Expedient Synthesis of an Atypical Oxazolidinone Compound Library

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Abstract

In order to address the current downturn in the drug discovery pipeline, initiatives are being undertaken to synthesise screening libraries of sp^3-rich, low molecular weight compounds. As part of the European Lead Factory initiative, the synthesis and derivatisation of a simple hexahydrooxazolo[5,4-*c*]pyridin-2(1H)-one bicyclic carbamate has been achieved. The synthetic route employed involved a telescoped hetero-Diels-Alder/[2,3]-sigmatropic rearrangement/cyclisation sequence to deliver the desired core scaffold containing two points for further diversification. When applied, this synthesis was found to be robust and scalable which allowed the production of a 155 compound library.

1. Introduction

The urgent need for drug discovery programmes to move away from identifying hit compounds using chemical libraries of flat, (hetero)aromatic constituents has been highlighted in a number of publications.[1] It is accepted that flat compounds contribute to high attrition rates due to poor pharmacokinetic profiles and late stage toxicity studies due to off-target effects. Chiral, three-dimensional compounds are more likely to form complementary interactions with specific biological targets, reducing off-target side-effects and potentially providing ligands for more challenging targets.[1] Initiatives have been realised which fund the compilation of new, innovative screening libraries with the aim of injecting novelty back into drug discovery pipelines to tackle the ensuing stalemate with regards to getting new, improved drugs to market.[2] Advances in sp^2-sp^2 coupling reactions led to the creation of the current available libraries and so it is imperative that similar robust and facile chemistry is implemented in analogous sp^3-rich collections. Approaches to the new libraries include fragment-based screening and diversity-orientated synthesis, often with a focus on the synthesis of sp^3-rich, three-dimensional core structures.[3] The aim of the work described herein was to synthesise a small library of sp^3-rich compounds based upon a fused oxazolidinone/piperidine ring scaffold, containing a *cis*-ring junction and at least two functional groups available for diversification.

Carbamates are well precedented in medicinal chemistry as physiologically stable peptidomimetics capable of penetrating cell membranes.[4] Cyclic carbamates, such as the oxazolidinones, are the most metabolically stable carbamates and are a widely known pharmacophore for antibacterial agents.[4] Linezolid (**1**, **Figure 1. A**) is the archetypal oxazolidonone antibiotic used for the treatment of Gram-

positive strains of methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus faecium (VRE).[5] Antibacterial activity in this series usually requires substitution at the 5-position of the oxazolidinone ring with predictable stereochemistry, as exemplified by the most well developed analogue of **1**, tedizolid (**2**, **Figure 1. A**) which displays activity in linezolid-resistant bacteria and was approved, as a phosphate prodrug, in 2014 in the USA to treat acute bacterial skin infections.[6] Aside from antibacterial activity, the oxazolidinone pharmacophore is present in rivaroxaban (**3**, **Figure 1. A**), a factor Xa inhibitor for the treatment of deep vein thrombosis and pulmonary embolism.[7]

It is hoped that inclusion of an oxazolidinone motif in the innovative bicycle **4** could potentially uncover a novel therapeutic opportunity (**Figure 1. B**). As an addition to our continued interest in scaffold synthesis, discussed herein are results pertaining to the synthesis and derivatisation of the chemical scaffold of the type **4**.[8] *N*-Functionalisation of the oxazolidinone ring nitrogen would provide scaffolds from which novel libraries of compounds could be synthesised, by further derivatisation of the piperidine ring nitrogen. Incorporation of nitrogen atoms as the handle for diversification is desired as this potentially gives access to functional groups such as amines, amides and sulfonamides through facile and high-throughput synthetic methods. The low molecular weight (142 Da) and cLogP (-1.2) of the unsubstituted scaffold, render this scaffold an excellent starting point for a drug discovery programme if found to possess any biological activity.[9]

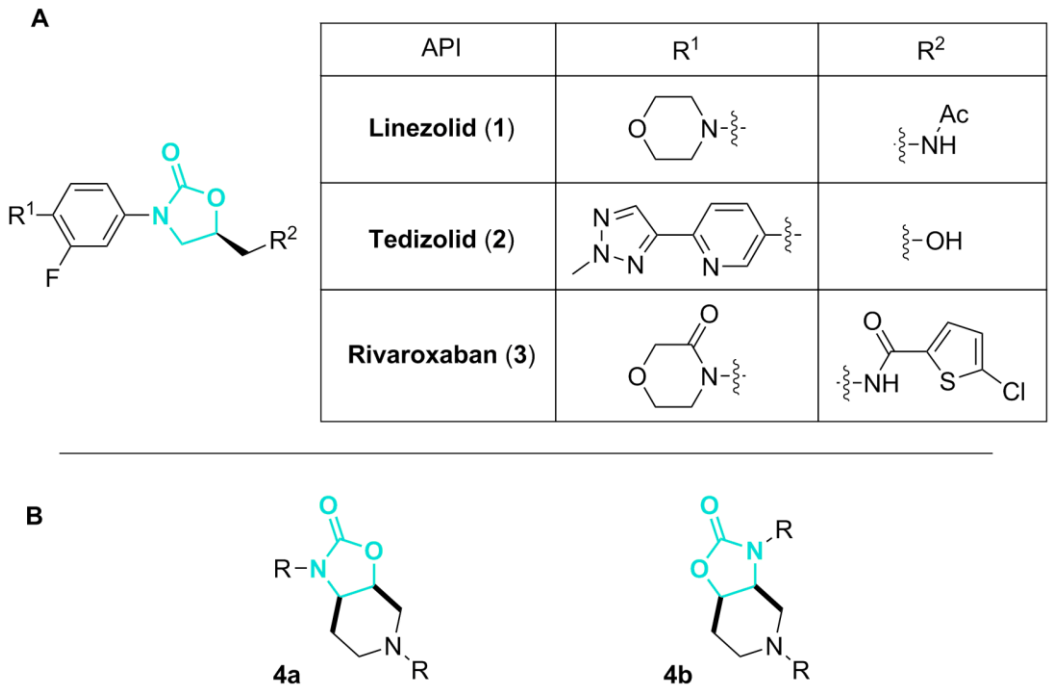
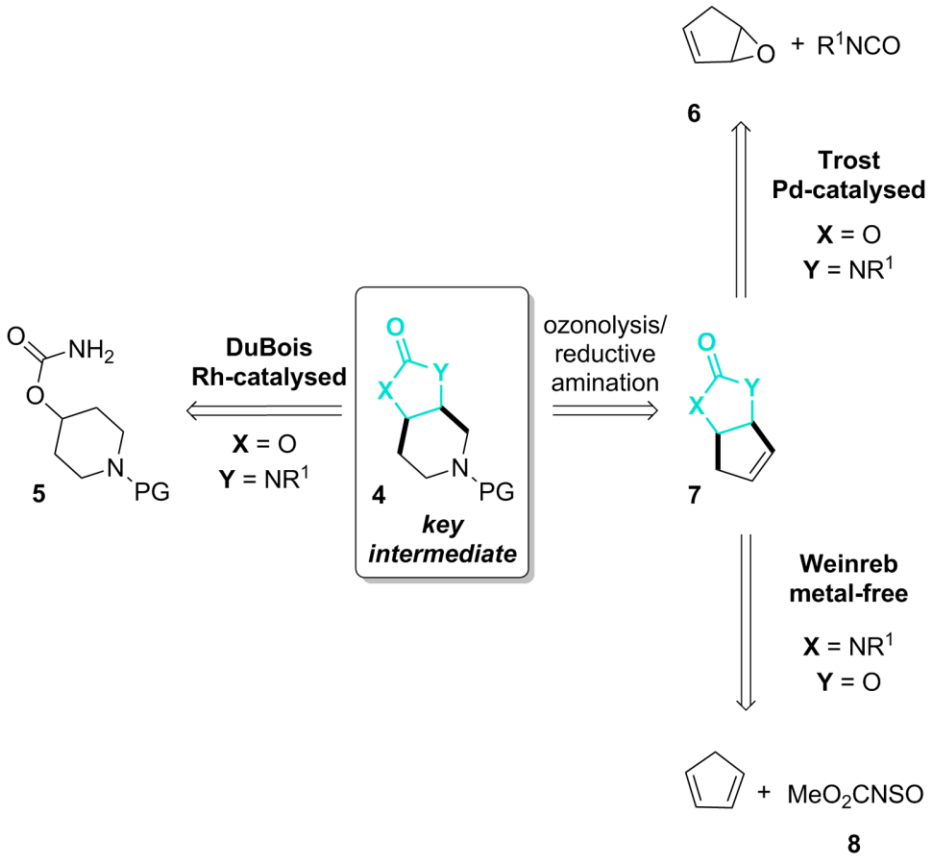


Figure 1. **A** - Known cyclic-carbamate containing pharmacophores (**1**-**3**). **B** - Targeted bicyclic potential pharmacophores **4a** and **4b**.

There are two regioisomers of the targeted scaffold which were highlighted as potential targets; **4a** (hexahydrooxazolo[5,4-*c*]pyridin-2(1H)-one) and **4b** (hexahydrooxazolo[4,5-*c*]pyridin-2(3H)-one). Several routes towards the synthesis of carbamates are known in the literature; however there significantly fewer published syntheses of fused bicyclic oxazolidinones of this class containing a *cis*-ring junction. In order to scale the synthesis of this scaffold to produce a library of hundreds of compounds, the

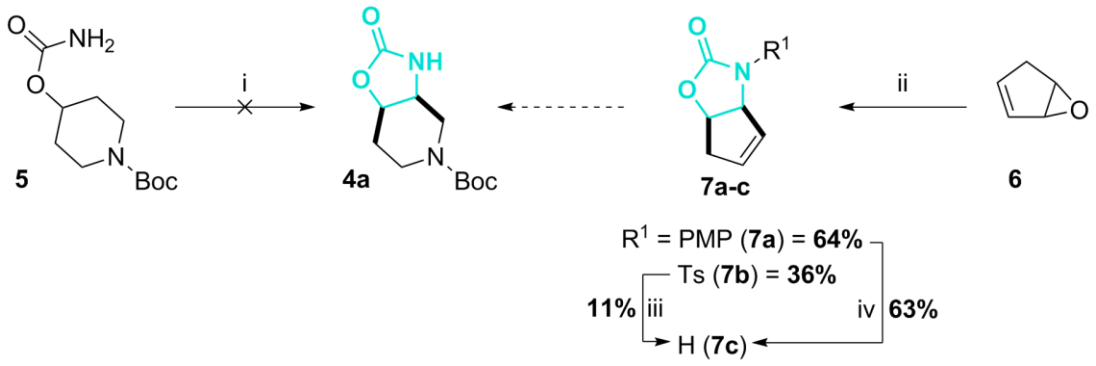
synthetic route chosen must be amenable in terms of cost, safety and expediency. Three potential syntheses towards intermediates **4a** and **4b** were identified (**Scheme 1**). The use of Du Bois' Rh-catalysed C-H insertion chemistry of a carbamate such as **5**,[10] a Trost-type Pd-catalysed reaction of a vinyl epoxide (**6**) and isocyanate,[11] which would both give rise to regioisomer **4b**, and finally Weinreb's metal-free allylic sulfoxide route which would give alternative regiochemistry seen in **4a** (**Scheme 1**).[12]



Scheme 1. Retrosynthetic analysis towards the synthesis of scaffold **4**.

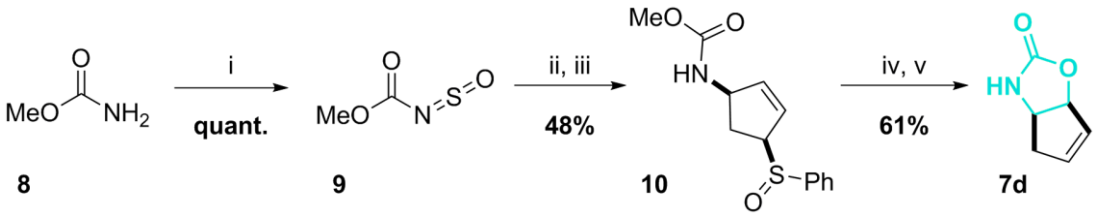
2. Results and Discussion

Our initial investigations focussed upon applying the two transition metal-catalysed routes to generate cores of the general structure **4a**. The Du Bois method was initially attempted with a number of appropriate carbamates (**5**), which were subjected to typical literature conditions for the C-H insertion reaction.[10] Unfortunately, the cyclised products **4** were not observed in appreciable quantities (**Scheme 2**). However, the palladium catalysed method for the generation of intermediate **7c**, a precursor to **4a**, was applied with more success. The relevant epoxide **6** was subjected to reaction with a small range of isocyanates.[9] Both the *N*-4-methoxyphenyl and *N*-4-toluenesulfonate protected intermediates **7a** and **7b** were synthesised in 64% and 36% yields respectively and could both be deprotected to provide **7c**. Despite this protocol being productive, reproducibility, purification and scalability issues caused by complex reaction mixtures were experienced. These problems forced us to abandon the use of this regioisomer in the remainder of the synthesis.



Scheme 2. Ineffective routes towards target core **4a**. Representative conditions: i - $Rh_2(OAc)_4$, $PhI(OAc)_2$, MgO, CH_2Cl_2, 40 °C, 36 h. ii - $Pd_2(dba)_3.CHCl_3$, $P(O^iPr)_3$, CH_2Cl_2, R_2NCO, RT, 18 h. iii - CAN, MeCN, 2 h, RT. iv - naphthalene, Na, DME, THF, -78 °C-RT, 18 h.

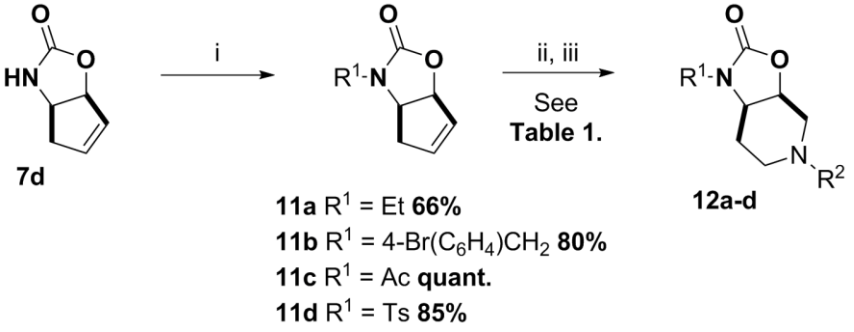
With these preliminary set-backs, the work then shifted to focus on a low cost, expedient synthesis of relevant intermediates which did not necessitate the use of expensive transition metal-catalysts at an early stage in the synthesis. A diastereoselective synthesis of **7d** (regioisomer of **7c**) was identified, which had previously been utilised in the synthesis of marine sponge alkaloid agelastatin A by Weinreb *et al.* (**Scheme 3**).[12b] Synthesis of sulfinyl carbamate **9** proceeded well as per the literature from thionyl chloride addition to *O*-methyl carbamate (**8**).[13] We found that, in agreement with Whitesell *et al*., handling the reaction mixture and product under strict anaerobic conditions gave optimal yields on multigram scale of this reportedly capricious reaction.[14] The one-pot Diels-Alder cycloaddition of sulfinyl carabamate **9** with cyclopentadiene and subsequent ring-opening of the unstable product with phenyl Grignard gave allylic sulfoxide **10** in 48% yield. Literature precedent demonstrates that the desired oxazolidinone **7d** can be obtained in two steps from **10**.[15] A thermal [2,3]-sigmatropic rearrangement to the corresponding sulfonate ester, followed by treatment of the rearranged product with HMPT facilitates ring closure to deliver **7d**. Use of toxic HMPT on scale was a health and safety concern, hence, after an assessment of a variety of phosphorus(III) reagents, it was found that trimethyl phosphite provided the key intermediate (**7d**) in a moderate yield of 61% over 2 steps (**Scheme 3**).



Scheme 3. Synthesis of **7d** *via* an allylic sulfoxide rearrangement. i - $SOCl_2$, Py, Et_2O, RT, 3 h. ii - cyclopentadiene, PhH, RT, 24 h. iii - PhMgBr, THF, RT, 20 min. iv - $P(OMe)_3$, EtOH, Δ, 36 h. v - KOH, MeOH, RT, 24 h.

With key intermediate **7d** in hand, functionalisation of the carbamate nitrogen could be performed to provide the library precursors (**Scheme 4**). Treatment with ^{n}BuLi at -78 °C followed by the addition of the relevant electrophile provided the *N*-ethyl, 4-bromobenzyl, acetyl and 4-toluenesulfonyl bearing derivatives (**11a-d**) in good yields (66-85%; **Scheme 4**). Each derivative was subjected to a one-pot

oxidative cleavage of the olefin under ozonolysis conditions followed by reductive amination of the intermediate ozonide with a small range of amines (**Scheme 4**, **Table 1**).



Scheme 4. *N*-Functionalisation and ring expansion of **7d**. i - ^{n}BuLi, R^1X, THF, -78 °C (X = I for **11a**, Br for **11b** and Cl for **11c** and **11d**). ii - O_3, MeOH, -78 °C. iii - $NaBH_3CN$, R^2NH_2, 0 °C.

Table 1. Synthesis of piperidines **12a-d**.

Entry	SM	R^1	R^2	Yield (%)	Prod.
1	**11a**	Et	4-Br(C_6H_4)CH_2	37	**12a**
2		Et	Me	25	**12b**
3		Et	^{t}Bu	0	-
4	**11b**	4-Br(C_6H_4)CH_2	4-Br(C_6H_4)CH_2	55	**12c**
5		4-Br(C_6H_4)CH_2	Me	29	**12d**
6	**11c**	Ac	4-Br(C_6H_4)CH_2	0	-
7	**11d**	Ts	Bn	9[1]	**13**

1 – By-product derived from the hydrolysis of the desired product.

Ring-expansion of *N*-ethyl scaffold **11a** was successful with two of three attempted amines, with *tert*-butylamine being too sterically hindered to succeed (**Table 1**, Entries 1-3). Similarly, the bromobenzylamine furnished substrate (**11b**) ring expansion proceeded well for two attempted amines (**Table 1**, Entries 4 and 5). We found the acetyl and 4-toluenesulfonyl functionalities were ineffective at generating the desired products under the ozonolysis reaction conditions; indeed, a side-product (**13**) was isolated from the reaction where R^1 = 4-toluenesulfonyl. Compound **13** was identified as a product of hydrolysis (due to the basic work-up) of the carbamate ring post ring expansion (**Table 1**, Entry 7). A single crystal X-ray structure of this product (**13**) was determined which provides evidence to support the *cis*-configuration of the ring junction in compounds **12a-l** (**Figure 2**).

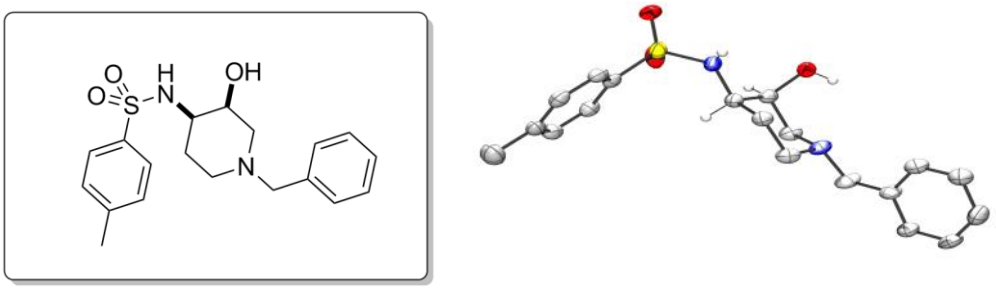
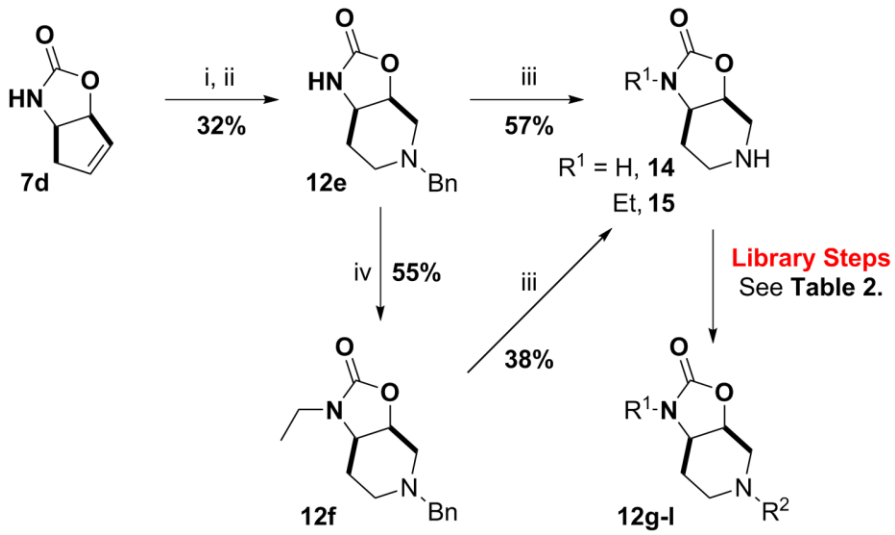


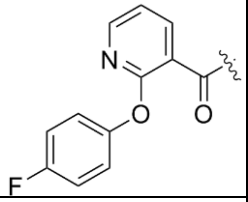
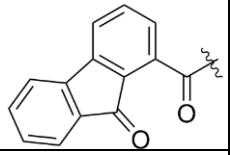
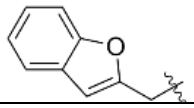
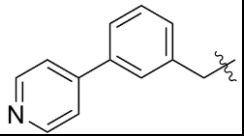
Figure 2. X-ray diffraction crystal structure of hydrolysis product (**13**) showing cis-configuration of C3 hydroxyl and C4 sulfonamide functionalities.

The synthetic route outlined in Scheme 4 demonstrated the facile nature by which carbamate functionalisation and *N*-alkyl piperidine generation can be performed. However, to improve the synthetic utility of the reaction sequence and therefore increase the potential diversity of the intended library, an orthogonal synthetic route was developed (**Scheme 5**). Unsubstituted intermediate **7d** was subjected to oxidative cleavage/reductive amination of the olefin with benzylamine to give the benzyl-protected piperidine **12e**. *N*-Functionalisation of the carbamate nitrogen can then be performed as exemplified by the synthesis of *N*-ethylated compound **12f**. Removal of the piperidine benzyl protecting group under acidic hydrogenolysis conditions allowed access to the secondary amines **14** and **15**. From these cores, a small exemplary compound library of 6 compounds (**12g-l**) was produced *via* standard amidation and reductive amination reactions (**Scheme 5**, Table 2). Both of these protocols are highly amenable to plated library synthesis allowing for the potential of rapid library synthesis.



Scheme 5. Alternative route to the synthesis of library compounds (**12**) from **7d**. i - O_3, MeOH, -78 °C. ii - $NaBH_3CN$, $BnNH_2$, 0 °C. iii – H_2 (1 atm.), Pd/C, HCl, MeOH, RT, 18 h. iv - ^{n}BuLi, EtI, THF, -78 °C.

Table 2. Examples of piperidine *N*-functionalisation library steps.

Entry	SM	R^1	R^2	Yield (%)	Prod.
1[1]	**14**	H		27	**12g**
2[1]	**15**	Et		67	**12h**
3[1]	**14**	H		30	**12i**
4[1]	**15**	Et		47	**12j**
5[2]	**14**	H		55	**12k**
6[2]	**14**			67	**12l**

1 – R^2CO_2H, HATU, NEt^iPr_2, DMF, RT, 18 h. 2 – R^2CHO, AcOH, $NaHB(OAc)_3$, NMP, RT, 18 h.

Each library compound synthesised was found to be chemically stable in DMSO (one week, ambient temperature, in sunlight) and consequently validated the carbamate/piperidine scaffold as a viable library structure. To this end, a proof of principle library of 155 unique compounds was synthesised; these have subsequently been added to the Joint European Compound Library (JECL).[16] Exemplary property data of the produced library is presented in **Figure 3** which demonstrates the range and diversity of this compound family.

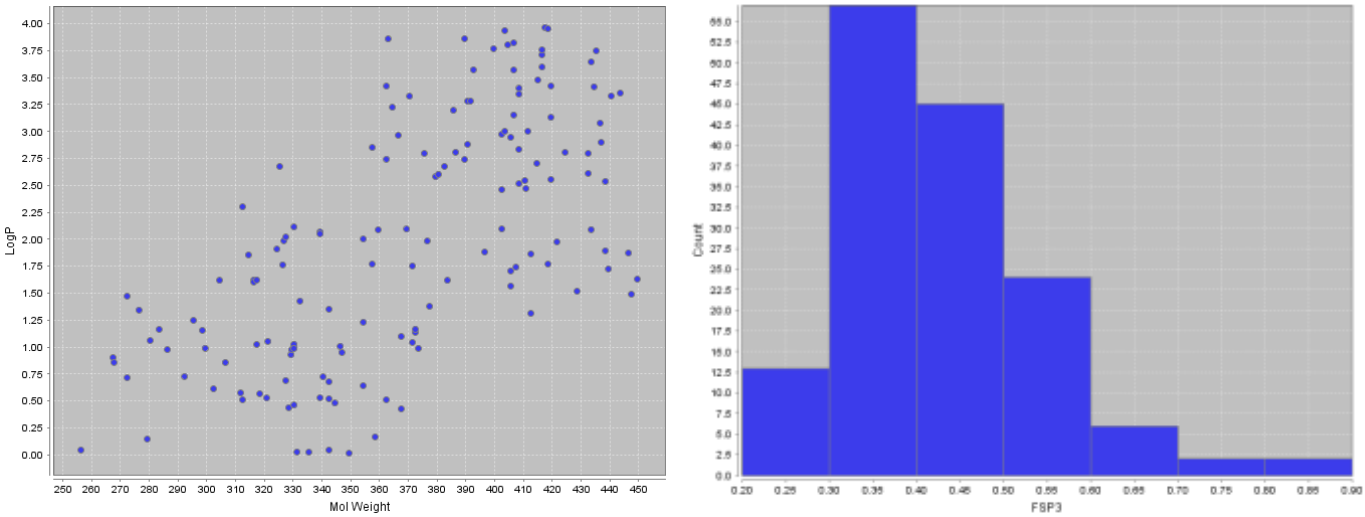


Figure 3. A – Chart of CLogP versus MW for a library of 155 compounds based on scaffold **4a**. **B** – Chart of demonstrating the distribution of compounds synthesised and their respective Fsp^3.

3. Conclusions

A low cost, expedient synthesis of a potential pharamacophore has been demonstrated. The innovative *cis*-fused oxazolidinone/piperidine ring system was synthesised in four synthetic steps from commercially available *O*-methyl carbamate. The use of an ozonolysis/reductive amination protocol enabled the rapid generation of a desired piperidine ring. Further to this, *N*-functionalisation of the carbamate nitrogen was demonstrated to be a facile process, which provided a number of scaffolds for further diversification on the piperidine ring nitrogen. The synthetic route described has provided a synthetic sequence that has enabled the synthesis of a library of compounds of the general structure **4a**. Importantly, a number of chemically stable library compounds, with appealing lipophilicity and molecular weight properties, were synthesised currently constitute a part of the openly accessible JECL for lead generation for both academia and industry.

4. Experimental

4.1 General experimental details

Nuclear Magnetic Resonance (NMR) spectra were recorded on a 400 (Bruker® DPX400, AV400, or AVIII400) NMR spectrometers in $CDCl_3$ or DMSO-d_6 at 300 K (unless stated otherwise). All spectra were referenced to the residual hydrogen solvent peaks for ^{1}H NMR ($CDCl_3$ δ = 7.26 ppm, DMSO-d_6 = 2.50) and the solvent peak for ^{13}C NMR ($CDCl_3$ δ = 77.0 ppm, DMSO-d_6 = 39.5). NMR Chemical shifts (δ) are reported in ppm; coupling constants (J) are reported in Hz; splitting patterns are assigned s = singlet, d = doublet, t = triplet, q = quartet, br = broad signal; and app = the apparent multiplicity. High resolution mass spectrometry (HRMS) data was obtained using a Bruker® MicroTOF spectrometer measured using electrospray ionization (ESI). Infrared spectroscopic data were recorded using a Bruker® Tensor27 FTIR spectrometer. Melting points were measured on a Stuart Scientific SMP3 apparatus and are uncorrected. Solvents, unless otherwise stated, were purchased in reagent grade or anhydrous quality and used as received. THF was distilled from Na/benzophenone immediately prior to use and diethyl ether was obtained from in-house purification towers. Reagents were either purchased directly from commercial suppliers or prepared according to literature procedures. Reactions were monitored using aluminium backed silica thin layer chromatography with a fluorescent dye (λ = 254 nm) and visualised under UV illumination or staining with basic $KMnO_4$ dye. Flash column chromatography was performed manually on silica gel (Fluka 60) with pressurised air flow (except where stated otherwise).

4.2 Procedure for the synthesis of compound 10

To a solution of methyl carbamate (20.0 g, 266 mmol) in diethyl ether (300 ml) was added $SOCl_2$ (21.0 mL, 288 mmol) at 0 °C, after stirring for 5 min the reaction mixture was allowed to warm to RT and stirred for a further 30 min. A solution of pyridine (40.9 mL, 506 mmol) in diethyl ether (60.0 mL) was added slowly over 1.5 h and then stirred for further 1.5 h. The resulting precipitate was filtered under N_2. The filtrate was concentrated *in vacuo* to give **9** (32.0 g, 264 mmol, Quant.) as yellow oil. The material was used without any further purification [^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (3H, s, CH_3)]. To a solution of methyl sulfinylcarbamate (**9**, 10.0 g, 83 mmol) in benzene (60.0 mL) was added freshly distilled cyclopentadiene (9.7 mL, 116 mmol) dropwise and the resulting solution was stirred for 20 h at RT. The solution was diluted with THF (110 mL) and phenylmagnesium bromide (1 M in THF, 83.0 mL, 83 mmol) was added over 45 min then stirred for 30 min before being quenched by addition of sat. aq. NH_4Cl (100 mL). Extracted with EtOAc (3 x 100 mL), combined organic phases were washed with brine (100 mL), dried

($MgSO_4$) and concentrated *in vacuo*. Purification (MPLC, Si, EtOAc/petrol, 80%) gave **10** as mixture of diastereomers in approx. 85% purity, which was used in the subsequent reaction (10.4 g, thick oil, estimated 48% yield taking into account small impurities).

4.2.1 Compound 10[12b]

Orange coloured oil. R_f = 0.72 (EtOAc); IR cm^{-1} 3011, 2360, 2341, 1716, 1516; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57-7.47 (5H, m, H-Ar), 6.17-5.99 (2H, m, H-2 and H-3), 5.83 (1H, d, *J* = 8.8 Hz, NH), 4.78 (1H, dd, *J* = 8.8 and 8.7 Hz, H-1), 3.84-3.78 (1H, m, H-4), 3.68 (3H, s, CH_3), 2.17 (1H, ddd, *J* = 15.3, 8.7 and 8.5 Hz, H-5), 1.78-1.73 (1H, m, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) 171.1 (CO_2Me), 156.3 (C-Ar), 142.0 (C-2 or C-3), 130.9 (C-Ar), 129.3 (C-Ar), 129.1 (C-Ar), 128.0 (C-2 or C-3), 124.0 (C-Ar), 71.2 (C-4), 53.4 (C-1), 52.0 (CH_3), 29.2 (C-5); HRMS ESI^+ *m/z* $C_{13}H_{15}NO_3S$ calculated: 288.0665 $[M+Na]^+$, found: 288.0654.

4.3 Procedure for the synthesis of 7d

To a solution of methyl (*Z*)-(5-(phenylsulfinyl)hex-3-en-2-yl)carbamate (**10**, 39.7 g, 135 mmol) in ethanol (200 mL) was added trimethyl phosphite (17.5 mL, 148 mmol) and the reaction heated to 80 °C for 36 h before the solvent was removed *in vacuo*. The crude mixture was stirred in a 10% solution of KOH in MeOH (100 mL) for 2 h. The mixture was then acidified by addition of 1 M HCl (250 mL) then extracted with EtOAc (4 x 200 mL). The combined organic phase was washed with brine (200 mL), dried ($MgSO_4$) and solvent removed *in vacuo*. Purification (MPLC, Si, EtOAc/isohexane 0-100%) followed by trituration with diethyl ether gave **7d** (2.9 g, 17% yield) as a white solid. The aqueous was concentrated *in vacuo* and the resulting solid was suspended in EtOAc (500 mL) and slurried for 1 h before filtering. The filtrate was concentrated *in vacuo* and then triturated with diethyl ether to give combined **7d** (10.2 g, 61%).

4.3.1 Compound 7d[12b]

A white solid. R_f = 0.63 (EtOAc 100%); M.p. 120-122 °C; IR cm^{-1} 3468, 3011, 1750; ^1H NMR (400 MHz, $CDCl_3$) δ 6.08-6.06 (1H, m, H-alkene), 5.89-5.85 (1H, m, H-alkene), 5.62 (1H, br s, NH), 5.58-5.55 (1H, m, H-5), 4.47-4.43 (1H, m, H-1), 2.76-2.68 (1H, m, H-2), 2.54-2.47 (1H, m, H-2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9 (CO), 135.3 (C-3 or 4), 128.5 (C-3 or 4), 86.2 (C-5), 53.3 (C-1), 40.7 (C-2); HRMS *m/z* $C_6H_7NO_2$ calculated: 148.0369 $[M+Na]^+$, found: 148.0366.

4.4 General procedure for functionalisation cyclic carbamates using ^{n}BuLi

To a solution of **7d** (1 mol. equiv.) in THF (1 mL/0.5 mmol) at -78 °C was added ^{n}BuLi (2.5 M in hexanes, 1.1 mol. equiv.) and stirred for 30 min before a solution of the appropriate halide (1.2 mol. equiv.) in THF (1 mL/0.5 mmol) was added dropwise. The solution was allowed to warm to RT overnight then heated to 70 °C for 12 h. Brine was added and extracted with EtOAc (3 x 1 mL/0.3 mmol), dried ($MgSO_4$) and concentrated *in vacuo*.

4.4.1 Compound 11a

Compound **11a** was prepared according to the general procedure (**4.4**): **7d** (200 mg, 1.6 mmol), THF (3.0 mL), ^{n}BuLi (2.5 M in hexanes, 0.7 mL, 1.8 mmol) and iodoethane (0.15 mL, 1.9 mmol) in THF (3.0

mL). Purification (MPLC, Si, EtOAc/petrol 60%) gave **11a** (160 mg, 66%) as a yellow oil. R_f = 0.33 (EtOAC/petrol 50%); IR cm^{-1} 3011, 2983, 2938, 1737; ^1H NMR (400 MHz, $CDCl_3$) δ 6.08-6.06 (1H, m, H-3), 5.86 (1H, dd app.t, *J* = 5.9, 2.2 and 2.1 Hz, H-4), 5.43-5.40 (1H, m, H-5), 4.39 (1H, ddd, *J* = 7.9, 5.9 and 2.0 Hz, H-1), 3.58 (1H, dt, *J* = 14.8 and 7.5 Hz, C*H*HCH$_3$), 3.05 (1H, dt, *J* = 14.5 and 7.2 Hz, CH*H*CH$_3$), 2.63-2.49 (2H, m, H-2), 1.18 (3H, t, *J* = 7.4 Hz, CH$_3$); ^{13}CNMR (101 MHz, $CDCl_3$) δ 157.0 (CO), 135.0 (C-3 or 4), 128.7 (C-3 or 4), 82.4 (C-5), 56.1 (C-1), 37.4 (C-2), 37.3 (*C*H$_2$CH$_3$), 12.4 (CH$_3$); HRMS *m/z* calculated for $C_8H_{12}N_1O_2$: 154.0863 $[M+H]^+$, found: 154.0861.

4.4.2 Compound 11b

Compound **11b** was prepared according to the general procedure (**4.4**): **7d** (200 mg, 1.6 mmol), THF (3.0 mL), ^{n}BuLi (2.5 M in hexanes, 0.7 mL, 1.8 mmol) and 4-bromobenzylbromide (475 mg, 1.9 mmol) in THF (3.0 mL). Purification (MPLC, Si, EtOAc/petrol 40%) gave **11b** (378 mg, 80%) as a yellow oil. R_f = 0.64 (EtOAc/petrol 50%); IR cm^{-1} 3011, 2933, 1739; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (2H, d, *J* = 8.4 Hz, H-Ar), 7.17 (2H, d, *J* = 8.4 Hz, H-Ar), 6.04-6.01 (1H, m, H-4), 5.87 (1H, ddd, *J* = 6.0, 2.2 and 2.1 Hz, H-3), 5.39-5.35 (1H, m, H-5), 4.68 (1H, d, *J* = 15.3 Hz, H-benzylic), 4.13 (1H, ddd, *J* = 7.9, 3.2 and 3.1 Hz, H-1), 4.07 (1H, d, *J* = 15.3 Hz, H-benzylic), 2.48-2.46 (2H, m, H-2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4 (CO), 135.1 (C-3 or C-4), 135.0 (C-3 or C-4), 132.0 (C-Ar), 130.0 (C-Ar), 128.7 (C-Ar), 122.0 (C-Ar), 82.8 (C-5), 56.3 (C-1), 46.3 (C-benzylic), 36.9 (C-2); HRMS *m/z* calculated for $C_{13}H_{12}BrNO_2$: 294.0124 $[M+H]^+$, found: 294.0115.

4.4.3 Compound 11c

Compound **11c** was prepared according to the general procedure (**4.4**): **7d** (200 mg, 1.6 mmol), THF (3.0 mL), ^{n}BuLi (2.5 M in hexanes, 0.7 mL, 1.8 mmol) and acetyl chloride (0.14 mL, 1.9 mmol) in THF (3.0 mL). Purification (MPLC, Si, EtOAc/petrol 40%) gave **11c** (272 mg, quantitative) as a pale orange oil. R_f = 0.69 (EtOAc/petrol 50%); ^1H NMR (400 MHz, $CDCl_3$) δ 6.14 (1H, m, H-4), 5.87 (1H, app dq, *J* = 6.3, 2.2 Hz, H-3), 5.45 (1H, app dt, *J* = 8.1, 2.1 Hz, H-5), 4.83 (1H, app td, *J* = 7.6, 2.1 Hz, H-1), 2.95 (1H, ddt, *J* = 18.7, 7.2, 2.4 Hz, H-2a), 2.58 (1H, dm, *J* = 18.7, 2.3 Hz, H-2b), 2.51 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7 (CO), 153.4 (CO-*Ac*), 137.6 (C4), 127.3 (C-3), 82.4 (C-5), 55.6 (C-1), 40.0 (C2), 23.8 (CH$_3$); HRMS *m/z* calculated for $C_8H_{11}NO_3$: 168.0655 $[M+H]^+$, found: 168.0655.

4.4.4 Compound 11d

Compound **11d** was prepared according to the general procedure (**4.4**): **7d** (200 mg, 1.6 mmol), THF (3.0 mL), ^{n}BuLi (2.5 M in hexanes, 0.7 mL, 1.8 mmol) and 4-toluenesulfonyl chloride (362 mg, 1.9 mmol) in THF (3.0 mL) to give **11d** (376 mg, 85%) as an orange coloured solid, used without further purification. R_f = 0.16 (EtOAc 100%); M.p. 112-114 °C; IR cm^{-1} 3631, 3011, 2945, 2839, 2360, 1777, 1602; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (2H, d, *J* = 8.5 Hz, H-Ar), 7.35 (2H, d, *J* = 8.5 Hz, H-Ar), 6.15-6.12 (1H, m, H-4), 5.83 (1H, ddd, *J* = 6.1, 4.3 and 2.2 Hz, H-3), 5.44-5.40 (1H, m, H-5), 4.87 (1H, app. dt, *J* = 8.5 and 4.3 Hz, H-1), 2.98-2.95 (2H, m, H-2), 2.45 (3H, s, CH$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9 (CO), 145.7 (C-Ar), 137.1 (C-4), 134.7 (C-Ar), 129.8 (C-Ar), 128.5 (C-Ar), 127.2 (C-3), 83.4 (C-5), 58.0 (C-1), 40.5 (C-2), 21.8 (CH$_3$); HRMS *m/z* calculated for $C_{13}H_{13}NO_4S$: 280.0638 $[M+H]^+$, found: 280.0637.

4.4.5 Compound 12f

Compound **12f** was prepared according to the general procedure (**4.4**): **12e** (500 mg, 2.2 mmol), THF (6.0 mL), ^{n}BuLi (2.5 M in hexanes, 1.0 mL, 2.5 mmol) and iodoethane (0.21 mL, 2.6 mmol) in THF (6.0 mL). Purification (MPLC, Si, EtOAC/petrol, 60%) gave **12f** (312 mg, 55%) as a colourless oil. R_f = 0.32 (EtOAc/petrol 50%); IR cm^{-1} 3631, 3469, 3011, 2945, 2839, 1744, 1603; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.24 (5H, m, H-Ar), 4.50 (1H, d app. t, *J* = 6.6 and 5.5 Hz, H-7), 3.80 (1H, d app. t, *J* = 6.6 and 5.0 Hz, H-2), 3.54 (2H, s, CH_2 benzylic), 3.50 (1H, dq, *J* = 14.3 and 7.2 Hz, C*H*HCH$_3$), 3.09 (1H, dq, *J* = 14.3 and 7.2 Hz, CH*H*CH$_3$), 2.83 (1H, dd, *J* = 12.3 and 5.5 Hz, H-6), 2.54 (1H, dd, *J* = 12.3 and 6.7 Hz, H-6), 2.44-2.43 (2H, m, H-4), 2.00-1.82 (2H, m, H-3), 1.15 (3H, t, *J* = 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5 (C=O), 137.7 (C-Ar), 128.9 (C-Ar), 128.4 (C-Ar), 127.3 (C-Ar), 71.4 (C-7), 62.5 (CH_2 benzylic), 54.1 (C-6), 52.1 (C-2), 48.1 (C-4), 36.3 (C-*C*H$_2$CH$_3$), 25.7 (C-3), 12.6 (C-CH$_3$); HRMS *m*/*z* calculated for $C_{15}H_{21}N_2O_2$: 261.598 $[M+H]^+$, found: 261.601.

4.5 General procedure for one-pot ozonolysis and reductive amination

A solution of the appropriate alkene (1 mol. equiv.) in CH_2Cl_2/MeOH (1:1 0.34 mL/mmol) at -78 °C was treated with ozone until a colour change was observed to blue. After 10 min, O_2 was bubbled through the solution until the solution was colourless then the flask was flushed with N_2. $NaCNBH_3$ (2.5 mol. equiv.) was added and stirred at -78 °C for 30 min before a solution of the appropriate amine (1 mol. equiv.) in MeOH (1.0 mL/mmol) was added dropwise at 0 °C and the mixture was allowed to warm to RT overnight. AcOH (7.5 mol. equiv.) was added and stirred for 1 h before the solution was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (15 mL/mmol), washed with sat. aq. $NaHCO_3$ (15.0 mL/mmol), brine, dried ($MgSO_4$) and concentrated *in vacuo*.

4.5.1 Compound 12a

Compound **12a** was prepared according to the general procedure (**4.5**): **11a** (50 mg, 0.33 mmol) in CH_2Cl_2/MeOH (2.0 mL/ 2.0 mL) followed by $NaCNBH_3$ (52 mg, 0.82 mmol) and 4-bromobenzylamine.HCl (69 mg, 0.31 mmol) in MeOH (0.3 mL). Purification (MPLC, Si, EtOAC/petrol, 50%) gave **12a** (41 g, 37%) as a pale yellow coloured oil. R_f = 0.42 (EtOAc/petrol 50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (2H, d, *J* = 8.5 Hz, H-Ar), 7.18 (2H, d, *J* = 8.5 Hz, H-Ar), 4.48 (1H, dd, *J* = 12.1 and 6.5 Hz, H-5), 3.78 (1H, dd, *J* = 12.1 and 5.0 Hz, H-1), 3.53-3.44 (3H, m, H-benzylic and C*H*HCH$_3$), 3.07 (1H, dq, *J* = 14.0 and 7.4 Hz, CH*H*CH$_3$), 2.78 (1H, dd, *J* = 12.3 and 5.4 Hz, H-4), 2.54 (1H, dd, *J* = 12.3 and 6.5 Hz, H-4), 2.38-2.30 (2H, m, H-3), 1.98-1.80 (2H, m, H-2), 1.14 (3H, t, *J* = 7.4 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4 (C=O), 136.8 (C-Ar), 131.5 (C-Ar), 130.5 (C-Ar), 121.1 (C-Ar), 71.3 (C-5), 61.7 (C-benzylic), 54.0 (C-4), 52.1 (C-1), 47.9 (C-3), 36.5 (C-*C*H$_2$CH$_3$), 25.7 (C-2), 12.7 (CH$_3$); HRMS *m*/*z* calculated for $C_{15}H_{19}BrN_2O_2$: 339.0703 $[M+H]^+$, found: 339.0700.

4.5.2 Compound 12b

Compound **12b** was prepared according to the general procedure (**4.5**): **11a** (50 mg, 0.33 mmol) in CH_2Cl_2/MeOH (2.0 mL/ 2.0 mL) followed by $NaCNBH_3$ (52 mg, 0.82 mmol) and methylamine.HCl (21 mg, 0.31 mmol) in MeOH (0.3 mL). Purification (MPLC, Si, MeOH/EtOAC, 15%) gave **12b** (15 g, 25%) as a pale orange coloured oil. R_f = 0.41 (MeOH/EtOAc 10%); IR cm^{-1} 2949, 2806, 1747, 1668; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 4.46 (1H, dd, *J* = 11.9 and 5.6 Hz, H-5), 3.76 (1H, dd, *J* = 11.9 and 6.0 Hz, H-1), 3.31-3.22 (1H, m, C*H*HCH$_3$), 3.01 (1H, dq, *J* = 14.1 and 7.1 Hz, CH*H*CH$_3$), 2.55 (1H, dd, *J* = 12.4 and 4.8 Hz, H-4), 2.39 (1H, dd, *J* = 12.4 and 5.6 Hz, H-4), 2.28-2.22 (1H, m, H-3), 2.18-2.12 (4H, m, H-3 and H-6), 1.94-1.86 (1H, m, H-2), 1.69-1.61 (1H, m, H-2), 1.04 (3H, t, *J* = 7.1 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4 (CO), 71.1 (C-5),

56.1 (C-4), 51.4 (C-1 or C-3), 50.3 (C-1 or C-3), 46.0 (CH$_2$CH$_3$), 36.4, 25.6, 12.6 (CH$_2$$CH_3$); HRMS m/z calculated for $C_9H_{16}N_2O_2$: 185.1285 $[M+H]^+$, found: 185.1284.

4.5.3 Compound 12c

Compound **12c** was prepared according to the general procedure (**4.5**): **11b** (100 mg, 0.34 mmol) in CH_2Cl_2/MeOH (3.0 mL/ 3.0 mL) followed by $NaCNBH_3$ (53 mg, 0.82 mmol) and 4-bromobenzylamine.HCl (72 mg, 0.32 mmol) in MeOH (0.5 mL). Purification (MPLC, Si, EtOAc/petrol, 80%) gave **12c** (91 mg, 55%) as a colourless sticky solid. R_f = 0.22 (EtOAc/petrol 50%); IR cm^{-1} 2360, 2342, 1750; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.42 (4H, m, H-Ar), 7.18-7.14 (4H, m, H-Ar), 4.63 (1H, d, J = 15.4 Hz, H- benzylic), 4.48 (1H, app. dd, J = 12.0 and 6.5 Hz, H-5), 4.09 (1H, d, J = 15.4 Hz, H- benzylic), 3.60 (1H, app. dd, J = 5.1 and 12.0 Hz, H-1), 3.46 (2H, s, H-benzylic), 2.77 (1H, dd, J = 12.4 and 5.2 Hz, H-4), 2.57 (1H, dd, J = 12.4 and 6.5 Hz, H-4), 2.29-2.22 (2H, m, H-3), 1.86-1.74 (2H, m, H-2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9 (CO), 136.5 (C-Ar), 135.0 (C-Ar), 131.9 (C-Ar), 131.5 (C-Ar), 130.5 (C-Ar), 129.9 (C-Ar), 121.9 (C-Ar), 121.2 (C-Ar), 71.7 (C-5), 61.6 (C-benzylic), 53.9, 52.2, 47.8, 45.5, 25.4 (C-2); HRMS m/z calculated for $C_{20}H_{20}Br_2N_2O_2$: 478.9964 $[M+H]^+$, found: 478.9967.

4.5.4 Compound 12d

Compound **12d** was prepared according to the general procedure (**4.5**): **11b** (100 mg, 0.34 mmol) in CH_2Cl_2/MeOH (3.0 mL/ 3.0 mL) followed by $NaCNBH_3$ (53 mg, 0.82 mmol) and methylamine.HCl (22 mg, 0.32 mmol) in MeOH (0.5 mL). Purification (MPLC, Si, MeOH/EtOAc, 10%) gave **12d** (32 mg, 29%) as a colourless oil. R_f = 0.35 (EtOAc 100%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (2H, d, J = 8.5 Hz, H-Ar), 7.17 (2H, d, J = 8.5 Hz, H-Ar), 4.64 (1H, d, J = 15.4 Hz, H-benzylic), 4.52 (1H, app. dd, J = 12.1 and 6.7 Hz, H-5), 4.08 (1H, d, J = 15.4 Hz, H-benzylic), 3.56 (1H, app. dd, J = 12.1 and 5.2 Hz, H-1), 2.78 (1H, dd, J = 12.4 and 5.4 Hz, H-4), 2.49 (1H, dd, J = 12.4 and 6.7 Hz, H-4), 2.33-2.19 (5H, m, H-3 and CH_3), 1.93-1.77 (2H, m, H-2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (CO), 135.0 (C-Ar), 132.0 (C-Ar), 129.9 (C-Ar), 122.0 (C-Ar), 71.3 (C-5), 55.9 (C-4), 51.4, 50.1, 45.8, 45.5, 25.2 (C-2); HRMS m/z calculated for $C_{14}H_{17}BrN_2O_2$: 325.0546 $[M+H]^+$, found: 325.0536.

4.5.5 Compound 12e

Compound **12e** was prepared according to the general procedure (**4.5**): **7a** (5.3 g, 42 mmol) in CH_2Cl_2/MeOH (50.0 mL/ 50.0 mL) (NB: colour change to green), followed by $NaCNBH_3$ (8.0 g, 127 mmol) and benzylamine (4.6 mL, 42 mmol) in MeOH (5.0 mL). The crude product was purified (MPLC, Si, EtOAc/isohexane 0-80%). Isocyanate, polymer bound 2% DVB, 200-400 mesh (5.0 g) was added into a solution of **12e** in CH_2Cl_2 (100 mL) and stirred gently at RT overnight. The suspension was filtered and the filtrate was *conc. in vacuo* to **12e** (3.1 g, 32% yield) as pale yellow gum. R_f = 0.32 (EtOAc/petrol, 75%); IR cm^{-1} 3448, 3009, 2953, 2820, 1760; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.25 (5H, m, H-Ar), 5.51 (1H, s, NH), 4.59 (1H, d app. t, J = 6.3 and 5.4 Hz, H-7), 3.91 (1H, app. q, J = 5.4 Hz, H-2), 3.55 (2H, s, CH_2 benzylic) 2.79 (1H, dd, J = 12.2 and 5.3 Hz, H-6), 2.67 (1H, dd, J = 12.2 and 6.2 Hz, H-6), 2.51-2.32 (2H, m, H-4), 2.00-1.79 (2H, m, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1 (C=O), 137.6 (C-Ar), 129.0 (C-Ar), 128.4 (C-Ar), 127.3 (C-Ar), 74.2 (C-7), 62.4 (C-CH_2 benzylic), 53.7 (C-6), 50.0 (C-2), 47.9 (C-4), 28.3 (C-3); HRMS m/z calculated for $C_{13}H_{17}N_2O_2$ $[M+H]^+$: 223.1285, found: 223.1279.

4.5.6 Compound 13

Compound **13** was prepared according to the general procedure (**4.5**): **11d** (350 mg, 1.3 mmol) in CH_2Cl_2/MeOH (12.0 mL/ 12.0 mL) followed by $NaCNBH_3$ (195 mg, 3.1 mmol) and benzylamine (0.13 mL, 1.2 mmol) in MeOH (0.5 mL). Purification (MPLC, Si, EtOAc/petrol, 80%) gave **13** (42 mg, 9%) as a pale yellow solid. R_f = 0.47 (EtOAc/petrol, 60%); M.p. 117-119 °C; IR cm^{-1} 3379, 2929, 2854, 1768; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (2H, d, *J* = 8.3 Hz, H-Ar), 7.33-7.24 (7H, m, H-Ar), 5.12 (1H, d, *J* = 9.0 Hz, OH), 3.54-3.46 (3H, m, H-benzylic, H-5), 3.27-3.20 (1H, m, H-1), 2.91-2.75 (2H, m, H-4, H-3), 2.44 (3H, s, CH_3), 2.14-1.97 (2H, m, H-4, H-3), 1.72-1.67 (2H, m, H-2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3 (C-Ar), 138.7 (C-Ar), 137.6 (C-Ar), 129.8 (C-Ar), 129.0 (C-Ar), 128.4 (C-Ar), 127.4 (C-Ar), 126.9 (C-Ar), 67.2 (C-5), 62.1 (C-benzylic), 58.0 (C-4), 53.4 (C-1), 51.7 (C-3), 28.3 (C-2), 21.5 (CH_3); HRMS *m/z* calculated for $C_{19}H_{24}N_2O_3S$: 361.1580 $[M+H]^+$, found: 361.1583.

4.6 Procedure for the synthesis of compound 14.HCl

To a solution of **12e** (400 mg, 1.7 mmol) in MeOH (15.0 mL) was added HCl (1 M in MeOH, 3.0 mL) and Pd/C (10% *w/w*, 200 mg, 0.2 mmol) and stirred under 1 atm. H_2 for 18 h at RT. The suspension was filtered through a pad of Celite, rinsed with MeOH, and the filtrates *conc. in vacuo*. CH_2Cl_2 (5.0 mL) was added and *conc. in vacuo* to give **14**.HCl (212 mg, 57%). Compound 14 can also be 'free based': A solution of *rel*-(3a*S*,7a*R*)-hexahydrooxazolo[5,4-*c*]pyridin-2(1*H*)-one hydrochloride (**14**.HCl) in MeOH was treated with solid supported $NaHCO_3$ for 10 min before being filtered and concentrated *in vacuo*.

4.6.1 Compound 14.HCl

A sand coloured solid which was used without further purification. M.p. 155 °C (dec.); IR cm^{-1} 3012, 2962, 2930, 2361, 2338, 1717; ^1H NMR (400 MHz, DMSO-d_6) δ 9.58 (1H, br s, NH), 8.89 (1H, br s, NH), 4.74 (1H, d app. t, *J* = 7.3 and 2.9 Hz, H-7), 3.92 (1H, app. dd, *J* = 12.7 and 6.3 Hz, H-2), 3.44-3.24 (2H, m, H-4), 3.08-2.91 (2H, m, H-6), 2.07-1.99 (1H, m, H-3), 1.65-1.57 (1H, m, H-3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.2 (CO), 70.3 (C-7), 47.1 (C-6), 41.6, 38.1, 25.1 (C-3); HRMS *m/z* calculated for $C_6H_1N_2O_2$: 143.0815 $[M+H]^+$, found: 143.0817.

4.7 Procedure for the synthesis of compound 15

To a solution of **12f** (400 mg, 1.5 mmol) in MeOH (15.0 mL) was added HCl (1 M in MeOH, 3.0 mL) and Pd/C (10%, 160 mg, 0.15 mmol) and stirred under 1 atm. H_2 for 18 h at RT. The suspension was filtered through a pad of Celite, rinsed with MeOH, and the filtrates *conc. in vacuo*. CH_2Cl_2 (5.0 mL) was added and *conc. in vacuo* to give **15** (121 mg, 38%).

4.7.1 Compound 15

A brown coloured solid which was used without further purification. M.p. 130 °C (dec.); IR cm^{-1} 3011, 2361, 2341, 1759; ^1H NMR (400 MHz, DMSO-d_6) δ 9.81 (1H, br s, NH), 9.10 (1H, br s, NH), 4.77 (1H, d app. t, *J* = 6.2 and 3.5 Hz, H-7), 4.07 (1H, app. dd, *J* = 12.6 and 6.2 Hz, H-2), 3.31-3.38 (3H, m, H-6 and C*H*HCH$_3$, under water peak, observed by COSY), 3.13-2.98 (3H, 3.13-2.98, m, H-4 and C*H*HCH$_3$), 2.21-2.13 (1H, m, H-4), 1.78-1.70 (1H, m, H-3), 1.12 (3H, t, *J* = 7.2 Hz, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.8

(CO), 68.8 (C-7), 50.1 (C-2), 41.2 (C-6), 37.8 (C-4), 36.6 (*C*H_2CH_3), 22.0 (C-3), 13.2 (CH_3); HRMS *m/z* calculated for $C_8H_{15}N_2O_2$: 171.1128 $[M+H]^+$, found: 171.1126.

4.8 General Procedure C: HATU-mediated amide coupling

A solution of the appropriate amine (1 mol. equiv.) in DMF (10.0 mL/mmol) was added to the appropriate carboxylic acid (1.2 mol. equiv.), followed by DIPEA (4 mol. equiv.) and a solution of HATU (1.2 mol. equiv.) in DMF (5.0 mL/mmol) and shaken at RT overnight.

4.8.1 Compound 12g

Compound **12g** was prepared according to the general procedure (**4.8**): **14**.HCl (22 mg, 0.1 mmol), DMF (1.0 mL), 2-(fluorophenoxy)nicotinic acid (28 mg, 0.12 mmol), DIPEA (70 µL, 0.4 mmol) and HATU (46 mg, 0.12 mmol) in DMF (0.5 mL). Purification (prep. HPLC) gave **12g** (7 mg, 27%) as a beige coloured solid. M.p. 210-212 °C; IR cm^{-1} 3674, 3033, 1769, 1635, 1602, 1504, 1421; ^1H NMR (400 MHz, DMSO-d_6, 363 K) δ 8.18 (1H, dd, *J* = 4.9 and 1.9 Hz, H-6), 7.75 (1H, dd, *J* = 7.3 and 1.9 Hz, H-8), 7.31 (1H, br s, NH), 7.21 (1H, dd, *J* = 7.3 and 4.9 Hz, H-7), 7.19-7.17 (4H, m, H-9 and H-10), 4.81-4.68 (1H, m, H-5), 4.08-4.06 (1H, m, H-1), 3.76-3.26 (4H, m, H-4 and H-3), 2.05-1.70 (2H, m, H-2); HRMS *m/z* calculated for $C_{18}H_{16}FN_3O_4$: 358.1198 $[M+H]^+$, found: 358.1196.

4.8.2 Compound 12h

Compound **12h** was prepared according to the general procedure (**4.8**): **15** (21 mg, 0.1 mmol), DMF (1.0 mL), 2-(fluorophenoxy)nicotinic acid (28 mg, 0.12 mmol), DIPEA (70 µL, 0.4 mmol) and HATU (46 mg, 0.12 mmol) in DMF (0.5 mL). Purification (prep. HPLC) gave **12h** (21 mg, 67%) as a beige solid. M.p. 117-118 °C; IR cm^{-1} 3691, 3005, 1752, 1634; ^1H NMR (400 MHz, DMSO-d_6, 363 K) δ 8.18 (1H, dd, *J* = 4.9 and 1.9 Hz, H-6), 7.74 (1H, dd, *J* = 7.3 and 1.9 Hz, H-8), 7.21 (1H, dd, *J* = 7.3 and 4.9 Hz, H-7), 7.19-7.17 (4H, m, H-9 and H-10), 4.75-4.65 (1H, m, H-5), 4.13-4.09 (1H, m, H-1), 3.66-3.49 (2H, m, H-4), 3.12-2.98 (4H, m, H-3 and C*H*$_2CH_3$), 2.10-1.86 (2H, m, H-2), 1.14-1.08 (3H, m, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.3 (CO amide), 156.5 (CO carbamate), 149.2 (C-Ar), 147.8 (C-6), 123.6 (C-Ar), 123.5 (C-Ar), 123.3 (C-Ar), 121.0 (C-Ar), 120.8 (C-Ar), 120.2 (C-Ar), 119.2 (C-Ar), 116.1 (c-Ar), 115.9 (C-Ar), 70.8 (C-5), 50.0 (C-1), 44.5 (C-4), 37.3 (C-3), 36.0 (*C*H_2CH_3), 22.5 (C-2), 12.4 (CH_3); HRMS *m/z* calculated for $C_{20}H_{20}FN_3O_4$ $[m+H]^+$: 386.1511, found: 386.1511.

4.8.3 Compound 12i

Compound **12i** was prepared according to the general procedure (**4.8**): **14**.HCl (22 mg, 0.1 mmol), DMF (1.0 mL), 2-(fluorophenoxy)nicotinic acid (28 mg, 0.12 mmol), DIPEA (70 µL, 0.4 mmol) and HATU (46 mg, 0.12 mmol) in DMF (0.5 mL). Purification (prep. HPLC) gave **12i** (8 mg, 30%) as a yellow sticky solid. IR cm^{-1} 3692, 3461, 3011, 1767, 1714, 1637, 1608, 1433; ^1H NMR (400 MHz, DMSO-d_6, 363 K) δ 7.80 (2H, d, *J* = 7.5 Hz, H-Ar), 7,67-7.58 (3H, m, H-Ar), 7.42-7.38 (1H, m, H-Ar), 7.34-7.12 (2H, m, H-Ar and NH), 4.87-4.56 (1H, m, H-5), 4.10-4.01 (1H, m, H-1), 3.77-3.54 (2H, m, H-4), 3.42-3.12 (2H, m, H-3), 2.07-1.81 (2H, m, H-2); ^{13}C NMR (101 MHz, DMSO-d_6) δ 191.9 (CO ketone), 167.3 (CO amide), 159.0 (CO carbamate), 143.8 (C-Ar), 143.4 (C-Ar), 135.7 (C-Ar), 135.4 (C-Ar), 134.1 (C-Ar), 132.9 (C-Ar), 129.8 (C-Ar), 128.6 (C-Ar), 127.7 (C-Ar), 124.0 (C-Ar), 121.4 (C-Ar), 72.8 (C-5), 47.5 (C-1), 44.2 (C-3), 36.7 (C-4), 23.6 (C-2); HRMS *m/z* calculated for $C_{20}H_{16}N_2O_4$: 349.1183 $[M+H]^+$, found: 349.1181.

4.8.3 Compound 12j

Compound **12j** was prepared according to the general procedure (**4.8**): **15** (21 mg, 0.1 mmol), DMF (1.0 mL), 2-(fluorophenoxy)nicotinic acid (28 mg, 0.12 mmol), DIPEA (70 µL, 0.4 mmol) and HATU (46 mg, 0.12 mmol) in DMF (0.5 mL). Purification (prep. HPLC) gave **12j** (13.2 mg, 47%) as an orange coloured solid. M.p. 201-203 °C; IR cm^{-1} 3691, 3007, 1751, 1714, 1635; ^{1}H NMR (400 MHz, DMSO-d_6, 363 K) δ 7.82-7.79 (2H, m, H-Ar), 7.67-7.58 (3H, m, H-Ar), 7.42-7.38 (1H, m, H-Ar), 7.17-7.10 (1H, m, H-Ar), 4.82-4.53 (1H, m, H-5), 4.14-4.03 (1H, m, H-1), 3.68-3.02 (6H, m, H-4, H-3 and CH_2CH$_3$), 2.13-1.85 (2H, m, H-2), 1.15-1.04 (3H, m, CH$_3$); ^{13}C NMR (101 MHz, DMSO-d_6) δ 191.3 (CO ketone), 167.3 (CO amide), 156.5 (CO carbamate), 143.8 (C-Ar), 143.4 (C-Ar), 135.7 (C-Ar), 135.5 (C-Ar), 134.1 (C-Ar), 132.9 (C-Ar), 129.8 (C-Ar), 128.7 (C-Ar), 127.6 (C-Ar), 123.9 (C-Ar), 121.5 (C-Ar), 121.4 (C-Ar), 70.8 (C-5), 50.1 (C-1), 44.2, 37.0, 36.0, 20.6 (C-2), 12.4 (CH$_3$); HRMS *m/z* calculated for $C_{22}H_{20}N_2O_4$: 399.1315 $[M+H]^+$, found: 399.1324.

4.9 Procedure for the synthesis of compound 12k

A solution of **14** (14 mg, 0.1 mmol) in NMP (1.0 mL) was added to benzofuran-2-carbaldehyde (18 mg, 0.12 mmol), followed by AcOH (11 µL, 0.2 mmol) and a solution of sodium triacetoxyborohydride (53 mg, 0.2 mmol) in NMP (0.5 mL) and shaken at RT overnight. Purification (prep. HPLC) gave **12k** (11 mg, 55%).

4.9.1 Compound 12k

A yellow coloured sticky solid. IR cm^{-1} 3691, 3448, 3007, 2955, 2824, 2784, 1761, 1603, 1455; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60-7.54 (3H, m, H-7, H-10 and NH), 7.29-7.20 (2H, m, H-8 and H-9), 6.79 (1H, s, H-6), 4.50 (1H, dd, *J* = 11.6 and 5.4 Hz, H-5), 3.76-3.73 (3H, m, H-1 and H-benzylic), 2.74 (1H, dd, *J* = 12.6 and 4.9 Hz, H-4), 2.63 (1H, dd, *J* = 12.6 and 5.4 Hz, H-4), 2.49-2.46 (1H, m, H-3), 2.35-2.29 (1H, m, H-3), 1.88-1.80 (1H, m, H-2), 1.62-1.54 (1H, m, H-2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (CO), 155.1 (C-Ar), 153.8 (C-Ar), 128.2 (C-Ar), 124.1 (C-9), 122.8 (C-8), 120.9 (C-7), 111.3 (C-10), 106.0 (C-6), 73.8 (C-5), 54.9 (C-benzylic), 53.5 (C-4), 49.8 (C-1), 47.7 (C-3), 28.0 (C-2); HRMS *m/z* calculated for $C_{15}H_{16}N_2O_3$: 273.1234 $[M+H]^+$, found: 273.1228.

4.10 Procedure for the synthesis of compound 12l

A solution of **14** (14 mg, 0.1 mmol) in NMP (1.0 mL) was added to 3-(pyridine-4-yl)benzaldehyde (22 mg, 0.12 mmol), followed by AcOH (11 µL, 0.2 mmol) and a solution of sodium triacetoxyborohydride (53 mg, 0.2 mmol) in NMP (0.5 mL) and shaken at RT overnight. Purification (prep. HPLC) gave **12l** (15 mg, 67%).

4.10.1 Compound 12l

A yellow coloured sticky solid. IR cm^{-1} 3693, 3448, 3000, 1760, 1702, 1598; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70-8.69 (1H, m, H-Ar), 8.64-8.62 (2H, m, H-Ar), 7.81-7.80 (1H, m, H-Ar), 7.71-7.69 (2H, m, H-Ar), 7.51-7.47 (1H, m, H-Ar), 7.42-7.39 (1H, m, H-Ar), 4.50 (1H, app. dd, *J* = 11.8 and 5.3 Hz, H-5), 3.77 (1H, dd, *J* = 11.8 and 5.9 Hz, H-1), 3.60 (2H, s, H-benzylic), 2.65 (1H, dd, *J* = 12.7 and 4.9 Hz, H-4), 2.58 (1H, dd, *J* = 12.7 and 5.3 Hz, H-4), 2.46-2.40 (1H, m, H-3), 2.27-2.21 (1H, m, H-3), 1.88-1.80 (1H, m, H-2), 1.63-1.55

(1H, m, H-2) ; ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.9 (CO), 154.8 (C-Ar), 154.3 (C-Ar), 128.0 (C-Ar), 123.9 (C-Ar), 122.7 (C-Ar), 120.8 (C-Ar), 111.0 (C-Ar), 105.4 (C-Ar), 72.9 (C-5), 53.8 (C-benzylic), 53.0 (C-4), 48.7 (C-1), 47.4 (C-3), 28.1 (C-2); HRMS *m/z* calculated for $C_{18}H_{19}N_3O_2$: 310.1550 $[M+H]^+$, found: 310.1547.

4.11 Procedure for the synthesis of compound 7a

A solution of 3,4-epoxycyclopent-1-ene (0.50 g, 6.09 mmol) in freshly distilled THF (50 mL) was cooled to 0 °C under Ar. Tris(dibenzylideneacetone)dipalladium(0) chloroform adduct ($(dba)_3Pd_2.CHCl_3$) (0.06 g, 0.06 mmol) was then added followed by the addition of triisopropyl phosphite (0.16 mL, 0.73 mmol) and *p*-methoxybenzyl isocyanate (0.87 mL, 0.01 mmol). The yellow reaction mixture was stirred for 18 h at RT and concentrated *in vacuo*. Purification by column chromatography over silica gel (eluting with 1:3-1:1 EtOAc/petrol) gave **7a** (0.90 g, 64 %).

4.11.1 Compound 7a

Yellow needle like crystals. M.p. 96.8-97.0 (EtOAc/hexane). IR cm^{-1} (nujol; cm^{-1}) 1720 (C=O); ^{1}H NMR (400MHz, $CDCl_3$) 7.46 (2H, m, Ar), 6.92 (2H, m, Ar), 6.05-6.00 (1H, m, H-3), 5.91-5.89 (1H, m, H-2), 5.22-5.12 (2H, m, H1 and H-5), 3.80 (3H, s, CH3), 2.90-2.79 (2H, m, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) 156.9 (C=O), 155.0 (Ar), 154.0 (Ar), 134.1 (C-2), 127.6 (Ar), 122.2 (C-3), 114.6 (Ar), 75.5 (C-1), 67.4 (C-5), 55.7 (CH_3), 39.8 (C-4); HRMS *m/z* calculated for $C_{13}H_{14}NO_3$: 232.0968 $[M+H]^+$, found: 232.0972.

4.12 Procedure for the synthesis of compound 7b

A solution of 3,4-epoxycyclopent-1-ene (1.0 g, 0.01 mol) in freshly distilled THF (50 mL) was cooled to 0 °C under Ar. Tris(dibenzylideneacetone)dipalladium(0) chloroform adduct ($(dba)_3Pd_2.CHCl_3$) (0.13 g, 0.12 mmol) was then added followed by the addition of triisopropyl phosphite (0.17 mL, 0.72 mmol) and *p*-toluenesulfonyl isocyanate (2.0 mL, 0.01 mol). The resulting yellow reaction mixture was stirred for 18 h at RT and concentrated *in vacuo*. Purification by column chromatography over silica gel (eluting with 1:4-1:1 EtOAc/petrol.) to give **7b** (1.2 g, 36%).

4.12.1 Compound 7b[17]

A white crystalline solid. ^{1}H NMR (400MHz, $CDCl_3$) 7.96 (2H, m, Ar), 7.36 (2H, m, Ar), 6.06-5.98 (2H, m, H-3 and H-3), 5.31-5.27 (1H, m, H-1), 5.14-5.10 (H, m, H-5), 2.86-2.66 (2H, m, H-4), 2.45 (3H, s, CH_3).

4.13 Procedure for the synthesis of compound 7c

A solution of **7a** (0.46 g, 1.99 mmol) in MeCN (7.0 mL) was cooled to 0 °C. An aqueous solution of ammonium cerium(IV) nitrate (1.64 g, 2.98 mmol, 7.0 mL of water) was then added. The reaction mixture was stirred for 2 h at RT and then concentrated *in vacuo*. The resulting solution was diluted with water (50 mL), extracted with EtOAc (3x100 mL), dried over $MgSO_4$ and *conc. in vacuo*. Purification by column chromatography over activity IV alumina (eluting with 3:1-1:1 petrol/EtOAc) gave **7c** (0.16 g, 63%) as a yellow oil. Alternatively: A solution of naphthalene (0.50 g, 3.90 mmol) in dry DME (20 mL) under argon was stirred at room temperature. Sodium (0.30 g, 0.01 mol) was then added in small portions and the resulting green solution was stirred for 18 h at RT. A solution of **7b** (0.20 g, 0.72 mmol) in THF (20 mL)

was cooled to -78 °C under argon and the reducing solution was transferred *via* a cannula until the reaction mixture turned green. The resulting solution was stirred for another 18 h at RT. Water (50 mL) was then added and the organic layer was separated. The aqueous layer was extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine, dried and *conc*. *in vacuo*. Purification by column chromatography over activity IV alumina (eluting with 1:1 hexane/EtOAc) gave **7c** (0.01 g, 11%).

4.13.1 Compound 7c[18]

A yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) 6.90 (1H, br s, NH), 5.94-5.90 (1H, m, H-3), 5.76-5.72 (1H, m, H-2), 5.24-5.18 (1H, m, H-5), 4.73-4.68 (1H, m, H-1), 2.84-2.68 (2H, m, H-4).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.xxxx/j.bmc.xxxx.xx.xxx.

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