ORGANIC LETTERS

2009
Vol. 11, No. 14
3108−3111

Concise Synthesis of the Bryostatin A-Ring via Consecutive C−C Bond Forming Transfer Hydrogenations

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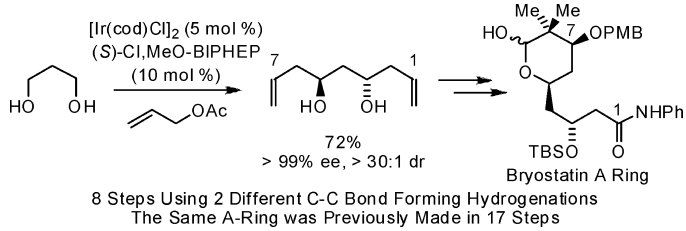
Received May 19, 2009

ABSTRACT



8 Steps Using 2 Different C-C Bond Forming Hydrogenations
The Same A-Ring was Previously Made in 17 Steps

Under the conditions of C−C bond forming transfer hydrogenation, 1,3-propanediol 1 engages in double asymmetric carbonyl allylation to furnish the C_2-symmetric diol 2. Double ozonolysis of 2 followed by TBS protection delivers aldehyde 3, which is subject to catalyst directed carbonyl reverse prenylation via transfer hydrogenation to deliver neopentyl alcohol 4 and, ultimately, the bryostatin A-ring 7. Through use of two consecutive C−C bond forming transfer hydrogenations, the Evans' bryostatin A-ring 7 is prepared in less than half the manipulations previously reported.

Originally isolated from the bryozoan Bugula neritina,[1] the bryostatins are a family of over 20 marine natural products that possess a polyacetate backbone and differ largely on the basis of substitution at C_7 and C_{21} (Figure 1, top).[2] The bryostatins exhibit a remarkable range of biological effects, including antineoplastic activity against diverse tumor cell lines, immunopotentiating activity, restoration of apoptotic function, and the ability to act synergistically with other chemotherapeutic agents.[3] More recently, the bryostatins have been found to exhibit exciting neurological effects, including activity against Alzheimer's disease,[4] neural growth and repair, and the reversal of stroke damage,[5] as well as memory enhancement.[6]

The natural abundance of bryostatins is insufficient to advance clinical studies and elucidate their precise mechanism of action.[7] Consequently, the *de novo* synthesis of various bryostatins and the design and preparation of non-natural functional analogues has been the topic of intensive

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10.1021/ol901096d CCC: $40.75
Published on Web 06/24/2009

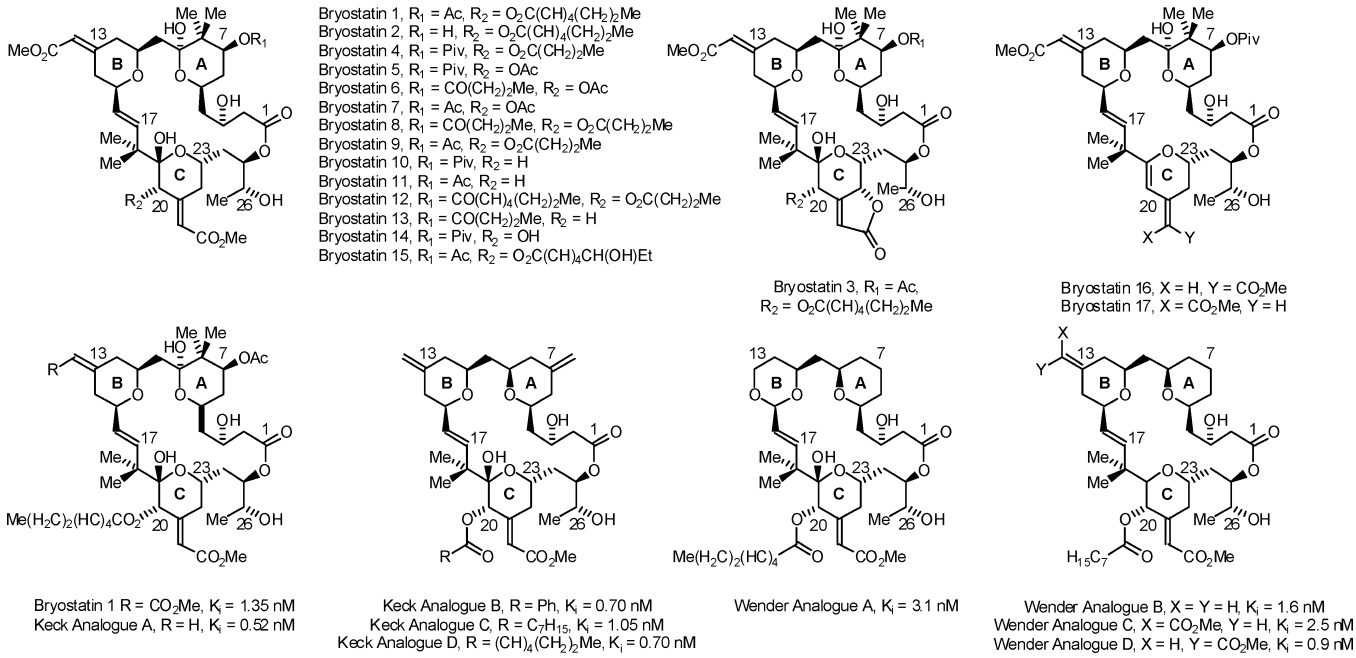

Figure 1. (Top) Structures of bryostatins **1**−**17**. (Bottom) Selected bryostatin analogues and binding affinities for PKCα.

investigation. To date, total syntheses of bryostatin 2, bryostatin 3, bryostatin 7, and bryostatin 16 have been reported by Evans,[8] Yamamura,[9] Masamune,[10] and Trost,[11] respectively. A formal synthesis of bryostatin 7 was reported by Hale.[12] Finally, several creative synthetic approaches to bryostatin fragments are reported by Hale,[13] Thomas,[14] Hoffman,[15] Vandewalle,[16] Burke,[17] and the present author.[18] Although impressive, these syntheses do not represent a practical source of material for clinical study. Hence, efforts led by Wender,[19,20] Keck,[21] and Hale[13b] have focused on the design of simplified structural analogues that possess enhanced functional capability and provide insight into key structural features of the bryostatins that confer unique biological activity (Figure 1, bottom).

As part of a broad program aimed at the development of hydrogen-mediated C−C bond formations,[22] enantioselective carbonyl allylations,[23a−c,f] crotylations,[23d] and reverse prenylations[23e] were recently achieved under the conditions of

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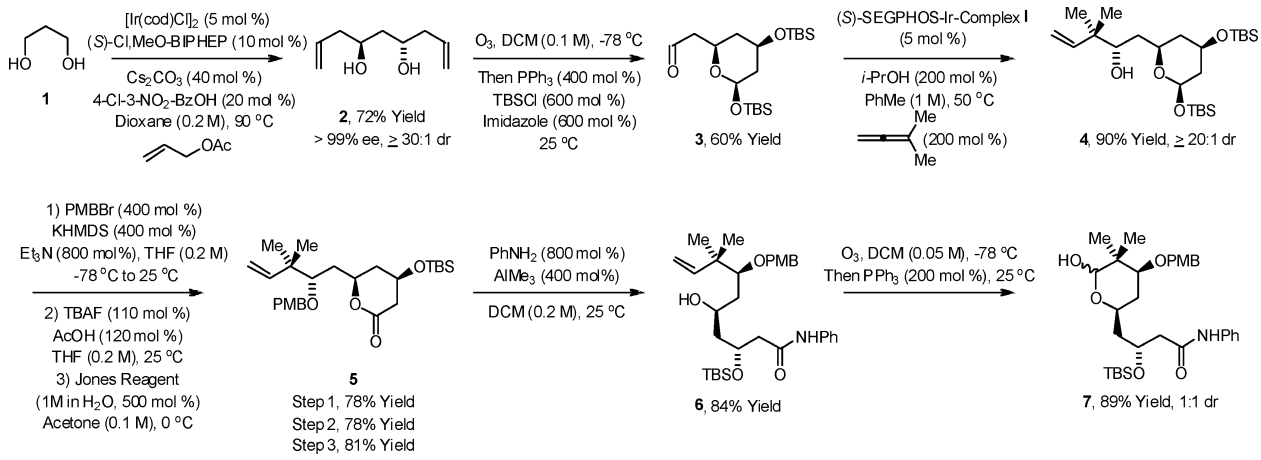
Scheme 1. Synthesis of the Bryostatin A-Ring Employing Consecutive C−C Bond Forming Transfer Hydrogenations



iridium catalyzed transfer hydrogenation. A long-term goal of these studies resides in defining a departure from preformed organometallic reagents in carbonyl and imine addition, thereby circumventing the excessive preactivation and waste generation associated with their use. Furthermore, the ability to achieve asymmetric carbonyl addition directly from the alcohol oxidation level, as established by the aforementioned processes, is inherently more redox-economic and, hence, step-economic than classical protocols. Given the longstanding challenges associated with defining concise routes to the bryostatins, this class of natural products was deemed an ideal vehicle to benchmark the utility of C−C bond forming hydrogenations and transfer hydrogenations developed in our laboratory. In prior work, enantioselective hydrogen-mediated alkyne-carbonyl reductive coupling was applied to the construction of the bryostatin C-ring. Here, using two different C−C bond forming transfer hydrogenations, we disclose a synthetic route to a known bryostatin A-ring fragment in less than half the steps previously required.[8]

Our initial step toward the bryostatin A-ring employs the double asymmetric carbonyl allylation of 1,3-propanediol **1** to furnish the C_2-symmetric diol **2**,[23c] which is obtained in >99% ee as the minor enantiomer of the monoadduct is converted to the *meso*-isomer of the *bis*-adduct.[24] Identical material was previously prepared in four steps from acetylacetone.[25] Notably, this particular carbonyl allylation cannot be achieved directly from the aldehyde oxidation level due to the instability of malondialdehyde. The C_2-symmetric diol **2** was subjected to double ozonolysis followed by protection *in situ* as the *bis*-TBS ether to deliver aldehyde **3**. Because the transient dialdehyde moieties that arise upon ozonolysis are homotopic, pyran **3** appears as a single isomer (Scheme 1).

The stage was now set for catalyst-directed prenylation of aldehyde **3** under previously disclosed transfer hydrogenation conditions.[23e] Upon exposure of aldehyde **3** to 1,1-dimethylallene and isopropanol in the presence of the iridium *C*,*O*-benzoate generated *in situ* from allyl acetate, *m*-nitrobenzoic acid, and (*R*)-SEGPHOS,[26] a 92% isolated yield of the prenylated adduct **4** was obtained as a 1:11 (*S*:*R*) ratio of epimers at 60 °C. Using the catalyst derived from (*S*)-SEGPHOS under otherwise identical conditions, the prenylated adduct **4** was obtained as a 16:1 (*S*:*R*) ratio of epimers. These data suggest that the catalysts derived from (*R*)- and (*S*)-SEGPHOS are mismatched and matched, respectively, with regard to the inherent diastereofacial bias of aldehyde **3**. Indeed, upon use of the corresponding achiral iridium complex derived from BIPHEP, the prenylated adduct **4** was obtained as a 1.4:1 (*S*:*R*) ratio of epimers corroborating a fortuitous bias of the substrate toward formation of the (*S*)-epimer. By isolating the catalyst derived from (*S*)-SEGPHOS and employing it at slightly lower temperature (50 °C), the prenylated adduct **4** was obtained in 90% isolated yield as a single (*S*)-epimer as determined by ^{1}H NMR (Scheme 2).

Transformation of the neopentyl alcohol **4** to the bryostatin A-ring was accomplished in five manipulations. In accordance with literature precedent,[27] the neopentyl alcohol **4** was converted to the corresponding *p*-methoxybenzyl ether in 78% isolated yield. Selective removal of the lactol TBS

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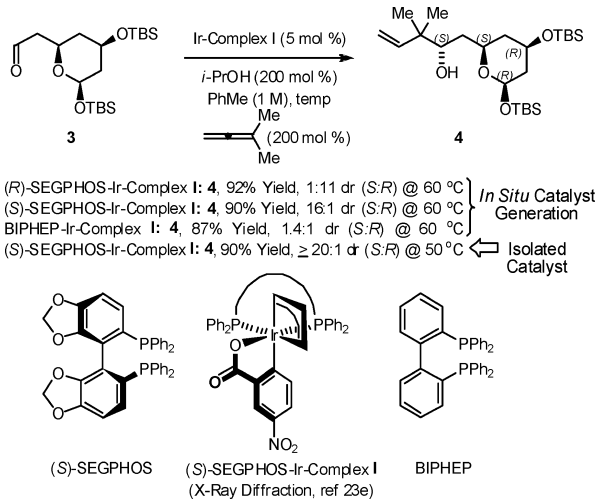
Scheme 2. Catalyst-Directed Diastereoselectivity in the Transfer Hydrogenative Reverse Prenylation of Aldehyde **3**



ether was achieved using TBAF-AcOH, also in 78% isolated yield.[28] Finally, Jones oxidation of the lactol delivers lactone **5** in 81% isolated yield.[29] Ring-opening of lactone **5** mediated by $AlMe_3$-$PhNH_2$ provides anilide **6** in 84% isolated yield,[8] which upon ozonolysis furnishes the previously reported bryostatin A-ring fragment **7**[8] in a total of eight manipulations from 1,3-propanediol **1** (Scheme 1).[30] Notably, this material was prepared previously in 12 steps from 2,2-dimethyl-4,4-diphenyl-3-butenal, which itself is prepared in five steps from 3-chloro-2-methylpropene,[31] thus representing a total of 17 steps from 3-chloro-2-methylpropene.

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To summarize, it is well-appreciated that new synthetic methods beget new synthetic strategies that can dramatically simplify the preparation of target substances. Here, through consecutive use of C−C bond forming transfer hydrogenations, a remarkably concise synthesis of a known bryostatin A-ring fragment was achieved in less than half the manipulations previously required. In earlier work utilizing hydrogen-mediated alkyne-carbonyl reductive coupling, a route to the bryostatin C-ring was established.[18] Future studies will focus on total syntheses of the bryostatins and simplified structural analogues that possess enhanced functional capability, taking advantage of the simplifications availed through C−C bond forming hydrogenation and transfer hydrogenation.

Acknowledgment. Acknowledgment is made to the Robert A. Welch Foundation and the NIH-NIGMS (RO1-GM069445) for partial support of this research. Dr. Oliver Briel of Umicore is thanked for the generous donation of $[Ir(cod)Cl]_2$. Takasago is thanked for the generous donation of SEGPHOS.

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

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(30) With regard to the assignment of relative and absolute stereochemistry, the optical rotation of C_2-symmetric diol **2** was correlated with reported data (see ref 25 and Supporting Information). In the reverse prenylation of **3**, the undesired diastereomer of adduct **4** obtained using (*R*)-SEGPHOS as ligand was used to complete the A-ring. As anticipated, the ^{1}H NMR data did not match the reported data. In contrast, the A-ring diastereomer obtained using (*S*)-SEGPHOS as ligand in the prenylation step matches the reported data, notwithstanding a small difference in the ratio of diastereomers at C9.

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