**1,4-Dioxamacrolides: Preparation and Sensory Properties**

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**Abstract:** The synthesis of 3-methyl-1,4-dioxacyclopentadecan-2-one (12c) and 3-methyl-1,4-dioxacyclohexadecan-2-one (12d), two new musk odorants, is described starting from methyl 2-bromopropanionic 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 (3R)-(+)- and (3S)-(−)-3-methyl-1,4-dioxacyclopentadecan-2-one as well as (3R)-(+)- and (3S)-(−)-3-methyl-1,4-dioxacyclohexadecan-2-one reveals that mainly the (3R)-(+) enantiomers are responsible for the powerful musk odor characteristic. Their synthesis starts from ethyl (2S)-2-hydroxypropanoate (14) or isobutyl (2R)-2-hydroxypropanoate (15) which were treated under acidic conditions with allyl trichloroacetimidate (16), followed by titnate mediated transesterification, ring-closing olefin metathesis and hydrogenation.

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

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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. Hence, the synthesis of new biodegradable macrocyclic musk odorants has become an important topic of current research interest in the flavor and fragrance industry. One of the most popular ingredients 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). The synthesis of 1,6-dioxacycloheptadecan-7-one (2) started with methyl 11-bromoundecanoate which was reacted with the monosodium salt of 1,4-butanediol. The resulting methyl 16-hydroxy-12-oxopalmimiate was condensed to the corresponding polyester, which was subsequently depolymerized. The 1,7-dioxo- (3) and 1,8-dioxo- (4) isomers were obtained in the same way from the corresponding hydroxy-oxa-acids.

Kraft et al. have described two strategies for the synthesis of 4-methyl-1,7-dioxacycloptadecan-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-dioxacycloptadecan-8-one (5).

Here we report the first approach to the oxamacrolides 11 and 12 from α-bromo carboxylic acids 6 and 1,0-alkenols 7 via 1,0-dienes 10. The key step in our short route is the macrocyclization reaction of 1,0-dienes 10 by ring-closing olefin metathesis (RCM), which was catalyzed by the ruthenium carbene complex. Variation of the numbers of methylene groups in 7 and 9 offers the advantage to synthesize 15- to 17-membered rings.

The synthesis of 1,0-dienes 10 started with a nucleophilic substitution of α-bromo carboxylic acids 6 and 1,0-alkenols 7 to generate 2-alkenylcarboxylic acids 8 (Scheme 1). This material 8 was transformed without any purification into the 1,0-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 1,0-dienes 10 failed to cyclize when treated with ruthenium carbene 13, due to the formation of 5- or 6-membered intramolecular chelate struc-
tured to the saturated 1,4-dioxamacrolides.

40 °C, 90–95%; (d) Pd/C (5 mol%), H₂, blocks under basic conditions 10 was not practical, because (Scheme 2). The ing materials for the enantioselective approach

R(S)chiral ethyl (2S)-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 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 (2S)-2-hydroxypropanoate (14) or isobutyl (2R)-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 (2S)- and (2R)-2-allyloxyesters 17 and 18 in 75% yield. Allyl trichloroacetimidate (16) was readily available from the corresponding allylic alcohol, trichloroacetointrile and a catalytic amount of sodium hydride. Thereafter, titanate mediated transesterification by means of 7 mol% Ti(i-PrO)₄ in 1,0-alkenol 9a or 9b12 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 of ≥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

<table>
<thead>
<tr>
<th>Compound</th>
<th>Sensory properties of 11 and 12</th>
<th>Musk intensity</th>
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</thead>
<tbody>
<tr>
<td>11a</td>
<td>musky, metallic, reminiscent of hot iron</td>
<td>+</td>
</tr>
<tr>
<td>11b</td>
<td>musky, woody, technical, metallic, reminiscent of hot iron</td>
<td>+</td>
</tr>
<tr>
<td>11c</td>
<td>musky, sweet-floral, erogenous ++</td>
<td></td>
</tr>
<tr>
<td>11d</td>
<td>musky, woody, erogenous, animalic ++</td>
<td></td>
</tr>
<tr>
<td>11e</td>
<td>musky, sweet-floral, erogenous ++</td>
<td></td>
</tr>
<tr>
<td>12a</td>
<td>musky, floral, erogenous, metallic ++</td>
<td></td>
</tr>
<tr>
<td>12b</td>
<td>musky, woody, erogenous, technical ++(+)</td>
<td></td>
</tr>
<tr>
<td>12c</td>
<td>musky, sweet-floral, ambergris, erogenous, reminiscent of musk ambrette +++</td>
<td></td>
</tr>
<tr>
<td>12d</td>
<td>musky, woody, ambergris, erogenous, animalic, reminiscent of nitro-musk +++</td>
<td></td>
</tr>
<tr>
<td>12e</td>
<td>musky, sweet-woody, ambergris, erogenous, reminiscent of musk ambrette ++(+)</td>
<td></td>
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</table>

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 (2S)-2-hydroxypropanoate (14) or isobutyl (2R)-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 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 (2S)-2-hydroxypropanoate (14) or isobutyl (2R)-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 (2S)- and (2R)-2-allyloxyesters 17 and 18 in 75% yield. Allyl trichloroacetimidate (16) was readily available from the corresponding allylic alcohol, trichloroacetointrile and a catalytic amount of sodium hydride. Thereafter, titanate mediated transesterification by means of 7 mol% Ti(i-PrO)₄ in 1,0-alkenol 9a or 9b12 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 of ≥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.
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 results are in good agreement with the results of other groups; e.g. Kraft et al. 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.

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 (CDCl3, TMS). GC–MS: HP MSD 5972 A (EI: 70 eV) Polarimetry: Schmidt and Haensch Polartronic 1 (CHCl3). Chiral GC: Carlo Erba 5300, 25 m × 0.25 mm DMTBS-β-cyclodextrin (Mega), 1.0 bar H2, 100–102 °C/min–180 °C.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Sensory Properties of 3-Methyl-1,4-dioxamacrolide Enantiomers.</th>
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</thead>
<tbody>
<tr>
<td>Compound</td>
<td>Sensory properties of 11 and 12</td>
</tr>
<tr>
<td>(R)-11c</td>
<td>musky, sweet-floral, ambergris, erogenous</td>
</tr>
<tr>
<td>(S)-11c</td>
<td>slightly musky, sweet-floral</td>
</tr>
<tr>
<td>(R)-11d</td>
<td>musky, woody, ambergris, erogenous, animalic</td>
</tr>
<tr>
<td>(S)-11d</td>
<td>slightly musky, woody, erogenous</td>
</tr>
<tr>
<td>(R)-12c</td>
<td>strong musky, sweet-floral, erogenous, animalic, ambergris</td>
</tr>
<tr>
<td>(S)-12c</td>
<td>musky, sweet-floral, erogenous</td>
</tr>
<tr>
<td>(R)-12d</td>
<td>strong musky, woody, erogenous, animalic, ambergris</td>
</tr>
<tr>
<td>(S)-12d</td>
<td>musky, woody, erogenous</td>
</tr>
</tbody>
</table>

Scheme 2 Synthesis of enantiomerically pure 3-methyl-1,4-dioxamacrolides.
Yield: 3.60 g (70%); colorless oil.

\( ^1 \text{H} \text{NMR} (200 \text{ MHz, CDCl}_3); \delta = 1.25–1.40 \text{ (m, 10 H)}, 1.42 \text{ (d, } J = 6.9 \text{ Hz, } 3 \text{ H}), 1.57–1.74 \text{ (m, 2 H)}, 1.97–2.13 \text{ (m, 2 H)}, 3.94 \text{ (dd}, J = 12.5, 5.9, 1.7 \text{ Hz, } 2 \text{ H}), 4.02 \text{ (q}, J = 6.7 \text{ Hz, } 1 \text{ H}), 4.14 \text{ (m, } 2 \text{ H}), 4.93 \text{ (dd}, J = 10.2, 2.2, 1.1 \text{ Hz, } 1 \text{ H}), 4.99 \text{ (dd}, J = 17.2, 2.2, 1.4 \text{ Hz, } 1 \text{ H}), 5.20 \text{ (dd}, J = 10.2, 1.7, 1.3 \text{ Hz, } 1 \text{ H}), 5.29 \text{ (dq}, J = 17.2, 1.7 \text{ Hz, } 1 \text{ H}), 5.81 \text{ (dd}, J = 17.2, 10.2, 6.7 \text{ Hz, } 1 \text{ H}), 5.93 \text{ (dddd}, J = 17.2, 10.2, 6.0, 5.2 \text{ Hz, } 1 \text{ H}).

\( ^13 \text{C} \text{NMR} (50 \text{ MHz, CDCl}_3); \delta = 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: mlc (%): 41 (C\text{6}H\text{7}+, 79), 43 (C\text{6}H\text{9}O+ , 39), 95 (C\text{6}H\text{7}O\text{2}+, 55), 97 (C\text{6}H\text{7}O\text{3}+, 43), 110 (C\text{6}H\text{7}O\text{4}+, 39), 124 (C\text{6}H\text{8}O\text{5}+, 36), 149 (M–C\text{2}H\text{5}O\text{8}, 184) (M–C\text{4}H\text{6}O\text{6}, 240) (M+, 2).}

(\pm)-3-Methyl-1,4-dioxacyclohexadecan-2-one (11a)

In a 500 mL, 3-necked flask fitted with condenser, dropping funnel and thermometer (\pm)-9-decenyl 2-(allyloxy)propanoate (10c) (187 mg, 0.70 mmol) and Ti(i-Pr)\text{O}(60.0 mg, 0.21 mmol) were dissolved in CH\text{2}Cl\text{2} (220 mL) under N\text{2} and the mixture was refluxed for 1 h. A solution of the ruthenium carbene 13b (16.4 mg, 0.02 mmol) in CH\text{2}Cl\text{2} (5 mL) was added and refluxed for 20 h. After the mixture had cooled to rt, 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, Rf 0.28) afforded 3-methyl-1,4-dioxacyclohexadecan-2-one (11c).

\text{Yield:} 3.6 g (70%); colorless oil.

\( ^1 \text{H} \text{NMR} (200 \text{ MHz, CDCl}_3); \delta = 1.30–1.51 \text{ (m, 14 H)}, 1.60–1.80 \text{ (m, 4 H)}, 3.52 \text{ (t}, J = 6.6 \text{ Hz, } 2 \text{ H}), 4.11 \text{ (s, } 2 \text{ H}), 4.22 \text{ (dd}, J = 5.1, 4.4 \text{ Hz, } 2 \text{ H}).

\( ^13 \text{C} \text{NMR} (50 \text{ MHz, CDCl}_3); \delta = 23.7, 24.7, 25.3, 25.5, 26.2, 26.6, 26.9, 27.7, 28.0, 63.9, 71.9, 171.3.

MS: mlc (%): 41 (C\text{6}H\text{7}+, 100), 55 (C\text{6}H\text{8}+, 83), 69 (C\text{7}H\text{13}O+ , 37), 83 (C\text{7}H\text{14}O+ , 27), 95 (C\text{7}H\text{15}O\text{2}+, 23), 109 (C\text{7}H\text{16}O\text{3}+, 9), 121 (C\text{7}H\text{17}O\text{4}+, 150) (M–C\text{6}H\text{9}O\text{7}, 168) (M–C\text{6}H\text{9}O\text{8}, 183) (M–C\text{6}H\text{9}O\text{9}, 228) (M+, 1).
(±)-3-Methyl-1,4-dioxacyclopentadecan-2-one (12d)

Average yield: 8.40 g (75%); colorless oil; 99.0% ee; 

The reaction mixture was allowed to cool and the Ti(isoPrO)4 was hydrolyzed by adding a small amount of water (10 drops). Flash chromatography (silica gel; cyclohexane–EtOAc, 20:1, Rf 0.31) afforded (2R,6S)-9-decenyloxy-2-allyloxy)propanoate ([R]-10c).

Yield: 4.20 g (80%); colorless oil; 99.0% ee; [α]20D +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-dioxacycloptadecan-2-one (12c).

(3R)/(–)-3-Methyl-1,4-dioxacycloptadecan-2-one (Z)-6-endo-2-one ([R]-11c)
Odor: musky, sweet-floral, ambergis, stronger musky and more erogenous than the racemate (±)-11c; [α]20D +20.0 (neat).

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

(3S)/(+) -3-Methyl-1,4-dioxacycloptadecan-2-one (E)-6-endo-2-one ([S]-11c)
Odor: slightly musky, sweet-floral, weaker than the racemate (±)-11c; [α]20D –20.0 (neat).

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

(3S)/(–)-3-Methyl-1,4-dioxacycloptadecan-2-one (S)-12c
Odor: musky, sweet-floral, ambergis, stronger musky, weaker than the racemate (±)-12c; 95.2% ee; [α]20D –23.0 (neat).

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

(3R)/(+)-3-Methyl-1,4-dioxacycloptadecan-2-one (E)-6-endo-2-one ([R]-11d)
Odor: musky, woody, ambergis, erogenous, stronger musky than the racemate (±)-11d; [α]20D +28.2 (neat).

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

(3S)/(–)-3-Methyl-1,4-dioxacycloptadecan-2-one (S)-12d
Odor: strong musky, woody, ambergis, erogenous, stronger musky than the racemate (±)-12d; 99.0% ee; [α]20D +15.4 (neat).

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

(3S)/(–)-3-Methyl-1,4-dioxacycloptadecan-2-one (S)-11d
Odor: slightly musky, woody, erogenous, weaker musky than the racemate (±)-11d and no ambergis undertone; [α]20D –23.0 (neat).

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

(3S)/(–)-3-Methyl-1,4-dioxacycloptadecan-2-one (S)-12d
Odor: musky, woody, erogenous, weaker musky than the racemate (±)-12d and no ambergis undertone; 95.2% ee; [α]20D –16.0 (neat).

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

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References

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