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Total Synthesis of Bryostatin 7 *via* C−C Bond-Forming Hydrogenation

Yu Lu, Sang Kook Woo, and Michael J. Krische*

University of Texas at Austin, Department of Chemistry and Biochemistry, Austin, Texas 78712, United States

Supporting Information

ABSTRACT: The marine macrolide bryostatin 7 is prepared in 20 steps (longest linear sequence) and 36 total steps with five C−C bonds formed using hydrogenative methods. This approach represents the most concise synthesis of any bryostatin reported, to date.

The bryostatins are a family of 20 marine natural products originally isolated from the bryozoan *Bugula neritina*[1] that possess a polyacetate backbone and differ largely on the basis of substitution at C7 and C20 (Figure 1).[2] The bryostatins display diverse biological effects, including antineoplastic activity, immunopotentiating activity, restoration of apoptotic function, and the ability to act synergistically with other chemotherapeutic agents.[3] Neurological effects also are evident, including activity against Alzheimer's disease,[4] neural growth and repair, and the reversal of stroke damage,[5] as well as memory enhancement.[6]

As their natural abundance is insufficient to advance clinical studies, the bryostatins have emerged as a vibrant testing ground for polyketide construction. To date, total syntheses of bryostatins 1,[7a] 2,[7b,c] 3,[7d,e] 7,[7f] 9,[7g] and 16[7h] have been reported. A formal synthesis of bryostatin 7[8a] and total syntheses of C20-*epi*-bryostatin 7[8b] and C20-deoxybryostatin[8c] have been disclosed. Simplified bryostatin analogues that retain high potency have been identified.[9−11]

Given the challenges associated with defining concise routes to the bryostatins, these products were deemed an ideal vehicle to benchmark the utility of the C−C bond-forming hydrogenations developed in our laboratory.[12] Retrosynthetically, a convergent assembly of the bryostatin 7 core from Fragments **A** and **B** employing the Keck−Yu pyran annulation[13,14] and Yamaguchi macrolactonization[15] was envisioned. For the synthesis of Fragment **A**, hydrogen-mediated reductive coupling of glyoxal **6** and 1,3-enyne **9** appeared strategic, as the key C20−C21 bond would be formed with control of the C20 carbinol stereochemistry and C21 olefin geometry.[16] The planned synthesis of Fragment **B**, which incorporates the A-ring, takes advantage of three transfer hydrogenative processes: enantioselective double allylation of 1,3-propanediol to form the C_2-symmetric diol **11**,[17a] subsequent aldehyde *tert*-prenylation[17b] to establish the C7 carbinol stereochemistry and install the C8 *gem*-dimethyl moiety, and finally, allylation[17c,d] at C9 to introduce the C11 aldehyde. The feasibility of these syntheses has been established in model systems (Scheme 1).[16,17e]

The synthesis of Fragment **A** begins with the hydroxymethylation of 3-methyl-2-butanone **1** to furnish the aldol product.[18] Moffatt−Swern oxidation of the aldol product provides ketoaldehyde **2**, which upon Horner−Wadworth−Emmons olefination delivers the α,β-unsaturated ester **3**. All compounds up to this point are isolated by vacuum distillation, expediting access to large quantities of material. Conversion of **3** to the enol silane followed by addition of $LiAlH_4$ to the reaction mixture directly provides the allylic alcohol **4**.[19] Treatment of crude **4** with *tert*-butyldimethylsilyl chloride followed by *N*-bromosuccinimide provides the α-bromoketone **5** in 84% yield over the 2-step sequence from α,β-unsaturated ester **3**. Finally, Kornblum oxidation of α-bromoketone **5** delivers the glyoxal **6** (Scheme 2).[20]

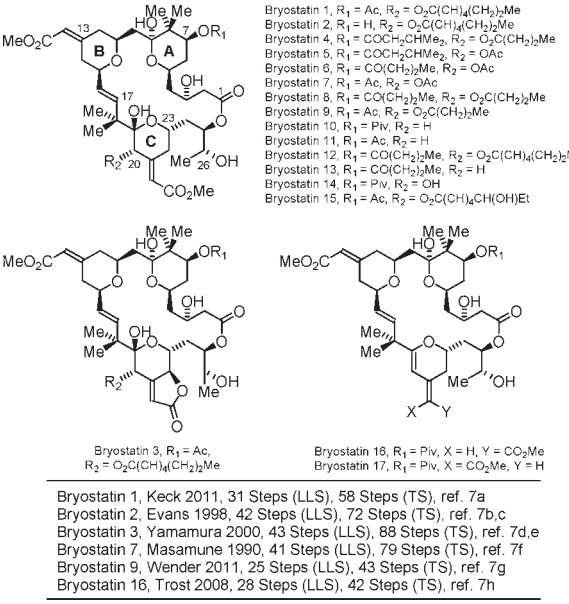

Figure 1. Bryostatins 1−17 and prior total syntheses. See SI for a graphical summary of prior syntheses.

Preparation of the 1,3-enyne **9** begins with Sharpless asymmetric dihydroxylation of crotononitrile **7**, which provides the diol in 86% enantiomeric excess.[21] The diol is converted to the acetonide and exposed to diisobutylaluminum hydride to provide the aldehyde **8**, which is a known compound previously prepared using a six-step sequence.[22] Chelation-controlled propargylzinc addition converts **8** to the homopropargylic alcohol, which is formed as a 5:1 mixture of diastereomers.[22] As described in the SI, the minor isomer is easily converted to the desired epimer by Mitsunobu inversion. Conversion of the homopropargylic alcohol to the TBDPS ether followed by Sonogashira coupling delivers **9** (Scheme 2).

To complete the synthesis of Fragment **A**, **6** and **9** are subjected to hydrogen-mediated reductive coupling to furnish the α-hydroxyketone in 77% yield as a 7:1 mixture of diastereomers.[16]

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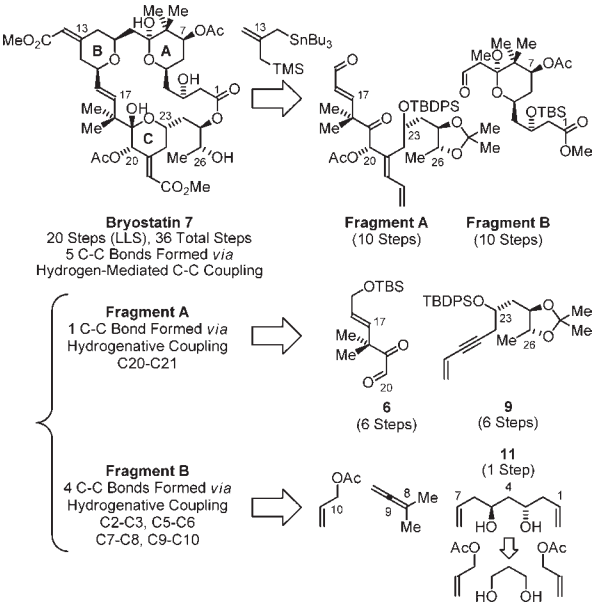
Notably, although the coupling product incorporates multiple points of unsaturation, over-reduction is not observed under the conditions of hydrogenative coupling. Exposure of α-hydroxy-ketone to acetic anhydride provides the acetate. Selective deprotection of the allylic TBS ether in the presence of the TBDPS ether, which is accomplished using HF-pyridine, provides the allylic alcohol. Finally, oxidation of allylic alcohol delivers the enal, Fragment **A**, in a total of 10 steps from 3-methyl-2-butanone **1** or crotononitrile **7** (Scheme 2).

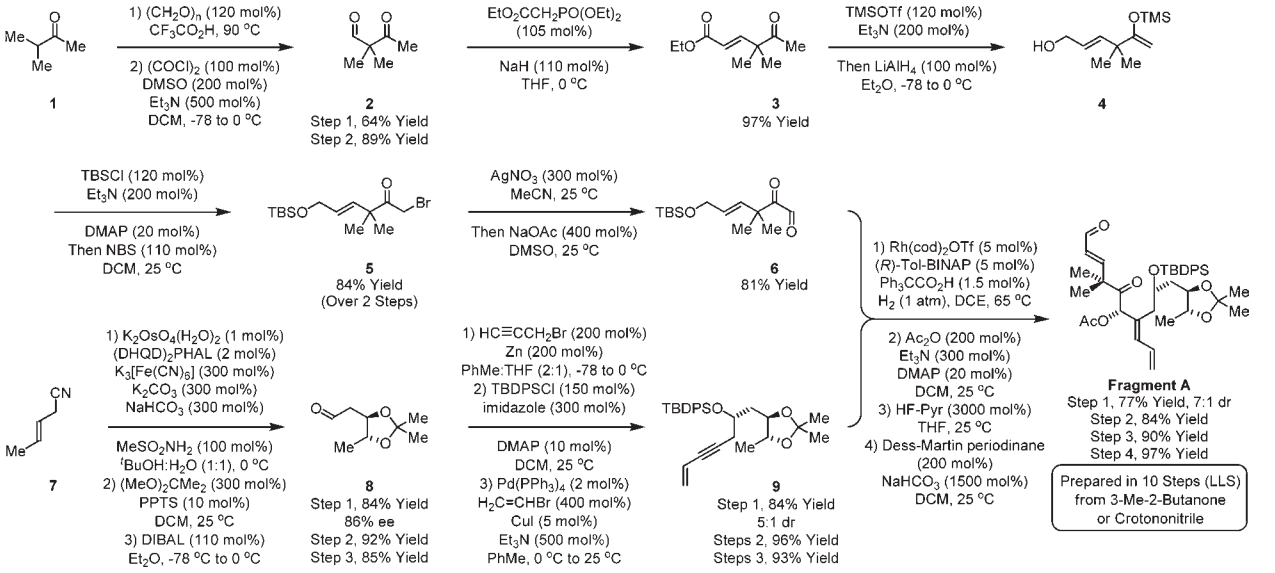
Efforts toward Fragment **B** begin with allyl acetate-mediated double allylation of 1,3-propanediol **10**[17a,e] to form C_2-symmetric diol **11**. This process employs an iridium catalyst generated *in situ* from $[Ir(cod)Cl]_2$, allyl acetate, 4-chloro-3-nitrobenzoic acid, and (*S*)-Cl,MeO-BIPHEP. Because the minor enantiomer of the mono-allylated intermediate is converted to the *meso*-diastereomer, **11** is obtained as a single enantiomer, as determined by chiral stationary phase HPLC analysis. Previously, the *mono*-TBS ether of **11** was prepared in 7 steps from 1,3-propanediol through iterative use of Brown's reagent for carbonyl allylation.[23a] Alternatively, a 4-step protocol for the preparation of **11** from acetylacetone is described.[23b] Ozonolysis of **11** delivers an unstable lactol, which is protected *in situ* as the *bis*-TBS ether to provide aldehyde **12** as a single isomer. Transfer hydrogenation of **12** in the presence of 1,1-dimethylallene promotes *tert*-prenylation[17b] to form neopentyl alcohol-**13**. In this process, the discrete iridium complex derived from $[Ir(cod)Cl]_2$, allyl acetate, *m*-nitrobenzoic acid, and (*S*)-SEGPHOS is used as catalyst. Complete levels of catalyst-directed diastereoselectivity are observed. Exposure of **13** to acetic anhydride followed by ozonolysis provides β-acetoxy aldehyde **14**. Reductive coupling of **14** and allyl acetate under transfer hydrogenation conditions results in the formation of homoallylic alcohol **15**. As the stereochemistry of this addition is irrelevant, an achiral iridium complex is employed as catalyst. Selective removal of the glycosidic silyl ether followed by concomitant Dess–Martin oxidation of the lactol and homoallylic alcohols provides β,γ-enone **16**. Treatment of a methanolic solution of **16** to pyridinium *p*-toluenesulfonate triggers sequential lactone ring-opening followed by formation of the cyclic ketal **17a**. Ozonolysis of **17a** provides Fragment **B** in a total of 10 steps from **10** (Scheme 3).

The union of Fragments **A** and **B** is achieved through Keck–Yu annulation to form the B-ring pyran.[13,14] The desired adduct **18a** is accompanied by the elimination product **18b**; however, both compounds participate in acidic methanolysis to form triol **19b**. Chemoselective hydrolysis of the C1 methyl ester in the presence of the C7 and C20 acetates employing trimethyltin hydroxide[24] followed by selective TES-protection of the triol reveals a hydroxy acid, which upon macrolactonization[15] provides tetraene **20**. Concomitant oxidative cleavage[25] of the olefinic termini of **20** in the presence of the neopentyl olefin at C16–C17 installs both the B-ring ketone and C-ring enal. Whereas Corey–Gilman oxidation

Scheme 1. Retrosynthetic Analysis of Bryostatin 7 Illustrating C–C Bonds Formed *via* Hydrogenative Coupling



Scheme 2. Synthesis of Fragment A *via* Hydrogen-Mediated Reductive Coupling of Glyoxal 6 and 1,3-Enyne 9[a]



[a] Indicated yields are of material isolated by silica gel chromatography or distillation. See SI for experimental details.

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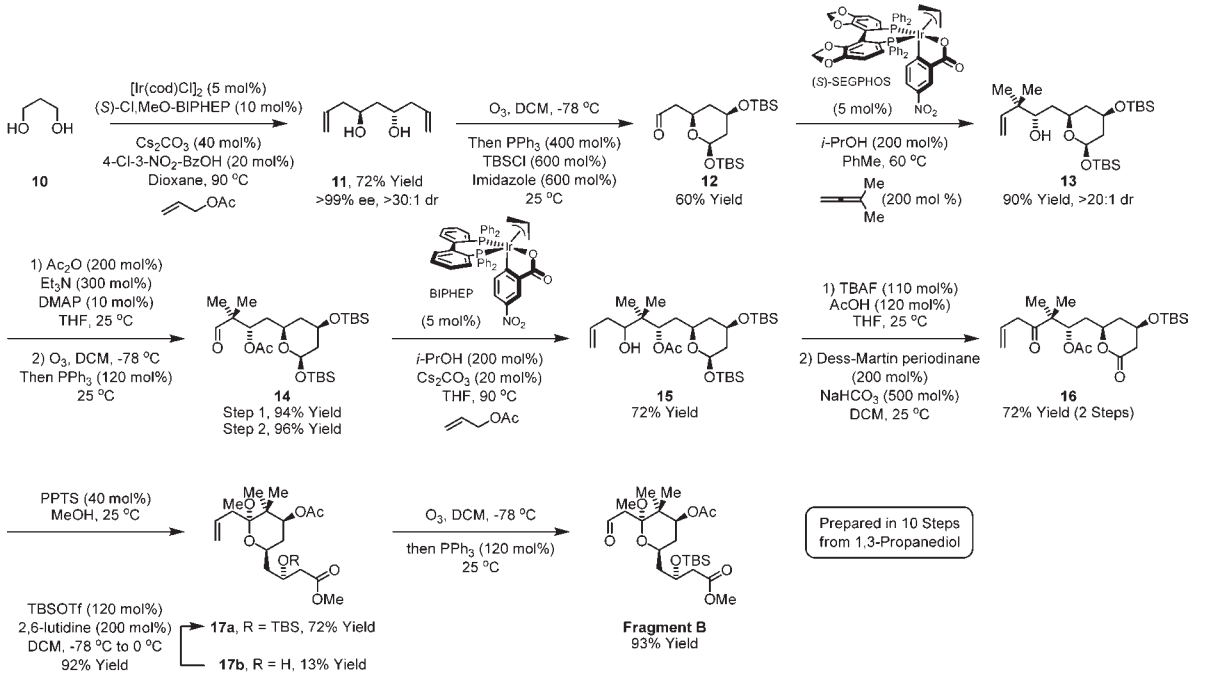
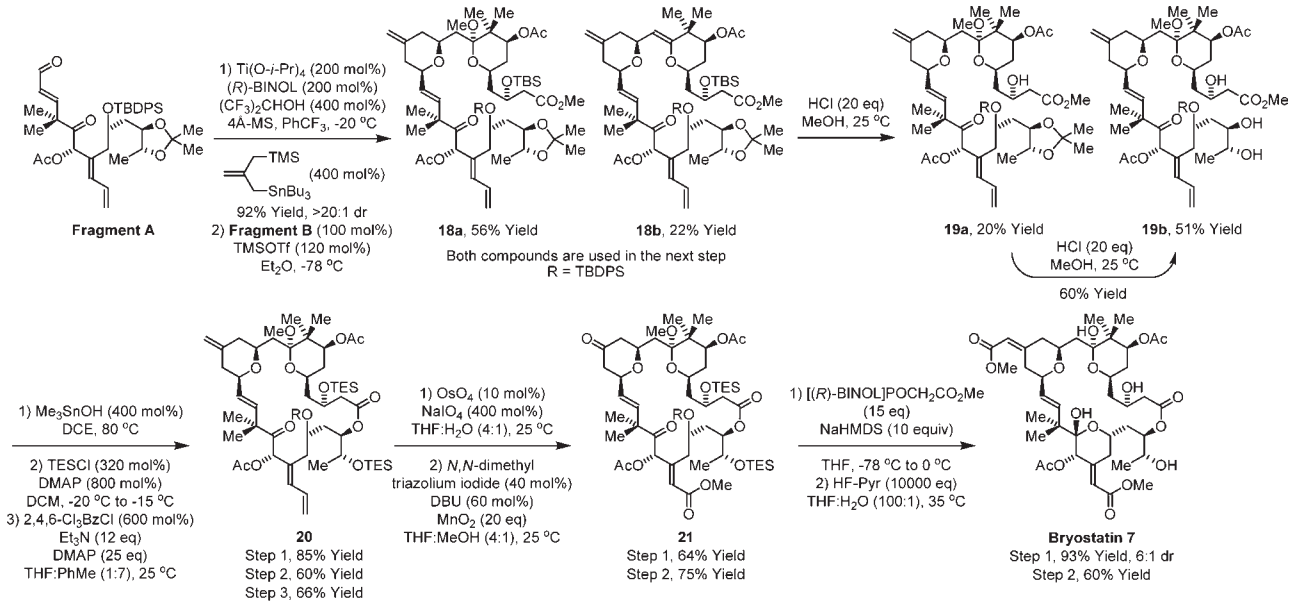
Scheme 3. Synthesis of Fragment B Employing Multiple Transfer Hydrogenative C−C Bond Formations[a]



[a] Indicated yields are of material isolated by silica gel chromatography. See SI for experimental details.

Scheme 4. Union of Fragment A and Fragment B and Total Synthesis of Bryostatin 7[a]



[a] Indicated yields are of material isolated by silica gel chromatography. See SI for experimental details.

of enal failed,[26] the corresponding *N*-heterocyclic carbene-promoted process provides the desired methyl ester **21** in good isolated yield.[27] Finally, as practiced in prior syntheses,[7a−d,g] asymmetric olefination of the B-ring ketone using Fuji's chiral phosphonate[28] followed by global deprotection using HF-pyridine provides bryostatin 7 (Scheme 4).

The present synthesis of bryostatin 7 is accomplished in 20 linear and 36 total steps, representing the most concise route to any bryostatin reported, to date. The step economy associated with this approach can be attributed to the rapid assembly of Fragments **A** and **B** through C−C bond-forming hydrogenations developed in our laboratory,[12] a technology that has enabled dramatic simplification in the synthesis of other polyketide natural products.[29] This work serves as a prelude to even shorter syntheses of bryostatins and their analogues. More broadly, the merged redox−construction events central to this study speak to an emerging retrosynthetic paradigm, wherein C−C bond construction is accompanied by withdrawal of hydrogen.[30,31]

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures; spectral, HPLC, and GC data; complete ref 10a. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
mkrische@mail.utexas.edu

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