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A FACILE SYNTHETIC ROUTE TO (±)-CHRYSANTHEMATE ANALOGUES[1]

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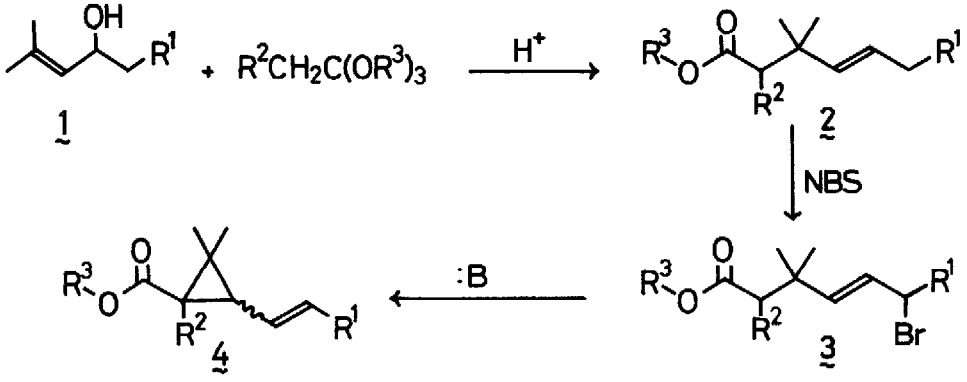
Recently, two new methods[2] on the preparation of chrysanthemic acid have been published. We now wish to report our own conceptually similar but different approach to this problem. The thorough and extensive study by Elliott and his coworkers[3] on the structure-activity relationship of pyrethroid analogues has demonstrated that modification of the dimethylvinyl group in chrysanthemic acid to 1-propenyl, 1-butenyl, or 1,3-butadienyl substituent significantly increases the insecticidal activity. These analogues were usually prepared from the parent chrysanthemate by ozonolysis followed by condensation of the resulting 2-formyl-3,3-dimethylcyclopropanecarboxylate with appropriate Wittig reagents[4].

We have found that the acid moieties of these potential pyrethroids including their α-substituted analogues[5] can easily be prepared by the following sequence of reactions.



The starting allylic alcohol 1 were prepared either by reduction of mesityl oxide with LAH (for R^1=H) or by the condensation of 3-methylcrotonaldehyde with appropriate Grignard reagents. Heating of a mixture of the above alcohol 1 and triethyl orthoacetate[6] in the presence of a catalytic amount of

phenol at 140° for 20∿24 hrs under continueous removal of by-produced ethanol from the system afforded the γ,δ-unsaturated esters 2 in good yields. The obtained ester 2 was then brominated with N-bromosuccinimide in CCl_4 (under reflux for 3∿5 hrs) in the presence of BPO to produce the ε-bromo-γ,δ-unsaturated esters 3. Treatment of the resulting ester 3 with potassium t-butoxide in THF gave finally the desired cyclopropanecarboxylates 4. The α-substituted analogues were prepared in the similar manner as described above starting from allylic alcohol 1 (R^1=H) and triethyl orthopropionate or triethyl orthobutyrate. The results and the reaction condition for cyclization step are summarized in Table I.

Table I. Analogues of Chrysanthemate

	R^1	R^2	R^3	Product Yields (%) 2	3	4	Reaction Cond. for cyclization	b.p. of Product[a]	
a	H	H	Et	64	91	85	t-BuOK/THF 60°C: 4 hr	2 3 4	100∿105°C/57mmHg ∿85°C/0.5mmHg 65∿75°C/25mmHg
b	Me	H	Et	85	91[b]	66[c]	t-BuOK/THF 0∿5°C: 4 hr	2 4	97∿103°C/38mmHg 86∿88°C/15mmHg
c	Et	H	Et	88	92[b]	69[c]	t-BuOK/THF -30°C: 1 hr	2 4	114∿116°C/38mmHg 88∿91°C/14mmHg
d	H	Me	Et	60	86[b]	77[c]	t-BuOK/THF -10°C: 1.5 hr	2 4	97∿99°C/37mmHg 80∿86°C/25mmHg
e	H	Et	Me	48	83	22[d]	t-BuOK/THF 0∿5°C: 6 hr	2 3 4	97∿100°C/30mmHg ∿90°C/1.7mmHg 78∿84°C/20mmHg

a: All new compounds gave IR, NMR, and mass spectra consistent with the assigned structures.
b: Crude yields. Crude products were used in next step without purification.
c: Isolated yields based on 2.
d: t-Butyl ether 5e as by-product was formed in 15% yield.

The cyclized ester was usually a mixture of cis and trans isomers. For example, the nmr spectrum of the crude product derived from 3a revealed that

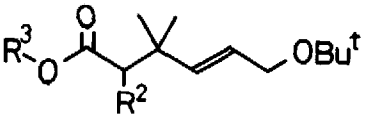
4a was almost 1:1 mixture of cis and trans isomers[7]. Further treatment of this mixture with t-butoxide in t-butanol at 80°[8], however, induced the smooth isomerization of cis isomer to the thermodynamically stable trans 4a. Infrared spectra of esters 4b and 4c exhibited a strong absorption at 960∿965 cm^{-1}. Therefore, the geometry of the olefinic bond attached to the cyclopropane ring would be predominantly trans, though the presence of cis isomer in the product as minor component could not be excluded.

Two side-reactions were observed in the cyclization from 3 to 4. The one was the 1,2-elimination of hydrogen bromide leading to diene, which occured in the reaction with 3b and 3c. The other was the substitution of halogen by alkoxy anion to afford t-butoxy substituted ester 5. The latter reaction was observed especially when the α-substituted analogues of 3 was exposed to the aforementioned cyclization. The competitive occurance of these reactions might be the result of insufficient acidity of the α-hydrogen in bromoester 3, especially in 3d and 3e. Both side-reactions, however, could effectively be suppressed by lowering the reaction temperature. An example of the temperature effect on the product selectivity is showen in Table II.

Table II. Product ratios* in the reaction of 3d with t-BuOK in THF

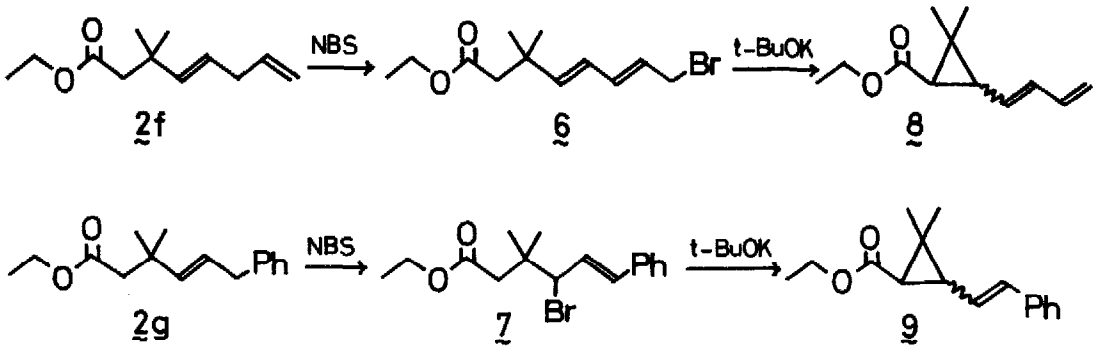
Reaction Temp.	4d : 5d
60°	1 : 1
r.t.	2 : 1
-10°	9 : 1

* Ratios were determined by comparing area of peaks in GC.



5 d: R^2=Me, R^3=Et
e: R^2=Et, R^3=Me

For the syntheses of butadienyl and styryl analogues, γ,δ-unsaturated esters 2f and 2g were prepared by the condensation of triethyl orthoacetate with allylic alcohols 1f (R^1=vinyl) and 1g (R^1=phenyl) in 87 and 75 % yields, respectively. The structure of the products obtained by the bromination of these unsaturated esters was not so simple. Inspection of their nmr spectra suggested that the major product from 2f was the ω-bromoester[9] 6 (94% yield) and that from 2g was the γ-bromoester 7 (85% yield). Treatment of these crude bromination products with potassium t-butoxide in THF below 0° produced the expected cyclopropanecarboxylates 8, b.p. 62∿65°/0.1 mmHg, and 9, b.p. 112∿118°/0.1 mmHg, in 59 and 58% yields based on 2, respectively.



Thus, the sequence of reactions, i.e., Claisen rearrangement, halogenation, and cyclization, has now been proved to be a useful alternative route to cyclopropanecarboxylates.

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