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# Total Synthesis of (−)-Dysithiazolamide

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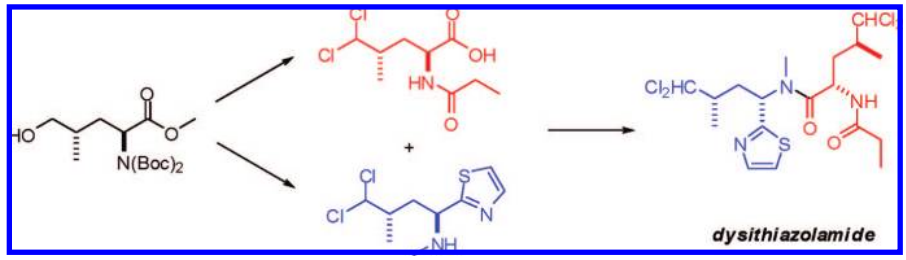
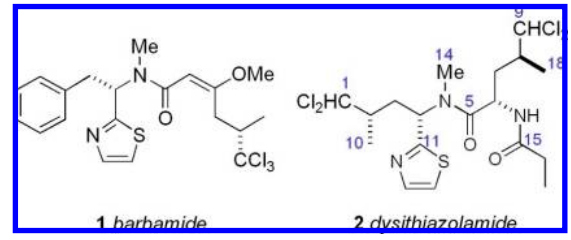
## ABSTRACT




**The tetrachlorinated natural product (−)-dysithiazolamide was synthesized from L-glutamic acid in a convergent way, confirming the previously proposed (2*S*,4*S*,6*S*,8*S*) absolute stereochemistry.**

More than 4500 natural products of both marine and terrestrial origin have in common some biohalogenation processes.[1] Very recently, Walsh and co-workers described a novel class of halogenating enzymes capable of carrying out halogenations at aliphatic carbon centers of peptidyl carrier protein-linked amino acid residues such L-leucines.[2] This mechanism of chlorination was first proposed by Gerwick et al. in the biosynthetic studies of barbamide (**1**),[3] a mixed polypeptide−polyketide natural product that contains a trichloromethyl group and whose biosynthetic gene cluster was isolated and characterized.[4] They have shown that the chlorination of the *pro-R* methyl group of leucine gives a dichloroleucine intermediate, which in turn is trichlorinated at the C5 methyl group of the amino acid attached to a peptidyl carrier.[2,5,6a]

Recently, we reported the structure of a new member of this class of compounds,[6] the tetrachlorinated dipeptide dysithiazolamide (**2**), the relative configuration of which was deduced through configurational analysis using proton−proton and proton-carbon coupling constants.[7] Furthermore, the absolute configuration was proposed by comparison with previous compounds isolated from *Dysidea* species. In order to confirm the absolute configurations of the four chiral centers present in **2**, in this paper we describe the total synthesis of (−)-(2*S*,4*S*,6*S*,8*S*)-dysithiazolamide.




The preparation of this kind of compounds, which contain a *gem*-dichloromethyl group, has hardly been described, probably due to the difficulty in the selective generation of this functionality. Some examples include the synthesis of

(1) (a) Gribble, G. W. *J. Chem. Educ.* **2004**, *81*, 1441–1449. (b) Gribble, G. W. *Am. Sci.* **2004**, *92*, 342–349. (c) Gribble, G. W. In *Natural Production of Organohalogen Compounds*; Gribble, G. W., Ed.; Springer-Verlag, New York, 2003. (d) Neidleman, S. L.; Geigert, J. *Biohalogenation: Principles, Basic Roles and Application*; Halsted: New York, 1986.

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(4) Chang, Z.; Flatt, P.; Gerwick, W. H.; Nguyen, V.-A.; Willis, C. L.; Sherman, D. H. *Gene* **2002**, *296*, 235–247.

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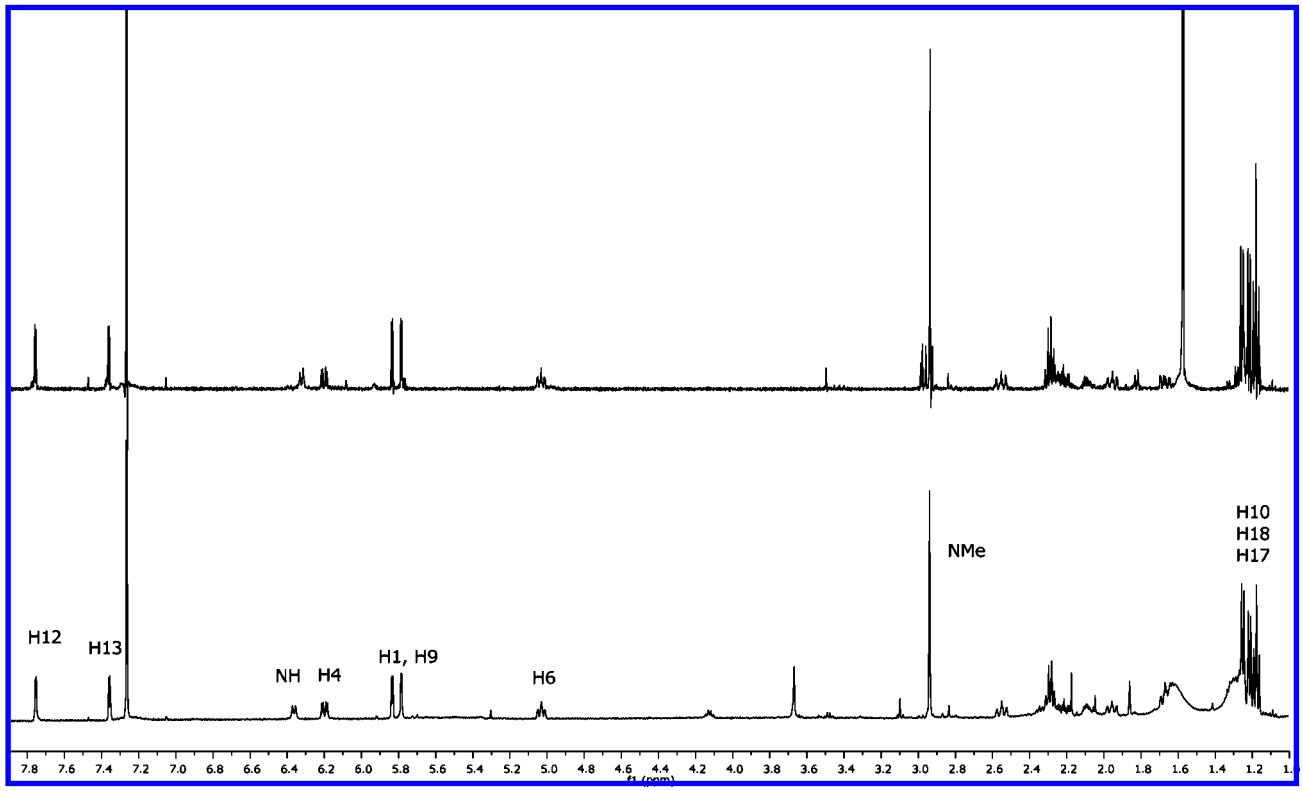
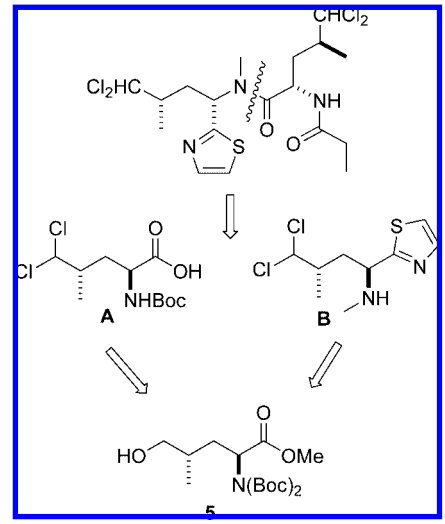



**Figure 1.** $^1$H NMR (500 MHz, $CDCl_3$) spectra of synthetic (top) and natural (bottom) dysithiazolamide.

dysamide B[8] and both *anti*- and *syn*-5,5-dichloroleucines reported by us,[9] in which the dichloromethyl group was introduced by treatment of an aldehyde with hydrazine and $CuCl_2$.[10]

Using this methodology, our overall retrosynthetic plan (Scheme 1) was supported by a convergent synthesis from fragments **A** and **B**, which can be obtained from a common precursor. To achieve this goal, compound **5** was found to be a good choice. It was easily accessible from L-glutamic acid in five steps (Scheme 2), and it allowed us the manipulation of all the functional groups in an orthogonal way. Having obtained compound **3** using a 1−3 asymmetric induction reported by Hanessian and co-workers,[11] a sterically bulky reductant was needed for the selective reduction of the $\gamma$-ester. At this stage, a second Boc protecting group was introduced on the nitrogen to avoid cyclization due to nucleophilic attack by nitrogen on the aldehyde.[12] Two different precursors to fragment **A** were easily accessible from compound **5**. The dichloromethyl was introduced after oxidation of the hydroxyl group to give the expected aldehyde (Scheme 3). Several methods are known for the conversion of aldehydes to dichlorides. In the same way as Willis and co-workers,[6] different methods were tried ($SOCl_2$, $PCl_5$ and $Ph_3P/CCl_4$), but in all cases products were not obtained. We recently reported a variation of the Takeda conditions in the synthesis of *gem*-dihalides, and these involve treatment of the aldehyde with hydrazine monohydrate in anhydrous MeOH followed by reaction with copper(II) chloride.[7] In this way, we converted aldehyde **6** into the target *gem*-dichloride **7** in moderate yield.

**Scheme 1**

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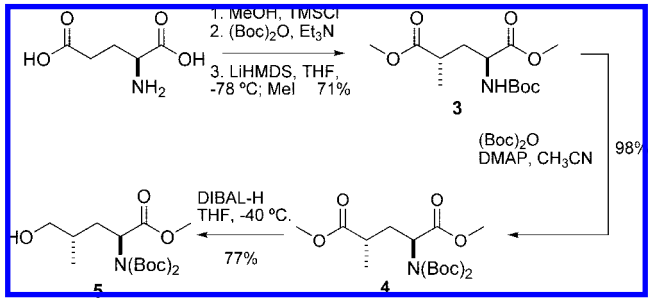
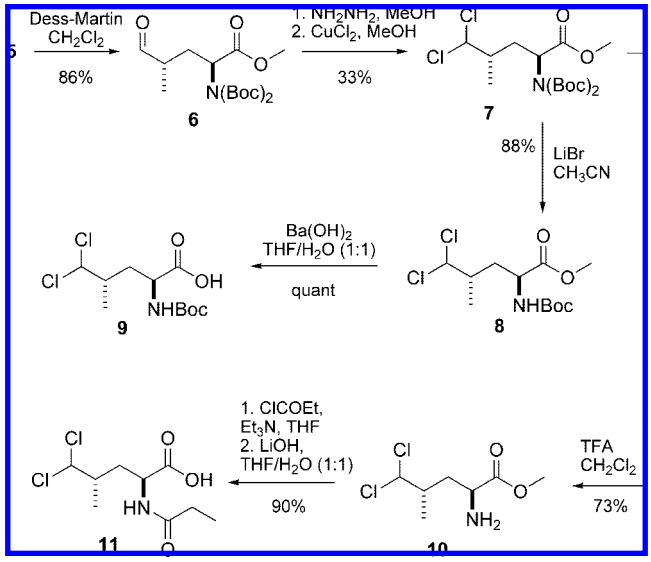
(6) (a) Flatt, P. M.; O'Connell, S. J.; McPhail, K. L.; Zeller, G.; Willis, C. L.; Sherman, D. H.; Gerwick, W. H. *J. Nat. Prod.* **2006**, *69*, 938–944. (b) Hartung, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 1209–1211.
(7) Ardá, A.; Rodriguez, J.; Nieto, R.; Bassarello, C.; Gomez-Paloma, L.; Bifulco, G.; Jiménez, C. *Tetrahedron* **2005**, *61*, 10093–10098.
(8) Durow, A. C.; Long, G. C.; O'Connell, S. J.; Willis, C. L *Org. Lett.* **2006**, *8*, 5401–5404.

**Scheme 2**




In order to obtain two possible fragments to test in the final coupling with fragment **B**, we carried out the syntheses of the corresponding acids **9** and **11**, with and without the *N*-propionyl group, respectively. Compound **9** was easily obtained from **7** by selective deprotection of one Boc group[13] and basic hydrolysis in $Ba(OH)_2$; meanwhile, total deprotection of the amine group in acidic media, introduction of the *N*-propionyl group, and basic hydrolysis gave **11** in very good yield.

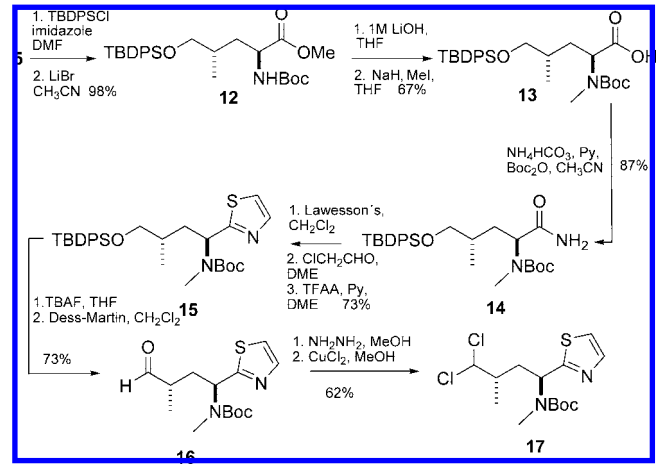
**Scheme 3**




For the synthesis of fragment **B** we needed to achieve three key transformations: the introduction of the methyl group at the nitrogen; the formation of the thiazole ring from the carbonyl function; and the synthesis of the dichloromethyl group from the aldehyde at position 5. Therefore, the alcohol group in **5** was protected with TBDPS and in order to reduce the acidity in the α-position, which could lead to side methylation, the corresponding methyl ester was hydrolyzed with LiOH in THF. Treatment of the acid with NaH and MeI in THF yielded compound **13**.

The synthesis of the thiazole ring was carried out using the Hantzsch methodology through reaction of chloroacetaldehyde (prepared from the corrresponding dimethyl acetal under reflux with 1.5 M $H_2SO_4$)[14] and the corresponding thiamide (Scheme 4). Therefore, carboxylic acid **13** was

**Scheme 4**




transformed into amide **14** with $Boc_2O$ in the presence of ammonium bicarbonate and pyridine.[15] Treatment of **14** with Lawesson's reagent gave the expected thiamide, which was then treated with chloroacetaldehyde in the presence of potassium bicarbonate in DME. This led to the isolation of the thiazoline while avoiding the imine−enamine tautomerization that would lead to epimerization at the chiral center adjacent to the thiazole ring. Dehydration with TFAA in DME and pyridine[16] allowed us to obtain the thiazolic compound **15**. After removal of the silyl protecting group we turned our attention to the oxidation of the alcohol with Dess−Martin periodinane, which gave the key aldehyde **16**. This compound was then converted to the *gem*-dichloride **17** in good yield.

With compounds **9**, **11**, and **17** in hand, we considered the final coupling to obtain dysithiazolamide. First, we investigated the most obvious coupling between **11** and the analogous amine derived from **17**. Acid-mediated removal of the Boc group from **17** followed by addition of 1.0 equiv of **11** in the presence of the coupling agent bromo-tris-

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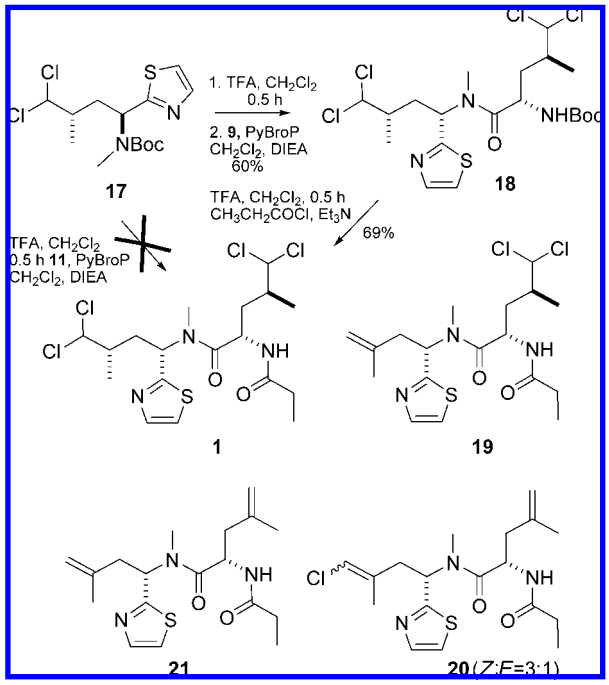
**Scheme 5**




pyrrolidinophosphoniumhexafluorophosphate, PyBroP, in DIEA did not give coupled product. However, under the same conditions the reaction between the amine derived from **17** and **9** gave the expected coupled compound **18**, which was used in the next synthetic step without further purification. Final substitution of the Boc nitrogen-protecting group for the propionyl moiety gave the natural compound **2**, along with four unexpected analogs, 1,1-didehydrochlorodysithiazolamide (**19**), 1,9,9-tridehydrochlorodysithiazolamide (**20** *Z*/*E*) in a 3:1 ratio and 1,1,9,9-tetradehydrochlorodysithiazolamide (**21**), all of which were identified by HR-ESIMS and 2D NMR spectroscopy.

The synthetic product **2** was spectroscopically indistinguishable from the natural material, showing a very similar optical rotation.[17] The dehydrochlorination products **19**−**21** can be explained as side products formed under the coupling conditions used for the union of **17** and **9**. Although this type of transformation has rarely been described in the literature,[18] it is a process that we also observed in our synthesis of (2*S*,4*R*)-5,5-dichloroleucine.[9b]

In conclusion, a practical and reasonably efficient synthesis of dysithiazolamide has been developed, confirming the initially proposed (2*S*,4*S*,6*S*,8*S*) absolute stereochemistry. It is also important to note the robustness and the extremely useful spectroscopic tool provided by the *J*-based configurational analysis, which almost 10 years after its disclosure to the scientific community is a widely used methodology for the assignment of relative configurations of polysubstituted acyclic carbon chains, including nitrogen-containing compounds.

**Acknowledgment.** This work was financially supported by the Ministerio de Educación y Ciencia, project CQT2005-00793, and the Xunta de Galicia (PGIDI06PXIC103118PN and PGIDIT05RMA10302PR). We also thank CESGA. R.G.S. and M.I.N. acknowledge the Xunta de Galicia for the Parga Pondal Program.

**Supporting Information Available:** Synthesis and spectroscopic data for all intermediates and copies of $^{1}H$ and $^{13}C$ NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Natural $[\alpha]^{25}_{D}$ −35 (*c* 0.08, $CH_2Cl_2$); **2** $[\alpha]^{25}_{D}$ −42 (*c* 0.28 $CH_2Cl_2$).

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