OPTICALLY ACTIVE CHRYSANTHEMIC ACID AND ITS ANALOGUES

L. Bets, Z. Ribkovskaia, L. Vlad, S. Pogrebnoi, F. Galin, F. Macaev*

Institute of Chemistry of the Academy of Sciences of Moldova,
Academy str. 3, MD-2028, Chisinau, Moldova

*Tel +373-22-739-754, Fax +373-22-739-954, *E-mail: flmacaev@cc.acad.md*
Institute of Organic Chemistry, Ufa Research Center of the Russian Academy of Sciences,
71 prosp. Oktyabrya, 450054 Ufa, Russian Federation.

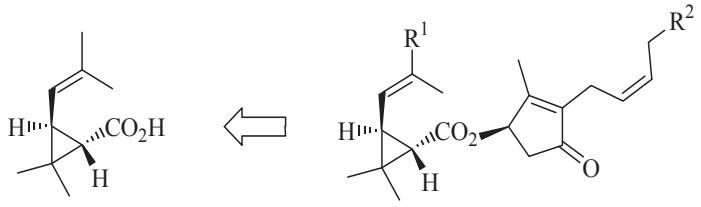
Dedicated to Professor Lupaşcu Tudor on his 60th birthday

Abstract: Optically active chrysanthemic acid and its analogues have received considerable attention in recent years due to their practical importance. This review will focus on describing the developments in the synthesis of optically active chrysanthemic acid and its analogues. The transformation that will be covered includes the chemistry of enantiomerically pure 2,2-dimethyl 1,3-disubstituted cyclopropanes derived from monoterpene (+)-3-carene.

Keywords: chrysanthemic acid, pyrethrins, pyrethroids, permetrin, cypermethrin, deltamethrin (decis), thigalotrin (cyhalothin), natural (+)-3-carene, organic synthesis.

1. Introduction

Optically active chrysanthemic acid **1** and its esters **2a-e** (pyrethrins) have been isolated from pyrethrum flowers (*Chrisanthemum cinerariaefolium*) [1-11]. For a long time pyrethrins have not found application as crop protection agents due to their photo lability and quick oxidization while in open air conditions.

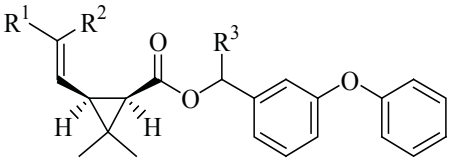


1 **2a-e**

2a R^1=-Me, R^2=-CH=CH_2; **2b** R^1=-CO_2Me, R^2=-CH=CH_2; **2c** R^1=-Me,R^2=-Me;
2d R^1=-CO_2Me,R^2=-Me; **2e** R^1=Me,R^2=-H;

Scheme 1

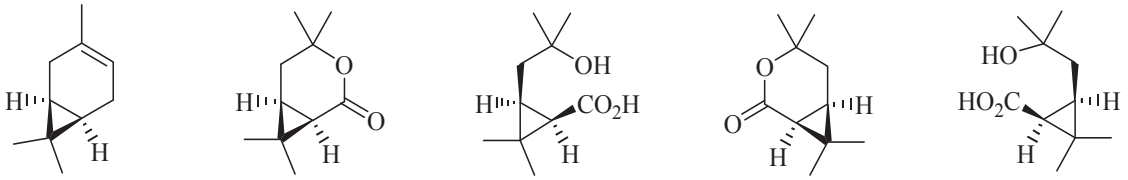
The synthesis of a stable and effective pyrethroid - permetrin **3a,** made in 1973 gave an impetus to the search for its structural analogues and, as a result, cypermethrin **3b**, deltamethrin (decis) **3c**, thigalotrin (cyhalothin) **3d** and several other compounds with higher insecticide activity were discovered [12-24].



3a R^1=R^2= CI, R^3= H;
3b R^1=R^2= CI, R^3= CN
3c R^1=R^2= Br, R^3= (*S*)CN
3d R^1= Cl, R^2= CF_3, R^3= (*S*)CN

Scheme 2

The present tendency of the pyrethroids chemistry developing is to carry out the guided synthesis of enantiomerically pure substances which, gradually, supplant the racemic ones. The syntheses of the optically active pyrethroids that represent ester are, in most cases, connected with the preparation of an enantiomerically pure acid component [25-29]. One of the ways of obtaining such acids is the using of the accessible natural (+)-3-carene **4** due to the renewable character of its sources, high enough optical purity, as well as the possibility for the synthesis of the products that belong to antipode series (see scheme 3).



4 **5a** **5b** **6a** **6b**

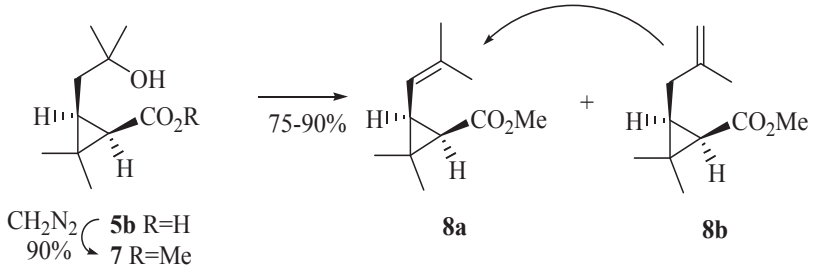
Scheme 3

The synthesis of pyrethroid acids from (+)-3-carene **4** has been thoroughly considered in [30-34]. Therefore, only the most important and newest data regarding the synthesis of chrysanthemic acid and its analogues from synthons on the basis of compound **4** will be dealt with in the review.

2. Synthesis, isomerization and separation of the chrysanthemic acid, its esters and analogues

Judging by the available data, more preferable initial substances in synthesizing these compounds are acid **5b** and lactone **5a**, as well as their antipodes **6a** and **6b**.

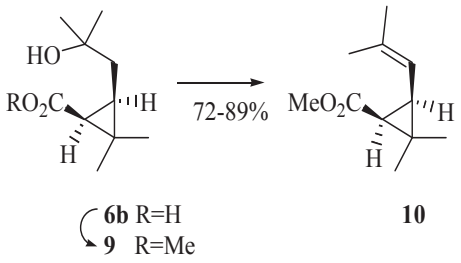
Dehydroxylation of alcohol **7** affords the mixture of methyl (1R,3S)-chrysanthemates **8a,b**.



Scheme 4

The transformation can be performed by refluxing with *p*-toluenesulfonic acid in toluene [28], xylene and benzene [35,36] or $POCl_3$ in Py [37]. Mixture **8a,b** can be separated only chromatographically on SiO_2 columns, impregnated with $AgNO_3$. However, during a prolonged heating of the reaction mixture, ester **8b** isomerizes into thermodynamically more stable ester **8a**.

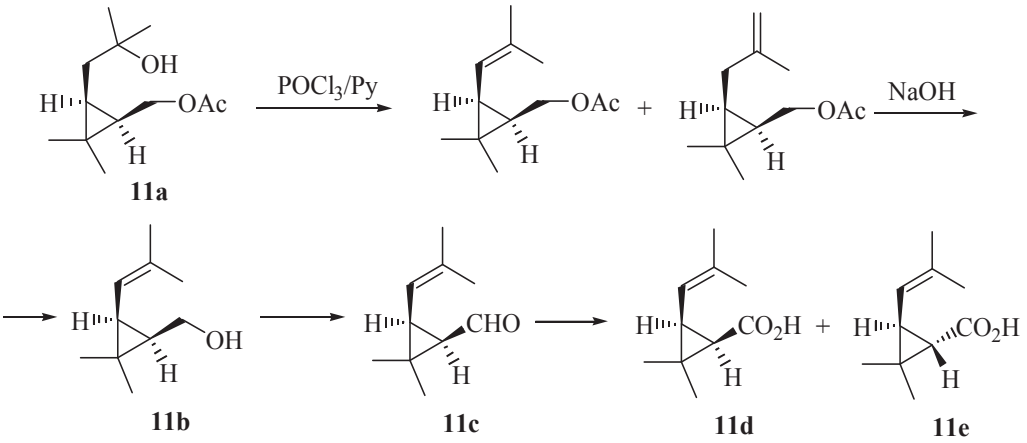
Similarly, alcohol **9** has been converted into methyl (+)-(1S,3R)-chrysanthemate **10** [6,38].



Scheme 5

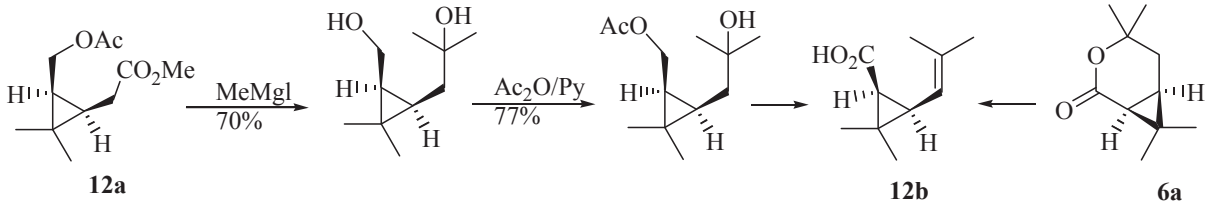
Acetate **11a** has served as initial compound for synthesizing the (-)-(1R,3S)-chrysanthemic acids **11d,e** [39].

It should be noted that dehydroxylation as well as oxidation proceeds non-specifically. Alcohol **11b** can be oxidized step-by-step, firstly in aldehyde **11c** by air oxygen on platinum catalysts [40] or CrO_3 [41]. In its turn, compound **11c** produces acid **11d,e** at the interaction with CrO_3 in pyridine [42,43], Jones's reagent [43] or silver oxide [40].



Scheme 6

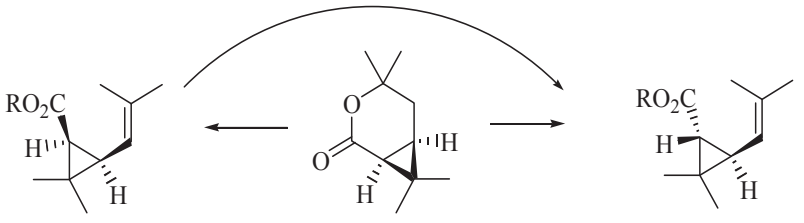
(-)-(1S)-*cis*-Chrysanthemic acid **12b** has been obtained from **12a** according to scheme **7** [44].



Scheme 7

As has been mentioned above, chrysanthemic acids can be obtained from dihydrochrysanthemolactone. Thus, (-)-lactone **6a** is easily converted into *cis*-chrysanthemic acid **12b** under the action of diluted H_2SO_4 [28,45,46], potassium *tert*-butoxide [28,45], potassium hydroxide [47] or SO_2Cl_2 [48]. This conversion, which ends the transformation of 3-carene **4** into acid **12b**, has served as a proof of its stereochemistry [49,50].

Compound **6a** with solution H_2SO_4 in *tert*-butanol affords ester **13a** (yield 95%) [51]. The authors [47] discovered that in more rigid condition (heating with sodium hydroxide in ethylene glycol at 225-230^{0}C for 5 hours) lactone **6a** immediately isomerizes into (+)-*trans*-acid **13a**.



12b R=H
12c R=Bu^t
12d R=Et

6a

13a R=H
13b R=Et
13c R=Bu^t

Scheme 8

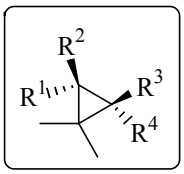
It should be noted that (-)-*cis*-acid **12b** can be also isomerized into (+)-*trans*-acid **13a** by heating its ethyl ester **12d** with NaOEt in ethanol in a soled tube followed by the saponification of **13b** with alkali [28,45]. A more convenient transformation of *cis*-esters into *trans*-esters under the action of potassium *tert*-butoxide is reported in patent [52].

Antipode **5a** can be turned into the corresponding (+)-*cis*-acid **11d** or (-)-*trans*-acid **11e** in the same way [28].

In the corresponding literature one can find a whole series of chrysanthemic acids and their esters analogues (see table). They have been mainly prepared by the schemes of the synthesis of chrysanthemic acids.

Table 1

Chrysanthemic acid esters and their analogues



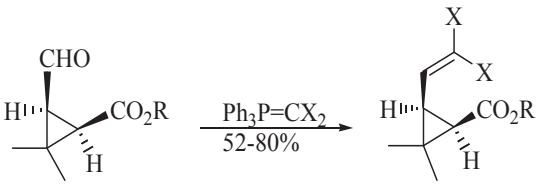
№	Substituents				Ref.
	R^1	**R^2**	**R^3**	**R^4**	
1.	H	CH=C(Ph)Me	H	H	35,60
2.	H	CO_2Me	CH=C(Ph)Me	H	53
3.	CO_2Me	H	CH=C(Ph)Me	H	54
4.	H	CH=C(4-MeC_6H_4)Me	CO_2Me	H	55
5.	CO_2Me	H	CH=C(4-MeC_6H_4)Me	H	55
6.	H	CH=C-C_6H_4Me	CO_2Me	H	56
7.	H	CH=C-(4-ClC_6H_4)Me	CO_2Me	H	56
8.	CO_2Me	H	CH=C(4-Cl-C_6H_4)Me	H	54
9.	CO_2Me	H	CH=C(CHO)Me	H	56, 57
10.	H	CH=C(CN)Me	CO_2Me	H	58
11.	H	CH=C(Cl)Me	CO_2Me	H	58
12.	CO_2Me	H	CH=C(Cl)Me	H	59
13.	H	CO_2Me	CH=C(Cl)Me	H	60
14.	CO_2Me	H	CH=C(Cl)Ph	H	61
15.	H	CH=C(Cl)Ph	CO_2Me	H	62
16.	H	CO_2Me	CH=C(Cl)Ph	H	63
17.	CO_2Me	H	CH=C(4-ClC_6H_4)Ph	H	64
18.	CO_2Me	H	CHC≡CCl	H	64
19.	H	CH=C(Cl)CH_2OH	CO_2Me	H	58
20.	H	CH=C(Cl)CHO	CO_2Me	H	58
21.	H	CO_2Me	C_2H_5	H	65
22.	H	CO_2Me	C_3H_7	H	66
23.	H	C_3H_7	CO_2Me	H	66
24.	H	CO_2Me	C_6H_{13}	H	65
25.	H	CO_2Me	$C_{10}H_{21}$	H	65
26.	CO_2Et	H	CH=C(Cl)CF_3	H	67,68
27.	CO_2Me	H	CH=CC_5H_{11}	H	52
28.	$CO_2{}^tBu$	H	CH=CHCl	H	54, 69,70
29.	CH=C(Me)Me	H	CO_2Me	H	69
30.	CH=C(Me)Et	H	CO_2Me	H	69
31.	CH=C(Me)C_3H_7	H	CO_2Me	H	69
32.	CH=C(Me)C_4H_9	H	CO_2Me	H	69
33.	CH=C(Me)-CH=CH_2	H	CO_2Me	H	69
34.	CH=C(Me)-CH=CMe_2	H	CO_2Me	H	69
35.	CH=C(Me)-CH=CHMe	H	CO_2Me	H	69
36.	CH=CH_2	H	CO_2Me	H	69
37.	CH=CHMe	H	CO_2Me	H	69
38.	CH=CH-CH=CH_2	H	CO_2Me	H	69
39.	CH=CH-C-CH=CHMe	H	CO_2Me	H	69

40.	$CH=CH-CH=CMe_2$	H	CO_2Me	H	69
41.	$CH=C(Me)-CH=CH_2$	H	CO_2Me	H	69
42.	$CH=CH-CH=CH-CH_3$	H	CO_2Me	H	69
43.	$CH=C(Me)-C_2H_5$	H	CO_2Me	H	69
44.	CO_2Me	H	$CH=CPh_2$	H	53
45.	CO_2Me	H	CH=CHPh	H	61

Two patents [70,71] also contained structural analogues, however, characteristic data were not given there.

Despite numerous analogues of chrysanthemic acids, 3-(2,2-dihalovinyl)-2,2-dimethylcyclopropanecarboxilic are the most important acids. Pyrethroids show the highest activity when *cis*-acid has 1*R*-configuration [30-34].

The interaction between aldehydes **14a,b,c** and dichloro- or dibromomethylene triphenylphosphoranes has been used for obtaining dihalovinyl-2,2-dimethylcyclopropanecarboxilic acids [26,33,34,69,71,72,75-80].

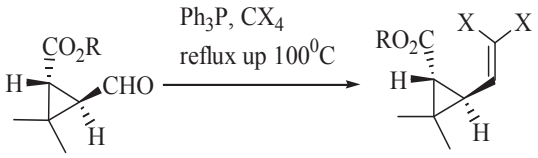


14a R=H
14b R=Me
14c R=^{t}Bu

15a R=H, X=Cl
15b R=Me, X=Cl
15c R=^{t}Bu, X=Cl
15d R=Me, X=Br
15e R=H, X=Br

Scheme 9

It is to be noted that phosphoranes can be obtained *in situ* from triphenylphosphine and CBr_4 or CCl_4 [72,76-79]. For example, the synthesis of *trans*-isomers **17a-e** from aldehydes **16a,b** has also been performed using Wittig reaction (scheme 10). In case of the synthesis of fluorinated analogues **17d**, sodium salt of chlorodifluoroneacetic acid [80] has been included in the reaction along with aldehyde **16a** and Ph_3P.



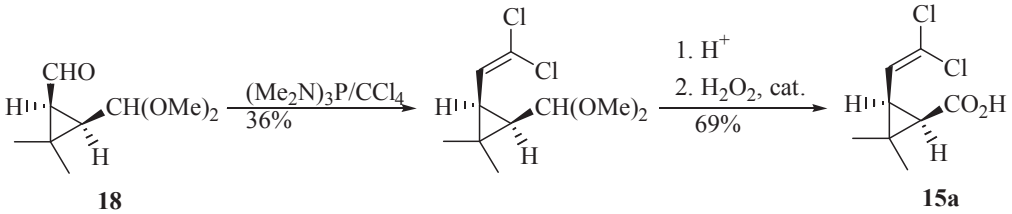
16a R=Me
16b R=^{t}Bu

17a R=^{t}Bu, X=Cl (61)%)
17b R=^{t}Bu, X=Br (60%)
17c R=^{t}Bu, X=I (54%)
17d R=Me, X=F (57%)
17e R=Et, X=Cl (80%)

Scheme 10

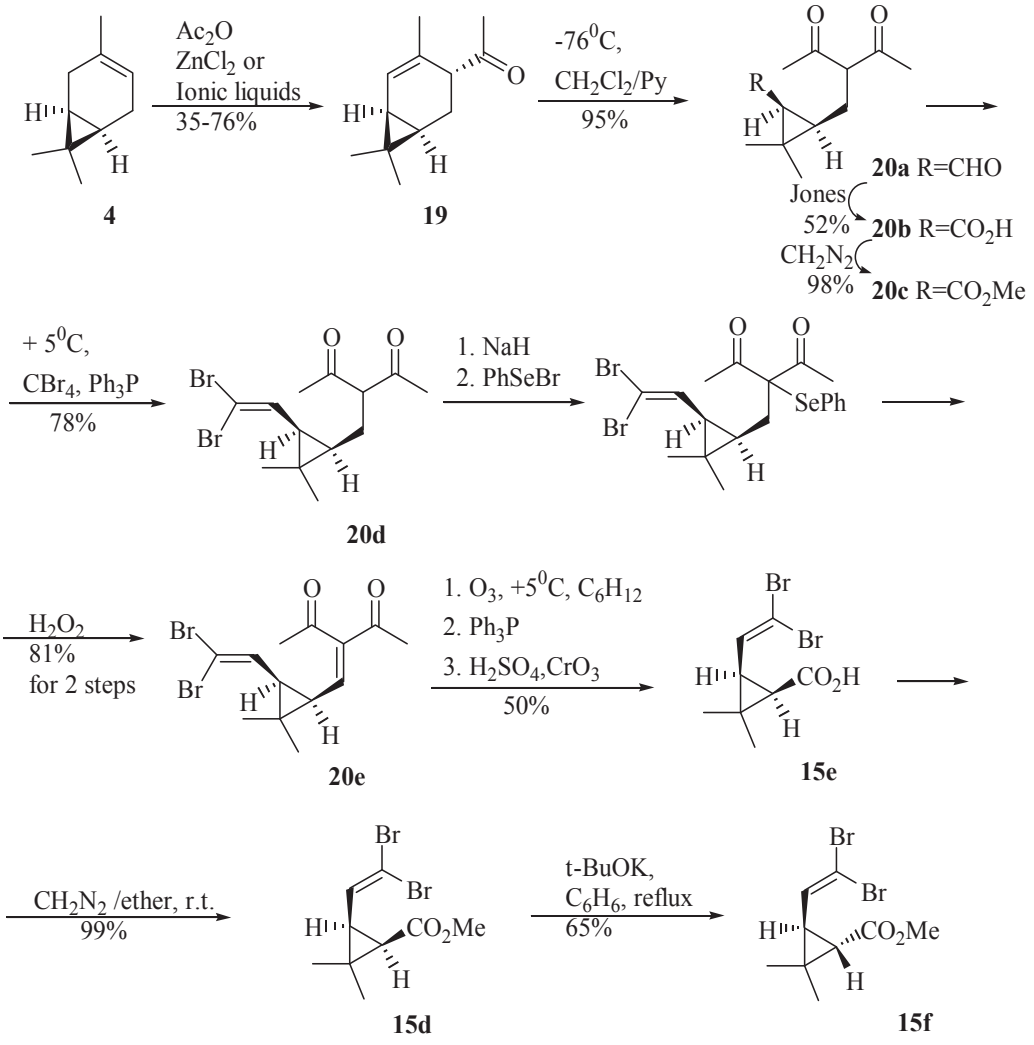
The afore-enumerated syntheses according to Wittig's reaction have several drawbacks: they offer a relatively low yield of products (about 60%), generate a partial epimerization of chiral centre at C_1 and partial cleavage of the cyclopropane ring. These drawbacks can be eliminated (unfortunately, only performing the reaction with small quantities of reagents), if *tris*-dimethylammoniumphosphine is used instead of Ph_3P and instead of CCl_4 – bromo(trichloro)methane [72,81]. The yield of *trans*-ester **17e** [81] and *cis*-esters **16b,c** has been about 80%.

It should be mentioned that the reaction of CCl_4 with *tris*-dimethylammoniumphosphine also proceeds. For example, ester **15b** [82,83] has been obtained by this way. The authors [84-87] have described another synthesis of *cis*-acid **15a** from aldehyde **18**.



Scheme 11

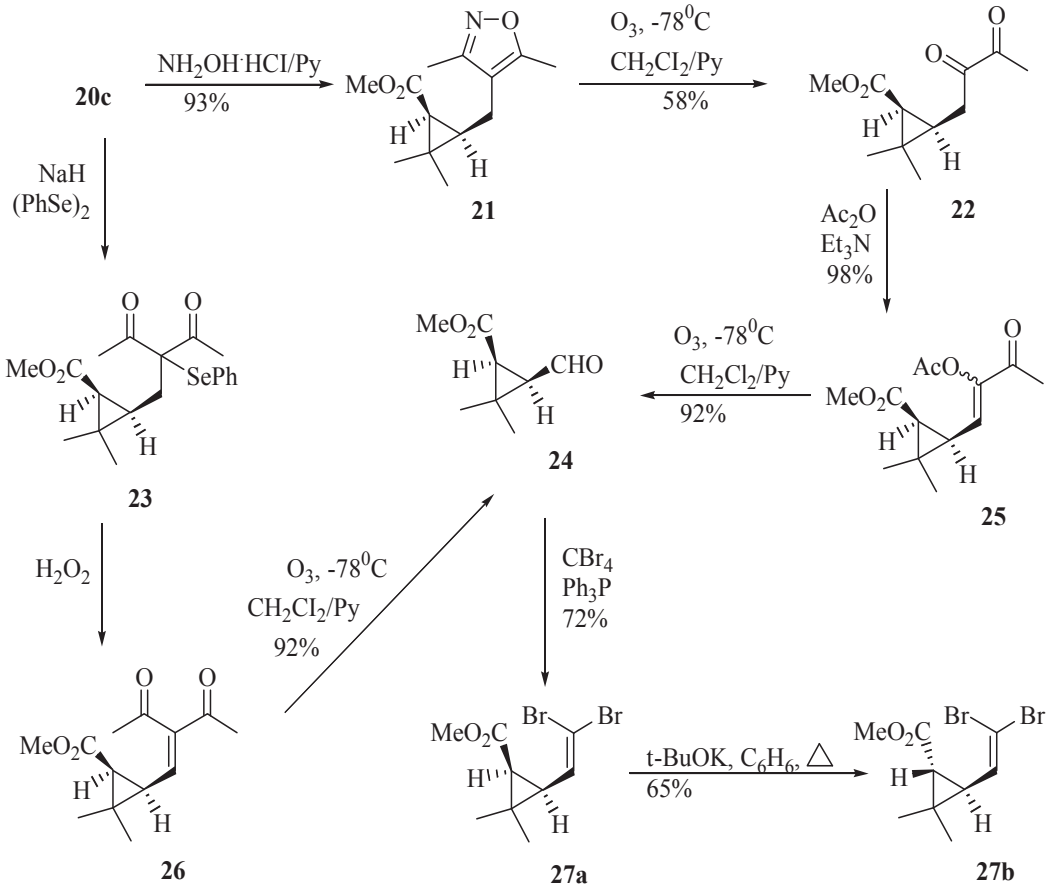
4α-Acetyl-2-carene **19** has been used for the synthesis of all four deltamethrinic acids (scheme 12) [76,77,87-89].



Scheme 12

Initial compound **19** has been converted into aldehyde **20a**, whose olefination produced dibromovinyl-2,2-dimethylcyclopropane **20d**. The preparation of diene **20e** includes a two-step dehydration. Ozonation of compound **20e** that followed oxidation has produced acid **15e**. Esterification of acid **15e** yielded (+)-1R-*cis*-ester **15d**. Product **15d** isomerizes rather smoothly into the thermodynamically more stable (+)-1S-*trans*-ester **15f**.

On the other hand, aldehyde **24**, is synthesized from β-diketone **20c** by two ways (scheme 13): **20c→21→22→25→24** and **20c→23→26→24** [90,91] has been used as intermediate in the synthesis of antipode **27a**.

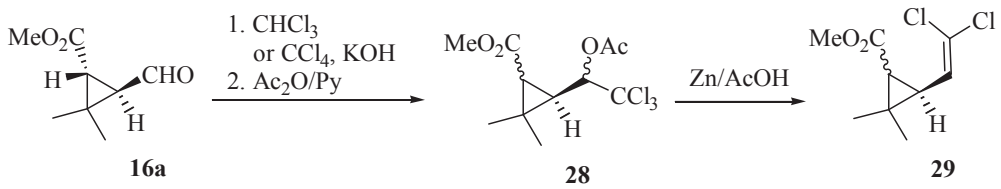


Scheme 13

cis-Product **27a** is formed at the interaction of aldehyde **24** with CBr_4 and Ph_3Ph. The enantiomer **27b** has been obtained from compound **27a** by boiling with potassium *tert*-butoxide in benzene.

Thus, enantiomeric 1*S*- and 1*R*-*trans*-2,2-dibromovinylcyclopropanes **15f** and **27b** have been obtained by epimerization of 1R- and 1S- *cis*-2,2-dibromvinylcyclopropanes **15d** and **27a**.

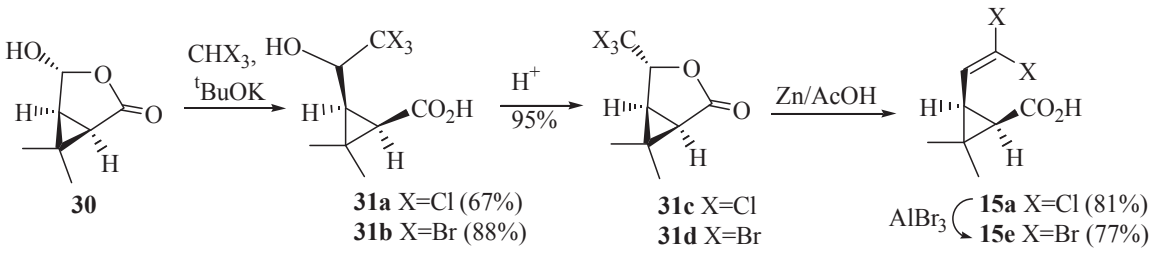
There has been worked out an alternative synthesis of dichlorovinyl-2,2-dimethylcyclopropanecarboxylic acid. For example, epimeric esters **29** have been obtained *via* the interaction of aldehyde **16a** with $CHCl_3$ or with CCl_4 in the presence of KOH in dimethoxyethane [92].



Scheme 14

The treatment of acetates **28** with zinc in acetic acid produces the epimers **29**. The total yield of the product reaction has been 29%.

Such a reaction has also been carried out with caronic aldehyde **30** (scheme 15) [93]. Caronic aldehyde **30** reacts with chloroform in DMF in the presence of potassium *tert*-butoxide generating the formation of hydroxyacid **31a** which is converted under the action of *p*-toluenesulfonic acid in lactone **31c**. At the interaction with zinc in acetic acid, lactone 31c turns into dichlorovinyl acid **15a**.

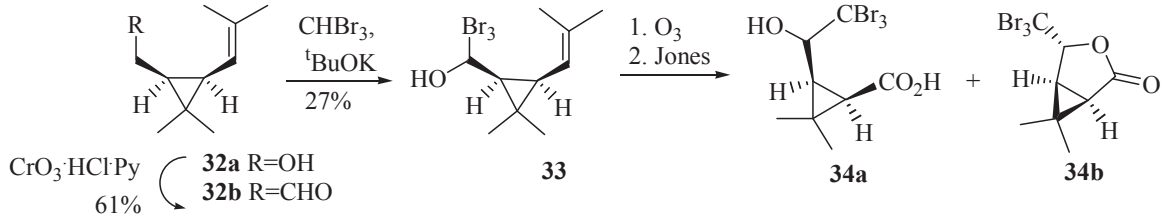


Scheme 15

Similarly, 1R-*cis*-acid **15e** has been obtained *via* substances **31b**, **31d** from acetal **30** [14,94,95].

The dibromovinyl acid **15e** can be obtained from dichlorovinyl acid **15a** when the latter is treated with $AlBr_3$ in 1,2-dibromomethane [88].

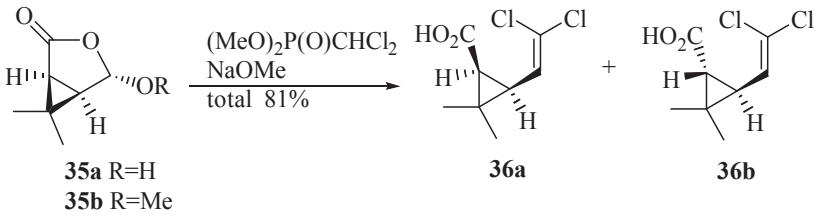
The Indian chemists [96] have described the synthesis of tribromoderivatives **34a**,**b** from alcohol **32a** by the scheme shown below.



Scheme 16

Alcohol **32a** is oxidized in aldehyde **32b**. Product **33** is ozonized and followed by transformation up to the mixture of acid **34a** (yield 15%) and lactone **34b** (yield 38%).

Permetrinic acids **36a,b** can be obtained from lactones **35a,b** also using the phosphate variant of Wittig's reaction [97].

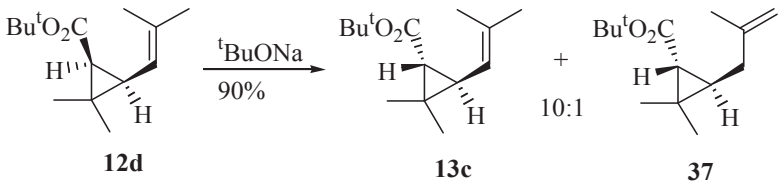


Scheme 17

It should be noted that patents [80,99] as well as the article [100] describe the isomerization of ester of 1*R*,3*R*-caronic aldehyde **16a** under the effect of NaOMe in methyl ester of 1*S*,3*R*-lactol **35b** which, when heated, easily hydrolyzes with aqueous 1,4-dioxane into semiacetal **35a**. Lactone **35b** has also been obtained from the same compound as a result of alkali saponification and the treatment of the product with acid in MeOH.

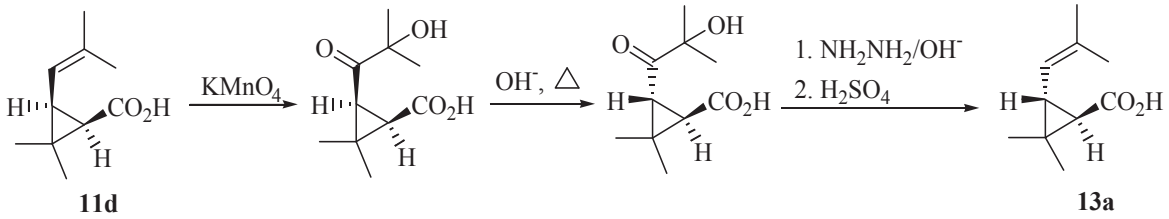
cis-Chrysanthemic acids, e.g. **12c,d** are isomerized into *trans*-isomer **13b,c** [28,34,52] under the action of alkali or when they are subjected to the action of Lewis's acids to chloro anhydride [95,101,102].

Dev S. has obtained ester (+)-*trans*-chrysanthemic acid **13c** in the mixture with its isomer **37** and the initial substance **12d** during the latter's isomerization with sodium *tert*-butoxide [47,51].



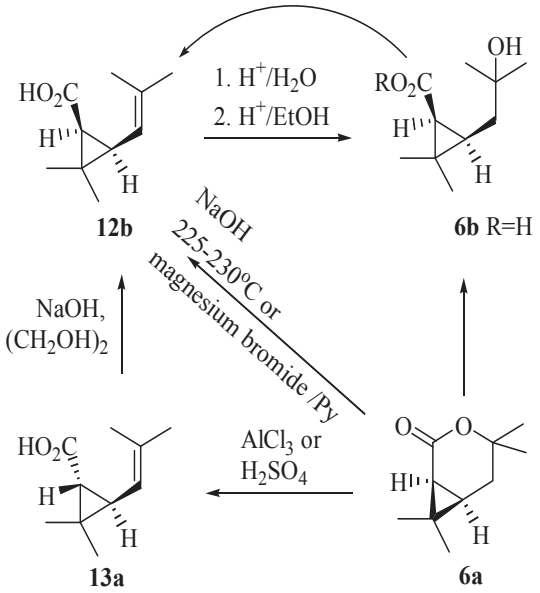
Scheme 18

cis-Acid **11d** can be isomerized into *trans*-isomer **13a** by scheme 19 [28,45].



Scheme 19

In this case epimerization occurs on the C_3 carbon atom. The transformation of *trans*-chrysanthemic acid **13a** into *cis*-isomer **12b** which can proceed by scheme 20 [43,48] is also possible.



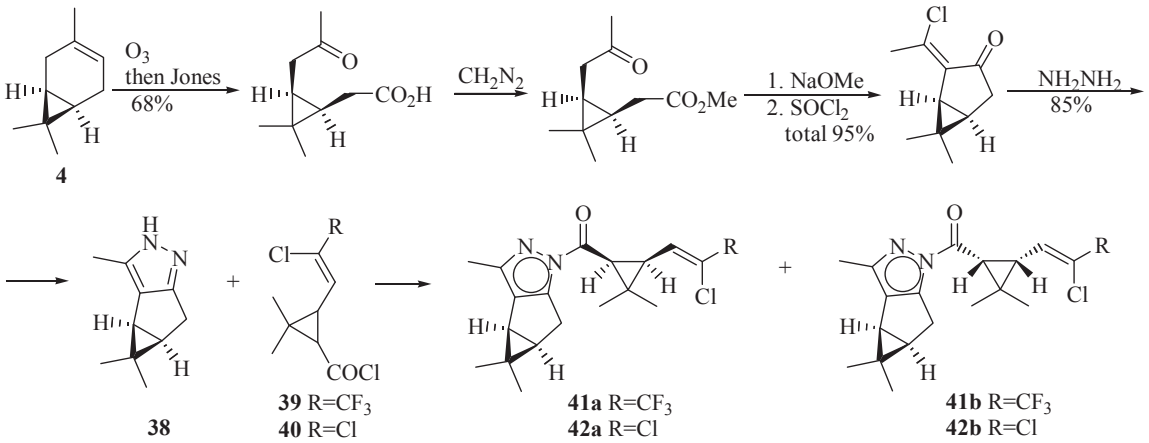
Scheme 20

Dihydrochrysanthemolactone **6a** can also be converted into *cis*-chrysanthemic acid **12b** by heating with magnesium bromide in pyridine [103]. If the above-mentioned conversion of lactone **6a** (heated with NaOH in diethylene glycol) into *trans*-acid **12b** is added, this scheme will be closed.

The set of modern crop protection agents is rather wide. Nevertheless, the investigations concerning the enlargement of their assortment and modernization of the methods of their obtaining are still under way. In the study of synthetic pyrethroids, a special emphasis is placed on the elaboration of new production technologies, including the isolation of diastereomers and enantiomers, which allows one to reduce the applied dozes and, thus, to decrease the chemical impact on the environment.

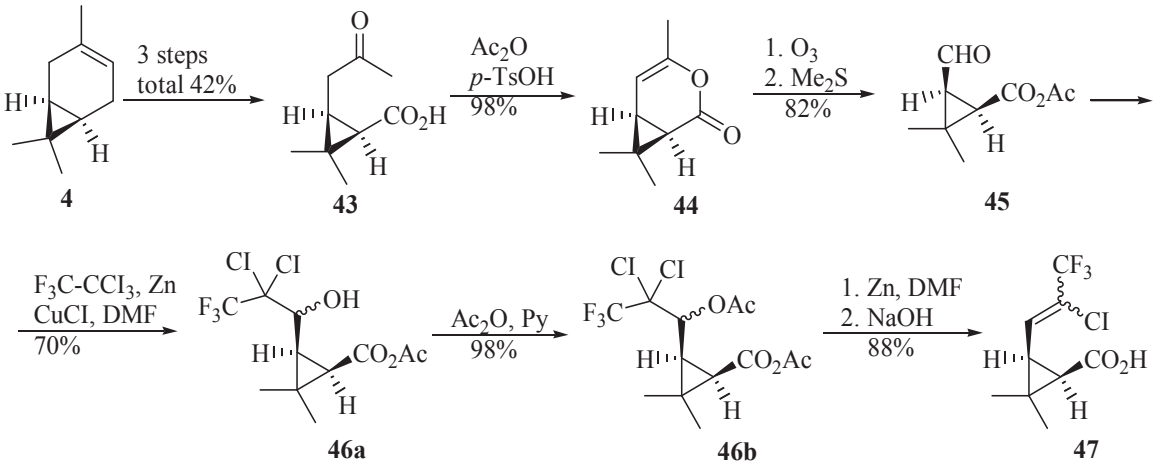
It is known that fluorine containing chrysanthemic acids analogues display a considerable insecticidal activity [67,68,104]. A variant for the separation of (±)-*cis*-thigalotrinic acid **39** and (±)-*cis*-permetrinic acid **40**, respectively, into antipodes *via* the acylation of chiral pyrazole **38** has been proposed [105-110].

In both cases 2*S*-derivatives **41a, 42a** have been completely separated from their antipodes by crystallization. Compounds **41b** as well as **42b** were obtained as oil.



Scheme 21

The mixture *E*- and *Z*- isomeric (-)-1*S*-*cis*-thigalotrinic acid **47** that constitutes an acid component of insecticide **3d** [111] can be obtained from (+)-3-carene **4** by scheme 22 [112,113].



Scheme 22

Acid **43** has been converted into anhydride **45** by the ozonation of lactone **44**. Aldehyde **45** interacts with F_3C-CCl_3 in the presence of zinc, producing a mixture of alcohols **46a** which, when treated with the mixture of acetic anhydride – pyridine, turns into a mixture of acetates **46b**. The reaction of the mixture of **46b** with zinc in DMF and the subsequent hydrolysis of the reaction product leads to the target mixture **47**.

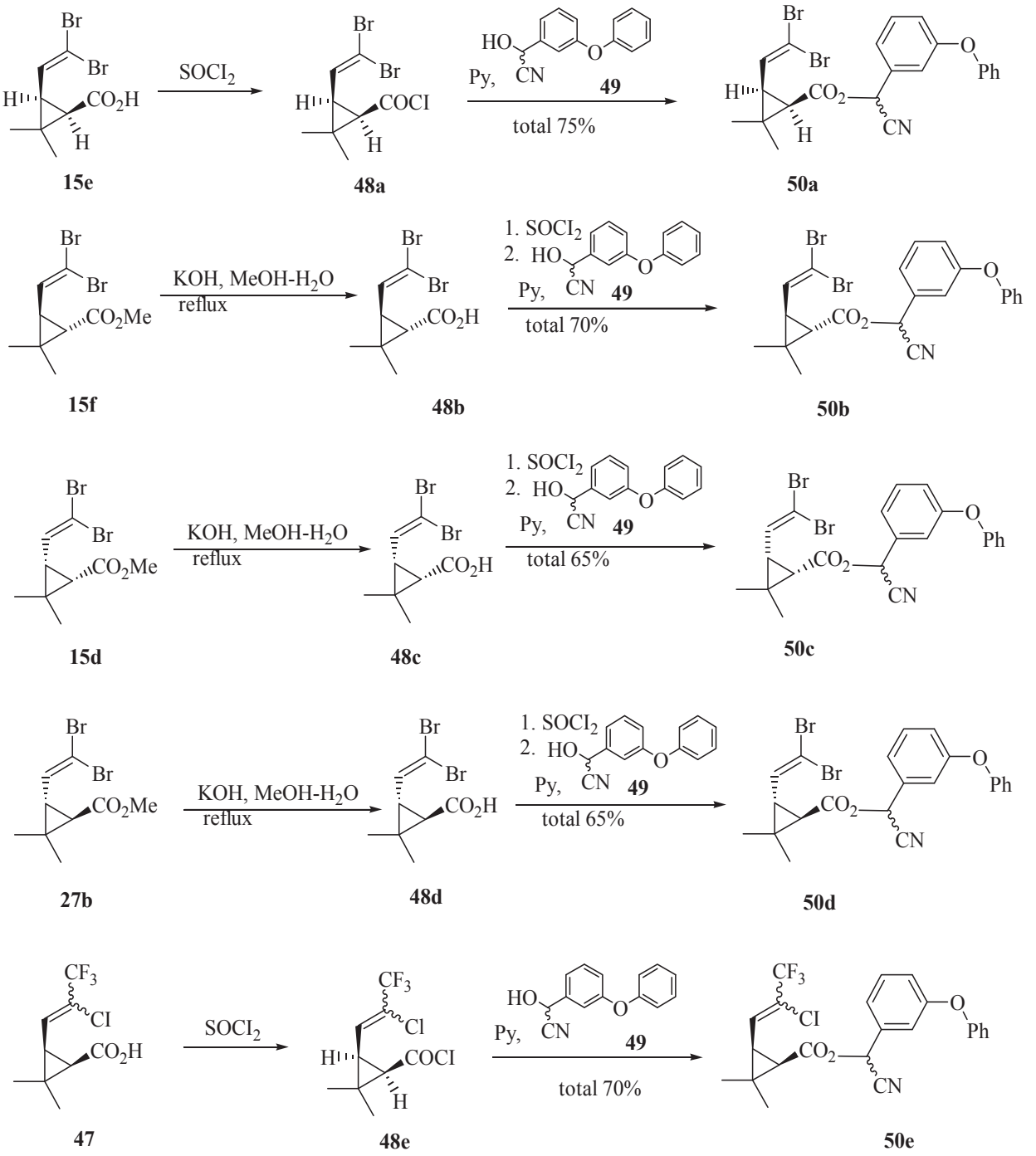
Esters **50a-e** have been synthesized for studying the relationship between stereochemistry and insecticide activity (scheme 23) [114].

Chloro anhydride **48a** has been directly treated with alcohol **49** in the presence of pyridine. Ester **50a** has been isolated with total yield 75%.

The reaction of anhydride **48e** with alcohol **49**, similar to the synthesis of ester **50b-d**, proceeds smoothly producing mixture **50e** with 16% yield from (+)-3-carene **4**.

The results of the laboratory tests on the insecticide impact upon the synthesized substances made against the room fly imago have shown that all synthetic products display a high insecticide activity. It has been established that the highest activity is displayed by product **50a** with 1*R*,3*S*- configuration of the cyclopropane ring carbon atoms. Further, the activity of stereoisomeric products decreases in the following order: 1*R*-*trans*- isomer **50d** > 1*S*-*trans*- isomer **50b** > 1*S*-*cis*- isomer **50c**. The insecticide activity of **49e** is lower than that of the standard – thigalotrin **3d**, however it takes the second place among the tested products.

The synthesis of 1*R*-*cis*-chrysanthemilamine **53** and azo-analogues **56a** of ciphenotrine **56b** was realized according to scheme 24 [115,116].

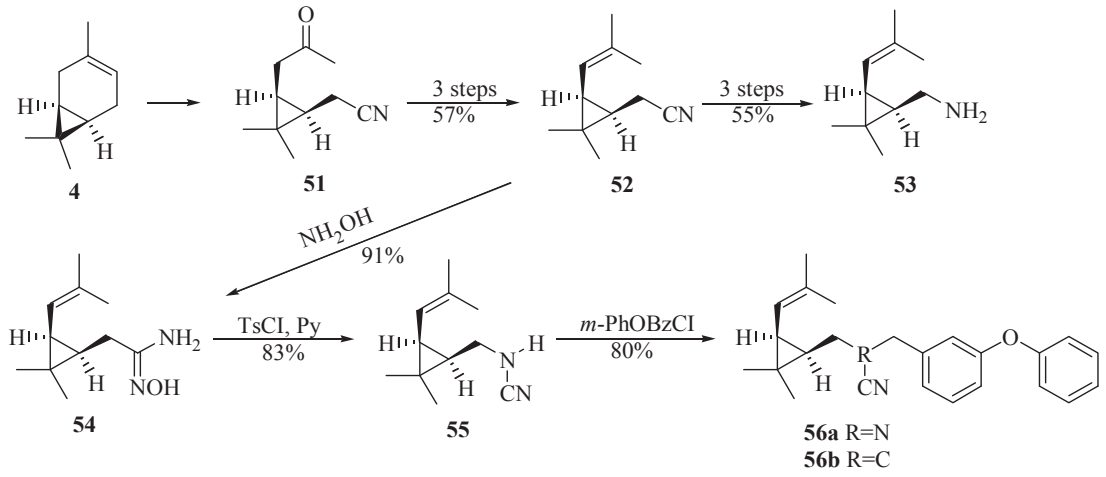


Scheme 23

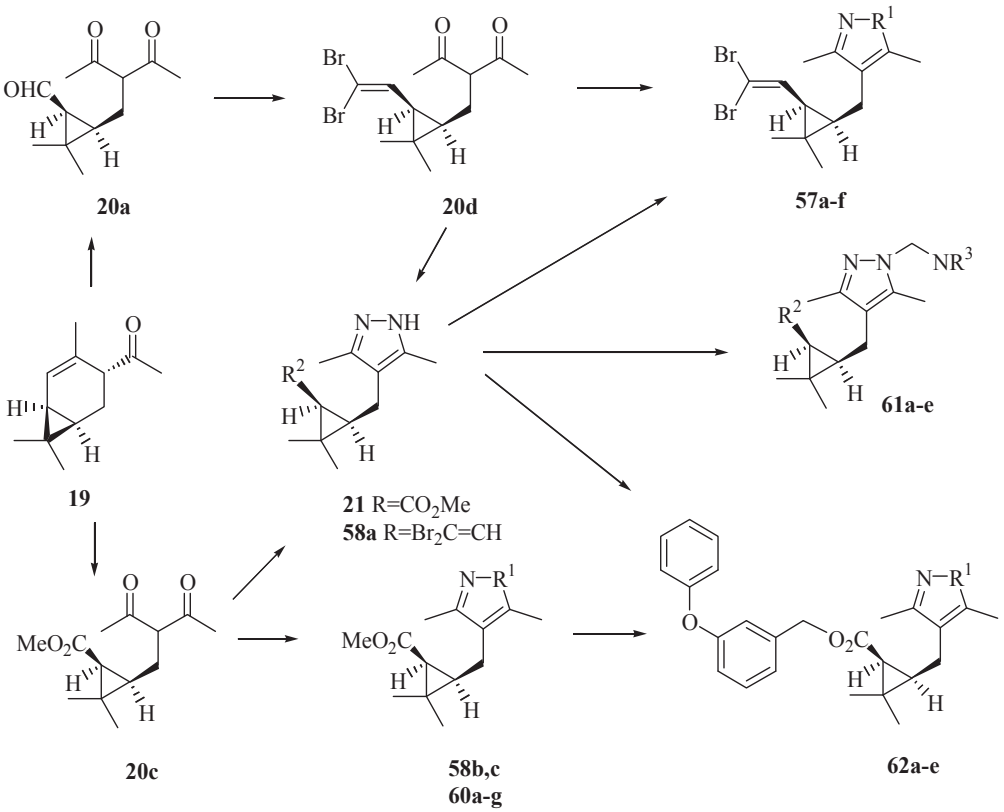
The reaction of nitrile **51** with MeMgI followed by dehydration yields nitrile **52**. The latter compound was converted into amine **53** with total yield 31%. Compound **52** interacts with NH_2OH forming amide oxime **54** which, through compound **55**, has been converted into azo-analogue **56a**.

(+)-4α-Acetyl-2-carene **19** is a convenient initial compound for the design of molecules, including fragments of various structural types with useful properties [117-125]. The assortment of the thus obtained products can be substituted and enlarged utilizing both the 1,3-disubstituted cyclopropanes **20a**, **20c**, and their transformation products **20d** and **21**.

The reaction of β-diketones **20c** with $NH_2OH{\cdot}HCl$ in aqueous solution Na_2CO_3 results in isoxazole **21** with 85% yield.



Scheme *24*



R^1=NEt (**58b**), (**57a**), (**62a**); R^1=O (**21**), (**57e**), (**62b**);
R^1=NPh (**57b**), (**60a**),(**62c**); R^1=CH_2Ph (**57f**);
R^1=2-MeC_6H_4(**57c**), (**60c**); R^1= 4-$MeC_6H_4SO_2$(**57d**), (**60e**);
R^1=4-$CO_2HC_6H_4$(**60d**); R^1= 4-$ClC_6H_4CH_2$(**60f**);
R^1=2-naphtyl (**60g**); R^1= 3-$PhOC_6H_4CH_2$(**60b**), (**62d**);
R^1= COPh (**60f**),(**62e**);
R^2=CO_2Me (**61a**), (**61b**), (**61c**);
R^2=Br_2C=CH (**57e**), (**61d**), (**61e**);
R^3=(-$(C_3H_7)_2$(**61a**); R_3=(-$(CH(Me)_2)_2$(**61b**); R^3= morpholinyl (**61c**);
R^3=Et_2(**61d**); R^3=imidazolyl (**61e**).

Scheme 25

At the interaction of compound **20c** with NH_2NH_2 or ethyl hydrazine in boiling ethanol pyrazoles **58a,b** are formed with 80 and 71% yield, respectively. Condensation reaction proceeds more effectively in the presence of neutral Al_2O_3 without solvent increasing the yield up to 97% and 81%, respectively. The speed of the reaction almost doubles and the reaction finishes in 5 hours. However, if the condensation reaction in the presence of Al_2O_3 is performed under ultrasonic irradiation, then the reaction time decreases to 30 minutes, the reaction products yields remaining the same as shown above.

Chiral pyrazoles **60a-g** have been obtained in a similar way. It is worth noting that pyrazoles **58b** and **60b** have been also synthesized by alkylation of pyrazole **58a** with EtBr and 1-bromomethyl-3-phenoxybenzene, respectively.

When interacting with 1-benzenecarbohydrazine in the conditions described above for the synthesis of pyrazoles **58b,c**, diketone **20c** does not yield the heterocyclic derivative **60f**. However, when the formed adduct is heated in alcohol alkali followed by the treatment with 1-bromomethyl-3-phenoxybenzene, compound **60d** is obtained with 66% yield.

Aminoalkylation of **58a** with formaldehyde and dipropyl- and di-*iso*-propyl amines, as well as with morpholine, results in pyrazoles **61a-e**.

Finally, a series of heterocyclic analogues **62a-e** of permetrin **3a** has been synthesized. Esters **60a-c**, **57b** and **60b** have been saponified followed by the treatment with 1-bromomethyl-3-phenoxybenzene. It should be noted that in the case of the sodium salt of compound **58a**, the reaction of NH-group hydrogen substitution with the formation of product **62d** (yield 40%) proceeded simultaneously.

The investigation of anti-inflammatory effect and anti-microbic activity of compounds **58a-c**, **57f**, **60b,e** has shown that these compounds have a pronounced anti-inflammatory effect at reduced anti-microbic effect. The analysis of these compounds group testing results regarding the fungicide effect has shown that compounds **21b**, **60g** and **61e** display a considerable fungicide effect [126-128].

3. Conclusion

From the given data, it follows that chemists pay a rather great attention to the questions of obtaining, the intermediates suitable for synthesizing an optically active chrysanthemic acid and its analogues on the basis of natural careens. The primary products of the afore-enumerated intermediate transformations were the substances containing 1,3-disubstituted-2,2-dimethylcyclopropane fragment. These products were later utilized in selective synthesis of chrysanthemic acid and its analogues. The availability in the 3-carene **4** of the *gem*-dimethyl fragment as well as the reactive C=C-double bond has called forth the search for transition variants from cheap compound **4** to chrysanthemic acid and its analogues. The chemical transformations of enantiomerically pure 3-carene whose chemistry has been discussed in the review can serve as an alternative variant for synthesizing such kinds of substances.

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