TOTAL SYNTHESIS OF (-)-EUDISTOMIN F

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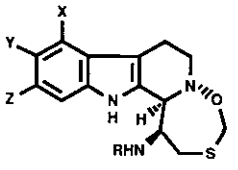
Abstract - (-)-Eudistomin F (**1d**) was synthesized in optically pure form from 6-bromo-5-methoxy-N_b-hydroxytryptamine (**10**) and D-cysteinal (**15**).

Eudistomins (**1**), a group of the first naturally occurring oxathiazepine-containing alkaloids, are known to be endowed with remarkable antiviral[1] and antitumor activity,[2] and are now the subjects of considerable interests as synthetic targets.[3] Recently, we have reported the efficient, N_b-hydroxytryptamine mediated, total synthesis of (-)-eudistomin L (**1a**) and (-)-debromoeudistomin L (**1f**).[4] In the present paper, we wish to report that the another member of the group, (-)-eudistomin F (**1d**) can be prepared from the corresponding substituted N_b-hydroxytryptamine. The challenge we thus faced in this synthesis was the regioselective introduction of the OH and Br groups to the required positions of the benzene ring. In the synthesis of (-)-eudistomin L (**1a**),[4] we have developed a method with which regioselective bromination was achieved *via* the tetracyclic compound **2a**, an intermediate of Pictet-Spengler reaction of N_b-hydroxytryptamine and cysteinal.[5] It was expected that similar methodology should be useful for the introduction of the OH and Br groups in the synthesis of (-)-eudistomin F (**1d**).

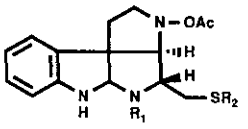
As a preliminary experiment, when treated the tetracyclic compound **2b** with $Pb(OAc)_4$ in the presence of TFA, the desired hydroxylated product **3** (44%, two steps) was obtained after reduction with Zn dust and hydrolysis of the acetate.[6] Bromination of **3** with NBS in CH_2Cl_2 provided the corresponding bromide **4** (23%). However, attempts to introduce OH and Br groups to sulfide **2a**, a precursor for the cyclization to oxathiazepine ring system, were unsuccessful. Oxidation of **2a** with $Pb(OAc)_4$ gave only the corresponding sulfoxide **5**.

As an alternative method, we prepared 6-bromo-5-methoxy-N_b-hydroxytryptamine **10** from which (-)-eudistomin F (**1d**) had been synthesized. Starting from 6-bromo-5-methoxyindole **6**,[7] **10** was synthesized in four steps. Thus, Vilsmeier-Haack reaction of **6** provided the 3-formylindole **7** in 97% yield. Condensation of **7** with $MeNO_2$ in the presence of $AcONH_4$ afforded the nitroolefin **8** (91%) which was then treated with $NaBH_4$

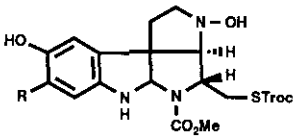


eudistomins 1

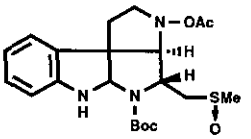
	X	Y	Z	R	
1a	H	Br	H	H	eudistomin L
1b	H	H	Br	H	eudistomin K
1c	H	OH	Br	H	eudistomin C
1d	H	OH	Br	CO_2Me	eudistomin F
1e	Br	OH	H	H	eudistomin E
1f	H	H	H	H	



2a R_1 = Boc R_2 = Me
2b R_1 = CO_2Me R_2 = Troc



3 R = H
4 R = Br



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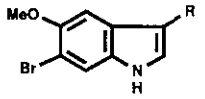
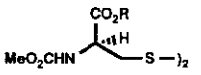
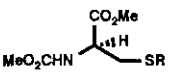


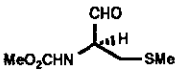
6 R = H
7 R = CHO
8 R = CH=CHNO$_2$
9 R = $CH_2CH_2NO_2$
10 R = CH_2CH_2NHOH



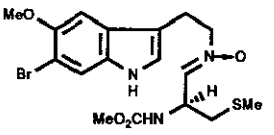
11 R = H
12 R = Me



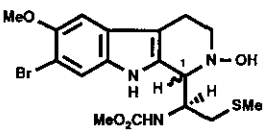
13 R = H
14 R = Me



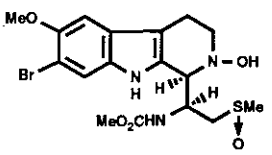
15



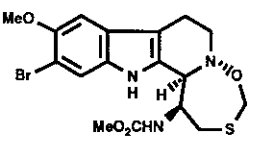
16



17a C_1 - H = α
17b C_1 - H = β



18



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in methanol to give **9** (96%). Reduction of **9** with Zn-NH_4Cl yielded the desired 6-bromo-5-methoxy-N_b-hydroxytryptamine **10**. The unstable N_b-hydroxytryptamine **10** was used immediately without purification for the next condensation with cysteinal **15** which was readily obtained from D-cystine in the sequence described below. D-Cystine was protected as N,N'-dimethoxycarbonylcystine **11** which was then converted into the corresponding methyl ester **12** (MeI, iPr_2NEt, CH_2Cl_2, room temperature, overnight, 94% from D-cystine). Reductive cleavage of the disulfide **12** with Zn dust (conc. HCl, MeOH) gave the D-cysteine derivative **13** which was then treated with MeI (iPr_2NEt, CH_2Cl_2, room temperature, 1 h) to give the methyl thioether **14** (75% from **12**). Subsequent reduction of **14** with DIBAL (toluene, -78°C, 2 h) afforded the optically pure D-cysteinal **15** (crude, 51%) which was used without purification.

Condensation of **10** with **15** in CH_2Cl_2 at room temperature without any catalyst cleanly afforded the nitrone **16**[8] (51% from **9**). According to our developed method,[4,9] **16** was treated with TFA (5 equiv.) in CH_2Cl_2 at -78°C for 2 h and N_b-hydroxy-β-carboline **17** was then obtained (96%) with high diastereoselectivity for **17a** (**17a** : **17b** = 10 : 1). Oxidation of the diastereoisomeric mixture (**17a** and **17b**) with mCPBA gave the desired sulfoxide **18**[10] after separation on silica gel. The acid-induced Pummerer-type cyclization of **18** (TsOH, 2 equiv., CH_2Cl_2, room temperature, 2 h) provided the oxathiazepine **19** (22%) together with the recovery of **18** (65%). Conversion of **19** to (-)-eudistomin F (**1d**) was accomplished by treatment with BBr_3 (33%). The synthetic (-)-eudistomin F (**1d**) was obtained as a colorless amorphous solid,[8] whose spectral data were identical with those of the natural (-)-eudistomin F (**1d**) by direct comparison. Further work on the total syntheses of other eudistomins is in progress.

ACKNOWLEDGMENT

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8. Spectra data of the nitrone **16** and synthetic (-)-eudistomin F. **16**: $[\alpha]_D^{19}$ - 41.0° (c 0.30, MeOH); λmax (EtOH) 227, 285^{sh}, 291.5, 303, 314^{sh} nm; νmax (KBr) 3300, 1700, 1530, 1470, 1235, 1040 cm^{-1}; δ (500 MHz, $CDCl_3$) 2.07 (3H, s, SCH_3), 2.71 (1H, dd, J = 6.9 Hz, 13.5 Hz, SCH_2), 2.87 (1H, dd, J = 6.9 Hz, 13.5 Hz, SCH_2), 3.32 (2H, m, CH_2), 3.65 (3H, s, $COOCH_3$), 3.94 (3H, s, OCH_3), 3.99 (2H, t, J = 6.7 Hz, NCH_2), 4.57 (1H, m, CONCH), 6.13 (1H, br s, NH), 6.61 (1H, br s, N=CH), 7.03 (1H, d, J = 2.5 Hz, α-CH), 7.06 (1H, s, arom H), 7.56 (1H, s, arom H), 8.04 (1H, br s, NH); m/z 445 (M^+ + 2), 443 (M^+). Synthetic (-) -eudistomin F: $[\alpha]_D^{20}$ - 67.5° (c 0.11, MeOH); λmax (EtOH) 229, 283, 287, 305, 317^{sh} nm; νmax (KBr) 3350, 2910, 1695, 1510, 1450 cm^{-1}; δ (500 MHz, CD_3CN) 2.70 (1H, m, CH_2), 2.80 (1H, m, SCH_2), 2.88 (1H, m, CH_2), 3.03 (1H, m, NCH_2), 3.27 (1H, d, J = 14.3 Hz, SCH_2), 3.28 (1H, s, $COOCH_3$), 3.41 (2H, s, $COOCH_3$), 3.54 (1H, br s, NCH_2), 4.14 (1H, s, CHNO), 4.52 (1H, br s, NCH), 4.79 (1H, d, J = 9.1 Hz, SCH_2O), 4.91 (1H, br s, SCH_2O; d, J = 9.1 Hz, at 50°C), 5.59 (1H, d, J = 9.5 Hz, CONH), 6.64 (1H, br s, OH), 6.95 (1H, s, arom H), 7.45 (1H, s, arom H), 8.80 (1H, br s, NH); m/z (%) 429 (M^+ + 2, 6), 427 (M^+, 6), 360 (36), 358 (19), 282 (99), 280 (100).

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10. The diastereoisomers of **18** could not be separated by tlc.

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