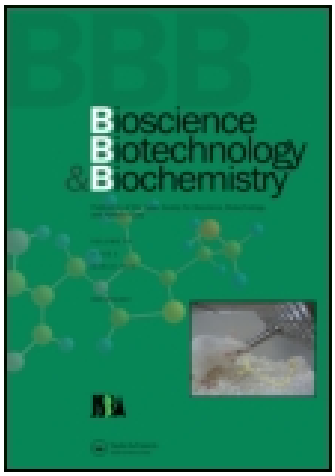

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Synthesis of 13-Oxo-(Z)-9-octadecenoic Acid and 15-Oxo-(Z)-11-icosenoic Acid, Arrestants of Oryzaephilus surinamensis L.

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Note

Synthesis of 13-Oxo-(*Z*)-9-octadecenoic Acid and 15-Oxo-(*Z*)-11-icosenoic Acid, Arrestants of *Oryzaephilus surinamensis* L.

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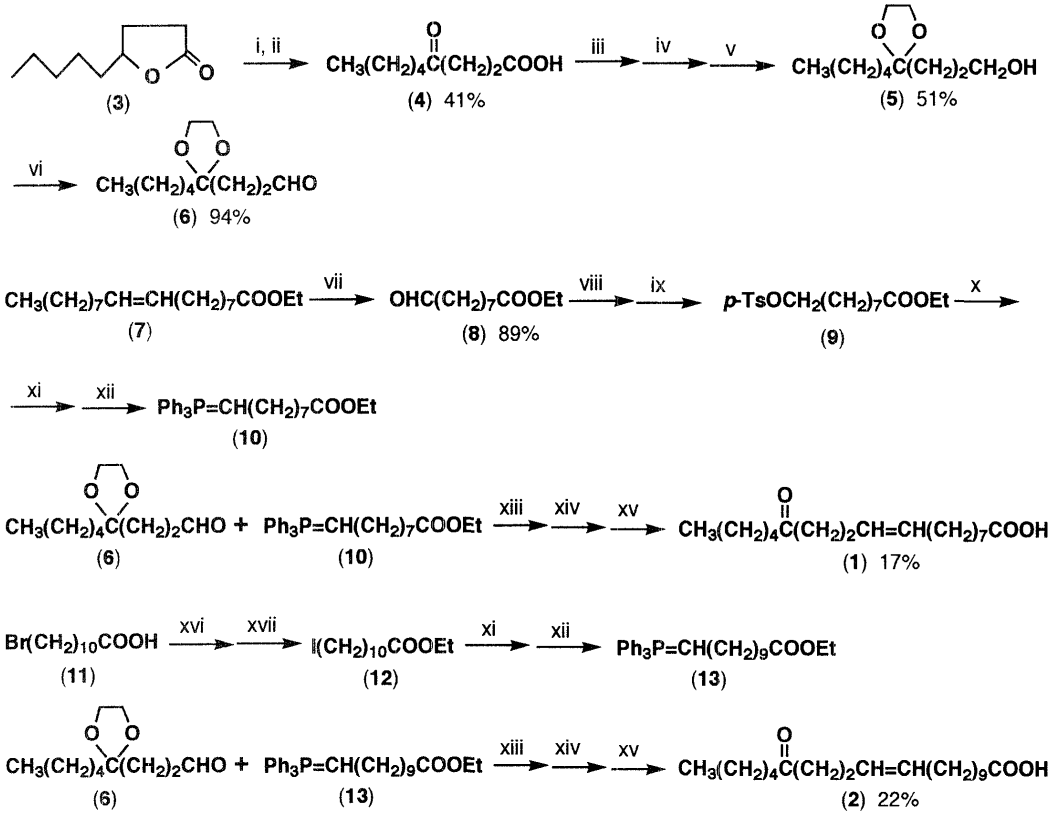
Two arrestants of the sawtoothed grain beetle (*Oryzaephilus surinamensis* L.), 13-oxo-(*Z*)-9-octadecenoic acid and 15-oxo-(*Z*)-11-icosenoic acid, were synthesized for the first time by utilizing a *Z*-selective Wittig reaction.

Key words: *Oryzaephilus surinamensis* L.; arrestant; 13-oxo-(*Z*)-9-octadecenoic acid; 15-oxo-(*Z*)-11-icosenoic acid

Oryzaephilus surinamensis L. (Coleoptera; Silvanidae) is one of the most infamous noxious insects which are globally distributed and is known to infest fresh wheat grain in particular. From a hexane extract of wheat flour infested by *O. surinamensis*, two compounds having arrestive activity toward the same beetle have already been isolated and identified as 13-oxo-(*Z*)-9-octadecenoic acid (**1**) and 15-oxo-(*Z*)-11-icosenoic acid (**2**) by us.[1] As the next step, confirming their structural integrity and supplying them in a sufficiently large quantity and pure state are required for further studies on their ecological aspects. Thus, this report describes the first synthesis of the two carboxylic acids to compare their spectral data (^{1}H-NMR and MS) with those of the natural products. As shown in the Scheme, the Wittig reaction was selected for the *Z*-predominant olefine synthesis by retro-synthetic considerations and the ready availability of the starting materials. Despite our repeated trials, however, the two phosphonium salts for ylides **10** and **13** did not crystallize by standing the viscous liquid. Throughout drying the salts, their ylides obtained were found to react with aldehydes, and the desired products (**1** and **2**) were obtained, although the yields were low.

Thus, the outline of the whole procedure is as follows: 4-Oxononanoic acid (**4**) was prepared from a commercially available γ-lactone (**3**) by bromine oxidation.[2] The acid was esterified with diazomethane, and the carbonyl group was protected as an oxolane, from which the aldehyde (**6**) was obtained by lithium aluminum hydride reduction and the Swern oxidation.[3] Ethyl oleate (**7**) was submitted to ozone oxidation at −20°C in methanol,[4] and fractional distillation gave an aldehyde (**8**), which was converted to an alcohol with sodium borohydride. This alcohol was converted to an ylide (**10**) *via* tosylation, iodination and phosphonium salt formation.[5,6] The ylide thus obtained was



Scheme Synthesis of 13-Oxo-(*Z*)-9-octadecenoic Acid and 15-Oxo-(*Z*)-11-icosenoic Acid.

Reagents and reaction conditions: i) H_2O, NaOH, room temp.; ii) Br_2, 0°C; iii) CH_2N_2 in ether, room temp.; iv) $HO(CH_2)_2OH$, *p*-TsOH in benzene; v) $LiAlH_4$ in ether, reflux; vi) $(COCl)_2$, DMSO in CH_2Cl_2, −78°C; vii) O_3 in MeOH, −20°C; viii) $NaBH_4$ in EtOH; ix) *p*-TsCl, pyridine, 0°C; x) LiI in acetone, reflux; xi) PPh_3 in benzene, reflux; xii) $LiN(Me_3Si)_2$ in THF, 0°C; xiii) in THF, −78°C; xiv) AcOH (60%, in H_2O), 60°C; xv) lipase in H_2O, room temp.; xvi) EtOH, H_2SO_4, reflux; xvii) NaI in 2-butanone, reflux.

submitted to the reaction with aldehyde **6** at −78°C. The usual work-up afforded the desired olefin. After being purified by silica gel column chromatography, the compound was submitted to a hydrolysis of the oxolane moiety and ethyl ester. Isolation of the hydrolysis product by silica gel column chromatography afforded the desired ketoenoic acid (**1**) in a 5% total yield. Details of the reactions are described for the major synthetic steps to compound **1** in the experimental section. The configurational abundance of the double bond was shown to be *Z*-predominant (*Z*:*E*=85:15) by ^{1}H-NMR data.

The synthesis of acid **2** was performed as follows, mostly by the same process as that just described: Commercially available 11-bromoundecanoic acid was converted to an iodide (**12**) *via* ethyl esterification and treatment with sodium iodide. An ylide (**13**) was condensed with aldehyde **6**, and the product was submitted to hydrolysis of the oxolane and ethyl ester to afford the desired acid (**2**). The *Z*-predominant configuration was calculated to be *Z*:*E*=89:11 by a ^{1}H-NMR analysis.

The methyl esters of compounds **1** and **2** were obtained by treating each with diazomethane. All signals of *Z*-form in the ^{1}H-NMR spectrum of the synthetic compound **1** methyl ester coincided with those of the natural compound **1** methyl ester. An EI-MS analysis of the synthetic **1** methyl ester gave a similar spectral pattern to that of the natural *Z*-form compound. These spectral similarities suggest that the chemical structure determined and reported in our previous communication[1] is reasonable for natural arrestant **1**. In the case of the synthetic **2** methyl ester, a similarity in the ^{1}H-NMR and EI-MS spectra was observed, suggesting that the *Z*-fraction in the synthetic **2** methyl ester and the natural compound had the same structure.

The assay for arrestive activity was done in a Petri dish with two paper disks, one of which was treated with a sample solution and the other remained blank. Here, the arrestive activity is defined as the number of the insects arrested on a paper disk impregnated with the sample solution (10 μg/disk) being tested. The percentage (%) response was calculated by the formula $100(T-B)/N$, where T and B were the number of beetles on the treated and blank disks, respectively, after 10 min at 26–28°C in the dark, and N was the total number of beetles used. Thus, the arrestive activity was found to be 12.0±4.9% for synthetic compound **1**. This value is comparable with that of 10.0±7.1% for natural **1** within the margins of experimental error in the biological experiment with the grain beetle in the present study.[1] On the other hand, synthetic **2** with 89% *Z*-predominance showed no significant activity, like natural **2**. These rough similarities in biological response between the synthetic and natural compounds are not incompatible with the results of the structural assignment of the natural arrestants through the present synthesis.

Experimental

^{1}H-NMR spectra were recorded with a Varian VXR500 SC-NMR spectrometer, and EI-MS data with D 300 and Automass 20 instruments (JEOL).

13-Oxo-(Z)-9-octadecenoic acid (**1**). A solution of *p*-toluenesulphonate (**9**; 7.5 g, crude) and lithium iodide (16 g, 94 mmol) in dry acetone (40 ml) was refluxed for 14 h. After this time, most of the acetone was evaporated under reduced pressure, and the residue was poured into water before being extracted 3 times with ether. The ethereal phase was dried over anhydrous sodium sulphate. After evaporating the solvent under reduced pressure, the crude product was purified by silica gel column chromatography (hexane/EtOAc) to give ethyl 9-iodononanoate (6.2 g, 60% from 9-hydroxynonanoate).

A solution of ethyl 9-iodononanoate (6.2 g, 20 mmol) and triphenylphosphine (5.2 g, 20 mmol) in dry benzene (25 ml) was refluxed for 10 h. Evaporation of the solvent under reduced pressure afforded the crude phosphonium salt (11.4 g).

To a stirred solution of this phosphonium salt (2.9 g, crude) in THF (15 ml) was added at 0°C lithium bis(trimethylsilyl)amide (6.2 ml, 6 mmol, 1 M in THF) to give an orange solution. The solution of the phosphorus ylide (**10**) was cooled to −78°C immediately after its generation. A solution of 3-(2-pentyl-1,3-dioxolan-2-yl)propanal (**6**; 1 g, 5 mmol) in THF (15 ml) was added. After stirring at −78°C for 12 h, the reaction mixture was allowed to warm to room temperature and then stirred for 10 h. The reaction mixture was adjusted to pH 5–6 with 0.2 N-HCl and extracted 4 times with hexane. The crude product was purified in a silica gel column (hexane/EtOAc) to give ethyl 12-(2-pentyl-1,3-dioxolan-2-yl)-(*Z*)-9-dodecenoate (391 mg, 21%).

A solution of ethyl 12-(2-pentyl-1,3-dioxolan-2-yl)-(*Z*)-9-dodecenoate (85 mg, 231 μmol) in acetic acid (3.6 ml, 60% in H_2O) was stirred at 60°C for 2 h. The reaction mixture was extracted 4 times with hexane, and the crude product was purified in a silica gel column (hexane/EtOAc) to afford 13-oxo-(*Z*)-9-octadecenoate (63 mg, 84%).

Lipase P (15 mg) was added to a solution of ethyl 13-oxo-(*Z*)-9-octadecenoate (44 mg, 136 μmol) in water (5 ml). After stirring at room temperature for 18 h, the solution was extracted 4 times with ether and then dried over anhydrous sodium sulphate. The crude product was purified in a silica gel column (hexane/EtOAc) to give title compound **1** (38 mg, 95%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=7 Hz, H(18)), 1.20–1.35 (12H, br.), 1.57 (2H, br. quintet, J=7.5 Hz, H(15)), 1.63 (2H, br. quintet, J=7.5 Hz, H(3)), 2.02 (2H, q, J=6 Hz, H(8)), 2.29 (2H, br. q, J=7 Hz, H(2)), 2.34 (2H, t, J=7.5 Hz, H(11)), 2.39 (2H, t, J=7.5 Hz, H(14)), 2.44 (2H, t, J=7.5 Hz, H(12)), 5.29 (1H, dtt, J=11, 7, 1.5 Hz, H(9)) and 5.37 (1H, dtt, J=11, 7, 1.5 Hz, H(10)); EI-MS *m/z*: 296 (M^+).

Methyl 13-oxo-(Z)-9-octadecenoate. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=7Hz, H(18)), 1.20–1.37 (12H, br.), 1.59 (4H, m, H(3), H(15)), 2.02 (2H, q, J=6 Hz, H(8)), 2.29 (2H, br. q, J=7 Hz, H(2)), 2.35 (2H, t, J=7.5 Hz, H(11)), 2.39 (2H, t, J=7.5 Hz, H(14)), 2.43 (2H, t, J=7.5 Hz, H(12)), 3.67 (3H, s, $-CO_2C\underline{H}_3$), 5.29 (1H, dtt, J=11, 7, 1.5 Hz, H(9)) and 5.37 (1H, dtt, J=11, 7, 1.5 Hz, H(10)); EI-MS *m/z*: 310 (M^+).

15-Oxo-(Z)-11-icosenoic acid (**2**). This compound was prepared in the same way as that used for the preparation of **1** (22% from **12**). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.89 (3H, t, J=7 Hz, H(20)), 1.20–1.35 (16H, br.), 1.57 (2H, br. quintet, J=7.5 Hz, H(17)), 1.63 (2H, br. quintet, J=7.5 Hz, H(3)), 2.02 (2H, q, J=6 Hz, H(10)), 2.29 (2H, br. q, J=7 Hz, H(2)), 2.35 (2H, t, J=7.5 Hz, H(13)), 2.39 (2H, t, J=7.5 Hz, H(16)), 2.44 (2H, t, J=7.5 Hz, H(14)), 5.29 (1H, dtt, J=11, 7, 1.5 Hz, H(11)) and 5.38 (1H, dtt, J=11, 7, 1.5 Hz, H(12)); EI-MS *m/z*: 324 (M^+).

Methyl 15-oxo-(Z)-11-icosenoate. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.89 (3H, t, J=7 Hz, H(20)), 1.20–1.36 (16H, br.), 1.58 (4H, m, H(3), H(17)), 2.02 (2H, q, J=6 Hz, H(10)), 2.29 (2H, br. q, J=7 Hz, H(2)), 2.35 (2H, t, J=7.5 Hz, H(13)), 2.38 (2H, t, J=7.5 Hz, H(16)), 2.43 (2H, t, J=7.5 Hz, H(14)), 3.67 (3H, s, $-CO_2C\underline{H}_3$), 5.29 (1H, dtt, J=11, 7, 1.5 Hz, H(11)) and 5.38 (1H, dtt, J=11, 7, 1.5 Hz, H(12)); EI-MS *m/z*: 338 (M^+).

Bioassay procedures. *O. surinamensis* beetles were reared on wheat flour containing 5% (w/w) brewer's yeast at 26–28°C in the dark, and were preconditioned without food for five days before the bioassay. The assay for arrestive activity was done in a Petri dish (ϕ4 cm) with two paper disks (ϕ0.5 cm), one of which was treated with a sample solution in ethyl acetate (1 μl), and the other with the solvent alone as a blank. The arrestive activity is defined as the number of insects arrested on the paper disk that had been impregnated with the sample solution to be tested. The percentage (%) response was calculated by the formula $100(T-B)/N$, when T and B are the number of beetles on the treated and blank disks, respectively, after 10 min at 26–28°C in the dark, and N is the total number of the beetles used.

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