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New Chiral Agents for Resolution of Racemic *cis*-Permethric and *cis*-Z-cyhalothric Acids.

Sergey A. Popov and Alexey V. Tkachev*

Novosibirsk Institute of Organic Chemistry, Novosibirsk 630090, Russia

Abstract: Resolution of racemic pyrethroid acids (*cis*-permethric and *cis*-Z-cyhalothric) using stable optically active amines derived from natural monoterpene (+)-3-carene and prepartion of optically active esters of the pyrethroid acids are described.

Optically active amines are known to be the most common used agents for resolution of racemic cyclopropanecarboxylic acids^{1,2,3}. In most cases these amines have poor stability on the open air and, besides, are readily soluble in water, so recycling of the optically active reagent is highly conjectural. Now we report the use of stable⁴ optically active amines 1 and 2 derived from natural monoterpene (+)-3-carene for the resolution of certain pyrethroid acids - (\pm) -cis-permethric (3) and (\pm) -cis-Z-cyhalothric (4) acids.



Due to their low basicity, amines 1 and 2 do not form stable salts with carboxylic acids. At the same time, when treated with chloroanhydrides of (\pm) -cis-permethric or (\pm) -cis-Z-cyhalothric acids, these amines form mixtures of diastereometric amides 5-8 that are easily separated by crystallization to give individual 2*R*- and 2*S* derivatives. In all the cases 2*S*-derivatives (>95% pure) are crystallized first and corresponding 2*R*-derivatives (ca. 90-95%) remain in mother liquor. NMR data for diastereometre 5-8 are given in Table 1.

Comparison of the data with NMR parameters for simple N-acyl derivative of pyrazole 1^5 shows cyclopropane carboxylic acid moiety to be attached to the N_b-atom of the pyrazole frame in both derivatives 7 and 8. In contrast to the menthol esters of pyrethroid acids that are also used for the separation of racemic cyclopropanecarboxylic acids and whose hydrolysis calls for rigid conditions⁶, acylated pyrazole 7-8 and enaminone derivatives 5-6 are hydrolyzed readily affording optically active pyrethroid acids and starting amine. Purity, melting points, yields and specific rotation of the compounds are collected in Table 2.

	5		6			7	8				
	2'S	2' <i>R</i>	2'S	2'R	2'S	2'R	2'S	2'R			
\mathbf{C}^{i}	δ C ', ppm										
C-1	29.41		29.34		12.78		12.80				
C-2	198.71		198.83		147.86		148.19				
C-3	116.20		116.60		130.92		131.20				
C-4	155.59		155.44		152.06	152.06 152.15		152.15 152.27			
0-5	33.92		24.00			27.14		34.91			
	24.39		32.90		25.64		25.63				
C-8	19.90		19.97		21.91 21.85		21.96 21.89				
C-9	25.95		25.96			26.21	26 19				
C-10	13.29		13.23		13.59		13.59				
C-1'	168.41		168.01		1	68.11	167.86				
C-2'	33.03		35.77		30.20	30.08	32.80	32.83			
C-3'	28.04		29.03			29.89		.87			
C-4'	34.6	57	31	.33	34.66	34.77	31.30	31.13			
C-5'	124.67		130.00		1	124.68		129.94*			
C-6'	120.26		121.34°		1	120.65		121.69°			
C-7'	28.40		28.41			28.34		28.33			
C-8'	14.54		14.57			14.68		14.66			
C-9'			120.29		1			120.36-			
H	δ Η ^{<i>i</i>} , ppm (<i>J</i> , Hz)										
3H-1	2.17 s		2.19 s		2	2.19 s		2.21 s			
αH-5	2.91 ddd (21.	0 2.5 1.5)	2.924 ddd (2	1.0 3.0 2.0)	2.806 ddd	2.775 ddd	2.803 ddd	2.783 ddd			
			2 2 2 2 1 1		(18.3	2.0 2.0)	(19.01	.5 1.5)			
βН-5	3.23 dd (21.0 8.0)		3.239 dd (21.0 7.5)		3.00 aaa	(18.5 5.5 2.5)	2.998 dad 3.013 dad				
	1.2		1 22 datus (8 0 8 0)			1.74 m		(19.0 7.0 2.0)			
H-0	1.4 m		$1.22 \ uan (0.00.0)$ 1.82 dd (7.5.3.0)		1 1	1.74 m		1.75 m			
л-/ 2Ц_0	1.00 aa (7.5 2.5)		1.62 uu (7.5 5.0)		1	1.74 m 1.06 s		1.73 m 1.07 c			
3H-10	0.76 s		0.78 s			0.67 s		0.670 \$ 0.673 \$			
H-2'	165 d (, 83)	1.80 d	(8.5)	3.259 d	3.280 d	3.405 d	3 474 d			
	1.05 4 (0.0)	1.00 0	(0.0)		(8.5)	(9.0	0)			
H-4'	1.996 dd	1.996 dd 2.011 dd		2.13 dd (9.0 8.5)		2.179 dd 2.192 dd		2.336 dd 2.358 dd			
	(9.0 8.3)				(8.5 8.5)		(9.0 9.0)				
H-5'	6.300 d 6.270 d		6.827 dq 6.800 dq		6.349 d	6.304 d	6.976 dq 6.921 dq				
	(9.0)		(9.0	1.2")		(8.5)	(9.0	l. 5')			
3H-7'	1.20 s	*	1.25	s*	1.264 s*	1.288 s*	1.304 s*	1.325 s*			
3H -8 '	1.21 s	*	1.27	s*	1.320 s*	1.313 s*	1.377 s*	1.370 s*			
N <u>H</u>	11.4 bi	r.s	11.5	br.s							

Table 1. ¹³C and ¹H NMR Data for Compounds 5-8^a.

^{*a*} chemical shifts are given for solutions in CDCl₃ (c = 80-120 mg/ml); assignments marked with an asterisk may have to be reversed; ^{*b*} ³J(C-F) = 4.4 Hz; ^{*c*} ²J(C-F) = 38 Hz; ^{*d*} ¹J(C-F) = 272 Hz; ^{*c*} ⁴J(F-H).

	5		6		7		8				
	2'S	2'R	2'S	2'R	2'S	2'R	2'S	2'R			
yield of the diastereomeric mixture	61-66%		61-66%		90-95%		90-95%				
m.p. (from CH ₃ OH)	112-113°	oil	103-104°	oil	153-154°	89-9 0°	179-180°	oil			
purity (based on NMR)	≥98%	85%	≥98%	85%	≥98%	95%	≥98%	90%			
specific rotation, $[\alpha]$	+274	+120	+152	+162	+138	+184	+56.6	+190			
c in CHCl ₃	2.3	2.7	4.8	4.5	1.9	11	2.4	9.9			
temperature, °C	23°	23°	23°	23°	25°	22°	19°	19°			
resulting pyrethroid acid:											
yield		90%			91%						
specific rotation, $[\alpha]$	-30.0	+24.2	-43.2	+36.8	-30.0	+29.0	-40.2	+39.5			
c in CHCl ₃	3.3	2.7	1.9	2.5	3.3	8.8	2.4	2.8			
temperature, °C	22	23	21	22	20°	21°	22°	20			
yield of the chiral amine recovered	80%				86%						

 Table 2.
 Purity, Melting Points, Yields and Specific Rotation for Compounds 5-8 and for the Resolved Pyrethroid Acids.

When treated with the apropriate alcohol in acidic medium, the pyrethroid acid amides may be easily transformed to the corresponding esters. Thus, treatment of 2'R-7 with 3-phenoxybenzyl alcohol leads directly to 1R-cis-permethrin which is known to be the most biologically active isomer³:



Using pyrazole 1 and enaminone 2, we have tried to resolve some other racemic acids such as (\pm) -2-(4chlorophenyl)-valeric acid, (\pm) -2-phenylbutiric acid, (\pm) -2-[4-(2-methylpropyl)-phenyl)-propionic acid (ibuprofen), but none of them forms crystalline adducts. We synthesized another optically active pyrazole 13 starting from the enaminone 11 derived from R-(+)-limonene. The synthesis was carried out via diketone 12 as described before for the carene-type derivatives⁵. In contrast to the related bicyclic diketone, NMR spectra of compound 12 shows 3 isomeric forms: 12A (two C2-epimers) and 12B. Comparison of the NMR parametres for 13 and its acylated derivative 14 with those of the pyrazole-type compounds of the carene series shows the formation of the only N-acylated derivative with the acetyl group being attached to the N_b- atom of the pyrazole frame. When treated with the racemic chloroanhydrides of the pyrethroid acids, enaminone 11 and pyrazole 13 form diastereomeric mixtures of N-acylated derivatives, but none of them are crystalline.



EXPERIMENTAL

See Ref.⁵ about General Experimental.

Compounds 1⁵ and 2⁷ were prepared according to the known procedures. Optically active enaminone 11 $([\alpha]^{23}$ -57.6, c=7.35 in CHCl₃) was prepared from *R*-(+)-limonene (Aldrich Chemical Co.) as described for racemate in ref.⁷.

Choloroanhydrides of Z-cyhalothric and cis-permethric acid were prepared from the acids and SOCl₂ (14 h at room temperature).

Cyhalothric acid derivatives 8. A solution of Z-cyhalothric acid chloroanhydride (prepared from 0.8 g, 3.3 mmol of the acid) in CH₂Cl₂ (5 ml) was added dropwise to a stirred solution of pyrazole 1 (1 g, 6.2 mmol) and pyridine (0.3 g, 3.8 mmol) in CH₂Cl₂ (5 mL) at 0°C. The reaction muxture was heated to room temperature and allowed to stay for 5 h. The solvent was removed at reduced pressure and the residue was extracted with ether (2×20 mL). The combined ethereal extracts were washed consequently with 5% aq. Na₂CO₃ (20 mL) and 1 M aq. HCl (2×20 mL), dried (Na₂SO₄) and concentrated at reduced pressure to give the *title compound* (1.2 g, 94%) as white powder; MS: m/z (%) = 386.13753 [(M)⁺, 23; calc. for C₁₉H₂₂ClF₃N₂O 386.13727], 351 (10), 203 (20), 189 (33), 162 (20), 174 (100), 106 (10), 83 (21). The acidic aqueous phase was treated with an excess of aq. NH₃ and extracted with CHCl₃ to give the unreacted pyrazole 1 (0.42 g 2.6 mmol).

Isolation of 2*R*-8. Crude mixture of diastereomers 8 (1.2 g, 3.1 mmol) was crystallised from benzenemethanol (20 mL, 1:1 v/v) and then twice from methanol (10 and 10 mL), each time the previous concentrated mother liqour was taken for further crystallisation. The final mother liquor was concentrated to give pale yellow oil (0.38 g, 0.98 mmol) containing more than 90% of 2'*R*-8 (¹H and ¹³C NMR).

Isolation of 2 S-8. Crude mixture of diastereomers 8 (1.2 g, 3.1 mmol) was crystallised twice from benzene-methanol (20 mL, 1:1 v/v; 10 mL, 1:1 v/v) to give white crystals (0.40 g, 1.03 mmol) which contained more than 95 % of 2'S-8 (¹H and ¹³C NMR).

Hydrolysis of amides 8. A solution of KOH (1g) in MeOH (5 mL) was added at vigorous stirring to a boiling suspension of 2'R-8 or 2'S-8 (0.160 g,0.45 mmol) in MeOH (5 mL). The reaction mixture became homogeneous immediatly, the stirring was continued for 5 min, water (5 mL) was added and the mixture was refluxed for 5 h. The solvent was removed at reduced pressure and the residue was diluted with water (50 mL) and extracted with CH₂Cl₂ (2×20 mL). The organic extracts were washed with water (20 mL), dried

 (Na_2SO_4) and concentrated to give pyrazole (0.062 g, 86 %) as pale yellow crystals. The combined aqueous solutions were treated with aq. 20 % HCl (5 mL), saturated with NaCl and extracted with CHCl₃ (3×15 mL) to give 1*R*- or 1*S*- (*cis*,*Z*)-2,2-dimethyl-3-(2-chloro-3,3,3-trifluoro-1-propenyl)cyclopropane carboxylic acid (cyhalothric acid, 0.092 g, 91%) as white crystals.

Permethric acid derivatives 7. Diastereomeric mixture 7 (1.53 g, 91%) as white powder was prepared from permethric acid (1 g, 4.78 mmol) and pyrazole 1 (1.5 g, 9.25 mmol) as described before for the preparation of the cyhalothric acid derivative; MS: m/z (%) = 352.10932 [(M)⁺, 28; calc. for C₁₈H₂₂Cl₂N₂O 352.11092], 317 (16), 203 (35), 189 (49), 162 (15), 147 (100), 127 (12), 106 (12), 91 (26), 83 (18), 77 (14), 41 (12).

Isolation of 2R-7. 2'R-7 (0.43 g, 1.21 mmol, more than 95% of the 2'R isomer according to NMR) as white crystals was prepared from the crude diastereomeric mixture (1.53 g, 4.35 mmol) by the same manner as described before for the isolation of the 2'R-8.

Isolation of 2'S-7. 2'S-7 (0.52 g, 1.47 mmol, more than 95% of the 2'S isomer) was prepared as described before for the 2'S-8.

Permethric acid derivatives 5. Reaction of permethric acid chloroanhydride (prepared from 0.3 g, 1.43 mmol of permethric acid) and enaminone 2 (1 g, 6.1 mmol) and pyridine (1.5 mL) in CH₂Cl₂ (10 mL) at room temperature for 24 h followed by column chromatography of the crude product (0.45 g) resulted in the *title compound* (0.33 g, 66 %) as pale yellow oil; MS: m/z (%) = 355.11056 [(M)⁺, 11; calc. for C₁₈H₂₃Cl₂NO₂ 355.11058], 191 (19), 165 (100), 150 (43), 127 (16), 122 (15), 91 (22), 43 (33).

Isolation of 2R-5. Crude mixture of diastereomers 5 (0.4 g, 1.12 mmol) was crystallised twice from methanol (5 and 5 mL) and then from aqueous methanol (5 mL, 1:4 v/v), each time the previous concentrated mother liquor was taken for further crystallisation. The final mother liquor was concentrated to give pale yellow oil (0.12 g, 0.34 mmol) containing more than 85% of 2'R-5 (¹H and ¹³C NMR).

Isolation of 2 S-5. Crystallization of the crude diastereomeric mixture 5 (0.4 g, 1.12 mmol) from methanol (twice, 5 and 5 mL) gave white crystals (0.14 g, 0.39 mmol) containing more than 95% of the 2 S permethric acid derivative.

Hydrolysis of amides 2R-5 and 2S-5 was carried as described for the hydrolysis of amides 8.

Cyhalothric acid derivatives 6. Preparation of the diastereomeric mixture 6 {MS: m/z (%) = 389.13565 [(M)⁺, 11; calc. for C₁₉H₂₃ClF₃NO₂ 389.13694], 225 (16), 165 (100), 150 (34), 122 (12), 43 (20)} and isolation of 2'*R*-6 and 2'*S*-6 were the same as it was described before for the permethric acid derivatives 5.

IR-cis-Permethric acid methyl ester 9. Dried gaseous HCl was blown into a boiling solution of amide 2R-5 (0.35 g, 1.0 mmol) in CH₃OH (5 mL) for 1.5 h. The reaction mixture was concentrated at reduced pressure, the residue was taken up into benzene and the resulting solution was washed with water (15 mL), 1N aq. HCl (15 mL), dried (Na₂SO₄). The solvent was evaporated at reduced pressure and the crude product was purified by column chromatography (Al₂O₃, benzene) to give methyl ester 9 (0.20 g, 83%). The acidic aqueous extract was treated with aq. NH₃ and extracted with CHCl₃ to recover pyrazole 1 (0.13 g, 80%).

IR-cis-Permethrin 10. Dried gaseous HCl was blown into a boiling solution of amide 2*R*-5 (0.50 g, 1.4 mmol) and 3-phenoxybenzyl alcohol (0.54 g, 2.8 mmol) in CHCl₃ (1.5 mL) for 1.5 h. Treatment of the reaction mixture and purification of the crude product as described above afforded *IR-cis*-permethrin 10 (0.43 g, 76%) and pyrazole 1 (0.19 g, 81%). Hydrolysis of the *IR-cis*-permethrin prepared resulted in *IR-cis*-permethric acid *IR-cis*-3 having $[\alpha]^{18}$ +29.9 (c 6.8, CHCl₃).

(4R)-2-Acetyl-4-(1-methyl-1-ethenyl)-cyclopentanone 12. A solution of enaminone 11 (3.00 g, 18.3 mmol) in a mixture of CH₃OH (5 mL) and 0.5N aq. H₂SO₄ (40 mL) was stirred at 80°C for 1 h to give the title compound (2.70 g, 88%); $[\alpha]^{23}$ -3.7 (c 2.17, CHCl₃). MS: m/z (%) = 166.1001 [(M)⁺, 55; calc. for C₁₀H₁₄O₂ 166.0994], 151 (28), 124 (25), 123 (100), 109 (33), 96 (35), 95 (41), 81 (53), 70 (55). NMR ¹³C (CDCl₃): 30 signals (3 isomeric forms). NMR ¹H (CDCl₃): 2.22 s and 2.24 s (CH₃CO-, cis- and transisomers of 12A), 1.89 s (CH₃CO-, 12B),

(7R)-4-Methyl-7-(1-methyl-1-ethenyl)-2, 3-diazabicyclo[3.3.0]octane 13. Reaction of diketone 11 (1.60 g, 9.6 mmol) with hydrazine hydrate (1.0 g, 20 mmol) in a boiling mixture of CH₃OH (20 mL) and glacial acetic acid (3 mL) for 20 min. resulted in *the title compound* (1.30 g, 84%); m.p. 70-71°C (after sublimation in vacuum); $[\alpha]^{23}$ -2.5 (c 3.67, CHCl₃). MS: m/z (%) = 162.1159 [(M)^{*}, 81; calc. for C₁₀H₁₄N₂ 162.1157], 161 (38), 148 (10), 147 (100), 134 (18), 121 (13), 120 (15), 106 (27), 79 (10), 77 (9). NMR ¹³C (CDCl₃): 10.34 q, 20.30 q, 27.64 t, 29.58 t, 52.42 d, 109.25 t, 121.09 s, 133.41 s, 147.57 s, 158.13 s. NMR ¹H (CDCl₃): 1.78 s 3H, 2.23 s 3H, 2.49 dd (J = 14.5 and 8.0 Hz) 1H, 2.67 dd (J = 15.0 and 8.0 Hz) 1H, 2.74 dd (J = 14.5 and 8.0 Hz) 1H, 2.88 dd (J = 15.0 and 8.0 Hz) 1H, 3.47 dddd (J = 8.0, 8.0, 8.0 and 8.0 Hz) 1H, 4.75 br.s 1H, 4.82 br.s 1H, 11.6 br. 1H.

(7R)-2-Acetyl-4-methyl-7-(1-methyl-1-ethenyl)-2, 3-diazabicyclo[3.3.0]octane 14. Reaction of pyrazole 13 with Ac₂O (0.13 g, 1.3 mmol) and pyridine (0.11 g, 1.4 mmol) at room temperature for 1 h gave the title compound (0.22 g, 90%) as colorless oil, $[\alpha]^{23}$ -25.4 (c 6.06, CHCl₃). MS: m/z (%) = 204.12617 [(M)⁺, 58; calc. for C₁₂H₁₆N₂O 204.12626], 162 (82), 161 (78), 147 (100), 133 (18), 120 (8), 109 (6); NMR ¹³C (CDCl₃): 12.60 q, 19.94 q, 21.25 q, 27.34 t, 31.82 t, 52.24 d, 109.55 t, 128.95 s, 146.46 s, 147.62 s, 149.89 s, 168.94 s. NMR ¹H (CDCl₃): 1.66 dd (J = 1.0 and 1.0 Hz) 3H, 2.10 s 1H, 2.34 dddd (J = 14.5, 7.5, 1.5 and 1.5 Hz) 1H, 2.48 s 3H, 2.59 ddd (J = 14.5, 8.5 and 1.5 Hz) 1H, 2.79 dddd (J = 17.0, 7.5, 1.5 and 1.5 Hz) 1H, 3.50 ddddd (J = 8.0, 8.0, 8.0 and 8.0 Hz) 1H, 4.65 br.s 1H, 4.70 br.s 1H.

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