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A study of polychlorinated leucine derivatives: synthesis of (2*S*,4*S*)-5,5-dichloroleucine

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Abstract—The first total synthesis of (2*S*,4*S*)-5,5-dichloroleucine has been achieved in 11 steps from L-pyroglutamic acid. A key step is the dichlorination process on the hydrazone of aldehyde **13** with $CuCl_2$ in triethylamine.
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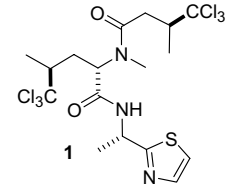
Dysidea herbacea is an Indopacific sponge that is able to produce several secondary metabolites belonging to a wide variety of structural types. These include polybrominated diphenyl ethers, nonhalogenated terpenes and a series of unique polychlorinated metabolites derived from amino acid precursors, particularly leucine.[1] One example of a compound belonging to this latter category is the hexachlorinated compound dysidenin (**1**),[1a–c] which is biosynthesised from an assemblage between the sponge and its associated symbiont—the filamentous cyanobacteria *Oscillatoria spongeliae*[2]—an involvement also found in the isolation of chlorinated diketopiperazine derivatives.[1h,3]



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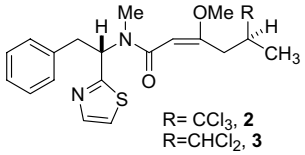

R= CCl_3, **2**
R=$CHCl_2$, **3**

Several studies have been aimed at determining the role of certain amino acids bearing aliphatic side chains in the inter and intramolecular hydrophobic interactions and the final tertiary structure of a polypeptide. It is known that leucine residues are important in such arrangements. For this reason it is very important to have synthetic routes to access different leucine-derived amino acids (labelled or unlabelled) in order to complete these studies.[4] In addition, it is believed that the majority of the halogen atoms found in marine natural products are incorporated through X^+ species, which can be related to haloperoxidases already isolated from several marine organisms.[5] In order to understand all of the halogen-incorporation processes, including the addition of chlorine to prochiral methyl groups, samples of diverse leucine derivatives labelled in different positions are required and a total synthesis of this type of compound also needs to be taken into account. Furthermore, there are several secondary metabolites of sponge and bacterial origin that possess halogenated moieties for which the electronic nature of the halogenating source remains unknown. Well known examples include barbamide (**2**)[6] and dechlorobarbamide (**3**),[7] both of which were isolated from the cyanobacteria *Lyngbya majuscula*. These metabolites have been biosynthetically studied through their production in laboratory cultures of *L. majuscula* and their precursors determined using stable-isotope biochlorination labelling methods via chloroleucine analogues.[7,8] Amino acids such as **4** and **5** have been very recently synthesised in a stereospecific way. Nevertheless, a synthesis has not been reported for dichloro derivatives such as (2*S*,4*S*)-5,5-dichloroleucine (**6**),[9] an amino acid that has only been isolated in nature from the hydrolysed

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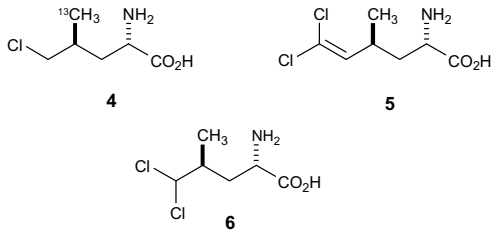
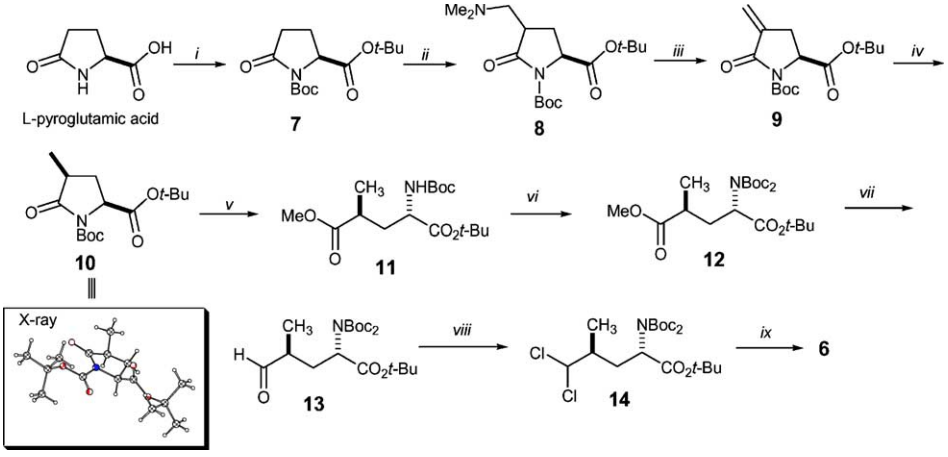
portion of the HV-Toxin M, a host-specific compound of the phytopathogenic fungus *Helminthosporium victoriae*,[10a] and also from an analogous phytotoxin, victorin, produced by the fungus *Cochiobolus victoriae*.[10b]

The route for the synthesis of **6** is shown in Scheme 1. Treatment of commercially available L-pyroglutamic acid with *tert*-butyl acetate in perchloric acid gave the ester, which was converted to the *N*-Boc derivative **7**. Our synthetic strategy was based on the studies of Nájera and co-workers for the synthesis of 4-methylene-L-glutamic acid,[11] and it included the conversion of the diprotected pyroglutamate **7** into *tert*-butyl *N*-Boc-4-methylenepyroglutamate (**9**) via the adduct **8**. The lithium lactam enolate of **7** was prepared by deprotonation with lithium hexamethyldisilazane and then reacted with commercially available Eschenmoser's salt to give **8**, which by subsequent in situ quaternisation with methyl iodide followed by elimination in basic conditions provided **9** in moderate yield. When olefin **9** was catalytically hydrogenated in EtOAc with Pd/C, *tert*-butyl (2*S*,4*S*)-*N*-(*tert*-butoxycarbonyl)-4-methylpyroglutamate (**10**) was obtained in a stereoselective manner in 95% yield. The structure of **10** was confirmed by X-ray analysis. At this point the stereocentre at C-4 was maintained by ring-opening hydrolysis of **10** with LiOH in THF at 0 °C; evidence of epimerisation was not found by NMR spectroscopy. The resulting acid was converted into the methyl ester **11** by treatment with methyl chloroformate in the presence of DMAP and triethylamine. After protecting the amide at C-2 as the di-*tert*-butoxycarbonyl derivative **12** using standard procedures, different attempts to directly convert the ester to the aldehyde **13**[12] gave negative results in that the aldehyde, starting material and alcohol were always present in the reaction mixture. This problem was circumvented by using an excess of DIBALH and the resulting alcohol was further oxidized with the Dess–Martin reagent.

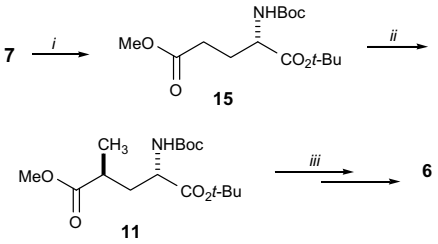


Having obtained the aldehyde, different approaches to the final *gem*-dichloroleucine analogue were examined. Several attempts involved treatment of **13** with Ph_3P/CCl_4 with different concentrations, temperatures and solvents—conditions also investigated by Willis and co-workers.[9] In all cases epimerisation at C-4 and a lack of reaction was observed by proton NMR spectroscopy. The final synthesis of **14** was achieved in moderate yield using a modification of Takeda's transformation of ketones and aldehydes to *gem*-dihalides via the hydrazone.[13] The preparation required stirring of the aldehyde with excess hydrazine monohydrate in anhydrous MeOH. Molecular sieves were added to the resulting hydrazone after the work-up and this compound was further converted in the desired dichloromethyl derivative **14** with copper(II) chloride and Et_3N as base. Epimerisation at C-4 was not observed and **14** was detected as the sole product after chromatographic separation.[14] Final hydrolysis in a standard acid medium gave the amino acid **6**.[15]

A different approach was also used to prepare **6** and this involved the hydrolysis of **7** and transformation into its methyl ester derivative **15**. 1,3-Diastereoselective induction of **15**, proposed by Hanessian and Margarita[16] gave the *anti* methylation product at C-4 (**11**) in good yield. This product was then converted to **6** in a similar way to that shown in Scheme 2. It is important to notice that this second route up compound



Scheme 1. Reagents and conditions: (i) (a) *t*-BuOAc, $HClO_4$; (b) Boc_2O, Et_3N, DMAP, DCM 46% (ii) LiHMDS, Eschenmoser salt, THF −78 °C, 74% (iii) (a) MeI, MeOH; (b) $NaHCO_3$, H_2O (Ref. 12) (iv) H_2, Pd/C 10%, EtOAc, 95% (v) (a) LiOH, THF, 0 °C; (b) $ClCO_2Me$, DMAP; Et_3N, DCM, 0 °C 70% (vi) Boc_2O, DMAP; CH_3CN; 71% (vii) (a) DIBALH, Et_2O −78 °C; (b) Dess–Martin, DCM, 66% (viii) (a) $NH_2NH_2{\cdot}H_2O$, 2 Å molecular sieves; (b) $CuCl_2$, Et_3N; MeOH, rt 40% (ix) HCl 4 N, reflux, 75%.



Scheme 2. Reagents and conditions: (i) (a) LiOH, THF, 0 °C; (b) $ClCO_2Me$, DMAP, Et_3N, DCM, 0 °C 50% (ii) HMDS, *n*-BuLi, THF −78 °C, then MeI, −78 °C, 68% (iii) Steps (vi–ix) in Scheme 1.

12 was used before by Gerwick et al. in the synthesis of **5**.[9]

The amino acid (2*S*,4*S*)-5,5-dichloroleucine (**6**) is present in several polychlorinated compounds isolated from sponges belonging to the genus *Dysidea*. These compounds include the monodechloro-demethylisodydesidenins,[1d] dysideathiazoles and its *N*-methyl derivatives,[1f,h,m] or the dysideaprolines and barbaleucamides.[10] The synthesis of **6** described here provides the opportunity to approach a total synthesis of these compounds and incorporate another metabolite in the feeding experiments aimed at discovering the biosynthesis of barbamide and dechlorobarbamide.

Acknowledgements

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12. Compound **13**: ^{1}H NMR (200 MHz, $CDCl_3$, δ_H ppm, m): 9.60 (1H, d, $J = 1.0$ Hz, H5); 4.82 (1H, dd, $J = 4.9$ and 9.3 Hz, H2); 2.46–2.32 (2H, m); 2.01 (1H, m); 1.50 (Boc_2, 18H, s); 1.45 (CO^{t}Bu, 9H, s); 1.13 (3H, d, $J = 6.7$ Hz, H2). ^{13}C NMR (50 MHz, $CDCl_3$, δ_c ppm): 203.7 (C5); 169.5 (C1); 152.3 (N($\mathbf{C}O_2^t$Bu)$_2$); 83.1 (Boc); 81.6 (CO_2^tBu); 56.7 (C2); 43.8 (C4); 30.1 (CH_2); 27.9 (CO_2^tBu); 27.8 (CO_2^tBu); 13.1 (C6).
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14. Compound **14**:^{1}H NMR (200 MHz, $CDCl_3$, δ_H ppm, m): 5.78 (1H, d, $J = 2.8$ Hz, H5); 4.79 (1H, dd, $J = 4.4$ and 10.6 Hz,); 2.29 (1H, m); 2.18–1.95 (2H, m); 1.51 (Boc_2, 18H, s); 1.45 (CO^{t}Bu, 9H, s); 1.19 (3H, d, $J = 6.3$ Hz, H6). ^{13}C NMR (50 MHz, $CDCl_3$, δ_c ppm): 169.4 (C1); 152.3 (Boc_2); 83.1(Boc_2); 81.4 (O^{t}Bu); 78.8 (C5); 56.6 (C2); 41.2 (C4); 31.4 (C3); 28.0 (Boc_2); 27.9 (O^{t}Bu); 14.9 (C6). LRFABMS (thioglycerol) m/z (%): 456 (18); 458 (11). $[\alpha]_D$ −25.5 (c 0.95, CH_2Cl_2).
15. Compound **6**: ^{1}H NMR (200 MHz, D_2O, δ_H ppm, m): 5.95 (1H, d, $J = 3.1$ Hz, H5); 3.61 (1H, dd, $J = 5.1$ and $J = 9.3$ Hz, H2); 2.21 (1H, m, H4); 1.95–1.83 (2H, m, H_23); 1.04 (3H, d, $J = 6.7$ Hz, H6). ^{13}C NMR (50 MHz, $CDCl_3$, δ_c ppm): 175.1 (C1); 79.2 (C5); 53.8 (C2); 41.1 (C4); 34.6 (C3); 15.5 (C6). ESI MS (positive ion) m/z (%): 200 (100); 202 (64). $[\alpha]_D$ −23.0 (c 0.16, HCl 1 N).
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