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Tandem Radical Cyclisations : Synthesis of Lysergic Acid Derivatives

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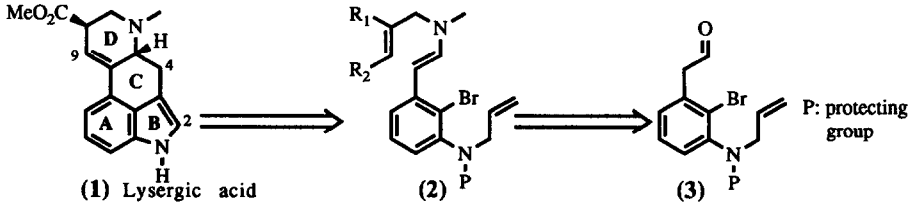
Abstract: A novel free radical cyclisation approach for the synthesis of lysergic acid analogues has been investigated. The homolytic cleavage of carbon-bromine bond, mediated by tri-n-butyltin hydride, led to the development of a method for the construction of 3,4-disubstituted dihydroindoles *via* single cyclisation; hexahydrobenz[cd]indoles *via* double tandem cyclisations and both octahydroindolo[6,5,4-cd]indoles and decahydroindolo[4,3-fg]quinolines *via* triple radical cyclisations. A successful tandem double 5-exo-trig,6-endo-trig cyclisation of aryl radical generated from N-3-[3-(N-acetyl-N-allylamino)-2-bromophenyl]-5-(carbomethoxy)-1,4,5,6-tetrahydro-N-methylpyridine afforded methyl 1-acetyl-2,3,9,10-tetrahydrolysergate.

Ergot alkaloids possess biological activity which is well documented[1]. Pharmacological activity of naturally occurring lysergic acid amides has been known since 1582 [2]. Synthetically prepared derivatives of lysergic acid (**1**) have also been shown to possess activity at 5-HT and adrenaline receptor sites [3], amongst others. The wide biological profile of ergot alkaloids, and the fact that lysergic acid (**1**) is the starting material for the synthesis of many of other ergot alkaloids in both bio and organic synthesis, stimulated the interest in this field, and eight total syntheses of lysergic acid (**1**) have appeared in the literature to date [4]. However none of these chemical syntheses can compete with the fermentation process that is used in the production of lysergic acid (**1**) because they are lengthy and expensive. Design and synthesis of new analogues of lysergic acid remains desirable in this field. In this respect, preparation of despyrrole analogues of ergot alkaloids [5], 9,10-dihydrolysergic acid derivatives [6], 6-alkyl-8-ergolenes and 6-methyl-8-amino ergolenes [7] are worthy of mention.

We previously reported [8] use of tandem radical cyclisation reactions for the construction of the lysergic acid framework. In this account we wish to give the full details of this work and to describe the synthesis of methyl 1-acetyl-2,3,9,10-tetrahydrolysergate.

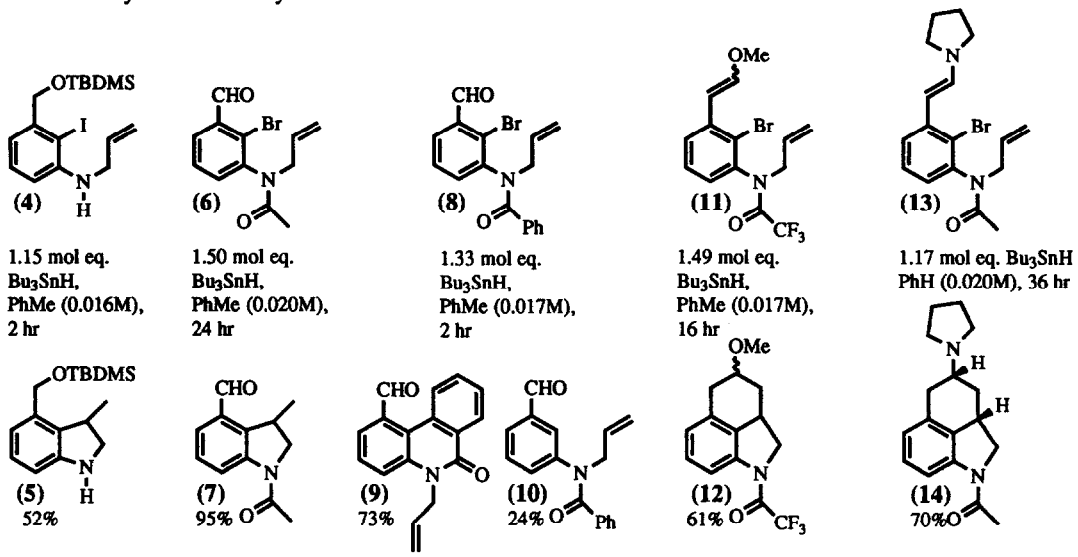
The retrosynthetic analysis for this programme is shown in scheme 1.



(**1**) Lysergic acid (**2**) (**3**)

Scheme 1

Free radical chemistry is one of the growing areas of the organic synthesis which has been extensively reviewed in recent years [9]. With careful planning and selection of conditions, the tandem radical cyclisation reaction can be used as a very versatile tool for making carbon-carbon bonds leading to complex molecules [10]. We anticipated that homolytic cleavage of the carbon-bromine bond in the enamine (2) ,where R_1 and R_2 groups represent different functional groups as shown later in the text, would create an aryl radical which would then commence the triple radical cyclisation. In order to test the utility of this approach, we first investigated single and double cyclisations of aryl radicals as shown in table 1.



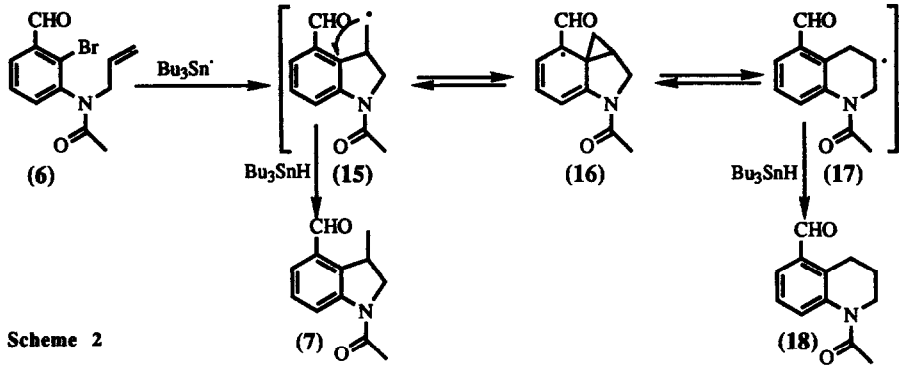
a) All cyclisations were performed using syringe pump technique in the presence of catalytic amounts of AIBN

Table 1: Single and Double Aryl Radical Cyclisations

In the first four entries, a range of protecting groups for the N-allyl amine moiety was tested in order to establish the best conditions for the proposed triple tandem radical cyclisation reactions. The allylic amine (**4**) bears no protecting group on the nitrogen atom, which did not alter the reaction process. The indoline (**5**) was obtained in good yield. A methyl doublet at 1.32 ppm in the proton n.m.r. spectrum clearly demonstrates that the aryl radical generated by the homolytic cleavage of the carbon-iodine bond cyclises *via* a 5-exo-trig pathway. In the second entry, N-acetyl protected N-allylamine (**6**) was tested; this gave the indoline (**7**) after a successful cyclisation reaction. No other product (**18**) arising from a possible neophyl rearrangement, as reported by Parker [11] for similar systems, was observed. This shows that even in very dilute solutions and under slow addition conditions (0.020M, 24 hr) the methyl radical (**15**) generated after the ring closure is short lived and does not add to the aromatic ring to initiate the ring expansion reaction as shown in scheme 2.

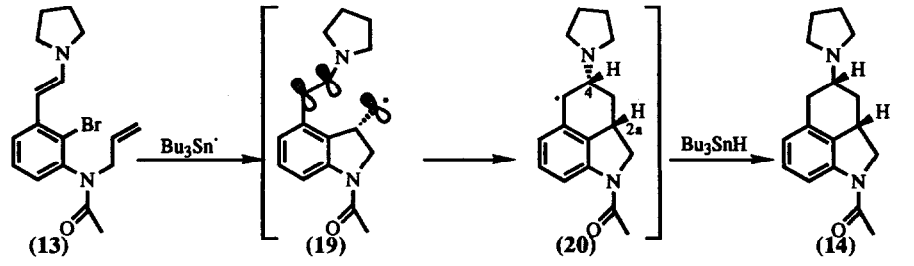
Apparently, the small acetyl group does not cause any problem related to restriction of rotation on the aryl carbon-nitrogen bond during the radical cyclisation. On the other hand, radical cyclisation of N-benzoyl protected N-allyl amine (**8**) gave the quinolone (**9**) as the major product along with the reduced product (**10**). No product arising from the usual 5-exo addition to the double bond was observed. This result was in agreement with the results of Togo [12] for similar systems, and was explained by conformational preference due to restricted

rotation on the carbon-nitrogen bond. As a result, there is a strong preference for a configuration with the radical centre close to the phenyl ring which results in addition to the aromatic ring to afford the product.



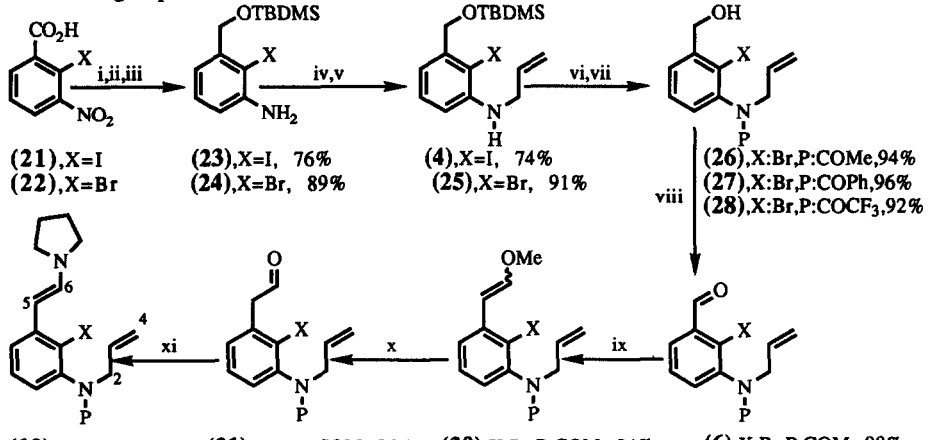
Scheme 2

With the single radical cyclisations tested, double tandem radical cyclisation reactions of the enol ether (**11**) and the enamine (**13**) were investigated. When a 1:1 mixture of Z and E enol ether (**11**) was subjected to radical cyclisation under the conditions described, the tricycle (**12**) was obtained as a 1:1 mixture of stereoisomers at the carbon atom bearing the methoxy group. The introduction of a N-trifluoroacetyl group also allowed the aryl radical to cyclise onto the double bond. The nucleophilic methyl radical generated after the first 5-exo cyclisation adds to the electron rich enol ether bond in a 6-endo fashion to afford the observed product (**12**). This is the first example of a N-trifluoroacetyl protecting group being used in aryl radical cyclisation reactions of 6-hexenyl systems containing heteroatoms at the side chain. Use of the trifluoroacetyl moiety as a protecting group offers an advantage which is its facile removal in the hydrolysis step. The last entry in table 1 demonstrates the use of enamine (**13**) which is the model study for the tandem cyclisations to construct the lysergic acid ring system. When the enamine (**13**) was treated with tri-n-butyltin hydride as described above, the hexahydrobenzindoline (**14**) was obtained *via* a 5-exo-trig,6-endo-trig pathway. By examination of molecular models, the relative stereochemistry of the protons at the ring junctions seems likely to be *cis*. The nucleophilic methyl radical (**19**) attacks the electron rich enamine double bond from below maintaining the maximum p-orbital overlap, and as a result H-4 is forced to the β face. The resulting benzylic radical (**20**) is then quenched to give the product (**14**). This deduction is supported by proton n.m.r.; the quartet at 1.40 ppm is typical of similar systems with H-2a,H-4 *cis* stereochemistry [13] (scheme 3).



Scheme 3

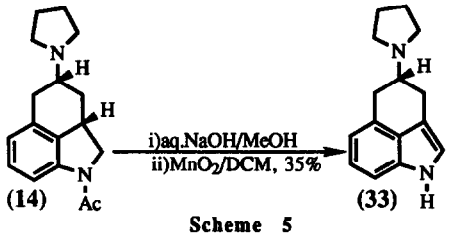
The enamine (13) was prepared from the aldehyde (31) and pyrrolidine, using molecular sieves (Linde 13X) as the drying agent. The aldehydes (31) and (32) served as starting materials for the other enamines which were used in the triple radical cyclisations. Preparation of the aldehydes (31) and (32) along with the starting materials used in the single double radical cyclisations is illustrated in scheme 4. The nitro benzene (21) was prepared in five steps from methyl anthranilate using standard organic procedures [14]. Corresponding bromo compound (22) was synthesized from 3-nitrophthalic acid by an orthometallation procedure [15]. Reduction of the carboxylic acid group in each of (21) and (22) was achieved with borane-THF complex in excellent yields to give the corresponding intermediate alcohols which were reduced with iron powder in acetic acid-ethanol followed by the protection of the alcohol functionality with t-butyldimethylsilylchloride to afford the anilines (23) and (24) respectively. Treatment of these anilines with lithium diisopropylamide at low temperatures in order to increase nucleophilicity at the nitrogen atom followed by quenching with allyl bromide gave amines (4) and (25). For the preparation of the other radical precursors, the synthesis was carried on with the bromo compound (25), because the iodo compound (4) gave unwanted side reactions at the Wittig olefination stage in this methodology. Treatment of the N-allyl amine (25) with different acid chlorides and acid anhydrides followed by deprotection of the alcohol moiety with aqueous hydrogen fluoride afforded the corresponding alcohols (26),(27) and (28) in good yields. PCC oxidation of the alcohols in dichloromethane using ultrasound activation[16] gave the aldehydes (6), (8) and (29) respectively. Subsequent Wittig reaction of the aldehydes (6) and (29) with methoxymethyl triphenylphosphonium chloride gave the enol ethers (11) and (30) as an inseparable 1:1 mixture of Z and E regioisomers. These were hydrolysed with aqueous hydrogen chloride in the next step to obtain the aldehydes (31) and (32). The resulting aldehydes could not be stored even as low as to -20°C, due to self polymerisation. Thus, their preparation was performed just prior their use in the forthcoming step.



Reagents: i)BH_3.THF/THF, ii)Fe/AcOH/EtOH/cat.HCl, iii)TBDMSCl/DMAP/imidazole/DMF, iv)LDA/THF/-78°C v)allyl bromide, vi)AcCl,or PhCOCl,or $(CF_3CO)_2O$/THF, vii)aq.HF/MeCN, viii)PCC/SiO_2/DCM/ultrasound, ix)HMDSLi/THF/$(Ph_3P^+CH_2OMe)Cl^-$, x)aq.HCl/THF, xi)pyrrolidine/PhH/mol sieves/rt

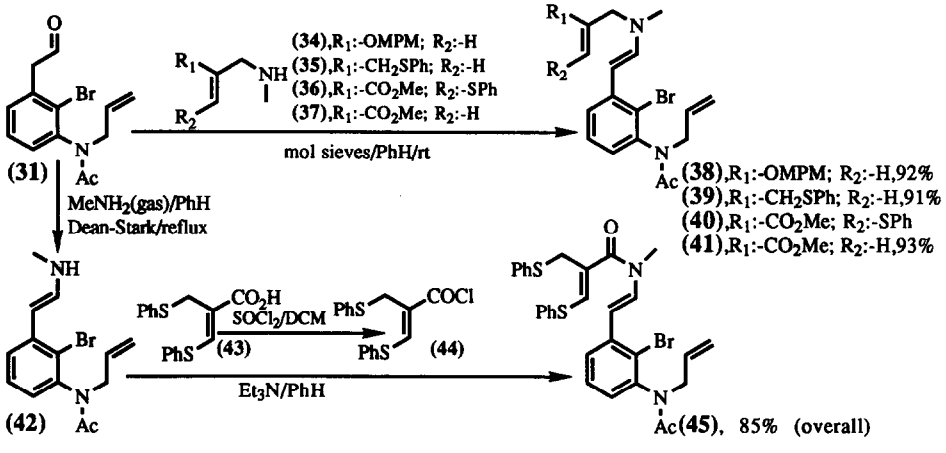
Scheme 4

Indoline (14) was converted to the corresponding indole (33) by reacting with aqueous alkali in methanol followed by oxidation of the resulting amine with activated manganese dioxide in dichloromethane under an atmosphere of nitrogen (Scheme 5). Amide hydrolysis whilst stirring in air for two weeks also gave the indole (33).



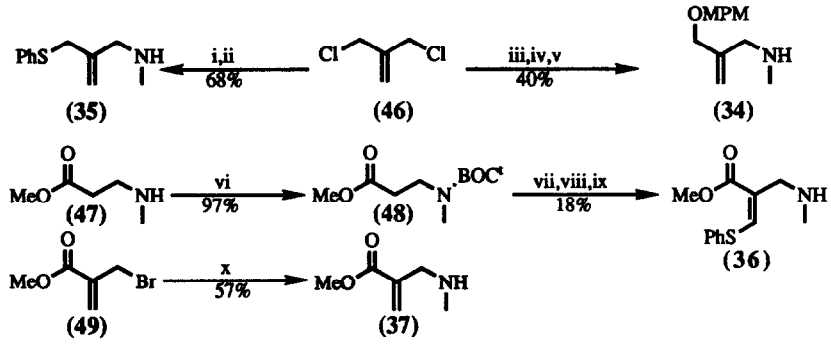
Scheme 5

Formation of the indole (33) from the enamine (13) shows the feasibility of the triple radical cyclisation approach for the construction of the lysergic acid framework. A range of enamines were prepared with the hope of making lysergic acid analogues. Preparation of these enamines was simple, and required coupling of the aldehydes (31) and (32) with suitable secondary amine fragments in the presence of molecular sieves. In many cases, the crude enamines were pure enough to be used in the cyclisation reactions, but nevertheless, were purified by column chromatography. Preparation of the enamines (38), (39), (40) and (41) is shown in scheme 6.



Scheme 6

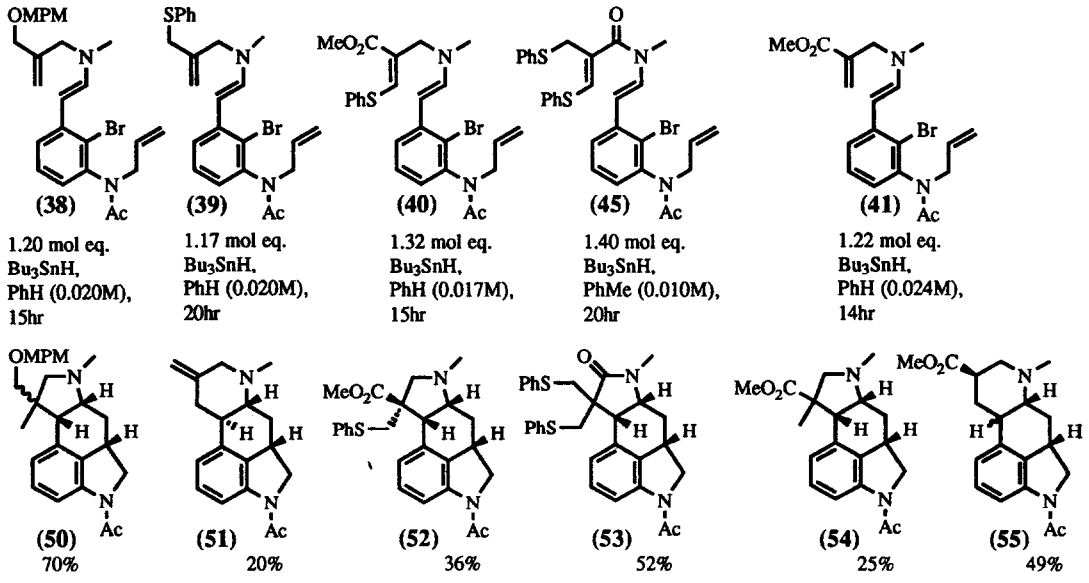
The enamide (45) was prepared from the methyl enamine (42) and the acid chloride (44) which was prepared from the known carboxylic acid (43) [17]. Synthesis of the amine fragments (34),(35),(36) and (37) is illustrated in scheme 7.



Reagents: i)n-BuLi/THF/PhSH, ii)$MeNH_2$/EtOH, iii)NaH/DMF/THF/4-methoxybenzyl alcohol, iv)PhH/K_2CO_3/NaOH/n-Bu_4NHSO_4/N-methylacetamide, v)aq.KOH/EtOH, vi)$(Bu^tOCO)_2O$/THF, vii)1.2eq LDA/THF, viii)$PhSCHCl_2$, ix)HCl/MeOH/MeOAc, x)$MeNH_2$(gas)/PhH/rt

Scheme 7

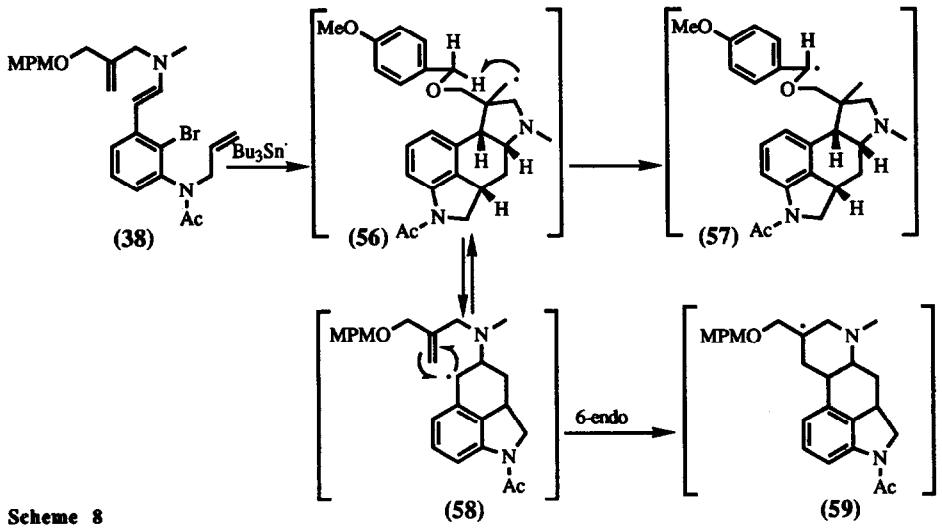
In order to obtain the lysergic acid framework, the proposed cascade radical cyclisation of the enamines should follow a 5-exo-trig,6-endo-trig,6-endo-trig pathway. The first two cyclisations have been established to follow the desired pathway. In the first cyclisation of the aryl radical, the rate of the favoured 5-exo cyclisation is further increased by the presence of nitrogen atom at the side chain, and the second cyclisation has to follow 6-endo pathway since the rigidity of the molecule does not allow 5-exo cyclisation to proceed. The remaining question is whether the final cyclisation of the triple radical ring closure would follow the desired 6-endo-trig pathway. Our results are summarized in table 2.



a) All reactions were performed using syringe pump technique in the presence of catalytic amounts of AIBN

Table 2: Triple Tandem Radical Cyclisations

When the enamine (38) was subjected to radical cyclisation, the tetracycle (50) was obtained in 70% yield as the only product of tandem 5-exo-trig,6-endo-trig,5-exo-trig ring closure. The result of the final cyclisation was perhaps not surprising since it follows the kinetically favoured pathway. On the other hand, under high dilution conditions the methyl radical (56), generated by the final 5-exo ring closure, should be able to revert to the more stable benzylic radical (58), which in turn should ultimately undergo to 6-endo-cyclisation to give thermodynamic product (59). Given that the thermodynamic product is not observed, suggests that the methyl radical (56) is short lived and does not revert to the benzyl radical (58). It may be that the methyl radical (56) is quenched intramolecularly to give the stable benzylic radical (57) leading to the observed product (scheme 8).



Scheme 8

Allyl sulphides have been used in radical cyclisations to control the regiochemistry in 6-endo ring closures [18]. This, indeed was found to be the case when the enamine (39) was subjected to radical cyclisation under high dilution conditions. The ergoline (51) was isolated after a successful 5-exo-trig,6-endo-trig,6-endo-trig cyclisation. Although the stereochemistry of C(10) was not assigned, molecular models suggests that the C,D-ring fusion should be *trans* if the final cyclisation adopts a chair rather than a boat, transition state (Figure 1). Formation of the ergoline (51),albeit in low yield, is encouraging. The yield of the reaction could not be improved by changing reaction conditions. This was thought to be the result of the self-destruction of the enamine (39) at high temperatures.

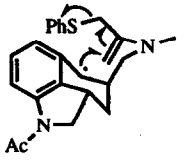
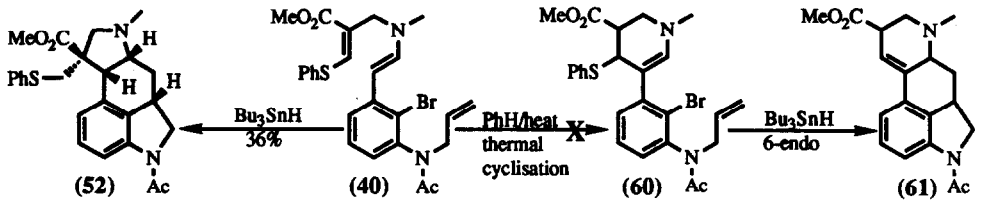


Figure 1

In the third entry, it was thought that thermal cyclisation of the D ring in enamine (40) would take place to give the pre-formed 6-membered ring prior to radical cyclisation as shown in scheme 9. Radical cyclisation of

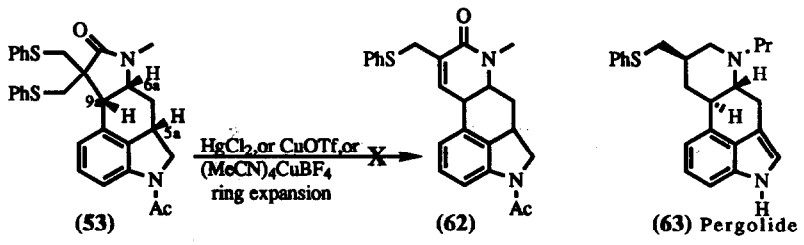
(60) would then occur *via* a 5-exo-trig,6-endo-trig pathway followed by ejection of phenylsulphenyl radical to give dihydroergoline (61) thus introducing the required 9,10-double bond in lysergic acid ring system. In practice, when the enamine (40) was heated for 5 days in boiling benzene and then subjected to radical cyclisation, the tetracycle (52) was obtained as the major product. This must arise *via* a 5-exo-trig cyclisation in the final step of tandem triple radical ring closure. Two points are evident from this result. Firstly, the thermal cyclisation of the D ring did not take place under the reaction conditions used and this may be due to the low reactivity of the α,β-unsaturated ester towards the enamine brought about by the mesomeric electron donation of sulphur. Secondly, since the final cyclisation follows a 5-exo pathway to give the kinetic product, it can be said that the electronic effect at the α,β-unsaturated ester appears not to guide the cyclisation in this case. Formation of a stable radical next to the sulphur atom after the final cyclisation should also favour the observed outcome of this reaction.



Scheme 9

If the 5 position in (40) is held further away from the intermediate benzyl radical then 6-endo-trig cyclisation should be encouraged especially if favourable electronic factors are present. It is known [19] that presence of an amide bond in radical precursors increases the amount of 6-endo product. In the fourth entry in table 2, radical cyclisation of the enamide (45) was investigated. It was hoped that after the first two cyclisations the final ring closure would be encouraged to follow 6-endo pathway by the geometry of the system brought about by the amide bond and by a possible ejection of phenylsulphenyl radical. On the other hand, presence of the α,β-amide bond would also guide the reaction in the desired direction. In practice, however, it was found that the radical cyclisation follows the kinetically favoured pathway, 5-exo-trig,6-endo-trig,5-exo-trig, to give the tetracycle (53). The relative stereochemistry of the hydrogens at the ring junctions was determined by n.O.e. experiments; thus, irradiation of the proton H-9a showed positive enhancements for the both protons H-5a and H-6a confirming the *cis* relationship assigned earlier on the basis of molecular models. Formation of a 5-membered ring by analogy to the previous result suggests that stabilisation of the final radical plays an important role in the reaction mechanism. Here, the radical formed after the 5-exo cyclisation is stabilised by a neighbouring sulphur atom which apparently overcomes the factors favouring 6-endo ring closure. Although formation of the tetracycle (53) was not desirable in relation to the lysergic acid framework, a possible cationic ring expansion reaction of (53) would provide the access to the ergot alkaloid ring system. Structural resemblance of the rearranged product (62) to pergolide (63), which is currently being evaluated clinically for the treatment of Parkinson's disease [20], was another attracting point for its synthesis.Unfortunately, the tetracyclic compound (53) was found to be inert to such conversion with different thiophiles used(scheme 10).

In the light of these results, the enamine (41) was prepared, which had mainly two advantages over the other radical cyclisation precursors; firstly, the electron deficient α,β–unsaturated ester would direct the radical

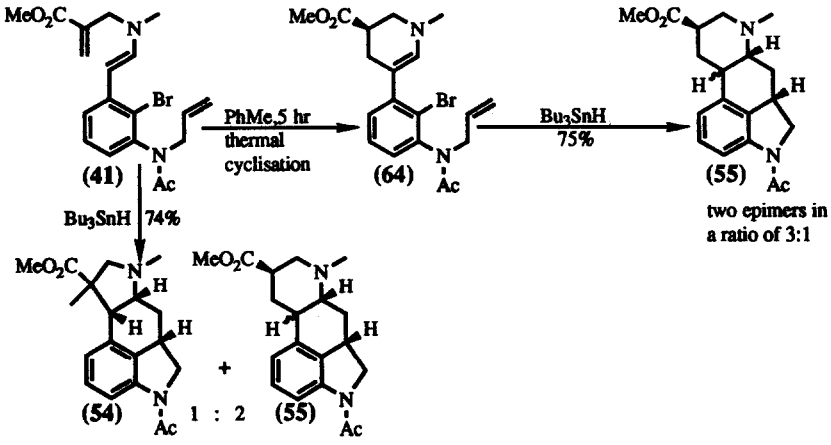


(53) (62) (63) Pergolide

Scheme 10

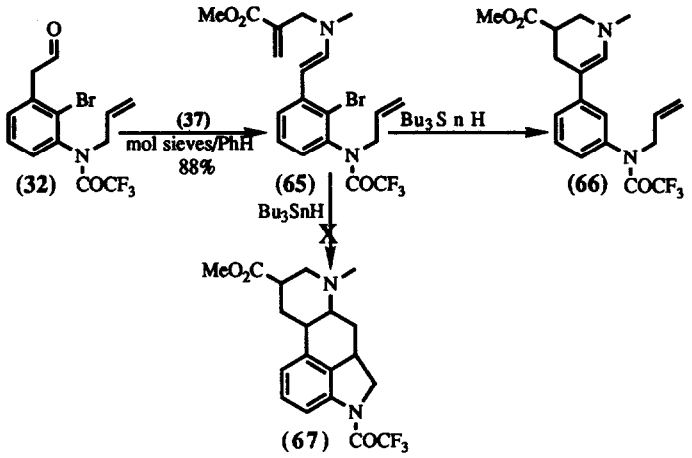
addition, and secondly, the 6-endo mode of cyclisation in the final stage could be accelerated by having no substitution at the terminal alkenic carbon atom. The probability of observing 6-endo cyclisation is also increased by the fact that there is no further stabilisation for the methyl radical after a possible 5-exo addition in the final stage of the cyclisation. This may mean that there is a greater chance for the methyl radical to revert to the more stable benzylic radical which was not observed in the previous examples.On the other hand, thermal cyclisation of the enamine (**41**) to form the 6-membered D ring prior to radical addition was a strong option, since no adverse effect of an electron releasing group as in the case of (**40**) is present. In fact, the enamine (**41**) was always obtained as a 1:1 mixture of cyclised (**64**) and uncyclised (**41**) enamines following the normal procedure. When the mixture of two enamines (**41**) and (**64**) was subjected directly to radical cyclisation, without any heating prior to radical addition to allow thermal cyclisation to take place, methyl tetrahydrolysergate derivative (**55**) and the tetracycle (**54**) was obtained in 2:1 ratio. We believe that the tetracycle (**54**) is the kinetic product of the enamine (**41**) which underwent a triple tandem radical cyclisation *via* 5-exo-trig,6-endo-trig,5-exo-trig pathway. Singlets at 1.32 ppm and 1.34 ppm in its proton n.m.r. and a quartet at 21.57 ppm in its carbon-13 n.m.r. support this structure. This shows once more that the α,β-unsaturated ester moiety does not play any leading role in the reaction mechanism.On the other hand, tetrahydrolysergate (**55**) must arise from a double tandem radical cyclisation of the cyclised enamine (**64**). The separation of these two products was achieved by using column chromatography and the tetracyclic compound (**54**) was found to be considerably less polar than (**55**).The product ratio from this reaction is interesting in terms of the ratio of the starting materials. It may be that the thermal cyclisation of the enamine (**41**) is taking place concurrently in the radical cyclisation process, thus causing an increase in the ratio of the 6-endo product. This was shown to be the case when the pure cyclised enamine (**64**), which was prepared by allowing the uncyclised enamine (**41**) to cyclise in boiling toluene for 5 hr before radical addition, was treated with tri-n-butyltin hydride in boiling toluene. Tetrahydrolysergate (**55**) was obtained as the only isolable product in 75% yield, as a 3:1 mixture of two epimers at C-10 (Scheme 11).

Analysis of the proton and carbon n.m.r. spectra supported the presence of two epimers; the major isomer gave a singlet at 3.66 ppm for the ester methyl, and a singlet at 2.33 ppm for the N-methyl group, whilst the minor isomer gave singlets at 3.68 and 2.35 ppm for the corresponding ester and N-methyl groups respectively. Double peaks were observed for each of C-8 and C-10 atoms in the carbon-13 spectrum. These and other observed peaks are consistent with the similar systems in the literature [21]. The relative stereochemistry of the protons at the ring junctions of B and C is expected to be *cis* by analogy to the previous results. However, the stereochemistry of the proton H-10 remains undefined, since the final benzylic radical can pick up hydrogen from tri-n-butyltin hydride from the both sides of the molecule which leads to two diastereoisomers.



Scheme 11

Hydrolysis of tetrahydrolysergate (**55**) was attempted using existing methods in the literature [22]. Unfortunately, it was found that under alkaline conditions (**55**) undergoes an extensive destruction to give a simple aromatic compound which was not identified. To tackle this problem, the enamine (**65**) was prepared with a protecting group which could be easily removed after the radical cyclisation step. When the enamine (**65**) was subjected to radical cyclisation it was observed that the expected product (**67**) had not formed; instead, reduction of the starting material to give (**66**) had taken place (Scheme 12).



Scheme 12

Although introduction of 9,10-double bond in lysergic acid framework (**1**) remains unaccomplished, the tandem radical cyclisation approach can be used in the synthesis of tetrahydrolysergic acid derivatives. With proper choice of starting materials, synthesis of other ergot alkaloids and their synthetic derivatives could be achieved using this novel approach.

EXPERIMENTAL

All m.ps. are uncorrected. IR spectra were recorded using Perkin-Elmer 298 and UV spectra obtained using Pye-Unicam SP800 spectrophotometers.NMR spectra were measured using Jeol JMM GX270, Bruker WM-250,WH-400, and VXR-500 spectrometers. Mass spectra were recorded on a VG analytical 70-250-SE normal geometry double focussing mass spectrometer.

2-Bromo-3-(tert-butyldimethylsilyloxymethyl)aniline **(24)**: A solution of borane-tetrahydrofuran complex (1.0 M, 100 ml, 0.100 moles) was added at 0°C over 3 minutes to the acid **(22)** (12.30 g, 0.050 moles) in dry THF (100 ml) under a nitrogen atmosphere with stirring. Stirring was continued at 0°C for 1 hr and then at room temperature for 3 hours. Water (20 ml) was added dropwise carefully, and the mixture was saturated with potassium carbonate, and the organic layer was separated. The aqueous layer was extracted several times with ether, and the combined extracts were dried over magnesium sulphate. The solvent was removed under reduced pressure to give intermediate 2-bromo-3-nitrobenzyl alcohol as pale yellow solid, m.p.74-76°C (CCl_4). The crude alcohol was dissolved in a mixture of glacial acetic acid (100 ml), absolute ethanol (100 ml) containing catalytic amount of conc. HCl (1.50 ml); and iron powder (11.00 g, 0.200 moles) was added. The resulting mixture was heated under reflux for 3 hours. After cooling, water (200 ml) was added and the solution was neutralized with solid sodium carbonate. The mixture was extracted with ethyl acetate (4x150 ml), the extracts were combined and washed with saturated sodium bicarbonate solution, dried with magnesium sulphate, and the solvent was removed in *vacuo* to give the crude product which was purified by column chromatography (silica gel, petroleum ether:ether 3:2) to give the corresponding intermediate 2-bromo-3-aminobenzyl alcohol as a white solid, m.p. 113-115°C (water). This amine was dissolved in dry DMF (60ml), and imidazole (4.125g, 60.00 mmol) and a catalytic amount of DMAP were added under a nitrogen atmosphere. The mixture was stirred and cooled in an ice bath. When the mixture was homogeneous *tert*-butyldimethylsilylchloride (8.30g, 55.00 mmol) was added and stirring was continued at room temperature for 18 hours. A saturated solution of sodium chloride (50 ml) was added, the mixture was extracted with ether, and the combined extracts were dried with magnesium sulphate. The solvent was removed at aspirator pressure, and the residue was purified by column chromatography (silica, petroleum ether : ether 4:1) to give the protected alcohol **(24)** (14.062 g, 89% overall) as an oil. υ_{max} (thin film, $CDCl_3$) : 3490 (m), 3390 (m), 1610 (s), 1470 (s); δ_H (270 MHz, $CDCl_3$) : 0.15 (s,6H,-$SiMe_2$),0.99(s,9H,-$SiCMe_3$),4.73(s,2H,-CH_2O-), 6.69-6.72 (m,1H,arom.), 6.96-6.99 (m,1H,arom.), 7.14 (dd,1H,Jax=Jax=7.92Hz,arom.); δ_C (67.94 MHz, $CDCl_3$) : -5.18 (q,-$SiMe_2$), 18.55(s,-SiC-), 26.10 (q,-$SiCMe_3$), 65.22 (t,-CH_2O-), 108.15 (s,-CBr), 114.35 (d,arom.), 117.24 (d,arom.), 127.85 (d,arom.), 141.71 (s,arom.), 143.85 (s,arom.);E.I. m/z : 315 and 317 (M^+, 8%), 260 (100), 258 (98), 230 (34), 228 (33).

Corresponding iodo derivative *2-iodo-3-(tert-butyldimethylsiloxymethyl)aniline* **(23)** was prepared in an overall 76% yield using the same procedure. υ_{max} (thin film, $CDCl_3$) :3480 (m), 3380 (m), 1610 (s); δ_H (270 MHz, $CDCl_3$) : 0.13 (s,6H), 0.96 (s,9H), 4.59 (s,2H), 6.63-6.67 (m,1H), 6.87-6.91 (m,1H), 7.12 (dd,1H,Jax=7.73 Hz); δ_C (67.94 MHz, $CDCl_3$) : -5.16(q), 18.58 (s), 26.14 (q), 70.26 (t), 86.10 (s), 113.53 (d), 117.44 (d), 128.90 (d), 143.85 (s), 146.53 (s); E.I. m/z : 363 (M^+,8%),306(36), 232(14), 179 (100), 164 (38); m/z (accurate mass): Found: 363.0538, Calc: 363.0515

2-Iodo-3-(tert-butyldimethylsiloxymethyl)-N-allylaniline **(4)**: A solution of LDA, prepared from N,N-diisopropyl amine (1.0 ml, 7.1 mmol) and *n*-BuLi (1.0 M, 5.0 ml, 5.00 mmol) in dry THF (25 ml) at room temperature (0.5 hr), was added with stirring to the amine **(23)** (1.577 g, 4.3mmol) in THF (40 ml) under a

nitrogen atmosphere at -78°C. The solution was allowed to warm to room temperature and a dark-yellow anion formed after stirring for 15 min. The solution was re-cooled to -78°C and allyl bromide (0.4 ml, 4.6 mmol) was added. The solution was stirred at -78°C for 30 min and at room temperature for 4 hours. A saturated solution of ammonium chloride (200 ml) was added, the mixture was extracted with ether (3x50 ml), and the combined extracts were dried over magnesium sulphate, concentrated in *vacuo*. The residue was purified by column chromatography (silica, CCl_4) to give the product (4) (1.294 g, 74%) as a yellow oil.υ_{max} (thin film, $CDCl_3$) : 3450(m); δ_H (270 MHz,$CDCl_3$) : 0.13 (s,6H), 0.90 (s,9H), 3.82-3.92 (m br,3H, NH and NHCH2), 4.60 (s,2H,CH_2OSi), 5.16-5.31 (m,2H,CH=CH_2), 5.88-5.97 (m,1H,CH=CH_2), 6.48(d,1H,J=8.12 Hz,arom.), 6.90 (d,1H,J=7.53 Hz,arom.), 7.18 (m,1H,arom.); δ_C (67.94 MHz,$CDCl_3$) : -5.15(q), 18.55 (s), 26.11 (q), 46.93 (t,NCH_2), 70.53 (t,CH_2O), 87.30 (s,CI,arom.),109.88 (d,CH=CH_2), 116.49 (t,CH=CH_2), 128.96 (d,arom.), 134.83(d,arom.), 143.68 (s,arom.), 146.64 (s,arom.); E.I. m/z: 403 (M^+,21%), 219(100); m/z (accurate mass): Found: 403.0828 Calc. 403.0828

Corresponding bromo derivative, *2-bromo-3-(tert-butyl-dimethysilyloxymethyl)-N-allylaniline* (**25**) was prepared by following the same procedure, but used in the next step as crude.

3-(N-Acetyl-N-allylamino)-2-bromobenzyl alcohol (**26**): The N-allyl amine (**25**), prepared from the amine (**24**) (9.40 g, 29.74 mmol) as described above, was dissolved in dry THF (100 ml), and acetyl chloride (7.5 ml, 100.0 mmol) was added and the mixture was stirred at room temperature for 3 hours. All volatiles were removed under reduced pressure, and the residue was dissolved in acetonitrile (200 ml) . Hydrogen fluoride solution (60 %, 300 drops) was added, and the solution was stirred at room temperature for overnight. A saturated solution of sodium bicarbonate was added and the solution was extracted with ethyl acetate. The combined extracts were dried with magnesium sulphate, and the solvent was removed at the aspirator pressure. The residue was purified by column (silica gel, ether : pentane 3:1) to afford the alcohol (**26**) (7.28 g, 88%, overall) as a yellow oil. υ_{max} (thin film, $CDCl_3$) : 3450 (m), 1660 (s); δ_H (270 MHz,$CDCl_3$) : 1.78 (s,3H,-NAc), 3.59-3.67 (m,1H, one of C(2)-H), 4.78 (s,2H,C(5)-H_2), 4.74-5.11 (m,3H,one of C(2)-H and C(4)-H_2), 5.79-5.91 (m, 1H, C(3)-H),7.11-7.65 (m,3H,arom.); δ_C (67.94 MHz,$CDCl_3$) : 22.31 (q,-NAc), 50.97 (t,C-3),64.38 (t,C-5),118.62 (t, C-4), 122.87 (s,C-11), 127.97 (d,arom.), 128.98 (d,arom.),129.15 (d,arom.), 132.46 (d,arom.), 140.96 (s,arom.), 143.11 (s, arom.), 170.71 (s,-CO,amide); E.I. m/z : 283 and 285 (M^+, 2%), 204 (100)

3-(N-Benzoyl-N-allylamino)-2-bromobenzyl alcohol (**27**): The title compound was prepared in a similar way to its N-acetyl analogue from crude N-allylamine (**25**) and benzoyl chloride in an overall 96% yield as a clear oil as described above. υ_{max} (thin film, $CDCl_3$) : 3409 (brs, -OH), 1645 (s, amide); δ_H (250 MHz, $CDCl_3$) : 3.00 (brs, 1H, -OH), 3.92 (q, 1H, J = 7.56 Hz,one of C(2)-H), 4.64 (s,2H, C(5)-H_2), 4.94 (dd,1H,J=5.41 Hz and J=9.21 Hz,one of C(2)-H), 5.90-6.10 (m, 1H,C(3)-H), 6.92-7.64 (m, 8H, arom.); δ_C (62.89 MHz, $CDCl_3$) : 52.06 (t,C-2), 64.66 (t,C-5), 118.75 (t,C-4), 127.71 (s, C-11), 127.27 (d,arom.), 127.56 (d, arom.), 127.83 (d,arom.), 129.76 (d,arom.), 130.50 (d,arom.), 132.36 (d, arom.),142.23 (d,arom.); m/z (accurate mass): Found : 345.0366, Calc: 345.0365.

3-(N-Trifluoroacetyl-N-allylamino)-2-bromobenzyl alcohol (**28**) : Reaction of the amine (**25**) with trifluoro acetic anhydride (5.65 ml, 40.0 mmol) as described above gave the title compound (**28**) in an overall 92% yield as a clear oil.υ_{max} (thin film,$CDCl_3$) : 3437 (brs), 1706 (s); δ_H (250 MHz, $CDCl_3$) : 3.15 (brs, 1H,-OH), 3.62 (q, 1H, J = 7.82 Hz, one of C(2)-H), 4.75 (s,2H,C(5)-H_2), 4.90 (dd,1H,J=3.06 Hz and J=7.87 Hz,one of C(2)-H), 5.05-5.20 (m,2H,C(4)-H_2), 5.90 (m,1H,C(3)-H), 7.14 (d,1H,J=7.85 Hz,arom.), 7.35 (t,1H,J=

7.73 Hz, arom.), 7.55-7.62 (m, 1H, arom.); δ_C (62.89 Hz,$CDCl_3$) : 53.10 (t,C-2), 64.54 (t, C-5), 120.41 (t, C-4), 122.81 (s,C-11), 127.18 (d, arom.), 127.56 (d,arom), 128.09 (d,arom.), 128.47 (d,arom.), 137.41 (s,arom.), 142.36 (s,arom.); m/z (accurate mass): Found: 336.9931, Calc: 336.9926.

3-(N-Acetyl-N-allylamino)-2-bromobenzaldehyde (**6**) : Commercial grade pyridinium chlorochromate (8.62 g, 40,0 mmol) was ground with silica gel (10.0 g) in a mortar. The resulting free-running solid was suspended in DCM (75 ml) at room temperature, and the reaction flask was placed in an ultrasound bath. Sonication of the mixture was followed by addition of the alcohol (**26**) (7.10 g, 25.0 mmol) in DCM (30 ml) in one portion. The reaction mixture was sonicated for 6 hours, and then stirred overnight at room temperature. The reaction mixture was filtered through celite, and the solid residue was washed several times with ethyl acetate. The filtrate and washings were combined, and the solvent was removed in *vacuo*. The residue was purified by column chromatography (silica, ether : petroleum ether 4:1) to give the aldehyde (**6**) (6.94 g, 98%) as white solid, m.p. 49-51°C (petroleum ether).υ_{max} (thin film, $CDCl_3$) : 1670 (s), 1600 (s); δ_H (270 MHz,$CDCl_3$) : 1.75 (s,3H,-NAc), 3.58-3.66 (m,1H,one of C(2)-H), 4.70-5.20 (m,3H,one of C(2)-H and C(4)-H_2), 5.70-6.00 (m,1H,C(3)-H), 7.40-7.60 (m,2H,arom.), 7.80-8.00 (m,1H,arom.), 10.34 (s,1H,-CHO); δ_C (67.94 MHz, $CDCl_3$) : 22.50 (q,-NAc), 50.88 (t,C-2), 119.14 (t,C-4), 128.70 (d,C-3), 129.65 (d,arom.), 132.33 (d,arom.), 135.50 (s, C-11), 136.56 (d,arom.), 142.48 (s,arom.), 169.78 (s,-CO,amide), 191.22 (s,-CHO); E.I. m/z : 281 and 283 (M^+,1%), 202 (100).

3-(N-Benzoyl-N-allylamino)-2-bromobenzaldehyde (**8**) :Oxidation of the alcohol (**27**) (1.96 g,5.66 mmol) in DCM (30 ml) with pyridinium chlorochromate (1.80 g, 8.00 mmol) and silica gel (2.00 g) as described above gave the desired aldehyde (**8**) (1.884 g, 97%) as a pale-yellow viscous oil after purification by column chromatography (silica gel, ether : petroleum ether 1:1). υ_{max} (thin film, $CDCl_3$) : 3066 (w), 2957 (w), 2870 (w), 1720 (s), 1691 (s), 1655 (s), 1601 (s), 1570 (s); δ_H (250 MHz, $CDCl_3$) : 3.97 (q, 1H,J = 6.93 Hz, one of C(2)-H), 4.93-5.22 (m, 3H, one of C(2)-H, and C(4)-H_2), 5.93-6.11 (m, 1H, C(3)-H), 7.05-8.20 (m, 8H, arom.), 10.30 (s, 1H, -CHO); δ_C (62.89 MHz,$CDCl_3$) : 51.97 (t,C-2), 119.33 (t, C-4), 127.83 (d,C-3), 127.97 (d,arom.), 128.30 (d,arom.), 128.59 (d,arom.), 128.92 (d,arom.), 130.05 (d,arom.), 132.03 (d,arom.), 133.18 (d,arom.), 133.33 (d,arom.), 135.15 (d,arom.), 137.30 (s,arom.), 191.13 (s, -CHO); m/z (accurate mass): Found: 343.0209 , Calc: 343.0208

3-(N-Trifluoroacetyl-N-allylamino)-2-bromobenzaldehyde (**29**): The title compound was prepared by following the same procedure, from the alcohol (**28**) (9.126g, 27.0mmol) in 95% yield after purification by column chromatography (silica gel, petroleum ether:ether 1:4) as a viscous yellow oil. υ_{max} (thin film, $CDCl_3$) : 1707 (s), 1701 (s); δ_H (250 MHz, $CDCl_3$) : 3.64 (q, 1H, J = 8.23 Hz, one of C(2)-H), 4.98 (dd,1H,J=5.37 Hz and J=9.06 Hz, one of C(2)-H), 5.10-5.26 (m, 2H, C(4)-H_2), 5.78-6.14 (m,1H,C(3)-H), 7.40-8.00 (m,3H, arom.), 10.42 (s,1H,-CHO); δ_C (62.89 MHz,CDCl3) : 52.98(t,C-2), 121.00(t,C-4), 128.03(s,C-11), 128.45 (d,C-3), 128.69(d,arom.), 130.45 (s,arom.), 130.74 (d,arom.), 135.27 (s, arom.), 136.65 (d,arom.), 190.55 (s,-CHO); m/z (accurate mass):Found: 334.9768, Calc: 334.9769

2-[(3'-N-Acetyl-N-allylamino)-2'-bromophenyl]ethenyl methyl ether (**30**): A solution of lithium hexamethyldisilazide, prepared from hexamethyl disilazane (0.74 ml, 3.50 mmol) and *n*-BuLi (1.0 M,3.50 ml, 3.50 mmol) in THF (5 ml), was added dropwise with stirring to a suspension of methoxymethyl triphenylphosphonium chloride (1.20 g, 3.50 mmol) in dry THF (10 ml) under a nitrogen atmosphere at -78°C. The red solution that formed was stirred for 90 min during which the temperature rose to 0°C. After cooling the solution of the ylide to -78°C , a solution of the aldehyde (**6**) (0.600 g, 2.12 mmol) in THF (5 ml) at -78°C was

added, and the resulting solution was stirred for 24 hours at room temperature. A saturated solution of ammonium chloride (100 ml) was added and the mixture was extracted with ethyl acetate. The combined extracts were dried with magnesium sulphate and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether : ether 1:1) to give the product (**30**) (0.620 g, 94%) as a yellow oil as a 1:1 mixture of E and Z isomers. υ_{max} (thin film, $CDCl_3$) : 1670 (s), 1600 (s); δ_H (270 MHz, $CDCl_3$) : 1.80 and 1.81 (2xs,3H,-NAc), 3.57-3.68 (m,1H, one of C(2)-H), 3.74 and 3.81 (s,3H,-OMe), 4.78-5.10 (m,3H,one of C(2)-H and C(4)-H_2), 5.65 (d,0.5H,J = 7.15 Hz, C(5)-H_{cis}), 5.81-5.97 (m,1H,C(3)-H), 6.14 (d,0.5H, J = 12.94 Hz,C(5)-H_{trans}), 8.08 (m,3H,arom.); δ_C (67.94 MHz, $CDCl_3$) : 22.08 (q,-NAc), 50.43 (t,C-2), 56.38 and 60.76 (2xq,-OMe),103.39 and 104.11 (2xd,C-5), 117.95 and 118.00 (2xt,C-4), 123.66 (s), 125.00 (d), 127.29 (d), 127.56 (d), 127.61 (d), 127.71 (d), 128.94 (s),129.62 (d), 132.60 (d), 132.63 (d), 137.18 (s), 138.58 (s), 141.14 (s), 141.59 (s), 149.79 (d), 169.19 and 169.69 (s,-CO,amide); E.I. m/z : 310 and 312 (MH^+,100%), 279 (24), 230 (35), 200 (31)

2-[(3'-N-Trifluoroacetyl-N-allylamino)-2'-bromophenyl]ethenyl methyl ether (**11**) : Reaction of the aldehyde (**29**) (3.36 g, 10.0 mmol) with the ylide prepared from methoxymethyl triphenylphosphonium chloride (6.00 g, 17.50 mmol) and lithium hexamethyldisilazide [prepared from hexamethyl disilazane (3.80 ml, 18.00 mmol) and n-BuLi (2.5 M, 8.00 ml, 19.00 mmol)] in THF (80 ml) as described for (**30**) gave the desired enol ether (**11**) (2.97 g, 82%) as a clear oil as a 1:1 mixture of E and Z isomers after column chromatography (silica gel, petroleum ether : ether, 4:1). υ_{max} (thin film, $CDCl_3$) : 2935 (w), 1703 (s), 1644 (s); δ_H (250 MHz, $CDCl_3$) : 3.60-3.90 (m,1H, one of C(2)-H), 3.72 and 3.77 (2xs, 3H,-OMe, two isomers), 4.90 (dd, 1H,one of C(2)-H), 5.10-5.30 (m,2H, C(4)-H_2), 5.62 (d,0.5H, C(5)-H_{cis}), 5.75-6.00 (m,1H,C(3)-H), 6.10 9d, 0.5H,C(5)-H_{trans}), 6.90-7.70 (m, 4H, arom., and C(6)-H); δ_C (62.89 MHz, $CDCl_3$) : 52.43 and 53.29 (2xt, C-2), 65.35 and 67.96 (2xq,-OMe), 104.12 (s,C-12), 116.24 (t, C-4), 120.11 (d), 126.06 (d), 127.18 (d), 128.14 (d), 128.25 (d), 130.29 (d), 130.71 (d), 131.82 (d), 131.98 (d) 151.44 (d); m/z (accurate mass): Found: 363.0081, Calc: 363.0082

3-(N-Acetyl-N-allylamino)-2-bromophenyl acetaldehyde (**31**) : Dilute HCl (10% w/v, 30 ml) was added to a solution of enol ether (**30**) (0.530 g, 1.71 mmol) in THF (15 ml) and the mixture was stirred for 24 hours. Sodium bicarbonate was added to saturate the aqueous layer and to neutralize the excess acid. The mixture was then extracted with ethyl acetate, the combined extracts were dried with magnesium sulphate. The solvent was removed in *vacuo* and the residue was purified by column chromatography (silica gel, ether) to give the product (**31**) (0.450g.89%) as a yellow oil. υ_{max} (thin film, $CDCl_3$) : 1730 (s), 1660 (s); δ_H (270 MHz, $CDCl_3$) : 1.82 (s,3H,-NAc), 3.63-3.71 (m,1H,one of C(2)-H), 4.00 (d,2H, J=1.35 Hz,C(5)-H_2), 4.78-4.85 (m,1H,one of C(2)-H), 5.03-5.13 (m,2H,C(4)-H_2), 5.82-5.97 (m,1H,C(3)-H), 7.03-7.44 (m,3H,arom.), 9.81 (t,1H,J = 1.55 Hz,-CHO); δ_C (67.94 MHz, $CDCl_3$) : 22.44 (q,-NAc), 50.82 (t,C-2), 51.41 (t,C-5), 118.61 (t,C-4), 126.00 (s,arom.), 128.40 (d), 130.20 (d), 131.57 (d), 132.66 (d), 135.37 (s), 142.19 (s), 170.00 (s,-CO,amide), 197.37 (s,-CHO); E.I. m/z : 295 and 297 (M^+, 1%), 216 (100); m/z (accurate mass): Found : 295.0228, Calc: 295.0208

3-(N-Trifluoroacetyl-N-allylamino)-2-bromophenyl acetaldehyde (**32**): Dilute HCl (10% w/v, 30 ml) was added to a solution of the enol ether (**11**) (1.00 g, 2.74 mmol) in THF (25 ml), and the mixture was stirred for 48 hrs at room temperature. Sodium bicarbonate was added to saturate the aqueous layer and neutralize the excess acid. The mixture was then extracted with ethyl acetate, and the combined extracts were dried with magnesium sulphate. The solvent was removed at aspirator pressure, and the residue was purified by column

chromatography (silica gel, petroleum ether : ether, 1:1) to give the aldehyde (32) (0.708 g, 74%) as a clear oil. υ_{max}(thin film:$CDCl_3$): 2927 (m), 1730 (s), 1702 (s), 1685 (s) ; δ_H(250 MHz, $CDCl_3$) : 3.68 (q,1H,J=8.30 Hz,one of C(2)-H), 4.06 (m,2H,C(5)-H_2), 4.82 (dd,1H,J=5.30 Hz and J=9.02 Hz, one of C(2)-H), 5.10-5.16 (m,2H,C(4)-H_2), 5.86-6.02 (m,1H,C(3)-H), 6.96-7.40 (m,3H,arom.), 9.96 (s,1H,-CHO); δ_C (62.89 MHz, $CDCl_3$) : 52.94(t,C-2), 53.36(t,C-5), 118.40(t,C-4), 125.48(s), 128.16(d,C-3), 129.96(d),131.00(d), 132.43 (d),135.20(s), 142.16(s), 167.60(s),196.44(s,-CHO); m/z (accurate mass): Found : 348.9929, Calc: 348.9925.

N-1-[2-(3'-N-Acetyl-N-allylamino)-2'-bromophenyl]ethenylpyrrolidine **(13)** : Pyrrolidine (0.12 ml, 1.40 mmol) was added to solution of the aldehyde (31) (0.430 g, 1.45 mmol) and molecular sieves (Linde 13X,2.60 g) in dry toluene (20 ml) under a nitrogen atmosphere. The resulting suspension was stirred for 4 hours at room temperature. The solution was filtered, and the solid residue was washed several times with ethyl acetate. The solvent was removed under reduced pressure to give the title enamine (13) (0.438 g, 90%) as a yellow oil. υ_{max} (thin film, $CDCl_3$) : 3078 (w), 2972 (m), 2852 (m), 1666 (s), 11626 (s); δ_H (250 MHz, $CDCl_3$) : 1.82 (s, 3H,-NAc), 1.92-1.97 (m, 4H,C(15)-H_2 and C(16)-H_2), 3.28-3.30 (m, 4H,C(13)-H_2 and C(14)-H_2), 3.58-3.66 (m, 1H, one of C(2)-H), 4.77-4.84 (m, 1H, one of C(2)-H), 5.02-5.09 (m,2H,C(4)-H_2), 5.35 (d, 1H, J=13.53 Hz,C(5)-H), 5,81-5.96 (m, 1H,C(3)-H), 6.73-6.77 (m, 1H, arom.), 7.07-7.35 (m, 3H, 2 aromatics and C(6)-H); δ_C (62.89 MHz, $CDCl_3$) : 22.43 (q,-NAc), 25.38 (t, C-15 and C-16), 49.15 (t, C-13 and C-14), 50.83 (t, C-2), 95.60 (d, C-5), 118.12 (t, C-4), 121.89 (s), 122.29 (d), 127.55 (d), 133.19 (d), 138.51 (d), 141.90 (s), 142.08 (s), 170.54 (s, amide carbonyl); E.I. m/z : 350 and 348 (M^+, 7 %), 269 (97), 228 (100) ;m/z (accurate mass): Found : 348.0815, Calc: 348.0837

2-(4'-Methoxybenzyloxymethyl)prop-2-enylmethylamine **(34)**: 4-Methoxybenzyl alcohol (5.0ml, 40.1mmol) was added to sodium hydride (60%, 1.625g, 40.6mmol) in dry THF (50ml) under a nitrogen atmosphere at room temperature. DMF (10ml) was added and the solution stirred for 30 minutes. The mixture was then added to a solution of dichloride (46) (7.0ml, 60.5mmol) in THF (50ml) with stirring for a total of 2 hours 15 minutes. A saturated solution of sodium dichloride (100ml) was added. The mixture was extracted with ether (3x150ml), the combined extracts dried with magnesiumsulphate and the solvent removed in vacuo to give a yellow oil. The product was purified by column chromatography (silica, 1.CCl_4; 2. petrol:ether 4:1) to give 2-chloromethyl-prop-2-enyl 4-methoxybenzyl ether which was used in the next step.

Powdered sodium hydroxide (5.62g,141mmol), powdered potassium carbonate (11.38g,80mmol) and tetrabutylammonium hydrogensulphate (1.41g,4.13mmol) were added to a solution of N-methylacetamide (2.98ml, 39.14mmol) in dry benzene (50ml) under a nitrogen atmosphere. The mixture was heated to reflux and stirred vigorously. 2-Chloromethyl-prop-2-enyl 4-methoxybenzyl ether in benzene (15ml) was added dropwise and the mixture was heated at reflux for 5 hours. After cooling, benzene (50ml) was added and the mixture extracted with water (3x50ml). The organic layer was separated and dried with magnesium sulphate. The solvent was removed in *vacuo*, and the residue was purified by column chromatography (silica; ethyl acetate) to give N-2-(4'-methoxybenzyloxymethyl)prop-2-enyl-N-methylacetamide as a light yellow oil which was dissolved in in ethanol (125ml). To this solution, a solution of potassium hydroxide (42.2g, 0.75mol) in water (125ml) was added and the mixture heated at reflux for 22 hours. After cooling, the solvent volume was reduced in *vacuo* to ca. 150 ml and the mixture extracted with ether (3x100ml). The combined extracts were dried with magnesium sulphate and the solvent removed in *vacuo*. The residue was purified by bulb-to-bulb distillation (250°C oven temp., 0.4mmHg) to give the title compound (34) (3.55g,40% overall) as a clear oil; υ_{max} ($CDCl_3$) : 3350 wbr, 1615 m; δ_H (270 MHz, $CDCl_3$) : 2.38 (s,3H,NMe), 3.21 (s,2H,NCH_2), 3.75 (s,3H,OMe), 3.98

(s,2H,OCH_2), 4.41 (s,2H,$ArCH_2$),5.08 and 5.13 (2xs,2H,$=CH_2$), 6.85 (d,2H,J=8.5Hz,arom.), 7.24 (d,2H,J=8.5Hz); δ_C (67.94 MHz, $CDCl_3$) : 35.78 (q,NMe), 54.09 (t,NCH_2), 54.94 (q,OMe), 71.47 (t,OCH_2), 71.57 (t,$ArCH_2$), 112.69 (t,$=CH_2$), 113.53 (d), 129.06 (d), 130.17 (s,$CH_2=C$), 144.04 (s), 158.95 (s); C.I. m/z: 222 (M^++1,100%), 121 (46)

2-(Phenylthiomethyl)prop-2-enylmethylamine **(35):** *n*-Butyllithium (10.0M,10.0ml,100mmol) was added dropwise with cooling to a solution of thiophenol (10.0ml,97mmol) in dry THF (50ml) under a nitrogen atmosphere. The solution was stirred at room temperature for 1 hour and was then added dropwise to dichloride **(46)** (17.0ml, 147mmol) in THF (50ml). The solution was stirred overnight and then water (50ml) was added. The mixture was extracted with ether (2x50ml), the combined extracts dried with magnesium sulphate and the solvent removed in *vacuo*. The residue was purified by column chromatography (silica; petrol) to give 2-chloromethylprop-2-enyl phenyl sulphide which was added to a solution of methylamine in absolute ethanol (33%w/v;30ml,0.32mol). The flask was sealed and the mixture stirred at room temperature overnight. The amine salts were neutralised with aqueous sodium bicarbonate and all volatile material removed in *vacuo*. The residue was purified by bulb-to-bulb distillation (water pump; 150-200°C) to give the title compound **(35)** (12.73g,68% overall) as a clear oil; υ_{max} ($CDCl_3$) : 1585 m; δ_H (270 MHz, $CDCl_3$) : 1.23 (sbr,1H,NH), 2.35 (s,3H,NMe), 3.26 (s,2H,NCH_2), 3.57 (s,2H,SCH_2),4.95 and 4.97 (2xs,2H,$=CH_2$), 7.09-7.34 (m,arom.); δ_H (67.94 MHz, $CDCl_3$) : 35.69 (q,NMe), 38.11 (t,SCH_2), 54.80 (t,NCH_2), 114.02 (t,$=CH_2$), 125.94 (d), 128.51 (d), 129.61 (d), 136.17 (s), 142.65 (s); E.I. m/z : 193 (M^+,6%), 109 (17), 83 (100)

Methyl(Z)-2-(N-methyl)aminomethyl-3-phenylthio-2-propenoate **(36):** Di-*tert*-butyl dicarbonate (2.36g, 10.1 mmol) in dry THF (10ml) was added dropwise over 40 minutes with stirring to amine **(47)** (1.47g, 12.8mmol) in dry THF (10ml) at 0°C. Stirring was continued at room temperature for 2 hours. The solvent was removed in *vacuo* and the residue distilled to give the carbamate **(48)** (2.11g,97%); b.pt. 85-87°C.The carbamate **(48)** was dissolved in dry THF (20 ml), and the resulting solution was added to a solution of LDA [prepared from diisopropyylamine (3.0ml, 21.4mmol) and n-butyllithium (1.6M,12.5ml,20.0mmol) at 0°C] in THF (20ml) with stirring under a nitrogen atmosphere at -78°C over 105 minutes.The solution was allowed to warm to -40°C over 20 minutes and was then recooled to -100°C.Dichloromethylphenylsulphide[23] 2.43g,12.6mmol) was added. The solution was stirred at -100°C for 15 minutes and at ambient temperature for 30 minutes.A saturated solution of ammonium chloride (50ml) was added,the mixture was extracted with ether (3x50ml) and the combined extracts dried with magnesium sulphate.The solvent was removed in *vacuo* to give a dark yellow oil.The sample was purified by column chromatography (silica; petrol:ether 3:1) to give methyl (z)-2-[(n-tert-butoxycarbonyl-N-methyl)amino]methyl-3-phenylthio-2-propenoate as a yellow oil which was used in the next step.Acetyl chloride (24ml,0.34mol) was added dropwise to methanol (16ml,0.4mol) with ice cooling. (CARE! very exothermic!).To the solution of hydrogen chloride thus prepared was added a solution of carbamate in methanol (10ml). After stirring at room temperature for 3 hours the solvent was removed in *vacuo*. The residue was partitioned between aqueous hydrochloric acid (2M,20ml) and dichloromethane. The organic layer was washed with aqueous hydrochloric acid (2M,20ml). The combined aqueous layers were neutralised with solid sodium bicarbonate and the solution extracted with ether (3x25ml). The combined organic extracts were dried with magnesium sulphate and the solvent removed in *vacuo* to give the title compound **(36)** (0.412g,18% overall) as an oil; υ_{max} (thin film, $CHCl_3$) : 3350 wbr,1695 s; δ_H (270 MHz, $CDCl_3$) : 2.44 (s,3H,NMe), 3.53 (s,2H,NCH_2), 3.84 (s,3H,OMe), 4.48 (br s,1H,NH), 7.32-7.54 (m,6H); δ_C (67.94 MHz, $CDCl_3$) : 34.44

(q,NMe), 51.83 (q,OMe), 52.40 (t,NCH_2), 120.80 (s),128.18 (d), 129.34 (d), 131.03 (d), 136.13 (s), 149.26 (d), 166.51 (s); E.I. m/z: 237 (M^+,4%), 163 (18), 128 (100)

Methyl 2-(N-methyl aminomethyl) acrylate **(37)** : Anhydrous methyl amine gas was bubbled through a solution of methyl α-bromomethyl acrylate (0.537 g, 3.00 mmol) in toluene (10 ml) for 15 min at room temperature, during which a white solid formed. Water was added , and the reaction mixture was extracted with ethyl acetate. The combined extracts were dried over magnesium sulphate , and the solvent was removed at aspirator pressure. The residue was purified by column chromatography (silica gel, pentane : ether, 1:1) which afforded the amine **(37)** (0.220 g, 57%) as a clear oil; υ_{max} (thin film, $CHCl_3$) : 3427 (w), 2953 (m), 2845 (m), 1727 (s); δ_H (250 MHz, $CDCl_3$) : 2.20 (s,3H,-NMe), 3.24 (s,2H,-NCH_2-), 3.75 (s,3H,-OMe), 5.82 (s,1H,one double bond proton), 6.26 (s,1H, one double bond proton); δ_C(62.89 MHz,$CDCl_3$) : 42.41 (q,-NMe), 51.73 (q, -OMe), 57.47 (t, -NCH_2-), 126.40 (t,-CH_2=C-), 137.82 (s,alkenic), 167.32 (s,-CO,ester); Accurate mass m/z: Found : 129.07897 Calc: 129.07903

N-2-[3-(N-Acetyl-N-allylamino)-2-bromophenyl]ethenyl-2-(4'-methoxyphenylmethyloxymethyl)prop-2-enylmethyl amine **(38)**: Amine **(34)** (0.395 g, 1.8 mmol) was added to a solution of the aldehyde **(31)** (0.529 g, 1.8 mmol) in dry benzene (20 ml) under a nitrogen atmosphere. Linde 13X molecular sieves (3.2 g) were added and the mixture was stirred for 4 hours. The solution was filtered and the solvent was removed in *vacuo* to give the enamine **(38)** (0.792 g, 92%) as a viscous oil. δ_H (250 MHz, $CDCl_3$) : 1.82 (s,3H,CH_3CO), 2.81 (s,3H,NMe),3.57-3.66(m,1H,oneC(2)-H),3.79(s,3H,OMe),3.81 (s,2H,C(8)-H_2), 3.94 (s,2H,CH_2OCH_2Ar), 4.42 (s,2H,CH_2OCH_2Ar), 4.78-4.85 (m,1H,one C(2)-H), 5.01-5.20 (m,4H,C(4)-H_2 and C(10)-H_2), 5.46 (d,1H,J=13.72Hz,C(5)-H), 5.81-5.96 (m,1H,C(3)-H), 6.77-6.91 (m,2H,one arom. and C(6)-H), 6.86 (d,2H,J=8.69Hz,arom), 7.08-7.35 (m2H,arom),7.24 (d,2H,J=8.69Hz,arom); δ_C (62.89 MHz, $CDCl_3$) : 21.77(q,COMe),36.00(q,NMe),50.18(t),54.48(q,OMe),58.04(t),70.32(t,CH_2OCH_2Ar),71.60(t,CH_2OCH_2Ar) ,96.19 (d,C-5), 113.37 (d), 114.08 (t,C=CH_2), 117.43 (t,C=CH_2), 122.30 (d), 122.53 (s), 124.79 (d), 126.89 (d), 127.93 (d), 128.79 (d), 129.60 (s), 133.56 (d), 141.22 (s), 141.68 (d), 141.97 (s), 142.49 (s), 158.91 (s), 167.73 (s); E.I. m/z : 500 and 498(M^+,3%), 419 (98), 121 (100); m/z (accurate mass):Found: 498.1530 Calc:498.1518

N-2-[3-(N-Acetyl-N-allylamino)-2-bromophenyl]ethenyl-2-(phenylthiomethyl) prop-2-enylmethylamine **(39)** : To a solution of the aldehyde **(31)** (0.375 g, 1.25 mmol) in toluene (15 ml) were added successively the allylic amine **(35)** (0.270 g, 1.40 mmol) in toluene (2 ml) and molecular sieves (Linde 13X, 1.50 g) under a nitrogen atmosphere.The reaction mixture was stirred at room temperature for 4 hours, and filtered to remove the solid residue. The solid residue was washed with ethyl acetate, and the filtrate and the washings were combined. The solvent was removed under reduced pressure to give the enamine **(39)** (0.532 g, 91%) as a yellow oil. υ_{max} (thin film, $CDCl_3$) : 3055 (w), 2957 (s), 2929 (s), 2870 (s), 1736 (s), 1717 (s); δ_H (270 MHz, $CDCl_3$) : 1.82 (s, 3H, -NAc), 2.78 (s, 3H, -NMe), 3.51 (s, 2H, C(11)-H_2), 3.57-3.65 (m, 1H, one of C(2)-H), 3.86 (s, 2H, C(8)-H_2), 4.78-4.85 (m, 1H, one of C(2)-H), 4.96-5.09 (m, 4H,C(4)-H_2 and C(10)-H_2), 5.49 (d, 1H, J = 13.72 Hz, C(5)-H), 5.81-5.93 (m, 1H, C(3)-H), 6.77-6.80 (m, 3H, arom.); δ_C (67.94 MHz,$CDCl_3$) : 22.33 (q,-NAc), 36.37 (q,-NMe), 37.83 (t,C-11), 50.69 (q,C-2), 58.60 (t,C-8), 96.05 (d,C-5), 116.03 (t,C-4), 118.02 (t, C-10), 122.28 (s,C-17), 122.70 (d), 124.86 (d), 126.63 (d), 127.49 (d), 128.85 (d), 130.46 (d), 133.08 (d), 135.50 (s), 140.64 (d), 141.56 (s), 141.77 (s), 142.04 (s), 170.20 (s,-CO, amide) ; E.I. m/z : 472 and 470(M^+, 3 %), 391 (100), 363 (66), 281 (34); m/z (accurate mass): Found: 470.1019, Calc: 470.1027

N-2-[3-(N-Acetyl-N-allylamino)-2-bromophenyl]ethenyl-2-(methoxycarbonyl) prop-2-enylmethylamine **(41):** Anhydrous methyl amine gas was bubbled through a solution of methyl α-bromomethyl acrylate (0.358 g, 2.00 mmol) in toluene (20 ml) for 20 min at 0°C. Excess methyl amine was removed by bubbling nitrogen through the solution for 4 hours , and by applying high vacuum for 10 min at room temperature. To this solution, a solution of freshly prepared aldehyde **(31)** (0.500 g, 1.61 mmol) in toluene (10 ml) and molecular sieves (Linde 13X,2.00 g) were added successively, and the resulting mixture was stirred for 2 hours at room temperature. The reaction mixture was filtered through a glass sinter, and the solid residue was washed several times with ethyl acetate. The filtrate and washings were combined. and the solvent was removed under reduced pressure to give the crude product which was further purified by column chromatography (silica gel, petroleum ether : ethyl acetate : tri-ethyl amine 1:1:0.1). The enamine **(41)** (0.607g, 93%) was obtained as a yellow oil; υ_{max} (thin film, $CHCl_3$) : 3056(w), 2952 (s), 2928 (s), 1727 (s,ester carbonyl), 1665(s,amide carbonyl),1649(s),1629 (s) 1577 (s); δ_H (250 MHz, $CDCl_3$) : 1.75 (s,3H,-NAc), 2.82 (s,3H,-NMe), 3.50-3.72 (m,1H, one of C(2)-H), 3.74 (s,3H,-OMe), 3.98 (s,2H,C(8)-H_2), 4.76 (dd, 1H, J = 5.29 Hz and J=9.42 Hz, one of C(2)-H), 4.95-5.10 (m,2H,C(4)-H_2), 5.37 (d, 1H, J_{trans}= 13.66 Hz,C(5)-H), 5.68 (d,1H,J = 1.11 Hz, one of C(10)-H), 5.75-5.92 (m,1H,C(3)-H), 6.21 (s,1H, one of C(10)-H), 6.74 (dd,1H, J = 1.32 and 4.53 Hz ,C(14)-H), 6,78 (d,1H, J_{trans} = 13.62 Hz, C(6)-H),7.08 (t,1H, J = 3.14 Hz,C(13)-H), 7.20-7.29 (m,1H,C(15)-H); δ_C (62.89 MHz, $CDCl_3$) : 22.19 (q,-NAc), 36.87 (q,-NMe), 50.64 (t,C-2), 51.75 (q,-OMe), 55.99 (t, C-8), 96.11 (d,C-5), 117.82 (t,C-4), 122.64 (d,C-3), 124.76 (d,C-15), 126.42 (t,C-10), 127.34 (d,C-13), 133.01 (d,C-14), 137.47 (s,C-17), 141.59 (d,C-6), 141.66 (s, C-16), 170.06 (s,-CO, amide), 174.13 (s,-CO, ester); E.I. m/z : 408 and 406 (M^+, 3%), 327 (100), 286 (20), 227 (30); m/z (accurate mass):Found: 407.0970, Calc: 407.0972.

3-[3-(N-Acetyl-N-allylamino)-2-bromophenyl]-5-(methoxycarbonyl)-1,4,5,6-tetrahydro-N-methylpyridine **(64):** Anhydrous methyl amine gas was bubbled through a solution of methyl α-bromomethyl acrylate **(49)** (0.179 g, 1.00 mmol) in benzene (10 ml) for 15 min at room temperature. Excess methyl amine was removed by bubbling nitrogen through the solution for 4 hours, and by applying high vacuum for 10 min at room temperature. A solution of freshly prepared aldehyde **(31)** (0.250 g, 0.80 mmol) in benzene (5 ml) was added dropwise. The solution was then heated under reflux for 6 hours with continuous azeotropic distillation of water. The mixture was cooled to room temperature, and the solvent was evaporated in *vacuo* . The residue was diluted with ethyl acetate (50 ml), and shaken with 2N HCl (50 ml). The aqueous layer was made alkaline with saturated sodium bicarbonate, and re-extracted with DCM. The combined extracts were dried with magnesium sulphate, and the solvent was removed at reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether : ethyl acetate : tri-ethyl amine, 2:1:0.1) to give the cyclised enamine **(64)** (0.215 g, 66%) as a mixture of two diastereoisomers (in a ratio of 4:1) as a yellow oil. Enamine **(64)** can also be prepared from its acyclic form **(41)** by thermal cyclisation. This was achieved practically by heating the crude enamine **(41)** in boiling dry-degassed toluene for 5 h prior to radical cyclisation. υ_{max} (thin film, $CDCl_3$) : 3080(w), 2953(s), 2926 (s), 2857 (s), 1735 (s, carbonyl, ester), 1656 (s) and 1650 (s, carbonyl, amide), 1631 (s), 1578 (s), 1466(s); δ_H (250 MHz, $CDCl_3$) : 1.78 (s,3H,-NAc), 2.18-2.28 (m,1H, C(9)-H), 2.83 and 2.86 (2xs,3H,-NMe,two isomers in a ratio of 4:1), 3.10-3.35 (m,2H,C(10)-H_2), 3.42-3.55 (m,3H,one of C(2)-H and C(8)-H_2), 3.63 and 3.66 (2xs, 3H,-OMe, two isomers in a ratio of 4:1), 4.78 (ddd,1H,J = 1.06 Hz,J=3.26 Hz and J=8.13 Hz,one of C(2)-H),4.99-5.10 (m,2H,C(4)-H_2), 5.77-5.94 (m,1H,C(3)-H), 6.71 (s,1H,C(6)-H), 6.75-6.81 (m,1H, arom.),7.10 (t,1H,J =7.69 Hz,arom.),7.27(dd,1H,J=1.65Hz and J=6.38Hz,arom.); δ_C (62.89 MHz, $CDCl_3$) : 22.23 (q,-NAc), 37.37 (q,-NMe), 43.91 (d,C-9), 50.67(t,C-2),

52.27(q,-OMe), 55.29(t, C-8), 117.92(t,C-4),122.89 (d,C-3),125.27(d,C-15),127.49(d,C-13),133.00 (d,C-14),141.21(d,C-6),141.85(s,C-16),170.04 (s,-CO, amide),173.43 (s,-CO,ester); E.I. m/z : 327 (M^+-Br, 10%), 277 (5), 171 (100), 149 (30); m/z (accurate mass): Found : 407.0970, Calc: 407.0972

N-2-[3-(N'-Acetyl-N-allylamino)-2-bromophenyl]ethenyl-N-methyl-2'-(phenylthiomethyl)-3'-phenylsulphenyl-2-propenamide **(45):** Anhydrous methyl amine gas was bubbled through a solution of the aldehyde **(31)** (0.400g, 1.35 mmol) in benzene (10ml) at room temperature for 3 hours over molecular sieves (Linde 13X, 2.00g). Excess methyl amine was removed by passing nitrogen through the solution for 4 hours at room temperature. The reaction mixture was cooled to 0°C and freshly prepared acid chloride **(47)** [24] (1.423g, 1.40mmol) in benzene (10 ml) and tri-ethyl amine (1.00 ml) were added; and the mixture was stirred overnight at room temperature. The solid residue was removed by filtration, and the filtrate was concentrated in vacuo. The residue was subjected to column chromatography (silica gel, ether:petroleum ether 5:1) which gave the enamide **(45)** (0.560 g, 85%) as a yellow oil. υ_{max} (thin film , $CDCl_3$): 1655 (s) and 1626 (s, amide); δ_H (250 MHz, $CDCl_3$): 1.76(s,3H,-NAc),2.86 (2xs,3H,-NMe),3.62 (m,1H,one of C(2)-H),3.95(s,2H,C(11)-H_2), 4.70-5.22 (m,3H,C(4)-H_2 and one of C(2)-H), 5.75-5.98 (m,1H,C(3)-H), 6.27 (m,1H,C(10)-H), 6.46(d,1H,J=21.15 Hz,C(5)-H), 7.10-7.50 (m,14H, arom. and C(6)-H); δ_C (62.89 MHz,$CDCl_3$):22.40(q,-NAc),26.62 (q,-NMe), 33.21(t,C-11),50.84(t,C-2), 89.20(d,C-5), 118.67(t,C-4), 122.06 , 122.07, 127.39, 127.50, 127.85, 128.92, 129.19, 129.62, 130.62, 131.07, 131.80, 132.77, 133.53, 139.45, 142.41, 166.47 (s,amide); E.I. m/z : 595 and 593(MH^+,3%),513(M^+-Br,10), 175(100), 147(58), 110(92); m/z (accurate mass):Found:592.0854,Calc: 592.0855

N-2-[3-(N-Trifluoroacetyl-N-allylamino)-2-bromophenyl]ethenyl-2-(methoxycarbonyl)prop-2-enylmethylamine **(65) :** Reaction of the allylic amine **(37)** prepared in-situ from methyl α-bromomethyl acrylate **(49)** (0.500 g, 2.79 mmol) and anhydrous methyl amine gas, with the freshly prepared aldehyde **(32)** (0.650 g, 1.85 mmol) over molecular sieves (Linde 13X, 1.50 g) as described, gave the enamine **(65)** (0.75 g, 88%) as a yellow oil. Crude enamine was used in the next step without further purification. υ_{max} (thin film, $CDCl_3$) : 2953 (w), 1702 (s), 1637 (s), 1578 (s); δ_H (250 MHz, $CDCl_3$) : 2.22 (s, 3H,-NMe), 3.60-3.90 (m,1H, one of C(2)-H), 3.71 (s,2H,C(8)-H_2), 3.73 (s,3H,-OMe), 4.90-5.27 (m,3H,one of C(2)-H and C(4)-H_2), 5.80-5.95 (m,1H,C(3)-H), 5.84 (s, 1H, one of C(10)-H), 6.05 (d, 1H, C(5)-H), 6.25 (s,1H, one of C(10)-H), 6.96-8.00 (m,4H, arom. and C(6)-H); δ_C (62.89 MHz, $CDCl_3$) : 38.61 (q, -NMe), 49.76 (q, -OMe), 51.62 (t,C-2), 57.60(t,C-8), 120.03 (t,C-4), 126.19 (t,C-10), 127.04 (d), 128.30 (d), 130.32 (d), 131.30 (d); m/z (accurate mass): Found : 460.0617 Calc: 460.0610

General Procedure for radical cyclisation reactions: To a boiling solution of reactants in dry-degassed solvent (diluted to 0.02 M or less) was added a solution of *tri*-n-butyltin hydride (1.2-1.4 mol eq) and catalytic amounts of azoisobisbutyronitrile (0.005g/10 ml of the solvent) in the same solvent (< 0.05 M) over a period of 2-36 hours by means of a syringe pump. After the addition was complete, the reaction mixture was refluxed another 1hr , and allowed to cool to room temperature. The solvent was removed in *vacuo* , and the residue was subjected to a column chromatography on silica gel. Tin residues were eluted first with petroleum ether (500 ml) and the indoline compounds were eluted with more polar solvent mixtures as stated for each individual product.

2,3-Dihydro-3-methyl-4-(tert-butyldimethylsilyloxymethyl)indole **(5):** After the addition of *tri*-n-butyltin hydride the solvent was removed in *vacuo* to give an oil which was twice purified by column chromatography (silica,1.petrol:ether 4:1,2.petrol:ether 1:1)to give the title compound as a white solid which rapidly decomposed υ_{max} (thin film, $CDCl_3$): 3455(w),1600(m); δ_H (270 MHz, $CDCl_3$): 0.10 (2xs,6H),0.94 (s,9H),1.24

(d,3H,J=6.96Hz,CH_3a),3.19(dd,1H,J=8.96 and 3.28Hz,C(2)-Ha),3.2-3.3(sbr,1HNH), 3.4-3.5 (m,1H,C(3)-Hb), 3.67 (t,1H,J=8.69Hz,C(2)-Hb), 4.68 and 4.75 (ABq,2H,CH_2OSi), 6.57 (d,1H,J_{AX}=7.7Hz,arom.), 6.79 (d,1H,J_{BX}=7.5Hz,arom.), 7.03 (dd,1H,J_{AX}=J_{BX}=7.7Hz; δ_C (67.94 MHz, $CDCl_3$): -5.10 (q), 18.60 (s), 19.51 (q), 26.14 (q), 35.57 (d), 55.34 (t), 62.93 (t), 108.76 (d), 117.54 (d), 127.71 (d), 131.40 (s), 137.41 (s), 150.98 (s); E.I. m/z: 277 (M^+,31%), 144 (100); m/z (accurate mass): Found: 277.1854 Calc: 277.1862

5(H)-5-Acetyl-6,7-dihydro-1-formyl indoline (**7**): The title compound (**7**)was obtained as a clear liquid after purification by column chromatography (silica gel, ether : petroleum ether 3 : 2). υ_{max} (thin film, $CDCl_3$) : 2966 (s), 2929(s), 1698(s), 1665(s), 1597(s), 1585(s); δ_H (250 MHz, $CDCl_3$) : 1.24 (d,3H,J=6.97, H-10), 2.22 (s, 3H,-NAc), 3.76 (dd,1H,J=9.40 and 1.00Hz,C(2)-H_a), 4.00 (m,1H, C(3)-H), 4.18 (t,1H,J=9.20Hz,C(2)-H_b), 7.35-7.51 (m, 2H,C(6)-H and C(7)-H), 8.50 (d,1H,J=6.86Hz,C(8)-H),10,08 (s, 1H,-CHO); δ_C (62.89 MHz, $CDCl_3$) : 21.56 (q,C-10), 24.09 (q,-NAc), 33.97 (d,C-3), 57,19(t,C-2),121.97(d,C-8),128.30(d,C-7), 131.54 (s, C-4), 137.90 (s, C-5), 143.14 (s, C-9), 169.06 (s, amide -CO), 191.79 (s, aldehyde -CO); E.I. m/z : 203 (MH^+, 100 %), 161 (65), 146 (85), 110 (95); m/z (accurate mass): Found: 203.0947 Calc : 203.0947

1-Allyl-10-formyl-2-quinolone (**9**); *and 3-(N-Benzoyl-N-allylamino) benzaldehyde* (**10**): After the radical reaction the solvent was removed under *vacuo* , and the residue was subjected directly to column chromatography on silica gel. Eluation with first petroleum spirit, and then with ether:petroleum spirit (6:4) afforded the quinolone (**9**) as the first fraction as an oil, and the benzaldehyde (**10**) as the second fraction. For (**9**) : υ_{max} (thin film, $CDCl_3$) : 3060 (s), 2980 (m), 1690 (m), 1660 (m), 1650 (m), 1645 (m); δ_H (250 MHz, $CDCl_3$) : 3.75-4.00 (m,1H,one of C(16)-H), 4.17 (dd,1H,J=10.73 Hz and J=8.27 Hz,one of C(16)-H), 5.02-5.26 (m,2H,C(18)-H_2), 5.90-6.06 (m,1H,C(17)-H), 7.09-7.81 (m,6H,arom.), 8.59 (dd,1H,J=7.41 Hz and J=1.43 Hz, C(13)-H); δ_C (62.89 MHz, $CDCl_3$) : 45.54 (t,C-16), 117.38 (t,C-18, one of the rotamers), 119.46 (t,C-18,the other rotamer), 119.81 (d), 123.48 (d), 125.70 (d), 126.88 (d), 127.19 (d), 127.94 (d), 128.13 (d), 128.31 (d), 128.55 (d), 128.71 (d), 128.93 (d), 129.04 (d), 129.13 (d), 129.26 (d), 129.96 (d), 130.17 (d), 130.68 (d), 131.31 (d), 132.17 (d), 135.23 (s), 135.61 (s), 137.41 (s), 138.18 (s), 160.98 (s,C-2), 191.23 (s,C-15) and 191.76 (s,C-15); m/z (accurate Mass): Found : 264.1025 Calc: 264.1024; For (**10**) : υ_{max} (thin film, $CDCl_3$) : 30.58 (w), 1714 (s), 1692 (s), 1655 (s); δ_H (250 MHz, $CDCl_3$) : 3.87 (q,1H,J=9.25 Hz,one of C(2)-H), 4.90 (dd,1H,J=9.25 Hz and J=5.48 Hz,one of C(2)-H), 4.98-5.17 (m,2H,C(4)-H_2), 5.95 (m,1H,C(3)-H), 6.92-8.05 (m,9H,arom.), 10.16 (s,1H,-CHO); δ_C (62.89 MHz, $CDCl_3$) : 52.11 (t,C-2), 118.81 (t,C-4), 122.90 (s), 125.68 (d), 127.38 (d), 127.64 (d), 128.33 (d), 128.50 (d), 128.77 (d), 129.82 (d), 130.71 (d), 132.46 (d,C-3), 135.75 (s), 142.13 (s), 170.61 (s,-COPh), 192.00 (d,-CHO); m/z (accurate Mass): Found : 266.1181 Calc: 266.1181

1-Trifluoroacetyl-4-methoxy-1,2,2a,3,4,5-hexahydrobenz[cd]indole (**12**):After the radical addition the reaction mixture was cooled to room temperature and the solvent was removed in *vacuo*. Chromatography of the residue on silica gel, first, with pentane, and then, with pentane:ether (4:1) afforded the both isomers of (**12**) as clear oil. For α-isomer : υ_{max} (thin film, $CDCl_3$) : 2962 (m), 2890 (m), 1702 (s); δ_H (250 MHz, $CDCl_3$) : 1.40-1.52 (m,1H,C(3)-H_a), 2.51 (td,1H,J=13.05 Hz and J=3.80 Hz,C(3)-H_b), 2.74-2.85 (m,1H,C(5)-H_a), 2.89 (d,1H,J=4.51 Hz,C(5)-H_b), 3.07 (d,1H,J=18.10 Hz,C(2a)-H_b), 3.43 (s,3H,-OMe), 3.52-3.66 (m,1H,C(2)-H_a),3.94-4.00 (m,1H,C(2)-H_b),4.55-4.65(m,1H,C(4)-H_b),6.97(d,1H,J=7.84 Hz,C(6)-H),7.21 (t,1H,J=7.92 Hz,C(7)-H),7.84 (d,1H,J=7.91 Hz,C(8)-H); δ_C (62.89 MHz,$CDCl_3$): 30.05(t,C-3),31.25(t,C-5),32.03(t,C-2a), 56.08 (t,C-2), 56.18 (q,-OMe), 74.67 (d,C-4), 115.00 (d,C-8), 125.29 (d,C-6), 128.38; (d,C-7), 131.70 (C-8b); m/z (accurate Mass): Found : 286.1055 Calc : 286.1054; For β-isomer: υ_{max} (thin film, $CDCl_3$) : 2966

(m), 2892 (m), 1706 (s); δ_H (250 Mhz, $CDCl_3$) : 1.32-1.52 (m,1H,C(3)-H_a), 2.49-2.58 (m,1H,C(3)-H_b), 2.64 (t,1H,J=4.75 Hz,C(5)-H_a), 3.30 (d,1H,J=6.29 Hz,C(5)-H_b), 3.37 (d,1H,J=6.45 Hz,C(2a)-H_b), 3.49 (s,3H,-OMe), 3.67-3.85 (m,2H,C(2)-H_a and C(2)-H_b), 4.51-4.62 (m,1H,C(4)-H_b), 6.97 (d,1H,J=7.61 Hz,C(6)-H), 7.22 (t,1H,J=7.89 Hz,C(7)-H), 7.84 (d,1H,J=7.94 Hz,C(8)-H); δ_C (62.89 MHz, $CDCl_3$) : 32.12 (t,C-3), 32.93 (t,C-5), 36.95 (d,C-2a), 55.84 (t,C-2), 56.38 (q,-OMe), 77.00 (d,C-4), 115.16 (d,C-8), 125.18 (d,C-6), 128.64 (d,C-7), 131.59 (s,C-8b), 132.63 (s,C-5a), 139.91 (s,C-8a), 153.45 (s,-$COCF_3$); m/z (accurate Mass) : Found : 286.1055 Calc: 286.1054

4-Pyrrolidinyl-1,3,4,5-tetrahydrobenz[cd]indole **(14):** The title compound was obtained after purification by column chromatography (silica, ether:Et_3N 9:1); υ_{max} (thin film, $CDCl_3$) : 3500(s), 1620(w); δ_H (360 MHz, $CDCl_3$) : 1.85-1.95 (m,4H), 2.75-2.87 (m,6H), 2.97-3.06 (m,1H,C(4)-Hβ), 3.26-3.34 (m,2H,C(3)-Hβ and C(5)-Hα), 6.85-6.88 (m,2H,arom.), 7.11-7.18 (m,2H,arom), 8.10 (sbr,1H,NH); δ_C (90.56 MHz, $CDCl_3$): 23.45 (t), 28.23 (t), 33.80 (t), 52.16 (t), 62.77 (d,C-4), 108.43 (d,C-2), 112.68 (s,C-2a), 117.80 (d), 123.07 (d), 127.07 (s), 130.46 (s), 133.63 (s); E.I. m/z: 226(M^+,100); m/z (accurate mass): Found: 226.1461 Calc: 226.1469

4-Pyrrolidinyl-1,3,4,5-tetrahydrobenz[cd]indole **(33):** Aqueous sodium hydroxide (25% w/v, 15ml) was added to a solution of **(14)** (0.102g, 0.38mmol) in methanol (25ml) and the mixture stirred for 2 weeks. The methanol was removed in *vacuo* and the aqueous solution extracted with dichloromethane. The combined extracts were dried with magnesium sulphate and the solvent removed in *vacuo* . The residue was purified by column chromatography (silica, ether:Et_3N 9:1) to give the title compound as an oil; υ_{max} (thin film, $CDCl_3$) : 3500(s), 1620(w); δ_H (360 MHz, $CDCl_3$) : 1.85-1.95 (m,4H), 2.75-2.87 (m,6H), 2.97-3.06 (m,1H,C(4)-Hβ), 3.26-3.34 (m,2H,C(3)-Hβ and C(5)-Hβ), 6.85-6.88 (m,2H), 7.11-7.18 (m,2H), 8.10 (sbr,1H,NH); δ_C (90.56 MHz, $CDCl_3$) : 23.45 (t), 28.23 (t), 33.80 (t), 52.16 (t), 62.77 (d,C4), 108.43 (d,C2), 112.68 (s,C2a), 116.20 (d), 117.80 (d), 123.07 (d), 127.07 (s), 130.46 (s), 133.63 (s); E.I. m/z: 226(M^+,100); m/z (accurate mass): Found: 226.1461 Calc: 226.1469

(4H)-4-Acetyl-9-(4'-methoxyphenylmethyloxy)methyl-9-methyl-5,5a,6,6a,7,8,9,9a-octahydroindolo[6,5,4-cd] indole **(50):** Radical cyclisation of the enamine **(38)** gave the title compound after purification by column chromatography (silica, ammoniacal ether:methanol 9:1 and acetone:methanol 17:3) as a semi-solid; υ_{max} (thin film, $CDCl_3$) : 1640 (s); δ_H (270 MHz, $CDCl_3$) : Major isomer: 0.84 (s,3H,CH_3C), 1.40 (m,1H,C(6)-Hα), 2.20 (s,3H,CH_3CO), 2.56 (m,1H,C(6)-Hβ), 2.60 (s,3H,CH_3N), 2.80 (m,1H,C(6a)-Hβ), 2.9-3.0 (m,2H,C(8)-Hα and C(8)-Hβ), 3.24 (m,1H,C(5a)-Hβ), 3.43-3.53 (m,3H,CH_2O and C(9a)-Hβ), 3.56-3.66 (m,1H,C(5)-Hα),3.81(s,3H,CH_3O),4.21(t,1H,J=9.37Hz,C(5)-Hβ),4.49 and 4.61 (ABq,2H,J=11.78Hz, $ArCH_2O$),6.75(d,1H,J=7.73Hz,C(1)H),6.90(d,2H,J=8,69Hz),7.09(t,1H,J=7.82Hz,C(2)H),7.29(d,2H,J=8.69Hz), 7.85 (d,1H,J=7.92Hz,C(3)-H); δ_C (67.94 MHz, $CDCl_3$): 20.44 (q,CH_3C), 24.01 (q,COMe), 29.76 (t,C-6), 36.12 (d,C5a), 41.12 (q,NMe), 43.15 (d,C(a), 45.97 (t,C8), 55.33 (q,OMe), 56.15 (t,C5), 65.39 (t,OCH_2), 66.54 (d,C3), 122.83 (d,C1), 128.27 (d,C2), 129.41 (d), 130.23 (s), 132.33 (s,C9c), 132.83 (s,C9b), 141.10 (s,C3a), 159.30 (s), 168.66(s); E.I. m/z: 420 (M^+,15%), 269(88), 199(100); m/z (accurate mass): 420.2398 Calc: 420.2412

1-Acetyl-6-methyl-8-methylidene-2,3-dihydroergoline **(51):** Radical cyclisation of the enamine **(39)** afforded the title compound after purification by column chromatography (1.ether, 2.ether:Et_3N 9:1 and acetone:methanol 7:3) as a viscous oil; υ_{max} (thin film, $CDCl_3$):1645(s); δ_H (270 MHz, $CDCl_3$): Major isomer 1.79 (q,1H,J=11.78Hz), 2.1-2.1 (m,2H,C(9)-Hα and C(9)-Hβ), 2.22 (s,3H,Me0),2.4-2.5 (m,1H,C(4)-Hβ), 2.53

(s,3H,NMe), 3.01 (d,1H,J=12.74Hz,C(7)-Hα), 3.1-3.3 (m,3H,C(7)-Hβ,C(10)-Hβ and C(5)-H), 3.3-3.5 (m,1H,C(3)-Hβ), 3.63 (t,1H,J=10.63Hz,C(2)-Hα), 4.22 (t,1H,J=8.96Hz,C(2)-Hβ), 4.81 (s,1H,alkenyl proton cis to CH_2N), 4.85 (s,1H,alkenyl proton trans to CH_2N), 6.86 (d,1H,J=7.72Hz,C(12)-H), 7.16 (t,1H,J=7.92Hz,C(13)-H), 7.84 (d,1H,J=7.72Hz,C(14)-H); δ_C (67.94 MHz, $CDCl_3$): 21.78 (t,C4), 24.06 (q,MeCO), 37.44 (d,C3), 38.50 (d,C10), 38.84 (t,C9), 42.51 (q,NMe), 54.71 (t,C7), 56.87 (t,C2), 60.64 (d,C5), 109.85 (t,=CH_2), 114.49 (d,C14), 122.41 (d,C12), 128.70 (d,C13), 130.33 (s,C16), 137.89 (s,C11), 142.83 (s,C15), 168.67 (s); E.I. m/z: 282 (M^+,100%), 267(18), 239(10); m/z (accurate mass): Found: 282.1723 Calc: 282.1732

(4H)-4-Acetyl-9-methoxycarbonyl-9-phenylthiomethyl-5,5a,6,6a,7,8,9,9a-octahydroindolo[6,5,4-cd]indole **(52):** Aldehyde **(31)** (0.494 g,1.69 mmol) and amine **(36)** (0.336 g, 1.41 mmol) were stirred together overnight in dry benzene (40ml) in the presence of molecular sieves (5.27g). The sieves were removed by filtration and then were washed with benzene (60ml). After heating at reflux for 5 days the solvent was removed in *vacuo* . The residue was dissolved in dry-benzene and the radical addition reaction was performed by following the general procedure. After cooling the solvent was removed in *vacuo* and the residue was purified twice by column chromatography (silica, EtOAc;Et_3N 9:1 and petrol:acetone 7:3) to give **(52)** (0.262g, 36% overall) as a white solid; υ_{max} (thin film, $CDCl_3$): 1740(s), 1640(s); δ_H (400 MHz, $CDCl_3$): Major isomer 1.24 (q,1H,J=11.74Hz,C(6)-Hα), 2.21 (s,3H,MeCO), 2.40-2.43 (m,1H,C(6)-Hβ), 2.46 (s,3H,NMe), 2.81 (d,1H,J=13.50Hz), 3.10-3.15 (m,1H,C(6a)-Hβ), 3.18 (d,1H,J=8.78Hz,C(8)-Hβ), 3.21-3.30 (m,1H,C(5a)-Hβ),3.32(d,1H,J=9.59Hz,C(8)-Hβ),3.37 (d,1H,J=13.50Hz), 3.62 (t,1H,J=10.33Hz,C(5)-Hα), 3.79 (s,3H, OMe),3.89(d,1H,J=10.99Hz,C(9a)-Hβ),4.22(t,1H,J=9.53Hz,C(5)-Hβ), 6.97 (d,1H,J=7.96Hz,C(1)-H), 7.10 (t,1H,J=7.17Hz), 7.15-7.27 (m,3H,C(2)-H), 7.35(d,2H,J=7.30Hz),7.89 (d,1H,C(3)-H); n.O.e. Irradiation at 1.25 ppm showed positive enhancement at 2.80 ppm indicating that the $PhSCH_2$ group is *cis* relative to C(6)-Hα; δ_C (100.63 MHz, $CDCl_3$): 23.84 (q,COMe), 30.84 (t,C6), 35.58 (d,C5a), 37.19 (t), 39.68 (q,NMe), 47.75 (d,C9a), 52.40 (q,OMe), 55.90 (t,C5), 61.70 (t,C8), 64.22 (d,C6a), 114.54 (d,C3), 122.64 (d,C1), 125.50 (d), 128.40 (d,C2), 128.58 (d), 128.88 (d), 130.89 (s,C9c), 133.10 (s,C9b), 137.87 (s), 141.16 (s,C3a), 168.45 (s), 174.87 (s); E.I. m/z: 436 (M^+,17%), 327(18),199 (68), 128(100); m/z (accurate mass): Found: 436.1809 Calc: 436.1821

4(H)-4-Acetyl-9,9-(bis)phenylthiomethyl-5,5a,6,6a,7,8,9,9a-octahydro indolo-[6,5,4-cd] indole **(53):** To a boiling solution of the enamide **(45)** (0.300 g, 051 mmol) in dry-degassed toluene (50 ml, 0.006M) was added a solution of tri-*n*-butyltin hydride (0.200 ml, 0.75 mmol) and a catalytic amount of AIBN (0.010 g) in toluene (20 ml, 0.037M) over a period of 20 hours at reflux, by means of a syringe pump. After the addition was complete, the reaction mixture was allowed to cool down to room temperature and the solvent was removed under *vacuo*. The residue was dissolved in a small amount of dichloromethane and subjected to column chromatography on silica gel. Tin residues were eluted first using large volume of petroleum ether, and then the product **(53)** (0.135 g, 52%) was eluted with ethyl acetate:petroleum ether:tri-ethyl amine (8:1:0.1) as a yellow powder , m.p.113-117°C; υ_{max} (thin film, $CDCl_3$) : 1686 (s, cyclic amide), and 1653 (s, amide); δ_H (400 MHz, $CDCl_3$) : 1.69 (m, 1H,C(6)-H_a), 2.20 (s, 3H, -NAc), 2.55 (m, 1H,C(6)-H_b), 2.92 (m, 1H, H_b proton of one of the -$PhSCH_2$ groups), 2.94 (s, 3H, -NMe), 2.96 (m, 1H, other H_b proton of the -$PhSCH_2$ groups), 3.29 (m, 2H,H_a proton of one of the -$PhSCH_2$ groups, and C(5a)-H_b), 3.52 (m, 1H, C(5)-H_a), 3.88 (m, 2H, other H_a proton of the $PhSCH_2$ groups, and C(6a)-H_b), 4.20 (t, 1H, J = 9.4 Hz, C(5)-H_b), 4.27 (d,1H, J = 8.87 Hz, C(9a)-H_b), 6.81 (d, 1H, J = 7.74 Hz, C(1)-H), 6.97-7.47 (m, 11H, 2x -SPh, and C(2)-H), 7.90

(d,1H, J = 7.90 Hz,C(3)-H); n.O.e. (400 MHz) : Irradiation at 4.27 ppm for the proton H_b-9a showed positive enhancements at 3.88 ppm for the proton H_b-6a and at 3.29 ppm for the proton H_b-5a showing that they occupy the same face of the molecule.; δ_C (100.63 MHz, $CDCl_3$) : 23.94 (q,-NAc), 28.94 (q, -NMe), 29.93 (t,C-6), 35.27 (d, C-5a), 38.14 (d, C-9a), 39.69 (t,-CH_2SPh), 43.38 (t,-CH_2SPh), 53.10 (s, C-9), 55.90 (t, C-5), 58.16 (d, C-6a), 115.02 (d, C-3), 122.07 (d,C-1), 126.08 and 126.87 (2xd, aromatic,p- to sulphur atom), 128.33 and 129.03 (2xd, aromatic, m- to sulphur atom), 129.34 and 130.78 (2xd, aromatic, o- to sulphur atom), 130.34 (s, C-9c), 131.71 (s, C-9b), 135.67 and 136.69 (2xs, aromatic, ipso to sulphur atom), 141.59 (s,C-3a), 168.51 (s, amide,-NAc), and 172.61 (s, amide, C-8); E.I. m/z : 514 (M^+,4%), 391 (54), 281 (40), 168 (31), 123 (60), 109 (35), 43 (100); m/z (accurate mass): Found : 514.1749 Calc: 514.1751

(4H)-4-Acetyl-9-methoxycarbonyl-9-methyl-5,5a-6,6a-7,8,9,9a-octahydro indolo [6,5,4-cd]indole **(54)** : To a boiling solution of the enamine **(41)** (0.500 g, 1.225 mmol) in dry-degassed benzene (50 ml, 0.024 M) and a catalytic amount of AIBN (0.010 g) was added a solution of tri-n-butyltin hydride (0.40 ml, 1.50 mmol) and AIBN (0.010 g) in benzene (20 ml, 0.075 M) over a period of 14 hours by a syringe pump. The reaction mixture was allowed to cool to room temperature, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 1. neat petroleum ether; 2. petroleum ether:ethyl acetate : tri-ethyl amine 1:2:0.1; 3. ethyl acetate:methanol 9:1), and the 6-endo product **(55)** (0.192 g, 49%) along with the 5-exo product **(54)** (0.100 g, 25%) were isolated. Only the spectroscopic data for **(54)** is given below: υ_{max} (thin film, $CDCl_3$) : 1732 (s), 1663 (s), 1639 (s), 1590 (s); δ_H (250 MHz, $CDCl_3$) : 1.32 and 1.34 (2xs, 3H, C(10)-H_3), 1.83-1.90 (m,1H), 2.20 (s, 3H,-NAc), 2.30 (s, 3H, -NMe), 2.50-2.70 (m,1H), 2.76-2.82 (m,1H), 3.00-3.20 (m,1H), 3.25-3.50 (m,1H), 3.60-3.70 (m,1H), 3.66 (s,3H,-OMe), 4.12 (t,1H), 6.70-7.15 (m,2H, arom.), 8.05 (d,1H, arom.); δ_C (62.89 MHz, $CDCl_3$) : 21.57 (q,C-10), 24.24 (q,-NAc), 26.92 (t, C-6), 33.77 (d, C-5a), 36.26 (d, C-9a), 38.38 (q, -NMe). 52.26 (q, -OMe), 57.31 (t, C-5), 57.44 (t, C-8), 81.96 (d, C-6a), 114.61 (d, C-3), 123.84 (d, C-1), 128.00 (d, C-2), 134.56 (s, C-9), 137.94 (s, C-9c), 139.37 (s, C-9b), 141.96 (s, C-9d), 168.62 (s, -CO, amide), 173.12 (s, -CO, ester); C.I. m/z : 329 (MH^+, 5%), 279 (40), 220 (50), 206 (100); m/z (accurate mass):Found:346.2130 for ($C_{19}H_{24}N_2O_3$ + NH_4), requires: 346.2132

Methyl 1-acetyl-2,3,9,10-tetrahydrolysergate **(55)** : Crude enamine **(41)** (0.154 g,0.38 mmol) was dissolved in dry toluene (25 ml, 0.0152M), and the mixture was de-oxygenated by bubbling nitrogen through the solution for 0.5 h at room temperature. The reaction mixture was heated under reflux for 4 hours to ensure the thermal cyclisation of **(41)** to give the desired enamine **(64)** was complete. Then, a solution of tri-n-butyltin hydride (1.1 mol equiv., 0.110 ml) and catalytic amount of AIBN (0.007 g) in toluene (10 ml, 0.040 M) was added over 20 hrs to the boiling reaction mixture by using a syringe pump under a nitrogen atmosphere. The solvent was then removed in *vacuo* to give an oil which was purified by column chromatography (silica gel, 1.neat petroleum ether; 2. ether:methanol 10:1) to give methyl 1-acetyl-2,3,9,10-tetrahydrolysergate **(55)** as sole product consisting of two diastereoisomers in a ratio of 3:1 by n.m.r, as a foamy solid, m.p. 80-83°C (with slow decomposition); υ_{max} (thin film, $CDCl_3$) : 1732 (s, carbonyl, ester), 1654 (s, carbonyl, amide), 1637 (s); δ_H (250 MHz,$CDCl_3$) : 1.23-1.52 (m,2H), 2.50-3.20 (m,6H), 3.26-3.33 (m,1H), 3.50-3.70 (m,2H), 4.14-4.24 (m,1H,C(2)-H_b), 6.78-6.92 (m,1H,C(12)-H), 7.11 (t, 1H,C(13)-H), 7.80 (d,1H,C(14)-H) ; also singlets at : 2.19 (s,3H,-NAc), 2.33 (s,3H,-NMe), 3.66 (s,3H,-OMe) for the major isomer, and at 2.23 (s,-NAc), 2,36 (s,-NMe), 3.68 (s,-OMe) for the minor isomer in a ratio of 3:1; δ_C (62.89 MHz, $CDCl_3$) : 23.78 (q, -NAc), 28.20 and 29.70 (t, C-4), 36.70 (q,-NMe), 37.85 (d, C-3), 42.40 and 44.20 (d, C-8), 44.30 and 44.90 (d, C-

10), 45.70 (t, C-9), 51.42 (q,-OMe), 54.16 and 55.83 (t, C-2), 58.40 and 58.70 (t, C-7), 60.61 (d, C-5), 113.89 (s, C-14), 123.07 (d, C-12), 128.15 (d, C-13), 131.54 (s, C-16), 133.10 (s, C-11), 141.22 (s, C-15), 168.36 (s,-CO, amide), 175.01 and 175.20 (s,-CO, ester) ; E.I. m/z : 328 (M^+, 5%), 283 (3), 243 (40), 199 (30), 156 (35), 131 (100); m/z (accurate mass): Found : 328.1787 for ($C_{19}H_{24}N_2O_3$), requires : 328.1788

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24. Acid chloride (**44**) was prepared from the carboxylic acid (**43**) *in situ* as follows: The carboxylic acid (**43**) (0.453g,1.50mmol) was dissolved in freshly distilled thionyl chloride (10ml), and the mixture was stirred at room temperature for 2 hours under a nitrogen atmosphere. Then, dry toluene (20ml) was added, and both the solvent and excess thionyl chloride were removed azeotropically in *vacuo*. This procedure was repeated with another 20ml portion of toluene to give the product which was used without isolation.

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