Synthesis of phenethylenamides and their radical cyclization to 3-benzazepines.

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Abstract

Synthetic approaches to enamides, intermediates of use in the synthesis of natural products, were studied as well as their 7-*endo-trig* radical cyclization to 3-benzazepines. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: enamides; benzazepines; radical reactions.

Introduction

The 3-benzazepine unit is present in a large number of alkaloids, including isopavines [1], indenobenzazepines [2], dibenzopyranazepines [3], isoindolobenzazepines [4] and cephalotaxine [5]. In connection with our interest in the synthesis of indenobenzazepine alkaloids, we have reported a new procedure for assembly of their 3-benzazepine unit by intramolecular addition of an aryl radical to the enamide double bond of **1** [6]. This cyclization took place stereoselectively in a 7-*endo* manner, giving *trans*-fused benz[*d*]indeno[1,2-b]azepines **2** in 40 to 85% yield, depending on the substituents in the benzo ring.

1   **2**
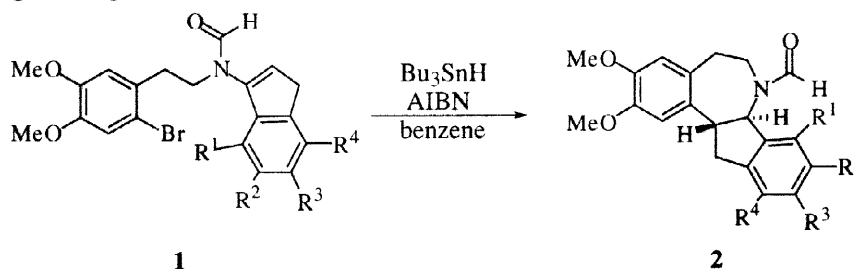
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Recently, we extended this approach to the preparation of isoindolo[1,2-*b*][3]benzazepines [7], this time by aryl radical cyclization onto the double bond of cyclic enamides **3** (Scheme 1). Cyclization of the dimethoxy-substituted methylenephthalimidine **3b** led directly to the alkaloid lennoxamine (**4b**), though the yield was lower than for the reaction of **3a** with a less electron-rich benzo ring.

Scheme 1

a R$_1$ = R$_2$ = OMe, R$_3$ = H

b R$_1$+ R$_2$ =OCH$_2$O, R$_3$ = OMe

4a, 81%

4b, 61%
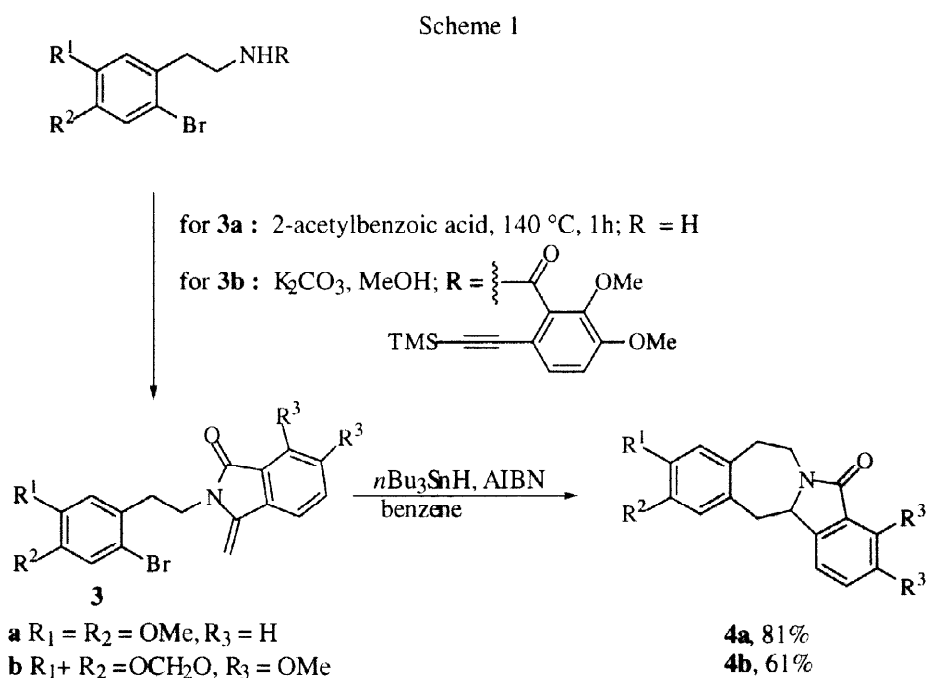
The starting unsubstituted methylenephthalimidine **3a** was prepared by heating 6-bromohomoveratrylamine with commercial 2-acetylbenzoic acid. However, this classical procedure is not suitable for the synthesis of aryl-substituted methylenephthalimidines because the required aromatic γ-ketoacids are not available. For the preparation of substituted methylenephthalimidines, exemplified by **3b**, we therefore developed an alternative approach to these compounds involving 5-*exo-dig* cyclization of an *o*-ethynylbenzamide. Specifically, treatment of the corresponding *o*-trimethylsilyl ethynylbenzamide with excess methanolic potassium carbonate leads to desilylation followed by spontaneous nucleophilic attack of the triple bond by the amide nitrogen, giving the cyclic enamide **3b** (Scheme 1) [8].

Results and Discussion

In this paper we describe the preparation of alkylidenephthalimidines and their radical cyclization to isoindolo[3]benzazepines. The most noteworthy result is the successful application of our methodology to an aliphatic enamide, since it provides a route to the tricyclic core of the pentacyclic alkaloid cephalotaxine, the parent compound of the antileukemic-active harringtonines [5].

The benzyloxy-substituted methylenephthalimidine **3c** was obtained in 72% yield by the classical acylation procedure. The benzylidene derivative **3d** was obtained in 91% yield by an alternative method [9] consisting of heating the appropiate phenethylamine with commercially available 3-benzalphthalide and then dehydrating the resulting hydroxylactam with acetic acid.
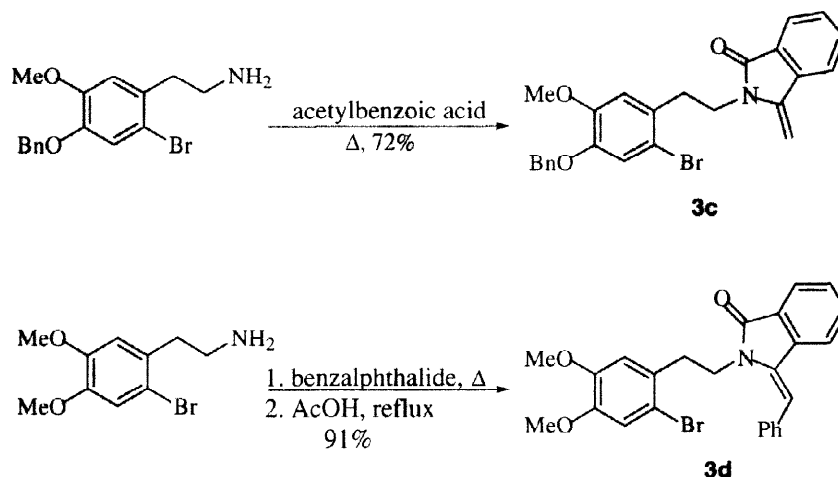
Next, we turned our attention to the preparation of non-phthalimidine enamides such as the aliphatic γ-methylene-γ-lactams **3e** and **3f**. Attempts to prepare **3f** by condensing homoveratrylamine and levulinic acid unexpectedly gave tricyclic lactam **5** as the major product (65% yield), presumably as the result of C–C bond formation through electrophilic attack of the intermediate acyliminium ion on the electron-rich aromatic ring, as shown in Scheme 2 [10].

Scheme 2
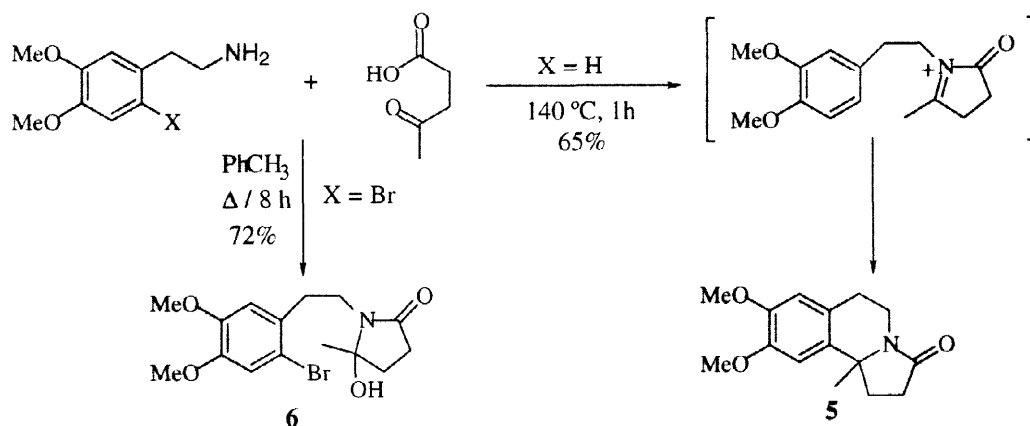
In the corresponding reaction of homoveratrylamine with its nucleophilic aromatic position blocked by a bromine atom, no dehydration of carbinolamide **6** to methylenelactam **3e** took place, and **6** was obtained in 72% yield. Similar results were obtained when the phenethylamines were condensed with γ-methylene-γ-butyrolactone. Thus, the easy
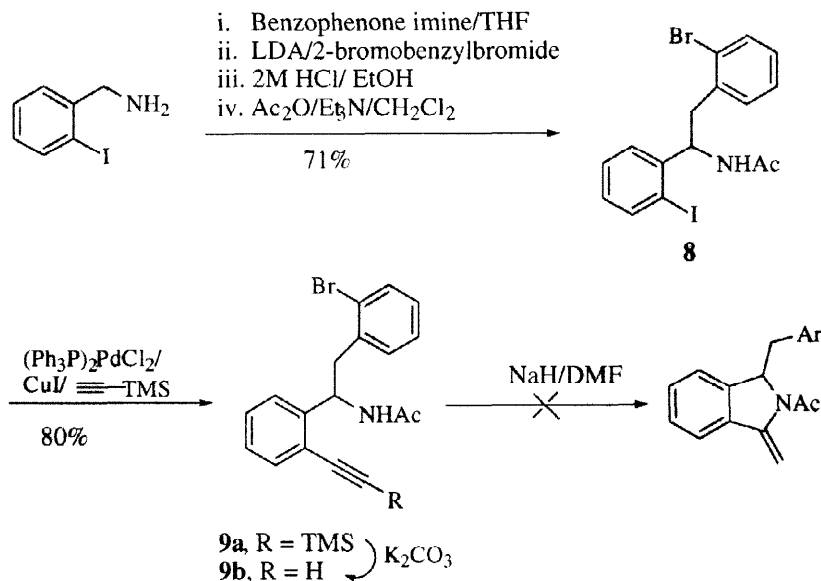
elimination that follows condensation of benzoic acid derivatives with phenethylamines (as in the preparation of **3c**), does not occur with aliphatic ketoacids, making this route unsuitable for preparation of these enamides.

In the light of these results, we decided to try the alternative procedure based on 5-*exo-dig* cyclization of acetylenic benzamides, which we had used previously to prepare phthalimidine **3b**. Thus, the appropiate amide **7**, which was easily prepared by condensation of 6-bromohomoveratrylamine with 4-pentynoic acid chloride, was treated with NaH in DMF for 2 hours at room temperature affording methylenelactam **3e** in 82% yield as the only product.

MeO \
    \
MeO   Br   **7**

NaH/DMF →

MeO \
    \
MeO   X

3e, X = Br, 82%
3f, X = H
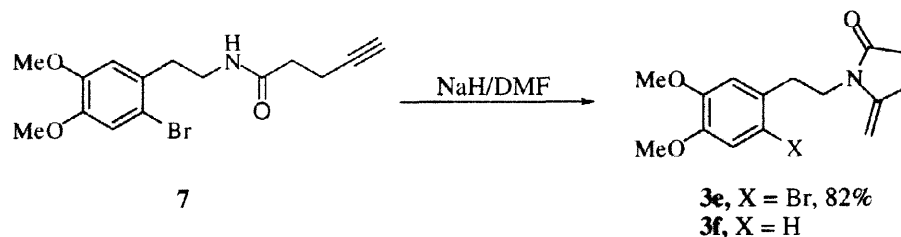
To examine the scope of this cyclization we applied it to the alternative system of an *o*-ethynylbenzylamide, as exemplified by **9**. Amide **9a** was prepared by α-alkylation of *o*-iodobenzylamine followed by chemoselective Pd–catalysed coupling with trimethylsilylacetylene (Scheme 3). Treatment of **9a** with either a catalytic amount or an excess of K_2CO_3 gave the desilylated compound **9b**. Attempts to promote the 5-*exo-dig* azacyclization on **9a** or **9b** by treatment with NaH/DMF resulted in decomposition.

Scheme 3

NH₂ \
   \
   I

i. Benzophenone imine/THF
ii. LDA/2-bromobenzylbromide
iii. 2M HCl/ EtOH
iv. Ac₂O/Et₃N/CH₂Cl₂

71%

Br \
   \

   NHAc
   \
   I
   8

(Ph₃P)₂PdCl₂/
Cu/ ≡—TMS

80% →

Br \
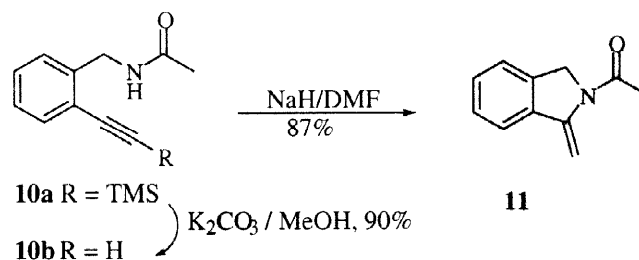   \

   NHAc
   \
   R

NaH/DMF
—✗→

Ar
 \
  NAc

9a, R = TMS ⎫ K₂CO₃
9b, R = H ⎭

The problem appears to be the α-substituent, since when **10a** was treated with K₂CO₃/MeOH under the same reaction conditions (or with 1 equiv. of KOH/MeOH), it was
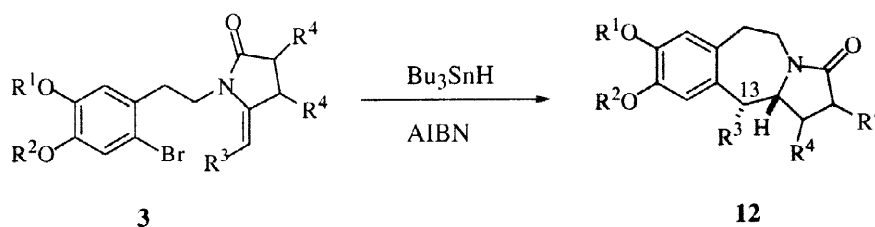
desilylated to **10b** (90% yield), which underwent 5-*exo-dig* cyclization upon treatment with NaH in DMF for 3 h, giving the desired enamide **11** in 87% yield.
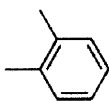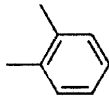
Scheme 4

Next, we proceeded with investigation of the 7-*endo-trig* radical cyclization of the phenethylenamides **3** to 3-benzazepines **12**. The radical cyclization was performed by dropwise addition of tributyltin hydride (2 equiv.) to a 5mM solution of **3** and AIBN (20% by weight) in benzene refluxing under argon. The results are shown in Scheme 5.

Scheme 5

3	R^1	R^2	R^3	R^4	Yield (%) of **12**
c	Me	Bn	H	(o-tolyl)	40
d	Me	Me	Ph	(o-tolyl)	93
e	Me	Me	H	H	75

The benzylidenephathalimidine **3d** and the aliphatic γ-methylenebutyrolactam **3e** produced the corresponding 3-benzazepines in good yield. The low yield of benzazepine **12c** may have been due to radical translocation to the benzyl group. The *cis* selectivity observed in the formation of **12d** may be the result of *n*Bu$_3$SnH hydrogen abstraction by the radical

intermediate through its less hindered face. Its *cis* stereochemistry was determined by X-ray analysis (Figure 1)[11]. Interesting features of the solid-state molecular structure are the chair conformation of the seven-membered ring, and the consequent pseudo-axial orientation of the phenyl group at position 13.

Figure 1. Chem3D representation of the X-ray structure of 12d
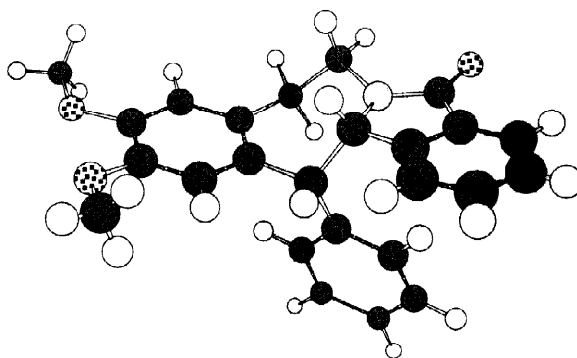
In summary, we have extended the 5-*exo-dig* cyclization of acetylenic benzamides to the preparation of N-substituted alicyclic enamides, and broadened the scope of the 7-*endo-trig* radical cyclization for the preparation of 3-benzazepines. The combination of both cyclizations allowed the synthesis of tricyclic **12e**, an analogue of which has been used as an intermediate in the synthesis of cephalotaxine [12].

Experimental Section

General: All reactions were carried out under argon. Solvents THF, toluene and benzene were dried by distillation from Na/benzophenone. Melting points are uncorrected. IR: Bruker IFS-28. NMR: ^{1}H and ^{13}C spectra were recorded in CDCl$_3$ with TMS as internal standard in Bruker AM 400 (400 MHz and 100.6 MHz, for 1H and 13C, respectively). MS: (70 eV).

N-[2-(4-benzyloxy-2-Bromo-5-methoxyphenyl)ethyl]-2,3-dihydro-3-methylene-1H-isoindol-1-one (**3c**): A mixture of 4-benzyloxy-2-bromo-5-methoxyphenethylamine (780 mg, 2.32 mmol) and 2-acetylbenzoic acid (400 mg, 2.44 mmol) was heated at 110 °C for 1h under argon. After the mixture was cooled to room temperature, treated with EtOAc (2 mL) and left at 0 °C overnight, it afforded as a crystalline solid isoindolone **3c** (778 mg, 72%). M.p. (EtOAc) 131 °C. IR (KBr): $\bar{\nu}$ = 1706 cm^{-1} (C=O). ^{1}H NMR: δ = 7.82 (d, J = 7.2 Hz, 1 H), 7.67 (d, J = 7.4 Hz, 1 H), 7.57 (dt, J =7.2 and 1.2 Hz, 1 H), 7.49 (dt, J = 7.4 and 1.2 Hz, 1 H), 7.40 (m, 5 H), 7.05 (s, 1 H), 6.71 (s, 1 H), 5.13 (d, J = 2.4 Hz, 1 H), 5.09 (s, 2 H), 4.95 (d, J = 2.4 Hz, 1 H), 3.98 (t, J = 7.5 Hz, 2 H), 3.68 (s, 3 H), 3.04 (t, J = 7.5 Hz, 2 H). ^{13}C NMR: δ = 167.5, 149.7, 148.2, 142.2, 136.9, 136.7, 132.3 (CH), 130.8, 129.8 (CH), 129.7,

129.0 (CH), 128.5 (CH), 127.8 (CH), 123.4 (CH), 120.3 (CH), 118.5 (CH), 114.5 (CH), 114.4, 89.5 (CH$_2$), 71.7 (CH$_2$), 56.5 (CH$_3$), 39.7 (CH$_2$), 34.9 (CH$_2$). MS; m/z (%): 384 (100) [M$^+$ – Br]. C$_{25}$H$_{22}$BrNO$_3$: calcd. C 64.66, H 4.78, N 3.02; found C 64.26, H 4.76, N 3.01.

N-[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]-3-benzylidene-2,3-dihydro-1H-isoindol-1-one (**3d**): A mixture of 6-bromohomoveratrylamine (500 mg, 1.92 mmol) and benzalphthalide (405 mg, 2.02 mmol) was heated at 140 °C for 3 min under argon. The resulting solid was treated with AcOH (2 mL) and refluxed for 2 h. The mixture was cooled and the solid precipitate that was formed was filtered out and identified as **3d** (405 mg, 91%). M.p. (EtOAc) 180 °C. IR (KBr): $\overline{\nu}$ = 1703 cm^{-1} (C=O). ^{1}H NMR: δ = 7.83 (d, *J* = 7.5 Hz, 1 H), 7.41-7.24 (m, 8 H), 6.99 (s, 1 H), 6.70 (s, 1 H), 6.59 (s, 1 H), 4.11 (t, J = 7.3 Hz, 2 H), 3.83 (s, 3 H), 3.64 (s, 3 H), 3.12 (t, *J* = 7.3 Hz, 2 H). ^{13}C NMR: δ = 166.6, 148.5, 136.0, 135.2, 135.0, 131.5 (CH), 130.2, 129.9, 129.5 (CH), 129.2 (CH), 128.6 (CH), 128.0, 127.8 (CH), 123.1 (CH), 123.0 (CH), 115.5 (CH), 114.2, 113.8 (CH), 110.7 (CH), 56.1 (CH$_3$), 55.9 (CH$_3$), 39.2 (CH$_2$), 34.5 (CH$_2$). MS; m/z (%): 465 (6) [M$^+$ + 2], 463 (6) [M$^+$], 244 (100), 242 (98). C$_{25}$H$_{22}$BrNO$_3$: calcd. C 64.66, H 4.78, N 3.02; found C 65.00, H 4.96, N 3.11.

8,9-Dimethoxy-10b-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3(2H)-one (**5**): A mixture of homoveratrylamine (200 mg, 1.1 mmol) and levulinic acid (150 mg, 1.2 mmol) was heated at 110 °C for 1 h. Flash chromatography (silica gel, 1:1 hexane/EtOAc) of the crude gave isoquinoline **5** as an oil (185 mg, 65%) with data identical to those reported in ref.10.

N-[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]-4-hydroxy-4-methyl-γ-butyro lactam (**6**): A mixture of 6-bromohomoveratrylamine (190 mg, 0.74 mmol) and levulinic acid (90 mg, 0.75 mmol) was refluxed in toluene (20 mL) for 8 h. After work-up amideketal **6** (190 mg, 72%) was isolated as a crystalline solid. M.p. (EtOAc) 99 °C. IR (KBr): $\overline{\nu}$ = 1668 cm^{-1} (C=O). ^{1}H NMR: δ = 6.99 (s, 1 H), 6.78 (s, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.45-3.36 (m, 2 H), 3.02-2.94 (m, 2 H), 2.54 (m, 1 H), 2.37 (m, 1 H), 2.13-2.03 (m, 2 H), 1.44 (s, 3 H). ^{13}C DEPT NMR: δ = 115.5 (CH), 113.7 (CH), 56.2 (CH$_3$), 39.2 (CH$_2$), 35.3 (CH$_2$), 34.8 (CH$_2$), 32.8 (CH$_2$), 29.1 (CH$_3$). MS; m/z (%): 359 (3) [M$^+$ + 2], 357 (3) [M$^+$], 244 (100), 242 (98). C$_{15}$H$_{20}$BrNO$_4$: calcd. 357.0575; found 357.0584.

N-[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]-4-methylene-γ-butyrolactam (**3e**): Sodium hydride (180 mg, 7.5 mmol) was added to a stirred solution of the acetylenic amide **7** (550 mg, 1.62 mmol) in dry DMF (5 mL) under argon, left at rt for 2 h, and then poured into water (50 mL). The resulting mixture was extracted with diethyl ether. The combined organic layers were washed with brine, dried (Na$_2$SO$_4$) and concentrated *in vacuo.*

The residue proved unstable on flash chromatography silica gel, so it was purified by recrystallization from EtOAc, affording methylene-γ-butyrolactam **3e** (450 mg, 82%). M.p. 101–103 °C. IR (KBr): $\bar{v}$ = 1715 cm^{-1} (C=O). ^{1}H NMR: δ = 7.01 (s, 1 H), 6.76 (s, 1 H), 4.42 (d, J = 1.8 Hz, 1H), 4.15 (d, J = 1.8 Hz, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.66 (t, J = 7.6 Hz, 2 H), 2.91 (t, J = 7.6 Hz, 2 H), 2.70 (m, 2 H), 2.46 (m, 2 H). ^{13}C NMR: δ = 176.2, 148.9, 148.8, 146.8, 130.2, 115.9 (CH), 114.6, 113.8 (CH), 84.9 (CH$_2$), 56.5 (CH$_3$), 40.2 (CH$_2$), 33.2 (CH$_2$), 29.4 (CH$_2$), 24.2 (CH$_2$). MS; m/z (%): 341 (3) [M$^+$ + 2], 339 (3) [M$^+$], 260 (100). C$_{15}$H$_{18}$BrNO$_3$: calcd. C 52.96, H 5.33, N 4.12; found C 53.14, H 5.50, N 3.97.

N-[2-(2-bromophenyl)-1-(2-iodophenyl)]ethylacetamide (**8**). A mixture of 2-iodobenzylamine (426 mg, 1.83 mmol) and benzophenone imine (330 mg, 1.83 mmol) in dry THF (1 mL) was heated at 50 °C under argon for 3 h. The resulting solution was added *via* cannula to a LDA solution (2.75 mmol) stirring at -70 °C, causing a deep purple colour to form. After 90 min, 2-bromobenzylbromide (460 mg, 1.83 mmol) was added and the reaction mixture was stirred for 4 h at rt. The solvent was evaporated and the residue was taken up in ether, washed with brine, and dried to give an oil. This was dissolved in a mixture of 1:1 EtOH/2M HCl (6 mL), refluxed for 30 min, and then poured into water (20 mL). After washing the aqueous layer with ether (3 x 30 mL), it was neutralized and extracted with ether (3 x 30 mL). These etheral extracts were dried and concentrated to give crude 1-(2-iodophenyl)-2-(2-bromophenyl) ethylamine (610 mg, 83%). This amine was dissolved in dichloromethane (20 mL) and cooled to 0 °C, and Et$_3$N (152 mg, 1.5 mmol) and acetic anhydride (203 mg, 2 mmol) were added. The reaction mixture was stirred at rt for 5 h, washed with water and then brine, dried and concentrated. The residue was purified by flash chromatography (1:1 EtOAc/hexane), which gave **8** (560 mg, 84%) as a crystalline solid. M.p. (EtOAc) 137 °C. IR (KBr): $\bar{v}$ = 1649 cm^{-1} (C=O). ^{1}H NMR: δ = 7.78 (d, J = 7.7 Hz, 1 H); 7.50 (d, J = 7.9 Hz, 1 H); 7.24 (m, 3 H); 7.06 (dt, J = 7.7 and 1.7 Hz, 1H); 6.90 (m, 2 H); 5.48 (q, J = 8.1Hz, 1 H); 3.15 (m, 2 H); 1.84 (s, 3 H). ^{13}C NMR: δ = 169.4, 143.9, 139.8 (CH), 136.9, 132.6 (CH), 131.1 (CH), 129.0 (CH), 128.5 (CH), 128.4 (CH), 127.6 (CH), 125.0, 98.7, 58.3 (CH), 40.6 (CH$_2$), 23.0 (CH$_3$). MS; m/z (%): 446 (0.3) [M$^+$ + 3], 444 (0.3) [M$^+$ + 1], 402 (0.3), 274 (100). C$_{16}$H$_{16}$BrINO: calcd. 445.9439; found 445.9448.

N-[2-(2-bromophenyl)-1-[2-(Trimethylsilyl)ethynyl]phenyl]ethylacetamide (**9a**). *N*-[2-(2-bromophenyl)-1-(2-Iodophenyl)]ethylacetamide (**8**, 0.11 g, 0.25 mmol), PdCl$_2$(Ph$_3$P)$_2$ (22 mg, 0.02 mmol), CuI (5 mg, 0.02 mmol) and trimethylsilylacetylene (52 mL, 0.36 mmol) were placed in a flask containing 6 mL of 1:1 Et$_3$N/THF and stirred under argon for 8 h at rt. The resulting suspension was vacuum filtered through a bed of Celite, the filtrate was concentrated, and the residue was dissolved in CH$_2$Cl$_2$, washed with 5% HCl, dried (Na$_2$SO$_4$)

and chromatographed on silica gel (1:1 EtOAc/hexane). Acetamide **9a** (88 mg, 85%) was obtained as colourless crystals . M.p. (EtOAc) 140 °C. IR (KBr): $\overline{v}$ = 1651 cm^{-1} (C=O). ^{1}H NMR: δ = 7.50 (t, J = 7.9 Hz, 2 H); 7.21 (m, 2 H); 7.17 (m, 3 H); 7.06 (m, 1 H); 6.80 (d, J = 8.7Hz, 1 H); 5.54 (m, 1 H); 3.35 (m, 2 H); 1.93 (s, 3 H); 0.33 (s, 9 H). ^{13}C NMR: δ = 168.8, 143.3, 137.5, 133.9 (CH), 132.7 (CH), 131.1 (CH), 128.9 (CH), 128.2 (CH), 127.8 (CH), 127.3 (CH), 127.1 (CH), 124.9, 120.6, 104.0, 100.2, 54.1 (CH), 41.0 (CH$_2$), 23.3 (CH$_3$), -0.1 (CH$_3$). MS; m/z (%): 416 (0.6) [M$^+$ + 3], 414 (0.63) [M$^+$ + 1], 402 (7), 400 (7), 244 (100). C$_{21}$H$_{25}$BrNOSi: calcd. 414.0889; found 414.0878.

N-[[2-(Trimethylsilyl)ethynyl]benzyl]acetamide (**10a**). N-(2-Iodobenzyl)acetamide (0.9 g, 3.27 mmol), PdCl$_2$(Ph$_3$P)$_2$ (0.2 g, 0.3 mmol), CuI (60 mg, 0.3 mmol) and trimethylsilylacetylene (0.47 mL, 3.33 mmol) were placed in a flask containing 60 mL of 1:1 Et$_3$N/THF and stirred under argon for 2h at rt. The resulting suspension was vacuum filtered through a bed of Celite, the filtrate was concentrated and dissolved in CH$_2$Cl$_2$, the residue was washed with 5% HCl, dried (Na$_2$SO$_4$) and chromatographed on silica gel (1:1 EtAcO/hexane). A mixture of two rotamers of acetamide **10a** (0.8 g, 99%) was obtained as colourless crystals. M.p. (EtOAc) 86 °C. IR (KBr): $\overline{v}$ = 1651 cm^{-1} (C=O). ^{1}H NMR: δ = 7.45 (d, J = 7.5 Hz, 1 H), 7.34-7.18 (m, 3 H), 6.09 (bs, 1 H), 4.57 and 4.55 (2xs, 2 H), 1.99 (s, 3 H), 0.27 (s, 9 H). ^{13}C NMR: δ = 170.1, 140.8, 133.0 (CH), 129.4 (CH), 128.9 (CH), 127.8 (CH), 122.6, 103.3, 100.2, 42.8 (CH$_2$), 23.6 (CH$_3$), 0.33 (CH$_3$). MS; m/z (%): 245 (28) [M$^+$], 230 (34), 202 (100). C$_{14}$H$_{19}$NOSi: calcd. 245.1236; found 245.1235.

N-[(2-Ethynyl)benzyl]acetamide (**10b**). Potassium carbonate (290 mg, 2.1 mmol) was added to a stirred solution of **10a** (220 mg, 0.9 mmol) in methanol (20 mL) and the mixture was left at rt for 5 min. The solid formed was filtered out and the filtrate was evaporated to dryness under reduced pressure. The resulting residue was chromatographed on silica gel (1:1 EtOAc/hexane), affording a mixture of two rotamers of acetamide **10b** (140 mg, 90%) as colourless crystals. M.p. (EtOAc) 91 °C. IR (KBr): $\overline{v}$ = 1651 cm^{-1} (C=O). ^{1}H NMR: δ = 7.50 (d, J = 7.4 Hz, 1 H), 7.38-7.30 (m, 2 H), 7.27-7.22 (m, 1 H); 6.13 (bs, 1 H); 4.56 and 4.57 (2xs, 2 H), 3.33 (s, 1 H), 2.00 (s, 3 H). ^{13}C NMR: δ = 170.3, 141.1, 133.3 (CH), 129.7 (CH), 129.0 (CH), 127.8 (CH), 121.6, 82.3 (CH), 81.9, 42.6 (CH$_2$), 23.6 (CH$_3$). MS; m/z (%): 173 (32) [M$^+$], 130 (100). C$_{11}$H$_{11}$NO: 173.0841; found 173.0845.

2-Acetyl-2,3-dihydro-1-methylene-1H-isoindole (**11**). Sodium hydride (27 mg, 1.1 mmol) was added to a solution of **10b** (106 mg, 0.61 mmol) in dry DMF (4 mL) stirring under argon and left at rt for 4 h. The resulting mixture was poured into water (40 ml) and extracted with ethyl ether. The combined organic layers were washed with brine, dried (Na$_2$SO$_4$) and concentrated *in vacuo*, affording an unstable residue that was identified as

enamide **11** (95 mg, 90%). IR (KBr): $\bar{v}$ = 1699 cm^{-1} (C=O). ^{1}H NMR: δ = 7.51 (m, 1 H), 7.31 (m, 3 H), 6.10 (s, 1 H); 5.17 (s, 1 H); 4.85 (s, 2 H), 2.45 and 2.29 (2xs, 3 H). ^{13}C NMR: δ = 169.7, 144.2, 136.1, 134.9, 128.8 (CH), 127.9 (CH), 122.3 (CH), 120.2 (CH), 91.3 (CH$_2$), 54.2 (CH$_2$), 24.6 (CH$_3$). MS; m/z (%): 173 (19) [M$^+$], 130 (100). C$_{11}$H$_{11}$NO: 173.0841; found 173.0841.

General procedure for the synthesis of the 3-benzazepines (**12**). *11-Benzyloxy-7,8,13,13a-tetrahydro-10-methoxy-5H-isoindolo[1,2-b][3]benzazepin-5-one* (**12c**).

n-Bu$_3$SnH (0.35 mL, 1.30 mmol) was added dropwise over 6 min to a solution of **3c** (300 mg, 0.65 mmol) and AIBN (60 mg, 20% by weight) in 70 mL of dry degassed benzene refluxing under argon. The mixture was refluxed for a further 6h, and then the benzene was evaporated under reduced pressure and the resulting residue was taken up in CH$_3$CN. This solution was washed with hexane, dried (Na$_2$SO$_4$), and concentrated, and the residue was chromatographed on silica gel (3:1 EtOAc/hexane). Benzazepine **12c** (0.11 g, 40%) was obtained as colourless crystals. M.p. (EtOAc) 134–135 °C. IR (KBr): $\bar{v}$ = 1686 cm^{-1} (C=O). ^{1}H NMR: δ = 7.87 (d, *J* = 7.5 Hz, 1 H), 7.59-7.41 (m, 8 H), 6.93 (s, 1 H), 6.79 (s, 1 H), 5.19 (s, 2 H), 4.83 (m, 1 H), 4.41 (d, *J* = 9.8 Hz, 1 H), 3.92 (s, 3 H), 3.17 (dd, *J* = 14.7, 1.6 Hz, 1 H), 3.15–2.81 (m, 4 H). ^{13}C NMR: δ = 167.9, 148.8, 147.0, 145.2, 137.6, 134.9, 132.4, 131.9 (CH), 129.7, 128.9 (CH), 128.8 (CH), 128.3 (CH), 127.8 (CH), 124.2 (CH), 122.4 (CH), 117.3 (CH), 114.6 (CH), 72.0 (CH$_2$), 61.7 (CH), 56.4 (CH$_3$), 42.5 (CH$_2$), 41.8 (CH$_2$), 36.3 (CH$_2$ MS; m/z (%): 385 (28) [M$^+$], 294 (42), 91 (100). C$_{25}$H$_{23}$NO$_3$: C 77.90, H 6.01, N 3.63; found C 77.53, H 5.94, N 3.77.

(13R*,13aS*)-7,8,13,13a-Tetrahydro-10,11-dimethoxy-13-phenyl-5H-isoindolo *[1,2-b][3]* *benzazepin-5-one* (**12d**). *n*Bu$_3$SnH (0.31 mL, 1.14 mmol) was added to a refluxing mixture of compound **3d** (260 mg, 0.55 mmol) and AIBN (50 mg) in benzene (80 mL) as described in the previous procedure. After work-up and purification, benzazepine **12d** (0.19 g, 93%) was obtained as colourless crystals. M.p. (EtOAc) 206 °C. IR (KBr): $\bar{v}$ = 1682 cm^{-1} (C=O). ^{1}H NMR: δ = 7.80 (d, *J* = 7.3 Hz, 1 H), 7.65 (d, *J* = 7.3 Hz, 1 H), 7.56 (t, *J* = 7.3 Hz, 1 H), 7.46 (t, *J* = 7.3 Hz, 1 H), 6.96 (m, 3 H), 6.80 (s, 1 H), 6.74 (s, 1 H), 6.59 (d, *J* = 6.7 Hz, 2 H), 5.18 (d, *J* = 1.8 Hz, 1 H), 4.82 (d, *J* = 1.8 Hz, 1 H), 4.35 (m, 1 H), 3.91 (s, 3 H), 3.86 (s, 3 H), 3.58 (m, 1 H), 3.01 (m, 2 H). ^{13}C NMR: δ = 168.6, 148.1, 148.0, 144.9, 138.8, 133.2, 132.4, 131.9 (CH), 128.9 (CH), 128.8 (CH), 128.3 (CH), 127.0 (CH), 124.2 (CH), 122.6 (CH), 115.1 (CH), 63.8 (CH), 56.5 (CH$_3$), 56.4 (CH$_3$), 54.0 (CH), 42.4 (CH$_2$), 34.1 (CH$_2$). MS; m/z (%): 385 (87) [M$^+$], 253 (100). C$_{25}$H$_{23}$NO$_3$: C 77.90, H 6.01, N 3.63; found C 77.51, H 6.35, N 3.57.

1,2,5,6,11,11a-Hexahydro-8,9-dimethoxy-3H-pyrrolo[2,1-b][3]benzazepin-3-one **(12e)**. *n*Bu3SnH (0.4 mL, 1.46 mmol) was added over 10 min to a refluxing mixture of compound **3e** (250 mg, 0.73 mmol) and AIBN (50 mg) in benzene (70 mL), as described in the above procedure. Addition of the alkylstannane has to be slow enough to avoid reductive debromination. After work-up and purification, benzazepine **12e** (0.14 g, 75%) was obtained as colourless crystals. M.p. (EtOAc) 124 °C. IR (KBr): $\overline{v}$ = 1681 cm^{-1} (C=O). ^{1}H NMR: δ = 6.65 (s, 2 H), 4.44 (ddd, J = 2.0, 5.4 and 13.3 Hz, 1 H), 3.84 (s, 6 H), 3.52 (m, 1 H), 2.96–2.57 (m, 5 H), 2.47–2.20 (m, 3 H), 1.72 (m, 1 H). ^{13}C NMR: δ = 174.4, 147.3, 147.0, 133.4, 130.4, 113.5 (CH), 113.2 (CH), 59.2 (CH), 56.0 (CH3), 55.9 (CH3), 44.0 (CH2), 42.0 (CH2), 35.3 (CH2), 30.0 (CH2), 25.4 (CH2). MS; m/z (%): 261 (52) [M$^+$], 246 (100). $C_{15}H_{19}NO_3$: C 68.94, H 7.33, N 5.36; found C 69.07, H 7.84, N 5.38.

Crystal structure analysis of **12d**.

Molecular formula, $C_{25}H_{22}NO_3$; Mr = 384.44. Monoclinic space group P2$_1$/a (No. 14); a = 9.6813 (16), b = 21.746 (5), c = 9.692 (3) Å; β= 94.554(2)°, V = 2034.8(8) Å^3, Z = 4. Dc = 1.259 gcm^{-3}, μ (Cu–Kα) = 0.658 mm^{-1}. Data were collected at 293 (2) K with a CAD4 Enraf–Nonius diffractometer using graphite monochromated Cu–Kα radiation λ = 1.54184 Å 4386 reflections in the theta range 4–75° (-12 ≤ h ≤ 12, 0 ≤ k ≤ 27, -12 ≤ 1 ≤ 0) were collected using the ω/2θ scan technique, of which 4141 were used for refinement.

The structure was solved by direct methods (SHELXS86) [13]. Full matrix least-squares refinement on F^2 was performed with anisotropic displacement parameters for all non-H atoms [14]. Hydrogen atoms belonging to methyl groups were refined at geometrically calculated positions; all other hydrogen atoms were located on the electron-density difference map and refined with isotropic temperature factors. The final agreement indices were R$_1$ = 0.0690 for observed reflections Y > 2σ (I), and WR$_2$ = 0.2258 for all reflections. Absorption coefficients and scattering factors were taken from International Tables for Crystallography [15].

Acknowledgements

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