

GM25459) and for a loan of $\text{IrCl}_3 \cdot 3\text{H}_2\text{O}$ 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

Masako Nakagawa,* Jin-Jun Liu, and Tohru Hino*

Faculty of Pharmaceutical Sciences
Chiba University, Yayoi-cho, Chiba-shi, 260, Japan

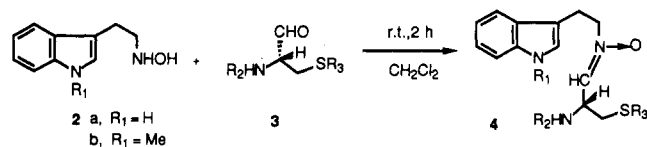
Received September 19, 1988

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 K² and the unsubstituted eudistomin 1e³ 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

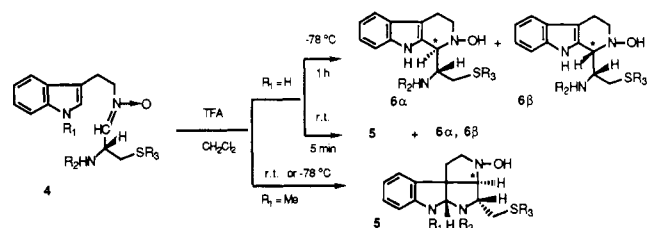
We wish to report the first total synthesis of (–)-eudistomin L (1a) and (–)-debromoeudistomin L (1e) in an optically pure form possessing the natural configuration. We have recently reported preliminary results on the Pictet–Spengler (PS) reaction of N_b -hydroxytryptamines 2 with the cysteinals 3.^{4e} Further investigations disclosed that the optically active nitrones 4⁵ can be isolated as the first intermediates of the PS reaction when 2 is reacted with L-cysteinyl 3 (CH_2Cl_2 , room temperature) (Scheme I, Table I).

When 4 ($R_1 = \text{H}$) 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 6 α and 6 β with high diastereoselectivity for 6 β . On the other hand, 4 ($R_1 = \text{Me}$) gave

Scheme I



Scheme II



Scheme III

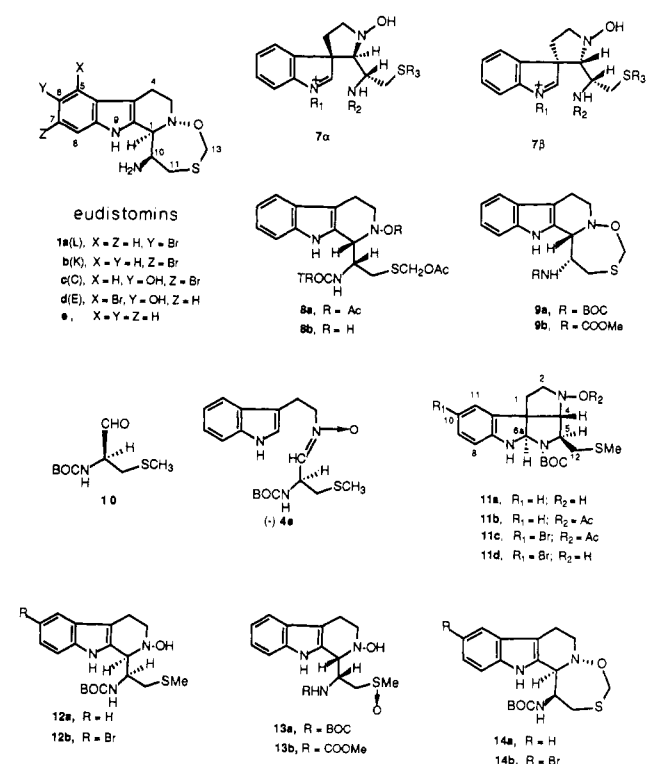


Table I. Isolation of the Optically Active Nitrones 4

entry	4	R ₁	R ₂	R ₃	yield (%)	$[\alpha]_D^{25}$ (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 ($R_1 = \text{H}$) with TFA in CH_2Cl_2 afforded 6 α and 6 β . The stereochemistry of *C position is reversed in the major carboline 6 β in contrast to that of 5.^{4e} Unlike 5 ($R_1 = \text{H}$), 5 ($R_1 = \text{Me}$) does not rearrange to 6, and the nitrone 4 ($R_1 = \text{Me}$, $R_2 = \text{COOMe}$, $R_3 = \text{MEM}$) was isolated (30%) when 5 ($R_1 = \text{Me}$, $R_2 = \text{COOMe}$, $R_3 = \text{MEM}$) was treated with ZnBr_2 . We believe that the mechanism of this PS reaction is qualitatively similar to the known mechanism⁶ which proceeds through the

(6) Ungemach, F.; Cook, J. M. *Heterocycles* 1978, 9, 1089. CF. related papers cited in ref 4e.

(1) (a) Rinehart, K. L., Jr.; Kobayashi, J.; Harbour, G. C.; Hughes, R. G., Jr.; Mizsak, S. A.; Scallion, T. A. *J. Am. Chem. Soc.* 1984, 106, 1524–1526. (b) Rinehart, K. L., Jr.; Kobayashi, J.; Harbour, G. C.; Gilmore, J.; Mascall, M.; Holt, T. G.; Shield, L. S.; Lafargne, F. *J. Am. Chem. Soc.* 1987, 109, 3378–3387.

(2) (a) Blunt, J. W.; Lake, R. J.; Munro, M. H. G. *Tetrahedron Lett.* 1987, 28, 1825–1826. (b) Lake, R. J.; Brennan, M. M.; Blunt, J. W.; Munro, M. H. G. *Tetrahedron Lett.* 1988, 29, 2255–2256.

(3) (a) Lake, R. J.; Blunt, J. W.; Munro, M. H. G. 16th International Symposium on the Chemistry of Natural Products, Abstracts, p 604. (b) Lake, R. J.; McCombs, J. D.; Blunt, J. W.; Munro, M. H. G.; Robinson, W. T. *Tetrahedron Lett.* 1988, 29, 4971–4972. (c) Blunt, J. W.; Munro, M. H. G., personal communication.

(4) (a) Han, S. Y.; Lakshmikantham, M. V.; Cava, M. P. *Heterocycles* 1985, 23, 1671–1673. (b) Behm, H.; Burskens, P. T.; Plate, R.; Ottenheijm, H. C. *J. Recl. Trav. Chim. Pays-Bas* 1986, 105, 238. (c) Nakagawa, M.; Liu, J. J.; Ogata, K.; Hino, T. *Tetrahedron Lett.* 1986, 27, 6087–6090. (d) Plate, R.; Van Hout, R. H. M.; Behm, H.; Ottenheijm, H. C. *J. J. Org. Chem.* 1987, 52, 555–560. (e) Nakagawa, M.; Liu, J. J.; Ogata, K.; Hino, T. *J. Chem. Soc., Chem. Commun.* 1988, 463–464.

(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 (–)-6a β 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 (±)-6a β , respectively.

Table II. Cyclization of the Nitrones 4

entry	4	R ₁	R ₂	R ₃	TFA (equiv)	condition	5 (%)	6 (%)	6 α :6 β
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 7 α and 7 β (Scheme III). The isomer 7 α could convert either to 5 via trapping by intramolecular cyclization or to 6 α by a competitive rearrangement. On the other hand, 7 β could only rearrange to 6 β 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 pathway⁸ at the indole 2-position under kinetically controlled conditions.

With the optically active key intermediates 5 and 6⁵ 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, chlorination⁹ of 6e β was carried out. Thus, when 6e β was treated with NCS (1.2 equiv, CCl₄, 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-H₂Cl₂, 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 (-)-4e⁵ [$[\alpha]_D$ -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, CCl₄, 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-catalyzed¹¹ 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 (CH₂Cl₂, -78 °C, 2 h, 4%) provides eudistomin 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, ¹³C 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.

Electrochemical Activation of Oxygenated Fe-Bleomycin

Reuel B. Van Atta, Eric C. Long,[†] and Sidney M. Hecht*

Departments of Chemistry and Biology
University of Virginia
Charlottesville, Virginia 22901

Gijs A. van der Marel and Jacques H. van Boom

Department of Organic Chemistry
University of Leiden, Leiden, The Netherlands
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

(7) Bailey, P. D. *J. Chem. Res.* 1987, 202.

(8) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* 1976, 734-735.

(9) (a) Wilson, G. E. *Tetrahedron* 1982, 38, 2567 and references therein.

(b) Chen, C. H.; Reynolds, G. A.; Van Allan, J. A. *J. Org. Chem.* 1977, 42, 2777.

(10) Other reagents such as *t*-BuOCl, NBS, SO₂Cl₂, etc. using a variety of solvents for the intramolecular Pummerer cyclization have also been examined but gave no satisfactory results.

(11) Ishibashi, H.; Sato, K.; Ikeda, M.; Maeda, H.; Akai, S.; Tamura, Y. *J. Chem. Soc., Perkin Trans. 1* 1985, 605-609.

[†] Present address: Department of Chemistry, Columbia University, New York, NY.

(1) *Metal Ion Activation of Dioxygen*; Spiro, T. G., Ed.; Wiley: New York, 1983.

(2) (a) Hecht, S. M. *Fed. Proc.* 1986, 45, 2784. (b) Stubbe, J.; Kozarich, J. W. *Chem. Rev.* 1987, 87, 1107.