J|A|C|S
COMMUNICATIONS

Published on Web 04/01/2006

Total Synthesis of (−)-Dictyostatin

Gregory W. O'Neil and Andrew J. Phillips*

Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado 80309-0215

Received February 9, 2006; E-mail: andrew.phillips@colorado.edu

Dictyostatin (**1**, Figure 1) is a marine-derived macrolide that inhibits the growth of a variety of cancer cell lines (including Taxol-resistant lines) at low nanomolar levels by a mechanism involving tubulin polymerization.[1] First isolated in small amounts by Pettit,[2] and more recently by Wright,[1] dictyostatin's structure is defined by a 22-membered macrolactone punctuated by 11 stereocenters, two dienes, and a *cis*-1,2-disubstituted olefin.[3] Its significant therapeutic potential and relationship to discodermolide has resulted in syntheses from the groups of Paterson[4] and Curran,[5] and in this communication, we describe our synthesis of dictyostatin.

To maximize convergency, our strategy called for the union of three subunits of similar complexity (compounds **2**, **3**, and **4**) by olefin metathesis at C10−C11, olefination at C17−C18, and a late stage macrocyclization by an intramolecular Still−Gennari-modified Horner−Wadsworth−Emmons reaction (Figure 1). This plan was further underpinned by our interest in evaluating the utility of our recently described (silyloxy)enyne cyclization in the context of complex polyketide synthesis.[6]

The synthesis of the C18−C26 subunit **4** is shown in Scheme 1 and commences with known alcohol **5**.[7] Silylation with (propynyl)-diisopropylbromosilane, followed by reduction to the primary alcohol ($LiBH_4$, 78%), and finally protection as the PMB ether ($PMBOC(=NH)CCl_3$, 82%) gave **6**. Using our previously reported conditions,[6] (silyloxy)enyne **6** was cyclized to siloxane **7** in 65% yield. Desilylation and acylation with acryloyl chloride led to **8** in 95% yield. Ring-closing metathesis with Grubbs' second generation catalyst[8] gave the expected lactone and was followed by in situ reduction to the lactol, then Wittig olefination to produce diene **9** in 85% yield for the three steps. Conversion of **9** to β-ketophosphonate **4** was achieved by a five-step sequence of straightforward transformations: (i) oxidation of the PMB ether to the PMP acetal (DDQ, 75%, **9** → **10**), (ii) acetal cleavage to the PMB ether, (iii) oxidation of the primary alcohol with Dess−Martin periodinane, (iv) reaction with lithiodimethylphosphonate, and (v) oxidation with Dess−Martin periodinane (60% from **10**).

The synthesis of **2** commenced with silylation of alcohol **11**[9] with (ethynyl)diisopropylbromosilane to give **12** in 95% yield (Scheme 2). Reductive (silyloxy)enyne cyclization with $ClTi(i\text{-}PrO)_3$-*i*-PrMgCl produced **13** in 73% yield and was followed by removal of the siloxane to give **2** in 95% yield. Acylation of the secondary alcohol with acid **3**[10] under Yamaguchi[11] conditions yielded **14** (90%) and set the stage for the formation of the $\Delta^{10,11}$ olefin by ring-closing metathesis.[12] Gratifyingly, treatment of a toluene solution of **14** under reflux with a total of 15 mol % of Grubbs' second generation catalyst (in 5 mol % batches at 6 h intervals) provided lactone **15** in 76% yield.

In advance of the introduction of the C18−C26 subunit, lactone **15** was converted to **16** in 73% yield by reduction to the hydroxy aldehyde with DIBAL-H and olefination with (carboethoxy) methylenetriphenylphosphorane. Further reduction to the allylic alcohol, diol silylation with TBSOTf, removal of the PMB ether (DDQ, aqueous buffer), and finally oxidation with Dess−Martin periodinane provided delicate aldehyde **17** (60% yield from **16**). Reaction with β-ketophosphonate **4** in the presence of $Ba(OH)_2$ in aqueous THF[13] resulted in the smooth union of these two key fragments to give enone **18** in 77% yield. After conjugate reduction of the C17−C18 double bond with Stryker's reagent[14] and removal of the PMB ether, 1-3-*syn*-reduction[15] ($Zn(BH_4)_2$, dr > 20:1) provided diol **19** in 88% yield. Selective silylation of the C19 alcohol (TBSOTf, 89%), followed by acylation of the C21 alcohol under Yamaguchi conditions[11] gave phosphonate **20** in 93% yield. Careful removal of the TBS ether from the allylic alcohol with aqueous acetic acid (78%), followed by oxidation to the enal with Dess−Martin periodinane provided the substrate for macrocyclization by an intramolecular Still−Gennari-modified Horner−Wadsworth−Emmons reaction.[16,17] To our delight, treatment with potassium

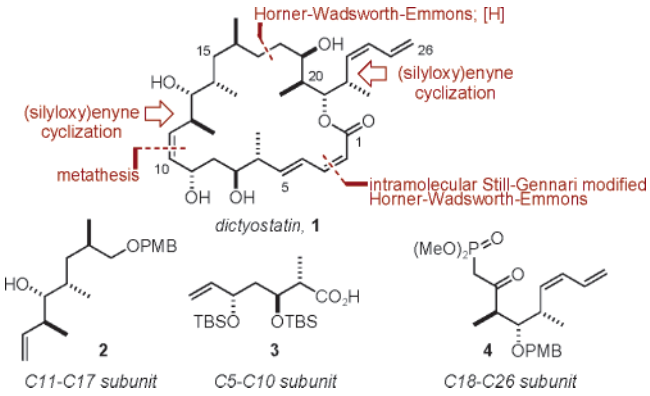
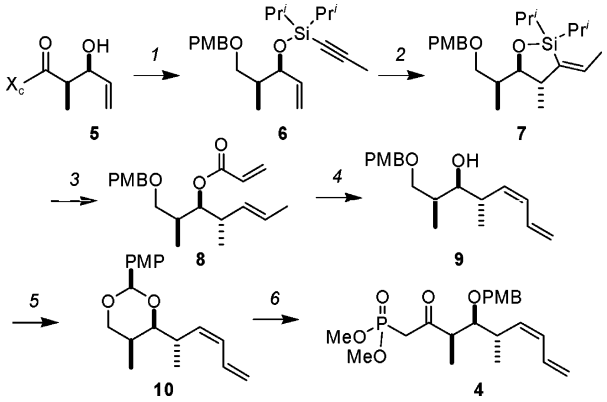


Figure 1. Synthesis strategy.

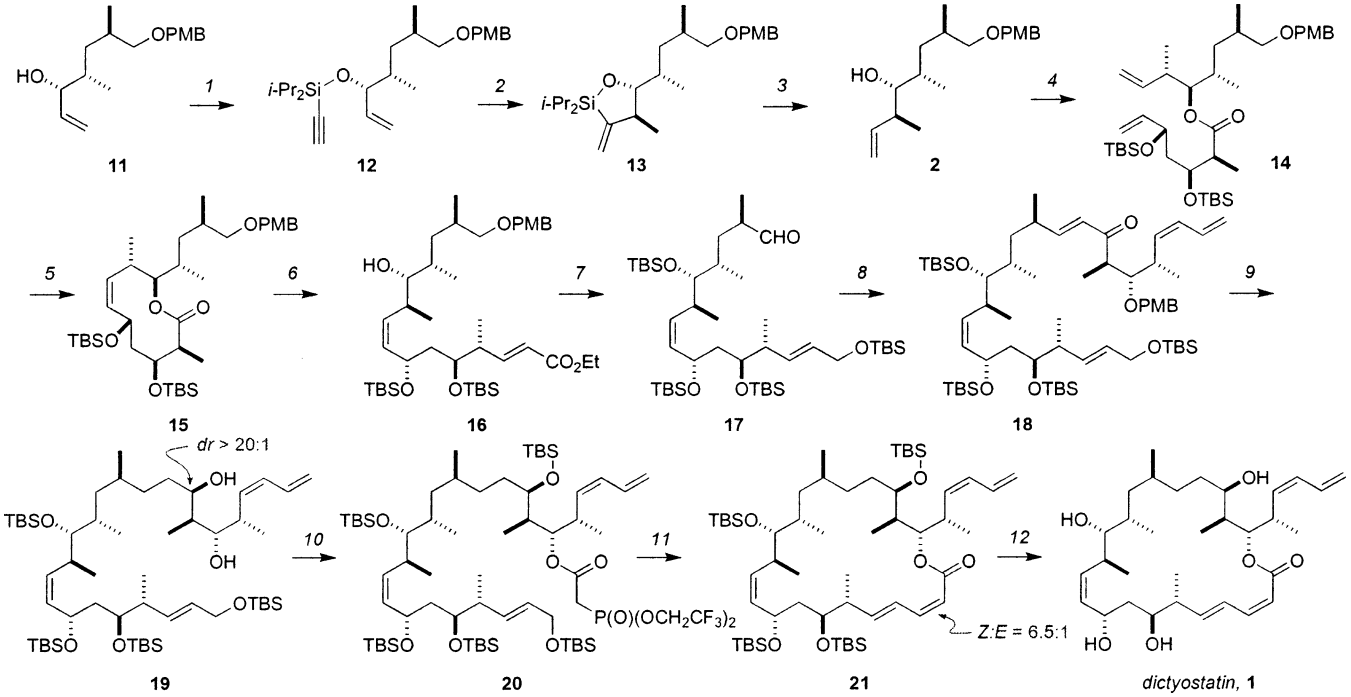
Scheme 1[a]



[a] Reagents and conditions: (1) (a) (propynyl)diisopropylbromosilane, imidazole, DMF, 97%, (b) $LiBH_4$, THF, 78%, (c) $PMBOC(=NH)CCl_3$, CSA, CH_2Cl_2, 82%; (2) $ClTi(i\text{-}PrO)_3$, *i*-PrMgCl, 65%; (3) TBAF, DMF then $H_2C{=}CHCOCl$, *i*-Pr_2NEt, CH_2Cl_2, 95%; (4) (a) 5 mol % of Grubbs II, PhH, 60 °C then cool to −78 °C, DIBAL-H, (b) Ph_3PCH_3I, *n*-BuLi, THF, 85% (from **8**); (5) DDQ, CH_2Cl_2, 4 Å MS, 75%; (6) (a) DIBAL-H, CH_2Cl_2, (b) Dess−Martin periodinane, CH_2Cl_2, (c) $(MeO)_2P(O)Me$, *n*-BuLi, THF, (d) Dess−Martin periodinane, CH_2Cl_2, 60% (from **10**). X_c = (*R*)-benzyloxazolidinone.

10.1021/ja0609708 CCC: $33.50

Scheme 2[a]



[a] Reagents and conditions: (1) (ethynyl)diisopropylbromosilane, imidazole, DMF, 95%; (2) $ClTi(i\text{-}PrO)_3$, *i*-PrMgCl, 73%; (3) TBAF, DMF, 65 °C, 95%; (4) **3**, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, PhMe, 90%; (5) 15 mol % of Grubbs II, PhMe, 110 °C, 76%; (6) DIBAL-H, CH_2Cl_2 then Ph_3PCHCO_2Et, 73%; (7) (a) DIBAL-H then TBSOTf, 2,6-lutidine, (b) DDQ, CH_2Cl_2, pH = 7 buffer, (c) Dess−Martin periodinane, CH_2Cl_2 (60% from **16**); (8) **4**, $Ba(OH)_2$, THF−H_2O, 80%; (9) (a) $[Ph_3P{\cdot}CuH]_6$, PhH, (b) DDQ, CH_2Cl_2−H_2O, 0 °C, (82% over 2 steps), (c) $Zn(BH_4)_2$, Et_2O, 88%; (10) (a) TBSOTf, CH_2Cl_2, 2,6-lutidine, 89%, (b) $(CF_3CH_2O)_2P(O)CH_2CO_2H$, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, PhMe, 93%; (11) (a) AcOH−THF−H_2O, 78%, (b) Dess−Martin periodinane, CH_2Cl_2, (c) K_2CO_3, 18-C-6, PhMe, rt, 85% (2 steps, 74% of desired diastereoisomer); (12) HF·pyridine, THF, 40 h, 67%.

carbonate and 18-crown-6 in toluene at room temperature resulted in clean cyclization to form **21** in excellent yield and with good diastereoselectivity (6.5:1 *Z*:*E* to *E*:*E*, 74% of desired over two steps). Removal of the four TBS ethers with HF·pyridine, followed by chromatography, produced (−)-dictyostatin in 67% yield. Synthetic dictyostatin was identical in all respects with physical and spectroscopic data provided for the natural product.[18]

In summary, a convergent synthesis of (−)-dictyostatin has been achieved in 26 steps via **11**. As well as providing an avenue for the preparation of larger amounts of the natural product, the synthesis also offers an evaluation of the use of (silyloxy)enyne cyclizations for the synthesis of *syn*−*anti* stereotriads in the context of complex polyketide synthesis.

Acknowledgment. We thank Professor Dennis Curran for copies of spectra for intermediates in their synthesis. Financial support was provided by the NCI (CA110246).

Supporting Information Available: Data and spectra for compounds **1**, **3**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Isbrucker, R. A.; Cummins, J.; Pomponi, S. A.; Longley, R. E.; Wright, A. E. *Biochem. Pharmacol.* **2003**, *66*, 75.
(2) (a) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Boyd, M. R.; Schmidt, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1111. (b) Pettit, G. R.; Cichacz, Z. A. WO 5430053, 1995; *Chem. Abstr.* **1995**, 733500.
(3) Stereochemical assignment: Paterson, I.; Britton, R.; Delgado, O.; Wright, A. E. *Chem. Commun.* **2004**, 632.
(4) Paterson, I.; Britton, R.; Delgado, O.; Meyer, A.; Poullennec, K. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4629.
(5) Shin, Y.; Fournier, J.-H.; Fukui, Y.; Bruckner, A. M.; Curran, D. P. *Angew. Chem., Int. Ed*. **2004**, *43*, 4634.
(6) O'Neil, G. W.; Phillips, A. J. *Tetrahedron Lett.* **2004**, *45*, 4253.
(7) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894.
(8) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
(9) Synthesized by a route analogous to that described in ref 6.
(10) For the synthesis of acid **3**, see the Supporting Information.
(11) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(12) Curran has recently described the cyclization of substrates related to **15** by RCM. See: Kangani, C. O.; Bruckner, A. M.; Curran, D. P. *Org. Lett.* **2005**, *7*, 379.
(13) (a) Sinisterra, J. V.; Mouloungui, Z.; Delmas, M.; Gaset, A. *Synthesis* **1985**, 1097. (b) Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774.
(14) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291.
(15) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338.
(16) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(17) For other recent examples of macrolide synthesis by *Z*-selective intramolecular Still−Gennari-modified Horner−Wadsworth−Emmons reaction, see: (a) Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597. (b) Smith, A. B.; Verhoest, P. R.; Minbiole, K. P.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942. (c) Williams, D. R.; Kiryanov, A. A.; Emde, U.; Clark, M. P.; Berliner, M. A.; Reeves, J. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 1258. (d) González, M. A.; Pattenden, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 1255. (e) Ghosh, A. K.; Wang, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11027.
(18) Synthetic $[\alpha]_D = -22.0$ (*c* 0.05, MeOH); natural $[\alpha]_D = -20.0$ (*c* 0.16, MeOH).[2] HRMS calculated for $C_{32}H_{52}O_6H^+$ 533.3836, found 533.3831. For a comparison of NMR data, see the Supporting Information.

JA0609708