Preparation of substituted tetrahydro-1-benzazepines by lithiation–trapping

Tahani Aeyad,[a] Callum G. Jones,[a] and Iain Coldham*[a]

Abstract: The tetrahydro-1-benzazepine or benzo[b]azepine ring system is found in a number of drug molecules although methods to access 2,2-disubstituted derivatives are rare. Here we report the preparation of *N*-*tert*-butoxycarbonyl-2-phenyltetrahydro-1-benzazepine followed by lithiation and trapping with electrophiles. The metallation reaction was optimized by using React-IR spectroscopy, and VT-NMR spectroscopy allowed the determination of the rate of rotation of the Boc group (approximate $\Delta G^{\ddagger}$ 63 kJ/mol at –50 °C). The resulting organolithium was quenched to give either 2,2-disubstituted products or, with certain electrophiles, the *ortho*-substituted products, presumably through an η^3-coordinated benzyllithium intermediate. The chemistry was shown to be amenable to extension to the 7-methoxy analog. Removal of the Boc group from the nitrogen atom led to amine products.

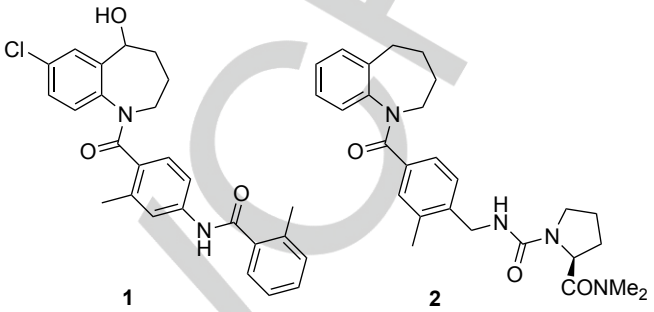


Figure 1. Biologically active 1-benzazepines.

Introduction

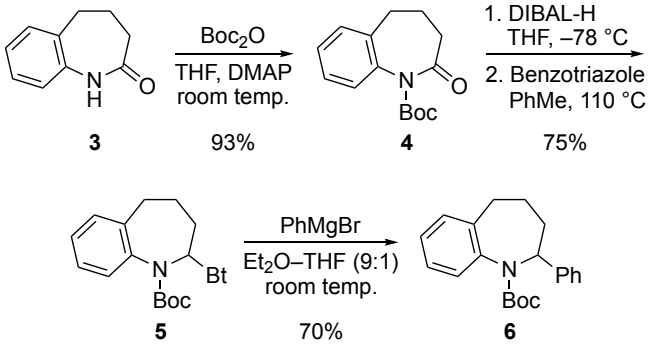
The tetrahydro-1-benzazepine ring system is found in a number of compounds with biological activity and has potential as a building block for drug discovery.[1] Some examples of 1-benzazepines include the vasopressin receptor antagonist tolvaptan (**1**) and the anti-diuretic fedovapagon (**2**) (Fig. 1).[2] Many routes have been developed for the synthesis of tetrahydro-1-benzazepines,[3] although the formation of 2,2-disubstituted derivatives is relatively rare.[4] Our research group has reported chemistry to prepare 2,2-disubstituted tetrahydroquinolines,[5] azepanes,[6] and other alpha-amino substituted compounds[7] by using a lithiation–trapping protocol. We were therefore interested to extend this chemistry to 1-benzazepines. Although lithiation next to a nitrogen atom followed by electrophilic quench is well-known for pyrrolidines and piperidines,[8] there is only one example, as far as we are aware, of this type of reaction with a tetrahydro-1-benzazepine, in which Meyers and Milot prepared a small selection of mono-substituted products.[9] The most popular directing group on the nitrogen atom is the *N*-*tert*-butoxycarbonyl (*N*-Boc) group which promotes lithiation alpha to the nitrogen atom and we therefore needed access to *N*-Boc-2-aryltetrahydro-1-benzazepines.

[a] *T. Aeyad, C. G. Jones, I. Coldham**
Department of Chemistry
University of Sheffield
Brook Hill, Sheffield S3 7HF
UK
E-mail: i.coldham@sheffield.ac.uk
https://www.sheffield.ac.uk/chemistry/staff/profiles/iain_coldham

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.201800868.

Results and Discussion

The tetrahydro-1-benzazepine compound **6** was prepared by the addition of phenylmagnesium bromide to the benzotriazole **5** (Scheme 1). The benzotriazole **5** was made from the commercially available lactam **3** by Boc protection to give lactam **4**, partial reduction with *i*Bu$_2$AlH (DIBAL-H) and reaction with benzotriazole, following literature precedent on a related lactam.[6,10] The partial reduction of lactam **4** provided a mixture of the alcohol and the ring-opened aldehyde product, but this mixture was amenable to conversion directly to the benzotriazole compound **5** in good overall yield (75%). The Grignard addition step was performed in Et$_2$O with some THF to aid solubility. Reaction in neat THF resulted in a lower yield of the product **6** and the reaction was best conducted in a mixture of Et$_2$O–THF. The structure of the tetrahydro-1-benzazepine **6** was verified by single crystal X-ray analysis (see SI). This showed a torsion angle between the fused aromatic ring and the N–CO bond of 67°, suggesting poor overlap between the nitrogen p-orbital and this aromatic ring.



Scheme 1. Preparation of the carbamate **6** (Bt = benzotriazolyl).

The lithiation of the 1-benzazepine **6** was successful by using *n*BuLi in THF. The optimum temperature and time was verified by *in situ* ReactIR spectroscopy (Fig. 2). The lithiation was slow at –78 °C but at –50 °C the reaction was complete in a few minutes, as judged by the formation of a new carbonyl stretch, $\nu_{C=O}$ at 1644 cm^{-1} for the lithiated compound.

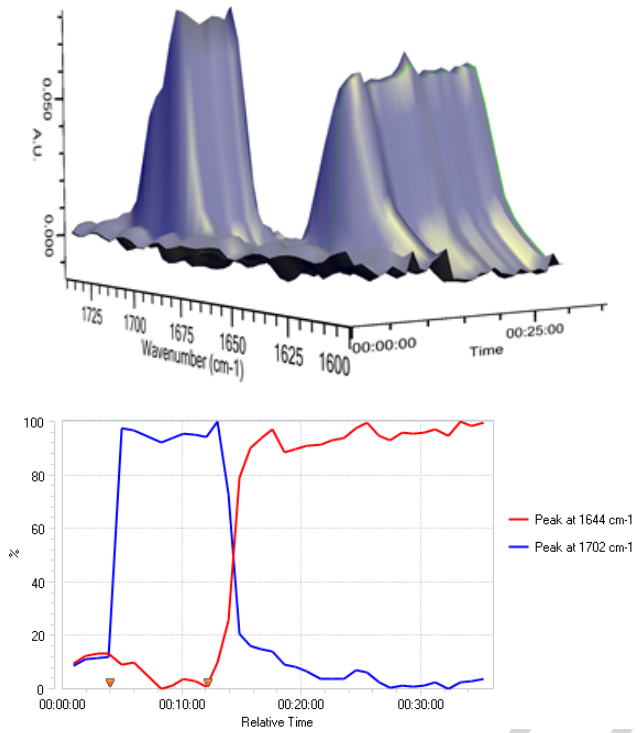


Figure 2. ReactIR spectra for lithiation of **6** with *n*BuLi added after about 12 min in THF at –50 °C; $\nu_{C=O}$ at 1702 cm^{-1} for **6** and $\nu_{C=O}$ at 1644 cm^{-1} for lithiated **6** (Time in h:min:sec).

The slow lithation at –78 °C is due to the slow rotation around the N–CO bond combined with the requirement for the carbonyl group to be directed towards the benzylic proton for lithiation to occur.[11] 1H NMR spectroscopy indicated that the two rotamers were present in about 1.2:1 ratio and variable temperature NMR spectroscopy was performed (Fig. 3). By using line shape analysis, the activation parameters can be estimated and this led to approximate values of $\Delta H^{\ddagger}$ 56 kJ/mol and $\Delta S^{\ddagger}$ –32 J/K·mol. These results, albeit in DMSO as the solvent (to allow for elevated temperatures to observe coalescence), give a half-life for rotation of about 2 h at –78 °C but only about 80 s at –50 °C. These data match those found using *in situ* ReactIR spectroscopy and verify that the best conditions for lithiation use the higher temperature.

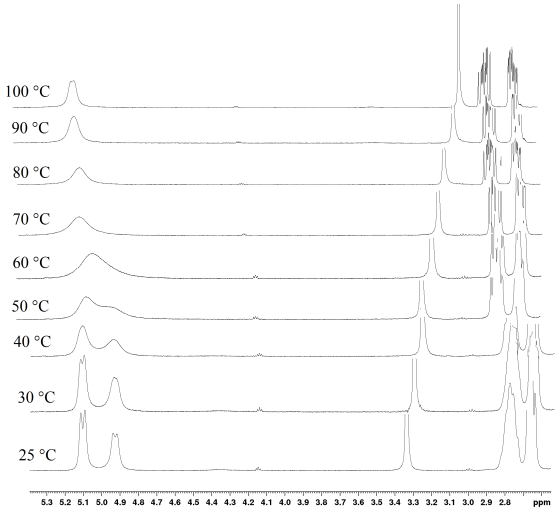
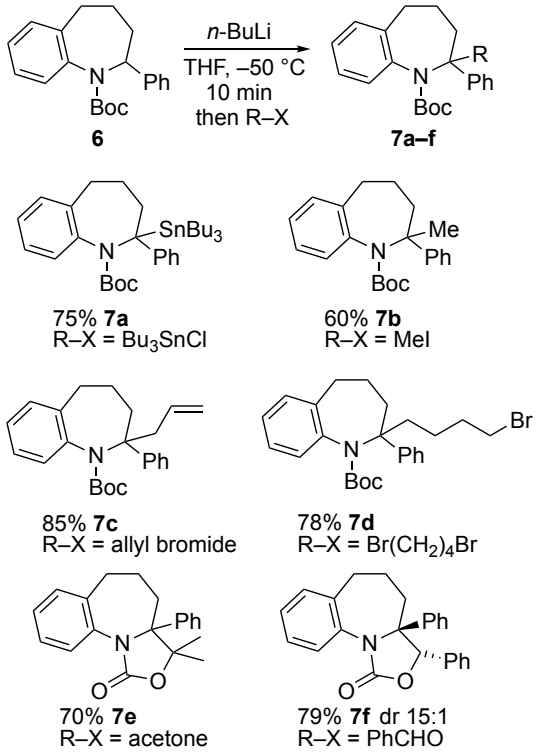


Figure 3. ^{1}H NMR spectra of 1-benzazepine **6** in D_6-DMSO showing region 5.30–2.60 ppm.

The barrier to rotation of the Boc group is about 63 kJ/mol at –50 °C and this is lower than that for the related azepane (approximate $\Delta G^{\ddagger}$ 71 kJ/mol at –50 °C).[5] The faster rate of rotation is likely due to at least partial conjugation of the nitrogen lone pair with the aromatic ring, thereby reducing the interaction with the carbonyl group. However this conjugation will be tempered by the lack of planarity and the value of 63 kJ/mol is significantly higher than that for the corresponding tetrahydroquinoline (approximate $\Delta G^{\ddagger}$ 47 kJ/mol at –50 °C) where the torsion angle is lower.[5]

Using the data above, we treated the 1-benzazepine **6** with *n*BuLi (1.2 equivalents) in THF at –50 °C. After 10 min, the organolithium intermediate was trapped with a range of different electrophiles to give the products **7a–f** (Scheme 2). The products **7a–f** were formed with good yields in which the electrophile adds at C-2 of the benzazepine ring. The reaction was successful for tributyltin chloride, alkyl and allyl halides, and for carbonyl electrophiles. In the latter case the intermediate alkoxide cyclizes on to the Boc group to give the cyclic carbamate. With benzaldehyde as the electrophile, the trapping occurred stereoselectively to give the product **7f** as the major (separable) isomer with the phenyl groups *trans* to each other. This was verified by single crystal X-ray analysis (Fig. 4).



Scheme 2. Lithiation–trapping to give the carbamates **7a–f**.

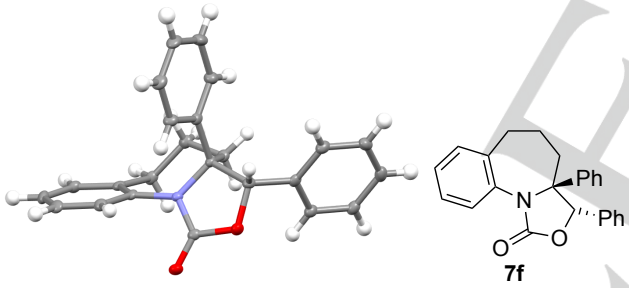
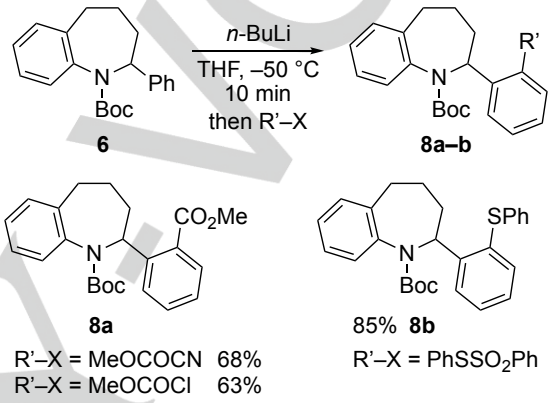


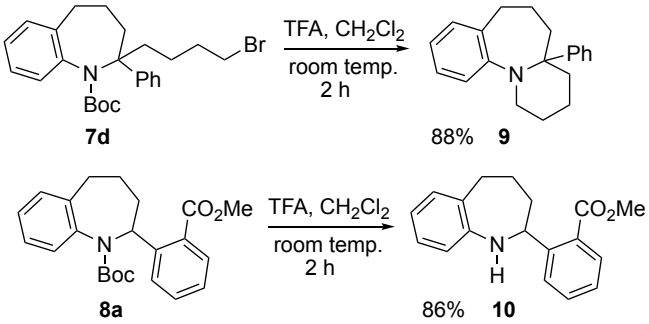
Figure 4. Crystal structure of the major isomer of the carbamate **7f**.

In previous work with *N*-Boc-2-phenylazepane and *N*-Boc-2-phenyltetrahydroquinoline, we had found that lithiation followed by addition of alkyl cyanoformate electrophiles provided the unusual *ortho*-substituted products.[5,6] We therefore tested this with methyl cyanoformate and found the same type of switch to the *ortho*-substituted product **8a** (Scheme 3). The same product **8a** was also formed by using methyl chloroformate as the electrophile. In addition, the *ortho*-substituted product **8b** was formed on using the electrophile $PhSSO_2Ph$. These data, combined with those from the ReactIR and Scheme 2, suggest that the lithium atom in the intermediate organolithium species (typically drawn as if located at C-2 of the benzazepine with coordination to the Boc carbonyl group) has η^3-coordination to the phenyl group. Both η^1- and η^3-coordination of benzyllithiums is known.[12] Density functional theory calculations with the related tetrahydroquinoline system suggest that coordination of a cyanoformate to the lithium atom alters the structure of the organolithium towards the η^3-coordination mode.[5] This is presumably also the case here with the 1-benzazepine not only with cyanoformates but also with certain other electrophiles (MeOCOCl and $PhSSO_2Ph$). After reaction at the *ortho* position, rearomatization would provide the products **8a–b**. In contrast, alkyl halides and aldehydes/ketones react at C-2 (Scheme 2) suggesting that the organolithium is located predominantly on C-2 and that these electrophiles interact differently (in comparison with, for example, formates) during reaction with the organolithium species.



Scheme 3. Lithiation–trapping to give the carbamates **8a–b**.

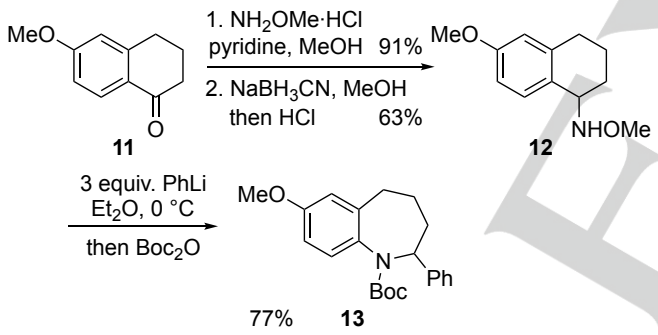
To illustrate the relevance of the chemistry, we treated the carbamates **7d** and **8a** with trifluoroacetic acid (TFA) at room temperature in CH_2Cl_2 to give new products **9** and **10** (Scheme 4). The secondary amine **10** was formed from carbamate **8a** although the amine product generated by removal of the Boc group from carbamate **7d** cyclized *in situ* with displacement of bromide to give the tricyclic amine product **9** in high yield. Fused tricyclic amines with an aryl group alpha to the nitrogen atom are of interest in synthetic and medicinal chemistry and are present in biologically active compounds such as antidepressants and *N*-methyl-D-aspartate receptor antagonists.[13]



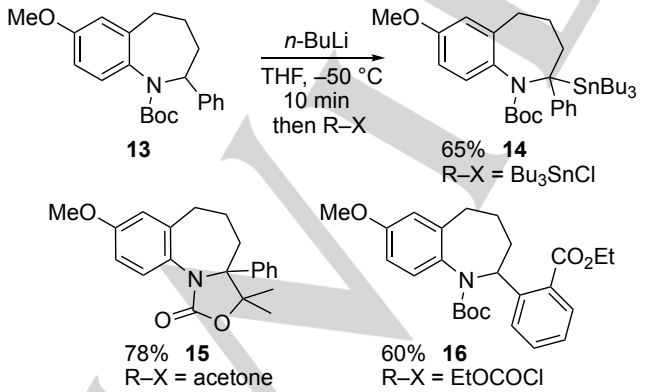
Scheme 4. Removal of the Boc group to give amines **9–10**.

Finally, we have demonstrated that the chemistry is amenable to a derivative, namely the 7-methoxy analog **13**. The carbamate **13** was prepared from the commercially available ketone **11** following related literature methods (Scheme 5).[14,15] Reduction of the oxime to give the hydroxylamine **12** is reported with sodium cyanoborohydride in acetic acid.[14] We found that the presence of acetic acid led to difficulties in isolation of hydroxylamine **12**, and it was preferable to use hydrochloric acid instead. The hydroxylamine **12** was treated with phenyllithium to promote loss of methoxide, rearrangement and addition of the phenyl group.[15] The lithiated secondary amine could be protonated according to the literature but the subsequent conversion to the carbamate **13** with a base and Boc_2O was unsatisfactory in terms of yield. However, rather than isolate the secondary amine, direct addition of Boc_2O to the lithiated intermediate resulted in a good yield for in situ one-pot formation of the carbamate **13**.

In the same way as the 1-benzazepine **6**, treatment of the 1-benzazepine **13** with *n*BuLi in THF at –50 °C for 10 min was followed by addition of a selection of electrophiles (Scheme 6). We were pleased to find that this gave good yields of the substituted products **14–16**. The reactivity matched that of the 1-benzazepine **6**, where addition of acetone gave the cyclic carbamate (**15**) and addition of ethyl chloroformate resulted in the *ortho*-substituted product (**16**).



Scheme 5. Preparation of the carbamate **13**.



Scheme 6. Lithiation–trapping of the carbamate **13**.

Conclusions

A selection of substituted 2-aryltetrahydro-1-benzazepines can be prepared by lithiation then trapping with different electrophiles. Variable temperature NMR spectroscopy, which provides knowledge of the rate of rotation of the Boc group, and *in situ* ReactIR spectroscopy were found to be suitable methods by which the lithiation reactions can be optimised. Alkyl halides, tributyltin chloride, aldehydes and ketones lead to the 2,2-disubstituted products. However, chloroformates, cyanoformates, and $PhSSO_2Ph$ lead to *ortho* substituted products. This may be due to a change in the structure (η^1 or η^3) of the organolithium as it reacts with/coordinates to the different electrophiles.[4] The products can be converted to amines by removal of the Boc group.

Experimental Section

General details: Reagents were obtained from commercial suppliers and were used without further purification except for methyl chloroformate, allyl bromide, benzaldehyde, and 1,4-dibromobutane that were used after distillation; *n*BuLi was titrated before use. Solvents were obtained from a Grubbs dry solvent system. Thin layer chromatography was performed on Merck silica gel $60F_{254}$ plates and visualised by UV irradiation at 254 nm or by staining with an alkaline $KMnO_4$ dip. Flash column chromatography was performed using DAVISIL or Geduran silica gel (40-63 micron mesh). Melting points were recorded on a Gallenkamp hot stage and were uncorrected. InfraRed spectra were recorded on a Perkin Elmer Spectrum RX Fourier Transform – IR System and only selected peaks are reported. ^{1}H NMR spectra were recorded on a Bruker AC400 (400 MHz) instrument. Chemical shifts are reported in ppm with respect to the residual solvent peaks, with multiplicities given as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants (*J* values) are quoted to the nearest 0.5 Hz with values in Hertz (Hz). ^{13}C NMR spectra were recorded on the above instrument at 100 MHz. Low and high resolution (accurate mass) mass spectra were recorded on a Walters LCT instrument for Electro–Spray (ES). ReactIR infrared spectroscopic monitoring was performed on a Mettler-Toledo ReactIR iC 4000 spectrometer equipped with a diamond-tipped (DiComp) probe.

***tert*-Butyl 2,3,4,5-Tetrahydro-2-oxobenzo[b]azepine-1-carboxylate 4:** Di-*tert*-butyl dicarbonate (4.7 g, 20 mmol) in dry THF (15 mL) was added to commercially available 2,3,4,5-tetrahydro-1H-1-benzazepin-2-one **3** (3.0 g, 19 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (2.5 g, 20 mmol) in dry THF (50 mL) at room temperature. After 3 h, the solvent was evaporated and EtOAc (50 mL) was added. The mixture was washed with aqueous HCl (3 × 50 mL, 0.5 M), saturated brine solution (3 × 25 mL) and saturated $NaHCO_3$ solution (3 × 25 mL). The organic layer was dried ($MgSO_4$) and the solvent was evaporated. Purification by flash silica chromatography, eluting with CH_2Cl_2–MeOH (95:5), gave the carbamate **4** (4.5 g, 93%) as an amorphous solid; m.p. 110–112 ºC; R_f 0.26 [petrol–EtOAc (70:30)]; FT-IR ν_{max} (film)/cm^{-1} 2980, 2930, 2860, 1765, 1715; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39–7.20 (3H, m, 3 × CH), 7.19–7.05 (1H, m, CH), 2.81 (2H, t, *J* = 7.0 Hz, CH_2), 2.28 (2H, t, *J* = 7.0 Hz, CH_2), 2.19–2.05 (2H, m, CH_2), 1.47 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.6, 151.4, 138.8, 135.5, 129.0, 127.8, 127.1, 126.1, 83.5, 34.7, 29.3, 27.8, 27.5; HRMS (ES) Found: MH$^+$, 262.1443. $C_{15}H_{20}NO_3$ requires MH$^+$, 262.1438; LRMS *m/z* (ES) 262 (5%, MH$^+$), 206 (100).

***tert*-Butyl-2-(1H-Benzo[d][1,2,3]triazol-1-yl)-2,3,4,5-tetrahydrobenzo[b]azepine-1-carboxylate 5:** DIBAL-H (21.4 mL, 21.4 mmol, 1 M in cyclohexane) was added dropwise to the carbamate **4** (4.0 g, 15 mmol) in dry THF (50 mL) at –78 ºC. After 1 h, the mixture was allowed to warm to room temperature over a further 1 h. Saturated aqueous potassium acetate solution (20 mL) was added slowly. The solids were removed by filtration and were washed with EtOAc (3 × 25 mL). The organic layers were combined, washed with saturated brine solution (4 × 25 mL), dried ($MgSO_4$), and the solvent was evaporated. Purification by flash silica chromatography, eluting with CH_2Cl_2–MeOH (95:5), gave a mixture of the 2-hydroxy compound and the aldehyde (3.6 g, 89%) (ratio 60:40) as an oil; R_f 0.50 (alcohol), 0.75 (aldehyde) [CH_2Cl_2–EtOAc (90:10)]; FT-IR ν_{max} (film)/cm^{-1} 3450, 3360, 2970, 2980, 2940, 2870, 1710, 1680; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of isomers) δ = 9.82 (0.4H, t, *J* = 1.0 Hz, C*H*O), 7.82 (0.4H, d, *J* = 8.0 Hz, CH), 7.25–7.19 (1.6H, m, CH), 7.17–7.11 (1.6H, m, CH), 7.04–7.01 (0.4H, m, CH), 6.80 (0.4H, br s, NH), 5.71–5.54 (0.6H, m, CH), 3.92 (0.6H, s, OH), 2.75 (0.6H, td, *J* = 13.0, 7.0 Hz, CH), 2.62–2.54 (2.4H, m, 4 × CH), 1.95–1.77 (2.2H, m, CH), 1.55 (3.7H, s, *t*-Bu), 1.54–1.52 (0.8H, m, CH), 1.40 (5.3H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of isomers) δ = 202.4, 155.5, 153.6, 137.1, 136.5, 136.1, 131.0, 129.4, 129.2, 128.9, 128.3, 127.1, 126.5, 123.9, 122.2, 80.8, 80.3, 78.9, 43.0, 30.6, 29.7, 29.4, 28.4, 28.3, 22.0, 21.2; HRMS (ES) Found: MNa^+, 286.1417. $C_{15}H_{21}NO_3Na$ requires MNa^+, 286.1414; LRMS *m/z* (ES) 286 (5%, MH^+), 190 (100), 146 (85). It was possible to separate the aldehyde from this mixture and its data are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.83 (1H, br s, C*H*O), 7.84 (1H, d, *J* = 8.0 Hz, CH), 7.25–7.20 (1H, m, CH), 7.13 (1H, d, *J* = 7.0 Hz, CH), 7.07–7.01 (1H, m, CH), 6.80 (1H, br s, NH), 2.63–2.54 (4H, m, 4 × CH), 1.95–1.84 (2H, m, 2 × CH), 1.55 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.3, 153.5, 136.0, 131.0, 129.4, 127.1, 123.9, 122.0, 80.3, 43.0, 30.6, 28.4, 22.0. Benzotriazole (2.0 g, 17 mmol) and $MgSO_4$ (0.5 g) were added to this mixture (3.0 g, 11 mmol) in toluene (70 mL). The mixture was heated under reflux for 18 h then was allowed to cool to room temperature, before washing with saturated aqueous $NaCO_3$ solution (3 × 20 mL) and saturated brine solution (3 × 20 mL). The organic layers were dried ($MgSO_4$) and the solvent was evaporated. Purification by flash silica chromatography, eluting with petrol–EtOAc (75:25), gave the carbamate **5** (3.50 g, 84%), as an oil; R_f 0.45 [petrol–EtOAc (70:30)]; FT-IR ν_{max} (film)/cm^{-1} 3025, 2970, 1690; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08–7.43 (3H, m, 3 × CH), 7.42–7.02 (5H, m, 3 × CH), 6.90–6.62 (1H, m, NCH), 3.06–2.93 (1H, m, CH), 2.83–2.68 (1H, m, CH), 2.54–1.84 (4H, m, 4 × CH), 1.33 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, the C=O could not be observed) δ = 143.9, 137.6, 136.8, 136.5, 128.7, 128.2, 127.3, 126.1, 123.9, 119.7, 118.5, 110.6, 79.0, 66.8, 29.9, 29.6, 29.1, 28.1; HRMS (ES) Found: MNa^+, 387.1793. $C_{21}H_{24}N_4O_2Na$, requires MNa^+, 387.1791; LRMS *m/z* (ES) 387 (15% MNa^+), 190 (28), 146 (100).

***tert*-Butyl 2,3,4,5-Tetrahydro-2-phenylbenzo[b]azepine-1-carboxylate 6:** Phenylmagnesium bromide solution (14.6 mL, 44 mmol, 3 M in Et_2O) was added dropwise to the carbamate **5** (4.0 g, 11 mmol) in dry Et_2O–THF (100 mL, 9:1) at 0 °C. After 20 h, the mixture was allowed to warm slowly to room temperature, then a saturated solution of NH_4Cl (10 mL) was added and was extracted with ether (3 × 25 mL). The combined organic layers were washed with saturated brine solution (4 × 25 mL), dried ($MgSO_4$), and the solvent was evaporated. Purification by flash silica chromatography, eluting with petrol–EtOAc (95:5), gave the carbamate **6** (2.48 g, 70%) as needles; m.p. 110–112 ºC; R_f 0.65 [petrol–EtOAc (80:20)]; FT-IR ν_{max} (film)/cm^{-1} 2980, 2945, 2855, 1690; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.54–7.19 (9H, m, 9 × CH), 5.17 (0.55H, br d, *J* = 12.0 Hz, NCH), 4.94 (0.45H, br d, *J* = 12.0 Hz, NCH), 3.08–2.89 (1H, m, CH), 2.65 (1H, dd, *J* = 13.0, 8.0 Hz, CH), 2.04–1.90 (1H, m, CH), 1.84–1.62 (2H, m, 2 × CH), 1.58–1.42 (1H, m, CH), 1.31 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.9, 154.6, 146.5, 144.9, 138.9, 138.8, 137.3, 137.2, 130.0, 129.8, 128.5, 128.4, 128.2, 128.1, 127.2, 127.1, 126.9, 126.6, 126.5, 126.4, 126.0, 80.5, 79.8, 61.0, 59.4, 32.1, 31.2, 29.7, 29.5, 28.3, 28.2, 23.7, 23.0; HRMS (ES) Found: MNa^+, 346.1779. $C_{21}H_{25}NO_2Na$ requires MNa^+, 346.1778; LRMS *m/z* (ES) 346 (5%, MNa^+), 268 (100%).

***tert*-Butyl 2-(Tributylstannyl)-2,3,4,5-tetrahydro-2-phenylbenzo[b]azepine-1-carboxylate 7a:** *n*BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexane) was added to the carbamate **6** (100 mg, 0.31 mmol) in dry THF (2 mL) at –50 ºC under nitrogen. After 10 minutes, tributyltin chloride (0.25 mL, 0.93 mmol) was added. The mixture was allowed to warm slowly to room temperature and MeOH (1 mL) was added. The solvent was evaporated and the mixture was absorbed onto silica then was purified by flash column chromatography on silica gel, eluting with petrol–EtOAc (99:1), to give the carbamate **7a** (142 mg, 75%) as an oil; R_f 0.75 [petrol–EtOAc (80:20)]; FT-IR ν_{max} (film)/cm^{-1} 2955, 2920, 2860, 1670; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24–6.94 (9H, m, 9 × CH), 2.99–2.86 (1H, m, CH), 2.60 (1H, dt, *J* = 9.0, 4.5 Hz, CH), 2.55–2.45 (1H, m, CH), 1.92–1.82 (2H, m, 2 × CH), 1.47–1.19 (22H, m, *t*-Bu, CH, 3 × CH_2CH_2), 0.87 (9H, t, *J* = 7.0 Hz, 3 × CH_3), 0.83–0.65 (6H, m, 3 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.8, 139.6, 138.4, 131.3, 130.3, 128.2, 127.8, 126.8, 126.0, 125.0, 123.8, 79.8, 61.8, 35.2, 32.5, 29.1, 28.3, 27.7, 22.6, 13.7, 13.5; HRMS (ES) Found: MNa^+, 636.2841. $C_{33}H_{51}NO_2{}^{120}Sn$ Na requires MNa^+, 636.2839; Found: MNa^+, 634.2863. $C_{33}H_{51}NO_2{}^{118}Sn$ Na requires MNa^+, 634.2860; LRMS *m/z* (ES) 636 (72%, MNa^+), 634 (50, MNa^+), 500 (35), 498 (25), 212 (100).

***tert*-Butyl 2,3,4,5-Tetrahydro-2-methyl-2-phenylbenzo[b]azepine-1-carboxylate 7b:** *n*BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexane) was added to the carbamate **6** (100 mg, 0.31 mmol) in dry THF (2 mL) at –50 ºC under nitrogen. After 10 minutes, iodomethane (0.06 mL, 0.93 mmol) was added. The mixture was allowed to warm slowly to room temperature and MeOH (1 mL) was added. The solvent was evaporated and the mixture was absorbed onto silica then was purified by flash column chromatography on silica gel, eluting with petrol–EtOAc (98:2), to give the carbamate **7b** (62 mg, 60%) as an oil; R_f 0.65 [petrol–EtOAc (80:20)]; FT-IR ν_{max} (film)/cm^{-1} 2960, 2930, 2860, 1695; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.56–7.15 (9H, m, 9 × CH), 3.20–2.87 (1H, m, CH), 2.72–2.60 (1H, m, CH), 2.12–1.89 (1H, m, CH), 1.81–1.43 (3H, m, 3 × CH), 1.31–1.02 (12H, m, *t*-Bu and CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 156.2, 154.7, 145.1, 145.0, 138.9, 138.7, 137.2, 136.7, 129.9, 129.5, 128.9, 128.2, 128.0, 127.2, 126.9, 126.7, 126.5, 126.3, 126.0, 125.9, 125.6, 124.7, 80.5, 79.8, 61.4, 61.0, 32.2, 31.2, 30.3, 29.7, 29.6, 28.3, 28.2, 28.0, 23.0, 21.6; HRMS (ES) Found: MH^+, 338.2112. $C_{22}H_{28}NO_2$ requires MH^+, 338.2115; LRMS *m/z* (ES) 338 (5%, MH^+), 282 (100).

***tert*-Butyl 2-Allyl-2,3,4,5-Tetrahydro-2-phenylbenzo[b]azepine-1-carboxylate 7c:** *n*BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexane) was added to the carbamate **6** (100 mg, 0.31 mmol) in dry THF (2 mL) at –50 ºC under nitrogen. After 10 minutes, allyl bromide (0.08 mL, 0.93 mmol) was added. The mixture was allowed to warm slowly to room temperature and MeOH (1 mL) was added. The solvent was evaporated and the mixture was absorbed onto silica then was purified by flash column chromatography on silica gel, eluting with petrol–EtOAc (98:2), to give the carbamate **7c** (94 mg, 85%) as an oil; R_f 0.68 [petrol–EtOAc (70:30)]; FT-IR ν_{max} (film)/cm^{-1} 2965, 2925, 2850, 1695; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.77–7.53 (1H, m, CH), 7.41–7.19 (8H, m, 8 × CH), 5.36–5.00 (1H, m, =CH), 4.99–4.58 (2H, m, =CH_2), 3.03–2.83 (1H, m, CH), 2.73–2.62 (1H, m, CH), 2.54–2.12 (3H, m, 3 × CH), 2.03–1.86 (1H, m, CH), 1.74–1.65 (1H, m, CH), 1.31 (3H, s, *t*-Bu), 1.12 (6H, s, *t*-Bu), 0.99–0.88 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.5, 143.1, 141.3, 134.7, 130.7, 129.1, 128.3, 127.5, 127.2, 126.6, 125.8, 125.4, 118.2, 80.5, 68.1, 29.7, 27.9, 23.6, 23.1, 22.1; HRMS (ES) Found: MH^+,

364.2272. $C_{24}H_{30}NO_2$ requires MH^+, 364.2271; LRMS *m/z* (ES) 364 (5%, MH^+), 308 (100).

***tert*-Butyl 2-(4-Bromobutyl)-2,3,4,5-tetrahydro-2-phenylbenzo[b]azepine-1-carboxylate 7d:** *n*BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexane) was added to the carbamate **6** (100 mg, 0.31 mmol) in dry THF (2 mL) at –50 ºC under nitrogen. After 10 minutes, 1,4-dibromobutane (0.11 mL, 0.93 mmol) was added. The mixture was allowed to warm slowly to room temperature and MeOH (1 mL) was added. The solvent was evaporated and the mixture was absorbed onto silica then was purified by flash column chromatography on silica gel, eluting with petrol–EtOAc (80:20), to give the carbamate **7d** (109 mg, 78%) as an oil; R_f 0.34 [petrol–EtOAc (80:20)]; FT-IR ν_{max} (film)/cm^{-1} 2950, 2925, 2860, 1700; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71–7.12 (9H, m, 9 × CH), 3.17–3.05 (2H, m, 2 × CH), 2.89–2.77 (1H, m, CH), 2.74–2.65 (1H, m, CH), 2.62–2.34 (2H, m, 2 × CH), 2.06–1.90 (1H, m, CH), 1.73–1.56 (2H, m, 2 × CH), 1.54–1.43 (2H, m, 2 × CH), 1.34–1.25 (3H, m, 3 × CH), 1.10 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, one CH_2 missing) δ = 153.4, 141.3, 134.1, 133.7, 130.6, 129.2, 128.5, 127.5, 126.7, 125.9, 125.3, 80.2, 66.0, 39.7, 33.7, 33.3, 32.8, 29.7, 27.9, 22.5; HRMS (ES) Found: MNa^+, 480.1507. $C_{25}H_{32}{}^{79}BrNO_2Na$ requires MNa^+, 480.1509; Found: MNa^+, 482.1489. $C_{25}H_{32}{}^{81}BrNO_2Na$ requires MNa^+, 482.1492; LRMS *m/z* (ES) 482 (10%, MNa^+), 480 (10, MNa^+), 404 (100), 402 (100).

5,5-Dimethyl-6-phenyl-4-oxa-2-azatricyclo[8.4.0.0^{2,6}]tetradeca-1(10),11,13-trien-3-one 7e: *n*BuLi (0.19 mL, 0.44 mmol, 2.4 M in hexane) was added to the carbamate **6** (100 mg, 0.31 mmol) in dry THF (2 mL) at –50 ºC under nitrogen. After 10 minutes, acetone (0.07 mL, 0.93 mmol) was added. The mixture was allowed to warm slowly to room temperature and MeOH (1 mL) was added. The solvent was evaporated and the mixture was absorbed onto silica then was purified by flash column chromatography on silica gel, eluting with petrol–EtOAc (95:5), to give the carbamate **7e** (66 mg, 70%) as an oil; R_f 0.37 [petrol–EtOAc (70:30)]; FT-IR ν_{max} (film)/cm^{-1} 2965, 2925, 2855, 1745; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58 (1H, d, *J* = 8.0 Hz, CH), 7.45–7.04 (8H, m, 8 × CH), 2.86–2.68 (3H, m, 3 × CH), 2.28–2.17 (1H, m, CH), 1.99–1.88 (1H, m, CH), 1.56 (3H, s, CH_3), 1.36–1.30 (1H, m, CH), 1.02 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.6, 139.5, 136.6, 136.5, 131.0, 130.6, 129.6, 128.3, 127.5, 127.4, 127.1, 85.1, 72.3, 36.3, 35.9, 26.2, 21.2, 21.1; HRMS (ES) Found: MH^+, 308.1648. $C_{20}H_{22}NO_2$ requires MH^+, 308.1645; LRMS *m/z* (ES) 330 (10%, MNa^+), 308 (100, MH^+).

5,6-Diphenyl-4-Oxa-2-azatricyclo[8.4.0.0^{2,6}]tetradeca-1(10),11,13-trien-3-one 7f: *n*BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexane) was added to the carbamate **6** (100 mg, 0.31 mmol) in dry THF (2 mL) at –50 ºC under nitrogen. After 10 minutes, benzaldehyde (0.09 mL, 0.93 mmol) was added. The mixture was allowed to warm slowly to room temperature and MeOH (1 mL) was added. The solvent was evaporated and a crude ^{1}H NMR spectrum showed the product as a mixture of stereoisomers (15:1). The mixture was absorbed onto silica then was purified by flash column chromatography on silica gel, eluting with petrol–EtOAc (75:25), to give the carbamate **7f** (82 mg, 75%) (with the phenyl groups *trans* as verified by X-ray crystallography, see page S-22) as needles; m.p. 93–94 °C; R_f 0.43 [petrol–EtOAc (70:30)]; FT-IR ν_{max} (film)/cm^{-1} 3065, 2925, 2850, 1750; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50 (1H, d, *J* = 8 Hz, CH), 7.43–7.26 (9H, m, 9 × CH), 7.16–7.05 (4H, m, 4 × CH), 5.62 (1H, s, CH), 2.89–2.68 (2H, m, 2 × CH), 1.96–1.83 (3H, m, 3 × CH), 1.56–1.45 (1H, m, CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.3, 140.0, 138.0, 135.2, 133.1, 131.0, 130.3, 128.8, 128.6, 128.5, 128.3, 128.2, 128.0, 127.8, 127.2, 126.8, 126.1, 125.9, 125.7, 88.8, 70.0, 35.4, 33.6, 20.6; HRMS (ES) Found: MH^+, 356.1645. $C_{24}H_{22}NO_2$ requires MH^+, 356.1645; LRMS *m/z* (ES) 356 (100%, MH^+).

***tert*-Butyl 2-(2-(Methoxycarbonyl)phenyl)-2,3,4,5-tetrahydrobenzo[b]azepine-1-carboxylate 8a:** *n*BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexane) was added to the carbamate **6** (100 mg, 0.31 mmol) in dry THF (2 mL) at –50 ºC under nitrogen. After 10 minutes, methyl cyanoformate (0.07 mL, 0.91 mmol) was added. The mixture was allowed to warm slowly to room temperature and MeOH (1 mL) was added. The solvent was evaporated and the mixture was absorbed onto silica then was purified by flash column chromatography on silica gel, eluting with petrol–EtOAc (95:5), to give the carbamate **8a** (71 mg, 68%) as an oil; R_f 0.43 [petrol–EtOAc (60:40)]; FT-IR ν_{max} (film)/cm^{-1} 2975, 2940, 2860, 1720, 1695; ^{1}H NMR (400 MHz, $CDCl_3$, rotamer ratio 7:3) δ = 7.92 (1H, d, *J* = 8.0 Hz, CH), 7.64–7.43 (3H, m, 3 × CH), 7.42–7.36 (1H, m, CH), 7.35–7.20 (3H, m, 3 × CH), 5.96 (0.3H, d, *J* = 12.0 Hz, CH), 5.81 (0.7H, d, *J* = 12.0 Hz, CH), 3.95 (3H, s, CH_3), 3.07–2.90 (1H, m, CH), 2.67 (1H, dd, *J* = 13.0, 7.0 Hz, CH), 2.16–2.03 (1H, m, CH), 1.96–1.87 (1H, m, CH), 1.70–1.59 (1H, m, CH), 1.39–1.32 (1H, m, CH), 1.28 (3H, s, *t*-Bu), 1.18 (6H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 167.6, 167.3, 154.7, 154.3, 150.6, 149.1, 139.7, 139.3, 137.9, 137.2, 132.5, 132.1, 130.6, 130.1, 129.7, 129.4, 128.6, 128.3, 128.0, 127.5, 127.1, 126.9, 126.8, 126.4, 126.0, 125.7, 125.5, 125.3, 80.3, 80.1, 57.2, 56.6, 52.3, 52.0, 31.8, 31.6, 29.7, 29.6, 28.2, 27.9, 24.0, 23.8; HRMS (ES) Found: MH^+, 382.1942. $C_{23}H_{28}NO_4$ requires MH^+, 382.1930; LRMS *m/z* (ES) 382 (100%, MH^+). Alternatively, compound **8a** was prepared by addition of methyl chloroformate (0.07 mL, 0.93 mmol), which gave the carbamate **8a** (66 mg, 63%) as an oil; data as above.

***tert*-Butyl 2,3,4,5-Tetrahydro-2-(2-(phenylthio)phenyl)benzo[b]azepine-1-carboxylate 8b:** *n*BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexane) was added to the carbamate **6** (100 mg, 0.31 mmol) in dry THF (2 mL) at –50 ºC under nitrogen. After 10 minutes, *S*-phenyl benzenethiosulfonate (0.23 mL, 0.93 mmol) was added. The mixture was allowed to warm slowly to room temperature and MeOH (1 mL) was added. The solvent was evaporated and the mixture was absorbed onto silica then was purified by flash column chromatography on silica gel, eluting with petrol–EtOAc (95:5), to give the carbamate **8b** (110 mg, 85%) as an amorphous solid; m.p. 94–96 ºC; R_f 0.42 [petrol–EtOAc (60:40)]; FT-IR ν_{max} (film)/cm^{-1} 2930, 2855, 1670; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.69–7.08 (13H, m, 13 × CH), 5.17 (0.5H, d, *J* = 12.0 Hz, CH), 4.93 (0.5H, d, *J* = 12.0 Hz, CH), 3.10–2.88 (1H, m, CH), 2.65 (1H, dd, *J* = 13.0, 8.0 Hz, CH), 2.04–1.89 (1H, m, CH), 1.83–1.62 (2H, m, 2 × CH), 1.57–1.43 (1H, m, CH), 1.30 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 154.9, 154.7, 146.6, 145.0, 143.0, 142.7, 138.9, 138.8, 137.3, 137.2, 136.6, 135.4, 133.6, 132.2, 131.6, 131.4, 130.4, 130.0, 129.8, 129.5, 129.3, 129.1, 129.0, 128.8, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.6, 127.2, 126.9, 126.6, 126.5, 126.0, 125.6, 125.4, 80.4, 79.8, 61.0, 59.4, 32.1, 31.2, 29.7, 29.5, 28.3, 28.2, 23.7, 23.0; HRMS (ES) Found: MH^+, 432.1909. $C_{27}H_{30}NO_2S$ requires MH^+, 432.1906; LRMS *m/z* (ES) 432 (100%, MH^+), 331 (45).

11-Phenyl-1-azatricyclo[9.4.0.0^{2,7}]pentadeca-2(7),3,5-triene 9: Trifluoroacetic acid (0.23 mL, 3.0 mmol) was added to the carbamate **7d** (100 mg, 0.31 mmol) in CH_2Cl_2 (1 mL) at room temperature. After 1 h, the solvent was evaporated then CH_2Cl_2 (2 mL) and aqueous NaOH (5 mL, 2 M) were added. After 15 min, the organic layer was separated, dried ($MgSO_4$), and the solvent was evaporated. Purification by flash silica chromatography, eluting with petrol–EtOAc (95:5), gave the amine **9** (53 mg, 88%) as an oil; R_f 0.46 [petrol–EtOAc (60:40)]; FT-IR ν_{max} (film)/cm^{-1} 2990, 2875, 2750, 1150; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60–6.82 (9H, m, 9 × CH), 3.55–3.25 (2H, m, 2 × CH), 3.13–2.85 (1H, m, CH), 2.79–2.46 (1H, m, CH), 2.34–2.08 (1H, m, CH), 1.91–1.83 (1H, m, CH), 1.76–1.68 (1H, m, CH), 1.64–1.47 (5H, m, 5 × CH), 1.35–1.22 (2H, m, 2 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.9, 137.3, 134.9, 133.8, 128.5, 128.2, 127.0, 125.7, 121.0, 120.3, 60.5, 47.9, 40.7, 30.6, 29.7, 26.2, 21.3,

19.8; HRMS (ES) Found: MH^+, 278.1906. $C_{20}H_{24}N$ requires MH^+, 278.1903; LRMS *m/z* (ES) 278 (100%, MH^+).

Methyl 2-(2,3,4,5-Tetrahydro-1H-benzo[b]azepin-2-yl)benzoate 10: Trifluoroacetic acid (0.20 mL, 2.6 mmol) was added to the carbamate **8a** (100 mg, 0.26 mmol) in CH_2Cl_2 (1 mL) at room temperature. After 1 h, the solvent was evaporated then CH_2Cl_2 (2 mL) and aqueous NaOH (5 mL, 2 M) were added. After 15 min, the organic layer was separated, dried ($MgSO_4$), and the solvent was evaporated. Purification by flash silica chromatography, eluting with petrol–EtOAc (95:5), gave the amine **10** (63 mg, 86%) as an oil; R_f 0.15 [petrol–EtOAc (70:30)]; FT-IR ν_{max} (film)/cm^{-1} 3350, 2960, 2920, 1700; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.03–7.78 (2H, m, 2 × CH), 7.66–7.34 (3H, m, 3 × CH), 7.14–7.04 (1H, m, CH), 6.99–6.69 (2H, m, 2 × CH), 4.50–4.40 (1H, m, CH), 3.86 (3H, s, CH_3), 2.95–2.83 (2H, m, 2 × CH), 2.22–2.02 (2H, m, 2 × CH), 1.97–1.83 (1H, m, CH), 1.59–1.51 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.2, 149.1, 146.3, 138.6, 133.9, 132.4, 130.6, 129.8, 128.3, 127.1, 126.8, 121.3, 120.3, 59.3, 52.3, 39.8, 35.8, 26.6; HRMS (ES) Found: MH^+, 282.1490. $C_{18}H_{20}NO_2$ requires MH^+, 282.1489; LRMS *m/z* (ES) 282 (100%, MH^+).

***N*,6-Dimethoxy-1,2,3,4-tetrahydronaphthalen-1-amine 12:** *O*-Methylhydroxylamine hydrochloride (2.83 g, 33.2 mmol) was added dropwise to 6-methoxy-1-tetralone **11** (4.87 g, 27.7 mmol) and pyridine (2.67 mL, 33.2 mmol) in methanol (60 mL) at room temperature. After 20 h, the solvent was evaporated and the mixture was poured into water (300 mL). Aqueous HCl (100 mL, 1 M) was added and the mixture was extracted with CH_2Cl_2 (3 × 150 mL). The organic layers were washed with water (300 mL), dried (Na_2SO_4), and the solvent was evaporated to give the oxime (*N*,6-dimethoxy-3,4-dihydro-2H-naphthalen-1-imine) (5.19 g, 91%) as an oil; R_f 0.41 [petrol–EtOAc (80:20)]; FT-IR ν_{max} (film)/cm^{-1} 2940, 1615, 1590; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.95 (1H, d, *J* = 9.0 Hz, CH), 6.78 (1H, dd, *J* = 9.0, 3.0 Hz, CH), 6.66 (1H, d, *J* = 3.0 Hz, CH), 3.99 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 2.78–2.70 (4H, m, 4 × CH), 1.90–1.81 (2H, m, 2 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.2, 153.9, 141.3, 125.8, 123.5, 112.9, 112.7, 61.8, 55.2, 30.1, 24.2, 21.5; HRMS (ES) Found: MH^+, 206.1176. $C_{12}H_{15}NO_2$, requires MH^+, 206.1176; LRMS *m/z* (ES) 206 (100%, MH^+). Sodium cyanoborohydride (3.08 g, 60 mmol) was added dropwise to this oxime (10.0 g, 48 mmol) in methanol (100 mL) at 15 ºC. Methyl orange was added as an indicator and aqueous HCl (2 M) was added until the solution turned red. The mixture was stirred at room temperature for 24 h then aqueous NaOH (50 mL, 2 M) was added and the mixture was extracted with CH_2Cl_2 (4 × 40 mL). The organic layers were combined and washed with water (2 × 40 mL) and brine (20 mL), then dried ($MgSO_4$). The solvent was evaporated to give hydroxylamine **12** (6.22 g, 63%) as an oil; R_f 0.44 [petrol–EtOAc (90:10)]; FT-IR ν_{max} (film)/cm^{-1} 2940, 3400, 1610; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.26 (1H, d, *J* = 8.5 Hz, CH), 6.75 (1H, dd, *J* = 8.5, 3.0 Hz, CH), 6.65 (1H, d, *J* = 3.0 Hz, CH), 4.10 (1H, t, *J* = 4.5 Hz, CH), 3.79 (3H, s, OCH_3), 3.60 (3H, s, OCH_3), 2.85–2.68 (2H, m, 2 × CH), 2.20–2.12 (1H, m, CH), 2.08–1.96 (1H, m, CH), 1.84–1.71 (2H, m, 2 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.7, 139.9, 130.7, 127.0, 113.6, 112.2, 62.3, 57.3, 55.2, 29.8, 26.4, 18.1; HRMS (ES) Found: M^+–$NHOCH_3$, 161.0962. $C_{11}H_{13}O$ requires M^+–$NHOCH_3$, 161.0961; LRMS *m/z* (ES) 161 (100%).

***tert*-Butyl 2,3,4,5-Tetrahydro-7-methoxy-2-phenylbenzo[b]azepine-1-carboxylate 13:** Phenyllithium (2.50 mL, 4.80 mmol, 1.9 M in Et_2O) was added dropwise to the hydroxylamine **12** (322 mg, 1.60 mmol) in dry Et_2O (10 mL) at 0 ºC. After 2 h, a solution of Boc_2O (1.00 g, 4.80 mmol) in Et_2O (10 mL) was added dropwise and the mixture was warmed to room temperature. After 16 h, Et_2O (10 mL) was added. The mixture was washed with water (3 × 15 mL), dried ($MgSO_4$), and the solvent was evaporated. Purification by flash silica chromatography, eluting with petrol–EtOAc (90:10), gave the carbamate **13** (420 mg, 77%) as needles, m.p. 98–100 °C; R_f 0.26 [petrol–EtOAc (80:20)]; FT-IR ν_{max} (film)/cm^{-1} 2930, 1690, 1600; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.38–7.20 (5.5H, m, CH), 7.07 (0.5H, d, *J* = 8.5 Hz, CH), 6.86 (0.5H, dd, *J* = 8.5, 3.0, CH), 6.80–6.72 (1.5H, m, CH), 5.16 (0.5H, dd, *J* = 12.0, 3.0 Hz, CH), 4.91 (0.5H, d, *J* = 12.0 Hz, CH), 3.84 (3H, s, CH_3), 3.03–2.88 (1H, m, CH), 2.64–2.54 (1H, m, CH), 2.01–1.89 (1H, m, CH), 1.83–1.65 (2H, m, 2 × CH), 1.56–1.47 (1H, m, CH), 1.33 (4H, s, *t*-Bu), 1.31 (5H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 158.5, 158.3, 155.1, 155.0, 138.8, 138.5, 132.2, 132.0, 131.6, 131.4, 130.8, 130.6, 128.3, 128.1, 126.65, 126.6, 126.5, 126.1, 114.0, 113.5, 111.8, 111.5, 79.6, 79.4, 60.8, 59.2, 55.4, 55.3, 32.0, 31.1, 30.1, 29.9, 28.3, 28.2, 23.6, 23.0; HRMS (ES) MNa^+, 376.1885. $C_{22}H_{27}NO_3Na$ requires MNa^+, 376.1883; LRMS *m/z* (ES) 376 (5%, MNa^+), 298 (100).

***tert*-Butyl 7-Methoxy-2-phenyl-2-(tributylstannyl)-4,5-dihydro-3H-1-benzazepine-1-carboxylate 14:** *n*BuLi (0.15 mL, 0.33 mmol, 2.4 M in hexane) was added to the carbamate **13** (100 mg, 0.28 mmol) in dry THF (2 mL) at –50 ºC under nitrogen. After 10 minutes, tributyltin chloride (0.22 mL, 0.84 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the mixture was adsorbed onto silica. Purification by flash column chromatography on silica gel, eluting with petrol–EtOAc (99:1), gave the carbamate **14** (118 mg, 65%) as needles; m.p. 86–88 ºC; R_f 0.53 [petrol–EtOAc (90:10)]; FT-IR ν_{max} (film)/cm^{-1} 2955, 1670, 1495; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.21 (2H, t, *J* = 8.0 Hz, 2 × CH), 7.12 (2H, br d, *J* = 8.0 Hz, CH), 6.98 (1H, t, *J* = 8.0 Hz, CH), 6.89 (1H, d, *J* = 9.0 Hz, CH), 6.62 (1H, d, *J* = 3.0 Hz, CH), 6.55 (1H, dd, *J* = 9.0, 3.0 Hz, CH), 3.74 (3H, s, OCH_3), 2.95–2.82 (1H, m, CH), 2.57–2.44 (2H, m, 2 × CH), 1.90–1.80 (2H, m, 2 × CH), 1.40–1.30 (16H, m, *t*-Bu, CH, 3 × CH_2), 1.28–1.21 (6H, m, 3 × CH_2), 0.86 (9H, t, *J* = 7.0 Hz, 3 × CH_3), 0.82–0.63 (6H, m, 3 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.0, 157.2, 139.6, 132.5, 130.9, 130.2, 128.8, 127.8, 123.7, 113.5, 110.8, 79.7, 68.2, 55.2, 30.4, 29.1, 28.3, 27.7, 23.8, 23.0, 13.7, 13.5; HRMS (ES) Found: MNa^+, 666.2972. $C_{34}H_{53}NO_3{}^{120}SnNa$ requires MNa^+, 666.2945; Found: MNa^+, 664.3000. $C_{34}H_{53}NO_3{}^{118}SnNa$ requires MNa^+, 664.2940; LRMS *m/z* (ES) 666 (100%), 664 (80).

12-Methoxy-5,5-dimethyl-6-phenyl-4-oxa-2-azatricyclo[8.4.0.0^{2,6}]tetradeca-1(10),11,13-trien-3-one 15: *n*BuLi (0.15 mL, 0.33 mmol, 2.4 M in hexane) was added to the carbamate **13** (100 mg, 0.28 mmol) in dry THF (2 mL) at –50 ºC under nitrogen. After 10 minutes, acetone (0.06 mL, 0.84 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the mixture was adsorbed onto silica. Purification by flash column chromatography on silica gel, eluting with petrol–EtOAc (70:30), gave the carbamate **15** (74 mg, 78%) as needles; m.p. 139–142 ºC; R_f 0.26 [petrol–EtOAc (60:40)]; FT-IR ν_{max} (film)/cm^{-1} 2935, 1750, 1610; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.48 (1H, d, *J* = 9.0 Hz, CH), 7.44–7.13 (5H, m, 5 × CH), 6.86 (1H, dd, *J* = 9.0, 3.0 Hz, CH), 6.59 (1H, d, *J* = 3.0 Hz, CH), 3.77 (3H, s, OCH_3), 2.86–2.74 (2H, m, 2 × CH), 2.67 (1H, dd, *J* = 13.0, 6.0 Hz, CH), 2.27–2.16 (1H, m, CH), 1.98–1.89 (1H, m, CH), 1.54 (3H, s, CH_3), 1.35–1.30 (1H, m, CH), 1.01 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.4, 156.9, 141.1, 136.4, 132.2, 129.2, 128.2, 127.9, 127.4, 115.6, 112.2, 84.9, 71.9, 55.3, 36.4, 36.2, 26.1, 21.3, 21.1; HRMS (ES) Found: MH^+, 338.1757. $C_{21}H_{24}NO_3$ requires MH^+, 338.1751; LRMS *m/z* (ES) 360 (10%, MNa^+), 338 (100, MH^+).

***tert*-Butyl 2-(2-(Ethoxycarbonyl)phenyl)-7-methoxy-2,3,4,5-tetrahydro-1-benzazepine-1-carboxylate 16:** *n*BuLi (0.15 mL, 0.33 mmol, 2.4 M in hexane) was added to the carbamate **13** (100 mg, 0.28 mmol) in dry THF (2 mL) at –50 ºC under nitrogen. After 10 minutes, ethyl chloroformate (0.08 mL, 0.84 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was

added. The solvent was evaporated and the mixture was adsorbed onto silica. Purification by flash column chromatography on silica gel, eluting with petrol–EtOAc (70:30), gave the carbamate **16** (72 mg, 60%) as an oil; R_f 0.52 [petrol–EtOAc (70:30)]; FT-IR ν_{max} (film)/cm^{-1} 2980, 1695, 1500; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ = 7.91 (1H, d, *J* = 8.0 Hz, CH), 7.59–7.57 (1H, m, CH), 7.52–7.48 (1H, m, CH), 7.23–7.20 (1H, m, CH), 6.99–6.57 (3H, m, CH), 5.94 (0.25H, d, *J* = 12.0 Hz, CH), 5.77 (0.75H, d, *J* = 12.0 Hz, CH), 4.45–4.37 (2H, m, OCH_2), 3.86–3.82 (3H, m, OCH_3), 3.79 (0.75H, s, OCH_3), 3.00–2.93 (1H, m, CH), 2.64–2.58 (1H, m, CH), 2.56–2.43 (1H, m, CH), 2.39–2.20 (1H, m, CH), 1.97–1.86 (2H, m, 2 × CH), 1.44 (3H, t, *J* = 7.0, Hz, CH_3), 1.35 (2.5H, s, *t*-Bu), 1.18 (6.5H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) δ = 167.2, 166.6, 158.3, 157.9, 155.0, 154.7, 150.4, 149.6, 138.5, 138.2, 132.3 (CH), 132.2 (CH), 130.8, 130.7, 130.1 (CH), 130.0 (CH), 129.4, 129.3, 127.4, 127.3, 127.0, 126.5, 125.9, 125.6, 113.9, 113.5, 111.7, 111.0, 80.1, 79.5, 61.1, 60.8, 57.0, 56.4, 55.4, 55.3, 31.8, 31.5, 29.9, 29.7, 28.2, 27.9, 23.9, 23.8, 14.3, 14.1; HRMS (ES) Found: MH^+, 426.2282. $C_{25}H_{32}NO_5$ requires MH^+, 426.2275; LRMS *m/z* (ES) 426 (25%, MH^+), 370 (100), 326 (60).

Acknowledgements

We thank the Ministry of Higher Education & Scientific Research, Libya and the University of Sheffield for support. We are grateful to Dr C. Robertson (University of Sheffield) for single crystal X-ray analysis for compounds **6** and **7f**, CCDC 1842826 and 1842827 respectively.

Keywords: Alkylation • Carbanions • Lithiation • Nitrogen heterocycles • Quaternary centers

[1] See, for example, a) S. Gómez-Ayala, J. A. Castrillón, A. Palma, S. M. Leal, P. Escobar, A. Bahsas, *Bioorg. Med. Chem.* **2010**, *18*, 4721; b) S. Soto, E. Vaz, C. Dell'Aversana, R. Álvarez, L. Altucci, A. R. de Lera, *Org. Biomol. Chem.* **2012**, *10*, 2101; c) M. C. Blanco, P. Escobar, S. M. Leal, A. Bahsas, J. Cobo, M. Nogueras, A. Palma, *Eur. J.. Med. Chem.* **2014**, *86*, 291.

[2] a) M. A. Konstam, M. Gheorghiade, J. C. Burnett, L. Grinfeld, A. P. Maggioni, K. Swedberg, J. E. Udelson, F. Zannad, T. Cook, J. Ouyang, C. Zimmer, C. Orlandi, *J. Am. Med. Assoc.* **2007**, *297*, 1319; b) K.-E. Andersson, P. Van Kerrebroeck, *Curr. Urol. Rep.* **2018**, *19*, 8.

[3] See, for example, L. Wu, Y. Meng, J. Ferguson, L. Wang, F. Zeng, *J. Org. Chem.* **2017**, *82*, 4121 and references therein.

[4] a) K. Hino, Y. Nagai, H. Uno, *Chem. Pharm. Bull.* **1988**, *36*, 2386; b) Z. Liang, L. Ju, Y. Xie, L. Huang, Y. Zhang, *Chem. Eur. J.* **2012**, *18*, 15816; c) L. Min, B. Pan, Y. Gu, *Org. Lett.* **2016**, *18*, 364; d) A. S. K. Raj, B. S. Kale, B. D. Mokar, R.-S. Liu, *Org. Lett.* **2017**, *19*, 5340; e) R. Wang, R.-X. Jin, Z.-Y. Qin, K.-J. Bian, X.-S. Wang, *Chem. Commun.* **2017**, *53*, 12229; f) A. Rahman, E. Xie, X. Lin, *Org. Biomol. Chem.* **2018**, *16*, 1367.

[5] N. Carter, X. Li, L. Reavey, A. J. H. M. Meijer, I. Coldham, *Chem. Sci.* **2018**, *9*, 1352.

[6] T. Aeyad, J. D. Williams, A. J. H. M. Meijer, I. Coldham, *Synlett* **2017**, *28*, 2765.

[7] a) R. A. Talk, A. Duperray, X. Li, I. Coldham, *Org. Biomol. Chem.* **2016**, *14*, 4908; b) E. J. Cochrane, L. A. Hassall, I. Coldham, *J. Org. Chem.* **2015**, *80*, 5964; c) X. Li, I. Coldham, *J. Am. Chem. Soc.* **2014**, *136*, 5551; d) E. J. Cochrane, D. Leonori, L. A. Hassall, I. Coldham, *Chem. Comm.* **2014**, *50*, 9910; e) X. Li, D. Leonori, N. S. Sheikh, I. Coldham, *Chem. Eur. J.* **2013**, *19*, 7724; f) N. S. Sheikh, D. Leonori, G. Barker, J. D. Firth, K. R. Campos, A. J. H. M. Meijer, P. O'Brien, I. Coldham, *J. Am. Chem. Soc.* **2012**, *134*, 5300; g) I. Coldham, D. Leonori, *J. Org. Chem.* **2010**, *75*, 4069; h) S. P. Robinson, N. S. Sheikh, C. A. Baxter, I. Coldham, *Tetrahedron Lett.* **2010**, *51*, 3642; i) I. Coldham, S. Raimbault, D. T. E. Whittaker, P. T. Chovatia, D. Leonori, J. J. Patel, N. S. Sheikh, *Chem. Eur. J.* **2010**, *16*, 4082.

[8] a) P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996**, *29*, 552; b) D. Stead, G. Carbone, P. O'Brien, K. R. Campos, I. Coldham, A. Sanderson, *J. Am. Chem. Soc.* **2010**, *132*, 7260.

[9] a) A. I. Meyers, G. Milot, *J. Org. Chem.* **1993**, *58*, 6538. For an alternative approach to tetrahydro-1-benzazepines by using organolithium chemistry, see b) Y. S. Park, E. K. Yum, A. Basu, P. Beak, *Org. Lett.* **2006**, *8*, 2667. For lithiation of *N*-methyl-2- or 3-benzazepines, see c) S. V. Kessar, P. Singh, K. N. Singh, P. Venugopalan, A. Kaur, M. Mahendru, P. Kapoor, *Tetrahedron Lett.* **2005**, *46*, 6753; d) K. N. Singh, P. Singh, E. Sharma, M. Kaur, Y. S. Deol, *Synthesis* **2015**, *47*, 3212.

[10] S. Madan, P. Milano, D. B. Eddings, R. E. Gawley, *J. Org. Chem.* **2005**, *70*, 3066.

[11] K. M. Bertini Gross, P. Beak, *J. Am. Chem. Soc.* **2001**, *123*, 315.

[12] a) H. Ahlbrecht, J. Harbach, T. Hauck, H.-O. Kalinowski, *Chem. Ber.* **1992**, *125*, 1753; b) T. Tatic, S. Hermann, M. John, A. Loquet, A. Lange, D. Stalke, *Angew. Chem. Int. Ed.* **2011**, *50*, 6666; c) M. G. Davidson, D. Garcia-Vivo, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, *Chem. Eur. J.* **2011**, *17*, 3364.

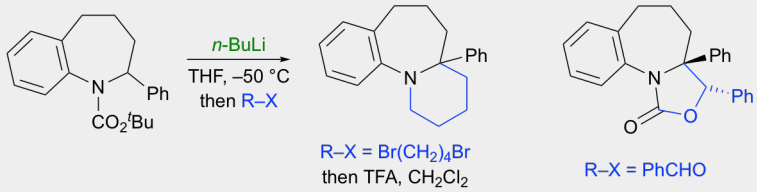
[13] a) B. E. Maryanoff, D. F. McComsey, J. F. Gardocki, R. P. Shank, M. J. Costanzo, S. O. Nortey, C. R. Schneider, P. E. Setler, *J. Med. Chem.* **1987**, *30*, 1433; b) G. A. R. Mealing, T. H. Lanthorn, D. L. Small, R. J. Murray, K. C. Mattes, T. M. Comas, P. Morley, *J. Pharm. Exp. Ther.* **2001**, *297*, 906; c) M. Chaumontet, R. Piccardi, O. Baudoin, *Angew. Chem. Int. Ed.* **2009**, *48*, 179; d) M. Rueping, L. Hubener, *Synlett* **2011**, 1243.

[14] D. Stierli, H. Walter, Patent WO 2012/093100 A1, **2012**.

[15] O. Miyata, T. Ishikawa, M. Ueda, T. Naito, *Synlett* **2006**, 2219.

Entry for the Table of Contents

FULL PAPER



React-IR and VT-NMR spectroscopy ($\Delta G^{\ddagger}$ 63 kJ/mol at –50 °C for Boc rotation) were used to optimise the lithiation of *N*-Boc-2-phenyltetrahydro-1-benzazepine. The intermediate organolithium was reacted with electrophiles to provide a selection of substituted products, with functionalisation either at C-2 or at the *ortho* position of the phenyl ring.

Organolithium reactions

*T. Aeyad, C. G. Jones, I. Coldham**

Page No. – Page No.

Preparation of substituted tetrahydro-1-benzazepines by lithiation–trapping