Preparation of Novel Polycyclic Heterocycles Using a Tin(II) Chloride Dihydrate-Mediated Deacetalisation–Bicyclisation Sequence

Alex N. Cayley,[a] Katherine A. Gallagher,[a] Cécilia Ménard-Moyon,[a] Jan Peter Schmidt,[a] Louis J. Diorazio,[b] Richard J. K. Taylor*[a]

[a] Department of Chemistry, University of York, Heslington, York YO10 5DD, UK
Fax +44(1904)434523; E-mail: rjkt1@york.ac.uk

[b] AstraZeneca, Process Research & Development, Silk Road Business Park, Macclesfield, Cheshire SK10 2NA, UK

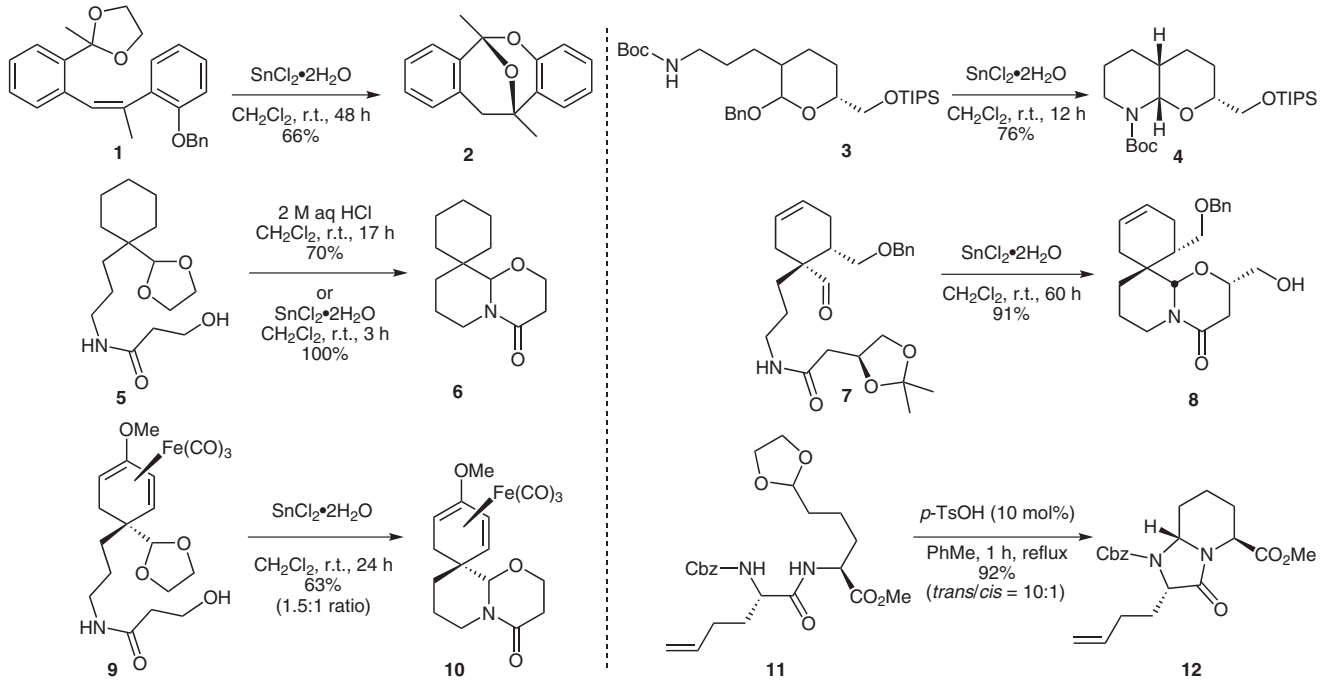
Received 12 August 2008

Abstract: Tin(II) chloride dihydrate-mediated deacetalisation–bicyclisation procedures for the construction of novel polycyclic heterocycles from amides possessing a pendant acetal group are reported. Optimisation and scoping studies are described; using this methodology, a range of known, and novel, ring-fused heterocyclic systems have been prepared, some in enantiomerically pure form.

Key words: heterocycles, tin(II) chloride dihydrate, deacetalisation, bicyclisation, tandem processes

The formation of novel polycyclic heterocycles is of great interest to the synthetic organic chemist. This interest is not purely of an academic nature but also based on the fact that polycyclic heterocycles are considered to be 'privileged structures' in the pharmaceutical and agrochemical industries.[1] Thus, new methods for the construction of such compounds with low molecular weights are invaluable in the search for bioactive lead compounds. In this paper we report the preparation of a range of polycyclic heterocyclic systems using a tin(II) chloride dihydrate ($SnCl_2{\cdot}2H_2O$) mediated deprotection–bicyclisation sequence in the key step. Tin(II) chloride is widely used as a reducing agent and as a Lewis acid catalyst[2] and, as its dihydrate, has been employed as a mild reagent for the deprotection of acetals.[3]

This research was inspired by recent natural product studies in our group which featured the use of $SnCl_2{\cdot}2H_2O$-mediated deprotection–cyclisation processes. As illustrated in Scheme 1, treatment of acetal **1** with $SnCl_2{\cdot}2H_2O$ gave the racemic [6,6,6,6]-tetracyclic core **2** of the HIV-1 integrase inhibitors integrastatins A and B via a presumed sequence of acetal deprotection, debenzylation, hemi-acetal formation, and alkene etherification.[4] More recently, in an effort directed towards the total synthesis of the macro-



Scheme 1

SYNTHESIS 2008, No. 23, pp 3846–3856
Advanced online publication: 30.10.2008
DOI: 10.1055/s-0028-1083214; Art ID: P08508SS

cyclic marine alkaloid 'upenamide,[5] it was found that $SnCl_2{\cdot}2H_2O$ can be employed in the key step for the construction of the core systems **4**,[6] **6**[7] and **8**[8] from the respective precursors **3**, **5** and **7**. The $SnCl_2{\cdot}2H_2O$ deacetalisation–bicyclisation procedure was subsequently employed by Han and Ong to prepare the iron tricarbonyl–cyclohexadiene analogue **10**,[9] thus establishing still further its mild nature and synthetic utility. It should be noted that a number of acid-catalysed deprotection–bicyclisation procedures have been reported leading to related O/N-bicyclic acetals[10] as well as to N/N-bicyclic systems.[11,12] For example (Scheme 1), in 2006, Blaauw and co-workers converted acetal **11** into bicycle **12**, which was subsequently transformed into the natural product (–)-dysibetaine PP.[11]

The generality and simplicity of the $SnCl_2{\cdot}2H_2O$ cyclisation procedures, coupled with the novelty of the heterocycles produced, encouraged us to investigate further applications of this methodology. Preliminary results were published in a recent communication.[13] We have since carried out additional optimisation and scoping studies and now present a more detailed discussion of this one-pot, tandem deprotection–bicyclisation procedure.

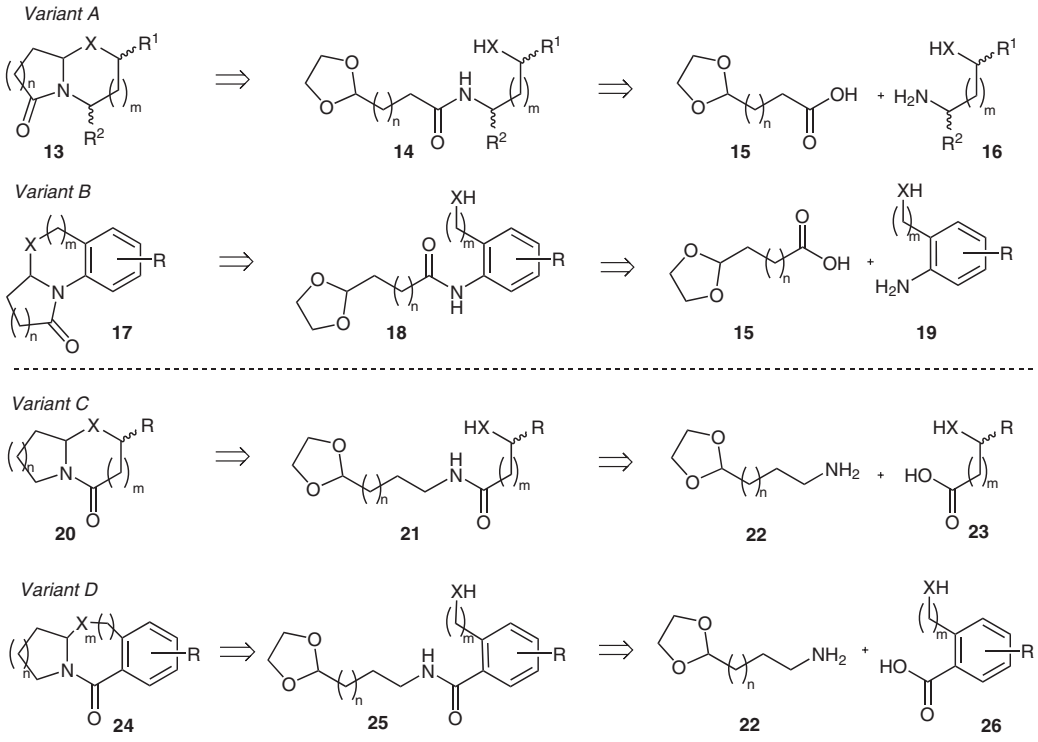
Four variants of the tandem deprotection–bicyclisation procedure were investigated and these are outlined in retrosynthetic form in Scheme 2. It was envisaged that the most useful, general coupling partners would be the dioxolane-acids **15** and the dioxolane-amines **22**. Thus, variants A and B would both utilise dioxolane-acids **15** as the coupling partner. In Variant A, bicycles **13** would be prepared from amides **14** which would in turn be prepared by coupling dioxolane-acids **15** with ω-functionalised aliphatic amines **16**. In Variant B, the benzannelated analogues, tricycles **17**, would be prepared via amides **18** from dioxolane-acids **15** with ω-functionalised aryl amines **19**.

Similarly, in Variant C, bicycles **20** would be prepared from amides **21**, which would in turn be obtained by coupling dioxolane-amines **22** with ω-functionalised aliphatic acids **23**. Variant D would then involve the preparation of the benzannelated analogues, tricycles **24**, from amides **25** derived from dioxolane-amines **22** and ω-functionalised aryl acids **26**.

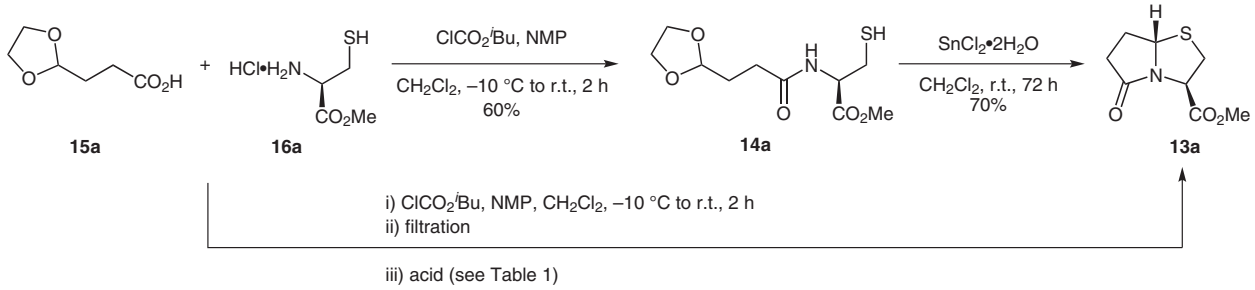
(i) Heterocycles via Variant A

Having identified four variants for the construction of novel polycyclic heterocycles by tandem deprotection–bicyclisation procedures, we initially decided to evaluate the feasibility of Variant A starting from L-cysteine methyl ester hydrochloride (**16a**; Scheme 3). Thus, coupling of the readily available dioxolane-acid **15a**[14] with amine **16a** using the mixed anhydride method gave the required amide **14a** in 60% purified yield. We were delighted to observe that treatment of amide **14a** with $SnCl_2{\cdot}2H_2O$ in dichloromethane for 72 hours gave methyl 5-oxohexahydropyrrolo[2,1-*b*]thiazole-3-carboxylate (**13a**)[15] in 70% yield. This one-pot tandem deprotection–bicyclisation process produced **13a** as a single diastereoisomer {$[\alpha]_D^{23}$ –250.7 (*c* 1.25, $CHCl_3$)}, which was tentatively assigned the (presumed thermodynamically preferred) 3*R*,7a*S*-configuration shown, on the basis of NMR studies.

Attempts to combine the two-step amide-formation–deprotection–bicyclisation sequence into a single one-pot



Scheme 2



Scheme 3

process failed. However, it was found that minimal purification (filtration through silica gel and removal of the volatiles in vacuo) of the intermediate amide **14a** prior to treatment with $SnCl_2·2H_2O$ in dichloromethane was sufficient to provide the bicycle **13a** in 68% isolated yield (as compared to the 42% overall yield for the two-step process involving purification of intermediate **14a**).

At this stage we screened a range of mineral, organic and Lewis acids in the deprotection–bicyclisation process (Table 1). In view of related cyclisation sequences, dilute hydrochloric acid[10] and *p*-TsOH·H_2O[11] were studied first (entries 1 and 2) but mixtures of products were obtained and the yields of compound **13a** were disappointing. The widely used Lewis acid, $BF_3·Et_2O$, gave a similarly low yield (entry 3), as did $SnBr_2$ and $SnCl_4$ (entries 4 and 5). Anhydrous $SnCl_2$ gave an improved yield (57%, entry 6) but the original procedure using $SnCl_2·2H_2O$ proved to be the best (68% over two steps from **15a**, entry 7). A likely rationale is that $SnCl_2·2H_2O$ slowly releases dilute hydrochloric acid to aid acetal cleavage in addition to the Lewis acidic Sn(II) to aid the bicyclisation process; this theory is supported by the fact that addition of potassium carbonate to the $SnCl_2·2H_2O$ reaction resulted in a dramatic loss of activity. However, it is noteworthy that $CuCl_2·2H_2O$, a reagent which efficiently hydrolyses acetals when used in ethanol,[16] proved to be totally ineffective in dichloromethane (entry 8).

It should be noted that the ability of tin(II) chloride to act as a reductant can also be exploited. Thus, processing of the disulfide, L-cysteine dimethyl ester dihydrochloride **27**, through the same coupling and $SnCl_2·2H_2O$ conditions via amide **28** gave the same heterocycle **13a** in 59% overall yield (Scheme 4). In the second step, the $SnCl_2·2H_2O$ is mediating the three-step disulfide reduction–deprotection–bicyclisation sequence.

Next, three further examples were explored in order to indicate the generality of the procedure (Scheme 5). Thus,

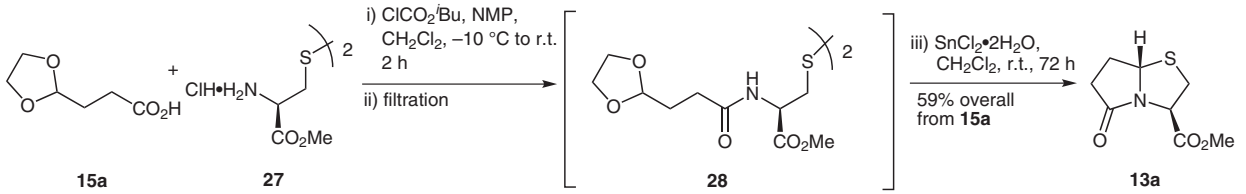
Table 1 Yields of **13a** from **15a** Using the Deprotection–Bicyclisation Process

Entry	Reagent	Solvent	Temp	Time (h)	Yield (%)
1	10% aq HCl	CH_2Cl_2	r.t.	72	39
2	*p*-TsOH·H_2O (cat)	PhMe	reflux	2	29
3	$BF_3·Et_2O$ (2 equiv)	CH_2Cl_2	r.t.	24	26
4	$SnBr_2$ (2 equiv)	CH_2Cl_2	r.t.	72	35
5	$SnCl_4$ (2 equiv)	CH_2Cl_2	r.t.	72	5
6	$SnCl_2$ (2 equiv)	CH_2Cl_2	r.t.	72	57
7	$SnCl_2·2H_2O$ (2 equiv)	CH_2Cl_2	r.t.	72	68
8	$CuCl_2·2H_2O$ (2 equiv)	CH_2Cl_2	r.t.	24	0

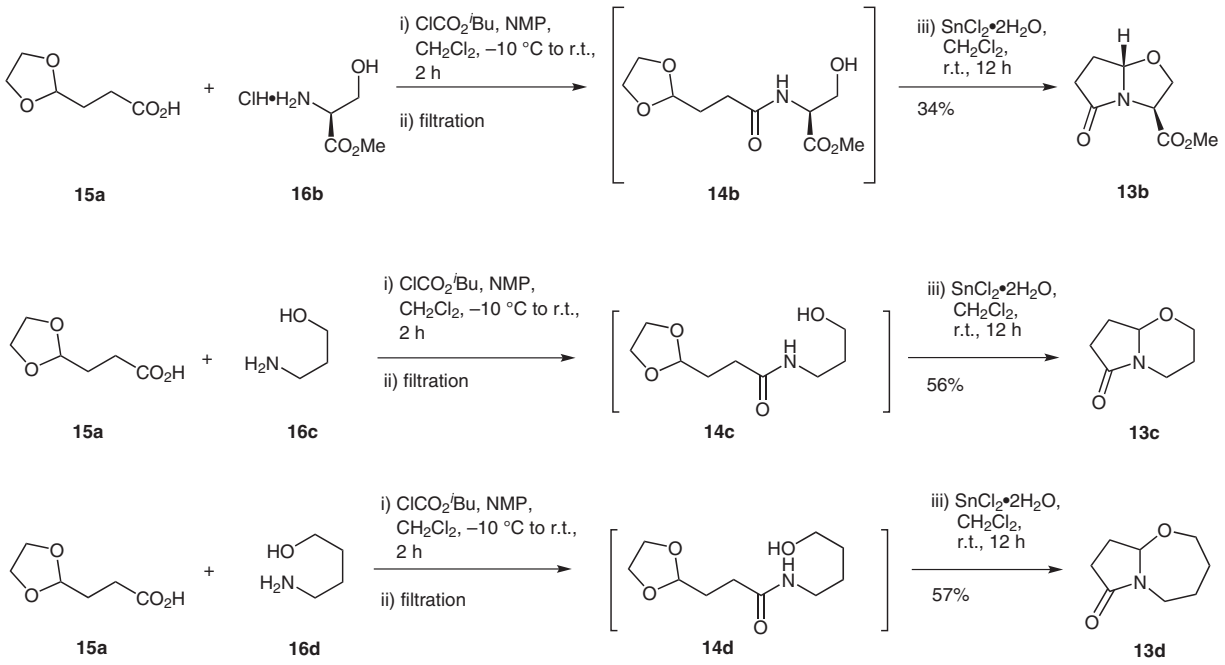
amide formation between acid **15a** and L-serine derivative **16b** followed by treatment with $SnCl_2·2H_2O$ induced the desired deacetalisation–bicyclisation reaction to give the novel heterocycle **13b** {$[\alpha]_D^{23}$ –124.3 (*c* 1.0, $CHCl_3$)} in moderate yield over the two-step process. In a similar manner, amide formation between acid **15a** and 3-aminopropanol (**16c**) followed by deacetalisation–bicyclisation gave the known heterocyclic system **13c**[17] {hemi-aminal proton: δ_H = 4.94 ppm, 1 H, dd, *J* = 6.5, 2.8 Hz; IR 1690 cm^{-1}; Lit.[17] δ_H = 4.94 ppm, 1 H, m; IR 1690 cm^{-1}}. The novel, higher homologue **13d** was then prepared from 4-aminobutanol (**16d**) in reasonable yield over the two steps.

(ii) Heterocycles via Variant B

Our attention next turned to the second combination of coupling partners outlined in Scheme 2, in which the same dioxolane-acid **15a** is coupled with ω-functionalised aryl amines **19** to generate benzannelated tricycles **17**, via amides **18**. The initial example explored was unsuccess-



Scheme 4



Scheme 5

ful: conversion of 2-aminophenol (**19a**) into amide **18a** was straightforward, but all attempts to effect the cyclisation to give **17a** failed (Scheme 6). On the assumption that this failure was due to the low nucleophilicity of the phenolic group and/or to ring strain in the product, ω-functionalised anilines **19b–d** were studied. In the case of the corresponding thiophenol **19b**, coupling again proceeded smoothly but in this example, treatment with $SnCl_2 \cdot 2H_2O$ promoted the desired deacetalisation–bicyclisation reaction to give the novel heterocycle **17b** accompanied by the cyclisation precursor **29**.

Encouraged by this partial success, we investigated the use of 2-aminobenzyl alcohol **19c** and the corresponding thiol **19d** (Scheme 6). In both cases, the coupling and deacetalisation–bicyclisation proceeded smoothly, giving the novel benzannelated heterocycles **17c** and **17d** in 80 and 86% overall yields, respectively. Finally, in a slight variation, the *N*-methylated diamine **30** was subjected to the coupling–deacetalisation–bicyclisation sequence to produce the linear tricyclic adduct **32** in 43% overall yield, further illustrating the potential of this methodology.

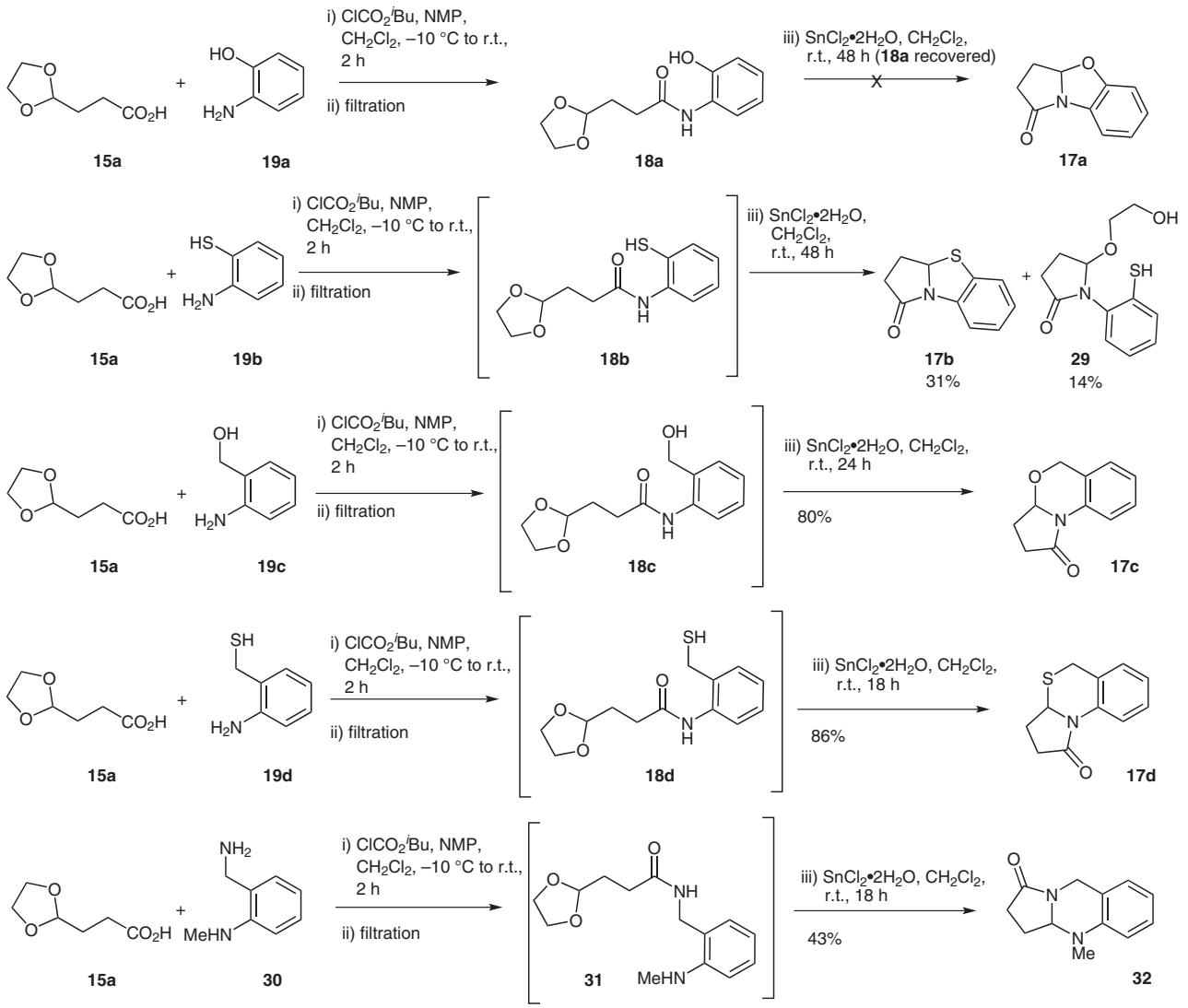
(iii) Heterocycles Via Variant C

Having established the viability of procedures utilising dioxolane-acid **15a** for heterocycle formation, we moved on to explore the potential of dioxolane-amines **22**, initially looking at their coupling with ω-functionalised aliphatic acids **23** (Scheme 7). In the initial example, amine **22a**[18] was coupled to (*R*)-mandelic acid **23a**; it was established that 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU)-mediated peptide coupling was preferable to the mixed anhydride method for the formation of amide **21a**. The $SnCl_2 \cdot 2H_2O$-mediated deacetalisation–bicyclisation proceeded cleanly, if in modest yield, to give the novel bicyclo[3.3.0]octane heterocyclic products **20a** as a separable mixture of two diastereoisomers. In a similar manner, *N*-Boc-L-alanine (**23b**) was converted into an inseparable mixture of novel diazabicyclo[3.3.0]octanes **20b** (ratio established by NMR spectroscopy).[19] In both **20a** and **20b**, the major diastereoisomer was tentatively assigned by inspection of molecular models (NMR and NOE studies were uninformative). Finally in this section, amine **22a** and *N*-Boc-L-serine **23c** gave the bicyclo[4.3.0]nonane adduct **20c** as a single diastereoisomer in 46% yield $\{[\alpha]_D^{22}$ +32.5 (*c* 0.95, $CHCl_3)\}$.

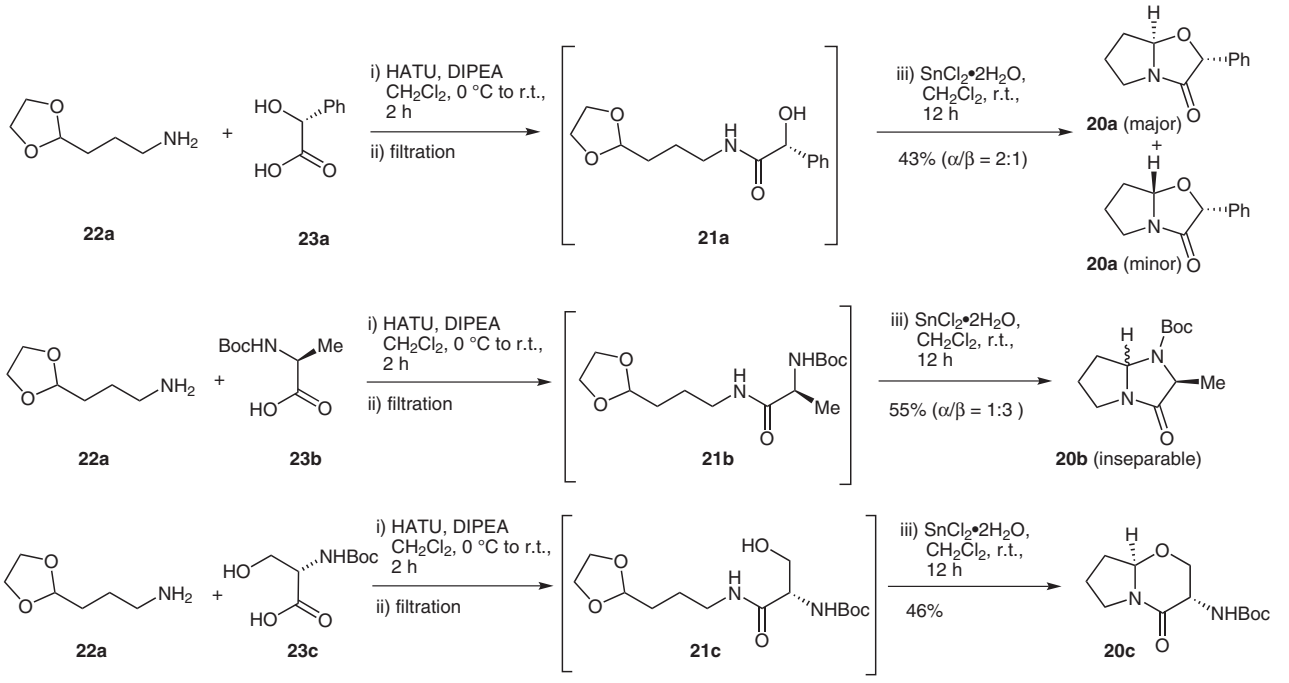
(iv) Heterocycles via Variant D

The final variant to be explored utilised dioxolane-amine **22a** and ω-functionalised aryl acids **26** (m = 0) to produce benzannelated products **24** (Scheme 8). Once again, the coupling procedure to produce the intermediate amides **25** proved problematic. Using 2-hydroxy-3-methylbenzoic acid (**26a**) to ultimately produce heterocycle **24a**, the mixed anhydride procedure ($ClCO_2{}^tBu$) gave no product and HATU gave the required product **24a** in only 45% yield. Turning to other activated acid derivatives, the acid chloride and methyl ester derived from **26a** gave only trace amounts of product **24a** after attempted coupling and treatment with $SnCl_2 \cdot 2H_2O$. However, we were delighted to find that the phenyl ester derivative **33** underwent efficient coupling to amine **22a** under microwave irradiation (MW) and deacetalisation–bicyclisation using $SnCl_2 \cdot 2H_2O$ gave the expected product **24a** in almost quantitative yield.

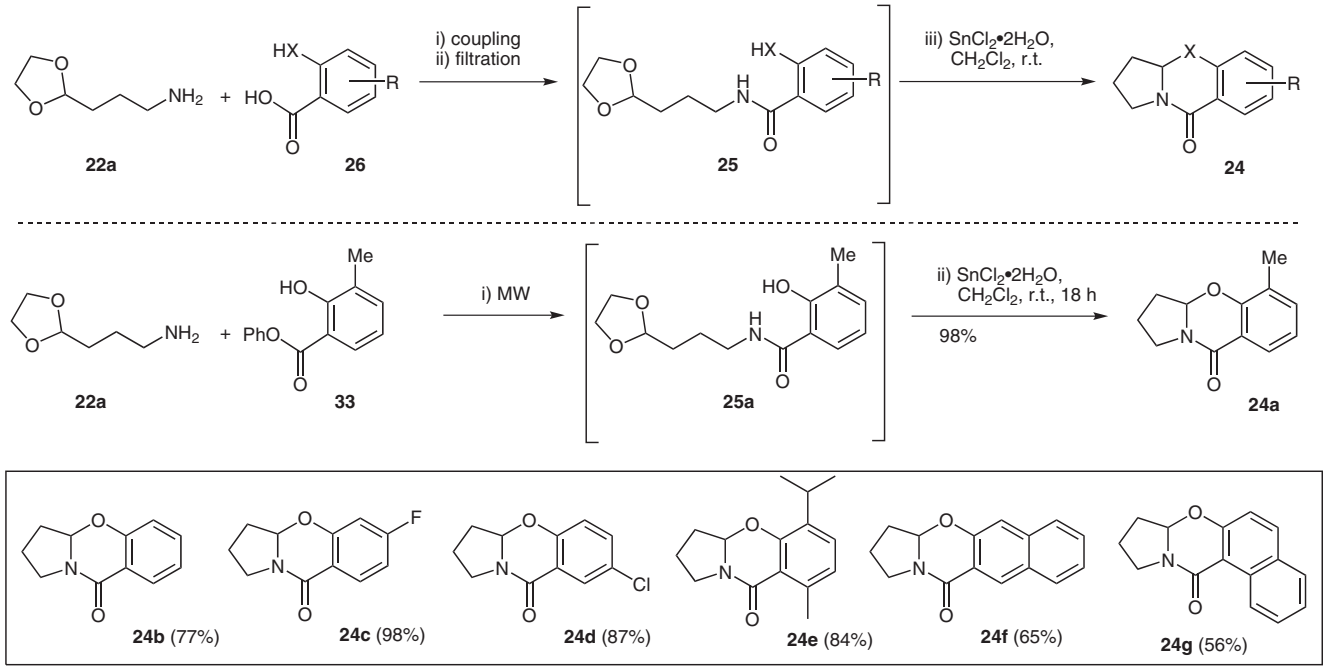
Attempts to develop a tandem process were unsuccessful; heating the mixture of **22a**, **33** and $SnCl_2 \cdot 2H_2O$ under microwave conditions resulted in complete degradation of the starting materials. However, a telescoped procedure



Scheme 6



Scheme 7



Scheme 8

was developed that proved to be extremely straightforward; after heating the amine and ester together neat in a microwave system, the resulting amide was then dissolved directly in dichloromethane and $SnCl_2 \cdot 2H_2O$ was added in a single portion. After stirring at room temperature, the desired heterocycles could then be isolated by flash chromatography. These conditions were then applied to a range of phenyl esters,[20] producing novel polycyclic heterocycles **24b–g** (Scheme 8). These heterocycles all show characteristic ^1H and ^{13}C NMR signals (hemi-aminal protons between δ = 5.33 and 5.65 ppm; hemi-aminal carbons at δ = 87.7–89.0 ppm; e.g. **24a**, δ_H = 5.46 ppm; δ_C = 88.4 ppm).

In summary, we have developed a mild, cheap and simple method of producing a diverse range of polycyclic heterocycles from commercially available or easily accessible starting materials using amide coupling followed by a tin(II) chloride mediated deacetalisation–bicyclisation sequence. The products, several of which have been obtained in diastereoselective processes, should be of interest both in their own right and as building blocks for the production of more complex target molecules. We are currently investigating the application of this methodology to complex natural product targets.

Et_2O was dried using an MBraun MPS solvent purification system. Anhydrous THF was obtained by distillation over sodium benzophenone. Petroleum ether (PE) refers to light petroleum ether, bp 40–60 °C. All reagents were used as supplied by the manufacturers, unless otherwise stated. $SnCl_2 \cdot 2H_2O$ was purchased from Aldrich and used without further purification. 3-[1,3]-Dioxolan-2-ylpropionic acid (**15a**) was prepared by the method of Shea and co-workers;[14] all data were in accordance with the assigned structure, and ^1H NMR data was in accordance with the literature.[14] 3-[1,3]-Dioxolan-2-ylpropylamine (**22a**) was prepared by the method of Shimizu and co-workers;[18] all data were in accordance with the assigned structure, and ^1H NMR data was in accordance with the literature.[18]

Flash column chromatography was performed using Fluka silica gel 60 at a low positive pressure. Analytical TLC was performed on aluminium sheets precoated with Merck silica gel 60 F_{254}, and visualised with ultraviolet light (254 nm), aq $KMnO_4$ or alcoholic vanillin solutions, as appropriate. Preparative TLC was performed on Whatman Partasil K6F precoated 60 Silica Gel Glass plates, and visualised under UV light (254 nm). SCX refers to prepacked Varian BondElut SCX columns (1 g). All melting points were taken on a Gallenkamp apparatus. ^1H NMR spectra were recorded at 400 MHz on a JEOL ECX 400 spectrometer or at 270 MHz on a JEOL ECX 270 spectrometer and are reported as follows: chemical shift (δ, ppm), multiplicity, coupling constant *J* (to the nearest 0.5 Hz), number of protons, assignment. Residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm) or DMSO (δ_H = 2.50 ppm) was used as an internal reference. ^{13}C NMR spectra were recorded at 100 MHz on a JEOL ECX 400 spectrometer or at 125 MHz on a Bruker AV500 spectrometer. The central peak of $CDCl_3$ (δ_C = 77.0 ppm) or DMSO (δ_C = 39.4 ppm) was used as an internal reference. ^{19}F NMR spectra were recorded at 376 MHz on a JEOL ECX 400 spectrometer. Chemical shifts are reported in parts per million (ppm) to the nearest 0.01 ppm for ^1H and the nearest 0.1 ppm for ^{13}C and ^{19}F. Infrared spectra were carried out on a ThermoNicolet IR100 spectrometer and are recorded as a liquid film or a Nujol® mull between NaCl disks. Absorption maxima are reported in wavenumbers (cm^{-1}) and only selected absorbencies are reported. Mass spectra and accurate mass measurements were recorded on a Micromass Autospec spectrometer.

Microwave irradiation refers to the use of a CEM 'Discovery' reactor, with reactions contained in 10 mL CEM tubes with Intellivent® caps.

Methyl 2-(3-[1,3]Dioxolan-2-ylpropionylamino)-3-mercaptopropanoate (14a)

Isobutyl chloroformate (44 μL, 0.34 mmol) was added dropwise to a solution of acid **15a**[14] (50 mg, 0.34 mmol) and *N*-methylpiperidine (41 μL, 0.34 mmol) in CH_2Cl_2 (4 mL) at –10 °C (acetone–ice bath). After exactly 2 min, an ice-cold solution of L-cysteine methyl ester

hydrochloride (**16a**; 62 mg, 0.36 mmol) and *N*-methylpiperidine (44 μL, 0.36 mmol) in CH_2Cl_2 (1 mL) was added dropwise and stirring was continued at –10 °C for 1 h and then the reaction mixture was slowly allowed to warm to r.t. and stirred for a further 1 h. The solution was then filtered through a short pad of silica gel, washing through with EtOAc (3 × 5 mL) and the volatiles removed from the filtrate in vacuo to give the crude amide **14a**, which was used immediately in the subsequent cyclisation reaction without further purification. If so desired, the crude amide **14a** could be purified by flash column chromatography (SiO_2, EtOAc), to give the title compound **14a**.

Yield: 54 mg (60%); clear colourless oil; $[\alpha]_D^{23}$ +41.9 (*c* 1.00, $CHCl_3$); R_f = 0.40 (EtOAc).

IR (neat): 3300 (br), 2955, 2886, 1740, 1659, 1531, 1439, 1242, 1215, 1140, 1042 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.36 (t, *J* = 9.0 Hz, 1 H, SH), 1.98–2.03 (m, 2 H, CH_2), 2.37 (t, *J* = 7.5 Hz, 2 H, CH_2C=O), 2.96 (dd, *J* = 9.0, 4.0 Hz, 2 H, C*H*$_2$SH), 3.76 (s, 3 H, CO_2CH_3), 3.82–3.87 (m, 2 H, OCH_2), 3.92–3.99 (m, 2 H, OCH_2), 4.86 (dt, *J* = 7.5, 4.0 Hz, 1 H, C*H*CO_2CH_3), 4.92 [t, *J* = 4.0 Hz, 1 H, C*H*$(OCH_2)_2$], 6.71 (br d, *J* = 7.5 Hz, 1 H, NHCO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.7, 28.9, 30.1, 52.7, 53.5, 64.9, 103.1, 170.6, 172.2.

MS (ESI): *m*/*z* (%) = 286 (20) $[M + Na]^+$, 264 (100) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{18}NO_5S$: 264.0900; found: 264.0907 (3.3 ppm error).

Methyl (3*R*,8*S*)-5-Oxohexahydropyrrolo[2,1-*b*]thiazole-3-carboxylate (13a)

*Method A: From Purified **14a***

Amide **14a** (100 mg, 0.38 mmol) was dissolved in CH_2Cl_2 (5 mL) and $SnCl_2{\cdot}2H_2O$ (0.17 g, 0.76 mmol) added. The reaction mixture was stirred for 72 h at r.t. then diluted with $CHCl_3$ (5 mL) and treated with K_2CO_3 (0.25 g, 1.8 mmol). Stirring was continued for a further 30 min then the mixture was filtered through a short pad of Celite®, washing through with $CHCl_3$ (3 × 10 mL). The filtrate was concentrated in vacuo and the crude product was purified by flash column chromatography (SiO_2, PE–EtOAc, 1:1), to give the title compound **13a**.

Yield: 53 mg (70%); clear colourless oil; $[\alpha]_D^{23}$ –250.7 (*c* 1.25, $CHCl_3$); R_f = 0.33 (PE–EtOAc, 1:1).

IR (neat): 2954, 1743, 1709, 1437, 1388, 1285, 1218, 1177 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.09–2.19 (m, 1 H, CH*H*), 2.48–2.59 (m, 2 H, CH*H*C=O, C*H*H), 2.60–2.73 (m, 1 H, C*H*HC=O), 3.33 (dd, *J* = 11.5, 4.5 Hz, 1 H CH*H*S), 3.38 (dd, *J* = 11.5, 7.5 Hz, 1 H, C*H*HS), 3.73 (s, 3 H, CO_2CH_3), 5.08 (dd, *J* = 7.5, 4.5 Hz, 1 H, C*H*CO_2CH_3), 5.19 (dd, *J* = 7.0, 4.0 Hz, 1 H, NCHS).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 31.0, 36.1, 52.7, 57.6, 66.3, 170.2, 176.3.

MS (ESI): *m*/*z* (%) = 202 (100) $[M + H]^+$, 142 (10) $[M – CO_2Me]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_8H_{12}NO_3S$: 202.0532; found: 202.0539 (3.3 ppm error).

Method B: Telescoped Procedure

Unpurified amide **14a** (see above) was redissolved in CH_2Cl_2 (5 mL). $SnCl_2{\cdot}2H_2O$ (0.17 g, 0.75 mmol) was added to this solution and the reaction mixture was stirred at r.t. for 72 h, whereupon it was diluted with $CHCl_3$ (5 mL) and then treated with K_2CO_3 (0.25 g, 1.8 mmol). Stirring was continued for a further 30 min then the mixture was filtered through a short pad of Celite®, washing through with $CHCl_3$ (3 × 10 mL). The filtrate was concentrated in vacuo and the crude product was purified by flash column chromatography (SiO_2, PE–EtOAc, 1:1), to give the title compound **13a**.

Yield: 46 mg (68% over two steps from **15a**); clear colourless oil.

*Method C: From Disulfide **27***

L-Cysteine dimethyl ester dihydrochloride (**27**; 128 mg, 0.37 mmol) and 3-[1,3]dioxolan-2-ylpropionic acid (**15a**; 100 mg, 0.68 mmol) were converted into amide **28** according to the procedure used for amide **14a** (see above). The unpurified amide **28** was then treated with $SnCl_2{\cdot}2H_2O$ (306 mg, 1.36 mmol) for 72 h following the procedure used in methods A and B above. The crude product was purified by flash column chromatography (SiO_2, Et_2O), to give the title compound **13a**.

Yield: 82 mg (59% over two steps); clear colourless oil.

Methyl (3*S*,8*S*)-5-Oxohexahydropyrrolo[2,1-b]oxazole-3-carboxylate (13b)

Prepared from L-serine methyl ester hydrochloride (**16b**; 56 mg, 0.36 mmol) and 3-[1,3]dioxolan-2-ylpropionic acid (**15a**; 50 mg, 0.34 mmol) according to the procedures described for the preparation of compound **13a**. The unpurified amide was stirred with $SnCl_2{\cdot}2H_2O$ (153 mg, 0.68 mmol) for 12 h and the crude product was purified by flash column chromatography (SiO_2, Et_2O), to yield the title compound **13b**.

Yield: 21 mg (34% over two steps); clear colourless oil; $[\alpha]_D^{23}$ –124.3 (*c* 1.0, $CHCl_3$); R_f = 0.24 (Et_2O).

IR (neat): 2956, 2921, 1719, 1403, 1279, 1212, 1173, 1007 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.06–2.17 (m, 1 H, CH*H*), 2.38–2.56 (m, 2 H, CH*H*C=O, C*H*H), 2.65–2.75 (m, 1 H, C*H*HC=O), 3.78 (s, 3 H, CO_2CH_3), 3.91 (dd, *J* = 8.5, 6.5 Hz, 1 H, CH*H*O), 4.36 (t, *J* = 8.5 Hz, 1 H, C*H*HO), 4.68 (dd, *J* = 8.5, 6.5 Hz, 1 H, C*H*CO_2CH_3), 5.20 (dd, *J* = 6.0, 2.0 Hz, 1 H, NCHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.8, 30.9, 52.7, 56.0, 69.5, 93.0, 170.6, 179.5.

MS (ESI): *m*/*z* (%) = 186 (100) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_8H_{12}NO_4$: 186.0761; found: 186.0761 (0.1 ppm error).

Tetrahydropyrrolo[2,1-*b*][1,3]oxazin-6-one (13c)

Prepared from 3-amino-1-propanol (**16c**; 55 μL, 0.71 mmol) and 3-[1,3]dioxolan-2-ylpropionic acid (**15a**; 100 mg, 0.68 mmol) according to the procedures described for the preparation of compound **13a**. The unpurified amide was stirred with $SnCl_2{\cdot}2H_2O$ (306 mg, 1.36 mmol) for 12 h, then the crude product was purified by flash column chromatography (SiO_2, MeOH–CH_2Cl_2, 5:95), to give the title compound **13c**.

Yield: 54 mg (56% over two steps); clear colourless oil; R_f = 0.46 (MeOH–CH_2Cl_2, 5:95).

IR (neat): 2960, 2864, 1690, 1451, 1277, 1076, 1053 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.44–1.50 (m, 1 H, C*H*HCNO), 1.74–1.93 (m, 2 H, CH_2), 2.22–2.39 (m, 2 H, CH*H*C=O, C*H*H), 2.45–2.54 (m, 1 H, C*H*HC=O), 3.08 (td, *J* = 13.0, 4.0 Hz, 1 H, CH*H*N), 3.71 (td, *J* = 12.0, 2.0 Hz, 1 H, CH*H*O), 4.06–4.12 (m, 1 H, C*H*HO), 4.15–4.21 (m, 1 H, C*H*HN), 4.94 (dd, *J* = 6.5, 2.5 Hz, 1 H, NCHO). Consistent with published data.[16]

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 24.7, 28.8, 38.6, 67.0, 88.0, 173.5.

MS (CI, NH_3): *m*/*z* (%) = 159 (80) $[M + NH_4]^+$, 142 (100) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_7H_{11}NO_2Na$: 164.0682; found: 164.0680 (1.3 ppm error).

Hexahydropyrrolo[2,1-*b*][1,3]oxazepin-7-one (13d)

Prepared from 4-amino-1-butanol (**16d**; 33 μL, 0.36 mmol) and 3-[1,3]dioxolan-2-ylpropionic acid (**15a**; 50 mg, 0.34 mmol) according to the procedure described for the preparation of compound **13a**.

The unpurified amide was stirred with $SnCl_2·2H_2O$ (153 mg, 0.68 mmol) for 12 h and the crude product was purified by flash column chromatography (SiO_2, MeOH–CH_2Cl_2, 5:95), to yield the title compound **13d**.

Yield: 30 mg (57% over two steps); clear colourless oil; R_f = 0.30 (MeOH–CH_2Cl_2, 5:95).

IR (neat): 2931, 1689, 1419, 1374, 1279, 1186, 1099 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.65–1.95 (m, 5 H, CH_2), 2.21–2.35 (m, 2 H, CH*H*C=O, C*H*H), 2.47–2.58 (m, 1 H, C*H*HC=O), 3.20 (ddd, *J* = 13.5, 6.5, 3.0 Hz, 1 H, CH*H*N), 3.46–3.53 (m, 1 H, CH*H*O), 3.57–3.66 (m, 1 H, C*H*HN), 3.82–3.89 (m, 1 H, C*H*HO), 5.06 (dd, *J* = 6.5, 2.5 Hz, 1 H, NCHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.6, 26.4, 29.4, 30.9, 42.5, 68.8, 90.3, 174.8.

MS (ESI): *m*/*z* (%) = 156 (100) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_8H_{14}NO_2$: 156.1019; found: 156.1018 (0.5 ppm error).

2,3,3a,5-Tetrahydro-1*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazin-1-one (17c)

Prepared from 2-aminobenzyl alcohol (**19c**; 89 mg, 0.72 mmol) and acid **15a** (100 mg, 0.72 mmol) according to the procedure described for the preparation of compound **13a**. The crude amide was stirred with $SnCl_2·2H_2O$ (324 mg, 1.44 mmol) for 24 h and the crude product was purified by flash column chromatography (SiO_2, Et_2O), to yield the title compound **17c**.

Yield: 104 mg (80%); colourless solid; mp 89–90 °C; R_f = 0.38 (Et_2O).

IR (neat): 1695, 1494, 1490, 1215, 1080 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 2.01–2.10 (m, 1 H, C*H*HCH$_2$C=O), 2.47–2.61 (m, 3 H, CH$_2$C=O, CH*H*CH$_2$C=O), 4.90 (d, *J* = 15.0 Hz, 1 H, Ar-CH$_2$O), 5.05 (d, *J* = 15.0 Hz, 1 H, Ar-CH$_2$O), 5.27 (dd, *J* = 7.0, 5.0 Hz, 1 H, OCHN), 7.02 (br d, *J* = 7.5 Hz, 1 H, Ar-H), 7.10 (td, *J* = 7.5, 1.0 Hz, 1 H, Ar-H), 7.26–7.27 (m, 1 H, Ar-H), 8.30 (d, *J* = 8.5 Hz, 1 H, Ar-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.8, 30.1, 58.1, 87.2, 119.6, 123.8, 124.3, 124.4, 127.7, 134.2, 172.0.

MS (ESI): *m*/*z* (%) = 212 (100) $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{11}NO_2Na$: 212.0682; found: 212.0687 (2.2 ppm error).

3,3a-Dihydro-2*H*,5*H*-pyrrolo[2,1-*a*][3,1]benzothiazine-1-one (17d)

Prepared from (2-aminophenyl)methane thiol[21] (**19d**; 106 mg, 0.75 mmol) and 3-[1,3]dioxolan-2-ylpropionic acid (**15a**; 100 mg, 0.68 mmol) according to the procedure for compound **13a**. The crude amide was stirred with $SnCl_2·2H_2O$ (306 mg, 1.36 mmol) for 18 h and the crude product was partially purified by flash column chromatography (MeOH–CH_2Cl_2, 3:97). The impure product was dissolved in MeOH and loaded onto an SCX column. Washing with MeOH then elution with ~0.5M methanolic ammonia and concentration gave the title compound **17d**.

Yield: 105 mg (86%); pale-yellow oil; R_f = 0.65 (MeOH–CH_2Cl_2, 1:10).

IR (neat): 3430, 2095, 1643, 1468, 1210, 1104 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.03–2.11 (m, 1 H, C*H*H), 2.57–2.68 (m, 3 H, CH$_2$=O, CH*H*), 3.70 (d, *J* = 17.0 Hz, 1 H, ArCH$_2$N), 4.30 (d, *J* = 17.0 Hz, 1 H, ArCH$_2$), 5.02–5.05 (m, 1 H, NCHS), 7.10 (br d, *J* = 8.0 Hz, 1 H, Ar-H), 7.15–7.17 (m, 1 H, Ar-H), 7.30 (br t, *J* = 8.0 Hz, 1 H, Ar-H), 8.25 (dd, *J* = 8.0, 1.0 Hz, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9, 30.5, 31.0, 60.9, 122.7, 123.5, 124.4, 127.6, 128.7, 135.9, 173.2.

MS (ESI): *m*/*z* (%) = 228 (100) $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{11}NOSNa$: 228.0454; found: 228.0459 (2.1 ppm error).

4-Methyl-3,3a,4,9-tetrahydro-2*H*-pyrrolo[2,1-*b*]quinazoin-1-one (32)

Prepared from 2-methylaminobenzylamine (**30**; 60 mg, 0.43 mmol)[22] and 3-[1,3]dioxolan-2-ylpropionic acid (**15a**; 58 mg, 0.39 mmol) according to the procedure described for the preparation of compound **13a**. The crude amide was stirred with $SnCl_2·2H_2O$ (175 mg, 0.78 mmol) for 18 h and the crude product was purified by preparative TLC (EtOAc–PE, 1:1) to yield the title compound **32**.

Yield: 35 mg (43%); colourless oil; R_f = 0.31 (EtOAc–PE, 1:1).

IR (neat): 1685, 1498, 1447, 1369, 1307, 1273, 1212 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.02–2.09 (m, 1 H, C*H*HCH$_2$C=O), 2.36–2.57 (m, 3 H, CH*H*CH$_2$C=O, CH$_2$C=O), 2.81 (s, 3 H, NCH$_3$), 4.25 (d, *J* = 17.0 Hz, 1 H, ArC*H*H), 4.56 (t, *J* = 6.0 Hz, 1 H, NCHN), 4.85 (d, *J* = 17.0 Hz, 1 H, ArCH*H*), 6.79–6.81 (m, 2 H, Ar-H), 7.03 (d, *J* = 7.5 Hz, 1 H Ar-H), 7.16 (t, *J* = 7.5 Hz, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.8, 29.5, 33.8, 41.1, 71.9, 113.7, 119.2, 119.6, 126.8, 128.0, 145.7, 173.5.

MS (ESI): *m*/*z* (%) = 225 (100) $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{14}N_2ONa$: 225.0998; found: 225.1006 (3.5 ppm error).

(2*R*)-2-Phenyltetrahydropyrrolo[2,1-*b*]oxazol-3-one (20a)

A solution of 3-[1,3]dioxolan-2-ylpropylamine (**22a**; 0.10 g, 0.76 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a solution of (*R*)-(–)-mandelic acid (**23a**; 0.12 g, 0.80 mmol) and DIPEA (0.16 mL, 0.91 mmol) in CH_2Cl_2 (5 mL) at 0 °C. This was followed immediately by the portionwise addition of HATU (0.32 g, 0.84 mmol) to the reaction. The yellow solution was stirred at 0 °C for 1 h and then allowed to slowly warm to r.t. and stirred for a further 1 h. The reaction was filtered through a short pad of silica, washing through with EtOAc (3 × 10 mL). The volatiles were removed from the filtrate under reduced pressure to yield the crude amide (contaminated with tetramethylurea). The unpurified amide was redissolved in CH_2Cl_2 (8 mL), $SnCl_2·2H_2O$ (0.38 g, 1.67 mmol) was added, and the reaction mixture was stirred at r.t. for 12 h. The mixture was diluted with $CHCl_3$ (8 mL) and then treated with K_2CO_3 (0.5 g, 3.6 mmol) and stirring was continued for a further 30 min. The mixture was filtered through a short pad of Celite®, washing through with $CHCl_3$ (3 × 10 mL). The filtrate was concentrated in vacuo and the crude product was purified by flash column chromatography (SiO_2, EtOAc), to give the title compound **20a**.

Yield: 54 mg (43% over two steps); mixture of diastereoisomers [2:1, separable by careful chromatography: R_f = 0.50 (major), 0.55 (minor) (EtOAc)]; clear colourless oil.

IR (neat): 2979, 2945, 2894, 1717, 1413, 1309, 1091, 911 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (mixture of diastereoisomers) = 1.69–2.26 (m, 4 H, CH_2), 3.07–3.17 (m, 1 H, CH*H*N), 3.74–3.84 (m, 1 H, C*H*HN), 5.38 [s, 1 H, CHC=O (minor)], 5.45 [s, 1 H, CHC=O (major)], 5.59–5.63 [m, 1 H, NCHO (major)], 5.66–5.70 [m, 1 H, NCHO (minor)], 7.30–7.50 (m, 5 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (minor diastereoisomer given in brackets) = 24.3, (24.0), 31.50, (31.45), 43.0, (42.4), 83.7, (83.3), (94.2), 92.7, 126.9, (125.6), 128.5, (128.4), 128.7, (128.6), (136.1), 135.6, (173.6), 173.1.

MS (ESI): *m*/*z* (%) = 204 (100) $[M + H]^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}NO_2$: 204.1019; found: 204.1020 (0.5 ppm error).

tert-Butyl (2*S*)-2-Methyl-3-oxohexahydropyrrolo[1,2-*a*]imidazole-1-carboxylate (20b)

Prepared from 3-[1,3]dioxolan-2-ylpropylamine (**22a**; 0.10 g, 0.76 mmol) and *N*-Boc-L-alanine (**23b**; 0.15 g, 0.80 mmol) according to the procedure described for the preparation of compound **20a**. The crude amide was stirred with $SnCl_2{\cdot}2H_2O$ (342 mg, 1.52 mmol) for 12 h and the crude product **20b** was purified by flash column chromatography (SiO_2, EtOAc), to yield the title compound **20b** as an inseparable mixture of diastereoisomers (3:1).

Yield: 0.10 g (55% over two steps); clear colourless oil; R_f = 0.45 (EtOAc).

IR (neat): 2977, 2933, 1705, 1477, 1450, 1418, 1175, 1136, 1043 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6, 80 °C): δ (mixture of diastereoisomers) = 1.33 [d, *J* = 7.0 Hz, 3 H, CH_3 (major)], 1.37 [d, *J* = 6.5 Hz, 3 H, CH_3 (minor)], 1.45 [s, 9 H, *t*-Bu (minor)], 1.45 [s, 9 H, *t*-Bu (major)], 1.26–1.50 (occluded m, 1 H, CH_2), 1.90–2.07 (m, 2 H, CH_2), 2.14–2.30 (m, 1 H, CH_2), 2.98–3.06 (m, 1 H, CH*H*N), 3.50–3.60 (m, 1 H, C*H*HN), 4.02 [q, *J* = 6.5 Hz, 1 H, CHC=O (minor)], 4.21 [q, *J* = 7.0 Hz, 1 H, CHC=O (major)], 5.06 [dd, *J* = 8.5, 5.5 Hz, 1 H, NCHN (major)], 5.08–5.10 [m, 1 H, NCHN (minor overlaying major diastereoisomer)].

^{13}C NMR (100 MHz, DMSO-d_6, 80 °C): δ (minor diastereoisomer given in brackets) = 17.7 (both diastereoisomers), 23.2, (23.3), 27.6, (27.61), 32.2 (both diastereoisomers), 40.9, (40.5), 56.4 (both diastereoisomers), 74.6, (74.4), 79.5, (79.3), 152.6 (both diastereoisomers), 172.3 (both diastereoisomers).

MS (ESI): *m*/*z* (%) = 263 (10) [M + Na]$^+$, 241 (100), [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{21}N_2O_3$: 241.1547; found: 241.1554 (2.9 ppm error).

tert-Butyl (3*S*,8a*R*)-(4-Oxohexahydropyrrolo[2,1-*b*][1,3]oxazin-3-yl)carbamate (20c)

Prepared from 3-[1,3]dioxolan-2-ylpropylamine (**22a**; 0.10 g, 0.76 mmol) and *N*-Boc-L-serine (**23c**; 0.16 g, 0.80 mmol) according to the procedure described for the preparation of compound **20a**. The crude amide was stirred with $SnCl_2{\cdot}2H_2O$ (342 mg, 1.52 mmol) for 12 h and the crude product **20c** was purified by flash column chromatography (SiO_2, EtOAc), to yield the title compound **20c**.

Yield: 90 mg (46% over two steps); colourless solid; single diastereoisomer; mp 104–106 °C; $[\alpha]_D^{22}$ 32.5 (*c* 0.95, $CHCl_3$); R_f = 0.30 (EtOAc).

IR (Nujol mull): 3343, 2922, 2853, 1724, 1666, 1519, 1458, 1252, 1165, 1000 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 9 H, *t*-Bu), 1.19–2.02 (m, 3 H, CH_2, C*H*HCHNO), 2.20–2.28 (m, 1 H, CH*H*CHNO), 3.35 (ddd, *J* = 11.5, 7.5, 5.5 Hz, 1 H, CH*H*N), 3.64 (dd, *J* = 13.5, 10.5 Hz, 1 H, CH*H*O), 3.82 (dt, *J* = 11.5, 7.0 Hz, 1 H, C*H*HN), 4.34–4.40 (m, 2 H, C*H*HO, CHC=O), 5.08 (t, *J* = 5.0 Hz, 1 H, NCHO), 5.53 (br s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 28.3, 32.5, 45.0, 49.0, 68.7, 80.1, 87.0, 155.8, 166.4.

MS (ESI): *m*/*z* (%) = 257 (40) [M + H]$^+$, 201 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{21}N_2O_4$: 257.1496; found: 257.1502 (2.4 ppm error).

8-Methyl-1,2,3,9a-tetrahydro-9-oxa-3a-azacyclopenta[*b*]naphthalen-4-one (24a)

A mixture of 3-[1,3]dioxolan-2-yl-propylamine (**22a**; 37 mg, 0.28 mmol) and phenyl 2-hydroxy-3-methylbenzoate (**33**; 50 mg, 0.22 mmol) in a sealed tube, was heated under microwave irradiation at 135 °C for 10 min (50 W input power). The resulting gum was allowed to cool to r.t., dissolved in CH_2Cl_2 (5 mL) and $SnCl_2{\cdot}2H_2O$ (100 mg, 0.44 mmol) was added in a single portion. The reaction was allowed to stir at r.t. for 18 h whereupon it was diluted with $CHCl_3$ (5 mL) and then treated with K_2CO_3 (130 mg, 0.94 mmol) and stirring was continued for a further 30 min. The mixture was filtered through a short pad of Celite®, washing with $CHCl_3$ (3 × 10 mL). The filtrate was concentrated in vacuo and purified by flash chromatography (SiO_2; Et_2O) to give the title compound **24a**.

Yield: 70 mg (98%); colourless solid; mp 111–113 °C; R_f = 0.25 (Et_2O).

IR (Nujol mull): 2955, 2924, 2855, 1669, 1440, 1073 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88–1.99 (m, 1 H, NCHOCH$_2$C*H*H), 2.07–2.16 (m, 1 H, NCHOCH$_2$CH*H*), 2.23 (s, 3 H, CH_3), 2.24–2.33 (m, 1 H, NCHOC*H*H), 2.39–2.49 (m, 1 H, NCHOCH*H*), 3.61 (ddd, *J* = 11.5, 8.0, 5.0 Hz, 1 H, CONC*H*H), 3.84 (dt, *J* = 11.5, 7.5 Hz, 1 H, CONCH*H*), 5.46 (t, *J* = 6.0 Hz, 1 H, NCHO), 6.99 (t, *J* = 7.5 Hz, 1 H, Ar-H), 7.26 (d, *J* = 7.5 Hz, 1 H, Ar-H), 7.76 (dd, *J* = 7.5, 1.0 Hz, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4, 21.4, 32.0, 44.3, 88.2, 119.4, 121.9, 125.4, 125.8, 134.9, 155.5, 161.3.

MS (ESI): *m*/*z* (%) = 204 (100) [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}NO_2$: 204.1019; found: 204.1023 (1.7 ppm error).

1,2,3,3a-Tetrahydropyrrolo[2,1-*b*][1,3]benzoxanin-9-one (24b)

Prepared from 3-[1,3]dioxolan-2-ylpropylamine (**22a**; 79 mg, 0.61 mmol), phenyl salicylate (**26b**; 100 mg, 0.47 mmol) and $SnCl_2{\cdot}2H_2O$ (212 mg, 0.94 mmol) according to the procedure described for compound **24a**. Flash chromatography (SiO_2; Et_2O), yielded the title compound **24b**.[23]

Yield: 68.5 mg (75%); colourless oil; R_f = 0.22 (Et_2O).

IR (neat): 2884, 1667, 1611, 1468, 1347 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.89–1.99 (m, 1 H, NCHOCH$_2$C*H*H), 2.07–2.16 (m, 1 H, NCHOCH$_2$CH*H*), 2.21–2.30 (m, 1 H, NCHOC*H*H), 2.40–2.47 (m, 1 H, NCHOCH*H*), 3.59–3.66 (m, 1 H, CONC*H*H), 3.81–3.88 (m, 1 H, CONCH*H*), 5.50 (t, *J* = 6.0 Hz, 1 H, NCHO), 6.96 (dd, *J* = 7.5, 1.0 Hz, 1 H, Ar-H), 7.11 (td, *J* = 7.5, 1.0 Hz, 1 H, Ar-H), 7.42 (td, *J* = 7.5, 2.0 Hz, 1 H, Ar-H), 7.93 (dd, *J* = 7.5, 1.5 Hz, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 31.9, 44.3, 88.4, 116.4, 119.7, 122.6, 127.9, 133.7, 157.2, 160.9.

MS (ESI): *m*/*z* (%) = 190 (100) [M + H]$^+$, 212 (8) [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{12}NO_2$: 190.0863; found: 190.0863 (0.2 ppm error).

6-Fluoro-1,2,3,3a-tetrahydro-pyrrolo[2,1-*b*][1,3]benzoxanin-9-one (24c)

Prepared from 3-[1,3]dioxolan-2-ylpropylamine (**22a**; 55 mg, 0.41 mmol), phenyl 4-fluoro-2-hydroxybenzoate (**26c**; 75 mg, 0.32 mmol) and $SnCl_2{\cdot}2H_2O$ (144 mg, 0.64 mmol) according to the procedure described for compound **24a**. Flash chromatography (SiO_2; Et_2O), yielded the title compound **24c**.

Yield: 70 mg (98%); colourless solid; mp 79–81 °C; R_f = 0.44 (Et_2O).

IR (neat): 1666, 1618, 1450, 1261 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84–1.94 (m, 1 H, NCHOCH$_2$C*H*H), 2.01–2.09 (m, 1 H, NCHOCH$_2$CH*H*), 2.14–2.23 (m, 1 H, NCHOC*H*H), 2.34–2.41 (m, 1 H, NCHOCH*H*), 3.51–3.57 (m, 1 H, CONC*H*H), 3.73–3.80 (m, 1 H, CONCH*H*), 5.45 (t, 1 H,

J = 6.0 Hz, NCHO), 6.60 (dd, J = 10.0, 2.0 Hz, 1 H, Ar-H), 6.74 (td, J = 10.0, 2.0 Hz, 1 H, Ar-H), 7.86 (dd, J = 7.0, 9.0 Hz, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 31.9, 44.3, 88.9, 104.3 (d, J = 25.0 Hz), 110.3 (d, J = 22.0 Hz), 116.2, 130.0 (d, J = 11.0 Hz), 158.9, 160.9, 164.6, 165.9 (d, J = 252.0 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.8 (ddd, J = 10.3, 10.2, 9.0 Hz).

MS (ESI): m/z (%) = 230 (100) $[M + Na]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{11}H_{10}NFO_2Na$: 230.0588; found: 230.0592 (1.9 ppm error).

7-Chloro-1,2,3,3a-tetrahydropyrrolo[2,1-*b*][1,3]benzoxanin-9-one (24d)

Prepared from 3-[1,3]dioxolan-2-ylpropylamine (**22a**; 120 mg, 0.60 mmol), phenyl 5-chloro-2-hydroxybenzoate (**26d**; 150 mg, 0.91 mmol) and $SnCl_2{\cdot}2H_2O$ (410 mg, 1.82 mmol) according to the procedure described for compound **24a**. Flash chromatography (SiO_2; Et_2O) yielded the title compound **24d**.

Yield: 125 mg (87%); sticky colourless solid; mp 63–64 °C; R_f = 0.36 (Et_2O).

IR (neat): 1669, 1609, 1451, 1413, 1346 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.86–1.95 (m, 1 H, $NCHOCH_2CHH$), 2.03–2.10 (m, 1 H, $NCHOCH_2CHH$), 2.16–2.24 (m, 1 H, $NCHOCHH$), 2.35–2.43 (m, 1 H, $NCHOCHH$), 3.53–3.59 (m, 1 H, $CONCHH$), 3.75–3.81 (m, 1 H, $CONCHH$), 5.43 (t, J = 5.5 Hz, 1 H, NCHO), 6.87 (d, J = 9.0 Hz, 1 H, Ar-H), 7.31 (dd, J = 9.0, 3.0 Hz, 1 H, Ar-H), 7.83 (d, J = 2.5 Hz, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 31.7, 44.2, 88.6, 118.0, 120.8, 127.5, 127.9, 133.5, 155.7, 159.7.

MS (ESI): m/z (%) = 224 (100) $[M + H]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $NaC_{11}H_{10}ClNO_2$: 246.0292; found: 246.0293 (0.2 ppm error).

5-Isopropyl-8-methyl-1,2,3,3a-tetrahydropyrrolo[2,1-*b*][1,3]benzoxanin-9-one (24e)

Prepared from 3-[1,3]dioxolan-2-ylpropylamine (**22a**; 67 mg, 0.51 mmol), phenyl 2-hydroxy-3-isopropyl-6-methylbenzoate (**26e**; 100 mg, 0.30 mmol) and $SnCl_2{\cdot}2H_2O$ (135 mg, 0.60 mmol) according to the procedure described for compound **24a**. Flash chromatography (SiO_2; Et_2O) yielded the title compound **24e**.

Yield: 81 mg (84%); colourless oil; R_f = 0.68 (Et_2O).

IR (neat): 2960, 1663, 1491, 1428 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (d, J = 7.0 Hz, 3 H, $CHCH_3$), 1.18 (d, J = 7.0 Hz, 3 H, $CHCH_3$), 1.87–1.94 (m, 1 H, $NCHOCH_2CHH$), 2.03–2.16 (m, 1 H, $NCHOCH_2CHH$), 2.21–2.29 (m, 1 H, $NCHOCHH$), 2.35–2.43 (m, 1 H, $NCHOCHH$), 2.61 (s, 3 H, CH_3), 3.18 [quint, J = 7.0 Hz, 1 H, $CH(CH_3)_2$], 3.49–3.55 (m, 1 H, $CONCHH$), 3.84–3.91 (m, 1 H, $CONCHH$), 5.33 (dd, J = 6.0, 5.0 Hz, 1 H, NCHO), 6.82 (d, J = 7.5 Hz, 1 H, Ar-H), 7.15 (d, J = 7.5 Hz, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7, 21.8, 22.5, 22.7, 26.7, 32.2, 44.7, 87.7, 118.4, 125.3, 129.3, 133.9, 138.3, 155.4, 162.0.

MS (ESI): m/z (%) = 246 (100) $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{20}NO_2$: 246.1489; found: 246.1493 (2.6 ppm error).

1,2,3,11a-Tetrahydro-11-oxa-3a-azacyclopenta[*b*]anthracen-4-one (24f)

Prepared from 3-[1,3]dioxolan-2-ylpropylamine (**22a**; 64 mg, 0.64 mmol), phenyl 3-hydroxynaphthalene-2-carboxylate (**26f**; 100 mg, 0.49 mmol) and $SnCl_2{\cdot}2H_2O$ (220 mg, 0.98 mmol) according to the procedure described for compound **24a**. Flash chromatography (SiO_2; Et_2O) yielded the title compound **24f**.

Yield: 59 mg (65%); colourless solid; mp 111–114 °C; R_f = 0.21 (Et_2O).

IR (neat): 1664, 1633, 1436 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91–2.02 (m, 1 H, $NCHOCH_2CHH$), 2.13–2.20 (m, 1 H, $NCHOCH_2CHH$), 2.24–2.33 (m, 1 H, $NCHOCHH$), 2.44–2.52 (m, 1 H, $NCHOCHH$), 3.66–3.72 (m, 1 H, $CONCHH$), 3.87–3.92 (m, 1 H, $CONCHH$), 5.54 (t, J = 11.0 Hz, 1 H, NCHO), 7.33 (m, 1 H, Ar-H), 7.38–7.42 (m, 1 H, Ar-H), 7.49–7.53 (m, 1 H, Ar-H), 7.73 (d, J = 8.0 Hz, 1 H, Ar-H), 7.90 (d, J = 8.0 Hz, 1 H, Ar-H), 8.51 (s, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 32.1, 44.5, 88.6, 112.1, 120.1, 125.1, 127.0, 128.5, 129.5 (3 × C), 136.4, 153.6, 161.1.

MS (ESI): m/z (%) = 262 (100) $[M + Na]^+$, 240 (30) $[M + H]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{15}H_{13}NO_2Na$: 262.0838; found: 262.0843 (0.9 ppm error).

7a,8,9,10-Tetrahydro-7-oxa-10a-azacyclopenta[*b*]phenanthrene-11-one (24g)

Prepared from 3-[1,3]dioxolan-2-yl-propylamine (**22a**; 64 mg, 0.64 mmol) and phenyl 2-hydroxynaphthalene-1-carboxylate (**26g**; 100 mg, 0.49 mmol) according to the procedure described for compound **24a**. Flash chromatography (SiO_2; Et_2O) yielded the title compound **24g**.

Yield: 51 mg (56%); colourless solid; mp 104–107 °C; R_f = 0.24 (Et_2O).

IR (neat): 1658, 1443, 763 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94–2.05 (m, 1 H, $NCHOCH_2CHH$), 2.13–2.22 (m, 1 H, $NCHOCH_2CHH$), 2.40–2.57 (m, 2 H, $NCHOCH_2$), 3.62–3.68 (m, 1 H, $CONCHH$), 3.87–3.93 (m, 1 H, $CONCHH$), 5.65 (t, J = 5.5 Hz, 1 H, NCHO), 7.49–7.59 (m, 3 H, Ar-H), 7.81 (d, J = 8.0, 1.0 Hz, 1 H, Ar-H), 7.92 (d, J = 9.0 Hz, 1 H, Ar-H), 8.20 (dd, J = 8.5, 1.0 Hz, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 32.1, 44.6, 89.1, 114.3, 122.1, 122.8, 123.2, 123.8, 126.3, 127.8, 128.5, 136.6, 154.8, 161.5.

MS (ESI): m/z (%) = 362 (100) $[M + Na]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{15}H_{13}NO_2Na$: 262.0838; found: 262.0840 (0.2 ppm error).

Acknowledgment

We are grateful to the University of York for studentship and PDRA support (J.P.S. and A.N.C., respectively), EPSRC Pharmasynth program for studentship (K.A.G.), AstraZeneca for further funding (J.P.S., K.A.G.) and the French Ministère des Affaires Etrangères for a Lavoisier Postdoctoral Fellowship (C.M.M.). We are also grateful to Dr Trevor Dransfield (University of York) for assistance with mass spectrometry and to Dr Rhona J. Cox (AstraZeneca) and Dr Mike Edwards (University of York) for helpful discussions.

References

(1) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893; and references therein.
(2) Faul, M. M. *Encyclopedia of Reagents for Organic Synthesis*, Vol. 7; Paquette, L. A., Ed.; Wiley: Chichester, **1995**, 4892.
(3) Ford, K. L.; Roskamp, E. J. *Tetrahedron Lett.* **1992**, *33*, 1135.
(4) Foot, J. S.; Giblin, G. M. P.; Taylor, R. J. K. *Org. Lett.* **2003**, *5*, 4441.

(5) Jiménez, J. I.; Goetz, G.; Mau, C. M. S.; Yoshida, W. Y.; Scheuer, P. J.; Williamson, R. T.; Kelly, M. *J. Org. Chem.* **2000**, *65*, 8465.
(6) Ménard-Moyon, C.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2007**, 3698.
(7) Reid, M.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 4181.
(8) Schmidt, J. P.; Beltrán-Rodil, S.; Cox, R. J.; McAllister, G. D.; Reid, M.; Taylor, R. J. K. *Org. Lett.* **2007**, *9*, 4041.
(9) Han, J. L.; Ong, C. W. *Tetrahedron* **2007**, *63*, 609.
(10) Winterfeld, K.; Michael, H. *Pharm. Ber. Dtsch. Pharm. Ges.* **1961**, 65.
(11) Ijzendoorn, D. R.; Botman, P. N. M.; Blaauw, R. H. *Org. Lett.* **2006**, *8*, 239.
(12) For related processes, see: (a) Mizutani, N.; Chiou, W.-H.; Ojima, I. *Org. Lett.* **2002**, *4*, 4575. (b) Armorde, S. M.; Judd, A. S.; Martin, S. F. *Org. Lett.* **2005**, *7*, 2031. (c) Vink, M. K. S.; Schortinghuis, C. A.; Mackova-Zabelinskaja, A.; Fechter, M.; Pöchlauer, P.; Castelijns, A. M. C. F.; van Maarseveen, J. H.; Hiemstra, H.; Griengl, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2003**, *345*, 483.
(13) Cayley, A. N.; Cox, R. J.; Ménard-Moyon, C.; Schmidt, J. P.; Taylor, R. J. K. *Tetrahedron Lett.* **2007**, *48*, 6556.
(14) Shea, K. J.; Wada, E. *J. Am. Chem. Soc.* **1982**, *104*, 5715.
(15) For similar systems, see: Meyers, A. I.; Lefker, B. A.; Sowin, T. J.; Westrum, L. J. *J. Org. Chem.* **1989**, *54*, 4243.
(16) (a) Iwata, M.; Ohrui, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2837. (b) Tanner, D.; Somfai, P. *Tetrahedron Lett.* **1988**, *29*, 2373.
(17) Okita, M.; Wakamatsu, T.; Mori, M.; Ban, Y. *Heterocycles* **1980**, *14*, 1089.
(18) Shimizu, M.; Ishikawa, M.; Komoda, Y.; Nakajima, T. *Chem. Pharm. Bull.* **1982**, *30*, 909.
(19) For similar systems, see: Griot, R. G.; Frey, A. J. *Tetrahedron* **1963**, *19*, 1661; see also reference 11.
(20) The phenyl esters were either commercially available (**26b**, **26f** and **26g**) or were prepared from the corresponding acids using standard conditions, see: Jeffery, E. A.; Bansal, R. K.; Andrews, L. J.; Keefer, R. M. *J. Org. Chem.* **1964**, *29*, 3365.
(21) (a) Kitamura, R. *J. Pharm. Soc. Jpn.* **1937**, *57*, 55; in practice, compound **19d** was prepared from 2-nitrobenzyl bromide according to the procedure of Leach and co-workers (ref. 21b), followed by reduction with $SnCl_2 \cdot 2H_2O$ in THF. (b) Leach, D. N.; Reiss, J. A. *J. Org. Chem.* **1978**, *43*, 2484.
(22) (a) Papot, S.; Bachmann, C.; Combaud, D.; Gesson, J. P. *Tetrahedron* **1999**, *55*, 4699; prepared via the alkylation of 2-aminobenzonitrile with *n*-BuLi and MeI (ref. 22b), then reduction with $LiAlH_4$ to afford the primary amine. (b) Barluenga, J.; Fañanás, F. J.; Sanz, R.; Fernández, Y. *Chem Eur. J.* **2002**, *8*, 2034.
(23) Bohme, H.; Boing, H. *Arch. Pharm.* **1961**, *294*, 556.