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Total Synthesis of Bryostatins. Development of Methodology for Atom-Economic and Stereoselective Synthesis of the C-ring Subunit

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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 stereoselective assembly of the C-ring 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 C-ring subunit of bryostatins.

Keywords

palladium; alkyne-alkyne coupling; bryostatin; atom economy; dihydropyran synthesis

Introduction

Isolation and Biology

Since their first isolation in 1968 by Pettit and coworkers from the marine bryozoan *Bugula neritina*,^{i, ii} bryostatins 1-20 (**1a-t**) (Figure 1), a class of structurally complex macrolides, have continuously attracted the attention of both chemists and biologists for almost 40 years. These marine natural products exhibit an exceptional range of biological activities, most notable is that the bryostatins can act as antineoplastic agents and exhibit excellent anticancer activity.ⁱⁱⁱ Biological experiments indicate that bryostatin 1 (**1a**) significantly inhibits the growth of a large number of tumor cell lines *in vivo* with low toxicity, such as murine leukemia, ovarian carcinoma, reticulum cell sarcoma, and B16 melanoma.^{iv, v, vi, vii} Recently, clinical application of bryostatin in combination with other chemotherapeutic agents has shown significant potential to treat some cancers with high potency.^{viii, ix}

Unlike other antineoplastic agents, however, bryostatin stimulates the immune and hematopoietic system,^x which has been suggested as a key factor for its anti-tumor action.^{xi} Furthermore, recent efforts have revealed that bryostatin significantly affects both cognition and memory enhancement in animals, which suggests potential use of bryostatin for the treatment of Alzheimer's disease, depression and other cognitive impairments.^{xii} Remarkably, Sun, Hongpaisan, Neslon and Alkon recently suggested that bryostatin could be a potential new treatment to reverse brain damage after a stroke.^{xiii} Due to these

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outstanding biological activities, bryostatin has been examined in numerous phase I and II clinical trials, including for the treatment of melanoma, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, sarcomas, and more recently for the treatment of Alzheimer's disease.^{xiv,xv,xvi,xvii,xviii,xix} Although its exact mode of action is still under debate, bryostatins' efficacy can be attributed to their strong affinity (picomolar) for protein kinase C (PKC) isozymes,^{xx} enzymes that phosphorylate serine and threonine residues in many target proteins that are often involved in cell-signal transduction pathways. Bryostatin activates PKC through binding to the same active sites as phorbol esters,^{xxi,xxii} however, unlike many phorbol esters, which are tumor promoters, bryostatin acts as an anti-tumor agent.

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, 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 synthesis,^{xxiii,xxiv,xxv} and formal syntheses of bryostatins have also been reported.^{xxvixxxvii} 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 total steps) have so far restrained them from serving as a practical supply source for this natural product.

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 development of convergent and chemoselective methods would enable us to synthesize the PHP rings in a more efficient fashion, and to shorten the synthesis ultimately. In this article, we report detailed studies on the development of methods and strategies for the chemo- and diastereoselective formation of the bryostatin C-ring.^{xxviii}

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 the C-ring was based on the unique reactivity of alkynes. We envisioned that the C-ring fragment could ultimately come from functionalization of a dihydropyran intermediate (**I**). The key dihydropyran (**I**) could be prepared via a highly atom-economic transformation from alkynes **III** and **VI**. By taking advantage of the different reactivities between 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 to generate the dihydropyran in one pot.

Our initial efforts were inspired by a previous method developed in this group, in which furans were synthesized via 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).^{xxix} If an ynoate bearing a hydroxyl group at the *homopropargylic* position were used in the tandem alkyne-alkyne coupling/6-*endo-dig* oxycyclization, 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 via transesterification.

To test the feasibility of the desired cyclization, the reaction of 1-heptyne (**2a**) and homopropargylic ynoate (**3a**) was chosen as a model system and examined under the conditions reported for furan formation. Initial experiments using 5 mol % of Pd(OAc)₂ and 2 mol% tri(2,6-dimethoxyphenyl)phosphine (TDMPP) gave dihydropyran **5a**, although the reaction time was rather long when 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 ca. 24 h. Elevated temperatures shortened the reaction times, but at the cost of selectivity and yield (entries 3-6). As the reaction temperature was raised, progressively higher proportions of lactone **6a** were observed. Fortunately, higher catalyst loading both accelerated the reaction to a reasonable time interval (60 h) and eliminated the formation of the lactone. 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 (entry 2).

For its application in the total synthesis of bryostatin, chemoselectivity and substrate scope of this method were next explored. Alkynes and ynoates^{xxx} with various functional groups and substitution patterns were subjected to the tandem coupling/cyclization reaction under the optimal 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 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 (entry 8). The excellent chemoselectivity was revealed by the observation that the relatively reactive primary chloride substitution was tolerated under these conditions (entry 4). Ynoates with the homopropargylic alcohol chain restricted within a ring (**3e** and **3f**)^{xxxi} failed to undergo the subsequent *O*-cyclization; only the cross-coupled products (**4e** and **4f**) were isolated (entries 5 and 7). In the case of **3e**, longer reaction times (7 d) gave the corresponding lactone (**6e**) without any detectable amount of dihydropyran in the reaction mixture (entry 6). The difficulty is likely caused by the *trans*-orientation of the substituents on the cyclohexane ring, which presents an unfavorable geometry for the endo cyclization. A donor alkyne with a branch at the propargyl position (**2b**) was also examined (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 the 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 5-*exo* product (**7**) was observed when the donor alkyne bearing an electron-withdrawing group was employed. The highest proportions of the 5-*exo* products were observed when an electronegative group was installed at the propargylic position (e.g. entries 1, 2 and 9), lesser amounts when the substitution was at the homoallylic position (entries 4 and 5), and none when the group was four carbons removed (entry 8). This unusual regioselectivity was presumably caused by the inductive effect of the electronegative substituents adjacent to the donor alkyne, as well as the dipole repulsion between the alcohol nucleophile and the electronegative substituent (Figure 2). Variation of reaction temperature, concentration, and order of addition had little to no effect on the *endo*/*exo* ratio in the reaction depicted in 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 (entry 9). Vinylsilane substitution^{xxxii} also caused

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

As the synthesis of bryostatin 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 the 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 a 14-day exposure to the typical reaction conditions (eq 1 and Table 4, entry 1).

To address this slow cyclization problem, 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, wherein increasing electrophilicity should increase the rate of cyclization. We have previously noted a dramatic enhancement of rate in formation of π -allylpalladium complexes from less nucleophilic alkenes when palladium trifluoroacetate was employed.^{xxxiii} 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).^{xxxiv}

(1)

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 directly employed as the oxypalladation catalyst. Indeed, by the 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 over 36 hours without isomerization of the exocyclic alkene (Table 4, entry 3), which is a significant improvement compared to 25 % yield over 14 days (entry 1).

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

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

(2)

(3)

A few substrates produced unusual results when subjected to the tandem reaction protocol. The ortho-alkynyl phenol **10**^{xxxv} 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).

(4)

(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 $\text{Pd}(\text{OAc})_2$ failed, as the cross-coupling step did not occur. When a cross-coupled enyne product of type **4** was treated with $\text{Pd}(\text{O}_2\text{CCF}_3)_2$ *without ligand*, no cyclization product was detected, which indicates the importance of ligand in the oxypalladation step. Finally, when an enyne **4** was subjected to $\text{Pd}(\text{O}_2\text{CCF}_3)_2$ (5 mol%) and ligand (2 mol%), oxypalladation occurs, but the reaction rate was slow. An investigation of palladium to phosphine ligand ratios as well as palladium acetate to palladium trifluoroacetate ratios revealed that the best results were obtained using the original conditions (i.e. 4 mol% $\text{Pd}(\text{OAc})_2$ /4 mol% TDMPP for cross-coupling, then 6 mol% $\text{Pd}(\text{O}_2\text{CCF}_3)_2$ for oxypalladation). It was also found that use of excess terminal alkyne (>1.1 equiv.) accelerated the cross-coupling step, but seriously compromised the efficiency of the oxypalladation step, making the competing lactonization a problem.

Synthesis of the C-ring 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 C-ring subunit of bryostatins. We envisioned that bryostatin could be divided into two fragments: the northern one containing the A- and B-rings and the southern one (**12**) containing the C-ring (Scheme 4). These two fragments could be sewn together via esterification to form the C1 ester and olefination reaction to form the C16-C17 alkene. The C-ring fragment **12** could be ultimately prepared from donor alkyne **13** and ynoate **14**.

Towards this end, a variety of donor alkynes with different functional handles were synthesized to examine in the tandem dihydropyran formation protocol targeting the C-ring of bryostatin (Scheme 5). 2,2-Dimethyl-3-butyn-1-ol (**13a**) was synthesized in two steps from commercially available 2-methyl-but-3-yn-2-ol **2k** according to a literature protocol,^{xxxvi} and then elaborated in various ways to 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.^{xxxvii} All these alkynes possess substituents appropriate for future coupling reactions with the northern fragments as outlined in Scheme 4.

Synthesis of the target ynoate partners of type **14** for the projected tandem cross-coupling/oxy cyclization sequence is shown in Scheme 6. Silyl ether **15a** was prepared in high enantiomeric purity over two steps from commercially available 1,4-*trans*-hexadiene according to a literature procedure.^{xxxviii}

After some experimentation, conditions were found to convert the terminal olefin to the corresponding diol in a diastereoselective fashion (Table 6). Surprisingly, when TBS substrate **15a** was subjected to the Sharpless asymmetric dihydroxylation (SAD) conditions, the observed stereochemical outcomes are exactly opposite to the prediction based on the Sharpless' mnemonic.^{xxxix} Using 'matched' DHQD ligand, a poor diastereoselectivity was obtained slightly favoring the undesired diastereomer (entry 2); however, use of the 'mismatched' DHQ ligand provided the desired diol isomer as the major product in about 6:1 dr (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 acetone substrate **15b** was consistent with prediction, albeit with a relatively poor diastereoselectivity (entries 3 and 4). Examination of other asymmetric dihydroxylation ligands was not fruitful (entries 5 and 6), despite evidence that the anthraquinone ligand is often superior to the DHQD series for terminal alkenes.^{xl} In addition, substrate-controlled dihydroxylation of substrate **15a** (no chiral ligand present) resulted in a 1.5:1 isomer mixture, slightly favoring the desired diastereomer (entry 7).

With pure diol **16a** in hand, conversion to the epoxide **17** was uneventful (Scheme 6). Opening the epoxide with the lithium anion of methyl propiolate provided target ynoate **18a** in 80% yield. Ynoates **18b** and **18c** 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 acetone **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 (eq 6).^{xli} This transformation proceeded very well on small

scale (0.5 mmol; 90 %); however, the yield was diminished on larger scale (12.2 mmol, 45 %), when problems arose with the temperature control 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 donor alkyne and ynoate partners, the stage was set to test them in the Pd-catalyzed tandem coupling/cyclization reaction. Donor alkynes were examined first using **3b** as a model ynoate (Table 7). Subjecting sulfone **13d** to the two-stage one-pot reaction conditions produced the desired dihydropyran **19d**, along with the 5-*exo* byproduct **20d** in a 3:1 ratio (entry 1). In contrast, sulfone **13e** produced mainly **20e** (3.5:1 ratio; entry 3). Thioacetate **13c** underwent cross coupling with ynoate **3b** (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 (entry 4). When silyl ether **13b** was the donor alkyne, the sequence was selective for **19b** (entry 5). From these studies, it seemed appropriate to select **13d** and **13b** (entries 1 and 5) as terminal alkyne partners for use during synthesis of fully functionalized dihydropyran **12** (see Scheme 4) necessary for the synthesis of the bryostatins.

Ynoates **18a**, **18b** and **18c** 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 ynoate most directly accessible (see Scheme 6), was unsuitable for two reasons: 1) even using the Pd(O₂CCF₃)₂ protocol, the reaction times were unreasonably long, and 2) a high proportion of lactone **30** was observed in the product mixture (entries 1 and 2, Table 8). 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 of **18a**, due to the two neighboring TBS ethers.

Substrate triol **18b** underwent rapid cyclization with very high selectivity (no byproducts **21** or **22** were detected by crude ¹H NMR). However, dihydropyran **12** could not be isolated without isomerization of the exocyclic enoate (entries 3 and 4). In addition, isolation of the enoate mixture revealed that the yield of the reaction was lower than other cases (ca 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 provide the best results in the tandem cyclization process (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 the sulfone **13d** was inferior with respect to the formation of the undesired products **21** and **22** (entries 1 and 5). Therefore, donor alkyne **13b** and ynoate **18c** clearly acted as the best combination as indicated in entry 6 for the synthetic route targeting bryostatin C-ring.

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 synthesis of alkyne **13b** and ynoate **18c**, improving efficiency and scalability.

A more effective synthesis of alkyne **13b** on large scale is described in Scheme 7. Commercially available 3-methyl-2-butanone was subjected to an acid-mediated aldol reaction with paraformaldehyde to provide alcohol **23**,^{xlii} which was then protected as a TBS-silyl ether. Subsequently, methyl ketone **24** was converted to terminal alkyne **13b** using a one-pot protocol developed by Negishi.^{xliii}

To avoid the cumbersome purification encountered when running the reaction on scale using the SAD route, we next developed an efficient ‘chiral pool’-based route to access ynoate **18c** (Scheme 8). Although it was partially adapted from a known route,^{xliv} the reaction parameters were carefully optimized for successful completion of this strategy (see supporting information for details). Towards this end, commercially available D-galactono-1,4-lactone was brominated at the primary hydroxyl function and then peracetylated.^{xlv} 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 bryostatin. 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 BF₃-mediated epoxide opening with the lithium acetylide derived from methyl propiolate. Multigram quantities of ynoate **18c** can be obtained from this chiral pool approach, 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, efforts were next taken to improve the efficiency of forming dihydropyran **12d**. As indicated in Table 8, use of the Pd(OAc)₂ and Pd(O₂CCF₃)₂ combination method provided the desired dihydropyran in acceptable yield. This protocol was reproducible at scales of 0.3 mmol; unfortunately, upon further scale-up sluggish reactions and the formation of different isomers was observed.

Closer investigation of the reaction products of the tandem reaction revealed the presence of four different products (Table 9). While the desired dihydropyran **12d** from a 6-*endo* cyclization was the major product, we also observed varying amounts of the double bond isomer **29**, the furan derivative **21d** resulting from the 5-*exo* cyclization and the lactone **22d**. Towards this end, we attempted to determine the relative kinetics of the formation of each product via 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 the enyne **30** was observed after 20 hours. Palladium trifluoroacetate (8 mol %) was added to the reaction mixture and aliquots of the reaction were analyzed by NMR after 24, 48 and 96 h (Table 9). The results suggested that the lactone formation was a strong 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 the side products, consequently, we performed a more detailed catalyst survey for the oxycyclization step. Towards this end, enyne **30** was isolated in 89% yield after quenching the reaction at the first stage (eq 7), and subsequently subjected to different catalyst conditions (Table 10).

(7)

Use of palladium trifluoroacetate as catalyst led only to only low selectivity towards favoring the desired product **12d**, and significant amounts of the olefin isomer **29** and 5-*exo* product **21d** were observed (entries 1 and 2). The addition of TDMPP as ligand afforded similar selectivities as in the two-stage one-pot sequence (entry 3). Silver salts have been described in the literature to catalyze the intermolecular addition of alcohols to alkynes,^{xlvi} but silver catalysis was not effective for this cyclization. High catalyst loadings of silver trifluoroacetate (60 mol%) were necessary to achieve cyclization (entries 4 and 5), and cyclization with AgOTf was inefficient and unselective. Interesting results were obtained when using PtCl₂ as catalyst.^{xlvi} 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 6-*endo* cyclization pathway (entry 6). No cyclization was observed in experiments using CpRu(CH₃CN)₃PF₆, [RuCl₂(p-cymene)]₂ and Rh(PPh₃)₃Cl as catalysts.

Utimoto and coworkers reported that PdCl₂(PhCN)₂ complex was able to catalyze intramolecular alcohol addition to alkynes (Table 10).^{xlvi} Reactions with this catalyst system were very fast (complete conversions within one hour) with no formation of lactone **22d** detectable by ¹H NMR (entries 7-11). Etheral solvents provided the best results (entries 8-11), and THF was chosen for the further optimisation. Cyclization with PdCl₂(MeCN)₂ led to similar results (entry 12). One major side reaction for this catalyst system was isomerization of the exocyclic olefin. One initial hypothesis was that this isomerization was mediated by protons or chloride ions generated from the catalyst in the course of the catalytic cycle. Using amine bases as a buffer resulted in complete inhibition of the oxycyclization, while ethylvinylether was somewhat effective as an acid trap (entry 13). Addition of solid inorganic bases seemed more promising, but only barium oxide and silver oxide gave complete conversion (entries 14 and 15). Finally, inspired by the results in the previous one-pot procedure, phosphines were investigated as additives to this PdCl₂(RCN)₂ catalyst system. Addition of TDMPP (1:1 to Pd) dramatically slowed the reaction, but use of a smaller amount of phosphine (3 mol%) provided complete conversion within 7 h and suppressed the formation of **21d** and **29** (entry 16). Use of other phosphines, such as dppf, and PPh₃, resulted in extremely low reactivity.

During the original oxycyclization studies on **30**, the most practical set of conditions found for dihydropyran formation involved use of PdCl₂(MeCN)₂ (5 mol %)/TDMPP (3 mol%), on 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).

(8)

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).

(9)

Pure alcohol **31** was isolated after removal of TBS group with TBAF from the mixture of TBS-ethers obtained in the $\text{PdCl}_2(\text{MeCN})_2/\text{TDMPP}$ -cyclization. To access α -hydroxyl ketal **32**, chemoselective epoxidation of the C19-C20 alkene followed by an *in situ* epoxide ring-opening with a methanol nucleophile was investigated.^{xxviii} The findings are shown in Table 11.

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 spectrum indicated that the 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 from 3:1 to 2:1 depending on the reaction conditions employed. The reactions at the lower temperature and the epoxidations with peroxyimides gave diastereomeric mixtures that also contained the alcohols inverted at C20. The absolute stereochemistry at C20 was assigned by converting **32** to tetrahydropyran **33** through reduction of the anomeric methoxy group with triethylsilane (eq 10 and Figure 3). The stereochemistry at the ketal center (C19) was tentatively assigned based on a similar epoxidation outcome in the Evans bryostatin synthesis.^{xxivb}

(10)

As the stereochemistry of the secondary alcohol at C20 had to be inverted to synthesize bryostatins, an oxidation-reduction approach was next explored (Scheme 9). 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. Use of IBX^{xlxi} 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 oxidationⁱ (DMSO, TFAA, TEA) gave an apparently clean reaction by TLC, however the crude NMR showed the presence of five different aldehyde products. Switching to oxalyl chloride as activating agent in the Moffatt-Swern oxidation afforded no improvement. Somewhat promising results were obtained when using Dess-Martin periodinane (DMP).^{li} 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)^{liii} led only to decomposition. Therefore, this approach was not pursued further.

Due to the labile nature of diol **32**, attempts were next made to oxidize the TBS-protected dihydropyran **12d** directly (Scheme 10). Subjecting **12d** (60 % purity, **22d** and **29** as minor components) to the optimal epoxidation conditions (trifluoroacetic acid;^{liii} 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 were assigned in analogy to **32**. Oxidation of the secondary alcohol with DMP cleanly afforded ketone **37**. Finally, a highly diastereoselective Luche reduction^{liv} of **37** followed by acylation of the resulting secondary alcohol (**38**) furnished the C-ring fragment **39** with the desired C20 stereochemistry in 45% yield over four steps.^{lv}

Conclusion

During the initial stage of our efforts towards the total synthesis of bryostatin, we have developed a distinct method for the stereoselective assembly of the C-ring 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 C-ring 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 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 chromatography on Florisil eluting with ether/petroleum ether.

General Procedure B for Dihydropyran Synthesis

A solution of Pd(OAc)₂ (4 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 reaction mixture: 0.7 M). The reaction was stirred until the ynoate was consumed and palladium trifluoroacetate (6 mol %) was 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 chromatography on Florisil eluting with ether/petroleum ether.

13b

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 up to rt for 1 h) in THF (40 ml) ketone **24** (4.60 g, 20 mmol) in THF (20 ml) is added at -78 °C. After the solution was stirred for 1 h at -78 °C, diethyl chlorophosphate (3.18 ml, 22 mmol) is added at -78 °C. After the reaction mixture was being warmed to rt during 90 min, it was added to a solution of LDA (45 mmol, prepared as above) in THF (40 ml) at -78 °C. Stirring is continued at this temperature for 1 h. After additional stirring for 1 h at rt the reaction mixture is quenched by addition of sat. aq. NH₄Cl (50 ml). Extraction with Et₂O (3 × 100 ml), washing of the combined organic phases with sat. aq. NaHCO₃, drying over MgSO₄, filtration and evaporation of the solvents affords a crude oil. Flash chromatography on silica gel (petroleum ether/Et₂O 50:1) affords **13b** (2.64 g, 62 %) as colourless oil. IR (film): 3313, 2957, 2931, 2899, 2859, 1472, 1410, 1391, 1362, 1254, 1106, 838, 776, 632 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ: 3.46 (s, 2H), 2.06 (s, 1H), 1.19 (s, 6H), 0.90 (s, 9H), 0.06 (s, 6H); ¹³C

NMR (75 MHz, CDCl_3) δ : 90.6, 71.1, 68.0, 33.3, 25.9, 25.3, 18.3, -5.4; Anal Calc'd for $\text{C}_{12}\text{H}_{24}\text{OSi}$: C, 67.86; H, 11.39. Found: C, 67.97; H, 11.60.

18c

HF (aq. 40 %, 4 ml) is added to a solution of silylether **18a** (2.52 g, 5.85 mmol) in acetonitrile (60 ml). After stirring 4h at rt the reaction is 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 affords a crude oil, that is used directly in the next reaction. It is dissolved in CH_2Cl_2 (50 ml), followed by addition of 2,2-dimethoxypropane (1.44 ml, 11.7 mmol) and *p*-toluenesulfonic acid (111 mg, 0.585 mmol). The reaction mixture is stirred 12h at rt, and quenched by addition of triethylamine (1 ml). Evaporation of the solvents and flash chromatography on silica gel (petroleum ether/EtOAc 2:1) affords **18c** (1.07 g, 72 %, over 2 steps) as colourless oil. IR (film): 3454, 2986, 2937, 2240, 1716, 1436, 1381, 1257, 1172, 1076, 999, 931, 869, 836, 754 cm^{-1} ; ^1H 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 (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; Anal Calc'd for $\text{C}_{13}\text{H}_{20}\text{O}_5$: C, 60.92; H, 7.87. Found: C, 60.87; H, 7.61. $[\alpha]^{23}_{\text{D}}$ 18.3 [*c* 1.20, CH_2Cl_2].

12d

$\text{Pd}(\text{OAc})_2$ (3.1 mg, 0.014 mmol, 4 mol%) and tris-(2,6-dimethoxyphenyl)phosphine (6.2 mg, 0.014 mmol, 4 mol%) were stirred for 30 minutes 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 added. The reaction mixture is stirred for 1 day at rt, complete conversion is observed (as judged by thin layer chromatography). $\text{Pd}(\text{OCOCF}_3)_2$ (8.7 mg, 0.027 mmol, 8 mol%) is added and stirring is continued for 2 days. Evaporation of the solvent and flash chromatography on silica gel (petroleum ether/Et₂O 10:1, 2 % triethylamine) affords **12d** (90 mg, 55 %) as a pale yellow oil. Minor impurities (double-bond isomer and 5-exo isomer were detected in the NMR). TLC R_f = 0.32 [petroleum ether/Et₂O 4:1]; IR (film): 2949, 2922, 2858, 1710, 1644, 1472, 1434, 1379, 1327, 1248, 1226, 1153, 1096, 1045, 1002, 925, 854, 838, 776 cm^{-1} ; ^1H 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 (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; Anal Calc'd for $\text{C}_{25}\text{H}_{44}\text{O}_6\text{Si}$: C, 64.06; H, 9.46. Found: C, 63.92; H, 9.65. $[\alpha]^{26}_{\text{D}}$ 14.3 [*c* 1.82, CH_2Cl_2].

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.

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 was added Na_2HPO_4 (1.33 g, 9.4 mmol). The suspension was stirred for 5 min before being treated with the above prepared trifluoroperacetic acid solution. The content was stirred at 0 °C for 40 min, quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$. 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 a quick flash silica gel chromatography to give 0.94 g of impure **36**. An analytically pure sample was obtained by further silica gel chromatography purification.

$[\alpha]_D^{29}$ -5.7 (*c* 1.20, CH₂Cl₂); ¹H NMR (400 MHz, C₆D₆) 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 (s, 3H). ¹³C NMR (100 MHz, C₆D₆) 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. TLC R_f 0.26 (petroleum ether/Et₂O 2:1). IR (film): 3339, 2949, 2886, 2859, 1714, 1660, 1474, 1438, 1371, 1364, 1252, 1225, 1166, 1089, 999, 836, 772 cm⁻¹; HRMS calcd for C₂₆H₄₈O₈Si [M+Na]⁺: 539.3016. Found: 539.3018.

37

To a solution of impure **36** (0.94 g) and pyridine (1.47 mL) in CH₂Cl₂ (30 mL) was added Dess-Martin periodinane in two portions (1.16 g + 0.39 g). The reaction was stirred at room temperature for 1 h and then quenched with 1:1 saturated aqueous NaHCO₃ and saturated aqueous Na₂S₂O₃. The mixture was extracted with CH₂Cl₂. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The residue was subjected to a quick flash silica gel chromatography to give 0.39 g impure ketone **37**. An analytically pure sample was obtained by further silica gel chromatography purification.

$[\alpha]_D^{24}$ -54.1 (*c* 0.84, CH₂Cl₂); ¹H NMR (400 MHz, C₆D₆) 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 (s, 3H). ¹³C NMR (100 MHz, C₆D₆) 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; TLC R_f 0.32 (petroleum ether/Et₂O 4:1). IR (film): 2932, 2858, 1727, 1710, 1634, 1471, 1435, 1379, 1252, 1215, 1171, 1130, 1093, 1043, 1004, 936, 838, 779 cm⁻¹; Anal Calcd for C₂₆H₄₆O₈Si: C, 60.67; H, 9.01. Found: C, 60.8; H, 8.97.

38

To a solution of the impure ketone **37** (0.39 g) in CH₃OH (15 mL) at -30 °C was added CeCl₃ · 7H₂O (141 mg, 0.38 mmol). The mixture was stirred for 20 min before being treated with NaBH₄ (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 MgSO₄, filtered, and concentrated. The residue was subjected to a quick flash silica gel chromatography to give 0.28 g impure alcohol **38**. An analytically pure sample was obtained by further silica gel chromatography purification.

$[\alpha]_D^{26}$ -9.8 (*c* 0.98, CH₂Cl₂); ¹H NMR (400 MHz, C₆D₆) 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 (s, 3H); ¹³C NMR (100 MHz, C₆D₆) 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; TLC R_f 0.20 (petroleum ether/ether 2:1); IR (film): 3339, 2931, 2859, 1719, 1469, 1455, 1433, 1374, 1223, 1170, 1091, 997, 948, 838, 780 cm⁻¹; Anal Calcd for C₂₆H₄₈O₈Si: C, 60.43; H, 9.36. Found: C, 60.51; H, 9.18.

39

To a solution of alcohol **38** (280 mg) in CH₂Cl₂ (6 mL) were added DMAP (6 mg, 0.049 mmol), pyridine (1.1 mL), and acetic anhydride (0.55 mL) sequentially. The mixture was stirred at room temperature for 3.5 h, and then directly purified by flash chromatography with 25% Et₂O/petroleum ether to give 260 mg of acetate **39** (45% yield over four steps) as a clear oil.

$[\alpha]_D^{23}$ -2.6 (c 1.1, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) 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 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) 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 (2); IR (neat film) 2988, 2955, 2929, 1755, 1721, 1658, 1468, 1434, 1227, 1155, 1092, 855, 834, 775; TLC R_f 0.39 (33% Et₂O in petroleum ether); HRMS calcd for C₂₅H₄₅O₇Si [M-C₂H₃O₂]⁺: 485.2934. Found: 485.2952.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Bryostatins

Figure 2.
5-*exo*-dig vs 6-*endo*-dig oxycyclization

Figure 3.
nOe data for tetrahydropyran **33**

Scheme 1.
Initial design of the bryostatin C-ring synthesis

Scheme 2.

Formation of Furans via Pd-Catalyzed Tandem Alkyne-Alkyne Coupling/5-*exo*-dig Oxy cyclization.

Scheme 3.

Formation of Dihydropyrans via Pd-Catalyzed Tandem Alkyne-Alkyne Coupling/6-*endo*-dig Oxycyclization.

Scheme 4.
Strategy for synthesis of ring C of bryostatins.

Scheme 5.

Synthesis of Donor Alkynes for Ring C Study

Reagents and Conditions: a) PBr₃, 66%; b) Al, HgCl₂ (cat.) (CH₂O)_n, 37%; c) TBSCl, imidazole, 99%; d) TsCl, pyridine, then AcSK, 61%; e) i) TsCl, pyridine, then NaSPh ii) *m*CPBA, 60% over two steps; f) i) 1-phenyl-1*H*-tetrazol-5-thiol, DIAD, PPh₃ ii) (H₄N)₆Mo₇O₂₄ H₂O₂, 71% over 2 steps

Scheme 6.
Synthesis of Ynoates for Ring C Synthesis

Scheme 7.
Improved synthesis of alkyne **13b**

Scheme 8.
Chiral pool-based synthesis of alkynoate **18c**

Scheme 9.
Oxidation-reduction approach to C20 inversion

Scheme 10.
Synthesis of C-ring fragment **39**

Table 1

Optimization for Dihydropyran Formation^[a]

entry	Pd(OAc) ₂ /TDMPP (mol %)	temp. (°C)	time (h)	ratio 5a:6a	yield (%)
1	5/2	rt	135	>20:1	61
2	10/4	rt	60	>20:1	61
3	5/2	rt-50 °C ^b	60	5.5:1	61
4	5/2	50 °C	54	5.5:1	57
5	5/2	rt-80 °C ^{b/}	36	1.8:1	30
6	5/2	80 °C	24	1.6:1	23

^[a] All reactions performed in benzene at a concentration of 0.7 M in substrates **2a** and **3a**.

^[b] Reaction run at ambient temperature for the first 24 h followed by heating to the stated temperature.

Table 2

Pd-Catalyzed Tandem Alkyne-Alkyne Coupling/*6-endo-dig* Oxycyclization^[a]

		time	product	yield ^[b]
entry	alkyne	ynoate				
1	2a			60 h		61%
2	2a			60 h		57%
3	2a			7 days		57%
4	2a			7 days		42%
5	2a			48 h		50%
6	2a			7 days		58%
7	2a			13 days		69%
8	2a			7 days		44%

Reaction scheme: $\text{C}_6\text{H}_{11}\text{C}\equiv\text{CH}$ (2a) or cyclopentyl-C≡CH (2b) + ynoate 3a-3g → product 5f

entry	alkyne	ynoate	time	product	yield ^[b]
9	2b		60 h		57%

^[a] Pd(OAc)₂ (5 mol%), TDMPP (2 mol%), benzene, 0.7 M, rt

^[b] Isolated yield.

Table 3Pd-Catalyzed Tandem Alkyne-Alkyne Coupling/6-*endo-dig* Oxycyclization^[a]

entry	donor alkyne	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, 0.7M, rt^[b] Isolated yields^[c] 4 mol% Pd(OAc)₂, 4 mol% TDMPP, then 6 mol% Pd(OCOCF₃)₂.

Table 4Stepwise dihydropyran formation^[a]

entry	reagents and conditions	time	yield
1	Pd(OAc) ₂ (10 mol%), TDMPP (4 mol%), benzene, rt	14 days	25
2	TFA (20 mol%)	24 h	59 ^[b]
3	Pd(OAc) ₂ (4 mol%), TDMPP (4 mol%), Pd(OCOCF ₃) ₂₂ (6 mol%), benzene, rt	36 h	62

^[a] Intermediate enyne **4q** was prepared using Pd(OAc)₂ (10 mol%), TDMPP (4 mol%) in benzene at ambient temperature

^[b] E/Z ratio was 1:1

Table 5

Tandem vs. Stepwise Reaction Conditions for Cyclization

entry	alkyne	R'	yield ^[a] (product: reaction time)	
			Method A	Method B
1	2a	H (3a) ^[b]	61% (5a ; 60 h)	63% (12 h)
2	2a	Me (3b)	57% (5b ; 52 h)	66% (30 h)
3	2a	CH ₂ OPMB (3c)	52% (5c ; 7 days)	58% (24 h)
4	2a	CH ₂ OTBS (3h)	52% (5r ; 7 days)	61% (36 h)
5	2m	Me (3b)	25% (5q ; 14 days)	62% (78 h)
6	2m	CH ₂ OPMB (3c)	- (5s ; 7 days) ^[c]	69% (9 days)
7	2m	CH ₂ OTBS (3h)	- (5t ; 7 days) ^[c]	50% (7 days) ^[d]

Method A: 10 mol% Pd(OAc)₂, 4 mol% TDMPP, benzene **Method B:** 4 mol% Pd(OAc)₂, 4 mol% TDMPP, then 6 mol% Pd(OCOCF₃)₂, benzene

^[a] Isolated yields.

^[b] Methyl ester was used.

^[c] No oxycyclization was observed after 7 days (enyne product of cross-coupling only).

^[d] 95% conversion. The yield of this reaction was 58% after 5 days (82% conversion).

Table 6

Dihydroxylation of Compound **15**^[a]

The reaction scheme shows compound **15**, which is a 1,3-diene with two OR groups and a methyl group, undergoing dihydroxylation to produce two diastereomeric products: **16-anti** and **16-syn**. In **16-anti**, the two hydroxyl groups are on opposite sides of the carbon chain, while in **16-syn**, they are on the same side.

entry	R	chiral ligand	ratio (<i>anti</i> : <i>syn</i>)
1	TBS (15a)	(DHQ) ₂ PHAL	6 : 1
2	TBS (15a)	(DHQD) ₂ PHAL	1 : 1.2
3	acetonide (15b)	(DHQ) ₂ PHAL	1 : 2.5
4	acetonide (15b)	(DHQD) ₂ PHAL	2 : 1
5	TBS (15a)	(DHQ) ₂ PYR	1.8 : 1
6	TBS (15a)	(DHQ) ₂ AQN	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]OsO₄ (10 mol %), NMO, Acetone/H₂O

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

entry	X	time	yield ^[b]	products (ratio)
1	SO ₂ Ph (13d)	4 days	54%	19d:20d (3:1)
2	SAc (13c)	--	--	[c]
3	(13e)	3 days	38%	19e:20e (1:3.5)
4	OH (13a)	2 days	[d]	19a:20a (1:1)
5	OTBS (13b)	6 days	58%	19b only

^[a] Pd(OAc)₂ (4 mol%), TDMPP (4 mol%), benzene, rt, then Pd(CO₂CF₃)₂, (6 mol%)^[b] Isolated yields^[c] cross-coupling product (enyne) only^[d] not determined

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

entry	R	X	time	products (ratio)
1	TBS (18a)	SO ₂ Ph (13d)	> 14 days	12a:21a:22a (4:1:4)
2	TBS (18a)	OTBS (13b)	> 24 days	12b:21b:22b (6:1:2) ^[b]
3	H (18b)	SO ₂ Ph (13d)	2.5 days	isomerization of exo-enoate
4	H (18b)	OTBS (13b)	1.5 days	
5	acetonide (18c)	SO ₂ Ph (13d)	3 days	12c:21c:22c (3:1:1) ^[b]
6	acetonide (18c)	OTBS (13b)	4 days	12d:21d:22d (12:1:1) ^[c]

^[a] Pd(OAc)₂ (4 mol%), TDMPP (4 mol%), benzene, rt, then Pd(CO₂CF₃)₂, (6 mol%)^[b] 54% isolated yield of **12c**^[c] 55-72% isolated yield of **12d**

Table 9

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

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

Table 10

Metal-catalyzed 6-*endo-dig* cyclization of Compound **30** ^[a], ^[b]

entry	catalyst	mol %	solvent	additive	time	30 (%)	12d (%)	29 (%)	21d (%)	22d (%)
1	Pd(O ₂ CCF ₃) ₂	10	benzene	-	12h	-	18	32	20	30
2	Pd(O ₂ CCF ₃) ₂	10	CH ₂ Cl ₂	-	14h	-	33	22	16	29
3	Pd(O ₂ CCF ₃) ₂	10	benzene	TDMPP (10 mol%)	12h	-	49	15	8	28
4 ^c	Ag(O ₂ CCF ₃)	30	CH ₂ Cl ₂	-	12h	41	32	5	4	18
5 ^c	Ag(O ₂ CCF ₃)	60	CH ₂ Cl ₂	-	16h	-	47	26	3	24
6	PdCl ₂	5	toluene	-	14h	-	29	14	57	-
7	PdCl ₂ (PhCN) ₂	5	benzene	-	45 min	-	30	21	49	-
8	PdCl ₂ (PhCN) ₂	5	Et ₂ O	-	45 min	-	45	24	31	-
9	PdCl ₂ (PhCN) ₂	5	THF	-	1h	-	47	26	27	-
10	PdCl ₂ (PhCN) ₂	5	dioxane	-	30 min	-	45	28	27	-
11	PdCl ₂ (PhCN) ₂	5	DME	-	30 min	-	50	30	20	-
12	PdCl ₂ (MeCN) ₂	5	THF	-	1h	-	44	35	26	-
13	PdCl ₂ (MeCN) ₂	5	THF	ethylvinylether (25 mol%)	1h	-	53	19	28	-
14	PdCl ₂ (MeCN) ₂	5	THF	BaO (50 mol %)	1h	-	50	15	35	-
15	PdCl ₂ (MeCN) ₂	5	THF	AgO (20 mol%)	1h	-	52	14	34	-
16	PdCl ₂ (MeCN) ₂	5	THF	TDMPP (3 mol%)	7h	-	62	10	28	-

^[a]Reactions were run at 25 °C unless otherwise noted.

^[b]The ratio of products was determined by ¹H NMR

^[c]reaction was run at 40 °C

^[d]reaction was run at 70 °C

^[e]reaction was run at 60 °C

Table 11

Oxidation of compound **31**

entry	conditions	result ^[a]
1	mCPBA (1.5 equiv), CH ₂ Cl ₂ /MeOH, 2h, rt	[b]/[c]
2	TFPAA (1.5 equiv), rt, 1 h, Na ₂ HPO ₄ , CH ₂ Cl ₂ /MeOH/CH ₃ CN	32 (48 %)
3	TFPAA (3.5 equiv), 0 °C, 15 min, Na ₂ HPO ₄ , CH ₂ Cl ₂ /MeOH/CH ₃ CN	32 (27 %)
4	TFPAA (1.5 equiv), -20 °C, 30 min, Na ₂ HPO ₄ , CH ₂ Cl ₂ /MeOH/CH ₃ CN	32 (41 %) ^[d]
5	DMDO, acetone, MeOH	no reaction
6	CF ₃ COCH ₃ , UHP, rt, 20 h, Na ₂ HPO ₄ , CH ₂ Cl ₂ /MeOH	no reaction
7	MTO (10 mol%), UHP (3 equiv), rt, 3h, CH ₂ Cl ₂ /MeOH	32 (28 %)
8	CCl ₃ CN (4 equiv), UHP (2 equiv), Na ₂ HPO ₄ , rt, 4h, CH ₂ Cl ₂ /MeOH	32 (52 %)

^[a]The yields in the 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**.