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Spirocyclic tetramates by sequential Knoevenagel and [1,5]-prototropic shift

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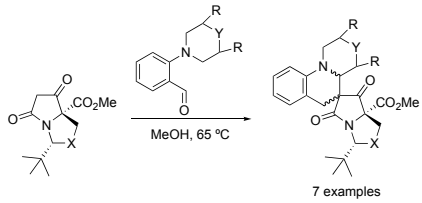
Keywords: Spirocycles; Tetramates; Antibacterial



Highly functionalised spirocyclic tetramates were prepared *via* a sequential Knoevenagel reaction and [1,5]-prototropic shift (T-reaction) of bicyclic tetramates. While these compounds isomerise in solution, stable analogues can be prepared *via* appropriate choice of substituents. Further modification of these compounds allows for introduction of aromatic groups, making them suitable as skeletons suitable for application in medicinal chemistry.

1. Introduction

It is now widely appreciated that the antibacterial drug pipeline is poorly populated,[1–3] that models for antibacterial drug development need revision,[4–8] and that the emergence of antibacterial resistance creates a constant need for new drugs.[9–11] Therefore, the identification of suitable and effective drug discovery paradigms has become urgent.[12–18] Recently, spiropyrimidinetrione PNU-286607 **1** (Figure 1) was reported to have a broad spectrum antibacterial activity, including against fluoroquinoline resistant strains, and a novel mode of action.[19] It was shown to target the β subunit of bacterial type II topoisomerases *via* a novel mechanism of inhibition. The common pharmacophore of the class has been extended to include **2**,[20,21] **3**[22] and AZD0914 **4**[23] (Figure 1). The (-)-enantiomer exhibits both the highest antibacterial activity along with the highest inhibitory effects, while the (+)-isomer is inactive. More recently, **4** has also shown high activity against the multidrug-resistant *Neisseria gonorrhoeae*, giving it the potential to combat the growing public health concern of gonorrhea.[24,25]

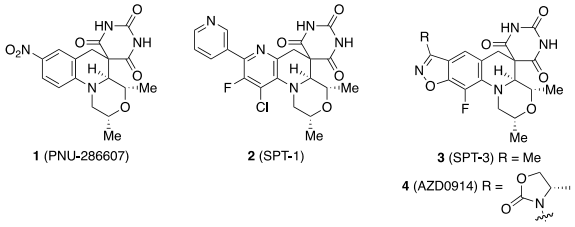
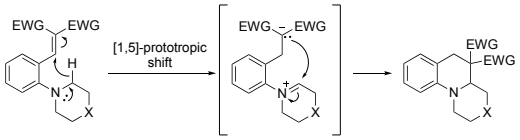


Figure 1. Examples of biologically active spiropyrimidinetriones.

The synthesis of these systems relies on a very effective intramolecular cyclisation, known as the "T-reaction" or the "*t*-amino effect",[26] which involves a suprafacial [1,5]-prototropic shift followed by carbon-carbon bond formation (Scheme 1). The transformation is promoted when a tertiary aromatic amine is substituted with an *ortho*-electron-poor double bond, and it has been successfully employed to access a range of tricyclic quinoline systems with multiple stereocentres.[27–30] The asymmetric synthesis of **1** has been developed by Hurd and co-workers,[31] where *trans*-dimethylmorpholine was used as a source of asymmetry, and the reaction was driven towards the thermodynamic product where the substituents in the morpholine ring were equatorial. This proceeded *via* isomerisation of the initial kinetic intermediate. While the barbiturate nucleus is well suited to this process,[31–33] given our interest in related tetramates both for antibacterial drug discovery[34] and for the generation of novel 3-D drug templates,[35] we examined them for their suitability in the T-reaction. Access to spirocyclic tetramates has been rarely reported.[36–39] In our case, an additional level complexity is added by the chiral nature of the tetramate, as opposed to the non-chiral barbiturate, which converts the spirocentre into yet another quaternary carbon.

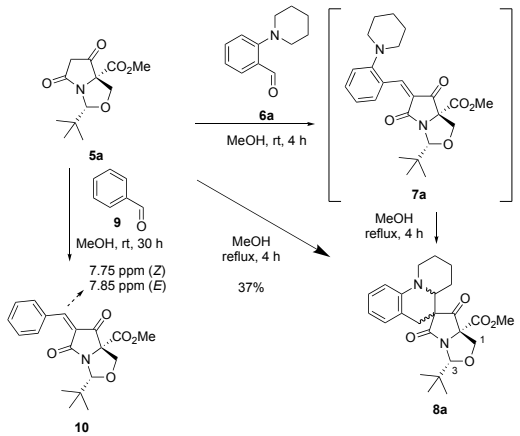


Scheme 1. Generalized T-reaction.

2. Results and Discussion

2.1. Synthesis of spirocyclic tetramates

The synthesis of the required bicyclic tetramate cores **5a,b** (Schemes 2 and 3), which are readily available from serine and cysteine, has been reported.[40] The required *o*-aminobenzaldehydes **6a-d** were obtained by reaction of cyclic amines with *o*-fluorobenzaldehyde using literature methodology (Scheme 3).[41]

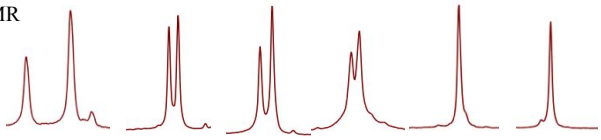


Scheme 2. Synthesis of spirocyclic tetramate **8a** and alkylidene **10**.

In the first attempt to access the spirocyclic tetramate, it was found that upon mixing tetramate **5a** with aldehyde **6a** in methanol at reflux and subsequent cooling, spontaneous

precipitation took place to afford spiro-tetramate **8a** (Scheme 2). The isolated product was found to be a mixture of diastereoisomers, which were quantified by the *H*(1) doublets and the *H*(3) singlet. Interestingly, the number of isomers and the diastereomeric ratio changed depending on the solvent used (Table 1). While non-polar solvents (C_6D_6, tol-d_8) gave a single isomer (minor isomer <2%), with DMSO and acetone 3 isomers were observed. These data suggest that **8a** obtained as a precipitate is a single isomer, but that it may isomerise upon dissolution.

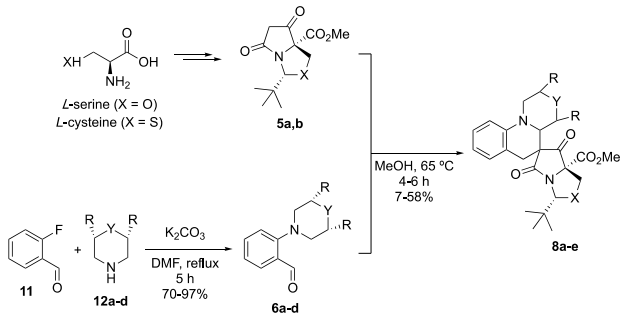
Table 1. Solvent dependence of the number of isomers of **8a**. Spectra recorded 5-10 min after dissolving the precipitate.

Solvent	DMSO-d_6	Acetone-d_6	$CDCl_3$	DCM-d_2	Tol-d_8	C_6D_6
No. isomers	3	3	2	2	1	1
H(3) NMR peaks*						
d.r.	3:6:1	5:5:1	4:6		-	-

*Only 4.8-5.2 ppm shown

In an attempt to isolate the presumed alkylidene intermediate **7a**, **5a** and **6a** were stirred at room temperature in methanol, but purification of **7a** proved challenging as it cyclised to **8a** both during *flash* column chromatography and in chloroform-*d*. That formation of **7a**, which would be expected from initial Knoevenagel condensation, was feasible, was shown by reaction of tetramate **5a** with benzaldehyde **9**. Under the same conditions, the alkylidene product **10** was isolated as a 1.2:1 mixture of the *E* and *Z* isomers (Scheme 2). The characteristic vinylic protons (7.75 – 7.85 ppm) of product **10** were not present in crude **8a**, which supports that the multiple products observed by NMR correspond to isomers of the spirocycle, and do not include intermediate **7a**.

Treatment of tetramates **5a,b** with a range of amines **6a-d** (prepared by the reaction of *o*-fluorobenzaldehyde with amines **12a-d**) following the same procedure (reflux in MeOH followed by precipitation and filtration) furnished spirocyclic tetramates **8a-e** in 7-58% yield (Scheme 3 and Table 2). The morpholine analogues **8c-e** were isolated at lower yields than that aliphatic derivatives **8a,b**.



Scheme 3. Synthesis of aromatic amines **6a-d** and spirocyclic tetramates **8a-e**.

Examination of the cyclisation under alternative literature procedures was made, but refluxing in either ^{n}butanol at 117 °C[31] or in EtOH/H_2O,[42] or adding pyrrolidine as a catalyst,[43] resulted in either lower yield or no isolated product.

Table 2. Synthesis of spirocyclic tetramates **8a-e**.

Compound	X	Y	R	Yield (%)	# isomers (C_6D_6)	d.r.
8a	O	CH_2	H	37	2	98:2
8b	O	-	H	58	1	-
8c	O	O	H	7	1	-
8d	O	O	CH_3	31	2	8:2
8e	S	O	CH_3	23	2	8:2

2.2. Investigation into isomerism

To investigate the stability of spirocycles **8a-e** in solution, the isolated precipitates where dissolved in C_6D_6, and NMR spectra were recorded over time (Figure 2). While all analogues had equilibrated to 4 diastereomers after 2 weeks, the rate of isomerisation and ratio of isomers was dependent on the nature of the azacycle. The fastest rates were observed for piperidine **8a**, which reached equilibrium after 24 h, and dimethyl-morpholine analogues **8d** and **8e**, where equilibration was reached after 3 days. For pyrrolidine **8b** and morpholine **8c**, new isomers were only observed after several days. Separation of the different isomers proved impossible, as the individual isomers had the same retention factors.

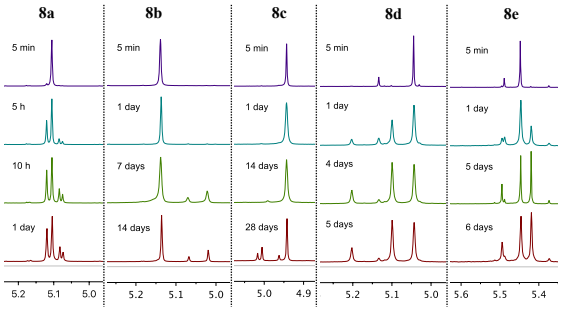
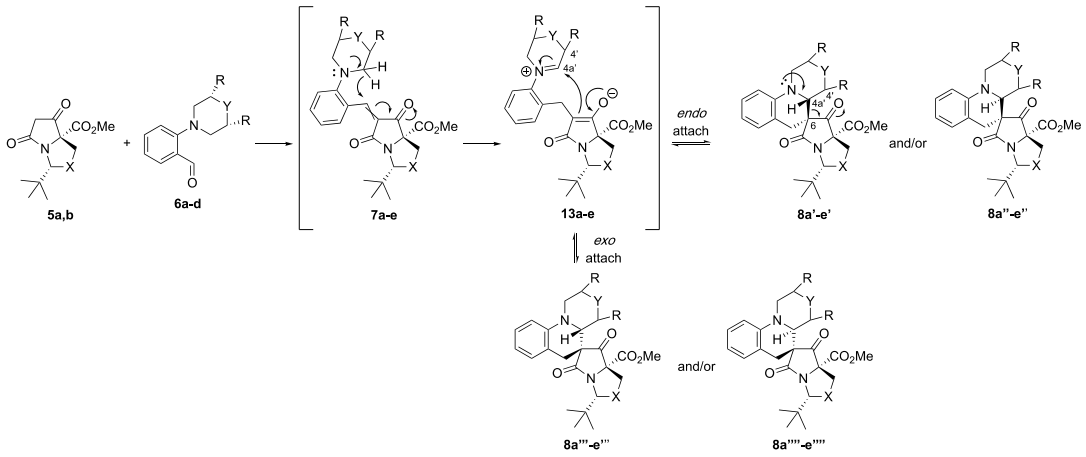


Figure 2. ^{1}H NMR spectra (in C_6D_6) of *H*(3) singlet of spirocyclic tetramates **8a-e** over time.

Isomerisation of these compounds probably involves an intramolecular mechanism where the spirocycle reverts to zwitterion **13** *via* a retro-Mannich type process, as indicated in Scheme 4. Such a phenomenon has been previously reported for related systems and has been utilised to access PNU-286607.[21,31] It should be noted that in that case, epimerisation also occurred at the morpholine methyl substituent ((*C*(4')-Me). For the spirocycles described herein, the formation of only 4 isomers for dimethyl-morpholine analogues **8d-e**, which is the same number as for the unsubstituted **8a-c**, suggests that no epimerisation at *C*(4') occurs and that only the 2 stereocentres *C*(4a') and *C*(6) epimerise. Importantly, Ruble *et al*. observed epimerisation only when the mixture was heated at temperatures over 80 °C,[31] and in our synthesis, spirocyclisation was performed at 65 °C.



Scheme 4. Suggested mechanism of cyclisation and isomerisation.

The observed tendency of these analogues to isomerise in solution led to the question of whether the initial isolated isomer obtained *via* precipitation was the kinetic product of the reaction, or whether it was the only isomer to precipitate under the reaction conditions. When solid **8d** was stirred in EtOAc at room temperature for 8 h, followed by concentration under vacuum, a mixture of 4 isomers was observed by NMR spectroscopy in C_6D_6 (Figure 3). Re-dissolution of the mixture in methanol led to the precipitation of only one of the isomers, and re-analysis of the filtrates indicated the presence of 3 isomers, including the precipitated one. These results seem to indicate that while all isomers could be formed during the reaction, only one of them precipitates out of methanol, and this could partly explain the low isolation yields.

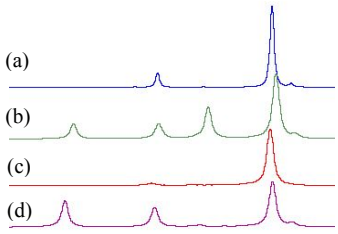
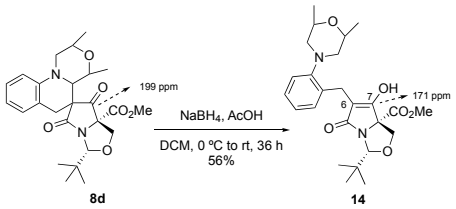


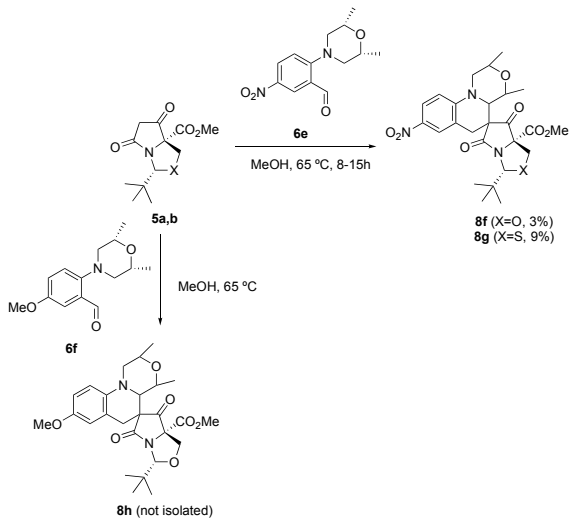
Figure 3. ^{1}H NMR spectra (in C_6D_6) of *H*(3) singlet of (a) precipitate **8d**, (b) **8d** stirred in EtOAc for 8 h, (c) mixture concentrated and precipitated in methanol, (d) the remaining filtrates.

An attempt was made to block the reverse process by reducing the tetramate ketone group, a reaction that can be conducted easily on simpler substrates.[40,44] However, reaction of **8d** with sodium borohydride gave not the desired alcohol, but instead ring opened product **14** (Scheme 5). The enol form was clearly indicated by the *C*(7) ^{13}C NMR chemical shift, as well as the lack of *C*(6) proton on the ^{1}H NMR spectrum. This product probably resulted from reduction of the iminium ion formed upon ring opening, and further supports that opening of the spirocycle is possible during isomerisation (Scheme 4).



Scheme 5. Reduction of ketone **8d**.

Of interest was the effect of the introduction of electron withdrawing or donating groups on the aromatic ring (Scheme 6). The nitro derivatives **8f** and **8g** were successfully synthesised using the previous method, but were isolated in low yields as 9:1 and 8:1 mixtures of diastereomers respectively. Nevertheless, these analogues did not isomerise in C_6D_6 over several weeks, and this is the first example of such a spirocyclic tetramate that is stable in solution. The electron withdrawing nitro groups could be deactivating the retro-Mannich reaction required to ring-open the spirocycle. A similar effect could also explain the lower yields of the transformation compared to the analogous **8d** and **8e**, as the low electron density on the amine can also decrease the rate of the initial [1,5]-hydride shift. Enhanced stability of the nitro analogues has also been previously observed in barbiturates.[45]



Scheme 6. Introduction of electron withdrawing (**8f,g**) and donating (**8h**) groups to spirocyclic tetramates.

On the other hand, no product precipitated from the reaction mixture for the methoxy derivative **8h**. NMR analysis of the

concentrated crude material showed a mixture of the alkylidene intermediate as well as a mixture of suspected isomers of the product, and it could be that the increased polarity of this analogue increases its solubility in methanol, preventing precipitation.

2.3. Stereochemical identification of the spirocyclic tetramates

Having shown that formation of spirocyclic tetramates is possible, of interest was the determination of their stereochemical identity. NOE analysis (Figure S1, SI) of the major isomer in the analogues where Z=H (**8a-c**) suggested that the azacycle is placed at the concave face of the bicyclic tetramate, as indicated by correlation between *H*(1)-*H*(4') or *H*(3)-*H*(4'). Conversely, for dimethyl-morpholine compounds **8d-g**, correlations were observed between *H*(1)-*H*(7') and/or *H*(3)-*H*(7'), indicative of the aromatic ring residing at the concave face of the bicycle.

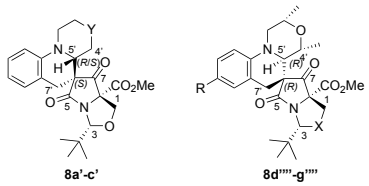


Figure 4. Major isomers of **8a-g** predicted from NOE interactions and CLIP-HSQMBC coupling constants.

Following the stereochemical determination at the spiro-centre, we turned our attention to the configuration of the other chiral centre, 5'. For this purpose, the isolated isomers were analysed by CLIP-HSQMBC. This NMR technique provides accurate measurements of long-range proton-carbon coupling constants,[46] which are dependent on the dihedral angle between the atoms.[47] A large ^3J (6 – 9 Hz) represents a dihedral angle tending to 180º, showing a pseudo-*trans* relationship, while a small ^3J is the result of a pseudo-*cis* relationship, with dihedral angles 20-70º. Samples were prepared in C_6D_6 directly before analysis. Analysis of the *H*(5')-*C*(5) and the *H*(5')-*C*(7) angles revealed that, in all compounds, *H*(5') is pseudo-cis to the amide carbonyl *C*(5), and pseudo-trans to ketone *C*(7) (Scheme 4).

To determine the stereochemistry of the additional chiral centres (2' and 4') in the analogues with a dimethyl-morpholine, the coupling constant between the 4' and 5' protons was examined. For all analogues, the ^3J was large (8.7 – 9.5 Hz), indicating a *trans*- configuration between the two protons, placing the methyl groups in the equatorial positions of the ring. Assuming that no epimerisation of these positions occurs during the reaction or upon isomerisation, both methyl groups should be *cis*- as in the starting amine **12d**.

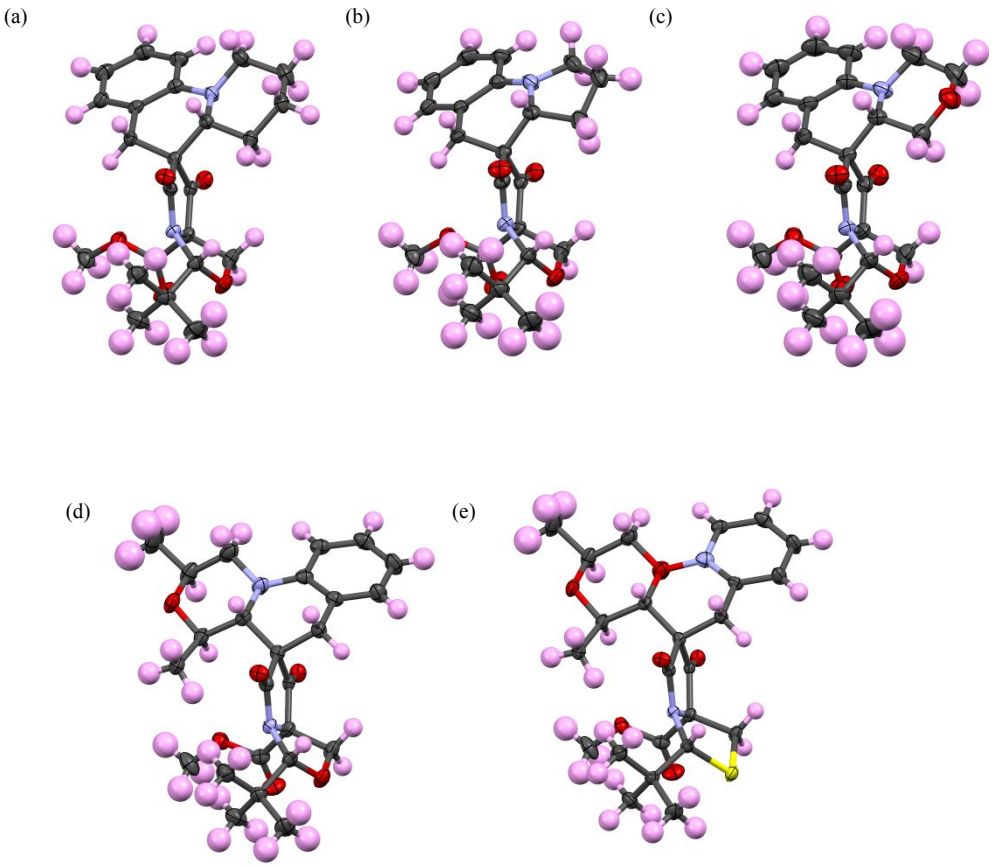


Figure 5. Structure of spirotetramates **8a** (a), **8b** (b), **8c** (c), **8d** (d) and **8e** (e) drawn from results of single crystal X-ray diffraction studies.[48] Displacement ellipsoids are drawn at 50% probability.

Therefore, the data from NOE correlations and the CLIP-HSQMBC coupling constants suggest that, when R=H, the major diasteroisomer corresponds to **8a-c**, while when R=Me the structure is **8d-g** (see Figure 4). The difference between these analogues could be due to the large steric hindrance when the additional methyl groups reside in the concave site of the bicycle, favouring in these latter cases the formation of a different isomer. It is worth noting that **8d** and **8e** had been shown to quickly isomerise in solution to an almost 1:1 mixture of another isomer. While the newly formed compounds could be the epimer at

spirocentre *C*(6), their complex NMR spectra impeded their precise stereochemical identification.

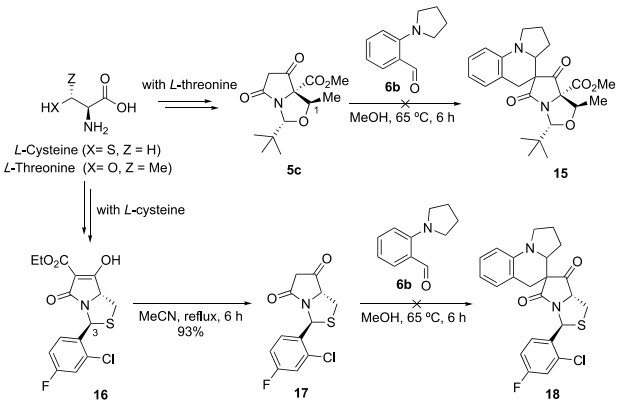
The absolute structure of the precipitates was determined using single crystal X-ray diffraction.[48] The stereochemistry at 5', 6, 2' and 4' were indeed as predicted for all the analogues, as shown in Figure 5. The torsion angles between *H*(5')-*C*(5) and *H*(5')-*C*(7) correlate with those calculated with CLIP-HSQMBC (Table S1).

2.4. Further functionalisation of the spirocyclic tetramates

Having prepared these examples of spirocyclic tetramates, and determined their stereochemistry, of interest was whether the methodology could be extended to (1) the preparation of different tetramate bicycles; (2) the introduction of acyclic amines; and (3) further modification of the aromatic ring.

2.4.1. Modification of the tetramate

Using *L*-threonine, the bicyclic tetramate can be prepared with an additional methyl group at *C*(1)[49] (Scheme 7). Treatment of tetramate **5c** with pyrrolidine aldehyde **6b** resulted in no precipitation of product, and NMR analysis of the crude mixture after removal of solvent showed recovered starting material. It appears that the extra methyl at the concave face of the bicycle imposes sufficient extra steric strain that formation of the spirocycle is prevented.

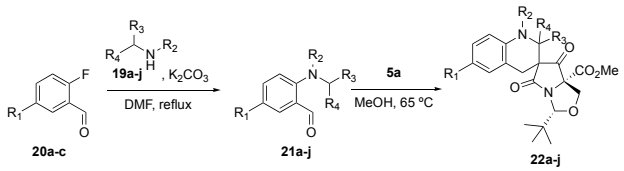


Scheme 7. Modification of the tetramate core *via* introduction of different groups at *C*(1) and *C*(3).

It has previously been shown that the tetramate **16** derived from cysteine may be prepared with aromatic groups at the *C*(3) position, and that in this case tetramate cyclisation leads to isomer **16**.[50] To obtain the *C*(6)-unsubstituted analogue suitable for spirocyclisation, ethyl ester **16** was refluxed to yield decarboxylated **17**. However, treatment with aldehyde **6b** resulted again in recovered starting material. These results differ from the observed rapid reaction of **5a,b** with aldehydes **6a-d**, and illustrate the strict steric requirements of these systems, where additional hindrance can lead to a complete loss of reactivity.

2.4.2. Introduction of acyclic amines

Thus far, the synthesised spirotetramates were derived from cyclic amines, and of interest was the extension to the introduction of non-cyclic amines. For this purpose, *o*-aminobenzaldehydes with a range of amines **19a-j** were synthesised (Scheme 8 and Table 3). Under the same conditions used to prepare **6a-d**, yields for **21a-j** were significantly reduced, and in particular as the size of the R groups increased. Thus, moving from R_2 = Me (**21b**) to Et (**21c**) led to a large drop in reactivity even at longer reaction times, and with ^{i}Pr (**21d**), only starting material was recovered. Other than steric constraints, substitution with these acyclic amines could also be less entropically favourable as compared to the cyclic ones.



Scheme 8. Preparation of spirotetramates with acyclic amines.

Table 3. Synthesis of spirotetramates **22** from acyclic amines **21**.

Entry	R_1	R_2	R_3	R_4	21		22	
					Yield [%]	Time [h]	Yield [%]	# isomers
a	H	Et	Me	H	18	24	7	2 (3:1)
b	H	Me	Me	Me	16	48	0	-
c	H	Et	Me	Me	traces	72	-	-
d	H	^{i}Pr	Me	Me	0	-	-	-
e	H	Me	Ph	H	12	48	0	-
f	H	Et	Ph	H	25	48	0	-
g	H	Me	Ph	Ph	0	-	-	-
h	H	Bn	Ph	H	7	24	43	4
i	NO_2	Et	Me	H	50	24	0	-
j	Br	Et	Me	H	47	24	0	-

With the aminobenzaldehydes in hand, spirocyclisation with **5a** was attempted under the previous reaction conditions. Unfortunately, in this case, no solid was formed upon cooling of the reaction mixture in any of the examples, and complex reaction mixtures were isolated after solvent evaporation. While the aldehyde had been consumed in all cases, some product by NMR and MS analysis was only seen in **21a** and **21h**, and these were purified by *flash* column chromatography to give **22a** and **22h** as a mixture of 2 and 4 isomers respectively. Product **22a** was chosen for stereochemical determination due to its simpler NMR spectrum. NOE analysis showed no correlations between protons *H*(1) or *H*(3) and *H*(5') or *H*(7'). It could be that the higher flexibility of the non-cyclic substituents leads to a less defined conformation, decreasing NOE correlations as compared to the cyclic **8a-g**. Having previously proven the reliability of CLIP-HSQMBC to predict the isomeric nature of **8a-g**, the same technique was employed for **22a**. The measured ^{3}J coupling constants of the major and minor isomers were compared to the predicted torsion angles of the favoured conformations obtained from the MM2 energy minimisation tool of ChemBio3D (Table S2, Figure S2). In this case, the major isomer was found to place the aromatic ring in the inner face of the ring (**22a**), and consistent with the previous observations, the minor isomer arises from isomerisation around the spirocentre to give **22a** (Figure 6).

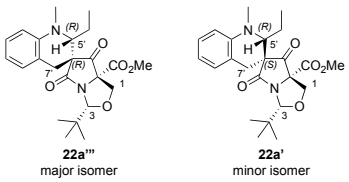
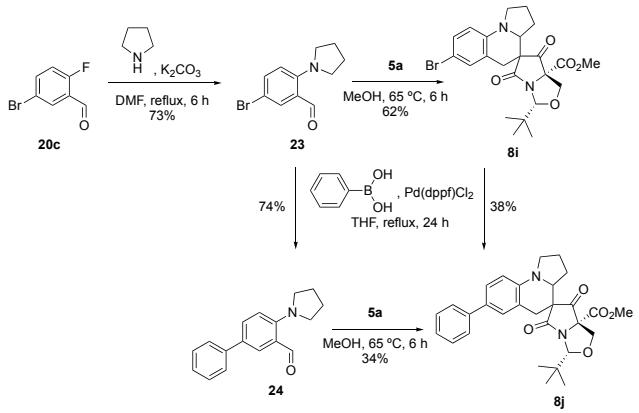


Figure 6. Isomers of **22a** based on the CLIP HSQMBC results.

2.4.3. Modification of the aromatic ring

Finally, it was also of interest to study the potential for functionalisation of the aromatic group. For this purpose, pyrrolidine aldehyde **23** was prepared, and reacted with tetramate **5a** to give spiro **8i** as a mixture of 4 diastereomers (Scheme 9). This could be converted by Suzuki coupling to phenyl derivative **8j** as a mixture of 4 diastereomers. When the order of the reactions was reversed by performing the Suzuki reaction first on **23** before spirocyclisation, the same mixture of 4 diastereomers was isolated, further confirming that these spirocyclic systems isomerise in solution.



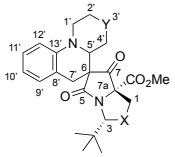
Scheme 9. Functionalisation of the aromatic ring *via* Suzuki coupling.

3. Conclusion

In summary, we have shown that the preparation of spirocyclic tetramates is possible, using a route that involves initial Knoevenagel condensation of tetramates **5a-c** with aminobenzaldehydes, followed by [1,5]-hydride shift. The products, which can be isolated as one major diastereomer, were found to isomerise in solution, and the stability was dependent on the solvent and on the nature of the azacycle. This equilibration can be blocked by introducing electron withdrawing groups onto the aromatic ring. The stereochemistry of the major isolated isomers was determined using NOE and CLIP-HSQMBC correlations, and confirmed by X-ray crystallography. Further modification of the tetramate moiety of these systems was challenging, but it was possible to introduce some acyclic amines and use Suzuki coupling.

4. Experimental section.

General methods. All reagents were obtained from commercial sources and used without further purification. Anhydrous solvents were dried by pre-storing them over activated 3 Å molecular sieves before being passed through an activated alumina column on a solvent tower under N_2 pressure. Analytical thin-layer chromatography (TLC) was carried out on Merck aluminum foil backed sheets precoated with 0.2 mm Kielselgel 60 F254. The spots were visualized by UV irradiation (λ 254 nm) and by staining with a $KMnO_4$ solution followed by heating. *Flash* column chromatography was performed on Kielselgel 60 silica gel (230−400 mesh particle size). Optical rotations were recorded at 25 °C on a polarimeter using the D line of sodium (589 nm) and a path length of 1 dm. Concentrations (c) are given in g/100 mL, and specific rotations ($[\alpha]_D^{25}$) are quoted in 10^{-1} deg cm^2 g^{-1}. Melting points were measured with a capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an FT-IR spectrometer; absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}) and only selected peaks are reported. ^{1}H NMR spectra were recorded 400, 500 and 600 MHz, and ^{13}C NMR spectra at 100 and 125 MHz. Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) and are referenced to the residual solvent peak ($CDCl_3$: δ 7.26 for ^{1}H NMR and δ 77.2 for ^{13}C NMR; C_6D_6: δ 7.16 for ^{1}H NMR and δ 128.1 for ^{13}C NMR). Coupling constants (*J*) are quoted in hertz. Two-dimensional COSY, NOE and HMBC experiments were recorded at 500 MHz. Low-resolution mass spectra (*m/z*) were recorded using electrospray ionization (ESI); selected peaks are reported in daltons and their intensities given as percentages of the base peak. High-resolution mass spectra (HRMS) were recorded using TOF (ESI, EI or CI). In the cases where the products exist as mixtures of tautomers or diastereomers, the ratio was calculated from the ^{1}H NMR spectrum. For the NMR assignment of the spirocyclic compounds, the following numbering has been employed to facilitate comparison between analogues. The bicyclic tetramate is numbered following IUPAC guidelines.



1.3 Synthetic procedures

Compounds **5a**,[51] **5b**,[52] **5c**[49] and **16**[50] were prepared using the reported methods.

General procedure A: Formation of *o*-aminobenzaldehydes

Potassium carbonate (1.2 equiv) and the desired amine (1.2 equiv) were added to a solution of the required *o*-fluorobenzaldehyde (1 equiv) in DMF (*c* 0.5 M). The reaction mixture was heated to reflux for 3-6 hours, and then left to cool to room temperature before being diluted with water. The aqueous layer was extracted with chloroform, and the organic layer was washed with water, dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The resulting oil was then eluted with 10% EtOAc in petrol through a silica plug to give the desired *o*-aminobenzaldehyde.

General procedure B: Spirocyclisation

The bicyclic tetramate **5a-c** (1 equiv) was added to a solution of *o*-aminobenzaldehyde (1.2 equi) in methanol (*c* 0.2 M) and the solution was heated to reflux for 2-6 h. The solution was then cooled to 0 °C and the product was precipitated out of solution. In the cases were no solid precipitates, the solvent was concentrated under reduced pressure.

2-(Piperidin-1-yl)benzaldehyde (6a)

General procedure A (5 h) from 2-fluorobenzaldehyde (170 μL, 1.61 mmol), piperidine (185 μL, 1.88 mmol) and potassium carbonate (263 mg, 1.88 mmol) to give **6a** (216 mg, 1.14 mmol, 71%) as a yellow oil. R_f (10% EtOAc in petrol) 0.53; ν_{max}/cm^{-1} 1685, 1595, 1452; ^{1}H NMR (400 MHz, $CDCl_3$) 10.30 (1H, s, C*H*O), 7.79 (1H, dd, *J* 7.6, 1.8, C(6)*H*), 7.49 (1H, ddd, *J* 8.6, 7.2, 1.7, C(4)*H*), 7.09 (1H, d, *J* 7.8, C(3)*H*), 7.06 (1H, t, *J* 7.4, C(5)*H*), 3.05 (4H, t, *J* 5.0, C(2')H_2), 1.76 (4H, quint, *J* 5.7, C(3')H_2), 1.54 – 1.65 (2H, m, C(4')H_2); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 191.8 (*C*HO), 157.1 (*C*(2)), 134.9 (*C*(4)), 129.3 (*C*(6)), 128.8 (*C*(1)), 122.1 (*C*(5)), 119.1 (*C*(3)), 55.7 (*C*(2')), 26.3 (*C*(3')), 24.2 (*C*(4')); *m/z* (ESI$^+$) 190.1 (MH$^+$, 100%); HRMS (EI$^+$) m/z: [M]+ Calcd for $C_{12}H_{15}NO$ 189.1154; Found 189.1155. Experimental data is in agreement with reported values.[53]

2-(Pyrrolidin-1-yl)benzaldehyde (6b)

General procedure A (5 h) from 2-fluorobenzaldehyde (270 μL, 2.60 mmol), pyrrolidine (260 μL, 3.13 mmol) and potassium carbonate (432 mg, 3.13 mmol) to give **6b** (441 mg, 2.52 mmol, 97%) as a yellow oil. R_f (5% EtOAc in petrol) 0.69; ν_{max}/cm^{-1} 1677, 1560, 1491, 1478; ^{1}H NMR (400 MHz, $CDCl_3$) 10.09 (1H, s, C*H*O), 7.70 (1H, dd, *J* 7.8, 1.8, C(6)*H*), 7.38 (1H, ddd, *J* 8.7, 7.0, 1.8, C(4)*H*), 6.87 – 6.76 (2H, m, C(3)*H* + C(5)*H*), 3.40 – 3.32 (4H, tm, C(2')H_2), 2.03 – 1.95 (4H, m, C(3')H_2); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 190.2 (*C*HO), 150.1 (*C*(2)), 134.3 (*C*(4)), 133.2 (*C*(6)), 123.1 (*C*(1)), 116.6 (*C*(5)), 114.6 (*C*(3)), 52.8 (*C*(2')), 26.1 (*C*(3')); *m/z* (ESI$^+$) 176.1 (MH$^+$, 100%); HRMS (ESI$^+$) m/z: [MH]+ Calcd for $C_{11}H_{14}NO$ 176.1070; Found 176.1069. Experimental data is in agreement with reported values.[53]

2-Morpholinobenzaldehyde (6c)

General procedure A (5 h) from 2-fluorobenzaldehyde (225 μL, 2.02 mmol), morpholine (210 μL, 2.42 mmol) and potassium carbonate (334 mg, 2.42 mmol) to give **6c** (268 mg, 1.40 mmol, 70%) as a yellow oil. R_f (20% EtOAc in petrol) 0.42; ν_{max}/cm^{-1} 1683, 1596; ^{1}H NMR (400 MHz, $CDCl_3$) 10.33 (1H, s, C*H*O), 7.81 (1H, dd, *J* 7.7, 1.7, C(6)*H*), 7.54 (1H, ddd, *J* 8.1, 7.3, 1.7, C(4)*H*), 7.17 – 7.12 (1H, m, C(5)*H*), 7.11 (1H, d, *J* 8.2, C(3)*H*), 3.99 – 3.86 (4H, m, C(3')*H*), 3.16 – 3.00 (4H, m, C(2')H_2); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 191.3 (*C*HO), 155.4 (*C*(2)), 135.2 (*C*(4)), 130.4 (*C*(6)), 128.8 (*C*(1)), 123.0 (*C*(5)), 119.0 (*C*(3)), 67.0 (*C*(3')), 54.3 (*C*(2')); HRMS (EI$^+$) m/z: [MH]+ Calcd for $C_{11}H_{13}NO_2$ 191.0946; Found 191.0944. Experimental data is in agreement with reported values.[53]

2-(*cis*-2,6-Dimethylmorpholino)benzaldehyde (6d)

General procedure A (5 h) from 2-fluorobenzaldehyde (170 μL, 1.61 mmol), 2-(*cis*-2,6-dimethyl)morpholine (230 μL, 1.88 mmol) and potassium carbonate (263 mg, 1.88 mmol) to give **6d** (291 mg, 1.33 mmol, 82%) as an orange solid. m.p. 106 – 108 °C; R_f (10% EtOAc in petrol) 0.45; ν_{max}/cm^{-1} 1727, 1597, 1453; ^{1}H NMR (400 MHz, $CDCl_3$) 10.31 (1H, d, *J* 0.7 C*H*O), 7.80 (1H, dd, *J* 7.7, 1.7, C(4)*H*), 7.52 (1H, ddd, *J* 8.2, 7.3, 1.8, C(6)*H*), 7.12 (1H, tt, *J* 7.4, 0.8, C(5)*H*), 7.08 (1H, dd, *J* 8.2, 0.6, C(3)*H*), 3.91 (2H, dqd, *J* 10.0, 6.3, 2.1, C(3')*H*), 3.10 – 3.03 (2H, m, C(2')H_AH$_B$), 2.64 (2H, dd, *J* 11.9, 10.1, C(2')H$_A$$H_B$), 1.22 (6H, d, *J* 6.3, C(3')CH_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 191.4 (*C*HO), 155.2 (*C*(2)), 135.2 (*C*(6)), 130.3 (*C*(4)), 128.8 (*C*(1)), 122.9 (*C*(5)), 119.1 (*C*(3)), 71.9 (*C*(3')), 59.8 (*C*(2')), 19.0 (C(3')*C*H$_3$); *m/z* (ESI$^+$) 220.1 (MH$^+$, 100%); HRMS (ESI-TOF) m/z: [MH]+ Calcd for $C_{13}H_{18}NO_2$ 220.1332; Found 220.1329. Experimental data is in agreement with reported values.[54]

2-(*cis*-2,6-Dimethylmorpholino)-5-nitrobenzaldehyde (6e)

General procedure A (6 h) from 2-fluoro-5-nitrobenzaldehyde (1.50 g, 8.87 mmol), 2-(*cis*-2,6-dimethyl)morpholine (1.32 mL, 10.6 mmol) and potassium carbonate (1.47 g, 10.6 mmol) to give **6e** (1.91 g, 7.23 mmol, 82%) as a yellow solid. m.p. 120 – 121 °C; R_f (50% EtOAc in petrol) 0.68; ν_{max}/cm^{-1} 2871, 1687, 1508, 1335; ^{1}H NMR (400 MHz, $CDCl_3$) 10.06 (1H, s, C*H*O), 8.61 (1H, d, *J* 2.8, C(6)*H*), 8.29 (1H, dd, *J* 9.1, 2.8, C(4)*H*), 7.06 (1H, d, *J* 9.1, C(3)*H*), 3.91 (2H, dqd, *J* 10.2, 6.2, 2.1, C(3')*H*), 3.40 – 3.22 (2H, m, C(2')H_AH$_B$), 2.82 (2H, dd, *J* 12.4, 10.2, C(2')H$_A$$H_B$), 1.24 (6H, d, *J* 6.3, C(3')CH_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 188.4 (*C*HO), 157.5 (*C*(2)), 141.1 (*C*(5)), 129.6 (*C*(4)), 129.1 (*C*(6)), 126.0 (*C*(1)), 118.4 (*C*(3)), 71.7 (*C*(3')), 58.6 (*C*(2')), 18.8 ((C(3')*C*H$_3$); *m/z* (ESI$^+$) 265.1 (MH$^+$, 28%); HRMS (ESI$^+$) m/z: [MH]+ Calcd for $C_{13}H_{16}N_2O_4$ 265.1183; Found 265.1183. Experimental data is in agreement with reported values.[20]

2-(*cis*-2,6-Dimethylmorpholino)-5-methoxybenzaldehyde (6f)

General procedure A (8 h) from 2-fluoro-5-methoxybenzaldehyde (1.03 mL, 8.30 mmol), 2-(*cis*-2,6-dimethyl)morpholine (880 μL, 9.73 mmol) and potassium carbonate (1.35 g, 9.73 mmol) to give **6f** (408 mg, 1.64 mmol, 20%) as a yellow oil. R_f (50% EtOAc in petrol) 0.50; ν_{max}/cm^{-1} 2868, 1684; ^{1}H NMR (400 MHz, $CDCl_3$) 10.42 (1H, s, C*H*O), 7.33 – 7.31 (1H, m, C(6)*H*), 7.15 – 7.08 (2H, m, C(3)*H* + C(4)*H*), 3.89 (2H, dqd, *J* 12.5, 6.2, 1.9, C(3')*H*), 3.82 (3H, s, OCH_3), 2.95 (2H, d, *J* 10.9, C(2')H_AH$_B$), 2.61 (2H, t, *J* 10.8, C(2')H$_A$$H_B$), 1.21 (6H, d, *J* 6.3, C(3')CH_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 191.6 (*C*HO), 156.0 (*C*(5)), 149.8 (*C*(2)), 130.2 (*C*(1)), 122.8 (*C*(4)), 121.4 (*C*(3)), 111.3 (*C*(6)), 72.0 (*C*(3')), 60.4 (*C*(2')), 55.8 (O*C*H$_3$), 19.0 (C(3')*C*H$_3$); *m/z* (ESI$^+$) 250.1 (MH$^+$, 88%); HRMS (ESI$^+$) m/z: [MH]+ Calcd for $C_{14}H_{20}NO_3$ 250.1438; Found 250.1438.

Methyl (3'*R*,4a*R*,5*S*,7a'*R*)-3'-(*tert*-butyl)-5',7'-dioxo-2,3,4,4a-tetrahydro-1*H*,1'*H*,3'*H*,5'*H*,6*H*-spiro[pyrido[1,2-*a*]quinoline-5,6'-pyrrolo[1,2-*c*]oxazole]-7a'(7'*H*)-carboxylate (major isomer of 8a)

General procedure B (6 h) from tetramate **5a** (500 mg, 1.96 mmol) and *o*-aminobenzaldehyde **6a** (408 mg, 2.15 mmol) to give spirocycle **8a** (309 mg, 0.724 mmol, 37%) as a red solid. m.p. 185 °C; R_f (25% EtOAc in petrol) 0.66; ν_{max}/cm^{-1} 1774, 1746, 1720, 1497, 1458, 1497, 1267; ^{1}H NMR (600 MHz, C_6D_6) 7.09 (1H, t, *J* 7.6, C(11')*H*), 6.82 (1H, d, *J* 7.4, C(9')*H*), 6.72 (1H, d, *J* 8.4, C(12')*H*), 6.67 (1H, t, *J* 7.3, C(10')*H*), 5.11 (1H, s, C(3)*H*), 4.75 (1H, d, *J* 8.9, C(1)H_AH$_B$), 3.76 – 3.70 (1H, m, C(1')H_AH$_B$), 3.41 – 3.36 (2H, m, C(7')H_AH$_B$ + C(5')*H*), 3.26 (1H, d, *J* 15.8, C(7')H$_A$$H_B$), 3.20 (1H, d, *J* 8.8, C(1)H$_A$$H_B$), 3.12 (3H, s, CO_2CH_3), 2.42 (1H, td, *J* 12.3, 4.4, C(1')H$_A$$H_B$), 1.50 – 1.44 (2H, m, C(3')H$_A$$H_B$ + C(4')H_AH$_B$), 1.32 – 1.27 (2H, m, C(2')H_AH$_B$), 1.12 – 1.06 (1H, m, C(3')H_AH$_B$), 1.04 (9H, s, C(CH_3)$_3$), 1.00 – 0.96 (1H, m, C(4')H$_A$H$_B$); ^{13}C{^{1}H} NMR (100 MHz, C_6D_6) 199.6 (*C*(7)), 178.6 (*C*(5)), 167.6 (*C*O$_2$CH$_3$), 146.2 (*C*(13')), 129.4 (*C*(9')), 127.9 (*C*(11')), 118.2 (*C*(8')), 118.0 (*C*(10')), 113.9 (*C*(12')), 99.2 (*C*(3)), 78.5 (*C*(7a)), 68.2 (*C*(1)), 59.0 (*C*(5')), 57.7 (*C*(6)), 52.9 (CO$_2$*C*H$_3$), 48.7 (*C*(1')), 36.9 (*C*(7')), 35.7 (*C*(CH$_3$)$_3$), 29.3 (*C*(4')), 25.6 (*C*(2')), 25.0 (*C*(CH$_3$)$_3$), 24.5 (*C*(3')); *m/z* (ESI$^+$) 427.2 (MH$^+$, 100%); HRMS (ESI$^+$) m/z: [MH]$^+$ Calcd for $C_{24}H_{31}N_2O_5$ 427.2228; Found 427.2212. Single Crystal Data: $C_{24}H_{30}N_2O_5$, tetragonal, $I4_1$, *a*=16.4812(2), *c*=16.0775(3) Å, *V*= 4367.13(11) Å^3, Data/restraints/parameters 4521/1/281, R_{int}=0.029, Flack *x*=0.00(11), Final R_1=0.0272, wR_2=0.0689 (I>2s(I)).

Methyl (3aR,3'R,4S,7a'R)-3'-(*tert*-butyl)-5',7'-dioxo-1,2,3,3a-tetrahydro-1'*H*,3'*H*,5*H*,5'*H*-spiro[pyrrolo[1,2-a]quinoline-4,6'-pyrrolo[1,2-*c*]oxazole]-7*a*'(7'*H*)-carboxylate (major isomer of 8b)

General procedure B (6 h) from tetramate **5a** (500 mg, 1.96 mmol) and *o*-aminobenzaldehyde **6b** (420 mg, 2.15 mmol) to give spirocycle **8b** (474 mg, 1.15 mmol, 58%) as an orange solid. m.p. 188 °C; R_f (25% EtOAc in petrol) 0.70; ν_{max}/cm^{-1} 1745, 1717; ^{1}H NMR (600 MHz, C_6D_6) 7.20 (1H, t, *J* 7.6, C(11')*H*), 6.93 (1H, d, *J* 7.4, C(9')*H*), 6.69 (1H, t, *J* 7.4, C(10')*H*), 6.49 (1H, d, *J* 8.0, C(12')*H*), 5.15 (1H, s, C(3)*H*), 4.76 (1H, d, *J* 8.9, C(1)H_AH$_B$), 3.82 (1H, dd, *J* 10.2, 5.6, C(5')*H*), 3.47 (1H, d, *J* 15.9, C(7')H_AH$_B$), 3.23 (1H, d, *J* 15.9, C(7')H$_A$$H_B$), 3.17 (1H, d, *J* 8.9, C(1)H$_A$$H_B$), 3.12 – 3.09 (1H, m, C(1')H_AH$_B$), 3.09 (3H, s, CO_2CH_3), 2.94 (1H, td, *J* 9.3, 7.0, C(1')H$_A$$H_B$), 1.71 (1H, dtd, *J* 11.4, 6.2, 1.7, C(4')H_AH$_B$), 1.48 – 1.37 (2H, m, C(2')$H_A$$H_B$), 1.04 (9H, s, C(C$H_3$)$_3$), 0.97 – 0.88 (1H, m, C(4')H$_A$H$_B$); ^{13}C{^{1}H} NMR (100 MHz, C_6D_6) 199.3 (*C*(7)), 178.5 (*C*(5)), 167.1 (*C*O$_2$CH$_3$), 143.9 (*C*(13')), 128.6 (*C*(9')), 128.2 (*C*(11')), 115.9 (*C*(10')), 115.3 (*C*(8')), 110.9 (*C*(12')), 98.7 (*C*(3)), 78.1 (*C*(7a)), 67.8 (*C*(1)), 60.1 (*C*(5')), 52.6 (CO$_2$*C*H$_3$), 52.4 (*C*(6)), 47.3 (*C*(1')), 37.7 (*C*(7')), 35.3 (*C*(CH$_3$)$_3$),

28.6 (*C*(4')), 24.6 (C(*C*H$_3$)$_3$), 23.5 (*C*(2')); *m/z* (ESI$^+$) 413.2 (MH$^+$, 100%); HRMS (ESI$^+$) m/z: [MH]+ Calcd for $C_{23}H_{29}N_2O_5$ 413.2071; Found 413.2065. Single Crystal Data: $C_{23}H_{28}N_2O_5$, tetragonal, $I4_1$, *a*=16.4674(2), *c*=15.6590(4) Å, *V*=4246.33(13) Å^3, Data/restraints/parameters 4405/1/272, R_{int}=0.030, Flack *x*=0.07(12), Final R_1=0.0277, wR_2=0.0706 (I>2s(I)).

Methyl (3*R*,4a'*S*,6*S*,7a*R*)-3-(*tert*-butyl)-5,7-dioxo-1',2',4',4a'-tetrahydro-1*H*,3*H*,5*H*,6'*H*-spiro[pyrrolo[1,2-*c*]oxazole-6,5'-[1,4]oxazino[4,3-*a*]quinoline]-7a(7*H*)-carboxylate (major isomer of 8c)

General procedure B (12 h) from tetramate **5a** (500 mg, 1.96 mmol) and *o*-aminobenzaldehyde **6c** (440 mg, 2.15 mmol) to give spirocycle **8c** (53 mg, 0.12 mmol, 7%) as a red solid. m.p. 172 – 175 °C; R_f (25% EtOAc in petrol) 0.46; ν_{max}/cm^{-1} 1773, 1747, 1718; ^{1}H NMR (500 MHz, C_6D_6) 7.09 (1H, t, *J* 7.8, C(11')*H*), 6.80 (1H, d, *J* 7.4, C(9')*H),* 6.70 (1H, t, *J* 7.0, C(10')*H*), 6.57 (1H, d, *J* 8.3, C(12')*H*), 4.95 (1H, s, C(3)*H*), 4.68 (1H, d, *J* 9.0, C(1)H_AH_B), 3.82 (1H, dd, *J* 10.1, 2.9, C(4')H_AH_B), 3.63 (1H, dd, *J* 10.2, 3.0, C(5')*H*), 3.58 – 3.54 (1H, m, C(2')H_AH_B), 3.37 (1H, d, *J* 16.2, C(7')H_AH_B), 3.34 (1H, td, *J* 11.5, 3.0, C(2')H_AH_B), 3.22 (1H, d, *J* 16.2, C(7')H_AH_B), 3.21 – 3.17 (1H, m, C(1')H_AH_B), 3.08 (3H, s, CO_2CH_3), 3.09 – 3.04 (2H, m, C(1)H_AH_B + C(4')H_AH_B), 2.60 (1H, td, *J* 11.9, 3.7, C(1')H_AH_B), 1.00 (9H, s, C(CH_3)$_3$); ^{13}C{^{1}H} NMR (125 MHz, C_6D_6) 199.6 (*C*(7)), 177.8 (*C*(5)), 167.5 (*C*O$_2$CH$_3$), 145.2 (*C*(13')), 129.6 (*C*(9')), 128.4 (*C*(11')), 118.8 (*C*(10')), 118.2 (*C*(8')), 113.1 (*C*(12')), 99.1 (*C*(3)), 78.6 (*C*(7a)), 68.4 (*C*(1)), 68.0 (*C*(4')), 66.9 (*C*(2')), 57.5 (*C*(5')), 53.8 (*C*(6)), 53.0 (CO$_2$*C*H$_3$), 46.4 (*C*(1')), 36.5 (*C*(7')), 35.6 (*C*(CH$_3$)$_3$), 25.0 (C(*C*H$_3$)$_3$); *m/z* (ESI$^+$) 429.2 (MH$^+$, 100%); HRMS (ESI$^+$) m/z: [MH]+ Calcd for $C_{23}H_{29}N_2O_6$ 429.2020; Found 429.2017. Single Crystal Data: $C_{23}H_{28}N_2O_6$, tetragonal, $I4_1$, *a*=16.3993(2), *c*=15.9819(3) Å, *V*=4298.12(13) Å^3, Data/restraints/parameters 4195/1/281, R_{int}=0.017, Flack *x*=0.01(13), Final R_1=0.0287, wR_2=0.0806 (I>2s(I)).[55]

Methyl (2'*S*,3*R*,4'*R*,4a'*R*,6*R*,7a*R*)-3-(*tert*-butyl)-2',4'-dimethyl-5,7-dioxo-1',2',4',4a'-tetrahydro-1*H*,3*H*,5*H*,6'*H*-spiro[pyrrolo[1,2-*c*]oxazole-6,5'-[1,4]oxazino[4,3-*a*]quinoline]-7a(7*H*)-carboxylate (major isomer of 8d)

General procedure B (8 h) from tetramate **5a** (2.25 g, 8.82 mmol) and *o*-aminobenzaldehyde **6d** (2.13 g, 9.70 mmol) to give spirocycle **8d** (1.24 g, 2.72 mmol, 31%) as a pink solid. m.p. 190 °C; R_f (50% EtOAc in petrol) 0.88; ν_{max}/cm^{-1} 1773, 1745, 1721; ^{1}H NMR (600 MHz, C_6D_6, 8:2 mixture of diastereomers) major isomer **8d'''''** 7.15 – 7.11 (1H, m, C(11')*H*), 6.80 (1H, d, *J* 7.4, 1.8, C(9')*H*), 6.76 (1H, td, *J* 7.2, 0.9, C(10')*H*), 6.61 (1H, d, *J* 8.4, C(12')*H*), 5.05 (1H, s, C(3)*H*), 4.65 (1H, d, *J* 8.9, C(1)H_AH_B), 3.72 (1H, dq, *J* 9.5, 6.0, C(4')*H*), 3.48 (1H, dqd, *J* 12.4, 6.1, 2.7, C(2')*H*), 3.42 (1H, dd, *J* 12.0, 2.7, C(1')H_AH_B), 3.31 (1H, d, *J* 16.5, C(7')H_AH_B), 3.30 (1H, d, *J* 9.5, C(5')*H*), 3.18 (3H, s, CO$_2$CH_3), 3.02 (1H, d, *J* 8.9, C(1)H_AH_B), 2.40 (1H, t, *J* 11.2, C(1')H_AH_B), 2.38 (1H, d, *J* 16.8, C(7')H_AH_B), 1.69 (3H, d, *J* 6.0, C(4')CH_3), 1.01 (9H, s, C(CH_3)$_3$), 0.99 (3H, d, *J* 6.2, C(2')CH_3); ^{13}C{^{1}H} NMR (125 MHz, C_6D_6) major isomer **8d'''''** 198.9 (*C*(7)), 179.4 (*C*(5)), 167.7 (*C*O$_2$CH$_3$), 145.3 (*C*(13')), 129.0 (*C*(9')), 128.4 (*C*(11')), 118.2 (*C*(10')), 118.0 (*C*(8')), 113.1 (*C*(12')), 100.3 (*C*(3)), 78.7 (*C*(7a)), 73.6 (*C*(4')), 70.9 (*C*(2')), 70.1 (*C*(1)), 63.7 (*C*(5')), 58.0 (*C*(6)), 52.8 (*C*(1')), 52.7 (CO$_2$*C*H$_3$), 37.6 (C(7')), 35.7 (*C*(CH$_3$)$_3$), 25.2 (C(*C*H$_3$)$_3$), 20.3 (C(4')*C*H$_3$), 19.0 (C(2')*C*H$_3$); *m/z* (ESI$^+$) 457.2 (MH$^+$, 100%); HRMS (ESI$^+$) m/z: [MH]+ Calcd for $C_{25}H_{33}N_2O_6$ 457.2333; Found 457.2324. Single Crystal Data: $C_{25}H_{32}N_2O_6$, orthorhombic, $P2_12_12_1$, *a*=9.0534(1), *b*=11.9701(2), *c*=22.0969(3) Å, *V*=2394.64(6) Å^3, Data/restraints/parameters 4966/0/299, R_{int}=0.039, Flack *x*=-0.07(12), Final R_1=0.0313, wR_2=0.0805 (I>2s(I)).

Methyl (2'*S*,3*R*,4'*R*,4a'*R*,6*R*,7a*R*)-3-(*tert*-butyl)-2',4'-dimethyl-5,7-dioxo-1',2',4',4a'-tetrahydro-1*H*,3*H*,5*H*,6'*H*-spiro[pyrrolo[1,2-*c*]thiazole-6,5'-[1,4]oxazino[4,3-*a*]quinoline]-7a(7*H*)-carboxylate (major isomer of 8e)

General procedure B (8 h) from tetramate **5b** (250 mg, 0.92 mmol) and *o*-aminobenzaldehyde **6d** (222 mg, 1.02 mmol) to give spirocycle **8e** (111 mg, 0.235 mmol, 23%) as an orange solid. m.p. 195 – 197 °C; R_f (50% EtOAc in petrol) 0.76; ν_{max}/cm^{-1} 1773, 1746, 1715; ^{1}H NMR (500 MHz, C_6D_6, 8:2 mixture of diastereomers) major isomer **8e''''** 7.14 – 7.10 (1H, m, C(11')*H*), 6.72 (1H, td, *J* 7.3, 0.9, C(10')*H*), 6.68 (1H, d, *J* 7.3, C(9')*H*), 6.59 (1H, d, *J* 8.4, C(12')*H*), 5.46 (1H, s, C(3)*H*), 3.69 – 3.63 (1H, m, C(4')*H*), 3.63 (1H, d, *J* 11.4, C(1)H_AH_B), 3.53 – 3.47 (1H, m, C(2')*H*), 3.44 (1H, dd, *J* 12.1, 12.7, C(1')H_AH_B), 3.35 (1H, d, *J* 9.4, C(5')*H*), 3.30 (1H, d, *J* 16.4, C(7')H_AH_B), 3.18 (3H, s, OCH_3), 2.51 (1H, d, *J* 11.5, C(1)H_AH_B), 2.42 (1H, dd, *J* 12.1, 10.5, C(1')H_AH_B), 2.33 (1H, d, *J* 16.4, C(7')H_AH_B), 1.68 (3H, d, *J* 6.0, C(4')CH_3), 0.98 (9H, s, C(CH_3)$_3$), 1.00 – 0.97 (3H, m, C(2')CH_3); ^{13}C{^{1}H} NMR (125 MHz, C_6D_6) major isomer **8e''''** 198.5 (*C*(7)), 179.1 (*C*(5)), 167.4 (*C*O$_2$CH$_3$), 145.0 (*C*(13')), 129.1 (*C*(9')), 128.5 (*C*(11')), 118.3 (*C*(10')), 118.1 (*C*(8')), 113.3 (*C*(12')), 82.9 (*C*(7a)), 76.2 (*C*(3)), 73.8 (*C*(4')), 71.2 (*C*(2')), 63.7 (*C*(5')), 53.2 (*C*(1')), 53.0 (CO$_2$*C*H$_3$), 51.9 (*C*(6)), 39.1 (*C*(7')), 37.4 (*C*(CH$_3$)$_3$), 36.3 (*C*(1)), 27.1 (C(*C*H$_3$)$_3$), 20.4 (*C*(4')*C*H$_3$), 19.1 (C(2')*C*H$_3$); *m/z* (ESI$^+$) 473.2 (MH$^+$, 100%); HRMS (ESI$^+$) m/z: [MH]+ Calcd for $C_{25}H_{33}N_2O_5S$ 473.2105; Found 473.2098. Single Crystal Data: $C_{25}H_{32}N_2O_6S_1$, orthorhombic, $P2_12_12_1$, *a*=9.2640(2), *b*=12.1677(3), *c*=21.5109(6) Å, *V*= 2424.74(10) Å^3, Data/restraints/parameters 5020/0/299, R_{int}=0.019, Flack *x*=-0.015(14), Final R_1=0.0320, wR_2=0.0879 (I>2s(I)).

Methyl (2'*S*,3*R*,4'*R*,4a'*R*,6*R*,7a*R*)-3-(*tert*-butyl)-2',4'-dimethyl-8'-nitro-5,7-dioxo-1',2',4',4a'-tetrahydro-1*H*,3*H*,5*H*,6'*H*-spiro[pyrrolo[1,2-*c*]oxazole-6,5'-[1,4]oxazino[4,3-*a*]quinoline]-7a(7*H*)-carboxylate (8f)

General procedure B (15 h) from tetramate **5a** (70 mg, 0.28 mmol) and *o*-aminobenzaldehyde **6e** (86 mg, 0.33 mmol) to give spirocycle **8f** (4 mg, 0.008 mmol, 3%) as an orange solid. m.p. 235 – 240 °C; R_f (25% EtOAc in petrol) 0.24; ν_{max}/cm^{-1} 1745, 1674 and 1607; ^{1}H NMR (500 MHz, C_6D_6, 9:1 mixture of diastereomers) major isomer **8f''''** 8.02 (1H, dd, *J* 9.3, 2.7, C(11')*H*), 7.74 (1H, d, *J* 2.7, C(9')*H*), 6.04 (1H, d, *J* 9.3, C(12')*H*), 5.04 (1H, s, C(3)*H*), 4.61 (1H, d, *J* 8.9, C(1)H_AH_B), 3.56 (1H, dq, *J* 9.6, 5.9, C(4')*H*), 3.25 – 3.19 (1H, m, C(2')*H*), 3.16 (3H, s, CO$_2$CH_3), 3.18 – 3.14 (1H, m, C(5')*H*), 3.09 (1H, dd, *J* 12.5, 2.7, C(1')H_AH_B), 2.96 (1H, d, J 9.0, C(1)H_AH_B), 2.86 (1H, d, *J* 16.5, C(7')H_AH_B), 2.21 (1H, dd, *J* 12.5, 10.8, C(1')H_AH_B), 2.02 (1H, d, *J* 16.7, C(7')H_AH_B), 1.61 (3H, d, *J* 6.0, C(4')CH_3), 0.99 (9H, s, C(CH_3)$_3$), 0.91 (3H, d, *J* 6.2, C(2')CH_3); ^{13}C{^{1}H} NMR (125 MHz, C_6D_6) major isomer **8f''''** 198.9 (*C*(7)), 178.0 (*C*(5)), 167.3 (*C*O$_2$CH$_3$), 149.3 (*C*(13')), 138.7 (*C*(10')), 124.8 (*C*(9')), 124.4 (*C*(11')), 117.3 (*C*(8')), 111.3 (*C*(12')), 100.2 (*C*(3)), 78.4 (*C*(7a)), 73.0 (*C*(4')), 70.3 (*C*(2')), 69.8 (*C*(1)), 62.9 (*C*(5')), 52.7 (CO$_2$*C*H$_3$), 51.8 (*C*(1')), 51.8 (*C*(6)), 36.5 (*C*(7')), 35.5 (*C*(CH$_3$)$_3$), 24.9 (C(*C*H$_3$)$_3$), 20.0 (C(4')*C*H$_3$), 18.6 (C(2')*C*H$_3$); *m/z* (ESI$^+$) 502.3 (MH$^+$, 73%); HRMS (ESI$^+$) m/z: [MH]+ Calcd for $C_{25}H_{32}N_3O_8$ 502.2184; Found 502.2186.

Methyl (2'*S*,3*R*,4'*R*,4a'*R*,6*R*,7a*R*)-3-(*tert*-butyl)-2',4'-dimethyl-8'-nitro-5,7-dioxo-1',2',4',4a'-tetrahydro-1*H*,3*H*,5*H*,6'*H*-spiro[pyrrolo[1,2-*c*]thiazole-6,5'-[1,4]oxazino[4,3-*a*]quinoline]-7a(7*H*)-carboxylate (8g)

General procedure B (8 h) from tetramate **5b** (75 mg, 0.28 mmol) and *o*-aminobenzaldehyde **6e** (88 mg, 0.33 mmol) to give spirocycle **8g** (13 mg, 0.024 mmol, 9%) as an orange solid. m.p. 236 – 238 °C; R_f (25% EtOAc in petrol) 0.41; ν_{max}/cm^{-1} 1744, 1718, 1685, 1316; ^1H NMR (500 MHz, C_6D_6, 8:1 mixture of diastereomers) major isomer **8g''''** 8.01 (1H, dd, *J* 9.3, 2.8, C(11')*H*), 7.63 (1H, d, *J* 2.7, C(9')*H*), 6.03 (1H, d, *J* 9.3, C(12')*H*), 5.41 (1H, s, C(3)*H*), 3.55 (1H, d, *J* 11.6, C(1)H_AH_B), 3.53 – 3.48 (1H, m, C(4')*H*), 3.21 (1H, d, *J* 9.6, C(5')*H*), 3.24 – 3.19 (1H, m, C(2')*H*), 3.16 (3H, s, CO_2CH_3), 3.15 – 3.09 (1H, m, C(1')H_AH_B), 2.85 (1H, d, *J* 16.4, C(7')H_AH_B), 2.39 (1H, d, *J* 11.5, C(1)H_AH_B), 2.21 (1H, dd. *J* 12.6, 10.7, C(1')H_AH_B), 1.96 (1H, d, *J* 16.5, C(7')H_AH_B), 1.60 (3H, d, *J* 6.0, C(4')CH_3), 0.97 (9H, s, $C(CH_3)_3$), 0.91 (3H, d, *J* 6.2, C(2')CH_3); $^{13}C\{^1H\}$ NMR (125 MHz, C_6D_6) major isomer **8g''''** 200.1 (*C*(7)), 176.3 (*C*(5)), 167.8 (CO_2CH_3), 149.7 (*C*(13')), 139.0 (*C*(10')), 125.2 (*C*(9')), 124.9 (*C*(11')), 117.6 (*C*(8')), 111.6 (*C*(12')), 82.7 (*C*(7a)), 76.1 (*C*(3)), 73.4 (*C*(4')), 70.7 (*C*(2')), 63.2 (*C*(5')), 53.1 (CO_2CH_3), 52.3 (*C*(1')), 51.1 (*C*(6)), 38.0 (*C*(7')), 37.4 ($C(CH_3)_3$), 36.2 (*C*(1)), 27.0 ($C(CH_3)_3$), 20.3 (C(4')CH_3), 18.9 (C(2')CH_3); HRMS ($APCI^+$) m/z: [MH]+ Calcd for $C_{25}H_{32}N_3O_7S$ 518.1956; Found 518.1959.

Methyl (3'*R*,7a'*R*)-7-bromo-3'-(*tert*-butyl)-5',7'-dioxo-1,2,3,3a-tetrahydro-1'*H*,3'*H*,5*H*,5'*H*-spiro[pyrrolo[1,2-*a*]quinoline-4,6'-pyrrolo[1,2-*c*]oxazole]-7a'(7'*H*)-carboxylate (8i)

General procedure B (6 h) from tetramate **5a** (100 mg, 0.392 mmol) and *o*-aminobenzaldehyde **23** (110 mg, 0.431 mmol) to give spirocycle **8i** (119 mg, 0.243 mmol, 9%) as a brown solid. R_f (25% EtOAc in petrol) 0.81; ν_{max}/cm^{-1} 1742, 1718, 1112; ^1H NMR (500 MHz, C_6D_6, 2.5:1.5:1:1 mixture of 4 diastereomers) major isomer 7.26 (1H, dd, *J* 8.6, 2.7, C(11')*H*), 7.08 (1H, d, *J* 2.3, C(9')*H*), 6.12 (1H, d, *J* 8.6, C(12')*H*), 5.11 (1H, s, C(3)*H*), 4.74 (1H, d, *J* 8.9, C(1)H_AH_B), 3.67 (1H, dd, *J* 10.3, 5.6, C(5')*H*), 3.28 (1H, d, *J* 16.1, C(7')H_AH_B), 3.14 (1H, d, *J* 8.9, C(1)H_AH_B), 3.05 (1H, d, *J* 16.3, C(7')H_AH_B), 3.04 (3H, s, CO_2CH_3), 2.91 (1H, ddd, *J* 8.2, 5.1, 2.9, C(1')H_AH_B), 2.82 – 2.74 (1H, m, C(1')H_AH_B), 1.69 – 1.60 (1H, m, C(4')H_AH_B), 1.49 (1H, m, C(2')H_AH_B), 1.43 – 1.38 (1H, m, C(2')H_AH_B), 1.01 (9H, s, $C(CH_3)_3$), 0.87 – 0.81 (1H, m, C(4')H_AH_B); $^{13}C\{^1H\}$ NMR (125 MHz, C_6D_6) major isomer 199.8 (*C*(7)), 178.4 (*C*(5)), 167.2 (CO_2CH_3), 143.1 (*C*(13')), 131.3 (*C*(9')), 131.2 (*C*(11')), 117.9 (*C*(8')), 112.8 (*C*(12')), 107.8 (*C*(10')), 99.0 (*C*(3)), 78.4 (*C*(7a)), 68.0 (*C*(1)), 60.4 (*C*(5')), 53.1 (CO_2CH_3), 52.3 (*C*(6)), 47.6 (*C*(1')), 37.3 (*C*(7')), 35.7 ($C(CH_3)_3$), 28.9 (*C*(4')), 25.0 ($C(CH_3)_3$), 23.8 (*C*(2')); *m/z* (ESI^+) 491.2 (MH^+, 100%); HRMS (ESI^+) m/z: [MH]+ Calcd for $C_{23}H_{28}BrN_2O_5$ 491.1176; Found 491.1174.

Methyl (3'*R*,7a'*R*)-3'-(*tert*-butyl)-5',7'-dioxo-7-phenyl-1,2,3,3a-tetrahydro-1'*H*,3'*H*,5*H*,5'*H*-spiro[pyrrolo[1,2-*a*]quinoline-4,6'-pyrrolo[1,2-*c*]oxazole]-7a'(7'*H*)-carboxylate (8j)

Bromospirocycle **8i** (100 mg, 0.20 mmol) and phenylboronic acid (37 mg, 0.30 mmol) were dissolved into THF (5 mL). To the stirring solution was added $Pd(dppf)Cl_2$ (195 mg in 0.2 mL H_2O, 0.01 mmol, 5 mol%). The mixture was stirred at room temperature for 40 minutes and then heated to reflux for 24 h. The reaction mixture was then diluted with EtOAc and filtered through a pad of Celite. The filtrates were collected and washed with brine and a saturated solution of $NaHCO_3$. Solvent was removed using rotary evaporation and the resulting residue was purified by *flash* column chromatography to yield the biaryl **8j** (38 mg, 0.078 mmol, 39%) as a mixture of 4 diastereomers as a yellow oil. R_f (25% EtOAc in petrol) 0.91; ν_{max}/cm^{-1} 1745, 1711, 1605, 1507, 1480, 1461, 1577; *m/z* (ESI^+) 489.2 (MH^+, 100%); HRMS (ESI^+) m/z: [MH]+ Calcd for $C_{29}H_{33}N_2O_5$ 489. 2384; Found 489.2382.

Methyl (3*R*,7a*R*)-6-benzylidene-3-(*tert*-butyl)-5,7-dioxodihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7a(5*H*)-carboxylate (10)

Tetramare **5a** (100 mg, 0.392 mmol) was added to a solution of benzaldehyde (440 µL, 0.429 mmol) in methanol (2.0 mL). The solution was then stirred at room temperature for 30 hours, and then concentrated *in vacuo*. Purification *via flash* column chromatography gave alkene **10** (47 mg, 0.14 mmol, 36%, 1.2:1 mixture of E/Z isomers) as a yellow oil. R_f (EtOAc) 0.41; ν_{max}/cm^{-1} 1700, 1622, 1475; ^1H NMR (500 MHz, $CDCl_3$) *E* isomer: 8.35 – 8.32 (2H, m, C(3')*H*), 7.92 (1H, s, C(1')*H*), 7.63 – 7.56 (1H, m, C(5')*H*), 7.53 – 7.48 (2H, m, C(4')*H*), 5.07 (1H, s, C(3)*H*), 4.90 (1H, d, *J* 9.0, C(1)H_AH_B), 3.78 (3H, s, CO_2CH_3), 3.57 (1H, d, *J* 9.0, C(1)H_AH_B), 0.97 (9H, s, $C(CH_3)_3$); *Z* isomer: 8.45 – 8.41 (2H, m, C(3')*H*), 7.82 (1H, s, C(1')*H*), 7.63 – 7.56 (1H, m, C(5')*H*), 7.53 – 7.48 (2H, m, C(4')*H*), 5.09 (1H, s, C(3)*H*), 4.90 (1H, d, *J* 8.5, C(1)H_AH_B), 3.79 (3H, s, CO_2CH_3), 3.58 (1H, d, *J* 8.5, C(1)H_AH_B), 0.97 (9H, s, $(CH_3)_3$); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) *E* isomer: 190.0 (*C*(7)), 172.1 (*C*(5)), 167.8 (CO_2CH_3), 154.1 (*C*(1')), 134.9 (*C*(5')), 134.4 (*C*(3')), 132.9 (*C*(2')), 129.1 (*C*(4')), 123.3 (*C*(6)), 99.3 (*C*(3)), 77.1 (*C*(7a)), 68.6 (*C*(1)), 53.6 (CO_2CH_3), 35.6 ($C(CH_3)_3$), 24.9 ($C(CH_3)_3$); *Z* isomer: 191.5 (*C*(7)), 170.3 (*C*(5)), 167.6 (CO_2CH_3), 152.2 (*C*(1')), 135.4 (*C*(3')), 134.5 (*C*(5')), 132.3 (*C*(2')), 129.1 (*C*(4')), 123.9 (*C*(6)), 99.0 (*C*(3)), 77.8 (*C*(7a)), 68.3 (*C*(1)), 53.6 (CO_2CH_3), 35.7 ($C(CH_3)_3$), 25.0 ($C(CH_3)_3$); *m/z* (ESI^+) 344.1 (MH^+, 100%); HRMS (ESI^+) m/z: [MH]+ Calcd for $C_{19}H_{22}NO_5$ 344.1492; Found 344.1486.

Methyl (3*R*,7a*R*)-3-(*tert*-butyl)-6-(2-(2,6-dimethylmorpholino)benzyl)-7-hydroxy-5-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7a(5*H*)-carboxylate (14)

Acetic acid (60 µL, 0.99 mmol) and spirotetramate **8d** (100 mg, 0.219 mmol) were dissolved in anhydrous DCM (600 µL). $NaBH_4$ was added portionwise at 0 °C and left to stir for 15 min before stirring at room temperature. After 36 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give **14** (56 mg, 0.12 mmol, 56%) as a pink oil. R_f (20% EtOAc in petrol) 0.53; ν_{max}/cm^{-1}; 2976, 1746, 1716, 1664; ^1H NMR (500 MHz, C_6D_6) 7.49 (1H, dd, *J* 7.2, 2.1, C(9')*H*), 6.98 – 6.88 (2H, m, C(10')*H* + C(11')*H*), 6.63 (1H, dd, *J* 7.6, 1.7, C(12')*H*), 4.92 (1H, d, *J* 8.3, C(1)H_AH_B), 4.90 (1H, s, C(3)*H*), 3.82 (1H, dqd, *J* 10.6, 6.2, 2.0, C(2')*H*), 3.70 (1H, dqd, *J* 10.6, 6.2, 2.0, C(2')*H*), 3.43 (1H, d, *J* 14.4, C(7')H_AH_B), 3.34 (1H, d, *J* 14.4, C(7')H_AH_B), 3.30 (3H, s, CO_2CH_3), 3.08 (1H, d, *J* 8.3, C(1)H_AH_B), 2.58 – 2.55 (1H, m, C(5')H_AH_B), 2.54 – 2.50 (1H, m, C(1')H_AH_B), 2.15 (1H, t, *J* 11.0, C(5')H_AH_B), 1.95 (1H, t, *J* 11.0, C(1')H_AH_B), 1.14 (9H, s, $C(CH_3)_3$), 0.93 (3H, d, *J* 6.2, C(4')CH_3), 0.87 (3H, d, *J* 6.3, C(2')CH_3); $^{13}C\{^1H\}$ NMR (125 MHz, C_6D_6) 178.7 (*C*(5)), 171.4 (*C*(7)), 169.5 (CO_2CH_3), 147.3 (*C*(12')), 134.8 (*C*(8')),132.7 (*C*(9')), 128.2 (*C*(10')), 127.2 (*C*(11')), 120.2 (*C*(12')), 107.0 (*C*(6)), 97.2 (*C*(3)), 74.2 (*C*(7a)), 70.6 (*C*(2')), 70.6 (*C*(4')), 70.2 (*C*(1)), 60.3 (*C*(1')), 58.8 (*C*(5')), 52.5 (CO_2CH_3), 35.6 ($C(CH_3)_3$), 25.2 ($C(CH_3)_3$), 24.6 (*C*(7')), 19.2 (C(4')CH_3), 19.1 (C(2')CH_3); *m/z* (ESI^+) 459.3 (MH^+, 100%).

(3*S*,7a*R*)-3-(2-Chloro-4-fluorophenyl)dihydro-3*H*,5*H*-pyrrolo[1,2-*c*]thiazole-5,7(6*H*)-dione (17)

To a stirred solution of tetramate **16** (185 mg, 0.52 mmol) in MeCN (5 mL) was added one drop of distilled water, and the reaction mixture was heated to reflux for 6 h. The solvent was removed *in vacuo* to yield tetramate **17** (138 mg, 0.483 mmol, 93%) as a dark orange oil, which was used in the following step without further purification. R_f (20% MeOH in EtOAc) 0.15; $[\alpha]_D^{25}$ -257.0 (*c* 0.25, $CHCl_3$); ν_{max}/cm^{-1} 2981, 1696, 1649, 1232,

728; ^{1}H NMR (400 MHz, $CDCl_3$) 7.29 (1H, dd, *J* 8.7, 5.8, C(6')*H*), 7.17 (1H, dd, *J* 8.2, 2.6, C(3')*H*), 6.99 (1H, td, *J* 8.2, 2.6, C(5')*H*), 6.74 (1H, s, C(3)*H*), 4.82 – 4.73 (1H, m, C(7a)*H*), 3.44 (1H, d, *J* 22.1, C(6)H_AH_B), 3.32 – 3.22 (2H, m, C(1)H_AH_B + C(6)H_AH_B), 3.09 (1H, dd, *J* = 10.9, 9.6 Hz, C(1)H_AH_B); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 202.2 (*C*(7)), 169.1 (*C*(5)), 162.3 (d, *J* 249.7, *C*(4')), 133.6 (d, *J* 4.1, *C*(2')), 126.6 (d, *J* 9.2, *C*(6')), 117.9 (d, *J* 25.1, *C*(3')), 114.5 (d, *J* 21.5, *C*(5')), 100.1 (*C*(1')), 72.5 (*C*(7a)), 60.4 (*C*(3)), 43.5 (*C*(6)), 33.3 (*C*(1)); *m/z* (ESI$^-$) 284.0 ([M-H]$^-$, 100%); HRMS (ESI$^-$) m/z: [M-H]$^-$ Calcd for $C_{12}H_8ClFNO_2S$ 283.9954; Found 283.9954.

2-(Diethylamino)benzaldehyde (21a)

General procedure A (24 h) from 2-fluorobenzaldehyde (300 μL, 4.75 mmol), diethylamine (565 μL, 5.46 mmol) and potassium carbonate (755 mg, 5.46 mmol) to give **21a** (150 mg, 0.846 mmol, 18%) as a brown oil. R_f (20% hexane in DCM) 0.48; ν_{max}/cm^{-1} 1683, 1594, 1482, 1450; ^{1}H NMR (400 MHz, $CDCl_3$) 10.4 (1H, s, C*H*O), 7.80 (1H, dd, *J* 7.7, 1.8, C(6)*H*), 7.49 (1H, ddd, *J* 8.2, 7.2, 1.8, C(4)*H*), 7.15 (1H, d, *J* 8.2, C(3)*H*), 7.13 – 7.03 (1H, m, C(5)*H*), 3.18 (4H, q, *J* 7.1, C(1')*H*), 1.05 (6H, t, *J* 7.1, C(2')*H*); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 192.3 (*C*HO), 154.7 (*C*(2)), 134.4 (*C*(4)), 130.9 (*C*(1)), 129.0 (*C*(6)), 122.4 (*C*(5)), 121.8 (*C*(3)), 49.0 (*C*(1')), 12.4 (*C*(2')); HRMS (CI$^+$) m/z: [MH]+ Calcd for $C_{11}H_{16}NO$ 178.1226; Found 178.1234. Experimental data is in agreement with reported values.[56]

2-(Isopropyl(methyl)amino)benzaldehyde (21b)

General procedure A (48 h) from 2-fluorobenzaldehyde (300 μL, 4.75 mmol), *N*-isopropyl methylamine (570 μL, 5.46 mmol) and potassium carbonate (755 mg, 5.46 mmol) to give **21b** (138 mg, 0.779 mmol, 16%) as a dark orange oil. R_f (20% hexane in DCM) 0.51; ν_{max}/cm^{-1} 1684, 1595, 1519, 1454; ^{1}H NMR (400 MHz, $CDCl_3$) 10.19 (1H, s, C*H*O), 7.77 (1H, dd, *J* 7.7, 1.8, C(6)*H*), 7.45 (1H, ddd, *J* 8.2, 7.2, 1.8, C(4)*H*), 7.07 (1H, d, *J* 8.1, C(3)*H*), 7.00 (1H, t, *J* 7.5, C(5)*H*), 3.46 (1H, hept, *J* 6.5, C(2')*H*), 2.72 (3H, s, C(1')H_3), 1.14 (6H, d, *J* 6.6, C(3')H_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 191.6 (*C*HO), 156.2 (*C*(2)), 134.4 (*C*(4)), 129.6 (*C*(6)), 128.9 (*C*(1)), 121.3 (*C*(5)), 120.3 (*C*(3)), 59.1 (*C*(2')), 32.4 (*C*(1')), 18.9 (*C*(3')); HRMS (ESI+) m/z: [MH]+ Calcd for $C_{11}H_{16}NO$ 178.1226; Found 178.1226.

2-(Benzyl(methyl)amino)benzaldehyde (21e)

General procedure A (48 h) from 2-fluorobenzaldehyde (1.0 mL, 9.5 mmol), *N*-benzylmethylamine (1.4 mL, 11 mmol) and potassium carbonate (1.51 g, 10.9 mmol) to give **21e** (246 mg, 1.09 mmol, 12%) as a yellow oil. R_f (20% hexane in DCM) 0.68; ν_{max}/cm^{-1} 1712, 1596, 1484, 1453; ^{1}H NMR (400 MHz, $CDCl_3$) 10.35 (1H, s, C*H*O), 7.77 (1H, dd, *J* 7.7, 1.7, C(6)*H*), 7.47 – 7.38 (1H, m, C(4)*H*), 7.30 – 7.26 (2H, m, C(5')*H*), 7.24 – 7.21 (3H, m, C(4')*H* + C(6')*H*), 7.05 (1H, d, *J* 8.5, C(3)*H*), 7.02 (1H, t, *J* 7.6, C(5)*H*), 4.29 (2H, s, C(2')H_2), 2.77 (3H, s, C(1')H_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 191.4 (*C*HO), 155.8 (*C*(2)), 137.5 (*C*(3')), 134.8 (*C*(4)), 130.3 (*C*(6)), 128.6 (*C*(5')), 128.2 (*C*(1)), 128.1 (*C*(4')), 127.5 (*C*(6')), 121.7 (*C*(5)), 119.6 (*C*(4)), 62.5 (*C*(2')), 42.4 (*C*(1')); *m/z* (ESI$^+$) 226.0 (MH$^+$, 100%); HRMS (ESI$^+$) m/z: [MH]+ Calcd for $C_{15}H_{16}NO$ 226.1226; Found 226.1226. Experimental data is in agreement with reported values.[57]

2-(Benzyl(ethyl)amino)benzaldehyde (21f)

General procedure A (48 h) from 2-fluorobenzaldehyde (1.0 mL, 9.5 mmol), *N*-ethylbenzylamine (1.6 mL, 11 mmol) and potassium carbonate (1.51 g, 10.9 mmol) to give **21f** (574 mg, 2.40 mmol, 25%) as a yellow oil, isolated as an inseparable mixture with aldehyde. R_f (20% hexane in DCM) 0.71; ν_{max}/cm^{-1} 1739, 1595, 1481, 1453; ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.50 (1H, d, *J* 0.5, C*H*O), 7.84 (1H, dd, *J* 7.7, 1.8, C(6)*H*)), 7.50 (1H, ddd, *J* 8.2, 7.2, 1.8, C(4)*H*), 7.35 – 7.25 (5H, m, C(5')*H* + C(6')*H* + C(7')*H*), 7.18 (1H, d, *J* 8.2, C(3)*H*), 7.12 (1H, t, *J* 7.5, C(5)*H*), 4.34 (2H, s, C(3')H_2), 3.20 (2H, q, *J* 7.1, C(1')H_2), 1.09 (3H, t, *J* 7.1, C(2')H_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 191.8 (*C*HO), 154.6 (*C*(2)), 137.9 (*C*(4')), 134.5 (*C*(4)), 130.4 (*C*(1)), 129.2 (*C*(6)), 128.5 (*C*(5') or *C*(6')), 128.4 (*C*(5') or *C*(6')), 127.4 (*C*(7')), 122.7 (*C*(5)), 122.1 (*C*(3)), 58.5 (*C*(3')), 49.7 (*C*(1')), 11.9 (*C*(2')); *m/z* (ESI$^+$) 240.2 (MH$^+$, 100%); HRMS (ESI$^+$) m/z: [MH]+ Calcd for $C_{16}H_{18}NO$ 240.1383; Found 240.1384. Experimental data is in agreement with reported values.[58]

2-(Dibenzylamino)benzaldehyde (21h)

General procedure A (24 h) from 2-fluorobenzaldehyde (500 μL, 4.75 mmol), dibenzylamine (1.0 mL, 5.5 mmol) and potassium carbonate (755 mg, 5.46 mmol). A complex mixture was obtained, which was used in the following step (formation of **22h**) without further purification.

2-(Diethylamino)-5-nitrobenzaldehyde (21i)

General procedure A (24 h) from 2-fluoro-5-nitrobenzaldehyde (500 mg, 2.96 mmol), diethylamine (350 μL, 3.40 mmol) and potassium carbonate (470 mg, 3.40 mmol) to give **21i** (326 mg, 1.47 mmol, 50%) as a yellow solid. R_f (20% hexane in DCM) 0.55; ν_{max}/cm^{-1} 1739, 1592, 1572, 1435; ^{1}H NMR (400 MHz, $CDCl_3$) 10.01 (1H, s, C*H*O), 8.59 (1H, d, *J* 2.8, C(6)*H*), 8.20 (1H, dd, *J* 9.3, 2.9, C(4)*H*), 7.02 (1H, d, *J* 9.3, C(3)*H*), 3.44 (4H, q, *J* 7.1, C(1')H_2), 1.23 (6H, t, *J* 7.1, C(2')H_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 188.5 (*C*HO), 156.9 (*C*(2)), 139.4 (*C*(5)), 128.7 (*C*(1)), 128.5 (*C*(4)), 125.3 (*C*(6)), 118.2 (*C*(4)), 48.1 (*C*(2')), 12.7 (*C*(1')); *m/z* (ESI$^+$) 223.0 (MH$^+$, 100%); HRMS (ESI$^+$) m/z: [MH]+ Calcd for $C_{11}H_{15}N_2O_3$ 223.1077; Found 223.1079.

5-Bromo-2-(diethylamino)benzaldehyde (21j)

General procedure A (24 h) from 5-bromo-2-fluorobenzaldehyde (300 μL, 2.53 mmol), diethylamine (300 μL, 2.91 mmol) and potassium carbonate (402 mg, 2.91 mmol) to give **21j** (304 mg, 1.19 mmol, 47%) as a yellow oil. R_f (20% hexane in DCM) 0.77; ν_{max}/cm^{-1} 1739, 1680, 1467, 1585; ^{1}H NMR (400 MHz, $CDCl_3$) 10.24 (1H, s, C*H*O), 7.89 (1H, d, *J* 2.6, C(6)*H*), 7.56 (1H, dd, *J* 8.7, 2.6, C(4)*H*), 7.03 (1H, d, *J* 8.7, C(3)*H*), 3.17 (4H, q, *J* 7.1, C(1')H_2), 1.05 (6H, t, *J* 7.1, C(2')H_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 190.7 (*C*HO), 153.5 (*C*(2)), 137.0 (*C*(4)), 132.1 (*C*(1)), 131.7 (*C*(6)), 123.7 (*C*(3)), 115.6 (*C*(5)), 49.1 (*C*(1')), 12.4 (*C*(2')); HRMS (CI$^+$) m/z: [M]+ Calcd for $C_{11}H_{15}BrNO$ 256.0332; Found 256.0333.

Methyl (2'*R*,3*R*,6*R*,7a*R*)-3-(*tert*-butyl)-1'-ethyl-2'-methyl-5,7-dioxo-1',4'-dihydro-1*H*,2'*H*,3*H*,5*H*-spiro[pyrrolo[1,2-*c*]oxazole-6,3'-quinoline]-7a(7*H*)-carboxylate (22a)

General procedure B (6 h) from tetramate **5a** (100 mg, 0.39 mmol) and 2-(diethylamino)benzaldehyde **21a** (76 mg, 0.43 mmol) to give spirocycle **22a** (11 mg, 0.027 mmol, 7%) *via in vacuo* concentration of reaction mixture instead of precipitation, isolated as a mixture of 2 diastereomers. R_f (5% MeOH in EtOAc) 0.91; ^{1}H NMR (600 MHz, C_6D_6, 3:1 mixture of diastereomers) major isomer **22a'''** 7.13 (1H, t, *J* 7.3, C(11')*H*), 7.04 (1H, d, *J* 7.4, C(9')*H*), 6.77 (1H, td, *J* 7.4, 1.1, C(10')*H*), 6.57 (1H, d, *J* 8.2, C(12')*H*), 5.13 (1H, s, C(3)*H*), 4.69 (1H, d, *J* 9.0, C(1)H_AH_B), 4.30 (1H, qd, *J* 6.5, 1.0, C(5')*H*), 3.48 (1H, d, *J* 17.4, C(7')H_AH_B), 3.22 (3H, s, CO_2CH_3), 3.19 – 3.10 (1H, m, C(1')H_AH_B), 3.02 (1H, d, *J* 9.0, C(1)H_AH_B), 2.93 (1H, dq, *J* 14.5, 7.2, C(1')H_AH_B), 2.50 (1H,

d, *J* 17.1, C(7')H_AH_B), 1.10 (3H, d, *J* 6.6, C(4')H_3), 1.03 (9H, s, C(CH_3)$_3$), 0.90 (3H, t, *J* 7.1, C(2')H_3); ^{13}C{^{1}H} NMR (125 MHz, C_6D_6) major isomer **22a'''** 199.5 (*C*(7)), 177.8 (*C*(5)), 168.1 (*C*O_2CH_3), 142.3 (*C*(13')), 129.7 (*C*(9')), 128.4 (*C*(11')), 117.4 (*C*(8')), 117.2 (*C*(10')), 112.2 (*C*(12')), 98.9 (*C*(3)), 78.6 (*C*(7a)), 69.7 (*C*(1)), 56.4 (*C*(6)), 56.2 (*C*(5')), 52.9 (CO_2CH_3), 45.6 (*C*(1')), 35.5 (*C*(CH$_3$)$_3$), 26.8 (*C*(7')), 25.1 (C(*C*H$_3$)$_3$), 15.3 (*C*(4')), 13.9 (*C*(2')); *m/z* (ESI$^+$) 415.0 (MH$^+$, 100%); HRMS (ESI$^+$) m/z: [MH]+ Calcd for $C_{23}H_{31}N_2O_5$ 415.2227; Found 415.2225.

Methyl (3*R*,7a*R*)-1'-benzyl-3-(*tert*-butyl)-5,7-dioxo-2'-phenyl-1',4'-dihydro-1*H*,2'*H*,3*H*,5*H*-spiro[pyrrolo[1,2-*c*]oxazole-6,3'-quinoline]-7a(7*H*)-carboxylate (22h)

General procedure B (6 h) from tetramate **5a** (50 mg, 0.20 mmol) and impure 2-(dibenzylamino)benzaldehyde **21h** (65 mg, 0.22 mmol) to give spirocycle **22h** (46 mg, 0.085 mmol, 43%) *via in vacuo* concentration of reaction mixture instead of precipitation, isolated as a mixture of 4 diastereomers. R_f (25% EtOAc in petrol) 0.71; ^{1}H NMR (400 MHz, C_6D_6, mixture of diastereomers) major isomer 7.36 – 7.29 (2H, m, Ar), 7.18 – 6.91 (10H, m, Ar), 6.78 (1H, t, *J* 7.4, C(10')*H*), 6.56 (1H, d, *J* 8.2, C(12')*H*), 5.49 (1H, s, C(5')*H*), 5.06 (1H, s, C(3)*H*), 4.74 (1H, d, *J* 9.0, C(1)H_AH_B), 4.39 (1H, d, *J* 17.6, C(1')H_AH_B), 4.06 (1H, d, *J* 17.6, C(1')H_AH_B), 3.53 (1H, d, *J* 17.2, C(7')H_AH_B), 3.10 (1H, d, *J* 8.6, C(1)H_AH_B), 2.94 (3H, s, CO_2CH_3), 2.62 (1H, d, *J* 17.2, C(7')H_AH_B), 1.02 (9H, s, C(CH_3)$_3$); ^{13}C{^{1}H} NMR (100 MHz, C_6D_6) major isomer 199.4 (*C*(7)), 175.4 (*C*(5)), 167.5 (*C*O_2CH$_3$), 144.7 (Ar), 138.6 (Ar), 129.6 (*C*(9')), 128.8 – 127.1 (Ar), 126.5 (Ar), 117.6 (*C*(8')), 111.0 (*C*(12')), 98.8 (*C*(3)), 79.0 (*C*(7a)), 70.0 (*C*(1)), 64.0 (*C*(5')), 57.8 (*C*(6)), 53.8 (*C*(1')), 53.0 (CO_2CH_3), 35.6 (*C*(CH$_3$)$_3$), 27.0 (*C*(7')), 25.2 (C(*C*H$_3$)$_3$); *m/z* (ESI$^+$) 539.2 (MH$^+$, 100%); HRMS (ESI$^+$) m/z: [MH]+ Calcd for $C_{33}H_{35}N_2O_5$ 539.2540; Found 539.2537.

5-Bromo-2-(pyrrolidin-1-yl)benzaldehyde (23)

General procedure A (6 h) from 5-bromo-2-fluorobenzaldehyde (300 µL, 2.53 mmol), pyrrolidine (250 µL, 3.04 mmol) and potassium carbonate (420 mg, 3.04 mmol) to give **23** (478 mg, 1.88 mmol, 74%) as a brown oil. R_f (5% EtOAc in petrol) 0.26; ν_{max}/cm^{-1} 1739, 1559, 1458, 1152; ^{1}H NMR (400 MHz, $CDCl_3$) 10.01 (1H, s, C*H*O), 7.78 (1H, d, *J* 2.5, C(6)*H*), 7.41 (1H, dd, *J* 9.0, 2.6, C(4)*H*), 6.71 (1H, d, *J* 9.0, C(3)*H*), 3.38 – 3.29 (4H, m, C(4')H_2), 2.02 – 1.96 (4H, m, C(3')H_2); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 188.9 (*C*HO), 149.0 (*C*(2)), 136.8 (*C*(4)), 134.7 (*C*(6)), 124.0 (*C*(1)), 116.6 (*C*(3)), 108.3 (*C*(5)), 53.0 (*C*(2')), 26.1 (*C*(1')); *m/z* (ESI$^+$) 254.0 (MH$^+$, 100%); HRMS (ESI$^+$) m/z: [MH]+ Calcd for $C_{11}H_{12}BrNO$ 254.0175; Found 254.0175.

4-(Pyrrolidin-1-yl)-[1,1'-biphenyl]-3-carbaldehyde (24)

5-bromo-2-(pyrrolidin-1-yl)benzaldehyde (430 mg, 1.68 mmol) and phenylboronic acid (310 mg, 2.52 mmol) were dissolved in anhydrous THF (20 mL). To the solution were added Pd(dppf)Cl_2 (62.8 mg, 0.216 mmol) and Cs_2CO_3 (1.65 g in 2 mL H_2O, 5.07 mmol). The mixture was stirred at room temperature for 40 min, and then heated to reflux for 48 h. The mixture was then allowed to cool to room temperature, diluted with EtOAc, filtered through Celite and concentrated. The residue was taken up into EtOAc, washed with brine and saturated aqueous $NaHCO_3$ (2 x 15 mL) and concentrated *in vacuo*, and then purified by *flash* column chromatography to give biphenyl **24** (267 mg, 1.06 mmol, 63%) as a yellow oil. R_f (5% EtOAc in petrol) 0.77; ν_{max}/cm^{-1} 1738, 1541, 1494, 1449; ^{1}H NMR (400 MHz, $CDCl_3$) 10.17 (1H, s, C*H*O), 7.96 (1H, d, *J* 2.4, C(3)*H*), 7.67 (1H, dd, *J* 8.8, 2.4, C(6)*H*), 7.62 – 7.56 (2H, m, C(5')*H*), 7.47 – 7.38 (2H, m, C(6')*H*), 7.35 – 7.27 (1H, m, C(7')*H*), 6.92 (1H, d, *J* 8.8, C(5)*H*), 3.47 – 3.37 (4H, m, C(2')*H*), 2.07 – 1.97 (4H, m, C(3')*H*); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 190.3 (*C*HO), 149.4 (*C*(3)), 140.0 (*C*(4')), 132.9 (*C*(6)), 131.3 (*C*(3)), 129.4 (*C*(2)), 128.9 (*C*(6')), 126.7 (*C*(7')), 126.3 (*C*(5')), 123.1 (*C*(4)), 115.3 (*C*(5)), 53.0 (*C*(2')), 26.1 (*C*(1')); HRMS (SI$^+$) m/z: [M]+ Calcd for $C_{17}H_{17}NO$ 251.1310; Found 251.1298.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.xxxx. ^{1}H and ^{13}C NMR spectra; calculated energies; X-ray crystallographic data (PDF).

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