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An approach to an asymmetric synthesis of stemofoline

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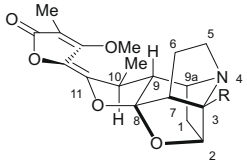
This paper is dedicated to Professor George Fleet, on the occasion of his 65th birthday.

ABSTRACT

A stereoselective Mannich reaction between an (*S*)-*tert*-butylsulfinimine and methyl (*S*)-4-benzyloxy-3-methylbutanoate followed by treatment with acid and N-protection was used to prepare methyl (2*R*,3*S*)-2-[(*S*)-2-benzyloxy-1-methylethyl]-3-*tert*-butoxycarbonylamino-6-methylenedecanoate. This was taken through to methyl (4*R*,5*S*)-4-[(*S*)-2-benzyloxy-1-methylethyl]-5-*tert*-butoxycarbonylamino-3,8-dioxododecanoate which on treatment with trifluoroacetic acid cyclised stereoselectively to give (1*R*,2*S*,4*R*,5*S*)-4-[(*S*)-2-benzyloxy-1-methylethyl]-1-butyl-2-methoxycarbonyl-8-*tert*-butoxycarbonyl-3-oxo-8-azabicyclo[3.2.1]octane, a potential precursor of stemofoline. Reduction and N-deprotection of this ketone gave (1*R*,2*S*,3*R*,4*R*,5*S*)-4-[(*S*)-2-benzyloxy-1-methylethyl]-1-butyl-2-methoxycarbonyl-8-azabicyclo[3.2.1]octan-3-ol the structure of which was confirmed by X-ray diffraction.

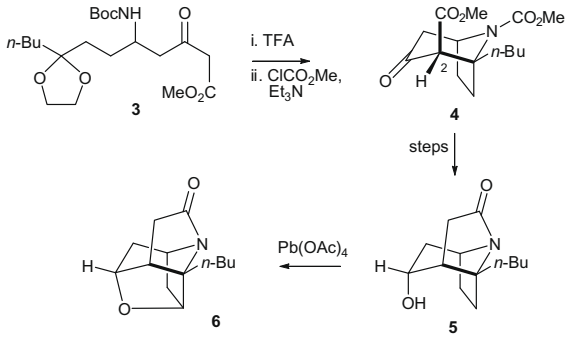
1. Introduction

The *Stemona* alkaloids have been isolated from extracts obtained from the roots and leaves of several *Stemonacea* used in traditional medicine in China, Japan and Thailand to treat respiratory illnesses and parasitic infections.[1] The more complex *Stemona* alkaloids include stemofoline **1** and asparagamine A **2**, which has also been isolated from *Asparagus racemosus*.[2] Many synthetic approaches to the Stemona alkaloids have been described including total syntheses of (±)-isostemofoline[3] [the (*E*)-isomer of stemofoline] and (±)-asparagamine together with its (*E*)-isomer.[4,5] No biosynthetic work has been reported for these alkaloids but a biogenetic route has been proposed.[1]



1 R=$(CH_2)_3CH_3$
2 R = $CH{=}CHCH_2CH_3$

Studies have been carried out on a synthetic approach to stemofoline, based on the modification of tropinone **4** prepared by a stereoselective cyclisation of a cyclic iminium ion generated from the racemic open-chain amido-ketone **3**.[6] Subsequent modification of the tropinone **4** gave the tricyclic hydroxylactam **5**, which was converted into ether **6**, which has the tetracyclic core structure of stemofoline, by regioselective remote oxidation. However, attempts to introduce fragments corresponding to the C(10)–C(11) side chain of stemofoline into bi- and tricyclic intermediates prepared from **4** and **5** were relatively low yielding.[6] Therefore, it was decided to study the synthesis and cyclisation of open-chain intermediates corresponding to the keto-ester **3** to which the C(10)-C(11) fragment had already been attached.



Keto-ester **7** which has three stereogenic centres corresponding to those at C(9a), C(9) and C(10) in stemofoline, was identified as the initial target and syntheses based on an asymmetric Mannich strategy were considered. The titanium(IV)-mediated addition of ester enolate anions to *N*-*tert*-butylsulfinimines developed by Ellman has proven to be a very useful asymmetric synthesis of β-amino-esters.[7] For the synthesis of the keto-ester **7** this would involve the reaction of ester **9** with the chiral sulfinimine **8** followed by further elaboration to develop the keto-ester functionality. In his case, both the sulfinimine and the ester are chiral, and so the

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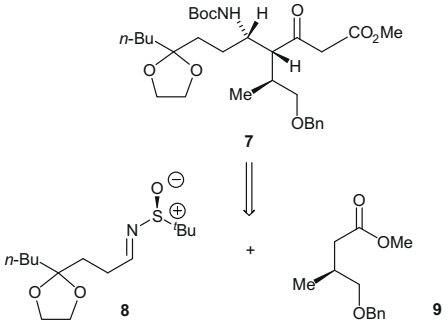
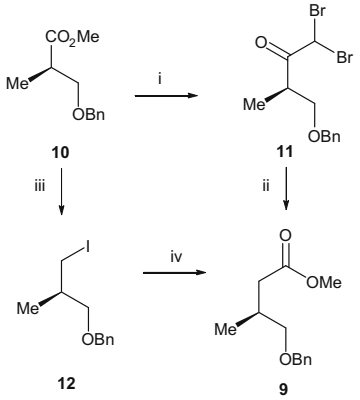
overall stereoselectivity would be affected by both the ester and the imine. Herein, we report preliminary studies into the use of the Ellman reaction to prepare intermediates analogous to keto-ester **7** and the stereoselective cyclisations of these to give 8-azabicyclo[3.2.1]octanes which may have use in an asymmetric synthesis of stemofoline.



2. Results and discussion

Two procedures were used to prepare methyl (*S*)-4-benzyloxy-3-methylbutanoate **9** from methyl (*R*)-3-benzyloxy-2-methylpropanoate **10**. The addition of lithiated dibromomethane gave dibromoketone **11**, which was converted into ester **9** by treatment with lithium hexamethyldisilazide and butyllithium.[8] Alternatively, ester **10** was taken through to iodide **12** by reduction and reaction of the resulting alcohol with iodine and triphenylphosphine. Iodide **12** was then converted into the required ester **9** by halogen–metal exchange using *tert*-butyllithium followed by the addition of methyl chloroformate (Scheme 1).



Scheme 1. Reagents and conditions: (i) CH_2Br_2, LiTMP, −78 °C, 30 min (50%); (ii) LiHMDS, −78 °C, 1 h, then ^{n}BuLi, −78 °C, 1 h, followed by AcCl, MeOH, 0 °C (52%); (iii) (a) DIBAL-H, hexanes, −78 °C, 1 h, rt 3 h (91%) (b) Ph_3P, imid., I_2, THF, 0 °C then rt, 3 h (93%); (iv) ^{t}BuLi, pentane, Et_2O, −78 °C, 5 min to rt, then $MeCO_2Cl$, −78 °C, 5 min (60%).

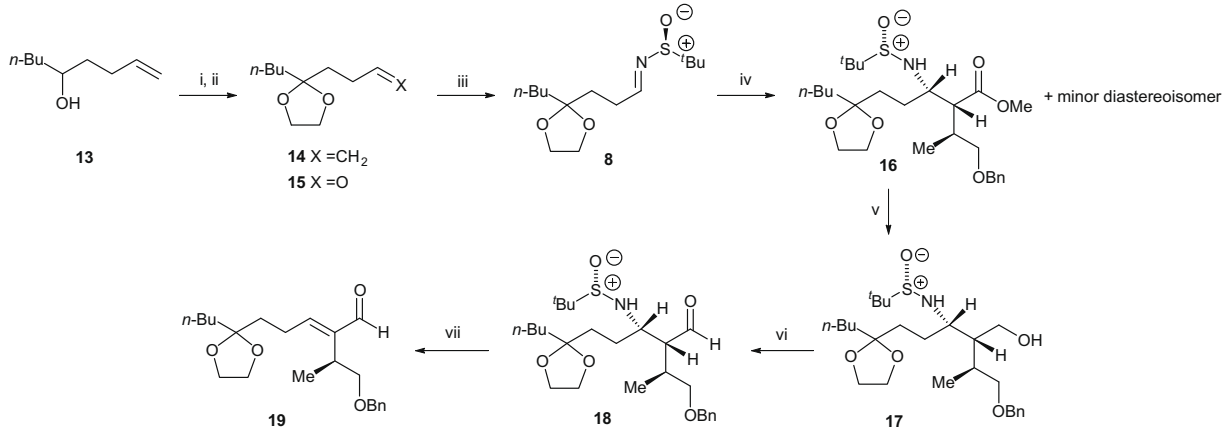
Non-1-en-5-ol **13**[9] was oxidised to the corresponding ketone which was protected as its acetal **14**. Ozonolysis gave the aldehyde **15** which was immediately converted into the sulfinimine **8** by treatment with (*S*)-*tert*-butyl sulfinamide, see Scheme 2.[10] The reaction of the titanium enolate of ester **9** with the sulfinimine **8** was then carried out at 60 °C and gave a mixture of two products which were isolated in yields of 66% and 11%. The major product was identified as the required diastereoisomer **17** on the basis of Ellman's mnemonic[7] and by comparison with similar products prepared later, vide infra. The minor product was identified as a diastereoisomer of the major product from spectroscopic data but its stereochemistry was not established.

At this point it was necessary to convert the ester **16** into a keto-ester analogous to **7**. However, the aldehyde **18** prepared from ester **16** by reduction followed by oxidation, was found to be unstable, and attempts to effect an aldol condensation with methyl acetate were thwarted by competing elimination to the α,β-unsaturated aldehyde **19**.

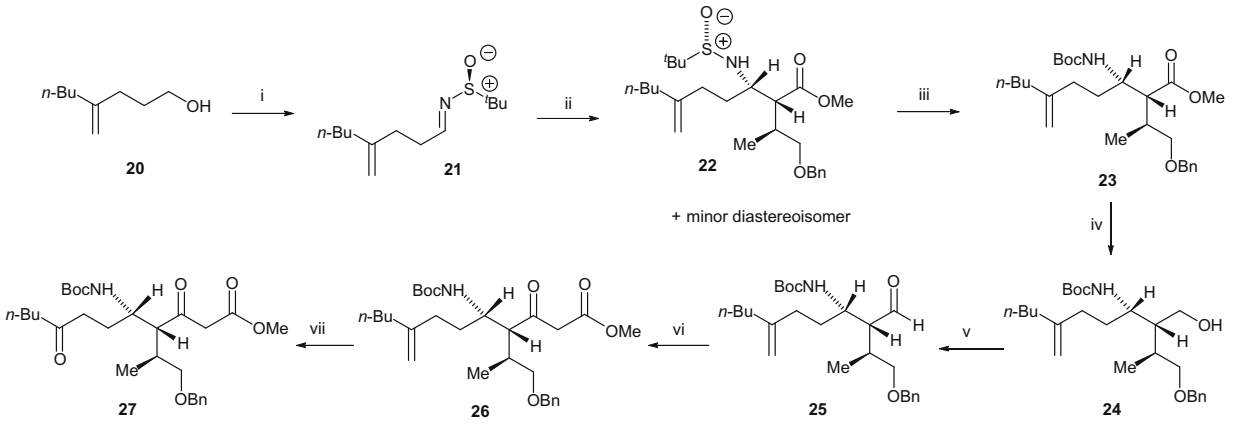
It would appear that the elimination of the sulfinamide group from the aldehyde is relatively facile. Attempts were made to remove the sulfinyl group from the Mannich product **16** under acidic conditions in methanol, but competing loss of the acetal was observed and complex mixtures of products were obtained.

It appeared necessary to use intermediates with a different functional group precursor for the ketone. 4-Methylene-octanal[11] was prepared from the alcohol **20** and condensed with (*S*)-*tert*-butyl sulfinamide to give the sulfinimine **21**, see Scheme 3. Reaction of the titanium(IV) enolate of ester **9** with the sulfinimine **21** gave mainly the required product **22**, 72% isolated yield, together with a mixture of other minor diastereoisomers which were not separated or formally characterised. The structure shown for the major Mannich product was assigned by analogy with Ellman's work and was confirmed by X-ray diffraction later in the synthesis.

The *tert*-butylsulfinyl auxiliary could now be removed under acidic conditions and the amine protected as its *tert*-butoxycarbonyl derivative **23**. This was taken through to aldehyde **25** by reduction followed by oxidation and condensation with methyl acetate to give keto-ester **26** after oxidation of the mixture of epi-



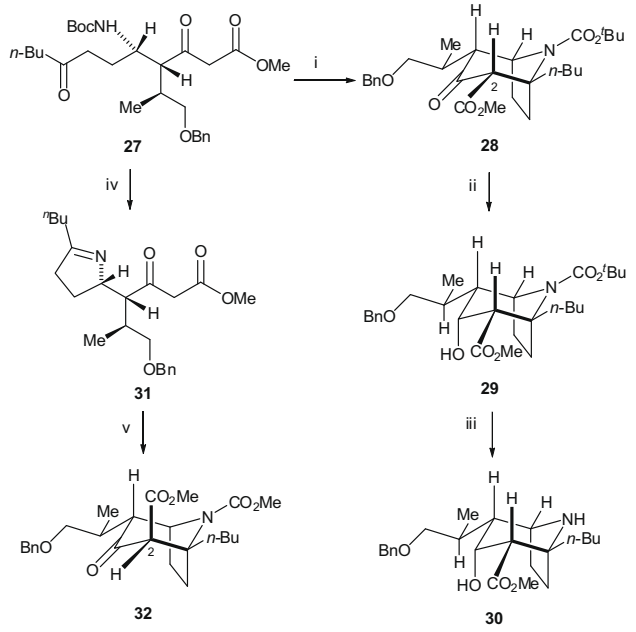
Scheme 2. Reagents and conditions: (i) (a) CrO_3, H_2SO_4, H_2O (71%), (b) $(CH_2OH)_2$, benzene, TsOH (cat.), heat under reflux, 18 h (98%); (ii) O_3, MeOH, −78 °C, 30 min, Me_2S, rt, 2 h; (iii) (S)-tert-butyl sulfinamide, CH_2Cl_2, $CuSO_4$, rt, 18 h (45% from 14); (iv) LDA, 9, −78 °C, 1 h, $TiCl(OiPr)_3$, −78 °C, 1 h, 8, −60 °C, 48 h (66% plus 11% of a second diastereoisomer); (v), $LiAlH_4$, 0 °C, 40 min, rt, 2 h (92%); (vi), Dess Martin periodinane, py., CH_2Cl_2, 0 °C, 3.5 h (70%); (vii) LDA, methyl acetate, −78 °C, 1 h (28%).



Scheme 3. Reagents and conditions: (i) (a) PDC, CH_2Cl_2, rt, 24 h (60%) (b) (*S*)-*tert*-butyl sulfinamide, $CuSO_4$, CH_2Cl_2, rt, 24 h (93%); (ii) LDA, **9**, −78 °C, 1 h, $TiCl(OiPr)_3$, −78 °C, **21**, −90 °C, 18 h (**22**, 72% plus 18% of a mixture of three other diastereoisomers); (iii) (a) HCl, dioxane, H_2O, MeOH, rt, 1 h (b) Et_3N, Boc-anhydride, THF, rt, 1 h (93% fom **22**); (iv) DIBAL-H, hexanes, THF, −78 °C, 1 h, rt, 20 min (85%); (v) Dess Martin periodinane, py., CH_2Cl_2, 0 °C, 3.5 h (81%); (vi) (a) LDA, methyl acetate, −78 °C, 1 h, add **25**, −78 °C, 2 h (82%) (b) PDC, 4 Å molecular sieves, CH_2Cl_2, rt, 24 h (86%); (vii) OsO_4, 4-methylmorpholine N-oxide, THF, *t*BuOH, H_2O, 0 °C, rt, 24 h (b) $NaIO_4$, MeOH, pH 7 phosphate buffer, rt, 1 h (75% from **26**).

meric aldol products. The double-bond was then cleaved by hydroxylation[12] followed by cleavage of the diol using sodium periodate to give diketo-ester **27**, the potential iminium ion cyclisation precursor (Scheme 3).

In the original work, acetal **3** had been treated with trifluoroacetic acid to remove the acetal and *tert*-butoxycarbonyl-protecting groups. This gave a cyclic imine which was induced to undergo further cyclisation to give the 8-azabicyclo[3.2.1]octanone **4** by treatment with methyl chloroformate and triethylamine. Of interest was the stereoselectivity of this process since the methoxycarbonyl group ended up in the axial position at C(2), probably due to thermodynamic control. However, when the Boc-protected amino-ketone **27** was treated with trifluoroacetic acid in dichloromethane at 0 °C, a relatively non-polar product, subsequently identified as the 8-azabicyclo[3.2.1]octanone **28**, started to appear within 5 min and was isolated in an 82% yield after 1 h, (Scheme 4).



Scheme 4. Reagents and conditions: (i) TFA, CH_2Cl_2, 0 °C, 1 h (82%); (ii) $NaBH_4$, MeOH, 0 °C, 30 min (99%); (iii) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 24 h (57%); (iv) TFA, 0 °C, rt, 20 min (79%); (v) $MeCO_2Cl$, CH_2Cl_2, −78 °C, Et_3N, −78 °C, 18 h (41%).

The product from this cyclisation reaction was identified as an 8-azabicyclo[3.2.1]octanone from its spectroscopic data. Although these data did not unambigously reveal the configuration at C(2), it was noticed that H(2) for the new compound, at δ 3.7, was significantly deshielded relative to H(2), in **4** which was observed at δ 3.33, and was observed as a broadened singlet, possibly due to hindered rotation involving the Boc-group. Reduction of ketone **28** using sodium borohydride was highly stereoselective and gave a single alcohol subsequently shown to be the axial alcohol **29**.

Structural and stereochemical assignments in this series were confirmed when the amine prepared by treatment of the Boc-protected amino-alcohol **29** with *tert*-butyldimethylsilyl triflate and 2,6-lutidine[13] was shown to have the structure **30** by X-ray diffraction. Figure 1 shows a projection of the amine which establishes its structure confirming both the proposed stereoselectivity of the Ellman reaction and the equatorial orientation of the 2-methoxycarbonyl substituent.

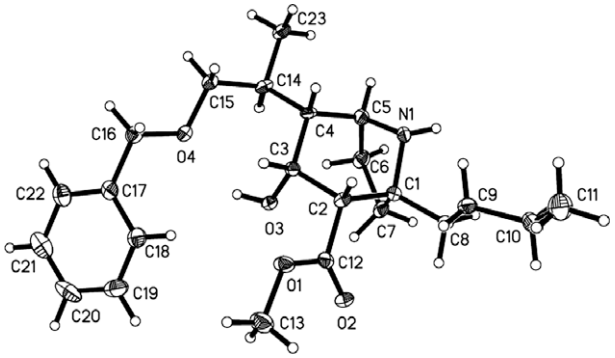
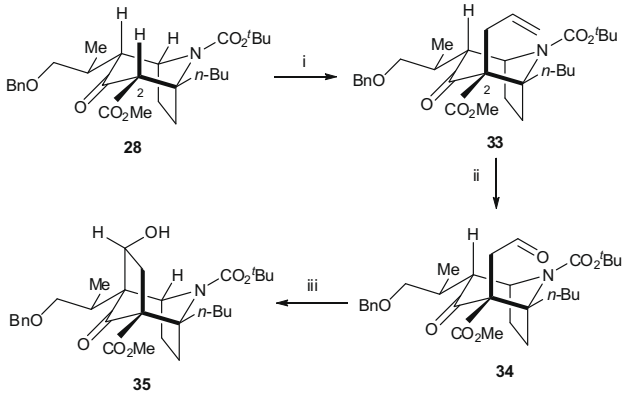


Figure 1. An ORTEP projection of the structure of amino-alcohol **30** as determined by X-ray diffraction.

The formation of tropinone **28**, in which the 2-methoxycarbonyl group is equatorial, contrasts with the formation of the axial epimer **4** in the cyclisation of keto-ester **3**. To probe the reasons for this dichotomy, the Boc-protected amino-ketone **27** was treated with neat trifluoroacetic acid at room temperature. Under these conditions, the loss of the *tert*-butoxycarbonyl group was observed and the cyclic imine **31** was isolated and characterised. This was now treated with methyl chloroformate and triethylamine. A fairly complex mixture of products was obtained from this reaction but the major product, which was isolated in a 41% yield, was identified as the tropinone **32** in which the 2-methoxycarbonyl group is axial, this assignment being made on the basis of spectroscopic data, for example, the chemical shift of H(2) at δ 3.35.

The formation of the equatorial product **28** from keto-ester **27** may be due to kinetic control, possibly involving the addition of the (Z)-enol of the keto-ester to the iminium ion formed by an acid-catalysed reaction of the Boc-protected amine and the 8-ketone functionality. The formation of the cyclic imine **31** must follow loss of the *tert*-butoxycarbonyl group either from the intermediate iminium ion or from the tropinone **28**. As the conversion of imine **31** into the tropinone **32** is carried out under more vigorous conditions than those used to prepare **28**, it may be that thermodynamic control is involved in this case.

The efficient formation of tropinone **28** with the equatorial 2-methoxycarbonyl group, and a side-chain corresponding to C(10) and C(11) of stemofoline, makes this an attractive intermediate for a synthesis of stemofoline. However, a new protocol is required for the introduction of the third ring incorporating C(5) and C(6) of stemofoline, (see structure **1**) since in the original work, the axial methoxycarbonyl group was used directly to form a bridge with the *N*-methoxycarbonyl group. Allylation of the tropinone **28** formed cleanly product **33** with the prop-2-enyl substituent in the axial position, see Scheme 5. Oxidative cleavage of the alkene then gave aldehyde **34** but attempts to remove the *tert*-butoxycarbonyl group from this keto-aldehyde led to an acid-catalysed intramolecular aldol condensation forming the hydroxy-ketone **35**. This was obtained as a single epimer at the hydroxyl bearing carbon, the configuration shown being tentatively assigned since in this epimer the hydroxy group should be able to undergo intramolecular hydrogen bonding with the carbamate.



Scheme 5. Reagents and conditions: (i) NaH, DMF, rt, 30 min, then TBAI, allyl bromide, THF, reflux, 24 h (83%); (ii) OsO_4, 2,6-lutidine, THF, H_2O, $NaIO_4$, rt, 5 h (80%); (iii) TFA, rt, 2 min (40%).

3. Conclusions

This work has provided examples of Mannich reactions involving a chiral ester as well as a chiral sulfinimine. Although aspects of matching and mismatching of the chiral reagent and chiral substrate were not investigated, the combination used gave useful stereoselectivity in the context of an asymmetric approach to stemofoline. The observation of different stereoselectivities in the iminium ion-induced cyclisations of the keto-ester **27** depending on the reaction conditions, possibly due to kinetic and thermodynamic control, is also of interest, and will be studied further. Finally, the C(10)–C(11) side-chain of stemofoline is present in both tropinones **28** and **32** which may prove to be useful stemofoline precursors. The completion of a total synthesis of stemofoline from these and related tropinones is currently under investigation.

4. Experimental

4.1. General procedures

Flash column chromatography was performed using Merck silica gel (60H; 40–60μ, 230–240 mesh). Petrol refers to light petroleum which was redistilled before use and refers to the fraction boiling between 40 and 60 °C. Tetrahydrofuran was dried over sodium-benzophenone and was distilled prior to use. Dichloromethane was dried over CaH_2 and distilled before use. Ether refers to diethyl ether. Reactions under non-aqueous conditions were carried out under an atmosphere of nitrogen or argon.

Electron impact (EI) or chemical ionisation using ammonia (CI) mass spectra were recorded using a Micromass Trio 200 spectrometer and high resolution mass spectra on a Kratos Concept IS spectrometer. Infra-red spectra were measured using a Genesis FTIR spectrometer on NaBr plates, either neat or as evaporated films unless otherwise stated. Nuclear magnetic resonance spectra were recorded in deuteriated chloroform unless otherwise indicated on either a Varian Unity 500 (500 MHz), Varian INOVA 400 (300 MHz), or a Varian INOVA 300 (300 MHz) spectrometer. Coupling constants (*J*) are given in hertz (Hz) and chemical shifts are relative to tetramethylsilane.

4.2. (*R*)-4-Benzyloxy-1,1-dibromo-3-methylbutan-2-one 11[8]

Lithium 2,2,6,6-tetramethylpiperidine (173.49 mmol) in THF (300 mL), prepared by treating 2,2,6,6-tetramethylpiperidine (35.5 mL, 208.2 mmol) in THF (300 mL) with ^{n}BuLi (1.6 M in hexanes, 108.43 mL, 173.49 mmol) at 0 °C, was added to methyl (*R*)-3-benzyloxy-2-methylpropanoate **10** (18.04 g, 86.74 mmol) and dibromomethane (12.3 mL, 173.49 mmol) in THF (290 mL) at −78 °C. After 30 min at – 78 °C, the solution was added to aqueous hydrogen chloride (1.2 M, 600 mL, 720 mmol) and the mixture was concentrated under reduced pressure. The residue was extracted with Et_2O (2 × 600 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using Et_2O (5%) in light petroleum gave the title compound **11** (15.18 g, 43.37 mmol, 50%), as a pale yellow oil, R_f = 0.62 in 10% Et_2O/light petroleum (Found: M^++NH_4, 365.9697. $C_{12}H_{18}NO_2Br_2$ requires *M*, 365.9699); $[\alpha]_D^{22} = -109.25$ (*c* 6.7, $CHCl_3$); ν_{max} 2957, 2934, 2861, 1740, 1455, 1436, 1369, 1250, 1194, 1176, 1095 and 702 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.30–7.19 (5H, m, ArH), 6.02 (1H, s, 1-H), 4.42 and 4.40 (each 1H, d, *J* 12, HC*H*Ph), 3.51–3.39 (3H, m, 4-H_2, 3-H) and 1.15 (3H, d, *J* 6.5, 3-CH_3); δ_C (125 Hz, $CDCl_3$) 198.39, 137.50, 128.49, 127.88, 127.65, 73.45, 73.18, 44.42, 41.67 and 14.62; *m/z* (ES^-) 347 (50%), 349 (100) and 351 (50).

4.3. Methyl (*S*)-4-benzyloxy-3-methylbutanoate 9

(a) Lithium hexamethyldisilazide (1 M in THF, 52.05 mL, 52.05 mmol) was added to the dibromoketone **11** (15.18 g, 43.37 mmol) in THF (430 mL) at −78 °C and the solution stirred at −78 °C for 1 h. *n*-Butyllithium (1.6 M in hexanes, 59.63 mL, 95.41 mmol) was added dropwise and the dark red solution stirred at −78 °C for 1 h then allowed to warm to 0 °C and stirred for 30 min before being added to acetyl chloride (75 mL) in anhydrous methanol (350 mL) at 0 °C. The mixture was concentrated under reduced pressure and the brown residue was diluted with Et_2O (200 mL) and washed with water (200 mL), saturated aqueous sodium hydrogen carbonate (200 mL) and brine (200 mL). After drying ($MgSO_4$) and concentration under reduced pressure, chromatography using Et_2O (20%) in light petroleum gave the title compound **9** (4.98 g, 22.43 mmol, 52%), as a colourless oil, R_f = 0.38 in 20% Et_2O/light petroleum {Found: M^++H, 223.1327. $C_{13}H_{19}O_3$

requires *M*, 223.1329); $[\alpha]_D^{22} = -7.3$ (*c* 7.1, $CHCl_3$)}; ν_{max} 2954, 2858, 1737, 1454, 1437, 1364, 1251, 1194, 1176, 1098, 738 and 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35–7.40 (5H, m, ArH), 4.55 (2H, s, CH_2Ph), 3.70 (3H, s, OMe), 3.43 (1H, dd, *J* 5.5, 9, 4-H), 3.35 (1H, dd, *J* 7, 9, 4-H′), 2.55 (1H, dd, *J* 6, 15, 2-H), 2.38 (1H, m, 3-H), 2.23 (1H, dd, *J* 7.5, 15, 2-H′) and 1.03 (3H, d, *J* 6.5, 3-CH_3); δ_C (75 Hz, $CDCl_3$) 173.78, 138.77, 128.61, 127.82, 127.79, 75.06, 73.24, 57.71, 38.77, 31.14 and 17.27; *m/z* (Cl^+) 223 (M^++1, 100%).

(b) *tert*-Butyllithium (1.7 M in pentane, 116.54 mL, 198.11 mmol) was added to the iodide **12**[14] (27.36 g, 94 mmol) in Et_2O (940 mL) at −78 °C. The yellow solution was stirred at −78 °C for 5 min, allowed to warm to room temperature over 1 h and then re-cooled to −78 °C. Methyl chloroformate (29.5 mL, 377 mmol) in Et_2O (470 mL) was added and the mixture stirred for 5 min before saturated aqueous ammonium chloride (1 L) was added. The aqueous phase was extracted with Et_2O (1 L) and the organic extracts were washed with water (2 L) and brine (2 L), and dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using 20% Et_2O in light petroleum gave the ester **9** (12.5 g, 56.4 mmol, 60%) as a colourless oil.

4.4. Non-1-en-5-one ethylene acetal 14

Chromic oxide (3.76 g, 37.65 mmol), concentrated sulfuric acid (3 mL) and water (11 mL) were added dropwise to non-1-en-5-ol **13** (4.86 g, 34.23 mmol) in acetone (13 mL) at 0 °C and the mixture was stirred for 30 min at 0 °C. Water (100 mL) was added and the mixture extracted with Et_2O (3 × 200 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a brown oil which was distilled to give non-1-en-5-one (3.41 g, 24.4 mmol, 71%) as a colourless oil, bp 75 °C at 15 mmHg, R_f = 0.75 in 20% Et_2O/light petroleum (Found: $M+H^+$, 140.1200. $C_9H_{16}O$, requires *M*, 140.1196); ν_{max} 2959, 2933, 2873, 1715, 1641, 1412, 1370, 1128, 996, 913 and 744 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.74 (1H, ddt, *J* 10, 17, 6.5, 2-H), 4.95 (1H, ddt, *J* 3, 17, 1.5, 1-H), 4.90 (1H, ddt, *J* 3, 10, 1.5, 1-H′), 2.44 (2H, t, *J* 7.5, 4-H_2), 2.34 (2H, t, *J* 7.5, 6-H_2), 2.27 (2H, m, 3-H_2), 1.47 (2H, tt, *J* 7.5, 8, 7-H_2), 1.25 (2H, tq, *J* 7.5, 8, 8-H_2) and 0.83 (3H, t, *J* 7.5, 9-H_3); δ_C (75 Hz, $CDCl_3$) 210.61, 137.20, 115.14, 42.63, 41.74, 27.78, 25.90, 22.35 and 13.86; *m/z* (Cl^+) 158 (M^++18, 100%) and 141 (M^++1, 20).

Ethylene glycol (1.5 mL, 26.80 mmol) followed by toluene *p*-sulfonic acid (5 mg) was added to non-1-en-5-one (3.41 g, 24.36 mmol) in benzene (34 mL) and the mixture heated under reflux for 18 h using a Dean Stark trap. After cooling to room temperature and concentrating under reduced pressure, Et_2O (100 mL) was added and the solution was washed with saturated aqueous sodium hydrogen carbonate (150 mL). The aqueous phase was extracted with Et_2O (100 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound **14** (4.4 g, 23.9 mmol, 98%) as a colourless oil, R_f = 0.75 in 20% Et_2O/light petroleum (Found: M^++H, 185.1531. $C_{11}H_{21}O_2$ requires *M*, 185.1536); ν_{max} 2955, 2875, 1642, 1453, 1213, 1155, 1079, 1043 and 910 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.76 (1H, ddt, *J* 10, 17, 6.5, 2-H), 4.97 (1H, ddd, *J* 1.5, 3.5, 17, 1-H), 4.87 (1H, ddd, *J* 1.5, 3.5, 10, 1-H′), 3.87 [4H, s, $O(CH_2)_2O$], 2.05 (2H, m, 3-H_2), 1.64 (2H, m, 4-H_2), 1.54 (2H, m, 6-H_2), 1.25 (4H, m, 7-H_2 and 8-H_2) and 0.83 (3H, t, *J* 7.5, 9-H_3); δ_C (125 Hz, $CDCl_3$) 138.63, 114.18, 111.51, 64.96, 37.02, 36.24, 28.13, 26.00, 23.00 and 14.08; *m/z* (Cl^+) 185 (M^++1, 100%).

4.5. (S_S)-*N*-(*tert*-Butylsulfinyl)-4-oxo-octanimine ethylene acetal 8

Ozonised air was bubbled through a solution of the alkene **14** (2 g, 10.87 mmol) in methanol (42 mL) at −78 °C for ca. 30 min until a pale blue colour persisted. Dimethyl sulfide (8.6 mL, 114 mmol) was added dropwise at −78 °C and the solution was allowed to warm to room temperature and was stirred for 2 h. After concentration under reduced pressure, the residue was taken up in Et_2O (100 mL) and the solution was washed with water (100 mL). The aqueous phase was extracted with Et_2O (3 × 100 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the aldehyde **15** as a colourless oil, δ_H (500 MHz, $CDCl_3$) 9.62 (1H, t, *J* 1.5, 1-H), which was azeotroped with benzene.

Copper sulfate and the aldehyde **15** (2 g, 10.87 mmol) were added to (*S*)-(−)-*tert*-butanesulfinamide (1.45 g, 11.96 mmol) in CH_2Cl_2 (24 mL) at room temperature and the suspension stirred for 18 h. The mixture was filtered through a pad of Celite and concentrated under reduced pressure. Chromatography of the residue using 50% Et_2O in light petroleum gave the title compound **8** (1.41 g, 4.89 mmol, 45% from **14**) as a colourless oil, R_f = 0.15 in 50% Et_2O/light petroleum (Found: $M+H^+$, 290.1790. $C_{14}H_{28}NO_3S$ requires *M*, 290.1784); $[\alpha]_D^{27} = +127.8$ (*c* 10.3, $CHCl_3$); ν_{max} 2957, 2873, 1733, 1624, 1458, 1364, 1182, 1143, 1085 and 949 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.01 (1H, t, *J* 4.5, 1-H), 3.86–3.67 [4H, m, $O(CH_2)_2O$], 2.52 (2H, m, 2-H_2), 1.90 (2H, m, 3-H_2), 1.55 (2H, m, 5-H_2), 1.26 (4H, m, 6-H_2, 7-H_2), 1.12 (9H, s, ^{t}Bu) and 0.83 (3H, t, *J* 7.5, 8-H_3); δ_C (75 Hz, $CDCl_3$) 169.50, 110.90, 65.00, 56.75, 56.57, 37.16, 33.90, 32.30, 26.97, 22.95, 22.33 and 13.85; *m/z* (Cl^+) 290 (M^++1, 100%).

4.6. Methyl (2*R*,3*S*)-2-[(*S*)-2-Benzyloxy-1-methylethyl]-3-[(S_S)-*tert*-butylsulfinylamino]-6-oxodecanoate ethylene acetal 16

n-Butyllithium (1.6 M in hexanes, 5.2 mL, 8.37 mmol) was added to di-isopropylamine (1.3 mL, 9.13 mmol) in THF (45 mL) at 0 °C and the solution stirred at 0 °C for 30 min before being cooled to −78 °C. The ester **9** (1.69 g, 7.61 mmol) in THF (40 mL) was added and the solution stirred at −78 °C for 1 h before chlorotitanium tri-isopropoxide (3.83 mL, 15.22 mmol) in THF (15 mL) was added. The bright yellow solution was stirred at −78 °C for 1 h and then the sulfinimine **8** (771 mg, 2.67 mmol) in THF (0.5 mL) was added. The reaction mixture was stirred at −60 °C for 48 h and saturated aqueous ammonium chloride (50 mL) was added. The mixture was diluted with water (50 mL) and extracted with Et_2O (3 × 100 mL). The organic extracts were washed with water (300 mL) and brine (300 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using 80% Et_2O in light petroleum gave the minor diastereomer (148 mg, 0.29 mmol, 10%) as a colourless oil, R_f = 0.35 in 80% Et_2O/light petroleum (Found: M^++H, 512.3035. $C_{27}H_{46}NO_6S$ requires *M*, 512.3040); $[\alpha]_D^{26} = +14.7$ (*c* 1.9, $CHCl_3$); ν_{max} 2956, 1718, 1455, 1362, 1170, 1071 and 736 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.26 (5H, m, ArH), 4.82 (1H, d, *J* 8, NH), 4.47 and 4.40 (each 1H, d, *J* 12.5, HC*H*Ph), 3.81 [4H, m, $O(CH_2)_2O$], 3.65 (1H, dd, *J* 4, 10, 2′-H), 3.62 (3H, s, OMe), 3.35 (1H, dd, *J* 3.5, 10, 2′-H′), 3.23 (1H, m, 3-H), 2.70 (1H, dd, *J* 3.5, 10, 2-H), 2.28 (1H, m, 1′-H), 1.61 (1H, m, 7-H), 1.53–1.46 (4H, m), 1.37 (2H, m, 5-H_2), 1.26–1.19 (3H, m), 1.16 (9H, s, ^{t}Bu), 0.90 (3H, d, *J* 7, 1′-CH_3) and 0.82 (3H, t, *J* 6.5, 10-H_3); δ_C (75 Hz, $CDCl_3$) 176.13, 138.89, 128.56, 127.89, 127.73, 111.70, 73.24, 71.72, 65.29, 65.15, 56.54, 56.14, 51.70, 50.74, 37.17, 33.92, 32.83, 31.25, 26.24, 23.22, 16.39 and 14.34; *m/z* (Cl^+) 512 (M^++1, 100%).

The second fraction was the title compound **16** (900 mg, 1.76 mmol, 66%) as a colourless oil, R_f = 0.24 in 80% Et_2O/light petroleum, $[\alpha]_D^{26} = +7.2$ (*c* 8.3, $CHCl_3$); ν_{max} 3436, 2872, 1733, 1455, 1364, 1261, 1196 and 1168 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.24 (5H, m, ArH), 4.41 and 4.36 (each 1H, d, *J* 12, HC*H*Ph), 4.00 (1H, d, *J* 8, NH), 3.83 [4H, m, $O(CH_2)_2O$], 3.56 (3H, s, OMe), 3.46 (1H, m, 3-H), 3.37 (1H, dd, *J* 5.5, 9.5, 2′-H), 3.23 (1H, dd, *J* 6.5, 9.5, 2′-H′), 2.76 (1H, dd, *J* 4.5, 9, 2-H), 2.24 (1H, m, 1′-H), 1.77 and 1.60 (each 1H, m, 5-H), 1.50 (3H, m, 4-H, 7-H_2), 1.23 (5H, m, 4-H′, 8-H_2, 9-H_2), 1.15 (9H, s, ^{t}Bu), 0.98 (3H, d, *J* 7, 1′-CH_3) and 0.82 (3H, t, *J* 7, 10-H_3); δ_C (125 Hz, $CDCl_3$)

173.46, 138.33, 128.28, 127.76, 127.47, 111.48, 74.10, 73.01, 64.93, 64.86, 56.46, 56.10, 53.93, 51.57, 36.93, 33.78, 32.68, 26.20, 26.05, 22.93, 22.77, 15.31 and 14.21.

4.7. (2*R*,3*S*)-2-[(*S*)-2-Benzyloxy-1-methylethyl]-3-[(S_S)-*tert*-butylsulfinylamino]-6-oxodecan-1-ol ethylene acetal 17

Lithium aluminium hydride (140 mg, 3.5 mmol) was added at 0 °C to the ester **16** (900 mg, 1.76 mmol) in THF (7 mL). The suspension was stirred at 0 °C for 40 min, allowed to warm to room temperature and stirred for a further 2 h. Ethyl acetate (30 mL) was added dropwise at 0 °C followed by water (30 mL). The aqueous layer was extracted with ethyl acetate (2 × 30 mL) and the organic extracts washed with brine (60 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using 2% methanol in Et_2O gave the title compound **17** (780 mg, 1.61 mmol, 91.5%) as a colourless oil, R_f = 0.25 in Et_2O (Found: M+H$^+$, 484.3102. $C_{26}H_{46}NO_5S$ requires *M*, 484.3091); $[\alpha]_D^{26} = +17.9$ (*c* 9.6, $CHCl_3$); ν_{max} 3370, 3259, 2956, 2873, 1455, 1365, 1073, 1043, 737 and 699 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.26 (5H, m, ArH), 5.02 (1H, d, *J* 8.5, NH), 4.46 (2H, s, CH_2Ph), 3.86 [4H, m, O(C*H*$_2$)$_2$O], 3.74 (1H, t, *J* 11, 1-H), 3.64 (1H, dd, *J* 3.5, 11, 1-H′), 3.40 (1H, m, 3-H), 3.28 (1H, t, *J* 9.5, 2′-H), 3.16 (1H, dd, *J* 4.5, 9.5, 2′-H′), 2.05 (1H, m, 1′-H), 1.83 (1H, m, 2-H), 1.76 (1H, m, 5-H), 1.58–1.43 (6H, m), 1.26 (3H, m), 1.05 (9H, s, ^{t}Bu), 0.90 (3H, d, *J* 7.5, 1′-CH_3) and 0.83 (3H, t, *J* 6.5, 10-H_3); δ_C (125 Hz, $CDCl_3$) 137.52, 128.51, 127.87, 127.69, 111.64, 73.44, 72.73, 64.89, 59.06, 57.51, 48.73, 34.41, 34.23, 30.77, 30.31, 28.72, 26.02, 22.97, 22.81, 18.08 and 14.13; *m*/*z* (CI$^+$) 484 (M$^+$+1, 30%), 422 (15), 365 (20), 129 (70) and 91 (100).

4.8. (2*R*,3*S*)-2-[(*S*)-2-Benzyloxy-1-methylethyl]-3-[(*S*)-*tert*-butylsulfinylamino)-6-oxodecanal ethylene acetal 18

Pyridine (5.8 mL, 17.71 mmol) and the Dess Martin periodinane (1.4 g, 3.28 mmol) were added at 0 °C to the alcohol **17** (780 mg, 1.61 mmol) in CH_2Cl_2 (11.5 mL). The solution was stirred at 0 °C for 3.5 h and then the mixture was diluted with Et_2O (100 mL) and poured into a mixture of sodium thiosulfite (25 g) and saturated aqueous sodium hydrogen carbonate (100 mL). The mixture was stirred at rt until all the solid had dissolved. The aqueous phase was extracted with Et_2O (2 × 100 mL) and the organic extracts washed with water (4 × 300 mL), brine (300 mL) and dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using Et_2O gave the title compound **18** (546 mg, 70%) as a colourless oil, R_f = 0.43 in Et_2O (Found: M+H$^+$, 482.2925. $C_{26}H_{44}NO_5S$ requires *M*, 482.2935); $[\alpha]_D^{24} = +12.8$ (*c* 5.3, $CHCl_3$); ν_{max} 3419, 3236, 2957, 2872, 1714, 1455, 1364, 1070, 739 and 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.71 (1H, d, *J* 3, 1-H), 7.28–7.19 (5H, m, ArH), 4.40 and 4.34 (each 1H, d, *J* 12, HC*H*Ph), 4.01 (1H, d, *J* 9, NH), 3.83 [4H, m, O(C*H*$_2$)$_2$O], 3.45 (1H, dd, *J* 4.5, 9, 2′-H), 3.42 (1H, m, 3-H), 3.28 (1H, dd, *J* 8, 9, 2″-H′), 2.56 (1H, m, 2-H), 2.33 (1H, m, 1′-H), 1.78 (1H, ddd, *J* 4, 11, 13.5, 4-H), 1.63 (1H, m, 4-H′), 1.50–1.46 (3H, m, 7-H_2, 5-H), 1.36 (1H, ddd, *J* 4.5, 11, 15, 5-H″), 1.23–1.18 (4H, m, 9-H_2, 8-H_2), 1.15 (9H, s, ^{t}Bu), 0.99 (3H, d, *J* 7, 1′-CH_3) and 0.82 (3H, t, *J* 6.5, 10-H_3); δ_C (75 Hz, $CDCl_3$) 206.01, 137.17, 128.41, 128.32, 127.70, 111.49, 74.18, 73.27, 64.87, 64.85, 60.13, 57.13, 56.22, 55.67, 36.86, 34.01, 32.83, 26.38, 25.95, 22.78, 15.25 and 14.08; *m*/*z* (CI$^+$) 482 (M$^+$+1, 10%), 290 (80) and 85 (100).

4.9. (*E*)-2-[(*S*)-2-Benzyloxy-1-methylethyl]-6-oxodecan-2-enal ethylene acetal 19

n-Butyllithium (1.6 M in hexane, 0.2 mL, 0.35 mmol) was added to di-isopropylamine (0.05 mL, 0.38 mmol) in THF (1 mL) at 0 °C and the solution stirred at 0 °C for 30 min before being cooled to −78 °C. Methyl acetate (0.26 mL, 0.32 mmol) in THF (0.8 mL) was added, followed, after 1 h at −78 °C, by the aldehyde **18** (120 mg, 0.25 mmol) in THF (0.5 mL). The solution was stirred for 1 h and then warmed to rt before saturated aqueous ammonium chloride (10 mL) was added. The mixture was diluted with Et_2O (10 mL) and the aqueous phase extracted with Et_2O (3 × 10 mL). The organic extracts were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue using 25% Et_2O in light petroleum gave the title compound **19** (25 mg, 0.069 mmol, 28%) as a colourless oil, R_f = 0.92 in 90% Et_2O/light petroleum; ν_{max} 3400, 2958, 2935, 2873, 2714, 1714, 1686, 1635, 1455, 1373, 1261, 1206, 1091, 1039, 949, 739 and 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.26 (1H, d, *J* 1.5, 1-H), 7.26–7.20 (5H, m, ArH), 6.43 (1H, t, *J* 7.5, 3-H), 4.40 (2H, s, CH_2Ph), 3.85 [4H, m, O(C*H*$_2$)$_2$O], 3.61 (1H, dd, *J* 8, 9, 2′-H), 3.53 (1H, dd, *J* 7, 9, 2′-H′), 2.99 (1H, m, 1′-H), 2.38 (2H, m, 4-H_2), 1.72 (2H, m, 5-H_2), 1.52 (2H, m, 7-H_2), 1.27–1.22 (4H, m, 8-H_2 and 9-H_2), 1.09 (3H, d, *J* 7.5, 1′-CH_3) and 0.83 (3H, t, *J* 7.5, 10-H_3); δ_C (75 Hz, $CDCl_3$) 194.47, 156.16, 143.33, 137.55, 127.24, 126.55, 126.40, 110.09, 71.96, 63.99, 62.67, 36.11, 31.44, 24.94, 22.46, 21.93, 21.29, 14.44 and 13.04; *m*/*z* (CI$^+$) 361 (M$^+$+1, 10%), 350 (25), 322 (50), 242 (20), 160 (65), 143 (95) and 106 (100).

4.10. (S_S)-*N*-(*tert*-Butylsulfinyl)-4-methylene-octanimine 21

4-Methylene-octanol **20** (3.25 g, 22.89 mmol) in CH_2Cl_2 (100 mL) was added to a suspension of pyridinium dichromate (21.97 g, 57.23 mmol) in CH_2Cl_2 (100 mL) and the resultant mixture stirred at room temperature for 24 h. Et_2O (200 mL) was added and the suspension filtered through a short column of silica gel (200 mL). The column was washed with Et_2O (5 × 200 mL) and the filtrate concentrated under reduced pressure. Chromatography of the residue using 5% Et_2O in light petroleum gave 4-methylene-octanal (1.83 g, 13.07 mmol, 60%) as a colourless oil, R_f = 0.82 in 40% Et_2O/light petroleum; ν_{max} 2930, 1730, 1646, 1454, 1262, 1138, 889 and 800 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.71 (1H, t, *J* 1.5, 1-H), 4.71 and 4.63 (each 1H, d, *J* 1, 4-CH), 2.57 (2H, td, *J* 7.5, 1.5, 2-H_2), 2.28 (2H, t, *J* 7.5, 3-H_2), 1.96 (2H, t, *J* 8, 5-H_2), 1.35 (2H, m, 6-H_2), 1.24 (2H, m, 7-H_2) and 0.84 (3H, t, *J* 7.5, 8-H_3); δ_C (125 Hz, $CDCl_3$) 202.33, 147.88, 109.45, 41.87, 36.02, 29.87, 28.07, 22.38 and 13.95.

Copper sulfate (3.58 g, 22.4 mmol) and 4-methylene-octanal (1.57 g, 11.2 mmol) in CH_2Cl_2 (30 mL) were added to (*S*)-(−)-*tert*-butanesulfinamide (1.5 g, 12.34 mmol) in CH_2Cl_2 (30 mL) at room temperature and the suspension stirred for 18 h. The mixture was filtered through a pad of Celite and concentrated under reduced pressure. Chromatography of the residue using 40% Et_2O in light petroleum gave the title compound **21** (2.53 g, 10.41 mmol, 93%) as a colourless oil (Found: M+H$^+$, 244.1739. $C_{13}H_{26}NOS$ requires *M*, 244.1730); $[\alpha]_D^{26} = +230$ (*c* 11.5, $CHCl_3$) ν_{max} 2958, 2929, 1645, 1622, 1456, 1363, 1088 and 889 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.01 (1H, t, *J* 4.5, 1-H), 4.71 and 4.67 both (1H, m, 4-CH), 2.60 (2H, m, 2-H_2), 2.27 (2H, t, *J* 7.5, 3-H_2), 1.97 (2H, t, *J* 7.5, 5-H_2), 1.35 (2H, m, 6-H_2), 1.25 (2H, m, 7-H_2), 1.12 (9H, s, ^{t}Bu) and 0.84 (3H, t, *J* 7.5, 8-H_3); δ_C (125 Hz, $CDCl_3$) 169.19, 147.89, 109.69, 56.54, 35.88, 34.22, 31.41, 29.86, 22.41, 22.34 and 13.97; *m*/*z* (CI$^+$) 244 (M$^+$+1, 100%).

4.11. Methyl (2*R*,3*S*)-2-[(*S*)-2-benzyloxy-1-methylethyl]-3-[(S_S)-*tert*-butylsulfinylamino]-6-methylenedecanoate 22

n-Butyllithium (1.6 M in hexanes, 32.78 mL, 52.45 mmol) was added to di-isopropylamine (7.5 mL, 53.48 mmol) in THF (250 mL) at 0 °C and the solution stirred for 30 min then cooled to −78 °C. The ester **9** (11.42 g, 51.4 mmol) in THF (250 mL) was

added and the mixture stirred for 1 h Chlorotitanium triisopropoxide (25.86 mL, 102.85 mmol) in THF (100 mL) was added and the solution was stirred at −78 °C for 1 h. The sulfinylimine **21** (5.0 g, 20.57 mmol) in THF (4 mL) was then added and, after 18 h at −90 °C, saturated aqueous ammonium chloride (500 mL) was added at −78 °C and the mixture allowed to warm to room temperature before being diluted with water (100 mL) and extracted with Et_2O (2 × 600 mL). The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using hexane–acetonitrile–CH_2Cl_2 (25:3:7 to 20:3:7) gave a mixture of minor products (1.72 g, 3.7 mmol, 18%), R_f = 0.59 in 80% Et_2O/light petroleum, followed by the title compound **22** (6.89 g, 14.81 mmol, 72%) as a colourless oil, R_f = 0.36 in 80% Et_2O/light petroleum (Found: M+H$^+$, 466.2992. $C_{26}H_{44}NO_4S$ requires *M*, 466.2986); $[\alpha]_D^{23} = +6.8$ (*c* 4.7, $CHCl_3$) ν_{max} 3311, 2955, 1733, 1644, 1455, 1364, 1194, 1168, 1074, 889, 737 and 698 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.27–7.18 (5H, m, ArH), 4.67 (1H, d, *J* 1, 6-CH), 4.62 (1H, s, 6-CH′), 4.41 and 4.37 (each 1H, d, *J* 12, HC*H*Ph), 3.98 (1H, d, *J* 9, NH), 3.56 (3H, s, OMe), 3.47 (1H, dddd, *J* 2.5, 4.5, 7, 9, 3-H), 3.36 (1H, dd, *J* 5.5, 9, 2′-H), 3.22 (1H, dd, *J* 4.5, 9, 2′-H′), 2.78 (1H, dd, *J* 4.5, 9, 2-H), 2.22 (1H, m, 1″-H), 2.13 (1H, ddd, *J* 4.5, 9.5, 14.5, 5-H), 1.92 (3H, m, 5-H′, 7-H_2), 1.61 (1H, dddd, *J* 2.5, 7, 9.5, 12, 4-H), 1.34–1.18 (5H, m, 4-H′, 8-H_2, 9-H_2), 1.16 (9H, s, ^{t}Bu), 0.97 (3H, d, *J* 7, 1″-CH_3) and 0.83 (3H, t, *J* 7, 10-H_3); δ_C (125 Hz, $CDCl_3$) 173.55, 148.94, 138.33, 128.27, 127.62, 127.45, 109.68, 74.15, 73.01, 56.12, 55.73, 53.89, 51.53, 35.69, 32.70, 32.54, 30.17, 29.92, 22.77, 22.40, 15.27 and 13.99; *m/z* (CI$^+$) 466 (M$^+$+1, 80%) and 91 (100).

4.12. Methyl (2*R*,3*S*)-2-[(*S*)-2-benzyloxy-1-methylethyl]-3-*tert*-butoxycarbonylamino-6-methylenedecanoate 23

Hydrogen chloride (4 M in dioxane, 18.51 mL, 74 mmol) was added to the sulfinamide **22** (6.89 g, 14.81 mmol) in methanol (150 mL) at room temperature and the solution stirred at room temperature for 1 h before being concentrated under reduced pressure. The residue was taken up in water (10 mL) and the solution cooled to 0 °C before triethylamine (4.75 mL, 34.1 mmol) and di-*tert*-butyl dicarboxylate (4.33 g, 19.25 mmol) in THF (7.4 mL) were added. The mixture was stirred at room temperature for 1 h, diluted with CH_2Cl_2 (100 mL) and washed with saturated aqueous sodium hydrogen sulfate (100 mL), water (100 mL) and brine (100 mL) then dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using 30% Et_2O in light petroleum gave the title compound **23** (6.35 g, 13.77 mmol, 93%) as a colourless oil, R_f = 0.20 in 15% Et_2O/light petroleum (Found: M+H$^+$, 462.3205. $C_{27}H_{44}NO_5$ requires *M*, 462.3214); $[\alpha]_D^{23} = -24.8$ (*c* 11.6, $CHCl_3$) ν_{max} 3364, 2958, 1713, 1645, 1513, 1454, 1366, 1170, 1099, 889, 737 and 698 cm^{-1}; δ_H (500 MHz, $CDCl_3$); 7.27–7.18 (5H, m, ArH), 4.65 and 4.63 (each 1H, s, 6-CH), 4.55 (1H, d, *J* 9.5, NH), 4.41 and 4.36 (each 1H, d, *J* 12, HC*H*Ph), 3.84 (1H, m, 3-H), 3.53 (3H, s, OMe), 3.43 and 3.25 (each, 1H, dd, *J* 6, 9.5, 2′-H), 2.58 (1H, dd, *J* 6.5, 7.5, 2-H), 2.17 (1H, m, 1′-H), 2.03 (1H, ddd, *J* 4.5, 10, 14.5, 5-H), 1.92 (3H, m, 5-H′, 7-H_2), 1.59 (1H, m, 4-H), 1.37 (9H, s, ^{t}Bu), 1.32 (1H, m, 4-H′), 1.30 (2H, m, 8-H_2), 1.22 (2H, m, 9-H_2), 0.96 (3H, d, *J* 7, 1′-CH_3) and 0.82 (3H, t, *J* 7, 10-H_3); δ_C (125 Hz, $CDCl_3$) 173.82, 155.43, 149.15, 138.40, 128.29, 127.61, 127.47, 109.19, 79.22, 73.81, 73.01, 52.90, 51.37, 49.79, 35.85, 32.89, 32.57, 29.94, 29.77, 28.39, 22.45, 15.48 and 14.00; *m/z* (ES$^+$) 462 (M$^+$+1, 100%).

4.13. (2*R*,3*S*)-2-[(*S*)-2-Benzyloxy-1-methylethyl]-3-*tert*-butoxycarbonylamino-6-methylenedecan-1-ol 24

Di-isobutylaluminium hydride (1 M in hexanes, 82.62 mL, 82.62 mmol) was added to the ester **23** (6.35 g, 13.77 mmol) in THF (51 mL) at −78 °C and the solution stirred at −78 °C for 1 h and at room temperature for 20 min. Saturated aqueous potassium sodium tartrate (150 mL) was added dropwise at 0 °C and the mixture was diluted with Et_2O (200 mL) then stirred for 18 h at room temperature. The aqueous phase was extracted with Et_2O (3 × 200 mL) and the organic extracts washed with water (800 mL) and brine (800 mL) then dried (Na_2SO_4). After concentration under reduced pressure, chromatography of the residue using 50% Et_2O in light petroleum gave the title compound **24** (5.07 g, 11.70 mmol, 85%) as a colourless oil, R_f = 0.18 in 30% Et_2O/light petroleum (Found: M+H$^+$, 434.3271. $C_{26}H_{44}NO_4$ requires *M*, 434.3265) $[\alpha]_D^{23} = -23.2$ (*c* 12.4, $CHCl_3$) ν_{max} 3407, 2959, 2929, 1688, 1511, 1454, 1365, 1249, 1172, 1092, 1075, 1043, 887 and 737; δ_H (500 MHz, $CDCl_3$) 7.27 (5H, m, ArH), 5.36 (1H, d, *J* 10, NH), 4.64 and 4.62 (each 1H, s, 6-CH), 4.45 and 4.41 (each 1H, d, *J* 11.5, HC*H*Ph), 3.82 (1H, m, 3-H), 3.66 (1H, dd, *J* 4.5, 9.5, OH), 3.54 (1H, ddd, *J* 4.5, 9.5, 12, 1-H), 3.48 (1H, ddd, *J* 4.5, 9, 12, 1-H′), 3.22 (2H, m, 2′-H_2), 2.05 (1H, m, 1′-H), 2.01–1.89 (4H, m, 7-H_2, 5-H_2), 1.62 (1H, m, 2-H), 1.54 (2H, dd, *J* 8, 15, 4-H_2), 1.37 (9H, s, ^{t}Bu), 1.31 (2H, m, 8-H_2), 1.23 (2H, m, 9-H_2), 0.93 (3H, d, *J* 7.5, 1′-CH_3) and 0.83 (3H, t, *J* 7.5, 10-H_3); δ_C (125 Hz, $CDCl_3$) 157.32, 149.50, 137.47, 128.51, 127.90,127.85, 108.96, 79.24, 73.47, 72.27, 65.87 58.98, 49.10, 48.95, 35.81, 33.04, 31.03, 29.96, 28.43, 22.45, 18.12 and 14.02; *m/z* (ES$^+$) 456 (M$^+$ + 23, 50%) and 434 (M$^+$+1, 100).

4.14. (2*R*,3*S*)-2-[(*S*)-2-Benzyloxy-1-methylethyl]-3-*tert*-butoxycarbonylamino-6-methylenedecanal 25

Pyridine (10.42 mL, 128.7 mmol) and the Dess Martin periodinane (10.42 g, 24.57 mmol) were added to the alcohol **24** (5.07 g, 11.70 mmol) in CH_2Cl_2 (84 mL) at 0 °C and the solution stirred at 0 °C for 3.5 h before being poured into a solution of sodium thiosulfate (25 g) in saturated aqueous sodium hydrogen carbonate (100 mL). The mixture was stirred at room temperature until all the solid had dissolved. The aqueous phase was then extracted with CH_2Cl_2 (2 × 100 mL) and the organic extracts were washed with water (4 × 300 mL) and brine (300 mL) and dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using 30% Et_2O in light petroleum gave the title compound **25** (4.08 g, 9.48 mmol, 81%) as a colourless oil, R_f = 0.58 in 50% Et_2O/light petroleum (Found: M+H$^+$, 432.3104. $C_{26}H_{42}NO_4$ requires *M*, 432.3108); $[\alpha]_D^{25} = -20.95$ (*c* 6.3, $CHCl_3$) ν_{max} 3367, 2959, 1712, 1510, 1453, 1365, 1247, 1170, 1097 and 736 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.64 (1H, d, *J* 3.5, 1-H), 7.29–7.19 (5H, m, ArH), 4.74 (1H, d, *J* 9.5, NH), 4.66 and 4.62 (each, 1H, s, 6-CH), 4.38 (2H, s, CH_2Ph), 3.95 (1H, ddd, *J* 3, 6, 9.5, 3-H), 3.44 (1H, dd, *J* 4.5, 9.5, 2′-H), 3.33 (1H, dd, *J* 7, 9.5, 2′-H′), 2.32 (1H, ddd, *J* 3.5, 6, 9.5, 2-H), 2.25 (1H, m, 1′-H), 2.04 (1H, ddd, *J* 4.5, 10, 15, 5-H), 1.95 (1H, dd, J 7, 10, 5-H′), 1.91 (2H, t, *J* 7.5, 7-H_2), 1.63 (2H, m, 8-H and 4-H), 1.36 (9H, s, ^{t}Bu), 1.34–1.19 (4H, m, 4-H′, 8-H′, 9-H_2), 0.99 (3H, d, *J* 7, 1′-CH_3) and 0.83 (3H, t, *J* 7, 10-H_3); δ_C (75 Hz, $CDCl_3$) 204.63, 155.52, 148.94, 137.89, 128.41, 128.34, 127.66, 109.31, 79.35, 73.44, 73.18, 59.55, 49.42, 35.85, 32.66, 32.63, 30.38, 29.93, 28.38, 22.45, 15.66 and 14.00; *m/z* (ES$^+$) 432 (M$^+$+1, 100%).

4.15. Methyl (4*R*,5*S*)-4-[(*S*)-2-benzyloxy-1-methylethyl]-5-*tert*-butoxycarbonylamino-8-methylene-3-oxododecanoate 26

n-Butyllithium (1.6 M in hexanes, 15.08 mL, 24.17 mmol) was added to di-isopropylamine (3.45 mL, 24.65 mmol) in THF (140 mL) at 0 °C and the solution stirred for 30 min then cooled to −78 °C. Methyl acetate (1.89 mL, 23.7 mmol) was added and the mixture stirred for 1 h. The aldehyde **25** (4.08 g, 9.48 mmol) in THF (19 mL) was added and the solution stirred at −78 °C for 2 h. Saturated aqueous ammonium chloride (200 mL) was added and the mixture extracted with Et_2O (3 × 200 mL). The organic extracts were washed with water (600 mL) and brine (600 mL),

dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using 40% Et_2O in light petroleum gave the aldol products (3.93 g, 7.77 mmol, 82%) as a 2:1 mixture of diastereomers, R_f = 0.33 (major) and 0.22 (minor) in 40% Et_2O/light petroleum (Found: M+H$^+$, 506.3464. $C_{29}H_{48}NO_6$, requires *M*, 506.3476); ν_{max} 3367, 2957, 1710, 1517, 1454, 1366, 1251, 1172, 1089, 887 and 736 cm^{-1}; δ_H (500 MHz, $CDCl_3$) major diastereomer 7.29–7.27 (5H, m, ArH), 5.86 (1H, d, *J* 9.5, *N*H), 4.65 (2H, s, 8-CH_2), 4.48 (2H, s, CH_2Ph), 4.02 (1H, m, 3-H), 3.61 (3H, s, OMe), 3.58 (1H, d, *J* 9, 2′-H), 3.55 (1H, m, 5-H), 3.30 (1H, dd, *J* 3.5, 9, 2′-H′), 3.21 (1H, br s, OH), 2.64 (1H, dd, *J* 1.5, 16.5, 2-H), 2.42 (1H, dd, *J* 9, 16.5, 2-H′), 2.12 (1H, m, 1′-H), 1.94 (4H, m, 7-H_2, 9-H_2), 1.62–1.51 (3H, m, 4-H, 6-H_2), 1.32 (9H, s, ^{t}Bu), 1.28–1.20 (4H, m, 10-H_2, 11-H_2), 1.03 (3H, d, *J* 7.5, 1′-CH_3) and 0.83 (3H, t, *J* 7.5, 11-H_3); minor diastereomer 7.25–7.20 (5H, m, ArH), 5.30 (1H, d, *J* 10, NH), 4.63 (2H, s, 8-CH_2), 4.49 and 4.42 (each 1H, d, *J* 12, HC*H*Ph), 4.15 (1H, m, 3-H), 3.62 (3H, s, OMe), 3.50 (1H, dd, *J* 8.5, 16.5, 2′-H), 3.35 (1H, m, 5-H), 3.26 (1H, m, 2′-H′), 3.21 (1H, br s, OH), 2.55–2.48 (2H, m, 2-H_2), 2.12 (1H, 1′-H), 2.06–1.97 (4H, m, 7-H_2, 9-H_2), 1.71–1.63 (3H, m, 4-H, 6-H_2), 1.46–1.38 (4H, m, 10-H_2, 11-H_2), 1.35 (9H, s, ^{t}Bu), 0.91 (3H, d, *J* 7, 1′-CH_3), 0.85 (3H, m, 12-H_3); *m/z* (CI$^+$) 506 (M$^+$+1, 50%) and 406 (100).

The aldol products (3.93 g, 7.77 mmol) in CH_2Cl_2 (32 mL) were added to a suspension of pyridinium dichromate (7.46 g, 19.4 mmol) and molecular sieves (8 g) in CH_2Cl_2 (33 mL) at room temperature and the suspension was stirred at room temperature for 24 h then filtered through a pad of silica and concentrated under reduced pressure. Chromatography of the residue using 50% Et_2O in light petroleum gave the title compound **26** (3.36 g, 6.68 mmol, 86%) as a colourless oil, R_f = 0.5 in 50% Et_2O/light petroleum (Found: M+H$^+$, 504.3322. $C_{29}H_{46}NO_6$, requires *M*, 504.3320); $[\alpha]_D^{26} = -50$ (*c* 6.4, $CHCl_3$) ν_{max} 3375, 2958, 1747, 1710, 1648, 1628, 1510, 1451, 1366, 1242, 1168, 1097, 890 and 738 cm^{-1}; δ_H (500 MHz, $CDCl_3$) keto-tautomer 7.29–7.21 (5H, m, ArH), 4.66 and 4.63 (each 1H, s, 8-CH), 4.63 (1H, d, *J* 10, NH), 4.37 and 4.33 (each 1H, d, *J* 12, HC*H*Ph), 3.81 (1H, m, 5-H), 3.62 (3H, s, OMe), 3.45 and 3.38 (each, 1H, d, *J* 16, 2-H), 3.31 and 3.27 (each 1H, dd, *J* 9, 5, 2′-H), 2.98 (1H, dd, *J* 5.5, 8.5, 4-H), 2.18 (1H, m, 1′-H), 2.01 (1H, m, 7-H), 1.94–1.85 (3H, m, 7-H′, 9-H_2), 1.64 and 1.40 (each 1H, m, 6-H), 1.37 (9H, s, ^{t}Bu), 1.33–1.30 (2H, m, 10-H_2), 1.26–1.18 (2H, m, 11-H_2), 0.91 (3H, d, *J* 7, 1′-CH_3) and 0.83 (3H, t, *J* 7, 12-H_3); minor peaks attributed to the enol tautomer (ca. 25%) 12.0 (1H, s, OH), 4.88 (1H, s, 2-H) and 3.66 (3H, s, OMe); δ_C (125 Hz, $CDCl_3$) 204.52, 171.69, 154.48, 147.82, 137.01, 127.34, 126.71, 126.39, 108.45, 78.43, 73.02, 72.70, 71.84, 57.05, 51.10, 50.18, 35.04, 34.72, 28.90, 28.03, 27.35, 21.60, 21.42, 13.94 and 12.97; *m/z* (ES$^+$) 526 (M+23, 100%) and 504 (40).

4.16. Methyl (4*R*,5*S*)-4-[(*S*)-2-benzyloxy-1-methylethyl]-5-*tert*-butoxycarbonylamino-3,8-dioxododecanoate 27

4-Methylmorpholine N-oxide (1.66 g, 13.76 mmol) and osmium tetroxide (85 mg, 0.33 mmol) were added to the alkene **26** (3.36 g, 6.68 mmol) in THF–^{t}BuOH–H_2O (44 mL; 20:20:4) at 0 °C and the reaction stirred at room temperature for 24 h. Sodium metabisulfite (2 g, 10.5 mmol) was added and the suspension was stirred for 4 h at room temperature then filtered through Celite which was washed with ethyl acetate (200 mL). The filtrate was washed with saturated aqueous sodium metabisulfite (200 mL), water (200 mL) and brine (200 mL) and dried (Na_2SO_4). Concentration under reduced pressure and chromatography of the residue using 10% ethyl acetate in Et_2O gave a mixture of diols (2.69 g, 5.01 mmol) (Found: M$^+$+Na, 560.3201. $C_{29}H_{47}NO_8Na$ requires *M*, 560.3194); *m/z* (ES$^+$) 560 (M$^+$+23, 100%). These were dissolved in a mixture of methanol (20 mL) and pH 7 aqueous phosphate buffer (10 mL). Sodium periodate (2.14 g, 10.02 mmol) was added and the suspension was stirred for 1 h then diluted with water (60 mL) and extracted with Et_2O (3 × 50 mL). The organic extracts were washed with brine (150 mL) and dried (Na_2SO_4). After concentration under reduced pressure, chromatography of the residue using 50% Et_2O in light petroleum gave the title compound **27** (2.53 g, 5.01 mmol, 75% from **26**) as a colourless oil, R_f = 0.16 in 50% Et_2O/light petroleum (Found: M+H$^+$, 506.3105. $C_{28}H_{44}NO_7$ requires *M*, 506.3112); $[\alpha]_D^{25} = -123.5$ (*c* 3.4, $CHCl_3$) ν_{max} 3368, 2960, 1747, 1710, 1512, 1453, 1367, 1245, 1165, 737 and 698 cm^{-1}; δ_H (500 MHz, C_6D_6) keto-tautomer 7.36–7.19 (5H, m, ArH), 5.04 (1H, d, *J* 9.5, NH), 4.32 and 4.30 (each 1H, d, *J* 12, HC*H*Ph), 4.17 (1H, m, 5-H), 3.56 and 3.52 (each 1H, d, *J* 16, 2-H), 3.45 (3H, s, OMe), 3.36 (1H, dd, *J* 2, 9.5, 2′-H), 3.26 (1H, dd, *J* 5, 9.5, 2′-H′), 3.07 (1H, dd, *J* 6.5, 7.5, 4-H), 2.38 (1H, m, 9-H), 2.31 (1H, m, 1′-H), 2.24 (1H, dd, *J* 7, 14, 9-H′), 2.18 (1H, t, *J* 7, 7-H), 2.05 (2H, m, 6-H, 7-H′), 1.74 (1H, m, 6-H′), 1.54 (9H, s, ^{t}Bu), 1.25 (4H, m, 10-H_2, 11-H_2), 1.09 (3H, d, *J* 7, 1′-CH_3) and 0.91 (3H, t, *J* 7.5, 12-H_3); minor peaks attributed to the enol tautomer (ca. 25%) 12.80 (1H, s, OH), 5.19 (1H, s, 2-H) and 3.41 (3H, s, OMe); δ_C (75 Hz, $CDCl_3$) 208.92, 204.79, 167.72, 155.69, 138.73, 128.48, 128.28, 127.38, 78.80, 73.99, 72.88, 58.73, 51.83, 51.61, 50.81, 42.42, 38.94, 33.76, 28.38, 25.99, 24.80, 22.49, 15.28 and 13.98; *m/z* (ES$^+$) 528 (M+23, 100%) and 506 (20).

4.17. (1*R*,2*S*,4*R*,5*S*)-4-[(*S*)-2-Benzyloxy-1-methylethyl]-1-butyl-2-methoxycarbonyl-8-*tert*-butoxycarbonyl-8-azabicyclo[3.2.1]octan-3-one 28

Trifluoroacetic acid (0.25 mL, 3.24 mmol) was added to the diketo-ester **27** (820 mg, 1.62 mmol) in CH_2Cl_2 (30 mL) at 0 °C and the mixture stirred at 0 °C for 1 h before saturated aqueous sodium hydrogen carbonate (30 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL) and the organic extracts were washed with water (90 mL) and brine (90 mL) before being dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using 5% Et_2O in light petroleum gave the title compound **28** (648 mg, 1.33 mmol, 82%) as a colourless oil which solidified upon standing to give a white amorphous solid, R_f = 0.37 in 20% Et_2O/light petroleum, mp = 55.9–58.3 °C (Found: M+Na$^+$, 510.2826. $C_{28}H_{41}NO_6Na$ requires *M*, 510.2826); $[\alpha]_D^{22} = -16.5$ (*c* 17, $CHCl_3$) ν_{max} 2959, 1748, 1703, 1456, 1358, 1318, 1259, 1161 and 739 cm^{-1}; δ_H (500 MHz, C_6D_6) 7.20–6.82 (5H, m, ArH), 4.34 (1H, m, 5-H), 4.10 and 4.06 (each 1H, d, *J* 12, HC*H*Ph), 4.00 (1H, br s, 2-H), 3.41 (1H, m, 2″-H), 3.25 (1H, m, 2″-H′), 3.25 (3H, s, OMe), 2.73 (1H, br d, *J* 5.5, 4-H), 2.62 (1H, ddd, *J* 6, 10, 14.5, 7-H), 2.11 (1H, m, 1″-H), 1.71 (2H, m, 7-H′, 1′-H), 1.50 (1H, m, 6-H), 1.35–1.05 (6H, m, 6-H′, 1′-H′, 2′-H_2, 3′-H_2), 1.22 (9H, s, ^{t}Bu), 0.83–0.74 (3H, d, *J* 7, 1″-CH_3) and 0.78 (3H, t, *J* 7, 4′-H_3); δ_C (75 Hz, $CDCl_3$) 204.65, 168.97, 154.22, 139.00, 128.49, 127.75, 127.63, 80.94, 74.30, 73.18, 68.02, 65.74, 59.94, 55.20, 52.08, 34.38, 30.33, 28.53, 25.46, 23.20, 23.19, 22.91, 14.85 and 14.48; *m/z* (ES$^+$) 511 (M+23, 25%), 510 (100) and 488 (20).

4.18. (1*R*,2*S*,3*R*,4*R*,5*S*)-4-[(*S*)-2-Benzyloxy-1-methyl-ethyl]-1-butyl-2-methoxycarbonyl-8-*tert*-butoxycarbon-yl-8-azabicyclo[3.2.1]octan-3-ol 29

Sodium borohydride (88 mg, 2.3 mmol) was added to the tropinone **28** (110 mg, 0.23 mmol) in methanol (13.3 mL) at 0 °C and the suspension was stirred at 0 °C for 30 min. After concentration under reduced pressure, the residue was taken up in ethyl acetate (20 mL) and the solution washed with water (20 mL) and brine (20 mL) and dried (Na_2SO_4). After concentration under reduced pressure, chromatography of the residue using 30% Et_2O in light petroleum gave the title compound **29** (110 mg, 0.22 mmol, 99.9%) as a colourless oil, R_f = 0.35 in 30% Et_2O/light petroleum (Found: M+Na$^+$, 512.2979. $C_{28}H_{43}NO_6Na$, requires *M*, 512.2983);

$[\alpha]_D^{22} = -48.05$ (*c* 35.3, $CHCl_3$); ν_{max} 3469, 2920, 1747, 1699, 1460, 1365 and 1171 cm^{-1}; δ_H (500 MHz, C_6D_6) 7.28–7.19 (5H, m, ArH), 4.43 and 4.40 (each 1H, d, *J* 11.5, HC*H*Ph), 4.24 (1H, m, 3-H), 4.14 (1H, br d, *J* 5.5, 5-H), 3.88 (1H, d, *J* 3.5, OH), 3.63 (3H, s, OMe), 3.45 (1H, dd, *J* 3, 9, 2″-H), 3.37 (1H, dd, *J* 8, 8.5, 2″-H′), 2.95 (1H, br s, 2-H), 2.57 (1H, m, 4-H), 1.96 (3H, m, 1″-H, 6-H_2), 1.82 (1H, m, 7-H), 1.74 (1H, m, 7-H′), 1.63 and 1.46 (each, 1H, m, 1′-H), 1.37 (9H, s, ^{t}Bu), 1.23 (4H, m, 2′-H_2, 3′-H_2), 0.92 (3H, d, *J* 7, 1″-CH_3) and 0.82 (3H, t, *J* 7, 4′-H_3); δ_C (75 Hz, $CDCl_3$) 173.19, 154.32, 137.68, 128.75, 128.21, 128.16, 79.60, 76.30, 73.95, 68.40, 64.37, 58.72, 51.60, 49.58, 34.69, 31.79, 30.32, 28.74, 28.74, 25.21, 23.43, 22.28, 16.15 and 14.63; *m/z* (ES^+) 512 (100%).

4.19. (1*R*,2*S*,3*R*,4*R*,5*S*)-4-[(*S*)-2-Benzyloxy-1-methyl-ethyl]-1-butyl-2-methoxycarbonyl-8-azabicyclo[3.2.1]-octan-3-ol 30

2,6-Lutidine (0.03 mL, 0.28 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.03 mL, 0.12 mmol) were added to the *tert*-butoxycarbamate **29** (34 mg, 0.07 mmol) in CH_2Cl_2 (0.23 mL) at 0 °C and the solution was allowed to warm to room temperature and stirred for 24 h. The reaction mixture was washed with saturated aqueous ammonium chloride (1 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using 1% methanol in CH_2Cl_2 gave the title compound **30** (16 mg, 0.04 mmol, 57%) as a white crystalline solid, mp = 74.2–75.5 °C, R_f = 0.43 in 10% MeOH/CH_2Cl_2 (Found: C, 70.4; H, 9.25; N, 3.4. $C_{23}H_{35}O_4N$ requires C, 70.9; H, 9.05; N, 3.6. Found: M^++H, 390.2638. $C_{23}H_{36}O_4N$, requires *M*, 390.2639); $[\alpha]_D^{26} = -48$ (*c* 0.5, $CHCl_3$); ν_{max} 3482, 2954, 2923, 2861, 1744, 1456, 1434, 1361, 1303, 1262, 1192, 1177, 1139, 1090, 1075, 745 and 699 cm^{-1}; δ_H (500 MHz, C_6D_6) 7.29–7.18 (5H, m, ArH), 4.43 and 4.40 (each 1H, d, *J* 11.5, HC*H*Ph), 4.26 (1H, m, 3-H), 3.70 (1H, d, *J* 3.5, OH), 3.64 (3H, s, OMe), 3.44 (1H, dd, *J* 2.5, 10, 2″-H), 3.40 (1H, br d, *J* 5.5, 5-H), 3.37 (1H, dd, *J* 7.5, 10, 2″-H′), 2.70 (1H, d, *J* 4.5, 2-H), 2.57 (1H, ddd, *J* 4.5, 9.5, 13, 7-H), 2.13 (1H, ddd, *J* 4, 9.5, 13, 7-H′), 1.98 (1H, m, 1″-H), 1.85 (1H, m, 1′-H), 1.58 (3H, m), 1.35 (2H, m), 1.21 (4H, m, 2′-H_2, 3′-H_2), 0.90 (3H, d, *J* 7, 1″-CH_3) and 0.81 (3H, d, *J* 7, 4′-H_3); δ_C (75 Hz, $CDCl_3$) 173.16, 137.39, 128.48, 127.98, 127.94, 76.32, 73.10, 67.91, 62.86, 56.34, 54.07, 51.26, 38.30, 32.50, 31.84, 26.83, 26.38, 23.32, 23.32, 16.19 and 14.08; *m/z* (ES^+) 412 (M^++23, 20%) and 390 (100).

4.20. Methyl (4*R*,5*S*)-6-(benzyloxy)-4-[(*S*)-5-butyl-3,4-dihydro-2*H*-pyrrolin-2-yl]-5-methyl-3-oxohexanoate 31

Trifluoroacetic acid (0.126 mL, 1.62 mmol) was added to the diketone **27** (50 mg, 0.01 mmol) at 0 °C and the solution allowed to warm to room temperature then stirred for 20 min. Saturated aqueous sodium hydrogen carbonate (5 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using 50% Et_2O in light petroleum gave the title compound **31** (30 mg, 0.078 mmol, 79%) as a colourless oil, R_f = 0.13 in 50% Et_2O/light petroleum (Found: M+H^+, 388.2481. $C_{23}H_{34}NO_4$ requires *M*, 388.2482); $[\alpha]_D^{26} = -18.4$ (*c* 6.3, $CHCl_3$); ν_{max} 2957, 1747, 1707, 1644, 1455, 1261, 1168, 1097, 1026, 801, 738 and 699 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.36–7.33 (5H, m, ArH), 4.50 and 4.44 (each 1H, d, *J* 12, HC*H*Ph), 4.36 (1H, m, 2′-H), 3.74 (1H, d, *J* 14, 2-H), 3.67 (3H, s, OMe), 3.55 (1H, d, *J* 14, 2-H′), 3.37 (2H, m, 6-H_2), 2.35 (2H, m), 2.22 (2H, m), 2.04–1.77 (2H, m), 1.68–1.33 (6H, m, 1″-H_2, 2″-H_2, 3″-H_2), 1.07 (3H, d, *J* 7, 5-CH_3) and 0.95 (3H, t, *J* 7.5, 4″-H_3); δ_C (75 Hz, $CDCl_3$) 207.06, 179.79, 167.97, 138.67, 128.57, 127.82, 127.67, 74.53, 73.25, 73.05, 57.08, 52.51, 52.09, 37.83, 33.99, 33.76, 28.68, 23.03, 22.93, 15.42 and 14.17; *m/z* (ES^+) 410 (M + 23, 90%) and 388 (100).

4.21. (1*R*,2*R*,4*R*,5*S*)-4-[(*S*)-2-Benzyloxy-1-methylethyl]-1-butyl-2,8-dimethoxycarbonyl-8-azabicyclo[3.2.1]octan-3-one 32

Methyl chloroformate (6 μL, 0.075 mmol) was added to the imine **31** (20 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) at −78 °C and the solution stirred at −78 °C for 30 min. Triethylamine (0.04 mL, 0.3 mmol) was added and reaction stirred at −78 °C for 18 h before being allowed to warm to room temperature. Saturated aqueous ammonium chloride (10 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using 20% Et_2O in light petroleum gave the title compound **32** (8 mg, 0.02 mmol, 41%) as a colourless oil, R_f = 0.50 in 50% Et_2O/light petroleum (Found: M+Na^+, 468.2355. $C_{25}H_{35}NO_6Na$ requires *M*, 468.2357); $[\alpha]_D^{29} = -37.7$ (*c* 5.1, $CHCl_3$) ν_{max} 2956, 1735, 1708, 1442, 1364, 1327, 1233, 1196, 1169, 1100, 738 and 698 cm^{-1}; δ_H (500 MHz, C_6D_6) 7.24 (2H, d, *J* 7, ArH), 7.10 (2H, m, ArH), 7.00 (1H, dd, *J* 7, 7.5, ArH), 4.56 (1H, br m, 5-H), 4.31 and 4.25 (each 1H, d, *J* 12, HC*H*Ph), 3.60 (1H, dd, *J* 3, 10, 2″-H), 3.58 (1H, dd, *J* 4, 10, 2″-H′), 3.38 (6H, s, 2 × OMe), 3.35 (1H, m, 2-H), 2.32 (1H, m, 1″-H), 2.18 (2H, br m, 7-H, 4-H), 1.47 (1H, td, *J* 12.5, 3.5, 7-H′), 1.28–1.08 (8H, m, 6-H_2, 1′-H_2, 2′-H_2 and 3′-H_2), 0.99 (3H, d, *J* 7, 1″-CH_3) and 0.83 (3H, t, *J* 7.5, 4′-H_3); δ_C (75 Hz, C_6D_6) 204.73, 168.22, 154.22, 139.55, 128.37, 127.52, 127.35, 74.57, 73.07, 67.68, 67.16, 58.81, 54.49, 51.95, 51.74, 35.48, 30.82, 30.11, 26.70, 23.41, 22.42, 14.64 and 14.17; *m/z* (ES^+) 468 (M^++23, 100%).

4.22. (1*R*,2*S*,4*R*,5*S*)-4-[(*S*)-2-Benzyloxy-1-methylethyl]-1-butyl-2-methoxycarbonyl-8-*tert*-butoxycarbonyl-2-prop-2-enyl-8-azabicyclo[3.2.1]octan-3-one 33

The tropinone **28** (200 mg, 0.41 mmol) in THF (1.4 mL) was added to a suspension of sodium hydride (18 mg, 0.45 mmol) in dimethylformamide (1.5 mL) at room temperature and the mixture stirred for 30 min. Tetrabutylammonium iodide (15 mg, 0.04 mmol) and allyl bromide (0.37 mL, 4.1 mmol) in THF (3 mL) were added and reaction mixture was heated under reflux for 24 h. Saturated aqueous ammonium chloride (6 mL) was added and the organic phase washed with water (6 mL) and brine (6 mL) and dried ($MgSO_4$). After concentration under reduced pressure, chromatography using 10% Et_2O in light petroleum gave the title compound **33** (180 mg, 0.34 mmol, 83%) as a colourless viscous oil, R_f = 0.40 in 20% Et_2O/light petroleum (Found: M+Na^+, 550.3149. $C_{31}H_{45}NO_6Na$, requires 550.3139); $[\alpha]_D^{26} = -56$ (*c* 75.1, $CHCl_3$) ν_{max} 2960, 1730, 1702, 1456, 1367, 1218, 1158, 1091, 994, 919, 736 and 698 cm^{-1}; δ_H (500 MHz, C_6D_6) 7.38 (2H, d, *J* 7.5, ArH), 7.28 (2H, m, ArH), 7.20 (1H, dd, *J* 7, 7.5, ArH), 6.12 (1H, dtd, *J* 4, 10, 17, 2″-H), 5.18 (1H, d, *J* 17, 3″-H), 5.07 (1H, d, *J* 10, 3″-H′), 4.71 (1H, m, 5-H), 4.39 (2H, s, CH_2Ph), 3.57 (2H, m, 2‴-H_2), 3.50 (2H, m, 1″-H_2), 3.47 (3H, s, OMe), 3.11 (1H, ddd, *J* 4.5, 10, 14), 3.06 (1H, dd, *J* 4, 9, 4-H), 2.90 (1H, br m), 2.44 (1H, m, 1‴-H), 2.01 (1H, dt, *J* 5, 13.5), 1.80–1.48 (3H, m), 1.52 (9H, s, ^{t}Bu), 1.43–1.37 (4H, m), 1.11 (3H, d, *J* 7, 1‴-CH_3), 1.03 (3H, t, *J* 7, 4′-H_3); δ_C (75 Hz, $CDCl_3$) 206.16, 170.48, 153.50, 139.16, 133.94, 128.46, 127.57, 127.53, 118.35, 74.51, 72.93, 72.67, 72.65, 58.63, 55.88, 52.37, 36.55, 31.82, 29.98, 29.97, 29.19, 28.63, 26.45, 23.42, 22.67, 14.76 and 14.52; *m/z* (ES^+) 550 (M^++23, 100%) and 518 (20).

4.23. (1*R*,2*S*,4*R*,5*S*)-4-[(*S*)-2-Benzyloxy-1-methylethyl]-1-butyl-2-formylmethyl-2-methoxycarbonyl-8-*tert*-butoxycarbonyl-8-azabicyclo[3.2.1]octan-3-one 34

2,6-Lutidine (0.03 mL) followed by osmium tetroxide (0.6 mg, 0.0025 mmol) and sodium periodate (107 mg, 0.5 mmol) was added to the tropinone **33** (65 mg, 0.123 mmol) in THF (2.25 mL)

containing water (0.75 mL). The suspension was stirred for 5 h, diluted with water (7 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using 20% Et_2O in light petroleum gave the title compound **34** (51 mg, 0.098 mmol, 80%) as a colourless oil, R_f = 0.13 in 20% Et_2O/light petroleum (Found: M+NH_4^+, 547.3369. $C_{30}H_{47}N_2O_7$, requires M, 547.3378); $[\alpha]_D^{29} = -25.5$ (*c* 12.4, $CHCl_3$) ν_{max} 2964, 2854, 1728, 1698, 1455, 1369, 1261, 1204, 1157, 1094, 889, 802 and 698 cm^{-1}; δ_H (500 MHz, C_6D_6) 9.46 (1H, t, *J* 1.5, 2″-H), 7.20 (2H, d, *J* 7.5, ArH), 7.08 (2H, t, *J* 7.5, ArH), 6.98 (1H, t, *J* 7.5, ArH), 4.53 (1H, m, 5-H), 4.35 and 4.24 (each 1H, d, *J* 12.5, HC*H*Ph), 3.54 (1H, br m, 2‴-H), 3.48 (1H, dd, *J* 2.5, 8.5, 2‴-H′), 3.17 (3H, s, OMe), 3.12 (1H, m, 1″-H), 3.09 (1H, m, 4-H), 2.87–2.77 (2H, m), 2.25 (1H, m, 1‴-H), 1.84 (1H, dt, *J* 5, 13), 1.60 and 1.47 (each 1H, m, 1′-H), 1.40 (1H, m), 1.26 (9H, s, ^{t}Bu), 1.23–1.16 (5H, m), 0.90 (3H, d, *J* 7, 1‴-CH_3) and 0.84 (3H, t, *J* 7.5, 4′-H_3); δ_C (125 Hz, $CDCl_3$) 204.65, 200.20, 168.94, 168.09, 137.96, 127.19, 126.41, 126.26, 72.69, 71.79, 70.12, 58.45, 51.63, 51.57, 43.48, 31.72, 31.67, 27.48, 27.47, 25.09, 25.0, 22.06, 21.56, 20.82, 13.41 and 13.24; *m/z* (ES^+) 552 (M^++23, 100%).

4.24. (*1R,2S,5S,6S*)-5-[(*S*)-2-Benzyloxy-1-methyl-ethyl]1-butyl-4-hydroxy-2-methoxycarbonyl-9-*tert*-butoxy-carbonyl-9-azatricyclo[4.2.1.1^{2,5}]decan-10-one 35

The aldehyde **34** (10 mg, 0.019 mmol) was stirred in trifluoroacetic acid (4 μL) at room temperature for 2 min. Saturated aqueous ammonium bicarbonate (5 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were washed with brine (15 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue using 50% Et_2O in light petroleum and then neat Et_2O gave the title compound **35** (4 mg, 0.008 mmol, 40%) as a colourless oil, R_f = 0.3 in 100% Et_2O; ν_{max} 3479, 2958, 1738, 1700, 1687, 1454, 1384, 1252, 1205, 1162, 1102, 1033, 734 and 699 cm^{-1}; δ_H (500 MHz, C_6D_6) 7.10 (2H, d, *J* 7, ArH), 7.05 (2H, m, ArH), 6.96 (1H, dd, *J* 7, 8, ArH), 4.79 (1H, d, *J* 12, OH), 4.56 (1H, m, 4-H), 4.39 (1H, dt, *J* 4, 8, 6-H), 4.15 (2H, s, CH_2Ph), 3.58 (1H, dd, *J* 4.5, 9, 2″-H), 3.36 (1H, dd, *J* 4, 9, 2″-H′), 3.45 (1H, m), 3.10 (3H, s, OMe), 3.06 (1H, dd, *J* 7, 12.5, 3-H), 2.85 (1H, dd, *J* 4, 7.5), 2.21 (1H, m, 1″-H), 2.02 (1H, ddd, *J* 2.5, 6.5, 9), 1.86 (1H, dd, *J* 8.5, 12.5, 3-H′), 1.67 (1H, m), 1.46 (1H, m), 1.40–1.18 (5H, m), 1.17 (9H, s, ^{t}Bu), 0.81 (3H, d, *J* 7.5, 1″-CH_3), 0.78 (3H, t, *J* 7, 4′-H_3); δ_C (100 Hz, $CDCl_3$) 208.24, 170.40, 152.32, 137.60, 127.26, 126.51, 126.44, 80.11, 73.44, 72.94, 71.98, 71.01, 54.50, 52.48, 51.42, 48.57, 41.74, 34.12, 31.61, 31.06, 28.34, 27.29, 21.90, 19.55, 14.28 and 13.18; *m/z* (ES^+) 530 (M^++1, 10%) and 547 (M^++18, 30).

4.25. Crystal data for tropinone 30

$C_{23}H_{35}NO_4$, MW 389.52, monoclinic, space group *C*2, *a* = 28.621(4), *b* = 8.2096(11), *c* = 9.3660(13) Å, *β* = 96.940(2)°, *V* = 2184.6(5) Å^3, *Z* = 4, D_c = 1.184 g cm^{-3}, μ(Mo Kα) = 0.080 mm^{-1}, *F*(000) = 848, *T* = 100 K. Crystal dimensions were 0.3 × 0.25 × 0.05 mm. 8829 reflections measured, 2431 independent reflections (R_{int} = 0.054), R_1 = 0.054 for the 2122 reflections with $I > 2\sigma(I)$, $wR(F^2)$ = 0.125 (all data). Atomic coordinates, bond lengths and angles and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, CCDC number 721348.

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