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Recently many bioactive indole alkaloids have been isolated from marine organisms. Many of them have novel ring systems which are not found in the indole alkaloids isolated from higher plants and molds on the land. We have chosen β-carboline alkaloids, eudistomins and manzamines, as targets for total synthesis.

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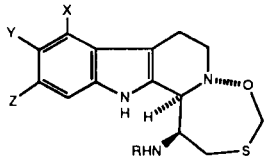
I Eudistomins.

Eudistomins have been isolated from various tunicates by Rinehart, Kobayashi and their group in 1984 [1]. They are β-carboline alkaloids and show anti-viral activity against HSV-1. Eudistomins are classified into two groups from their structures. The first one is the tetrahydro-β-carboline fused with a oxathiazepine (Scheme 1). Another

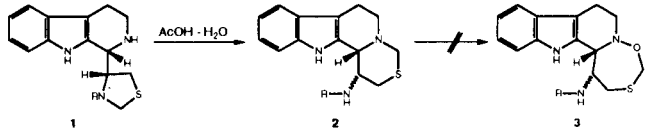


	X	Y	Z	R
Eudistomin	H	H	H	H
Eudistomin L	H	Br	H	H
Eudistomin K	H	H	Br	H
Eudistomin C	H	OH	Br	H
Eudistomin E	Br	OH	H	H
Eudistomin F	H	OH	Br	$C_2H_3O_2$

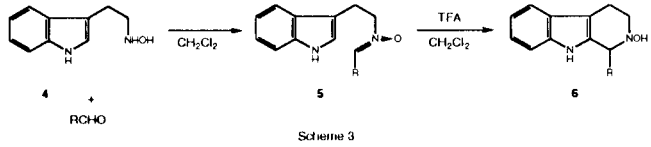
Scheme 1

one is the aromatic β-carboline having a substituent at the 1-position. We have synthesized both types of eudistomins, but we will discuss only the former type in this article. This is the first example that the oxathiazepine ring is found in natural products. Furthermore, the absolute configuration of these eudistomins was established as shown in the scheme by their CD spectral data [1] and the X-ray analysis of eudistomine K-oxide [2]. This configuration showed eudistomins may be derived from D-cysteine.

For the total synthesis of these eudistomines constructions of the β-carboline with correct stereochemistry and the oxathiazepine are the major problems. Furthermore, introduction of particular substituents at the benzene ring of β-carboline is laborious work even after the method of construction of the ring system is established. After unsuccessful approaches to the oxathiazepine **3** from thiaindoloquinolizidine **2** obtained by ring transformation of **1** by rearrangement, *via* its *N*-oxide [3] (Scheme 2), we examined the Pictet-Spengler reaction of N_b-hydroxytryptamine with aldehydes which is not so popular, but has a precedent.[4]. N_b-Hydroxytryptamine was prepared by the partial reduction of 3-nitroethylindole with aluminium amalgam or zinc-ammonium chloride. Reaction of N_b-hydroxytryptamine **4** with aldehydes in methylene chloride smoothly gave nitrones **5** which were stable compounds and gave 2-hydroxytetrahydro-β-carbolines **6** on treatmentment with trifluoroacetic acid (Scheme 3) [5].



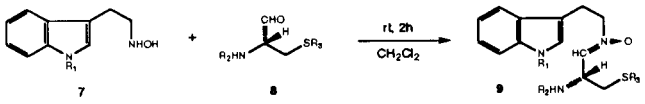
Scheme 2



Scheme 3

The *N*-hydroxytetrahydro-β-carboline is a rather stable compound and a reaction with acetic anhydride gave only an *O*-acetyl derivative. However, 3,4-dihydro-β-carboline was obtained on treatment with trifluoroacetic anhydride in boiling benzene [5]. Further examples of Pictet-Spengler reactions of *N*-hydroxytryptophans were reported by the Ottenheijm group [6] and the Cook group [7].

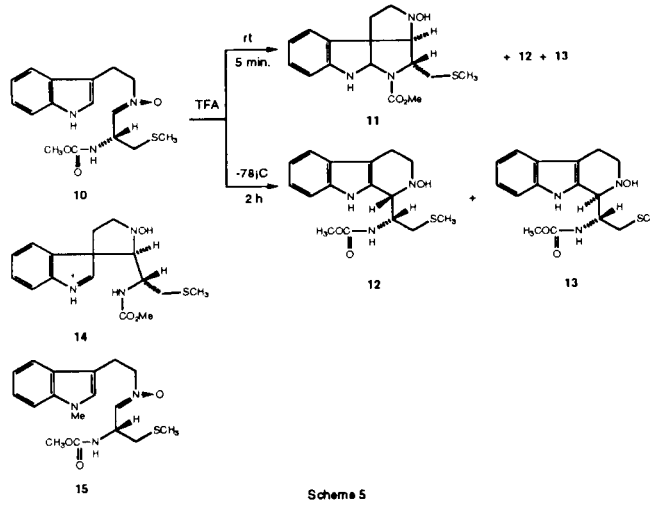
The Pictet-Spengler reaction of N_b-hydroxytryptamine with D-cysteinal will provide a tetrahydro-β-carboline promising precusor for the formation of the oxathiazepine ring. Before using expensive D-cysteinal, we examined the reaction applying L-cysteinal, the inexpensive counterpart. Reduction of L-cysteine esters variously protected at the nitrogen and at the thiol groups with DIBAH at low temperature gave the corresponding cysteinals **8** in moderate yield contaminated with the corresponding alcohol. The cysteinal could be purified on a silica gel column, but resulted in racemization. The reaction of crude cysteinal **8** with *N*-hydroxytryptamine **7** in methylene chloride at room temperature gave the optically active nitrones which were purified by a silica gel column without racemization in good yields. (Scheme 4) [8]. A single isomer of nitrone **9** was obtained in each case. The stereochemistry of these nitrones was established as the *Z*-isomer by X-ray analysis of the nitrone [9].



Entry	9	R_1	R_2	R_3	Yield (%)	$[\alpha]_D$ (i)
1	a	H	COOMe	Me	97.0	+56.9
2	b	H	Troc	Z	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
6	f	H	COOMe	Troc	95.4	+30.0

Scheme 4

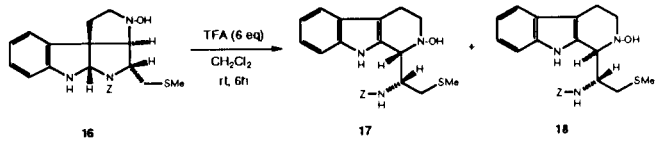
When the nitrone **10** was treated with TFA in methylene chloride at room temperature for 5 minutes the desired β–carboline (1α-H(**13**):1β-H(**12**) = 1:7) to our surprise was obtained in 24% yield (Scheme 5). The major product was the tetracyclic compound **11** probably derived from a spiroindolenine intermediate **14.** Only one isomer was isolated unlike the case of β–carbolines. In contrast, the reaction at -78° gave only β–carboline (1α(**13**):1β(**12**) = 1:41) in 97% yield and stereospecificity was higher than that at room temperature. Furthermore



Scheme 5

the similar reaction of the N_a-methyl derivative **15** gave only the corresponding tetracyclic compounds in excellent yield either at room temperature or at -78°. We have obtained similar results in the reaction of the nitrones in which the nitrogen and the sulfur atom of the cysteinal moiety was protected by various groups [8,9]. In every case the reaction at low temperature (-78°) gave the β-carbolines (the 1-βH isomer was predominant), and both the β-carbolines and tetracyclic compound (major) were obtained in the reaction at room temperature.

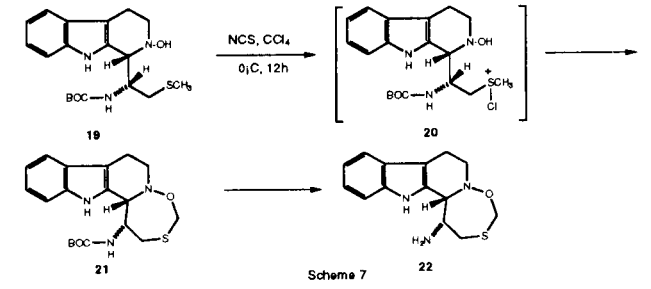
The tetracyclic compound **16** was found to be converted smoothly to the β–carbolines **17** and **18** on treatment with trifluoroacetic acid (6 molar equivalents) in methylene chloride at room temperature (Scheme 6). The fact that the predominant isomer of β–carboline obtained by this transformation was 1-βH isomer **17**, discloses that this conversion was not the simple migration of the C-C bond in the spiroindoleninium intermediate (*cf* **14**), but the formation of the β–carboline from the corresponding nitrone which was obtained by further reversion [8,9].



Scheme 6

Thus we have found two types of products in the Pictet-Spengler reaction and we established the conditions of formation of both compounds. Furthermore, formation of the tetracyclic compounds **11** and **16** was evidence of the presence of the spiroindolenine intermediate in the Pictet-Spengler reaction of *N*-hydroxytryptamine. As the tetracyclic compound can be converted to the β–carboline, both compounds may serve as a candidate for the precursor of the oxathiazepine ring [9].

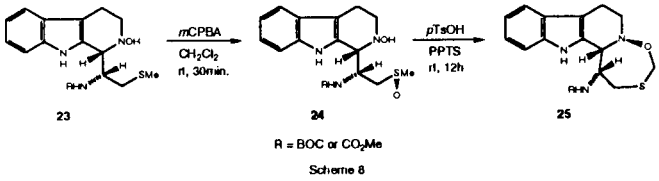
Various attempts to construct the oxathiazepine ring from the tetracyclic compounds having various protective groups at the sulfur atom and the oxygen atoms failed. Furthermore, some trials of the formation of the oxathiazepine ring from the β–carboline which has a free thiol and a free hydroxy group using one carbon equivalent were also unsuccessful. Finally, treatment of the β–carboline **19** having a methylthio group and an hydroxy group with *N*-chlorosuccinimide in carbon tetrachloride at 0°, gave the desired oxathiazepine **21** in low yield (4%) probably *via* the sulfonium chloride **20** (Scheme 7). The formation of oxathiazepine ring **21** was clearly disclosed



Scheme 7

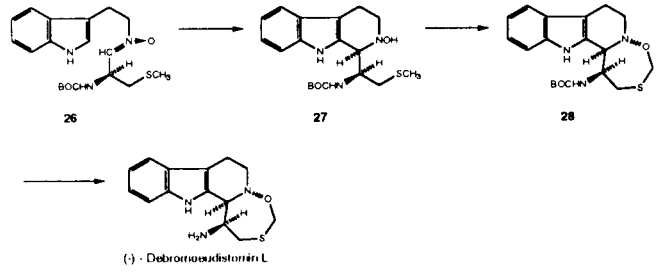
by the presence of a characteristic low field quartet due to the methylene group between the oxygen and the sulfur in the nmr spectrum. Deprotection of the BOC group gave unnatural (+)-debromoeudistomin L **22** whose spectral data were identical with those of the natural product except optical rotation. The yield of the cyclization to the oxathiazepine was improved (10-17%) by using a modified Pummerer reaction of the *S*-oxide **24** using *p*-toluenesulfonic acid-PPTS (Scheme 8) (**23**→**24**→**25**).

Although the yield of the cyclization was not satisfactory, we began the synthesis of the natural products using



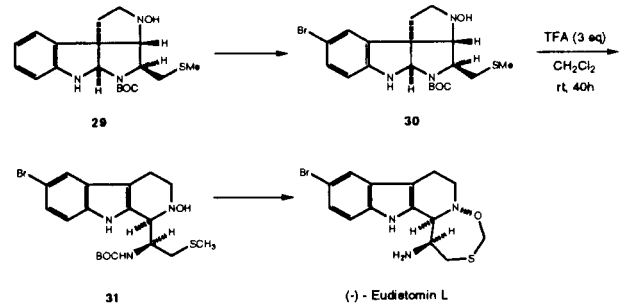
Scheme 8

D-cysteinals (Scheme 9). The reaction of N_b-hydroxytryptamine and *N*-BOC-*S*-methyl-D-cysteinal obtained by the DIBAH reduction of the corresponding ester gave the nitrone **26** in good yield. The cyclization of the nitrone with TFA (5 equivalents) in methylene chloride at -78° smoothly gave the 1-αH-β–carboline **27** in 90% yield along with the 1-βH isomer in 4% yield. Treatment of the β–carboline **27** with NCS-CCl_4 or peracid oxidation and rearrangement with *p*-toluenesulfonic acid-PPTS gave the oxathiazepine **28**. Deprotection and purification of the oxathiazepine **28** afforded (-)-debromoeudistsomine L which was identified by comparison with the natural product including the specific rotation [10].



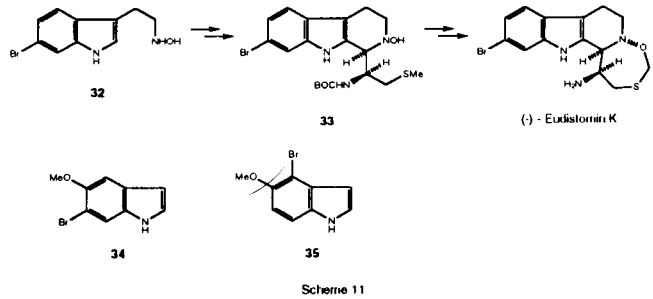
Scheme 9

Other eudistomins having the oxathiazepine ring possess substituents such as a bromine and/or a hydroxy group on the benzene ring. The next problem was how to synthesize these substituted natural products which show stronger anti-viral activity. The first resolution came from our previous work on the cyclic tautomer of tryptamine and tryptophans [11]. The tetracyclic compound **29** obtained by the Pictet-Spengler reaction at room temperature is a derivative of the cyclic tautomer, pyrrolo[2,3-*b*]indole, which is an indoline and not an indole. Therefore the 5-position of the indoline is a reactive position for electrophilic substitution such as bromination (Scheme 10). This tactic may open a way to (-)-eudistomin L from the tetracyclic compound **29**. The protection of the hydroxy group of the tetracyclic compound **29** with acetic anhydride and pyridine, bromination with NBS in acetic acid, and deprotection of the acetoxy group gave the desired brominated compound **30** in 75% yield. The ring transformation of the brominated tetracyclic compound **30** with TFA gave the corresponding β–carboline **31** having correct stereochemistry as the major product (33% yield). Similar treatment with NCS-CCl_4 followed by the deprotection afforded the natural (-)-eudistomin L.



Scheme 10

For the synthesis of eudistomin K possessing a bromine atom at the 6 position of the indole, our previous method [12] might be applied after some modification. However, we chose the ring forming reaction to prepare 6-bromo-3-formylindole from *p*-bromobenzaldehyde. 6-Bromo-*N*-hydroxytryptamine **32** was prepared from the aldehyde and treated with D-cysteinal as above to give the corresponding β-carboline **33** which afforded (-)-eudistomin K (Scheme 11). Furthermore 6-bromo-5-methoxyindole **34** and 4-bromo-5-methoxyindoles **35** were prepared from 3-bromo-4-methoxyaniline and these indoles were derived from the corresponding hydroxytryptamines. These *N*-hydroxytryptamines gave (-)-eudistomin C, E, and F [13].

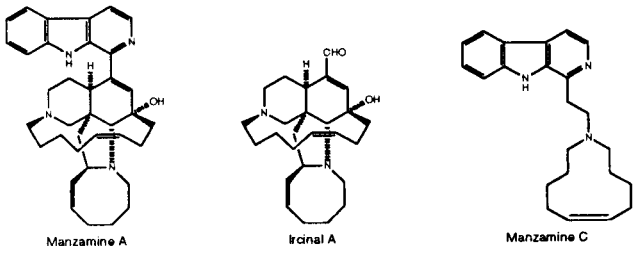


Scheme 11

Thus most of the natural eudistomins having an oxathiazepine ring have been prepared and identified with the natural products (spectral data and specific rotation) These syntheses clearly demonstrated that the natural eudistomin is derived from D-cysteine.

II Manzamines.

Manzamines (A-F) have been isolated from Okinawan sponges by the Higa group and the Kobayashi group [14]. These structures were established by X-ray analysis. (Scheme 12). These manzamines possess an aromatic β–carboline ring and other heterocycles, furthermore they show cytotoxicity against tumor-cells. Recently ircinal A and B which have similar novel azacycles as those of the manzamines but lack the β–carboline ring, have been isolated from similar sponges [15]. Recently hypothetical biogenesis of these manzamines is proposed by Baldwin [16].

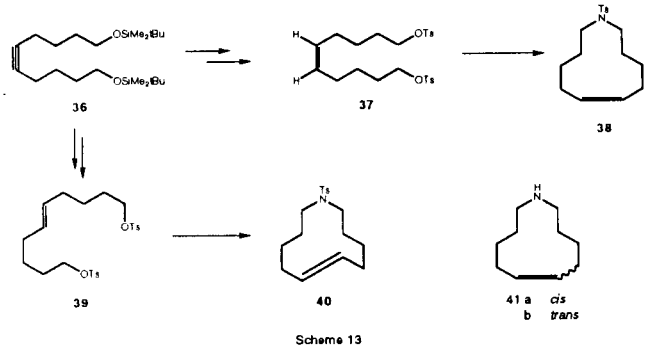


Scheme 12

Our first target for the synthesis of the manzamine family was naturally towards manzamine C, a simple structure with moderate cytotoxicity. Our synthetic plan towards manzamine C was combination of an azacycloundecene and β–carboline-1-acetic acid, by plain retrosynthesis. (*Z*)-6-Azacycloundecene has not been found in natural products previously.

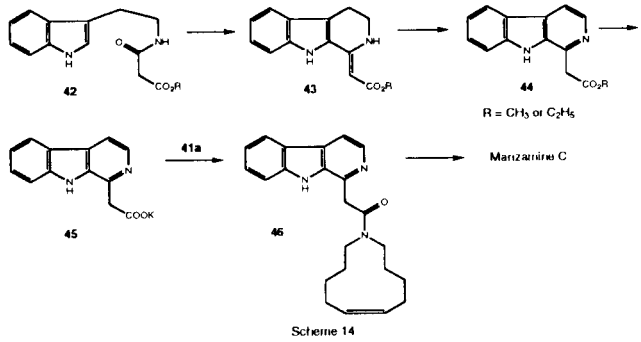
As the (*Z*)-6-azacycloundecene (**41a**) has C_2 symmetry, 5-decyne-1,10-diol **36** was supposed to be an appropriate intermediate. (*Z*)-5-Decene-1,10-diol ditosylate **37** was prepared by a conventional method from *O*-protected 5-decyne-1,10-diol **36** (Scheme 13). Cyclization of the *cis* ditosylate **37** with tosylamide under phase transfer conditions using tetrabutylammonium iodide [17] as the catalyst gave (*Z*)-*N*-tosyl-6-azacycloundecene **38** in 70% yield. A better yield was obtained than that of the saturated example [17] due to the presence of the *cis* double bond.

Lithium aluminium hydride reduction of 5-decyne-1,10-diol gave the (*E*)-5-decene-1,10-diol **39** which afforded (*E*)-6-azacycloundecene **40** by similar reactions as above. Detosylation of the *cis* unsaturated azacycle **38** did occur by Red-Al reduction in refluxing toluene to give (*Z*)-azacycloundecene **41a,** but the reduction with sodium naphthalenide in dimethoxyethane at -78° [18] gave excellent results.



Scheme 13

A similar reduction of the *E*-isomer **40** gave the NH compound in excellent yield. The β-carboline moiety, β-carboline-1-acetic acid, was prepared from tryptamine as follows. Bischler-Napieralsky cyclization of the amide **42** prepared from tryptamine and methyl malonyl chloride, with an excess of phosphorous oxychloride at room temperature, gave the enamine type of dihydro-β–carboline **43.** Aromatization of the dihydro-β-carboline **43** with 10% Pd/C in boiling *p*-cymene smoothly gave desired β–carboline-1-acetate **44** (70% yield). With both components now in our hands, we next examined the condensation of the ester **44** and the amine **41a** in boiling toluene. The desired amide **46** was obtained in 67% yield after 130 hours at reflux. Trimethylaluminium as a catalyst did not improve the yield. We next examined the DPPA method (Scheme 14). Hydrolysis of the acetate **44** with potassium hydroxide followed by the usual work-up to obtain the acid gave harman, a decarboxylated product, and not the 1-acetic acid. Therefore, the potassium salt **45** and (*Z*)-6-azacycloundecene **41a** was condensed using DPPA in dimethylformamide to give the amide **46** in excellent yield. The lithium aluminium hydride reduction of the amide **46** in tetrahydrofuran gave the manzamine C whose spectral data were identical with those of natural product [19].

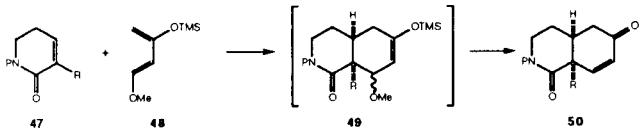


Scheme 14

By similar treatment the *trans* and dihydro isomers of manzamine C were also prepared [19]. Various manzamine C analogues having different azacycles instead of azacycloundecene have been prepared for the evaluation of cytotoxicity.

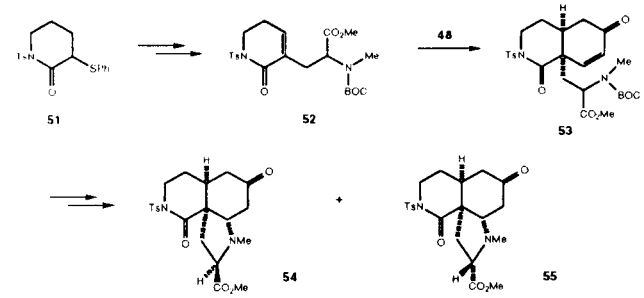
Manzamine A possesses complicated fused azacycles containing 5, 6, 6, 8, and 13 membered rings besides β-carboline. As the ircinal A and B were isolated and they are converted to manzamine A and B [15], targets of the synthesis were focused at the fused azascycles. The central part of these fused azacycles is the pyrrolo[2,3-*i*]isoquinoline moiety which is a polysubstituted *cis*-isoquinoline. Therefore, the Diels-Alder approach was the first choice for the construction of this azacycle.

We have examined Diels-Alder reactions of various dihydropyridinones **47** with the Danishefsky diene **48** to determine the appropriate functional group at the nitrogen atom (Scheme 15). A Diels-Alder reaction of *N*-benzoyl-5,6-dihydro-2-pyridinone (**47**, P = PhCO, R = H) with the



Scheme 15

Danishefsky diene **48** did occur in boiling xylene, while the reaction of the *N*-benzyl or the *N*-BOC derivative did not proceed. However, the reaction of the *N*-benzoyl-3-substituted-2-dihydropyridinone **47** with diene **48** did not occur in boiling xylene [20]. On the other hand, the reaction of *N*-toluenesulfonyl-3-methyl-5,6-dihydro-2-pyridinone (**47**, P = p-Ts, R = CH_3) with diene **48** gave the corresponding adduct in a boiling cymene. These results showed that the *p*-toluenesulfonyl group or its equivalent was a candidate for an activating group in these particular Diels-Alder reactions, and this was supported by LUMO energy calculation by MNDO. The first approach [21] to the pyrrolo[2,3-*i*]isoquinoline ring system started from the Michael reaction of *N*-tosyl-3-phenylthiopiperidone **51** with methyl *N*-methyl-*N*-BOC-aminoacrylate in the presence of base (Scheme 16). Oxidative removal of the phenylthio group in the Michael adduct afforded the desired dienophile **52.** The reaction of the dienophile **52** with the Danishefsky diene **48** in boiling *p*-cymene gave the adduct which gave the enone **53** in 30% yield on



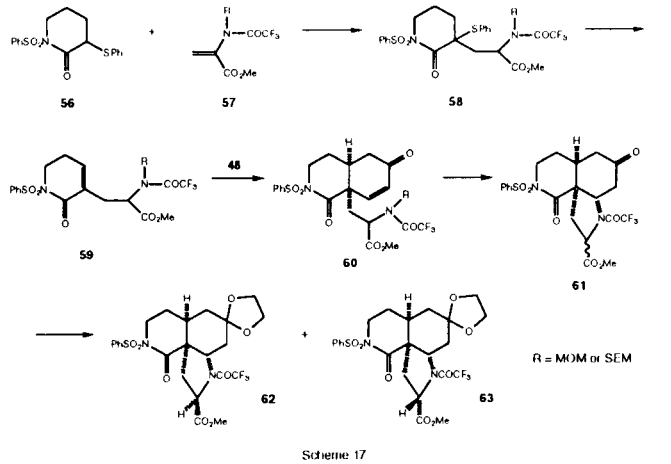
Scheme 16

treatment with camphorsulfonic acid. Much better results were obtained by the reaction under super high pressure conditions (11 Kb) in toluene at ambient temperature for 90 hours. The enone **53** gave a mixture of diastereomers of pyrrolo[2,3-*i*]isoquinoline **54**, **55** on treatment with TFA (removal of BOC group) and potassium carbonate (cyclization) in 60% yield from the dienophile **52**. These diastereomers were separated and their stereochemistry was confirmed as shown in the scheme by X-ray analysis of the 2-β–H isomer **55** [22].

Extension of this tricyclic pyrrolo[2,3-*i*]isoquinoline **54** to a tetracyclic compound by the formation of the 8-membered ring or the 13-membered ring met with some difficulties. The amide carbonyl group in *N*-tosyllactam was found to be susceptable to attack by a nucleophile or a base, and this makes the reaction conditions limited to further elaborations. Removal of the *N*-methyl group in the tricyclic compound was found to be difficult. Therefore we sought to find a better dienophile for the tricyclic compound with appropriate protective groups for further elaborations.

The Michael reaction of *N*-benzenesulfonyl-3-phenylthio-2-piperidone **56** with methyl *N*-MOM (or SEM)-*N*-trifluoroacetylacrylate **57** using potassium bis-(trimethylsilyl)amide as a catalyst at low temperature gave the adduct **58** in quantitative yield (Scheme 17) [23]. This result was much better than that of the reaction with methyl *N*-methyl-*N*-BOC-aminoacrylate. The adduct gave the corresponding dienophile **59** on peracid oxidation. Diels-Alder reaction of this dienophile with the Danishefsky diene **48** proceeded smoothly to give **60** in boiling *p*-cymene, not like the previous case, and not requiring super high pressure. After the usual work-up with acid and removal of the MOM or the SEM group, the Diels-Alder adduct gave the tricyclic compounds **61** as a mixture of diastereomers in good yield. Each of the diastereomers **62**, **63** could be separated after the ketalization and the stereochemistry was determined from the nmr spectra.

To construct the eight membered ring on the tricyclic compound **62,** we removed the benzenesulfonyl group on the nitrogen atom in **62** by sodium anthracenide in dimethoxyethane at -65° (Scheme 18). Reduction of the NH compound **64** with lithium borohydride-trimethyl

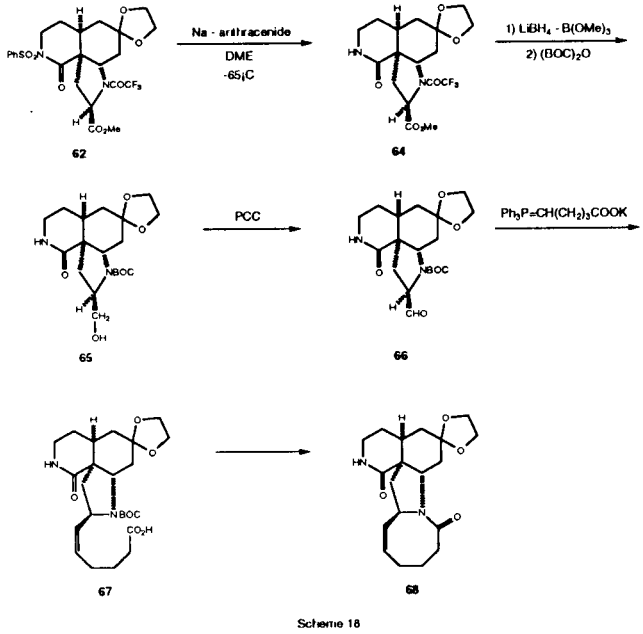


Scheme 17

borate removed the trifluoroacetyl group and gave the primary alcohol **65.** PCC oxidation of the primary alcohol **65** gave the aldehyde **66**. The Wittig reaction of the aldehyde **66** with the ylid gave the carboxylic acid **67** in which the *cis* and *trans* double bonds are present in a ratio of 5:2. Purification of its pentafluorophenol ester gave the *cis* isomer. The *cis* ester was warmed at 80° in dioxan in the presence of 4-dimethylaminopyridine after

removal of the BOC group to give the desired 8-membered lactam **68** in good yield. The structure of the tetracyclic compound **68** was confirmed by nmr spectra and X-ray analysis [24].

In this article we described our results on the synthesis of eudistomins and manzamines [25, 26].



Scheme 18

Acknowledgements.

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