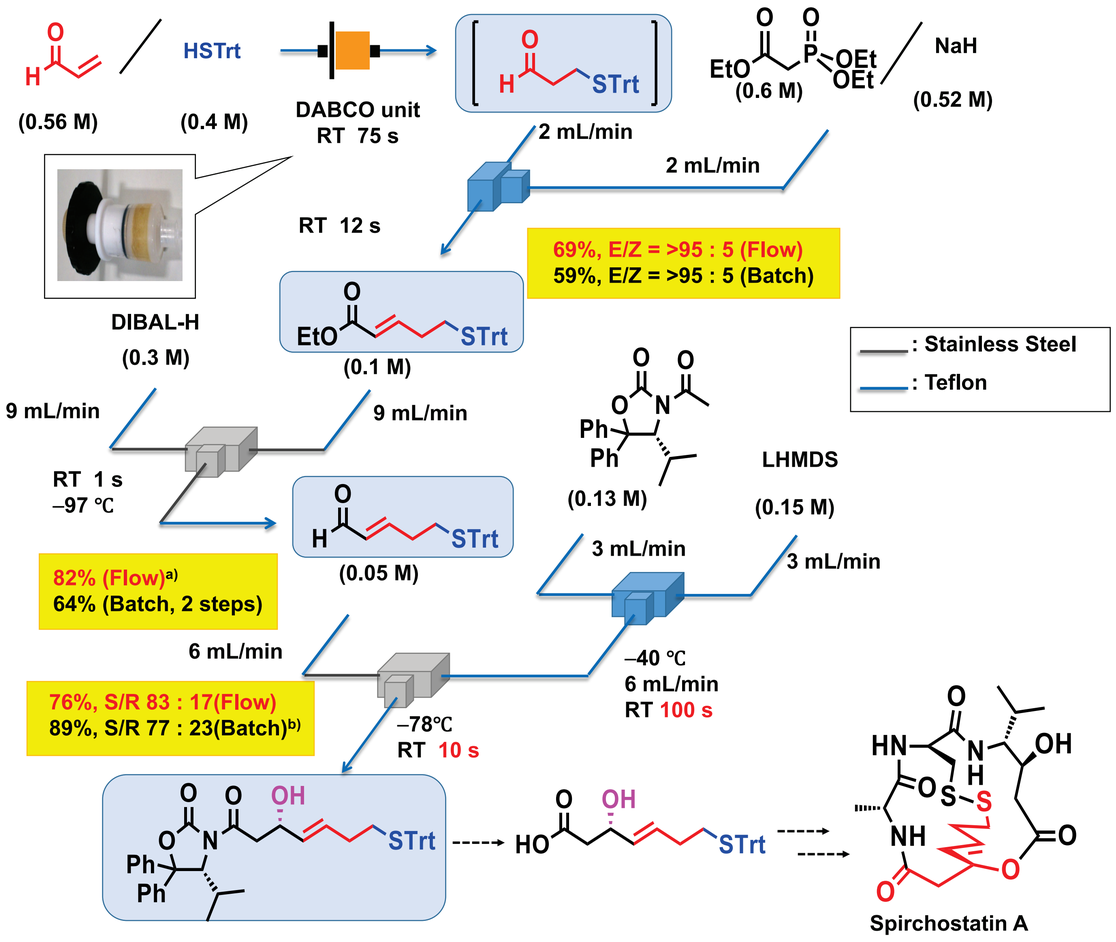
反応集積化が導く中分子戦略：
高次細胞機能制御を可能とする非天然型アミノ酸含有環状ペプチド中分子の創製

（東北大院薬）土井隆行

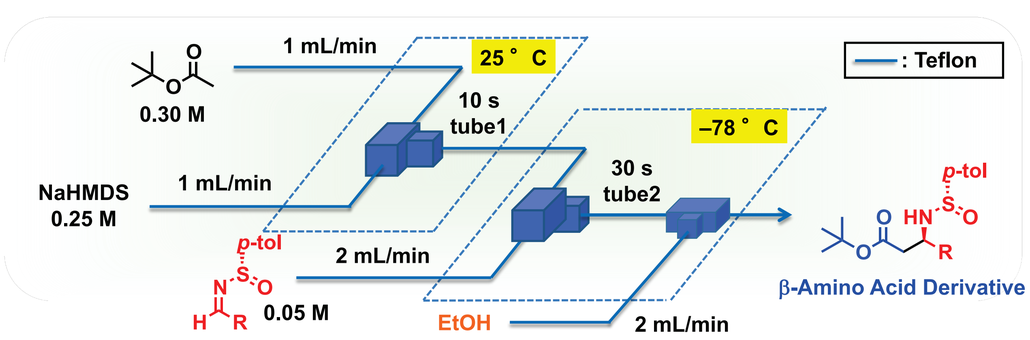
1.1 Asymmetric Flow Synthesis of 3-Hydroxyacid in Spiruchostatin A



- Michael addition through base-polymer support in flow
- Horner-Wadsworth-Emmons reaction in flow
- Partial reduction with DIBAL at –97 ° C in flow
- Asymmetric aldol reaction in flow

a) Yoshida, M.; Otaka, H.; Doi, T. *Eur. J. Org. Chem.* 2014, 6010.
b) Doi, T.; Otaka, H.; Umeda, K.; Yoshida, M. *Tetrahedron* 2015, *71*, 6463.

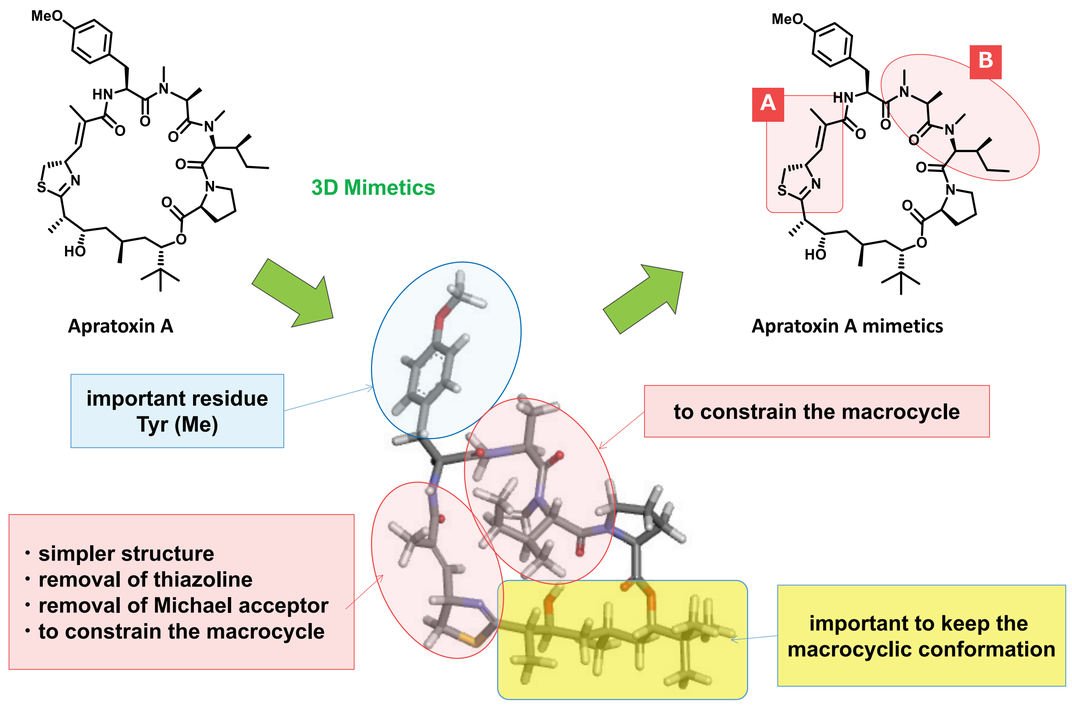
1.2 Asymmetric Mannich Reaction in Continuous-Flow System



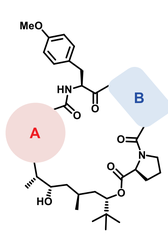
- Asymmetric Mannich reaction in flow

c) Yoshida, M.; Umeda, K.; Doi, T. *Bull. Chem. Soc. Jpn.*2017, 90, 1157.

2.1 Design and Synthesis of Apratoxin A Mimetics

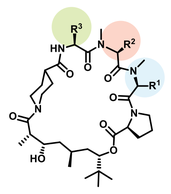


2.2 Cytotoxicity against HCT 116 Cells by WST Assay



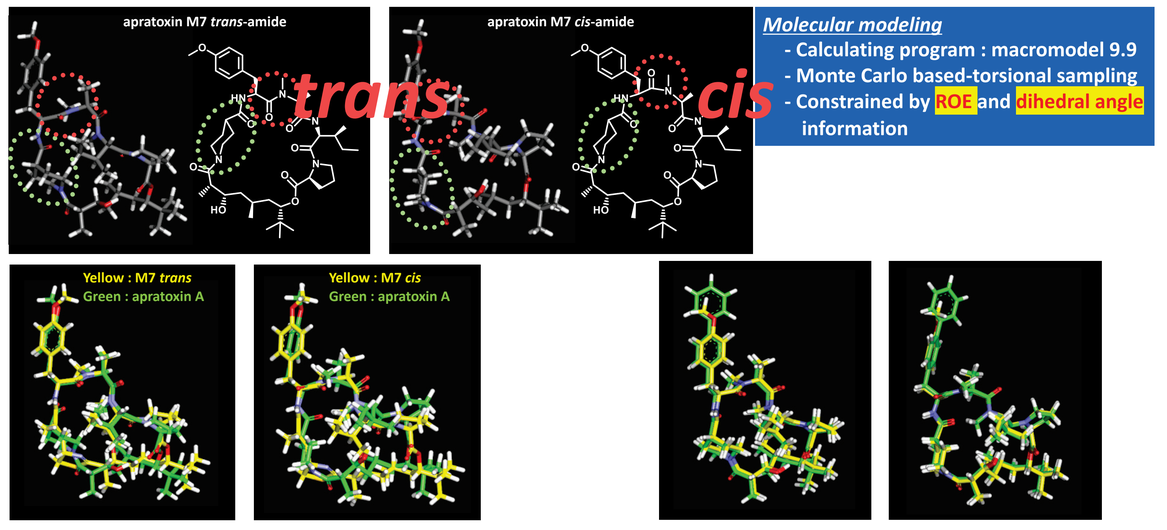
HCT116 cell
IC $_{50}$ (nM)

A \ B		trans	cis
	2.0 Apratoxin A	-	-	-
	820 APT055	>10000	>10000	>10000
	2600 APT M1	>10000	5700	>10000
	120 APT M7	4400	>10000	>10000



		–
710	130	7500
1600	360	850
APT M16	APT M15	
1.1	69	490

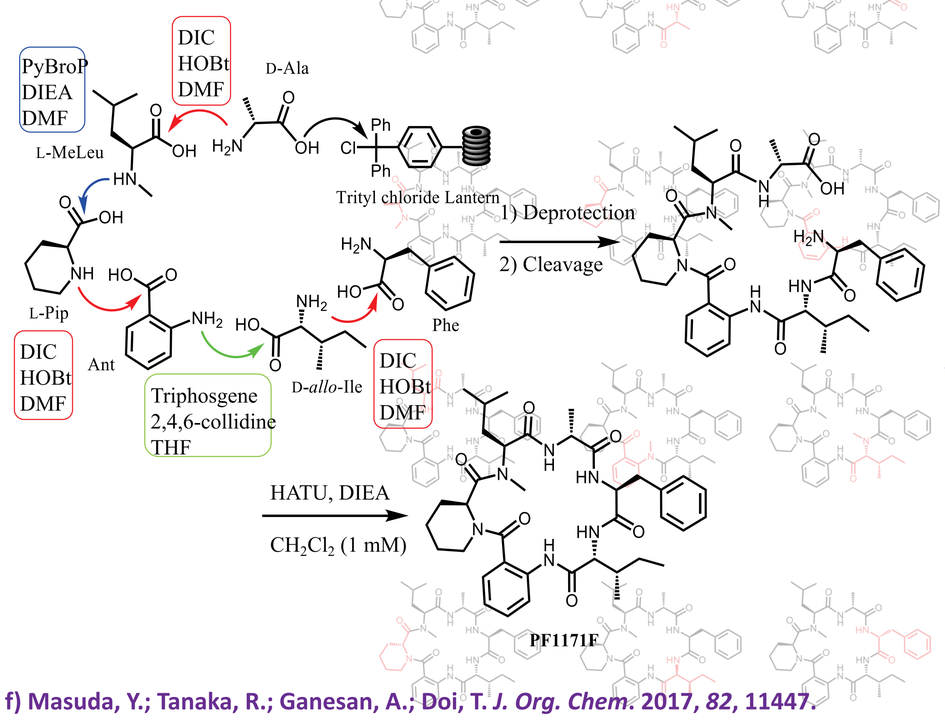
2.3 Molecular Modeling of Apratoxin M7 and M16



- Apratoxin M7: similar to apratoxin A
- Apratoxin M16: similar to apratoxin M7

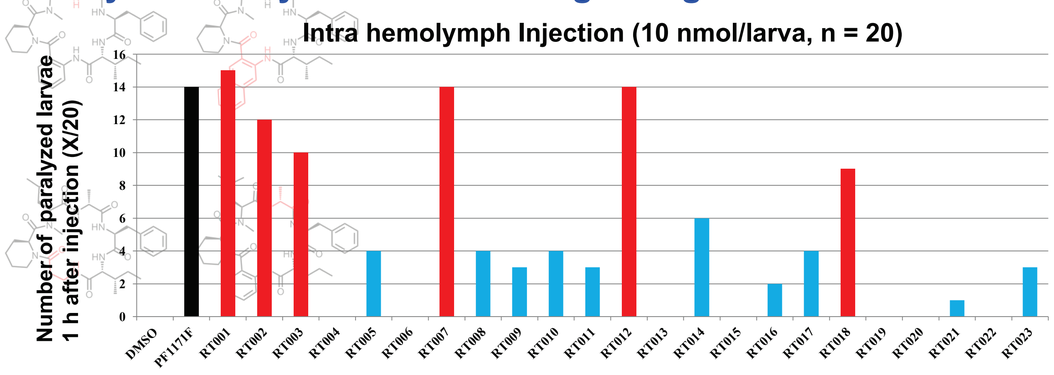
d) Onda, Y.; Masuda, Y.; Yoshida, M.; Doi, T. *J. Med. Chem.* 2017, *60*, 6751.
e) Onda, Y.; Fukushi, K.; Ohsawa, K.; Yoshida, M.; Masuda, Y.; Doi, T. *Heterocycles* 2020, *101*, 679.

3.1 Solid-phase Parallel Synthesis of PF1171F Analogues

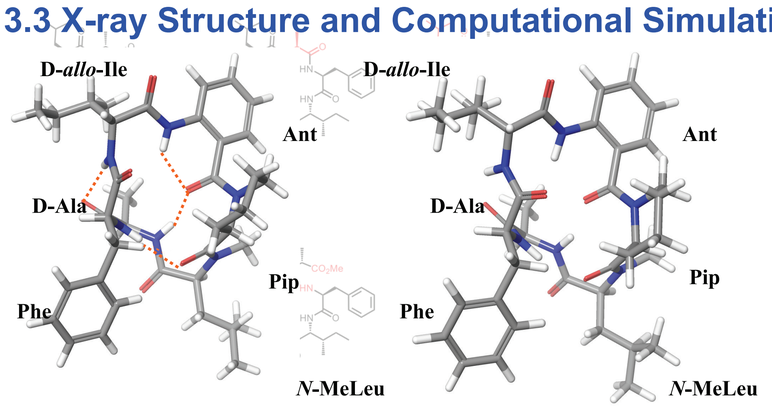


f) Masuda, Y.; Tanaka, R.; Ganesan, A.; Doi, T. *J. Org. Chem*. 2017, *82*, 11447.

3.2 Paralytic Activity of PF1171 Analogues against Silkworm



3.3 X-ray Structure and Computational Simulation Based on NMR Study



- Synthesis: 24 PF1171F analogues
- The bioactive conformation is probably different from that of the crystal structure.
- The MeLeu residue including its chirality is not significant for biological activity.
- PAMPA analysis