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THE HYDROAZOCINE ROUTE TO HIGHLY FUNCTIONALIZED PYRROLIZIDINES[a]

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Abstract—Studies of the preparation of 1,8-dihydroazocines and transannular cyclization of hydroazocines to produce functionalized pyrrolizidines are described. Results are presented which demonstrate that unsymmetrically substituted acetylenes bearing at least one electron withdrawing groups undergo efficient cycloaddition to 1 - β - styryl - 1,2 - dihydropyridine producing in a regio-selective fashion 3,4 - disubstituted - 1,8 - dihydroazocines. The dihydroazocines generated in this manner can be converted to 1 - formyl - $\Delta^{4,5}$ - epoxyazocines which undergo interesting rearrangement reactions to form pyrrolizidines when subjected to methoxide deformylation followed by acid treatment. In addition, 1,6,7,8 - tetrahydroazocines can be converted to pyrrolizidines under bromination conditions. The intriguing chemical process which occur under the conditions outlined above are described.

Compounds containing the pyrrolizidine heterocyclic ring system occur naturally and possess wide spectra of physiological activities.[2] Perhaps the most interesting of these are the mitomycins owing to their interesting biological properties.[3] As a result, the pyrrolizidine alkaloids have served as targets for a large number of synthetic investigations. Approaches to this interesting ring system have followed a number of different strategies including those in which the heterobicyclic framework is created by intramolecular amine alkylation,[4] intramolecular pyrrole or pyrrolidine acylation,[5] Dieckmann reaction,[6] ylid cycloaddition,[7] activated cyclopropane addition,[8] hydroazocine transannular cyclization,[9] and by a variety of other interesting methods.[10] Moreover, a rather modest effort has been expended in the development of general procedures to prepare highly functionalized pyrrolizidines which can serve as basic skeletal units for members of the senecio alkaloid family and the antitumor, antibacterial mitomycins.[11]

As part of our earlier studies targeted at the development of synthetic methods to prepare the mitosene ring system, we explored several sequences to generate functionalized pyrrolizidines.[9e] The strategy of these approaches was to employ transannular displacement reactions of appropriately functionalized hydroazocines to construct the key heterocyclic system. One of the attractive features of sequences of this type resides in the availability of 1,8-dihydroazocines through 1,2 - dihydropyridine-acetylene cycloadditions.[12] Indeed, in prior investigations we had found that 1 - β - styryl - 1,2 - dihydropyridine[13] (**1**) undergoes smooth cycloaddition with dimethyl acetylenedicarboxylate to form the 1,8-dihydroazocine **2** which can be transformed to the N - formyl - $\Delta^{4,5}$ - epoxyazocine **3**. Transannular cyclization of **3** to produce the pyrrolizidine diester **5** can be affected by deformylation and acid catalyzed cyclodehydration via the amino ether **4** (Scheme 1).

Our continuing efforts have focused on a further exploration of this methodology in order to develop efficient approaches to the mitosene skeleton based on the synthetic design outlined in Scheme 2. In this report, we describe the results of studies of several aspects of this sequence concerning cycloadditions of unsymmetric acetylenes to the dihydroazocine 1, and the preparation and transannular cyclizations of 4,5-disubstituted hydroazocines.

Acetylene-1,2-dihydropyridine cycloaddition regiochemistry

Application of the approach outlined above for synthesis of the mitosene skeleton is dependent upon the availability of methods for preparation of highly functionalized hydroazocines via regiochemically rational routes. A key feature of the design concerns the deployment of appropriate substituents at the azocine ring C-3 and C-4 positions which would be transformed into the quinone A-ring and methylene carbamate of the mitosenes, respectively. Thus, attention was given initially to a study of the regiochemical course of unsymmetric acetylene additions to the useful 1 - β - styryl - 1,2 - dihydropyridine, since it is at this stage that descrimination between substitution at C-3 and C-4 is required. Specifically, cycloaddition of the acetylenes **6a–10a** to dihydropyridine **1** were conducted under identical conditions (25°, C_6H_6, N_2, silica gel tlc) producing the 1,8-dihydroazocines **6a–10b** in the yields summarized in Table 1.

Regiochemical assignments to the products of these reactions were made on the basis of their ^{1}H-NMR spectra (see Table 1). The spectrum of the 3,4-dicarbomethoxy substituted system **2** has a singlet for H-2 at 7.72 ppm and a doublet at 6.85 for H-5. Substitution of a group capable of more electron withdrawal than carbomethoxy at C-3 or C-4 should cause the H-2 or H-5 resonances to experience a downfield shift. This is seen in the case of the product derived from the blocked propargyl acetylacetylene **10a**, where the ^{1}H-NMR shows a singlet 7.65 ppm for H-2 and broad doublet for H-5 at 6.18 pp. Similar observations are made in the ^{13}C-NMR spectra of these substances (Table 1).

[a] A preliminary report of these results has been presented.[1]
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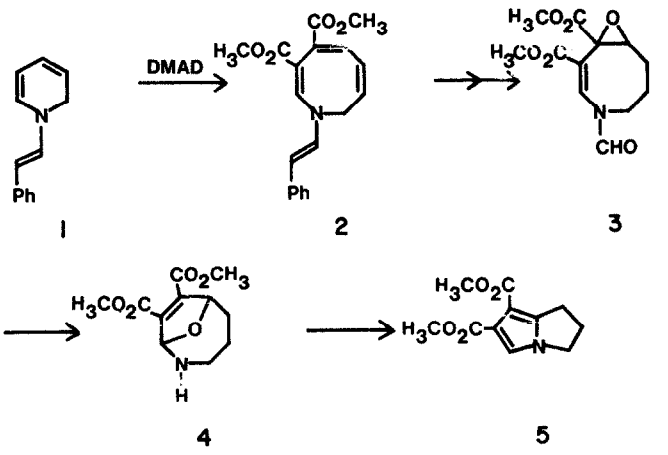
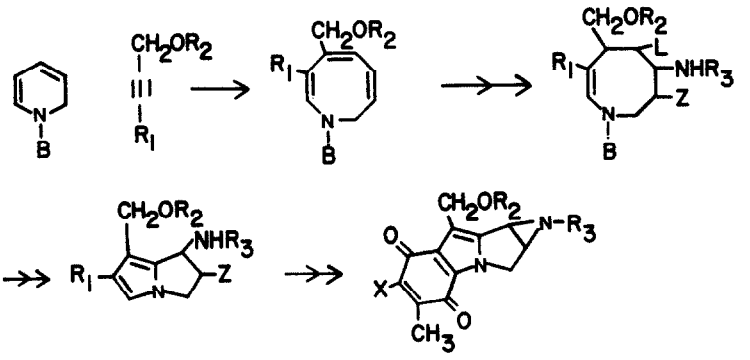


Scheme 1.



Scheme 2.

The mechanism proposed earlier by Acheson[12] to account for addition of dimethyl acetylenedicarboxylate to a variety of 1,2-dihydroazocines appears to account nicely for the regioselectivities observed. Accordingly the direction of addition to produce the azabicyclooctadiene intermediates **12** should be controlled by substituents which facilitate nucleophilic attack on the acetylene. The zwitterions **11** having the substituents with greater anion stabilizing properties at the anionic centers, thus, would be formed preferentially and transformed to 1,8-dihydroazocines with these substituents located at C-3.

Preparation of properly substituted 1,8 - *dihydroazocines*

The above results suggest that cycloaddition reactions of unsymmetric acetylenes to N-styryldihydropyridine might serve as a useful method for regiochemically rational syntheses of 3,4 - disubstituted - 1,8 - dihydroazocines. Our attention turned next to the design and synthesis of acetylenes which contain required C-3 and C-4 side chains for eventual elaboration of the quinone A-ring and carbamate side chain found in the mitosenes. We envisaged that a methyl succinoyl grouping at C-3 of the dihydroazocine **13** might be useful for the former purpose, since intramolecular acylation followed by

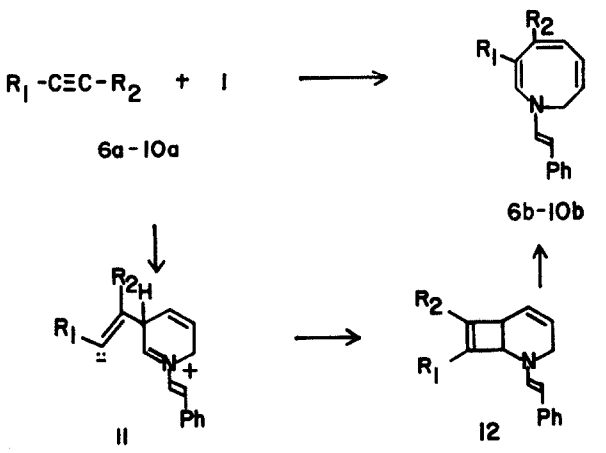


Table 1. Results of the addition of unsymmetric acetylenes **5a–10a** to 1-β-styryl-1,2-dihyropyridine (**1**)

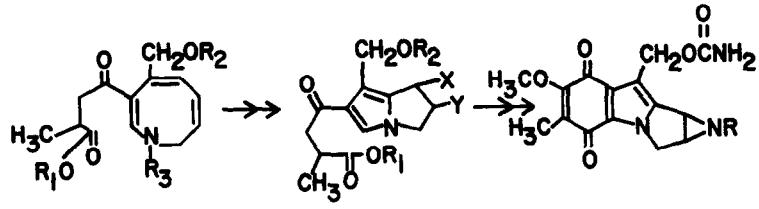
Acetylene or 1,8-Dihydroazocine	R_1	R_2	Yield[a]	NMR Data ^1H-NMR[b] H-2	H-5	^{13}C-NMR[b] C-2	C-5
2	CO_2CH_3	CO_2CH_3	69%	7.72	6.85	145.3	135.2
6	$COCH_3$	$CO_2CH_2CH_3$	56%	7.69	7.03	145.8	135.3
7	$CO(CH_2)_2CH_3$	$CO_2CH_2CH_3$	65%	7.69	7.05	144.9	135.1
8	$COCH{=}C(CH_3)_3$	$CO_2CH_2CH_3$	50%	7.71	7.01	146.3	135.3
9	$CO_2CH_2CH_3$	$COCH{=}C(CH_3)_2$	10%	7.95	-	145.9	136.3
10	$COCH_3$	CH_2OTHP	34%	7.65	6.18	144.9	125.5

[a] Isolated yields of pure materials

[b] Chemical shifts in ppm relative to TMS

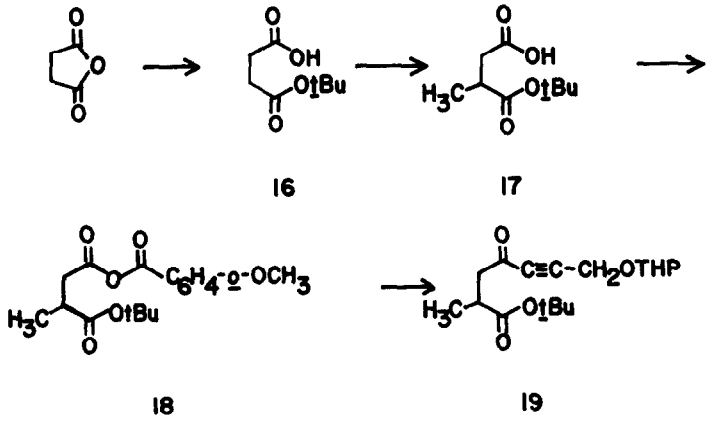
hydroxylation-oxidation should transform a pyrrolizidine precursor **14** into a key tricyclic-quinone intermediate **15**. The carbamate function should be readily derived from an appropriately blocked hydroxymethyl grouping (Scheme 3). Two acetylenes which appear to be compatible with the specifications outlined above and to contain the required CO functionality to be reactive with dihydropyridines are the blocked-propargyl succinoyl acetylenes **19** and **26**.

Preparation of these substances was accomplished through addition of appropriate propargylacetylides to activated methylsuccinoyl monoesters (Schemes 4 and 5), starting with succinic anhydride. The key feature of these routes is the method selected for differentiation between the two methylene groups of intermediate succinate monoesters. Kofron[14] has shown that monoesters of succinic acids can be converted by the use of two equivalents of amide ion in liquid ammonia to dianions in which the propon α to the ester moiety is selectively ionized and that the dianions react with alkyl halides to yield single alkylated products. The sequence used for preparation of the acetylenic ketoester **19** was modeled after Kofron's approach and began with mono-t-butyl succinate **16**, prepared from succinic anhydride by the four step procedure of Buchi[15] (60%) or directly by reaction with lithium t-butoxide (30%). Attempts at generation and methylation of the dianion of **16** with lithium diisopropylamide followed by treatment with



13 14 15

Scheme 3.



16 17 18 19

Scheme 4.

methyliodide met with failure. However, alkylation was successfully accomplished by using lithium bis-(trimethylsilyl)amide (2 h, 25°) followed by quenching with methyliodide (2 h, 25°) and provided t-butyl methylsuccinate **17** in a 77% yield. That monoalkylation had occurred under these conditions was evidenced by the spectroscopic properties. Characteristic was the appearance in the ^{1}H-NMR spectrum of a Me doublet at 1.19 ppm and a multiplet in the 2.3–3.0 ppm region for the succinoyl methylene and methine protons. At this stage, it was not possible to conclusively prove that methylation had occurred α to the ester CO since only minor differences were expected in spectroscopic properties for the two regioisomers.

Activation of the carboxylic acid function of **17**, required for coupling to blocked propargyl acetylides, was attempted through conversion to the acid chloride. Treatment of **17** under thionyl chloride [16] or oxalyl chloride[17] chlorination conditions gave only either the bis-acid chloride of succinic acid or mixtures of products. A more fruitful approach was developed modeled after the mixed anhydride procedure of Terasawa.[18] Accordingly, reaction of *o*-anisoyl chloride with the monoester **17** in the presence of triethylamine (−15°, THF) gave the mixed anhydride **18** which was used without purification typically. A tetrahydrofuran solution of this material was reacted directly with the lithium acetylide of 2-propargyloxytetrahydropyran[19] (n-BuLi, THF, −78°). The yield of desired acetylenic ketone **19** generated in this way was maximal at 42% when the lithium acetylide was added slowly to a THF solution of **18**. Structure proof for the acetylene **19** rests on firm spectroscopic evidence. In particular, the strong bands at 2230, 1725 and 1680 cm^{-1} in the IR spectrum are characteristic of the unsymmetric acetylene, ester CO and α,β-unsaturated CO groups present in **19**. Careful scrutiny of the mass spectrometric fragmentation patterns and ^{13}C-NMR spectrum of this acetylene allowed the first opportunity in this sequence for clear assignment of Me regiochemistry in the succinoyl side chain. The fragment at *m/e* 73.02887 of composition $C_3H_5O_2$ (requires 73.02895) appears best rationalized in terms of structure **21** produced by decomposition of the parent ion with a Me substituent at the ester α-carbon through a pathway involving β-cleavage of the radical ion **20** formed by the expected loss of isobutylene.[20] Comparisons of the ^{13}C-NMR chemical shifts of the succinoyl methylene and methine carbons of **19** and its precursor **17** provided further support. The methine carbons in ketone and acid resonate at 35.7 and 37.5 ppm, respectively. On the other hand, the chemical shifts for the methylene carbons in the ketone and acid differ greatly (48.4 and 36.7 respectively) in way expected for the change in the nature of the adjacent CO group.

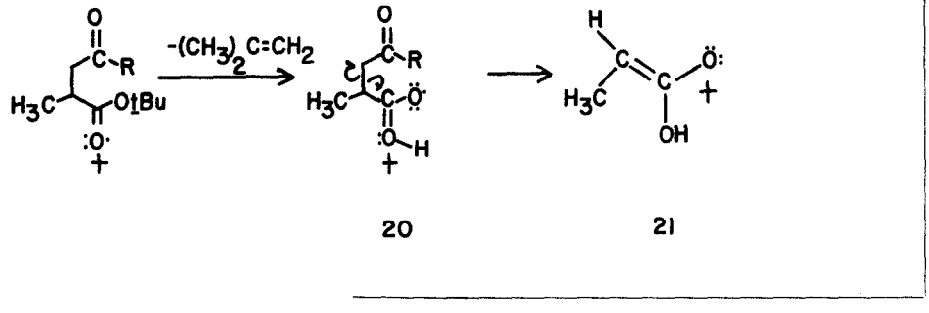
The alternate acetylene synthon **26** was prepared through the sequence shown in Scheme 5 starting with mono-n-butyl succinate **22**. Alkylation was performed by using lithium diisopropylamide (−78°, THF, MeI) giving the methylated material **23** (83%) which was converted to its acid chloride ($SOCl_2$, 35°, 78%). Dimethyl-t-butylsilyl blocked propargyl alcohol **25** (M=H) (propargylalcohol, imidazole, DMF, 25°) was converted to its silveracetylide **25** (M=Ag) by treatment with aqueous-ethanolic silver nitrate-ammoniumhydroxide, which was reacted with **24** (CCl_4, reflux) giving the desired acetylenic ketone **26** in a 74% yield.

As anticipated on the basis of our earlier results, both of the acetylenes **19** and **26** underwent cycloaddition to 1 - β - styryl - 1,2 - dihydropyridine (50°, THF, 4d) generating regiospecifically the respective 1,8-dihydroazocines **29** and **44** in modest yields (34–40%). The C-3 C-4 regiochemistry is readily assignable on the basis of the H-2 and H-5 proton chemical shifts of 7.55 and 6.60 ppm, respectively (Table 1).

Transannular cyclization methods

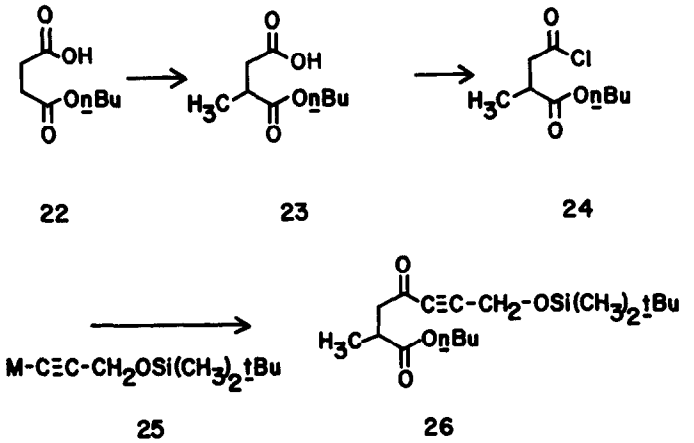
With the styrylazocines **29** and **44** in hand, we next addressed the problem of transannular cyclization to produce the pyrrolizidine ring system with correct functionality and side chain structure needed for eventual elaboration of the mitosenes. Our previous studies[9e] had shown that the approach outlined in Scheme 6 for conversion of hydroazocine to pyrrolizidines, involving through space (a) or through bond (b) assistance[a] of C-L bond cleavage, is useful for this purpose. Accordingly, we explored variations of this approach with azocine epoxides and bromonium ions of general structures **27** and **28**, produced from tetrahydroazocine precursors.

The first test of this plan commenced with selective ozonolysis of the styrylazocine **29** (−50°, MeOH) followed by reductive work-up (DMS) giving the N-formyl derivative **30** (65%). Introduction of ozone in this process had to be carefully monitored in order to prevent destruction of the azocine ring. Selective functionalization of the $\Delta^{6,7}$-π bond of **30** with electrophilic reagents is important in eventual applications of this methodology to mitosene syntheses. Earlier results had demonstrated that 1,8-dihydroazocines possessing electron withdrawing groups at C-3 and C-4 undergo both hydrogenation and bromination selectively at this unsaturated center.

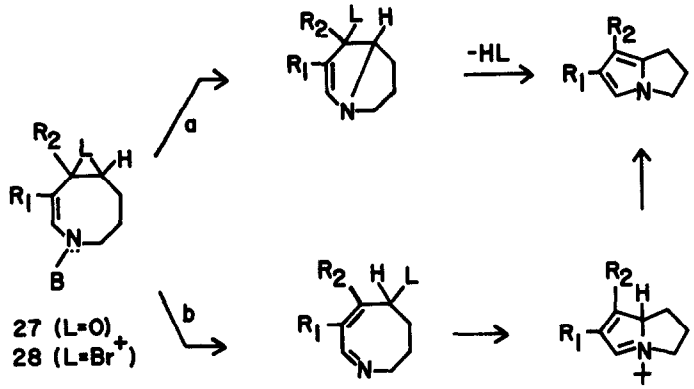


20 21

[a]Through bond assistance has been termed frangomeric assistance.[21]



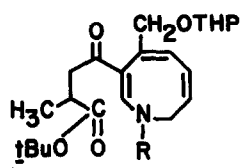
Scheme 5.



Scheme 6.

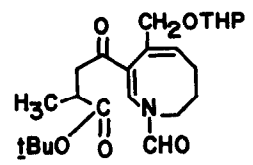
Significantly, systems lacking C-4 substituents which deactivate the $\Delta^{4,5}$-π bond appear to also undergo addition at the $\Delta^{6,7}$-center. Accordingly, catalytic hydrogenation of **30** (10% Pd/C, EtOH, 55 psi) yields quantitatively the N-formyltetrahydroazcine **31**.

The sequence outlined thusfar demonstrates how three of the four olefinic π-bonds of the N-styryldihydroazocines can be differentiated chemically in a manner compatible with our synthetic strategy. The final challenge involving discrimination of the $\Delta^{2,3}$ and $\Delta^{4,5}$-unsaturation



29 (R=CH=CHPh)

30 (R=CHO)



31

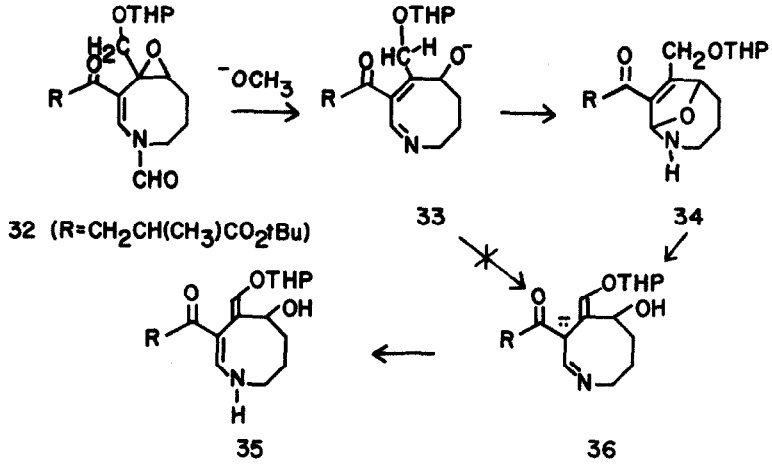
appears to be easily overcome. Introduction of the oxirane bridge at the $\Delta^{4,5}$-position is achieved by treatment of the tetrahydroazocine **31** with *m*-chloropherbenzoic acid (Na_2HPO_4, 0°, CH_2Cl_2, 89%) giving separable (Silica Gel tlc) pairs of diastereomeric epoxides **32**.[b] Following the procedure developed earlier,[9e] the epoxides, either separately or as a mixture, were reacted with

[b]The dihydro and tetrahydroazocines **29–31** consist of a mixture of diastereomers due to the chiral centers in the THP and succinoyl side chains. Introduction of two new correlated chiral centers at C-4 and C-5 leads to the possibility of four diastereomers assuming the oxirane ring is cis-fused. The pairs of inseparable isomers probably consist of epimers at the succinoyl methine carbon.

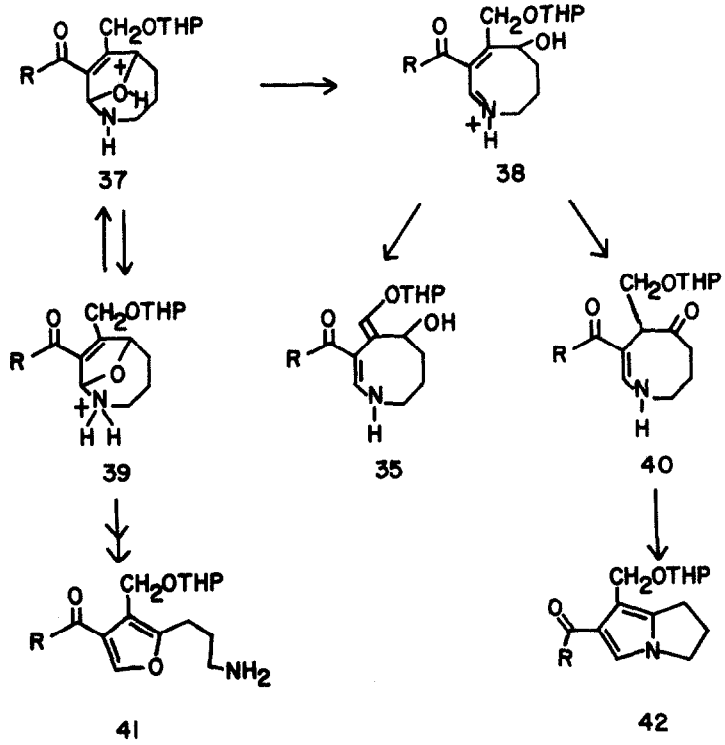
sodium methoxide in methanol at 0° for 15 min producing a mixture of diastereomeric bicyclic aminoethers **34**. Several key spectroscopic parameters serve as indicators of the structural changes occurring in this process.

In particular, the H-2 and H-5 bridgehead protons appear as a singlet and doublet of doublets at the characteristic positions 5.80 and 5.06 ppm, respectively. Also, the CO and olefin stretching bands at 1680 and 1630 cm^{-1} are evidence for the presence of an α,β-unsaturated ketone moiety in **34**. When the methoxide induced deformylation of **32** is conducted at 25° for extended time periods, (>30 min) a new substance identified as the allylic alcohol **35** is produced along with the bicyclic aminoether. Conversion to this material, which can also be generated from **34** by treatment with methoxide, is complete after 5 h (62%). Thus, it is clear that the allylic alcohol is a secondary product produced from the bicyclic ether by base induced elimination forming the stabilized enolate **36**. The alternate route to **35** via **36** involving intramolecular proton transfer in the alkoxide **33** is less likely since in the conformation required for this process the methylene proton to be transferred would not be acidic. This feature most probably accounts for the preferential formation of **34** under kinetic conditions.

Thus, by a judicious choice of reaction conditions the outcome of the epoxide deformylation reaction can be controlled to obtain the desired bicyclic ether. Unfortunately, the presence of the methylene group at C-4 of the azocine ring has an uncontrollable effect on the pyrrolizidine ring forming transformation. Previous studies have shown that the acid catalyzed (pyridine · HCl, 50°) rearrangement of the 3,4-dicarbomethoxy analog of **34** to the corresponding pyrrolizidine is high yielding. In



Scheme 7.



Scheme 8.

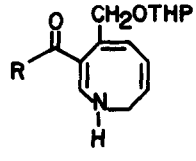
contrast, a mixture of products consisting of the desired pyrrolizidine **42** (6%) previously characterized allylic alcohol **35** (11%) and a substance tentatively identified as the furan **41** (1%) are isolated after reaction of **34** under these acid catalyzed reaction conditions and chromatography. Pyrrolizidine **42** shows stretching bands in the IR at 1509 and 1452 cm^{-1} characteristic of the pyrrole ring. Its ^{1}H-NMR spectrum contains a singlet at 7.13 ppm for the pyrrole α-proton, a triplet 3.86 ppm for the methylene protons α to nitrogen and other resonances consistent with the presence of the succinoyl and methylene-THP side chains. Interestingly the diastereotopic oxymethylene protons are significantly different, appearing as doublets at 4.62 and 4.86 ppm (J = 11 Hz).

The possible origin of the three products formed can be understood by considering the possible sites of protonation in **34** and reaction pathways available (Scheme 8). Oxygen protonation and cleavage would give the stabilized carbenium ion **38** which can undergo two likely transformations, Pinacol rearrangement to **40** followed by precedented cyclodehydration[9b–9e] yielding **42** or loss of a proton from the α-methylene group to produce the allylic alcohol **35**. Alternate protonation on nitrogen of **34** followed by C–N bond cleavage would serve as initial steps in the conversion to furan **41**.

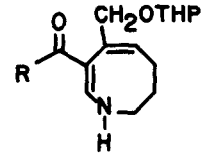
Another approach to transannular cyclization of hydroazocines was clearly needed. Wilson's studies[9a] of hexahydroazocine brominations suggested an alternate method involving internal capture of an intermediate bromonium ion like **28** by the ring nitrogen. The requisite systems required to test this methodology are the amines **44** and **48** which were found to be readily available starting with the N-styryldihydroazocines synthesized earlier. Sodium methoxide deformylation (EtOH, 0°, 10 min, 74%) of the N - formyl - 1,8 - dihydroazocine **30** provided the free amine **43** which was then converted to the tetrahydroazocine **44** by catalytic hydrogenation (10% Pd/C, EtOH, 83%). Alternatively, deformylation of the N-formyltetrahydroazocine **31** (NaMe, MeOH, 0°, 15 min, 90%) produced **44** directly. The differently blocked tetrahydroazocine **48** was prepared by a related sequence from **45**. Careful ozonolytic cleavage of the styryl double bond generated the N-formyl compound (62%) which was selectively hydrogenated yielding **47** (74%) and deformylated (95%) to give the desired amine **48**.

It was envisaged that treatment of the azocines **44** with bromine would produce the bromonium ion **49** which should be capable of undergoing transannular cyclization and loss of hydrogen bromide to yield the sought after pyrrolizidine **42**. However, when reaction of **44** was conducted by using bromine in methylene chloride, the azocinylaldehyde **51** was produced as the only isolable product. This aldehyde, which could also be produced by treatment of the allylic alcohol **35** under modified Moffat oxidation conditions[22] (Ac_2O, DMSO, K_2CO_3, 50%), was characterized on the basis of spectroscopic data, in particular, the ^{1}H-NMR spectrum which showed an aldehydic proton singlet at 9.32 ppm, a doublet of doublets at 6.32 ppm for H-5 and a collapsible (D_2O) doublet at 7.38 ppm for H-2. Apparently, the presence of the strongly acidic hydrogen bromide in the reaction medium causes cleavage of the tetrahydropyranylether function following bromonium ion ring opening by through bond rather than through space participation of the nitrogen lone pair to produce the intermediate allylic bromide **50** (Scheme 9). Accordingly, the reaction conditions were adjusted to prevent THP cleavage and thus provide the allylic bromide **50** with an opportunity for transannular cyclization. As expected, the pyrrolizidine **42** was produced as the major product when **44** was treated with methanolic solutions of bromine at 0° in the presence of triethylamine. This reaction is best carried out to less than complete conversion. In this way the yield of **42** based upon recycled starting material is a modest 52%. Quite surprisingly, the differently blocked tetrahydroazocine **48** provided the corresponding pyrrolizidine **42** (R_1=$CH_2CH(Me)CO_2n$-Bu; R_2=$Si(Me)_2t$-Bu) in only low yields.

In summary, the synthetic routes investigated in these studies appear to provide modest yielding procedures for preparation of highly functionalized pyrrolizidines from readily available N - blocked - 1,8 - dihydroazocines. The sequences have considerable flexibility in the elaboration of structure and the regiocontrolled placement of substituents. Future studies will be directed at the development of synthetic routes to the mitosenes based upon the methodology developed.



43 (R=$CH_2CH(CH_3)CO_2t$Bu)



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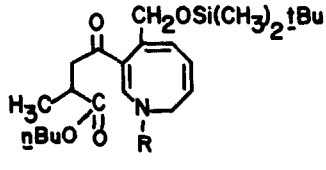
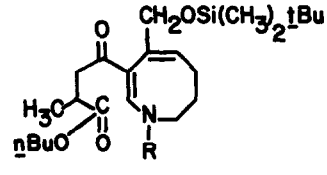


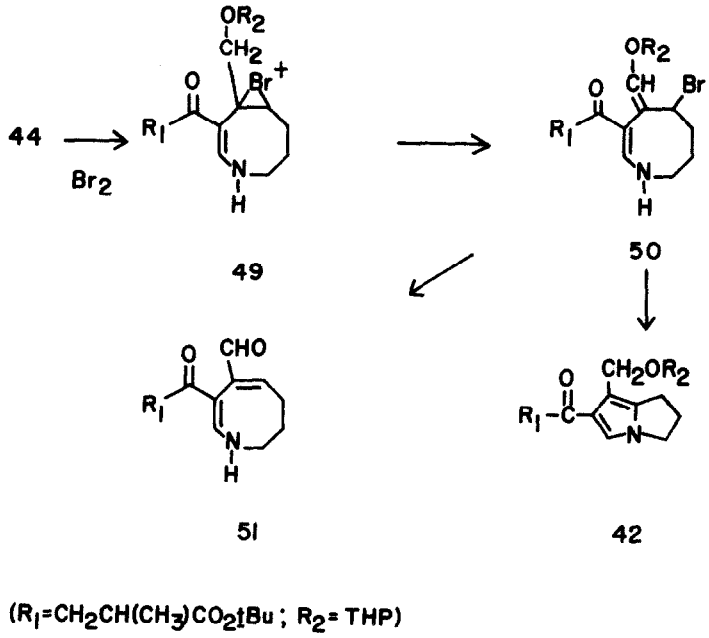
45 (R=CH=CHPh)

46 (R=CHO)



47 (R=CHO)

48 (R=H)



Scheme 9.

EXPERIMENTAL

General. ^{1}H-NMR spectra were taken on a Varian EM-360, T-60, HA-100, or Varian XL-100 FT NMR spectrometer and recorded in ppm relative to TMS as an internal standard. ^{13}C-NMR spectra were obtained from JEOL PS-100 NMR or Varian XL-100 spectrometers at an operating frequency of 25.0345 MHz and are recorded in ppm relative to Me_4Si as an internal standard. Mass spectra were taken on a Du Pont CEC21-110B high resolution or a Bell and Howell 21-492 mass spectrometer. UV data were obtained from Beckman Model ACTA III or Mac-Phearson 711 spectrometers. IR spectra were recorded on a Perkin-Elmer 237B, Beckman IR8, or Beckman IR12 spectrophotometer.

M.ps were taken on a Griffin Mel-Temp 110-V capillary m.p. apparatus and are reported uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Preparative chromatographic work was done with either Baker "tlc" silica gel 7GF, Grace silica gel, Davison grade 923, or Merck 230–400 mesh silica gel. Hydrogenations were carried out on a Parr low-pressure hydrogenation apparatus. Ozonolyses were performed by using a Welsbach T-408 laboratory ozonator. Unless otherwise mentioned drying during workup of crude mixtures involved washing with NaCl aq and drying with Na_2SO_4. Molecular distillations were performed on a Kugelrohr apparatus.

2-Carboethoxyethynyl silver. To a soln of 40 mL water, 80 mL MeOH and 3.4 g (20.0 mmol) $AgNO_3$ was added NH_4OH until the initially formed ppt dissolved, followed by an additional 5 drops. Ethyl propiolate (2.07 mL, 20.0 mmol) in 5 mL MeOH was added at 25° over a period of 30 min. The mixture was stirred an additional 2 h and then extracted with 50% CCl_4–$CHCl_3$. The organic extracts were concentrated *in vacuo* giving 3.82 g (93%) of 2-carboethoxyethynyl silver: IR ($CHCl_3$) 2990 (m), 2050(m) and 1675 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.30 (q, 2H, J = 8.0 Hz),1.35 (t, 3H, J = 8.0 Hz); mass spectrum (70 ev) *m/e* (relative intensity) 205 (< 1, M^+), 107 (8); ^{13}C-NMR ($CDCl_3$) 101.1 (s, C1) 112.7 (s, C2), 151.7 (s, CO), 62.3 (t, CH_2), 14.1 (q, CH_3). (Found: C, 28.97; H, 2.40. Calc. for $C_5H_5O_2Ag$: C, 29.27; H, 2.44%.)

Ethyl 3-oxo-1-butyne-1-carboxylate (**6a**). To 1.93 g (9.5 mmol) of 2-carboethoxynyl silver in 15 mL CH_2Cl_2 at 0°, under N_2 was added rapidly 0.74 mL (9.5 mmol) acetyl chloride in 10 mL CH_2Cl_2 with stirring. The reaction was then stirred at 25° for 10 h and filtered. Concentration of the filtrate gave the desired acetylene (1.1 g, 88%). An analytical sample was obtained by distillation at 35° (0.1 mm): IR (liquid film) 2990 (m) and 1710 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.40 (s, 3H, CH_3), 4.30 (q, 2H, CH_2), 1.18 (t, 3H, CH_3); mass spectrum (70 ev) *m/e* (relative intensity) 140 (< 1, M^+), 96 (16) 67 (10), 43 (63); UV max (EtOH) 232 nm (ϵ 9300); ^{13}C-NMR ($CDCl_3$) 32.3 (q, α-CH_3), 182.4 (s, CO), 80.8 (s, C3 acetylene), 77.8 (s, C4 acetylene), 152.2 (s, ester), 63.0 (t, CH_2), 13.9 (q, CH_3). (Found: C, 58.29; H, 5.91. Calc. for $C_7H_8O_3$: C, 60.00; H, 5.71%.)

Ethyl 3-oxo-1-hexyne-1-carboxylate (**7a**). To 1.85 g (9.0 mmol) of 2-carboethoxyethynyl silver in 20 mL CH_2Cl_2 was added 1.00 g (9.0 mmol) butyryl chloride in 10 mL CH_2Cl_2 at 0°, under N_2, with stirring. The reaction was stirred at 25° for 24 h and filtered. Concentration of the filtrate *in vacuo* gave 0.86 g (57%) of the desired acetylene: IR ($CHCl_3$) 1810 (m) and 1710 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (t, 3H, J = 7.0 Hz, CH_3), 1.7 (m, 2H), 2.6 (t, 2H, J = 7.0 Hz, α-CH_2), 4.37 (q, 2H, J = 7.0 Hz, OCH_2), 1.35 (t, 3H, J = 7.0 Hz, CH_3); mass spectrum (70 ev) *m/e* (relative intensity) 168 (< 1, M^+), 140 (20), 123 (17), 95 (31), 83 (100), 71 (97); UV max (95% EtOH) 230 nm (ϵ 11,200); ^{13}C-NMR ($CDCl_3$) 185.9 (s, CO), 152.2 (s, ester), 80.6 (s, acetylene), 78.1 (s, acetylene), 63.0 (t, OCH_2), 37.1 (t, α-CH_2), 17.2 (t, CH_2), 14.0 (Q, CH_3), 13.4 (q, CH_3). (Found: C, 64.52; H, 7.28. Calc. for $C_9H_{12}O_3$: C, 64.28; H, 7.14%.)

Ethyl 5-methyl-3-oxohex-4-ene-2-yne-1-carboxylate (**8a**). To 1.934 g (9.5 mmol) of 2-carboethoxyethynyl silver in 15 mL CH_2Cl_2 at 0° under N_2 was added 1.121 g (9.5 mmol) of β,β-dimethylacryloyl chloride in 10 mL CH_2Cl_2 with stirring. The mixture was then stirred at 25° for 10 h and filtered. Concentration of the filtrate *in vacuo*, gave a residue which was distilled (40°, 0.1 mm) to give 1.39 g (76%) of the desired acetylene: IR (liquid film) 2950 (m), 1774 (s) and 1715 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.26 (s, 3H, allylic CH_3), 2.00 (s, 3H, allylic CH_3), 6.23 (s, 1H, methine), 4.32 (q, 2H, CH_2), 1.33 (t, 3H, CH_3); mass spectrum (70 eV) *m/e* (relative intensity) 180 (< 1, M^+), 135 (24), 108 (48); UV max (EtOH) 269 nm (ϵ 12,000); ^{13}C-NMR ($CDCl_3$) 152.4 (s, ester), 173.8 (s, ketone), 162.0 (s), 124.6 (d, methine), 76.6 (s, acetylene), 82.8 (s, acetylene), 62.8 (t, CH_2), 28.0 (q, CH_3), 21.6 (q, CH_3), 13.9 (q, CH_3). (Found: C, 66.86; H, 6.55. Calc. for $C_{10}H_{12}O_3$: C, 66.67; H, 6.67%.)

1 - *Styryl* - 3 - *acetyl* - 4 - *carboethoxy* - 1,8 - *dihydroazocine* (**6b**). A soln of 200 mg (1.1 mmol) of 1 - styryl - 1,2 - dihydropyridine and 155 mg (1.1 mmol) of ethyl 3 - oxo - 1 - butyne - 1 - carboxylate in 20 mL benzene were stirred under N_2 at 25°, for 4 days. The solvent was removed *in vacuo* and the produce purified by chromatography (silica gel, 50:50 ether:hexane) to give the desired azocine—(200 mg, 56%): IR ($CHCl_3$) 2975 (m) and 1710 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.69 (s, 1H, H2), 7.03 (d, 1H, J = 4.0 Hz, H5), 6.66 (dd, 1H, J = 4.0 and 10.0 Hz, H6), 6.38 (dt, 1H, J = 10.0 and 7.0 Hz, H7), 4.40 (dbd, 2H, J = 7.0 Hz, NCH_2), 6.95 (d, 1H, J = 14.0 Hz, styryl AB quart.), 6.09 (d, 1H, J = 14.0 Hz, stryrl AB quart.), 7.31 (s, 5H, aromatic), 2.30 (s, 3H, CH_3CO), 4.28 (q, 2H, J = 7.5 Hz, OCH_2), 1.32 (t, 3H, J = 7.5, CH_3); mass spectrum (70 eV) *m/e* (relative intensity) 323 (31, M^+), 280 (100), 250 (7), 91 (29), 77 (43); UV max (95% EtOH) 337 nm (ϵ 9100), 270 (5100), 229 (7800); ^{13}C-NMR ($CDCl_3$) 145.8 (d, C2), 113.2 (s, C3), 136.1 (s, C4), 135.3 (d, C5), 128.9 (d, C6), 134.3 (d, C7), 44.6 (t, C8), 134.9 (d), 108.8 (d), 133.2 (s), 125.3 (d), 128.8 (d), 126.3 (d), 25.7 (q, α-CH_3), 196.0 (s, CO), 167.7 (s, ester), 61.1 (t, OCH_2), 14.2 (q, CH_3); high resolution mass spectrum *m/e* 323.153043 ($C_{20}H_{21}NO_3$ requires 323.152125).

1 - *Styryl* - 3 - *butanoyl* - 4 - *carboethoxy* - 1,8 - *dihydroazocine* (**7b**). A soln of 200 mg (1.1 mmol) of 1 - styryl - 1,2 - dihydropyridine and 185 mg (1.1 mmol) of ethyl 3 - oxo - 1 - hexyne - 1 - carboxylate in 20 mL benzene was stirred at 25° under N_2 for 4 days. The solvent was removed *in vacuo* and the desired azocine **7b** was purified by chromatography (silica gel 50:50 ether:hexane) to give 250 mg (65%): IR ($CHCl_3$) 2975 (m) and 1715 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.69 (s, 1H, H2), 7.05 (d, 1H, J = 4.0 Hz, H5), 6.69 (dd, 1H, J = 4.0 and 10.0 Hz, H6), 6.40 (dt, 1H, J = 10.0 and 7.0 Hz, H7), 4.40 (dbd, 2H, J = 7.0 Hz, NCH_2), 6.91 (d, 1H, J = 14.0 Hz, styryl AB quart), 6.05 (d, 1H, J = 14.0 Hz, styryl AB quart.), 7.32 (s, 5H, aromatic), 1.00 (t, 3H, J = 7.0 Hz), 1.69 (m, 2H), 2.55 (t, 2H, J = 7.0 Hz, α-CH_2), 4.25 (q, 2H, J = 7.5 Hz, OCH_2), 1.32 (t, 3H, J = 7.5 Hz, CH_3); mass spectrum (70 eV) *m/e* (relative intensity) 351 (23, M^+), 280 (100), 104 (72), 91 (24), 77 (37), 71 (37); UV max (95% EtOH) 340 nm (ϵ 12600) 271 (6600), 230 (10000); ^{13}C-NMR ($CDCl_3$) 144.9 (d, C2), 112.9 (s, C3), 136.2 (s, C4), 135.2 (d, C5), 129.0 (d, C6), 134.5 (d, C7), 44.6 (t, C8), 135.3 (d), 108.7 (d), 133.3 (s), 125.3 (d), 128.8 (d), 126.3 (d), 14.1 (q), 18.9 (t), 39.5 (t), 198.6 (s, CO), 167.8 (s, ester), 61.1 (t, OCH_2), 13.6 (q); high resolution mass spectrum *m/e* 351.182218 ($C_{22}H_{25}NO_3$ requires 351.183425).

1 - *Styryl* - 4 - *carboethoxy* - 3 - (3,3 - *dimethylacrylo* - [1 - *yl*]) - 1,8 - *dihydroazocine* (**8b**) *and the regioisomer* (**9b**). A soln of 1 - styryl - 1,2 - dihydropyridine (5.0 g, 0.027 mol) and ethyl 5 - methyl - 3 - oxohex - 4 - ene - 1 - yne - 1 - carboxylate (5 mL, 0.027 mol) in 25 mL benzene was stirred for 2 days under N_2 at 25°. The solvent was removed *in vacuo* and the product purified by chromatography (alumina, 50:50 ether:hexane) giving 4.922 g (50%) of **8b**, the faster moving, and 0.96 g (9%) of **9b**, the slower moving, azocine: (**8b**) IR ($CHCl_3$) 2940 (m) and 1710 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.92 (s, 3H, allylic CH_3), 2.03 (s, 3H, allylic CH_3), 6.10 (s, 1H), 7.71 (s, 1H, H-2), 7.01 (d, 1H, J = 4.0 Hz, H-5), 6.72 (dd, 1H, J = 4.0 and 10.0 Hz, H-6), 6.45 (dt, 1H, J = 10.0 and 7.5 Hz, H-7), 4.49 (dbd, 2H, J = 7.5 Hz, NCH_2), 6.88 (d, 1H, J = 14.0 Hz, styryl AB quart.), 6.02 (d, 1H, J = 14.0 Hz, styryl AB quart.), 7.31 (s, 5H, aromatic), 4.25 (q, 2H, J = 7.0 Hz, OCH_2), 1.35 (t, 3H, J = 7.0 Hz, CH_3); mass spectrum (70 eV) *m/e* (relative intensity) 363 (9, M^+), 280 (55), 103 (18), 91 (20), 83 (100), 77 (31); UV max (EtOH) 366 nm (ϵ 13,200), 266 nm (ϵ 12,600); ^{13}C-NMR ($CDCl_3$) 146.3 (d, C2), 113.7 (s, C3), 136.3 (s, C4), 135.3 (d, C5), 129.5 (d, C6), 134.3 (d, C7), 44.5 (t, C8), 135.1 (d), 108.2 (d), 133.3 (s), 125.3 (d), 128.8 (d), 126.2 (d), 20.6 (q), 26.8 (q), 122.9 (d), 192.4 (s, CO), 167.9 (s, ester), 61.1 (t, OCH_2), 14.1 (q), 149.2 (s); high resolution mass spectrum *m/e* 363.182155 ($C_{23}H_{25}NO_3$ requires 363.183425); (**9b**) IR ($CHCl_3$) 2990 (m), 1695 (s) and 1610 (m) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.95 (s, 1H, H2), 6.69 (dd, 1H, J = 4.0 and 10.0 Hz, H6), 6.35 (dt, 1H, J = 10.0 and 7.0 Hz, H7), 4.41 (dbd, 2H, J = 7.0 Hz, NCH_2), 6.89 (d, 1H, J = 14.0 Hz, styryl AB quart.), 5.95 (d, 1H, J = 14.0 Hz, styryl AB quart.), 7.30 (s, 5H, aromatic), 4.15 (q, 2H, J = 7.5 Hz, OCH_2), 1.21 (t, 3H, J = 7.5 Hz, CH_3), 6.45 (s, 1H), 1.99 (s, 3H, allylic CH_3), 2.25 (s, 3H, allylic CH_3); mass spectrum (70 eV) *m/e* (relative intensity) 363 (16, M^+), 280 (48), 91 (18), 83 (100), 77 (34); UV max (95% EtOH) 336 nm (ϵ 5100), 244 (ϵ 8500); ^{13}C-NMR ($CDCl_3$) 145.9 (d, C2), 101.7 (s, C3), 142.5 (s, C4), 136.3 (d, C5), 129.2 (d, C6), 134.3 (d, C7), 44.2 (t, C8), 135.5 (d), 107.7 (d), 131.3 (s), 125.2 (d), 128.7 (d), 126.1 (d), 20.9 (q), 27.7 (q), 122.3 (d), 193.5 (s, CO), 168.0 (s, ester), 60.5 (t, OCH_2), 14.1 (q), 155.4 (s); high resolution mass spectrum *m/e* 363.185015 ($C_{23}H_{25}NO_3$ requires 363.183425).

1 - *Styryl* - 3 - *acetyl* - 4 - *hydroxymethyl* - 1,8 - *dihydroazocine* - *tetrahydropyranyl ether* (**10b**). A soln of 1 - hydroxy - 4 - oxopent - 2 - yne tetrahydropyranyl ether (1.78 g, 7.5 mmol) and 1 - styryl - 1,2 - dihydropyridine 0.46 g (2.5 mmol) in benzene was stirred at 25°, under N_2 for 8 days. The solvent was removed *in vacuo* and the reaction was purified by chromatography (silica gel, 75:25 ether:hexane) to give 0.301 g (34%) of the desired **10b** IR (CHl) 2990 (m) and 1640 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.65 (s, 1H, H2), 7.30 (s, 5H, aromatic), 6.80 (d, 1H, J = 14.0 Hz, styryl AB quart.), 6.00 (d, 1H, J = 14.0 Hz, styryl AB quart.), 6.00–6.70 (m, 3H), 4.78 (m, 1H, pyran methine), 4.18–4.67 (m, 4H, OCH_2's), 3.28–4.54 (m, 2H, pyran OCH_2), 2.30 (s, 3H, CH_3), 1.70 (m, 6H, pyran CH_2); mass spectrum (70 eV) *m/e* (relative intensity) 365 (6, M^+), 322 (6); UV max (MeOH) 358 nm (ϵ 14100) 268 (10200); ^{13}C-NMR ($CDCl_3$) 19.6 (t, pyran CH_2), 25.4 (t, CH_2), 26.2 (t, CH_2), 30.7 (q, CH_3), 45.6 (t, NCH_2), 62.3 (t), 70.3 (t, OCH_2), 98.3 (d, pyran methine), 108.8 (d, β-styryl), 116.2 (s, C3), 138.8 (s), 144.9 (d), 196.4 (s, CO); high resolution mass spectrum *m/e* 365.200557 ($C_{23}H_{27}NO_3$ requires 365.199015).

t-Butyl 2-*methylsuccinate* (**17**). To a soln of lithium hexamethyldisilazide (from 4.31 mmol n-BuLi and 4.31 mmol hexamethyldisilizane) at 0° was added 10 mL anhyd THF and 0.396 g (2.28 mmol) of mono-t-butyl succinate in 10 mL dry THF. The mixture was stirred at 25° for 2 h. MeI (1.43 mL, 32 mmol, 10 eq) was added rapidly and the mixture was stirred for 2 h, cooled to 0°, poured into 0° cooled 5% NaOH. The resulting soln was washed twice with CH_2Cl_2, acidified to pH 3 with HCl, and extracted with CH_2Cl_2. The organic layer was dried and concentrated *in vacuo* to give an oil which on distillation (0.05 mm, 110°) gave 0.290 g of the desired crystalline ester (77%), m.p. 55–57°: IR ($CHCl_3$) 3100 (sbd), 2990 (m), 1720 (s) and 1160 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 10.6 (s, 1H, CO_2H), 2.3–3.0 (m, 3H, succinoyl), 1.45 (s, 9H, t-Bu), 1.19 (d, 3H, J = 9.0 Hz, CH_3); mass spectrum (70 eV) *m/e* (relative intensity) 173 (1), 115 (17), 87 (8), 73 (1), 59 (35), 57 (100), 56 (9), 55 (1); ^{13}C-NMR ($CDCl_3$) 177.3 (s, CO_2H), 174.6 (s, CO_2t-Bu), 80.7 (s, $\underline{C}Me_3$), 37.5 (d, CH), 36.7 (t, CH_2), 27.9 (q, $C\underline{Me}_3$), 16.9 (q, CH_3); high resolution mass spectrum of P-15 *m/e* 173.08120 ($C_8H_{13}O_4$ requires 173.08137).

t - Butyl 2 - *methyl* - 4 - *oxo* - 7 - *hydroxyhept* - 5 - *ynoate tetrahydropyranyl ether* (**19**). A soln of Et_3N (3.44 mL, 24.7 mmol), *o*-anisoyl chloride (4.22 g, 24.7 mmol), and t-butyl 2-methylsuccinate (4.60 g, 24.7 mmol) in 90 mL anhyd THF was stirred at − 10° under argon for 1 h and filtered. In another flask a soln of 3 - tetrahydropyranyloxy - 1 - propyne (3.46 g, 24.7 mmol) in 60 mL anhyd THF and n-BuLi (16.0 mL, 24.7 mmol) was stirred at 0° under argon for 1 h. The resulting lithium acetylide soln was added rapidly to the soln of the mixed anhydride at − 78° under argon and then allowed to stir 45 min. The mixture was warmed to 0° and $NaHCO_3$ aq was added. The mixture was extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and concentrated *in vacuo* to give an oil which was chromatographed on silica gel (30:70 ether:hexane) to give the desired **19** (3.24 g, 42%): IR ($CDCl_3$) 2985 (s), 2955 (s), 2230 (m), 1725 (s), 1680 (s), 1225 (sbd) and 1150 (s), cm^{-1}; ^{1}H-NMR (CDCl) δ 3.41–3.98 (m, 2H, THP OCH_2), 1.50–1.78 (m, 6H, THP methylenes), 4.81 (s, 1H, THP methine), 4.23 (s, 2, $C{\equiv}C\underline{CH}_2$), 2.41–3.11 (m, 3H, succinoyl), 1.17 (d, 3H, J = 7.0 Hz, CH_3), 1.46 (s, 9H, t-Bu); mass spectrum (70 eV) *m/e* (relative intensity) 310 (1, M^+), 237 (5), 57 (100), 56 (7), 55 (7); UV max (EtOH) 270 (ϵ 4570), 216 (13700); ^{13}C-NMR ($CDCl_3$) 27.9 (q, $C\underline{Me}_3$), 80.4 (s, $\underline{C}Me_3$), 174.0 (s, $\underline{C}O_2$t-Bu), 35.7 (d, succinoyl methine), 48.4 (t, succinoyl methylene), 184.7 (s, ketone), 84.5 (s, $\underline{C}{\equiv}CCH_2$), 88.2 (s, $C{\equiv}\underline{C}CH_2$), 61.8 (t, $C{\equiv}C\underline{C}H_2$), 97.1 (d, THP methine), 30.1 (t, THP C2), 18.9 (t, THP C3), 25.3 (t, THP C4), 53.7 (t, THP C5), 16.9 (q, CH_3); high resolution mass spectrum of M-73 *m/e* 237.11163 ($C_{13}H_{17}O_4$ requires 237.11267).

Mono-n-butyl succinate (**22**). Succinic anhydride (100 g,

1.0 mol) was refluxed with n-BuOH (12 mL, 1.3 mol) for 3 h. The mixture was then distilled (120°, 1.5 mm) to give the desired **22** (130 g, 76%) (Lit.[23] b.p. 136.5°).

Mono-n-butyl 2-methylsuccinate (**23**). Mono-n-butyl succinate (*10.0 g, 57.5 mmol*) in 50 mL of dry THF was added to a soln of lithium diisopropylamide (from diisopropylamine, 17.8 mL, 126.5 mmol) and n-BuLi (81.6 mL, 126.5 mmol) and the mixture was stirred for 1 h at −78°. MeI (10.7 mL, 172.5 mmol) was added and the mixture was stirred an additional 1 h at −78°. The mixture was then warmed to 0° and quenched with water (0°). This mixture was washed with $CHCl_3$. The aqueous layer was acidified to pH 3 with HCl and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and concentrated *in vacuo* giving a residue which was distilled (120°, 2 mm) to give the desired **23** (8.86 g, 83%): IR ($CHCl_3$) 2960 (s), 3000 (sbrd), 1710 (s), 1730 (s) and 1178 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 10.10 (s, 1H, CO_2H), 4.11 (t, 2H, J = 6.0 Hz, OCH_2), 2.18–3.13 (m, 3H, succinoyl), 0.63–1.82 (m, 7H, $CH_2CH_2CH_3$), 1.24 (d, 3H, J = 7.0 Hz, methyl); mass spectrum (70 eV) *m/e* (relative intensity) 133 (6, M^+), 129 (3), 115 (100), 101 (16), 87 (101), 73 (16), 57 (17), 56 (17); ^{13}C-NMR ($CDCl_3$) 177.5 (s, CO_2H), 174.8 (s, ketone), 64.6 (t, OCH_2), 37.3 (t, C2), 35.7 (d, C3), 30.7 (t, OCH_2CH_2), 19.1 (t, $OCH_2CH_2CH_2$), 16.9 (q, C3 methyl), 13.8 (q, n-butyl CH_3); high resolution mass spectrum of M-73 *m/e* 115.039807 ($C_5H_7O_3$ requires 115.039505).

1 - *Propyn* - 3 - *yl dimethyl* - *t* - *butylsilyl ether* (**25**). To a soln of imidazole (9.63 g, 141.5 mmol) and propargyl alcohol (3.17 g, 56.6 mmol) in 5 mL of anhyd DMF at 25° was added a soln of dimethyl - t - butylsilyl chloride (10.3 g, 67.9 mmol) in 10 mL dry DMF. The resulting mixture was stirred for 36 h diluted with pentane, washed with water, dried and fractionally distilled (45°, 10 mm) to give the desired **25** (8.56 g, 89% yield): IR ($CHCl_3$) 3308 (s), 2900 (s), 2130 (w), 1392 (m), 1368 (s), 1260 (s), 1090 (vs), 1004 (s), 840 (vs) and 630 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.32 (d, 2H, J = 3.0 Hz, CH_2), 2.38 (t, 1H, J = 3.0 Hz, CH), 0.94 (s, 9H, t-Bu), 0.14 (s, 6H, CH_3); ^{13}C-NMR ($CDCl_3$) 72.8 (d, acetylene), 82.5 (s, acetylene), 51.6 (t, CH_2O), 25.9 (q, *t*-butyl), 18.5 (s, $\underline{C}Me_3$), −5.1 (q, $SiMe_2$); mass spectrum (70 eV) *m/e* (relative intensity) 169 (71), 113 (18), 57 (51); high resolution mass spectrum of P-1 *m/e* 169.1036 ($C_9H_{17}SiO$ requires 169.1049).

n - *Butyl* 2 - *methyl* - 4 - *oxo* - 7 - *dimethyl* - *t* - *butylsilyloxyhept* - 5 - *ynoate* (**26**). Acid chloride **24** was prepared by heating a soln of **23** (5.49 g, 29.5 mmol) in $SOCl_2$ (4.3 mL, *59.0 mmol*) at 35° for 3 h followed by distillation (88°, 2.6 mm) yielding 4.72 g (78%). The silver acetylide of acetylene **25** was prepared as follows: 32 mL water and $AgNO_3$ (2.01 g, 11.8 mmol) in 32 mL MeOH, precipitated and redissolved by addition of conc NH_4OH. To this soln, in the dark, with stirring and under an argon atmosphere, was added actylene **25** (1.91 g, 11.2 mmol) in 4 mL MeOH. The mixture was stirred at 25° for 2 h and filtered. The ppt was washed with water and dried *in vacuo* yielding 2.57 g (78%) of the desired silver acetylide. Synthesis of the desired **26** was then accomplished by heating the silver acetylide (2.87 g, 10.4 mmol) with **24** (2.12 g, 10.4 mmol) in 10 mL anhyd CCl_4 for 4 h in the dark. The mixture was filtered and distilled (125°, 0.05 mm) to give the desired acetylenic ketone (2.53 g, 74%): IR ($CHCl_3$) 2970 (s), 2223 (m), 1730 (s), 1685 (s), 1260 (s), 1165 (s), 1100 (s) and 840 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.49 (s, 2H, $C{\equiv}C\underline{C}H_2$), 4.10 (t, 2H, J = 7.0 Hz, $O\underline{C}H_2Pr$), 2.44–3.22 (m, 3H, succinoyl), 1.21 (d, 2H, J = 7.0 Hz, succinoyl Me), 0.96–1.74 (m, OCH_2Pr), 0.93 (s, 9H, t-Butyl), 0.15 (s, 6H, $SiMe_2$); mass spectrum (70 eV) *m/e* (relative intensity) 283 (20), 267 (10), 209 (5), 143 (5), 73 (65), 57 (100); ^{13}C-NMR ($CDCl_3$) 184.0 (s, ketone), 174.3 (s, ester), 90.3 (s, $CO\underline{C}{\equiv}C$), 83.3 (s, $COC{\equiv}\underline{C}$), 64.4 (t, $O\underline{C}H_2Pr$), 51.5 (t, $C{\equiv}C\underline{C}H_2O$), 48.3 (t, succinoyl), 34.8 (d, succinoyl), 30.8 (t, $OCH_2\underline{C}H_2Et$), 25.8 (q, t-Butyl), 19.2 (t, $O(CH_2)_2\underline{C}H_2CH_3$), 18.1 (s, $\underline{C}$-Me_3), 16.9 (q, succinoyl methyl), 13.8 (q, $O(CH_2)_3\underline{C}H_3$), −5.1 (q, $SiMe_2$); high resolution mass spectrum of M-57 *m/e* 238.137535 ($C_{14}H_{23}O_4Si$ requires, 238.136544).

3 - [*t* - *Butyl* 2 - *methylsuccinoyl*] - 4 - *tetrahydropyranyloxymethyl* 1 - *styryl* - 1,8 - *dihydroazocine* (**29**). A soln of t-butyl 2 - methyl - 4 - oxo - 7 - tetrahydropyranyloxyhept - 5 - ynoate (3.24 g, 10.4 mmol) and 1 - styryl - 1,2 - dihydropyridine (1.90 g, 10.4 mmol) in 3 mL anhyd THF was stirred at 50° under argon for 4 days. An additional 2.3 g (12.6 mmol) of the dihydropyridine was added and stirring continued for 4 days. Concentration *in vacuo* gave a residue which was chromatographed on silica gel (50:50 ether:hexane) to give the desired **29**. (2.03 g, 40%): IR ($CHCl_3$) 3005 (s), 2985 (s), 1725 (s), 1650 (m), 1590 (sbd) and 1030 (sbd) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.28 (s, 5H, Ph), 5.98 (d, 1H, J = 13.5, PhC$\underline{H}$), 7.55 (s, 1H, C2), 6.10 (m, 1H, C5), 6.60 (dd, 1H, J = 3.0 and 10.0 Hz, C6), 6.10 (m, 1H, C7), 4.10–4.56 (m, 4H, C8, $C\underline{H}_2OTHP$), 4.69 (s, 1H, THP methine), 1.48–1.90 (m, 6H, THP C2), 3.36–4.10 (m, 2H, THP C5), 2.18–3.16 (m, 3H, succinoyl), 1.15 (d, 2H, J = 7.0, CH_3), 1.46 (s, 9H, t-Bu); mass spectrum (70 eV) *m/e* (relative intensity) 493 (4, M^+), 420 (2), 57 (50); UV max (EtOH) 365 (ϵ 14,000), 270 (ϵ 7,600), 228 (ϵ 11,000); ^{13}C-NMR ($CDCl_3$) 144.1 (d, C2), 115.8 (s, C3), 138.8 (s, C4), 125.1 (d, C5), 134.8 (d, C6), 126.0 (d, C7), 45.4 (t, C8), 196.4 (s, ketone), 41.2 (t, succinoyl methylene), 36.7 (d, succinoyl methine), 175.4 (s, ester), 79.7 (s, $\underline{C}Me_3$), 28.0 (q, CMe_3), 17.3 (q, CH_3), 62.2 (t, $\underline{C}H_2OTHP$), 98.2 (d, THP C1), 30.7 (t, THP C2), 19.6 (t, THP C3), 25.4 (t, THP C4), 70.2 (t, THP C5), 108.4 (d, Ph$\underline{C}$H), 136.4 (s, Ph Cl); high-resolution mass spectrum *m/e* 493.285101 ($C_{30}H_{39}NO_5$ requires 493.282795).

3 - [*t* - *Butyl* 2 - *methylsuccinoyl*] - 4 - *hydroxymethyltetrahydropyranyloxymethyl* 1 - *formyl* - 1,8 - *dihydroazocine* (**30**). O_3 in an oxygen stream was bubbled through a soln of 0.576 g (1.17 mmol) of 3 - [t - butyl 2 - methylsuccinoyl] - 4 - tetrahydropyranyloxymethyl - 1 - stryryl - 1,8 - dihydroazocine in 100 mL andyd MeOH at −50°. After 1 equivalent of O_3 had been added, 10 mL Me_2S in 10 mL anhyd MeOH was introduced and the mixture was warmed to 25°, and conc *in vacuo*. The product was purified by preparative tlc on silica gel (75:25 ether:hexane) giving 0.319 g (65%) of the desired **30**: IR ($CHCl_3$) 3040 (m), 3005 (s), 2975 (s), 2950 (s), 1710 (s), 1600 (sbd), 1150 (sbd) and 1030 (sbd) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.53, 8.19, 8.12 (s, s, s, 1H, formyl), 7.56 (s, 1H, C2), 5.80–6.27 (m, 1H, C5), 6.57 (dd, 1H, J = 2.0 and 10.0 Hz, C6), 5.80–6.27 (m, 1H, C7), 3.98–4.80 (m, 4H, C8, $C\underline{H}_2OTHP$), 4.66 (s, 1H, THP methine), 1.53–1.92 (m, 6H, THP methylenes), 3.38–3.98 (m, 2H, THP C5), 2.44–3.20 (m, 3H, succinoyl), 1.16 (d, 3H, J = 7.0 Hz, CH_3), 1.44 (s, 9H, t-Bu); mass spectrum (70 eV) *m/e* (relative intensity) 419 (1, M^+), 317 (1), 85 (100), 57 (65), 56 (3), 55 (4); UV max (MeOH) 238 nm (ϵ 11,800), 291 (ϵ 7640); ^{13}C-NMR ($CDCl_3$) 138.5 (d, C2), 121.7, 123.2 (s, s, C3), 137.5 (s, C4), 127.0 (d, C5), 136.1 (d, C6), 126.1 (d, C7), 38.4, 41.5 (t, t, C8), 163.6, 163.7 (d, d, CHO), 198.3, 198.5 (s, s, ketone), 42.0 (t, succinoyl methylene), 36.3 (d, succinoyl methine), 80.0 (s, $\underline{C}Me_3$), 28.0 (q, t-Bu CH_3), 17.3 (q, CH_3), 62.2 (t, $\underline{C}H_2OTHP$), 98.4 (d, THP methine), 30.5 (t, THP C2), 19.4 (t, THP C3), 25.4 (t, THP C4), 69.9 (t, THP C5), 175.1 (s, ester); high resolution mass spectrum of M-102 *m/e* 317.163124 ($C_{18}H_{23}NO_4$ requires 317.162685).

3 - [*t-Butyl* 2 - *methylsuccinoyl*] - 4 - *tetrahydropyranyloxymethyl* - 1 - *formyl* - 1,6,7,8 - *tetrahydroazocine* (**31**). A soln of 3 - [t - butyl 2 - methylsuccinoyl] - 4 - tetrahydropyranyloxymethyl - 1 - formyl - 1,8 - dihydroazocine (1.05 g, 2.51 mmol) in 140 mL EtOH containing 0.18 g 10% PdC was hydrogenated at 55 psi in a Parr apparatus. After uptake of 1 equiv H_2, the catalyst was removed by filtration. Concentration of the filtrate *in vacuo* followed by preparative tlc on silica gel (75:25 ether:hexane) gave the desired **31** (1.08 g, 100%): IR ($CHCl_3$) 3010 (s), 2985 (s), 1700 (s), 1610 (s), 1590 (s) and 1220 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.50, 8.13 (s, s, 1H, CHO), 7.09 (d, 1H, J = 7.0 Hz, C2), 5.77 (t, 1H, J = 8.0 Hz, C5), 4.63 (s, 1H, THP methine), 1.58 (m, 6H, THP methylenes), 1.14 (d, 3H, J = 7.0 Hz, CH_3), 1.43 (s, 9H, t-Bu); mass spectrum (70 eV) *m/e* (relative intensity) 421 (3, M^+), 348 (2), 57 (65), 56 (10), 55 (14); UV max (MeOH) 228 nm (ϵ 11,900), 288 nm (ϵ 14,800), ^{13}C-NMR ($CDCl_3$) 138.5 (d, C2), 119.0, 119.8 (s, s, C3), 135.4 (s, C4), 129.5, 128.8 (d, d, C5), 24.4 (t, C6), 20.9 (t, C7), 37.9 (t, C8), 163.8, 163.0 (d, d, CHO), 1.99.0 (s, ketone), 42.5 (t, succinoyl methylene), 36.2, 36.8 (d, d, succinoyl methine), 175.0 (s, ester), 79.9 (s, $\underline{C}Me_3$), 27.8 (q, CMe_3), 17.1 (q, CH_3), 61.9, 62.3 (t, t, $\underline{C}H_2OTHP$), 97.6, 99.1 (d, d, THP methine), 31.0 (t, THP C2), 19.4 (t, THP C3), 25.1 (t, THP C4), 69.0, 70.3 (t, THP C5); high resolution mass spectrum *m/e* 421.247403 ($C_{23}H_{35}NO_6$ requires 421.246405).

3 - [*t* - *Butyl* 2 - *methylsuccinoyl*] - 4 - *tetrahydropyranyloxy-*

methyl - 1 - formyl - 4,5 - epoxy - 1,4,5,6,7,8 - hexahydroazocine (**32**). To a soln of 0.118 g (0.280 mmol) of 3 - [t - butyl 2 - methylsuccinoyl] - 4 - tetrahydropyranyloxymethyl - 1 - formyl - 1,6,7,8 - tetrahydroazocine in 3 mL CH_2Cl_2 containing dry disodium hydrogen phosphate (43.7 mg, 0.308 mmol) at 0° was added a soln of 53.1 mg (0.280 mmol) *m*-chloroperoxygenzoic acid in 8 mL CH_2Cl_2 over a period of 75 min. Disodium hydrogen phosphate was added periodically to maintain neutrality. After stirring for 30 h the mixture was poured into 10% Na_2SO_3 aq. The separated organic layer was dried and conc *in vacuo*. Purification by preparative tlc on silica gel (80:20 ether:hexane) gave two separable mixtures of the diastereomeric epoxides **32** (91 mg, 89% based on recovered starging material): (Diastereomers R_f 0.32) IR ($CHCl_3$) 2940 (m), 1720 (s), 1685 (m), 1625 (m) and 1165 (m) cm^{-1}; ^{1}H-NMR ($CDCl_3$)δ 8.61 (s, 1H, CHO), 7.86 (s, 1H, C2), 1.58 (m, 6H, THP methylenes), 1.46 (s, 9H, t-Bu), 1.19 (d, 3H, J = 7.0 Hz, CH_3); mass spectrum (70 eV) *m/e* (relative intensity) 408 (2), 364 (3), 57 (37), 56 (3), 55 (6); UV max (EtOH) 272 nm (ϵ 6,500); ^{13}C-NMR ($CDCl_3$) 141.3, 141.0 (d, d, C2), 114.3, 114.5 (s, s, C3), 57.3, 57.5 (s, s, C4), 60.2, 61.0 (d, d, C5), 25.5 (t, C6), 24.8 (t, C7), 38.6 (t, C8), 164.1 (d, CHO), 197.8 (s, ketone), 43.2 (t, succinoyl methylene), 36.0 (d, succinoyl methine), 175.2 (s, ester), 79.9 (s, $\underline{C}Me_3$), 27.9 (q, CMe_3), 17.3 (q, CH_3), 61.5, 61.8 (t, t, $\underline{C}H_2OTHP$), 98.5, 99.1 (d, d, THP methine), 30.1 (t, THP C2), 19.1 (t, THP C3), 25.1 (t, THP C4), 70.5, 72.4 (t, t, THP C5); high resolution mass spectrum of M-29 *m/e* 408.2393 ($C_{22}H_{34}NO_6$ requires 408.2386). (Diastereomers R_f 0.43) IR ($CDCl_3$) 2950 (m), 1720 (s), 1690 (s) and 1145 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.62 (s, 1H, CHO), 7.80 (s, 1H, C2), 1.61 (m, 6H, THP methylenes), 1.46 (s, 9H, t-Bu), 1.20 (d, 3H, J = 7.0 Hz, CH_3); mass spectrum (70 eV) *m/e* (relative intensity) 437 (0.3, M^+), 408 (1), 364 (3), 57 (52), 56 (5), 55 (10); UV max (EtOH) 272 nm (ϵ 7400); ^{13}C-NMR ($CDCl_3$) 141.1, 141.4 (C2), 113.4, 113.5 (C3), 56.9, 57.4 (C4), 59.9, 61.0 (C5), 25.2 (C6), 24.4 (C7), 38.0, 38.2 (C8), 164.0 (CHO), 197.5 (ketone), 43.0 (succinoyl methylene), 35.8 (succinoyl methine), 174.8 (ester), 79.5 ($\underline{C}Me_3$), 27.6 (CMe_3), 16.9 (CH_3), 61.5, 61.9 ($\underline{C}H_2OTHP$), 98.0, 98.8 (THP methine), 29.8 (THP C2), 18.7, 19.0 (THP C3), 24.8 (THP C4), 71.8, 69.6 (THP C5); high resolution mass spectrum of M-29 *m/e* 408.2389 ($C_{22}H_{34}NO_6$ requires 408.2386).

7 - Tetrahydropyranyloxymethyl - 8 - [t - butyl 2 - methylsuccinoyl] - 9 - oxa - 2 - azabicyclo[4.2.1]non - 7 - ene (**34**). A soln of 3 - [t - butyl 2 - methylsuccinoyl] - 4 - tetrahydropyranyloxy - 1 - formyl - 4,5 - epoxy - 1,4,5,6,7,8 - hexahydroazocine (diasteriomers R_f 0.32 151 mg, 0.346 mmol) in 10 mL benzene and 4 mL MeOH containing NaOMe (0.830 mmol) was stirred at 0° for 15 min. The mixture was poured into ice water and extracted with CH_2Cl_2. The organic extracts were dried and conc giving a residue which was subjected to preparative tlc on silica gel (ether) giving the desired **34** (106 mg, 75%): IR ($CHCl_3$) 3250–3600 (m), 3360 (m), 2980 (s), 1720 (s), 1680 (s), 1630 (s), 1230 (sbd) and 1150 (sbd) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.80 (s, 1H, C2), 5.06 (dd, 1H, J = 2.0 and 6.0 Hz, C5), 4.70 (s, 1H, THP methine), 4.51 (s, 1H, CH_2OTHP), 3.28–3.86 (m, 2H, THP C5), 2.30–3.22 (m, 5H, succinoyl, NCH_2), 1.40–1.80 (m, 6H, THP methylenes), 1.40 (s, 9H, t-Bu), 1.12 (d, 3H, J = 7.0 Hz, CH_3); mass spectrum (70 eV) *m/e* (relative intensity) 294 (10), 57 (32), 56 (32), 55 (75); UV max (EtOH) 240 nm (ϵ 5910); ^{13}C-NMR ($CDCl_3$) 94.5 (d, C2), 128.7, 129.2 (s, s, C3), 158.4, 158.8 (s, s, C4), 82.4, 82.6 (d, d, C5), 30.3 (t, C6), 29.1 (t, C7), 45.0 (t, C8), 62.2 (t, CH_2OTHP), 98.5, 98.9 (d, d, THP methine), 30.7 (t, THP C2), 19.3 (t, THP C3), 25.2 (t, THP C4), 63.1, 63.8 (t, t, THP C5), 195.4 (s, ketone), 42.5 (t, succinoyl methylene), 35.2 (d, succinoyl methine), 17.1 (q, CH_3), 174.9 (s, ester), 79.9 (s, $\underline{C}Me_3$), 27.8 (q, CMe_3); high resolution mass spectrum M-101 *m/e* 294.1710 ($C_{16}H_{24}NO_4$ requires 294.1705).

3 - [t - Butyl 2 - methylsuccinoyl] - 4 - tetrahydropyranyloxymethylene - 5 - hydroxy - 1,5,6,7,8 - pentahydroazocine **35**. A soln of **34** (87 mg, 0.213 mmol) and NaOMe (0.426 mmol) in 5 mL anhyd MeOH was stirred at 25° under argon for 4.5 h. The reaction was quenched with water (0°) and acidified to pH 8 with 10% HCl. This mixture was extracted with $CHCl_3$, the layers were dried and conc *in vacuo*. The crude mixture was purified by chromatography on silica gel (Et_2O) giving the desired **34** (56 mg, 62%): IR ($CHCl_3$) 3459 (s), 3370 (m, brd), 3005 (m), 2940 (s), 2862 (m), 1715 (s), 1372 (m) and 1160 (sbrd) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.66 (m, 1H, C2), 5.94, 5.97 (s, s, 1H, vinyl), 5.54 (brds, 1H, NH), 5.02 (brds, 1H, C5), 4.90 (s, 1H, THP methine), 3.26–4.44 (m, 2H, THP OCH_2), 2.16–3.24 (m, 3H, succinoyl), 3.26–4.44 (m, 2H, NCH_2), 1.40 (s, 9H, t-butyl), 1.11, 1.14 (d, d, 3H, J = 7.0 Hz, Me); mass spectrum (70 eV) *m/e* (relative intensity) 409 (10, M^+), 336 (26), 159 (48), 80 (6), 57 (54), 56 (8), 55 (12); UV max (EtOH) 307 nm (ϵ 9600), 243 (3500); ^{13}C-NMR ($CDCl_3$) 198.1, 198.3 (s, s, ketone), 176.0 (s, ester), 149.8, 149.6 (d, d, C2), 144.8, 144.1(d, d, vinyl), 118.0, 117.7 (s, s, C3), 104.8 (s, C4), 98.7 (d, THP methine), 79.7 (s, $\underline{C}Me_3$), 68.7 (d, C5), 61.9 (t, THP OCH_2), 40.2 (t, succinoyl C2), 40.1 (t, NCH_2), 37.0 (d, succinoyl C3), 29.6, 29.5 (d, d, C6, C7), 28.0 (q, t-butyl), 25.1 (t, THP CH_2), 17.1 (q, methyl); high resolution mass spectrum *m/e* 409.2457 ($C_{33}H_{35}NO_6$ requires 409.2464).

3 - [t-Butyl 2 - methylsuccinoyl] - 4 - tetrahydropyranyloxymethyl - 1 - azabicyclo[3.3.0]octa - 2,4 - diene (**42**)

Acid catalyzed rearrangement of 7 - tetrahydropyranyloxymethyl - 8 - [t - butyl 2 - methylsuccinoyl] - 9 - oxa - 2 - azabicyclo[4.2.1]non - 7 - ene. A soln of 42 mg (0.103 mmol) of the bicyclic amino ether in 5 mL dry pyridine saturated with pyridinium hydrochloride was stirred under argon at 25° for 4 days. The mixture was poured into 0° cooled $NaHCO_3$ aq and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and conc *in vacuo* giving a residue which was purified by preparative tlc on silica gel (Et_2O) giving recovered starting **34** (1.4 mg, 3%), **35** (4.1 mg, 11%), and the desired **42** (2.4 mg, 6%): **42** IR ($CHCl_3$) 3010 (m), 2943 (s), 1720 (s), 1509 (m), 1452 (m), 1391 (m), 1368 (s), 1155 (s) and 695–790 (mbd) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.13 (s, 1H, pyrrole), 4.62, 4.86 (d, 2H, J = 11, hydroxymethylene), 4.69 (s, 1H, THP methine), 3.86 (t, 2H, J = 7.0 Hz, C8), 3.27–3.70 (m, 2H, THP OCH_2), 2.18–3.24 (m, 3H, succinoyl), 2.86 (t, 2H, J = 7.0 Hz, C6), 2.43 (t, 2H, J = 7.0 Hz, C7), 1.44–1.80 (m, 6H, THP CH_2), 1.41 (s, 9H, t-Bu), 1.15 (d, 3H, J = 7.0 Hz, CH_3); mass spectrum (70 eV) *m/e* (relative intensity) 391 (20, M^+), 318 (17), 306, (50), 290 (17), 57 (77), 56 (20), 55 (25); UV max (EtOH) 260 nm (ϵ 7600); high resolution mass spectrum for P-THP *m/e* 306.1744 ($C_{17}H_{24}NO_4$ requires 306.1756).

3 - [t - Butyl 2 - methylsuccinoyl] - 4 - tetrahydropyranyloxymethyl - 1,8 - dihydroazocine (**43**). A soln of NaOEt (5 mL, 0.75 mmol) in EtOH at 0° containing 0.103 g (0.246 mmol) of 3 - [t - butyl 2 - methylsuccinoyl] - 4 - tetrahydropyranyloxymethyl 1 - formyl - 1,8 - dihydroazocine was stirred under argon for 10 min, poured into $NaHCO_3$ aq and extracted with ether. The ethereal extracts were dried and conc *in vacuo* giving a residue which was subjected to preparative tlc on silica gel (70:30 ether:hexane) giving 71.5 mg (0.183 mmol, 74%) of the desired **43**: IR ($CHCl_3$) 3460 (m), 3380 (mbd), 3010 (s), 2985 (s), 1710 (s), 1590 (s), 1150 (mbd) and 1075 (sbd) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.42 (d, 1H, J = 9.0 Hz, C2), 6.57 (dd, 1H, J = 2.0 and 10.0 Hz, C6), 5.63–6.20 (m, 2H, C5, C7), 4.65 (s, 1H, THP methine), 1.45–2.00 (m, 6H, THP methylenes), 5.03–5.59 (m, 1H, NH), 2.12–3.08 (m, 3H, succinoyl), 1.41 (s, 9H, t-Bu), 1.15 (d, 3H, J = 7.0 Hz, CH_3); mass spectrum (70 eV) *m/e* (relative intensity) 391 (5, M^+), 318 (5), 57 (90), 56 (17), 55 (29) cm^{-1}; UV max (EtOH) 223 nm (ϵ 7,610), 285 (6,730), 309 (6,880); ^{13}C-NMR ($CDCl_3$) δ 147.0 (d, C2), 112.2 (s, C3), 139.1 (s, C4), 127.9 (d, C5), 136.3 (d, C6), 125.3 (d, C7), 40.4 (t, C8), 195.4 (s, ketone), 41.8 (t, succinoyl methylene), 37.0 (d, succinoyl methine), 175.8 (s, ester), 79.9 (s, $\underline{C}Me_3$), 28.0 (q, CMe_3), 17.3 (q, CH_3), 62.4 (t, $\underline{C}H_2OTHP$), 98.3 (d, THP methine), 30.8 (t, THP C2), 19.7 (t, THP C3), 25.5 (t, THP C4), 70.3 (t, THP C5); high resolution mass spectrum *m/e* 391.234394 ($C_{22}H_{33}NO_5$ requires 391.235845).

3 - [t - Butyl 2 - methylsuccinoyl] - 4 - tetrahydropyranyloxymethyl - 1,6,7,8 - tetrahydroazocine (**44**)

Hydrogenation of 3 - [t - butyl 2 - methylsuccinoyl] - 4 - tetrahydropyranyloxymethyl - 1,8 - dihydroazocine. A soln of **43** (55 mg, 0.14 mmol) containing 10% Pd/C (44 mg) in 100 mL absolute EtOH was hydrogenated in a Parr apparatus for 20 min. Filtration followed by conc *in vacuo* gave an oil which was subjected to tlc on silica gel (Et_2O) affording the desired **44** (46 mg, 83%): IR ($CHCl_3$) 3440 (m), 3250 (mbr), 3000 (m), 2920 (s), 1715 (s), 1595 (s), 1365 (m) and 1150 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ

7.53, 7.45 (d, d, 1H, J = 4, 4 Hz, C2), 5.73 (brds, 1H, NH), 5.53 (t, 1H, J = 8.0 Hz, C5), 4.70 (s, 1H, THP methine), 4.57 (s, 2H, CH_2OTHP), 1.57–2.00 (m, 6H, THP methylenes), 1.44 (s, 9H, t-butyl), 1.21 (d, 3H, J = 7.0 Hz, methyl); mass spectrum (70 eV) *m/e* (relative intensity) 393 (1.5, M^+), 85 (58), 57 (83), 56 (67), 55 (92); UV max (EtOH) 303 nm (ϵ 12,800) ^{13}C-NMR ($CDCl_3$) 196.0 (s, ketone), 175.7 (s, ester), 148.2 (d, C2), 137.8 (s, C4), 126.6 (d, C5), 108.3 (s, C3), 97.6 (d, THP methine), 79.7 (s, $\underline{C}Me_3$), 70.9 (t, THP OCH_2), 62.4 (t, CH_2OTHP), 40.8 (t, succinoyl C2), 39.9 (t, NCH_2), 37.0 (d, succinoyl C3), 30.7 (d, THP CH_2), 25.4 (t, THP CH_2), 24.7 (t, C6), 22.6 (t, C7), 19.8 (t, THP CH_2), 17.3 (q, methyl); high resolution mass spectrum of M-1 *m/e* 391.235394 ($C_{22}H_{35}NO_5$ requires 391.235845).

Sodium methoxide deformylation of 3 - [*t - butyl* 2 - *methylsuccinoyl*] - 4 - *tetrahydropyranyloxymethyl* - 1 - *formyl* - 1,8 - *dihydroazocine.* A soln of **31** (254 mg, 0.603 mmol) in 6 mL dry MeOH containing 1.206 mmol NaOMe was stirred under argon for 15 min. The mixture was poured into water (0°), acidified to pH 8 with 10% HCl, and extracted with $CHCl_3$. The $CHCl_3$ layers were dried and conc *in vacuo* giving pure desired **44** (229 mg, 90%).

3 - [*n - Butyl* 2 - *methylsuccinoyl*] - 4 - *dimethyl* - *t* - *butylsilyloxymethyl* 1 - *styryl* - 1,8 - *dihydroazocine* (**45**). A mixture of **26** (103 mg, 0.313 mmol) and 1 - styryl - 1,2 - dihydropyridine (290 mg) and 3 mL anhyd THF was stirred under argon at 50° for 4 days. The mixture was cooled to 25° and stirred in the open air for 4 h to destroy the excess dihydropyridine. Concentration of the mixture gave a residue which was chromatographed on silica gel (60:40 petroleum ether:ether) giving the desired **45** (56 mg, 34%): IR ($CHCl_3$) 2945 (s), 1720 (s), 1640 (m), 1585 (s), 1160 (s) and 833 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.54 (s, 1H, C2), 7.28 (s, 5H, Ph), 6.80 (d, 1H), (J = 4.0 Hz, NCH=CHPh), 6.61 (d, 1H, J = 11.0 Hz, C5), 6.06 (m, 2H, C6, C7), 5.95 (d, 1H, J = 14.0 Hz, NCH=CHPh), 4.22 (s, 2H, CH_2OSi) 4.14 (m, 2H, NCH_2), 4.07 (t, 2H, J = 7.0 Hz, OCH_2Pr), 2.46–3.08 (m, 3H, succinoyl), 1.98–1.78 (m, 7H, $OCH_2\underline{Pr}$), 1.17 (d, 3H, J = 7.0 Hz, succinoyl methyl), 0.95 (s, 9H, t-butyl), 0.08 (s, 6H, $SiMe_2$); mass spectrum (70 eV) *m/e* (relative intensity) 523 (2, M^+), 412 (24), 384 (3), 145 (7), 115 (29), 75 (100), 73 (58), 57 (30); UV max (EtOH) 362 nm (ϵ 11000), 272 (5970), 231 (10700); ^{13}C-NMR ($CDCl_3$) 196.1 (s, ketone), 176.0 (s, ester), 143.8 (d, C2), 141.2 (s, C4), 134.7 (d, C6), 136.9 (d, NCH=CHPh), 136.3 (s, Ph), 126.0 (d, C7), 123.8 (d, C5), 128.5, 125.4, 125.0 (d, d, d, Ph), 115.4 (s, C3), 108.8 (d, NCH=CHPh), 66.0 (t, CH_2OSi), 64.2 (t, OCH_2Pr), 41.3 (t, succinoyl), 35.8 (d, succinoyl), 30.7 (t, $OCH_2\underline{C}H_2Et$), 25.9 (q, $\underline{C}Me_3$), 19.3 (t, $O(CH_2)_2\underline{C}H_2CH_3$), 18.3 (s, $\underline{C}Me_3$), 17.3 (q, succinoyl methyl), 13.7 (q, $\overline{O(CH_2)_3CH_3}$),−5.2 (q, $SiMe_2$); high resolution mass spectrum *m/e* 523.3107 ($C_{31}H_{45}NSiO_4$ requires 523.3118).

3 - [*n - Butyl* 2 - *methylsuccinoyl*] - 4 - *dimethyl* - *t* - *butylsilyloxymethyl* - 1 - *formyl* - 1,8 - *dihydroazocine* (**46**). O_3 in an oxygen stream was passed through a soln of 3 - [n - Butyl 2 - methylsuccinoyl] - 4 - dimethyl - t - butyl - silyloxymethyl - 1 - styryl - 1,8 - dihydroazocine (378 mg, 0.723 mmol) in 15 mL anhyd MeOH at −78°. After addition of one equiv O_3 a methanol soln of Me_2S (2 mL in 2 mL MeOH) was added. The mixture was warmed to 25°, and solvent was removed *in vacuo.* Silica gel chromatography (50:50 ether:petroleum ether) gave the desired **46** (202 mg, 62%): IR ($CHCl_3$) 2945 (s), 2920 (s), 1700 (sbrd), 1612 (s), 1249 (m), 1150 (sbrd), 1070 (m) and 832 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.50, 8.19, 8.13 (s, s, s, 1H, CHO), 7.49 (s, 1H, C2), 6.58 (brdd, 1H, J = 10.0 Hz, C5), 6.19 (m, 1H, C7), 5.90 (dd, 1H, J = 4.0 and 10.0 Hz, C6), 4.53 (m, 2H, C8), 4.21 (m, 2H, $SiOCH_2$), 4.08 (t, 2H, J = 6.5 Hz, CO_2CH_2), 2.37–3.04 (m, 3H, succinoyl), 1.17–1.67 (m, 7H, $CH_3CH_2CH_2$), 1.22 (d, 3H, J = 7.0 Hz, CH_3), 0.91 (s, 9H, *t*-Bu), 0.07 (s, 6H, $SiMe_2$); mass spectrum (70 eV) *m/e* (relative intensity) 449 (18), 392 (42), 376 (15), 115 (64), 73 (100), 57 (36); UV max (EtOH) 237 nm (ϵ 10,400), 290 (8000); ^{13}C-NMR ($CDCl_3$) 203.3 (s, ketone), 175.6 (s, ester), 162.1, 162.8 (d, d, CHO), 139.5 (d, C2), 139.5 (s, C4), 135.9 (d, C5), 126.1 (d, C7), 124.5 (d, C6), 120.9 (s, C3), 65.2 (t, $SiOCH_2$), 64.0 (t, CO_2CH_2), 41.9 (t, C8), 25.7 (q, t-Bu), 19.0 (t, $CO_2CH_2\underline{C}H_2CH_2$), 14.0 (q, *n*-Bu CH_3), −5.5 (q, $SiMe_2$); high resolution mass spectrum *m/e* 449.2582 ($C_{24}H_{39}NSiO_5$ requires 449.2596).

3 - [*n - Butyl* 2 - *methylsuccinoyl*] - 4 - *dimethyl* - *t* - *butylsilyloxymethyl* - 1 - *formyl* - 1,6,7,8 - *tetrahydroazocine* (**47**). 3 - [n - Butyl 2 - methylsuccinoyl] - 4 - dimethyl- t - butylsilyloxymethyl - 1 - formyl - 1,8 - dihydroazocine (221 mg, 0.492 mmol) in 100 mL EtOH was hydrogenated in a Parr apparatus over 10% Pd/C. After 20 min at 50 psi the soln was filtered, the filtrate conc *in vacuo.* The residue was purified by chromatography on silica gel (40:60 ether:Petroleum ether) giving the desired **47** as a light yellow oil (166 mg, 74%): IR ($CDCl_3$) 2955 (s), 1708 (sbd), 1612 (s), 1250 (m), 1060 (s) and 835 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.7, 8.51 (s, s, 1H, CHO), 7.50, 7.57 (s, s, 1H, C2), 5.77 (m, 1H, C5), 4.27 (s, 2H, $SiOCH_2$), 4.07 (t, 2H, J = 7.0 Hz, CO_2CH_2), 0.88 (s, 9H, t-Bu), 0.04 (s, 6H, $SiMe_2$); high resolution mass spectrum (70 eV) *m/e* (relative intensity) 523 (13, M^+), 466 (3), 57 (56), 56 (10); UV max (EtOH) 287 nm (10700) 228 (7880); ^{13}C-NMR ($CDCl_3$) 198.6 (s, ketone), 175.6 (s, ester), 139.6, 139.1 (d, d, C2), 118.9, 118.8 (s, s, C3), 138.1, 138.0 (s, s, C4), 127.5 (d, C5), 24.5 (t, C6), 21.7 (t, C7), 38.0 (t, C8), 163.9, 163.3 (d, d, CHO), 65.5 (t, $\underline{C}H_2OSi$), 64.3 (t, $CO_2\underline{C}H_2$), 42.6 (t, succinoyl), 35.6 (d, succinoyl), 30.7 (t, $OCH_2\underline{C}H_2$), 19.2 (t, $OCH_2CH_2\underline{C}H_2$), 13.7 (q, n-Bu $\underline{C}H_3$), 25.9 (q, $\underline{C}Me_3$), 18.1 (s, $\underline{C}Me_3$), −5.2 (q, $SiMe_2$); high resolution mass spectrum *m/e* 451.2661 requires 451.2754).

3 - [*n - Butyl* 2 - *methylsuccinoyl*] - 4 - *dimethyl* - *t* - *butylsilyoxymethyl* - 1,6,7,8 - *tetrahydroazocine* (**48**). To 3 - [n - Butyl 2 - methylsuccinoyl] - 4 - dimethyl - t - butylsilyloxymethyl - 1 - formyl - 1,6,7,8 - tetrahydroazocine (264 mg, 0.585 mmol) in 4 mL anhyd MeOH under N_2 at 0° was added NaOMe (30 mg, 1.29 mmol) in 1.2 mL anhyd MeOH. The mixture was stirred for 5 min and quenched with cold water. The aqueous soln was acidified to pH 3 with HCl and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and conc *in vacuo.* Chromatographic purification of the residue on silica gel (Et_2O) gave the desired **48** as a yellow oil (234 mg, 95%): IR ($CHCl_3$) 3445 (m), 3340 (brdw), 2945 (s), 2930 (s), 1720 (s), 1250 (m), 1170 (m), 1060 (m), 835 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.31 (m, 1H, C2), 5.55 (t, 1H, J = 8.0 Hz, C5), 4.76 (brds, 1H, NH), 4.00–4.42 (m, 2H, C8), 4.32 (s, 2H, $SiOCH_2$), 4.07 (t, J = 6.0 Hz, CO_2CH_2), 2.71–3.13 (m, 3H, succinoyl), 1.15 (d, 3H, J = 7.0 Hz); mass spectrum (70 eV) *m/e* (relative intensity) 423 (20, M^+), 381 (3), 75 (100), 73 (97), 57 (43); UV max (EtOH) 304 nm (ϵ 13,500); ^{13}C-NMR ($CDCl_3$) 195.8 (s, ketone), 176.6 (s, ester), 147.9, 148.1 (d, d, C2), 108.2 (s, C3), 140.1 (s, C4), 124.4, 124.7 (d, d, C5), 24.6 (t, C6), 23.3 (t, C7), 39.9 (t, C8), 65.9 (t, $\underline{C}H_2OSi$), 64.1 (t, $CO_2\underline{C}H_2$), 40.9 (t, succinoyl), 36.1 (d, succinoyl), 30.6 (t, $CO_2CH_2\underline{C}H_2$) 25.9 (q, $\underline{C}Me_3$), 18.3 (s, $\underline{C}Me_3$), 19.1 (t, $OCH_2\underline{C}H_2CH_2$), 17.3 (q, CH_3), 13.7 (q, n-Bu CH_3), −5.1 (q, $SiMe_2$); high resolution mass spectrum *m/e* 423.279276 ($C_{23}H_{41}NSiO_4$ requires 423.280464).

Bromination of 3 - [*t - butyl* 2 - *methylsuccinoyl*] - 4 - *tetrahydropyranyloxymethyl* - 1,6,7,8 - *tetrahydroazocine.* A soln of Br_2 (0.026 mL, 0.509 mmol) in 3 ml anhyd MeOH was added over a period of 1 h with stirring to a soln of **44** (125 mg, 0.32 mmol) in 4 ml anhyd MeOH and 0.44 mL Et_3N at 0°. After stirring for an additional 30 min solvent was removed *in vacuo* and the residue obtained was purified by tlc on silica gel (Et_2O) giving the desired **42** (46 mg, 37%) and starting material (36 mg).

3 - [*n - Butyl* 2 - *methylsuccinoyl*] - 4 - *dimethyl* - *t* - *butylsilyloxymethyl* - 1 - *azabicyclo*[3.3.0]*octa* - 2,4 - *diene* (**42**). To 3 - [n - butyl 2 - methylsuccinoyl] - 4 - dimethyl - t - butylsilyloxymethyl - 1,6,7,8 - tetrahydroazocine (68 mg, 0.16 mmol) in 2 mL anhyd MeOH at 0° under N_2, was added Et_3N (2 mL, 160 mmol) in 4 mL anhyd MeOH. After stirring for 5 min, solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel (ether) giving 37 mg of starting material and 14 mg of a product mixture which contained approximately 30% of the desired **42** (NMR analysis approx. 10% yield): IR ($CHCl_3$) 2957 (s), 1768 (s), 1725 (s), 1505 (m), 1070 (s) and 839 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.26 (s, 1H, pyrrole), 4.96 (s, 2H, $\underline{C}H_2OSi$), 4.05 (t, 2H, J = 6.0 Hz, $CO_2\underline{C}H_2$), 3.90–4.13 (m, 2H, $NC\underline{H}_2$), 0.89 (s, 9H, t-Bu), 0.09 (s, 6H, $SiMe_2$).

3 - [*t - Butyl* 2 - *methylsuccinoyl*] - 4 - *formyl* - 1,6,7,8 - *tetrahydroazocine* (**51**). *Moffat oxidation of azocine* **35**. To a soln of K_2CO_3 (210 mg, 1.52 mmol) in 1.5 mL anhyd DMSO argon was added Ac_2O (0.29 mL, 3.0 mmol) followed by **35** (6.23 mg,

0.152 mmol) in 1.5 mL anhyd DMSO. The mixture was stirred at 25° for 6 h, cooled to 0°, quenched with cold $NaHCO_3$ aq, stirred 30 min and extracted with $CHCl_3$. Concentration of the $CHCl_3$ layer *in vacuo* gave a crude product which was purified by preparative tlc (silica, Et_2O) to give 29.1 mg (50%) of **51**: IR ($CHCl_3$) 1710 (s), 1680 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.32 (s, 1H, CHO), 6.32 (dd, 1H, J = 8.0 and 8.2 Hz, C5), 7.38 (d, 1H, J = 8.0 Hz C2), 4.92 (bds, 1H, NH), 1.34 (s, 9H, t-Bu), 1.04 (d, 3H, J = 7.0 Hz, CH_3); UV max (EtOH) 294 nm (ϵ 5600); high-resolution mass spectrum *m/e* 307.1789 ($C_{17}H_{24}NO_4$ requires 307.1783).

Bromination of azocine **44**. To **44** (46.1 mg, 0.117 mmol) in 5 mL anhyd CH_2Cl_2 under argon at 0° was added Br_2 (6 mL, 0.177 mmol) in 0.5 mL dry CH_2Cl_2 with stirring. After 15 min a few drops of Et_3N were added followed by addition of cold $NaHCO_3$ aq and the resulting mixture was extracted with $CHCl_3$. The $CHCl_3$ layers were dried and conc *in vacuo* to give an oil which was purified by preparative tlc (silica gel, Et_2O) to give **51** (8.2 mg, 23%).

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