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PAPER

Synthesis of dysideaproline E using organocatalysis†

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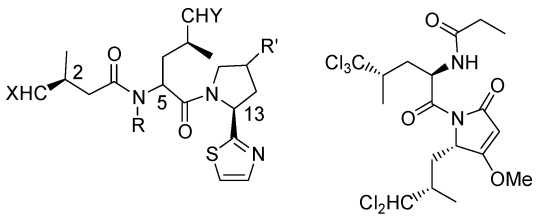
(*S*)-4,4-Dichloro-3-methylbutanoic acid was prepared in 51% overall yield from commercially available starting materials using an organocatalytic transfer hydrogenation to 4,4-dichloro-3-methylbut-2-enal in the key step. The (*S*)-dichloro acid was used as an intermediate in the first total synthesis of dysideaproline E and a diastereomer confirming the structure of the natural product.

Introduction

An intriguing feature of many biologically active natural products is the presence of halogens. In the majority of cases these are located at sites in accord with biohalogenation occurring *via* electrophilic species, and haloperoxidases which catalyze such reactions have been widely studied.[1] However an interesting family of chlorinated natural products exist in which the halogens are located at aliphatic positions remote from activating groups. The mechanism of biohalogenation *via* a remarkable direct chlorination of the pro-*R* methyl group of leucine has been a topic of much recent interest.[2] Examples of such compounds are six related chlorinated natural products, dysideaprolines A to F (**1–6**) isolated from extracts of Dysidea sp (NCI 1517) collected in the Philippines (Fig. 1).[3] The peptide structures (**1–6**) were determined by extensive spectroscopic methods and with the exception of dysideaproline D, **4**, all contain the 4,4-dichloro-3-methylbutanoic acid **8** moiety. This was assigned the *S* configuration by analogy with other chlorinated natural products isolated from *Dysidea* sp.[4] Degradation studies on dysideaproline A, **1**, revealed the *S*-configuration for C-13 but C-5 was not assigned. Further degradation studies on dysideproline E, **5**, and Marfey analysis indicted that it is assembled on an *N*-methyl-D-leucine core *i.e.* C-5 has the *R*-configuration.[3] Interestingly X-ray studies have revealed that sintokamide A (Fig. 1), a further polychlorinated natural product isolated from *Dysidea* sp., contains both D-trichloroleucine and L-dichloroleucine derived fragments and is an inhibitor of the androgen receptor in prostate cancer.[5]

Since these polychlorinated natural products are produced in only small quantities the development of methods for their synthesis is an important goal for structure confirmation and to provide material for full biological assessment. Herein we describe a practical and efficient synthesis of (*S*)-4,4-dichloro-3-methylbutanoic acid **8** using organocatalysis and its use in the first total synthesis of dysideaproline E **5** and the diastereomer **7**



1 X = Y = Cl_2, R = CH_3, R' =H
2 X = Y = Cl_2, R = R' = CH_3
3 X = Y = Cl_2, R = R' = H
4 X = H_2, Y = Cl_2, R = CH_3, R' =H
5 X = Cl_2, Y = H_2, R = CH_3, R' =H
6 X = Cl_2, Y = ClH, R = CH_3, R' =H

Fig. 1 Examples of chlorinated natural products.

Results and discussion

Retrosynthetic analysis of dysideaproline E **5** gives three fragments (**8–10**) which could be coupled *via* standard peptide chemistry. A similar strategy was proposed for the synthesis of diastereomer **7** assembled on an *N*-methyl L-leucine core required for comparison with the natural product **5** (Scheme 1).

The first goal was to develop an efficient synthetic approach to (*S*)-dichloro acid **8**. Previous syntheses of natural products containing a dichloromethyl group have introduced the halogens either by direct conversion of an aldehyde to a dichloride *e.g.* in the synthesis of (2*S*,4*S*)-5,5-dichloroleucine,[6] dysithiazolamide,[7] sintokamide C[8] and nakiteropiosin[9] or *via* enolate chemistry to prepare an α,α-dichloro acid followed by decarboxylation as in the synthesis of dysamide B.[10]

We proposed that an α,α-dichlorination/decarboxylation strategy could be adopted for the synthesis of the target dichloro acid **8** using a conjugate addition to chiral crotonate **11** to create the required stereocentre (Scheme 2). Thus **11** was treated

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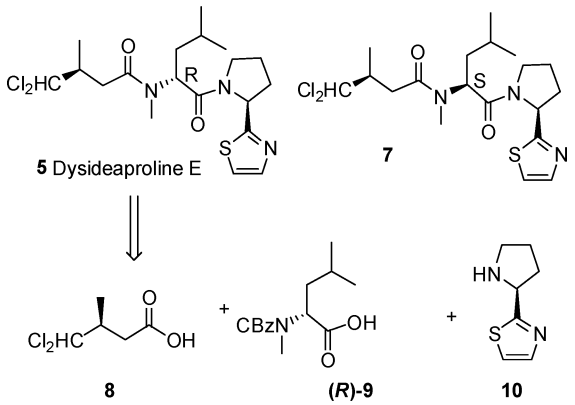
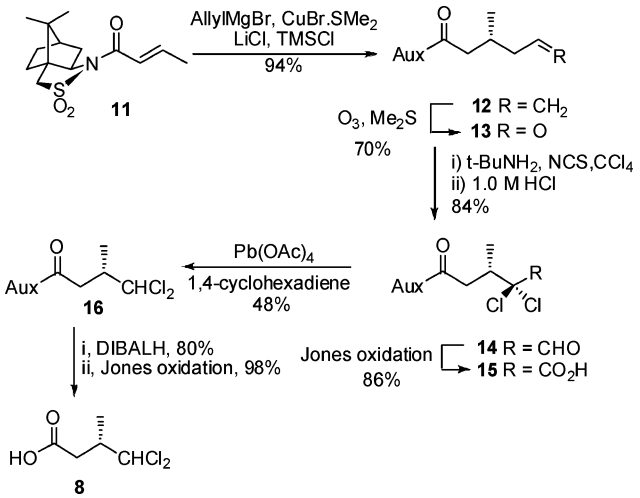
† Electronic supplementary information (ESI) available: Determination of the enantiopurity of acid **8**; NMR spectra of **7**, **8**, **18**, **20** and dysideaproline E **5**. See DOI: 10.1039/c0ob00617c



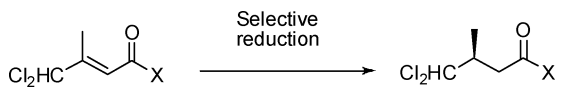
Scheme 1 Retrosynthesis of dysideaproline E.



Scheme 2 Preparation of (*S*)-4,4-dichloro-3-methylbutanoic acid **8**.

with allylmagnesium bromide, $CuBr{\cdot}SMe_2$, LiCl and TMSCl under the conditions reported by Lipshutz and co-workers[11] to give the known[12] alkene **12** in 94% yield. Oxidative cleavage of alkene **12** to aldehyde **13** followed by α,α-dichlorination using *N*-chlorosuccinimide and *tert*-butylamine[13] gave, after hydrolysis, dichloroaldehyde **14** in good yield. Oxidation of **14** gave acid **15** required for the key decarboxylation step in the presence of a hydride source which would not reduce the dichloride moiety. Treatment of **15** with $Pb(OAc)_4$ and 1,4-cyclohexadiene generated the required dichloride **16** and finally cleavage of the auxiliary gave the target dichloro acid **8** in 7 steps and 18% overall yield from crotonyl sultam **11**.

Whilst the above method gave the target **8**, a more concise approach was required to prepare large quantities of the dichloro acid for use in total synthesis. Hence a new strategy was proposed involving the asymmetric reduction of an unsaturated carbonyl compound already containing the requisite dichloromethyl group (Scheme 3). However such a reduction would be challenging as it would be necessary to effect a selective asymmetric conjugate reduction without either competing S_N2' attack (leading to

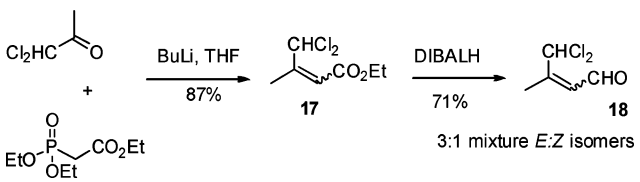


Scheme 3 Proposed new strategy to dichloro acid **8**.

formation of a vinyl chloride) or concomitant reduction of the dichloride.

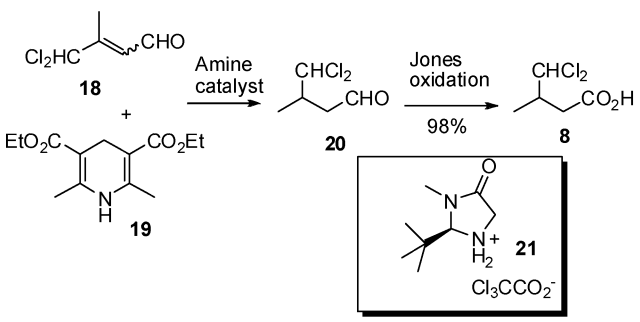
Inspired by biological processes which use enzyme mediated reductions with dihydropyridine cofactors such as NADH to perform highly stereoselective reductions, several research groups have successfully replaced the enzymes and co-factors by small molecule organocatalysts and dihydropyridine analogues. For example List and MacMillan have shown that Hantzsch esters can be used in the presence of chiral amine catalysts to reduce β,β-disubstituted-α,β-unsaturated aldehydes in good yields and high enantioselectivities.[14] The method is versatile and a series of unsaturated aldehydes with aromatic, heteroaromatic and aliphatic groups at the β-position have been reduced successfully.[14,15] Hence we questioned whether the enantio- and chemoselective reduction of a β-dichloromethyl-β-methyl-α,β-unsaturated aldehyde (X═H, Scheme 3) could be achieved using the biomimetic reaction with an inexpensive hydride source and an air stable chiral catalyst.

The required substrate **18** was prepared in 2 steps and 62% overall yield using a Horner–Wadsworth–Emmons chain extension of commercially available α,α-dichloroacetone with triethyl phosphonoacetate followed by DIBALH reduction of the resultant ester **17** (Scheme 4). From the ^{1}H-NMR spectrum of **18** it was apparent that a 3 : 1 mixture of isomers had been formed, with the minor isomer showing an nÖe between the methyl group and olefinic proton in accord with the *Z*-geometry.



Scheme 4 Synthesis of unsaturated aldehyde **18**.

The chemoselectivity of the key reduction step was investigated by treating unsaturated aldehyde **18** with dihydropyridine **19** in the presence of dibenzylamine TFA salt as the catalyst in THF at room temperature (Method 1, Scheme 5). Dichloroaldehyde **20** was isolated as the sole product in a pleasing 80% yield confirming that the required conjugate reduction had occurred selectively. Aldehyde **20** was readily oxidized to acid **8** using Jones reagent. Having established a short and efficient approach to dichloro acid **8**, the reduction of **18** was repeated using dihydropyridine **19** and

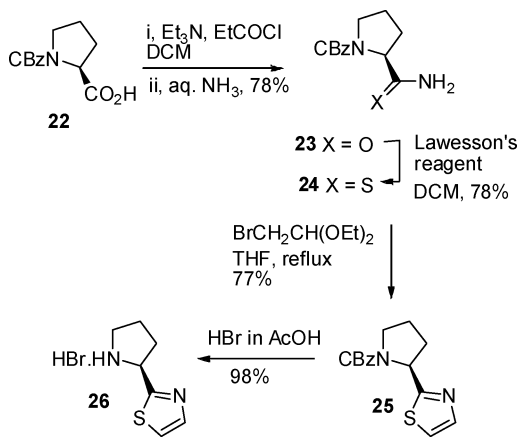


Method 1, Dibenzylamine TFA salt, THF, rt, 80% yield
Method 2, L-proline TFA salt, $CHCl_3$, -30 °C- rt, 82% yield, 34% ee
Method 3, Imidazoline **21**, $CHCl_3$, -20 °C, 85% yield, 90% ee

Scheme 5 Reduction of unsaturated aldehyde **18**.

with L-proline TFA salt as a chiral catalyst (Method 2, Scheme 5) and the resultant aldehyde oxidized to acid **8**. The enantiopurity of acid **8** was determined by coupling to a thiazolidinethione chiral auxiliary (see ESI†) revealing a 34% ee. Hence a more effective chiral catalyst was required. Imidazolines have been used to good effect in the organotransfer hydrogenation of enals.[15,16] In this case reduction of unsaturated aldehyde **18** using imidazolidinone **21** as the catalyst gave significantly better enantioselectivity (90% ee) than with L-proline TFA salt (Method 3, Scheme 5). The absolute configuration was confirmed by comparison with material prepared using the Oppolzer camphorsultam (Scheme 2). Thus a short and efficient synthetic route has been developed giving (*S*)-dichloro acid **8** in 4 steps and 51% overall yield from commercially available starting materials.

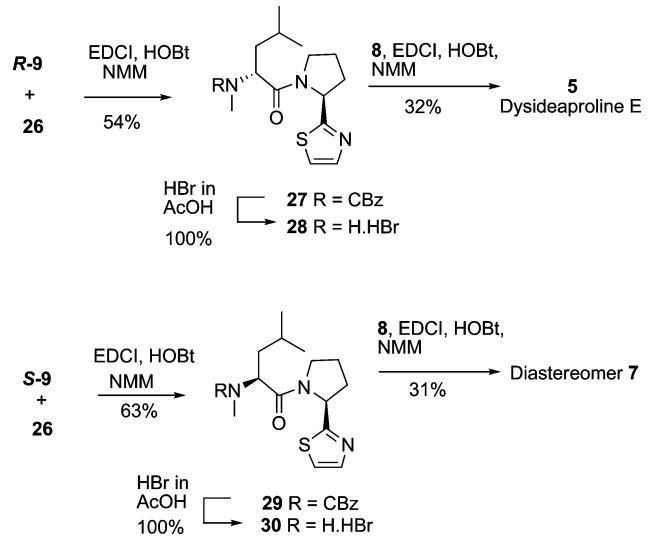
The second component common to both dysideaproline E **5** and its diastereomer **7** was the salt of thiazole **10** which was prepared *via* a modified Hantzsch method (Scheme 6). First CBz L-proline **22** was converted to amide **23** *via* a mixed anhydride and reaction with aqueous ammonia,[17] then treatment with Lawesson's reagent in CH_2Cl_2 at room temperature[18] in dichloromethane gave the required thioamide **24** in 61% overall yield from acid **22**. Reaction of thioamide **24** with α-bromoacetaldehyde diethyl acetal in THF at reflux gave thiazole **25** and finally removal of the CBz protecting group with hydrobromic acid yielded the required proline derivative **26**.



Scheme 6 Preparation of L-proline thiazoline **26**.

To confirm that the stereochemical integrity at C-2 had been maintained throughout the synthetic route the product **26** was compared with racemic material by chiral HPLC. The final compounds needed for the total synthesis of dysideaproline E **5** and diastereomer **7** were *N*-CBz-*N*-methyl D- and L- leucines (***R*-9**) and (***S*-9**). We have previously prepared *S*-**9** from L-leucine in two steps and 74% yield *via* CBz protection followed by *N*-methylation with NaH/MeI in MeCN[10] and the same approach was used herein to prepare both enantiomers.

With all the necessary building blocks in hand for the total synthesis of dysideaproline E **5** and the diastereomer **7**, the first coupling to be investigated was *N*-CBz *N*-methyl D-leucine *R*-**9** with salt **26**. Several standard coupling conditions were explored and EDCI, HOBt, NMM in DCM–DMF gave the best yield (54%) of dipeptide **27** (Scheme 7).



Scheme 7 Completing the total synthesis of dysideaproline E **5** and the diastereomer **7**.

Reaction of the L-leucine derivative *S*-**9** with **26** under the same conditions gave **29** in 63% yield. Deprotection of dipeptides **27** and **29** using hydrobromic acid proceeded cleanly to give the salts **28** and **30** in quantitative yield which were coupled with (*S*)-dichloro acid **8** giving the target compounds **5** and **7**. There was an excellent correlation of the ^{1}H- and ^{13}C- NMR data for synthetic **5** with that of the natural product and the optical rotation, $[\alpha]_D$ +43.8 (*c* 0.02, MeOH) was in accord with the literature value[3] of $[\alpha]_D$ +45.5 (*c* 0.02, MeOH) for dysideaproline E. In contrast diastereomer **7** assembled on the *N*-methyl-L-leucine core had an optical rotation $[\alpha]_D$ –42.6 (*c* 1.0, MeOH).

Conclusions

In conclusion two different strategies for the synthesis of (*S*)-4,4-dichloro-3-methylbutanoic acid **8** have been explored. An operationally simple and efficient approach used an organocatalytic transfer hydrogenation to 4,4-dichloro-3-methylbut-2-enal **18** in the key step giving the target **8** in 51% overall yield from commercially available starting materials. Dichloro acid **8** was used as an intermediate in the first total synthesis of dysideaproline E **5** and its diastereomer **7** confirming the structure of the natural product. This organocatalytic transfer methodology will be of value in the total synthesis of further polychlorinated natural products.

Experimental

General details

All commercially available compounds were used without further purification except where stated. All moisture or air sensitive reactions were carried out in oven-dried glassware under a positive pressure of nitrogen using standard syringe/septa techniques. Anhydrous solvents were obtained by passing through a modified Grubbs system of alumina columns, manufactured by Anhydrous Engineering. When stated, DMF was dried sequentially over three

portions of 10% w/v 3 Å MS beads for 24 h each, and then stored under nitrogen. Petroleum ether is of the 40–60 °C boiling point range. Routine monitoring of reactions was performed using precoated Merck–Kieselgel 60 F_{254} aluminium backed TLC plates. The spots were visualised by UV_{254} light, or potassium permanganate. Flash column chromatography was performed using silica gel (obtained from Fluorochem Ltd.) as the adsorbent. Melting points were determined on an electrothermal apparatus and are uncorrected. Optical rotations were recorded using with the sodium D line (λ = 589 nm) on a Bellingham and Stanley ADP220 polarimeter and the $[\alpha]_D$ values are quoted in units 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer in the solid or liquid state. ^1H and ^{13}C NMR spectra were recorded at using either a Jeol Delta/GX 400 MHz or a Jeol Eclipse 400 MHz spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (J) are in Hertz (Hz). Tetramethylsilane was used as the internal reference for proton and carbon chemical shifts. DEPT 135, COSY, HBQC and HMBC NMR spectra we were routinely used to definitively assign the signals of ^1H and ^{13}C NMR spectra. Electron impact (EI) and chemical ionisation (CI) mass spectra were recorded on a VG Analytical Autospec mass spectrometer. Electrospray (ESI) mass spectra were recorded on a Micromass LCT mass spectrometer or a VG Quattro mass spectrometer. Methane was the ionisation gas used for chemical ionisation.

(1*S*,2*R*)-*N*-[(3′*R*)-Methylhex-5′-enyl]-bornane-10,2-sultam 12

$CuBr{\cdot}Me_2S$ (1.5 eq, 106 mmol, 21.79 g) and LiCl (1.5 eq, 106 mmol, 4.49 g) in THF (100 ml) were pre-stirred for 0.5 h before adding to a solution of allyl magnesium bromide (1.4 eq, 98.84 mmol, 98.84 ml) in THF (300 ml) at −78 °C under N_2. TMSCl (1.5 eq, 106 mmol, 13.45 ml) was added to the reaction mixture followed by the immediate addition of the crotonyl auxiliary **11** (20 g, 70.6 mmol) in THF (140 ml). The reaction mixture was stirred for 4 h before quenching with NH_4Cl/NH_4OH (pH 8, 120 ml) and warming to room temperature overnight. Water (50 ml) and Et_2O (50 ml) were added and the layers separated. The aqueous phase was extracted with Et_2O (3 × 150 ml) and the combined organic layer was washed with water (2 × 70 ml) and brine (70 ml). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. Purification by column chromatography (0–5% EtOAc/petrol) gave alkene **12** as a white solid and single diastereomer (21.6 g, 94%); m.p. 74–76 °C; $[\alpha]_D$ −75.3 (*c* 3.4, $CHCl_3$); lit.[12b] $[\alpha]_D$ −88 (*c* 3.6, $CHCl_3$), δ_H (400 MHz) 0.95 (3H, d, *J* 6, CH_3), 0.96 and 1.18 (each 3H, s, 8-H_3 and 9-H_3), 1.2–2.2 (10H, m, 3-H_2, 4-H, 5-H_2, 6-H_2, 3′-H and 4′-H_2), 2.49 (1H, dd, *J* 16, 8, 2′-*H*H), 2.76 (1H, dd, *J* 16, 6, 2′-H*H*), 3.41 and 3.49 (each 1H, d, *J* 14, 10-H_2). 3.87 (1H, t, *J* 6, 2-H), 5.0 (2H, m, 6′-H_2), 5.75 (1H, ddt, *J* 18, 10, 7, 5′-H); δ_C (100 MHz) 19.6 (CH_3), 19.9 and 20. 9 (C-8 and C-9), 26.5 (C-5), 29.8 (C-3′), 32.9 (C-6), 38.6 (C-2′), 40.9 (C-3), 42.4 (C-4′), 44.8 (C-4), 47.8 (C-1), 48.4 (C-7), 53.1 (C-10), 65.3 (C-2), 116.6 (C-6′), 136.5 (C-5′), 171.5 (CO); ν_{max}/cm^{-1} 3019, 2964, 1720, 1693, 1330 and 1166; *m*/*z* (CI) 326 (MH^+, 100%), 284 (8), 218 (12), 135 (100); found C 62.4, H 8.72, N 3.45, S 9.91, $C_{17}H_{27}NO_3S$ requires C 62.74, H 8.36, N 4.3, S 9.85.

(1*S*,2*R*)-*N*-[(3′*R*)-Methylpent-5′-al]-bornane-10,2-sultam 13

Ozone was bubbled through a solution of alkene **12** (21.6 g, 66.36 mmol) in DCM (200 ml) at −78 °C until a permanent blue colour persisted. DMS (10 eq, 663.7 mmol, 50 ml) was added and the reaction mixture warmed to room temperature before heating under reflux overnight. The reaction mixture was allowed to cool before adding water (50 ml). The layers were separated and the aqueous layer extracted with DCM (3 × 60 ml). The combined organic layer was washed with water (35 ml), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. Purification by column chromatography (20% EtOAc/petrol) gave aldehyde **13** as a white solid (15.03 g, 70%); m.p. 60–72 °C; $[\alpha]_D$ −83.8 (*c* 2.1, $CHCl_3$); δ_H (400 MHz) 0.96 and 1.15 (each 3H, s, 8-H_3 and 9-H_3), 1.05 (3H, d, *J* 6, CH_3), 1.8–2.2 (7H, m, 3-H_2, 4-H, 5-H_2 and 6-H_2), 2.34–2.4 (1H, m, 3-H′), 2.5 (1H, ddd, *J* 16, 7, 2, 4′-*H*H), 2.72 (3H, m 4′-H*H* and 2′-H_2), 3.41 and 3.49 (each 1H, d, *J* 14, 10-H_2), 3.87 (1H, t, *J* 6, 2-H), 9.7 (1H, t, *J* 2, 5′-H); δ_C (100 MHz) 14.2 (CH_3), 19.9 and 20.8 (C-8 and C-9), 25 (C-3′), 26.5 (C-5), 32.9 (C-6), 38.6 (C-3), 41.9 (C-2′), 44.7 (C-4), 47.8 (C-7), 48.5 (C-1), 50.3 (C-4′), 53 (C-10), 65.3 (C-2), 170.5 and 201.5 (CO); ν_{max}/cm^{-1} 2962, 1705, 1326 and 1166; *m*/*z* (CI) 328 (MH^+, 53%), 257 (13), 135 (46) and 113 (100); Found C 58.38, H 7.57, N 3.93, S 9.7, $C_{16}H_{25}NO_4S$ requires C 58.69, H 7.7, N 4.28, S 9.79.

(1*S*,2*R*)-*N*-[(3′S)-Methylpent-4′4′-dichloro-5′-al]-bornane-10,2-sultam 14

tert-Butylamine (1eq, 29.95 mmol, 3.15 g) was added to a solution of aldehyde **13** (9.81 g, 29.95 mmol) in CCl_4 (100 ml) in the presence of molecular sieves (4 Å). The reaction mixture was stirred for 1.5 h before adding additional CCl_4 (20 ml) and magnesium sulfate. The reaction mixture was filtered and NCS (2.2 eq, 65.89 mmol, 8.80 g) was added in one portion and the reaction mixture stirred overnight. The succinimide was removed by filtration and the filtrate concentrated *in vacuo*. The product was hydrolysed by stirring in HCl (0.1 M, 260 ml) for 48 h. After this time, Et_2O (250 ml) was added and the layers separated. The aqueous layer was extracted with Et_2O (3 × 150 ml), the combined organic layers were washed with water (70 ml), dried over anhydrous magnesium sulfate and the solvent removed *in vacuo* to give dichlorinated aldehyde **14** as a white solid (9.89 g, 84%); m.p. 98–101 °C; $[\alpha]_D$ −72 (*c* 2, $CHCl_3$); δ_H (400 MHz) 0.99 and 1.1 (each 3H, s, 8-H_3 and 9-H_3), 1.13 (3H, d, *J* 7, CH_3), 1.2–2.1 (7H, m, 3-H_2, 4-H, 5-H_2 and 6-H_2), 2.8 (1H, dd, *J* 17, 8, 2′-*H*H), 3.13 (1H, dd, *J* 17, 4, 2′-H*H*), 3.20 (1H, m, 3′-H), 3.45 and 3.53 (each 1H, d, *J* 14, 10-H_2), 3.87 (1H, dd, *J* 8, 5, 2-H), 9.15 (1H, s, 5′-H); δ_C (100 MHz) 16.0 (CH_3), 19.9 and 20.8 (C-8 and C-9), 26.5 (C-5), 32.9 (C-6), 38.3 (C-3), 38.4 (C-2′), 38.8 (C-3′), 44.7 (C-4), 47.9 (C-7), 48.6 (C-1), 53 (C-10), 65.3 (C-2), 93.5 (C-4′), 169 and 184 (CO); ν_{max}/cm^{-1} 2969, 1740, 1694, 1333 and 1135; *m*/*z* (CI) 396 (MH^+, 92%), 362 (52), 216 (30), 135 (100); $C_{16}H_{24}Cl_2NO_4$ requires 396.0803, found 396.0800.

(1*S*,2*R*)-*N*-[(3′*S*)-4′,4′-Dichloro-3′-methylpentan-5′-oic acid]-bornane-10,2-sultam 15

Dichlorinated aldehyde **14** (7.79 g, 19.66 mmol) was dissolved in acetone (130 ml) and Jones reagent (20 ml) was added. The reaction was monitored by TLC and after 3 h had reached completion.

The reaction mixture was quenched with MeOH (25 ml) and the solvent removed *in vacuo*. Water (40 ml) was added and the aqueous layer extracted with EtOAc (3 × 70 ml). The combined organic layer was washed with water (2 × 30 ml), dried over anhydrous magnesium sulfate and the solvent removed *in vacuo*. Purification by column chromatography (20–50% EtOAc/petrol) gave acid **15** as a white solid (7.03 g, 86%); m.p. 174–176 °C; $[\alpha]_D$ −80.4 (*c* 2.1, $CHCl_3$), δ_H (400 MHz) 0.97 and 1.15 (each 3H, s, 8-H_3 and 9-H_3), 1.2 (3H, d, *J* 7, CH_3), 1.3–2.1 (7H, m, 3-H_2,4-H, 5-H_2, 6-H_2), 2.9 (1H, dd, *J* 17, 9, 2′-*H*H), 3.13 (1H, dd, *J* 17, 2, 2′-H*H*), 3.3 (1H, m, *J* 3, 3′-H), 3.44 and 3.54 (each 1H, d, *J* 14, 10-H_2), 3.9 (1H, dd, *J* 8, 5, 2-H), 9.4 (1H, br s, CO_2H); δ_C (100 MHz) 16.2 (CH_3), 19.3 and 20.9 (C-8 and C-9), 26.5 and 26.7 (C-3 and C-5), 32.9 (C-6), 38.4 (C-2′), 41.8 (C-3′), 44.7 (C-4), 47.9 (C-7), 48.6 (C-1), 53.1 (C-10), 65.4 (C-2), 88.8 (C-4′), 167.5 and 169.8 (CO); ν_{max}/cm^{-1} 2971, 1739, 1670, 1371 and 1136; *m*/*z* (CI) 412 (MH^+, 10%), 376 (6), 339 (8), 295 (46), 135 (100), 216 (40); Found C 46.9, H 5.69, N 3.41, S 7.52, Cl 17.01, $C_{16}H_{23}Cl_2NO_5S$ requires C 46.61, H 5.62, N 3.4, S 7.78, Cl 17.2.

(1*S*,2*R*)-*N*-[(3′*S*)-4′,4′-Dichloro-3′methylbutane]-bornane-10,2-sultam 16

Dichlorinated acid **15** (0.54 g, 1.3 mmol) was dissolved in MeCN (15 ml) under N_2 and stirred for 5 mins. $Pb(OAc)_4$ (1eq, 1.3 mmol, 0.581 g) and 1,4-cyclohexadiene (1.2 eq, 1.6 mol, 0.15 ml) were then added and the reaction mixture heated at reflux for 2 h. After this time the reaction mixture was cooled before adding further $Pb(OAc)_4$ (1 eq) and 1,4-cyclohexadiene (1.2 eq) and heating at reflux for an additional 1 h. The reaction mixture was diluted with Et_2O (20 ml) and washed with perchloric acid (7%, 2 × 15 ml). The aqueous layer was extracted with Et_2O (2 × 15 ml) and the combined organic layer was washed with $NaHCO_3$ (2 × 20 ml). The aqueous layer was extracted with Et_2O (1 × 20 ml) and the combined organic layers were washed with water (10 ml). The combined organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. Purification by column chromatography (5–10% EtOAc/petrol) gave dichloride **16** as a white solid (0.32 g, 48%); m.p. 132–135 °C; $[\alpha]_D$ −82.9 (*c* 2.2, $CHCl_3$); δ_H (400 MHz) 0.97 and 1.15 (each 3H, s, 8 and 9-CH_3), 1.2 (3H, d, *J* 6, CH_3), 1.3–2.1 (7H, m, 3-H_2, 4-H, 5-H_2 and 6-H_2), 2.79–2.85 (2H, m, 3-H′ and 2′-*H*H), 3.0 (1H, dd, *J* 19, 8, 2′-H*H*), 3.44 and 3.51 (each 1H, d, *J* 14, 10-H_2), 3.87 (1H, dd, *J* 8, 5, 2-H), 5.97 (1H, d, *J* 3, 4′-H); δ_C (100 MHz) 15.1 (CH_3), 19.9 and 20.8 (C-8 and C-9), 26.5, 26.7 and 32.9 (C-3, C-5 and C-6), 38.6 (C-2′), 40.3 (C-3′), 44.7 (C-2), 47.9 (C-4), 48.6 (C-7), 53 (C-10), 65.3 (C-1), 76.7 (C-4′), 169.8 (CO); ν_{max}/cm^{-1} 2963, 1691, 1328 and 1133; *m*/*z* (CI) 368 (MH^+, 94%), 332 (80), 151 (42) and 135 (100); $C_{15}H_{24}Cl_2NO_3S$ requires 368.0849, found 368.0853.

Ethyl 4,4-dichloro-3-methylbut-2-enoate 17

Triethyl phosphonoacetate (0.78 ml, 3.9 mmol) in THF (10 ml) was cooled to 0 °C under nitrogen and n-butyllithium in hexane (2.5 M, 1.58 ml, 3.9 mmol) was added dropwise. The solution was stirred for 20 min and dichloroacetone (0.5 g, 3.9 mmol) in THF (10 ml) was added dropwise. The solution was stirred at room temperature and monitored by TLC. After 2 h it was quenched with water (15 ml). The mixture was extracted with EtOAc (3 × 30 ml), dried over $MgSO_4$, filtered and the solvent evaporated *in vacuo* to give the crude product which was purified by column chromatography using EtOAc/petroleum ether 1 : 9 as the eluent to give ester **17** as a 3 : 1 mixture of *E*/*Z* isomer (0.67 g, 87%); ν_{max}/cm^{-1} 2979, 1745, 1320, 750; major isomer δ_H (400 MHz, $CDCl_3$), 1.29 (3H, t, *J* 7.0, OCH_2CH_3), 2.45 (3H, s, CH_3), 4.21 (2H, q, *J* 7.0, OCH_2CH_3), 6.0 (1H, br. s), 6.18 (1H, s); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 77.1 (C-4), 118.3 (C-2), 151.9 (C-3), 165.4 (CO); minor isomer, δ_H (400 MHz, $CDCl_3$), 1.29 (3H, t, *J* 7.0, OCH_2CH_3), 2.34 (3H, s, CH_3), 4.21 (2H, q, *J* 7.0, OCH_2CH_3), 5.71 (1H, s), 7.99 (1H, s); δ_C (100 MHz, $CDCl_3$) 13.2 (CH_3), 67.3 ($CHCl_2$), 118.0 (C-2), 151.7 (C-3), 164.7 (CO); *m*/*z* (CI) 201 (4%), 199 (25), 197 (MH^+ 38), 196 (8), 161 (68), 133 (69), 85 (65), 83 (100); $C_7H_{11}O_2Cl_2$ requires 197.0129, found 197.0136.

4,4-Dichloro-3-methylbut-2-enal 18

Diisobutylaluminium hydride (3.28 ml, 3.28 mmol, 1.1 eq) was added to a stirring solution of ester **17** (0.588 g, 2.98 mmol) in dry dichloromethane (10 ml) at −78 °C, under nitrogen over a period of 15 min. The reaction mixture was stirred at −78 °C for 0.5 h and was then quenched with Rochelle's salt (5 ml). The mixture was allowed to stir for 3 h at room temperature, the layers separated and the aqueous layer extracted with ethyl acetate (3 × 10 ml). The organic layers were combined, washed with brine (50 ml) and dried over magnesium sulfate. The solvent was removed *in vacuo* to give the crude product which was purified using column chromatography eluting with 5% ethyl acetate/petrol to give unsaturated aldehyde **18** as a 3 : 1 mixture of *E*/*Z* isomers as yellow oil (0.32 g, 71%); ν_{max}/cm^{-1} 2789, 1738, 1645, 750; major isomer, δ_H (400 MHz, $CDCl_3$), 2.45 (3H, d, *J* 1.3, CH_3), 6.08 (1H, br d, *J* 7.3, 2-H), 6.18 (1H, s, 4-H) 10.06 (1H, d, *J* 7.3, 1-H); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 79.6 (C-4), 128.7 (C-2), 156.3 (C-3), 193.3 (CO); minor isomer, δ_H (400 MHz, $CDCl_3$), 2.34 (3H, d, *J* 1.3, CH_3), 5.94 (1H, br. d, *J* 5.3, 2-H), 7.46 (1H, s, 4-H), 9.90 (1H, d, *J* 5.3, 1-H); δ_C (100 MHz, $CDCl_3$) 13.2 (CH_3), 79.0 ($CHCl_2$), 128.5 (C-2), 155.5 (C-3), 189.4 (CO); *m*/*z* (CI) 157 (8%),155 (22), 153 (MH^+ 58), 117 (85), 113 (52), 97 (79), 89 (100); $C_5H_7O^{35}Cl_2$ requires 152.9870, found 152.9874.

(*S*)-4,4-Dichloro-3-methylbutanal 20

A solution of unsaturated aldehyde **18** (0.814 g, 5.32 mmol) dissolved in chloroform (5 ml) was cooled to −20 °C in a dry ice/acetone bath. To this solution was added the trichloroacetic acid salt of (*R*)-2-*tert*-butyl-3-methylimidazolidin-4-one **21** (0.287 g, 1.06 mmol) and Hantzsch ester **19** (1.98 g, 6.33 mmol). The resulting yellow suspension was stirred at −20 °C for 4 h and allowed to warm room temperature overnight. The reaction mixture was poured into HCl solution (10%, 30 ml) and diluted with ether (30 ml). The organic layer was washed 4 times with HCl solution (10%, 30 ml) and once with a saturated aqueous solution of $NaHCO_3$ (30 ml). The resulting organic solution was dried with magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography using 5% ether in pentane to give aldehyde **20** as a yellow oil (0.694 g, 85%); $[\alpha]_D^{23}$ −6.0 (*c* 1, $CHCl_3$). ν_{max}/cm^{-1} 2789, 1730, 750; δ_H (270 MHz, $CDCl_3$), 1.25 (3H, d, *J* 6.8, CH_3), 2.45 (1H, dd, *J* 10.5, 7.3, 2-*H*H), 2.84–2.95 (2H, m, 2-H*H*, 3-H), 5.89 (1H, d, *J* 3.3, 4-H), 9.81 (1H, br. s, 1-H),

δ_C (67.5 MHz, $CDCl_3$), 15.8 (CH_3), 38.4 (C-3), 46.4 (C-2), 76.6 (*C*HCl_2), 199.8 (C-1), *m/z* (CI) 157 (5%), 155 (MH^+ 10), 117 (55), 89 (55), 83 (100); $C_5H_9OCl_2$ requires 155.0025, found 155.0030

4,4-Dichloro-3-methylbutanoic acid 8

Jones reagent was prepared by dissolving chromium trioxide (25 g, 250 mmol) in a solution of concentrated sulfuric acid (20 ml) and distilled water (70 ml). Aldehyde **20** (0.077 g, 0.49 mmol) was dissolved in acetone (10 ml) and Jones reagent was added dropwise until an orange colour persisted. The reaction was stirred for 15 min, after which time methanol (5 ml) was added dropwise to quench the reaction followed by water (5 ml). The solvent was removed *in vacuo* and the green-black residue diluted with water (5 ml) and extracted with ethyl acetate (3 × 10 ml). The combined organic extract was dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. Purification by column chromatography (20% EtOAc/petrol + 1% AcOH) gave dichlorinated acid **8** as a clear liquid (0.083 g, 98%); $[\alpha]_D^{23}$ −8.2 (*c* 1, $CHCl_3$), $[\alpha]_D^{23}$ −7.8 (*c* 1, Et_2O) ν_{max}/cm^{-1} 3400–3200, 2979, 1705, 750; δ_H (270 MHz, $CDCl_3$), 1.25 (3H, d, *J* 6.9, CH_3), 2.45 (1H, dd, *J* 10.5, 7.3,2-*H*H), 2.61–2.80 (2H, m, 2-H*H*, 3-H), 5.89 (1H, d, *J* 3.3, 4-H), 10.5 (1H, br s, OH), δ_C (100 MHz, $CDCl_3$), 15.4 (CH_3), 36.7 (C-3), 40.5 (C-2), 76.6 (*C*HCl_2), 178.1 (C-1), *m/z* (CI) 175 (2%) 173 (10), 171 (MH^+ 15),135 (35), 99 (100), 83 (65); $C_5H_9O_2{}^{35}Cl_2$ requires 170.9972, found 170.9980

***N*-Methyl-*N*-(benzyloxycarbonyl)-D-leucine (*R*)-9**

Cbz-D-Leucine (5 g, 18 mmol) was dissolved in acetonitrile (60 ml) and cooled to 0 °C. Sodium hydride (2.17 g, 56.5 mmol) was added followed by dropwise addition of methyl iodide (8 ml, 128 mmol) to form a thick liquid. The reaction mixture was stirred overnight. EtOAc (70 ml) and water (25 ml) were added and the solvent evaporated off. The crude mixture was dissolved in ether (30 ml) and water (30 ml), the layers were separated and the aqueous layer was washed with ether (2 × 20 ml). The organic layers were combined and washed with saturated $NaHCO_3$ (2 × 15 ml). All the aqueous layers were combined and acidified to pH 2 using HCl (1 M), extracted with EtOAc (3 × 35 ml) and all organic layers were combined and washed with water (15 ml), dried over magnesium sulfate and the solvent evaporated to give a dark orange viscous oil. This was purified by column chromatography (loaded on in DCM) using eluent 20% EtOAc:petrol to give **(*R*)-9** as a white solid (4.7 g, 90% yield); mp 64–69 °C (no lit. mp reported); $[\alpha]_D^{23}$ + 25.4 (*c* 1, EtOH) [lit.[10] +23 (*c* 1, EtOH)]; δ_H (400 MHz), major rotamer) 0.95 and 0.98 (each 3H, d, *J* 6, 2 × CH_3), 1.58 (1H, m, 4-H), 1.63–1.80 (2H, m, 3-H_2), 2.89 (3H, s, N-CH_3), 4.93 (1H, t, *J* 7.9 (minor rotamer, dd, *J* 10,5 and 4.5), 2-H), 5.1–5.2 (2H, m, OCH_2), 7.3–7.4 (5H, m, PhH); δ_C (100 MHz both rotamers) 21.0 and 21.3 (CH_3), 23.1 (CH_3), 24.7 and 24.9 (C-4), 30.4 and 30.7 (NCH_3), 37.3 and 37.7 (C-3), 56.6 and 56.8 (C-2), 67.6 (OCH_2) 127.7–128.4 (PhH), 136.5 (*ipso*), 157.2 and 177.3 (CO).

***N*-(Benzyloxycarbonyl)-L-proline thiazole 25**

Method 1. α-Chloroacetaldehyde (0.168 g, 2.27 mmol) and potassium hydrogen carbonate (ground, 0.227 mg, 2.27 mmol) were added to a solution of the crude thioamide **24** (0.15 g, 0.57 mmol) in dimethoxyethane (5 ml) and stirred at room temperature overnight under nitrogen. LCMS showed starting material remaining and the mixture was therefore stirred for a further 6 h at room temperature. Again starting material was still remaining, so further $KHCO_3$ (1.14 g, 11.36 mmol) and $ClCH_2CHO$ (0.084 g, 1.14 mmol) were added. The reaction mixture was left to stir at room temperature for a further 48 h. LCMS analysis showed no starting material remaining. The reaction mixture was then passed through a pad of celite and rinsed with diethyl ether (15 ml). The solution was concentrated to give a yellow oil which was dissolved in DME (5 ml) and cooled to 0 °C. Trifluoroacetic anhydride (2.36 ml, 17.04 mmol) was added followed by pyridine (2.021 ml, 24.99 mmol). The reaction mixture turned a dark red and was concentrated *in vacuo* after 10 min. The residue was taken up in chloroform (10 ml) and washed with water (2 × 10 ml), and dried over magnesium and evaporated to give the crude product which was purified by column chromatography using 20% acetone:petrol to give thiazole **25** as a brown liquid (1.19 g, 69%); $[\alpha]_D^{23}$ −76.8 (*c* 1, $CHCl_3$); ν_{max}/cm^{-1} 3404, 2976, 2883, 1705, 1499 and 1110; δ_H (400 MHz, both rotamers) 1.99 (2H, m, 4-H_2), 2.33 (2H, m, 3-H_2), 3.57–3.72 (2H, m, 5-H_2), 5.1–5.18 (2H, m, O-CH_2), 5.31 (1H, m, 2-H), 7.15–7.38 (6H, m, PhH and 7-H), 7.71 (1H, m, 6-H); δ_C (100 MHz, both rotamers) 22.9 and 23.9 (C-4), 32.7 and 34.1 (C-3), 46.7 and 47.1 (C-5), 59.2 (C-2), 67.0 (OCH_2), 118.4 and 118.6 (C-7), 127.7–128.4 (10 × C-Ph), 136.4 and 136.7 (C-*ipso*), 142.0 (C-6), 155.1 and 155.1 (CO), 174.5 and 173.4 (C-1); LCMS-*m/z* (ESI) 289 (MH^+), $C_{15}H_{17}O_2$ requires 289.099 found 289.1011.

Method 2. A solution of thioamide **24** (0.75 g, 2.8 mmol) and diethyl bromoacetaldehyde acetal (0.43 ml, 2.8 mmol) in THF was heated to reflux for 7 h. After the solvent had then been evaporated, the residual oil was washed with petroleum ether (30 ml) to remove the excess acetal. The mixture was diluted with aqueous sodium bicarbonate (10 ml) and extracted with ethyl acetate (3 × 20 ml). The combined organic extract was washed with water, dried over $MgSO_4$ and the solvent was evaporated. The product was purified by column chromatography using 20% acetone:petrol to give thiazole **25** (621 mg, 77%).

2-((*S*)-2-Pyrrolidinyl)-1,3-thiazole hydrobromic salt 26[19]

Thiazole **25** (222 mg, 0.77 mmol) was dissolved in HBr (3 ml, 33% in acetic acid) and stirred for 4 h at room temperature. The reaction mixture was concentrated *in vacuo* and dried in the vacuum oven at 60 °C overnight to give salt **26** as an orange solid (179 mg, 98%); $[\alpha]_D^{23}$ +28.5 (*c* 1, H_2O); ν_{max}/cm^{-1} 2860, 2440, 1564, 1368 and 1286 δ_H (400 MHz, D_2O) 2.21–2.48 (3H, m, 3H*H* and 4-H_2), 2.65–2.77 (1H, m, 3*H*H), 3.54–3.63 (2H, m, 5-H_2), 5.23 (1H, t, *J* 7.8, 2-H), 7.77 (1H, d, *J* 3.4, 7-H), 7.93 (1H, d, *J* 3.4, 6-H); δ_C (100 MHz) 23.5 (C-4), 30.9 (C-3), 45.9 (C-5), 59 (C-2), 122.3 (C-7), 142.8 (C-6), and 164.4 (C-1); *m/z* (ESI) 289 (MH^+); $C_{15}H_{17}O_2NS$ requires 289.0999 found 289.1011.

***N*-Methyl-[(*R*)-3-methyl-1-((*S*)-thiazol-2-yl-pyrrolidine-1-carbonyl)-butyl]-carbamic acid benzyl ester 27**

L-Proline thiazole hydrobromic salt **26** (170 mg, 0.72 mmol) and *N*-Cbz-*N*-Me-D-leucine (*R*)-**9** (180 mg, 0.72 mmol) formed a suspension with DCM–DMF (5 : 1 ratio, 11 ml). The reaction mixture was cooled to 0 °C and EDCI (2 eq, 277 mg, 1.45 mmol),

HOBt (1.1 eq, 108 mg, 0.79 mmol) and NMM (1.5 eq, 0.12 ml, 1.08 mmol) were added and the reaction mixture was stirred at 0 °C for 1 h and then at room temperature overnight. The reaction was quenched with HCl (1 M, 5 ml) and diluted with EtOAc (15 ml). The mixture was separated and the organic layer was then washed with $NaHCO_3$ (10 ml), brine (10 ml), water (10 ml), dried over magnesium sulfate and the solvent evaporated *in vacuo* to give the crude product which was purified with flash chromatography eluting with 20% acetone/petrol to give **27** as viscous white oil (156 mg, 54%); $[\alpha]_D^{23}$ +18.8 (*c* 1, MeOH); ν_{max}/cm^{-1} 2955, 2875, 1697, 1654; δ_H (400 MHz, major rotamer) 0.95 and 0. 97 (6H, 2 × d, *J* 6.6, 2 × CH_3), 1.3 and 1.73 (2H, m, 3-H_2), 1.5 (1H, m, 2-H), 1.97 (2H, m, 10-H_2), 2.05–2.39 (2H, m, 9-H_2), 2.83 (3H, s, N-CH_3), 3.45–3.78 (2H, m, 11-H_2), 5.09 (1H, m, 4-H), 5.22 (2H, m, OCH_2), 5.5 (1H, dd, *J* 7.9, 2.8, 8-H), 7.17 (1H, d, *J* 3.3, 14-H), 7.67 (1H, d, *J* 3.3, 13-H); δ_C (100 MHz major rotamer) 22.3 (C-1), 23.0 (C-7), 24.4 (C-10), 24.5 (C-2), 29.3 (C-6), 31.5 (C-9), 37.3 (C-3), 46.7 (C-11), 54.6(C-4), 58.6 (C-8), 67.3 (OCH_2), 118.7 (C-14), 127.6-128.8 (PhH), 136.7 (*ipso*-C), 142.2 (C-13), 156.6 (CO_2CH_2), 170 (CO), 172.2 (C-12), *m*/*z* (ESI) 416 (MH^+); $C_{22}H_{30}O_3N_3S$ requires 416.2008 found 416.2005.

N-Methyl-[(*S*)-3-methyl-1-((*S*)-thiazol-2-yl-pyrrolidine-1-carbonyl)-butyl]-carbamic acid benzyl ester 29

The above method was repeated with *N*-Cbz-*N*-Me-L-leucine (*S*)-**9** to give **29** as a viscous yellow oil (182 mg, 63%); $[\alpha]_D^{23}$ −99.1 (*c* 1, MeOH); ν_{max}/cm^{-1} 2955, 2875, 1697, 1654; δ_H (400 MHz, major rotamer) 0.95 and 0. 97 (6H, 2 × d, *J* 6.6, 2 × CH_3), 1.57 (1H, m, 2-H), and 1.56 and 1.72 (2H, m, 3-H_2), 1.5–1.64 and 2.0–2.16 (2H, m, 10-H_2), 1.96–2.08 and 2.2–2.35 (2H, m, 9-H_2), 2.05–2.39 (2H, m, 9-H_2), 2.97 (3H, s, N-CH_3), 3.78 (2H, m, 11-H_2), 5.12 (1H, dd, J 9.7, 5.2, 4-H), 5.17 (2H, m, OCH_2), 5.5 (1H, dd, *J* 7.9, 2.8, 8-H), 7.17 (1H, d, *J* 3.3, 14-H), 7.67 (1H, d, *J* 3.3, 13-H); δ_C (100 MHz major rotamer) 22.3 (C-1), 23.0 (C-7), 24.4 (C-10), 24.5 (C-2), 29.3 (C-6), 31.5 (C-9), 37.3 (C-3), 46.7 (C-11), 54.6(C-4), 58.6 (C-8), 67.3 (OCH_2), 118.7 (C-14), 127.6–128.8 (PhH), 136.7 (*ipso*-C), 142.2 (C-13), 156.6 (CO_2CH_2), 170 (CO), 172.2 (C-12), *m*/*z* (ESI) 416 (MH^+); $C_{22}H_{30}O_3N_3S$ requires 416.2008 found 416.2005.

4-(*R*)-4-*N*-Methyl-2-methylamino-1-((*S*)-2-thiazol-2-yl-pyrrolidin-1-yl)-pentan-1-one 28

Amide **27** (167 mg, 0.4 mmol) was dissolved in HBr (2.5 ml, 33%w/w in acetic acid) and stirred at room temperature for 4 h. The acetic acid was evaporated off and the residue dried in the vacuum oven at 60 °C for 3 days to give **28** as an orange sticky solid in quantitative yield (139 mg, 100%); ν_{max}/cm^{-1} 3323, 2955, 1651, 1551, 1385 and 1102; δ_H (400 MHz, D_2O) 1.06 and 1.09 (6H, 2 × d, *J* 6, 2 × CH_3), 1.86 (3H, m, 2-H and 3-H_2), 2.24 (3H, m, 9*H*H and 10-H_2), 2.55 (1H, m, 9H*H*), 2.74 (3H, s, N-CH_3), 3.78 (1H, m, 11-*H*H), 4.16 (1H, m, 11-H*H*), 4.41 (1H, dd, *J* 7.6, 5, 4-H), 5.61 (1H, dd, *J* 8, 2.4, 8-H), 7.74 (1H, d, *J* 3.5, 14-H), 7.92 (1H, d, *J* 3.5,13-H); δ_C (100 MHz) 20.91 (C-1), 22.23 (C-7), 23.54 (C-10), 23.85 (C-2), 32.07 (C-6), 32.29 (C-9), 38.39 (C-3), 47.76 (C-11), 59.11(C-4), 59.65 (C-8), 67.5 120.9 (C-14), 139.6 (C-13), 168.0 (CO), 173.67 (CN), *m*/*z* (ESI) 282 (MH^+); $C_{14}H_{24}ON_3S$ requires 282.1640 found 282.1637.

4-(*S*)-4-*N*-Methyl-2-methylamino-1-((*S*)-2-thiazol-2-yl-pyrrolidin-1-yl)-pentan-1-one 30

The above method was repeated with **29** (151 mg, 0.376 mmol) to give **30** as an orange sticky solid (130 mg, 100%); ν_{max}/cm^{-1} 3387, 2959, 1643, 1551, 1332 and 1111; $[\alpha]_D^{23}$ −57.9 (*c* 1, H_2O); δ_H (400 MHz, D_2O) 1.03 and 1.07 (6H, 2 × d, *J* 6, 2 × CH_3), 1.83 (3H, m, 2-H and 3-H_2), 2.25 (3H, m, 9*H*H and 10-H_2), 2.57 (1H, m, 9H*H*), 2.80 (3H, s, N-CH_3), 3.96 (2H, m, 11-H_2), 4.38 (1H, t, *J* 6.5, 4-H), 5.64 (1H, dd, *J* 8.5, 3.7, 8-H), 7.70 (1H, d, *J* 3.5, 14-H), 7.90 (1H, d, *J* 3.5,13-H); δ_C (100 MHz) 21.1 (C-1), 21.8 (C-7), 23.9 (C-2), 24.05 (C-10), 32.0 (C-6), 32.1 (C-9), 38.8 (C-3), 48.0 (C-11), 58.8 (C-4), 59.0 (C-8), 67.5 120.0 (C-14), 140.6 (C-13), 168.4 (CO), 173.2 (CN), *m*/*z* (ESI) 282 (MH^+); $C_{14}H_{24}ON_3S$ requires 282.1640 found 282.1637.

Dysideaproline E 5

L-Proline thiazole hydrobromic salt **28** (157 mg, 0.45 mmol) and (*S*)-4,4-dichloro-3-methylbutanoic acid **8** (116 mg, 0.676 mmol, 1.5 eq) formed a suspension with DCM–DMF (5 : 1 ratio, 11 ml). The reaction mixture was cooled to 0 °C and EDCI (2 eq, 173 mg, 0.9 mmol), HOBt (1.1 eq, 67 mg, 0.49 mmol) and NMM (1.5 eq, 0.1 ml, 0.676 mmol) were added and the reaction mixture was stirred at 0 °C for 1 h and then at room temperature overnight. The reaction was quenched with HCl (1 M, 5 ml) and diluted with EtOAc (15 ml). The mixture was separated and the organic layer was then washed with $NaHCO_3$ (10 ml), brine (10 ml), water (10 ml), dried over $MgSO_4$ and solvent evaporated to give crude **5** which was purified with flash chromatography eluting with 20% acetone/petrol to give dysideaproline E **5** as viscous clear oil (66 mg, 32%); $[\alpha]_D^{23}$ +43.8 (*c* 0.02, MeOH), [lit.[3] +45.5 (*c* 0.02, MeOH)]; ν_{max}/cm^{-1} 2955, 2871, 1695, 1650, 1453 and 1153; δ_H (400 MHz, major rotamer) 0.87 (3H, d, *J* 7.0, CH_3), 0. 88 (3H, d, *J* 7.0, CH_3), 1.09 (3H, d, *J* 6.6, CH_3), 1.35 (1H, m, 7-H), 1.51 (1H, m, 6*H*H), 1.51 (1H, m, 6H*H*), 1.89 (1H, m, 15*H*H), 1.96 (1H, m, 15H*H*), 2.06 (1H, m, 14*H*H), 2.23 (1H, m, 14H*H*), 2.46 (1H, dd, J 7.6, 16.3, 3H*H*), 2.57 (1H, dd, *J* 7.6, 16.3, 3*H*H), 2.69 (1H, m, 2H), 2.81 (3H, s, *N*-CH_3), 3.40 (1H, m, 16*H*H), 3.55 (1H, m, 16H*H*), 5.30 (1H, dd, *J* 3.2, 8.2, 13-H), 5.37 (1H, dd, *J* 6.6, 8.3, 5-H), 6.41 (1H, d, *J* 3.2, 11-H), 7.57 (1H, d, *J* 3.3, 19-H), 7.70 (1H, d, *J* 3.3, 18-H); δ_C (100 MHz, DMSO) 14.5 (C-1), 22.1 (C-9), 23.0 (C-8), 23.9 (C-15), 24.0 (C-7), 30.2 (C-10), 31.5 (C-14), 35.6 (C-3), 36.9 (C-6), 40.2 (C-2), 46.4 (C-16), 51.7 (C-5), 58.4 (C-13), 79.1 (C-11), 119.5 (C-19), 142.1 (C-18), 169.2 (C-4), 170.2 (C-12) and 172.6 (C-17); *m*/*z* 438 (2%),436 (6),434 (10), 362(45), 280 (100), 100 (65); $C_{19}H_{30}N_3O_2S^{35}Cl_2$ requires 434.1425 found 434.1436.

Diastereomer 7

L-Proline thiazole hydrobromic salt **30** (157 mg, 0.45 mmol) and (*S*)-4,4-dichloro-3-methylbutanoic acid **8** (116 mg, 0.676 mmol, 1.5 eq) formed a suspension with DCM–DMF (5 : 1 ratio, 11 ml). The reaction mixture was cooled to 0 °C and EDCI (2 eq, 173 mg, 0.9 mmol), HOBt (1.1 eq, 67 mg, 0.49 mmol) and NMM (1.5 eq, 0.1 ml, 0.676 mmol) were added and the reaction mixture was stirred at 0 °C for 1 h and then at room temperature overnight. The reaction was quenched with HCl (1 M, 5 ml) and diluted with EtOAc (15 ml). The mixture was separated and the organic layer was then washed with $NaHCO_3$ (10 ml), brine (10 ml), water

(10 ml), dried over $MgSO_4$ and solvent evaporated to give crude **7** which was purified with flash chromatography eluting with 20% acetone/petrol to give **7** as viscous clear oil (61 mg, 31%); $[\alpha]_D^{23}$ –42.6 (*c* 1, MeOH); 2955, 2871, 1695, 1650, 1453 and 1153; δ_H (400 MHz, major rotamer), 0.87 (3H, d, *J* 7.0, CH_3), 0. 88 (3H, d, *J* 7.0, CH_3), 1.09 (3H, d, *J* 6.6, CH_3), 1.35 (1H, m, 7-H), 1.51 (1H, m, 6*H*H), 1.51 (1H, m, 6H*H*), 1.89 (1H, m, 15*H*H), 1.96 (1H, m, 15H*H*), 2.06 (1H, m, 14*H*H), 2.23 (1H, m, 14H*H*), 2.46 (1H, dd, *J* 7.6, 16.3, 3H*H*), 2.57 (1H, dd, *J* 7.6, 16.3, 3*H*H), 2.69 (1H, m, 2H), 2.81 (3H, s, *N*-CH_3), 3.40 (1H, m, 16*H*H), 3.55 (1H, m, 16H*H*), 5.30 (1H, dd, *J* 3.2, 8.2, 13-H), 5.37 (1H, dd, *J* 6.6, 8.3, 5-H), 6.41 (1H, d, *J* 3.2, 11-H), 7.57 (1H, d, *J* 3.3, 19-H), 7.70 (1H, d, *J* 3.3, 18-H); δ_C 14.5 (C-1), 22.1 (C-9), 23.0 (C-8), 23.9 (C-15), 24.0 (C-7), 30.2 (C-10), 31.5 (C-14), 35.6 (C-3), 36.9 (C-6), 40.2 (C-2), 46.4 (C-16), 51.7 (C-5), 58.4 (C-13), 79.1 (C-11), 119.5 (C-19), 142.1 (C-18), 169.2 (C-4), 170.2 (C-12) and 172.6 (C-17); *m*/*z* 438 (2%),436 (6),434 (10), 362(45), 280 (100), 100 (65); $C_{19}H_{30}N_3O_2S^{35}Cl_2$ requires 434.1425 found 434.1436

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