

Title: Synthesis of new chiral *cis*-cyclooctenes

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Date: January 2020

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Trans-cyclooctenes (TCOs) have been used for many different applications e.g., as a probe compound for labelling in live cells, radiochemistry and for the creation of patterned hydrogels and biomimetic fibres. The number of applications with TCOs has increased the need for TCO production on large scale. The way to get them is with a click reaction with a tetrazine because this reaction is the fastest known; the rate is $k = 3.3 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ in water at 25 °C.

Click reactions can be bioorthogonal and nowadays, this field is being used a lot. The concept of click chemistry refers to attach a substrate of interest to a specific biomolecule. In our case, an inverse electron demand Diels-Alder reaction (IEDDA) is used (see Figure 1). IEDDA is a cycloaddition between an electron-rich dienophile and an electron-poor diene and possesses both fast kinetics and bioorthogonal properties. Therefore, it is one of the most relevant click reactions for *in vivo* applications.

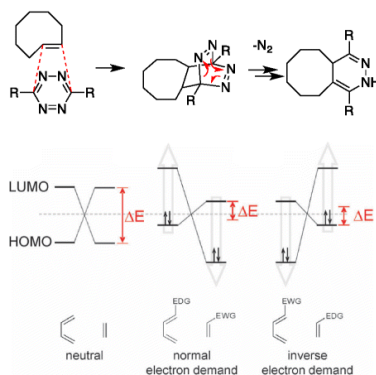


Figure 1. Mechanism of IEDDA and orbital interaction explanation of the inverse electron reaction better than the normal one.

As we can see in Figure , electron withdrawing substituents attached to the TCO confer increased reaction rates between the dienophile and diene because the HOMO orbital has less energy than without a withdrawing group.

The goal of this research was to synthesize novel bi-functionalized CCOs with one of the substituents on the allylic position (see Figure 2). Once the CCO is obtained, the obtention of TCO to do the click reaction with a tetrazines is easier than the other way around.

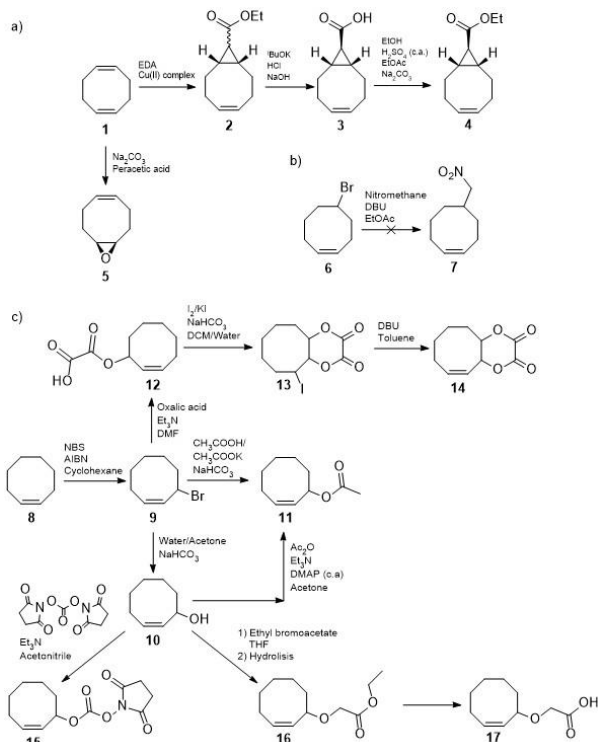


Figure 2. a) All the synthetic routes done from the 1,5-cyclooctadiene to get different TCOs. These procedures were taken from another student. b) Reaction to include the nitrate as a substituent on the TCO. c) All the synthetic routes done from the *cis*-cyclooctene to get derivate TCOs.

Almost all of the molecules were gotten. The bromination was quite successful with a 44% of yield, which was because of the volatility of this compound. The hydrolysis finally was obtained with a very quickly procedure with a 62.5% of yield. The acetate was better obtained from the bromide than from the alcohol because the reaction takes only 4 hours head-on 16 hours. The yield was around 65%.

After all, the Fischer esterification of oxalic acid with (*Z*)-3-bromocyclooct-1-ene seemed to work. The yield was 48%. Unfortunately, the activated ester with the N,N'-disuccinimidyl carbonate was not gotten pure because another side-product was too close to the desire product. Finally, compound **17** was not gotten because there was not more time to do it.