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REGIO- AND STEREO-SELECTIVE SYNTHESES OF CYCLIC NATURAL PRODUCTS BY INTRAMOLECULAR CYCLOADDITION- AND ENE-REACTIONS

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Abstract - The utility of intramolecular cycloaddition- and ene-reactions in terms of entropy effects, regio- and stereo-selectivity is illustrated by the following recent syntheses of natural products :

1) Optically pure (+)-estradiol has been synthesized from 2-methyl-2-cyclopentenone by a sequence of 9 steps in high overall yield. The key steps are a regioselective deprotonation/alkylation of 5-(1,3-dihydroisothianaphthen-2,2-dioxide)-carbonitrile with an easily accessible, functionalized, enantiomerically pure ring D-unit and a subsequent thermolysis which involves SO_2-extrusion and intramolecular trapping of the transient *ortho*-quinodimethane giving the *trans-anti-trans* steroid skeleton in 66% overall yield.

2) Starting from indol-4-carboxaldehyde the otherwise not easily accessible ergot alkaloids (±)-chanoclavine I and for the first time its even scarcer isomer (±)-isochanoclavine I have been prepared by a sequence of 11 synthetic operations in overall yields of 14% and 2.4%. The key step is a regio- and stereo-selective intramolecular addition of a transient nitrone to a 4-indolylacrylic ester.

3) (-)-(S)-2-Cyclopenten-2-carboxylic acid has been converted to the optically pure sesquiterpenes (+)-longifolene and (+)-sativene via a common tricyclic 1,5-diketone intermediate in overall yields of 24% and 9%. These syntheses are centered on an efficient regio-selective intramolecular (2+2)-photocycloaddition followed by a retrolaldolisation.

4) The neurophysiologically interesting cyclic amino diacid (+)-α-allokainic acid as well as its (-)-antipode have been prepared enantioselectively from β-chloroacrylates by a series of 4 synthetic operations in over 15% overall yield. The crucial step is an intramolecular ene reaction of a 1,6-diene. Treatment of the latter with a mild Lewis-acid promotes a dramatically accelerated, highly diastereo- and enantiostereoselective cyclization. This is the first examples of an "ene-type" reaction proceeding with high asymmetric induction followed by regeneration of the auxiliary chirality directing group.

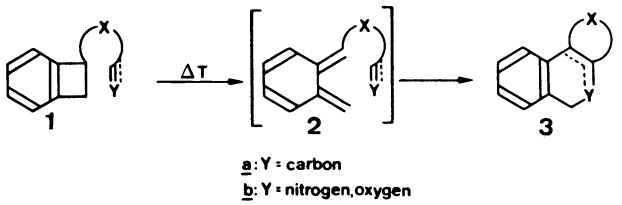
INTRODUCTION

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 complex cyclic molecules has become generally recognized, as is apparent by the rapid development of this field (Ref. 1 , 2). Today I would like to outline some recent applications of intramolecular versions of Diels-Alder and nitrone additions, photo-additions and ene reactions to the synthesis of natural products.

INTRAMOLECULAR DIELS-ALDER REACTIONS : SYNTHESES OF AROMATIC STEROIDS

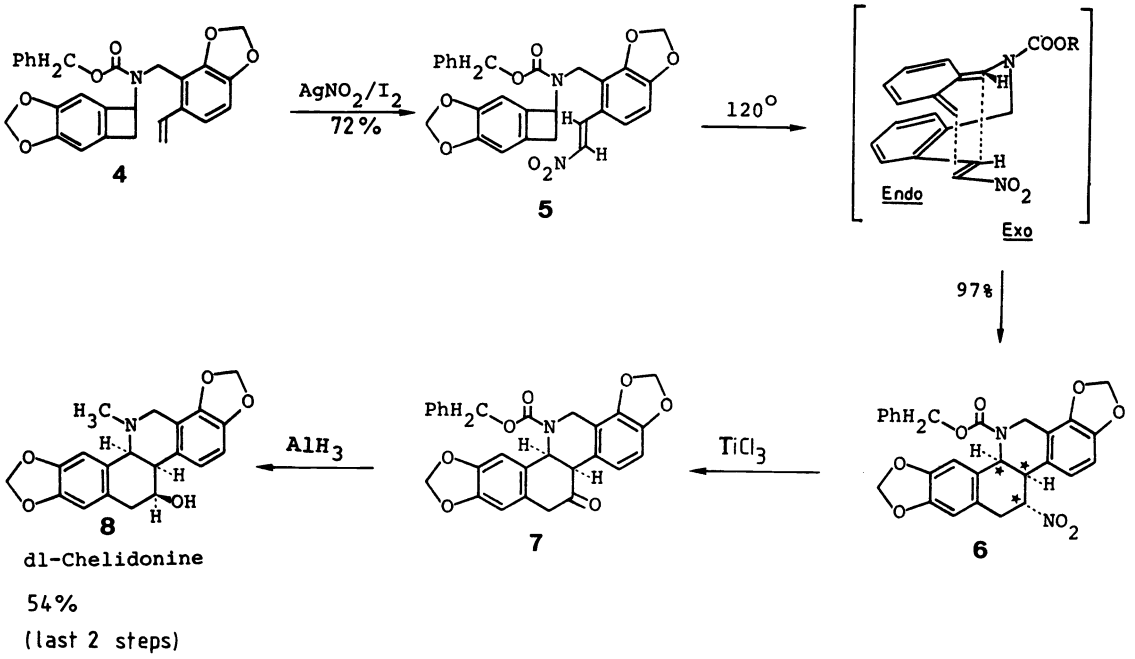
It is well established that a variety of polycyclic annelated systems 3 are readily obtained by heating benzocyclobutenes carrying an unsaturated chain in position 1 (Scheme 1, Ref. 2). Initial thermal opening of the four-membered

Scheme 1



ring leads to the transient (E)-*ortho*-quinodimethanes 2 which are then trapped by the suitably positioned multiple bond. Nearly 9 years ago we have reported the synthesis of (±)-chelidonine 8 which constitutes the first application of this reaction sequence in natural product synthesis (Ref. 3). In the meantime we have improved this approach considerably as shown in Scheme 2. Introduction of the nitro group into the known styrene 4 by reaction with silver nitrite in the presence of iodine and potassium acetate gave the nitrostyrene 5 in 72% yield. Heating of 5 in xylene at 120° for 2 hours gave after crystallisation the *cis*-fused adduct 6 in 97% yield. Not even a trace of any other stereo-

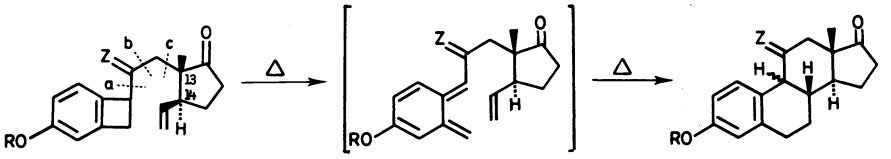
Scheme 2



isomer was found in the mother liquor. This remarkable stereoselectivity of the addition 5 → 6 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 6 with $TiCl_3$ furnished under mild conditions the sensitive ketone 7. Concomitant reduction of the carbonyl and urethane group of crude 7 with aluminum hydride gave (±)-chelidonine, identical to a natural sample of (±)-8, in 54% yield from 6 (Ref. 4). It goes without saying that intramolecular quinodimethane-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 docu-

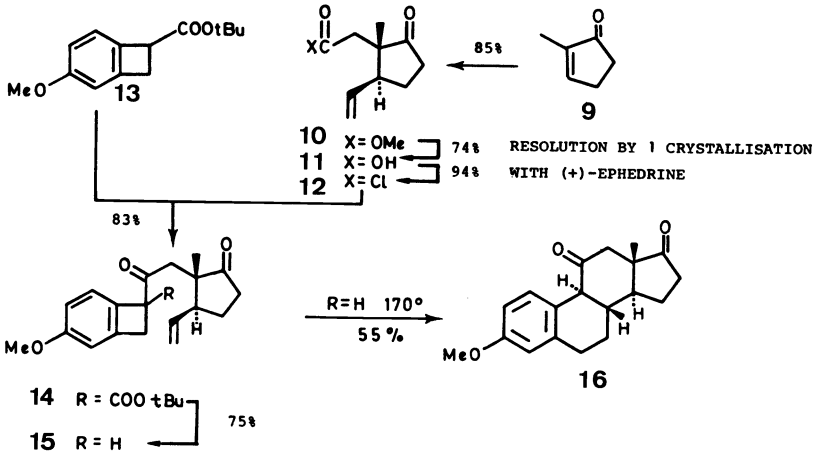
mented (Scheme 3, Ref. 2 & 5). However, for some time a major problem using this approach concerned the enantioselective assemblage of the preformed

Scheme 3



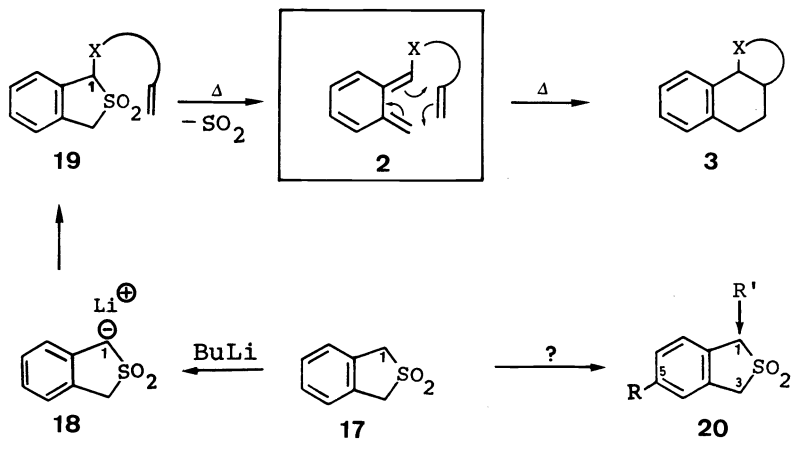
ring-D unit containing chiral centers C-13 and C-14 as well as the joining of this unit with the benzocyclobutene. An intriguingly simple solution to this problem, reported by us 2 years ago (Ref. 6, Scheme 4), involves conjugate addition of a mixed vinyl cuprate to methylcyclopentenone (9) and subsequent trapping of the nonisolated enolate with methyl bromoacetate. The racemic

Scheme 4



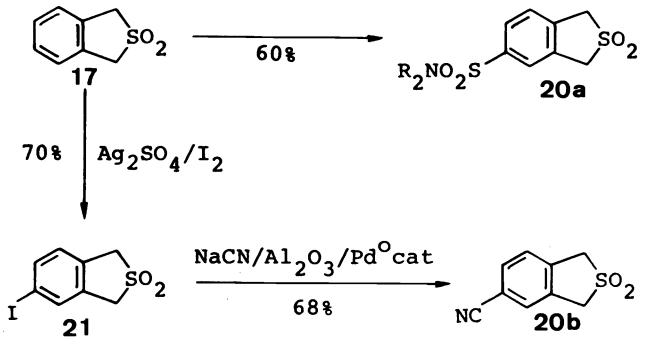
ester, thus obtained in 85% yield was saponified and the resulting acid crystallized once with (+)-ephedrine to give the optically pure acid 11. Acylation of the enolate derived from 13 with the acid chloride 12 led to 14 in high yield. After heating a solution of the dione 15 in decane under pure argon the optically pure *trans-anti-trans*-11-oxo-estrone 16 crystallized from the cooled reaction mixture in 56% yield. 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, we have recently reported the deprotonation and alky-

Scheme 5



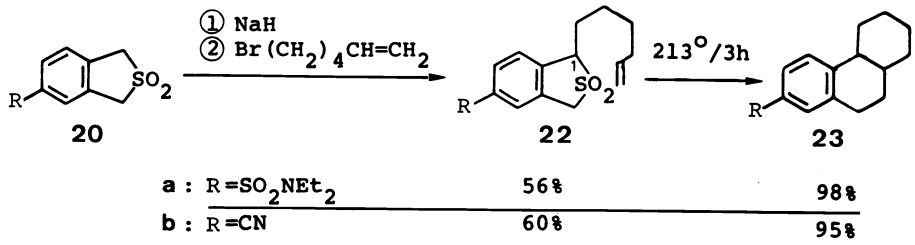
lation or acylation of the isothianaphthene dioxide 17 followed by thermolysis of the monosubstituted sulfones 19, giving the polycyclic products 3 in good yields (Ref. 7, Scheme 5). This evidence as well as independent work (Ref. 8) indicates the isothianaphthene dioxide 17 to be a useful functionalisable masked quinodimethane unit. However, there remains one problem : How to direct the electrophilic introduction of the dienophile side chain selectively into position 1 of 5-substituted 1,3-dihydroisothianaphthene-2,2-dioxides 20 ? As 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 deprotonation at C-1 by means of an electron-attracting substituent R in the para-position C-5 of 20. For reasons of practicability and flexibility, introduction of R into the readily available sulfone 17 seemed preferable to an *ab-initio* construction of the aryl-substituted heterocycle. The sulfonamide 20a was easily prepared by classical procedures invol-

Scheme 6



ving chlorosulfonation of 17. To introduce the more interesting nitrile group (17 → 20b) we used newer methodology such as the iodination of 17 followed by a palladium-catalyzed iodide/cyanide exchange using a solid alumina support (Scheme 6). Although simple nitration of 17 afforded smoothly the corresponding 5-nitro-isothianaphthene dioxide, subsequent treatment with various bases led only to intractable tars. On the other hand, both the sulfonamide 20a and the nitrile 20b came up to our expectations; successive treatment of 20a or

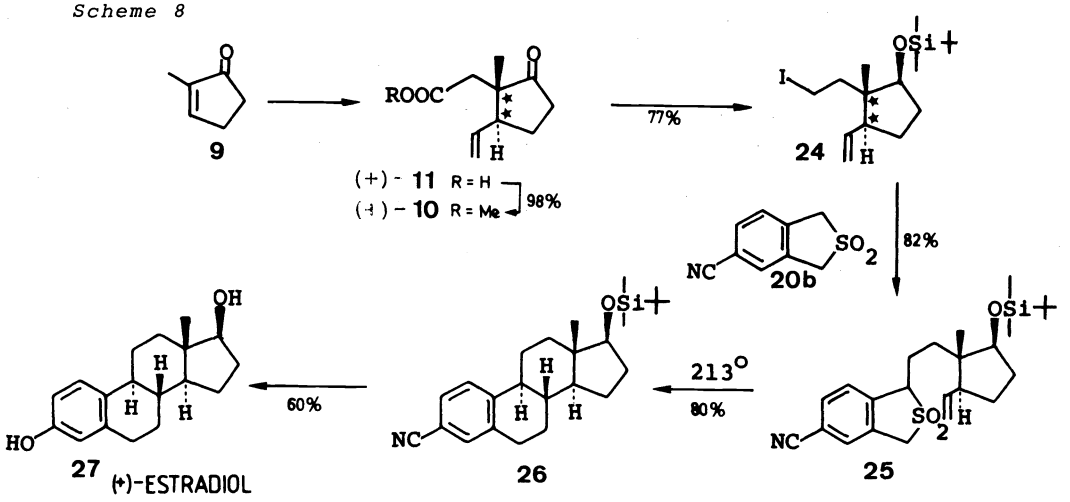
Scheme 7



20b with sodium hydride and 1-bromo-5-hexene furnished exclusively the 1-substituted sulfones 22. Thermolysis of 22 in boiling trichlorobenzene gave the desired adducts 23 in nearly quantitative yield (Scheme 7, Ref. 9).

Having solved the problem of regioselective 1,5-functionalization of the sulfone 17 we now turned our attention to the synthesis of (±)-estradiol (Scheme 8). The optically pure acid (+)-11 was converted to the iodide 24 by

Scheme 8

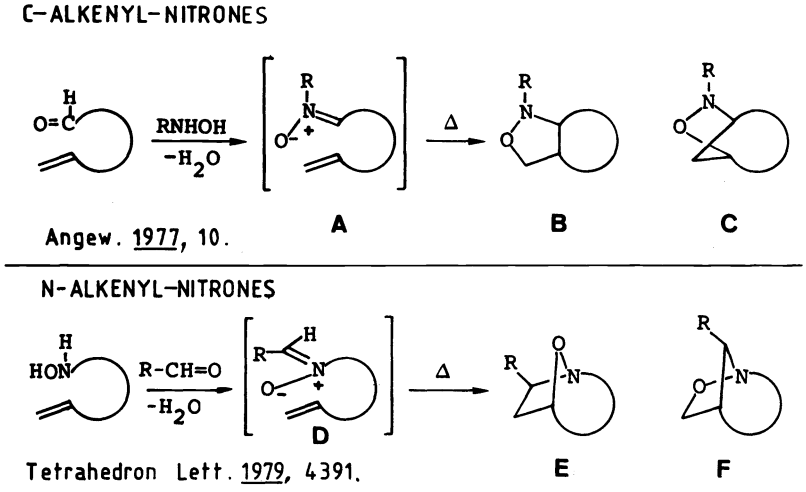


a few conventional steps in 77% overall yield. Alkylation of 20b with 24 led to the selective and efficient (82% yield) joining of the masked quinodimethane and the ring-D unit. Thermolysis of the resulting olefinic sulfone 25 in boiling trichlorobenzene yielded smoothly the crystalline *trans-anti-trans* steroid 26 in 80% yield. 26 was easily transformed to (+)estradiol (60% yield) (27) by successive addition of methyllithium, Baeyer-Villiger oxidation of the resulting methyl ketone, and acidic hydrolysis (Ref. 9).

INTRAMOLECULAR NITRONE-OLEFIN-ADDITIONS : SYNTHESES OF (±)-CHANOCLAVINE I AND (±) - ISOCHANOCLAVINE I

Intramolecular additions of C-alkenyl- as well as N-alkenyl-nitrones (Scheme 9) have received ever increasing attention in the field of natural product synthesis in recent years (Ref. 1). This has been nicely illustrated

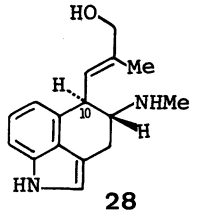
Scheme 9



inter alia by the efficient syntheses of the alkaloids (+)-luciduline (Ref. 10) and (±)-cocaine (Ref. 11) exploiting in each case a regioselective addition of a N-alkenyl-nitrone D. In continuation of our earlier work on analogous additions to styrenes (Ref. 12) we have now exploited an intramolecular cycloaddition of a nitrone A containing a 4-vinylindole-unit for the synthesis of

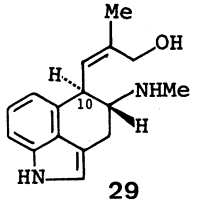
the ergot alkaloids chanoclavine I and isochanoclavine I. Chanoclavine I 28, was first isolated at the Sandoz company in Basel. It occurs in *Claviceps purpurea* together with two other alkaloids, isochanoclavine I (29) and

Scheme 10



28

Chanoclavine I



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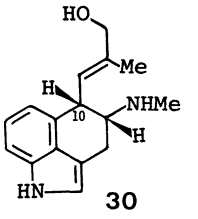
Isochanoclavine I



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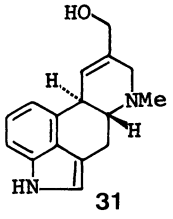
Chanoclavine II



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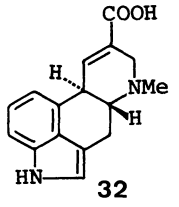
Elymoclavine



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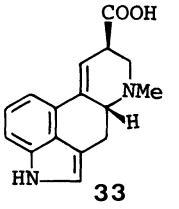
Paspalic Acid

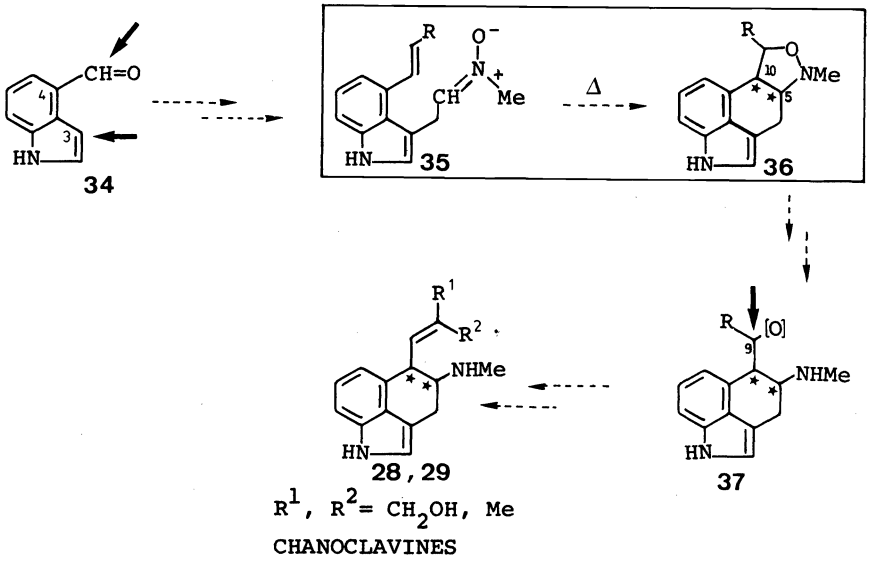


33

Lysergic Acid

chanoclavine II (30), which differ from 28 in their olefinic geometry or their chirality at C-10 respectively (Ref. 13). Chanoclavine I has been shown to be a biosynthetic precursor of elymoclavine 31 and hence of other tetracyclic ergolines such as paspalic and lysergic acids (Ref. 14). Whereas three different syntheses of lysergic acid (33) are known (Ref. 15), only one non-stereoselective approach to chanoclavine I (28) has been reported (Ref. 16) giving the racemic alkaloid in about 0.3% overall yield starting from 5-nitro-2-naphthol. After completion of this work another multi-step synthesis of chanoclavine I was published (Ref. 17). Our basic strategy centers on the nitrone-addition 35 → 36 (Scheme 11).

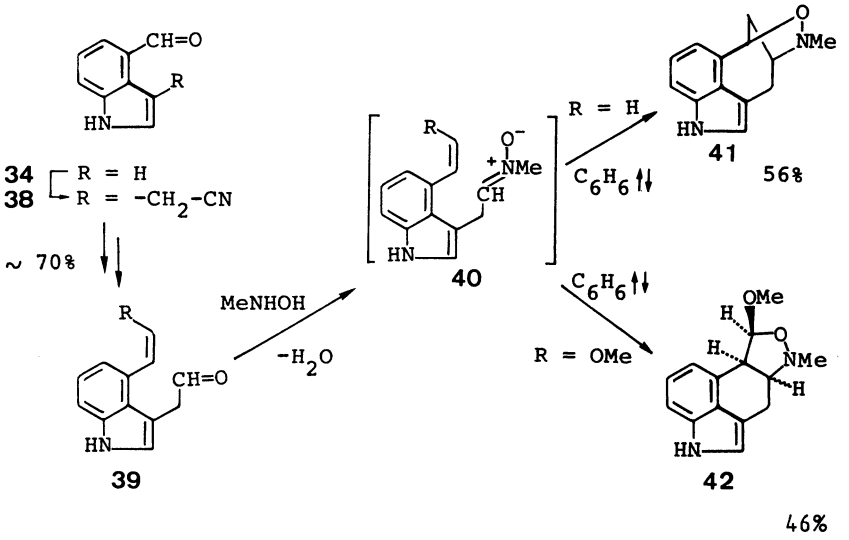
Scheme 11



The known aldehyde 34 was chosen as a bifunctional starting material which

allows the elaboration of the dipolarophile at the aldehyde group and the introduction of the dipole chain at position 3. Thus in contrast to most other syntheses of ergolines the unprotected indole nucleus should be carried intact throughout the synthesis. This strategy parallels the biosynthesis of chanoclavine I insofar as the latter starts from tryptophan and also involves C(5)-C(10) bond formation of a 3,4-disubstituted indole intermediate (Ref. 14). Final conversion of the key cycloadduct 36 to 28 would be accomplished by N/O-cleavage and subsequent functionalization of the oxygenated center C-9. Starting from 34, a conventional Mannich reaction followed by a cyanide displacement furnished the cyanide 38. Wittig reaction of the aryl-aldehyde group in 38 and successive reduction of the nitrile with diisobutylaluminum hydride led to the olefinic aldehydes 39. Condensation of 39, R = H which N-methylhydroxylamine followed by heating the solution of the intermediate nitrone 40,

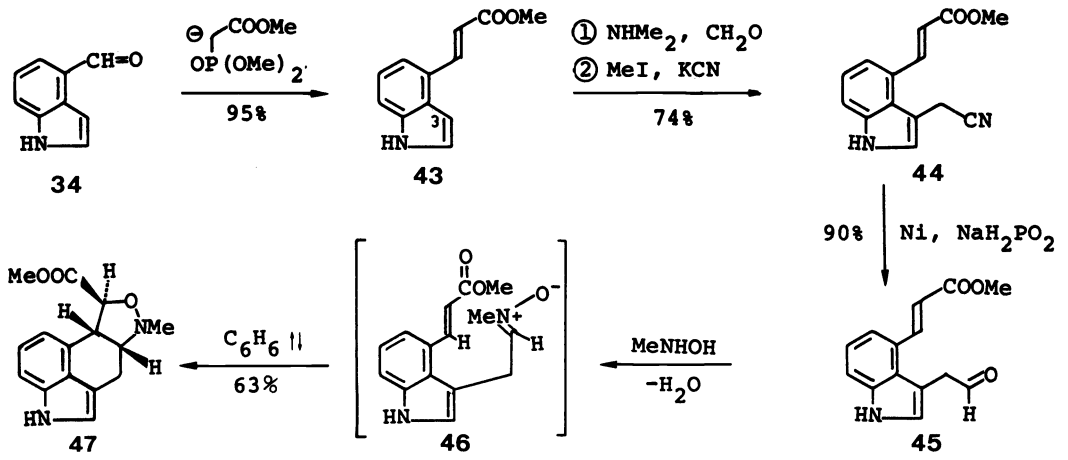
Scheme 12



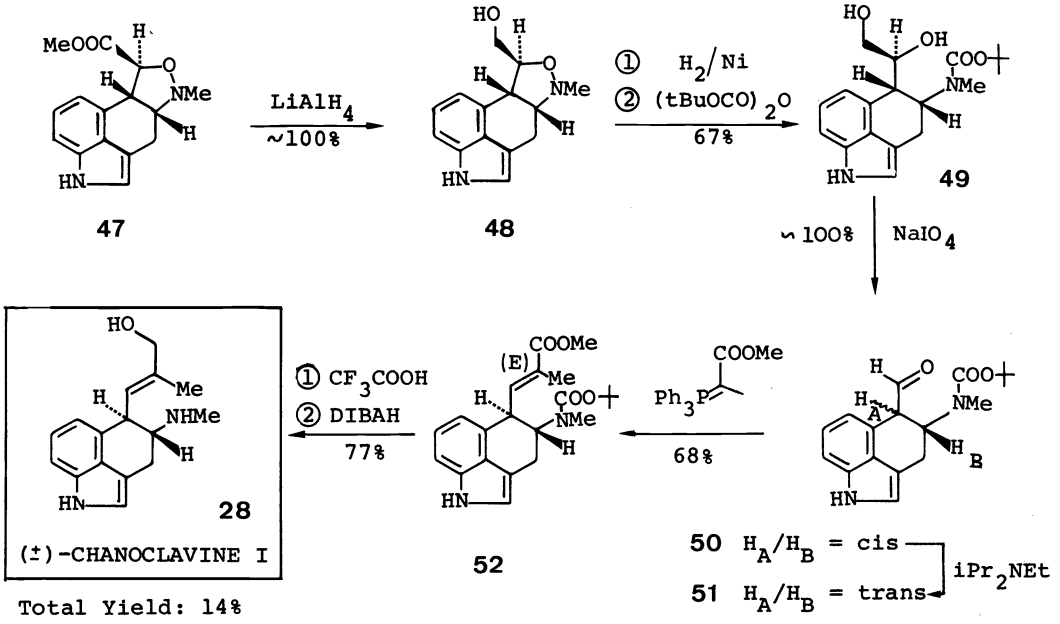
R = H in refluxing benzene gave the bridged cycloadduct 41 as the only isolable product. This undesired regioselectivity was not unexpected in view of the orientational bias of the aryl-substituent on the near end of the alkene unit in 40, R = H. Placing either an electron-donating or withdrawing group 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 39, R = OMe led exclusively to a mixture of stereoisomers 42 indicating complete reversal of the regiochemistry (Scheme 12).

The actual synthesis of chanoclavine I was then started (Scheme 13) by a Horner reaction 34 → 43 followed by the C-3-functionalization 43 → 44. Reduction of the nitrile 44 to the aldehyde 45 was accomplished in high yield with Raney-nickel/sodium hypophosphite in pyridine/acetic acid/water. Now the stage was set for the crucial cycloaddition step : Consecutive treatment of 45 with N-methylhydroxylamine and heating of the transient nitrone 46 furnished exclusively the *cis*-fused isoxazolidine 47 in 63% yield. To convert the key cycloadduct 47 to chanoclavine I (Scheme 14) the ester 47 was reduced to the alcohol 48 which underwent smooth hydrogenolysis of the N,O-bond in the presence of Raney nickel. Selective protection of the resulting methylamine using di-tert-butyldicarbonate gave the diol carbamate 49 in 67% overall yield from 47. Oxidation of the diol 49 with sodium metaperiodate in aqueous methanol at 0° yielded initially the pure *cis*-aldehyde 50 which epimerized slowly on standing to the more stable *trans*-isomer 51. After complete epimerization of 50 to 51 by treating 50 with ethyl-diisopropylamine in chloroform at 20° for 3 hours, the pure *trans*-aldehyde 51 was subjected to a Wittig reaction using cristalline (α-carbomethoxyethylidene) triphenylphosphorane in CH_2Cl_2 at 60°

Scheme 13



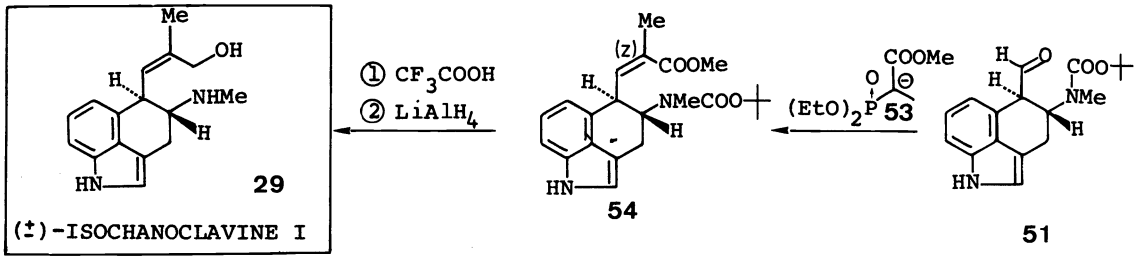
Schema 14



for 2 days, which yielded exclusively the (E)-olefin 52 in 68% yield. No trace of the corresponding (Z)-olefin was observed. Mild removal of the tert-butoxycarbonyl group by treatment of 52 with trifluoroacetic acid and subsequent reduction of the ester with diisobutylaluminum hydride furnished (±)-chanoclavine in 77% yield. The crystalline racemic alkaloid showed IR(KBr), ^{1}H-NMR (360 MHz), MS and UV spectra identical to those of the natural product kindly supplied by Sandoz Ltd/Basel (Ref. 18).

It was rather surprising to find that the Horner reaction of the aldehyde 51 with the phosphonate 53 gave no trace of the (E)-olefin 52 but only the (Z)-isomer 54 although in low yield (25%) (Scheme 15). Consecutive treatment

Scheme 15

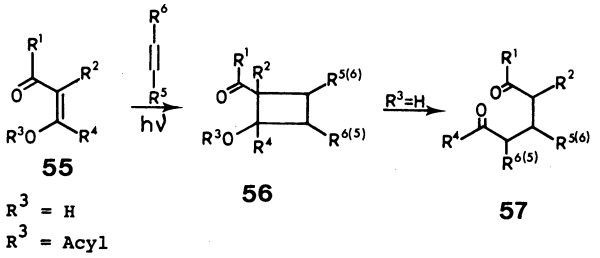


of the protected ester 54 with trifluoroacetic acid and lithium aluminum hydride furnished (±)-isochanoclavine I (29), identified by comparison with a sample of natural origin, kindly provided by Professor D. Arigoni (Ref. 18).

INTRAMOLECULAR DE MAYO REACTIONS : SYNTHESES OF (+)-LONGIFOLENE AND (+)-SATIVENE

The synthetic potential of the bimolecular photoaddition retroaldol reaction sequence (De Mayo reaction) depicted in Scheme 16 is well documented and a valuable method for preparing 1,5-diketones starting from 1,3-diketones (Ref. 19). One of the drawbacks of the bimolecular reaction however,is the

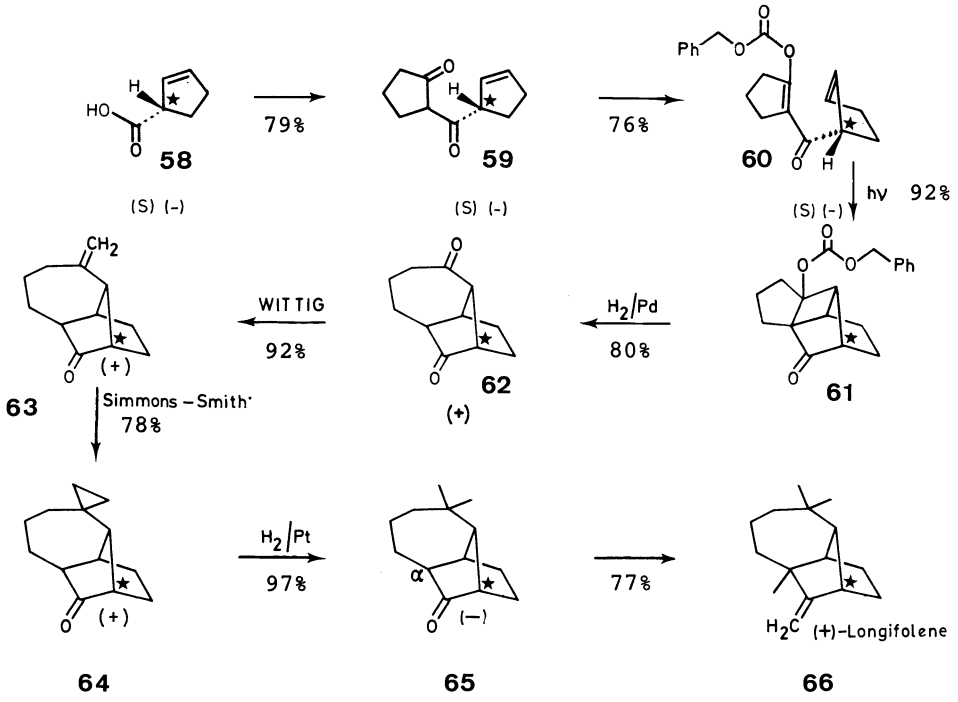
Scheme 16



poor predictability of the regio-chemistry in the photo-2+2-cycloaddition step. On the other hand, intramolecular variants starting from 1,3-diketones or their enol derivatives 55 bearing olefinic substituents R^1, R^2 or R^4, strongly neglected until recently, should be highly regioselective. Two years ago, we reported the first example of one of these intramolecular alternatives which constitutes the key reaction leading to a ready synthesis of racemic longifolene (Ref. 20). The intricate carbon network of this sesquiterpene (66) has served as a challenging test case for synthetic methodology and planning throughout the past 15 years (Ref. 21). The crucial step of our approach, depicted in Scheme 17 (60 → 61), is in fact a highly efficient and regioselective photo-2+2-addition followed by hydrogenolysis of the protecting carbonate which triggers off a spontaneous retroaldol cleavage 61 → 62 giving the skeleton of longifolene in high overall yield. The subsequent steps deal mainly with the functionalization of the sterically discriminated carbonyl groups of 62 giving racemic longifolene in about 25% overall yield starting from this easily accessible acid chloride derived from 58.

Challenged by the general importance of enantioselectivity in synthesis we could not resist the temptation to synthesize the natural (+)-longifolene starting from the known(S)-(-)-carboxylic acid 58. In fact, the crucial tricyclic 1,5-diketone 62 was obtained in over 85% optical purity starting from

Scheme 17

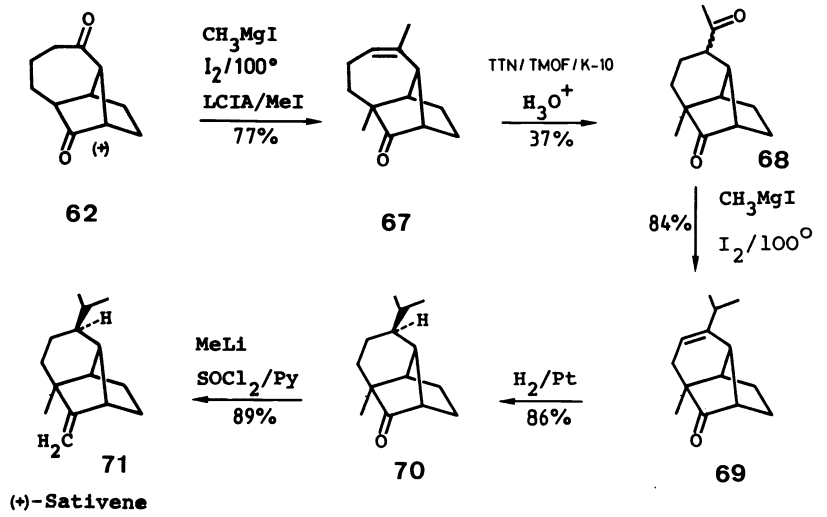


96% optically pure carboxylic acid 58. Thus very little racemization had occurred during the first tedious steps like acid chloride formation, enamine-acylation giving 59 and acylation of the carbonyl group. Crystallization of the crude 1,5-diketone 62 furnished the 100% optically pure key intermediate which was then transformed to (+)-longifolene obtained in overall yield of 24% starting from 58 (Ref. 22).

Having thus achieved the first enantioselective synthesis of (+)-longifolene we envisaged furthermore to use the optically pure tricyclic 1,5-diketone-key-intermediate 62 for the synthesis of other natural products such as sativene (71).

This approach (Scheme 18) obviously requires a ring-contraction of the 7-membered ring and a stereoselective introduction of an equatorial isopropyl group. To this end the diketone 62 was first converted to the keto-olefin 67 by addition of methylmagnesium iodide and subsequent iodine-catalyzed dehydration. Ring contraction of 67 using thallium trinitrate in the presence of trimethylorthoformate was disappointingly unsuccessful. In contrast using $Tl(NO_3)_3$ supported on the Montmorillonit clay K-10 (Ref. 23) and subsequent acidic hydrolysis of the non-isolated acetal, the ring-contracted diketone was obtained in respectable yield as a mixture of stereoisomers. To convert this mixture to isomerically pure sativene, the remaining methyl group was introduced by a Grignard addition. Dehydration of the resulting alcohol and concomitant olefin isomerisation with iodine led in high yield directly to the trisubstituted olefin 69. Stereoselective hydrogenation 69 → 70 from the unhindered exo-side, addition of methyllithium and subsequent dehydration gave the optically pure (+)-sativene (71), identified by comparison with a sample of (-) sativene, kindly provided by Professor D. Arigoni (Ref. 22).

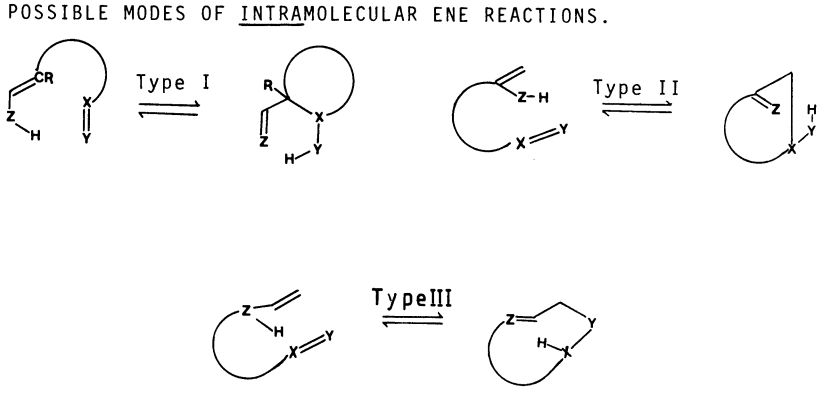
Scheme 18



INTRAMOLECULAR ENE-TYPE REACTIONS : SYNTHESIS OF (+)-α-ALLOKAINIC ACID

After having demonstrated the utility of intramolecular (either concerted or non-concerted) cycloaddition reactions in synthesis, I would like to draw your attention to the intramolecular ene reactions. As indicated in Scheme 19, as

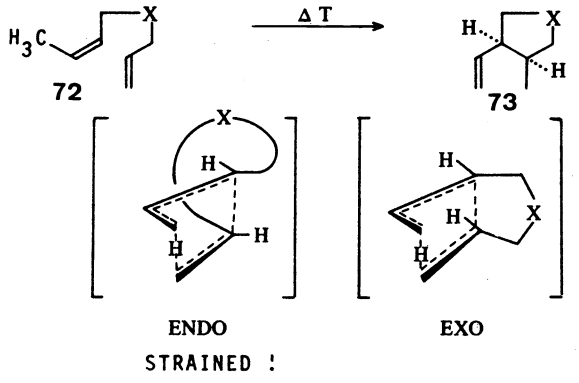
Scheme 19



well as in a recent review article (Ref. 24), there are 3 possible types of such cyclizations in which the enophile is linked by an appropriate bridge either to the olefinic terminal (type I), the central atom (type II), or the allylic terminal (type III) of the ene unit. So far the most interesting variant deals with reactions of type I, particularly the regioselective formation of 5-membered rings by thermolysis of 1,6-dienes (Scheme 20; X may be carbon or a heretoatom). Several years ago we studied systematically the influence of the ene geometry on the configuration of the newly formed centers. Already model considerations show that a concerted *supra-supra*-facial hydrogen-transfer from a *cis*-ene 72 should lead to *cis*-substituted 5-membered rings 73 via an *exo*-transition state since the *endo*-orientation is highly strained. Indeed, kinetically controlled cyclizations of the *cis*-dienes 72 furnished *cis*-substi-

tuted products 73 with 100% stereoselectivity (Ref. 24).

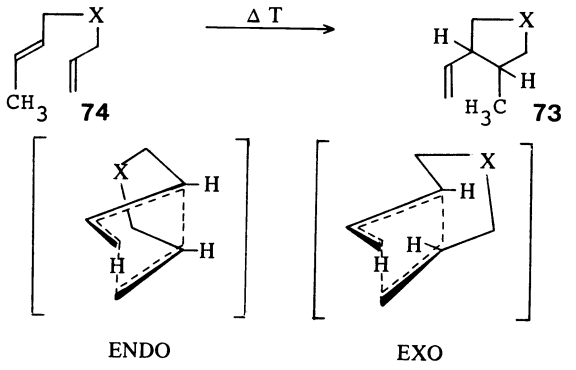
Scheme 20



∴Exclusive Formation of cis-substituted 5-membered rings.

Analogous cyclizations of the *trans*-dienes 74 (Scheme 21) gave mainly but not exclusively the *cis*-products 73 which indicates that the *endo*-transition state is preferred over the *exo*-orientation (ref. 24).

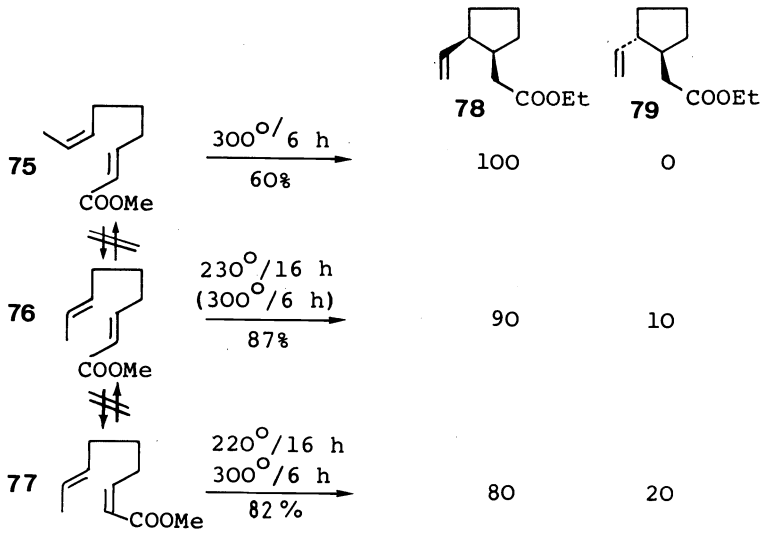
Scheme 21



Both, Endo and Exo-Orientation Possible.

We then exploited these findings for the stereoselective syntheses of cyclopentanoid sesquiterpenes like acoranes (Ref. 25) and isocomene (Ref. 26). More recently we obtained a related stereoselectivity in the thermal cyclizations of 1,6-dienes where the enophile is substituted by a carbomethoxy group (Scheme 22). Despite reaction temperatures of 230° high yields of *cis*-substituted cyclopentanes 78 were obtained. The observed stereoselectivity is again 100% starting from the *cis*-ene 75 and 80 to 90% starting from the trans-enes 77 and 76 showing little influence of the enophile geometry. No significant acceleration of these reactions was found in the presence of a variety of Lewis-acids (Ref. 27).

Scheme 22

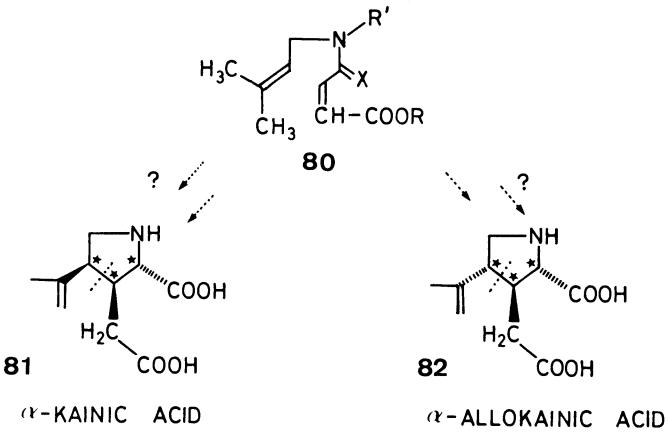


No acceleration by Lewis acid

($AlCl_3$, $AlEtCl_2$, $AlEt_2Cl$, $SnCl_4$, $TiCl_4$)

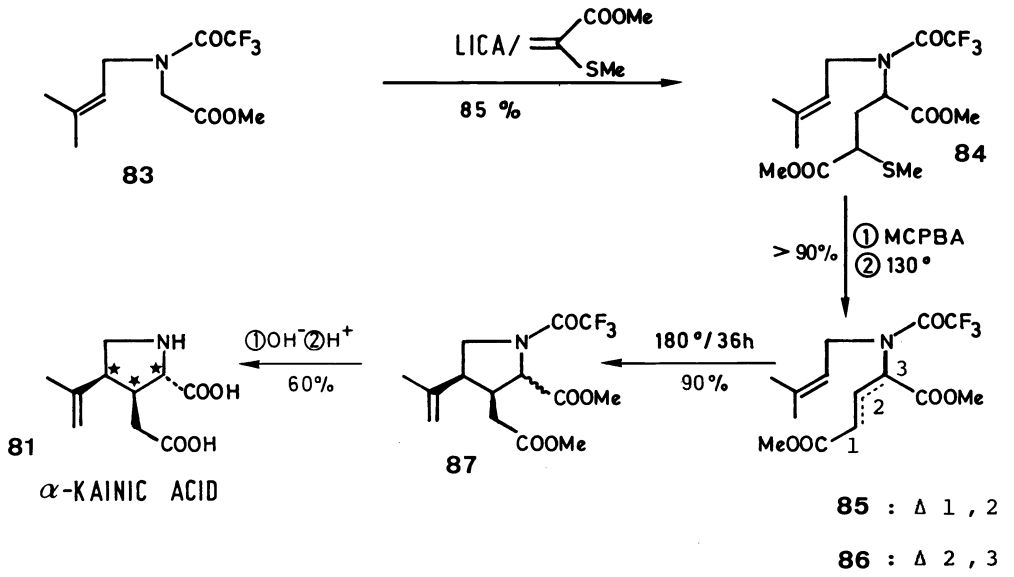
One of the reasons for these studies is depicted in Scheme 23 showing a very direct strategy to synthesize the naturally occuring α-kainic acid (81) and α-allokainic acid (82). Both amino acids are of considerable neurophysiological

Scheme 23



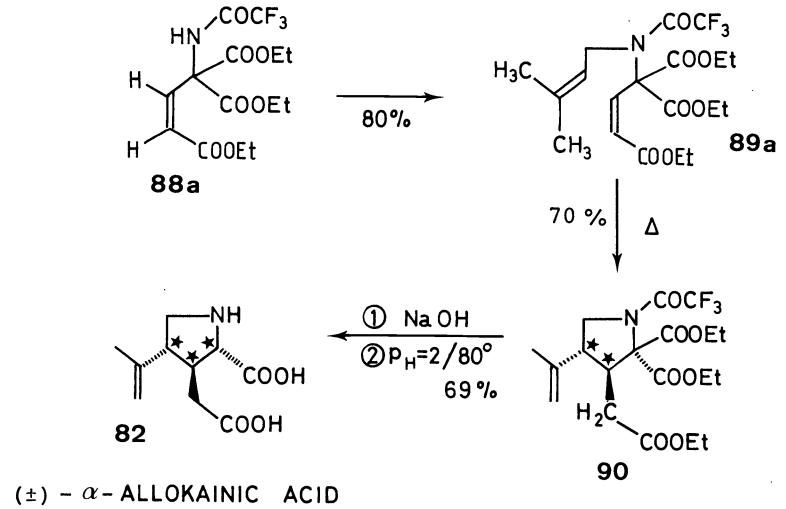
interest and differ only in their configuration with the acetic acid and isopropenyl groups *trans* in α-allokainic acid and *cis* in α-kainic acid. The basic question was to what extent a 1,6-diene 80 carrying a masked carboxyl-equivalent X would cyclize to a pyrrolidine with *cis*- or *trans*-positioned hydrogen donor and acceptor sites. In fact, we have obtained the potent neurotoxine α-kainic acid with good selectivity by the reaction sequence depicted in Scheme 24 (Ref. 28). The key step is the thermolysis of the diene 86 which apparently isomerized to the 1,6-diene 85, prior to the ene reaction leading selectively to 87 showing again *cis*-related H-donor and acceptor sites.

Scheme 24



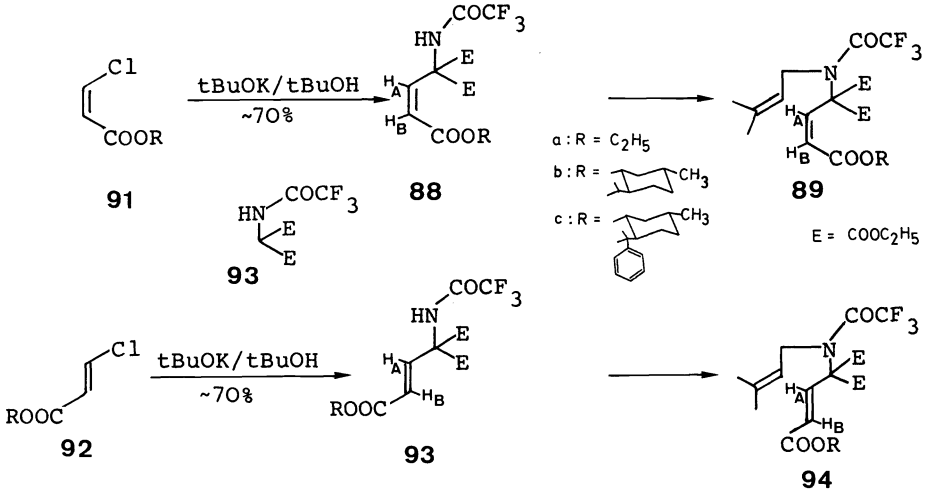
By contrast (Scheme 25), the analogous 1,6-diene 89a carrying a malonic ester moiety gave mainly the *trans*-substituted pyrrolidine 90 which after hydrolysis and subsequent decarboxylation furnished the racemic α-allokainic acid (Ref. 29). After we had reported this work in a preliminary note we re-examined the crucial ene reaction. First, as we soon found out, the thermal cyclization of 89a furnished the *trans*-product 90 not exclusively but a 3:1-mixture of 90 and its *cis*-isomer 95. Nevertheless, the unusual predominance of the *trans*-product 90 was still significant and raised the question as to how far this diastereoselectivity depends on the enophile geometry in 89a.

Scheme 25



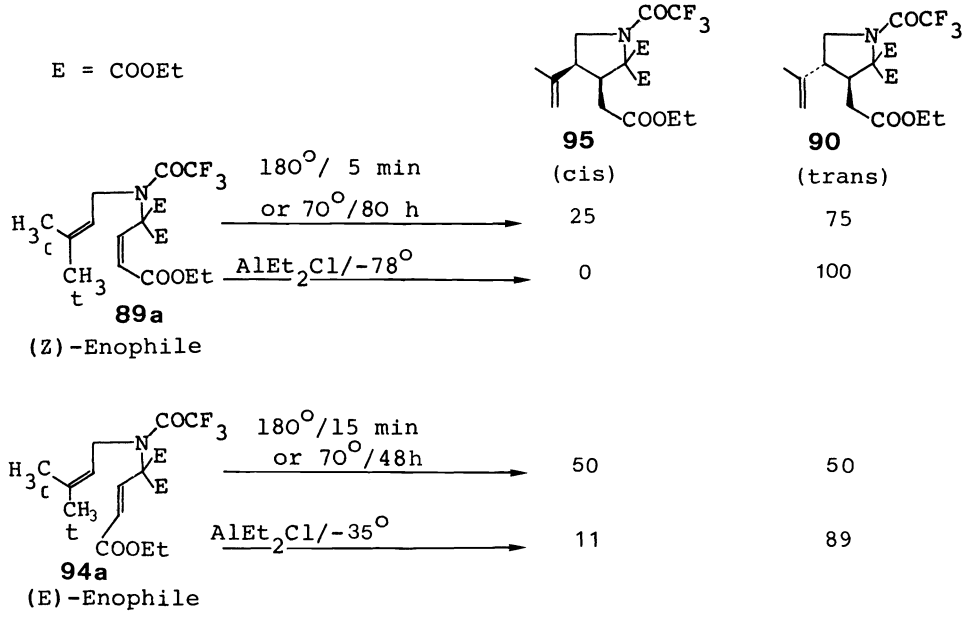
The (Z)-diene 89a was easily accessible (Scheme 26) *via* treatment of the *cis*-β-chloroacrylate 91a with the acylaminomalonic ester 93 in the presence of 1 molequiv. of tert-BuOK followed by N-alkylation of 88a. Analogous Michael-

Scheme 26



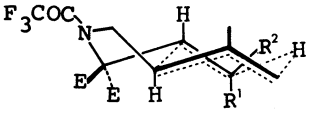
addition and subsequent alkylation starting from the *trans*-β-chloroacrylate 92a furnished stereospecifically the (E)-ester 94a. We then appreciated that P.D. Kennewell informed us about independent careful studies of the thermolyses of the (Z)- and (E)-dienes 89a and 94a, prepared by Michael-addition of 93 to ethyl priopiolate giving a 1:3 mixture of 88a and 93a. which was separated by HPLC prior to alkylation (Ref. 30). The British authors obtained the pyrrolidines 95 and 90 also in a ratio of 25:75 from 89a but in a ratio of 53:47 from 94a, and furthermore, characterized the products 95 and 90 after their separation by HPLC. Having a convenient stereospecific route to the (E)-diene 94a in hand, we readily confirmed the lack of diastereoselectivity on thermolysis of 94a irrespective of the reaction temperature (+ 70° and + 180°) indicating a kinetic control of the stereochemistry (Scheme 27).

Scheme 27



However, the situation changed dramatically when we carried out the cyclization of 89a and 94a in the presence of an excess of diethylaluminium chloride (a mild Lewis-acid and HCl-scavenger similar to $EtAlCl_2$ and Me_2AlCl which have been recently used by B.B. Snider as catalysts in bimolecular ene reactions : see Ref. 31). Thus, addition of Et_2AlCl (3 equiv.) to a solution of the (Z)-diene 89a in dry CH_2Cl_2 at -78° and quenching of the reaction with water at -78° after 8 hours, yielded exclusively ($\geq$ 90% yield) the *trans*-substituted pyrrolidine 90. Not even a trace of the *cis*-isomer 95 was found.
More conveniently the reaction was carried out with 3 equiv. of Et_2AlCl at -35°; the same diastereoselectivity was observed at -78° and at -35°. We were also pleased to find that the (E)-diene 94a cyclized at -35° with 89% diastereoselectivity to the *trans*-product 90 in the presence of 3 equiv. of Et_2AlCl. The reaction 94a → 90 proceeded somewhat slower than the cyclization of 89a requiring 6 hours at -35° for completion (78% yield). The kinetic nature of the Lewis-acid promoted diastereoselectivity in the reactions 89a → 90 and 94a → 90 was supported by the observation that a 1:1-mixture of 90 and 95 remained virtually unchanged on treatment with 30 equiv. of Et_2AlCl in CH_2Cl_2 at 25° for 10 min. Accordingly, we attempted to rationalize the observed stereochemistry of the thermal and Et_2AlCl-mediated cyclizations of 89a and 94a by examination of the possible transition states (Scheme 28).

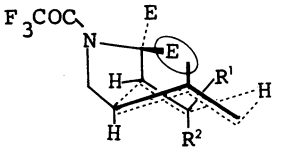
Scheme 28



t-Ene ⟶ **90** (trans)

A: (Z)-Enophile (R^1=COOEt)

B: (E)-Enophile (R^2=COOEt)

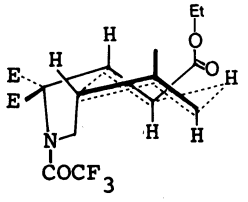


t-Ene ⟶ **95** (cis)

C: (Z)-Enophile (R^1= COOEt)

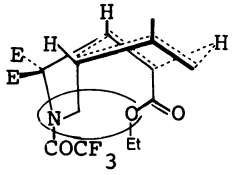
D: (E)-Enophile (R^2= COOEt)

strong repulsion



F: c-Ene ⟶ **95** (cis)

(E)-Enophile



E: c-Ene ⟶ **95** (cis)

(Z)-Enophile

moderate repulsion

As a working model we have postulated a chair-like transition state for the ene reaction. This differs from the traditional model (Ref. 32), mainly in the assumption that the migrating hydrogen does not lie on the axis which joins the termini of the ene and the enophile. A chair-like transition state has also been proposed for the aldol reaction (Ref. 33), which may be regarded as a version of the ene reaction. This analysis accounts for H-transfer from the allylic *trans*-methyl (t-ene) as well as *cis*-methyl (c-ene) groups; the latter is forced by angle strain to yield only the *cis*-substituted product 95 whereas

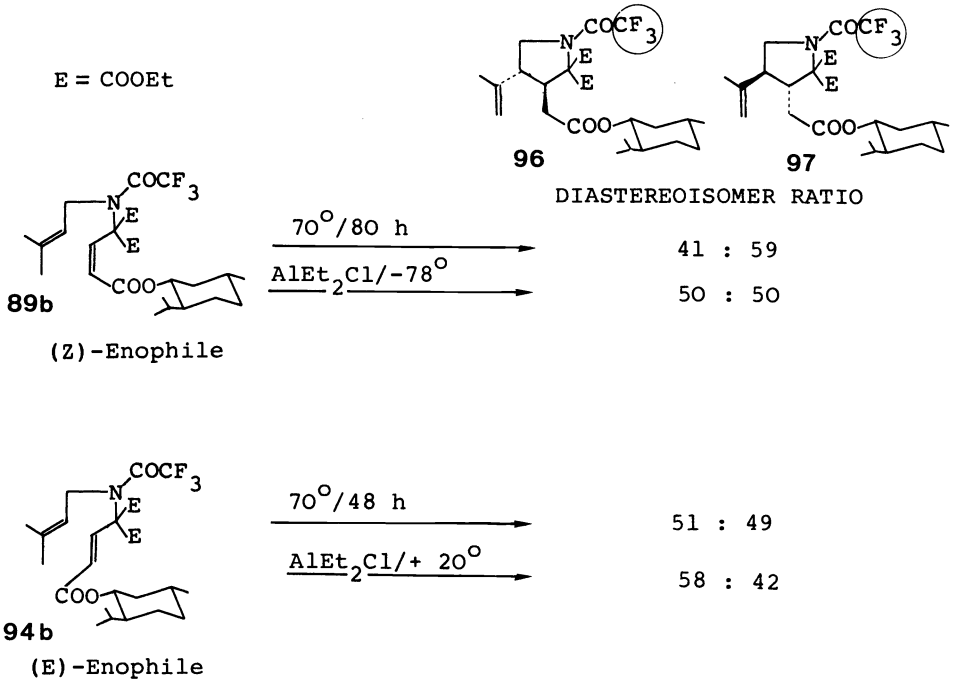
the former may in principle lead to both *trans*- and *cis*-pyrrolidines 90 and 95. However, formation of the *cis*-product 95 *via* a t-ene unit (transition states C and D) invariably shows a strong repulsion between one of the malonic ester groups and the olefinic methyl substituent regardless of the enophile geometry. Transition state E is disfavored by 1,3-diaxial perturbation which is absent in transition state F; the transition states A and B are virtually free from non-bonding interactions. It thus follows that in the thermal cyclization of 89a (containing a (Z)-enophile) transition state A should be preferred over C and E explaining the predominant formation of 90. Thermal ene-reaction of 94a (containing an (E)-enophile) indicates the compatibility of the non-encumbered transition states B and F since 90 and 95 were formed in equal amounts.

Although the operation of concerted ene reactions in the Lewis-acid-induced cyclizations of 89a and 94a remains to be proved, it agrees with the observed stereochemistry. Thus, complexation of the ester and amide units increases their steric bulk, and therefore, the repulsions in the states C, D, E and, somewhat less, in F. Consequently it appears that in the presence of Et_2AlCl the *trans*-product 90 is formed from 89a exclusively *via* transition state A and from 94a preferentially *via* transition state B (Ref. 34).

Having solved the diastereoselectivity problem, we turned our attention to the possibility of carrying out the crucial ene reaction in an enantioselective manner. This perspective seemed to be of general interest in synthesis since very little is known about asymmetric induction in ene reactions. We only know about one study allowing recyclization of the chirality directing group which deals with the Lewis-acid-catalyzed addition of menthylglyoxalate to 1-pentene; the corresponding adducts were obtained in only modest optical yields in spite of wide variations of temperature, solvent and catalyst (Ref. 35).

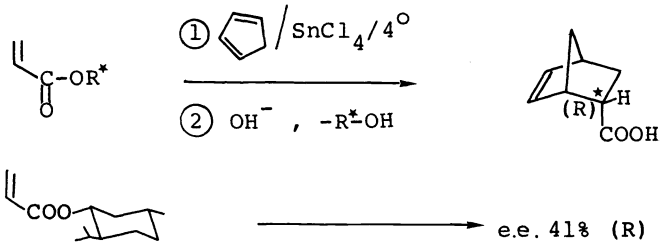
First, the esters derived from (-)-menthol, 89b and 94b were prepared *via* the routes 91b → 88b → 89b and 92b → 93b → 94b by analogy to the preparation of 89a and 94a (Scheme 26). Disappointingly, thermal and $AlEt_2Cl$-mediated cyclizations of 89b or 94b led to little if any (≤ 18 % e.e.) optical induction at the newly formed centers in 96 and 97 as shown by NMR-evidence (Scheme 29).

Scheme 29

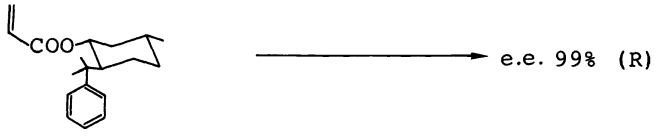


Then, in view of the known asymmetric Diels-Alder additions of 8-phenylmenthyl acrylates (Scheme 30, Ref. 36) we envisaged "ene-type" cyclizations of the dienes 89c and 94c.

Scheme 30



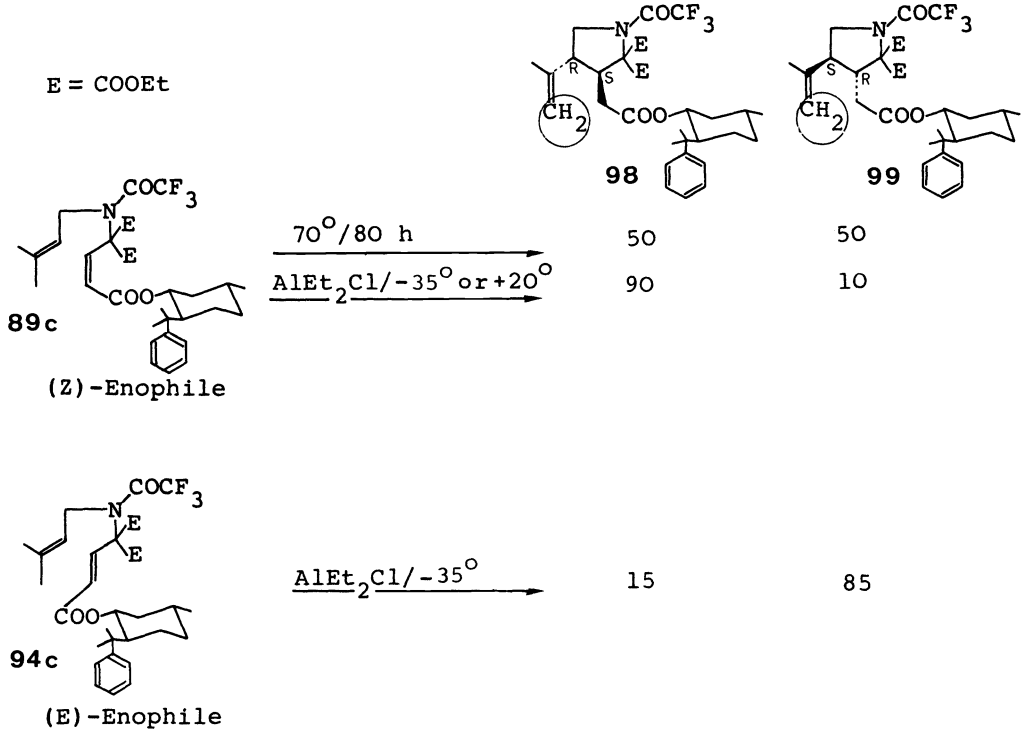
R.F. Farmer & J. Hamer, J. Org. Chem. 31, 2418 (1966).



E.J. Corey & H.E. Ensley, J. Amer. Chem. Soc. 97, 6908 (1975).

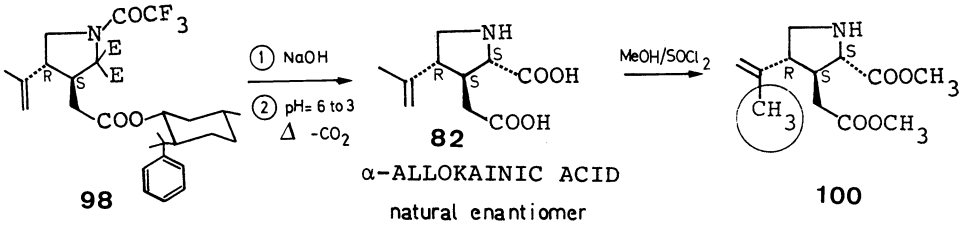
(-)-8-Phenylmenthol, prepared from natural (+)-pulegone, was esterified with *cis*- and *trans*-β-chloroacrylic acids to give the esters 91c and 92c. Subsequent conjugate addition/elimination followed by alkylation (Scheme 26) furnished

Scheme 31



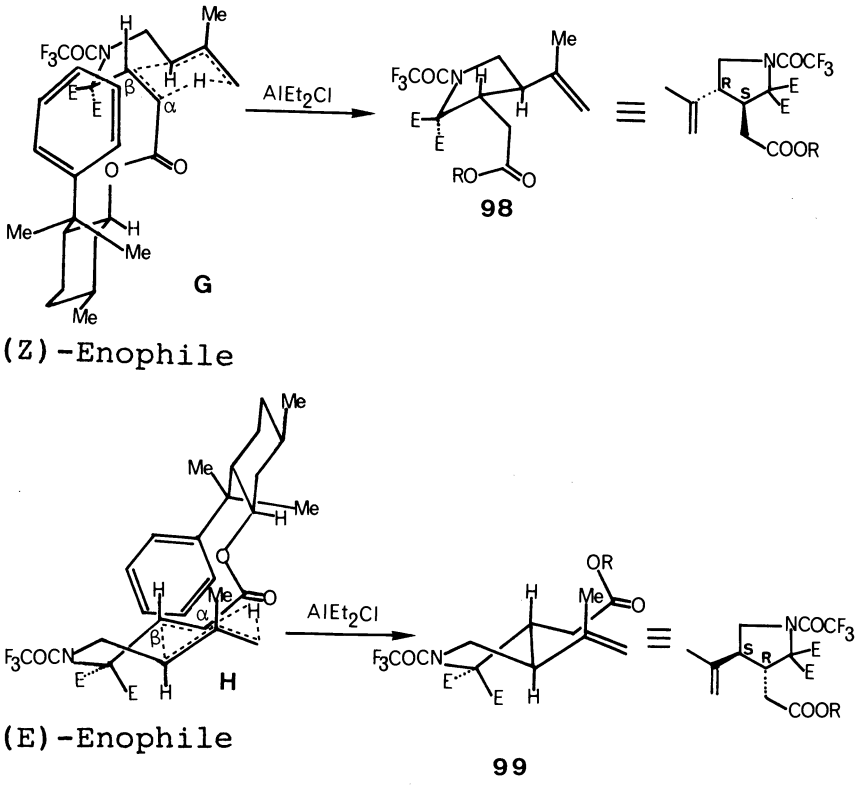
the (Z)-diene 89c in 40% overall yield from 91c and the (E)-diene 94c in 60% yield from 92c. Heating the (Z)-diene 89c at 70° for 80 hours gave a 1:1-mixture of the diastereoisomers 98 and 99 (Scheme 31), readily assessed by 360 MHz-^{1}H-NMR-evidence which shows the two singlets of the olefinic protons at 4.83/4.90 ppm for 98 and at 4.96/5.02 ppm for its isomer 99. On the other hand, we were delighted to find that treatment of the (Z)-phenylmenthylester 89c with 3 molequiv. of Et_2AlCl in dry CH_2Cl_2 at -35° for 18 hours furnished the isomers 98 and 99 in a ratio of 9:1. This assignment is based on the conversion of the 9:1-mixture to (+)-α-allokainic acid 82, carried out in the following manner (Scheme 32). Alkaline saponification furnished on extraction

Scheme 32



the unchanged starting (-)-8-phenylmenthol. Successive decarboxylation of the non-isolated malonic acid at pH = 6 to 3, precipitation of the copper salt of 82 and its decomposition with aq. H_2S gave the enantiomerically pure (+)-α-allokainic acid (82 in 73% yield from 98). The synthetic amino acid 82 was shown to be enantiomerically pure and identical with natural 82, kindly provided by Professor H. Morimoto, by conversion to the dimethylester 100 ($MeOH/SOCl_2$) and subsequent comparison of the chromatographic properties, IR and ^{1}H-NMR-spectra particularly using a chiral shift reagent. The strikingly high asymmetric induction in the Et_2AlCl-promoted "ene-type" reaction 89c → 98 agrees nicely with a transition state geometry resembling G (Scheme 33).

Scheme 33



Invoking antiplanar conjugated $C_\alpha = C_\beta$ / C = O bonds and a synplanar arrangement of the alkoxy-hydrogen and the carbonyl oxygen in 89c, the phenyl group is smoothly positioned over the enophile-double bond. In support of this conformation, the phenylmenthylester 89c shows in the ^{1}H-NMR-spectrum the signal of H-C_α shifted up-field by 1.01 and 1.04 ppm from its position in the ethyl- and menthylesters 89a and 89b. Association of the acrylate unit with the Lewis-acid may lead to a charge-transfer complex which could account for the slower cyclization of 89c in comparison with 89a and 89b. This interaction of the enophile with the phenyl group blocking the *si*-face of C-β could direct the attack of the ene to the Cβ-*re*-face in agreement with experiment.

Similar stereochemical analysis of the Lewis-acid induced cyclization of the (E)-phenylmenthylester 94c (transition state H) predicts shielding of the enophile-*re*-face by the phenyl group and, consequently, ene-attack from the *si*-face. Indeed, treatment of 94c with Et_2AlCl (3 molequiv., CH_2Cl_2, - 35°, 18 hours) gave the isomers 98 and 99 in a ratio of 15:85 in perfect agreement with our prediction (Scheme 31). In summary, the cyclization 89c → 98 and 94c → 99 are the first examples of "ene-type" reactions proceeding with high asymmetric induction, allowing recyclization of the chirality directing group (Ref. 37). This, together with the possibility to manipulate the absolute sense of induction by variation of the enoate geometry, may prove of further value in synthesis.

Acknowledgement - It is a pleasure to pay credit to my very able collaborators Mr. Christian Robbiani, Dr. David Anthony Roberts, Dr. J. Ian Grayson, Dr. Thierry Godel and Mr. Kurt Bättig, who made the realization of this work possible. Their names are cited in the appropriate references. Generous financial support of this work by the Swiss National Science Foundation, Sandoz Ltd, Basel and Givaudan S.A., Vernier is gratefully acknowledged.

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