Diastereoselective radical cyclization reactions; the synthesis of *O*-methylcorytenchirine

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Dedicated to Professor Rod Rickards on the occasion of his 70th birthday

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Abstract

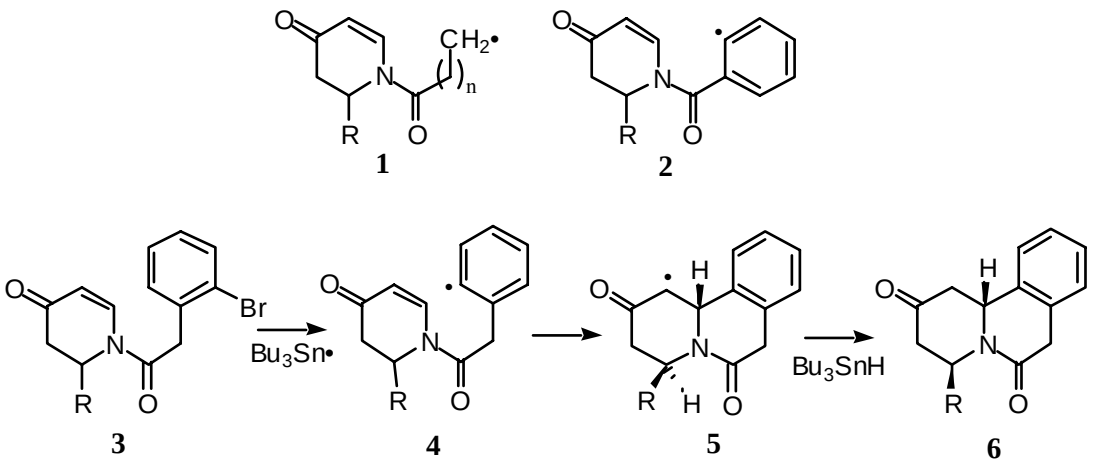
Highly diastereoselective cyclization of radicals such as **4** provides a model for the synthesis of 8-substituted berbines. Thus the reaction of 6,7-dimethoxyisoquinoline **21** with the acid chloride **19** affords the key intermediate **22**, which undergoes free radical cyclization on treatment with tributylstannane to give (±)-**23** as the sole product. Reduction of **23** affords (±)-*O*-methylcorytenchirine **14**. The carbamate **24** does not undergo radical cyclization when treated with tributylstannane, but the acetyl pyridine **33** affords the cyclized products **37** and **38** in reasonable yield and with good diastereoselectivity.

Keywords: Radical cyclization, diastereoselectivity, alkaloids, *O*-methylcorytenchirine

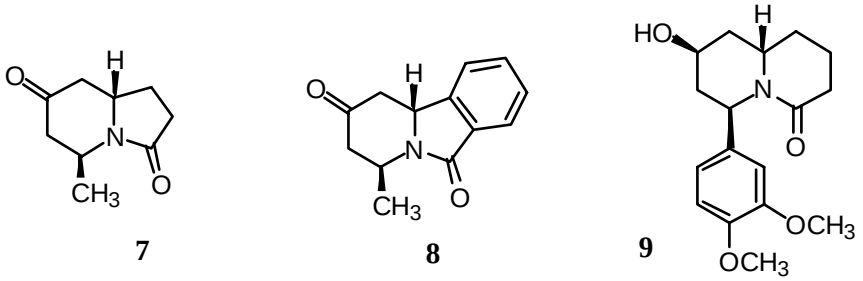
Introduction

In an earlier communication[1] we briefly described the intramolecular addition reactions of radicals of the general type **1** (n = 1 or 2) and **2** and used molecular mechanics calculations to support the notion that non-bonded interactions between the amide carbonyl group and the substituent R in the transition structures account for the very high diastereoselectivity exhibited by such processes. For example, treatment of the bromide **3a** with tributyl-stannane gave **6a** in good yield (91%), while **6b** was the sole product of the cyclization of **3b** (Scheme 1).

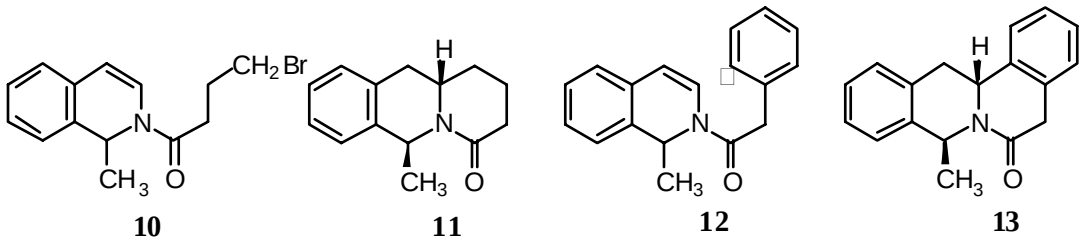
Indolizidines such as **7** and **8** were similarly prepared in high yield by treatment of the appropriate bromides. The high diastereoselectivity of these reactions underpinned other work in the field,[2] while their synthetic utility was illustrated by the efficient syntheses of (±)-lasubine **9**. These results indicate that the reaction mechanism involves intermediate radicals such as **4b** that undergo ring closure exclusively trans to the phenyl substituent to give **5b**. Hydrogen atom transfer from the stannane to **5b** then affords **6b**.



Scheme 1. a: R= Me; b: R = Ph.



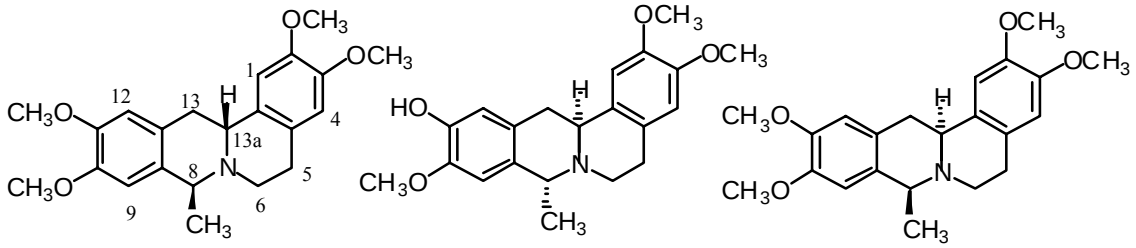
An important feature of the earlier work[1] was that the dihydroquinoline **10** also undergoes highly diastereoselective radical cyclization to afford **11** (90%) as the only detectable product. This observation suggested that related aryl radicals such as **12** should undergo similarly diastereoselective ring closure to afford products e.g. **13** in which the substituent at C8 is cis to the proton at the ring junction.



Since this stereochemistry is a unique feature of the dibenzoquinazoline alkaloids containing a substituent on C8 it seemed possible that radical cyclization might provide a useful method for their synthesis. We now demonstrate the validity of this hypothesis by the preparation of the alkaloid (±)-*O*-methylcorytenchirine **14**. In addition, we examine the cyclization behaviour of some related radicals that may also find use in alkaloid synthesis.

Results and Discussion

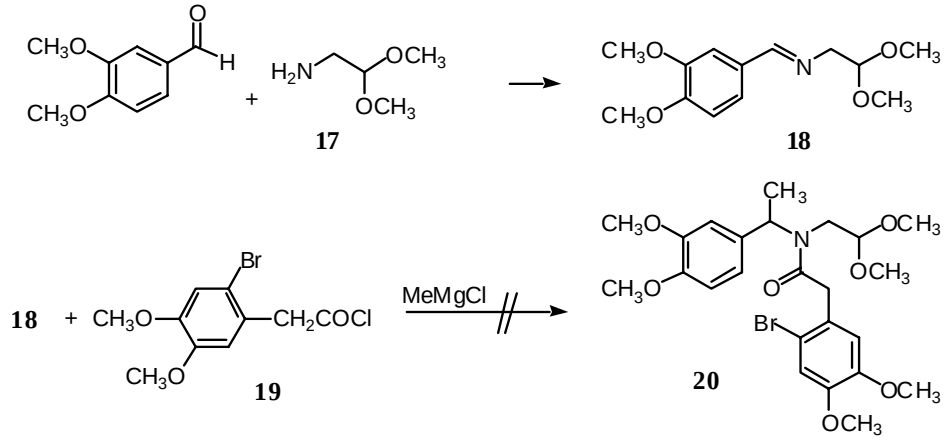
(−)-Corytenchirine **15** was first isolated in 1975 by Kametani *et al.*[3,4] from a biennial herb, *corydalis ochotensis*. This was the first report of an 8-substituted berbine alkaloid although the isolation of many 13-methyl substituted alkaloids having the same basic heterocyclic frame work had previously been reported.[5] More recently a number of new 8-substituted berbines have been described.[6] Coralydine **16**, a diastereomer of **14**, has also been synthesized[7] but appears not to occur in nature.



14 **15** **16**

There are relatively few reported syntheses of corytenchirine (−)-**15** and its *O*-methylated derivative. Immediately following the isolation of **15**, Brossi[8] described the first preparation of (±)-*O*-methylcorytenchirine **14** and Kametani reported the first total synthesis of (±)-corytenchirine **15** by two different routes.[9] Other syntheses have more recently been reported.[7]

The sequence we eventually employed for the synthesis of (±)-*O*-methyl corytenchirine **14** is illustrated in Scheme 3. Initially we planned to obtain the key intermediate **22** by acid catalyzed cyclization of the amide **20**. Condensation of 3,4-dimethoxybenzaldehyde with the amino acetal **17** under Dean-Stark conditions gave the imine **18** in good yield. However, when **18** was treated sequentially with the acid chloride **19** and methylmagnesium chloride as previously described[10] only starting material was recovered. Reverse addition of the two reagents i.e. the Grignard reagent followed by the acid chloride, was similarly unsuccessful (Scheme 2).

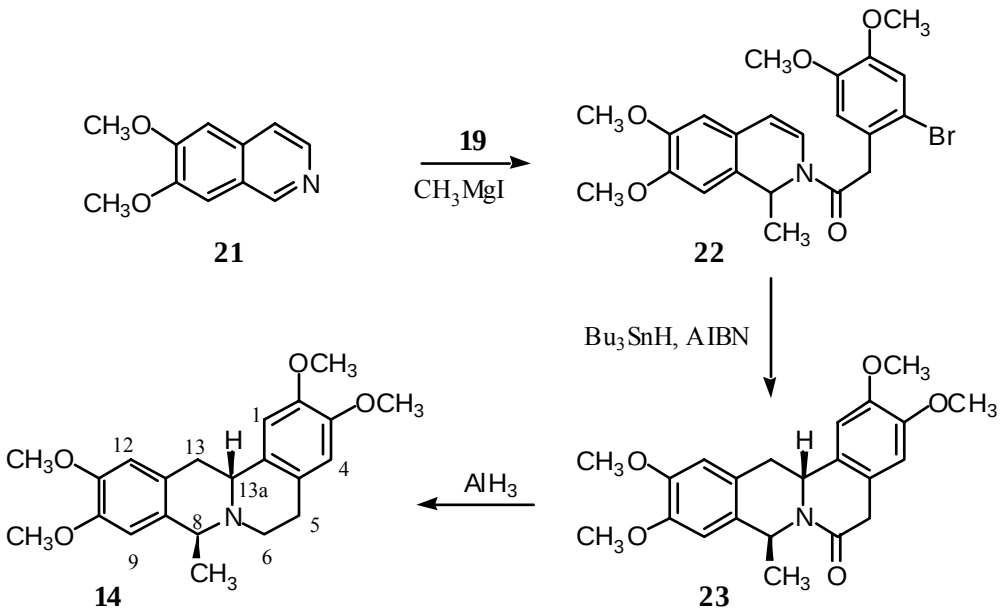


17 **18** **19** **20**

Scheme 2

In view of our failure to successfully prepare the proposed intermediate **20** we decided to investigate the formation of **22** directly from 6,7-dimethoxyisoquinoline **21** which was obtained in good yield (86%) by dropwise addition of **18** in trifluoroacetic anhydride to a solution of boron trifluoride acetic acid complex in trifluoroacetic anhydride following the published procedure.[11] When **21** was treated with the acid chloride **19** in THF at -23ºC and stirred for 1h a precipitate was formed (presumably an isoquinolinium quaternary salt) which redissolved on the addition of methylmagnesium iodide. Chromatography of the crude product gave **22** in good yield (92%).

The spectral characteristics of the isolated product were found to be in full agreement with those expected for **22**. Thus the mutually coupled AB system of doublets with a *J* value of 8 Hz in the ^{1}H NMR spectrum at δ 5.86 and 6.55 established the presence of the double bond essential for the radical ring closure step, while the presence of the methyl substituent and the adjacent benzylic proton was confirmed by the quartet at δ 5.81 coupled (*J* = 7 Hz) with a three proton doublet at δ 1.28 assigned to the C1 methyl protons.



Scheme 3

Treatment of the radical precursor **22** with tributylstannane and AIBN over 6 hours in benzene at reflux proceeded smoothly to give **23** as the single product in good yield (76%). Spectroscopic methods and elemental analysis confirmed the structure of **23**. The absence of the mutually coupled doublets assigned to the C3-C4 vinylic protons of **22** in the ^{1}H NMR spectrum of the single product isolated from the radical reaction was indicative of ring closure. In addition an ABX system was observed. The two AB signals centred at δ 2.84 and 3.03 assigned to the C13 methylene protons have the characteristics of two geminal and diastereotopic protons, the former relationship evident from a large coupling constant (*J* = 16 Hz) and the latter revealed by

the diminished intensity of the outer signals. As expected, the signal at δ 4.83 assigned to the C13*a* proton has a large (*J* = 12 Hz) coupling arising from an axial - axial interaction with one benzylic proton and a small (*J* = 3 Hz) arising from axial - equatorial interaction with the other. These observations conform to X-ray data for model compounds[12] which indicate that the equivalent proton in compounds related to **23** assumes a *pseudo*-axial conformation.

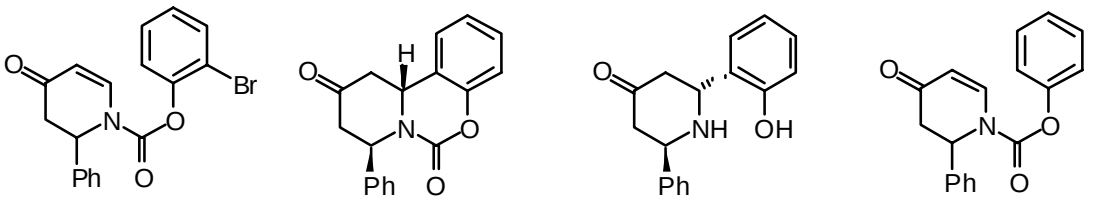
Confirmation of the stereochemical outcome of the above reaction was established by nOe difference spectroscopy. As expected upon irradiation of the signal assigned to the C13*a* proton there was a 16% enhancement of the methyl signal and 4% enhancement of the C8 proton. Saturation of the C8 proton resulted in a 11% enhancement of the methyl signal but only 2% of the C13*a* signal. Thus, these two experiments alone provide unequivocal evidence of the *syn* disposition of the C13*a* proton and the methyl group. Similar but less reliable confirmation was obtained by saturation of the methyl signal, which provided enhancements of 5 and 7% to C13*a* and C8 signals respectively.

Having in hand a precursor **23** with the required stereochemistry, we addressed the reduction of the C6 carbonyl function necessary to complete the preparation of **14**. $LiAlH_4$ is often used for the reduction of amides to amines. However, there was no reaction when **23** in THF was stirred with $LiAlH_4$ for 24 hours at room temperature, while heating of the mixture led to decomposition resulting in highly polar baseline material. On the basis of previous work with similar compounds,[1] the amide **23** was treated with AlH_3 generated *in situ* by addition of a third of a molar equivalent of $AlCl_3$ to a suspension of $LiAlH_4$. Reduction of the C6 carbonyl was rapid and efficient as observed on TLC. Purification of the crude residue by column chromatography over basified alumina afforded (±)-*O*-methylcorytenchirine **14** in 43% overall yield from 3,4-dimethoxybenzaldehyde and the amino acetal **17**.

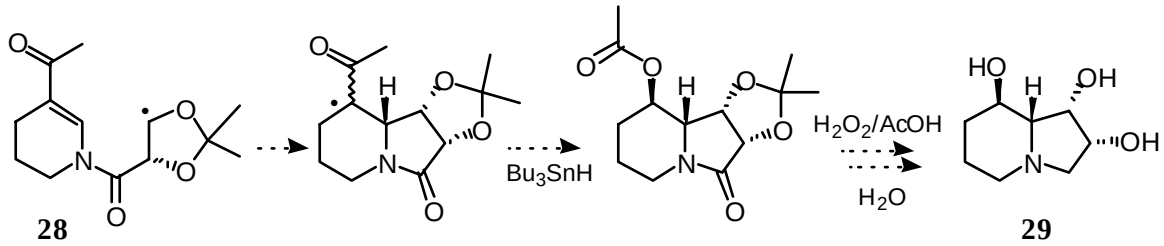
(±)-*O*-methylcorytenchirine **14** thus obtained had all the expected spectral and the analytical characteristics. The ^{1}H NMR spectrum agreed closely with the published data.[3] The assignment of the signals is given in the experimental section. The ^{13}C APT NMR spectrum consisted of three methylene signals at δ 29.46, 35.63, and 47.16 that confirmed the complete reduction of the carbonyl function and were assigned to C5, C13 and C6 respectively with the aid of heteronuclear correlation spectroscopy. In addition the spectrum displayed one methyl signal (δ 17.97), two methine carbons (δ 50.35 and 59.22), two signals for the four methoxy carbons (δ 55.81, 55.93), signals for the four aromatic methine carbons (δ 109.08, 109.75, 111.11, 111.39) and five quaternary carbon signals. The molecular ion at *m/z* 369 together with exact mass calculations as given in the experimental section confirmed the identity of (±)-*O*-methyl-corytenchirine **14**.

The successful preparation of (±)-*O*-methylcorytenchirine via diastereoselective radical cyclization encouraged us to examine the synthetic potential of similar processes. For example cyclization of **24** similar to that of its carbon analog **3b** might be expected to give **25**, hydrolysis of which would afford the trans 3,6-disubstituted product **26**. The successful development of such a reaction series would allow simple access to a wide variety of alkaloids, e.g. the selenopsines,[13] andrachamine[14] and andrachcine.[15]

The radical precursor **24** was readily prepared from 4-methoxypyridine by treatment with 2-bromophenylacetyl chloroformate and phenylmagnesium bromide following standard procedures.[16] However, syringe pump slow addition of tributylstannane to **24** in benzene or *t*-butylbenzene at 80°C or 110°C afforded only the directly reduced product **27**. It is clear from these observations that the radical derived from **24** undergoes cyclization too slowly to compete effectively with hydrogen atom transfer from the stannane under the conditions employed to give **27**.

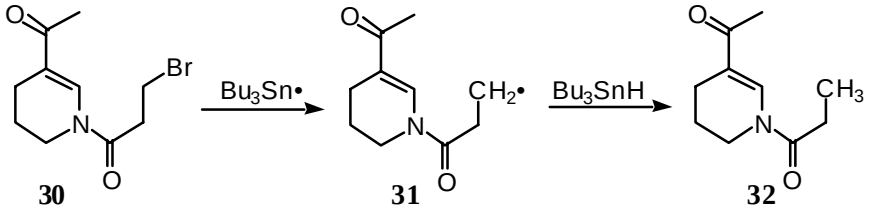


We next turned to reactions of the radicals containing a carbonyl activating group exocylic to the ring. Diastereoselective cyclization of a suitably constituted radical such as **28** could provide a key step in a simple synthesis of polyhydroxylated indolizidine alkaloids such as swainsonine **29** (Scheme 4).



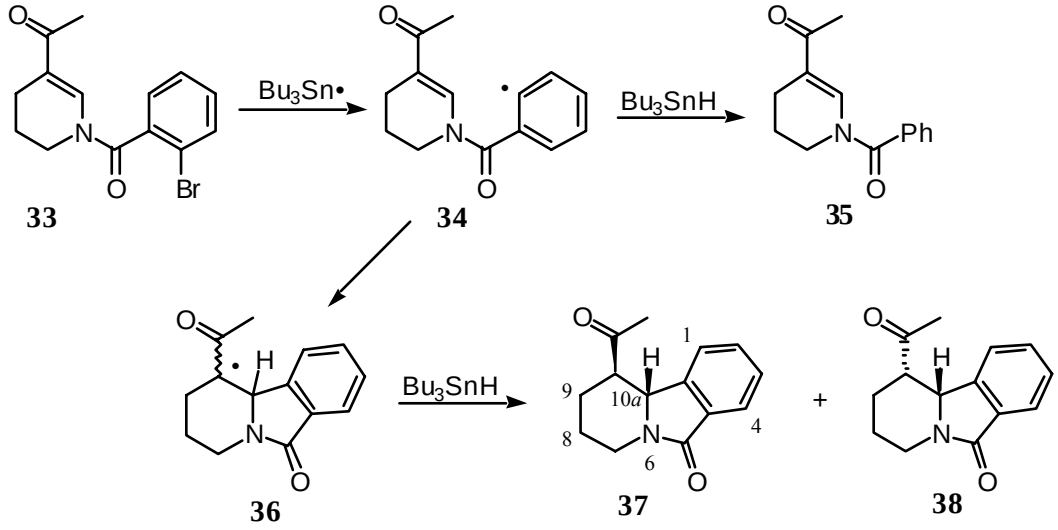
Scheme 4

The two radicals chosen for model studies to test this hypothesis were **31** and **34**. The precursors **30** and **33** were readily prepared from 3-acetylpyridine by *N*-acylation of the lithio-enamide with the appropriate acid chlorides. Unfortunately treatment of **30** with tributylstannane gave solely the directly reduced product **32** (Scheme 5)**.** Once again it appears that under our conditions cyclization of the radical **31** is too slow to compete with hydrogen atom transfer from stannane under the conditions employed.



Scheme 5

More encouraging results were obtained with the aryl radical precursor **33**. Treatment of **33** with tributylstannane in benzene (Scheme 6) at 80°C gave three products identified as the uncyclized compound **35** (35%), the indolizidine **37** (55%) and its diastereoisomer **38** (6%). The assignment of structure to **37** and **38** rests on spectral data. The key data were the signals attributable to the C10a protons. For the major isomer the doublet coupling of J = 10.5 Hz is indicative of axial - axial doublet coupling with the C10 proton, an orientation that is diagnostic of structure **37**. The doublet coupling for the C10a proton of J = 4.5 Hz in the minor isomer **38** is diagnostic of the expected axial - equatorial coupling.



Scheme 6

Although the yield of the major cyclized product **37** is modest, the relatively high diastereoselectivity (9:1) of the atom transfer step **36** → **37** leading to its formation indicates that this type of reaction could be synthetically useful. Further theoretical studies designed to determine the factors controlling the conformations of the radicals involved in the reactions described above, and their relative rates of hydrogen atom transfer and cyclization are in hand and will be separately reported.

Experimental Section

General Procedures. All reactions were carried out under an atmosphere of dry nitrogen in pre-dried glassware unless specified otherwise. The solvents used in the reactions were distilled and dried prior to use. Benzene for radical reactions was freshly distilled over sodium wire under nitrogen and degassed by purging with a stream of argon for 15 minutes.

Merck Kieselgel 60 (230-400 mesh ASTM) was used for Flash chromatography. Preparative radial chromatography was conducted on a Chromatotron model 7924 with 1, 2 and 4 mm plates

prepared from Merck Kieselgel 60 PF_{254} (with gypsum). Preparative liquid chromatography was performed using glass backed precoated with Kieselgel with PF_{254} indicator. TLC was conducted on glass backed Whatman MK6F precoated silica microscopic slide plates with 254 nm indicator. The solvents used for chromatography are specified in each experiment. Petroleum spirits refer to the fraction bp 60-80°C unless indicated otherwise.

^{1}H NMR spectra (300, 500 MHz) and ^{13}C(75, 125 MHz) were measured in $CDCl_3$ with tetramethylsilane (TMS) and residual $CHCl_3$ as internal standards (in some cases signals for two rotamers were detected). Low resolution EIMS were recorded at 70 *eV* on either a VG7070F or a VGZAB-2SEQ spectrometer. All elemental analyses were carried out by the microanalytical unit at the Research School of Chemistry. The melting points are uncorrected and were determined on a Reichert microscopic Kofler hot-stage apparatus.

***N*-[(3,4-Dimethoxyphenyl)methylene]-2,2-dimethoxy-ethanamine (18).** A solution of amino-acetaldehyde dimethylacetal **17** (5.78 g, 55 mmol) and 3,4-dimethoxy-benzaldehyde (8.31 g, 50 mmol) benzene (150 mL) was heated at reflux under a Dean-Stark apparatus. After the theoretical amount of water (0.9 mL) had been collected, the solution was cooled to room temperature and the solvent removed under reduced pressure to yield the solid imine **18** (12.62 g, 49.8 mmol, quant.); ^{1}H NMR δ 3.42 (s, 6H, 2 x OCH_3), 3.75 (d, 2H, J = 5, NCH_2), 3.91 (s, 3 H, $ArOCH_3$), 3.94 (s, 3 H, $ArOCH_3$), 4.75 (t, 1H, J = 5, acetal-CH), 6.88 (d, 1H, J = 8, 5-ArH), 7.17 (dd, 1H, J = 2 and 8, 6-ArH), 7.44 (d, 1H, J = 2, 2-ArH), 8.20 (s, 1H, imine-H); ^{13}C NMR δ 53.86, 55.65 (4 x OCH_3), 63.20 (NCH_2), 103.67 (acetal-CH), 100.45, 110.05, 123.05 (3 x ArCH), 129.06 (ArC_q), 148.97, 151.14 (2 x Ar$C_q$$OCH_3$), 162.77 (imine-CH); MS *m/z*: 253(M^+,17%), 222(42), 190(12), 178(40), 177(27), 165(28), 162(13), 151(84), 147(20), 137(14), 136(26), 120(13), 111(15), 107(30), 106(23), 92(49), 91(100), 90(23), 89(22); Anal. Calcd. for $C_{13}H_{19}NO_4$: C, 61.64;H, 7.56; N, 5.53. Found: C, 61.93;H, 7.85; N, 5.63.

6,7-Dimethoxyisoquinoline (21). Trifluoroacetic anhydride (50 mL) was added dropwise into 50 mL of boron trifluoride diacetic acid complex [$BF_3.2(CH_3CO_2H)$] at 0°C. The solution was stirred for 10 minutes at 0°C before the imine **18** (25.3 g, 100 mmol), dissolved in 38 mL of trifluoroacetic anhydride was introduced by dropwise addition over about 10 min. The cherry red solution was stirred for 2 hours at 0°C and then for 5 hours at room temperature. Ice and 20% aqueous NaOH (300 mL) were added and the mixture was extracted with chloroform (10 x 100 mL). The crude product obtained by acid extraction was chromatographed on silica gel (10% methanol in ethyl acetate) to afford dimethoxyisoqinoline[17] (16.25 g, 86 mmol, 86%), mp 91-93°C; ^{1}H NMR δ 3.90 (s, 6H, 2 x OCH_3), 6.93 (s, 1H, 5-ArH), 7.06 (s, 1H, 8-ArH), 7.38 (d, 1H, J = 6, 4-ArH), 8.28 (d, 1H, J = 6, 3-ArH), 8.92 (s, 1H, 1-ArH); ^{13}C NMR δ 55.66, 55.71 (2 x OCH_3), 104.17 (5-ArCH), 104.90 (8-ArCH), 118.91 (4-ArCH), 124.39 (4*a*-ArC_q), 132.16 (8*a*-ArC_q), 141.58 (3-ArCH), 149.58 (1-ArCH), 149.91 and 152.60 (2 x Ar$C_q$$OCH_3$); *m/z*: 190(M+1, 12%), 189(M^+, 100%), 174(13), 146(68), 117(34), 116(38), 103(49), 91(32), 89(20), 88(10), 77(13), 76(51), 75(24), 74(14), 63(21), 62(29), 51(22), 50(44); Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.93; H, 6.02; N, 7.13.

2-Bromo-4,5-dimethoxyphenylacetyl chloride (19). A solution of bromine (20.78 g, 130 mmol) in chloroform (40 mL) was added dropwise to a cooled solution (ice/acetone) 3,4-dimethoxyphenylacetic acid (19.62 g, 100 mmol) in $CHCl_3$ (60 mL). The ice bath was then removed, and the mixture was stirred for 6h at room temperature. Extraction with 10% aqueous NaOH (100 mL) afforded 2-bromo-4,5-dimethoxyphenylacetic acid[18] (32.22 g, 117 mmol, 90%); ^{1}H NMR δ 3.76 (s, 2H, CH_2CO), 3.85 (s, 6H, 2 x OCH_3), 6.78, 7.03(2s, each 1H, ArH), 10.98 (bs, 1H, CO_2H); ^{13}C NMR δ 40.68 (benzylic CH_2), 55.86, 55.91 (2 x OCH_3), 113.68, 115.20 (ArCH), 114.85 (ArC_q), 124.99 (ArC_qBr), 148.16, 148.73 (2 x ArC_qO), 176.99 (CO).
A drop of DMF was added to the acid (32.00 g, 116.3 mmol) in $SOCl_2$ (50 mL) and the solution was heated at reflux for 3 h. Removal of excess $SOCl_2$ under reduced pressure gave the acid chloride **19** as a thick oil (34.01 g, 115.8 mmol, 99%) which was used without further purification.

***N*-(2-Bromo-4,5-dimethoxyphenylacetyl)-6,7-dimethoxy-1-methyl-1,2-dihydro-isoquinoline (22).** Freshly prepared 2-bromo-4,5-dimethoxyphenylacetyl chloride **19** (0.660 g, 2.4 mmol) in THF (10 mL) was added dropwise to 6,7-dimethoxyisoquinoline **21** (0.378 g, 2 mmol) in THF (20 mL) at −23°C. The mixture was stirred for 1h during which time a suspension of the quaternary isoquinolinium salt was formed. Methylmagnesium bromide (3 mmol, 3M solution in diethyl ether) was added and stirring was continued for 1h at −23°C. Saturated aqueous NH_4Cl (100 mL) was added and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The solution of the combined organic extracts was dried with Na_2SO_4, filtered, and the solvent removed under reduced pressure. The residue was purified by radial preparative layer chromatography (50% ethyl acetate in light petroleum) to give **22** as a colourless solid (0.85 g, 1.84 mmol, 92%); mp 149-150°C; ^{1}H NMR δ 1.28 (d, 3H, J = 7, CH_3), 3.80, 3.87, 3.88 (s, 14H, 4 x OCH_3 and the benzylic-CH_2), 5.81 (q, 1H, J = 7, 1-CH), 5.86 (d, 1H, J = 8, 4-CH), 6.55 (d, 1H, J = 8, 3-CH), 6.62, 6.65, 6.78, 7.04 (4s, 1H each, ArH); ^{13}C NMR δ 20.62 (CH_3), 40.12, 40.25 (benzylic-CH_2), 43.70 (4-CH), 108.01, 108.20, 110.31, 110.43, 112.74, 115.18, 115.23, 121.86 (4-CH, 4 x ArCH), 114.41, 121.99, 126.09, 127.59 (ArC_q), 148.06, 148.39, 148.42, 148.52 (4 x ArO*C*H_3), 167.98 (CO); *m/z*: 463(M+2, 4%), 461(M^+, 3%), 448(5), 446(5), 231(7), 229(8), 204(3), 191(11), 190(100), 146(3), 91(2), 89(3), 77(5), 64(2), 63(4), 51(3); Anal. Calcd. for $C_{22}H_{24}NO_5Br$: C, 57.15; H, 5.23; N, 3.03; Br, 17.28. Found: C, 57.40; H, 5.20; N, 3.14; Br, 17.38.

(8RS,13*a*SR)-8-Methyl-2,3,10,11-tetramethoxy-5,8,13,13a-tetrahydrodibenzo-[a,g]quinolizine-6-one (23). A solution of the amide **22** (231mg, 0.5 mmol) in deoxygenated benzene (5 mL) was placed in a flask under an inert atmosphere and heated at reflux. A solution of Bu_3SnH (218 mg, 0.75 mmol) and AIBN (40 mg, 0.28 mmol) in degassed benzene (4 mL) was then added dropwise with a syringe pump over 6 h. The solution was then stirred at reflux for a further 4 h before it was cooled to room temperature and the solvent removed under reduced pressure. The residue was purified by radial preparative layer chromatography (60% ethyl acetate in light petroleum) to afford the cyclized product **23** as a solid (145 mg, 0.38 mmol, 76%) mp 198-200°C; 1H NMR δ 1.55 (d, 3H, J = 7, CH3), 2.84 (dd, 1H, J = 12 and 16, 13-H*ax*),

3.03 (dd, 1H, *J* = 3 and 16, 13-H*eq*), 3.63 (d, 2H, *J* = 21, 5-H), 3.86, 3.89 and 3.91 (4s, 3H each, 4 x OCH_3), 4.83 (dd, 1H, *J* = 12, *J* = 3, 13*a*-H), 5.97 (q, 1H, *J* = 7, 8-H), 6.59, 6.63, 6.67, 6.76 (4s, 1H each, 4 x ArH); ^{13}C NMR δ 21.91 (CH_3), 34.95 (5-CH_2), 38.86 (13-CH_2), 48.02 (8-CH), 52.92 (14-CH), 55.79 and 55.86 (4 x OCH_3), 108.35, 108.47, 109.76, 110.87 (1, 4, 9, 12-ArCH), 122.15, 124.76, 124.95, 129.99 (4*a*, 8*a*, 12*a*, 13*b*-ArC_q), 147.42, 147.82, 147.94, 148.58 (2, 3, 10, 11-ArC_qOCH_3), 166.15 (6-CO); *m/z*: 383(M^+, 9%), 369(2), 368(9), 206(2), 179(12), 178(100), 163(9), 135(5), 117(3), 115(2), 107(2), 105(3), 103(3), 91(7), 79(4), 77(4), 65(2); Anal. Calcd. for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found; C, 69.15; H, 6.91; N, 3.78.

(8RS,13*a*SR)-8-Methyl-5,8,13,13a-tetrahydro-2,3,10,11-tetramethoxy-6*H*-dibenzo-[a,g]quinolizine [(±)-*O*-Methylcorytenchirine] (14). A solution of $AlCl_3$ (160 mg, 1.2 mmol) in diethyl ether (12 mL) was added dropwise to a suspension of ice cooled $LiAlH_4$ (137 mg, 3.6 mmol) in diethyl ether (12 mL), the ice bath was removed and the solution was stirred for 30 min at room temperature. The tetracyclic amide **23** (575 mg, 1.5 mmol) in THF (12 mL) was then slowly added with stirring. After 3h the mixture was filtered through a thin pad of silica and washed with methanol (20 mL). The filtrate was concentrated and purified by radial preparative layer chromatography to yield (±)-*O*-methylcorytenchirine (390 mg, 1.06 mmol, 71%) as an oil; ^{1}H NMR δ 1.41 (d, 3H, *J* = 7, CH_3), 2.79 (dd, 1H, *J* = 16.5 and 11, 13-H_{ax}), 2.85-3.00 (m, 4H, 5-CH_2 and 6-CH_2), 3.06 (dd, 1H, *J* = 4.5 and 16.5 Hz, 13H_{eq}), 3.85, 3.87, 3.89 (3s, 12H, 4 x OCH_3), 4.11 (q, 1H, *J* = 7, 8-H_{eq}), 4.24 (dd, 1H, *J* = 4.5 and 11, 13*a*-H), 6.59, 6.60, 6.62, 6.70 (4 x ArH); ^{13}C NMR δ 17.97 (CH_3), 29.46 (5-CH_2), 35.63 (13-CH_2), 47.16 (6-CH_2), 50.35 (8*a*-CH), 55.81, 55.93 (4 x OCH_3), 59.22 (13*a*-CH), 109.08, 109.75, 111.11, 111.39 (1, 4, 9, 12-ArCH), 125.26, 126.45, 130.68, 131.78 (4*a*, 8*a*, 12*a,* 13*b*-ArC_q), 174.26 (2, 3, 11, 10-Ar*C*$_q$$OCH_3$); *m/z*: 369($M^+$, 5%), 355(4), 354(18), 192(5), 190(2), 180(2), 179(18), 178(100), 177(4), 176(3), 164(2), 163(12), 146(2), 135(8),.133(2), 117(4), 115(2), 107(3), 105(4), 104(3), 103(6), 92(3), 91(14), 79(7), 78(3), 77(9), 65(4), 55(3), 53(3), 51(4); HRMS exact mass calcd. for $C_{22}H_{27}NO_4$ 369.1940, found 369.1922; Anal. Calcd. for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found; C, 71.09; H, 7.64; N, 3.50.

1-(2-Bromophenoxycarbonyl)-2-phenyl-2,3-dihydro-4-pyridone (24). Treatment of 4-methoxypyridine with 2-bromophenoxycarbonyl chloride and phenylmagnesium bromide by the procedure described above for **22** and purification of the crude product by column chromatography (30% ethyl acetate in petroleum spirits) gave the required product as a colourless solid (89%); mp 85-88°C; ^{1}H NMR ($CDCl_3$) δ 2.90 (d, 1 H, *J* = 17 Hz, 3-CH_{ax}), 3.26 (dd, 1 H, *J* = 17 and 7 Hz, 3-H_{eq}), 5.52 (d, 1 H, *J* = 8 Hz, 5-CH), 5.91 (d, 1 H, *J* = 7 Hz, 2-CH), 7.15 (d, 1 H, *J* = 8 Hz, 6-CH), 7.11-7.33 (m, 7 H, 7 x ArH), 7.59 (d, 1 H, *J* = 7 Hz, ArH), 8.11 (d, 1 H, *J* = 7 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ 41.67, 41.75, 41.78 (3-CH_2), 56.35, 56.43 (2-CH), 109.28 (5-CH), 115.77, 137.73, 147.56 (3 x ArC_q), 123.47, 125.93, 127.83, 128.10, 128.55, 128.80, 133.32 (9 x ArCH), 141.73 (6-C), 151.86 (NCO) and 191.63 (4-CO); *m/z* : 274(M+3, 5%), 273(M+2, 16%), 272(M+1, 5%), 271(M^+, 16%), 292(3), 269(3), 267(3), 169(76), 200(31), 104(28), 96(100), 84(10), 77(10), 49(13). Anal. Calcd. for $C_{18}H_{14}NO_3Br$: C, 58.08; H, 3.79; N, 3.76; Br, 21.47. Found: C, 58.01; H, 3.51; N, 3.70; Br, 21.76.

3-Acetyl-1-(3-bromopropanoyl)-1,4,5,6-tetrahydropyridine (30). A round bottom flask containing a solution of 3-acetyltetrahydropyridine (1.25 g, 10 mmol) in THF (60 mL) was sealed with a septum and purged with nitrogen. The solution was cooled to −78 °C (ice/acetone) and *n*-butyl lithium (6.6 mL, 1.6 M, 10.5 mmol) was then added dropwise during approximately 10 min. A white precipitate was rapidly formed. After the mixture had been stirred for 30 min at −78°C 3-bromopropanoyl chloride (2.06 g, 12 mmol) was rapidly added. The solution gradually became clear (1-2 minutes) and was stirred for a further 30 min. before 40 mL of saturated aqueous NaCl was added. The organic portion was separated and the aqueous part was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated. Chromatography of the residue with 50% ethyl acetate in petroleum spirits afforded the title compound **30** as an oil (1.87 g, 7.19 mmol, 72%); ^{1}H NMR δ 1.88 (m, 2H, 5-CH_2), 2.33 (m, 5H, 4-CH_2 and $COCH_3$), 3.15 (m, 2H, 6-CH_2), 3.64 (m, 4H, 2' and 3'-CH_2), 7.72 and 8.33 (s each, 1H, 2-CH); ^{13}C NMR δ 19.78, 20.21, 20.24, 20.27, 20.33 (4 and 5-CH_2), 24.83 and 25.19 CO*C*H$_3$ rotamers), 25.40 (2'-CH_2), 36.40 and 37.27 (3'-CH_2), 40.91, 43.58 (6-CH_2), 121.87 (3-C_q), 134.55, 134.77 (2-CH rotamers), 168.93 and 169.11 (NCO, rotamers), 195.78 (3-CO); *m/z:* 261(M+2, 26%), 259(M^+, 26%), 246(7), 244(7), 215(5), 180(7), 179(27), 164(9), 126(9), 125(68), 124(8), 111(11), 110(100), 109(14), 107(15), 82(30), 80(9), 73(24), 55(41). Anal. Calcd. for $C_{10}H_{14}NO_2Br$: C, 46.17; H, 5.42; N, 5.38; Br, 30.72. Found: C, 46.54; H, 5.75; N, 5.24; Br, 30.56.

Bu_3SnH reduction of 3-Acetyl-1-(3-bromopropanoyl)tetrahydropyridine (30). 3-Acetyl-1-(3-bromopropanoyl)-tetrahydropyridine **30** (0.61 g, 2.33 mmol) and AIBN (50 mg, 0.35 mmol) were introduced into an oven-dried flask fitted with a reflux condenser. De-oxygenated benzene (25 mL) was added and the mixture was heated at reflux. A solution of Bu_3SnH (1.02 g, 3.5 mmol) and AIBN (85 mg, 0.6 mmol) in 12.5 mL of degassed benzene was added to the heated substrate and AIBN solution over 5-6 hours with the aid of a syringe pump. On completion of addition the solution was left to stir for 12 hours at the same temperature. The residue obtained by removal of benzene under reduced pressure was purified by radial preparative chromatography with 75% ethyl acetate in petroleum spirits to afford *N*-propanoyltetrahydropyridine **32** (0.41 g, 2.26 mmol, 97%) as a thick oil; ^{1}H NMR δ 1.23 (m, 3H, 3'-CH_3), 1.86 (b, 2H, 5-CH_2), 2.30 (bs, 5H, 4-CH_2 and $COCH_3$), 2.58 (b, 2H, 6-CH_2), 3.64 (b, 2H, 2'-CH_2), 7.80 and 8.38 (bs each, 1H, 2-CH); ^{13}C NMRδ 8.75 (3'-CH_3), 19.86, 19.89, 19.96, 20.01, 20.23, 20.26, 20.28, 20.39, 20.61, 20.69, 20.81 (4 & 5-CH_2), 24.74 and 24.79 ($COCH_3$), 26.50, 26.59, 26.65, 26.68, 26.76, 26.83, 26.91, 27.20, 27.42, 27.65 (2'-CH_2), 40.53, 40.64, 43.21, 43.36 (6-CH2 rotamers), 121.73 (3-Cq), 1 35.36, 135.48, 135.85 (2-CH), 172.53 and 172.57 (NCO), 196.52, 197.72 (3-CO); m/z: 182(M+1, 10%), 181(M, 35%), 126(9), 125(42), 111(15), 110(100), 96(5), 82(33), 81(8), 80(15), 67(7), 57(44); HRMS exact mass calcd. for $C_{10}H_{15}NO_2$ 181.1103. found 181.1102.

3-Acetyl-1-(2-bromobenzoyl)-1,4,5,6-tetrahydropyridine (33). THF (5 mL) was added to 3-acetyltetrahydropyridine (0.63 g, 5 mmol) in a flask purged with nitrogen, the solution was cooled to −78 °C (ice/acetone). and *n*-BuLi (3.25 mL, 1.6 M, 5.2 mmol) was added dropwise by

a syringe during 10 min. After the solution had been stirred for 0.5 h a solution of 2-bromobenzoyl chloride (1.21 g, 5.5 mmol) in THF (2.5 mL) was added with continued stirring. The mixture was left for a further 0.5 h then brought to room temperature and quenched with brine (10 mL). The organic layer was separated and the aqueous portion extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated at reduced temperature. Chromatography of the residue with 30% ethyl acetate in petroleum spirits afforded 3-acetyl-1-(2-bromobenzoyl)-1,4,5,6-tetrahydropyridine **33** (1.24 g, 4 mmol, 80%); ^{1}H NMR ($CDCl_3$) δ 1.84 and 1.93 (m, each 1H, 5-CH_2), 1.99 (s, 3H, $COCH_3$), 2.38 (m, 3H, 4 and 5-CH_2), 3.30, 3.46 and 3.89 (rotamer m, each 2H, 6-CH_2), 7.28-8.45 (m, 5 H, 2-CH and 4 x ArH); ^{13}C NMR (rotamer signals detected) δ 19.97, 20.42, 20.50, 20.93 (4 and 5-CH_2), 24.46 and 24.98 (3-CO<u>C</u>H$_3$), 40.95, 45.16, 43.21, 43.36 (6-CH_2), 119.40 (3-C_q), 120.78 (ArC_q), 127.69, 127.90, 127.96, 128.80, 131.09, 132.87, 132.99, 134.29, 137.08 (2-CH and ArCH rotamers), 135.84 (ArC_q), 168.85 (NCO), 196.04 (3-CO); *m/z:* 309(M+2, 34%), 307(M^+, 34%), 186(13), 185(98), 184(14), 183(100), 157(26), 155(26), 139(10), 105(19), 86(52), 84(69), 77(14), 76(16), 75(14), 71(13), 67(15), 51(35), 49(94); HRMS exact mass calcd. for $C_{14}H_{14}NO_2{}^{79}Br$ 307.0208, found 307.0207; Anal. Calcd. for $C_{14}H_{14}NO_2Br$: C, 54.56; H, 4.58; N, 4.55, Br, 25.93. Found: C, 54.73; H, 4.55; N, 4.80; Br, 25.61.

Bu_3SnH reduction of 3-acetyl-1-(2-bromobenzoyl)-tetrahydropyridine (33). The bromo compound (0.62 g, 2 mmol) and AIBN (43 mg, 0.3 mmol) were introduced to an oven dried round bottom flask fitted with a condenser, which was then purged with nitrogen and sealed with septa. De-oxygenated benzene (20 mL) was added and the solution heated at reflux. Heating was continued while a solution of Bu_3SnH (0.87 g, 3 mmol) and AIBN (71 mg, 0.5 mmol) in deoxygenated benzene (10 mL) was added over 6h through a syringe pump. Upon completion of addition the yellow solution was allowed to stir at reflux for 12 h. The solution was then cooled to room temperature and the solvent removed under reduced pressure. Radial preparative chromatography of the residue with ethyl acetate in petroleum spirit gave the following products:

i) 3-Acetyl-1-benzoyl-1,4,5,6-tetrahydropyridine (35). (0.161 g, 0.70 mmol, 35%); ^{1}H NMR δ 1.91 (m, 2H, 5-CH_2), 2.15 (s, 3H, $COCH_3$), 2.39 (m, 2H, 4-CH_2), 3.76 (m, 2H, 6-CH_2), 7.48-7.57 (m, 5H, ArH), 7.91 (b, 1H, 2-CH); ^{13}C NMR δ 20.46, 20.61 (4 and 5-CH_2), 24.66 (CO<u>C</u>H$_3$), 43.32 (b, 6-CH_2), 120.34 (3-ArC_q), 128.13, 128.60, 131.18 (5 x ArCH), 133.69 (ArC_q), 137.74 (2-CH), 170.16 (NCO), 196.51 (<u>C</u>OCH$_3$); *m/z:* 230(M+1, 12%), 229(M^+, 49%), 106(12), 105(100), 84(24), 78(7), 77(62), 57(6); HRMS exact mass calcd. for $C_{14}H_{15}NO_2$ 229.1103, found 229.1103.

ii) *trans*-10-Acetyl-1,2,3,5,6,7,8,8a-octahydrobenzo[a]indolizine-5-one (37). (0.251 g, 1.10 mmol, 55%). ^{1}H NMR δ 1.53 (m, 1H, 8-H_{ax}), 1.62 (m, 1H, 9-H_{ax}), 1.94 (m, 1H, 8-H_{eq}), 2.20-2.30 (m, 1H, 9-H_{eq}), 2.26 (s, 3H, $COCH_3$), 2.33 (Ddi, 1H, J = 3, 10.5 and 12 Hz, 10-H_{ax}), 2.95 (dt, 1H, J = 3.5 and 13 Hz, 7-H_{ax}), 4.52 (m, 1H, 7-H_{eq}), 4.70 (d, 1H, J = 10.5 Hz, 10*a*-H_{ax}), 7.28-7.31 (m, 1H, 1-ArH), 7.43-7.50 (m, 2H, 2 and 3-ArH), 7.84-7.87 (m, 1H, 4-ArH); ^{13}C NMR δ 24.86 (8-CH_2), 27.94 (9-CH_2), 29.88 (CO*C*H$_3$), 38.79 (7-CH_2), 55.42 (10-CH), 58.63 (10*a*-CH), 122.86, 123.65, 128.35, 131.35 (4 x ArCH), 132.18 (10*b*-C_q), 144.41 (4*a*-C_q), 165.97

(NCO), 209.60 (N*C*OCH$_3$); *m/z:* 230(M+1, 12%), 229(M$^+$, 60%), 214(18), 200(12), 187(19), 186(100), 184(13), 159(25)158(22), 146(7), 132(6), 131(7), 130(14), 117(7), 105(8), 104(15), 90(7), 89(6), 77(10), 76(7); HRMS exact mass calcd. for $C_{14}H_{15}NO_2$ is 229.1103, found 229.1103; Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34;H, 6.59; N, 6.11. Found: C, 73.04; H, 6.37; N, 5.81.]

iii) *cis*-10-Acetyl-1,2,3,5,6,7,8,8a-octahydrobenzo[a]indolizine-5-one (38). (0.029 g, 0.13 mmol, 6%). ^{1}H NMR δ 1.68-1.74 (m, 1H, 8-H$_{ax}$ and 9-H$_{ax}$), 1.87 (s, 3H, COCH$_3$), 1.96-2.07 (m, 1H, 8-H$_{eq}$), 2.21-2.27 (m, 1H, 9-H$_{eq}$), 2.01 (m 1H, 7-H$_{ax}$), 3.44 (m, 1H, 10-H$_{eq}$), 4.44 (d, 1H, J = 4.5 Hz, 10*a*-H$_{ax}$), 4.52 (m, 1H, 7-H$_{eq}$), 7.35-7.52 (m, 2H, 1, 2 and 3-ArH), 7.84-7.87 (m, 1H, 4-ArH); ^{13}C NMR δ 20.02 (8-CH$_2$), 25.81 (9-CH$_2$), 30.88 (CO<u>C</u>H$_3$), 39.06 (7-CH$_2$), 47.57 (10-CH), 58.67 (10*a*-CH), 120.86, 123.71, 128.19, 130.97 (4xArCH), 133.52 (10*b*-C$_q$), 143.19 (4*a*-C$_q$), 166.50 (NCO), 206.54 (<u>C</u>OCH$_3$); *m/z:* 230(M+1, 23%), 229(M$^+$, 54%), 214(27), 200(20), 187(30), 186(100), 184(28), 160(36), 159(48), 158(43), 149(25), 146(23), 132(25), 131(29), 130(39), 117(21), 105(29), 104(45), 90(25), 89(20), 77(34), 76(30), 71(23), 57(22); HRMS exact mass calcd. for $C_{14}H_{15}NO_2$ 229.1103, found 229.1104.

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