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APPLICATION OF OLEFIN METATHESIS TO ORGANIC SYNTHESIS. SYNTHESES OF CIVETONE AND MACROLIDES

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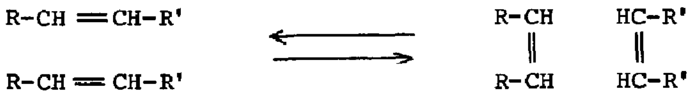
Summary: Diethyl 9-octadecene-1,18-dioate was obtained in 87% yield based on 50% theoretical conversion by the olefin metathesis reaction catalyzed by $WOCl_4$-Cp_2TiMe_2. The Dieckmann condensation of this diester using potassium hydride afforded 2-ethoxycarbonylcyclo-9-heptadecenone, which was converted by hydrolysis and decarboxylation to cyclo-9-heptadecenone (civetone) as a mixture of *cis* and *trans* isomers (1.3 : 1) in 54% yield. Also 9-octadecen-18-olide was obtained in 17.9% by the metathesis of oleyl oleate.

Olefin metathesis expressed by the following general scheme is a truly unique reaction catalyzed by homogeneous and heterogeneous tungsten, molybdenum and rhenium catalysts.[1)]

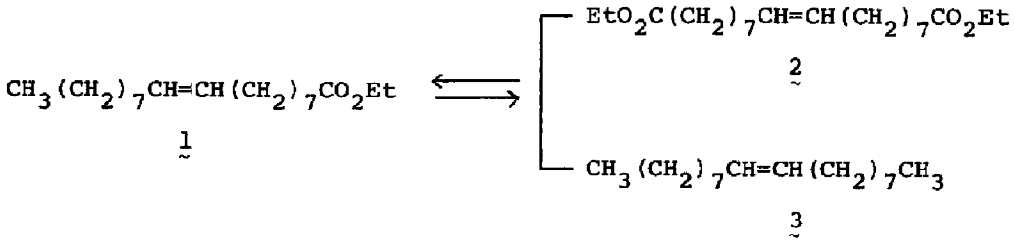


$$\begin{array}{c} R\text{-}CH=CH\text{-}R' \\ R\text{-}CH=CH\text{-}R' \end{array} \quad \rightleftarrows \quad \begin{array}{cc} R\text{-}CH & HC\text{-}R' \\ \| & \| \\ R\text{-}CH & HC\text{-}R' \end{array}$$

The reaction seems to be potentially useful in organic synthesis. However, one drawback in applying olefin metathesis to organic synthesis is the fact that common catalysts for olefin metathesis prepared from tungsten or molybdenum chlorides and organoaluminum compounds can not be used for olefins with functional groups. In order to exploit the metathesis reaction as a truly useful synthetic methodology, it is essential to discover a new catalyst system which can tolerate the presence of functional groups in olefin molecules. In this connection, the Boelhouwer's discovery that the catalyst prepared from WCl_6 and $SnMe_4$ can be used for the metathesis of olefins with functional groups such as ester group is an important breackthrough.[2,3)] We have carried out screening experiments on the activity of tungsten catalysts prepared from tungsten chlorides and various alkylating agents, and found that catalysts prepared from $WOCl_4$ or WCl_6 and dimethyltitanocene (Cp_2TiMe_2) are active catalysts for unsaturated esters.[5)]

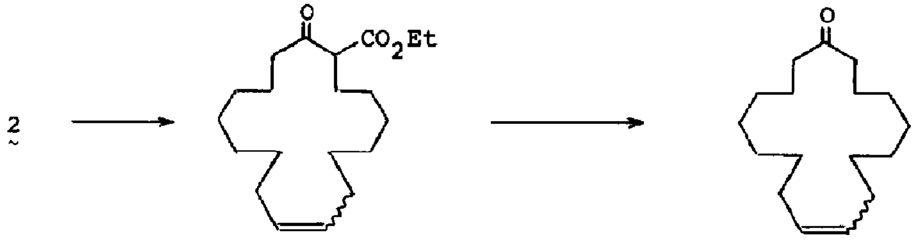
We have chosen civetone (5) as a target molecule. It is possible to synthesize this 17-membered unsaturated cyclic ketone by the cyclization of 9-octadecene 1,18-dioate (2), which can be obtained in one step by the metathesis of easily available oleate (1).[6)] The metathesis reaction is equilibrium control and the

reaction mixture always contains oleate (1), the diester 2 and the olefin 3. B
their separation can be done easily by column chromatography.



$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2Et \rightleftarrows EtO_2C(CH_2)_7CH{=}CH(CH_2)_7CO_2Et + CH_3(CH_2)_7CH{=}CH(CH_2)_7CH_3$

1 2 3



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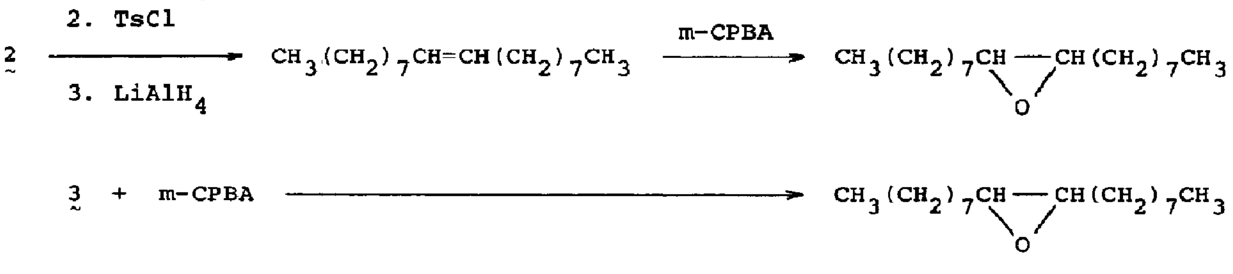
A catalyst solution was prepared in benzene by mixing $WOCl_4$ (10 mol% for olefin
and Cp_2TiMe_2 (1.2 equiv. for $WOCl_4$) under argon atmosphere at room temperature.
A benzene solution of purified ethyl oleate (1) was added to the catalyst and t
reaction was carried out at 70°C for 20 h. The catalyst was quenched with 10%
NaOH solution. After the usual workup, a mixture of ethyl oleate (1), diethyl
19-octadecene-1,18-dioate (2), and 9-octadecene (3) was subjected to silica gel
column chromatography. The diester and 9-octadecene were isolated in 87% yield
based on theoretical conversion of 50%.

It is known that *cis-trans* double bond isomerization takes place during th
metathesis reaction. Although the ethyl oleate (1) used as the starting materi
is predominantly *cis*, the *cis* to *trans* isomerization took place during the reaction. Then ratios of the *cis-trans* double bonds in the products were determine
by converting 2 and 3 by the following sequences of reactions to epoxides as
reported by Baker.[7)]



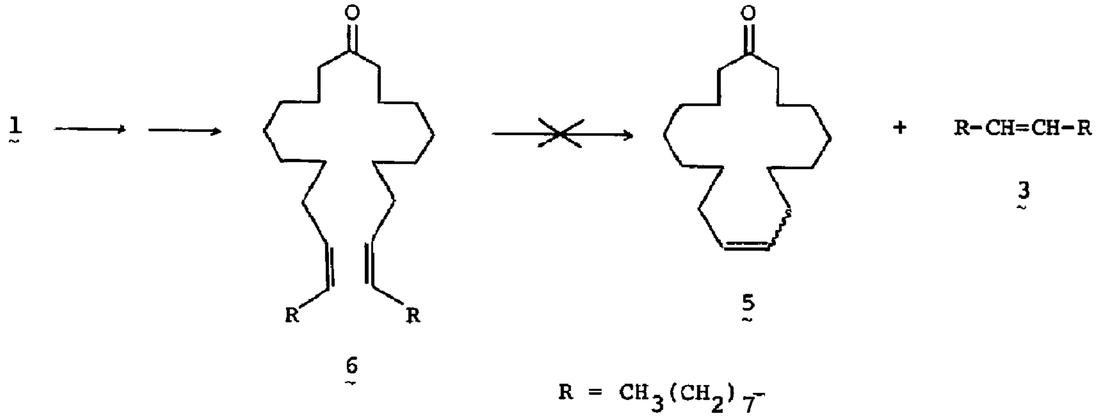
$$2 \xrightarrow[\text{3. LiAlH}_4]{\text{1. LiAlH}_4 \quad \text{2. TsCl}} CH_3(CH_2)_7CH{=}CH(CH_2)_7CH_3 \xrightarrow{\text{m-CPBA}} CH_3(CH_2)_7\underset{\diagdown O \diagup}{CH{-}CH}(CH_2)_7CH_3$$

$$3 + \text{m-CPBA} \longrightarrow CH_3(CH_2)_7\underset{\diagdown O \diagup}{CH{-}CH}(CH_2)_7CH_3$$

Gas chromatographic analyses of the epoxides showed that the *cis-trans* ratios in the diester and octadecene were 1.3 : 1. By the same analysis, it was found that the *cis-trans* ratio of ethyl oleate before the reaction was 10.3 : 1. But the ratio of the recovered oleate was 2.8 : 1.

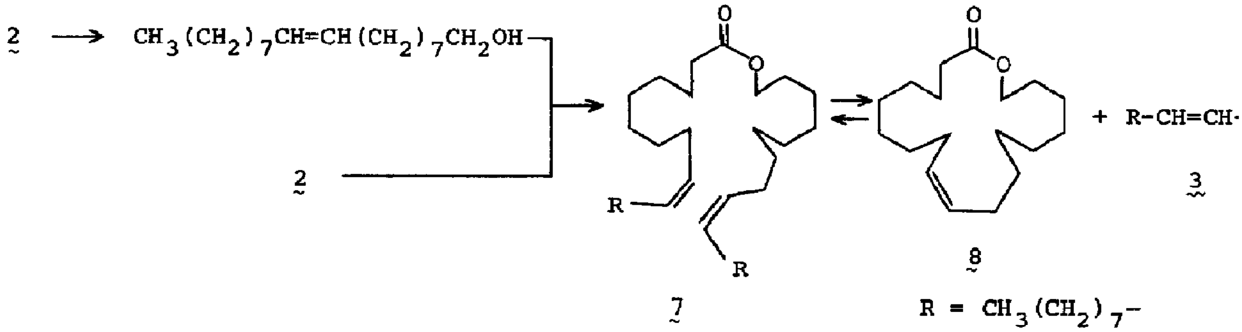
Then the Dieckmann condensation of the diester 2 was carried out. Potassium hydride (370 mg, 2.30 mmol) was suspended in dry benzene (40 ml) and the solution of the diester 2 (425 mg, 1.15 mmol) in benzene (10 ml) was added slowly in 2.5 h at 55°C. After the reaction, the crude keto ester 4 was isolated and subjected tc hydrolysis with sodium hydroxide in a mixture of ethanol and THF at refluxing temperature for 5 h. After decarboxylation with sulfuric acid, the crude product was subjected to column chromatography and cyclo-9-heptadecenone (civetone) (5) was obtained in 54.5%. Since there is no possibility of the *cis-trans* isomerization during the cyclization, it is assumed that the civetone thus prepared is a mixture of the *cis* and *trans* forms in the ratio of 1.3 : 1. They could not be separated. The structure of the civetone was determined by mass spectrum (m/e 250 M$^+$), and comparison of NMR and IR data with those of an authentic sample of *cis*-civetone prepared in this laboratory.[8]

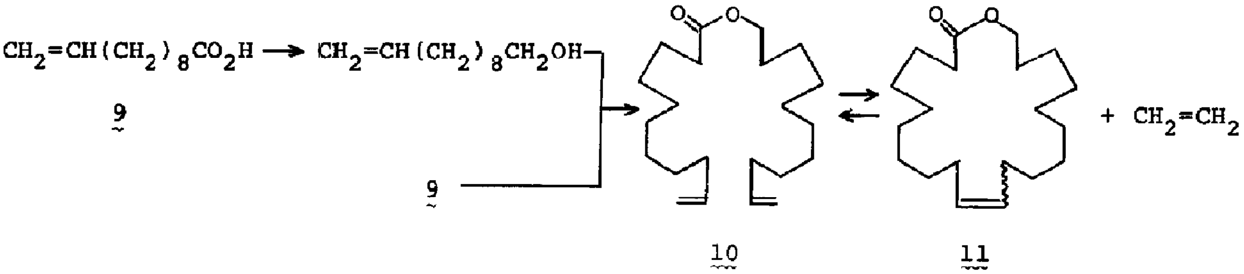
Also we have attempted, without success, another synthetic method of civetone (5) by cyclization based on intramolecular metathesis reaction of di(8-heptadecenyl)ketone (6) as shown below. Both our catalyst and the Boelhouwer's one could not tolerate the presence of ketone and its acetal.



As another attempt, we have carried out a preliminary study of macrolide synthesis based on cyclization by intramolecular metathesis reaction of oleyl oleate (7). The substrate 7 was prepared easily from oleic acid and oleyl alcohol The metathesis reaction carried out in benzene using WCl$_6$ (20 mol%) and Cp$_2$TiMe$_2$ (24 mol%) afforded 9-octadecen-18-olide (8) in 17.9% yield. Although the yield was still unsatisfactory, the method is simple, and the separation of the product and recovery of the starting material are easy. Therefore, this method may be a good synthetic method of macrolides by further improvement. Also 10-eicosen-20-olide (11) was obtained in 12% yield by the metathesis of 10-undecenyl

10-uncecenoate (10). The ester 10 was prepared from commercially available undecenoic acid (9).





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