Preparation and structural analysis of (±)-*cis*-ethyl 2-sulfanylidenedecahydro-1,6-naphthyridine-6-carboxylate and (±)-*trans*-ethyl 2-oxooctahydro-1*H*-pyrrolo[3,2-*c*]pyridine-5-carboxylate

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Bicycle ring closure on a mixture of (4a*S*,8a*R*)- and (4a*R*,8a*S*)-ethyl 2-oxodecahydro-1,6-naphthyridine-6-carboxylate, followed by conversion of the separated *cis* and *trans* isomers to the corresponding thioamide derivatives, gave (4a*SR*,8a*RS*)-ethyl 2-sulfanylidenedecahydro-1,6-naphthyridine-6-carboxylate, $C_{11}H_{18}N_2O_2S$. Structural analysis of this thioamide revealed a structure with two crystallographically independent conformers per asymmetric unit (Z' = 2). The reciprocal bicycle ring closure on (3a*RS*,7a*RS*)-ethyl 2-oxooctahydro-1*H*-pyrrolo[3,2-*c*]pyridine-5-carboxylate, $C_{10}H_{16}N_2O_3$, was also accomplished in good overall yield. Here the five-membered ring is disordered over two positions, so that both enantiomers are represented in the asymmetric unit. The compounds act as key intermediates towards the synthesis of potential new polycyclic medicinal chemical structures.

Keywords: **X-ray crystal structure**; **privileged structure**; **bicycle formation**; **biologically active compounds**; **NMR evaluation**; **medicinal chemistry**; **GPCRs**; **polycyclic scaffolds**.

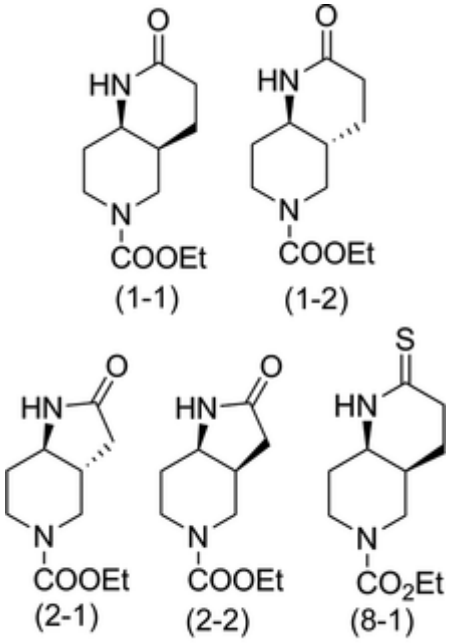
CCDC references: 1032904; 1032903

PowerPoint slides

1. Introduction

The bicyclic lactams (1-1), (1-2), (2-1) and (2-2) (see Scheme 1) represent both interesting chemical scaffolds and important synthetic precursors to novel polycyclic scaffolds for application in medicinal chemistry drug discovery programmes.

The resulting polycyclic compounds derived from these bicyclic scaffolds could be used in the design of molecules to modulate various biological targets and therefore represent a new class of privileged structures (Welsch *et al.*, 2010; DeSimone *et al.*, 2004) for targeting, for example, G protein-coupled receptors (GPCRs). GPCRs are 7-transmembrane receptors whose function is to regulate multiple disease states and represent one of the major target families for currently prescribed drugs in the clinic (Filmore, 2004). Continued efforts to discover new compounds that modulate these important biological targets therefore remain of great importance to the biopharmaceutical industry.

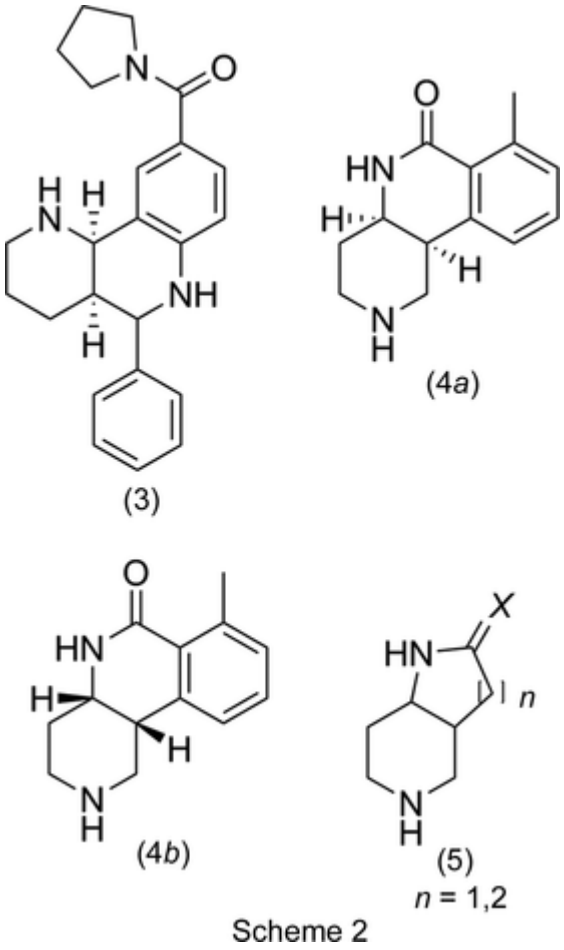


Scheme 1

The chemical scaffolds (1-1), (1-2), (2-1) and (2-2) themselves appear underrepresented in the medicinal chemical literature and therefore warrant further investigation. It had been reported that compound (3) (Scheme 2) targets the bradykinin receptor (Hu *et al.*, 2005), which is a member of the GPCR family and has a key role as a pro-inflammatory mediator (Hall, 1997; Yogi *et al.*, 2009). Compounds (4*a*) and (4*b*) (Scheme 2) act as serotonin 5HT receptor ligands (Fevig *et al.*, 2006). The serotonin receptors are found in the central and peripheral nervous system and mediate both excitatory and inhibitory neurotransmission (Wang *et al.*, 2013; Wacker *et al.*, 2013; Raote *et al.*, 2007).

We were interested in the synthesis of the core bicyclic molecular scaffolds [*e.g.* compounds of type (5) (see Scheme 2), where *X* = O] contained within these biologically active compounds,

which therefore necessitated the synthesis, separation and full characterization of the resulting diastereoisomers obtained from our synthetic sequence. So far no robust synthetic procedure has been reported for the interesting bicyclic 6,6-lactam scaffolds (1-1) and (1-2) (see Scheme 1). However, the 6,5-system, *e.g.* compounds (2-1) and (2-2) (see Scheme 1), was recently reported in the literature (Martini *et al.*, 2011). Unfortunately, in our hands, we were unable to repeat the published synthetic procedure and so we needed to further investigate both the synthesis and structural assignment of these key bicyclic intermediates. Upon completion of our robust and high-yielding synthetic sequence to both the 6,5- and 6,6-bicyclic ring systems, we were unable to assign the relative stereochemistries of the separated *cis* and *trans* isomers by NMR spectroscopic analysis due to the complexity of the overlapping proton signals and therefore we required final structural confirmation through X-ray crystallographic analysis.



Scheme 2

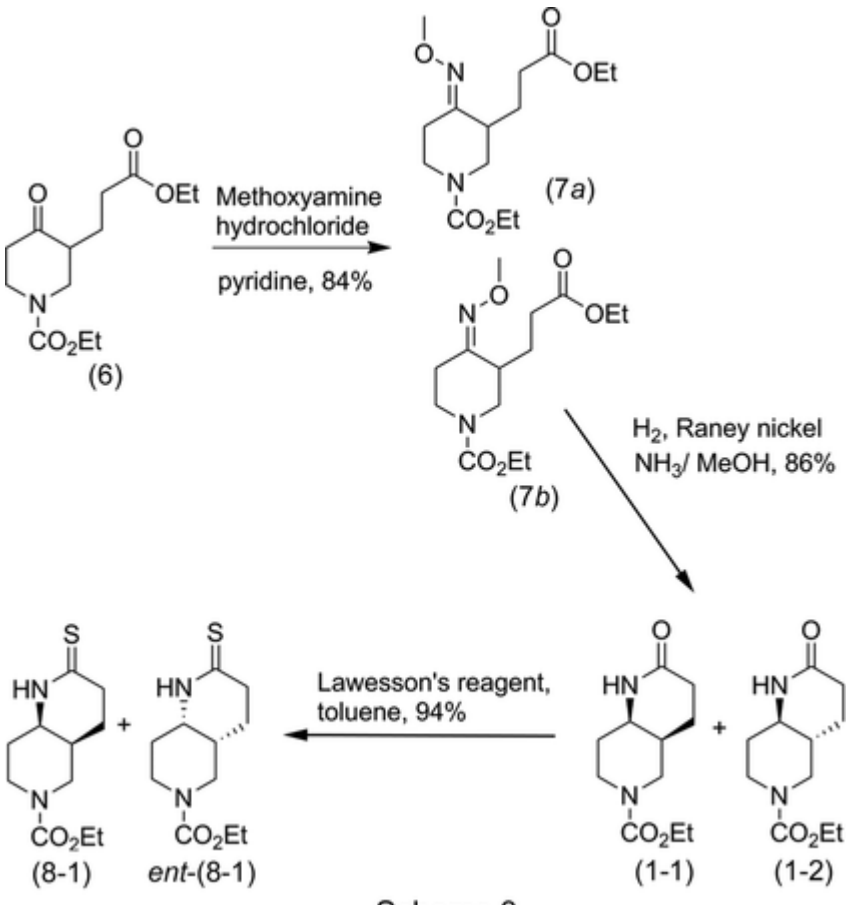
2. Experimental

We embarked on a racemic synthesis of compounds (1) [isomers (1-1) and (1-2)] and (2) [isomers (2-1) and (2-2)] (see Scheme 1). In our synthetic strategy, no enantioselective conditions were used to synthesize the bicyclic ring systems. As a consequence, each of the resulting separated diastereoisomers exists as a pair of enantiomers, which are for simplicity drawn as one single stereoisomer. Our initial attempts to obtain crystals of sufficient quality for X-

ray crystallographic analysis from the separated amide compounds (1-1) or (1-2) were unprofitable. However, from isomer (1-1), it was subsequently discovered that the corresponding thiolactam (8-1) (see Scheme 3) was highly crystalline and delivered crystals of sufficient quality for X-ray crystallographic structure determination.

2.1. Synthesis and crystallization of thiolactam (8-1) (see Scheme 3)

The synthesis started from the known ethyl ester ethyl 3-(3-ethoxy-3-oxopropyl)-4-oxopiperidine-1-carboxylate, (6) (Borne *et al.*, 1984), which was converted into the methoxime derivative ethyl 3-(3-ethoxy-3-oxopropyl)-4-(methoxyimino)piperidine-1-carboxylate, (7), using *O*-methyl-hydroxylamine hydrochloride in pyridine to yield a 1:1.5 mixture of diastereomers (see Scheme 3). Subsequent conversion to the bicyclic lactams ethyl (4a*SR*,8a*RS*)-2-oxodecahydro-1,6-naphthyridine-6-carboxylate, (1-1), and ethyl (4a*SR*,8a*SR*)-2-oxodecahydro-1,6-naphthyridine-6-carboxylate, (1-2), was accomplished with Raney nickel in methanolic 7 *N* NH_3 under an atmosphere of hydrogen. Final thioamide formation on the separated lactam diastereoisomer (1-1) was achieved using Lawesson's reagent [*i.e.* 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithia-diphosphetane 2,4-disulfide; Occhiato *et al.*, 2004], giving the thiolactams (4a*SR*,8a*RS*)-ethyl 2-sulfanylidenedecahydro-1,6-naphthyridine-6-carboxylate, (8-1), and *ent*-(8-1) (see Scheme 3).



Scheme 3

2.1.1. Ethyl 3-(3-ethoxy-3-oxopropyl)-4-(methoxyimino)piperidine-1-carboxylate, (7)

To a solution of ketone (6) (3.0 g, 11.0 mmol, 1.0 equivalent) in pyridine (21 ml) was added *O*-methylhydroxylamine hydrochloride (1.11 g, 13.3 mmol, 1.2 equivalents) and the reaction was stirred at room temperature under a nitrogen atmosphere overnight. The reaction mixture was evaporated and diluted with diethyl ether (150 ml) and water (150 ml). The organic phase was washed with hydrochloric acid (1 *M*, 60 ml) and brine (150 ml). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to yield ethyl 3-(3-ethoxy-3-oxopropyl)-4-(methoxyimino)piperidine-1-carboxylate, (7*a*)/(7*b*), as a yellow/orange oil (yield 2.80 g, 84%; 1:1.5 diastereomeric mixture).

R_F (petroleum ether/ethyl acetate, 2:1 *v*/*v*) = 0.56; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.16–4.08 (4H, *m*), 3.85 (2H, *s*), 3.81 (1H, *s*), 3.61 (1H, *m*), 3.39 (1H, *m*), 3.23 (1H, *m*), 2.92–2.67 (2H, *m*), 2.43–2.21 (4H, *m*), 1.95 (1H, *m*), 1.82–1.72 (1H, *m*), 1.26, 1.25 (6H, 2*t*, *J* = 7.47 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 173.0, 157.1, 155.7, 61.7, 61.5, 61.3, 60.5, 48.4, 44.3, 42.7, 40.6, 31.9, 24.9, 24.8, 14.7, 14.3; HRMS *m*/*z* ($C_{14}H_{24}N_2O_5$): calculated 301.1758 [*M*+ H]$^+$, found 301.1699.

2.1.2. Ethyl 2-oxodecahydro-1,6-naphthyridine-6-carboxylate, (1-1 and 1-2)

To a stirred solution of (7*a*)/(7*b*) (200 mg, 0.66 mmol, 1 equivalent) in methanolic NH_3 (7 *N*, 5 ml) was added Raney nickel (50 mg, 50% slurry in water) and the resulting mixture was stirred under a hydrogen atmosphere overnight. The reaction mixture was filtered through Celite and the filter cake was washed with methanol (3 × 10 ml). The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (ethyl acetate/petroleum ether/methanol 9:1:2 *v*/*v*/*v*) to yield two isomers of ethyl 2-oxodecahydro-1,6-naphthyridine-6-carboxylate, *viz.* (1-1) (yield 40 mg, 26%; colourless oil) and (1-2) (yield 90 mg, 60%; colourless oil) (combined yield 130 mg, 86%).

Isomer 1, *viz.* (1-2): R_F (petroleum ether/ethyl acetate, 10:1 *v*/*v* + 15% MeOH) = 0.36; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.20 (1H, *bs*), 4.24, (2H, *bm*), 4.12 (2H, *q*, *J* = 7.6, 14.8 Hz), 3.06 (1H, *dddd*, *J* = 4.0, 9.8, 12.3 Hz), 2.81–2.74 (1H, *m*), 2.52–2.34 (3H, *m*), 1.83–1.76 (2H, *m*), 1.55–1.41 (3H, *m*), 1.24 (3H, *t*, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 155.4, 61.7, 56.4, 47.3, 42.3, 38.9, 32.2, 30.9, 24.5, 14.7. HMRS *m*/*z* ($C_{14}H_{19}N_2O_3$): calculated 227.1390 [*M* + H]$^+$, found 227.1265.

Isomer 2, *viz.* (1-1): R_F (petroleum ether/ethyl acetate, 10:1 *v*/*v* + 15% MeOH) = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (1H, *bs*), 4.11–4.04 (2H, *m*), 3.57–3.51 (3H, *m*), 3.40–3.36 (1H, *m*), 3.26–3.20 (1H, *m*), 3.15 (2H, *t*, *J* = 6.9 Hz), 2.03–1.98 (1H, *m*), 1.86–1.62 (4H, *m*), 1.20 (3H, *t*, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 155.6, 61.7, 50.6, 44.7, 40.5, 32.7, 30.5, 28.9, 22.0, 14.9; HRMS *m*/*z* ($C_{14}H_{19}N_2O_3$): calculated 227.1390 [*M* + H]$^+$, found 227.1229.

2.1.3. Ethyl 2-sulfanylidenedecahydro-1,6-naphthyridine-6-carboxylate, (8-1) and *ent*-(8-1)

To a solution of (1-1) (80 mg, 0.35 mmol, 1 equivalent) in toluene (1 ml) was added Lawesson's reagent (71 mg, 0.17 mmol, 0.5 equivalents) and the mixture was refluxed for 20 min. The reaction mixture was evaporated under reduced pressure and purified by flash chromatography (ethyl acetate/petrol ether/methanol, 10:1:0.5 *v*/*v*/*v*) to yield ethyl 2-sulfanylidenedecahydro-1,6-naphthyridine-6-carboxylate [(8-1) and *ent*-(8-1)] as a colourless waxy oil (yield 80 mg, 94%). The resulting oil was dissolved in a mixture of ethyl acetate and diethyl ether and the solvent was allowed to evaporate slowly. After evaporation of half of the solvent, diisopropyl ether was added and the solvent was allowed to evaporate slowly to afford clear colourless crystals, which were used for X-ray structural determination that allowed us an unambiguous assignment of the regiochemistry of the separated isomers (Fig. 1).

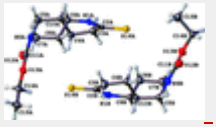
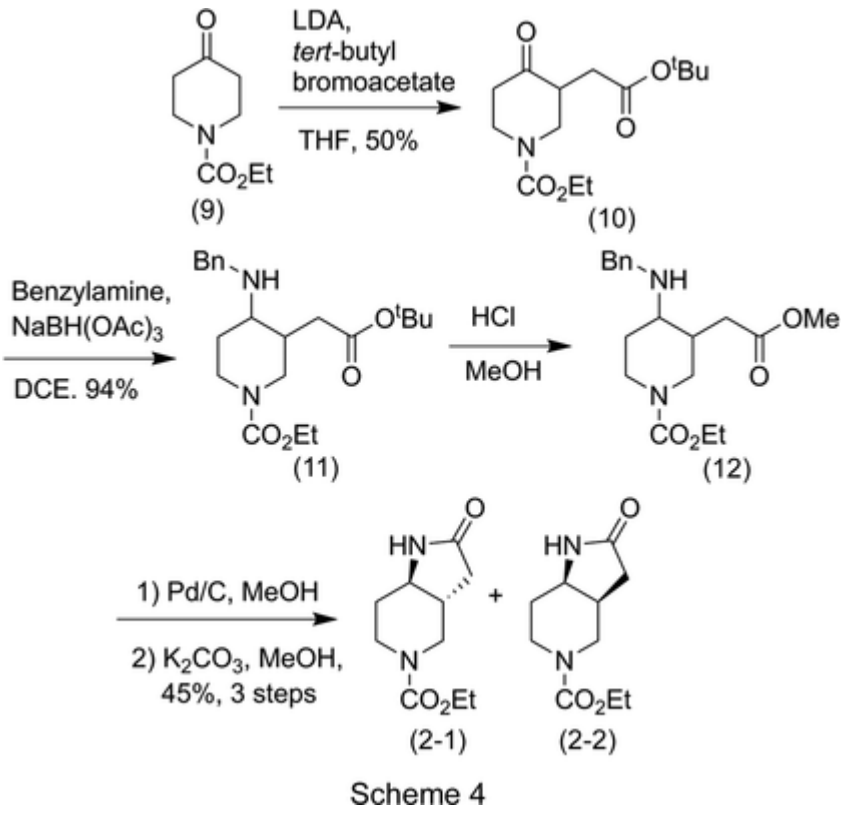


Figure 1
The molecular structures of the two rotamers of (4a*SR*,8a*RS*)-(8-1). Displacement ellipsoids are drawn at the 50% probability level.

R_F (petroleum ether/ethyl acetate, 10:1 *v*/*v*) = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (1H, *bs*), 4.12 (2H, *dq*, *J* = 2.3, 7.2, 14.4 Hz), 3.64–3.52 (3H, *m*), 3.46–3.42 (1H, *m*), 3.33–3.27 (1H, *m*), 2.93 (2H, *qt*, *J* = 7.1, 19.6, 40.4 Hz), 2.10–2.06 (1H, *m*), 1.88–1.72 (4H, *m*), 1.25 (3H, *t*, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.1, 155.7, 61.7, 53.1, 44.9, 40.6, 37.7, 31.7, 29.3, 21.4, 14.9; m.p. 401–403 K; HRMS *m*/*z* ($C_{11}H_{19}H_2O_2S$): calculated 243.1162 [*M*+ H]$^+$, found 243.1003.

2.2. Synthesis and crystallization of bicyclic lactam (2-1) (see Scheme 4)

Commercial ethyl 4-oxopiperidine-1-carboxylate, (9), was converted into the *tert*-butyl ester ethyl 3-(2-*tert*-butoxy-2-oxyethyl)-4-oxopiperidine-1-carboxylate, (10), using LDA and *tert*-butyl bromoacetate. The *tert*-butyl ester (10) was converted to the substituted benzylamine ethyl 4-benzylamino-3-(2-*tert*-butoxy-2-oxoethyl)piperidine-1-carboxylate, (11), *via* a reductive amination reaction using benzylamine and sodium triacetoxyborohydride in dichloroethane. Compound (11) was transesterified with 0.6 *M* HCl in methanol to yield the ester ethyl 4-benzylamino-3-(2-methoxy-2-oxoethyl)piperidine-1-carboxylate, (12), which was catalytically deprotected (Pd/C in MeOH under an atmosphere of hydrogen). The final ring closure to the key bicyclic lactams ethyl 2-oxo-octahydro-1*H*-pyrrolo[3,2-*c*]pyridine-5-carboxylate, *viz.* (2-1) and (2-2), was carried out with potassium carbonate in methanol (see Scheme 4). Unlike the 6,6-membered-ring compound (1), the 6,5-membered-ring compound (2) did not need further elaboration to the thioamide to obtain high-quality crystals.



Scheme 4

2.2.1. Ethyl 3-(2-*tert*-butoxy-2-oxyethyl)-4-oxopiperidine-1-carboxylate, (10)

To a solution of diisopropylamine (5.6 g, 7.8 ml, 55.6 mmol, 1.9 equivalents) in tetrahydrofuran (THF; 175 ml) at 273 K was added *n*-BuLi (18.5 ml, 2.5 *M* in hexane, 46.2 mmol, 1.6 equivalents) and the mixture was stirred for 30 min. The mixture was cooled to 195 K and ethyl 4-oxo-piperidine-1-carboxylate, (16) (5.0 g, 4.4 ml, 29.2 mmol, 1 equivalent), was added and the mixture was stirred for an additional 30 min at 195 K. A solution of *tert*-butyl bromoacetate (9.2 g, 7.0 ml, 47.2 mmol, 1.62 equivalents) in THF (17.5 ml) and hexamethylphosphoramide (HMPT; 2.9 ml) was added and the yellow reaction mixture was warmed gradually to room temperature overnight. The mixture was quenched with saturated aqueous NH_4Cl (200 ml), the phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 200 ml). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 3:1 *v*/*v*) to yield *tert*-butyl ester (10) in 50% yield.

R_F (petroleum ether/ethyl acetate, 3:1 *v*/*v*) = 0.28; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.34 (2H, *bs*), 4.13 (2H, *q*, *J* = 7.0, 14.5 Hz), 3.21 (1H, *m*), 2.94–2.80 (2H, *m*), 2.64–2.50 (2H, *m*), 2.39 (0.68 H, *t*, *J* = 3.9 Hz), 2.35 (0.32 H, *t*, *J* = 4.3 Hz), 2.25–2.18 (1H, *m*), 1.45 (9H, *s*), 1.28 (3H, *t, J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.2, 170.6, 155.2, 80.9, 61.9, 47.9, 46.5, 43.6, 40.7, 32.7, 28.0, 14.6.

2.2.2. Ethyl 4-benzylamino-3-(2-*tert*-butoxy-2-oxoethyl)piperidine-1-carboxylate, (11)

To a solution of *tert*-butyl ester (10) (1.43 g, 5.01 mmol, 1 equivalent) in dichloroethane (22 ml) was added benzylamine (0.65 ml, 0.63 g, 5.90 mmol, 1.17 equivalents) and sodium triacetoxyborohydride (1.80 g, 8.53 mmol, 1.70 equivalents). The resulting mixture was stirred overnight under an atmosphere of dry nitrogen. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (150 ml) and the aqueous phase was extracted with ethyl acetate (3 × 150 ml). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 1:5 *v*/*v*) to yield (10) as a clear colourless oil (yield 1.77g, 94%).

R_F (ethyl acetate/petroleum ether 6:1 *v*/*v*) = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.31, 7.29–7.23 (5H, *m*), 4.12 (2H, *q*, *J* = 7.1, 14.3 Hz), 4.04–3.69 (4H, *m*), 3.11–2.89 (1H, *m*), 2.86–2.81 (1H, *m*), 2.74–2.46 (1H, *m*), 2.37–2.30 (1H, *m*), 2.18–2.12 (1H, *m*), 1.91–1.76 (1H, *m*), 1.56–1.46 (1H, *m*), 1.45 (9H, *s*), 1.24 (3H, *t*, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 155.8, 155.4, 140.6, 140.4, 128.4, 128.3 (2), 128.1 (2), 126.9 (2), 82.6, 80.4, 80.3, 62.2, 61.5, 61.2, 59.2, 50.9, 50.4, 45.9, 42.5, 42.4, 28.2, 14.7 (2); HRMS *m*/*z* ($C_{22}H_{33}N_2O_4$): calculated 377.2435 $[M + H]^+$, found 377.2422.

2.2.3. Ethyl 2-oxooctahydro-1*H*-pyrrolo[3,2-*c*]pyridine-5-carboxylate, (2-1) and (2-2)

To a solution of (11) (1.70 g, 4.52 mmol, 1.0 equivalents) in MeOH (50 ml) was added hydrochloric acid (0.6 *M*, 4 ml) and the reaction mixture was stirred for 4 d. A further aliquot of hydrochloric acid (concentrated, 1 ml) was added and the mixture was stirred for a further 2 d. The reaction mixture was evaporated under reduced pressure and subsequently diluted with MeOH (30 ml) and dilute hydrochloric acid (0.5 *M*, 2 ml). The reaction was stirred for 48 h at room temperature. After evaporation, the crude product was obtained as the hydrochloride salt and was used without further purification. To a solution of the hydrochloride salt (550 mg, 1.49 mmol, 1 equivalent) in MeOH (15 ml) was added Pd/C (10% *w*/*w*, 100 mg) and the reaction mixture was stirred at room temperature overnight under an atmosphere of hydrogen. The reaction mixture was filtered through Celite, the filter cake was washed with MeOH (3 × 10 ml) and the filtrate was evaporated to give (11) which was used without further purification. To a solution of the crude product 1-ethoxycarbonyl-3-(2-methoxy-2-oxoethyl)piperidin-4-aminium chloride in MeOH (6 ml) was added anhydrous K_2CO_3 (200 mg) and the reaction mixture was stirred overnight at room temperature. The reaction mixture was quenched with water (30 ml) and the aqueous phase was extracted with ethyl acetate (3 × 30 ml). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether/methanol, 10:1:1 *v*/*v*/*v*) to yield ethyl 2-oxooctahydro-1*H*-pyrrolo[3,2-*c*]pyridine-5-carboxylate which was separated by flash column chromatography to afford two isomers, *viz.* (2-1) (yield 168 mg, 16%) and (2-2) (yield 286 mg, 28%) (combined yield 454 mg, 45%), that slowly crystallized on standing. Crystals suitable for the

X-ray crystallographic analysis were grown by slow evaporation of an ethyl acetate solution and it was found that isomer (2-1) afforded crystals of sufficient quality to allow the unambiguous assignment of the regiochemistry (Fig. 2).

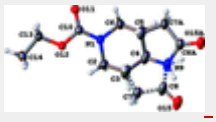


Figure 2
An overlay of the two rotamers of isomer (2-1) in the asymmetric unit, showing the major (solid bonds) and minor (dashed bonds) disorder components. Displacement ellipsoids are drawn at the 50% probability level.

Isomer 1, (2-1): R_F (ethyl acetate/petroleum ether/methanol, 10:1:1 *v*/*v*/*v*) = 0.27; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.29 (1H, *bs*), 4.34 (2H, *bm*), 4.12 (2H, *q*, *J* = 7.4, 13.3 Hz), 3.19 (1H, *dddd*, *J* = 3.7, 10.2 Hz), 2.84–2.74 (2H, *m*), 2.32 (1H, *dd*, *J* = 6.7, 15.7 Hz), 2.08 (1H, *dd*, *J* = 12.9, 15.7 Hz), 2.01–1.87 (1H, *m*), 1.54 (1H, *dddd*, *J* = 4.4, 12.9, 24.5 Hz), 1.25 (3H, *t*, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.2, 156.2, 61.5, 60.4, 59.5, 46.4, 43.8, 42.5, 34.9, 14.7, m.p. 377–378 K, HRMS *m*/*z* ($C_{10}H_{17}N_2O_3$): calculated 213.1234 $[M + H]^+$, found 213.0807.

Isomer 2, (2-2): R_F (ethyl acetate/petroleum ether/methanol 10:1:1 *v*/*v*/*v*) = 0.20; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (1H, *bs*), 4.05 (2H, *q*, *J* = 7.4, 14.4 Hz), 3.80 (1H, *q*, *J* = 4.8, 11.5 Hz), 3.60 (1H, *dd*, *J* = 5.1, 13.9 Hz), 3.46–3.41 (1H, *m*), 3.24 (1H, *dddd*, *J* = 3.6, 9.7, 13.4 Hz), 3.15 (1H, *dd*, *J* = 7.1, 13.8 Hz), 2.52 (1H, *bs*), 2.38 (1H, *dd*, *J* = 10.6, 17.9 Hz), 1.97 (1H, *dd*, *J* = 4.7, 16.6 Hz), 1.87–1.78 (1H, *m*), 1.70–1.62 (1H, *m*), 1.18 (3H, *t*, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.4, 155.5, 61.5, 51.1, 43.6, 39.3, 34.9, 27.6, 21.2, 14.7; HRMS *m*/*z* ($C_{10}H_{16}KN_2O_3$): calculated 251.0793 $[M + K]^+$, found 251.0761.

2.3. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 1. Upon initial refinement of the structure of (2-1), it became obvious that the five-membered ring was disordered over two possible positions and that both enantiomers were present in the asymmetric unit. The reflection data and raw frames were examined and no signs of larger cells or twinning could be found. Structure solution was also attempted in the space groups $P2_1$ and *Pn*; in both cases, the disorder was still present. The structure was further examined for twinning with the *PLATON* (Spek, 2009) routine TWINROTMATR; again, no signs of twinning were found. During refinement, the occupancies of the two disorder components were refined competitively, converging at a ratio of 0.533 (3):0.467 (3). Although no geometric restraints were applied to the C, N and O atoms, it was necessary to restrain the N—H distances of (2-1) to 0.88 (2) Å, and also to restrain the C···H distances of this amine H atom to be approximately equal. The positions of the H atoms bound to atom C6 in (2-1) and to atoms N1*A* and N1*B* in (8-1) were refined, but all other H atoms of both (2-1) and (8-1) were placed in idealized positions and refined in riding modes,

with C—H distances of 0.98, 0.99 and 1.00 Å for CH_3, CH_2 and CH groups, respectively. U_{iso}(H) values were set at 1.5U_{eq}(C) for CH_3groups and at 1.2U_{eq}(C,N) for all other H atoms.

Table 1

Experimental details

	(2-1)	**(8-1)**
Crystal data		
Chemical formula	$C_{10}H_{16}N_2O_3$	$C_{11}H_{18}N_2O_2S$
M_r	212.25	242.33
Crystal system, space group	Monoclinic, $P2_1/n$	Orthorhombic, $Pna2_1$
Temperature (K)	120	120
a, b, c (Å)	8.5204 (6), 6.4089 (4), 19.5921 (16)	15.06714 (17), 8.30759 (8), 19.5481 (2)
α, β, γ (°)	90, 96.381 (8), 90	90, 90, 90
V (Å^3)	1063.22 (14)	2446.87 (5)
Z	4	8
Radiation type	Cu $K\alpha$	Cu $K\alpha$
μ (mm^{-1})	0.82	2.26
Crystal size (mm)	0.33 × 0.14 × 0.08	0.15 × 0.12 × 0.05
Data collection		
Diffractometer	Agilent Technologies GV1000 diffractometer with an Atlas detector	Agilent Technologies GV1000 diffractometer with an Atlas detector
Absorption correction	Gaussian (*CrysAlis PRO*; Agilent, 2013)	Gaussian (*CrysAlis PRO*; Agilent, 2013)
T_{min}, T_{max}	0.906, 1.120	0.769, 0.976
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	6951, 2130, 1748	21836, 5117, 5030
R_{int}	0.040	0.026
(sin θ/λ)$_{max}$ (Å^{-1})	0.626	0.634
Refinement		
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.048, 0.136, 1.06	0.034, 0.091, 1.07
No. of reflections	2130	5117
No. of parameters	177	297
No. of restraints	5	1
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.22, −0.21	0.61, −0.20

Absolute structure	–	Flack *x* determined using 2311 quotients $[(I^+) - (I^-)]/[(I^+) + (I^-)]$ (Parsons & Flack, 2004)
Absolute structure parameter	–	0.067 (6)

Computer programs: *CrysAlis PRO* (Agilent, 2013), *OLEX2.SOLVE* (Bourhis *et al.*, 2014), *SHELXL2014* (Sheldrick, 2008), *SHELXL2013* (Sheldrick, 2008) and *OLEX2* (Dolomanov *et al.*, 2009).

3. Results and discussion

The X-ray crystal structures of the separated isomers of lactam (2-1) and thiolactam (8-1) were required to confirm the relative stereochemistries of the two separated *cis* and *trans* isomers as the ^{1}H NMR spectra could not categorically assign the relative stereochemistries of the synthesized and separated bicyclic ring systems.

In the case of compound (1-1), it was discovered that obtained thiolactam (8-1) proved highly crystalline and formed crystals of sufficient quality for X-ray crystallographic analysis. The synthesis of thioamide (8-1) was achieved from ethyl 3-(3-ethoxy-3-oxopropyl)-4-oxopiperidine-1-carboxylate, (6), following a literature procedure (Shah *et al.*, 2005), which was converted in a three-step synthesis (68% yield) to thiolactam (8-1) (see Scheme 3).

The coupling constant $^3J_{HH}$ for the *syn*-H atoms should be found in a range of 0–5 Hz and for the *anti*-H atoms in the range of 7–15 Hz (Reich, 2013).

The ^{1}H NMR spectra for the lactams displayed a clear difference for the ring-junction H atoms in both isomers (1-1) and (1-2) (Fig. 3). However, analysis of the ^{1}H NMR spectrum proved inconclusive as the spectrum clearly showed that only one coupling constant for the proton H_A of the isomer could be fully determined with $^3J_{HH}$ = 9.8 Hz.

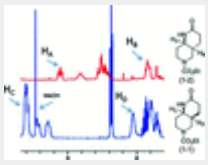


Figure 3
^{1}H NMR data for compound (1), showing isomer (1-2) in the upper spectrum and isomer (1-1) in the lower spectrum.

Thiolactam (8) showed two molecules in the asymmetric unit related by a noncrystallographic axis of rotation, although they have different conformations of the carbamate chain (Fig. 4). The overall packing of the crystal appears to be driven by the interaction of the carbamate and the lactam groups (Fig. 5 and Table 2).

Table 2

Hydrogen-bond geometry (Å, °) for (8-1)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1*A*—H1*A*···O12*A*^{i}	0.87 (4)	2.02 (4)	2.867 (3)	165 (3)
N1*B*—H1*B*···O12*B*^{ii}	0.83 (4)	2.12 (4)	2.891 (3)	155 (3)

Symmetry codes: (i) $x+\frac{1}{2},-y+\frac{3}{2},z$; (ii) $x-\frac{1}{2},-y+\frac{1}{2},z$.

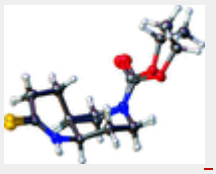


Figure 4
An overlay of the two molecules of isomer (8-1) in the asymmetric unit, showing the different conformations of the carbamate chain. Displacement ellipsoids are drawn at the 50% probability level.

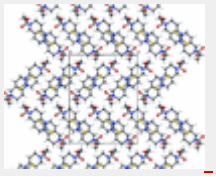


Figure 5
The packing of isomer (8-1) in the *ac* plane. The one-dimensional hydrogen-bonded chains extend along the *a* axis.

The crystal structure showed typical C—S bond lengths of 1.679 (2) and 1.686 (3) Å for the molecules with atom labels *A* and *B*, respectively (Wiberg & Wang, 2011). The piperidine ring adopts a chair conformation with the carbamate group in an equatorial position, with C5—N6—C11 angles of 119.3 (2)/121.5 (2)° and C7—N6—C11 angles of 123.5 (2)/123.8 (2)° for molecules *A*/*B*, respectively.

The torsion angles N1—C9—C10—C4 [46.2 (3)/−46.8 (3)°], C8—C9—C10—C4 [−76.4 (2)/76.8 (3)°] and C8—C9—C10—C5 [49.2 (3)/−48.9 (3)°] are all synclinal, and from the torsion angles N1—C9—C10—C5 [171.73 (19)/−172.60 (19)°] and the resulting antiperiplanar conformation it can be seen that the H atoms are arranged in a *gauche* conformation, giving rise to the chair-like conformation of the piperidine ring and the synclinal orientation of atoms H9 and H10.

For isomers (2-1) and (2-2), another synthetic route had to be established as stable *tert*-butyl ester (10) gave no direct conversion to bicyclic lactam (2-1) or (2-2). Ethyl 3-(2-*tert*-butoxy-2-oxoethyl)-4-oxopiperidine-1-carboxylate, (9), was synthesized following the literature procedure for the BOC-protected compound (Hubschwerlen *et al.*, 2008). The starting material was converted *via* a four-step synthesis into the desired isomers of the bicyclic lactam in an overall yield of 21%. It was found that diastereomeric lactams (2-1) and (2-2) could be separated easily by flash chromatography.

Once more the ^{1}H NMR spectra for separated lactams (2-1) and (2-2) showed clear differences (Fig. 6). In this case, the coupling constant for H_A was $^{3}J_{HH}$ = 10.1 Hz, which was the only measurable coupling constant due to extensive overlap of the other NMR signals (Fig. 6).

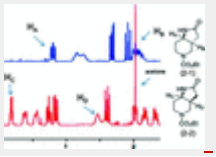


Figure 6
^{1}H NMR data for compound (2), showing isomer (2-1) in the upper spectrum and isomer (2-2) in the lower spectrum.

Compound (2-1) was recrystallized slowly from ethyl acetate to afford crystals of sufficient quality for structure determination. The compound was found to crystallize in the centrosymmetric space group $P2_1/n$, with one molecule in the asymmetric unit.

Interestingly, the five-membered ring is disordered over two possible positions, so both enantiomers are represented in the asymmetric unit due to the piperidine ring flip. In this case, the overall packing of the crystal appears to be driven by the interactions of both the carbamate and the lactam functional groups. The molecules form hydrogen-bonded dimers (Table 3), which pack in a classic herringbone fashion (Fig. 7). The piperidine ring in the crystal has a chair-like conformation and the C8—O15/C8*A*—O15*A* bond lengths [1.234 (5)/1.237 (4) Å] are in the typical range. The N9—C4—C3/N9—C4—C5 bond angles are 112.06 (15)/109.21 (16)° and the C7—C3—C4/C7*A*—C5—C4 bond angles are 98.9 (2)/100.46 (18)°.

Table 3
Hydrogen-bond geometry (Å, °) for (2-1)

D*—H···*A	***D*—H**	**H···*A***	***D*···*A***	***D*—H···*A***
N9—H9*A*···O15^{i}	0.87 (2)	2.03 (2)	2.889 (4)	174 (4)
N9—H9*B*···O15*A*^{i}	0.87 (2)	1.97 (2)	2.841 (3)	176 (3)

Symmetry code: (i) -*x*+2, -*y*, -*z*+1.

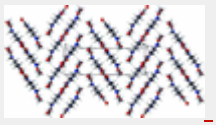


Figure 7
The herringbone packing of isomer (2-1) in the *bc* plane.

The torsion angles are synclinal for C7—C3—C4—N9/C7*A*—C5—C4—N9 [−36.2 (2)/34.4 (2)°] and C2—C3—C4—C5/C6—C5—C4—C3 [62.8 (2)/−63.0 (2)°]. With the antiperiplanar torsion angles of −158.0 (2)/157.79 (19)° for C7—C3—C4—C5/C7*A*—C5—C4—C3 and −175.51 (15)/173.55 (16)° for C2—C3—C4—N9/C6—C5—C4—N9, the antiperiplanar positon of atoms H4 and H3*A*/H5*B*, and hence the relative stereochemistry of the molecule was determined.

In conclusion, we have unambiguously determined the stereochemical outcome for the separated disatereomers of the molecular scaffolds (8-1)/(8-2) and (2-1)/(2-2) using X-ray crystallography. The crystal structure analyses showed clearly the relative configuration of the bicyclic ring systems, resulting in a synclinal orientation for the 6,6-bicyclic ring system and an antiperiplanar configuration for the 6,5-ring system. The ^{1}H NMR comparison of compounds (2-1)/(2-2) and (8-1)/(8-2) showed a clear difference in the chemical shifts of the separated diastereoisomers, but

could not be used to unambiguously to assign the relative configurations of the separated *cis* and *trans*diastereoisomers.

Supporting information

CCDC references: 1032904; 1032903

Crystal structure: contains datablocks I, II. DOI: 10.1107/S205322961402436X/ky3066sup1.cif

Structure factors: contains datablock csmsab.
DOI: 10.1107/S205322961402436X/ky3066Isup2.hkl

Structure factors: contains datablock II. DOI: 10.1107/S205322961402436X/ky3066IIsup4.hkl

Supplementary crystallographic information

3D view

- **(I) (±)-*cis*-Ethyl 2-sulfanylidenedecahydro-1,6-naphthyridine-6-carboxylate**
- **(II)**

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