10-2017

Progress toward the Development of a "Catch/Release" Strategy for Isolating Salvinorin A, From Plant Materails Including Microwave Promotion

Douglas Armstrong
Olivet Nazarene University, darmstrg@olivet.edu

Logan Smith

Progress Toward the Development of a "Catch/Release" Strategy for Isolating Salvinorin A From Plant Materials, Including Microwave Promotion

Dr. Douglas Armstrong and Logan Smith
Olivet Nazarene University
Bourbonnais, IL 60914
darmstrg@olivet.edu/815-939-5393

MACTLAC 2017: The 65th Annual Meeting of the Midwest Association of Chemistry Teachers in Liberal Arts Colleges, Oct. 13-14

Proposal and Background

We are investigating using the Diels-Alder (DA) and the retro-Diels-Alder (RDA) reactions as a potential "catch/release" strategy for isolating Salvinorin A from plant samples (Salvia divinorum), hopefully to improve the current method of isolating it, which is very long and laborious. The background for our work is related to the work of Tom Prisinzano (1). Erin Carlson developed a "catch/release" strategy for isolating natural products containing –OH groups, in which alcohols, or phenols, or carboxylic acids are bound to a polymer, which is then rinsed with certain solvents, and then the original compound is released (2). Yli-Kauhaluoma published a review of many DA reactions carried out on solid supports (3).

The synthesis of Salvinorin A is also very long (20 or more steps). (4)

Discussion

Salvinorin A has analgesic activity by activating the kappa opioid receptor, not the mu receptor (1), and thus it has potential for being developed into a non-addicting analgesic.

Strategy and Progress Report

Our strategy focuses on the DA reaction involving the furan ring of Salvinorin A (Fig. 1), as the "diene", with polymer-bound DEAD (Fig. 2) (diethyl azodicarboxylate), as the dienophile, which is extremely expensive. See below.

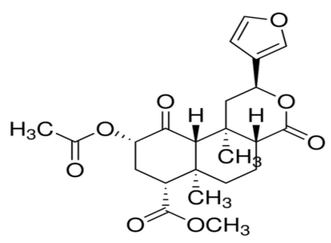


Fig. 1: Salvinorin A

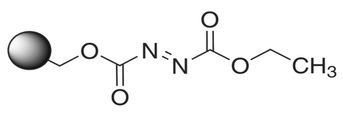


Fig. 2: Polymer-Bound DEAD

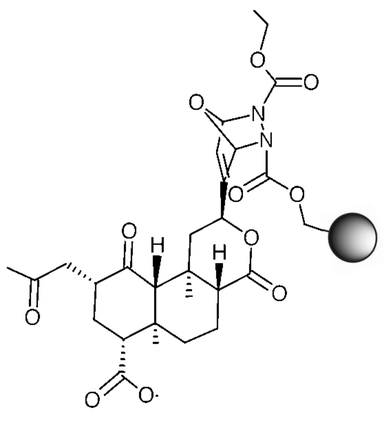
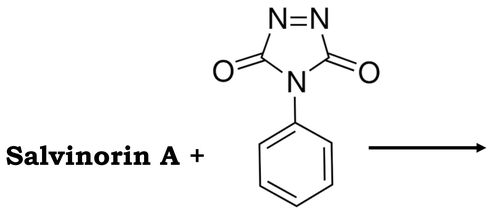


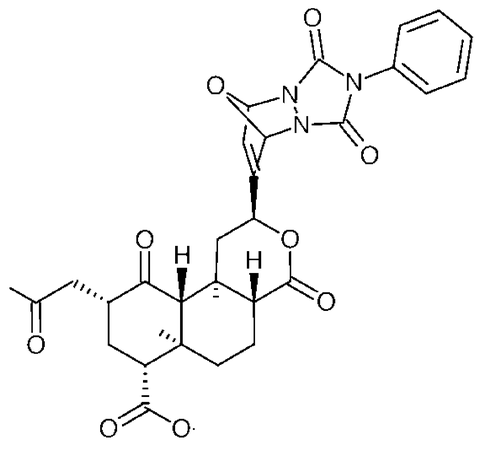
Fig. 3: Polymer-bound Salvinorin A

Hopefully, our expected product (polymer-bound Salvinorin A, Fig. 3), will allow extraneous compounds and other substances to be rinsed away with suitable solvents, and then hopefully RDA can produce quite pure Salvinorin A. Progress so far includes the IR of the product which lends support to that product, but which we have not had time to fully prove yet.

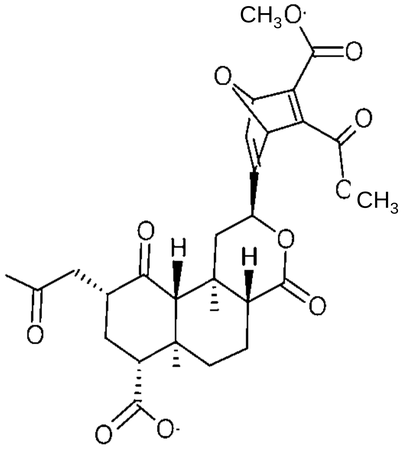
Prior to doing the above work, we did a "pilot" study, in which we ran DA reactions on Salvinorin A with various dienophiles. One example is the closely related 4-phenyl-1,2,4-triazoline-3,5-dione, PTAD, below, with the expected product shown below, for which we have some evidence (e.g., red color of PTAD disappearing, even at room temperature, and the disappearance of the 1745 cm^{-1} IR peak of PTAD), but not enough time for complete proof of the product.



(PTAD)



Another dienophile example was dimethyl acetylenedicarboxylate, similar to Prisinzano's work (1) with microwave promotion, using our Biotage "Initiator" model microwave instrument, with the product (below) being suggested by IR data, but not enough time for complete proof.



Future Research

We now need to finish the proof of the polymer-bound Salvinorin A, and then do the RDA reaction on it. If that fails, we will try the same process using polymer-bound dimethyl acetylenedicarboxylate.

Another future endeavor would be to treat polymer-bound DEAD with an extract of the plant (Salvia divinorum) which was unavailable to us.

References

1. Tom Prisinzano (et al.) : Journal of Natural Products, 2011, 74, 718-726.
2. Erin Carlson (et al.) : Chem. Sci., 2011, 2, 760; Org. Lett., 2011, 13, 5652; and Mol. Biosyst., 2012, 8, 2484.
3. Yli-Kauhaluoma, Tetrahedron, 2001, 57, 7053-7071.
4. Jonathan R. Scheerer, et al., J. Am. Chem. Soc, **2007**, 129 (29), 8968-8969.

Acknowledgements

- ONU Honors Program for undergraduate students
- HCIR Margaret Messer Student Research Grant
- Dr. Tom Prisinzano, University of Kansas