DOI: 10.1002/chem.201002932

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

Barry M. Trost,* Hanbiao Yang, and Guangbin Dong[a]

Abstract: Herein, we report 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. Ring-closing metathesis was utilized to form the 31-membered ring macrocycle of the analogue. These ring-expanded bryostatin analogues possess anticancer activity against several cancer cell lines. Given the difficulty in forming the C16–C17 olefin at a late stage, we also describe our development of a new-generation strategy to access the C7–C27 fragment, containing both the ring B and C subunits.

Keywords: bryostatins · domino reactions · metathesis · palladium · ruthenium

Introduction

In previous papers, we have described our development of chemoselective and atom-economical methods for the stereoselective assembly of the bryostatin ring A, B, and C subunits (Scheme 1). Consequently, efforts have been made towards the total synthesis of the bryostatins by taking advantage of these methods.[1] Herein, we report a full account of our synthesis and biological evaluation of two novel ring-expanded bryostatin analogues by using ring-closing metathesis (RCM) as the macrocyclization method. Given the difficulty in forming the C16–C17 olefin in the late stages of the synthesis, we also describe the development of a new-generation strategy to access the C7–C27 fragment containing the ring B and C subunits.

Results and Discussion

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

In our two preceding articles, we described our efforts to develop atom-economic transformations for the synthesis of the ring A, B, and C subunits of the bryostatins. Importantly, a high degree of stereocontrol of the geometry of the exocyclic methyl enoate 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 enoates towards both acids and bases. The impressive progress of strategies for performing RCM reactions in organic synthesis and the mildness of the reaction conditions prompted us to evaluate its use for our bryostatin total synthesis (Scheme 2).[7]

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

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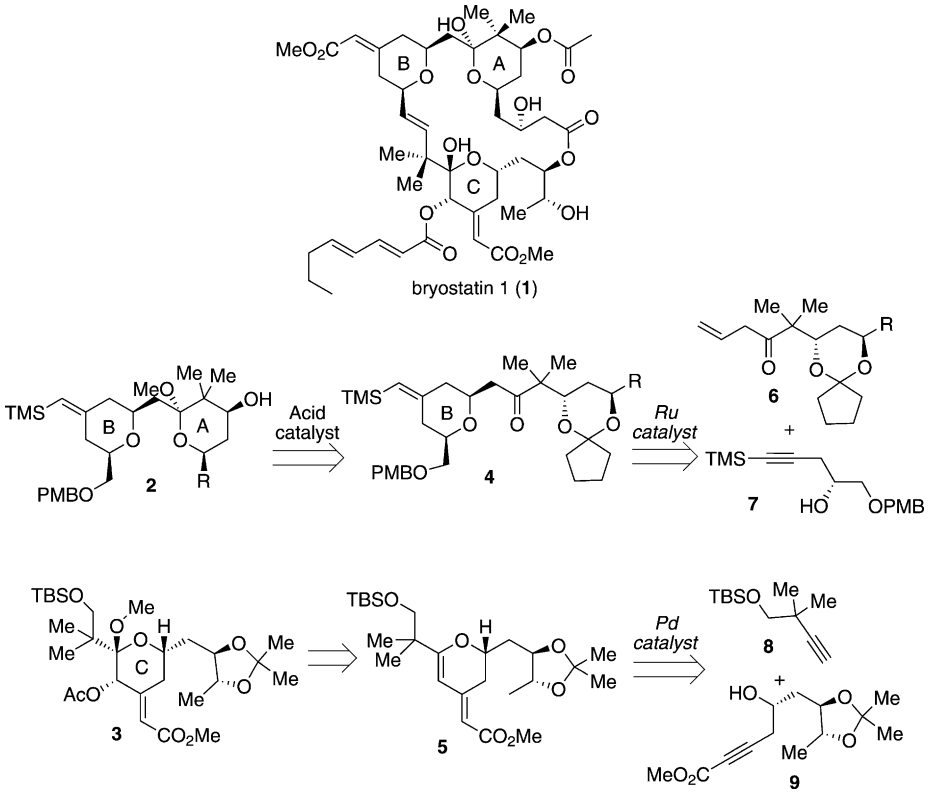
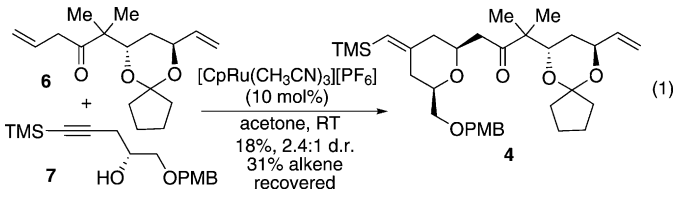
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201002932.



Scheme 1. Stereoselective assembly of the bryostatin ring A, B, and C subunits.

Synthesis of the northern C1–C16 fragment: Our synthesis of

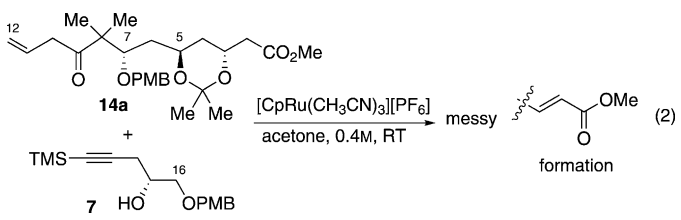


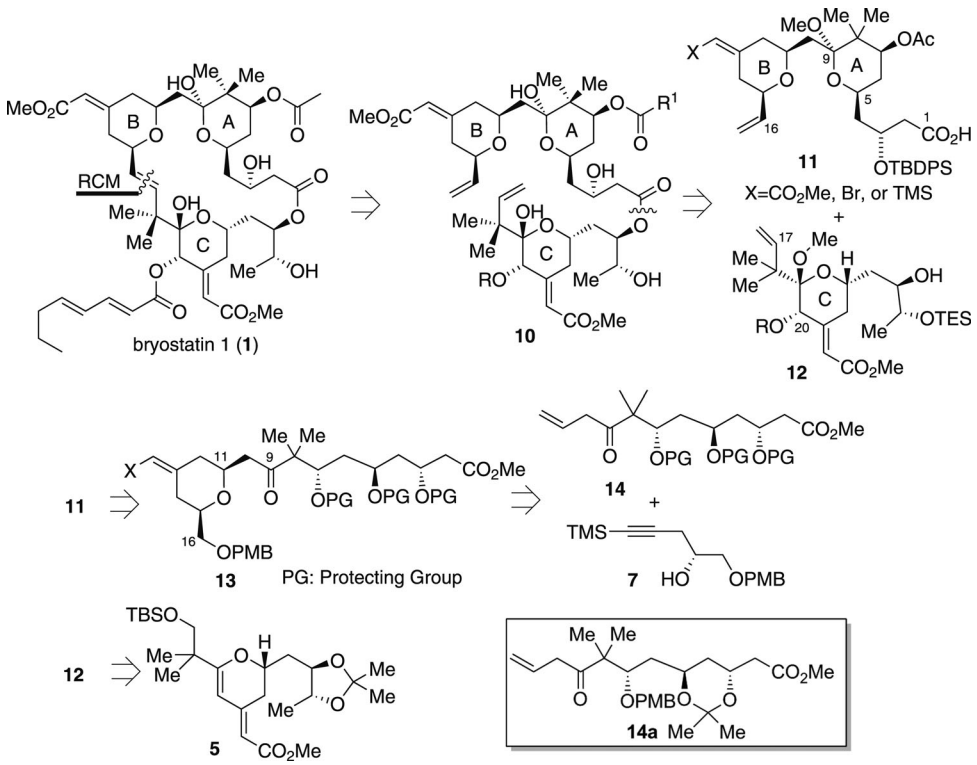
14a (Scheme 3) commenced with (*R*)-pantolactone, which was converted to alcohol **15** in five steps [exhaustive reduction with lithium aluminum hydride (LAH), selective protection of the C7 and C9 alcohols as a 4-methoxylbenzaldehyde acetal, TEMPO-catalyzed oxidation[10] of the C5 alcohol, Wittig olefination, and diisobutylaluminum hydride (DIBAL-H) reduction] following a procedure by White et al. and Mukaiyama et al.[11,12] *tert*-Butyl silyl (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 $[Ti(OiPr)_2Cl_2]$-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 et al.[13] Subsequent hydroxyl-directed *anti*-reduction[14] ($Me_4NBH(OAc)_3$, $AcOH/CH_3CN$, −35°C) set the C3 stereochemistry with excellent yield (96%) and diastereoselectivity (≈15:1).

To proceed, 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, although 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, $NaHCO_3$, CH_2Cl_2) resulted in β,γ-enone **14a**.

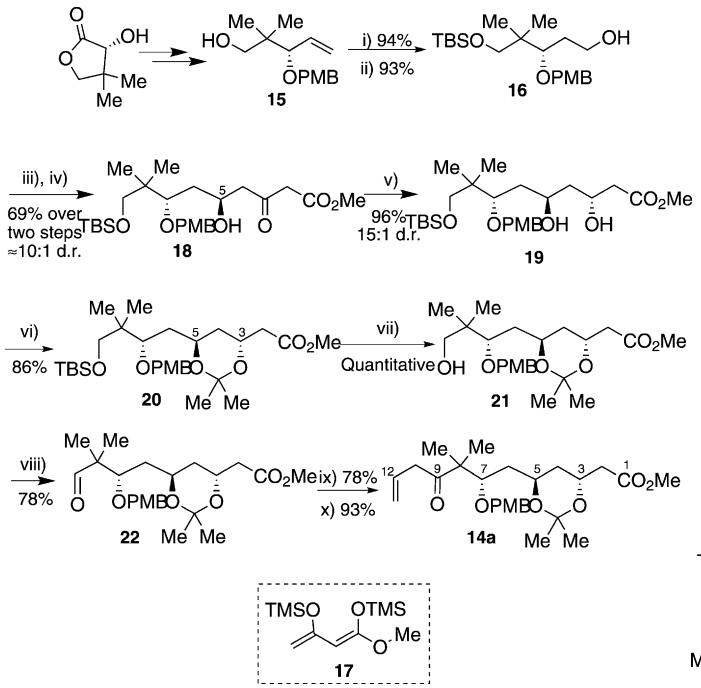
With enone **14a** in hand, the Ru-catalyzed tandem coupling reaction of **7** with **14a** was then investigated [Eq. (2)]. Unfortunately, the reaction provided a complex mixture and none of the desired coupling product was obtained. Nevertheless, we were able to identify an apparent signal at 6.69 ppm ($CDCl_3$, dt, $J=10.5$, 17.0 Hz) in the crude ^1H NMR spectrum, which indicated the formation of a *trans*-α,β-unsaturated ester during the reaction.

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 to-



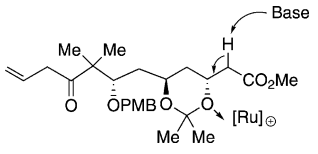


Scheme 2. Retrosynthetic analysis of the bryostatins.



Scheme 3. Synthesis of compound **14a**. i) Tributylsilyl triflate (TBSOTf), Et_3N; ii) 9-borabicyclo[3.3.1]nonane (9-BBN); iii) 2,2,6,6-tetramethylpiperadin-1-yl)oxyl (TEMPO), KBr, NaOCl, CH_2Cl_2/H_2O; iv) **17**, [Ti(O-*i*Pr)$_2$Cl$_2$], $PhCH_3$, −78 °C; v) $(CH_3)_4NBH(OAc)_3$, $AcOH/CH_3CN$, −35 °C; vi) 2,2-dimethoxypropane, pyridinium *p*-toluenesulfonate (PPTS), DMF, RT; vii) $Et_3N{\cdot}3HF$, THF, RT; viii) Dess–Martin Oxidation; ix) allyl iodide, In, DMF; x) Dess–Martin Oxidation.

wards β-alkoxy elimination (Scheme 4). The C5-oxygen could consequently be deprotected and then participate in

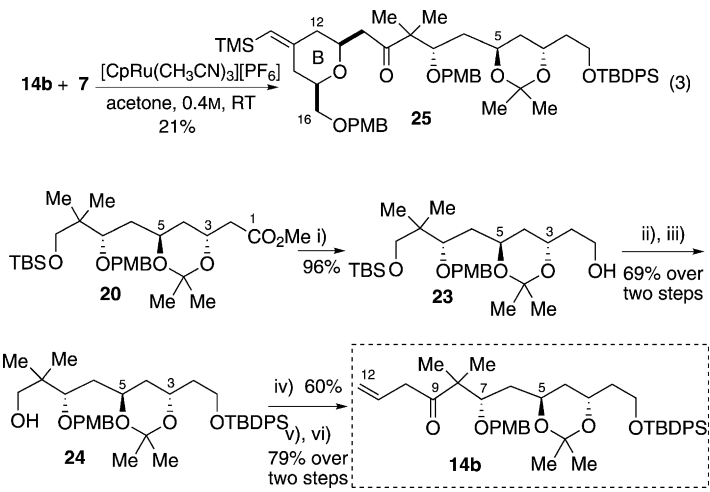


Scheme 4. The β-alkoxy elimination of **14a**.

other reactions, such as the formation of a hemiketal. If this hypothesis is correct, removal of the ester group should minimize the β-alkoxy-elimination pathway.

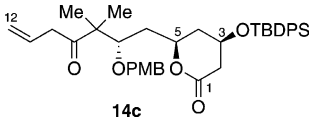
To this end, the synthesis of a new β,γ-enone **14b** was pursued (Scheme 5). Methyl ester **20** was converted into alcohol **24** through a straightforward three-step transformation (LAH reduction, deprotection of the TBS ether, and selective protection of the C1-hydroxyl group with TBDPSCl). The β,γ-enone was installed in three steps as previously described (Dess–Martin oxidation, indium-mediated allylation, and Dess–Martin oxidation) to furnish **14b**.

To our delight, treatment of **14b** and alkyne **7** with $[CpRu(CH_3CN)_3][PF_6]$ under the optimized conditions (0.4 M in acetone, 40 h) gave the desired dihydropyran **25**, although the in low yield [21 %; Eq. (3)].



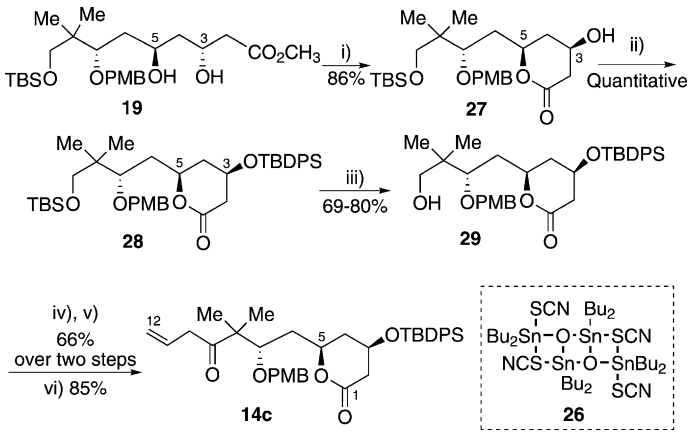
Scheme 5. Synthesis of **14b**. i) LAH, THF; ii) $Et_3N{\cdot}3HF$, THF; iii) *t*-butyldiphenylsilyl chloride (TBDPSCl), DMF; iv) Dess–Martin Oxidation; v) allyl iodide, In, DMF; vi) Dess–Martin Oxidation.

It is likely that the problem was caused by the acid sensitivity of the acetonide in **14a** and **b**, 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 (Scheme 6). Both the lactone and the TBDPS ether moieties in **14c** were expected to be stable under the reaction conditions. Furthermore, the lactone would protect both the C5-hydroxyl group and the C1-ester moiety, thus minimizing protecting group manipulations.



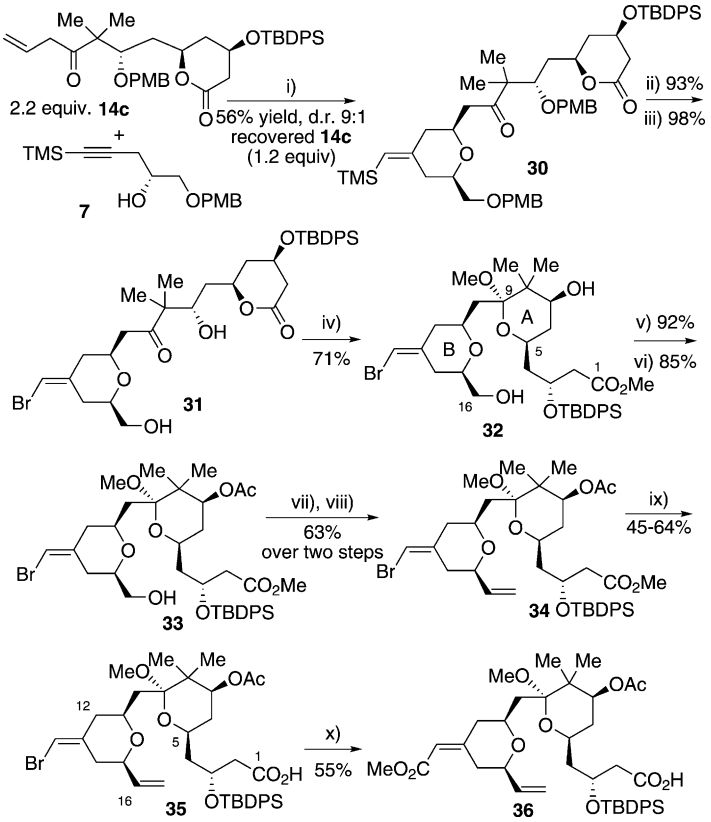
Scheme 6. A new enone substrate.

The synthesis of enone **14c** is outlined in Scheme 7. Starting from diol **19**, the two hydroxyl groups at C3 and C5 were differentiated by lactonization, which was best achieved with the Otera catalyst (**26**).[17] The use of PPTS gave inferior results in terms of both yield and conversion. Protection of the C3 alcohol (TBDPSCl, DMF, imidazole) required heating (50 °C) as 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 (56% over three steps).



Scheme 7. Synthesis of **14c**. i) **26** (10 mol%), hexane, reflux; ii) TBDPSCl, imidazole, DMF, 50 °C; iii) AcOH/H_2O (4:1); iv) Dess–Martin oxidation; v) allyl iodide, In, DMF, RT; vi) Dess–Martin oxidation.

With enone **14c** in hand, the crucial Ru-catalyzed tandem coupling was investigated (Scheme 8). 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 (minor) and 5.38 ppm (major) and

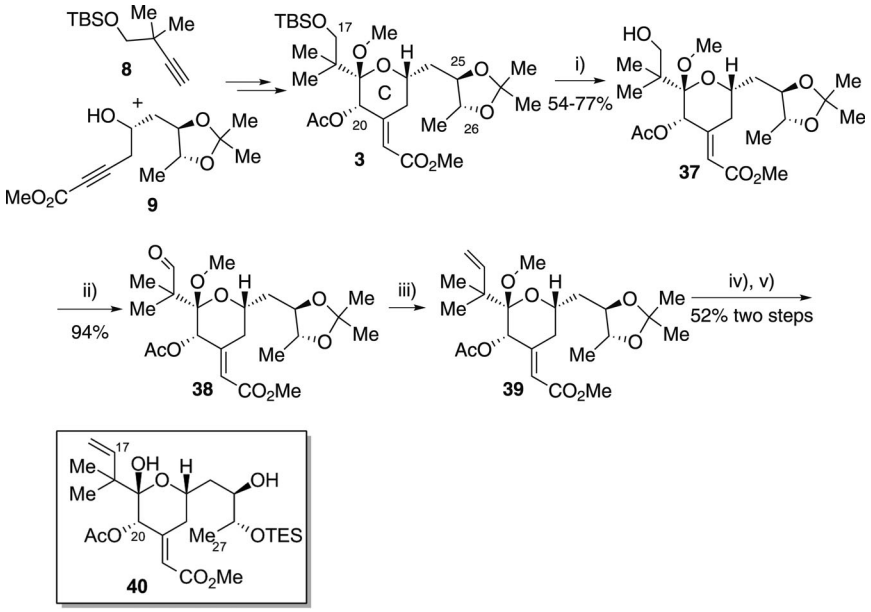


Scheme 8. Synthesis of the C1–C16 fragment. i) $[CpRu(CH_3CN)_3][PF_6]$ (10 mol%; Cp = cyclopentadienyl), acetone, RT; ii) *N*-bromosuccinimide (NBS), DMF; iii) $BF_3{\cdot}OEt_2$, CH_2Cl_2, $HS(CH_2)_3SH$, 0 °C; iv) PPTS, CH_3OH, $CH(OCH_3)_3$, reflux; v) triethylsilyl chloride (TESCl), 4-dimethylaminopyridine (DMAP) then pyridine, Ac_2O; vi) PPTS, CH_3OH; vii) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C to RT; viii) Ph_3PCH_3Br, *n*BuLi; ix) $(CH_3)_3SnOH$, 1,1-dichloroethene (DCE), 140 °C, microwave; x) $[Pd(PPh_3)_4]$, CO, DMF/CH_3OH, 85 °C.

the incorporation of two PMB groups in the ^1H NMR spectrum (500 MHz, C_6D_6) suggested a successful coupling. This was later confirmed by ^{13}C NMR spectroscopy and elemental analysis. Assignment of the $\delta = 5.38$ ppm signal (belonging to the vinylsilane proton) as the *cis*-isomer was based on previous model studies and later confirmed by 2D NMR experiments on late stage compounds. Furthermore, we were able to reduce the enone/alkyne ratio to 2.2:1 and recover 1.2 equivalents 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 by using $BF_3{\cdot}Et_2O$ and 1,3-propanedithiol in CH_2Cl_2 at 0 °C to give diol **31**. The shift of the vinyl proton resonance from 5.38 to 6.04 ppm, disappearance of both PMB groups in the ^1H NMR spectrum, and appearance of a broad peak at 3436 cm^{-1} in the IR spectrum support the structural assignment. Furthermore, the incorporation of a bromine atom into the molecule was confirmed by mass spectrometry. Diol **31** was subsequently subjected to a tandem methanolysis/ketalization reaction with PPTS in refluxing $CH_3OH/CH(OCH_3)_3$ to afford methyl ketal **32**, in which both rings A and B are installed.[18] The assignment of

the stereochemistry of the C9 methyl ketal was based on a similar precedent in the literature.[4a]

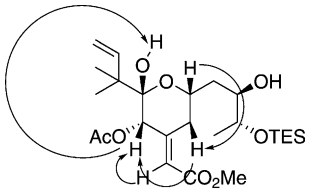
At this point, the remaining task was to acetylate the C7 hydroxyl group, hydrolyze the C1 methyl ester, and install a terminal olefin at C16. To this end, the C7 hydroxyl group was selectively acetylated in two steps involving the temporary protection of the C16 hydroxyl as a TES ether, one-pot acetylation of the C7 hydroxyl moiety, and deprotection of the C16 hydroxyl group to give compound **33**. The resultant alcohol was then oxidized (Moffatt–Swern oxidation) and olefinated (Wittig olefination) to afford terminal alkene **34** in 63% yield over two steps. Surprisingly, saponification of the methyl ester in compound **34** was troublesome; for example, the use of LiOH in aqueous THF or *n*PrSLi in HMPA[19] gave a complex mixture. It was eventually found that the use of $(CH_3)_3SnOH$[20] resulted in acid **35** in 45–64% yield together with 10–15% of recovered methyl ester **34**. A large excess of $(CH_3)_3SnOH$ (15 equiv) and heating under microwave conditions were required to achieve high conversion. Pd-catalyzed carbonylation[21] of acid **35** with $[Pd(PPh_3)_4]$ in DMF/CH_3OH furnished the requisite α,β-unsaturated methyl ester **36** in 55% yield. Note that both acids **35** and **36** could be used as the RCM precursor. Moreover, the use of vinyl bromide **35** as an RCM precursor could be advantageous because in principle it allows late-stage diversification through cross-coupling reactions to provide novel bryostatin analogues.



Scheme 9. Synthesis of C17–C27 fragment **40**. i) $Et_3N{\cdot}HF$, THF, RT; ii) Dess–Martin Oxidation; iii) see Table 1; iv) $AcOH/H_2O$ (3:1), RT; vi) TESCl, Et_3N, DMF, −30 °C.

Synthesis of the southern C17–C27 fragment: The synthesis commenced with tetrahydropyran **3**, which was prepared in 5 or 6 steps from terminal alkyne **8** and ynoate **9** (see Reference [1c]). Removal of the C17 TBS ether in **3** was best effected by using $Et_3N{\cdot}3HF$ in THF (60–77% yield, ≈10% of **3** recovered; Scheme 9). An excess of reagents (15 equiv $Et_3N{\cdot}3HF$) and a 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 group 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 of the classical olefination methods failed (see Table 1), likely due to the neopentyl nature of the aldehyde and sensitivity of the dihydropyran core towards bases. Eventually, employment of $[Cp_2Ti(CH_3)_2]$ (Petasis reagent)[23] as the olefination reagent solved the problem, and terminal alkene **39** was obtained in 58% yield (70% based on recovered starting material, Table 1, entry 7). Under the reaction conditions, a byproduct derived from olefination of one of the ester groups was also observed (5–10% yield). Cleavage of the acetonide with 75% aqueous acetic acid, followed by selective protection of the C26 hydroxyl with a TES group furnished fully functionalized southern fragment **40** in 52% yield over two steps.

The stereochemistry in tetrahydropyran **40** was confirmed by ROESY experiments (Scheme 10). The selectivity for the mono-TES protection was predicted according to literature precedent[4a] and confirmed by 2D NMR experiments.

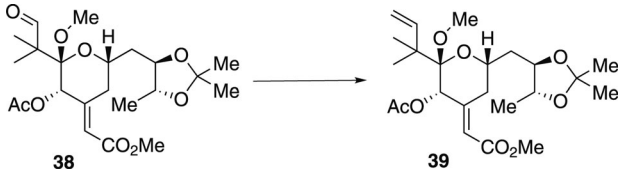


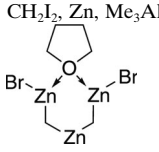
40

Scheme 10. Key ROESY correlations observed for **40**.

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 (EDCl) 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 effort was made to identify the

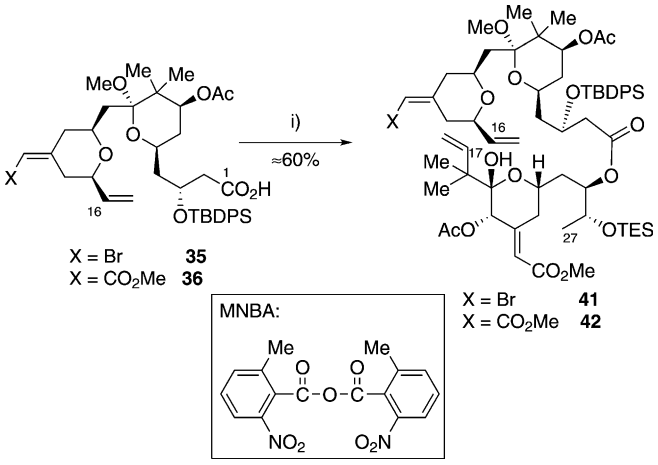
Table 1. Olefination of **38**.



	Conditions	Observation	Yield [%]
1	$Ph_3P{=}CH_2$, −30–0 °C	unkown byproduct	0
2	CH_2I_2, Zn, Me_3Al, 25 °C	mainly **38**	trace
3	CH_2I_2, Zn, PbI_2, $TiCl_4$, 0–25 °C	decomposition of **38**	0
4	$[TMSCH_2CeCl_2]$, THF, −78 °C	only **38**	0
5	CH_2I_2, Zn, Me_3Al, $BF_3{\cdot}OEt_2$, 25 °C	**38** + decomposition	0
6		**38** + decomposition	0
7	$[Cp_2Ti(CH_3)_2]$	**39** + a byproduct from ester olefination	58

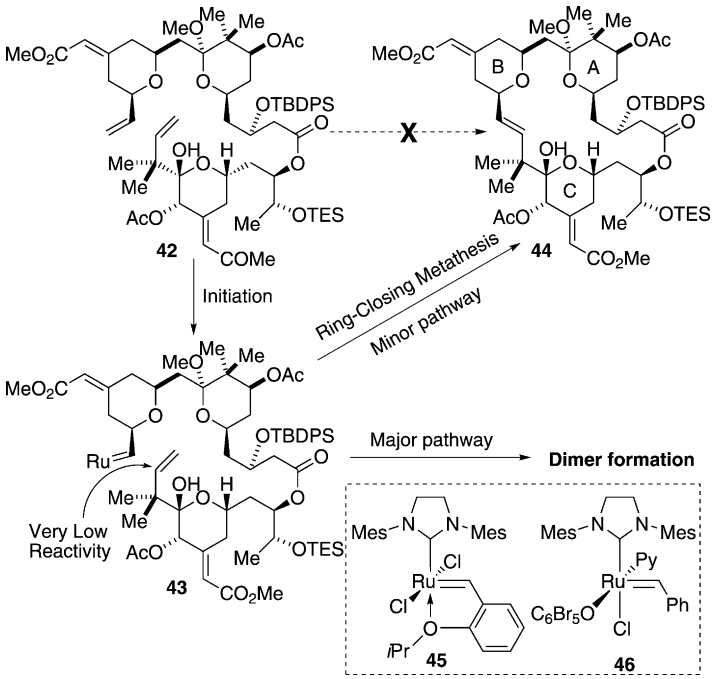
other product. The most satisfactory results were obtained by employing 2-methyl-6-nitrobenzoic anhydride (MNBA) in the method developed by Shiina et al. (Scheme 11).[24] Ester **42** was isolated in around 60% yield with the majority of the excess alcohol (**40**) recovered.[25] In addition, under the same esterification conditions, acid **35** was coupled with alcohol **40** to give ester **41** in a similar yield.

Consequently, the RCM reaction of both esters **41** and **42** was investigated. Our initial attempts were carried out with the Grubbs–Hoveyda catalyst **45**[26] or pseudohalide catalyst **46**[27] in either refluxing CH_2Cl_2 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 major isolated product was much more polar than the corresponding starting materials. ^{1}H NMR analysis supported the fact that the polar



Scheme 11. Synthesis of **41** and **42**. i) Et_3N, DMAP, MNBA, CH_2Cl_2 then **40**.

product could be a dimer: the double bond at C16 disappeared whereas the one at C17 remained intact. Based upon these observations, a possible explanation for the failure of the RCM reaction is outlined in Scheme 12. Both terminal



Scheme 12. Unsuccessful RCM: a possible explanation.

double bonds at C16 and C17 are deactivated towards Ru–alkylidene formation due to 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 concentrations (≈0.0005 M). Concurrently, a similar observation was reported by Thomas and co-workers during their investigation of an RCM approach to the bryostatins.[28]

It was anticipated that the conformation of the RCM precursor would have a dramatic impact on the efficiency of the RCM reaction. The X-ray crystal structure of bryostatin 1 (Figure 1)[2a] clearly shows that the C3 OH group helps to organize the macrocycle by serving as a hydrogen bonding acceptor for the C19 lactol hydroxyl group (O···H–O bond length of 2.71 Å) and donors for both the 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 the two terminal olefins together. Therefore, deprotection of the TBDPS ether at C3 was undertaken [Eq. (4)]. Unfortunately, only a complex mixture was obtained under the three reaction conditions attempted (TBAF, HF in pyridine, and NH_4F in CH_3OH). To circumvent this problem, it

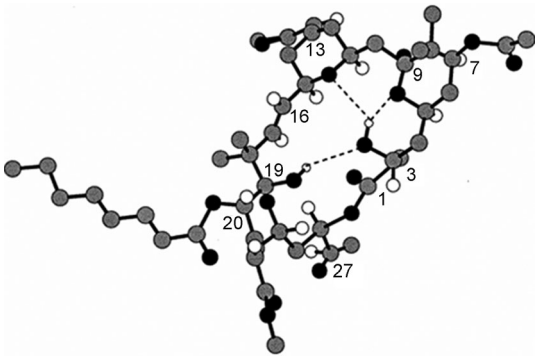
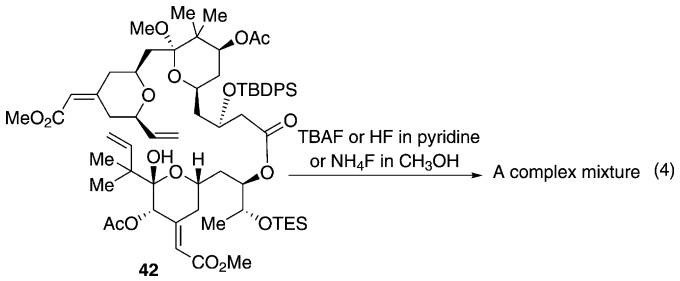


Figure 1. X-ray crystal structure of bryostatin 1 from reference [2a].

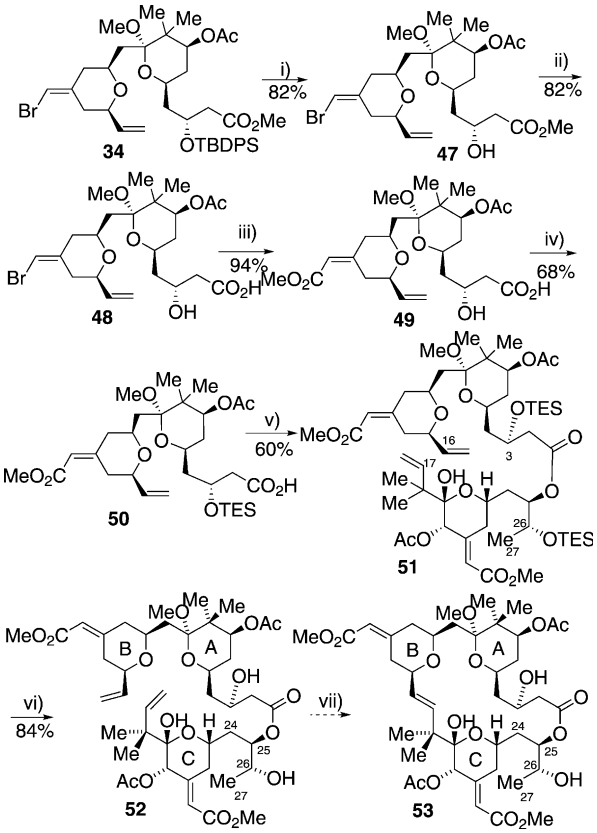
was decided to remove the TBDPS group at an earlier stage in the synthesis.

Treatment of vinyl bromide **34** with TBAF led to smooth deprotection of the C3 TBDPS ether to give alcohol **47** in



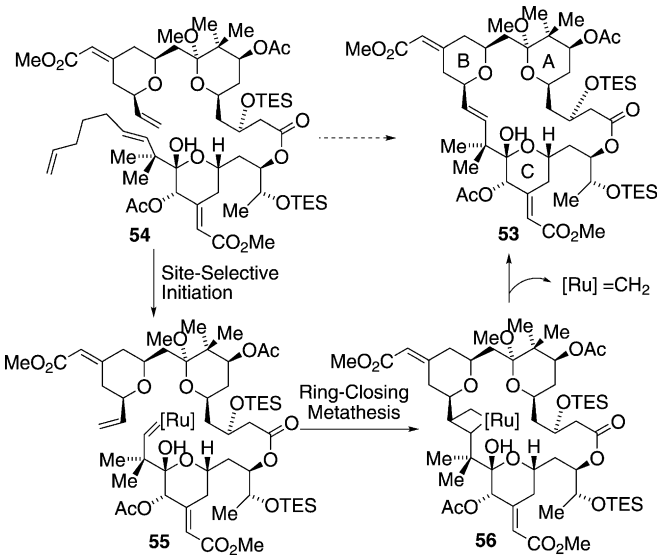
82% yield (Scheme 13). In contrast to the hydrolysis of methyl ester **34** (Scheme 8, 45–50% yield with 15 equivalents of $(CH_3)_3SnOH$, 140°C, microwave, 1.5 h), the saponification of **47** was much simpler. Under the identical conditions, the reaction went to completion in 40 min to deliver hydroxy acid **48** in 86% yield. Presumably, the hydrolysis of the C1 methyl ester was facilitated by pre-coordination (or complexation) of the C3 hydroxyl group with $(CH_3)_3SnOH$.[29] Next, carbonylation of the vinyl bromide moiety followed by selective protection of the C3 hydroxyl group (TESOTf, CH_2Cl_2, 0°C) converted **49** into acid **50**, which was subsequently acylated with alcohol **40** to give ester **51**. Removal of the 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 compound **52** was subjected to RCM reactions in the presence of the Grubbs–Hoveyda catalyst (**45**), no reaction was observed in refluxing CH_2Cl_2 and heating to reflux in benzene only led to decomposition. It is evident from these studies that the low reactivity of the double bond at C17 is the source of the problem. Thus, we decided to initiate the ruthenium alkylidene formation onto the C17 double bond through relay ring-closing metathesis (RRCM).[30] If this could be accomplished, it was anticipated



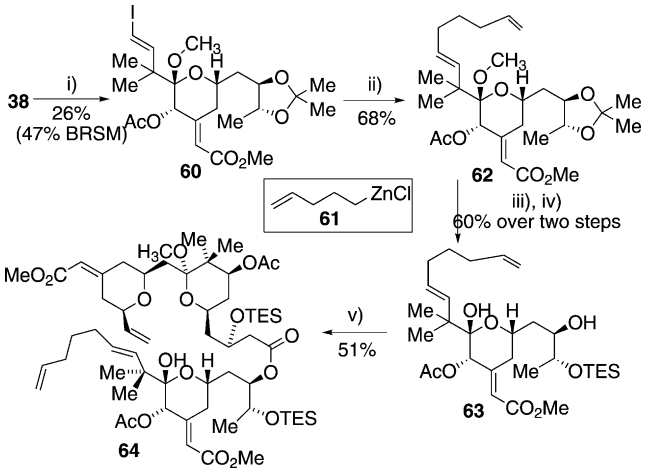
Scheme 13. i) Tetra-*n*-butylammonium fluoride (TBAF), THF; ii) $(CH_3)_3SnOH$, DCE, 140°C, microwave; iii) $[Pd(PPh_3)_4]$, CO, DMF/CH_3OH, 85°C; iv) TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C; v) Et_3N, DMAP, MNBA then **40**; vi) PPTS, THF/H_2O; vii) Grubbs–Hoveyda catalyst (**45**).

that the resulting ruthenium alkylidene **55** would cyclize onto the C16 double bond to form macrocycle **53** (Scheme 14).



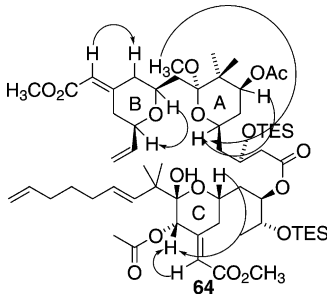
Scheme 14. Relay ring-closing metathesis: a possible solution.

An RRCM Strategy: Although direct installation of a relay moiety onto the southern fragment through Takai olefination[31] [Eq. (5)] or olefin cross-metathesis[32] [Eq. (6)] was difficult, this problem was solved with a two-step procedure: initial Takai olefination of aldehyde **38** with iodoform,[33] followed by a Negishi cross-coupling[34] gave compound **60** (Scheme 15). The quality of the $CrCl_2$ utilized was crucial

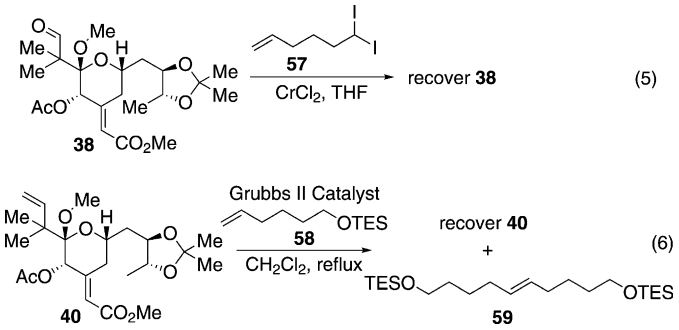


Scheme 15. Synthesis of precursor **64** for relay ring-closing metathesis. i) $CrCl_2$, CHI_3, THF, RT (BRSM = based on recovered starting material); ii) **61**, $[Pd(PPh_3)_4]$, THF; iii) $AcOH/H_2O$ (4:1); iv) TESCl, DMF, Et_3N, 0 °C to RT; v) **50**, MNBA, DMAP, Et_3N, CH_2Cl_2.

for the Takai olefination reaction, and a high chromium loading (≈15 equiv) was necessary for full conversion of the starting material.[35] The yield (26%, 47% based on recovered starting material) was moderate, perhaps 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** into mono-TES ether **63**, which was then acetylated with northern fragment **50** to give RRCM precursor **64** in 51% yield. The structure of compound **64** was determined by ^1H, ^{13}C, and 2D NMR experiments. In particular, the observed ROESY correlations confirmed our previous stereochemical assignments for rings A, B, and C (Scheme 16).



Scheme 16. Key ROESY correlations observed for **64**.

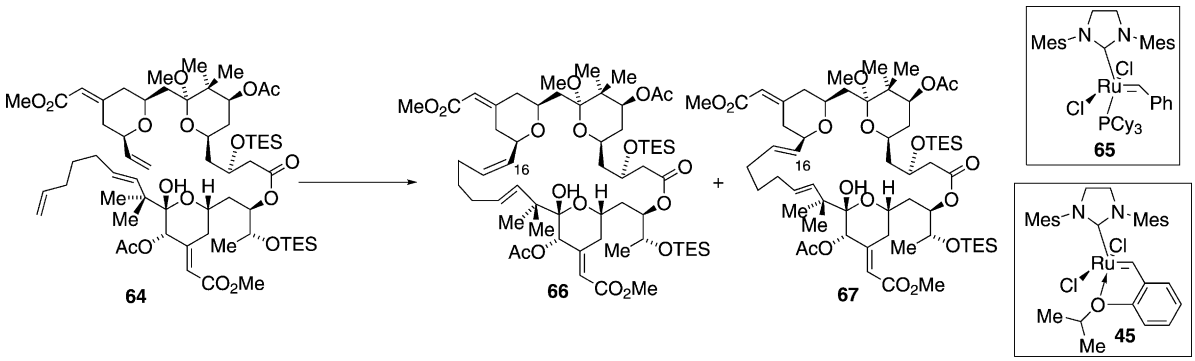


With polyolefin **64** in hand, the RRCM reaction was next investigated (Table 2). To avoid the undesired dimerization, the solution of **64** was added dropwise through a syringe pump to a solution of the Grubbs–Hoveyda catalyst (**45**; 18 mol%) in benzene at 50 °C and then the bath temperature was raised to 80 °C. The starting material disappeared within one hour (Table 2, entry 1). However, 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 the direct RCM products was supported by high-resolution mass spectrometry and 2D NMR experiments. Changing the order of addition (adding **45** to a solution of **64** in benzene) gave the same product ratio. However, employing 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 (Table 2, entry 2).[36]

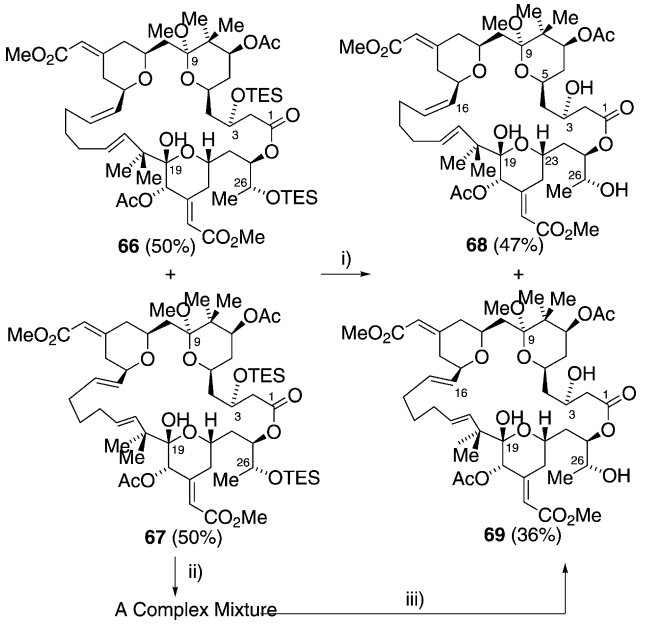
Treatment of the mixture of macrocycles **66** and **67** with PPTS in anhydrous MeOH cleanly removed both TES groups (Scheme 17). At this stage, diols **68** and **69** were separated by preparative TLC, and their structures were determined by IR, HRMS, ^1H, ^{13}C, and 2D NMR experiments. Note that 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 probably caused by the rapid tautomerization of the C9 hemiketal (Scheme 18).

Biological evaluation of the new ring-expanded bryostatin analogues: Compounds **68** and **69** contain all of the functionality present in the bryostatins except that they have an unusual 31-membered macrolactone ring. As almost all previous efforts to synthesize 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 (SARs) of the bryostatins. To this end, macrocycles **68** and **69** and acyclic compound **52** were tested against several cancer cell lines (Table 3). Interestingly, whereas 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-

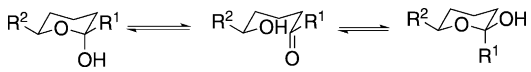
Table 2. Relay ring-closing metathesis studies of compound **64**.



	Conditions	Results
1	Hoveyda catalyst **45** (18 mol%), benzene, 50–80°C, N_2 sparging	80% yield (**66**/**67**, 1:1)
2	second generation Grubbs catalyst **65** (≈20 mol%), toluene, reflux, N_2 sparging	small scale reaction, clean by TLC and NMR (**66**/ **67**, 1:2.3)



Scheme 17. Final deprotection of **66** and **67**. i) PPTS, CH_3OH; ii) PPTS, THF/H_2O (3:1); iii) PPTS, CH_3OH.



Scheme 18.

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 for which the IC_{50} value was as low as 123 nM.[37]

Development of a new-generation strategy to access the C7–C27 fragment: We have disclosed the synthetic challenges to installing the C16–C17 olefin at a late stage through either a

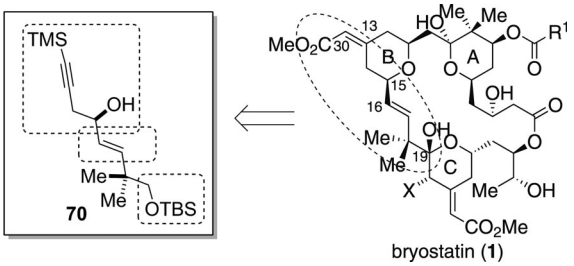
Table 3. Biological activities of bryostatin analogues.[a]

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

[a] The numbers are the half maximal inhibitory concentrations (IC_{50}) for **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.

macrocyclic RCM or RRCM strategy. Indeed, previous syntheses have noted the difficulties in forming this double bond,[4] which led us to conceive a new strategy for the installation of 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 of the subunits together (Scheme 19). The function of fragment **70** is three-fold:

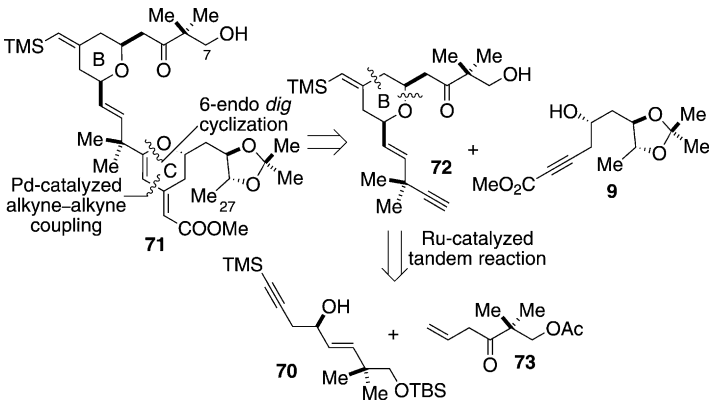


Scheme 19. Linchpin: fragment **70**.

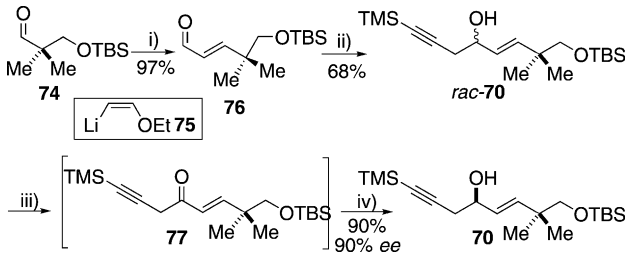
1) the homopropargyl alcohol moiety could permit the use of a Ru-catalyzed tandem enyne coupling/Michael addition to construct bryostatin ring B; 2) it provides the C16–17 olefin directly; and 3) the TBS protected primary alcohol could serve as a masked terminal alkyne, so that fragment **70** could also provide a link to build bryostatin ring C

through Pd-catalyzed alkyne–alkyne coupling and then 6-*endo-dig* cyclization.

As substrates with an allylic alcohol moiety have not previously been examined in the Ru-catalyzed enyne coupling/Michael addition reaction and it is known that allylic alcohols are able to participate in various Ru-catalyzed transformations, such as redox isomerizations,[38] the issue of chemoselectivity needed to be investigated prior to use of enyne **70** as the substrate. On the other hand, the Pd-catalyzed alkyne–alkyne coupling and 6-*endo-dig* cyclization have also not been previously tested on 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 ring B and C entities, was designed as the model target molecule (Scheme 20).



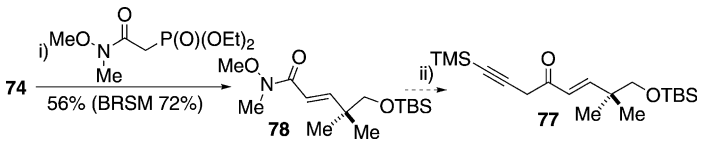
Scheme 20. Retrosynthetic analysis of compound **71**.



Scheme 21. Asymmetric synthesis of fragment **70**. i) **75**, Me_2Zn, Et_2O, −78 °C then $NaHSO_4$; ii) 1-trimethylsilyl-3-bromoprop-1-yne, In/InF_3, 66 °C; iii) Dess–Martin periodinane (DMP), $NaHCO_3$; iv) (*S*)-Corey–Bakshi–Shibata catalyst ((*S*)-CBS; 5 mol%), catecholborane, CH_2Cl_2, −78 °C.

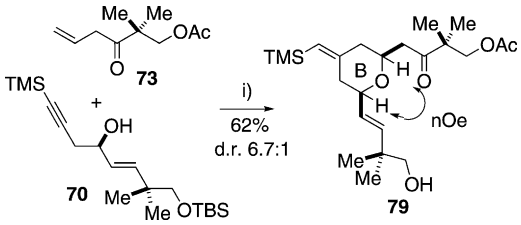
Enantioselective synthesis of TMS-alkyne **70** is described in Scheme 21. Aldehyde **74**[39] was treated with *cis*-2-ethoxyvinyl lithium **75** and Me_2Zn followed by an acidic aqueous workup, providing α,β-unsaturated aldehyde **76** in 97% yield.[40] $NaHSO_4$ was selected as a mild acid source; if HCl (1 N) was used, a much lower yield (51%) was observed. Following a protocol described by Loh et al.,[41] treatment of aldehyde **76** with indium metal, TMS-propargyl bromide and a catalytic amount of InF_3 in refluxing THF afforded racemic homopropargyl alcohol **70** in 68% yield. Dess–Martin oxidation[42] of the allylic alcohol followed by CBS-reduction[43] of corresponding ketone **77** afforded **70** in 90% *ee* and 90% yield over two steps. 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** was also explored, since it could potentially shorten the synthesis by one step (Scheme 22). Weinreb-amide **78** was synthesized in 56% yield through Horner–Wadsworth–Emmons (HWE) olefination[45] of aldehyde **74**. Although subsequent allenyl lithium addition was able to provide desired ketone **77**, the impurity in the crude (compound **77** cannot be purified by chromatography) did not permit the CBS reduction, especially on a large scale. Therefore, this route was abandoned.



Scheme 22. A Weinreb–amide route. i) $Ba(OH)_2$, THF/H_2O; ii) 1-trimethylsilylprop-1-yne, *n*BuLi, tetramethylethylenediamine (TMEDA), Et_2O, 0 °C to RT.

The other fragment, β,γ-unsaturated ketone **73**, was prepared according to our previously published 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 23). The

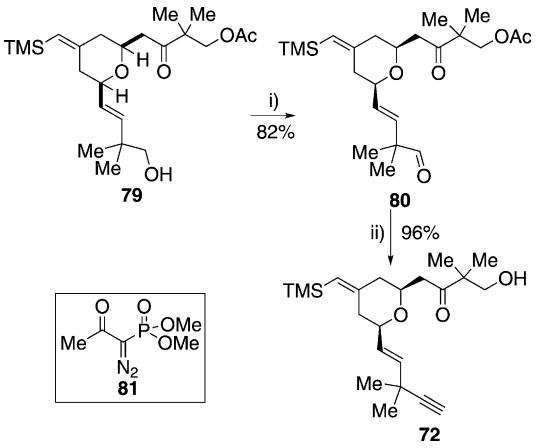


Scheme 23. Synthesis of **79**. i) $[CpRu(CH_3CN)_3][PF_6]$, (10 mol%), CH_2Cl_2, 0 °C to RT then HF·pyridine.

$[CpRu(CH_3CN)_3][PF_6]$ complex (10 mol%) was employed as the catalyst, and three equivalents 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 in the product conversion. Under the original reaction conditions, in which acetone was used, tetrahydropyran **79** was only isolated in 32% yield;[46] however, upon switching to CH_2Cl_2, a much higher conversion and a much cleaner reaction was

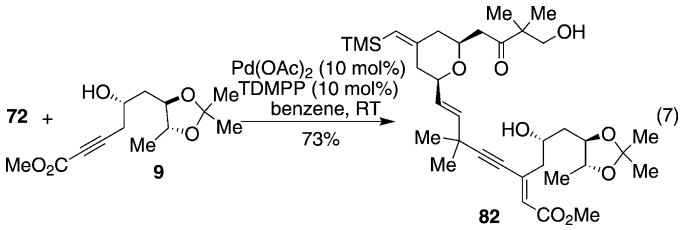
observed, with an isolated yield of 62% over two steps, almost doubling that of the reaction in acetone. We rationalize that as CH_2Cl_2 is a much less coordinating solvent than acetone, it enhances the reactivity of $[CpRu(CH_3CN)_3][PF_6]$. The diastereoselectivity ratio (d.r.) for this cyclization was around 6.7:1 (determined by integration of peaks in the ^1H NMR spectrum; $\delta_{major} = 2.91$ and $\delta_{minor} = 2.80$ ppm), favoring the *cis*-isomer.

Advancement of compound **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 24).

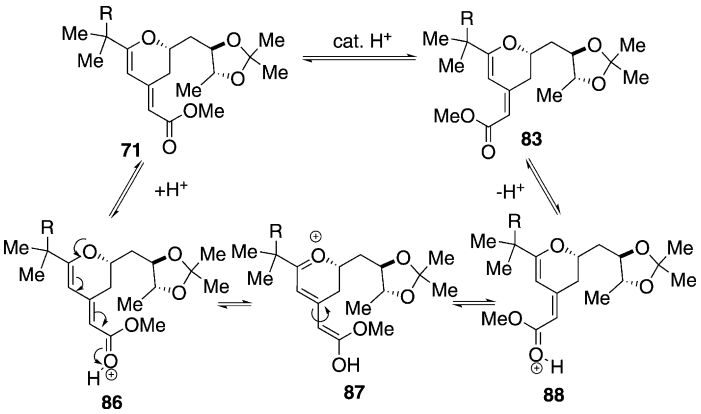


Scheme 24. Synthesis of alkyne **72**. i) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to RT; ii) **81**, K_2CO_3, MeOH.

The stage was now set to test the Pd-catalyzed alkyne–alkyne coupling reaction. Acceptor alkyne **9** was synthesized in six steps from commercially available D-galactonic acid-1,4-lactone (see Reference [1c]). The coupling between alkynes **72** and compound **9** proceeded well by using $Pd(OAc)_2$ (10 mol%)/tris(2,6-dimethoxyphenyl)phosphine (TDMPP) as the catalyst [Eq. (7)]; enyne **82** was isolated in 73% yield. The primary alcohol, vinylsilane, and *trans* olefin remained intact under the reaction conditions, which demonstrates excellent chemoselectivity for the Pd-catalyzed alkyne–alkyne coupling reaction.

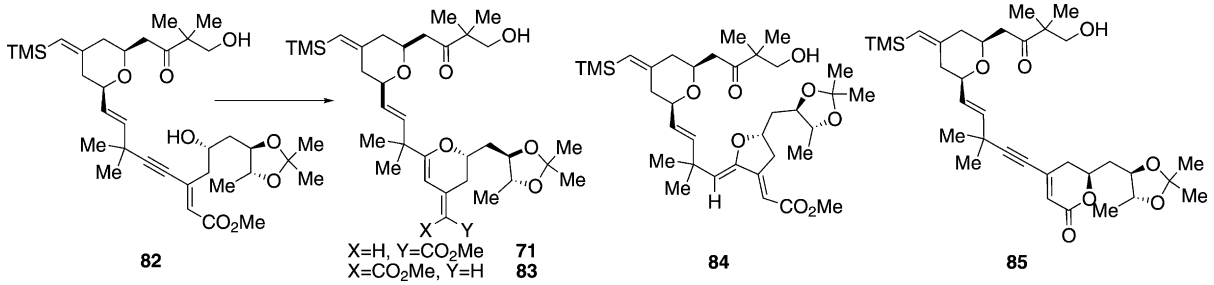


A metal-catalyzed 6-*endo-dig* cyclization of enyne **82** was next required to construct ring C of bryostatin (Table 4). As shown in our previous paper (see Reference [1c]), this cyclization could be very challenging because a number of possible byproducts can be formed. For example, if the alkyne is 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 25).[48] Moreover, the secondary alcohol could attack the ester, instead of the alkyne, to give the 6-



Scheme 25. Bronsted acid catalyzed olefin isomerization.

Table 4. The 6-*endo-dig* cyclization of enyne **82**.

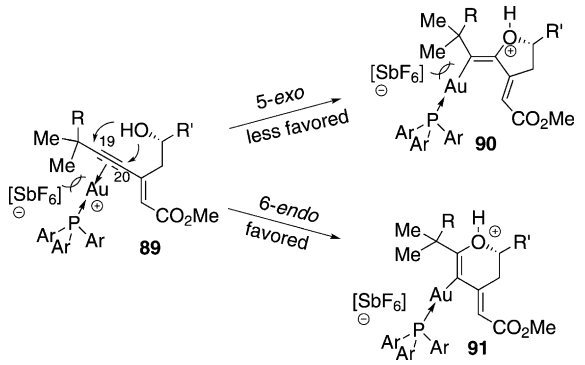


	Conditions	Results
1	$[PdCl_2(CH_3CN)_2]$ (17 mol%), TDMPP (10 mol%), THF, RT	6-*endo*(**71**+**83**)/5-*exo* (**84**) ≈1:1
2	$Pd(OAc)_2$ (20 mol%), TDMPP (20 mol%) then $Pd(TFA)_2$ (30 mol%), benzene, RT	**71**/**83**/**84** 1.5:0.5:1 (≈10% **82** + ≈30% **85**)
3	$[Au(PPh_3)]^+[SbF_6]^-$ (20 mol%), CH_3CN, $NaHCO_3$, RT	53% yield (**71**/**83**/**84** 5.1:1:1.3)

membered lactone. Given these concerns, we decided to revisit this 6-*endo-dig* cyclization issue.

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). If enyne **82** was subjected to the previously optimized conditions ($[PdCl_2(CH_3CN)_2]$ (17 mol%), TDMPP (10 mol%), THF, RT), the products from 6-*endo* (**71**+**83**) and 5-*exo* (**84**) cyclization pathways were isolated in a ratio of around 1:1 (Table 4, entry 1). A slightly better 6-*endo*/5-*exo* ratio (around 2:1) was observed by using $Pd(OAc)_2$/TDMPP/$Pd(TFA)_2$ as the catalyst and by using benzene as the solvent; however, this reaction gave incomplete conversion and lactone **85** was formed in around a 30% yield (Table 4, entry 2). Eventually, the most satisfactory result was found when using cationic gold(I) complex $[Au(PPh_3)]^+[SbF_6]^-$ as the catalyst in CH_3CN (Table 4, entry 3).[49] The product ratio of **71**/**83**/**84** was enhanced to 5.1:1:1.3, which is equal to around 5:1 6-*endo*/5-*exo* regioselectivity. $NaHCO_3$ was employed as a buffer to minimize the acid-catalyzed olefin isomerization. The only drawback to these conditions was that the reaction proceeded relatively slowly (53% yield over 4 days). If the Au-catalyzed reaction was conducted in CH_2Cl_2, 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 ^{1}H 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 26, when Au



Scheme 26. 5-*exo* vs. 6-*endo* addition.

binds to the alkyne, the steric interaction between the substituted *t*Bu-like group and the [Au(PPh$_3$)] cation and 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 advantage of two tandem methods, Ru-catalyzed enyne coupling/Michael addition and Pd-catalyzed diyne coupling/6-*endo* cyclization, we were able to furnish fully functionalized northern and southern fragments of bryostatins. An esterification/olefin metathesis strategy has been investigated to unite the two fragments and to advance them to the natural products. Although formation of the C16–C17 olefin through olefin metathesis was unsuccessful, we were able to synthesize two new bryostatin analogues with a ring-expanded backbone. These analogues retain almost all the functionalities in the bryostatins, as well as their biological activities against several cancer cell lines, including NCI-ADR (the cell line containing multi-drug resistant pumps).

To overcome this "olefination problem", a new strategy was developed to install the C16–C17 olefin at an earlier stage. Enyne **70** was designed and synthesized to serve as a "linchpin" to connect both the northern and southern parts together. To test this strategy, model substrate **71**, containing the C7–C27 carbon skeleton and rings B and C of the bryostatins, was synthesized in only six steps. During this study, several chemoselectivity issues were addressed, including the functional group tolerance of the Ru-catalyzed tandem alkene–alkyne coupling/Michael addition reaction and the Pd-catalyzed alkyne–alkyne coupling. Moreover, a cationic gold complex was found to be a superior catalyst for the challenging 6-*endo-dig* cyclization. Therefore, our ring-expanded analogue synthesis, along with the new linchpin strategy described in this article, should provide key support for our subsequent accomplishment of the total synthesis of bryostatins.

Experimental Section

All reactions were run under a nitrogen atmosphere unless otherwise indicated. Anhydrous solvents were transferred through an 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 indicted, solvents were degassed through freezing in liquid nitrogen and thawing under high vacuum. The above cycle was repeated three times, unless otherwise indicated. Analytical thin layer chromatography (TLC) was carried out by using 0.2 mm commercial silica gel plates (DC–Fertigplatten Krieselgel 60 F_{254}). 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 centimeters (cm^{-1}). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded by using a Varian UI-600 (600 MHz), Varian UI-500 (500 MHz), or Varian MERC-400 (400 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) or in ppm relative to the singlet at 7.26 ppm for chloroform. Coupling constants are reported in Hertz (Hz). The following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), and

m (multiplet). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded by using a Varian UI-600 (150 MHz), Varian UI-500 (125 MHz), or Varian MERC-400 (100 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) relative to the center line of the triplet at 77.1 ppm for deuterochloroform. ^{13}C 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.

Synthesis of compound 30: Acetone (freshly distilled over calcium sulfate, 3 mL) was added 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. 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 $[CpRu(CNCH_3)_3][PF_6]$ (65 mg, 0.15 mmol). The reaction was stirred at room temperature for 40 h and the solvent removed under reduced pressure. The residue was purified by flash column chromatography on silica gel with EtOAc/petroleum ether (10%, 12.5%, 15%, 17.5%, and 20%) to give **30** as a pale yellow foam (0.81 g, 56%, 9:1 d.r. determined by integrating peaks at 5.38 and 5.36 ppm). Significant amounts of both alkene **14c** and alkyne **7** were recovered as an inseparable mixture (1.02 g, **14c**/**7**, 7:1). R_f = 0.37 (20% EtOAc/petroleum ether); $[\alpha]_D^{23} = -35.5$ (c = 0.6 in CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): 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 ppm (s, 9H); ^{13}C NMR (125 MHz, C_6D_6): 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 ppm; IR (neat film): $\tilde{\nu}$ = 3075, 3042, 1742, 1705, 1609, 1585, 1510, 1484, 1427, 1386, 1361, 1303, 1245, 1170, 1108, 1091, 1033, 839, 818, 739, 702 cm^{-1}; elemental analysis calcd (%) for $C_{54}H_{72}O_9Si_2$: C 70.40, H 7.88; found: C 70.21, H 7.80.

Synthesis of compound 32: A solution of diol **31** (0.62 g, 0.9 mmol) and pyridinium *p*-toluenesulfonate (99 mg, 0.39 mmol) in CH_3OH (15 mL) and trimethyl orthoformate (0.75 mL) was heated at reflux for 2 h. The contents were cooled to room temperature, poured into saturated aqueous $NaHCO_3$, and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel with EtOAc/petroleum ether (30%, 40%, and 50%) to give **32** as a clear colorless oil (0.47 g, 71%). R_f = 0.50 (50% EtOAc/petroleum ether); $[\alpha]_D^{23} = -30.5$ (c = 1.4 in CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): 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 ppm (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): 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 ppm; IR (neat film): $\tilde{\nu}$ = 3446, 3073, 3047, 1734, 1632, 1588, 1472, 1428, 1388, 1357, 1260, 1105, 953, 821, 736, 701 cm^{-1}; HRMS calcd for $C_{37}H_{53}BrNaO_8Si$: 755.2591 $[M+Na]^+$; found: 755.2592.

Synthesis of compound 39: Dimethyltitanocene (**75**; Petasis reagent) in THF (0.52 M, 5.3 mL, 2.76 mmol) was added to a solution of aldehyde **38** (0.33 g, 0.75 mmol) in THF (1.3 mL) in a pressure tube at room temperature. The tube was sealed and the reaction was heated at 90 °C for 2.5 h. The contents were cooled to room temperature and the solvent was removed in vacuo. The residue was purified by flash column chromatography on silica gel with Et_2O/petroleum ether (20%, 30%, and 40%) to give olefin **39** (0.193 g, 58%). R_f = 0.59 (20% EtOAc/petroleum ether); $[\alpha]_D^{24} = +3.3$ (c = 0.5 in CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): 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), 1.37–1.31 (m, 1H), 1.36 (s, 3H), 1.35 (s, 3H), 1.23 (s, 3H), 1.22 (s, 3H), 1.08 ppm (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): 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 ppm; IR (neat film): $\tilde{\nu}$ = 3076, 2996, 2931, 1746, 1719, 1664, 1460, 1433, 1370, 1230, 1157, 1094, 1048, 1021, 994 cm^{-1}; HRMS calcd for $C_{22}H_{32}O_7^+$: 408.2148 $[M-CH_4O]^+$; found: 408.2129.

Synthesis of compound 40:

Acetonide cleavage: Compound **39** (40 mg, 0.09 mmol) in aqueous acetic acid (75% (v/v); 7 mL) was stirred at room temperature for 6 h. The contents were poured into ice-cooled saturated aqueous Na/K tartrate, neutralized with saturated aqueous Na_2CO_3, and extracted three times with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel with Et_2O/petroleum ether (50%) followed by CH_3OH/CH_2Cl_2 (6%) to give a triol (34 mg) contaminated with a small amount (<10%) of an impurity. R_f = 0.18 (6% CH_3OH/CH_2Cl_2); $[\alpha]_D^{24} = -11.1$ (c = 0.55 in CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): 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 ppm (d, J = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): 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 ppm; IR (neat film): $\tilde{\nu}$ = 3438 (br), 3076, 1743, 1721, 1683, 1635, 1437, 1410, 1369, 1234, 1152, 1080, 1031, 1017, 745, 728 cm^{-1}; HRMS calcd for $C_{14}H_{21}O_8$: 317.1236 $[M-C_5H_9]^+$; found: 317.1240.

TES protection: Et_3N (0.12 mL, 0.86 mmol) and then TESCl (16.3 μL, 0.097 mmol) were added to a solution of the triol formed above (34 mg, 0.088 mmol) in DMF (2.5 mL) at −30 °C. The reaction was stirred at −30 °C for 30 min and the contents were poured into saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel with EtOAc/petroleum ether (20% and 30%) to give **40** (23 mg, 52% over the two steps). R_f = 0.52 (40% EtOAc/petroleum ether); $[\alpha]_D^{22} = -7.5$ (c = 0.75 in CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): 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 (quin, 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), 1.60–1.54 (m, 1H), 1.59 (s, 3H), 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 ppm (q, J = 7.9 Hz, 6H); ^{13}C NMR (125 MHz, C_6D_6): 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 ppm; IR (neat film): 3408 (br), 3082, 1741, 1718, 1662, 1434, 1369, 1230, 1174, 1155, 1086, 1030 cm^{-1}; HRMS calcd for $C_{25}H_{42}O_7$: 482.2700 $[M-H_2O]^+$; found: 482.2698.

Synthesis of compound 48: A mixture of **47** (40 mg, 0.075 mmol) and trimethyltin hydroxide (135 mg, 0.75 mmol) in CH_2Cl_2 (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 column chromatography on silica gel with EtOAc/petroleum ether (40%) followed by CH_3OH/CH_2Cl_2 (6% and 12%) to give **48** (32 mg, 82%). R_f = 0.42 (8% CH_3OH/CH_2Cl_2); $[\alpha]_D^{23} = +75.0$ (c = 0.3 in CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): 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 ppm (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): 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 ppm; IR (thin film): $\tilde{\nu}$ = 3499 (br), 3077, 1735, 1434, 1365, 1245, 1159, 1129, 1060, 1021 cm^{-1}.

Synthesis of compound 60: A solution of **38** (470 mg, 1.06 mmol) and CHI_3 (2.53 g, 6.38 mmol) in THF (6 mL and 2×2 mL rinse) was added through a cannula to a suspension of anhydrous $CrCl_2$ (99.99% from Aldrich, 2.0 g, 16.26 mmol) in freshly distilled THF (10 mL) at 0 °C. The ice bath was removed and the brown suspension was stirred at room temperature in the dark for 20 h before being poured into a brine/H_2O mixture (1:1). The mixture was extracted with EtOAc. The combined organic extracts were concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/petroleum ether (5%, 10%, and 20%) to give vinyl iodide **60** (158 mg, 26%) and recovered aldehyde **38** (208 mg; 44% yield of **60** based on recovered starting material). R_f = 0.35 (16% EtOAc/petroleum ether); $[\alpha]_D^{23} = -9.7$ (c = 0.9 in CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): 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 ppm (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): 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 ppm; IR (neat film): $\tilde{\nu}$ = 3072, 1745, 1719, 1662, 1596, 1433, 1380, 1367, 1227, 1165, 1095, 1042 cm^{-1}; HRMS calcd for $C_{23}H_{35}IO_8$: 551.1142 $[M-CH_3]^+$; found: 551.1165.

Synthesis of compound 62: tBuLi (1.7 in pentane, 3.44 mL, 5.84 mmol) was added to cooled Et_2O (6 mL) at −78 °C and then 5-boromo-1-pentene (0.3 mL, 2.95 mmol) was added dropwise. 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 through a cannula. The yellow–green color disappeared upon addition of the zinc chloride. The cold bath was removed and the contents were warmed to room temperature during which time it became a cloudy white solution. The reaction was then stirred at room temperature for 45 min and the solvent removed in vacuo. The residue was dissolved in THF (10 mL) to give 4-pentenyl zinc chloride **61** (0.3 M in THF). Zinc reagent **61** (5 mL + 2 mL THF rinse) was then added to a mixture of vinyl iodide **60** (157 mg, 0.277 mmol) and [Pd(PPh_3)$_4$] (32 mg, 0.03 mmol) at room temperature. The contents were stirred at room temperature for 7 h, poured into phosphate buffer (pH 7), and extracted with EtOAc. The combined organic extracts were concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/petroleum ether (8% and 10%) to give triene **62** (62 mg, 47%) and a 5:1 mixture of **62** and **39** (27 mg, 68% combined yield). R_f = 0.47 (15% EtOAc/petroleum ether); $[\alpha]_D^{22} = -12.7$ (c = 0.65 in CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): 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), 1.29 (s, 3H), 1.11 ppm (d, J = 6 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): 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 ppm; IR (neat film): $\tilde{\nu}$ = 3077, 1745, 1719, 1663, 1638, 1496, 1377, 1364, 1228, 1155, 1091, 1049, 1023 cm^{-1}; HRMS calcd for $C_{27}H_{41}O_7$: 477.2852 $[M-CH_3O]^+$; found: 477.2818.

Synthesis of compound 64: CH_2Cl_2 (3.4 mL) and Et_3N (0.042 mL, 0.3 mmol) were added to a mixture of DMAP (1.2 mg, 0.01 mmol) and 2-methyl-6-nitrobenzoic anhydride (MNBA; 34.4 mg, 0.1 mmol) at room temperature. The contents were stirred at room temperature for 5 min, after which a homogeneous light yellow solution had 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 CH_2Cl_2). The mixture was stirred at room temperature for 15 min, and then a solution of alcohol **63** (26.7 mg, 0.047 mmol) was added to the vial through a cannula. The reaction was stirred at room temperature for 16 h and the contents were purified by flash column chromatography on silica gel with EtOAc/petroleum ether (5%, 10%, 15%, 20%, and 30%) to give **64** (23 mg, 51% yield). R_f = 0.63 (20% EtOAc/petroleum ether); $[\alpha]_D^{23} = +12.7$ (c = 0.3 in CH_2Cl_2); ^{1}H NMR (600 MHz, C_6D_6): 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 (quin, 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 ppm (m, 12H); ^{13}CNMR (125 MHz, C_6D_6): 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 ppm; IR (thin film): $\tilde{\nu}$ = 3508, 3077, 1744, 1718, 1655, 1462, 1435, 1368, 1233, 1152, 1112, 1080, 1027, 910, 874, 744, 726 cm^{-1}; HRMS calcd for $C_{61}H_{106}O_{17}Si_2N$: 1180.6999 $[M+NH_4]^+$; found: 1180.6974.

Synthesis of compounds 66 and 67: The Hoveyda catalyst **65** (4.5 mg, 18 mol%) in benzene (2 mL) was added over 5 min through a syringe to a solution of **64** (20 mg, 0.018 mmol) in benzene (8 mL) at 50 °C with N_2 sparging. The contents were stirred at 50 °C for 30 min before heating the oil bath to 80 °C. Stirring was continued for 15 min at 80 °C. The contents were then 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 **66** and **67** (16 mg, 80% combined yield) as a 1:1 mixture (as shown by integrating the peaks at 3.36 and 3.32 ppm in the ^{1}H NMR spectrum). HPLC: t_r = 5.72 min and 7.07 min (Alltech–Econosphere silica 3 micro column; 99:1 heptane/isopropanol; 254 nm; 1 mL min^{-1}); ^{1}H 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 ppm (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 ppm; IR (thin film): $\tilde{\nu}$ = 3510, 1721, 1650, 1431, 1370, 1232, 1156, 1113, 1080, 1023, 728, 724 cm^{-1}; HRMS calcd for $C_{59}H_{98}O_{17}Si_2Na$: 1157.6240 $[M+Na]^+$; found: 1157.6104.

Synthesis of compounds 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 contents were 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 **68** (2.6 mg) and **69** (2 mg; 82% combined yield).

*Characterization for **68***: R_f = 0.44 (75% EtOAc/petroleum ether); $[\alpha]_D^{24} = +72.2$ (c = 0.53 in CH_2Cl_2); ^{1}H 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 s, 1H), 3.66–3.62 (m, 1H), 3.60–3.56 (m, 1H), 3.51 (quin, J = 6.0 Hz, 1H), 3.46 (s, 3H), 3.33 (s, 3H), 3.17 (br s, 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 ppm (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, 69.9, 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, 20.9, 20.8, 20.6, 19.5, 16.3 ppm; IR (film): $\tilde{\nu}$=3482, 1718, 1652, 1434, 1365, 1234, 1155, 1025, 983, 872 cm^{-1}; HRMS calcd for $C_{47}H_{70}O_{17}Na$: 929.4513 [M+Na]$^+$; found: 929.4535.

Characterization for ***69***: R_f=0.63 (75% EtOAc/petroleum ether); $[\alpha]_D^{23}$=+36.6 (c=0.24 in 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 (quin, J=6.6 Hz, 1H), 3.46 (brs, 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 ppm (d, J=6.6 Hz, 3H); IR (film): $\tilde{\nu}$=3454, 1718, 1648, 1434, 1369, 1234, 1155, 1030, 974 cm^{-1}, HRMS calcd for $C_{47}H_{70}O_{17}Na$: 929.4513 [M+Na]$^+$; found: 929.4597.

Synthesis of 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 CH_2Cl_2 (66 mL) at 0 °C. The reaction was stirred at RT for 30 min, before being quenched with saturated $Na_2S_2O_3$ and saturated $NaHCO_3$. The mixture was extracted with ethyl acetate (3×150 mL), and the combined organic extracts were dried over Na_2SO_4. The solvent was removed, and the crude ketone was dissolved with CH_2Cl_2 (112 mL). This solution was cooled to −78 °C, and (*S*)-2-methyl-CBS-oxazaborolidine (0.78 mL, 1 M 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 warmed to 0 °C. The reaction was stirred at 0 °C for 1 h, before being quenched with NaH_2PO_4 (1 M). The mixture was extracted with ethyl acetate and the combined organic extracts were dried over Na_2SO_4. Compound (*R*)-**70** was purified by silica gel flash column chromatography (5% 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^{-1}, 99.5:0.5 heptane/*i*PrOH, t_{major}=7.9, t_{minor}=7.2 min). R_f=0.35 (10% Et_2O/petroleum ether, 1:9 v/v); $[\alpha]_D^{20}$=+4.86 (c=0.64 in CH_2Cl_2); ^{1}H 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 (brs, 1H), 0.97 (s, 3H), 0.88 (s, 12H), 0.15 (s, 9H), 0.00 ppm (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 ppm; IR (film): $\tilde{\nu}$=3336 (br), 2958, 2858, 2178, 1464, 1250, 1099, 843 cm^{-1}; HRMS calcd for $C_{15}H_{29}O_2Si_2$+*t*Bu: 297.1706 [M−*t*Bu]$^+$; found: 297.1684.

Synthesis of compound 79: $[CpRu(CH_3CN)_3]^+[PF_6]^-$ (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 CH_2Cl_2 (0.5 mL) at 0 °C. The resulting yellow solution was stirred at room temperature for 12 h. The tetrahydropyran was isolated by silica gel flash column chromatography as a mixture contaminated with (*R*)-**70**. THF (0.4 mL) was added to this mixture and the resulting solution was cooled to 0 °C before HF·pyridine (5 drops) was added. The reaction mixture was stirred vigorously for 5 h at RT, before being quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate (3× 20 mL), and the combined organic extracts were dried over Na_2SO_4. Compound **79** was purified by silica gel flash column chromatography (4:1 then 3:2 petroleum ether/ethyl acetate) to give a colorless oil (8.3 mg, 62%, d.r. 6.7:1, δ_{major}=2.91, δ_{minor}=2.80 ppm). R_f=0.35 (40% ethyl acetate in petroleum ether); $[\alpha]_D^{23}$=−1.5 (c=0.40 in CH_2Cl_2); ^{1}H 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 ppm (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 ppm; IR (film): $\tilde{\nu}$=3473, 2956, 1747, 1702, 1624, 1472, 1375, 1247, 1140, 1046, 974, 840 cm^{-1}; HRMS calcd for $C_{23}H_{40}O_5Si$: 447.2543 [M+Na]$^+$; found: 447.2545.

Synthesis of compound 71: Dry CH_2Cl_2 (0.4 mL) was added to a mixture of $[Au(PPh_3)_3Cl]$ (10.2 mg, 0.020 mmol) and $AgSbF_6$ (7.0 mg, 0.020 mmol) 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 buffer (pH 7.0), and the mixture was extracted with ethyl acetate four times and the combined organic extracts were dried over Na_2SO_4. The dihydropyran products were isolated by 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 ^{1}H NMR peaks at δ=5.34, 6.80, and 6.05 ppm, respectively). R_f=0.60 (40% ethyl acetate/petroleum ether); $[\alpha]_D^{23}$=16.1 (c=0.24 in CH_2Cl_2); see the Supporting Information for the NMR data; IR (film): $\tilde{\nu}$=34854 (br), 2953, 2931, 1708, 1610, 1379, 1226, 1153, 1094, 840 cm^{-1}; HRMS calcd for $C_{35}H_{56}O_8Si$: 655.3642 [M+Na]$^+$; found: 655.3636.

Acknowledgements

We thank the National Institutes of Health (GM13598) and NSF for their generous support of our programs. H.Y. thanks Amgen and Bristol–Myers Squibb for fellowships. G.D. thanks Stanford University for a Graduate Fellowship. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California, San Francisco, supported by the NIH Division of Research Resources. Palladium and ruthenium salts were generously supplied by Johnson–Matthey.

[1] a) For a preliminary report of a portion of our work, see: B. M. Trost, H. Yang, O. R. Thiel, A. J. Frontier, C. S. Brindle, *J. Am. Chem. Soc.* **2007**, *129*, 2206–2207; b) for our synthesis of bryostatin rings A and B, see: B. M. Trost, H. Yang, C. S. Brindle, G. Dong, *Chem. Eur. J.* **2011**, *17*, 9777–9788; c) for our synthesis of bryostatin ring C, see: B. M. Trost, A. J. Frontier, O. R. Thiel, H. Yang, G. Dong, *Chem. Eur. J.* **2011**, *17*, 9762–9776.

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Received: October 11, 2010
Revised: April 26, 2011
Published online: July 21, 2011

