Chemistry of Natural Compounds and Bioorganic Chemistry

Synthesis of 3(*Z*)-dodecen-12-olide — an aggregation pheromone of the flat grain beetle *Cryptolestes pusillus* (Coleoptera: *Cucujidae*)

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3(*Z*)-Dodecen-12-olide, an aggregation pheromone of the flat grain beetle, was obtained using 1,4-*cis*-hydrogenation of ethyl 12-hydroxydodeca-2,4-dienoate as a key step. The dienoic ester was synthesized from 10-hydroxydec-2-enal, which, in turn, was prepared from its saturated precursor *via* acetal α-bromination followed by phenylselenation/oxidative elimination/hydrolysis.

Key words: acetals, bromination, selenation, 3(*Z*)-dodecen-12-olide, 10-hydroxydec-2-enal, aldehydes, organoselenium compounds, 1,4-*cis*-hydrogenation.

1,4-*cis*-Hydrogenation of conjugated dienes catalyzed by (arene)tricarbonylchromium complexes is a convenient method for the preparation of olefins with a specific configuration (for a review see Ref. 1). Previously, we have developed[2—6] flexible protocols for the stereocontrolled synthesis of some olefinic insect pheromones using this reaction as a key step. As compared to other methods for (*Z*)-olefin formation, the merits of this approach are determined by the availability of the starting conjugated dienes. We recently reported[7,8] efficient access to conjugated dienoic esters *via* α-(4-methoxyphenyl)selenation of γ,δ-unsaturated esters, followed by oxidative elimination of the arylseleno group (Scheme 1, route *a*). In earlier works[2,3,6] we used for this purpose the simpler and cheaper Horner—Emmons olefination of saturated aldehydes with phosphonocrotonates (Scheme 1, route *b*). However, the target dienoic esters were often obtained in only moderate yields, depending on the conditions used. An alternative version of the Horner—Emmons reaction, involving condensation of a conjugated unsaturated aldehyde with a trialkyl phosphonoacetate (Scheme 1, route *c*), would also seem worth considering.[2,3,9]

Among the numerous methods for the preparation of α,β-unsaturated carbonyl compounds,[10] the introduction of the double bond into the saturated analog looks attractive. The well recognized α-selenation — oxidative elimination protocol[11—13] for aldehydes requires expensive electrophilic organoselenium reagents though or conversion to enol ethers or enamines prior to selenation. Recently, we have demonstrated[14—16] that the reaction sequence as outlined is a reliable protocol for the con-

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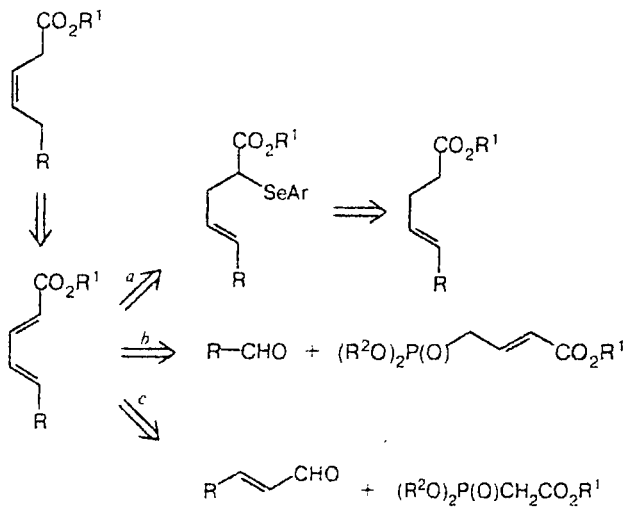
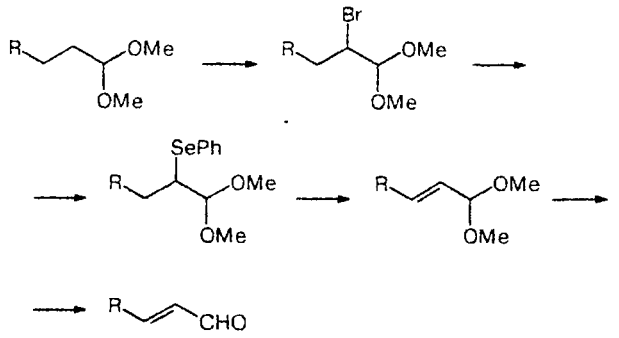
Scheme 1



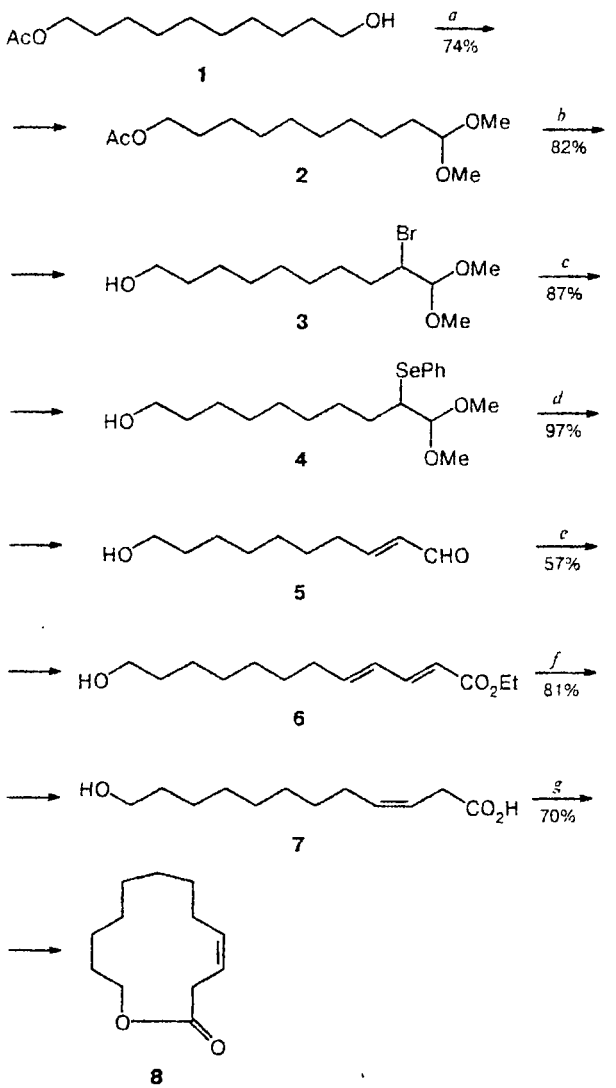
version of aldehyde acetals to α,β-unsaturated aldehydes:



The application of this scheme allowed us to accomplish a simple and efficient synthesis of 10-hydroxydec-2-enal (**5**), which was employed as a key intermediate for the preparation of 3(*Z*)-dodecen-12-olide (**8**) — an aggregation pheromone of the flat grain beetle *Cryptolestes pusillus*[17] (Scheme 2; for other preparations of compound **8**, see Refs. **18—21**).

The primary alcohol grouping in readily available decane-1,10-diol monoacetate (**1**)[22,23] was subjected to electrochemical oxidation in an undivided cell containing NaBr—$NaHCO_3$—4-acetamido-2,2,6,6-tetramethylpiperidin-1-yl-1-oxyl (4-AcNH-TEMPO).[24—26] Treatment of the crude aldehyde with trimethyl orthoacetate afforded acetal **2** in 74% yield. The same compound in slightly lower yield (70%) was obtained by PCC oxidation of **1** followed by acetalization. α-Bromination of acetal **2** occurred cleanly in CH_2Cl_2 upon slow addition of bromine in the same solvent. After removal of the acetate protecting group, α-bromo-ω-hydroxyacetal **3** was isolated in 82% yield. Considerable amounts of transacetalization products were formed during attempted

Scheme 2



Reagents and conditions: *a*) 1) NaBr/$NaHCO_3$ aq/CH_2Cl_2/4-AcNH-TEMPO (−2e, 4.5 $F\,mol^{-1}$); 2) $MeC(OMe)_3$, H^+;
b) 1) Br_2/CH_2Cl_2; 2) $MeOH/K_2CO_3$;
c) PhSeK, DMSO, 90 °C, 8 h;
d) 1) H_2O_2, THF; 2) H_3O^+;
e) $(EtO)_2P(O)CH_2CO_2Et$, K_2CO_3, H_2O, 20 °C, 5 h;
f) 1) $H_2/(MeO_2CPh)Cr(CO)_3$/acetone, 120 °C, 3 h;
2) KOH/MeOH/H_2O, HCl;
g) Ph_3P/DEAD, toluene, 20 °C.

bromination of unprotected 1-hydroxy-10,10-dimethoxydecane. The secondary bromine in acetal **3** was cleanly replaced with a phenylseleno group (87% yield of selenide **4**) by heating in DMSO (90 °C, 8 h) with a small excess of PhSeK generated as described earlier.[27] The selenide **4** thus obtained was subjected to oxidative elimination. Hydrolysis of the acetal group afforded 10-hydroxydec-2-enal (**5**) as an *E*- and *Z*-isomers mixture (9 : 1) in 89% yield. Horner—Emmons olefination[9]

of the aldehyde **5** (57% yield), *cis*-1,4-hydrogenation of the dienoic ester **6** formed, and hydrolysis of the β,γ-unsaturated ester thus obtained led to acid **7** in 81% yield, whose macrolactonization (70% yield) furnished the desired macrolide **8**.

In conclusion, we have developed a convenient and efficient scheme for the total synthesis of 3(*Z*)-dodecen-12-olide (**8**). The overall yield from decane-1,10-diol monoacetate (**3**) was 16.5% over eleven steps (in our previous synthesis,[8] the yield of compound **8** was 10.5% over nine steps).

Experimental

All melting points are uncorrected. NMR spectra were registered in $CDCl_3$ at 299.903 MHz (^1H) and at 75.419 MHz (^{13}C) using a Varian XL-300 spectrometer. Elemental analyses were performed by Analytical Laboratories (Lindlar, Germany). Decane-1,10-diol monoacetate (**1**)[22] and (η^6-methylbenzoate)tricarbonylchromium[28] were prepared according to known procedures. Pentane, AcOEt, THF, and CH_2Cl_2 were distilled prior to use. DMSO, decane-1,10-diol (Reakhim), 4-AcNH-TEMPO (production of Novocherkassk Polytechnical Institute), $MeC(OMe)_3$, Ph_2Se_2, PPh_3, and DEAD (Aldrich) were used as purchased. TLC analysis was performed using Kieselgel 60 F_{254} plates (Merck Cat. No. 1.05554), eluent — 40% AcOEt in hexane. Silica gel L (100/160 μm) was used for column chromatography.

1-Acetoxy-10,10-dimethoxydecane (2). An undivided glass cell, equipped with a magnetic stirring bar and an outer cooling jacket, was charged with compound **1** (0.97 g, 4.5 mmol), 4-AcNH-TEMPO (0.026 g) in CH_2Cl_2 (20 mL), and an aqueous solution containing 25% NaBr and 5% $NaHCO_3$ by weight. The cathode (stainless steel, 15×25 mm) and anode (graphite plate, 13×25 mm) were immersed, at a depth of 10 mm, into the upper aqueous layer of the biphasic system. The mixture was then subjected to electrolysis under a constant current of 100 mA with outer cooling and moderate magnetic stirring of the lower phase. The electrolysis was continued for 5.5 h until the starting material had practically disappeared (TLC monitoring, R_f 0.35 for **1** and 0.78 for **2**); this required 4.5 F mol^{-1} with respect to alcohol **1**. The lower organic layer was separated, the aqueous phase was extraced with CH_2Cl_2, and the combined extracts were dried ($MgSO_4$) and concentrated to furnish 0.86 g (89%) of essentially pure 10-acetoxydecanal as a yellowish oil. The aldehyde was immediately dissolved in a mixture of $MeC(OMe)_3$ (0.6 g, 5 mmol) and anhydrous methanol (1 mL), one crystal of *p*-TsOH was added, and the mixture was kept for 2 h. The volatile components were evaporated, toluene was added to the the residue and evaporated again (×2), and the residue was then dried *in vacuo* (1 Torr) for 1 h. The product **2** thus obtained (0.866 g of oil, 74% with respect to compound **1**) was used in the next step without further purification. ^1H NMR, δ: 1.27 (m, 12 H, CH_2); 1.56 (m, 4 H, CH_2); 2.02 (s, 3 H, Me); 3.29 (s, 6 H, OMe); 4.02 (t, 2 H, OCH_2, J = 6.8 Hz); 4.33 (t, 1 H, OCHO, J = 5.8 Hz). ^{13}C NMR, δ: 21.0 (Me), 24.5, 25.8, 28.5, 29.2, 29.3, and 32.4 (CH_2), 52.5 (OMe), 64.6 (OCH_2), 104.5 (OCHO), 171.2 (C=O).

9-Bromo-10,10-dimethoxydecan-1-ol (3). Br_2 (0.544 g, 3.4 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 30 min to a stirred solution of **2** (0.866 g, 3.33 mmol) in CH_2Cl_2 (8 mL), keeping temperature below 30 °C. MeOH (4 mL) was added to the yellow solution with cooling and stirring and three minutes later the mixture was poured into an aqueous solution of Na_2CO_3, containing Na_2SO_3. The organic layer was separated, the aqueous phase was extracted with ether, and the combined extracts were dried ($CaCl_2$) and concentrated. The residue was dissolved in MeOH (20 mL), solid K_2CO_3 (1 g) was added, and the mixture was stirred at ~20 °C for 4 h (TLC monitoring, R_f 0.75 for the acetate and 0.36 for alcohol **3**) until complete removal of the acetate group. Methanol was evaporated; the residue was treated with water and extracted with ether. After drying (Na_2SO_4) and concentration *in vacuo*, the crude material was purified by column chromatography (eluent — 5, 20, and finally 30% EtOAc in pentane), affording 0.812 g (82%) of the title compound as a colorless oil. Found (%): C, 48.44; H, 8.41. $C_{12}H_{25}BrO_3$. Calculated (%): C, 48.49; H, 8.48. ^1H NMR, δ: 1.31 (m, 10 H, CH_2); 1.56 (m, 3 H, CH_2 and OH); 1.74 and 1.92 (both m of 1 H, $H_2C(3)$); 3.44 (s, 6 H, OMe); 3.63 (t, 2 H, OCH_2, J = 6.7 Hz); 3.96 (ddd, 1 H, CHBr, J = 10.1 Hz, J = 5.6 Hz, J = 3.2 Hz); 4.37 (d, 1 H, OCHO, J = 5.7 Hz). ^{13}C NMR, δ: 25.7, 27.2, 28.9, 29.2, 29.3, 32.7, and 32.8 (CH_2), 54.9 and 55.0 (OMe), 55.5 (CHBr), 63.0 (OCH_2), 106.3 (OCHO).

10,10-Dimethoxy-9-phenylselenodecan-1-ol (4). To a vacuum-degassed (with periodic filling of the flask with nitrogen) mixture of bromoacetal **3** (0.202 g, 0.68 mmol), Ph_2Se_2 (0.125 g, 0.4 mmol), freshly powdered K_2CO_3 (0.5 g), and DMSO (1.5 mL) $N_2H_4 \cdot H_2O$ (0.15 mL) was injected with a syringe under nitrogen and the temperature was gradually raised to 90 °C. Reduction of the diselenide was accompanied by decoloration and occurred within 10—15 min. The mixture was stirred at 90 °C for 8 h, then cooled, diluted with water, and extracted with ether. The extract was washed with NaCl solution, dried (Na_2SO_4), and concentrated *in vacuo*, and the residue was subjected to chromatography on SiO_2 (eluent — 5, 20, and 35% EtOAc in pentane).The selenide **4** (0.221 g, 87%) was obtained as a colorless oil. Found (%): C, 57.64; H, 7.96. $C_{18}H_{30}O_3Se$. Calculated (%): C, 57.90; H, 8.10. ^1H NMR, δ: 1.20—1.45 (m, 10 H, CH_2), 1.56 (m, 4 H, 3 H from CH_2 and OH), 1.79 (m, 1 H, H from CH_2), 3.22 (m, 1 H, CHSe), 3.38 and 3.41 (both s of 3 H, OMe), 3.62 (t, 2 H, OCH_2, J = 6.7 Hz), 4.38 (d, 1 H, OCHO, J = 4.8 Hz), 7.25 (m, 3 H, CH_{arom}), 7.59 (m, 2 H, *o*-CH_{arom}). ^{13}C NMR, δ: 25.7, 27.6, 29.2, 29.3, 30.1, and 32.8 (CH_2), 48.8 (CHSe), 55.4 (both OMe), 63.0 (OCH_2), 107.5 (OCHO), 127.3 (*p*-CH_{arom}), 128.8 (*m*-CH_{arom}), 129.8 (C—Se), 134.7 (*o*-CH_{arom}).

10-Hydroxydec-2-enal (5). A mixture of selenide **4** (2.057 g, 5.51 mmol), THF (40 mL), Et_3N (3 mL), and 30% H_2O_2 (5 mL) was stirred at 20 to 25 °C for 5 h. Hexane (40 mL) was added and the mixture was treated with saturated $NaHCO_3$ (aq). The organic layer was separated, washed with a NaCl solution, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was dissolved in 80% aqueous acetone containing oxalic acid (0.1 g) and the mixture was kept at ~20 °C for 1 h. Acetone was evaporated; the remaining slurry was treated with $NaHCO_3$ (aq) and extracted with ether. The extracts were washed with NaCl solution, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was the title compound **5** as a mixture (9 : 1) of (*E*) and (*Z*)-isomers. Yield 0.913 g (97%). ^1H NMR spectrum data for the (*E*)-isomer were in close agreement with the literature.[29] ^{13}C NMR, δ: 25.5, 27.6, 28.9, 29.0, 32.5, 32.6 (CH_2), 62.8 (OCH_2), 132.9 (=CH), 159.1 (=CH), 194.2 (C=O). (*Z*)-Isomer: ^1H NMR, δ (characteristic peaks): 2.58 (q, 2 H, CH_2, J = 7.8 Hz); 5.93 (ddt, 1 H, HC(2), J = 11.2 Hz, J = 8.0 Hz, J = 1.6 Hz); 6.61 (dt, 1 H, HC(3), J = 11.3 Hz, J = 8.3 Hz); 10.0 (d, 1 H, CHO, J = 8.1 Hz).

Ethyl 12-hydroxydodeca-2,4-dienoate (6). A mixture of aldehyde **5** (0.913 g, 5.36 mmol), $(EtO)_2P(O)CH_2CO_2Et$ (1.382 g, 6.61 mmol), water (1.07 mL), and K_2CO_3 (1.516 g)

was stirred at −20 °C for 5 h (TLC control, R_f 0.27 for **5** and 0.33 for **6**) according to a known procedure.[9] The mixture was diluted with water and extracted with ether and the extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Compound **6** (0.731 g, 57%) was isolated by column chromatography (eluent — 5%, then 30% EtOAc in pentane) as a mixture (9 : 1) of 2(*E*),4(*E*)- and 2(*E*),4(*Z*)-isomers. 2(*E*),4(*E*)-Isomer: ^{1}H NMR, δ: 1.10—1.60 (several peaks, 14 H, CH_2, Me, OH), 2.14 (q, 2 H, $H_2C(6)$, J = 6.8 Hz), 3.61 (t, 2 H, OCH_2, J = 6.4 Hz), 4.17 (q, 2 H, OCH_2Me, J = 7.2 Hz), 5.76 (d, 1 H, HC(2), J = 15.2 Hz), 6.07 (m, 2 H, HC(4) and HC(5)), 7.23 (dd, 1 H, HC(3), J = 15.2, J = 11.8 Hz). ^{13}C NMR, δ: 14.3 (Me), 25.6, 28.6, 29.1, 29.2, 32.7, and 32.9 (CH_2), 60.1 (OCH_2Me), 62.9 (OCH_2), 119.1, 128.3, 144.6, 145.0 (=CH), 167.3 (C=O). 2(*E*),4(*Z*)-Isomer: ^{1}H NMR, δ (characteristic peaks): 2.28 (q, 2 H, J = 6.8 Hz), 5.84 (d, 1 H, HC(2), J = 15.0 Hz), 7.59 (dd, 1H, HC(3), J = 15.0 Hz, J = 11.8 Hz).

12-Hydroxydodec-3(*Z*)-enoic acid (7). A solution of dienoic ester **6** (0.730 g) and (η^6-methylbenzoate)tricarbonylchromium (0.18 g) in acetone (20 mL, distilled under argon) was charged into a stainless steel autoclave under an atmosphere of argon. The vessel was sealed and filled/evacuated three times with H_2 (at 10 atm) to remove traces of O_2, the hydrogen pressure was then adjusted to 50 atm, and hydrogenation was carried out at 120—125 °C for 3 h. The autoclave was cooled and opened, acetone was evaporated from the reaction mixture, and the remaining slurry was subjected to column chromatography (gradient 0→40% EtOAc in pentane) to afford the ethyl ester of acid **7** (0.612 g, 83%). The product was dissolved in MeOH (12 mL), 10% KOH (aq) (4 mL) was added, and the mixture was kept for 1.5 h. Methanol was evaporated, water (10 mL) was added, and impurities were extracted with ether. The aqueous phase was then acidified with 5% HCl (pH 1) and the carboxylic acid was extracted with ether. The extract was dried ($MgSO_4$) and concentrated *in vacuo* to afford 0.545 g (81%) of acid **7**, containing in total 5% of 2(*E*)- and 3(*E*)-isomers (characteristic signals of impurities in the ^{1}H NMR spectrum, δ: for 3(*E*) 3.03 (d, J = 5.5 Hz); for 2(*E*) 5.80 (d, J = 15.7 Hz), 7.08 (dt, J = 15.7 Hz, J = 7.9 Hz)). Pure acid **7** (m.p. 38—39 °C) was obtained by crystallization from a toluene—pentane mixture at −15 °C. ^{1}H and ^{13}C NMR data were in close agreement with those reported earlier.[21]

3(*Z*)-Dodecen-12-olide (8) was obtained by lactonization of hydroxy acid **7** (0.189 g, 0.88 mmol) in the presence of PPh_3 and diethyl azodicarboxylate (DEAD) in toluene as previously described.[21] Yield 0.121 g (70%), ^{1}H and ^{13}C NMR data were in close agreement with the literature.[21]

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