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# PARTIALLY FLUORINATED ANALOGS OF *(Z)*-9-DODECENYL ACETATE: PROBES FOR PHEROMONE HYDROPHOBICITY REQUIREMENTS

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***Summary***: Allylic difluoromethylene, terminal trifluoromethyl, and pentafluoroethyl analogs of *(Z)*-9-dodecenyl acetate were synthesized to probe the requirements for hydrophobicity of the alkyl terminus in pheromone activity. These compounds show unexpected and varied behavioral activities in assays using the European grape berry moth.

Blends of simple saturated and unsaturated fatty alcohols, acetates, and aldehydes act as sex attractant pheromones in moths. Each component is perceived in a specialized olfactory cell involving sensillum-specific binding and catabolic proteins.[1] Subtle changes in chain length, branching, alkene position or geometry, or functional group can result in nearly complete loss of biological activity.[2] Electrophysiological responses to analogs of the turnip moth pheromone component (*Z*)-5-decenyl acetate can be correlated with calculated differences in the conformational energies relative to a *cis*-oid receptor site model.[3] Although the terminal methyl group is a key to pheromone activity in virtually all pheromones, the relative importance of the overall hydrophobicity of the terminal alkyl moiety is unknown. We now describe the preparation of four polyfluorinated analogs[4] (Figure 1) designed to more accurately map the receptor requirements for a simple alkenyl acetate, *(Z)*-9-dodecenyl acetate (1).

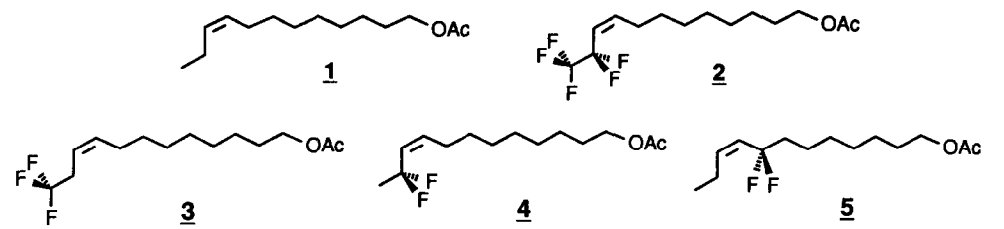


**Figure 1.** Structure of fluorinated analogs of *Z*9-12:Ac

The synthesis of perfluoroethyl analog, 11,11,12,12,12-pentafluoro-*Z*9-12:Ac (2) was achieved in four steps in 27% overall yield (Figure 2). (Note: *Z*9-12:Ac is an accepted shorthand for (*Z*)-9-dodecenyl

acetate). Heating 9-decyn-1-ol (6) (from an acetylene zipper reaction[5]) and $C_2F_5I$ with AIBN as catalyst afforded an 82% yield of the alkenyl iodides (9) as a 92:8 *E*:*Z* mixture[6], and the isomers were separated at this stage by MPLC. Lithium-halogen exchange and quenching at low-temperature[7] gave perfluoroethyl-*Z*9-12:OH (8) in 85% yield. Acetylation of (8) provided the pentafluoro pheromone analog (2).

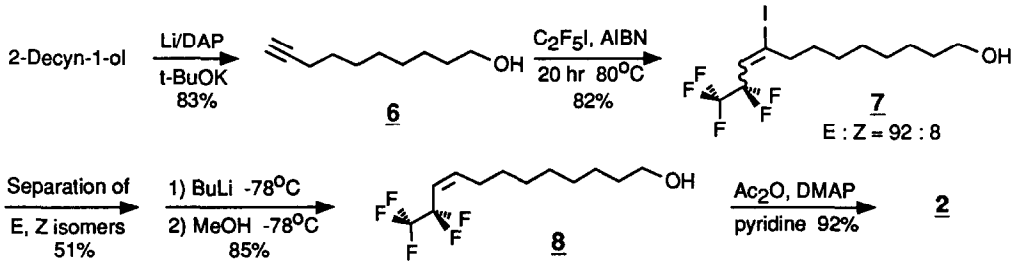


**Figure 2.** Synthesis of 11,11,12,12,12-pentafluoro-*Z*9-12:Ac (2)

Initial attempts to synthesize 12,12,12-trifluoro-*Z*9-12:Ac (3) via radical coupling of 9-decyn-1-ol and 2,2,2-trifluoroethyl iodide with AIBN failed, as did the attempts at metal-catalyzed reductive coupling of the 2,2,2-trifluoroethyl iodide or tosylate with the lithium acetylide of (12). Successful synthesis of the trifluoromethyl analog (3) was accomplished by a *cis*-selective Wittig olefination[8] (Figure 3). Thus, the triphenylphosphonium salt prepared from 3,3,3-trifluoropropyl iodide was converted to the ylid, and the protected aldehyde (10) was added at -78 °C. After warming to 25 °C for 10 h, the expected 12,12,12-trifluoro-*Z*9-12:OTBDMS (11) was obtained in 60% yield. Capillary GC and $^1H$ NMR of the chromatographically purified TBDMS ether indicated exclusive (>99%) formation of the desired (*Z*)-alkene. Deprotection and acetylation afforded 12,12,12-trifluoro-*Z*9-12:Ac (3) in 25% overall yield.

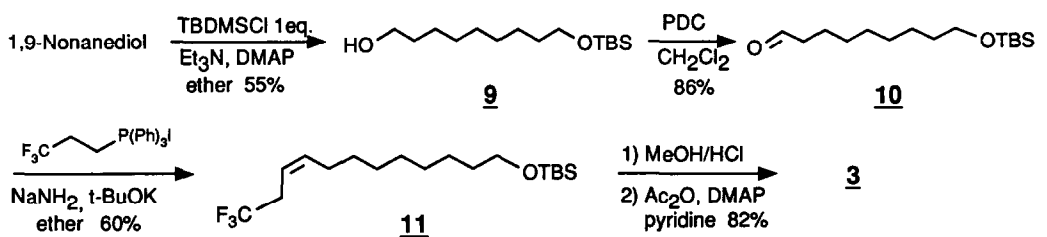


**Figure 3.** Synthesis of 12,12,12-trifluoro-*Z*9-12:Ac (3)

The 11,11-difluoro analog (4) was synthesized in 7 steps, also starting from 2-decyn-1-ol, in 21% overall yield (Figure 4). Thus, addition of the lithium acetylide of the TBDMS ether protected 9-decyn-1-ol (12) to acetaldehyde provided the propargylic alcohol (13), which was then oxidized by PDC to the corresponding ketone. Deprotection with methanolic HCl followed by acetylation gave the ynone acetate (14) in 85% yield. Fluorination with excess diethylaminosulfur trifluoride (DAST) at 55 °C for 8 h provided the 11,11-difluoroalkyne (15) in 60% yield. The difluoroalkyne (15) was semihydrogenated to the *Z*-alkene

using quinoline-poisoned $Pd/BaSO_4$ in pyridine. Lindlar catalyst was ineffective and omitting quinoline or replacing pyridine with pentane, ethyl acetate, or methanol gave undesired side products (capillary GC analysis).

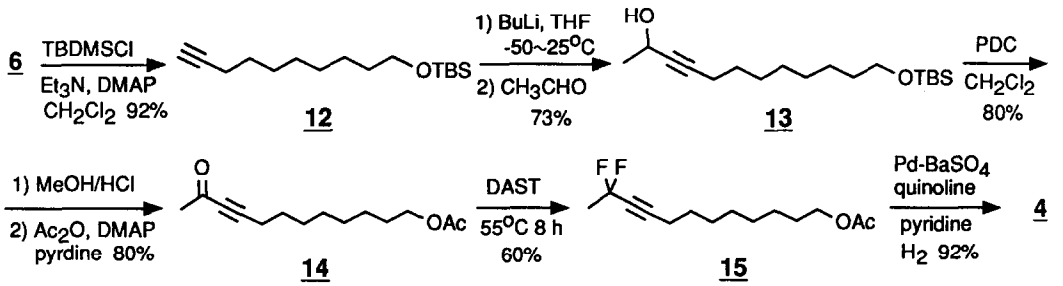


**Figure 4.** Synthesis of 1,11-difluoro-*Z*9-12:Ac (4)

The 8,8-difluoro analog (5) was synthesized following the successful route for the allylic difluoride (Figure 5). The lithium acetylide of butyne, generated in ether at -30 °C from 1-butyne and *n*-BuLi, was added to the TBDMS ether of 8-hydroxyoctanal (16) in THF at -30 °C; the resulting propargylic alcohol (17) was then oxidized to the ketone by PDC. Deprotection, acetylation, and then fluorination with DAST gave the 8,8-difluoroalkyne. Semihydrogenation with quinoline-poisoned $Pd/BaSO_4$ in pyridine gave the desired 8,8-difluoro-*Z*-9-12:Ac (5) in 15% overall yield starting from 1,8-octanediol.

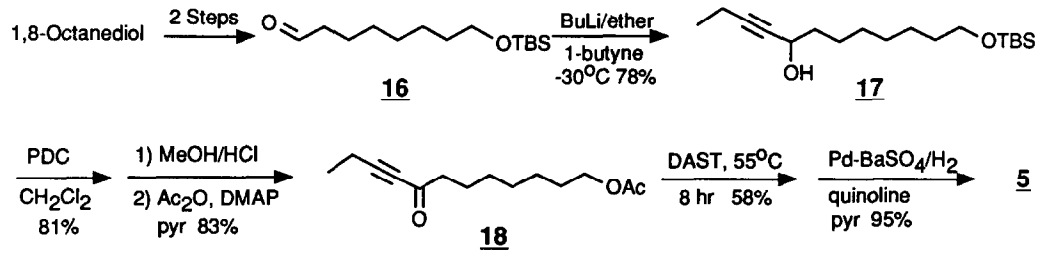


**Figure 5.** Synthesis of 8,8-difluoro-*Z*9-12:Ac (5)

The ability of fluorine to masquerade sterically as hydrogen leads to analogs of pharmaceuticals and agrochemicals with altered bioavailability, biochemical activity, and metabolic fate.[9] Selectively fluorinated analogs of pheromones have been examined by our group[10], the Barcelona group[11], and the Rothamsted group.[12] These analogs have gross physical and biological properties similar to those of the parent compounds. However, substitution of perfluorobutyl and perfluorohexyl groups for terminal *n*-butyl and *n*-hexyl chains dramatically increased volatility and reduced specific single cell responses in several moth species.[13] The unexpected behavioral responses to three of the analogs described herein will be described in detail elsewhere.[14]

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4. Key spectral and analytical data follow for compounds **2**, **3**, **4**, and **5**. **2**: $^1$H NMR δ 6.11 (dtt, H-9, $J_{H9-H10}$ = 12.0 Hz, $J_{H9-H8}$ = 7.9 Hz, $J_{H9-F11}$ = 2.4 Hz, 1 H), 5.45 (m, H-10, 1 H), 4.05 (t, $J$ = 6.7 Hz, 2 H), 2.28 (br, 2 H), 2.04 (s, 3 H), 1.56-1.32 (br m, 12 H). $^{19}$F NMR ϕ 91.50 (t, $J$ = 2.0 Hz, 3 F), 115.62 (m, 2 F). Calcd. for $C_{14}H_{21}F_5O_2$: C, 53.16; H, 6.69; F, 30.02. Found: C, 53.62; H, 6.68; F, 30.12. **3**: $^1$H NMR δ 5.70 (crude q, 1H), 5.38 (crude qt, 1H), 4.04 (t, $J$ = 6.7 Hz, 2 H), 2.83 (m, H-11, 2 H), 2.04 (s and br, H-8 and H-acetate, 5 H), 1.58 (br, 2 H), 1.29 (br, 12 H). $^{19}$F NMR ϕ 70.78 (t, $J$ = 10.8 Hz). Calcd. for $C_{14}H_{23}F_3O_2$: C, 59.98; H, 8.27; F, 20.33. Found: C, 60.17; H, 8.19; F, 20.30. **4**: $^1$H NMR δ 5.67 (dtt, H-9, $J_{H9-H8}$ = 7.7 Hz, $J_{H9-H10}$ = 12.0 Hz, $J_{H9-F11}$ = 1.4 Hz, 1 H), 5.50 (dt, H-10, $J_{H10-H9}$ = 12.0 Hz, $J_{H10-F11}$ = 13.6 Hz, 1 H), 4.05 (t, $J$ = 6.8 Hz, 3 H), 2.25 (m, 2 H), 2.04 (s, 3 H), 1.70 (t, H 12, $J$ = 18.0 Hz, 3 H), 1.6-1.3 (br m, 12 H). $^{19}$F NMR ϕ 87.85 (m). Calcd. for $C_{14}H_{24}F_2O_2$: C, 64.09; H, 9.22; F, 14.48. Found: C, 65.03; H, 9.35; F, 14.58. **5**: $^1$H NMR δ 5.69 (dtt, H-10, $J_{H10-H9}$ = 11.8 Hz, $J_{H10-H11}$ = 7.7 Hz, $J_{H10-F8}$ = 1.9 Hz, 1 H), 5.43 (td, H-9, $J_{H9-H10}$ = 12 Hz, $J_{H9-F8}$ = 14.3 Hz, 1 H), 4.04 (t, H-1, $J$ = 6.7 Hz, 2 H), 2.19 (m, H-11, 2 H), 2.05 (s, 3 H), 1.82 (m, 2 H), 1.6-1.3 (m br, 10 H), 1.00 (t, H-12, $J$ = 7.5 Hz, 3 H). $^{19}$F NMR ϕ 95.26 (q, $J$ = 15.2 Hz). Calcd. for $C_{14}H_{24}F_2O_2$: C, 64.09; H, 9.22; F, 14.48. Found: C, 64.20; H, 9.26; F, 14.45. $^1$H shifts were downfield relative to $(CH_3)_4Si$; $^{19}$F shifts were upfield relative to $CCl_3F$.

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