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Total Synthesis of Bryostatin 9

Paul A. Wender* and Adam J. Schrier

Departments of Chemistry and Chemical and Systems Biology, Stanford University, Stanford, California 94305-5080, United States

Supporting Information

ABSTRACT: The total synthesis of bryostatin 9 was accomplished using a uniquely step-economical and convergent Prins-driven macrocyclization strategy. At 25 linear and 42 total steps, this is currently the most concise and convergent synthesis of a potent bryostatin.

The bryostatins are a family of 20 structurally complex natural products[1] putatively produced by a bacterial symbiont[2] of the marine bryozoan *Bugula neritina*. In 1968, Pettit and co-workers[3] found that extracts of this organism have potent anticancer activity, but it was not until 1981 that the structure of bryostatin 1, the prototypical member of this family, was elucidated (Figure 1).[4] Structurally characterized by a 20-membered macrolactone core containing three densely functionalized pyran rings, members of this family differ primarily in the identity (or absence) of acyloxy substituents at positions 7 and 20. Additional diversity is observed in the C ring: bryostatins 16 and 17 contain a dihydropyran C ring in lieu of the more common tetrahydropyran, and bryostatins 3, 19, and 20 possess a C22 oxygen that engages the C21 exocyclic enoate as a butenolide.

The bryostatins exhibit a uniquely rich and diverse portfolio of biological activities. Bryostatin 1, the most thoroughly investigated congener, has been found to restore apoptotic function in cancer cells, stimulate the immune system,[5] and reverse multidrug resistance.[1] In anticancer clinical trials,[6] bryostatin 1 has demonstrated the ability to enhance the activities of known oncolytic agents at remarkably low doses (~50 $\mu g/m^2$).[7] Of further significance, bryostatin 1 has been shown to induce the formation of synapses,[8] improve memory and learning in animal models,[9] and enhance the α-secretase processing of amyloid precursor protein,[10] suggesting its possible use as a novel Alzheimer's disease[11] or poststroke[12] therapeutic. These activities are believed to result in part from bryostatin's extraordinary affinity for protein kinase C (PKC) and other C1-domain-containing proteins.[13]

Impressive total syntheses of five bryostatins have been reported (Figure 1): bryostatin 7 in 1990 by Masamune and co-workers,[14] bryostatin 2 in 1998 by Evans and co-workers (a formal synthesis of bryostatin 1),[15] bryostatin 3 in 2000 by Yamamura and co-workers,[16] bryostatin 16 in 2008 by Trost and Dong,[17] and, most recently, bryostatin 1 by Keck and co-workers.[18] Additionally, a formal total synthesis of bryostatin 7 was reported by Hale and colleagues in 2006.[19] Several additional groups have contributed significantly to this field, including those of Thomas, Vandewalle, Roy, Burke, Krische, Hoffmann, Yadav, and others.[20]

Of those bryostatins that have been prepared by total synthesis, bryostatins 1, 2, 3, and 7 are highly potent ligands for PKC

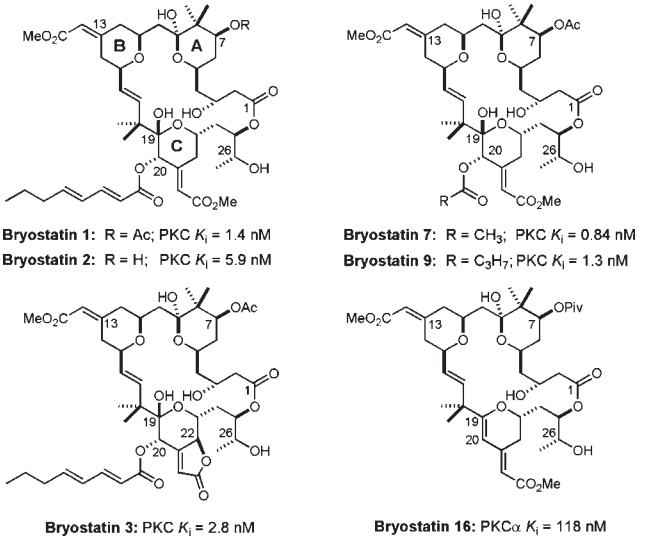

Figure 1. Bryostatins that have been prepared by total synthesis.

(K_i < 10 nM[21]). Each congener contains a C-ring tetrahydropyran motif with attendant C19 hemiketal and C20 acyloxy groups. Bryostatin 16, which lacks these structural elements, is much less active (PKCα K_i = 118 nM). While the early syntheses reported by Masamune, Evans, and Yamamura provided a starting point for accessing the potent bryostatins (42-45 linear, >75 total steps), further development of these routes has not been reported. In addition, the points of convergence of these syntheses necessitate a further 14−21 linear steps to elaborate each target following assembly of their respective pyran-containing backbones, thus limiting step-economical access to diverse analogues.

Keck's synthesis of bryostatin 1, which requires 31 linear and an estimated 57 total steps, is a notable advance.[18] This strategy utilized an intermolecular Prins cyclization to anneal the B ring, which was then followed by 11 additional steps to elaborate the macrocycle (via lactonization) and other peripheral functionality.

In 1988, in collaboration with the groups of Pettit and Blumberg, we advanced a computer-based structure−function hypothesis in which the northern A/B-ring architecture of bryostatin is proposed to conformationally restrict the southern-fragment functionality required for effective recognition by PKC.[22] This analysis guided our design of the first simplified functional analogues of bryostatin,[23] exemplified by **1** (Figure 2),[24] which demonstrated that bryostatin-like potency can be achieved and even exceeded with great simplification of the northern-fragment

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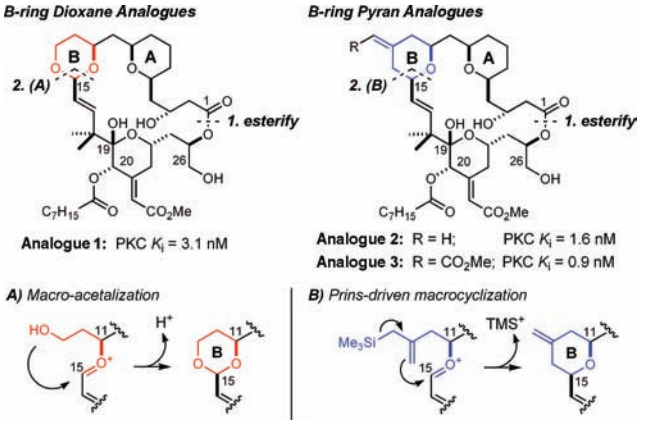

Figure 2. Representative bryostatin analogues **1**, **2**, and **3** and strategies for their synthesis.

functionality. Strategically, a design element common to this and numerous related bioactive analogues[25] was the incorporation of a dioxane B ring as a pyran surrogate, which enabled assembly of the macrocycle by esterification and subsequent macroacetalization of a diol−acid northern fragment with an aldehyde-containing southern fragment to produce in sequence the ester (lactone) and B-ring dioxane (Figure 2A). This mild sequence tolerates fully functionalized coupling partners, thereby enabling excellent overall convergence (e.g., **1** was accessed in one step following fragment coupling).

We recently reported that this B-ring annulation strategy accommodates a Prins-driven macrocyclization (Figure 2B) to provide the corresponding B-ring tetrahydropyran architecture, as exemplified by analogues **2** and **3**.[26] Like the macroacetalization precedent, this mild macrocyclization tolerates sensitive C-ring functionality, thereby enabling the synthesis of **2** in only three steps following esterification of a hydroxyallylsilane-containing northern piece with the same southern-fragment aldehyde employed in the synthesis of **1**.

While the excellent PKC affinity and bioactivity of **1**−**3** and related analogues support a scaffolding role of bryostatin's northern A/B-ring motif, recent work by us and Keck's group has shown additional structure−function relationships associated with this region. For example, we found that A/B-ring structural variation influences PKC isoform selectivity,[27] and Keck, Blumberg, and co-workers found that modifications of the A ring influence activity against certain cancer cell lines.[28]

Prompted by the importance of elucidating these structure−function−selectivity relationships, the therapeutic potential of these agents, and the scarcity of the natural products, we sought a facile, maximally convergent route to variably and systematically functionalized northern-fragment analogues. Our designed analogues included those possessing the full complement of functionality present in the natural product family, an area that has been largely unexplored because of scarce supply. Toward this end, we report herein the first total synthesis of bryostatin 9. This natural product has excellent affinity for PKC (K_i = 1.3 nM) and was first isolated in 1986[29] by Pettit and co-workers in 0.000027% yield. Our synthesis proceeds in 25 linear steps using a Prins-driven macrocyclization strategy. This is the most step-economical and convergent total synthesis of a potent bryostatin (PKC K_i < 10 nM), underscoring the strategic value of this functionality-tolerant macrocyclization reaction. Recent notable examples of Prins macrocyclizations have also been described by the groups of Scheidt, Lee, Rychnovsky, and Yadav.[30]

With this disconnection approach, the synthesis of bryostatin 9 was simplified to accessing hydroxyallylsilane-containing northern fragment **4** and aldehyde-containing southern fragment **5**. The synthesis of **4** commenced with the benzylation of C1−C9 lactone **6** (Scheme 1A), a versatile A-ring intermediate available in seven steps from acrolein that we had previously disclosed for the synthesis of several A-ring bryologues.[27b] The C10−C13 carbon fragment was installed by addition of the ethyl acetoacetate dienolate, and equilibration of the resulting C9 lactol epimers to the anomeric methyl ketal was accomplished using PPTS in MeOH. Reduction of C11 with $NaBH_4$ favored hydroxyester **8** (78:22 dr), which was isolated in 61% yield.

Silylation and double nucleophilic addition[31] of $TMSCH_2MgCl$ mediated by $CeCl_3 \cdot 2LiCl$[32] provided alcohol **10**. Knochel's soluble cerium salt provided the optimal yield (65%) for this challenging reaction; conventionally dried anhydrous $CeCl_3$ (from its heptahydrate) gave poorer yields (∼45%). Peterson olefination of **10** with NaHMDS furnished the corresponding allylsilane.

Debenzylation was cleanly effected using lithium naphthalenide to provide C1,C7 diol **11** in 87% yield, and the C1 hydroxyl group was oxidized using a combined TEMPO/$PhI(OAc)_2$/$NaClO_2$ system. Acetylation followed by alkaline aqueous workup provided the fully elaborated northern fragment **4** in 57% yield over two steps and in ∼2% overall yield over a 17-step sequence.

The preparation of bryostatin 9 southern fragment **5** (Scheme 1B) began with olefin **12**,[24] an intermediate available in eight steps from 2,2-dimethyl-1,3-propanediol. Ozonolysis provided the corresponding ketoaldehyde, which was then chemoselectively olefinated using Takai's protocol[33] to provide a 93:7 mixture of (*E*)- and (*Z*)-ethylidene isomers **13**. Although these isomers were not separable via chromatography at this or subsequent stages, the undesired *Z* component was ultimately removed in the dihydroxylation step (see below).

Aldol condensation of **13** with methyl glyoxylate installed the C21 enoate motif in 81% yield, and Luche reduction followed by butanoylation provided ester **14** in 91% yield. Desilylation with $3HF \cdot Et_3N$ followed by Dess−Martin oxidation then gave a C17 aldehyde that was homologated in one step to unsaturated aldehyde **15** using the dimethylzincate reagent derived from (*Z*)-2-lithio-1-ethoxyethylene.

At this stage, the C25/C26 (*R*,*R*)-diol subunit was installed with 83:17 dr in 78% combined yield via Sharpless' dihydroxylation. The undesired C25/C26 (*Z*)-olefin carried through to this point (∼8 mol %) was less reactive under these conditions, and the recovered starting material was enriched in this isomer.[34] The mixture of (*R*,*R*)- and (*S*,*S*)-glycols was then subjected to aqueous *p*-TsOH to hydrolyze the C19 methyl ketal, and selective silylation of the C26 hydroxyl group provided recognition domain **5** as a single diastereomer in 64% yield over two steps. This domain was thereby accessed in ∼2% yield over a 19-step longest linear sequence. Esterification of **5** with 1 equiv of northern fragment **4** proceeded in 82% yield using Yamaguchi's protocol (Scheme 2), thus setting the stage for the Prins macrocyclization.

In our previous report detailing the syntheses of **2** and **3**,[26] the triethylsilyl-protected macrocyclization precursor analogous to **17** was desilylated and the corresponding hydroxyallylsilane cyclized using TMSOTf in Et_2O.[35] However, for functionalized A-ring substrates more closely related to **17**, those conditions

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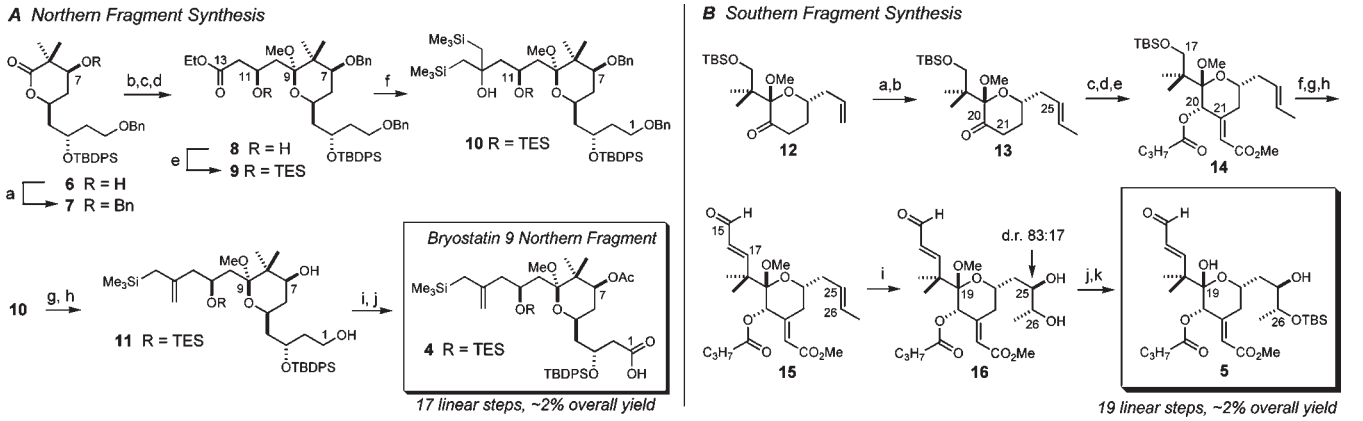
Scheme 1. Synthesis of the Bryostatin 9 Northern and Southern Fragment Coupling Partners[a]



[a] Reagents and conditions in (A): (a) BnBr, NaHMDS, 5:1 THF/DMF, 0 °C, 90%. (b) Ethyl acetoacetate (2.5 equiv), LDA (5.0 equiv), THF, −78 °C. (c) PPTS, MeOH, 40 °C, 84% over three steps. (d) $NaBH_4$, EtOH, −15 °C, 78:22 dr, 61% isolated **8**. (e) TESCl, imidazole, CH_2Cl_2, rt, 97%. (f) $CeCl_3 \cdot 2LiCl$, $TMSCH_2MgCl$, THF, rt, 65%. (g) NaHMDS, THF, 0 °C, 91%. (h) Lithium naphthalenide, THF, −30 → −10 °C, 87%. (i) TEMPO (30 mol %), $PhI(OAc)_2$ (3 equiv), 4:1 $MeCN/H_2O$; then NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, 0 °C. (j) Ac_2O, DMAP, CH_2Cl_2, 0 °C; then $NaHCO_3$(aq), 57% over two steps. Reagents and conditions in (B): (a) O_3, CH_2Cl_2, −78 °C; then PPh_3, rt, 98%. (b) I_2CHCH_3, $CrCl_2$, DMF, THF, 0 °C, 76%, 93:7 *E*:*Z*. (c) K_2CO_3, methyl glyoxylate, THF/MeOH, rt, 81%. (d) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −49 °C. (e) Butyric anhydride, DMAP, CH_2Cl_2, rt, 91% over two steps. (f) $3HF \cdot Et_3N$, THF, rt. (g) Dess−Martin periodinane, CH_2Cl_2, rt. (h) (*Z*)-1-Bromo-2-ethoxyethylene, *t*-BuLi, Me_2Zn, Et_2O, −78 °C; then H_3O^+, 64% over three steps. (i) $K_2OsO_4 \cdot 2H_2O$ (~0.5 mol %), $DHQD_2PYR$ (1.5 mol %), K_2CO_3, $K_3Fe(CN)_6$, 4 °C, 78%, 83:17 (*R*,*R*):(*S*,*S*). (j) *p*-TsOH, 4:1 $MeCN/H_2O$, rt. (k) TBSCl, imidazole, CH_2Cl_2, 64% over two steps as a single diastereomer.

yielded a significant amount of a spirocyclic byproduct that resulted from activation of the methyl ketal at C9.[36] We therefore investigated alternative reaction conditions and found that treatment of **17** with catalytic PPTS in anhydrous MeOH provided macrocyclization product **18** in a single step (65% yield). Notably, these mild conditions obviated the need for a separate C11 desilylation step, as the reactive hydroxyallylsilane was revealed in situ.

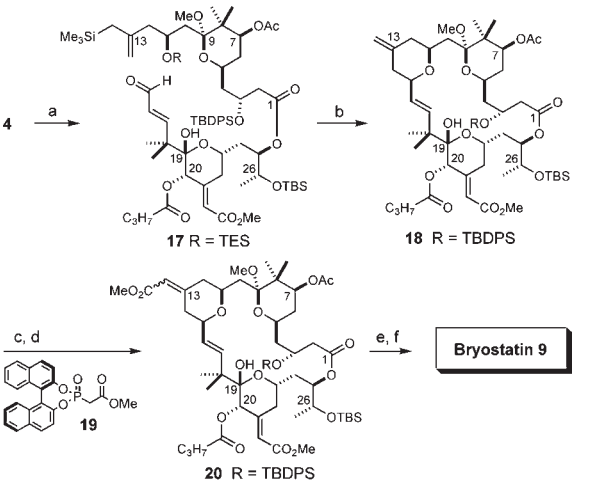
The exocyclic B-ring enoate was then installed in two steps: oxidative cleavage of the C13 methylidene with stoichiometric ozone (72% yield) and olefination of the resulting ketone with phosphonoacetate **19** (82% yield, 79:21 *Z*:*E*).[37] The selectivity of this olefination is in good accord with that observed by Evans, Yamamura, and Keck. The reaction with trimethyl phosphonoacetate lacked appreciable selectivity (48:52 *Z*:*E*).

Global desilylation and C9 ketal hydrolysis was accomplished in two steps and 76% combined yield by treatment of enoate mixture **20** with HF·pyridine followed by aqueous PPTS,[38] thereby providing pure bryostatin 9 in 52% yield.

We conclusively established the identity of our synthetic material by comparison with an authentic sample kindly provided by Prof. G. R. Pettit. All analytical data for the synthetic sample were found to be in agreement with published or observed data for the natural product (see the Supporting Information).

This synthesis provided bryostatin 9 in 25 linear and 42 total steps. Significantly, the fragment syntheses can be readily scaled to produce gram quantities of the advanced intermediates, which, because of the potency of these agents, have clinical supply potential. This approach enables access to the complete and highly functionalized bryostatin oxycarbocyclic ring system (e.g., **18**) in only two steps from similarly complex northern fragment **4** and southern fragment **5**. More generally, the macro-Prins and macroacetalization strategies provide potentially general and functional-group-tolerant approaches to natural or unnatural pyran-containing macrocycles and their dioxane analogues. The flexibility, convergence, scalability, and step economy of these strategies

Scheme 2. Completion of Bryostatin 9[a]



[a] Reagents and conditions: (a) 2,4,6-Trichlorobenzoyl chloride, Et_3N, $PhCH_3$; then alcohol **5**, DMAP, 82%. (b) PPTS (20 mol %), MeOH, [**17**] = 0.02 M, rt, 22 h, 65%. (c) O_3, CH_2Cl_2, −78 °C; then thiourea, 1:1 CH_2Cl_2/MeOH, rt, 72%. (d) **19**, NaHMDS, THF, −78 → 4 °C, 79:21 *Z*:*E*, 82%. (e) HF·py, THF, rt. (f) PPTS, 20% H_2O in THF, rt, 76% combined yield, 80:20 *Z*:*E*, 52% isolated bryostatin 9.

enable access to natural and designed bryostatin analogues that are critically needed for ongoing mode-of-action, structural, and preclinical studies.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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AUTHOR INFORMATION

Corresponding Author
wenderp@stanford.edu

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