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The use of enantiomerically pure ketene dithioacetal bis(sulfoxides) in highly diastereoselective intramolecular nitrone cycloadditions. Application in the total synthesis of the β-amino acid (−)-cispentacin and the first asymmetric synthesis of *cis*-(3*R*,4*R*)-4-amino-pyrrolidine-3-carboxylic acid

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Received 3rd January 2003, Accepted 12th January 2003
First published as an Advance Article on the web 30th January 2003

Intramolecular 1,3-dipolar nitrone cycloaddition onto an enantiomerically pure ketene dithioacetal dioxide using a three-carbon tether gave the corresponding 5,5-disubstituted isoxazolidine as a single diastereomer in good yield. This reaction has been used as the key step in an asymmetric synthesis of the naturally occurring antibiotic, (−)-cispentacin. An asymmetric synthesis of 4-amino-pyrrolidine-3-carboxylic acid has also been carried out using the intramolecular nitrone cycloaddition as the stereocontrolling step.

Introduction

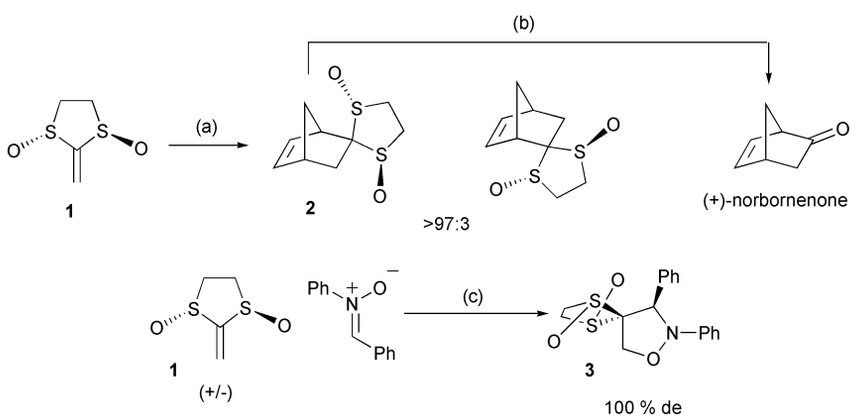
Since Staudinger established that ketenes do not undergo cycloaddition reactions with dienes to give [4 + 2] products, but instead react to give the products of [2 + 2] cycloaddition,[1–4] synthetic organic chemists have developed reagents that are able to act as ketene equivalents by undergoing [4 + 2] cycloaddition onto dienes, after which the carbonyl group is unmasked.[5–7] Later the goal of enantioselective natural product synthesis provided an impetus for the development of chiral ketene equivalents which undergo diastereoselective cycloadditions onto dienes.[8–15] We have developed the use of *trans*-dioxides of cyclic ketene thioacetals as highly selective chiral ketene equivalents. A range of cyclic ketene thioacetals have been studied in Diels–Alder reactions, where **1** was found to be the most reactive and selective. Compound **1** can be prepared in >98% ee in four steps and undergoes cycloaddition with a range of dienes. For example, reaction with cyclopentadiene at −78 °C using $BF_3{\cdot}OEt_2$ gave **2** as a single diastereomer (Scheme 1).[16]

We have also studied intermolecular nitrone cycloadditions with **1** and found that, unusually for 1,1-disubstituted alkenes, the 4,4-disubstituted isoxazolidines (*e.g.* **3**) were formed in high yield and with >18 : 1 diastereoselectivity.[17] From a synthetic point of view a 5,5-disubstituted product obtained by cycloaddition of a nitrone onto a ketene equivalent may be a useful intermediate in the synthesis of β-amino acids, which are biologically important compounds.[18,19] Indeed Overton *et. al.* have used this approach in an attempted asymmetric synthesis of aspartame.[20,21]

We realised that, in our case, a 5,5-disubstituted isoxazolidine (**5**) could be accessed by linking the cycloaddition components with a suitable tether (**4**). Intramolecular cycloaddition with a three-carbon tether should result in the diastereoselective formation of the *cis*-fused [3.3.0]isoxazolidine **5**, according to a wealth of literature precedent.[22–25]

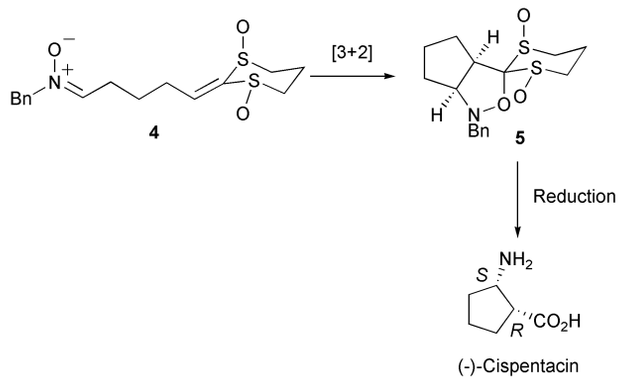
Although dithiolane **1** had been employed in intermolecular nitrone cycloadditions we chose to work on the dithiane derivative **4** as the synthesis of such substituted alkenes had already been successfully achieved by Horner–Wadsworth–Emmons olefination.[26] Following hydrogenolysis of the N–O and N–Bn bonds the thioacetal moiety should collapse and directly furnish the naturally occurring β-amino acid, cispentacin (Scheme 2).

In fact such a process would be the first example of an intramolecular cycloaddition in which a chiral ketene equivalent is employed. Our initial aim was to establish conditions that would promote intramolecular cycloaddition with high diastereoselectivity.[27] However at the outset of this project the stereochemical course of any intramolecular cycloaddition was not clear. The only precedent came from our work in the



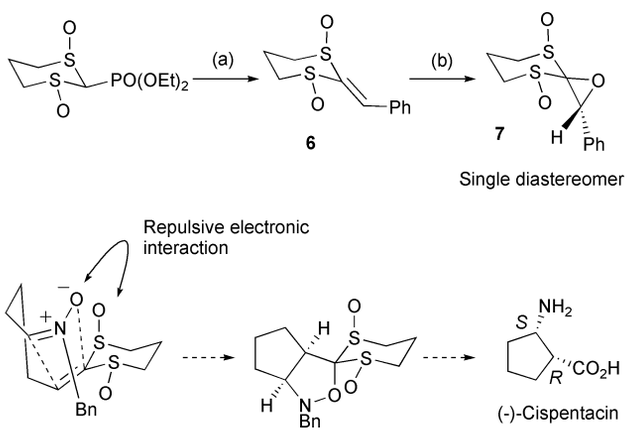
Scheme 1 (a) Cyclopentadiene, $BF_3{\cdot}Et_2O$, −78 °C, EtCN, 20 min, 74%. (b) (i) TFAA, NaI, CH_3CN, 2 h, 0 °C, 90% (ii) $CuCl_2$, SiO_2, H_2O, CH_2Cl_2, 4 days, 81%. (c) CH_2Cl_2, rt, 15 h, 64%.

DOI: 10.1039/b212719a



Scheme 2

nucleophilic epoxidation of related ketene thioacetals, in which high levels of diastereoselectivity were observed.[26] For example, nucleophilic epoxidation of ketene dithioacetal **6** gave the spirocyclic epoxide **7** as a single diastereomer in good yield (Scheme 3).



Scheme 3 *Reagents and conditions:* (a) PhCHO, $LiOH{\cdot}H_2O$, THF, 70 °C, 4 h, 70%. (b) H_2O_2 (3 equiv.), NaOH (0.5 equiv.), 30% DCM–MeOH, −10 °C, 20 min, 81%.

X-Ray crystallography had established that the preferred conformation of ketene dithioacetal **6** in the solid state is that in which the more bulky phenyl substituent is held away from the equatorial oxygen atom, thereby minimising $A^{1,3}$ strain.[28] The nucleophilic peroxide anion attacked the top (*re*) face of **6** to give spirocyclic epoxide **7** after ring-closure.

The diastereoselectivity of an intramolecular nitrone cycloaddition might be controlled effectively by similar factors. However, the approach of the (*Z*)-nitrone[29,30] onto the face of the ketene thioacetal which is preferred in epoxidation places the negatively charged oxygen atom of the nitrone and the axial sulfinyl oxygen atom in close proximity.[31] Clearly this repulsive electronic interaction will destabilize the sterically favoured transition state. We therefore wished to establish whether steric or electronic control would dominate the cycloaddition process.

The stereochemistry of the cycloaddition may be established by conversion of the isoxazolidine to cispentacin. (−)-Cispentacin, (1*R*,2*S*)-2-aminocyclopentane-1-carboxylic acid was isolated from *Bacillus cereus*[32] and *Streptomyces setonii*[33] and was found to exhibit potent *in vivo* activity against several *Candida* species in mice. As a result of its biological activity and the inactivity of the unnatural (1*S*,2*R*) enantiomer several asymmetric syntheses have been reported.[34–38]

Results and discussion

Nitrone **4** should be easily accessible by condensation of the corresponding aldehyde with *N*-benzylhydroxylamine at room temperature. Intramolecular [3 + 2] dipolar cycloaddition onto the ketene dithioacetal may then occur without additional heating.[24]

Our synthesis began with 1,3-dithiane **8**, which was converted into the 2-phosphonate and oxidised to give the (1*R*,3*R*) phosphonate dioxide **9** with >98% ee.[26] A preliminary study employing the Horner–Wadsworth–Emmons olefination of glutaraldehyde with phosphonate **9** gave only low yields of the mono-olefinated product along with the bis(ketene) dithioacetal side-product.[39] Instead the readily accessible, terminally differentiated aldehyde 5,5-dimethoxypentanal was employed.[40,41] Horner–Wadsworth–Emmons olefination of 5,5-dimethoxypentanal with (+)-phosphonate, using a slight deficiency of base, gave ketene thioacetal **10**. Horner–Wadsworth–Emmons olefination using an excess of lithium hydroxide monohydrate gave the corresponding allyl sulfoxide, resulting from formation of the ketene thioacetal and subsequent base-catalysed isomerisation. The thermodynamic instability of vinyl sulfoxides with respect to allyl sulfoxides was established by O′Connor and Lyness and provides evidence that ground-state bonding interactions between the unoccupied sulfur atom d-orbitals and the π-bond are not significant.[42]

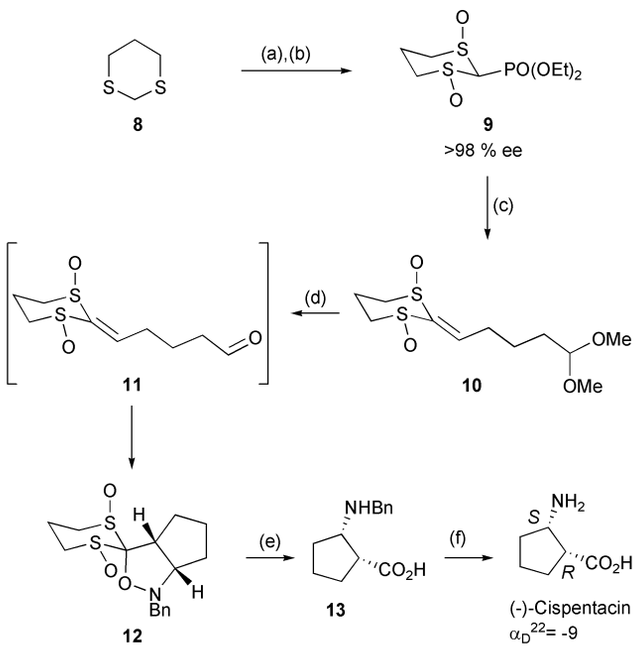
For the hydrolysis of the dimethoxyacetal **10** the method of Lipshutz *et. al.* was preferred,[43] which led to transketalisation with only 1 mol% $PdCl_2(CH_3CN)_2$ in refluxing acetone to give aldehyde **11** in excellent yield after column chromatography. Although aldehyde **11** can be isolated and characterised we preferred to use the crude transketalisation reaction mixture for the formation of nitrone **4**. Thus, once the transketalisation reaction was complete *N*-benzylhydroxylamine hydrochloride (1.3 equiv.) and sodium hydrogen carbonate (3 equiv.) were added to the reaction mixture at room temperature and after stirring at room temperature for 16 hours and purification by column chromatography isoxazolidine **12** was isolated as a single diastereomer, as determined by ^{1}H NMR. This sequence of reactions occurred in high yield (70%) and with complete diastereoselectivity, according to high-field ^{1}H NMR spectroscopy of the crude reaction mixture. Cyclisation of nitrone **4** at room temperature prevented its isolation and characterisation. The facial selectivity of the cycloaddition could not be determined at this stage as **12** was not crystalline and data from ^{1}H NMR spectroscopy could not provide useful stereochemical information. To establish which diastereomer of the isoxazolidine was formed conversion to the known *cis*-2-aminocyclopentane-1-carboxylic acid would be required in order to compare a_D values.

A number of reagents have been used to carry out reductive cleavage of the N–O bond of an isoxazolidine, including zinc in acetic acid,[44,45] molybdenum hexacarbonyl,[46,47] nickel boride[48–50] and catalytic hydrogenation over palladium[47,51] or Raney nickel.[49] Hydrogenation of **12** over palladium on carbon (10 mol%) in acetic acid under 7 atm hydrogen pressure furnished *cis*-*N*-benzyl-2-aminocyclopentane-1-carboxylic acid (**13**) in 65% yield after 48 hours.

We had hoped that cleavage of the N–Bn bond would occur in the same pot to give cispentacin directly, however hydrogenation of the isoxazolidine failed to cleave the *N*-benzyl group. The inertness of the N–Bn bond to hydrogenolysis and the sluggish N–O bond cleavage are attributed to poisoning of the palladium catalyst by the sulfide by-products of the dithiane hydrolysis. The material obtained from column chromatography was not spectroscopically clean and a single recrystallisation from ethanol was required to remove all traces of sulfide impurities from the *cis*-*N*-benzyl-2-aminocyclopentane-1-carboxylic acid. Debenzylation was then carried out at atmospheric pressure using Pearlman's catalyst in ethanol with 5 mol% triethylamine additive at 40 °C. Spectroscopically clean (−)-cispentacin was obtained in 85% yield following a single recrystallisation from water–acetone. When the debenzylation was first attempted using palladium on carbon or Pearlman's catalyst in ethanol a mixture of 2-aminocyclopentane-1-carb-

oxylic acid and its *N*-ethyl derivative was obtained. However, with 5 mol% triethylamine debenzylation was faster, and none of the *N*-ethyl by-product was observed. The reason for the rate acceleration is not clear, but evidently a more powerfully reducing system is formed.[52]

The absolute stereochemistry of the 2-aminocyclopentane-1-carboxylic acid was established as being (1*R*,2*S*) from the sign of the optical rotation: $[\alpha]_D^{22}$ −9.0, *c* = 1.1 in H_2O. Lit;[53] $[\alpha]_D^{20}$ −8.9, *c* = 1.0 in H_2O (Scheme 4).



Scheme 4 *Reagents and conditions:* (a) (i) NCS, benzene, rt, 24 h (ii) $P(OEt)_3$, 60 °C, 4 h, 78% yield. (b) $PhC(CH_3)_2OOH$ (4 equiv.), $Ti(O^iPr)_4$ (0.5 equiv.), (+)-DET (2 equiv.), DCM, 72 h, 43% yield, >98% ee. (c) 5,5-Dimethoxypentanal (1.5 equiv.), $LiOH{\cdot}H_2O$ (0.99 equiv.), THF, 80 °C, 4 h, 80% yield. (d) $PdCl_2(CH_3CN)_2$ (1 mol%), acetone, 60 °C, 1 h then $BnNH_2OH{\cdot}Cl$ (1.3 equiv.) and $NaHCO_3$ (3 equiv.), rt, 16 h, 70% yield. (e) Pd/C (10 mol%), AcOH, H_2 (7 atm), 48 h, 65% yield. (f) $Pd(OH)_2$–C (10 mol%), NEt_3 (10 mol%), EtOH, 40 °C, H_2 (1 atm), 4 h, 85% yield. (+)-DET = diethyl tartrate.

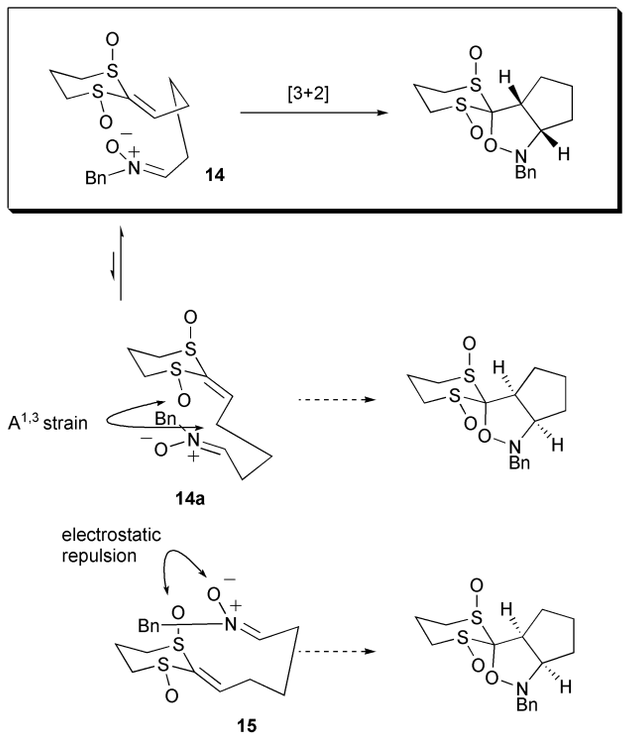
The formation of (−)-(1*R*,2*S*)-cispentacin indicated that the nitrone prefers to approach the *si* face of the double bond. This diastereoselectivity can be understood by considering the conformation of the dithiane dioxide ring and the facial approach of the nitrone. The preferred conformation of the ketene dithioacetal is **14**, as **14a** suffers from severe $A^{1,3}$ strain.

It is clear from the observed facial selectivity that cyclisation transition state **14**, in which the nitrone approaches the sterically more hindered face according to the results obtained from nucleophilic epoxidation, is preferred to **15**. Clearly transition state **15** is destabilised by a severe electronic repulsion between the negatively charged oxygen atoms of the (*Z*)-nitrone and the axial sulfinyl oxygen to such an extent that this interaction directs the approach of the nitrone onto the *si* face (Scheme 5).

At this stage we had gained an insight into the stereochemistry of the cycloaddition process and we were pleased that the diastereoselectivity was high as it allowed an efficient asymmetric synthesis of the naturally occuring antibiotic (−)-cispentacin to be carried out.

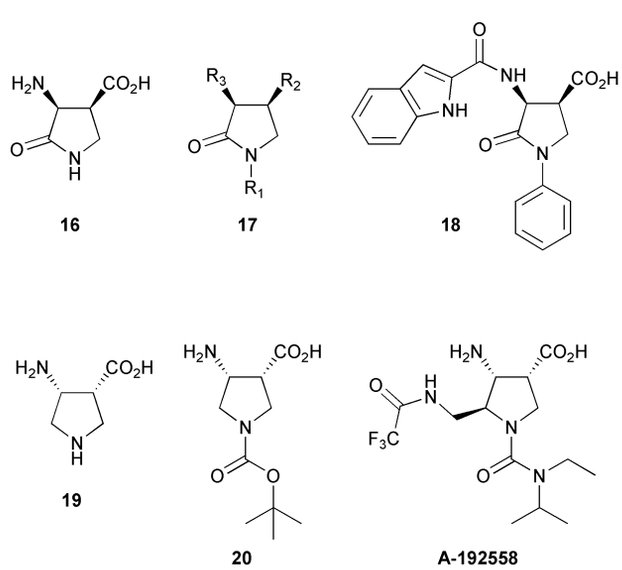
Asymmetric synthesis of (+)-4-amino-β-proline

We wanted to apply this chemistry to the asymmetric synthesis of medicinally interesting heterocyclic analogues of cispentacin. For example, *cis*-4-amino-5-oxopyrrolidine-3-carboxylic acid (**16**) is the core structure in a number of biologically interesting compounds that have been identified as potent and selective CCK-A antagonists,[54] based on the 1,3,4-trisubsti-



Scheme 5 Competing cycloaddition transition states.

tuted pyrrolidin-2-one scaffold **17**. A focused library of rationally designed cholecystokinin mimics was screened for antagonism of the CCK-A receptor and, for example, pyrrolidinone **18**, wherein R_1, R_2 and R_3 mimicked phenylalanine, aspartic acid and tryptophan residues respectively, was found to be a potent CCK-A antagonist (Scheme 6). Libraries of related peptidomimetic compounds have been made by Boger *et. al.* by solution phase parallel synthesis.[55]



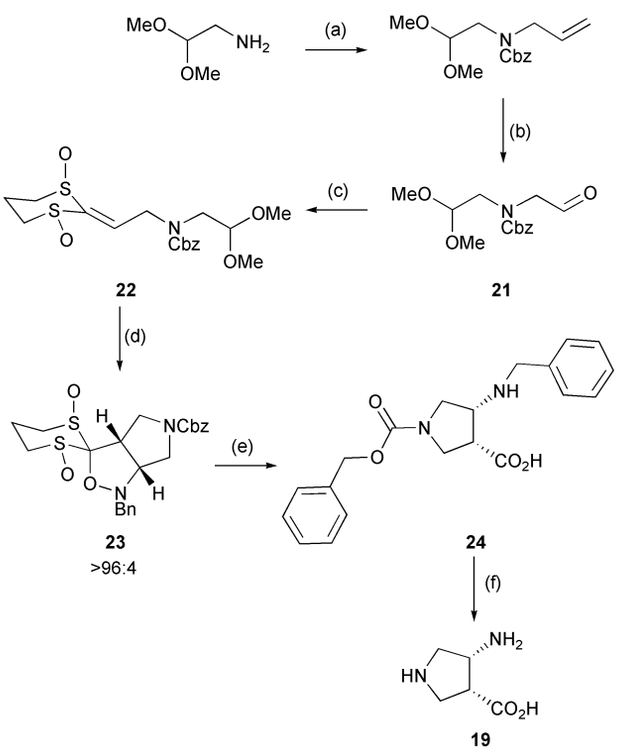
Scheme 6

4-Aminopyrrolidine-3-carboxylic acid (**19**) has been synthesised as a racemic mixture and has been used to probe the structure of the GABA receptor.[56] More recently workers at Abbott Laboratories have used the carbamate derivative **20** as a lead structure for the synthesis of libraries of compounds that were screened for inhibition of influenza neuraminidase (NA). This led to the discovery of A-192558, a sub-micromolar NA inhibitor.[57]

Clearly both *cis*-4-amino-5-oxopyrrolidine-3-carboxylic acid (**16**) and 4-aminopyrrolidine-3-carboxylic acid (**19**) may be used

as building blocks in the design and synthesis of compounds for biological testing and an asymmetric synthesis that allows access to either enantiomer of a potential drug candidate may be of considerable benefit. Moreover, recently Gellman *et al.* have included (3*S*,4*R*)-*trans*-3-aminopyrrolidine-4-carboxylic acid in β-peptides and have discovered some interesting structural and biological properties.[18,58]

An asymmetric synthesis of *cis*-4-aminopyrrolidine-3-carboxylic acid (**19**) has not been reported and we aimed to be able to provide efficient access to either enantiomer using the chemistry developed for the synthesis of cispentacin, in which the nitrone was introduced by condensation of *N*-benzylhydroxylamine with an aldehyde derived from acetal hydrolysis. Our synthesis began with aminoacetaldehyde dimethyl acetal, which was converted to the carboxybenzoyl carbamate,[59] alkylated with allyl bromide and ozonolysed to aldehyde **21**. Horner–Wadsworth–Emmons olefination using enantiomerically pure (+)-phosphonate gave the ketene thioacetal **22**. Hydrolysis of the acetal with $PdCl_2(CH_3CN)$ in acetone failed, as the catalyst was reduced to palladium metal in the reaction. However, transketalisation was achieved by using one equivalent of toluene-*p*-sulfonic acid in hot acetone to give a solution of the corresponding aldehyde (Scheme 7).



Scheme 7 *Reagents and conditions:* (a) (i) BnOCOCl, K_2CO_3, diethyl ether–water (1 : 1), rt, 18 h, 98%. (ii) NaH (1.1 equiv.), DMF, allyl bromide (1.2 equiv.), rt, 24 h, 75%. (b) O_3, CH_2Cl_2, −78 °C then Me_2S (excess), rt, 4 h, 67%. (c) (+)-**9**, LiOH·H_2O (0.99 equiv.), THF, 70 °C, 4 h, 75%. (d) (i) TsOH (1 equiv.), acetone, 60 °C, 3 h (ii) $NaHCO_3$ (6 equiv.), rt. (iii) BnNHOH·HCl (1.1 equiv.), rt, 14 h, 73% overall yield. (e) Pd/C (10 mol%), AcOH, H_2 (7 atm), rt, 24 h, 65%. (f) $Pd(OH)_2$/C (25 mol%), EtOH, 40 °C, H_2 (1 atm), 2 h, 85%.

As in the synthesis of cispentacin, the nitrone was formed in the same pot by addition of excess base followed by *N*-benzylhydroxylamine hydrochloride at room temperature. The nitrone could not be isolated as cyclisation occurred without additional heating. Isoxazolidine **23** was isolated in good yield with a >96 : 4 ratio of diastereomers observed in the ^{1}H NMR spectrum. The relative stereochemistry of **23** is assigned by analogy with the asymmetric synthesis of (−)-cispentacin.

High-pressure hydrogenolysis of **23** over palladium on carbon in acetic acid for 24 hours gave a good yield of the *N*-protected amino acid **24**. Clearly the palladium catalyst is poisoned by the sulfide by-products of dithiane hydrolysis to such an extent that hydrogenolysis of the normally highly labile Cbz group is not possible. Subsequent hydrogenolysis of both protecting groups was carried out in a separate step to give the *cis*-4-aminopyrrolidine-3-carboxylic acid in good yield. The absolute stereochemistry is assigned as being (3*R*,4*R*) by analogy with the asymmetric synthesis of (−)-cispentacin.

Conclusions

Intramolecular cycloaddition of a nitrone onto a ketene dithioacetal dioxide using a three-carbon tether gave the corresponding 5,5-disubstituted isoxazolidine as a single diastereomer in good yield. When the facial selectivity of this process is compared to that observed for nuclephilic epoxidation it becomes clear that the cyclisation proceeds through a transition state in which the nitrone approaches the more sterically hindered face of the double bond. This unexpected stereoselectivity must be due to severe electronic repulsion between the negatively charged oxygen atoms of the (*Z*)-nitrone and the axial sulfinyl oxygen, which prevents cyclisation onto the less hindered face. This reaction has been used as the key step in an asymmetric synthesis of the naturally occurring antibiotic, (−)-cispentacin. This methodology has been applied to the first asymmetric synthesis of (4*R*)-aminopyrrolidine-(3*R*)-carboxylic acid. Again the intramolecular nitrone cycloaddition provided excellent stereocontrol of the two stereogenic centres in the final target.

Experimental

General

Reactions requiring anhydrous conditions were performed in vacuum flame-dried glassware under a nitrogen atmosphere. Air- and moisture-sensitive liquids and solutions were transferred *via* syringe or cannula into the reaction vessels through rubber septa. ^{1}H and ^{13}C NMR spectra were recorded at the specified field strength using a Joel JNM-GX 400 FT spectrometer. Chemical shifts (δ_H) are quoted in parts per million (ppm). Coupling constants are quoted in Hertz (Hz). Melting points were recorded using a Kofler Hot Stage Micro Melting Point Apparatus. Optical rotations were measured using a Perkin-Elmer 241 MC Polarimeter. $[\alpha]_D^{22}$ values are given in 10^{-1} deg cm^2 mg^{-1}. Infrared spectra were recorded on a Perkin-Elmer Spectrum-One FT-IR spectrometer. Low resolution mass spectra (*m*/*z*) were recorded on either VG platform or VG Prospec spectrometers, with only molecular ions (M^+ or MH^+) and major peaks being reported with relative intensities quoted. High-resolution mass spectra were recorded on a VG Prospec spectrometer. Analytical TLC was performed on Merck Kieselgel 60F_{254} aluminium plates which were visualised using standard visualising agents: ninhydrin/Δ, phosphomolybdic acid/Δ, potassium permanganate/Δ, *p*-anisaldehyde/Δ. Flash chromatography was performed using Kieselgel 60F_{254}, 40–63 micron silica gel.

Purification of reagents

Anhydrous THF, DCM and hexane were obtained from a purification column composed of activated alumina (A-2).[60] Anhydrous benzene and anhydrous DMF were used as provided by Aldrich Chemical Company. Anhydrous triethylamine and diisopropylamine were purified by distillation from calcium hydride at atmospheric pressure. Triethylphosphite and titanium(IV) isopropoxide were purified by distillation under reduced pressure. All other reagents were used as supplied.

Experimental procedures and compound characterisation

Diethyl 1,3-dithian-2-ylphosphonate. To a solution of 1,3-dithiane (6.0 g, 50 mmol) in anhydrous benzene (150 mL) was

carefully added *N*-chlorosuccinimide (6.7 g, 50 mmol) in three portions. The mixture was stirred under nitrogen for 24 hours at room temperature. Distilled triethyl phosphite (10.3 mL, 60 mmol) was then added dropwise and the solution warmed to 60 °C for 4 hours. The cold reaction mixture was filtered to remove succinimide as a white solid. The solvent was removed *in vacuo* and the residue triturated with diethyl ether, any white solid precipitated was then removed by filtration. Solvent was removed *in vacuo* to give the crude product as a yellow oil. Column chromatography (1 : 1 petrol : ethyl acetate) afforded diethyl 1,3-dithian-2-ylphosphonate as a low melting white solid (10.47 g, 78%); R_f 0.35 (1 : 1 petrol : ethyl acetate); ν_{max} (thin film)/cm^{-1} 1237, 1019; δ_H (400 MHz, $CDCl_3$) 1.37 (6H, t, *J* 7.2, $(CH_2CH_3)_2$), 1.91–2.03 (1H, m, 5-H), 2.08–2.16 (1H, m, 5-H), 2.55 (2H, ddd, *J* 13.8, 5.3, 3.1, 4-H_{eq} and 6-H_{eq}), 3.45–3.55 (2H, m, 4-H_{ax} and 6-H_{ax}), 3.52 (1H, d, $^2J_{HP}$ 19.6, 2-H), 4.20 (4H, dq, $^3J_{HP}$ 7.2, $^3J_{HH}$ 7.2, $(CH_2CH_3)_2$).

Diethyl (1*RS*,3*RS*)-1,3-dioxo-1,3-dithian-2-ylphosphonate. Sodium metaperiodate (41.0 g, 192 mmol) was added to a solution of diethyl 1,3-dithian-2-ylphosphonate (12.3 g, 47.9 mmol) in methanol (160 mL) and water (55 mL). After 4 days stirring at room temperature under nitrogen the sodium metaperiodate was filtered off and the methanol removed under reduced pressure. The residue was diluted with water (100 mL) and extracted with chloroform (10 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as a bright orange oil. Column chromatography immediately following the work-up (10% EtOH in DCM) afforded racemic dioxide as a white solid (5.05 g, 53%); mp 102–103 °C (DCM–EtOAc, lit; [26]105–106 °C); R_f 0.20 (10% EtOH in $CHCl_3$); ν_{max} (cm^{-1}) 1250, 1164, 1062, 999; δ_H (400 MHz, $CDCl_3$) 1.38 (3H, t, *J* 7.3, CH_3), 1.40 (3H, t, *J* 7.3, CH_3), 2.54–2.65 (1H, m, 5-H), 2.67–2.78 (1H, m, 5-H), 3.04–3.19 (2H, m, 4-H and 6-H), 3.51–3.59 (1H, m), 3.79–3.87 (1H, m), 4.24–4.37 (4H, m, 2×CH_2), 4.42 (1H, d, $^2J_{HP}$ 17.1, 2-H).

(+)-Diethyl [(1*R*,3*R*)-1,3-dioxo-1,3-dithian-2-yl]phosphonate 9. (+)-Diethyl tartrate (6.7 mL, 39.1 mmol) and titanium (IV) isopropoxide (2.9 mL, 9.77 mmol) were dissolved in anhydrous dichloromethane (115 mL) at room temperature under nitrogen and stirred for 20 minutes. Diethyl 1,3-dithian-2-ylphosphonate (5.00 g, 19.5 mmol) was added and the reaction mixture was cooled to −40 °C and stirred for one hour. Cumene hydroperoxide (14.9 mL of an 80% solution in hexanes, 78.1 mmol) was added dropwise *via* syringe and the resulting yellow solution was stirred at −40 °C for 10 minutes. The flask was then placed in a freezer (−22 °C) for 72 hours. Distilled water (7 mL) was added to the cold reaction mixture and the mixture was allowed to warm to room temperature with vigorous stirring for one hour. The resultant gel was filtered through a large Celite pad, which was subsequently washed with dichloromethane (500 mL). The filtrate was dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. Column chromatography immediately following work-up (10 : 1 DCM : EtOH) afforded dioxide **9** (2.40 g, 43%) with spectroscopic data identical to that of the racemic material; mp 97–98 °C (DCM–EtOAc);[26] $[\alpha]_D^{22}$ +153 (c = 1.1 in $CHCl_3$).

5,5-Dimethoxypentanal. A 500 mL, three-necked, round-bottomed flask was fitted with a glass frit to admit ozone, a calcium hydride drying tube, a glass stopper and a magnetic stirrer bar and was charged with cyclopentene (5.11 g, 75 mmol), anhydrous dichloromethane (250 mL) and anhydrous methanol (50 mL). The flask was cooled to −78 °C and ozone was bubbled through the solution with stirring until a blue colour remained. Nitrogen was passed through the solution until the blue colour was discharged and then the cold bath was removed. The drying tube and ozone inlet were replaced with a glass stopper and a rubber septum and toluene-*p*-sulfonic acid monohydrate (1.1 g, 5.78 mmol, 10% w/w) was added. The solution was allowed to warm to room temperature and stirred under nitrogen for 90 minutes. Anhydrous sodium hydrogencarbonate (1.94 g, 23.1 mmol) was added to the flask and the mixture was stirred for 15 minutes after which time dimethyl sulfide (12 mL, 150 mmol) was added. After stirring for 12 hours the heterogeneous mixture was concentrated *in vacuo*. Dichloromethane (100 mL) was added and the mixture was washed with water (75 mL). The aqueous layer was extracted with dichloromethane (2 × 100 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (2 : 1 petroleum ether 40–60: diethyl ether) on silica gel gave 4.79 g (44%) of 5,5-dimethoxypentanal as a colourless oil; R_f 0.20 (2 : 1 petroleum ether 40–60); ν_{max} (thin film)/cm^{-1} 1723 (C=O), 1453, 1387, 1127, 1050; δ_H (270 MHz, $CDCl_3$) 1.57–1.79 (4H, m), 2.44–2.52 (2H, m), 3.32 (6H, s, 2×OCH_3), 4.37 (1H, t, *J* 5.6, $CH(OMe)_2$), 9.77 (1H, t, *J* 1.3, CHO); *m*/*z* (EI$^+$) 145 (M$^+$-1, 25), 115 (M$^+$-OMe, 80), 75 (100).

(−)-[1*R*,3*R*]-2-(5,5-Dimethoxypentylidene)-1,3-dioxo-1,3-dithiane 10. To a stirring solution of 5,5-dimethoxypentanal (1.44 g, 9.85 mmol) in anhydrous THF (160 mL) under nitrogen at room temperature was added (+)-(*R*,*R*)-phosphonate (1.89 g, 6.57 mmol) and lithium hydroxide monohydrate (273 mg, 6.50 mmol). The stirring reaction mixture was heated at 70 °C for 4 hours after which time the reaction mixture was allowed to cool to room temperature and the solvent was removed *in vacuo* to give a white solid residue. Column chromatography of the residue (4% EtOH in DCM) afforded **10** as a colourless oil (1.55 g, 85%); Found: C, 47.7; H, 7.4, $C_{11}H_{20}O_4S_2$ requires C, 47.1; H, 7.2; $[\alpha]_D^{22}$ −5.12 (c = 1.25 in CH_2Cl_2); R_f 0.36 (9 : 1 DCM : EtOH); ν_{max} (thin film)/cm^{-1} 2945, 1733, 1614, 1434, 1387, 1126, 1040 (S–O); δ_H (400 MHz, $CDCl_3$) 1.53–1.73 (4H, m, 2 × CH_2), 2.30–2.43 (1H, m), 2.44–2.56 (1H, m), 2.56–2.73 (2H, m), 2.73–2.86 (1H, m), 3.02–3.15 (1H, m), 3.17–3.25 (1H, m), 3.32 (6H, s, 2×OCH_3), 3.60–3.67 (1H, m), 4.36 (1H, t, *J* 5.2, OC*H*O), 6.68 (1H, t, *J* 7.7, C=C*H*); δ_C (100 MHz, $CDCl_3$) 14.9, 24.0, 28.8, 32.0, 49.0, 53.1, 53.2, 55.6, 104.3 (O*C*HO), 140.4 (C=*C*H), 145.0 (*C*=CH); *m*/*z* (EI$^+$) 295 (71), 280 (M$^+$, 60), 249 (88), 231 (38), 71 (100); Found: M$^+$, 280.0802. $C_{11}H_{20}O_4S_2$ requires 280.0803.

(+)-[1*R*,5*S*][1′*R*,3′*R*]-4-Benzyl-1′,3′-dioxo-4-aza-3-oxa-bicyclo[3.3.0]octane-2-spiro-2′-(1′,3′-dithiane) 12. Bis(acetonitrile)palladium(II) chloride (13 mg, 4.92×10^{-5} mol, 1 mol%) was added to a stirring 0.01M solution of (−)-(*R*,*R*)-acetal **10** (1.38 g, 4.92 mmol) in distilled acetone (500 mL) under nitrogen. The orange reaction mixture was heated under reflux at 65 °C for 1 hour after which time no acetal was remaining according to TLC observation. *N*-benzylhydroxylamine hydrochloride (1.02 g, 6.40 mmol) and sodium hydrogencarbonate (1.24 g, 14.8 mmol) were then added to the cool reaction mixture, which was stirred at room temperature under nitrogen for 16 hours. The heterogeneous reaction mixture was filtered through a small Celite pad and washed with dichloromethane. The solvent was removed under reduced pressure to give the crude product as an orange oil. Column chromatography (20 : 1 DCM : EtOH) yielded the optically pure (+)-isoxazolidine **12** as a yellow oil (1.16 g, 70%); $[\alpha]_D^{22}$ +138 (c = 1.3 in CH_2Cl_2); R_f 0.48 (9 : 1 DCM : EtOH); Found: C, 56.6; H, 6.5; N, 4.0. $C_{16}H_{21}NO_3S_2$ requires C, 56.6; H, 6.2; N, 4.1; ν_{max} (thin film)/cm^{-1} 1053 (S–O); δ_H (400 MHz, $CDCl_3$) 1.55–1.61 (1H, m), 1.66–1.82 (2H, m), 1.99–2.16 (3H, m), 2.51–2.60 (1H, m), 2.63–2.72 (2H, m), 2.86–3.01 (2H, m), 3.19 (1H, m), 3.68 (1H, td, *J* 7.2, 1.9), 3.76 (1H, dt, *J* 8.6, 7.0), 4.01 (1H, d, *J* 13.9, CH_aH_bPh), 4.13 (1H, d, *J* 13.9, CH_aH_bPh), 7.25–7.34 (5H, m, C_6H_5); δ_C (100 MHz, $CDCl_3$) 13.3 (t), 25.5 (t), 26.4 (t), 29.5 (t), 42.7 (t), 46.6 (t), 55.2 (d), 61.7 (t), 73.3 (d), 103.4 (q), 127.1 (d,

Ar), 128.0 (d, Ar), 128.3 (d, Ar), 136.4 (q, Ar); *m*/*z* (CI^+) 340 (MH^+, 20), 220 (32), 218 (100), 202 (27), 200 (32); Found: MH^+, 340.1035. $C_{16}H_{22}NO_3S_2$ requires 340.1041.

(+)-(1*R*,2*S*)-*N*-Benzyl-2-aminocyclopentane-1-carboxylic acid 13. A solution of (+)-isoxazolidine **12** (1.11 g, 3.27 mmol) in glacial acetic acid (30 mL) was transferred to a miniclave fitted with a magnetic stirrer bar. Palladium (10% on carbon, 350 mg, 0.327 mmol, 10 mol%) was added to the reaction mixture and the vessel was sealed. After flushing three times with hydrogen the reaction mixture was placed under 7 atmospheres of hydrogen pressure and the vigorously stirring reaction mixture was heated at 40 °C for 48 hours. The cooled reaction mixture was filtered through a Celite pad and washed thoroughly with methanol. The solvent was removed *in vacuo* to give a brown oil. Column chromatography on silica gel (9 : 1 DCM : MeOH) gave the amino acid **13** as an off-white solid (460 mg, 65%). Recrystallisation from hot ethanol gives spectroscopically clean material suitable for debenzylation (360 mg, 50%); mp (EtOH) 179–181 °C; Found: C, 71.2; H, 7.8; N, 6.3, $C_{13}H_{17}NO_2$ requires C, 71.2; H, 7.8; N, 6.4; $[\alpha]_D^{22}$ +8.0 (*c* = 1.0 in CH_3OH); R_f 0.15 (9 : 1 DCM : MeOH); ν_{max} (cm^{-1}) 1584, 1541, 1379; δ_H (400 MHz, CD_3OD) 1.60–1.71 (1H, m), 1.76–1.90 (2H, m), 1.95–2.14 (3H, m), 2.81 (1H, q, *J* 6.9, C*H*CO_2^-), 3.54 (1H, q, *J* 6.9, C*H*NH_2Bn), 4.17 (2H, s, NCH_2Ph), 7.40–7.50 (5H, m, Ph); δ_C (62.9 MHz, D_2O) 21.1 (t), 27.9 (t), 29.0 (t), 45.3 (d), 50.0 (t), 59.2 (d), 129.3 (Ar), 129.6 (Ar), 131.1 (Ar), 181.2 (q); *m*/*z* (EI^+) 91 (100), 106 (82), 132 (27), 146 (100), 190 (11), 219 (M^+, 13); Found: M^+, 219.1249. $C_{13}H_{17}NO_2$ requires 219.1259.

(−)-(1*R*,2*S*)-2-Aminocyclopentane-1-carboxylic acid (cispentacin).[32,33,53] (+)-*cis*-*N*-benzyl-2-aminocyclopentane-1-carboxylic acid **13** (150 mg, 0.685 mmol) and Pearlman's catalyst (50 mg, 0.0685 mmol) were placed in a 250 mL three-neck round-bottomed flask with a magnetic stirrer bar. The flask was fitted with a three-way tap, leading to a balloon of hydrogen, and two rubber septa. After the flask was flushed with nitrogen, ethanol (75 mL) and triethylamine (10 μL, 0.0685 mmol, 10 mol%) were added *via* syringe. The flask was flushed with hydrogen three times and the vigorously stirring reaction mixture was heated at 40 °C for three hours or until no starting material was visible by TLC. After cooling to room temperature the reaction mixture was filtered through a Celite pad and washed with methanol to give a white solid after removal of solvent *in vacuo*. Recrystallisation from a small volume of hot water and acetone followed by filtration and drying *in vacuo* gave 70 mg (80%) of spectroscopically clean (−)-*cis*-2-aminocyclopentane-1-carboxylic acid as a white powder; mp (water–acetone) 194–197 °C (decomp.); $[\alpha]_D^{22}$ −9.0 (*c* = 1.1 in H_2O); Lit;[32] $[\alpha]_D^{20}$ −8.9 (*c* = 1.0 in H_2O); R_f 0.20 (1 : 1 DCM : MeOH); ν_{max}/cm^{-1} 1623, 1580, 1505, 1410, 1386, 1337, 1311, 1122, 1073; δ_H (400 MHz, D_2O, TMS salt) 1.65–1.86 (4H, m), 2.01–2.13 (2H, m), 2.76–2.85 (1H, m, C*H*CO_2H), 3.66–3.73 (1H, m, C*H*NH_2); *m*/*z* (CI^+) 130 (MH^+, 72), 112 (100).

Benzyl (2,2-dimethoxyethyl) carbamate.[59] To a stirred solution of aminoacetaldehyde dimethyl acetal (3.26 mL, 29.9 mmol) in ether (150 mL) was added water (150 mL) and potassium carbonate (12.4 g). The reaction mixture was cooled to 0 °C and benzyl chloroformate (4.28 mL, 29.9 mmol) was slowly added. The reaction mixture was allowed to warm slowly to room temperature and stirring was continued for a further 14 hours, after which time the organic layer was separated and the aqueous layer extracted with ether (3 × 50 mL). The organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated. Column chromatography (1 : 1 petrol : ether) yielded 6.76 g (95%) of the carbamate as a colourless oil; R_f 0.20 (1 : 1 petrol : ether); ν_{max} (thin film/cm^{-1}) 3341 (NH), 1704 (C=O), 1527, 1245, 1060; δ_H (400 MHz, $CDCl_3$) 3.40 (2H, t, *J* 5.8, NCH_2), 3.39 (6H, s, 2×OMe), 4.38 (1H, t, *J* 5.8, C*H*$(OMe)_2$), 4.96 (1H, br, NH), 5.11 (2H, s, OCH_2Ph), 7.30–7.38 (5H, Ph); *m*/*z* (EI^+) 239 (M^+, 1), 207 (12), 164 (10), 91 (65), 75 (100).

Allyl-(2,2-dimethoxyethyl)carbamic acid benzyl ester. A vigorously stirring suspension of freshly washed sodium hydride (1.62 g of a 60% dispersion in mineral oil, 40.6 mmol) in dry DMF (80 mL) was treated with benzyl (2,2-dimethoxyethyl)-carbamate (8.82 g, 36.9 mmol) as a solution in dry DMF (50 mL) at 25 °C by slow addition *via* cannula, under nitrogen. After gas evolution had ceased, the resultant yellow solution was cooled to 0 °C and allyl bromide (3.83 mL, 44.3 mmol) was added drop-wise. The reaction mixture was allowed to warm slowly to room temperature and was stirred under nitrogen for 15 hours, after which time water (50 mL) was added to the reaction mixture and the aqueous layer was extracted with diethyl ether (4 × 100 mL). The organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated. Column chromatography (2 : 1 petrol : ether) furnished 7.40 g (72%) of the alkylated carbamate as a colourless oil; R_f 0.39 (1 : 1 petrol: ether); Found: C, 64.7; H, 7.6; N, 5.2; $C_{15}H_{21}NO_4$ requires C, 64.5; H, 7.6; N, 5.0; ν_{max} (thin film/cm^{-1}) 1678 (C=O), 1456, 1413, 1241, 1122, 1071; δ_H (400 MHz, $CDCl_3$, isolated as a 1 : 1 mixture of rotamers) 3.29–3.42 (8H, m, 2 × OMe and NCH_2-CH$(OMe)_2$), 3.94–4.30 (2H, m, NCH_2CH=), 4.41 (0.5H, t, *J* 4.8, C*H*$(OMe)_2$), 4.52 (0.5H, t, *J* 4.8, C*H*$(OMe)_2$), 5.06–5.20 (4H, m, C=CH_2 and OCH_2Ph), 5.70–5.84 (1H, m, C*H*=CH_2), 7.28–7.40 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 48.2 (t), 48.9 (t), 50.7 (t), 54.7 (CH_3), 67.3 (t), 103.5 (d), 104.0 (d), 116.5 (t), 117.0 (t), 127.8 (d), 128.0 (d), 128.5 (d), 133.6 (d), 133.7 (d), 136.8 (q); *m*/*z* (EI^+) 279 (M^+, 7), 248 (45), 204 (80), 75 (100); Found: M^+, 279.1461. $C_{15}H_{21}NO_4$ requires 279.1471.

***N*-(2,2-Dimethoxyethyl)-*N*-(2-oxoethyl) carbamic acid benzyl ester 21.** A 500 mL 3-necked, round-bottomed flask fitted with a magnetic stirrer bar was charged with allyl-(2,2-dimethoxyethyl)-carbamic acid benzyl ester (5.0 g, 17.9 mmol) and dry DCM (250 mL) under nitrogen. The solution was cooled to −78 °C and ozone was passed through the stirring reaction mixture, which was fitted with a bubbler, using a glass frit for approximately 30 minutes until a pale blue colour persisted in the reaction mixture. Dimethyl sulfide (1.6 mL, 21.5 mmol) was then added to the cold reaction mixture *via* syringe and the reaction mixture was allowed to warm to room temperature and stirred under nitrogen for a further 3 hours. The reaction mixture was washed with water (2 × 50 mL) and the aqueous layer was extracted with DCM (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography (2 : 1 petrol : EtOAc) to give 3.02 g (60%) of the clean aldehyde, isolated as a 1 : 1 mixture of rotamers; R_f 0.21 (2 : 1 petrol : EtOAc); ν_{max} (thin film/cm^{-1}) 1698 (CH=O), 1453, 1120; δ_H (400 MHz, $CDCl_3$, 1 : 1 mixture of rotamers) 3.30 (3H, s, 2 × OMe), 3.38 (3H, s, 2 × OMe), 3.42 (1H, d, *J* 5.1, NCH_2CH$(OMe)_2$), 3.47 (1H, d, *J* 5.1, NCH_2CH$(OMe)_2$), 4.05 (1H, s, NCH_2CHO), 4.09 (1H, s, NCH_2CHO), 4.36 (0.5H, t, *J* 5.1, C*H*$(OMe)_2$), 4.44 (0.5H, t, *J* 5.1, C*H*$(OMe)_2$), 5.13 (1H, s, CH_2Ph), 5.19 (1H, s, CH_2Ph), 7.28–7.38 (5H, m, Ph), 9.49 (0.5H, s, CHO), 9.53 (0.5H, s, CHO); δ_C (100 MHz, $CDCl_3$) 50.6 (t), 51.0 (t), 54.7 (CH_3), 55.0 (CH_3), 58.6 (t), 59.0 (t), 67.8 (t), 67.9 (t), 103.8 (d), 104.0 (d), 128.0 (d), 128.1 (d), 128.2 (d), 128.6 (d), 136.0 (q), 156.1 (q), 156.3 (q), 198.6 (CHO), 198.7 (CHO); *m*/*z* (EI^+) 281 (M^+, 10), 250 (20), 206 (30), 130 (60), 75 (100); Found: M^+, 281.1264. $C_{14}H_{19}NO_5$ requires 281.1263.

(−)-*N*-[2-(1,3-Dioxo-1λ^4,3λ^4-dithian-2-ylidene)ethyl]-*N*-(2,2-dimethoxyethyl)carbamic acid benzyl ester 22. To a stirring solution of aldehyde **21** (1.68 g, 5.98 mmol) in THF (100 mL) under nitrogen was added (+)-phosphonate **9** (1.33 g, 4.60 mmol) and lithium hydroxide monohydrate (190 mg, 4.55 mmol). The flask

was then fitted with a reflux condenser and the stirring reaction mixture was heated at 70 °C under nitrogen for 4 hours, after which time the reaction mixture was allowed to cool to room temperature and concentrated. The residue was then purified by column chromatography (3% MeOH in DCM) to give 1.34 g (71%) of ketene thioacetal **22** as a colourless, viscous oil; $[a]_D^{22}$ −29 (c = 4.6 in $CHCl_3$); R_f 0.40 (9 : 1 DCM : MeOH); Found: C, 51.5; H, 6.2; N, 3.4; $C_{18}H_{25}NO_6S_2$ requires C, 52.0; H, 6.1; N, 3.4; ν_{max} (thin film/cm^{-1}) 1695 (C=O), 1044 (S–O); δ_H (400 MHz, $CDCl_3$, *ca.* 1 : 1 mixture of rotamers) 2.16–2.34 (1.5H, m), 2.61–2.78 (1H, m), 2.86–3.14 (2.5H, m), 3.34–3.50 (8H, m, 2×OCH_3 and $NCH_2CH(OMe)_2$), 3.51–3.63 (1H, m, C*H*SO), 4.04 (0.5H, dd, *J* 15.6, 5.4, NCH_2CH=C), 4.29–4.44 (1.5H, m, NCH_2CH=C and C*H*$(OMe)_2$), 4.48 (0.5H, t, *J* 4.9, C*H*$(OMe)_2$), 4.61 (0.5H, dd, *J* 15.6, 5.4, NCH_2CH=C), 5.07–5.21 (2H, m, OCH_2Ph), 6.56–6.65 (1H, m, CH=C), 7.31–7.40 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.8 (t), 15.0 (t), 46.5 (t), 47.0 (t), 49.0 (t), 49.2 (t), 50.4 (t), 54.8 (CH_3), 55.0 (CH_3), 55.2 (t), 56.1 (t), 67.7 (t), 68.0 (t), 103.7 (d), 103.9 (d), 128.0 (d), 128.3 (d), 128.6 (d), 128.7 (d), 133.2 (d), 136.0 (q), 136.2 (q), 148.0 (q), 155.6 (q); *m*/*z* (EI^+) 430 (70), 415 (M^+, 10), 398 (60), 384 (30), 91 (100); Found: M^+, 415.1125. $C_{18}H_{25}NO_6S_2$ requires 415.1123.

(+)-[1′*R*,3′*R*]-1-Benzyl-1′,3′dioxospiro[1′,3′-dithiane-2′,3-pyrrolo[3,4-*c*]isoxazole]-5-carboxylic acid benzyl ester 23. To a stirring solution of acetal **22** (985 mg, 2.37 mmol) in distilled acetone (250 mL) was added toluene-*p*-sulfonic acid monohydrate (451 mg, 2.37 mmol) under nitrogen. The reaction mixture was heated at 60 °C under a condenser for 3 hours, until no starting material was visible by TLC. The stirring reaction mixture was then cooled to room temperature, after which sodium hydrogencarbonate (1.19 g, 14.2 mmol) was added, followed by *N*-benzylhydroxylamine hydrochloride (416 mg, 2.61 mmol). The reaction mixture was stirred under nitrogen for a further 16 hours at room temperature, after which time the reaction mixture was filtered through a short pad of Celite, washed with DCM and concentrated. The residue was purified by column chromatography (2% MeOH in DCM) to give 820 mg (73%) of isoxazolidine **23** as a white foam; $[a]_D^{22}$ +2 (c = 1.1 in $CHCl_3$); R_f 0.5 (9 : 1 DCM : MeOH); Found: C, 57.7; H, 6.0; N, 5.8; $C_{23}H_{26}N_2O_5S_2$ requires C, 58.2; H, 5.5; N, 5.9; ν_{max} (thin film/cm^{-1}) 1698 (C=O), 1414, 1346, 1049 (S–O); δ_H (300 MHz, $CDCl_3$, 1 : 1 mixture of rotamers) 1.17–1.29 (0.5H, m, SCC*H*CH_2N), 2.07–2.16 (1H, m, SCH_2CH_2), 2.60–2.85 (2H, m), 2.94–3.05 (2H, m), 3.20–3.42 (1H, m), 3.43–3.69 (1.5H, m, SCC*H*CH_2N and BnNC*H*), 3.98–4.16 (4H, m, NCH_2Ph and CH_2NCbz), 4.23–4.40 (2H, m, CH_2NCbz), 5.09–5.21 (2H, m, NCO_2CH_2Ph), 7.28–7.39 (10H, m, Ar); δ_C (100 MHz, $CDCl_3$) 13.7 (t), 15.2 (d), 16.8 (d), 43.8 (t), 45.5 (t), 45.9 (t), 47.3 (t), 49.0 (t), 49.3 (t), 52.8 (d), 53.2 (d), 53.8 (t), 63.0 (t), 67.0 (t), 67.3 (t), 69.5 (d), 70.0 (d), 70.9 (d), 73.0 (t), 104.1 (q), 127.9 (d), 128.2 (d), 128.6 (d), 128.6 (d), 136.0 (q), 136.5 (q), 154.4 (q); *m*/*z* (CI^+) 473 (M^+-1, 40), 427 (40), 383 (60), 337 (92), 311 (72), 293 (82), 286 (40), 245 (95), 196 (90), 91 (100); Found: MH^+, 475.1363. $C_{23}H_{27}N_2O_5S_2$ requires 475.1361.

(+)-*cis*-(4*S*,3R)-4-Benzylaminopyrrolidine-1,3-dicarboxylic acid-1-benzyl ester 24. A solution of (+)-isoxazolidine **23** (292 mg, 0.616 mmol) in glacial acetic acid (12 ml) was transferred to a miniclave fitted with a magnetic stirrer bar. Palladium (10% on carbon, 65 mg, 0.0616 mmol, 10 mol%) was added to the reaction mixture and the vessel was sealed. After flushing three times with hydrogen the reaction mixture was placed under 7 atmospheres of hydrogen pressure and vigorously stirred at room temperature for 24 hours, after which time the reaction mixture was filtered through a Celite pad and washed thoroughly with methanol. The solvent was removed *in vacuo* to give a yellow oil which was purified by column chromatography (6 : 1 DCM : MeOH) to give 144 mg (65%) of the *N*-protected amino acid as a white powder; mp 194–196 °C (MeOH); $[a]_D^{22}$ +176 (c = 0.5 in DMSO); Found: C, 67.7; H, 6.3; N, 8.0; $C_{20}H_{22}N_2O_4$ requires C, 67.8; H, 6.3; N, 7.9; R_f 0.57 (4 : 1 DCM : MeOH); ν_{max} (cm^{-1}) 1698 (C=O), 1586, 1412, 1358, 1099; δ_H (300 MHz, DMSO-d_6) 3.01–3.12 (1H, m, C*H*CO_2H), 3.28–3.68 (5H, m, C*H*NBn and 2×CbzNCH_2), 3.88 (2H, d, *J* 5.7, NCH_2Ph), 5.04–5.08 (2H, m, NCO_2CH_2Ph), 7.30–7.40 (10H, m, Ar); δ_C (75 MHz, DMSO-d_6) 44.2 (d), 45.0 (d), 46.9 (t), 47.4 (t), 49.0 (t), 49.4 (t), 50.2 (t), 50.3 (t), 56.5 (d), 57.4 (d), 65.9 (t), 127.4 (d), 127.4 (d), 127.5 (d), 127.6 (d), 127.8 (d), 128.4 (d), 128.4 (d), 128.5 (d), 128.5 (d), 137.0 (q), 137.9 (q), 138.1 (q), 153.9 (q), 172.9 (q), 173.1 (q); *m*/*z* (CI^+) 355 (MH^+, 60), 91 (100); Found: M^+, 354.1585. $C_{20}H_{22}N_2O_4$ requires 354.1580.

(+)-*cis*-(4*R*,3*R*)-4-Aminopyrrolidine-3-carboxylic acid 19. Carbamate **24** (177 mg, 0.5 mmol) and palladium hydroxide on carbon (90 mg, 25 mol%, 0.125 mmol) were placed in a 250 mL three-neck round bottomed flask under nitrogen with a magnetic stirrer bar. Ethanol (90 mL) was added and the flask was flushed three times with hydrogen gas. The suspension was stirred vigorously and heated at 40 °C for two hours, or until the reaction had gone to completion according to TLC observations. The reaction was allowed to cool to room temperature, filtered through a short Celite pad and washed with methanol. The reaction mixture was concentrated *in vacuo* to give a pale pink oil which was triturated with ethanol until fine crystals were formed. The crystals were triturated with methanol and ethanol and dried *in vacuo* to give 55 mg (85%) of amino acid **25** as white crystals; mp 166–167 °C (1 : 1 MeOH : EtOH); $[a]_D^{22}$ +25.9 (c = 0.9 in MeOH); Found: C, 45.9; H, 7.7; N, 21.1; $C_5H_{10}N_2O_2$ requires C, 46.1; H, 7.7; N, 21.5; R_f 0.18 (3 : 1 : 1 *n*-BuOH:AcOH:H_2O); ν_{max} (cm^{-1}) 2438, 1549, 1398, 1281; δ_H (400 MHz, CD_3OD) 3.02–3.09 (1H, m), 3.12 (1H, dd, *J* 12.1, 4.0), 3.29–3.38 (2H, m), 3.50 (1H, dd, *J* 11.7, 8.4), 3.79 (1H, dd, *J* 10.3, 5.9); δ_C (100 MHz, CD_3OD) 46.5, 51.3, 52.5, 53.3, 177.0; *m*/*z* (electrospray) 131 (MH^+, 91), 115 (22), 101 (46).

Although the HBr salt of the racemate has been described,[56] this is the first report of the free base.

Acknowledgements

We would like to thank Celltech R + D Ltd and the EPSRC for a CASE studentship to S. J. R.

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