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Total Synthesis of Bryostatins: The Development of Methodology for the Atom-Economic and Stereoselective Synthesis of the Ring C Subunit

Barry M. Trost,* Alison J. Frontier, Oliver R. Thiel, Hanbiao Yang, and Guangbin Dong[a]

Abstract: Bryostatins, a family of structurally complicated macrolides, exhibit an exceptional range of biological activities. The limited availability and structural complexity of these molecules makes development of an efficient total synthesis particularly important. This article describes our initial efforts towards the total synthesis of bryostatins, in which chemoselective and atom-economical methods for the stereoselective assembly of the ring C subunit were developed. A Pd-catalyzed tandem alkyne–alkyne coupling/6-*endo*-*dig* cyclization sequence was explored and successfully pursued in the synthesis of a dihydropyran ring system. Elaboration of this methodology ultimately led to a concise synthesis of the ring C subunit of bryostatins.

Keywords: alkynes · atom economy · bryostatins · cross-coupling · dihydropyran synthesis · palladium

Introduction

Isolation and biology: Since their first isolation in 1968 by Pettit and co-workers from the marine bryozoan *Bugula neritina*,[1,2] bryostatins 1–20 (**1a**–**t**), a class of structurally complex macrolides, have continuously attracted the attention of both chemists and biologists. These marine natural products exhibit an exceptional range of biological activities, the most notable being that bryostatins can act as antineoplasic agents and exhibit excellent anticancer activity.[3] Biological experiments indicate that bryostatin 1 (**1a**) significantly inhibits the growth of a large number of tumor cell lines in vivo with low toxicity, including murine leukemia, ovarian carcinoma, reticulum cell sarcoma, and B16 melanoma.[4,5,6,7] Recently, the clinical application of bryostatin 1 in combination with other chemotherapeutic agents has shown significant potential to treat some cancers with high potency.[8,9]

Unlike other antineoplasic agents, however, bryostatin 1 stimulates the immune and hematopoietic system,[10] which has been suggested as a key factor for its antitumor action.[11] Furthermore, recent efforts have revealed that bryostatin 1 significantly enhances both cognition and memory in animals, which suggests a potential use of bryostatin 1 for the treatment of Alzheimer's disease, depression, and other cognitive impairments.[12] Remarkably, Sun et al. recently suggested that bryostatin 1 could be a potential new treatment to reverse brain damage after a stroke.[13] Due to these outstanding biological activities, bryostatin 1 has been examined in numerous phase I and II clinical trials, including for the treatment of melanoma, non-Hodgkin's lymphoma, chronical lyphocytic leukemia, sarcomas, and more recently for the treatment of Alzheimer's disease.[14–19] Although their exact mode of action is still under debate, bryostatins' efficacy can be attributed to their strong affinity (picomolar) for protein kinase C (PKC) isozymes,[20] enzymes that phosphorylate serine and threonine residues in many target proteins that are often involved in cell-signal transduction pathways. Bryostatins activate PKC through binding to the same active sites as phorbol esters,[21,22] however, unlike many phorbol esters, which are tumor promoters, bryostatins act as antitumor agents.

Synthetic challenge and previous efforts: The structures of the bryostatins constitute significant synthetic challenges, which include a 26-membered lactone fused by three heavily substituted polyhydropyran (PHP) rings, two acid/base-sensitive *exo*-cyclic unsaturated esters, and one congested C16–C17 *trans*-olefin, as well as numerous oxygen-containing functionalities and stereogenic centers. Previously, three of the twenty bryostatins have been accessed by total syntheses,[23,24,25] and formal syntheses of bryostatins have also been reported.[26,27] These elegant syntheses have illustrated the power of organic synthesis for the creation of molecules of extreme complexity, however, their lengths (>40 steps in the longest linear sequence and >70 steps in total) have so far restrained them from serving as a practical source for these natural products.

One of the main reasons for the length of the reported synthetic sequences is the large number of steps devoted to protecting group manipulations and functional group transformations, necessitated by the complexity of the bryostatin structure. We envisioned that the development of conver-

[a] Prof. Dr. B. M. Trost, Prof. Dr. A. J. Frontier, Dr. O. R. Thiel, Dr. H. Yang, Dr. G. Dong
Department of Chemistry, Stanford University
Stanford, California 94305-5080 (USA)
Fax: (+1) 650-725-0002
E-mail: bmtrost@stanford.edu

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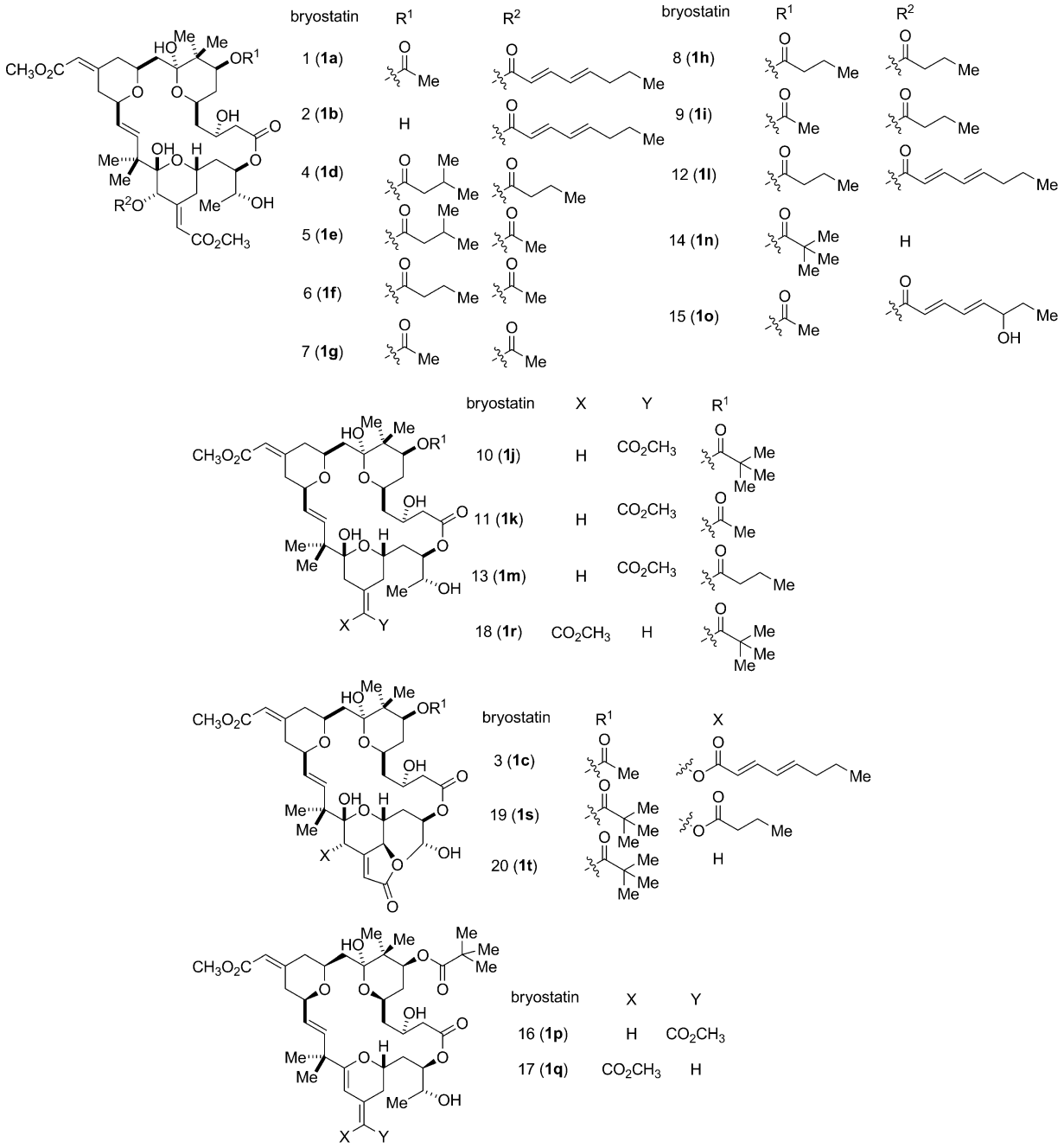
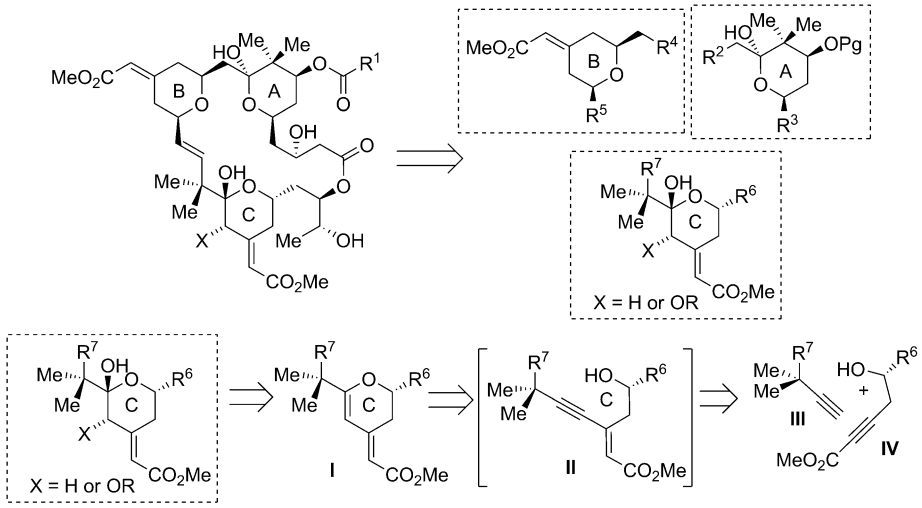


gent and chemoselective methods would enable us to synthesize the PHP rings in a more efficient fashion, and ultimately to shorten the syntheses. Herein, we report detailed studies on the development of methods and strategies for the chemo- and diastereoselective formation of bryostatin ring C.[28]

Results and Discussion

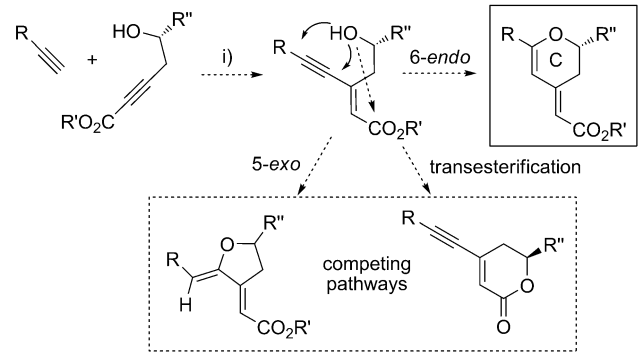
Initial design: As a key structural feature, bryostatins contain three multi-substituted polyhydropyran rings, and each of them has a unique substitution pattern (Scheme 1). Our initial strategy for the assembly of ring C (see Scheme 1) was based on the unique reactivity of alkynes. We envisioned that the ring-C fragment could ultimately come from functionalization of dihydropyran intermediate **I**. The key dihydropyran (**I**) could be prepared through a highly atom-economic transformation from alkynes **III** and **IV**. By taking advantage of the different reactivities of a terminal alkyne and an ynoate, we could develop a Pd-catalyzed tandem sequence: alkyne–alkyne coupling to give enyne intermediate **II** followed by a 6-*endo-dig* O-cyclization reaction to generate the dihydropyran in a one-pot process.



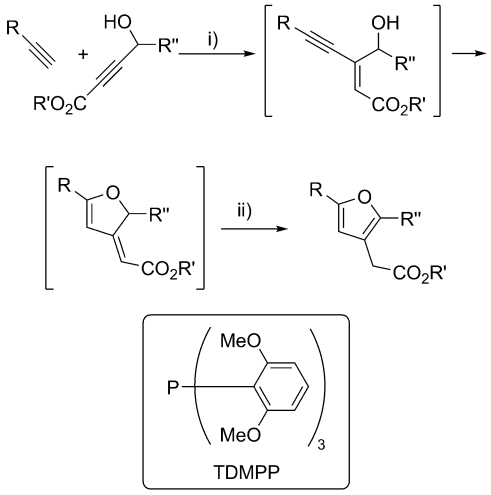
Scheme 1. The initial design of the synthesis of ring C in bryostatins. Pg = protecting group.

Our initial efforts were inspired by a previous method developed in this group, in which furans were synthesized through the palladium-catalyzed cross-coupling of terminal alkynes and ynoates with a propargyl alcohol, followed by intramolecular 5-*endo-dig* oxypalladation and then olefin migration (Scheme 2).[29] If an ynoate bearing a hydroxyl group at the homopropargylic position was used in the tandem alkyne–alkyne coupling/6-*endo-dig* oxycyclization reaction, a dihydropyran ring system would be obtained (Scheme 3). Two possible competing pathways would be expected: 1) the alcohol could attack the alkyne in a 5-*exo* fashion to give polyhydrofurans; or 2) the alcohol could attack the ester group to provide a 6-membered lactone through transesterification.

To test the feasibility of the desired cyclization, the reaction of 1-heptyne (**2a**) and homopropargylic ynoate **3a** was chosen as the model system and examined under the conditions reported for furan formation. Initial experiments by using Pd(OAc)$_2$ (5 mol%) and tri(2,6-dimethoxyphenyl)phosphine (TDMPP; 2 mol%) gave dihydropyran **5a**, although the reaction time was rather long if the reaction was run at room temperature (7 days, Table 1, entry 1). It was possible to isolate the simple cross-coupling product **4a** after ≈24 h. Elevated temperatures shortened the reaction time, but at a cost of selectivity and yield (Table 1, entries 3–6). As the reaction temperature was raised, progressively higher proportions of lactone **6a** were observed. Fortunately, a higher catalyst loading both accelerated the reaction to a reasonable time interval (60 h) and eliminated

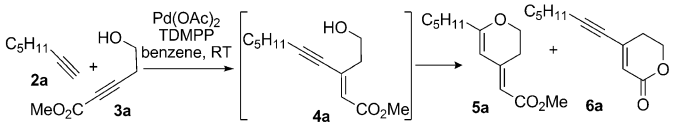


Scheme 3. The formation of dihydropyrans through Pd-catalyzed tandem alkyne–alkyne coupling/6-*endo-dig* oxycyclization. i) Pd(OAc)$_2$ (5 mol%), TDMPP (2 mol%).



Scheme 2. The formation of furans through Pd-catalyzed tandem alkyne–alkyne coupling/5-*exo-dig* oxycyclization. i) Pd(OAc)$_2$ (5 mol%), TDMPP (2 mol%); ii) 1,8-diazabicycloundec-7-ene (DBU).

Table 1. Optimization of the dihydropyran formation reaction.[a]



	Pd(OAc)$_2$/TDMPP [mol%]	*T* [°C]	*t* [h]	Ratio of **5a**:**6a**	Yield [%]
1	5:2	RT	135	>20:1	61
2	10:4	RT	60	>20:1	61
3	5:2	RT–50[b]	60	5.5:1	61
4	5:2	50	54	5.5:1	57
5	5:2	RT–80[b]	36	1.8:1	30
6	5:2	80	24	1.6:1	23

[a] All reactions were performed in benzene at a concentration of 0.7 M of substrate **3a**. [b] Reaction run at ambient temperature for the first 24 h, followed by heating to the stated temperature.

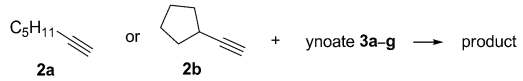
the formation of the lactone. By using 10 mol% $Pd(OAc)_2$ and 4 mol% TDMPP in benzene (0.7 M in ynoate) at room temperature, dihydropyran **5a** was isolated in 61% yield (Table 1, entry 2).

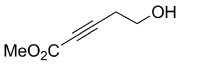
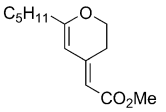
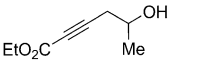
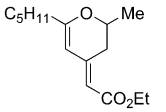
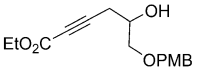
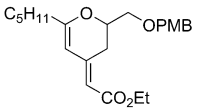
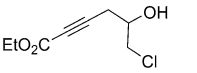
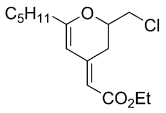
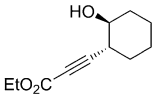
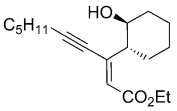
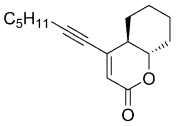
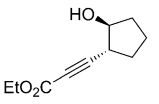
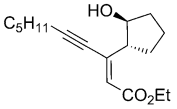
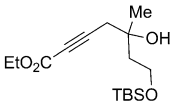
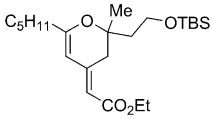
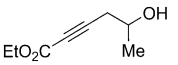
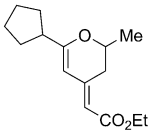
For its application in the total synthesis of bryostatins, the chemoselectivity and substrate scope of this method were next explored. Alkynes and ynoates[30] with various functional groups and substitution patterns were subjected to the tandem coupling/cyclization reaction under the optimal reaction conditions (Tables 2 and 3).

As indicated in Table 2, ynoates bearing primary, secondary, and tertiary alcohols all underwent cyclization without incident. It is not unexpected that the reaction with a tertiary alcohol substrate (**3g**) was markedly slower, but gratifyingly, still able to provide the desired dihydropyran in 44% yield, despite the high levels of steric hindrance (Table 2, entry 8). The excellent chemoselectivity was revealed by the observation that the relatively reactive primary chloride substituent was tolerated under these conditions (Table 2, entry 4). Ynoates with the homopropargylic alcohol chain restricted within a ring (**3e** and **f**)[31] failed to undergo the subsequent O-cyclization reaction; only the cross-coupled products (**4e** and **f**) were isolated (Table 2, entries 5 and 7). In the case of **3e**, a longer reaction time (7 d) gave the corresponding lactone (**6e**) without any detectable amount of the dihydropyran in the reaction mixture (Table 2, entry 6). This difficulty is likely caused by the *trans*-orientation of the substituents on the cyclohexane ring, which presents an unfavorable geometry for the *endo* cyclization reaction. A donor alkyne with a branch at the propargylic position (**2b**) was also examined (Table 2, entry 9), and the cross-coupling/cyclization sequence was comparable to the unsubstituted cases.

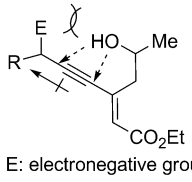
Next, we investigated the functional group compatibility and electronic effects of substitution on this transformation. Studies shown in Table 3 reveal that free alcohols, nitriles, acetals, and vinyl silanes are compatible with the reaction conditions. The electronic nature of the substituents on the donor alkynes proved to affect the regioselectivity of the oxypalladation step. A minor amount of 5-*exo* product (**7**) was observed if a donor alkyne bearing an electron-withdrawing group was employed. The highest proportions of the 5-*exo* products were observed if an electronegative group was installed at the propargylic position (e.g., Table 3, entries 1, 2, and 9), with lesser amounts observed if the substitution was at the homoallylic position (Table 3, entries 4 and 5), and none if the group was four carbons removed from the alkyne (Table 3, entry 8). This unusual regioselectivity was presumably caused by the inductive effect of the electronegative substituents adjacent to the donor alkyne, as well as dipole repulsion between the alcohol nucleophile and the electronegative substituent (Scheme 4). Variation of the reaction temperature, concentration, and order of addition had little to no effect on the *endo*/*exo* ratio of the reaction depicted in Table 3, entry 1. However, use of 2-methyl-3-butyne-2-ol **2k** as the alkyne partner led to a reversal of the product ratios, presumably due to a combination of both electronic and steric effects (Table 3, entry 9). Vinylsilane substitution[32] also caused for-

Table 2. The Pd-catalyzed tandem alkyne–alkyne coupling/6-*endo*-*dig* oxycyclization.[a] (PMB = *p*-methoxybenzyl)



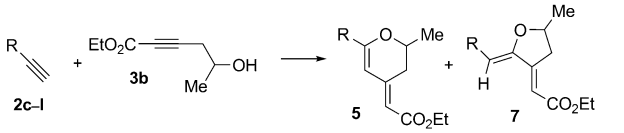
	Alkyne	Ynoate		*T*	Product		Yield [%][b]
1	**2a**		**3a**	60 h		**5a**	61
2	**2a**		**3b**	60 h		**5b**	57
3	**2a**		**3c**	7 d		**5c**	57
4	**2a**		**3d**	7 d		**5d**	42
5	**2a**		**3e** (*rac*)	48 h		**4e**	50
6	**2a**		**3e** (*rac*)	7 d		**6e**	58
7	**2a**		**3f** (*rac*)	13 d		**4f**	69
8	**2a**		**3g**	7 d		**5g**	44
9	**2b**		**3b**	60 h		**5f**	57

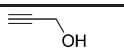
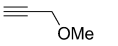
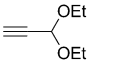
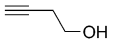
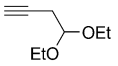
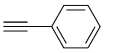
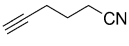
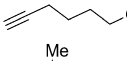
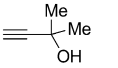
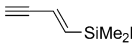
[a] $Pd(OAc)_2$ (5 mol%), TDMPP (2 mol%), benzene, 0.7 M in ynoate **3**, RT. [b] Isolated yield.



Scheme 4. The 5-*exo*-*dig* versus 6-*endo*-*dig* oxycyclization pathways.

Table 3. Pd-catalyzed tandem alkyne–alkyne coupling/6-*endo-dig* oxycyclization.[a]

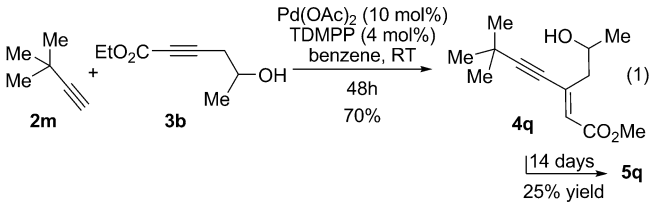


	Donor alkyne		Product ratio	Yield[b] (**5**+**7**) [%]
1		**2c**	2.3:1 (**5h**/**7h**)	50
2		**2d**	1.9:1 (**5i**/**7i**)	18
3		**2e**	–	–
4		**2f**	7.5:1 (**5j**/**7j**)	69
5		**2g**	9.3:1 (**5k**/**7k**)	35
6		**2h**	6.2:1 (**5l**/**7l**)	59
7		**2i**	6.9:1 (**5m**/**7m**)	52
8		**2j**	>20:1 (**5n**)	51
9		**2k**	1:4.2 (**5o**/**7o**)	41
10[c]		**2l**	2:1 (**5p**/**7p**)	55

[a] $Pd(OAc)_2$ (10 mol%), TDMPP (4 mol%), benzene, 0.7 M in ynoate **3b** RT. [b] Isolated yield. [c] $Pd(OAc)_2$ (4 mol%), TDMPP (4 mol%), then $Pd(OCOCF_3)_2$ (6 mol%).

mation of the *exo*-product (Table 3, entry 10), likely due to the ability of silicon to stabilize a positive charge at the β-position.

As the synthesis of bryostatins requires the use of a donor alkyne with a propargylic all-carbon quaternary center (see Scheme 1), 3,3-dimethylbutyne (**2m**) was then employed as the model substrate. Although enyne (**4q**) was produced in 70% yield within 48 h [Eq. (1)], the oxypalladation step was quite sluggish. The 6-*endo-dig* product dihydropyran **5q** formed very slowly (25% yield) after exposure to the typical reaction conditions for 14 days [Eq. (1) and Table 4, entry 1].



To address this problem of slow cyclization, methods for accelerating the oxypalladation step of the reaction sequence were next examined. Envisioning that the cyclization was also a palladium-catalyzed reaction, its rate should depend on the electrophilicity of the palladium(II) species, and thus increasing the electrophilicity should increase the rate of cyclization. We have previously noted a dramatic enhancement in the rate of formation of π-allylpalladium complexes from less nucleophilic alkenes when palladium trifluoroacetate was employed.[33] In the initial experiment, the trifluoroacetate salt was generated in situ by simply adding trifluoroacetic acid to palladium acetate. Indeed, the cyclization rate increased significantly (complete cyclization within 24 h), but a 1:1 mixture of the exocyclic alkene isomers of **5q** was isolated in 59% yield (Table 4, entry 2).[34]

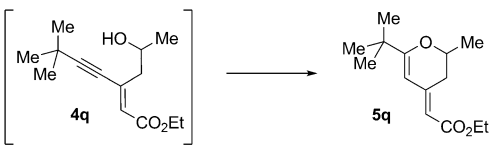
Ancillary experiments revealed that *E*/*Z* isomerization of the double bond was catalyzed by Brønsted acids. To solve the olefin isomerization problem, the more electrophilic palladium trifluoroacetate was employed directly as the oxypalladation catalyst. Indeed, by addition of palladium trifluoroacetate (6 mol%) after the initial cross-coupling with $Pd(OAc)_2$ and TDMPP in a 1:1 ratio (4 mol% each), we were able to obtain the desired dihydropyran in 62% yield after 36 h without isomerization of the exocyclic alkene (Table 4, entry 3), which is a significant improvement compared to a 25% yield over 14 days (Table 4, entry 1).

In general, this new procedure provides rapid direct conversion of the two alkyne starting materials into the dihydropyrans in a one-pot fashion. A direct comparison of these two methods (Table 5) demonstrates that a considerably reduced reaction time and increased yield was observed with this new two-stage, one-pot method. Furthermore, this procedure permits the cyclization of substrates that had undergone only the cross-coupling reaction under the Method A reaction conditions (Table 5, entries 6 and 7).

By using this two-stage protocol, synthetically useful bicyclic systems were generated from cyclic ynoates **3e** and **f** [Eq. (2)], a cyclization that did not proceed in the absence of palladium trifluoroacetate (see Table 2, entries 5 and 7). The formation of seven-membered rings [Eq. (3)] also became possible by using this combination of catalysts.

A few substrates produced unusual results when subjected

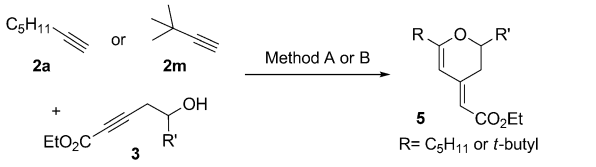
Table 4. Stepwise dihydropyran formation.[a]



	Reagents and conditions	*T*	Yield [%]
1	$Pd(OAc)_2$ (10 mol%), TDMPP (4 mol%), benzene, RT	14 d	25
2	$Pd(OAc)_2$ (10 mol%), TDMPP (4 mol%), benzene, RT then TFA (20 mol%)	24 h	59[b]
3	$Pd(OAc)_2$ (4 mol%), TDMPP (4 mol%), $Pd(OCOCF_3)_2$ (6 mol%), benzene, RT	36 h	62

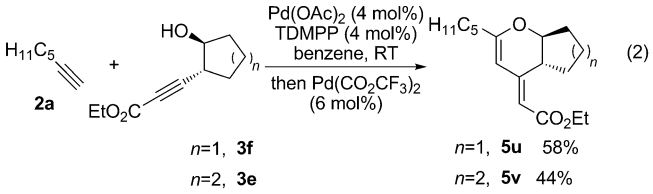
[a] Intermediate enyne **4q** was prepared by using $Pd(OAc)_2$ (10 mol%), TDMPP (4 mol%) in benzene at ambient temperature. [b] *E*/*Z* ratio was 1:1

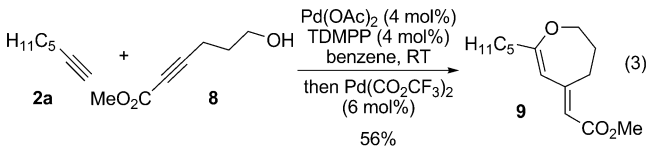
Table 5. Tandem versus stepwise reaction conditions for cyclization.



	Alkyne	R′		Product	Yield [%][a] (*t*) Method A[b]	Method B[c]
1	**2a**	H	**3a**[d]	**5a**	61 (**5a**; 60 h)	63 (12 h)
2	**2a**	Me	**3b**	**5b**	57 (**5b**; 52 h)	66 (30 h)
3	**2a**	CH_2OPMB	**3c**	**5c**	52 (**5c**; 7 d)	58 (24 h)
4	**2a**	CH_2OTBS	**3h**	**5r**	52 (**5r**; 7 d)	61 (36 h)
5	**2m**	Me	**3b**	**5q**	25 (**5q**; 14 d)	62 (78 h)
6	**2m**	CH_2OPMB	**3c**	**5s**	– (**5s**; 7 d)[e]	69 (9 d)
7	**2m**	CH_2OTBS	**3h**	**5t**	– (**5t**; 7 d)[e]	50 (7 d)[f]

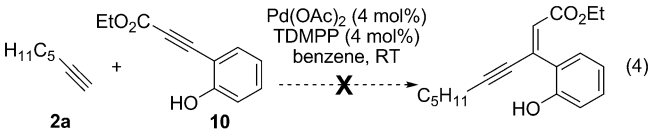
[a] Isolated yields. [b] Method A: $Pd(OAc)_2$ (10 mol%), TDMPP (4 mol%), benzene. [c] Method B: $Pd(OAc)_2$ (4 mol%), TDMPP (4 mol%), then $Pd(OCOCF_3)_2$ (6 mol%), benzene. [d] The methyl ester was used. [e] No oxycyclization was observed after 7 days (enyne product of the cross-coupling only). [f] 95% conversion. The yield of this reaction was 58% after 5 days (82% conversion).

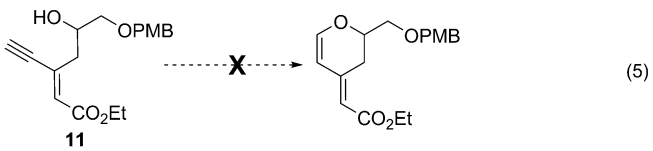




to the tandem reaction protocol. The *ortho*-alkynyl phenol **10**[35] failed to undergo the initial cross-coupling reaction [Eq. (4)]. It is also surprising that terminal enyne **11** did not undergo the oxycyclization, and only the lactone product was observed [Eq. (5)].

To gain insight into the role of each reagent during the two-stage, one-pot sequence, a series of control experiments





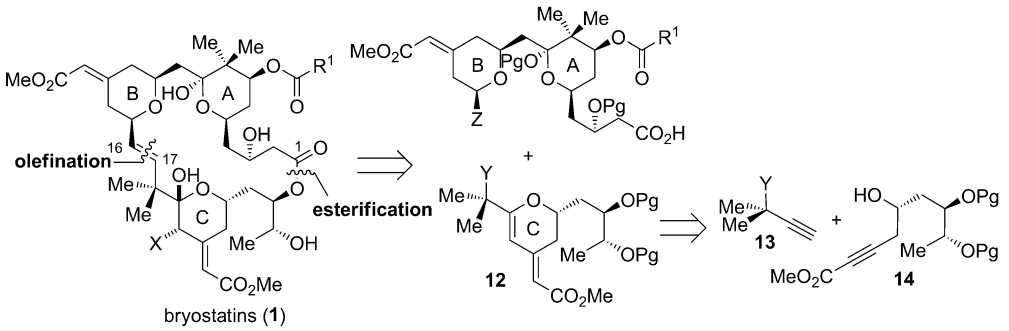
were conducted. Attempts to trigger the reaction sequence without $Pd(OAc)_2$ failed, as the cross-coupling step did not occur. If a cross-coupled enyne product of type **4** was treated with $Pd(O_2CCF_3)_2$ without a ligand, no cyclization product was detected, which indicates the importance of ligands in the oxypalladation step. Finally, if an enyne **4** was subjected to $Pd(O_2CCF_3)_2$ (5 mol%) and a ligand (2 mol%), the oxypalladation occurs, but the reaction rate is slow. An investigation into palladium to phosphine ligand ratios, as well as palladium acetate to palladium trifluoroacetate ratios, revealed that the best results are obtained by using the original conditions (i.e., $Pd(OAc)_2$ (4 mol%)/TDMPP (4 mol%) for the cross-coupling and then $Pd(O_2CCF_3)_2$ (6 mol%) for the oxypalladation). It was also found that the use of an excess of the terminal alkyne (>1.1 equiv) accelerated the cross-coupling step, but seriously compromised the efficency of the oxypalladation step, making the competing lactonization a problem.

Synthesis of the ring C subunit of bryostatins: With this new Pd-catalyzed tandem coupling/cyclization method in hand, the stage was set to apply this method to the synthesis of the ring C subunit of bryostatins. We envisioned that bryostatins could be divided into two fragments: the northern fragment containing rings A and B and the southern fragment (**12**) containing ring C (Scheme 5). These two fragments could then be sewn together through esterification to form the C1 ester and an olefination reaction to form the C16–C17 alkene. The ring C fragment **12** could be ultimately prepared from donor alkyne **13** and ynoate **14**.

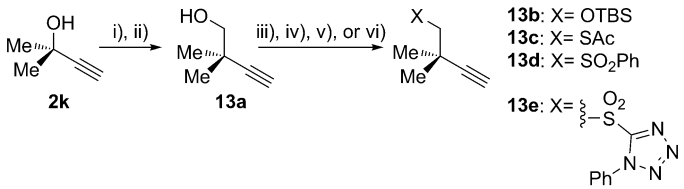
To this end, a variety of donor alkynes with different functional handles were synthesized to examine in the tandem dihydropyran formation protocol targeting ring C of bryostatins (Scheme 6). 2,2-Dimethyl-3-butyn-1-ol (**13a**) was synthesized in two steps from commercially available 2-methylbut-3-yn-2-ol **2k** according to a literature protocol,[36] and then elaborated in various ways to form other substituted terminal alkynes. Simple silylation of the primary alcohol gave *tert*-butyldimethylsilyl ether **13b**. S_N2 displacement of the corresponding tosylate with potassium thioacetate gave thioacetate **13c** and with thiophenol provided the sulfide, which was subsequently oxidized to produce sulfone **13d**. Sulfone **13e** was produced by the Mitsunobu reaction with 1-phenyl-1*H*-tetrazol-5-thiol followed by oxidation.[37] All of these alkynes possess substituents appropriate for future coupling reactions with the northern fragments, as outlined in Scheme 5.

The synthesis of the target ynoate partners of type **14** for the projected tandem cross-coupling/oxycyclization sequence is shown in Scheme 7. Silyl ether **15a** was prepared in high enantiomeric purity over two steps from commercially available 1,4-*trans*-hexadiene according to a literature procedure.[38]

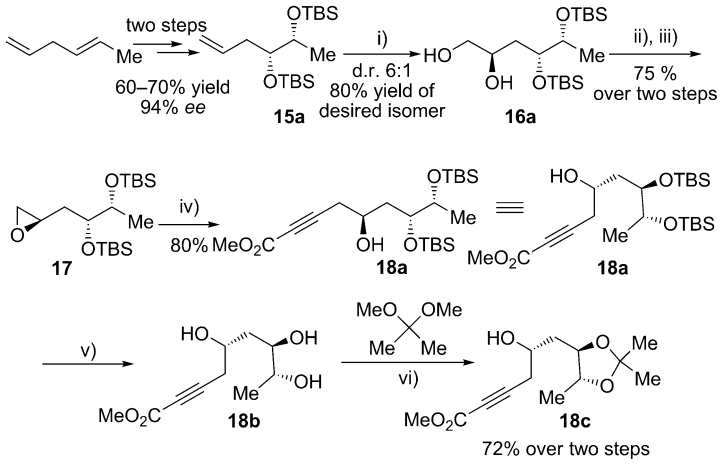
After some experimentation, conditions were found to convert the terminal olefin into the corresponding diol in a diastereoselective fashion (Table 6). Suprisingly, when TBS substrate **15a** was subjected to the Sharpless asymmetric di-



Scheme 5. Strategy for the synthesis of ring C in bryostatins.



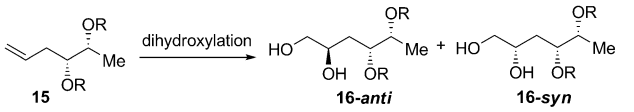
Scheme 6. The synthesis of donor alkynes for the ring C study. i) PBr_3, 66%; ii) Al, $HgCl_2$ (cat.), $(CH_2O)_n$, 37%; iii) *tert*-butyldimethylsilyil chloride (TBSCl), imidazole, 99% yield of **13b**; iv) *p*-toluenesulfonyl chloride (TsCl), pyridine, then AcSK, 61% yield of **13c**; v) TsCl, pyridine, then NaSPh followed by *m*-chloroperoxybenzoic acid (mCPBA), 60% yield of **13d** over the two steps; vi) 1-phenyl-1*H*-tetrazol-5-thiol, diisopropyl azodicarboxylate (DIAD), PPh_3 followed by $[(H_4N)_6Mo_7O_{24}]\cdot H_2O_2$, 71% yield of **13e** over the two steps.



Scheme 7. The synthesis of ynoates for the synthesis of ring C. i) AD-mix α, *t*BuOH/H_2O; ii) TsCl, pyridine; iii) NaOMe, MeOH; iv) $LiCCCO_2Me$, $BF_3\cdot OEt_2$, THF, −78 °C; v) aqueous HF, CH_3CN; vi) *p*-toluenesulfonic acid (PTSA).

hydroxylation (SAD) conditions, the observed stereochemical outcomes were exactly the opposite of the prediction based on the Sharpless mnemonic.[39] By using the 'matched' DHQD ligand, a poor diastereoselectivity was obtained that slightly favored the undesired diastereomer (Table 6, entry 2); however, use of the 'mismatched' DHQ ligand provided the desired diol isomer as the major product in about

Table 6. Dihydroxylation of compound **15**.[a]



	R		Chiral ligand	Ratio (*anti*:*syn*)
1	TBS	**15a**	$(DHQ)_2PHAL$	6:1
2	TBS	**15a**	$(DHQD)_2PHAL$	1:1.2
3	acetonide	**15b**	$(DHQ)_2PHAL$	1:2.5
4	acetonide	**15b**	$(DHQD)_2PHAL$	2:1
5	TBS	**15a**	$(DHQ)_2PYR$	1.8:1
6	TBS	**15a**	$(DHQ)_2AQN$	2.7:1
7	TBS	**15a**	none[b]	1.5:1

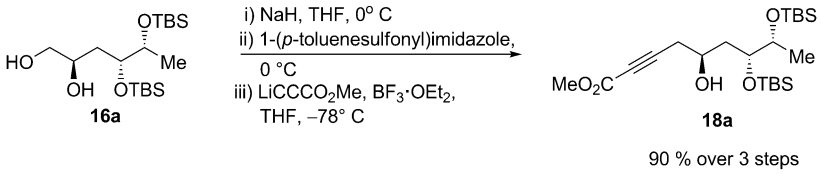
[a] The Sharpless AD-mix protocols were used when possible for the dihydroxylation reactions. [b] OsO_4 (10 mol %), *N*-methyl morpholine-*N*-oxide (NMO), acetone/H_2O.

a 6:1 d.r. (Table 6, entry 1). It is likely that **15a** is too sterically crowded to fit into the chiral pocket properly. On the other hand, the stereochemistry of the diol after SAD of acetonide substrate **15b** was consistent with the prediction, albeit with a relatively poor diastereoselectivity (Table 6, entries 3 and 4). Examination of other asymmetric dihydroxylation ligands was not fruitful (Table 6, entries 5 and 6), despite evidence that the anthraquinone ligand is often superior to the DHQD series for terminal alkenes.[40] In addition, substrate-controlled dihydroxylation of substrate **15a** (no chiral ligand present) resulted in a 1.5:1 mixture of isomers, slightly favoring the desired diastereomer (Table 6, entry 7).

With pure diol **16a** in hand, conversion to epoxide **17** was uneventful (Scheme 7). Opening the epoxide with the lithium anion of methyl propiolate provided target ynoate **18a** in 80 % yield. Ynoates **18b** and **c** were also synthesized to examine their performance in the subsequent tandem alkyne coupling/cyclization sequence. The silyl groups were removed under acidic conditions to give triol **18b**. Subsequently, triol **18b** was selectively reprotected at the 1,2-diol by treatment with 2,2-dimethoxypropane to give acetonide **18c** (72 % yield from bis(silyl ether) **18a**).

Attempts were made to streamline the synthesis of ynoate **18a** from diol **16a** by adopting a protocol developed by Forsyth and Cink [Eq. (6)].[41] This transformation proceeded

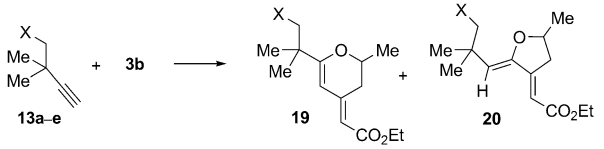
very well on a small scale (0.5 mmol; 90%); however, the yield was diminished on a larger scale (12.2 mmol, 45%) when problems arose with the control of the temperature of the reaction. Furthermore, efficient stirring during the epoxide-opening stage was difficult to achieve, due to the presence of the salts formed in the first stage of the reaction.

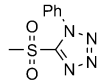


(6)

With routes to access both the donor alkyne and the ynoate partners, the stage was set to test them in the Pd-catalyzed tandem coupling/cyclization reaction. Donor alkynes were examined first by using **3b** as the model ynoate (Table 7). Subjecting sulfone **13d** to the two-stage, one-pot

Table 7. Palladium-catalyzed tandem reaction between alkynes **22** and **13b**.[a]



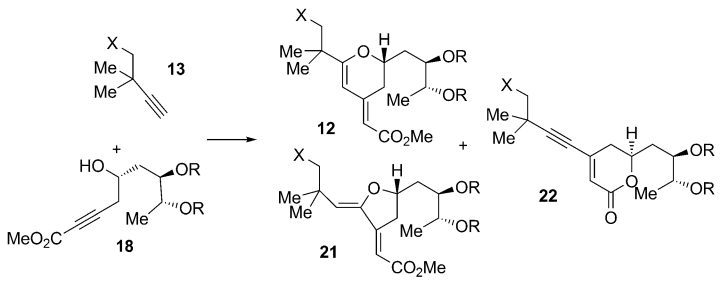
	X		*t* [d]	Yield [%][b]	Products (ratio)
1	SO_2Ph	**13d**	4d	54	**19d**:**20d** (3:1)
2	SAc	**13c**	–	–	–[c]
3		**13e**	3	38	**19e**:**20e** (1:3.5)
4	OH	**13a**	2	–[d]	**19a**:**20a** (1:1)
5	OTBS	**13b**	6	58	**19b** only

[a] $Pd(OAc)_2$ (4 mol%), TDMPP (4 mol%), benzene, RT, then $Pd(CO_2CF_3)_2$, (6 mol%). [b] Isolated yield. [c] Cross-coupling product (enyne) only [d] Not determined.

reaction conditions produced the desired dihydropyran **19d**, along with 5-*exo* byproduct **20d** in a 3:1 ratio (Table 7, entry 1). In contrast, sulfone **13e** produced mainly **20e** (3.5:1 ratio; Table 7, entry 3). Thioacetate **13c** underwent cross-coupling with ynoate **3b** (Table 7, entry 2), but no dihydropyran **19c** was formed, even after an extended reaction period; the only product isolated was the lactone byproduct. When alkyne **13a** (free alcohol) was subjected to the reaction conditions, a mixture of **19a** and **20a** was observed (Table 7, entry 4). However, when silyl ether **13b** was the donor alkyne, the sequence was selective for **19b** (Table 7, entry 5). From these studies, it seemed appropriate to select **13d** and **b** (Table 7, entries 1 and 5) as the terminal alkyne partners for use during the synthesis of the fully functionalized dihydropyran **12** (see Scheme 5) that is necessary for the synthesis of the bryostatins.

Ynoates **18a–c** were next examined in the context of the tandem cross-coupling oxypalladation process with donor alkynes, sulfone **13d** and silyl ether **13b** (Table 8). Ynoate **18a**, the most directly accessible ynoate (see Scheme 7), was unsuitable for two reasons: 1) even by using the $Pd(O_2CCF_3)_2$ protocol, the reaction times were unreasonably long, and 2) a high proportion of lactone **22** was observed in the product mixture (Table 8, entries 1 and 2). The formation of this undesired byproduct, as well as the sluggishness of the reaction process may be attributed to the extremely hindered nature of the homopropargylic alcohol in **18a**, due to the two neighboring TBS ethers.

Table 8. Palladium-catalyzed tandem coupling/cyclization of alkynes **13** and **18**.[a]



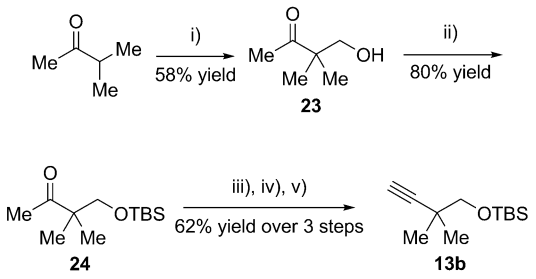
	R		X		*t* [d]	Products (ratio)
1	TBS	**18a**	SO_2Ph	**13d**	>14	**12a**:**21a**:**22a** (4:1:4)
2	TBS	**18a**	OTBS	**13b**	>24	**12b**:**21b**:**22b** (6:1:2)[b]
3	H	**18b**	SO_2Ph	**13d**	≤2.5	isomerization of the *exo*-
4	H	**18b**	OTBS	**13b**	≥1.5	enoate
5	acetonide	**18c**	SO_2Ph	**13d**	3	**12c**:**21c**:**22c** (3:1:1)
6	acetonide	**18c**	OTBS	**13b**	4	**12d**:**21d**:**22d** (12:1:1)[c]

[a] $Pd(OAc)_2$ (4 mol%), TDMPP (4 mol%), benzene, RT, then $Pd(CO_2CF_3)_2$ (6 mol%). [b] 54% isolated yield of **12b**. [c] 55–72% isolated yield of **12d**.

Substrate **18b** underwent rapid cyclization with very high selectivity (no byproducts **21** or **22** were detected by ^1H NMR spectroscopy of the crude products). However, dihydropyran **12** could not be isolated without isomerization of the exocyclic enoate (Table 8, entries 3 and 4). In addition, isolation of the enoate mixture revealed that the yield of the reaction was lower than for other cases (≈40%). It was decided that ynoate **18b** was too reactive to perform reliably in the cyclization. Acetonide ynoate (**18c**) proved to have the proper reactivity and provided the best results in the tandem cyclization process (Table 8, entries 5 and 6). In general, the reaction with silyl ether **13b** as the donor alkyne proceeded without significant formation of the 5-*exo* cyclization product. It seems that sulfone **13d** was inferior with respect to the formation of the undesired products **21** and **22** (Table 8, entries 1 and 5). Therefore, donor alkyne **13b** and ynoate **18c** clearly acted as the best combination as

indicated in Table 8, entry 6 for the synthetic route targeting bryostatin ring C.

Second generation approaches for the synthesis of donor alkyne 13b and ynoate 18c: Having identified the optimal coupling partners for the tandem cyclization, we next optimized the syntheses of alkyne **13b** and ynoate **18c**, improving both efficiency and scalability. A more effective synthesis of alkyne **13b** on a large scale is described in Scheme 8.



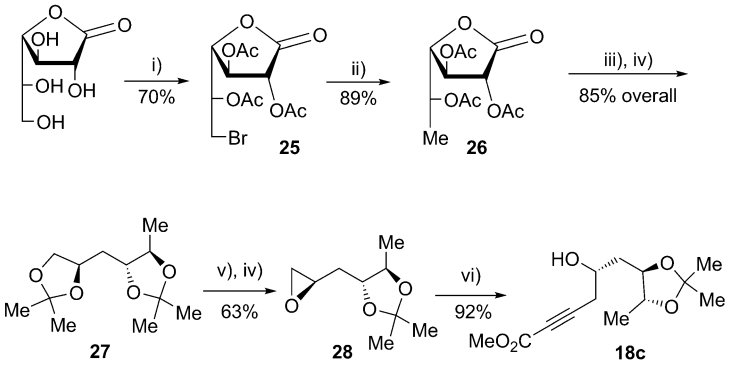
Scheme 8. An improved synthesis of alkyne **13b**. i) CH_2O, CF_3COOH; ii) TBSCl, imidazole, DMF; iii) lithium diisopropylamide (LDA), THF, −78 °C; iv) $ClPO(OEt)_2$, −78 °C to RT; v) LDA, −78 °C to RT.

Commercially available 3-methyl-2-butanone was subjected to an acid-mediated aldol reaction with paraformaldehyde to provide alcohol **23**,[42] which was then protected as a TBS ether. Subsequently, methyl ketone **24** was converted to terminal alkyne **13b** by using a one-pot protocol developed by Negishi.[43]

To avoid the cumbersome purification encountered when running the reaction on a large scale by using the SAD route, we next developed an efficient 'chiral-pool'-based route to access ynoate **18c** (Scheme 9). Although it was partially adapted from a known route,[44] the reaction parameters were carefully optimized for successful completion of this strategy (see the Supporting Information for details). To this end, commercially available D-galactono-1,4-lactone was brominated at the primary hydroxyl functional group and then peracetylated.[45] Subsequent global hydrogenation catalyzed by palladium on charcoal reduced the bromine and led to intermediate **26**, which contains all three stereogenic centers of the C22–C27 moiety of the bryostatins. Exhaustive reduction with lithium borohydride was followed by acetonide formation to give bisacetonide **27**. The sterically less hindered terminal acetonide was chemoselectively cleaved, and the ensuing diol was converted to the known epoxide **28** by activation of the primary alcohol with *N*-(2,4,6-triisopropylbenzenesulfonyl)imidazole followed by base-mediated ring closure. Finally, synthesis of ynoate **18c** was furnished by BF_3-mediated epoxide ring opening with the lithium acetylide derived from methyl propiolate. Multigram quantities of ynoate **18c** can be obtained from this chiral-pool approach, the product of which is spectroscopically identical to the one that was derived from tetraol **16a**; furthermore, this approach also proves our previous stereochemical assignment of the SAD intermediates from the first generation route.

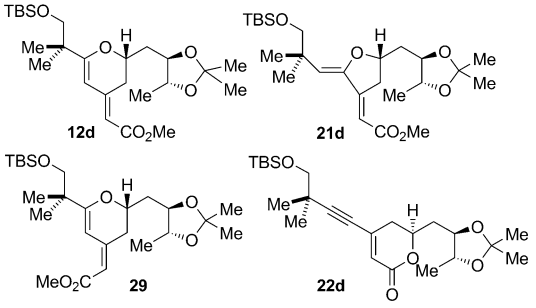
With high yielding and scalable routes to access both coupling fragments, our efforts were directed towards improving the efficiency of the formation of dihydropyran **12d**. As indicated in Table 8, the use of the $Pd(OAc)_2$ and $Pd(O_2CCF_3)_2$ combination provided the desired dihydropyran in an acceptable yield. This protocol was reproducible at scales of 0.3 mmol; unfortunately, upon further scaling up, sluggish reactions and the formation of different isomers was observed.

A closer investigation of the reaction products of the tandem reaction revealed the presence of four different products (Table 9). Although the desired dihydropyran **12d** from a 6-*endo* cyclization was the major product, we also observed varying amounts of its double-bond isomer **29**, the furan derivative **21d**, resulting from the 5-*exo* cyclization, and the lactone **22d**. Consequently, we attempted to deter-



Scheme 9. A chiral-pool-based synthesis of alkynoate **18c**. i) HBr, AcOH then Ac_2O; ii) H_2, Pd/C, Et_3N; iii) $LiBH_4$, THF then Amberlyst 15; iv) 2,2-dimethoxypropane, PTSA, THF; v) I_2, CH_3OH, 66% (87% based on recovered starting material (BRSM)); vi) NaH, THF, then *N*-(2,4,6-triisopropylbenzenesulfonyl)imidazole; vii) $LiCCCO_2CH_3$, $BF_3{\cdot}OEt_2$, THF, −78 °C.

Table 9. NMR study on the ratio of the products from the one-pot coupling/cyclization of alkyne **13b** and ynoate **18c**.



	t [h]	**30** [%]	**12d** [%]	**29** [%]	**21d** [%]	**22d** [%]
1	24	56	15	1	2	26
2	48	19	35	2	4	40
3	96	0	49	5	5	41

mine the relative kinetics of the formation of each product through NMR studies. Alkyne **13b** and ynoate **18c** were treated with $Pd(OAc)_2$ (4 mol%) and TDMPP (4 mol%) in benzene (0.5 M) at RT. Complete conversion to enyne **30** was observed after 20 h. Palladium trifluoroacetate (8 mol%) was added to the reaction mixture and aliquots of the reaction were analyzed by NMR spectroscopy after 24, 48, and 96 h (Table 9). The results suggested that lactone formation was a very competitive pathway, mostly occurring directly after addition of palladium trifluoroacetate. The 6-*endo*-cyclization was favored over the other two competing pathways, but the reaction was relatively slow. Catalytic turnover was still observed after 2 days, indicating good catalyst stability.

Having identified all of the side products, we performed a more detailed catalyst survey for the oxycyclization step. To this end, enyne **30** was isolated in 89% yield after quenching the reaction at the first stage [Eq.(7)], and subsequently subjected to different catalytic conditions (Table 10).

The use of palladium trifluoroacetate as the catalyst led to only low selectivity towards the desired product **12d**, and significant amounts of olefin isomer **29** and 5-*exo* product **21d** were observed (Table 10, entries 1 and 2). The addition of TDMPP as a ligand afforded similar selectivities as in the two-stage, one-pot sequence (Table 10, entry 3). Silver salts have been described in the literature to catalyze the intermolecular addition of alcohols to alkynes,[46] but silver catalysis was not effective for this cyclization. High catalyst loadings of silver trifluoroacetate (60 mol%) were necessary to achieve cyclization (Table 10, entries 4 and 5), and cyclization with AgOTf was inefficient and unselective. Interesting results were obtained by using $PtCl_2$ as the catalyst.[47] Complete conversion was observed in toluene at 60°C without formation of lactone **22d**. Interestingly, this reaction showed a strong preference for the 5-*exo* versus the 6-*endo* cyclization pathway (Table 10, entry 6). No cyclization was observed in experiments that used $[CpRu(CH_3CN)_3PF_6]$ (Cp = cyclopentadienyl), $[\{RuCl_2(p\text{-cymene})\}_2]$, or $[Rh(PPh_3)_3Cl]$ as the catalyst.

Utimoto and co-workers reported that $[PdCl_2(PhCN)_2]$ was able to catalyze intramolecular alcohol addition to alkynes (Table 10).[48] Reactions with this catalyst system were very fast (complete conversions within one hour) with no detectable formation of lactone **22d** by ^{1}H NMR spectroscopy (Table 10, entries 7–11). Ethereal solvents provided the best results (Table 10, entries 8–11), and THF was chosen for further optimization. Cyclization with $[PdCl_2(MeCN)_2]$ led to similar results (Table 10, entry 12). One major side reaction for this catalyst system was isomerization of the exocyclic olefin. An initial hypothesis was that this isomerization was mediated by protons or chloride ions generated from the catalyst in the course of the catalytic cycle. The use of amine bases as a buffer resulted in complete inhibition of the oxycyclization, although ethylvinylether was somewhat effective as an acid trap (Table 10, entry 13). The addition of solid inorganic bases seemed more promising, but only barium oxide and silver oxide gave complete conversion (Table 10, entries 14 and 15). Finally, inspired by the results in the previous one-pot procedure, phosphines were investigated as additives to this $[PdCl_2(RCN)_2]$ catalyst system. The addition of TDMPP (1:1 to Pd) dramatically slowed the reaction, but the use of a smaller amount of phosphine (3 mol%) provided complete conversion within 7 h and suppressed the formation of both **21d** and **29** (Table 10, entry 16). The use of other phosphines, such as 1,1′-bis(diphenylphosphino)ferrocene (dppf) and PPh_3, resulted in extremely low reactivity.

During the original oxycyclization studies on **30**, the most practical set of conditions

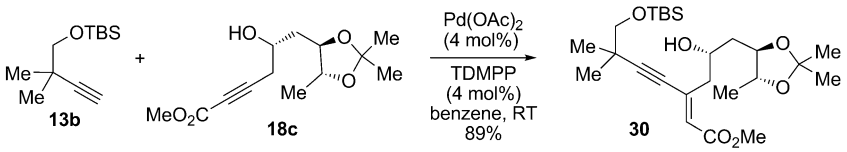


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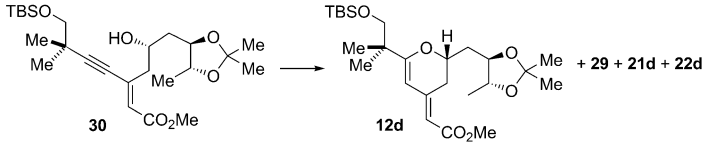
Table 10. Metal-catalyzed 6-*endo-dig* cyclization of compound **30**.[a,b]



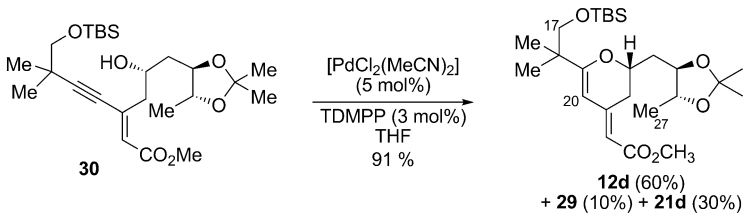
	Catalyst	[mol%]	Solvent	Additive ([mol%])	*t* [h]	**30** [%]	**12d** [%]	**29** [%]	**21d** [%]	**22d** [%]
1	$Pd(O_2CCF_3)_2$	10	benzene	–	12	–	18	32	20	30
2	$Pd(O_2CCF_3)_2$	10	CH_2Cl_2	–	14	–	33	22	16	29
3	$Pd(O_2CCF_3)_2$	10	benzene	TDMPP (10)	12	–	49	15	8	28
4[c]	$Ag(O_2CCF_3)$	30	CH_2Cl_2	–	12	41	32	5	4	18
5[c]	$Ag(O_2CCF_3)$	60	CH_2Cl_2	–	16	–	47	26	3	24
6[d]	$PtCl_2$	5	toluene	–	14	–	29	14	57	–
7	$PdCl_2(PhCN)_2$	5	benzene	–	0.75	–	30	21	49	–
8	$PdCl_2(PhCN)_2$	5	Et_2O	–	0.75	–	45	24	31	–
9	$PdCl_2(PhCN)_2$	5	THF	–	1	–	47	26	27	–
10	$PdCl_2(PhCN)_2$	5	dioxane	–	0.5	–	45	28	27	–
11	$PdCl_2(PhCN)_2$	5	DME	–	0.5	–	50	30	20	–
12	$PdCl_2(MeCN)_2$	5	THF	–	1	–	44	35	26	–
13	$PdCl_2(MeCN)_2$	5	THF	ethylvinylether (25)	1	–	53	19	28	–
14	$PdCl_2(MeCN)_2$	5	THF	BaO (50)	1	–	50	15	35	–
15	$PdCl_2(MeCN)_2$	5	THF	AgO (20)	1	–	52	14	34	–
16	$PdCl_2(MeCN)_2$	5	THF	TDMPP (3)	7	–	62	10	28	–

[a] Reactions were run at 25°C unless otherwise noted. [b] The ratio of products was determined by ^{1}H NMR spectroscopy. [c] This reaction was run at 40°C. [d] This reaction was run at 60°C.

found for dihydropyran formation involved the use of $[PdCl_2(MeCN)_2]$ (5 mol%)/TDMPP (3 mol%), on a 7 mmol scale [Eq. (8)]. This protocol provided a good isolated yield of the product mixture (91%) with a selectivity that reflected our small-scale experiments (Table 10, entry 16, **12d**/**29**/**21d** = 6:1:3).

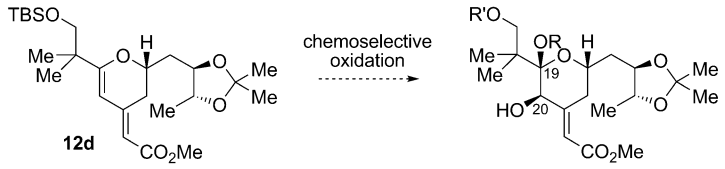
With scalable access to dihydropyran **12d**, the remaining challenge was to install the C19 and C20 oxygen functionalities in a chemoselective and diastereoselective fashion [Eq. (9)].

Pure alcohol **31** was isolated after removal of the TBS group with TBAF from the mixture of TBS ethers obtained in the $[PdCl_2(MeCN)_2]$/TDMPP cyclization reaction. To access α-hydroxyl ketal **32**, chemoselective epoxidation of the C19–C20 alkene, followed by an in situ epoxide ring-opening procedure with a methanol nucleophile was investigated. Use of mCPBA as the oxidant was inefficient (Table 11, entry 1). Switching to the more reactive trifluoroperacetic acid (TFPAA),[49a] the dihydropyran was oxidized



(8)

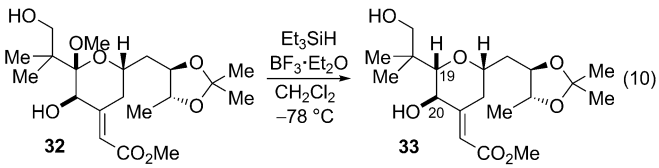
instantly at 0°C. Using acetonitrile/DCM/MeOH as the mixed-solvent system, alcohol **32** was isolated as the major product in 34–48% yield (Table 11, entries 2–4). Increasing the amount of TFPAA increased the formation of byproducts (Table 11, entry 3). The selectivity of the reaction seemed to be slightly improved when it was performed at −20°C (Table 11, entry 4), although incomplete conversion was observed. When MTO was used as a catalyst along with urea hydrogen peroxide (UHP) as the oxidant, the desired product was obtained but the yield was poor (Table 11, entry 7).[49b–d] Switching to trichloroacetonitrile gave similar results (Table 11, entry 8). Oxidations using $Mo(CO)_6$ and $VO(acac)_2$[49e] as catalysts gave mainly recovered **31**, as did experiments using dioxiranes (Table 11, entries 5 and 6). The findings are shown in Table 11.



(9)

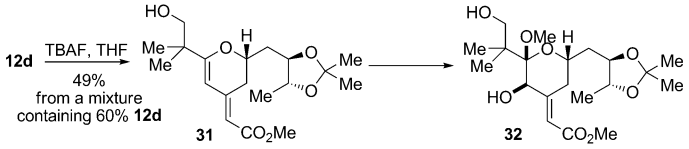
Interpretation of the NMR spectrum of **32** was complicated by the presence of diastereomers. The stereoisomers at C19 and C20 were formed in varying amounts depending on the conditions. The NMR spectra indicated that peracid oxidations at ambient temperature provided exclusive formation of the C20 diastereomer depicted as structure **32**, with the ratio of diastereomers at the anomeric position between 3:1 and 2:1 depending on the reaction conditions employed. The reactions at lower temperatures and the epoxidations with peroxyimidates gave diastereomeric mixtures that also contained the alcohols inverted at C20. The absolute stereochemistry at C20 was assigned by converting **32** into tetrahydropyran **33** through reduction of the anomeric methoxy group with triethylsilane [Eq. (10) and Scheme 10]. The stereochemistry at the ketal center (C19) was tentatively assigned based on a similar epoxidation outcome in the Evans bryostatin synthesis.[24b]

As the stereochemistry of the secondary alcohol at C20 had to be inverted to synthesize bryostatins, an oxidation–reduction approach was explored next (Scheme 11). However, diol **32** is a very sensitive compound and it decomposed quickly in the presence of acid (even in $CDCl_3$), and even on standing as a neat substance (0°C, under argon). Nonetheless, the oxidation of **32** to **34** was attempted under a variety of conditions. The use of 2-iodoxybenzoic acid (IBX)[50a] at RT in THF/DMSO led to no conversion, and oxidation with IBX in acetonitrile at 80°C caused complete decomposition of diol **32**. Moffatt–Swern oxidation[50b] (DMSO, trifluoroacetic anhydride (TFAA), triethylamine (TEA)) gave an apparently clean reaction by TLC, however, the crude NMR spectrum showed the presence of five different aldehyde products. Switching to oxalyl chloride as the activating agent in the Moffatt–Swern oxidation afforded no improvement. Somewhat promising results were obtained by using the Dess–Martin periodinane (DMP).[51] Aldehyde **34** was obtained in 44% yield in an impure form; however, subjection of **34** to the standard Luche reduction conditions ($CeCl_3$, $NaBH_4$, MeOH)[52] only led to decomposition. Therefore, this approach was not pursued further.



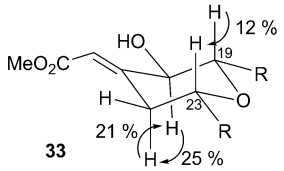
(10)

Table 11. Oxidation of compound **31**. TBAF = tetra-*n*-butylammonium fluoride, TFPAA = trifluoroperacetic acid, DMDO = dimethyldioxirane, UHP = urea hydrogen peroxide, MTO = methyltrioxorhenium.

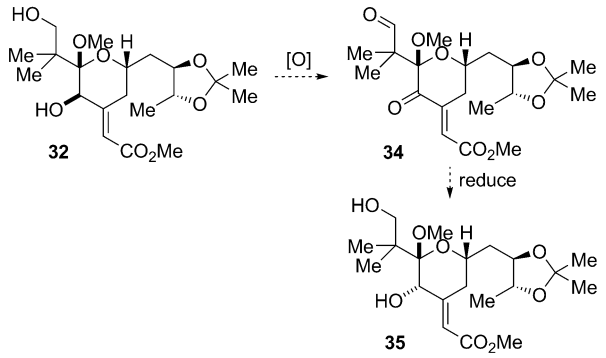


	Conditions	Product (yield [%])[a]
1	mCPBA (1.5 equiv), CH_2Cl_2/MeOH, RT, 2 h	–[b,c]
2	TFPAA (1.5 equiv), Na_2HPO_4, CH_2Cl_2/MeOH/CH_3CN, RT, 1 h	**32** (48)
3	TFPAA (3.5 equiv), Na_2HPO_4, CH_2Cl_2/MeOH/CH_3CN, 0 °C, 15 min	**32** (27)
4	TFPAA (1.5 equiv), Na_2HPO_4, CH_2Cl_2/MeOH/CH_3CN, −20 °C, 30 min	**32** (41)[d]
5	DMDO, acetone, MeOH, RT, 3 h	no reaction
6	CF_3COCH_3, UHP, Na_2HPO_4, CH_2Cl_2/MeOH, RT, 20 h	no reaction
7	MTO (10 mol %), UHP (3 equiv), CH_2Cl_2/MeOH, RT, 3 h	**32** (28)
8	CCl_3CN (4 equiv), UHP (2 equiv), Na_2HPO_4, CH_2Cl_2/MeOH, RT, 4 h	**32** (52)

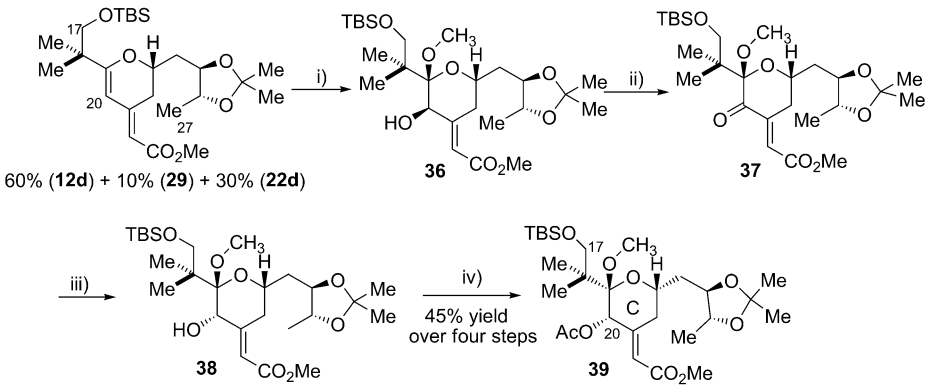
[a] The yields in parenthesis are isolated yields. [b] A complex mixture of products was observed. [c] Poor conversion was observed. [d] Yield of **32** was 53 % based on recovered **31**.



Scheme 10. The nOe data for tetrahydropyran **33**.



Scheme 11. The oxidation–reduction approach to C20 inversion.



Scheme 12. The synthesis of ring C fragment **39**. i) TFPAA, Na_2HPO_4, CH_3CN/DCM, MeOH, 0 °C; ii) DMP; iii) $NaBH_4$, $CeCl_3$, CH_3OH, −30 °C; iv) Ac_2O, 4-dimethylaminopyridine (DMAP), pyridine, CH_2Cl_2.

Due to the labile nature of diol **32**, attempts were next made to oxidize the TBS-protected dihydropyran **12d** directly (Scheme 12). Subjecting **12d** (60 % purity, **22d** and **29** as minor components) to the optimal epoxidation conditions (trifluoroperacetic acid;[53] see Table 11) provided alcohol **36** in 30 % yield, which corresponds to a 50 % yield for this step adjusting for the purity of the starting material. The stereochemistry of the C19 and C20 centers was assigned in analogy with compound **32**. Oxidation of the secondary alcohol with DMP cleanly afforded ketone **37**. Finally, a highly diastereoselective Luche reduction[54] of **37**, followed by acylation of the resulting secondary alcohol (**38**), furnished ring C fragment **39** with the desired C20 stereochemistry in 45 % yield over four steps.[55]

Conclusion

During the initial stage of our efforts towards the total synthesis of bryostatins, we have developed a distinct method for the stereoselective assembly of the ring C subunit, which features a Pd-catalyzed tandem alkyne–alkyne coupling/6-*endo-dig* cyclization sequence. This method is both chemoselective and atom economic, and utilization of this method successfully resulted in a concise enantioselective synthesis of the ring C fragment.

Experimental Section

General procedure A for dihydropyran synthesis: A solution of $Pd(OAc)_2$ (10 mol %) and tris-2,6-dimethoxyphenylphosphine (TDMPP; 4 mol %) in benzene was stirred at RT for 20 min. A solution of ynoate (1.0 equiv) and alkyne (1.1 equiv) in benzene was added (concentration of the reaction mixture: 0.7 M). The reaction was stirred until the addition product was consumed and the solvent was removed in vacuo. The residue was purified by flash column chromatography on Florisil eluting with a diethyl ether/petroleum ether mixture.

General procedure B for dihydropyran synthesis: A solution of $Pd(OAc)_2$ (4 mol %) and TDMPP (4 mol %) in benzene was stirred at RT for 20 min. A solution of ynoate (1.0 equiv) and alkyne (1.1 equiv) in benzene was added (concentration of reaction the

mixture: 0.7 M). The reaction was stirred until the ynoate was consumed, palladium trifluoroacetate (6 mol%) was then added and the reaction stirred until the cross-coupling product was consumed. The solvent was removed in vacuo and the residue was purified by flash column chromatography on Florisil eluting with a diethyl ether/petroleum ether mixture.

Synthesis of 13b: Ketone **24** (4.60 g, 20 mmol) in THF (20 mL) was added to a solution of LDA [prepared by addition of *n*BuLi (13.1 mL, 21 mmol, 1.6 M in hexanes) to diisopropylamine (2.94 mL, 21 mmol) at −78 °C and warming to RT for 1 h] in THF (40 mL) at −78 °C. After the solution was stirred for 1 h at this temperature, diethyl chlorophosphate (3.18 mL, 22 mmol) was added. After the reaction mixture was warmed to RT over 90 min, it was added to another solution of LDA (45 mmol, prepared as above) in THF (40 mL) at −78 °C. Stirring was continued at this temperature for 1 h. After additional stirring for 1 h at RT the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (50 mL). Extraction with Et_2O (3×100 mL), washing of the combined organic phases with saturated aqueous $NaHCO_3$, drying over $MgSO_4$, filtration, and evaporation of the solvents afforded a crude oil. Flash column chromatography on silica gel (petroleum ether/Et_2O, 50:1) afforded **13b** (2.64 g, 62%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.46 (s, 2H), 2.06 (s, 1H), 1.19 (s, 6H), 0.90 (s, 9H), 0.06 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 90.6, 71.1, 68.0, 33.3, 25.9, 25.3, 18.3, −5.4 ppm; IR (film): $\tilde{\nu}$ = 3313, 2957, 2931, 2899, 2859, 1472, 1410, 1391, 1362, 1254, 1106, 838, 776, 632 cm^{-1}; elemental analysis calcd for $C_{12}H_{24}OSi$: C 67.86, H 11.39; found: C 67.97, H 11.60.

Synthesis of 18c: HF (aq. 40%, 4 mL) was added to a solution of silylether **18a** (2.52 g, 5.85 mmol) in acetonitrile (60 mL). After stirring for 4 h at RT, the reaction was quenched by careful addition of solid $NaHCO_3$. Dilution with CH_2Cl_2 (250 mL), drying over $MgSO_4$, filtration through a pad of Celite and evaporation of the solvents afforded a crude oil that was used directly in the next reaction. This oil was dissolved in CH_2Cl_2 (50 mL) and then 2,2-dimethoxypropane (1.44 mL, 11.7 mmol) and *p*-toluenesulfonic acid (111 mg, 0.585 mmol) were added. The reaction mixture was stirred for 12 h at RT and quenched by addition of triethylamine (1 mL). Evaporation of the solvents and flash column chromatography on silica gel (petroleum ether/EtOAc, 2:1) afforded **18c** (1.07 g, 72%, over the 2 steps) as a colorless oil. $[\alpha]_D^{23}$ = 18.3 (c = 1.20 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.17–4.09 (m, 1H), 3.82–3.74 (m, 2H), 3.77 (s, 3H), 3.05 (d, J = 5.0 Hz, 1H), 2.59 (d, J = 6.2 Hz, 2H), 1.89–1.82 (m, 1H), 1.76–1.69 (m, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 1.27 ppm (d, J = 5.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.9, 108.2, 85.8, 79.0, 76.4, 74.6, 67.0, 52.6, 37.1, 27.4, 27.2, 27.1, 16.9 ppm; IR (film): $\tilde{\nu}$ = 3454, 2986, 2937, 2240, 1716, 1436, 1381, 1257, 1172, 1076, 999, 931, 869, 836, 754 cm^{-1}; elemental analysis calcd for $C_{13}H_{20}O_5$: C 60.92, H 7.87; found: C 60.87; H 7.61.

Synthesis of 12d: $Pd(OAc)_2$ (3.1 mg, 0.014 mmol, 4 mol%) and TDMPP (6.2 mg, 0.014 mmol, 4 mol%) were stirred for 30 min in benzene (0.5 mL) to obtain a homogenous solution. Alkyne **13b** (82 mg, 0.38 mmol) and ynoate **18c** (87 mg, 0.34 mmol) are then added. The reaction mixture was stirred for 1 day at RT, that is, until complete conversion was observed (as judged by thin layer chromatography). $Pd(OCOCF_3)_2$ (8.7 mg, 0.027 mmol, 8 mol%) was then added and stirring was continued for 2 days. Evaporation of the solvent and flash column chromatography on silica gel (petroleum ether/Et_2O, 10:1, 2% triethylamine) afforded **12d** (90 mg, 55%) as a pale yellow oil. Minor impurities, the double-bond isomer and the 5-*exo* isomer, were detected in the NMR spectrum. R_f = 0.32 (petroleum ether/Et_2O, 4:1); $[\alpha]_D^{26}$ = 14.3 (c = 1.82 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.44 (s, 1H), 5.40 (s, 1H), 4.16–4.08 (m, 1H), 3.82–3.76 (m, 1H), 3.74–3.68 (m, 1H), 3.66 (s, 3H), 3.56 (dd, J = 17.2, 3.2 Hz, 1H), 3.46 (d, J = 11.2 Hz, 1H), 3.43 (d, J = 11.2 Hz, 1H), 2.45 (ddd, J = 17.2, 12.0, 2.0 Hz, 1H), 1.86 (ddd, J = 14.0, 10.0, 2.0 Hz, 1H), 1.70 (ddd, J = 14.0, 9.6, 2.8 Hz, 1H), 1.38 (s, 3H), 1.37 (s, 3H), 1.26 (d, J = 6.4 Hz, 3H), 1.07 (s, 3H), 1.06 (s, 3H), 0.86 (s, 9H), 0.00 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 167.9, 150.3, 108.0, 107.8, 102.0, 78.4, 76.8, 73.3, 69.4, 50.7, 41.7, 37.5, 31.8, 27.3, 27.2, 25.8, 22.5, 22.4, 18.2, 17.1, −5.4, −5.6 ppm; IR (film): $\tilde{\nu}$ = 2949, 2922, 2858, 1710, 1644, 1472, 1434, 1379, 1327, 1248, 1226, 1153, 1096, 1045, 1002, 925, 854, 838, 776 cm^{-1}; elemental analysis calcd for $C_{25}H_{44}O_6Si$: C 64.06, H 9.46; found: C 63.92, H 9.65.

Synthesis of 36: Trifluoroacetic anhydride (TFAA, 0.99 mL, 7.05 mmol) was added to a suspension of urea hydrogen peroxide (0.705 g, 7.49 mmol) in CH_3CN (23.4 mL) at 0 °C and stirred for 50 min to obtain a homogeneous trifluoroperacetic acid solution. Na_2HPO_4 (1.33 g, 9.4 mmol) was added to a solution of **12d** (1.1 g, ≈50% purity, 1.18 mmol) in a mixture of CH_2Cl_2 (23.4 mL) and CH_3OH (23.4 mL) at 0 °C. The suspension was stirred for 5 min before being treated with the above prepared trifluoroperacetic acid solution. This mixture was stirred at 0 °C for 40 min and then quenched with saturated $Na_2S_2O_3$. The mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash column chromatography on silica gel to give impure **36** (0.94 g). An analytically pure sample was obtained by further column chromatography on silica gel. R_f = 0.26 (petroleum ether/Et_2O, 2:1); $[\alpha]_D^{29}$ = −5.7 (c = 1.20 in CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6): δ = 6.64 (t, J = 1.8 Hz, 1H), 4.40 (dd, J = 13.7, 2.3 Hz, 1H), 4.35 (dd, J = 7.2, 1.8 Hz, 1H), 3.88–3.82 (m, 1H), 3.81 (d, J = 9.9 Hz, 1H), 3.64 (d, J = 7.2 Hz, 1H), 3.52–3.46 (m, 1H), 3.43 (d, J = 8.2 Hz, 1H), 3.39 (s, 3H), 3.28–3.25 (m, 1H), 3.26 (s, 3H), 1.83–1.76 (m, 1H), 1.46–1.36 (m, 2H), 1.36 (s, 6H), 1.16 (s, 3H), 1.15 (s, 3H), 1.09 (d, J = 6.0 Hz, 3H), 0.95 (s, 9H), 0.03 (s, 3H), 0.02 ppm (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ = 167.3, 158.5, 127.9, 113.2, 107.8, 103.7, 78.7, 77.1, 73.6, 69.4, 68.7, 51.2, 50.5, 45.8, 38.4, 35.4, 27.5, 27.4, 26.0, 25.9, 22.9, 22.3, 18.5, 17.1, −5.5, −5.6 ppm; IR (film): $\tilde{\nu}$ = 3339, 2949, 2886, 2859, 1714, 1660, 1474, 1438, 1371, 1364, 1252, 1225, 1166, 1089, 999, 836, 772 cm^{-1}; HRMS: m/z calcd for $C_{26}H_{48}O_8Si$: 539.3016 $[M+Na]^+$; found: 539.3018.

Synthesis of 37: The Dess–Martin periodinane (DMP) was added in two portions (1.16 g and 0.39 g) to a solution of impure **36** (0.94 g) and pyridine (1.47 mL) in CH_2Cl_2 (30 mL). The reaction mixture was stirred at RT for 1 h and then quenched with a mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ (1:1). The mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was subjected to flash column chromatography on silica gel to give impure ketone **37** (0.39 g). An analytically pure sample was obtained by further column chromatography on silica gel. R_f = 0.32 (petroleum ether/Et_2O, 4:1); $[\alpha]_D^{24}$ = −54.1 (c = 0.84 in CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6): δ = 6.89–6.87 (m, 1H), 4.17–4.09 (m, 1H), 3.92–3.85 (m, 2H), 3.55 (d, J = 10.0 Hz, 1H), 3.54–3.48 (m, 1H), 3.45–3.39 (d, J = 17.8 Hz, 1H), 3.34 (s, 3H), 3.30 (s, 3H), 2.74 (ddd, J = 17.8, 12.7, 3.4 Hz, 1H), 1.42–1.22 (m, 2H), 1.35 (s, 3H), 1.34 (s, 3H), 1.26 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H), 0.91 (s, 9H), 0.01 (s, 3H), 0.00 ppm (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ = 195.9, 166.2, 148.3, 122.4, 108.0, 104.7, 78.4, 77.2, 70.3, 68.5, 52.0, 51.2, 46.6, 38.7, 36.1, 27.5, 27.4, 26.2, 26.0, 20.3, 19.9, 18.7, 17.1, −5.4, −5.6 ppm; IR (film): 2932, 2858, 1727, 1710, 1634, 1471, 1435, 1379, 1252, 1215, 1171, 1130, 1093, 1043, 1004, 936, 838, 779 cm^{-1}; elemental analysis calcd for $C_{26}H_{46}O_8Si$: C 60.67, H 9.01; found: C 60.8, H 8.97.

Synthesis of 38: $CeCl_3{\cdot}7H_2O$ (141 mg, 0.38 mmol) was added to a solution of the impure ketone **37** (0.39 g) in CH_3OH (15 mL) at −30 °C. The mixture was stirred for 20 min before being treated with $NaBH_4$ (57 mg, 1.5 mmol). The yellow solution turned clear within 10 min. After stirring for another 10 min at −30 °C, brine was added. The mixture was warmed to room temperature and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash column chromatography on silica gel to give impure alcohol **38** (0.28 g). An analytically pure sample was obtained by further column chromatography on silica gel. R_f = 0.20 (petroleum ether/ether, 2:1); $[\alpha]_D^{26}$ = −9.8 (c = 0.98 in CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6): δ = 6.57 (m, 1H), 5.89 (d, J = 7.4 Hz, 1H), 4.62 (d, J = 7.4 Hz, 1H), 4.21–4.14 (m, 1H), 3.98 (d, J = 10.0 Hz, 1H), 3.92–3.86 (m, 1H), 3.55–3.48 (m, 1H), 3.43 (s, 3H), 3.40–3.34 (m, 1H), 3.30 (s, 3H), 2.91–2.82 (m, 1H), 1.43–1.26 (m, 3H), 1.37 (s, 6H), 1.13 (d, J = 5.9 Hz, 3H), 1.06 (s, 3H), 1.05 (s, 3H), 0.94 (s, 9H), 0.00 (s, 3H), −0.01 ppm (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ = 167.0, 161.0, 127.9, 113.6, 107.8, 104.2, 78.7, 77.2, 70.0, 69.8, 68.2, 50.5, 49.7, 47.2, 39.0, 36.2, 27.5, 27.5, 25.9, 22.0, 21.5, 18.4, 17.1, −5.6, −5.8 ppm; IR (film): 3339, 2931, 2859, 1719, 1469, 1455, 1433,

1374, 1223, 1170, 1091, 997, 948, 838, 780 cm^{-1}; elemental analysis calcd for $C_{26}H_{48}O_8Si$: C 60.43, H 9.36; found: C 60.51, H 9.18.

Synthesis of 39: DMAP (6 mg, 0.049 mmol), pyridine (1.1 mL), and acetic anhydride (0.55 mL) were sequentially added to a solution of alcohol **38** (280 mg) in CH_2Cl_2 (6 mL). The mixture was stirred at room temperature for 3.5 h, and then directly purified by flash column chromatography (Et_2O/petroleum ether, 1:3) to give acetate **39** (260 mg, 45% yield over four steps) as a clear oil. R_f=0.39 (Et_2O/petroleum ether, 1:3); $[\alpha]_D^{23}=-2.6$ (c=1.1 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ=5.88 (s, 1H), 5.58 (s, 1H), 4.13 (t, J=10.7 Hz, 1H), 3.85 (td, J=2.2, 9.2 Hz, 1H), 3.69 (s, 3H), 3.69 (m, 1H), 3.56 (d, J=9.4 Hz, 1H), 3.54 (d, J=9.4 Hz, 1H), 3.44 (dd, J=1.5, 14.1 Hz, 1H), 3.34 (s, 3H), 2.39 (t, J=13.3 Hz, 1H), 2.11 (s, 3H), 1.77–1.72 (m, 1H), 1.70–1.64 (m, 1H), 1.36 (s, 3H), 1.35 (s, 3H), 1.27 (d, J=6.0 Hz, 1H), 1.01 (s, 3H), 0.97 (s, 3H), 0.88 (s, 9H), 0.01 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=168.9, 166.5, 152.7, 116.4, 107.8, 102.7, 78.2, 76.9, 72.2, 68.1, 67.3, 51.1, 50.8, 47.1, 38.4, 33.4, 27.3, 27.1, 25.9, 21.1, 20.6, 18.4, 17.0, −5.5 ppm (2); IR (film): 2988, 2955, 2929, 1755, 1721, 1658, 1468, 1434, 1227, 1155, 1092, 855, 834, 775 cm^{-1}; HRMS calcd for $C_{25}H_{45}O_7Si$: 485.2934 $[M-C_2H_3O_2]^+$; found: 485.2952.

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