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Strategies for the Construction of Morphinan Alkaloid AB-Rings: Regioselective Friedel-Crafts-type Cyclisations of γ-Aryl-β-benzoylamido Acids with Asymmetrically Substituted γ-Aryl Rings

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ABSTRACT

The regioselectivity of the Friedel-Crafts-type cyclisation of a range of γ-aryl-β-benzoylamido acids, bearing oxy substituents at the C(3)- and C(4)-positions of the γ-aryl ring, has been investigated. In all of the cases examined (with 3,4-dimethoxy, 3,4-methylenedioxy and 3-hydroxy-4-methoxy substituents) the Lewis acid promoted cyclisation proceeds with exclusive regioselectivity for attack at the C(6)-position rather than at the C(2)-position, and furnishes the corresponding, *N*- and *O*-protected 3-amino-6,7-dihydroxy-1-tetralone derivatives. This inherent regioselectivity can be overturned by the regioselective introduction of chlorine as a blocking group for the C(6)-position; subsequent Lewis acid promoted cyclisation then proceeds with exclusive regioselectivity for attack at the C(2)-position to deliver the corresponding *N*- and *O*-protected 3-amino-5-chloro-7,8-dihydroxy-1-tetralone derivative. These complementary cyclisation protocols represent useful methods for the preparation of these benzo-fused carbocyclic ring systems, which are the functionalised AB-rings of a range of morphinan alkaloids.

1. Introduction

Morphinan **1** is the archetypal molecular framework of a number of alkaloids, including opiates, which are of significant importance. It comprises a partially reduced phenanthrene core with only one of the rings (denoted the A-ring) remaining aromatic; the other two rings (denoted the B- and C-rings) are saturated. An additional six-membered ring (denoted the D-ring) is fused through carbon atoms 9 and 13, and contains an endocyclic nitrogen atom (at position 17). The structures of the morphinan alkaloids themselves are somewhat diverse. The A-ring is usually substituted with two vicinal oxy functionalities (which bear a variety of substituents) either at the C(2)- and C(3)-positions, e.g., 2,3-dimethoxy as in *O*-methylpallidinine **2**,[1] sebiferine **5**[2-5] and tannagine **8**,[6] 2,3-methylenedioxy as in meconoquintupline **3**,[7-9] amurine **6**[10-14] and nudaurine **9**,[11,13] and 2-hydroxy-3-methoxy as in pallidinine **4**[1] and pallidine **7**,[15] or at the C(3)- and C(4)-positions, e.g., 3-methoxy-4-hydroxy as in sinoacutine **10**[16-18] (the regioisomer of pallidine

7). In cases where the C(4)-position is oxy-substituted, a formal etherification to link carbon atoms 4 and 5 and hence close an additional ring (denoted the E-ring) gives further alkaloids, e.g., the opiates morphine **11**,[19,20] codeine **12**,[20] and thebaine **13**.[20] The B-ring and C-ring can be either *cis*- or *trans*-fused, and there is significant structural variation within the C-ring (which generally contains partial unsaturation) as shown by the structures of *O*-methylpallidinine **2**,[1] sebiferine **5**[2-5] and tannagine **8**,[6] or meconoquintupline **3**,[7-9] amurine **6**[10-14] and nudaurine **9**[11,13] (Figure 1).

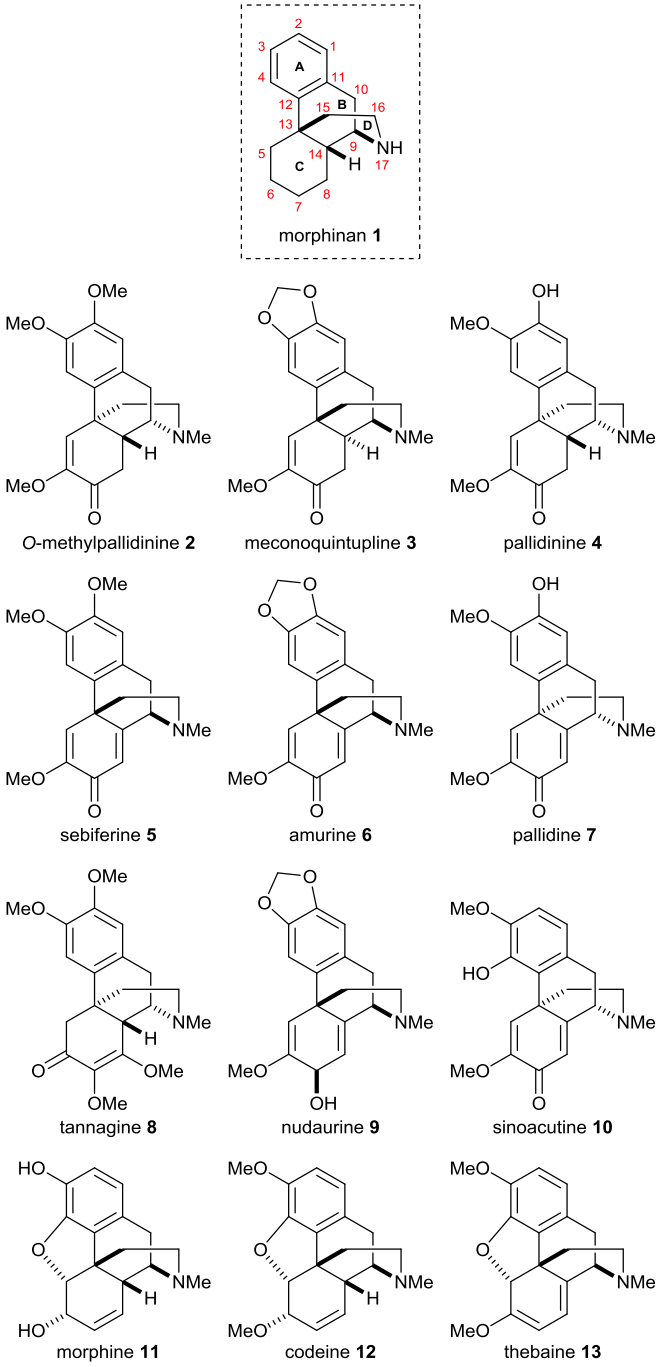
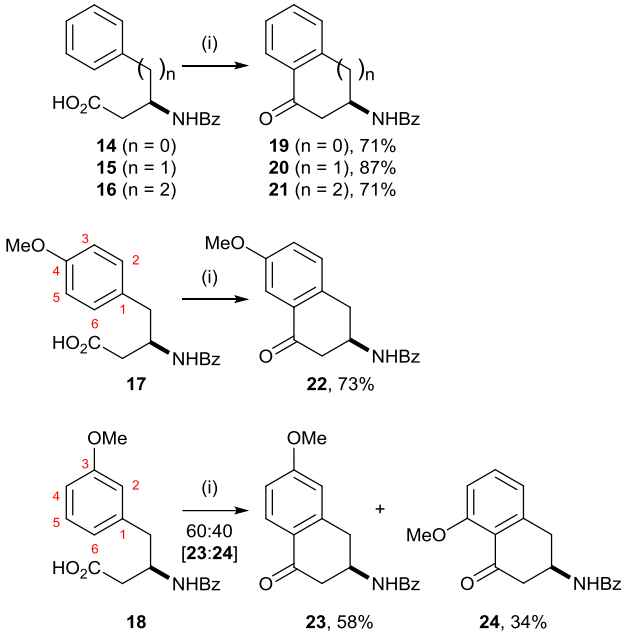


Figure 1. Structure and numbering convention of morphinan **1**, and structures of representative morphinan alkaloids **2**–**13**.

We have recently reported the Fridel-Crafts-type cyclisation of a range of ω-aryl-β-benzoylamido acids (e.g., **14**–**18**) for the construction of 3-amino-substituted, benzo-fused carbocycles: 1-indanones, e.g., **19** (n = 0), 1-tetralones, e.g. **20** and **22**–**24** (n = 1), and 1-benzosuberones, e.g., **21** (n = 2).[21,22] Mixtures of

regioisomeric products were observed in cases where the ω-aryl ring was not symmetrically substituted: whilst cyclisation of **17** proceeded to give 1-tetralone **22** as the sole product [cyclisation onto either C(2) or C(6) being equivalent] which was isolated in 73% yield, analogous reaction of **18** gave a 60:40 mixture of the regioisomers **23** and **24** [resulting from cyclisation onto either C(6) or C(2), respectively] which were separated and isolated in 58% and 34% yield, respectively[21] (Scheme 1).



Scheme 1. Reagents and conditions: (i) $(COCl)_2$, DMF, CH_2Cl_2, rt, 30 min, then add $AlCl_3$, 0 °C, 16 h.

Described herein are the results of our studies concerning the application of this methodology to the cyclisation of a range of γ-aryl-β-benzoylamido acids **25** bearing two oxy substituents at the C(3)- and C(4)-positions of the γ-aryl ring. The range of γ-aryl-β-benzoylamido acids **25** was chosen such that the commonly occurring substitution patterns encountered within the morphinan alkaloids were represented: $R_1 = R_2$ = Me; $R_1 = R_2$ = -CH_2-; R_1 = OMe, R_2 = OH. It was anticipated that cyclisation of these substrates would proceed preferentially onto the least sterically congested C(6)-position, which would also be electronically promoted by the C(3)-oxy substituent, to give the corresponding 1-tetralones **26**. For the same reasons, the introduction of a blocking group (e.g., a halogen) was expected to proceed regioselectively at C(6) to give the corresponding C(6)-substituted derivatives **27**; subsequent cyclisation was then predicted to proceed preferentially onto the unsubstituted C(2)-position, thus giving 1-tetralones **28**. Both families of 1-tetralones **26** and **28**, which should be accessible via this strategy, represent useful 3-amino-substituted benzo-fused carbocyclic templates comprising the functionalised AB-ring scaffolds of a number of morphinan alkaloids **29** (Figure 2).

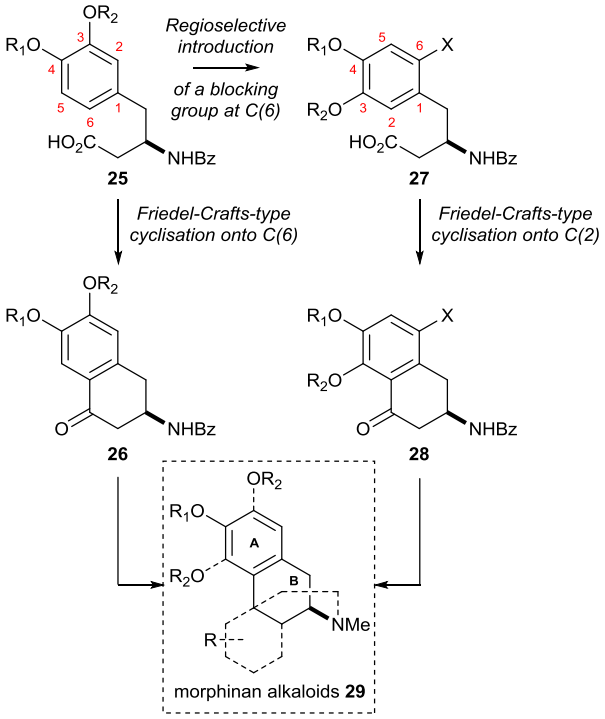
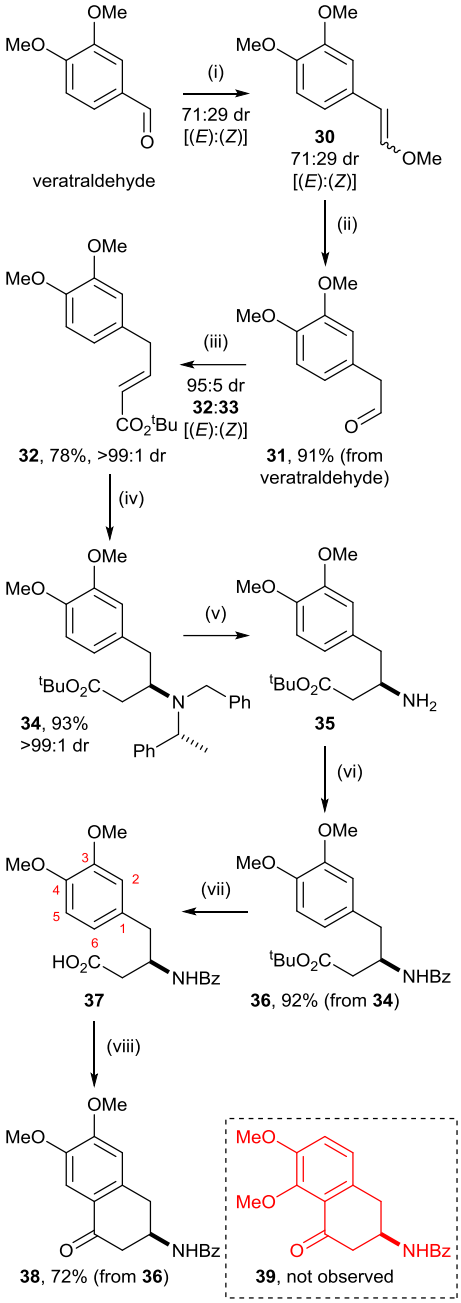


Figure 2. Proposed strategy for the synthesis of a range of 1-tetralones **26** and **28**, the AB-ring scaffolds of morphinan alkaloids **29**.

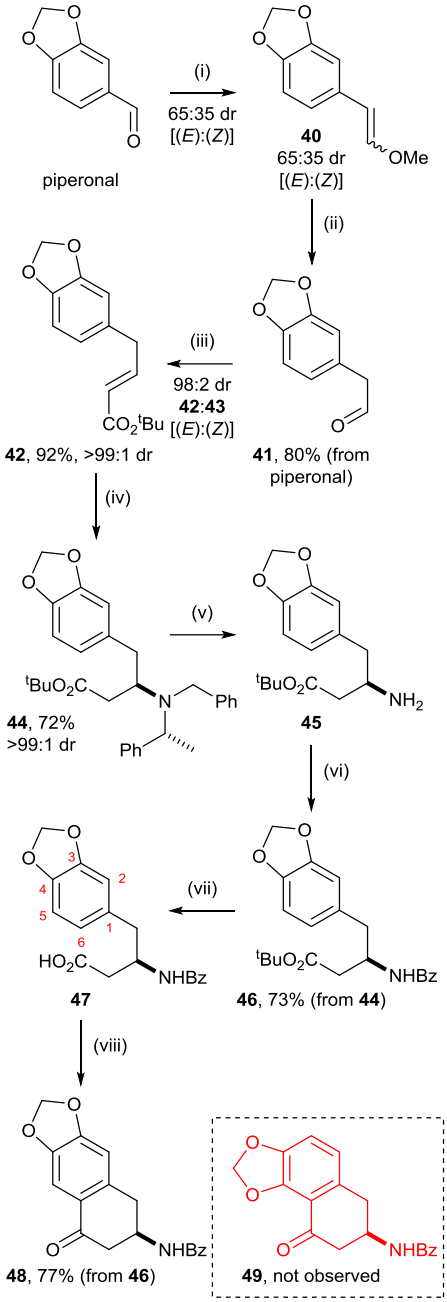
2. Results and Discussion

Our strategy for the syntheses of the range of γ-aryl-β-benzoylamido acids **25** was identical to that used for the preparation of the mono-methoxy substituted analogues **17** and **18**.[21] The aldehydes with the requisite substitution patterns (R_1 = R_2 = Me; R_1 = R_2 = -CH_2-; R_1 = OMe, R_2 = OH) are all commercially available, *viz.* veratraldehyde, piperonal and isovanillin. However, to ensure success in the latter of these cases, it was decided to employ an *O*-protecting group strategy from the outset: commercially available *O*-benzylisovanillin was thus used as the starting material in this case. Hence, veratraldehyde, piperonal and *O*-benzylisovanillin were homologated[23] by Wittig reaction with Ph_3P=CHOMe followed by hydrolysis of the resultant vinyl ethers **30**, **40** and **50**, to give aldehydes **31**, **41** and **51** in 91%, 80% and 57% overall yields, respectively. Next, olefination of **31**, **41** and **51** with Ph_3P=$CHCO_2{}^tBu$ gave mixtures of the corresponding, diastereoisomeric (*E*)- and (*Z*)-α,β-unsaturated esters {**32**:**33**, 95:5 dr [(*E*):(*Z*) ratio]; **42**:**43**, 88:12 dr [(*E*):(*Z*) ratio]; **52**:**53** >95:5 dr [(*E*):(*Z*) ratio]} from which **32**, **42** and **52** were isolated in 78%, 49% and 71% yields, respectively. In the case of **42**, the yield was compromised by the isolation of a mixed fraction in 47% yield {**42**:**43**, 78:22 dr [(*E*):(*Z*) ratio]}. However, application of the Masamune-Roush conditions[24] to effect olefination of **41** gave superior diastereoselectivity {**42**:**43**, 98:2 dr [(*E*):(*Z*) ratio]}, allowing **42** to be isolated in 92% yield after chromatography. With **32**, **42** and **52** in hand, conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (>99% ee) furnished the corresponding β-amino esters **34**, **44** and **54**, which were isolated in 93%, 72% and 47% yields, respectively, and in >99:1 dr in all three cases. The

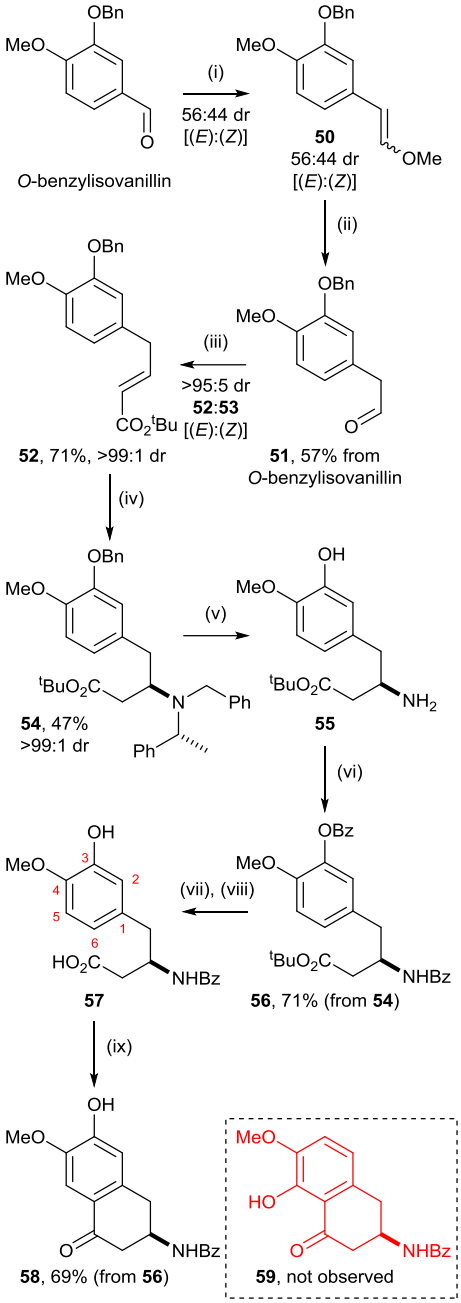
relative (and absolute) configurations within **34**, **44** and **54** were assigned by reference to the transition state mnemonic that we have developed to reliably predict the stereochemical outcome of this lithium amide in its conjugate addition reaction.[25] Palladium-mediated hydrogenolysis of **34** and **44** was followed by *N*-benzoylation of the resultant primary amines **35** and **45** to give **36** and **46** in 92% and 73% yields from **34** and **44**, respectively. Meanwhile, hydrogenolysis of **54** cleaved the *O*-benzyl, *N*-benzyl and *N*-α-methylbenzyl protecting groups to give **55**. It was envisaged that the primary amino functionality within **55** could be selectively protected upon treatment with 1 equiv of PhCOCl, leaving the less reactive phenol functionality free. However, reaction of **55** (unpurified) under these conditions gave a 25:21:54 mixture of starting material **55**, di-*N*,*O*-protected **56** and the corresponding mono-*N*-protected species, respectively. When 2 equiv of PhCOCl was used, **56** was produced as the only product, which was isolated in 71% yield (from **54**). Cleavage of the *tert*-butyl esters within **36** and **46** with neat TFA then gave γ-aryl-β-benzoylamido acids **37** and **47**, whilst treatment of **56** with NaOMe in MeOH cleaved the *O*-benzoyl protecting group, and the *tert*-butyl ester was then cleaved with neat TFA to give γ-aryl-β-benzoylamido acid **57**. Activation of γ-aryl-β-benzoylamido acids **37**, **47** and **57** upon treatment with $(COCl)_2$ was followed by addition of $SnCl_4$ to the reaction flask, which resulted in formation of 1-tetralones **38**, **48** and **58** as a single regioisomers in all three cases. Chromatographic purification gave **38**, **48** and **58** in 72%, 77% and 69% isolated yields from **36**, **46** and **56**, respectively. The regiochemistries of **38**, **48** and **58** were easily established by the presence of two aryl hydrogen singlets at δ_H ~6.7 ppm and δ_H ~7.5 ppm [corresponding to C(5)*H* and C(8)*H*, respectively] in the ^{1}H NMR spectra of the crude reaction mixtures (and isolated products); no traces of the regioisomeric 1-tetralones **39**, **49** and **59** were observed in the ^{1}H NMR spectra of the crude reaction mixtures. These results are consistent with a mechanism whereby either (i) cyclisation of **37**, **47** and **57** is promoted directly onto the least sterically congested C(6)-position by the action of the C(3)-oxy group, or (ii) cyclisation of **37**, **47** and **57** is promoted onto the C(1)-position by the action of the C(4)-oxy group to form a 5,6-spirocyclic intermediate,[26] with subsequent regioselective dienone-phenol-type rearrangement of the acyl group to the least sterically congested C(6)-position giving the same intermediate; in both cases rearomatisation by loss of a proton then results in the formation of 1-tetralones **38**, **48** and **58** (Schemes 2−4).



Scheme 2. *Reagents and conditions:* (i) $[MeOCH_2PPh_3]^+[Cl]^-$, KO^{t}Bu, THF, rt, 12 h; (ii) HCO_2H, CH_2Cl_2, rt, 48 h; (iii) $Ph_3P{=}CHCO_2{}^t$Bu, CH_2Cl_2, 0 °C to rt, 12 h; (iv) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h; (v) Pd/C, H_2, MeOH, AcOH, H_2O, rt, 12 h; (vi) PhCOCl, Et_3N, CH_2Cl_2, rt, 16 h; (vii) TFA, rt, 1 h; (viii) $(COCl)_2$, CH_2Cl_2, DMF, rt, 30 min, then $SnCl_4$, 0 °C to rt, 16 h.

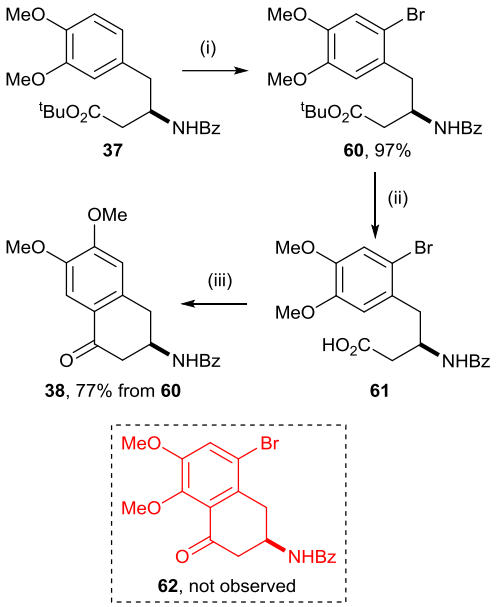


Scheme 3. *Reagents and conditions:* (i) $[MeOCH_2PPh_3]^+[Cl]^-$, KO^{t}Bu, THF, rt, 12 h; (ii) HCO_2H, CH_2Cl_2, rt, 48 h; (iii) $(EtO)_2P(O)CH_2CO_2{}^t$Bu, $^i Pr_2NEt$, LiCl, MeCN, rt, 48 h; (iv) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h; (v) $Pd(OH)_2/C$, H_2, EtOAc, rt, 12 h; (vi) PhCOCl, Et_3N, CH_2Cl_2, rt, 16 h; (vii) TFA, rt, 1 h; (viii) $(COCl)_2$, CH_2Cl_2, DMF, rt, 30 min, then $SnCl_4$, 0 °C to rt, 16 h.



Scheme 4. *Reagents and conditions:* (i) $[MeOCH_2PPh_3]^+[Cl]^-$, KO^{t}Bu, THF, rt, 12 h; (ii) HCO_2H, CH_2Cl_2, rt, 48 h; (iii) $Ph_3P{=}CHCO_2{}^t$Bu, CH_2Cl_2, 0 °C to rt, 12 h; (iv) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h; (v) Pd/C, H_2, MeOH, AcOH, H_2O, rt, 16 h; (vi) PhCOCl, Et_3N, CH_2Cl_2, rt, 16 h; (vii) NaOMe, MeOH, 5 °C, 1 h; (viii) TFA, rt, 1 h; (ix) $(COCl)_2$, CH_2Cl_2, DMF, rt, 30 min, then $SnCl_4$, 0 °C to rt, 16 h.

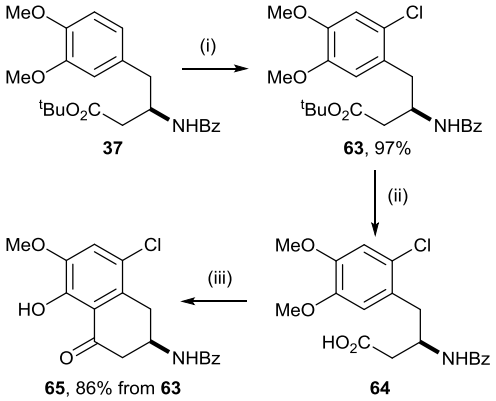
Having effected the regioselective cyclisation of the range of γ-aryl-β-benzoylamido acids **37**, **47** and **57** to give the corresponding *O*-protected 3-benzoylamido-6,7-dihydroxy-1-tetralone derivatives **38**, **48** and **58**, respectively, attention turned to effecting the cyclisation to give the alternative, regioisomeric *O*-protected 3-benzoylamido-7,8-dihydroxy-1-tetralone derivatives. To this end, the use of a blocking group was considered. In this approach, a temporary substituent is introduced regioselectively onto the more reactive position of an aromatic nucleus, such that an ensuing reaction is directed to an alternative position. Bromine has been a useful and suitably robust blocking group in related cyclisation reactions.[27] The production of γ-aryl-β-benzoylamido acid **61** was therefore targeted. Treatment of **37** with Br_2 in $CHCl_3$ was found to give exclusive C(6)-bromination, furnishing **60** in 97% isolated yield. Cleavage of the *tert*-butyl ester then gave **61**, which upon carbonyl activation and then treatment with $SnCl_4$ gave tetralone **38** as the sole product, i.e., the same product resulting from reaction of **37** (without introduction of the bromine blocking group) under the same reaction conditions; purification gave **38** in 77% isolated yield. The same result was observed when **61** was heated at 90 °C for 5 h in polyphosphoric acid: tetralone **38** was the sole product and was isolated in 68% yield (Scheme 5).



Scheme 5. *Reagents and conditions*: (i) Br_2, $CHCl_3$, rt, 30 min; (ii) TFA, rt, 1 h; (iii) $(COCl)_2$, CH_2Cl_2, DMF, rt, 30 min, then $SnCl_4$, 0 °C to rt, 16 h.

It is apparent that the subtle interplay between steric and electronic effects coupled with blocking group identity is insufficient, in this case, to overturn the inherent regioselectivity and effect direction of the cyclisation reaction onto the C(2)-position; thus, addition occurs to the C(6)-position to which the bromine is attached. Although bromine is often the reagent of choice, chlorine has also been applied as a blocking group.[28] Its use has, however, been hampered by the difficulties associated with handling and dispensing of stoicheiometric quantities of the gas: chlorine is a strong electrophile and reacts rapidly and often unselectively with aromatic compounds, unless the stoicheiometry can be carefully controlled. In contrast,

sulfuryl chloride (SO_2Cl_2) is a relatively weak electrophile[29] and monochlorinates activated arenes in reactions which are generally high yielding when other functionalities that are present are compatible with this reagent.[30] Following this precedent, treatment of **37** in CH_2Cl_2 with 1 equiv of SO_2Cl_2 gave C(6)-chlorinated adduct **63**. It was noted that the use of a stoicheometric amount of SO_2Cl_2 was important, since any slight excess of reagent resulted in polychlorination. Ensuing *tert*-butyl ester cleavage of **63** in neat TFA furnished **64**. Attempts to cyclise **64** by sequential treatment with $(COCl)_2$ and $SnCl_4$, or by heating in polyphosphoric acid, gave no reaction, with only starting material being isolated. However, this was not considered a negative result, since both sets of conditions had previously led to the cyclisation of **61** to give the unwanted regioisomer **38**. Given these positive implications regarding the efficacy of the new blocking group, attempting the reaction using $AlCl_3$ as the Lewis acid catalyst furnished **65** as the sole product, in which the regioselective cyclisation onto the C(2)-position had been accompanied by a selective *O*-demethylation; chromatographic purification enabled the isolation of **65** in 86% yield (from **63**). The exact order of events leading to **65** is likely ring-closure and re-aromatisation followed by Lewis acid assisted dealkylation of the vinylogous ester (Scheme 6).



Scheme 6. *Reagents and conditions*: (i) SO_2Cl_2 (1.0 equiv), CH_2Cl_2, rt, 1 h; (ii) TFA, rt, 1 h; (iii) $(COCl)_2$, CH_2Cl_2, DMF, rt, 30 min, then $AlCl_3$, 0 °C to rt, 16 h.

3. Conclusion

In conclusion, a range of γ-aryl-β-benzoylamido acids, bearing oxygen substituents at the C(3)- and C(4)-positions of the aromatic ring, has been prepared; this range incorporates differential *O*-protection. In all of the cases investigated, the cyclisation proceeds with exclusive regioselectivity for attack at the C(6)-position rather than C(2)-position of the γ-aryl ring, regardless of the nature of the *O*-protecting groups, and furnishes the corresponding *N*- and *O*-protected 3-amino-6,7-dihydroxy-1-tetralone derivatives. This inherent regioselectivity may be overturned by the use of chlorine as a blocking group for the C(6)-position of the γ-aryl ring within a γ-aryl-β-benzoylamido acid. Cyclisation of this species delivers an *N*- and *O*-protected 3-amino-5-chloro-7,8-dihydroxy-1-tetralone derivative, in which cyclisation has been directed exclusively via

the C(2)-position of the γ-aryl ring. These complementary cyclisation protocols represent useful methods for the preparation of the corresponding, functionalised 1-tetralones, which represent the functionalised AB-ring systems of a number of morphinan alkaloids.

4. Experimental Section

4.1. General Experimental Details

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[31] Water was purified by an Elix® UV-10 system. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica or on an automated flash column chromatography platform.

Melting points are uncorrected. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded as a thin film on NaCl plates (film), as a KBr disc (KBr), or using an ATR module (ATR), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. ^{1}H-^{1}H COSY and ^{1}H-^{13}C HMQC analyses were used to establish atom connectivity.

4.2. Experimental Procedures and Characterisation Data

4.2.1. 3,4-Dimethoxyphenylacetaldehyde 31

Step 1: KO^{t}Bu (11.8 g, 0.10 mol) was added portionwise to a stirred suspension of $[MeOCH_2PPh_3]^+[Cl]^-$ (37.7 g, 0.11 mol) in THF (100 mL) at 0 °C. The resultant mixture was stirred for 30 min at rt and then a solution of veratraldehyde (16.6 g, 0.10 mol) in THF (100 mL) was added dropwise. The resultant mixture was stirred at rt for 12 h and then quenched by addition of satd aq NH_4Cl (100 mL). The aqueous layer was extracted with Et_2O (3 × 150 mL) and the combined organics were washed with brine (2 × 200 mL), then dried and concentrated *in vacuo*. Pentane (100 mL) was added to the residue and the resultant suspension was stirred at rt for 30 min. The resultant solution was filtered and the filtrate was concentrated in vacuo. This trituration process was repeated three times to give **30** {71:29 dr, [(*E*):(*Z*) ratio]} as a pale yellow oil (19.3 g).

Step 2: Formic acid (50 mL) was added to a stirred solution of the residue of **30** (19.3 g) in CH_2Cl_2 (200 mL) at rt. The resultant solution was stirred in the dark for 48 h. H_2O (100 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organics were washed with brine (2 × 500 mL), then dried and concentrated in vacuo. Purification by vacuum distillation gave **31** as a colourless oil (16.4 g, 91% from veratraldehyde); bp 126-130 °C (0.6 mmHg); δ_H (400 MHz, $CDCl_3$) 3.61 (2H, d, *J* 2.5, C*H*$_2$CHO), 3.85 (6H, app s, O*Me*), 6.68-6.77 (2H, m, C(2)*H*, C(6)*H*), 6.85 (1H, d, *J* 8.1, C(3)*H*), 9.70 (1H, t, *J* 2.5, CH_2C*H*O).

4.2.2. *tert*-Butyl (*E*)-4-(3′,4′-dimethoxyphenyl)but-2-enoate 32

A solution of **31** (5.41 g, 30.0 mmol) in CH_2Cl_2 (50 mL) was added dropwise to a stirred solution of Ph_3P=$CHCO_2{}^tBu$ (13.6 g, 36.0 mmol) in CH_2Cl_2 (200 mL) at 0 °C. The resultant solution was stirred at rt for 12 h and then concentrated in vacuo. The residue was suspended in a mixture of Et_2O (50 mL) and pentane (50 mL), and the resultant suspension was stirred at rt for 30 min. The resultant solution was filtered and the filtrate was concentrated in vacuo. This trituration process was repeated three times to give a 95:5 mixture of **32** and **33**, respectively. Purification via flash column chromatography (eluent 5→10→20% Et_2O in pentane) gave **33** as a colourless oil {309 mg, 4%, >99:1 dr [(*E*):(*Z*) ratio]}; ν_{max} (film) 2977, 2935, 2835, 1712, 1638, 1606, 1591, 1515, 1465, 1262, 1236, 1152, 1030, 825; δ_H (400 MHz, $CDCl_3$) 1.52 (9H, s, C*Me*$_3$), 3.87 (3H, s, O*Me*), 3.88 (3H, s, O*Me*), 3.93 (2H, dd, *J* 7.6, 1.6, C(4)*H*$_2$), 5.76 (1H, dt, *J* 11.5, 1.6, C(2)*H*), 6.25 (1H, dt, *J* 11.5, 7.6, C(3)*H*), 6.76-6.82 (3H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 34.5 (*C*(4)), 55.8, 55.9 (O*Me*), 80.4 (*C*Me$_3$), 111.3, 111.9 (*C*(2′), *C*(5′)), 120.4 (*C*(6′)), 121.5 (*C*(2)), 132.3 (*C*(1′)), 146.6 (*C*(3)), 147.5, 149.0 (*C*(3′), *C*(4′)), 165.9 (*C*(1)); *m/z* (CI^+) 296 ($[M+NH_4]^+$, 5%), 240 (100%), 222 (30%); HRMS (CI^+) $C_{16}H_{26}NO_4^+$ ($[M+NH_4]^+$) requires 296.1856; found 296.1876. Further elution gave **32** as a pale yellow solid {6.48 g, 78%, >99:1 dr, [(*E*):(*Z*) ratio]}; mp 58-60 °C; ν_{max} (KBr) 3063, 3004, 2973, 2935, 2834, 1705, 1651, 1592, 1516, 1467, 1263, 1149, 1028, 911, 733; δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, C*Me*$_3$), 3.42 (2H, dd, *J* 6.8, 1.5, C(4)*H*$_2$), 3.86 (3H, s, O*Me*), 3.88 (3H, s, O*Me*), 5.71 (1H, dt, *J* 15.5, 1.5, C(2)*H*), 6.67 (1H, d, *J* 1.7, C(2′)*H*), 6.71 (1H, dd, *J* 8.1, 1.7, C(6′)*H*), 6.81 (1H, d, *J* 8.1, C(5′)*H*), 6.97 (1H, dt, *J* 15.5, 6.8, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 37.9 (*C*(4)), 55.8, 55.9 (O*Me*), 80.2 (*C*Me$_3$), 111.4, 112.0 (*C*(2′), *C*(5′)), 120.8 (*C*(6′)), 123.8 (*C*(2)), 130.4 (*C*(1′)), 146.3, 147.8, 149.0 (*C*(3), *C*(3′), *C*(4′)), 165.8 (*C*(1)); *m/z* (CI^+) 296 ($[M+NH_4]^+$, 10%), 278 (20%), 240 (100%), 222 (20%); HRMS (CI^+) $C_{16}H_{26}NO_4^+$ ($[M+NH_4]^+$) requires 296.1856; found 296.1860.

4.2.3. *tert*-Butyl (*R*,*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(3′,4′-dimethoxyphenyl)butanoate 34

BuLi (2.5 M in hexanes, 2.16 mL, 5.40 mmol) was added dropwise via syringe to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.14 g, 5.40 mmol, >99% ee) in THF (20 mL) at −78 °C. The resultant pink solution was stirred for 30 min at −78 °C. A solution of **32** {500 mg, 1.80 mmol, >99:1 dr [(*E*):(*Z*) ratio]} in THF (5 mL) at −78 °C was then added dropwise via cannula. The resultant solution was stirred at −78 °C for 2 h then quenched with satd aq NH_4Cl (20 mL). The resultant mixture was diluted with Et_2O (20 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organics were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 5→10% Et_2O in pentane) gave **34** as a colourless oil (855 mg, 93%, >99:1 dr); $[\alpha]_D^{25}$ −14.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3084, 3062, 3027, 2975, 2934, 2835, 1723, 1454, 1262, 1145, 1030, 912, 733; δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 8.0, C(α)*Me*), 1.43 (9H, s, C*Me*$_3$), 2.06 (2H, app d, *J* 6.5, C(2)*H*$_2$), 2.61 (1H, dd, *J* 13.7, 5.7, C(4)*H*$_A$), 2.72 (1H, dd, *J* 13.7, 8.2, C(4)*H*$_B$), 3.63 (1H, d, *J* 15.2, NC*H*$_A$H$_B$Ph), 3.95 (1H, d, *J* 15.2, NCH$_A$*H*$_B$Ph), 3.68 (1H, m, C(3)*H*), 3.84 (3H, s, O*Me*), 3.91 (3H, s, O*Me*), 3.88 (1H, q, *J* 8.0, C(α)*H*), 6.65 (1H, d, *J* 1.5, *Ar*), 6.73 (1H, dd, *J* 8.2, 1.5, *Ar*), 6.82 (1H, d, *J* 8.2, *Ar*), 7.22-7.46 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.0 (C(α)*Me*), 28.1 (C*Me*$_3$), 37.5 (*C*(2)), 39.4 (*C*(4)), 50.0 (N*C*H$_2$Ph), 55.7, 55.9 (O*Me*), 56.7 (*C*(3)), 58.3 (*C*(α)), 80.1 (*C*Me$_3$), 110.9, 112.7, 121.5 (*C*(2′), *C*(5′), *C*(6′)), 126.6, 126.8, 127.8, 128.0, 128.2 (*o,m,p-Ph*), 133.0 (*C*(1′)), 141.5, 143.1 (*i-Ph*), 147.2, 148.4 (*C*(3′), *C*(4′)), 171.9 (*C*(1)); *m/z* (ESI^+) 512 ($[M+Na]^+$, 10%), 490 (100%); HRMS (ESI^+) $C_{31}H_{39}NNaO_4^+$ ($[M+Na]^+$) requires 512.2771; found 512.2778.

4.2.4. *tert*-Butyl (*R*)-3-benzamido-4-(3′,4′-dimethoxyphenyl)butanoate 36

Step 1: Pd/C (165 mg, 20% w/w substrate) was added to a stirred, degassed solution of **34** (825 mg, 1.69 mmol) in MeOH (20 mL), AcOH (2 mL) and H_2O (0.5 mL). The reaction vessel was charged with H_2 (1 atm) and the resultant suspension was stirred rapidly for 12 h. The suspension was filtered through a pad of Celite® (eluent MeOH) and the filtrate was concentrated in vacuo to give **35** as a pale yellow oil. Purification of an aliquot via flash column chromatography (eluent Et_2O) gave an analytically pure sample of **35** as a colourless oil; $[\alpha]_D^{25}$ +1.07 (*c* 0.75 in $CHCl_3$); ν_{max} (film) 3377, 2976, 2934, 2835, 1723, 1607, 1590, 1516, 1465, 1367, 1262, 1238, 1149, 1030; δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, C*Me*$_3$), 1.59 (2H, br s, N*H*$_2$), 2.25 (1H, dd, *J* 15.9, 8.7, C(2)*H*$_A$), 2.42 (1H, dd, *J* 15.9, 4.2, C(2)*H*$_B$), 2.53 (1H, dd, *J* 13.5, 8.3, C(4)*H*$_A$), 2.72 (1H, dd, *J* 13.5, 5.5, C(4)*H*$_B$), 3.42 (1H, m, C(3)*H*), 3.86 (3H, s, O*Me*), 3.88 (3H, s, O*Me*), 6.74-6.77 (2H, m, *Ar*), 6.82 (1H, d, *J* 7.9, *Ar*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 43.1, 43.3 (*C*(2), *C*(4)), 49.7 (*C*(3)), 55.8, 55.9 (O*Me*), 80.6 (C*Me*$_3$), 111.3, 112.4, 121.3 (*C*(2′), *C*(5′), *C*(6′)), 131.2 (*C*(1′)), 147.6, 148.9 (*C*(3′), *C*(4′)),

171.8 (*C*(1)); *m/z* (ESI$^+$) 318 ([M+Na]$^+$, 10%), 296 (80%), 240 (100%); HRMS (ESI$^+$) $C_{16}H_{25}NNaO_4^+$ ([M+Na]$^+$) requires 318.1676; found 318.1679.

Step 2: Et_3N (0.53 mL, 3.83 mmol) and benzoyl chloride (0.18 mL, 1.56 mmol) were added sequentially to a stirred solution of the residue of **35** (454 mg, 1.53 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The resultant solution was stirred at 0 °C for 10 min, then allowed to warm to rt and stirred for an additional 16 h. 10% aq HCl (40 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organics were dried and concentrated *in vacuo*. Purification via recrystallisation (25% Et_2O in pentane) gave **36** as a white solid (562 mg, 92% from **34**); mp 68-70 °C; $[\alpha]_D^{25}$ +30.3 (*c* 1.6 in $CHCl_3$); ν_{max} (KBr) 3349, 3061, 2977, 2933, 2838, 1724, 1639, 1603, 1589, 1580, 1518, 1446, 1366, 1290, 1262, 1237, 1152, 1027; δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, C*Me*$_3$), 2.46 (1H, dd, *J* 15.8, 5.2, C(2)*H*$_A$), 2.52 (1H, dd, *J* 15.8, 5.1, C(2)*H*$_B$), 2.83 (1H, dd, *J* 13.6, 8.6, C(4)*H*$_A$), 3.04 (1H, dd, *J* 13.6, 5.7, C(4)*H*$_B$), 3.84 (3H, s, O*Me*), 3.87 (3H, s, O*Me*), 4.61 (1H, m, C(3)*H*), 6.76-6.82 (3H, m, *Ar*), 7.12 (1H, d, *J* 8.6, N*H*), 7.27-7.52 (3H, m, *Ph*), 7.75-7.78 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 37.7 (*C*(2)), 39.4 (*C*(4)), 48.0 (*C*(3)), 55.8, 55.9 (O*Me*), 81.4 (*C*Me$_3$), 111.2, 112.3, 121.4 (*C*(2′), *C*(5′), *C*(6′)), 126.8, 128.6, 130.2 (*o,m,p-Ph*), 131.5 (*C*(1′)), 134.5 (*i-Ph*), 147.7, 148.9 (*C*(3′), *C*(4′)), 166.5 (N*C*OPh), 171.6 (*C*(1)); *m/z* (ESI$^+$) 422 ([M+Na]$^+$, 25%), 400 (30%), 344 (100%); HRMS (ESI$^+$) $C_{23}H_{30}NO_5^+$ ([M+H]$^+$) requires 400.2118; found 400.2128.

4.2.5. (*R*)-3-Benzamido-6,7-dimethoxy-1-tetralone 38

Step 1: TFA (3 mL) was added dropwise to **36** (300 mg, 0.75 mmol) at rt, and the resultant solution was stirred at rt for 1 h. Volatiles were then removed in vacuo to give **37** as a white solid (254 mg, quant); mp 162-164 °C; $[\alpha]_D^{25}$ +39.6 (*c* 1.0 in DMSO); ν_{max} (KBr) 3687-2481, 3302, 2938, 2837, 1695, 1643, 1519, 1490, 1465, 1443, 1419, 1263, 1157, 1027, 807, 695; δ_H (400 MHz, d_6-DMSO) 2.46 (1H, dd, *J* 15.4, 7.6, C(2)*H*$_A$), 2.53 (1H, dd, *J* 15.4, 6.2, C(2)*H*$_B$), 2.72-2.85 (2H, m, C(4)*H*$_2$), 3.63 (3H, s, O*Me*), 3.66 (3H, s, O*Me*), 4.46 (1H, m, C(3)*H*), 6.73 (1H, dd, *J* 8.1, 1.8, *Ar*), 6.81 (1H, d, *J* 1.8, *Ar*), 6.84 (1H, d, *J* 8.1, *Ar*), 7.42-7.55 (3H, m, *Ph*), 7.77-7.79 (2H, m, *Ph*), 8.32 (1H, d, *J* 8.2, N*H*); δ_C (100 MHz, d_6-DMSO) 39.7 (*C*(2)), 40.6 (*C*(4)), 49.1 (*C*(3)), 56.0, 56.2 (O*Me*), 112.5, 113.8, 122.0 (C(2′), *C*(5′), *C*(6′)), 128.0, 129.0, 131.9, 132.0 (*o,m,p-Ph*, *C*(1′)), 135.5 (*i-Ph*), 148.1, 149.2 (*C*(3′), *C*(4′)), 166.5 (N*C*OPh), 173.4 (*C*(1)); *m/z* (ESI$^+$) 366 ([M+Na]$^+$, 20%), 344 (100%); HRMS (ESI$^+$) $C_{19}H_{22}NO_5^+$ ([M+H]$^+$) requires 344.1492; found 344.1504.

Step 2: Oxalyl chloride (0.10 mL, 1.10 mmol) was added dropwise to a stirred solution of the residue of **37** (170 mg, 0.50 mmol) in CH_2Cl_2 (10 mL) at rt, followed by one drop of DMF. Stirring was continued at rt until all the solid dissolved and the evolution of gas ceased (≈ 30 min). The resultant solution was then

cooled to 0 °C and $SnCl_4$ (0.20 mL, 1.75 mmol) was added dropwise. The resultant solution was allowed to warm to rt and stirred at rt for 16 h. H_2O (5 mL) was then added and the resultant mixture was stirred vigorously for 10 min. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organics were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 10→20→40% EtOAc in pentane) gave **38** as a pale yellow crystalline solid (117 mg, 72% from **36**); mp 124-126 °C; $[\alpha]_D^{25}$ −20.0 (*c* 0.45 in $CHCl_3$); ν_{max} (KBr) 3308, 3062, 2944, 2841, 1667, 1636, 1602, 1580, 1537, 1513, 1368, 1277, 1217, 1050, 693; δ_H (400 MHz, $CDCl_3$) 2.77 (1H, dd, *J* 16.8, 8.4, C(2)H_A), 2.99 (1H, dd, *J* 16.8, 4.1, C(2)H_B), 3.04 (1H, dd, *J* 15.0, 7.6, C(4)H_A), 3.37 (1H, dd, *J* 15.0, 4.0, C(4)H_B), 3.93 (3H, s, O*Me*), 3.96 (3H, s, O*Me*), 4.83 (1H, m, C(3)*H*), 6.35 (1H, d, *J* 7.5, N*H*), 6.71 (1H, s, C(5)*H*), 7.40-7.52 (3H, m, *Ph*), overlapping 7.52 (1H, s, C(8)*H*), 7.70-7.72 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 35.3 (*C*(4)), 43.8 (*C*(3)), 46.2 (*C*(2)), 55.9, 56.0 (O*Me*), 108.3 (*C*(8)), 110.9 (*C*(5)), 125.2 (*C*(8a)), 126.8, 128.5, 131.6 (*o*,*m*,*p*-*Ph*), 134.0 (*i*-*Ph*), 135.4 (*C*(4a)), 148.4, 154.2 (*C*(6), *C*(7)), 167.0 (N*C*OPh), 194.3 (*C*(1)); *m/z* (ESI^+) 348 ($[M+Na]^+$, 70%), 326 (100%); HRMS (ESI^+) $C_{19}H_{20}NO_4^+$ ($[M+H]^+$) requires 326.1387; found 326.1397.

4.2.6. 3,4-Methylenedioxyphenylacetaldehyde 41

Step 1: KO^tBu (6.48 g, 66.6 mmol) was added portionwise to a stirred suspension of $[MeOCH_2PPh_3]^+[Cl]^-$ (12.6 g, 36.6 mmol) in THF (50 mL) at 0 °C. The resultant mixture was stirred for 30 min at rt and then a solution of piperonal (5.00 g, 33.3 mmol) in THF (50 mL) was added dropwise. The resultant mixture was stirred at rt for 12 h and then quenched by addition of satd aq NH_4Cl (50 mL). The aqueous layer was extracted with Et_2O (3 × 75 mL) and the combined organics were washed with brine (2 × 100 mL), then dried and concentrated *in vacuo*. Pentane (50 mL) was added to the residue and the resultant suspension was stirred at rt for 30 min. The resultant solution was filtered and the filtrate was concentrated in vacuo. This trituration process was repeated three times to give **40** {65:35 dr [(*E*):(*Z*) ratio]} as a pale yellow oil (5.93 g).
Step 2: Formic acid (12.5 mL) was added to a stirred solution of the residue of **40** (5.93 g) in CH_2Cl_2 (50 mL) at rt. The resultant solution was stirred in the dark for 48 h. H_2O (25 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 35 mL). The combined organics were washed with brine (2 × 100 mL), then dried and concentrated in vacuo. Purification by vacuum distillation gave **41** as a pale yellow oil (4.37 g, 80% from piperonal); δ_H (400 MHz, $CDCl_3$) 3.61 (2H, d, *J* 2.3, CH_2CHO), 5.97 (2H, s, OCH_2O), 6.66-6.70 (2H, m, C(2)*H*, C(5)*H*), 6.81 (1H, d, *J* 7.8, C(6)*H*), 9.72 (1H, app td, *J* 2.3, 0.6, C*H*O).

4.2.7. *tert*-Butyl (*E*)-4-(3′,4′-methylenedioxyphenyl)but-2-enoate 42

$(EtO)_2P(O)CH_2CO_2{}^tBu$ (9.63 mL, 41.0 mmol), LiCl (9.70 g, 229 mmol) and $^iPr_2NEt$ (6.55 mL, 37.6 mmol) were added sequentially to a stirred solution of **41** (5.61 g, 34.2 mmol) in MeCN (100 mL) at rt. The resultant suspension was stirred at rt for 48 h and then quenched by addition of H_2O (100 mL). The resultant mixture was extracted with EtOAc (3 × 100 mL) and the combined organics were washed with brine (100 mL), dried and concentrated *in vacuo* to give a 98:2 mixture of **42** and **43**, respectively. Purification via flash column chromatography (eluent 2.5% Et_2O in pentane) gave **42** as a colourless oil {8.25 g, 92%, >99:1 dr [(*E*):(*Z*) ratio]}; ν_{max} (film) 1712; δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, C*Me*$_3$), 3.41 (2H, dd, *J* 6.7, 1.4, C(4)*H*$_2$), 5.71 (1H, dt, *J* 15.5, 1.4, C(2)*H*), 5.95 (2H, s, OC*H*$_2$O), 6.63 (1H, dd, *J* 7.9, 1.4, C(6′)*H*), 6.66 (1H, d, *J* 1.4, C(2′)*H*), 6.66 (1H, d, *J* 7.9, C(5′)*H*), 6.85 (1H, dd, *J* 15.5, 6.7 C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 38.0 (*C*(4)), 80.2 (*C*Me$_3$), 100.9 (O*C*H$_2$O), 108.3 (*C*(5′)), 109.3 (*C*(2′)), 121.7 (*C*(6′)), 123.9 (*C*(2)), 131.6 (*C*(1′)), 146.1 (*C*(3′)), 146.2 (*C*(4′)), 147.8 (*C*(3)), 165.8 (*C*(1)); *m/z* (ESI^+) 285 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{15}H_{18}NaO_4^+$ ($[M+Na]^+$) requires 285.1097; found 285.1097.

4.2.8. *tert*-Butyl (*R*,*R*)-3-[*N*-benzyl-*N*-(α-methylbenyl)amino]-4-(3′,4′-methylenedioxyphenyl)butanoate 44

BuLi (2.5 M in hexanes, 1.65 mL, 2.65 mmol) was added dropwise via syringe to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (577 mg, 2.73 mmol, >99% ee) in THF (20 mL) at −78 °C. The resultant pink solution was stirred for 30 min at −78 °C. A solution of **42** {448 mg, 1.71 mmol, >99:1 dr [(*E*):(*Z*) ratio]} in THF (5 mL) at −78 °C was then added dropwise via cannula. The resultant solution was stirred at −78 °C for 2 h then quenched with satd aq NH_4Cl (20 mL). The resultant mixture was diluted with Et_2O (20 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organics were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 5% Et_2O in pentane) gave **44** as a colourless oil (582 mg, 72%, >99:1 dr); $[\alpha]_D^{20}$ −7.7 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 1724; δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 7.0, C(α)*Me*), 1.42 (9H, s, C*Me*$_3$), 1.99 (1H, dd, *J* 14.3, 4.4, C(2)*H*$_A$), 2.04 (1H, dd, *J* 14.3, 7.1, C(2)*H*$_B$), 2.55 (1H, dd, *J* 13.6, 6.0, C(4)*H*$_A$), 2.69 (1H, dd, *J* 13.6, 8.0, C(4)*H*$_B$), 3.62 (1H, d, *J* 15.0, NC*H*$_A$H$_B$Ph), 3.85 (1H, q, *J* 7.0, C(α)*H*), 3.90 (1H, d, *J* 15.0, NCH$_A$*H*$_B$Ph), 4.32 (1H, app dd, *J* 10.4, 4.7, C(3)*H*), 5.96 (2H, s, OC*H*$_2$O), 6.61 (1H, dd, *J* 7.8, 1.5, C(6')*H*), 6.64 (1H, d, *J* 1.5, C(2')*H*), 6.75 (1H, d, *J* 7.8, C(5')*H*), 7.24-7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.8 (C(α)*Me*), 28.1 (C*Me*$_3$), 37.6 (*C*(2)), 39.4 (*C*(4)), 50.0 (N*C*H$_2$Ph), 53.1 (*C*(α)), 59.6 (*C*(3)), 80.2 (*C*Me$_3$), 100.9 (O*C*H$_2$O), 108.8 (*C*(5')), 109.1 (*C*(2')), 121.9 (*C*(6')), 126.4, 126.8, 128.0, 128.3 (*o*,*m*,*p*-*Ph*), 134.1 (*C*(1')), 137.1, 145.4, 145.9, 147.4 (*C*(3'), *C*(4'), *i*-

Ph), 171.4 (*C*(1)); *m/z* (ESI$^+$) 474 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{36}NO_4^+$ ([M+H]$^+$) requires 476.2639; found 476.2639.

4.2.9. *tert*-Butyl (*R*)-3-benzamido-4-(3',4'-methylenedioxyphenyl)butanoate 46

Step 1: $Pd(OH)_2/C$ (1.85 g, 50% w/w substrate) was added to a stirred, degassed solution of **44** (3.70 g, 7.81 mmol) in EtOAc (100 mL). The reaction vessel was charged with H_2 (1 atm) and the resultant suspension was stirred rapidly for 12 h. The suspension was filtered through a pad of Celite® (eluent EtOAc) and the filtrate was concentrated in vacuo to give **45** as a pale yellow oil (1.77 g). Purification of an aliquot via flash column chromatography (eluent Et_2O) gave an analytically pure sample of **45** as a pale yellow oil; $[\alpha]_D^{25}$ −1.8 (*c* 0.8 in $CHCl_3$); ν_{max} (film) 1724; δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, C*Me*$_3$), 2.22 (1H, dd, *J* 15.8, 8.8, C(2)*H*$_A$), 2.40 (1H, dd, *J* 15.8, 4.2, C(2)*H*$_B$), 2.51 (1H, dd, *J* 13.5, 8.2, C(4)*H*$_A$), 2.67 (1H, dd, *J* 13.5, 5.5, C(4)*H*$_B$), 3.33-3.40 (1H, m, C(3)*H*), 5.94 (2H, s, OC*H*$_2$O), 6.65 (1H, dd, *J* 7.9, 1.6, C(6')*H*), 6.70 (1H, d, *J* 1.6, C(2')*H*), 6.75 (1H, d, *J* 7.9, C(5')*H*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 43.0 (*C*(2)), 43.5 (*C*(4)), 49.8 (*C*(3)), 80.7 (*C*Me$_3$), 100.9 (OCH$_2$O), 108.4 (*C*(5')), 109.6 (*C*(6')), 127.3 (*C*(2')), 132.4 (*C*(1')), 146.1 (*C*(4')), 147.7 (*C*(3')), 171.8 (*C*(1)); *m/z* (ESI$^+$) 280 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{22}NO_4^+$ ([M+H]$^+$) requires 280.3389, found 280.1543.

Step 2: Et_3N (2.21 mL, 15.8 mmol) and benzoyl chloride (0.77 mL, 6.65 mmol) were added sequentially to a stirred solution of the residue of **45** (1.77 g, 6.34 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The resultant solution was stirred at 0 °C for 10 min, then allowed to warm to rt and stirred for an additional 16 h. 10% aq HCl (50 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were dried and concentrated *in vacuo*. Purification by flash column chromatography (eluent 5% Et_2O in pentane) gave **46** as a colourless oil (2.19 g, 73% from **44**); $[\alpha]_D^{25}$ −8.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1724, 1663; δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, C*Me*$_3$), 2.43 (1H, dd, *J* 15.8, 5.6, C(2)*H*$_A$), 2.49 (1H, dd, *J* 15.8, 5.2, C(2)*H*$_B$), 2.77 (1H, dd, *J* 13.6, 8.2, C(4)*H*$_A$), 2.96 (1H, dd, *J* 13.6, 6.0, C(4)*H*$_B$), 4.52-4.60 (1H, m, C(3)*H*), 5.87 (2H, s, OC*H*$_2$O), 6.63-6.71 (3H, m, C(2')*H*, C(5')*H*, C(6')*H*), 7.19 (1H, d, *J* 8.6, *Ph*), 7.34-7.38 (2H, m, *Ph*), 7.74 (2H, d, *J* 7.3, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 38.0 (*C*(2)), 39.7 (*C*(4)), 48.2 (*C*(3)), 81.3 (*C*Me$_3$), 100.8 (OCH$_2$O), 108.2 (*C*(5')), 109.4 (*C*(6')), 122.3 (*C*(2')), 126.9, 128.5, 131.4 (*o,m,p-Ph*), 131.5 (*C*(1')), 134.6 (*i-Ph*), 146.3 (*C*(3')), 147.7 (*C*(4')), 166.6 (N*C*OPh), 171.4 (*C*(1)); *m/z* (ESI$^+$) 442 ([M+NH$_4$+MeCN]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{25}NNaO_5^+$ ([M+Na]$^+$) requires 406.1625; found 406.1622.

4.2.10. (*R*)-3-Benzamido-6,7-methylenedioxy-1-tetralone 48

Step 1: TFA (20 mL) was added dropwise to **36** (2.19 g, 5.71 mmol) at rt, and the resultant solution was stirred at rt for 1 h. Volatiles were then removed in vacuo to give **47** as a white solid (1.87 g, quant); mp 74-78 ºC (dec); $[\alpha]_D^{25}$ +31.4 (*c* 0.8 in $CHCl_3$); ν_{max} (film) 1731, 1633; δ_H (400 MHz, *d*$_4$-MeOH) 2.60 (2H, app d, *J* 6.8, C(2)*H*$_2$), 2.87 (2H, app d, *J* 7.3, C(4)*H*$_2$), 4.57-4.64 (1H, m, C(3)*H*), 5.89 (2H, s, OC*H*$_2$O), 6.71 (2H, app d, *J* 1.0, *Ar*), 6.78 (1H, app t, *J* 1.0, *Ar*), 7.40-7.45 (2H, m, *Ph*), 7.48-7.52 (1H, m, *Ph*), 7.71-7.74 (2H, m, *Ph*); δ_C (100 MHz, *d*$_4$-MeOH) 38.2 (*C*(2)), 40.0 (*C*(4)), 49.2 (*C*(3)), 101.2 (O*C*H$_2$O), 108.1 (*C*(6')), 109.6 (*C*(2')), 122.5 (*C*(5')), 127.3, 128.5, 131.6 (*o,m,p-Ph*), 132.2 (*C*(1')), 134.9 (*i-Ph*), 146.7 (*C*(4')), 148.1 (*C*(3')), 168.9 (N*C*OPh), 174.1 (*C*(1)); *m/z* (ESI^-) 326 ($[M-H]^-$, 100%); HRMS (ESI^+) $C_{18}H_{17}NNaO_5^+$ ($[M+Na]^+$) requires 350.0999; found 350.0997.

Step 2: Oxalyl chloride (0.15 mL, 1.73 mmol) was added dropwise to a stirred solution of the residue of **47** (200 mg, 1.58 mmol) in CH_2Cl_2 (10 mL) at rt, followed by one drop of DMF. Stirring was continued at rt until all the solid dissolved and the evolution of gas ceased (≈ 30 min). The resultant solution was then cooled to 0 °C and $SnCl_4$ (0.58 mL, 3.15 mmol) was added dropwise. The resultant solution was allowed to warm to rt and stirred at rt for 16 h. H_2O (5 mL) was then added and the resultant mixture was stirred vigorously for 10 min. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organics were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 25% EtOAc in pentane) gave **48** as a white solid (517 mg, 77% from **46**); mp 197-200 °C; $[\alpha]_D^{25}$ −16.5 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 1724, 1660; δ_H (400 MHz, $CDCl_3$) 2.74 (1H, dd, *J* 16.8, 8.7, C(2)*H*$_A$), 2.98 (1H, dd, *J* 16.8, 3.8, C(2)*H*$_B$), 3.01 (1H, dd, *J* 16.0, 7.9, C(4)*H*$_A$), 3.32 (1H, dd, *J* 16.0, 4.1, C(4)*H*$_B$), 4.78 (1H, app tq, *J* 8.3, 4.2, C(3)*H*), 6.04 (2H, s, OC*H*$_2$O), 6.38 (1H, d, *J* 7.5, N*H*), 6.69 (1H, s, C(5)*H*), 7.41 (2H, app t, *J* 7.5, *Ph*), 7.46 (1H, s, C(8)*H*), 7.49 (1H, tt, *J* 7.5, 2.0, *Ph*), 7.71 (2H, app d, *J* 7.1, *Ph*); δ_C (100 MHz, $CDCl_3$) 35.9 (*C*(4)), 44.1 (*C*(2)), 46.1 (*C*(3)), 101.9 (O*C*H$_2$O), 106.2 (*C*(8)), 108.7 (*C*(5)), 126.9, 128.6, 131.7 (*o,m,p-Ph*), 127.6 (*C*(8a)), 134.1 (*i-Ph*), 137.6 (*C*(4a)), 147.6, 152.8 (*C*(6), *C*(7)), 167.2 (N*C*OPh), 193.9 (*C*(1)); *m/z* (ESI^+) 322 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{18}H_{15}NNaO_4^+$ ($[M+Na]^+$) requires 322.0893; found 322.0893.

4.2.11. 3-Benzyloxy-4-methoxyphenylacetaldehyde 51

Step 1: KO^{t}Bu (2.32 g, 20.6 mmol) was added portionwise to a stirred suspension of $[MeOCH_2PPh_3]^+[Cl]^-$ (7.78 g, 22.7 mmol) in THF (50 mL) at 0 °C. The resultant mixture was stirred for 30 min at rt and then a solution of *O*-benzylisovanillin (5.00 g, 20.6 mmol) in THF (50 mL) was added dropwise. The resultant mixture was stirred at rt for 12 h and then quenched by addition of satd aq NH_4Cl (50 mL). The aqueous layer was extracted with Et_2O (3 × 75 mL) and the combined organics were washed with brine (2 × 100 mL),

then dried and concentrated *in vacuo*. Pentane (100 mL) was added to the residue and the resultant suspension was stirred at rt for 30 min. The resultant solution was filtered and the filtrate was concentrated in vacuo. This trituration process was repeated three times to give **50** {56:44 dr [(*E*):(*Z*) ratio]} as a white powder (3.17 g).

Step 2: Formic acid (12.5 mL) was added to a stirred solution of the residue of **40** (3.17 g) in CH_2Cl_2 (50 mL) at rt. The resultant solution was stirred in the dark for 48 h. H_2O (25 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 35 mL). The combined organics were washed with brine (2 × 100 mL), then dried and concentrated in vacuo. Purification by vacuum distillation gave **51** as a colourless oil (3.00 g, 57% from *O*-benzylisovanillin); ν_{max} (film) 1722; δ_H (250 MHz, $CDCl_3$) 3.60 (2H, s, C*H*$_2$CHO), 3.92 (3H, s, O*Me*), 5.17 (2H, s, OC*H*$_2$Ph), 6.79 (1H, dd, *J* 8.2, 2.1, C(6)*H*), 6.83 (1H, d, *J* 2.1, C(2)*H*), 6.93 (1H, d, *J* 8.2, C(5)*H*), 7.34-7.49 (5H, m, *Ph*), 9.70 (1H, app t, *J* 2.4, C*H*O); δ_C (62.5 MHz, $CDCl_3$) 50.4 (*C*H_2CHO), 56.5 (O*Me*), 71.5 (O*C*H_2Ph), 112.6 (*C*(2)), 115.8 (*C*(5)), 122.9 (*C*(6)), 124.4 (*C*(1)), 127.8, 128.4, 129.0 (*o,m,p-Ph*), 137.3 (*i-Ph*), 148.9, 149.6 (*C*(3), *C*(4)), 200.0 (*C*HO); *m/z* (GC ToF CI$^+$) 274 ([M+NH_4]$^+$, 100%), 257 (61%); HRMS (GC ToF CI$^+$) $C_{16}H_{17}O_3^+$ ([M+H]$^+$) requires 257.1172; found 257.1178.

4.2.12. *tert*-Butyl (*E*)-4-(3′-benzyloxy-4′-methoxyphenyl)but-2-enoate 52

A solution of **51** (3.02 g, 11.8 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a stirred solution of $Ph_3P{=}CHCO_2{}^tBu$ (4.44 g, 11.8 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The resultant solution was stirred at rt for 12 h and then concentrated in vacuo. The residue was suspended in a mixture of Et_2O (10 mL) and pentane (10 mL), and the resultant suspension was stirred at rt for 30 min. The resultant solution was filtered and the filtrate was concentrated in vacuo. This trituration process was repeated three times to give a >95:5 mixture of **52** and **53**, respectively. Purification via flash column chromatography (eluent 10% Et_2O in pentane) gave **52** as a colourless oil {2.96 g, 71%, >99:1 dr [(*E*):(*Z*) ratio]}; ν_{max} (film) 1709; δ_H (400 MHz, $CDCl_3$) 1.50 (9H, s, C*Me*$_3$), 3.39 (2H, dd, *J* 6.7, 1.5, C(4)*H*$_2$), 3.87 (3H, s, O*Me*), 5.14 (2H, s, OC*H*$_2$Ph), 5.70 (1H, dt, *J* 15.5, 1.5, C(2)*H*), 6.73-6.76 (2H, m, C(2′)*H*, C(6′)*H*), 6.85 (1H, d, *J* 8.6, C(5′)*H*), 6.97 (1H, dt, *J* 15.5, 6.7, C(3)*H*), 7.31-7.47 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.3 (C*Me*$_3$), 34.4 (*C*(4)), 56.1 (O*Me*), 71.1 (O*C*H_2Ph), 80.1 (*C*Me$_3$), 112.1 (*C*(5′)), 115.0 (*C*(2′)), 121.5 (*C*(6′)), 123.8 (*C*(2)), 127.4, 127.9, 128.6 (*o,m,p-Ph*), 130.4 (*C*(1′)), 137.1 (*i-Ph*), 146.3 (*C*(3)), 148.2 (*C*(4′)), 148.5 (*C*(3′)), 165.9 (*C*(1)); *m/z* (ESI$^+$) 377 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{26}NaO_4^+$ ([M+Na]$^+$) requires 377.1723; found 377.1726.

4.2.13. *tert*-Butyl (*R*,*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(3′-benzyloxy-4′-methoxyphenyl)butanoate 54

BuLi (2.5 M in hexanes, 5.28 mL, 8.44 mmol) was added dropwise via syringe to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.85 g, 8.71 mmol, >99% ee) in THF (40 mL) at −78 °C. The resultant pink solution was stirred for 30 min at −78 °C. A solution of **52** {1.94 g, 5.44 mmol, >99:1 dr [(*E*):(*Z*) ratio]} in THF (10 mL) at −78 °C was then added dropwise via cannula. The resultant solution was stirred at −78 °C for 2 h then quenched with satd aq NH_4Cl (20 mL). The resultant mixture was diluted with Et_2O (50 mL). The aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organics were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 5% Et_2O in pentane) gave **54** as a colourless oil (2.03 g, 47%, >99:1 dr); $[\alpha]_D^{25}$ +24.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1725; δ_H (400 MHz, $CDCl_3$) 1.11 (3H, d, *J* 7.1, C(α)*Me*), 1.43 (9H, s, C*Me*$_3$), 2.00-2.03 (2H, m, C(2)*H*$_2$), 2.55 (1H, dd, *J* 13.6, 5.8, C(4)*H*$_A$), 2.67 (1H, dd, *J* 13.6, 8.1, C(4)*H*$_B$), 3.60-3.64 (2H, m, C(3)*H*, NC*H*$_A$H$_B$Ph), 3.83 (1H, q, *J* 7.1, C(α)*H*), 3.89-3.93 (1H, m, NCH$_A$*H*$_B$Ph) overlapping 3.92 (3H, s, O*Me*), 5.07 (1H, d, *J* 12.1, OC*H*$_A$H$_B$Ph), 5.11 (1H, d, *J* 12.1, OCH$_A$*H*$_B$Ph), 6.72-6.75 (1H, m, C(2′)*H*), 6.84-6.87 (1H, m, C(6′)*H*), 7.22-7.50 (16H, m, C(5′)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.8 (C(α)*Me*), 28.1 (C*Me*$_3$), 37.6 (*C*(2)), 39.2 (*C*(4)), 50.0 (N*C*H$_2$Ph), 56.2 (O*Me*), 56.7 (*C*(3)), 58.1 (*C*(α)), 70.9 (O*C*H$_2$Ph), 80.0 (*C*Me$_3$), 111.6 (*C*(5')), 115.4 (*C*(2')), 122.2 (*C*(6')), 126.6, 126.9, 127.4, 127.8, 127.9, 128.1, 128.2, 128.5, 133.3 (*Ar*), 137.3, 141.5, 143.1 (*i-Ph*), 147.8 (*C*(3')), 147.9 (*C*(4')), 171.9 (*C*(1)); *m/z* (ESI$^+$) 566 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{37}H_{44}NO_4^+$ ([M+H]$^+$) requires 566.3265; found 566.3266.

4.2.14. *tert*-Butyl (*R*)-3-benzamido-4-(3′-benzoyloxy-4′-methoxyphenyl)butanoate 56

Step 1: Pd/C (406 mg, 20% w/w substrate) was added to a stirred, degassed solution of **54** (2.03 g, 3.59 mmol) in MeOH (60 mL), AcOH (6 mL) and H_2O (1.5 mL). The reaction vessel was charged with H_2 (1 atm) and the resultant suspension was stirred rapidly for 12 h. The suspension was filtered through a pad of Celite® (eluent MeOH) and the filtrate was concentrated in vacuo to give **55** as a pale yellow oil. Purification of an aliquot via flash column chromatography (eluent 40% CH_2Cl_2 in MeOH) gave an analytically pure sample of **55** as a colourless oil; $[\alpha]_D^{25}$ +2.9 (*c* 1.3 in $CHCl_3$); ν_{max} (film) 1724; δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, C*Me*$_3$), 2.25 (1H, dd, *J* 16.1, 8.6, C(2)*H*$_A$), 2.39 (1H, dd, *J* 16.1, 4.2, C(2)*H*$_B$), 2.48 (1H, dd, *J* 13.4, 8.1, C(4)*H*$_A$), 2.63 (1H, dd, *J* 13.4, 5.5, C(4)*H*$_B$), 3.32-3.38 (1H, m, C(3)*H*), 3.79 (1H, s, O*Me*), 6.61 (1H, d, *J* 8.1, C(5′)*H*), 6.70 (1H, d, *J* 1.5, C(2′)*H*), 6.74 (1H, dd, *J* 8.1, 1.5, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 42.4 (*C*(2)), 42.6 (*C*(4)), 49.6 (*C*(3)), 55.8 (O*Me*), 80.6 (*C*Me$_3$), 111.1 (*C*(6′)), 116.2 (*C*(2′)), 120.3

(*C*(5′)), 131.4 (*C*(1′)), 146.0 (*C*(3′)), 146.2 (*C*(4′)), 171.8 (*C*(1)); *m/z* (ESI$^+$) 282 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{24}NO_4^+$ ([M+H]$^+$) requires 282.1700; found 282.1701.

Step 2: Et_3N (1.22 mL, 8.71 mmol) and benzoyl chloride (0.42 mL, 3.66 mmol) were added sequentially to a stirred solution of the residue of **55** (490 mg, 1.74 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The resultant solution was stirred at 0 °C for 10 min, then allowed to warm to rt and stirred for an additional 16 h. 10% aq HCl (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent pentane/EtOAc/Et_3N, 75:25:1) gave **56** as a colourless oil (605 mg, 71% from **54**); $[\alpha]_D^{25}$ +2.9 (*c* 1.6 in $CHCl_3$); ν_{max} (film) 1731, 1644; δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, C*Me*$_3$), 2.50 (1H, dd, *J* 15.7, 5.5, C(2)H_A), 2.54 (1H, dd, *J* 15.7, 5.1, C(2)H_B), 2.86 (1H, dd, *J* 13.7, 8.5, C(4)H_A), 3.06 (1H, dd, *J* 13.7, 5.8, C(4)H_B), 3.79 (3H, s, O*Me*), 4.59-4.67 (1H, m, C(3)*H*), 6.96 (1H, d, *J* 8.5, C(5′)*H*), 7.07 (1H, d, *J* 2.1, C(2′)*H*), 7.13 (1H, dd, *J* 8.5, 2.1, C(6′)*H*) 7.40-7.53 (5H, m *Ph*), 7.61-7.65 (1H, m, *Ph*), 7.77-7.78 (2H, m, *Ph*), 8.19-8.21 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 37.9 (*C*(2)), 38.1 (*C*(4)), 48.1 (*C*(3)), 56.0 (O*Me*), 81.4 (*C*Me$_3$), 112.6 (*C*(5′)), 114.1 (*C*(2′)), 124.1, 126.9, 127.1, 127.6, 128.5, 129.4, 130.2, 131.4 (*o,m,p-Ph*, *C*(1′), *C*(6′)), 133.5, 134.5 (*i-Ph*), 139.8 (*C*(3′)), 150.1 (*C*(4′)), 164.7 (O*C*OPh), 166.6 (N*C*OPh), 171.5 (*C*(1)); *m/z* (ESI$^+$) 512 ([M+Na]$^+$, 100%), 490 (85%); HRMS (ESI$^+$) $C_{29}H_{31}NNaO_6^+$ ([M+Na]$^+$) requires 512.2044, found 512.2042.

4.2.15. (*R*)-3-Benzamido-6-hydroxy-7-methoxytetral-1-one 58

Step 1: NaOMe was prepared by the slow addition of small pieces of sodium (20 mg, 0.89 mmol) to MeOH (5 mL), stirring at rt. Once the sodium had reacted (*ca* 10 min), the resultant solution was colled to 5 °C and a solution of **56** (87 mg, 0.18 mmol) in MeOH (4 mL) was added dropwise. The resultant solution was stirred at 5 ºC for 1 h, then poured into a solution of 10% aq. citric acid (25 mL). The resultant slurry was extracted with EtOAc (3 ×20 mL) and the combined organics were washed with brine (30 mL), dried and concentrated *in vacuo*. TFA (1 mL) was added dropwise to the residue and the resultant solution was stirred at rt for 1 h. Volatiles were then removed in vacuo to give **57** as a colourless oil (59 mg, quant); $[\alpha]_D^{25}$ +2.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3395, 1667, 1641, 1585; δ_H (400 MHz, d_4-MeOH) 2.59 (2H, d, *J* 6.8, C(2)H_2), 2.79-2.95 (2H, m, C(4)H_2), 3.81 (3H, s, O*Me*), 4.57-4.64 (1H, m, C(3)*H*), 6.70 (1H, dd, *J* 8.1, 1.6, C(6′)*H*), 6.76 (1H, d, *J* 1.6, C(2′)*H*), 6.83 (1H, d, *J* 8.1, C(5′)*H*), 7.41-7.52 (3H, m, *Ph*), 7.73 (2H, d, *J* 7.3, *Ph*); δ_C (100 MHz, d_4-MeOH) 39.6 (*C*(2)), 42.9 (*C*(4)), 49.2 (*C*(3)), 55.5 (O*Me*), 111.8 (*C*(5′)), 116.4 (*C*(2′)), 120.7 (*C*(6′)), 127.8, 128.5, 131.0 (*o,m,p-Ph*), 131.6 (*C*(1′)), 135.0 (*i-Ph*), 146.4 (*C*(4′)), 146.8 (*C*(3′)), 168.1 (N*C*OPh), 176.7 (*C*(1)); *m/z* (ESI$^-$) 328 ([M−H]$^-$, 100%); HRMS (ESI$^+$) $C_{18}H_{19}NNaO_5^+$ ([M+Na]$^+$) requires 352.1155; found 352.1155.

Step 2: Oxalyl chloride (0.02 mL, 0.24 mmol) was added dropwise to a stirred solution of the residue of **57** (39 mg, 0.12 mmol) in CH_2Cl_2 (10 mL) at rt, followed by one drop of DMF. Stirring was continued at rt until all the solid dissolved and the evolution of gas ceased (≈ 30 min). The resultant solution was then cooled to 0 °C and $SnCl_4$ (0.03 mL, 0.24 mmol) was added dropwise. The resultant solution was allowed to warm to rt and stirred at rt for 16 h. H_2O (5 mL) was then added and the resultant mixture was stirred vigorously for 10 min. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organics were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 25% EtOAc in pentane) gave **58** as a colourless oil (25 mg, 69% from **56**); $[\alpha]_D^{25}$ −10.4 (*c* 0.6 in $CHCl_3$); ν_{max} (film) 3402, 1721, 1662, 1591; δ_H (400 MHz, $CDCl_3$) 2.72 (1H, dd, *J* 15.7, 8.4, C(2)H_A), 2.92 (1H, dd, *J* 15.7, 4.2, C(2)H_B), 3.07 (1H, dd, *J* 16.0, 7.7, C(4)H_A), 3.30 (1H, dd, *J* 16.0, 5.1, C(4)H_B), 3.79 (3H, s, O*Me*), 4.76-4.79 (1H, m, C(3)*H*), 6.42 (1H, br d, *J* 7.6, N*H*), 6.70 (1H, s, C(5)*H*), 7.40-7.43 (2H, m, *Ph*), 7.47 (1H, s, C(8)*H*), 7.46-7.48 (1H, m, *Ph*), 7.73 (2H, app d, *J* 7.5, *Ph*); δ_C (100 MHz, $CDCl_3$) 34.9 (*C*(4)), 44.5 (*C*(2)), 47.8 (*C*(3)), 56.2 (O*Me*), 105.9 (*C*(8)), 108.8 (*C*(5)), 126.7, 128.5, 131.5 (*o*,*m*,*p*-*Ph*), 127.4 (*C*(8a)), 134.4 (*i*-*Ph*), 137.3 (*C*(4a)), 152.4 (*C*(6)), 154.6 (*C*(7)), 167.3 (N*C*OPh), 195.7 (*C*(1)); *m/z* (ESI^-) 310 ($[M-H]^-$, 100%); HRMS (ESI^+) $C_{18}H_{17}NNaO_4^+$ ($[M+Na]^+$) requires 334.1050; found 334.1058.

4.2.16. *tert*-Butyl (*R*)-3-benzamido-4-(3′,4′-dimethoxyphenyl-6′-bromo)butanoate 60

A solution of bromine (320 mg, 2.00 mmol) in $CHCl_3$ (10 mL) was added dropwise to a solution of **37** (400 mg, 1.00 mmol) in $CHCl_3$ (25 mL) at rt. The resultant solution was stirred at rt for 30 min and then H_2O (20 mL) was added. The aqueous layer was separated and extracted with $CHCl_3$ (3 × 20 mL). The combined organics were washed with satd aq $Na_2S_2O_4$ (30 mL), then dried and concentrated *in vacuo*. Purification via recrystallisation (25% Et_2O in pentane) gave **60** as a white solid (502 mg, 97%); $C_{23}H_{28}BrNO_5$ requires C, 57.75; H, 5.9; N, 2.9%; found C, 58.1; H, 6.1; N, 3.0%; mp 132-134 °C; $[\alpha]_D^{25}$ +80.7 (*c* 0.30 in DMSO); ν_{max} (KBr) 3291, 3061, 2999, 2978, 2934, 2909, 1715, 1640, 1603, 1579, 1533, 1511, 1260, 1222, 1166, 1036, 800, 698; δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, CMe_3), 2.58 (1H, dd, *J* 15.1, 5.1, C(2)H_A), 2.64 (1H, dd, *J* 15.1, 4.9, C(2)H_B), 3.07 (1H, dd, *J* 13.9, 7.7, C(4)H_A), 3.14 (1H, dd, *J* 13.9, 7.0, C(4)H_B), 3.80 (3H, s, O*Me*), 3.85 (3H, s, O*Me*), 4.68-4.72 (1H, m, C(3)*H*), 6.82 (1H, s, *Ar*), 7.00 (1H, s, *Ar*), 7.18 (1H, d, *J* 8.7, N*H*), 7.41-7.52 (3H, m, *Ph*), 7.76 (2H, d, *J* 7.2, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.1 (CMe_3), 38.4 (*C*(2)), 39.2 (*C*(4)), 47.6 (*C*(3)), 56.0, 56.1 (O*Me*), 81.5 (*C*Me$_3$), 113.5, 114.6, 115.3 (*C*(2′), *C*(5′), *C*(6′)), 126.9, 128.6, 129.4 (*o*,*m*,*p*-*Ph*), 131.5 (*C*(1′)), 134.4 (*i*-*Ph*), 148.1, 148.4 (*C*(3′), *C*(4′)), 166.6 (N*C*OPh), 171.5 (*C*(1)); *m/z* (ESI^+) 478 ($[M+H]^+$, 70%), 422 (100%); HRMS (ESI^+) $C_{23}H_{29}BrNO_5^+$ ($[M+H]^+$) requires 478.1224; found 478.1229.

4.2.17. Attempted preparation of (*R*)-3-benzamido-5-bromo-7,8-dimethoxy-1-tetralone 62

Step 1: TFA (5 mL) was added dropwise to **60** (500 mg, 1.05 mmol) at rt, and the resultant solution was stirred at rt for 1 h. Volatiles were then removed in vacuo to give **61** as a white solid (440 mg, quant); $C_{19}H_{20}BrNO_5$ requires C, 54.0; H, 4.8; N, 3.3%; found C, 53.8; H, 4.9; N, 3.2%; mp 188-190 °C; $[\alpha]_D^{25}$ +78.8 (*c* 0.95 in DMSO); ν_{max} (KBr) 3491-2821, 3280, 3001, 2960, 2934, 2841, 1714, 1646, 1604, 1579, 1539, 1506, 1440, 1382, 1260, 1242, 1223, 1205, 1167, 1036, 873, 797, 702; δ_H (400 MHz, d_6-DMSO) 2.52 (1H, dd, *J* 15.2, 7.7, C(2)H_A), 2.59 (1H, dd, *J* 15.2, 6.1, C(2)H_B), 2.88 (1H, dd, *J* 13.8, 9.1, C(4)H_A), 2.96 (1H, dd, *J* 13.8, 5.3, C(4)H_B), 3.61 (3H, s, O*Me*), 3.71 (3H, s, O*Me*), 4.60 (1H, m, C(3)*H*), 6.95 (1H, s, *Ar*), 7.07 (1H, s, *Ar*), 7.42-7.52 (3H, m, *Ph*), 7.75-7.77 (2H, m, *Ph*), 8.34 (1H, d, *J* 8.7, N*H*); δ_C (100 MHz, d_6-DMSO) 40.2, 40.4 (*C*(2), *C*(4)), 47.6 (*C*(3)), 56.2, 56.6 (O*Me*), 114.8, 115.3, 116.2 (*C*(2′), *C*(5′), *C*(6′)), 127.9, 129.1, 130.5 (*o,m,p-Ph*), 132.0 (*C*(1′)), 135.3 (*i-Ph*), 148.6, 148.8 (*C*(3′), *C*(4′)), 166.6 (N*C*OPh), 173.2 (*C*(1)); *m/z* (ESI^+) 422 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{21}BrNO_5^+$ ($[M+H]^+$) requires 422.0598; found 422.0623.

Step 2: Oxalyl chloride (0.07 mL, 0.79 mmol) was added dropwise to a stirred solution of the residue of **61** (150 mg, 0.36 mmol) in CH_2Cl_2 (5 mL) at rt, followed by one drop of DMF. Stirring was continued at rt until all the solid dissolved and the evolution of gas ceased (≈ 30 min). The resultant solution was then cooled to 0 °C and $SnCl_4$ (0.09 mL, 0.79 mmol) was added dropwise. The resultant solution was allowed to warm to rt and stirred at rt for 16 h. H_2O (5 mL) was then added and the resultant mixture was stirred vigorously for 10 min. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organics were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 10→20→40% EtOAc in pentane) gave **38** as a pale yellow crystalline solid (90 mg, 77%).

4.2.18. *tert*-Butyl (*R*)-3-benzamido-4-(3′,4′-dimethoxyphenyl-6′-chloro)butanoate 63

SO_2Cl_2 (0.10 mL, 1.25 mmol) was added dropwise to a solution of **37** (500 mg, 1.25 mmol) in CH_2Cl_2 (30 mL) at rt. H_2O (20 mL) was added after 1 h, and the aqueous layer was separated and extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were washed with brine (30 mL), then dried and concentrated *in vacuo*. Purification via recrystallisation (25% Et_2O in pentane) gave **63** as a white solid (498 mg, 94%); $C_{23}H_{28}ClNO_5$ requires C, 63.7; H, 6.5; N, 3.2%; found C, 63.6; H, 6.8; N, 3.3%; mp 134-136 °C; $[\alpha]_D^{25}$ +57.4 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 3350, 3060, 2969, 2933, 2841, 1715, 1639, 1604, 1580, 1532, 1516, 1458, 1439, 1389, 1366, 1264, 1222, 1208, 1168, 1143, 1045, 975, 812, 697; δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, CMe_3), 2.57 (1H, dd, *J* 16.4, 5.3, C(2)H_A), 2.62 (1H, dd, *J* 16.4, 5.1, C(2)H_B), 3.06 (1H, dd, *J* 14.0, 7.6, C(4)H_A), 3.12 (1H, dd, *J* 14.0, *J* 7.4, C(4)H_B), 3.80 (3H, s, O*Me*), 3.84 (3H, s, O*Me*), 4.66-4.70 (1H, m,

C(3)*H*), 6.80 (1H, s, *Ar*), 6.84 (1H, s, *Ar*), 7.18 (1H, d, *J* 8.5, N*H*), 7.41-7.51 (3H, m, *Ph*), 7.75-7.77 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 36.7 (*C*(4)), 38.3 (*C*(2)), 47.6 (*C*(3)), 56.1 (O*Me*), 81.4 (*C*Me$_3$), 112.3, 113.5, 125.1 (*C*(2′), *C*(5′), *C*(6′)), 126.8, 127.5, 128.6 (*o,m,p-Ph*), 131.5 (*C*(1′)), 147.9, 148.3 (*C*(3′), *C*(4′)), 166.6 (N*C*OPh), 171.5 (*C*(1)); *m/z* (ESI^+) 434 ($[M+H]^+$, 70%), 378 (100%); HRMS (ESI^+) $C_{23}H_{29}ClNO_5^+$ ($[M+H]^+$) requires 434.1729; found 434.1731.

4.2.19. (*R*)-3-Benzamido-5-chloro-7-methoxy-8-hydroxy-1-tetralone 65

Step 1: TFA (5 mL) was added dropwise to **63** (400 mg, 0.92 mmol) at rt, and the resultant solution was stirred at rt for 1 h. Volatiles were then removed in vacuo to give **64** as a white solid (343 mg, quant); $C_{19}H_{20}ClNO_5$ requires C, 60.4; H, 5.3; N, 3.7%; found C, 60.2; H, 5.1; N, 3.9%; mp 202-204 °C; $[\alpha]_D^{25}$ +74.6 (*c* 1.0 in DMSO); ν_{max} (KBr) 3281, 2999, 2960, 2935, 2842, 1712, 1642, 1604, 1579, 1536, 1506, 1441, 1387, 1262, 1242, 1224, 1206, 1169, 1039, 873, 701; δ_H (400 MHz, d_6-DMSO) 2.52 (1H, dd, *J* 15.2, 7.7, C(2)H_A), 2.59 (1H, dd, *J* 15.2, *J* 6.3, C(2)H_B), 2.87 (1H, dd, *J* 13.7, 9.0, C(4)H_A), 2.97 (1H, dd, *J* 13.7, 5.2, C(4)H_B), 3.62 (3H, s, O*Me*), 3.75 (3H, s, O*Me*), 4.57-4.61 (1H, m, C(3)*H*), 6.93 (1H, s, *Ar*), 6.95 (1H, s, *Ar*), 7.49-7.56 (3H, m, *Ph*), 7.75-7.77 (2H, m, *Ph*), 8.35 (1H, d, *J* 8.7, N*H*); δ_C (100 MHz, d_6-DMSO) 37.7 (*C*(4)), 40.3 (*C*(2)), 47.6 (*C*(3)), 56.3, 56.6 (O*Me*), 113.3, 115.3, 125.0 (*C*(2′), *C*(5′), *C*(6′)), 128.0, 128.6, 129.0 (*o,m,p-Ph*), 132.0 (*C*(1′)), 135.4 (*i-Ph*), 148.1, 148.7 (*C*(3′), *C*(4′)), 166.4 (N*C*OPh), 173.2 (*C*(1)); *m/z* (ESI^+) 378 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{21}ClNO_5^+$ ($[M+H]^+$) requires 378.1103; found 378.1107.

Step 2: Oxalyl chloride (0.08 mL, 0.41 mmol) was added dropwise to a stirred solution of the residue of **61** (140 mg, 0.37 mmol) in CH_2Cl_2 (10 mL) at rt, followed by one drop of DMF. Stirring was continued at rt until all the solid dissolved and the evolution of gas ceased (≈ 30 min). The resultant solution was then cooled to 0 °C and $AlCl_3$ (172 mg, 1.30 mmol) was added portionwise. The resultant solution was allowed to warm to rt and stirred at rt for 16 h. H_2O (5 mL) was then added and the resultant mixture was stirred vigorously for 10 min. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organics were dried and concentrated in vacuo. Purification via recrystallisation (20% EtOAc in pentane) gave **65** as a pale yellow crystalline solid (110 mg, 86%); mp 218-220 °C (dec); $[\alpha]_D^{25}$ −3.7 (*c* 0.60 in DMSO); ν_{max} (KBr) 3420, 3290, 3057, 3025, 2962, 2944, 2903, 2836, 1641, 1603, 1579, 1529, 1467, 1437, 1334, 1250, 827, 814, 727, 694; δ_H (400 MHz, $CDCl_3$) 2.92 (1H, dd, *J* 17.2, 8.8, C(2)H_A), 3.11 (1H, dd, *J* 17.2, 3.2, C(2)H_B), 3.03 (1H, dd, *J* 16.8, 8.0, C(4)H_A), 3.43 (1H, dd, *J* 16.8, *J* 4.0, C(4)H_B), 3.91 (3H, s, O*Me*), 4.79-4.83 (1H, m, C(3)*H*), 6.23 (1H, d, *J* 7.1, N*H*), 7.10 (1H, s, C(6)*H*), 7.42-7.55 (3H, m, *Ph*), 7.72-7.74 (2H, m, *Ph*), 12.73 (1H, s, O*H*); δ_H (400 MHz, d_6-DMSO) 2.92-3.00 (3H, m, C(2)H_2, C(4)H_A), 3.25 (1H, dd, *J* 16.4, 4.3, C(4)H_B), 3.82 (3H, s, O*Me*), 4.50-4.54 (1H, m, C(3)*H*), 7.34 (1H, s, C(6)*H*), 7.43-7.57 (3H, m, *Ph*), 7.85-

7.87 (2H, m, *Ph*), 8.78 (1H, d, *J* 7.2, N*H*), 12.67 (1H, br s, O*H*); δ_C (100 MHz, d_6-DMSO) 32.8 (*C*(4)), 44.2 (*C*(2)), 45.5 (*C*(3)), 57.1 (O*Me*), 117.7, 122.3 (*C*(5), *C*(8a)), 119.6 (*C*(6)), 128.3, 129.1, 130.4, 132.2 (*C*(4a), *o,m,p-Ph*), 135.0 (*i-Ph*), 147.9, 152.3 (*C*(7), *C*(8)), 167.1 (N*C*OPh), 204.8 (*C*(1)); *m/z* (ESI^+) 368 ($[M+Na]^+$, 100%), 346 ($[M+H]^+$, 65%), 279 (40%), 225 (40%); HRMS (ESI^+) $C_{18}H_{17}ClNO_4^+$ ($[M+H]^+$) requires 346.0841; found 346.0856.

References and Notes

[1] Vecchietti, V.; Casagrande, C.; Ferrari, G.; Danieli, B.; Palmisano, G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 578.

[2] Sivakumaran, M.; Gopinath, K. W. *Indian. J. Chem.* **1976**, *14B*, 150.

[3] Bhakuni, D. S.; Mangla, V. K.; Singh, A. N.; Kapil, R. S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 267.

[4] Bhakuni, D. S.; Singh, A. N. *Tetrahedron* **1979**, *35*, 2365.

[5] Sebiferine is also known as *O*-methylflavinantine; see: (a) Kametani, T.; Kukumoto, K.; Satoh, F.; Yagi, H. *J. Chem. Soc. C* **1969**, 520. (b) Bick, I. R. C.; Leow, H. W.; Preston, N. W.; Wright, J. J. *Austral. J. Chem.* **1973**, *26*, 455. (c) Tackie, A. N.; Dwuma-Badu, D.; Knapp, J. E.; Slatkin, D. J.; Schiff Jr., P. L. *Phytochemistry* **1974**, *13*, 2884.

[6] Charles, B.; Guinaudeau, H.; Bruneton, J.; Cabalion, P. *Can. J. Chem.* **1989**, *67*, 1257.

[7] Shang, X. Y.; Shi, J. G.; Yang, Y.C.; Liu, X.; Li, C.; Zhang, C. Z. *Yaoxue Xuebao* **2003**, *38*, 276.

[8] Ünsal, Ç. Eroğlu, E.; Şerbetçi, T.; Mat, A.; Sarıyar, G. *Biochem. Syst. Ecol.* **2008**, *36*, 497.

[9] The isolation of "racemic 8,14-dihydroamurine" (albeit without relative stereochemistry) from *Papaver nudicale* L. has also been reported, see: Philipov, S.; Istatkova, R.; Yadamsurenghiin, G.-O.; Samdan, J.; Dangaa, S. *Nat. Prod. Res.* **2007**, *21*, 852.

[10] Boit, H.-G.; Flentje, H. *Naturwiss.* **1959**, *46*, 514.

[11] Boit, H.-G.; Flentje, H. *Naturwiss.* **1960**, *47*, 180.

[12] Flentje, H.; Döpke, W.; Jeffs, P. W. *Naturwiss.* **1965**, *52*, 259.

[13] Döpke, W.; Flentje, H. *Tetrahedron* **1968**, *24*, 4459.

[14] Öztekin, A.; Hocquemiller, Cavé, A. *J. Nat. Prod.* **1984**, *47*, 560.

[15] Kametanim, T.; Ihara, M.; Honda, T. *J. Chem. Soc. D, Chem. Commun.* **1969**, 1301.

[16] Chu, J.-H.; Lo, S.-Y.; Chu, Y.-L. *Acta Chimica Sinica* **1964**, *30*, 265.

[17] Hsu, J.-S.; Lo, S.-Y.; Chu, J.-H. *Scientia Sinica* **1964**, *13*, 2016.

[18] Stuart, K. L.; Chambers, C.;Byfield, D. *J. Chem. Soc. C* **1969**, 1681.

[19] Sertuerner, F. *Trommsdorff's Journal der Pharmazie* **1805**, *13*, 234.

[20] Rice, K. C. in *The Chemistry and Biology of Isoquinoline Alkaloids*, Eds Phillipson, J. D.; Roberts, M. F.; Zenk, M. H. **1985**, pp191.

[21] Davies, S. G.; Goddard, E. C.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Synlett* **2015**, *26*, 1541.

[22] For other applications of this approach to these carbocylces, see: (a) Horton, W. J.; Thompson, G. *J Am. Chem. Soc.* **1954**, *76*, 1909. (b) Zymalkowski, P.; Dornhege, E. *Tetrahedron Lett.* **1968**, *55*, 5743. (c) Fries, D. S.; Bertelli, D. J. *J. Med. Chem.* **1982**, *55*, 216. (d) Rault, S; Dallemange, P.; Robba. *Bull. Soc. Chim. Fr.* **1987**, *6*, 1079. (e) Gmeiner, P.; Hummel, E. *Synthesis* **1994**, 1026. (f) Kimbara, K.; Katsumata, Y.; Saigo, K. *Chem Lett.* **2002**, 266.

[23] Levine, S. G. *J. Am. Chem. Soc.* **1958**, *80*, 6150.

[24] Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

[25] Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1999.

[26] For instance, see: (a) Coote, S. J.; Davies, S. G.; Middlemiss, D.; Naylor, A. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2223. (b) Coote, S. J.; Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Chem. Asian J.* **2010**, *5*, 589.

[27] Cyclisation of 3-phenyl-4-(3′-methoxyphenyl)butanoic acid proceeds exclusively at the C(6′)-position (i.e., *para* to the OMe group), see: (a) Malik, M. S.; Rastogi, S. N. *Indian J. Chem.* **1984**, *23B*, 834. However, the related cyclisation of 3-methyl-4-(3′-methoxy-6′-bromophenyl)butanoic acid proceeds exclusively at the C(2′)-position (i.e., *ortho* to the OMe group), see: (b) Nishiyama, T.; Kameoka, H. *Chem. Express* **1991**, *6*, 109.

[28] Cyclisation of 3-(3′,4′-dimethoxy-6′-chlorophenyl)butanoic acid proceeds exclusively at the C(2′)-position, see: (a) Gosh, R.; Robinson, R. *J. Chem. Soc.* **1944**, 506. (b) Trauner, D.; Bats, J. W.; Werner, A.; Mulzer, J. *J. Org. Chem.* **1998**, *63*, 5908.

[29] Bolton, R.; de la Mare, P. B. D. *J. Chem. Soc. B* **1967**, 1044.

[30] For examples, see: (a) Watson, W. D. *J. Org. Chem.* **1985**, *50*, 2145. (b) Reiter, L.; Berg, G. E. *Heterocycles* **1992**, *34*, 771. (c) Smith, K.; Tzimas, M.; Brown, C. M.; Payne, K. *Sulfur Lett.* **1999**, *22*, 89.

[31] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.