Synthesis of 1-(N-carbobenzoxythiazolidinyl)-2-hydroxy-3-ethoxycarbonyl-1,2,3,4-tetrahydro-β-carboline

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Pictet-Spengler reaction of the N-hydroxytryptophan ethyl ester (**4**) with N-protected thiazolidine aldehyde (**8**) has been carried out. The product, compound (**9b**), might be a possible precursor for the eudistomins C, E, K, and L.

Introduction

Eudistomins C, E, K, and L have been isolated from the colonial tunicate *Eudistoma olivaceum*, one of marine species assayed during the 1978 Alpha Helix Carribean Expedition (AHCE 1978), and were reported to inhibit the growth of *Herpes simplex* virus, type 1 (HSV-1)[1].

Since their unique structures containing the condensed oxathiazepine ring were reported[2,3] in 1984 (Figure 1), a variety of approaches to the synthesis of eudistomins have been attempted[4-7]. Most of them were focused on forming oxathiazepine ring rather than introducing substituents to the benzene ring of 1,2,3,4-tetrahydro-β-carboline. Recently, Plate *et al.*[4] proposed that a possible precursor for the synthesis of the eudistomins C, E, K, and L should be derived from Pictet-Spengler reaction of N-hydroxytryptophan ethyl ester with a cysteinal derivative. In this reaction, a mixture of *cis/trans* stereoisomers was obtained, and the chirality of N-hydroxytryptophan ethyl ester was used to control the stereochemistry at $C_{(1)}$ of the 1,2,3,4-tetrahydro-β-carboline ring. The ethoxycarbonyl group, having fulfilled its function, was removed with easy.

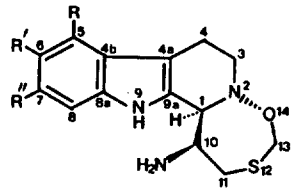
In the present study, we have tried to obtain a precursor for synthesis of eudistomins C, E, K, and L by the expansion of the five-membered thiazolidine ring to a seven-membered oxathiazepine ring.

Results and Discussion

Our retro-synthetic plan is shown is Scheme 1.

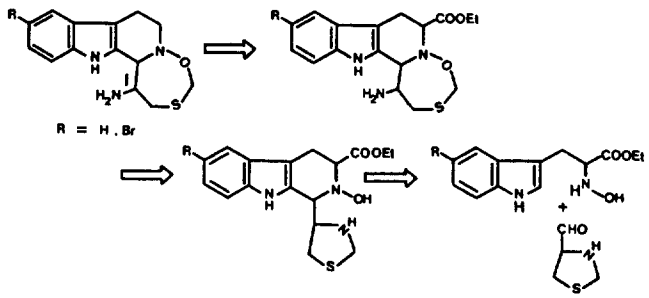
First, we have synthesized two derivatives of N-hydroxytryptophan ester. When bromo-oxime (**1**) was reacted with indole or 5-bromoindole in alkaline solution by the procedure of Gilchrist *et al.*[8], indole oximes (**2**, **3**) were obtained in 62% and 65% yield, respectively. Reduction of indole oximes (**2**, **3**) with trimethylamine-borane complex gave N-hydroxytryptophan esters (**4**, **5**) (Scheme 2).

The thiazolidine carboxylic acid methyl ester (**6**) was also prepared in 66% yield from (R)-(−)-thiazolidine-4-carboxylic acid. The reactive amino group of methyl ester (**6**) was protected with bulky carbobenzoxy (Cbz) group to increase steric hindrance, and reduced with diisobutylaluminiumhydride (DIBAL) in dry toluene at isopropyl alcohol-dry ice bath

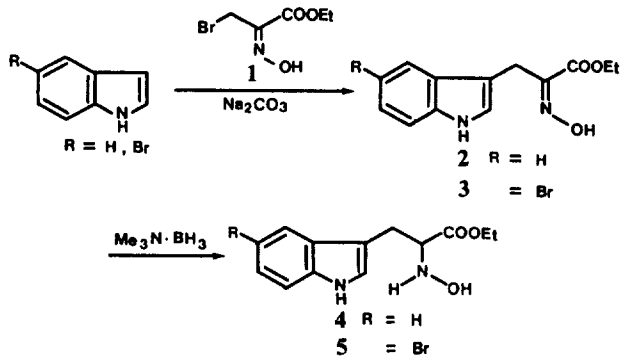


	R	R′	R″
Eudistomin C	H	OH	Br
" E	Br	OH	H
" K	H	H	Br
" L	H	Br	H

Figure 1. Structures of Eudistomins C, E, K, and L.



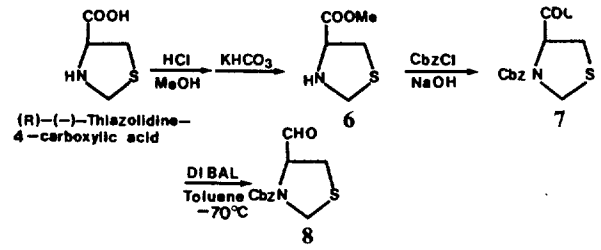
Scheme 1.



Scheme 2.

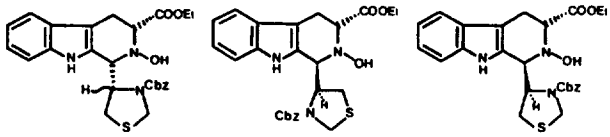
(−70℃) to give N-protected aldehyde (**8**) in 38% yield. In a ^{1}H-NMR spectrum the signal for proton of aldehyde appeared at δ 9.80 ppm (Scheme 3).

Pictet-Spengler reaction of N-protected aldehyde (**8**) with ethyl 2-hydroxyamino-3-(indol-3-yl)propanoate (**4**) was performed in the presence of CF_3COOH and, as expected, a mixture of diastereomers were obtained. Three spots on TLC



Scheme 3.

(silica gel, benzene/ethyl acetate=85/15) were obtained. These diastereomers **9a**, **9b**, and **9c** were separated by preparative HPLC with the product ratio of 2:1:1. Their polarities were **9a**, **9b**, and **9c** in increasing order. Their relative stereochemistry was assigned on the basis of ^{13}C-NMR data. The structure of compound (**9a**) having the greatest chemical shift values for the $C_{(1)}$ and $C_{(3)}$ was assigned to the *cis* isomers, considering the compression effect resulting from 1,3-diaxial interaction. The structure of the *trans* isomer showing more shielded $C_{(1)}$ and $C_{(3)}$ carbon atoms was assigned to compound (**9b**), which was expected to show a bit greater compression effect than the compound (**9c**). The specific ro-

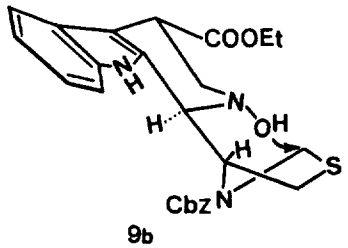


9a **9b** **9c**

tation of compound (**9a**) or the mixture of compound (**9b**) and (**9c**) was zero, indicating that the aldehyde racemized under the conditions of its preparation.

The Pictet-Spengler reaction of N-protected aldehyde (**8**) with ethyl 2-hydroxyamino-3-(5-bromoindol-3-yl)propanoate (**5**) was also carried out, but the similar three products would not be identified due to some unidentifiable peaks on their NMR spectra.

In conclusion, we have synthesized the probable eudistomins C, E, K, and L intermediate (**9b**) according to Scheme



9b

1. The chirality of tryptophan ester (**4**) was exploited to separate the *trans* isomers (**9a** and **9b**) from the *cis* products (**9a**). In the meantime, ring transformation with compound (**9b**) in aqueous acetic acid was attempted to form oxathiazepine ring, but we were not able to obtain any identifiable products. We are currently investigating other conditions.

Experimental

Infrared spectra were recorded with Shimadzu IR-440 spectrometer. All NMR spectra were taken on a bruker 300 MHz spectrometer using TMS as an internal standard. Mass spectra were obtained by use of a thermospray interface of HP 1090 A HPLC and HP 5988 A Mass (Hewlett Packard). Optical rotations were measured by Jasco DIP-360 polarimeter. Analytical thin layer chromatography was performed on a silica gel platè (0.25 mm, 60F-254, E. Merck). All solvents and liquids were distilled before use.

Ethyl 2-hydroxyimino-3-(indol-3-yl)propanoate (2). Ethyl bromopyruvate 2-oxime (10.5 g, 0.05 mol) was dissolved in dry CH_2Cl_2 (100 m*l*) with indole (23.4 g, 0.20 mol). Anhydrous Na_2CO_3 (42.4 g, 0.20 mol) was then added and the suspension was stirred for 25 h at room temperature. The solution was filtered through celite, and the solvent removed under reduced pressure. The column chromatographic separation ($CHCl_3$/n-Hexane=1 : 1) gave hydroxyimine (**2**, 7.6 g, 62%): mp. 155-157℃ (Lit.[8] 156-157℃)

Ethyl 2-hydroxyimino-3-(5-bromoindol-3-yl)propanoate (3). Ethyl bromopyruvate 2-oxime (21.0 g, 0.1 mol) was dissolved in dry CH_2Cl_2 (250 m*l*) with 5-bromoindole (19.6 g, 0.1 mol). Anhydrous Na_2CO_3 (11.7 g, 0.11 mol) was then added and the suspension was stirred for 10 h at room temperature. The solution was filtered through celite, and the solvent removed under reduced pressure. The column chromatographic purification (CH_2Cl_2/CH_3OH=99/1) gave hydroxyimine (**3**, 21.1 g, 65%): mp. 149-150℃; ^{1}H-NMR (DMSO-d_6) δ 7.95-7.21 (m, 4H, indole $C_{(2)}H$ and $C_{(4)}$-$C_{(7)}H$), 4.21 (q, 2H, CH_2CH_3), 4.03 (s, 2H, $C_{(3)}CH$), 1.24 (t, 3H, CH_2CH_3); MS m/e 344, 342 (MNH_4^+, 92), 327, 325 (MH^+, 26), 297, 295 (6), 210, 208 (7); IR (KBr) 3410, 3251 (br), 3018, 2982 cm^{-1}.

Ethyl 2-hydroxyamino-3-(indol-3-yl)propanoate (4). To a stirred solution of ethyl 2-hydroxyimino-3-(indol-3-yl) propanoate (**2**, 0.8 g, 7.4 mmol) and $(CH_3)_3N\cdot BH_3$ (Tokyo Kasei, 0.6 g, 8.0 mmol) in ethanol (200 m*l*) was added dropwise a solution of HCl in ethanol (12 m*l* of a 7 N solution) at room temperature under dry N_2 atmosphere. The mixture was stirred for 5 h, concentrated to dryness, and the residue was dissolved in CH_2Cl_2. The solution was treated with a large excess of $NaHCO_3$, filtered, washed with 0.1 N HCl, dried over anhydrous Na_2SO_4, filtered and concentrated. Column chromatographic separation (CH_2Cl_2/CH_3OH=94/6) gave hydroxyamine (**4**, 0.58 g, 32%): mp. 117-118℃ (Lit.[9] 118-119℃)

Ethyl 2-hydroxyamino-3-(5-bromoindol-3-yl)propanoate (5). A solution of HCl in ethanol (80 m*l* of a 7 N solution) was added dropwise to a stirred solution of hydroxyimine (**3**, 16.2 g, 50 mmol) and $(CH_3)_3N\cdot BH_3$ (Tokyo Kasei, 4.0 g, 55 mmol) in ethanol (200 m*l*) at room temperature under dry N_2 atmosphere. The mixture was stirred for 3 h, concentrated to dryness, and the residue was dissolved in CH_2Cl_2. The solution was treated with a large excess of $NaHCO_3$, filtered, washed with 0.1 N HCl, dried over anhydrous Na_2SO_4, filtered, and concentrated. Column chromatographic separation (CH_2Cl_2/CH_3OH=94/6) gave hydroxyamine (**5**, 13.6 g, 42%): mp. 122℃ (dec.); ^{1}H-NMR (DMSO-d_6) δ 7.73-7.10 (m, 4H, indole $C_{(2)}H$ and $C_{(4)}$-$C_{(7)}H$), 4.34 (q, 2H, CH_2CH_3), 4.07 (1H, indole $C_{(3)}CH_2CH$), 3.28 and 3.26 (2H, indole $C_{(3)}CH_2CH$), 1.25 (t, 3H, CH_2CH_3); MS m/e 329, 327 (MH^+, 93), 311, 309(50), 297, 295(25), 254, 252(4), 242, 240(4), 210, 208 (5); IR (KBr) 3315 (br), 3223, 2917, 1719 cm^{-1}.

N-Carbobenzoxythiazolidine-4-carboxylic acid methyl ester (7). To a suspension of thiazolidine-4-carboxylic

acid methyl ester (**6**, 14.7 g, 0.1 mol) and NaOH (4.0 g, 0.1 mol) in dry CH_2Cl_2 (40 m*l*) was added dropwise carbobenzoxy chloride (17.1 g, 0.1 mol) slowly at room temperature with constant stirring and then allowed to stand overnight. The solvent was removed under reduced pressure. Column chromatographic separation ($CHCl_3/CH_3OH$=99/1) gave N-protected methyl ester (**7**, 20.0 g, 71%); ^{1}H-NMR ($CDCl_3$) δ 7.40 (s, 5H, C_6H_5), 5.19 (s, 2H, OCH_2), 4.83 (m, 1H, NCH), 4.76 (q, 2H, NCH_2), 3.81 (s, 3H, OCH_3), 3.30 (dd, 2H, SCH_2 CH); MS m/e 299 (MNH_4^+, 95), 282 (MH^+, 10), 238(10); IR (NaCl) 3442, 3004, 2910, 1701 cm^{-1}.

N-Carbobenzoxythiazolidine aldehyde (8). To a cooled (−70℃) and stirred solution of N-protected methyl ester (**7**, 14.1 g, 50 mmol) in dry toluene (200 m*l*) was added dropwise diisobutylaluminium hydride (37 m*l*, 1 M solution in n-hexane, Fluka) over a period of 1 h in an dry N_2 atmosphere. After the mixture was stirred for another 1 h at −70 ℃, the excess of reagent was decomposed by careful addition of a mixture of ethanol/concentrated aqueous HCl(20 m*l*, 10/1, v/v). Water was added (500 m*l*) and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to give yellow viscous liquid (**8**, 4.8 g, 38%): ^{1}H-NMR ($CDCl_3$) δ 9.80 (s, 1H, CHO), 7.40 (s, 5H, C_6H_5), 5.34 (s, 2H, $CH_2C_6H_5$), 5.01 (m, 1H, NCH), 4.78 (q, 2H, NCH_2), 3.32 (dd, 2H, SCH_2CH); MS m/e 269 (MNH_4^+, 94), 252 (MH^+, 42), 208(11); IR (NaCl) 3402, 3001, 2970, 1703 cm^{-1}.

1-N-Carbobenzoxythiazolidinyl-2-hydroxy-3-ethoxycarbonyl-1,2,3,4-tetrahydro-β-carboline (9). To a stirred solution of aldehyde (**8**, 1.3 g, 5 mmol) and hydroxyamine (**4**, 1.2 g, 5 mmol) in dry CH_2Cl_2(15 m*l*) was added dropwise CF_3COOH (2.3 g, 20 mmol) at room temperature in a dry N_2 atmosphere. After overnight, the reaction mixture was concentrated to dryness and the residue was dissolved in CH_2Cl_2 (250 m*l*). The resulting solution was washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness to give a yellow oil consisting mainly of three compounds, which were separated by means of preparative HPLC (silica gel, benzene/ethylacetate=85/15). The product ratio of **9a**, **9b**, and **9c** determined by analytical HPLC was 2:1:1; 0.75 g of **9a** (31%, Rf 0.45), 0.34 g of **9b** (14%, Rf 0.41), 0.31 g of **9c** (13%, Rf 0.36).

Compound **9a**: mp. 76-77℃; UV (MeOH) 224, 280 (λ_{max}), 246 (λ_{min}); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.5 (C(O)OCH_2CH_3), 165.5 (C(O)N), 138.8 ($C_{(8a)}$), 137.1 ($C_{(9a)}$), 136.1, 130.2, 130.2, 128.4, 128.4, 127.9 (C_6H_5), 126.5 ($C_{(4b)}$), 122.0 ($C_{(7)}$), 119.8 ($C_{(6)}$), 117.8 ($C_{(5)}$), 111.2 ($C_{(8)}$), 108.0 ($C_{(4a)}$), 67.8 ($CH_2C_6H_5$), 71.4 ($C_{(3)}$), 63.1 ($C_{(1)}$), 62.5 ($NCHCH_2$), 61.8 (NCH_2S), 61.5 (CH_2 CH_3), 21.4 ($C_{(4)}$), 14.5 (CH_2CH_3); ^{1}H-NMR ($CDCl_3$) δ 8.72 (brs, 1H, $N_{(9)}H$), 7.58-7.19 (m, 9H, $C_{(5)}$-$C_{(8)}H$ and C_6H_5), 6.21 (s, 1H, NOH), 5.28 (s, 2H, $CH_2C_6H_5$), 5.04 (m, 1H, NCH), 4.86 (d, 1H, $C_{(1)}H$), 4.27 (q, 2H, OCH_2CH_3), 3.84 (s, 2H, SCH_2N), 3.43 (t, 1H, $C_{(3)}H$), 3.21 (d, 2H, SCH_2CH), 3.00 (d, 2H, $C_{(4)}H_2$), 1.13 (t, 3H, OCH_2CH_3); MS m/e 482 (MH^+, 76), 464(18), 330 (35), 267(30), 243(88).

Compound **9b**: mp. 161℃; UV (MeOH) 224, 280 (λ_{max}), 246 (λ_{min}); ^{13}C-NMR ($CDCl_3$) δ 172.6 (C(O)OCH_2CH_3), 165.5 (C(O)N), 138.5 ($C_{(8a)}$), 137.2 ($C_{(9a)}$) 136.5, 130.3, 130.3, 128.4, 128.4, 127.8 (C_6H_5), 126.7 ($C_{(4b)}$), 122.0 ($C_{(7)}$), 120.4 ($C_{(6)}$), 118.1 ($C_{(5)}$), 111.3 ($C_{(8)}$), 108.1 ($C_{(4a)}$), 68.1 ($CH_2C_6H_5$), 63.2 ($C_{(3)}$), 62.5 ($NCHCH_2$), 62.4 ($C_{(1)}$), 61.7 (NCH_2S), 61.5 (CH_2CH_3), 21.1 ($C_{(4)}$), 14.5 (CH_2CH_3); ^{1}H-NMR ($CDCl_3$) δ 8.08 (brs, 1H, $N_{(9)}H$), 7.50-7.09 (m, 9H, $C_{(5)}$-$C_{(8)}H$ and C_6H_5), 6.35 (s, 1H, NOH), 5.22 (s, 2H, $CH_2C_6H_5$), 5.02 (m, 1H, NCH), 4.87 (d, 1H, $C_{(1)}H$), 4.23 (q, 2H, OCH_2CH_3), 4.10 (s, 2H, SCH_2N), 3.73 (t, 1H, $C_{(3)}H$), 3.28 (d, 2H, SCH_2CH), 2.80 (d, 2H, $C_{(4)}H_2$), 1.13 (t, 3H, OCH_2CH_3); MS m/e 482 (MH^+, 82), 464(43), 374(12), 356(31), 267(96), 241(68), 215(41).

Compound **9c**: mp. 164℃; UV (MeOH) 224, 280 (λ_{max}), 246 (λ_{min}); ^{13}C-NMR ($CDCl_3$) δ 172.6 (C(O)OCH_2CH_3), 165.5 (C(O)N), 138.5 ($C_{(8a)}$), 137.2 ($C_{(9a)}$), 136.5, 130.3, 130.3, 128.4, 128.4, 127.8 (C_6H_5), 126.7($C_{(4b)}$), 122.0 ($C_{(7)}$), 120.4 ($C_{(6)}$), 118.1 ($C_{(5)}$), 111.3 ($C_{(8)}$), 108.1 ($C_{(4a)}$), 68.1 ($CH_2C_6H_5$), 65.1 ($C_{(3)}$), 62.5 ($NCHCH_2$), 62.4 ($C_{(1)}$), 61.7 (NCH_2S), 61.5 (CH_2CH_3), 22.0 ($C_{(4)}$), 14.5 (CH_2CH_3); ^{1}H-NMR ($CDCl_3$) δ 7.97 (brs, 1H, $N_{(9)}H$), 7.48-7.06 (m, 9H, $C_{(5)}$-$C_{(8)}H$ and C_6H_5), 6.20 (s, 1H, NOH), 5.23 (s, 2H, $CH_2C_6H_5$), 5.01 (m, 1H, NCH), 4.87 (d, 1H, $C_{(1)}H$), 4.23 (q, 2H, OCH_2CH_3), 4.17 (s, 2H, SCH_2N), 3.61 (t, 1H, $C_{(3)}H$), 3.16 (d, 2H, SCH_2CH), 2.82 (d, 2H, $C_{(4)}H_2$), 1.13 (t, 3H, OCH_2CH_3); MS m/e 482 (MH^+, 93), 466(67), 330 (11), 267(58), 241(62).

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References

1. K. L. Rinehart, Jr., P. D. Shaw, L. S. Sheld, J. B. Gloer, G. C. Harbour, M. E. S. Koker, D. Samain, R. E. Schwartz, A. A. Tymiak, D. L. Weller, G. T. Carter, M. H. G. Munro, R. G. Hughes, Jr., H. E. Renis, E. B. Swynenberg, D. A. Stringfellow, J. J. Vavra, J. H. Coats, G. E. Zurenko, S. L. Kuentzel, L. H. Li, G. J. Bakus, R. C. Brusca, L. L. Craft, D. N. Young, and J. L. Connor, *Pure Appl. Chem.*, **53**, 795 (1981).
2. K. L. Reinhart Jr., J. Kobayashi, G. C. Harbour, R. G. Hughes, Jr., S. A. Mizsak, and T. A. Scahill, *J. Am. Chem. Soc.*, **106**, 1524 (1984).
3. J. Kobayashi, G. C. Harbour, J. Gilmore, and K. L. Reinhart Jr., *J. Am. Chem. Soc.*, **106**, 1526 (1984).
4. R. Plate, R. H. M. Van Hout, H. Behm, and H. C. J. Ottenheijm, *J. Org. Chem.*, **52**, 555 (1987).
5. S. Y. Han, M. V. Lakshmikantham, and M. P. Cava, *Heterocycles*, **23**, 1671 (1985).
6. P. H. H. Hermkens, J. H. V. Maarseveen, C. G. Kruse, and H. W. Scheeren, *Tetrahedron Lett.*, **30**, 5009 (1989).
7. M. Nakagawa, J. J. Liu, and T. Hino, *J. Am. Chem. Soc.*, **111**, 2721 (1989).
8. T. L. Gilchrist and T. G. Roberts, *J. Chem. Soc. Perkin Trans. I*, 1283 (1983).
9. R. Plate, P. H. H. Hermkens, J. M. M. Smits, and H. C. J. Ottenheijm, *J. Org. Chem.*, **51**, 309 (1986).