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C_3 EPIMERIZATION AND SELECTIVE C_2-C_3 BOND FISSION OF ALKYL CHRYSANTHEMATE

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Summary: Treatment of alkyl chrysanthemate with Lewis acid leads to C_3 epimerization, while protonic acid treatment gives rise to selective C_2-C_3 bond cleavage. The latter method is successfully applied to the synthesis of optically active tetrahydrolavandulol.

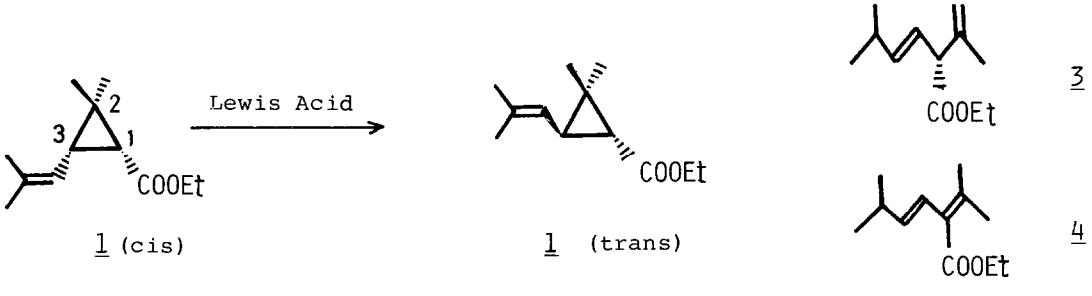
Interconversion of stereoisomers of chrysanthemic acid and its derivatives has been investigated as a method for the preparation of biologically most active stereoisomer, (+)-trans form. Although several papers dealing with C_1 epimerization have been presented,[1] no study has been reported on direct C_3 epimerization.[2,3]

In this communication we wish to report the first observation of C_3 epimerization of alkyl chrysanthemate.

Treatment of (+)-cis ethyl chrysanthemate 1 with 30 mol% of Lewis acid such as $AlCl_3$, $FeCl_3$ or $BF_3 \cdot OEt_2$ in heptane at 70°C for 2 hr afforded (+)-trans/(+)-cis isomeric mixture (94:6)[4] together with C_2-C_3 bond cleaved product 3 and 4. The formation of (+)-trans isomer from (+)-cis chrysanthemate clearly demonstrates that the isomerization is C_3 epimerization.

The results are summarized in the following Table.

Scheme 1:



1 (cis) 1 (trans) 3 4

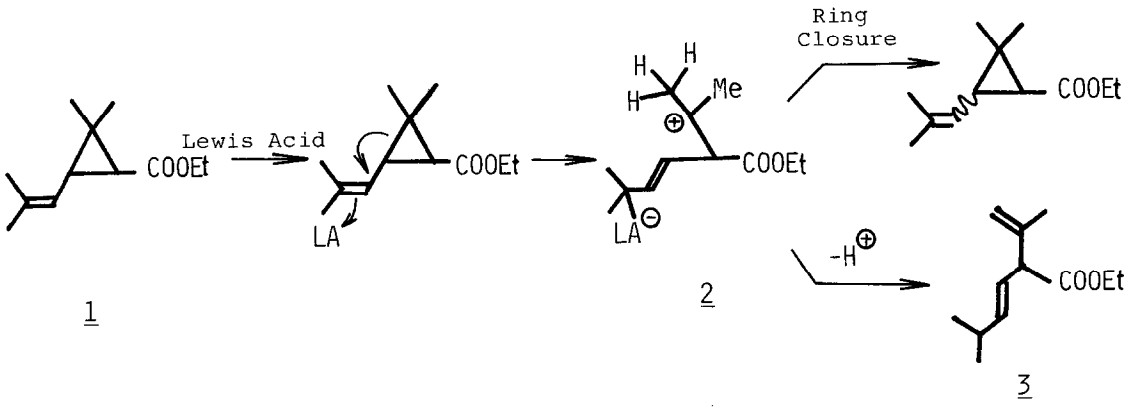
Table: C_3 epimerization of cis ethyl chrysanthemate

catalyst	temp(°C)	trans content(%)	yield(%)
$AlCl_3$	70	93.0	69
$FeCl_3$	70	94.4	60
$BF_3 \cdot Et_2O$	70	94.0	70

The present method enabled increasing trans content of (+)-trans/(+)-cis mixture of chrysanthemate, which is obtained by optical resolution of synthetic (±)-trans/cis chrysanthemic acid[5] followed by esterification, without loss of optical purity. Thus 65:35 (+)-trans/cis ester could be converted into 94:6 (+)-trans/cis ester by the same treatment as mentioned above.

Although actual reaction mechanism is not clearly elucidated yet, we assumed that both C_3 epimerization and C_2-C_3 bond cleavage are resulted from a common intermidiate 2. Ring closure of 2 gives C_3 epimerized product, and on the other hand, elimination of proton from 2 causes C_2-C_3 bond fission to give 3.[6]

Scheme 2:



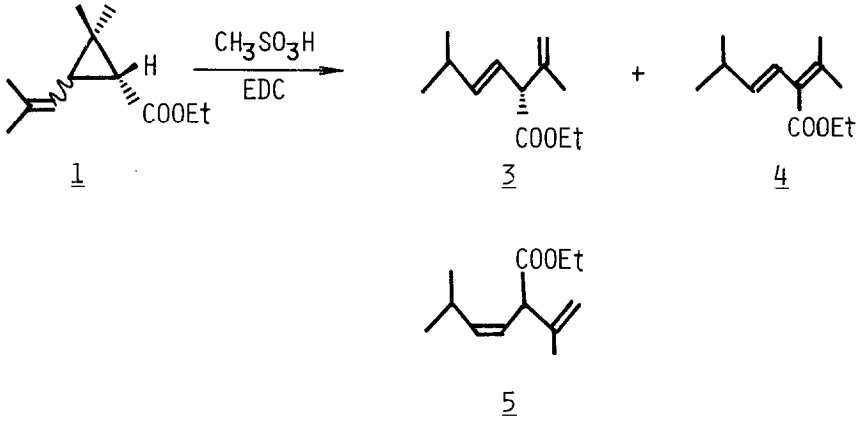
Since reported method for C_2-C_3 bond cleavage of chrysanthemate requires high reaction temperature (500°C),[7] we focused our attention to exploring mild reaction conditions.

We found that an employment of protonic acid instead of Lewis acid brings about the formation of ring cleaved product selectively.

Treatment of ethyl chrysanthemte (c/t=20/80, 10.0g, 51mmol) with methanesulfonic acid (1.8g, 19mmol) in 1,2-dichloroethane at 70°C for 2 hr gave esters 3 and 4 in 47% and 46% yields respectively (Sheme 3). Ester 3 was found to have E configuration in contrast to Z configuration of ester 5 obtained by thermal C_2-C_3 bond cleavage.[7] Ester 4 was resulted from double bond migration of ester 3.

As the reaction conditions were mild, optically active ester 3 (α_D -18.0°, neat) was obtained from optically active ethyl chrysanthemate with complete retention of configuration at the C_1 position.[4,8]

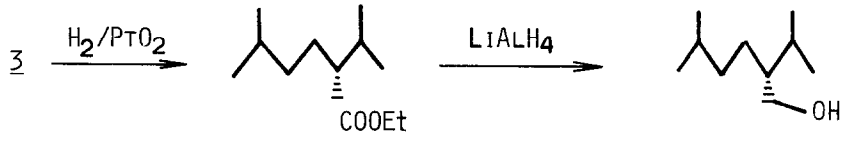
Sheme 3:



1 3 4 5

This method was successfully applied to the synthesis of optically active tetrahydrolavandulol. The synthtic route is illustrated in Sheme 4. Double bond of ester 3 was reduced with H_2/PtO_2 to afford ester 6(86%), which was further reduced with $LiAlH_4$ to give tetrahydrolavandulol 7(87%). The optical rotation of the product(α_D +12.8°, neat) agreed with the reported value.[9]

Sheme 4:



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References and Notes

1) (a) M. Elliot and N. F. Janes, "Pyrethrum", ed. by J. E. Casida, Academic Press, New York and London, 1973, p.76.
(b) G. Suzukamo, M. Fukao, T. Nagase, and H. Yoshioka, Japanese Pat., 55-16568 (1980); G. Suzukamo, M. Fukao, T. Nagase, and H. Yoshioka, Japanese Pat., 56-12625 (1981).

2) J. L. Williams and M. Rettig reported Pd-complex catalyzed cis/trans isomerization of chrysanthemic acid: Tetrahedron Lett., 22, 385 (1981). Our detailed study on the method employing optically active acid revealed that the isomerization was C_3 epimerization.

3) For multi-step conversion of (+)-cis chrysanthemic acid to (+)-trans form by C_3 epimerization see: M. Matsui, H. Yoshioka, H. Yamada, H. Sakamoto, and T. Kitahara, Agr. Biol. Chem., 29, 784 (1965).

4) The isomer ratio was determined by gas chromatography after conversion into (+)-2-octyl ester: colomn; silicon DC QF-1, 15 m x 0.25 mmI.D. (glass capillary), column temp.; 125°C, carrier gas; N_2 1 ml/min, detector; FID.

5) I. Miyamoto, H. Yoshioka, K. Fujimoto, T. Kadota, and Y. Okuno, Sumitomo Kagaku, Special Issue II, 1 (1973), and references cited therein.

6) H. -U. Reissig proposed ring opening/ring closure mechanism for cis/trans isomerization of methyl 2-trimethylsilyloxycyclopropane carboxylates: Tetrahedron Lett., 24, 715 (1983).

7) G. Ohloff, Tetrahedron Lett., 3795 (1965). We verified that the product was (Z)-2-isopropenyl-5-methyl-3-hexanoate 5 by NMR study.

8) The optical purity of ring opened product 5 prepared from optically active ethyl chrysanthemate according to Ohloff's method was only 12 %.

9) O. Kumada, "Koryokagakusoran II", Hirokawa syoten, Japan, 1968, p.550.

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