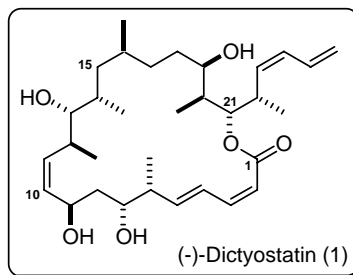


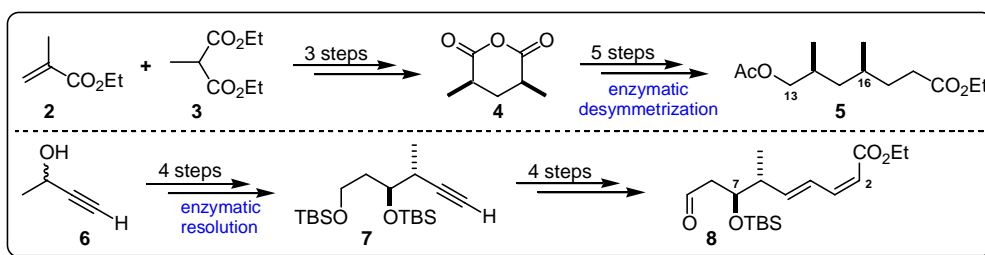
Total Synthesis of the Marine Macrolactone (-)-Dictyostatin

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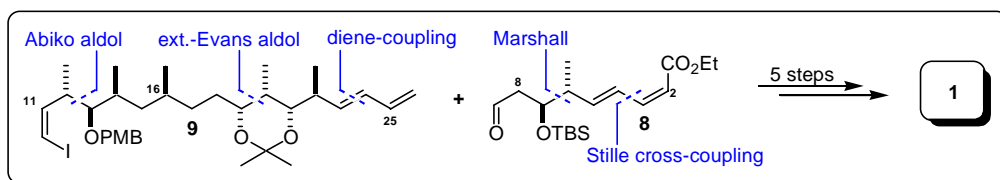
The macrolactone (-)-dictyostatin was first isolated by G. R. Pettit from a Maldives marine sponge *Spongia sp.* in 1994.¹ In 2001 Wright and co-workers showed, that it strongly inhibits the growth of human cancer cells by stabilizing the microtubules preventing the depolymerisation to tubulin heterodimers.²



The purpose of this project is the development of a convergent synthetic strategy which allows rapid access to (-)-dictyostatin, and its analogs. Avoiding the use of the costly Roche ester, the main precursors were prepared by employing enzymatic desymmetrisation and resolution, only using cheap, achiral compounds as starting materials.³



Starting from ester **5** the stereocenters at C12/C13 were introduced by Abiko aldol reaction. These at C19-C22 could be easily obtained in only two steps by extended-Evans aldol reaction directly followed by *syn*-reduction. The terminal diene was made by Cr(II)-mediated coupling, well known from the synthesis of discodermolide.⁴ Wittig reaction led to (*Z*)-vinyl iodide **9**, which was coupled under Nozaki-Kishi conditions with aldehyde **8**. Yamaguchi lactonisation of the free acid with the deprotected C21-alcohol and global deprotection completed the total synthesis.



¹ G. R. Pettit, Z. A. Cichacz, F. Gao, M. A. Boyd, J. M. Schmidt, *J. Chem. Soc. Chem. Comm.* **1994**, 1111-1112

² A. E. Wright, J. Cummins, S. A. Pomponi, R. E. Longley, R. A. Isbrucker, *Dictyostatin compounds for stabilizing of microtubules*, WO 0162239, **2001** [*Chem. Abstr.* **2001**, 635882]

³ a) E. Prusov, H. Röhm, M. E. Maier, *Org. Lett.* **2005**, 8 (6), 1025-1028; b) J. Jägel, M. E. Maier, *Synlett* **2006**, 5, 693-696

⁴ I. Paterson, O. Delgado, G. J. Florence, *J. Org. Chem.* **2005**, 70, 150-160