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

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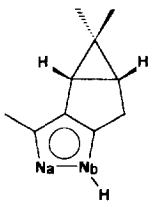
Abstract: Resolution of racemic pyrethroid acids (*cis*-permethric and *cis-Z*-cyhalothric) using stable optically active amines derived from natural monoterpene (+)-3-carene and prepartion of optically active esters of the pyrethroid acids are described.

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 stable[4] optically active amines **1** and **2** derived from natural monoterpene (+)-3-carene for the resolution of certain pyrethroid acids - (±)-*cis*-permethric (**3**) and (±)-*cis-Z*-cyhalothric (**4**) acids.



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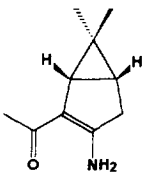

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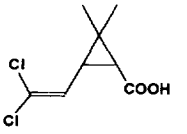

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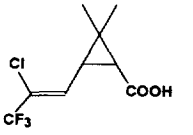

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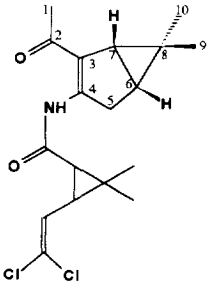

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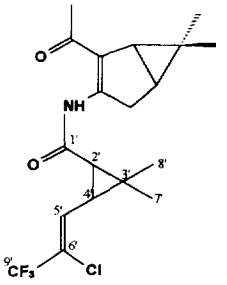

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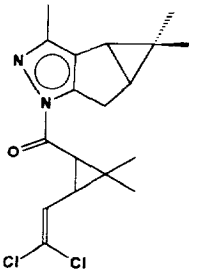

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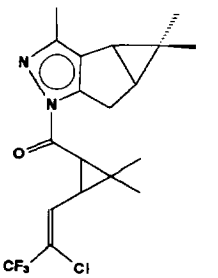

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Due to their low basicity, amines **1** and **2** do not form stable salts with carboxylic acids. At the same time, when treated with chloroanhydrides of (±)-*cis*-permethric or (±)-*cis-Z*-cyhalothric acids, these amines form mixtures of diastereomeric amides **5-8** that are easily separated by crystallization to give individual *2R*- and *2S* derivatives. In all the cases *2S*-derivatives (>95% pure) are crystallized first and corresponding *2R*-derivatives (ca. 90-95%) remain in mother liquor. NMR data for diastereomers **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 conditions[6], 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.

Table 1. **^{13}C and ^{1}H NMR Data for Compounds 5-8[a].**

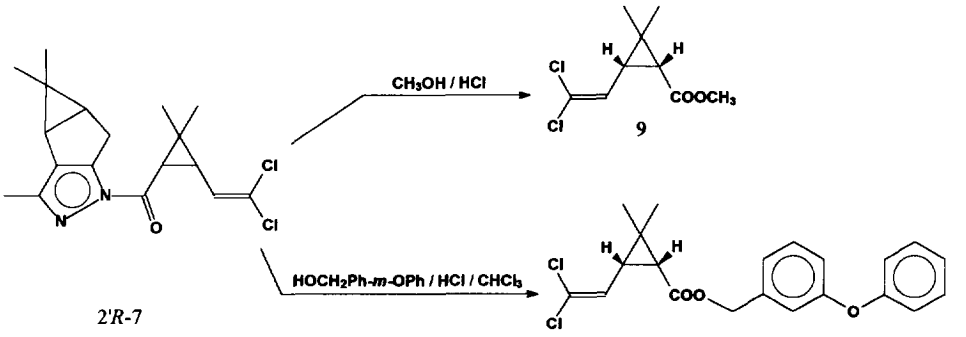
	5		**6**		**7**		**8**	
	2'*S*	2'*R*	2'*S*	2'*R*	2'*S*	2'*R*	2'*S*	2'*R*
C^i	**δC^i, ppm**							
C-1	29.41		29.34		12.78		12.80	
C-2	198.71		198.83		147.86		148.19	
C-3	116.20		116.60		130.92		131.20	
C-4	155.59		155.44		152.06	152.15	152.15	152.27
C-5	33.92		34.00		27.14		27.13	
C-6	24.59		24.71		34.89		34.91	
C-7	32.77		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		168.11		167.86	
C-2'	33.03		35.77		30.20	30.08	32.80	32.83
C-3'	28.04		29.03		29.89		30.87	
C-4'	34.67		31.33		34.66	34.77	31.30	31.13
C-5'	124.67		130.00[b]		124.68		129.94[b]	
C-6'	120.26		121.34[c]		120.65		121.69[c]	
C-7'	28.40		28.41		28.34		28.33	
C-8'	14.54		14.57		14.68		14.66	
C-9'			120.29[d]				120.36[d]	
H^i	**δH^i, ppm (*J*, Hz)**							
3H-1	2.17 *s*		2.19 *s*		2.19 *s*		2.21 *s*	
αH-5	2.91 *ddd* (21.0 2.5 1.5)		2.924 *ddd* (21.0 3.0 2.0)		2.806 *ddd* (18.5 2.0 2.0)	2.775 *ddd*	2.803 *ddd* (19.0 1.5 1.5)	2.783 *ddd*
βH-5	3.23 *dd* (21.0 8.0)		3.239 *dd* (21.0 7.5)		3.00 *ddd* (18.5 5.5 2.5)		2.998 *ddd* (19.0 7.0 2.0)	3.013 *ddd*
H-6	1.2 *m*		1.22 *ddm* (8.0 8.0)		1.74 *m*		1.75 *m*	
H-7	1.80 *dd* (7.5 2.5)		1.82 *dd* (7.5 3.0)		1.74 *m*		1.75 *m*	
3H-9	1.05 *s*		1.07 *s*		1.06 *s*		1.07 *s*	
3H-10	0.76 *s*		0.78 *s*		0.67 *s*		0.670 *s*	0.673 *s*
H-2'	1.65 *d* (8.3)		1.80 *d* (8.5)		3.259 *d* (8.5)	3.280 *d*	3.405 *d* (9.0)	3.424 *d*
H-4'	1.996 *dd* (9.0 8.3)	2.011 *dd*	2.13 *dd* (9.0 8.5)		2.179 *dd* (8.5 8.5)	2.192 *dd*	2.336 *dd* (9.0 9.0)	2.358 *dd*
H-5'	6.300 *d* (9.0)	6.270 *d*	6.827 *dq* (9.0 1.2[e])	6.800 *dq*	6.349 *d* (8.5)	6.304 *d*	6.976 *dq* (9.0 1.5[e])	6.921 *dq*
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**
NH	11.4 *br.s*		11.5 *br.s*					

[a] chemical shifts are given for solutions in **$CDCl_3$** (*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; [e] **^4J(F-H)**.

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

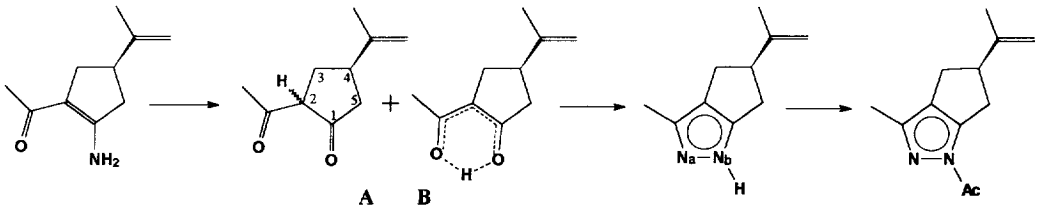
	5		6		7		8	
	2'*S*	2'*R*	2'*S*	2'*R*	2'*S*	2'*R*	2'*S*	2'*R*
yield of the diastereomeric mixture	61-66%		61-66%		90-95%		90-95%	
m.p. (from **CH_3OH**)	112-113°	*oil*	103-104°	*oil*	153-154°	89-90°	179-180°	*oil*
purity (based on NMR)	≥98%	85%	≥98%	85%	≥98%	95%	≥98%	90%
specific rotation, [α]	+274	+120	+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, [α]	-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%			

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 1*R*-*cis*-permethrin which is known to be the most biologically active isomer[3]:



Using pyrazole **1** and enaminone **2**, we have tried to resolve some other racemic acids such as (±)-2-(4-chlorophenyl)-valeric acid, (±)-2-phenylbutiric acid, (±)-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 derivatives[5]. 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.



11 **12** **13** **14**

EXPERIMENTAL

See Ref.[5] about General Experimental.

Compounds **1**[5] and **2**[7] were prepared according to the known procedures. Optically active enaminone **11** ($[\alpha]^{23}$ −57.6, *c*=7.35 in **$CHCl_3$**) 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 **$SOCl_2$** (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 **CH_2Cl_2** (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 **CH_2Cl_2** (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. **Na_2CO_3** (20 mL) and 1 M aq. **HCl** (2×20 mL), dried (**Na_2SO_4**) 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 $C_{19}H_{22}ClF_3N_2O$ 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. **NH_3** and extracted with **$CHCl_3$** 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 benzene-methanol (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** (^{1}**H** and ^{13}**C** 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** (^{1}**H** and ^{13}**C** 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 **CH_2Cl_2** (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 **$CHCl_3$** (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 $C_{18}H_{22}Cl_2N_2O$ 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 2′R-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 **CH_2Cl_2** (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 $C_{18}H_{23}Cl_2NO_2$ 355.11058], 191 (19), 165 (100), 150 (43), 127 (16), 122 (15), 91 (22), 43 (33).

Isolation of 2′R-**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 liqour 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** (^{1}**H** and ^{13}**C** 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 *2′R*-**5** and *2′S*-**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 $C_{19}H_{23}ClF_3NO_2$ 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**.

1R-cis-Permethric acid methyl ester **9**. Dried gaseous **HCl** was blown into a boiling solution of amide *2′R*-**5** (0.35 g, 1.0 mmol) in **CH_3OH** (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 (**Na_2SO_4**). The solvent was evaporated at reduced pressure and the crude product was purified by column chromatography (Al_2O_3, benzene) to give methyl ester **9** (0.20 g, 83%). The acidic aqueous extract was treated with aq. **NH_3** and extracted with **$CHCl_3$** to recover pyrazole **1** (0.13 g, 80%).

1R-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 **$CHCl_3$** (1.5 mL) for 1.5 h. Treatment of the reaction mixture and purification of the crude product as described above afforded *1R-cis*-permethrin **10** (0.43 g, 76%) and pyrazole **1** (0.19 g, 81%). Hydrolysis of the *1R-cis*-permethrin prepared resulted in *1R-cis*-permethric acid *1R-cis*-**3** having $[\alpha]^{18}$+29.9 (*c* 6.8, **$CHCl_3$**).

(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 **CH_3OH** (5 mL) and 0.5N aq. **H_2SO_4** (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, **$CHCl_3$**). MS: *m/z* (%) = 166.1001 [$(M)^+$, 55; calc. for $C_{10}H_{14}O_2$ 166.0994], 151 (28), 124 (25), 123 (100), 109 (33), 96 (35), 95 (41), 81 (53), 70 (55). NMR ^{13}C (**$CDCl_3$**): 30 signals (3 isomeric forms). NMR ^1H (**$CDCl_3$**): 2.22 *s* and 2.24 *s* (**CH_3CO-**, *cis-* and *trans-*isomers of **12A**), 1.89 *s* (**CH_3CO-**, **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 **CH_3OH** (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, **$CHCl_3$**). MS: *m/z* (%) = 162.1159 [$(M)^+$, 81; calc. for $C_{10}H_{14}N_2$ 162.1157], 161 (38), 148 (10), 147 (100), 134 (18), 121 (13), 120 (15), 106 (27), 79 (10), 77 (9). NMR ^{13}C (**$CDCl_3$**): 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 (**$CDCl_3$**): 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 Ac_2O (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, **$CHCl_3$**). MS: *m/z* (%) = 204.12617 [$(M)^+$, 58; calc. for $C_{12}H_{16}N_2O$ 204.12626], 162 (82), 161 (78), 147 (100), 133 (18), 120 (8), 109 (6); NMR ^{13}C (**$CDCl_3$**): 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 (**$CDCl_3$**): 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, 3.09 *ddd* (J = 17.0, 8.5 and 1.5 Hz) 1H, 3.50 *dddd* (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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