Pergamon

Tetrahedron 57 (2001) 4999–5007

TETRAHEDRON

# Synthesis of a novel thiabicyclo[3.2.0]heptan-6-one analogue of penicillin

Domnic H. Martyres,[a,†] Jack E. Baldwin,[a,*] Robert M. Adlington,[a] Victor Lee,[a] Mike R. Probert[b] and David J. Watkin[b]

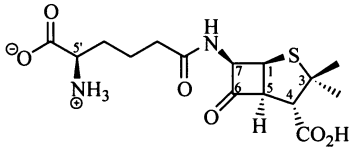
[a]*The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, UK*
[b]*Chemical Crystallography Laboratory, University of Oxford, 9 Parks Road, Oxford OX1 3PD, UK*

Received 23 February 2001; revised 30 March 2001; accepted 12 April 2001

**Abstract**—Synthesis of (1*SR*, 4*SR*, 5*SR*, 7*RS*)-7-(*tert*-butoxycarbonylamino)-2-thiabicyclo[3.2.0]heptan-6-one-4-carboxylic acid ethyl ester, a novel cyclobutanone analogue of a β-lactam antibiotic is described. This was achieved by [2+2] cycloaddition of a 2,3-dihydrothiophene with dichloroketene, followed by conversion to a cyclobutanol and use of an intramolecular nitrene insertion strategy to install nitrogen functionality at C-7 with *endo* stereochemistry. © 2001 Elsevier Science Ltd. All rights reserved.

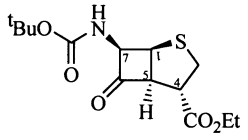
During cephalosporin biosynthesis, a step involving ring expansion of penicillin N to deacetoxycephalosporin C takes place.[1] This transformation is catalysed in eukaryotic organisms by the enzyme deacetoxycephalosporin C/deacetylcephalosporin C synthase (DAOC/DACS) and in prokaryotic organisms by the enzyme deacetoxycephalosporin C synthase (DAOCS)—also known as ring expandase (REX).[2] A common mechanism for this step involving radical intermediates has been proposed.[3]

Ongoing studies in this area required the synthesis of (1*S*, 4*S*, 5*S*, 5′*R*, 7*R*)-7-[5′-amino-5′-carboxy pentanamido]-3,3-dimethyl-2-thiabicyclo[3.2.0]heptan-6-one-4-carboxylate **1**, a hydrolytically stable analogue of penicillin N designed as a mechanistic probe.[4]



**1**

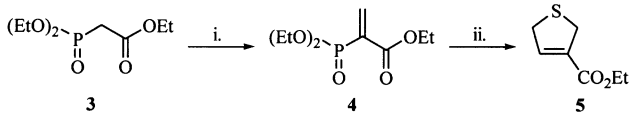
Dmitrienko et al.[5] and Tomczuk et al.[6] have reported syntheses of 2-thiabicyclo[3.2.0]heptan-6-ones bearing a 4-carboxylic acid group as in **1**, but have been unsuccessful in installing a *gem*-dimethyl group at C-3 or an *endo*-acylamino side chain at C-7. Herein we report synthesis of (1*SR*, 4*SR*, 5*SR*, 7*RS*)-7-(*tert*-butoxycarbonylamino)-2-thiabicyclo-[3.2.0]heptan-6-one-4-carboxylic acid ethyl ester **2**.



**2**

This molecule possesses an acylamino side chain at C-7 with the requisite *endo* stereochemistry, allowing entry to novel analogues of penicillin, in which the β-lactam nitrogen has been replaced with a carbon atom, and the *gem*-dimethyl group at C-3 is omitted.

Our synthetic strategy to **2** centred on a [2+2] cycloaddition reaction between a 2,3-dihydrothiophene **9** and dichloroketene. Synthesis of the dihydrothiophene commenced with Knövenagel condensation with commercially available triethylphosphonoacetate **3** and paraformaldehyde. Cracking of this polymeric source of formaldehyde in refluxing basic methanol was followed by reflux in toluene with catalytic tosic acid under Dean–Stark conditions. This provided a 10:1 mixture of alkenylphosphonate **4** and starting material **3**. The mixture was reacted with the dimer of mercaptoaldehyde following a literature procedure[7] which



**3** **4** **5**

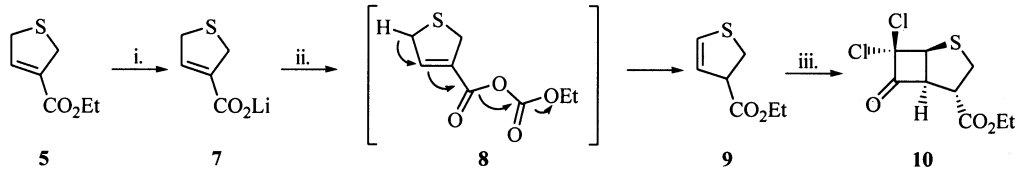
**Scheme 1.** *Reagents and conditions*: (i) (a) $(H_2CO)_x$, piperidine (cat.), MeOH, reflux, 15 h; (b) TsOH (cat.), toluene, reflux, 15 h, 74%; (ii) $Et_3N$, 1,4-dithiane-2,5-diol, DCM, reflux, 3 h, 76%.

*Keywords*: cycloaddition; ketene; β-lactam; nitrene; penicillin.

* Corresponding author. Tel.: +44-1865-275-671; fax: +44-1865-275-632; e-mail: jack.baldwin@chem.ox.ac.uk

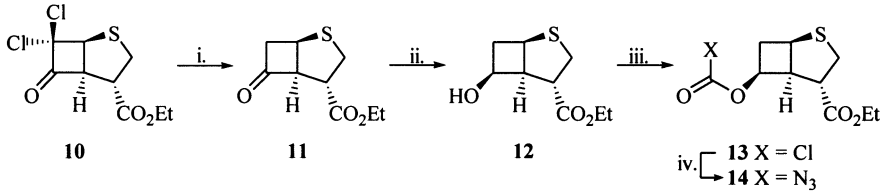
† Present address: Bayer AG, Crop Protection Business Group, Agriculture Centre Monheim, D-51368 Leverkusen, Germany.


PII: S0040-4020(01)00430-6



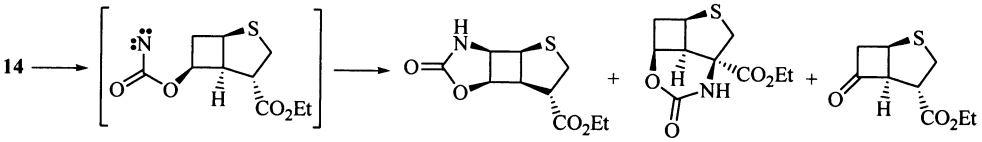

5 7 8 9 10

**Scheme 2.** *Reagents and conditions*: (i) $LiOH{\cdot}H_2O$, THF–$H_2O$, rt, 1.5 h, 80%; (ii) EtOCOCl, $Et_3N$, THF, rt, 13 h, 93%; (iii) $Cl_2CHCOCl$, $Et_3N$, $CCl_4$, rt, 72 h, 80%.




10 11 12

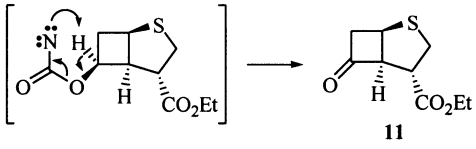
**Scheme 3.** *Reagents and conditions*: (i) Zn, AcOH, 50°C, 15 h, 82%; (ii) $NaBH_4$, MeOH, 0°C to rt, 30 min, 75%; (iii) triphosgene, pyridine, DCM, 0°C to rt, 2 h, 79%; (iv) $NaN_3$, DMF, 0°C to rt, 3 h, 63%.




15 16 11

| Entry | Conditions | | | | | |
|---|---|---|---|---|---|---|
| 1 | Δ, (sealed tube), 3.5 h, 130-135°C, DCM | 6 | : | 1 | : | 1 |
| 2 | Δ, (sealed tube), 15 h, 130-135°C, DCM | 3 | : | 2 | : | 1 |
| 3 | hν, (300nm), 20 h, 22°C, DCM | 9 | : | 1 | : | 0 |
| 4 | hν, (400nm), 22 h, 22°C, DCM | 10 | : | 1 | : | 0 |
| 5 | sonication, 5 h, 22°C, TCE | | | no reaction | | |
| 6 | Δ, 15 h, 50°C, TCE | | | no reaction | | |
| 7 | Δ, 15 h, 110°C, TCE | 2 | : | 1 | : | 0 |
| 8 | Δ, 16 h, 130°C, TCE | 4 | : | 2 | : | 1 |
| 9 | Δ, (reflux), 3 h, 147°C, TCE | 4 | : | 2 | : | 1 |
| 10 | Δ, (reflux), 0.5 h, 147°C, TCE | 14 | : | 5 | : | 1 |

**Scheme 4.**

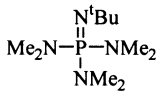



11

**Scheme 5.**

effected a Horner–Wadsworth–Emmons cyclisation to afford 2,5-dihydrothiophene **5** isomeric with the ketenophile **9** required for cycloaddition (Scheme 1).

In order to obtain the required 2,3-dihydrothiophene, a direct isomerisation was attempted, based on a literature procedure[8] involving the Schwesinger phosphazene base **6**.

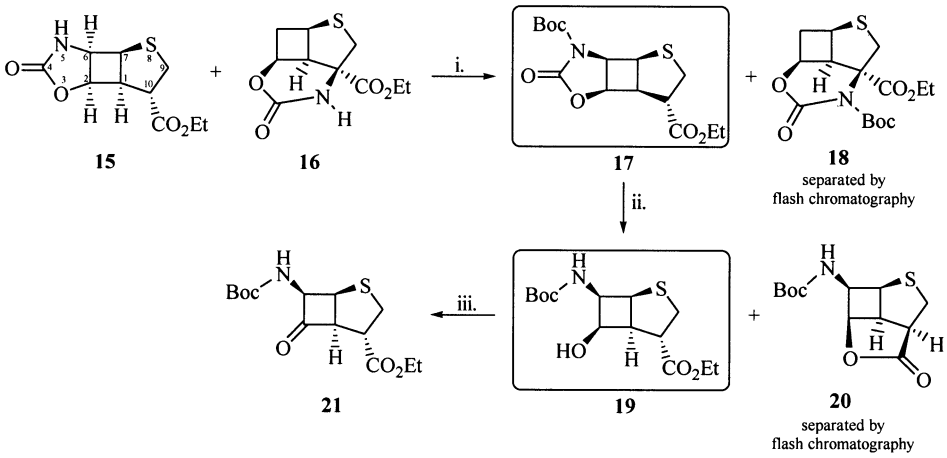



**6**

However, this was unsuccessful and thus **5** was instead saponified with lithium hydroxide to the carboxylate salt **7**, and isomerised via the mixed anhydride intermediate **8** under conditions employed by Dmitrienko et al.[5] to afford **9** in 80% yield (Scheme 2).

[2+2] Cycloaddition reaction between dihydrothiophene **9** and a suitable ketene was investigated next.[‡] We chose to use dichloroketene, prepared in situ from dichloroacetylchloride and triethylamine, as the cycloaddition partner to **9** carrying out the reaction in carbon tetrachloride at ambient temperature. Careful optimisation of this reaction afforded the desired cycloadduct **10** in 80% yield (Scheme 2). Critical to obtain a good yield for this reaction was prevention of ketene polymerisation. This was achieved by dropwise addition of a dilute solution of triethylamine

[‡] An azaketene was not attempted as it had been previously reported that azidoketene and phthalimidoketene failed to give the desired cycloadducts with similar olefins.[5,6,9]




**Scheme 6.** *Reagents and conditions*: (i) $Boc_2O$, $Et_3N$, DMAP, THF, rt, 1 h, 19% for **17** (from **14**); (ii) $Cs_2CO_3$, EtOH, rt, 3 h, 74% for **19**; (iii) IBX, DMSO, rt, 15 h, 91%.

(30 mg/cm$^3$) over 48 h. $^1$H NMR of **10** confirmed the stereochemistry at C-4, in which H-4 appears as a doublet coupling only to *endo*-H-3. Absence of coupling to *exo*-H-3 and H-5 is consistent with an *exo*-carboxylate group placing H-4 at a 90° dihedral angle to both *exo*-H-3 and H-5.

Introduction of an acylamino side chain was achieved by following a modified procedure involving an intramolecular *O*-acyl nitrene insertion that had been used by Lowe et al. on 2-oxabicyclo[3.2.0]heptan-6-one derivatives.[9] Reductive dechlorination of **10** was achieved with zinc and acetic acid at 50°C, in good yield to provide the cyclobutanone **11**. This was reduced with complete stereoselectivity using sodium borohydride in methanol at 0°C. The expected *endo*-cyclobutanol **12** was obtained on account of the *exo*-face being more easily accessible to the hydride reagent, which arises from the envelope conformation of the bicyclic ring system.

Treatment of **12** with triphosgene provided the corresponding chloroformate **13** and displacement of chloride on treatment with sodium azide (*caution*) in dimethylformamide (DMF) gave the azidoformate **14** in 31% overall yield from **10** (Scheme 3).

Generation of the *O*-acyl nitrene from **14** under various reaction conditions, led to 3 products including the cyclic carbamate **15** from C–H insertion at C-7 (Scheme 4). An optimal yield of 29% for **15** was found to occur when the nitrene was formed by refluxing **14** for 30 min in 1,1,2,2-tetrachloroethane (TCE) (entry 10).

Carbamate **15** was produced together with the isomeric structure **16** (formed by insertion at C-4), as an inseparable mixture. Also produced in the reaction was the oxidised compound **11** believed to come from the pericyclic mechanism shown in Scheme 5, or by rearrangement of the nitrene to an alkoxyisocyanate followed by elimination of isocyanic acid. This compound (**11**) was easily separated from the mixture.

The remaining steps of the synthesis are shown in Scheme 6. The isomeric mixture of carbamates was treated with Boc-anhydride affording the Boc-derivatives **17** and **18**, which were easily separated by chromatography on silica gel.

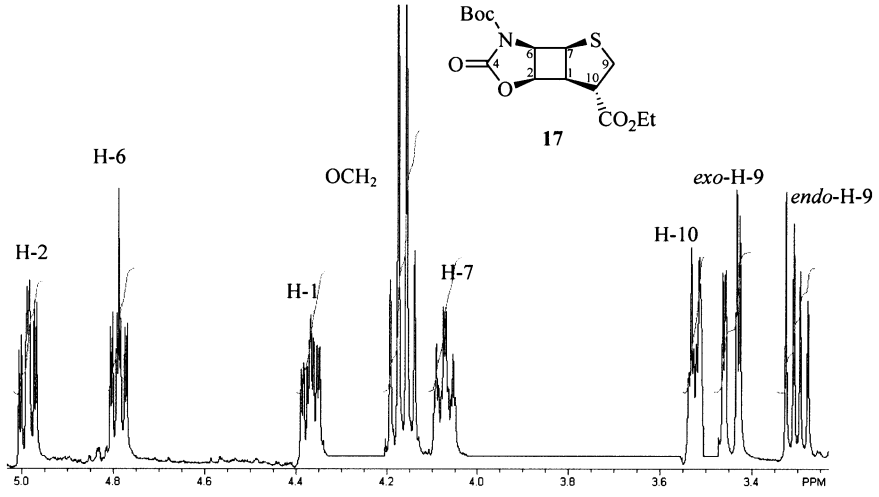



**Figure 1.**

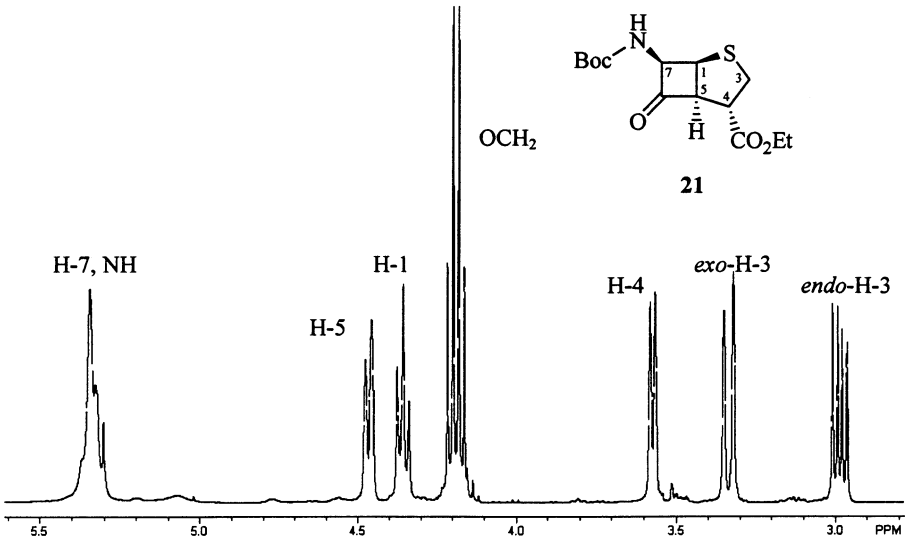



**Figure 2.**

The relative stereochemistry of the tricyclic system in the Boc-protected tricyclic carbamate **17** is borne out by its $^{1}$H NMR spectrum, which shows quite elegantly that the cyclobutyl ring protons H-1, H-2, H-6 and H-7 are all *exo* on account of their similar splitting patterns. All four of these signals appear as apparent triplets-of-doublets showing two *cis*-vicinal couplings with almost identical coupling constants (ca. 8.5 Hz), and one 'w' coupling of ca. 3.0 Hz (Fig. 1).

The carbamate **17** was hydrolysed using a modified literature procedure[10] that employed caesium carbonate in ethanol. This furnished the *vic*-aminoalcohol **19** in a mixture with the tricyclic lactone **20** in a 5:1 ratio. The lactone was believed to arise from epimerisation at C-4 under the basic conditions, followed by lactonisation by the C-6 alcohol. However, the lactone **20** was easily separated from **19** and in fact, fortuitously allowed removal of the epimer of **19** which might have otherwise proved difficult. The final step in the sequence was oxidation to the cyclobutanone **21**, which was achieved in excellent yield (91%) by treatment with *o*-iodoxybenzoic acid (IBX)[11] in dimethylsulphoxide (DMSO) at ambient temperature. $^{1}$H NMR shows H-1, H-5 and H-7 shifting downfield by ca. 0.5 ppm in accordance with the increased electrophilicity at C-6 (Fig. 2). X-ray analysis of **21** (CCDC 159592) confirmed that the relative stereochemistry at C-7 had been achieved (Fig. 3).

## 1. Conclusions

To our knowledge, this is the first synthesis of a 2-thiabicyclo[3.2.0]heptan-6-one analogue of penicillin, bearing an acylamino side chain at C-7. Through side chain manipulation, this route allows entry to this new class of penicillin analogues in which the β-lactam nitrogen has been replaced with a carbon atom. Furthermore, this route is amenable to analogues possessing a *gem*-dimethyl group at C-3, and work is in progress towards producing these carbocyclic penicillin analogues.

## 2. Experimental

### 2.1. General procedures

All reactions were carried out under a positive atmosphere of argon at room temperature unless otherwise stated. Chemical reagents were used as supplied by commercial suppliers or, where appropriate, purified by distillation or

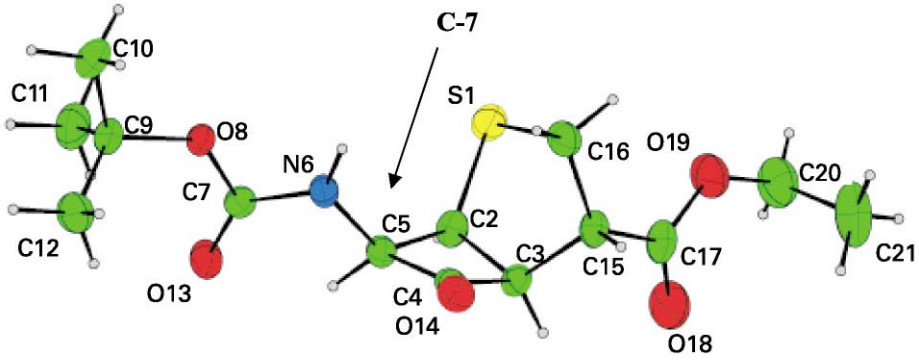



**Figure 3.**

recrystallisation according to literature methods.[12] Solvents were distilled before use. Anhydrous dichloromethane (DCM) was obtained by refluxing over calcium hydride under a positive atmosphere of argon, followed by distillation under those conditions. Anhydrous diethyl ether and anhydrous tetrahydrofuran (THF) were obtained by distillation from sodium/benzophenone ketyl under a positive atmosphere of nitrogen. Anhydrous hexane was obtained by distillation at atmospheric pressure and deoxygenated by purging with argon through a micro porous stainless steel frit for 60 min. Anhydrous *N*,*N*-dimethylformamide (DMF) and dimethyl sulphoxide (DMSO) were prepared by distillation under reduced pressure, and stored over 4 Å molecular sieves. Anhydrous tetrachloromethane and 1,1,2,2-tetrachloroethane (TCE) were prepared by distillation from phosphorus pentoxide, and stored over 4 Å molecular sieves. Pyridine was prepared by distillation at atmospheric pressure and stored over 4 Å molecular sieves. Triethylamine was prepared by distillation under reduced pressure and stored over potassium hydroxide pellets. 'Petroleum ether' (PE) refers to the fraction of light petroleum ether having a boiling range of 30–40 or 40–60°C, which was purified by distillation before use. Where drying of organic layers was carried out, this was done using anhydrous sodium or magnesium sulphate crystals. Solvents were evaporated at 40°C or below on a Büchi R-114 Rotavapor equipped with water condenser, Büchi B-480 water bath and Vacubrand MZ 2C pump fitted with CVC2 vacuum controller. Removal of trace amounts of solvent was carried out by using a glass vacuum manifold connected to an Edwards vacuum pump at pressures between 1 and 5 mmHg. Where removal of solvent from a solution of a volatile compound was necessary, this was achieved by Kugelröhr distillation using a Büchi B-580 distillation apparatus, performed at the recorded chamber temperature and pressure. Analytical thin layer chromatography (TLC) was performed using Merck silica gel 60 $F_{254}$ pre-coated glass-backed plates and components were visualised by quenching of ultra-violet fluorescence ($\lambda_{max}$ 254 nm), or by staining with one of the following: potassium permanganate solution (1% w/v in water with 6% potassium carbonate), ammonium molybdate solution (10% w/v in 2 M sulphuric acid), iodine crystals, or ninhydrin solution (0.3% w/v in 97:3 *n*-butanol/acetic acid), followed by heating. Retention factors ($R_f$) are quoted to the nearest 0.05. Silica-gel flash and 'dry-flash' chromatography were carried out using Merck silica gel 60 $F_{254}$ (230–400 mesh ASTM). All melting points (mp) are recorded on either a Reichert–Jung Gallen™ III Melting Point Microscope or a Gallenkamp Griffin™ capillary melting point apparatus to the nearest °C and are uncorrected. Proton ($^1$H) and carbon ($^{13}$C) nuclear magnetic resonance (NMR) spectra were recorded at 200, 400 and 500 MHz on a Brüker AC200, Brüker DPX400 and Brüker AMX500 spectrometer, respectively. These spectra were recorded as solutions in deuterochloroform unless stated otherwise. Chemical shifts are referenced to the NMR solvent deuterium lock and quoted in parts per million (ppm) and coupling constant (*J*) values are given in Hertz (Hz), rounded to the nearest 0.5 Hz. $^{13}$C NMR spectra were recorded at 50, 100 and 125 MHz on a Brüker AC200, Brüker DPX400 and Brüker AMX500 spectrometer, respectively. Infrared (IR) absorption spectra were recorded on a Perkin–Elmer 1750 FT-IR instrument as thin films between NaCl plates or as KBr discs. Absorbance ($\nu_{max}$) is quoted in wavenumbers ($cm^{-1}$) as strong (s), medium (m) or weak (w) intensity peaks. Low resolution mass spectrometry was carried out on Micromass Platform, Masslab 20-250, or V.G. BIO-Q spectrometers, using the following ionisation methods: atmospheric pressure chemical ionisation (APCI+ or APCI−), electron impact (EI+ or EI−) or electrospray (ES+ or ES−), as specified. Major peaks are listed as mass-to-charge (*m*/*z*) values with relative heights given as a percentage of the base peak. High resolution mass spectrometry (HRMS) was carried out by the Dyson Perrins mass spectrometry service and exact mass measurements were typically made on $M^+$, $M^-$, $MH^+$, or $M-H^-$ ions, and are quoted to four decimal places. Gas chromatography–mass spectrometry (GCMS) was carried out on a Fisons Trio-1 instrument, using the aforementioned ionisation methods, and retention times ($R_t$) are quoted in minutes. Elemental analyses were performed at the Dyson Perrins Laboratory, the Inorganic Chemistry Laboratory and by Elemental Microanalysis Ltd (Okehampton). Elemental compositions are quoted to the nearest 0.01% for carbon, hydrogen and nitrogen.

**2.1.1. Ethyl-2-(diethoxyphosphoryl)-acrylate (4).**[13] To a solution of paraformaldehyde (3.30 g) in methanol (225 $cm^3$) with 15 drops of piperidine (made homogeneous by refluxing for 0.5 h), was added triethylphosphonoacetate (13.30 $cm^3$, 66.9 mmol) and the solution heated to reflux. After 15 h, the solution was concentrated in vacuo. The crude oil was then dissolved in toluene (150 $cm^3$) and *p*-toluenesulphonic acid monohydrate (0.64 g, 5 mol%) was added and the mixture heated to reflux under a Dean–Stark separator. After 15 h, the reaction was complete, and the solution was concentrated in vacuo to provide the title compound **4** as a clear oil (12.93 g, 74%), shown to be a 10:1 mixture of product/starting material (by $^1$H NMR) which was used without further purification: $R_f$ (2:1 EtOAc/PE 40–60) 0.4; IR (NaCl plates) $\nu_{max}$: 2985s (CH), 1731s (C═O), 1608 (C═C); $\delta_H$ (200 MHz $CDCl_3$): 1.26–1.39 (9H, m, $P(O)(OCH_2CH_3)_2$ and $CO_2CH_2CH_3$), 4.12–4.36 (6H, m, $P(O)(OCH_2CH_3)_2$ and $CO_2CH_2CH_3$), 6.76 (1H, dd, $^3J_P$=20.0 Hz, $J$=1.5 Hz, *cis*-H of C = $CH_2$), 7.01 (1H, dd, $^3J_P$=42.0 Hz, $J$=2.0 Hz, *trans*-H of C = $CH_2$); *m*/*z* (APCI+): 237 ($[MH]^+$, 44%), 191 ($[M-OEt]^+$, 46%), 163 ($[M-CO_2Et]^+$, 67%), 135 (100%).

**2.1.2. 2,5-Dihydrothiophene-3-carboxylic acid ethyl ester (5).** To a stirred solution of 1,4-dithiane-2,5-diol (9.20 g, 60.4 mmol) in toluene (150 $cm^3$) containing triethylamine (25.00 $cm^3$, 177.8 mmol) was added crude ethyl-2-(diethoxyphosphoryl)-acrylate (**4**) (91% pure, 18.46 g, 71.1 mmol), and the solution heated to reflux. After 3 h, the reaction was complete. The solution was cooled to room temperature and acidified with HCl (aq.) (5%) to pH 6. Water (100 $cm^3$) was added and the mixture extracted with DCM (3×80 $cm^3$). The combined organic layers were washed with HCl (aq.) (5%, 50 $cm^3$) and water (2×50 $cm^3$), then dried and concentrated in vacuo. Dry flash chromatography (8:1 PE 30–40/$Et_2O$) afforded the title compound (**5**) (8.55 g, 76%) as a colourless oil: $R_f$ (8:1 PE 30–40/$Et_2O$) 0.4; found C, 53.14%; H, 6.41%. $C_7H_{10}O_2S$ requires C, 53.14%; H, 6.37%; IR (NaCl plates) $\nu_{max}$: 2981m (CH), 1715s (C═O), 1648m (C═C); $\delta_H$ (200 MHz $CDCl_3$):

1.24 (3H, t, $J$=7.0 Hz, $CO_2CH_2CH_3$), 3.80–3.91 (4H, m, $SCH_2CH$, $SCH_2CCO_2$), 4.16 (2H, q, $J$=7.0 Hz, $CO_2CH_2CH_3$), 6.82–6.87 (1H, m, $SCH_2CH$); $\delta_C$ (50 MHz $CDCl_3$): 14.05 ($OCH_2CH_3$), 36.99 ($SCH_2CH$), 38.88 ($SCH_2CCO_2$), 60.77 ($OCH_2CH_3$), 135.80 ($CH{=}CCO_2$), 140.68 (C=CH), 164.08 (C=O); $m/z$ (GCMS, EI+): 158 ($[M]^+$, 40%), 129 ($[M-Et]^+$, 30%), 111 (100%), 85 (90%).

**2.1.3. Lithium 2,5-dihydrothiophene-3-carboxylate (7).** To a stirred solution of 2,5-dihydrothiophene-3-carboxylic acid ethyl ester (**5**) (40.23 g, 254.3 mmol) in THF (100 $cm^3$) was added a solution of lithium hydroxide monohydrate (10.67 g, 254.3 mmol) in 3:1 (v/v) water–THF (200 $cm^3$). Care was taken to ensure that the solution was completely miscible. After 1.5 h, the reaction was complete, and was concentrated in vacuo. The remaining solid residue was then freeze-dried to give the title compound (**7**) (27.52 g, 80%) as a crude orange solid, which was used without further purification. For characterisation purposes, an acidic work up on a small amount of the salt followed by recrystallisation (EtOAc/*n*-pentane) afforded the free acid as an off-white crystalline solid: Mp (EtOAc/*n*-pentane) 174–176°C; $R_f$ (2:1 EtOAc/PE 40–60) 0.3; found: C, 46.35%; H, 4.65%. $C_5H_6O_2S$ requires C, 46.14%; H, 4.65%; IR (NaCl plates) $\nu_{max}$: 2922brs (OH), 1684s (C=O); $\delta_H$ (200 Hz $CD_3OD$): 3.86 (4H, brs, $SCH_2CCO_2H$, $SCH_2CH$), 6.85–6.89 (1H, m, C=CH); $\delta_C$ (50 MHz $CD_3OD$): 36.26 ($SCH_2CH$), 38.11 ($SCH_2CCO_2H$), 135.92 ($CH{=}CCO_2H$), 141.11 (C=CH), 166.03 (C=O); $m/z$ (APCI−): 129 ($[M-H]^-$, 100%).

**2.1.4. (3*SR*)-2,3-Dihydrothiophene-3-carboxylic acid ethyl ester (9).** To a stirred solution of lithium 2,5-dihydrothiophene-3-carboxylate (**7**) (27.52 g, 202.21 mmol) in THF (400 $cm^3$) was added triethylamine (70.50 $cm^3$, 505.5 mmol) dropwise. After 20 min, the reaction was cooled to 0°C and ethyl chloroformate (48.3 $cm^3$, 505.5 mmol) added dropwise, resulting in a pink suspension. After addition was complete, the reaction was allowed to stir at room temperature. After 13 h, the reaction was complete and the mixture was acidified to pH 2 with HCl (aq.) (5%) and diluted with water (300 $cm^3$). An extraction was then carried out with diethyl ether (3×100 $cm^3$) and the ethereal extracts combined, dried and concentrated in vacuo. Flash chromatography (8:1 PE 30–40/$Et_2O$) afforded the title compound (**9**) (29.76 g, 93%) as a fluorescent yellow oil: $R_f$ (2:1 EtOAc/PE 40–60) 0.8; found: C, 53.16%; H, 6.45%. $C_7H_{10}O_2S$ requires C, 53.14%; H, 6.37%; IR (NaCl plates) $\nu_{max}$: 2982m (CH), 1732s (C=O), 1190m, 1048m, 600w; $\delta_H$ (400 MHz $CDCl_3$): 1.29 (3H, t, $J$=7.0 Hz, $OCH_2CH_3$), 3.40 (1H, dd, $J$=11.5, 10.0 Hz, one of $SCH_2$), 3.63 (1H, dd, $J$=11.5, 10.0 Hz, one of $SCH_2$), 3.89–4.02 (1H, m, $SCH_2CH$), 4.20 (2H, q, $J$=7.0 Hz, $OCH_2CH_3$), 5.61 (1H, dd, $J$=6.0, 3.0 Hz, SCH=CH), 6.29 (1H, dd, $J$=6.0, 2.0 Hz, SCH=CH); $\delta_C$ (100.6 MHz $CDCl_3$): 14.01 ($OCH_2CH_3$), 33.06 ($SCH_2$), 52.82 ($SCH_2CH$), 61.16 ($OCH_2CH_3$), 120.30 (SCH=CH), 128.67 (SCH), 172.28 (C=O); $m/z$ (GCMS, CI+): 159 ($[MH]^+$, 32%), 158 ($[M]^+$, 47%), 85 ($[SCH{=}CHCHCH_2]^+$, 100%); HRMS: calculated for $C_7H_{11}O_2S$ $[MH]^+$: 159.0481; found: 159.0480.

**2.1.5. (1*S*, 4*S*, 5*S*)- and (1*R*, 4*R*, 5*R*)-7,7-Dichloro-2-thiabicyclo[3.2.0]heptan-6-one-4-carboxylic acid ethyl ester (10).** To a stirred solution of dichloroacetylchloride (10.10 $cm^3$, 104.7 mmol) and 2,3-dihydrothiophene-3-carboxylic acid ethyl ester (**9**) (11.05 g, 69.8 mmol) in dry tetrachloromethane (1000 $cm^3$) was added a solution of triethylamine (14.60 $m^3$, 104.7 mmol) in tetrachloromethane (350 $cm^3$) over a period of 48 h. After the addition was complete, the reaction was allowed to stir at room temperature for a further 24 h. The pale yellow precipitate formed was filtered off and washed with DCM (50 $cm^3$). The combined filtrate was then washed in ca. 500 $cm^3$ batches with water (100 $cm^3$), saturated $NaHCO_3$ (aq.) (2×100 $cm^3$) and saturated brine (100 $cm^3$). The organic layers were then combined, dried and concentrated in vacuo. Distillation at atmospheric pressure yielded a green oil (Bp 150–156°C). Dry flash chromatography (9:1 PE 40–60/$Et_2O$) afforded the title compound (**10**) (15.02 g, 80%) as a colourless liquid: $R_f$ (5:1 PE 40–60/$Et_2O$) 0.25; found C, 40.01%; H, 3.47%. $C_9H_{10}Cl_2O_3S$ requires C, 40.16%; H, 3.74%; IR (NaCl plates) $\nu_{max}$: 2983w (CH), 1810s (cyclobutanone C=O), 1736s (ester C=O), 1213m, 1184m, 1028w; $\delta_H$ (400 MHz $CDCl_3$): 1.30 (3H, t, $J$=7.0 Hz, $OCH_2CH_3$), 3.06 (1H, dd, $J$=12.5, 6.0 Hz, *endo*-H of $SCH_2$), 3.46 (1H, dd, $J$=12.5, 1.0 Hz, *exo*-H of $SCH_2$), 3.67 (1H, brd, $J$=6.0 Hz, $SCH_2CH$), 4.22 (2H, q, $J$=7.0 Hz, $OCH_2CH_3$), 4.54 (1H, d, $J$=8.0 Hz, SCH), 5.09 (1H, brd, $J$=8.0 Hz, SCHCH); $\delta_C$ (100.6 MHz $CDCl_3$): 14.07 ($OCH_2CH_3$), 35.61 ($SCH_2$), 50.08 ($SCH_2CH$), 58.89 (SCH), 62.16 ($OCH_2CH_3$), 67.37 (SCHCH), 89.25 ($CCl_2$), 169.85 (ester C=O), 194.87 (cyclobutanone C=O); $m/z$ (CI+): 272 ($[M(^{37}Cl_2)]^+$, 9%), 270 ($[M(^{35}Cl+^{37}Cl)]^+$, 38%), 268 ($[M(^{35}Cl_2)]^+$, 55%), 218 ($[M(^{35}Cl_2)-^{35}Cl-CH_3]^+$, 100%), 208 (50%), 128 (52%), 111 (73%).

**2.1.6. (1*R*, 4*S*, 5*S*)- and (1*S*, 4*R*, 5*R*)-2-Thiabicyclo[3.2.0]-heptan-6-one-4-carboxylic acid ethyl ester (11).** To a stirred solution of (1*S*, 4*S*, 5*S*)- and (1*R*, 4*R*, 5*R*)-7,7-dichloro-2-thiabicyclo[3.2.0]heptan-6-one-4-carboxylic acid ethyl ester (**10**) (9.74 g, 36.2 mmol) in glacial acetic acid (150 $cm^3$) at 50°C, was added zinc powder (11.80 g, 180.9 mmol) portion wise. After 15 h, the reaction mixture was cooled and filtered and the zinc residue washed with glacial acetic acid (20 $cm^3$). The filtrate was then concentrated in vacuo and taken up in ethyl acetate (50 $cm^3$). The solution was washed with water (20 $cm^3$), saturated $NaHCO_3$ (aq.) (3×20 $cm^3$) and saturated brine (20 $cm^3$), and the organic layer was dried and concentrated in vacuo to yield a pale yellow oil. Flash chromatography (2:1 PE 40–60/$Et_2O$) afforded the title compound (**11**) (5.94 g, 82%) as a pale green oil: $R_f$ (2:1 PE 40–60/$Et_2O$) 0.4; found C, 53.85%; H, 5.98%. $C_9H_{12}O_3S$ requires C, 53.98%; H, 6.04%; IR (NaCl plates) $\nu_{max}$: 2982m (CH), 1785s (cyclobutanone C=O), 1732 (ester C=O), 1369w, 1215m, 1027m; $\delta_H$ (400 MHz $CDCl_3$): 1.20 (3H, t, $J$=7.0 Hz, $CO_2CH_2CH_3$), 2.90 (1H, dt, $J$=18.5, 3.5 Hz, *endo*-H of $SCHCH_2$), 3.14 (1H, dd, $J$=12.0, 6.0 Hz, *endo*-H of $SCH_2$), 3.38 (1H, dd, $J$=12.0, 1.0 Hz, *exo*-H of $SCH_2$), 3.50 (1H, brd, $J$=6.0 Hz, $SCH_2CH$), 3.58 (1H, ddd, $J$=18.5, 8.5, 3.5 Hz, *exo*-H of $SCHCH_2$), 4.06–4.15 (3H, m, $CO_2CH_2CH_3$ and SCH), 4.56 (1H, m, SCHCH); $\delta_C$ (100.6 MHz $CDCl_3$): 14.03 ($CO_2CH_2CH_3$), 35.41 ($SCH_2$), 37.03 (SCH), 50.11 ($SCH_2CH$), 56.51 ($SCHCH_2C(O)$), 61.51 ($CO_2CH_2CH_3$), 71.61 (SCHCH), 170.82 (ester C=O), 208.43 (cyclobutanone C=O); $m/z$ (APCI+): 201

([MH]$^+$, 9%), 155 ([M−OEt]$^+$, 36%), 127 ([M−$CO_2$Et]$^+$, 23%).

**2.1.7. (1*R*, 4*S*, 5*S*, 6*S*)- and (1*S*, 4*R*, 5*R*, 6*R*)-2-Thiabicyclo-[3.2.0]heptan-6-ol-4-carboxylic acid ethyl ester (12).** To a stirred solution of (1*R*, 4*S*, 5*S*)- and (1*S*, 4*R*, 5*R*)-2-thiabicyclo[3.2.0]heptan-6-one-4-carboxylic acid ethyl ester (**11**) (2.00 g, 10.0 mmol) in methanol (60 cm$^3$) at 0°C was added sodium borohydride (0.40 g, 10.5 mmol) portionwise. After addition was complete, the reaction was allowed to warm to room temperature. After 30 min stirring at room temperature, water (20 cm$^3$) was added and the mixture acidified to pH 2 with $H_2SO_4$ (aq.) (1 M, 2 cm$^3$). Sodium chloride (ca. 4 g) was added to the mixture and this was extracted with DCM (4×30 cm$^3$). The organic layers were combined and washed with saturated brine (2×20 cm$^3$) then dried and concentrated in vacuo to yield a green oil. Flash chromatography (1:1 PE 40–60/$Et_2O$) afforded the title compound (**12**) (1.51 g, 75%) as a green oil: $R_f$ (4:1 EtOAc/$Et_2O$) 0.5; IR (NaCl plates) $\nu_{max}$: 3441 brs (OH), 2979s (CH), 2936s (CH), 1732brs (C═O), 1444m, 1369m, 1182s, 1030s; $\delta_H$ (400 MHz $CDCl_3$): 1.21 (3H, t, $J$=7.0 Hz, $OCH_2CH_3$), 1.91 (1H, brdt, $J$=14.5, 6.5 Hz, *endo*-H of $SCHCH_2$), 2.18 (1H, brs, O*H*), 2.85–2.91 (1H, m, *exo*-H of $SCHCH_2$), 3.28 (1H, dd, $J$=12.0, 6.0 Hz, *endo*-H of $SCH_2$), 3.36 (1H, dd, $J$=12.0, 5.0 Hz, *exo*-H of $SCH_2$), 3.52–3.61 (3H, m, S*CH*, $SCH_2CH$, and SCH*CH*), 4.10 (2H, q, $J$=7.0 Hz, $OCH_2CH_3$), 4.33 (1H, brq, $J$=7.0 Hz, C*H*OH); $\delta_C$ (100.6 MHz $CDCl_3$): 14.15 ($OCH_2CH_3$), 36.91 ($SCH_2$), 39.32 (S*CH*), 41.91 ($SCHCH_2$), 48.06 ($SCH_2CH$), 53.90 (SCH*CH*), 61.21 ($OCH_2CH_3$), 62.11 (*C*HOH), 173.20 (*C*═O); *m*/*z* (APCI+): 203 ([MH]$^+$, 100%), 158 ([MH−OEt]$^+$, 25%); HRMS: calculated for $C_9H_{15}O_3S$ [MH]$^+$: 203.0742; found: 203.0742.

**2.1.8. (1*R*, 4*S*, 5*S*, 6*S*)- and (1*S*, 4*R*, 5*R*, 6*R*)-4-Ethoxycarbonyl-2-thiabicyclo[3.2.0]heptane-6-chloroformate (13).** To a stirred solution of (1*R*, 4*S*, 5*S*, 6*S*)- and (1*S*, 4*R*, 5*R*, 6*R*)-2-thiabicyclo[3.2.0]heptan-6-ol-4-carboxylic acid ethyl ester (**12**) (1.40 g, 6.9 mmol) in DCM (30 cm$^3$) was added a solution of triphosgene (0.74 g, 2.5 mmol) and pyridine (0.56 cm$^3$, 6.9 mmol) in DCM (30 cm$^3$) dropwise at 0°C. After addition was complete, the reaction was allowed to warm to room temperature and stirred for a further 2 h. The reaction mixture was then concentrated in vacuo. Ethyl acetate (40 cm$^3$) was then added to the orange residue and this solution was washed with water (20 cm$^3$) and saturated brine (20 cm$^3$). The organic layer was dried and concentrated in vacuo to yield the title compound (**13**) (1.44 g, 79%) as a yellow oil, which was used without further purification: $R_f$ (1:1 PE 40–60/$Et_2O$) 0.3; IR (NaCl plates) $\nu_{max}$: 2983s (CH), 1778s (chloroformate C═O), 1732s (ester C═O), 1446m, 1372m; $\delta_H$ (400 MHz $CDCl_3$): 1.29 (3H, t, $J$=7.0 Hz, $OCH_2CH_3$), 2.27 (1H, dt, $J$=13.0, 7.0 Hz, *endo*-H of $SCHCH_2$), 3.09 (1H, dtd, $J$=13.0, 7.0, 3.0 Hz, *exo*-H of $SCHCH_2$), 3.36 (1H, dd, $J$=11.5, 5.5 Hz, *endo*-H of $SCH_2$), 3.46 (brq, $J$=5.5 Hz, $SCH_2CH$), 3.51 (1H, dd, $J$=11.5, 5.5 Hz, *exo*-H of $SCH_2$), 3.73 (1H, q, $J$=7.0 Hz, S*CH*), 3.92–3.96 (1H, m, SCH*CH*), 4.18 (2H, q, $J$=7.0 Hz, $OCH_2CH_3$), 5.23 (1H, q, $J$=7.0 Hz, $SCHCH_2CH$); $\delta_C$ (100.6 MHz $CDCl_3$): 14.07 ($OCH_2CH_3$), 37.01 ($SCH_2$), 39.32 ($SCHCH_2$), 40.04 (S*CH*), 48.86 ($SCH_2CH$), 51.86 (SCH*CH*), 61.51 ($OCH_2CH_3$), 71.72 ($SCHCH_2CH$), 149.50 (chloroformate *C*═O), 171.72 (ester *C*═O); *m*/*z* (APCI+): 185 ([M−OC(O)Cl]$^+$, 60%), 150 (67%), 111 (100%).

**2.1.9. (1*R*, 4*S*, 5*S*, 6*S*)- and (1*S*, 4*R*, 5*R*, 6*R*)-4-Ethoxycarbonyl-2-thiabicyclo[3.2.0]heptane-6-azidoformate (14).** To a stirred solution of (1*R*, 4*S*, 5*S*, 6*S*)- and (1*S*, 4*R*, 5*R*, 6*R*)-4-ethoxycarbonyl-2-thiabicyclo[3.2.0]heptane-6-chloroformate (**13**) (1.40 g, 5.3 mmol) in dry DMF (30 cm$^3$) was added sodium azide (1.73 g, 26.5 mmol) in one portion at 0°C. After 20 min, the reaction was allowed to warm to room temperature followed by 3 h further stirring. Water (20 cm$^3$) was added and the mixture extracted with diethyl ether (3×20 cm$^3$). The combined organic extracts were washed with water (2×30 cm$^3$) and saturated brine (2×30 cm$^3$), and the organic layer was dried and concentrated in vacuo to yield a yellow oil. Flash chromatography (2:1 PE 40–60/$Et_2O$) afforded the title compound (**14**) (0.91 g, 63%) as a pale green oil: $R_f$ (1:1 PE 30–40/$Et_2O$) 0.65; IR (NaCl plates) $\nu_{max}$: 2984s (CH), 2942m (CH), 2187s ($N_3$), 2139s ($N_3$), 1732brs (2xC═O); $\delta_H$ (400 MHz $CDCl_3$): 1.27 (3H, t, $J$=7.0 Hz, $OCH_2CH_3$), 2.18 (1H, dtd, $J$=14.0, 8.0, 1.5 Hz, *endo*-H of $SCHCH_2$), 3.06 (1H, dtd, $J$=14.0, 8.0, 3.0 Hz, *exo*-H of $SCHCH_2$), 3.22 (1H, dd, $J$=11.5, 6.0 Hz, *endo*-H of $SCH_2$), 3.41 (1H, brq, $J$=4.0 Hz, $SCH_2CH$), 3.48 (1H, dd, $J$=11.5, 4.5 Hz, *exo*-H of $SCH_2$), 3.72 (1H, q, $J$=7.0 Hz, S*CH*), 3.90–3.96 (1H, m, SCH*CH*), 4.16 (2H, q, $J$=7.0 Hz, $OCH_2CH_3$), 5.14 (1H, q, $J$=7.0 Hz, $SCHCH_2CH$); $\delta_C$ (100.6 MHz $CDCl_3$) 14.06 ($OCH_2CH_3$), 36.94 ($SCH_2$), 39.34 ($SCHCH_2$), 40.19 (S*CH*), 48.68 ($SCH_2CH$), 51.84 (SCH*CH*), 61.43 ($OCH_2CH_3$), 68.13 ($SCHCH_2CH$), 156.47 (azidoformate *C*═O), 171.89 (ester *C*═O); *m*/*z* (APCI+): 244 [(MH−$N_2$]$^+$, 100%), 111 (53%); HRMS: calculated for $C_{10}H_{14}N_3O_4S$ [MH]$^+$: 272.0705; found: 272.0711.

**2.1.10. (1*S*, 2*R*, 6*R*, 7*S*, 10*S*)- and (1*R*, 2*S*, 6*S*, 7*R*, 10*R*)-10-Ethoxycarbonyl-5-aza-3-oxa-8-thiatricyclo[5.3.0.0]-decan-4-one (15).** A stirred solution of (1*R*, 4*S*, 5*S*, 6*S*)- and (1*S*, 4*R*, 5*R*, 6*R*)-4-ethoxycarbonyl-2-thiabicyclo[3.2.0]heptane-6-azidoformate (**14**) (200 mg, 0.74 mmol) in 1,1,2,2-tetrachloroethane (400 cm$^3$) was heated to 147°C. After 30 min, the reaction was allowed to cool to room temperature and was then concentrated in vacuo to give a brown solid residue. Flash chromatography (3:1 $Et_2O$/EtOAc) afforded a mixture of the title compound (**15**) (52 mg, 29%) and the isomeric carbamate (**16**) in a 14:5 (w/w) ratio. Further purification of a sample of this mixture for characterisation purposes provided pure (**15**) as a pale yellow oil: $R_f$ ($Et_2O$) 0.2; IR (NaCl plates) $\nu_{max}$: 3340m (NH), 2982m (CH), 1732brs (urethane C═O and ester C═O), 1371m, 1211m, 1094m, 1027w; $\delta_H$ (400 MHz $CD_3OD$): 1.27 (3H, t, $J$=7.0 Hz, $OCH_2CH_3$), 3.31 (1H, dd, $J$=12.0, 7.0 Hz, *endo*-H of $SCH_2$), 3.45 (1H, dd, $J$=12.0, 2.0 Hz, *exo*-H of $SCH_2$), 3.54 (1H, dd, $J$=7.0, 2.0 Hz, $SCH_2CH$), 4.08–4.18 (1H, m, $SCH_2CHCH$), 4.16 (2H, q, $J$=7.0 Hz, $OCH_2CH_3$), 4.27 (1H, ddd, $J$=9.0, 5.0, 2.0 Hz, S*CH*), 4.48 (1H, ddd, $J$=9.0, 5.0, 2.0 Hz, C*H*NH), 5.15 (1H, ddd, $J$=7.0, 6.0, 2.0 Hz, C*H*OC(O)NH); $\delta_C$ (100.6 MHz $CDCl_3$): 14.09 ($OCH_2CH_3$), 38.78 ($SCH_2$), 48.32 ($SCH_2CH$), 51.93 ($SCH_2CHCH$), 52.08 (S*CH*), 54.40 (*C*HNH), 62.80 ($OCH_2CH_3$), 74.77 (*C*HOC(O)NH), 163.90 (urethane (*C*═O), 174.20 (ester *C*═O); *m*/*z* (APCI+): 244 ([MH]$^+$, 100%), 198 ([M−OEt]$^+$, 25%),

114 (15%); HRMS: calculated for $C_{10}H_{14}NO_4S$ $[MH]^+$: 244.0639; found: 244.0644.

**2.1.11. (1*S*, 2*R*, 6*R*, 7*S*, 10*S*)- and (1*R*, 2*S*, 6*S*, 7*R*, 10*R*)-10-Ethoxycarbonyl-5-(*tert*-butoxycarbonyl)-3-oxa-8-thiatricyclo[5.3.0.0]decan-4-one (17).** To a stirred solution of a 14:5 (w/w) mixture of (1*S*, 2*R*, 6*R*, 7*S*, 10*S*)- and (1*R*, 2*S*, 6*S*, 7*R*, 10*R*)-10-ethoxycarbonyl-5-aza-3-oxa-8-thiatricyclo-[5.3.0.0]decan-4-one (**15**) and the isomeric carbamate (**16**) (310 mg) in THF (35 $cm^3$) was added di-*tert*-butyldicarbonate (0.55 g, 2.5 mmol), triethylamine (0.35 $cm^3$, 2.5 mmol) and 4-(dimethylamino)pyridine (0.05 g, 0.4 mmol). The reaction was stirred at room temperature for 1 h followed by the addition of water (10 $cm^3$) and HCl (aq.) (9%, 10 $cm^3$). The aqueous layer was extracted with diethyl ether (3×20 $cm^3$) and the combined ethereal layers washed successively with water (2×15 $cm^3$) and saturated brine (2×15 $cm^3$). The organic layers were dried and concentrated in vacuum to give an off-white solid. Flash chromatography (18:1 DCM/$Et_2O$) afforded two pure products.

The title compound (**17**) (216 mg, 19% from (**14**)) as a white powder: Mp 157–160°C; $R_f$ (2:1 $Et_2O$/EtOAc) 0.45; found C, 52.05%; H, 5.83%; N, 4.01%. $C_{15}H_{21}NO_6S$ requires C, 52.40%; H, 6.16%; N, 4.08%; IR (NaCl plates) $\nu_{max}$: 2981w (CH), 2923w (CH), 1806s (urethane C═O), 1725s (ester C═O); $\delta_H$ (400 MHz $CDCl_3$) (Fig. 1): 1.24 (3H, t, *J*=7.0 Hz, $OCH_2CH_3$), 1.50 (9H, s, $C(CH_3)_3$), 3.31 (1H, dd, *J*=12.0, 6.5 Hz, *endo*-H of $SCH_2$), 3.44 (1H, dd, *J*=12.0, 2.5 Hz, *exo*-H of $SCH_2$), 3.53 (1H, dt, *J*=6.5, 2.5 Hz, $SCH_2CH$), 4.07 (1H, ddt, *J*=8.5, 6.0, 2.5 Hz, SC*H*), 4.16 (2H, q, *J*=7.0 Hz, $OCH_2CH_3$), 4.37 (1H, ddd, 8.5, 6.0, 2.5 Hz, $SCH_2CHCH$), 4.79 (1H, brt, *J*=8.5 Hz, NC*H*), 4.99 (1H, dddd, *J*=8.5, 6.0, 2.5, 1.0 Hz, NC(O)OC*H*); $\delta_C$ (100.6 MHz $CDCl_3$): 13.88 ($OCH_2CH_3$), 27.71 ($C(CH_3)_3$), 39.07 ($SCH_2$), 48.35 ($SCH_2CH$), 50.49 (SCH), 51.72 ($SCH_2CHCH$), 55.89 (SCHCHN), 61.47 ($OCH_2CH_3$), 71.38 (CHOC(O)N), 83.83 ($C(CH_3)_3$), 148.79 (*tert*-butoxycarbonyl *C*═O), 153.31 (cyclic urethane *C*═O), 171.94 (ester C═O); *m*/*z* (APCI+): 287 ($[MH-{}^tBu]^+$, 100%), 243 ($[MH-CO_2{}^tBu]^+$, 69%).

The isomeric Boc-protected tricyclic carbamate (**18**) (51 mg, 4% from (**14**)) as a white solid: $R_f$ (18:1 DCM/$Et_2O$) 0.35; IR (NaCl plates) $\nu_{max}$: 3458w, 2982m (CH), 1740brs (2×C═O), 1370m, 1278s; $\delta_H$ (400 MHz $CDCl_3$): 1.28 (3H, t, *J*=7.0 Hz, $OCH_2CH_3$), 1.42 (9H, s, $C(CH_3)_3$), 2.45 (1H, dt, *J*=14.0, 6.5 Hz, *endo*-H of $SCHCH_2$), 3.04 (1H, dtd, *J*=14.0, 8.0, 2.5 Hz, *exo*-H of $SCHCH_2$), 3.49 (1H, d, *J*=13.5 Hz, *endo*-H of $SCH_2$), 3.52 (1H, brt, *J*=9.5 Hz, SCHCH), 3.76 (1H, q, *J*=7.5 Hz, SC*H*), 3.89 (1H, d, *J*=13.5 Hz, *exo*-H of $SCH_2$), 4.25 (2H, q, *J*=7.0 Hz, $OCH_2CH_3$), 4.81 (1H, q, *J*=7.5 Hz, CHOC(O)N); $\delta_C$ (100.6 MHz $CDCl_3$): 13.89 ($OCH_2CH_3$), 27.63 ($C(CH_3)_3$), 38.02 (SCH), 40.98 ($SCHCH_2$), 42.57 ($SCH_2$), 51.89 (SCHCH), 62.74 ($OCH_2CH_3$), 66.34 (CHOC(O)N), 73.93 ($SCH_2C$), 84.98 ($C(CH_3)_3$), 151.08 (*tert*-butoxycarbonyl *C*═O), 153.21 (cyclic urethane *C*═O), 169.61 (ester *C*═O); *m*/*z* (APCI+): 244 ($[MH-CO_2C_4H_8]^+$, 100%), 218 (50%); HRMS: calculated for $C_{15}H_{22}NO_6S$ $[MH]^+$: 344.1168; found: 344.1175.

**2.1.12. (1*S*, 4*S*, 5*S*, 6*R*, 7*R*)- and (1*R*, 4*R*, 5*R*, 6*S*, 7*S*)-7-(*tert*-Butoxycarbonylamino)-2-thiabicyclo[3.2.0]heptan-6-ol-4-carboxylic acid ethyl ester (19).** To a stirred solution of (1*S*, 2*R*, 6*R*, 7*S*, 10*S*)- and (1*R*, 2*S*, 6*S*, 7*R*, 10*R*)-10-ethoxycarbonyl-5-(*tert*-butoxycarbonylamino)-3-oxo-8-thiatricyclo[5.3.0.0]decan-4-one (**17**) (0.10 g, 0.3 mmol) in ethanol (10 $cm^3$) was added caesium carbonate (20 mg, 60 μmol) in one portion and the reaction stirred at room temperature. After 3 h, the reaction was complete and citric acid (aq.) (1 M) was added to acidify the reaction to pH 7. The mixture was extracted with chloroform (3×5 $cm^3$) and the organic layers were combined, dried and concentrated in vacuo to yield an off-white solid. Flash chromatography (6:1 DCM/$Et_2O$) afforded the title compound (**19**) (68 mg, 74%) as a white powder: Mp 115–117°C; $R_f$ (6:1 DCM/$Et_2O$) 0.15; IR (NaCl plates) $\nu_{max}$: 3422brm (OH, NH), 2979m (CH), 1716s (ester C═O), 1689s (urethane C═O); $\delta_H$ (400 MHz $CDCl_3$): 1.25 (3H, t, *J*=7.0 Hz, $OCH_2CH_3$), 1.44 (9H, s, $C(CH_3)_3$), 2.45 (1H, brs, O*H*), 3.30–3.32 (2H, m, $SCH_2$), 3.46–3.48 (1H, m, $SCH_2CH$), 3.79 (1H, brt, *J*=7.5 Hz, $SCH_2CHCH$), 4.14 (2H, q, *J*=7.0 Hz, $OCH_2CH_3$), 4.21 (1H, brt, *J*=7.5 Hz, SC*H*), 4.27–4.30 (1H, m, CHNH), 4.54–4.57 (1H, m, CHOH), 5.41 (1H, brs, N*H*); $\delta_C$ (100.6 MHz $CDCl_3$): 14.09 ($OCH_2CH_3$), 28.27 ($C(CH_3)_3$), 38.09 ($SCH_2$), 48.38 ($SCH_2CH$), 49.26 ($SCH_2CHCH$), 49.45 (CHNH), 49.96 (SCH), 61.12 ($OCH_2CH_3$), 67.66 (CHOH), 79.96 ($C(CH_3)_3$), 155.82 (urethane *C*═O), 172.89 (ester *C*═O); *m*/*z* (APCI+): 273 ($[MH-OEt]^+$, 10%), 244 ($[M-CO_2Et]^+$, 5%), 218 ($[MH-CO_2C_4H_8]^+$, 100%), 172 (23%).

Also isolated from this reaction was the Boc-protected tricyclic lactone (**20**) (12 mg, 15%) as a white solid: Mp 136–139°C; $R_f$ (6:1 DCM/$Et_2O$) 0.3; IR (NaCl plates) $\nu_{max}$: 3406brm (NH), 2977s (CH), 1770s (lactone C═O), 1716s (urethane C═O); $\delta_H$ (400 MHz $CDCl_3$): 1.44 (9H, s, $C(CH_3)_3$), 3.22 (1H, dd, *J*=11.5, 5.0 Hz, *exo*-H of $SCH_2$), 3.37 (1H, d, *J*=11.5 Hz, *endo*-H of $SCH_2$), 3.52 (1H, ddd, *J*=8.0, 5.0, 0.5 Hz, $SCH_2CH$), 3.65 (1H, brq, *J*=8.0 Hz, CHCHCO), 4.43 (1H, td, *J*=8.0, 2.5 Hz, SC*H*), 4.67 (1H, brq, *J*=8.0 Hz, CHNH), 5.13–5.16 (1H, m, CHOC(O)), 5.45 (1H, d, *J*=8.0 Hz, N*H*); $\delta_C$ (100.6 MHz $CDCl_3$): 28.25 ($C(CH_3)_3$), 38.6 ($SCH_2$), 44.20 (CHCHCO), 48.29 (CHNH), 49.99 (CHCO), 79.57 (CHOC(O)), 80.2 ($C(CH_3)_3$), 154.5 (urethane *C*═O), 178.9 (lactone *C*═O); *m*/*z* (APCI+): 216 ($[MH-C_4H_8]^+$, 13%), 172 ($[MH-CO_2C_4H_8]^+$, 100%).

**2.1.13. (1*S*, 4*S*, 5*S*, 7*R*)- and (1*R*, 4*R*, 5*R*, 7*S*)-7-(*tert*-Butoxycarbonylamino)-2-thiabicyclo[3.2.0]heptan-6-one-4-carboxylic acid ethyl ester (21).** To a stirred solution of (1*S*, 4*S*, 5*S*, 6*R*, 7*R*)- and (1*R*, 4*R*, 5*R*, 6*S*, 7*S*)-7-(*tert*-butoxycarbonylamino)-2-thiabicyclo[3.2.0]heptan-6-ol-4-carboxylic acid ethyl ester (**19**) (20 mg, 63 μmol) in DMSO (1 $cm^3$) was added *o*-iodoxybenzoic acid (IBX) (25 mg, 89 μmol) and the reaction was stirred at room temperature for 15 h. The reaction was quenched with water (5 $cm^3$) and the white precipitate formed was removed by filtration. The filtrate was then extracted with diethyl ether (3×5 $cm^3$) and the organic layers were combined, dried and concentrated in vacuo to yield a colourless oil. Flash chromatography (1:1 hexane/$Et_2O$) followed by recrystallisation from hexane–diethyl ether afforded the title compound (18 mg, 91%) as colourless crystals: Mp 130–135°C; $R_f$ (1:1 hexane/$Et_2O$)

0.35; IR (NaCl plates) $\nu_{max}$: 3368brs (NH), 2980m (CH), 1788s (cyclobutanone C═O), 1716 brs (urethane and ester C═O); $\delta_H$ (400 MHz $CDCl_3$) (Fig. 2): 1.28 (3H, t, $J$=7.0 Hz, $OCH_2CH_3$), 1.45 (9H, s, $C(CH_3)_3$), 2.99 (1H, dd, $J$=12.0, 6.5 Hz, *endo*-H of $SCH_2$), 3.34 (1H, brd, $J$=12.0 Hz, *exo*-H of $SCH_2$), 3.57 (1H, brd, $J$=6.5 Hz, $SCH_2CH$), 4.19 (2H, q, $J$=7.0 Hz, $OCH_2CH_3$), 4.36 (1H, t, $J$=8.0 Hz, SC*H*), 4.47 (1H, brd, $J$=8.0 Hz, $SCH_2CHCH$), 5.30–5.38 (2H, m, N*H* and C*H*NH); $\delta_C$ (100.6 MHz $CDCl_3$): 14.07 ($OCH_2CH_3$), 28.19 ($C(CH_3)_3$), 34.88 ($SCH_2$), 45.58 (SCH), 48.54 ($SCH_2CH$), 61.74 ($OCH_2CH_3$), 65.33 ($SCH_2CHCH$), 66.12 (*C*HNH), 80.58 ($C(CH_3)_3$), 154.19 (urethane *C*═O), 170.90 (ester *C*═O), 205.70 (cyclobutanone *C*═O); *m/z* (APCI+): 260 ($[MH-C_4H_8]^+$, 5%), 216 ($[MH-CO_2C_4H_8]^+$, 100%), 199 (31%), 170 (24%), 142 (44%); X-ray Fig. 3.

## Acknowledgements

We would like to thank the BBSRC for a studentship (to D. H. M.) and are grateful to Dr T. Claridge and Dr B. Odell for their assistance with high-field NMR experiments. We also thank S. Romeril for a sample of IBX.

## References

1. Cooper, R. D. G. *Bioorg. Med. Chem.* **1993**, *1*, 1–17.
2. Baldwin, J. E.; Singh, P. D.; Yoshida, M.; Sawada, Y.; Demain, A. L. *Biochem. J.* **1980**, *186*, 889–895.
3. Valegard, K.; Terwisscha van Scheltinga, A. C.; Lloyd, M. D.; Hara, T.; Ramaswamy, S.; Perrakis, A.; Thompson, A.; Lee, H.; Baldwin, J. E.; Schofield, C. J.; Hajdu, J.; Andersson, I. *Nature* **1998**, *394*, 805–809.
4. Martyres, D. H. DPhil Thesis, University of Oxford, 2000.
5. Dmitrienko, G. I. *Tetrahedron Lett.* **1985**, *26*, 1791–1794.
6. Tomczuk, B. E. *Diss. Abst. Int. B* **1980**, *41*, 576.
7. McIntosh, J. M.; Hayes, I. E. E. *Can. J. Chem.* **1987**, *65*, 110–113.
8. Kim, S. H.; Figueroa, I.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 2601–2604.
9. Lowe, G.; Swain, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 391–398.
10. Yuan, P.; Driscoll, M. R.; Raymond, S. J.; Hansen, D. E.; Blatchly, R. A. *Tetrahedron Lett.* **1994**, *35*, 6195–6198.
11. Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272–7276.
12. Perrin, D. D.; Armarego, W. F. L. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: New York, 1988.
13. McIntosh, J. M.; Seiler, R. A. *Can. J. Chem.* **1978**, *56*, 226–231.