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Total Synthesis of Poisonous *Aconitum* Alkaloids Empowered by a Fragment Coupling Strategy

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Convergent total synthesis of highly complex bridged alkaloids through key fragment coupling.

It is no mean feat to synthesize such complex natural products as the C_{19} diterpene alkaloids (C_{19} DTAs), featuring unique polycyclic and bridged structures (Figure 1). In this issue of *ACS Central Science,* Reisman and co-workers take on this considerable challenge, employing a fragment coupling strategy to synthesize (−)-talatisamine (**1**), (−)-liljestrandisine (**2**), and (−)-liljestrandinine (**3**).[1] A series of highly chemoselective transformations was used to forge the polycyclic bridged skeleton of the natural products, one of which was structurally revised (**2** vs **4**).

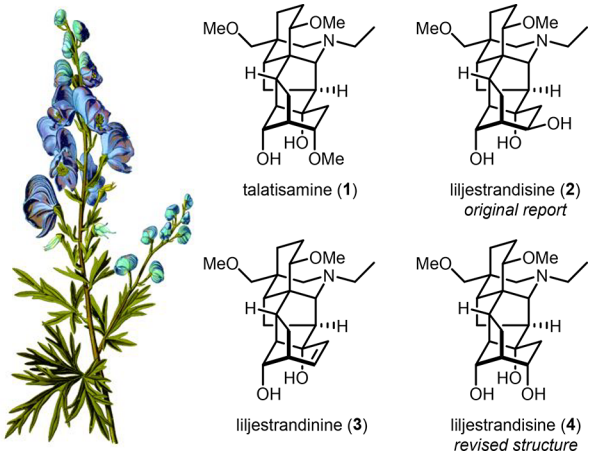

Figure 1. Structure of C_{19} diterpene alkaloids and an *Aconitum* plant from which they can be isolated (Picture Credit: Peter H. Raven Library/Missouri Botanical Garden).

> In fact, Reisman et al. solved this synthetic puzzle in a distinctly different manner, by coupling together two complex fragments that were separately assembled.

The *Aconitum* plants are well-known for their ability to biosynthesize neurotoxic C_{19} DTAs.[2] The plants themselves were used in medicinal preparations or as poison for hunting, due to the properties of the natural products to block cation channels in neurons, and to exhibit anti-inflammatory, antihypertensive, pain relief, or antiarrhythmic activities. The structure of these complex compounds results from peculiar biosynthetic transformations, especially a semipinacol rearrangement of the denudatine-type (**5**) into the aconitine-type (**6**) skeletons (Figure 2a).[3] This reaction has inspired the synthetic strategy of many chemists, starting with Wiesner's total synthesis of talatisamine **1** in the 1970s.[4−7] Besides, the retrosynthetic logic classically advises to unravel the complexity of bridged compounds by disconnecting the maximally bridged cycles.[5,8]

In fact, Reisman et al. solved this synthetic puzzle in a distinctly different manner, by coupling together two complex fragments that were separately assembled (Figure 2b). Such convergent approaches are well-known to empower the total synthesis of complex structures by making the synthetic route more flexible.[9] Fragment **A** was made from phenol thanks to a stereoselective *meta*-photocycloaddition, while fragment **B** was enantioselectively constructed from cyclopentenone. Both intermediates were coupled through a unique sequence of 1,2-addition followed by a high-yielding semipinacol rearrangement to deliver 4 g of intermediate **7**, which allows the stereoselective formation of the C-11

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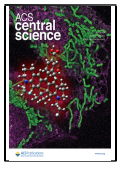

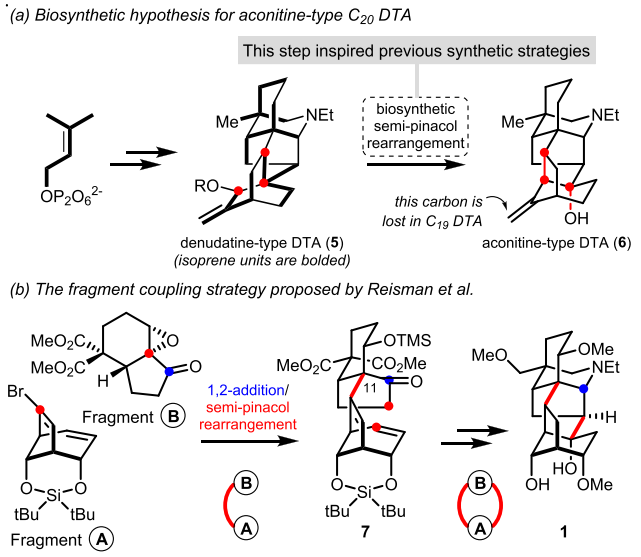

Figure 2. (a) Biosynthesis of *Aconitum* diterpene alkaloids and (b) the fragment coupling approach proposed by Reisman et al.

quaternary center at the same time. Unfortunately, the later key step involving a straightforward challenging *N*-radical cascade failed to construct the complete carbocyclic core of the natural product, thereby imposing a modification of the initial strategy. To solve these difficulties, a stepwise approach was adopted, and numerous chemoselective reactions were applied to finally afford the natural products. The reader will surely thrive on the many clever transformations that were used for this work.

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Thus, complex C_{19} DTAs were stereoselectively delivered in about 30 steps (1−3 mg each). While this achievement is not to compete with the phytochemical extraction from the plant (100 mg of **2** were isolated from 8 kg of plant through a complex purification process),[10] the preparative goal of total synthesis is by far not the only output that can be expected from such projects. First, challenging total syntheses closely correlate with the development of modern robust and reliable synthetic methods, many of which were developed and applied by Reisman and co-workers. Second, working on natural product synthesis leads to the preparation of complex synthetic intermediates that can be natural product analogues for additional prospects in biology. This is particularly relevant with such biologically active series. Third, the comparison of synthetic compounds with the natural products can occasionally lead to structure revision. This is a striking result of this new work: to revise the stereochemistry of liljestrandisine, initially reported as **2**, into structure **4**. Fourth and to conclude this discussion, there is well-established evidence that the field of total synthesis participates in the education of the next generation of organic chemists. In that context, synthetic targets as complex as the C_{19} DTA natural products certainly offer one of the best playgrounds to stimulate our creativity and challenge our capabilities.

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