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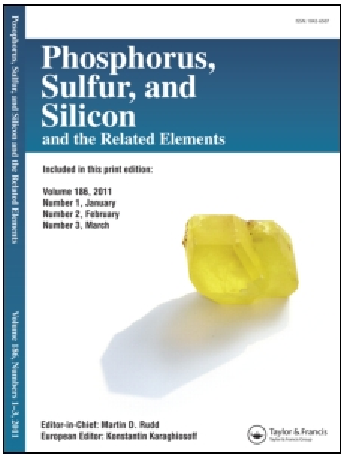

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Sulphur in the Strategy of Natural Products Synthesis

H. C. J. Ottenheijm[a]
[a] Laboratory of Organic Chemistry, University of Nijmegen, ED NIJMEGEN, The Netherlands

To cite this Article Ottenheijm, H. C. J.(1985) 'Sulphur in the Strategy of Natural Products Synthesis', Phosphorus, Sulfur, and Silicon and the Related Elements, 24: 1, 129 — 150

To link to this Article: DOI: 10.1080/03086648508073399

URL: http://dx.doi.org/10.1080/03086648508073399

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Phosphorus and Sulfur, 1985, Vol. 24, pp. 129-150
0308-664X/85/2401-0129/$25.00/0

SULPHUR IN THE STRATEGY OF NATURAL PRODUCTS SYNTHESIS

H.C.J. OTTENHEIJM
Laboratory of Organic Chemistry, University of Nijmegen, Toernooiveld, 6525 ED NIJMEGEN, The Netherlands

Abstract Syntheses of secondary metabolites of α- and β-mercapto aminoacids are described. The strategy in the first class of compounds consists of using N-hydroxy-α-amino acid derivatives as intermediates and of converting them into α-functionalized, in particular thiol-substituted amino acids; as examples serve syntheses in the gliotoxin and sporidesmin series. In the second class of compounds the cycloaddition products of indole derivatives, having sulfide substituents, and nitroso olefins are transformed into indole alkaloids, in particular tryptathionins, by rearrangement and further reactions.
The antitumor agent sparsomycin has been synthesized via an amino sultine and its stereospecific nucleophilic ring opening. Bioassays done with this compound and sixteen of its structural analogs gave insight in the structural features that are required for sparsomycin's antitumor activity.

Introduction

When the organic chemist uses the term "natural products", he usually means secondary metabolites. These secondary metabolites are distinct from primary metabolites in that they are frequently of relatively complex structure; in addition their distribution is restricted and more characteristic of specific sources. Whereas there are no sharp lines delimiting either class of compounds primary metabolites are nearly universal in their distribution; they are the products of, and participants in, the cellular activities of nearly all living organisms, from microorganisms to man.

Sulphur-containing amino acids fit very well into this classification. A vast number of sulphur-containing compounds that occur in nature is derived from cysteine and - to a smaller degree - methionine. These common amino acids - in their L-configuration - fall into the category of primary metabolites; their occurrence - e.g. as constituents of proteins - is widespread in all living cells, see Figure 1.

Other sulphur-containing amino acids, not found as constituents of proteins but widespread in plants and microorganisms, can be accomodated within the general structures 1 and 2.

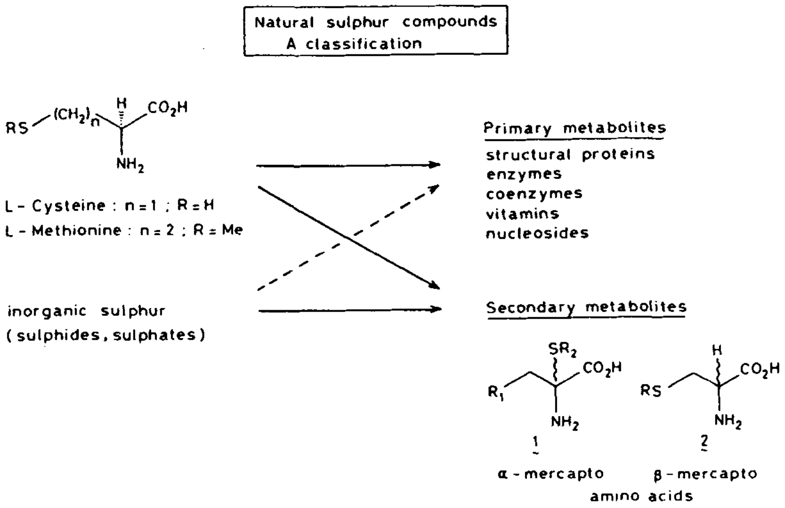

Fig. 1

Some illustrative examples of secondary metabolites characterized by structure 1 are given in Figure 2.

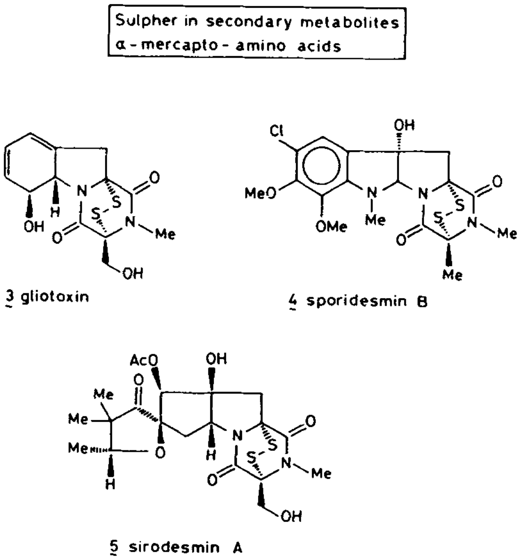

Fig. 2

Several examples of secondary metabolites containing the β-mercapto amino acid derivative 2 are presented in Figure 3.

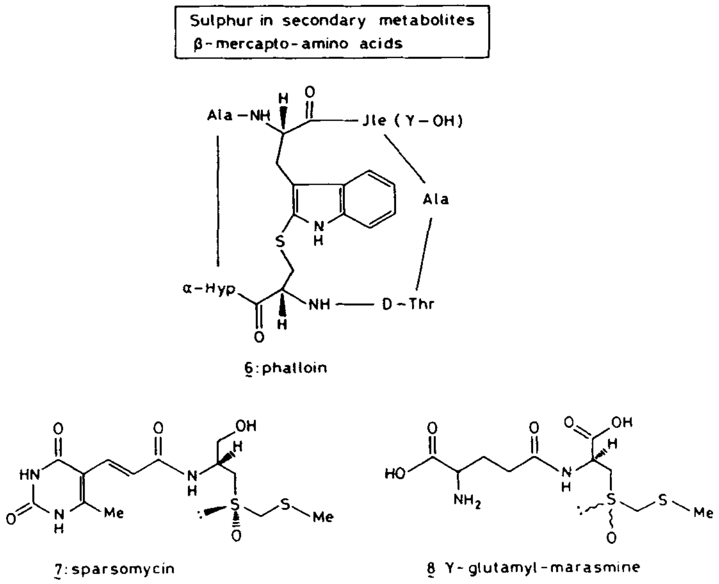

Fig. 3

We have embarked upon the application of novel synthetic methods directed towards all of the compounds listed. Herein we wish to summarize our efforts aimed at two characteristic examples of each class mentioned above, i.e. compounds 3,4,6 and 7.

α-MERCAPTO-α-AMINO ACID DERIVATIVES 1

A biogenetic approach

One of the targets that we settled upon originally was gliotoxin (3), in part because of its structure and in part because of its biological activity: it inhibits reverse transcriptase, an enzyme characteristic for RNA-viruses.

Gliotoxin can be viewed as an oxidized condensation product of two α-mercapto-α-amino acid derivatives 9 (Figure 4). However, neither of these derivatives is evidently capable of independent existence; unacylated α-mercapto-α-amino acids could not yet be synthesized.

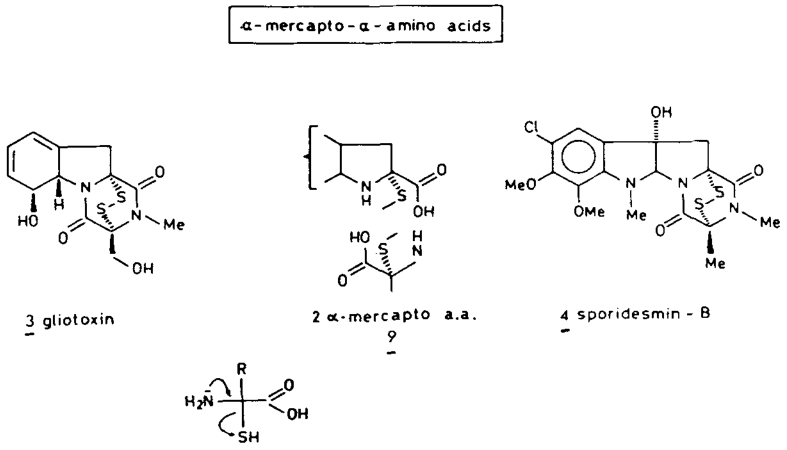

Fig. 4

Accordingly, we felt that a synthetic procedure for gliotoxin analogs would have to create a functional group at the indoline C(2) position, convertible to a mercapto group, simultaneously with the acylation of the indoline nitrogen by an α-mercapto-α-amino acid equivalent. Our initial, successful approach[1] involved the addition of pyruvoyl chloride[2] to the imine bond of an indolenine and the intramolecular cyclization of an amide nitrogen with the pyruvoyl α-carbonyl group (see 10; Figure 5).

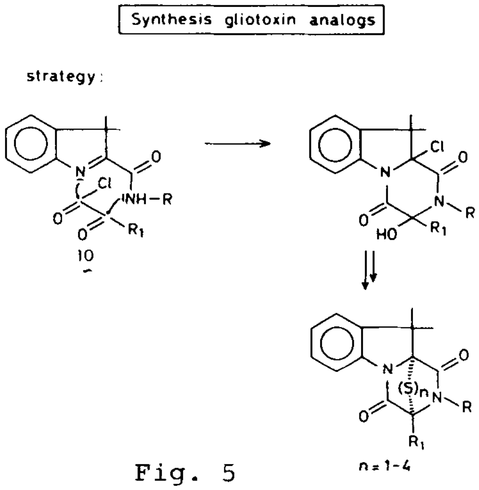

Fig. 5

This approach - which is certainly not biogenetic - led us to speculate on the biosynthesis of gliotoxin. Cyclo-L-Phe-L-Ser has been shown to be an efficient precursor of gliotoxin (3), and further labeling studies have demonstrated that the N-methyl group is derived from methionine, whereas the sulfur atoms are delivered by cysteine[3]. The most likely explanation for the formation of the dihydroaromatic system has been provided by Neuss et al[4], who invoked the intermediacy of a benzene oxide 11 (Figure 6).

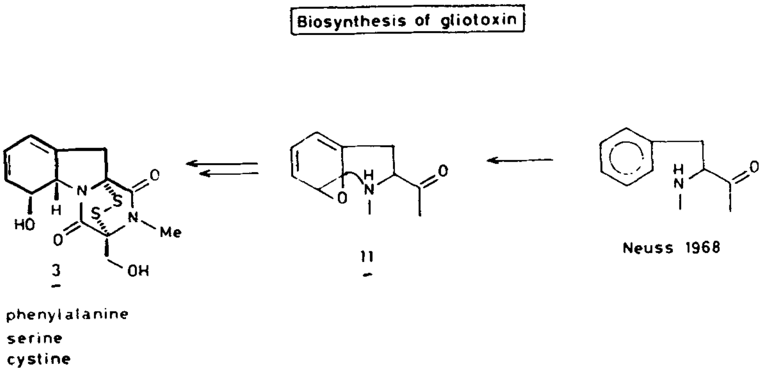

Fig. 6

We have proposed a mechanism for the introduction of the sulfur bridge [5]. This proposal features oxidation of the dioxopiperazine amide nitrogen in 12 to form the hydroxamic acid 13 followed by dehydration to the acylimine 14 (Figure 7).

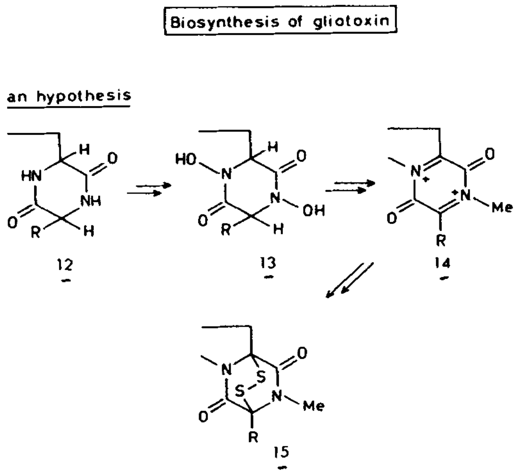

Fig. 7

We reasoned that the proposed role of N-hydroxy-α-amino acids 13 in the biosynthetic conversion of α-amino acids 12 into α-functionalized α-amino acids 15 might gain in probability if the latter could be obtained chemosynthetically by starting from N-hydroxy-α-amino acids. In Figure 8 some results toward this directive are depicted, which lent support to our hypothesis.

Selective reduction [6] of the oxime C=N bond of 16 and subsequent N-acylation of 17 yielded N-hydroxy-α-amino acid derivatives 18. Treatment with base (t-BuOK in MeOH) afforded the α-methoxy-α-amino acid derivatives 21, a reaction for which we proposed the acylimine 19 as an intermediate [7]. If this acylimine is formed in the absence of a nucleophile (DBU in dioxane) it rearranges [8] into a dehydro-α-amino acid 20 [9].

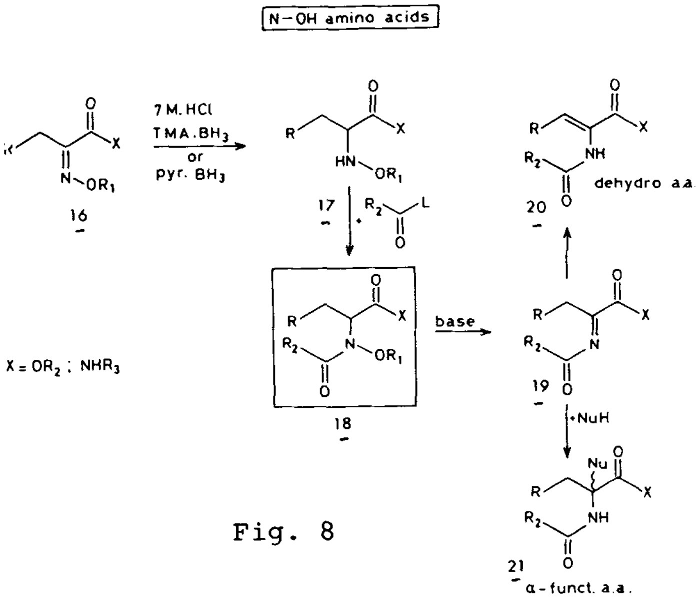

Fig. 8

Subsequently we were able to show [5] that this approach for α-functionalization by transposition of an N-functionality could also be achieved in dioxopiperazines, e.g. 22 as outlined in Figure 9.

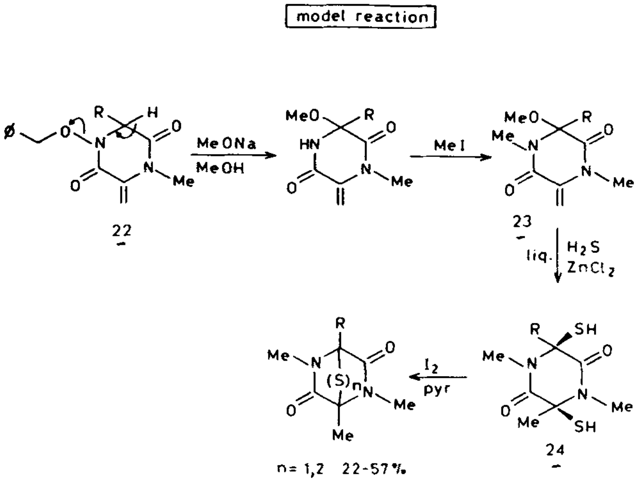

Fig. 9

The conversion 23→24 deserves an explanation. The Markownikoff-type H_2S addition to the exo-methylene bond of 23 was found to proceed in a diastereoselective fashion; only the cis-dithiol 24 could be detected. This zinc chloride-catalyzed reaction could be explained in the following way (Figure 1o).

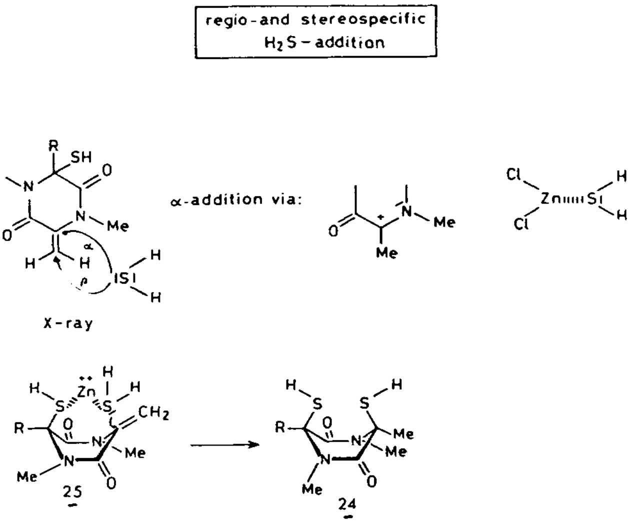

Fig. 1o

A zinc complex with the SH-group in 25 might direct the incoming SH-group from the same face by complexation, yielding 24. A second role for the catalyst is to convert H_2S into a stronger acid; when 25 is exposed to H_2S in the absence of zinc chloride no reaction took place [1].

Presently, the conversion of di-N-hydroxydioxopiperazines [10] (26) into sulfur bridged dioxopiperazines 27 is being studied (Figure 11).

applications

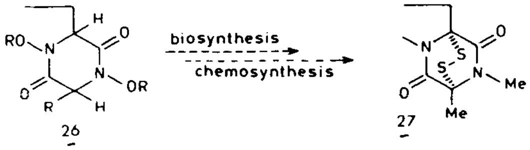

Fig. 11

Encouraged by these results, we selected sporidesmin B (4) as our next target and focussed on the conversion of N-hydroxytryptophan 28 into the corresponding α-functionalized amino acid (Figure 12).

Chemistry of N-OH Trp

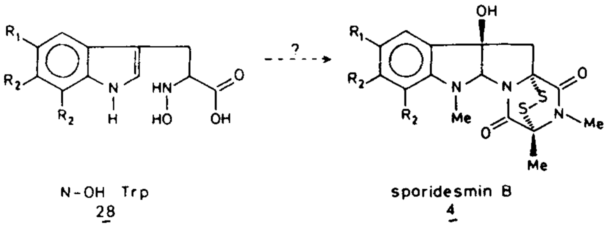

Fig. 12

Two syntheses of 28 were developed [11]. One procedure started from indole-3-pyruvic acid which was converted into the corresponding O-benzyl oxime ethyl ester. Methylation of the indole nitrogen and reduction of the oxime C=N bond with $(CH_3)_3N{-}BH_3$, afforded the N-benzyloxy amino acid ester (cf $16 \longrightarrow 17$). The second route (Figure 13) features[12] the reaction of N-methylindole (29, R_1 = H) with the transient nitroso olefin 31, prepared from 3o. The adduct 32 cannot be isolated; base catalyzed rearomatization afforded 33. Reduction gave 34 in good yields.

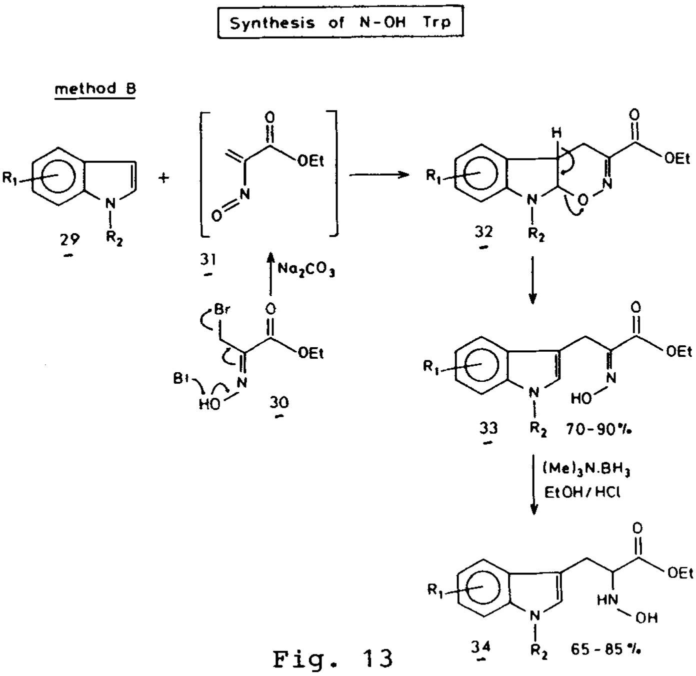

Fig. 13

Pyruvoyl chloride[2] and 34 in CH_2Cl_2/ether reacted at room temperature to form 35 (Figure 14); no O-acylation was observed. About 24 hrs. after mixing the intermediate was converted completely into 36. When stirred for several days after the addition of methanol, the corresponding α-methoxy derivative is formed, which was benzylated to give 37. Diastereomeric induction was observed; the indolyl group and methyl group are in a cis-relationship in the major isomer (9o%).

An approach to sporidesmin

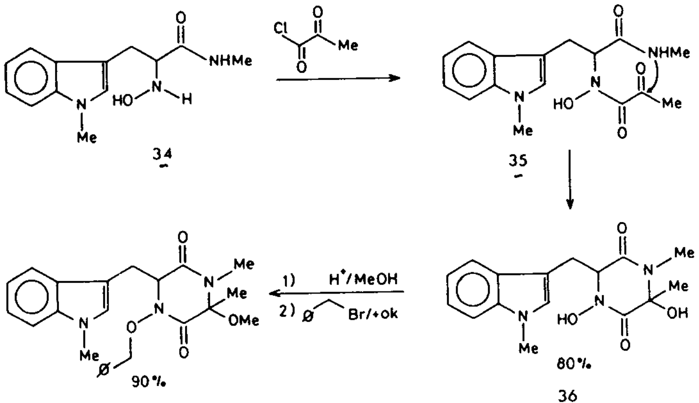

Fig. 14

Transposition of the N-functionality in 37 to an α-functionality (⟶38) was achieved by treatment with CH_3ONa/CH_3OH (Figure 15). The diastereomers were separated and each diastereomer was subjected to the following reaction. For closing of the five membered ring singlet oxy-

An approach to sporidesmin

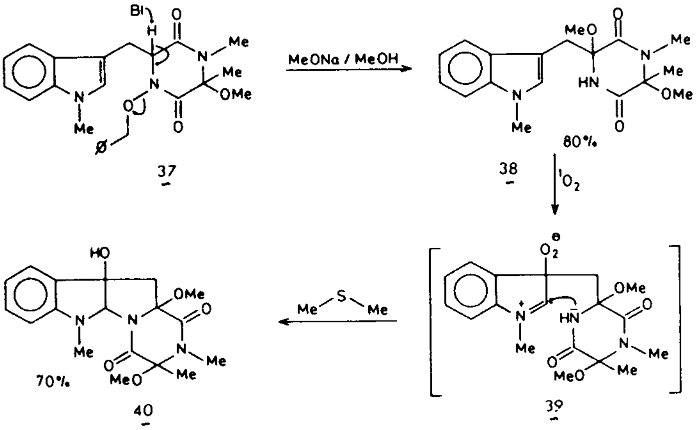

Fig. 15

gen was used [13]. A reliable procedure involves methylene blue as sensitizer and a reaction temperature of -78°C; reduction of the peroxo function in 39 led smoothly to 4o as outlined in Figure 15.

Hopefully the remaining stages will directly follow the sequence outlined in Figure 9 to allow conversion of 4o into the corresponding disulfide bridged dioxopiperazine. A total synthesis of sporisdesmin B (4) seems then feasible by using the properly substituted indole derivative [14] instead of 29 (see Figure 13).

β-MERCAPTO-α-AMINO ACID DERIVATIVES 2

Indole alkaloids

In the synthesis of the N-hydroxytryptophan derivative 34 from indole (29) we have seen the primarily formed cycloadduct 32 as an intermediate that escaped isolation (Figure 13). Intrigued by the potential usefulness of this adduct for other reaction schemes we have explored the chemistry of 42 formed by reaction of the corresponding indole derivative 41 and the nitroso olefin 31, Figure 16. I will summarize some results that are pertinent to the topic of this lecture.

We found that the stability of the cycloadduct 42 is related to the migratory aptitude of the substituent X.

When X is a fast-migrating group, e.g. an alkylthio substituent, not the cycloadduct 42a was isolated but a rearranged product 43 instead. This C(3) to C(2) migration occurs in good yields under mild reaction conditions (room temperature, CH_2Cl_2, Na_2CO_3). Stable cycloadducts are formed when the substituent X has a low migratory aptitude, e.g. when X is an alkyl or acetoxy group (42b). However, it was gratifying to observe that

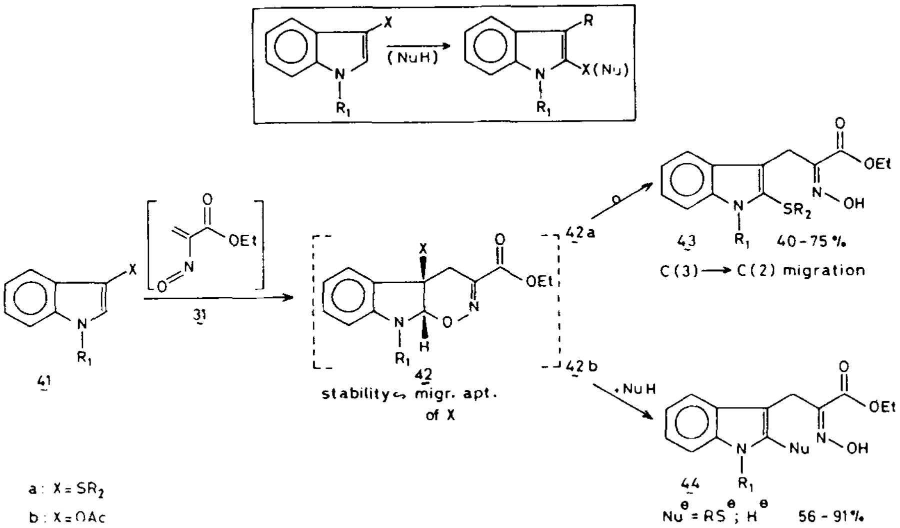

Fig. 16

the dihydro-1,2-oxazin ring of 42b is susceptible to nucleophilic attack: e.g. treatment with hydrides and mercaptides afforded the indole derivative 44. A mechanistic rationale for these reactions is presented in Figure 17. The indolenine derivative 45a - in equilibrium with 42a - forms the episulphonium 46, which undergoes rearomatization to yield 43. In case of X=OAc (42b), the intermediate indolenine 45b has a lower tendency to rearrange so that an external nucleophile can be added instead to yield 47. Subsequent elimination of AcOH yields 44.

We have employed [16] both reaction schemes for a novel approach to the 2-(S-cysteinyl)tryptophan derivative 51, a characteristic structural element of the toxic principles (e.g. Phalloin 6) of members of the genus Amanita. The results are summarized in Figures 18 and 19.

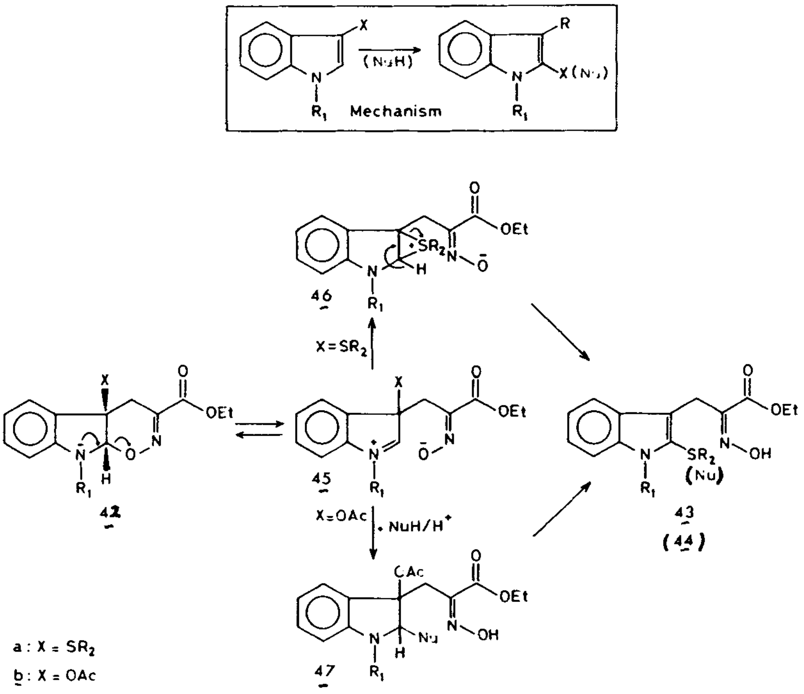

Fig. 17

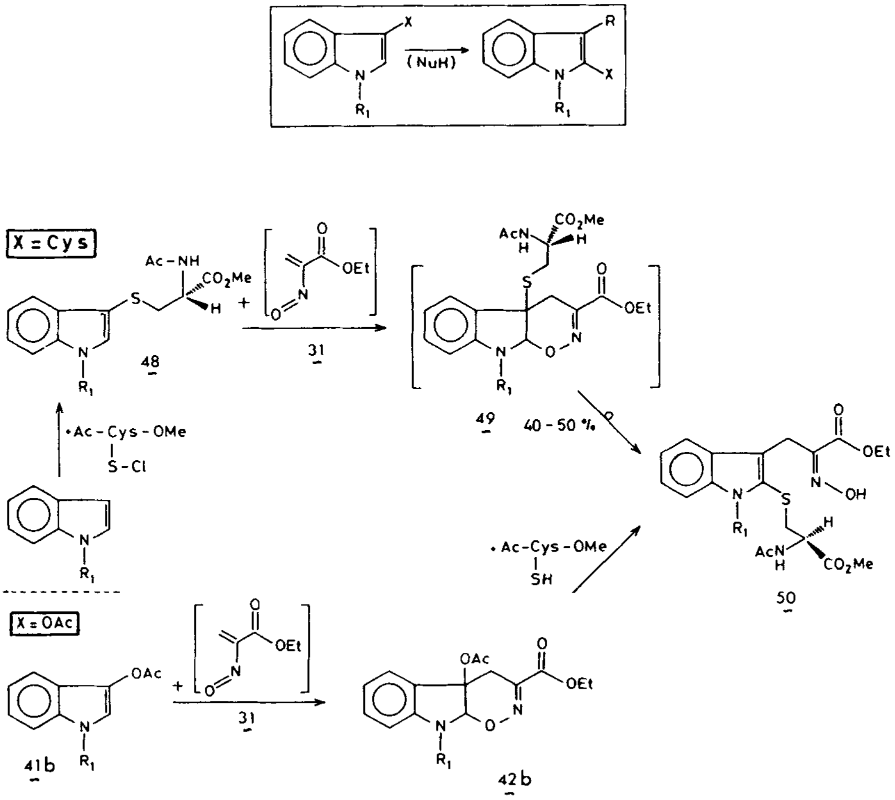
X
(NuH)
R
X
R₁
X = Cys
Ac-NH
CO₂Me
S
H
48
31
OEt
AcN
H
O
N
49
40 - 50 %
•Ac-Cys-OMe
S-Cl
•Ac-Cys-OMe
SH
N-OH
50
X = OAc
OAc
41b
42b

Fig. 18

Synthesis of Tryptathionine

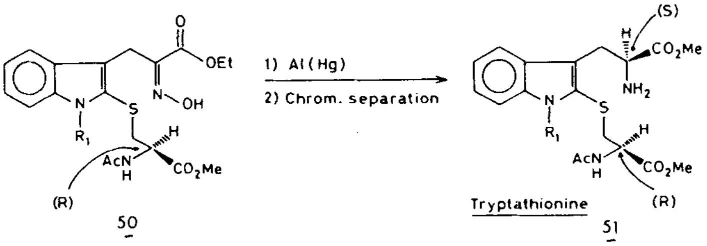
OEt
N-OH
S
AcN
H
CO₂Me
(R)
50
1) Al(Hg)
2) Chrom. separation
(S)
H
CO₂Me
NH₂
Tryptathionine
(R)
51

Fig. 19

In conclusion the adduct 42 opens a new approach to indole alkaloids, both in terms of strategy and methodology.

Sparsomycin: synthesis and structure-activity-relationship studies

Sparsomycin (17), a metabolite of Streptomyces sparsogenes or Streptomyces cuspidospores, has attracted much attention, partly because of its unusual structure - notice the in nature rarely encountered $-S(O)CH_2S-$moiety - and partly because of its biological activity of which the antitumor activity and the inhibition of protein biosynthesis are the most striking properties [17]. On the **basis** of spectroscopic and degradation studies [18] the presently accepted structure 7 was proposed; however, the chirality of the sulfoxide sulfur atom remained undetermined in these studies.

In an analysis of the synthetic problem (Figure 2o) sparsomycin can be considered as an amide derived from the acid component 52 and the amine component 53. The latter can be viewed as a derivative of D-cysteine having its $-CO_2H$-function reduced and its -SH function alkylated and oxidized.

Component 52 could be prepared by using a Wittig condensation [17]. More challenging was the synthesis of component 53, since the unsymmetrically substituted $-S(O)CH_2S-$moiety is acid labile and may also undergo β-elimination - thermal or base-induced - to which sulfoxides are prone. An attractive approach to a protected derivative of 53, i.e. 53A appeared to be nucleophilic ring opening of a cyclic sulfinate ester 54, a γ-sulfine (Figure 21). This compound has a sulfur atom activated

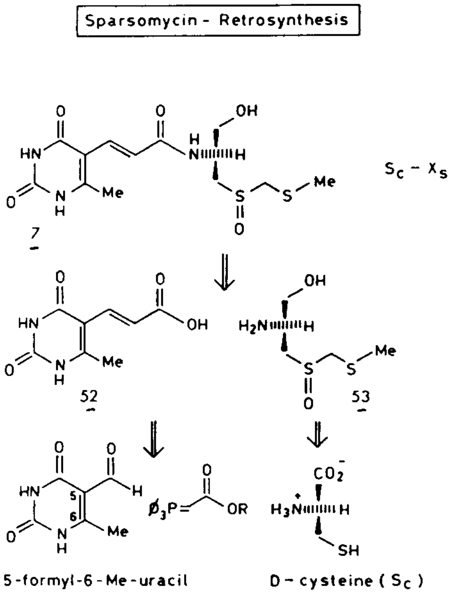

Fig. 2o

toward nucleophilic attack as well as a protected alcohol function. This approach was a viable one: we have synthesized sultines of type 54 starting from D-cysteine and have studied their ring opening reactions with nucleophiles (Figure 22).

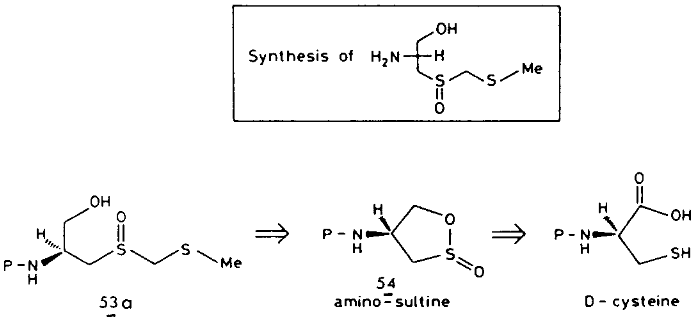

Fig. 21

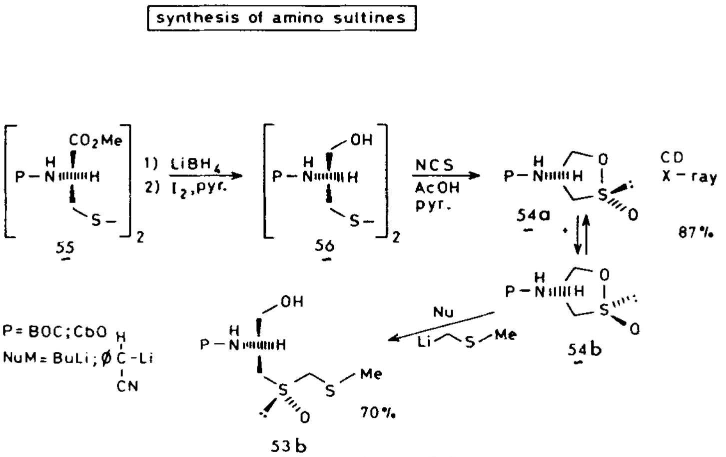
synthesis of amino sultines

Fig. 22

The N-protected D-cystinol derivative 56, prepared from 55 by $LiBH_4$ reduction followed by I_2 oxidation, was treated with three equiv of NCS in AcOH to afford 54A and 54B (1:1 ratio) in 87% yield[19]. The structures - including the absolute configuration of the sulfur atoms - were assigned by CD spectroscopy and X-ray crystallographic analysis[19,20].

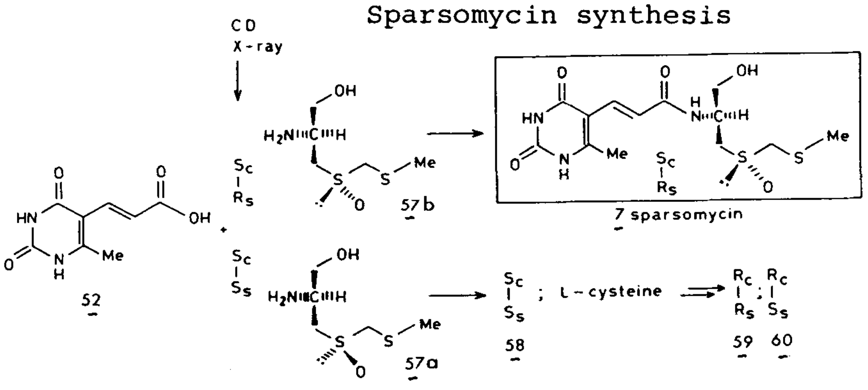
Sparsomycin synthesis

Fig. 23

We were pleased to find that the sultines underwent nucleophilic ring opening smoothly and with inversion at sulfur: e.g. treatment of 54B with $MeSCH_2Li$ gave 53B in 7o% yield. The amino alcohol 57B (Figure 23) was prepared quantitatively by treatment of 53B (P = t-BOC) with CF_3CO_2H at 0°C and subsequent deprotonation with an ion-exchange resin. Coupling of 52 with 57B was achieved by means of DCC and hydroxybenzotriazole to yield a compound that was identical with sparsomycin in all respects. From this we concluded that sparsomycin's sulfoxide sulfur atom must have the R-chirality.

Sparsomycin's three stereomers 58-6o were prepared using the same approach. Finally, the synthesis of sparsomycin was optimized by making use of the finding [21] that sultines 54A and 54B undergo a clean epimerization at the sulfur atom when heated at 12o-13o°C. Consequently, the 'wrong' isomer 54A was recycled by conversion into a 1:1 mixture of 54A and 54B, out of which 54B was readily isolated by flash column chromatography.
In the course of our synthetic work on 54, we found [16,19] that selective cleavage of the S-OR bond in sultines can be achieved by a wide variety of nucleophiles ($n\text{-}Bu^-$, CH_2CN^-, $CH_2CO_2Bu^{t-}$, $CH_2P(O)(OEt)_2^-$, $C_6H_5C(H)CN^-$ and $C_6H_5C(CH_3)CN^-$). With the last two nucleophiles asymmetric induction on the prochiral carbon atom was observed; in order to understand this induction we studied [22] the conformation of 54A and 54B in solution by ^1H-NMR. We also studied [21] the thermolytic SO_2-extrusion of the functionalized sultines. Flash vacuum thermolysis yielded a Z/E-mixture of the corresponding N-protected enamides, a reaction we explained by a novel migration of the benzamide group involving a Claisen-type rearrangement.

The aforementioned approach to 53 and another one we had published previously [17] was flexible enough to allow the synthesis of 16 structural analogs of sparsomycin. Sparsomycin and these analogs were tested in cell-free systems for their ability to inhibit the protein synthesis [16] as well as in an in vitro clonogenic assay for their antitumor activity [23]. The results of these assays indicate that sparsomycin's antitumor activity is primarily due to an inhibition of the protein biosynthesis. In addition, we were able to draw conclusions about the structural features that are required for sparsomycin's antitumor activity. These conclusions are summarized in Figure 24.

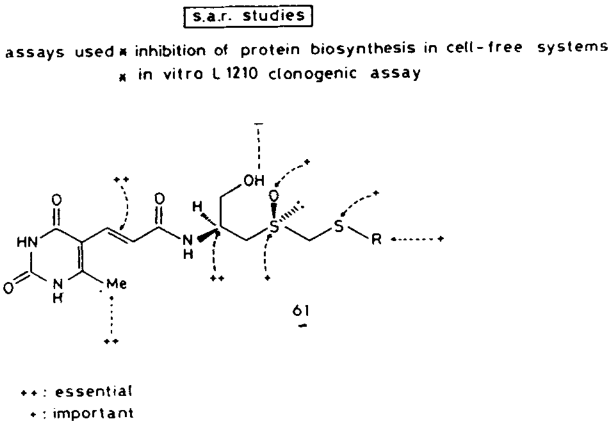

Fig. 24

These results lend support [24] to a mechanistic rationale for sparsomycin's activity on a molecular basis: it has been proposed [25] that the inhibitory activity might be due to a Pummerer-like reaction involving sparsomycin's sulfoxide moiety causing an irreversible blocking of the growing peptide chain.

Finally, our approach resulted - for the time being - in the synthesis of two analogs - benzylsparsomycin (61, R=$CH_2C_6H_5$) and octylsparsomycine (61, R=nC_8H_{17}) - that have a higher cytostatic activity and a lower toxicity than sparsomycin (61, R=Me). Work is in progress to obtain additional arguments for the introduction of the most promising analog of sparsomycin into the clinic as an antitumor agent.

In conclusion, these results underline our view that a flexible synthesis of a biologically active compound is a prerequisite for an analysis of the structural features that are essential for an optimal activity as well as for a study of the mode of action of that compound.

Acknowledgements

I wish to thank my coworkers for their patience and dedication in collaborating in the work I have described. I am particularly indebted to Dr. J.D.M. Herscheid, Dr. R.M.J. Liskamp and to Mr. R. Plate. We are grateful to Prof. Dr. R.J.F. Nivard for his support.

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