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Synthesis of the Bryostatin 1 Northern Hemisphere (C1–C16) via Desymmetrization by Ketalization/ Ring-Closing Metathesis

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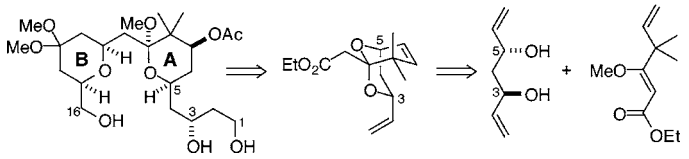
ABSTRACT



Synthesis of the northern hemisphere (C1–C16) of bryostatin 1, a potent anticancer agent, has been accomplished in 14 steps and 11% overall yield via desymmetrization by ketalization/ring-closing metathesis. A 2,9-dioxabicyclo[3.3.1]nonane template facilitated stereoselective A-ring functionalization, while an efficient hetero-Diels–Alder reaction was used to elaborate the B-ring.

We recently reported desymmetrization by ketalization/ring-closing olefin metathesis (K/RCM) as an efficient means to access the 6,8-dioxabicyclo[3.2.1]octane ring system in the context of natural product total synthesis[1] and spiroketal construction.[2] Each of these endeavors has highlighted the remarkable selectivity that can be accomplished using a rigid bicyclic ketal template for functional group introduction. To expand the utility and generality of our strategy, we sought to extend the method to 2,9-dioxabicyclo[3.3.1]nonane ring systems. Toward the goal of developing a practical synthetic route to the clinically significant bryostatins, we describe herein a short and efficient synthesis of the bryostatin 1 (**1**, Figure 1) northern hemisphere, comprising the C1−C16, AB-ring subunit, further validating the K/RCM strategy for rapidly accessing complex synthetic targets.

Bryostatin 1 is currently under investigation as a potent antineoplastic agent in numerous human clinical trials alone or in combination with other chemotherapies.[3] As one of 18 naturally occurring bryostatins, the anticancer activity and low toxicity of bryostatin 1 has stimulated considerable synthetic efforts toward the bryostatins and analogues.[4,5] In particular, total syntheses of bryostatins 7, 2, and 3 by Masamune,[6] Evans,[7] and Yamamura,[8] respectively, have provided important precedent for further synthetic efforts. Despite the variety of bryostatin synthetic studies, an efficient and general northern hemisphere synthesis remains an

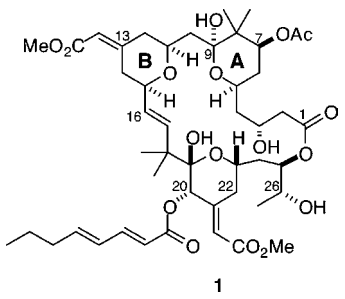


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Figure 1. Bryostatin 1.

(1) (a) Burke, S. D.; Müller, N.; Beaudry, C. M. *Org. Lett.* **1999**, *1*, 1827. (b) Burke, S. D.; Voight, E. A. *Org. Lett.* **2001**, *3*, 237. (c) Voight, E. A.; Rein, C.; Burke, S. D. *Tetrahedron Lett.* **2001**, *42*, 8747. (d) Voight, E. A.; Rein, C.; Burke, S. D. *J. Org. Chem.* **2002**, *67*, 8489.

(2) Keller, V. A.; Martinelli, J. R.; Strieter, E. R.; Burke, S. D. *Org. Lett.* **2002**, *4*, 467.

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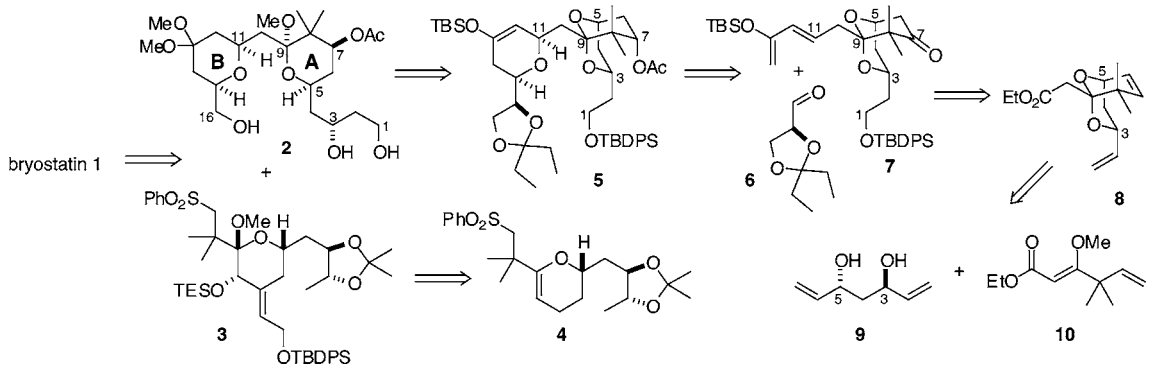


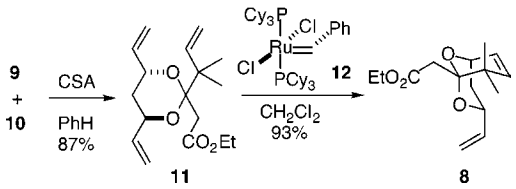
Figure 2. Retrosynthetic analysis of bryostatin 1.

important goal, especially one capable of delivering C7 ester derivatives. Since C7 and C20 are the only primary points of diversity among the naturally occurring bryostatins, access to many bryostatins and analogues could be enabled by such a general route.

Our retrosynthetic analysis of bryostatin 1 is shown in Figure 2, beginning with disconnection of the C16−C17 olefin as in previous bryostatin total syntheses.[6−8] A C16 aldehyde derived from **2** was seen as a suitable coupling partner for southern hemisphere phenyl sulfone **3**. We recently reported a formal synthesis of **3** via Hale's intermediate, glycal **4**,[9] which was prepared in only six steps from (*R*)-2-(benzyloxy)propanal.[10] The bryostatin northern hemisphere was seen as coming from A-ring bridged bicycle **5**. The B-ring could be derived from pentylidene-protected glyceraldehyde[11] (**6**) and siloxydiene **7** via a Lewis-acid-catalyzed hetero-Diels−Alder reaction. Ring-closing metathesis (RCM) product **8**, the precursor to **7**, would be derived from C_2-symmetric (*R,R*)-1,6-heptadiene-3,5-diol **9**[12] and vinylogous carbonate **10**[13] via desymmetrization by K/RCM.[1,2]

To begin the synthesis, diene diol **9**[12] was heated with vinylogous carbonate **10**[13] in refluxing benzene with 5 mol % camphorsulfonic acid for 1 h with a Dean−Stark trap, giving ketal **11** in 87% yield (Scheme 1). Notably, when a

Scheme 1. Synthesis of RCM Product **8**



β-keto ester was used for this reaction, no ketalization product was observed, presumably because of the quaternary center adjacent to the reacting carbon. With triene substrate **11** in hand, ring-closing metathesis proceeded readily using 5 mol % of Grubbs' first generation catalyst **12** (Scheme 1).[14] This reaction was best performed by adding the catalyst in CH_2Cl_2 slowly over 4 h to a room-temperature solution of **11** in CH_2Cl_2 (0.01 M). After an additional 2 h, bridged bicyclic ketal **8** was obtained in 93% yield.

With the 2,9-dioxabicyclo[3.3.1]nonane template constructed, differentiation of the two olefins in diene **8** was required (Scheme 2). This was accomplished efficiently by hydroboration with disiamyl borane (2 equiv, 0 °C, 3 h) followed by oxidative workup with aqueous sodium perborate (8 equiv, 1 h). The primary alcohol thus obtained was protected using *tert*-butylchlorodiphenylsilane, giving TBDPS-protected **13** in 90% yield over two steps. Attempted

(3) For current information on bryostatin 1 clinical trials, see: http://www.cancer.gov/search/clinical_trials/.

(4) For reviews, see: (a) Pettit, G. R. The Bryostatins. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Ed.; Springer-Verlag: New York, 1991; Vol. 57, p 153. (b) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041. (c) Mutter, R.; Wills, M. *Bioorg. Med. Chem.* **2000**, *8*, 1841. (d) Hale, K. J.; Hummersone, M. G.; Manaviazar, S.; Frigerio, M. *Nat. Prod. Rep.* **2002**, *19*, 413.

(5) For analogue studies, see ref 4d and: (a) Wender, P. A.; Baryza, J. L.; Bennett, C. E.; Bi, C.; Brenner, S. E.; Clarke, M. O.; Horan, J. C.; Kan, C.; Lacôte, E.; Lippa, B.; Nell, P. G.; Turner, T. M. *J. Am. Chem. Soc.* **2002**, *124*, 13648. (b) Wender, P. A.; Mayweg, A. V. W.; VanDeusen, C. L. *Org. Lett.* **2003**, *5*, 277. (c) Hale, K. J.; Frigerio, M.; Manaviazar, S.; Hummersone, M. G.; Fillingham, I. J.; Barsukov, I. G.; Damblon, C. F.; Gescher, A.; Roberts, G. C. K. *Org. Lett.* **2003**, *5*, 499.

(6) Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990**, *112*, 7407.

(7) Evans, D. A.; Carter, P. H.; Carreira, E. M.; Charette, A. B.; Prunet, J. A.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540.

(8) (a) Ohmori, K.; Ogawa, Y.; Obitsu, T.; Ishikawa, Y.; Nishiyama, S.; Yamamura, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2290. (b) Ohmori, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 875.

(9) Hale, K. J.; Frigerio, M.; Manaviazar, S. *Org. Lett.* **2003**, *5*, 503.

(10) Voight, E. A.; Roethle, P. A.; Burke, S. D. *J. Org. Chem.* **2004**, *69*, 4534.

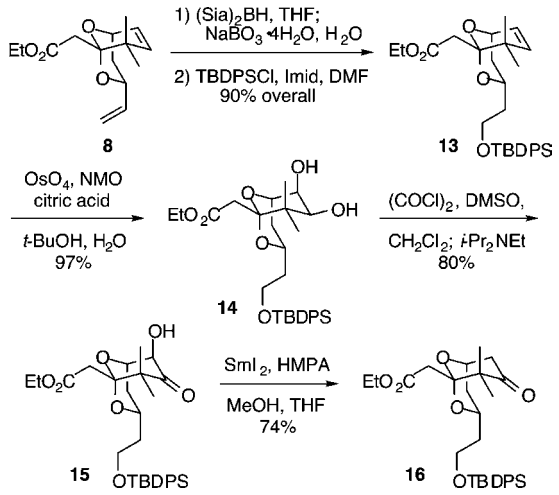
(11) Schmid, C. R.; Bradley, D. A. *Synthesis* **1992**, 587.

(12) The enantiomer of **9** has been prepared previously: Hoffmann, R. W.; Kahrs, B. C.; Schiffer, J.; Fleischhauer, J. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2407. We used D-(−)-diethyltartrate in place of L-(+)-diethyltartrate in the double Sharpless asymmetric epoxidation step of the published sequence to obtain the desired enantiomer.

(13) Obtained by treatment of ethyl 4,4-dimethyl-3-oxo-5-hexenoate (b) with (trimethylsilyl)diazomethane (a): (a) Harris, C. R.; Kuduk, S. D.; Balog, A.; Savin, K.; Glunz, P. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 7050. (b) Aurell, M. J.; Gil, S.; Mestres, R.; Parra, M.; Parra, L. *Tetrahedron* **1998**, *54*, 4357. (c) Shibuya, M.; Kubota, S. *Heterocycles* **1980**, *14*, 601. See the Supporting Information for details.

(14) For recent reviews, see: (a) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (d) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141. (e) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (f) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371.

Scheme 2. Synthesis of Keto Ester **16**



dihydroxylation of the remaining olefin in **13** using catalytic osmium tetraoxide/*N*-methylmorpholine *N*-oxide[15] was extremely sluggish, and catalytic ruthenium(III) chloride/sodium periodate[16] gave low yields. However, when 1.5 equiv of citric acid was added to the OsO_4-catalyzed reaction in 1:1 *tert*-butyl alcohol/water a dramatic rate enhancement was observed, and diol **14** was obtained in 97% yield after 8 h at room temperature.[17] Notably, no *endo*-diol was observed from this reaction, consistent with previous dihydroxylation results with 6,8-dioxabicyclo[3.2.1]octane ring systems.[1b,d,2] The equatorial alcohol of diol **14** was oxidized selectively[18] using standard Swern conditions, giving a 6:1 ratio of readily separable regioisomeric keto alcohols in 74% yield. After one recycle of recovered starting material, the desired keto alcohol **15** was obtained in 80% yield. Again, the locked conformation of the bicyclic ketal facilitated this selectivity. Excision of the undesired hydroxyl in **15** was accomplished using samarium diiodide (5 equiv) and MeOH (10 equiv) in THF/HMPA (5:1) at 0 °C for 10 min.[19] The axial orientation of the alcohol in **15** assured optimal orbital overlap in the reductive elimination step, providing keto ester **16** in 74% yield.

To confirm the structure of **16**, regioisomeric ketone **17** was prepared[20] and NOE studies were carried out (Figure 3). Irradiation of the bridgehead proton of **16** (H_a) showed a significant enhancement for each α-keto proton, while irradiation of H_a in **17** showed very little α-keto proton NOE. The most convincing NOE data were realized when H_b was irradiated, giving little to no NOE in **16** but a 7.4% NOE

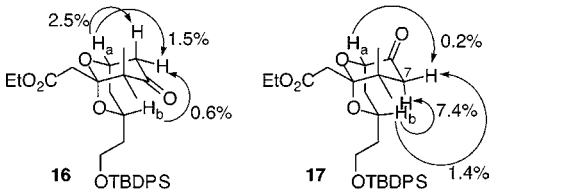


Figure 3. Selected NOE data.

for the axial, concave face C7 proton in **17**. Furthermore, significant shielding of H_b was observed in **16**, with δ H_b (**16**) 3.93 ppm vs δ H_b (**17**) 4.37 ppm, indicating close proximity to the ketone carbonyl for H_b (**16**). These data also provide support for the chair-chair conformation drawn for bridged bicyclic compounds up to this point in the synthesis.[21]

Continuing with the synthesis, the hindered ketone in **16** proved less reactive toward reducing agents than the ethyl ester. Therefore, it was possible to selectively reduce ester **16** with diisobutylaluminum hydride (1.2 equiv) in CH_2Cl_2 (0.1 M) at −90 °C over 30 min. When the anion of diethyl-2-(oxopropyl)phosphonate in THF (0.2 M) was added to the reaction mixture, Horner−Wadsworth−Emmons olefination took place after 10 min at reflux. α,β-Unsaturated ketone **18** could then be isolated in 75% yield. In preparation for the key hetero-Diels−Alder reaction, siloxydiene **19** was prepared using diisopropylethylamine (3 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (2 equiv) in Et_2O (0.1 M) for 1 h at 0 °C. When boron trifluoride diethyl etherate (1.2 equiv) was added to a −78 °C solution of **7** and aldehyde **6**[11] (1.5 equiv) in Et_2O (0.1 M), a hetero-Diels−Alder reaction took place in 91% yield to give an easily separable 15:4:1 mixture of diastereomers. On the basis of extensive literature precedence indicating excellent Cram selectivity in hetero-Diels−Alder reactions with ketal-protected glyceraldehyde derivatives[22] and NMR coupling constants (vide infra), the major isomer was assigned as B-ring silyl enol ether **19**.

With the B-ring constructed successfully, it remained to introduce the correct C7 stereocenter, convert the silyl enol ether to a ketal, effect methanolysis of the bridged bicyclic ketal, and deprotect and oxidatively cleave the pentylidene-protected diol. Ketone **19** was reduced with lithium aluminum hydride, and acetylation of the resulting secondary alcohol gave acetate **5** in 87% yield over two steps (Scheme 3). At this stage, the concave face C3 proton was significantly deshielded (δ 4.96 ppm), more than 1 ppm downfield relative to its ketone precursors. Only *endo*-acetate was observed in

(15) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973.

(16) See: Plietker, B.; Niggemann, M. *Org. Lett.* **2003**, *5*, 3353 and references therein.

(17) Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B. *Adv. Synth. Catal.* **2002**, *344*, 421. Sharpless has suggested that citric acid assists osmium-catalyzed dihydroxylations by (1) lowering the pH to prevent formation of an essentially inert 18-electron diooxoosmate dianion (which causes the brown color in the original Upjohn process, ref 15) and (2) by preventing Os(VI) disproportionation through bidentate chelation.

(18) Sasaki, M.; Murae, T.; Takahashi, T. *J. Org. Chem.* **1990**, *55*, 528.

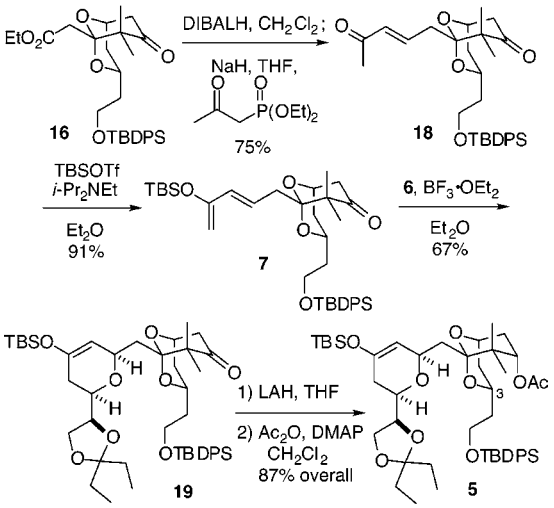
(19) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Org. Chem.* **1998**, *63*, 6200.

(20) See the Supporting Information for details.

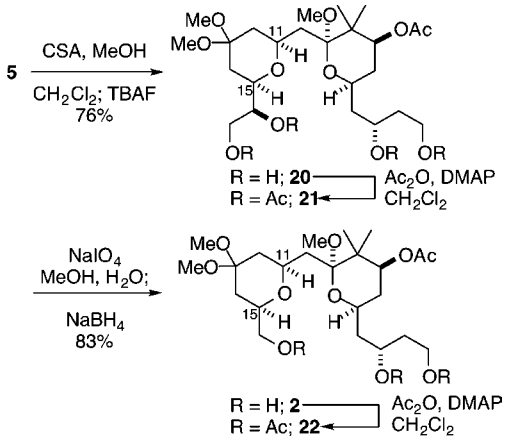
(21) (a) Lynch, V. M.; Lee, W.-C.; Martin, S. F.; Davis, B. E. *Acta Crystallogr.* **1994**, *C50*, 1467. (b) Peters, J. A.; Baas, J. M. A.; Van de Graaf, B.; Van der Toorn, J. M.; Van Bekkum, H. *Tetrahedron* **1978**, *34*, 3313.

(22) (a) Martín, M.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *Synlett* **2001**, 117. (b) Mujica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *J. Org. Chem.* **1998**, *63*, 9728. (c) Cink, R. D.; Forsyth, C. J. *J. Org. Chem.* **1997**, *62*, 5672. (d) Danishefsky, S. J.; Kobayashi, S.; Kerwin, J. F. *J. Org. Chem.* **1982**, *47*, 1981.

Scheme 3. Synthesis of AB-Ring Intermediate **5**



Scheme 4. Northern Hemisphere Completion



this reaction, again due to the steric requirements of the bicyclic ketal.

Treatment of **5** with CSA (0.5 equiv) in 1:1 MeOH/CH_2Cl_2 (0.025 M) at room-temperature overnight and 1 h at reflux, followed by treatment with TBAF to complete TBDPS cleavage, gave tetraol **20** in 76% yield (Scheme 4). Five transformations were accomplished in this single operation, including (1) silyl enol ether methanolysis, (2) dimethyl ketal formation, (3) A-ring bicyclic ketal opening, (4) pentylidene ketal methanolysis, and (5) TBDPS cleavage. The first two steps took place rapidly, followed by A-ring opening,[23] then pentylidene and TBDPS cleavage happened at similar rates. Importantly, before the fourth axial substituent was introduced on the A-ring (i.e., **19** → **5**), bicyclic ketal opening was virtually impossible. Treatment of tetraol **20** with sodium periodate (1.5 equiv) in 1:1 MeOH/H_2O (0.05 M) for 15 min at 0 °C, followed by addition of sodium borohydride (20 equiv), gave triol **2** in 83% yield to complete the bryostatin northern hemisphere (C1−C16) architecture. Both **20** and **2** were characterized as the corresponding pentaacetate (**21**) and tetraacetate (**22**), respectively, and the 2,6-*cis* B-ring relative configuration was confirmed by the large *trans*-diaxial vicinal coupling constants ($J = 12-12.5$ Hz) observed for the C11 and C15 methine protons.

In conclusion, a short (14 step) and efficient (11% overall yield) synthesis of the bryostatin 1 northern hemisphere intermediate **2** has been realized starting from diene diol **9** via desymmetrization by K/RCM. A-Ring functionalization was facilitated by the steric and conformational constraints imposed by the rigid 2,9-dioxabicyclo[3.3.1]nonane template. Protecting group interconversion was avoided due to the internal keto diol protection inherent in K/RCM sequences. Furthermore, the C7 acetylation step could be replaced by an alternative esterification, providing ready access to other natural and nonnatural bryostatins. Efforts toward completing the total synthesis of bryostatin 1 continue and will be reported in due course.

(23) A product with TBDPS and pentylidene ketal still present could be isolated in 55% yield after 1 h, 45 min under these conditions.

Acknowledgment. We thank the NIH [Grant Nos. GM069352 and CA108488 (S.D.B.) and CBI Training Grant 5 T32 GM08505 (E.A.V.)], the Abbott Laboratories Fellowship in Synthetic Organic Chemistry (E.A.V.), and the Hilldale Foundation (P.A.R.) for generous support of this research. The NIH (1 S10 RR0 8389-01) and NSF (CHE-9208463) are acknowledged for their support of the NMR facilities at the University of Wisconsin—Madison Department of Chemistry. We also thank Dr. Charles Fry for obtaining NOE data for compounds **16** and **17**.

Supporting Information Available: Experimental procedures and characterization data for compounds **2**, **5**, **7**, **8**, **10**, **11**, and **13**−**22**; ^1H and ^{13}C NMR spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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