Total Synthesis of Bryostatin 3

First isolated by Pettit from the marine bryozoan, are a family of 21 macrolides.

- Potent antineoplastic, immunopotentiating, synaptogenesis inducing, and latent HIV-modulating activity.
- Beneficial effects as a post-stroke treatment and for restoring the blood-brain barrier after traumatic blast injuries.
- 26-membered lactone and three highly functionalized tetrahydropyrans integrated in the macrocycle.

Bryostatin 3: PKC Ki = 2.75 nM
Yamamura 2000, 43 steps (LLS), 88 steps (TS)
This work, 22 steps (LLS), 31 steps (TS)

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Total Synthesis Presentation
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Retrosynthetic analysis of Bryostatin 3

Bryostatin 3

- Carbonylative esterification
- Epoxidation & installation of side chain

1. [Au] 6-Endo-Dig Cyclization
2. [Pd] Alkyne/Alkyne Coupling
3. [Ru] Alkene/Alkyne Coupling
4. Michael Addition
5. [Pd] Yamaguchi Macrolactonization
Synthesis of Fragment 3

From 6 to 7:

From 9 to 10:

From 7 to 9:
Synthesis of Fragment 3

From 10 to 11: Wittig Olefination

Ph$_3$P$^+$I

Ph$_3$P=CH$_2$H$^-$ 

Base

From 11 to 12: Negishi cross-coupling

PdCl$_2$(dpf)

(dpf)Pd+

oxidative addition

transmetalation

reductive elimination

then ZnBr$_2$

LDA

then ZnBr$_2$

K$_2$OsO$_2$(OH)$_4$ (25 mol%), (DHQ)$_2$PHAL (60 mol%), K$_3$Fe(CN)$_6$, K$_2$CO$_3$, NaHCO$_3$, MeSO$_2$NH$_2$

H$_2$O/BuOH (1:1)

0 °C, 30 min 90%, 3:1 dr

HO$_-$

Me$_2$CO
Synthesis of Fragment 2

[Chemical reactions and structures depicted in the image]

Reductive Elimination

Alkene coupling:

β-hydride Elimination

Oxidative Coupling

From 21 to 22:
Synthesis of Fragment 2

**From 22 to 23:**

1. **22**
2. **23**

**From 23 to 2:**

1. **23**
2. **2**
Completion of bryostatin 3 synthesis

From 29 to 1: Yamaguchi Esterification

From 1 to 30:
Completion of bryostatin 3 synthesis

From 30 to 31 & 32:

From 31 to 33:
Completion of bryostatin 3 synthesis

From 33 to 34:

1. HF (aq.)/MeCN
2. TFA/H₂O/CH₂Cl₂
60% over 2 steps
Synthesis of Fragment 5
