Total Synthesis of Bryostatin 7 via C–C Bond-Forming Hydrogenation


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Current Literature
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The Bryostatin Family

• The Bryostatin family was first isolated by Pettit and coworkers from the bryozoan Bugula neritina. (Pettit et al. J. Am. Chem. Soc. 1982, 104, 6846.)

• Recently, it was reported that the bryostatins are produced by an uncultured bacteria E. sertula. The proposed biosynthetic gene cluster and biosynthetic hypothesis are reported in the following reference: Sudek et al. J. Nat. Prod. 2007, 70, 67.

15 members with this core (varying at \( R_1 \) and \( R_2 \)).

**Bryostatin 7:** \( R_1 = \text{Ac}, R_2 = \text{OAc} \)

**Bryostatin 16:** \( R_1 = \text{Piv}, X = H, Y = \text{CO}_2\text{Me} \)

**Bryostatin 17:** \( R_1 = \text{Piv}, X = \text{CO}_2\text{Me}, Y = H \)

**Bryostatin 3**
Biological Significance

The bryostatins are being applied to several biological problems including Alzheimer’s disease and applications in chemotherapy.

Bryostatin 1 is well studied; 18 g of bryostatin 1 were isolated from 13,000 kg of source organism!1,2

Bryostatin 1 exhibits high affinity binding to the regulatory C1 domains of protein kinase C (PKC). These domains regulate cellular processes including proliferation and apoptosis.1,3

Efforts by Keck3 and Wender4 have led to the development of bryostatin analogs that maintain efficacy:

![Bryostatin 1 structure](image)

**Bryostatin 1**

PKC $K_i = 1.35$ nm

$R = \text{Me}; \, \text{PKC } K_i = 3.4$ nm

$R = \text{H}; \, \text{PKC } K_i = 0.25$ nm

$R = \text{Ph}; \, \text{PKC } K_i = 0.70$ nm

$R = \text{C}_7\text{H}_{15}; \, \text{PKC } K_i = 1.05$ nm

$R = \text{Ph} = \text{C}_7\text{H}_{15}$

PKC $K_i = 0.70$ nm

Previous Approaches

Wender, Keck: Convergent Pyran Annulation Strategy (Wender synthesis shown):

Evans (1998): 42 steps LLS, 72 steps total
Masamune (1990): 41 steps LLS, 79 steps total
Yamamura (2000): 43 steps LLS, 88 steps total

“...the points of convergence of these syntheses necessitate a further 14-21 linear steps to elaborate each target following assembly of their respective pyran-containing backbones, thus limiting step-economical access to diverse analogs.” (Wender1)

Wender (2011): 25 steps LLS, 43 steps total
Keck (2010): 31 steps LLS, 58 steps total

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See also Keck et al. J. Am. Chem. Soc. 2010, 133, 744.
Previous Approaches

Trost: Transition-metal mediated, atom-economical approach:

**Key Features:**
1) Pd-catalyzed reaction of alkynes to form a macrocycle
2) Au-catalyzed dihydropyran formation

**28 steps LLS, 42 steps total**

Retrosynthetic Analysis: Application of Hydrogenative C-C Bond Formation

**Fragment A:** 1 C-C bond using hydrogenative coupling

**Fragment B:** 4 C-C bonds using hydrogenative coupling
Reductive C-C Bond Formation

“Old” chemistry: hydroformylation (carbonylative hydrogenation):

\[
R_1 \equiv + \overset{\text{MLn (cat.)}}{\text{O}} \overset{\text{H}_2 (1 \text{ atm})}{\rightarrow} R_1 \overset{\text{H}}{\text{O}} \overset{\text{H}}{\text{O}}
\]

Krische group methodology: C-C coupling via hydrogenation or transfer hydrogenation:

\[
R_1 \equiv \ldots R_2 + \overset{\text{MLn (cat.)}}{\text{X}} \overset{\text{H}_2 (1 \text{ atm})}{\rightarrow} R_1 \overset{\text{XH}}{\ldots} R_2 R_3
\]

or

\[
R_1 \equiv \ldots R_2 + \overset{\text{MLn (cat.)}}{\text{XH}} \overset{i-\text{PrOH}}{\rightarrow} R_1 \overset{\text{XH}}{\ldots} R_2 R_3
\]

\[
X = O, N
\]


Condensation of Aldehydes and Alkynes

Main concept: heterolytic activation of elemental hydrogen by cationic Rh catalysts:

\[ \text{H}_2 + \text{Rh}^{+X^-} \rightarrow \text{Rh-H} + \text{HX} \]

Iridium-Catalyzed Transfer Hydrogenative Coupling

I. Allylation Reactions: polarity reversal of π-allyl iridium species:

**O- Allylation (conventional substitution):**

\[
\text{Nucleophile} + \text{Electrophile} \xrightarrow{\text{IrLn (cat.) Base (1 equiv)}} \text{Product}
\]

**C- Allylation (Transfer Hydrogenative Coupling):**

\[
\text{Electrophile} + \text{Nucleophile} \xrightarrow{\text{IrLn (cat.) Base (cat.)}} \text{Product}
\]

Proposed Mechanism for Iridium-Catalyzed Carbonyl Allylation

“Organic molecules, by definition, are composed of carbon and hydrogen. Hence, the ability to direct C-C coupling through the use of catalytic hydrogenation and transfer hydrogenation evokes numerous possibilities for the construction of diverse molecular architectures, circumventing use of preformed organometallic reagents.” (Kim, I. S.; N, N-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891.)

Utility of the Methodology

Synthesis of C₂-Symmetric Diol (use as a dialdehyde equivalent):

\[
\text{OH} \quad \text{OH} \\
\text{+} \\
\text{OAc} \\
\text{CH}_2 \\
\text{CHO} \\
\text{[Ir(cod)Cl]}_2 (5 \text{ mol\%}) \\
(S)-\text{Cl,MeO-BIPHEP} (10 \text{ mol\%}) \\
\text{Cs}_2\text{CO}_3 (40 \text{ mol\%}) \\
4-\text{Cl-3-NO}_2\text{-BzOH} (20 \text{ mol\%}) \\
\text{Dioxane, 90 °C} \\
72\%, >99\% \text{ ee}, >30:1 \text{ dr}
\]


Alternative synthesis (classical route):


The methodology led to a concise synthesis of the polyketide natural product (+)-Roxaticin using iterative transfer hydrogenation reactions:

Synthesis of Fragment A

1. AD-mix-β, MeSO₂NH₂, tBuOH/H₂O, 1:1, 0 °C (84%, 86% ee)
2. (MeO)₂CMe₂, PPTS, CH₂Cl₂, 25 °C (92%)
3. DIBAL, Et₂O, -78 °C to 0 °C (85%)

1. (CH₂O)ₙ, TFA, 90 °C (64%)
2. (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C to 0 °C (89%)
3. NaH, THF, 0 °C (97%)

1. (CH₂O)ₙ, TFA, 90 °C (64%)
2. (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C to 0 °C (89%)
3. NaH, OEt, PhMe, 0 °C (97%)
4. TMSOTf, Et₃N, CH₂Cl₂, -78 °C to 0 °C (81%)

1. H = C = Br
2. TBDPSCI, imid. DMAP, CH₂Cl₂, 25 °C (96%)
3. Pd(PPh₃)₄, Cul, Et₃N, PhMe, 0 °C to 25°C
Synthesis of Fragment A

Fragment B Synthesis:

**References and Notes:**

*5 mol%*
Synthesis of Fragment B

BIPHEP-Ir complex*

1. TBAF, AcOH, THF
2. DMP, NaHCO₃, CH₂Cl₂

(72%, 2 steps)

R = TBS, 72%
R = H, 13%

O₃, CH₂Cl₂, -78 °C
then PPh₃, 25 °C
93%
Uniting the Fragments and End Game

1. Ti(O-iPr)_4 (2 equiv) (R)-BINOL (2 equiv) (CF_3)_2CHOH (4 equiv) 4 Å MS, PhCF_3, -20 °C

2. MeO OAc

TMSOTf, Et_2O, -78 °C

R = TBDPS

56%

(carried on mixture) 22%

HCl, MeOH 25 °C

1. Me_3SnOH DCE (85%)

2. TESCl, DMAP CH_2Cl_2 (60%)

3. Cl Cl Cl

Et_3N DMAP (66%)

20%

51%

HCl, MeOH (60%)
End Game (Continued)

1. OsO₄
NaIO₄
THF:H₂O, 4:1 (64%)

2. DBU, MnO₂
THF/MeOH, 4:1 (75%)

1. [(R)-BINOL]POCH₂CO₂Me
NaHMDS (93%, 6:1 dr)

2. HF•pyr, THF:H₂O, 35 °C
   (60%)

20 Linear steps
36 Total steps

Bryostatin 7
Summary

• The Krische group has published the shortest synthesis of a bryostatin to date.

• The point of convergence is earlier in the Krische synthesis than in the Wender synthesis

• The use of C-C bond forming hydrogenation in complex molecule synthesis showcases the utility of the methodology.