Communications

Natural Products Synthesis

Total Synthesis of (–)-Dictyostatin: Confirmation of Relative and Absolute Configurations**

Youseung Shin, Jean-Hugues Fournier, Yoshikazu Fukui, Arndt M. Brückner, and Dennis P. Curran*

The macrolactone (–)-dictyostatin was isolated in small quantities from a Maldives marine sponge *Spongia sp.* by Pettit and co-workers in 1994.^[1a] Dictyostatin strongly inhibits the growth of human cancer cells with a GI_{50} in the 50 pM to 1 nM range, and in a subsequent patent it was assigned a partial structure **1a** shown.^[1b] Wright and co-workers isolated dictyostatin from *Corallistidea* sponges,^[2] and showed that it stabilized microtubules in the same way as discodermolide (by preventing the depolymerization to tubulin heterodimers). Studies on taxol-resistant cell lines and other experiments also suggested that dictyostatin could be useful against multidrug-resistant tumors. Despite these exciting results, further study of dictyostatin has been retarded because it is scarce and its structure is not known with certainty.

Dictyostatin is structurally related to discodermolide 2,^[3] and in 2002 we reported the syntheses of the first discodermolide–dictyostatin hybrid molecules and suggested that the absolute configuration of dictyostatin should be inverted so that it more closely resembles discodermolide.^[4] The synthesis of hybrids such as **3** taught us how to make the lower dienyl ester chain of the dictyostatins, including the macrolactone ring.

In further work, we began to doubt the relative stereochemical assignments in $\mathbf{1a}$.^[5] For example, we recently made an isomer of dictyostatin with the structure $\mathbf{1c}$ ("dictyostatin 5") that has discodermolide-like configurations in the "upper" and "middle" fragments (solid boxes) and the dictyostatin configurations proposed by Pettit and co-workers in the "lower" fragment (dashed box). The resonances of the protons from the "upper" and "middle" fragments resembled those for dictyostatin very closely, but those of the "lower"

[*] Y. Shin, Dr. J.-H. Fournier, Dr. Y. Fukui, Dr. A. M. Brückner, Prof. Dr. D. P. Curran
Department of Chemistry
University of Pittsburgh
Pittsburgh, PA 15260 (USA)
Fax: (+1) 412-624-9861
E-mail: curran@pitt.edu

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Supporting information for this article (comparison of ¹H and ¹³C NMR spectroscopic data for natural and synthetic samples of dictyostatin) is available on the WWW under http://www.angewandte.org or from the author.





1b, dictyostatin

Paterson/Wright structure

2004

1a original Pettit structure, 1995 (C14, C17 not assigned)



a discodermolide/dictyostatin hybrid 2002



fragment (especially 3-H–5-H) were very different.^[5] Likewise, we made **1d** ("dictyostatin 2"),^[5] which is one of the four candidate structures originally proposed; this was not dictyostatin either, and the resonances for its "lower" fragment protons resembled those of **1c**, not dictyostatin.

Very recently, Paterson and Wright conducted a detailed ¹H NMR spectroscopic analysis to assign configurations to dictyostatin fragments, and then used molecular modeling to assemble the fragments.^[6] They arrived at structure **1b** in which the 10 stereocenters that dictyostatin shares with discodermolide all have the same relative configurations (C14^[7] of dictyostatin is not a stereocenter in discodermolide, and was assigned the *S* configuration). We report herein the synthesis of dictyostatin, and confirm that structure **1b** is correct. Concurrently, Paterson and co-workers report their synthesis and have reached the same conclusion.^[8]

Scheme 1 summarizes key elements of the strategic plan to make **1b**. Because of the uncertainties with configurations, stereochemical flexibility is a key design element.^[5] The molecule breaks down into three key fragments as indicated by the wavy lines in **1b**. With the preparation of analogues in mind, we intentionally designed a less convergent synthesis



Scheme 1. Summary of the synthetic strategy to make **1b**. TBS = *tert*-butyldimethylsilyl, PMP = *p*-methoxyphenyl, Tr = triphenylmethyl.

that introduces both dienes after coupling of the fragments. Compound **4** became a key intermediate in this strategy and was built from fragments **5**, **6**, and **7**. In turn, the fragments were made by building on prior work in the discodermolide area,^[3,9] including our own routes to simplified discodermolide analogues.^[10] A key element of the synthesis was our decision to change from a Wittig approach^[9] to the synthesis of the C8–C9 Z alkene to a more reliable alkyne addition to make the C7–C8 bond.^[11]

The syntheses of fragments **5**, **6**, and **7** are summarized in Scheme 2. Fragment **5** was prepared from known Weinreb ester $8^{[9a,b]}$ by addition of LiCH₂P(=O)(OMe)₂. The C14 stereocenter of fragment **6** was introduced by conversion of alcohol **9** into a sensitive iodide,^[12] followed by direct Myers alkylation.^[13] This gave **10** in 87% yield as a single stereoisomer. Cleavage of the auxiliary group and protection of the alcohol function were followed by removal of the PMB group, oxidation, Corey–Fuchs olefination, and elimination to install the alkyne on the other end of the backbone. Fragment **7** was prepared by a straightforward sequence of functional-group transformations from the ester **11**.^[14]

The union of the fragments and the completion of the synthesis are shown in Scheme 3. Metalation of alkyne 6 and addition of Weinreb ester 7 provided an alkynyl ketone (not shown). The asymmetric reduction of this ketone according to Noyori and co-workers^[11,15] followed by Lindlar hydrogenation gave **12** as a single isomer. Protection of the secondary alcohol followed by deprotection of the primary TBS ether, oxidation, and Wittig–Horner coupling with **5** provided key enone **4**. The conjugated double bond of **4** was reduced with nickel boride, and the ketone was then reduced with sodium borohydride to give a readily separable mixture of epimers **13** (β/α 2.4:1).^[16] The major β epimer was silylated, the PMP acetal was opened, and the terminal diene was introduced by a standard procedure used in the synthesis of discodermolide^[17] to give **14**. Detritylation of **14** followed by oxidation,



Scheme 2. A) a) $(MeO)_2P(O)CH_3$, BuLi, -78 °C, 85%. B) a) LiH_2NBH_3 , THF, 96%; b) TBSCI, imidazole, 4-DMAP, 95%; c) DDQ, 99%; d) SO₃-py, Et₃N, DMSO; e) CBr₄, PPh₃, 2,6-lutidine, 73% over two steps; f) BuLi, THF, 95%. C) a) DIBAL-H, CH₂Cl₂, 97%; b) TrCl, 4-DMAP, pyridine; c) HF/py, pyridine, THF, 89% over two steps; d) 1) SO₃-py, Et₃N, DMSO/CH₂Cl₂; 2) NaClO₂, NaHPO₄, 2-methyl-2-butene, THF/H₂O; e) NH(Me) (OMe)HCl, DCC, Et₃N, DMAP, CH₂Cl₂, 73% (three steps). DIPEA = diisopropylethylamine, DMAP = dimethyl-aminopyridine, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMSO = dimethyl sulfoxide, DIBAL-H = diisobutylaluminum hydride, DCC = dicyclohexylcarbodiimide.

Still–Gennari olefination,^[18] and removal of the PMB group provided the E/Z dienyl ester **15**.

The final key steps follow directly from our previous syntheses.^[4,5] Saponification, Yamaguchi lactonization,^[19] and global desilylation provided about 3 mg of **1b** as a white solid after purification by HPLC. Extensive high-field ¹³C and ¹H NMR data are available for both natural samples, and our data match these well.^[20] Pettit and co-workers report that natural dictyostatin has an optical rotation of -20 (c = 0.12, MeOH),^[1] whereas our sample has a rotation of -23 (c = 0.18, MeOH). From these data, we conclude that dictyostatin has structure **1b**. The longest linear sequence of 34 steps runs through fragment **6** and provides **1b** in 1% overall yield from (2*S*)-3-hydroxy-2-methylpropionic acid methyl ester (Roche ester).^[9b]

The confirmation of the structure of dictyostatin clears the way for further development in this exciting area. Despite being a macrolactone, dictyostatin presumably has a similar shape to discodermolide, and indeed we had even designed macrocyclic discodermolide analogues before we were aware of dictyostatin.^[4] Armed with the knowledge of the structure of dictyostatin, we now know that discodermolide/dictyostatin hybrids such as **3** are much closer to dictyostatin than was originally expected. Our present synthesis is flexible and is

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Scheme 3. a) *n*BuLi, THF, 93%; b) *S*,*S* Noyori catalyst (20 mol%), *i*PrOH, 79%; c) Lindlar catalyst, H₂ (balloon), toluene, 91%; d) TBSOTf, 2,6-lutidine, CH₂Cl₂, 99%; e) HF/py, pyridine, THF, 0°C, 1 day, 67%; f) 1) Dess–Martin oxidation; 2) Ba(OH)₂, **5**, THF/H₂O, 80% (two steps); g) NiCl₂, NaBH₄, MeOH/THF, 76%; h) NaBH₄, MeOH/THF, 70% (β), 29% (α); i) TBSOTf, 2,6-lutidine, CH₂Cl₂, 99%; j) DIBAL-H, CH₂Cl₂, 88%; k) 1) Dess–Martin oxidation; 2) CH₂=CHCH(TMS)Br, CrCl₂, THF; 3) NaH, THF, 89% (three steps); l) ZnBr₂, CH₂Cl₂/MeOH, 69%; m) 1) Dess–Martin oxidation; 2) (CF₃CH₂O)₂P(O)CH₂CO₂Me, KHMDS, [18]crown-6, THF, 86% (two steps); n) DDQ, CH₂Cl₂/H₂O, 88%; o) KOH (1 N), EtOH/THF; p) 2,4,6-trichlorobenzoyl chloride, Et₃N, THF then 4-DMAP(10 equiv), toluene, 78% (two steps); q) HCl/MeOH (3 N), THF, 55%. Tf=tri-fluoromethanesulfonyl, TMS = trimethylsilyl, HMDS = hexamethyldisilazide.

suitable for making other kinds of analogues as well. Increased quantities of dictyostatin are also needed for testing. Although it has two more backbone carbon atoms, dictyostatin lacks three of the stereocenters of discodermolide, therefore it will probably be easier to make in the long run. We are currently investigating ways to increase the convergence of the current synthesis as a prelude to making more dictyostatin.

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