PREPARATION AND USE OF NITROGEN- OR SULFUR CONTAINING HETEROCYCLES IN ORGANIC SYNTHESIS.

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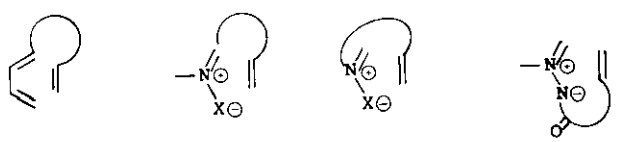
ABSTRACT

The utility of intramolecular cycloadditions of ortho-quinodimethanes for the synthesis of complex polycyclic molecules is illustrated: 1) by the stereoselective synthesis of the natural alkaloid (±)-chelidonine starting from a benzocyclobutene; 2) by the efficient preparation of various polycyclic carbon skeletons using 1,3-dihydroisothianaphthen-2,2-dioxide as a simple building block. Furthermore, the total syntheses of the ergolines chanoclavine I and isochanoclavine I, exploiting a regio- and stereo-selective intramolecular nitrone-olefin-addition, is described.

INTRODUCTION

Over the last 12 years a major part of our research has been focused on intramolecular cycloaddition and ene reactions. By now the utility of these reactions for the efficient synthesis of polycyclic molecules has become generally recognized, as is apparent by the rapid development of this field.[1,2]
Today I would like to outline some aspects of intramolecular Diels-Alder and nitrone additions with emphasis on important features such as regio- and stereo-

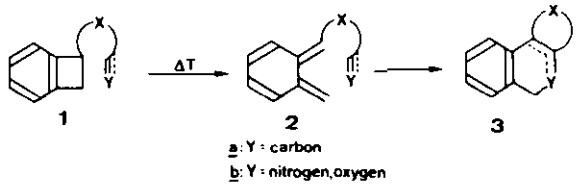


- Scheme 1 -

selectivity, and last but not least, the accessibility of the key precursors.

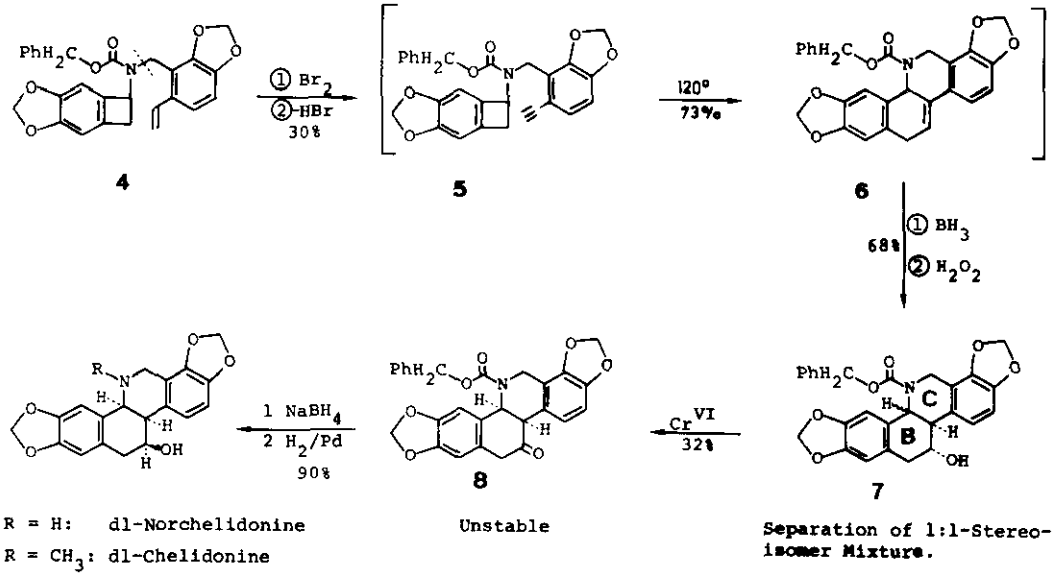
INTRAMOLECULAR DIELS-ALDER REACTIONS

It is well established that a variety of polycyclic annelated systems 3 are readily obtained by heating benzocyclobutenes carrying an unsaturated chain in position 1[2]. Initial thermal opening of the four-membered ring leads to the transient



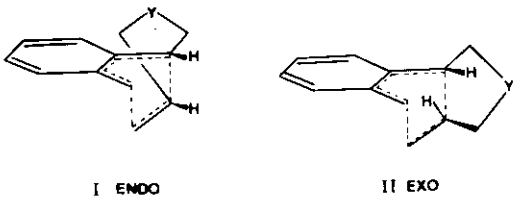
- Scheme 2 -

(E)-ortho-quinodimethanes 2 which are then trapped by the suitably positioned multiple bond. Nearly 9 years ago we reported the synthesis of (±)-chelidonine 10 which constitutes the first application of this reaction sequence in natural



- Scheme 3 -

product synthesis[3]. Although the key step 5 → 6 efficiently provides the skeleton of the target molecule the attraction of this synthesis is severely diminished by the poor yields of the transformations 4 → 5 and 7 → 8. In particular the non-stereoselective hydroboration 6 → 7 requiring chromatographic separation and loss of the undesired trans-fused alcohol 7 is clearly unacceptable. We therefore tried to establish the desired B/C-cis-fusion by conformational control of the cyclo-addition step (Scheme 4) instead of elaborating the stereochemistry at a later

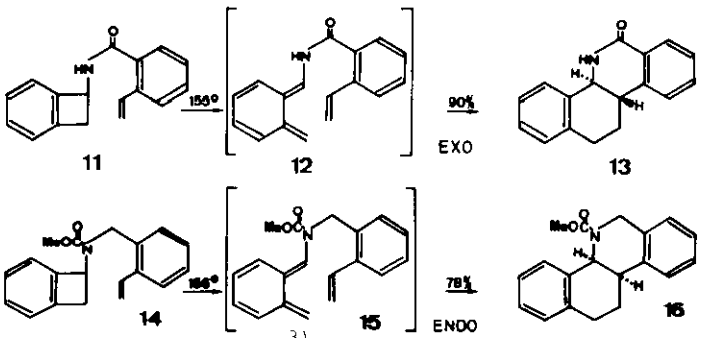


I ENDO II EXO

- Scheme 4 -

stage of the synthesis. In fact, model studies showed that the amide 11 furnished selectively the trans-fused exo-adduct 13. By contrast the cis-fused endo-product 16 was obtained preferentially in high yield from the closely related urethane 14

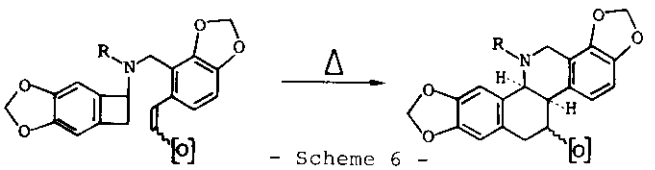
- Scheme 5 -



11 12 EXO 13

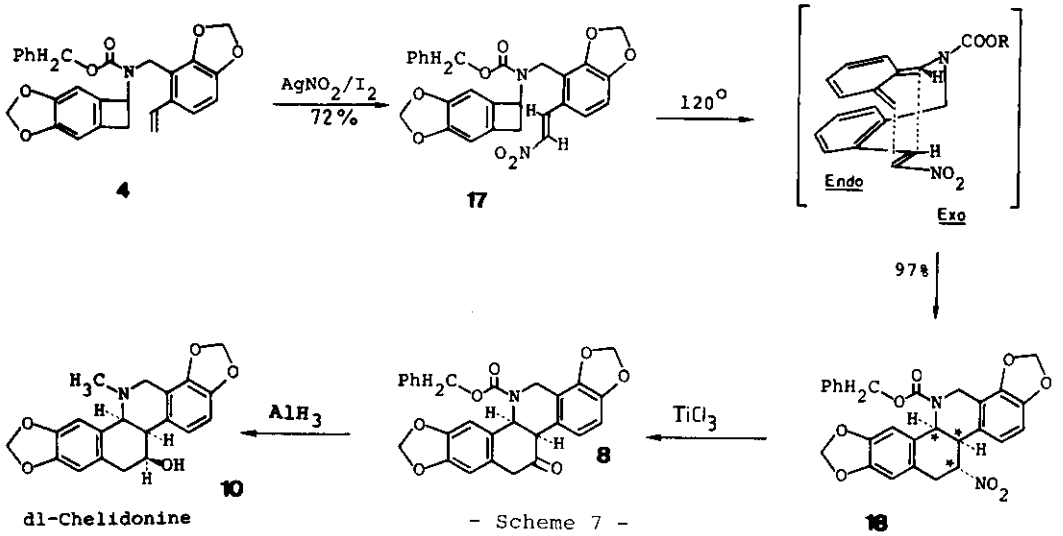
14 15 ENDO 16

under identical reaction conditions[3]. Accordingly the synthetic plan for chelidonine was modified (Scheme 6) by using an olefin carrying an oxygen or equivalent



- Scheme 6 -

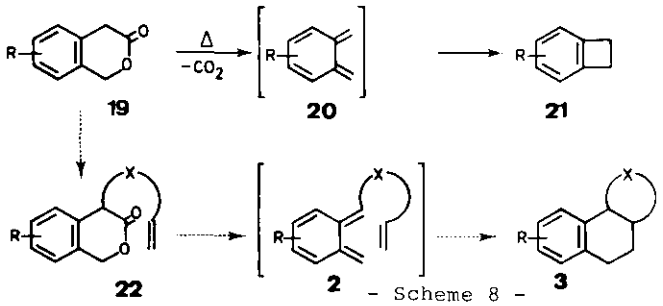
functionality as dienophile. As indicated in Scheme 7, the nitro group served



4 17 Endo Exo 18 8 10 dl-Chelidonine

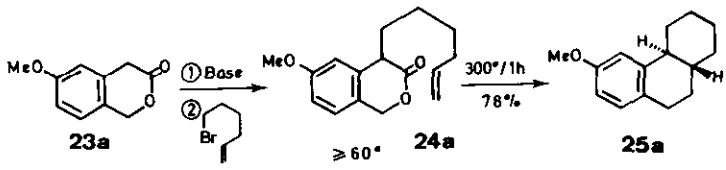
- Scheme 7 -

perfectly in this context as a masked oxygen substituent. First, it was readily introduced into the known styrene 4 by reaction with silver nitrate in the presence of iodine and potassium acetate[4], giving the nitrostyrene 17 in 72% yield. Heating of 17 in xylene at 120° for 2 hrs gave after crystallisation the cis-fused adduct 18 in 97% yield. Not even a trace of any other stereoisomer was found in the mother liquor. This remarkable stereoselectivity of the addition 17 → 18 reflects a transition state with the nitro group in the unusual exo-orientation and demonstrates nicely the power of intramolecular control of stereochemistry. Treatment of the nitro compound 18 with $TiCl_3$[5] furnished under mild conditions the sensitive ketone 8. Concomitant reduction of the carbonyl and urethane groups of crude 8 with aluminum hydride gave (±)-chelidonine (identical to a natural sample of (±)-10) in 54% yield from 18[6]. It goes without saying that intramolecular quinodimethan-additions are not only useful for the synthesis of complex heterocycles but also for the stereoselective construction of polycyclic carbon skeletons. Thus, the value of this reaction for the synthesis of aromatic steroids is amply documented[2,7]. Although benzocyclobutenes are versatile starting materials their preparation requires several steps. It seemed therefore worthwhile to exploit further routes to quinodimethanes using heterocyclic precursors. For example, 3-isochromanones 19 are efficiently converted to benzocyclobutenes 21 on heating, probably via non-isolated ortho-quinodimethanes 20[8].



- Scheme 8 -

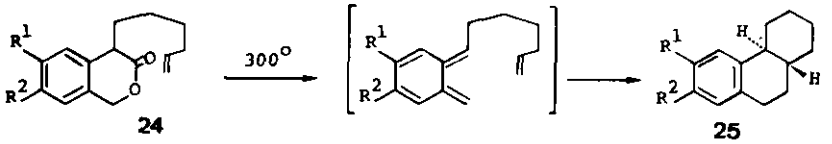
It thus appeared promising to functionalize the isochromanone (19 → 22) and to combine the Diels-Alder-cycloreversion 22 → 2 with an intramolecular trapping of the intermediate diene 2 → 3. Indeed, alkylation of the enolate derived from the isochromanone 23a with 1-bromo-5-hexene allowed the smooth introduction of an



- Scheme 9 -

olefinic chain. Subsequent thermolysis of 24a in diethyl phthalate gave directly the trans-fused octahydrophenanthrene 25a in high yield. However, as shown in

Scheme 10, the efficiency of this cycloreversion-cycloaddition-sequence seems to depend on the aromatic substitution of the precursors 24; the products 25



24 25

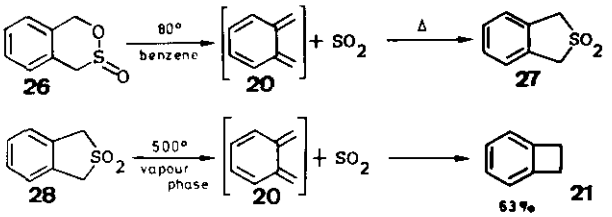
	R^1	R^2	Yield
a	OMe	H	78%
b	OMe	OMe	60%
c	O	CH_2-O	52%
d	H	H	20%
e	H	OMe	19%

- Scheme 10 -

were obtained in fair to good yields only when R^1 in isochromanone 24 was an alkoxy-substituent[9].

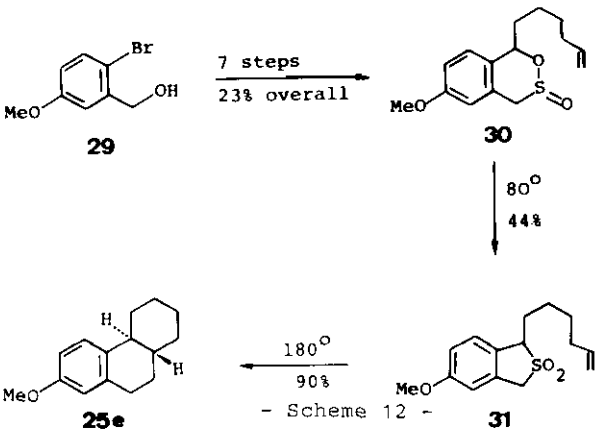
With the aim of finding a functionalisable masked quinodimethane unit of more general applicability we turned our attention to cyclic sulfinates and sulfones.

- Scheme 11 -



26 20 27 28 20 21

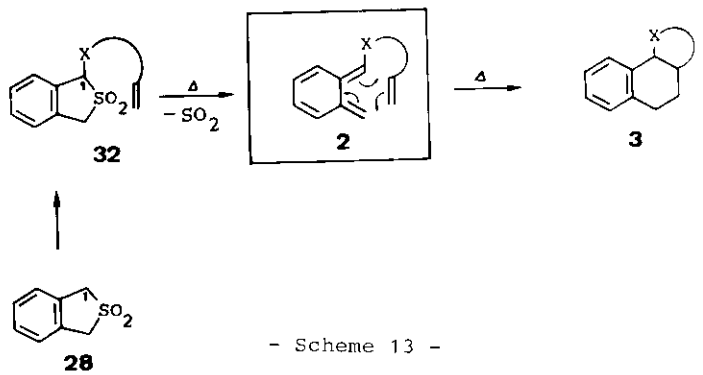
Both cycloreversion of the oxathiine 26[10] as well as chelotropic SO_2- extrusion from the isothianaphthen dioxide 28[11] were already described as giving the unstable quinodimethane 20. As a logical extension of this work the sulfinate 30 was prepared from the bromide 29 by a sequence of 7 steps. However, heating the



29 30 25e 31

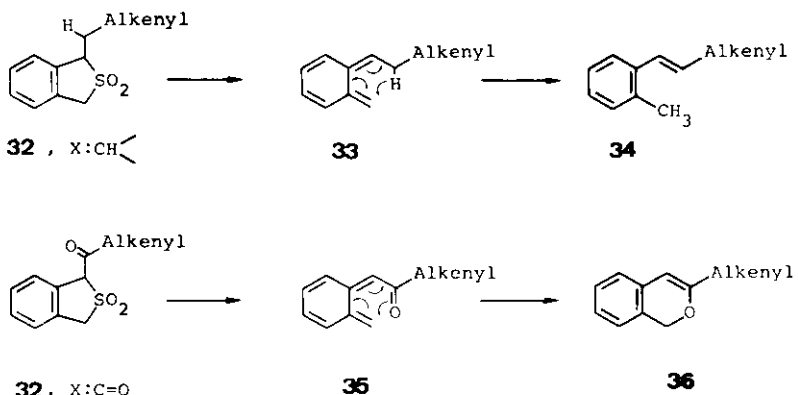
- Scheme 12 -

sulfinate 30 in refluxing benzene gave no trace of the expected adduct 25e. Instead the sulfone 31 was obtained as the sole product. On the other hand we were pleased to find that SO_2- extrusion of 31 at 180° furnished the adduct 25e in 90% yield[9]. In view of this result it seemed worthwhile to explore a more direct approach to olefinic isothianaphthen dioxides. Accordingly, we anticipated that the readily available sulfone 28 would afford the monosubstituted isothianaphthen dioxide 32 by consecutive deprotonation and alkylation or acylation (Scheme 13). Encouraged by the efficient conversion 31 → 25 (Scheme 12),



- Scheme 13 -

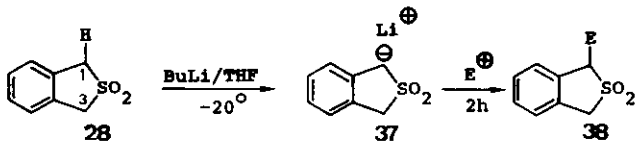
we expected that the thermal SO_2-elimination would lead predominantly to the (E)-quinodimethanes 2, ideally suited for the cycloaddition 2 → 3. There remained, nevertheless, some uncertainty as to what extent (Z)-quinodimethanes might be formed, such as 33 and 35 (or the corresponding diradicals), which would easily

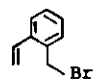
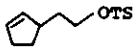


- Scheme 14 -

undergo 1,5-H-shift 33 → 34 or cyclisation 35 → 36.

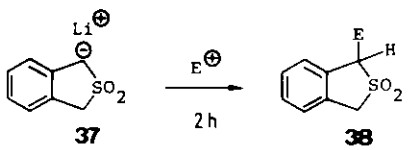
The sulfone 28 was most conveniently deprotonated with butyllithium at -20°. Alkylation of the resulting anion 37 with alkenyl bromides and tosylates gave

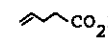
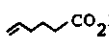


	Electrophile	Yield
a		76%
b		61%
c		53%
d		45%

- Scheme 15 -

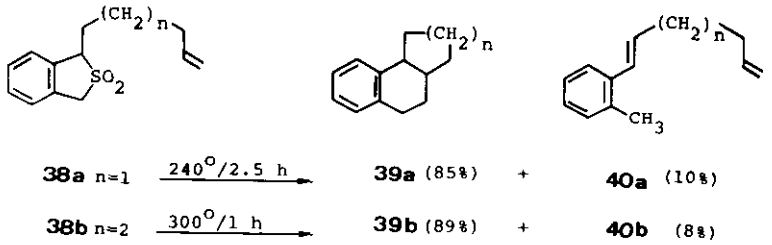
mainly the monosubstituted sulfones 38 in satisfactory yields after separation from minor amounts of 1,3-dialkylated products and unchanged 28. Acylation of the anion 37 by carboxylic esters required two mol. of 37 per mol. of ester owing to the acidic nature of the acylsulfone products 38 which were obtained in excellent yields. Similarly, sulfenylation of 37 with 0.5 mol-equiv. of a disulfide fur-



	Electrophile	Yield
e		95%
f		91%
g		80%
h	PhSSPh	81%
i	MeSSMe	86%

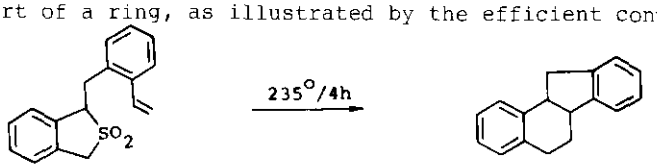
- Scheme 16 -

nished smoothly the thioethers 38h and 38j. Having developed a practical route to various olefinic sulfones 32, the stage was set to study the thermolyses 32 → 2 → 3. On heating the pentenyl-sulfone 38a in diethyl phthalate at 240° for 3 h the desired adduct 39a was obtained in 85% yield as a mixture of two stereoisomers.

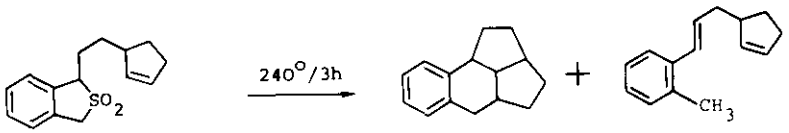


- Scheme 17 -

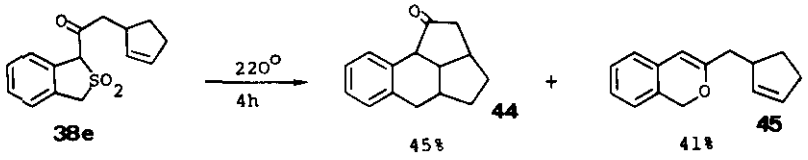
The formation of a small amount of the styrene 40a reflects the intermediacy of some (Z)-quinodimethane (or the corresponding diradical). Similar yields of 39b and 40b were obtained by the analogous pyrolysis of the homologous hexenyl-sulfone 38b. Tetracyclic ring systems may be readily formed when the bridge to the olefinic bond 32 is part of a ring, as illustrated by the efficient conversions 38c → 41 and 38d → 42.



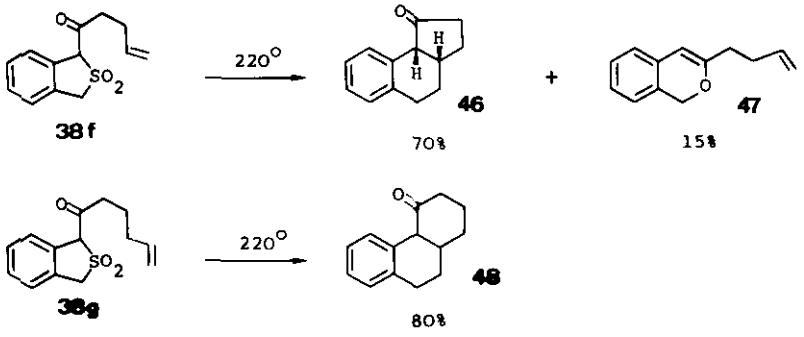
- Scheme 18 -



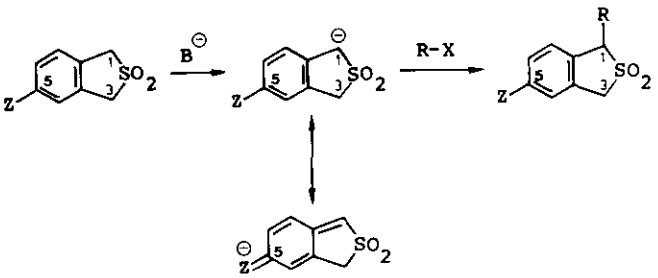
Thermolysis of the acylated sulfones 38e, 38f and 38g in refluxing trichlorobenzene furnished the desired adducts 44, 46 and 48 in fair to good yields depending on the extent of competitive isochromene formation.



- Scheme 19 -

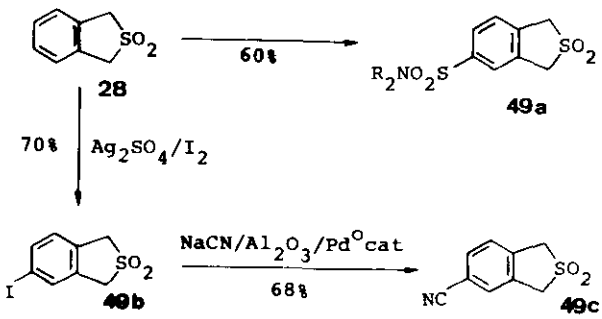


The evidence presented here[12] as well as independent work from the laboratory of K.C. Nicolaou[13] indicates isothianaphthen dioxides 32 to be useful building blocks for the synthesis of polycyclic molecules. However, there remains one nasty little problem: How to direct the electrophilic substitution of 5-substituted isothianaphthenes selectively into the 1-position ? However insignificant this problem appears at first sight, its solution is absolutely indispensable for the general use of isothianaphthenes in the synthesis of natural products such as steroids. We therefore studied the possibility of favoring selective deprotona-



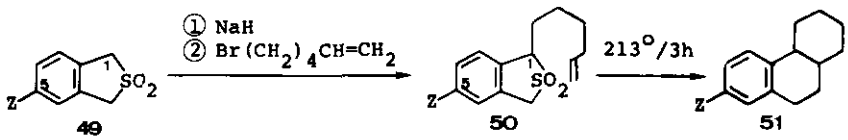
- Scheme 20 -

tion at C-1 by means of an electron-attracting substituent Z in the para-position C-5 (Scheme 20). For reasons of practicability and flexibility, introduction of Z into the readily available sulfone 28 seemed preferable to an ab-initio construction of the aryl-substituted heterocycle. The sulfonamide 49a was easily prepared



- Scheme 21 -

by classical procedures involving chlorosulfonation of 28. Introduction of the more interesting nitrile group (28 → 49c) required newer methodology such as the iodination[14] of 28 followed by a palladium-catalyzed iodine/cyanide exchange using a solid alumina support[15]. Although simple nitration of 28 afforded smoothly the corresponding 5-nitro-isothianaphthen dioxide, subsequent treatment with various bases led only to intractable tars. On the other hand, both the sulfonamide 49a and the nitrile 49c came up to our expectations; successive treatment of 49a or 49c with sodium hydride and 1-bromo-5-hexene furnished exclusively

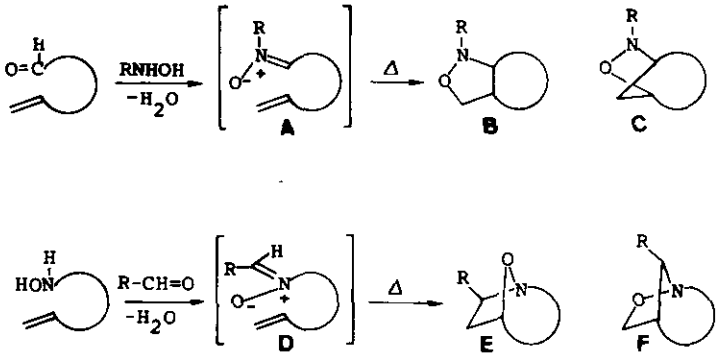


- Scheme 22 -

the 1-substituted sulfones 50. Thermolysis of 50 in boiling trichlorobenzene gave the desired adducts 51 in nearly quantitative yield[16].

Having solved the problem of regioselective 1,5-functionalization of the sulfone 28 we are now ready to apply these findings to the synthesis of (+)-estrone and other natural products.

INTRAMOLECULAR NITRONE-OLEFIN-ADDITIONS:

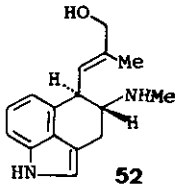


- Scheme 23 -

There is ample evidence for the potential of intramolecular nitrone-olefin additions in the synthesis of nitrogen-containing heterocycles[1a,b]. This has been nicely illustrated inter alia by the efficient syntheses of the alkaloids (+)-luciduline[17] and (±)-cocaine[18] exploiting in each case a regioselective addition of a N-alkenyl-nitrone D. Further insight into the regiochemistry of this process gained by a recent study[19] may prove of value in directing the additions of D towards either the products E or F. Despite numerous contributions from several research teams including our laboratory the reaction A → B has been rarely used in the field of natural product synthesis.

We now report a new synthesis of the ergot alkaloid Chanoclavine I based on the crucial addition of a C-alkenyl-nitrone A.

- Scheme 24 -



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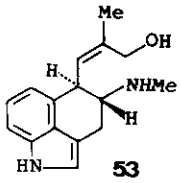
Chanoclavine I



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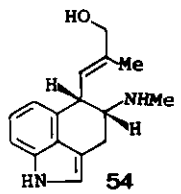
Isochanoclavine I



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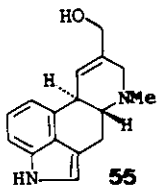
Chanoclavine II



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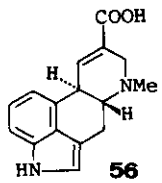
Elymoclavine



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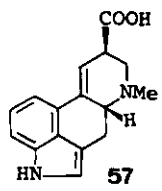
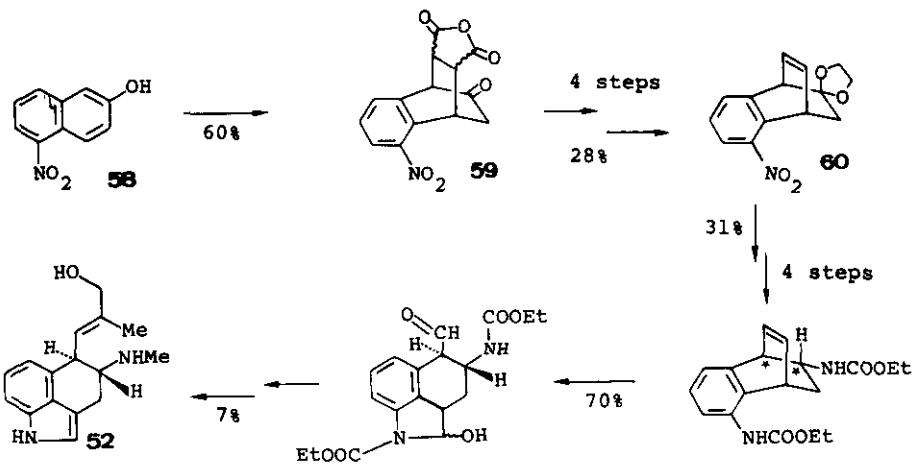
Paspalic Acid



57

Lysergic Acid

Chanoclavine I (52) was first isolated at the Sandoz company in Basel. It occurs in Claviceps purpurea together with two other alkaloids, isochanoclavine I (53) and chanoclavine II (54), which differ from 52 in their olefinic geometry or their chirality at C-10 respectively[20]. Chanoclavine I has been shown to be a biosynthetic precursor of elymoclavine 55 and hence of other tetracyclic ergolines such as paspalic and lysergic acids[21]. Whereas three different syntheses of lysergic acid (57) are known[22], only one non-stereoselective approach to chanoclavine I (52) has been reported by Plieninger and Schmalz[23]. The crucial steps are the Diels-Alder addition 58 → 59 and the ozonolysis 61 → 62 which leads

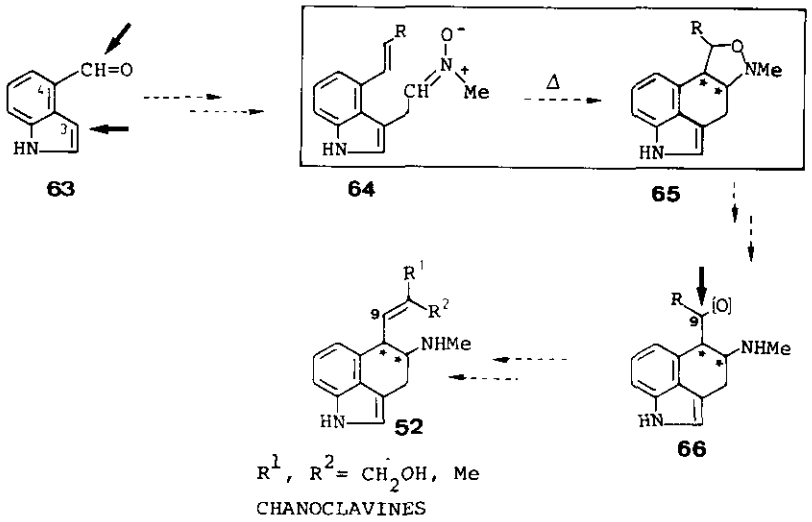


(±)-CHANOCLAVINE I

Total yield: 0.25%

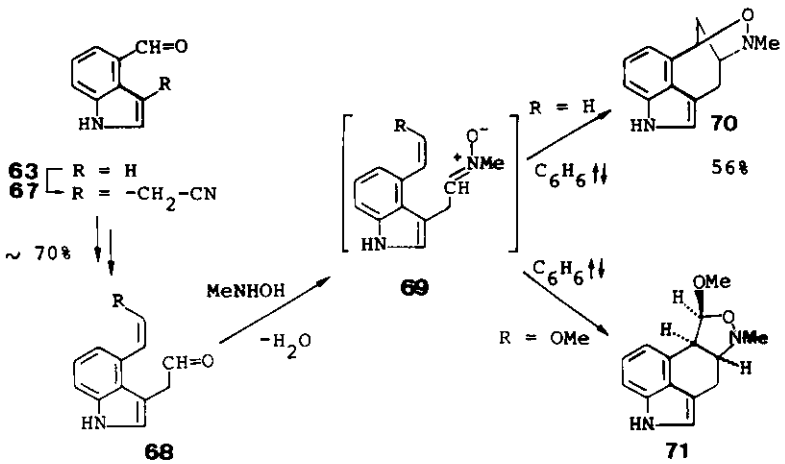
- Scheme 25 -

to the unstable key intermediate 62. Despite the original design of this synthesis the difficulty of the task becomes apparent by the number of steps and the low overall yield of 52. In contrast to all known syntheses of ergolines we envisaged an approach to chanoclavine I which carries the intact indole nucleus throughout the synthesis as indicated in Scheme 26. The basic



- Scheme 26 -

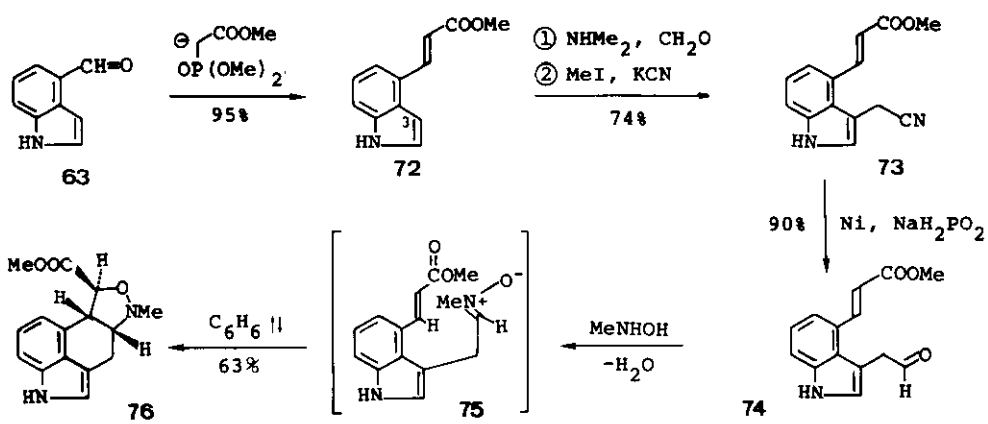
strategy centers on the nitrone 64 → 65. The known aldehyde 63[24] was chosen as a bifunctional starting material allowing the elaboration of the dipolarophile at the aldehyde group and the introduction of the dipolar chain at the 3-position of the indole nucleus. Final conversion of the key cycloadduct 65 to 52 would be accomplished by N/O-cleavage and subsequent functionalization of the oxygenated center C-9.



- Scheme 27 -

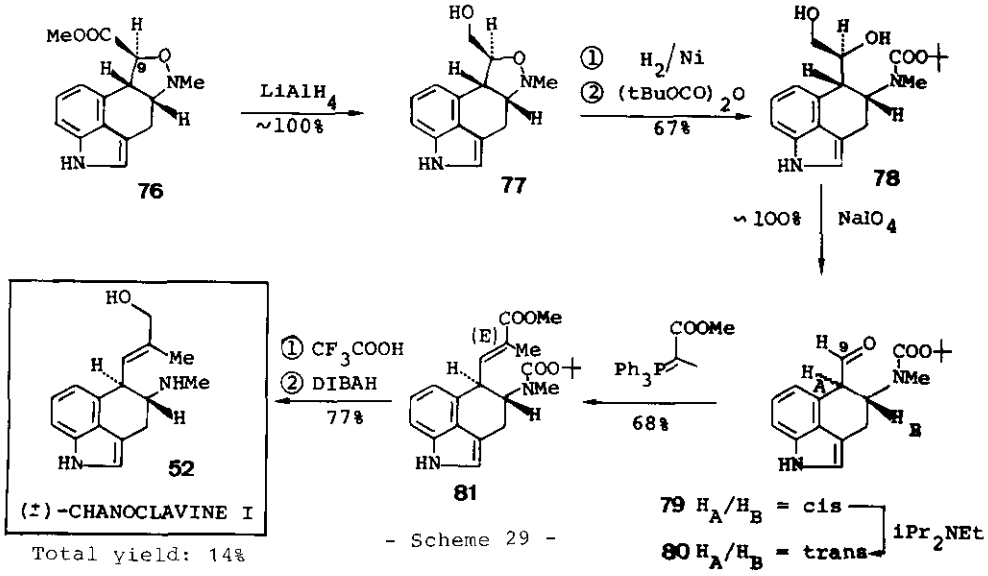
Starting from 63 , a conventional Mannich reaction followed by a cyanide displacement furnished the cyanide 67. Wittig reaction of the aryl-aldehyde group in 67 and successive reduction of the nitrile with diisobutylaluminum hydride led to the olefinic aldehydes 68. Condensation of 68, R=H with N-methylhydroxylamine followed by heating the solution of the intermediate nitrone 69, R=H in refluxing benzene gave the bridged cycloadduct 70 as the only isolable product. This undesired regioselectivity was not unexpected in view of the orientational bias of the aryl-substituent on the nearer end of the alkene unit in 69[25]. Placing either an electron-donating or withdrawing group R at the terminus of the vinyl moiety should direct the regiochemistry towards the desired ring-fused isoxazolidines. Indeed, this proved to be the case: Analogous preparation and thermolysis of the enol ether 69, R= OMe led exclusively to a mixture of stereoisomers 71 indicating complete reversal of the regiochemistry.

The actual synthesis of chanoclavine I was then started by a Horner reaction 63 → 72 followed by the C-3-functionalization 72 → 73. Reduction of the nitrile 73



- Scheme 28 -

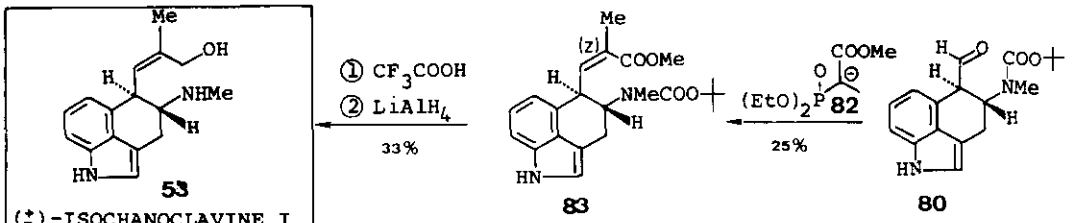
to the aldehyde 74 was accomplished in high yield with Raney-nickel/sodium hypophosphite in pyridine/acetic acid/ water[26]. Now the stage was set for the crucial cycloaddition step: Consecutive treatment of 74 with N-methylhydroxylamine and heating of the transient nitrone 75 furnished exclusively the cis-fused isoxazolidine 76 in 63% yield. To convert the key cycloadduct 76 to chanoclavine I the ester 76 was reduced to the alcohol 77 which underwent smooth hydrogenolysis



Total yield: 14%

- Scheme 29 -

of the N,O-bond in the presence of Raney nickel. Selective protection of the resulting methylamine using tert-butyldicarbonate gave the diol carbamate 78 in 67% overall yield from 77. Oxidation of the diol with sodium metaperiodate in aqueous methanol at 0° yielded initially the pure cis-aldehyde 79 which epimerized slowly on standing to the more stable trans-isomer 80. After complete epimerization of 79 to 80 by treating 79 with ethyldiisopropylamine in chloroform at 20° for 3 h, the pure trans-aldehyde 80 was subjected to a Wittig reaction using crystalline (α-carbomethoxyethylidene) triphenylphosphorane[23] in CH_2Cl_2 at 60° for 2 days, which yielded exclusively the (E)-olefin 81 in 68% yield. No trace of the corresponding (Z)-olefin was observed. Mild removal of the tert-butoxycarbonyl group by treatment of 81 with trifluoroacetic acid and subsequent reduction of the ester with diisobutylaluminum hydride furnished (±) chanoclavine in 77% yield[27]. The crystalline racemic alkaloid shows IR(KBr), ^{1}H-NMR (360 MHz), MS and UV spectra identical to those of the natural product kindly supplied by Sandoz Ltd/Basel. It was rather surprising to find that the Horner reaction of the aldehyde 80 with the phosphonate 82 gave no trace of the (E)-olefin 81 but only the (Z)-isomer 83



- Scheme 30 -

although in low yield (25%). Consecutive treatment of the protected ester 83 with trifluoroacetic acid and lithium aluminum hydride furnished (±)-isochanoclavine I (53)[27], identified by comparison with a sample of natural origin, kindly provided by Professor D. Arigoni.

It is a great pleasure to thank my very able collaborators Mr. Christian Robbiani, Dr. Bernard Delpech, Dr. David A. Roberts and Dr. Ian Grayson for their skilful and crucial contributions to this work. Their names are cited in the appropriate references. We are indebted to the Swiss National Science Foundation, Sandoz Ltd, Basel and Givaudan SA, Vernier for generous financial support.

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