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Total Synthesis of Antitumor Depsipeptide (−)-Doliculide

Arun K. Ghosh* and Chunfeng Liu

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607

arunghos@uic.edu

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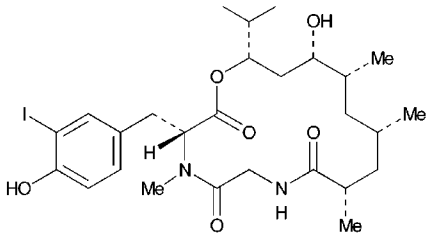
ABSTRACT



(-)-Doliculide (1)

(−)-Doliculide, a potent antitumor agent, is synthesized stereoselectively in a convergent manner. The key strategy involves a stereoselective synthesis of the polyketide unit and synthesis of the D-tyrosine derivative, followed by assembly of the fragments by an esterification and cycloamidation reaction sequence. The synthesis of the polyketide fragment was achieved by an iterative asymmetric synthesis to install stereoselectively both 1,3-dimethyl groups and the 1,3-diol unit by utilizing asymmetric cyclopropanations and Sharpless asymmetric epoxidations as the key steps.

(−)-Doliculide (**1**), a novel 16-membered depsipeptide, has been recently isolated from the Japanese sea hare *Dolabella auricularia* (Aplysiidae).[1] Doliculide exhibited exceedingly potent cytotoxicity against HeLa-S_3 cells with an IC_{50} value of 1 ng/mL.[2] The structure of **1** was initially established by NMR studies, and its absolute configuration has been confirmed by a stereoselective total synthesis by Yamada and co-workers.[3] Doliculide possesses a unique 15-carbon polyketide unit and a substituted D-tyrosine derivative. Apart from its important biological significance, the unique structural features and structure−function studies of doliculide became of interest to us. Herein, we report a convergent and enantioselective synthesis of (−)-doliculide.

As depicted in Figure 1, our convergent strategy to **1** relies upon stereoselective synthesis of the polyketide unit **2**, synthesis of D-tyrosine derivative **3**, and its conversion to a tyrosine−glycine dipeptide, followed by assembly of the fragment by an esterification and cycloamidation reaction sequence. Our approach to the synthesis of polyketide fragment **2** involved an iterative asymmetric synthesis to

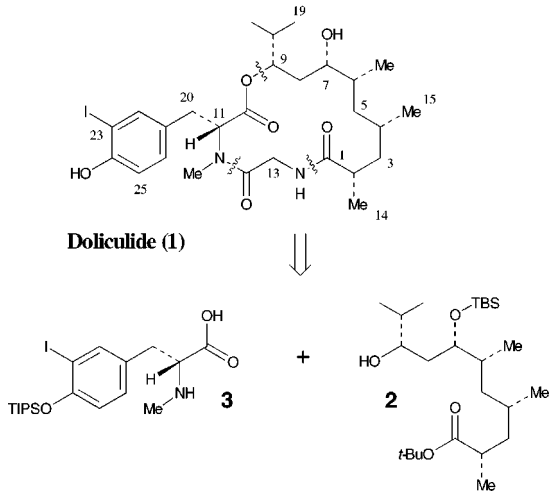


Figure 1.

(1) Ishiwata, H.; Nemoto, T.; Ojika, M.; Yamada, K. *J. Org. Chem.* **1994**, *59*, 4710.
(2) Ishiwata, H.; Sone, H.; Kigoshi, H.; Yamada, K. *Tetrahedron* **1994**, *50*, 12853.
(3) Ishiwata, H.; Sone, H.; Kigoshi, H.; Yamada, K. *J. Org. Chem.* **1994**, *59*, 4712.

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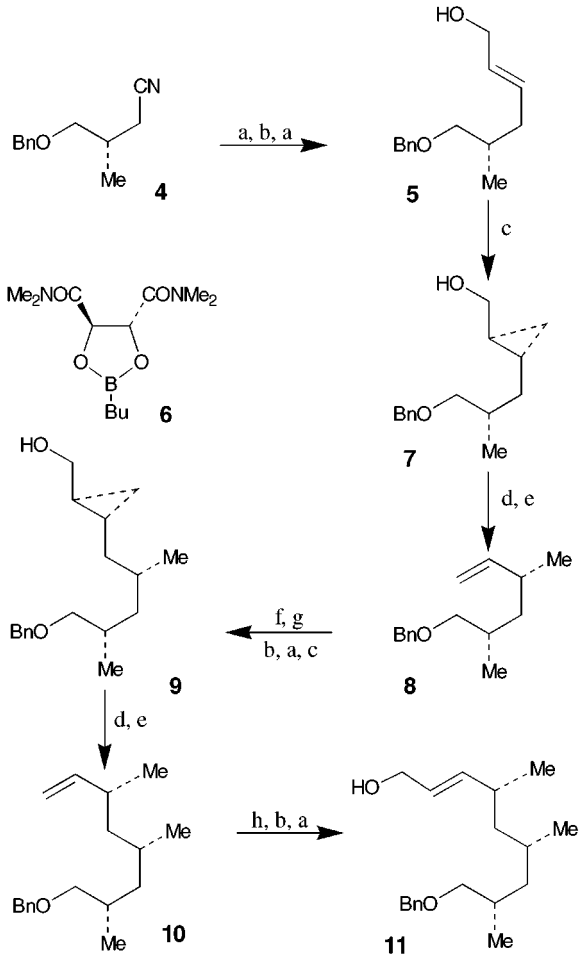
install stereoselectively both 1,3-dimethyl groups and the 1,3-diol unit. The 1,3-dimethyl groups would be constructed by iterative Charette asymmetric cyclopropanations[4] followed by opening of the cyclopropane rings, also utilizing Charette's protocol.[5] Stereoselective elaboration of the 1,3-diol unit would be achieved by Sharpless asymmetric epoxidations[6] followed by regioselective epoxide opening reactions.

The synthesis of the polyketide unit **2** began with the optically active cyanide **4** prepared in multigram quantities following a previously described procedure.[7] Cyanide **4** was converted to allylic alcohol **5** in a three-step sequence involving (1) Dibal reduction at 0 °C, (2) Horner−Emmons olefination of the resulting aldehyde, and (3) Dibal reduction of the α,β-unsaturated ester to provide the allylic alcohol **5** in 66% yield after chromatography. Charette asymmetric cyclopropanation of **5** using the amphoteric chiral dioxaborolane ligand **6** and $Zn(CH_2I)_2$·DME complex provided the cyclopropane derivative **7** in near quantitative yield and with high diastereoselectivity (91% de).[4] Among a number of different protocols surveyed for selective opening of the cyclopropane ring, Charette's protocol provided the best results.[5] Thus, reaction of **7** with PPh_3, imidazole, and iodine provided the iodide, which upon treatment with *n*-BuLi at −78 °C in the presence of TMEDA and molecular sieves afforded the alkene **8** in 72% yield over two steps.[8,9] Hydroboration of alkene **8** with 9-BBN in THF followed by Swern oxidation of the resulting alcohol provided the corresponding aldehyde. Following an iterative sequence as described for **7**, the resulting aldehyde was converted to cyclopropane **9** diastereoselectively. Thus, Horner−Emmons homologation of the aldehyde, Dibal reduction, and Charette asymmetric cyclopropanation of the resulting allylic alcohol with dioxaborolane **6** afforded the cyclopropane **9** in 55% overall yield from **8**.[11] Cyclopropane derivative **9** was converted to olefin **10** in 72% yield by following the same reaction protocol as **8**. Ozonolysis of **10** in CH_2Cl_2 at −78 °C followed by reductive workup with Ph_3P furnished the corresponding aldehyde. Horner−Emmons olefination followed by Dibal reduction of the resulting α,β-unsaturated ester afforded the allylic alcohol **11** in 59% yield (from **10**). Stereoselective construction of the 1,3-diol unit was achieved utilizing Sharpless asymmetric epoxidation as the key step.[6] As shown in Scheme 2, Sharpless epoxidation of allylic alcohol **11** was carried out with (−)-DET at −23 °C for 20 h. Epoxide **12** and its diastereomer were isolated as a mixture

Scheme 1[a]



[a] (a) Dibal, CH_2Cl_2; (b) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF, 0 to 23 °C (85−90%); (c) **6** (cat.), $Zn(CH_2I)_2$·DME, CH_2Cl_2, −15 °C (99%); (d) I_2, PPh_3, imidazole, CH_2Cl_2; (e) *n*-BuLi, TMEDA, Et_2O, molecular sieves, −78 °C (72%); (f) 9-BBN, THF, H_2O_2, OH^-, 0 °C; (g) Swern oxidation; (h) O_3, CH_2Cl_2, −78 °C, Ph_3P.

(5:1) in 90% yield. The presence of the mismatch chirality is most likely responsible for the somewhat lower observed diastereoselectivity. The mixture could not be separated and was used directly for the subsequent transformation. Thus, Swern oxidation of **12** followed by Wittig homologation of the resulting aldehyde with the stabilized ylide $Ph_3P{=}C(CH_3)CO_2C_2H_5$ in benzene at reflux provided the α,β-unsaturated ester **13** as an *E*:*Z* mixture (96:4) in 81% yield for two steps. Without separation, the mixture was exposed to regioselective epoxide opening with HCOOH−NEt_3 in the presence of a catalytic amount (0.06 equiv) of $Pd_2(dba)_3$·$CHCl_3$ and *n*-Bu_3P to stereoselectively provide the *anti* alcohol **14** in 90% yield after chromatography.[12] Protection of the alcohol as a TBDMS ether and then Dibal reduction followed by Sharpless epoxidation with (+)-DET afforded epoxy alcohol **15** as a single isomer in 91% yield. Attempts to directly open the oxirane ring using known procedures

(4) (a) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651. (b) Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081 and references therein.

(5) Charette, A. B.; Naud, J. *Tetrahedron Lett.* **1998**, *39*, 7259.

(6) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993; pp 103−158.

(7) (a) LeBel, N. A.; Banucci, E. G. *J. Org. Chem.* **1971**, *36*, 2440. (b) Ghosh, A. K.; Wang, Y. *Tetrahedron Lett.* **2000**, *41*, 2319.

(8) Ozonalytic cleavage of **8**, $NaBH_4$ reduction of the resulting aldehyde, and formation (BnBr/NaH) of benzyl ether afforded a meso dibenzyl diether.

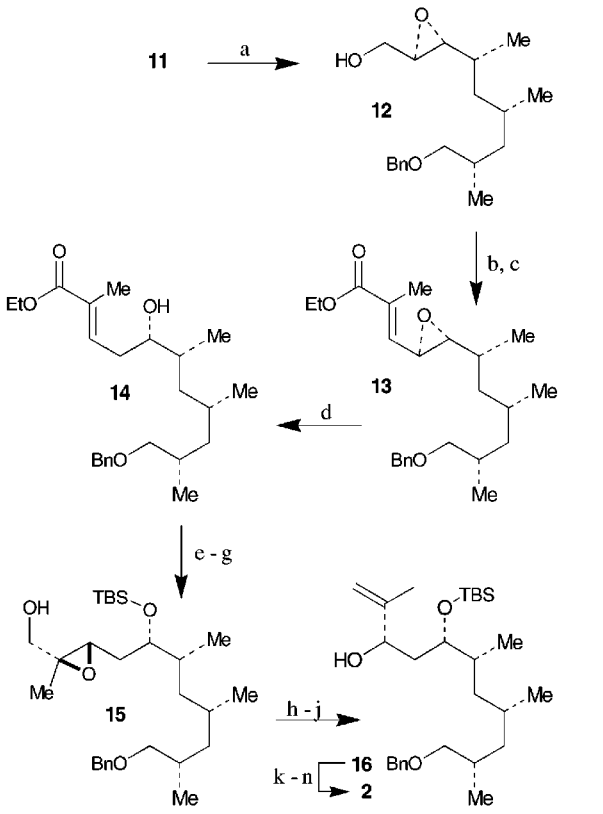
(9) Hydroboration of **8** and formation of TIPS ether of the resulting alcohol provided the known[10] TIPS ether. Diastereoselectivity of the cyclopropanation reaction was determined to be 91% de by ^{13}C NMR analysis.

(10) Hanessian, S.; Murry, P. J. *Can. J. Chem.* **1984**, *64*, 2231.

(11) ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) analysis have shown a 90% de.

(12) Oshima, M.; Yamazaki, H.; Shimizu, I.; Nisar, M.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, *111*, 6280.

Scheme 2[a]



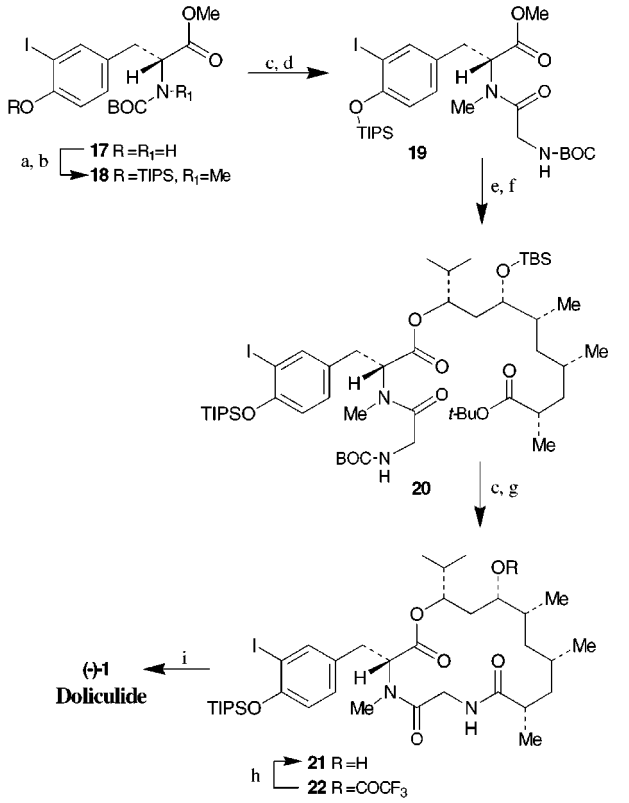
[a] (a) Ti(O^{i}Pr)$_4$, (−)-DET, *t*-BuOOH, −23 °C (90%); (b) Swern oxidation; (c) $Ph_3P{=}C(Me)CO_2Et$, PhH, 84 °C (81%); (d) $Pd_2(dba)_3{\cdot}CHCl_3$ (cat.), Bu_3P, HCO_2H, Et_3N, Dioxane, 23 °C (90%); (e) TBSOTf, Et_3N, CH_2Cl_2; (f) DIBAL-H, CH_2Cl_2, −40 °C (80%); (g) Ti(O^{i}Pr)$_4$, (+)-DET, *t*-BuOOH, −23 °C (91%); (h) MsCl, Et_3N, DMAP (cat.), CH_2Cl_2; (i) NaI, butanone, reflux; (j) *n*-BuLi, TMEDA, Et_2O, −78 °C (84%); (k) H_2, 10% Pd−C (cat.), THF (84%); (l) TPAP (cat.), NMO, CH_2Cl_2, 23 °C; (m) $NaClO_2$, methylbutene, *t*-BuOH−H_2O, 23 °C; (n) BOC_2O, DMAP (cat.), *t*-BuOH, 30 °C (51%).

were unsuccessful.[13] We then devised an alternative procedure in which **15** was first converted to its iodide by mesylation and subsequent displacement of the resulting mesylate with sodium iodide. Treatment of this iodide with *n*-BuLi at −78 °C in the presence of TMEDA effected lithium−iodide exchange followed by epoxide opening to furnish the allyllic alcohol **16** in 84% overall yield (from **15**).[1] To complete the synthesis of the polyketide fragment **2**, hydrogenation of **16** over 10% Pd−C resulted in debenzylation as well as saturation of the olefin. The resulting diol was transformed into the *tert*-butyl ester **2** by a three-step sequence involving (1) selective TPAP oxidation of the primary alcohol to an aldehyde, (2) $NaClO_2$ oxidation of the resulting aldehyde, and (3) esterification of the resulting acid with BOC_2O and a catalytic amount of DMAP (51% yield from **16**).

(13) Attempted Cp_2TiCl-mediated opening of epoxide **15** resulted in a trace amount of desired allylic alcohol **16** (<10% yield). For procedure, see: Yadav, J. S.; Shekharam, T.; Gadgil, V. R. *J. Chem. Soc. Chem. Commun.* **1990**, 8443 and references therein.

Our next synthetic strategy called for the synthesis of Tyr−Gly dipeptide **19** followed by linking with the polyketide unit. Commercial D-tyrosine was iodinated with iodine in a mixture of ethanol and aqueous ammonia as described by

Scheme 3[a]



[a] (a) TIPSCl, imidazole, DMF, 23 °C (98%); (b) NaH, MeI, DMF−THF, 60 °C; (c) CF_3CO_2H, CH_2Cl_2, 0 to 23 °C; (d) *N*-BOC-Gly, EDC, HOBt, DMF, 0 to 23 °C (90%); (e) aq. LiOH, THF, 0 °C; (f) **2**, DCC, DMAP, CH_2Cl_2, −20 °C (98%); (g) BOP, DMAP, CH_2Cl_2, 0 to 23 °C (82%); (h) aq. NH_3, MeOH, 23 °C (88%); (i) *n*-$Bu_4N^+F^-$, THF, 0 °C, 15 min (98%).

Pitt-Rivers.[15] Esterification of the resulting *meta*-iodo tyrosine derivative with dry HCl in methanol and BOC protection provided **17** in 50% overall yield. Protection of the phenolic group as a TIPS ether followed by *N*-methylation with sodium hydride and methyl iodide in a mixture (10:1) of THF and DMF furnished the *N*-methylated tyrosine derivative **18**. Removal of the BOC group by treatment with trifluoroacetic acid and coupling of the resulting amine with *N*-BOC-glycine in the presence of EDC and HOBT under standard conditions afforded the dipeptide **19**. Selective hydrolysis of the methyl ester with LiOH in aqueous THF at 0 °C for 1 h gave the crude acid, which was subjected to esterification with polyketide **2** to provide the diester **20** in 98% yield. Treatment of **20** with trifluoroacetic acid effected deprotection of the TBDMS group, *N*-BOC, and *tert*-butyl ester.

(14) For related procedures, see: Burke, S. D.; Buchanan, J. L.; Rovin, J. D. *Tetrahedron Lett.* **1991**, *32*, 3961 and references therein.

(15) Pitt-Rivers, R. *Chem. Ind.* **1956**, 21.

To effect selective cycloamidation, the resulting amino acid was reacted with BOP reagent in the presence of DMAP in CH_2Cl_2 at 0 to 23 °C for 20 h to afford the desired cycloamide **21** in 82% yield along with a minor trifluoroacetate derivative **22** (10% yield).[16] Treatment of **22** with aqueous ammonia in MeOH at 23 °C for 1 h readily converted **22** to **21** in 88% yield. Removal of the TIPS ether in **21** by exposure to *n*-$Bu_4N^+F^-$ in THF afforded the synthetic (−)-doliculide **1** {$[\alpha]^{23}_D$ −25.4 (*c* 0.28, MeOH); lit.[1] $[\alpha]^{23}_D$ −25.5 (*c* 0.67, MeOH)} in 98% yield. Spectral data (^{1}H and ^{13}C NMR) for synthetic **1** are in full agreement with that reported by Yamada and co-workers[1] for the natural (−)-doliculide. Thus, a stereocontrolled synthesis of (−)-doliculide has been accomplished. Structure−activity and biological studies of **1** are the subject of future investigation.

(16) The C-7 trifluoacetate derivative was formed during the treatment of **20** with trifluroacetic acid at 0 to 23 °C.

Acknowledgment. Financial support by the National Institutes of Health (GM 55600) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectral data (^{1}H and ^{13}C NMR) for compounds **1**, **2**, **4**−**16**, and **19**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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