SYNTHESIS OF (*Z*)-14-HEPTADECEN-4-OLIDE AND (*Z*)-11-PENTADECEN-4-OLIDE, SEX PHEROMONE ANALOGUES OF *Ostrinia nubilalis* AND *Cydia molesta*

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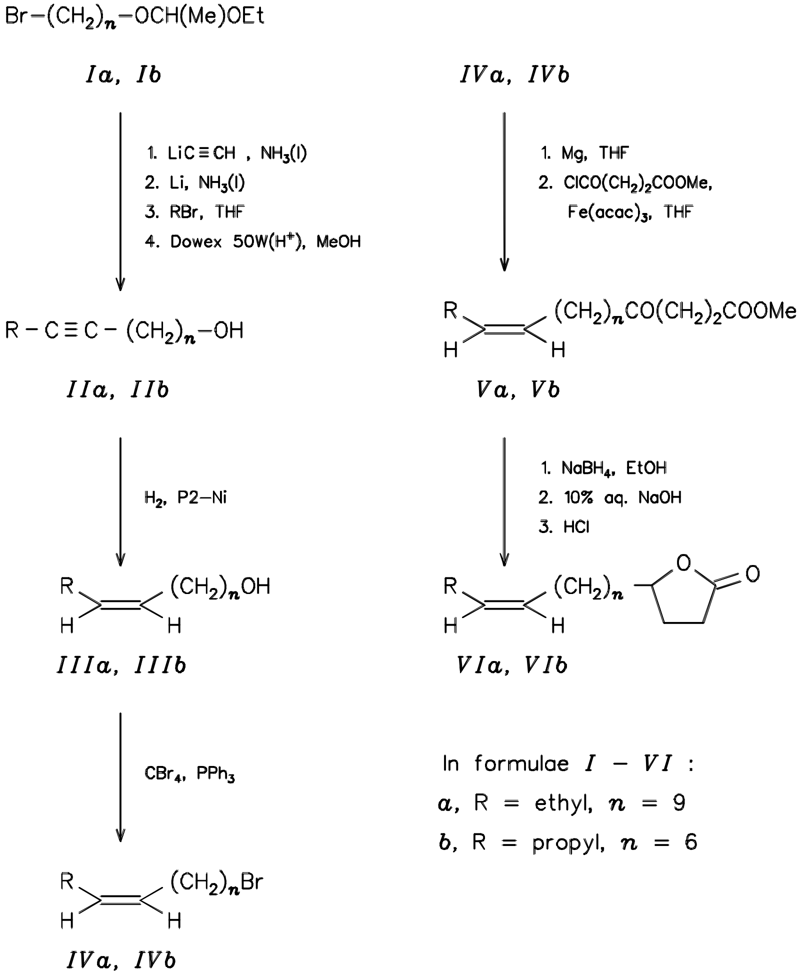
The key step in the preparation of racemic (*Z*)-14-heptadecen-4-olide (*VIa*) and (*Z*)-11-pentadecen-4-olide (*VIb*), sex pheromone analogues of *Ostrinia nubilalis* and *Cydia molesta*, was efficient cross-coupling reaction of 3-methoxycarbonylpropanoyl chloride with corresponding (*Z*)-alkenylmagnesium bromides. The methyl 4-oxo-(*Z*)-14-heptadecenoate (*Va*) and methyl 4-oxo-(*Z*)-11-pentadecenoate (*Vb*) prepared in this way were converted by one-pot reaction using sodium borohydride in an ethanolic solution to the required (*Z*)-alken-4-olides (*VIa,VIb*).

In the search for new biorational pesticides based on semiochemicals, we focused our attention to a synthesis of butyrolactone analogues of the European corn borer (*Ostrinia nubilalis*) and the Oriental fruit moth (*Cydia molesta*) sex pheromones[1].

Five-membered enol lactones bearing a halogen at the vinylic position are known[2] to be mechanism-based inhibitors (suicide inhibitors) of serine hydrolases. Similarly, ynenol lactones are featured as suicide inhibitors of serine proteinase. We expect that due to their alkylating properties even the more simple butyrolactones could exhibit similar inhibition effects. In our case the acetate group of the parent pheromone molecules, (*Z*)-11-tetradecen-1-yl acetate (*Ostrinia nubilalis*) and (*Z*)-8-dodecen-1-yl acetate (*Cydia molesta*), was replaced by a five membered lactone moiety.

The key moment of the synthesis (Scheme 1) of the target compounds, (*Z*)-14-heptadecen-4-olide (*VIa*) and (*Z*)-11-pentadecen-4-olide (*VIb*), is a preparation of the 4-oxoesters *Va* and *Vb*. For the synthesis of these compounds we tested a “classical” method, based on the two-step alkylation of diethyl 3-oxopentanedioate (3-oxoglutarate)[3,4]. Unfortunately, this way is relatively complicated (4 steps) and the total yield of the synthesis was not higher than 30 – 40%. Therefore, the synthesis of 4-oxoesters *Va* and *Vb* was performed by applying the tris(2,4-pentadionato-*O,O′*)iron(III) (Fe(acac)$_3$) catalyzed cross-coupling reaction[5,6] between acyl chlorides and Grignard reagents. This method has been successfully applied[5,6] to the synthesis of some functionalized ketones and oxo esters which are not easily prepared by other known procedures.

The isolated yield of the coupling of 3-methoxycarbonylpropanoyl chloride with the corresponding (*Z*)-alkenylmagnesium bromides is about 40%. This yield is lower than described (70 – 85%) in original papers[5,6], where only short-chain and/or reactive



SCHEME 1

Grignard reagents were used. The coupling of Grignard reagents, prepared from 1-bromo-(*Z*)-10-tridecene (*IVa*) and 1-bromo-(*Z*)-7-undecene (*IVb*), gave relatively low yields, however this one-step way is more advantageous than the four-step synthesis via diethyl 3-oxopentanedioate.

The preparation of 1-bromo-(*Z*)-10-tridecene (*IVa*) and 1-bromo-(*Z*)-7-undecene (*IVb*) is based on alkyne chemistry[7 – 10]. Alkynols *IIa* and *IIb* were prepared from protected ω-bromoalkanols[11] *Ia* and *Ib* by a two-step alkylation of acetylene. Hydrogenation of alkynols *IIa* and *IIb* over P2–Ni catalyst[12] gave (*Z*)-alkenols *IIIa* and *IIIb* in isomeric purity >98% (GLC). Treatment of (*Z*)-enols *IIIa* and *IIIb* with carbon tetrabromide and triphenylphosphine[13] furnished the corresponding 1-bromoalkenes *IVa* and *IVb* in high yields.

In the final step of the synthesis the 4-oxoalkenoates *Va* and *Vb* were converted to the racemic target lactones *VIa* and *VIb* by a reduction using an ethanolic solution of sodium borohydride[14]. The overall yields of the synthesis were 11% for lactone *VIa* and 12% for lactone *VIb*.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ solution on Varian UNITY-500 spectrometer, operating at 499.5 MHz and absorptions are expressed in δ (ppm) scale relative to TMS. The NMR data of all synthesized compounds are given in Tables I – IV. The IR spectra (ν, in cm^{-1}) were recorded on a Bruker IFS 88 FT-IR spectrometer in tetrachloromethane. GLC analyses were performed on a Hewlett–Packard HP 5880A chromatograph equipped with a FID detector and a 25 m capillary column (internal diameter 0.3 mm, HP5-5% phenyl methyl silicone, cross-linked). Preparative medium pressure liquid chromatography (pMPLC) separations were made on Merck 60 silica gel (0.040 – 0.063 mm) using a Büchi B-680 Prep LC System with stepwise gradient of diethyl ether in light petroleum.

10-Tridecyn-1-ol (*IIa*)

Into a stirred suspension of freshly prepared lithium acetylide[7] (0.3 mol) in liquid ammonia (1 000 ml) dry DMSO (400 ml) was added carefully. After stirring for 5 min, 14-bromo-4-methyl-3,5-dioxatetradecane[9,10] (*Ia*) (75 g, 0.254 mol) was added dropwise and stirring was continued for 4 h. Ammonia was evaporated on standing overnight and the residue was decomposed with brine (1 500 ml). The mixture was extracted with ether–light petroleum (1 : 1) (4 × 250 ml) and the combined extracts were dried over K_2CO_3. Evaporation of solvents gave 45 g of a yellow oil. This oil (45 g) was added dropwise to a stirred suspension of $LiNH_2$ (prepared from 13.9 g, 0.2 mol of lithium) in 1 000 ml of liquid ammonia. After stirring for 1 h, 1-bromoethane (21.8 g, 0.2 mol) was added dropwise and stirring was continued for 4 h. Ammonia was evaporated on standing overnight and the residue was decomposed with ice cold water (1 000 ml). The mixture was extracted with ether (4 × 250 ml), the combined extracts were dried over K_2CO_3. Evaporation of the solvents furnished 40 g of a red oil that was dissolved in methanol (1 000 ml) and treated with Dowex 50W (H^+ form, 20 g) for 20 h. The ion-exchanger was filtered off and the solvents were removed in vacuo. Purification of the residue by pMPLC gave 32.6 g (63%) of alkynol *IIa*.

7-Undecyn-1-ol (IIb) was synthesized analogously from 11-bromo-3,5-dioxa-4-methyl-undecane[9,10] (*Ib*) (92.1 g, 0.363 mol), LiC≡CH, $LiNH_2$ and 1-bromopropane (0.33 mol, 35.9 g). Yield 43.5 g (72 %).

(Z)-10-Tridecen-1-ol (*IIIa*)

1,2-Diaminoethane (600 μl) and alkynol *IIa* (32.0 g, 0.164 mol) were added to a suspension of P2–Ni (prepared from 1.25 g of nickel(II) acetate) in ethanol (500 ml) and hydrogenated with stirring at 25 °C. The hydrogenation was monitored by analyzing aliquots of the solution by GLC. Preparative medium

TABLE I

^1H NMR chemical shifts (δ, ppm) and coupling constants (in parentheses, *J*, Hz) of compounds *IIa* – *VIa* in $CDCl_3$ (499.5 MHz, tetramethylsilane as internal standard)

Position	*IIa*	*IIIa*	*IVa*	*Va*	*VIa*
1	3.63 t (6.6)	3.63 t (6.5)	3.41 t (6.8)	–	–
2	1.56 m	1.56 m	1.85 m	2.72 m	2.53 m
3	1.26	1.25	1.25	2.58 m	1.85 ddd (8.0, 12.7, 19.0) 2.32 ddd (6.6, 7.4, 19.0)
4				–	4.48 ddt (5.6, 6.6, 2 × 7.8)
5				2.44 t (7.1)	1.58 m 1.73 m
6				1.58 m	1.24
7				1.24	
8		1.37 m	1.46 m		
9	1.40 m	2.03 m	2.03 m		
10	2.13 tt (2.5, 7.1)	5.29	5.29		
11	2.16 tt (2.4, 6.6)	5.39 m	5.39 m		
12	1.47 m	2.03 m	2.03 m	1.35 m	1.44 m
13	1.11 t (7.3)	0.95 t (7.6)	0.96 t (7.6)	2.02 m	2.03 m
14	–	–	–	5.28	5.29
15	–	–	–	5.38 m	5.38 m
16	–	–	–	2.02 m	2.03 m
17	–	–	–	0.95 t (7.6)	0.96 t (7.6)
$COOCH_3$				3.67 s	

pressure liquid chromatography of the crude product afforded 30.4 g (94%) of pure (GLC) (*Z*)-alkenol *IIIa*.

(Z)-7-Undecen-1-ol (IIIb) was prepared analogously from 43.5 g (0.258 mol) of alkynol *IIb*. Yield 38.7 g (87%).

1-Bromo-(Z)-10-tridecene (*IVa*)

Triphenylphosphine (41.8 g, 0.160 mol) in dry dichloromethane (200 ml) was added dropwise to a solution of *IIIa* (30.0 g, 0.151 mol) and tetrabromomethane (50.1 g, 0.151 mol) in dry dichloromethane (300 ml) at 0 – 3 °C. The mixture was warmed to 20 °C over 1 h. After stirring for 4 h the solvent

TABLE II

^{1}H NMR chemical shifts (δ, ppm) and coupling constants (in parentheses, *J*, Hz) of compounds *IIb* – *VIb* in $CDCl_3$ (499.5 MHz, tetramethylsilane as internal standard)

Position	*IIb*	*IIIb*	*IVb*	*Vb*	*VIb*
1	3.64 t (6.6)	3.64 t (6.7)	3.41 t (7.1)	–	–
2	1.58 m	1.57 m	1.86 m	2.72 m	2.53 m
3	1.33	1.24	1.29	2.58 m	1.85 ddd (8.0, 12.7, 19.0) 2.32 ddd (6.6, 7.4, 19.0)
4				–	4.48 m (5.6, 6.6, 2 × 7.8)
5		1.37 m	1.40 m	2.44 t (7.5)	1.14
6	1.46 m	2.01 m	2.02 m	1.58 m	
7	2.12 tt (2.5, 7.1)	5.32	5.30	1.24	
8	2.16 tt (2.4, 6.6)	5.39 m	5.50 m		
9	1.33 – 1.46 m	2.01 m	2.02 m	1.35 m	1.78 m
10	1.50 m	1.37 m	1.37 m	2.01 m	2.01 m
11	0.97 t (7.1)	0.90 t (7.3)	0.90 t (7.3)	5.31	5.32
12	–	–	–	5.39 m	5.38 m
13	–	–	–	2.01 m	2.01 m
14	–	–	–	1.24 – 1.40 m	1.14 – 1.78 m
15	–	–	–	0.90 t (7.3)	0.90 t (7.3)
$COOCH_3$				3.67 s	

was removed on a rotary evaporator and light petroleum (400 ml) was added to the residue. The mixture was cooled to a 0 °C and filtered. The solid residue (Ph_3PO) was washed with ice-cold light petroleum and the filtrate was concentrated in vacuo. The crude residue was purified by pMPLC. The bromoalkene *IVa* was obtained as a colorless oil (39.3 g, 84%). For $C_{13}H_{25}Br$ (261.3) calculated: 59.8% C, 9.7% H, 30.6% Br; found: 59.6% C, 9.7% H, 30.7% Br.

1-Bromo-(Z)-7-undecene (IVb). In the same manner as described above, *IIIb* (38.7 g, 0.227 mol) was brominated with tetrabromomethane (75.3 g, 0.227 mol) and triphenylphosphine (60.3 g, 0.23 mol) to give 45.0 g (85%) of *IVb*. For $C_{11}H_{21}Br$ (233.2) calculated: 56.7% C, 9.1% H, 34.3% Br; found: 56.8% C, 9.1% H, 34.1% Br.

Methyl 4-Oxo-(*Z*)-14-heptadecenoate (*Va*)

A solution of (*Z*)-7-tridecenyl-1-magnesium bromide [freshly prepared from *IVa* (13.82 g, 53.2 mmol) and magnesium turnings (1.32 g, 53.2 mmol) in THF (30 ml)] was added dropwise (10 min) under argon, to a stirred solution of 3-methoxycarbonylpropanoyl chloride (8.0 g, 53.2 mmol) and tris(2,4-pentadionato-*O,O′*)iron(III) (0.6 g, 1.6 mmol) in 250 ml of dry THF at room temperature.

TABLE III
^{13}C NMR chemical shifts (δ, ppm) of compounds *IIa* – *VIa* in $CDCl_3$ ($CDCl_3$ = 77.00 ppm as internal standard)

Position	*IIa*	*IIIa*	*IVa*	*Va*	*VIa*
1	62.94 t	63.05 t	34.02 t	173.29 s	177.29 s
2	32.72 t	32.77 t	32.83 t	36.96 t	35.57 t
3	25.67 t	25.71 t	28.16 t	42.77 t	29.73 t
4	29.42 t	29.73 t	29.72 t	209.10 s	81.05 d
5	29.32 t	29.55 t	29.40 t	23.76 t	25.20 t
6	29.07 t	29.44 t	29.40 t	29.71 t	29.46 t
7	29.03 t	29.39 t	29.21 t	29.43 t	29.46 t
8	28.77 t	29.23 t	28.75 t	29.38 t	29.43 t
9	18.66 t	27.06 t	27.07 t	29.33 t	29.31 t
10	79.50 s	129.29 d	129.26 d	29.20 t	29.22 t
11	81.55 s	131.51 d	131.55 d	29.15 t	28.85 t
12	12.36 t	20.48 t	20.50 t	27.68 t	27.99 t
13	14.32 q	14.36 q	14.38 q	27.04 t	27.06 t
14	–	–	–	129.25 d	129.28 d
15	–	–	–	131.47 d	131.52 d
16	–	–	–	20.45 t	20.48 t
17	–	–	–	14.34 q	14.37 q
$COOCH_3$				51.71 q	

After complete addition, the stirring continued for 1 h at the same temperature. Then, the reaction was quenched with 10% aqueous HCl (500 ml) and extracted with ether (4 × 100 ml). The combined ethereal extracts were washed with aqueous $NaHCO_3$, water, and dried over $MgSO_4$. The solvent was removed and the residue was purified by pMPLC to give 6.3 g (40%) of oxoester *Va*. For $C_{18}H_{32}O_3$ (296.5) calculated: 72.9% C, 10.9% H; found: 73.1% C, 11.0% H.

Methyl 4-oxo-(Z)-11-pentadecenoate (Vb) was synthesized analogously from *IVb* (12.41 g, 53.2 mmol), magnesium (1.32 g, 53.2 mmol), 3-methoxycarbonylpropanoyl chloride (8.0 g, 53.2 mmol) and tris(2,4-pentadionato-*O,O′*)iron(III) (0.6 g, 1.6 mmol). Yield 5.5 g (38%). For $C_{16}H_{28}O_3$ (268.4) calculated: 71.6% C, 10.2% H; found 71.8% C, 10.7% H.

(*Z*)-14-Heptadecen-4-olide (*VIa*)

To a mixed solution of $NaBH_4$ (189 mg, 5.0 mmol) and $Na_2HPO_4 \cdot 12\ H_2O$ (193 mg, 0.517 mmol) in ethanol (20 ml) was added dropwise 4-oxo-(*Z*)-14-heptadecenoate (*Va*) (1.36 g, 4.59 mmol) with cooling and stirring, and the mixture was stirred for 5 h at room temperature. Then, a 10% aqueous solution of NaOH (20 ml) was added and stirring was continued for 1 h at room temperature. The mixture was acidified to pH 1 – 2 with concentrated HCl, stirring for 1 h at 0 °C, then extracted with ether (3 × 25 ml), dried ($MgSO_4$), and evaporated to give 0.93 g the crude lactone *VIa*. Further purification by pMPLC gave 0.63 g (52%) of pure (GLC) product *VIa*. For $C_{17}H_{30}O_2$

TABLE IV
^{13}C NMR chemical shifts (δ, ppm) of compounds *IIb* – *VIb* in $CDCl_3$ ($CDCl_3$ = 77.00 ppm as internal standard)

Position	*IIb*	*IIIb*	*IVb*	*Vb*	*VIb*
1	62.94 t	63.02 t	33.96 t	173.31 s	177.27 s
2	32.64 t	32.76 t	32.80 t	36.99 t	35.36 t
3	25.24 t	25.62 t	29.50 t	42.77 t	29.58 t
4	29.04 t	29.68 t	29.30 t	209.08 s	81.02 d
5	28.55 t	29.27 t	28.37 t	23.76 t	25.18 t
6	18.64 t	29.04 t	28.06 t	29.53 t	29.28 t
7	80.17 s	129.88 d	129.91 d	29.27 t	29.21 t
8	80.17 s	129.77 d	129.72 d	29.08 t	29.05 t
9	20.74 t	27.12 t	27.05 t	29.00 t	28.84 t
10	22.51 t	22.86 t	22.87 t	27.12 t	27.11 t
11	13.44 q	13.78 q	13.79 q	129.85 d	129.83 d
12	–	–	–	129.77 d	129.80 d
13	–	–	–	27.70 t	27.99 t
14	–	–	–	22.86 t	22.86 t
15	–	–	–	13.78 q	13.78 q
$COOCH_3$				51.75 q	

(266.4) calculated: 76.6% C, 11.4% H; found: 76.5% C, 11.4% H. IR spectrum: 3 005 m [(C–H), *cis*-double bond], 1 782 vs [(C=O), lactone], 1 653 w (C=C).
(Z)-11-pentadecen-4-olide (VIb) was prepared analogously from *Vb* (1.00 g, 3.73 mmol). Yield 0.51 g (57.4%). For $C_{15}H_{26}O_2$ (238.4) calculated: 75.6% C, 11.0% H; found: 75.4% C, 10.9% H. IR spectrum: 3 005 m ((C–H), *cis*-double bond], 1 781 vs [(C=O), lactone], ≈ 1 653w (C=C).

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