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Atom-Economic and Stereoselective Syntheses of the Ring A and B Subunits of the Bryostatins

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

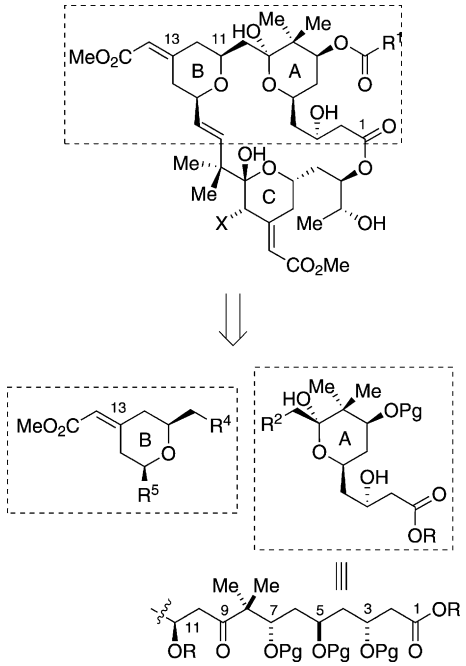
Abstract: This article describes chemoselective and atom-economic methods for the stereoselective assembly of the ring A and B subunits of bryostatins. A Ru-catalyzed tandem alkene–alkyne coupling/Michael addition reaction was developed and applied to the synthesis of bryostatin ring B. We explored an acetylide-mediated epoxide-opening/6-*exo-dig* cyclization route to access the bryostatin ring A, although ring A was eventually furnished through an acid-catalyzed tandem transketalization/ketalization sequence. In addition, a dinuclear zinc-catalyzed methyl vinyl ketone (MVK) aldol strategy was evaluated for the construction of the polyacetate moiety. Utilization of these methods ultimately led to the rapid assembly of the northern bryostatin fragment containing both the ring A and B subunits.

Keywords: aldol reaction · asymmetric synthesis · chemoselectivity · diastereoselectivity · enantioselectivity · enynes · Michael addition · natural products

Introduction

As part of our continuing efforts towards the total synthesis of bryostatins,[1] we explored new methods and strategies for assembling rings A and B (Scheme 1). The structure of bryostatin ring B features a 2,6-*cis*-disubstituted tetrahydropyran with a geometrically defined exocyclic conjugated methyl ester at the C13 position (bryostatin numbering). Controlling the olefin geometry of this α,β-unsaturated ester has been one of the major challenges in syntheses of ring B of bryostatins.[2] The use of a chiral Horner–Wadsworth–Emmons (HWE) reagent developed by Evans et al.[2a] proved to be effective in the syntheses of bryostatins 2 and 3; however, a stoichiometric amount of the expensive chiral reagent was required for this non-asymmetric transformation and the *E*/*Z* ratio was only 6:1 to 8:1 (Scheme 2). We envisioned that by utilizing our Ru-catalyzed enyne coupling reaction with multi-functionalized substrates, we would be able to generate the required ring-B motif in a highly regio- and chemoselective fashion. A single olefin isomer is expected and this approach would also be catalytic and atom economic.

The bryostatin ring-A region contains multiple 1,3-*anti* diol units, and thus an aldol approach seems to be one of the most straightforward ways to provide this motif. Indeed, in all previous total syntheses aldol reactions have been employed for the synthesis of ring A; moreover, these aldol reactions all relied on the generation of a stoichiometric amount of metal enolates.[3] For example, in the synthesis by Masamune et al., boron enolates were utilized to form the C10–C11 and C2–C3 bonds;[3a,b] in the synthesis by Evans et al., a boron enolate was used to form the C6–C7 bond and a titanium enolate was used to form the C4–C5 bond;[2a] and in the synthesis of bryostatin 3 by Ohmori et al., a lithi-



Scheme 1. Retrosynthetic analysis of the ring A and B subunits of bryostatins. Pg = protecting group.

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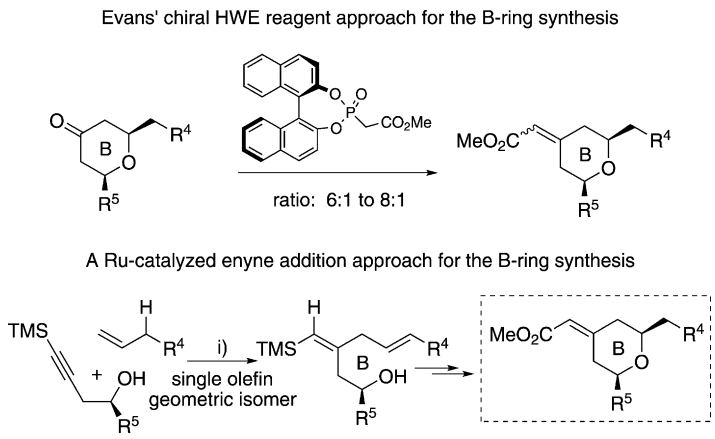
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201002930. It contains experimental details for the synthesis of compounds **5**, **16**–**19**, **24**, **25**, **27**, **28**, **46**, **49a**–**g**, **50a**, **53**–**60**, **62**, **63**, and **67**, as well as spectral data.



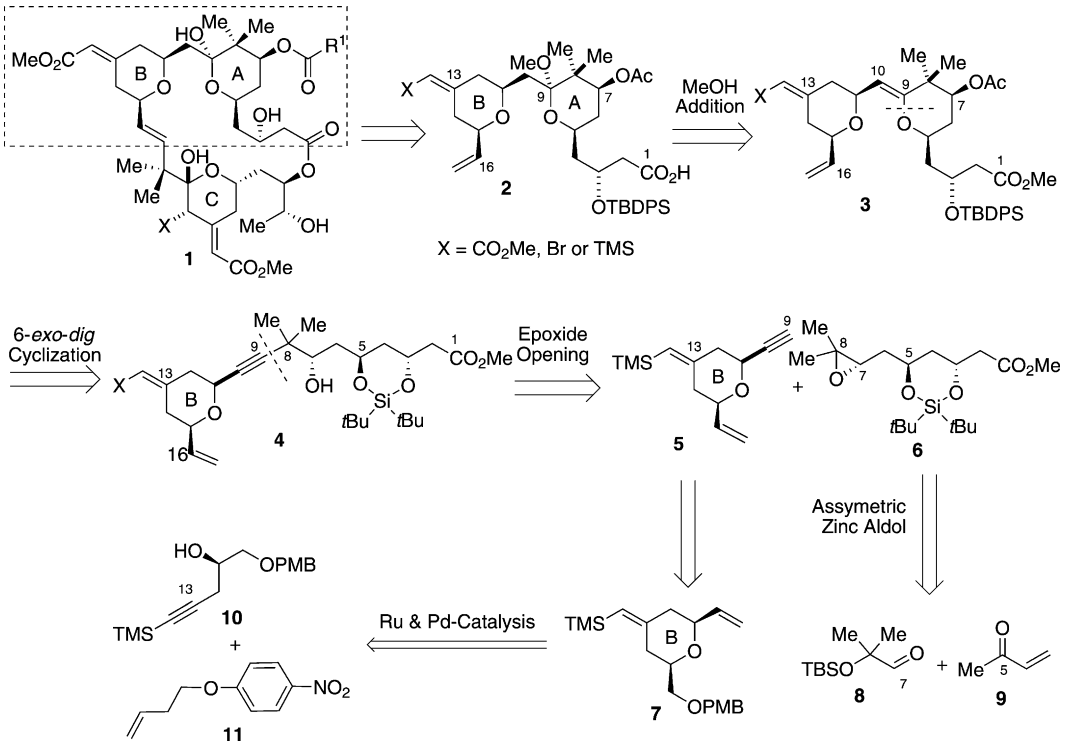
Scheme 2. Installation of the geometrically defined *exo*-enoate of bryostatins. i) $[CpRu(CH_3CN)_3][PF_6]$ (cat.; Cp = cyclopentadienyl). TMS = trimethylsilyl.

um enolate was employed to form the C4–C5 bond.[3c,d] From an atom-economy viewpoint, the use of a catalytic asymmetric direct aldol reaction would allow access to these poly-1,3-diol units in a more efficient manner. Recently, we have developed a highly enantioselective dinuclear Zn-catalyzed direct aldol reaction in which methyl vinyl ketone (MVK) was used as a bifunctional nucleophile (Scheme 3).[4] With this method, we envisioned that the C3–C9 fragment along with the C5 and C7 stereocenters would be constructed in a rapid fashion; meanwhile, an olefin as a precursor for C3–C4 as in enone **9** could provide a functional handle for further elaboration and union with the other fragments. Herein, we describe our detailed efforts towards developing methods for the atom-economic and stereoselective syntheses of bryostatin rings A and B.[5]

Results and Discussion

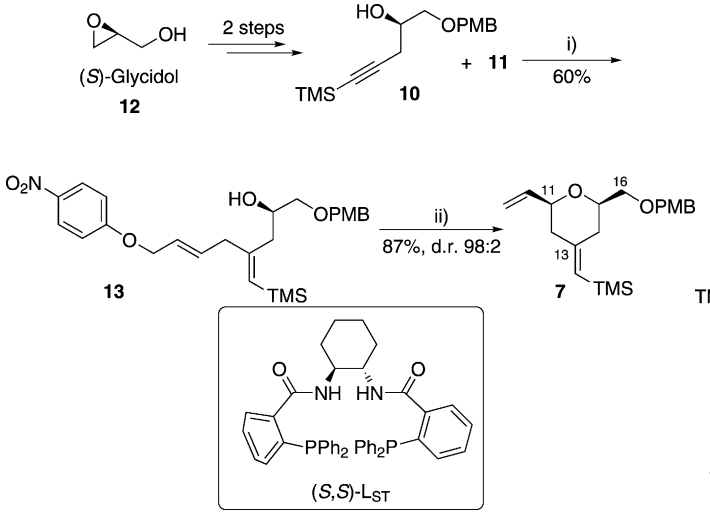
First generation strategy: Our initial strategy for the synthesis of the northern rings A and B is shown in Scheme 3. We envisioned that the C9 methyl ketal in compound **2** could arise from the addition of CH_3OH to the C9–C10 enol ether in **3** under acidic conditions. Enol ether **3** could be obtained through a 6-*exo-dig* oxypalladation cyclization from homopropargyl alcohol **4**. Inspection of intermediate **4** suggested disconnection at the C8–C9 bond, resulting in fragments **5** and **6**. In the forward direction, by using a nucleophile derived from alkyne **5**, attack at the C8 terminus of epoxide **6** was expected to furnish secondary alcohol **4** in the presence of a Lewis acid. Alkyne fragment **5**, containing the ring B subunit would be derived from alkene **7**, which can be ultimately prepared from a Ru-catalyzed alkene–alkyne coupling followed by a Pd-catalyzed cyclization. Epoxide fragment **6** could be prepared from a dinuclear zinc–ProPhenol-catalyzed aldol addition between aldehyde **8** and MVK (**9**).

*Synthesis of alkyne fragment **5***: The synthesis of terminal alkyne **5** commenced with (*S*)-glycidol **12**, which was converted into alkynyl alcohol **10** in two straightforward steps consisting of PMB protection followed by epoxide opening



Scheme 3. First generation approach for the construction of rings A and B of bryostatins. TBDPS = *tert*-butyldiphenylsilyl, PMB = *para*-methoxybenzyl.

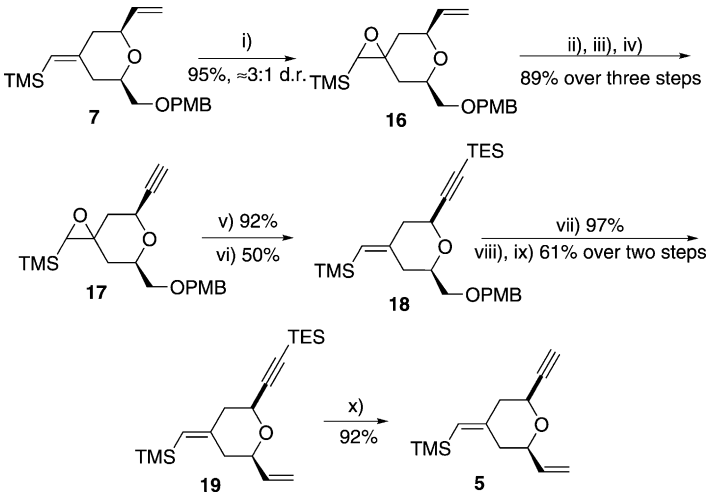
with lithium (trimethylsilyl)acetylide (Scheme 4).[6] The coupling between alkyne **10** and alkene **11** by using the tandem procedure[7] of alkene–alkyne coupling followed by Pd-catalyzed asymmetric allylic alkylation (AAA) proceeded uneventfully to give tetrahydropyran **7**. However, an excess of alkene **11** (5 equiv) was needed for complete consumption of alkyne **10**, and tetrahydropyran **7** had the same R_f value as diene **11**. Thus, a two-step procedure was used to facilitate product purification. It is noteworthy that the stereochemistry at C11 is under ligand control: if the standard Trost ligand (*R,R*)-L_{ST} was employed, the product was obtained as a 97:3 diastereomeric mixture favoring the thermodynamically disfavored 2,6-*trans*-tetrahydropyran, whereas (*S,S*)-L_{ST} gave a 98:2 ratio favoring *cis*-tetrahydropyran **7**. Interestingly, the use of 1,2-bis(diphenylphosphino)ethane (dppe) as a ligand gave a nearly 1:1 ratio of a *cis*/*trans* isomeric mixture. By following this procedure, tetrahydropyran **7** was obtained on a gram scale.



Scheme 4. A tandem Ru-catalyzed ene–yne coupling/Pd-catalyzed allylic alklylation strategy for the formation of ring B. i) $[CpRu(CH_3CN)_3][PF_6]$ (10 mol%), acetone, RT; ii) $[Pd_2(dba)_3]\cdot CHCl_3$ (dba = dibenzylideneacetone; 2 mol%), (*S,S*)-L_{ST} (6 mol%), triethylamine (TEA), CH_2Cl_2.

An efficient way to convert alkene **7** into alkyne **5** would be to oxidatively cleave the terminal alkene, followed by alkynylation of the resulting aldehyde, and then transformation of the OPMB ether into an olefin (Scheme 5). Unfortunately, the electron-rich disubstituted vinylsilane was also reactive under the dihydroxylation conditions. Despite the use of a variety of oxidative cleavage conditions, we were unable to achieve the selective oxidation of the terminal olefin with OsO_4 (**7**→**14**).[8] Given the electron-rich nature of the vinylsilane in diene **7** and relative insensitivity of the epoxidation reaction with peracids towards steric factors, we decided to protect the vinylsilane as an epoxysilane. Treatment of vinylsilane **7** with mCPBA (1.5 equiv) at 0°C gave epoxysilane **16** in 95% yield as a 3:1 diastereomeric mixture (Scheme 6). Oxidative cleavage of the monosubstituted olefin followed by alkyne formation[9] went smoothly to deliver alkyne **17** in 83% yield over three steps.

Scheme 5. Attempted direct functionalization of the terminal olefin proved non-selective.



Scheme 6. Protection of the vinyl silane as an epoxide to achieve selective functionalization of the terminal olefin. i) *meta*-Chloroperoxybenzoic acid (mCPBA), Li_2CO_3 (30%), CH_2Cl_2, 0°C ; ii) OsO_4, *N*-methylmorpholine *N*-oxide (NMO), acetone/H_2O; iii) $NaIO_4$, THF/H_2O; iv) Ohira–Bestmann reagent, K_2CO_3, CH_3OH; v) Sodium hexamethyldisilazane (NaHMDS), triethylsilyl chloride (TESCl), THF, −78°C; vi) $[Rh_2(OAc)_4]$, dimethyl diazomelonate, C_6H_6, 80°C; vii) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), CH_2Cl_2/H_2O; viii) 2-iodoxybenzoic acid (IBX), CH_3CN, 80°C; ix) $Ph_3P{=}CH_2$, toluene, 0°C; x) tetra-*n*-butylammonium fluoride (TBAF), THF/H_2O (95:5), RT.

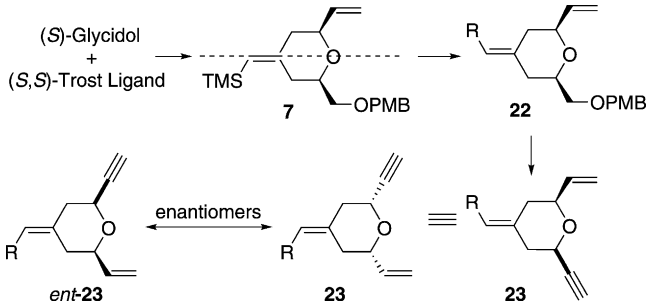
A deoxygenation reaction at this stage to unmask the exocyclic vinylsilane proved to be nontrivial (Table 1). Martin and Ganem reported a mild Rh-catalyzed deoxygenation of epoxides with dimethyl diazomalonate in refluxing benzene with retention of olefin geometry.[10] Under their conditions the deoxygenation of **17** gave the desired vinylsilane **21** as a single isomer (Table 1, entry 1), albeit in low yield (15%). Switching the solvent to chlorobenzene gave only trace amounts of product (Table 1, entry 2). The use of alumina with a catalytic amount of $HgCl_2$ in refluxing toluene/isopropanol[11] led to clean deoxygenation by both TLC and crude ^1H NMR analysis (Table 1, entry 3). Unfortunately, the product was obtained as an inseparable mixture of exocyclic vinylsilane isomers. Deoxygenation employing low valent tungsten, originally reported by Sharpless and Umbreit,[12] gave

Table 1. Deoxygenation studies for compounds **17** and **20**.

	X	Conditions	Product	Yield [%]
1	H	$[Rh_2(OAc)_4]$ (10 mol%), C_6H_6, 80 °C	**21**	15
2	H	$[Rh_2(OAc)_4]$ (10 mol%), C_6H_5Cl, 80 °C	**21**	trace
3	H	Al/$HgCl_2$, C_6H_6/*i*PrOH, reflux	**21** + double bond isomer	clean reaction
4	H	WCl_6, *n*BuLi (3 equiv), −78 °C→RT	baseline material	0
5	H	$(PhO)_3PCH_3I$, BF_3·OEt_2, RT	recovered **17**	0
6	TES	$[Rh_2(OAc)_4]$ (10 mol%), C_6H_6, 80 °C	**18**	52

no reaction at −78 °C and decomposition upon warming (Table 1, entry 4). Treatment with $(PhO)_3PCH_3I$[13] in the presence of BF_3·OEt_2 resulted in no reaction at room temperature (Table 1, entry 5). As the low yield in Table 1, entry 1 was likely caused by reaction between the terminal alkyne and a Rh carbenoid, the terminal alkyne was protected with a TES group and the resulting silylalkyne **20** was subjected to the Rh-catalyzed deoxygenation ($[Rh_2(OAc)_4]$, benzene, 80 °C). Gratifyingly, the desired vinylsilane (**18**) was obtained in 52% yield. With compound **18** in hand, alkyne **5** was obtained smoothly by using a four-step sequence of PMB cleavage, IBX oxidation, Wittig olefination, and TES removal.

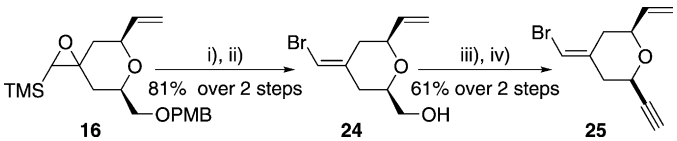
Alternatively, the ring B alkyne subunit could be synthesized by taking advantage of the internal symmetry present in pyran **7** (Scheme 7). If the exocyclic double-bond geometry is inverted, the terminal alkene can be mapped onto the product. To obtain alkyne **5** with the desired absolute stereochemistry for the bryostatin synthesis, (*R*)-glycidol and the (*R,R*)-Trost ligand would be needed.



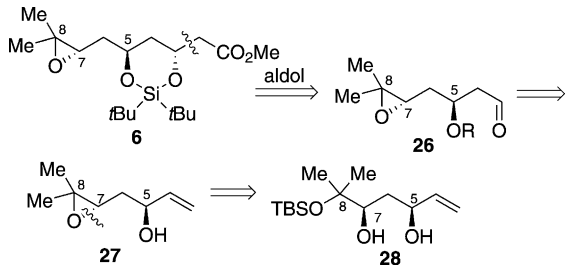
Scheme 7. Route to the desired enyne through the enantiomer of diene **7**.

This route was explored by use of the previously prepared epoxysilane **16** (Scheme 8). Bromide **24** was obtained from epoxide **16** in a two-step sequence (bromohydrin formation and siloxy elimination) in 81% yield.[14] Subsequent oxidation followed by alkyne formation gave alkyne **25**, which possessed all the required functionalities for the epoxide coupling strategy (see Equations (1) and (2), given later) but with the opposite stereochemistry.[15] Changing the starting glycidol and Trost ligand would allow access to the desired enantiomer.

*Efforts towards the synthesis of epoxide fragment **6***: We envisioned that epoxide fragment **6** could be accessed by an ester aldol or Reformatsky reaction from aldehyde **26** (Scheme 9). Aldehyde **26** could be derived from allyl alcohol intermediate **27**, which can ultimately be prepared from diol **28**.



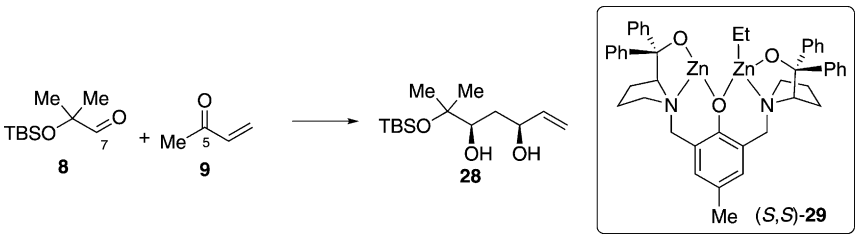
Scheme 8. Inversion of the olefin geometry through manipulation of the epoxide. i) HBr, Et_2O, −50 °C; ii) BF_3·Et_2O, RT; iii) IBX, CH_3CN, 60 °C; iv) Ohira–Bestmann reagent, K_2CO_3, CH_3OH.



Scheme 9. Retrosynthetic analysis of the 1,3-*anti*-diol **6** region of bryostatins. TBS = *tert*-butyldimethylsilyl.

In the forward direction, by utilizing the dinuclear zinc-catalyzed direct aldol addition reaction[4] followed by *cis*-reduction of the crude aldol adduct, diol **28** was rapidly obtained from aldehyde **8** and MVK **9** (Table 2). The yield, d.r. and enantioselectivity were carefully optimized as shown in Table 2. Initially, the effect of temperature was examined (Table 2, entries 1–3). The reaction showed a small inverse relationship between temperature and enantioselectivity, a trait that has been observed previously with this catalyst system.[16] The reaction gave a better yield at higher temperatures, though at ambient temperature the product was obtained impurely (Table 2, entry 3). Longer reaction times caused increased decomposition and lower isolated yields (Table 2, entries 3–5). Increasing the reaction temperature to 50 °C only led to decomposition (Table 2, entry 6). Surprisingly, the use of undistilled MVK at 4 °C led to an improvement in the isolated yield (Table 2, entry 7). As commercial MVK contains a small amount of acetic acid and hy-

Table 2. Optimization of the dinuclear zinc-catalyzed direct aldol addition reaction.[a]



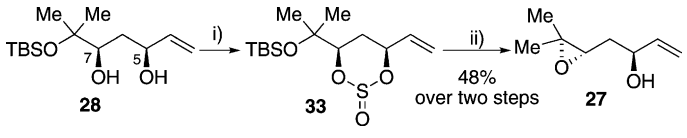
	Catalyst [mol%]	T [°C]	T [h]	Additives	Yield [%][b]	*ee* [%][c]	d.r.[d]
1	10	−15	7	*i*PrOH (5 equiv)	20	93	24:1
2	10	4	7	*i*PrOH (5 equiv)	25	97	22:1
3	10	25	7	*i*PrOH (5 equiv)	41	97	18:1
4	10	25	9	*i*PrOH (5 equiv)	25	96	38:1
5	10	25	24	*i*PrOH (5 equiv)	25	98	26:1
6	10	50	9	*i*PrOH (5 equiv)	0	–	–
7	10	4	7	*i*PrOH (5 equiv), AcOH (0.6%), hydroquinone (3%)	45	98	35:1
8	10	4	7	*i*PrOH (5 equiv), AcOH (1.6%), hydroquinone (3%)	52	97	31:1
9	5	4	7	*i*PrOH (5 equiv), AcOH (1.6%), hydroquinone (3%)	50	90	25:1
10	10	25	7	*i*PrOH (5 equiv), AcOH (1.6%), hydroquinone (3%)	32	98	17:1
11	10	25	4	*i*PrOH (5 equiv), AcOH (1.6%), hydroquinone (3%)	40	92	50:1
12	10	4	20	*i*PrOH (5 equiv), AcOH (1.6%), hydroquinone (3%)	trace	–	–
13	10	4	7	methyl β-hydroxypropionate (16 equiv)	16	84	25:1

[a] Conditions: (*S*,*S*)-**29**, toluene, 4 Å molecular sieves, then Et_2BOMe, $NaBH_4$. [b] Isolated yield. [c] *ee* was determined by HPLC. [d] d.r. was determined by ^1H NMR spectroscopy.

droquinone to prevent polymerization, acetic acid is probably responsible for the increase in yield. Indeed, adding an additional 1% acetic acid gave an even better result (Table 2, entry 8). It is likely that acetic acid could serve as a buffer for the system, thus mitigating the undesired elimination pathway. Lowering the catalyst loading gave a slightly reduced yield, with only a modest drop in enantioselectivity (Table 2, entry 9). Raising the temperature gave a poor yield, even after shorter reaction times (Table 2, entries 10–11). Increasing the amount of added acetic acid to 2% resulted in the observation of only trace amounts of product (Table 2, entry 12). The use of methyl β-hydroxypropionate, an achiral additive that found some success in a similar system, gave little conversion.[16] From these studies, the most practical set of conditions emerged as those shown in Table 2, entry 8, and the desired reduced adduct **28** was obtained in 52% yield over two steps with 97% *ee* and 31:1 d.r. in favor of the desired diastereomer. This method provides a facile route for the installation of two of the stereocenters in epoxide fragment **6**.

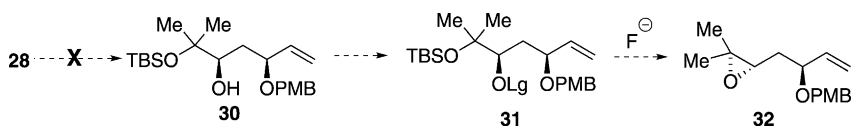
Protection of the less hindered allylic alcohol as a PMB ether was envisioned to differentiate the two alcohols, which vary in their steric environment (Scheme 10). After PMB installation, transformation of the more hindered alcohol into a leaving group would allow for epoxide formation. Unfortunately, chemoselective PMB protection of the allylic alcohol proved problematic. For example, treatment of **28** with PMBCl and sodium hydride in DMF, or use of PMB trichloroacetimidate with catalytic trifluoromethanesulfonic acid, gave only recovered starting material. Attempted formation of the tin acetal was also unsuccessful, even after reflux for 36 h. The use of catalytic tetrabutylammonium iodide (TBAI) to further activate the PMBCl in situ gave no desired product at ambient temperature, but did give the desired product at reflux, though as a mixture of the two isomeric products.

Consequently, an alternative approach was undertaken in which the diol was transformed into the diastereomeric cyclic sulfites **33**, thus activating the C7 alcohol for intramolecular S_N2 inversion to form the epoxide, while differentiating the two alcohols by tying them into a ring and thus preventing attack of the tertiary alcohol at the allylic C5 site (Scheme 11). After generation of the



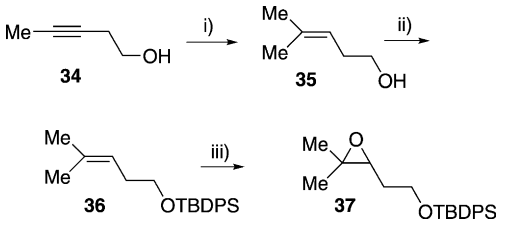
Scheme 11. Epoxide formation. i) $SOCl_2$, Et_3N, CH_2Cl_2, 0°C; ii) TBAF, THF, reflux.

diastereomeric sulfites, a variety of conditions were attempted for the desilylation to form desired epoxide **27**. Treatment with an anhydrous fluoride source, tetrabutylammonium triphenyldifluorosilicate (TBAT) or $3HF{\cdot}NEt_3$, did not give the desired product or recovered starting material. If TBAF was used as the fluoride source in THF, the desired product was isolated in an 18% yield at ambient temperature, and 48% yield under reflux. The reaction was shown to be successful by TLC, but the isolated yield was low. This is probably caused by the volatility of product **27**, or the instability of the compound, as it was found to decompose upon storage at −15°C. In an effort to solve both of these problems, the epoxide was subjected to silylation conditions with TBDPSCl and imidazole in DMF, but this resulted in decomposition.



Scheme 10. Failed elaboration of diol **28**. Lg = leaving group.

Meanwhile, we conducted a parallel study to investigate the feasibility of the proposed alkyne–epoxide coupling reaction (see Scheme 3). Sterically, although the C8 position is more substituted and therefore more hindered than C7, nucleophilic attack at C7 would also be difficult due to its pseudoneopentyl nature (next to C8). Accordingly, the steric difference between C7 and C8 during nucleophilic attack could be small. On the other hand, when Lewis acids are employed in the reaction, their coordination to the epoxide will weaken the C8–O bond more than the C7–O bond because of the relief of steric congestion around C8, and the ability of a tertiary carbon to stabilize a positive charge. Therefore, electronically, nucleophilic attack at the C8 terminus of the epoxide would be favored. A recent publication by Zhao and Pagenkopf provides further support for this analysis.[17] To this end, model epoxide **37** was synthesized from 3-pentyne-1-ol **34** in three steps (Scheme 12).[18] Carbometallation of 3-pentyne-1-ol **34**

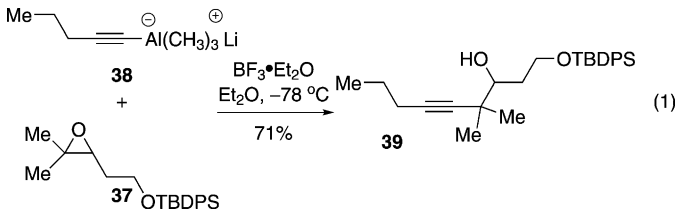


Scheme 12. Preparation of model epoxide **37**. i) $Al(CH_3)_3$, $TiCl_4$, THF, CH_2Cl_2, −78 °C; ii) TBDPSCl, imidazole, DMF; iii) mCPBA, CH_2Cl_2.

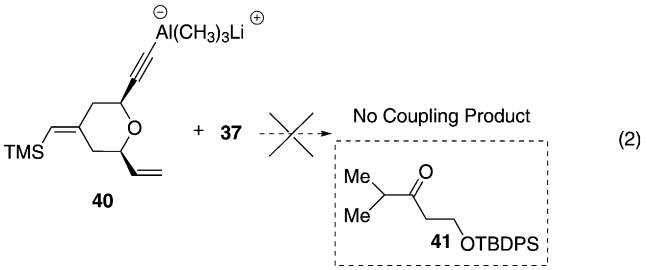
($TiCl_4$, $Al(CH_3)_3$, CH_2Cl_2/THF, −78 °C) was clean but incomplete. The product was obtained as a mixture of starting material **34** and olefin **35** in approximately a 1:2 ratio, which was carried over two steps (TBDPS protection and epoxidation) to provide epoxide **37**.

This set the stage for examination of the proposed epoxide-opening reaction. Following the procedure by Zhao and Pagenkopf,[17] lithium acetylide trimethylaluminum ate complex **38** (derived from pentyne) reacted with trisubstituted epoxide **37** in the presence of $BF_3{\cdot}OEt_2$, providing secondary alcohol **39**, which indicates that the attack at the more hindered position was indeed favored [Eq. (1)]. Formation of the other regioisomer could not be completely excluded since the ^{1}H NMR spectrum was not very clean; however, the major signal at 3.64 ppm ($CDCl_3$, ddd, J = 1.5, 4.0, 10.5 Hz, assigned to the proton next to the hydroxyl group in **39**) indicated that secondary alcohol **39** was the major component (>85 %). The use of the trimethylaluminum ate complex is crucial since lithiated pentyne resulted in no reaction.

Encouraged by this model study, the coupling between alkyne **5** and epoxide **37** was subsequently attempted. Unfortunately, under the Zhao and Pagenkopf conditions, no reaction occurred. Upon warming, epoxide **37** underwent rearrangement to give ketone **41** [Eq. (2)]. Changing the solvent (THF, hexane, or toluene), the Lewis acid ($Al(CH_3)_3$,

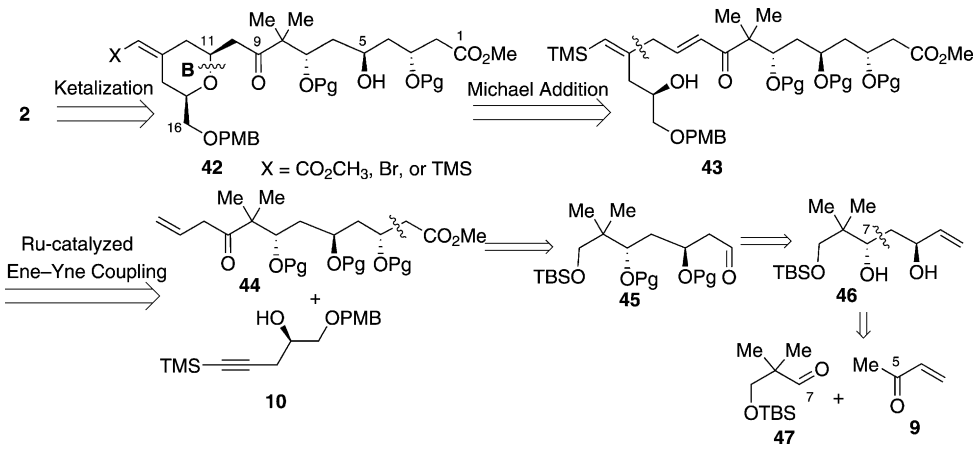


$Zn(OTf)_2$, $Al(OTf)_3$, or $B(C_6F_5)_3$), or the order of addition did not provide promising results.



Second generation strategy: Although there are other possible ways to carry out the epoxide-opening strategy, the difficulties associated with the ring-opening reaction prompted us to re-evaluate our approach to the northern fragment. At the outset, we decided to form the hindered C8–C9 bond early in the synthesis. Our alternative, second-generation strategy is shown in Scheme 13. We envisioned that the ring A moiety, along with the C9 methyl ketal in **2**, could be installed through an acid-catalyzed ketalization reaction with CH_3OH from hydroxyketone **42**. The presence of the C–O bond at C11, which is β to the C9 ketone, suggested that a Michael addition would construct the C11–O bond and ring B simultaneously. The requisite α,β-unsaturated ketone **43** contains a 1,4-diene, which is the characteristic functionality obtained from our Ru-catalyzed alkene–alkyne coupling reaction. Enone fragment **44** could be derived from aldehyde **45** through functional group manipulations in which the C2–C3 bond could be formed by either an ester aldol or a Reformatsky reaction. In analogy with our first-generation strategy, the aldehyde intermediate (**45**) would be prepared from diol **46**, which could be efficiently synthesized through a dinuclear Zn-catalyzed direct aldol reaction from aldehyde **47** and MVK **9**.

This new strategy revealed a novel enyne coupling reaction to construct ring B of bryostatins because one of the coupling partners, the β,γ-enone, had never before been used in the Ru-catalyzed ene reaction. One immediate concern was the stability of β,γ-enones in the presence of the cationic Ru catalyst since they are prone to isomerization in the presence of Brønsted or Lewis acids. Thus, we decided to address these issues with a model system [Eq. (3)].[15] The initial model studies gave surprising but gratifying results (Table 3). If a 1:1 mixture of alkyne **10** and β,γ-enone **48a**

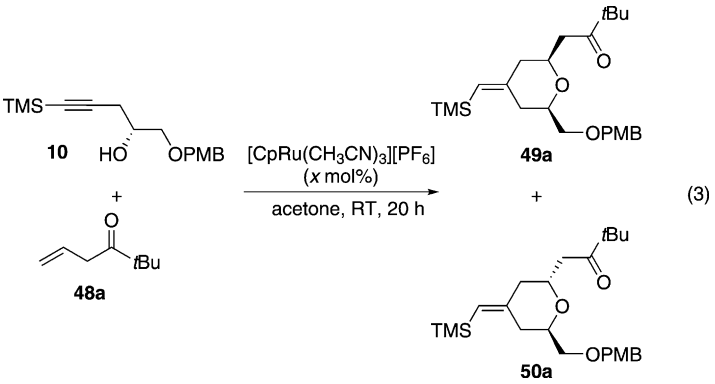


Scheme 13. Retrosynthetic analysis featuring an ene–yne coupling/Michael addition reaction.

was treated with $[CpRu(CH_3CN)_3][PF_6]$ (10 mol%) in acetone at room temperature, diene **51a** was not observed. Instead the cyclized product, 2,6-*cis*-dihydropyran **49a**, was isolated in a 31% yield (Table 3, entry 1). The *cis* configuration was confirmed by nOe studies. The potential minor product **50a** (2,6-*trans*) was not isolated in this case. To achieve both reasonable conversion and yield, excess enone was employed (Table 3, entry 2). Higher concentrations led to increased conversion, as typically expected for a bimolecular reaction (Table 3, entry 3). Interestingly, increased catalyst loading did not improve the yield substantially (Table 3, entry 4). The best yield was achieved by using 3 equivalents of enone with acetone as the solvent at 0.4 M concentration of alkyne (Table 3, entry 5; recovery of enone **48a** was not attempted due to its volatility.)

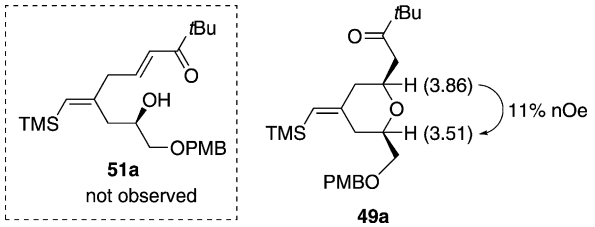
Encouraged by this model study, we decided to probe the scope and limitations of this reaction, with an emphasis on substrates that may prove useful for the construction of rings A and B of bryostatins. Accordingly, a variety of homopropargylic alcohols and β,γ-enones were prepared (Scheme 14). In general, the homopropargylic alcohols were synthesized through epoxide opening with lithium (trimethylsilyl)acetylide (method A; Scheme 14); β,γ-enones were accessed either through a two-step sequence (method B: allylation then oxidation; Scheme 14) or a $BiCl_3$–NaI or $BiCl_3$–ZnI_2 catalyzed Friedel–Crafts acylation reported by Le Roux and Dubac[19] (method C; Scheme 14).

The propargylic alcohols and β,γ-enones were then subjected to the optimized coupling/cyclization conditions. The results are summarized in Table 4. A variety of functional groups, including PMB, TBS, and acetyl

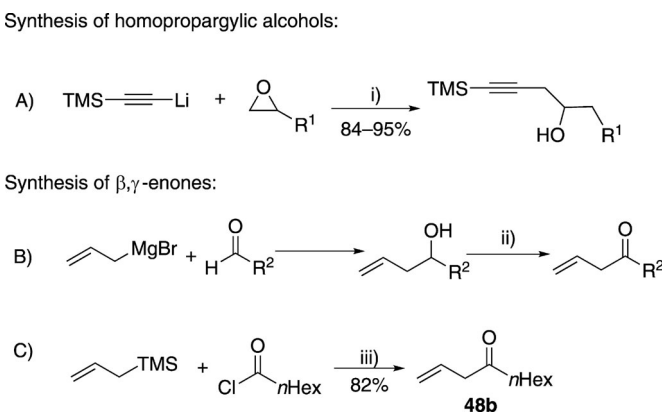


are tolerated in this reaction. Since excess enone was necessary to achieve a reasonable conversion and yield, the ability to recover the unreacted enone was crucial. To our delight, enones with *tert*-alkyl groups could be mostly recovered (Table 4, entries 3, 5, and 6), which boded well for our bryostatin synthesis. On the other hand, if dec-1-ene-4-one

Table 3. Optimization of the Ru-catalyzed ene–yne/Michael addition reaction.

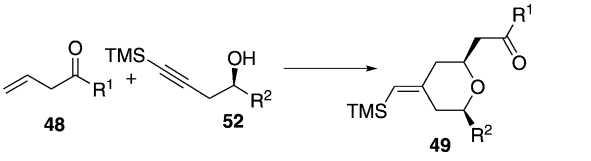


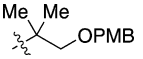
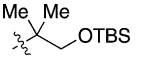
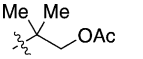
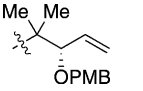
	Concentration [M]	Catalyst loading [mol%]	**48a**:**10**	Yield **49a** [%] (**50a** [%])
1	0.1	10	1:1	31
2	0.1	10	1.8:1	43 (6)
3	0.4	10	1.2:1	41 (6)
4	0.1	30	1:1	36
5	0.4	10	3:1	68 (15)



Scheme 14. Synthesis of substrates for the ene–yne coupling reaction. i) BF_3·Et_2O, THF, −78°C; ii) Dess–Martin Oxidation; iii) $BiCl_3$ (2.5 mol%), NaI (7.5 mol%), CH_2Cl_2, RT (*n*Hex = *n*-hexyl).

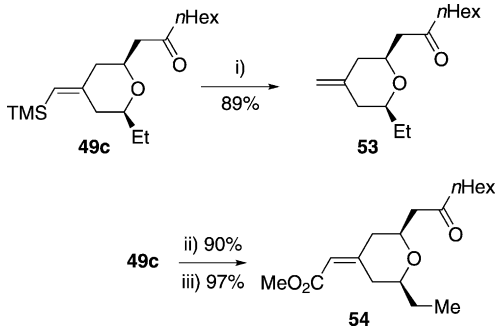
Table 4. Tandem alkyne–enone coupling/Michael addition reaction.[a]



	R^1	R^2	Yield **49** [%] (recovered **48** [equiv])
1	*t*Bu	Et	80
2	*n*Hex	Et	62
3		CH_2OPMB (**10**)	69 (1.8)
4		CH_2OPMB (**10**)	58
5		CH_2OPMB (**10**)	77 (1.9)
6		CH_2OPMB (**10**)	39 (1.9)

[a] **48** (3 equiv), **52** (1 equiv), $[CpRu(CH_3CN)_3][PF_6]$ (10 mol%), acetone (0.5 M), RT, 40 h.

was used, it was recovered together with 15–20% of the α,β-enone isomer as an inseparable mixture (Table 4, entry 2). Interestingly, complete chemoselectivity was observed in the reaction of a compound with two different types of double bond (Table 4, entry 6). No product derived from the coupling of the alkyne with the double bond bearing an allylic oxygen was detected. The *cis*/*trans* ratios ranged from 5:1–8:1. Preliminary studies suggested that the *cis*- and *trans*-isomers were not equilibrating under the reaction conditions. Attempts to establish the thermodynamic ratio were thwarted by acid- and base-mediated decomposition.



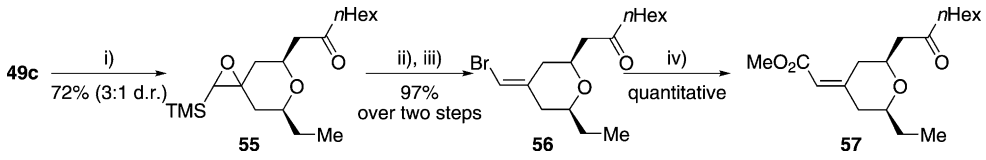
Scheme 15. Functionalization of the vinyl silane. i) Trifluoroacetic acid (TFA), toluene, 0°C to RT; ii) *N*-iodosuccinimide (NIS), CH_3CN; iii) $[PdCl_2(PhCN)_2]$, 1,1′-bis(diphenylphosphino)ferrocene (dppf), CH_3OH, CO.

The geometrically defined exocyclic vinylsilane resulting from the ruthenium-catalyzed enyne-coupling/Michael addition provides a convenient handle for further functionalization (Scheme 15). Protiodesilylation of **49c** went smoothly to give terminal alkene **53** without double-bond migration. Vinyl iodide formation also proceeded efficiently and the product was subsequently carbonylated to give α,β-unsaturated methyl ester **54**. Furthermore, we were able to invert the double-bond geometry through an epoxidation, bromohydrin formation, and siloxy elimination sequence to give inverted bromide **56** (Scheme 16), which was then carbonylated to give methyl enoate **57** with high efficiency. Thus, from one geometrically defined vinylsilane, either geometric isomer of the exocyclic enoate is cleanly available.

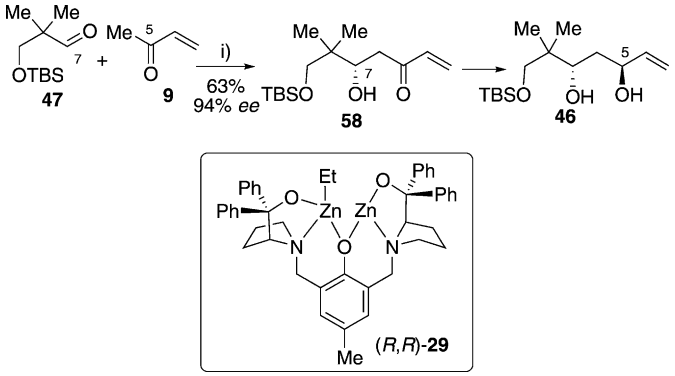
*Synthesis of β,γ-enone fragment **44***: Efforts were next directed towards the synthesis of the β,γ-enone fragment for the real system. Aldol adduct **58** is available in good yield and excellent enantioselectivity from the dinuclear zinc-catalyzed MVK aldol reaction with aldehyde **47** (containing one more methylene unit than aldehyde **8** used for the epoxide-opening strategy).[20] The opposite enantiomer of the catalyst [(*R*,*R*)-**29**] was used for this reaction, as the C7 stereocenter would not be inverted in this strategy (Scheme 17).

To obtain the desired stereochemistry at the C5 position, a *trans* reduction of β-hydroxyl ketone **58** was required. The Evans acetoxyborohydride reagent is a commonly employed strategy for the synthesis of *anti* diols from β-hydroxyketones.[21] However, this reaction proceeds slowly at low temperature, but gives poorer selectivities at higher temperature. To balance reactivity and selectivity, a brief survey of reaction conditions was undertaken (Table 5). The use of sodium acetoxyborohydride at −10°C gave incomplete conversion and moderate selectivity (Table 5, entry 1). Switching to the more reactive tetramethylammonium counterion, the reaction temperature could be lowered to −20°C, and both the yield and diastereoselectivity were improved (Table 5, entry 2). Increasing the amount of the reducing agent increased the conversion and yield, though it lowered the diastereoselectivity (Table 5, entry 3).

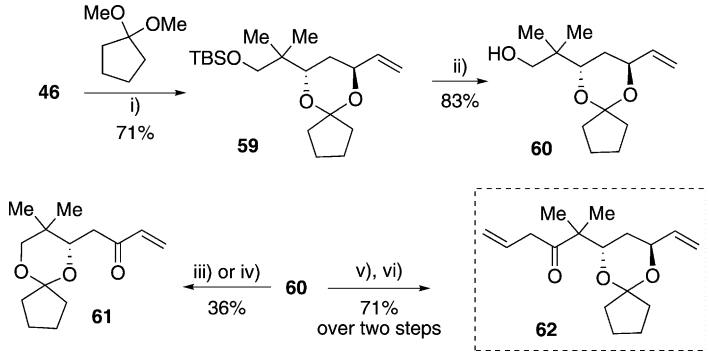
Diol **46** was then protected with a cyclopentanone-derived ketal (Scheme 18). Subsequent removal of the silyl group provided free alcohol **60**, which set the stage for the installation of the β,γ-unsaturated ketone. Unexpectedly, oxidation of the primary alcohol by using IBX or TPAP/NMO caused rearrangement of the cyclic acetal, and the resultant allylic



Scheme 16. Inversion of the olefin geometry. i) mCPBA, Li_2CO_3, CH_2Cl_2; ii) aqueous HBr, CH_3OH, −78°C; iii) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −50 to 10°C; iv) $[Pd(PPh_3)_4]$, DMF, CH_3OH, CO, 85°C.



Scheme 17. ProPhenol–zinc-catalyzed asymmetric aldol reaction. i) (*R*,*R*)-**29**, toluene, 4 Å molecular sieves, *i*PrOH (5 equiv), −15 °C.



Scheme 18. i) Camforsulfonic acid (CSA; 1 mol%), CH_2Cl_2, 0 °C; ii) TBAF, THF; iii) IBX, AcCN; iv) tetrapropylammonium perruthenate (TPAP), NMO; v) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C, then allylMgBr, Et_2O; vi) Dess–Martin periodinane (DMP), $NaHCO_3$, CH_2Cl_2.

Table 5. The *trans* reduction of β-hydroxyl ketone.

	Conditions	Yield **46** [%] (recovered **58** [%])[a]	d.r.[b]
1	$NaB(OAc)_3H$ (5 equiv), AcOH/acetone, −10 °C	56 (11)	5:1
2	$NMe_4B(OAc)_3H$ (5 equiv), AcOH/acetone, −20 °C	54 (26)	9:1
3	$NMe_4B(OAc)_3H$ (10 equiv), AcOH/acetone, −20 °C	69 (0)	5:1

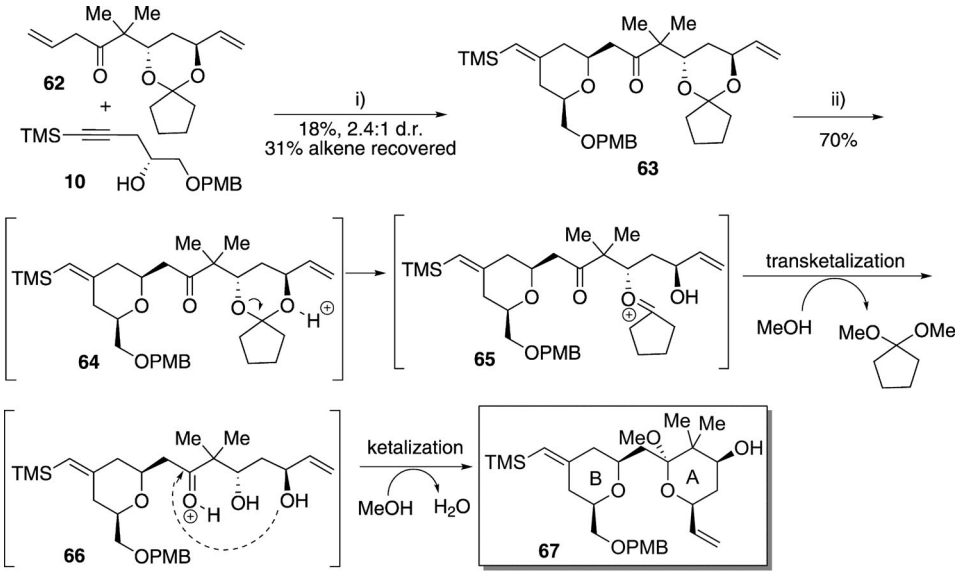
[a] Isolated yield. [b] d.r. was determined by ^1H NMR spectroscopy.

alcohol was oxidized to give enone **61**. Fortunately, oxidation under Moffat–Swern conditions, followed by quenching with allylmagnesium bromide, provided the desired homoallylic alcohol. Oxidation of the resulting diastereomeric alcohols with DMP furnished the desired β,γ-unsaturated ketone **62** in 71% yield over the two steps.

Proof of principle: Synthesis of fragment 67, containing both the ring A and B subunits: At this stage, we investigated the ene–yne coupling/1,4-addition reaction to construct bryostatin ring B (Scheme 19). Gratifyingly, submission of β,γ-unsaturated ketone **62** and alkyne **10** to the reaction conditions developed earlier (see Tables 3 and 4) afforded desired tetrahydropyran **63**, in spite of the presence of a second terminal olefin. A portion of starting alkene **62** could be recovered. The low yield of this reaction was attributed to the instability of the ketal moiety to the Lewis acidic ruthenium catalyst, as well as competitive binding of the allyl ether double bond with the catalyst. Since this was only a proof-of-principle, no effort was made to optimize the yield for this example. Nevertheless, the success of this method in uniting the two components and forming the desired bryostatin ring B proved the utility of the Ru-catalyzed tandem coupling/cyclization reaction as a viable strategy for bryostatin synthesis. Subsequently, treatment of tetrahydropyran **63** with a catalytic amount of CSA in MeOH resulted in a tandem transketalization/ketalization sequence that ultimately provided compound **67**, containing both rings A and B of bryostatins.

Conclusion

During our continuing efforts towards the total synthesis of the bryostatin family, we have developed methods for the stereoselective assembly of the ring A and B subunits. For the synthesis of bryostatin ring B, a new method for the ste-



Scheme 19. Completion of rings A and B of bryostatins. i) $[CpRu(CH_3CN)_3][PF_6]$ (10 mol%), acetone, RT; ii) CSA (10 mol%), MeOH.

reoselective synthesis of tetrahydropyran rings was disclosed, which features a Ru-catalyzed tandem alkene–alkyne coupling/Michael addition sequence. For the assembly of the bryostatin ring A subunit, a dinuclear zinc-catalyzed MVK aldol strategy was explored for the construction of the polyacetate entities. Furthermore, an acid-catalyzed cascade transketalization/ketalization sequence provided an advanced intermediate containing both rings A and B. All of these highly chemoselective and/or atom-economical methods set the stage for further advances towards the total synthesis of the bryostatins.[22]

Experimental Section

General procedure for carrying out the Ru-catalyzed alkyne–β,γ-enone coupling reaction: A point-shaped vial equipped with a stirring bar and capped with a rubber septum was flame-dried and cooled under an argon atmosphere. The septum was temporarily removed to allow the addition of the alkyne (0.25 mmol), enone[22] (0.75 mmol), and acetone (0.5 mL). After stirring at room temperature for 5 min to ensure the formation of a homogeneous solution, the septum was again removed and [CpRu-$(CH_3CN)_3$][PF_6] (11 mg, 0.025 mmol) was added quickly. The vial was sealed and the septum was wrapped with black electric tape. The reaction mixture 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 to give the desired product.

Compound ***49a***: R_f=0.38 (6% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.25 (d, J=8.6 Hz, 2H), 6.87 (d, J=8.8 Hz, 2H), 5.27 (s, 1H), 4.49 (dd, J=11.8, 15.5 Hz, 2H), 3.88–3.83 (m, 1H), 3.80 (s, 3H), 3.53–3.49 (m, 1H), 3.49–3.42 (m, 2H), 2.91 (dd, J=5.7, 16.7 Hz, 1H), 2.54 (dd, J=7.0, 17.0 Hz, 1H), 2.38 (dt, J=2.0, 13.5 Hz, 1H), 2.24 (dt, J=2.0, 13.0 Hz, 1H), 1.98–2.02 (m, 2H), 1.12 (s, 9H), 0.08 ppm (s, 9H); ^{13}C NMR (125 MHz, CCl_3): δ=213.5, 159.1, 152.4, 130.3, 129.2, 123.9, 113.7, 77.4, 75.1, 72.9, 72.8, 55.2, 45.0, 44.2, 43.1, 36.4, 26.1, 0.2 ppm; IR (neat film): $\tilde{\nu}$=1701, 1615, 1585, 1512, 1473, 1460, 1362, 1245, 1099, 1035, 837 cm^{-1}; HRMS calcd for $C_{20}H_{29}O_4Si$: 361.1835 $[M-C_4H_9]^+$; found: 361.1835.

Compound ***50a***: R_f=0.28 (6% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.26 (d, J=8.7 Hz, 2H), 6.87 (d, J=8.7 Hz, 2H), 5.27 (s, 1H), 4.47 (dd, J=11.6, 13.9 Hz, 2H), 4.36–4.32 (m, 1H), 3.94–3.89 (m, 1H), 3.80 (s, 3H), 3.52 (dd, J=5.9, 9.8 Hz, 1H), 3.44 (dd, J=5.5, 9.8 Hz, 1H), 2.72 (d, J=6.5 Hz, 2H), 2.43 (dd, J=3.3, 13.1 Hz, 1H), 2.38 (dd, J=4.4, 13.7 Hz, 1H), 2.21 (dd, J=6.5, 13.4 Hz, 1H), 2.02 (dd, J=6.2, 13.2 Hz, 1H), 1.12 (s, 9H), 0.09 ppm (s, 9H); ^{13}C NMR (125 MHz, CCl_3): δ=213.4, 159.2, 150.3, 129.4, 125.9, 113.7, 73.1, 72.1, 71.2, 69.6, 55.3, 44.3, 43.8, 40.2, 35.6, 26.2, 26.1, 0.2 ppm; IR (film): $\tilde{\nu}$=1703, 1611, 1582, 1509, 1461, 1364, 1301, 1242, 1170, 1097, 1029, 835 cm^{-1}; HRMS calcd for $C_{20}H_{29}O_4Si$: 361.1835 $[M-C_4H_9]^+$; found: 361.1833.

Synthesis of compound 28:

Catalyst preparation: *S*,*S*-ProPhenol ligand **29** (70.2 mg, 0.11 mmol) was added to a flame-dried test tube containing a stirring bar. The ligand was then azeotroped three times with benzene (1 mL each) and dissolved in toluene (0.40 mL). Diethylzinc (1 M in hexanes, 0.20 mL, 0.20 mmol) was added slowly. Isopropanol (0.4 mL, 5.22 mmol) and acetic acid (0.1 mL, 1 M in toluene, 0.01 mmol) were then added and the catalyst was allowed to stir at ambient temperature for 30 min.

Aldol reaction: Aldehyde **8**[23] (202.8 mg, 1.00 mmol) and methyl vinyl ketone **9** (undistilled, 0.50 mL, 6.2 mmol) were added to a flame-dried test tube equipped with molecular sieves (4 Å; 203 mg) and a stirring bar. The catalyst solution was then added and the reaction was stirred at 4 °C for 7 h. The reaction mixture was then poured into phosphate buffer (1 M, pH 7) and extracted with petroleum ether/diethyl ether (1:1). The organic layer was then washed twice with phosphate buffer (1 M, pH 7) and once with brine. The aqueous layers were extracted twice with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to give the aldol adduct as a yellow oil, which was used directly in the following reaction. ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.38 (dd, J=10.4, 17.6 Hz, 1H), 6.23 (dd, J=1.2, 17.6 Hz, 1H), 5.86 (dd, J=1.2, 10.4 Hz, 1H), 3.82 (dd, J=2.4, 9.6 Hz, 1H), 2.83 (dd, J=2.4, 16.4 Hz, 1H), 2.64 (dd, J=9.6, 16.4 Hz, 1H), 1.23 (s, 3H), 1.21 (s, 3H), 0.85 (s, 9H), 0.10 (s, 3H), 0.09 ppm (s, 3H); IR (thin film): $\tilde{\nu}$=3423, 2952, 2929, 2860, 1677, 1590, 1460, 1404, 1363, 1252, 1155, 1122, 1090, 1044, 831, 771 cm^{-1}.

Reduction reaction: The crude aldol adduct from above was dissolved in 20% methanol/THF (10.0 mL) and then diethylmethoxyborane (0.8 mL, 6.09 mmol) was added. The reaction vessel was cooled to −78 °C and sodium borohydride (49.2 mg, 1.30 mmol) was added. The reaction mixture was stirred for 2.5 h, quenched with glacial acetic acid (0.1 mL) and warmed to ambient temperature. The mixture was then poured into diethyl ether and washed four times with saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, concentrated in vacuo, and then chromatographed with a solvent gradient (0–1% v/v diethyl ether/petroleum ether) to give **28** (141.7 mg, 52% yield over two steps, 97% *ee*, 31:1 d.r.) as a yellow oil. Chiral GC (Cyclosil B): 100 °C for 20 min then ramped up at 5 °C min^{-1} to 200 °C: t_r (major enantiomer, minor diastereomer)=35.81 min, t_r (minor enantiomer, minor diastereomer)=35.91 min, t_r (minor enantiomer, major diastereomer)=36.09 min, t_r (major enantiomer, major diastereomer)=36.25 min; R_f=0.8 (10% v/v ethyl acetate/petroleum ether); $[\alpha]_D^{25}$=−1.2 (c=1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=5.85 (ddd, J=5.4, 10.5, 17.1 Hz, 1H) 5.30 (dt, J=17.2, 1.5 Hz, 1H), 5.11 (dt, J=10.5, 1.3 Hz, 1H), 4.37–4.42 (m, 1H), 3.67 (dd, J=2.8, 11.4 Hz, 1H), 2.01 (dt, J=13.8, 2.8 Hz, 1H), 1.45 (ddd, J=2.4, 11.4, 13.8 Hz, 1H), 1.23 (s, 3H), 1.16 (s, 3H), 0.83 (s, 9H), 0.07 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=139.33, 114.49, 77.92, 74.70, 71.84, 33.00, 27.24, 25.78, 24.11, 18.11, 7.77, −2.16 ppm; IR (thin film): $\tilde{\nu}$=2958, 2931, 2884, 2858, 1740, 1673, 1648, 1614, 1472, 1463, 1392, 1354, 1326, 1292, 1254, 1216, 1169, 1138, 1091, 1044, 1006, 989, 925, 903, 835, 812, 774, 708, 694, 680, 653 cm^{-1}; elemental analysis calcd (%) for: C 61.26, H 11.02; found: C 61.47 H 11.01.

Synthesis of compound 27: Diol **28** (119.3 mg, 0.435 mmol) was dissolved in CH_2Cl_2 (3.3 mL, 0.1 M) and triethylamine (0.3 mL, 2.15 mmol) was then added. The reaction was cooled to 0 °C and then thionyl chloride (0.75 M in CH_2Cl_2, 1.2 mL, 0.9 mmol) was added. The reaction was stirred for 10 min and then quenched with water, diluted with CH_2Cl_2, washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to give the crude diastereomeric cyclic sulfites, which were used without purification. The crude cyclic sulfites were dissolved in THF (6.5 mL) and then TBAF (1 M in THF, 2.2 mL, 2.2 mmol) was added. The solution was heated to reflux for 15 min, after which it was cooled to ambient temperature, diluted with diethyl ether, washed with water and brine, dried (Na_2SO_4), filtered, concentrated in vacuo, and chromatographed with a solvent gradient (10–20% v/v ethyl acetate/petroleum ether) to give epoxide **27** (29.8 mg, 48% yield over 2 steps) as a dark orange oil. $[\alpha]_D^{25}$=−3.2 (c=0.56 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=5.92 (ddd, J=5.5, 10.5, 17.5 Hz, 1H), 5.27 (d, J=17.5 Hz, 1H), 5.12 (d, J=10.5 Hz, 1H), 4.34 (br q, J=5.5 Hz, 1H), 2.93 (dd, J=4.5 Hz, 7.5 Hz, 1H), 2.12 (br s, 1H), 1.81 (ddd, J=4.5, 7.5, 14.5 Hz, 1H), 1.67 (ddd, J=4.5, 7.5, 14.5 Hz, 1H), 1.29 (s, 3H), 1.25 ppm (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$): δ=140.5, 114.7, 70.9, 61.2, 58.3, 35.8, 24.7, 18.9 ppm; IR (thin film): $\tilde{\nu}$=3426, 3082, 2964, 2926, 1708, 1645, 1459, 1427, 1380, 1325, 1252, 1206, 1123, 1053, 993, 923, 898, 848, 784, 760, 679 cm^{-1}; LRMS calcd for $C_8H_{15}O_2$: 143.1; found: 143.1.

Synthesis of compound 58:

Catalyst preparation: (*R*,*R*)-ProPhenol ligand **29** (35.9 mg, 0.056 mmol) was added to a flame-dried test tube containing a stirring bar. The ligand was azeotroped three times with benzene (1 mL each) and then dissolved in toluene (0.20 mL), and diethylzinc was added slowly (1 M in hexanes, 0.10 mL, 0.10 mmol). Isopropanol (0.2 mL, 2.6 mmol) was then added and the catalyst solution was allowed to stir at ambient temperature for 30 min.

Aldol reaction: Aldehyde **47**[24] (111.7 mg, 0.52 mmol) and methyl vinyl ketone **9** (freshly distilled, 0.50 mL, 6.2 mmol) were added to a flame-

dried test tube equipped with molecular sieves (4 Å; 110.7 mg) and a stirring bar. The catalyst was then added and the reaction was stirred at 4 °C for 7 h. The reaction mixture was then poured into phosphate buffer (1 M, pH 7) and extracted with petroleum ether/diethyl ether (1:1). The organic layer was washed twice with phosphate buffer (1 M, pH 7) and once with brine. The aqueous layers were extracted twice with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo, and chromatographed with a solvent gradient (2–10 % v/v diethyl ether/petroleum ether) to give compound **58** (93.1 mg, 63 % yield, 94 % *ee*) as a light yellow oil. HPLC: AD column, 230 nm, 1.0 mL min^{-1}, 99.5:0.5 heptane/isopropanol, t_r (minor) = 11.124 min, t_r (major) = 12.918 min; R_f = 0.65 (20 % ethyl acetate/petroleum ether); $[\alpha]_D^{24} = -26.0$ (c = 2.69 in CH_2Cl_2,); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.37 (dd, J = 10.5, 17.5 Hz, 1H), 6.21 (dd, J = 1.1, 17.5 Hz, 1H), 5.81 (dd, J = 1.1, 10.5 Hz, 1H), 4.03 (dt, J = 9.6, 2.9 Hz, 1H), 3.61 (d, J = 3.2 Hz, 1H), 3.44–3.46 (m, 2H), 2.72 (dd, J = 9.6, 16.0 Hz, 1H), 2.63 (dd, J = 2.7, 15.9 Hz, 1H), 0.88 (s, 3H), 0.85 (s, 9H), 0.81 (s, 3H), 0.020 (s, 3H), 0.019 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.0, 136.9, 128.5, 74.2, 71.9, 41.9, 38.4, 25.8, 21.8, 19.2, 18.2, −5.6, −5.7 ppm; IR (thin film) $\tilde{\nu}$ = 3500, 2926, 2855, 1746, 1681, 1619, 1590, 1464, 1391, 1363, 1252, 1098, 1006, 984, 837, 776, 669 cm^{-1}; HRMS calcd for $C_{15}H_{31}O_3Si$: 287.2042 $[M+H]^+$; found: 287.2014.

Synthesis of compound 46: Tetramethylammonium triacetoxyborohydride (2.8919 g, 10.99 mmol) was dissolved in acetic acid (5.5 mL) and then cooled to −20 °C. Enone **58** (311.9 mg, 1.089 mmol) was then added as a solution in acetone (5.5 mL) and the reaction was stirred for 17 h. Sodium potassium tartrate (saturated aqueous solution, ≈100 mL) was then added, as well as CH_2Cl_2 (≈100 mL) and the thick mixture was stirred for 2.5 h. The layers were then separated and the aqueous layer was further extracted three times with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, concentrated in vacuo, and chromatographed with a solvent gradient (10–20 % diethyl ether/petroleum ether) to give diol **46** (215.6 mg, 69 % yield, 5:1 d.r., as judged by integration of the olefin peak at 5.11 vs. 5.06 ppm for the diastereomer) as a yellow oil. R_f = 0.43 (20 % v/v ethyl acetate/petroleum ether); $[\alpha]_D^{24} = -3.62$ (c = 2.98 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93 (ddd, J = 5.0, 10.5, 17.2 Hz, 1H), 5.30 (dt, J = 17.1, 1.7 Hz, 1H), 5.11 (dt, J = 10.5, 1.5 Hz, 1H), 4.45 (br s, 1H), 4.09 (d, J = 2.9 Hz, 1H), 3.82 (dt, J = 12.0, 2.7 Hz, 1H), 3.50 (d, J = 9.8 Hz, 1H), 3.46 (d, J = 9.8 Hz, 1H), 3.12 (d, J = 6.4 Hz, 1H), 1.72 (ddd, J = 3.5, 11.0, 14.0 Hz, 1H), 1.56 (ddd, J = 1.4, 6.9, 14.0 Hz, 1H), 0.88 (s, 9H), 0.86 (s, 3H), 0.80 (s, 3H), 0.06 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.1, 113.9, 76.3, 73.7, 70.5, 37.8, 37.1, 25.8, 22.3, 18.9, 18.1, −5.71, −5.69 ppm; IR (thin film): $\tilde{\nu}$ = 3452, 2927, 2856, 1744, 1717, 1472, 1404, 1363, 1327, 1293, 1254, 1161, 1094, 1006, 990, 922, 837, 777, 669 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{32}O_3Si$: C 62.45, H 11.18; found: C 62.66, H 10.97.

Synthesis of compound 63: Alkene **62** (134.7 mg, 0.484 mmol) and alkyne **10** (49.7 mg, 0.17 mmol)[6] were dissolved in acetone (0.4 mL) in a flame-dried microwave vial. $[CpRu(MeCN)_3][PF_6]$ (7.7 mg, 0.018 mmol) was then added and the reaction was stirred at ambient temperature for 22 h. The reaction was then concentrated in vacuo and chromatographed with a solvent gradient (5–30 % v/v diethyl ether/petroleum ether) to give **63** (17.6 mg, 18 % yield, 2.4:1 d.r.), recovered alkene **62** (39.5 mg, 31 % recovery) and recovered alkyne **10** (2.8 mg, 7 % recovery). R_f = 0.55 (10 % v/v ethyl acetate/petroleum ether); $[\alpha]_D^{24} = -3.2$ (c = 1.24 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23 (d, J = 7.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 5.83 (ddd, J = 17.3, 10.5, 5.9 Hz, 1H), 5.25 (br s, 1H), 5.19 (dt, J = 17.3, 1.6 Hz, 1H), 5.10 (ddd, J = 10.5, 3.3, 1.5 Hz, 1H), 4.49 (d, J = 11.8 Hz, 1H), 4.46 (d, J = 11.8 Hz, 1H), 4.19–4.23 (m, 1H), 3.97 (dd, J = 9.5, 6.3 Hz, 1H), 3.78–3.85 (m, 1H), 3.78 (s, 3H), 3.45–3.50 (m, 1H), 3.45 (dd, J = 10.1, 5.2 Hz, 1H), 3.42 (dd, J = 10.0, 4.3 Hz, 1H), 2.94 (ddd, J = 17.5, 10.0, 5.2 Hz, 1H), 2.58 (dd, J = 17.3, 7.3 Hz, 1H), 2.37 (br d, J = 13.4 Hz, 1H), 2.20–2.24 (m, 2H), 1.95–2.00 (m, 3H), 1.86–1.42 (m, 8H), 1.302 (s, 3H), 1.298 (s, 3H), 0.06 ppm (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 212.5, 159.1, 152.5, 138.4, 130.3, 129.2, 123.8, 115.2, 113.7, 100.5, 77.4, 75.0, 72.9, 72.8, 70.9, 69.8, 68.1, 55.3, 50.6, 45.6, 45.1, 36.5, 32.2, 30.3, 25.3, 24.2, 20.3, 18.9, 0.3 ppm; IR (thin film): $\tilde{\nu}$ = 2954, 2895, 2854, 1706, 1618, 1587, 1514, 1466, 1364, 1331, 1302, 1248, 1224, 1173, 1092, 1037, 991, 923, 840, 768, 717, 689 cm^{-1}; HRMS calcd for $C_{33}H_{50}O_6Si$: 570.3377; found: 570.3388.

Synthesis of compound 67: Ketal **63** (16.1 mg, 0.028 mmol) was dissolved in methanol (0.5 mL). Camphor sulfonic acid (0.8 mg, 0.003 mmol) was added at ambient temperature and the reaction was stirred for 3 h. The solution was then poured over aqueous $NaHCO_3$, diluted with diethyl ether, washed with brine, dried ($MgSO_4$), filtered, concentrated in vacuo, and isocratically chromatographed (25 % v/v diethyl ether/petroleum ether) to give compound **67** (10.2 mg, 70 % yield) as a yellow oil. R_f = 0.17 (10 % v/v ethyl acetate/petroleum ether) $[\alpha]_D^{25} = 9.8$ (c = 0.98 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 5.83 (ddd, J = 17.3, 10.6, 5.1 Hz, 1H), 5.25 (dt, J = 17.2, 1.6 Hz, 1H), 5.21 (br s, 1H), 5.06 (dt, J = 10.6, 1.5 Hz, 1H), 4.53 (d, J = 11.7 Hz, 1H), 4.49 (d, J = 11.7 Hz, 1H), 3.98–4.02 (m, 2H), 3.79 (s, 3H), 3.59 (ddt, J = 11.0, 2.2, 5.0 Hz, 1H), 3.53–3.40 (m, 3H), 3.15 (s, 3H), 2.35–2.42 (m, 2H), 2.09 (dd, J = 15.9, 5.1 Hz, 1H), 2.01–2.13 (m, 2H), 1.90–1.98 (m, 2H), 1.78 (dd, J = 16.0, 5.2 Hz, 1H), 1.74 (ddd, J = 12.4, 4.5, 3.1 Hz, 1H), 1.03 (s, 3H), 0.95 (s, 3H), 0.07 ppm (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.7, 138.4, 130.6, 129.1, 123.0, 114.2, 113.7, 104.1, 77.5, 75.5, 73.0, 72.9, 71.3, 68.9, 55.3, 47.9, 47.0, 43.1, 39.2, 36.6, 35.6, 29.7, 20.6, 15.5, 0.3 ppm; IR (thin film): $\tilde{\nu}$ = 3456, 2952, 2925, 2854, 1618, 1514, 1465, 1362, 1302, 1248, 1114, 1038, 843 cm^{-1}; HRMS calcd for $C_{28}H_{43}O_6Si$: 503.2829 $[M-CH_3]$; found: 503.2829.

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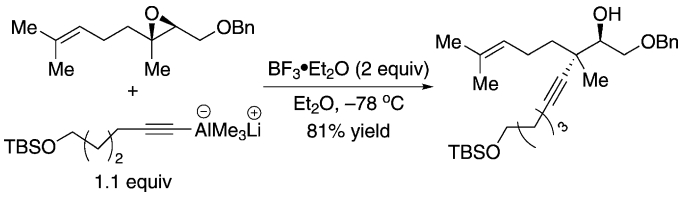

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