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Ring-Closing Metathesis Approach to Dictyostatin†

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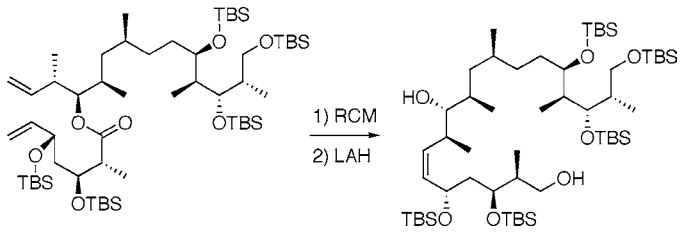
ABSTRACT



An esterification/ring-closing metathesis approach to dictyostatin and discodermolide is introduced. The approach provides for facile fragment coupling of two main segments of these natural products at the C10–C11 alkene with high to complete *Z*-selectivity.

Dictyostatin is a potent antitumor agent that acts by microtubule stabilization. It was first isolated in 1994 by Pettit and co-workers,[1a] who correctly proposed the two-dimensional structure from data collected on a very small sample (about 1 mg). Later, Wright and co-workers isolated dictyostatin from a different source, and their exciting biological results[1c,d] further demonstrated the need for total synthesis both to secure the structure and to provide material for additional biological testing.

Early on, Pettit and Cichacz proposed partial stereostructure **1** for dictyostatin (Figure 1).[1b] Very recently, Wright and Paterson suggested that dictyostatin had structure **2**,[2] and this proposal has just been confirmed by independent total syntheses from Paterson's group[3a] and ours.[3b,4] Thus, dictyostatin is a "tied back" analogue of the important antitumor agent discodermolide **3**.[5] The scarcity and high biological activity of dictyostatin encourage continued development of

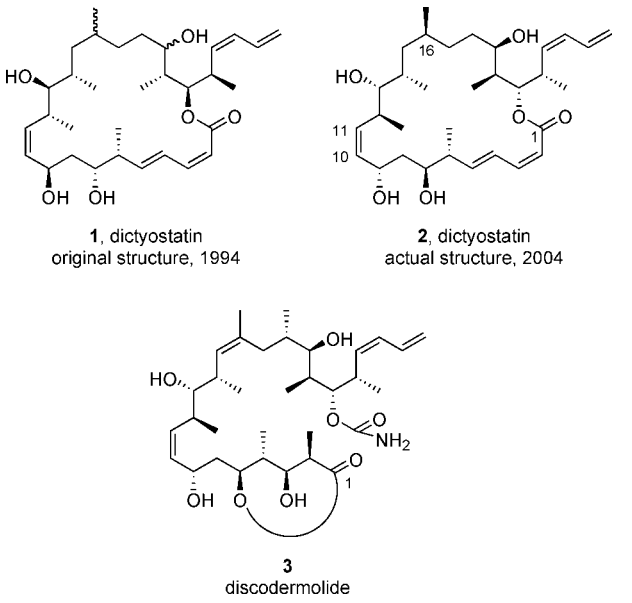


Figure 1. Structures of dictyostatin and discodermolide.

† Dedicated to Prof. Jeremiah P. Freemen in tribute to his 25 years of tenure as Secretary of Organic Syntheses.

(1) (a) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Boyd, M. R.; Schmidt, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1111−1112. (b) Pettit, G. R.; Cichacz, Z. A. Isolation and structure of dictyostatin 1 PCT WO5430053, 1995; *Chem. Abstr.* **1995**, 733500. (c) Wright, A. E.; Cummins, J. L.; Pomponi, S. A.; Longley, R. E.; Isbrucker, R. A. Dictyostatin compounds for stabilization of microtubules. PCT WO 0162239, 2001; *Chem. Abstr.* **2001**, 635882. (d) Isbrucker, R. A.; Cummins, J.; Pomponi, S. A.; Longley, R. E.; Wright, A. E. *Biochem. Pharm.* **2003**, *66*, 75−82.

(2) Paterson, I.; Britton, R.; Delgado, O.; Wright, A. E. *Chem. Commun.* **2004**, 632−633.

(3) (a) Paterson, I.; Britton, R.; Delgado, O.; Meyer, A.; Poullennec, K. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4629−4633. (b) Shin, Y.; Fournier, J.-H.; Fukui, Y. Brückner, A. M.; Curran, D. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 4634−4637.

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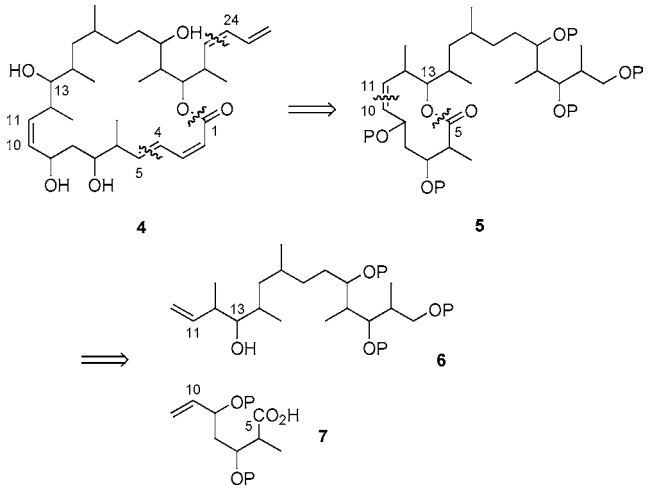


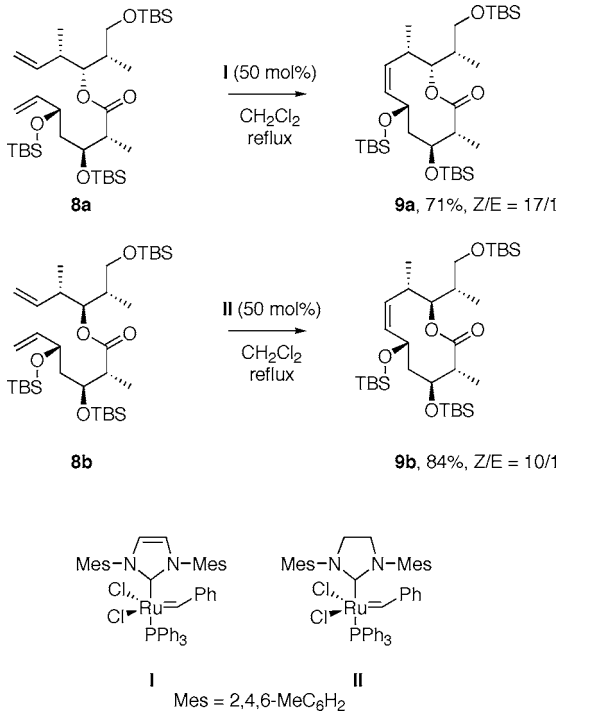
Figure 2. Esterification/ring-closing metathesis strategy.

more efficient synthetic approaches to the natural product and analogues.

Stereoselective construction of the C10−C11 (*Z*)-alkene is a crucial concern in the synthesis of both discodermolide and dictyostatin, and a number of successful approaches have been implemented in a fragment coupling setting.[5] We originally favored a Wittig approach for simplified discodermolide analogue synthesis[6] similar to that implemented by Smith in the total synthesis of discodermolide.[7] But the approach proved unreliable when we attempted to extend it to dictyostatin,[8] and we ultimately adapted the strategy to make the C9−C10 bond by fragment coupling instead.[3b] We report herein a series of simple and sophisticated model studies probing a ring-closing metathesis[9] approach to the C10−C11 (*Z*)-alkene. The results suggest considerable promise for extending this route to dictyostatin or discodermolide synthesis.

Figure 2 highlights the metathesis strategy in a dictyostatin setting and omitting stereochemical concerns. Retrosynthetically, the *E*,*Z*-diene of **4** is terminated at C23, and the C1−C4 fragment of the dienyl ester is excised with concomitant lactonization of the new terminus C5 onto the C13 hydroxyl group to give 10-membered lactone **5**. This lactone in turn can be made from alcohol **6** and acid **7** by esterification and ring-closing metathesis. Will the metathesis reaction succeed given the relatively crowded substitution pattern of the alkene?[9] If it succeeds, will it provide for stereocontrol in the alkene formation?[9,10]

Scheme 1. RCM Reactions of **8a**,**b**



To bring experimental evidence to bear on these questions, we selected model substrates **8a** and **8b** to study the ring-closing metathesis (Scheme 1). These substrates were made by esterification reactions from readily available alcohol and acid fragments, as described in the Supporting Information. Cyclization of **8a** with 50 mol % of catalyst **I** provided **9a** in 71% yield as an inseparable 17/1 mixture of *Z*/*E* isomers. Similar treatment of **8b** this time with second-generation Grubbs catalyst **II** provided **9b** in 84% yield as a 10/1 *Z*/*E* mixture. Reactions with 10% catalyst were not as successful, and starting material was recovered along with the target lactones. These encouraging results suggest that acceptable yields and good stereocontrol are possible.

We next extended these studies to prepare a large subunit of dictyostatin, as summarized in Scheme 2. The relative stereostructure was targeted based on originally proposed structure **1**, which we converted to its enantiomer to make it more similar to discodermolide.[4a] The alcohol **10** was

(4) Dictyostatin analogues and fragment synthesis: (a) Shin, Y.; Choy, N.; Balachandran, R.; Madiraju, C.; Day, B. W.; Curran, D. P.; Turner, T. R. *Org. Lett.* **2002**, *4*, 4443−4446. (b) O'Neil, G. W.; Phillips, A. J. *Tetrahedron Lett.* **2004**, *45*, 4253−4256.

(5) (a) Myles, D. C. In *Annual Reports In Medicinal Chem*; Doherty, A. M., Ed.; Academic Press: San Diego, CA, 2002; Vol. 37, 125−132. (b) Paterson, I.; Florence, G. J. *Eur. J. Org. Chem.* **2003**, 2193−2208.

(6) (a) Curran, D. P.; Furukawa, T. *Org. Lett.* **2002**, *4*, 2233−2235. (b) Choy, N.; Shin, Y.; Nguyen, P. Q.; Curran, D. P.; Balachandran, R.; Madiraju, C.; Day, B. W. *J. Med. Chem.* **2003**, *46*, 2846−2864. (c) Minguez, J. M.; Giuliano, K. A.; Balachandran, R.; Madiraju, C.; Curran, D. P.; Day, B. W. *Mol. Cancer. Therapeut.* **2002**, *1*, 1305−1313. (d) Minguez, J. M.; Kim, S.-Y.; Giuliano, K. A.; Balachandran, R.; Madiraju, C.; Day, B. W.; Curran, D. P. *Bioorg. Med. Chem.* **2003**, *11*, 3335−3357.

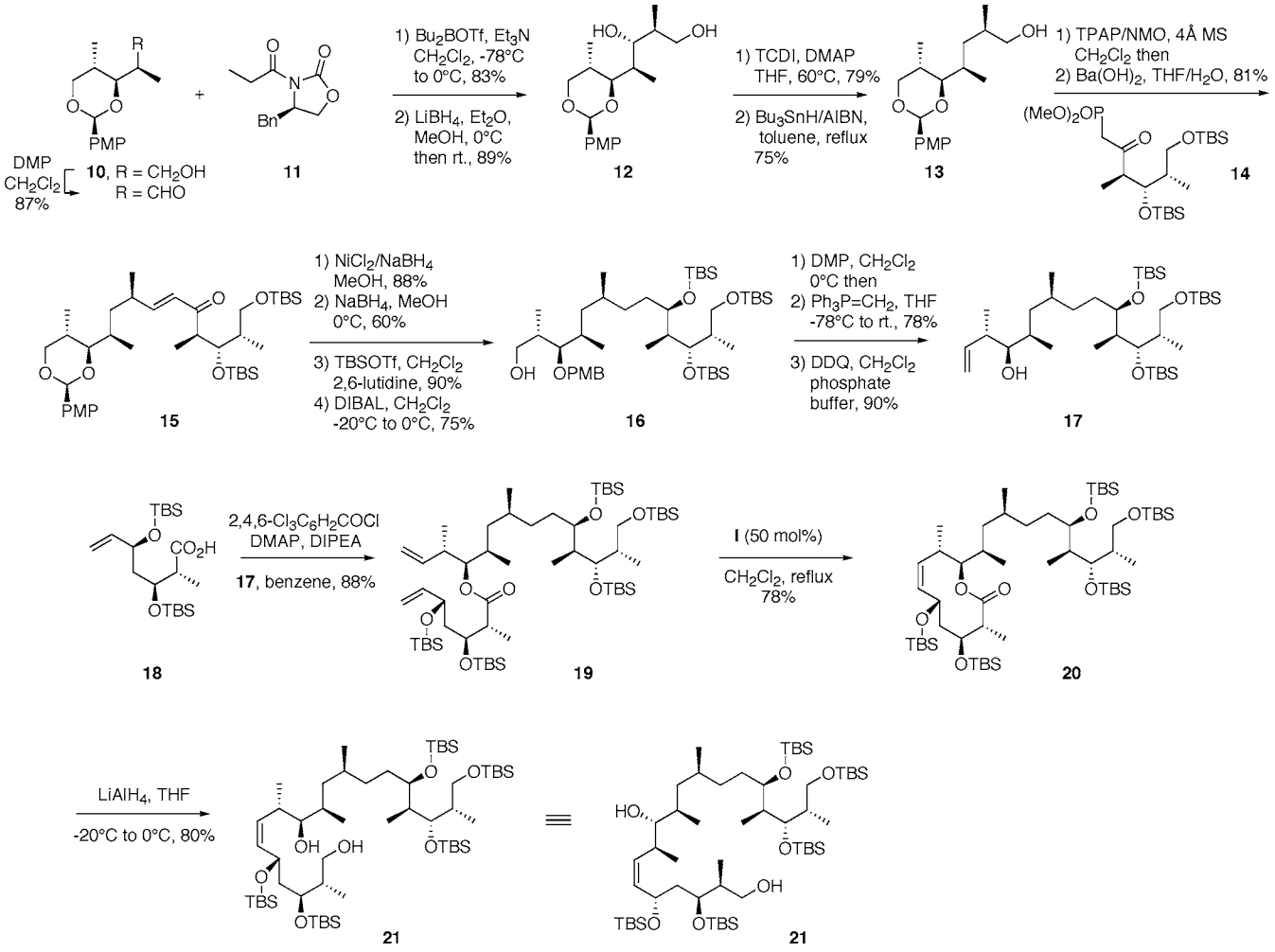
(7) (a) Smith, A. B.; Freeze, B. S.; Brouard, I.; Hirose, T. *Org. Lett.* **2003**, *5*, 4405−4408. (b) Smith, A. B.; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y. P.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654−8664.

(8) Shin, Y. Ph.D. Thesis, University of Pittsburgh, 2005.

(9) (a) Fürstner, A. *Alkene Metathesis in Organic Synthesis*; Springer: New York, 1998; Vol. 1, pp 37−72. (b) *Handbook of Metathesis*; Han, S.-Y., Chang, S., Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vol. 1, pp 5−119 (see especially sections 2.2.2.2, 2.2.6.2 and 2.2.7.1−2.2.7.3 for syntheses of medium and large rings).

(10) Variable stereoselectivities have been observed in medium ring formation. See, for example: (a) Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061−7069. (b) Liu, D.; Kozmin, S. A. *Org. Lett.* **2002**, *4*, 3005−3007. (c) Murga, J.; Falomir, E.; Garcia-Fortanet, J.; Carda, M.; Marco, J. A. *Org. Lett.* **2002**, *4*, 3447−3449. (d) Fink, B. E.; Kym, P. R.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 4334−4344.

Scheme 2. RCM Model Study



oxidized to the corresponding aldehyde,[11] which was immediately reacted with Evans (*R*)-oxazolidinone **11** to provide diol **12** after reductive removal of the oxazolidinone. Formation of the cyclic thionocarbonate from **12** with thiocarbonyl diimidazole (TCDI) followed by selective Barton−McCombie deoxygenation with Bu_3SnH provided alcohol **13**.[12]

The sequence now follows steps similar to those that were ultimately used in the successful synthesis of dictyostatin.[3] Oxidation of **13** with TPAP and Horner−Wadsworth−Emmons coupling[13] with readily available phosphonate **14**[14] provided enone **15**. 1,4-Reduction of the enone with $NiCl_2$/$NaBH_4$[15] followed by 1,2-reduction with $NaBH_4$ provides a readily separable mixture of alcohols. The major β-epimer was taken on by silylation with TBSOTf followed by DIBAL-induced acetal opening to provide **16**. Now, oxidation, Wittig reaction, and deprotection with DDQ[16] provide the key alcohol fragment **17**.

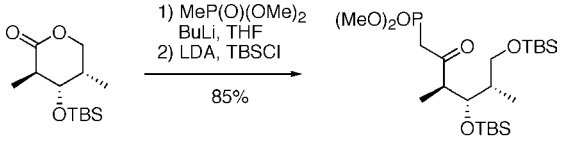
Coupling of **17** with acid **18** under Yamaguchi conditions[17] provided **19** in 88% yield. Ring-closing metathesis as above with catalyst **I** gave lactone **20** in 78% yield. In this case, the reaction was highly *Z*-selective, and there was no spectroscopic or chromatographic evidence for formation of

(11) Toshima, K.; Jyojima, T.; Yamaguchi, H.; Noguchi, Y.; Yoshida, T.; Murase, H.; Nakata, M.; Matsumura, S. *J. Org. Chem.* **1997**, *62*, 3271−3284.

(12) (a) Barton, D. H. R.; Subramanian, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1718−1723. (b) Barton, D. H. R.; McCombie, S. *J. Chem. Soc., Perkin. Trans. 1* **1975**, 1574−1585. (c) The enantiomer of this compound was recently reported: Lautens, M.; Colucci, J. T.; Hiebert, S.; Smith, N. D.; Bouchain, G. *Org. Lett.* **2002**, *4*, 1879−1882.

(13) Paterson, I.; Yeung, K. S.; Smaill, J. B. *Synlett* **1993**, 774−776.

(14) The phosphonate was prepared from the lactone shown below (Day, B. W.; Kangani, C. O.; Avor, K. S. *Tetrahedron: Asymmetry* **2002**, *13*, 1161−1165) as follows. See the Supporting Information for details.



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(15) (a) Satoh, T.; Nanba, K.; Suzuki, S. *Chem. Pharm. Bull.* **1971**, *19*, 817−820. (b) Abe, N.; Fujisaki, F.; Sumoto, K.; Miyano, S. *Chem. Pharm. Bull.* **1991**, *39*, 1167−1170.

(16) (a) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593−1596. (b) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885−892.

(17) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1995.

the *E*-isomer. Finally, LAH reduction cleaved the lactone to provide advanced intermediate **21**.

In the end, the further elaboration of **21** was discontinued because we learned from parallel studies[3] that this would not lead to dictyostatin (configurations are incorrect at C6 and C14). Nonetheless, the viability of the esterification/ring-closing metathesis approach stands, and this approach could potentially be applied to advantage in either the dictyostatin or discodermolide series. While catalyst loadings in the key metathesis step need to be reduced before the approach can be used for scale-up, the strategy appeals because of its ease and high *Z*-selectivity. It could provide a more convenient and reliable approach to C10−C11 bond construction than the Wittig reaction.

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Supporting Information Available: Complete experimental details and compound characterization data, as well as copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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