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Enantioselective Reductive Coupling of Alkynes and α-Keto Aldehydes via Rhodium-Catalyzed Hydrogenation: An Approach to Bryostatin Substructures

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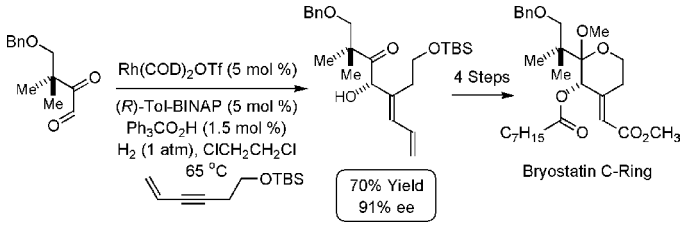
ABSTRACT



Hydrogen-mediated reductive coupling of glyoxal 2 and 1,3-enyne 3 provides α-hydroxy ketone 4 in 70% yield and 91% enantiomeric excess. Notably, the benzylic ether and diene side chain of 4 remain intact under the conditions of hydrogen-mediated coupling. In four steps, α-hydroxy ketone 4 is converted to pyrans 8 and 9, which embody key structural features of the bryostatin recognition domain.

The bryostatins are a family of marine natural products possessing a polyacetate backbone that were originally isolated from the bryozoan *Bugula neritina*.[1] Presently, 20 naturally occurring bryostatins are known, which differ primarily on the basis of substitution at C_7 and C_{21} (Figure 1).[2] The bryostatins and related structural analogues exhibit a range of extraordinary biological properties, which include antineoplastic activity against a broad range of tumor cell lines, immunopotentiating activity, the restoration of apoptotic function, and the ability to act synergistically with other chemotherapeutic agents.[3] While the mechanism of action of the bryostatins remains unclear, it is believed that the ability of the bryostatins to inhibit protein kinase C *without* tumor promotion plays an important role.[3h] Due to these remarkable features, clinical evaluation of bryostatin 1 is currently in progress.

The total synthesis of bryostatin 2, bryostatin 3 and bryostatin 7 have been reported by Evans,[4] and Yamamura,[5] and Masamune,[6] respectively. Though impressive, these syntheses require over 60 steps and, hence, do not represent an effective source of material for clinical study. This fact, coupled with the low natural abundance of the bryostatins, has stimulated efforts toward the preparation and evaluation of simplified analogous by Wender[7] and Keck.[8] Finally, a

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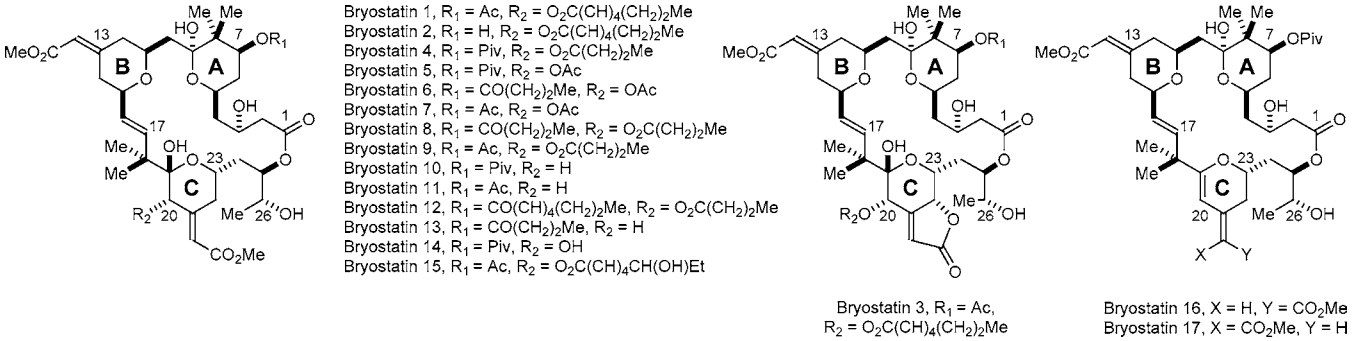
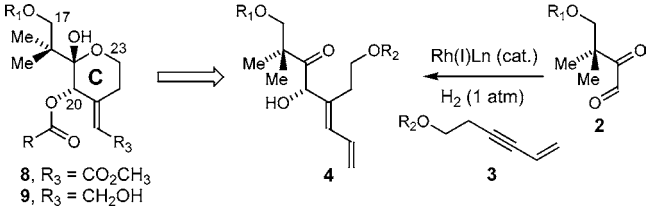


Figure 1. Structure of bryostatins **1**−**17**.

number of creative synthetic approaches to various bryostatin fragments are reported by Hale,[9] Thomas,[10] Hoffman,[11] Vandewalle,[12] and Burke.[13]

As part of a broad program in hydrogen-mediated C−C bond formation,[14] the catalytic reductive coupling of conjugated alkynes with carbonyl[14f,g,k] and imine[14j] partners was recently reported from our laboratory. This reductive coupling method was deemed applicable to the synthesis of the bryostatin C-ring derivatives **8** and **9** on the following basis: (a) the reductive coupling of 1,3-enynes to glyoxals provides β,γ-unsaturated α-hydroxy ketones—an oxidation pattern matching that found in C_{19}−C_{21} of bryostatin 1 and the majority of other bryostatins; (b) the geometry of the trisubstituted alkene derived upon enyne−glyoxal reductive coupling is consistent with the geometry of the alkylidene moiety at C_{21} of the bryostatin C-ring; and finally, (c) through the use of chirally modified rhodium catalysts, it should be possible to address absolute stereochemistry. The following retrosynthetic analysis, which involves the reductive coupling of gloxal **2** to enyne **3** to afford the β,γ-unsaturated α-hydroxy ketone **4**, illustrates these features (Scheme 1).

Scheme 1. Retrosynthetic Analysis of the Bryostatin C-Ring via Hydrogen-Mediated Reductive Coupling



To explore the feasibility of an enantioselective variant, the reductive coupling of glyoxal **2**[15] to enyne **3** using $Rh(COD)_2OTf$ (5 mol %) and Ph_3CCO_2H (5 mol %) as additive at ambient temperature and pressure was performed in the presence of assorted chiral phosphine ligands (Table 1). Among the chiral ligands assayed, (*R*)-Tol-BINAP proved superior. Through variation of the reaction temperature, 65 °C was identified as the ideal temperature, affording a 58% yield of **4** in 78% enantiomeric excess (Table 1, entry 6). Interestingly, a striking dependence of enantiomeric excess upon the reaction temperature was observed. This result may be explained by a Curtin−Hammett-type effect akin to that observed in the asymmetric hydrogenation of dehydro-α-amino acids, which also employs a cationic rhodium catalyst.[16] While use of Ph_3CCO_2H as a substoichiometric

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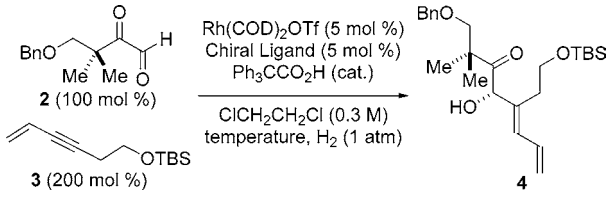
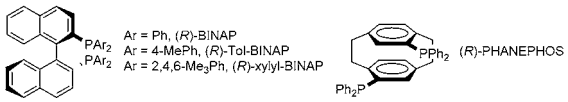
(15) The α-keto aldehyde **2** was prepared via oxidation of the corresponding methyl ketone. See the Supporting Information for detailed experimental procedures.

Table 1. Enantioselective Hydrogen-Mediated Reductive Coupling of Glyoxal **2** to 1,3-Enyne **3**[a]



entry	chiral ligands	temp.	Ph_3CCO_2H	ee %	yield
1	(*R*)-PHANEPHOS	25 °C	5.0 mol %	4%	15%
2	(*R*)-BINAP	25 °C	5.0 mol %	41%	36%
3	(*R*)-xylyl-BINAP	25 °C	5.0 mol %	23%	28%
4	(*R*)-Tol-BINAP	25 °C	5.0 mol %	48%	37%
5	(*R*)-Tol-BINAP	45 °C	5.0 mol %	67%	55%
6	(*R*)-Tol-BINAP	65 °C	5.0 mol %	78%	58%
7	(*R*)-Tol-BINAP	65 °C	2.5 mol %	86%	64%
8	**(*R*)-Tol-BINAP**	**65 °C**	**1.5 mol %**	**91%**	**70%**
9	(*R*)-Tol-BINAP	65 °C	---	90%	32%

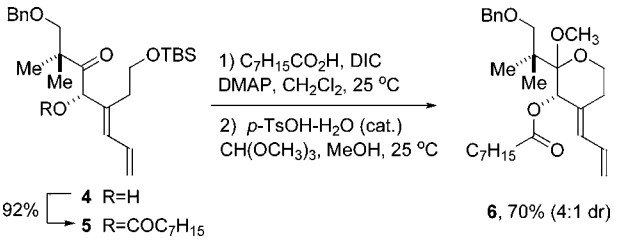


[a] The cited yields are of pure material isolated by silica gel chromatography. See the Supporting Information for detailed experimental procedures.

additive has been found to accelerate the reaction rate in the Rh-catalyzed reductive coupling of conjugated alkynes and carbonyl partners,[14k] it was speculated that an acidic species of this type may deprotect the TBS groups of enyne **3** or the coupling product **4**. Indeed, when the loading of Ph_3CCO_2H is decreased to 1.5 mol %, the coupling product **4** is obtained in 70% isolated yield and 91% enantiomeric excess (Table 1, entry 8). Under otherwise identical conditions, but in the absence of Ph_3CCO_2H, the reductive coupling product **4** was obtained in only 32% yield and 90% enantiomeric excess (Table 1, entry 9).

Elaboration of coupling product **4** to bryostatin C-ring derivatives **8** and **9** is achieved in four steps. Esterification of the reductive coupling product **4** with $C_7H_{15}CO_2H$ using diisopropylcarbodiimide and DMAP in dichloromethane[17] provides the ester **5** in 92% yield. An initial attempt to achieve the direct conversion of ester **5** to cyclic ketal **6** involved exposure of **5** to *p*-TsOH·H_2O (5 mol %) and $CH(OCH_3)_3$ (350 mol %) in methanol.[18] Under these conditions, deprotection of the TBS ether of ester **5** occurs in situ and the resulting primary alcohol spontaneously cyclizes to give the ketal **6** in 48% yield as a 4:1 mixture of diastereomers. Under otherwise identical conditions, but using of 20 equiv of $CH(OCH_3)_3$, the ketal **6** is obtained in 70% yield (Scheme 2). The stereochemistry at the anomeric carbon is irrelevant,

Scheme 2. Synthesis of Ketal **6** via Acid-Catalyzed TBS Deprotection−Cyclization of **5**[a]



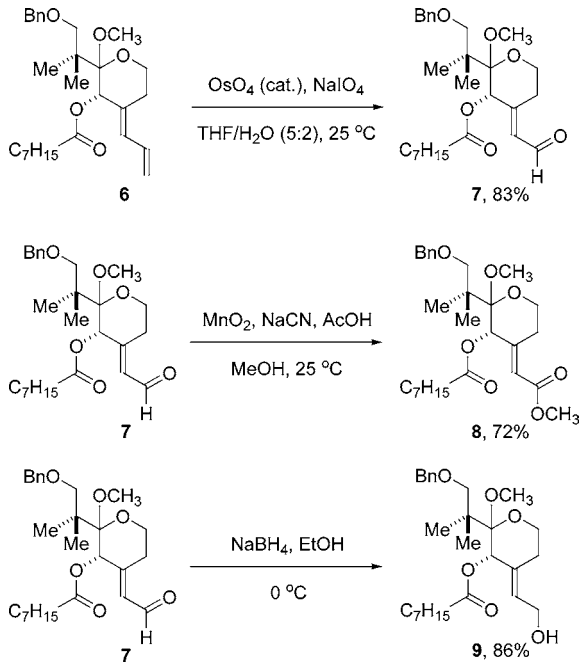
[a] See the Supporting Information for detailed experimental procedures.

as the configuration of this position is ultimately established by the anomeric effect under conditions of thermodynamic control in bryostatin and related structures.

To complete the preparation of bryostatin C-ring derivatives **8** and **9**, a regioselective oxidative cleavage of the diene moiety is required. Whereas ozonolytic cleavage gives a complex distribution of products,[19] exposure of **6** to substoichiometric quantities of OsO_4 in the presence of $NaIO_4$ provides the desired enal product **7** in 83% yield.[20] Oxidation of the enal **7** with manganese oxide and sodium cyanide in methanol gave the methyl enoate **8** in 72% yield. Sodium borohydride reduction of enal **7**, carried out with in ethanol at 0 °C, provides the allylic alcohol **9** in 86% yield (Scheme 3).

Hydrogen-mediated C−C bond formation enables direct reductive coupling of highly functionalized π-unsaturated

Scheme 3. Synthesis of the Enoate **8** and the Enol **9** via Regioselective Oxidation of Diene of **6**[a]



[a] See Supporting Information for detailed experimental procedures.

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substrates to carbonyl and imine acceptors, providing access to functional group arrays that are otherwise difficult to prepare.[14] To highlight the synthetic utility of hydrogen-mediated C−C bond formation, the first highly enantioselective reductive coupling of glyoxals and enynes was developed and applied strategically in a concise approach to $C_{17}-C_{23}$ of the bryostatin recognition domain. Future studies will be devoted to the discovery and development of new reductive C−C bond formations mediated by hydrogen.

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Supporting Information Available: Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, and HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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