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Intramolecular Pictet-Spengler reaction of N-alkoxy tryptamines I. Synthesis of (±)-Deamino-debromo-Eudistomin L.

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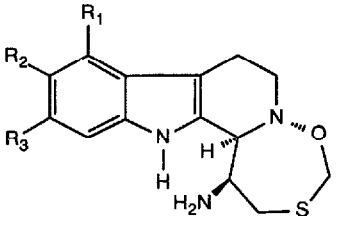
Abstract: The Eudistomin analogue **1f** was prepared in four steps with high overall yield (50%) from N-hydroxytryptamine **3a**. The key step in this reaction sequence is an intramolecular Pictet-Spengler cyclization reaction.

The increased research on secondary metabolites with interesting pharmacological activities has led to the discovery of the class of indole alkaloids containing a tetrahydro-β-carboline fragment annulated with a oxathiazepine unit. These compounds -*the Eudistomins* (**1a-1e**)- were isolated from *Eudistoma olivaceum*[1] and more recently also from *Ritterella sigillinoides*[2,4b]. They display potent activity against *Herpes simplex* Type 1 (HSV-1) and *Polio* vaccine Type I viruses. Because of its unique structure and the antiviral activity, this class of compounds constitute a major challenge for total synthesis[3]. Common in the present approaches is the first step, to construct the C-ring by a



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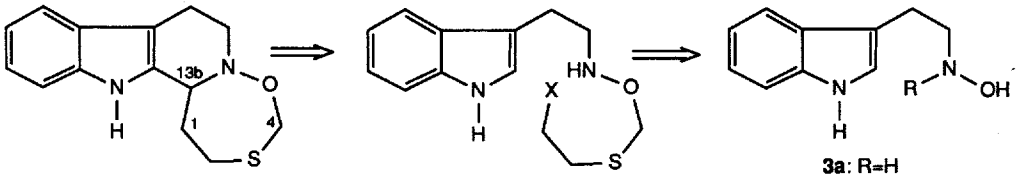
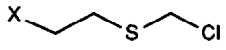
		R_1	R_2	R_3
Eudistomin L	**a:**	H	Br	H
K	**b:**	H	H	Br
C	**c:**	H	OH	Br
E	**d:**	Br	OH	H
	e:	H	H	H

Pictet-Spengler reaction of **3a** and a cysteinal derivative. However, subsequent ringclosure of the oxathiazepine ring appeared a difficult task and only recently two reports appeared of a total synthesis of eudistomin L[4].

We have demonstrated[5] by the synthesis of corynanthe analogs with a terahydro 1,2-oxazines-D-ring that an intramolecular Pictet-Spengler ringclosure of N-alkoxytryptamine derivatives is an appropriate method for constructing the tetracyclic N-oxo-β-carboline alkaloid framework with a high overall yield. In this approach ring C and D are formed simultaneously. We reasoned that this methodology for constructing tetracyclic indole alkaloids could also be suitable for an approach to the Eudistomin series. We now report the synthesis of (±)-Deamino-debromo-Eudistomin L (**1f**) via an intramolecular Pictet-Spengler reaction of **2a** or **2b** (see, retrosynthetic scheme below).

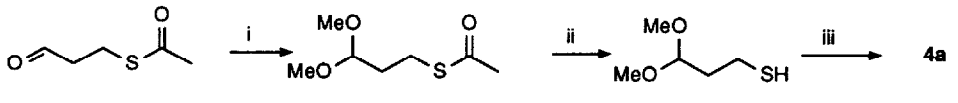
As the retrosynthetic scheme shows the intermediate for the intramolecular cyclization **2** could be build up by a coupling reaction of **3a** and the α-chloromethylsulfides **4**. It has been demonstrated[5] that TEOC-protected N-hydroxytryptamine (**3b**) can be O-alkylated by alkylhalogenides in the presence of NaI, followed by deprotection to give N-alkoxytryptamines in good yields in a one-pot synthesis. Treatment of **3a** with 2-(trimethylsilyl)ethylchloroformate in dichloromethane/dioxan at room temperature gave **3b** (96% yield).





4a: X=CH(OMe)$_2$
b: X=COOMe

The α-chloromethyl sulfide **4a** could be prepared in 3 steps starting from the thioacetate **5**[7]. A stirred solution of **5**, trimethyl orthoformate and a few drops of TFA (MeOH, 24h) gave the dimethylacetal **6** (81% yield). Dropwise addition of a methanolic 1N NaOMe solution (1 equiv.) to **6** in methanol gave the thiol **7** (70% yield). A phase-transfer alkylation reaction of **7** with bromochloromethane using powdered KOH (1.4 equiv.), catalyzed by triethylbenzylammoniumchloride (TEBAC) (0.1 equiv.) resulted in the quantitative formation of **4a**. The α-chloromethyl sulfide **4b** was prepared in an



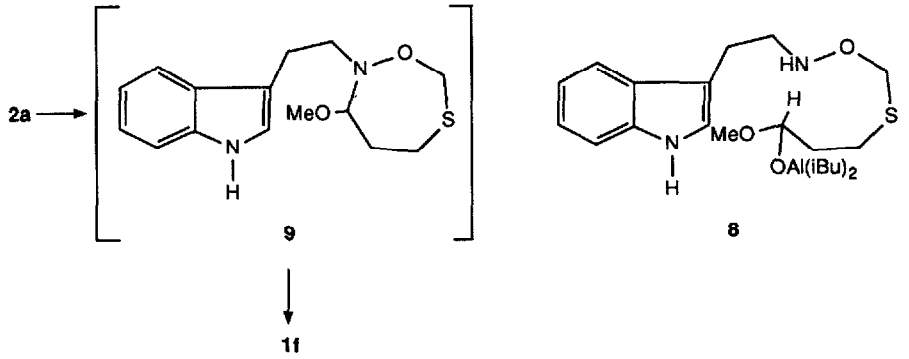
analogous fashion from methyl 3-mercaptopropionate (98% yield).

The freshly prepared anion of the N-hydroxyurethane derivative **3b** (DME/NaH(1.1 equiv.), 0°C) was added dropwise to the functionalized α-chloromethylsulfides **4a** or **4b** in the presence of NaI in DME at roomtemperature. The alkylated products were not isolated, but deprotected immediately by adding Bu_4NF (2 equiv.) to give the compounds **2a** and **2b** in an overall yield of 70% and 81%, respectively.

An intramolecular Pictet-Spengler reaction occurred on treatment of **2a** in dichloromethane with trifluoroacetic acid (2 equiv.). After stirring for 3 days at roomtemperature, (±)-Deamino-debromo-Eudistomin L (**1f**) was isolated in a reasonable yield of 71%. The NMR data of **1f** shows a great resemblance with **1e**[4b] as far as characteristic shifts and coupling constants are

concerned.

After the reduction of the methylester of **2b** with DIBAL (2 equiv.) at -70°C in toluene, TFA (3 equiv.) was added and intramolecular cylization of intermediate **8** occurred at -70°C within 15 minutes to give **1f** (61% yield). The difference in reactivity between the cyclization of **2a** and the intermediate **8** is enormous. Both cyclizations may proceed via **9**. In this case formation of **9** from **8** should be much faster than from **2a**. However, the difference in reactivity can also be explained by



supposing that the cyclization of **8** proceeds via an aldehyde intermediate.

In conclusion the successful synthesis of the model compound **1f**, demonstrates that the intramolecular Pictet-Spengler approach is suitable for constructing of the 7 membered oxathiazepine ring of the Eudistomin derivatives. Further work on the total synthesis of **1e** and **1a** is in progress and will be the subject of a full paper.

Acknowledgment

We thank Ad Swolfs for taking the 400 MHz COSY NMR spectrum of **1f**, through which proton assignment was possible. This work was supported by the Technology Foundation of the Netherlands (STW).

Spectroscopic data and Physical constants:

Compound 6: bp 74-75°C/4mm; η^{25} 1.4697; EIMS m/z 178 (M^+); ^1H NMR δ 4.45 (t, 1H, $HC(OMe)_2$), 3.34 (s, 6H, $2xOCH_3$), 2.92 (t, 2H, CH_2S), 2.35 (s, 3H, $COCH_3$), 1.84 (m, 2H, CH_2CH_2S).

Compound 7: bp 49°C/4mm; η^{25} 1.4571; EIMS m/z 136 (M^+); ^1H NMR δ 4.43 (t, 1, $HC(OMe)_2$), 3.27 (s, 6H, $2xOCH_3$), 2.47 (m, 2H, CH_2S), 1.92 (m, 2H, CH_2CH_2S), 1.40 (t, 1H, SH)

Compound 4a: bp 75-78 °C/3.5 mm; η^{25} 1.4970; ^1H NMR δ 4.73 (s, 2H, SCH_2Cl), 4.45 (t, 1H, $HC(OMe)_2$), 3.30 (s, 6H, $2xOCH_3$), 2.77 (t, 2H, CH_2S), 1.91 (m, 2H, CH_2CH_2S).

Compound 4b: CIMS m/z 184 ($[M+2]^+$), 182 (M^+), ^1H NMR δ 4.80 (s, 2H, SCH_2Cl), 3.73 (s, 3H, OCH_3), 3.18-2.58 (m, 4H, CH_2CH_2).

Compound 2a: Oil; Rf 0.56 ($CHCl_3$/MeOH, 97/3, v/v); CIMS m/z 325 ($[M+1]^+$), 292 ($[M-MeOH]^+$), 261 ($[C_{14}H_{17}N_2OS]^+$), 189 ($[C_{11}H_{13}N_2O]^+$), 130 ($[C_9H_8N]^+$); ^1H NMR δ 8.03 (br s, 1H, indole NH), 7.67-7.08 (m, 5H, indole C(2)H and C(4)-C(7)H), 5.89 (br s, 1H, NH), 4.87 (s, 2H, OCH_2S), 4.50 (t, 1H, $CH(OMe)_2$), 3.40 (s, 6H, $2xOCH_3$), 3.38 (m, 2H, CH_2N), 3.05 (m, 2H, indole $C(3)CH_2$), 2.72 (t,

2H, CH_2S), 1.99 (m, 2H, $CH_2CH(OMe)_2$).

Compound 2b: Oil; Rf 0.51 ($CHCl_3$/MeOH, 97/3, v/v); EIMS 308 (M^+), 188 ($[C_{11}H_{12}N_2O]^+$), 130 ($[C_9H_8N]^+$), 86 ($[C_4H_6O_2]^+$); ^1H NMR δ 8.03 (br s, 1H, indole NH), 7.62-7.00 (m, 5H, indole C(2)H and C(4)-C(7)H), 5.89 (br s, 1H, NH), 4.83 (s, 2H, OCH_2S), 3.64 (s, 3H, OCH_3), 3.07 (br t, 2H, CH_2N), 3.07-2.56 (m, 6H, indole C(3)CH_2 and SCH_2CH_2).

Compound 1f: mp 158-160°C (EtOAc/n-hexane); Rf 0.59 (n-hexane/EtOAc, 60/40, v/v); UV (MeOH) λmax 225, 274.5(sh), 281, 289.5 nm; CIMS (100 eV) m/z (relative intensity) 261 ($[M+1]^+$, 53), 260 (M^+, 100), 230 ($[C_{13}H_{14}N_2S]^+$, 34), 144 ($[C_{10}H_{10}N]^+$, 72), 130 ($[C_9H_8N]^+$, 86); ^1H NMR (400 MHz) δ 7.65 (br s, 1H, NH), 7.47 (d, 1H, ^3J=7.7 Hz, C(12)H), 7.31 (d, 1H, ^3J=7.7 Hz, C(9)H), 7.18-7.08 (m, 2H, C(10)-C(11)H), 5.08 and 5.01 (AB spectrum, 2H, ^2J=9.9 Hz, C(4)H_2), 4.12 (br s, 1H, C(13b)H), 3.67 (m, 1H, C(7)H_A), 3.11 (m, 1H, C(7)H_B), 3.09 (m, 1H, C(2)H_A), 3.05 (m, 1H, C(8)H_A), 2.82 (m, 1H, C(2)H_B), 2.78 (m, 1H, C(8)H_B), 2.65 (m, 1H, C(1)H_A), 2.10 (m, 1H, C(1)H_B); ^{13}C NMR (400 MHz) δ 136.38 C(12a), 133.07 C(13a), 126.59 C(8b), 121.75 C(11), 119.65 C(10), 118.31 C(9), 110.78 C(12), 108.13 C(8a), 73.44 C(4), 63.05 C(C13b), 54.06 C(7), 37.96 C(2), 26.49 C(8), 20.17 C(1); Anal.Calc. for $C_{14}H_{16}N_2OS$ (Mw 260.360): C, 64.59; H, 6.19; N, 10.76. Found: C, 64.25; H, 6.17; N, 10.68.

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