Table SA1: Compound **31** relative energies (kcal mol^{-1}) and populations (percentages) obtained from theoretical calculations at the B3LYP-D3/6-311+G** level.

Conformer	Δ*E*	Δ*H*	Δ*G*	%P(Δ*E*)	%P(Δ*H*)	%P(Δ*G*)
31-1	0.00	0.00	1.29	21.1	16.1	2.6
31-2	0.49	0.23	0.57	9.2	10.9	8.8
31-3	0.60	0.11	0.00	7.6	13.4	22.7
31-4	0.45	0.34	0.38	9.8	9.0	12.0
31-5	0.75	0.47	0.49	5.9	7.3	10.0
31-6	1.19	0.92	0.95	2.8	3.4	4.6
31-7	0.68	0.37	0.25	6.7	8.6	14.9
31-8	1.16	1.05	1.43	3.0	2.7	2.0
31-9	2.05	2.22	2.78	0.7	0.4	0.2
31-10	1.08	1.09	1.63	3.4	2.5	1.5
31-11	0.73	0.65	1.18	6.1	5.4	3.1
31-12	1.63	1.52	2.32	1.3	1.2	0.5
31-13	1.40	1.51	2.27	2.0	1.3	0.5
31-14	1.04	0.96	1.22	3.6	3.1	2.9
31-15	1.75	1.70	2.33	1.1	0.9	0.4
31-16	2.03	2.01	2.63	0.7	0.5	0.3
31-17	2.63	2.50	1.87	0.2	0.2	1.0
31-18	3.01	3.26	4.69	0.1	0.1	0.0
31-19	1.39	1.12	1.08	2.0	2.4	3.7
31-20	1.24	1.16	1.68	2.6	2.3	1.3
31-21	1.39	1.44	2.20	2.0	1.4	0.6
31-22	1.64	1.68	2.58	1.3	0.9	0.3
31-23	1.97	2.16	2.74	0.8	0.4	0.2
31-24	1.41	1.33	1.90	2.0	1.7	0.9
31-25	1.62	1.39	1.27	1.4	1.5	2.7
31-26	2.79	2.93	4.08	0.2	0.1	0.0
31-27	2.12	2.00	1.95	0.6	0.5	0.8
31-28	1.96	1.77	1.92	0.8	0.8	0.9
31-29	2.18	2.12	2.85	0.5	0.4	0.2
31-30	2.38	2.31	2.17	0.4	0.3	0.6

Table SA2: Compound **30** relative energies (kcal mol^{-1}) and populations (percentages) obtained from theoretical calculations at the B3LYP-D3/6-311+G** level.

Conformer	Δ*E*	Δ*H*	Δ*G*	%P(Δ*E*)	%P(Δ*H*)	%P(Δ*G*)
30-1	2.02	2.19	2.03	0.6	0.6	0.7
30-2	1.22	1.55	1.95	2.4	1.7	0.8
30-3	0.06	0.09	0.41	17.0	20.2	11.3
30-4	2.26	2.65	2.46	0.4	0.3	0.4
30-5	0.00	0.00	0.00	18.8	23.4	22.4
30-6	0.70	1.09	1.30	5.8	3.7	2.5
30-7	1.21	1.78	2.71	2.4	1.2	0.2
30-8	2.34	2.69	2.90	0.4	0.3	0.2
30-9	0.83	0.96	0.97	4.7	4.6	4.4
30-10	1.22	1.43	1.57	2.4	2.1	1.6
30-11	0.50	0.65	0.53	8.2	7.8	9.1
30-12	1.44	1.75	2.05	1.7	1.2	0.7
30-13	1.29	1.30	1.00	2.1	2.6	4.1
30-14	0.87	1.24	1.63	4.3	2.9	1.4
30-15	0.94	0.85	0.19	3.8	5.6	16.2
30-16	1.71	2.00	2.05	1.0	0.8	0.7
30-17	0.83	0.96	0.97	4.7	4.6	4.4
30-18	1.76	1.98	1.64	1.0	0.8	1.4
30-19	0.94	1.12	1.51	3.8	3.5	1.7
30-20	0.85	1.00	0.80	4.5	4.4	5.8
30-21	1.56	1.83	1.78	1.4	1.1	1.1
30-22	2.64	2.94	2.86	0.2	0.2	0.2
30-23	1.73	1.90	1.21	1.0	0.9	2.9
30-24	1.23	1.63	2.22	2.4	1.5	0.5
30-25	2.45	2.70	2.38	0.3	0.2	0.4
30-26	1.23	1.53	1.62	2.4	1.8	1.4
30-27	1.62	1.96	1.75	1.2	0.9	1.2
30-28	2.11	2.14	1.54	0.5	0.6	1.7
30-29	2.44	2.65	2.47	0.3	0.3	0.3
30-30	2.34	2.62	2.58	0.4	0.3	0.3

Table SA3: Compound **29** relative energies (kcal mol^{-1}) and populations (percentages) obtained from theoretical calculations at the B3LYP-D3/6-311+G** level.

Conformer	Δ*E*	Δ*H*	Δ*G*	%P(Δ*E*)	%P(Δ*H*)	%P(Δ*G*)
29-1	0.42	1.84	1.43	5.9	1.2	1.7
29-2	0.00	0.64	0.41	12.0	9.1	9.8
29-3	0.23	1.48	1.13	8.1	2.2	2.9
29-4	0.36	0.24	0.15	6.5	18.0	15.2
29-5	0.21	0.45	0.25	8.5	12.6	12.8
29-6	0.38	1.88	1.43	6.3	1.1	1.7
29-7	0.34	1.72	1.28	6.8	1.5	2.2
29-8	0.69	1.71	1.36	3.7	1.5	2.0
29-9	0.76	0.95	0.73	3.3	5.4	5.7
29-10	1.03	2.32	1.99	2.1	0.5	0.7
29-11	0.57	1.36	1.01	4.6	2.7	3.5
29-12	2.46	4.21	3.58	0.2	0.0	0.0
29-13	0.66	0.00	0.00	4.0	26.9	19.5
29-14	0.72	1.64	1.26	3.6	1.7	2.3
29-15	0.78	1.04	0.76	3.2	4.6	5.4
63-16	0.75	2.10	1.64	3.4	0.8	1.2
29-17	1.10	2.36	2.03	1.9	0.5	0.6
29-18	1.43	2.03	1.63	1.1	0.9	1.2
29-19	0.83	1.30	1.00	3.0	3.0	3.6
29-20	0.60	1.98	1.61	4.4	1.0	1.3
29-21	1.30	2.07	1.66	1.3	0.8	1.2
29-22	1.04	3.34	2.89	2.1	0.1	0.1
29-23	1.74	3.37	2.83	0.6	0.1	0.2
29-24	1.73	3.98	3.54	0.7	0.0	0.0
29-25	2.85	2.49	1.91	0.1	0.4	0.8
29-26	1.63	1.86	1.63	0.8	1.2	1.2
29-27	1.79	4.68	4.23	0.6	0.0	0.0
29-28	3.76	2.55	2.12	0.0	0.4	0.5
29-29	1.79	2.05	1.70	0.6	0.8	1.1
29-30	1.73	1.91	1.58	0.6	1.1	1.4

Table SA4: Compound **28** relative energies (kcal mol^{-1}) and populations (percentages) obtained from theoretical calculations at the B3LYP-D3/6-311+G** level.

Conformer	Δ*E*	Δ*H*	Δ*G*	%P(Δ*E*)	%P(Δ*H*)	%P(Δ*G*)
28-1	0.71	0.94	1.78	5.0	0.9	3.5
28-2	0.00	0.00	0.38	16.7	9.7	17.0
28-3	1.62	1.69	0.25	1.1	1.9	1.0
28-4	1.84	1.92	2.05	0.7	0.6	0.7
28-5	1.93	2.11	2.18	0.6	0.5	0.5
28-6	2.59	2.92	3.89	0.2	0.0	0.1
28-7	1.03	1.11	1.93	2.9	0.7	2.6
28-8	1.59	1.85	2.80	1.1	0.2	0.7
28-9	0.14	0.01	0.00	13.2	18.6	16.7
2810	0.34	0.31	0.08	9.4	16.2	10.1
28-11	1.82	1.84	2.18	0.8	0.5	0.8
28-12	0.76	0.97	1.47	4.6	1.5	3.3
28-13	0.37	0.30	0.27	9.0	11.9	10.2
28-14	0.86	0.99	1.38	3.9	1.8	3.2
28-15	0.78	0.71	0.65	4.5	6.2	5.1
28-16	2.12	2.50	3.50	0.5	0.1	0.2
28-17	0.66	0.67	0.59	5.4	6.9	5.5
28-18	1.66	1.77	1.99	1.0	0.6	0.9
28-19	1.13	1.25	2.03	2.5	0.6	2.1
28-20	2.18	2.34	1.78	0.4	0.9	0.3
28-21	1.92	2.30	3.36	0.7	0.1	0.4
28-22	1.33	1.55	2.10	1.8	0.5	1.2
28-23	1.02	1.14	1.31	3.0	2.0	2.5
28-24	2.44	2.74	2.65	0.3	0.2	0.2
28-25	2.05	2.20	1.92	0.5	0.7	0.4
28-26	1.35	1.38	1.35	1.7	1.9	1.7
28-27	2.23	2.57	2.91	0.4	0.1	0.2
28-28	1.04	0.87	0.38	2.9	9.9	3.9
28-29	1.00	0.97	1.18	3.1	2.5	3.3
28-30	1.24	1.28	1.47	2.1	1.6	1.9

Table SA5: Compound (*E*)-**34** relative energies (kcal mol^{-1}) and populations (percentages) obtained from theoretical calculations at the B3LYP-D3/6-311+G** level.

Conformer	**Δ*E***	**Δ*H***	**Δ*G***	**%P(Δ*E*)**	**%P(Δ*H*)**	**%P(Δ*G*)**
(*E*)-**34-1**	0.38	0.82	1.06	8.9	5.5	3.1
(*E*)-**34-2**	0.25	0.50	0.74	11.1	9.6	5.3
(*E*)-**34-3**	1.58	1.79	2.08	1.2	1.1	0.6
(*E*)-**34-4**	1.17	1.47	1.87	2.4	1.8	0.8
(*E*)-**34-5**	1.56	1.73	1.67	1.2	1.2	1.1
(*E*)-**34-6**	0.08	0.18	0.38	14.9	16.5	9.7
(*E*)-**34-7**	0.70	0.96	0.96	5.2	4.4	3.7
(*E*)-**34-8**	0.00	0.00	0.00	17.0	22.2	18.5
(*E*)-**34-9**	0.45	0.58	0.23	7.9	8.3	12.5
(*E*)-**34-10**	1.84	2.25	2.60	0.8	0.5	0.2
(*E*)-**34-11**	2.29	2.41	2.00	0.4	0.4	0.6
(*E*)-**34-12**[a]	2.29	2.41	2.00	---	---	---
(*E*)-**34-13**	0.86	0.94	0.75	4.0	4.5	5.2
(*E*)-**34-14**	2.70	3.16	3.79	0.2	0.1	0.0
(*E*)-**34-15**	1.26	1.54	1.48	2.0	1.6	1.5
(*E*)-**34-16**	0.69	0.62	0.15	5.3	7.7	14.3
(*E*)-**34-17**	1.07	1.52	1.61	2.8	1.7	1.2
(*E*)-**34-18**[a]	1.07	1.52	1.61	---	---	---
(*E*)-**34-19**	3.09	3.41	3.25	0.1	0.1	0.1
(*E*)-**34-20**	2.67	2.88	2.50	0.2	0.2	0.3
(*E*)-**34-21**	2.44	2.65	2.24	0.3	0.3	0.4
(*E*)-**34-22**	0.88	1.12	0.63	3.8	3.3	6.4
(*E*)-**34-23**	3.06	3.26	2.32	0.1	0.1	0.4
(*E*)-**34-24**	2.31	2.59	2.78	0.3	0.3	0.2
(*E*)-**34-25**	0.95	1.12	0.59	3.4	3.3	6.9
(*E*)-**34-26**	1.95	2.21	2.01	0.6	0.5	0.6
(*E*)-**34-27**	2.02	2.21	1.89	0.6	0.5	0.8
(*E*)-**34-28**	1.23	1.55	1.30	2.1	1.6	2.1
(*E*)-**34-29**	1.02	1.32	0.98	3.0	2.4	3.5
(*E*)-**34-30**	2.31	2.61	2.75	0.3	0.3	0.2

[a]Conformers (*E*)-**34-12** and (*E*)-**34-18** interconvert to the most stable conformer geometries **(**(*E*)-**34-11** and (*E*)-**34-17**, respectively, and are not taken into account for conformer population values.

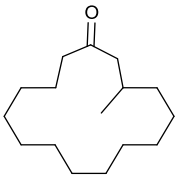
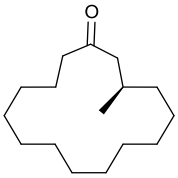
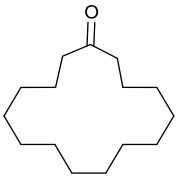
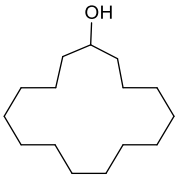
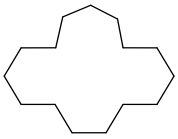
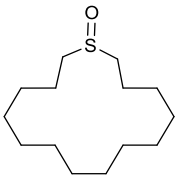
Table SA6: Compound (*Z*)-**34** relative energies (kcal mol^{-1}) and populations (percentages) obtained from theoretical calculations at the B3LYP-D3/6-311+G** level.

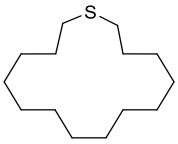
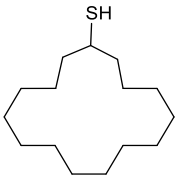
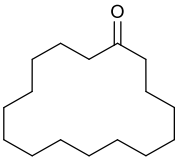
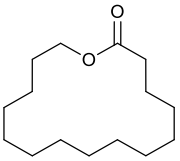
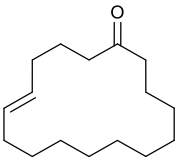
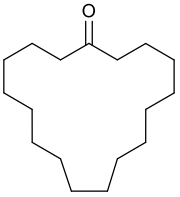
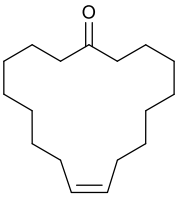
Conformer	**Δ*E***	**Δ*H***	**Δ*G***	**%P(Δ*E*)**	**%P(Δ*H*)**	**%P(Δ*G*)**
(*Z*)-**34-1**	0.00	0.00	0.00	15.7	21.0	51.8
(*Z*)-**34-2**	0.97	1.25	2.51	3.0	2.6	0.7
(*Z*)-**34-3**	1.05	1.37	2.52	2.6	2.1	0.7
(*Z*)-**34-4**	0.74	0.92	2.34	4.5	4.4	1.0
(*Z*)-**34-5**	1.37	1.58	2.49	1.6	1.5	0.8
(*Z*)-**34-6**	0.62	0.92	2.14	5.5	4.4	1.4
(*Z*)-**34-7**	0.27	0.23	0.87	9.9	14.2	11.9
(*Z*)-**34-8**	1.59	1.82	2.71	1.1	1.0	0.5
(*Z*)-**34-9**	0.43	0.65	1.34	7.5	7.0	5.4
(*Z*)-**34-10**[a]	0.43	0.65	1.34	---	---	---
(*Z*)-**34-11**	1.45	1.59	2.60	1.3	1.4	0.6
(*Z*)-**34-12**	1.26	1.55	2.76	1.9	1.5	0.5
(*Z*)-**34-13**	0.49	0.69	1.62	6.8	6.5	3.4
(*Z*)-**34-14**	0.31	0.64	1.91	9.3	7.1	2.1
(*Z*)-**34-15**	0.68	0.81	1.32	4.9	5.4	5.6
(*Z*)-**34-16**	2.39	2.75	3.97	0.3	0.2	0.1
(*Z*)-**34-17**	1.12	1.54	2.61	2.4	1.5	0.6
(*Z*)-**34-18**	0.63	0.85	1.45	5.4	5.0	4.4
(*Z*)-**34-19**	0.97	1.19	2.12	3.0	2.8	1.4
(*Z*)-**34-20**	1.68	1.93	2.63	0.9	0.8	0.6
(*Z*)-**34-21**	1.00	1.31	2.30	2.9	2.3	1.1
(*Z*)-**34-22**	1.37	1.87	2.58	1.5	0.9	0.7
(*Z*)-**34-23**	0.85	1.17	2.05	3.7	2.9	1.6
(*Z*)-**34-24**	3.43	3.79	4.83	0.0	0.0	0.0
(*Z*)-**34-25**	2.27	2.50	3.46	0.3	0.3	0.2
(*Z*)-**34-26**	1.60	1.69	1.88	1.0	1.2	2.1
(*Z*)-**34-27**	3.17	3.50	4.57	0.1	0.1	0.0
(*Z*)-**34-28**	1.69	2.02	3.33	0.9	0.7	0.2
(*Z*)-**34-29**	1.69	2.04	3.03	0.9	0.7	0.3
(*Z*)-**34-30**	1.75	2.13	3.37	0.8	0.6	0.2

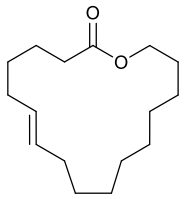
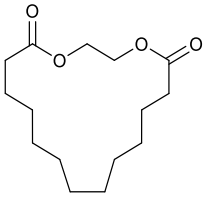
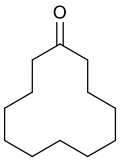
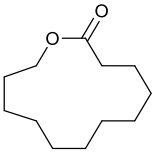
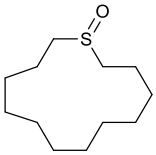
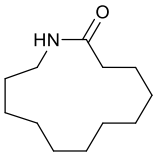
[a] Conformer (*Z*)-**34-10** interconverts to the most stable conformer geometry (*Z*)-**34-9** and is not taken into account for conformer population value

Table S1. (A) Macrocyclic, (B) nitro, and (C) polycyclic musk-smelling and analog compounds used.

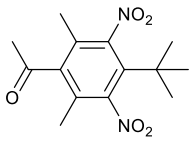
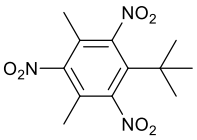
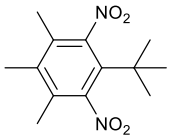
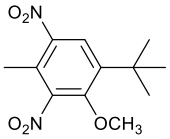
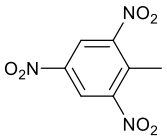
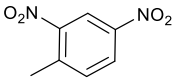
A

Ring	IUPAC name (common name)	Code	Structure	Source
15	3-Methylcyclopentadecan-1-one (Racemic muscone)	**1**		Santa Cruz
	(*R*)-3-Methylcyclopentadecan-1-one (*R*)-Muscone)	(*R*)-**1**		In-house synthesis
	Cyclopentadecanone (Exaltone)	**2**		Sigma-Aldrich
	Cyclopentadecanol	**3**		Sigma-Aldrich
	Cyclopentadecane	**4**		In-house synthesis
	Thiacyclopentadecane 1-oxide	**5**		In-house synthesis

	Thiacyclopentadecane	**6**		In-house synthesis
	Cyclopentadecanethiol	**7**		In-house synthesis
	Cyclohexadecanone (Isomuscone)	**8**		Sigma-Aldrich
16	Oxacyclohexadecan-2-one (ω-Pentadecalactone) (Exaltolide)	**9**		Sigma-Aldrich
	Cyclohexadec-5-en-1-one (Ambretone)	**10**		TCI
	Cycloheptadecanone (Dihydrocivetone)	**11**		In-house synthesis
17				
	Cycloheptadec-9-en-1-one (Civetone)	**12**		In-house synthesis

	1-Oxacycloheptadec-7-en-2-one (Ambrettolide)	**13**		Sigma-Aldrich
	1,4-Dioxacycloheptadecane-5,17-dione (Ethylene brassylate) (Astrotome)	**14**		Sigma-Aldrich
12	Cyclododecanone	**15**		Sigma-Aldrich
	Oxacyclotridecan-2-one	**16**		Sigma-Aldrich
13	Thiacyclotridecane-1-oxide	**17**		In-house synthesis
	Azacyclotridecan-2-one	**18**		Sigma-Aldrich

B

IUPAC name (common name)	Code	Structure	Source
1-(4-*tert*-Butyl-2,6-dimethyl-3,5-dinitrophenyl)ethanone (Musk ketone)	**19**		Sigma-Aldrich
1-*tert*-Butyl-3,5-dimethyl-2,4,6-trinitrobenzene (Musk xylene)	**20**		Chemsky
1-*tert*-Butyl-3,4,5-trimethyl-2,6-dinitrobenzene (Musk tibetene)	**21**		Sigma-Aldrich
1-*tert*-Butyl-2-methoxy-4-methyl-3,5-dinitrobenzene (Musk ambrette)	**22**		Sigma-Aldrich
2-Methyl-1,3,5-trinitrobenzene (Trinitrotoluene) (TNT)	**23**		J&K
1-Methyl-2,4-dinitrobenzene (2,4-Dinitrotoluene) (DNT)	**24**		Sigma-Aldrich

C

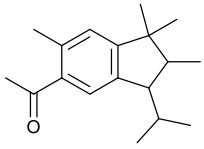
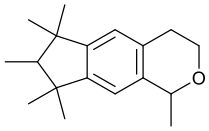
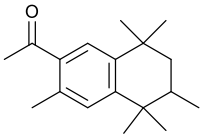
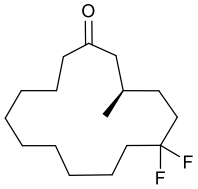
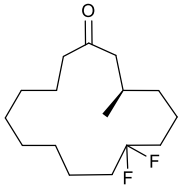
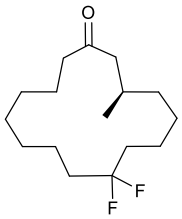
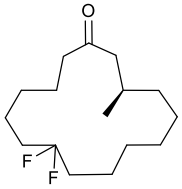
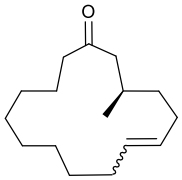
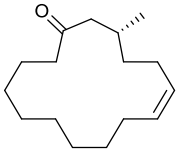
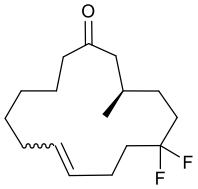
IUPAC name (common name)	Code	Structure	Source
1-(1,1,2,6-Tetramethyl-3-propan-2-yl-2,3-dihydroinden-5-yl)ethanone (Traseolide)	**25**		TRC
4,6,6,7,8,8-Hexamethyl-1,3,4,7-tetrahydrocyclopenta[g]isochromene (Galaxolide)	**26**		Sigma-Aldrich
1-(3,5,5,6,8,8-Hexamethyl-6,7-dihydronaphthalen-2-yl)ethanone (Tonalide)	**27**		Sigma-Aldrich

Table S2. EC_{50} and top values of the dosage-response curves in Figures 2 and S1. EC_{50} values are given in μM. The number after "/" indicates previously published data from Sato-Akuhara *et al*. The responses of OR5AN1 are normalized to the highest value of racemic muscone, and the responses of OR1A1 to musk ambrette. Grey boxes indicate little or no response where no meaningful EC_{50} or top values can be obtained.

Ring	Odorant	Code	OR5AN1		OR1A1	
			EC_{50}	top	EC_{50}	top
	Racemic muscone	**1**	14.21/12.5	1.22		
	Cyclopentadecanone	**2**	7.32	1.20		
	Cyclopentadecanol	**3**	9.05	0.32		
15	Cyclopentadecane	**4**				
	Thiacyclopentadecane 1-oxide	**5**	10.58	0.41		
	Thiacyclopentadecane	**6**				
	Cyclopentadecanethiol	**7**				
	Isomuscone	**8**	19.00	1.11		
16	ω-Pentadecalactone	**9**	4.78	0.32		
	Ambretone	**10**	9.15	1.21		
	Dihydrocivetone	**11**	5.23	0.50		
17	Civetone	**12**	3.43	0.41		
	Ambrettolide	**13**				
	Ethylene brassylate	**14**				
12	Cyclododecanone	**15**				
	Oxacyclotridecan-2-one	**16**				
13	Thiacyclotridecane 1-oxide	**17**				
	Azacyclotridecan-2-one	**18**				
	Musk ketone	**19**	0.02/0.8	1.34		
	Musk xylene	**20**	1.28/16.7	1.04	15.71	0.35
nitro	Musk tibetene	**21**	1.74	1.27	16.67	0.26
	Musk ambrette	**22**			7.69	1.21
	Trinitrotoluene	**23**				
	2,4-Dinitrotoluene	**24**				
	Traseolide	**25**				
poly	Galaxolide	**26**				
	Tonalide	**27**				

Table S3. Fluorinated muscone-related analogues used.

IUPAC name (common name)	Code	Structure	Source
(*R*)-6,6-Difluoro-3-methylcyclopentadecan-1-one ((*R*)-6,6-Difluoromuscone)	**28**		In-house synthesis
(*R*)-7,7-Difluoro-3-methylcyclopentadecan-1-one ((*R*)-7,7-Difluoromuscone)	**29**		In-house synthesis
(*R*)-8,8-Difluoro-3-methylcyclopentadecan-1-one ((*R*)-8,8-Difluoromuscone)	**30**		In-house synthesis
(*R*)-10,10-Difluoro-3-methylcyclopentadecan-1-one ((*R*)-10,10-Difluoromuscone)	**31**		In-house synthesis
(*R*)-3-Methylcyclopentadec-6-en-1-one E:Z = 10:1 ((*R*)-6,7-Dehydromuscone (E:Z = 10:1))	**32**		In-house synthesis
(*R,Z*)-3-Methylcyclopentadec-6-en-1-one ((*R,Z*)-6,7-Dehydromuscone)	(*Z*)-**32**		In-house synthesis
(*R*)-6,6-Difluoro-3-methylcyclopentadec-8-en-1-one *E*:*Z* = 3:2 (*R*)-9,10-Dehydro-6,6-difluoromuscone (*E*:*Z* 3:2)	**33**		In-house synthesis

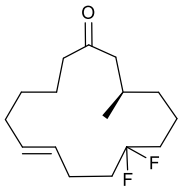
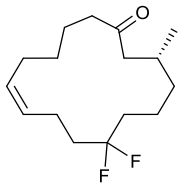
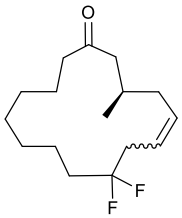
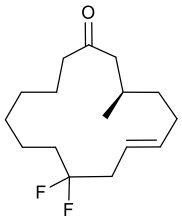
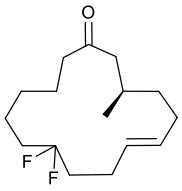
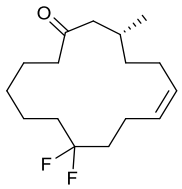
(*R*,*E*)-7,7-Difluoro-3-methylcyclopentadec-10-en-1-one ((*R*,*E*)-10,11-Dehydro-7,7-dilfuoromuscone)	(*E*)-**34**		In-house synthesis
(*R*,*Z*)-7,7-Difluoro-3-methylcyclopentadec-10-en-1-one ((*R*,*Z*)-10,11-Dehydro-7,7-difluoromuscone)	(*Z*)-**34**		In-house synthesis
(*R*)-8,8-Difluoro-3-methylcyclopentadec-5-en-1-one *E:Z* = 10:1 ((*R*)-5,6-Dehydro-8,8-difluoromuscone) (*E:Z* =10:1)	**35**		In-house synthesis
(*R*,*E*)-9,9-Difluoro-3-methylcyclopentadec-6-en-1-one ((*R*,*E*)-6,7-Dehydro-9,9-difluoromuscone)	(*E*)-**36**		In-house synthesis
(*R*,*E*)-10,10-Difluoro-3-methylcyclopentadec-6-en-1-one ((*R*,*E*)-6,7-Dehydro-10,10-difluoromuscone)	(*E*)-**37**		In-house synthesis
(*R*,*Z*)-10,10-Difluoro-3-methylcyclopentadec-6-en-1-one ((*R*,*Z*)-6,7-Dehydro-10,10-difluoromuscone)	(*Z*)-**37**		In-house synthesis

Table S4. EC_{50} and top values of the dosage-response curves in Figure 4. EC_{50} values are given in μM. The responses of OR5AN1 are normalized to the highest value of (*R*)-muscone.

Odorant		OR5AN1	
	Code	EC_{50}	Top
(*R*)-Muscone	(*R*)-**1**	19.94	1.09
(*R*)-6,6-Difluoromuscone	**28**	4.63	0.60
(*R*)-7,7-Difluoromuscone	**29**	12.56	0.73
(*R*)-8,8-Difluoromuscone	**30**	3.23	1.00
(*R*)-10,10-Difluoromuscone	**31**	11.20	0.28
(*R*)-6,7-Dehydromuscone (*E:Z* = 10:1)	**32**	15.47	0.84
((*R*,*Z*)-6,7-Dehydromuscone	(*Z*)-**32**	17.25	0.76
(*R*)-9,10-Dehydro-6,6-difluoromuscone (*E:Z* = 3:2)	**33**	10.75	0.46
(*R*,*E*)-10,11-Dehydro-7,7-dilfuoromuscone	(*E*)-**34**	0.03	1.26
(*R*,*Z*)-10,11-Dehydro-7,7-dilfuoromuscone	(*Z*)-**34**	3.77	1.40
(*R*)-5,6-Dehydro-8,8-difluoromuscone (*E:Z* = 10:1)	**35**	0.27	0.84
(*R, E*)-6,7-Dehydro-9,9-difluoromuscone	(*E*)-**36**	14.07	0.87
(*R, E*)-6,7-Dehydro-10,10-difluoromuscone	(*E*)-**37**	7.22	0.37
(*R, Z*)-6,7-Dehydro-10,10-difluoromuscone	(*Z*)-**37**	23.33	0.39

Table S5. Docking results for OR5AN1.

OR5AN1	Odorants	Code	Glide docking score	EC50 µM
	Musk ketone	**19**	-5.50	0.02
	Musk xylene	**20**	-5.75	1.28
	Musk tibetene	**21**	-5.89	1.74
	Civetone	**12**	-6.51	3.43
	ω-Pentadecalactone	**9**	-6.55	4.78
	Dihydrocivetone	**11**	-6.74	5.23
	Cyclopentadecanone	**2**	-6.37	7.32
	Cyclopentadecanol	**3**	-6.85	9.05
	Ambretone	**10**	-7.28	9.15
	Thiacyclopentadecane 1-oxide	**5**	-5.62	10.58
	(*R*)-Muscone	(*R*)-**1**	-6.80	19.94
	(*S*)-Muscone	(*S*)-**1**	-6.85	-
	Isomuscone	**8**	-6.24	19.0
	(*R*)-6,6-Difluoromuscone	**28**	-7.24	4.63
	(*R, E*)-9,10-Dehydro-6,6-difluoromuscone	(*E*)-**33**		10.75
	(*R*)-7,7-Difluoromuscone	**29**	-7.08	12.56
	(*R, Z*)-10,11-Dehydro-7,7-difluoromuscone	(*Z*)-**34**	-6.72	3.77
	(*R, E*)-10,11-Dehydro-7,7-difluoromuscone	(*E*)-**34**	-7.06	0.03
	(*S, E*)-10,11-Dehydro-7,7-difluoromuscone	-	-7.20	-
	(*R*)-8,8-Difluoromuscone	**30**	-7.42	3.23
	(*S*)-8,8-Difluoromuscone	**-**	-7.30	-
	(*R, Z*)-5,6-Dehydro-8,8-difluoromuscone	(*Z*)-**35**	-6.77	0.27
	(*R,E*)-6,7-Dehydro-9,9-difluoromuscone	(*E*)-**36**	-7.37	14.07
	(*R*)-10,10-Difluoromuscone	**31**	-7.09	11.20
	(*R, E*)-6,7-Dehydro-10,10-difluoromuscone	(*E*)-**37**	-7.41	7.22
	(*R, Z*)-6,7-Dehydro-10,10-difluoromuscone	(*Z*)-**37**	-6.89	23.33
	(*R, E*)-6,7-Dehydromuscone	(*E*)-**32**	-7.07	15.47
	(*R,Z*)-6,7-Dehydromuscone	(*Z*)-**32**	-7.02	17.25

Table S6. Predicted activities of the training and test set molecules.

Odorants	Code	QSAR Set
(*R*)-9,10-Dehydro-6,6-difluoromuscone	(*E*)-**33**	training
(*R*)-7,7-Difluoromuscone	**29**	training
(*R*,*Z*)-10,11-Dehydro-7,7-difluoromuscone	(*Z*)-**34**	training
Cyclopentadecanone	**2**	test
Thiacyclopentadecane 1-oxide	**5**	test
Civetone	**12**	test
Musk ketone	**19**	training
Musk xylene	**20**	training
Dihydrocivetone	**11**	training
ω-Pentadecalactone	**9**	training
Ambretone	**10**	training
(*R*)-8,8-Difluoromuscone	**30**	training
(*R*)-5,6-Dehydro-8,8-difluoromuscone	(*Z*)-**35**	training
(*R*)-6,7-Dehydro-9,9-difluoromuscone	**36**	training
(*R*,*E*)-10,11-Dehydro-7,7-difluoromuscone	(*E*)-**34**	training
(*R*)-10,10-Difluoromuscone	**31**	training
(*R*,*E*)-6,7-Dehydro-10,10-difluoromuscone	(*E*)-**37**	training
(*R*,*Z*)-6,7-Dehydro-10,10-difluoromuscone	(*Z*)-**37**	training
(*R*)-6,7-Dehydromuscone	(*E*)-**32**	test
(*R*,*Z*)-6,7-Dehydromuscone	(*Z*)-**32**	training
(*R*)-6,6-Difluoromuscone	**28**	training
Musk tibetene	**21**	test
Isomuscone	**8**	training
Cyclopentadecanol	**3**	training
(*R*)-Muscone	(*R*)-**1**	test

Table S7. ONIOM extrapolated energies for the optimized OR5AN1 model in complex with musk odorants.

OR5AN1	Odorants	Code	ONIOM Extrapolated energy (a.u.)
	Musk ketone	**19**	-1584.93977773
	Musk xylene	**20**	-1636.7829038
	Musk tibetene	**21**	-1471.60850711
	Civetone	**12**	-1296.27446906
	ω-Pentadecalactone	**9**	-1294.10033567
	Dihydrocivetone	**11**	-1297.50679115
	Cyclopentadecanone	**2**	-1218.79721278
	Cyclopentadecanol	**3**	-1220.03172238
	Ambretone	**10**	-1256.95243294
	Thiacyclopentadecane 1-oxide	**5**	-1578.91272652
	(*R*)-Muscone	(*R*)-**1**	-1258.16192466
	Isomuscone	**8**	-1258.16333633
	(*R*)-6,6-Difluoromuscone	**28**	-1456.65485542
	(*R*)-9,10-Dehydro-6,6-difluoromuscone	(*E*)-**33**	-1455.4266909
	(*R*)-7,7-Difluoromuscone	**29**	-1456.64419226
	(*R, Z*)-10,11-Dehydro-7,7-difluoromuscone	(*Z*)-**34**	-1455.44207584
	(*R, E*)-10,11-Dehydro-7,7-difluoromuscone	(*E*)-**34**	-1455.43586371
	(*R*)-8,8-Difluoromuscone	**30**	-1456.6500194
	(*R*)-5,6-Dehydro-8,8-difluoromuscone	(*Z*)-**35**	-1455.42865372
	(*R*)-6,7-Dehydro-9,9-difluoromuscone	(*E*)-**36**	-1455.41311478
	(*R*)-10,10-Difluoromuscone	**31**	-1456.65265928
	(*R, E*)-6,7-Dehydro-10,10-difluoromuscone	(*E*)-**37**	-1455.41329544

	(*R, Z*)-6,7-Dehydro-10,10-difluoromuscone	(*Z*)-**37**	-1455.41903509
	(*R*)-6,7-Dehydromuscone	(*E*)-**32**	-1256.96734884
	(*R,Z*)-6,7-Dehydromuscone	(*Z*)-**32**	-1256.94202006
OR1A1	Musk tibetene	**21**	-2026.14185747
	Musk xylene	**20**	-2191.28727834
	Musk ambrette	**22**	-2062.07382608