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Enantioselective Formal Total Synthesis of the Antitumor Macrolide Bryostatin 7

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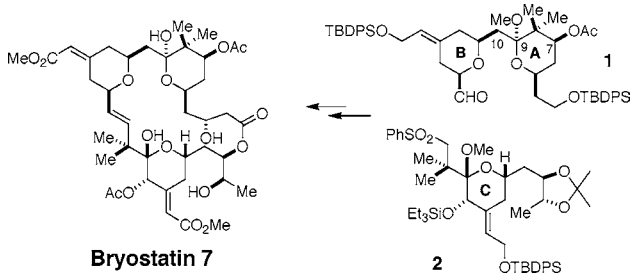
ABSTRACT



A new enantioselective synthesis of Masamune's AB fragment (1) for bryostatin 7 is described. Key steps in the new route include a Meerwein–Ponndorf–Verley reduction to set the O(7) stereocenter and an alkylative union between the dithiane 6 and iodide 5 to construct the C(9)–C(10) bond. Because we have previously published a synthesis of Masamune's C-ring phenyl sulfone 2, our new route to 1 constitutes a formal total synthesis of bryostatin 7; it also corrects the previously reported spectral data for 1 in $CDCl_3$.

The bryostatins are a structurally novel family of tripyranylated antitumor macrolides whose prototype, bryostatin 1, was first reported by Pettit and co-workers more than two decades ago.[1] Ever since that time, biological interest in the bryostatins[2,3] has risen steadily, mainly because of their powerful anticancer effects in vivo and their ability to potently activate and modulate aberrant protein kinase C (PKC) expression and signaling within human tissues.

Although the extremely low natural abundance of the bryostatins did for a long time hamper their human clinical development as antitumor drugs, this situation changed quite dramatically in 2000 when Mendola announced[4] that aquaculture could supply bryostatin 1 economically on a large scale (100−200 g annually). Despite this important advance, clinical interest in bryostatin 1 as a single-agent antitumor drug has now largely abated, primarily because of its poor clinical efficacy against solid tumors in man.[5] Notwithstanding this setback, the search for new "bryostatin-like" drug entities continues, mainly because of their potential for preventing Alzheimer's disease onset in animal models.[6] As a consequence, new synthetic routes to the bryostatins remain of interest due to the novel analogues they can potentially deliver.

To date, three bryostatin total syntheses have been reported. The first of these was the landmark total synthesis of bryostatin 7 by Masamune and co-workers in 1990.[7] This was followed eight years later by Evans' majestic synthetic route to bryostatin 2[8] and, not long after this, by Nishiyama and Yamamura's excellent enantiospecific total synthesis of bryostatin 3[9] which, remarkably, delivered 25 mg of the final natural product for biological testing.

(1) Bryostatin 1 isolation and structure determination: Pettit, G. R.; Herald, C. L.; Clardy, J.; Arnold, E.; Doubek, D. L.; Herald, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 6848.

(2) For reviews on bryostatin chemistry and biology, see: (a) Norcross, R.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041. (b) Mutter, R.; Wills, M. *Bioorg. Med. Chem.* **2000**, *8*, 1841. (c) Hale, K. J.; Hummersone, M. G.; Manaviazar, S.; Frigerio, M. *Nat. Prod. Rep.* **2002**, 413.

(3) Bryostatin 20: Lopanik, N.; Gustafson, K. R.; Lindquist, N. *J. Nat. Prod.* **2004**, *67*, 1412.

(4) Mendola, D. In *Drugs from the Sea*; Fusetani, N., Ed.; Karger: Basel, 2000; p 20.

(5) Some phase II human clinical trials include: (a) Madhusan, S.; Protheroe, A.; Propper, D.; Han, C.; Corrie, P.; Earl, H.; Hancock, B.; Vasey, P.; Turner, A.; Balkwill, F.; Hoare, S.; Harris, A. L. *Br. J. Cancer* **2003**, *89*, 1418. (b) Brockstein, B.; Samuels, B.; Humerickhouse, R.; Arietta, R.; Fishkin, P.; Wade, J.; Sosman, J.; Vokes, E. E. *Invest. New Drugs* **2001**, *19*, 249. (c) Pagliaro, L.; Daliani, D.; Amato, R.; Tu, S.-M.; Jones, D.; Smith, T.; Logothetis, C.; Millikan, R. *Cancer* **2000**, *89*, 615.

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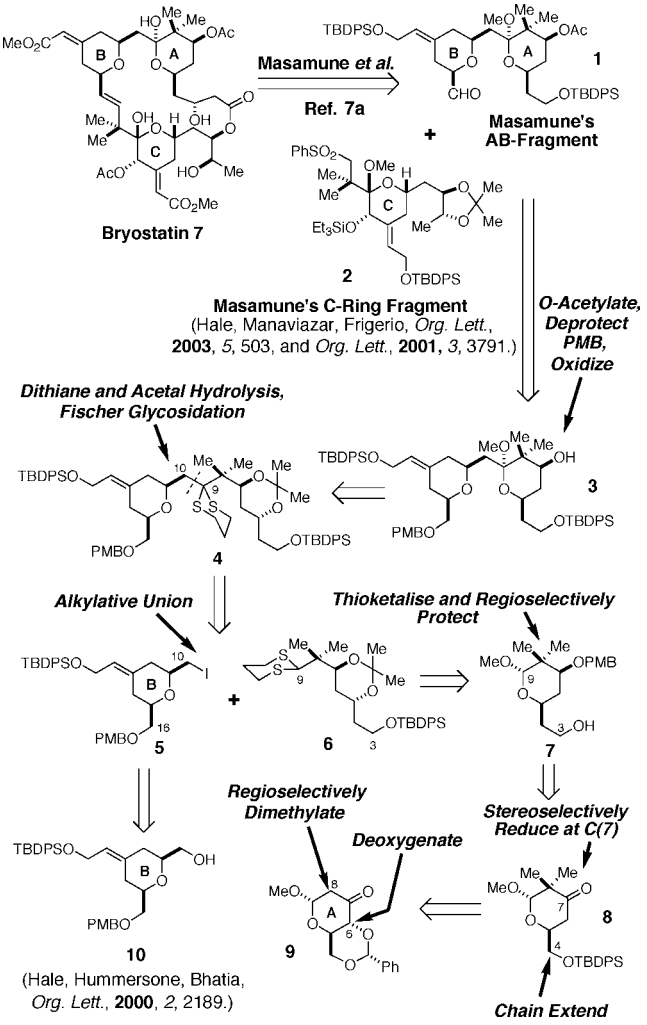
Our own group's synthetic efforts in the bryostatin area[10] have so far culminated in new and fully stereocontrolled asymmetric routes to Masamune's bryostatin 7 C-ring phenyl sulfone **2**[10a−c] (Scheme 1) and our own B-ring synthon **10**[10d]

Scheme 1. Our Retrosynthetic Strategy for Masamune's Bryostatin 7 Advanced AB Intermediate **1**



(Scheme 1). In continuation of this work, we now report on a stereocontrolled pathway to Masamune's bryostatin 7 AB fragment **1** which, given our recent synthesis of **2**, constitutes a new formal enantiospecific total synthesis of bryostatin 7. We note here that although our new formal total synthesis of bryostatin 7 does actually proceed in the same overall number of steps as that of Masamune (64 steps in total) it does have the added advantage that it much more readily generates complex BC analogues.[11,12] Currently, these are not readily accessible via the existing Masamune route, which forges the B-ring domain out of a linear, open-chain, A-ring precursor. Our new total synthesis of bryostatin 7 thus augments Masamune's earlier work on this compound and offers many exciting new opportunities for probing how the BC regions[11] of the bryostatins interact with different PKCs to mediate their powerful in vivo biological effects.

The retrosynthetic strategy that we favored for accessing **1** was based upon the alkylative union[9,13] of dithiane **6** with iodide **5** to forge thioketal **4** (Scheme 1). The latter would thereafter be converted into the methyl glycoside **3** by thioketal hydrolysis, O-deacetalation, and Fischer glycosidation. O-Acetylation, O-debenzylation, and C(16) primary alcohol oxidation would then transform **3** into **1** and allow intersection with Masamune's total synthesis.

We envisioned preparing dithiane **6** from the methyl glycoside **7** by debenzylative thioketalization and site-selective protection of the intermediary triol. Compound **7** would itself be prepared from the pyranone **8** by stereoselective ketone reduction, O-benzylation (with PMBCl), and one-carbon homologation at C(4). An attractive progenitor of ketone **8** was considered to be the known 2-deoxy-3-ketoglycoside **9**. The conversion of **9** into **8** would require a site-selective geminal dimethylation at C(8) and an excision of the surplus oxygen functionality at C(6). With this picture of the proposed route in mind, we will now describe the pathway that was eventually developed to **1** in more detail in Schemes 2−4.

Our sequence to dithiane **6** (see Schemes 2 and 3) commenced with the low-temperature double alkylation of **9**[14] with KH and methyl iodide which, when performed at −20 °C in THF with reasonably pure starting ketone, gave the desired product **11**[14] fairly cleanly in 62% yield after SiO_2 flash chromatography. Starting with much less pure **9** (see Supporting Information), ketone **11** was generally obtained in a lower but, nevertheless, highly reproducible 46% yield on a 15 g scale. It is presumed that the enolization and double methylation process occur regioselectively at C(8) (bryostatin numbering) due to the alternative mode of enolization at C(6) producing a significantly more strained enolate during both

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(9) Total synthesis of bryostatin 3: Ohmori, K.; Ogawa, Y.; Obitsu, T.; Ishikawa, Y.; Nishiyama, S.; Yamamura, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2290.

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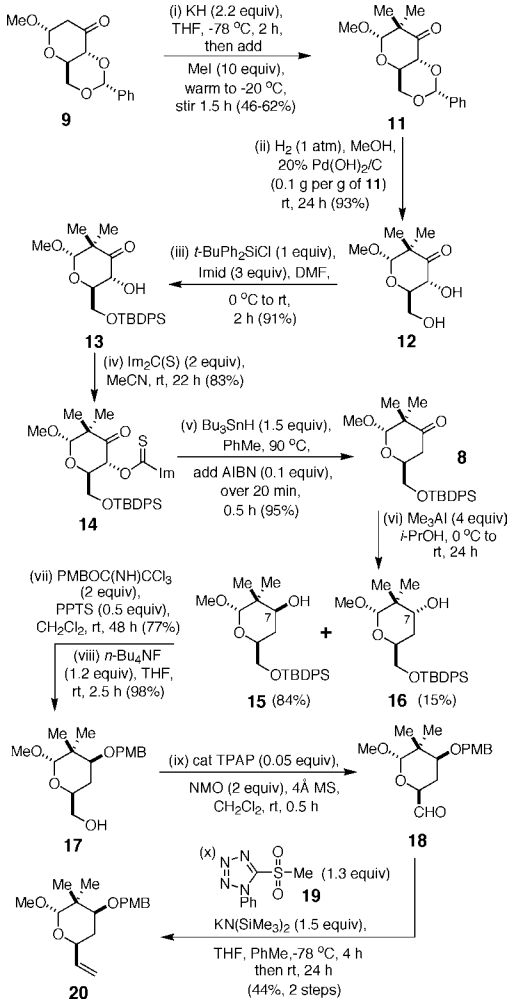
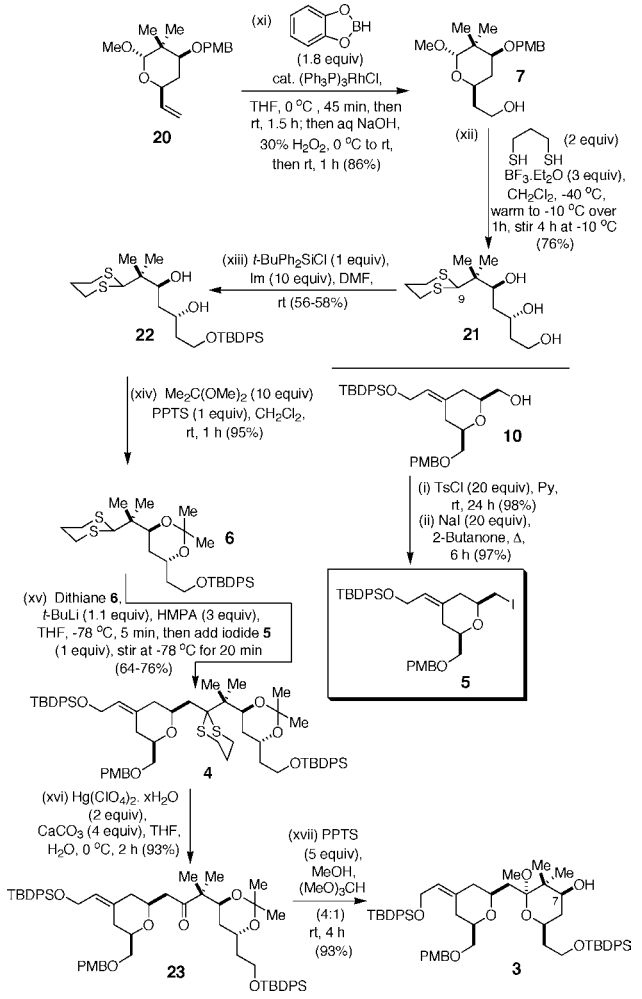
(13) For other dithiane alkylation strategies for constructing the C(9)−C(10) bond of the bryostatins, see: (a) Vakalopoulos, A.; Lampe, T. F. J.; Hoffmann, H. M. R. *Org. Lett.* **2001**, *3*, 929. (b) Ref 9.

(14) (a) Chapleur, Y. *Chem. Commun.* **1983**, 141. (b) Hong, C. Y.; Kishi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 9693. (c) Generally, we have found it more convenient and far less sacrificial to conduct this C-methylation with ketone **9** that has only been recrystallized twice. Generally, two recrystallizations provide material that is approximately 90% pure; the other main contaminant appears to be 1-phenylpentan-2-ol.

Scheme 2. Synthesis of Alkene **20**



Scheme 3. Conversion of Alkene **20** into Dithiane **6**, Union of **6** with **5**, and Elaboration of **4** into Glycoside **3**



alkylation steps. With the desired ketone **11** in hand, we set about excising the C(6)-oxygen atom that lay α to the ketone. For this, we needed to hydrogenolytically cleave off the *O*-benzylidene acetal from **11** using Pearlman's catalyst in MeOH, and thereafter, we selectively O-silylated the product diol **12** with *t*-BuPh$_2$SiCl. A Barton deoxygenation[15] was then effected on the thiocarbonylimidazolide **14** derived from **13**. The desired C(6)-deoxy ketone **8** was obtained in 67% overall yield for the four steps.

A range of hydride reducing agents were screened for their ability to stereoselectively reduce the C(7)-ketone to give the desired equatorial alcohol **15**. After much effort, we eventually discovered that a Meerwein−Ponndorf−Verley (MPV) reduction with Al(OPr-*i*)$_3$ in *i*-PrOH[16a] gave the best results with regard to reaction yield and stereoselectivity (typically **15** was formed with ca. 5.6:1 selectivity). We attribute this stereochemical outcome to the reversible nature of the MPV reaction and predominating thermodynamic control, which clearly would favor formation of the equatorial alcohol **15** (Scheme 2).[16b] Significantly, the minor, undesired product alcohol **16** could be reoxidized to **8** with TPAP/NMO[17] and recycled back into the synthesis.

The newly introduced hydroxyl group of **15** was next protected as a PMB ether with *p*-methoxybenzyl trichloroacetimidate (2 equiv) and PPTS (0.5 equiv) in CH_2Cl_2 for 48 h; the desired PMB−ether was isolated in 77% yield along with a 19% yield of recovered starting alcohol **15**, which was recycled. The use of PMBCl/NaH for this alkylation proved problematic and gave vastly inferior results. Because the primary TBDPS group had served its purpose, it was cleaved from the etherified product with *n*-Bu$_4$NF in THF; the expected alcohol **17** was isolated in 98% yield.

Several unsuccessful methods were explored for homologating the C(4) position of **17** by one extra carbon before it was eventually discovered that this could best be achieved by sequential TPAP oxidation[17] and Kocienski−Julia olefin-

(15) Barton, D. H. R.; Motherwell, W. B.; Stange, A. *Synthesis* **1981**, 743.

(16) (a) Kocienski, P.; Narquizian, R.; Raubo, P.; Smith, C.; Farrugia, L. J.; Muir, K.; Boyle, F. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2357. (b) Coordination of the Al(OPr-*i*)$_3$ reagent with the anomeric OMe would also favor delivery of hydride to the underside of **8** to give **15**, but a referee has argued against this proposal on the basis that, if it did occur, it would most likely cause loss of the acid-labile C(9)−OMe.

(17) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

ation[18] with **19**;[19] this combined sequence provided the desired alkene **20** in 44% overall yield. By way of contrast, the Wittig reaction of aldehyde **18** with $Ph_3P{=}CH_2$ gave totally unsatisfactory results, and cyanide displacement of the iodide derived from **17** was equally problematic.

Of the various hydroboration protocols that were examined for converting **20** into **7** (see Scheme 3), Evans' rhodium-catalyzed procedure with catecholborane[20] proved the most successful, furnishing **7** exclusively in 86% yield after oxidative workup. By way of contrast, borane−THF was poorly regioselective in this reaction, leading to a 2:1 mixture of 1°:2° alcohols enriched in **7**. We next converted alcohol **7** into the triol **21** by reacting it with 1,3-propanedithiol and excess $BF_3{\cdot}Et_2O$.[21] Selective O-silylation of the primary OH in **21** thereafter provided **22** which was transformed into **6** by O-isopropylidenation.

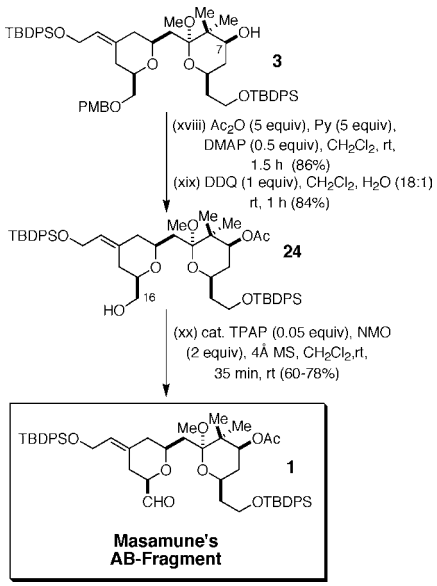
To our great delight, the all-important alkylative union[9,13] between iodide **5** and dithiane **6** proceeded smoothly when conducted in THF at −78 °C with HMPA as an additive;[10d] the desired coupling product **4** was isolated in 64−76% yield on a multigram scale (Scheme 3). Iodide **5** was itself prepared from the previously synthesized alcohol **10**[10d] by displacement of the derived *O*-tosylate with NaI in butan-2-one at reflux (Scheme 3). Surprisingly, the Ph_3P, I_2, imidazole method failed to give satisfactory results in this system.

Having successfully united the B- and A-ring fragments **5** and **6**, we hydrolytically cleaved the dithiane unit from **4** to access ketone **23**; $Hg(ClO_4)_2$ and $CaCO_3$ in aqueous THF proved optimal for effecting this conversion[10d] (Scheme 3). Ketone **23** was thereafter subjected to a tandem acetal exchange/Fischer glycosidation reaction with PPTS and MeOH in the presence of $(MeO)_3CH$[9] to obtain the methyl glycoside **3** (Scheme 3). Surprisingly, the omission of $(MeO)_3CH$ from the reaction mixture led to the hemiketal being formed rather than the anticipated glycoside **3**.

The final stages of our formal total synthesis of bryostatin 7 were O-acetylation of the C(7)-hydroxyl in **3**, DDQ-mediated removal of the C(16)-OPMB group from the resulting product, and TPAP/NMO[17] oxidation of **24** to give **1** (Scheme 4). The latter three steps proceeded in approximately 43−56% overall yield.

Significantly, the 500 MHz ^1H NMR spectrum of our synthetic **1** in $CDCl_3$ confirmed its proposed structure but did not match up with the 300 MHz ^1H NMR spectral data that were reported for **1** in $CDCl_3$ by Masamune.[7a] In Part 3 of our Supporting Information, we will present the new and completely revised chemical shifts and *J* values for **1** in $CDCl_3$. We will show that the originally published[7a] ^1H NMR data for **1** were not actually gathered in $CDCl_3$, as was originally stated, but were instead recorded in C_6D_6. In this regard, the chemical shifts that we have tabulated for **1** in C_6D_6 in the Supporting Information show an excellent agreement with the chemical shifts that were previously published for **1** in $CDCl_3$ by Masamune and co-workers in their 1990 JACS paper Supporting Information (see Table 1 in Part 3 of our Supporting Information).

Scheme 4. Completion of Our Formal Total Synthesis of Bryostatin 7



In summary, a new enantiospecific route to Masamune's AB fragment[22] **1** has been completed which, given our previous synthesis of **2**, constitutes a new enantioselective formal total synthesis of bryostatin 7. The primary advantage of our new pathway to bryostatin 7 lies in its ability to generate tailored BC analogues and in its generally high levels of stereocontrol throughout. Our synthetic work on **1** has also led to the originally published $CDCl_3$ spectral data[7a] for the AB fragment **1** being revised. Comprehensive details of the authentic ^1H NMR spectrum for **1** in $CDCl_3$ are presented in Part 3 of the Supporting Information, which also describes our unambiguous structure determination of the UCL version of **1**.

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Supporting Information Available: Full experimental procedures and detailed spectral data of all key compounds are reported. Copies of 500 MHz ^1H and 125 MHz ^{13}C spectra are additionally provided, along with HRMS data. This material is available free of charge via the Internet at http://pubs.acs.org.

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