Total Synthesis of the Lycorenine-Type Amaryllidaceae Alkaloid (±)-Clivonine via a Biomimetic Ring-Switch from a Lycorine-Type Progenitor

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Amaryllidaceae Alkaloids

- Amaryllidaceae family: ca. 85 genera and 1100 species distributed throughout tropic and warm temperate regions

- Widely used in folk medicine

- Nearly 500 structurally diverse alkaloids isolated so far

- 18 different skeleton types

- Biological activities: antitumor, antibacterial, antifungal, antimalarial, antiviral, analgesic and AChE inhibitory activity

- Biosynthetically originate from norbelladine

Clivonine:
- Isolated from Clivia miniata (bush lily) in 1956 by Wildman
- Structure determined by Jeffs in 1971


http://en.wikipedia.org/wiki/Amaryllidaceae
Sir Derek H. R. Barton

- Conformational analysis (Nobel prize 1969)
- Discovery of cis-elimination
- Photochemical reactions (synthesis of aldosterone by nitrite photolysis)
- Radical chemistry: Barton-McCombie deoxygenation
- Radical decarboxylation

Barton’s hypothesis (1957): Phenolic oxidative coupling is critical diversifying step in alkaloid biosynthesis!

Pumerer’s ketone structure

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\text{Barton, D. H. R. Some Recollections of Gap Jumping, American Chemical Society: Washington 1991.}
\]
Biosynthesis of Morphine

Robinson, 1931.

Schöpf, 1952. (based on the wrong structure of Pummerer's ketone)

Barton and Cohen (1957)

Bentley, K. W. Kurtze Mitteilungen – Brief Reports 1956, 251.
Biosynthesis of Tazettine and Lycorenine-Type Alkaloids

- Norbelladine is biosynthesized from tyrosine and phenylalanine
- Further transformations of norbelladine first proposed by Barton in 1957 – tazettine is formed by intermolecular phenolic coupling
- Revised in 1960 – “ring switching” proposed
- Confirmed by Wildman by tritium feeding experiments
- Biomimetic protocol for the synthesis of pretazettine known since 1969
- No biomimetic protocol for the conversion of lycorine to lycorenine-type skeleton until now

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Wildman’s Biomimetic Conversion of Haemanthididine to Tazettine and Pretazettine

Irie’s Synthesis of Clivonine

Oppolzer’s Synthesis of (+)-Trianthine

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Conclusions

• Total synthesis of (±)-clivonine was achieved in 12 steps (6.1% overall yield)

• Biomimetic transformation of lycorine-type intermediate to lycorenine-type product corroborated Barton’s 50 years old hypothesis

• Synthesis of other members of this type of Amaryllidaceae alkaloids is currently being explored

• Sir Derek H. C. Barton on alkaloid biosynthesis:

  “…the last paper on this subject was in 1974. One day this theme will be developed elsewhere. It was, however, very satisfying to see how much elegant work came out of my original disbelief in the long-accepted formula of Pumerer’s ketone.”