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FUNCTIONALIZED NITROALKANES IN SYNTHESIS OF 1,6-DIOXASPIRO[4.5]DECANE COMPONENTS OF *PARAVESPULA VULGARIS* PHEROMONE ≠

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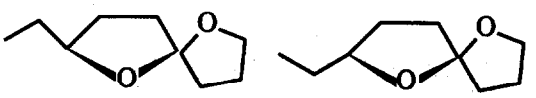
Abstract: (E)-2-,(Z)-2-, and (E)-7-Methyl-1,6-dioxa[4.5]decane isomers which are components of odours of *Paravespula vulgaris* have been prepared by two practical and efficient procedures starting from easily available functionalized nitroalkanes.

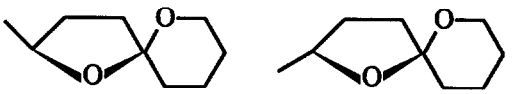
The spiroketal moiety plays a very important role as structural element of many biologically active natural products. Avermectins and milbemycins,[1-4] macrocyclic lactones which have exceptional pesticidal activity; polyether antibiotics[5,6] such as monensin, narasin and lonomycin; antitumoral agents including okadaic acid[7] and phyllantocin;[8] toxins (talaromycins)[9] and steroidal compounds (sapogenins)[10] are representative structures exhibiting a spiroketal moiety. However, the discovery that simple spiroketals are components of insect pheromones is a recent achievement of W. Francke and his coworkers that confirms the great importance of the acetal and ketal groups in well-known semiochemicals. 1.6-Dioxaspiro[4.4]nonanes, 1.6-dioxaspiro[4.5]decanes, 1.7-dioxaspiro[5.5]undecanes and 1.7-dioxaspiro[5.6]dodecanes were identified as basic structures of components of volatile secretions from, respectively, *Pityogenes chalcographus*,[11] *Paravespula vulgaris*,[12] *Dacus oleae*,[13] *Andrena wilkella*[14] *and Andrena haemorrhoa*[15] (Table 1).

Not surprisingly, the wide occurrence of such structures has prompted a very large amount of work in which a number of imaginative variations on the theme of building spiroketal rings

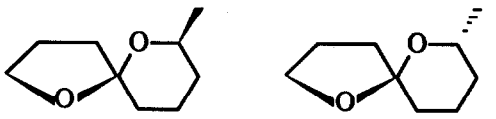
≠ This work was presented by G.R. as a part of his lecture, on invitation, at the "Symposium on the Chemistry and Biochemistry of Insect Pheromones" held in occasion of the Third Chemical Congress of North America - Toronto - June 5-10 1988.

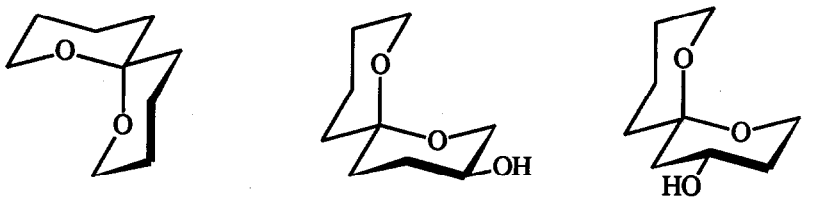


principal aggregation pheromone of *Pityogenes chalcografus (L.)*

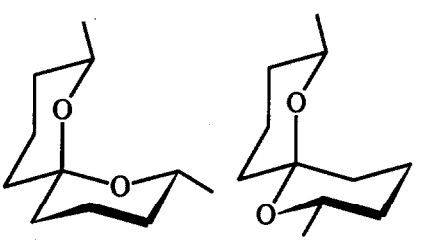


components of pheromone bouquet of workers of the common wasp *Paravespula vulgaris (L.)*





components of the sex pheromone of the olive fruit fly *Dacus oleae (G.)*



main components of mandibular gland secretion of bees *Andrena wilkella*

component of the volatile secretion from the mandibular glands of *Andrena haemorrhoa (F.)*

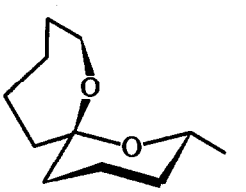
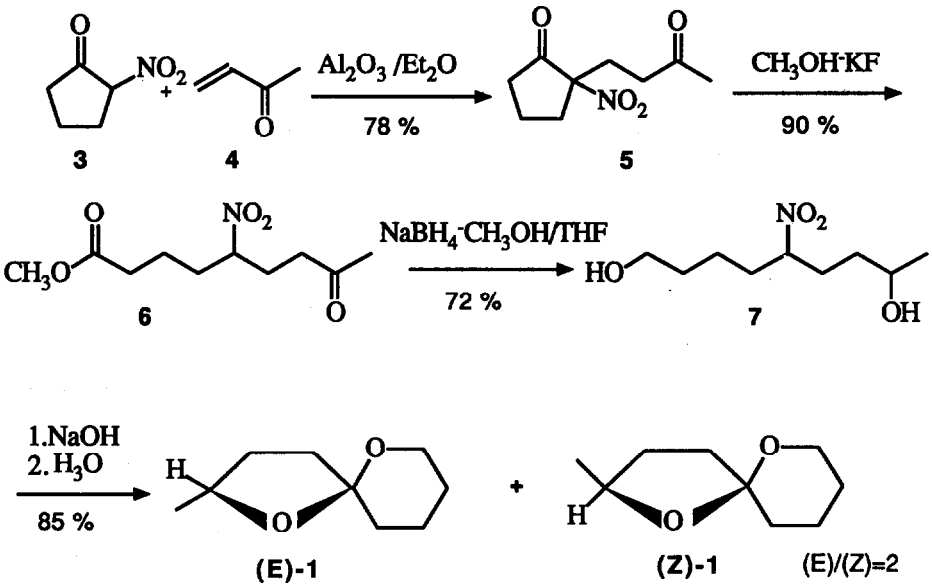


Table 1. Spiroketal components of pheromones of insects.

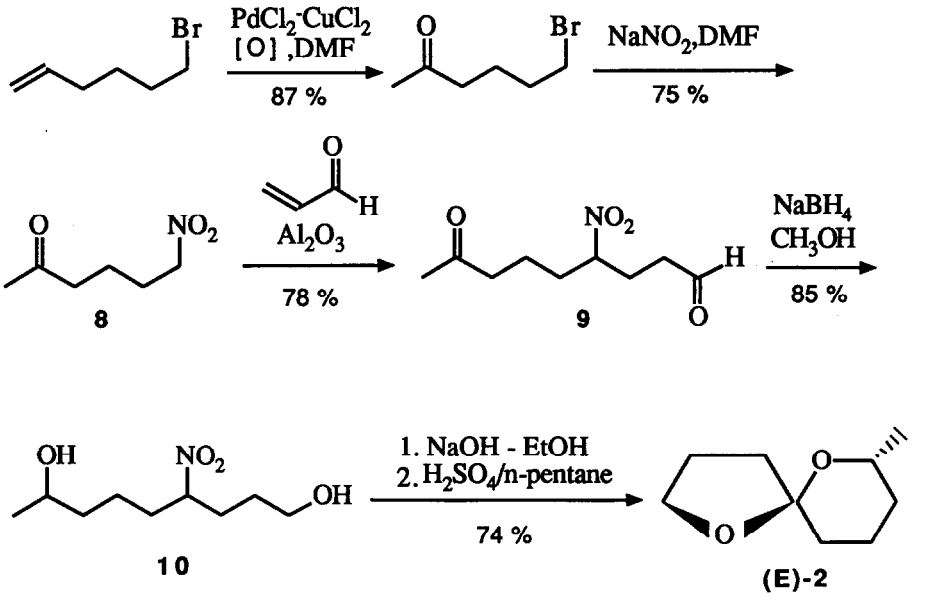
with correct sizes and specific arrangement of substituents have been played.[6,16-19] Recently, we reported[20] a new approach to the synthesis of 1,6-dioxaspiro[4.4]nonane derivatives based on the utilization of nitromethane as a d^1,d^1 multiple coupling reagent corresponding to a carbonyl dianion synthon. 2-Ethyl-1,6-dioxaspiro[4.4]nonane (chalcogran), the main component in the aggregation pheromone of the bark beetle *Pytyogenes chalcographus (L.)*[11] was obtained in 20% overall yield in a four steps procedure. Continuing our efforts to verify the utility of functionalized nitroalkanes as reagents for alkyl and acyl anion synthons,[21] we have worked out a solution to the synthesis of 1,6-dioxaspiro-[4.5]decanes (1) and (E)-7-methyl-1,6-dioxaspiro[4.5]decane (2). These compounds are important components of odours of the common wasp *P. vulgaris*[12] which might serve as repellants or aggregation inhibitors.

The starting material in our synthesis of (E)-1 and (Z)-1 (Scheme 1) was 2-nitrocyclopentanone (3), which was readily obtainable in high yield by nitration of the enol acetate of cyclopentanone with nitric acid in acetic anhydride.[22] The 1:4 addition of 3 to 1-buten-3-one (4) was carried out in diethyl ether, at room temperature in the presence of alumina.[23] The cyclic dicarbonyl derivative 5, containing all carbon atoms needed for the construction of 1, was obtained in 78% yield after a very simple work-up of the reaction mixture. It is well known that the C-C bond between the carbonyl group and the nitro substituted carbon atom of cyclic 2-nitroketones can be selectively cleaved by nucleophilic agents under mild reaction conditions.[24] The key open-chain nitro derivative 6 was obtained in 90% yield by a very efficient reaction with methanol using catalytic amounts of potassium fluoride as a base.[25] We now had to face the problem of chemoselective reduction of both ester and ketone groups of 6 to the correpsonding primary and secondary hydroxyl groups without modification of the nitro group. This crucial step was overcome by adding (dropwise) methanol to a refluxing tetrahydrofuran solution of 6 and sodium borohydride.[26] 5-Nitro-1,8-nonandediol (7) was obtained in 72% yield. The transformation of carbon bearing nitro group into a carbonyl group was efficiently achieved according to a recently improved two-layer method of the Nef reaction.[27] Under these conditions spontaneous spiroketalization occurred to give in good yield compound 1 as a 2:1 mixture of (E)- and (Z)-isomers. This composition is identical with that reported for the natural material and with that observed after equilibration at the spiro center under acidic conditions.[28]

We chose 1-nitro-hexan-5-one (8) as reagent for the 5-oxo-hexyl anion synthon needed for the synthesis of 7-methyl-1,6-dioxaspiro[4.5]decane summarized in Scheme 2. This



Scheme 1. Preparation of (E)- and (Z)-2-methyl-1,6-dioxaspiro[4.5]decanes .



Scheme 2. Preparation of (E)-7-methyl-1.6-dioxaspiro[4.5]decane .

specific C-6 fragment was obtained by oxidation of commercially available 1-bromo-5-hexene with palladium(II)chloride-copper(II)chloride/benzoquinone[29] and subsequent displacement of bromine with sodium nitrite in dimethylformamide (DMF).[30] The conjugate addition of primary nitroderivative **8** to an equimolar amount of acrolein was performed on Amberlist A-21 without solvent at room temperature. Under these conditions 4-nitro-1,8-dioxononane (**9**) was obtained in 78% yield. This was reduced to the corresponding dihydroxy derivative **10** by conventional treatment with sodium borohydride in ethanol. The conversion of **10** into the corresponding 4-carbonyl derivative and its concomitant spiroketalization was easily performed by the above reported procedure via solvolysis of aci-nitronate in a two-layer solution of aqueous sulfuric acid and n-pentane.[27] In this case the cyclization occurred to give a good yield of the single (E)-**2** isomer.

This high stereoselectivity in spiroketalization of **10** was not unexpected in view of previously reported findings of several authors on this field. In fact, the strong conformational stabilization by which the methyl group of a pyranose ring prefers an equatorial position whereas the oxygen atom of the neighboring ring occupies an axial site has been recognized as depending on stereoelectronic effects and steric interactions between the oxygen lone pair and the anti bonding orbitals of adjacent bonds and is well known as the "anomeric effect"[30,31] The decrease in stereoselectivity of spiroketalization of 2-ethyl-1,6-dioxaspiro[4.4]nonane and 2-methyl-1.6-dioxaspiro[4.5]decane in which an alkyl substituent is on the carbon adjacent to the oxygen of a tetrahydrofuran ring reflects the smaller energy difference between axial and equatorial orientation of substituents in this system.

In conclusion, the syntheses of (E)-**1**, (Z)-**1**, (E)-**2** described in this article as well as the previously reported preparation of "chalcogran"[20] illustrate a progressive evolution of a synthetic methdology that involves practical utilization of functionalized nitroalkanes as strategic tools for spiroketal synthesis.

EXPERIMENTAL

^{13}C and ^{1}H NMR spectra were obtained on a Varian VXR 300 MHZ spectrometer for deuteriochloroform solutions with tetramethylsilane as internal standard. IR spectra were recorded on a Perkin-Elmer 257 spectrophotometer as liquid films. Mass spectra were determined on a Hewlett-Packard GS/MS 5988A. Vapor-phase chromatography analyses were performed on a Carlo Erba Fractovap H160 using capillary column of fused silica (0.4-0.45 mm x 25 m) packed with Carbowax 20 M. Microanalyses were performed using C,H,N Analyzer Model 185 from Hewlett-Packard Co.

2-Nitro-2-(3'-oxobutyl)cyclopentanone (5).- A 500 ml, two-necked flask was equipped with a mechanical stirrer, charged with 2-nitrocyclopentanone (3) (16.5 g, 0.128 mol) in diethyl ether (200 ml) and cooled with an ice/water bath. Methyl vinyl ketone (17.92 g, 0.256 mol) was added and the mixture stirred for 5 min. Chromatographic alumina (activity I, 50 g) was added and stirring was continued for 3 h. at room temperature. The reaction mixture was passed through a short pad of Florisil to give a clear solution. This solution was evaporated to give 2-nitro-2-(3'-oxobutyl)cyclopentanone (5) (19.87 g, 78%, >97% pure by GLC) as an oil: IR (neat) 1760, 1715 (CO), 1545 (NO_2) cm^{-1}: ^1H NMR δ (90MHz): 2.85-1.9 (m, 10H); 2.12 (5.34). Found: C, 54.35; H, 6.71; N, 6.85; $C_9H_{13}O_4N$ requires C, 54.26; H, 6.58; N, 7.03 %.

Methyl 5-Nitro-8-oxononanoate (6). To a solution of compound 5 (12 g, 60 mmol) in dry methanol (300 ml), potassium fluoride (1.5 g, 25.8 mmol) was added at room temperature. The solution was refluxed for 1.5 h and then evaporated. The residue was treated with water, extracted with ether, dried (Na_2SO_4) and evaporated. Methyl 5-nitro-8-oxononanoate (6) was obtained (12.60, 90%, 100% pure by GLC) as an oil: IR (neat) 1740, 1720 (CO), 1550 (NO_2) cm^{-1}; ^1H NMR δ (90 MHz): 4.75-4.32 (m, 1H); 3.68 (s, 3H); 2.15 (s, 3H); 2.85-1.40 (m, 10H). Found: C, 51.85; H, 7.38; N, 5.97; $C_{10}H_{17}O_5N$ requires C, 51.94; H, 7.41; N, 6.06 %.

5-Nitro-1,8-nonanediol (7). Methanol (40 ml) was added dropwise over a period of 2h to a refluxing mixture of 6 (3.5 g, 41 mmol) and sodium borohydride (7.8 g, 205 mmol) in tetrahydrofuran (80 ml). The mixture was refluxed for 30 min, then after cooling to room temperature, water (50 ml) was added and the mixture was acidified with 2N hydrochloric acid. Most of the organic solvents were evaporated under reduced pressure. Water layer was extracted with chloroform (3x50 ml). This solution was dried (Na_2SO_4) and the solvent was removed at reduced pressure to give 5-nitro-1,8-nonanediol (7) (6.08 g, 72%) as an oil: IR (neat) 3340 (OH), 1545 (NO_2) cm^{-1}; ^1H NMR δ (90 MHz): 4.60-4.45 (m, 1H); 3.9-3.71 (m, 1H); 3.64 (t, 2H, J = 6.3 Hz); 2.20-1.32 (m, 10 H); 1.2 (d, 3H, J= 6.1 Hz). Found: C, 51.57; H, 8.12; N, 5.89; $C_{10}H_{19}O_5N$ requires C, 51.49; H, 8.21; N, 6.01 %.

(E)- and (Z)-2-Methyl-1,6-dioxaspiro[4.5]decanes: (E)-1 and (Z)-1. A solution of 5-nitro-1,8-nonanediol (7) (2.8 g, 13.6 mmol) in absolute ethanol (30 ml) was added dropwise to a solution of NaOH (2.2 g, 54 mmol) in ethanol (30 ml) under nitrogen at room temperature. The mixture was stirred for 5 min and the solvent was evaporated at room temperature under reduced pressure. A solution of the resulting salt in water (60 ml) was slowly added (dropwise) to the two-layer mixture of sulfuric acid (6.8 ml of conc sulfuric acid in 70 ml of water) and n-pentane (60 ml) with stirring under ice-water bath cooling. When the addition was complete, stirring was continued for 1 h at 0°C and the pentane layer was separated out. The aqueous layer was then extracted with pentane. Organic solutions were combined, dried (Na_2SO_4) and distilled (bp = 120°C/75 torr by Kugelrohr) to give a mixture of (E)- and (Z)- isomers of 2-methyl-1.6-dioxaspiro[4.5]decanes (1.48 g, 70%, E/Z = 63/37): ^1H NMR δ(300 MHz): 4.28-4.12 (m, 1H); 3.98-3.5 (m, 2H); 2.18-1.32 (m, 10H); 1.30 (d, 3H, J=6.2 Hz) for Z isomer; 1.22 (d, 3H, J= 6.2 Hz) for E isomer. ^{13}C (300 MHz): 105.78; 105.57; 76.71; 73.96; 61.57; 61.43; 38.98; 37.75; 34.18; 34.05; 31.70; 31.37; 25.37; 25.28; 23.18; 21.26; 20.35; 20.38 ppm. MS (m/z): (E)-isomer: 156(3%, M^+), 141 (4); 128 (5); 111 (15); 101 (100); 98 (57); 83 (45); 70 (5); 56 (19); 55 (26); 43 (13); (Z)-isomer: 156 (3%, M^+), 141 (4), 128 (4), 111 (9), 101 (100), 98 (40), 83 (37), 70 (4), 56 (14), 55 (21); 43 (9). Found: C, 69.35; H, 10.28; $C_9H_{16}O_2$ requires C, 69.19; H, 10.32 %.

4-Nitro-1,8-dioxononane (9). A 100 ml two-necked flask equipped with a mechanical stirrer was charged with 1-nitrohexan-5-one (8) (2.7 g, 18.6 mmol) and cooled with an ice-water

bath. Acrolein (1.04 g, 18.6 mmol) was added and the mixture stirred for 5 min. Amberlist-A21 (3 g) was added and stirring was continued for additional 4 h. The reaction mixture was evaporated and the residue was purified by chromatography with ethyl acetate/hexane (1:1) as eluent to give 4-nitro-1,8-dioxononane (2.16 g, 58%) as an oil: IR (neat) 1730 (CHO), 1710 (CO), 1550 (NO_2) cm^{-1}; ^1H NMR δ (90 MHz): 9.76 (S, 1H); 4.6-4.5 (m, 1H); 2.60-2.32 (m, 4H); 2.12 (s, 3H); 2.1-1.5 (m, 6H). Found C, 53.63; H, 7.38; N, 6.87; $C_9H_{15}O_4N$ requires C, 53.72; H, 7.51, N, 6.96 %.

4-Nitro-1,8-nonanediol (10). A solution of compound 9 (1.32 g, 6.5 mmol) in ethanol (60 ml) was cooled at 0°C, then sodium borohydride (0.62 g, 16 mmol) was added. The mixture was stirred for 30 min, then water (20 ml) was added and the solution was acidified with 2N HCl. Most of the organic solvent was evaporated under reduced pressure. Aqueous layer was extracted with ether (3x30 ml). The ethereal layers were combined, dried (Na_2SO_4), and after evaporation under reduced pressure gave a residue which was purified by column chromatography (silica gel ethyl acetate/hexane/ethanol 7:2.5:0.5) to give 4-nitro-1,8-nonanediol (10) as pure product (1.14 g, 85%): IR (neat) 3370 (OH), 1550 (NO_2) cm^{-1}. ^1H NMR δ (90 MHz): 4.62-4.48 (m, 1H); 3.9-3.6 (m, 3H); 1.18 (d, 3H, J=6.1 Hz); 2.15-1.15 (m, 10H). Found: C, 58.25; H, 10.61; N, 7.12; $C_9H_{19}O_H$ N requires C, 57.11; H, 10.12; N, 7.40 %.

(E)-7-Methyl-1,6-dioxaspiro[4.5]decane (2). 4-Nitro-1.8-nonanediol (10) (5.0 g, 24.4 mmol) in absolute ethanol (60 ml) was added dropwise to a solution of NaOH (3.9 g, 97 mmol) in ethanol (40 ml) under nitrogen at room temperature. After stirring for 5 min the solvent was evaporated under reduced pressure and at room temperature. The resulting sodium salt was dissolved in water (120 ml) and was slowly added to the two-layer mixture of sulfuric acid (12 ml of conc H_2SO_4 in 14 ml of water) and n-pentane (150 ml) with stirring under ice-water cooling. The mixture was stirred for 1 h at 0°C, then the n-pentane layer was separated. Aqueous layer was extracted again with n-pentane. The organic layers were combined dried (Na_2SO_4) and distilled to give (E)-7-methyl-1.6-dioxaspiro[4.5]decane (2) (2.8 g, 74%) as an oil: bp 95° C/36 torr by Kugelrohr. IR ($CHCl_3$) 2900, 1050 cm^{-1}. ^1H NMR δ_{13} (300 MHz): 3.95-3.81 (m+t, 3H, J= 7.11 Hz); 2.10-1.12 (m, 10H); 1.11 (d, 3H, J= 6.32 Hz). ^{13}C (300 MHz) 105.99; 66.77; 66.45; 37.97; 32.82; 32.62; 23.76; 22.03; 20.43. MS (m/z) = 156 (3%, M^+); 115 (5); 112 (12); 97 (21); 87 (100); (86 (13); 85 (10); 84 (96); 73 (5); 72 (5); 70 (6); 69 (13); 57 (9); 56 (20); 55 (31); 53 (5); 45 (7); 43 (29); 42 (29); 41 (28); 39 (16); 29 (10); 28 (5); 27 (9). Found: C, 69.28; H, 10.45; $C_9H_{16}O_2$ requires C, 69.19; H, 10.32 %.

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