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A CONCISE ROUTE TO THE OXATHIAZEPINE CONTAINING EUDISTOMIN SKELETON AND SOME CARBA-ANALOGS

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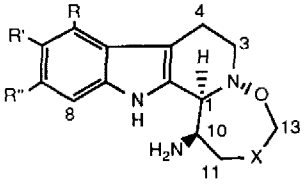
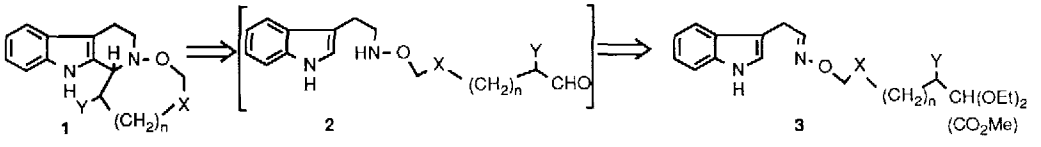
Summary: *The unsubstituted Eudistomin skeleton containing the oxathiazepine D ring was prepared along with a series of unsubstituted and amino-substituted carba-analogs, using an intramolecular Pictet-Spengler condensation.*

Since the report by Rinehart and co-workers of a series of β-carboline alkaloids possessing considerable antiviral,[1,2] and calmodulin antagonist activity,[3] much interest has been shown in these compounds as synthetic targets.[4-8]



Eudistomins
C. X=S, R=H, R'=OH, R"=Br
E. X=S, R=Br, R'=OH, R"=H
K. X=S, R=R'=H, R"=Br
L. X=S, R=R"=H, R'=Br
K(sulfoxide). X=SO, R=R'=H, R"=Br

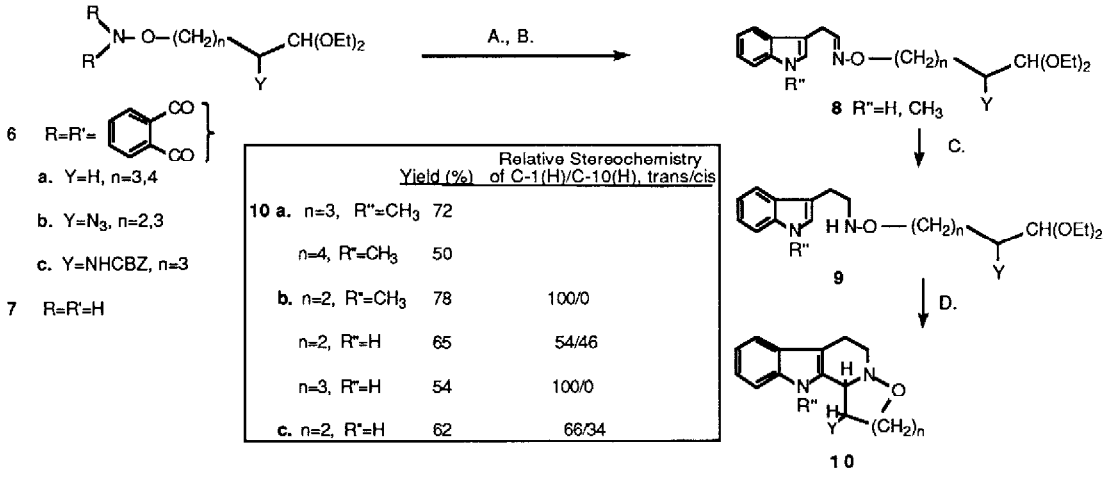
The greatest challenge has been the construction of the unusual 1,3,7-oxathiazepine ring appearing in Eudistomins C, E, K, and L. The recent successful synthesis of N(10)-acetyleudistomin L by Still and Strautmanis[7] and (-)-Eudistomin L by Nakagawa and coworkers[8], both involving the formation of the -O-CH_2- bond in the final step, were the first reported syntheses of this ring system.



In this paper we present a preliminary account of our own studies which have resulted in a convenient route to the unsubstituted tetracycle **1** (Y=H; X=S; n=1), as well as a series of carba-analogs **1** (X=CH_2; Y=H, N_3, $NHCO_2Me$).Our strategy was to construct **1**, from the open chain 3-substituted indole **2**, via an intramolecular Pictet-Spengler condensation. In reality, this proved to be a convenient route to this ring system; even the 8-membered tetracycle **10a** (n=4) is available using this methodology. In the case of the carba-analogs, alkyloxyphthalimides **6**[9] (SCHEME 1) were treated with hydrazine in THF, and the resulting aminooxy derivatives **7** were condensed with indole-3-acetaldehyde to efficiently generate the oximes **8**[10]. The intermediate oximes were then reduced with sodium cyanoborohydride to form the alkoxytryptamines **9** in good yield. These were then treated with TFA in methylene chloride to give the tetracycles **10**. Interestingly, indole-N-substitution, chain length and the presence of an azido function dramatically affected the product stereochemistry. In the N-methylindole series, when **9b** (n=2; R"=CH_3) was cyclized in methylene chloride in the

presence of a trace of TFA, a single diastereoisomer, azide **10b** (n=2; R"=CH_3) was produced, whereas the N-H indole series gave a mixture of diastereoisomers in a ratio of approximately 1:1. When the chain length was increased by one carbon, **9b** (n=3, R"=H) cyclized under the same conditions to give only one diastereoisomer, **10b** (n=3; R"=H), in which the C-1 and C-10 protons (Eudistomin numbering) are trans (unnatural configuration).

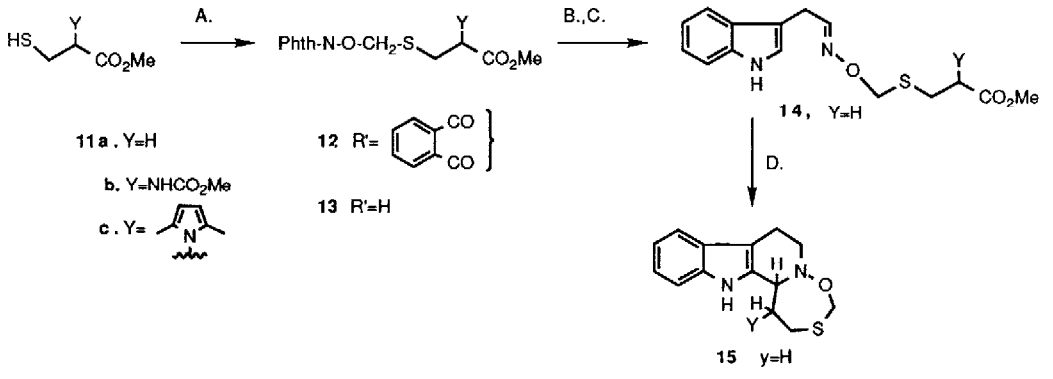
SCHEME 1



		Yield (%)	Relative Stereochemistry of C-1(H)/C-10(H), trans/cis
10 a.	n=3, R"=CH_3	72	
	n=4, R"=CH_3	50	
b.	n=2, R"=CH_3	78	100/0
	n=2, R"=H	65	54/46
	n=3, R"=H	54	100/0
c.	n=2, R"=H	62	66/34

A. **6**, H_2NNH_2, THF, B. **7**, indole-3-acetaldehyde, or N-methylindole-3-acetaldehydeTHF, C. **8**, $NaCNBH_3$, HOAc, D. **9**,TFA, CH_2Cl_2

SCHEME 2



A. **11**, Chloromethoxyphthalimide, Et_3N,THF. B. **12**, H_2NNH_2, THF. C. **13**, indole-3-acetaldehyde.
D. **14**, 2.2 eq. DiBAlH, toluene, -78°C then silica gel.

SCHEME 2 shows an extension of this methodology to give the parent ring system **15**. Sulfide **12** was prepared by reaction of N-Chloromethoxyphthalimide[17] with the appropriate thiol **11**. When **12** was treated with anhydrous hydrazine in THF and, without isolation of the intermediate alkoxylamine **13**, added directly to a solution of freshly prepared indole-3-acetaldehyde, the oxime **14** was obtained in good yield. When oxime **14a**[11,12] (SCHEME 2) was treated with 2.2 equiv.

of DiBALH at -78°C in toluene,[13] the major product, isolated in 26% yield, was compound **15a** the structure of which was determined by detailed ^{1}H and ^{13}C NMR studies[14] and confirmed by X-ray crystallography [15]. The X-ray data indicates very clearly the existence of both the α– and β– conformers about the N-O bond.

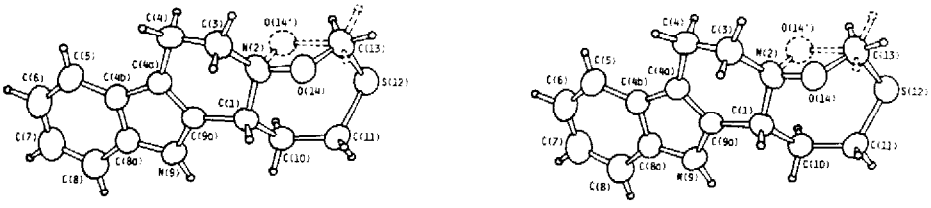


Fig. 1. Stereoview of one enantiomer of (**15a**); small circles represent hydrogen atoms and the broken lines indicate atoms of the minor (26%) conformer.

Crystals of racemic (**15a**) contain a mixture of α- and β-N-O conformers (26%:74%) as shown in Fig. 1. The seven-membered ring in each case approximates to a chair form with the mirror plane of symmetry passing through C(1) and the mid-point of the S(12)-c(13) bond in the major conformer whereas the corresponding plane in the minor conformer passes through S(12) and the mid-point of the C(1)-N(2) bond.

Although several suitably N-protected-S-(phthalimidooxymethyl)cysteine methyl esters (**11b,c**) were prepared, the rate of hydrazinolysis of these derivatives was slowed considerably and the expected aminooxymethylsulfides (**13,b,c**) decomposed in the reactions, to give the thiol **11b,c**. Further study of this problem is ongoing and will be the subject of a future publication.

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9. Prepared from the corresponding terminal chloroalkyl dimethyl or diethyl acetals by reaction with the sodium salt of N-hydroxyphthalimide in DMF. The α- azido acetals were prepared in a four step sequence from the terminal chloroalkylcarboxylic acids by reacting them with iodine and thionyl chloride[16], followed by methanol workup. These terminal chloro- α-iodoesters were then reacted with sodium azide in DMF, reduced with 1.1 equivalents of DiBAlH and then treated with methanol/HCl to give the corresponding azidoacetals. These were then reacted with N-hydroxyphthalimide to give the derivatives **6 b**.

10. Removal of the phthaloyl groups was accomplished by reacting **6** with anhydrous hydrazine (1.1 eq.) in THF. Removal of phthalhydrazide by filtration and then reaction with freshly prepared indole-3-acetaldehyde in toluene gave the corresponding oximes **8**.

11. To a stirred solution of methyl-3-mercaptoproprionate (280mg., 2.3 mmoles) in methylene chloride (10mL), was added chloromethoxyphthalimide[17] (500 mg., 2.39 mmoles) followed by triethylamine (252 mg.,2.5 mmoles) in methylene chloride. The reaction mixture was kept at r.t. for 1.5 hrs., then washed with water (15 mL), dried ($MgSO_4$) and stripped of solvent under vacuum. Chromatography on silica gel (5% Et_2O, methylene chloride), gave 420 mg (1.48 mmoles, 65%) of the product **12a.** This method works equally well for the thiols **11b** and **c.**

12. The phthalimidoester **12a** (3.7 gm., 18.8 mmoles), was dissolved in THF (10 mL) and anhydrous hydrazine (0.6 gm, 0.6 mL, 18.75 mmoles), was added to the stirred reaction mixture at 5°C. The phthalhydrazide precipitated almost immediately and was rapidly removed by filtration. The filtrate was reacted with a freshly prepared solution of indole-3-acetaldehyde in toluene. After 30 min. the solvent was removed under vacuum and the residue was chromatographed on silica gel (5% Et_2O, CH_2Cl_2) to give 4.3 gm (75% yield) of oxime **14a**.

13. The oxime **14a** (1.45 gm., 4.74 mmoles) in toluene, was treated with 10 mL of 1M DiBALH in toluene (Aldrich) at -78° C with stirring under nitrogen.After 45 min., 5 mL of methanol was added , the cold bath was removed and 5 mL of brine was added. The mixture was stirred rapidly for 3 hrs. The ppt. was removed by filtration through celite and washed with ether. Several grams of silica gel were added to the filtrate and the mixture was stirred under nitrogen for 30 min. The silica gel was removed by filtration, the filtrate was dried ($MgSO_4$), stripped of solvent under vacuum and the residue was purified by preparative HPLC (Whatman partisil, 1% EtOAc, $CHCl_3$) to give 320 mg (1.23 mmoles, 26% yield) of the oxathiazepine **15**. Recrystallization from Et_2O/hexane afforded crystals (mp 157-159° C) of sufficient quality for x-ray analysis[15].

14. **^{1}H NMR** ($CDCL_3$): δ = 2.14 (1H, q of mult.); 2.65 (1H, m); 2.80(2H, m); 3.10 (3H, m); 3.68(1H, m); 4.13 (1H,dd, J=10.1, 7.1 Hz); 5.02 (1H, d, J=10.1 Hz); 7.14 (2H, pair of dt, J= 1.2, 7.3 Hz); 7.29 (1H, d, J= 7.3 Hz); 7.48 (1H, d, J= 7.4Hz). **^{13}C NMR** ($CDCl_3$) : d = 20.3 (t); 26.8 (t); 38.1 (t); 54.2 (t); 63.2 (d); 73.8 (t); 108.4 (s); 110.9 (d); 118.4 (d); 119.8 (d); 121.9 (s); 133.3 (s); 136.7 (s).

15. **Crystal data**. (**15a**) , $C_{14}H_{16}N_2OS$, M = 260.36, monoclinic, space group $P2_1/c$, a = 10.612(2), b = 6.436(1), c = 20.087(6) Å, β = 109.90 (2)°, V = 1290(1) Å^3 (from 25 orientation refls., 42° <θ <66°), Z = 4, D_c = 1.341 g cm^{-3}, μ(Cu-Kα radiation, λ = 1.5418 Å) = 20.9 cm^{-1}; crystal size: 0.10 x 0.14 x 0.40 mm. Intensity data (+h,+k,+/-l; 2303 refls., $\theta_{max.}$ = 67°) were recorded on an Enraf-Nonius Cad-4 diffractometer (Cu-Kα radiation, graphite monocrometer; ω-2θ scans). The structure was solved by direct methods (MULTAN11/82). Full-matrix least-squares refinement (Enraf-Nonius SDP) of atomic positional and thermal parameters [anisotropic C, N, O, S; isotropic H; occupancy factors of 0(14) and 0(14')] converged at R + 0.047 (R_w = 0.068) over 1802 absorption-corrected reflections with I> 3.0σ (I). Atomic parameters, bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre.

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