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Synthesis of Dolastatin G and Nordolastatin G, Cytotoxic 35-Membered Cyclodepsipeptides of Marine Origin

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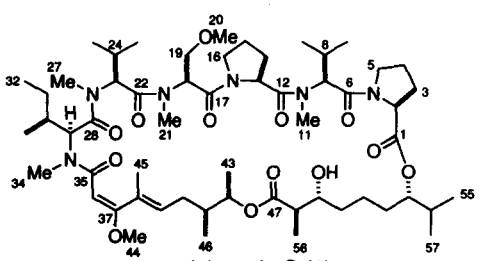
Abstract: The synthesis of dolastatin G (**1**) and nordolastatin G (**2**), new cytotoxic cyclodepsipeptides from the Japanese sea hare *Dolabella auricularia*, was achieved enantioselectively, and the present result confirmed their stereostructures unambiguously. Copyright © 1996 Elsevier Science Ltd

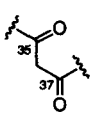
Recently we isolated dolastatin G (**1**) and nordolastatin G (**2**) from the Japanese sea hare *Dolabella auricularia*, which exhibited cytotoxicities against HeLa S_3 cells with IC_{50} values of 1.0 and 5.3 μg/mL, respectively.[1] The stereostructures of dolastatin G (**1**) and nordolastatin G (**2**) were elucidated to be novel 35-membered cyclodepsipeptides, as depicted in formulas **1** and **2**, on the basis of spectral analysis and an organic synthetic method.[1] We describe herein the synthesis of dolastatin G (**1**) and nordolastatin G (**2**), and the present result confirms their stereostructures unambiguously.

Synthesis of dolastatin G (**1**) and nordolastatin G (**2**) was carried out by a convergent approach: hexapeptide **3**, β-keto ester **4**, and the protected dihydroxy acid **5** were synthesized, respectively; subsequently, they were combined to give a seco acid, which was cyclized to afford nordolastatin G (**2**) and then dolastatin G (**1**).

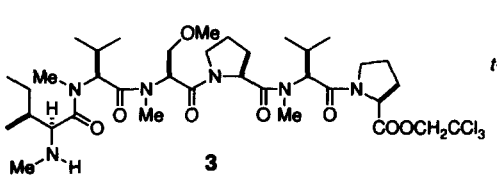
Synthesis of hexapeptide **3**[2] was carried out starting from L-proline benzyl ester hydrochloride in a stepwise manner in 65% overall yield (Scheme 1).



dolastatin G (**1**)



nordolastatin G (**2**)



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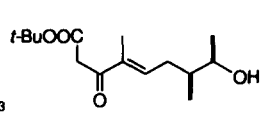

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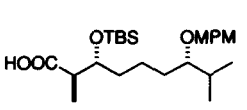

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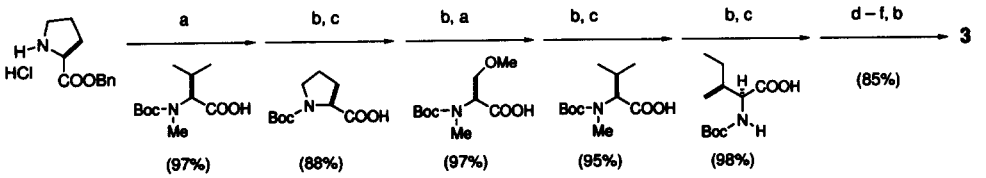
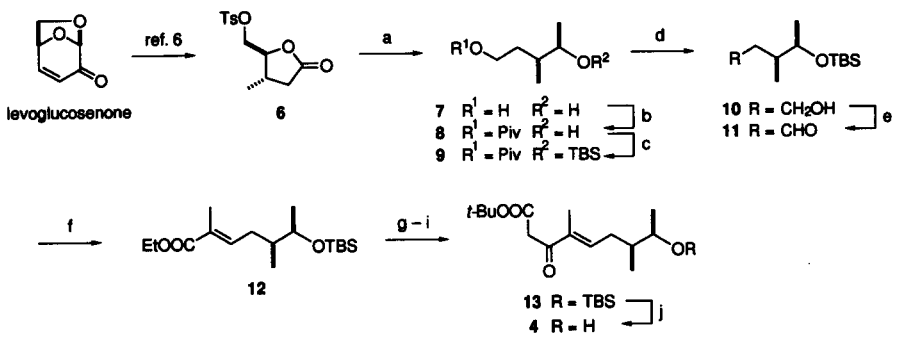


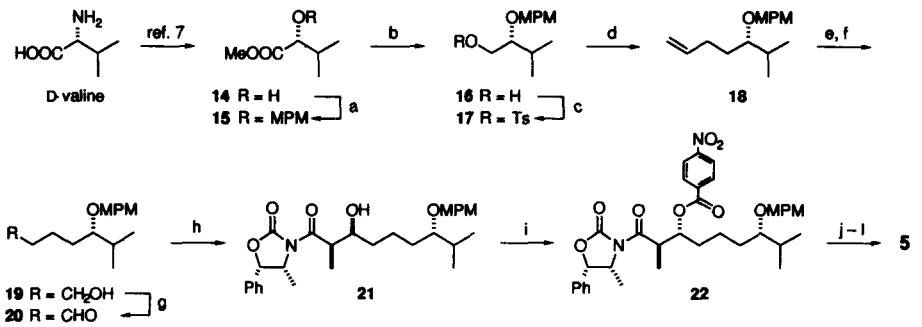
Scheme 1. Reagents and conditions: (a) DEPC,[3] Et_3N, DMF, 23 °C; (b) TFA, CH_2Cl_2, 0 °C; (c) PyBOP,[4] *i*-Pr_2NEt, CH_2Cl_2, 23 °C; (d) MeI, NaH, DMF, 0 °C; (e) H_2, Pd/C, EtOH, 23 °C; (f) $HOCH_2CCl_3$, EDCI·HCl,[5] DMAP, CH_2Cl_2, 23 °C.



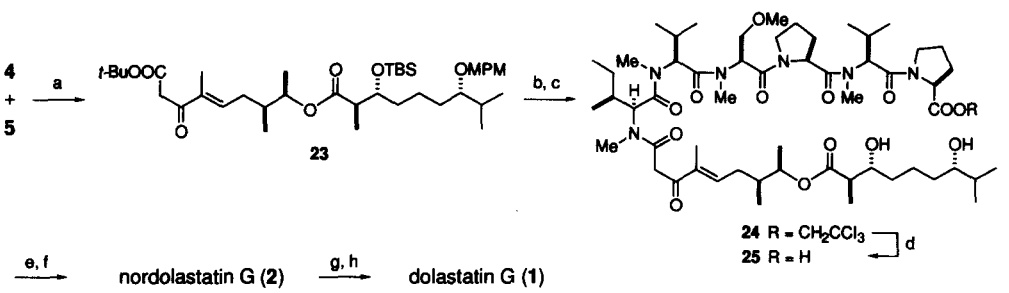
Scheme 2. Reagents and conditions: (a) $LiAlH_4$, THF, 23 °C; (b) Me_3CCOCl (PivCl), pyr, 0 °C (68%, 2 steps); (c) TBSCl, imidazole, DMF, 23 °C; (d) DIBAL, CH_2Cl_2, –78 °C (92%, 2 steps); (e) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, –78 °C → 0 °C; (f) $(EtO)_2P(O)CH(Me)COOEt$, NaH, DME, 23 °C (80%, 2 steps); (g) LiOH, MeOH, H_2O, 23 °C; (h) carbonyl diimidazole, THF, 23 °C; (i) *t*-BuOAc, LDA, THF, –78 °C (84%, 3 steps); (j) HF, H_2O, MeCN, 23 °C (90%).

β-Keto ester **4** was synthesized from commercially available levoglucosenone as follows (Scheme 2). Levoglucosenone was converted into tosylate **6**[6] by a four-step sequence of reactions. Reduction of the lactone and tosyloxy groups in **6** afforded diol **7**, the primary hydroxyl group of which was protected to provide ester **8** (68% from **6**). Protection of the secondary hydroxyl in **8** led to silyl ether **9**, reduction of which provided alcohol **10** (92% from **8**). Swern oxidation of **10** gave aldehyde **11**, Horner-Emmons reaction of which with triethyl 2-phosphonopropionate afforded olefin **12** (80% from **10**). Hydrolysis of the ester group in **12** followed by reaction with carbonyl diimidazole gave an imidazolide, which was coupled with $LiCH_2COO$-*t*-Bu to yield β-keto ester **13**. Deprotection of the silyl ether group of **13** afforded β-keto ester **4** (76% from **12**).

The protected dihydroxy acid **5** was synthesized from D-valine, which was converted into methyl (*R*)-2-hydroxy-3-methylbutanoate (**14**)[7] in two steps (Scheme 3). The hydroxyl group of **14** was protected to give *p*-methoxybenzyl (MPM) ether **15**. Reduction of **15** afforded alcohol **16**, which was transformed into tosylate **17** (56% from **14**). Allylation of **17** with allylmagnesium bromide in the presence of CuI provided olefin **18** (95%), which was converted into alcohol **19**. Oxidation of alcohol **19** gave aldehyde **20**, Evans aldol reaction of which with (4*R*,5*S*)-4-methyl-5-phenyl-3-propionyl-2-oxazolidinone afforded aldol **21** (89% from **18**). Under the Mitsunobu reaction conditions aldol **21** was converted into *p*-nitrobenzoate **22** (67%). Both the *p*-nitrobenzoyl group and the chiral auxiliary group in **22** were removed under basic conditions to provide a β-hydroxy acid, which, in turn, was converted into the protected dihydroxy acid **5** (88% from **22**).



Scheme 3. Reagents and conditions: (a) *p*-$MeOC_6H_4CH_2OC(=NH)CCl_3$, TfOH, Et_2O, 23 °C (58%); (b) $LiAlH_4$, THF, 0 °C (98%); (c) TsCl, pyr, 0 °C (98%); (d) allylmagnesium bromide, CuI, Et_2O, 0 °C (95%); (e) 9-BBN, THF, 23 °C; (f) 30% H_2O_2, NaOH, THF, H_2O, 23 °C (97%, 2 steps); (g) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, –78 °C → 0 °C (94%); (h) Bu_2BOTf, Et_3N, (4*R*,5*S*)-4-methyl-5-phenyl-3-propionyl-2-oxazolidinone, CH_2Cl_2, –78 °C (98%); (i) (*i*-PrOOC-N=)$_2$, PPh_3, *p*-$NO_2C_6H_4COOH$, benzene, 23 °C (67%); (j) LiOH, 30% H_2O_2, THF, H_2O, 23 °C; (k) TBSOTf, Et_3N, CH_2Cl_2, 0 °C; (l) K_2CO_3, MeOH, H_2O (88%, 3 steps).



Scheme 4. Reagents and conditions: (a) DCC, DMAP, CSA, CH_2Cl_2, 23 °C (85 %); (b) TFA, CH_2Cl_2, 0 °C; (c) **3**, PyBroP, *i*-Pr_2NEt, CH_2Cl_2, 0 °C (83%, 2 steps); (d) Zn, NH_4OAc, THF, H_2O, 50 °C (96%); (e) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 23 °C; (f) DMAP, toluene, reflux (3%, 2 steps); (g) montmorillonite K 10, $HC(OMe)_3$, MeOH, CCl_4, 23 °C; (h) toluene, reflux (29%, 2 steps).

Coupling reaction of β-keto ester **4** and the protected dihydroxy acid **5** was effected under the Keck conditions[8] to give β-keto ester **23** in 85% yield (Scheme 4). Treatment of β-keto ester **23** with acid led to an unstable β-keto acid, which was immediately condensed with hexapeptide **3** to afford trichloroethyl ester **24** (83% from **23**). Reduction of trichloroethyl ester **24** with Zn gave seco acid **25** (96%). Attempts were made to cyclize seco acid **25** under a variety of conditions (for example, the Keck[8] and Corey[9] conditions) and it was found that the desired 35-membered lactone, nordolastatin G (**2**), was obtained only under the Yamaguchi lactonization conditions,[10] although the yield was very low.[11,12] The final task for the synthesis of dolastatin G (**1**) was construction of an enol ether structure (C36–C37). After extensive investigation on the formation of the enol ether group in **2**, we found montmorillonite K 10 (Aldrich) to be an effective catalyst for this purpose.[13] Nordolastatin G (**2**) was allowed to react with montmorillonite K 10 that was treated with trimethyl orthoformate and methanol prior to use to give a mixture of dolastatin G (**1**) and a dimethyl acetal, which was converted into dolastatin G (**1**) on heating (total yield; 29% from **2**).

Synthetic dolastatin G (**1**) and nordolastatin G (**2**) thus obtained were found to be identical with natural **1** and **2**, respectively, by comparison of the spectral (UV, IR, ^1H NMR, MS, α_D) and chromatographic

properties. Thus, the stereostructures of dolastatin G (**1**) and nordolastatin G (**2**) including the absolute stereochemistry were confirmed unambiguously.

Acknowledgment. This work was supported in part by Grants-in-Aid for Scientific Research on Priority Areas (Asymmetric Synthesis of Chiral Molecules No. 05234102, Natural Supramolecules No. 06240103) and for COE research (No. 07CE2004) from the Ministry of Education, Science, and Culture, Japan, the Fujisawa Foundation, and Ono Pharmaceutical Co. We thank Minoru Kiryu and Hiroyuki Sato for technical assistance.

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11. The major products were the C2 epimer **i** (11%) and the 31-membered lactone epimeric at C2, **ii** (10%). The stereochemistry of C2 in **i** and **ii** was determined by chiral HPLC analysis of proline obtained from the acid hydrolysis of **i** and **ii**: L- and D-forms of proline were produced in the ratio of 1:1. [Note that the acid hydrolysis of dolastatin G (**1**) gave only L-proline.[1]]
    One of referees pointed out the possibility that the racemization of the C-terminal L-proline residue may occur during the preparation of **3**. This possibility is excluded by the fact that the acid hydrolysis of **3** gave only L-proline.
12. Studies were also made to construct the 35-membered cyclodepsipeptide structure by macrolactamization of a seco acid. Treatment of compound **iii** with trifluoroacetic acid gave an unstable β-keto acid, which, under macrolactamization conditions (for example: Bop-Cl,[14] Et_3N, CH_2Cl_2, 23 °C), afforded not the desired macrocyclic compound, nordolastatin G (**2**), but a complex mixture containing a compound resulting from decarboxylation of the β-keto acid portion.
13. For the use of montmorillonite K 10 in the preparation of a dimethyl acetal group, see: Tayler, E. C.; Chiang, C. C. *Synthesis* **1977**, 467.
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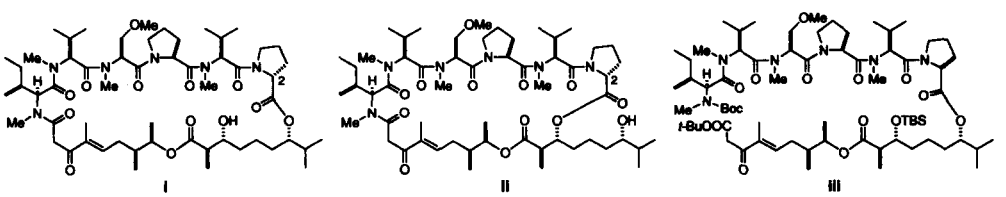

I II III

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