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Total synthesis of lyngbyabellin A, a potent cytotoxic metabolite from the marine cyanobacterium *Lyngbya majuscula*

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Abstract—The first total synthesis of lyngbyabellin A, a novel peptolide from the marine cyanobacterium *Lyngbya majuscula*, is described. Both functionalized thiazole carboxylic acid units were synthesized using our CMD (chemical manganese dioxide) oxidation from the corresponding thiazolidines. The asymmetric synthesis of the dichlorinated β-hydroxy acid was achieved by the chiral oxazaborolidinone mediated aldol reaction. Finally, fragment condensation followed by the macrolactamization provided lyngbyabellin A.

Lyngbyabellin A (**1**) was isolated from the marine cyanobacterium *Lyngbya majuscula* collected at Apra Harbor, Guam.[1,2] It has exhibited attractive cytotoxic properties against the human cancer cell lines and shown to be a potent disrupter of the cellular microfilament network. This novel peptolide is structurally related to dolabellin (**2**), another compound originally isolated from the sea hare *Dolabella auricularia* (Fig. 1).[3] While both compounds consist of two functionalized thiazole carboxylic acid units and a dichlorinated β-hydroxy acid, the structural modifications including the presence of two amino acid units (glycine and isoleucine), hydroxylation of C-27, and its cyclic nature make **1** interesting and distinctive. Our interest in the total synthesis of the thiazole-based marine natural products[4] led us to investigate the synthesis of lyngbyabellin A (**1**). In this letter, we wish to report the first total synthesis of lyngbyabellin A (**1**).

In our convergent strategy, lyngbyabellin A (**1**) is separated into the two thiazole fragments (**3** and **4**), the dichlorinated β-hydroxy acid **5**, and Boc-glycine (**6**). Subsequent segment condensation of these fragments and macrolactamization gives the desired macrocycle (Scheme 1).

For the preparation of the thiazole amino acid fragment **3**, we applied our CMD (chemical manganese dioxide) oxidation for the conversion of thiazolidine to thiazole (Scheme 2).[4a,5] The coupling of (*S*)-Boc-isoleucine (**7**) with *N*,*O*-dimethylhydroxyl amine using diethyl phosphorocyanidate (DEPC, $(EtO)_2P(O)CN$)[6] afforded the amide **8** in 81% yield. Reduction of the amide **8** with lithium aluminum hydride[7] followed by condensation of the resulting aldehyde with the cysteine methyl ester gave the thiazolidine **9** in 69% yield. Subsequent CMD oxidation of the thiazolidine **9** provided the thiazole fragment **3** in 58% yield without epimerization at the α-chiral center of the thiazole ring.

Next, we attempted the synthesis of the α,β-dihydroxy thiazole fragment **4** according to the same CMD methodology. Condensation of 3,3-dimethylacrolein (**10**) with the cysteine methyl ester gave the corresponding thiazolidine, which was directly used for the CMD oxidation to afford the desired thiazole **11** in 7% yield. Although we were unable to improve the yield of the oxidation due to the instability of the thiazolidine, the thiazole **11** was obtained in only two steps from the commercially available aldehyde **10**. Alternatively, we synthesized the thiazole **11** via the thiazoline **15** from the cysteine *N*-amide **14**. The fully protected cysteine *N*-amide **14** was prepared from (*R*)-Fmoc-*S*-trityl cys-

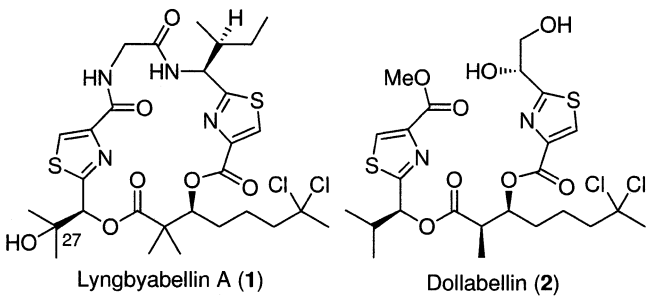

Figure 1. Structures of lyngbyabellin A and dollabelin.

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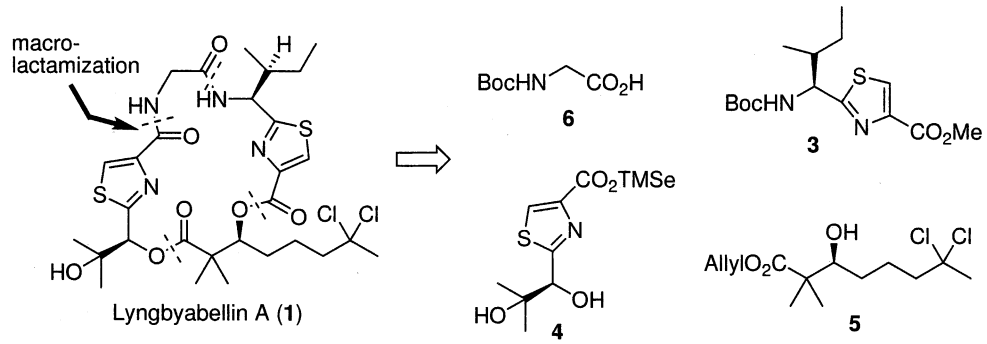
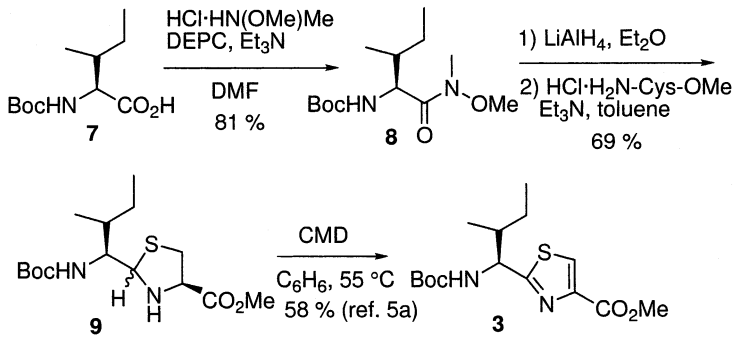


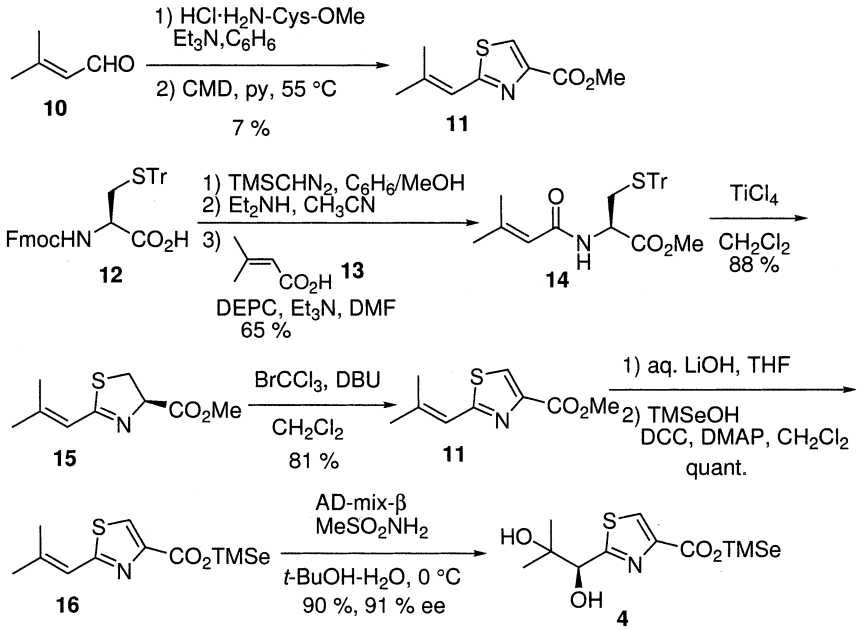
Scheme 1. Retrosynthetic analysis of lyngbyabellin A.



Scheme 2. Synthesis of Boc-Ile-Thz-OMe (**3**).

teine (**12**) through (1) methyl esterification using $TMSCHN_2$,[8] (2) deprotection of the Fmoc group, and (3) coupling with 3-methylcrotonic acid (**13**) using DEPC in 65% yield. The titanium (IV)-mediated tandem deprotection–dehydrocyclization of **14**[9] produced the thiazoline **15** in 88% yield, which was dehydrogenated with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU)/$BrCCl_3$[10] to give the thiazole **11** in 81% yield. Replacement of the methyl ester function with the trimethylsilyl ethyl (TMSe) one quantitatively afforded **16** in two steps. Asymmetric dihydroxylation[11] of the thiazole **16** with Sharpless' AD-mix-β in the presence of methanesulfonamide gave the required α,β-dihydroxy thiazole fragment **4** with 91% enantiomeric excess (ee)[12] in 90% yield (Scheme 3).

The stereoselective synthesis of the dichlorinated β-hydroxy acid fragment was achieved by the enantioselective aldol reaction developed by Kiyooka.[13] The aldol reaction of the aldehyde **17**[3] with commercially



Scheme 3. Synthesis of the α,β-dihydroxy thiazole **4**.

available methyl trimethylsilyl ketene acetal (**18**) using a stoichiometric amount of the chiral oxazaborolidinone **19** derived from (*R*)-valine in THF proceeded to give the (*S*)-β-hydroxy ester **20** with 97% ee in 58% yield.[14] The absolute configuration of **20** was ascertained by transformation into the corresponding (*S*)- and (*R*)-MTPA esters **21**, and comparison of the ^{1}H NMR spectra as shown in Fig. 2.[15] Finally, replacement of the methyl ester with the allyl ester provided the desired β-hydroxy acid fragment **5** in 94% yield (Scheme 4).

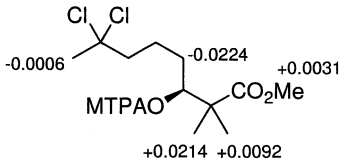
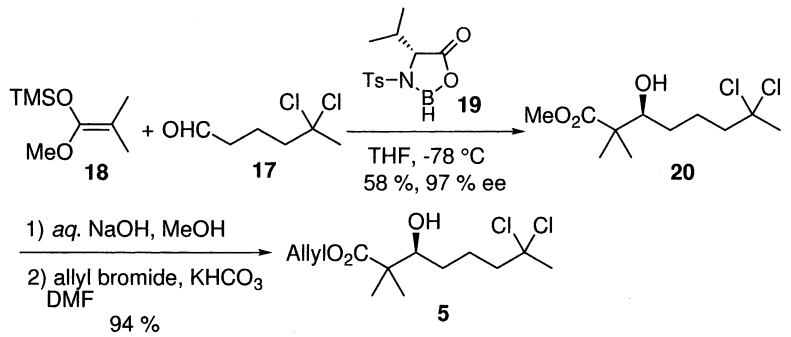
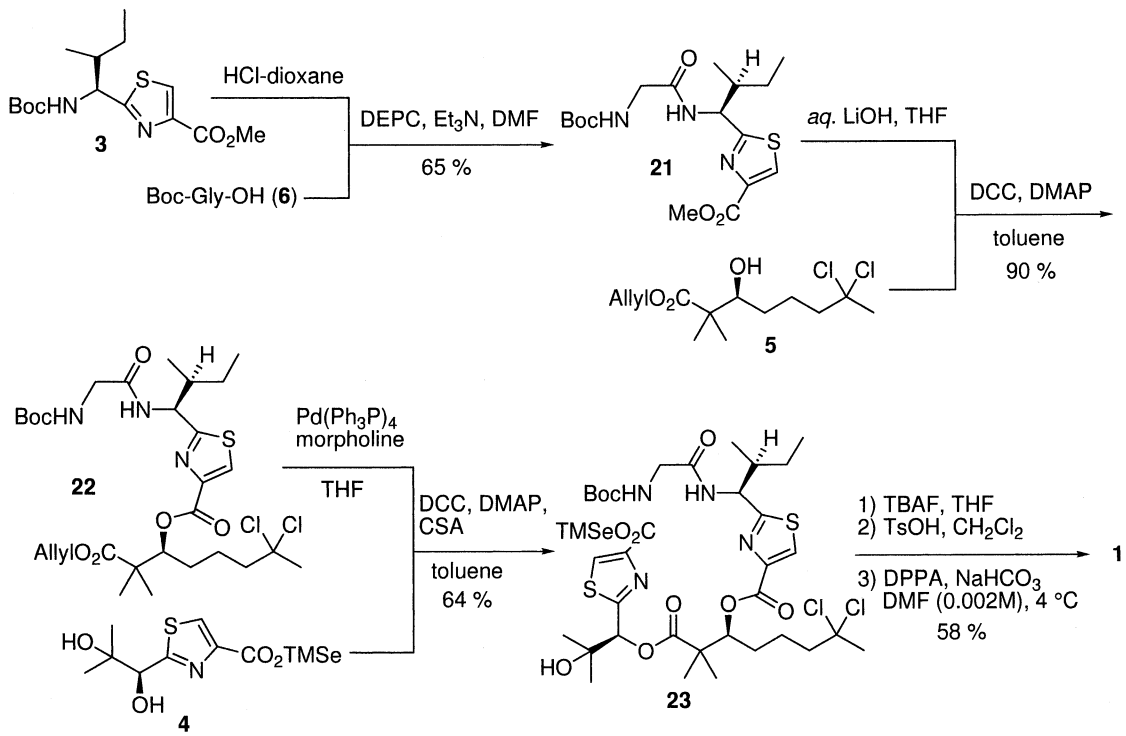


Figure 2. $\Delta\delta$ ($\delta S-\delta R$) values (ppm) obtained from ^{1}H NMR spectral data in $CDCl_3$.

The segment condensation was initiated by deprotection of the Boc group in **3** with hydrogen chloride followed by coupling with Boc-glycine (**6**) using DEPC to give the dipeptide **21** in 65% yield. Ester saponification of **21** followed by condensation with the β-hydroxy acid fragment **5** using dicyclohexyl carbodiimide (DCC) in the presence of *N*,*N*-(dimethylamino)pyridine (DMAP) produced the depsipeptide **22** in 90% yield. After cleavage of the allyl ester in **22** with $Pd(Ph_3P)_4$ in the presence of morpholine, coupling of the resulting carboxylic acid with the α,β-dihydroxy thiazole fragment **4** required considerable optimization of the yields and was accomplished under Keck conditions[16] to produce the linear precursor **23** in 64% yield. Finally, after removal of the TMSe group at the C-terminus of **23** by tetra *n*-butylammonium fluoride (TBAF) and then deprotection of the Boc group at the *N*-terminus with *p*-toluenesulfonic acid (TsOH), the macrolactamization was efficiently achieved using diphenyl phosphorazidate (DPPA, $(PhO)_2P(O)N_3$)[17,18] in the presence of sodium hydrogen carbonate to provide lyngbyabellin A (**1**) in



Scheme 4. Synthesis of the dichlorinated β-hydroxy acid **5**.



Scheme 5. Total synthesis of lyngbyabellin A (**1**).

58% yield. The ^{1}H and ^{13}C NMR spectra as well as the specific rotation of our synthetic lyngbyabellin A (**1**) were completely identical with those published for the natural product (Scheme 5).

In summary, we have developed an efficient and convergent strategy for the total synthesis of the structurally and biologically attractive lyngbyabellin A (**1**). Application of this strategy to the synthesis of lyngbyabellin B[2] is currently underway in our laboratory.

Acknowledgements

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