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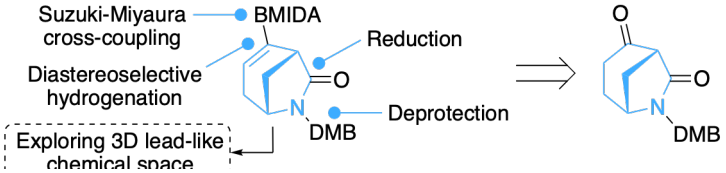

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Synthesis and functionalisation of a bifunctional normorphan 3D building block for medicinal chemistry†

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ABSTRACT

A multi-gram-scale synthetic route to a novel, bifunctional normorphan 3D building block bearing orthogonally reactive vinyl MIDA boronate and *N*-2,4-dimethoxybenzyl (DMB) amide functional handles has been developed. Synthetic manipulation at each of the functional handles has been demonstrated including Suzuki-Miyaura cross-coupling, *exo*-diastereoselective hydrogenation, *N*-DMB group removal and lactam reduction. Normorphan cores derived from the building block satisfied AstraZeneca's 'rule of 2' for building blocks and had a high fraction of sp^3 hybridised carbon atoms (Fsp^3). A virtual lead-like library of 344 compounds derived from the building block had attractive lead-like properties. The 3D building block has been commercialised by Redbrick Molecular and is currently available for purchase.

1. Introduction

The advent of high-throughput screening has dramatically increased the capacity to survey compound-target interactions within medicinal chemistry. As a result, synthetic chemists have been challenged to match this new capability with more *and* better-designed compounds in order to efficiently explore medicinal chemistry space.[1] This in turn has led to the introduction of a number of diverse design concepts which include lead-oriented synthesis,[2] increasing the fraction of sp^3 hybridised carbon atoms (Fsp^3),[3] conformational restriction[4] and scaffold hopping.[5] In each of these approaches, building blocks find great utility and this has driven synthetic interest in building block development, with a number of recent reports on new structural families.[6-9] Alongside this, there is now a recognition that the availability of 'high quality' building blocks is pivotal to the construction of compound screening collections that will deliver both good success rates in high-throughput screening and 'high quality' hits for development into potential drug candidates.[10-12] In this context, as part of AstraZeneca's 'strategic reagent initiative', Goldberg *et al.* have parametrised building block quality in the form of a 'rule of 2' for key metrics: MW < 200, clogP < 2, hydrogen bond donor count (HBD) ≤ 2 and hydrogen bond acceptor count (HBA) ≤ 4.[10]

As part of our ongoing interest in exploring 3D lead-like[13,14] and fragment[15,16] medicinal chemistry space, we have become interested in the design, synthesis and further functionalisation of bifunctional 3D building blocks for use in medicinal chemistry. With building block design in mind, the normorphan core was of particular interest as a result of its rigidity, 3-dimensionality, high Fsp^3 and low molecular weight. In addition, derivatives of this scaffold have been shown to exhibit a variety of pharmacological activities[17-20] (Figure 1A, normorphan scaffold highlighted in blue). Thus, using the normorphan framework as inspiration, 3D building block **1** (Figure 1B) was designed; it is equipped with an *N*-protected amide and a cross-coupling handle, namely a vinyl methyliminodiacetic acid (MIDA) boronate group (Figure 1B). These are orthogonally reactive functional handles that could be exploited in *N*-functionalisation (after *N*-group removal) and Suzuki-Miyaura cross-coupling reactions, two of the most commonly used reactions in medicinal chemistry.[21] Of note, amines and aryl boronates were functional groups that were often present in the building blocks selected in the AstraZeneca 'strategic reagent initiative'; aryl boronates had an especially high usage probably due to their particular aptitude for parallel synthesis.[10] Furthermore, there are limited examples[22,23] of 3D

† This paper is dedicated to Professor Richard J. K. Taylor, my friend, mentor and colleague, to celebrate all of his creative scientific contributions and to highlight the spectacular mentoring of the Taylor research group – what a wonderful legacy!

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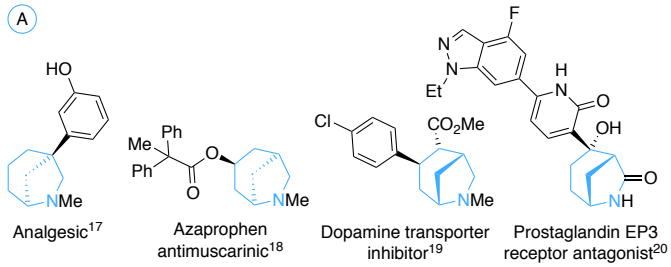
building blocks that are equipped with cross-coupling potential – this is a key design feature of 3D building block **1**.

From a synthetic perspective, there are several additional aspects to the design of building block **1**. First, we anticipated that the vinyl BMIDA group in **1** could be forged from 2,4-dimethoxybenzyl (DMB) protected keto-lactam **2** *via* enol triflate formation, Miyaura borylation with B_2pin_2 and transesterification with MIDA (Figure 1B); Bonjoch and co-workers had reported the preparation of the analogous *N*-benzyl keto-lactam.[24] Second, the DMB group was selected to facilitate downstream removal of the amide protecting group under either acidic or oxidative conditions since *N*-benzyl lactams can be difficult to cleave using hydrogenolysis. Third, building block **1** presents a range of reactivity and functionalisation opportunities. At the outset, we envisaged (i) Suzuki-Miyaura cross-coupling of the vinyl BMIDA group followed by diastereoselective *exo* face hydrogenation; (ii) *N*-DMB group removal and subsequent *N*-functionalisation of the NH lactam; (iii) lactam reduction to the corresponding amine and subsequent *N*-functionalisation. Fourth, the BMIDA group, introduced by Burke, often confers crystallinity and bench-stability to its derivatives whilst also undergoing effective sp^2-sp^2 cross-coupling *via* a slow-release of the corresponding *in situ*-generated boronic acid.[25]



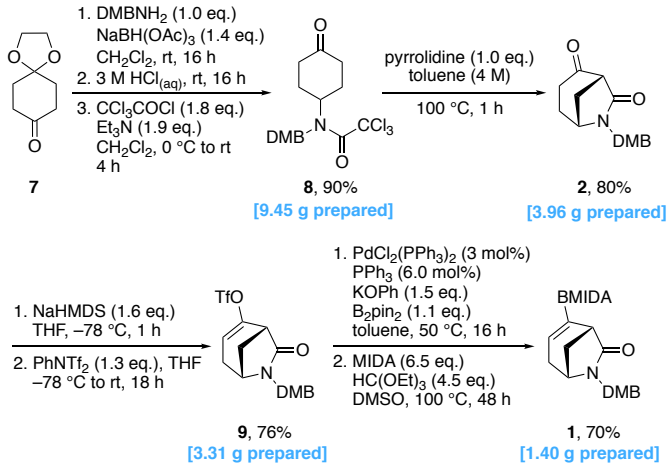
	3	4	5	6
MW	123.16	125.17	109.17	111.19
clogP	–0.38	–0.10	0.77	1.25
HBD	1	1	1	1
HBA	1	1	1	1
Fsp^3	0.57	0.86	0.71	1.00

Figure 1. A. Exemplar pharmacologically active normorphans. **B.** Bifunctional normorphan 3-D building block **1**. **C.** 'Rule of 2 analysis'. DMB = 2,4-dimethoxybenzyl.

In order to verify the potential utility of building block **1** for use in medicinal chemistry, we analysed the properties of two lactam scaffolds (**3**, **4**) and two amine scaffolds (**5**, **6**) derived from **1** (Figure 1C). Specifically, all four of the normorphan cores **3**-**6** fell within AstraZeneca's 'rule of 2' guidelines, whilst also possessing high Fsp^3 values, indicating that building block **1** is likely to yield derivatised products with desirable lead-like properties (which was subsequently confirmed, *vide infra*). Herein, we report the gram-scale synthesis of novel normorphan 3D building block **1** together with successful examples of Suzuki-Miyaura cross-coupling, alkene hydrogenation, DMB protecting group removal and lactam reduction.

2. Results and discussion

In order to develop a practical and useful 3D building block, a robust, scalable synthesis of **1** was required. Our overall, optimised gram-scale synthesis of **1** is summarised in Scheme 1. For the construction of the key intermediate, DMB protected keto-lactam **2**, we slightly modified an elegant approach to the analogous *N*-benzyl normorphan skeleton reported by Bonjoch *et al.*[24] To start, reductive amination of 1,4-cyclohexadione monoethylene acetal **7** with 2,4-dimethoxybenzylamine gave an intermediate crude DMB-amine which was subjected to ketal hydrolysis and *N*-acylation with trichloroacetyl chloride to afford trichloroacetamido-ketone **8** in 90% yield over the three steps after purification by chromatography (~26 mmol scale). It was also found that chromatography could be avoided altogether: trichloroacetamido-ketone **8** was successfully triturated from Et_2O (60% yield of **8** on ~26 mmol scale). Next, the key cyclisation reaction was explored following Bonjoch's approach in which an enamine derived from **8** attacked the carbonyl in the trichloroacetamide group. In our hands, slight modifications to the literature procedure[24] were required to improve the efficiency. Thus, reaction of pyrrolidine (1.0 eq.) with trichloroacetamido-ketone **8** in toluene at 100 °C in a sealed tube for 1 h gave DMB protected normorphan keto-lactam **2** in 80% yield (on ~17 mmol scale).



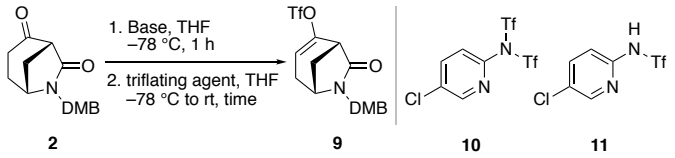
Scheme 1. Optimised gram-scale synthesis of normorphan building block **1**. DMB = 2,4-dimethoxybenzyl.

The next step in the synthesis, namely conversion of keto-lactam **2** into enol triflate **9**, required some optimisation (Table 1). An initial attempt at enol triflate formation following a procedure for a structurally related bridged carbocyclic ketone[26] using LDA and $PhNTf_2$ afforded enol triflate **9** in only 30% yield (entry 1). This result led us to survey a range of analogous strong bases in conjunction with either $PhNTf_2$ or Comins' reagent **10**[27] (entries 2–5), which identified the combination of NaHMDS with Comins' reagent **10** to be the most promising: enol triflate **9** was isolated in 54% yield (entry 4). However, the product from this reaction was isolated as an 85:15 mixture of enol triflate **9** and sulfonamide **11**,[28] the by-product formed from Comins' reagent, that could not be separated by chromatography. It has been reported that washing with cold 1 M $NaOH_{(aq)}$ in the work-up can be effective at removing side-products from the triflating agent.[29] Although this approach did give pure enol triflate **9**, a lower yield (36%) was obtained (entry 6), potentially due to degradation during the work-up. To avoid formation of the inseparable sulfonamide **11**, $PhNTf_2$ was used in combination with NaHMDS (1.8 eq.) which gave enol triflate **9** in 61% yield (entry 7). Finally, decreasing the amount of NaHMDS from 1.8 eq. to 1.6 eq. led to an improved yield of 76%

on a ~10 mmol scale (entry 8). This represented our optimised conditions for the formation of enol triflate **9** (Scheme 1).

The two-step conversion of enol triflate **9** into building block **1** *via* Miyaura borylation and BMIDA formation proceeded smoothly. Miyaura borylation was best accomplished using $PdCl_2(PPh_3)_2$, PPh_3, KOPh[30,31] and B_2pin_2; under these conditions, enol triflate **9** was efficiently converted into the corresponding vinyl pinacol boronate (Scheme 1). However, there was evidence of vinyl pinacol boronate decomposition during chromatography. Hence, in subsequent experiments, we elected to omit purification at this stage and the crude vinyl pinacol boronate was directly submitted to MIDA boronate formation with an excess of MIDA and $HC(OEt)_3$ at 100 °C in DMSO.[32] From this sequence, building block **1** was generated in 70% yield over the two steps on a ~5 mmol scale (Scheme 1). A larger scale (~8.5 mmol) two-step sequence delivered **1** in 68% yield after chromatography and recrystallisation from EtOAc. In summary, the synthesis of normorphan building block **1** was achieved in 38% overall yield on a multi-gram scale from commercially available 1,4-cyclohexadione monoethylene acetal **7**.

Table 1. Optimisation of the formation of enol triflate **9**.

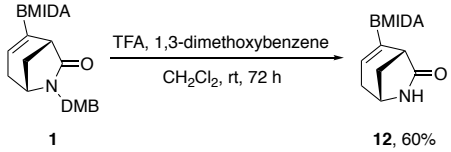


2 **9** **10** **11**

Entry	Base (eq.)	Tf Source (eq.)	Time (h)	Yield (%)[a]
1	LDA (1.2)[b]	$PhNTf_2$ (1.4)	18	30
2	LDA (1.2)[b]	**10** (1.3)	72	33[c]
3	LiHMDS (1.4)	**10** (1.3)	18	10[d]
4	NaHMDS (1.3)	**10** (1.3)	18	54[e]
5	KHMDS (1.3)	$PhNTf_2$ (1.4)	18	8
6	NaHMDS (1.8)	**10** (1.3)	18	36[f]
7	NaHMDS (1.8)	$PhNTf_2$ (1.3)	18	61[g]
8	NaHMDS (1.6)	$PhNTf_2$ (1.3)	18	76[h]

a) Yield after chromatography, entries 1-6 on 0.30-0.85 mmol scale; b) Prepared *in situ* by the addition of *n*-BuLi to *i*-Pr_2NH; c) Isolated as an 80:20 mixture of **9** and **11**; d) Estimated by ^1H NMR spectroscopy; e) Isolated as an 85:15 mixture of **9** and **11**; f) Cold 1 M $NaOH_{(aq)}$ wash in the work-up; g) 12.3 mmol scale; h) 10.4 mmol scale.

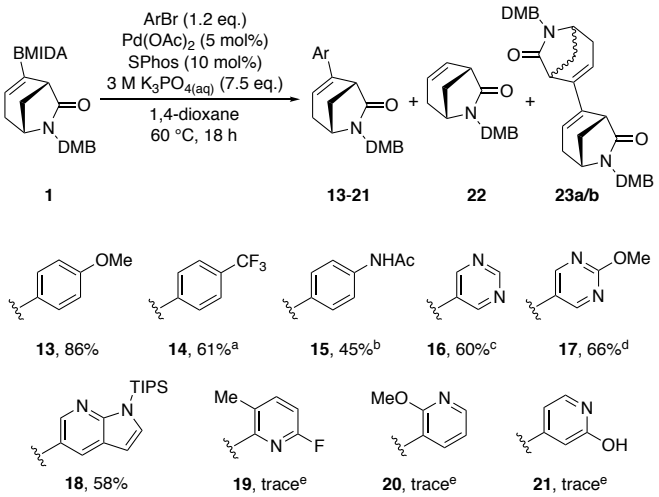
With the synthesis of building block **1** in hand, attention turned to elaboration at the two orthogonal functional handles. To start with, we considered whether it would be possible to carry out *N*-DMB group removal and *N*-functionalisation of the lactam in the presence of the vinyl BMIDA functionality. Given that the vinyl BMIDA group would likely be converted into the boronic acid under aqueous acid conditions,[33] 1,3-dimethoxybenzene and anhydrous TFA were explored.[34] Under these conditions, *N*-DMB removal was slow but, nevertheless, reaction of **1** at rt for 72 h delivered lactam **12** in 60% yield (Scheme 2). Unfortunately, lactam **12** suffered from very low solubility in a range of organic solvents and it was thus concluded that this would be too limiting for its use in further elaboration chemistry.



1 **12**, 60%

Scheme 2. *N*-DMB group removal from building block **1**.

As a result, Suzuki-Miyaura cross-coupling reactions on the vinyl BMIDA functionality in building block **1** were explored, with a view to carrying out subsequent *N*-functionalisations. A range of aryl bromides of relevance to medicinal chemistry were selected for the Suzuki-Miyaura cross-coupling reactions including aryl bromides with electron donating/withdrawing groups and heteroaryl bromides with pyrimidine, aza-indole and pyridine groups (Scheme 3). Several FragLites were also included in our scoping studies. Fraglites, recently introduced by Waring *et al.* as a new element for fragment-based drug discovery,[35] are compounds with paired hydrogen bonding motifs designed to identify ligand binding sites on proteins through productive drug-like interactions. Thus, using conditions reported by Burke *et al.* for the *in situ* slow-release of the vinyl boronic acid,[25,33] building block **1** was reacted with the selected aryl bromides in the presence of $Pd(OAc)_2$, SPhos and $K_3PO_{4(aq)}$ in dioxane at 60 °C for 18 h (Scheme 3). In most cases, the reactions worked well and good yields of aryl normorphans **13-18** were obtained (45-86%). However, only trace quantities of aryl normophans **19-21** were observed from the reactions with the pyridine-containing heteroaryl bromides; other catalyst/ligand combinations were not explored in this preliminary scoping study. The purification of most reactions by chromatography was complicated by the co-production of protodeborylated alkene **22** and heterodimeric, diastereomeric bis-normorphans **23a/b** (details provided in Scheme 3). Nevertheless, it is clear that normorphan **1** is a viable Suzuki-Miyaura cross-coupling partner with much potential as a 3D building block.



1 **13-21** **22** **23a/b**

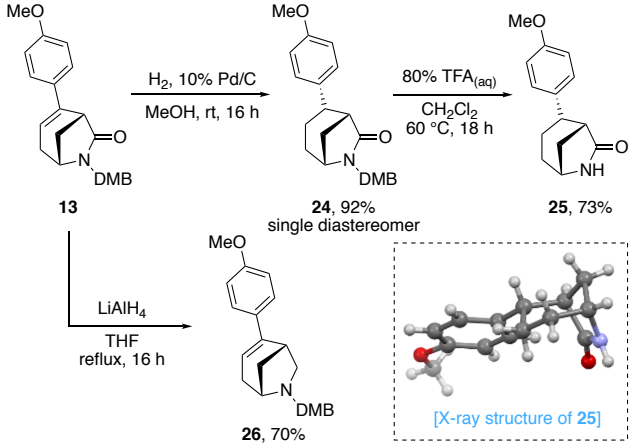
13, 86% **14**, 61%[a] **15**, 45%[b] **16**, 60%[c] **17**, 66%[d]

18, 58% **19**, trace[e] **20**, trace[e] **21**, trace[e]

Scheme 3. Suzuki-Miyaura cross-coupling reactions of building block **1**. a) Also isolated: **22** 20%, **23a/b** 6%; b) **15** isolated as a 90:10 mixture with **23b**, also isolated: **22** 40%, **23a** 3%; c) Also isolated: **22** 5%, **23a/b** 10%; d) **17** isolated as a 95:5 mixture with **23a**, also isolated: **22** 6%, **23b** 7%; e) product formation evidenced by ^1H NMR spectroscopy of the reaction mixture following work-up.

Next, we briefly explored further elaboration chemistry with aryl normorphan **13** (Scheme 4, Table 2). Hydrogenation (using 10% Pd/C in MeOH) of aryl normorphan **13** occurred on the *exo* face with complete diastereoselectivity to give saturated normorphan **24** in 92% yield (the other diastereomer was not detected by ^1H NMR spectroscopy) without the need for chromatography. Subsequent removal of the *N*-DMB group was accomplished using aqueous TFA in THF at 60 °C for 18 h and lactam **25** was isolated in 73% yield (Scheme 4, Table 2, entry 3). Crystals of **25** suitable for X-ray crystallography were grown and this confirmed the relative stereochemistry of both **24** and **25**. Other conditions for the *N*-DMB group removal were also

explored (Table 2). Using DDQ/water,[36] only a 25% yield of lactam **25** was obtained (entry 1) due to the formation of several unidentified by-products. Reaction of *N*-DMB lactam **24** with aqueous TFA or anhydrous TFA/1,3-dimethoxybenzene at rt was slow and, after 72 h, lactam **25** was isolated in 68% (entry 2) and 52% (entry 4) yields respectively. Finally, lactam reduction in aryl normorphan **13** was investigated. Reaction of aryl normorphan **13** with $LiAlH_4$ in THF at reflux gave amine **26** in 70% yield after chromatography. Further *N*-functionalisation chemistry was not explored; there are numerous reported examples of *N*-functionalisation of the normorphan scaffold including acylation,[37] sulfonylation,[38] reductive amination,[39] alkylation,[40] nucleophilic aromatic substitution[41] and Buchwald-Hartwig arylation.[42]



Scheme 4. Synthetic elaboration of aryl normorphan **13**.

Table 2. Investigation of *N*-DMB removal from **24** to give **25**.

Entry	Conditions	Temp (°C)	Time (h)	Yield[a] (%)
1	DDQ, H_2O, CH_2Cl_2	rt	24	25
2	80% $TFA_{(aq)}$, CH_2Cl_2	rt	72	68
3	80% $TFA_{(aq)}$, THF	60	18	73
4	TFA, 1,3-dimethoxybenzene, CH_2Cl_2	rt	72	52

a) Yield after chromatography. $TFA_{(aq)}$ = aqueous trifluoroacetic acid.

In order to further demonstrate the suitability of normorphan cores **3–6** (see Figure 1) derived from building block **1** for drug discovery, we assessed their suitability for generating lead-like compounds.[2] Such compounds provide optimal starting points for a wide range of drug discovery programs due to favorable molecular properties, namely MW of 200-350 Da and logP values of –1 to +3. The Fsp^3 value is also crucial since drug candidates with a high degree of unsaturation are more likely to suffer problems in development and may ultimately fail.[3]

Thus, a virtual library of compounds was enumerated from the four normorphan cores **3–6** (see Figure 1C). Virtual Suzuki-Miyaura cross-coupling and *N*-diversification was performed with a range of medicinally relevant capping groups,[43] to generate a library of 344 virtual compounds (see Supporting Information for full details). A plot of clogP versus MW is shown in Figure 2. The library had a mean MW of 300 and a mean clogP of 1.68, which are both within the lead-likeness parameters and 80% of the compounds fell within lead-like space, better than many targeted lead-oriented synthesis libraries.[44] In comparison, only 23% of the ZINC database of commercially available screening compounds fall within lead-like space.[43] Furthermore, it was found that the mean Fsp^3 was 0.46 (compared to 0.33 for ZINC) indicating that this virtual library is more saturated than most commercially available screening compounds.

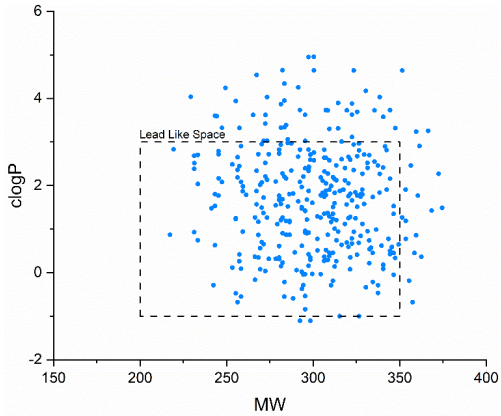


Figure 2. Molecular properties of the virtual library. Lead-like chemical space is indicated by the black box.

3. Conclusion

In summary, an efficient seven-step synthesis of bifunctional normorphan 3D building block **1** has been developed, offering multi-gram access to this scaffold (38% overall yield, only four isolations required). The synthetic route hinges on ketone reactivity to both close the normorphan ring (*via* enamine formation) and to install the vinyl MIDA boronate functionality (*via* enolate formation and *O*-triflation). Of note, using the two orthogonal synthetic handles, a range of functionalisation chemistry starting from building block **1** has been demonstrated. Specifically, Suzuki-Miyaura cross-coupling with a variety of medicinally-relevant aryl and heteroaryl bromides proceeded in good yields. Subsequent *exo*-diastereoselective hydrogenation, *N*-DMB removal and lactam reduction all worked well to deliver different scaffolds for further *N*-functionalisation *via* known[37-42] methods. Normorphan cores **3–6** derived from building block **1** were found to satisfy AstraZeneca's 'rule of 2' for building blocks and to have high Fsp^3 values suggesting that **1** has the qualities of an attractive building block for library generation. Indeed, a virtual lead-like library of 344 compounds embodying the four normorphan cores **3–6** and bearing aryl and *N*-capping groups of medicinal relevance was found to have attractive lead-like properties. Alongside our design and synthetic work on building block **1**, we have also commercialised **1** through Redbrick Molecular; it is currently available for purchase. We envisage that bifunctional normorphan building block **1** will prove to be a useful asset for exploring 3D lead-like chemical space for drug discovery.

4. Experimental

4.1. General

All non-aqueous reactions were carried out under oxygen-free Ar atmosphere using flame-dried glassware. THF was freshly distilled from sodium and benzophenone. Alkyllithiums were titrated against *N*-benzylbenzamide before use.[45] Et_3N, *i*-Pr_2NH and pyrrolidine were distilled over CaH_2 before use. Brine refers to a saturated $NaCl_{(aq)}$ solution. Water is distilled water. Flash column chromatography was carried out according to standard techniques using silica gel (60 Å, 220-440 mesh particle size 40–63 μm) purchased from Sigma-Aldrich or Fluka silica gel, 35–70 μm, 60 Å and the solvent system as stated. Thin layer chromatography was carried out using Merck TLC Silica gel 60G F254 aluminium backed plates (100390 Supelco). Proton (400 MHz) and carbon (101 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument using an internal deuterium lock. For samples recorded in $CDCl_3$, chemical shifts are quoted in parts per million relative to $CHCl_3$ (δ_H 7.26) and $CDCl_3$ (δ_C 77.0, central line of triplet). For samples recorded in d_6-DMSO, chemical shifts are

quoted in parts per million relative to DMSO (δ_H 2.50, central line of quintet) and d_6-DMSO (δ_C 39.5, central line of septet). For samples recorded in d_6-acetone, chemical shifts are quoted in parts per million relative to acetone (δ_H 2.05, central line of quintet) and d_6-acetone (δ_C 29.8, central line of septet). Carbon NMR spectra were recorded with broad band proton decoupling and assigned using DEPT experiments. Coupling constants (*J*) are quoted in Hertz. Melting points were carried out on a Gallenkamp melting point apparatus. Infrared spectra were recorded on a PerkinElmer UATR 2 FT-IR spectrometer. Electrospray high and low resonance mass spectra were recorded at room temperature on a Bruker Daltronics microOTOF spectrometer.

4.2. General Procedure A: Suzuki-Miyaura cross coupling of vinyl MIDA boronate 1

A solution of vinyl MIDA boronate **1** (100 mg, 0.234 mmol, 1.0 eq), $Pd(OAc)_2$ (3.00 mg, 0.012 mmol, 0.05 eq), SPhos (10.0 mg, 0.023 mmol, 0.1 eq) and the aryl bromide (0.28 mmol, 1.2 eq) in dioxane (2.35 mL) in a sealed tube was stirred at rt for 15 min under Ar. 3 M $K_3PO_{4(aq)}$ (0.59 mL, 1.755 mmol, 7.5 eq), degassed by sparging with Ar, was added and the resulting mixture was stirred and heated at 60 °C in a sealed tube for 20 h. H_2O (5 mL) was added and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

4.3. 2,2,2-Trichloro-*N*-(2,4-dimethoxybenzyl)-*N*-(4-oxocyclohexyl)acetamide 8

A solution of 1,4-cyclohexadione monoethylene acetal **7** (4.00 g, 25.6 mmol, 1.0 eq), 2,4-dimethoxybenzylamine (3.90 mL, 25.6 mmol, 1.0 eq) and $NaBH(OAc)_3$ (7.60 g, 35.9 mmol, 1.4 eq) in CH_2Cl_2 (100 mL) was stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added. Then, 1 M $NaOH_{(aq)}$ was added until pH ≈ 10 was reached. The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (50 mL) dried (Na_2SO_4) and evaporated under reduced pressure to give the crude amine as a pale yellow oil. To the crude amine was added 3 M $HCl_{(aq)}$ (140 mL) and the resulting solution was stirred at rt for 48 h. Solid Na_2CO_3 was added until pH ≈ 9 was reached and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude amino ketone as a pale yellow oil. The crude amino ketone was dissolved in CH_2Cl_2 (80 mL). The resulting solution was cooled to 0 °C and Et_3N (6.80 mL, 48.6 mmol, 1.9 eq) was added under Ar. Then, trichloroacetyl chloride (5.20 mL, 45.0 mmol, 1.8 eq) was added dropwise and the solution was allowed to warm to rt. The resulting solution was stirred at rt for 4 h and then poured into water (30 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:6 to 7:3 Et_2O-hexane as eluent gave trichloroacetamide **8** (9.45 g, 90%) as a white solid, mp 122-124 °C; R_F (4:6 Et_2O-hexane) 0.22; IR (ATR) 2956, 1717 (C=O, ketone), 1674 (C=O, amide), 1615, 1507, 1417, 1259, 1208, 1157, 1123, 1036, 825, 812, 730, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (65:35 mixture of rotamers) δ 7.25–7.15 (m, 0.35H, Ar), 6.96 (d, *J* = 8.5 Hz, 0.65H, Ar), 6.52–6.35 (m, 2H, Ar), 5.00 (br t, *J* = 12.0 Hz, 0.65H, NCH), 4.93–4.79 (m, 0.35H, NCH), 4.60–4.52 (m, 1.3H, NCHAr), 4.04–3.92 (m, 0.35H, NCHAr), 3.84–3.74 (m, 6.35H, NCHAr, OMe), 2.49–2.37 (m, 3.3H, CH), 2.36–2.21 (m, 0.7H, CH), 2.21–2.10 (m, 2.05H, CH), 2.10–1.91 (m, 1.95H, CH); ^{13}C NMR (101 MHz, $CDCl_3$) (mixture of rotamers) δ 208.4 (C=O, ketone), 160.7 (C=O, amide), 160.1 (*ipso*-Ar), 157.2 (*ipso*-Ar), 128.7 (Ar, only resolved in HMQC), 127.1 (Ar), 117.4 (*ipso*-Ar), 104.3 (*ipso*-Ar), 98.5 (Ar), 93.8 (CCl_3), 57.2 (NCH), 55.5 (OMe), 46.9 (NCH), 42.1 (NCH_2), 39.8 (CH_2), 29.3 (CH_2) (1 × OMe resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{17}H_{20}{}^{35}Cl_3NO_4$ $(M + Na)^+$ 430.0350, found 430.0344 (+1.4 ppm error).

4.4. 6-(2,4-Dimethoxybenzyl)-6-azabicyclo[3.2.1]octane-2,7-dione 2

A mixture of trichloroacetamide **8** (7.00 g, 17.1 mmol, 1.0 eq) and pyrrolidine (1.43 mL, 17.1 mmol, 1.0 eq) in toluene (4.30 mL) was stirred and heated at 100 °C in a sealed tube for 1 h. The crude mixture was directly purified by flash column chromatography on silica with 1:1 to 4:1 EtOAc-hexane as eluent to give normorphan **2** (3.96 g, 80%) as a red oil, R_F (1:1 EtOAc-hexane) 0.17; IR (ATR) 2953, 1723 (C=O, ketone), 1689 (C=O, amide), 1613, 1588, 1508, 1418, 1295, 1209, 1158, 1125, 1034, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24–7.21 (m, 1H, Ar), 6.48–6.44 (m, 2H, Ar), 4.60 (d, *J* = 14.5 Hz, 1H, NC*H*H'), 4.43 (d, *J* = 14.5 Hz, 1H, NCH*H'*), 3.85–3.78 (m, 7H, OMe, NCH), 3.18 (d, *J* = 5.0 Hz, 1H, C(O)CH), 2.56 (dddd, *J* = 11.5, 5.0, 5.0, 2.5 Hz, 1H, CH-4), 2.45–2.32 (m, 2H, C(O)CHH'), 2.08–2.00 (m, 1H, CH-2), 1.98 (d, *J* = 11.5 Hz, 1H, CH-4), 1.79 (dddd, *J* = 13.5, 8.5, 8.5, 1.5 Hz, 1H, CH-2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.0 (C=O, ketone), 170.8 (C=O, amide), 160.9 (*ipso*-Ar), 158.7 (*ipso*-Ar), 131.3 (Ar), 116.8 (*ipso*-Ar), 104.4 (Ar), 98.6 (Ar), 58.3 (*C*HCO), 55.5 (OMe), 54.8 (NCH), 39.5 (NCH_2), 36.2 (CH_2-4), 35.1 (CH_2CO), 27.6 (CH_2-2) (1 × OMe resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{16}H_{19}NO_4$ $(M + H)^+$ 290.1383, found 290.1387 (+1.4 ppm error).

4.5. 6-(2,4-Dimethoxybenzyl)-7-oxo-6-azabicyclo[3.2.1]oct-2-en-2-yl trifluoromethanesulfonate 9

NaHMDS (16.6 mL of a 1 M solution in THF, 16.6 mmol, 1.6 eq) was added dropwise to a stirred solution of normorphan **2** (3.00 g, 10.4 mmol, 1.0 eq) in THF (25 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, a solution of $PhNTf_2$ (4.82 g, 13.5 mmol, 1.3 eq) in THF (17 mL) was added and resulting the solution was allowed to warm slowly to rt. The solution was stirred at rt for 18 h. Saturated $NH_4Cl_{(aq)}$ (30 mL) was added and the mixture was extracted with Et_2O (4 × 30 mL). The combined organic extracts were washed with brine (120 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 3:2 Et_2O-hexane as eluent gave enol triflate **9** (3.31 g, 76%) as a clear oil, R_F (3:2 Et_2O-hexane) 0.22; IR (ATR) 2959, 1703 (C=O), 1662 (C=C), 1589, 1508, 1415, 1206, 1138, 878, 834, 609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14–7.08 (m, 1H, Ar), 6.47–6.40 (m, 2H, Ar), 5.56–5.51 (m, 1H, =CH), 4.50 (d, *J* = 14.5 Hz, 1H, NC*H*H'), 4.29 (d, *J* = 14.5 Hz, 1H, NCH*H'*), 3.83–3.77 (m, 6H, OMe), 3.76–3.71 (m, 1H, NCH), 2.98–2.94 (m, 1H, CH-5), 2.36–2.23 (m, 3H, CH_2-2, CH-4), 1.90 (d, *J* = 10.5 Hz, 1H, CH_2-4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (C=O), 160.8 (*ipso*-Ar), 158.5 (*ipso*-Ar), 148.4 (=C), 130.9 (Ar), 118.6 (q, *J* = 320.0 Hz, CF_3), 117.2 (*ipso*-Ar), 114.8 (=CH) , 104.5 (Ar), 98.6 (Ar), 55.5 (OMe), 55.4 (OMe), 53.0 (NCH), 44.7 (*C*HCO), 38.4 (NCH_2), 34.1 (CH_2-4), 28.3 (CH_2-2); HRMS (ESI) *m/z* calcd for $C_{17}H_{18}F_3NO_6S$ $(M + Na)^+$ 444.0699, found 444.0706 (–1.8 ppm error).

4.6. 8-(6-(2,4-Dimethoxybenzyl)-7-oxo-6-azabicyclo[3.2.1]oct-2-en-2-yl)-4-methyldihydro-4λ⁴,8λ⁴-[1,3,2]oxazaborolo[2,3-*b*][1,3,2]oxazaborole-2,6(3*H*,5*H*)-dione 1

A solution of enol triflate **9** (1.98 g, 4.70 mmol, 1.0 eq), $PdCl_2(PPh_3)_2$ (97.0 mg, 0.14 mmol, 0.03 eq), PPh_3 (73.0 mg, 0.28 mmol, 0.06 eq), KOPh (931 mg, 7.05 mmol, 1.5 eq) and B_2pin_2 (1.31 g, 5.17 mmol, 1.1 eq) in toluene (30 mL) under Ar was stirred

and heated at 50 °C for 16 h. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give the crude pinacol boronate. The crude pinacol boronate was dissolved in DMSO (24 mL) and MIDA (4.49 g, 30.5 mmol, 6.5 eq) and $HC(OEt)_3$ (3.70 mL, 21.1 mmol, 4.5 eq) were added. The resulting mixture was stirred and heated at 100 °C under Ar for 48 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the mixture was extracted with EtOAc (4 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 to 7:3 CH_2Cl_2-acetone as eluent gave vinyl MIDA boronate **1** (1.40 g, 70%) as an off-white crystalline solid, mp 80-82 °C; R_F (4:1 CH_2Cl_2-acetone) 0.29; IR (ATR) 2958, 1760 (C=O, ester), 1673 (C=O, amide), 1614, 1508, 1457, 1292, 1180, 1036, 823 cm^{-1}; ^1H NMR (400 MHz, d_6-acetone) δ 7.08 (d, J = 8.5 Hz, 1H, Ar), 6.53 (d, J = 2.5 Hz, 1H, Ar), 6.45 (dd, J = 8.5, 2.5 Hz, 1H, Ar), 5.98 (ddd, J = 3.0, 3.0, 3.0 Hz, 1H, =CH), 4.41 (d, J = 15.0 Hz, 1H, NC*H*H'), 4.27–4.07 (m, 4H, NCH*H'*, CHH'CO_2), 3.96 (d, J = 17.0 Hz, 1H, CH*H'*CO_2), 3.81 (s, 3H, OMe), 3.78–3.71 (m, 4H, OMe, NCH), 2.84 (s, 3H, NMe), 2.64 (d, J = 4.5 Hz, 1H, CH-5), 2.24–2.17 (m, 2H, CHH'-2), 2.16 (ddd, J = 10.5, 5.5, 4.5 Hz, 1H, C*H*H'-4), 1.67 (d, J = 10.5 Hz, 1H, CH*H'*-4); ^{13}C NMR (101 MHz, d_6-acetone) δ 177.0 (C=O, amide), 169.2 (C=O, ester), 167.9 (C=O, ester), 160.7 (*ipso*-Ar), 158.6 (*ipso*-Ar), 134.1 (=CH), 130.0 (Ar), 117.8 (*ipso*-Ar), 104.6 (Ar), 98.2 (Ar), 62.0 (*C*H_2CO_2), 61.3 (*C*H_2CO_2), 55.0 (OMe), 54.8 (OMe), 54.3 (NCH), 45.8 (NMe), 41.8 (CH-5), 37.6 (NCH_2), 33.7 (CH_2-4), 28.8 (CH_2-2, only resolved in DEPT-135) (=C-B resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{21}H_{25}{}^{11}BN_2O_7$ $(M + Na)^+$ 451.1647, found 451.1654 (–0.2 ppm error). After chromatography (if necessary), vinyl MIDA boronate **1** can be further purified by recrystallisation from EtOAc to give **1** as colourless microcrystals.

4.7. 4-Methyl-8-(-7-oxo-6-azabicyclo[3.2.1]oct-2-en-2-yl)dihydro-4λ⁴,8λ⁴-[1,3,2]oxazaborolo[2,3-b][1,3,2]oxazaborole-2,6(3H,5H)-dione 12

TFA (800 µL, 7.01 mmol, 30 eq) was added to a stirred solution of vinyl MIDA boronate **1** (100 mg, 0.23 mmol, 1.0 eq) and *m*-dimethoxybenzene (60.0 µL, 0.46 mmol, 2 eq) in CH_2Cl_2 (1.15 mL) at rt. The resulting mixture was stirred at rt for 72 h. The solvent was evaporated under reduced pressured. The residue was suspended in toluene (5 mL) and the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 to 8:2 CH_2Cl_2-acetone as eluent gave free amide **12** (39.0 mg, 60%) as a white crystalline solid. mp 280-282 °C (decomposition); R_F (2:8 CH_2Cl_2-acetone) 0.31; IR (ATR) 3388 (NH), 1755 (C=O, ester), 1671 (C=O, amide), 1322, 110, 1039, 558 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO) δ 7.55 (s, 1H, NH), 5.86 (ddd, J = 3.0, 3.0, 1.5 Hz, 1H, =CH-1), 4.25 (d, J = 17.5 Hz, 1H, C(O)C*H*H'), 4.13 (d, J = 16.5 Hz, 1H, C(O)C*H*H'), 3.91 (d, J = 17.5 Hz, 1H, C(O)CH*H'*), 3.90 (d, J = 16.5 Hz, 1H, C(O)CH*H'*), 3.68–3.65 (m, 1H, NCH), 2.64 (s, 3H, NMe), 2.41 (d, J = 5.0 Hz, 1H, CH-5), 2.32 (ddd, J = 19.0, 3.0, 3.0 Hz, 1H, C*H*H'-2), 2.07 (ddd, J = 10.5, 5.0, 5.0 Hz, 1H, C*H*H'-4), 2.02 (ddd, J = 19.0, 3.0, 1.5 Hz, 1H, CH*H'*-2), 1.52 (d, J = 10.5 Hz, 1H, CH*H'*-4); ^{13}C NMR (101 MHz, d_6-DMSO) δ 179.7 (C=O, amide), 170.4 (C=O, ester), 169.2 (C=O, ester), 134.1 (=CH), 62.2 (*C*H_2CO_2), 61.6 (*C*H_2CO_2), 49.8 (NCH), 46.6 (NMe), 41.5 (CH-5), 34.9 (CH_2-4), 33.2 (CH_2-2) (=C-B resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{12}H_{15}{}^{11}BN_2O_5$ $(M + H)^+$ 301.0966, found 301.0966 (+0.8 ppm error).

4.8. 6-(2,4-Dimethoxybenzyl)-2-(4-methoxyphenyl)-6-azabicyclo[3.2.1]oct-2-en-7-one 13

Using general procedure A, MIDA boronate **1** (750 mg, 1.75 mmol, 1.0 eq), $Pd(OAc)_2$ (20.0 mg, 0.09 mmol, 5 mol%), SPhos (72.0 mg, 0.17 mmol, 10 mol%), 4-bromoanisole (0.27 mL, 2.11 mmol, 1.2 eq) and 3 M $K_3PO_{4(aq)}$ (5.74 mL, 17.2 mmol, 7.5 eq), in dioxane (28 mL) gave the crude product. Purification by flash column chromatography on silica with 1:1 EtOAc-hexane as eluent gave arylated normorphan **13** (565 mg, 86%) as a clear oil, R_F (3:2 EtOAc-hexane) 0.49; IR (ATR) 2938, 2835, 1686 (C=O), 1609, 1508, 1244, 1032, 835, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.44 (m, 2H, Ar), 7.15–7.11 (m, 1H, Ar), 6.89–6.84 (m, 2H, Ar), 6.45–6.41 (m, 2H, Ar), 5.70–5.63 (m, 1H, =CH), 4.57 (d, J = 15.0 Hz, 1H, NC*H*H'), 4.25 (d, J = 15.0 Hz, 1H, NCH*H'*), 3.81–3.76 (m, 9H, OMe), 3.76– 3.73 (m, 1H, NCH-3), 3.23 (d, J = 5.0 Hz, 1H, CH-5), 2.63–2.27 (m, 2H, CH_2-2), 2.24 (ddd, J = 10.0, 5.0, 5.0 Hz, 1H, C*H*H'-4), 1.84 (d, J = 10.0 Hz, 1H, CH*H'*-4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8 (C=O), 160.4 (*ipso*-Ar), 158.9 (*ipso*-Ar), 158.6 (*ipso*-Ar), 139.8 (=C), 133.5 (*ipso*-Ar), 130.5 (Ar), 126.5 (Ar), 119.7 (=CH), 118.0 (*ipso*-Ar), 113.9 (Ar), 104.3 (Ar), 98.5 (Ar), 55.5 (OMe), 55.4 (OMe), 53.9 (NCH), 44.3 (*C*HCO), 38.0 (NCH_2), 34.1 (CH_2-4), 28.8 (CH_2-2) (1 × OMe resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{23}H_{25}NO_4$ $(M + H)^+$ 380.1856, found 380.1858 (–0.4 ppm error).

4.9. 6-(2,4-Dimethoxybenzyl)-2-(4-(trifluoromethyl)phenyl)-6-azabicyclo[3.2.1]oct-2-en-7-one 14

Using general procedure A, vinyl MIDA boronate **1** (100 mg, 0.234 mmol, 1.0 eq), $Pd(OAc)_2$ (3.00 mg, 0.012 mmol, 0.05 eq), SPhos (10.0 mg, 0.023 mmol, 0.1 eq), 4-bromobenzotrifluoride (63.0 mg, 0.280 mmol, 1.2 eq) and 3 M $K_3PO_{4(aq)}$ (0.59 mL, 1.755 mmol, 7.5 eq) in dioxane (2.34 mL) gave the crude product. Purification by flash column chromatography on silica with 4:1 to 3:2 hexane-EtOAc as eluent gave arylated normorphan **14** (60.0 mg, 61%) as a clear oil, R_F (3:2 hexane-EtOAc) 0.32; IR (ATR) 2941, 2837, 1687 (C=O), 1613, 1588, 1507, 1322, 1109, 818, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.63 (m, 2H, Ar), 7.60–7.55 (m, 2H, Ar), 7.16–7.11 (m, 1H, Ar), 6.47–6.39 (m, 2H, Ar), 5.85 (ddd, J = 3.5, 3.0, 1.5 Hz, 1H, =CH-1), 4.57 (d, J = 15.0 Hz, 1H, NC*H*H'), 4.26 (d, J = 15.0 Hz, 1H, NCH*H'*), 3.83–3.67 (m, 7H, OMe, NCH), 3.24 (d, J = 4.5 Hz, 1H, CH-5), 2.42–2.31 (m, 2H, CHH'-2), 2.27 (ddd, J = 10.0, 5.0, 4.5 Hz, 1H, C*H*H'-4), 1.86 (d, J = 10.0 Hz, 1H, CH*H'*-4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4 (C=O), 160.6 (*ipso*-Ar), 158.6 (*ipso*-Ar), 144.2 (*ipso*-Ar), 139.6 (=C), 130.7 (Ar), 129.1 (q, J = 32.5 Hz, *ipso*-Ar), 125.6 (Ar), 125.5 (q, J = 4.0 Hz, Ar), 124.4 (q, J = 272.0 Hz, CF_3), 123.8 (=CH), 117.8 (*ipso*-Ar), 104.3 (Ar), 98.5 (Ar), 55.5 (OMe), 53.7 (NCH), 44.2 (CH-5), 38.2 (NCH_2), 34.0 (CH_2-4), 29.1 (CH_2-2) (1 × OMe resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{23}H_{22}F_3NO_3$ $(M + Na)^+$ 440.1444, found 440.1442 (+0.4 ppm error), alkene **22** (12.0 mg, 20%) as a clear oil, R_F (9:1 hexane-acetone) 0.1; IR (ATR) 2940, 2835, 1685 (C=O), 1612, 1587, 1506, 1411, 1206, 1031, 832, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.09–7.03 (m, 1H, Ar), 6.42–6.34 (m, 2H, Ar), 6.07 (dddd, J = 9.0, 7.0, 1.0, 1.0 Hz, 1H, =CH-6), 5.51 (dddd, J = 9.0, 3.5, 3.0, 1.5 Hz, 1H, =CH-1), 4.50 (d, J = 15.0 Hz, 1H, NC*H*H'), 4.16 (d, J = 15.0 Hz, 1H, NCH*H'*), 3.76–3.71 (m, 6H, OMe), 3.66–3.62 (m, 1H, NCH), 2.75 (dd, J = 7.0, 4.5 Hz, 1H, CH-5), 2.17 – 2.04 (m, 3H, CHH'-2, C*H*H'-4), 1.71 (d, J = 10.0 Hz, 1H, CH*H'*-4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.5 (C=O), 160.4 (*ipso*-Ar), 158.5 (*ipso*-Ar), 130.3 (Ar), 129.2 (=CH-6), 126.0 (=CH-1), 117.8 (*ipso*-Ar), 104.3 (Ar), 98.4 (Ar), 55.4 (OMe), 54.3 (NCH), 40.8 (CH-5), 37.8 (NCH_2), 33.9 (CH_2-4), 28.3 (CH_2-2) (1 × OMe resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{16}H_{19}NO_3$ $(M+Na)^+$ 296.1257, found 296.1250 (+2.7 ppm error), and a 75:25 mixture (by ^1H NMR spectroscopy) of bis-normorphan **23a** and SPhos (2.00 mg, i.e. 1.50 mg (2%) of **23a**) as a clear oil, R_F (3:2 hexane-acetone) 0.2; IR (ATR) 2928, 1689 (C=O), 1613, 1588,

1508, 1208, 1034, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) for **23a** δ 7.14–7.06 (m, 2H, Ar), 6.48–6.39 (m, 4H, Ar), 5.85 (s, 2H, =CH), 4.51 (d, *J* = 15.0 Hz, 2H, NC*H*H'), 4.18 (d, *J* = 15.0 Hz, 2H, NCH*H'*), 3.82–3.75 (m, 12H, OMe), 3.67 (d, *J* = 5.0 Hz, 2H, NCH), 3.08 (d, *J* = 5.0 Hz, 2H, CH-5), 2.36–2.20 (m, 4H, CHH'-2), 2.16 (ddd, *J* = 10.5, 5.0, 5.0 Hz, 2H, C*H*H'-4), 1.71 (d, *J* = 10.5 Hz, 2H, CH*H'*-4); ^{13}C NMR (101 MHz, $CDCl_3$) for **23a** δ 176.4 (C=O), 160.4 (*ipso*-Ar), 158.7 (*ipso*-Ar), 139.2 (=C), 130.5 (Ar), 119.4 (=CH), 118.0 (*ipso*-Ar), 104.2 (Ar), 98.5 (Ar), 55.5 (OMe), 53.5 (NCH), 42.3 (CH-5), 38.1 (NCH_2), 34.1 (CH_2-4), 28.5 (CH_2-2) (1 × OMe resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{32}H_{36}N_2O_6$ $(M + Na)^+$ 567.2466, found 567.2455 (+1.9 ppm error), and a 95:5 mixture (by ^1H NMR spectroscopy) of bis-normorphan **23b** and SPhos (3.00 mg i.e. 2.85 mg (4%) of **23b**) as a clear oil, R_F (3:2 hexane-acetone) 0.09; IR (ATR) 2929, 1764, 1678 (C=O), 1613, 1508, 1208, 1035, 835, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) for **23b** δ 7.13–7.09 (m, 2H, Ar), 6.46–6.40 (m, 4H, Ar), 6.05–5.62 (m, 2H, =CH), 4.55 (d, *J* = 15.0 Hz, 2H, NC*H*H'), 4.16 (d, *J* = 15.0 Hz, 2H, NCH*H'*), 3.84–3.76 (m, 12H, OMe), 3.72–3.67 (m, 2H, NCH), 3.16 (d, *J* = 5.0 Hz, 2H, CH-5), 2.35–2.30 (m, 4H, CHH'-2), 2.14 (ddd, *J* = 10.0, 5.0, 5.0 Hz, 2H, C*H*H'-4), 1.76 (d, *J* = 10.0 Hz, 2H, CH*H'*-4); ^{13}C NMR (101 MHz, $CDCl_3$) for **23b** δ 176.6 (C=O), 160.4 (*ipso*-Ar), 158.6 (*ipso*-Ar), 138.0 (=C), 130.6 (Ar), 120.1 (=CH), 117.9 (*ipso*-Ar), 104.3 (Ar), 98.5 (Ar), 55.5 (OMe), 53.7 (NCH), 41.2 (CH-5), 37.9 (NCH_2), 33.6 (CH_2-4), 28.7 (CH_2-2) (1 × OMe resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{32}H_{36}N_2O_6$ $(M + Na)^+$ 567.2466, found 567.2466 (0 ppm error).

4.10. *N*-(4-(-6-(2,4-Dimethoxybenzyl)-7-oxo-6-azabicyclo[3.2.1]oct-2-en-2-yl)phenyl)acetamide 15

Using general procedure A, vinyl MIDA boronate **1** (100 mg, 0.234 mmol, 1.0 eq), $Pd(OAc)_2$ (3.00 mg, 0.012 mmol, 0.05 eq), SPhos (10.0 mg, 0.023 mmol, 0.1 eq), 4-bromoacetanilide (63.0 mg, 0.280 mmol, 1.2 eq) and 3 M $K_3PO_{4(aq)}$ (0.59 mL, 1.755 mmol, 7.5 eq) in dioxane (2.34 mL) gave the crude product. Purification by flash column chromatography on silica with 2:8 to 1:99 hexane-EtOAc as eluent gave a 90:10 mixture (by ^1H NMR spectroscopy) of arylated normorphan **15** and bis-normorphan **23b** (48.0 mg, i.e. 43.2 mg (45%) of **15** and 4.80 mg (7%) of **23b**) as a clear oil, R_F (1:99 hexane-EtOAc) 0.3; IR (ATR) 3309 (NH), 2939, 2836, 1669 (C=O), 1613, 1591, 1508, 1208, 1035, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) for **15** δ 8.82 (br s, 1H, NH), 7.52–7.49 (m, 2H, Ar), 7.43–7.39 (m, 2H, Ar), 7.09 (d, *J* = 8.5 Hz, 1H, Ar), 6.47–6.40 (m, 2H, Ar), 5.77–5.74 (m, 1H, =CH), 4.59 (d, *J* = 15.0 Hz, 1H, NC*H*H'), 4.25 (d, *J* = 15.0 Hz, 1H, NCH*H'*), 3.84–3.73 (m, 7H, OMe, NCH), 3.27 (d, *J* = 4.5 Hz, 1H, CH-5), 2.38–2.22 (m, 3H, CHH'-2, C*H*H'-4), 2.07 (s, 3H, Me), 1.88 (d, *J* = 10.5 Hz, 1H, CH*H'*-4); ^{13}C NMR (101 MHz, $CDCl_3$) for **15** δ 177.1 (C=O, lactam), 169.1 (C=O, NHC(O)), 160.6 (*ipso*-Ar), 158.6 (*ipso*-Ar), 139.7 (*ipso*-Ar), 138.0 (*ipso*-Ar), 135.6 (=C), 130.2 (Ar), 125.7 (Ar), 120.5 (=CH), 120.0 (Ar), 117.6 (*ipso*-Ar), 104.3 (Ar), 98.6 (Ar), 55.5 (OMe), 55.4 (OMe), 54.0 (NCH), 44.1 (C-5), 38.3 (NCH_2), 34.1 (CH_2-4), 28.8 (CH_2-2), 24.4 (Me); HRMS (ESI) *m/z* calcd for $C_{24}H_{26}N_2O_4$ $(M + Na)^+$ 429.1785, found 429.1782 (+0.7 ppm error), alkene **22** (26.0 mg, 40%) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above and a 75:25 mixture (by ^1H NMR spectroscopy) of bis-normorphan **23a** and SPhos (3.00 mg, i.e. 2.30 mg (3%) of **23a**) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above.

4.11. 6-(2,4-Dimethoxybenzyl)-2-(pyrimidin-5-yl)-6-azabicyclo[3.2.1]oct-2-en-7-one 16

Using general procedure A, vinyl MIDA boronate **1** (100 mg, 0.234 mmol, 1.0 eq), $Pd(OAc)_2$ (3.00 mg, 0.012 mmol, 0.05 eq), SPhos (10.0 mg, 0.023 mmol, 0.1 eq), 5-bromo-pyrimidine (45.0 mg, 0.280 mmol, 1.2 eq) and 3 M $K_3PO_{4(aq)}$ (0.59 mL, 1.755 mmol, 7.5 eq) in dioxane (3.9 mL) gave the crude product. Purification by flash column chromatography on silica with 99:1 to 9:1 Et_2O-MeOH as eluent gave arylated normorphan **16** (50.0 mg, 60%) as a clear oil, R_F (9:1 Et_2O-MeOH) 0.27; IR (ATR) 2942, 2866, 1687 (C=O), 1613, 1507, 1412, 1208, 1033, 903, 823, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H, Ar), 8.85 (s, 2H, Ar), 7.15–7.07 (m, 1H, Ar), 6.45–6.37 (m, 2H, Ar), 5.90 (dd, *J* = 3.5, 3.5 Hz, 1H, =CH), 4.54 (d, *J* = 15.0 Hz, 1H, NC*H*H'), 4.23 (d, *J* = 15.0 Hz, 1H, NCH*H'*), 3.77 (s, 7H, OMe, NCH), 3.19 (d, *J* = 5.0 Hz, 1H, CH-5), 2.41–2.32 (m, 2H, CHH'-2), 2.28 (ddd, *J* = 10.5, 5.0, 5.0 Hz, 1H, C*H*H'-4), 1.86 (d, *J* = 10.5 Hz, 1H, CH*H'*-4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8 (C=O), 160.6 (*ipso*-Ar), 158.6 (*ipso*-Ar), 157.3 (Ar), 153.5 (Ar), 135.0 (=C), 133.8 (*ipso*-Ar), 130.7 (Ar), 125.6 (=CH), 117.5 (*ipso*-Ar), 104.4 (Ar), 98.5 (Ar), 55.5 (OMe), 53.4 (NCH), 43.6 (CH-5), 38.2 (NCH_2), 33.8 (CH_2-4), 29.1 (CH_2-2) (1 × OMe resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{20}H_{21}N_3O_3$ $(M + Na)^+$ 374.1475, found 374.1471 (+0.9 ppm error), alkene **22** (3 mg, 5%) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above, a 75:25 mixture (by ^1H NMR spectroscopy) of bis-normorphan **23a** and SPhos (2.00 mg, i.e. 1.50 mg (3%) of **23a**) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above and a 90:10 mixture (by ^1H and ^{13}C NMR spectroscopy) of bis-normorphan **23b** and SPhos (4.00 mg, i.e. 3.60 mg (7%) of **23b**) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above.

4.12. 6-(2,4-Dimethoxybenzyl)-2-(2-methoxypyrimidin-5-yl)-6-azabicyclo[3.2.1]oct-2-en-7-one 17

Using general procedure A, vinyl MIDA boronate **1** (100 mg, 0.234 mmol, 1.0 eq), $Pd(OAc)_2$ (3.00 mg, 0.012 mmol, 0.05 eq), SPhos (10.0 mg, 0.023 mmol, 0.1 eq), 5-bromo-2-methoxy-pyrimidine (53.0 mg, 0.280 mmol, 1.2 eq) and 3 M $K_3PO_{4(aq)}$ (0.59 mL, 1.755 mmol, 7.5 eq) in dioxane (2.34 mL) gave the crude product. Purification by flash column chromatography on silica with 99:1 to 9:1 Et_2O-MeOH as eluent gave a 95:5 mixture (by ^1H NMR spectroscopy) of arylated normorphan **17** and bis-normorphan **23a** (62.0 mg, i.e. 58.9 mg (66%) of **17** and 3.10 mg (5%) of **23a**) as a clear oil, R_F (95:5 Et_2O-MeOH) 0.46; IR (ATR) 2955, 2836, 1686 (C=O), 1613, 1589, 1471, 1412, 1207, 1032, 823 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) for **17** δ 8.60 (s, 2H, Ar), 7.08 (d, *J* = 8.0 Hz, 1H, Ar), 6.46–6.35 (m, 2H, Ar), 5.78 (dd, *J* = 3.5, 2.5 Hz, 1H, =CH), 4.49 (d, *J* = 15.0 Hz, 1H, NC*H*H'), 4.19 (d, *J* = 15.0 Hz, 1H, NCH*H'*), 3.95 (s, 3H, OMe), 3.81–3.71 (m, 7H, OMe, NCH), 3.10 (dd, *J* = 5.0, 1.0 Hz, 1H, CH-5), 2.38–2.29 (m, 2H, CHH'-2), 2.25 (dddd, *J* = 10.0, 5.5, 4.5, 1.0 Hz, 1H, C*H*H'-4), 1.85 (d, *J* = 10.5 Hz, 1H, CH*H'*-4); ^{13}C NMR (101 MHz, CD_2Cl_2) for **17** δ 175.8 (C=O), 164.9 (*ipso*-Ar), 160.6 (*ipso*-Ar), 158.6 (*ipso*-Ar), 155.9 (Ar), 134.6 (*ipso*-Ar), 130.2 (Ar), 128.0 (=C), 122.9 (=CH), 117.8 (*ipso*-Ar), 104.3 (Ar), 98.3 (Ar), 55.41 (OMe), 55.36 (OMe), 54.8 (NCH), 43.7 (CH-5), 38.0 (NCH_2), 33.6 (CH_2-4), 28.8 (CH_2-2) (1 × OMe resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{21}H_{23}N_3O_4$ $(M + Na)^+$ 404.1581, found 404.1583 (–0.4 ppm error), alkene **22** (4.00 mg, 6%) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above, and a 90:10 mixture (by ^1H NMR spectroscopy) of bis-normorphan **23b** and SPhos (5.00 mg, i.e. 4.50 mg of **23b**, 7%) as a clear oil, identical (by ^1H and ^{13}C NMR spectroscopy) to that described above.

4.13. 6-(2,4-Dimethoxybenzyl)-2-(1-(triisopropylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-6-azabicyclo[3.2.1]oct-2-en-7-one 18

Using general procedure A, MIDA boronate **1** (200 mg, 1.47 mmol, 1.0 eq), $Pd(OAc)_2$ (6.00 mg, 0.025 mmol, 0.05 eq), SPhos (20.0 mg, 0.047 mmol, 0.1 eq), 5-bromo-1-triisopropylsilanyl-1*H*-

pyrrolo[2,3-b]pyridine (198 mg, 0.56 mmol, 1.2 eq) and 3 M $K_3PO_{4(aq)}$ (1.52 mL, 4.59 mmol, 7.5 eq) in dioxane (7.5 mL) gave the crude product. Purification by flash column chromatography on silica with 1:4 EtOAc-hexane as eluent gave arylated normorphan **18** (178 mg, 58%) as a clear oil, R_F (1:4 EtOAc-hexane) 0.15; IR (ATR) 2945, 2866, 2244, 1686 (C=O), 1613, 1507, 1465, 1385, 1207, 1154, 906, 726, 648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 2.0 Hz, 1H, Ar), 8.10 (d, *J* = 2.0 Hz, 1H, Ar), 7.27 (d, *J* = 3.5 Hz, 1H, Ar), 7.21–7.13 (m, 1H, Ar), 6.55 (d, *J* = 3.5 Hz, 1H, Ar), 6.49–6.40 (m, 2H, Ar), 5.78 (dd, *J* = 3.5, 3.5 Hz, 1H, =CH), 4.61 (d, *J* = 15.0 Hz, 1H, NC*H*H'), 4.29 (d, *J* = 15.0 Hz, 1H, NC*H*H'), 3.91–3.72 (m, 7H, OMe, NCH), 3.33 (d, *J* = 5.0 Hz, 1H, CH-5), 2.43–2.30 (m, 2H, CHH'-2), 2.29 (ddd, *J* = 10.0, 5.0, 5.0 Hz, 1H, C*H*H'-4), 1.91 (d, *J* = 10.0 Hz, 1H, CH*H'*-4), 1.85 (sept, *J* = 7.5 Hz, 3H, SiCH), 1.121 (d, *J* = 7.5 Hz, 9H, SiCH*Me*$_2$), 1.117 (d, J = 7.5 Hz, 9H, SiCH*Me*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8 (C=O), 160.5 (*ipso*-Ar), 158.6 (*ipso*-Ar), 153.4 (*ipso*-Ar), 140.3 (Ar), 139.0 (=C), 131.6 (Ar), 130.6 (Ar), 129.1 (*ipso*-Ar), 124.7 (Ar), 122.0 (*ipso*-Ar), 120.5 (=CH), 118.0 (*ipso*-Ar), 104.3 (Ar), 103.4 (Ar), 98.5 (Ar), 55.5 (OMe), 53.9 (NCH), 44.6 (CH-5), 38.0 (NCH_2), 34.2 (CH_2-4), 29.0 (CH_2-2), 18.3 (SiCH*Me*$_2$), 12.4 (SiCH) (1 × OMe resonance not resolved); HRMS (ESI) *m/z* calcd for $C_{32}H_{44}N_3O_3$ $(M + H)^+$ 546.3146, found 546.3147 (–0.1 ppm error).

4.14. 6-(2,4-Dimethoxybenzyl)-2-(4-methoxyphenyl)-6-azabicyclo[3.2.1]octan-7-one 24

10% Pd/C (61.0 mg, 0.06 mmol, 10 mol%) was added to a stirred solution of arylated normorphan **12** (215 mg, 0.57 mmol, 1 eq) in MeOH (3 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times and then with H_2 three times. The resulting mixture was stirred under a balloon of H_2 (760 mmHg) for 18 h. The solids were removed by filtration through Celite® and washed with MeOH (10 mL). The filtrate was evaporated under reduced pressure to give hydrogenated normorphan **24** (200 mg, 92%) as a clear oil, R_F (3:2 EtOAc-hexane) 0.49; IR (ATR) 2936, 2835, 1680 (C=O), 1611, 1587, 1508, 1243, 1032, 825, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.33 (m, 2H, Ar), 7.22 (d, *J* = 8.5 Hz, 1H, Ar), 6.87–6.82 (m, 2H, Ar), 6.47–6.42 (m, 2H, Ar), 4.64 (d, *J* = 14.5 Hz, 1H, NC*H*H'), 4.30 (d, *J* = 14.5 Hz, 1H, NCH*H'*), 3.84–3.74 (m, 9H, OMe), 3.61 (dd, *J* = 5.5, 4.5 Hz, 1H, NCH), 2.84 (ddd, *J* = 12.0, 5.0, 1.5 Hz, 1H, CH-6), 2.64 (d, *J* = 5.5 Hz, 1H, CH-5), 2.28 (dddd, *J* = 11.0, 5.5, 5.5, 1.5 Hz, 1H, C*H*H'-4), 1.85 (ddd, *J* = 14.0, 5.0, 5.0 Hz, 1H, C*H*H'-1), 1.79–1.61 (m, 3H, CH*H'*-1, C*H*H'-2, CH*H'*-4), 1.52 (ddd, *J* = 12.0, 11.5, 5.0 Hz, 1H, CH*H'*-2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3 (C=O), 160.5 (*ipso*-Ar), 158.7 (*ipso*-Ar), 158.2 (*ipso*-Ar), 136.5 (*ipso*-Ar), 131.0 (Ar), 128.7 (Ar), 117.9 (*ipso*-Ar), 113.7 (Ar), 104.2 (Ar), 98.4 (Ar), 55.5 (OMe), 55.4 (OMe), 55.3 (OMe), 54.8 (NCH), 46.2 (CH-5), 44.0 (CH-6), 39.7 (CH_2-4), 38.6 (NCH_2), 27.5 (CH_2-1), 26.4 (CH_2-2); HRMS (ESI) *m/z* calcd for $C_{23}H_{27}NO_4$ $(M + Na)^+$ 404.1832, found 404.1837 (–1.2 ppm error). The relative stereochemistry was established by X-ray crystallography: CCDC 2043548.

4.15. 2-(4-Methoxyphenyl)-6-azabicyclo[3.2.1]octan-7-one 25

80% v/v $TFA_{(aq)}$ (8 mL) was added to a stirred solution of *N*-DMB-amide **24** (100 mg, 0.26 mmol, 1.0 eq) in CH_2Cl_2 (1 mL) at rt. The resulting mixture was stirred and heated at 60 °C for 18 h. The solvent was evaporated under reduced pressure. The residue was suspended in toluene (10 mL) and the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 to 7:3 EtOAc-hexane as eluent gave amide **25** (44.0 mg, 73%) as an off-white crystalline solid, mp 140-142 °C; R_F (7:3 EtOAc-hexane) 0.20; IR (ATR) 3231 (NH), 2934, 1693 (C=O), 1611, 1514, 1247, 1181, 1035, 835, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.27 (m, 2H, Ar), 6.88–6.79 (m, 2H, Ar), 6.69 (br s, 1H, NH), 3.85–3.69 (m, 4H, OMe, NCH), 2.88 (ddd, *J* = 12.5, 6.0, 2.0 Hz, 1H, CH-6), 2.53 (d, *J* = 5.5 Hz, 1H, CH-5), 2.44 (dddd, *J* = 11.5, 6.0, 5.5, 2.0 Hz, 1H, C*H*H'-4), 2.09–1.88 (m, 2H, C*H*H'-1, C*H*H'-2), 1.88–1.73 (m, 2H, CH*H'*-1, CH*H'*-4), 1.68 (ddd, *J* = 12.5, 12.5, 6.0 Hz, 1H, CH*H'*-2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0 (C=O), 158.2 (*ipso*-Ar), 136.2 (*ipso*-Ar), 128.5 (Ar), 113.8 (Ar), 55.3 (OMe), 51.2 (NCH), 45.8 (CH-5), 43.8 (CH-6), 41.0 (CH_2-4), 29.1 (CH_2-1), 26.8 (CH_2-2); HRMS (ESI) *m/z* calcd for $C_{14}H_{17}NO_2$ $(M + H)^+$ 232.1332, found 232.1334 (–0.8 ppm error).

4.16. 6-(2,4-Dimethoxybenzyl)-2-(4-methoxyphenyl)-6-azabicyclo[3.2.1]oct-2-ene 26

A solution of arylated normorphan **12** (200 mg, 0.53 mmol, 1.0 eq) in THF (7.5 mL), was added dropwise to a stirred suspension of $LiAlH_4$ (80.0 mg, 2.11 mmol, 4 eq) in THF (3.5 mL) at rt under Ar. The resulting mixture was stirred and heated at reflux for 16 h under Ar. After allowing the mixture to cool to rt, H_2O (0.15 mL), 2 M $NaOH_{(aq)}$ (0.32 mL) and $MgSO_4$ (250 mg) were added and the resulting mixture was stirred for 15 min. The solids were removed by filtration through Celite® and the filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 99:1 to 9:1 EtOAc-MeOH as eluent gave amine **26** (136 mg, 70%) as a clear oil, R_F (9:1 EtOAc-MeOH) 0.3; IR (ATR) 2934, 2832, 1607, 1507, 1240, 1152, 1032, 819 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.5 Hz, 1H, Ar), 7.31–7.27 (m, 2H, Ar), 6.87–6.82 (m, 2H, Ar), 6.48 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar), 6.44 (d, *J* = 2.5 Hz, 1H, Ar), 5.72 (ddd, *J* = 3.5, 3.5, 1.5 Hz, 1H, =CH), 3.87–3.80 (m, 2H, NCHH'Ar), 3.81–3.79 (m, 9H, OMe), 3.48–3.42 (m, 1H, NCH), 3.12–3.02 (m, 2H, NCHH'-7), 3.00 (dd, *J* = 5.0, 4.5 Hz, 1H, CH-5), 2.48 (ddd, *J* = 18.5, 3.5, 2.0 Hz, 1H, C*H*H'-2), 2.30 (ddd, *J* = 18.5, 3.5, 3.5 Hz, 1H, CH*H'*-2), 2.04 (ddd, *J* = 10.5, 5.0, 5.0 Hz, 1H, C*H*H'-4), 1.84 (d, *J* = 10.5 Hz, 1H, CH*H'*-4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6 (*ipso*-Ar), 158.6 (*ipso*-Ar), 158.2 (*ipso*-Ar), 144.2 (=C), 134.1 (*ipso*-Ar), 130.2 (Ar), 126.2 (Ar), 121.3 (*ipso*-Ar), 119.6 (=CH), 113.8 (Ar), 103.9 (Ar), 98.4 (Ar), 63.2 (NCH_2-7), 58.2 (NCH), 55.45 (OMe), 55.43 (OMe), 55.38 (OMe), 52.6 (NCH_2Ar), 38.6 (CH-5), 34.3 (CH_2-2), 33.6 (CH_2-4); HRMS (ESI) *m/z* calcd for $C_{23}H_{27}NO_3$ $(M + H)^+$ 366.2064, found 366.2066 (–0.5 ppm error).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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