



## CHEMISTRY

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## The Total Synthesis of Monoalizeamine D

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**Abstract:** We report the first total synthesis of the supernatural product monoalizeamine D via a 14-step pathway. Our synthetic approach relies heavily on photocatalysis and radical intermediates. By preparing both *E* and *Z* isomers of this compound, we have conclusively resolved the ambiguity concerning the orientation of the C15–C16 olefin.

## Introduction

The structure of monoalizeamine D has captivated chemists for decades. R. B. Woodward, the chemical savant, isolated it from the sea sponge *Gioconda vinciades* in 1975 and deduced its structure from a single UV-Vis spectrum.<sup>1</sup> It features a bold, unsaturated frame, with subtly curvaceous alkynes hinting at the vortex of steric impulses within (Fig. 1A). Delicate 6-4-5 and 8-8 ring systems nestle beneath a sumptuous hydroxydecalin core, with a cheeky furan on the side. Most striking of all are the peroxidal oxygens. These iconic chalcogens fix the viewer with a captivating stare, which seems to follow you around the room. In equal parts beguiling, provocative, wry, and melancholy, not even the sternest inorganic chemist can remain unmoved by their piquant allure, and penned one of his finest verses in their honour<sup>2</sup>:

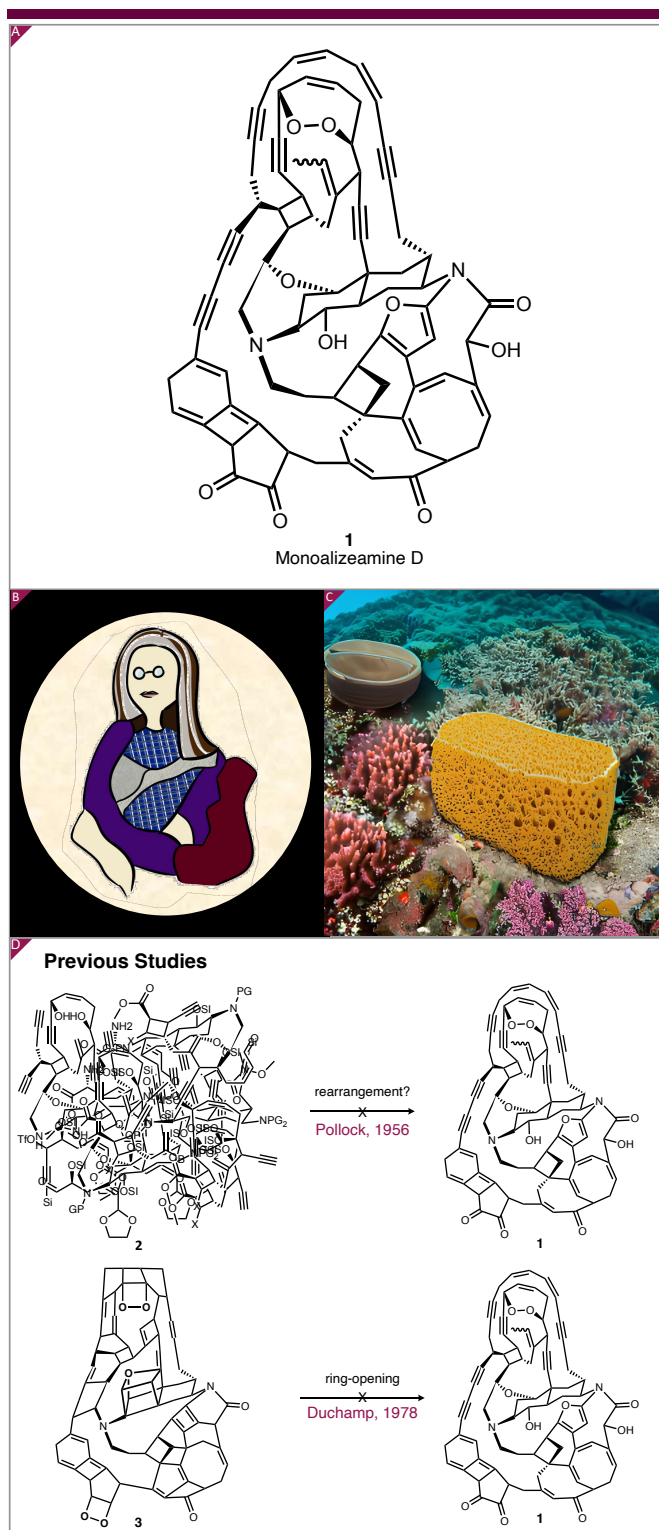
*As I browsed a journal's page  
A pair of circles caught my gaze  
The brightest eyes I'd ever seen  
In the face of monoalizeamine*

Noted artist Sasha Sundstrom immortalised monoalizeamine's countenance in "Lisa MSc." a molecular portrait created with BODIPY pigments on 5-speed Waterman filter paper (Fig. 1B). Frank Furious, on the other hand, claims that monoalizeamine looks like Alphonse Elric from Fullmetal Alchemist.<sup>3</sup>

*Gioconda vinciades* is endemic to the Venetian Lagoon, where it grows plentifully on submerged ruins, jetties and the undersides of gondolas (Fig. 1C).<sup>4</sup> The purpose for which *G. vinciades* produces the monoalizeamines is not known, but an extract of the sponge has been used as an attractant for fish since ancient times. Pliny the Elder recorded in his *Naturalis Historia* that "even a small piece [of *G. vinciades*], when placed in water, will draw copious fishes to it, which thereafter remain trancelike in their fascination with it, and thus may easily be caught."<sup>5</sup>

Monoalizeamines are psychoactive in humans.<sup>6</sup> Some test subjects report experiencing euphoria when treated with them, while others experienced a mild lachrymatory effect. However, more than 40% of test subjects experienced no effects at all, except mild irritation at having to wait in line at the clinic. More detailed studies on the activity of the monoalizeamines have been hampered by a lack of material, as the compounds are only present in minute amounts in *G. vinciades* extract.

This deficiency has been the motivation for several previous attempts at the synthesis of these supernatural products. In 1952, the Pollock group attempted to capture the essence of 1



**Figure 1:** A) The structure of monoalizeamine D, as determined by Woodward. B) "Lisa MSc." by Sasha Sundstrom. C) *G. vinciades* in the Venetian Lagoon. D) Previous attempts at the total synthesis of 1.

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in their work “*Di Poles*”.<sup>7</sup> Conducted 23 years before the structure of **1** was determined, this study began with grand aspirations but culminated in a lot of brown tar splattered over some glassware. Shortly after Woodward completed his structural assignment of **1**, the Duchamp group at La Sorbonne attempted to access monoalzeamine D via a series of ring-opening reactions from intermediate **3**.<sup>8</sup> The strain energy of the central oxocubonium proved too great to control, however, and again the synthesis was unsuccessful.

We envisaged a linear synthesis, building first upon a stark and minimalist canvas, thenceforth layering complexity and detail into the molecular structure. A successful synthesis of Monoalzeamine D must be, by definition, radical. As such, we anticipated the frequent use of single-electron pathways and photocatalysis. We drew inspiration from chemists noted for their use of light, such as Micky Caravaggio, Pawlski Cézanne and Pete Ruben, in the design of our synthesis.

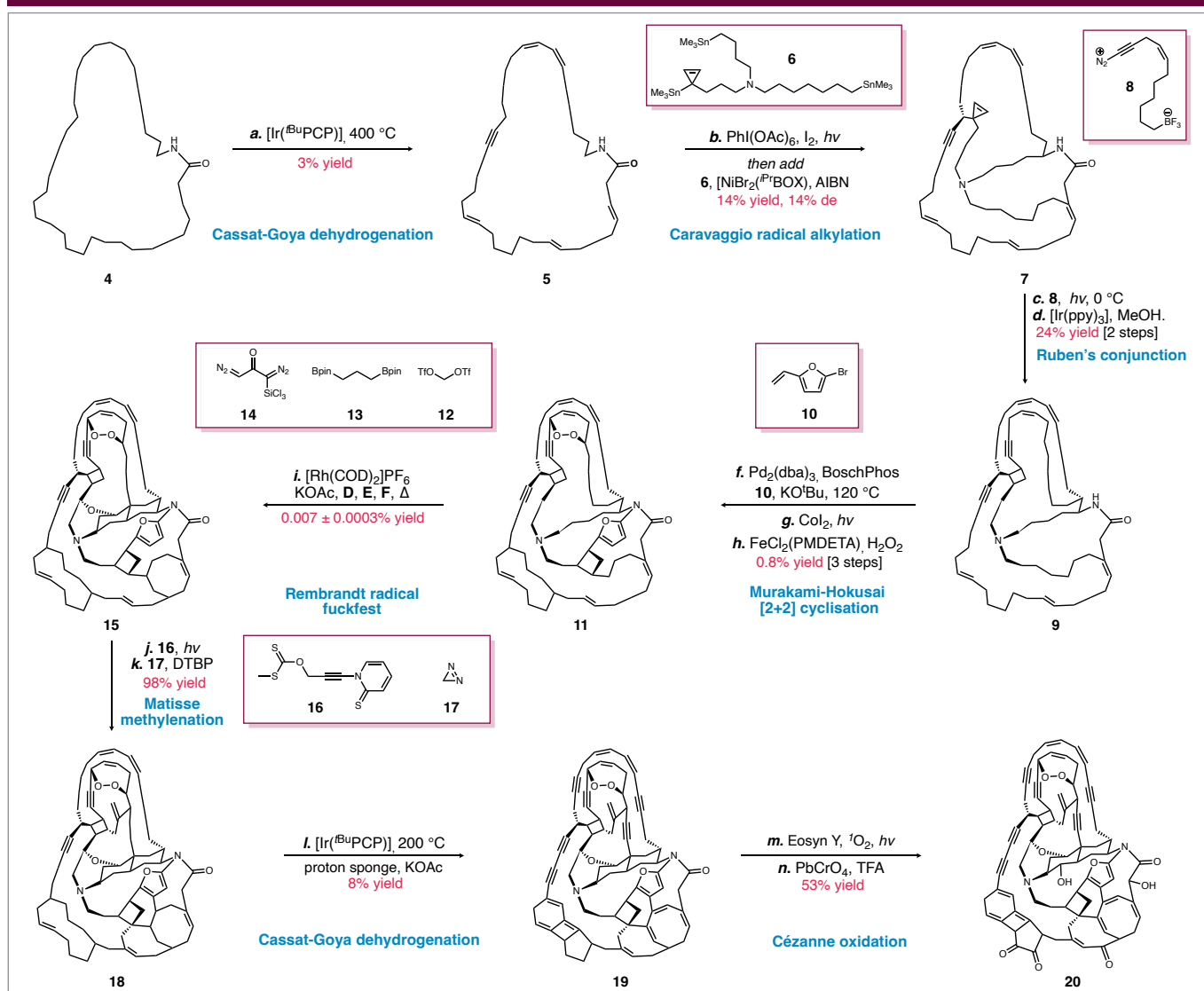
Our synthesis began with rothkolactam (**4**), which was subjected to a Cassat-Goya dehydrogenation (Scheme 1). This transformation installed akenes and alkynes at random positions around the ring. Isolation of the desired product (**5**) was accomplished by preparatory scale gas chromatography. With this reaction accomplished, the time had come to draw the rest of the fucking owl.<sup>9</sup>

This process began with Caravaggio’s asymmetric radical alkylation, which installed the broad features of **1**’s profile. Ruben’s conjunction with zwitterion **8** outlined the face, and a subsequent Cluckwald-Birchtwig coupling installed the furan. Hironimus’ BoschPhos ligand was essential to the success of this reaction. A cobalt catalysed Murakami-Hokusai [2+2] cyclisation generated the second cyclobutane ring, and a Fenton-type oxidation installed the eyes.

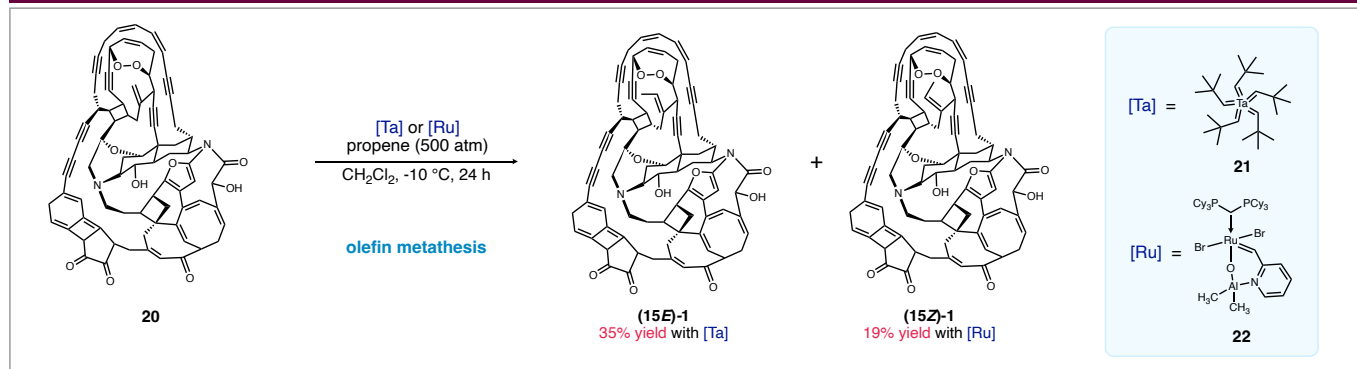
With the outlines of **1** now established, it was necessary to fill in the details. Regrettably, this required the use of Rembrandt’s radical fuckfest reaction, which goes exactly like it sounds. A prime example of directionless C-H activation, preparatory GC was insufficient to purify the product (**15**) of this reaction, and we had to resort to preparatory mass spectrometry.

Matisse’s methyleneation was used to round off the left hand, and Munch ester **16** was employed to sketch monoaleziamine’s jawline. A second dehydrogenation, this time under milder conditions was used to install the remaining alkenes and alkynes, and a final pair of oxidations delivered the penultimate intermediate (**20**).

With **20** in hand, we proceeded to investigate the enigmatic nature of the C15–C16 olefin. Even the mighty Woodward was unable to definitively assign an *E* or *Z* configuration from the UV-Vis data available to him. Later spectroscopic studies have also



**Scheme 1:** The 13-step synthetic sequence to reach penultimate intermediate **20**. This highly radical chemistry makes use of light in both visible and invisible shades to accentuate the reactivity at targeted sites around the molecule. Both organic and metallic pigments have been blended to achieve this goal.



**Scheme 2:** The olefin metathesis of compound **20** to form both isomers of monoalizeamine D. Schreck-type tantalum complex **21** was selective for the *E* isomer, and Darthoveyda–Grubbs Catalyst® M107 was selective for the *Z* isomer.

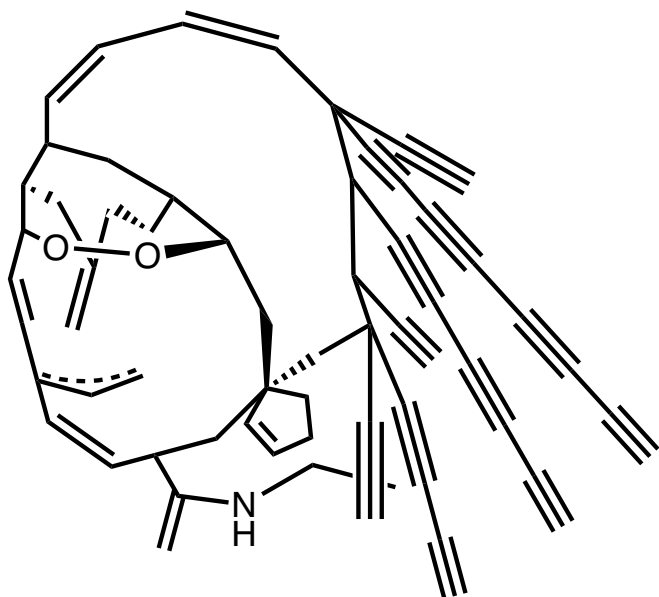
been inconclusive, as the crucial  $^1\text{H}$  NMR signals are obscured by “every other fucking alkene in that god-awful molecule”.<sup>10</sup>

The final step in our synthetic sequence was an olefin metathesis with propene, to install the olefin described above. After considerable optimisation, we found we were able to obtain acceptable selectivity between the *E* and *Z* isomers of **1** with careful choice of catalyst (Scheme 2). Schreck-type complexes such as **21** delivered (15*E*)-**1** as the predominant product, while Darthoveyda–Grubbs Catalyst M107® (**22**) gave primarily 15*Z*-monoalizeamine D.

The  $^1\text{H}$  NMR spectra for both products look like the Swiss alps in profile, but deconvolution with the chemical AI “Chat- $\text{C}_{sp^3}$ ” allowed us to match the *E*-isomer of our product with an authentic sample of monoalizeamine D.

### Conclusion

We have conducted the first successful synthesis of monoalizeamine D in  $2.3 \times 10^{-11}\%$  yield over 14 steps. We have also determined that naturally occurring monoalizeamine D is the 15*E* isomer, which resolves the long-running controversy regarding the enigmatic nature of monoalizeamine’s smile. Future work in our group will focus on the synthesis of the other monoalizeamines. Work on monoalizeamine A (aka “The Girl with the Cyclopentene”, Fig. 2) is currently underway in our laboratory.



**Figure 1:** The Girl with the Cyclopentene.

### Acknowledgements

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### Conflicts of Interest

G.S. admits that he proof-read this manuscript in some haste, as he was running late for the pub.

### Notes and references

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