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Total synthesis of a novel 2-thiabicyclo[3.2.0]heptan-6-one analogue of penicillin N

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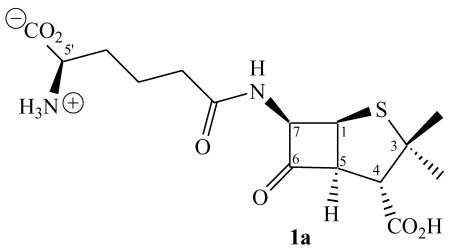
Abstract—A route has been developed which allows synthesis of novel cyclobutanone analogues of penicillin. This is illustrated by the synthesis of (1*R*,4*R*,5*R*,5′*R*,7*S*)-(**1b**) and (1*S*,4*S*,5*S*,5′*R*,7*R*)-7-[5′-amino-5′-carboxy]pentanamido]-2-thiabicyclo[3.2.0]heptan-6-one-4-carboxylate (**1a**), an analogue of penicillin N. The key steps in the synthesis were the formation of the bicyclic structure via a [2+2] cycloaddition and the introduction of nitrogen at C7 via an intramolecular nitrene insertion.

1. Introduction

The biosynthesis of penicillins and cephalosporins have been the subject of extensive investigation, as it is these processes which permit viable production of these antibiotics on a commercial scale.[1] In cephalosporin-producing organisms, the enzyme isopenicillin N/penicillin N epimerase converts isopenicillin N to penicillin N. This biosynthesis proceeds towards cephalosporin C by a ring expansion and subsequent hydroxylation. These biotransformations occur differently in prokaryotes and eukaryotes. In eukaryotes, the two steps are carried out by a single bifunctional enzyme deacetoxycephalosporin C/deacetylcephalosporin C synthase (DAOC/DACS) whereas in prokaryotes, the enzymes are distinct; deacetoxycephalosporin C synthase (DAOCS)[2] and deacetylcephalosporin C synthase (DACS) respectively.

The mechanism of the ring-expansion has been investigated and a free radical pathway proposed.[3] Ongoing studies would be greatly enhanced by a crystal structure of an DAOCS–substrate complex, which would represent an extremely useful mechanistic probe. The β-lactam moiety of penicillin N has proved to be hydrolytically unstable to the aqueous crystallisation conditions and as such was unsuitable for this purpose. It was therefore envisaged that the carbocyclic analogue (**1**) would be a suitable and hydrolytically stable mimic, since PM3 calculations predicted close structural similarity (Fig. 1).[4] It is noteworthy that related fully carbocyclic bicyclo[3.2.0]heptan-6-ones have recently been reported by Fairlamb et al., for use as a squalene synthase enzyme probe.[5]

The synthesis of 2-thiabicyclo[3.2.0]heptan-6-ones bearing a 4-carboxylic acid functionality has previously been reported by Dimentriko et al.,[6] and Tomczuk,[7] but these attempts were unsuccessful in the installation of an acylamino side chain at C7, and a *gem*-dimethyl group at C3. We recently reported the synthesis of a 2-thiabicyclo[3.2.0]heptan-6-one derivative (**2**) bearing a carboxyl group at C4 and a carbamate side chain at C7 (Fig. 2).[8] Herein we report an extension of our methodology which has enabled further incorporation of both a *gem*-dimethyl group at C3 and the D-α-aminoadipoylamino group at C7 to provide a cyclobutanone analogue of penicillin N.



1a

Figure 1. 1a (**1b**—1*R*,4*R*,5*R*,5′*R*,7*S* diastereomer).

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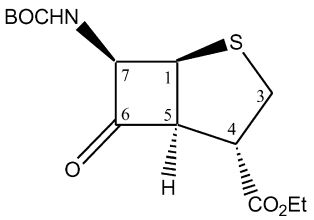


2

Figure 2. (1*R*,4*R*,5*R*,7*S*)- and (1*S*,4*S*,5*S*,7*R*)-7-(*tert*-butyoxycarbonyl-amino)-2-thiabicyclo[3.2.0]heptan-6-one-4-carboxylic acid ethyl ester.

2. Results and discussion

Our synthetic strategy was developed from our previous investigations.[8] The key steps in the synthesis proved to be formation of the bicyclic nucleus by a [2+2] cycloaddition between dichloroketene and a dihydrothiophene, and installation of an acylamino moiety at C7, which was effected by an intramolecular nitrene insertion reaction.

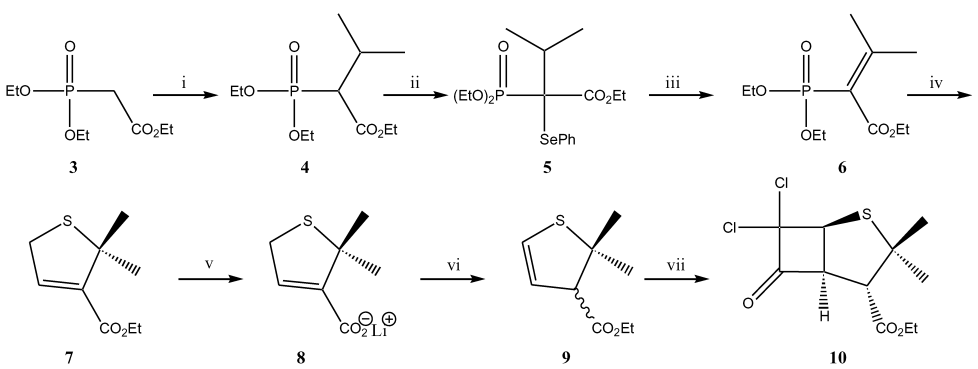
The dihydrothiophene structure was produced according to literature procedures[8] (Scheme 1). Assembly of the alkene (**6**) commenced with the alkylation of commercially available triethylphosphono acetate (**3**) with 2-iodopropane in 87% yield.[9] The alkylated product (**4**) was then subjected to a selenation/selenoxide elimination sequence in 77 and 83% yield, respectively.[10] Synthesis of dihydrothiophene (**7**) was achieved by a modified Horner–Wadsworth–Emmons cyclisation in 78% yield,[10,11] the mercaptaldehyde generated in situ from its dimer, 1,4-dithiane-2,5-diol. Isomerisation to the kinetic isomer (**9**) was achieved by saponification to the lithium salt (**8**) in 98% yield, followed by the formation of a mixed anhydride/ketene intermediate which undergoes a decarboxylative elimination and subsequent readdition of ethoxide to afford the kinetic isomer (**9**) in 74% yield. The bicyclic structure racemic (±)-(**10**) was then accessible in 96% yield via a [2+2] cycloaddition; the dichloroketene was generated in situ by the slow addition of triethylamine to a solution of the dihydrothiophene and dichloroacetyl chloride over 4 days (Scheme 1).[5,10]

Having constructed the first key bicyclic intermediate, the second key step was introduction of the acylamino side chain at C7. A route was proposed involving an intramolecular *o*-acyl nitrene insertion to provide a cyclic carbamate which could be hydrolysed to a *cis* amino alcohol (Scheme 2).

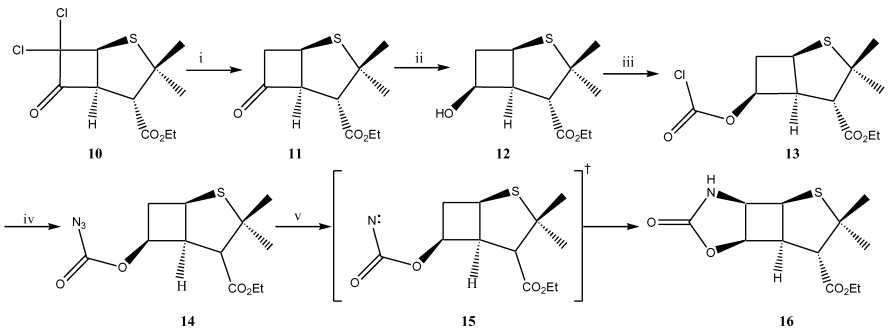
To this end, reductive dechlorination was effected by heating the bicyclic adduct (**10**) in a suspension of zinc and acetic acid, under reflux to afford the ketone (**11**) in 82% yield.[10] This was used without purification owing to instability on silica. The *endo*-cyclobutanol (**12**) was accessed stereoselectively using sodium borohydride, which delivers hydride from the more accessible *exo* face.[10] The yields were increased to 83% by quenching the reaction with the silica onto which it was adsorbed for flash chromatography, bypassing extraction. This was presumably due to the alcohol having some solubility in water. Treatment of the *endo*-cyclobutanol (**12**) with triphosgene and pyridine in CCl_4 furnished the chloroformate (**13**), which proved unstable to silica and therefore was converted into the azidoformate without purification. Reaction with sodium azide in DMF afforded the azidoformate (**14**) in 67% yield. X-Ray crystallography provided explicit means of proving the relative stereochemistry (Fig. 3).

Azidoformates are known to thermally decompose to *o*-acyl nitrenes, e.g. (**15**), which can insert into available C–H bonds. We have previously reported that an intramolecular nitrene insertion was possible in 29% yield in the synthesis of the desmethyl analogue (**2**). This yield was low and it was of concern that the 3,3-*gem*-dimethyl group may hinder the reaction in this synthesis, as a result of its increased steric bulk. In addition to this, it was anticipated that insertion at C4 might be a strongly competing reaction. Nonetheless, the reaction was optimised and the most efficient conditions found to be highly dilute, to prevent intermolecular reaction, rigorously anhydrous and anaerobic to prevent competing nitrene reactions and with the dropwise introduction of the azidoformate to the solvent at 147°C. As a result of these optimised conditions the tricyclic structure (**16**) was isolated in 28% yield, comparable to the yields obtained by Lowe et al. on an oxygen analogue of penicillin G.[12] A crystal structure of (**16**) clearly indicated that the insertion had occurred on the *endo* face, as required (Fig. 4).

After protection of the nitrogen functionality using di-*tert*-butyl dicarbonate, triethylamine and a catalytic amount of 4-dimethyl amino pyridine (DMAP) in 79% yield, the cyclic



Scheme 1. (i) KO^{t}Bu, 2-iodopropane, DMSO, 60°C, 87%. (ii) NaH, PhSeCl, THF, 77%. (iii) H_2O_2, DCM, 83%. (iv) LiCl, 1,4-dithiane-2,5-diol, DBU, MeCN, 78%. (v) LiOH·H_2O, THF, H_2O, 98%. (vi) Ethyl chloroformate, Et_3N, 74%. (vii) Et_3N, dichloroacetylchloride, CCl_4, 5 days, 96%.



Scheme 2. (i) Zn, AcOH, reflux, 82%. (ii) $NaBH_4$, MeOH 83%. (iii) Triphosgene, pyridine, carbon tetrachloride, 50°C, quantitative. (iv) NaN_3, DMF, 50°C, 67%. (v) TCE, 147°C, 15 min, 28%.

carbamate (**17**) was hydrolysed using caesium carbonate in ethanol to afford the *cis*-amino alcohol (**18**) in 90% yield.

A careful protecting group strategy was required in order to couple the D-(α)-aminoadipic acid side chain efficiently. The final selection was made on the evidence of model studies (Fig. 5). Deprotection of the *para*-nitrobenzyl protected molecule[13] (**22a**) and alloc protected molecule[14] (**22b**) proved unsuccessful owing to decomposition under deprotection conditions. It was proposed that the palladium involved in the deprotection was coordinating to the sulfur, causing structural degradation. However viable deprotection of the acid labile diphenylmethyl protecting group[13] could be achieved, leaving the ring system structurally intact. On this basis the diphenylmethyl protecting group was utilised in protection of the 4-carboxyl functionality, and the BOC and PMB groups used to protect the 5′ amino and 5′ carboxyl functionalities of D-α-aminoadipic acid respectively.[15] There remained concern however, that on final deprotection of (**24**) enolisation of the cyclobutanone may result in racemistion at C7.[12]

The synthetic route proceeded with saponification of the ethyl ester (**18**) to the carboxylic acid (**19**) with 1 equiv. of $LiOH{\cdot}H_2O$. The reaction did not proceed to completion, however the product was isolated by acid/base extraction in 75% yield and the residual starting material recycled. The 4-carboxyl group was then protected to afford the diphenylmethyl ester (**20**) in 66% yield by stirring with diphenyl diazomethane[13] in acetonitrile at ambient temperature. The amine functionality was then revealed by removal of the BOC protecting group, stirring with 1 equiv. of *p*-toluene sulfonic acid monohydrate at room temperature to afford the tosylate salt (**21**) in 59% yield (Scheme 3).

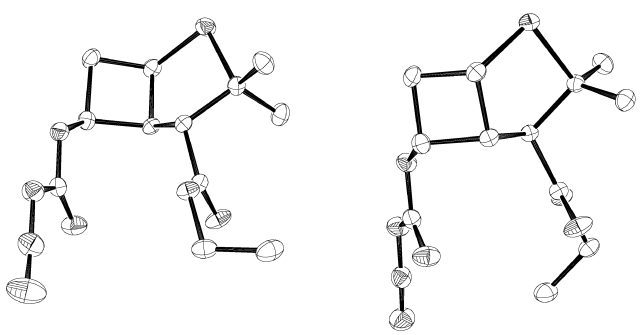


Figure 3. The crystal structure of (1*S*,4*R*,5*R*,6*R*)- and (1*R*,4*S*,5*S*,6*S*)-3,3-dimethyl-4-carboxethyl-2-thiabicyclo[3.2.0]heptane-6-azidoformate (**14**).

Having obtained the tosylate salt it was then necessary to couple the amino acid side chain. It was decided to use the tosylate salt directly in the coupling reaction and liberate the amine in situ, to maximise efficiency on the small scale. Activation with EDCI and HOBt proved effective in the acylation of the free amino function and coupling to the protected D-α-aminoadipic acid. This afforded the fully protected cyclobutanol (**23**) as a mixture of diastereomers, in 82% yield. (Compounds (**23**), (**24**), (**25**) and (**1**) are depicted as the (1*S*,4*S*,5*S*,5′*R*, (6*R*),7*R*) isomer.) At this stage the cyclobutanol (**23**) was oxidised with *o*-iodoxybenzoic acid (IBX) in 90% yield to the cyclobutanone (**24**). Deprotection was achieved by stirring in a solution of TFA/anisole/toluene (3:1:20) for 0.5 h at ambient temperature to afford the target compound in 71% yield (Scheme 4).

The product (**1a/1b**) was identified by ^1H and ^{13}C NMR. The stereochemistry was proven to be as required by synthesising the deprotected cyclobutanol (**25**) by two different methods. The first was via borohydride reduction of the cyclobutanone (**1**), and the second via deprotection of the cyclobutanol (**23**) (Scheme 5). An NMR doping experiment proved the products to be identical.

Deuterium exchange at C7 was observed when (**1a/1b**) was left standing in D_2O for 5 days, clearly indicating that enolisation of the cyclobutanone was occurring. However the ^1H NMR spectrum did not show any additional set of signals which would have resulted from an additional pair of diastereomers. It followed, therefore that the enolisation and reprotonation was proceeding with total retention to give (**1a/1b**).

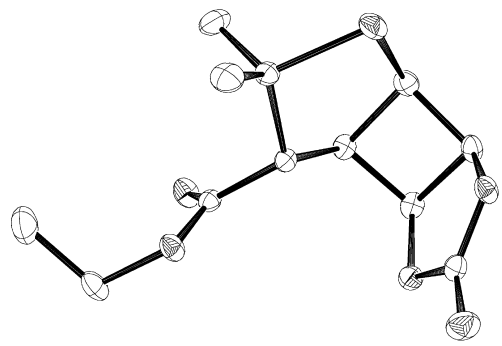
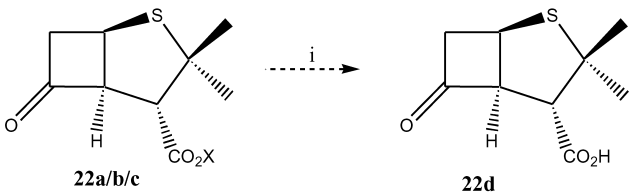


Figure 4. The crystal structure of (1*R*,2*S*,6*S*,7*R*,10*R*)- and (1*S*,2*R*,6*R*,7*S*,10*S*)-10-ethoxycarbonyl-5-aza-9,9-dimethyl-3-oxo-8-thiatricyclo[5.3.0.0]decan-4-one (**16**).

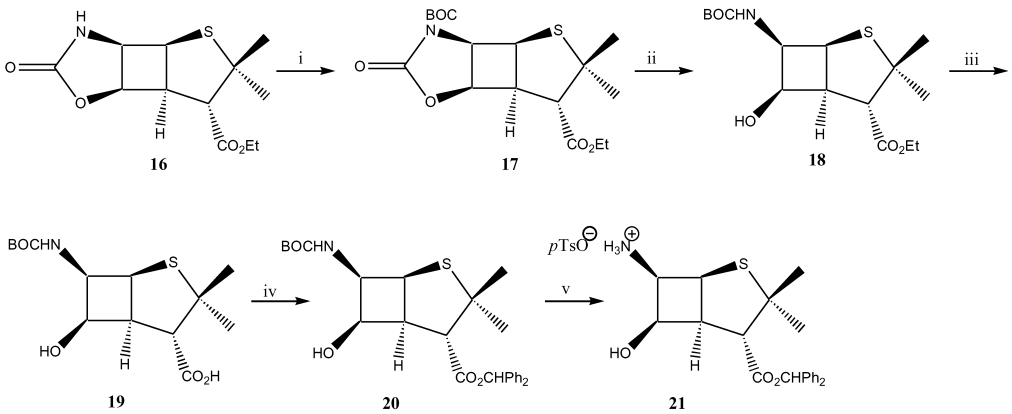


22a X = PNB i) = 10% Pd/C, $NaHCO_3$, H_2, THF:H_2O 2:1.

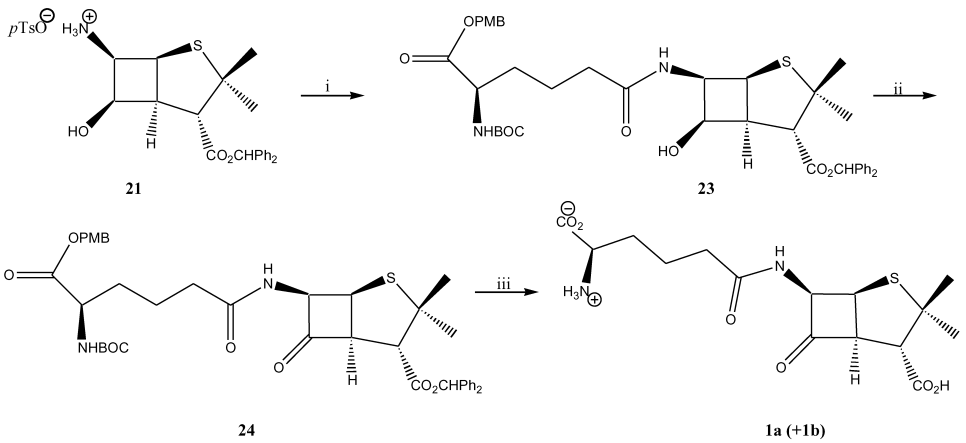
22b X = Allyl i) = 1,3-Dimethyl barbituric acid, tetrakis-(triphenylphosphine) palladium(0), THF.

22c X= $CHPh_2$ i) = TFA:Anisole:Toluene (3:1:20).

Figure 5. Model studies to select a protecting group strategy.



Scheme 3. (i) Di-*tert*-butyl dicarbonate, Et_3N, DMAP, THF, 79%. (ii) Cs_2CO_3, EtOH, 90%. (iii) LiOH·H_2O, DMF, H_2O, 70°C, 75%. (iv) Ph_2CN_2, MeCN, 66%. (v) *p*-TsOH, MeCN, 59%.

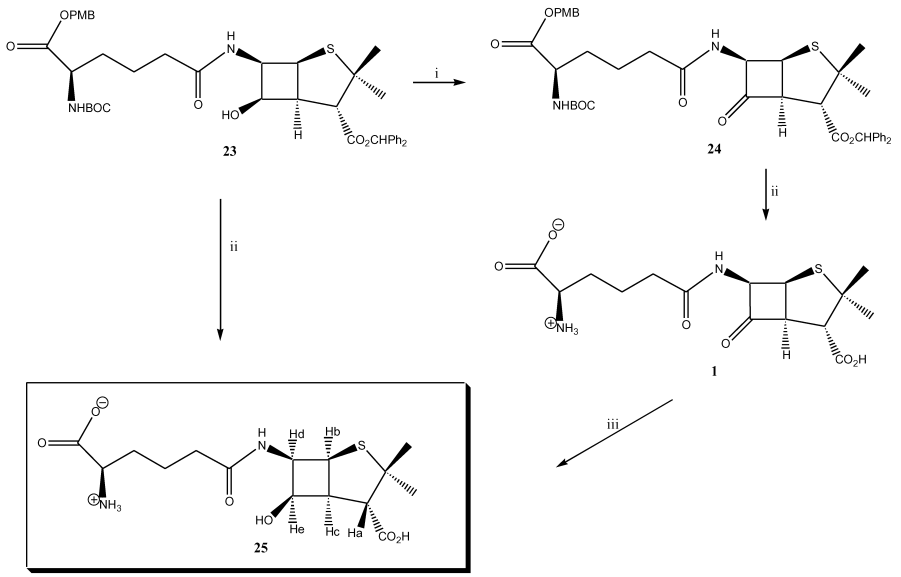


Scheme 4. (i) EDCI, HOBt, *N*-*tert*-butyloxycarbonyl-D-α-aminoadipic acid-α-*p*-methoxybenzyl ester, DCM, Et_3N, 82%. (ii) IBX, DMSO, 90%. (iii) TFA/anisole/toluene (3:1:20) 71%.

Quantitative NOE studies of (**25a/25b**) were consistent with the structure drawn. The NOEs between H^b and H^c, H^d and H^b, H^c and H^e, and H^d and H^e are large, i.e integrals of 6 or greater, indicating that these protons are all orientated *cis* to each other. The integral between H^a and H^c is less than 50% of that expected for a *cis* relationship, suggesting that this relationship is *trans*. NOEs between protons across the diagonals of the cyclobutanone were not observed, but it is probable that the conformation of the molecule is such that the through-space distance is too large (Table 1).

Table 1. Comparison of NOE integrals for (1*S*,4*S*,5*S*,5′*R*,6*R*,7*R*)- and (1*R*,4*R*,5*R*,5′*R*,6*S*,7*S*)-7-[5′-amino-5′-carboxypentanamido]-3,3-dimethyl-2-thiabicyclo[3.2.0]heptan-6-ol-4-carboxylate (**25**)

Proton irradiated	NOE integrals				
	H^a	H^b	H^c	H^d	H^e
H^a	–	0	2.4	0	0
H^b	0	–	7.4	6.8	0
H^c	2.5	9.0	–	0	6.9
H^d	0	11.2	0	–	7.7
H^e	0	0	9.2	7.9	–



Scheme 5. Synthesis of (1*S*,4*S*,5*S*,5′*R*,6*R*,7*R*)- and (1*R*,4*R*,5*R*,5′*R*,6*S*,7*S*)-7-[5′-amino-5′-carboxypentanamido]-3,3-dimethyl-2-thiabicyclo[3.2.0]heptan-6-ol-4-carboxylate (**25**). (i) IBX, DMSO. (ii) TFA/anisole/toluene (3:1:20). (iii) $NaBH_4$, D_2O.

3. Conclusion

To our knowledge, this is the first synthesis of the 2-thiabicyclo[3.2.0]heptan-6-one analogue of penicillin N. The synthesis produced the target compound as a diasteromeric pair. However, it is not anticipated that this will be a problem for biological testing, as it is hoped that the enzyme will select for the correct diastereomer. A positive α-ketogluterate binding assay[16] indicated that this compound binds in the active site of DAOCS which leaves us in a strong position to commence crystallisation trials.

4. Experimental

4.1. General

Chemical reagents were used as supplied by commercial suppliers unless otherwise stated. Where necessary, solvents were dried and purified according to recommended methods.[17] TCE was prepared freshly by distillation from a suspension of phosphorus pentoxide. Ether refers to diethyl ether. PE 40–60 refers to light petroleum in the boiling range 40–60°C. DCM refers to dichloromethane. Organic solutions were dried over $MgSO_4$ unless otherwise stated. Flash chromatography refers to the method of Still et al.[18] Solvents were evaporated at 40°C or below using a Buchi R114 Rotavapor equipped with a water condenser, Buchi B480 water bath and a Vacubrand MZ 2C pump fitted with a CVC2 vacuum controller. Analytical TLC was performed on Merck silica gel 60 F254 precoated aluminium-backed plates. Proton (^1H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded on Bruker DPX 200, DPX 250, Bruker DQX 400 and Bruker AMX 500 spectrometers.

4.1.1. (2*RS*)-Ethyl 2-(diethoxyphosphoryl)-3-methylbutanoate (4).[9] To a stirred solution of potassium *tert*-butoxide (105.3 g, 0.94 mol) in DMSO (380 mL) was added triethylphosphono acetate (150.0 g, 0.67 mol). This was stirred at room temperature for 1 h. The mixture was cooled to 0°C and 2-iodopropane (108.5 mL, 1.09 mol) was added dropwise. The reaction was then stirred at ambient temperature for 18 h, quenched with pH 7 phosphate buffer (550 mL) and extracted into DCM (5×300 mL). The organic extract was washed with brine (200 mL), dried and concentrated in vacuo to yield a pale orange oil. This was purified by distillation under reduced pressure to yield the title compound as a colourless oil (155.1 g, 87%): bp 92–93°C (0.6 Torr); R_f 0.3 (EtOAc/PE 40–60 2:1); IR (NaCl plates) ν_{max} 2928 (m, CH), 1732 (s, C=O); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, dd, J=6.5, 1.5 Hz, methyl of $CH(CH_3)_2$), 1.09 (3H, dd, J=6.5, 1.5 Hz, methyl of $CH(CH_3)_2$), 1.21–1.41 (9H, m, $P(O)(OCH_2CH_3)_2$ and $CO_2CH_2CH_3$), 2.25–2.36 (1H, m, $CH(CH_3)_2$), 2.66 (1H, dd, ^2J_P=10.0, 9.5 Hz, $CHCH(CH_3)_2$), 4.05–4.18 (6H, m, $P(O)(OCH_2CH_3)_2$ and $CO_2CH_2CH_3$); δ_C (100.63 MHz, $CDCl_3$) 14.06 ($CO_2CH_2CH_3$), 16.30 $P(O)(OCH_2CH_3)_2$, 21.45 (one of $CH(CH_3)_2$, 21.55 (one of $CH(CH_3)_2$, 28.20 ($CH(CH_3)_2$), 52.66 (d, ^1J_P=132.0 Hz, $CHCH(CH_3)_2$), 61.02 ($CO_2CH_2CH_3$), 62.29 ($P(O)(OCH_2CH_3)_2$), 169.17 (C=O); *m/z* (APCI$^+$) 289 ($[MNa]^+$, 15%), 267 ($[MH]^+$, 100%), 221 ($[M-OEt]^+$, 6%).

4.1.2. (2*RS*)-Ethyl 2-(diethoxyphosphoryl)-2-phenylselenyl-3-methyl-butanoate (5).[10] To a stirred solution of sodium hydride (7.94 g of a 60% dispersion, 199 mmol) in THF (50 mL) at −78°C was added a solution of (2*RS*)-ethyl 2-(diethoxyphosphoryl)-3-methylbutanoate (**4**) (33.0 g, 124 mmol) in THF (50 mL) dropwise over 1 h. This was allowed to warm to ambient temperature and stirred for 20 h. The solution was cooled to −78°C and a solution of phenyl selenenyl chloride (25.0 g, 131 mmol) in THF (100 mL) was added to the reaction mixture. The reaction was again allowed to warm to ambient temperature and stir for 15 h. The reaction was quenched with acetic acid (10%, 300 mL) and extracted with EtOAc (4×400 mL). The organic extract was washed with saturated $NaHCO_{3(aq)}$

(100 mL), brine (100 mL) and concentrated in vacuo to yield a brown oil. Flash chromatography on silica afforded the title compound as a pale green oil (40.3 g, 77%): R_f 0.3 (EtOAc/PE 40–60 1:1); IR (NaCl plates) ν_{max} 2980 (s, CH), 1721 (s, C=O); δ_H (200 MHz, $CDCl_3$) 1.08–1.38 (15H, m, P(O)(OCH_2CH_3)$_2$, $CO_2CH_2CH_3$ and $CH(CH_3)_2$), 2.49–2.66 (1H, dquin, J=26.0, 7.0 Hz, $CH(CH_3)_2$), 3.90 (2H, qd, J=7.0, 3.5 Hz, $CO_2CH_2CH_3$), 4.09–4.32 (4H, m, P(O)(OCH_2CH_3)$_2$), 7.26–7.39 (3H, m, Ar*H*), 7.75–7.81 (2H, m, Ar*H*); δ_C (100.63 MHz, $CDCl_3$) 13.73 (one of $CH(CH_3)_2$), 16.40 (P(O)(OCH_2CH_3)$_2$), 19.47 ($CO_2CH_2CH_3$), 20.37 (one of $CH(CH_3)_2$), 34.08 ($CH(CH_3)_2$), 61.54 ($CO_2CH_2CH_3$), 63.27 (P(O)(OCH_2CH_3)$_2$), 127.39 (P(O)*C*SePh), 128.44, 129.35, 138.11 (C_{Ar}), 168.70 (*C*=O); *m/z* (APCI$^+$) 445 ([M(^{80}Se)Na]$^+$, 100%), 443 ([M(^{78}Se)Na]$^+$, 43%), 442 ([M(^{77}Se)Na]$^+$, 20%), 441 ([M(^{76}Se)Na]$^+$, 15%), 289 ([MNa−SePh]$^+$, 90%), 273 (85%), 199 (35%), 160 (37%).

4.1.3. Ethyl 2-(diethoxyphosphoryl)-3-methyl-but-2-enoate (6).[10] To a stirred solution of (2*RS*)-ethyl 2-(diethoxyphosphoryl)-2-phenylselenyl-3-methyl-butanoate (**5**) (27.6 g, 65.0 mmol) in DCM (200 mL) at 0°C was added H_2O_2 (18.8 mL, 30% aq, 170 mmol) dropwise. The solution was allowed to warm to ambient temperature and after 2 h the reaction was quenched with saturated $NaHCO_{3(aq)}$ solution (100 mL) and the organic layer separated and washed with water (100 mL), dried and concentrated *in vacuo* to yield a yellow oil. Flash chromatography on silica (EtOAc/PE 40–60 2:1) afforded the title compound as a colourless oil (14.2 g, 83%): R_f 0.35 (EtOAc/PE 40–60 2:1); IR (NaCl plates) ν_{max} 2983 (m, CH), 1723 (s, br, C=O), 1624 (m, C=C); δ_H (200 MHz, $CDCl_3$) 1.21–1.41 (9H, m, P(O)C(OCH_2CH_3)$_2$ and $CO_2CH_2CH_3$), 1.81 (3H, d, J=2.0 Hz, one of C=C(CH_3)$_2$), 2.07 (3H, d, J=3.0 Hz, one of C=C(CH_3)$_2$), 3.97–4.22 (6H, m, P(O)(OCH_2CH_3)$_2$ and $CO_2CH_2CH_3$); δ_C (100.63 MHz, $CDCl_3$) 13.99 ($CO_2CH_2CH_3$), 16.27 (P(O)(OCH_2CH_3)$_2$), 22.65 (d, J=8.0 Hz, P–C=C(CH_3)$_2$), 24.37 (d, J=18.0 Hz, P–C=C(CH_3)$_2$), 61.37 (d, J=22.0 Hz, P(O)(OCH_2CH_3)$_2$), 62.11 (d, J=5.0 Hz, $CO_2CH_2CH_3$), 135.63 (d, J=9.0 Hz, $C(CH_3)_2$), 157.95 (d, J=6.0 Hz, P–*C*), 167.26 (d, J=4.0 Hz, *C*=O); *m/z* (APCI$^+$) 287 ([MNa]$^+$, 100%).

4.1.4. 2,5-Dihydrothiophene-2,2-dimethyl-3-carboxylic acid ethyl ester (7).[11] To a suspension of flame dried lithium chloride (4.86 g, 115 mmol) in MeCN (210 mL) were added 1,4-dithiane-2,5-diol (8.75 g, 57.5 mmol) and then ethyl 2-(diethyoxyphosphoryl)-3-methyl-but-2-enoate (**6**) (30.6 g, 116 mmol). This mixture was cooled to 0°C and 1,8-diazabicyclo[5.4.0]undec-7-ene (17.6 mL, 117 mmol) was added. This solution was allowed to warm to ambient temperature and stirred for 8 h. The mixture was acidified to pH 6 with acetic acid (25% aq) and extracted into EtOAc (8×75 mL). The combined organic extracts were washed with saturated $NaHCO_{3(aq)}$ (50 mL), brine (50 mL), dried and concentrated in vacuo. The residue was purified by flash chromatography on silica (PE 40–60) to afford the title compound as a yellow oil (16.8 g, 78%): R_f 0.25 (PE 40–60/Et_2O 15:1); IR (NaCl plates) ν_{max} 2967 (m, CH), 1716 (s, C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, J=6.5 Hz, OCH_2CH_3), 1.70 (6H, s, C(CH_3)$_2$), 3.78 (2H, d, J=3.0 Hz, SCH_2CH), 4.22 (2H, q, J=6.5 Hz, OCH_2CH_3), 6.85 (1H, t, J=3.0 Hz, SCH_2CH=CH); δ_C (100.63 MHz, $CDCl_3$) 14.16 (OCH_2CH_3), 31.35 (SC(CH_3)$_2$), 35.12 (SCH_2), 59.24 (SC(CH_3)$_2$), 60.44 (OCH_2CH_3), 139.91 (SCH_2CH), 142.54 (CH=$CCO_2CH_2CH_3$), 163.50 (*C*=O); *m/z* (APCI$^+$) 187 ([MH]$^+$, 10%), 157 ([M−Et]$^+$, 50%), 113 ([M−CO_2Et]$^+$, 100%).

4.1.5. 2,5-Dihydrothiophene-2,2-dimethyl-3-carboxylic acid lithium salt (8). To a stirred solution of 2,5-dihydrothiophene-2,2-dimethyl-3-carboxylic acid ethyl ester (**7**) (18.8 g, 0.10 mmol) in anhydrous THF (200 mL) was added LiOH·H_2O (4.23 g, 0.10 mmol) in water (200 mL). This was heated under reflux for 24 h. The solvent was removed and the product dried in a dessicator for 48 h to yield the title compound, isolated as the lithium salt, as a yellow solid (16.2 g, 98%): R_f (acid) 0.25 (EtOAc/PE 40–60 2:1); IR (NaCl plates) ν_{max} 3434 (s, br, OH), 1642 (s, C=O); δ_H (200 MHz, CD_3OD) 1.60 (6H, s, C(CH_3)$_2$), 3.63 (2H, d, J=2.5 Hz, SCH_2CH), 6.52 (1H, t, J=2.5 Hz, SCH_2CH); δ_C (100.63 MHz, CD_3OD) 31.32 (S(CH_3)$_2$), 33.98 (SCH_2), 67.17 (SC(CH_3)$_2$), 132.17 (SCH_2CH), 150.27 (CH=CCO_2H), 171.56 (*C*=O); *m/z* (APCI$^-$) 157 ([M−H]$^-$, 78%), 113 (98%).

4.1.6. (3*RS*)-2,3-Dihydrothiophene-2,2-dimethyl-3-carboxylic acid ethyl ester (9). To a solution of the lithium salt (**8**) (4.00 g, 24.4 mmol) in THF (200 mL) was added triethylamine (8.32 mL, 59.6 mmol). This solution was stirred at ambient temperature for 0.5 h. The solution was then cooled to 0°C and ethyl chloroformate (6.31 mL, 65.9 mmol) was added dropwise. The solution was allowed to warm to ambient temperature and stirred for a further 24 h. The solvent was removed and water (50 mL) was added. The solution was acidified to pH 6 with HCl (5%, aq) and the product extracted with EtOAc (4×75 mL). The combined organic layers were then washed with saturated $NaHCO_{3(aq)}$ (50 mL), brine (50 mL), dried and concentrated in vacuo to yield a crude brown residue. This was purified by flash chromatography on silica (PE 40–60/Et_2O 10:1) to yield the title compound as a fluorescent green oil (3.35 g, 74%): R_f 0.25 (PE 40–60/Et_2O 10:1); IR (NaCl plates) ν_{max} 3978 (m, CH), 1735 (s, C=O); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, J=6.5 Hz, OCH_2CH_3), 1.40 (3H, s, one methyl of C(CH_3)$_2$), 1.70 (3H, s, one methyl of C(CH_3)$_2$), 3.69 (1H, t, J=2.5 Hz, $CHCO_2$Et), 4.12 (2H, q, J=6.5 Hz, OCH_2CH_3), 5.52 (1H, dd, J=6.5, 2.5 Hz, SCH=CH), 6.32 (1H, dd, J=6.5, 2.5 Hz, SCH=CH); δ_C (100.63 MHz, $CDCl_3$) 14.24 (OCH_2CH_3), 25.80 (one of SC(CH_3)$_2$), 29.35 (one of SC(CH_3)$_2$), 58.38 (SC(CH_3)$_2$), 60.79 (OCH_2CH_3), 63.14 ($CHCO_2$Et), 120.42 (SCH=CH), 127.83 (SCH=CH), 171.01 (*C*=O); *m/z* (APCI$^+$) 203 ([MNH_4]$^+$, 100%), 157 ([M−Et]$^+$, 57%), 113 ([M−CO_2Et]$^+$, 20%).

4.1.7. (1*R*,4*R*,5*R*)- and (1*S*,4*S*,5*S*)-7,7-Dichloro-3,3-dimethyl-2-thiabicyclo[3.2.0]heptan-6-one-4-carboxylic acid ethyl ester (10).[12] To a stirred solution of (3*RS*)-2,3-dihydrothiophene-2,2-dimethyl-3-carboxylic acid ethyl ester (**9**) (13.5 g, 72.5 mmol) and dichloroacetyl chloride (10.41 mL, 108 mmol) in carbon tetrachloride (1100 mL) was added a solution of triethylamine (15.0 mL, 108 mmol) in carbon tetrachloride (360 mL) dropwise over 4 days. After a further 24 h the reaction was quenched with water (100 mL) and the product extracted into carbon tetrachloride

(6×150 mL). The organic layer was washed with saturated $NaHCO_{3(aq)}$ (200 mL), brine (200 mL), dried and concentrated in vacuo to yield the title compound as a crude brown oil. This was purified by flash chromatography on silica (DCM/Et_2O 4:1) to afford the title compound as an orange oil (20.6 g, 96%): R_f 0.25 (DCM/Et_2O 4:1); IR (NaCl plates) ν_{max} 2950 (w, CH), 1802 (s, cyclobutanone C═O), 1736 (s, ester C═O); δ_H (400 MHz, $CDCl_3$) 1.26 (3H, t, J=7.0 Hz, OCH_2CH_3), 1.39 (3H, s, *endo*-methyl of $SC(CH_3)_2$), 1.59 (3H, s, *exo*-methyl of $SC(CH_3)_2$), 3.34 (1H, d, J=4.5 Hz, $CHCO_2Et$), 4.11–4.28 (2H, m, OCH_2CH_3), 4.62 (1H, d, J=8.0 Hz, SC*H*), 5.04 (1H, dd, J=8.0, 4.5 Hz, $CHC(O)CCl_2$); δ_C (100.63 MHz, $CDCl_3$) 14.20 (OCH_2CH_3), 27.68 (*exo*-methyl of $SC(CH_3)_2$), 28.31 (*endo*-methyl of $SC(CH_3)_2$), 57.65 (S*C*H), 60.19 (OCH_2CH_3), 63.08 ($C(CH_3)_2$), 69.07 ($CHC(O)CCl_2$), 85.02 (CCl_2), 169.23 (ester *C*═O), 193.85 (cyclobutanone *C*═O); *m/z* (EI^+) 298 ($[M^{37}Cl+^{35}Cl]^+$, 6%), 296 ($[M^{35}Cl_2]^+$, 19%), 201 (36%), 163 (78%), 113 (75%).

4.1.8. (1*S*,4*R*,5*R*)- and (1*R*,4*S*,5*S*)-3,3-Dimethyl-2-thiabicyclo[3.2.0]heptan-6-one-4-carboxylic acid ethyl ester (11). To a stirred solution of (1*R*,4*R*,5*R*) and (1*S*,4*S*,5*S*)-7,7-dichloro-3,3-dimethyl-2-thiabicyclo [3.2.0] heptan-6-one-4-carboxylic acid ethyl ester (**10**) (19.5 g, 65.7 mmol) in acetic acid (600 mL) was added zinc powder (18.0 g, 275 mmol). This mixture was heated under reflux for 15 h. The mixture was filtered and the zinc residue washed with acetic acid (100 mL). The filtrate was concentrated in vacuo. The residue was dissolved in EtOAc (600 mL) and washed with saturated $NaHCO_{3(aq)}$ (100 mL), brine (100 mL), dried and concentrated in vacuo to afford the title compound as an orange oil which was used without further purification, (12.3 g, 82%): R_f 0.25 (DCM/Et_2O 4:1); IR (NaCl plates) ν_{max} 2980 (w, CH), 1802 (s, cyclobutanone C═O), 1735 (s, ester C═O); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, t, J=7.0 Hz, OCH_2CH_3), 1.31 (3H, s, *endo*-methyl of $C(CH_3)_2$), 1.57 (3H, s, *exo*-methyl of $C(CH_3)_2$), 2.94 (1H, dt, J=18.0, 3.0 Hz, *endo*-H of $SCHCH_2$), 3.21 (1H, d, J=6.0 Hz, $CHCO_2Et$), 3.44 (1H, ddd, J=18.0, 7.5, 3.0 Hz, *exo*-H of $SCHCH_2$), 4.09–4.25 (3H, m, OCH_2CH_3, SC*H*), 4.72 (1H, m, SCHC*H*); δ_C (100.63 MHz, $CDCl_3$) 14.22 (OCH_2CH_3), 27.47 (*endo*-methyl of $C(CH_3)_2$), 27.99 (*exo*-methyl of $C(CH_3)_2$), 36.04 (S*C*H), 52.51 ($SCHCH_2$), 60.94 ($CHCO_2Et$), 61.25 (OCH_2CH_3), 64.27 ($SC(CH_3)_2$), 73.34 (SCH*C*H), 169.85 (ester *C*═O), 207.38 (cyclobutanone *C*═O); *m/z* ($APCI^+$) 229 ($[MH]^+$, 5%), 183 ($[M-OEt]^+$, 10%), 155 ($[M-CO_2Et]^+$, 5%), 201 (36%), 163 (78%), 113 (75%); HRMS: calculated for $C_{11}H_{17}O_3S$ $[MH]^+$: 229.0898; found: 229.0893.

4.1.9. (1*S*,4*R*,5*R*,6*R*)- and (1*R*,4*S*,5*S*,6*S*)-3,3-Dimethyl-2-thiabicyclo[3.2.0]heptan-6-ol-4-carboxylic acid ethyl ester (12). To a stirred solution of (1*S*,4*R*,5*R*) and (1*R*,4*S*,5*S*)-3,3-dimethyl-2-thiabicyclo[3.2.0]heptan-6-one-4-carboxylic acid ethyl ester (**11**) (12.6, 55.2 mmol) in MeOH (200 mL) at 0°C was added sodium borohydride (2.28 g, 60.2 mmol). The solution was allowed to warm to ambient temperature and stirred for a further 5 h. The product was adsorbed onto silica by solvent evaporation and purified by flash chromatography (DCM/Et_2O 8:1) to afford the title compound as a pale yellow oil (10.5 g, 83%): R_f 0.25 (DCM/Et_2O 8:1); IR (NaCl plates) ν_{max} 3448 (s, br, O–H), 2979, 2932 (C–H), 1728 (C═O); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, t, J=7.0 Hz, OCH_2CH_3), 1.29 (3H, s, *exo*-methyl of $C(CH_3)_2$), 1.64 (3H, s, *endo*-methyl of $C(CH_3)_2$), 2.11–2.21 (1H, dtd, J=12.0, 7.5, 1.0 Hz, *endo*-H of $SCHCH_2$), 2.49 (1H, d, J=4.0 Hz, O*H*), 2.86–2.92 (1H, ddd, J=12.0, 7.5, 2.0 Hz, *exo*-H of $SCHCH_2$), 3.46 (1H, q, J=7.5 Hz, SC*H*), 3.58 (1H, d, J=10.0 Hz, $CHCO_2Et$), 3.73–3.82 (1H, m, SCHC*H*), 4.09–4.29 (2H, m, OCH_2CH_3), 4.40–4.49 (1H, qd, J=7.5, 4.0 Hz, C*H*OH); δ_C (100.63 MHz, $CDCl_3$) 14.25 (OCH_2CH_3), 28.18 (*endo*-methyl of $C(CH_3)_2$), 28.55 (*exo*-methyl of $C(CH_3)_2$), 34.36 (S*C*H), 42.43 ($SCHCH_2$), 54.48 (SCH*C*H), 57.22 ($CHCO_2Et$), 60.08 ($SC(CH_3)_2$), 60.89 (OCH_2CH_3), 62.24 (*C*HOH), 172.09 (*C*═O); *m/z* ($APCI^+$) 231 ($[MH]^+$, 43%), 213 ($[M-H_2O]^+$, 100%), 187 ($[MH_2-OEt]^+$, 85%).

4.1.10. (1*R*,4*S*,5*S*,6*S*)- and (1*S*,4*R*,5*R*,6*R*)-3,3-Dimethyl-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*)-3,3-dimethyl-2-thiabicyclo[3.2.0]heptan-6-ol-4-carboxylic acid ethyl ester (**12**) (3.00 g, 13.0 mmol) in carbon tetrachloride (60 mL) was added a suspension of triphosgene (1.58 g, 5.32 mmol) in pyridine (1.20 mL, 14.9 mmol) and carbon tetrachloride (60 mL). This solution was stirred at 50°C for 3 h. The reaction mixture was cooled to ambient temperature and DCM (100 mL) added. This was washed with water (2×50 mL), brine (50 mL), dried and evaporated to afford the title compound as a yellow brown oil in quantitative yield. This was used without further purification: R_f 0.30 (PE 40–60/Et_2O 3:1); IR (NaCl Plates) ν_{max} 2987 (s, CH), 1778 (s, C═O, chloroformate), 1731 (s, C═O ester); δ_H (200 MHz, $CDCl_3$) 1.30 (3H, t, J=7.0 Hz, OCH_2CH_3) 1.32 (3H, s, *exo*-methyl of $C(CH_3)_2$), 1.63 (3H, s, *endo*-methyl of $C(CH_3)_2$), 2.43 (1H, dtd, J=15.0, 7.0, 2.0 Hz, *exo*-H of $SCHCH_2$), 2.97 (1H, dddd, J=15.0, 8.0, 7.0, 3.0 Hz, *endo*-H of $SCHCH_2$), 3.45 (1H, d, J=9.5 Hz, $CHCO_2Et$), 3.53 (1H, q, J=7.0 Hz, SC*H*), 3.92–4.07 (1H, m, SCHC*H*), 4.21 (2H, q, J=7.0 Hz, OCH_2CH_3), 5.26 (1H, q, J=8.0 Hz, $SCHCH_2CH$); δ_C (400 MHz, $CDCl_3$) 14.23 (OCH_2CH_3), 27.93 (*endo*-methyl of $C(CH_3)_2$), 28.46 (*exo*-methyl of $C(CH_3)_2$), 34.78 (S*C*H), 40.52 ($SCHCH_2$), 53.00 (SCH*C*H), 60.70 ($SC(CH_3)_2$), 61.12 (OCH_2CH_3), 70.88 ($SCHCH_2CH$), 149.41 (chloroformate *C*═O), 170.12 (ester *C*═O).

4.1.11. (1*R*,4*S*,5*S*,6*S*)- and (1*S*,4*R*,5*R*,6*R*)-3,3-Dimethyl-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*)-3,3-dimethyl-4-carbonyl-2-thiabicyclo[3.2.0] heptane-6-chloroformate (**13**) (3.80 g, 13.0 mmol) in DMF (20 mL) was added NaN_3 (4.23 g, 65.1 mmol). This solution was stirred at 50°C for 2 h, then allowed to cool to ambient temperature and then concentrated in vacuo. The product was dissolved in EtOAc (75 mL) and the organic solution was washed with water (2×20 mL) and brine (20 mL), dried and concentrated in vacuo. The residue was purified by flash chromatography on silica (PE 40–60/Et_2O 15:1) to afford the title compound as a yellow oil which crystallised on standing. (2.6 g, 67%): R_f 0.65 (PE 40–60/Et_2O 3:1); mp 31.5–32.0°C; IR (NaCl plates) ν_{max} 2978 (s, CH), 2186, 2136 (N_3), 1731 (s, br, C═O azidoformate and C═O ester); δ_H (500 MHz, $CDCl_3$) 1.28 (3H, t, J=7.5 Hz, OCH_2CH_3), 1.31 (3H, s, *exo*-methyl of $C(CH_3)_2$), 1.61 (3H, s,

endo-methyl of C(CH_3)$_2$), (1H, dtd, *J*=13.0, 8.0, 1.0 Hz, *exo*-H of SCHCH_2), 3.03 (1H, dtd, *J*=13.0, 7.5, 3.0 Hz, *endo*-H of SCHCH_2), 3.44 (1H, d, *J*=10.5 Hz, C*H*CO$_2$Et), 3.48 (1H, q, *J*=7.5 Hz, SC*H*), 3.99 (1H, m, SCHC*H*), 4.13–4.24 (2H, q, *J*=7.5 Hz, OCH_2CH$_3$), 5.18 (1H, q, *J*=8.0 Hz, SCHCHC*H*); δ_C (100.63 MHz, CDCl$_3$) 14.1 (OCH$_2$*C*H$_3$), 27.1 (*endo*-methyl of C(*C*H$_3$)$_2$), 28.4 (*exo*-methyl of C(*C*H$_3$)$_2$), 34.9 (S*C*H), 40.6 (SCH*C*H$_2$), 52.8 (SCH*C*H), 60.8 (S*C*(CH$_3$)$_2$), 61.1 (O*C*H$_2$CH$_3$), 67.4 (SCHCH$_2$*C*H), 156.0 (azidoformate *C*=O), 170.2 (ester *C*=O); *m/z* (CI(NH$_3$)) 317 ([MNH$_4$]$^+$, 100%), 300 ([MH]$^+$, 15%), 213 (80%), 113 (30%).

4.1.12. (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-9,9-dimethyl-3-oxo-8-thiatricyclo[5.3.0.0]decan-4-one (16). A stirred volume of dry TCE (700 mL) was degassed using a flow of argon through a glass pipette for 0.5 h. This was heated under reflux at 147°C. To this a solution of (1*R*,4*S*,5*S*,6*S*)- and (1*S*,4*R*,5*R*,6*R*)-3,3-dimethyl-4-ethoxycarbonyl-2-thiabicyclo [3.2.0]heptane-6-azidoformate (**14**) (250 mg, 0.84 mmol) in dry TCE (10 mL) was added dropwise over 3 min and the solution was stirred for a further 15 min. The solution was then cooled in an ice bath and concentrated in vacuo to yield a brown oil. This was purified by flash chromatography on silica (DCM/Et$_2$O 4:1) to afford the title compound as a white solid (63 mg, 28%): R_f 0.25 (PE 40–60/Et$_2$O 1:1); mp 135–135.5°C; IR (NaCl plates) ν_{max} 3361 (m, NH), 2970 (m, CH), 1744 (C=O), 1717 (s, C=O); δ_H (500 MHz, CDCl$_3$) 1.29 (6H, t and s, *J*=7.0 Hz, OCH$_2$C*H*$_3$ and *exo*-methyl of C(CH_3)$_2$), 1.70 (3H, s, *endo*-methyl of C(CH_3)$_2$), 3.40 (1H, d, *J*=6.0 Hz, C*H*CO$_2$Et), 4.05–4.37 (4H, m, SC*H*, SCHC*H*CHCO$_2$Et, OCH_2CH$_3$), 4.32 (1H, dddd *J*=7.5, 4.0, 2.0, 0.5 Hz, C*H*NH), 5.17 (1H, dt, *J*=6.0, 2.0 Hz, C*H*O(CO)NH), 5.21 (1H br s, N*H*); δ_C (100.63 MHz, CDCl$_3$) 14.2 (OCH$_2$*C*H$_3$), 27.4 (*exo*-methyl of C(*C*H$_3$)$_2$), 28.5 (*endo*-methyl of C(*C*H$_3$)$_2$), 47.0 (S*C*H), 51.2 (SCH*C*HCHCO$_2$Et), 52.7 (SCH*C*HNH), 57.0 (*C*HCHCO$_2$-Et), 60.3 (S*C*(CH$_3$)$_2$), 61.1 (O*C*H$_2$CH$_3$), 72.6 (O*C*H), 159.9 (urethane *C*=O), 170.0 (ester *C*=O); *m/z* (APCI$^+$) 272 ([MH]$^+$ 100%), 226 (40%) 198 (25%); HRMS calculated for C$_{12}$H$_{17}$NO$_4$S [MH]$^+$: 271.0878; found 271.0877.

4.1.13. (1*S*,2*R*,6*R*,7*S*,10*S*)- and (1*R*,2*S*,6*S*,7*R*,10*R*)-10-Ethoxycarbonyl-9,9-dimethyl-5-(*tert*-butyloxycarbonyl-3-oxo-8-thiatricyclo[5.3.0.0]decan-4-one (17). To a stirred solution of (1*R*,2*S*,6*S*,7*R*,10*R*)- and (1*S*,2*R*,6*R*,7*S*,10*S*)-10-ethoxycarbonyl-5-aza-9,9-dimethyl-3-oxo-8-thiatricyclo [5.3.0.0]decan-4-one (**16**) (238 mg, 0.88 mmol) in THF (24 mL) were added di-*tert*-butyl dicarbonate (396 mg, 1.81 mmol), triethylamine (0.25 mL, 1.79 mmol) and 4-(dimethylamino)pyridine (33.4 mg, 0.28 mmol). This solution was stirred at ambient temperature for 4 h and then concentrated in vacuo. The residue was dissolved in EtOAc (40 mL), washed with water (10 mL), brine (10 mL), dried and concentrated in vacuo to afford the title compound as a brown solid. This was triturated with hexane to yield an off-white solid (258 mg, 79%): R_f 0.25 (PE 40–60/Et$_2$O 1:1); IR (NaCl plates) ν_{max} 2980 (m, CH), 1809 (s, urethane C=O) 1734 (s, ester C=O); δ_H (500 MHz, (CD$_3$)$_2$C(O) 1.28 (6H, t, *J*=7.0 Hz, OCH$_2$C*H*$_3$, *exo*–methyl of C(CH_3)$_2$), 1.50 (9H, s, C(CH_3)$_3$), 1.59 (3H, s, *endo*-methyl of C(CH_3)$_2$), 3.12 (1H, d, 9.0 Hz, C*H*CO$_2$Et), 4.28–4.06 (3H, m, SC*H*, OCH_2CH$_3$), 4.43–4.48 (1H, ddd, *J*=9.0, 5.0, 2.0 Hz, SCHC*H*CHCO$_2$Et), 4.79–4.83 (1H, ddd, *J*=7.0, 5.0, 2.0 Hz, C*H*NBOC), 5.12–5.16 (1H, ddd, *J*=7.0, 6.5, 2.0 Hz, C*H*OC(O)); δ_C (100.63 MHz, (CD$_3$)$_2$C(O)) 14.02 (OCH$_2$*C*H$_3$), 27.4 (*exo*-methyl of C(*C*H$_3$)$_2$), 27.91 (C(*C*H$_3$)$_3$), 28.6 (*endo*-methyl of C(*C*H$_3$)$_2$), 47.0 (S*C*H), 50.3 (SCH*C*HCHCO$_2$Et), 55.2 (SCH*C*HN), 57.4 (*C*HCHCO$_2$Et), 59.7 (S*C*(CH$_3$)$_2$), 61.2 (O*C*H$_2$CH$_3$), 69.6 (O*C*H), 82.9 (*C*(CH$_3$)$_3$), 148.8 (BOC *C*=O), 153.2 (*C*=O), 170.0 (*C*=O); *m/z* (CI$^+$) 389 ([MNH$_4$]$^+$, 10%), 333 (15%), 289 (100%), 272 (35%), 186 (27%), 113 (23%); HRMS calculated for C$_{17}$H$_{29}$N$_2$O$_6$S [MNH$_4$]$^+$: 389.1746; found 389.1752.

4.1.14. (1*S*,4*S*,5*S*,6*R*,7*R*)- and (1*R*,4*R*,5*R*,6*S*,7*S*)-7-(*tert*-Butyloxycarbonylamino)-3,3-dimethyl-2-thiabicyclo [3.2.0]heptan-6-ol-4-carboxylic acid ethyl ester (18). To a stirred solution of (1*R*,2*S*,6*S*,7*R*,10*R*)- and (1*S*,2*R*,6*R*, 7*S*,10*S*)-10-ethoxycarbonyl-9,9-dimethyl-5-(*tert*-butyloxy-carbonyl-3-oxo-8-thiatricyclo[5.3.0.0]decan-4-one (**17**), (50 mg, 0.135 mmol) in ethanol (5 mL) was added caesium carbonate (9 mg, 27.6 μmol). This solution was stirred at ambient temperature for 3 h. The volatile components were removed in vacuo and the residue dissolved in water (2 mL) and neutralised to pH 7 with citric acid (5%, aq). The product was extracted into DCM (3×15 mL), dried and concentrated in vacuo. The residue was purified by flash chromatography on silica (DCM/Et$_2$O 3:1) to afford the title compound (42.0 mg, 90%): R_f 0.45 (DCM/Et$_2$O 3:1); IR (NaCl plates) ν_{max} 3429 (br, NH, OH) 2980 (w, CH), 2961, 2925, (s, CH), 1729 (s, C=O ester) 1694 (s, urethane C=O); δ_H (400 MHz, CDCl$_3$) 1.28 (6H, t, *J*=7.0 Hz, OCH$_2$C*H*$_3$ and s, *exo*-methyl of C(CH_3)$_2$), 1.50 (9H, s, C(CH_3)$_3$), 1.59 (3H, s, *endo*-methyl of C(CH_3)$_2$), 2.89 (1H, d, *J*=4.5 Hz, CHO*H*), 3.33 (1H, d, *J*=8.5 Hz, C*H*CO$_2$Et), 3.74 (1H, q, *J*=8.5 Hz, SCHC*H*CHCO$_2$Et), 3.93– 4.16 (4H, m, OCH_2CH$_3$, C*H*NH, SC*H*), 4.52 (1H, q, *J*=6.0 Hz, C*H*OH), 5.12–5.16 (1H, br s N*H*); δ_C (100.63 MHz, CDCl$_3$) 14.22 (OCH$_2$*C*H$_3$), 27.82 (*exo*-methyl of C(*C*H$_3$)$_2$) 28.31 (*endo*-methyl of C(*C*H$_3$)$_2$), 28.47 (C(CH_3)$_3$), 43.75 (S*C*H), 50.03 (*C*HNH), 50.88 (SCH*C*H), 57.98 (*C*HCO$_2$Et), 59.45 (S*C*(CH$_3$)$_2$), 61.27 (O*C*H$_2$CH$_3$), 65.75 (HO*C*H), 79.84 (*C*(CH$_3$)$_3$), 155.86 (urethane *C*=O), 170.91 (ester *C*=O); *m/z* (CI$^+$) 346 ([MH]$^+$, 10%), 290 (100%), 246 (40%), 120 (28%); HRMS calculated for C$_{16}$H$_{28}$N$_1$O$_5$S [MH]$^+$:346.1671; found 346.1688.

4.1.15. (1*R*,4*R*,5*R*,6*S*,7*S*)- and (1*S*,4*S*,5*S*,6*R*,7*R*)-7-(*tert*-Butyloxycarbonylamino)-3,3-dimethyl-2-thiabicyclo [3.2.0]heptan-6-ol-4-carboxylic acid (19). 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*-butyloxycarbonylamino)-3,3-dimethyl-2-thiabicyclo[3.2.0] heptan-6-ol-4-carboxylic acid ethyl ester (**18**) (88.0 mg, 0.255 mmol) in DMF (2 mL) was added a solution of LiOH·H$_2$O (18.0 mg, 0.43 mmol) in water (2 mL). This solution was stirred at 70°C for 18 h and was then acidified to pH 2 with HCl (1 M, aq) and extracted into EtOAc (3×10 mL). The organic layer was extracted into saturated NaHCO$_{3(aq)}$ (3×10 mL). This was then acidified with HCl (1 M, aq) and extracted into EtOAc (3×10 mL). The organic layer was dried and concentrated *in vacuo* to afford the title compound as a white solid (60.7 mg, 75%): R_f 0.75 (Et$_2$O); mp (dec. 150°C); IR (NaCl plates) ν_{max} 3382 (m, NH, OH), 2974, 2931, (s, CH), 1667 (br, s, urethane C=O and C=O

acid); δ_H (500 MHz, CD_3OD) 1.28 (3H, s, *exo*-methyl of $C(CH_3)_2$), 1.43, (9H, s, $C(CH_3)_3$), 1.60 (3H, s, *endo*-methyl of $C(CH_3)_2$), 3.43 (1H, d, J=7.0 Hz, $CHCO_2H$), 3.75 (1H, q, J=7.0 Hz, $SCHCHCHCO_2H$), 4.02 (1H, t, J=7.0 Hz, SCH), 4.17 (1H, t, J=6.0 Hz, $CHNH$), 4.56 (1H, t, J=7.0 Hz, $CHOH$); δ_C (100.63 MHz, CD_3OD) 26.99 (*endo*-methyl of $C(CH_3)_2$), 27.62 ($C(CH_3)_3$), 28.02 (*exo*-methyl of $C(CH_3)_2$), 45.05 (SCH), 51.19 ($CHNH$), 51.70 ($SCHCH$), 58.61 ($CHCO_2H$), 60.3 ($SC(CH_3)_2$), 64.19 ($CHOH$), 79.53 ($C(CH_3)_3$), 156.39 (urethane C=O), 173.49 (acid C=O); *m/z* (APCI$^-$) 316.4 ([M−H]$^-$, 100%) 242 (10%), 216 (10%), 113 (35%); HRMS calculated for $C_{14}H_{23}NO_5S$ [MH]$^+$: 318.1375; found 318.1369.

4.1.16. (1*S*,4*S*,5*S*,6*R*,7*R*)- and (1*R*,4*R*,5*R*,6*S*,7*S*)-7-(*tert*-Butyloxycarbonylamino)-3,3-dimethyl-2-thiabicyclo [3.2.0]heptan-6-ol-4-carboxylic acid diphenylmethyl ester (20). 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*-butyloxycarbonylamino)-3,3-dimethyl-2-thiabicyclo[3.2.0]heptan-6-ol-4-carboxylic acid (**19**) (149 mg, 0.47 mmol) in acetonitrile (3 mL) was added a solution of diphenyldiazomethane (91.2 mg, 0.47 mmol) in acetonitrile (3 mL). This solution was stirred at ambient temperature for 1 h. The volatile components were removed in vacuo. The residue was taken up into EtOAc (20 mL) and acetic acid (0.1 mL) added to quench any residual diphenyldiazomethane. The mixture was washed with water (2×2 mL), saturated $NaHCO_{3(aq)}$ (2 mL), brine (2 mL), dried and concentrated in vacuo. The residue was purified by flash chromatography on silica (DCM/Et_2O 3:1) to yield the title compound as a pale yellow oil (150 mg, 66%): R_f (DCM/Et_2O) 0.3; IR (NaCl plates) ν_{max} 3389 (s, OH), 2975 (CH), 1713 (ester C=O), 1689 (urethane C=O); δ_H (400 MHz, $CDCl_3$) 1.12 (3H, s, *exo*-methyl of $C(CH_3)_2$), 1.44 (9H, s, $C(CH_3)_3$), 1.61 (3H, s, *endo*-methyl of $C(CH_3)_2$), 2.55–2.62 (1H, br s, OH), 3.55 (1H, d, J=9.0 Hz, $CHCO_2CHPh_2$), 3.82 (1H, qd, J=9.0, 1.0 Hz, $SCHCH$), 4.07 (1H, br t, J=7.0 Hz, SCH), 4.12 (1H, br m, $CHNH$), 4.57 (1H, t, J=7.0 Hz, $CHOH$), 5.50 (1H, br d, J=4.5 Hz, NH), 6.89 (1H, s, $CHPh_2$), 7.30–7.40 (10H, m, $CHPh_2$); δ_C (400 MHz, $CDCl_3$) 27.75 (*endo*-C of $C(CH_3)_2$), 28.32 (*exo*-C of $C(CH_3)_2$ and $C(CH_3)_3$), 43.71 (SCH), 51.11 ($CHNH$), 53.72 ($SCHCH$), 57.17 ($CHCO_2CHPh_2$), 59.63 ($C(CH_3)_2$), 65.79 ($CHOH$), 77.66 ($CHPh_2$), 126.72, 127.64, 127.83, 128.15, 128.47, 128.54 (C_{Ar}), 139.85 (urethane C=O), 170.02 (ester C=O); *m/z* (ES$^+$) 506 ([MNa]$^+$, 100%), 484 ([MH]$^+$, 25%), 428 (7%); HRMS calculated for $C_{27}H_{33}NO_5S^{23}Na$: 506.1977; found 506.1990.

4.1.17. (1*S*,4*S*,5*S*,6*R*,7*R*)- and (1*R*,4*R*,5*R*,6*S*,7*S*)-7-Amino-3,3-dimethyl-2-thiabicyclo[3.2.0]heptan-6-ol-4-carboxylic acid diphenylmethyl ester *p*-toluenesulfonic acid salt (21). To a stirred solution of (1*R*,4*R*,5*R*,6*S*,7*S*)- and (1*S*,4*S*,5*S*,6*R*,7*R*)-7-(*tert*-butyloxycarbonylamino)-3,3-dimethyl-2-thiabicyclo[3.2.0]heptan-6-ol-4-carboxylic acid diphenylmethyl ester (**20**) (149 mg, 0.31 mmol) in MeCN (3 mL) was added *p*-toluene sulfonic acid monohydrate (59 mg, 0.31 mmol). This solution was stirred at ambient temperature for 10 h. Ether (5 mL) was added and the tosylate salt filtered and dried in a dessicator to yield the title compound as a white solid (102 mg, 59%): R_f (DCM/EtOAc 3:1) 0.05; δ_H (400 MHz, CD_3OD) 1.11 (3H, s, *exo*-methyl of $C(CH_3)_2$), 1.60 (3H, s, *endo*-methyl of $C(CH_3)_2$), 2.35 (3H, s, $CH_3C_6H_4$), 3.86 (1H, d, J=7.5 Hz, $CHCO_2CHPh_2$), 3.94 (1H, td, J=7.0, 2.0 Hz, $CHNH_3^+$), 4.03 (1H, qd, J=7.5, 2.0 Hz, $SCHCH$), 4.12 (1H, dt, J=7.0, 2.0 Hz, SCH), 4.69 (1H, dt, J=7.0, 2.0 Hz, $CHOH$), 6.89 (1H, s, $CHPh_2$), 7.20 (2H, d, J=8.0 Hz, $CH_3(C_6H_4)SO_3$), 7.20–7.50 (10H, $CHPh_2$), 7.72 (2H, d, J=8.0 Hz, $CH_3(C_6H_4)SO_3$); δ_C (100.63 MHz, CD_3OD) 20.0 ($CH_3(C_6H_4)$, 26.15 (*endo*-methyl of $C(CH_3)_2$), 27.0 (*exo*-methyl of $C(CH_3)_2$), 40.35 (SCH), 50.79 ($SCHCH$), 53.14 ($CHNH$), 56.94 ($CHCO_2CHPh_2$), 61.55 ($CHOH$), 78.0 ($CHPh_2$), 125.97, 126.69, 127.76, 127.85, 128.26, 128.47, 128.57, 128.79 (C_{Ar}), 170.1 ester (C=O); Found C, 62.28%; H, 6.02%. $C_{29}H_{33}NO_6S_2$ requires C, 62.28%, H, 5.99%; *m/z* (ES$^+$) 384 ([M−*p*TsO$^-$]+, 3%), 167 (100%); HRMS calculated for $C_{22}H_{26}NO_3S$ [M−*p*TsO$^-$]+: 384.1633; found 384.1633.

4.1.18. (1*S*,4*S*,5*S*,5′*R*,6*R*,7*R*)- and (1*R*,4*R*,5*R*,5′*R*,6*S*,7*S*)-7-[5′(*tert*-Butyloxycarbonylamino)-5′-(*p*-methoxybenzyl-oxycarbonyl)pentanamido]-3,3-dimethyl-2-thiabicyclo [3.2.0]heptan-6-ol-4-carboxylic acid diphenylmethyl ester (23). 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-amino-3,3-dimethyl-2-thiabicyclo[3.2.0] heptan-6-ol-4-diphenylmethyl ester *p*-toluenesulfonic acid (**21**) (160 mg, 0.29 mmol) in DCM (1 mL) was added a solution of *N*-*tert*-butyloxycarbonyl-D-α-aminoadipic acid α-*p*-methoxybenzyl ester[13] (113 mg, 0.29 mmol) in DCM (2 mL) and a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (71.6 mg, 0.37 mmol) and 1-hydroxybenzotriazole (HOBt) (65 mg, 0.48 mmol) in DCM (2 mL). Triethylamine (101 μL, 0.72 mmol) was added dropwise and the mixture stirred at ambient temperature for 15 h. The volatile components were removed in vacuo and the residue dissolved in EtOAc (10 mL). This was washed with HCl (5%, aq, 2 mL), saturated $NaHCO_{3(aq)}$ (2 mL), brine (2 mL), dried and concentrated in vacuo to yield a pale yellow oil which was purified by flash chromatography on silica (DCM/Et_2O 3:1) to yield a white foam (177 mg, 82%): R_f 0.3 (DCM/Et_2O 3:1); IR (NaCl plates) ν_{max} 3365 (m, NH), 2972 (s, CH), 1731 (s, br, ester C=O), 1651 (amide C=O); δ_H (400 MHz, $CDCl_3$) 1.10 (6H, s, *exo*-methyl of $C(CH_3)_2$ diastereomers A and B), 1.40 (18H, s, $C(CH_3)_3$ diastereomers A and B), 1.61 (6H, s, *endo*-methyl of $C(CH_3)_2$, diastereomers A and B), 1.62–1.73 (6H, m, $NHCHCH_2$ diastereomers A and B and $NHCHCH_2CH_2$ diastereomer A), 1.74–1.90 (2H, br m, $NHCHCH_2CH_2$ diastereomer B) 2.20–2.42 (4H, m, $NHCHCH_2CH_2CH_2$ diastereomers A and B) 3.56 (2H, 2d, J=9.0, 7.0 Hz, $CHCO_2CHPh_2$ diastereomers A and B) 3.80 (6H, s, OCH_3 diastereomers A and B) 3.87 (2H, q, 8.0 Hz, $SCHCH$ diastereomers A and B), 4.03 (2H, t, J=8.0 Hz, SCH diastereomers A and B), 4.30 (2H, br m, ^tBuO-$CONHCH$ diastereomers A and B), 4.42 (2H, m, $SCHCHNH$ diastereomers A and B), 4.60 (2H, br m, $CHOH$ diastereomers A and B), 5.06 (4H, m, $pMeO(C_6H_4)CH_2$ diastereomers A and B), 5.23 (2H, m, $NHCHCH_2$, diastereomers A and B), 6.46 (2H, m, $NHCHCHOH$ diastereomers A and B), 6.88 (6H, m, 2H from $CHPh_2$ diastereomers A and B and 4H from $pMeO(C_6H_4)CH_2$ diastereomers A and B), 7.21–7.40 (24H, m, 20H from $CHPh_2$ and 4H from $pMeO(C_6H_4)CH_2$ diastereomers A and B); δ_C (400 MHz, $CDCl_3$) 21.41 ($NHCHCH_2CH_2$), 27.87 (*endo*-methyl of $C(CH_3)_2$), 28.31 (*exo*-methyl of $C(CH_3)_2$ and $C(CH_3)_3$), 31.85

(NHCHCH$_2$CH$_2$*C*H$_2$), 35.36, 35.46 (NHCH*C*H$_2$CH$_2$CH$_2$), 43.07, 43.44 (S*C*H), 49.26 (SCH*C*HNH), 50.97, 51.20 (NH*C*HCH$_2$), 53.23 (SCH*C*HCHCO$_2$CHPh$_2$), 55.27 (O*C*H$_3$), 57.17 (*C*HCO$_2$CHPh$_2$) 59.67, 59.72 (*C*(CH$_3$)$_2$), 65.28 (*p*MeO(C$_6$H$_4$)C*H*$_2$) 65.40 (*C*HOH), 66.94 (*C*(CH$_3$)$_3$), 77.66 (*C*HPh$_2$), 113.95 (two of *p*MeO(*C*$_6$H$_4$)CH$_2$), 126.69, 127.48, 127.63, 127.82, 128.15, 128.47, 130.19, 139.79, 139.85 (*C*$_{Ar}$), 159.72 (urethane *C*=O), 169.77 (amide *C*=O), 172.47, 172.56 (2×ester *C*=O); *m/z* (ES$^+$) 747 ([MH]$^+$, 100%), 610 (10%); HRMS calculated for $C_{41}H_{51}N_2O_9S$: 747.3315; found 747.3298.

4.1.19. (1*R*,4*R*,5*R*,5′*R*,7*S*)- and (1*S*,4*S*,5*S*,5′*R*,7*R*)-7-[5′-(*tert*-Butyloxycarbonylamino)-5′-(*p*-methoxybenzyloxycarbonyl)pentanamido]-3,3-dimethyl-2-thiabicyclo-[3.2.0]heptan-6-one-4-carboxylic acid diphenylmethyl ester (24). To a stirred solution of (1*S*,4*S*,5*S*,5′*R*,6*R*,7*R*)- and (1*R*,4*R*,5*R*,5′*R*,6*S*,7*S*)-7-[5′(*tert*-butyloxycarbonylamino)-5′-(*p*-methoxybenzyloxycarbonyl)pentanamido]-3,3-dimethyl-2-thiabicyclo[3.2.0]heptan-6-ol-4-carboxylic acid diphenylmethyl ester (**23**) (89 mg, 0.12 mmol) in DMSO (2 mL) was added *o*-iodoxybenzoic acid (IBX) (36.7 mg, 0.13 mmol) in one portion. This was stirred at room temperature for 1.5 h. Water (5 mL) was added and the product extracted into ethyl acetate (3×20 mL). The organic layer was washed with saturated NaHCO$_{3(aq)}$ (3×5 mL) and brine (2×5 mL). The organic layer was dried over sodium sulfate and then concentrated in vacuo to afford the title compound as a pale yellow foam. This was purified by flash chromatography on silica (DCM/Et$_2$O 4:1) to afford the title compound as an off-white foam (80 mg, 90%): R_f 0.65 (DCM/Et$_2$O 3:1); IR (NaCl plates) ν_{max} 3315 (m, NH), 2965, 2950 (s, CH), 1789 (s, cyclobutanone C=O), 1731 (s, br, ester C=O); δ_H (400 MHz, C$_6$D$_6$) 1.05 (6H, s, *exo*-methyl of C(C*H*$_3$)$_2$, diastereomers A and B), 1.40 (18H, s, C(C*H*$_3$)$_3$, diastereomers A and B), 1.43 (6H, s, *endo*-methyl of C(C*H*$_3$)$_2$, diastereomers A and B), 1.48–1.52 (12H, br m, NHCHC*H*$_2$C*H*$_2$C*H*$_2$ diastereomers A and B), 3.30 (6H, s, OC*H*$_3$ diastereomers A and B), 3.47 (2H, 2d, *J*=4.0 Hz, C*H*CO$_2$CHPh$_2$ diastereomers A and B), 3.86–3.98 (2H, br t, SC*H* diastereomers A and B), 4.28–4.31 (1H, br m, SCHC*H*CHCO$_2$), 4.42–4.55 (2H, m NHC*H*CH$_2$ diastereomers A and B), 4.80–5.10 (4H, br, m, *p*MeO(C$_6$H$_4$)C*H*$_2$ diastereomers A and B), 5.09–5.18 (2H, q, *J*=10.0 Hz, CH$_2$N*H*CCO$_2$ diastereomers A and B), 5.40–5.51 (2H, q, *J*=9.0 Hz, SCHC*H*NH diastereomers A and B), 5.77–5.93 (2H, 2d, *J*=8.5, 9.0 Hz, N*H*CHCH diastereomers A and B), 6.75 (6H, m, 2H from C*H*Ph$_2$ diastereomers A and B and 4H from *p*MeO(C$_6$*H*$_4$)CH$_2$ diastereomers A and B), 6.91–7.43 (24H, m, 20H from CH*Ph*$_2$ and 4H from *p*MeO(C$_6$*H*$_4$)CH$_2$ diastereomers A and B); δ_C (100.63 MHz, CDCl$_3$) 21.14 (NHCHCH$_2$*C*H$_2$), 27.51, 28.25, 28.32 (*exo* and *endo*-C of C(*C*H$_3$)$_2$ and C(*C*H$_3$)$_3$), 32.01 (NHCH*C*H$_2$CH$_2$CH$_2$), 35.09 (NHCHCH$_2$CH$_2$*C*H$_2$), 45.24 (S*C*H), 55.27 (NH*C*HCH$_2$), 59.57 (SCHCHCHCO$_2$), 60.4 (*C*(CH$_3$)$_2$), 62.46 (*C*(CH$_3$)$_3$), 62.52 (SCH*C*HNH), 66.98 (*p*MeO(C$_6$H$_4$)*C*H$_2$), 67.19 (SCH*C*HCHCO$_2$CHPh$_2$), 78.26 (*C*HPh$_2$), 113.96 (two of *p*MeO(*C*$_6$H$_4$)CH$_2$), 126.67, 127.43, 127.78, 128.02, 128.40, 128.56, 128.63, 130.17 (16 *C*$_{Ar}$), 159.73 (*C*=O urethane), 168.97 (*C*=O amide), 172.01, 172.46 (2×ester *C*=O), 205.36 (cyclobutanone *C*=O); *m/z* (ES$^+$) 745 ([MH]$^+$, 100%), 689 (10%), 645 (5%), 610 (5%), 536 (8%); HRMS calculated for $C_{41}H_{49}N_2O_9S$: 745.3152; found 745.3159.

4.1.20. (1*S*,4*S*,5*S*,5′*R*,7*R*)- and (1*R*,4*R*,5*R*,5′*R*,7*S*)-7-[5′-Amino-5′-carboxypentanamido]-3,3-dimethyl-2-thiabicyclo[3.2.0]heptan-6-one-4-carboxylate (1a/1b). To a solution of (1*S*,4*S*,5*S*,5′*R*,7*R*)- and (1*R*,4*R*,5*R*,5′*R*,7*S*)-7-[5′(*tert*-butyloxycarbonylamino)-5′-(*p*-methoxybenzyloxycarbonyl)pentanamido]-3,3-dimethyl-2-thiabicyclo[3.2.0]heptan-6-one-4-carboxylic acid diphenylmethyl ester (**24**) (19 mg, 0.026 mmol) in TFA/anisole/toluene (3:1:20) (7 mL) was stirred for 0.5 h at ambient temperature. This solution was concentrated in vacuo and the residue dissolved in H$_2$O (10 mL). The aqueous solution was washed with EtOAc (3×2 mL) and lyophilised to yield the title compound as a white solid (6.60 mg, 71%): δ_H (400 MHz, D$_2$O) 1.28 (2×3H, s, *exo*-methyl of C(C*H*$_3$)$_2$ diastereomers A and B), 1.47 (2×3H, s, *endo*-methyl of C(C*H*$_3$)$_2$ diastereomers A and B), 1.50–1.68 (2×2H, m, NHCHCH$_2$C*H*$_2$ diastereomers A and B), 1.68–1.87 (2×2H, m, NHCHC*H*$_2$CH$_2$ diastereomers A and B), 2.24–2.34 (2×2H, m, NHCHCH$_2$CH$_2$C*H*$_2$ diastereomers A and B), 3.10 (2×1H, 2d, *J*=3.5 Hz, C*H*CO$_2$H diastereomers A and B), 3.80 (2×1H, t, *J*=7.0 Hz, C*H*(NH)CH$_2$ diastereomers A and B), 4.47–4.58 (2×2H, m, SC*H*C*H*CO$_2$H diastereomers A and B), 5.32–5.41 (2×1H, 2d, *J*=2.5 Hz, SCHC*H*NH diastereomers A and B); δ_C (100.63 MHz, D$_2$O) 21.1 (NHCHCH$_2$*C*H$_2$), 27.2 (*exo*-C of C(*C*H$_3$)$_2$), 28.2, (*endo*-C of C(*C*H$_3$)$_2$), 29.8 (NHCH*C*H$_2$CH$_2$CH$_2$), 34.6 (NHCHCH$_2$-CH$_2$*C*H$_2$), 44.8 (S*C*H), 54.20 (*C*H(NH)CH$_2$), 60.1 (*C*HCO$_2$H), 62.7 (*C*(CH$_3$)$_2$), 63.1 (SCH*C*HNH), 67.2 (SCH*C*HCHCO$_2$H), 174.3 (amide *C*=O), 175.7 (2×acid *C*=O), 208.4, 208.9 (cyclobutanone *C*=O); *m/z* (ES-) 357 ([M−H]$^-$, 100%), 283 (9%), 279 (10%), 255 (10%); HRMS calculated for $C_{15}H_{21}N_2O_6S$: 357.1120; found 357.1137.

4.1.21. (1*S*,4*S*,5*S*,5′*R*,6*R*,7*R*)- and (1*R*,4*R*,5*R*,5′*R*,6*S*,7*S*)-7-[5′-Amino-5′-carboxypentanamido]-3,3-dimethyl-2-thiabicyclo[3.2.0]heptan-6-ol-4-carboxylate (25). *Method 1*: To a solution of (1*S*,4*S*,5*S*,5′*R*,7*R*)- and (1*R*,4*R*,5*R*,5′*R*,7*S*)-7-[5′-amino-5′-carboxypentanamido]-3,3-dimethyl-2-thiabicyclo[3.2.0]heptan-6-one-4-carboxylate (**1a/1b**) (6 mg, 0.017 mmol) in D$_2$O (5 mL) was added sodium borohydride (0.7 mg, 0.019 mmol). The product was observed directly by NMR.

Method 2: (1*S*,4*S*,5*S*,5′*R*,6*R*,7*R*)- and (1*R*,4*R*,5*R*,5′*R*,6*S*,7*S*)-7-5′(*tert*-butyloxycarbonylamino)-5′-(*p*-methoxybenzyloxycarbonyl)pentanamido]-3,3-dimethyl-2-thiabicyclo[3.2.0]heptan-6-ol-4-carboxylic acid diphenylmethyl ester (**23**) (5 mg, 0.007 mmol) in a TFA/anisole/toluene (3:1:20) (0.5 mL) was stirred for 0.5 h at ambient temperature. This solution was concentrated in vacuo and the residue dissolved in H$_2$O (2 mL). This aqueous solution was washed with EtOAc (1×0.5 mL) and lyophilised to yield the title compound as a white solid (1.2 mg, 48%).

For (**25**): δ_H (400 MHz, D$_2$O) 1.12 (2×3H, s, *exo*-methyl of C(C*H*$_3$)$_2$ diastereomers A and B), 1.48 (2×3H, s, *endo*-methyl of C(C*H*$_3$)$_2$ diastereomers A and B), 1.50–1.73 (4×2H, m, NHCHCH$_2$C*H*$_2$ diastereomers A and B and NHCHC*H*$_2$CH$_2$ diastereomers A and B), 2.02–2.37 (2×2H, m, NHCHCH$_2$CH$_2$C*H*$_2$ diastereomers A and B), 2.97 (2×1H, 2d, *J*=4.5 Hz, C*H*CO$_2$H diastereomers A and B), 3.30 (2×1H, br m, C*H*(NH)CH$_2$ diastereomers A and B), 3.56 (2×1H, q, *J*=8.0 Hz, SCHC*H*CO$_2$H diastereomers A

and B), 3.97 (2×1H, t, J=5.0 Hz, SC*H*CHCO$_2$H diastereomers A and B), 4.53 (2×1H, t, J=7.0 Hz, SCHC*H*NH diastereomers A and B).

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