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A NEW APPROACH TO THE SYNTHESIS OF 4,4-DISUBSTITUTED -2-CYCLOHEXENONE

D. Becker and J. Kalo

Department of Chemistry, Israel Institute of Technology, Haifa, Israel

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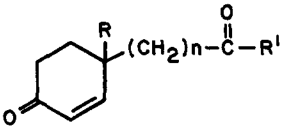
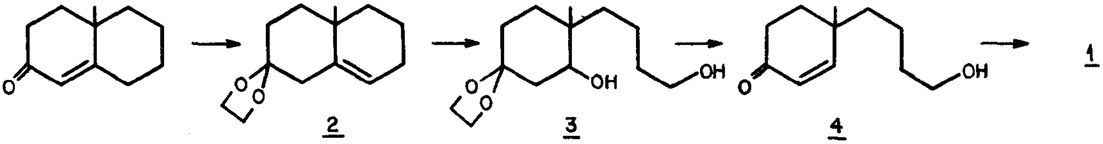
We wish to report a new simple route for the synthesis of compounds 1, 5-7, required in our laboratory.



1 n = 3; R = CH_3; R' = OH
5 n = 3; R = CH_3; R' = CH_3
6 n = 3; R = CO_2Et; R' = OH
7 n = 2; R = Me; R' OH

Since neither of the synthetic approaches developed by Stork (1), Yamada (2), or by Birch (3) suited our needs, we have had to develop a new approach.

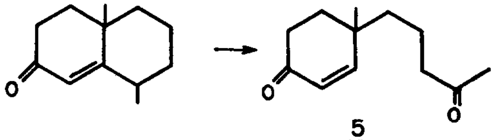
We have synthesized known bicyclo[m.n.o]alkenones which contain all of the carbon atoms that are present in the end product. Ketalization was used to shift the double bond to the required position for subsequent cleavage (4,5). Ozonolysis followed by sodium borohydride reduction and acid treatment of the crude ketal-dialcohol afforded the 2-cyclohexenone system in high yield. Compound 1 was synthesized from 10-methyl-1(9)-octal-2-one(6) by the following steps:



2 3 4 1

The ketal 2 was prepared in 80% yield by refluxing the conjugated ketone for 43 hours in benzene, ethylene glycol, p-toluenesulfonic acid 1% with azeotropic removal of water. Ozonolysis of 2 in methylene chloride : methanol (3:1) at -78° C with ozone for 15 min. was followed by addition of sodium borohydride to the reaction mixture at -78° C. The crude ketal-dialcohol 3 was refluxed for 3 hours in a solution of 10% aqueous oxalic acid : tetrahydrofuran (1:1). The conjugated keto alcohol 4 (7) was isolated in 76% yield.

Jones oxidation of 4 by inverse addition gave 1 (7) in 60% yield. We have similarly obtained 5 (7) and 6 (7) in good yields from trans-8,10-dimethyl-1(9)-octal-2-one(3) and 10-carbethoxy-1(9)-octal-2-one, respectively.



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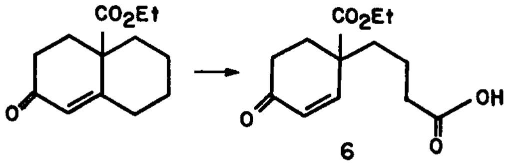

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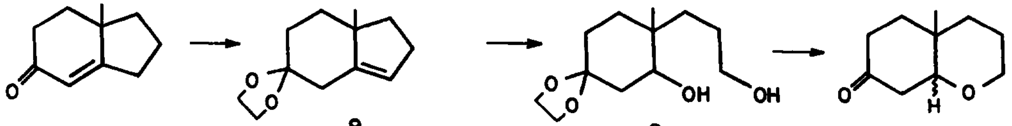
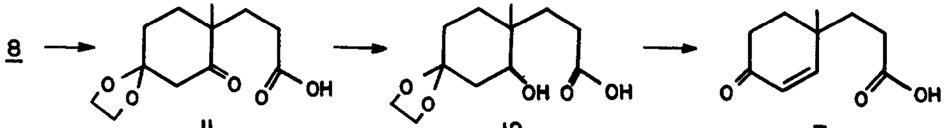
The same approach was followed in order to prepare the known keto acid 7 (3). It was found that the crude ketal-dialcohol 9 cyclized under mild acidic conditions to give a very stable keto ether 10 (7), m.p. 42.5°.



8 9 10

Because the keto acid 7 is known to be stable under acidic conditions (9), cyclization can be avoided in this case:



11 12 7

The ketal 8 was dissolved in methylene chloride and oxidized with ozone at -78° C. The solvent was removed at 0° and the crude ozonide was oxidized with Jones' reagent. Compound 11 was reduced by sodium borohydride and the resulting 12 was treated with 10% oxalic acid solution. The keto acid 7 was isolated in 40% yield and was identical to the keto acid which was prepared according to Birch's procedure (3).

This is a general method for a synthesis of 4,4-disubstituted-2-cyclohexenones which are of high synthetic potential. Some of their uses are currently under investigation in our laboratory.

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9. The keto-acid 7 was **prepared** from the ketone-methyl ester by refluxing for 3 hours in H_2O : AcOH : HCl (1:1:1).