

Synthesis and biological evaluation of (–)-16-normethyldictyostatin: a potent analog of (–)-dictyostatin

Youseung Shin,^a Charitha Madiraju,^b Raghavan Balachandran,^b Brianne S. Raccor,^a Guangyu Zhu,^a Michael C. Edler,^c Ernest Hamel,^c Billy W. Day,^{a,b*} Dennis P. Curran^{a*}

^aDepartment of Chemistry and ^bDepartment of Pharmaceutical Sciences, University of Pittsburgh, Pittsburgh, PA 15261 USA, and ^cScreening Technologies Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute at Frederick, National Institutes of Health, Frederick, MD 21702 USA, curran@pitt.edu

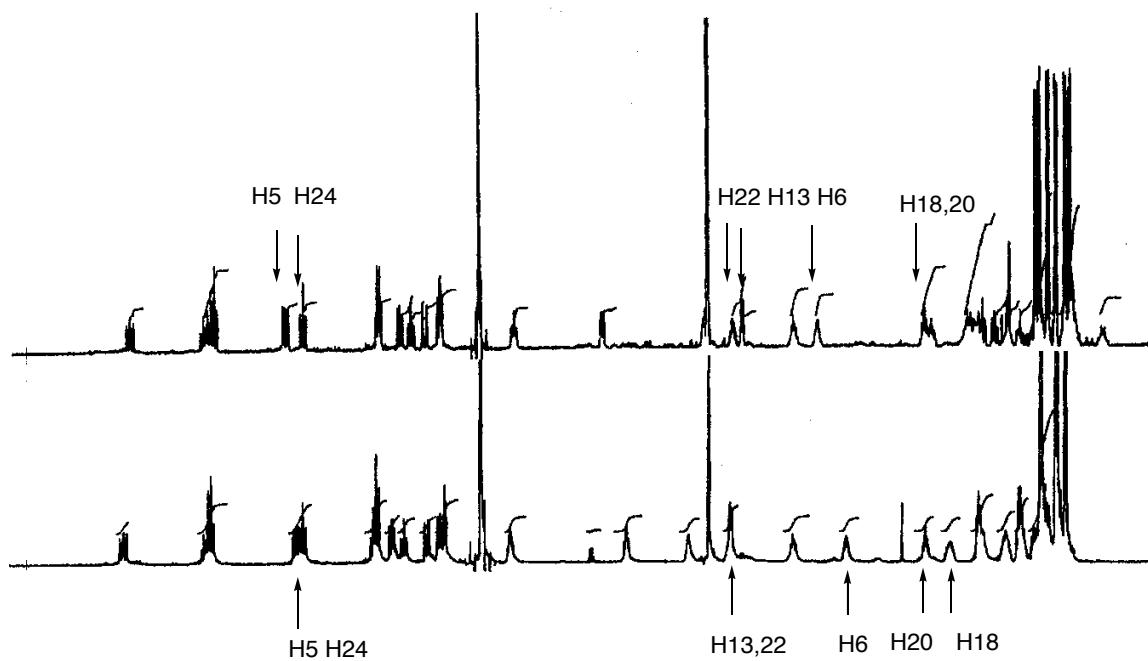
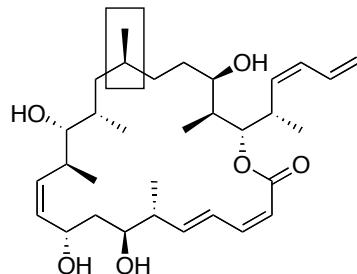
Supporting Information

Table of Contents

Spectroscopic and physical data for 1b	2
Comparison of 600 MHz ¹ H NMR spectra of 1a and 1b	3
Copies of ¹ H and ¹³ C NMR spectra of 1b (YSS698-2)	4
Copies of HH COSY and HMQC spectra of 1b	5

(8S,10S,14R,20R)-Tetrahydroxy-(7R,13S,15S,21S)-tetramethyl-(22S)-((1S)-methylpent-2,4-dienyl)-oxacyclodocosa-3,5,11-trien-2-one (16-normethyldictyostatin, 1b). The product was purified by flash column chromatography (EtOAc/hexane 3:7) and was isolated as a colorless oil (25 mg, 24%): IR (CHCl₃) 3414, 2965, 2930, 1708, 1637, 1454, 1375, 1273, 1182, 1046, 968 cm⁻¹; ¹H NMR (600 MHz, CD₃OD) δ 7.22 (dd, *J* = 15.4, 11.2 Hz, 1H), 6.67 (ddd, *J* = 17.3, 11.0, 10.5 Hz, 1H), 6.64 (dd, *J* = 11.4, 11.4 Hz, 1H), 6.07 (dd, *J* = 15.4, 7.7 Hz, 1H), 6.02 (dd, *J* = 10.9, 10.9 Hz, 1H), 5.55 (t, *J* = 10.6 Hz, 1H), 5.52 (d, *J* = 11.4 Hz, 1H), 5.43 (dd, *J* = 10.9, 9.0 Hz, 1H), 5.35 (dd, *J* = 10.7, 10.6 Hz, 1H), 5.20 (d, *J* = 16.7 Hz, 1H), 5.12 (d, *J* = 10.2 Hz, 1H), 5.08 (dd, *J* = 5.9, 5.9 Hz, 1H), 4.64 (m, 1H), 3.86 (ddd, *J* = 8.4, 4.7, 4.5 Hz, 1H), 3.43 (m, 1H), 3.16 (m, 1H), 3.14 (dd, *J* = 8.1, 2.6 Hz, 1H), 2.73 (m, 1H), 2.37 (m, 1H), 1.84 (m, 1H), 1.68 (m, 1H), 1.51-1.45 (m, 3H), 1.31 (m, 1H), 1.20 (m, 1H), 1.14-1.11 (m, 1H), 1.08 (d, *J* = 6.9 Hz, 6H), 1.07-1.01 (m, 2H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.95 (m, 1H), 0.92 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CD₃OD) δ 168.2, 146.6, 144.8, 134.3, 133.8, 133.4, 132.2, 131.3, 129.1, 118.5, 118.0, 79.9, 79.3, 72.4, 71.0, 65.5, 44.9, 41.7, 40.7, 37.9, 36.0, 35.4, 35.2, 33.9, 27.4, 27.2, 19.5, 18.3, 16.4, 15.1, 10.1; LRMS (ESI) 541.3 [M + Na]⁺, 483.3; HRMS (ESI) calcd for C₃₁H₅₀O₆Na 541.3505 [M + Na]⁺, found 541.3521; [α]²⁰_D -34.4 (*c* 0.18, MeOH).

dictyostatin
(600MHz, CD₃OD)



16-normethyldictyostatin
(600MHz, CD₃OD)

