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The synthesis of pyrrolizidine alkaloids

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THE SYNTHESIS OF PYRROLIZIDINE ALKALOIDS

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The synthesis of pyrrolizidine alkaloids

by

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INTRODUCTION

The pyrrolizidine alkaloids have attracted considerable attention over the last several decades due to their widespread occurrence and interesting range of biological effects. A number of the naturally occurring alkaloids are hepatotoxic and carcinogenic, but some derivatives have potentially useful physiological properties. These include anesthetic and antiviral activities. A wide range of pharmaceuticals, including anti-inflammatory drugs, have been prepared. Some of the quaternary pyrrolizidine salts are powerful parasiticides.

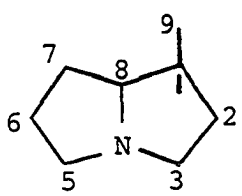
This manuscript will detail the results of a program to use the amidoalkylation reaction in the synthesis of some pyrrolizidine alkaloids.

HISTORICAL

The pyrrolizidine alkaloids constitute an exceptionally large class of naturally occurring compounds found in various families of Compositae, Boraginaceae, Leguminosae, Santalaceae, and Gramineae (1-6).

Although the title pyrrolizidine alkaloids is the most descriptive, frequently members of this group have been designated as Senecio alkaloids derived from the fact that various alkaloids of this group were first discovered in the generea Senecio of the family Compositae. This practice appears to be losing support, however.

There are approximately 125 pyrrolizidine alkaloids of known structure. All contain the methyl pyrrolizidine nucleus 1 as the distinguishing skeletal feature. The pyrrolizidine nucleus itself (the necine) possesses one or more hydroxyl groups esterified by organic acids (the necic acids), e.g., Dicrotatine (2).



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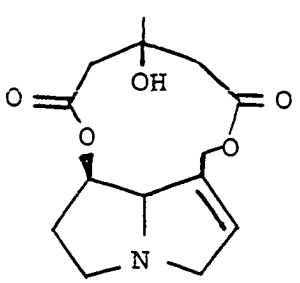

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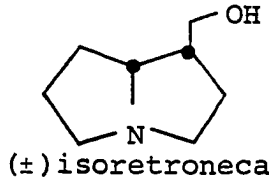
The structures of a number of representative necines are shown in Figure 1. The alkaloids fall into three main categories: monoesters of the necine with a monocarboxylic

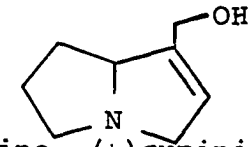


(±)isoretronecanol

3

(±)trachelanthamidine

4



(±)supinidine

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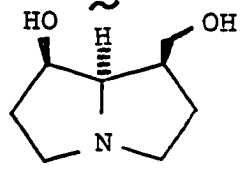
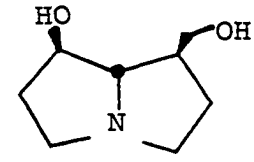


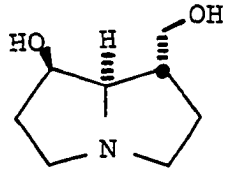
platynecine

6



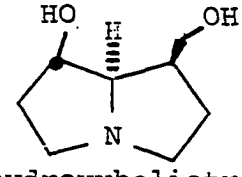
hastanecine

7



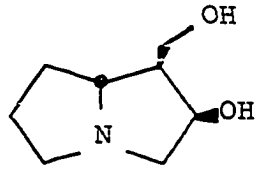
turniforcidine

8



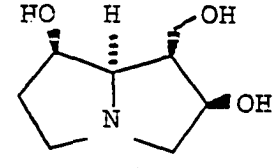
dihydroxyheliotridane

9



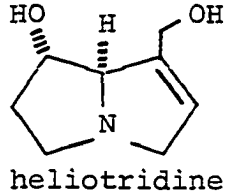
macronecine

10



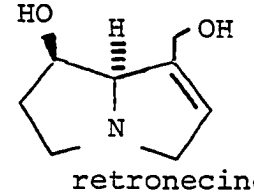
rosmarinecine

11



heliotridine

12



retronecine

13

Figure 1. Structures of representative necines

necic acid, diesters of the necine with two different monocarboxylic necic acids, and cyclic diesters of the necine with a dicarboxylic necic acid. The last category represents a highly interesting group of compounds, of wide natural occurrence, containing rings of medium size: the bislactone is part of an eleven or twelve membered ring.

Biosynthetically the necine arises from two C_4 units derived from ornithine 14, by the sequence shown in Figure 2 (7).

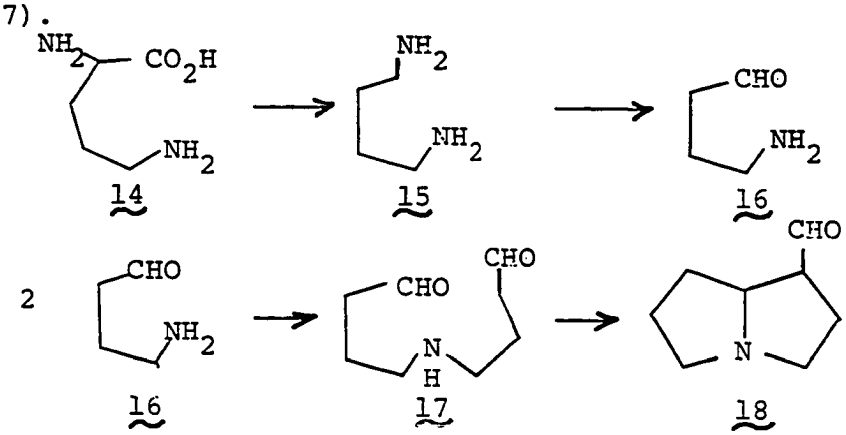


Figure 2. Biosynthesis of the necine

Pharmacologically, most of the alkaloids are toxic and have been shown to be responsible for cirrhosis of the liver in animals and occasionally for "bread poisoning" in human beings. The pharmacological effects of the pyrrolizidine alkaloids have been known since ancient times. Many of the findings made in ancient times and in the middle ages were summarized by A. Müller (8) in 1924. From the work of Dioscorides (69 B.C.), Muller reports that the Senecio leaves and flowers have a cooling effect, and when applied to inflammations, inflamed wounds and ulcers they

act curatively. Drinking the fresh extract from flowers produces a stifling effect, whereas the boiled extract from the whole plant has a beneficial action upon gastric pains. Plinius (23 to 79 A.D.) mentioned the beneficial effect of an extract of Senecio as a means against worms, epileptic seizures, jaundice, and liver and heart diseases.

It was only by the end of the nineteenth century, however, that the alkaloids contained in the plants were recognized as the biologically active principles. In 1867, Theissier (9) was the first to draw attention to the presence of alkaloids in the toxic Mexican plant Senecio canidices. He also obtained the first crystalline, though not fully identified, alkaloid from Senecio totutanus. Thirty years later two other alkaloids were isolated by Dalche and Heim (10) who suggested that these substances could be applied as hemostatica; they were also used for a long time in gynecology.

The isolation of toxic pyrrolizidine alkaloids from Senecio plants has led to the clarification of the etiology of a disease of domestic animals caused by consumption of these plants. The plants containing the alkaloids responible for the disease have been called in common terminology, "poisonous ragwort" (England), and the disease has been variously term Pictou disease (Canada), Winton disease (New Zealand), horse staggers and Molteno disease (South Africa),

walking disease and Missouri River bottom disease (United States), Schweinsberger disease (Germany), siraskaye disease (Norway), and the Zdar disease (Bohemia).

The plants are unpalatable, and are therefore eaten only in small quantities at a time, but are eaten especially when other food is in short supply. The disease is progressive; deaths of the animals commonly occur weeks or months after consumption of the poison plant. The principal and consistent feature of the disease is cirrhosis of the liver, in conjunction with disorders of the liver function. It is believed the alkaloids act on the parenchymal cells of the liver to produce an irreversible change which is additive and essentially antimitotic. As a terminal event, the liver fails to synthesize urea adequately, and death of the animal is commonly produced by ammonia intoxication of the central nervous system.

The lesion is usually confined to the liver which becomes fibrotic, but in some instances lesions in the lungs and in the kidneys also occur.

It is believed that the alkaloid molecule is changed by the hepatic microsomal enzymes and some part of the product, a so called metabolite, acts on the liver cell and usually does not escape into the general circulation. When lung and kidney lesions develop, they may be produced by a metabolite gaining access to the general circulation.

The suspected metabolites causing the liver lesions are believed to be dehydropyrrolizidine analogues (in abbreviation called pyrroles) of the corresponding alkaloids. Culvenor et al. (11) proposed that the organism is able to metabolize the pyrrolizidine alkaloids to the so called "metabolic pyrrols" by dehydrogenation of the unsaturated alkaloid (Figure 3). It should be emphasized that only alkaloids with a 1,2 double bond and a C-9 (allylic) ester are hepatotoxic.

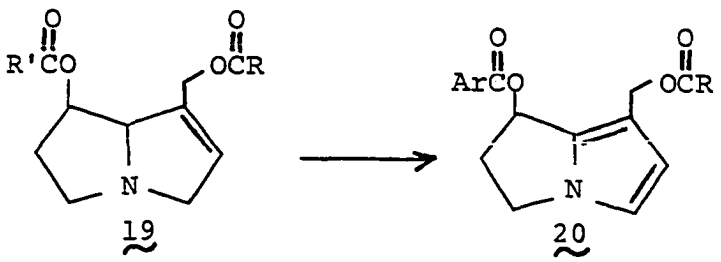


Figure 3. Formation of toxic metabolite

The resulting pyrrols are very reactive and have a high alkylating ability. Culvenor et al. (11) undertook chemically to prepare, in vitro, the dehydropyrrolizidine analogues of the corresponding alkaloids. He found their alkylating capacity is comparable with that of nitrogen mustard or mitomycin C, which were found to inhibit mitosis by bonding to both DNA chains (12).

The alkylating capability of the pyrrols depends on the ability of the lone pair of electrons on nitrogen to aid in the ionization of the primary (C-9) ester group (Figure 4).

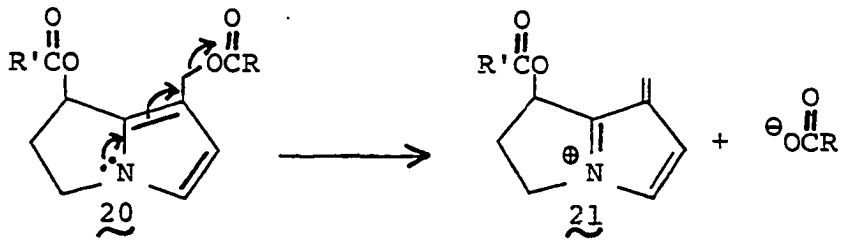
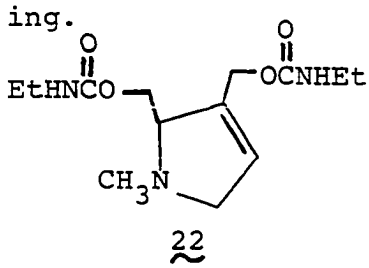
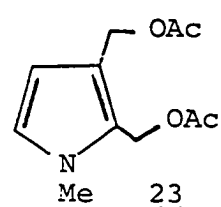


Figure 4. Ionization of primary ester group

This intermediate 21 is the probable alkylating agent. According to Shoental (13), intermediate 21 then forms a covalent bond with a coenzyme in the hepatic cell.

In connection with the toxicity of the pyrrolizidine alkaloids, the toxic effects have been reproduced by dosing experimental animals with synthetic compounds. Because the most toxic alkaloids are esters which are resistant to enzymatic hydrolysis, and which are converted in vivo into pyrrole derivatives, it was expected that simpler pyrroline esters would prove to exhibit the same toxic properties. This expectation was realized (14) when it was shown that the dicarbamate 22 is also toxic, and further, that the tissue damaged produced is histologically similar to that observed in cases of pyrrolizidine alkaloid poisoning.

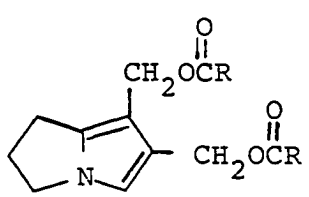




In further experiments (14) the synthetic pyrrole derivative 23 was also shown to produce the characteristic toxic effects of the poisonous pyrrolizidine alkaloids.

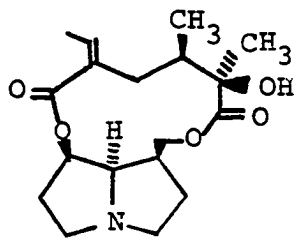
Recent work has finally settled a longstanding debate as to whether the pyrrolizidine alkaloids are truly carcinogenic (6). It has now been clearly established that malignant tumors arise in various organs of experimental animals following administration of sublethal doses of pyrrolizidine alkaloids (15-18). Rats injected with dehydroretronecine (a pyrrole) developed tumors at the site of injection (18).

The studies of the antimitotic effect of pyrrolizindine alkaloids also led to the investigation of their antitumor effect. The antitumor activity of many pyrrolizidine alkaloids could be experimentally confirmed. The testing of the alkaloids on experimentally produced standard tumors was carried out by Cancer Chemotherapy National Service Center in Bethesda and by the Abbot Laboratories in North Chicago. The results were published by Culvenor (19). A number of synthetic dehydropyrrolizidines 24 have also been prepared (20). Many of the diesters 24 showed significant antileukemic activity, particularly when R = NHMe.



24

Currently, the antitumor activity of pyrrolizidine alkaloids has not found wider use because of the numerous side effects, particularly the hepatotoxic activity. A non-hepatotoxic alkaloid platyphylline (25) is widely used in the U.S.S.R. for the treatment of hypertension and of internal ulcers.

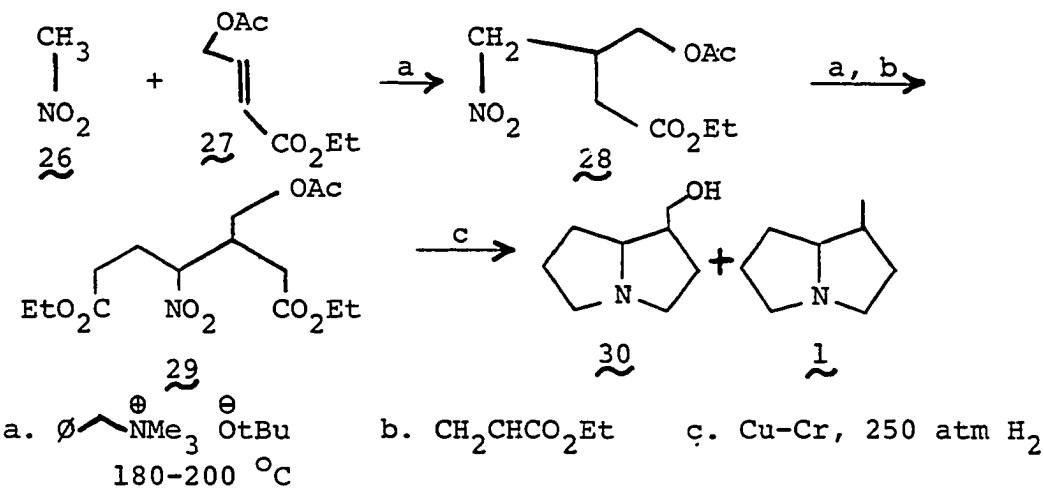


25

The large number of naturally occurring pyrrolizidine alkaloids, their deceptively simple structural features, and an interesting range of biological effects have all served to make these materials unusually attractive synthetic targets. Approximately thirty conceptually different syntheses of hydroxypyrrolizidines have been published, attesting to their synthetic appeal.

The first synthetic approaches to compounds containing the pyrrolizidine system were made as soon as the complete structures of a number of pyrrolizidine alkaloids were established. The first reported synthesis of the pyrrolizidine bicyclic system was by Menshikoff in 1937 (21). He synthesized 1-methylpyrrolizidine 1, but in very poor yield.

The first synthesis of a naturally occurring 1-hydroxymethylpyrrolizidine (30) was published by Leonard and Felley in 1950 (22) (Scheme 1). Nitromethane (26) when

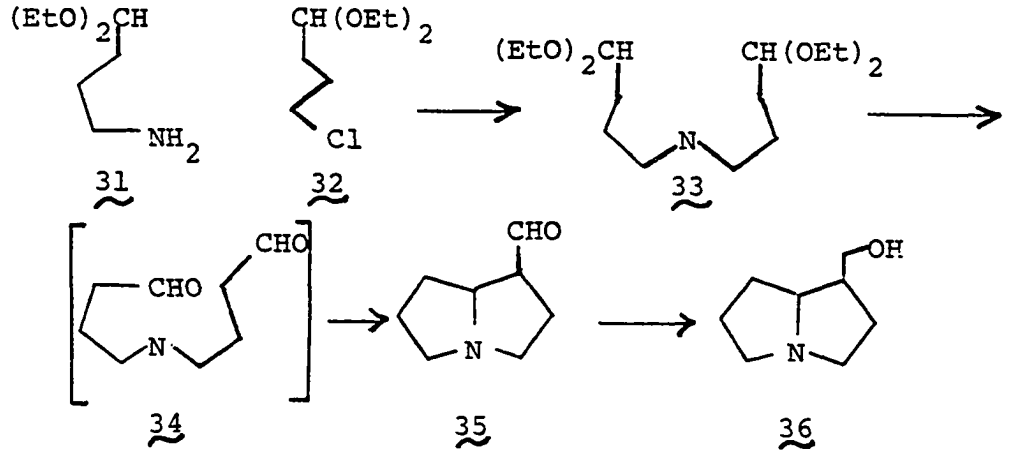


Scheme 1

condensed with ethyl γ-acetoxycrotonate (27) afforded the corresponding addition product 28, which was converted into diethyl β-acetoxymethyl-γ-nitropimelate (29) by condensation with ethyl acrylate. Reductive cyclization of 29 resulted in only trace amounts of 1-hydroxymethyl-pyrrolizidine (30) which was isolated as its picrate. This was probably a consequence of the drastic conditions that resulted in hydrogenolysis of the hydroxymethyl group. Less drastic conditions resulted in a negligible yield of the product formed by reductive cyclization.

An interesting synthesis of a 1-hydroxypyrrolizidine via a biogenetic pathway was proposed by Leonard and Blum

(23) and by Babor et al. (24) (Scheme 2). The bis-diethyl-acetal of di-(4-oxo-n-butyl)amine (33) was obtained from γ-aminobutyraldehyde diethyl acetal (31) and γ-chlorobutyr-

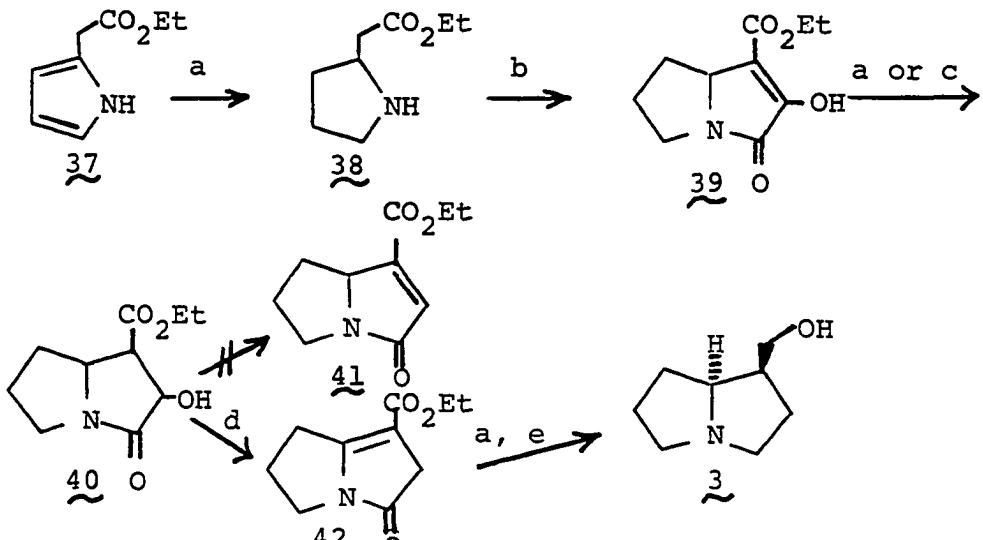


31 32 33 34 35 36

Scheme 2

aldehyde acetal (32). After removal of acetal protecting groups it was converted into 1-formylpyrrolizidine (35) without isolation of the intermediates. The final condensation was achieved by Babor et al. (24), in ca. 10-15% yield, at pH = 4-4.5. Hydrogenation of the compound over platinum afforded 1-hydroxymethylpyrrolizidine 36 which they claimed to be (±)isoretronecanol (3). Conversely, Leonard and Blum (23) carried out the same condensation at pH = 7 and reduced the resultant aldehyde with sodium borohydride. The 1-hydroxymethylpyrrolizidine 36 was isolated as 1-benzoyloxymethylpyrrolizidine in ca. 50% yield. According to Leonard the amino alcohol 36 is (±)trachelanthamidine (4).

An interesting stereospecific synthesis of (±)isoretronecanol (3) was published in 1961 by Adams et al. (25). The synthesis is based on closure of the pyrrolizidine ring by a reaction involving simultaneous ester condensation and N-acylation (Scheme 3).



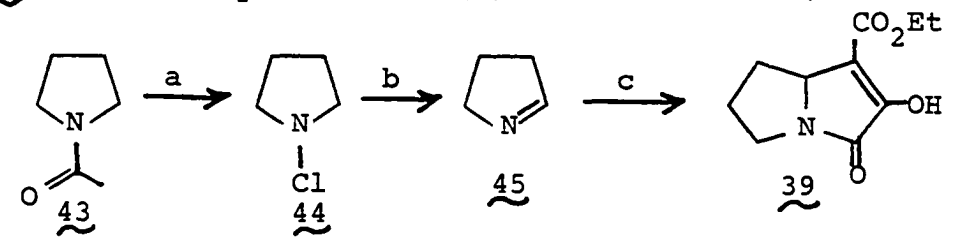
a. H_2, Rh-Al_2O_3 b. $(EtO_2C)_2$, NaOEt c. Zn, HOAc
d. TsCl, pyr. e. $LiAlH_4$

Scheme 3

Condensation of ethyl 2-pyrrolidylacetate (38) with diethyl oxalate in the presence of sodium ethoxide results in a high yield of the bicyclic amide 39. The latter can be reduced to give the saturated compound 40, which upon dehydration with p-toluenesulfonyl chloride in pyrridine yields compound 42 and not the expected compound 41. Catalytic hydrogentation followed by reduction with lithium aluminum hydride leads to (±)isoretronecanol (3). The authors erroneously claimed (25) that the unsaturated ester

had structure 41. As demonstrated later (26), however, the correct structure must be formulated as 42. This explains their failure to reduce the compound to supinidine (5).

Goldschmidt (26) reported another route to intermediate 39 in Adam's synthesis of (±)isoretronecanol (Scheme 4).



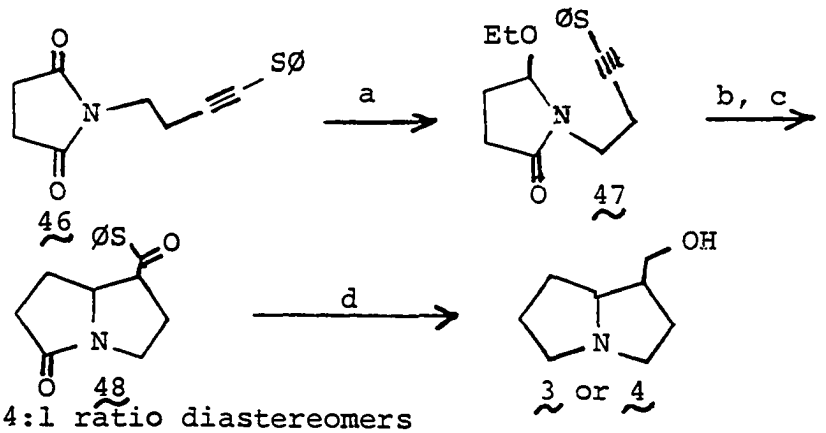
43 44 45 39

a. NaOCl b. KOH/EtOH c. $EtO_2CCH=C(OH)CO_2Et$

Scheme 4

Treatment of pyrrolidine acetate (43) with sodium hypochlorite gave N-chloropyrrolidine (44), which upon careful treatment with alcoholic potassium hydroxide yielded 1-pyrroline 45 (27). Refluxing a diethyl ether/ethanol solution of 1-pyrroline in the presence of diethyloxalyl-acetate resulted in a 64% yield of the bicyclic ring system 39.

This example closely resembles our own amidoalkylation route to the pyrrolizidine alkaloids. Another synthetic strategy parallelling our route is Speckamp and Nossin's (28) synthesis of (±)trachelanthanidine (4) and (±)isoretronecanol (3) (Scheme 5). The imide 46, obtained via the oxidation-reduction coupling technique (29) ($Ø_3P$, diethyl azodicarboxylate (DEAD)) of succinimide and the acetylenic alcohol, was reduced with sodium borohydride.

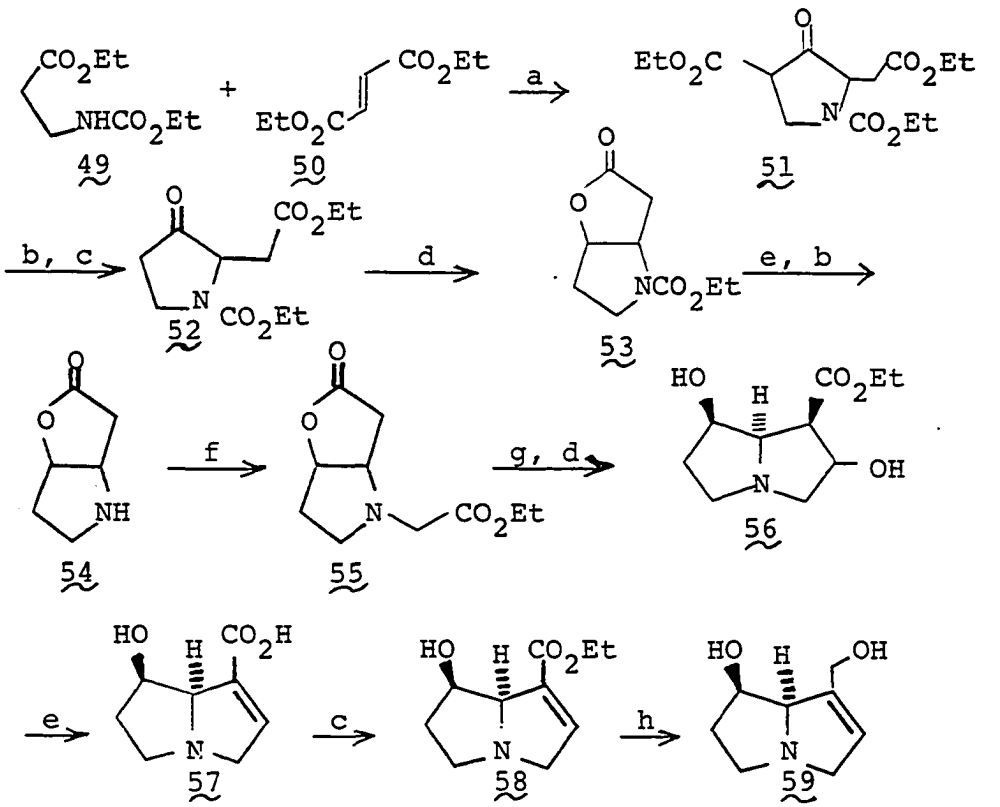


Scheme 5

Acidification of the alcoholic reaction mixture yielded the ethoxylactam 47. Cyclization of the ethoxylactam 47 in formic acid and subsequent acid hydrolysis furnished a 4:1 mixture of epimeric compounds. Lithium aluminum hydride reduction of the separated epimers yielded (±)trachelanthamidine (4) from the major product of the cyclization, and (±)isoretronecanol (3) from the minor product.

Total syntheses of pyrrolizidine alkaloids containing more than one hydroxyl group are not nearly as plentiful; only a few have been disclosed.

In 1962, Geissman and Waiss (30) published a stereospecific total synthesis of (±)retronecine (13) (Scheme 6). Condensation of N-carboethoxy-β-aminopropionate (49) with fumarate (50) in the presence of sodium followed by



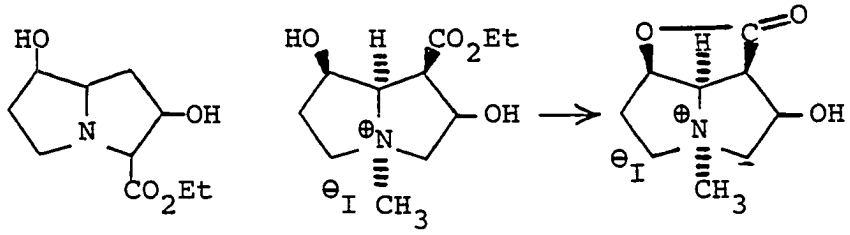
a. Na, C_6H_6 b. HCl, H_2O c. EtOH, $H^{\oplus}$ d. H_2, Pt

e. $Ba(OH)_2$ f. $BrCH_2CO_2Et$ g. KOEt, C_6H_6 h. $LiAlH_4$

Scheme 6

saponification, decarboxylation, and esterification of the resulting keto-ester 51 yielded ketone 52. Platinum catalyzed reduction of 52 afforded hydroxypyrrolidine, which was transformed without isolation into lactone 53. Reduction of 52 with sodium borohydride led to a mixture of lactone 53 and the corresponding hydroxyester (probably with the carboethoxy and hydroxyl groups in the trans orientation). Lactone 54, obtained by hydrolysis and subsequent relactonization of 53, was alkylated with ethyl

bromoacetate. The N-carboethoxymethyl lactone 55 was subjected to cyclization in the presence of potassium ethylate in benzene. Hydrogenation over platinum gave the hydroxyester 56. Had the Dieckmann cyclization proceeded in the other possible direction, one would have expected structure 60. To establish its structure, 56 was converted into the corresponding methiodide 61, which readily yielded lactone 62. This ready lactonization, together with the

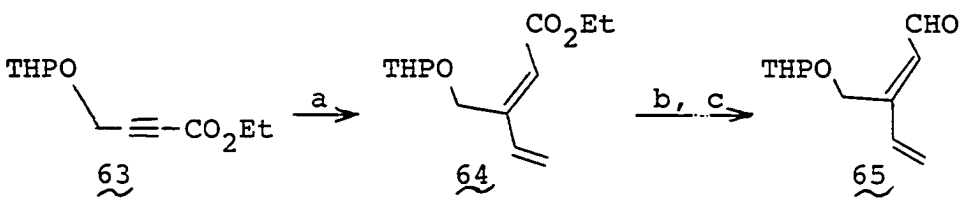


60 61 62

I.R. spectrum of the lactone, indicated that it was butyrolactone, providing evidence in favor of structure 56 and against 60. On the other hand, the readiness of lactonization suggests a retronecine-like (i.e., trans) configuration of the hydroxyl group at C-7 and the hydrogen at C-8 in hydroxyester 56. Treatment of 56 with barium hydroxide resulted in both hydrolysis of the ester grouping and in dehydration to yield unsaturated acid 57. The ethyl ester 58 was reduced with lithium aluminum hydride to afford the final product, (±)retronecine (13).

Keck and Nickell (31) recently reported the synthesis of retronecine (13) and heliotridine (12) using an intramolecular dienophile transfer technique to simultaneously form one carbon-nitrogen bond (N-C_8 pyrrolizidine numbering), establish the $\Delta^{1,2}$ double bond, and functionalize C_3 for eventual formation of the N-C_3 bond.

Addition of lithium divinylcuprate to the acetylenic ester 63 yielded diene ester 64 as a single isomer in quantitative yield. Reduction of 64 with diisobutylaluminum hydride to the dienol followed by oxidation with active manganese dioxide afforded the labile dienal 65.

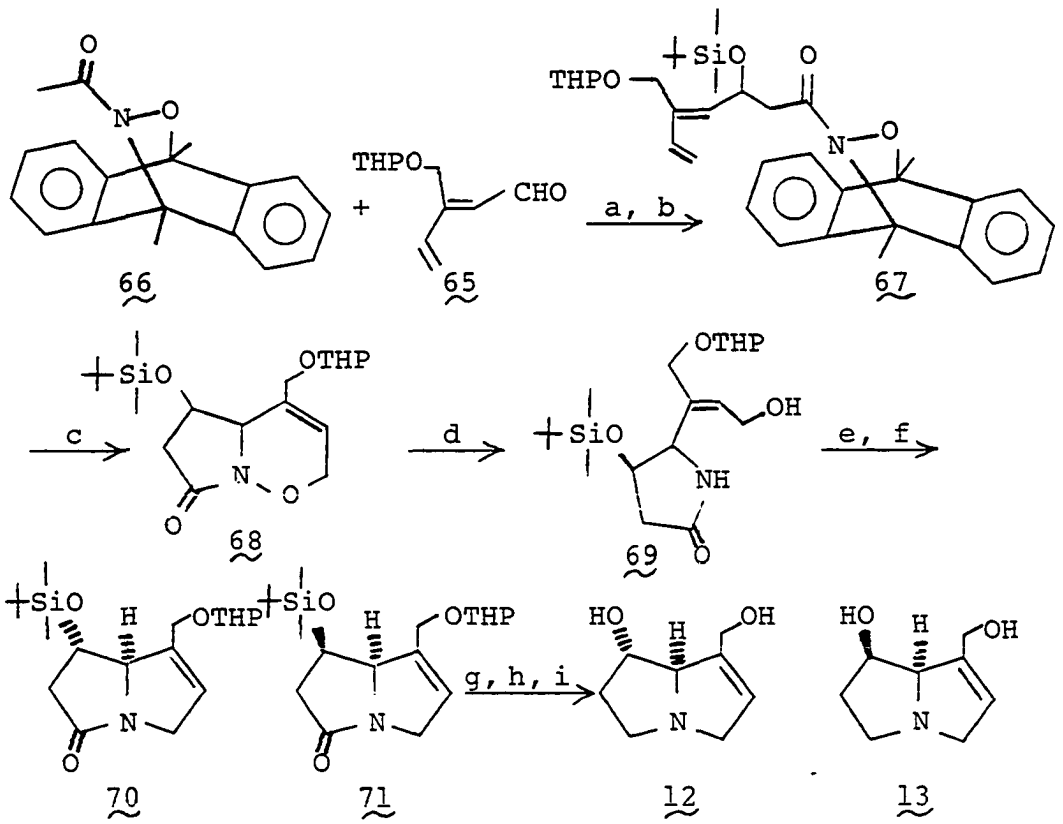


a. $(CH_2{=}CH)_2CuLi$ b. i-Bu_2AlH c. MnO_2

Scheme 7

Addition of aldehyde 65 to the lithium enolate of 66 cleanly afforded the alcohol. This was converted into its tert-butyldimethylsilyl ether derivative 67. Intramolecular transfer of the acylnitroso dienophile was cleanly effected by thermolysis (benzene, 80 °C, 4.5 hrs.) of 67 to afford the 1,2 oxazine derivative 68. Oxazine 68 was formed as an inseparable 1.3:1 mixture of stereoisomers, reflecting little stereoselectivity in the intramolecular

Diels-Alder process. Reductive cleavage of the nitrogen-oxygen bond in 68 was cleanly effected with excess 6% sodium amalgam to afford hydroxylactam 69. The hydroxylactam 69 was converted into easily separable bicyclic lactams 70 and 71 by adding a mixture of the mesylates to a solution of lithium diisopropylamide (LDA) at -78 °C followed by warming to room temperature. The separated isomers 70 and 71 were taken on to (±)heliotridine 12 and

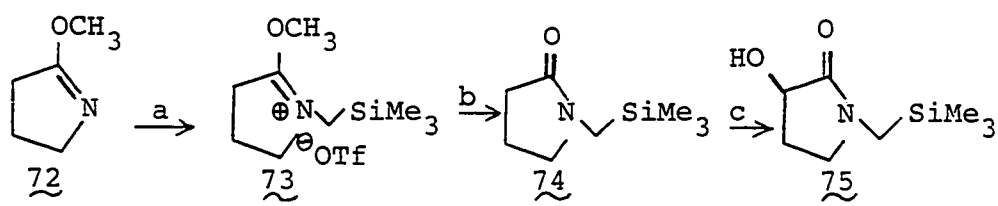


a. LDA, THF-HMPA b. t-Bu, Me_2SiCl, imidazole c. benzene, 80 °C, 4.5 hr. d. 6% Na-Hg e. CH_3SO_2Cl, Et_3N f. LDA g. PTSA, MeOH h. n-Bu_4NF i. $LiAlH_4$

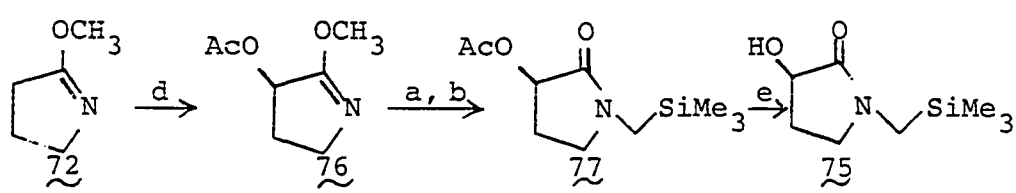
Scheme 8

and retronecine 13 by removal of the protecting groups, followed by lithium aluminum hydride reduction.

Vedejs and Martinez (32) recently reported another synthesis of retronecine (13) by an imidate methylide cycloaddition sequence. The retronecine sequence depends on the availability of hydroxy lactam 75. Vedejs developed two routes to 75. The shortest route started with alkylation of imidate 72 by trimethylsilylmethyltriflate to give salt 73 (not isolated) which was demethylated with 1,4-diazobicyclo[2.2.2]octane (Dabco) give the lactam 74. Enolate hydroxylation of 74 using the LDA, $MoO_5 \cdot Py \cdot HMPA$ method (33) afforded 75.



a. $CF_3SO_3CH_2SiMe_3$ b. Dabco c. LDA, $MoO_5 \cdot Py \cdot HMPA$
d. NBS, Et_4NOAc e. $NaOCH_3$

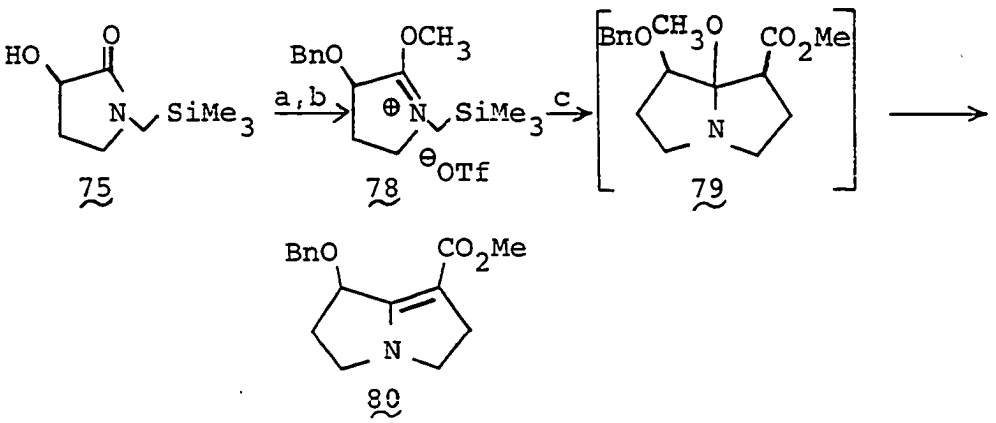


Scheme 9

An alternative route which had some advantages on a large scale was based on the conversion of 72 into 76 via bromination and nucleophilic displacement with tetraethylammonium acetate. Treatment of 76 with trimethylsilylmethyl triflate

and Dabco followed by acetate hydrolysis gave hydroxy lactam 75.

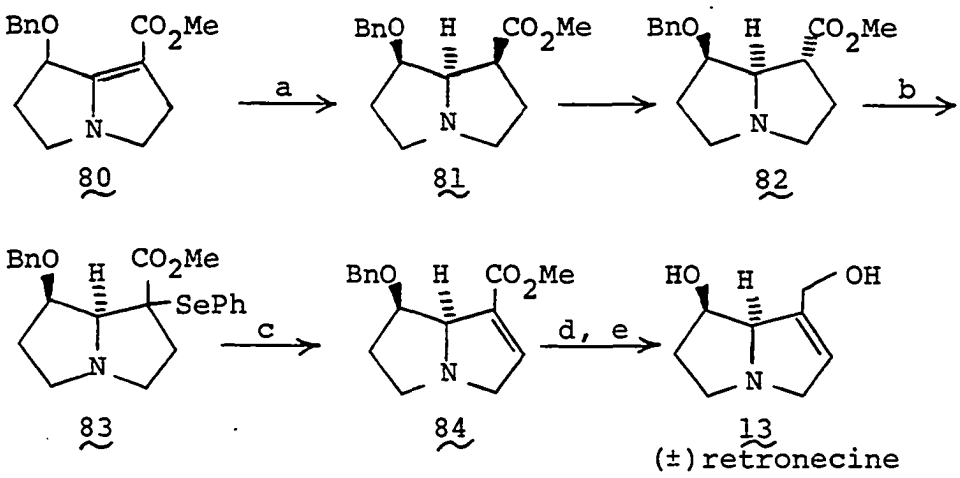
The hydroxy group in 75 was protected as the benzyl ether, followed by O-alkylation of the lactam to yield the imidate 78. The crude salt was dissolved in dimethoxyethane (DME) and stirred at 20 °C with methyl acrylate and anhydrous cesium fluoride to effect the 1,3 dipolar cycloaddition. Catalytic reduction of 80 gave a single reduction product 81 which spontaneously epimerized to



a. NaH, $BrCH_2Ph$ b. $CH_3OSO_2CF_3$ c. CsF, $CH_2=CHCO_2CH_3$

Scheme 10

isomer 82. Similar endo- to exo-isomerizations have been reported previously (34) among pyrrolizidine alkaloids. Final transformation of 82 to (±)retronecine (13) involved a selenium-based elimination to form the $\Delta^{1,2}$ double bond,



80 81 82 83 84 13 (±)retronecine

a. H_2, Pd/C b. LDA, PhSeSePh c. MCPBA d. Dibal
e. Li, NH_3

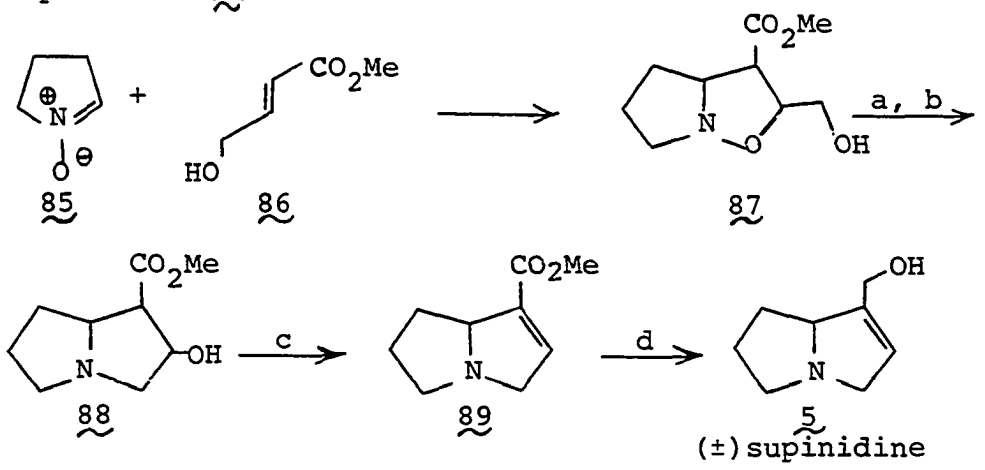
Scheme 11

reduction of the unsaturated ester to an allylic alcohol, and removal of the benzyl protecting group.

Few of the pyrrolizidine alkaloid syntheses are sufficiently adaptable that they may be extended to the synthesis of both the monohydroxy and dihydroxy pyrrolizidine alcohols. To date, only Tufariello and Tette (35), Tufariello and Lee (36), and Danishefsky et al. (37, 38) have been able to accomplish this feat.

Tufariello used the 1,3-dipolar reactivity of 1-pyrroline-1-oxides (nitrones) to synthesize (±)supinidine (5) and (±)retronecine (13). Addition of nitrone 85 to methyl γ-hydroxycrotonate (86) gave the hydroxy-substituted isoxazolidine 87, which was converted into the mesylate and subjected to palladium catalyzed hydrogenolysis. The

product 88, formed by internal alkylation of the amine by the primary mesylate, was dehydrated and reduced to yield (±)supinidine (5).



85 86 87 88 89 5

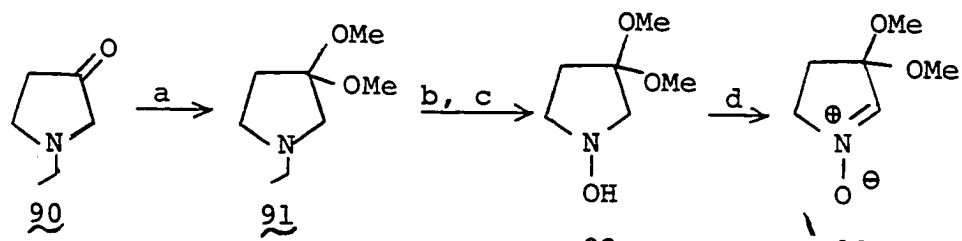
a. $MeSO_2Cl$ b. H_2-Pd/C c. $POCl_3$ e. $LiAlH_4$-$AlCl_3$

Scheme 12

To extend the 1,3-dipolar cycloaddition strategy to (±)retronecine (13), Tufariello and Lee (36) needed a functionalized nitrone that would allow introduction of the C-7 hydroxyl group.

The nitrone ketal 93 was chosen as a logical starting material. Its preparation parallels that of the simpler 1-pyrroline-1-oxide 85. N-Ethylpyrrolidin-3-one (90) was transformed into the corresponding dimethyl ketal 91 and thence into the hydroxylamine 92 by an N-oxidation-Cope elimination sequence. The mecuric oxide mediated oxidation of 92 proceeded regiospecifically to give nitrone 93. This remarkable selectivity was attributed to a diminuation

of eclipsing interactions (i.e., to a more favorable dihedral angle relationship) in proceeding from 92 to 93.

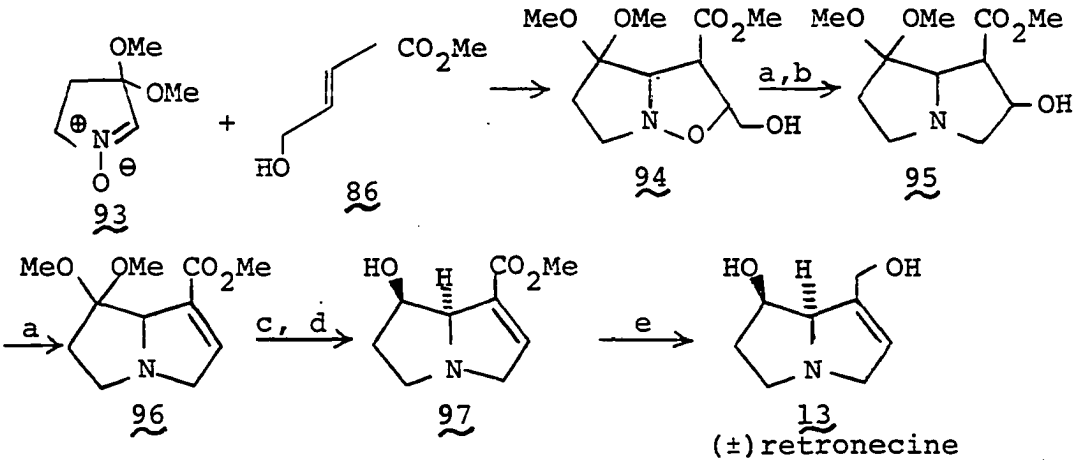


a. $(MeO)_3CH$, HCl b. 30% H_2O_2 c. 146 °C d. HgO

Scheme 13

Nitrone 93 underwent a 1,3-dipolar cycloaddition with methyl γ-hydroxycrotonate (86) to provide isoxazolidine 94. Mesylation of the primary alcohol, hydrogenolysis of the nitrogen-oxygen bond, and dehydration led to the α,β-unsaturated ester 96. Ketal hydrolysis, followed by reduction with sodium borohydride, and finally reduction with alane yielded (±)retronecine (13).

Danishefsky and co-workers have developed a novel route to saturated pyrrolizidine alcohols (37, 38). Stereospecific synthesis of (±)trachelanthamidine (4) and (±)isoretronecanol (3) are shown in Scheme 15 (37). The (Z)-diazomalonate 100 was prepared in a number of steps from the lithium salt of propargyl alcohol tetrahydropyranyl ether 98. Cyclopropanation with copper bronze in refluxing toluene gave syn-addition of the carbenoid to the (Z)-double bond. Treatment of the activated cyclopropane 101



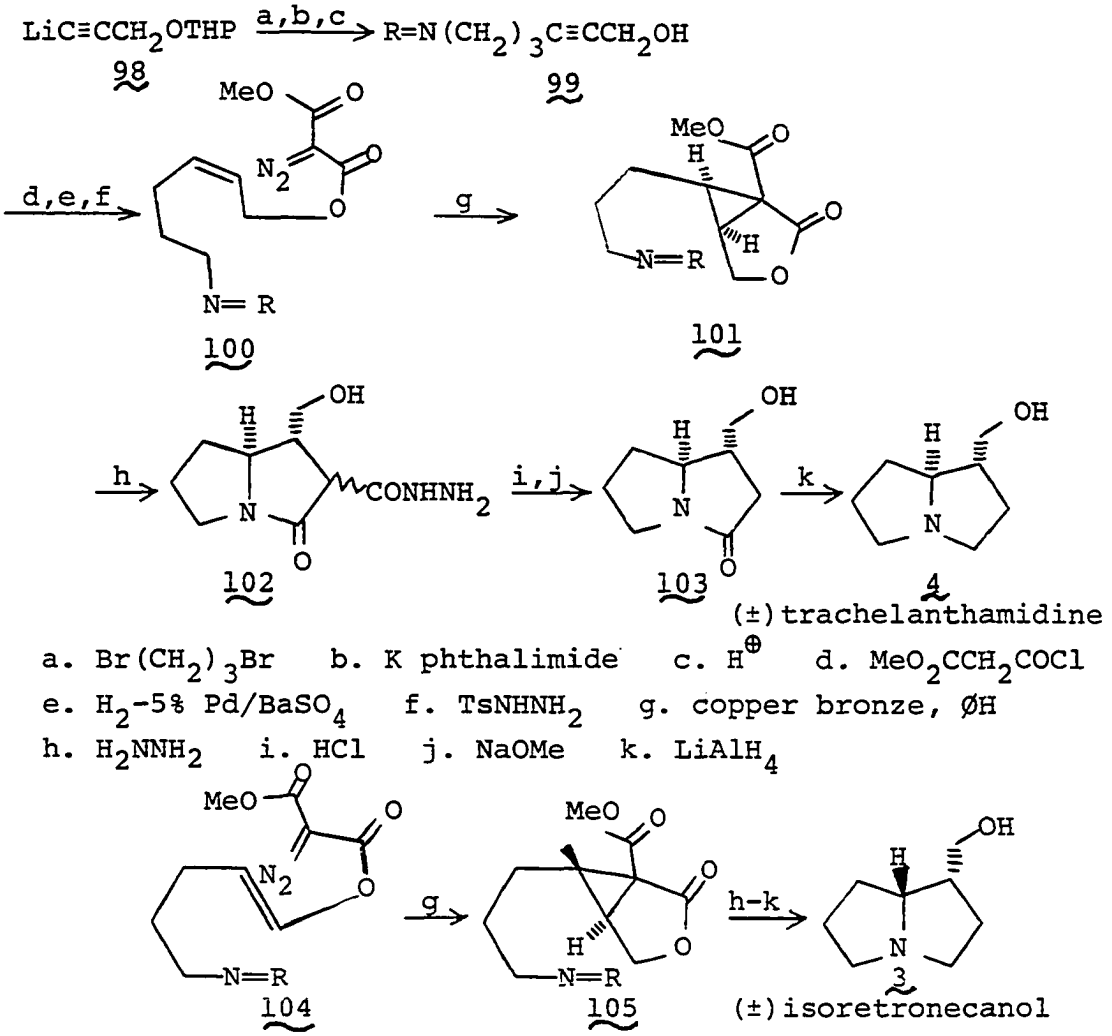
a. MsCl, Et_3N b. Pd/C, $-H_2$ c. 37% HCl, DME

d. $NaBH_4$ e. $LiAlH_4$-$AlCl_3$

Scheme 14

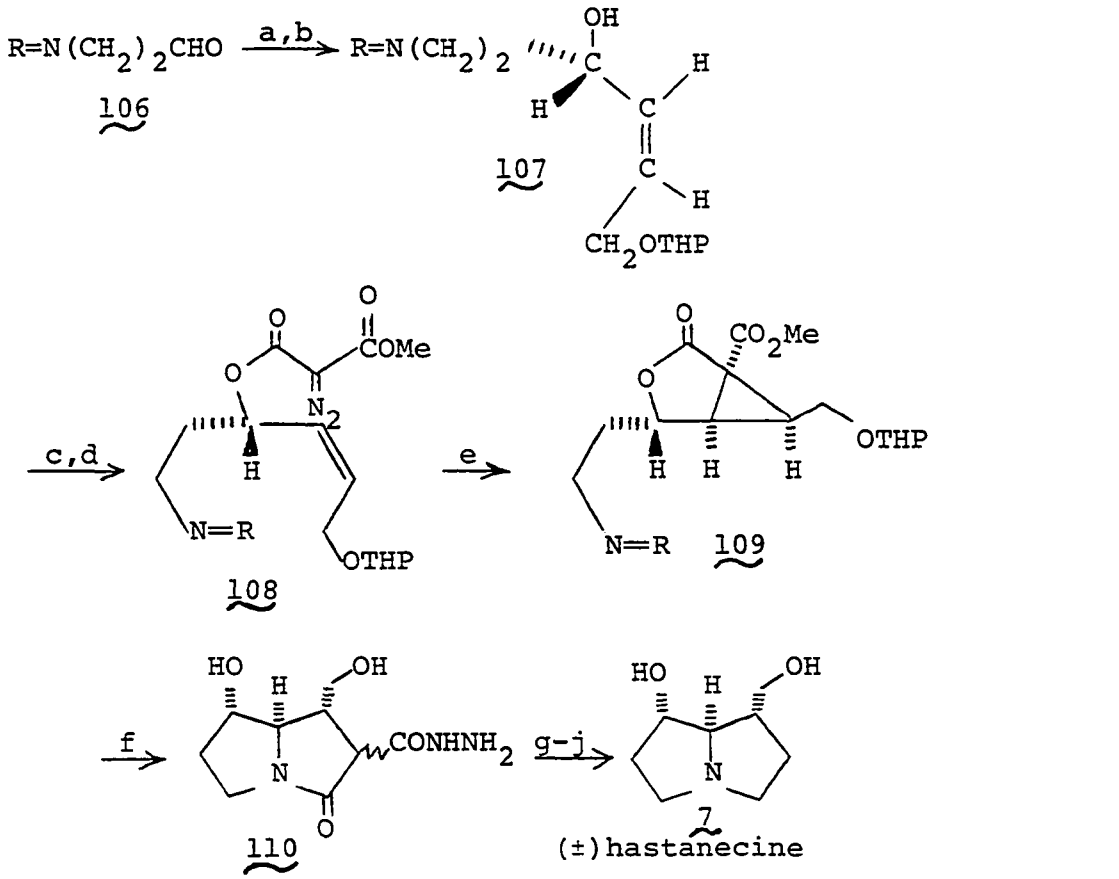
with excess hydrazine released the free amine, which underwent intramolecular homoconjugate addition with complete inversion of stereochemistry to give the pyrrolizidine hydrazide 102. Removal of the hydrazide function of 102 and reduction yielded (±)trachelanthamidine (4). Analogous treatment of the (E)-isomer 104 afforded (±)isoretronecanol (3).

Danishefsky et al. (38) used this strategy to synthesize necines with hydroxyl functions at C-7, namely (±)hastanecine (7) and (±)dihydroxyheliotridane (9). This route is outlined in Scheme 16. Production of the diazomalonate 108 from the (Z)-olefin 107 was carried out in a manner related to their previous syntheses (37).



Scheme 15

Intramolecular carbene insertion of the carbenoid derived from 108 was again highly stereospecific, yielding the bicyclo[3.1.0]oxahexanone system 109 with the phthalimidoethyl group in the exo-configuration. Ring opening of the cyclopropane 109 again occurred with inversion of configuration. Hastanecine (7) was formed in a parallel fashion

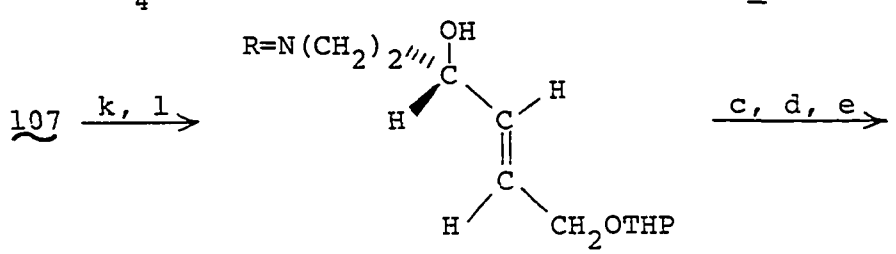


a. $Mg(C{\equiv}CCH_2OTHP)_2$ b. H_2 5% $Pd/BaSO_4$, quinoline

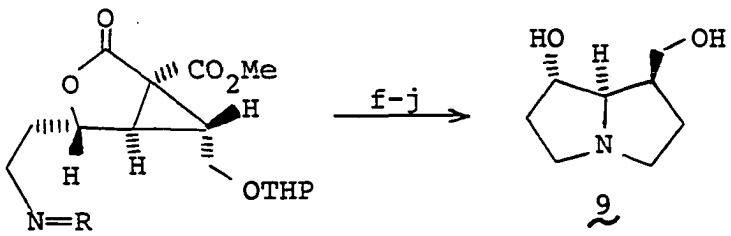
c. MeO_2CCH_2COCl d. $TsNHNH_2$ e. copper bronze f. NH_2NH_2

g. HCl h. NaOMe i. Ac_2O j. $LiAlH_4$ k. $PyrHCrO_3Cl$

l. $NaBH_4$ THP = tetrahydropyranyl; R = o-phthaloyl



Scheme 16



112 9

(±)dihydroxyheleotridine

Scheme 16 continued

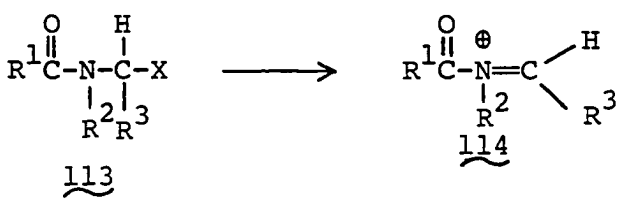
to (±)trachelanthamidine (4) (37). In order to prepare the epimeric pyrrolizidine, dihydroxyheliodridine 9, the (Z)-olefin 107 was converted into the (E)-isomer via the (E)-enone (39), followed by reduction with sodium borohydride. Analogous treatment of the (E)-isomer eventually yielded dihydroxyheliotridine 9.

RESULTS AND DISCUSSION

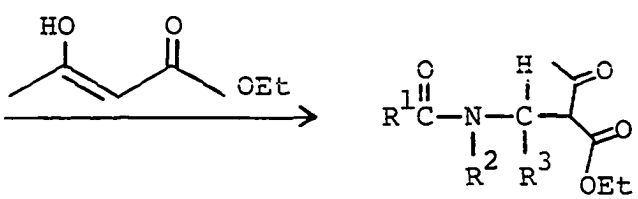
Electrophilic Amidoalkylation

Electrophilic amidoalkylation is a well-documented procedure (40, 41). It includes any reaction which leads to the formation of a new carbon-carbon bond by replacement of X from the electrophilic reagent $R^1CONR^2\text{-}CHR^3\text{-}X$. The X can be halogen, -OH, -OR, -OCOR, -NHCOR, $-NR_2$, or $-\overset{\oplus}{N}R_3$.

The mechanism of this reaction initially involves departure of leaving group X to yield an α-acyliminium ion 114. This α-acyliminium ion then undergoes an electro-



113 114



115

philic addition with a weak nucleophile (e.g., the enol of ethyl acetoacetate) to give the amidoalkylation product 115.

Compounds bearing carbon atoms sufficiently nucleophilic to be susceptible to attack by the amidoalkylating

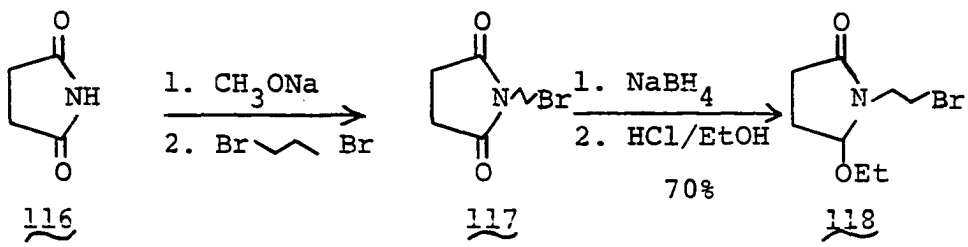
agents represent a wide variety of structural types. They include aromatic compounds, olefins, acetylenes, ketenes, carbenoids, active methylene compounds, Grignard reagents, and other organometallics.

Surprisingly this reaction has received little attention in the synthesis of natural products. This is due primarily to the harsh reaction conditions often employed (strong acid, base, or heat), but may also be due to difficulties encountered in the synthesis of suitable electrophilic reagents. Recently, Speckamp and Schoemaker (42) and Evans and Thomas (43) reported the amidoalkylation of an acetylene in their syntheses of perhydrohistrionicotoxin. Speckamp and Nossin (28) also utilized this reaction for the synthesis of isoretronecanol (3) and trachelanthamidine (4) (vide supra).

To investigate this potentially useful reaction, we decided to apply it to the synthesis of the pyrrolizidine alkaloids. The pyrrolizidine alkaloids were chosen for several reasons. The large number of known structures and their differing degrees of complexity would allow for syntheses of varying sophistication. Since most of the diastereomers are known, any questions concerning stereochemistry could be answered by comparing the product with the naturally occurring compound.

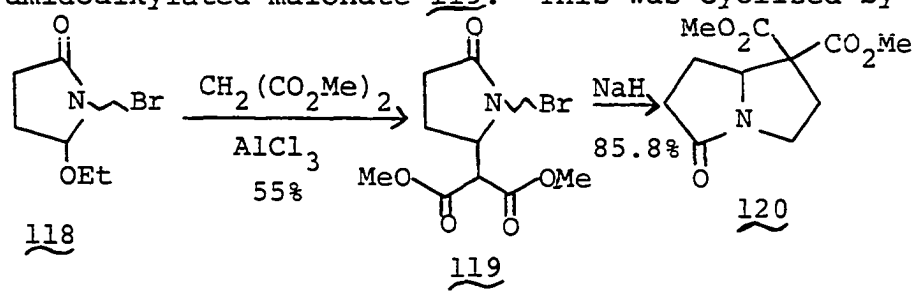
1-Hydroxymethyl-pyrrolizidines

For the synthesis of the functionalized pyrrolizidine alkaloids (isoretronecanol (3) and trachelanthamidine (4)) we needed a 5-ethoxy-pyrrolidinone as our electrophilic reagent. The pH controlled sodium borohydride reduction of succinimide or N-alkyl succinimide (44) allowed us to prepare a number of N-substituted-5-ethoxypyrrolidinones for use in amidoalkylations. The most useful of these for making the bicyclic pyrrolizidine skeleton proved to be 1-(2-bromoethyl)-5-ethoxy-2-pyrrolidinone (118). This was easily prepared from succinimide (116) and dibromoethane (45) followed by sodium borohydride reduction.



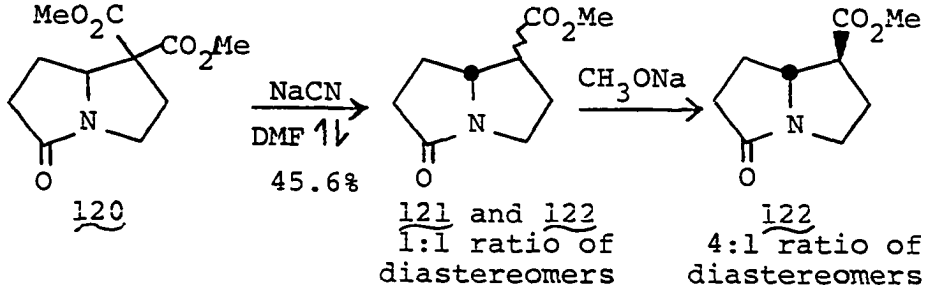
116 117 118

Amidoalkylation with 118 using Malmberg and Nyberg's (46) conditions (dimethyl malonate, $AlCl_3$) gave the amidoalkylated malonate 119. This was cyclized by

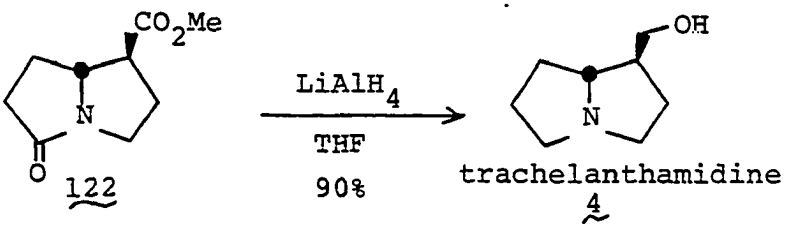


118 119 120

treatment with sodium hydride to give the bicyclic ring system 120. Completion of the synthesis required the removal of an ester group followed by reduction with lithium aluminum hydride. Decarboxylation of the diester proved to be a difficult task (probably due to steric hindrance around this center). A number of different conditions were tried (48% HBr (47); NaCN, DMF (48); NaCN, Me_2SO (49); NaCN, HMPA (50); PhSSPh, NaI, HMPA (51)) with limited success. The best yield (45.6%) was achieved using sodium cyanide in refluxing dimethyl formamide (DMF) (48) to give monoesters 121 and 122 as a 1:1 mixture of diastereomers. Treatment of this 1:1 diastereomeric



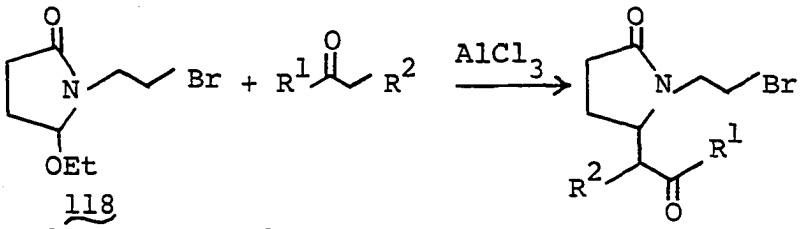
mixture with sodium methoxide in methanol resulted in partial epimerization to a 4:1 mixture with the exo ester (trachelanthamidine structure) predominating. The diastereomers could be separated by careful column chromatography and reduced with lithium aluminum hydride to give the naturally occurring pyrrolizidine alkaloids trachelanthamidine (4) and isoretronecanol (3).



122 trachelanthamidine 4

The difficulty encountered with the decarboxylation of 120 prompted us to revise our synthetic strategy to avoid this step. A number of different active methylene compounds were tried in the amidoalkylation reaction and the results are shown in Table 1.

Table 1. Amidoalkylation results



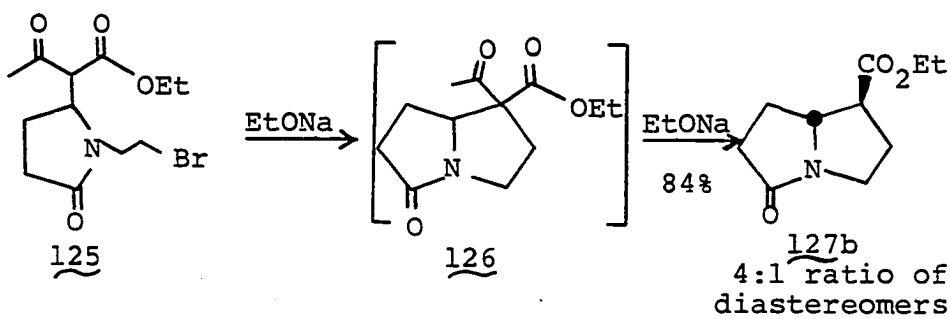
118

R^1	R^2	Yield (%)	
-OMe	$-CO_2Me$	55	119
-OMe	$-NO_2$	67	123
-OEt	$-CO_2CH_2Ph$	37	124
-OEt	-COMe	54	125
-OEt	$-O_2SC_6H_4CH_3$	0	
$-CH_3$	$-O_2SC_6H_4CH_3$	0	

Unfortunately, both β-ketosulfones and β-carboethoxy-sulfones failed to yield amidoalkylation products. This failure might be ascribed to the extremely low enol content of both compounds. Pyrrolysis of the sulfone moiety would

have served to introduce unsaturation at carbons 1 and 2 which is found in more complex pyrrolizidine alkaloids.

The solution to the decarboxylation problem was the amidoalkylation product of ethyl acetoacetate 125. This could be cyclized with sodium hydride in the same manner as the malonate ester adduct. However, if adduct 125 was treated with two equivalents of sodium ethoxide in ethanol, lactam 127 could be isolated directly. The first equivalent of sodium ethoxide abstracts the remain-



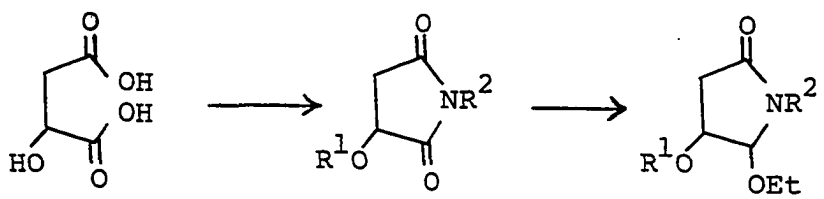
ing acidic proton of the ethyl acetoacetate residue. This then undergoes intramolecular alkylation to give the bicyclic ring system 126. The methyl ketone and the ethyl ester are attached to a quaternary carbon and are capable of undergoing the known β-keto ester cleavage at the ketone function (52). The sodium ethoxide also serves to epimerize the monoester to a 4:1 mixture of diastereomers.

This sequence (intramolecular alkylation, decarboxylation, and epimerization) greatly simplifies the

preparation of the less complex pyrrolizidine alkaloids. The synthesis of trachelanthamidine (4) and isoretronecanol (3) required only 4 steps from N-(2 bromoethyl) succinimide (115) and proceeded in an overall yield of 28.5%.

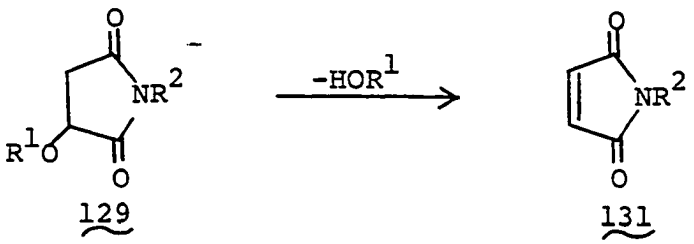
1-Hydroxymethyl-7-hydroxy-pyrrolizidines

To extend the amidoalkylation route to the pyrrolizidine alkaloids with a C-7 hydroxyl group, we hoped to reduce the imide 129 (prepared from malic acid (128)) to form pyrrolidone 130. Since both enantiomers of malic



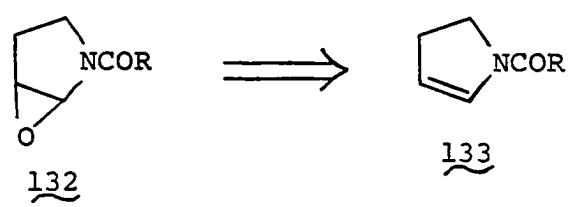
128 129 130

acid 128 are commercially available, this route would have allowed us to prepare enantiomerically pure pyrrolizidine alkaloids. We hoped that coordination of the reducing agent with the hydroxyl group (or protected hydroxyl) would produce only one regioisomer from the reduction. Unfortunately, our previous conditions ($NaBH_4$) or diisobutyl aluminum hydride gave only the elimination product 131. This happened even if the hydroxyl was protected (R^1 = H, acyl, alkyl).



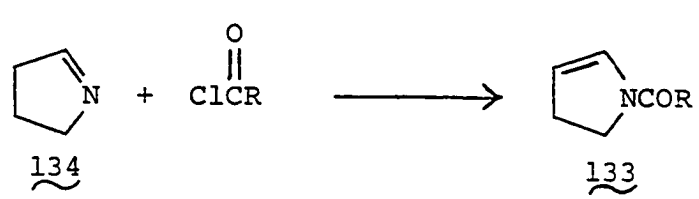
129 131

From these results it is obvious that the second acyl group would have to be moved out of the ring. Putting the acyl group on the N-side chain (R^2) would provide a workable alternative. The N-acyl epoxypyrrolidine 132, which might be obtained from the N-acyl-2-pyrroline 133 appeared to offer a promising solution to the problem.



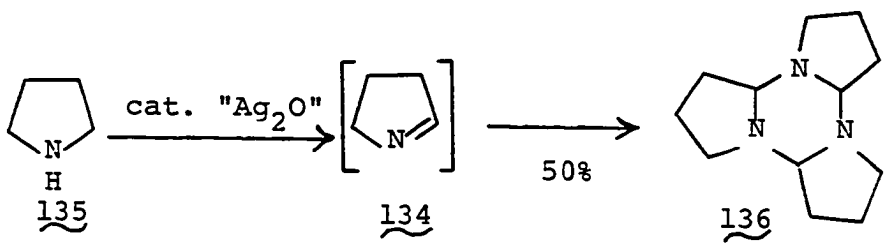
132 133

Attempted cyclization of N-acyl aminobutyraldehyde dimethyl acetal to N-acyl-2-pyrroline (53) proceeded in very low yield. We decided to explore the possibility of acylating 1-pyrroline (134) with an acid chloride or alkyl chlorocarbonate. This reaction is well-known for acyclic imines (54).



134 133

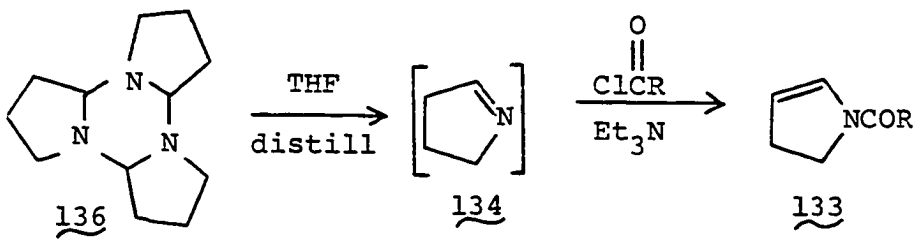
However, 1-pyrroline (134) is unstable and has been little studied (26, 27, 55). The trimer of 1-pyrroline (136) is readily available by oxidation of pyrrolidine (135) with sodium peroxydisulfate and 0.5% silver nitrate (56) and has been used as a synthetic equivalent of 1-pyrroline (57).



135 134 136

Treating the trimer 136 directly with acetyl chloride and triethyl amine in refluxing dichloroethane resulted in low yields of N-acetyl-2-pyrroline. Better yields were obtained by flow pyrolysis of a tetrahydrofuran (THF) solution of the trimer 136 at 320 °C followed by reaction with an acid chloride and triethyl amine. Unfortunately this was accompanied by much decomposition.

Nomura et al. (56) had noted that the trimer of 1-pyrroline (136) "decomposed" at 50 °C. This observation prompted us to distill a 0.1 M THF solution of the 1-pyrroline trimer (136) into a flask precooled to -70 °C. The addition of triethyl amine and an acid chloride afforded the N-acyl-2-pyrroline in good yield. Presumably the trimer dissociates in the refluxing tetrahydrofuran



136 134 133

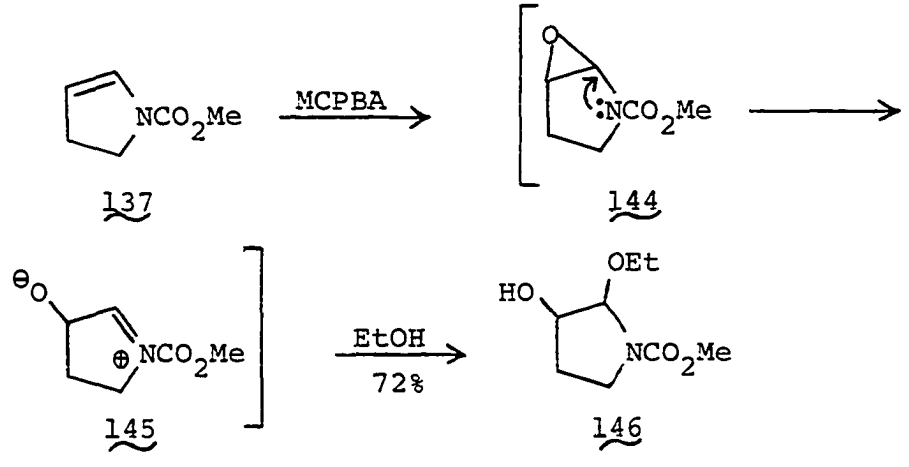
(THF) solution and 1-pyrroline codistills with the tetrahydrofuran. After distillation, approximately 40-45% of the 1-pyrroline trimer (136) remained in the flask as a polymeric residue. It is not clear if the polymer was initially present in the trimer or whether the polymerization occurred upon distillation. A number of different acylating agents were employed and the yields are shown in Table 2.

Table 2. Preparation of N-acyl-2-pyrrolines

Acylating Agent	Yield[a] (%)	
MeOCOCl	78	137
EtOCOCl	79	138
CH_3COCl	71	139
$PhCH_2OCOCl$	74	140
$ClCH_2COCl$	57	141
Cl_3CCH_2OCOCl	39	142
EtOCOCOCl	0	143

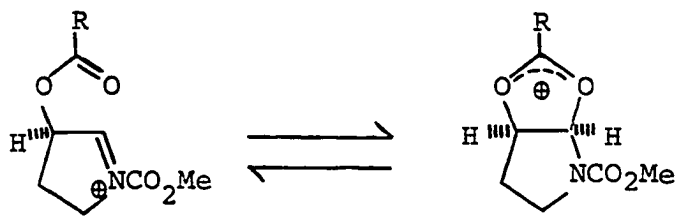
[a]Yield is based on consumed trimer. Typically 55-60% of the trimer is consumed on a 50 mmole scale.

Based on the yields of the N-acyl-2-pyrrolines and the need to remove the acyl group at a later stage, we chose to work with N-methoxycarbonyl-2-pyrroline (137). Attempted epoxidation of this enamide with m-chloroperbenzoic acid (MCPBA) in methylene chloride yielded none of the epoxide. Instead, most of the product arose from opening of the initially formed epoxide 144 and addition of m-chlorobenzoic acid or m-chloroperbenzoic acid to the acyliminium ion 145. To simplify the procedure and increase the yield, the epoxidations were conducted in ethanol to give N-methoxycarbonyl-2-ethoxy-3-hydroxy pyrrolidine (146).

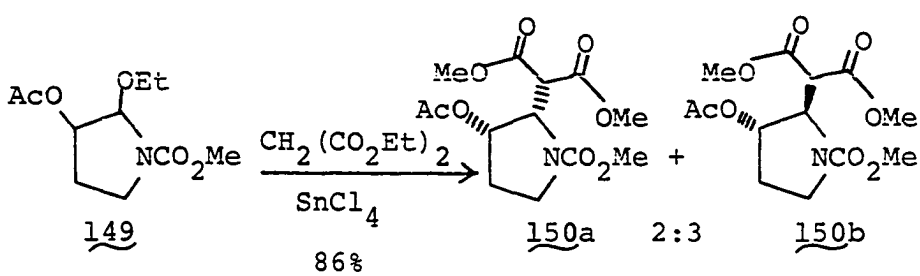


We expected the product distribution of the amidoalkylation would be strongly influenced by variation of the protecting group placed on the 3-hydroxyl group. This influence could take two forms. One involves steric

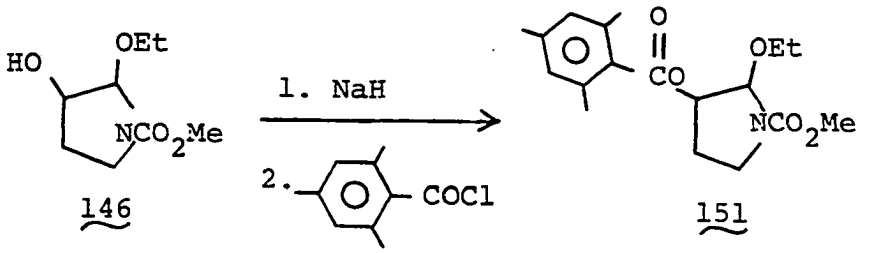
hindrance to the incoming nucleophile. Larger protecting groups on the neighboring hydroxyl group would favor the trans-amidoalkylation product. Another argument would invoke neighboring group participation. It was felt that an adjacent ester group could help stabilize the acyliminium ion 147 by forming bridged bicyclic intermediate 148. This intermediate would promote amidoalkylation on the convex side (i.e., trans-to the ester group).



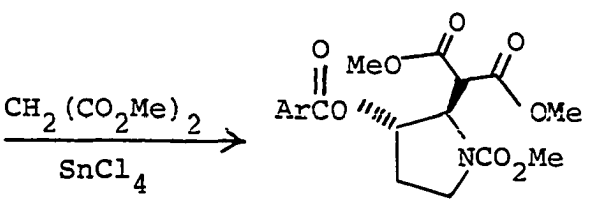
Subsequent trials seemed to indicate that the major stereochemical influence came from steric factors rather than neighboring group participation. The 3-hydroxyl group was protected as the acetate with acetic anhydride. Amidoalkylation of the 3-acetoxy-2-ethoxy pyrrolidine 149 with dimethyl malonate and tin tetrachloride ($SnCl_4$)



gave a 2:3 mixture of diastereomers. Using a t-butyl-dimethylsilyl ether as a protecting group gave a 1:15 ratio of diastereomers. Unfortunately, the overall yield was only 19%. This is most likely due to the instability of the silyl ether to the reaction conditions. Treating alcohol 146 with sodium hydride and mesityl chloride (58) gave the mesitoate ester 151. Amidoalkylation of 151 with dimethyl malonate and tin tetrachloride gave a 1:7.4 ratio of diastereomers in 87% yield.



146 151

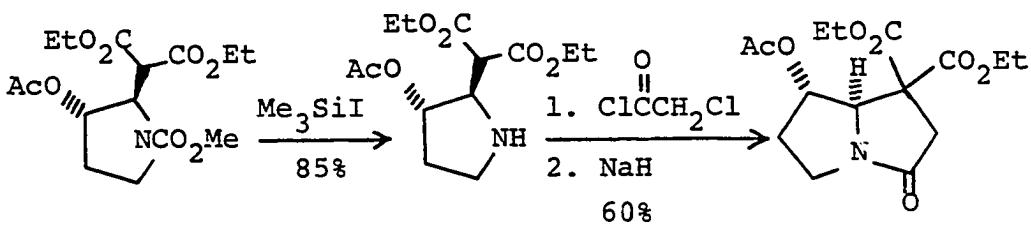


152b
7.4:1 ratio of diastereomers

Tin tetrachloride ($SnCl_4$) was used as the Lewis acid in the above examples. Aluminum trichloride ($AlCl_3$) had been used previously. It was found that tin tetrachloride gave better yields than aluminum trichloride and was operationally more convenient.

Surprisingly the amidoalkylation with ethyl acetoacetate did not work and gave no identifiable products. This was unfortunate since the ethyl acetoacetate adduct 125 had allowed us to circumvent the decarboxylation problem in the less complex system.

The dimethyl malonate adduct 150b was treated with trimethylsilyl iodide (59) to selectively remove the N-acyl group in the presence of three esters.



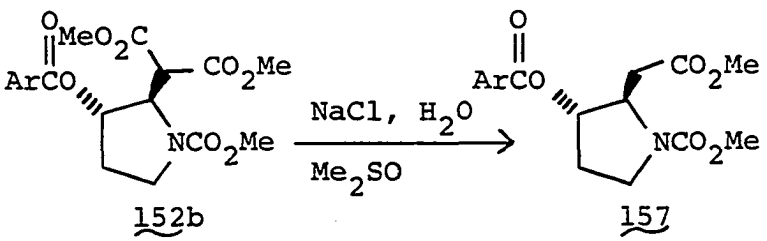
150b 153 155

Acylating the amine 153 with chloroacetyl chloride followed by cyclization with sodium hydride gave the bicyclic ring system 155. Decarboxylation of the 1,1-diester 155 proved to be as difficult as decarboxylation of 1,1-diester 120. The best yield obtained was only 31%.

Because of the difficulties encountered in decarboxylating hindered diesters on quaternary carbons, it seemed prudent to remove one of the esters before forming the bicyclic ring system.

Heating a dimethyl sulfoxide solution of the malonate ester 152b for 2 hours at 160 ^{o}C with sodium chloride and

water (60) gave a 66% yield of the decarboxylated product 157. It also gave a 23.7% yield of methyl mesitoate as a byproduct. It appeared that the methanol formed in the

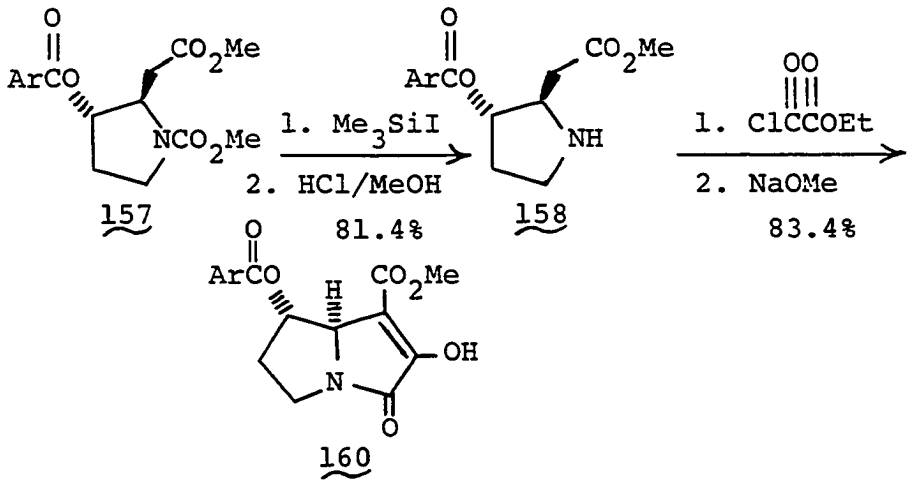


152b 157

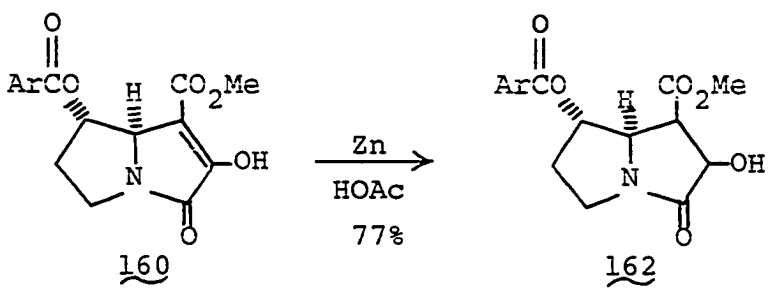
decarboxylation reaction attacked the mesitoyl ester to give methyl mesitoate and an unstable alcohol that was never isolated. To avoid this unwanted side reaction, the solution was heated only for 30 minute periods, cooled, and the methanol formed was removed under vacuum. The reaction was heated for four 30 minute periods to yield 85% of the decarboxylated product 157. Heating for longer periods of time gave increasing amounts of methyl mesitoate and a lower yield of 157.

To form the bicyclic ring system it was necessary to remove the N-acyl group. Treating the urethane 157 with trimethylsilyl iodide (60) as before, afforded the free amine 158. The reaction was quenched with acidic methanol to re-esterify any methyl ester that had been saponified.

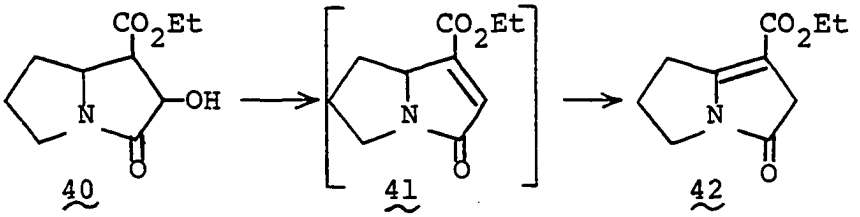
Acylating the amine 158 with ethyl oxalyl chloride followed by cyclization with sodium methoxide gave bicyclic ring system 160. This was similar to an intermediate



reached by Adams et al. (25b) and by Goldschmidt (26) (vide supra 39). Compound 160 appeared to be a promising intermediate for completion of the synthesis of heliotridine (12). The enol 160 was easily reduced to the alcohol 162 by treating the compound with zinc in acetic acid (61).



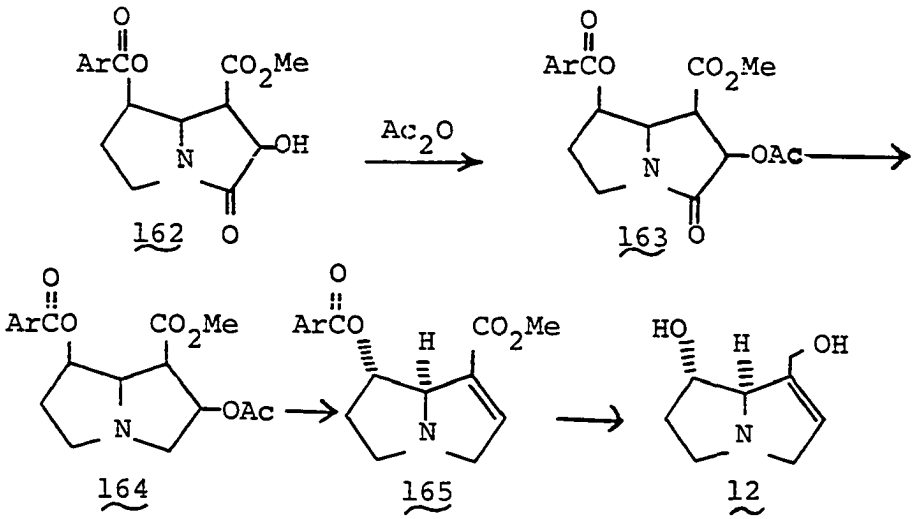
Unfortunately, previous investigators (26, 61) had found that if this type of compound was dehydrated to form the $\Delta^{1,2}$ double bond, the double bond would isomerize to the $\Delta^{1,8}$ position.



40 41 42

We wanted to avoid this pitfall for several reasons. First, we would lose the stereochemistry at C-8 (introduced by the amidoalkylation reaction). Once the double bond had migrated, it would be difficult to isomerize back to the $\Delta^{1,2}$ position and would have to be reduced instead.

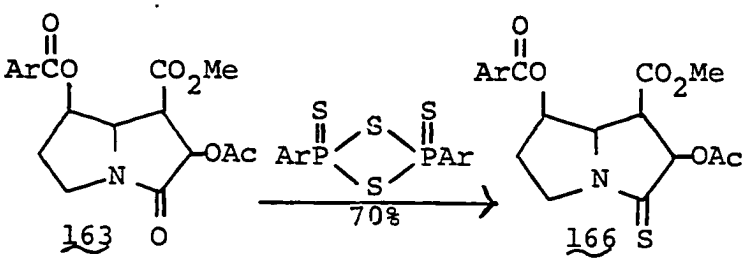
To prevent double bond migration, the amide must be reduced prior to dehydration. We first protected the α-hydroxy-amide 162 with acetic anhydride. The acetate seemed an ideal protecting group as it would be stable to most reduction conditions and it could be eliminated later to form the $\Delta^{1,2}$ bond.



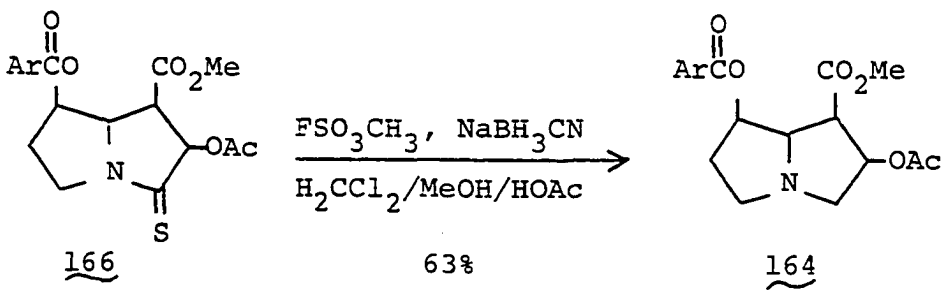
162 163 164 165 12

Attempted reduction of amide 163 under a variety of conditions [BH_3 (62); $POCl_3$, $NaBH_4$ (63); FSO_3CH_3, $NaBH_4$ (64)] was unsuccessful. The problem appeared to be competing attack on the esters present in the molecule.

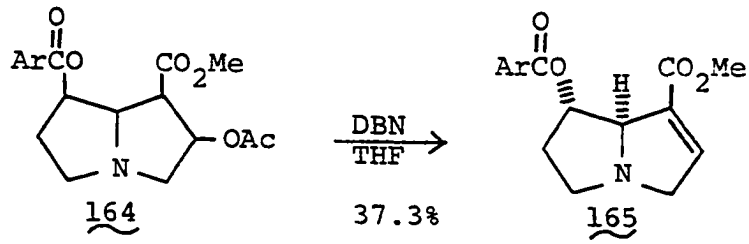
To make the amide more reactive it was converted to the thioamide using Lawesson's reagent (65). Attempted reduction of thioamide 166 under a variety of conditions



[BH_3; MeI, $NaBH_4$ (66); MeI, $NaBH_3CN$; Raney nickel (67); FSO_3CH_3, $NaBH_4$] was again unsuccessful. The reduction was finally achieved by a modification of Raucher and co-worker's procedure (68) to yield amine 164.



Elimination of acetic acid to form the unsaturated ester 167 was accomplished with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN).



164 165

Completion of the synthesis of heliotridine 12 requires only reduction of the methyl ester to an alcohol and removal of the mesityl protecting group.

CONCLUSION

The utility of the amidoalkylation reaction has been demonstrated. This reaction was used successfully in the syntheses of pyrrolizidine alkaloids. It should also find general applicability in other alkaloid systems.

The simple pyrrolizidines, trachelanthamidine and isoretronecanol, were prepared from succinimide. The synthesis required only five steps and proceeded in good overall yield. The synthesis is the most direct and operationally convenient route yet reported.

An intermediate for the synthesis of heliotridine was also prepared. The synthetic route gave good stereochemical control of the key asymmetric centers. Completion of the synthesis requires only reduction of a methyl ester and removal of a mesityl protecting group.

EXPERIMENTAL

General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Diethyl ether, tetrahydrofuran (THF), and benzene were distilled from $LiAlH_4$ prior to use. Triethyl amine was distilled from sodium. Pyridine was distilled from CaH_2. Infrared spectra were obtained on a Beckman IR 4250 or Acculab 2 spectrometer. The NMR spectra were recorded using a Varian EM-360, A-60, or HA-100 spectrometer or a Hitachi-Perkin Elmer R20-B spectrometer. Carbon-13 NMR spectra were determined on a JEOL FX-90Q Fourier Transform spectrometer. Both proton and carbon chemical shifts are expressed in parts per million (δ) downfield from internal tetramethylsilane. High resolution mass spectra were recorded on an AEI MS-902 mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected.

Preparation of 1-(2-Bromoethyl)-2,5-pyrrolidinedione (117)

A 2.0 M methanol solution of succinimide (116) (36.64 g, 400 mmoles) was added dropwise to a stirred 2.0 M methanol solution of NaOMe (9.2 g of Na, 400 mmoles). The methanol was evaporated and the residue redissolved in 500 mL of dimethylformamide (DMF). Dibromoethane (93.93 g, 500 mmoles)

was added and the reaction stirred for 48 hours. The reaction mixture was concentrated in vacuo, redissolved in ethyl acetate, and extracted with water and with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to yield 38.24 g (185 mmoles) of imide 117 as an off-white solid. mp 52-54 °C. NMR ($CDCl_3$) δ 2.77 (s, 4H), 3.53 (m, 2H), 3.90 (m, 2H). IR (nujol) 1685 cm^{-1}.

Preparation of 1-(2-Bromoethyl)-5-ethoxy-2-pyrrolidinone (118)

Sodium borohydride (7.06 g, 186.4 mmoles) was added portionwise to an ice cold solution of imide 117 (10.3 g, 50 mmoles) and 565 mL of absolute ethanol. Every 5 minutes, 3 drops of 2 N HCl in ethanol were added to maintain a constant pH. After 5 hours, the solution was acidified to pH 3.5 with 97 mL of 2 N HCl in ethanol. After stirring 3 hours at 0 °C, the solution was neutralized with 160 mL of 1% KOH in ethanol. The solvent was evaporated, and the residue was washed with $HCCl_3$. The $HCCl_3$ washings were filtered through celite and concentrated in vacuo. The residue was chromatographed on silica gel (1/10, w/w) using ethyl acetate/hexane (1/2) as the solvent to yield 7.87 g (33 mmoles) of 118 (66%) as a colorless oil. IR (film) 1700 cm^{-1}. NMR ($CDCl_3$) δ 1.25 (t, 3H, J = 7 Hz), 1.82-2.78 (envelope, 4H), 3.40-3.98 (envelope, 6H), 5.10 (m, 1H). C-13 NMR ($CDCl_3$) δ 14.7, 24.3, 28.0, 28.6, 42.1, 61.2, 89.2,

174.3. High resolution mass spectrum for C_6H_8NOBr ($M^{\cdot+}$-$HOCH_2CH_3$) requires m/e 188.97892, measured 188.97905.

Preparation of [1-(2-Bromoethyl)-2-oxo-5-pyrrolidinyl] Propanedioic Acid Dimethyl Ester (119)

A solution of the ethoxylactam 118 (9.44 g, 40 mmoles), dimethyl malonate (6.34 g, 48 mmoles), and 30 mL of H_2CCl_2 was added dropwise to a stirred suspension of $AlCl_3$ (7.47 g, 56 mmoles) and 40 mL of H_2CCl_2. The reaction was stirred at room temperature for 20 hours, diluted with H_2CCl_2, and extracted with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (1/20, w/w) using ethyl acetate/hexane (1/1) as solvent to yield 7.08 g (22 mmoles) of 119 (55%). IR (film) 1730, 1685 cm^{-1}. NMR ($CDCl_3$) δ 2.05-2.55 (envelope, 4H), 3.15-4.20 (envelope, 5H), 3.75 (s, 3H), 3.79 (s, 3H), 4.43 (m, 1H). C-13 NMR ($CDCl_3$) δ 21.8, 28.2, 29.0, 42.6, 52.6, 53.2, 57.0, 167.2, 175.3. High resolution mass spectrum for $C_{11}H_{16}N_1O_5Br$ requires m/e 321.02119, measured 321.02123.

Preparation of Hexahydro-5-oxo-1H-pyrrolizine-1,1-dicarboxylic Acid Dimethyl Ester (120)

A 0.2 M ether solution of malonate 119 (3.22 g, 10 mmoles) was added dropwise to an ice cold suspension of oil free NaH (0.3 g, 12.5 mmoles) and 62.5 mL of ether. The

reaction was stirred 12 hours at room temperature, diluted with ethyl acetate, and extracted with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (1/20, w/w) using hexane/ethyl acetate as solvent to yield 2.07 g (8.58 mmoles) of 120 (85.8%). IR (film) 1730, 1695 cm^{-1}. NMR ($CDCl_3$) δ 1.78-2.84 (envelope, 6H), 3.18 (t of d, 1H, J = 10.5 Hz, 4 Hz), 3.77 (s, 3H), 3.79 (s, 3H), 3.86 (m, 1H), 4.42 (m, 1H). C-13 NMR ($CDCl_3$) δ 21.0, 32.4, 34.2, 40.3, 52.2, 60.1, 65.1, 169.2, 169.3, 175.0. High resolution mass spectrum for $C_{11}H_{15}NO_5$ requires m/e 241.09503, measured 241.09461.

Preparation of *cis*- and *trans*-Hexahydro-5-oxo-1H-pyrrolizine-1-carboxylic Acid Methyl Esters (121) and (122)

A solution of 0.964 g (4 mmoles) of diester 120, NaCN (0.282 g, 5.77 mmoles), and 4.44 mL DMF was refluxed for 2 hours. After cooling, the solvent was removed *in vacuo* and the residue taken up in $HCCl_3$ and water. The layers were separated and the water layer washed with $HCCl_3$. The combined organic layers were extracted with brine, dried over Na_2SO_4, filtered, and concentrated to yield 0.334 g (1.82 mmoles) of the monoesters 121 and 122 (45.6%). Treatment of the 1:1 mixture of diastereomers 121 and 122 with sodium methoxide effected a partial isomerization of

121 to 122 (endo- to exo-ester) to yield a 1:4 mixture of diastereomers. Compound 121 (endo-ester): R_f = 0.11 (EtOAc). IR (film) 1725, 1690 cm^{-1}. NMR ($CDCl_3$) δ 1.50-3.30 (envelope, 7H), 3.70 (s, 3H), 3.55-4.38 (envelope, 3H). C-13 NMR ($CDCl_3$) δ 22.2, 30.1, 33.7, 41.0, 45.1, 51.6, 63.0, 172.7, 175.3. Compound 122 (exo-ester): R_f = 0.17 (EtOAc). IR (film) 1730, 1690 cm^{-1}. NMR ($CDCl_3$) δ 1.6-2.85 (envelope, 6H), 2.85-4.28 (envelope, 4H), 3.75 (s, 3H).

Preparation of 2-[1-(2-Bromoethyl)-2-oxo-5-pyrrolidinyl]-3-oxo-butanoic Acid Ethyl Ester (125)

A solution of ethoxylactam 118 (3.54 g, 15 mmoles), ethyl acetoacetate (2.34 g, 18 mmoles), and 11.25 mL of H_2CCl_2 was added dropwise to a stirred suspension of $AlCl_3$ (2.8 g, 21 mmoles) and 15 mL of H_2CCl_2. The reaction was stirred 15 hours at room temperature, diluted with H_2CCl_2, and extracted with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (1/20, w/w) using ethyl acetate/hexane (1/1) as solvent to yield 2.59 g (8.1 mmoles) of 125 (54%) as a mixture of diastereomers. IR(film) 1730, 1715, 1690 cm^{-1}. The NMR spectra are complicated as 125 is a diastereomeric mixture. NMR ($CDCl_3$) δ 1.27 and 1.29 (t, 3H, J = 7.5 Hz), 2.0-2.6 (envelope, 4H), 2.29 (s, 3H), 3.05-4.1 (envelope, 5H), 4.21 and 4.23 (q, 2H, J = 7.5 Hz), 4.42 (m, 1H). C-13 NMR ($CDCl_3$) δ 13.7,

21.2, 23.0, 28.0, 28.2, 28.9, 29.5, 29.8, 42.4, 42.7, 56.1, 56.4, 60.1, 61.6, 61.8, 62.2, 167.2, 167.3, 175.1, 200.5. High resolution mass spectrum for $C_{12}H_{18}NO_4Br$ requires m/e 319.041978, measured 319.04141.

Preparation of cis- and trans-Hexahydro-5-oxo-1H-pyrrolizine-1-carboxylic Acid Methyl Esters (127a) and (127b)

To 1.95 g (6.09 mmoles) of 125 was added 14.6 mL of a 1.04 M solution of NaOEt in ethanol (15.2 mmoles). After stirring at room temperature for 26 hours, the reaction was neutralized with 2 N HCl in ethanol and the solvent evaporated. The residue was redissolved in ethyl acetate and water and the layers separated. The aqueous layer was extracted two times more with ethyl acetate. The combined organic layers were extracted with brine, dried over Na_2SO_4, filtered, and concentrated to yield 1.00 g (5.08 mmoles) of 127a and 127b (83%) as a 1:4 mixture of diastereomers. The diastereomers could be separated by chromatography on silica gel using ethyl acetate/hexane as solvent. Compound 127a (endo-ester): R_f = 0.11 (EtOAc). IR (film) 1725, 1690 cm^{-1}. NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7 Hz), 1.5-3.3 (envelope, 8H), 3.55-4.38 (envelope, 2H), 4.13 (q, 2H, J = 7 Hz). C-13 NMR δ 14.1, 22.1, 30.2, 33.8, 41.1, 45.5, 60.7, 63.1, 172.3, 175.4. Compound 127b (exo-ester): R_f = 0.16 (EtOAc). IR (film) 1730, 1690 cm^{-1}. NMR ($CDCl_3$) δ 1.3 (t, 3H, J = 7 Hz), 1.5-2.7 (envelope, 7H), 2.7-4.2 (envelope,

3H), 4.18 (q, 2H, $\underline{J}$ = 7 Hz). C-13 NMR ($CDCl_3$) δ 13.7, 25.3, 30.1, 33.7, 40.3, 49.0, 60.3, 63.7, 171.4, 174.2. High resolution mass spectrum for $C_{10}H_{15}NO_3$ requires m/e 197.105198, measured 197.104206.

Preparation of (±)Trachelanthamidine (4)

A solution of 1.02 g (5.57 mmoles) of the lactam ester 127b, in 6.79 mL of THF, was added dropwise to a suspension of $LiAlH_4$ (0.423 g, 11.15 mmoles) and 13.7 mL of THF. The reaction was refluxed 17 hours and cooled. The reaction was worked up by successive addition of 0.423 mL of H_2O, 0.423 mL of 15% NaOH, and 1.27 mL of H_2O. Evaporation of the volatiles left a residue which was leached with ether. The ether solution, after filtration of the salts, was dried over Na_2SO_4, filtered, and concentrated to give .707 g (5.01 mmoles) of (±)trachelanthamidine (4). Picrate mp 168-171 °C (lit. (1) 174 °C). NMR ($CDCl_3$) δ 1.1-2.22 (envelope, 7H), 2.22-2.8 (envelope, 2H), 2.8-3.3 (envelope, 2H), 3.55 (m, 3H), 6.15 (br s, 1H). C-13 NMR ($CDCl_3$) 25.0, 29.7, 31.3, 48.1, 53.9, 54.1, 64.1, 67.1.

Preparation of (±)Isoretronecanol (3)

The reaction conditions were identical to the ones used for the reduction of 127b (vide supra). C-13 NMR ($CDCl_3$) δ 25.3, 25.8, 26.7, 43.7, 53.4, 55.0, 62.0, 65.6. The C-13 NMR spectrum is identical with one furnished by H. W. Pinnick.

Preparation of Dodecahydrotripyrrolo[1,2-a:1',2'-c:1",2"-e][1,3,5] Triazine (136)

To an ice cold solution of NaOH (48.98 g, 1.2 moles), 600 mL H_2O, and pyrrolidine (42.6 g, 600 mmoles) was added about 50 mL of a solution made from 145.7 g (600 mmoles) of sodium peroxodisulfate ($Na_2S_2O_8$) and 426 mL of H_2O. To this was added 0.510 g (3 mmoles) of $AgNO_3$ dissolved in a small amount of water. The remainder of the $Na_2S_2O_8$ solution was then added dropwise through an addition funnel. The ice bath was removed and the reaction stirred 7 hours at room temperature. The aqueous layer was extracted three times with H_2CCl_2. The combined organic layers extracted with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was composed of two products: an orange oil and a dark polymer. The orange oil was separated from the polymer via pipet to yield 21.10 g (102 mmoles) of 1-pyrroline trimer (136) (51%). NMR ($CDCl_3$) δ 1.5-2.2 (envelope, 12H), 2.2-2.8 (envelope, 3H), 2.9-3.2 (envelope, 6H). There were also peaks resulting from an impurity that constantly appeared in the spectra δ 3.87 (complex multiplet), 7.62 (br s). C-13 NMR ($CDCl_3$) δ 20.1, 27.7, 45.7, 81.8.

General Procedure For Preparation of N-Acyl-2-pyrrolines

A 0.1 M THF solution of 1-pyrroline trimer (136) was distilled through a short path distillation apparatus into

a flask precooled to -70 °C. (After distillation, approximately 40-45% of the 1-pyrroline trimer remained in the flask as a polymeric residue.) To the distillate was added triethyl amine (2.2 equivalents/trimer) followed by dropwise addition of an acid chloride (2.2 equivalents/-trimer). The suspension was warmed to room temperature and stirred overnight. The reaction mixture was filtered through a pad of celite to remove the salts and concentrated in vacuo. The residue was purified by distillation or chromatography.

2,3-Dihydro-1H-pyrrole-1-carboxylic acid methyl ester (137)

Reaction of 19.88 g (96 mmoles) of 1-pyrroline trimer (136) yielded 14.9 g (117 mmoles) of 137 (40.6%) as a colorless oil. Bp 76 °C/11 mm Hg. IR (film) 1700, 1620 cm^{-1}. NMR ($CDCCl_3$) δ 2.66 (br t, 2H, J = 9 Hz), 3.72 (s, 3H), 3.74 (t, 2H, J = 9 Hz), 5.14 (m, 1H, J = 2 Hz, 4 Hz), 6.55 (br m, 1H). C-13 NMR ($CDCl_3$) δ 28.1, 44.5, 51.6, 107.6, 128.6, 152.2. High resolution mass spectrum for $C_6H_9NO_2$ requires 127.06333, measured 127.06346.

2,3-Dihydro-1H-pyrrole-1-carboxylic acid ethyl ester (138)

Reaction of 10.35 g (50 mmoles) of 1-pyrroline trimer (136) yielded 11.0 g (78 mmoles) of 136 (52%) as a colorless oil. IR (film) 1700, 1620 cm^{-1}. NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7 Hz), 2.62 (br t, 2H, J = 9 Hz), 3.77 (br t, 2H, J =

9 Hz), 4.17 (q, 2H, J = 7 Hz), 5.00 (m, 1H), 6.52 (m, 1H). C-13 NMR ($CDCl_3$) δ 14.4, 28.6, 44.8, 66.9, 107.8, 129.2.

2,3-Dihydro-1H-pyrrole-1-carboxylic acid benzyl ester (140)

Reaction of 4.76 g (23 mmoles) of 1-pyrroline trimer (136) yielded 5.35 g (26.4 mmoles) of 140 (38.3%). IR (film) 1705, 1620 cm^{-1}. NMR ($CDCl_3$) δ 2.67 (br t, 2H, J = 9 Hz), 3.80 (t, 2H, J = 9 Hz), 5.10 (m, 1H), 5.19 (s, 2H), 6.60 (m, 1H), 7.36 (s, 5H). C-13 NMR δ 28.6, 45.1, 66.9, 108.6, 128.0, 128.4, 129.1, 136.6.

2,3-Dihydro-1H-pyrrole-1-carboxylic acid 2,2,2-trichloroethyl ester (142)

Reaction of 9.66 g (46.63) of 1-pyrroline trimer (136) yielded 7.17 g (29.3 mmoles) of 142 (21%). IR (film) 1715, 1620 cm^{-1}. NMR ($CDCl_3$) δ 2.56 (br t, 2H, J = 9 Hz), 3.70 (br t, 2H, J = 9 Hz), 4.60 (s, 2H), 5.02 (m, 1H), 6.44 (m, 1H).

1-Acetyl-2,3-dihydro-1H-pyrrole (139)

From 4.9 g (23.67 mmoles) of 1-pyrroline trimer (136) was obtained 3.02 g (27.2 mmoles) of 139 (38.3%) after bulb to bulb distillation (Kügelrohr 70 °C/1 mm Hg). IR (film) 1640, 1610 cm^{-1}. The NMR spectra are complicated as 139 exists as a rotameric pair. NMR ($CDCl_3$) δ 2.07 and 2.17 (s, 1H), 2.72 (m, 2H), 3.87 (t, 2H, J = 9 Hz), 5.26 (m, 1H), 6.50 and 6.93 (m, 1H). C-13 NMR ($CDCl_3$) δ 21.1, 21.5, 27.8, 29.6, 44.2, 45.7, 110.1, 111.1, 128.4, 128.9, 165.6. The

high resolution mass spectrum requires m/e 111.06842, measured 111.06798.

1-Chloroacetyl-2,3-dihydro-1H-pyrrole (141)

Reaction of 2.07 g (10 mmoles) of 1-pyrroline trimer (136) yielded 0.72 g (4.9 mmoles) of 141 (16%). The general reaction conditions were modified so that Dabco (diazobicyclooctane) was used instead of triethyl amine. IR (film) 1655, 1615 cm^{-1}. The NMR spectrum is complicated as 141 exists as a rotomeric pair. NMR ($CDCl_3$) δ 2.7 (m, 2H), 4.04 and 4.10 (s, 2H), 4.88 (m, 2H), 5.33 (m, 1H), 6.65 and 6.85 (m, 1H).

Preparation of 2-Ethoxy-3-hydroxy-1-pyrrolidinecarboxylic Acid Methyl Ester (146)

m-Chloroperbenzoic acid (10.79 g, 50 mmoles) was added portionwise to an ice cold 0.2 M ethanol solution of 137 (6.35 g, 50 mmoles). The reaction was stirred 10 hours at room temperature and the solvent evaporated. The residue was dissolved in saturated $NaHCO_3$ and H_2CCl_2. The layers were separated and the aqueous layer was extracted twice with H_2CCl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel using ethyl acetate/hexane as solvent to yield 6.85 g (36 mmoles) of 146 (72%) as a colorless oil. IR (film) 3450, 1705, 1690

cm^{-1}. The NMR spectra are complicated because 146 is a mixture of diastereomers. NMR ($CDCl_3$) δ 118 and 1.23 (t, 3H, J = 7 Hz), 1.72-2.43 (m, 2H), 3.2-3.75 (envelope, 4H), 4.16 (m, 1H), 5.07 (m, 1H), 5.11 (br s, 1H). C-13 NMR ($CDCl_3$) δ 15.0, 15.2, 29.9, 30.4, 42.6, 43.9, 52.4, 63.4, 63.7, 73.6, 74.4, 92.2, 92.7, 156.2, 156.9. High resolution mass spectrum for $C_8H_{15}NO_4$ requires m/e 189.10011, measured 189.10095.

Preparation of 3-Acetoxy-2-ethoxy-1-pyrrolidinecarboxylic Acid Methyl Ester (149)

A 0.5 M H_2CCl_2 solution of alcohol 146 (2.84 g, 15 mmoles) was treated with dimethylaminopyridine (DMAP) (0.183 g, 1.5 mmoles), pyridine (1.39 mL, 18 mmoles), and acetic anhydride (1.70 mL, 18 mmoles). After stirring 8 hours at room temperature, the solution was diluted with H_2CCl_2 and extracted with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to yield 3.40 g (14.7 mmoles) of 149 (98%) as a colorless oil. The NMR spectra are complicated as 149 is a 2:1 mixture of diastereomers. NMR ($CDCl_3$) δ 1.17 and 1.20 (t, 3H, J = 6.5 Hz), 1.8-2.5 (m, 2H), 2.05 and 2.1 (s, 3H), 3.3-3.85 (envelope, 4H), 3.75 (s, 3H), 4.8 (t of d) 5.0-5.22 (m), and 5.37 (br m)(2H). C-13 NMR δ 14.8, 14.9, 20.2, 20.5, 27.1, 28.0, 41.4, 43.7,52.0, 63.5, 63.8, 75.8, 76.6,

89.5, 90.1, 155.1, 155.8, 169.5, 169.8. IR (film) 1740, 1710 cm^{-1}. High resolution mass spectrum for $C_9H_{14}NO_4$ ($M^{\cdot+}-OCH_3$) requires m/e 200.09229, measured 200.09195.

Preparation of cis- and trans-3-Acetoxy-2-(propanedioic acid diethyl ester)-1-pyrrolidinecarboxylic Acid Methyl Ester (150a) and (150b)

Tin tetrachloride (2.11 g, 18 mmoles) was added dropwise to a 0.5 M H_2CCl_2 solution of 149 (3.63 g, 15 mmoles) and diethyl malonate (2.64 g, 16.5 mmoles). The reaction was stirred 10 hours at room temperature, diluted with H_2CCl_2, and extracted twice with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (1/50, w/w) with ethyl acetate/hexane (1/5) as solvent to yield two diastereomers in a combined yield of 86%. The minor diastereomer 150a (1.77 g, 5.13 mmoles) had an R_f = 0.39 (1/1, EtOAc/hexane). IR (film) 1740, 1710 cm^{-1}. NMR ($CDCl_3$) δ 1.27 (t, 6H, J = 7 Hz), 1.7-2.45 (m, 2H), 1.96 (s, 3H), 3.25-3.85 (envelope, 3H), 3.64 (s, 3H), 4.13 and 4.17 (q, 4H, J = 7 Hz), 4.7 and 4.77 (d, 1H, J = 6 Hz), 5.49 (q, 1H, J = 6 Hz). The major diastereomer 150b (2.66 g, 7.71 mmoles) had an R_f = 0.45 (1/1, EtOAc/hexane). NMR ($CDCl_3$) δ 1.26 (t, 6H, J = 7 Hz), 1.75-2.5 (m, 2H), 2.03 (s, 3H), 3.22-3.7 (envelope, 3H), 4.17 (q, 4H, J= 7 Hz), 4.4 (d, 1H, J = 6 Hz), 5.48 (m, 1H).

Preparation of trans-3-Acetyl-2-pyrrolidinyl Propanedioic Acid Diethyl Ester (153)

Trimethylsilyl iodide (1.65 mL, 11.57 mmoles) was added dropwise to an ice cold 0.2 M H_2CCl_2 solution of urethane 150b. The reaction was stirred for 48 hours at room temperature and quenched with ethanol (0.52 g, 11.57 mmoles). The reaction mixture was diluted with H_2CCl_2 and extracted with saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and concentrated to yield 1.97 g (6.86 mmoles) of crude amine 153 (86%). IR (film) 3360, 1735 cm^{-1}. NMR ($CDCl_3$) δ 1.28 (t, 6H, J = 7 Hz), 1.5-2.5 (m, 2H), 2.03 (s, 3H), 2.85-3.2 (m, 2H), 3.27 (br s, 1H), 3.5-3.8 (m, 2H), 4.18 (q, 4H, J = 7 Hz), 5.0-5.3 (m, 1H).

Preparation of trans-3-Acetoxy-1-chloroacetyl-2-pyrrolidinyl Propanedioic Acid Diethyl Ester (154b)

Chloroacetyl chloride (0.930 g, 8.23 mmoles) was added dropwise to an ice cold 1 M H_2CCl_2 solution of crude amine 153 (1.97 g, 6.86 mmoles), DMAP (0.084 g, 0.686 mmoles), and pyridine (0.67 mL, 8.23 mmoles). The reaction was stirred 8 hours at room temperature, diluted with H_2CCl_2, and extracted with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel using ethyl acetate/hexane as the solvent to yield 1.99 g (5.4 mmoles)

of 154b (80%). IR (film) 1735, 1660 cm^{-1}. NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7 Hz), 1.9-2.7 (m, 2H), 2.04 (s, 3H), 3.73 (m, 2H), 4.08 (s, 2H), 4.17 (q, 4H, J = 7 Hz), 4.27 (d, 1H, J = 6 Hz), 4.58 (br d, 1H, J = 5 Hz), 5.55 (m, 1H).

Preparation of cis-3-Acetoxy-1-chloroacetyl-2-pyrrolidinyl Propanedioic Acid Diethyl Ester (154a)

The reaction conditions were identical to those used for the preparation of 154b (vide supra). NMR ($CDCl_3$) δ 1.26 (t, 3H, J = 7 Hz), 1.28 (t, 3H, J = 7 Hz), 1.9-2.5 (m, 2H), 1.98 (s, 3H), 3.58-3.88 (m, 2H), 3.96 (d, 1H, J = 7 Hz), 4.1 and 4.11 (s, 2H), 4.17 (q, 2H, J = 7 Hz), 4.19 (q, 2H, J = 7 Hz), 4.83 (t, 1H, J = 6.5 Hz), 5.58 (m, 1H).

Preparation of Hexahydro-7-acetoxy-3-oxo-1H-pyrrolizine-1,1-dicarboxylic Acid Diethyl Ester (155)

A 0.5 M THF solution of malonate 154b (1.99 g, 5.4 mmoles) was added dropwise to an ice cold suspension of oil free NaH (0.156 g, 6.48 mmoles) and 13 mL of THF. The reaction was stirred 9 hours at room temperature, diluted with ethyl acetate, and extracted with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to yield 1.32 g (4.05 mmoles) of 155 (75%). IR (film) 1735, 1710 cm^{-1}. NMR ($CDCl_3$) δ 1.26 and 1.28 (t, 6H, 7 Hz), 1.8-2.5 (m, 2H), 2.07 (s, 3H), 3.0 (s, 2H), 2.95-3.3 (m, 1H),

3.68-3.95 (m, 1H), 4.22 (q, 2H, $\underline{J}$ = 7 Hz), 4.24 (q, 2H, $\underline{J}$ = 7 Hz), 4.48 (d, 1H, $\underline{J}$ = 5 Hz), 5.18 (m, 1H). C-13 NMR ($CDCl_3$) δ 13.5, 20.5, 32.5, 40.3, 41.2, 57.2, 61.9, 62.2, 68.4, 72.2, 168.1, 168.3, 169.5, 171.4.

Preparation of Hexahydro-7-acetoxy-3-oxo-1H-pyrrolizine-1-carboxylic Acid Ethyl Ester (156)

A 0.5 M Me_2SO solution of diester 155 (0.088 g, 0.269 mmoles), NaCl (0.0265 g, 0.47 mmoles), and H_2O (0.01 mL, 0.74 mmoles) was heated 5 hours at 175 °C. The reaction was diluted with ethyl acetate and extracted with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to yield 0.021 g (0.08 mmoles) of 156 (30.6%). IR (film) 1740, 1710 cm^{-1}. NMR ($CDCl_3$) δ 1.32 (t, 3H, $\underline{J}$ = 7 Hz), 2.05 (s, 3H), 2.0-2.5 (m, 2H), 2.6-2.95 (m, 2H), 3.0-3.3 (m, 2H), 3.6-3.9 (m, 1H), 3.95-4.2 (m, 1H), 4.19 (q, 2H, $\underline{J}$ = 7 Hz), 4.9 (m, 1H). C-13 NMR ($CDCl_3$) δ 14.1, 20.7, 32.3, 37.7, 40.4, 44.6, 61.3, 68.0, 76.5, 170.4, 171.8, 172.8. High resolution mass spectrum for $C_{10}H_{14}O_4N$ ($M^{+\cdot}-COCH_3$) requires m/e 212.09229, measured 212.09256.

Preparation of 2-Ethoxy-3-(1,3,5-trimethylbenzoyloxy)-1-pyrrolidinecarboxylic Acid Methyl Ester (151)

A 1 M THF solution of alcohol 146 (6.3 g, 33.33 mmoles) was added dropwise to a stirred suspension of oil

free NaH (1.12 g, 46.67 mmoles) in 67 mL of THF. The reaction was stirred 2 hours at room temperature and then a 1 M THF solution of mesityl chloride (58) was added dropwise. The reaction was stirred 24 hours at room temperature, diluted with ethyl acetate, and extracted with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (1/20, w/w) with ethyl acetate/hexane (1/5) as solvent to yield 9.53 g (28.4 mmoles) of 151 (85.4%) as a colorless oil. IR (film) 1705 cm^{-1}. The NMR spectra are complicated as 151 is a mixture of two diastereomers. NMR ($CDCl_3$) δ 1.17 and 1.24 (t, 3H, J = 7 Hz), 1.92-2.52 (m, 2H), 2.3 and 2.38 (s, 9H), 3.4-3.9 (envelope, 4H), 3.72 and 3.76 (s, 3H), 4.97 (t of d, J = 9 Hz, 4 Hz), 5.2-5.42 (m) and 5.61 (br d, J = 4 Hz) (2H), 6.84 (s, 2H). C-13 NMR ($CDCl_3$) δ 14.8, 19.2, 20.5, 26.9, 27.9, 43.7, 52.0, 63.3, 63.7, 76.1, 76.9, 89.4, 89.8, 128.1, 129.8, 134.9, 139.2, 154.9, 155.7, 168.4. High resolution mass spectrum for $C_{18}H_{25}NO_5$ requires m/e 335.17328, measured 335.17418.

Preparation of *cis*- and *trans*-2-(Propanedioic acid dimethyl ester)-3-(2,4,6-trimethylbenzoyloxy)-1-pyrrolidinecarboxylic Acid Methyl Ester (152a) and (152b)

Tin tetrachloride (8.33 g, 31.99 mmoles) was added dropwise to a 0.5 M H_2CCl_2 solution of 151 (8.93 g, 26.66

mmoles) and dimethyl malonate (3.87 g, 29.32 mmoles). The reaction was stirred 12 hours at room temperature, diluted with H_2CCl_2, and extracted twice with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (1/30, w/w) with ethyl acetate/hexane (1/5) as the solvent to yield two diastereomers in a combined yield of 87%. The minor diastereomer 152a, isolated as colorless crystals in 10.4% yield, had an R_f = 0.09 (1/3 EtOAc/hexane). mp 114-116 °C. IR ($HCCl_3$) 1735, 1710 cm^{-1}. NMR ($CDCl_3$) δ 2.08-2.5 (m, 2H), 2.29 (s, 9H), 3.23 (s, 3H), 3.35-3.9 (envelope, 3H), 3.58 (s, 3H), 3.68 (s, 3H), 4.80 (t, 1H, J = 7 Hz), 5.75 (q, 1H, J = 6 Hz), 6.83 (s, 2H). C-13 NMR 19.4, 20.7, 29.4, 43.9, 50.5, 51.4, 52.3, 58.1, 73.6, 128.1, 129.7, 135.0, 139.3, 155.0, 167.4, 168.0. High resolution mass spectrum for $C_{21}H_{27}NO_8$ requires m/e 421.17368, measured 421.17340. The major diastereomer 152b, isolated as colorless crystals in 77% yield, had an R_f = 0.17 (1/3 EtOAc/hexane). mp 114-116 °C. IR ($HCCl_3$) 1735, 1710 cm^{-1}. NMR ($CDCl_3$) δ 2.15-2.55 (m, 2H), 2.28 (s, 3H), 2.30 (s, 6H), 3.42-3.73 (envelope, 2H), 3.69 (s, 3H), 3.76 (s, 3H), 3.78 (s, 3H), 4.02-4.3 (m, 1H), 4.66 (m, 1H), 5.75 (m, 1H), 6.86 (s, 2H). C-13 NMR δ 19.6, 21.1, 30.3, 45.3, 52.7, 63.2, 76.6, 128.5, 130.5, 135.1, 139.6, 155.4, 167.3, 167.8, 168.9. High resolution mass spectrum for $C_{21}H_{27}NO_8$

requires m/e 421.17368, measured 421.17257. Anal. calcd. for $C_{19}H_{21}NO_6$: C, 59.86; H, 6.41; N, 3.33. Found: C, 60.03; H, 6.61; N, 3.27.

Preparation of trans-2-(Acetic acid methyl ester)-3-(2,4,6-trimethylbenzoyloxy)-1-pyrrolidinecarboxylic Acid Methyl Ester (157)

A solution of malonate ester 152b (2.11 g, 5 mmoles), NaCl (0.512 g, 8.75 mmoles), 0.5 mL of H_2O, and 10 mL of Me_2SO was heated to 160 °C for four 20-minute periods. Between each heating period, the solution was cooled, the methanol that formed was removed under vacuum, and another 0.5 mL of H_2O was added. The solution was diluted with ethyl acetate and extracted with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (1/20, w/w) using ethyl acetate/hexane (1/2) as the solvent to yield 1.54 g (4.25 mmoles) of 157 (85%) as a colorless solid. mp 85-87 °C. IR (film) 1730, 1705 cm^{-1}. NMR ($CDCl_3$) δ 2.05-2.6 (envelope, 4H), 2.27 (s, 3H), 2.3 (s, 6H), 3.4-3.75 (m, 2H), 3.67 (s, 3H), 3.70 (s, 3H), 4.23-4.47 (m, 1H), 5.42 (m, 1H), 6.82 (s, 2H). C-13 NMR ($CDCl_3$) δ 19.6, 21.1, 29.5, 37.2, 44.6, 51.8, 52.5, 60.5, 77.5, 128.4, 130.3, 135.1, 139.6, 155.2, 169.1, 170.6. High

resolution mass spectrum for $C_{19}H_{25}NO_6$ requires m/e 363.16820, measured 363.16865.

Preparation of trans-[3-(2,4,6-Trimethylbenzoyloxy)]-2-pyrrolidinyl Acetic Acid Methyl Ester (158)

Trimethylsilyl iodide (1.07 mL, 7.5 mmoles) was added dropwise to an ice-cold 1 M H_2CCl_2 solution of urethane 157. The reaction was stirred 44 hours at room temperature and quenched by the dropwise addition of 5 mL of 2 M HCl in methanol. This was stirred an additional 8 hours and the solvent evaporated. The residue was redissolved in ethyl acetate and extracted with saturated $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate and the combined organic layers extracted with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to yield 1.24 g (4.07 mmoles) of crude amine 158 (81.4%). IR (film) 3360, 1730 cm^{-1}. NMR ($CDCl_3$) δ 1.8-2.6 (envelope, 4H), 2.25 (s, 3H), 2.3 (s, 6H), 2.65 (m, 1H), 3.05 (m, 1H), 3.22 (br s, 1H), 3.46-3.75 (m, 1H), 3.66 (s, 3H), 5.13 (m, 1H), 6.8 (s, 2H).

Preparation of trans-2-(Acetic acid methyl ester)-3-(2,4,6-trimethylbenzoyloxy)-1-pyrrolidineglyoxylic Acid Ethyl Ester (159)

Ethyl oxalylchloride (0.55 mL, 4.88 mmoles) was added dropwise to an ice-cold 0.5 M H_2CCl_2 solution of the amine

158 (1.24 g, 4.07 mmoles), DMAP (0.0496 g, .407 mmoles), and pyrridine (0.39 mL, 4.88 mmoles). The reaction mixture was stirred 8 hours at room temperature, diluted with H_2CCl_2, extracted with dilute HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (1/15, w/w) using ethyl acetate/hexane (1/2) as the solvent to yield 1.64 g (4.05 mmoles) of 159 (99.5%). The NMR spectrum are complicated as 159 exists as a rotomeric pair. NMR ($CDCl_3$) δ 1.36 (t, 3H, J = 7 Hz), 2.2-2.7 (envelope, 4H), 2.28 (s, 3H), 2.33 (s, 6H), 2.98 and 3.02 (t, 1H, J = 15 Hz), 3.55-4.0 (m, 1H), 3.74 and 3.75 (s, 3H), 4.31 and 4.33 (q, 2H, J = 7 Hz), 4.5-4.86 (m, 1H), 5.48 (m, 1H), 6.87 (s, 2H). C-13 NMR ($CDCl_3$) δ 14.1, 19.9, 21.3, 27.5, 30.1, 35.3, 38.3, 44.6, 46.0, 52.1, 52.2, 61.0, 61.3, 62.4, 62.6, 76.4, 77.9, 128.7, 130.3, 135.4, 140.0, 159.0, 161.8, 169.1, 170.1, 170.6.

Preparation of 5,6,7,8-Tetrahydro-2-hydroxy-3-oxo-7-(2,4,6-trimethylbenzoyloxy)-3H-pyrrolizine-1-carboxylic Acid Methyl Ester (160)

A 0.1 M methanol solution of 159 (.92 g, 2.27 mmoles) was stirred for 18 hours at room temperature with 2.72 mmoles of sodium methoxide. The solvent was evaporated and the residue redissolved in H_2O. The water layer was

acidified with 5 mL of 1 M HCl and extracted 3 times with H_2CCl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to yield the bicyclic ring system 160 (.68 g, 1.89 mmoles) as an off-white solid (83.4%). mp 174-176 °C, discolors at 150 °C. Anal. calcd. for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 62.14; H, 5.96; N, 3.76. High resolution mass spectrum for $C_{18}H_{18}NO_5$ (M^+-OCH_3) requires m/e 328.11850, measured 328.11932. IR (H_2CCl_2) 3050, 2990, 1725, 1685, 1640, 1610 cm^{-1}. For further identification, the nearly insoluble enol 160 was converted into the soluble enol ether 161.

Preparation of 5,6,7,8-Tetrahydro-2-methoxy-3-one-7-(2,4,6-trimethylbenzoyloxy)-3H-pyrrolidine-1-carboxylic Acid Methyl Ester (161)

An ethereal suspension of 160 was treated with an excess of diazomethane and stirred until the solid had dissolved (2 hours). The ether was evaporated to yield 161 as a yellow oil. IR (film) 1720, 1640, 1610 cm^{-1}. NMR ($DCCl_3$) δ 2.08-2.7 (m, 2H), 2.32 (s, 3H), 2.89 (s, 6H), 3.16-3.55 (m, 1H), 3.72-4.07 (m, 1H), 3.78 (s, 3H), 4.32 (s, 3H), 4.54 (d, 1H, J = 5 Hz), 5.28 (m, 1H), 6.88 (s, 2H). C-13 NMR ($DCCl_3$) δ 19.8, 21.0, 34.9, 41.9, 51.7, 59.6, 64.6, 74.1, 116.1, 128.5, 129.9, 135.3, 139.7, 154.3,

162.5, 168.8. High resolution mass spectrum for $C_{19}H_{20}NO_5$ (M^{+}-OCH_3) requires m/e 342.13415, measured 342.13474.

Preparation of Hexahydro-2-hydroxy-3-oxo-7-(2,4,6-trimethylbenzoyloxy)-1H-pyrrolizine-1-carboxylic Acid Methyl Ester (162)

A 0.5 M acetic acid solution of 160 (0.180 g, 0.5 mmoles) was stirred for 36 hours with 0.216 g (3.3 mmoles) of zinc powder. The reaction was diluted with methanol, filtered through a pad of celite, and the solvent was evaporated. The residue was redissolved in ethyl acetate and brine. The layers were separated and the aqueous layer extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to yield 0.139 g (0.39 mmoles) of 162 (77%). IR (film) 1720, 1640 cm^{-1}. NMR ($CDCl_3$) δ 2.1-2.65 (m, 2H), 2.32 (s, 9H), 3.1-3.35 (envelope, 2H), 3.81 (s, 3H), 3.68-4.13 (envelope, 3H), 4.8 (d, 1H, J = 10 Hz), 5.24 (m, 1H), 6.86 (s, 2H). C-13 NMR ($CDCl_3$) δ 19.8, 21.1, 31.6, 41.0, 52.6, 54.8, 64.2, 75.4, 77.1, 128.6, 129.7, 135.4, 139.9, 169.5, 171.6, 173.2.

Preparation of Hexahydro-2-acetoxy-3-oxo-7-(2,4,6-trimethylbenzoyloxy)-1H-pyrrolizine-1-carboxylic Acid Methyl Ester (163)

Acetic anhydride (0.05 mL, 0.56 mmoles) was added dropwise to an ice cold solution of alcohol 162 (0.17 g, 0.47 mmoles), and DMAP (0.0689 g, 0.56 mmoles) in 3 mL of H_2CCl_2. The reaction was stirred for 20 minutes, diluted with ethyl acetate, and extracted with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to yield 0.188 g (0.47 mmoles) of acetate 163 (99%). The NMR spectrum is complicated as 163 is a mixture of diastereomers. NMR ($CDCl_3$) δ 2.07 and 2.17 (s, 3H), 2.29 (s, 9H), 2.29-2.65 (m, 2H), 3.05-3.63 (envelope, 2H), 3.68 and 3.77 (s, 3H), 3.85-4.22 (m, 1H), 4.32-4.62 (m, 1H), 4.87-5.3 (m, 1H), 5.65 (d, 1H, J = 7 Hz), 6.88 (s, 2H).

Preparation of Hexahydro-2-acetoxy-3-thio-7-(2,4,6-trimethylbenzoyloxy)-1H-pyrrolizine-1-carboxylic Acid Methyl Ester (166)

A benzene (1.5 mL) solution of amide 163 (0.188 g, 0.47 mmoles) and Lawesson's reagent (68) (0.11 g, 0.28 mmoles) was refluxed for 6 hours, cooled, and the solvent evaporated. The residue was chromatographed on silica gel (1/50, w/w) using ethyl acetate/hexane (1/5) as the solvent

to yield 0.135 g (0.32 mmole) of thioamide 166 (69%) as an off-white solid. mp 166-168 °C. The NMR spectra are complicated as 166 is a mixture of diastereomers. NMR ($CDCl_3$) δ 2.08 and 2.22 (s, 3H), 2.31 (s, 9H), 2.4-2.9 (m, 2H), 3.1-5.28 (envelope, 5H), 6.05 (d, 1H, J = 6 Hz), 6.9 (br s, 2H). C-13 NMR ($CDCl_3$) δ 19.9, 20.5, 20.7, 21.1, 30.6, 31.9, 43.6, 44.0, 51.2, 52.3, 52.6, 53.6, 69.4, 71.9, 74.7, 75.3, 82.7, 83.6, 128.6, 129.0, 135.6, 135.8, 140.1, 168.0, 168.8, 169.3, 169.5, 170.0, 192.3, 193.5. High resolution mass spectrum for $C_{21}H_{25}NO_6S$ requires m/e 419.14027, measured 419.14057.

Preparation of Hexahydro-2-acetoxy-7-(2,4,6-trimethyl-benzoyloxy)-1H-pyrrolizine-1-carboxylic Acid Methyl Ester (164)

Magic methyl (FSO_3CH_3) (0.16 mL, 2 mmoles) was added dropwise to an ice cold 0.5 M H_2CCl_2 solution of thioamide 166 (0.419 g, 1 mmole). After stirring for 15 minutes, a 1 M MeOH solution of $NaBH_3CN$ (0.314 g, 5 mmoles) was added dropwise. After addition of acetic acid (0.51 mL, 9 mmoles), the resultant solution was stirred 9 hours at room temperature. The reaction was diluted with H_2CCl_2 and extracted with saturated $NaHCO_3$. The aqueous layer was extracted once with H_2CCl_2 and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated

in vacuo. The residue was chromatographed on silica gel using ethyl acetate/hexane as the solvent to yield two diastereomers in a combined yield of 0.244 g (0.63 mmoles) (63%). Diastereomer 164a: R_f = 0.19 (1/1 EtOAc/hexane). NMR ($CDCl_3$) δ 1.0-4.0 (envelope, 7H), 2.08 (s, 3H), 2.3 (s, 3H), 2.33 (s, 6H), 3.77 (s, 3H), 4.27 (m, 1H), 5.3-5.6 (envelope, 2H), 6.84 (s, 2H). C-13 NMR ($CDCl_3$) δ 19.7, 20.9, 21.0, 31.2, 52.2, 53.0, 54.0, 58.7, 73.2, 77.8, 79.3, 128.4, 130.3, 135.2, 139.4, 169.7, 169.9, 171.8. Diastereomer 164b: R_f = 0.09 (1/1 EtOAc/hexane). NMR ($CDCl_3$) δ 1.0-4.0 (envelope, 7H), 2.05 (s, 3H), 2.28 (s, 3H), 2.33 (s, 6H), 3.7 (s, 3H), 4.12 (d of d, 1H, J = 9 Hz, 4 Hz), 5.26 (br q, 1H, J = 3 Hz), 5.67 (br t, 1H, J = 4 Hz), 6.84 (s, 2H). C-13 NMR ($CDCl_3$) δ 19.7, 20.8, 21.0, 31.3, 52.0, 52.6, 60.0, 70.6, 76.3, 78.9, 128.4, 130.3, 135.3, 139.4, 169.3, 169.6, 170.2.

cis-2,3,5,8-Tetrahydro-1-(2,4,6-trimethylbenzoyloxy)-1H-pyrrolizine-7-carboxylic Acid Methyl Ester (165)

A 1.0 M THF solution of 164 (0.244 g, 0.63 mmoles) was treated with 1.1 equivalents of DBN. The reaction was stirred 2 hours at room temperature, diluted with ethyl acetate and extracted with saturated $NaHCO_3$. The aqueous layer was extracted with ethyl acetate and the combined organic layers extracted with brine. The organic

layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel using ethyl acetate/hexane as the solvent to yield 0.0773 g (0.235 mmoles) of 165 (37.3%). IR (film) 1725, 1650, 1613 cm^{-1}. 300 MHz NMR ($CDCl_3$) δ 1.93-2.14 (envelope, 2H), 2.28 (s, 3H), 2.33 (s, 6H), 2.81-2.88 (m, 1H), 3.17-3.26 (m, 1H), 3.52 (d of d of d, 1H, J = 18.4, 5.1, 2.0 Hz), 3.77 (s, 3H), 4.14 (d of t, 1H, J = 18.4, 2.4 Hz), 4.5 (m, 1H), 5.5 (m, 1H), 6.80 (m, 1H), 6.86 (s, 2H). C-13 NMR ($CDCl_3$) δ 19.6, 20.9, 31.3, 51.6, 53.9, 62.0, 75.6, 77.5, 128.3, 130.7, 132.9, 135.0, 139.2, 141.2, 163.2, 169.1.

REFERENCES

1. Leonard, N. J. In "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1949; Vol. I, Chapter 4.

2. Leonard, N. J. In "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1960; Vol. VI, Chapter 3.

3. Warren, F. L. In "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1970; Vol. XII, Chapter 4.

4. Kochetkov, N. K.; Likhosherstov, A. M. In "Advances in Heterocyclic Chemistry"; Katritzky, A. R., Ed.; Academic Press: New York, 1965; Vol. 5, Chapter 6.

5. Robins, D. J. In "Advances in Heterocyclic Chemistry"; Katritzky, A. R.; Boulton, A. J., Ed.; Academic Press: New York, 1979; Vol. 24, Chapter 7.

6. Bull, L. B.; Culvenor, C. C. J.; Dick, A. T. "The Pyrrolizidine Alkaloids"; North-Holland Publishing Co.: Amsterdam, 1968.

7. Grue-Sørensen, G.; Spenser, I. D. J. Am. Chem. Soc. 1981, 103, 3208-3210.

8. Müller, A. Heil-und-Gewurz-Pflanzen 1924, 7, 1.

9. Note in: Müller, A. Heil-und-Gewurz-Pflanzen 1924, 7, 1.

10. Dalche, R.; Heim, F. Therap. Monatsh. 1897, 275.

11. Culvenor, C. C. J.; Dann, A. T.; Dick, A. T. Nature 1962, 195, 570.

12. McLean, E. K. Pharmacol. Rev. 1970, 22, 429.

13. Shoental, R. FEBS Lett. 1976, 61, 111.

14. Mattocks, A. R. Nature 1971, 232, 476.

15. McLean, E. K. Isr. J. Med. Sci. 1974, 10, 436.

16. Shoental, R. Cancer Res. 1975, 35, 2020; Biochem. Soc. Trans. 1975, 3, 292.

17. Newbern, P. M.; Rogers, A. E. Plant Foods for Man 1973, 1, 23.

18. Allen, J. R.; Hsu, I. C.; Carstens, L. A. Cancer Res. 1975, 35, 997.

19. Culvenor, C. C. J. J. Pharm. Sci. 1968, 57, 1112.

20. Anderson, W. K.; Corey, P. F. J. Med. Chem. 1977, 20, 812.

21. Menshikoff, G. P. Izv. Akad. Nauk SSSR, Otd. Khim. Nauk 1937, 1035; Chem. Abstr. 1938, 32, 2944.

22. Leonard, N. J.; Felley, D. J. Am. Chem. Soc. 1950, 72, 2537.

23. Leonard, N. J.; Blum, S. J. Am. Chem. Soc. 1960, 82, 502.

24. Babor, K.; Jezo, J.; Kalac, V.; Karvas, M. Chem. Zvesti 1959, 163.

25. (a) Adams, R.; Nair, M. D. J. Org. Chem. 1961, 26, 3059. (b) Adams, R.; Mijano, S.; Nair, M. D. J. Am. Chem. Soc. 1961, 83, 3323.

26. Goldschmidt, B. M. J. Org. Chem. 1962, 27, 4057.

27. Fuhlhage, D. W.; VanderWerf, C. A. J. Am. Chem. Soc. 1958, 80, 6249.

28. Speckamp, W. N.; Nossin, P. M. M. Tetrahedron Lett. 1979, 4411.

29. Mitsunobu, O.; Wada, M.; Sano, T. J. Am. Chem. Soc. 1972, 94, 679.

30. Geissman, J. A.; Waiss, A. C. J. Org. Chem. 1962, 27, 139.

31. Keck, G. E.; Nickell, D. G. J. Am. Chem. Soc. 1980, 102, 3632.

32. Vedejs, E.; Martinez, G. R. J. Am. Chem. Soc. 1980, 102, 7993.

33. Vedejs, E.; Engler, D. A.; Telschow, J. E. J. Org. Chem. 1978, 43, 188.

34. Likhosherstov, A. M.; Kulkov, V. N.; Kochetkov, N. K. Zh. Obshch. Khim. 1964, 34, 2798.

35. (a) Tufariello, J. J.; Tette, J. P. J. Chem. Soc., Chem. Commun. 1971, 469. (b) Tufariello, J. J.; Tette, J. P. J. Org. Chem. 1975, 40, 3866.

36. Tufariello, J. J.; Lee, G. E. J. Am. Chem. Soc. 1980, 102, 373.

37. Danishefsky, S.; McKee, R.; Singh, R. K. J. Am. Chem. Soc. 1977, 99, 4783.

38. Danishefsky, S.; McKee, R.; Singh, R. K. J. Am. Chem. Soc. 1977, 99, 7711.

39. Corey, E. J.; Suggs, J. W. Tetrahedron Lett. 1975, 2647.

40. Zaugg, H. E. Synthesis 1970, 49.

41. Zaugg, H. E.; Martin, W. B. In "Organic Reactions"; John Wiley and Sons, Inc.: New York, 1965; Vol. 14, Chapter 2.

42. Speckamp, W. N.; Schoemaker, H. E. Tetrahedron Lett. 1978, 4841.

43. Evans, D. A.; Thomas, E. W. Tetrahedron Lett. 1979, 411.

44. Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. Tetrahedron 1975, 31, 1437. A new procedure has recently been published for this reduction. Atta-ur-Rahman; Ghazala, M.; Sultana, N.; Bashir, M. Tetrahedron Lett. 1980, 1773.

45. Gibson, M. S.; Bradshaw, R. W. Angew. Chem., Int. Ed. Engl. 1968, 7, 919.

46. Malmberg, M.; Nyberg, K. J. Chem. Soc., Chem. Commun. 1979, 167.

47. Mayer, R. In "Newer Methods of Preparative Organic Chemistry"; Foerst, W., Ed; Academic Press: New York, 1963; Vol. 2, pp. 101-131.

48. Dolby, L. J.; Biere, H. J. Org. Chem. 1970, 35, 3843.

49. Krapcho, A. P.; Glynn, G. A.; Grenon, B. J. Tetrahedron Lett. 1967, 215.

50. For a review on ester cleavages via S_N2-type dealkylations see: McMurry, J. In "Organic Reactions"; John Wiley and Sons, Inc.: New York, 1976; Vol. 24, Chapter 2.

51. Asaoka, M.; Miyake, K.; Takei, H. Bull. Chem. Soc. Jpn. 1978, 51, 3008.

52. House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin, Inc.: Menlo Park, CA, 1972; pp. 517.

53. (a) Sato, S. Nippon Kagaku Zasshi 1969, 90, 404. (b) Becker, Y.; Eisenstadt, A.; Stille, J. K. J. Org. Chem. 1980, 45, 2145.

54. (a) Yang, N. C.; Lenz, G. R. Tetrahedron Lett. 1967, 4897. (b) Breederveld, H. Recl. Trav. Chim. Pays-Bas 1960, 79, 1197.

55. Giddy, A.; Todd, A. J. Chem. Soc. 1959, 2087.

56. Nomura, Y.; Ogawa, K.; Takeuchi, Y.; Tomoda, S. Chem. Lett. 1977, 693.

57. Petrillo, E. W.; Spitzmiller, E. R. Tetrahedron Lett. 1979, 4929.

58. Drake, N. L., Ed. "Organic Synthesis"; John Wiley and Sons, Inc.: New York, 1941; Vol. 21, pp. 77.

59. Jung, M. E.; Lyster, M. A. J. Chem. Soc., Chem. Commun. 1978, 315.

60. Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Stephens, W. P. J. Org. Chem. 1978, 43, 138.

61. Aasen, A. J.; Culvenor, C. C. J. J. Org. Chem. 1969, 34, 4143.

62. Kornet, M. J.; Thio, P. A.; Tan, S. I. J. Org. Chem. 1968, 33, 3637.

63. Pinnick, H. W.; Chang, Y. H. J. Org. Chem. 1978, 43, 4662.

64. Borch, R. F. Tetrahedron Lett. 1968, 61.

65. Scheibye, S.; Pedersen, B. S.; Nilsson, N. H.: Lawesson, S. O. Bull. Soc. Chim. Belg. 1978, 87, 229.

66. Raucher, S.; Klein, P. Tetrahedron Lett. 1980, 4061.

67. Kornfeld, E. C. J. Org. Chem. 1951, 16, 131.

68. Raucher, S.; Macdonald, J. E.; Lawrence, R. F. J. Am. Chem. Soc. 1981, 103, 2419.

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