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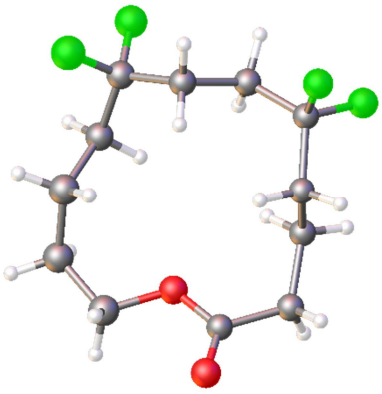

Fluorine in pheromones: Synthesis of fluorinated 12-dodecanolides as Emerald Ash Borer pheromone mimetics

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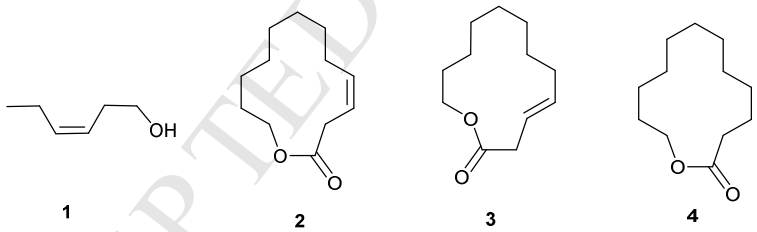
ABSTRACT
A series of five 12-dodecanolides have been synthesised containing CF_2 groups at C5, C6, C7, C8 and in one case a double substitution at C5 & C8, as a strategy to bias the conformational space accessed by these macrocycles, and to assess if the analogues may act as mimetics for 12-decenolide pheromones associated with the Emerald Ash Borer. Accordingly individual syntheses of 5,5-difluoro- **5**, 6,6-difluoro- **6**, 7,7-difluoro- **7**, 8,8-difluoro- **8** and 5,5,8,8-tetrafluoro- **9**, 12-decanolides is outlined and X-ray structural data was obtained for three (**5**, **8** and **9**) of these compounds. The structures show clearly that the CF_2 groups occupy 'corner' locations in the macrocycle consistent with their ability to bias accessible conformations. The fluorine containing 12-dodecanolides all generated an electro-antennogram response in female beetles.

Keywords:
Insect pheromones
Emerald ash borer
Organofluorine chemistry
12-Decanolides
Electroantennogram (EAD) analyses

1. Introduction

Fluorine is rarely encountered in natural products [1] and there are no examples known of insect pheromones containing fluorine; its occurrence in organic chemistry is almost exclusively anthropogenic. In that context fluorine has been widely and successfully employed to improve properties and efficacy in the design of pharmaceuticals products [2] and it would seem reasonable by extension that the strategic incorporation of fluorine into insect pheromone analogues may offer prospects as a design strategy for improving the efficacy of pheromone analogues. Such practice has however been slow to gain traction, and where fluorine has been explored in this context, outcomes have been mixed and unpredictable [3]. Almost always the fluorine has directly replaced an aliphatic hydrogen

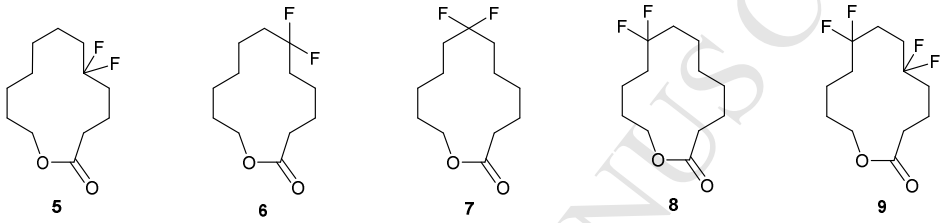
and clear cut improvements are rare [3 - 8]. This has much to do with the pheromones themselves already being optimal as they are highly evolved natural products and fluorine not being a very good hydrogen mimetic from a steric and electronic perspective. Differences in molecular volatility must also be anticipated with the molecular weight increase. Undeterred we have explored a new approach incorporating the fluorine as a means to limit the conformational flexibility of a macrocyclic pheromone and we report our synthesis and preliminary evaluation of the efficacy of a series of analogues in this paper. The emerald ash borer (EAB), *Agrilus planipennis* Fairmaire (Coleoptera: Buprestidae), is a wood boring beetle native to East Asia, however it has become a serious invasive pest in North America, causing extensive mortality to ash trees when it emerged on the continent in 2002 [9]. Currently it has spread to 31 States in the U.S. and across five Canadian Provinces. Western Europe is also under threat with its recent emergence in Russia [10]. The plant volatiles and pheromones such as **1** - **4** which stimulate the EAB have become relevant for developing strategies for monitoring and control [11]. (3*Z*)-Dodecen-12-olide **2** was identified as a key antennally-active compound produced primarily by females to attract males [11,12]. Similarly, the non-natural stereoisomer (3*E*)-dodecen-12-olide **3**, and the saturated dodecanolactone **4**, also showed similar activities towards male EAB [13].



1 2 3 4

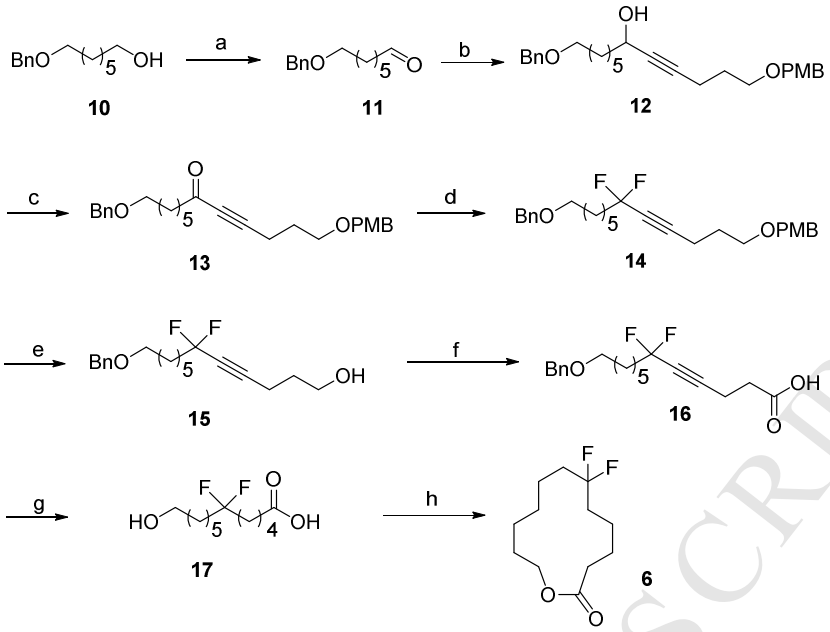
Fluorine has advantages as a hydrogen mimetic for bioactives in that it is sterically compact, and it does not enter into strong intermolecular interactions [14]. However the introduction of fluorine is never neutral. Fluorine is significantly larger than hydrogen based on van der Waals radii (F = 1.47Å versus H = 1.2Å) [15] and we have established that the -CF_2- group tends to dictate corner positions when it is incorporated into aliphatic rings, and particularly in medium sized macrocyclic ring compounds [16]. This is a consequence of the larger size of fluorine over hydrogen, avoiding transannular interactions relative to hydrogen, and also the electronegativity of fluorine changing the hybridisation towards sp^2 at the directly bound carbon and widening the C-CF_2-C angle, often close to sp^2 hybridisation [16b]. We have recently explored replacing one or two CH_2 groups by CF_2 in various macrocyclic lactones

such that the stereoelectronic influence of the fluorines might limit conformational flexibility and help provide some insight into favoured bioactive conformations of fragrance lactone and ketones such as muscone [17a] and musk lactones [17b,c]. We now report the synthesis of the CF_2 containing 12-dodecanolides **5-9** (Figure 4), where the CF_2 groups are variously positioned around the lactone ring. The fluorines should place conformational constraints into these molecules at different locations, as an alternative strategy to introducing double bonds of defined geometry such as is found in **2** and **3**. Compounds **5 - 9** underwent preliminary electroantennography (EAG) analyses, comparing the relative sensitivity of the fluorinated lactones to female beetles.

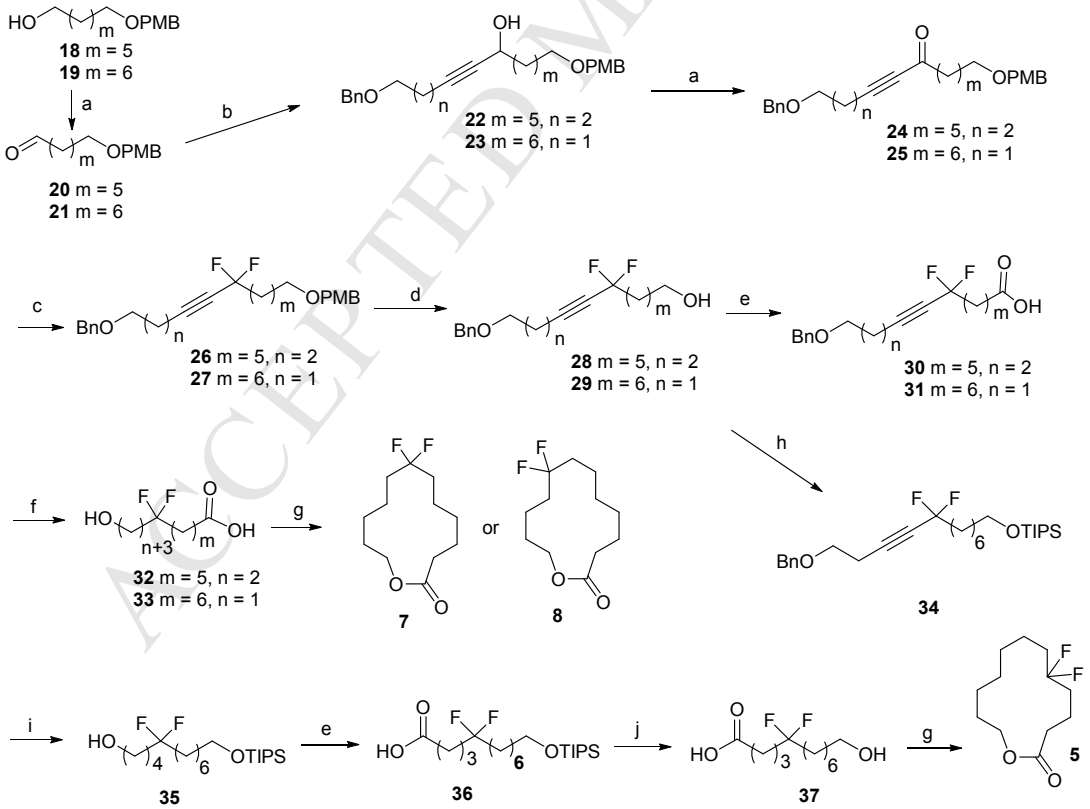


2. Result and Discussion

Synthesis: The synthesis of the 12-dodecanolide **6**, was accomplished as illustrated in Scheme 1. Full experimental details are given in the extensive Supplementary Information. A key reaction involved DAST treatment of propargylic ketone **13** to generate difluoromethylene **14**, following previously developed protocols [18]. Orthogonal deprotection allowed release of alcohol **15** which was oxidised to carboxylic acid **16**. Hydrogenation then released an alcohol at the other terminus of the chain, with concomitant reduction of the acetylene to generate fatty acid **17**, which was cyclised to generate 12-dodecanolide **6**. The routes to analogues **7** and **8** are illustrated in Scheme 2. Their syntheses were accomplished in a similar manner to that described for target **6**, but differed by manipulating the chain lengths of the aldehydes and terminal acetylenes used to generate propargylic alcohols **22** and **23**. In order to access 12-dodecanolide **5**, the protecting group strategy was controlled by introducing a triisopropylsilyl ether (TIPS group) [19], such that oxidation could be achieved at the opposite end of the chain with respect to the previous syntheses.



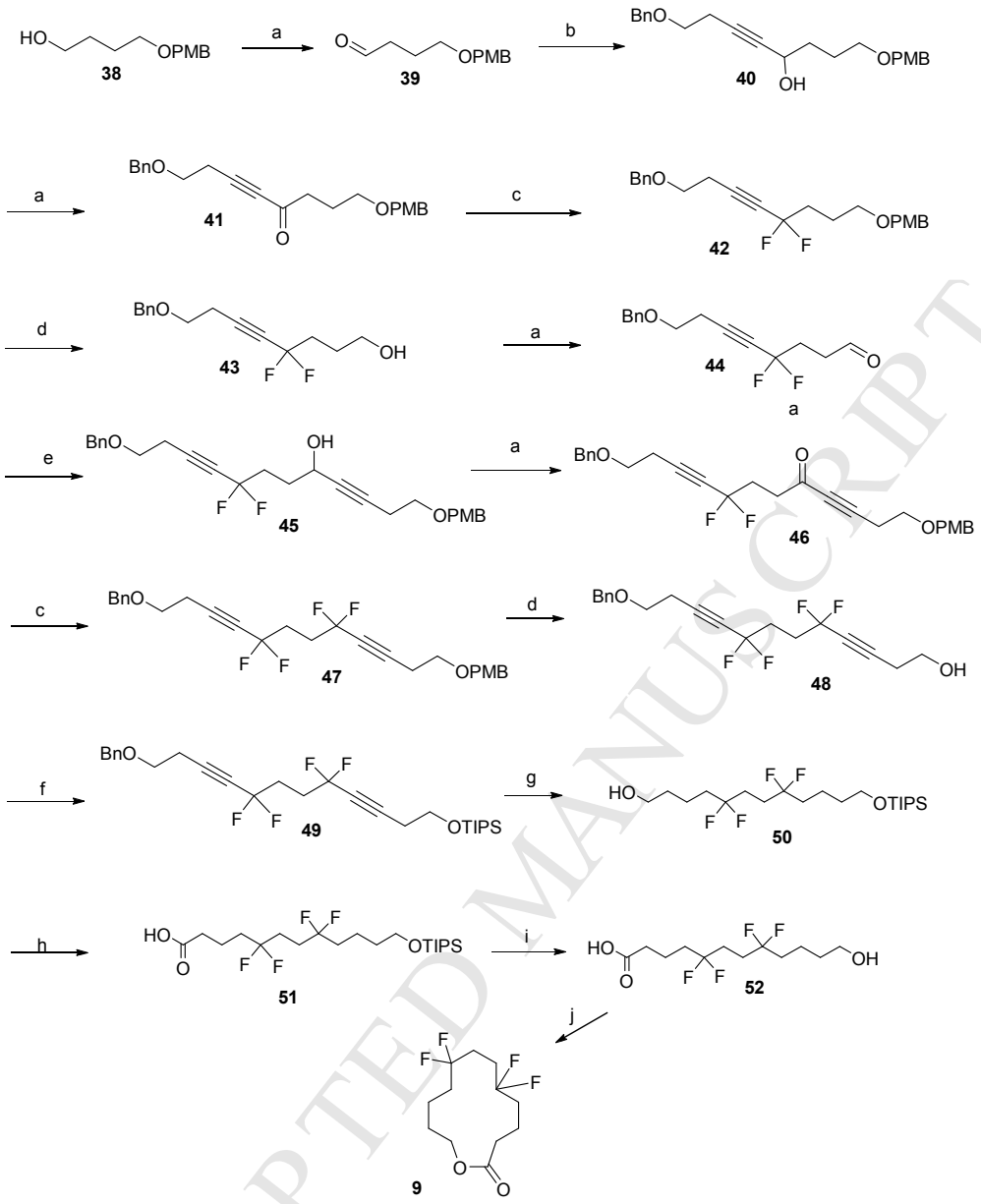
Scheme 1. Preparation of 6,6-difluorododecanolactone. *Reagents and conditions:* a) PCC, DCM, rt, 52%; b) $PMBO(CH_2)_3C{\equiv}CH$, BuLi, THF, -78°C to rt, 87%; c) IBX, DMSO, rt, overnight, 80%; d) DAST, 50°C, 42%; e) DDQ, wet DCM, rt, 23%; f) $PhI(OAc)_2$, TEMPO, CH_3CN/H_2O, 44%; g) H_2, 10% Pd/C, THF, 100%; h) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene, rt, 44%.



Scheme 2. Preparation of 7,7- , 8,8- and 5,5-difluorododecanolactone **7**, **8**, **5**. *Reagents and conditions:* a) IBX, DMSO, rt, 64% for **20**, 83% for **21**, 92% for **24**, 78% for **25**; b) $BnO(CH_2)_3C{\equiv}CH$ or $BnO(CH_2)_2C{\equiv}CH$, BuLi, THF, -78°C to rt, 60% for **22**, 70% for **23**; c) DAST, 50°C, 55% for **26** and **27**; d) CAN, CH_3CN, H_2O, rt, 82%

for **28**, 81% for **29**; e) $PhI(OAc)_2$, TEMPO, CH_3CN/H_2O, 80% for both **30** and **31,** 90% for **36**; f) H_2, 5% Pd/C, THF, 71% for **32** and 57% for **33**; g) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene, rt, 52% for **7**, 63% for **8**, 32% for **5**; h) triisopropylsilyl chloride, imidazole, DCM, rt, 90%; i) H_2, 10% Pd/C, THF, 76%; j) TBAF, THF, 50°C, 79%.

The preparation of 5,5,8,8-tetrafluorolactone **9** proved to be the most demanding synthesis certainly in terms of the length of the linear sequence and the route is illustrated in Scheme 3. The difluoromethylene groups were introduced also by DAST reaction of a propargyl ketone [18] in a sequential manner to generate the orthogonally protected diacetylene **47**, with both difluoromethylene groups installed. The *p*-methoxybenzyl group (PMB) was removed and replaced by TIPS and then a key hydrogenation step, using palladium on carbon cleaved the terminal benzyl ether with concomitant saturation of both acetylene bonds, to generate aliphatic alcohol **50**. An oxidation to carboxylic acid **51**, ω-deprotection to alcohol **52** and then cyclisation gave the desired macrolide **9**.



Scheme 3. Preparation of 5,5,8,8-tetrafluorododecanolactone **9**. *Reagents and conditions:* a) IBX, DMSO, rt, 75% for **39**, 78% for **41**, 72% for **44,** 60% for **46**; b) $BnO(CH_2)_2C{\equiv}CH$, BuLi, THF, -78°C to rt, 83%; c) DAST, 50°C, 43% for **42**, 75% for **47**; d) CAN, CH_3CN, H_2O, rt, 96% for **43**, 77% for **48**; e) $PMBO(CH_2)_2C{\equiv}CH$, BuLi, THF, -78°C to rt, 49%; f) triisopropylsilyl chloride, imidazole, DCM, rt, 97%; g) H_2, 10% Pd/C, THF, 2h, 47%; h) $PhI(OAc)_2$, TEMPO, CH_3CN/H_2O, 64%; i) HF-pyridine, THF, 50%; j) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene, rt, 50%.

X-Ray structure analysis: Of the five compounds prepared in this study, **6** and **7** were colourless oils, **5** and **8** were semi-solids at room temperature and notably 12-dodecanolide **9**, with two CF_2 groups, was a crystalline solid. In the event the three lactones **5**, **8** and **9** proved amenable to X-ray analysis and the resultant structures are shown in Figure 1. It is clear from these structures that in all cases the CF_2 groups occupy corner locations, certainly

in the solid state, consistent with our previous conclusions on thermodynamically favoured location of the CF_2 groups in rings. Compounds **5** and **9** have a common $C(5)F_2$ group and they adopt almost identical solid state conformations.

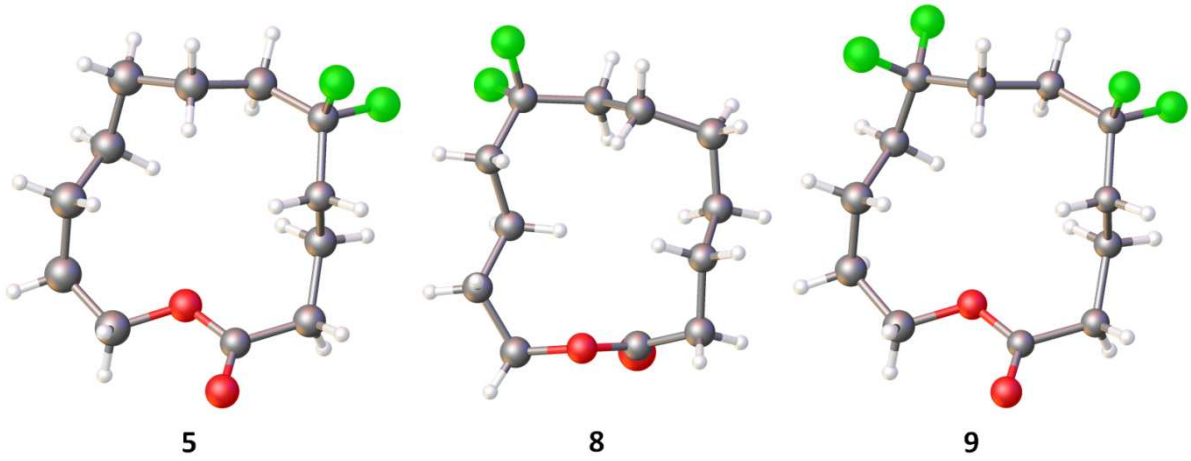


Fig. 1 Representations of the X-ray derived structure of 12-dodecanolides **5**, **8** and **9**. In all cases the CF_2 groups adopt corner locations in the solid state.

Bioactivity screening: Electroantennogram-detection (EAD) analyses [13] were conducted to determine if one or more of the 12-dodecanolides were detectable to adult female *A. planipennis* beetles. Ten adult insects (7-10 days old) were used in the study. All five 12-dodecanolides **5-9** as well as a hexane (Sigma Aldrich, 99%) control and the female pheromone, (*3*Z)-dodecen-12-olide **2** were used for each antenna. Concentrations of the 12-fluorine containing dodecanolides **5-9** and pheromone **2** were about 4mM (1mg/ml) with the stimulus source concentration for each compound at 3 µg. The order in which the compounds were applied to each antenna was randomly assorted for each antennal preparation.

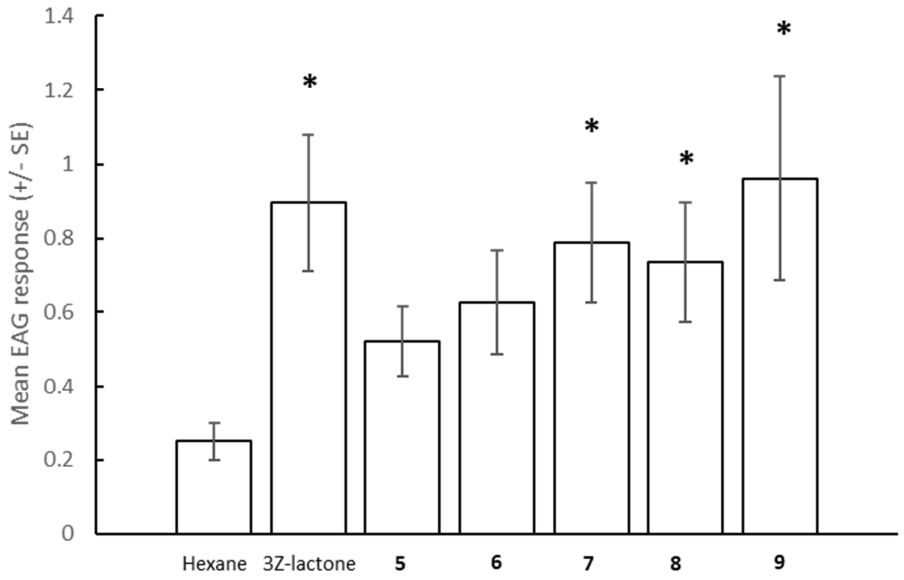


Fig 2. Electroantennogram-detection (EAD) analyses of 12-dodecanolides **5**-**9** of the antennae of female *A. planipennis* beetles against hexane and the pheromone, 3Z-lactone **2**.

After Log transformation of multiple measurements followed by a one-way ANOVA analysis, a post-hoc Tukey HSD test was then applied to compare pairs of compounds, to identify which pair-wise comparisons gave significantly different responses. This analysis demonstrated significant stimulatory differences for all of the fluorinated 12-decanolides relative to the hexane control, with the most significant responses being detected for decanolides **7**, **8** and **9**. Notably there was a significant difference between 12-decanolides **5** and **9** despite having similar solid state conformations, the latter having an additional CF_2 at C-8. This difference may indicate a poorer performance for the more conformationally flexible decanolide **5**.

3. Conclusion

In this study we have synthesised five 12-decanolides **5**-**9** each carrying CF_2 groups at different locations around the macrolide ring. These compounds are new analogues of the pheromones of the Emerald Ash Borer, a significant pest in North American and Canadian forests. Three of these compounds were amenable to X-ray structure analysis and reinforced the hypothesis that the CF_2 groups will adopt corner locations in aliphatic ring systems, placing limitations on the accessible conformational space in each case. In the event all of the compounds gave a positive EAD response with female EAB beetle antenna, with several showing similar levels of stimulatory activity to the natural pheromone, (*3*Z)-dodecen-12-

olide **2**. Thus the fluorines do not have a significantly negative effect and indeed the analogue **9** carrying four fluorines, with two conformationally biasing CF_2 groups, recorded a similar stimulatory response to pheromone **2**. This analogue might have been expected to suffer most detrimentally in the context of reduced volatility. The results provide some support to the developing hypothesis that correctly biasing conformation, in this case with CF_2 group, can improve pheromone efficacy.

4. Experimental Section

General procedure for the last step of the synthesis of 12-decanolides 5-9. Triethylamine (15.0 equiv.) and 2,4,6-trichlorobenzoyl chloride (10.0 equiv.) were added to a solution of 12-hydroxydodecanoic acid bearing CF_2 group(s) (**17**, **32**, **33**, **37**, **52**) (1.0 equiv., 2 mM) in dry THF at room temperature under an argon atmosphere. The reaction mixture was stirred for 2 h and then the mixture was diluted with dry toluene (half volume of THF) and added over 2 h using syringe pump to a solution of 4-DMAP (20 equiv., 70 mM) in dry toluene. The reaction mixture was stirred at room temperature for 12 h and then quenched with sat. aq. $NaHCO_3$ solution and diluted with DCM. The organic layer was separated and the aqueous was extracted into DCM. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 15:1) gave the lactones **5-9**.

X-ray diffraction data for **5**, **8** and **9** were collected at 173 K using a Rigaku MM-007HF High Brilliance RA generator/confocal optics with XtaLAB P100 diffractometer [Cu Kα radiation (λ = 1.54187 Å)]. Intensity data were collected using both ω and φ steps accumulating area detector images spanning at least a hemisphere of reciprocal space. Data for all compounds analysed were collected and processed (including correction for Lorentz, polarization and absorption) using CrystalClear [20]. Structures were solved by direct methods (SIR2011) [21] and refined by full-matrix least-squares against F2 (SHELXL-2016/4) [22]. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined using a riding model. All calculations were performed using the CrystalStructure [23] interface. CCDC 1891108-1891110 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

5,5-Difluorododecanolactone (5). Colourless wax (32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.38-1.97 (m, 16H, 8 × CH_2), 2.40-2.43 (m, 2H, CH_2CO), 4.17-4.19 (m, 2H, CH_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 19.1 (t, $^{3}J_{CF}$ = 5.7 Hz CH_2,), 20.8 (t, CH_2, $^{3}J_{CF}$ = 5.7 Hz), 24.6 (CH_2), 25.9 (CH_2), 26.5 (CH_2), 27.2 (CH_2), 33.3 (t, $^{2}J_{CF}$ = 25.2 Hz, CH_2), 34.2 (t, $^{2}J_{CF}$ = 25.7 Hz, CH_2), 65.5 (CH_2O), 125.9 (t, $^{1}J_{CF}$ = 246.9 Hz, CF_2), 172.8 (C=O); ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ_F -91.2 (s, CF_2), ^{19}F NMR (377 MHz, $CDCl_3$) δ_F -91.2 (p, J = 15.0 Hz, CF_2); HRMS (ESI$^+$) 257.1322 $[M+Na]^+$, $C_{12}H_{20}F_2O_2Na$ requires 257.1329.

X. Ray data; $C_{12}H_{20}F_2O_2$, M = 234.29, monoclinic, a = 12.188(3), b = 6.4319(10), c = 16.142(3) Å, β = 106.701(6) °, U = 1212.0(4) Å^3, T = 173 K, space group $P2_1/n$ (no. 14), Z = 4, 12204 reflections measured, 2185 unique (R_{int} = 0.0986), which were used in all calculations. The final R_1 [$I > 2\sigma(I)$] was 0.0550 and wR_2 (all data) was 0.1402.

6,6-Difluorododecanolactone (6). Colourless oil (44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.37-1.55 (m, 8H, 4 × CH_2), 1.66-1.77 (m, 4H, 2 × CH_2), 1.82-1.97 (m, 4H, 2 × CH_2CF_2), 2.38-2.41 (m, 2H, CH_2CO), 4.16-4.18 (m, 2H, CH_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 20.2 (t, $^{3}J_{CF}$ = 5.6 Hz, CH_2), 22.0 (t, $^{3}J_{CF}$ = 5.6 Hz, CH_2), 24.2 (CH_2), 24.5 (CH_2), 26.6 (CH_2), 27.1 (CH_2), 32.7 (t, $^{2}J_{CF}$ = 25.3 Hz, CH_2), 33.8 (CH_2), 34.3 (t, $^{2}J_{CF}$ = 25.7 Hz, CH_2), 64.9 (CH_2O), 126.4 (t, $^{1}J_{CF}$ = 239 Hz, CF_2), 173.6 (C=O); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ_F -90.5 (s, CF_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -90.5 (p, J = 15.2 Hz, CF_2); HRMS (ESI$^+$) 257.1322 $[M+Na]^+$, $C_{12}H_{20}F_2O_2Na$ requires 257.1324.

7,7-Difluorododecanolactone (7). Colourless oil (52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.42-1.59 (m, 8H, 4 × CH_2), 1.71-1.77 (m, 4H, 2 × CH_2), 1.84-1.97 (m, 4H, 2 × CH_2CF_2), 2.41-2.44 (m, 2H, CH_2CO), 4.20-4.22 (m, 2H, CH_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 21.3 (t, $^{3}J_{CF}$ = 5.6 Hz, CH_2), 21.8 (t, $^{3}J_{CF}$ = 5.6 Hz, CH_2), 23.6 (CH_2), 25.8 (CH_2), 26.6 (CH_2), 27.5 (CH_2), 33.1 (t, $^{2}J_{CF}$ = 25.3 Hz, CH_2), 34.1 (t, $^{2}J_{CF}$ = 25.7 Hz, CH_2), 34.3 (CH_2), 65.7 (CH_2O), 126.6 (t, $^{1}J_{CF}$ = 240.2 Hz, CF_2), 173.8 (C=O); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ_F -89.3 (s, CF_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -89.3 (p, J = 15.2 Hz, CF_2); HRMS (ESI$^+$) 215.1447 $[M-F]^+$, $C_{12}H_{20}FO_2$ requires 215.1447.

8,8-Difluorododecanolactone (8). Colourless gum (63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.39-1.56 (m, 8H, 4 × CH_2), 1.69-1.79 (m, 4H, 2 × CH_2), 1.82-1.98 (m, 4H, 2 × CH_2CF_2),

2.39-2.42 (m, 2H, CH_2CO), 4.19-4.22 (m, 2H, CH_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 19.2 (t, $^3J_{CF}$ = 5.7 Hz, CH_2), 20.3 (t, $^3J_{CF}$ = 5.5 Hz, CH_2), 24.2 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 27.1 (CH_2), 32.5 (t, $^2J_{CF}$ = 25.3 Hz, CH_2), 34.3 (t, $^2J_{CF}$ = 25.7 Hz, CH_2), 34.6 (CH_2), 63.0 (CH_2O), 126.4 (t, $^1J_{CF}$ = 240.2 Hz, CF_2), 173.8 (C=O); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ_F -90.8 (s, CF_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -90.8 (p, J = 15.2 Hz, CF_2); HRMS (ESI^+) 215.1439 $[M\text{-}F]^+$, $C_{12}H_{20}FO_2$ requires 215.1447.

X. Ray data; $C_{12}H_{20}F_2O_2$, M = 234.29, monoclinic, a = 11.2700(19), b = 8.3223(14), c = 12.952(2) Å, β = 96.450(4) °, U = 1207.1(3) Å^3, T = 173 K, space group $P2_1/n$ (no. 14), Z = 4, 11813 reflections measured, 2151 unique (R_{int} = 0.0730), which were used in all calculations. The final R_1 [$I > 2\sigma(I)$] was 0.0562 and wR_2 (all data) was 0.1918.

5,5,8,8-Tetrafluorododecanolactone (9). Colourless solid (50%). ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.49-1.57 (m, 2H, CH_2), 1.74-1.80 (m, 2H, CH_2), 1.84-1.87 (m, 2H, CH_2),1.90-2.11 (m, 8H, 4 × CH_2), 2.46 (t, 2H, $^3J_{CF}$ = 5.8 Hz, CH_2CO), 4.22 (t, 2H, $^3J_{CF}$ = 5.4 Hz, CH_2O); δ_C 19.3 (t, $^3J_{CF}$ = 6.2 Hz, CH_2), 19.7 (t, $^3J_{CF}$ = 5.5 Hz, CH_2), 27.3 (CH_2), 28.4 (tt, $^3J_{CF}$ = 5.5 Hz, $^2J_{CF}$ = 27.5 Hz, CH_2), 28.8 (tt, $^3J_{CF}$ = 5.8 Hz, $^2J_{CF}$ = 27.1 Hz, CH_2), 33.8 (t, $^2J_{CF}$ = 26.0 Hz, CH_2), 34.0 (CH_2), 33.99 (t, $^2J_{CF}$ = 25.6 Hz, CH_2), 64.1 (CH_2O), 125.0 (t, $^1J_{CF}$ = 241.2 Hz, CF_2), 125.1 (t, $^1J_{CF}$ = 241.2 Hz, CF_2), 172.2 (C=O); $\{^1H\}^{19}F$ (377 MHz, $CDCl_3$) –92.7 (br s), -92.5 (t, $^5J_{F,F}$ = 1.3 Hz); MS (ESI^+) 293.11398 $[M+Na]^+$, $C_{12}H_{18}F_4O_2Na$ requires 293.1141. M.pt 99-103^{o}C.

X. Ray data; $C_{12}H_{18}F_4O_2$, M = 270.27, monoclinic, a = 12.2019(12), b = 6.5194(6), c = 16.2763(15) Å, β = 107.805(2) °, U = 1232.7(2) Å^3, T = 173 K, space group $P2_1/n$ (no. 14), Z = 4, 12544 reflections measured, 2219 unique (R_{int} = 0.0542), which were used in all calculations. The final R_1 [$I > 2\sigma(I)$] was 0.0414 and wR_2 (all data) was 0.1103.

The experimental procedures for the synthesis and analysis of the intermediates/precursors can be obtained in the Supplementary Section (Appendix)

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Appendix Supplementary data

Supplementary data to this article can be found on line at ….

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