Total Synthesis of Bryostatins

(Previous Achievement and Krische’s Work)

Literature seminar (2018.02.14)
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1. Introduction
Introduction

Isolation:
From the marine bryozoan *Bugula neritina* (フサコケムシ)

Biosynthesis:
*Candidatus* Endobugula sertula
(Symbiotic bacterium of *Bugula neritina*)

Biological activity:
- Potent modulator of protein kinase C (PKC)
- Anti-cancer effect
- Anti-HIV effect
- Life-prolonging effect on Alzheimer’s disease
Introduction

Structure features:

- A family of 20 marine natural products
- Three heavily substituted tetrahydropyran rings
- Two acid/base-sensitive exo-cyclic unsaturated esters
- One congested C16-C17 $trans$-alkene
- Numerous oxygen-containing functionalities on a 26-membered lactone
2. Previous work
Development of Bryostatin’s Total Synthesis

Synthesis points:

1. Exo-cyclic unsaturated esters
2. Congested C16-C17 trans-alkene
3. Macrolactonization
4. Complex steric structure
Total Synthesis of Bryostatin 7 by Masamune (1990) (1)

- First total synthesis of Bryostatin
- Bryostatin 7 was divided into 4 fragments and chiral enolate reagent 7 controlled enantioselectivity of the product
- 41 steps in total

Total Synthesis of Bryostatin 7 by Masamune (1990) (2)

Total Synthesis of Bryostatin 7 by Masamune (1990) (3)

Total Synthesis of Bryostatin 2 by Evans (1998) (1)

- Rings A-C were derived from the same set of acyclic precursors, each of which contains a common anti-1,3-diol subunit.
- This stereochemical motif can be effectively synthesized by sequential aldol and reduction reactions.
- 42 steps in total.

Total Synthesis of Bryostatin 2 by Evans (1998) (2)

Total Synthesis of Bryostatin 2 by Evans (1998) (3)

Total Synthesis of Bryostatin 3 by Yamamura (2000) (1)

- The best condition for introducing a methoxycarbonylmethylene unit to the C13 position stereocontrolledly was studied
- 43 steps in total

Total Synthesis of Bryostatin 3 by Yamamura (2000) (2)


**Table 1. Horner-Wadsworth-Emmons reaction of 8 with various reagents.**

<table>
<thead>
<tr>
<th>Phosphonate</th>
<th>Yield [%]</th>
<th>Z:E ratio of 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO_2_CH_2_CO_2_Me</td>
<td>94</td>
<td>1.6:1</td>
</tr>
<tr>
<td>PhO_2_CH_2_CO_2_Me</td>
<td>90</td>
<td>2.0:1</td>
</tr>
<tr>
<td>PhO_2_</td>
<td>92</td>
<td>4.0:1</td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>2.3:1</td>
</tr>
</tbody>
</table>

NaH, phosphonate
THF, -78 → 0 ℃

(Z)-9

(E)-9
Total Synthesis of Bryostatin 3 by Yamamura (2000) (3)

Total Synthesis of Bryostatin 3 by Yamamura (2000) (4)

Total Synthesis of Bryostatin 16 by Trost (2008)

- Pd-catalysed chemoselective alkyne-alkyne coupling followed by Au-catalysed 6-endo-dig cyclization efficiently produced both the macrocycle and the C ring of Bryostatin 16
- Ru-catalysed tandem alkene-alkene coupling / Michael addition generated cis-tetrahydropyran 6
- 28 steps in total

A strategy of combining an A-ring hydroxyallylsilane and a C-ring aldehyde was selected for an attempted synthesis of Bryostatin 1.

A spirocyclic structure formed via intramolecular cyclization of the silane at the C9 position was a major byproduct.

31 steps in total.

Total Synthesis of Bryostatin 1 by Keck (2011) (2)
Total Synthesis of Bryostatin 1 by Keck (2011) (3)

An intermolecular Prins cyclization to anneal the B ring was investigated, which prevented the spirocyclic byproduct from synthesizing.

25 steps in total.
Total Synthesis of Bryostatin 9 by Wender (2011) (2)

Total Synthesis of Bryostatin 9 by Wender (2011) (3)

3. Total synthesis of Bryostatin 7 by Krische
Retrosynthetic Analysis of Bryostatin 7

Bryostatin 7
20 Steps (LLS), 36 Total Steps
5 C-C Bonds Formed via Hydrogen-Mediated C-C Coupling

Fragment A
1 C-C Bond Formed via Hydrogenative Coupling C20-C21

Fragment B
4 C-C Bonds Formed via Hydrogenative Coupling C2-C3, C5-C6, C7-C8, C9-C10

Krische’s Work (Key Reaction)

Classical C=O Addition - Stoichiometric Metals

\[ \text{Feedstock} \xrightarrow{[M]} \text{no cat/cat} \xrightarrow{\text{Then H}_2\text{O}} \text{R}^1\text{OH} \xrightarrow{\text{Metal Salts}} \text{R}^1\text{R}^2 \]

Metal Catalyzed C=O Reductive Coupling

\[ \text{R}^1\text{O} \xrightarrow{\text{MLn (cat)}} \text{R}^1\text{OH} \xrightarrow{\text{Reductant}} \text{R}^1\text{R} \]

H\text{2 or 2-PrOH} \text{Our Work}

Redox-Triggered C=O Coupling via H\text{2 Transfer}

\[ \text{Feedstock} \xrightarrow{\text{MLn (cat)}} \text{R}^1\text{OH} \xrightarrow{\text{Exclusively}} \text{R}^1\text{OH} \xrightarrow{\text{Our Work}} \text{R}^1\text{R} \]

Conception of Krische’s Work

Enantioselective Ir-Catalyzed Carbonyl Allylation via Transfer Hydrogenative Coupling of Allyl Acetate

Effect of Basic and Acidic Additives and Iridium Source in the Transfer Hydrogenative Allylation


\[
\begin{align*}
\text{Additive} & \quad \text{Iridium Source} & \text{Yield (\%)} \\
\hline
1 & \text{Cs}_2\text{CO}_3 & m-\text{NO}_2\text{BzOH} & [\text{Ir(cod)}\text{Cl}]_2 & 80 \\
2 & \text{K}_2\text{CO}_3 & m-\text{NO}_2\text{BzOH} & [\text{Ir(cod)}\text{Cl}]_2 & 21 \\
3 & \text{Na}_2\text{CO}_3 & m-\text{NO}_2\text{BzOH} & [\text{Ir(cod)}\text{Cl}]_2 & 15 \\
4 & \text{Li}_2\text{CO}_3 & m-\text{NO}_2\text{BzOH} & [\text{Ir(cod)}\text{Cl}]_2 & 12 \\
5 & -- & -- & [\text{Ir(cod)}\text{Cl}]_2 & \leq 5 \\
6 & \text{Cs}_2\text{CO}_3 & -- & [\text{Ir(cod)}\text{Cl}]_2 & 47 \\
7 & -- & -- & [\text{Ir(cod)}\text{Cl}]_2 & 10 \\
8 & -- & m-\text{NO}_2\text{BzOCs} & [\text{Ir(cod)}\text{Cl}]_2 & 72 \\
9 & \text{Cs}_2\text{CO}_3 & m-\text{NO}_2\text{BzOCs} & [\text{Ir(cod)}\text{Cl}]_2 & 79 \\
10 & \text{Cs}_2\text{CO}_3 & o-\text{NO}_2\text{BzOH} & [\text{Ir(cod)}\text{Cl}]_2 & 39 \\
11 & \text{Cs}_2\text{CO}_3 & p-\text{NO}_2\text{BzOH} & [\text{Ir(cod)}\text{Cl}]_2 & 49 \\
12 & \text{Cs}_2\text{CO}_3 & \text{BzOH} & [\text{Ir(cod)}\text{Cl}]_2 & 39 \\
13 & \text{Cs}_2\text{CO}_3 & p-\text{MeOBzOH} & [\text{Ir(cod)}\text{Cl}]_2 & 42 \\
14 & \text{Cs}_2\text{CO}_3 & m-\text{FBzOH} & [\text{Ir(cod)}\text{Cl}]_2 & 41 \\
15 & \text{Cs}_2\text{CO}_3 & m-\text{NO}_2\text{BzOMe} & [\text{Ir(cod)}\text{Cl}]_2 & 47 \\
16 & \text{Cs}_2\text{CO}_3 & -- & [\text{Ir(cod)}\text{(BIPHEP)}][\text{BARF}] & 41 \\
17 & \text{Cs}_2\text{CO}_3 & m-\text{NO}_2\text{BzOH} & [\text{Ir(cod)}\text{(BIPHEP)}][\text{BARF}] & 72
\end{align*}
\]
Effect of Substitution of $m$-Nitrobenzoic Acid in the Transfer Hydrogenative Allylation

Substituents of $m$-NO$_2$BzOH are important for enantioselectivity

R1 is the preferred site of cyclometalation and the enantioselectivity would be reversed if it is blocked

Catalytically Active ortho-cyclometalated iridium(Ⅲ)-π-allyl complex V

Experiments Corroborating Intervention of *Ortho*-Cyclometalated Iridium(III)-π-Allyl Complex(V) as a Catalytically Relevant Entity

![Chemical structures and reaction conditions](image)

- Carbonyl allylation products are also accessible from aldehydes when employing isopropanol as a hydrogen donor.
- Complex V serves as an active catalyst in the transfer hydrogenative carbonyl allylation of aldehyde 2n under standard conditions, suggesting that complex V is indeed catalytically relevant.

Proposed Stereochemical Model

Favored Mode of Addition

Disfavored Mode of Addition

Ir-Catalyzed Transfer Hydrogenative Allylation of Benzylic Alcohol Employing Isotopically Labeled Allyl Acetate

- Intervention of rapid interconversion of allyl haptomers through the agency of a symmetric π-allyl is supposed

Experiments Establishing Rapid Redox Equilibration in Advance of Carbonyl Addition

A very similar product distribution and yield are obtained, establishing rapid redox equilibration in advance of C-C coupling.

Proposed Catalytic Mechanism

Dehydrogenation of the secondary alcohol products is prevented by internal chelation of the homoallylic olefin

Survey of Enantioselective Alcohol C-H Allylations via Iridium-Catalyzed Hydrogen Transfer

Retrosynthetic Analysis of Bryostatin 7

Bryostatin 7
20 Steps (LLS), 36 Total Steps
5 C-C Bonds Formed via Hydrogen-Mediated C-C Coupling

Fragment A
1 C-C Bond Formed via Hydrogenative Coupling C20-C21

Fragment B
4 C-C Bonds Formed via Hydrogenative Coupling C2-C3, C5-C6, C7-C8, C9-C10

Synthesis of Fragment A

Synthesis of Fragment B Employing Multiple Transfer Hydrogenative C-C Bond Formations (1)

\[
\text{OH} \quad \text{OH}
\]

10

\[
[\text{Ir(cod)Cl}_2 \ (5 \text{ mol%}) \quad \text{(S)-Cl,MeO-BIPHEP} \ (10 \text{ mol%})]
\]

\[
\text{Cs}_2\text{CO}_3 \ (40 \text{ mol%}) \quad 4-\text{Cl-3-NO}_2-\text{BzOH} \ (20 \text{ mol%}) \\
\text{Dioxane, } 90 ^\circ \text{C}
\]

\[
\text{OAc} \quad (72\%)
\]

\[
\text{OH} \quad \text{OH} \quad \text{OAc}
\]

11

\[
(>99\% \text{ ee, } >30:1 \text{ dr})
\]

\[
\text{Ozonolysis}
\]

\[
\text{TBSCI} \quad \text{Imidazole} \ (60\%)
\]

\[
\text{OTBS}
\]

12

\[
\text{(S)-SEGPHOS} \ (5 \text{ mol%})
\]

\[
\text{i-PrOH} \ (200 \text{ mol%}) \quad \text{PhMe, } 60 ^\circ \text{C}
\]

\[
\text{Me} \quad \text{Me}
\]

13

\[
(>20:1 \text{ dr})
\]

\[
1) \text{Ac}_2\text{O}, \text{Et}_3\text{N}, \text{DMAP} \\
\text{THF} \ (94\%)
\]

\[
2) \text{Ozonolysis} \ (96\%)
\]

\[
\text{OTBS}
\]

14

Synthesis of Fragment B Employing Multiple Transfer Hydrogenative C-C Bond Formations (2)

Union of Fragment A and Fragment B and Total Synthesis of Bryostatin 7 (1)

Keck-Yu annulation
1) Ti(O-i-Pr)$_4$ (R)-BINOL (CF$_3$)$_2$CHOH 4A-MS, PhCF$_3$
2) Fragment B TMSOTf Et$_2$O
(92%, >20:1 dr)

Both compounds are used in the next step
R = TBDPS

acidic methanolysis

Union of Fragment A and Fragment B and Total Synthesis of Bryostatin 7 (2)

- Prepared in 20 steps (longest linear sequence) and 36 total steps, representing the most concise route to any bryostatin reported, to date
- Carbonyl allylation products could generate in a single manipulation and form as single enantiomers by utilizing hydrogenative methods
- Hydrogenative methods could bypass the requirement of stoichiometric metals

4. Summary
Summary

- Bryostatins are potent modulators of protein kinase C with promising biological activity.

- Total synthesis of Bryostatins 1, 2, 3, 7, 9, and 16 has been reported.

- Multiple transfer hydrogenative C-C bond formations reported by Krische, which was utilized in the total synthesis of Bryostatin 7 in 2011 simplified the total synthesis of Bryostatins.
Appendix
Appendix 1. Structure of Bryostatins (1)

1: \( R_1 = \text{Ac}, R_2 = \text{OOCCH}_2\text{CH(CH}_3\text{)}_2 \)
2: \( R_1 = \text{H}, R_2 = \text{OOCCH}_2\text{CH(CH}_3\text{)}_2 \)
4: \( R_1 = \text{OOCCH}_2\text{CH(CH}_3\text{)}_2, R_2 = \text{OOC(CH}_2\text{)}_2\text{CH}_3 \)
5: \( R_1 = \text{OOCCH}_2\text{CH(CH}_3\text{)}_2, R_2 = \text{OAc} \)
6: \( R_1 = \text{OOC(CH}_2\text{)}_2\text{CH}_3, R_2 = \text{OAc} \)
7: \( R_1 = \text{OAc}, R_2 = \text{OAc} \)
8: \( R_1 = \text{OOC(CH}_2\text{)}_2\text{CH}_3, R_2 = \text{OOC(CH}_2\text{)}_2\text{CH}_3 \)
9: \( R_1 = \text{Ac}, R_2 = \text{OOC(CH}_2\text{)}_2\text{CH}_3 \)
10: \( R_1 = \text{Piv}, R_2 = \text{H} \)
11: \( R_1 = \text{Ac}, R_2 = \text{H} \)
12: \( R_1 = \text{CO(CH}_2\text{)}_2\text{CH}_3, R_2 = \text{OOCCH}_2\text{CH(CH}_3\text{)}_2 \)
13: \( R_1 = \text{CO(CH}_2\text{)}_2\text{CH}_3, R_2 = \text{H} \)
14: \( R_1 = \text{Piv}, R_2 = \text{OH} \)
15: \( R_1 = \text{Ac}, R_2 = \text{OOCCH}_2\text{CH(CH}_3\text{)}_2 \)
Appendix 1. Structure of Bryostatins (2)

3: $R_1 = \text{Ac}$, $R_2 = \text{OCH}_2\text{CH}=$
20: $R_1 = \text{Piv}$, $R_2 = \text{H}$

Bryostatin 16

Bryostatin 17

Bryostatin 18

Bryostatin 19
Appendix 2. Biosynthesis of Bryostatin (2)

Appendix 3. Hypothetical pathway of PKC synthesis and downregulation by bryostatin 1

Appendix 4. Effect of Allyl Acetate Loading, Solvent, and Ligand in the Transfer Hydrogenative Allylation

Appendix 5. Effect of Chiral Ligand and Temperature in the Transfer Hydrogenative Allylation

Appendix 6. Chiral Ligands

(R)-MeO-BIPHEP

(R)-BINAP

(R)-tol-BINAP

(-)-TMBTP

(S)-Cn-TUNEPHOS

(R)-H8-BINAP

(S)-BIPHEMP

CTH-(S)-P-PHOS

(R)-SOLPHOS

(S)-SEGPHOS

(R)-SYNPHOS

\[
\text{Ene-Yne Coupling} \quad \text{Michael Addition}
\]

Proposed Tetrahydropyran Synthesis

Appendix 8. Mechanistic Proposal for Ru-Catalyzed Alkene-Alkyne Addition

Scheme 1. Mechanistic Proposal for Ru-Catalyzed Alkene—Alkyne Addition


- Pd catalyst chemoselectively inserts into the carbon-hydrogen bond of the terminal alkyne

- Au catalyst gives 6-endo-dig cyclization product selectively

Appendix 10. 5-exo-dig & Z-isomer Selectivity of Gold-Catalyzed Cyclization

Condition A: 1% AuCl₃, in CH₂Cl₂  
Condition B: 1% (PPh₃)AuCl, 1% AgOTf, in THF

<table>
<thead>
<tr>
<th>enynol</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>R₅</th>
<th>condition</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Me</td>
<td>Me</td>
<td>o-ClC₆H₄</td>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>A, 3h</td>
</tr>
<tr>
<td>1b</td>
<td>Me</td>
<td>Me</td>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>Cy c</td>
<td>A, 1h</td>
</tr>
<tr>
<td>1c</td>
<td>Me</td>
<td>Me</td>
<td>p-FC₆H₄</td>
<td>Ph</td>
<td>Ph</td>
<td>Bu</td>
<td>A, 1h</td>
</tr>
<tr>
<td>1d</td>
<td>Me</td>
<td>Me</td>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
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</tr>
<tr>
<td>1e</td>
<td>Me</td>
<td>Me</td>
<td>p-FC₆H₄</td>
<td>C₃H₇</td>
<td>C₃H₇</td>
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<td>Me</td>
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<td>Ph</td>
<td>p-MeC₆H₄</td>
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<td>1g</td>
<td>Me</td>
<td>Me</td>
<td>o-ClC₆H₄</td>
<td>Ph</td>
<td>Ph</td>
<td>Bu</td>
<td>A, 1h</td>
</tr>
</tbody>
</table>

- In all cases, only 5-exo-dig cyclization occurred and stereoisomerically pure compounds (Z)-2 were found to be the only reaction products
Appendix 11. Evans Aldol Reaction

- \( R\text{CHO} + \text{Bn\text{-}}N\text{C\text{-}}\text{O\text{-}}\text{Bn} \xrightarrow{^n\text{Bu}_2\text{BOTf, Et}_3\text{N}} \text{OH}\text{-}\text{Bn}\text{-}N\text{C\text{-}}\text{Bn} \quad \text{"Evans Syn"}

- \( R\text{CHO} + \text{Bn\text{-}}N\text{C\text{-}}\text{S\text{-}}\text{S\text{-}}\text{Bn} \xrightarrow{\text{TiCl}_4, \text{sparteine (1eq.)}} \text{OH}\text{-}\text{S\text{-}}\text{S\text{-}}\text{Bn}\text{-}N\text{C\text{-}}\text{S\text{-}}\text{S\text{-}}\text{Bn} \quad \text{"Non-Evans Syn"}

- \( R\text{CHO} + \text{Bn\text{-}}N\text{C\text{-}}\text{O\text{-}}\text{Bn} \xrightarrow{\text{MgCl}_2 \text{ (cat.)}, \text{Et}_3\text{N, TMSCl}} \text{OH}\text{-}\text{Bn}\text{-}N\text{C\text{-}}\text{O\text{-}}\text{Bn} \quad \text{"Non-Evans Anti"}

- \( R\text{CHO} + \text{Bn\text{-}}N\text{C\text{-}}\text{S\text{-}}\text{S\text{-}}\text{Bn} \xrightarrow{\text{MgBr}_2 \text{ (cat.)}, \text{Et}_3\text{N, TMSCl}} \text{OH}\text{-}\text{S\text{-}}\text{S\text{-}}\text{Bn}\text{-}N\text{C\text{-}}\text{S\text{-}}\text{S\text{-}}\text{Bn} \quad \text{"Evans Anti"}