Total Synthesis

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Total Synthesis of Bryostatin 8 Using an Organosilane-Based Strategy

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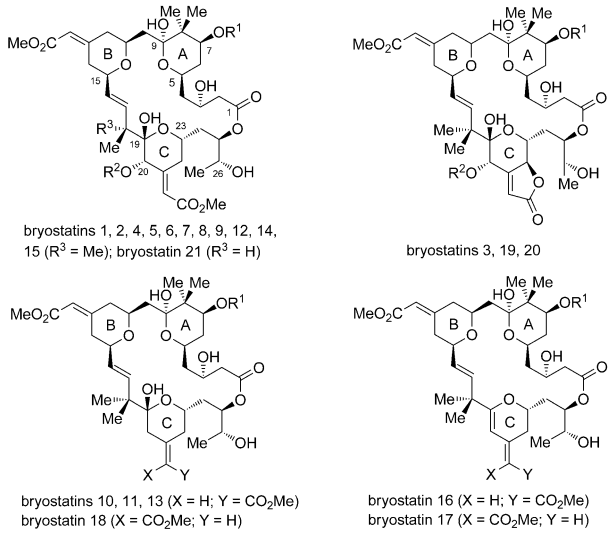
Abstract: *Convergent total synthesis of bryostatin 8 has been accomplished by an organosilane-based strategy. The C ring is constructed stereoselectively through a geminal bis(silane)-based [1,5]-Brook rearrangement, and the B ring through geminal bis(silane)-based Prins cyclization, thus efficiently joining the northern and southern parts of the molecule.*

Bryostatins[1] are a family of 21 complex macrolides produced by a bacterial symbiont of the marine bryozoan *Bugula neritina* (Scheme 1). Ever since Pettit and co-workers isolated the first family member, bryostatin 1, in 1982,[2] these marine natural products have attracted substantial interest for their wide range of potent bioactivities. Bryostatin 1, the most studied member, has shown remarkable activity against a wide range of cancers.[3] It also shows synergism with established oncolytic agents such as Taxol, which has led to numerous clinical trials for cancer therapy.[4] Recent studies have also uncovered promising potential in the treatment of other conditions such as ischemic stroke,[5] diabetes,[6] Alzheimer's disease,[7] and HIV infection.[8] It has been suggested that the unique biological activity of the bryostatins is associated with the solvent-exposed portion of the A and B rings,[9] while the C ring simply binds to the C1 domain of isoforms of protein kinase C.[10]



Scheme 1. Structure of bryostatins 1–21.

Bryostatins cannot be obtained in significant amounts from their marine source. Bryostatin 1, for example, is extracted at a final yield of 0.00014 %.[11] This low yield has motivated significant efforts toward their total syntheses[12] as well as the generation of functional analogues by simplification of the northern part of the molecule.[13] The complex structures of the bryostatins pose obvious synthetic challenges: they possess three pyran rings (A, B, and C) in distinct oxidation states, multiple stereocenters, and numerous functionalities such as alkene, alcohol, ether, hemiketal, and ester. Masamune and co-workers achieved the total synthesis of bryostatin 7,[12a] and later seven groups independently succeeded in synthesizing six members of this family.[12] Most recently, Wender and co-workers developed a state-of-the-art strategy, thus leading to a scalable synthesis of bryostatin 1.[12k] Despite these successes, new strategies for synthesizing bryostatins are still needed to facilitate the discovery of superior derivatives and drug leads.

We aimed to design a unique organosilane-based strategy for the synthesis of the bryostatins on the basis of our findings that geminal bis(silane)s, which contain two bulky silyl groups attached to a single carbon center, are quite useful as bifunctional synthons.[14] We reasoned that it should be possible to synthesize the A, B, and C rings, having different oxidation states, by using three different organosilane reactions. We planned to construct the B and C rings using our geminal bis(silane) chemistry, while the northern part, containing the A ring, would be prepared by hydrosilylation/Fleming–Tamao oxidation (Scheme 2).[15] We predicted that the geminal bis(silyl) homoallylic alcohol **1** and an aldehyde could undergo [1,5]-Brook rearrangement/addition[16] to construct the C-ring precursor **2** with γ-*E* selectivity, while the same types of substrates could also undergo Prins cyclization[17] to give the B-ring **3** with *cis*-*Z* stereochemical control, thereby connecting the northern and southern parts of the bryostatins. By using this unified geminal bis(silyl) approach, we report here detailed studies of the total synthesis of bryostatin 8.[18]

Synthesis of the northern part, containing the A ring, commenced with transformation of D-(−)-pantolactone (**4**) into the C5–C11 fragment **6** (Scheme 3). Protection with benzylbromide with subsequent reduction of the lactone and conversion of the resulting hemiacetal into a terminal alkyne

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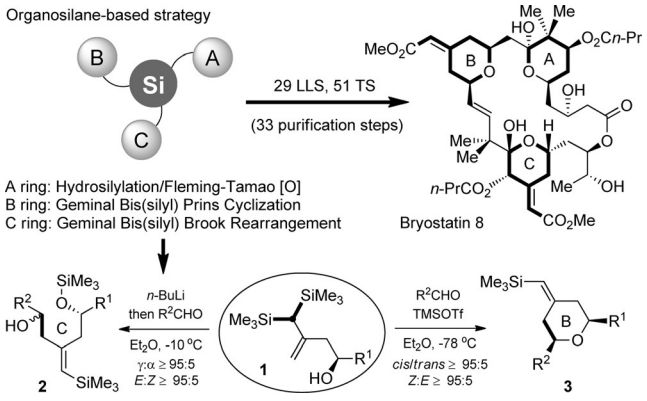
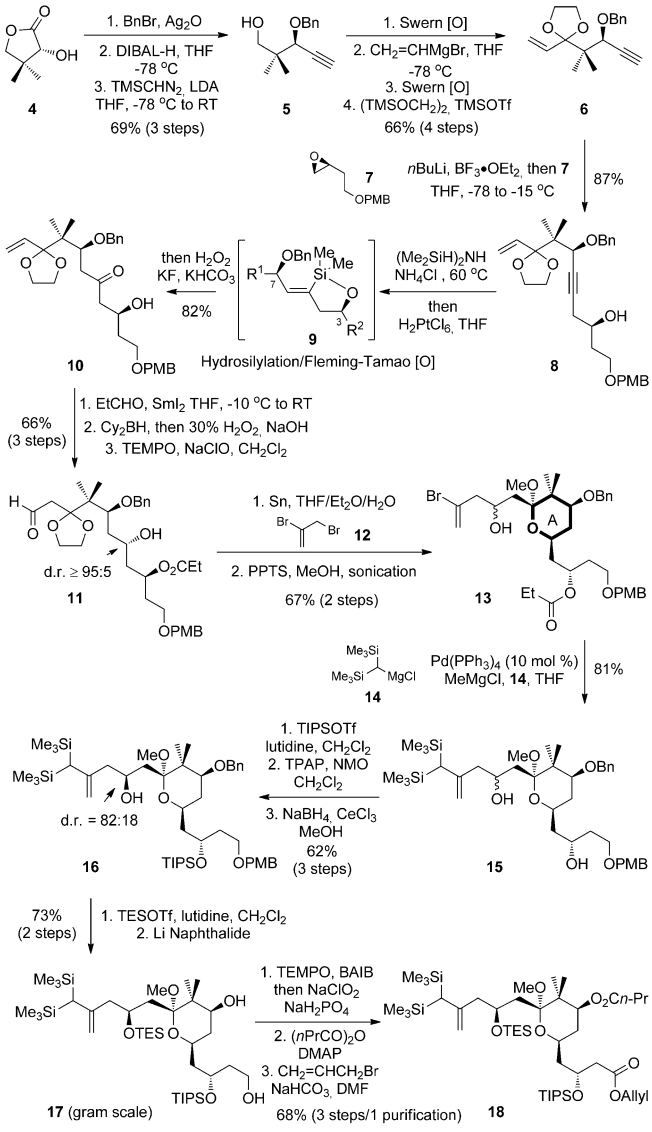


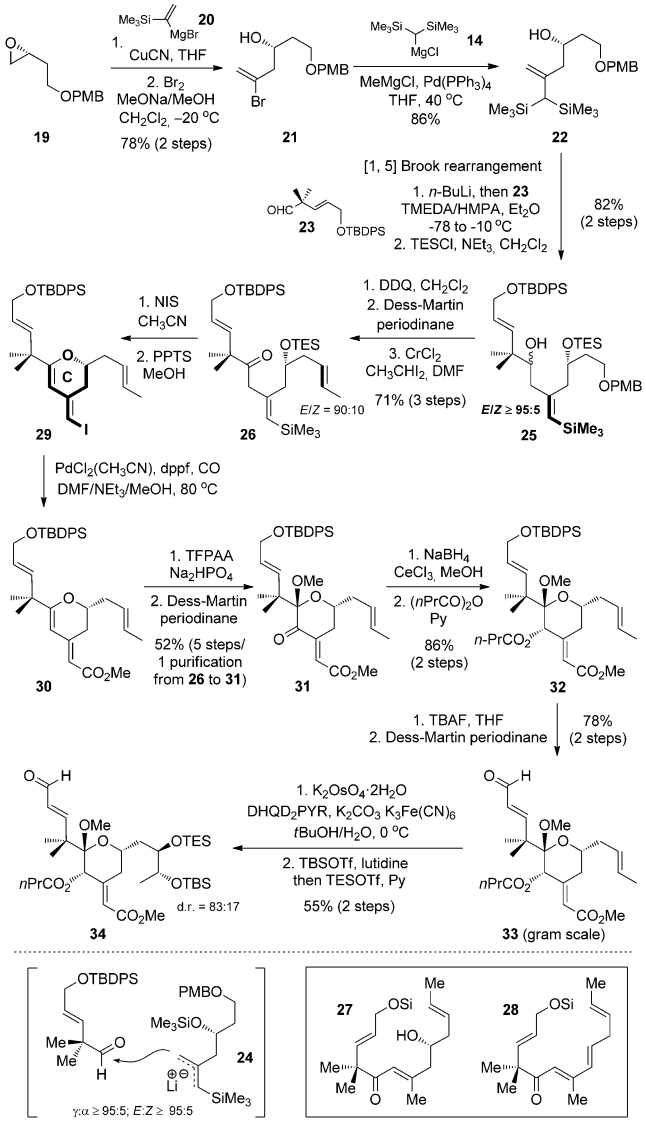
Scheme 2. Organosilane-based strategy for the total synthesis of bryostatin 8. Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.



Scheme 3. Synthesis of the northern part, containing the A ring, of the bryostatins. BAIB = = [bis(acetoxy)iodo]benzene, DIBAL-H = diisobutylaluminum hydride, DMF = *N*,*N*-dimethylfirmamide, LDA = lithium diisopropylamide, NMO = *N*-methylmorpholine-*N*-oxide, PMB = *para*-methoxybenzyl, TEMPO = , TES = triethylsilyl, THF = tetrahydrofuran, TIPS = triisopropylsilyl, TPAP = tetra-n-propylammonium perruthenate.

led to **5**. Sequential oxidation/addition/oxidation/protection gave rise to the alkyne **6**. The lithium acetylide of **6** was used to open the ring of the known epoxide **7** (C1–C4 fragment),[19] thus furnishing the C1–C11 fragment **8**, in 87% yield, in a convergent manner. Although synthesis of **8** from **4** required eight steps, the well-known operations and 45% overall yield make the process very practical for the preparation of **8** on a 10-gram scale. Hydrosilylation/Fleming–Tamao oxidation transformed the alkyne moiety into a ketone, thus delivering **10** in 82% yield via the vinylsilane intermediate **9** in a convenient sequential operation. The OH at C5 was introduced diastereoselectively ($\geq$95:5 d.r.) by an Evans–Tishchenko reduction using SmI_2.[20] Reduction using $Me_4NBH(OAc)_3$, $NaBH(OAc)_3$, or $LiAlH(O\textit{t}\text{-}Bu)_3$ gave only moderate d.r. values of 75:25. Hydroboration/oxidation of the terminal alkene and subsequent selective oxidation of the primary alcohol provided the aldehyde **11** in 66% yield over three steps. Allylation of **11** with 2-bromo allyl bromide or its variants did not proceed with adequate stereocontrol despite extensive testing under various asymmetric conditions.[21] Thus, a traditional Barbier reaction was performed to give a 1:1 mixture of two C11 diastereomers. PPTS-catalyzed ketalization led to the A ring, thus giving **13** in 67% yield over two steps. $Pd(PPh_3)_4$-catalyzed Kumada cross-coupling of **13** with the bis(trimethylsilyl)methyl magnesium chloride **14** installed the bis(silyl) moiety and generated **15** in 81% yield.[22] Protection of OH group at C3 with TIPS, and C11−OH oxidation and reduction afforded **16** in 62% with a d.r. value of 87:13. TES protection of C11−OH and removal of the Bn and PMB groups gave the diol **17**, which was oxidized to the acid,[23] butyrylated at C7−OH, and converted into an allyl ester to yield the northern part **18**. Only two purifications were required during the last five steps, thus affording **18** in 50% overall yield.

The synthesis of the southern part, containing the C ring, commenced with the known epoxide **19**.[24] Epoxide ring opening with the vinyl magnesium bromide **20**, followed by bromination, afforded **21** in 78% overall yield (Scheme 4).[25] $Pd(PPh_3)_4$-catalyzed Kumada cross-coupling of **21** with **14** provided the homoallylic alcohol **22** in 86% yield. [1,5]-Brook rearrangement of a geminal bis(silyl), developed by our group,[16] was used to assemble **22** and **23**. The reaction proceeded by C-to-O migration of one silyl group, thus generating the allyl anion **24**, which was stabilized by the unmigrated silyl group. Subsequent addition to **23**[26] proceeded with complete γ-regioselectivity and *E*-stereoselectivity to afford the C15–C25 fragment **25** in 82% yield after formation of the TES ether. Removal of the PMB group, Dess–Martin oxidation, and a Takai reaction[27] installed the C25–C26 olefin with an *E*/*Z* ratio of 90:10. Initial cyclization of **26** to the dihydropyran produced only the undesired **27** and **28** by elimination of the $SiMe_3$ and/or C23 hydroxy groups, together with a double-bond shift. Therefore, iodination of the vinylsilane was carried out first with configurational retention. The resulting *E*-configured vinyliodide underwent cyclization cleanly to give the dihydropyran **29**, which was transformed into **30**, containing an exocyclic *E*-enoate, by palladium-catalyzed carbonylation. Because the *E*-enoate moiety in **30** was vulnerable to isomerization, **30** was

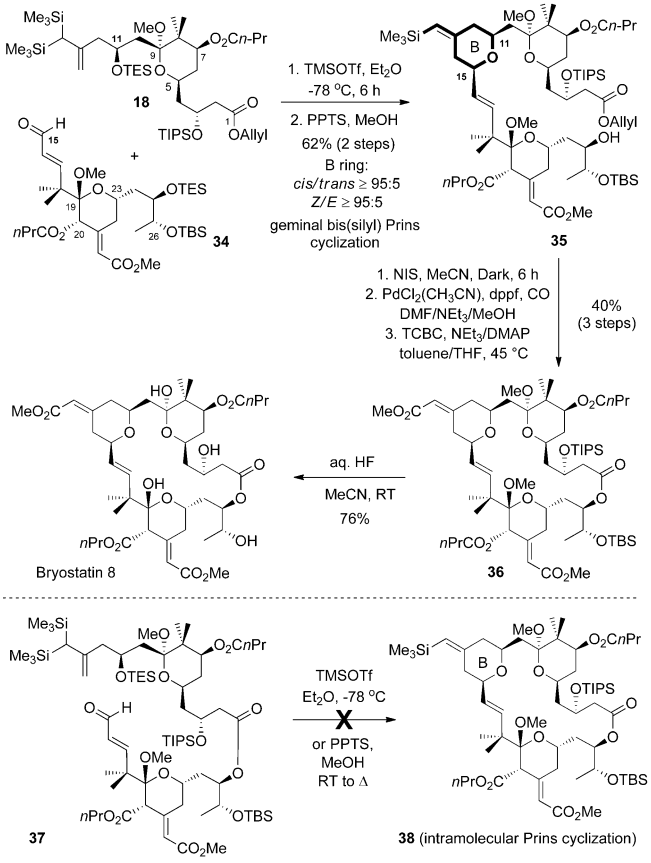


Scheme 4. Synthesis of the southern part, containing the C ring, of the bryostatins. HMPA = hexamethylphosphoric triamide, PPTS = *para*-toluenesulfonic acid, TBAF = tetra-n-butylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, TFPAA = trifluoroperacetic acid, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

subjected to TFPAA-mediated epoxidation of the C19–C20 double bond,[12g] in situ epoxide ring opening at C19, and Dess–Martin oxidation. The ketone **31** was synthesized from **26** in 52% overall yield over five steps, with only one purification at the last step. Reduction with $NaBH_4/CeCl_3$ and butyrylation installed the desired functionality at C20 in **32**. Removal of the TBDPS group and Dess–Martin oxidation afforded the enal **33** in 78% yield.[12i] Finally, Sharpless' dihydroxylation and sequential TBS/TES disilylation of the resulting C25/C26 diol (d.r. = 83:17) afforded the southern part **34**.

The strategy for coupling **18** and **34** relied on the geminal bis(silyl) Prins cyclization developed by our group.[17] We knew from our previous work that this reaction proceeds in high yields with good stereocontrol in simple systems, but we had never examined the reaction efficiency with structurally complex substrates such as the highly oxygenated **18** and **34**. To our delight, the desired intermolecular cyclization occurred readily with TMSOTf in Et_2O at −78 °C after 6 hours. The B ring was constructed with complete *cis*/*Z* selectivity, thus giving **35** in 62% yield (Scheme 5). A similar Prins cyclization for bryostatin synthesis was devised independently by the groups of Keck,[12h] Krische (intermolecular cyclization),[12j] and Wender (intramolecular cyclization).[12i,k] These cyclizations are less effective than ours because the unsubstituted, the exocyclic alkene in the resulting pyrans must be transformed into pyranone and then into the B ring by Fuji's asymmetric Horner–Wadsworth–Emmons reaction, which typically gives moderate *Z*/*E* ratios when generating the exocyclic enoate.[28] Separation of the *Z*/*E* mixture requires preparative thin-layer chromatography or HPLC. Instead, our strategy allowed us to install the enoate more efficiently by an iodination/carbonylation sequence, which proceeded with complete retention of the *Z* configuration. Subsequent Yamaguchi macrolactonization[29] gave **36** in 40% yield over three steps. Finally, two methyl ketals and two silyl ethers were removed with aq. HF in CH_3CN, thus providing bryostatin 8 in 76% yield.

Inspired by Wender's Prins macrocyclization,[12i] we also tested the intramolecular version of our geminal bis(silyl) Prins cyclization. Unfortunately, desired cyclization of **37** into **38** was detected neither under our optimal reaction conditions



Scheme 5. Union of the northern and southern parts by geminal bis(silyl) Prins cyclization to form the B ring of the bryostatins.

using TMSOTf in Et_2O, nor under Wender's conditions using PPTS in MeOH at room temperature or 50 °C (Scheme 5). The main transformations appeared to be acetalization at C9 and C11 with the aldehyde, as observed by Keck. We also observed other side-reactions, such as elimination of one silyl group from the geminal bis(silyl) allyl moiety and intramolecular cyclization between C9 and C14.

The data from the ^{1}H NMR and ^{13}C NMR spectroscopy in $CDCl_3$, high-resolution mass spectra, and optical rotation for our synthetic bryostatin 8 were in agreement with those reported for the natural product. Those data were kindly provided by Prof. G. R. Pettit, who isolated bryostatin 8 first in 1985.[18a,b] The identity of the synthetic sample was further established by the excellent consistency between our ^{1}H NMR, ^{13}C NMR, and DEPT spectra in CD_3OD and those kindly provided by Prof. H. W. Lin, who isolated bryostatin 8 later in 2001 (see the Supporting Information).[18c]

In summary, we have used an organosilane-based strategy to accomplish a convergent total synthesis of bryostatin 8 in 29 steps (longest linear sequence) and 51 total steps (33 purification steps). The synthesis highlights the power of the geminal bis(silane) chemistry, which was employed as a unified strategy for constructing the C ring by [1,5]-Brook rearrangement, and the B ring by Prins cyclization, thus leading to union of the northern and southern parts. This approach affords some structurally new and versatile intermediates, such as dihydropyran **29**, which may be a useful scaffold for synthesizing C-ring analogues by functionalization of the enol and vinyliodide moieties. A similar strategy could also be used to modify the B ring by functionalization of the vinylsilane in **35**. Our success with geminal bis(silyl) Prins cyclization and its reliable stereospecificity lead us to suggest that it may be possible to generate the *E*-(C13) analogues of the bryostatins, which differ in their preference for protein kinase C isoforms.[12k] This task would require exchanging the geminal bis(silyl) homoallylic alcohol and aldehyde in the northern and southern parts. We are investigating this possibility in our group.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cyclization · natural products · pyrans · rearrangements · total synthesis

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[1] For selected reviews on bryostatins, see: a) K. J. Hale, M. G. Hummersone, S. Manaviazar, M. Frigerio, *Nat. Prod. Rep.* **2002**, *19*, 413–453; b) "Beyond Natural Products: Synthetic Analogues of Bryostatin 1": P. A. Wender, J. L. Baryza, M. K. Hilinski, J. C. Horan, C. Kan, V. A. Verma in *Drug Discovery Research*: *New Frontiers in the Post-Genomic Era* (Ed.: Z. Huang), Wiley, Hoboken, **2007**, pp. 127–162; c) K. J. Hale, S. Manaviazar, *Chem. Asian J.* **2010**, *5*, 704–754; d) "Bryostatin 7": Y. Lu, M. J. Krische in *Total Synthesis of Naural Products* (Eds.: J. Li, E. J. Corey), Springer, Berlin, Heidelberg, **2012**, pp. 103–130; e) "Rethinking the Role of Natural Products: Function-Oriented Synthesis Bryostatin, and Bryologs": P. A. Wender, *Products in Medicinal Chemistry* (Ed.: S. Hanessian), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2014**, pp. 475–543; f) P. Kollár, J. Rajchard, Z. Balounová, J. Pazourek, *Pharm. Biol.* **2014**, *52*, 237–242; For isolation of the latest member of bryostatin 21, see: g) H.-B. Yu, F. Yang, F. Sun, G.-Y. Ma, J.-H. Gan, W.-Z. Hu, B.-N. Han, W.-H. Jiao, H.-W. Lin, *J. Nat. Prod.* **2014**, *77*, 2124–2129.

[2] G. R. Pettit, C. L. Herald, D. L. Doubek, D. L. Herald, E. Arnold, J. Clardy, *J. Am. Chem. Soc.* **1982**, *104*, 6846–6848.

[3] J. Kortmansky, G. K. Schwartz, *Cancer Invest.* **2003**, *21*, 924–936.

[4] G. K. Schwartz, M. A. Shah, *J. Clin. Oncol.* **2005**, *23*, 9408–9421.

[5] M.-K. Sun, J. Hongpaisan, T. J. Nelson, D. L. Alkon, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 13620–13625.

[6] K. J. Way, N. Katai, G. L. King, *Diabetic Med.* **2001**, *18*, 945–959.

[7] a) P. Williams, A. Sorribas, M.-J. R. Howes, *Nat. Prod. Rep.* **2011**, *28*, 48–77; b) C. Xu, Q.-Y. Liu, D. L. Alkon, *Neuroscience* **2014**, *268*, 75–86; c) T. J. Nelson, M.-K. Sun, C. Lim, A. Sen, T. Khan, F. V. Chirila, D. L. Alkon, *J. Alzheimer's Dis.* **2017**, *58*, 521–535.

[8] a) N. M. Archin, D. M. Margolis, *Curr. Opin. Infect. Dis.* **2014**, *27*, 29–35; b) G. M. Laird, C. K. Bullen, D. I. S. Rosenbloom, A. R. Martin, A. L. Hill, C. M. Durand, J. D. Siliciano, R. F. Siliciano, *J. Clin. Invest.* **2015**, *125*, 1901–1912.

[9] M. J. Krische, J. M. Ketcham, I. Volchkov, T.-Y. Chen, P. M. Blumberg, N. Kedei, N. E. Lewin, *J. Am. Chem. Soc.* **2016**, *138*, 13415–13423 and references therein.

[10] a) M. G. Kazanietz, N. E. Lewin, F. Gao, G. R. Petit, P. M. Blumberg, *Mol. Pharmacol.* **1994**, *46*, 374–379; b) E. M. Griner, M. G. Kazanietz, *Nat. Rev. Cancer* **2007**, *7*, 281–294; c) D. J. Lew, M. P. Rout, *Curr. Opin. Cell Biol.* **2009**, *21*, 1–3.

[11] D. E. Schaufelberger, M. P. Koleck, J. A. Beutler, A. M. Vatakis, A. B. Alvarado, P. Andrews, L. V. Marzo, G. M. Muschik, J. Roach, J. T. Ross, et al., *J. Nat. Prod.* **1991**, *54*, 1265–1270.

[12] For total synthesis of the bryostatins, see: bryostatin 7: a) M. Kageyama, T. Tamura, M. H. Nantz, J. C. Roberts, P. Somfai, D. C. Whritenour, S. Masamune, *J. Am. Chem. Soc.* **1990**, *112*, 7407–7408; bryostatin 2: b) D. A. Evans, P. H. Carter, E. M. Carreira, J. A. Prunet, A. B. Charette, M. Lautens, *Angew. Chem. Int. Ed.* **1998**, *37*, 2354–2359; *Angew. Chem.* **1998**, *110*, 2526–2530; c) D. A. Evans, P. H. Carter, E. M. Carreira, J. A. Prunet, A. B. Charette, M. Lautens, *J. Am. Chem. Soc.* **1999**, *121*, 7540–7552; bryostatin 3: d) K. Ohmori, Y. Ogawa, T. Obitsu, Y. Ishikawa, S. Nishiyama, S. Yamamura, *Angew. Chem. Int. Ed.* **2000**, *39*, 2290–2294; *Angew. Chem.* **2000**, *112*, 2376–2379; formal synthesis of bryostatin 7: e) A. E. Aliev, K. J. Hale, *Org. Lett.* **2006**, *8*, 4477–4480; bryostatin 16: f) B. M. Trost, G. Dong, *Nature* **2008**, *456*, 485–488; g) B. M. Trost, G. Dong, *J. Am. Chem. Soc.* **2010**, *132*, 16403–16416; bryostatin 1: h) G. E. Keck, Y. B. Poudel, T. J. Cummins, A. Rudra, J. A. Covel, *J. Am. Chem. Soc.* **2011**, *133*, 744–747; bryostatin 9: i) P. A. Wender, A. J. Schrier, *J. Am. Chem. Soc.* **2011**, *133*, 9228–9231; bryostatin 7: j) Y. Lu, S. K. Woo, M. J. Krische, *J. Am. Chem. Soc.* **2011**, *133*, 13876–13879; bryostatin 1: k) P. A. Wender, C. T. Hardman, S.

Ho, M. S. Jeffreys, J. K. Maclaren, R. V. Quiroz, S. M. Ryckbosch, A. J. Shimizu, J. L. Sloane, M. C. Stevens, *Science* **2017**, *358*, 218 – 223.

[13] For the latest studies on bryostatin analogues, see: a) B. M. Trost, H. Yang, O. R. Thiel, A. J. Frontier, C. S. Brindle, *J. Am. Chem. Soc.* **2007**, *129*, 2206 – 2207; b) P. A. Wender, J. L. Baryza, S. E. Brenner, B. A. DeChristopher, B. A. Loy, A. J. Schrier, V. A. Verma, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 6721 – 6726; c) B. M. Trost, H. Yang, G. Dong, *Chem. Eur. J.* **2011**, *17*, 9789 – 9805; d) P. A. Wender, B. A. DeChristopher, A. C. Fan, D. W. Felsher, *Oncotarget* **2012**, *3*, 58 – 66; e) G. E. Keck, N. Kedei, A. Telek, A. M. Michalowski, M. B. Kraft, W. Li, Y. B. Poudel, A. Rudra, M. E. Petersen, P. M. Blumberg, *Biochem. Pharmacol.* **2013**, *85*, 313 – 324; f) P. A. Wender, Y. Nakagawa, K. E. Near, D. Staveness, *Org. Lett.* **2014**, *16*, 5136 – 5139; g) G. E. Keck, M. B. Kraft, Y. B. Poudel, N. Kedei, N. E. Lewin, M. L. Peach, P. M. Blumberg, *J. Am. Chem. Soc.* **2014**, *136*, 13202 – 13208; h) M. J. Krische, I. P. Andrews, J. M. Ketcham, P. M. Blumberg, N. Kedei, N. E. Lewin, M. L. Peach, *J. Am. Chem. Soc.* **2014**, *136*, 13209 – 13216; i) G. E. Keck, J. S. Kelsey, C. Cataisson, J. Chen, M. A. Herrmann, M. E. Petersen, D. O. Baumann, K. M. McGowan, S. H. Yuspa, P. M. Blumberg, *Mol. Carcinog.* **2016**, *55*, 2183 – 2195.

[14] For latest progress, see: a) Z. J. Liu, X. L. Lin, N. Yang, Z. S. Su, C. W. Hu, P. H. Xiao, Y. Y. He, Z. L. Song, *J. Am. Chem. Soc.* **2016**, *138*, 1877 – 1883; b) Z. W. Chu, K. Wang, L. Gao, Z. L. Song, *Chem. Commun.* **2017**, *53*, 3078 – 3081.

[15] a) I. Fleming, R. Henning, H. Plaut, *J. Chem. Soc. Chem. Commun.* **1984**, 29 – 31; b) K. Tamao, M. Akita, M. Kumada, *J. Organomet. Chem.* **1983**, *254*, 13 – 22; c) J. A. Marshall, M. M. Yanik, *Org. Lett.* **2000**, *2*, 2173 – 2175; d) J. A. Marshall, K. C. Ellis, *Org. Lett.* **2003**, *5*, 1729 – 1732; e) W. Tu, P. E. Floreancig, *Angew. Chem. Int. Ed.* **2009**, *48*, 4567 – 4571; *Angew. Chem.* **2009**, *121*, 4637 – 4641.

[16] L. Gao, J. Lu, X. L. Lin, Y. J. Xu, Z. P. Yin, Z. L. Song, *Chem. Commun.* **2013**, *49*, 8961 – 8963.

[17] J. Lu, Z. L. Song, Y. B. Zhang, Z. B. Gan, H. Z. Li, *Angew. Chem. Int. Ed.* **2012**, *51*, 5367 – 5370; *Angew. Chem.* **2012**, *124*, 5463 – 5466.

[18] a) G. R. Pettit, Y. Kamano, R. Aoyagi, C. L. Herald, D. L. Doubek, J. M. Schmidt, J. J. Rudole, *Tetrahedron* **1985**, *41*, 985 – 994; b) G. R. Pettit, F. Gao, D. Sengupta, J. C. Coll, C. L. Herald, D. L. Doubek, J. M. Schmidt, J. R. van Camp, J. J. Rudloe, R. A. Nieman, *Tetrahedron* **1991**, *47*, 3601 – 3610; c) H. W. Lin, Y. H. Yi, X. S. Yao, H. M. Wu, *Chin. J. Mar. Drugs* **2001**, *20*, 1 – 6.

[19] S. V. Ley, M. J. Gaunt, A. S. Jessiman, P. Orsini, H. R. Tanner, D. F. Hook, *Org. Lett.* **2003**, *5*, 4819 – 4822.

[20] D. A. Evans, A. H. Hoveyda, *J. Am. Chem. Soc.* **1990**, *112*, 6447 – 6449.

[21] a) S. Hara, A. Suzuki, *Tetrahedron Lett.* **1991**, *32*, 6749 – 6752; b) M. Kurosu, M.-H. Lin, Y. Kishi, *J. Am. Chem. Soc.* **2004**, *126*, 12248 – 12249; c) Z. Zhang, J. Huang, B. Ma, Y. Kishi, *Org. Lett.* **2008**, *10*, 3073 – 3076; d) W. Q. Chen, Q. Yang, T. Zhou, Q. S. Tian, G. Z. Zhang, *Org. Lett.* **2015**, *17*, 5236 – 5239.

[22] D. R. Williams, Á. I. Morales-Ramos, C. M. Williams, *Org. Lett.* **2006**, *8*, 4393 – 4396.

[23] P. L. Anelli, C. Biffi, F. Montanari, S. Quici, *J. Org. Chem.* **1987**, *52*, 2559 – 2562.

[24] C. W. Wullschleger, J. Gertsch, K. Altmann, *Org. Lett.* **2010**, *12*, 1120 – 1123.

[25] A. Fürstner, S. Flügge, O. Larionov, Y. Takahashi, T. Kubota, J. Kobayashi, *Chem. Eur. J.* **2009**, *15*, 4011 – 4029.

[26] Aldehyde **23** was prepared from the known diol by 2 steps. F. A. Gimalova, N. K. Selezneva, Z. A. Yusupov, M. S. Miftakhov, *Russ. J. Org. Chem.* **2005**, *41*, 1183 – 1186. See the Supporting Information for details.

[27] T. Okazoe, K. Takai, K. Utimoto, *J. Am. Chem. Soc.* **1987**, *109*, 951 – 953.

[28] K. Tanaka, Y. Ohta, K. Fuji, *Tetrahedron Lett.* **1993**, *34*, 4071 – 4074. Wender and co-workers discoved that dimethyl-BINOL phosphonate gave a significantly higher *Z*/*E* ratio (11:1) than the corresponding unsubstituted reagent (3:1). See Ref. [11k] for details.

[29] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989 – 1993.

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