Total Synthesis of Doliculide, a Potent Cytotoxic Cyclodepsipeptide from the Japanese Sea Hare *Dolabella auricularia*

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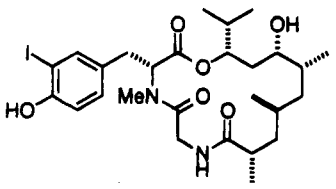
Received May 27, 1994®

Summary: The total synthesis of doliculide (**1**), a potent cytotoxic cyclodepsipeptide from the Japanese sea hare, has been achieved.

We have recently isolated doliculide (**1**) from the Japanese sea hare *Dolabella auricularia*, have elucidated the gross structure of **1** on the basis of spectral analysis, and have deduced the stereostructure of **1** by NOE experiments and chemical means.[1] We report herein the efficient synthesis of doliculide (**1**), and the present result confirms the stereostructure of **1** unambiguously.



doliculide (**1**)

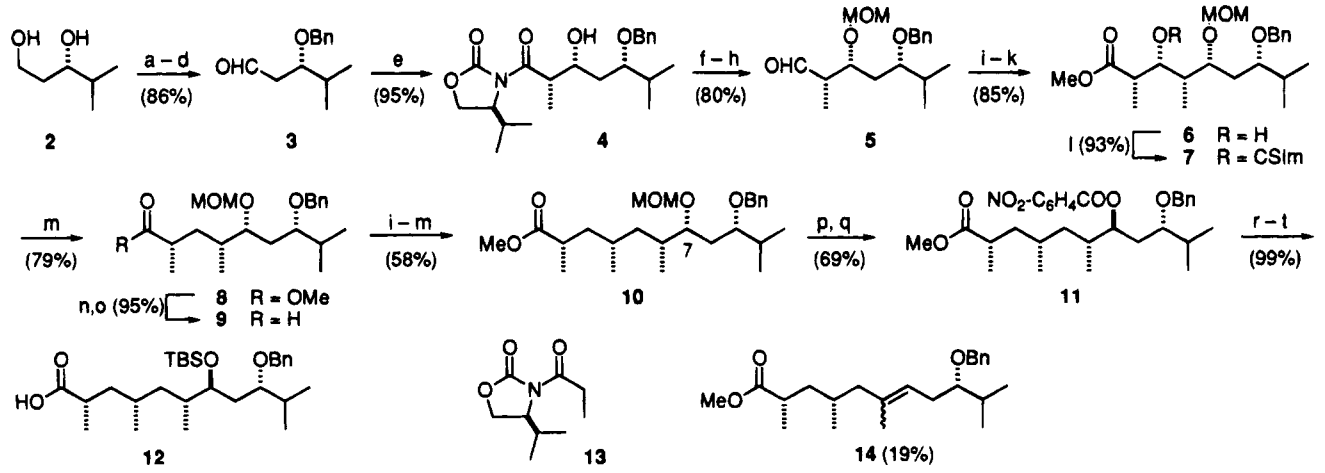
Preparation of the dihydroxy acid moiety of **1** began with (*S*)-4-methyl-1,3-pentanediol (**2**),[2] which was converted into aldehyde **3** in four steps (Scheme 1). Reaction of aldehyde **3** with imide **13**[3] under Evans conditions gave aldol **4**, which was transformed into aldehyde **5** by a three-step sequence. The Evans aldol reaction between **5** and **13**,[3] followed by removal of the chiral auxiliary and reaction with diazomethane, afforded methyl ester **6**, deoxygenation of which was effected by reduction[4] of the corresponding thionoimidazolide **7** to give methyl ester **8**, having a 1,3-*syn*-dimethylalkane structure. Methyl ester **8** was transformed into aldehyde **9** by two steps. The same sequence of reactions described above was applied to **9** to furnish methyl ester **10**, which possesses the 1,3,5-*syn*,*syn*-trimethylalkane structure. The protecting methoxymethyl group in **10** was removed, and the resulting hydroxyl group at C-7 was inverted by a Mitsunobu reaction[5] to afford *p*-nitrobenzoate **11**, along with olefin **14**. Hydrolysis of **11** gave a hydroxy acid, which was converted into silyl ether **12**.

Seco acid **17**, prepared from **12** and dipeptide **16**, was subjected to macrolactonization by Yamaguchi[6] or Keck[7] conditions, resulting in the complete epimerization of the tyrosine moiety to give cyclic compound **18** (Scheme 2). Thus, we investigated an alternative route, using macrolactamization for the synthesis of **1** (Scheme 3).

Coupling between **12** and glycine *tert*-butyl ester hydrochloride was effected with diethyl phosphorocyanidate[8] (DEPC) to provide amide **19**, which was converted into alcohol **20** (Scheme 3).

3-Iodo-*N*-methyl-D-tyrosine methyl ester (**21**)[9] was converted into *N*-Boc-3-iodo-*N*-methyl-*O*-TBS-D-tyrosine (**22**) by four steps (Scheme 3). Esterification of **20** with **22** gave fully protected seco acid **23**, treatment of which with trifluoroacetic acid provided amino acid **24** (Scheme 3). Macrolactamization of **24** was effected with bis(2-oxo-3-oxazolidinyl)phosphinic chloride[10] (BOP-Cl) to afford lactam **25** (74% from **23**) and trifluoroacetate **26** (10%

Scheme 1[a]



[a] Key: (a) TrCl, Et_3N, DMAP, CH_2Cl_2, 20 °C, 13 h; (b) BnBr, NaH, DMF, rt, 2.5 h; (c) concd HCl, MeOH, THF, 30 °C, 4 h; (d) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C, 20 min → 0 °C, 15 min; (e) **13**, Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C, 30 min → 0 °C, 1 h; (f) Me(MeO)NH·HCl, Me_3Al, THF, −19 → −6 °C, 2 h; (g) $MeOCH_2Cl$, *i*-Pr_2NEt, 0 °C → rt, 2 h; (h) DIBAL, THF, −78 °C, 10 min; (i) **13**, Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C, 30 min → 0 °C, 1 h; (j) LiOH, H_2O_2, THF, H_2O, 0 °C, 1.5 h; (k) CH_2N_2, ether, $CHCl_3$, rt, 5 min; (l) Im_2CS, THF, reflux, 10 h; (m) Bu_3SnH, toluene, reflux, 13 min; (n) $LiAlH_4$, THF, 0 °C, 10 min; (o) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C, 10 min → 0 °C, 10 min; (q) concd HCl, MeOH, 50 °C, 2 h; (r) Ph_3P, *p*-$NO_2C_6H_4COOH$, $(EtOOCN)_2$, ether, rt, 17.5 h; (s) NaOH, MeOH, H_2O, 45 °C, 2 h; (t) TBSOTf, Et_3N, CH_2Cl_2, 0 °C, 15 min; (u) K_2CO_3, MeOH, THF, H_2O, 40 °C, 1 h.

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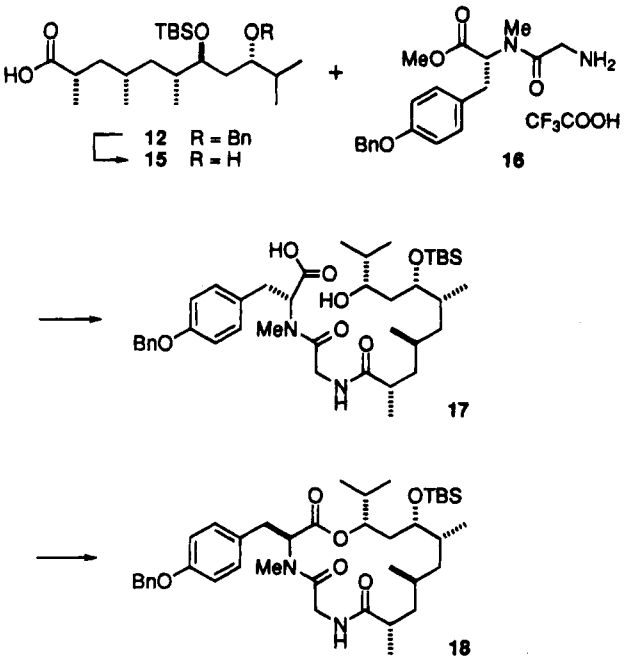
Scheme 2



from **23**), and the latter was transformed into the former on treatment with aqueous ammonia in methanol. Finally, the silyl group of **25** was removed to give doliculide (**1**). Synthetic doliculide (**1**) was found to be identical with natural **1** in all respects, including spectroscopic (mp, UV, IR, ^1H and ^{13}C NMR, MS, α_D) and chromatographic properties and cytotoxicity.

In conclusion, an efficient total synthesis of doliculide (**1**) has been achieved and the stereostructure of doliculide has been confirmed to be **1**. The overall yield of the synthesis, based on the longest linear sequence, is 11%.

Acknowledgment. This work was supported in part by Grants-in-Aid for Scientific Research (No. 04403009) and for Scientific Research on Priority Areas (Asymmetric Synthesis of Chiral Molecules) from the Ministry of Education, Science, and Culture, Japan, and Kowa Co. Ltd. We thank Dr. H. Ekimoto and Ms. R. Tanaka for the biological evaluation of synthetic doliculide (**1**). We are also grateful to Mr. T. Nemoto for his technical assistance. A fellowship of the Japan Society for the Promotion of Science for Japanese Junior Scientists to H.S. is gratefully acknowledged.

Supplementary Material Available: Modified preparation of **2**[2] and experimental procedures and spectral data (except for **17**) for new compounds (54 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

[⊗] Abstract published in *Advance ACS Abstracts,* July 1, 1994.

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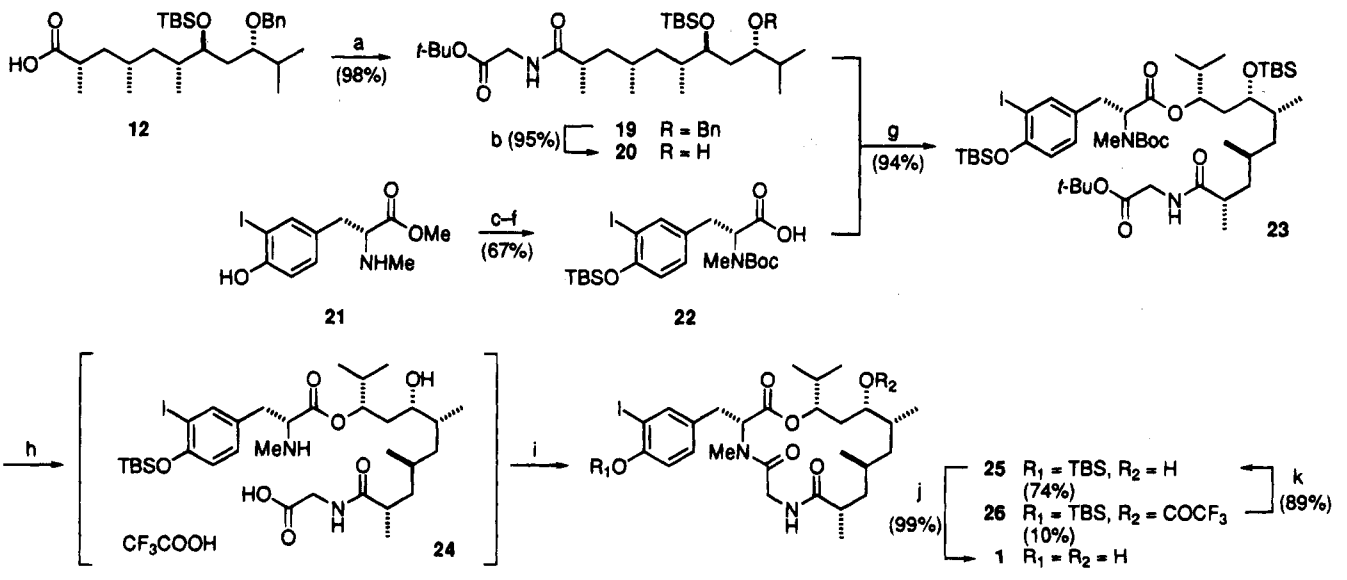
Scheme 3[a]



[a] Key: (a) glycine *tert*-butyl ester hydrochloride, DEPC, Et_3N, DMF, 0 °C, 30 min; (b) H_2, 20% $Pd(OH)_2/C$, dioxane, 40 °C, 1.5 h; (c) Boc_2O, Et_3N, CH_2Cl_2, 5 °C, 14 h; (d) LiOH, THF, H_2O, rt, 1 h; (e) TBSCl, imidazole, DMF, 50 °C, 1 h; (f) K_2CO_3, H_2O, MeOH, THF, rt, 30 min; (g) DCC, DMAP, CH_2Cl_2, −20 °C, 2 h; (h) CF_3COOH, CH_2Cl_2, rt, 3 h; (i) BOP-Cl, Et_3N, CH_2Cl_2, 0 °C → 25 °C, 19 h; (j) Bu_4NF, THF, 0 °C, 5 min; (k) concd NH_3, MeOH, rt, 1 h.