Synthesis of Deuterated-(C9)-11-*cis*-Retinal

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Introduction

It has been shown that the dimerization of 2 vitamin A molecules with an Ethanolamine molecule leads to the formation of a molecule labeled as A2E. The latter is a phototoxic molecule and has been shown to be a major contributor to the detrimental eye condition, Age-related Macular Degeneration, AMD (1). Even though vitamin A dimerization is a contributor to this AMD condition, vitamin A is the very molecule that is necessary and key for human vision, hence it cannot be eliminated. It is been demonstrated experimentally that once carbon 20 of vitamin A was deuterated, the dimerization of vitamin A was reduced (1). Synthesis of retinal, one of many forms of vitamin A, has been well established (2, 3) and can be used to study vitamin A structure. Using similar synthetic routes and methods, we were able to introduce deuterium on carbon 9 of 11-*cis*-retinal.

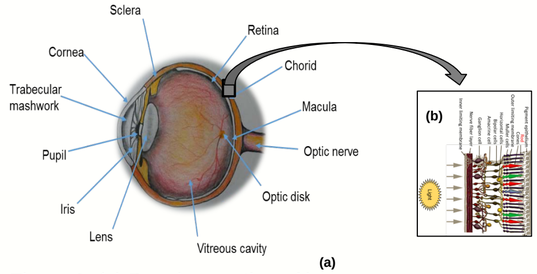


Figure 1. (a) Drawing section of human eye. (b) Schematic enlargement of the retina (5).

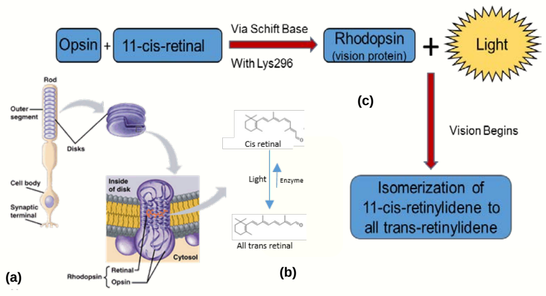


Figure 2. (a) Rod and schematic enlargement of rod disk (6). (b) *cis* and *trans* retinal. (c) Scheme on how vision begins.

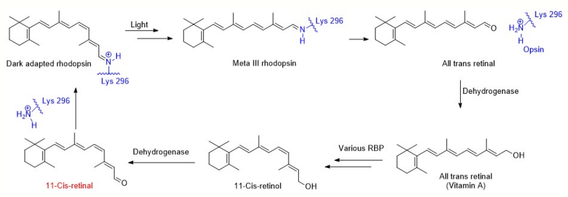
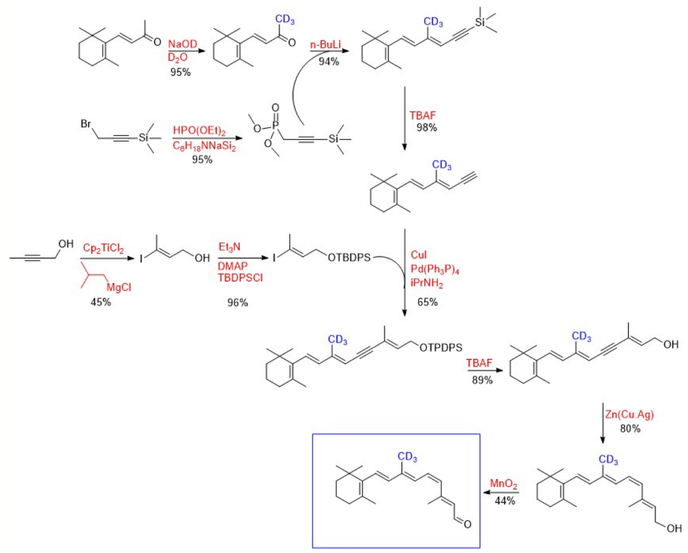


Figure 3. Mammalian visual cycle.

Methods

There are ten steps in total to make β-ionone into deuterated-(C9)-11-cis- retinal (Scheme 1).



Scheme 1. Synthetic route

Results and Discussion

The deuteration of C9 of β-ionone was highly successful. The singlet representing the methyl group of C9 seen prior to deuteration completely disappeared once C9 was deuterated indicating that the deuteration of C9 was completely done.

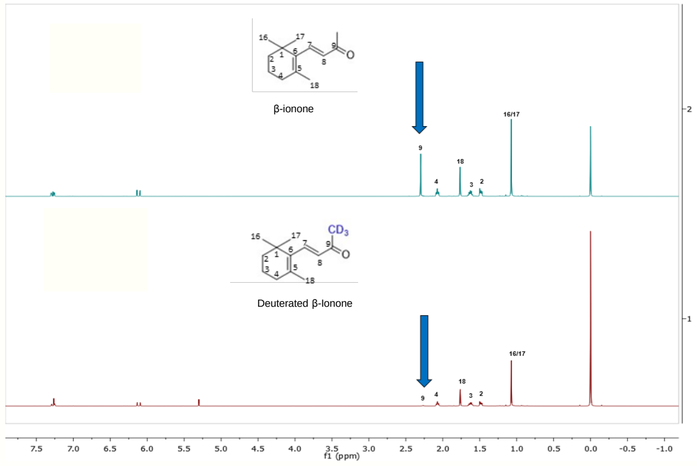


Figure 2. NMR characterization of β-ionone and deuterated β-ionone.

The last step was successful on given the right product; however, the yield was low (45%). This indicates that the oxidation agent used (MnO_2) was not the best fit for this reaction.

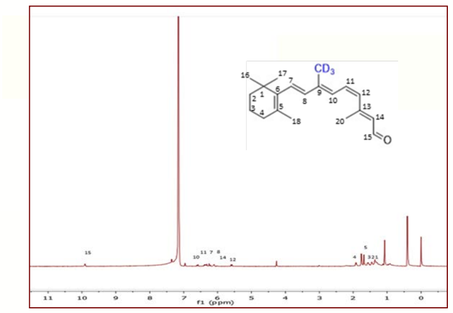


Figure 4. NMR characterization of the final product: deuterated (C9)-cis-Retinal.

Conclusions

The final deuterium enriched product resulting from this project was successfully used by our collaborators at the University of Arizona: Professor Michael F Brown and his group to study biochemical interaction between the binding pocket of rhodopsin and its covalently bound ligand, retinal, using solid state NMR (4).

Improvements

Tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine N-oxide (NMO) are better oxidation agent (2) than MnO_2 used on the last synthesis step. Therefore, the yield for the final product will be improved.

Future Experiments

- Deuteration of retinal could be experienced in different carbons;
- Retinal synthesized in this experiment could be analyzed under different lights in order to farther understand the behavior of retinal in light.

Acknowledgements

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