1,4-Dioxamacrolides: Preparation and Sensory Properties

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Abstract: The synthesis of 3-methyl-1,4-dioxacylopentadecan-2-one (**12c**) and 3-methyl-1,4-dioxacylohexadecan-2-one (**12d**), two new musk odorants, is described starting from methyl 2-bromopropionic acid (**6b**) and allylic alcohol, respectively. The key step of the synthesis is the ring-closing olefin metathesis (RCM) to the unsaturated 1,4-dioxamacrolides. Insight into the structure–odor relationship (SOR) is provided by the synthesis of ten related unsubstituted or methyl substituted oxamacrolides. Finally, a four step enantioselective synthesis of both (3*R*)-(+)- and (3*S*)-(–)-3-methyl-1,4-dioxacyclopentadecan-2-one as well as (3*R*)-(+)- and (3*S*)-(–)-3-methyl-1,4-dioxacyclohexadecan-2-one reveals that mainly the (3*R*)-(+) enantiomers are responsible for the powerful musky odor characteristic. Their synthesis starts from ethyl (2*S*)-2-hydroxypropanoate (**14**) or isobutyl (2*R*)-2-hydroxypropanoate (**15**) which were treated under acidic conditions with allyl trichloroacetimidate (**16**), followed by titanate mediated transesterification, ring-closing olefin metathesis and hydrogenation.

Key words: macrocycles, metathesis, lactones, ring closure, musk odorants, fragrance, structure–odor relationship

Due to low production cost, nitro-musks and polycyclic musks became the dominating musk fragrances in perfumery. However, the use of nitro-musks and polycyclic musks was subsequently reduced in recent years because of their poor biodegradability.[1] Hence, the synthesis of new biodegradable macrocyclic musk odorants has become an important topic of current research interest in the flavor and fragrance industry.[2] One of the most popular ingredient in perfume oils with musk odor is the macrocyclic lactone 15-pentadecanolide (cyclopentadecanolide®) (**1**). However, not only simple lactones can be of importance, other interesting materials can bear an additional heteroatom, e.g. an oxygen atom in the ring.

1,6-Dioxacycloheptadecan-7-one (**2**), 1,7-dioxacycloheptadecan-8-one (**3**) and 1,8-dioxacycloheptadecan-9-one (**4**) are strong smelling musk odorants and their odor tonality is comparable to that of cyclopentadecanolide® (**1**), but less intense (Figure 1).[3] The synthesis of 1,6-dioxacycloheptadecan-7-one (**2**) started from methyl 11-bromoundecanoate which was reacted with the monosodium salt of 1,4-butanediol. The resulting methyl 16-hydroxy-12-oxopalmitate was condensed to the corresponding polyester, which was subsequently depolymerized.[4] The 1,7-dioxa- (**3**)[5] and 1,8-dioxa - (**4**) isomers were obtained in the same way from the corresponding hydroxy-oxa acids.

Kraft et al.[2i,6] have described two strategies for the synthesis of 4-methyl-1,7-dioxacyclopentadecan-8-one (**5**), a powerful musk odorant, which possesses the floral aspects of some nitro-musks. Both strategies use the polymerization–depolymerization protocol to close the ring in the final step.

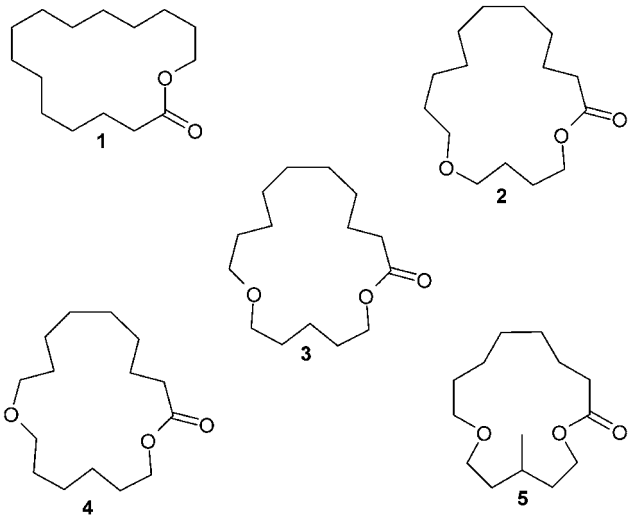

Figure 1 Cyclopentadecanolide® (**1**); 1,6-dioxacycloheptadecan-7-one (**2**); 1,7-dioxacycloheptadecan-8-one (**3**); 1,8-dioxacycloheptadecan-9-one (**4**); 4-methyl-1,7-dioxacyclopentadecan-8-one (**5**).

Here we report the first approach to the oxamacrolides **11** and **12** from α-bromo carboxylic acids **6** and 1,ω-alkenols **7** via 1,ω-dienes **10**. The key step in our short route is the macrocyclization reaction of 1,ω-dienes **10** by ring-closing olefin metathesis (RCM), which was catalyzed by the ruthenium carbene complex **13**.[7] Variation of the numbers of methylene groups in **7** and **9** offers the advantage to synthesize 15- to 17-membered rings.

The synthesis of 1,ω-dienes **10** started with a nucleophilic substitution of α-bromo carboxylic acids **6** and 1,ω-alkenols **7** to generate 2-alkenylcarboxylic acids **8** (Scheme 1).[8] This material **8** was transformed without any purification into the 1,ω-diene **10**, which was done by azeotropic esterification in the presence of 0.05 equiv *p*-TsOH. The yields over these two transformations vary between 61% and 69%. The 1,ω-dienes **10** failed to cyclize when treated with ruthenium carbene **13**, due to the formation of 5- or 6-membered intramolecular chelate struc-

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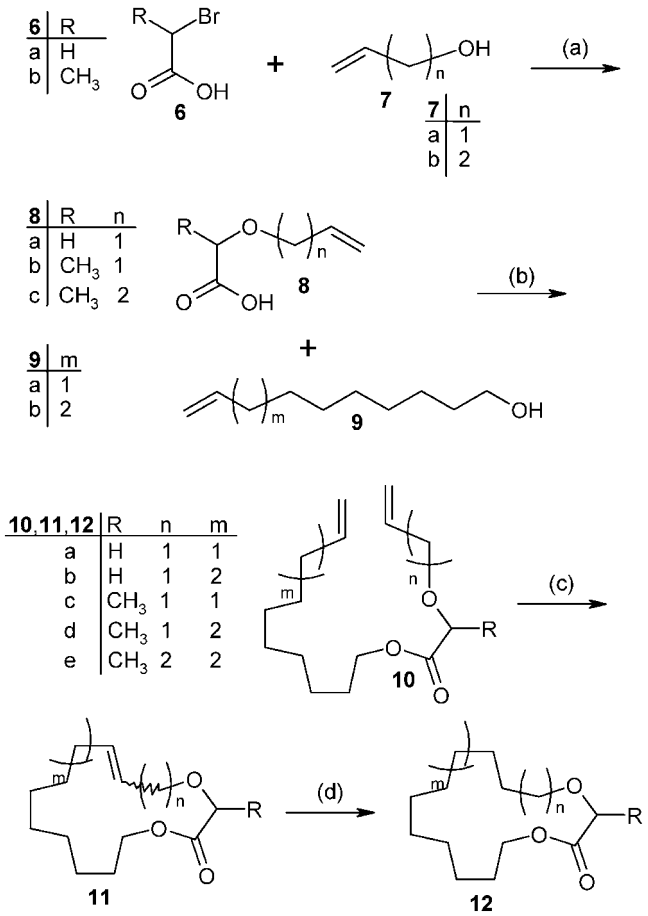
tures, which were formed from the polar ester group with the evolving carbene species. However, **10** reacted smoothly when exposed to catalytic amounts of **13** in the presence of catalytic amounts of Ti(*i*-PrO)$_4$.[9] Cycloalkenes **11** were obtained in excellent yield (90–95%) as mixtures of *E*- and *Z*-isomers, which were finally hydrogenated to the saturated 1,4-dioxamacrolides **12**.



Scheme 1 (a) NaH (2.0 equiv), THF, 66 °C; (b) *p*-TsOH (0.05 equiv), toluene, Dean–Stark, 6 h, 2 steps 61–69%; (c) $Cl_2(Cy_3P)_2Ru{=}CHPh$ (**13**, 3 mol%), Ti(*i*-PrO)$_4$ (0.3 equiv), CH_2Cl_2, 40 °C, 90–95%; (d) Pd/C (5 mol%), H_2, *i*-PrOH, 72–80%.

We noticed different sensory properties for **11** and the saturated counterparts **12**, as well as for the unsubstituted and methyl substituted molecules.

The macrocycles **12c**,**d** show an interesting odor profile, and they possess a stereogenic center (Table 1). Therefore it seemed to be of interest to investigate which enantiomers are responsible for the very pleasant odor of the racemates (±)-**12c**,**d**.

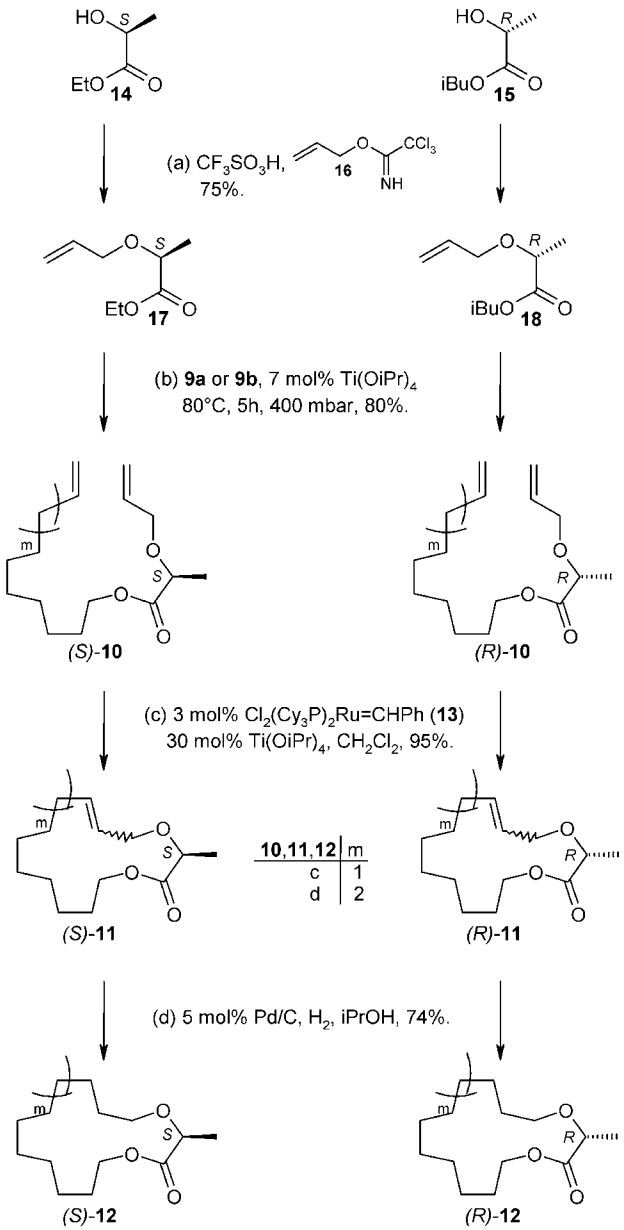
The synthesis of the enantiomerically pure macrocycles (*S*)- and (*R*)-**12c**, as well as (*S*)- and (*R*)-**12d** started from chiral ethyl (2*S*)-2-hydroxypropanoate (**14**) or isobutyl (2*R*)-2-hydroxypropanoate (**15**) which are suitable starting materials for the enantioselective approach (Scheme 2). The *O*-alkylation of these chiral building blocks under basic conditions[10] was not practical, because

Table 1 Sensory Properties of Musk 1,4-Dioxamacrolides.

Compound	Sensory properties of **11** and **12**	Musk intensity
11a	musky, metallic, reminiscent of *hot iron*	+
11b	musky, woody, technical, metallic, reminiscent of *hot iron*	+
11c	musky, sweet-floral, erogenous	++
11d	musky, woody, erogenous, animalic	++
11e	musky, sweet-floral, erogenous	++
12a	musky, floral, erogenous, metallic	++
12b	musky, woody, erogenous, technical	++(+)
12c	musky, sweet-floral, ambergris, erogenous, reminiscent of *musk ambrette*	+++
12d	musky, woody, ambergris, erogenous, animalic, reminiscent of *nitro-musk*	+++
12e	musky, sweet-woody, ambergris, erogenous, reminiscent of *musk ambrette*	++(+)

racemization can take place. In contrast, *O*-alkylation under acidic conditions with trichloroacetimidate was reported to give the ether in good yield and without racemization.[11] In order to preserve the chiral information, the etherification of ethyl (2*S*)-2-hydroxypropanoate (**14**) or isobutyl (2*R*)-2-hydroxypropanoate (**15**) was carried out with allyl trichloroacetimidate (**16**) and in the presence of catalytic amounts of trifluoromethanesulfonic acid. Using this procedure we obtained the (2*S*)- and (2*R*)-2-allyloxyesters **17** and **18** in 75% yield. Allyl trichloroacetimidate (**16**) was readily available from the corresponding allylic alcohol, trichloracetonitrile and a catalytic amount of sodium hydride. Thereafter, titanate mediated transesterification by means of 7 mol% Ti(*i*-PrO)$_4$ in 1,ω-alkenol **9a** or **9b**[12] provided dienes (*S*)- and (*R*)-**10c**, as well as (*S*)- and (*R*)-**10d** as suitable cyclization precursors. Under these conditions the (*S*)- and (*R*)- terminal dienes (**10**) were isolated in 80% yield and an enantiomeric excess ≥95%, which was measured by chiral GC (for detailed description see Experimental section). RCM was then effected in the presence of catalytic amounts of ruthenium carbene complex **13** as described before, to obtain the (*S*)- and (*R*)- unsaturated oxamacrolides **11** in excellent yields of 95%. Subsequent hydrogenation with Pd/C as catalyst in *i*-PrOH afforded the (*S*)- and (*R*)- oxamacrolides **12** in 75% yield and an enantiomeric excess ≥95%, which was also measured by chiral GC.

All (*R*)-enantiomers possess an intense and stronger musk odor than the corresponding (*S*)-antipodes, and in addition



Scheme 2 Synthesis of enantiomerically pure 3-methyl-1,4-dioxamacrolides.

the (*R*)-enantiomers shows ambergris nuances in combination with stronger erogenous undertones (Table 2). It can be concluded that mainly the (*R*)-enantiomers are responsible for the typical odor of the racemates. These result is in good agreement with the results of other groups;[13] e.g. Kraft et al.[2i,6] has examined the odor properties of (*R*)- and (*S*)-**5**, and it could be shown, that the (*R*)-(–)-enantiomer (*R*)-**5** was the odor vector of the racemate (±)-**5**; its enantiomer (*S*)-**5** was odorless on GC/olfactometry.

In summary, we have achieved a four-step synthesis to saturated oxamacrolides with a 1,4-dioxa substructure in racemic and enantiomerically pure form. The advantage of this approach is that the synthetic route is short and flexible enough to synthesize various analogs for the study of structure–odor relationships. Finally, it is worth mentioning that: (i) all synthesized 1,4-dioxamacrolides possess musky odor; (ii) a methyl substitution at the C3-position gives these molecules an unique ambergris note; and (iii) the (*R*)-enantiomers are responsible for the typical odor of the racemates.

Table 2 Sensory Properties of 3-Methyl-1,4-dioxamacrolide Enantiomers.

Compound	Sensory properties of **11** and **12**	Musk intensity
(*R*)-**11c**	musky, sweet-floral, ambergris, erogenous	++
(*S*)-**11c**	slightly musky, sweet-floral	+
(*R*)-**11d**	musky, woody, ambergris, erogenous, animalic	++
(*S*)-**11d**	slightly musky, woody, erogenous	+
(*R*)-**12c**	strong musky, sweet-floral, erogenous, animalic, ambergris	+++
(*S*)-**12c**	musky, sweet-floral, erogenous	++
(*R*)-**12d**	strong musky, woody, erogenous, animalic, ambergris	+++
(*S*)-**12d**	musky, woody, erogenous	++

Reagents and solvents were purchased from Sigma–Aldrich (Deisenhofen, Germany) or Acros Organics (Schwerte, Germany) and used without purification. FC: Biotage Flash 40 equipment with disposable pre-packed columns. NMR: Varian VXR400S or Gemini 2000 ($CDCl_3$, TMS). GC–MS: HP MSD 5972 A (EI: 70 eV) Polarimetry: Schmidt and Haensch Polartronic 1 ($CHCl_3$). Chiral GC: Carlo Erba 5300, 25 m × 0.25 mm DMTBS-β-cyclodextrin (Mega), 1.0 bar H_2, 100–102 °C/min–180 °C.

(±)-3-Methyl-1,4-dioxacyclopentadecan-2-one (12c)
(±)-2-(Allyloxy)propanoic Acid (8b)

In a 100 mL, 3-necked flask fitted with condenser, dropping funnel and thermometer were placed NaH (60% in mineral oil, 2.40 g, 60.0 mmol) and THF (40 mL). Under N_2, allyl alcohol (**7a**) (4.40 g, 75.0 mmol), dissolved in THF (10 mL), was added with stirring at r.t. Subsequently 2-bromopropanoic acid (**6b**) (7.60 g, 50.0 mmol), dissolved in THF (10 mL), was added and the slurry was heated to reflux. After 6 h the mixture was allowed to cool and quenched with HCl (2 M; 40 mL). The aq layer was separated and extracted with EtOAc (3 × 100 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated on a rotary evaporator to give crude (±)-2-(allyloxy)propanoic acid (90%) (**8b**: 6.60 g, 92%). The crude product was used in subsequent reactions without purification.

(±)-9-Decenyl 2-(allyloxy)propanoate (10c)

A mixture of crude (±)-2-(allyloxy)propanoic acid (90%) (**8b**) (3.30 g, 23.0 mmol), 9-decen-1-ol (**9a**) (5.50 g, 35.0 mmol) and *p*-TsOH·H_2O (0.38 g, 2.00 mmol) in toluene (40 mL) was refluxed in a Dean–Stark apparatus for 5 h. After the mixture had cooled to r.t. the organic layer was neutralized by washing with sat. aq $NaHCO_3$ (30 mL), the layers were separated, the organic layer was dried (Na_2SO_4) and the solvent was removed on a rotary evaporator. The crude product was purified by flash chromatography (silica gel; cyclohexane–EtOAc, 20:1, R_f 0.31) affording (±)-9-decenyl 2-(allyloxy)propanoate (**10c**).

Yield: 3.60 g (70%); colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.25–1.40 (m, 10 H), 1.42 (d, *J* = 6.9 Hz, 3 H), 1.57–1.74 (m, 2 H), 1.97–2.13 (m, 2 H), 3.94 (ddd, *J* = 12.5, 5.9, 1.7 Hz, 2 H), 4.02 (q, *J* = 6.7 Hz, 1 H), 4.14 (m, 2 H), 4.93 (ddd, 1 H, *J* = 10.2, 2.2, 1.1 Hz, 1 H), 4.99 (ddd, *J* = 17.2, 2.2, 1.4 Hz, 1 H), 5.20 (ddd, *J* = 10.2, 1.7, 1.3 Hz, 1 H), 5.29 (dq, *J* = 17.2, 1.7 Hz, 1 H), 5.81 (ddd, *J* = 17.2, 10.2, 6.7 Hz, 1 H), 5.93 (dddd, *J* = 17.2, 10.2, 6.0, 5.2 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.7, 25.8, 28.5, 28.8, 29.0, 29.1, 29.3, 33.7, 64.9, 71.0, 74.0, 114.1, 117.7, 134.1, 139.1, 173.4.

MS: *m*/*z* (%) = 41 ($C_3H_5^+$, 79), 43 ($C_2H_3O^+$, 64), 55 ($C_4H_7^+$, 29), 69 ($C_5H_9^+$, 11), 83 ($C_6H_{11}^+$, 10), 85 ($C_5H_9O^+$, 100), 138 ($C_{10}H_{18}^+$, 4).

(±)-3-Methyl-1,4-dioxacyclopentadec-(*E*/*Z*)-6-en-2-one (11c)

In a 500 mL, 3-necked flask fitted with condenser, dropping funnel and thermometer (±)-9-decenyl 2-(allyloxy)propanoate (**10c**) (187 mg, 0.70 mmol) and Ti(*i*-PrO)$_4$ (60.0 mg, 0.21 mmol) were dissolved in CH_2Cl_2 (220 mL) under N_2 and the mixture was refluxed for 1 h. A solution of the ruthenium carbene **13** (16.4 mg, 0.02 mmol) in CH_2Cl_2 (5 mL) was added and refluxed for 20 h. After the mixture had cooled to r.t. the organic layer was washed with aq HCl (1 M; 50 mL), the layers were separated and the organic layer was filtered through a short pad of silica gel, and the solvent was removed on a rotary evaporator. Flash chromatography (silica gel; cyclohexane–EtOAc, 30:1, R_f 0.26) afforded 3-methyl-1,4-dioxacyclopentadec-(*E*/*Z*)-6-en-2-one (**11c**).

Yield: 160 mg (95%); colorless oil; odor: musky, sweet-floral, erogenous; ratio of isomers *E*–*Z* = 2.8:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23–1.46 (m, 10 H), 1.40 (d, *J* = 6.9 Hz, 3 H), 1.57–1.74 (m, 2 H), 1.91–2.14 (m, 2 H), 3.86–4.12 (m, 2 H), 4.01 (q, *J* = 6.9 Hz, 1 H), 4.20–4.44 (m, 2 H), 5.46–5.67 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.7, 23.3, 24.8, 26.0, 26.3, 26.8, 27.6, 31.0, 64.4, 71.3, 72.8, 127.1, 135.4, 173.7.

MS: *m*/*z* (%) = 41 ($C_3H_5^+$, 87), 54 ($C_4H_6^+$, 100), 67 ($C_5H_7^+$,90), 81 ($C_6H_9^+$, 66), 95 ($C_7H_{11}^+$, 36), 123 ($C_9H_{15}^+$, 8), 149 ($M^+ - C_3H_7O_3$, 8), 167 ($M^+ - C_3H_5O_2$, 3), 184 ($M^+ - C_3H_4O$, 6), 240 (M^+, 2).

(±)-3-Methyl-1,4-dioxacyclopentadecan-2-one (12c)

In the presence of 10% Pd/C (0.01 g, 0.01 mmol, 1.00 mol%) a solution of 3-methyl-1,4-dioxacyclopentadec-(*E*/*Z*)-6-en-2-one (**11c**) (240 mg, 1.00 mmol) in *i*-PrOH (10 mL) was hydrogenated with H_2 (1 bar) over 3 h. The catalyst was removed by vacuum filtration over a pad of Celite, and the filtrate was concentrated in a rotary evaporator. Flash chromatography (silica gel; cyclohexane–EtOAc, 30:1, R_f 0.28) afforded 3-methyl-1,4-dioxacyclopentadecan-2-one (**12c**).

Yield: 177 mg (74%); colorless oil; odor: musky, sweet-floral, ambergris, erogenous, reminiscent of *musk ambrette*.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.20–1.50 (m, 14 H), 1.40 (d, *J* = 6.8 Hz, 3 H), 1.57–1.80 (m, 4 H), 3.50 (m, 2 H), 3.99 (q, *J* = 6.8 Hz, 1 H), 4.20 (ddd, *J* = 6.1, 4.7, 1.3 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.6, 23.3, 24.5, 24.9, 25.2, 26.2, 26.3, 26.5, 27.7, 28.2, 64.9, 70.4, 75.6, 174.1.

MS: *m*/*z* (%) = 41 ($C_3H_5^+$, 100), 55 ($C_4H_7^+$, 96), 69 ($C_5H_9^+$, 56), 83 ($C_6H_{11}^+$, 39), 97 ($C_7H_{13}^+$, 22), 110 ($C_8H_{14}^+$, 6), 124 ($C_9H_{16}^+$, 3), 169 ($M^+ - C_3H_5O_2$, 1), 183 ($M^+ - C_2H_3O_2$, 3), 199 ($M^+ - C_2H_3O$, 1).

Compounds **8a**,**c**, **10a**,**b**,**d**,**e**–**12a**,**b**,**d**,**e** were prepared according to the same procedures as described for (±)-3-methyl-1,4-dioxacyclopentadecan-2-one (**12c**), and purified by flash chromatography (silica gel).

1,4-Dioxacyclopentadec-(*E*/*Z*)-6-en-2-one (11a)

R_f 0.31 (cyclohexane–EtOAc, 30:1); odor: musky, metallic, reminiscent of *hot iron*; ratio of isomers *E*–*Z* = 3.5:1.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.20–1.50 (m, 10 H), 1.55–1.80 (m, 2 H), 2.0–2.16 (m, 2 H), 4.09 (s, 2 H), 4.11–4.33 (m, 4 H), 5.43–5.75 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.1, 25.2, 26.1, 26.5, 27.3, 27.5, 31.2, 64.2, 65.7, 72.6, 126.6, 136.6, 171.2.

MS: *m*/*z* (%) = 41 ($C_3H_5^+$, 100), 55 ($C_4H_7^+$, 75), 67 ($C_5H_7^+$,61), 81 ($C_6H_9^+$, 40), 95 ($C_7H_{11}^+$, 19), 109 ($C_8H_{13}^+$, 9), 123 ($C_9H_{15}^+$, 6), 148 ($M^+ - C_2H_6O_3$, 2), 166 ($M^+ - C_2H_4O_2$, 1), 184 ($M^+ - C_2H_2O$, 2), 198 ($M^+ - CO$, 1).

1,4-Dioxacyclopentadecan-2-one (12a)

R_f 0.33 (cyclohexane–EtOAc, 30:1); odor: musky, floral, metallic, erogenous.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30–1.51 (m, 14 H), 1.60–1.80 (m, 4 H), 3.52 (t, *J* = 6.6 Hz, 2 H), 4.11 (s, 2 H), 4.22 (dd, *J* = 5.1, 4.4 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.7, 24.7, 25.3, 25.5, 26.2, 26.6, 26.9, 27.7, 28.0, 65.3, 69.3, 71.9, 171.3.

MS: *m*/*z* (%) = 41 ($C_3H_5^+$, 100), 55 ($C_4H_7^+$, 83), 69 ($C_5H_9^+$,47), 83 ($C_6H_{11}^+$, 27), 95 ($C_7H_{11}^+$, 23), 109 ($C_8H_{13}^+$, 9), 121 ($C_9H_{13}^+$, 6), 150 ($M^+ - C_2H_6O_3$, 1), 168 ($M^+ - C_2H_4O_2$, 1), 183 ($M^+ - C_2H_5O$, 1), 228 (M^+, 1).

1,4-Dioxacyclohexadec-(E/Z)-6-en-2-one (11b)

R_f 0.29 (cyclohexane–EtOAc, 30:1); odor: musky, woody, technical, metallic, reminiscent of *hot iron*; ratio of isomers *E*–*Z* = 2.8:1.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.20–1.50 (m, 12 H), 1.61–1.78 (m, 2 H), 2.00–2.20 (m, 2 H), 4.07–4.14 (m, 2 H), 4.10 (s, 2 H), 4.18–4.29 (m, 2 H), 5.41–5.76 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.3, 25.9, 26.4, 26.9, 27.6, 27.7, 27.9, 31.6, 64.7, 64.8, 70.8, 125.8, 137.3, 170.5.

MS: *m*/*z* (%) = 41 ($C_3H_5^+$, 100), 55 ($C_4H_7^+$, 70), 67 ($C_5H_7^+$, 54), 81 ($C_6H_9^+$, 39), 95 ($C_7H_{11}^+$, 25), 109 ($C_8H_{13}^+$, 8), 121 ($C_9H_{13}^+$, 8), 162 ($M^+ - C_2H_6O_3$, 1), 180 ($M^+ - C_2H_4O_2$, 1), 198 ($M^+ - C_2H_2O$, 1).

1,4-Dioxacyclohexadecan-2-one (12b)

R_f 0.29 (cyclohexane–EtOAc, 30:1); odor: musky, woody, technical, metallic, erogenous.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.25–1.51 (m, 16 H), 1.55–1.75 (m, 2 H), 3.53 (t, *J* = 5.8 Hz, 2 H), 4.08 (s, 2 H), 4.24 (dd, *J* = 5.2, 5.1 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.2, 24.3, 25.3, 25.4, 26.5, 26.6, 26.8, 26.9, 28.1, 28.5, 64.8, 69.0, 71.2, 170.5.

MS: *m*/*z* (%) = 41 ($C_3H_5^+$, 100), 55 ($C_4H_7^+$, 85), 69 ($C_5H_9^+$,43), 83 ($C_6H_{11}^+$, 33), 95 ($C_7H_{11}^+$, 22), 109 ($C_8H_{13}^+$, 9), 121 ($C_9H_{13}^+$, 6), 153 ($M^+ - C_3H_5O_3$, 1), 171 ($M^+ - C_3H_3O_2$, 1), 183 ($M^+ - C_2H_3O_2$, 1), 197 ($M^+ - C_2H_5O$, 1).

(±)-3-Methyl-1,4-dioxacyclohexadec-(*E*/*Z*)-6-en-2-one (11d)

R_f 0.25 (cyclohexane–EtOAc, 30:1); odor: musky, woody, erogenous, animalic; ratio of isomers *E*–*Z* = 1.9:1.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.22–1.53 (m, 12 H), 1.40 (d, *J* = 6.8 Hz, 3 H), 1.65 (m, 2 H), 2.11 (m, 2 H), 3.96–4.36 (m, 4 H), 4.10 (q, *J* = 6.8 Hz, 1 H), 5.48–5.69 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.2, 24.9, 25.4, 26.1, 26.3, 27.1, 27.5, 28.0, 31.3, 64.6, 69.8, 71.5, 126.4, 135.7, 173.4.

MS: *m*/*z* (%) = 41 ($C_3H_5^+$, 100), 55 ($C_4H_7^+$, 83), 67 ($C_5H_7^+$,68), 81 ($C_6H_9^+$, 50), 95 ($C_7H_{11}^+$, 31), 109 ($C_8H_{13}^+$, 11), 121 ($C_9H_{13}^+$, 8), 163

($M^+ - C_3H_7O_3$, 2), 181 ($M^+ - C_3H_5O_2$, 1), 198 ($M^+ - C_3H_4O$, 2), 239 ($M^+ - CH_3$, 1), 254 (M^+, 1).

(±)-3-Methyl-1,4-dioxacyclohexadecan-2-one (12d)
R_f 0.27 (cyclohexane–EtOAc, 30:1); odor: musky, woody, ambergris, erogenous, animalic, reminiscent of *nitro-musk*.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.25–1.50 (m, 16 H), 1.40 (d, *J* = 6.7 Hz, 3 H), 1.53–1.76 (m, 4 H), 3.31–3.63 (m, 2 H), 3.99 (q, *J* = 6.7 Hz, 1 H), 4.21 (dd, *J* = 5.6, 5.0 Hz, 2 H)

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.1, 24.2, 24.6, 25.4, 26.5, 26.6, 26.7, 26.8, 26.9, 28.4, 28.7, 64.8, 69.9, 75.5, 173.6.

MS: *m*/*z* (%) = 41 ($C_3H_5^+$, 78), 55 ($C_4H_7^+$, 100), 69 ($C_5H_9^+$,67), 83 ($C_6H_{11}^+$, 55), 97 ($C_7H_{13}^+$, 30), 111 ($C_8H_{15}^+$, 11), 125 ($C_9H_{17}^+$, 3), 166 ($M^+ - C_3H_6O_3$, 3), 197 ($M^+ - C_2H_3O_2$, 5), 241 ($M^+ - CH_3$, 1), 256 (M^+).

(±)-3-Methyl-1,4-dioxacycloheptadec-(E/Z)-7-en-2-one (11e)
R_f 0.27 (cyclohexane–EtOAc, 30:1); odor: musky, sweet-woody, erogenous; ratio of isomers *E*–*Z* = 1.8:1.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.20–1.44 (m, 12 H), 1.40 (d, *J* = 6.8 Hz, 3 H), 1.60–1.75 (m, 2 H), 1.98–2.10 (m, 2 H), 2.25–2.37 (m, 2 H), 3.34–3.60 (m, 2 H), 4.00 (q, *J* = 6.8 Hz, 1 H), 4.15–4.28 (m, 2 H), 5.40–5.50 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.5, 25.8, 27.1, 27.5, 27.7, 27.8, 28.6, 28.7, 31.6, 32.9, 65.0, 70.5, 75.5, 126.0, 132.9, 173.6.

MS: *m*/*z* (%) = 41 ($C_3H_5^+$, 43), 55 ($C_4H_7^+$, 88), 67 ($C_5H_7^+$, 100), 81 ($C_6H_9^+$, 74), 96 ($C_7H_{12}^+$, 44), 110 ($C_8H_{14}^+$, 20), 121 ($C_9H_{13}^+$, 18), 135 ($C_{10}H_{15}^+$, 15), 149 ($C_{11}H_{17}^+$, 8), 178 ($M^+ - C_3H_6O_3$, 13), 197 ($M^+ - C_3H_3O_2$, 1), 225 ($M^+ - C_2H_3O$, 1), 268 (M^+, 1).

(±)-3-Methyl-1,4-dioxacycloheptadecan-2-one (12e)
R_f 0.28 (cyclohexane–EtOAc, 30:1); odor: musky, sweet-woody, ambergris, erogenous, reminiscent of *musk ambrette*.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.26–1.44 (m, 18 H), 1.40 (d, *J* = 6.8 Hz, 3 H), 1.55–1.75 (m, 4 H), 3.38–3.60 (m, 2 H), 3.79 (q, *J* = 6.8 Hz, 1 H), 4.10–4.30 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.6, 24.7, 25.3, 26.1, 26.4, 26.6, 26.7, 27.1, 27.3, 27.4, 28.6, 28.7, 64.9, 70.3, 75.5, 173.7.

MS: *m*/*z* (%) = 41 ($C_3H_5^+$, 91), 55 ($C_4H_7^+$, 100), 69 ($C_5H_9^+$, 65), 83 ($C_6H_{11}^+$, 54), 97 ($C_7H_{13}^+$, 37), 111 ($C_8H_{15}^+$, 14), 123 ($C_9H_{15}^+$, 6), 137 ($C_{10}H_{17}^+$, 15), 152 ($C_{11}H_{20}^+$, 2), 180 ($M^+ - C_3H_6O_3$, 1), 197 ($M^+ - C_3H_5O_2$, 1), 211 ($M^+ - C_2H_3O_2$, 5), 241 ($M^+ - CHO$, 1), 270 (M^+, 1).

(3*R*)-(+)-3-Methyl-1,4-dioxacyclopentadecan-2-one [(*R*)-12c]
(2*R*)-(+)-Isobutyl-2-(allyloxy)propanoate (18)
Under N_2 atmosphere (2*R*)-(+)-isobutyl-2-hydroxypropanoate (**15**) (8.80 g, 60.0 mmol) was dissolved in cyclohexane (120 mL) and allyl 2,2,2-trichloroethanimidoate (**16**) (25.0 g, 120 mmol), dissolved in cyclohexane (30 mL), was added. Additionally, trifluoromethanesulfonic acid (900 mg, 6.00 mmol, 0.55 mL) was added at r.t. Stirring of the reaction mixture over 16 h at r.t. was followed by filtration and extraction of the filtrate with sat. aq $NaHCO_3$ (75 mL). The layers were separated and the organic layer was dried (Na_2SO_4), and the solvent was removed on a rotary evaporator. Flash chromatography (silica gel; cyclohexane–EtOAc, 15:1, R_f 0.26) afforded (2*R*)-(+)-isobutyl-2-(allyloxy)propanoate (**18**).

Yield: 8.40 g (75%); colorless oil; 99.0% ee; $[\alpha]_D^{20}$ +56.1 (neat).

(2*R*)-(+)-9-Decenyl-2-(allyloxy)propanoate [(*R*)-10c]
(2*R*)-(+)-Isobutyl-2-(allyloxy)propanoate (**18**) (3.50 g, 19.0 mmol), 9-decen-1-ol (**9a**) (4.50 g, 28.5 mmol) and Ti(*i*-PrO)$_4$ (0.56 g, 2.00 mmol) were heated to 80 °C under vacuum (400 mbar). After 5 h the reaction mixture was allowed to cool and the Ti(*i*-PrO)$_4$ was hydrolyzed by adding a small amount of water (10 drops). Flash chromatography (silica gel; cyclohexane–EtOAc, 20:1, R_f 0.31) afforded (2*R*)-(+)-9-decenyl-2-(allyloxy)propanoate [(*R*)-**10c**].

Yield: 4.20 g (80%); colorless oil; 99.0% ee; $[\alpha]_D^{20}$ +48.2 (neat).

The spectral data were identical to those of the racemate (±)-**10c**.

The following RCM and the final hydrogenation were carried out according to the procedures as described for (±)-3-methyl-1,4-dioxacyclopentadecan-2-one (**12c**).

(3*R*)-(+)-3-Methyl-1,4-dioxacyclopentadec-(*E*/*Z*)-6-en-2-one [(*R*)-11c]
Odor: musky, sweet-floral, ambergris, erogenous, stronger musky and more erogenous than the racemate (±)-**11c**; $[\alpha]_D^{20}$ +20.0 (neat).

The spectral data were identical to those of the racemate (±)-**11c**.

(3R)-(+)-3-Methyl-1,4-dioxacyclopentadecan-2-one [(*R*)-12c]
Odor: musky, sweet-floral, ambergris, erogenous, animalic, reminiscent of *musk ambrette*, stronger musky than the racemate (±)-**12c**; 99.0% ee; $[\alpha]_D^{20}$ +20.4 (neat).

The spectral data were identical to those of the racemate (±)-**12c**.

Compounds (*S*)-**11c,d**, (*S*)-**12c,d**, (*R*)-**11d** and (*R*)-**12d** were prepared according to the same procedures as described for (3*R*)-(+)-3-methyl-1,4-dioxacyclopentadecan-2-one [(*R*)-**12c**], and purified by flash chromatography (silica gel). In all cases the spectral data of the enantiomers were identical to those of the corresponding racemates.

(3*S*)-(–)-3-Methyl-1,4-dioxacyclopentadec-(*E*/*Z*)-6-en-2-one [(*S*)-11c]
Odor: slightly musky, sweet-floral, weaker than the racemate (±)-**11c**; $[\alpha]_D^{20}$ –20.0 (neat).

The spectral data were identical to those of the racemate (±)-**11c**.

(3*S*)-(–)-3-Methyl-1,4-dioxacyclopentadecan-2-one [(*S*)-12c]
Odor: musky, sweet-floral, ambergris, erogenous, animalic, reminiscent of *musk ambrette*, weaker than the racemate (±)-**12c**; 95.2% ee; $[\alpha]_D^{20}$ –23.0 (neat).

The spectral data were identical to those of the racemate (±)-**12c**.

(3*R*)-(+)-3-Methyl-1,4-dioxacyclohexadec-(*E*/*Z*)-6-en-2-one [(*R*)-11d]
Odor: musky, woody, ambergris, erogenous, animalic, stronger musky than the racemate (±)-**11d**; $[\alpha]_D^{20}$ +28.2 (neat).

The spectral data were identical to those of the racemate (±)-**11d**.

(3*R*)-(+)-3-Methyl-1,4-dioxacyclohexadecan-2-one [(*R*)-12d]
Odor: strong musky, woody, ambergris, erogenous, animalic, reminiscent of *musk ambrette*, stronger musky than the racemate (±)-**12d**; 99.0% ee; $[\alpha]_D^{20}$ +15.4 (neat).

The spectral data were identical to those of the racemate (±)-**12d**.

(3*S*)-(–)-3-Methyl-1,4-dioxacyclohexadec-(*E*/*Z*)-6-en-2-one [(*S*)-11d]
Odor: slightly musky, woody, erogenous, weaker musky than the racemate (±)-**11d** and no ambergris undertone; $[\alpha]_D^{20}$ –23.0 (neat).

The spectral data were identical to those of the racemate (±)-**11d**.

(3S)-(–)-3-Methyl-1,4-dioxacyclohexadecan-2-one [(*S*)-12d]
Odor: musky, woody, erogenous, weaker musky than the racemate (±)-**12d** and no ambergris undertone; 95.2% ee; $[\alpha]_D^{20}$ –16.0 (neat).

The spectral data were identical to those of the racemate (±)-**12d**.

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