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Total Synthesis of the Chlorinated Marine Natural Product Dysamide B

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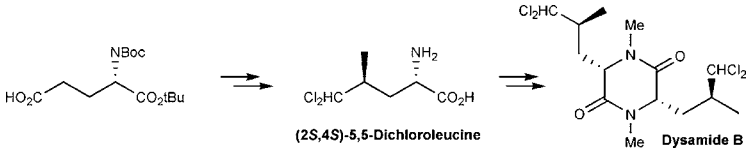
ABSTRACT



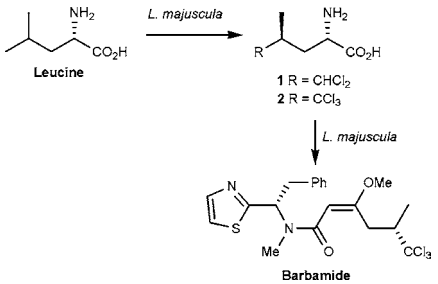
Two approaches to the synthesis of (2*S*,4*S*)-5,5-dichloroleucine are compared, and the parent amino acid was used in the first total synthesis of the polychlorinated marine natural product, dysamide B. A key step was the lead tetraacetate-mediated decarboxylation of an α,α-dichloro acid in the presence of 1,4-cyclohexadiene to generate the dichloromethyl group.

Biological halogenation occurs on a wide range of organic scaffolds including polyketides, terpenes, and non-ribosomal peptides, and more than 4500 halogenated natural products have been reported.[1] In the majority of cases, the halogens are incorporated into positions in accord with biohalogenation occurring via electrophilic species, and indeed, haloperoxidases which catalyze such reactions have been widely studied.[2] However, an intriguing family of chlorinated marine natural products exist in which the halogens are located at aliphatic positions remote from activating groups and for which the mechanism of halogenation is a topic of current interest.[3] For example, it has been shown that during the biosynthesis of barbamide, isolated from the cyanobacterium *Lyngbya majuscula*, chlorination of the pro-*R* methyl group of leucine occurs giving dichloroleucine **1** which in turn is converted to trichloroleucine **2** and hence to barbamide (Scheme 1).[4]

The isolation and characterization of the gene cluster encoding barbamide biosynthesis has been reported,[5] and recently, a mechanism for the reaction was proposed.[6]

As well as *L. majuscula*, extracts of the marine sponge−cyanobacteria symbionts, *Lamellodysidea*−*Oscillatoria* (formerly *Dysidea*−*Oscillatoria*), have proven to be a prolific source of unusual polychlorinated compounds. In 1993, symmetrical polychlorinated diketopiperazines (dysamides A and B; Figure 1) were isolated from extracts of *Lamellodysidea fragilis* (formerly *Dysidea fragilis*) and their structures were determined by spectroscopic methods.[7] The absolute configuration of dysamide A (**4**),[7] a dimer of *N*-methyl (2*S*,4*S*)-trichloroleucine, was determined by X-ray crystallography and used as a reference in the structure elucidation of other isolated diketopiperazines. Although not

Scheme 1. Biosynthesis of Barbamide in *L. majuscula*



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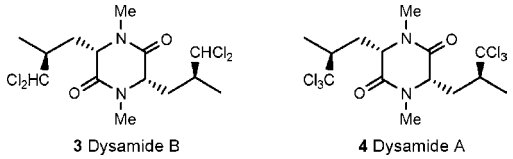
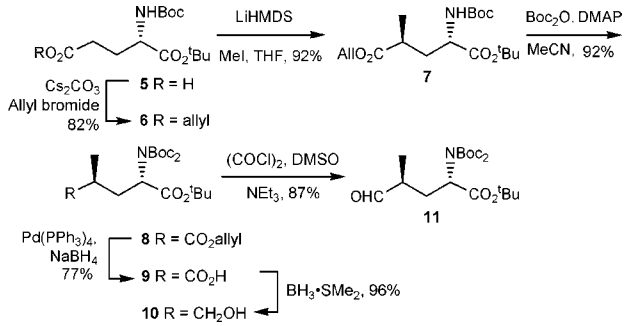


Figure 1. Structure of dysamides A and B.

proven, it is reasonable to propose that the chlorinated leucines **1** and **2** are biosynthetic precursors to diketopiperazines **3** and **4**, respectively. Further members of this family have been isolated,[8] but to date, the synthesis of none of these natural products has been reported. Herein, we describe two approaches for the preparation of (2*S*,4*S*)-dichloroleucine **1** as well as the first total synthesis of dysamide B **3**.

Because dysamide B is a symmetrical dimer based on *N*-methyl (2*S*,4*S*)-dichloroleucine, our studies began with the synthesis of the parent amino acid. Two approaches were explored via a common intermediate, aldehyde **11**. We have previously reported the synthesis of the analogous methyl ester[9] in which the asymmetric center at C-4 was generated via a directed alkylation of the lithium enolate of the N-protected glutamate[10] giving the (2*S*,4*S*)-diastereomer with excellent stereocontrol. However, we had found that the selective reduction of the terminal ester to the required aldehyde was capricious and good yields could only be obtained reliably when fresh DIBALH was employed. To overcome the problem, we now favor the use of selective reduction of a terminal acid rather than reduction of the ester with DIBALH as shown in Scheme 2. First, the known

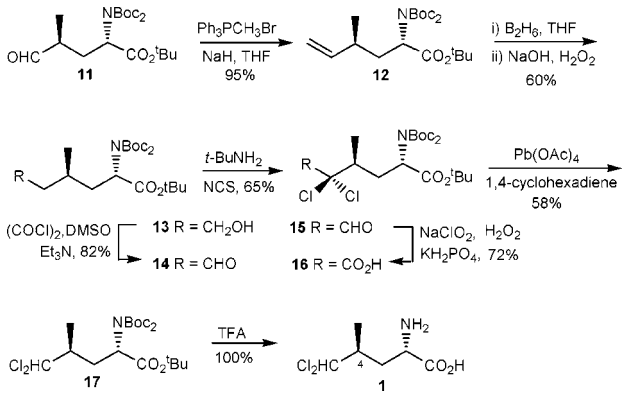
Scheme 2. Synthesis of Aldehyde **11**



glutamic acid derivative **5**[11] was temporarily protected as an allyl ester **6** by treatment with allyl bromide and cesium carbonate prior to the required alkylation which proceeded to give **7** in an excellent 92% yield with complete stereocontrol. Following conversion of **7** to the diBoc derivative **8**, the ester was cleaved via a π-allyl complex using Pd(PPh$_3$)$_4$/NaBH$_4$.[12] Reduction of acid **9** with a borane dimethylsulfide complex gave alcohol **10** which was oxidized under Swern conditions[13] to give the required aldehyde **11** in 59% overall yield from **7**.

The first approach to the synthesis of (2*S*,4*S*)-dichloroleucine relied upon a decarboxylation of α,α-dichloro acid **16** as the pivotal step using cyclohexadiene as the hydride source to access the required dichloromethyl group (Scheme 3). The substrate was readily prepared by a straightforward

Scheme 3. Synthesis of (2*S*,4*S*)-5,5-Dichloroleucine **1**



series of transformations beginning with an initial Wittig reaction under salt-free conditions to give alkene **12** in 95% yield. Hydroboration of **12** followed by Swern oxidation of the resultant primary alcohol **13** cleanly gave aldehyde **14**. α,α-Dichlorination of **14** was achieved using *tert*-butylamine and *N*-chlorosuccinimide,[14] and optimum yields were obtained when the reaction was conducted in the presence of molecular sieves giving dichloro aldehyde **15**. Williard and de Laszlo[15] have reported the use of KMnO$_4$ to oxidize an α,α-dichloro aldehyde, but in the case of oxidation of **15**, we found that sodium chlorite with hydrogen peroxide proved more reliable.

The penultimate step in the synthesis of dichloroleucine was decarboxylation of acid **16**. Halodecarboxylation of carboxylic acids has been achieved under a variety of conditions including the classical Hunsdiecker reaction (treatment of the silver salt of the acid with bromine)[16] or the Kochi reaction using Pb(OAc)$_4$ and lithium chloride.[17] Barton and co-workers[18] described the formation of noralkanes from carboxylic acids under radical conditions by irradiation of the *N*-hydroxythione derivative with tri-*n*-

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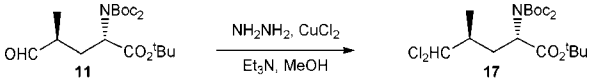
butylstannane. To prepare the target dichloride, decarboxylation of acid **16** was required in the presence of a hydride source which would not lead to concomitant reduction of the dichloride. The key to the success of this reaction was treatment of **16** with $Pb(OAc)_4$ in the presence of 1,4-cyclohexadiene generating the required dichloromethyl product **17** in 58% yield.

A more succinct approach to the required *gem*-dichloride is directly from aldehyde **11**. Several methods are known for the conversion of aldehydes to dichlorides; however, we have found, for example, that use of $Ph_3P/CCl_4/Et_3N$ led to a vinyl dichloride,[9] whereas under more forcing conditions, e.g., $SOCl_2$/DMF or PCl_5, decomposition occurred. Recently, Rodríguez[19] reported a valuable modification of the Takeda conditions (involving treatment of an aldehyde with hydrazine monohydrate in anhydrous MeOH followed by reaction with copper(II) chloride[20]) in the synthesis of dichloroleucine which has been used by the group of Walsh[6a] as well as by Gerwick Sherman, Willis, and co-workers in biosynthetic studies on barbamide.[6b] Using this method, we converted aldehyde **11** directly to the required dichloride **17**; however, we found that the reaction was capricious and yields varied from 30 to 45% (Scheme 4). Other solvents were examined

Scheme 4. Synthesis of Protected 5,5-Dichloroleucine **17**



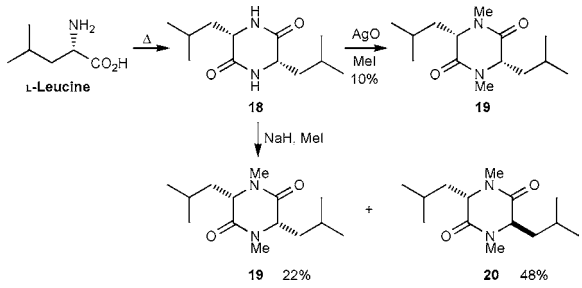
including dichloromethane, toluene, and isobutanol, but these gave a lower yield of the required *gem*-dichloride.

The final stage of the synthesis of dichloroleucine **1** was removal of the Boc group and hydrolysis of the *tert*-butyl ester. Interestingly, treatment of **17** with concentrated HCl under reflux led to the formation of a quantity (ca. 15%) of a byproduct tentatively identified as vinyl chloride (^{1}H NMR δ1.82, d, J = 1.5 Hz, 4-CH_3 and δ6.15, br. s, =CHCl; ^{13}C NMR δ141.2, C-4 and δ110.0, C-5), an observation also noted by Macko et al.[21] in the hydrolysis of the fungal phytotoxin victorin C. It was possible to avoid formation of this unwanted byproduct by carrying out the deprotection in neat TFA giving **1** in quantitative yield after ion-exchange chromatography. With quantities of (2*S*,4*S*)-dichloroleucine **1** in hand, next we turned to the synthesis of dysamide B (**3**).

Several methods have been reported for the synthesis of diketopiperazines,[22] and although dysamide B is symmetrical, our goal was to investigate a general approach which could be adapted for the synthesis of a series of symmetrical and unsymmetrical dysamides. Interestingly, in 1978 Wells and co-workers reported the isolation of a series of secondary metabolites from *Dysidea herbacea* including chlorinated diketopiperazines which, on reduction, gave a symmetrical diketopiperazine assembled from *N*-methylleucine.[23] The absolute and relative stereochemistry of the product was not assigned.

Matsunari and co-workers have reported the only synthesis of such a symmetrical diketopiperazine, and their approach began with a thermal dehydration of L-leucine to give diketopiperazine **18** (Scheme 5). N-Methylation of **18** with

Scheme 5. Synthesis of Diketopiperazines **19** and **20**[24]



MeI and silver oxide gave the cis product **19** in 10% yield, and with NaH and MeI, approximately a 1:2 mixture of *cis*- and *trans*-diketopiperazines **19** and **20** was obtained which were separated by fractional crystallization.[24] Thus, **19** was selected as our initial target to develop the synthesis of diketopiperazines by an approach which could be adapted for the preparation of symmetrical and unsymmetrical products

The strategy involved coupling of two orthogonally protected *N*-methyl amino acids **23** and **24** followed by deprotection and cyclization (Scheme 6). First, N-methylation was achieved by treatment of Cbz-L-leucine **21** with sodium hydride and methyl iodide in either CH_3CN or THF/DMF to give the known acid **24** and methyl ester **22**, respectively.[25] Removal of the Cbz group in **22** with HBr/AcOH gave the required secondary amine **23** in 88% yield. With both the orthogonally protected amino acids **23** and **24** in hand, next it was necessary to couple them using conditions which would not lead to racemization. Several standard coupling conditions were investigated (including HOAt, EDCI, $NaHCO_3$ and HOBt, and DCC)[26] which indeed gave the required dipeptide **25**, but the optimum yield was achieved using $BOPCl/Et_3N$ to give **25** as a single diastereomer.[27] To complete the synthesis of the model diketopiperazine **19**, the Cbz group was removed from **25** using HBr/AcOH followed

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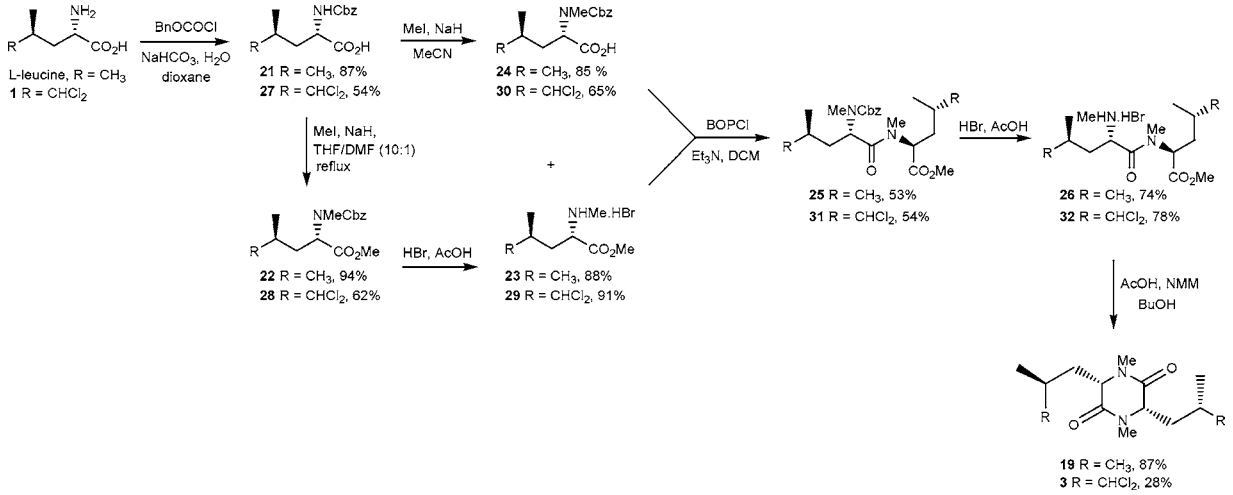
Scheme 6. Synthesis of Diketopiperazines **3** and **19**



by cyclization of amino ester **26** with AcOH/butanol/NMM.[28] This synthetic route gave diketopiperazine **19** as a single diastereomer in six steps from L-leucine and 26% overall yield.

The same approach was used for the synthesis of dysamide B **3** from (2*S*,4*S*)-dichloroleucine **1** giving the target compound as a white crystalline solid (Scheme 6). The synthetic material had the same melting point (mp 147−149 °C) as that reported for the natural product, and their spectral data correlated well. There are two papers which describe the isolation of dysamide B **3** from different sponges, namely, *Lamellodysidea (Dysidea) fragilis* and *Lamellodysidea (Dysidea) chlorea*.[29] However, although the spectral data for **3** are in good agreement, the optical rotation values are very different: $[\alpha]_D$ +13.7 (*c* 0.117 in MeOH)[7] and $[\alpha]_D$ −31 (*c* 0.8 in EtOH).[8a] Hence, the optical rotation of the synthetic material was recorded in both solvents giving $[\alpha]_D$ +11.4 (*c* 1.6 in MeOH) and $[\alpha]_D$ +20 (*c* 1.6 in EtOH) which is in accord with the value for the natural product reported in the original paper.[7]

In conclusion, two approaches to the synthesis of (2*S*,4*S*)-dichloroleucine **1** have been described which have led to the synthesis of a series of novel protected amino acids **12**−**16** as well as a new method for the decarboxylation of an α,α-dichloro acid to a dichloride using $Pb(OAc)_4$ and 1,4-cyclohexadiene as the hydride source. The first total synthesis of dysamide B **3** has been reported confirming the structure and absolute configuration of the marine natural product.

Acknowledgment. We are grateful to the BBSRC (A.C.D.) and EPSRC (G.C.L. and S.J.O.) for funding this work.

Supporting Information Available: Preparation and characterization of the compounds described in the paper. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062279F

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(29) It is now believed that the chlorinated natural products may indeed be metabolites of the symbiont cyanobacteria (*Oscillatoria*) rather then from the sponge itself.