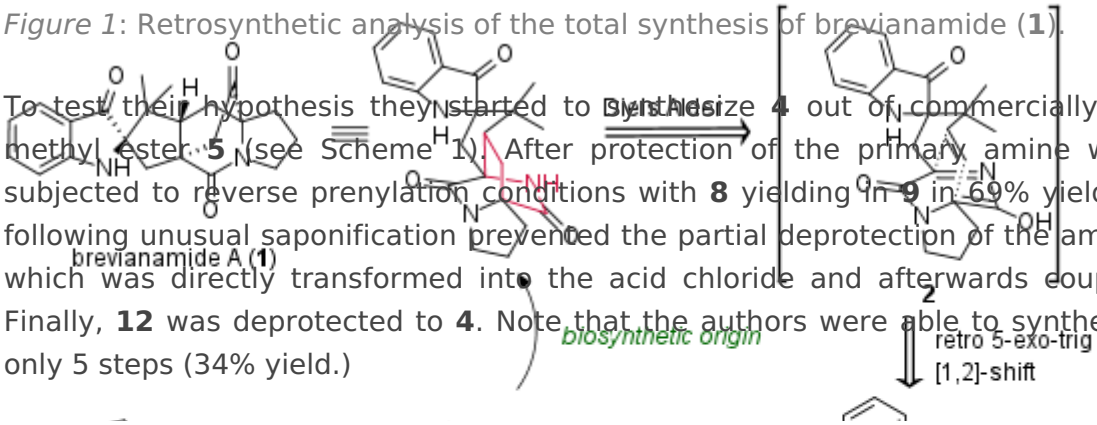
Bioinspired Total Synthesis of Brevianamide (A. Lawrence, 2020)

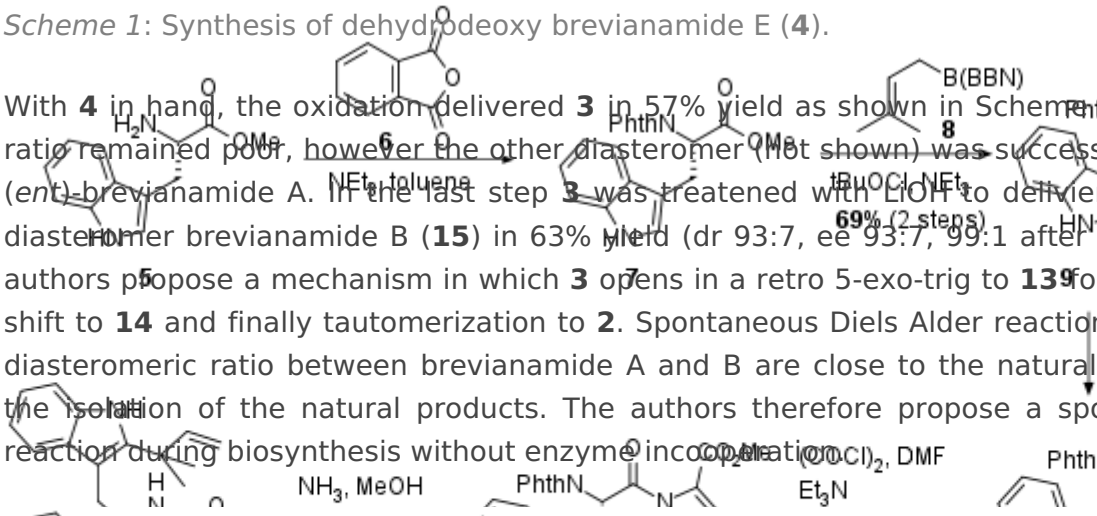
Although already isolated by Birch *et al.* in 1969, it took 50 years for the first total synthesis of brevianamide A (**1**). Published in Nature Chemistry from the research group of Andrew Lawrence (University of Edingburgh, Scotland, UK), the authors not only present a synthetic access, they also make a new proposal for the biosynthetic origin of this complex alkaloid. As shown in Figure 1, they envisioned that the oxidation of the natural occuring dehydroxydeoxy-brevianamide E (**4**) could deliver **3**. This intermediate then should undergo a retro 5-exo-trig cyclixation and a [1,2] alkyl shift yielding in Diels Alder precursor **2**.

Figure 1: Retrosynthetic analysis of the total synthesis of brevianamide (**1**).



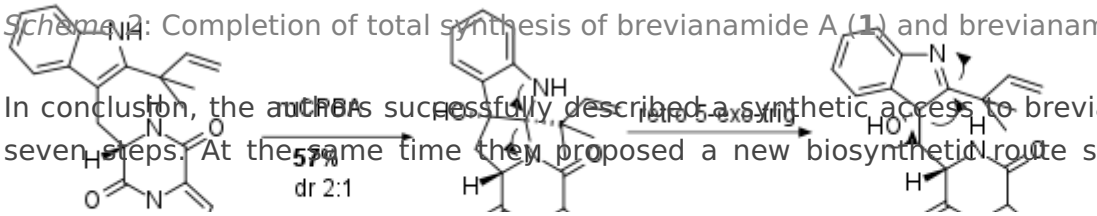
To test their hypothesis they started to synthesize **4** out of commercially available tryptophan methyl ester **5** (see Scheme 1). After protection of the primary amine with **6**, indole **7** was subjected to reverse prenylation conditions with **8** yielding in **9** in 69% yield over two steps. The following unusual saponification prevented the partial deprotection of the amine and delivered **10** which was directly transformed into the acid chloride and afterwards coupled with amine **11**. Finally, **12** was deprotected to **4**. Note that the authors were able to synthesize this precursor in only 5 steps (34% yield.)

Scheme 1: Synthesis of dehydrodeoxy brevianamide E (**4**).



With **4** in hand, the oxidation delivered **3** in 57% yield as shown in Scheme 2. The diastereomeric ratio remained poor, however the other diasteromer (not shown) was successfully transformed into (*ent*)-brevianamide A. In the last step **3** was treated with LiOH to deliver **1** together with the diastereomer brevianamide B (**15**) in 63% yield (dr 93:7, ee 93:7, 99:1 after recrystallization). The authors propose a mechanism in which **3** opens in a retro 5-exo-trig to **13** followed by a [1,2]-alkyl shift to **14** and finally tautomerization to **2**. Spontaneous Diels Alder reaction then delivers **1**. The diasteromeric ratio between brevianamide A and B are close to the natural occuring ratio during the isolation of the natural products. The authors therefore propose a spontaneous Diels Alder reaction during biosynthesis without enzyme incorporation.

Scheme 2: Completion of total synthesis of brevianamide A (**1**) and brevianamide B (**15**).



In conclusion, the authors successfully described a synthetic access to brevianamide A (**1**) in only seven steps. At the same time they proposed a new biosynthetic route starting from **4** to the

alkaloid based on their synthetic experiences.

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