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Polychlorinated Leucine Derivatives: Synthesis of (2*S*,4*R*)-5,5-Dichloroleucine and Its *J*-Based Analysis

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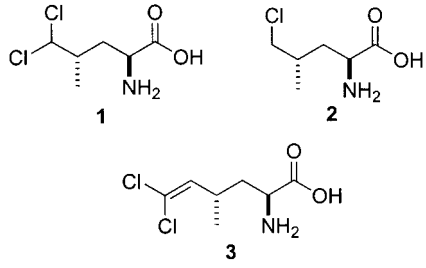
Keywords: Amino acids / Density functional calculations

A total synthesis of (2*S*,4*R*)-5,5-dichloroleucine is reported in 13 steps from (*S*)-methyl 2-(hydroxymethyl)propanoate. A density functional *J*-based analysis of this compound and a comparison with that of its (2*S*,4*S*) epimer is also performed in order to complete our study of *J*-configurational assignments in 1,3-nitrogen-containing acyclic moieties.

Introduction

Apart from proteinogenic and other naturally occurring amino acids, non-natural synthetic amino acids have received increasing attention due to their enzyme inhibitory and anti-metabolite properties and their ability to induce a certain conformation when incorporated into proteins. Among these, halogen α-amino acids have been shown to frequently act as antagonists of naturally occurring α-amino acids.[1] Furthermore, they are present in nature, either as free amino acids or as constituents of peptides, and have been isolated from different natural sources.[2] For example, a 5,5-dichloroleucine (**1**) was found and characterised without configuration assignment from the hydrolysed portion of victorin, also known as HV-toxin, isolated from the fungus *Helminthosporium victoriae*.[3] Sponges of the *Dysidea* genus are also a rich source of unique polychlorinated metabolites derived from amino acids.[4] It has been postulated that these chlorinated peptides are actually biosynthesised by blue-green algae living in association with the sponge.[5] However, the incorporation of chlorine in such compounds is intriguing and efforts have been made to establish the mechanism of biochlorination.[1a,6–8] Some precursors that have been used for feeding experiments are amino acids **2** and **3**, which along with **1** have been recently synthesised in a stereospecific way by different research groups.[9,10] The preparation of more leucine derivatives could be very helpful for further biosynthesis experiments.



The use of *J*-based analysis, also known as Murata's method, has become one of the best tools for the elucidation of the relative stereochemistry in acyclic compounds. Although many examples have been published with compounds bearing oxygenated or alkyl substituents, few compounds carrying chiral nitrogen-substituted acyclic systems have been reported.[11] For this reason, more examples are needed in order to obtain a new set of values to build up reliable curves, especially for $^2J_{C,H}$,[12] which may describe angular dependence vs. heteronuclear coupling constants.

Results and Discussion

Very recently, we reported a new structure from the sponge *Dysidea* sp., namely the polychlorinated dipeptide dysithiazolamide (**6**),[11e] whose relative configuration was proposed on the basis of the *J*-based analysis configuration.[13,14] The stereochemistry elucidation implied the application of Murata's methodology, first to the new amino acid derivative **5**, which was used as a model, and then to the natural product.[11e] In order to complete our study of *J*-configurational assignments to 1,3-nitrogen-containing acyclic moieties of this type, we now want to report the synthesis of its epimer, (2*S*,4*R*)-dichloroleucine (**4**), using chiral auxiliary strategies, and the corresponding *J*-based analysis along with QM calculations (Figure 1).

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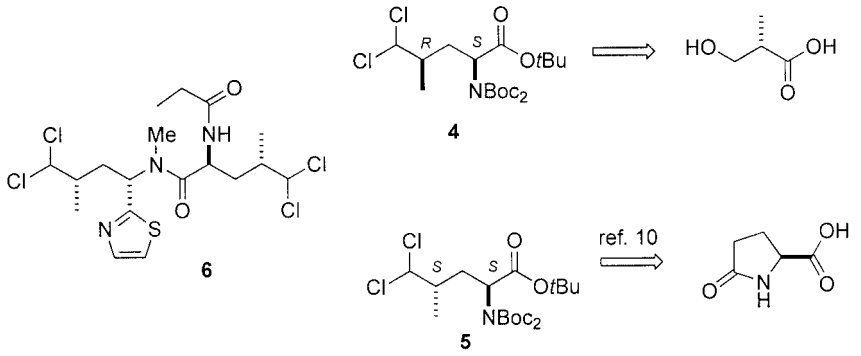


Figure 1. Retrosynthetic analysis of *syn*- and *anti*-5,5-dichloroleucines.

We have synthesised the α-azide carboximide **11** in five steps from commercially available (*S*)-methyl 2-(hydroxymethyl)propanoate (**7**) following a similar route to that described for the synthesis of cyclomarin;[15] for the dichlorination process we used Takeda's transformation of aldehydes into *gem*-dihalides via the hydrazone.[16,17]

The synthetic strategy begun with a silyl protection of **7** followed by reduction and subsequent Wadsworth–Emmons condensation of the resulting aldehyde with the chiral auxiliary phosphonate **8**, which was simultaneously prepared from L-phenylglycine.[18] The second stereogenic centre at C2 was introduced in a stereocontrolled *syn* manner by electrophilic azidation of the potassium enolate of the oxazolidinone **10** with trisyl azide at low temperature, according to Evans' procedure,[19] to afford **11** as a single diastereomer. After reduction of the azide moiety in **11** and Boc protection of the resulting amine group, removal of the chiral auxiliary was achieved by treatment with lithium hydroxyperoxide to provide compound **12** in a very good yield. Esterification of the resulting acid as its *tert*-butyl ester, and introduction of a second Boc group under more drastic conditions, afforded ester **13**. The poor conversion of the latter reaction (37%)[20] was overcome by recovering the unreacted starting material and recycling it.

Removal of the silyl ether group in **13** by treatment with TBAF in THF under standard conditions produced epi-

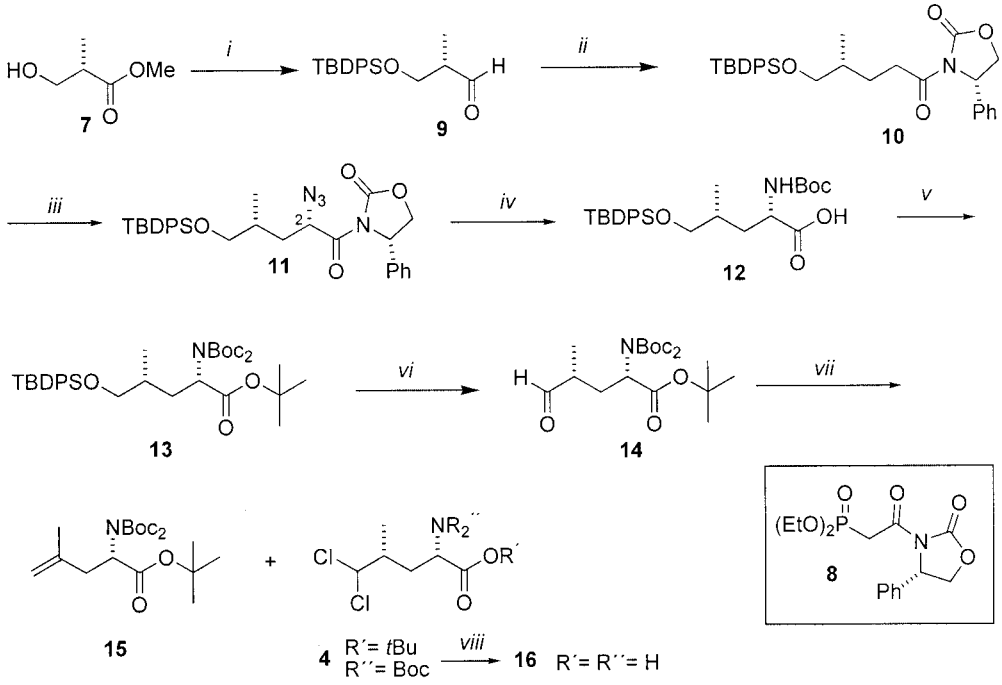
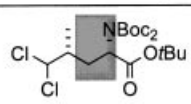
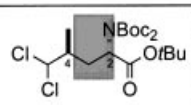
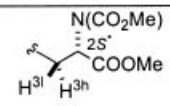
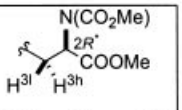
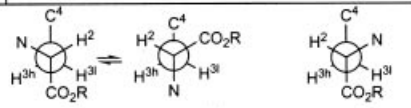
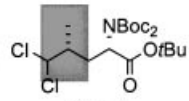
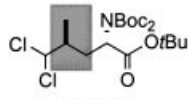
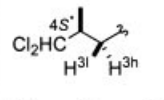
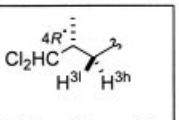
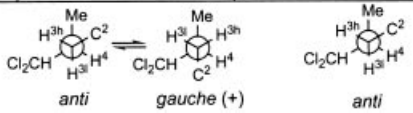


Figure 2. Reagents and conditions: *i*: (a) TBDPSCl, imidazole, DMF, 0 °C→room temp., 92%. (b) DIBAL-H, Et_2O, –80 °C, 93%; *ii*: (a) LiCl, iPr_2NEt, **8**, CH_3CN, 0 °C, 24 h, 70%. (b) H_2, 10% Pd/C, EtOAc, quantitative; *iii*: (a) KHMDS, THF, –80 °C, trisyl azide, –80 °C. (b) AcOH, 68%; *iv*: (a) H_2, 10% Pd/C. (b) Boc_2O, EtOAc, 99%. (c) LiOH, H_2O_2, THF/H_2O, 91%; *v*: (a) Boc_2O, DMAP, *t*BuOH, 75%. (b) Boc_2O, DMAP, Et_3N, 1,4-dioxane, 100 °C (37%, along with recovered starting material); *vi*: (a) TBAF, AcOH, THF, quantitative. (b) Dess–Martin periodinane, CH_2Cl_2, 87%; *vii*: (a) $NH_2NH_2{\cdot}H_2O$, MeOH. (b) 4-Å molecular sieves. (c) $CuCl_2$, Et_3N, MeOH, room temp., 35%; *viii*: TFA, CH_2Cl_2, 50%.

merisation at C2, although when the reaction was performed in the presence of acetic acid it resulted in the total retention of chirality.[21] The resulting primary alcohol was then oxidized with the Dess–Martin reagent to give aldehyde **14**, which was transformed into its hydrazone by treatment with $NH_2NH_2{\cdot}H_2O$, with further water removal using 4 Å molecular sieves. This hydrazone was quickly treated with $CuCl_2$ in dry methanol in the presence of triethyl-

Table 1. $^{3}J_{H,H}$ and $^{2,3}J_{C,H}$ values [Hz] around the C2–C3 and C3–C4 bonds for epimers **4** (*syn*) and **5** (*anti*) and comparison with the predicted values for the six possible staggered rotamers for each bond.

	Experimental			DFT					
C2-C3 bond	 **4 (*syn*)**		 **5 (*anti*)**						
				anti	***g-***	***g+***	***anti***	***g-***	***g+***
$^{3}J(H^{2},H^{3l})$	6.3[b], 5.9[c], 5.8[d]		11.0	11.3	3.6	1.8	4.8	4.5	6.5
$^{3}J(H^{2},H^{3h})$	8.4[b], 8.5[c], 8.6[d]		4.3	3.5	4.9	9.8	11.1	1.7	2.6
	HETLOC	***J-HMBC***[e]							
$^{3}J(C^{1},H^{3l})$	-	1.9	2.4	2.4	1.1	7.3	0.4	0.8	8.6
$^{3}J(C^{1},H^{3h})$	-	3.5	0.8	0.8	8.7	4.7	2.8	2.2	1.4
$^{3}J(C^{4},H^{2})$	1.7	1.8	2.8	2.1	7.4	3.9	1.3	5.5	6.3
$^{2}J(C^{2},H^{3l})$	-3.6	-3.7	-6.9	-6.5	-2.1	-4.8	-0.6	-3.4	-2.7
$^{2}J(C^{2},H^{3h})$	-6.0	-5.9	-2.5	-1.3	-4.0	-5.5	-6.2	-3.3	0.3
MAD (4, syn)				2.98	3.09	2.37	1.40	2.48	3.77
MAD (5, anti)				**0.49**	4.01	4.25	4.07	2.73	3.36
Main conformer/s	 *anti* *gauche (-)* *anti*								

	Experimental			DFT					
C3-C4 bond	 **4 (*syn*)**		 **5 (*anti*)**						
				anti	***g-***	***g+***	***anti***	***g-***	***g+***
$^{3}J(H^{4},H^{3l})$	6.5[b], 7.0[c], 7.0[d]		3.0	2.2	2.7	9.9	8.5	2.6	3.6
$^{3}J(H^{4},H^{3h})$	6.4[b], 5.6[c], 5.3[d]		11.0	10.3	5.8	5.2	0.8	1.8	4.0
	HETLOC	***J-HMBC***[e]							
$^{3}J(C^{5},H^{3l})$	n.o.	4.7	3.4	1.9	*11.2*	1.4	0.0	*11.6*	2.6
$^{3}J(C^{5},H^{3h})$	n.o.	6.8	3.2	3.9	0.8	*12.3*	7.5	3.3	*14.1*
$^{3}J(Me,H^{3l})$	3.9.	4.0	6.2	7.0	3.2	3.6	5.3	3.0	2.8
$^{3}J(Me,H^{3h})$	3.5	3.7	3.0	3.4	7.4	1.5	5.6	1.6	7.4
$^{3}J(H^{4},C^{2})$	3.8	3.7	3.6	3.4	8.4	0.5	3.0	3.2	8.1
$^{2}J(C^{4},H^{3l})$	n.m.	-5.4	-4.5	-3.7	-3.5	-2.0	-4.4	0.1	-3.0
$^{2}J(C^{4},H^{3h})$	-4.4	-4.1	-5.4	-2.7	-1.6	-4.7	-2.6	-2.5	-2.2
MAD (4, syn)				2.29	3.41	2.53	2.20	2.24	3.19
MAD (5, anti)				***0.83***	3.51	3.68	3.37	2.38	4.07
Main conformer/s	 *anti* *gauche (+)* *anti*								

[a] For DFT calculations see ref.[11e]. [b] At 298 K. [c] At 263 K. [d] At 243 K. [e] The sign of the coupling constant in the *J*-HMBC experiment is based on the HETLOC experiment. MAD = $(\sum|J_{exp.} - J_{theor.}|)/n$, where n = number of measured coupling constants; n.o. = coupling not observed; n.m. = coupling not measured for overlapped signals.

amine[11,16] to give, after HPLC purification, the desired dichloro amino acid derivative **4** in 35% yield, along with an unexpected alkene **15** in 7% yield. Final removal of the Boc groups was achieved by hydrolysis with trifluoroacetic acid to yield the free amino acid **16** (Figure 2).

At this point, in order to complete the NMR *J*-based analysis of this type of system we compared the $^{3}J_{H,H}$ and $^{2,3}J_{C,H}$ values of **4** (*syn*) with those of its epimer **5** (*anti*). Firstly, the $^{3}J_{H,H}$ measurements, obtained directly from their ^{1}H NMR spectra, show important differences. The medium/large values obtained around the C2–C3 (6.3 and 8.4) and C3–C4 (6.5 and 6.4 Hz) bonds in compound **4** indicate the presence of two main conformers for each bond in fast interconversion. This situation clearly differs from that for compound **5**, where only the *anti* conformer is present around both C2–C3 and C3–C4.

Next, the heteronuclear couplings were measured in HETLOC and *J*-HMBC experiments.[22] For the C2–C3 bond in **4**, the small values found for $^{3}J_{C^1,H^{3l}}$ and $^{3}J_{C^4,H^2}$ show a *gauche* relation for this pair of atoms. The large $^{2}J_{C^2,H^{3h}}$ value suggests that H3h is *gauche* to the nitrogen. Finally, the medium values found for $^{3}J_{C^1,H^{3h}}$ and $^{2}J_{C^2,H^{3l}}$ are in agreement with an equilibrium between the *anti* and the *gauche* (–) conformers shown in Table 1, where the population of the first one should be higher than that of the second one. The homonuclear coupling constants measured at low temperature agree with the situation in which population of the *anti* conformer increases while that of the *gauche* conformer (–) decreases. DFT calculations using the B3LYP functional and 6-311G(d,p) basis set were used to compare coupling constants for the six possible staggered rotamers. The mean absolute deviation (MAD)[23] values obtained for **4** (*syn* epimer) confirmed the lack of a major conformer, in contrast to compound **5** (*anti* epimer), where the MAD value of 0.49 is in agreement with the presence of a major rotamer.

Around the C3–C4 bond, the intermediate values found for $^{3}J_{H^4,H^{3l}}$, $^{3}J_{H^4,H^{3h}}$, $^{3}J_{Me,H^{3l}}$, along with the large one for $^{2}J_{C^4,H^{3h}}$ and the small one for $^{3}J_{Me,H^{3h}}$ suggest the presence of a more complex equilibrium with a slight predominance for that represented in Table 1. This situation is also in agreement with the inspection of the $^{3}J_{H^4,H^{3l}}$ and $^{3}J_{H^4,H^{3h}}$ values at low temperature. These values change from intermediate to larger, in the case of $^{3}J_{H^4,H^{3l}}$, and to smaller in the case of $^{3}J_{H^4,H^{3h}}$. The coupling constants involving carbon C5 ($^{3}J_{C^5,H^{3l}}$ and $^{3}J_{C^5,H^{3h}}$) seem, however, to be larger than expected from this equilibrium, as $^{3}J_{C^5,H^{3l}}$ should be small and $^{3}J_{C^5,H^{3h}}$ medium. These values can also be explained when attention is paid to the values predicted by DFT. The coupling of C5 with its proton in the *anti* position clearly shows larger values (11–14 Hz, italicized in Table 1) than the usual 7–10 Hz. This α-substitution effect has already been reported by others[24] and depends on the substituent's orientation with respect to the coupled hydrogen. Again, a comparison of the DFT and experimental values do not allow us to extract any conclusions about the main conformer/s due to the existence of a complex conformational equilibrium around the C3–C4 bond. A combination of the predicted conformers and the experimental coupling constants leads to the correct *syn* configuration of compound **4**.

There has been a notable difficulty in classifying the *J* values in this type of system due to a poorly defined range for the $^{2,3}J_{C,H}$ coupling constant. Even though dihedral-angle dependence is the main factor, other effects such as substituents, electronegativity, position and orientation, nonbonded electrons, through-space interactions, hydrogen bonding, etc. may produce deviations from the expected values obtained from the Karplus equation. The DFT calculations permitted us to predict these deviations and to classify the coupling constants into a range of values that can shift slightly depending on the system.[25] However, when two or more conformers coexist in rapid equilibrium, the values predicted by DFT do not allow us to identify them by comparison with the experimental values. When a major rotamer is present the comparison allowed us to identify this conformer directly.

In conclusion, we have been able to apply the *J*-based methodology to *syn* and *anti* 5,5-dichloroleucine derivatives; the results are merely a demonstration of the use of computational techniques among heteronuclear coupling constants for the determination of the relative stereochemistry in acyclic 1,3-nitrogen-containing moieties. The inconveniences found in having wide ranges of $^{2,3}J_{C,H}$ values in this type of system can be overcome through a systematic, and consequently reliable, study of suitable models with a known relative configuration in order to better describe the angular dependences of heteronuclear coupling constants.

Experimental Section

General: Most reactions were run under an inert atmosphere (argon) with strict exclusion of moisture in oven-dried vessels. Solvents were distilled prior to use: THF and diethyl ether from Na/benzophenone; acetonitrile, ethyl acetate and triethylamine from CaH_2; pyridine from KOH; methanol from Na followed by molecules sieves (4 Å). DMF, *t*BuOH and 1,4-dioxane were purchased as anhydrous grade. Trisyl azide was dried under vacuum prior to use; all other reagents were commercial and were used without any purification. TLC was carried out on pre-coated sheets (silica gel 60 F254, Merck). Spot visualisation was accomplished by illumination with UV light and/or spraying with phosphomolybdic acid solution. Flash chromatography was performed using the indicated solvents on Merck silica gel 60 (0.04–0.063 mm). NMR spectra were recorded with a Bruker AC 200F, Bruker Avance 300 MHz or Bruker Avance 500 MHz spectrometer. Chemical shifts are reported in ppm relative to the signals due to the solvent. ESI+ spectra were obtained using a Thermo Navigator or Thermo ESI-FTMS APEXIII mass spectrometers. Optical rotations were recorded with a JASCO digital polarimeter. Melting points were measured with a Bibby Stuart Scientific SMP3.

QM Calculations: Calculations were carried out using the Gaussian03W software package (ver. C-2).[26] The structures and energies of the species considered were optimised at the DFT levels using the functionals B3LYP and mPW1PW91 and the 6-31G(d) or 6-311G (d) basis set.

The coupling constants were calculated using a GIAO approach by DFT methods employing the B3LYP and mPW1PW91 functionals. For each of the approaches considered, the 6-31G(d,p) and 6-311G(d,p) basis sets were utilized.

Synthesis of (*R*)-3-*tert*-Butyldiphenylsilyloxy-2-methylpropanal (9): *tert*-Butyldiphenylsilyl chloride (17.5 mL, 67.3 mmol, 1.6 equiv.) and imidazole (13.7 g, 4.8 equiv.) were added to a solution of (*S*)-methyl 2-(hydroxymethyl)propanoate (5 g, 1 equiv.) in DMF (42 mL) at 0 °C. The reaction was allowed to reach room temp. and was stirred for 20 h. 5% HCl aqueous solution was then added and the aqueous layer was extracted three times with diethyl ether. The organic layers were washed with water and brine, and dried with $MgSO_4$. After solvent evaporation, the residue was purified by chromatography on silica gel, with hexane/ethyl acetate (9.5:0.5→9:1) as eluent, to provide (*R*)-methyl 2-(*tert*-butyldiphenylsilyloxymethyl)propanoate (13.8 g, 92%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.71–7.66 (m, 4 H, TBDPS), 7.44–7.43 (m, 6 H, TBDPS), 3.83 (m, 2 H, CH_2O), 3.71 (s, 3 H, CH_3O), 2.75 (m, 1 H, CHCO), 1.90 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CH_3), 1.07 (s, 3 H, TBDPS) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 175.3 (C-1), 135.6, 133.5, 129.7, 127.7 (all TBDPS), 65.9 (C3), 51.5 ($CO\mathit{C}H_3$), 42.4 (C-2), 26.7 (TBDPS), 13.5 (C-4) ppm. MS (ESI+, MeOH): *m*/*z* 379 $[M + Na]^+$. HR-ESI-MS calcd. for $C_{21}H_{28}O_3NaSi$: 379.16999; found 379.17046. $C_{21}H_{28}O_3Si$ (356.53): calcd. C 70.74, H 7.92; found C 70.50, H 8.63.

DIBAL-H (1 M in toluene; 18.7 mL, 1.6 equiv.) was slowly added, over 20 min, to a solution of (*R*)-methyl 2-(*tert*-butyldiphenylsilyloxymethyl)propanoate (4.1 g, 1 equiv.) in diethyl ether at –80 °C and the mixture was stirred for 1.25 h. The reaction was quenched by addition of water, and, once it had warmed to room temp., was filtered through a pad of celite. An oil was obtained after solvent evaporation, which was purified by chromatography on silica gel, using hexane/ethyl acetate (9:1→8:2) as eluent, to provide **9** as a colourless oil (3.4 g, 93%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 9.81 (s, 1 H, CHO), 7.73–7.70 (m, 4 H, TBDPS), 7.46–7.43 (m, 6 H, TBDPS), 3.94 (m, 2 H, CH_2O), 2.61 (m, 1 H, CH), 1.15 (d, $J_{H,H}$ = 6.8 Hz, 3 H, CH_3), 1.11 (s, 9 H, TBDPS) ppm.

Synthesis of (4*S*)-3-[(4*R*)-5-*tert*-butyldiphenylsilyloxy-4-methylpentanoyl]-4-phenyl-2-oxazolidinone (10): *i*Pr_2NEt (0.97 mL, 1 equiv.) was added to a solution of **9** (1.85 g, 1 equiv.), (4*S*)-*N*-diethoxyphosphonoacetyl-4-phenyloxazolidin-2-one (2.2 g, 6.45 mmol, 1.1 equiv.) and LiCl (2.3 g, 9.6 equiv.) in CH_3CN (35 mL) at 0 °C. The solution was allowed to reach room temp. and stirred for 24 h. The mixture was partitioned between water and diethyl ether and the organic layer was washed with brine and dried with Na_2SO_4. Removal of the solvent followed by chromatography on silica gel, using hexane/ethyl acetate (8:2→1:2) as eluent, provided (4*S*)-3-[(4*R*,2*E*)-5-*tert*-butyldiphenylsilyloxy-4-methyl-2-pentenoyl]-4-phenyl-2-oxazolidinone (2.04 g, 70%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.72–7.63 (m, 4 H, TBDPS), 7.43–7.27 (m, 12 H, TBDPS, Ph and 7-H), 7.12 (dd, $J_{H,H}$ = 6.8 and 15.1 Hz, 1 H, 8-H), 5.51 (dd, $J_{H,H}$ = 8.5 and 3.6 Hz, 1 H, 4-H), 4.70 (t, $J_{H,H}$ = 6.8 Hz, 1 H, 5-H), 4.28 (dd, $J_{H,H}$ = 8.7 and 3.4 Hz, 1 H, 5-H), 3.62 (m, 2 H, 10-H), 2.65 (m, 1 H, 9-H), 1.11 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, 11-H), 1.06 (s, 9 H, TBDPS) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0 (C-6), 153.8 (C-2), 139.2, 135.6, 133.5, 129.6, 129.1 128.6 127.6, 125.9 133.5, 129.7, 127.7 (TBDPS and Ph), 119.9 (C-7), 69.9 (C-5), 67.5 (C-10), 57.7 (C-9), 39.6 (C-4), 26.8 (TDBPS), 19.3 (TBDPS), 15.6 (C-11) ppm. MS (ESI+, MeOH): *m*/*z* 536 $[M + Na]^+$. HR-ESI-MS calcd. for $C_{31}H_{35}NO_4NaSi$: 536.22275; found 536.22386.

(4*S*)-3-[(4*R*,2*E*)-5-*tert*-Butyldiphenylsilyloxy-4-methyl-2-pentenoyl]-4-phenyl-2-oxazolidinone (2.0 g, 1 equiv.) and 10% Pd/C (0.9 g) were dissolved in EtOAc (45 mL) and the black slurry was stirred at room temp. under H_2. After 18 h the mixture was filtered through a pad of celite, and the solvent was evaporated to afford **10** (2.0 g, quantitative) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.69 (m, 4 H, TBDPS), 7.43–7.27 (m, 11 H, TBDPS and Ph), 5.43 (dd, $J_{H,H}$ = 8.7 and 3.5 Hz, 1 H, 4-H), 4.68 (t, $J_{H,H}$ = 8.7 Hz, 1 H, 5-H), 4.27 (dd, $J_{H,H}$ = 8.7 and 3.5 Hz, 1 H, 5-H), 3.51 (m, 2 H, 10-H), 2.65 (m, 1 H, 9-H), 3.07–2.87 (m, 2 H, 7-H), 1.89–1.65 (m, 2 H), 1.54–1.43 (m, 1 H), 1.08 (s, 9 H, TBDPS), 0.94 (d, $J_{H,H}$ = 6.6 Hz, 3 H, 11-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.2 (C-6), 152.9 (C-2), 153.8 (C-2), 139.3, 134.0, 133.9, 129.6, 129.3, 128.7, 127.7, 126.0 (TBDPS and Ph), 70.0 (C-5), 68.6 (C-10), 57.6 (C-4), 35.2 (C-9), 33.5 (C-7), 27.6 (C-8), 26.9 (TDBPS), 19.4 (TBDPS), 16.6 (C-11) ppm. $[\alpha]_D^{22}$ = +32.8 (*c* = 1.63, $CHCl_3$). MS (ESI+, MeOH): *m*/*z* 538 $[M + Na]^+$. HR-ESI-MS calcd. for $C_{31}H_{37}NNaO_4Si$: 538.23841; found 538.23878. $C_{31}H_{37}NO_4Si$ (515.72): calcd. C, 72.20, H 7.23, N 2.72; found C 72.20, H 8.24, N 2.40.

Synthesis of (4*S*)-3-[(2*S*,4*R*)-2-Azido-5-*tert*-butyldiphenylsilyloxy-4-methylpentanoyl]-4-phenyl-2-oxazolidinone (11): A solution of **10** (110 mg, 1 equiv.) in THF (1 mL) was added to a solution of KHMDS (0.5 M in toluene; 0.518 mL, 1.2 equiv.) in THF (1 mL) at –80 °C. After 40 min a solution of trisyl azide (1.2 equiv.) in THF (1.5 mL) prepared over molecular sieves was added followed, 4 min later, by acetic acid (61 μL). The mixture was then warmed to room temp. and stirred overnight. Diethyl ether and brine were added, and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and brine. After drying over $MgSO_4$, the solvent was evaporated and the residue obtained purified by chromatography on silica gel, using hexane/ethyl acetate (9.5:0.5→8:2) as eluent, to give compound **11** as a colourless oil (81.6 g, 68%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.71–7.68 (m, 4 H, TBDPS), 7.45–7.27 (m, 11 H, TBDPS and Ph), 5.40 (dd, $J_{H,H}$ = 8.3 and 3.9 Hz, 1 H, 4-H), 5.06 (dd, $J_{H,H}$ = 4.8 and 8.8 Hz, 1 H, 7-H), 4.69 (t, $J_{H,H}$ = 8.7 Hz, 1 H, 5-H), 4.31 (dd, $J_{H,H}$ = 8.7 and 3.9 Hz, 1 H, 5-H), 3.67–3.49 (m, 2 H, 10-H), 2.12–1.88 (m, 2 H), 1.73–1.57 (m, 1 H), 1.09 (s, 9 H, TBDPS), 1.05 (d, $J_{H,H}$ = 6.8 Hz, 3 H, 11-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.0 (C-6), 152.9 (C-2), 138.1, 135.6, 133.7, 129.6, 129.3, 128.9, 127.6, 125.8 (TBDPS and Ph), 70.3 (C-5), 68.1 (C-10), 58.7 (C-4), 57.8 (C-7), 34.2 (C-8), 33.3 (C-9), 26.8 (TDBPS), 19.4 (TBDPS), 17.3 (C-11) ppm. MS (ESI+, MeOH): *m*/*z* 579 $[M + Na]^+$. HR-ESI-MS calcd. for $C_{31}H_{36}N_4NaO_4Si$: *m*/*z* 579.23980; found 579.24039.

Synthesis of (2*S*,4*R*)-2-*tert*-Butoxycarbonylamino-5-*tert*-butyldiphenylsilyloxy-4-methylpentanoic Acid (12): Boc_2O (213.8 mg, 2 equiv.) and 10% Pd/C (71.1 mg) were added to a solution of **11** (272.8 mg, 1 equiv.) in EtOAc (4.8 mL) and the mixture was stirred under H_2 atmosphere at room temp. for 15 h. After filtration through a pad of celite the solvent was evaporated and the obtained oil was purified by chromatography on silica gel, using hexane/ethyl acetate (6:1→4:1) as eluent, to give (4*S*)-3-[(2*S*,4*R*)-2-*tert*-butoxycarbonylamino-5-*tert*-butyldiphenylsilyloxy-4-methylpentanoyl]-4-phenyl-2-oxazolidinone (306 mg, 99%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.68 (m, 4 H, TBDPS), 7.43–7.33 (m, 11 H, TBDPS and Ph), 5.49 (br. m, 7-H), 5.38 (m, 1 H, 4-H), 5.32 (br. m, 1 H, NH), 4.69 (t, $J_{H,H}$ = 8.7 Hz, 1 H, 5-H), 4.25 (dd, $J_{H,H}$ = 8.7 and 3.9 Hz, 1 H, 5-H), 3.60 and 3.52 (m, 2 H, 10-H), 1.97–1.86 (m, 2 H), 1.62–1.50 (m, 1 H), 1.36 (s, 9 H, Boc), 1.06 (s, 9 H, TBDPS), 0.95 (d, $J_{H,H}$ = 6.6 Hz, 3 H, 11-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8 (C-6), 155.4 (C-2), 153.0, 138.4, 153.0, 138.4, 137.7, 129.7, 122.2, 127.7 (TBDPS and Ph), 79.8 (Boc), 70.4 (C-5), 68.0 (C-10), 58.2 (C-4), 51.7 (C-7), 35.2 (C-8), 33.0 (C-9), 28.3 (Boc), 27.0 (TDBPS), 19.4 (TBDPS), 17.4 (C-11)

ppm. $[\alpha]_D^{22}$ = +40.2 (c = 0.24, $CHCl_3$). MS (ESI+, MeOH): m/z 653 $[M+Na]^+$. HR-ESI-MS calcd. for $C_{36}H_{46}N_2NaO_6Si$: 653.30173; found 653.30315.

LiOH (1 M; 0.87 mL, 8 equiv.) and 30% aqueous H_2O_2 (0.34 mL, 2 equiv.) were added successively to a solution of (4*S*)-3-[(2*S*,4*R*)-2-*tert*-butoxycarbonylamino-5-*tert*-butyldiphenylsilyloxy-4-methylpentanoyl]-4-phenyl-2-oxazolidinone (274 mg, 1 equiv.) in THF/H_2O (5:1.5 mL) at 0 °C, and the reaction mixture was stirred for 24 h at room temp. The solution was acidified at 0 °C with a 1 M aqueous solution of $KHSO_4$, and extracted three times with EtOAc. The organic layer was dried with $MgSO_4$ and the solvent evaporated. Purification was carried out by crystallisation of the product from hexane/diethyl ether (1:1) containing 1% acetic acid. Evaporation of the solvent under vacuum afforded compound **12** (192 mg, 92%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 10.1 (br. s, 1 H, OH), 7.68 (m, 4 H, TBDPS), 7.43–7.33 (m, 11 H, TBDPS and Ph), 5.34 (m, 1 H, NH), 4.36 (m, 1 H, 2-H), 3.54 (m, 2 H, 5-H), 2.06 (m, 1 H), 1.88 (m, 1 H), 1.59 (m, 1 H), 1.44 (s, 9 H, Boc), 1.08 (s, 9 H, TBDPS), 0.96 (d, $J_{H,H}$ = 5.8 Hz, 3 H, 6-H) ppm. MS (ESI+, MeOH): m/z 508 $[M+Na]^+$. HR-ESI-MS calcd. for $C_{27}H_{39}NNaO_5Si$: 508.24897; found 508.24965.

Synthesis of (2*S*,4*R*)-*tert*-Butyl 2-Di-*tert*-butoxycarbonylamino-5-*tert*-butyldiphenylsilyloxy-4-methylpentanoate (13): Compound **12** (101.8 mg, 1 equiv.), Boc_2O (91.5 mg, 2 equiv.) and DMAP (7.6 mg, 0.3 equiv.) were dissolved in *tert*-butanol (2 mL), and the mixture was stirred for 30 min at room temp. The solvent was then removed under vacuum, and the residue purified by chromatography on silica gel, using hexane/ethyl acetate (2%→5%→10%) as eluent, to afford (2*S*,4*R*)-*tert*-butyl 2-di-*tert*-butoxycarbonylamino-5-*tert*-butyldiphenylsilyloxy-4-methylpentanoate as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.67–7.65 (m, 4 H, TBDPS), 7.42–7.38 (m, 6 H, TBDPSO), 5.13 (br. d, $J_{H,H}$ = 7.8 Hz, 1 H, NH), 4.22 (m, 1 H, 2-H), 3.59 (dd, $J_{H,H}$ = 10.0 and 5.1 Hz, 1 H, 5-H), 3.47 (dd, $J_{H,H}$ = 10.0 and 5.6 Hz, 1 H, 5-H), 2.01 (m, 1 H), 1.82 (m, 1 H), 1.48 (s, 9 H, Boc), 1.44 (s, 9 H, O*t*Bu), 1.07 (s, 9 H, TBDPS), 0.98 (d, $J_{H,H}$ = 6.3 Hz, 3 H, 6-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.3 (C-1), 155.3 (Boc), 135.6, 133.6, 129.5, 127.6, (TBDPS), 81.5 [Boc and $(CH_3)_3$], 79.4 (TBDPSO), 67.8 (C-5), 52.6 (C-2), 36.3 (C-3), 32.5 (C-4), 28.3 [$(CH_3)_3$], 27.9 (Boc), 26.8 (TDBPS), 19.2 (TBDPSO), 17.1 (C-6) ppm. MS (ESI+, MeOH): m/z 564 $[M+Na]^+$. HR-ESI-MS calcd. for $C_{31}H_{47}NNaO_5Si$: 564.31157; found 564.31225.

Et_3N (0.05 mL, 1.2 equiv.) was added to a solution of (2*S*,4*R*)-*tert*-butyl 2-*tert*-butoxycarbonylamino-5-*tert*-butyldiphenylsilyloxy-4-methylpentanoate (179 mg, 1 equiv.) and DMAP (9 mg, 0.2 equiv.) in 1,4-dioxane (3 mL) and the mixture was heated to 100 °C. A solution of Boc_2O (136 m, 2 equiv.) in 1,4-dioxane (1.5 mL) was then added, and the reaction was stirred at that temperature for 12 h. After cooling, the solvent was evaporated under vacuum. Purification by chromatography on silica gel, using hexane/ethyl acetate (9:1) as eluent, gave compound **13** (45.6 mg, 23%) along with some recovered starting material (106 mg), which was re-used in subsequent reactions. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.67–7.65 (m, 4 H, TBDPSO), 7.42–7.38 (m, 6 H, TBDPSO), 4.77 (dd, $J_{H,H}$ = 8.7 and 5.3 Hz, 1 H, 2-H), 3.61 (dd, $J_{H,H}$ = 9.7 and 4.4 Hz, 1 H, 5-H), 3.50 (dd, $J_{H,H}$ = 10.1 and 5.8 Hz, 1 H, 5-H), 2.32 (m, 1 H), 1.88–1.56 (m, 2 H), 1.48 (s, 18 H, Boc), 1.45 (s, 9 H, O*t*Bu), 1.06 (s, 9 H, TBDPS), 1.00 (d, $J_{H,H}$ = 6.3 Hz, 3 H, 6-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.9 (C-1), 152.3 (Boc), 135.6, 133.9, 129.4, 127.5 (TBDPSO), 82.5 [Boc and $(CH_3)_3$], 80.9 (TBDPS), 67.8 (C-5), 57.4 (C-2), 33.1 (C-4), 32.9 (C-3), 27.9 [$(CH_3)_3$ and Boc], 26.8 (TDBPS), 19.3 (TBDPS), 17.6 (C6) ppm. MS (ESI+, MeOH): m/z 664 $[M+Na]^+$. HR-ESI-MS calcd. for $C_{36}H_{55}NNaO_7Si$: 664.36400; found 664.36466.

Synthesis of (2*S*,4*R*)-*tert*-Butyl 2-Di-*tert*-butoxycarbonylamino-5-formyl-4-methylpentanoate (14): Acetic acid (56 μL, 2.2 equiv.) and TBAF (1 M in THF; 0.37 mL, 4.1 equiv.) were added to a solution of compound **13** (57 mg, 1 equiv.) in THF and the mixture was stirred at room temp. for 3 d. The solution was then partitioned between ethyl acetate and an aqueous solution of NH_4Cl. The organic layer was washed with aqueous NH_4Cl and dried with $MgSO_4$. Purification by chromatography on silica gel, using hexane/ethyl acetate (8.5:1.5→7:3) as eluent, provided (2*S*,4*R*)-*tert*-butyl 2-di-*tert*-butoxycarbonylamino-5-hydroxy-4-methylpentanoate (15 mg, quantitative) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 4.80 (m, 1 H, 2-H), 3.51 (m, 2 H, 5-H), 2.23 (m, 1 H), 1.82–1.57 (m, 2 H), 1.51 (s, 18 H, Boc), 1.44 (O*t*Bu), 0.97 (d, $J_{H,H}$ = 6.5 Hz, 3 H, 6-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.4 (C-1), 152.5 (Boc), 82.9 (Boc), 81.6 (O*t*Bu), 67.3 (C-5), 57.54 (C-2), 33.5 (C-4 and C-3), 28.0 [$(CH_3)_3$-Boc], 17.7 (C-6) ppm. MS (ESI+, MeOH): m/z 426 $[M+Na]^+$. HR-ESI-MS calcd. for $C_{20}H_{37}NNaO_7$: 426.24622; found 426.24636.

Dess–Martin periodinane (59 mg, 1.4 equiv.) was added to a solution of (2*S*,4*R*)-*tert*-butyl 2-di-*tert*-butoxycarbonylamino-5-hydroxy-4-methylpentanoate (40 mg, 1 equiv.) in CH_2Cl_2 (2 mL), and the reaction mixture was stirred at room temp. for 30 min. The mixture was then poured into a solution of $Na_2S_2O_3$ in saturated $NaHCO_3$ (12 mg in 50 mL) and diluted with diethyl ether. The organic layer was dried with $MgSO_4$ and, after solvent evaporation, purification by chromatography on silica gel, using hexane/ethyl acetate (8:2) as eluent. afforded **14** (34.5 mg, 87%) as a colourless oil that rapidly crystallised. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 9.66 (s, 1 H, CHO), 4.82 (dd, $J_{H,H}$ = 4.8 and 9.1 Hz, 1 H, 2-H), 2.62–2.47 (m, 2 H), 1.86 (t, $J_{H,H}$ = 9.1 Hz, 1 H), 1.50 (s, 18 H, Boc), 1.45 (O*t*Bu), 1.14 (d, $J_{H,H}$ = 6.8 Hz, 3 H, 6-H) ppm.

Synthesis of (2*S*,4*R*)-*tert*-Butyl 2-Di-*tert*-butoxycarbonylamino-5,5-dichloro-4-methylpentanoate (4): Hydrazine monohydrate (0.035 mL, 10 equiv.) was slowly added to a solution of **14** (40 mg, 1 equiv.) in methanol and the reaction was stirred for 2 h at room temp. Molecular sieves (4 Å) were added and were then filtered off; they were washed with diethyl ether. After solvent evaporation, the excess of hydrazine was removed under vacuum at 30 °C. A solution of the hydrazone in MeOH (0.25 mL) was added to a solution of anhydrous $CuCl_2$ (80 mg, 6 equiv.) and Et_3N (41 μL, 3 equiv.) in MeOH (0.5 mL) at 0 °C. The reaction was stirred at room temp. for 1 h and was then quenched by addition of a 3.5% aqueous solution of NH_3 and extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, and the solvent removed under vacuum. Purification by chromatography on silica gel using hexane/ethyl acetate (9.5:0.5→9:1→8:2) as eluent afforded a mixture of compounds, which were separated by reverse-phase HPLC on a Whatman column with MeOH/6% H_2O at 1 mL min^{-1}. The peak at 37.9 min corresponds to compound **4** (15.9 mg, 35%), which was obtained as a clear oil that crystallised. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 6.03 (d, $J_{H,H}$ = 2.7 Hz, 1 H, 5-H), 4.76 (dd, $J_{H,H}$ = 6.3 and 8.4 Hz, 1 H, 2-H), 2.38 (m, 1 H, 3-H), 2.28 (m, 1 H, 4-H), 1.83 (m, 1 H, 3-H), 1.52 (s, 18 H, Boc_2), 1.46 (s, 9 H, CO*t*Bu), 1.19 (d, $J_{H,H}$ = 6.5 Hz, 3 H, 6-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.3 (C-1), 152.3 (Boc_2), 83.3 (Boc_2), 81.7 (O*t*Bu), 77.9 (C-5), 56.5 (C-2), 40.9 (C-4), 33.4 (C-3), 28.1 (Boc_2), 28.1 (O*t*Bu), 14.4 (C-6) ppm. MS (ESI+, MeOH): m/z 478/480 $[M+Na]^+$, 378/380 $[M+Na-100]^+$. $[\alpha]_D^{22}$ = –14.3 (c = 0.465, CH_2Cl_2). M.p. 60 °C (uncorrected). HR-ESI-MS calcd. for $C_{20}H_{35}{}^{35}Cl_2NNaO_6$/$C_{20}H_{35}{}^{35}Cl^{37}ClNNaO_6$: 478.17336/479.175900; found 478.17403/479.17742.

The HPLC peak at 36.2 min was identified as compound **15** (2.6 mg, 7%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.97 (dd, $J_{H,H}$ = 10.0 and 5.5 Hz, 1 H, 2-H), 4.80 (s, 1 H, 5-H), 4.72 (s, 1 H, 5-H), 2.70 (m, 2 H, 3-H), 1.76 (s, 3 H, 6-H), 1.50 (s, 18 H, Boc), 1.46 [$(CH_3)_3$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.8 (C-1), 152.4 (Boc), 141.8 (C-4), 113.8 (C-5), 82.6 (Boc), 81.7 [$(CH_3)_3$], 56.9 (C-2), 37.4 (C-3), 28.0 (Boc), 27.9 [$(CH_3)_3$], 21.9 (C-6) ppm. MS (ESI+, MeOH): *m/z* 408 $[M + Na]^+$.

Synthesis of (2*S*,4*R*)-2-Amino-5,5-dichloro-4-methylpentanoic Acid (16): TFA (0.1 mL) was added to a solution of **4** (3 mg) in CH_2Cl_2 (1 mL) and the reaction was stirred for 24 h. The solvent was then removed under vacuum and the unreacted TFA was removed azeotropically by evaporating with diethyl ether. Purification on a silica gel microcolumn eluting with isobutyl alcohol/acetic acid/water (8:2:2) afforded compound **16** (1.1 mg, 50%) as its trifluoroacetate salt. ^{1}H NMR (200 MHz, D_2O, 25 °C): δ = 5.92 (d, $J_{H,H}$ = 2.8 Hz, 1 H, 5-H), 3.62 (m, 1 H, 2-H), 2.28 (m, 1 H), 2.05 (m, 1 H), 1.61 (m, 1 H), 1.02 (d, $J_{H,H}$ = 6.5 Hz, 3 H, 6-H) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 174.3 (C-1), 163.0 (q, $COCF_3$), 116.2 (q, CF_3), 77.9 (C-5), 52.8 (C-2), 39.9 (C-4), 33.2 (C-3), 14.6 (C-6) ppm. $[\alpha]_D^{22}$ = –11.6 (*c* = 0.13, H_2O).

Supporting Information (see also the footnote on the first page of this article): ^{1}H, ^{13}C and DEPT NMR spectra of the product of silylation of **7**, compounds **10**, **11** and **13**, the product of deprotection of **13**, and compounds **14** (^{1}H NMR), **4** and **5**.

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