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不饱和螺环缩酮的合成及对桔小实蝇(*Bactrocera dorsalis*)性引诱活性与构效关系研究

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摘要 螺环缩酮结构片段广泛存在于许多具有不同来源的生物活性天然产物中, 该片段往往对生物活性起着重要作用. 合成了两类结构新颖的螺环缩酮类化合物, 并以甲基丁香酚为标准品对照, 测试其对桔小实蝇(*Bactrocera dorsalis*)的电生理活性. 结果表明: 雄性和雌性桔蝇对大部分化合物小实有明显的电生理响应. 螺环缩酮的立体化学和其苯环上取代基对电生理响应有一定的影响.

关键词 螺环缩酮; 性引诱剂; 桔小实蝇; 触角电位反应

Synthesis, Biological Evaluation, and Structure-Activity Relationship Study of Unsaturated Spiroacetals as Potential Sex Attractants to Oriental Fruit Flies (*Bactrocera dorsalis*)

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Abstract Spiroacetal motif is widely distributed in many bioactive natural products of different origins and essentially contributes to various bioactivities. In this paper, two series of spiroacetals were synthesized and biologically evaluated as insect sex attractant towards oriental fruit flies (*Bactrocera dorsalis*) using methyleugenol as the standard. Biological evaluation demonstrated that a large part of the tested compounds triggered apparent electrophysiological responses from both male and female fruit flies. The stereochemistry of the spiroacetals and the substitution on their phenyl rings influenced the responses to some degree.

Keywords spiroacetals; sex attractant; oriental fruit fly (*Bactrocera dorsalis*); electroantennogram response

1 Introduction

The oriental fruit fly, *Bactrocera dorsalis* (Hendel) (Diptera: Tephritidae), is a notorious pest of agricultural crops across East Asia, India and the Pacific.[1] It attacks a broad range of tropical, subtropical, and temperate species of suitable host plants including many types of commercial fruits, such as carambola, peach, citrus, mandarin and mango, as well as a wide variety of other agricultural products such as coffee, chilli pepper, and wild hosts.[2] Its infestation can cause severe crop losses if not well controlled.

Present approaches to suppress the oriental fruit fly populations depend mainly on broad-spectrum pesticide sprays.[3] However, this fly has been found to evolve apparent resistance and cross-resistance to many insecticides.[4] For example, flies in southern China have developed resistance to organophosphate-, pyrethroid- and antibiotic-based pesticides.[5] Pheromone traps along with annihilation are found to be effective to control this pest. Methyleugenol (ME) is an extremely potent and specific

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attractant for the oriental fruit fly, but only effective to male flies.[6]

Spiroacetals structures are widely distributed in numerous bioactive natural products of different origins including plants, fungi, and marine organisms. These natural products vary greatly in structural complexity and biological activity, acting as insect pheromones, antibacterial, antifungal, and anti-proliferative agents.[7] To date, more than 30 different structures with spiroacetal moiety represent volatile, less polar constituents of insect secretions. The spiroacetal moiety essentially contributes to the bioactivities as insect sex pheromones.[8] For example, chalcogran (2*S*,5*R*)-2-ethyl-1,6-dioxaspiro[4.4]nonane (**1**) is a key component of male produced aggregation pheromones of the spruce bark beetle, *Pityogenes chalcographus*.[9] Racemic olean (1,7-dioxaspiro[5.5]undecane) (**2**) is a female produced sex pheromone of the olive fly, *Bactrocera* (*Dacus*) *oleae*.[10] (2*S*,6*R*,8*S*)-2,8-Dimethyl-1,7-dioxaspiro[5.5]undecane (**3**) serves as an aggregation pheromone of solitary bee, *Andrena wilkella*.[11] Three spiroacetals, (*E*,*E*)-2,8-dimethyl-l,7-dioxaspiro-[5.5]undecane, (*E*,*E*)-2-ethyl-8-methyl-l,7-dioxaspiro-[5.5]undecane and 2-*n*-propyl-8-methyl-1,7-dioxaspiro-[5.5]undecane, have been identified from the volatile secretions of sexually mature female *B. dorsalis*.[12] In this paper, we would like to report the synthesis, biological evaluation, and structure-activity relationship study of an unprecedented unsaturated spiroacetal **4** and **5** as potential sex attractant with similar function to sex pheromones of *B. dorsalis*.

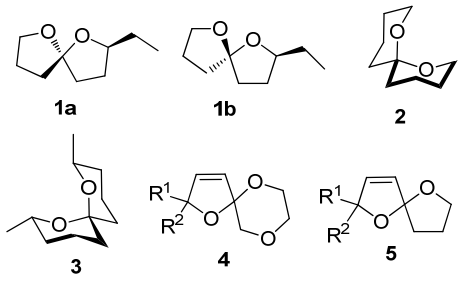


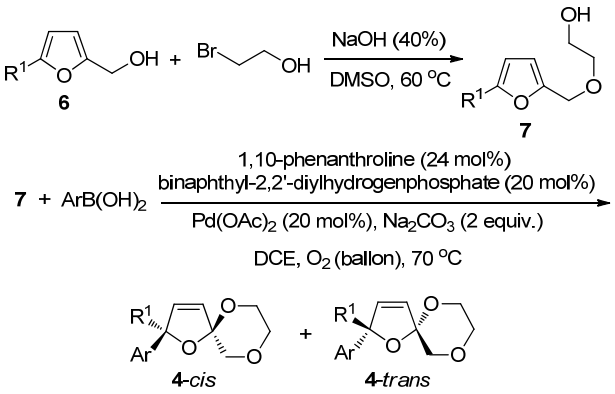
Figure 1 Spiroacetals as insect pheromones **1**～**3** and proposed unsaturated spiroacetals **4** and **5**

2 Results and discussion

2.1 Synthesis

The synthetic route to the unsaturated **4** was outlined in Table 1. A series of novel unsaturated [5.6]spiroacetals **4** was synthesized in 20%～49% isolated yields by Pd-catalyzed coupling of boronic acids with biomass-derived *α*-hydroxyalkylfurans using O_2 as the terminal oxidant. The two diasteroisomers of **4** are separable by silica flash chromatography. The ratios of **4**-*trans*/**4**-*cis* range from 1∶1 to 2.1∶1. The chemical structures of the target compounds were confirmed by ^{1}H NMR and ^{13}C NMR, HRMS and NOESY experiments. Spiroacetals **5** were synthesized according to reference.[13]

Table 1 Synthesis of unsaturated spiroacetals **4**[a]



R^1	Ar	**4**	Yield[b]%	*trans*/*cis*[c]
Me	Ph	**4a**	(44)	1.3∶1
Me	4-MeC_6H_4	**4b**	(45)	1∶1
Me	4-MeOC_6H_4	**4c**	(49)	1.5∶1
Me	3-MeC_6H_4	**4d**	(45)	1.1∶1
Me	3-MeOC_6H_4	**4e**	(39)	1∶1
Me	3,5-$Me_2C_6H_3$	**4f**	(36)	1.3∶1
Et	Ph	**4g**	(37)	2.1∶1
Me	4-FC_6H_4	**4h**	(37)	1∶1
Me	3-FC_6H_4	**4i**	(51)	1.1∶1
Me	4-ClC_6H_4	**4j**	(35)	1.2∶1
Me	4-BrC_6H_4	**4k**	(44)	1∶1
Me	4-OHCC_6H_4	**4l**	(27)	1.1∶1
Me	3-Me-4-FC_6H_3	**4m**	(45)	1.3∶1
Me	4-FC_6H_4	**4n**	(37)	1∶1

[a] The *cis* isomer is the isomer in which the phenyl group is on the same side of dihydrofuran ring as the oxygen group. [b] Isolated yields. [c] *trans*/*cis* ratios were determined by ^{1}H NMR spectroscopy of the crude products.

2.2 Electroantennogram (EAG) response

A series of diastereoisomeric [5,6]spiroacetals **4**-*cis* and **4**-*trans* were tested for the antennal activity of male and female *Bactrocera dorsalis* (Table 2), respectively. Quite a few compounds elicited moderate responses in male and female flies compared with ME as the standard. Antennal responses to spiroacetals varied between 0.05 and 0.67 mV for male fly and between 0.06 and 1.05 mV for female fly at a dose of 100 μg. In general, female flies showed slightly greater sensitivity than male flies to the same compound. Among the tested spiroacetals, compound **4d**-*trans* elicited the greatest responses. The stereochemistry and the substituent(s) on the phenyl ring of the spiroacetals influenced electrophysiological responses to a certain extent. In general, *trans*-isomers elicited greater responses than the corresponding *cis* isomers although the difference might not be statistically significant. The spiroacetals (*cis*- and *trans*-isomers) in which the phenyl ring was unsubstituted (**4a**-*cis*, **4g**-*cis*), or substituted with 4-formyl (**4l**-*cis*), 3-Me-4-F (**4m**-*cis*) triggered slightly higher responses in both male and female flies. Furthermore, the responses to the *trans*-isomers with phenyl ring substituted with moderate electron-donating group of Me (**4b**-*trans* and **4d**-*trans*) were relatively high (＞0.30 mV). In contrast, the responses

Table 2 The EAG response of *B. dorsalis* flies to Compounds **4** and **8a** (* indicates significant difference in EAG response between male and female flies)

Compound	EAG/mV			Compound	EAG/mV		
	Male fly	Female fly	Significance		Male fly	Female fly	Significance
4a-*cis*	0.25±0.051	0.31±0.031		**4a**-*trans*	0.38±0.032	0.45±0.025	
4b-*cis*	0.44±0.038	0.28±0.027	*	**4b**-*trans*	0.19±0.052	0.11±0.042	
4c-*cis*	0.13±0.012	0.04±0.012	*	**4c**-*trans*	0.19±0.049	0.05±0.008	*
4d-*cis*	0.11±0.016	0.23±0.016	*	**4d**-*trans*	0.67±0.090	1.05±0.141	*
4e-*cis*	0.23±0.036	0.19±0.020		**4e**-*trans*	0.19±0.036	0.16±0.018	
4f-*cis*	0.13±0.033	0.19±0.019		**4f**-*trans*	0.17±0.036	0.18±0.038	
4g-*cis*	0.28±0.069	0.36±0.029		**4g**-*trans*	0.15±0.031	0.07±0.030	
4h-*cis*	0.09±0.030	0.08±0.030		**4h**-*trans*	0.16±0.040	0.10±0.028	
4i-*cis*	0.15±0.030	0.15±0.021		**4i**-*trans*	0.13±0.037	0.24±0.013	*
4j-*cis*	0.20±0.044	0.13±0.025		**4j**-*trans*	0.12±0.033	0.09±0.023	
4k-*cis*	0.08±0.028	0.03±0.017		**4k**-*trans*	0.04±0.016	0.06±0.026	
4l-*cis*	0.27±0.059	0.37±0.031		**4l**-*trans*	0.27±0.074	0.46±0.065	
4m-*cis*	0.27±0.018	0.28±0.033		**4m**-*trans*	0.24±0.029	0.17±0.027	
8a-*cis*	0.06±0.018	0.11±0.008	*				
ME	1.89±0.079						

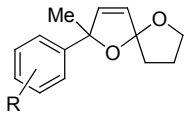
to spiroacetals with phenyl ring substituted with halide group of F (**4h**-*trans*, **4i**-*trans*), Cl (**4j**-*trans*) or Br (**4k**-*trans*) were relatively low (<0.30 mV). The *endo*-cyclic double bond plays an important role in triggering significant EAG response. Compound **8a**-*cis*, the hydrogenated product of **4a**-*cis*, elicited much lower EAG response than compound **4a**-*cis*. Among the 27 compounds tested, **4d**-*trans* elicited greatest responses from both male and female flies. Compounds **4d**-*cis*, **4d**-*trans*, **4i**-*trans*, **8a**-*cis* triggered significantly greater EAG response in female flies than that in male flies. In contrast, compounds **4b**-*cis*, **4c**-*cis*, **4c**-*trans* triggered significantly greater EAG response in male flies than that in female flies. These sexual differences at electrophysiological level suggest possibility to develop sex attractant from these compounds, such as compound **4d**-*trans*, for management of *B. dorsalis*.[14]

The synthesis of [5.5]-spiroacetals **5** was performed according to reference.[15] Due to the failure in separating two diasteroisomers by silica flash chromatography, compound **5** as a mixture of two diastereoisomers was tested for EAG response from both male and female *B. dorsalis* flies. As shown in Table 3, most of the tested compounds **5** elicited significant responses varied between 0.14 and 0.40 mV for male fly and between 0.21 and 0.75 mV for female fly at a dose of 100 μg. All compounds elicited much higher responses in female flies than that in male flies. The differences in EAG responses between female and male flies to **5a**, **5c**, **5d** were statistically significant. Furthermore, the differences to **5b**, **5j** and **5n** were marginally significant as their *P* values ranged 0.05～0.1, *i.e.*, 0.0901, 0.0575, 0.0548, respectively.

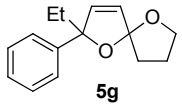
3 Conclusions

In summary, we reported the synthesis, biological evaluation, and structure-activity relationship study of unprecedented unsaturated spiroacetals as potential sex attractant for oriental fruit flies (*Bactrocera dorsalis*). A large part of the tested compounds demonstrated apparent responses from both male and female fruit flies. Convenient synthesis from sustainable furan derivative along with moderate to good biological-activities suggests the potential of unsaturated spiroacetal as a lead compound for further exploration of insect sexual attractants.

Table 3 The EAG response of **5** from both the male and female antennae of *Bactrocera dorsalis* (* indicates significant difference in EAG response between male and female flies)



5a: R = H
5b: R = 4-Me
5c: R = 4-MeO
5d: R = 3-Me
5e: R = 3-MeO
5f: R = 3,5-di-Me



5g

5i: R = 3-F
5j: R = 4-Cl
5m: R = 2-MeO
5n: R = 2,4-di-Me
5o: R = 3,5-di-MeO

Compound (*trans*∶*cis*)[a]	EAG/mV		
	Male fly	Female fly	Significance
5a (1.6∶1)	0.20±0.053	0.72±0.117	*
5b (1.5∶1)	0.45±0.115	0.96±0.154	
5c (1.4∶1)	0.61±0.121	1.13±0.104	*
5d (2.4∶1)	0.35±0.076	0.81±0.136	*
5e (1.4∶1)	0.31±0.053	0.70±0.138	
5f (1.8∶1)	0.21±0.065	0.32±0.063	
5g (1.5∶1)	0.49±0.130	0.46±0.082	
5i (1.3∶1)	0.50±0.122	0.35±0.077	
5j (1.9∶1)	0.23±0.106	0.73±0.133	
5m (1.4∶1)	0.29±0.144	0.47±0.101	
5n (3.3∶1)	0.28±0.061	0.72±0.115	
5o (1.2∶1)	0.32±0.138	0.61±0.090	
ME	1.89±0.079		

[a] Ratios in parentheses refer to *trans*/*cis* ratios determined by ^{1}H NMR spectroscopy of the crude products.

4 Experimental section

4.1 Chemicals and instruments

All reactions were performed under a nitrogen atmosphere. Unless specified otherwise, all reagents and starting materials were purchased from commercial suppliers and used as received. Solvents were purified by means of standard literature procedures. ^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra were recorded using $CDCl_3$ as a solvent, and product ratios were determined from ^{1}H NMR spectra. Analytical thin-layer chromatography was performed on silica gel with a mixture of petroleum ether and ethyl acetate as the eluent. High-resolution mass spectra (HRMS) were obtained with an LC/MS-IT-TOF mass spectrometer.

4.2 General procedure for the synthesis of intermediate 7

To a solution of furfuryl alcohol (12.5 mmol), NaOH (2.5 mL, 40%, 31.0 mmol) in dimethyl sulfoxide (DMSO, 30 mL) under nitrogen atmosphere was added slowly a solution of 2-bromoethanol (2.16 g, 18.8 mmol) in dimethyl sulfoxide (DMSO, 5 mL) at room temperature. After stirring for 2 h, H_2O (10 mL) was added to the reaction mixture. The resulting mixture was extracted with ethyl acetate (10 mL×3). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (using ethyl acetate/petroleum ether (V∶V=1∶2) as the eluent) to give **7**[15].

2-((5-Methylfuran-2-yl)methoxy)ethanol (**7a**): Slight yellow oil (1.5 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.18 (d, J=15.9 Hz, 1H, C=CH), 5.89 (d, J=15.3 Hz, 1H, C=CH), 4.43 (s, 2H, OCH_2), 3.71 (s, 2H, OCH_2), 3.58 (d, J=3.7 Hz, 2H, OCH_2), 2.53 (s, 1H, OH), 2.28 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.7, 149.7, 110.4, 106.2, 71.1, 65.1, 61.7, 13.5; IR (KBr film) v: 3366, 3061, 3029, 2937, 1692, 1649, 1447, 1428, 1366, 1254, 1159, 1057, 1014 cm^{-1}; HRMS (ESI) calcd for $C_8H_{12}NaO_3$ [M+Na]$^+$ 179.0786, found 179.0674.

2-((5-Ethylfuran-2-yl)methoxy)ethanol (**7b**): Slight yellow oil (1 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.21 (d, J=3.0 Hz, 1H, C=CH), 5.92 (d, J=2.8 Hz, 1H, C=CH), 4.49～4.40 (m, 2H, OCH_2), 3.71～3.72 (m, 2H, OCH_2), 3.60～3.56 (m, 2H, OCH_2), 2.63 (q, J=7.6 Hz, 2H, CH_2CH_3), 2.55 (s, 1H, OH), 1.22 (t, J=7.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.4, 149.5, 110.3, 104.6, 71.1, 65.1, 61.7, 21.4, 12.0; IR (KBr film) v: 3368, 3065, 3032, 2943, 1695, 1649, 1446, 1426, 1368, 1252, 1160, 1059, 1014 cm^{-1}; HRMS (ESI) calcd for $C_9H_{14}NaO_3$ [M+Na]$^+$ 193.0843, found 193.0832.

4.3 General synthetic procedures for 4

7 (0.6 mmol) was added to an 25-mL dried Schlenk tube charged with aryl boronic acids (1.5 mmol), $Pd(OAc)_2$ (0.3 mmol, 26.9 mg), 1,10-phenanthroline (0.375 mmol, 29.7 mg), Na_2CO_3 (1.2 mmol, 127.2 mg), 1,1'-binaphthyl-2,2'-diylhydrogenphosphate (0.12 mmol, 41.8 mg) and 1,2-dichloroethane (3.5 mL). The resulting solution was heated to 70 ℃ for 40 h under O_2 atmosphere (in balloon) until the disappearance of **7** detected by thin-layer chromatography (TLC). H_2O (5 mL) was added to quench the reaction. The resulting mixture was extracted with AcOEt (5 mL×3). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by neutral aluminium oxide chromatography (using ethyl acetate/petroleum ether (V/V=30/1) as the eluent) to afford **4**.

cis-2-Methyl-2-phenyl-1,6,9-trioxaspiro[4.5]dec-3-ene (**4a**-*cis*): Yellow oil (26.4 mg, 19%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42～7.38 (m, 2H, C_6H_5), 7.38～7.32 (m, 2H, C_6H_5), 7.29～7.25 (m, 1H, C_6H_5), 6.39 (d, J=5.8 Hz, 1H, CH=CH), 5.77 (d, J=5.8 Hz, 1H, CH=CH), 4.10～3.90 (m, 4H, OCH_2), 3.73～3.67 (m, 1H, OCH_2), 3.59～3.63 (m, 1H, OCH_2), 1.61 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.7, 136.9, 129.4, 128.5, 127.5, 125.0, 112.4, 93.3, 77.9, 74.3, 67.2, 27.4; HRMS (ESI) calcd for $C_{14}H_{17}O_3$ [M+H]$^+$ 233.1099, found 233.1168.

trans-2-Methyl-2-phenyl-1,6,9-trioxaspiro[4.5]dec-3-ene (**4a**-*trans*): Yellow oil (34.8 mg, 25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44～7.40 (m, 2H, C_6H_5), 7.36～7.31 (m, 2H, C_6H_5), 7.26～7.22 (m, 1H, C_6H_5), 6.37 (d, J=5.8 Hz, 1H, CH=CH), 5.77 (d, J=5.8 Hz, 1H, CH=CH), 4.36～4.27 (m, 1H, OCH_2), 3.82～3.70 (m, 5H, OCH_2), 1.77 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.5, 141.3, 128.4, 127.1, 124.8, 124.8, 107.6, 91.5, 71.8, 66.0, 62.3, 29.4; HRMS (ESI) calcd for $C_{14}H_{17}O_3$ [M+H]$^+$ 233.1099, found 233.1170.

cis-2-Methyl-2-(*p*-tolyl)-1,6,9-trioxaspiro[4.5]dec-3-ene (**4b**-*cis*): Yellow oil (32.5 mg, 22%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (d, J=8.1 Hz, 2H, C_6H_4), 7.17 (d, J=8.0 Hz, 2H, C_6H_4), 6.37 (d, J=5.8 Hz, 1H, CH=CH), 5.76 (d, J=5.8 Hz, 1H, CH=CH), 4.08～3.89 (m, 4H, OCH_2), 3.70 (dd, J=4.7, 4.5 Hz, 1H, OCH_2), 3.58～3.60 (m, 1H, OCH_2), 2.33 (s, 3H, $C_6H_4CH_3$), 1.60 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.8, 137.2, 137.0, 129.2, 125.0, 112.4, 93.2, 77.9, 74.3, 67.2, 27.4, 21.0; HRMS (ESI) calcd for $C_{15}H_{19}O_3$ [M+H]$^+$ 247.1256, found 247.1326.

trans-2-Methyl-2-(*p*-tolyl)-1,6,9-trioxaspiro[4.5]dec-3-ene (**4b**-*trans*): Yellow oil (33.9 mg, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (d, J=8.1 Hz, 2H, C_6H_4), 7.17 (d, J=8.1 Hz, 2H, C_6H_4), 6.38 (d, J=5.8 Hz, 1H, CH=CH), 5.79 (d, J=5.8 Hz, 1H, CH=CH), 4.37～4.29 (m, 1H, OCH_2), 3.84～3.72 (m, 5H, OCH_2), 2.35 (s, 3H, $C_6H_4CH_3$), 1.78 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.6, 141.4, 136.8, 129.0, 124.7, 124.6, 107.6, 91.4, 71.8, 66.0, 62.3, 29.4, 21.0; HRMS (ESI) calcd for $C_{15}H_{18}NaO_3$ [M+Na]$^+$ 269.1148, found 269.1148.

cis-2-(4-Methoxyphenyl)-2-methyl-1,6,9-trioxaspiro-[4.5]dec-3-ene (**4c**-*cis*): White solid (31.4 mg, 20%), m.p. 125 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36～7.31 (m, 2H, C_6H_4), 6.93～6.89 (m, 2H, C_6H_4), 6.39 (d, J=5.8 Hz, 1H, CH=CH), 5.78 (d, J=5.8 Hz, 1H, CH=CH), 4.09～3.92 (m, 4H, OCH_2), 3.82 (s, 3H, OCH_3), 3.75～3.69 (m, 1H, OCH_2), 3.61～3.63 (m, 1H, OCH_2), 1.62 (s, 3H, CH_3); ^{13}C

NMR (100 MHz, $CDCl_3$) δ: 159.0, 137.0, 132.9, 129.2, 126.2, 113.9, 112.4, 92.9, 77.9, 74.2, 67.2, 55.3, 27.4; HRMS (ESI) calcd for $C_{15}H_{19}O_4$ $[M+H]^+$ 263.1205, found 263.1275.

trans-2-(4-Methoxyphenyl)-2-methyl-1,6,9-trioxaspiro-[4.5]dec-3-ene (**4c**-*trans*): White solid (45.6 mg, 29%), m.p. 121 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.33 (d, J=8.6 Hz, 2H, C_6H_4), 6.86 (d, J=8.7 Hz, 2H, C_6H_4), 6.34 (d, J=5.8 Hz, 1H, CH=CH), 5.77 (d, J=5.8 Hz, 1H, CH=CH), 4.37～4.19 (m, 1H, OCH_2), 3.82～3.66 (m, 8H, OCH_2, OCH_3), 1.75 (s, 3H, CH_3); ^{13}C NMR (100MHz, $CDCl_3$) δ: 158.7, 141.5, 136.5, 126.1, 124.6, 113.7, 107.5, 91.2, 71.9, 66.0, 62.3, 55.3, 29.1; HRMS (ESI) calcd for $C_{15}H_{19}O_4$ $[M+H]^+$ 263.1205, found 263.1275.

cis-2-Methyl-2-(*m*-tolyl)-1,6,9-trioxaspiro[4.5]dec-3-ene (**4d**-*cis*): Yellow oil (31.0 mg, 21%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.25 (d, J=4.8 Hz, 1H, C_6H_4), 7.23～7.19 (m, 2H, C_6H_4), 7.09 (d, J=7.3 Hz, 1H, C_6H_4), 6.39 (d, J=5.8 Hz, 1H, CH=CH), 5.77 (d, J=5.8 Hz, 1H, CH=CH), 4.08～3.89 (m, 4H, OCH_2), 3.70 (dd, J=4.7, 4.6 Hz, 1H, OCH_2), 3.58～3.60 (m, 1H, OCH_2), 2.36 (s, 3H, $C_6H_4CH_3$), 1.61 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.7, 138.2, 136.9, 129.3, 128.4, 128.2, 125.7, 122.1, 112.4, 93.3, 78.0, 74.3, 67.2, 27.4, 21.6; HRMS (ESI) calcd for $C_{15}H_{19}O_3$ $[M+H]^+$247.1256, found 247.1327.

trans-2-Methyl-2-(*m*-tolyl)-1,6,9-trioxaspiro[4.5]dec-3-ene (**4d**-*trans*): Yellow oil (35.4 mg, 24%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.22 (d, J=4.6 Hz, 3H, C_6H_4), 7.08～7.02 (m, 1H, C_6H_4), 6.37 (d, J=5.8 Hz, 1H, CH=CH), 5.76 (d, J=5.8 Hz, 1H, CH=CH), 4.35～4.28 (m, 1H, OCH_2), 3.82～3.69 (m, 5H, OCH_2), 2.35 (s, 3H, $C_6H_4CH_3$), 1.75 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.4, 141.4, 138.0, 128.3, 127.9, 125.5, 124.7, 121.9, 107.6, 91.5, 71.8, 66.0, 62.3, 29.5, 21.6; HRMS (ESI) calcd for $C_{15}H_{19}O_3$ $[M+H]^+$ 247.1256, found 247.1331.

cis-2-(3-Methoxyphenyl)-2-methyl-1,6,9-trioxaspiro-[4.5]dec-3-ene (**4e**-*cis*): Yellow oil (29.9 mg, 19%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.27～7.29 (m, 1H, C_6H_4), 7.03 (s, 1H, C_6H_4), 6.96 (d, J=7.7 Hz, 1H, C_6H_4), 6.83～6.85 (m, 1H, C_6H_4), 6.39 (d, J=5.9 Hz, 1H, CH=CH), 5.79 (d, J=5.8 Hz, 1H, CH=CH), 4.13～3.91 (m, 4H, OCH_2), 3.83 (d, J=3.2 Hz, 3H, $C_6H_4OCH_3$), 3.73 (dd, J=4.7, 4.5 Hz, 1H, OCH_2), 3.61～3.63 (m, 1H, OCH_2), 1.64 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.8, 142.4, 136.8, 129.5, 129.4, 117.3, 112.7, 112.4, 111.1, 93.2, 77.9, 74.3, 67.2, 55.2, 27.4; HRMS (ESI) calcd for $C_{15}H_{19}O_4$ $[M+H]^+$ 263.1205, found 263.1277.

trans-2-(3-Methoxyphenyl)-2-methyl-1,6,9-trioxaspiro-[4.5]dec-3-ene (**4e**-*trans*): Yellow oil (31.4 mg, 20%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.28～7.24 (m, 1H, C_6H_4), 6.99 (dd, J=4.3, 2.2 Hz, 2H, C_6H_4), 6.78 (dd, J=8.0, 2.2 Hz, 1H, C_6H_4), 6.35 (d, J=5.8 Hz, 1H, CH=CH), 5.77 (d, J=5.8 Hz, 1H, CH=CH), 4.33～4.25 (m, 1H, OCH_2), 3.80 (s, 3H, $C_6H_4OCH_3$), 3.79～3.69 (m, 5H, OCH_2), 1.75 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.7, 146.2, 141.1, 129.4, 124.8, 117.2, 112.2, 111.0, 107.6, 91.4, 71.8, 65.9, 62.3, 55.2, 29.4; HRMS (ESI) calcd for $C_{15}H_{19}O_4$ $[M+H]^+$ 263.1205, found 263.1276.

cis-2-(3,5-Dimethylphenyl)-2-methyl-1,6,9-trioxaspiro-[4.5]dec-3-ene (**4f**-*cis*): Yellow oil (25.0 mg, 16%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.00 (s, 2H, C_6H_3), 6.92 (s, 1H, C_6H_3), 6.39 (d, J=5.8 Hz, 1H, CH=CH), 5.76 (d, J=5.8 Hz, 1H, CH=CH), 4.08～3.89 (m, 4H, OCH_2), 3.70 (dd, J=4.6, 4.4 Hz, 1H, OCH_2), 3.57～3.59 (m, 1H, OCH_2), 2.32 (s, 6H, $C_6H_3C_2H_6$), 1.61 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.7, 138.1, 137.0, 129.2, 122.8, 112.3, 93.3, 78.1, 74.3, 67.21, 27.4, 21.4; HRMS (ESI) calcd for $C_{16}H_{21}O_3$ $[M+H]^+$ 261.1412, found 261.1484.

trans-2-(3,5-Dimethylphenyl)-2-methyl-1,6,9-trioxaspiro[4.5]dec-3-ene (**4f**-*trans*): Yellow oil (31.2 mg, 20%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.02 (s, 2H, C_6H_3), 6.88 (s, 1H, C_6H_3), 6.36 (d, J=5.8 Hz, 1H, CH=CH), 5.74 (d, J=5.8 Hz, 1H, CH=CH), 4.36～4.27 (m, 1H, OCH_2), 3.82～3.69 (m, 5H, OCH_2), 2.31 (s, 6H, $C_6H_3C_2H_6$), 1.74 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.4, 141.5, 137.9, 128.8, 124.6, 122.5, 107.5, 91.5, 71.8, 66.0, 62.2, 29.5, 21.5; HRMS (ESI) calcd for $C_{16}H_{21}O_3$ $[M+H]^+$ 261.1412, found 261.1483.

cis-2-Ethyl-2-phenyl-1,6,9-trioxaspiro[4.5]dec-3-ene (**4g**-*cis*): Yellow oil (17.7 mg, 12%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.42 (d, J=7.5 Hz, 2H, C_6H_5), 7.35 (t, J=7.6 Hz, 2H, C_6H_5), 7.29～7.26 (m, 1H, C_6H_5), 6.50 (d, J=5.9 Hz, 1H, CH=CH), 5.77 (d, J=5.9 Hz, 1H, CH=CH), 4.09～3.90 (m, 4H, OCH_2), 3.72 (dd, J=4.6, 4.5 Hz, 1H, OCH_2), 3.60～3.61 (m, 1H, OCH_2), 1.90～1.81 (m, 2H, CH_3CH_2), 0.80 (t, J=7.5 Hz, 3H, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.7, 137.2, 128.5, 128.4, 127.4, 125.3, 115.2, 93.3, 78.4, 74.4, 67.1, 32.8, 8.5; HRMS (ESI) calcd for $C_{15}H_{19}O_3$ $[M+H]^+$ 247.1256, found 247.1325.

trans-2-Ethyl-2-phenyl-1,6,9-trioxaspiro[4.5]dec-3-ene (**4g**-*trans*): Yellow oil (36.9 mg, 25%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.41 (d, J=7.9 Hz, 2H, C_6H_5), 7.33 (t, J=7.6 Hz, 2H, C_6H_5), 7.23 (t, J=7.3 Hz, 1H, C_6H_5), 6.37 (d, J=5.8 Hz, 1H, CH=CH), 5.72 (d, J=5.8 Hz, 1H, CH=CH), 4.40～4.30 (m, 1H, OCH_2), 3.84～3.64 (m, 5H, OCH_2), 2.04～1.87 (m, 2H, CH_3CH_2), 0.88 (t, J=7.4 Hz, 3H, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.0, 139.8, 128.3, 126.8, 125.2, 125.0, 107.4, 94.8, 71.9, 66.0, 62.3, 35.0, 8.7; HRMS (ESI) calcd for $C_{15}H_{19}O_3$ $[M+H]^+$ 247.1256, found 247.1325.

cis-2-(4-Fluorophenyl)-2-methyl-1,6,9-trioxaspiro[4.5]-dec-3-ene (**4h**-*cis*): Yellow oil (27.0 mg, 18%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.39～7.34 (m, 2H, C_6H_4), 7.07～7.01 (m, 2H, C_6H_4), 6.36 (d, J=5.8 Hz, 1H, CH=CH), 5.79 (d, J=5.8 Hz, 1H, CH=CH), 4.07～3.88 (m, 4H, OCH_2), 3.70 (dd, J=4.7, 4.5 Hz, 1H, OCH_2), 3.57～3.59 (m, 1H, OCH_2), 1.60 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4, 160.9, 136.6, 129.6, 126.8, 126.7, 115.4, 115.2, 112.5, 92.9, 77.8, 74.3, 67.2, 27.4; HRMS (ESI) calcd for $C_{14}H_{16}FO_3$ $[M+H]^+$ 251.1005, found 251.1076.

trans-2-(4-Fluorophenyl)-2-methyl-1,6,9-trioxaspiro-[4.5]dec-3-ene (**4h**-*trans*): Yellow oil (28.5 mg, 19%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.43～7.37 (m, 2H, C_6H_4), 7.06～6.99 (m, 2H, C_6H_4), 6.36 (d, J=5.8 Hz, 1H, CH=

CH), 5.80 (d, J=5.8 Hz, 1H, CH=CH), 4.36～4.29 (m, 1H, OCH_2), 3.84～3.71 (m, 5H, OCH_2), 1.77 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.1, 160.7, 141.1, 140.3, 126.6, 126.6, 125.0, 115.2, 115.0, 107.6, 91.0, 71.8, 65.9, 62.2, 29.3; HRMS (ESI) calcd for $C_{14}H_{16}FO_3$ $[M+H]^+$ 251.1005, found 251.1075.

cis-2-(3-Fluorophenyl)-2-methyl-1,6,9-trioxaspiro[4.5]-dec-3-ene (**4i**-*cis*): Yellow oil (36.0 mg, 24%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.35～7.28 (m, 1H, C_6H_4), 7.18～7.11 (m, 2H, C_6H_4), 7.00～6.93 (m, 1H, C_6H_4), 6.35 (d, J=5.8 Hz, 1H, CH=CH), 5.79 (d, J=5.8 Hz, 1H, CH=CH), 4.07～3.88 (m, 4H, OCH_2), 3.71 (dd, J=4.7, 4.5 Hz, 1H, OCH_2), 3.58～3.59 (m, 1H, OCH_2), 1.61 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 161.7, 143.5, 143.4, 136.3, 130.0, 130.0, 129.8, 120.6, 120.6, 114.5, 114.2, 112.5, 112.5, 112.3, 92.9, 77.7, 74.3, 67.2, 27.4; HRMS (ESI) calcd for $C_{14}H_{16}FO_3$ $[M+H]^+$ 251.1005, found 251.1074.

trans-2-(3-Fluorophenyl)-2-methyl-1,6,9-trioxaspiro-[4.5]dec-3-ene (**4i**-*trans*): Yellow oil (40.5 mg, 27%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.34～7.27 (m, 1H, C_6H_4), 7.20～7.12 (m, 2H, C_6H_4), 6.96～6.90 (m, 1H, C_6H_4), 6.34 (d, J=5.8 Hz, 1H, CH=CH), 5.79 (d, J=5.8 Hz, 1H, CH=CH), 4.34～4.28 (m, 1H, OCH_2), 3.83～3.69 (m, 5H, OCH_2), 1.75 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.1, 161.7, 147.2, 147.2, 140.7, 129.9, 129.9, 125.3, 120.4, 120.4, 114.1, 113.8, 112.2, 112.0, 107.7, 91.0, 71.7, 65.9, 62.3, 29.3; HRMS (ESI) calcd for $C_{14}H_{16}FO_3$ $[M+H]^+$ 251.1005, found 251.1077.

cis-2-(4-Chlorophenyl)-2-methyl-1,6,9-trioxaspiro[4.5]-dec-3-ene (**4j**-*cis*): Yellow oil (25.6 mg, 16%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36～7.30 (m, 4H, C_6H_4), 6.35 (d, J=5.8 Hz, 1H, CH=CH), 5.79 (d, J=5.8 Hz, 1H, CH=CH), 4.06～3.88 (m, 4H, OCH_2), 3.70 (dd, J=4.7, 4.5 Hz, 1H, OCH_2), 3.56～3.58 (m, 1H, OCH_2), 1.59 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.3, 136.4, 133.4, 129.8, 128.6, 126.5, 112.5, 92.9, 77.7, 74.3, 67.2, 27.4; HRMS (ESI) calcd for $C_{14}H_{16}ClO_3$ $[M+H]^+$ 267.0710, found 267.0780.

trans-2-(4-Chlorophenyl)-2-methyl-1,6,9-trioxaspiro-[4.5]dec-3-ene (**4j**-*trans*): Yellow oil (30.3 mg, 19%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.35 (d, J=8.6 Hz, 2H, C_6H_4), 7.29 (d, J=8.7 Hz, 2H, C_6H_4), 6.33 (d, J=5.8 Hz, 1H, CH=CH), 5.77 (d, J=5.8 Hz, 1H, CH=CH), 4.34～4.26 (m, 1H, OCH_2), 3.82～3.68 (m, 5H, OCH_2), 1.74 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.1, 140.8, 132.9, 128.5, 126.3, 125.2, 107.7, 91.0, 71.7, 65.9, 62.3, 29.4; HRMS (ESI) calcd for $C_{14}H_{15}ClNaO_3$ $[M+Na]^+$ 289.0710, found 289.0602.

cis-2-(4-Bromophenyl)-2-methyl-1,6,9-trioxaspiro[4.5]-dec-3-ene (**4k**-*cis*): Yellow oil (40.9 mg, 22%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.51～7.46 (m, 2H, C_6H_4), 7.30～7.26 (m, 2H, C_6H_4), 6.34 (d, J=5.8 Hz, 1H, CH=CH), 5.79 (d, J=5.8 Hz, 1H, CH=CH), 4.06～3.88 (m, 4H, OCH_2), 3.70 (dd, J=4.7, 4.5 Hz, 1H, OCH_2), 3.55～3.57 (m, 1H, OCH_2), 1.59 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.8, 136.3, 131.6, 129.8, 126.9, 121.5, 112.5, 92.9, 77.7, 74.3, 67.2, 27.4; HRMS (ESI) calcd for $C_{14}H_{16}BrO_3$ $[M+H]^+$ 311.0205, found 311.0274.

trans-2-(4-Bromophenyl)-2-methyl-1,6,9-trioxaspiro-[4.5]dec-3-ene (**4k**-*trans*): Yellow oil (40.9 mg, 22%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.47 (d, J=8.6 Hz, 2H, C_6H_4), 7.32 (d, J=8.6 Hz, 2H, C_6H_4), 6.35 (d, J=5.8 Hz, 1H, CH=CH), 5.79 (d, J=5.8 Hz, 1H, CH=CH), 4.36～4.29 (m, 1H, OCH_2), 3.85～3.70 (m, 5H, OCH_2), 1.75 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.6, 140.7, 131.5, 126.7, 125.2, 121.1, 107.7, 91.0, 71.7, 65.9, 62.3, 29.4; HRMS (ESI) calcd for $C_{14}H_{16}BrO_3$ $[M+H]^+$ 311.0205, found 311.0273.

cis-2-Methyl-1,6,9-trioxaspiro[4.5]dec-3-en-2-yl)benz-aldehyde (**4l**-*cis*): Yellow oil (20.3 mg, 13%). ^1H NMR (400 MHz, $CDCl_3$) δ: 10.03 (s, 1H, CHO), 7.90 (d, J=8.3 Hz, 2H, C_6H_4), 7.61 (d, J=8.2 Hz, 2H, C_6H_4), 6.42 (d, J=5.8 Hz, 1H, CH=CH), 5.85 (d, J=5.8 Hz, 1H, CH=CH), 4.13～3.91 (m, 4H, OCH_2), 3.74 (dd, J=4.7, 4.4 Hz, 1H, OCH_2), 3.60～3.62 (m, 1H, OCH_2), 1.64 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.8, 147.4, 135.9, 135.7, 130.3, 130.0, 125.80, 112.6, 93.3, 77.6, 74.3, 67.2, 27.4; HRMS (ESI) calcd for $C_{15}H_{17}O_4$ $[M+H]^+$ 261.1049, found 261.1117.

trans-2-Methyl-1,6,9-trioxaspiro[4.5]dec-3-en-2-yl)-benzaldehyde (**4l**-*trans*): Yellow oil (21.8 mg, 14%). ^1H NMR (400 MHz, $CDCl_3$) δ: 10.04～9.95 (m, 1H, CHO), 7.86 (d, J=8.3 Hz, 2H, C_6H_4), 7.61 (d, J=8.3 Hz, 2H, C_6H_4), 6.39 (d, J=5.8 Hz, 1H, CH=CH), 5.80 (d, J=5.8 Hz, 1H, CH=CH), 4.37～4.29 (m, 1H, OCH_2), 3.85～3.70 (m, 5H, OCH_2), 1.78 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.9, 151.3, 140.2, 135.4, 130.0, 125.7, 125.4, 107.8, 91.28, 71.7, 66.0, 62.3, 29.6; HRMS (ESI) calcd for $C_{15}H_{17}O_4$ $[M+H]^+$ 261.1049, found 261.1118.

cis-2-(4-Fluoro-3-methylphenyl)-2-methyl-1,6,9-trioxaspiro[4.5]dec-3-ene (**4m**-*cis*): Yellow oil (31.8 mg, 20%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.23～7.14 (m, 2H, C_6H_3), 6.97 (t, J=8.9 Hz, 1H, C_6H_3), 6.36 (d, J=5.9 Hz, 1H, CH=CH), 5.78 (d, J=5.8 Hz, 1H, CH=CH), 4.06～3.88 (m, 4H, OCH_2), 3.70 (dd, J=4.7, 4.5 Hz, 1H, OCH_2), 3.55～3.58 (m, 1H, OCH_2), 2.28 (d, J=1.5 Hz, 3H, $C_6H_3CH_3$), 1.60 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.9, 159.4, 136.7, 136.3, 129.5, 128.2, 125.0, 124.8, 124.0, 115.0, 114.8, 112.4, 92.8, 77.9, 74.3, 67.2, 27.4, 14.7; HRMS (ESI) calcd for $C_{15}H_{18}FO_3$ $[M+H]^+$ 265.1162, found 265.1233.

trans-2-(4-Fluoro-3-methylphenyl)-2-methyl-1,6,9-trioxaspiro[4.5]dec-3-ene (**4m**-*trans*): Yellow oil (39.6 mg, 25%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.23～7.16 (m, 2H, C_6H_3), 6.94 (t, J=8.9 Hz, 1H, C_6H_3), 6.33 (d, J=5.8 Hz, 1H, CH=CH), 5.77 (d, J=5.8 Hz, 1H, CH=CH), 4.34～4.26 (m, 1H, OCH_2), 3.82～3.69 (m, 5H, OCH_2), 2.26 (d, J=1.3 Hz, 3H, $C_6H_3CH_3$), 1.74 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.7, 159.2, 141.2, 139.9, 130.9, 128.8, 128.1, 128.0, 124.9, 124.7, 124.5, 123.8, 114.8, 114.6, 107.6, 91.0, 71.8, 65.9, 62.2, 29.3, 14.7; HRMS (ESI) calcd for $C_{15}H_{18}FO_3$ $[M+H]^+$ 265.1162, found 265.1236.

4.4 Electroantennography (EAG) experiment

The EAG sensitivity of male and female flies was determined by conventional EAG methods.[16] Briefly, the reference glass electrode was connected to the neck of an isolated head of a fly, and the recording electrode was connected to the cut tip of the arista. The analogue signal was detected through a PRG-3 probe, amplified with a data acquisition controller IDAC-4, and analyzed with software EAG 2000 (all from Syntech, Kirchzarten, Germany). Each synthesized spiroacetal as well as the standard compound, ME, was diluted in hexane to give a 10 μg/μL solution. A 10 μL aliquot of each test compound impregnated to a piece of filter paper (40 mm×4 mm, Whatman no. 1) was delivered as 0.2 s puffs at a humidified flow rate of 1000 mL/min generated by an air stimulus controller CS-55 (Syntech, Kirchzarten, Germany). Hexane was used as the solvent control.

EAG recordings were obtained from eight antennal preparations for each test compound. For analyses, EAG response to the solvent control was deducted from the EAG amplitudes elicited by the test compounds. The corrected EAG data were analyzed using one-way analysis of variance (ANOVA) to establish significant differences among the test compounds. Means across all compounds were compared by the Tukey-Kramer honestly significant difference (HSD) comparison test ($P<0.05$).

Supporting Information Spectra copies of **7a**, **7b**, **4a**～**4m**, and HMQC, HMBS spectra for **4a**-*trans*. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

References

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