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Synthesis of the marine natural product barbamide

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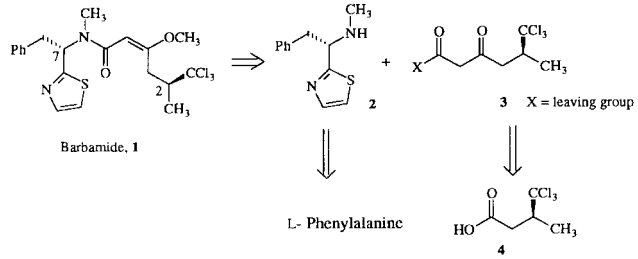
The first total synthesis of the trichlorinated natural product barbamide is described. The convergent approach involves coupling (*S*)-3-trichloromethylbutanoyl chloride with Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) to give 15 followed by addition of the novel secondary amine *N*-methyl-(*S*)-dolaphenine 2 (prepared in 6 steps and 24% overall yield from *N*-Cbz-L-phenylalanine) to give the β-keto amide 16 which was converted directly to the required (*E*)-enol ether.

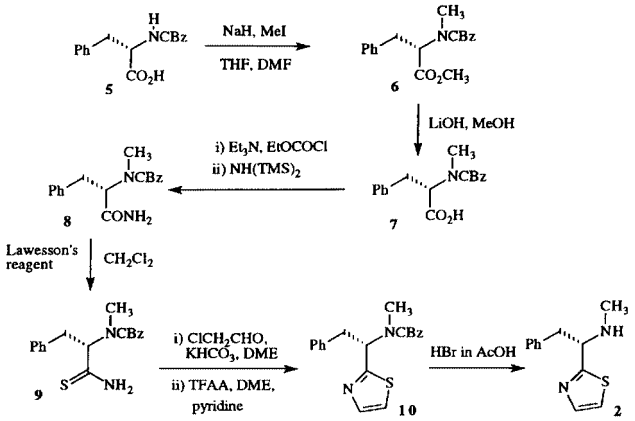
An interesting feature of many biologically active marine-derived natural products is the covalent inclusion of chlorine and bromine. Several compounds which contain a trichloromethyl group have been isolated from sponges of the genus *Dysidea* which have symbiotic association with cyanobacteria.[1] The polychlorinated natural products include, for example, the dysamides,[2] dysidin,[3] dysidenin,[4] herbacic acid[5] and herbamide A.[6] It has been suggested that sponge-based dysidenins are biosynthesised from associated cyanobacteria and indeed in 1996 a new natural product, barbamide, was found in the extracts of the cyanobacterium *Lyngbya majuscula*.[7] From extensive spectrocopic studies, it was proposed that barbamide has the structure **1** encompassing a trichloromethyl group, a thiazole ring as well as the methyl enol ether of a β-keto amide. Barbamide is an intriguing natural product in that the trichloromethyl group derives from the *pro-R* methyl group of leucine without detectable activation to facilitate a potential nucleophilic or electrophilic chlorination process. Hence, we have proposed that biochlorination occurs through a novel process, possibly involving radical chemistry.[8] In the majority of halogenated natural products the halogens are incorporated into positions which are suggestive of their biochemical reaction involving electrophilic species and indeed haloperoxidases which catalyse such reactions have been widely studied.[9]

Herein we report the first total synthesis of barbamide which confirms the structure of the natural product. Degradation studies have indicated that the configuration at C-7 is *S*.[8] Our retrosynthetic analysis is shown in Scheme 1 and involves cleavage of the amide bond to give two fragments: (*S*)-*N*-methyldolaphenine **2** which would be derived from L-phenylalanine and ketone **3** from (*S*)-3-trichloromethylbutanoic acid **4**.

The route for the synthesis of (*S*)-*N*-methyldolaphenine **2** is shown in Scheme 2. Treatment of commercially available *N*-Cbz-L-phenylalanine **5** with an excess of sodium hydride and



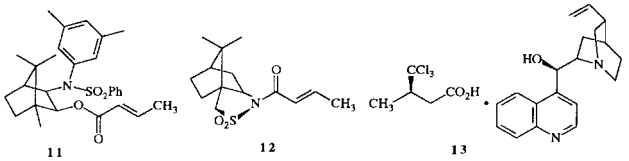
Scheme 1 Retrosynthetic analysis of barbamide.



Scheme 2 Synthesis of (*S*)-*N*-methyldolaphenine.

methyl iodide gave the *N*-methyl methyl ester **6** which was hydrolysed to the corresponding acid **7** in 80% yield over the 2 steps. A modified Hantsch method was used to form the thiazole ring in which the acid **7** was first converted to an amide **8** *via* a mixed anhydride using the approach described by Pellegata and coworkers.[10] Treatment of amide **8** with Lawesson's reagent at room temperature in dichloromethane[11] gave thioamide **9** in 71% yield over the two steps from acid **7**. Reaction of **9** with α-chloroacetaldehyde (prepared from the corresponding dimethyl acetal[12]) in DME in the presence of potassium hydrogen carbonate followed by dehydration using trifluoroacetic anhydride[13] gave (*S*)-*N*-Cbz-*N*-methyldolaphenine **10** as a yellow oil. Finally removal of the Cbz protecting group with hydrobromic acid in acetic acid gave an analytically pure sample of the novel secondary amine **2** with $[\alpha]_D$ −3.02† (*c* 0.65 in $CHCl_3$). To ensure that the stereochemical integrity at C-2 of **2** had been maintained throughout the synthetic route a sample of the (*R*,*R*)-tartrate salt was prepared in $CD_3OD:D_2O$ (4:1).[14] The ^{1}H-NMR spectrum of the product showed a downfield shift of the signal assigned to 2-H from δ 4.22 for amine **2** to δ 4.97 in the salt, there was no trace of the other diastereomer which was clearly apparent in a control experiment with the (*R*,*R*)-tartrate salt of racemic amine.

With the required amine **2** in hand, we next turned our attention to the synthesis of ketone **3** for which multigram quantities of **4** were needed (Scheme 1). Several methods have been reported for the preparation of **4** and the most direct is conjugate addition of a trichloromethyl anion to the chiral crotonyl derivatives **11** and **12**.[15,16] Unfortunately, despite



several attempts to repeat these reactions on a synthetically useful scale, in our hands generation of either trichloromethylmagnesium chloride[15] or trichloromethyllithium[16] at low temperature for reaction with **11** and **12** respectively did not

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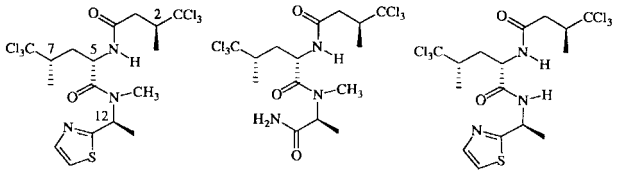
give acceptable yields of the required product. A more satisfactory approach proved to be resolution of the racemic acid.

Racemic trichloromethylbutanoic acid has been prepared previously *via* radical addition of bromotrichloromethane to crotonic acid followed by treatment of the resultant α-bromo acid with zinc.[17] The acid may then be resolved by separation of the corresponding (−)-(*R*)-α-phenylglycinol derivatives by HPLC giving **4** with 81% ee. However, there is some confusion in the literature with the sign of the optical rotation for (*S*)- and (*R*)-trichloromethylbutanoic acid.[18] Thus, in order to remove any possible ambiguity, the cinchonidine salt of **4** was prepared and repeated crystallisation of the salt from methanol and water[16] gave a single diastereomer as determined by ^{1}H- and ^{13}C-NMR spectroscopy. X-Ray crystallography revealed the (*R*)-configuration for C-3 of the trichloromethylbutanoic acid portion of the salt **13**. Treatment of the salt with potassium hydroxide followed by 2 M HCl gave, after work up, (*R*) (+)-**4** with $[\alpha]_D$ +25 (*c* 1.8 in EtOH).

For the synthesis of **4**, the (4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone[19] derivative of racemic trichloromethylbutanoic acid was prepared and the diastereomers were separated by column chromatography on silica. Following hydrolytic cleavage with lithium hydroxide–hydrogen peroxide the required (*S*)-**4** ($[\alpha]_D$ −28.9, *c* 0.96 in EtOH; lit.[15] −28.09, *c* 2.12 in EtOH) was isolated as well as recovered auxiliary, both in quantitative yield. From the retrosynthetic analysis shown in Scheme 1, the next stage of the synthesis of barbamide required a two carbon homologation of (*S*)-trichloromethylbutanoic acid **4** to give a β-keto acid derivative **3** with a suitable leaving group for reaction with (*S*)-*N*-methyldolaphenine **2**. Several approaches were investigated to achieve these final steps and the most direct route proved to be conversion of acid **4** to the corresponding acid chloride **14** with thionyl chloride followed by coupling **14** with Meldrum's acid to give the intermediate **15** (Scheme 3).[20] Treatment of **15** with **2** gave **16** with the framework of barbamide in 51% yield over the three steps from **4**. Finally, the (*E*)-enol ether was formed by reaction of β-keto amide **16** with sodium hydride and dimethyl sulfate in the presence of HMPA. A 1 : 1 mixture of two products was formed in this final stage of the synthesis due to epimerisation at C-7 under the basic reaction conditions. These compounds were readily separated by HPLC[21] giving the less polar product barbamide **1** and 7-epibarbamide **17**, $[\alpha]_D$ +73.4 (*c* 1.13 in CH_3OH). The ^{1}H- and ^{13}C-NMR and mass spectra of the synthetic material **1** were found to be identical with those of the natural product.[7] The optical rotation of synthetic barbamide was $[\alpha]_D$ −81.9 (*c* 0.95 in CH_3OH) whilst that of an authentic sample of the natural product gave $[\alpha]_D$ −82 (*c* 1.2 in CH_3OH).

Recently three further metabolites (pseudodysidenin **18**, dysidenamide **19** and nordysidenin **20**) containing the 3-trichloromethylbutanyl unit have been isolated from *L. majuscula*.[22] Unlike barbamide which is biosynthesised from L-trichloroleucine and a derivative of L-phenylalanine,[8] it is apparent that these metabolites are assembled from L-trichloroleucine and an L-alanine derivative (as determined by degradation studies). The 2*S*,5*S*,7*S* configurations of **18**, **19** and **20** were assigned by chiral HPLC and comparison of their optical rotations (which were all negative) to other polychlorinated natural products.[22] The synthetic studies described herein confirm that barbamide **1** isolated from extracts of *L. majuscula*, encompasses the (3*S*)-trichloromethylbutanyl unit which is in accord with the assignment of the configuration of the 2*S* and 7*S* stereocentres in these new structurally related metabolites **18**, **19** and **20** which have been isolated more recently from *L. majuscula*.



Pseudodysidenin, **18** Dysidenamide, **19** Nordysidenin, **20**

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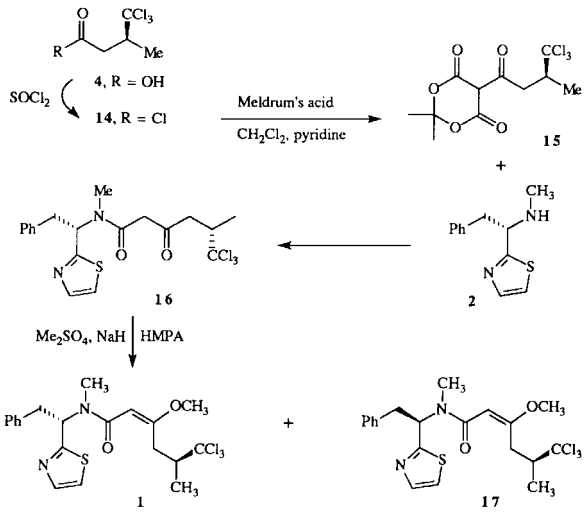

Scheme 3

Notes and references

† Units of $[\alpha]_D$ are 10^{-1} deg cm^2 g^{-1} throughout.

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