STUDIES ON *m*-CYCLOPHANE FORMATION FROM THE PHOTOLYSIS OF CHLOROACETAMIDE DERIVATIVES

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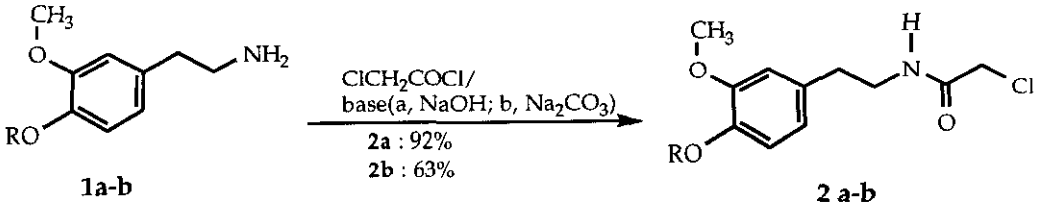
Abstract - The synthesis of 12-hydroxy-2-oxa-6-azabicyclo[7.3.1.]trideca-1(13),9,11-trien-5-one **(4)** is described. Two routes to **(4)** based on the photolysis of *N*-[2-(3,4-dimethoxyphenyl)ethyl]chloroacetamide **(2b)** and *N*-[2-(4-*t*-butyldimethylsiloxy-3-methoxyphenyl)ethyl]-chloroacetamide **(2c)** followed by *O*-demethylation or *O*-desilylation, were developed. Extension of the work has given the new *m*-cyclophane ester derivative **(9)**, whose structure has been confirmed by X-ray crystallography.

Amongst the products from the photolysis of *N*-[2-(3,4-dimethoxyphenyl)ethyl]chloroacetamide, Witkop and co-workers reported[1] the isolation of a *m*-cyclophane derivative **(3b)** in very low yield; analogous products were also obtained from other related photolyses as noted in the review by Sundberg.[2]

As part of a programme aimed at developing potential new pro-drugs for dopamine[4] based on the *m*-cyclophane skeleton in **3b** , we have sought ways to increase the photochemical yield of this system. In particular we wished to prepare initially the new derivative, 12-hydroxy-2-oxa-6-azabicyclo[7.3.1.]trideca-1(13),9,11-trien-5-one **(4)**, from **3b** by *O*- demethylation or from **3c** by *O*-

desilylation, as earlier work[3] had established that with a phenolic group present, no *m*-cyclophane derivative was obtained. The results are presented in this paper together with the preparation of an ester derivative of **3b**.

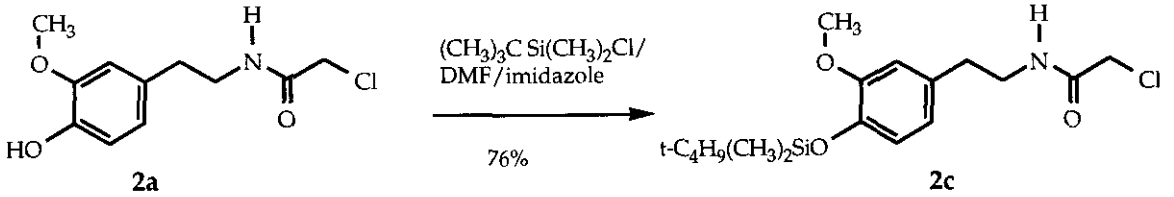
The precursor chloroacetamides **(2a-d)** were prepared in generally high yields by acylation of the appropriate amines by chloroacetyl chloride (Scheme 1), followed by silylation with *tert*-butyldimethylsilyl chloride (TBDMSC) in the case of **2c** (Scheme 2). A side product **(2d)** resulted from the alkylation of imidazole in this latter reaction when a larger excess of imidazole was used and the reaction was allowed to run for a longer period of time.



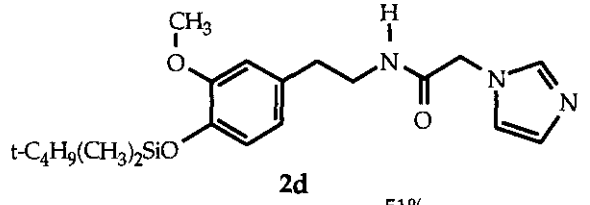
1a-b **2 a-b**

1-2	R
a	H
b	CH_3

Scheme 1



2a **2c**



2d 51%

Scheme 2

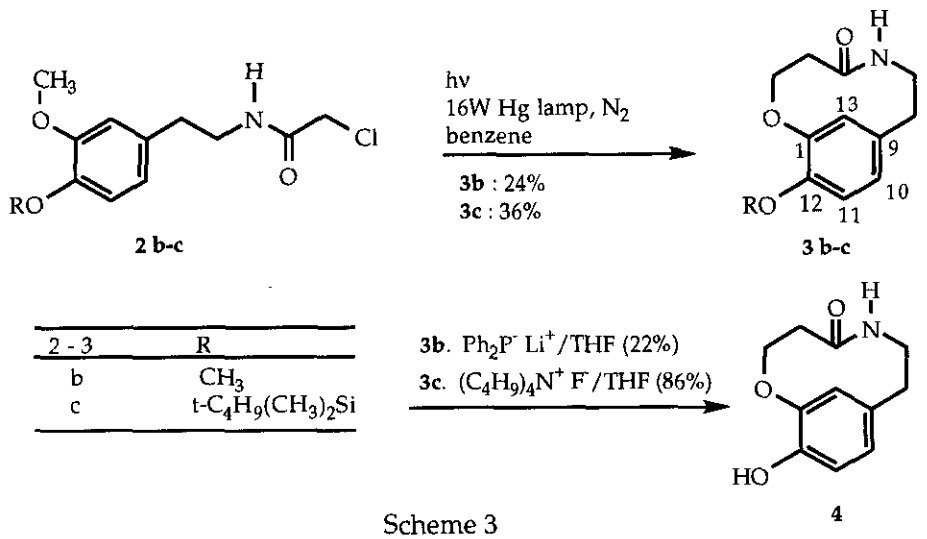
Photolyses of the chloroacetamides **(2b-c)** were conducted in benzene using a 16W mercury lamp (Scheme 3). The compound **(3b)** was isolated in 24% yield, which was an improvement on the

yield (12%) obtained[1] previously in THF. The reason is thought to be due to an increased effectiveness of the solvent cage[6] in the slightly more viscous solvent,[5] benzene. The low polarity of the solvent is also believed to contribute to the higher yield of the product **(3b)** obtained, since it retards the formation of other radical ion derived-products such as 7,8-dimethoxy-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one,[1] which was isolated in only 6.5% yield.[7,8] The possible formation of other isomers in benzene was suspected but not observed.

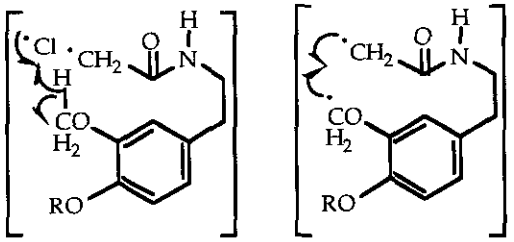
Distinguishing signals in the ^{1}H-nmr spectrum of the compound **(3b)** were produced by the oxymethylene and methoxy groups with a multiplet at δ 4.27 - 4.34 and a singlet at δ 3.88 in an integration ratio of 2 to 3 respectively; *ortho* coupling was observed for the 10, 11-aromatic hydrogens and *meta* coupling for the 10, 13-aromatic hydrogens. In the ^{13}C-nmr spectrum, the lactam carbonyl group resonated at 172.2 ppm.

Photolysis of the silylated chloroacetamide **(2c)** gave a higher yield (36%) of the analogous cyclolactam **(3c)**. The ^{1}H-nmr spectrum of **3c** showed a singlet for the *t*-butyl group at δ 1.02 and two singlets for each methyl group attached to the silicon atom at δ 0.18 and 0.24. In the ^{13}C-nmr spectrum, the signal at 172.1 ppm was ascribed to the carbonyl group.

The mechanism leading to products **(3b)** and **(3c)** most probably involves homolytic cleavage of the C-Cl bond.[5] This then gives rise to a chlorine radical and an amido methylene radical. The chlorine radical may then abstract a hydrogen atom from the 3-methoxy group **(A 3b-c)** to form a diradical intermediate. Subsequently the intramolecular combination of the diradical **(B 3b-c)** forms the cyclolactams **(3b)** and **(3c)**. It is possible that the *t*-butyldimethylsiloxy group at the 4 position in **2c** has an effect upon the conformation of the methoxy group at the 3 position. This sterically demanding group may orient the 3-methoxy group a little closer to the chloroacetyl group, resulting in more hydrogen abstraction from the methoxy group and subsequently formation of **3c** in a higher yield; the bulky siloxy group may also slow radical diffusion from the solvent cage. Furthermore, with **2c** the possible problem of competitive hydrogen abstraction from a saturated C-H group adjacent to oxygen at the 4-position is removed.

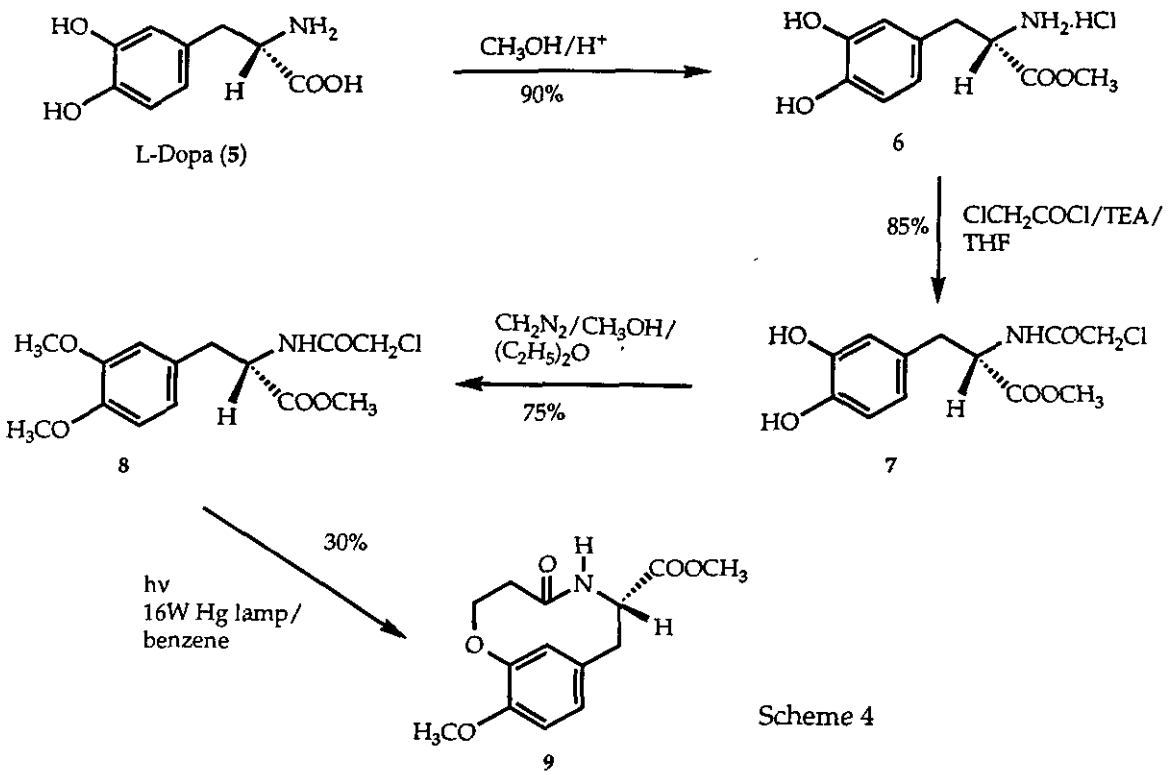


Scheme 3



Compounds **(3b)** and **(3c)** were converted to **4** by *O*-demethylation and *O*-desilylation (Scheme 3) using lithium diphenylphosphide and TBAF respectively. The structure of **4** was confirmed by the spectroscopic data.

In an extension of the work, photolysis of the chloroacetamide **(8)** derived from L-Dopa gave the new *m*-cyclophane analogue **(9)** (Scheme 4) in a good converted yield. The structure of **9** was confirmed unequivocally by X-ray crystallography.[11, 12] The structure obtained is shown in Figure 1 and non-hydrogen atom co-ordinates and equivalent isotropic thermal parameters are given in Table 1.



Scheme 4

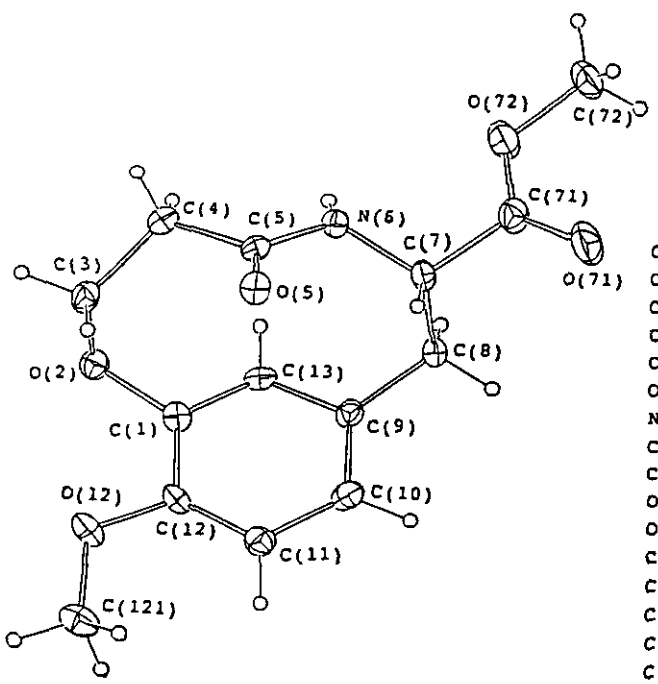


Figure1. Molecular projection of **9** normal to the phenyl ring; 20% thermal ellipsoids are shown for the non-hydrogen atoms, together with skeletal ring numbering. Hydrogen atoms have arbitrary radii of 0.1 Å.

Table 1. Non-hydrogen atom coordinates and equivalent isotropic thermal parameters of **9**. *y*(c(1)) defines the origin.

Atom	*x*	*y*	*z*	10^2U_{eq}Å^2
C(1)	0.039(2)	1.0(-)	0.8501(5)	0.041(4)
O(2)	0.087(1)	0.938(1)	0.9282(3)	0.050(3)
C(3)	-0.049(2)	0.785(2)	0.9379(5)	0.051(4)
C(4)	0.052(2)	0.643(2)	0.8865(5)	0.044(3)
C(5)	-0.054(2)	0.643(2)	0.7979(5)	0.035(3)
O(5)	-0.294(1)	0.662(1)	0.7816(3)	0.044(2)
N(6)	0.129(1)	0.616(1)	0.7429(4)	0.035(3)
C(7)	0.079(2)	0.674(2)	0.6598(5)	0.044(3)
C(71)	0.167(2)	0.559(2)	0.5958(6)	0.058(4)
O(71)	0.090(2)	0.572(2)	0.5260(4)	0.127(5)
O(72)	0.331(2)	0.450(1)	0.6215(4)	0.087(4)
C(72)	0.417(3)	0.334(2)	0.5612(6)	0.103(6)
C(8)	0.213(2)	0.844(2)	0.6477(5)	0.042(4)
C(9)	0.113(2)	0.962(2)	0.7077(5)	0.040(4)
C(10)	-0.093(2)	1.070(2)	0.6897(5)	0.049(4)
C(11)	-0.224(2)	1.150(2)	0.7507(5)	0.048(4)
C(12)	-0.169(2)	1.109(1)	0.8307(5)	0.038(3)
O(12)	-0.299(1)	1.166(1)	0.8954(3)	0.056(3)
C(121)	-0.479(2)	1.294(2)	0.8824(6)	0.061(4)
C(13)	0.191(2)	0.938(1)	0.7896(5)	0.036(3)

In summary, photolyses of chloroacetamides under suitable conditions thus provide a convenient route to oxaza-*m*-cyclophane derivatives.

EXPERIMENTAL PROCEDURE

General Procedures:

All melting points were determined using a Gallenkamp Melting Point apparatus and are uncorrected. The infrared spectra were recorded using a Digilab FTS-7 spectrophotometer and NaCl disks on mulls in nujol or hexachloro-1,3-butadiene (HCB). The peak positions were recorded in wave numbers (cm^{-1}). The ^1H nuclear magnetic resonance spectra (nmr) were determined at 400 MHz with a Varian Unity-400 spectrometer. ^{13}C nmr spectra were recorded using the same instrument at 100 MHz. Unless otherwise stated, the spectra were obtained on solutions in $CDCl_3$ and referenced to TMS. Chemical shifts of the outer peaks are given for specified multiplet patterns in the ^1H-nmr spectra. Ultra-violet/visible spectra were recorded on a Shimadzu UV-visible 160 spectrophotometer. Mass spectra (EI) were obtained using Vacuum General 12-12, Vacuum General - Quattro, or MAT-44 spectrometers and the direct insertion technique, with an electron beam energy of 70 eV and a source temperature of 200°C. The peak intensities, in parentheses, are expressed as the percentage abundance. In the CI mass spectra, methane was used as the ionising gas. High resolution mass spectra were run in the Research School of Chemistry, Australian National University, by Dr. J.K. MacLeod using a VG 70-70 double focussing mass spectrometer, or in the Central Science Laboratory, University of Tasmania by Dr. N. Davies, using a Kratos Concept ISQ or a VG 7070F mass spectrometer. The optical rotation was determined on a JASCO digital polarimeter, Model DIP-370. Elemental microanalyses of samples were carried out at the Australian National University and the University of Queensland. Analytical thin layer chromatography (tlc) was performed on Merck Kieselgel 60PF_{254} silica on aluminium sheets. R_f values were recorded from the centre of spots. All chromatographic solvent proportions are volume for volume. Column chromatography was performed using Merck silica gel under medium pressure. Dry DMF was distilled from BaO, and dry THF was distilled from sodium metal and benzophenone. Light petroleum had a boiling point range of 60-80°C. Solvents were removed under reduced pressure by rotary evaporation, and organic solvent extracts were dried with anhydrous Na_2SO_4.

General Information for the Photolyses:

The photolyses were conducted in a large quartz immersion well reactor (model RQ 400) supplied by Photochemical Reactors Ltd., U.K. The lamp (16W) was housed internally in a vycor glass sleeve and the solution was saturated with N_2 before and during photolysis.

_N_-[2-(4-Hydroxy-3-methoxyphenyl)ethyl]chloroacetamide (2a):

To a stirred solution of **1a**[9] (200 mg, 0.98 mmol) in THF (20 ml) was added NaOH (3.5 ml, 5M). The solution was then cooled in an ice bath to 5°C. Chloroacetyl chloride was added dropwise until a white precipitate was observed. The ice bath was removed and the stirring allowed to continue overnight. The solution was then basified to pH 9 (1M NaOH, 9 ml) and acidified to pH 6.5 (1M HCl). This solution was extracted with DCM (3 x 35 ml). The combined organic extracts were washed with water (2 x 30 ml) and dried. The organic solvent was then removed to give the *chloroacetamide* **(2a)** as colourless crystals after recrystallization from ethanol/ether (220 mg, 92%); mp 103-104°C. Ir (Nujol) υ_{max}: 3420 (OH), 3310 (NH), 1635 (C=O) cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 2.78 (t, J = 8.4 Hz, 2H, CH_2Ar), 3.54 (dt, J = 8.4, J = 6.0 Hz, 2H, $C\underline{H}_2NH$), 3.89 (s, 3H, CH_3O), 4.00 (s, 2H, CH_2Cl), 6.69-6.71 (m, $2H_{arom}$), 6.86-6.88 (m, $1H_{arom}$). Ms (CI) m/z (%): 244 (100, M^++1), 210 (25), 191 (7), 150 (32), 137 (9); (EI) (M^+; accurate mass 243.0663, $C_{11}H_{14}NO_3{}^{35}Cl$ requires 243.0662). Anal. Calcd for $C_{11}H_{14}NO_3Cl$: C, 54.22; H, 5.79; N, 5.75. Found: C, 54.34; H, 5.92; N, 5.67.

_N_-[2-(3,4-Dimethoxyphenyl)ethyl]chloroacetamide (2b):

To a stirred mixture of **1b** (10.0 g, 55.17 mmol) and anhydrous Na_2CO_3 (6.0 g, 56.63 mmol) in light petroleum (60 ml) was added chloroacetyl chloride (6.8 g, 60.21 mmol, 4.8 ml) dropwise over 10 min. The solution was allowed to stir for 15 h. The solvent was then removed to give a brown residue. The residue was extracted with DCM (100 ml) and filtered to remove the Na_2CO_3. The resulting solution was washed with a solution of Na_2CO_3 (20 gl^{-1}, 2 x 30 ml). The organic layer was dried and evaporated to give a brown residue. Recrystallization from MeOH and H_2O gave the chloroacetamide **(2b)** as colourless crystals (8.95g, 63%); mp 97-98°C (lit.,[10] 96°C).

***N*-[2-(4-*t*-Butyldimethylsiloxy-3-methoxyphenyl)ethyl)]chloroacetamide (2c):**

To a stirred solution of **2a** (200 mg, 0.821 mmol) in dry DMF (5 ml) was added TBDMSC (633 mg, 4.105 mmol) under anhydrous conditions and N_2. To the resulting solution was added imidazole (120 mg, 2.053 mmol) and the mixture was then allowed to stir for 15 h. The solution was concentrated under reduced pressure and then extracted with EtOAc (70 ml). The extract was washed with water (3x15 ml), dried and evaporated to yield a pale brown oil. The oil was chromatographed on a column of silica gel. Elution with DCM followed by evaporation of the solvent gave the *silylated chloroacetamide* **(2c)** as a colourless crystalline solid (223 mg, 76%); R_f 0.39 (DCM); mp 69-70^{0}C. ^{1}H-Nmr ($CDCl_3$) δ: 0.15 (s, 6H, 2x CH_3Si), 1.00 (s, 9H, $(CH_3)_3CSi$), 2.78 (t, J = 6.8 Hz, 2H, CH_2Ar), 3.54 (dt, J = 6.8, J = 6.0 Hz, 2H, $C\underline{H}_2NH$), 3.80 (s, 3H, CH_3O), 4.02 (s, 2H, CH_2Cl), 6.65 (dd, J = 8.0, J = 2.4 Hz, 1H, 6-H_{arom}), 6.68 (d, J= 2.0, 1H, 2-H_{arom}), 6.799 (d, J = 8.0 Hz, 1H, 5-H_{arom}). ^{13}C-Nmr ($CDCl_3$) δ: -4.7 (2x CH_3Si), 18.4 (CSi), 25.7 ($(\underline{C}H_3)_3CSi$), 35.1 (CH_2Ar) 41.0 (CH_2NH), 42.7 (CH_3O), 55.5 (CH_2Cl), 112.6 (ArC-H), 120.8 (ArC-H), 121.1 (ArC-H), 131.6 (Ar$\underline{C}$-CH_2), 143.8 (Ar$\underline{C}$-OSi), 151.0 (Ar$\underline{C}$-OCH_3), 165.7 (CO). Ms (EI) m/z (%): 357 (0.3, M^+; accurate mass 357.153, $C_{17}H_{28}NO_3{}^{35}Cl^{28}Si$ requires 357.1525), 342 (0.6), 322 (0.2), 300 (30), 192 (100).

***N*-[2-(4-*t*-Butyldimethylsiloxy-3-methoxyphenyl)ethyl]-2-(1-imidazolyl)acetamide (2d):**

To a stirred solution of **2a** (500 mg, 2.05 mmol) and imidazole (1.39, 20 mmol) in dry DMF (10 ml) was added TBDMSC (1.543 g, 10 mmol). The solution was allowed to stir for 58 h. The resulting solution was concentrated under reduced pressure, extracted with EtOAc (80 ml), the extract washed with water (3x15 ml), and then dried. The organic solvent was evaporated to give a pale brown oil. The crude oil was then crystallized from light petroleum and EtOAc (4:1) to afford *N-[2-(4-t-butyldimethylsiloxy-3-methoxyphenyl)ethyl]-2-(1-imidazolyl)acetamide* **(2d)** as a colourless crystalline powder (390 mg, 49%); mp 116-117°C. ^{1}H-Nmr ($CDCl_3$) δ: 0.15 (s, 6H, 2x CH_3Si), 1.00 (s, 9H, $(CH_3)_3CSi$), 2.68 (t, J = 6.8 Hz, 2H, CH_2Ar), 3.46 (dt, J= 6.8, J = 6.0 Hz, 2H, CH_2NH), 3.78 (s, 3H, CH_3O), 4.60 (s, 2H, CH_2N), 6.48-6.51 (dd, J = 8.0, J = 1.8 Hz, 1H, 6-H_{arom}), 6.58 (d, J = 1.6 Hz, 1H, 2-H_{arom}), 6.75 (d, J = 8 Hz, 1H, 5-H_{arom}), 6.81 (d, J = 1.6 Hz, 1H, Im H), 7.11 (d, J = 1.6 Hz, 1H, Im H), 7.46 (s, 1H, N-CHN). ^{13}C-Nmr ($CDCl_3$) δ: 4.6 (2x CH_3Si), 18.4 (CSi), 25.7 ($(\underline{C}H_3)_3CSi$), 34.8 (CH_2Ar), 40.7 (CH_2NH), 50.1 (CH_3O), 55.5 (CH_2N), 112.4 (ArC-H), 119.5 (Im $\underline{C}$-H), 120.7 (ArC-H), 121.0 (ArC-H), 130.8 (Im $\underline{C}$-H), 131.3 (Ar$\underline{C}$-CH_2), 138.0 (NCHN), 143.8 (ArC-OSi),

151.1 (ArC-OCH_3), 166.7 (CO). Ms(CI) m/z (%): 390 (62, M^++1), 374 (5), 332 (100), 193 (40), 179 (31). Anal. Calcd for $C_{20}H_{31}N_3O_3Si$: C, 61.66; H, 8.02; N 10.79. Found: C, 61.58; H, 8.24; N, 11.06.

Photocyclization of *N*-[2-(3,4-Dimethoxyphenyl)ethyl]chloroacetamide (2b):

A solution of **2b** (200 mg, 0.78 mmol) in benzene (300 ml) was photolysed for 10 h at room temperature. The organic solvent was then evaporated *in vacuo* at 40-45°C. The residual pale brown oil was dissolved in EtOAc (80 ml) and washed with saturated aqueous NaCl (3x15 ml). The EtOAc layer was dried and evaporated to leave a pale brown oil. Crystallization from EtOH gave the cyclolactam **(3b)** as colourless, needle-like crystals (31 mg); R_f 0.19 (MeOH : DCM, 3 : 97); mp 246-248°C (lit.,[1] 247-250°C). ^{1}H-Nmr ($CDCl_3$) δ: 2.32 (dd, J = 13.6, J = 2.8 Hz, 1H, CHCO), 2.48 (dt, J = 13.2, J = 5.2 Hz, 1H, CHAr), 2.62 (ddd, J = 13.2, J = 8.8, J = 4.0 Hz, 1H, CHAr), 2.80 (ddd, J = 13.6, J = 3.6, J = 1.2 Hz, 1H, CHCO), 3.11 (dd, J = 13.6, J = 4.8 Hz, 1H, CHNH), 3.44 (ddd, J = 13.6, J = 12.0, J = 4.0 Hz, 1H, CHNH), 3.88 (s, 3H, CH_3O), 4.27-4.34 (m, 2H, CH_2O), 5.23 (d, J = 11.6 Hz, NH), 6.87-6.95 (d, J =2.0 Hz, 1H, 13-H_{arom}), 6.87 (d, J= 7.6 Hz, 1H, 11-H_{arom}), 6.94 (dd, J = 8.0, J = 2.0 Hz, 1H, 10-H_{arom}). The ethanolic mother liquor was evaporated and the residue was re-crystallized from ethanol to give 7,8-dimethoxy-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one as colourless crystals (11 mg, 6.5 %); mp 192-193°C (lit.,[1] 191-193°C). The ethanolic mother liquor from the crystallization of **3b** was concentrated again and chromatographed on a column of silica gel (2.1 x 36 cm). Elution with DCM/ 1% MeOH, then 2% MeOH gave two fractions. The first fraction was the starting material **(2b)** (20 mg, 10%). The solvent in the second fraction was evaporated and the residue was recrystallized from EtOH to give further cyclolactam **(3b)** as colourless needles (10 mg) (total yield of 41 mg, 24%).

Photolysis of *N*-[2-(4-*t*-Butyldimethylsiloxy-3-methoxyphenyl)ethyl]chloroacetamide (2c):

A solution of **2c** (200 mg, 0.56 mmol) in benzene (280 ml) was irradiated for 10 h at room temperature. The organic solvent was evaporated *in vacuo* at 45-50°C. The residual brown oil was dissolved in EtOAc (80 ml) and washed with brine (3 x 15 ml). The EtOAc layer was dried and evaporated to leave a pale brown oil. Crystallization from light petroleum gave the *silylated cyclolactam* **(3c)** as colourless crystals (64 mg, 36%); R_f 0.18 (MeOH:DCM, 2 : 98); mp 175-176°C. Ir (HCB) υ_{max}: 3291 (NH); 2925 (Ar-H); 1651 (C=O) cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.18 (s, 3H, CH_3Si), 0.24

(s, 3H, CH_3Si), 1.02 (s, 9H, $(CH_3)_3CSi$), 2.30 (dd, J = 14.2, J = 4.0, 1H, CHCO), 2.38 (dt, J = 13.2, J = 4.8 Hz, 1H, CHAr), 2.61 (dt, J = 13.2, J = 4.8 Hz, 1H, CHAr), 2.80 (dd, J = 14.2, J = 3.6 Hz, 1H, CHCO), 3.11 (dd, J = 13.0, J = 5.0 Hz, 1H, CHNH), 3.45 (ddd, J = 13.2, J = 12.0, J = 5.2 Hz, 1H, CHNH), 4.16-4.24 (m, 1H, CHO) 4.26-4.34 (m, 1H, CHO), 5.23 (d, J = 12.0 Hz, 1H, NH), 6.82-6.83 (m, $3H_{arom}$). ^{13}C-Nmr ($CDCl_3$) δ: -5.0 (CH_3Si), -4.6 (CH_3Si), 25.7 ($(CH_3)_3CSi$), 38.4 (CH_2Ar), 40.0 (CH_2CO), 44.3 (CHNH), 71.2 (CH_2O), 123.0 (ArC-H), 124.8 (ArC-H), 128.5 (Ar-H), 130.1 (ArC-CH_2), 146.9 (ArC-OSi), 148.0, (ArC-OCH_2), 172.1 (CO). Ms (CI) m/z (%): 322 (30, M^++1), 321 (10, M^+; accurate mass 321.1761 in EI, $C_{17}H_{27}O_3N^{28}Si$ requires 321.1760), 305 (32), 264 (100), 236 (100), 219 (57), 207 (55), 193 (100), 179 (100). Anal. Calcd for $C_{17}H_{27}NO_3Si$: C, 63.51; H, 8.46; N, 4.36. Found: C, 63.39; H, 8.65; N, 4.61.

Demethylation of the Methoxycyclolactam (3b):

To a stirred mixture of Li (20 mg, 2.724 mmol) and dry THF (5 ml) under a N_2 flow in a three-necked flask, fitted with two rubber septa and a ground-glass stopper, Ph_2PCl (253 mg, 0.206 ml, 1.362 mmol) was added by a syringe through the septum . The mixture was allowed to stir for about 2 h until a deep orange colour was observed and almost all the Li was dissolved. The needle-like crystals of the cyclolactam **(3b)** (100 mg, 0.452 mmol) were added slowly to the solution. A stronger N_2 flow was maintained throughout the addition, which required about 15 min, and the deep orange coloured solution was allowed to stir for a further 18 h. To the resultant solution was added H_2O (2 ml) and a saturated solution of NH_4Cl until the pH was adjusted to 8.5. The solution was then extracted with DCM (3 x 20 ml). The combined extracts were washed with brine (1 x 20 ml), dried and evaporated to give a pale yellow oil. The residue was chromatographed on a column of silica gel. Elution with DCM and MeOH (93 : 7) gave two fractions.

Fraction A contained diphenylphosphine oxide as detected by ms. Evaporation of the DCM/MeOH (93 : 7) solution of fraction B gave *12-hydroxy-2-oxa-6-azabicyclo[7.3.1.]trideca-1(13),9,11-trien-5-one* **(4)** as a colourless crystalline powder, mp 217-218°C (21 mg, 23%); R_f 0.11 (DCM : MeOH, 93 : 7). ^{1}H-Nmr (CD_3OD) δ: 2.20 (d, J = 15.0, Hz, 1H, CHCO), 2.52 (dt, J = 12.8, J = 4.4 Hz, 1H, CHAr), 2.71 (dd, J = 12.8, J = 4.0 Hz, 1H, CHAr), 2.74-2.82 (m, 1H, CHCO), 3.04-3.08 (m, 1H, CHNH), 3.22-3.35 (m, 1H, CHNH), 4.19-4.21 (m, 2H, CH_2O), 6.71 (d, 1H, J = 8.4 Hz, 11-H_{arom}), 6.76 (dd, J = 8.0, J = 2.0 Hz, 1H, 10-H_{arom}), 6.88 (d, J = 2.0 Hz, 1H, 14-H_{arom}), 7.44-7.46 (m, NH). ^{13}C-Nmr

(CD_3OD) δ: 36.5 (CH_2Ar), 37.8 (CH_2CO), 43.0 (CH_2NH), 57.7 (CH_3O) 69.8 (CH_2O), 116.4 (ArC-H), 123.7 (ArC-H), 127.2 (ArC-H), 128.5 (Ar<u>C</u>-CH_2), 143.4 (ArC-OH), 146.9 (Ar<u>C</u>-OCH_2), 173.2 (CO). Ms (EI) m/z (%): 207 (18, M^+; accurate mass 207.0895, $C_{11}H_{13}O_3N$ requires 207.0885), 178 (15), 150 (42), 136 (38), 122 (85), 55 (100). Anal. Calcd for $C_{11}H_{13}NO_3 . 0.4H_2O$: C, 61.65; H, 6.58; N, 6.54. Found: C, 61.95; H, 6.41; N, 6.39.

Desilylation of 3c:

To a stirred solution of the silylated cyclolactam **(3c)** (26.5 mg, 0.083 mmol) in dry THF (0.5 ml) was added TBAF (30 mg, 0.115 mmol) at room temperature The mixture was allowed to stir for 55 min. To the resultant solution was added a saturated solution of NH_4Cl (2 ml, pH~8), saturated aqueous NaCl (3 ml), and a small amount of NaCl. The mixture was then extracted with EtOAc (4 x 15 ml). The combined extracts were washed with brine (1 x 10 ml), dried and evaporated to leave a pale yellow oil. The residual oil was then chromatographed on a silica gel column. Elution with DCM and MeOH (96 : 4) gave the desired fraction. The solvent was removed to give the phenolic cyclolactam **(4)** as a colourless crystalline powder (14 mg, 82%); R_f 0.11 (DCM : MeOH, 93 : 7).

L-Dopa Methyl Ester Hydrochloride (6)

Hydrogen chloride was bubbled into a refluxing solution of L-dopa **(5)** (1.0 g, 5.07 mmol) in methanol (40 ml) for 5.5 h. The solvent was then removed *in vacuo* and the residue was dried under high vacuum to give **6** (1.1g, 90%) as colourless hygroscopic crystals. ^{1}H-Nmr (D_2O) δ: 2.94 (dd, J=14.0, J=6.8 Hz, 1H, CHAr), 3.10 (dd, J=14.0, J=5.6 Hz, 1H, CHAr), 3.68 (s, 3H, $COOCH_3$), 4.15-4.21 (m, 1H, C<u>H</u>NH_2), 6.53 (dd, J=8.0, J=2.0, Hz, 1H, 6-H_{arom}), 6.62 (d, J=2.0 Hz, 1H, 2-H_{arom}), 6.74 (d, J=8.0 Hz, 1H, 5-H_{arom}).

Methyl 2-Chloroacetamido-3-(3, 4-dihydroxyphenyl)propanoate (7)

To a solution of **6** (810 g, 3.27 mmol) in dry THF (40 ml) were added triethylamine (0.91 ml, 6.54 mmol) and chloroacetyl chloride (0.388 g, 0.28 ml, 3.50 mmol). The solution was then stirred at room temperature for 48 h. Water (20 ml) was then added and the solution was extracted with DCM (3 x 40 ml). The combined organic extracts were washed with water (3 x 10 ml) and then

dried. The organic solvent was removed to give a yellow oil. The oil was chromatographed (MeOH : DCM, 4 : 96) to give **7** as a pale yellow oil (799 mg, 85%); R_f 0.20 (MeOH : DCM, 4 : 96). ^{1}H-Nmr ($CDCl_3$) δ: 2.97 (dd, J=14.0, J=6.8 Hz, 1H, CHAr), 3.06 (dd, J=14.0, J=5.6 Hz, 1H, CHAr), 3.74 (s, 3H, $COOCH_3$), 4.06 (s, 2H, CH_2Cl), 4.78-4.83 (m, 1H, C<u>H</u>NH), 6.50 (dd, J=8.0, J=2.0, Hz, 1H, 6-H_{arom}), 6.65 (d, J=2.0 Hz, 1H, 2-H_{arom}), 6.75 (d, J=8.0 Hz, 1H, 5-H_{arom}), 7.12 (d, J=8.4 Hz, 1H, NH). ^{13}C-Nmr ($CDCl_3$) δ: 37.2 (CH_2Ar), 42.3 ($COO\underline{C}H_3$), 52.7 (CH_2Cl), 53.7 (CHNH), 115.4 (ArC-H), 116.0 (ArC-H), 121.4 (ArC-H), 127.4 (Ar<u>C</u>-CH_2), 143.4 (ArC-OH), 144.1 (ArC-OH), 166.5 (<u>C</u>OCH_2), 171.6 (<u>C</u>OOCH_3). Ms (EI) m/z (%): 287 (1, M^+; accurate mass 287.0571, $C_{12}H_{14}NO_5{}^{35}Cl$ requires 287.0561), 228 (2, M^+1), 194 (50), 163 (15), 123 (100).

Methyl 2-Chloroacetamido-3-(3, 4-dimethoxyphenyl)propanoate (8)

To a solution of **7** (800 mg, 2.78 mmol) in MeOH (10 ml) was added diazomethane in ether (30 ml). The solution was kept at 1°C for 10 h and then at room temperature for 40 h. The organic solvent was then removed by rotary evaporation and then further MeOH (10 ml) and diazomethane (in excess) in ether (30 ml) was added. The solution was kept at 1°C overnight. The organic solvent was evaporated *in vacuo* to give a colourless solid. The solid was recrystallized from ethanol/ether to give **8** (660 mg, 75%) as colourless crystals; mp 106-107°C. ^{1}H-Nmr ($CDCl_3$) δ: 3.10 (d, J=6.0 Hz, 2H, CH_2Ar), 3.75 (s, 3H, $COOCH_3$), 3.856 (s, 3H, Ar-OCH_3), 3.861 (s, 3H, Ar-OCH_3), 4.02 (d, J=15.2 Hz, 1H, CHCl), 4.06 (d, J=15.2 Hz, 1H, CHCl), 4.83-4.87 (m, 1H, C<u>H</u>NH), 6.64 (dd, J=5.6, J=2.0 Hz, 1H, 6-H_{arom}), 6.68 (d, J=2.4 Hz, 1H, 2-H_{arom}), 6.80 (d, J=8.0 Hz, 1H, 5-H_{arom}), 7.02 (d, J=8.0 Hz, 1H, NH). ^{13}C-Nmr ($CDCl_3$) δ: 37.2 (CH_2Ar), 42.3 ($COO\underline{C}H_3$), 52.4 (CH_2Cl), 53.3 (CHNH), 55.7(Ar-OCH_3), 111.1 (ArC-H), 112.1 (ArC-H), 121.2 (ArC-H), 127.6(Ar<u>C</u>-CH_2), 148.1 (Ar<u>C</u>-OCH_3), 165.4 (<u>C</u>OCH_2Cl), 171.2 (<u>C</u>OOCH_3). Ms (EI) m/z (%): 315 (2, M^+, ^{35}Cl), 222 (35), 191 (5), 151 (100), 137 (5). Anal. Calcd for $C_{14}H_{18}NO_5Cl$: C, 53.25; H, 5.75; N, 4.44. Found: C, 53.27; H, 5.85; N, 4.34.

Photolysis of Methyl 2-Chloroacetamido-3-(3, 4-dimethoxyphenyl)propanoate (8)

(i) A solution of **8** (200 mg, 0.634 mmol) in benzene (300 ml) was irradiated for 5 h. The organic solvent was evaporated *in vacuo* to give a pale yellow oil. The oil was then chromatographed (ethyl acetate : hexane, 70 : 30) to give two fractions after solvent evaporation. The first fraction

was the starting material (130 mg, 65%). The second fraction was recrystallized from ethanol to give **9** (37 mg, 21%; 60% based on recovered starting material) as colourless needle-like crystals; mp 234-236°C; $[\alpha]_D^{20°}$ = +105.0° (c. 1g/100ml, $CHCl_3$). ^{1}H-Nmr ($CDCl_3$) δ: 2.28-2.33 (m, 1H, CHCO), 2.54 (dd, J=13.0, J=11.6 Hz,1H, CHAr), 2.65-2.72 (ddd, J=13.6, J=9.6, J=4.0 Hz, 1H, CHCO), 3.22 (dd, J=13.0, J=3.2 Hz, 1H, CHAr), 3.81 (s, 3H, $COOCH_3$), 3.88 (s, 3H, $ArOCH_3$), 4.28-4.30 (m, 2H, CH_2O), 4.35 (dt, J=11.2, J=3.6 Hz, 1H, CHNH), 5.96 (d, J=10.8, 1H, NH), 6.88 (d, J=8.0 Hz, 1H, 11-H_{arom}), 6.97(d, J=2.0 Hz, 13-H_{arom}), 7.00 (dd, J=8.0, J=2.0 Hz, 1H, 10-H_{arom}). ^{13}C-Nmr ($CDCl_3$) δ: 39.6 (CH_2CO), 41.8 (CH_2Ar), 52.6 (CHNH), 55.9 ($COOCH_3$), 57.3 (Ar-OCH_3), 71.7 (CH_2O), 133.6 (ArC-H), 125.3 (ArC-H), 128.3 (ArC-H), 128.6 (ArC-CH_2), 146.3 (ArC-OCH_3), 151.5 (ArC-OCH_2), 170.9 ($COCH_2$), 172.1 ($COOCH_3$). Ms (EI) m/z (%): 279 (10, M^+), 262 (5), 220 (5), 223 (46), 192 (45), 164 (100), 149 (46), 137 (50), 121 (20), 108 (70). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.45; H, 6.33; N, 4.86.

(ii) A solution of **8** (150 mg, 0.475 mmol) in benzene (300 ml) was irradiated for 10 h. The organic solvent was evaporated *in vacuo* to give a pale yellow oil. The oil was chromatographed as above to give the stating material (40 mg, 11%) and **9** (40 mg, 30%; 39% based on recovered starting material) after recrystallization from ethanol.

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7. Some of this benzazepin-2-one could conceivably also arise by direct attack on the aromatic ring by the amidomethylene radical shown in **A 3b-c**, followed by hydrogen abstraction and re-aromatisation.
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11. Structure Determination: $C_{14}H_{17}NO_5$, M=279.3. Monoclinic, $P2_1/c$, a=4.993(5), b=8.236(2), c=16.478(4) Å. β=93.15(5)°,U=676.6 Å^3. D_c(Z=2)=1.37 g.cm-3. F(000)=296. The structure was refined to R=0.047, R' (statistical weights)=0.043 for 629 'observed' diffractometer reflections out of 1021 independent reflections to $2\theta_{max}$ 45° (Mo Kα radiation, λ=0.7107$_3$ Å). Anisotropic thermal parameters were refined for C, N, O; (x, y, z, Uiso)$_H$ were estimated. Non hydrogen interatomic distances, interbond angles, and anisotropic thermal parameters, as well as hydrogen atom parameters and structure factor amplitudes are available from the Cambrige Crystallographic Data Centre.
12. Macrocycle torsion angles (degrees) for the atom string of **9**, numbered as in Figure 1, are as follows; beginning with bond C(1)-C(2): 93(1), 66(1), -80(1), 134(1), -156(1), 95(1), -57(1), 68(1), -156(1), 164(1). (Note the substantial deviation of the last two, associated with the phenyl ring, from 180°). The C(5).....C(13) distance is 2.73(2) Å.

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