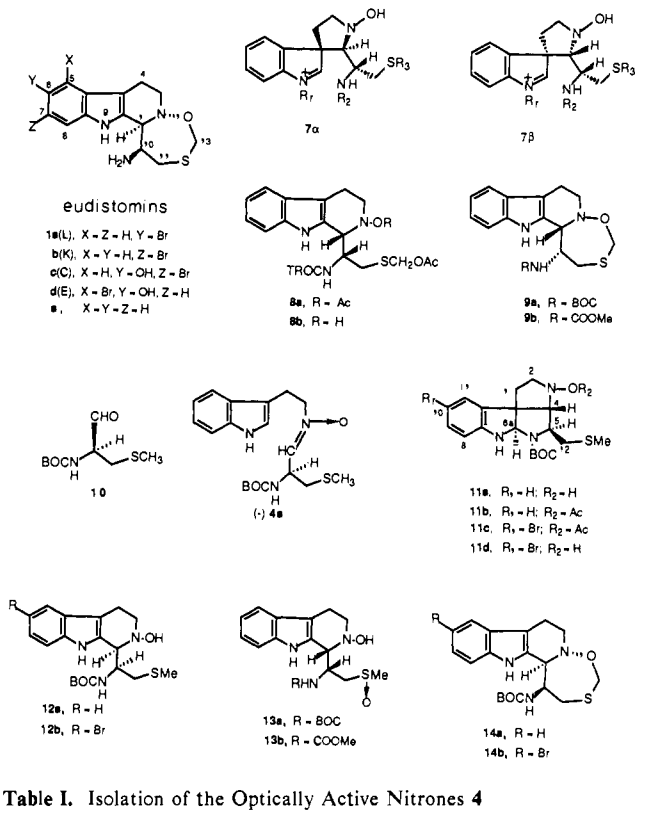


Table I. Isolation of the Optically Active Nitrones **4**

entry	4	R_1	R_2	R_3	yield (%)	$[\alpha]_D$[a] (deg)	mp (°C)
1	a	H	COOMe	Me	97.0	+56.9	
2	b	H	TROC	CBZ	77.6	+21.1	
3	c	H	BOC	TROC	96.7	+35.5	
4	d	H	TROC	Me	92.0	+41.0	
5	e	H	BOC	Me	92.8	+67.3	135.5–136.5
6	f	Me	COOMe	TROC	95.4	+30.0	96–97

[a] In MeOH.

5 regardless of the reaction temperature (Table II, entries 12–15). Subsequent treatment of **5** (R_1 = H) with TFA in CH_2Cl_2 afforded **6α** and **6β**. The stereochemistry of *C position is reversed in the major carboline **6β** in contrast to that of **5**.[4e] Unlike **5** (R_1 = H), **5** (R_1 = Me) does not rearrange to **6**, and the nitrone **4** (R_1 = Me, R_2 = COOMe, R_3 = MEM) was isolated (30%) when **5** (R_1 = Me, R_2 = COOMe, R_3 = MEM) was treated with $ZnBr_2$. We believe that the mechanism of this PS reaction is qualitatively similar to the known mechanism[6] which proceeds through the

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(5) The optical purity of the products **4** and **6** were determined from their ^1H NMR spectra by use of a shift reagent. The ^1H NMR spectra of (−)-**4e** and (−)-**6aβ** using tris[3-heptafluoropropylhydroxymethylene-*d*-camphorate] derivative of europium(III) in $CDCl_3$ showed the absence of the other enantiomers by comparisons with those of (±)-**4e** and (±)-**6aβ**, respectively.

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Table II. Cyclization of the Nitrones **4**

entry	4	R_1	R_2	R_3	TFA (equiv)	condition	5 (%)	6 (%)	6α:6β
1	**a**	H	COOMe	Me	2	−78 °C/1 h		**a** (97)	1:41
2	**b**	H	TROC	CBZ	5	−78 °C/2 h		**b** (82)	1:8
3	**c**	H	BOC	TROC	5	−78 °C/2 h		**c** (94)	1:10
4	**d**	H	TROC	Me	5	−78 °C/2 h		**d** (96)	1:21
5	**e**	H	BOC	Me	2	−78 °C/1 h		**e** (96)	1:10
6	**g**	H	COOMe	TROC	2	−78 °C/1 h		**g** (100)	1:12
7	**h**	H	CBZ	TROC	2	−78 °C/1 h		**h** (97)	1:12
8	**a**	H	COOMe	Me	1	rt/5 min	**a** (75)	**a** (24)	1:7
9	**e**	H	BOC	Me	1	rt/5 min	**e** (70)	**e** (21)	1:5
10	**g**	H	COOMe	TROC	1	rt/5 min	**g** (33)	**g** (56)	1:6
11	**h**	H	CBZ	TROC	2	rt/1 h	**h** (28)	**h** (67)	1:4
12	**f**	Me	COOMe	TROC	1	rt/5 min	**f** (90)		
13	**i**	Me	COOMe	Me	1	rt/5 min	**i** (90)		
14	**f**	Me	COOMe	TROC	5	−78 °C/1 h	**f** (93)		
15	**i**	Me	COOMe	Me	5	−78 °C/1 h	**i** (90)		

spiroindolenine intermediates 7α and 7β (Scheme III). The isomer 7α could convert either to **5** via trapping by intramolecular cyclization or to 6α by a competitive rearrangement. On the other hand, 7β could only rearrange to 6β due to the instability of the cis diastereoisomer of **5**. These results provide evidence for the involvement of a rapid equilibrium between **4**, **5**, and **6** in the PS reaction.[7] The reaction at low temperature suggests direct electrophilic attack via a favored 6-endo-trig pathway[8] at the indole 2-position under kinetically controlled conditions.

With the optically active key intermediates **5** and **6**[5] in hand, the intramolecular Pummerer cyclization of **6d**β was examined. Treatment of the sulfoxide of **6d**β with acetic anhydride gave the diacetate **8a** which was selectively O-deacetylated to yield **8b**. However, **8b** does not undergo the desired cyclization.

In order to prevent the acetylation of the hydroxyl group and to favor the desired cyclization via a more reactive intermediate, chlorination[9] of **6e**β was carried out. Thus, when **6e**β was treated with NCS (1.2 equiv, CCl_4, 0 °C, 12 h), the desired cyclization occurred to give the oxathiazepine **9a** {$[\alpha]_D$ +93.2° (21 °C, *c* 0.25, MeOH), 4%}. Deprotection of the BOC group (50% TFA-C-H_2Cl_2, room temperature, 20 min; IRA-400) afforded the enantiomeric debromoeudistomin L (+)-**1e** {$[\alpha]_D$ +105.8° (21 °C, *c* 0.19, MeOH), quantitative} (Scheme III).

Likewise, the condensation of **10**, prepared from D-cysteine, with **2a** gave (−)-**4e**[5] {$[\alpha]_D$ −68.6° (23 °C, *c* 0.50, MeOH), mp 135.5-136.5 °C, 90%} which was cyclized (TFA, −78 °C) to give **12a** (enantiomer of **6e**β, 90%) and the enantiomer of **6e**α (4%). Treatment of **12a** with NCS (1.2 equiv, CCl_4, 5-10 °C, 1.5 h, 8%) afforded **14a** {$[\alpha]_D$ −99.0° (22 °C, *c* 0.10, MeOH), mp 197-198 °C}. Deprotection of **14a** provided debromoeudistomin L (**1e**) as a TFA salt which on treatment with IRA-400 gave debromoeudistomin L (1e) {$[\alpha]_D$ −96.3° (22 °C, *c* 0.08, MeOH), 94%; lit.[3c] $[\alpha]_D$ −58.3° (*c* 0.06, MeOH)}.

After an extensive survey of this final oxidative cyclization,[10] the *p*-TsOH-catalyzed[11] cyclization (*p*-TsOH, 2.0 equiv; PPTS, 1.0 equiv, room temperature, 12 h) of the sulfoxide **13** (mCPBA, 94-99%) increased the yield of **9** {**9a**, 10%; **9b**, $[\alpha]_D$ +87.3° (23 °C, *c* 0.51, MeOH), 17%}.

The unexpected formation of **5** from **4** could now be used to modify the benzene ring for the synthesis of eudistomins carrying substituents on the benzene ring. Thus, the PS reaction of (−)-**4e** at room temperature gave **11a** {$[\alpha]_D$ +138.3° (24 °C, *c* 0.47, MeOH), 69.8%}. Bromination of **11b**, obtained by selective acetylation of **11a**, with NBS (1.2 equiv, room temperature, 20 min) proceeded regioselectively to give **11c** which afforded **11d** {$[\alpha]_D$ +171.3° (23 °C, *c* 0.40, MeOH), 3 steps from **11a**, 75%} on O-deacetylation. Rearrangement of **11d** with TFA (3 equiv, room temperature, 40 h, 33%) yields the desired β-carboline **12b**. Final cyclization of **12b** with NCS (CH_2Cl_2, −78 °C, 2 h, 4%) provides eudistomine L (**1a**) {$[\alpha]_D$ −58.3° (22 °C, *c* 0.06, MeOH), 76%; lit.[1] $[\alpha]_D$ −77° (25 °C, *c* 0.2, MeoH)}, via **14b** {$[\alpha]_D$ −24.0° (24° C, *c* 0.10, MeOH)}.

Synthetic eudistomins, **1a** and **1e**, exhibited identical spectroscopic data (HRMS, ^{13}C and ^1H NMR) to reported spectra.[1,3c] The synthesis also provides direct evidence for the absolute configuration of eudistomins. Further efforts for the improvement of the final cyclization step are currently underway in our laboratory.

Acknowledgment. We are grateful for support of this research by a Grant-in Aid for Scientific Research (62470134 and 63105005) from the Ministry of Education, Science, and Culture, Japan and Uehara Memorial Foundation. We are also grateful to Professors Blunt and Munro for the spectral data of **1e** and for invaluable information. We also thank Dr. K. Hirayama and S. Akashi, Central Research Laboratories, Ajinomoto Co. Inc., for high resolution mass spectral analysis.

Supplementary Material Available: Spectral and physical data (mp, $[\alpha]_D$, λ_{max}, ν_{max}, *m/z*, and δ ppm) for **1a**, **1e**, (+)- and (−)-**4e**, (+)-**4f**, **5e**, **6e**β, **11a**, **11d**, **12a**, **12b**, **14a**, and **14b** (5 pages). Ordering information is given on any current masthead page.

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Electrochemical Activation of Oxygenated Fe·Bleomycin

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Received October 25, 1988

Oxygen activation in metal ion-based biochemical systems has received considerable attention in recent years.[1] Intensively studied ligands include bleomycin (BLM),[2] an antitumor antibiotic whose conversion to one or more reactive intermediates involves

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