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SYNTHESIS AND PHEROMONAL PROPERTIES OF (Z)-7,7-DIFLUORO-8-DODECENYL ACETATE, A DIFLUORO DERIVATIVE OF THE SEX PHEROMONE OF THE ORIENTAL FRUIT MOTH

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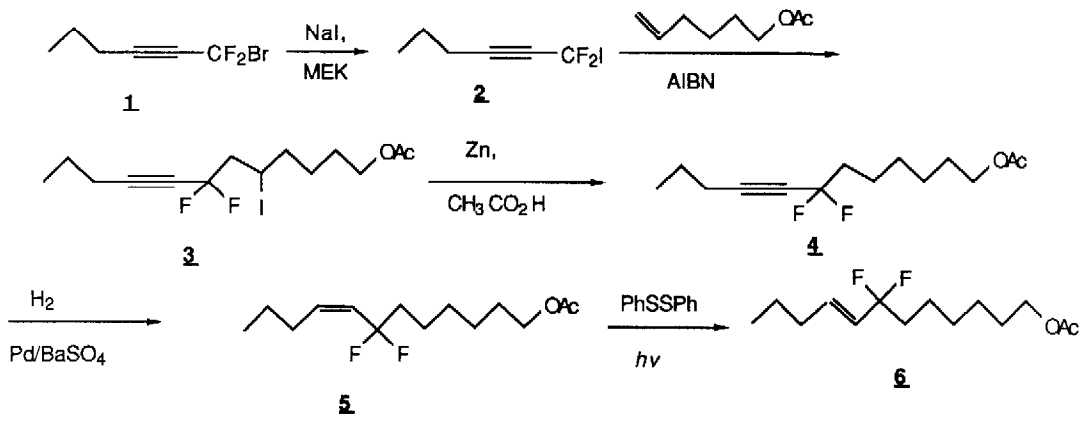
Summary: A synthesis of allylic difluorides is described, exemplified by the preparation of the title compound, which was shown to elicit the biological responses characteristic of (Z)-8-dodecenyl acetate, the pheromone of the Oriental fruit moth. It is concluded that the geometry of the double bond rather than its chemical reactivity is essential for biological activity.

Many insect pheromones contain double and triple bonds as an essential feature of their structure.[1] We recently reported on a general synthesis of (Z,Z)-3,3-difluoro-1,4-dienes and acetylenes in connection with the synthesis of fluorinated arachidonic acids.[2] It occurred to us that some of that methodology could also be utilized for the synthesis of allylic difluoromonoenes, thereby affording the opportunity to prepare pheromones in which a methylene group α to the double bond is replaced by a CF_2 group. No such methodology was available prior to this work. Such substitution would have no significant effect on the geometry of the pheromone, yet exert a pronounced influence on the reactivity of the double bond with the potential of altering the interaction of the pheromone with its exquisitely sensitive receptor. The biological consequences of such a change in structure were sufficiently intriguing to test this concept. Other investigators[3,4] have prepared and tested fluorinated pheromones, in which fluorine is substituted at vinylic carbons.

We chose to synthesize (Z)-10,10-difluoro-8-dodecenyl acetate (**5**), the difluoro-analog of the pheromone of the oriental fruit moth, Grapholita molesta, whose behavioral responses to the pheromone have been studied in depth.[5] 1-Bromo-1,1-difluoro-2-hexyne (**1**) was prepared[2] from 1-pentynyl lithium and CF_2BrCl as a difficultly separable mixture containing 10% of 1-bromo-1-pentyne, which was directly converted to the 1-iodide **2** with sodium iodide in refluxing methyl ethyl ketone for 20 hours. Fractional distillation (b.p. 85° at 65 Torr.) gave the pure iodide (**2**)[6] in 62% yield. Radical addition[7] of **2** (5.7 mmole) to 5-hexen-1-ol acetate (12.2 mmole) in benzene (1 ml) with AIBN (0.12 mmole) in a sealed tube at



80° for 6 hours gave after silica gel chromatography 5-iodo-7,7-difluoro-8-dodecyn-1-ol acetate (3)[8] in 82% yield without attack at the triple bond. Deiodination with Zn in acetic acid at 80-85° for 6 hours followed by filtration through silica gel and distillation (b.p. 129° at 2.5 Torr.) afforded 4[9] in 77% yield. The triple bond was reduced with $Pd/BaSO_4$ in pyridine to yield the desired cis-olefin 5[10] in quantitative yield. The observation that admixture of about 8% of the (E)-isomer of the pheromone to the (Z)-isomer resulted in a significant increase in potency[11] prompted the preparation of the corresponding difluoro analog 6. Irradiation of 5 with diphenyldisulfide[12] in hexane with a medium pressure mercury lamp at 0-5° resulted in complete conversion[13] to the trans isomer 6[14] in 95% yield.

The (Z)-isomer 5 was subjected to a number of assay procedures. In flight tunnel experiments using a three component blend with the pheromone as the main component substitution of 5 for (Z)-8-dodecenyl acetate showed no difference in the male's response to this blend and that containing the natural pheromone. This includes a complete behavioral sequence of activation: orienting to the plume, flying upwind, landing and hairpencilling. In the EAG the response was quite similar in amplitude and recovery of response to baseline for both the natural and difluoro compounds. The natural pheromone showed an average response of 6.6 mV compared to 5.9 mV for 5 (N = 18). These experiments indicate that the change in chemical reactivity (nucleophilicity) of the double bond caused by fluorine substitution plays little if any role in the interaction of the pheromone with its receptor. On the other hand, the maintenance of the geometry in the fluorine analog appears to be essential for biological activity.

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6. **2**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.33 (tt, 2H, J = 7.3, 5.0 Hz, H-4), 1.63 (sext., 2H, J = 7.3 Hz, H-5), 1.03 (t, 3H, J = 7.3 Hz, H-6); ^{19}F NMR (188 MHz,$CDCl_3$): Φ 25.48 (t, J = 5.0 Hz); $C_6H_7F_2I$: Calcd.: C, 29.52; H, 2.89; Found: C, 29.45; H, 2.97.

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8. **3**: ^{1}H NMR (500 MHz,$CDCl_3$): δ 4.32 (m, 1H, H-5), 4.08 (t, 2H, J = 6.3 Hz, H-1), 2.87 (ddt, J = 16.5, 15.0,5.0 Hz,H-6); 2.72 (ddt, 1H, J = 15.0, 11.5, 9.0 Hz, H-6), 2.27 (tt, 2H, J = 7.0, 5.2 Hz, H-10), 2.06 (s, 3H, $COCH_3$), 1.83 (qu, 2H, J = 6.4Hz,H-4),1.72-1.42 (m, 6H, H-2, H-3, H-11), 1.02 (t, 3H, J=7.4 Hz,H-12); ^{19}F NMR (188 MHz, $CDCl_3$): Φ 78.34 (dddt, J = 270, 14.5, 11.7, 5.2 Hz), 79.67 (dddt, J = 270, 16.4, 14.0, 5.2 Hz); $C_{14}H_{21}O_2F_2I$: Calcd.: C, 43.53; H, 5.48; F, 9.84; Found: C, 43.55; H, 5.44; F, 9.69;m/z: 259 (M-I), 239 (M-I-HF).

9. **4**: ^{1}H NMR (500 MHz,$CDCl_3$): δ 4.05 (t, 2H, J = 6.7 Hz, H-1), 2.25 (tt, 2H, J = 7.0, 5.0 Hz, H-10), 2.04 (s, 3H, $COCH_3$), 2.00 (m, 2H, H-6), 1.67-1.53 (m, 6H, H-2, H-5, H-11), 1.38 (m, 4H, H-3, H-4), 1.00 (t, 3H, J=7.4 Hz,H-12);^{19}F NMR (188 MHz, $CDCl_3$): Φ 81.48 (tt, J = 14.6, 5.0 Hz); $C_{14}H_{22}O_2F_2$: Calcd.: C, 64.54; H, 8.52; F, 14.60; Found: C, 64.83; H, 8.58; F, 14.23.

10. **5**: ^{1}H NMR (500 MHz,$CDCl_3$): δ 5.69 (m, 1H, H-9), 5.45 (qu, 1H, J = 13.6 Hz, H-8), 4.05 (t, 2H, J = 6.0 Hz, H-1), 2.23 (m, 2H, H-10), 2.05 (s, 3H, $COCH_3$), 1.91 (m, 2H, H-6),1.64 (m, 2H, H-5), 1.55-1.36 (m, 6H, H-2, H-3, H-4), 0.94 (t, 3H, J = 7.3 Hz, H-12); ^{19}F NMR ($CDCl_3$, 188 MHz): Φ 91.14 (qu, J =15.0Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 171.19 (s, $COCH_3$), 137.84 (t, J = 6.1 Hz, C-9), 124.81 (t, J = 26.1 Hz, C-8), 122.65 (t, J = 236.7 Hz, C-7), 63.43 (s, C-1), 38.41 (t, J =26.86Hz, C-6), 30.24 (s, C-10), 28.93 (s, C-2 or C-3), 28.42 (s, C-2 or C-3), 25.73 (s, C-4), 22.57 (s, C-11), 22.22 (t, J = 6.1 Hz, C-5), 21.00 (s, CH_3CO), 13.70 (s, C-12); $C_{14}H_{24}O_2F_2$: Calcd.: C, 64.09; H, 9.23; F, 14.49; Found: C, 64.13; H, 9.11; F, 14.30.

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13. Irradiation for 6 hours with a 2:1 molar ratio of cis olefin and diphenyl disulfide gave 90% conversion (by NMR). Complete isomerization was achieved after addition of disulfide and continued irradiation.

14. **6**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.03 (m, 1H, H-9), 5.52 (dt, 1H, J = 15.7, 11.0 Hz, H-8) 4.05 (t, 2H, J = 6.7 Hz, H-1), 2.08 (m, 2H, H-10), 2.05 (s, 3H, $COCH_3$) 1.88 (m, 2H, 6-H), 1.63 (m, 2H, H-2), 1.45 (m, 4H, H-5, H-11), 1.37 (m, 4H, H-3, H-4), 0.93 (t, 3H, J = 7.4 Hz, H-12); ^{19}F NMR (376 MHz, $CDCl_3$): Φ 95.28 (qu, J = 12.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 171.23 (s, $COCH_3$),135.64 (t, J = 6.8 Hz, C-9), 125.28 (t, J = 27.3 Hz, C-8), 121.66 (t, J = 236.1 Hz, C-7), 64.44 (s, C-1), 37.39 (t, 26.7 Hz, C-6), 33.83 (s, C-10), 28.93 (s, C-2 or C-3), 28.44 (s, C-2 or C-3),25.74 (s, C-4), 22.35 (t, J = 2.7 Hz, C-5), 21.72 (s, C-11), 21.00 (s, $COCH_3$), 13.60 (s, C-12); $C_{14}H_{24}O_2F_2$: Calcd.: C, 64.09; H, 9.23; Found: C, 64.00; H, 9.27.

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