Tetrahedron Letters,Vol.26,No.35,pp 4261-4264,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF ALKENOIC ACID DERIVATIVES CONTAINING CYCLOPROPANE RING, NEW JUVENILE HORMONE ANALOGS[1]

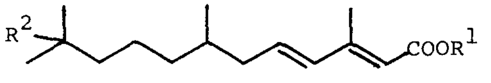
Gábor Baán[a], Péter Vinczer[a], Lajos Novák[b] and *Csaba Szántay[a,b]

[a]Central Research Institute for Chemistry of the
Hungarian Academy of Sciences, H-1525 Budapest, Hungary

[b]Institute for Organic Chemistry, Technical University of
Budapest, H-1111 Budapest, Hungary

Abstract: *A synthetic method is described for the preparation of new type juvenoids* [2].

In the last twenty years hundreds of chemical structures with juvenil hormone activity have been synthesized and investigated[2]. Among these juvenoids, the alkyl (2E,4E)-3,7,11-trimethyl-2,4-dodecadienoates are the most effective insect growth regulators[3]. Hydroprene [1a] and methoprene [1b] are successfully used in controlling important agricultural pest species.



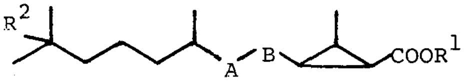
1

1a: $R^1 = C_2H_5$; $R^2 = H$
1b: $R^1 = CH(CH_3)_2$; $R^2 = OCH_3$

Detailed structure-biological activity studies showed that the structure and geometry (E,E configuration) of the C_{1-5} unit of 1 were important in point of effectivity[2b,4a]. A substantial enhancement of biological activity could be realized by introducing rigid structural element into this part of the molecule[4].

Now we report a simple synthesis of new type of juvenoids [2] in which the alkenoic acid has an internal cyclopropane ring close to the carboxylic group[5,6,7].

In the synthesis of 2 we started from the readily available substituted dihydro-citronellal [3]. Thiazolium ion catalysed[8] conjugate addition reaction[9] of 3 to alkyl 2-oxo-3-methyl-3-butenoate[10] [4] yielded 2,5-dioxo-dodecanoic acid



2

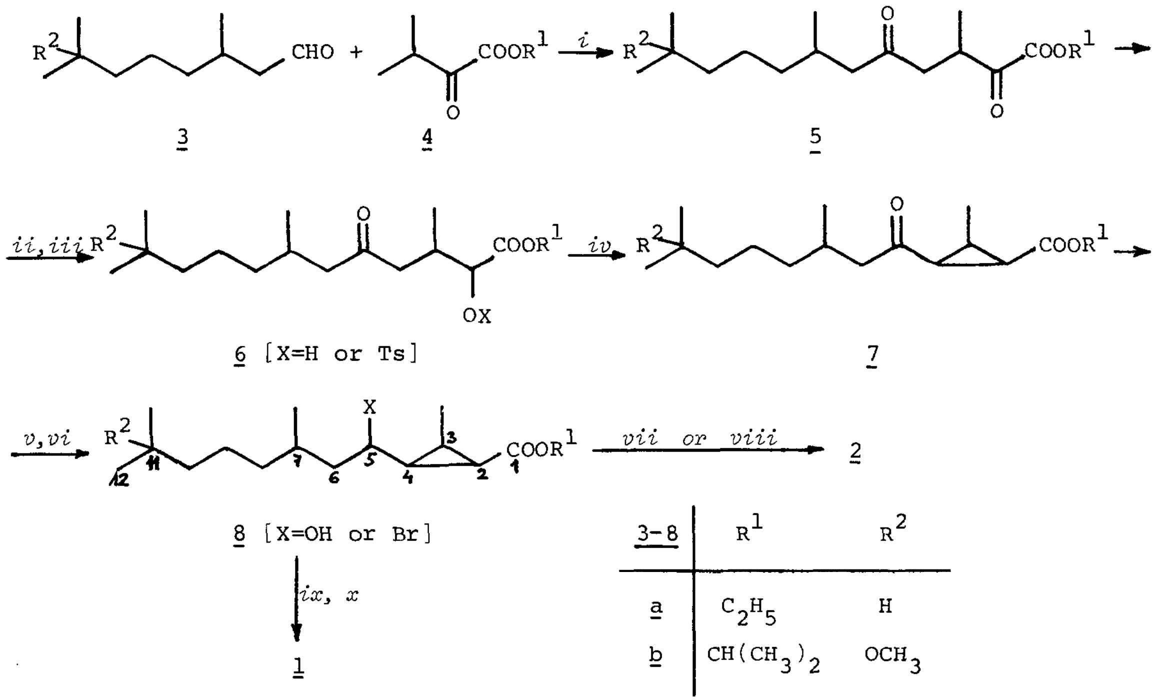
2	R^1	R^2	A-B
a	C_2H_5	H	$-\underset{H}{C}=\overset{H}{C}-$
b	$CH(CH_3)_2$	OCH_3	$-\underset{H}{C}=\overset{H}{C}-$
c	C_2H_5	H	$-CH_2-CH_2-$
d	$CH(CH_3)_2$	OCH_3	$-CH_2-CH_2-$

derivative[11] [5] (*20hr, 95-100°C*) which was selectively reduced at the α-carbonyl group with sodium borohydride (*0,6 mol in THF 0°C, 1hr*) in high yield. The resulting alcohol [6: X=H] was converted to the corresponding tosylate [6:X=Ts] by p-toluenesulfonyl chloride in the presence of pyridine (*24hr, 25°C*). Treatment of the crude tosylate with potassium t-butoxid (*2 ekv in benzene, r.t., 30 min*) in the presence of catalitic amount of 18-Crown-6 afforded a diastereomeric mixture of 7 [12], which was not separated. The carbonyl group of 7 was reduced with sodium borohydride at the boiling point of the appropriate alcohol (*ethanol or isopropanol, 4hr*) and the resulting alcohol [8: X=OH] was halogenated with phosphorous tribromide (*LiBr, 2,4,6-collidine, 3hr, -40 to 0°C*)[13]. Treatment of the resulting bromo ester [8: X=Br][14] with DBU (*50°C, 2hr*) to effect elimination of hydrogen bromide afforded target compounds 2a,b[15]. Finally, reduction of bromo ester [8: X=Br] with sodium cyanoborohydride (*4 ekv in HMPT, 70°C, 3hr*) yielded compounds 2c,d.

Furthermore, intermediates 8 [X=Br] were easily converted to hydroprene [1a] and methoprene [1b], respectively, by homoallylic rearrangement (*$ZnBr_2$ in ether, -40 to 0°C, 2hr*)[17] followed by base-catalysed elimination (*DBU, 50°C, 2hr*).

The biological screening of compounds 2a-d is currently being carried out.

Acknowledgements: The authors wish to thank to EGIS Pharmaceutical Works for partial financial support, E.Baitz-Gács and M.Kajtár-Peredy for ^1H- and ^{13}C-NMR, J.Tamás for MS measurements, and Mrs. M. Roczkov and Mrs. B. Moór for technical assistance.



3-8	R^1	R^2
a	C_2H_5	H
b	$CH(CH_3)_2$	OCH_3

i: N-(2-Hydroxyethyl)-thiazolium bromide/Et_3N/Dioxane; *ii:* $NaBH_4$/THF; *iii:* TsCl/Pyridine; *iv:* $KOBu^t$/Benzene/18-Crown-6; *v;* $NaBH_4/R^1OH$; *vi:* PBr_3/LiBr/2,4,6-collidine; *vii:* DBU; *viii:* $NaBH_3CN$/HMPT; *ix:* $ZnBr_2$/ether; *x:* DBU

References and Notes:

1/ Taken in part from P.Vinczer Ph.D. Dissertation; Technical University of Budapest, 1984.

2/ a: SEHNAL, F.: Juvenile Hormone Analogues, in "Endocrinology of Insects" New York, A.R.Liss Inc., 1983, p. 657-672; b: HENRICK, C.A.: Juvenile Hormone Analogs: Structure-activity Relationships, in "Insecticidal Modes of Action" /Ed. J.R. COATS/, New York, Acad.Press, 1982, p. 315-402

3/ a: HENRICK, C.A.; STAAL, G.B.; SIDDALL, J.B.: *J.Agr.Food.Chem.*, 1973, *21*, 354; b: HENRICK, C.A.; WILLY, W.E.; STAAL, G.B.: *J.Agr.Food.Chem.*, 1976, *24*, 207; c: HENRICK, C.A.; WILLY, W.E.; BAUM, J.W.; BAER, T.A.; GARCIA, B.A.; MASTRE, T.A.; CHANG, S.M.: *J.Org.Chem.* 1975, *40*, 1; d: HENRICK, C.A.; WILLY, W.E.; McKEAN, D.R.; BAGGIOLINI, E.; SIDDALL, J.B.: *J.Org.Chem.*, 1975, *40*, 8; e: HENRICK, C.A.; ANDERSON, R.J.; STAAL, G.B.; LUDVIK, G.F.: *J.Agr.Food. Chem.*, 1978, *26*, 542.

4/ a: HENRICK, C.A.; STAAL, G.B.; SIDDALL, J.B.: Structure Activity Relationships in Some Juvenile Hormone Analogs, in "The Juvenile Hormones" (Ed. L.I. GILBERT), New York, Plenum Press, 1976, p. 48-60. b: HENRICK, C.A.; LABOVITZ, J.N.; GRAVES, V.L.; STAAL, G.B.: *Bioorganic Chem.*, 1978, *7*, 235; c: NOVÁK, L.; ROHÁLY, J.; KOLONITS, P.; FEKETE, J.; VARJAS, L.; SZÁNTAY, Cs.: *Liebigs Ann. Chem.* 1982, 1173.

5/ Dodecanoates with exo-cyclopropane ring [2,3-methano-dodecanoates (Cyclopren)]: a/ KOCOR, M.; SOBOTKA, W.; STERZYCKY, R.; STYCZYNSKA, B.; *Rocz.Chem.*, 1976, *50*, 1337; b: SOBOTKA, W.; ZABZA, A.: Juvenoids with Alicyclic System, in "Regulation of Insect Development and Behaviour" (Eds. SEHNAL, F.; ZABZA, A.; MEN, J.J.; CYMBOROWSKY, B.), Wroclaw Techn. Univ. Press. 1981, 275-288.

6/ DeMEIJERE, A.: *Angew.Chem.Int.Ed.Eng.*, 1979, *18*, 809.

7/ NAKAYAMA, A.; IWAMURA, H.: FUJITA, T.: *J.Med.Chem.*, 1984, *27*, 1493.

8/ a: NOVÁK, L.; BAÁN, G.; MAROSFALVI, J., SZÁNTAY, Cs.: *Chem.Ber.*, 1980, *113*, 2939, b: STETTER, H.: *Angew.Chem.*, 1976, *88*, 695.

9/ a: LEVER, O.W.: *Tetrahedron*, 1971, *32*, 1943; b: SEEBACH, D.; KOLB, M.: *Chem. and Ind.* 1974, 687; c: SEEBACH, D.; *Angew.Chem.Int.Ed.Engl.* 1979, *18*, 239; d: MARTIN, S.F.; *Synthesis*, 1979, 633.

10/ Compounds 4a,b were prepared by MnO_2 oxidation of the appropriate alkyl 2-hydroxy-3-methyl-3-butenoates[18,19].

11/ Characteristic spectral data of 5: IR [film] ν_{max}:1740 cm^{-1}; ^1H-NMR [100 MHz, $CDCl_3$] δ: 3,61 (m,1H,C^3-H); 2,1-3,1 (m,4H,CH_2-C^5O-CH_2); 1,15 (d,J=7Hz,3H,C^3-CH_3); 0,86 (d,J=7Hz, 3H,C^7-CH_3); 1,0-1,6 (m,CH_2); ^{13}C-NMR [25,2 MHz, $CDCl_3$] δ : 160,7 (C^1); 196,6 (C^2); 37,2 (C^3); 15,8 ($C^{3'}$); 46,9(C^4); 208,6 (C^5); 49,9 (C^6); 27,9 (C^7); 19,8 ($C^{7'}$) ppm.

12/ Characteristic spectral data of diastereomeric mixutre of 7: IR[film] ν_{max}: 1700, 1735 cm^{-1}; ^1H-NMR [100 MHz, $CDCl_3$]δ : 2,1-2,7(m,4H,CH_X-CO); 1,1-2,0 (m,CH_2); 1,24 (d,J=7Hz,3H,C^3-CH_3);0,83 (d,J=7Hz,C^7-CH_3); ^{13}C-NMR [25,2 MHz, $CDCl_3$] δ : 169,8 (C^1); 30,2 (C^2); 25,7 (C^3); 11,3 ($C^{3'}$); 35,8 (C^4); 207,8 (C^5); 51,7 (C^6); 27,9 (C^7); 19,9 ($C^{7'}$) ppm.

13/ BRADY, F.S.; ILTON, M.A.; JOHNSON, W.S.: *J.Am.Chem.Soc.*, 1968, *90*, 2882.

14/ Characteristic spectral data of 8 (e.g.: R^1=iPr, R^2=OMe; X=Br): IR [film] ν_{max} : 1735 cm^{-1}; ^1H-NMR [100 MHz, $CDCl_3$] δ : 4,98 (h, J=6Hz, 1H, COOCH); 4,0-4,15 (m,1H, CHBr); 3,16 (s,3H, CH_3O); 1,05-1,9 (m,12H); 1,21 (d,J=6Hz,6H,$CH(CH_3)_2$); 1,12 (s,6H,$C^{11}(CH_3)_2$); 0,92 (dd,J=6Hz,6H,CH_3) ppm; MS: m/z 377(1), [M_1^+-15, ^{81}Br]; 375(1), [M^+-15, ^{79}Br]; 279(6) [M-(HBr+OMe)]; 237(8),[[279-iPr^+]; 191(6); 73 (100).

15/ Characteristic spectral data of 2b (e.g.: R^1=iPr,R^2 = OMe): IR [film] ν_{max}: 1735 cm^{-1}; ^1H-NMR [100 MHz, $CDCl_3$] δ : 5,45 (m,2H,CH=); 4,97 (h, J=6Hz,1H,COOCH=); 3,16 (s,3H,CH_3O); 1,05-2,1 (m, 9H); 1,21 (d, J=6Hz,6H, $CH(CH_3)_2$); 1,12 (s,6H,$C^{11}(CH_3)_2$); 0,9 (dd,J=6Hz,6Hz,6H,CH_3).

16/ HUTCHINS, R.O.; MARYANOFF, B.E.; MILEWSKI,C.A.; *Chem.Commun.*, 1971, 1097.

17/ McCORMICK, J.P.; BARTON, D.L.: *J.Org.Chem.*, 1980, *45*, 2566.

18/ VOGEL, E.; SCHINZ, H.: *Helv.Chim.Acta.*, 1950, *33*, 116.

19/ FATIADI, A.J.: *Synthesis*, 1976, 65, 113.

(Received in UK 19 June 1985)