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Total Synthesis of Bryostatin 16 using a Pd-Catalyzed Diyne Coupling as Macrocyclization Method and Synthesis of C20-*epi*-Bryostatin 7 as a Potent Anticancer Agent

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1. Introduction

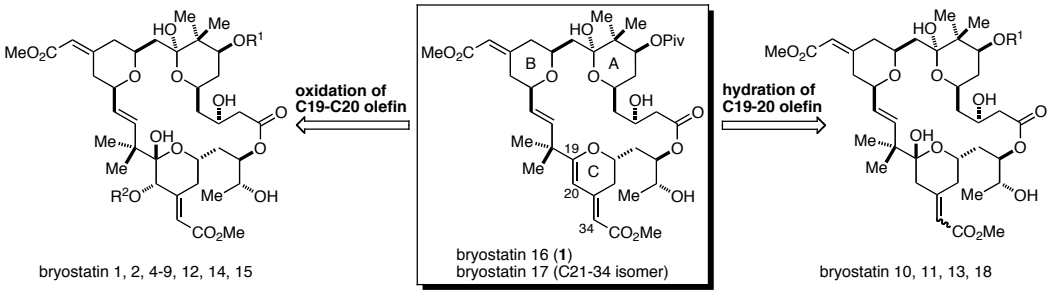
1-1. Bryostatin Family (bryostatin 1-20)

- Isolated from the marine bryozoan *Bugula neritina* (コケムシ)
- Biological activities including antineoplastic activity (anti-cancer)
- 26-membered lactone, acid/base sensitive esters, congested olefin, and numerous O-containing functionality and stereogenic centers
- Only 3 members (bryostatin 2, 3 and 7) were synthesized.

1-2. Bryostatin 16 (target compounds)

- Almost all bryostatin family can be accessed from bryostatin 16 (Scheme 1)
- Retrosynthetic analysis (Scheme 2): Pd-catalyzed tandem alkyne-alkyne coupling[1] is a key step (**5** → **3** or **4**)

Scheme 1. Bryostatins



1-3. This work

- The author reports the total synthesis of bryostatin 16 first time
- Bryostatin analogue 20-*epi*-bryostatin 7 (Fig. 1) can be synthesized from a common intermediate
- Three substituted PHP rings were formed through chemoselective and/or atom-economical approach

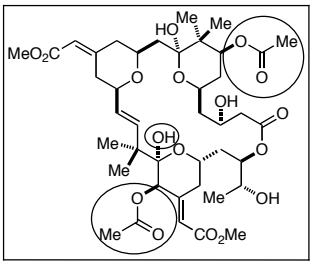
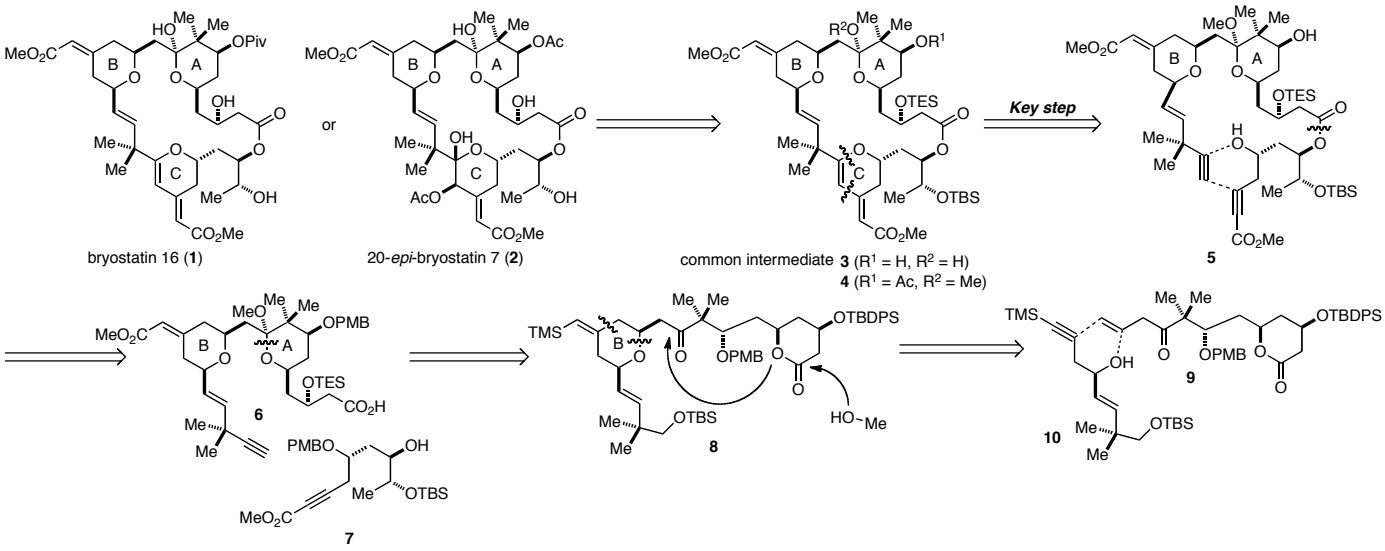


Figure 1. 20-epi-bryostatin

Scheme 2. Retrosynthesis

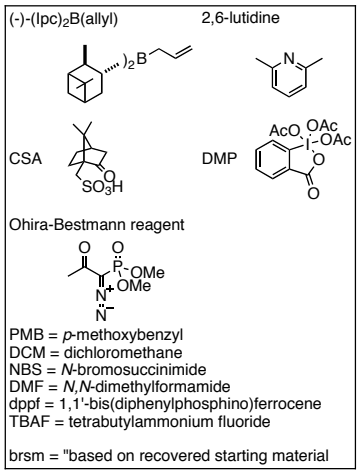


2. Results and discussion

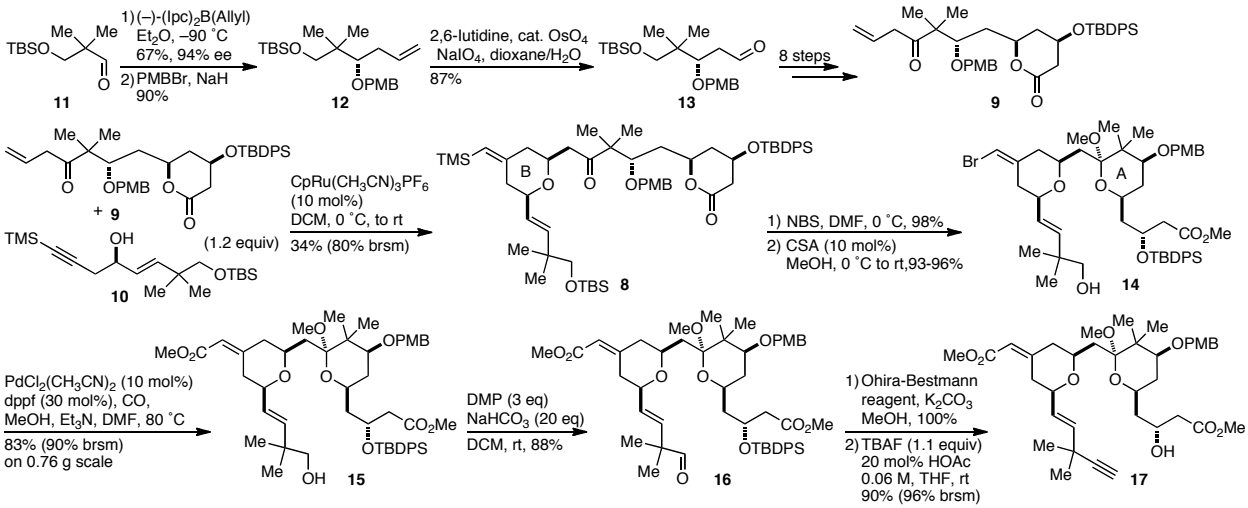
2-1. Synthesis of Bryostatin 16

2-1-1. Construction of rings A and B (Scheme 3)

- The synthesis of alkene **9** from aldehyde **13** and the synthesis of alkyne **10** were Previously reported[2,3]
- Ring B was formed through Ru-catalyzed alkene-alkyne coupling/Michael addition methodology (**9**+ **10** → **8**)
- Ring A was formed through acid-catalyzed tandem transesterification followed by methyl ketal formation (**8** → **14,** procedure 2)



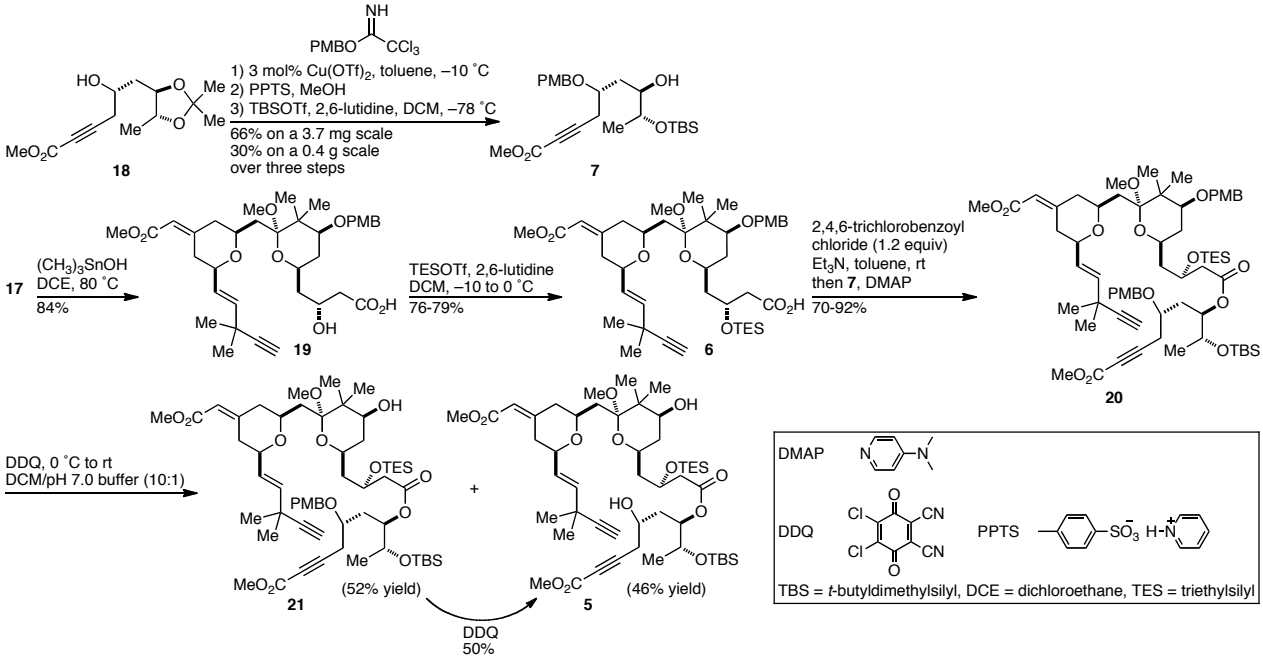
Scheme 3. Synthesis of β-hydroxy methyl ester **17** (construction of ring A and B)



2-1-2. Synthesis of diyne 5 (Scheme 4)

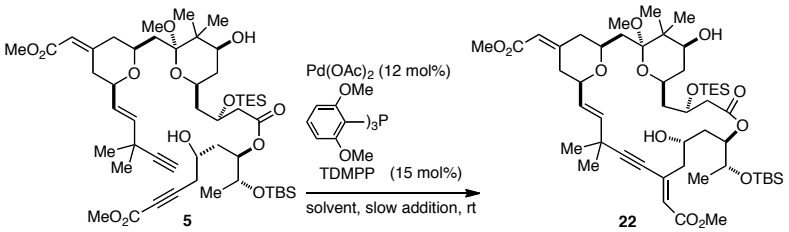
- Methyl ester **17** was hydrolyzed chemoselectively to acid **19**
- Acetonide intermediate **18** was synthesized according to literature[2]
- Treatment of ester **20** with excess DDQ gave a mixture containing mono-deprotection **21** and diyne **5.** Mono-deprotection **21** could be recycled and provided more diol.

Scheme 4. The synthesis of diyne **5**



2-1-3. Pd-catalyzed tandem alkyne-alkyne coupling (key step)

Scheme 5. Pd-catalyzed tandem alkyne-alkyne coupling



entry	solvent	yield, %
1	benzene	22 (44% brsm)
2	THF	23
3	toluene	56
4[a]	toluene	36 (57% brsm)

Reaction was carried out on 3.2 mg scale
[a] On 45 mg scale

- Pd-catalyzed tandem alkyne-alkyne coupling was employed for the macrocyclization
- Use of toluene as the solvent proved to be most effective
- On a 45 mg scale, the conversion was lower than the smaller scale reaction

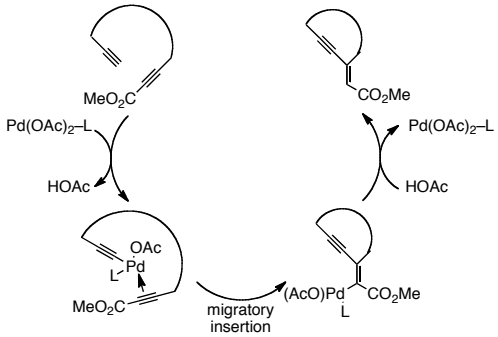
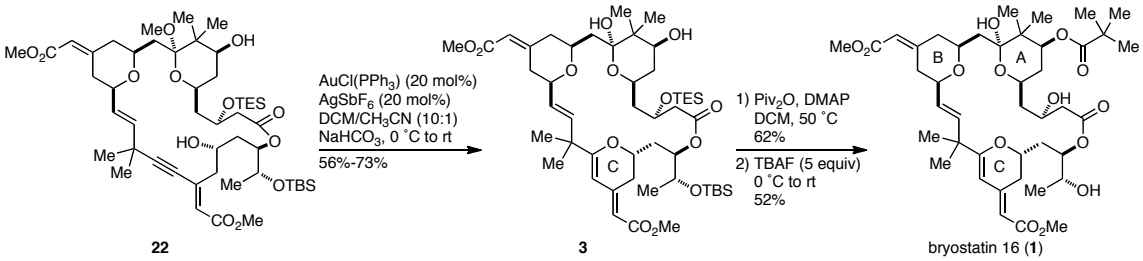


Figure 2. Plausible catalytic cycle

2-1-4. Construction of ring C (the end game of the synthesis of bryostatin 16)

- A cationic gold catalyst was used for the formation of ring C

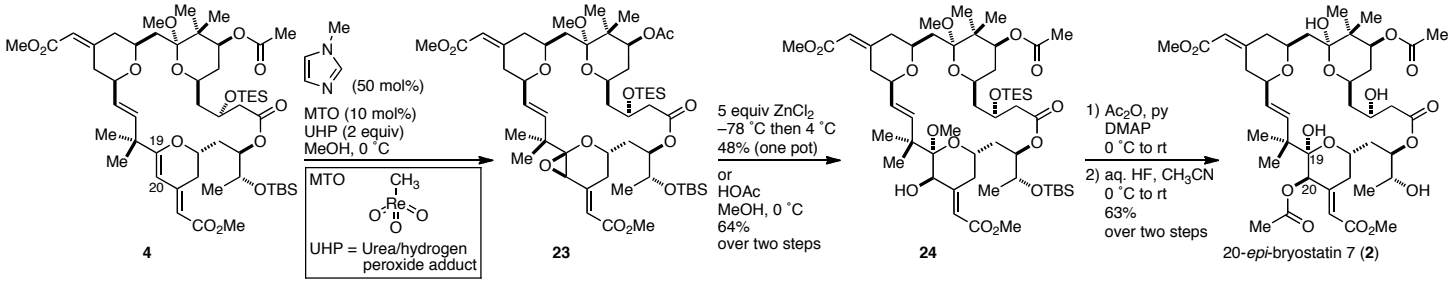
Scheme 6. Construction of ring C (end game of the synthesis of bryostatin 16)



2-2. Synthesis of Bryostatin analogue 2 via a common intermediate 4

- Start from the common intermediate **4**
- C19–C20 olefin was chemoselectively epoxidized
- Synthesized analogue **2** could be a potential anti-cancer drug

Scheme 7. The synthesis of 20-*epi*-Bryostatin 7 (**2**)



3. Conclusions

- Bryostatin 16 was synthesized from aldehyde **11** in 26 steps in the longest linear sequence, 39 total steps
- A Pd-catalyzed alkyne-alkyne coupling was employed for the first-time as a macrocyclization method in natural product synthesis
- Three PHP rings were formed by chemoselective and/or atom- economical approaches
- It was demonstrated that bryostatin analogues can be derived from Bryostatin 16-like intermediate **4**

4. References

1) Trost, B. M.; Frontier, A. J. *J. Am. Chem. Soc.* **2000**, *122*, 11727–11728
2) Trost, B. M.; Yang, H.; Thiel, O. R.; Frontier, A. J.; Brindle, C. S. *J. Am. Chem. Soc.* **2007**, *129*, 2206–2207
3) Trost, B. M.; Dong, G. *Nature* **2008**, *456*, 485–488