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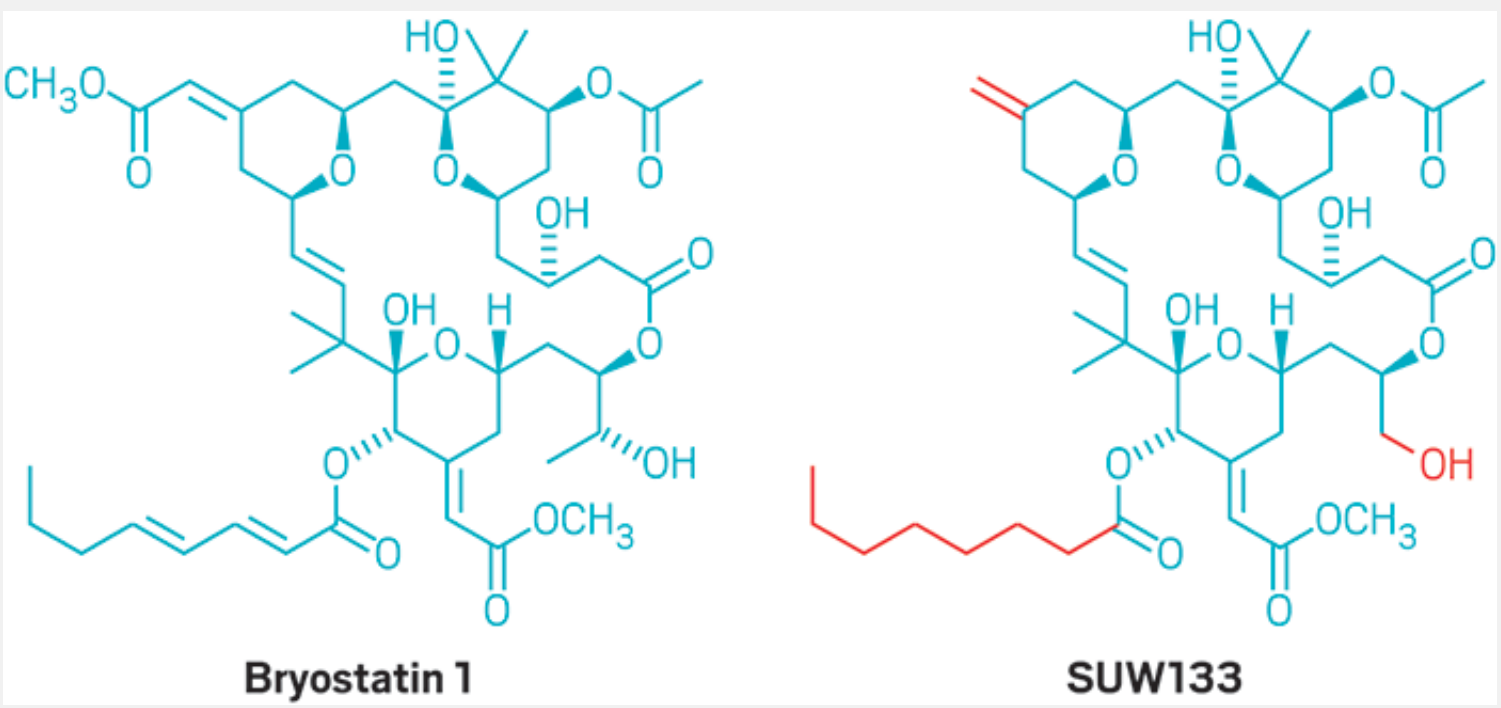
Bryostatin advances: A shorter synthesis and an HIV takedown

29-step route promises to boost dwindling supply of bryostatin 1, while an analog kicks latent virus out of cells and kills it

*By **Bethany Halford***



The marine natural product bryostatin 1 **has shown promise <https://cen.acs.org/articles/89/i43/BryostatinsTale.html>** as a treatment for cancer, Alzheimer's disease, and **HIV <https://cen.acs.org/articles/90/i29/Bringing-HIV-Hiding.html>** . But neither the compound nor its analogs have become approved drugs. One of the problems that has dogged bryostatin 1 is its scarce supply. Now, chemists at Stanford University led by **Paul A. Wender <http://web.stanford.edu/group/pawender/>** have developed a shortened synthesis of bryostatin 1 capable of supplying sufficient amounts of

the compound for clinical trials.

In the late 1980s, chemists at the National Cancer Institute took 12,700 kg of the tiny sea creature *Bugula neritina*—roughly the same weight as a school bus—and isolated from it just 18 g of bryostatin 1—not enough to even fill a salt shaker. The lion's share of that material has been used to supply more than three dozen clinical trials as a cancer chemotherapy, which ultimately didn't pan out.

Wender's new 29-step synthesis of bryostatin 1, which nearly halves the number of steps in the only other synthesis of the compound, from Gary Keck's lab at the University of Utah, could replenish supplies for clinical trials in other treatment areas where bryostatin 1 has proven promising (*Science* 2017, **DOI: 10.1126/science.aan7969 <http://dx.doi.org/10.1126/science.aan7969>**).

"The recent work from the Wender group marks a significant advance in resolving supply issues that will enable full clinical evaluation of bryostatins as chemotherapeutic agents. Specifically, gram quantities of bryostatin 1 are now available by total synthesis," notes Frank Fang, deputy president of Eisai's Andover innovative Medicines Institute. "The route described has several attractive features—convergence, telescoped steps, a crystalline final compound—that augur well for developing an eventual manufacturing route."

Wender says there was no particular synthetic breakthrough that helped his group to **whittle down the synthesis <https://cen.acs.org/articles/95/i30/Chemists-champion-future-2017-National.html>** of bryostatin 1, just clever chemistry and hard work. "It's kind of like running a marathon," he says. "What's important is how you start, what the middle of the race looks like, and how you cross the finish line." He is currently in discussions with potential partners to modestly scale up the synthesis using current good manufacturing practices so the material can be used in the clinic.

Bryostatin 1 has been given the go-ahead for testing in human clinical trials, but Wender still thinks many of the bryostatin analogs may ultimately be more useful as drugs. In recent work with the University of California, Los Angeles' Jerome A. Zack and colleagues, he has shown that the analog SUW133 can coax latent HIV out of cells and kill the virus more effectively

than bryostatin 1 in an animal model (*PLOS Path.* 2017, **DOI: 10.1371/journal.ppat.1006575 <http://dx.doi.org/10.1371/journal.ppat.1006575>**).

“Among the many findings of their work, two are especially relevant for the purpose of curing HIV: the absence of persistent immune activation after the reversal of HIV-1 latency by the drug, and the killing of a significant percentage of cells after the reactivation of latent HIV-1,” comments Santiago Moreno, an infectious disease expert at Madrid’s Ramón y Cajal Hospital. “If these results are confirmed in humans, apparently a single drug could do all the work needed.”

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