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Total Syntheses of Bryostatins. Syntheses of Two Ring-Expanded Bryostatin Analogues and Development of a New-Generation Strategy to Access the C7-C27 Fragment

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Abstract

This paper reports the synthesis of novel ring-expanded bryostatin analogues. By carefully modifying the substrate, a selective and high-yielding Ru-catalyzed tandem enyne coupling/Michael addition was employed to construct the northern fragment. A ring-closing metathesis was utilized to form the 31-membered macrocycle of the analogue. These ring-expanded bryostatin analogues possess anticancer activity against several cancer cell lines. Given the difficulty of forming the C16-17 olefin in the late stage, we also describe our development of a new-generation strategy to access the C7-C27 fragment containing both the B- and C-ring subunits.

Keywords

bryostatin; Ru catalysis; ring-closing metathesis; tandem reaction; Pd catalysis

Introduction

In the previous papers, we described our development of chemoselective and atom-economical methods for stereoselective assembly of bryostatin A-, B- and C-ring subunits (Figure 1). Consequently, efforts have been undertaken toward total synthesis of the bryostatins by taking advantage of these methods.^[1] In this article, we report a full account of our synthesis and biological evaluation of two novel ring-expanded bryostatin analogues using the ring-closing metathesis (RCM) as the macrocyclization method. Given the difficulty of forming the C16-17 olefin in the late stage, we also describe the development of a new-generation strategy to access the C7-C27 fragment containing the B- and C-ring subunits.

Results and Discussion

I. Synthesis of Two Ring-Expanded Bryostatin Analogues

Retrosynthetic Analysis—The 26-membered macrolactone embedded in the bryostatins presents a significant synthetic challenge.^[2] All three previously reported total syntheses relied upon a Julia olefination to unite a southern and a northern hemisphere followed by a macrolactonization to close the macrocycle.^[3–6] However, due to the basic nature of the Julia olefination reaction, the two exo-cyclic α,β -unsaturated enoates had to be masked and

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revealed after macrocyclization, resulting in lengthy syntheses (> 40 longest linear steps and >70 total steps).

In the two preceding articles, we described our efforts on the development of atom-economic transformations for the synthesis of A-, B- and C-ring subunits of the bryostatins. Importantly, a high degree of stereocontrol of the exocyclic methyl enoate geometry was achieved, which is mechanism-based. However, utilization of these methodologies for the total synthesis of bryostatins necessitates a more chemoselective strategy for the macrocycle synthesis due to the sensitive nature of exocyclic methyl enoate towards both acids and bases. The impressive progress of RCM in organic synthesis and the mildness of the reaction conditions prompted us to evaluate its use for our bryostatin total synthesis (Scheme 1).^[7]

We envisioned that the 26-membered macrocycle of **1** could be formed by a RCM reaction from a diene precursor **10**, which can be synthesized from two fragments, **11** and **12**, via esterification. Southern fragment **12** containing the C-ring subunit could be accessed from dihydropyran **5**.^[8] Northern fragment **11** could be prepared from protected polyol **13**, and synthesis of the B-ring in **13** would ultimately come from a Ru-catalyzed tandem alkyne-ene coupling/Michael addition reaction^[9] between alkene **14** and alkyne **7**. The feasibility of such a transformation has been previously established in a model system (eq 1), albeit with a low yield and diastereoselectivity likely caused by the liability of the cyclopentanone ketal and the presence of two terminal olefins in **6**. We anticipated that the nature of protecting groups in the alkene partner **14** would have an impact on the outcome of the Ru-catalyzed tandem coupling reaction. Thus, alkene **14a** with a more robust acetonide moiety was chosen as an initial coupling partner.

(1)

Synthesis of the Northern C1-C16 Fragment—Our synthesis (Scheme 2) commenced with (*R*)-pantolactone, which was converted to alcohol **15** in 5 steps (exhaustive reduction with LAH, selective protection of the C7, C9 diols as a 4-methoxybenzaldehyde acetal, TEMPO-catalyzed oxidation^[10] of the C5 alcohol, Wittig olefination, and DIBAL-H reduction) following a procedure from White and Mukaiyama.^[11,12] TBS protection of **15** followed by hydroboration/oxidation furnished the desired alcohol in high yield (90% overall). Oxidation of alcohol **16** was best accomplished by using TEMPO-catalyzed oxidation with bleach. The crude aldehyde was used without purification in the Ti(*O*-*i*-Pr)₂Cl₂-mediated Mukaiyama aldol reaction with bis(trimethylsilyl) dienol ether **17** to give secondary alcohol **18** in 68% yield over two steps as a ~10:1 diastereomeric mixture at C5. The stereochemical assignment of the newly formed C5-hydroxyl group (bryostatin numbering) was based upon similar precedent reported by Evans.^[13] Subsequent hydroxyl-directed *anti*-reduction^[14] (Me₄NBH(OAc)₃, AcOH/CH₃CN, -35 °C) set the C3 stereochemistry with excellent yield (96%) and diastereoselectivity (ca. 15:1).

To move forward, the C3 and C5 hydroxyl groups were protected as an acetonide, and the TBS group was removed with triethylamine-HF. Upon oxidation of the resultant neopentyl alcohol, the stage was set for allylation of aldehyde **22**. A variety of allylation reagents, such as allylmagnesium chloride, allylzinc bromide, and B-allyl-9-BBN, gave a complex mixture

due to the sensitivity of the aldehyde, while tetraallyl tin^[15] gave no reaction. On the other hand, indium-mediated allylation^[16] with allyl iodide (DMF, room temperature) provided a satisfactory 78% yield of the corresponding secondary alcohols as a 1:1 diastereomeric mixture at C9. The diastereoselectivity of this process is inconsequential as this stereocenter is subsequently obliterated. Interestingly, replacing allyl iodide with allyl bromide gave no reaction, even with the aid of sonication. Subsequent oxidation (Dess-Martin periodinane, NaHCO₃, CH₂Cl₂) resulted in β,γ -enone **14a**.

With enone **14a** in hand, the Ru-catalyzed tandem coupling reaction of **7** with **14a** was then investigated (eq 2). Unfortunately, the reaction provided a complicated mixture and no desired coupling product was obtained. Nevertheless, we were able to identify an apparent signal at 6.69 ppm (CDCl₃, dt, $J = 10.5, 17.0$ Hz) in the crude ¹H NMR, which indicated the formation of trans- α,β -unsaturated ester during the reaction.

(2)

This result was in striking contrast to our preliminary model studies. We hypothesize that coordination of the C3-oxygen in **14a** with the cationic Ru species activated it towards β -alkoxy-elimination (Figure 2). The C5-oxygen could consequently get deprotected and then participate in other reactions, such as formation of a hemiketal. If this hypothesis was correct, removal of the ester group should alleviate the β -alkoxy-elimination pathway.

To this end, the synthesis of a new β,γ -enone **14b** was pursued (Scheme 3). Methyl ester **20** was converted to alcohol **24** via a straightforward three-step transformation (LAH reduction, deprotection of the TBS ether, and selective protection of the C1-hydroxyl group with TBDPSCI). The β,γ -enone was installed in three steps as previously described (Dess-Martin oxidation, indium-mediated allylation, and Dess-Martin oxidation) to furnish **14b**.

Treatment of **14b** and alkyne **7** with [CpRu(CH₃CN)₃]PF₆ under the optimized conditions (0.4 M in acetone, 40 h), to our delight, indeed gave the desired dihydropyran **25**, although the yield was low (21%, eq 3).

(3)

It is likely that the problem was caused by the acid sensitivity of the acetonide in **14a** and **14b**, which could be enhanced by the presence of the C9 ketone moiety. For example, the deprotected C5 alcohol could undergo cyclization to form a hemi-ketal. To overcome this issue, a new enone **14c** was proposed (Figure 3). Both the lactone and the TBDPS ether moieties in **14c** were expected to be stable under the reaction conditions. Furthermore, the

lactone protected both the C5-hydroxyl group and C1-ester, thus minimizing protecting group manipulations.

The synthesis of enone **14c** is outlined in Scheme 4. Starting from diol **19**, the two hydroxyl groups at C3 and C5 were differentiated by lactonization, which was best achieved with Otera's catalyst **26**.^[17] Use of PPTS gave inferior results in terms of both the yield and the conversion. Protection of the C3 alcohol (TBDPSCI, DMF, imidazole) required heating (50 °C) while no reaction was observed at room temperature. The primary TBS ether in lactone **28** was selectively deprotected with aqueous acetic acid (80%, 4:1 v/v) to give alcohol **29** in good yield (69% – 80%). The β,γ -enone functionality was installed as previously described without incident to give the desired enone **14c** in good overall yield (85% over three steps).

With enone **14c** in hand, the crucial Ru-catalyzed tandem coupling was investigated (Scheme 5). To our delight, the reaction went smoothly, delivering tetrahydropyran **30** in 56% yield as a 9:1 *cis* : *trans* diastereomeric mixture. The appearance of a singlet at 5.45 ppm (minor) and 5.38 ppm (major) and the incorporation of two PMB groups in ¹H NMR (500 MHz, C₆D₆) suggested a successful coupling. This was later confirmed by ¹³C NMR and elemental analysis. Assignment of the 5.38 ppm signal (belonging to the vinylsilane proton) as the *cis*-isomer was based on the previous model studies and later confirmed by 2D NMR experiments on late stage compounds. Furthermore, we were able to reduce the ratio of enone : alkyne to 2.2:1 and recover 1.2 equiv. of **14c**, and up to 5.5 g of **30** was synthesized. Thwarted by acid-mediated protodesilylation of the vinylsilane moiety, compound **30** was brominated with NBS in DMF and then deprotected using BF₃•Et₂O and 1, 3-propanedithiol in CH₂Cl₂ at 0 °C to give diol **31**. Shift of the vinyl proton resonance from 5.38 to 6.04 ppm, disappearance of both PMB groups in ¹H NMR, and appearance of a broad peak at 3436 cm⁻¹ in IR supported the structural assignment. Furthermore, the incorporation of a bromine atom into the molecule was confirmed by mass spectroscopy. Diol **31** was subsequently subjected to a tandem methanolysis/ketalization reaction with PPTS in refluxing CH₃OH/CH(OCH₃)₃ to afford methyl ketal **32** with both A- and B-rings installed.^[18] The assignment of C9-methyl ketal stereochemistry was based on a similar literature precedent.^[4a]

At this point, the remaining task was to acetylate the C7-hydroxyl, hydrolyze the C1-methyl ester, and install a terminal olefin at C16. To this end, the C7-hydroxyl was selectively acetylated in two steps involving the temporary protection of the C16-hydroxyl with TES ether, one-pot acetylation of the C7-hydroxyl, and deprotection of the C16-hydroxyl to give compound **33**. The resultant alcohol was then oxidized (Moffatt-Swern oxidation) and olefinated (Wittig olefination) to afford the terminal alkene **34** in 63% yield over two steps. Surprisingly, saponification of the methyl ester in **34** was troublesome; for example, use of LiOH in aqueous THF or *n*-PrSLi in HMPA^[19] only gave a complex mixture. It was eventually found that the use of (CH₃)₃SnOH^[20] gave acid **35** in 45–64% yield together with 10–15% of recovered methyl ester **34**. A large excess of (CH₃)₃SnOH (15 equiv) and heating under microwave conditions were required for achieving high conversion. Pd-catalyzed carbonylation^[21] of acid **35** with Pd(PPh₃)₄ in DMF/CH₃OH furnished the requisite α,β -unsaturated methyl ester **36** in 55% yield. Note that both acids **35** and **36** could be used as a RCM precursor. But, use of vinyl bromide **35** as a RCM precursor could be advantageous because in principle it allows late-stage diversifications through cross-coupling reactions to provide novel bryostatin analogues.

Synthesis of the Southern C17-C27 Fragment—The synthesis commenced with tetrahydropyran **3** that was prepared in 5 or 6 steps from terminal alkyne **8** and ynoate **9** (see Part I). The removal of the C17-TBS ether in **3** was best effected by using Et₃N•3HF in THF (60–77% yield, ca 10% of the recovered **3**) (Scheme 6). Excess reagents (15 equiv of

Et₃N•3HF) and long reaction time (12 h) were necessary to achieve reasonable conversion of **3**.^[22] Other deprotection methods, such as TBAF, TBAF buffered with acetic acid, HF in pyridine, and aqueous HF in acetonitrile, gave inferior results. After oxidation of the C17-hydroxyl to the corresponding aldehyde, the stage was set for the introduction of a double bond at C17. This transformation turned out to be non-trivial, and almost all the classical olefination methods failed (see Table 1), likely caused by the neopentyl nature of the aldehyde and sensitivity of the dihydropyran core towards bases. Eventually, employment of Cp₂Ti(CH₃)₂ (Petasis reagent)^[23] as the olefination reagent solved the problem, and the terminal alkene **39** was obtained in 58% yield (70% based on recovered starting material, entry 7). Under the reaction conditions, a by-product derived from olefination of one of the ester groups was observed (5–10% yield). Cleavage of the acetonide with 75% aqueous acetic acid, followed by selective protection of the C26-hydroxyl with the TES group furnished the fully functionalized southern fragment **40** in 52% yield over two steps.

(4)

The stereochemistry of tetrahydropyran **40** was confirmed by ROESY experiment (Figure 4). The selectivity for the mono-TES protection was predicted according to the literature precedent^[4a] and confirmed by 2D NMR experiments.

Investigation of the Ring-Closing Metathesis Approach—With acid **36** and alcohol **40** in hand, the stage was set for their union. Initial efforts with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) as the coupling reagent were plagued by the formation of two inseparable products in a 1:1 ratio, one of which was later identified as the desired ester **42**. No efforts were made to identify the other product. The most satisfactory results were obtained by employing the 2-methyl-6-nitrobenzoic anhydride (MNBA) method developed by Shiina.^[24] Ester **42** was isolated in around 60% yield with the majority of the excess alcohol **40** recovered.^[25] In addition, under the same esterification conditions, acid **35** was also coupled with alcohol **40** to give ester **41** in a similar yield.

Consequently, the RCM reaction of both esters **41** and **42** were investigated. Our initial attempts were carried out with the Grubbs-Hoveyda catalyst **45**^[26] or the pseudohalide catalyst **46**^[27] in either refluxing CH₂Cl₂ or benzene. Unfortunately, these reactions were sluggish. Prolonged heating (> 12 h) was required for the conversion of either **41** or **42**, even in refluxing benzene. Furthermore, the isolated major product was much more polar than the corresponding starting materials. That the polar product could be a dimer was supported by ¹H NMR analysis: the double bond at C16 disappeared while the one at C17 remained intact. Based upon these observations, a possible explanation for the failure of the RCM reaction is outlined in Scheme 8. Both terminal double bonds at C16 and C17 are deactivated towards Ru-alkylidene formation due to the unfavorable steric and electronic factors. At elevated temperature, the Ru-alkylidene selectively initiated attack on the C16 double bond. Since the C17 double bond has very low reactivity, presumably due to steric congestion, intermediate **43** preferred to react with another molecule of **42** to form a dimer even at a very low substrate concentration (~0.0005 M). Concurrently, a similar observation

was also reported by Thomas and co-workers during their investigation of a RCM approach towards the bryostatins.^[28]

It was anticipated that the conformation of the RCM precursor would have a dramatic impact on the RCM efficiency. The X-ray crystal structure of bryostatin 1 (Figure 5)^[2a] clearly showed that the C3-OH group helps to organize the macrocycle by serving as a hydrogen bonding acceptor for the C19 lactol hydroxyl (O-H-O bond length of 2.71 Å) and donors for both C5 and C11 pyran oxygens (O-H-O bond length of 3.00 and 2.84 Å, respectively). If this holds true for the immediate RCM precursor, one would expect that a free hydroxyl group at C3 in either **41** or **42** would facilitate the RCM reaction by bringing two terminal olefins together. Therefore, deprotection of the TBDPS ether at C3 was undertaken (eq 5). Unfortunately, only a complex mixture was obtained under the three reaction conditions attempted (TBAF, HF in pyridine, and NH₄F in CH₃OH). To circumvent this problem, it was decided to deprotect the TBDPS group at an earlier stage of the synthesis.

(5)

Treatment of vinyl bromide **34** led to a smooth deprotection of the C3-TBDPS ether to give alcohol **47** in 82% yield (Scheme 9). In contrast to the hydrolysis of methyl ester **34** (Scheme 5, 45–50% yield with 15 equivalents of (CH₃)₃SnOH, 140 °C, microwave, 1.5 h), the saponification of **47** was much more facile. Under the identical reaction conditions, the reaction went to completion in 40 minutes to deliver the hydroxyacid **48** in 86% yield. Presumably, the hydrolysis of the C1-methyl ester was facilitated by precoordination (or complexation) of the C3-hydroxyl with (CH₃)₃SnOH.^[29] Next, carbonylation of the vinyl bromide moiety followed by selective protection of the C3-hydroxyl (TESOTf, DCM, 0 °C) converted **49** to acid **50**, which was subsequently acylated with alcohol **40** to give ester **51**. Deprotection of both TES groups at C3 and C26 with PPTS in aqueous THF provided diol **52**, the structure of which was fully determined by COSY, ROESY, HSQC, and HMBC experiments.

Unfortunately, when **52** was subjected to RCM reactions in the presence of the Grubbs-Hoveyda catalyst **45**, no reaction was observed in refluxing CH₂Cl₂ while refluxing in benzene only led to decomposition. It was evident from these studies that the low reactivity of the double bond at C17 was the source of the problem. Thus, we decided to initiate the ruthenium alkylidene formation onto the C17 double bond via relay ring-closing metathesis (RRCM).^[30] If this could be accomplished, it was anticipated that the resulting ruthenium alkylidene **55** would cyclize onto the C16 double bond to form macrocycle **53** (Scheme 10).

A RRCM Strategy—Although direct installation of a relay moiety onto the southern hemisphere via Takai olefination^[31] (eq 6) or olefin cross-metathesis^[32] (eq 7) was difficult (eq 6 and 7), this problem was solved with a two-step procedure: a Takai olefination of aldehyde **38** with iodoform^[33] followed by a Negishi cross coupling^[34] gave **60** (Scheme

11). The quality of CrCl_2 was crucial for the Takai olefination reaction, and high chromium loading (~15 equiv) was necessary for full conversion of the starting material.^[35] The yield (26%, 47% based on the recovered starting material) was moderate likely due to the steric congestion around the aldehyde. Subsequent deprotection (80% aqueous AcOH) followed by selective TES protection (TESCl, DMF, Et_3N , 0 °C to rt) converted **62** to mono-TES ether **63**, which was then acetylated with the northern hemisphere segment **50** to give RRCM precursor **64** in 51% yield. The structure of compound **64** was determined by ^1H , ^{13}C , 2D NMR experiments. In particular, the observed ROESY correlations confirmed our previous stereochemical assignment for the A-, B-, and C-rings (Figure 6).

(6)

(7)

With polyolefin **64** in hand, the RRCM was next investigated (eq 8). To avoid the undesired dimerization, a solution of **64** was added in a dropwise fashion via a syringe pump to a solution of the Grubbs-Hoveyda catalyst **45** (18 mol%) in benzene at 50 °C and then the bath temperature was raised to 80 °C. The starting material disappeared within one hour (entry 1). No RRCM product was observed. Surprisingly, the direct RCM products were isolated as a mixture of 1:1 *E/Z* isomers (**66** and **67**) in a very high yield (80%). The assignment of direct RCM products was supported by high-resolution mass spectroscopy and 2D NMR experiments. Changing the order of addition (adding **45** to a solution of **64** in benzene) gave the same product ratio. Furthermore, employing the second generation Grubbs catalyst **65** and running the reaction in refluxing toluene improved the product ratio of **66/67** to 1:2.3 favoring the *E*-isomer (entry 2).^[36]

(8)

Consequently, treatment of macrocycles **66/67** with PPTS in anhydrous MeOH cleanly removed both TES groups (Scheme 12). At this stage, diol **68/69** was separated by preparative TLC, and their structures were determined by IR, HRMS, ^1H , ^{13}C and 2D NMR experiments. Note that in the presence of water the global deprotection only resulted in a complex mixture; however, treatment of this mixture with PPTS in dry MeOH provided the same mixture (**68** and **69**) as above. We rationalize that this interesting phenomena was likely caused by the rapid tautomerization of the unprotected C9 hemiketal (Figure 7).

Biological evaluation of novel ring-expanded bryostatin analogues—

Compounds **68** and **69** contain all the functionalities present in the bryostatins except that they have an unusual 31-membered macrolactone. As almost all the previous efforts on the synthesis of bryostatin analogues have been centered on the 26-membered macrocycle backbone, we envisioned that these “ring-expanded bryostatins” could serve as a family of new analogues to further probe the structure-activity-relationships (SAR) of the bryostatins. Toward this end, macrocycles **68** and **69** and acyclic compound **52** were tested against several cancer cell lines (Table 3). Interestingly, while acyclic compound **52** is completely inactive, 31-membered lactones **68** and **69** exhibit activities against a range of cancer cell lines, including SKBR3—a breast cancer cell line, SKOV3—an ovarian cancer cell line, and NCI-ADR—a breast cancer cell line with added multi-drug resistant pumps. Remarkably, analogue **69** was effective at nm levels against all three cell lines, most notably with respect to NCI-ADR where the IC_{50} value was as low as 123 nm.^[37]

II. Development of a New-Generation Strategy to Access the C7-C27 Fragment

We have disclosed the synthetic challenges to install the C16-C17 olefin at a late stage via either a macrocyclic RCM or a RRCM strategy. Indeed, previous syntheses noted the difficulties of forming this double bond^[4], which led us to conceive of a new strategy to install this sterically hindered *trans* alkene at an earlier stage.

We envisioned that enyne fragment **70** could serve as a linchpin to allow us to “glue” all the subunits together (Figure 8). The function of fragment **70** is three-fold: 1) the homopropargyl alcohol moiety could permit the usage of a Ru-catalyzed tandem enyne coupling/Michael addition to construct the bryostatin B-ring; 2) it provides the C16-17

olefins directly; 3) the TBS protected primary alcohol could serve as a masked terminal alkyne, so that fragment **70** could also provide a linkage to build the bryostatin C-ring via Pd-catalyzed alkyne-alkyne coupling then 6-*endo-dig* cyclization.

As substrates with an allylic alcohol moiety have not been examined in the Ru-catalyzed enyne coupling/Michael addition reaction previously and it is known that allylic alcohols are able to participate in various Ru-catalyzed transformations, such as redox isomerization,^[38] the issue of chemoselectivity needed to be investigated for use of enyne **70** as the substrate. On the other hand, the Pd-catalyzed alkyne-alkyne coupling and 6-*endo-dig* cyclization have not been previously tested on rather complex substrates. Therefore, it was necessary to build a model system to address these chemoselectivity issues. Consequently, compound **71**, with the C7-C27 bryostatin skeleton as well as the B-ring and C-ring entities, was designed as the model target (Scheme 13).

Enantioselective synthesis of TMS-alkyne **70** is described in Scheme 14. Aldehyde **74**^[39] was treated with *cis*-2-ethoxyvinyl lithium **75** and Me₂Zn followed by acidic aqueous workup, providing homologated α,β -unsaturated aldehyde **76** in 97% yield.^[40] NaHSO₄ was selected as a mild acid source; when 1N HCl was used, a much lower yield (51%) was observed. According to a protocol described by Loh et al.,^[41] treatment of aldehyde **76** with indium metal, TMS-propargyl bromide and a catalytic amount of InF₃ in refluxing THF, afforded the racemic homopropargyl alcohol **70** in 68% yield. Dess-Martin oxidation^[42] of the allylic alcohol followed by CBS-reduction^[43] of the corresponding ketone **77** afforded **70** in 90% ee and 90% yield over two steps. The homopropargyl ketone **77** proved to be quite unstable and extremely sensitive to acids,^[44] hence after aqueous workup, it was directly subjected to the subsequent reduction without any purification.

A Weinreb-amide route to ketone **77** has also been explored, since it could potentially shorten the synthesis by one step (Scheme 15). The Weinreb-amide **78** was synthesized in 56% yield via Horner-Wadsworth-Emmons (HWE) olefination^[45] of aldehyde **74**. Although subsequent allenyllithium addition was able to provide the desired ketone **77**, the impurity in the crude (compound **77** cannot be purified by chromatography) did not permit the following CBS reduction, especially on large scale. Therefore, this route was abandoned.

The other fragment, β,γ -unsaturated ketone **73**, was prepared according to our earlier procedure.^[9] With both alkene **73** and alkyne **70** in hand, the conditions for the Ru-catalyzed tandem alkene-alkyne coupling-Michael addition were next examined (Scheme 16). [CpRu(CH₃CN)₃]PF₆ complex (10 mol%) was employed as the catalyst, and three equiv of alkene **73** were used to ensure good conversion. As the initial cyclization product was difficult to separate from the starting materials, the TBS group was subsequently removed with HF in pyridine to give primary alcohol **79**, which could be easily purified. We found that the solvent plays an important role on the product conversion. Under the original reaction conditions, in which acetone was used, the tetrahydropyran **79** was only isolated in 32% yield;^[46] however, upon switching to DCM, a much higher conversion and a much cleaner reaction were observed with an isolated yield of 62% yield over two steps, almost doubling that of the reaction in acetone. We rationalize that as DCM is a much less coordinating solvent than acetone, thus enhancing the reactivity of [CpRu(CH₃CN)₃]PF₆. The diastereoselectivity ratio (dr) for this cyclization was around 6.7:1 (determined by ¹H NMR integration of peaks δ_{major} 2.91 ppm and δ_{minor} 2.80 ppm), favoring the *cis*-isomer.

Advancement of **79** to terminal alkyne **72** was achieved in two steps. Dess-Martin oxidation of the primary alcohol, followed by Ohira-Bestmann alkynylation^[47] of the corresponding aldehyde, provided alkyne **72** in 79% yield over two steps (Scheme 17).

The stage was now set to test the Pd-catalyzed alkyne-alkyne coupling. The acceptor alkyne **9** was synthesized in 6 steps from commercially available *D*-galactonic acid-1,4-lactone (see Part I). The coupling between alkynes **72** and **9** proceeded well when using 10 mol% Pd(OAc)₂/tris(2,6-dimethoxyphenyl)phosphine (TDMPP) as the catalyst (eq 9); enyne **82** was isolated in 73% yield. The primary alcohol, the vinylsilane and the *trans* olefin remained intact under the reaction conditions, which demonstrates excellent chemoselectivity of the Pd-catalyzed alkyne-alkyne coupling.

(9)

A metal-catalyzed 6-*endo-dig* cyclization of enyne **82** was next required to construct the C-ring of bryostatin (eq 10). As shown in our previous paper (Part I), this cyclization could be very challenging because a number of possible by-products can be formed. For example, if the alkyne were substituted with a bulky group, such as a *t*-Bu group, formation of the 5-*exo* addition product would be competitive. In addition, acids can catalyze the isomerization of the external olefin of the 6-*endo-dig* product, giving the other geometric isomer (Scheme 18).^[48] Moreover, the secondary alcohol could attack the ester, instead of the alkyne, to give the 6-membered lactone. Given these concerns, we decided to revisit this 6-*endo-dig* cyclization issue.

(10)

With the goal of achieving good regio- and chemoselectivity, the conditions for this 6-*endo-dig* cyclization were optimized and a number of catalysts were surveyed (Table 4). When enyne **82** was subjected to the previously optimized conditions ([PdCl₂(CH₃CN)₂ (17 mol %), TDMPP (10 mol %), THF, rt), the products from 6-*endo* (**71**+**83**) and 5-*exo* (**84**) pathways were isolated with a ratio around 1:1 (entry 1). A slightly better 6-*endo*/5-*exo* ratio (around 2:1) was observed when using Pd(OAc)₂-TDMPP-Pd(TFA)₂ as the catalyst and using benzene as the solvent; however, this reaction gave incomplete conversion and around

30 % lactone **85** was formed (entry 2). Eventually, the most satisfactory result was found when using cationic gold(I) complex $[\text{Au}(\text{PPh}_3)]^+\text{SbF}_6^-$ as the catalyst in CH_3CN (entry 3).^[49] The product ratio among **71** : **83** : **84** was enhanced to 5.1 : 1 : 1.3, which is equal to ca 5 : 1 6-*endo*/5-*exo* regioselectivity. NaHCO_3 was purposely employed as a buffer to minimize the acid-catalyzed olefin isomerization. The only drawback to these conditions was that the reaction proceeded relatively slow (53% yield over 4 days). When the Au-catalyzed reaction was conducted in DCM, a much higher rate was observed; however the reaction became messy and many unidentified byproducts were formed. The structure of the final model study product **71** was confirmed by ^1H NMR, IR, HRMS and 2D NMR experiments.

The exact reason why the cationic gold catalyst gave much higher regio- and chemoselectivity is unclear. We rationalize that the higher chemoselectivity could be attributed to gold's unique affinity for alkynes;^[50] and the higher regioselectivity may relate to the ionic nature and linear structure of the Au^{I} catalyst. As shown in Scheme 19, when Au binds to the alkyne, the steric interaction between the substituted *t*-Bu-like group and $[\text{Au}(\text{PPh}_3)]^+$ cation plus the adjacent SbF_6^- anion would largely disfavor the 5-*exo* addition, because this interaction would become much worse in intermediate **90** than in **91**. Hence, the 6-*endo* pathway is preferred.

Conclusion

By taking advantages of the two tandem methods, Ru-catalyzed enyne coupling/Michael addition and Pd-catalyzed diyne coupling/6-*endo* cyclization, we were able to furnish fully functionalized both northern and southern fragments of bryostatin. An esterification/olefin metathesis strategy has been investigated to unit the two fragments and to advance them to the natural product. Although formation of the C16-17 olefin via olefin metathesis was unfruitful, we were able to synthesize two new bryostatin analogues with a ring-expanded backbone. These analogues retain almost all the functionalities in the bryostatins, and their biological activities against several cancer cell lines, including NCI-ADR (the one with multi-drug resistant pumps).

To overcome this “olefination problem”, a new strategy was developed to install the C16-17 olefin at an earlier stage. Enyne **70** was designed and synthesized to serve as a “linchpin” to connect both northern and southern parts together. By elaborating this strategy, model substrate **71**, containing the C7-27 carbon skeleton and the B,C-rings of bryostatin, was synthesized in only 6 steps. During these studies, several chemoselectivity issues were addressed, including the functional group tolerance in the Ru-catalyzed tandem alkene-alkyne coupling/Michael addition, and the Pd-catalyzed alkyne-alkyne coupling. Moreover, a cationic gold complex was found to be a superior new catalyst for the challenging 6-*endo-dig* cyclization. Therefore, our ring-expanded analogue synthesis along with this new linchpin strategy described in this article should provide key supports for our subsequent accomplishment of the total synthesis of bryostatins.

Experimental Section

All reactions were run under an atmosphere of nitrogen unless otherwise indicated. Anhydrous solvents were transferred via oven-dried syringe or cannula. Flasks were flame-dried under vacuum and cooled under a stream of nitrogen or argon. Tetrahydrofuran (THF), dimethoxyethane (DME), Benzene, pyridine, diisopropylamine, triethylamine, diisopropylethylamine, dimethylsulfoxide, acetonitrile, hexane, toluene, diethyl ether, and dichloromethane were purified with a Solv-Tek solvent purification system by passing

through a column of activated alumina. Acetone was distilled from calcium sulfate. Methanol was distilled from magnesium methoxide.

Where indicated, solvents are degassed via freezing in liquid nitrogen and thawing under high vacuum. The above cycle is repeated three times, unless otherwise indicated. Analytical thin layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F₂₅₄). Melting points were determined on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. Absorbance frequencies are reported in reciprocal centimetres (cm⁻¹).

Proton nuclear magnetic resonance (¹H NMR) spectra were recorded using a Varian UI-600 (600 MHz), UI-500 (500 MHz) or Varian MERC-400 (400 MHz). Chemical shifts are reported in delta (δ) units, part per million (ppm) downfield from tetramethylsilane (TMS) or in ppm relative to the singlet at 7.26 ppm for deuteriochloroform. Coupling constants are reported in Hertz (Hz). The following abbreviations are used: s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet.

Carbon-13 nuclear magnetic resonance (¹³C NMR) spectra were recorded using a Varian UI-600 (150 MHz), Varian UI-500 (125 MHz) or Varian MERC-400 (100 MHz). Chemical shifts are reported in delta (δ) units, part per million (ppm) relative to the center line of the triplet at 77.1 ppm for deuteriochloroform. ¹³C NMR spectra were routinely run with broadband decoupling. Optical rotation data was obtained with a Jasco DIP-360 digital polarimeter at the sodium D line (589 nm) in the solvent and concentration indicated.

Compound 30: To a mixture of alkene **14c** (2.09 g, 3.33 mmol) and alkyne **7** (0.442 g, 1.51 mmol) in a V-shaped vial with a septum was added acetone (freshly distilled over calcium sulfate, 3 mL). The mixture was stirred at room temperature for 5 min to ensure formation of a homogeneous solution, and the septum was quickly removed to allow the addition of [CpRu(CNCH₃)₃]PF₆ (65 mg, 0.15 mmol) all at once. The reaction was stirred at room temperature for 40 h and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (10%, 12.5%, 15%, 17.5%, and 20%) to give 0.81 g of **30** as a pale yellow foam (56% yield, 9:1 dr determined by integrating peaks at 5.38 and 5.36 ppm). Significant amount of both alkene **14c** and alkyne **7** were recovered as an inseparable mixture (1.02 g, **14c/7** 7:1). [α]_D²³ -35.5 (c 0.6, CH₂Cl₂); ¹H NMR (500 MHz, C₆D₆) δ 7.66-7.61 (m, 4H), 7.23-7.17 (m, 10H), 6.80 (d, J = 8.6 Hz, 2H), 6.74 (d, J = 8.6 Hz, 2H), 5.38 (s, 1H), 4.50 (d, J = 11.6 Hz, 1H), 4.38-4.35 (m, 3H), 4.22-4.16 (m, 1H), 4.03 (dd, J = 1.7, 10.3 Hz, 1H), 3.81-3.75 (m, 1H), 3.69-3.63 (m, 2H), 3.53 (dd, J = 5.2, 10.0 Hz, 1H), 3.41 (dd, J = 5.3, 10.0 Hz, 1H), 3.29 (s, 3H), 3.27 (s, 3H), 3.07 (dd, J = 7.0, 17.3 Hz, 1H), 2.66 (d, J = 13.2 Hz, 1H), 2.40 (dd, J = 5.2, 17.3 Hz, 1H), 2.34 (dd, J = 5.2, 16.5 Hz, 1H), 2.29 (d, J = 12.6 Hz, 1H), 2.21 (dd, J = 5.6, 16.4 Hz, 1H), 2.09 (q, J = 12.3 Hz, 2H), 1.56-1.30 (m, 4H), 1.13 (s, 3H), 1.08 (s, 9H), 1.04 (s, 3H), 0.17 (s, 9H); ¹³C NMR (125 MHz, C₆D₆) δ 210.9, 168.9, 159.7, 153.7, 136.0, 135.9, 133.9, 133.7, 131.4, 131.0, 130.3, 130.2, 129.6, 129.3, 128.3, 128.1, 127.9, 123.6, 114.0, 80.1, 77.7, 75.3, 73.3, 73.0, 72.7, 65.7, 54.8, 54.7, 52.8, 45.6, 45.3, 39.6, 38.9, 38.3, 37.4, 26.9, 21.5, 20.4, 19.2, 0.4; IR (neat film) 3075, 3042, 1742, 1705, 1609, 1585, 1510, 1484, 1427, 1386, 1361, 1303, 1245, 1170, 1108, 1091, 1033, 839, 818, 739, 702 cm⁻¹, TLC R_f 0.37 (20% EtOAc/petroleum ether); EA Calcd for C₅₄H₇₂O₉Si₂: C, 70.40; H, 7.88. Found: C, 70.21; H, 7.80.

Compound 32: A solution of diol **31** (0.62 g, 0.9 mmol) and pyridinium p-toluenesulfonate (99 mg, 0.39 mmol) in CH₃OH (15 mL) and trimethyl orthoformate (0.75 mL) was heated under reflux for 2 h. The content was cooled to room temperature, poured into saturated

aqueous NaHCO₃, and extracted with EtOAc. The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (30%, 40%, and 50%) to give 0.47g of **32** as an oil (71% yield). [α]_D²³ –30.5 (c 1.4, CH₂Cl₂); ¹H NMR (500 MHz, C₆D₆) δ 7.82–7.77 (m, 4H), 7.24–7.20 (m, 6H), 5.83 (t, J = 2.1 Hz, 1H), 4.54–4.49 (m, 1H), 3.73–3.69 (m, 1H), 3.43–3.31 (m, 3H), 3.33 (s, 3H), 3.14–3.10 (m, 1H), 2.83 (s, 3H), 2.71–2.62 (m, 3H), 2.01–1.94 (m, 3H), 1.83–1.75 (m, 1H), 1.67–1.49 (m, 4H), 1.18–1.15 (m, 2H), 1.16 (s, 9H), 1.06 (s, 3H), 0.9 (s, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 171.6, 140.3, 136.3, 134.4, 134.2, 130.1, 128.3, 104.0, 100.8, 77.3, 74.4, 70.4, 69.4, 66.2, 65.8, 51.2, 48.0, 44.4, 43.4, 43.2, 42.0, 38.8, 36.5, 32.7, 27.1, 20.9, 19.5, 15.8; IR (neat film) 3446, 3073, 3047, 1734, 1632, 1588, 1472, 1428, 1388, 1357, 1260, 1105, 953, 821, 736, 701 cm^{–1}; TLC R_f 0.50 (50% EtOAc/petroleum ether); HRMS calcd for C₃₇H₅₃BrNaO₈Si [M+Na]⁺: 755.2591. Found: 755.2592.

Compound **39**: To a solution of aldehyde **38** (0.33 g, 0.75 mmol) in THF (1.3 mL) in a pressure tube at room temperature was added dimethyltitanocene (Petasis reagent)**75** in THF (0.52 M, 5.3 mL, 2.76 mmol). The tube was sealed and the reaction was heated at 90 °C for 2.5 h. The content was cooled to room temperature and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel with Et₂O/petroleum ether (20%, 30%, and 40%) to give 0.193 g of olefin **39** (58% yield). [α]_D²⁴ +3.3 (c 0.5, CH₂Cl₂); ¹H NMR (500 MHz, C₆D₆) δ 6.43 (dd, J = 10.8, 17.7 Hz, 1H), 6.21 (t, J = 1.0 Hz, 1H), 5.77 (s, 1H), 4.87 (dd, J = 1.5, 17.7 Hz, 1H), 4.82 (dd, J = 1.5, 10.8 Hz, 1H), 4.13 (ddt, J = 2.8, 5.5, 12.7 Hz, 1H), 3.91 (ddd, J = 1.2, 8.4, 10.5 Hz, 1H), 3.76 (dd, J = 1.8, 15.8 Hz, 1H), 3.48 (dq, J = 6.0, 8.4 Hz, 1H), 3.32 (s, 3H), 3.31 (s, 3H), 2.47 (ddd, J = 2.2, 11.8, 14.8 Hz, 1H), 1.61 (s, 3H), 1.48 (ddd, J = 2.1, 10.0, 12.2 Hz, 1H), 1.36 (s, 3H), 1.35 (s, 3H), 1.37–1.31 (m, 1H), 1.23 (s, 3H), 1.22 (s, 3H), 1.08 (d, J = 6.0 Hz, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 168.5, 166.4, 153.2, 146.6, 117.5, 108.8, 107.9, 103.0, 78.5, 77.2, 72.2, 68.8, 51.2, 50.7, 47.0, 38.6, 33.3, 27.5, 27.4, 24.3, 23.0, 20.8, 17.0; IR (neat film) 3076, 2996, 2931, 1746, 1719, 1664, 1460, 1433, 1370, 1230, 1157, 1094, 1048, 1021, 994 cm^{–1}; TLC R_f 0.59 (20% EtOAc/petroleum ether); HRMS calcd for C₂₂H₃₂O₇ [M–CH₄O]⁺: 408.2148. Found: 408.2129.

Compound **40**: A mixture of **39** (40 mg, 0.09 mmol) in 75% (v/v) aqueous acetic acid (7 mL) was stirred at room temperature for 6 h. The content was poured into ice-cooled saturated aqueous Na/K tartrate, neutralized with saturated aqueous Na₂CO₃, and extracted with EtOAc three times. The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography on silica gel with Et₂O/petroleum ether (50%) followed by CH₃OH/CH₂Cl₂ (6%) to give 34 mg of a triol contaminated by small amount (<10%) of impurity. [α]_D²⁴ –11.1 (c 0.55, CH₂Cl₂); ¹H NMR (500 MHz, C₆D₆) δ 6.43 (dd, J = 10.5, 14.0 Hz, 1H), 6.34 (d, J = 1.5 Hz, 1H), 5.54 (s, 1H), 4.94–4.89 (m, 2H), 4.33 (t, J = 10.6 Hz, 1H), 4.07 (dd, J = 2.1, 13.8 Hz, 1H), 3.77–3.73 (m, 1H), 3.44 (q, J = 6.2 Hz, 1H), 3.32 (s, 3H), 2.33 (t, J = 13.7 Hz, 1H), 1.80–1.74 (m, 1H), 1.67–1.61 (m, 1H), 1.61 (s, 3H), 1.28 (s, 3H), 1.23 (s, 3H), 1.05 (d, J = 6.1 Hz, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 168.8, 166.8, 152.2, 145.4, 120.3, 110.8, 100.1, 73.8, 72.8, 71.3, 67.1, 50.9, 45.7, 39.6, 23.0, 21.8, 21.0, 20.2, 19.5; IR (neat film) 3438 (br), 3076, 1743, 1721, 1683, 1635, 1437, 1410, 1369, 1234, 1152, 1080, 1031, 1017, 745, 728 cm^{–1}; TLC R_f 0.18 (6% CH₃OH/CH₂Cl₂); HRMS calcd for C₁₄H₂₁O₈ [M–C₅H₉]⁺: 317.1236. Found: 317.1240.

To a solution of the above triol (34 mg, 0.088 mmol) in DMF (2.5 mL) at –30 °C was added Et₃N (0.12 mL, 0.86 mmol), followed by TESCl (16.3 μ L, 0.097 mmol). The reaction was stirred at –30 °C for 30 min and the content was poured into saturated aqueous NaHCO₃. The mixture was extracted with EtOAc. The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography on

silica gel with EtOAc/petroleum ether (20% and 30%) to give 23 mg of **40** (52% yield over two steps). $[\alpha]_D^{22} -7.5$ (c 0.75, CH₂Cl₂); ¹H NMR (500 MHz, C₆D₆) δ 6.41-6.36 (m, 1H), 6.36 (s, 1H), 5.55 (s, 1H), 4.88 (d, J = 18.1 Hz, 1H), 4.87 (d, J = 11.6 Hz, 1H), 4.52 (t, J = 10.3 Hz, 1H), 4.20 (dd, J = 2.3, 13.9 Hz, 1H), 3.82-3.79 (br m, 1H), 3.57 (s, 1H), 3.51 (pent, J = 6.1 Hz, 1H), 3.30 (s, 3H), 2.65 (br d, J = 4.8 Hz, 1H), 2.40 (ddd, J = 2.0, 11.6, 13.6 Hz, 1H), 1.72-1.67 (m, 1H), 1.59 (s, 3H), 1.60-1.54 (m, 1H), 1.27 (s, 3H), 1.16 (s, 3H), 1.05 (d, J = 6.1 Hz, 3H), 0.95 (t, J = 7.9 Hz, 9H), 0.53 (q, J = 7.9 Hz, 6H); ¹³C NMR (125 MHz, C₆D₆) δ 168.6, 166.5, 152.0, 145.2, 120.4, 111.4, 99.6, 74.0, 72.0, 67.3, 50.7, 45.7, 39.8, 32.0, 22.4, 22.1, 21.0, 20.0, 7.1, 5.2; IR (neat film) 3408 (br), 3082, 1741, 1718, 1662, 1434, 1369, 1230, 1174, 1155, 1086, 1030 cm⁻¹; TLC R_f 0.52 (40% EtOAc/petroleum ether); HRMS calcd for C₂₅H₄₂O₇ [M-H₂O]⁺: 482.2700. Found: 482.2698.

Compound **48**: A mixture of **47** (40 mg, 0.075 mmol) and trimethyltin hydroxide (135 mg, 0.75 mmol) in CH₂Cl₂ (3.2 mL) in a sealed vial was heated with a microwave at 140 °C for 40 min. The mixture was cooled to room temperature and directly purified by flash chromatography on silica gel with EtOAc/petroleum ether (40%) followed by CH₃OH/CH₂Cl₂ (6% and 12%) to give 32 mg of **48** (82% yield). $[\alpha]_D^{23} +75.0$ (c 0.3, CH₂Cl₂); ¹H NMR (500 MHz, C₆D₆) δ 6.02 (s, 1H), 5.82 (ddd, J = 5.0, 11.0, 17.5 Hz, 1H), 5.51 (dd, J = 4.5, 11.3 Hz, 1H), 5.26 (d, J = 17.0 Hz, 1H), 5.01 (d, J = 11.0 Hz, 1H), 4.31 (t, J = 9.0 Hz, 1H), 3.86-3.82 (m, 1H), 3.74-3.69 (m, 1H), 3.58-3.53 (m, 1H), 3.05 (s, 1H), 3.04 (s, 3H), 2.94 (d, J = 13.0 Hz, 1H), 2.35-2.13 (m, 4H), 1.77-1.64 (m, 4H), 1.70 (s, 3H), 1.43 (q, J = 12.5 Hz, 1H), 1.36-1.30 (m, 1H), 1.30-1.23 (m, 1H), 1.10 (s, 3H), 1.04 (s, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 170.1, 140.6, 138.7, 114.8, 104.1, 100.6, 77.4, 74.5, 73.9, 65.3, 64.9, 48.3, 42.4, 42.3, 42.1, 41.8, 38.9, 36.9, 32.8, 20.8, 20.7, 17.0; IR (thin film) 3499 (br), 3077, 1735, 1434, 1365, 1245, 1159, 1129, 1060, 1021 cm⁻¹; TLC R_f 0.42 (8% CH₃OH/CH₂Cl₂).

Compound **60**: To a suspension of anhydrous CrCl₂ (99.99% from Aldrich, 2.0 g, 16.26 mmol) in freshly distilled THF (10 mL) at 0 °C was added a solution of **38** (470 mg, 1.06 mmol) and CHI₃ (2.53 g, 6.38 mmol) in THF (6 mL + 2 × 2 mL rinse) via cannula. The ice bath was removed and the brown suspension was stirred at room temperature in dark for 20 h before being poured into 1:1 brine/H₂O. The mixture was extracted with EtOAc. The combined organic extracts were concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (5%, 10%, and 20%) to give 158 mg of the vinyl iodide **60** (26% yield) and 208 mg of recovered aldehyde **38** (47% yield based on recovered starting material). $[\alpha]_D^{23} -9.7$ (c 0.9, CH₂Cl₂); ¹H NMR (500 MHz, C₆D₆) δ 7.08 (d, J = 15.0 Hz, 1H), 6.10 (s, 1H), 5.82 (s, 1H), 5.72 (d, J = 15.0 Hz, 1H), 4.07 (dddd, J = 2.5, 2.5, 5.0, 12.5 Hz, 1H), 3.81 (ddd, J = 2.0, 8.5, 10.5 Hz, 1H), 3.49-3.43 (m, 2H), 3.36 (s, 3H), 3.26 (s, 3H), 2.49 (dd, J = 12.0, 15.5 Hz, 1H), 1.75 (s, 3H), 1.354 (s, 3H), 1.352 (s, 3H), 1.34-1.28 (m, 3H), 1.24-1.18 (m, 2H), 1.07 (d, J = 6 Hz, 3H), 1.04 (s, 3H), 0.99 (s, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 168.8, 166.3, 153.8, 153.2, 116.4, 107.9, 102.2, 78.3, 77.2, 73.0, 71.0, 68.7, 50.7, 50.6, 50.4, 38.3, 34.3, 27.5, 23.1, 22.6, 20.9, 17.0; IR (neat film) 3072, 1745, 1719, 1662, 1596, 1433, 1380, 1367, 1227, 1165, 1095, 1042 cm⁻¹; TLC R_f 0.35 (16% EtOAc/petroleum ether); HRMS Calcd for C₂₃H₃₅IO₈ [M-CH₃]⁺: 551.1142. Found: 551.1165.

Compound **62**: To a cooled Et₂O (6 mL) at -78 °C was added *t*BuLi (1.7 in pentane, 3.44 mL, 5.84 mmol), followed by dropwise-addition of 5-bromo-1-pentene (0.3 mL, 2.95 mmol). The resultant yellow-green solution was stirred at -78 °C for 40 min and a solution of zinc chloride (0.41 g, 3.0 mmol, freshly flamed under a slow stream of nitrogen) in THF (6 mL) was added via cannula. The yellow-green colour disappeared upon the addition of zinc chloride. The cold bath was removed and the content was warmed to room temperature during which it turned cloudy white. The reaction was stirred at room temperature for 45

min and then the solvent was removed *in vacuo*. The residue was dissolved in THF (10 mL) to give 4-pentenyl zinc chloride **61** (0.3 M in THF).

To a mixture of vinyl iodide **60** (157 mg, 0.277 mmol) and Pd(PPh₃)₄ (32 mg, 0.03 mmol) at room temperature was added the above zinc reagent **61** (5 mL + 2 mL THF rinse). The content was stirred at room temperature for 7 h, poured into pH 7 phosphate buffer, and extracted with EtOAc. The combined organic extracts were concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (8% and 10%) to give 62 mg of triene **62** and 27 mg of **62** and **39** as a 5:1 mixture (68% combined yield).

$[\alpha]_D^{22}$ -12.7 (c 0.65, CH₂Cl₂); ¹H NMR (500 MHz, C₆D₆) δ 6.20 (s, 1H), 5.97 (d, J = 15.5 Hz, 1H), 5.81 (s, 1H), 5.76 (dddd, J = 7.0, 7.0, 10.5, 17.0 Hz, 1H), 5.33 (ddd, J = 6.5, 6.5, 13.0 Hz, 1H), 5.04 (dq, J = 2.0, 17.5 Hz, 1H), 4.98 (d, J = 10.5 Hz, 1H), 4.16 (dddd, J = 2.5, 2.5, 5.5, 13.0 Hz, 1H), 3.93 (ddd, J = 2.0, 8.5, 10.5 Hz, 1H), 3.65 (d, J = 15.5 Hz, 1H), 3.52-3.46 (m, 1H), 3.35 (s, 3H), 3.34 (s, 3H), 2.55-2.49 (m, 1H), 2.01-1.95 (m, 4H), 1.64 (s, 3H), 1.51-1.30 (m, 4H), 1.372 (s, 3H), 1.369 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H), 1.11 (d, J = 6 Hz, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 168.6, 166.4, 153.7, 138.9, 138.0, 125.8, 116.8, 114.8, 107.9, 103.0, 78.5, 77.2, 72.2, 68.6, 51.0, 50.7, 46.4, 38.6, 34.0, 33.8, 32.8, 29.0, 27.52, 27.46, 24.8, 24.2, 20.6, 17.1; IR (neat film) 3077, 1745, 1719, 1663, 1638, 1496, 1377, 1364, 1228, 1155, 1091, 1049, 1023 cm⁻¹; TLC R_f 0.47 (15% EtOAc/petroleum ether); HRMS Calcd for C₂₇H₄₁O₇ [M-CH₃O]⁺: 477.2852. Found: 477.2818.

Compound 64: To a mixture of DMAP (1.2 mg, 0.01 mmol) and MNBA (2-methyl-6-nitrobenzoic anhydride, 34.4 mg, 0.1 mmol) at room temperature was added CH₂Cl₂ (3.4 mL) and Et₃N (0.042 mL, 0.3 mmol). The content was stirred at room temperature for 5 min, after which a homogeneous light yellow solution was formed. The above prepared solution (1.5 mL) was added to acid **50** (23.7 mg, 0.039 mmol) in a V-shaped vial (rinsed with 0.3 mL of CH₂Cl₂). The mixture was stirred at room temperature for 15 min, and a solution of alcohol **63** (26.7 mg, 0.047 mmol) was added to the vial via cannula. The reaction was stirred at room temperature for 16 h and the content was purified by flash chromatography on silica gel with EtOAc/petroleum ether (5%, 10%, 15%, 20%, and 30%) to give 23 mg of **64** (51% yield). $[\alpha]_D^{23}$ +12.7 (c 0.3, CH₂Cl₂); ¹H NMR (600 MHz, C₆D₆) δ 6.33 (s, 1H), 6.14 (d, J = 15.6 Hz, 1H), 6.01 (s, 1H), 5.90-5.80 (m, 2H), 5.55 (td, J = 4.8, 11.4 Hz, 2H), 5.51 (s, 1H), 5.44 (dt, J = 6.6, 16.2 Hz, 1H), 5.38 (d, J = 17.4 Hz, 1H), 5.08 (dd, J = 1.2, 15.6 Hz, 1H), 5.02 (d, J = 10.8 Hz, 2H), 4.40 (quin, J = 4.8 Hz, 1H), 4.31 (d, J = 13.8 Hz, 1H), 4.11 (d, J = 13.8 Hz, 1H), 4.07 (t, J = 10.8 Hz, 1H), 3.97 (pent, J = 6.0 Hz, 1H), 3.88 (dd, J = 2.4, 11.4 Hz, 1H), 3.80-3.74 (m, 2H), 3.46 (s, 3H), 3.33 (s, 3H), 3.15 (s, 3H), 2.99 (s, 1H), 2.81 (dd, J = 4.2, 16.2 Hz, 1H), 2.60 (dd, J = 7.2, 16.2 Hz, 1H), 2.40-2.36 (m, 2H), 2.23 (dd, J = 6.0, 15.6 Hz, 1H), 2.15-2.12 (m, 2H), 2.09-2.04 (m, 2H), 1.99 (t, J = 12.6 Hz, 1H), 1.91-1.76 (m, 4H), 1.71 (s, 3H), 1.63-1.59 (m, 1H), 1.60 (s, 3H), 1.57-1.48 (m, 2H), 1.42 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H), 1.21 (d, J = 6.0 Hz, 3H), 1.20 (s, 3H), 1.10 (s, 3H), 1.07-1.01 (m, 18H), 0.69-0.63 (m, 12H); ¹³C NMR (125 MHz, C₆D₆) δ 172.0, 169.9, 168.6, 166.6, 166.5, 157.7, 152.2, 138.9, 138.8, 136.9, 120.5, 115.1, 114.8, 114.6, 104.5, 99.5, 77.9, 74.9, 74.3, 73.7, 73.6, 68.7, 67.9, 66.3, 66.2, 50.8, 50.6, 48.3, 45.2, 44.2, 44.0, 43.3, 42.4, 39.4, 35.9, 35.0, 33.8, 32.8, 31.7, 30.4, 30.2, 29.3, 23.7, 22.3, 20.93, 20.90, 20.7, 18.6, 16.9, 7.21, 7.19, 5.5, 5.2; IR (thin film) 3508, 3077, 1744, 1718, 1655, 1462, 1435, 1368, 1233, 1152, 1112, 1080, 1027, 910, 874, 744, 726 cm⁻¹; TLC R_f 0.63 (20% EtOAc/petroleum ether); HRMS calcd for C₆₁H₁₀₆O₁₇Si₂N [M+NH₄]⁺: 1180.6999. Found: 1180.6974.

Compound 66 and 67: To a solution of **64** (20 mg, 0.018 mmol) in benzene (8 mL) at 50 °C with N₂ sparging was added Hoveyda catalyst **65** (4.5 mg, 18 mol%) in benzene (2 mL) via

a syringe over 5 min. The content was stirred at 50 °C for 30 mins before raising the bath temperature to 80 °C. Stirring was continued for 15 min at 80 °C. The content was cooled to room temperature. The solvent was removed under reduced pressure and the residue was purified by preparative TLC with EtOAc/petroleum ether (16%) to give 16 mg of **66** and **67** (80% combined yield) as 1:1 mixture by integrating peaks at 3.36 and 3.32 ppm in ^1H NMR. HPLC retention time: 5.72 min and 7.07 min (Alltech-Econosphere silica 3 micro column; 99:1 heptane:isopropanol; 254 nm; 1 mL/min); ^1H NMR (500 MHz, C_6D_6) δ 6.34-6.33 (m), 6.09 (s), 6.02-5.97 (m), 5.90-5.84 (m), 5.79-5.75 (m), 5.67-5.62 (m), 5.59-5.53 (m), 5.52 (s), 5.46 (s), 5.45-5.34 (m), 4.67-4.61 (m), 4.52 (t, J = 9.0 Hz), 4.41-4.29 (m), 4.20-4.14 (m), 4.08 (d, J = 12.0 Hz), 4.04-3.87 (m), 3.82-3.76 (m), 3.45 (s), 3.43 (s), 3.36 (s), 3.32 (s), 3.19 (s), 3.13 (s), 3.12 (s), 3.02 (s), 2.85 (d, J = 4.5 Hz), 2.82 (d, J = 4.0 Hz), 2.57-2.46 (m), 2.39-2.32 (m), 2.25-1.67 (m), 1.50 (d, J = 6.5 Hz), 1.46 (d, J = 10.0 Hz), 1.37 (s), 1.18 (d, J = 7.5 Hz), 1.14 (d, J = 6.5 Hz), 1.08-0.95 (m), 0.69-0.52 (m); ^{13}C NMR (125 MHz, C_6D_6) δ 172.0, 170.8, 170.2, 169.9, 168.7, 168.2, 166.7, 166.49, 166.47, 166.40, 158.2, 157.5, 152.0, 151.9, 136.6, 135.8, 132.32, 132.25, 131.8, 131.0, 125.8, 121.1, 120.3, 115.4, 114.6, 104.5, 103.9, 100.3, 99.0, 78.4, 74.8, 74.7, 74.42, 74.39, 74.25, 73.5, 73.4, 69.2, 68.4, 67.8, 66.5, 66.4, 66.2, 66.0, 64.5, 50.79, 50.74, 50.6, 50.4, 48.9, 47.8, 45.5, 45.3, 44.2, 44.0, 43.6, 43.2, 43.0, 42.95, 42.2, 40.4, 39.7, 36.5, 36.2, 35.8, 35.0, 34.3, 33.9, 33.3, 32.0, 31.6, 31.2, 30.9, 30.4, 30.3, 30.2, 28.1, 27.2, 26.1, 25.4, 25.0, 21.6, 21.3, 20.8, 19.4, 18.5, 17.7, 15.6, 7.25, 7.19, 7.10, 6.0, 5.8, 5.2; IR (thin film) 3510, 1721, 1650, 1431, 1370, 1232, 1156, 1113, 1080, 1023, 728, 724 cm^{-1} ; HRMS calcd for $\text{C}_{59}\text{H}_{98}\text{O}_{17}\text{Si}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 1157.6240. Found: 1157.6104.

Compound **68** and **69**: A solution of **66** and **67** (7 mg, 0.006 mmol) and PPTS (8 mg, 0.032 mmol) in CH_3OH was stirred at room temperature for 4 h. The content was poured into saturated NaHCO_3 and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by preparative TLC (60% EtOAc/PE) to give 2.6 mg of **68** and 2 mg of **69** (82% combined yield). Characterization for **68**: $[\alpha]_{\text{D}}^{24} +72.2$ (c 0.53, CH_2Cl_2); ^1H NMR (600 MHz, C_6D_6) δ 6.34 (d, J = 1.8 Hz, 1H), 5.92 (d, J = 16.2 Hz, 1H), 5.87 (s, 1H), 5.75 (dd, J = 7.2, 10.8 Hz, 1H), 5.47 (s, 1H), 5.46-5.42 (m, 2H), 5.39-5.34 (m, 1H), 5.32 (ddd, J = 3.0, 6.0, 10.8 Hz, 1H), 4.49 (t, J = 9.0 Hz, 1H), 4.37-4.33 (m, 2H), 4.20 (tt, J = 2.4, 11.4 Hz, 1H), 4.11 (dd, J = 1.8, 13.8 Hz, 1H), 3.90 (br, 1H), 3.66-3.62 (m, 1H), 3.60-3.56 (m, 1H), 3.51 (pent, J = 6.0 Hz, 1H), 3.46 (s, 3H), 3.33 (s, 3H), 3.17 (br, 1H), 2.82 (s, 3H), 2.30-2.14 (m, 7H), 2.12-2.07 (m, 1H), 2.03 (d, J = 12.6 Hz, 1H), 1.99 (dd, J = 3.0, 13.2 Hz, 1H), 1.86 (t, J = 13.2 Hz, 1H), 1.76 (s, 3H), 1.72-1.56 (m, 5H), 1.62 (s, 3H), 1.53-1.51 (m, 1H), 1.44-1.40 (m, 1H), 1.41 (s, 3H), 1.37 (s, 3H), 1.15-1.11 (m, 1H), 1.11 (s, 3H), 1.07-1.03 (m, 1H), 1.00 (s, 3H), 0.92 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 170.8, 169.9, 168.5, 166.7, 156.9, 152.2, 136.7, 132.0, 131.3, 129.4, 120.3, 115.4, 104.7, 99.4, 75.3, 74.97, 74.93, 69.93, 66.6, 66.4, 65.8, 50.64, 50.62, 47.9, 45.3, 44.6, 44.2, 42.5, 40.6, 39.0, 36.8, 36.3, 31.7, 31.2, 30.9, 28.5, 26.7, 25.2, 21.5, 10.9, 20.8, 20.6, 19.5, 16.3; TLC R_f 0.44 (75% EtOAc in petroleum ether); IR (film) 3482, 1718, 1652, 1434, 1365, 1234, 1155, 1025, 983, 872 cm^{-1} ; HRMS calcd for $\text{C}_{47}\text{H}_{70}\text{O}_{17}\text{Na}$ $[\text{M}+\text{Na}]^+$: 929.4513. Found: 929.4535. Characterization for **69**: $[\alpha]_{\text{D}}^{23} +36.6$ (c 0.24, CH_2Cl_2); ^1H NMR (600 MHz, C_6D_6) δ 6.49 (d, J = 1.2 Hz, 1H), 5.97 (d, J = 15.6 Hz, 1H), 5.84-5.80 (m, 2H), 5.73 (s, 1H), 5.55 (s, 1H), 5.56-5.48 (m, 2H), 5.23 (ddd, J = 1.8, 6.6, 11.4 Hz, 1H), 4.30-4.24 (m, 3H), 4.13 (dd, J = 2.4, 13.8 Hz, 1H), 3.94 (d, J = 9.6 Hz, 1H), 3.83-3.71 (m, 3H), 3.52 (pent, J = 6.6 Hz, 1H), 3.46 (br s, 1H), 3.39 (s, 3H), 3.26 (s, 3H), 3.09 (s, 3H), 2.35-2.30 (m, 1H), 2.20 (dd, J = 7.8, 16.8 Hz, 1H), 2.14-2.10 (m, 2H), 2.09-1.98 (m, 4H), 1.92 (dd, J = 3.0, 13.2 Hz, 1H), 1.86 (d, J = 13.8 Hz, 1H), 1.74 (s, 3H), 1.71-1.67 (m, 1H), 1.62 (s, 3H), 1.61-1.53 (m, 5H), 1.48-1.43 (m, 1H), 1.42 (s, 3H), 1.27 (s, 3H), 1.23-1.19 (m, 1H), 1.14 (s, 3H), 1.08-1.04 (m, 1H), 1.05 (s, 3H), 0.97 (d, J = 6.6 Hz, 3H); TLC R_f 0.63 (75% EtOAc in petroleum ether); IR (film) 3454, 1718, 1648, 1434, 1369,

1234, 1155, 1030, 974 cm^{-1} , HRMS calcd for $\text{C}_{47}\text{H}_{70}\text{O}_{17}\text{Na}$ $[\text{M}+\text{Na}]^+$: 929.4513. Found: 929.4597.

Compound (*R*)-**70**: Dess–Martin periodinane (6.95 g, 16.4 mmol) was added to a mixture of *rac*-**70** (5.49 g, 15.6 mmol) and NaHCO_3 (4.2 g, 49.9 mmol) in DCM (66 ml) at 0 °C. The reaction was stirred at rt for 30 min, before being quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$ and saturated NaHCO_3 . The mixture was extracted with ethyl acetate (150 ml $\times$ 3), and the combined organic fraction was dried over Na_2SO_4 . The solvent was removed, and the crude ketone was dissolved with DCM (112 ml). The above solution was cooled to -78 °C, and (*S*)-2-methyl-CBS-oxazaborolidine (0.78 ml, 1M in toluene) was added. The reaction was stirred at -78 °C for 20 min before catechol borane (2.8 g, 23.4 mmol) was added. The resulting solution was stirred at -78 °C for 4 h, and then it was warmed to 0 °C. The reaction was stirred at 0 °C for 1h, before being quenched with 1M NaH_2PO_4 . The mixture was extracted with ethyl acetate and the combined organic fractions were dried over Na_2SO_4 . Compound (*R*)-**70** was purified via silica gel flash column chromatography (5% Et_2O /petroleum ether, then 10% Et_2O /petroleum ether) to give a colorless oil (4.9 g, 90% over two steps, 90% ee, determined by chiral HPLC, OD 205 nm, 0.8 ml/min, 99.5:0.5 heptane/*i*PrOH, $t_{\text{major}} = 7.9$ min, $t_{\text{minor}} = 7.2$ min). $[\alpha]_{\text{D}}^{20}$: +4.86 (c 0.64, DCM). R_f : 0.35 (10% Et_2O /petroleum ether, 1:9 v/v); ^1H NMR (CDCl_3 , 500 MHz) δ 5.72 (dd, $J = 1.0$, 20 Hz, 1H), 5.47 (dd, $J = 8.0$, 20 Hz, 1H), 4.20 (m, 1H), 3.28 (s, 2H), 2.45 (dd, $J = 2.5$, 7.5 Hz, 2H), 2.02 (br, 1H), 0.97 (s, 3H), 0.88 (s, 12H), 0.15 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 140.1, 128.0, 103.0, 87.5, 71.7, 71.1, 38.2, 29.4, 26.0, 24.0, 18.4, 0.2, -5.4 ; IR (film): 3336 (br), 2958, 2858, 2178, 1464, 1250, 1099, 843 cm^{-1} ; HRMS ($\text{C}_{15}\text{H}_{29}\text{O}_2\text{Si}_2+\text{tBu}$): Calcd. 297.1706 $[\text{M}-\text{tBu}]^+$, Found 297.1684.

Compound **79**: $[\text{CpRu}(\text{CH}_3\text{CN})_3]^+\text{PF}_6^-$ (1.4 mg, 0.0032 mmol) was added to a solution of compound (*R*)-**70** (11.2 mg, 0.032 mmol) and compound **73** (17.4 mg, 0.094 mmol) in DCM (0.5 ml) at 0 °C. The resulting yellow solution was stirred at room temperature for 12 h. The tetrahydropyran was isolated via silica gel flash column chromatography as a mixture contaminated with (*R*)-**70**. To the above mixture was added THF (0.4 ml), and the resulting solution was cooled to 0 °C before $\text{HF}\cdot\text{py}$ (5 drops) was added. The reaction mixture was stirred vigorously for 5h at rt, before being quenched with saturated aqueous NaHCO_3 . The mixture was extracted with ethyl acetate (20 ml $\times$ 3), and the combined organic fractions were dried over Na_2SO_4 . Compound **79** was purified via silica gel flash column chromatography (petroleum ether/ethyl acetate = 4/1, and then 3/2) as a colorless oil (8.3 mg, 62%, dr 6.7:1, δ_{major} : 2.91 ppm, δ_{minor} : 2.80 ppm): R_f : 0.35 (40% ethyl acetate in petroleum ether); $[\alpha]_{\text{D}}^{20}$: -1.5 (c 0.40, DCM); ^1H NMR (CDCl_3 , 500 MHz) δ 5.60 (dd, $J = 1.0$, 16 Hz, 1H), 5.48 (dd, $J = 5.5$, 16 Hz, 1H), 5.29 (s, 1H), 4.10 (dd, $J = 11$, 24 Hz, 2H), 3.88 (m, 1H), 3.76 (m, 1H), 3.33 (s, 2H), 2.91 (dd, $J = 6.0$, 17 Hz, 1H), 2.53 (dd, $J = 7.0$, 17 Hz, 1H), 2.41 (dt, $J = 2.0$, 13.5 Hz, 1H), 2.24 (d, $J = 13$ Hz, 1H), 2.03 (s, 3H), 2.02–1.93 (2H), 1.16 (s, 3H), 1.15 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H), 0.10 (s, 9H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 210.9, 171.1, 152.4, 138.2, 129.9, 124.3, 79.0, 75.0, 71.7, 70.0, 47.8, 45.2, 44.1, 40.7, 38.5, 24.1, 23.8, 21.7, 21.67, 21.1, 0.5; IR (film) 3473, 2956, 1747, 1702, 1624, 1472, 1375, 1247, 1140, 1046, 974, 840 cm^{-1} ; HRMS ($\text{C}_{23}\text{H}_{40}\text{O}_5\text{Si}$): Calcd. 447.2543 for $[\text{M}+\text{Na}]^+$, Found 447.2545.

Compound **71**: To a mixture of $\text{Au}(\text{PPh}_3)_3\text{Cl}$ (10.2 mg, 0.020 mmol) and AgSbF_6 (7.0 mg, 0.020 mmol) was added dry DCM (0.4 ml) at room temperature under N_2 . The resulting mixture was stirred in the dark for 15 min, and a purple precipitate was formed. The supernatant solution (0.030 ml, ca 0.0015 mmol, 20 mol%) was added to a mixture of compound **82** (4.5 mg, 0.0071 mmol) and NaHCO_3 (2.0 mg, 0.021 mmol) in CH_3CN (0.10 ml) at 0 °C under N_2 . The resulting reaction mixture was stirred vigorously in the dark at room temperature for 4 days. The suspension was poured into pH 7.0 buffer, and the mixture

was extracted with ethyl acetate four times and the combined organic fractions were dried over Na_2SO_4 . The dihydropyran products were isolated via silica gel flash column chromatography (20%, 30%, 40% then 50% ethyl acetate/petroleum ether) as a light-yellow oil (2.4 mg, 53%, ratio of **71** : **83** : **84** = 5.1 : 1 : 1.3, based on the integration of ^1H NMR peaks δ 5.34, 6.80, 6.05 ppm respectively); R_f : 0.60 (40% ethyl acetate in petroleum ether); $[\alpha]_D$: 16.1 (c 0.24, DCM); For NMR data, see the supporting information. IR (film) 34854 (br), 2953, 2931, 1708, 1610, 1379, 1226, 1153, 1094, 840 cm^{-1} ; HRMS ($\text{C}_{35}\text{H}_{56}\text{O}_8\text{Si}$): Calcd. 655.3642 for $[\text{M}+\text{Na}]^+$, Found 655.3636.

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36. Compounds **66** and **67** could still lead to bryostatin if they undergo further reaction with Ru-alkylidene catalysts. However, treatment of macrocycle **66** and **67** under forced metathesis conditions did not provide any desired 26-membered product.
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Figure 1.
Stereoselective assembly of bryostatin A-, B- and C-ring subunits.

Figure 2.

Figure 3.
A new enone substrate.

Figure 4.
Key ROESY correlations observed for **40**.

Figure 5.
X-ray crystal structure of bryostatin 1 from ref 2a.

Figure 6.
Key ROESY correlations observed for **64**.

Figure 7.

Figure 8.
Linchpin: fragment **70**.

Scheme 1.
Retrosynthetic analysis.

Scheme 3.
Synthesis of **14b**.

Scheme 4.
 Synthesis of **14c**.

Scheme 5.
Synthesis of the C1-C16 fragment.

Scheme 6.
Synthesis of the C17-C27 fragment **40**.

Scheme 7.
Synthesis of **41** and **42**.

Scheme 8.
Unsuccessful RCM: a possible explanation.

Scheme 9.

Scheme 10.
Relay ring-closing metathesis: a possible solution.

Scheme 11.
Synthesis of precursor **64** for relay ring-closing metathesis.

Scheme 12.
Final deprotection of **66** and **67**.

Scheme 13.
Retrosynthetic analysis of compound **71**.

Scheme 14.
Asymmetric synthesis of fragment **70**.

Scheme 15.
A Weinreb-amide route.

Scheme 16.
Synthesis of **79**.

Scheme 17.
Synthesis of alkyne **72**.

Scheme 18.
Bronsted acids-catalyzed olefin isomerization.

Scheme 19.
5-*exo* vs 6-*endo* addition.

Table 1Olefination of **38**.

Entry	Conditions	Observation	Yield
1	$\text{Ph}_3\text{P}=\text{CH}_2$, $-30\text{ }^\circ\text{C}$ – $0\text{ }^\circ\text{C}$	an unknown byproduct	0
2	CH_2I_2 , Zn, Me_3Al , $25\text{ }^\circ\text{C}$	mainly 38	trace
3	CH_2I_2 , Zn, PbI_2 , TiCl_4 , $0\text{ }^\circ\text{C}$ – $25\text{ }^\circ\text{C}$	decomposition of 38	0
4	$\text{TMSCH}_2\text{CeCl}_2$, THF, $-78\text{ }^\circ\text{C}$	Only 38	0
5	CH_2I_2 , Zn, Me_3Al , $\text{BF}_3\cdot\text{OEt}_2$, $25\text{ }^\circ\text{C}$	38 + decomposition	0
6		38 + decomposition	0
7	$\text{Cp}_2\text{Ti}(\text{CH}_3)_2$	39 + a byproduct from ester olefination	58%

Table 2Relay ring-closing metathesis studies of compound **64**.

Entry	Conditions	Results
1	18 mol% Hoveyda catalyst 45 , benzene, 50 –80 °C, N ₂ sparging	80% yield (66 : 67 = 1:1)
2	ca 20 mol% the second generation Grubbs Catalyst 65 , toluene, reflux, N ₂ sparging	Small scale reaction, clean by TLC and NMR (66 : 67 = 1:2.3)

Table 3

Biological activities of bryostatin analogues..

Sample	SKBR3	SKOV3	NCI-ADR
68	560 nM	840 nM	1100 nM
69	52 nM	66 nM	123 nM

The numbers are the half maximal inhibitory concentrations (IC₅₀) of **68** and **69** in cell growth inhibition assays. SKBR3: a breast cancer cell line. SKOV3: an ovarian cancer cell line. NCI-ADR: a breast cancer cell line with multi-drug resistant pumps.

Table 46-*Endo-dig* cyclization of enyne **82**.

Entry	Conditions	Results
1	PdCl ₂ (CH ₃ CN) ₂ (17 mol%), TDMPP (10 mol%), THF, rt	6- <i>endo</i> (71 + 83):5- <i>exo</i> (84) ca 1:1
2	Pd(OAc) ₂ (20 mol%), TDMPP (20 mol%), then Pd(TFA) ₂ (30 mol%), benzene, rt	71 : 83 : 84 = 1.5:0.5:1 (ca 10% 82 + ca 30% 85)
3	[Au(PPh ₃)] ⁺ SbF ₆ ⁻ (20 mol%) CH ₃ CN, NaHCO ₃ , rt	53% yield (71 : 83 : 84 = 5.1:1:1.3)