PICTET–SPENGLER REACTIONS OF *Nb*-HYDROXY-TRYPTAMINES AND THEIR APPLICATION TO THE SYNTHESIS OF EUDISTOMINS †

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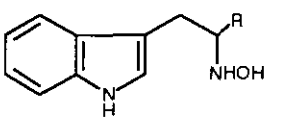
Abstract — Methods for preparing *Nb*-hydroxytryptamines, their Pictet–Spengler reactions with various aldehydes *via* nitrones, and their asymmetric inductions are reviewed. Syntheses of oxathiazepine-containing eudistomins and related natural products which incorporate these reactions are also reviewed.

Contents :

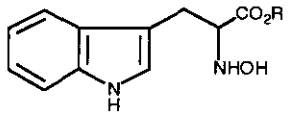
I Introduction

† This review is dedicated to Dr. Bernhard Witkop on the occasion of his 80 th birthday.

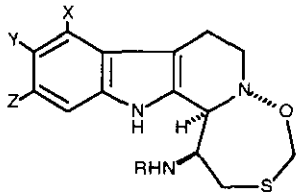
Until recently, *Nb*-hydroxytryptamines and -tryptophans were not as popular as their parent tryptamines and tryptophans, although the former compounds were proposed as intermediates in the metabolism of tryptophan to its dehydroamino acid and indoleacetic acid.[1] However, these compounds have attracted attention of synthetic organic chemists since the isolation of β-carboline alkaloids, eudistomins, from marine tunicates as potential antivirus agents in 1984.[2] The Pictet–Spengler(P–S) reaction of these hydroxytryptamines not only gave 2-hydroxytetrahydro–β–carbolines, which represent the eudistomin skeleton, but also reveal variations of P–S reactions with regard to reactivity and stereochemistry. (Scheme1) In this report, we survey the P–S and related reactions of *Nb*-hydroxytryptamines and the synthesis of oxathiazepine-containing eudistomins and other natural products by these reactions.



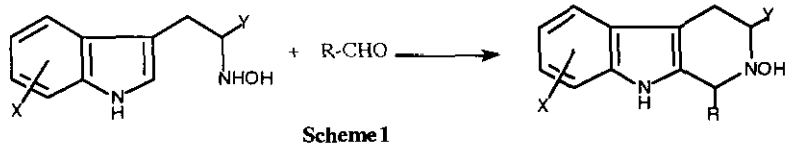
N-hydroxytryptamines



N-hydroxytryptophans



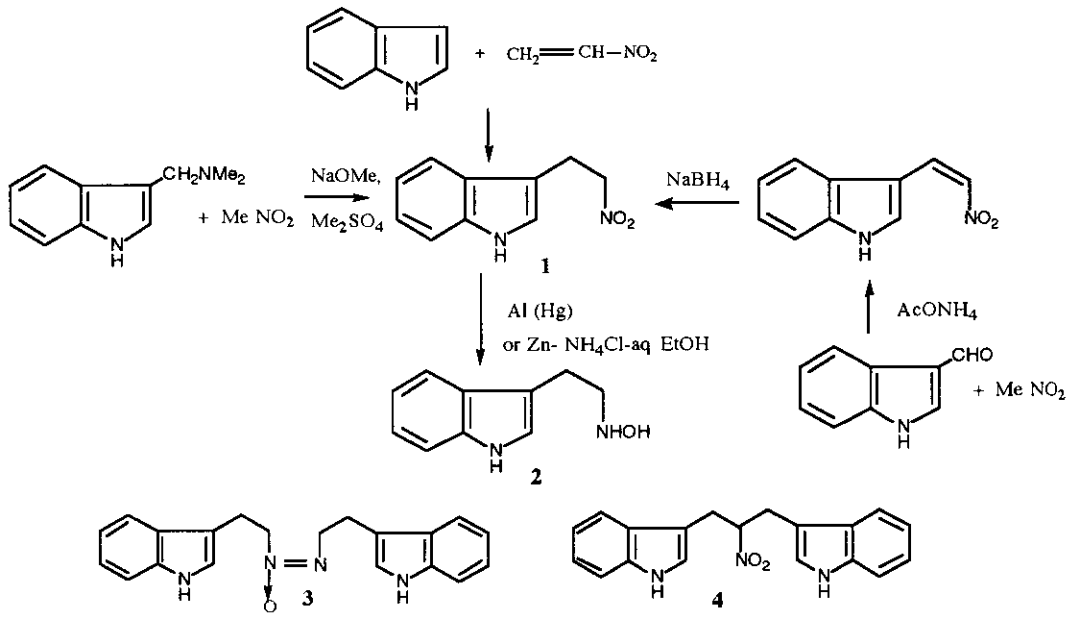
eudistomins	X	Y	Z	R
	H	H	H	H
L	H	Br	H	H
K	H	H	Br	H
C	H	OH	Br	H
E	Br	OH	H	H
F	H	OH	Br	$C_2H_3O_2$



Scheme1

II. Preparation of *Nb*-hydroxytryptamines

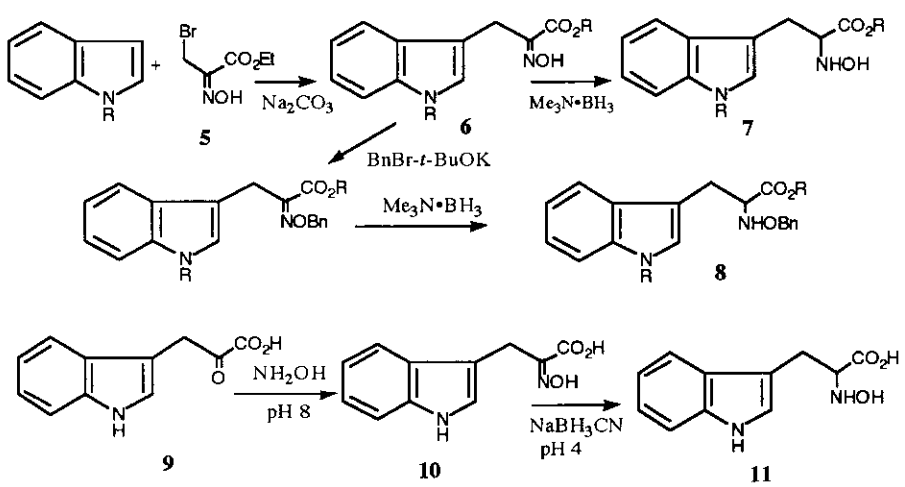
Nb-Hydroxytryptamine(**2**) was prepared by the partial reduction of 3-nitroethylindole(**1**) with zinc–ammonium chloride[3a] or aluminum amalgam.[3b] Although the azoxy compound(**3**), which was previously assigned to the oxime of 3-indolylacetaldehyde,[3a] was isolated as a by-product in the former method[4] and the latter method usually gave a better yield, the former method was preferred due to limitations of the use of mercury. The nitroethylindole(**1**) has been obtained by three different methods. The first is the Michael addition of nitroethylene to indole,[5] although preparation of nitroethylene is troublesome. The second method is condensation of gramine with nitromethane *via* 3-methyleneindolenine. [6] A by-product(**4**) was isolated when nitromethane was not used in large excess.[6b,c] Similar reactions with nitroalkanes gave corresponding α-substituted nitroethylindoles.[7] The third method is partial reduction[8a] of the double bond in 3-nitroethyleneindole obtained by condensation of nitromethane with 3-formylindole [8b] (Scheme 2). Several substituted *Nb*-hydroxytryptamines were also prepared from benzene-substituted indoles and nitroalkanes in alkaloid synthesis using the above methods (*vide infra*).



Scheme2

The resulting *Nb*-hydroxytryptamines could be purified by recrystallization from benzene, but were not stable enough to be purified by a chromatography. They gradually changed to the azoxy compound(**3**) during a column chromatography or left solution under atmospheric conditions. [4]

Syntheses of *Nb*-hydroxytryptophan derivatives have been reported mostly by Ottenheijm, Hermkens and coworkers.[8] They prepared **7** and **8** by the partial reduction of ethyl 3-(3-indolyl)pyruvate oximes(**6**), which were prepared by Michael addition of indoles to ethyl 3-bromopyruvate oxime(**5**), with trimethylamine–borane complex. The similar Michael addition of 3-methylthio or 3-ethylthioindoles has also been reported. [8b]



Scheme3

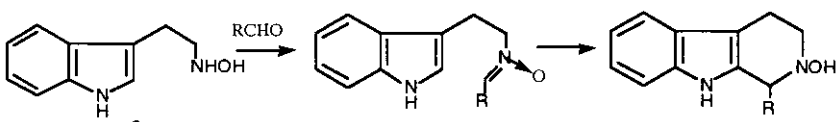
The free amino acid(**11**) was prepared by oximation and subsequent reduction with sodium borocyanohydride of 3-indolepyruvic acid(**9**) while controlling the pH.[9]

III. Pictet–Spengler reactions of *Nb*-hydroxytryptamines with simple aldehydes

Soon after the structure of eudistomins was reported, Cava and his group reported the first P–S reaction of *Nb*-hydroxytryptamine to form *Nb*-hydroxytetrahydro–β–carbolines(**13**).[3b] The reaction of *Nb*-hydroxytryptamine(**2**) with various simple aliphatic and aromatic aldehydes in MeOH–AcOH in a refrigerator gave the nitrones(**12**), but not the β-carboline, in good yields. On the other hand, the reaction with refluxing in MeOH–HCl for 34 h gave the desired *Nb*-hydroxytetrahydro–β–carbolines(**13**) in excellent yields. We later examined similar reactions as model reactions towards the synthesis of eudistomins.[4] Reactions of *Nb*-hydroxytrypamine(**2**) with various saturated and unsaturated aldehydes in dichloromethane gave the corresponding nitrones(**12**) in excellent yields, while the addition of a trace amount of TFA is required for unsaturated aldehydes. These nitrones(**12**) were readily converted to *Nb*-hydroxytetrahydro–β–carbolines(**13**) with TFA in dichloromethane, while unsaturated nitrones required a slighly more vigorous conditions to form β-carbolines(**13**). The direct formation of *Nb*-hydroxytetrahydro–β–carbolines(**13**) by the reaction of hydroxytryptamine(**2**) with aldehydes in dichloromethane–TFA is also possible under conditions milder than those described by Cava. However, this direct reaction with unsaturated aldehydes gave a poor yield of the *Nb*-hydroxy–β–carblines(**13**) . The two-step reaction to form β-carbolines is preferable in these cases.[4] These results are summarized in Tables 1 and 2.

These results show that the P–S reaction of *Nb*-hydroxytryptamine with aldehydes proceeds more readily than that of tryptamines. The reaction with unsaturated aldehydes is characteristically successful, while that with tryptamine fails. An important point in this reaction is the formation of stable nitrone intermediates(**12**), which are prepared under mild conditions and can be purified easily. This point is important for labile *Nb*-hydroxytryptamines. The nitrone prepared from labile *Nb*-hydroxytryptamine with aldehyde can be purified before cyclization.[4]

Table 1 Pictet–Spengler reactions of *Nb*-hydroxytryptamine(**2**) with simple aldehydes *via* nitrones (**12**)



2 **12** **13**

2 + RCHO R	condition	yield % (**12**)	condition of ring closure of **12**	yield % (**13**)	ref.
Me-	MeOH-AcOH 12 h *	100			3b
Et-	"	72			"
n-Pr-	"	76			"
p-MeO-Ph-	"	90			"
p-Cl-Ph-	"	89			"
o-Br-Ph-	"	69			"

Ph-	benzene reflux 2 h	90	TFA-CH_2Cl_2 rt, 2 h	83	4
Me_2CHCH_2-	CH_2Cl_2 rt, 1 min	90	TFA-CH_2Cl_2 rt, 10 min	88	"
$Me(CH_2)_4$-	CH_2Cl_2 rt, 1 min	84	TFA-CH_2Cl_2 rt, 15 min	92	"
Me_2C=CH-	CH_2Cl_2 rt +TFA, 20 min	79	TFA-CH_2Cl_2, reflux, 6 h	63	"
PhCH=CH-	CH_2Cl_2 rt +TFA, 1 h	59	TFA-CH_2Cl_2, reflux, 6.5 h	64	"
2-pyrrolyl-	CH_2Cl_2 +TFA, reflux 1.5 h	93	TFA rt, 3 h	89	"

* in a refrigerator

Table 2 Pictet–Spengler reactions of *Nb*-hydroxytryptamine(**2**) with aldehydes

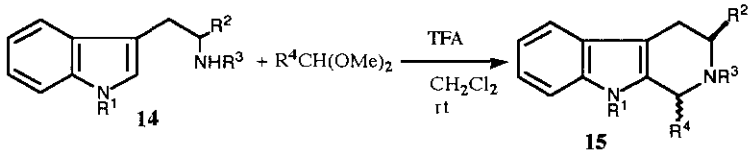
2 + RCHO	conditions for cyclization	yield % of **13**	ref.
Me-	MeOH-HCl reflux, 34 h	60	3b
Et-	"	72	"
n-Pr-	"	66	"
p-MeO-Ph-	"	90	"
p-Cl-Ph-	"	79	"
o-Br-Ph-	"	90	"
Ph	CH_2Cl_2-TFA(3 equiv.), rt, 1.5 h	91	4
Me_2CHCH_2-	CH_2Cl_2-TFA(3 equiv.), rt, 20 min	89	"
$Me(CH_2)_4$	CH_2Cl_2-TFA(3 equiv.), rt, 30 min	80	"
Me_2CH=CH-	CH_2Cl_2-TFA(3 equiv.), rt, 3 h	23	"
PhCH=CH-	CH_2Cl_2-TFA(3 equiv.), reflux, 5.5 h	27	"

Another characteristic of the P–S reaction of *Nb*-hydroxytryptamines is that the Z-isomer of the nitrone is stable, while the isomers of the imine are interconvertible.

The P–S reaction of *Nb*-hydroxytryptophan raises new problems. The stereoselectivity of 1,3-stereoisomers and the rate of the reaction are interesting when they are compared with those in normal P–S reactions of tryptophan ester. Ottenheijm and his group examined the P–S reaction of *Nb*-hydroxytryptophan with acetaldehyde and benzaldehyde dimethyl acetals.[10] They reported that the reaction gave more 1,3-*cis* isomer than that of *Nb*-benzyltryptophan esters.[11] Following this report Cook and his group reported the stereoselectivity and ease of the P–S reaction of *Nb*-substituted tryptophans under similar conditions.[12] These results are summarized in Table 3. The P–S reaction of the *Nb*-hydroxytryptophan proceeded more rapidly than that of *Nb*-alkyl derivatives (entries 1–6 and 7–10), perhaps due to the formation of stronger electrophilic immonium intermediates from hydroxylamine with lower pKa values than those from aliphatic amine.[12] The 1,3-*trans* stereoselectivity in the P–S reaction of *Nb*-alkyl-**14** with acetaldehyde acetal increased from 25 to 84% in the order *Nb*-H< Me <Bn < phenethyl, while that in the reaction of *Nb*-alkoxy **14** increased from 25 to 50% in the order *Nb*-H< *Nb*-OH < *Nb*-OBn. Thus, less dramatic increase was observed in the *Nb*-alkoxy series. The *cis* selectivity is greater for *Nb*-OBn

(entry 9) than for *Nb*-phenetyl (entry 4) derivatives, although these substituents are isosterers each other. Trans selectivity increased along with the size of the substituent at the *Nb*-position, but the oxygen atom also has an electronic contribution. This gives similar *cis* and *trans* selectivity in the reactions of *Nb*-hydroxy and *Nb*-methyl derivatives (entries 2 and 7). Increasing the steric effect by *Na*-methylation in the P–S reaction resulted in formation of more 1,3-*trans* isomers (entries 2 and 6).

Table 3 Pictet–Spengler reaction of tryptophans and their *Nb*-hydroxy derivatives (**14**) with acetals.

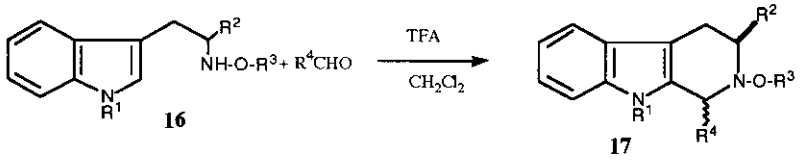


14 **15**

	14			$R^4CH(OMe)_2$		**15**	**15**	
entry	R^1	R^2	R^3	R^4	reaction time	total yield %	1,3 *cis* : *trans* ratio	ref.
1	H	CO_2Me	H	Me	48 h		75 : 25	12
2	"	"	Me	Me	24 h		66 : 34	"
3	"	"	Bn	Me	72 h		16 : 84	"
4	"	"	CH_2CH_2Ph	Me	168 h		16 : 84	"
5	"	"	Bn	Ph	48 h		0 : 100	"
6	Me	"	Me	Me	288 h		16 : 84	"
7	H	CO_2Et	OH	Me	3 h	95	67 : 33	10,12
8	"	"	OH	Ph	6 h	77	40 : 60	"
9	"	"	OBn	Me	3 h	96	50 :50	"
10	"	"	OH	H	3 h	91	-	8c

Table 4 summarizes the effects of aldehydes (R^4), and the substituents at the α-(R^2), *Na*- (R^1), and *Nb*-positions (R^3) in the P–S reaction of *Nb*-hydroxytryptophans(**16**) with aldehydes.[6b] Reactions with aliphatic aldehydes gave the 1,3-*cis* isomer as the major isomer, while those with benzaldehyde gave the *trans* isomer as the major isomer (entries 1–5). However, some deviations were observed in reactions with thienyl aldehyde and 3,4,5-trimethoxybenzaldehyde (entries 6 and 7). The 1,3-stereoselectivity of the reaction was not affected by replacing the ester group(R^2) with a methyl or a phenyl group (entries 8–13), except that *cis* preference was observed in entry 12. The reactions of *Nb*-alkoxytryptophans gave higher proportins of 1,3-trans isomers than those of *Nb*-hydroxy derivatives (entries 16–22 with 1 and 5), which supports the presence of steric hindrance during the P–S reaction. A substituent at the *Na* position increased 1,3-*trans* selectivity (entry 14), while the reaction did not proceed with the *Na*-Boc derivative(entry 15).

Table 4 Pictet–Spengler reactions of *Nb*-hydroxytryptophans (**16**) with various aldehydes.



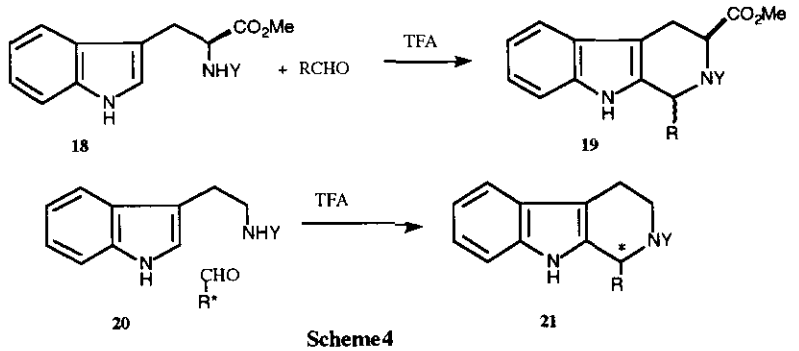
16 **17**

entry	16 R^1	16 R^2	16 R^3	R^4CHO R^4	condition °C, time	17 total yield%	17 1,3-*cis*: *trans* ratio	ds *3
				1. The effect of the structure(R^4) of aldehydes				
1	H	CO_2Et	H	Me	25°C, 5 h	98	70:30	40
2	"	"	"	n-Pr	" 2 d	98	60:40	20
3	"	"	"	Bn	" 2 d	98	58:42	16
4	"	"	"	*1	" 1 h	99	71:29	42
5	"	"	"	Ph	" 3 h	85	43:57	-14
6	"	"	"	2-thienyl	" 2 d	79	58:42	16
7	"	"	"	*2	" 4 d	76	50:50	0
				2. The effect of the substituents (R^2) at α-position and R^4				
8	H	Ph	H	Me	25°C, 2 h	94	70:30	40
9	"	Me	"	"	" 12 h	87	86:14	72
10	"	H	"	"	" 24 h	83	-	-
11	"	Ph	"	Ph	" 3 h	91	45:55	-10
12	"	Me	"	Ph	40°C, 24 h	97	63:37	26
13	"	Me	"	*2	" 24 h	97	66:34	32
				3. The effect of the substituent (R^1) at the *Na*-position				
14	Me	CONH-Me	H	Ph	25°C,3h	95	0:100	-100
15	BOC	Me	"	"	competition between deprotection and condensation			
				4. The effect of the *Nb*-alkoxy group (R^3)				
16	H	CO_2Et	Me	Me	25°C,1 h	95	47:53	-6
17	"	"	Bn	"	" 3 h	96	50:50	0
18	"	"	i-Pr	"	" 1 h	80	42:58	-16
19	"	"	n-Bu	"	" 1 h	87	43:57	-14
20	"	"	Me	Ph	" 1 h	97	18:82	-64
21	"	"	i-Pr	"	" 1 h	96	21:79	-58
22	"	"	n-Bu	"	" 1 h	93	25:75	-50

*1 : CH_2CH_2SAc *2 : 3,4,5-trimethoxyphenyl- *3 : diastereoselectivity (*cis-trans*/ *cis* + *trans*)

IV. Asymmetric P–S reactions of *Nb*-hydroxytryptamines

Optically active 1-substituted tetrahydro–β–carbolines (**19** and **21**) have generally been prepared by the P–S reaction of optically active tryptophan derivatives (**18**) with aldehydes and the P–S reaction of tryptamines (**20**) with chiral aldehydes.[11] (Scheme 4)

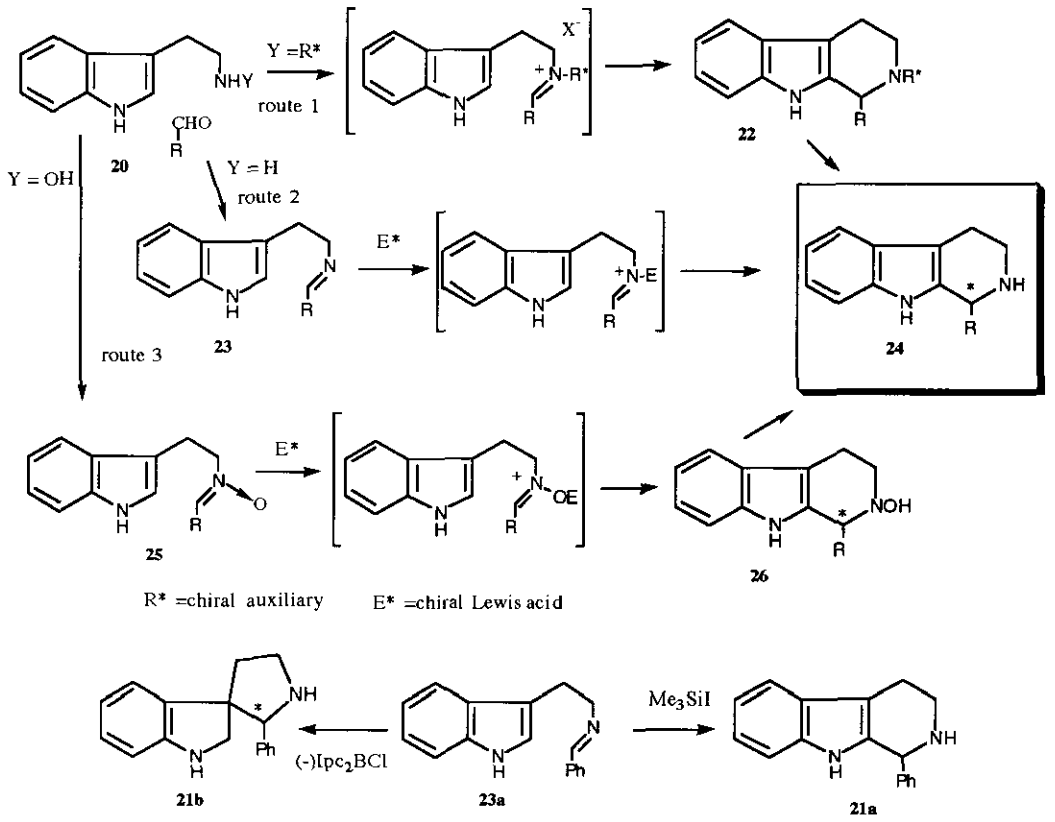


Scheme4

The reaction of *Nb*-hydroxytryptamine with optically active cysteinals will be discussed later.

Other asymmetric P–S reactions of tryptamine to form optically active 1-substituted tetrahydro–β–carbolines(**24**) are shown in Scheme 5.

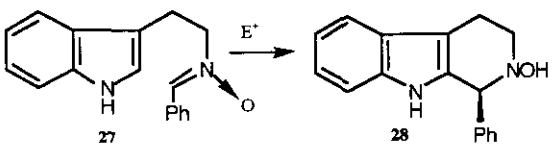
Route 1 is the P–S reaction of a tryptamine with a chiral auxiliary at the *Nb* position. Waldman,[13] Cook, [14] and we[15] have reported several examples using *Nb*-substituted tryptamines.



Scheme 5 Asymmetric Pictet-Spengler Reaction

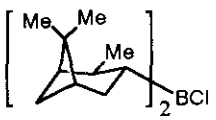
Route 2 is the P–S reaction of imines(**23**) with a chiral Lewis acid(E*). Although many mineral and organic acids are used as catalysts in the P–S reaction, there is little information available regarding the use of a Lewis acid. We found that the P–S reaction of the imine(**23a**) prepared from tryptamine and benzaldehyde with trimethylsilyl iodide-pyridine or bromodimethylborane gave the corresponding 1-phenyltetrahydro–β–carboline(**21a**) in excellent yield.[16] Therefore, we examined (–)Ipc2BCl, a known reducing agent, as a chiral Lewis acid. Optically active 3,3-spiroindoline derivatives(**21b**) were obtained, probably by reduction of the 3,3-spiroindolenine intermediate. The desired β-carboline(**21a**) was isolated in poor yield (2%) as a racemate.[16] We prepared chiral 2,5-dimethylborolane chloride and examined the reaction. The reaction proceeded to give β-carboline(**21a**), but the optical purity of the product was poor.[17]

Table 5 Asymmetric cyclization of the nitrone (**27**) with diisocamphenylborane derivatives (Ipc_2BX)

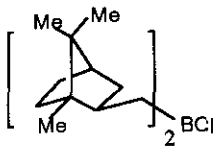


27 **28**

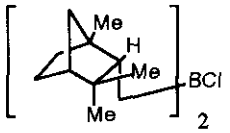
entry	E	solvent	temp °C	react time	**28** yield %	ee %	abs conf
1	(+)Ipc_2BCl	CH_2Cl_2	rt	2 h	97	25	S
2	"	"	0	1 h	97	48	"
3	"	"	-20	1 h	97	58	"
4	"	"	-78	6 h	92	75	"
5	"	"	-98	12 h	31	87	"
			enantiomer				
6	(–)-Ipc_2BCl	"	-78	3.5 h	94	83	R
			effect of solvent				
7	(+)Ipc_2BCl	Et_2O	-78	6 h	17	72	S
8	"	THF	"	48 h	61	79	"
9	"	toluene	"	9 h	44	74	"
			effect of halogen				
10	(+)Ipc_2BBr	CH_2Cl_2	"	24 h	69	67	"
11	(+)Ipc_2BOTf	"	"	28 h	78	55	"
			other terpenes				
12	**29**	"	"	2 h	98	3	S
13	**30**	"	"	1 h	95	4	R



Ipc_2BCl



29



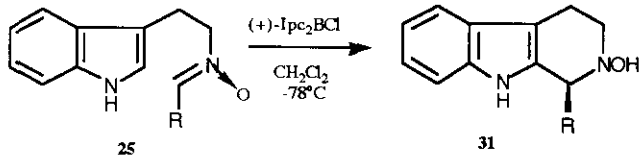
30

However, the situation is different in the case of the nitrone(**25**), since it may remain in the stable Z-form and is more chemically stable than the imines. A chiral Lewis acid may give optically active β–carboline (**26**), which is a precursor to **24**. (Route 3 in Scheme 5)

We examined the P–S reaction of the nitrone(**27**) prepared from benzaldehyde and *Nb*-hydroxytryptamine with (+)-Ipc_2BCl in dichloromethane at room temperature.[18] The reaction proceeded smoothly to give 1(*S*)-phenyl-2-hydroxytetrahydro–β–carboline(**28**) in excellent yield, but with low enantioselectivity. When the temperature was lowered to –78°C, the ee increased to 75%, which is currently the best result ; at -98°C, although the ee % of the reaction increased to 87%, the chemical yield dropped to 31%. Under similar conditions, enantiomeric (–)-Ipc_2BCl gave the (*R*)–β–carboline. The enantioselectivity of the

reaction did not improve when the solvent was changed to ether or toluene and the halogen in the reagent was changed to bromine or a tosyloxy group. (Table 5) We made two new chiral boron reagents (**29**, **30**) from (+)-camphor and (+)-fenchone. The reactions using these reagents proceeded smoothly, but the ee was poor.[19]

Table 6 Asymmetric cyclization of nitrones (**25**)



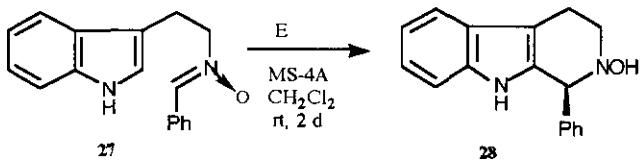
25 **31**

entry	**25** R	react time	**31** yield %	ee % (*S*)
1	Ph	6 h	92	75
2	*p*-MeO-Ph	3 h	65	90
3	*p*-NO_2-Ph	1 h	81	0.6
4	1-naphthyl	1 h	94	86
5	Me	3 h	91	43
6	*i*-Bu	4 h	75	35

The reaction was extended to other nitrones(**25**) prepared from various aldehydes.[18] The reactions of nitrones(**25**) prepared from 4-methoxybenzaldehyde or 1-naphthaldehyde under similar conditions gave good results, while those of nitrones(**25**) prepared from 4-nitrobenzaldehyde or aliphatic aldehydes showed poor results.[19] (Table 6) Both steric and electronic effects played important roles in these reactions, but the details are not clear.

We also used boron reagents derived from binaphthol derivatives. Three (*S*)-binaphthols(**32 a, b, c**) were prepared from dialkoxyboron fluoride by the known method[20] and applied to the P–S reaction of the nitrone(**27**). The reaction proceeded slowly even at room temperature and the chemical yield and ee were poor.(Table 7) Yamamoto and his coworkers introduced Brønsted acid-assisted chiral Lewis acids derived from the binaphthol as catalysts for asymmetric Diels–Alder reaction and alkylations of imines and reported excellent results.[21]

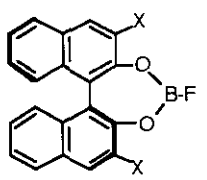
Table 7 Asymmetric cyclization of nitrone (**27**) with chiral binaphthols



27 **28**

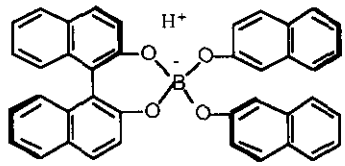
entry	reagent (2.0 mol) E	condition	chem yield **28** %	ee %
1	**32a**	rt, 2 d	42	64 (*R*)
2	**32b**	"	22	4 (*S*)

3	**32c**	"	70	2 (*S*)
4	**33**	"	81	73 (*S*)
5	**34**	"	82	77 (*R*)

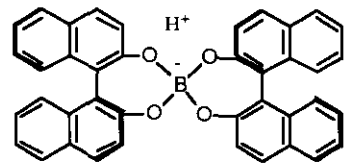


32

a : X = H ; **b**: X = Br ; **c** : X = Cl



33 : (*R*)-form



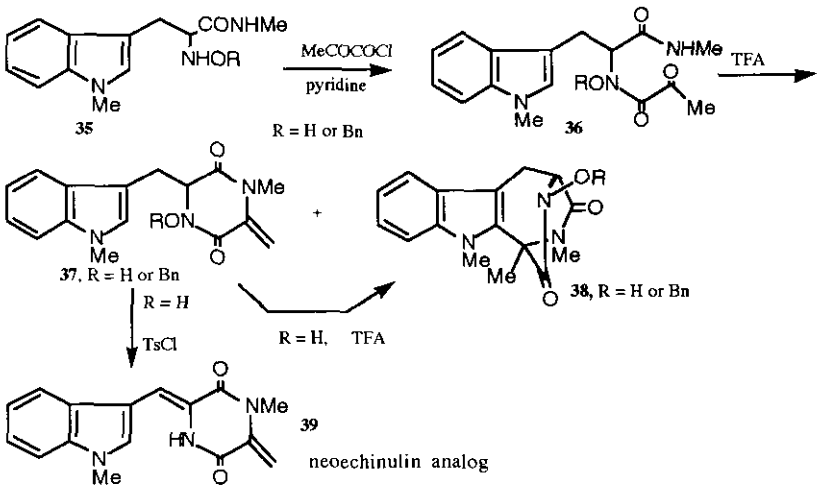
34 : (*S*)-form

We examined the P–S reaction with these Lewis acids(**33**,**34**). The reaction proceeded slowly, but gave better selectivity than those of alkoxyborane fluorides, although the results are not yet satisfactory.[19] (Table 7) Interestingly, the P–S reaction of benzylidenetryptamine(**23a**) with these reagents (**32a**,**33**) gave poor results.[19] Thus, although problems in the enantioselective P–S reaction of nitrones remain to be solved to achieve a high ee, better results were obtained than with imines, which is a characteristic feature of nitrones. Removal of the 2-hydroxy group in **28** to give optically active 1-phenyltetrahydro-β-carboline (**21a**) with Zn–MeOH–NH_3 (reflux) or $TiCl_3$–MeOH (at 0°C) proceeded smoothly and was accompanied by a slight racemization.[19]

V. Application of the P–S reaction of *Nb*-hydroxytrypamines to the synthesis of natural products

V–1. Synthesis of neoechinulin analog

As described earlier, *Nb*-hydroxytryptophan was believed to be an intermediate to α,β-dehydrotryptophan in biological systems. Ottenheijm's group[8a] showed biomimetic approaches to neoechinulin analogs from



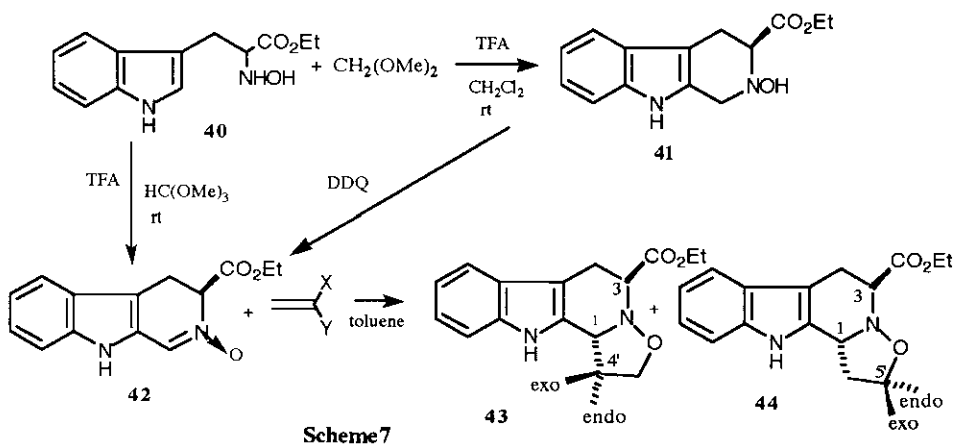
Scheme6

Nb-hydroxytryptophans. Selective acylation of hydroxytryptophan amide(**35**) with pyruvic acid chloride-

pyridine gave *Nb*-acylated compound(**36**), while acylation in the presence of triethylamine gave the *O,Nb*-diacyl derivative. Cyclization of **36** (R = H or Bn) with TFA gave the *Nb*-hydroxy-diketopiperazine(**37**, R =H or Bn) and **38** (R =H or Bn). Compound (**37**)(R =H) gave **38** (R = H) upon treatment with TFA. Dehydration of **37**(R =H) with tosyl chloride gave neoechinulin analog(**39**). [8a]

V-2. Synthesis of verruculogen TR-2 and fumitremorgin C[22]—1,3-Dipolar cycloadditions of nitrones derived from *Nb*-hydroxytryptophanes

The P–S reaction of racemic *Nb*-hydroxytryptophan ester(**40**) with formaldehyde dimethylacetal in the prfesence of TFA gave the corresponding *Nb*-hydroxytetrahydro–β–carboline(**41**), which in turn gave the nitrone(**42**) by oxidation with DDQ. The same nitrone(**42**) was readily obtained by the Bischler–Napieralski reaction of **40** with an orthoformate in the presence of TFA.[8c] The nitrone (**42**) gave fused isoxazolo-carbolines (**43**,**44**) by 1,3-dipolar cycloaddition with various alkenes, as shown in Scheme 7 and Table 8. The 5'-isoxazolo derivatives (**44**) were obtained as the sole product with electron-rich alkenes (entries 1 and 2), while the 4'-isoxazolo derivative (**43**) was obtained as the major product in the reaction with an electron-deficient alkene(entry 4). The stereochemistry at the 1- and 3-positions was always *trans* because the alkenes could approach the nitrone from the bottom of the ester group.[8c]

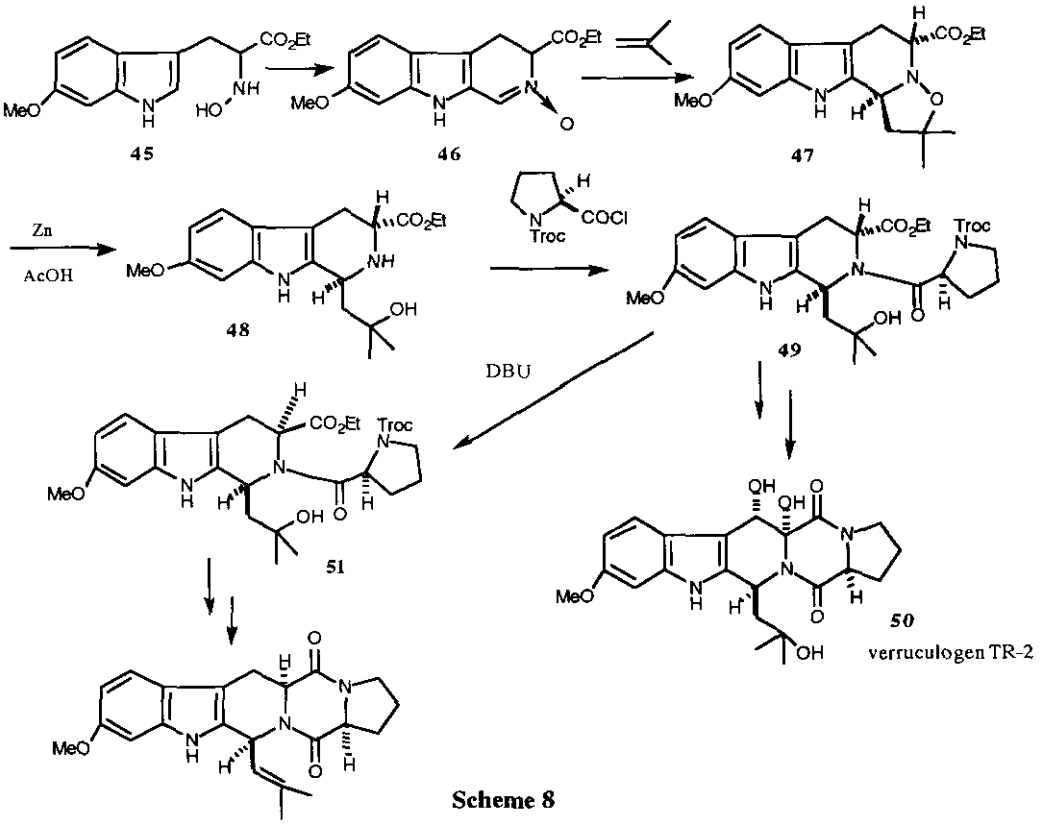


Scheme7

Table 8 1,3-Dipolar cycloaddition of the nitrone (**42**) with alkenes

entry	alkenes X	alkenes Y	reaction condition	**43**+**44** total yield %	**43** endo:exo ratio	**44** endo : exo ratio
1	Me	Me	120°C, 4 h, 9 bar	100		100
2	H	CH_2CO_2H	80°C, 24 h	80		100(exo)
3	H	Ph	110°C, 1.5 h	85	3(exo), 10(endo)	85(exo), 2(endo)
4	H	CO_2Me	+MeOH, rt, 5 h	93	12(exo), 52(endo)	31(exo), 5(endo)
5	cyclohexene		110°C, 6 d	86	100(exo)	
6	cyclohexenone		70°C, 1 h	93	100 (C=O at 4')	

The fused isoxazolo derivative(**43**) is a protected form of 1-(2-hydroxyisobutyl)tetrahydro-β-carboline(**48**), which is a promising intermediate in the synthesis of verruculogen TR-2, a tremorgenic mycotoxin, and is believed to be unobtainable by the typical P–S reaction of tryptophan ester with 3-hydroxy-3-methylbutanal. Therefore, the group of Ottenheijm and Hermkens *synthesized* TR-2(**50**) and fumitremorgin C(**52**) from racemic 6-methoxy-*Nb*-hydroxytryptophan ester(**45**).[23] 1,3-Dipolar cycloaddition of the nitrone (**46**) obtained from **45** with isobutylene gave the corresponding fused isoxazolo derivative(**47**). Hydrogenolysis of the *Nb*–O bond in **47** by zinc and acetic acid gave the desired hydroxy-β-carboline(**48**). Coupling with the L-proline derivative gave the optically active intermediate(**49**). Cyclization, dehydrogenation, and further elaboration of **49** gave TR-2(**50**). Epimerization at the 3-position of **49** and further elaboration including dehydration of the hydroxy group gave FTC(**52**). [22]

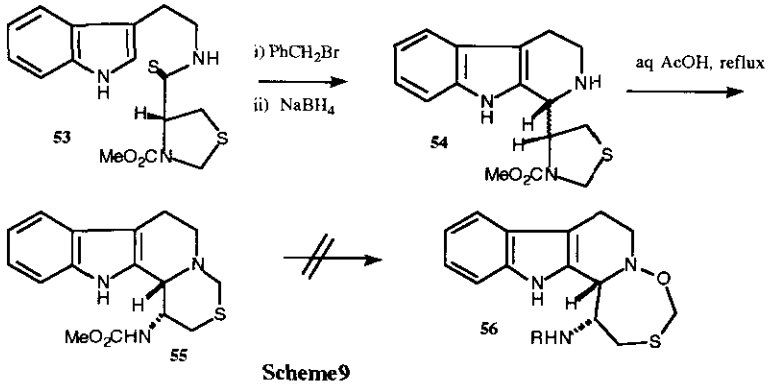


Scheme 8

V-3 Synthesis of oxathiazepine-containing eudistomins

Immediately after the structure of eudistomines was reported in 1984, we examined the ring transformation of 1-thiazolinyl-tetrahydro-β-carboline(**54**) to thiazolizino-β-carboline(**55**) as a precursor of a unique oxathiazepine fused with β-carboline(**56**). Transformation of **54** obtained from the optically active **53** to

55 was successful in refluxing aqueous acetic acid . However, oxidative transformation of **55** to the oxathiazepine(**56**) was unsuccessful. [24]



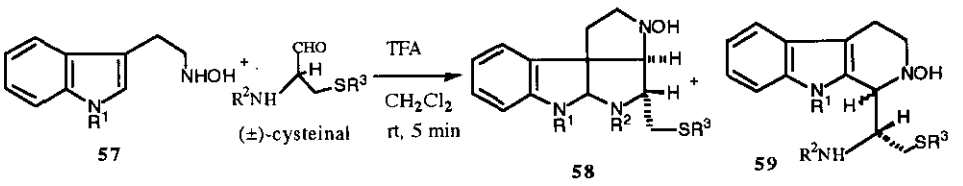
Scheme9

V-3-1 Pictet–Spengler reactions of *Nb*-hydoxytryptamines with cysteinals.—Trapping of the 3,3-spiroindolenine intermediate as a tetracyclic compound

We next examined the P–S reactions of *Nb*-hydroxytryptamines with cysteinals to form 2-hydroxytetrahydro-β-carboline, a promising precursor to the oxathiazepine ring, since we have used the P–S reaction of optically active tryptophan esters in the total synthesis of fumitremorgins.[22] Since the proposed structure of eudistomins was a D-cysteine-derived compound, it would be useful to confirm this absolute configuration by synthesis. Therefore, it is important to start with D-cysteine to eudistomins. There are few examples obtaining optically active β-carbolines by the P–S reaction of tryptamine with chiral aldehydes. At the beginning of our research, cysteinals were prepared by DIBALH reduction of the corresponding methyl esters derived from L-cysteine, but the cysteinals obtained after purification were completely racemic.[25] We used these racemic cysteinals as model compounds to examine the P–S reaction with *Nb*-hydroxytrypatmine.[26] The P–S reaction of *Nb*-hydroxytryptamine with various racemic N, S-protected cysteinals in dichloromethane at room temperature proceeded rapidly to give a mixture of the unexpected tetracyclic pyrroloindole derivatives(**58**) and tetrahydro–β–carboline(**59**). The results are summarized in Table 9. The structures of **58** and **59** have been confirmed by X-Ray analysis.[26] The reaction proceeded more rapidly than that with tryptamine. A single isomer was isolated in tetracyclic compounds(**58**), while 1-α and 1-β diastereomers were isolated in β-carbolines(**59**). The 1-β isomer was obtained as the major product in all cases. The ratio of tetracyclic compounds(**58**) to β-carboline(**59**) seems to depend upon the size of the substituents at R^2 and R^3 in the cysteinal, and the β–carboline(**59**) became the major product when both substituents were bulky. The substituent at the *Na*-position had a strong effect and the tetracyclic compound (**58**) was the sole product in the reaction of *Na*-methyl derivatives. (Table 9)

The racemic tetracyclic compound (**60**) can be transformed into a mixture of the corresponding β-carboline compounds (**61**, **62**) with TFA in dichloromethane, which shows that the tetracyclic compound may be an intermediate to the β-carboline, although this transformation requires a longer reaction time than the original

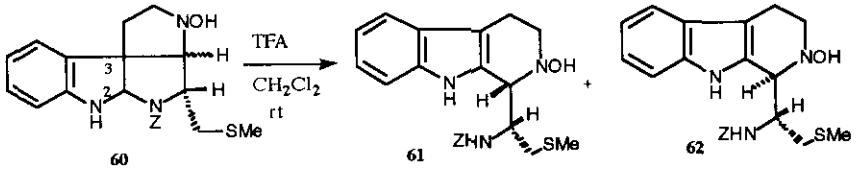
Table 9 The P–S reaction of **57** with racemic cysteinals.



entry	**57**	cysteinal		**58**	**59**	**59**
	R^1	R^2	R^3	%	%	α : β
1	H	CO_2Me	Me	75	24	1 : 6 a
2	"	Z	CO_2Me	39	51	1 : 4 a
3	"	"	Me	76	18	1 : 8 a
4	"	Troc	CO_2Me	21	62	1 : 8 b
5	'	CO_2Me	Z	47	34	1 : 5 b
6	"	"	Troc	33	56	1 : 6 b
7	Me	"	MEM	88	-	-
8	"	"	Troc	90	-	-

a: by isolation ; b : by NMR

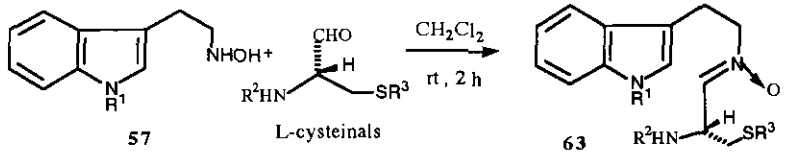
reaction . Examination of the stereochemistry of these β-carbolines showed that the major β-carboline (**61**) has a β-hydrogen at the 1-position. This indicated that this transformation is not a simple migration of the bond from the 3- to the 2-position, since the configuration of the 1-position of the major isomer of carboline is different from that of the tetracyclic compound(**60**). On the other hand, transformation to the β-carboline did not occur in the *Na*-methyl-tetracyclic compound (**58**, R^1 = Me) under similar conditions.



Scheme 10

We have found that the crude cysteinal obtained by DIBALH reduction of the corresponding ester is optically active, but racemize during a column purification. Therefore, we prepared nitrones by reacting the crude *Nb*-hydroxytryptamine with crude cysteinals. These nitrones were optically active and could be purified by a column chromatography. Various optically active nitrones were obtained in excellent yield.[26,27] (Table 10)

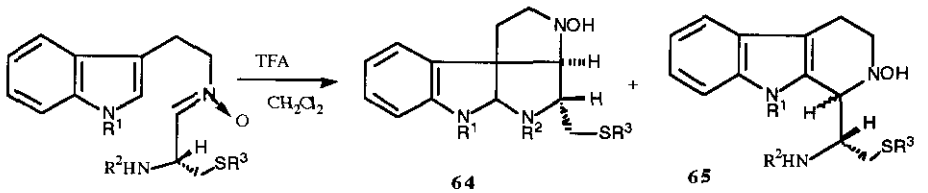
Table 10 Optically active nitrones (**63**)



entry	**57** L-cysteinal R^1	R^2	R^3	**63** yield %	$[\alpha]_D$
1	H	CO_2Me	Me	97	+56.9
2	"	"	Troc	91	+13.5
3	Me	"	"	95	+30
4	H	Boc	"	97	+35
5	"	Troc	Me	92	+41
6	"	Boc	"	93	+67.3
7	"	Troc	Z	78	+21

Ring-closure of these nitrones (**63**) with TFA in dichloromethane proceeded even at –78°C, and the reaction showed a temperature-dependent.[26–28] (Table 11) Only tetrahydro–β–carbolines(**65**) were obtained in the reaction at –78°C, and both compounds (**64,65**) were obtained at room temperature. The tetracyclic compound was obtained as the sole product in the reaction of *Na*-methylated nitrones at either –78°C or room temperature. Cyclization also proceeded with *p*-toluenesulfonic acid instead of TFA, but the ratio of the products was different from that obtained with TFA (entry 14).[28]

Table 11 Cyclization of optically active nitrones (**63**)

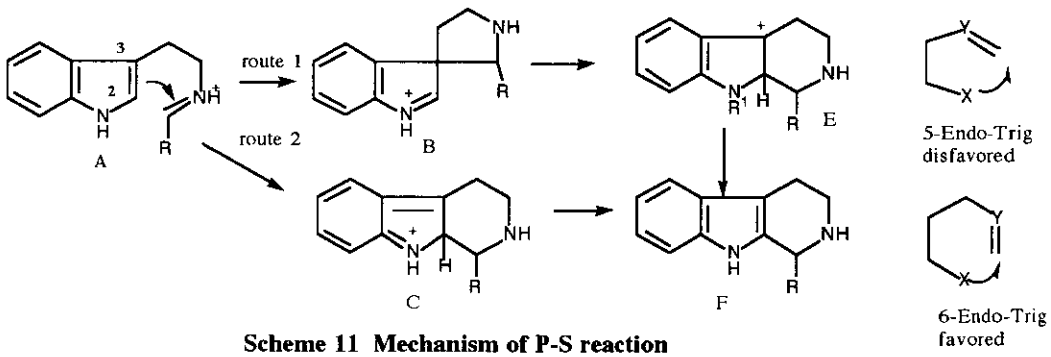


63 nitrones from L-cysteinals **64** **65**

entry	**63** R^1	R^2	R^3	TFA(eq)	condition °C / h	**64** %	**65** %	**65** α : β ratio
1	H	CO_2Me	Me	2	-78/ 1 h	-	97	1 : 41 a
2	"	Boc	"	2	"	-	96	1 : 10 b
3	"	CO_2Me	Troc	2	"	-	100	1 : 12 b
4	"	Boc	"	5	"/ 2 h	-	94	1 : 10 b
5	"	Z	"	2	"/ 1 h	-	97	1 : 12 b
6	"	Troc	Me	5	"/ 2 h	-	96	1 : 21 a
7	"	"	Z	5	"/1 h	-	82	1 : 8 b
8	"	CO_2Me	Me	1	rt/ 5 min	75	24	1 : 7 a
9	:	Boc	Me	"	"	70	21	1 : 5 b
10	"	CO_2Me	Troc	"	"	35	59	1 : 6 b
11	"	Boc	Troc	"	"	49	48	1 : 5 b
12	"	Z	"	2	"/ 1 h	28	67	1 : 4 b
13	"	Troc	Me	1	"/ 5 min	68	25	1 : 6 a
14	"	"	Z	" c	" / 1 h	23	58	3 : 5 b
15	Me	CO_2Me	Troc	"	" / 5 min	90	-	
16	"	"	Me	"	"	90	-	
17	"	"	Troc	5	-78/1 h	93	-	
18	"	"	Me	"	"	90	-	

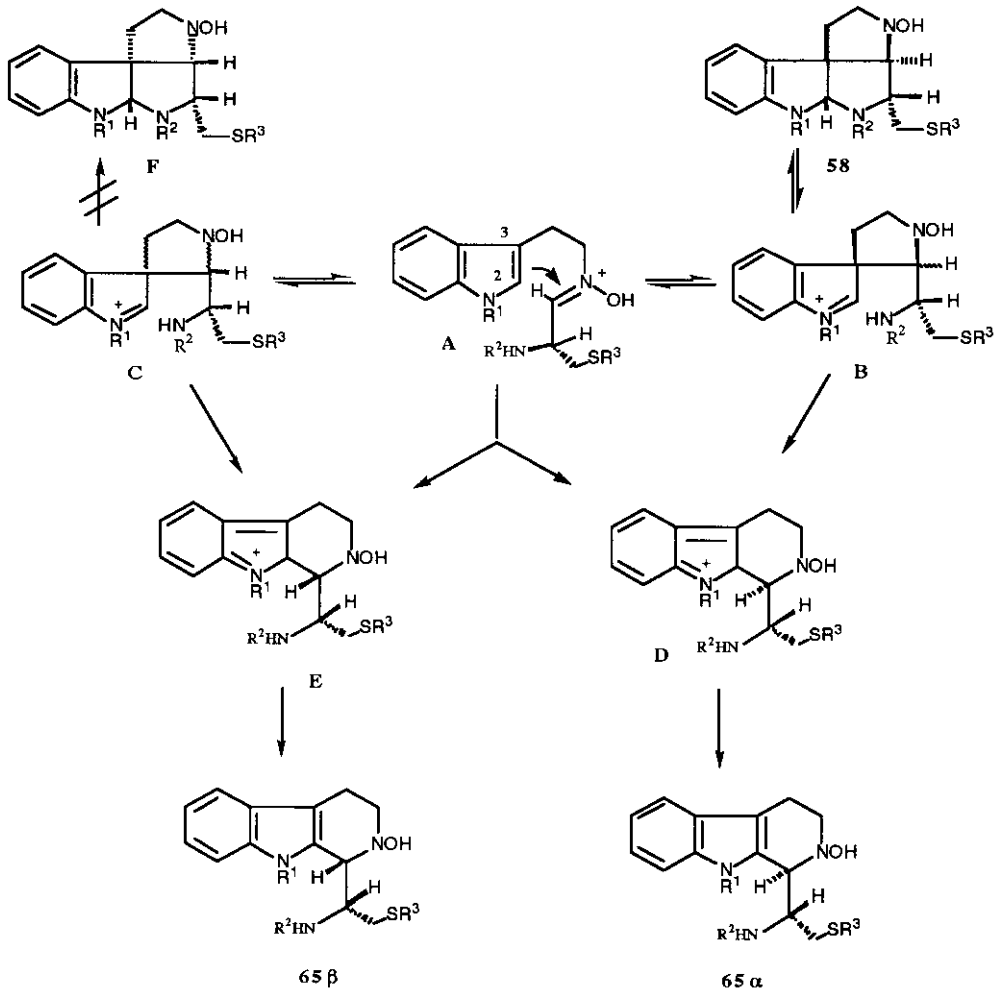
a: ratio by isolation. b: ratio by NMR c: TsOH instead of TFA

The P–S reaction is generally understood in terms of the sequence shown in Scheme 11. The electron-rich indole ring may attack at the immonium carbon in A at either the 3- or the 2-position to form a spiroindolenium B or a β-carboline-type immonium C. These intermediates (B, C) may transform tino the tetrahydro–β–carboline(F) by rearrangement and aromatization. The stability of the intermediate, B or C, prefers route 1, while Baldwin's rule [29] prefers route 2 by 6-endo-Trig cyclization to form C. However, clear evidence to support one of these routes is not yet available. A recent report on the MINDO calculation for this process supports route 2. [30]



Scheme 11 Mechanism of P-S reaction

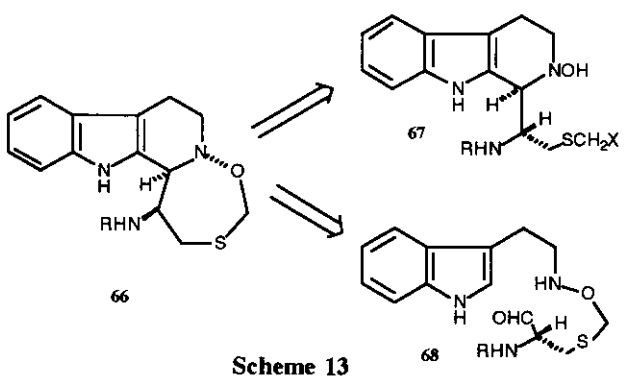
We proposed a pathway for the cyclization of the protonated nitrone (A), as shown in Scheme 12.[28] The probable conformation of the protonated nitrone (L-cysteine series is shown) may be similar to A, due to allylic strain ($A^{1,3}$-strain). At low temperature, cyclization proceeds by attack of the 2-position of the indole ring to form E and D, which may lead to **65β** and **65α**. The preferential formation of **65β** *via* E may be due to the influence of the chiral center in A. Attack of the 3-position of the indole ring at the immonium carbon in A from the upper or lower side may produce spiroindolenium ions (B and C) . Intermediate B may be trapped as **58**, but C can not cyclize to F due to severe steric hindrance in F. The equilibrium between C, A, B, and **58** was confirmed by the conversion of **58** to **65β** (major) and **65α** (minor) at room temperature. The formation of E and D may also be possible *via* C and B by rearrangement. The isolation of **58** is a strong evidence of the participation of the spiroindolenines (B and C) in the P–S reaction. However, we can not exclude the possibility that B and C take part in an equilibrium between A, B, and C without leading to **65**. The cyclization of A (R^1 = Me) to D and E may be difficult due to the greater steric hindrance than in the cyclization to B, which leads to **58**. Further investigations are required to establish the detailed mechanism of this reaction.



Schem 12 A proposed mechanism of cyclization of the nitrone

V-3-2 Oxathiazepine ring formation from substituted β-carbolines

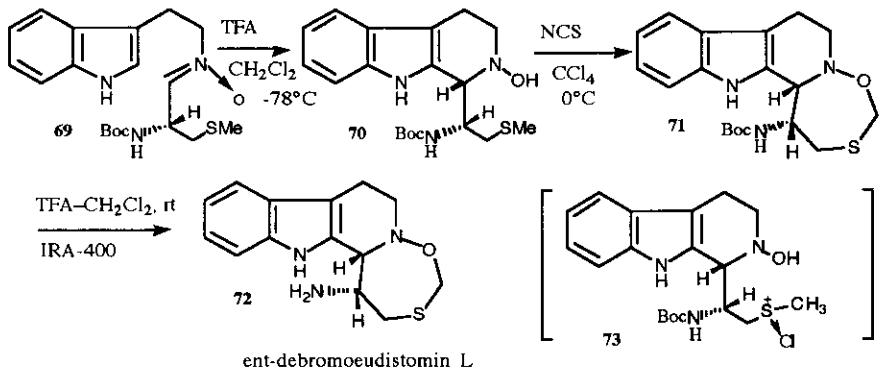
Oxathiazepine (**66**), a unique ring system found in eudistomins, is constructed by two ways; i.e., the ring-closure of properly 1,2-substituted β-carbolines(**67**), and the intramolecular P–S reaction



Scheme 13

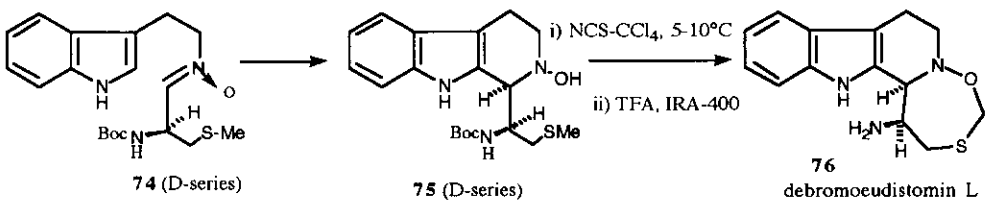
of *N, O*- substituted *Nb*-hydroxytryptamines(**68**), which forms the β-carboline ring and the oxathiazepine ring simultaneously. (Scheme 13)

After various attempts, we succeeded in cyclization of the *S*-methyl *N*-Boc protected *Nb*-hydroxy-β-carboline (**70**) to an oxathiazepine (**71**). (Scheme 14)



Scheme 14

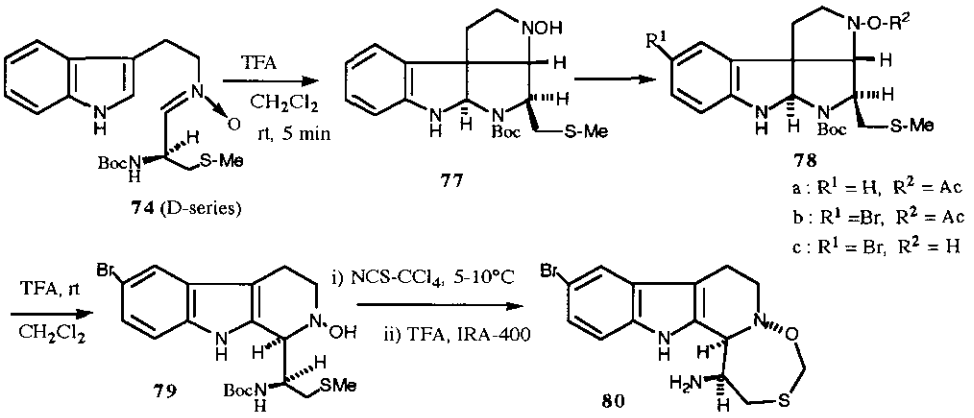
The P–S reaction of the nitrone (**69**) derived from an L-cysteine derivative with TFA at –78°C gave the tetrahydro–β–carboline (**70**) stereoselectively as shown previously. Treatment of **70** with NCS in carbon tetrachloride at 0°C gave the desired oxathiazepine(**71**), but in rather poor yield (4%). This Pummerer-type cyclization probably proceeded *via* a sulfonium chloride intermediate (**73**). Deprotection of the *Nb*-Boc group with TFA gave enantiomeric debromoeudistomin L(**72**).[27] The yield of cyclization improved to 10 % by treatment of the corresponding sulfoxide obtained by oxidation of **70** with *p*-toluenesulfonic acid and pyridinium *p*-toluenesufonate.[27,31] Further improvement of the yield to 17% was observed when the methoxycarbonyl group was used to protect the amino function. These results encouraged us to synthesize the natural compound.



Schem e 15

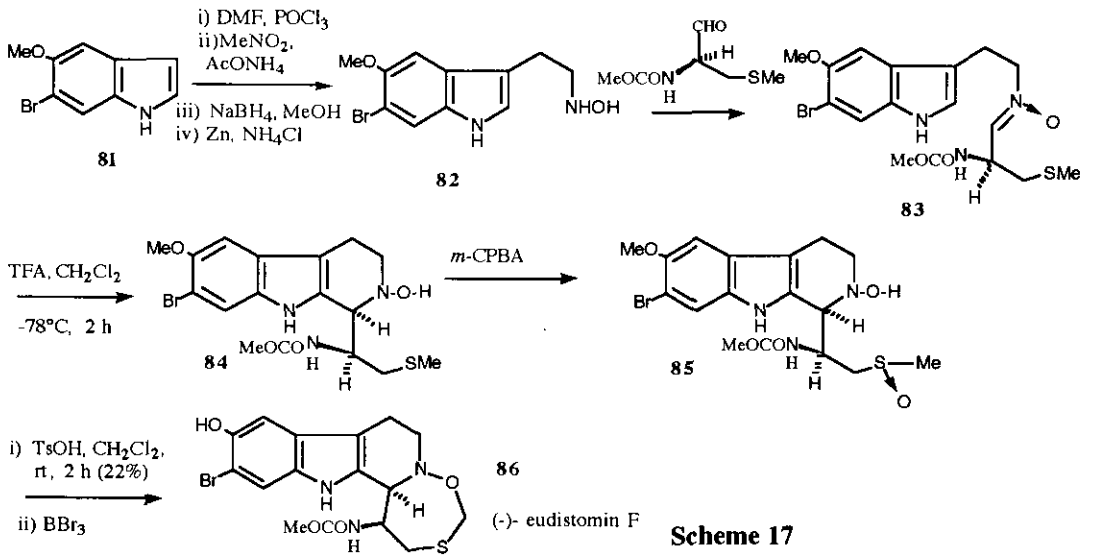
In a similar manner, the P–S reaction of the nitrone(**74**) derived from D-cysteine selectively gave the 1α-tetrahydro-β-carboline(**75**). The Pummerer-type cyclization of **75** with NCS gave the oxathiazepine in a yield of 8% as crystals. Deprotection gave natural (–)-debromoeudistomin L(**76**) in 94% yield. (Scheme 15)

To prepare eudistomin L, a bromine atom must be introduced at the 5-position of the indole ring. We used the tetracyclic compound(**77**) obtained from the nitrone(**74**), since **77** is an indoline and can be brominated at the 5-position of the indole when functional groups are properly protected. (Scheme 16)



Scheme 16

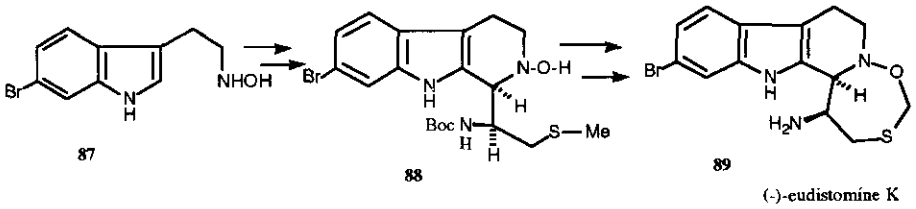
Acetylation of **77** followed by bromination with NBS and deprotection gave the desired brominated compound (**78c**) in 75% yield via **78a** and **78b**. Ring-transformation to β-carboline(**79**), ring-closure to oxathiazepine ring (8%), and removal of the Boc group gave the natural (–)-eudistomin L(**80**) for the first time. [27,31]



Scheme 17

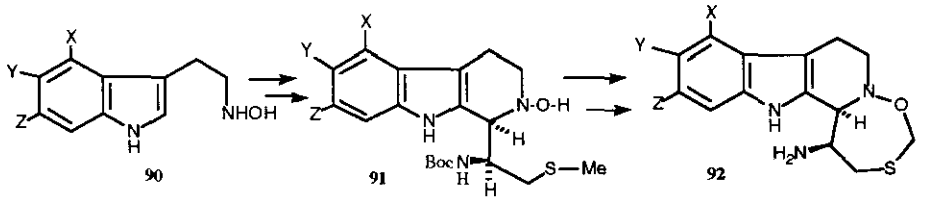
Natural eudistomin F was prepared as shown in Scheme 17. [31,32] Condensation of substituted hydroxytryptamine(**82**) prepared from 5-methoxy-6-bromoindole(**81**) [4] with a D-cysteinal prepared from *N*-methoxycarbonyl-*S*-methyl-D-cysteine ester smoothly gave the corresponding nitrone (**83**). The P–S

reaction of **83** with TFA at –78°C gave 1-α-β-carboline (**84**) in excellent yield in addition to a small amount of the 1-β-isomer. Ring-closure of its *S*-oxide (**85**, a mixture of diastereomers) to oxathiazepine with *p*-toluenesulfonic acid in dichloromethane at room temperature gave the product in 22% yield. Removal of the methyl group on the phenol with boron tribromide smoothly gave (–)-eudistomin F(**86**).



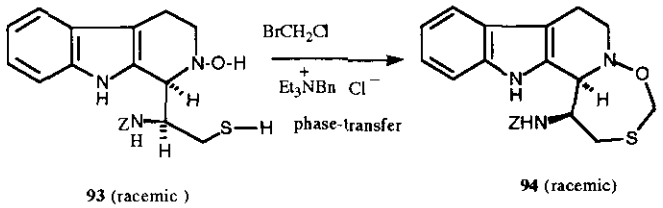
Scheme 18

Since it was not easy to introduce a bromine at the 6-position of indole *via* a tetracyclic intermediate, we prepared 6-bromoindole from *p*-bromobenzaldehyde and ethyl azidoacetate as described in the literature.[33] The corresponding *Nb*-hydroxytryptamine(**87**) was prepared from 6-bromoindole as descried above. The P–S reaction of the nitrone derived from **87** and the D-cysteinal at low temperature gave the 1-α-β-carboline(**88**) in 90% yield. Oxidation and ring-closure with *p*-toluenesulfonic acid and pyridinium *p*-toluenesulfonate gave the oxathiazepine in 15% yield, which in turn gave (–)-eudistomin K(**89**) as crystals upon removal of the Boc group. [31,34]



Scheme 19

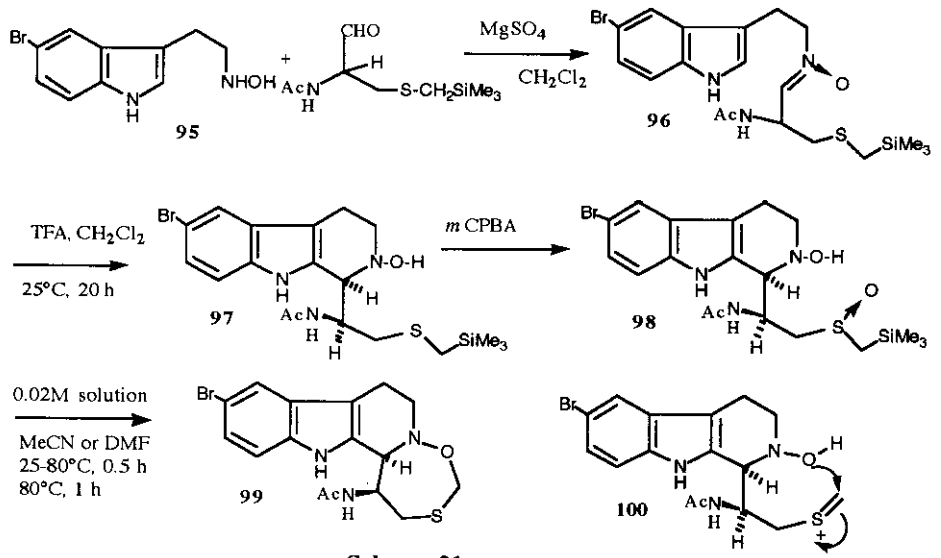
We have prepared (–)-eudistomin C and E in a similar manner.[31,34] (Scheme 19) Thus, all of the natural oxathiazepine-containing eudistomins were synthesized and identified, and we have shown that natural eudistomin is derived from D-cysteine.[31]



Scheme 20

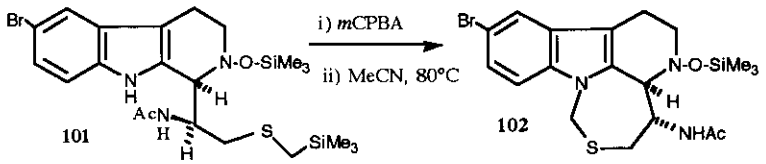
Yoon and his coworkers reported an improved ring-closure of racemic β-carboline(**93**), prepared by our procedure, to the oxathiazepine(**94**) by the alkylation under phase-transfer conditions in 50% yield, although they did not succeed in removing the protective group. [7d] (Scheme 20)

On the other hand, Still and Strautmanis[7c,35] reported a new cyclization method for oxathiazepine which applies the sila-Pummerer reaction. (Scheme 21) They prepared 5-bromo-*Nb*-hydroxytryptamine(**95**) in five steps from 5-bromoindole in excellent yield. The cysteinal was prepared from L-cysteine by analogy to our method, except that an acetyl group was used to protect the amino function. Condensation of **95** with the cysteinal in the presence of magnesium sulfate smoothly gave the racemic nitrone(**96**), but this could not be purified, unlike our results. The P–S reaction of this nitrone(**96**) with TFA in dichloromethane at 25°C gave the 1-α-tetrahydro–β–carboline(**97**) in 24% yield from **95**. Although this yield was not good, only a single isomer was obtained. The corresponding tetracyclic compound was not isolated even at room temperature, probably because the acetamido group is less nucleophilic than the carbamate groups in our case. Oxidation of silylmethyl sulfide(**97**) with *m*-CPBA gave the sulfoxide (**98**), which provided the desired racemic acetyleudistomin L(**99**) in 20% yield by Pummerer-type rearrangement upon warming in acetonitrile or dimethylformamide *via* a sulfonium ion(**100**). Unfortunately, they could not remove the acetyl group. [7c,35]



Scheme 21

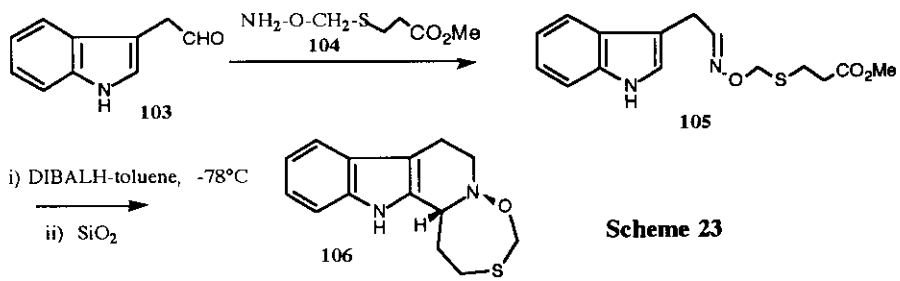
This sila-Pummerer-type rearrangement gave a different ring system when *Nb*-hydroxygroup was protected by a trimethylsilyl group. The new tetracyclic compound(**102**) was obtained in 17% yield when the β-carboline(**101**)was heated in acetonitrile. [35] (Scheme 22)



Scheme 22

V-3-3. Intramolecular P–S reaction to form a oxathiazepino-β–carboline

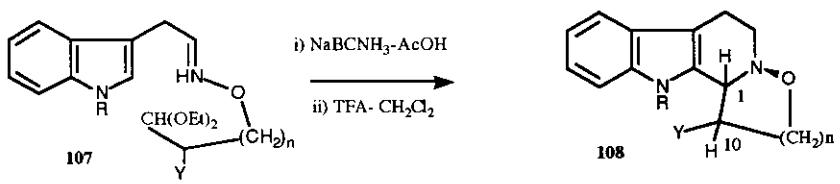
Another approach to the oxathiazepine ring is the intramolecular P–S reaction , which forms β-carboline and oxathiazepine rings simultaneously. Two groups, Kirkup and his coworkers and Hermkens and his coworkers, published preliminary reports in 1989. Kirkup's group prepared the hydroxylamine derivative(**104**) from *N*-chloromethoxyphthalimide and methyl β-mercaptopropionate. The condensation of 3-indoleacetaldehyde (**103**) with **104** gave the oxime (**105**), which in turn gave a fused oxathiazepine (**106**) in 24% yield upon treatment with DIBALH in toluene at –78°C followed by the addition of silica gel. (Scheme 23) They failed to prepare the amino-substituted oxathiazepine by similar methods. The corresponding carba-analogs were prepared similarly and this intramolecular P–S reaction was shown to be effective for the formation of not only 7-membered, but also 8-membered rings. (Table 12)



Scheme 23

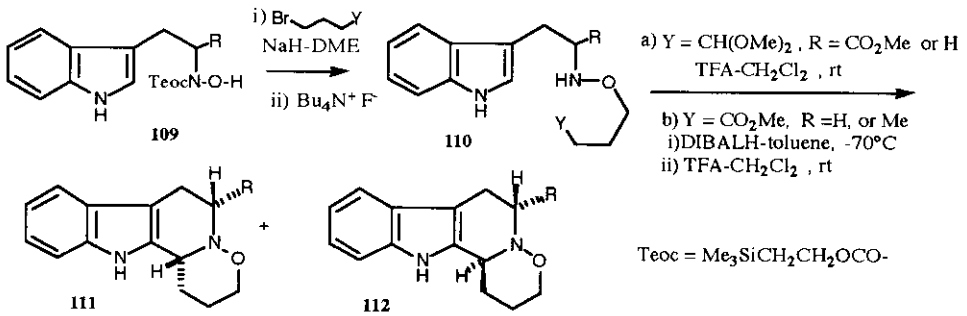
The P–S reaction of the hydroxylamine obtained by reduction of the oxime derivatives(**107**) with TFA gave carba-analogs(**108**). The relative stereochemistry of the major products at C-1 and C-10 was *trans*, and the *cis* :*trans* ratio varied with the substituents. Such stereoselectivity of the intramolecular P–S reaction is consistent with the results of Hermken' group. This group has not reported any further investigations.[42] (Table 12)

Table 12 Intramolecular P–S Reaction



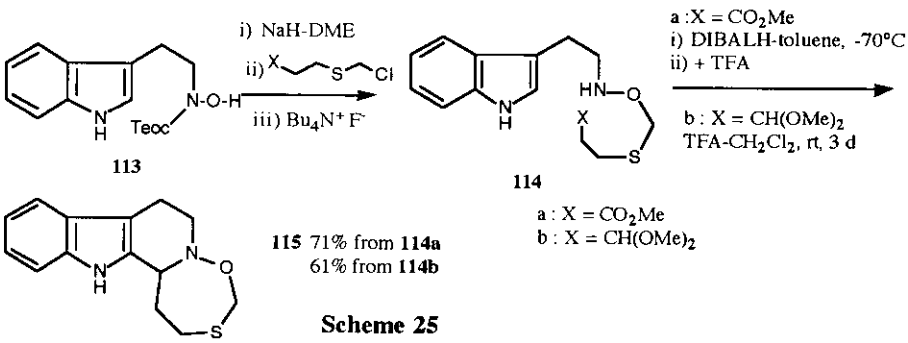
entry	Y	107 n	R	108 yield %	108 *trans* / *cis* C1-C10
1	H	3	Me	72	-
2	"	4	"	50	-
3	N3	2	"	78	100 / 0
4	"	"	H	65	54 / 46
5	"	3	"	54	100 / 0
6	NNZ	2	"	62	66 / 34

Hermkens' group also reported examples of the intramolecular P–S reaction of *Nb*-alkoxytryptamine (**110**) to form oxazine rings (**111,112**).[37] (Scheme 24)



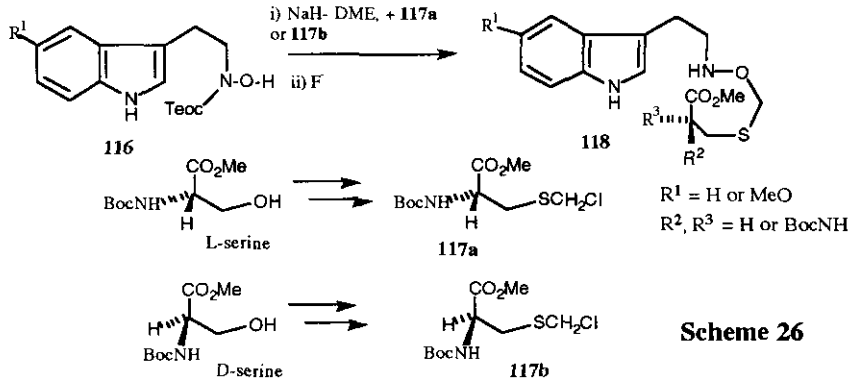
Scheme 24

O-Alkykated *Nb*-hydroxytryptamines (**110**) were prepared by the alkylation of *Nb*-trimethylsilylethoxycarbonyl(Teoc)-*Nb*-hydroxytryptamine (**109**) followed by deprotection of the Teoc group. The P–S reaction of the acetal (**110a,** Y = $CH(OMe)_2$) or the aldehyde (**110**, R = CHO) obtained by DIBALH reduction of **110b** (R = CO_2Me) with TFA in dichloromethane at room temperature smoothly gave oxazino–β–carboline(**111**, **112**) in good yield, and the1,3-*cis* isomer (**111**) was obtained as the major product in each reaction. (Scheme 24) Reduction of the fused compound with zinc and acetic acid gave 1-hydroxypropyl-tetrahydro–β–carbolines. [37b] They examined similar cyclizations of **114a** and **114b** to give a fused oxathiazepine ring (**115**) , similar to the results reported by Kirkup.[37a] (Scheme 25)



Scheme 25

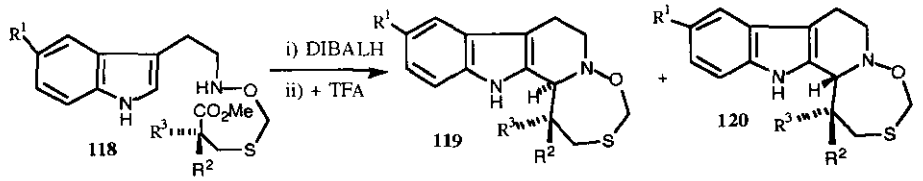
Since the intramolecular P–S reaction proceeded as expected, Hermkens' group prepared optically active *S*-chloromethylcysteine derivatives (**117a,b**) from L- and D-serine.[38] *O*-Alkylation of *Nb*-trimethylsilylethoxycarbonyl(Teoc)*Nb*-hydroxytryptamines **116**) with these *S*-chloromethylcysteine esters (**117a, 117b**) proceeded smoothly and gave substrates (**118**) for the intramolecular P–S reaction after deprotection by tetrabutylammonium chloride and KF (naked fluoride ion). However, the coupling reaction of **116** with the similar *Nb*-Troc-cysteine derivatives did not proceed.[38]



Scheme 26

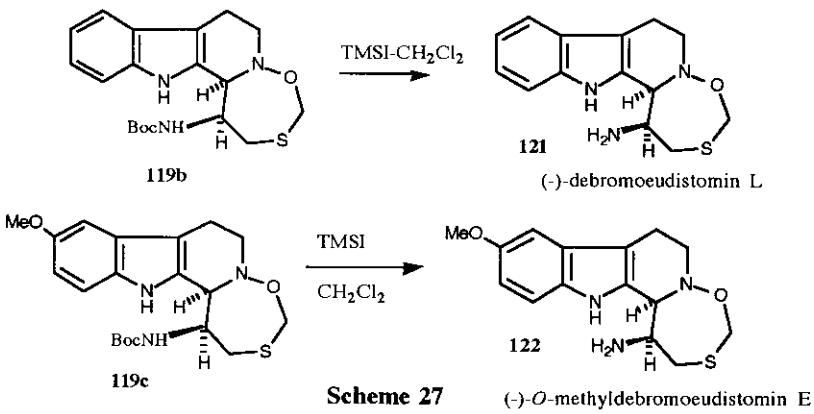
DIBALH reduction of these *Nb*-alkoxytryptamines(**118**) followed by treatment with TFA under various conditions gave the expected fused oxathiazepines(**119,120**), as summarized in Table 13 . However, the desired *cis* isomer was obtained only as a minor product in all cases. The *cis* : *trans* ratio did not change with the solvent or temperature, but the conditions in entry 5 gave the maximum proportion of *cis* . Cyclization of the corresponding dimethyl acetal, instead of the methyl ester, with TFA did not give the desired product, but instead gave the cyclic carbamate, which decomposed upon further treatment with the acid.[38]

Table 13 Intramolecular P–S reactions (1)



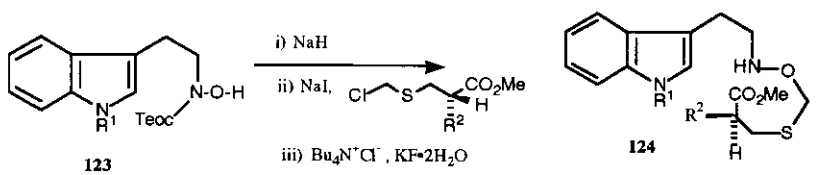
entry **118**	R^1	**118** R^2	R^3	solvent	condition	TFA (eq)	**119+120** yield %	**119 + 120** *cis* : *trans* ratio	
1 **(118a)**	H	H	NHBoc	toluene	-70°C,3 h	5	52	29 : 71 **(120a) (119a)**	L-series
2	"	"	"	"	rt, 1 h	"	41	39 : 61	
3	"	"	"	DME	-70°C,3 h	"	70	13 : 87	
4	"	"	"	CH_2Cl_2	"	"	52	31 : 69	
5	"	"	"	"	-90°C, 0.5 h	15	58	41 : 59	
6 **(118b)**	H	NHBoc	H	"	"	"	53	34 : 66 **(119b) (120b)**	D-series
7 **(118c)**	MeO	"	"	"	"	"	81	30 : 70 **(119c) (120c)**	

The minor products of entries 6, (**119b**) and 7 (**119c**) in Table 13 were converted to debromoeudistomin L (**121**) and *O*-methyl-debromoeudistomin E (**122**), respectively, after deprotection with trimethylsilyl iodide in good yield. The enantio-excess of the debromoeudistomin was determined to be 89%, and that of eudistomin E was 86%. The stereochemistry of the major isomer(**120c**) of entry 7 was confirmed by X-Ray analysis. [38] (Scheme 27)



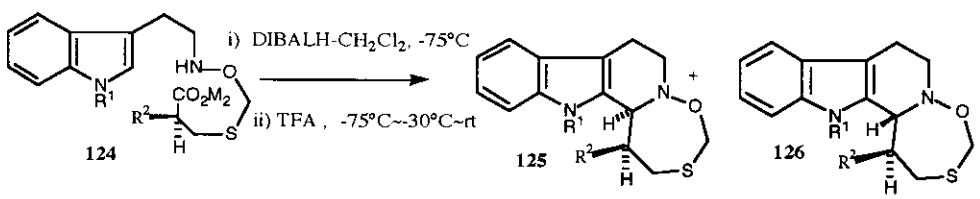
Scheme 27

To further examine the stereoselectivity of the intramolecular P–S reaction, they prepared variously substituted substrates(**124**) by *O*-alkylation of the *Nb*-hydroxytryptamines(**123**) with chloromethyl sulfides obtained from ethyl D-glycerate or D-serine. (Scheme 28) The *Na*-methyl-*Nb*-hydroxytryptamine (**123**, R^1 = Me) was prepared by the methylation of *Nb*-Teoc-*Nb*-allyloxytrypamine followed by removal of the allyl group. Intramolecular cyclization of **124** after reduction gave **125** and **126**, and the latter was obtained as the major isomer. (Table 14)



Scheme 28

Table 14 Intramolecular P–S reactions (2)

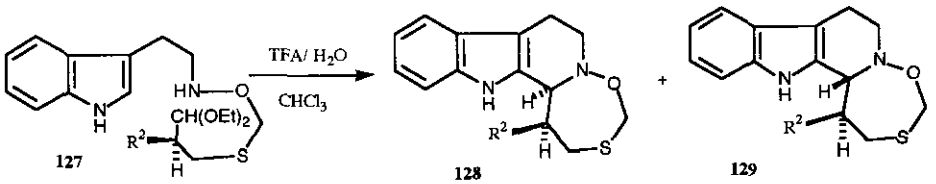


entry	**124** R^1	R^2	**125 +126** yield %	**125 : 126** *cis* : *trans*
1	H	OMe	91	10 : 90
2	"	OMTP*	98	11 : 89
3	"	OH	66	38 : 62
4	"	Me	69	0 : 100
5	"	NH_2	75	9 : 91
6	Me	NH_2	66	18 : 82
7	H	NHBoc	73	30 : 70
8	Me	"	79	31 : 69
9	Boc	"	0	-

* MTP : 4-(4-methoxytetrahydropyranyl)

They carried out the P–S reaction of the diethylacetals(**127**) to examine temperature dependence using slow two-phase hydrolysis (chloroform-TFA-water) and rapid cyclization, since the aldehyde obtained by the DIBALH reduction of ester may cyclize quickly even at low temperature with the addition of TFA. The diastereoselectivity did not change at room temperature and refluxing temperature, as shown in Table 15. [39]

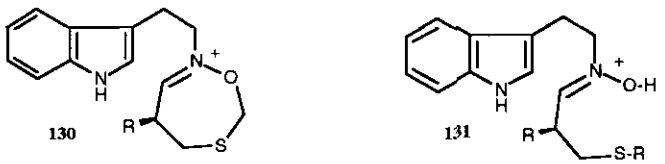
Table 15 Intramolecular P–S reaction : the temperature dependence



entry	**127** R^2	reaction time	yield **128+129**	*cis* : *trans* **128 : 129**
1) room temperature				
1	NHBoc	7 d	71%	29 : 71
2	NHAloc*	9 d	48%	23 : 77
3	Me	90 min	92%	0 : 100
4	NH_2	9 d	5% conv	–
2) reflux				
5	NHBoc	8 h	32%	6 : 94
6	NHAloc*	8 h	83%	10 : 90
7	Me	15 min	95%	0 : 100
8	NH_2	9 h	44%	5 : 95

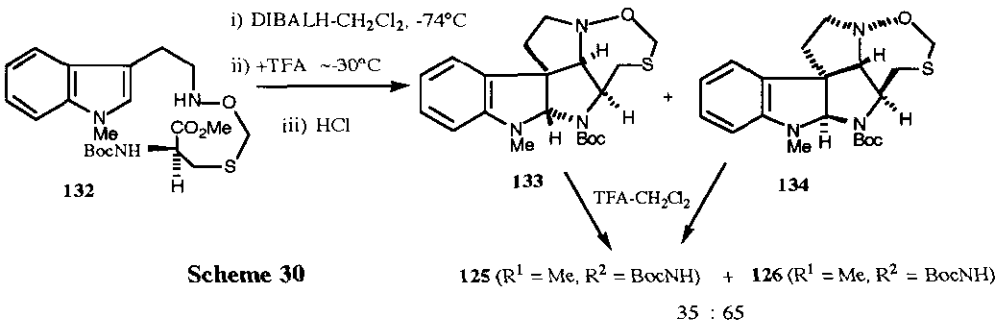
* Aloc : allyloxycarbonyl

They concluded that the *trans* isomer was the major product in the intramolecular P–S reaction , probably because the cyclic imminium ion intermediate(**130**) exhibits less freedom than the acyclic imminium intermediate (**131**).[39]



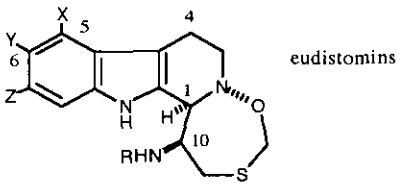
Scheme 29

Hermkens' group isolated pentacyclic compounds(**133**,**134**), corresponding to our tetracyclic compound in the cyclization of entry 8 in Table 14 under a slightly different conditions as by-products.[39] These compounds are acid-labile and were converted to the respective fused oxathiazepine compounds (**125**, **126**) in the same ratio of *cis* (**125**, R^1 = Me, R^2 = Boc NH) and *trans* (**126**, R1 = Me, R2 = BocNH) (35 : 65) , indicating that these transformations proceeded by the same intermediate(such as **130**). (Scheme 30) However, the intermolecular P–S reaction of *Na*-methylnitrones(**63**, R^1 = Me) gave only tetracyclic compounds(**64**), and the carbolines(**65**) were not formed with acid treatment (*vide supra*). Although this discrepancy remains to be resolved, it may be due to the differences in the structures of the substrates.



Scheme 30

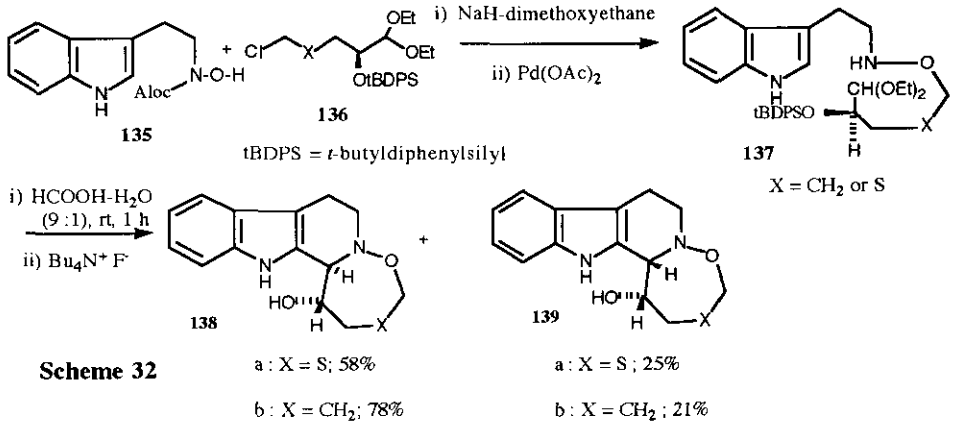
The *in vitro* antiviral and antitumor activities of these compounds have been evaluated. The natural stereochemistries at C1 and C10 and the presence of the 10-amino group are important for expression of these activities. The 6-methoxy derivative is highly potent with regard to both antiviral and antitumor activity. The substituents at the benzene ring also strongly affect the activity.[40] (Scheme 30)



Scheme31

Hermkens' group attempted to convert the *trans* isomer to the *cis* isomer by the Mitsunobu reaction of 10-hydroxy derivatives(**138**). They prepared fused hydroxy-oxathiazepines(**138a**,**139a**) and their carba-analogs (**138b**, **139b**) by the intramolecular P–S reaction of the diethylacetal(**137**) with formic acid instead of TFA.[41] (Scheme 32)

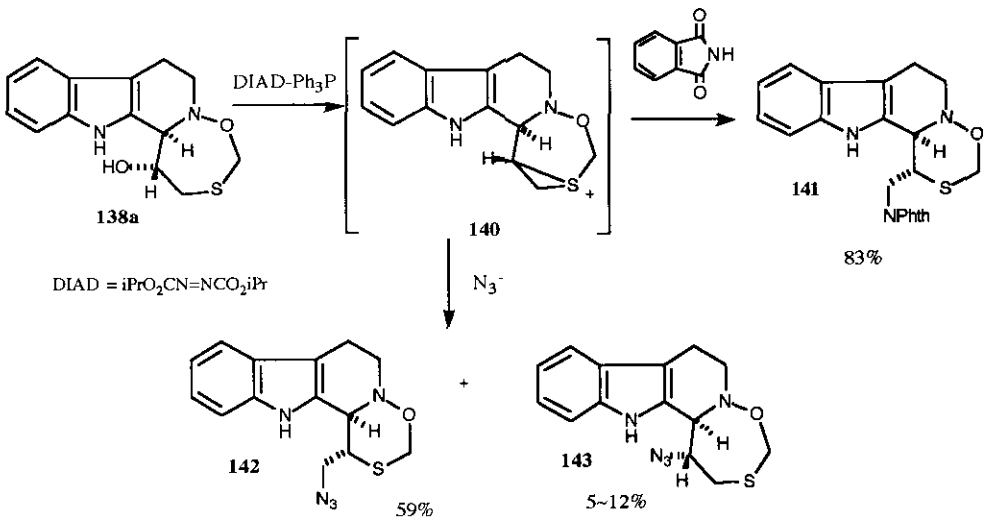
The *trans* isomers(**138**) were obtained as the major product, as expected. The Mitsunobu reaction of this 10-hydroxyoxathiazepine (**138a**) with diisopropyl diazocarboxylate and triphenylphosphine in the presence of phthalimide gave the phthalimidomethyloxazine derivative (**141**) as the sole product instead of the desired *cis* phthalimino-oxathiazepine derivative, *via* the episulfonium intermediate(**140**). A similar reaction in the presence of zinc azide gave a mixture of azidomethyloxathiazine (**142**) and azido-oxathiazepine(**143**).(Scheme 33)



Scheme 32

a : X = S; 58% b : X = CH_2; 78% a : X = S ; 25% b : X = CH_2 ; 21%

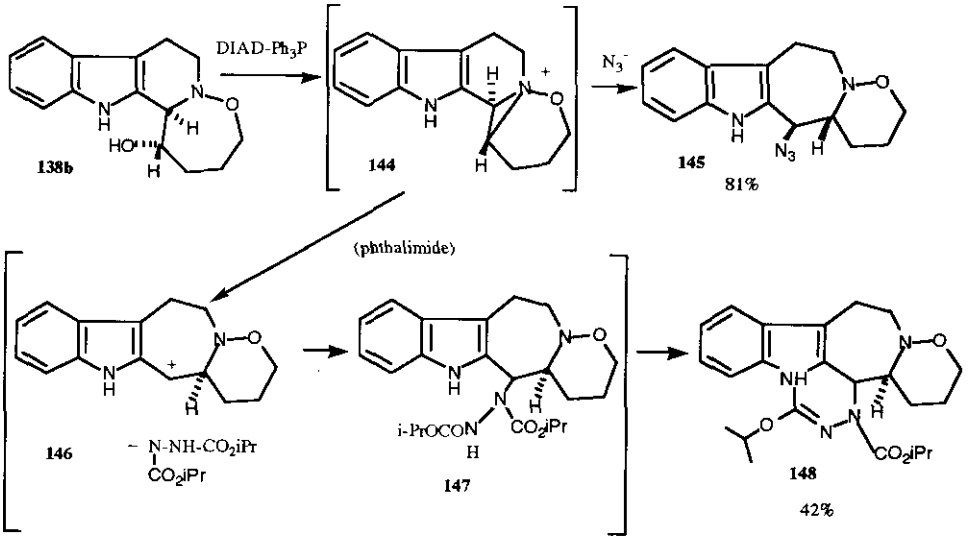
A similar Mitsunobu reaction of the carba-analog(**138b**) in the presence of azide ion gave the azido-azepinoindole derivative(**145**) *via* the aziridinium intermediate(**144**). However, the reaction in the presence of phthalimide gave a pentacyclic compound(**148**) by participation of the diazadicarboxylate anion instead of phthalimide on the carbocation(**146**) derived from the aziridinium intermediate(**144**), followed by cyclization. [41](Scheme 34)



Scheme 33

CONCLUSION

The P–S reaction of *Nb*-hydroxytryptamines varies from the normal P–S reaction. This reaction has been applied to formation of the oxathiazepine moiety of eudistomins with intermolecular or intramolecular manner.



Scheme 34

ACKNOWLEDGEMENTS

We acknowledge with gratitude the contributions of our coworkers, whose names appear in the literature citations.

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