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A Concise, Selective Synthesis of the Polyketide Spacer Domain of a Potent Bryostatin Analogue

Paul A. Wender,* Alexander V. W. Mayweg, and Christopher L. VanDeusen

Department of Chemistry, Stanford University, Stanford, California 94305-5080

wenderp@leland.stanford.edu

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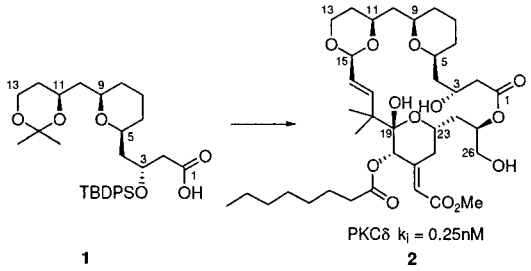
ABSTRACT



A concise, asymmetric synthesis of the polyketide spacer domain portion (C1–C13) of a highly potent bryostatin analogue was developed. The route utilizes asymmetric hydrogenation methodology to install the C3, C5, and C11 stereocenters, while a substrate directed syn reduction sets the C9 stereocenter. The spacer domain 1 is obtained in 10 steps with a 25% overall yield and is readily incorporated into the synthesis of 2.

The bryostatins are a family of structurally novel and complex marine macrolides exhibiting a unique set of biological activities, including induction of apoptosis, reversal of multidrug resistance, and immune system enhancement. They also synergize the effect of other cancer therapeutic agents.[1] Bryostatin **1** is in phase I and phase II clinical trials due to its promising antineoplastic activity, both as a single agent and in combination with other agents.[2] However, the low abundance and difficult isolation of bryostatin **1** has significantly limited its supply as well as access to potentially superior clinical derivatives.[1] To circumvent these problems, we have been involved in the de novo design and synthesis of simplified bryostatin analogues. Recently, this effort has resulted in the identification and synthesis of a bryostatin analogue **2** (Figure 1) that exhibits in vitro and in vivo biological activities comparable to or better than bryostatin **1** in various assays.[3,4]

Our previous synthesis of **2** was based on the two-step combination of the polyketide spacer domain **3** and recognition domain **4** (Figure 1). The route to **3** in turn was designed

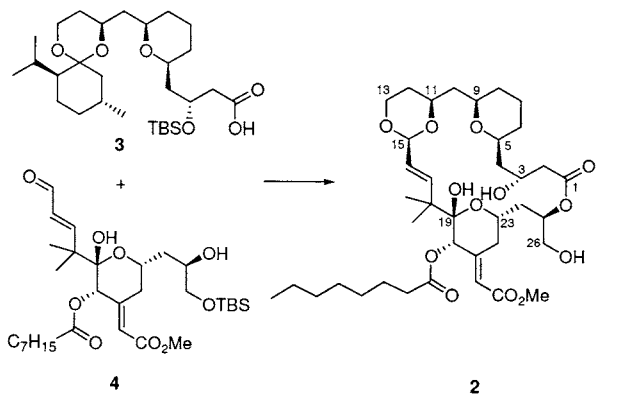


Figure 1. Convergent assembly of analogue **2** from spacer domain **3** and recognition domain **4**.

(1) (a) Mutter, R.; Wills, M. *Bioorg. Med. Chem.* **2000**, *8*, 1841−1860. (b) Pettit, G. R. *J. Nat. Prod.* **1996**, *59*, 812−821. (c) Hale, K. J.; Hummersone, M. G.; Manaviazar, S.; Frigerio, M. *Nat. Prod. Rep.* **2002**, *19*, 413−453.

(2) For current information, see: http://clinicaltrials.gov

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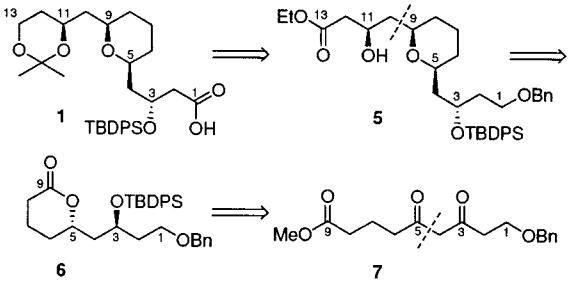
to allow rapid access to structures needed to test our pharmacophore hypothesis and proceeded in 11 linear steps and 11% yield, affording **3**, but with only 60% selectivity.[3] With the potency of analogue **2** now established, our attention turned to an improvement of its synthesis with respect to overall yield, selectivity, and scalability. This has led to a new strategy for the synthesis of a spacer domain in the form of **1** (Scheme 1) and its conversion to **2**.

Scheme 1. Retrosynthetic Analysis of Modified Spacer Domain **1**

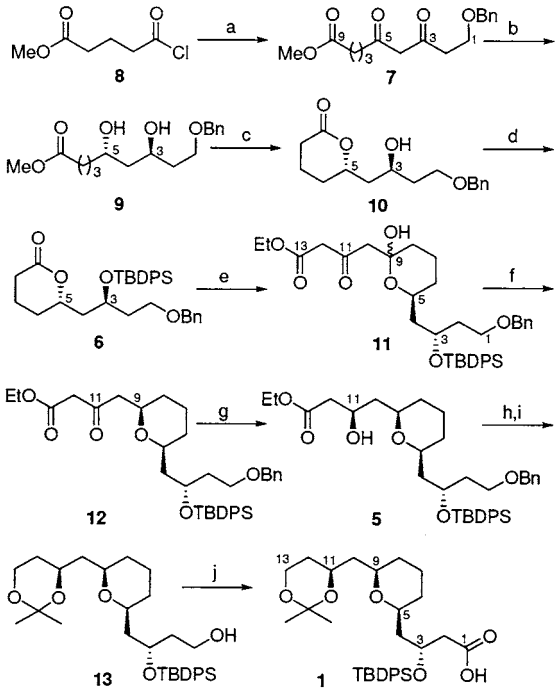


The strategy for accessing our new spacer domain (Scheme 1: **1**) is based on the conjunction and asymmetric elaboration of three commercially available building blocks. Our synthesis started with the acylation of the anion of commercially available 4-benzyloxy-2-butanone with the commercially available acid chloride **8**, which afforded diketone **7** in 68% yield (Scheme 2).

At this stage, in one of the key transformations of this sequence, the C3 and C5 stereocenters were set through a Noyori asymmetric diketone hydrogenation that proceeded in excellent yield and in greater than 95:5 enantioselectivity (as determined by Mosher's ester analysis) and complete syn selectivity to provide diol **9**.[5,6] The secondary alcohols in **9** were then differentiated through a lactonization of the C5 alcohol with the proximate ester group, affording after C3 protection, lactone **6**.

The third set of backbone carbons (C10−C13) of the spacer domain were then introduced by addition of the dianion of ethyl acetoacetate to lactone **6**. The resultant lactol **11** was subsequently reduced without further purification, thus setting the C9 stereocenter and providing the desired syn tetrahydropyran **12** in good yield.[7] At this stage, the C11

Scheme 2. Synthesis of Spacer Domain **1**[a]



[a] Reagents and conditions: (a) LDA, 4-benzyloxy-2-butanone, −78 °C, 10 min, 68%; (b) Ru-(*S*)-BINAPCl_2, MeOH, H_2, (95 atm), 30 °C, 78 h, 92% (97% BORSM); (c) silica, PhMe, 12 h, reflux, 95%; (d) TBDPSCl, imidazole, DMF, 2 h, 85%; (e) ethylacetoacetate, LDA (2 equiv), −78 °C; (f) Et_3SiH, TFA, −30 °C, 4 h, 70% over two steps; (g) Ru-(*R*)-BINAPCl_2, EtOH, H_2 (78 atm), 96 h, 91%; (h) H_2, $Pd(OH)_2$, Et_2O, 1 h, then $LiBH_4$, 1 h, 96%; (i) 2,2-dimethoxypropane, TsOH, DMF, then silica, DCM, 4 h, 93%; (j) TEMPO, NaOCl, $NaClO_2$, MeCN, 50 °C, 4 h, 92%.

stereocenter was set through a second asymmetric hydrogenation, affording the hydroxyester **5** in excellent yield and greater than 99% de.[8] It was found that **5** can be transformed to the corresponding triol in a one-operation procedure involving a hydrogenolysis with Pd/C under 1 atm of hydrogen followed by a $LiBH_4$ reduction. Protection of the triol as the acetonide **13** followed by oxidation of the alcohol with the Merck TEMPO/NaOCl/$NaClO_2$ procedure afforded the new spacer domain **1** in 10 steps, 25% overall yield, and greater than 95:5 selectivity.[9]

The new spacer domain **1**, incorporating a simpler diol protecting group relative to **3** (acetone in **1** vs menthone in **3**), was then tested as a substrate for coupling to the recognition domain **4** (Scheme 3). Toward this end, **1** was first coupled to **4** by using a PyBroP-mediated esterification to afford the richly functionalized ester **14**.[10] Gratifyingly,

(3) Wender, P. A.; Baryza, J. L.; Bennett, C. E.; Bi, F. C.; Brenner, S. E.; Clarke, M. O.; Horan, J. C.; Kan, C.; LaCote, E.; Lippa, B. S.; Nell, P. G.; Turner, T. M. *J. Am. Chem. Soc.* **2002**, *124*, 13648−13649.

(4) (a) Wender, P. A.; Hinkle, K. W.; Koehler, M. F. T.; Lippa, B. *Med. Res. Rev.* **1999**, *19*, 388−407. (b) Wender, P. A.; MartinCantalejo, Y.; Carpenter, A. J.; Chiu, A.; DeBrabander, J.; Harran, P. G.; Jimenez, J. M.; Koehler, M. F. T.; Lippa, B.; Morrison, J. A.; Muller, S. G.; Muller, S. N.; Park, C. M.; Shiozaki, M.; Siedenbiedel, C.; Skalitzky, D. J.; Tanaka, M.; Irie, K. *Pure Appl. Chem.* **1998**, *70*, 539−546. (c) Unpublished results.

(5) (a) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumabayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629−631. (b) For general reviews on 1,3-dicarbonyl reductions with ruthenium biarylbisphosphine catalysts see: (i) Noyori, R.; Kitamura, M.; Ohkuma, T. Asymmetric Hydrogenation. In *Catalytic Asymmetric Synthesis*, 2nd ed.: Ojima, I., Ed.; Wiley-VCH: New York, 2000. (ii) Ager, D. J.; Laneman, S. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3327−3355.

(6) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519.

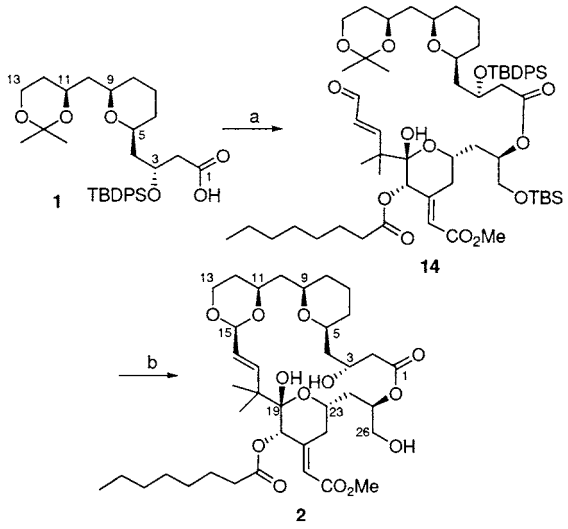
(7) (a) The selectivity of this step was determined to be greater than 95:5 by ^1H NMR. (b) Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Chem. Soc., Chem. Commun.* **1986**, 1568−1569.

(8) (a) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856−5858. (b) We believe this to be one of the more complex examples of a reduction of this type.

(9) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564−2566.

(10) Coste, J.; Frérot, E.; Jouin, P. *J. Org. Chem.* **1994**, *59*, 2437−2446.

Scheme 3. Synthesis of Analogue **2** from New Spacer Domain **1** and Recognition Domain **4**[a]



[a] Reagents and conditions: (a) PyBroP, Hünig's base, recognition domain **4**, DMAP, DCM, 70%; (b) HF·py, THF, 16 h, 90%.

this ester efficiently underwent deprotection and macro-transacetalization upon exposure to HF/pyridine, affording the desired analogue **2**, identical (^{1}H NMR, HPLC, MS) with a sample of the analogue obtained with use of the previous spacer domain. This establishes the compatibility of the new spacer domain with the existing synthesis of analogue **2**. It also provides a further example of the generality of this macroacetalization strategy in which C3 and C26 are deprotected and the stereochemistry at C15 is set under thermodynamic control in one operation in the presence of a diverse array of functionality.

In summary, a selective and concise new strategy for the synthesis of the polyketide-like spacer domain of our bryostatin analogue **2** has been realized. The synthesis utilizes three commercially available building blocks to establish the 13-carbon backbone of the spacer domain and asymmetric hydrogenation to control its relative and absolute stereochemistry. This approach offers enhanced efficiency and selectivity over the previous route to **2** and potential cost and scalability benefits. This spacer domain is currently being paired with new modified recognition domains. Further results will be reported in due course.

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Supporting Information Available: Experimental conditions and spectral data for compounds**1**, **2**, and **5**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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