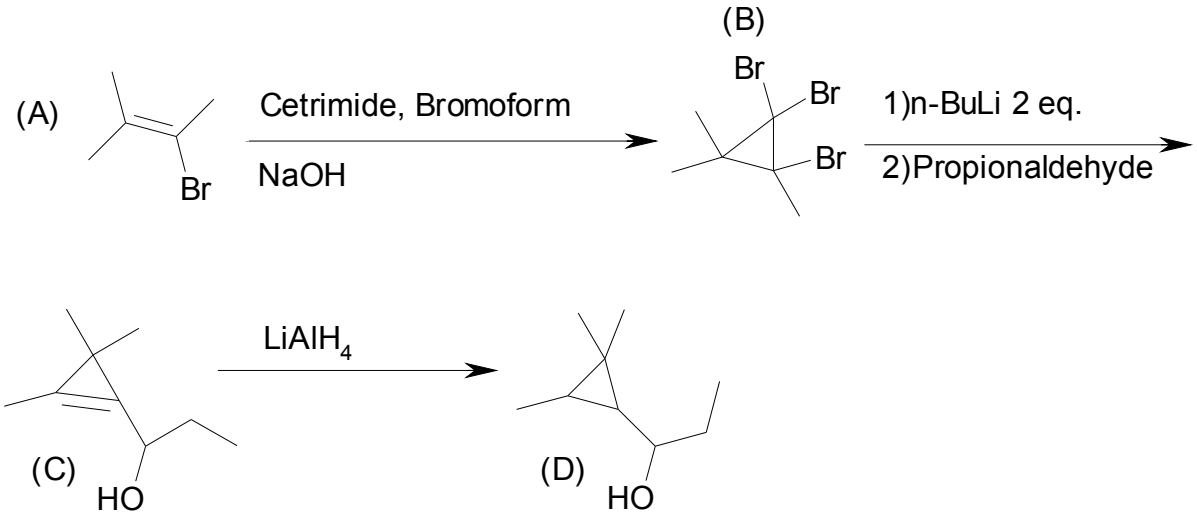
# Final project in the course of Organic Chemistry
## Lab 2:
## The diastereoselective preparation of 1-(2,2,3-trimethyl-cyclopropyl)-propan-1-ol

By: Azazel
ID: 5717
Tutor: TA that thinks that I don't know jacksh$%.

# A general description of the project:



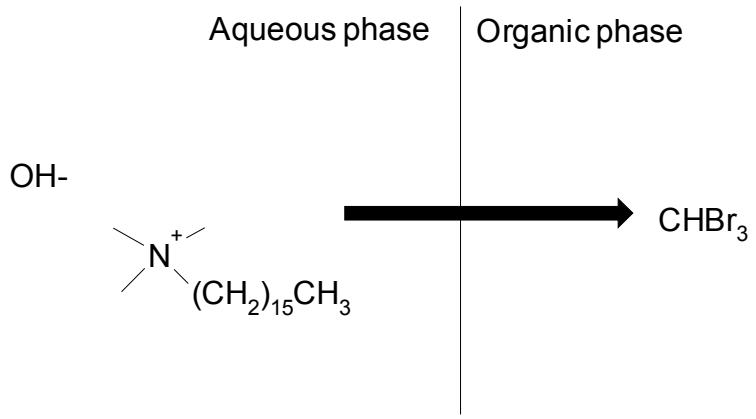

# Introduction:

The goal of the project was to synthesize a tetra-substituted cyclopropane in a diastereoselective manner. The best way to accomplish this is by the reduction of the suitable cyclopropene (C) by $LiAlH_4$, in the proper solvent. (C) is the product of the lithiation of (B) by lithium-bromine exchange (with the first eqivalent of n-BuLi creating the double bond, and the second one creating the reagent), and the following reaction of the organometallic reagent with Propionaldehyde.(B) in it's turn is synthesized by the reaction of the reaction of (A) with Bromoform in a very basic enviroment (~25M NaOH in the aqueous phase). The Creation of the needed carbene was accomplished by using a Phase Transfer Catalyst, Cetrimide.

## **Stage I:** The preparation of 1,1,2-tribromo-2,3,3-trimethylcyclopropane (B)

### **Description of the experiment:**

The phase transfer catalyst, cetrimide is an ammonium salt. The quarternary ammonium cation establishes a non-covalent bond with the hydroxide anion, and the long aliphatic chain enables it to enter the organic phase undisturbed.

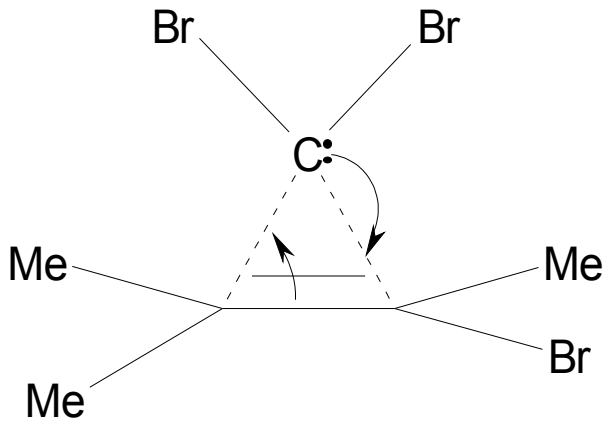



After the trasnfer of the hydroxide ion into the organic phase by the PTC, a pretty straightforward deprotonation of the Bromoform occurs by the hydroxide, and the anion C $Br_3$- is created. A Bromide anion leaves , and the carben C Br2 is created(1), with the bromide leaving for the aqueous phase.

$$CHBr_3 + OH^- \longrightarrow CBr_3^- + H_2O$$

$$CBr_3^- \longrightarrow CBr_2: + Br^-$$

What follows is the creation of the polysubstituted cyclopropane (B) (1):




The reactive carbene lone pair creates a bond with an vinylic carbon, while the electron pair that creates the π bond on the olephine shifts to a bond with the carbene.

**Experimental[2]:**

-a solution of 2-bromo-3-methyl-but-2-ene (3.215 gr, 2.5ml) and cetrimide (0.33 gr) in Bromoform (33 ml) was created in a 100(ml) flask, and rapidly stirred.
-Sodium Hydroxide (6.5gr) was dissolved in water ( 6.5ml), and then added to the flask.
-The Combined phases were put for 3 hrs at 65°C, and later were extracted by dicholormethane (3x15 ml), dried over $MgSO_4$.
-The solvent was removed at 100 (mmHg), and a crude sample was analyzed by NMR spectroscopy (Suppliment 1A).
-The product solution was purified by coloumn chromatography on silica gel with hexane as eluent, and a second NMR sample of the solution was sent. ( Suppliment 1B).
-The remaining solvent was removed at ( $10^{-2}$ mmHg), and the product was recrystallized.

**Results:**

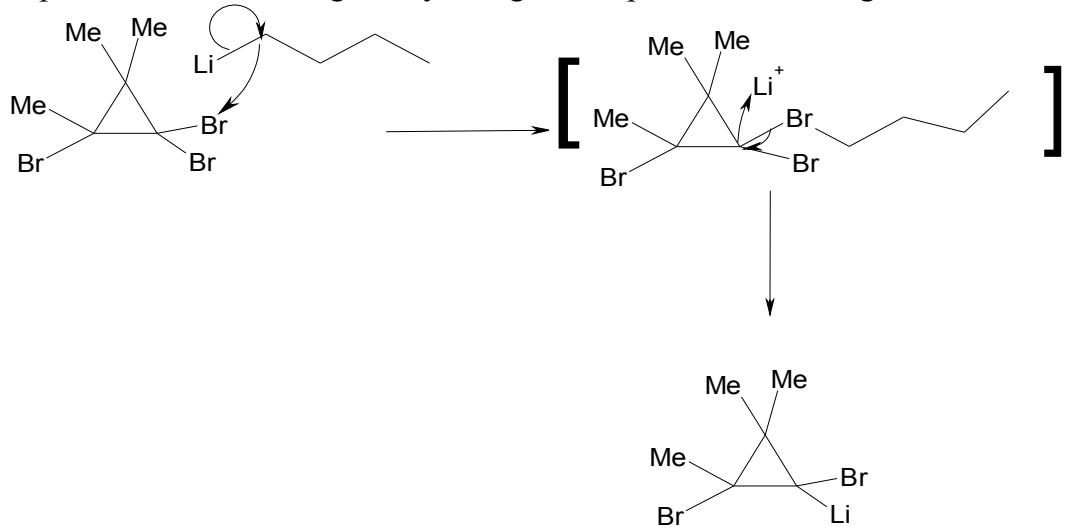
-from the 1st and the 2nd NMR samples, it'se quite easy to see we have got our product (B) in a bromoform solution. A rather strong vacuum was needed to evaporate the solvent.
-We've got 2.6 (gr) recrystallized, which at the MW of ~321(gr/mol) gives us 8.1(mmol) of product, and at 21.5(mmol) of reactant that gives us a yield of 37.6%, which is substantially lower than the one documented in the literature[2] . This can be explained by the differing methods of product purification, and recrystallization:for example, the high vacuum extraction of bromoform, and no recrystallization in ethanol as documented. No purification by coloumn chromatography is documented in literature, as well[2].

## Stage II: The preparation of 1-(2,2,3-trimethyl-cycloprop-1-enyl)-propan-1-ol (C):

**Description of the experiment:**

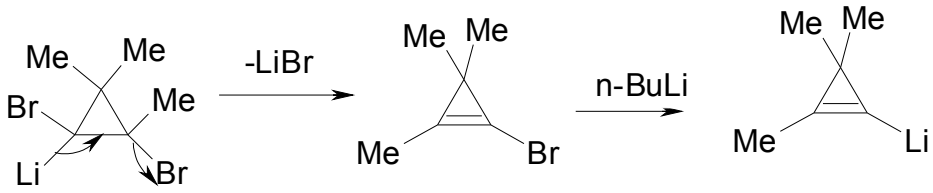
The exact mechanism of the lithium-Bromine exchange in alkyl halides is not yet fully described, some experimental evidence points to the radical-driven Single Electron Transfer mechanism while other evidence, like stereochemistry suggests a polar mechanism[3], unlike Aryl halides, in which the "ate-complex" is considered generally the more accepted one.

If we follow the ate-complex mechanism, the lithium is heterolytically separated from the butyl group, which creates a negatively charged complex with the reagent.

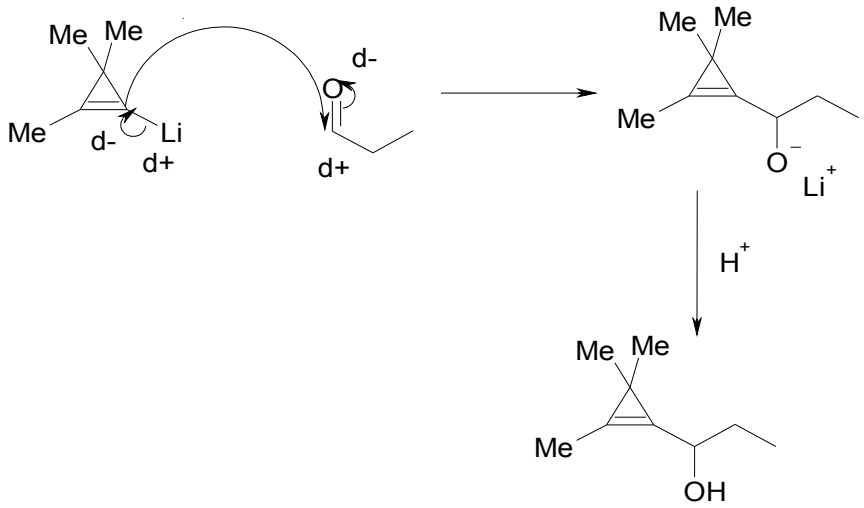



The initial creation of the complex through the bromine that has another bromine in the geminal position is preferred due to the stabilization of the negative charge by the geminal bromine, a σ-acceptor.

At that point, the electron pair on the lithium leaves and creates the π bond, and the bromine recieves it's bond electrons, and leaves. The ate complex mechanism is then repeated on the last remaining bromide group through the second equivalent of n-BuLi.




At this point, the propionaldehyde is added to the mixture, and a simple nucleophilic attack occurs on the Carbonyl group of the aldehyde, and the quenching of the reaction with water completes the process.




## **Experimental[4]:**

-6.7 (ml) of a 1.4(M) solution of n-BuLi in hexane were continuously added to a stirred solution of 1,1,2-tribromo-2,3,3-trimethyl-cyclopropane (1.3gr, 4.1mmol) in $Et_2O$ (25ml) under constant positive pressure of Argon at -80ºC.

-The mixture then heated up to -10ºC, and after 1 hr at that temperature, was cooled back to -50ºC.

-Propionaldehyde (0.5ml) was added to the mixture, and the mixture was kept at -50ºC for additional 15 mins, and then left at room temperature for 3 hours.

-The mixture was then quenched by 10ml of water, and the aqueous was extracted with $Et_2O$ (10ml x3).

-The combined organic layers were then washed with water ( 2x10 ml), dried over $MgSO_4$, and the solvent was extracted at 100 (mmHg). A crude sample was sent to NMR spectroscopy, and the spectrum was analyzed. ( Suppliment 2A).

-The product was purified by coloumn chromatography over silica gel, using hexane/ethyl acetate 15:1 mixture as eluent.

-The phases were combined in a previously weighed flask, and then were evaporated at 100 (mmHg). the flask was weighed once again, to measure the weight of the product, to calculate yield. The weight differential was 0.23(gr), putting the yield of the reaction at 52.8% . A sample of the purified product was sent to NMR spectroscopy ( Suppliment 2B).

**Results:**

-The product weighed 0.23 (gr) at 140(gr/mol), the yield is 52.8%

-While a weight differential was measured, the quality of the yield result is questionable to say the least: The weight measurement varied depending on the used instrument, and a more precise instrument was unable to measure the weight of the big flask that was used to colected the eluent from the coloumn.

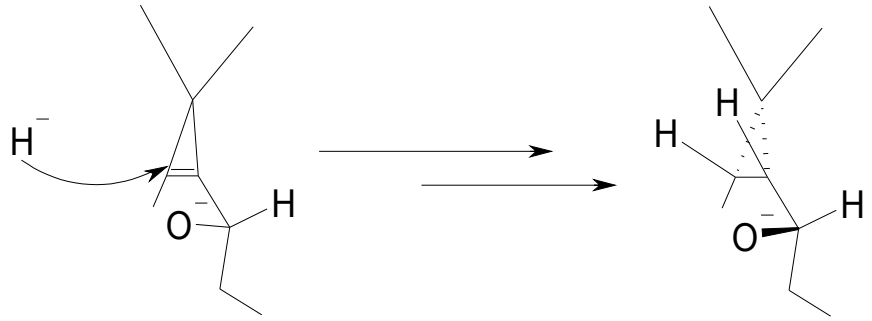
-The NMR Spectrum shows clearly the presense of the product ( Supp. 2A, 2B). However, it also shows impurities, which render the yield incorrect.

-In any case, the amount of product of this stage is clearly insufficient to proceed with the last stage. Thus, the next stage will be described in a purely theoretical manner.

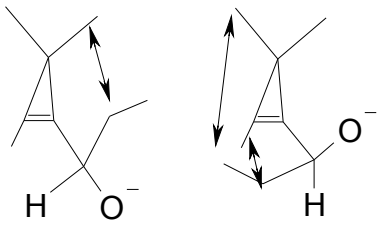
## **Stage III:** The diastereoselective preparation of the *anti* cyclopropyl alcohol (D):

**Description of the experiment:**

The reduction itself is produced by hydride anions from $LiAlH_4$,which is able to reduce double bonds if they're close to polar groups, while the diastereoselective guidance for this reduction reaction is created by the steric interference of the ethyl group. The oxygen angle ( the oxygen will be deprotonated by the hydrides prior to the beginning of the reduction of the double bond) thus is the most suitable to the reduction of the double bond.




This is because the alternative configuarations needed for the creation of the syn stereoisomer have steric collisions in them between the alkyl groups[4]:




(the arrows represent the steric collisions in an arrangements needed for the creation of the syn isomer)

## Suppliment 1A:

(H-NMR peaks of (B) given by the literature(2

1.98,s,3H
1.50,s,3H
1.36,s,3H

Peaks on the H-NMR Spectrum (all numbers are in ppm):

1.184
1.303 , s, 1H <-product
1.449 , s, 1H <-product
1.502
1.687
1.789
1.794
1.936, s, 1H <-product
2.207
5.238 <-dicholoromethane
~6.755 m >>1H <-bromoform

## Suppliment 1B:

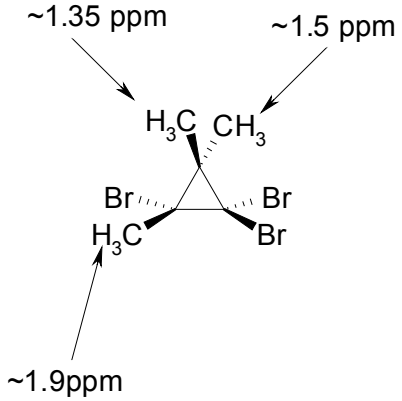
(H-NMR peaks of (B) given by the literature(2

1.98,s,3H
1.50,s,3H
1.36,s,3H

Peaks on the H-NMR Spectrum (all numbers are in ppm):

1.339, s, 1H <-product
1.482, s, 1H <-product
1.972, s, 1H <-product
~6.793 m >>1H <-bromoform.

In both cases, the values of the theoretical H-NMR cannot be calculated through charts, and thus, assigning the peaks to the proper hydrogens takes some educated guesswork:
The hydrogens on the methyl which has a Bromine in the geminal position will probably experience the biggest electron de-shielding, and thus will be further downfield. (~1.9 ppm). Whilst the the ones sitting geminally on the methyl will be upfield.



## Suppliment 2A:

H-NMR peaks of (C) given by the literature(4):
0.93,t,3H
1.08,s,6H
1.64,q,2H
1.97,s,3H
4.5,t,1H

approx. Peaks on the crude NMR Spectrum ( most peaks are multiplets, due to impurities, and the remaining Di-ethyl ether):

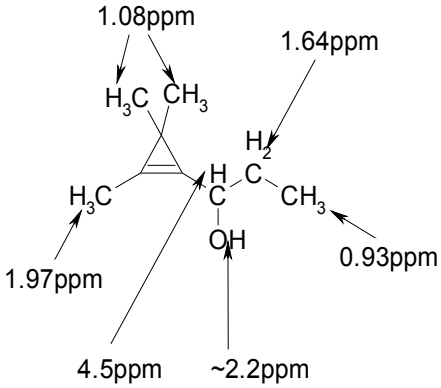
| | |
|---|---|
| 0.02 | <-silicon grease |
| 0.94 | <-product |
| 1.1 | <-product |
| 1.6 | <-product |
| 1.95 | <-product |
| 3.4 | <-$Et_2O$ |
| 4.49,t | <-product |

## Suppliment 2B:

H-NMR peaks of (C) given by the literature(4):
0.93,t,3H
1.08,s,6H
1.64,quintet,2H
1.97,s,3H
4.5,t,1H

Peaks on the H-NMR Spectrum (all numbers are in ppm): ( the solvent/eluent mixture is ethyl acetate, and hexane )

| | |
|---|---|
| 0.027 | <-silicon grease |
| 0.87,t+?, Integr.:9.094 | <-product overlapping remains of eluent. |
| 1.04,d+s ,Int:7.634 | <-product overlapping remains of eluent |
| 1.23 m | <-remains of eluent |
| 1.35 m | <-remains of eluent |
| 1.5 | |
| 1.51 quintet+? Int:2.832 | <-product |
| 1.97 s+? Int:4.528 | <-product |
| 2.2 (?) | <product (-OH)? |
| 3.4 (unmarked) | <-Ethyl acetate |
| 4.4, t, Int:1 | <-product |



References:

1)W. von E. Doering, A. Kentaro Hoffmann *J. Am. Chem. Soc.;* **1954**; 76(23); 6162-6165.
2)M.S. Baird, H.H. Hussain, W. Nethercott, *J. Chem. Soc. Perkin Trans. 1*. **1986**; 1845-53.
3)Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**,*352*, 1.
4)E. Zohar, I. Marek, *Organic Letters* **2004** Vol.6, No.3, 341-343., and supplimentary materials.