(4*E*,8*Z*)-12-Methyloxacyclotetradeca-4,8-dien-2-one and Its 7a-Homologue: Conformationally Constrained Double-Unsaturated Macrocyclic Musks by Ring-Closing Alkyne Metathesis

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Abstract: The double-unsaturated macrocyclic lactones (4*E*,8*Z*)-12-methyloxacyclotetradeca-4,8-dien-2-one and its 7a-homologue (4*E*,9*Z*)-13-methyloxacyclopentadeca-4,9-dien-2-one, designed as new potent musk odorants by molecular modeling, were synthesized by ring-closing alkyne metathesis in the presence of 10 mol% of Schrock's alkylidyne catalyst, and subsequent Lindlar hydrogenation. Demethylation of citronellol, induced by nitrous acid, afforded the 3-methyloct-6-yn-1-ol building block. The substrates for the alkyne metathesis were prepared by Steglich esterification of citronellol with the 3*E*-configured non-3-en-7-ynoic and dec-3-en-8-ynoic acids, accessible by β,γ-selective Knoevenagel condensation from the corresponding alkynals hept-5-ynal and oct-6-ynal, which were synthesized by Eschenmoser–Ohloff fragmentation of the epoxide of 2-methylcyclohex-2-enone, and methylation of hex-5-yn-1-ol, respectively. Both target structures, (4*E*,8*Z*)-12-methyloxacyclotetradeca-4,8-dien-2-one and its 7a-homologue, emanated most pleasant and powerful musk odors.

Key words: odorants, macrocycles, metathesis, musks, ring closure

By providing a sweet, warm, and erogenous sensation, musk odorants confer on perfumes that certain sensuality that distinguishes them from being merely floral bouquets or potpourris. Consequently, there is probably not a single fragrance on the market that does not contain any musk odorant.[2] Macrocycles constitute the only class of musks that occurs in nature: as ketones in the animal and as lactones in the plant kingdom. Despite a relatively high price, their authenticity and natural character makes them highly appreciated in perfumery.[3] Today, the ketone muscenone (**1**)[4] and the lactone Nirvanolide® (**2**),[2] both of which bear a methyl substituent and one double bond, constitute the most efficient macrocyclic musks used in perfumery (Figure 1). Their musk odors depend critically on both the position and configuration of the double bond[2,5] and that of the methyl substituent.[3] Most decisive is the latter, and the methyl group is best be situated on a different *trans*-configured edge than is the carbonyl osmophore, which acts as the hydrogen-bond acceptor on the receptor binding site. Placed that way, a methyl substituent will not hinder the receptor interaction, but will instead imitate a larger ring, without lowering the vapor pressure as much as would result from a correspondingly large perimeter.[3]

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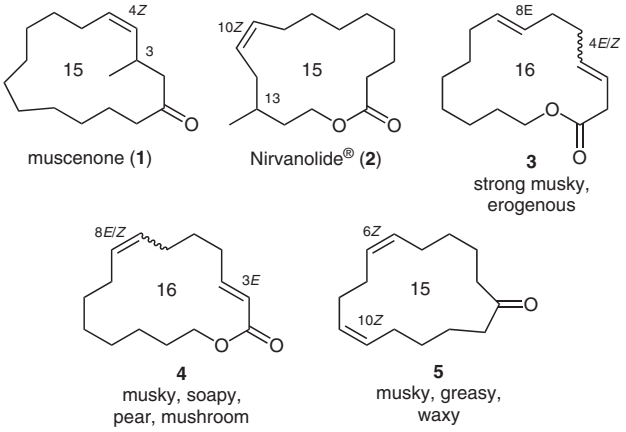


Figure 1 The most powerful macrocyclic musks muscenone (**1**) and Nirvanolide® (**2**) in comparison with the known double-unsaturated macrocyclic musks **3**–**5**

Double bonds constitute electronegative elements that can intensify the binding of an odorant to a complementary receptor site,[2] but they are also of major importance in restricting the conformational space of the macrocycles. However, as long as only one double bond is present, the ring remains quite flexible. This situation changes when two double bonds are introduced, especially if one of these is *E*-configured.

As shown in Figure 1 for macrocycles **3**–**5**, the odor of double-unsaturated macrocycles changes dramatically with the position and configuration of the double bonds. The strong, very erogenous animal musk note with sweet, warm sandalwood accents[6] that (4*E*/*Z*,8*E*)-oxacyclohexadeca-4,8-dien-2-one (**3**) emanates becomes soapy with unpleasant pear- and mushroom-like undertones in the (3*E*,8*E*/*Z*)-isomer **4** (Figure 1).[7] Only one other double-unsaturated macrocyclic musk has been reported in the literature, the 6*Z*,10*Z*-configured cyclopentadeca-6,10-dienone (**5**) (Figure 1), which Fehr et al.[8] obtained elegantly upon iterative fragmentation of a 1,3,5-functionalized tricyclic system. However, its greasy, waxy, relatively weak musk odor was rather disappointing.

To avoid transannular interactions, the gauche atoms in a macrocyclic ring tend to be separated as far as possible from one another. They form the corners of a regular polygon, the edges of which consist of *trans*-configured aliphatic chains.[9] An ester moiety tends to be accommodated in the middle of such a zigzag chain, just where an *E*-con-

figured double bond would prefer to be situated. Both favor the longest edge, but an *E*-configured double bond wins energetically over an ester function. Whenever possible, a *Z*-configured double bond will replace one gauche corner and thereby reduce the overall torsional (Pitzer) strain in the ring. In the minimum-energy conformer of Nirvanolide® (**2**), delineated in Figure 2, the 10*Z*-double bond thus defines one corner, the ester moiety a *trans*-configured edge of three bonds, and the methyl substituent comes to lie on an *all-trans* side situated in between, imitating a larger ring on the receptor, even if the corner atoms move by one position. According to the Dale system,[9] these configurations of macrocyclic rings are designated by stating the number of bonds between the corner atoms in square brackets, starting with the shortest *trans*-configured methylene chain and moving in the direction of the next shortest. The sum of the numbers in square brackets thus corresponds to the respective ring size (Figure 2).

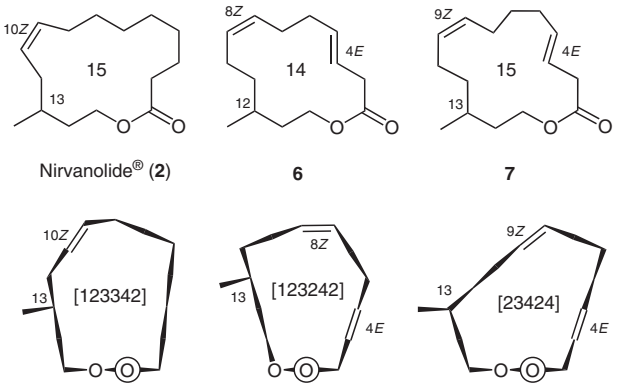
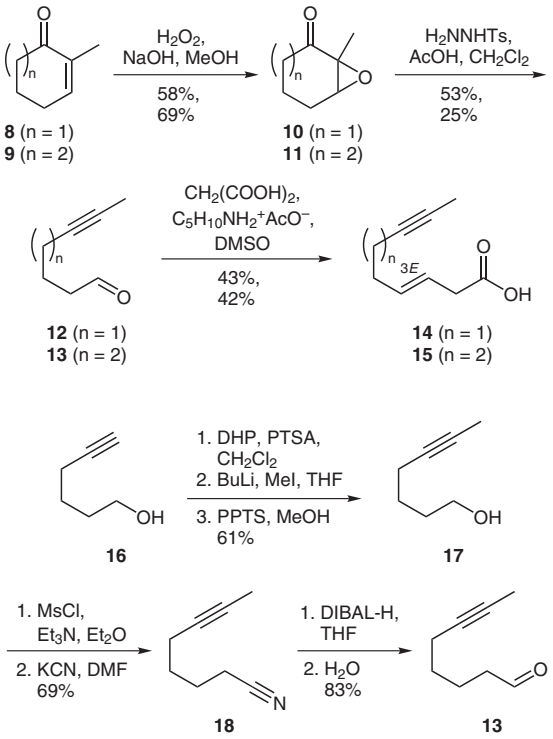


Figure 2 Minimum-energy conformation (PM3) of Nirvanolide® (**2**), and the two target structures **6** and **7** with their respective global energy minima (PM3)

To maximize the latitudinal dimensions, it was desired to fix the 13-methyl group by further restricting the flexibility of the macrocyclic ring. Introducing a 4*E*-double bond in the edge adjacent, and a *Z*-double bond opposite to the carbonyl group should force the methyl substituent to protrude from the side opposite to the *E*-configured double bond, thereby imitating a larger ring (Figure 2). To take full advantage of this effect, a high vapor pressure must, however, be ensured. Consequently, the target structures should possess a 14- or 15-membered ring, which are the smallest to occur in macrocyclic musks. These reflections led to the design of (4*E*,8*Z*)-12-methyloxacyclotetradeca-4,8-dien-2-one (**6**) and (4*E*,9*Z*)-13-methyloxacyclopentadeca-4,9-dien-2-one (**7**) as target molecules (Figure 2). And indeed, in accord with these conformational considerations, PM3 calculations confirmed that the 13-methyl substituent extends the latitudinal dimensions of both macrocyclic rings in the [123242] and [23424] conformations that were found to be the global energy minima of the target structures **6** and **7**, respectively (Figure 2).

Retrosynthetic analysis suggested the introduction of the *Z*-configured double bond by Lindlar hydrogenation of the corresponding oxacycloalkenynones, which could be accessible by ring-closing alkyne metathesis as, for instance, applied by Fürstner and Seidel in their elegant civetone synthesis.[10] There are quite a few examples for the compatibility of alkyne metathesis with double bonds such as those present in 1,3-enynes,[11,12] terminal alkenes,[13,14] styrenes,[15] enoates, non-conjugated exocyclic alkenes,[16] and β,γ-unsaturated esters.[15] In the synthesis of prostaglandin-E_2-1,15-lactone[17] and various analogues[18] by alkyne metathesis, Fürstner et al.[19] even employed substrates with a 1,6-enyne moiety. Therefore, the mechanistic differences between alkyne and enyne metathesis[20] seemed sufficiently pronounced to allow alkyne metathesis on substrates with a 1,5- or 1,6-enyne relation, even without the double bond being deactivated by conjugation with a carbonyl function. So, this synthetic plan seemed to us a promising approach.

The 4*E*-configured double bond on the corresponding carboxylic acid building block should be accessible by Knoevenagel condensation of hept-5-ynal (**12**) and oct-6-ynal (**13**) with malonic acid in the presence of piperidinium acetate (Scheme 1).[21] This latter reagent catalyzes the dehydration of the intermediate hydroxymalonic acid and the subsequent isomerization to the β,γ-unsaturated dicarboxylic acid, which then decarboxylates. Under standard reaction conditions, the α,β-unsaturated dicarboxylic acid cannot decarboxylate, so that the equilibrium is shifted towards the β,γ-unsaturated system.[21] The other re-



Scheme 1 Synthesis of the 3*E*-configured alk-3-en-(ω–2)-ynoic acids **14** and **15** from alkynals **12** and **13**, obtained by Eschenmoser–Ohloff fragmentation of **10**, and elongation of hex-5-yn-1-ol (**16**), respectively

quired building block should, for instance, be accessible from citronellol (**19**, Scheme 2) by ozonolysis and Corey–Fuchs reaction.

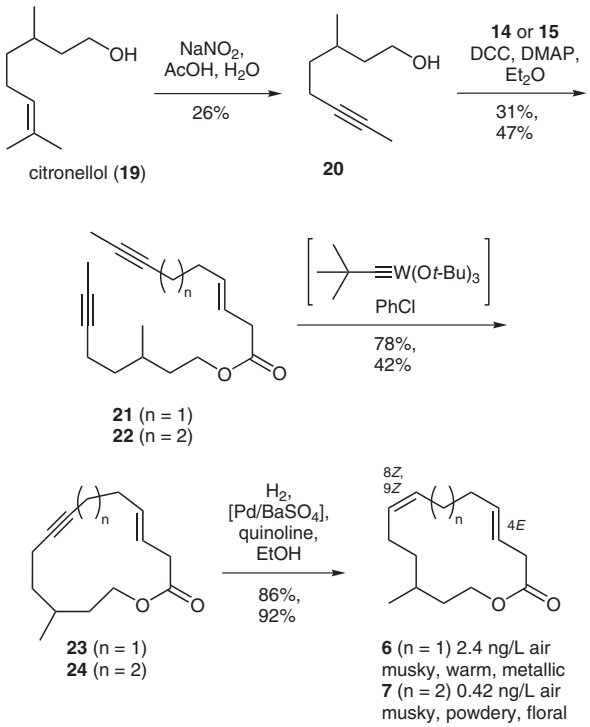
As outlined in Scheme 1, the synthesis of the 3*E*-configured non-3-en-7-ynoic acid (**14**) commenced with the Weitz–Scheffer epoxidation[22] of commercially available 2-methylcyclohex-2-enone (**8**), which afforded the 2,3-epoxy ketone **10** in 58% yield. We obtained hept-5-ynal (**12**) in a good 53% yield from **10** by employing the standard conditions of the Eschenmoser–Ohloff fragmentation (Scheme 1).[23,24] The alkynal **12**, however, turned out to be very sensitive to even traces of acids, and decomposed partly upon chromatographic purification on silica gel or alumina. Upon storage it also underwent slow rearrangement into the corresponding allene, and thus was later directly employed, as crude material, in the next step.

In analogy to the synthesis of **12**, it was first attempted to prepare the homologous oct-6-ynal (**13**) from 2-methylcyclohept-2-enone (**9**), which was accessible by α-methylation of suberone (77%),[25] bromination (73%), and subsequent dehydrohalogenation with lithium carbonate (60%).[26] The Weitz–Scheffer epoxidation of **9**, followed by an analogous Eschenmoser–Ohloff fragmentation of the 2,3-epoxy ketone **11** gave, however, a poor 17% total yield for oct-6-ynal (**13**) from **9** (Scheme 1), which corresponds to a yield of only 6% from suberone.

It was therefore decided to follow the alternative synthetic scheme of Herndon and co-workers,[27] which was modified by protection of the hydroxy function during the methylation step. Commercially available hex-5-yn-1-ol (**16**) was protected as a tetrahydropyran-2-yl (THP) ether by reaction with 3,4-dihydro-2*H*-pyran (DHP) and then methylated with iodomethane to furnish hept-5-yn-1-ol (**17**) in 61% yield after cleavage (Scheme 1). Cyanation via the mesylate afforded the corresponding nitrile **18** in 69% yield, which after reduction with diisobutylaluminum hydride and aqueous workup provided oct-6-ynal (**13**) in 83% yield (Scheme 1). With a total yield of 36% from hex-5-yn-1-ol (**16**), this route was thus far more efficient for preparing the homologous aldehyde **13**. In addition, oct-6-ynal (**13**) proved to be significantly more stable than hept-5-ynal (**12**), and thus could be stored for a prolonged period of time.

The Knoevenagel condensation of the alkynals **12** and **13** with malonic acid in the presence of catalytic amounts of piperidinium acetate (Scheme 1)[21] took the expected course and provided the desired β,γ-unsaturated acids **14** and **15** in good to excellent Δ^3/Δ^2 selectivities of 98:2 (**14**) and 70:30 (**15**) for the crude materials. The undesired conjugated isomers were removed by chromatography, which furnished **14** and **15** in 43% and 42% yield, respectively (Scheme 1).

For the synthesis of the required alcohol component **20**, it was originally intended to make use of a Corey–Fuchs reaction[28] starting from *rac*-citronellol (**19**) (Scheme 2) as an inexpensive perfumery raw material of prominent rose odor. After THP protection of the hydroxy function, ozonolysis of the monoterpene alcohol **19** furnished the corresponding aldehyde in 96% yield after reductive workup with dimethyl sulfide. Corey–Fuchs reaction[28] in the presence of an eightfold excess of triethylamine, with quenching by addition of iodomethane, then provided 3-methyloct-6-yn-1-ol (**20**) in 41% overall yield after deprotection. The eightfold excess of triethylamine was necessary to prevent cleavage of the THP protecting group, which would otherwise lead to the corresponding bromide by Appel–Lee reaction with the reactants present. However, independent of carrying out the methylation step in the Corey–Fuchs reaction or separately on the terminal alkyne, the 3-methyloct-6-yn-1-ol (**20**) isolated was always accompanied by an additional 10% yield of 3-methylhept-6-yn-1-ol from incomplete methylation. It turned out to be impossible to remove this terminal alkyne completely by all means tried, also not as the THP ether or on the following ester stage. Coutelier and Mortreux[29] had reported that alkyne metathesis of terminal alkynes was possible in the presence of quinuclidine, but in our hands this did not work. Thus, the Corey–Fuchs route to alkynol **20** was abandoned.



Scheme 2 Synthesis of 3-methyloct-6-yn-1-ol (**20**) from citronellol (**19**), and completion of the synthesis of the target structures **6** and **7**

An alternative access to 3-methyloct-6-yn-1-ol (**20**), free from any terminal alkyne, was found in the nitrous acid induced demethylation of the isopropylidene group discovered by Abidi,[30] which allowed the direct conversion of citronellol (**19**) into 3-methyloct-6-yn-1-ol (**20**) (Scheme 2).[30a] Although we were not able to reproduce the reported 95% yield of Abidi,[30a] the reaction provided a direct access to the desired compound **20**. In accordance

with the 25–33% yield Corey et al.[31] and the 10–15% yield Zard and co-workers[32] had obtained in their mechanistic studies of the reaction, we isolated 3-methyloct-6-yn-1-ol (**20**) in 26% yield after chromatographic purification (Scheme 2). The mechanism of this unusual demethylation is believed to involve an *N*-hydroxypyrazole *N*-oxide, which is further nitrosated. Tautomerization and cleavage then leads to a pyrazolone di-*N*-oxide, which is prone to open hydrolytically with subsequent loss of carbon dioxide and nitrous oxide to afford the desired alkynol **20**.[32] Steglich esterification[33] of 3-methyloct-6-yn-1-ol (**20**) with the 3*E*-configured alk-3-en-(ω–2)-ynoic acids **14** and **15** afforded the diyne esters **21** and **22**, respectively (Scheme 2). Although GC monitoring indicated complete conversion, the yields of esters **21** and **22** were only 31% and 47%, respectively. It is believed that decomposition occurred during chromatography or even upon esterification.

Ring-closing metathesis employing 10 mol% of Schrock's alkylidyne catalyst [*t*-BuC≡W(O*t*-Bu)$_3$][34] in refluxing chlorobenzene[35] furnished **23** and **24** in spot-to-spot reactions in 78% and 42% yield, respectively. Notably, enyne metathesis on (3*E*,6′*E*/*Z*)-3′-methyl-7′-phenylhept-6′-enyl dec-3-en-8-ynoate and (3*E*)-3′-methylhept-6′-enyl dec-3-en-8-ynoate in the presence of Grubbs' first-generation (5–10 mol%) or second-generation catalyst (5–25 mol%) under an argon or ethene atmosphere[20,36] did not provide **7** or other macrocyclic products. This, indeed, confirms the different mechanistic pathways proposed for alkyne and enyne metathesis.[37]

The synthesis of the target compounds **6** and **7** was completed by standard Lindlar hydrogenations in ethanol in the presence of the Cram–Allinger catalyst system.[38] The 4*E*,8*Z*-configured 12-methyloxacyclotetradeca-4,8-dien-2-one (**6**) and its 7a-homologue **7** were isolated in 86% and 92% yield, respectively.

While the cycloalkenynones **23** and **24** were only very weak and uncharacteristic in smell, both target compounds **6** and **7** emanated pronounced pleasant and very powerful musk notes. In the case of (4*E*,8*Z*)-12-methyloxacyclotetradeca-4,8-dien-2-one (**6**), the powdery musk scent was accompanied by a warm-metallic hot-iron note as well as herbaceous and floral facets. The musk tonality of its 7a-homologue **7** was also powdery, but sweeter, and more distinct, while at the same time also containing floral facets in the direction of jasmine, with slightly green aspects being more apparent. With a GC–odor threshold of 0.42 ng/L air it was clearly stronger than **6**, for which a threshold of 2.4 ng/L air was measured.

Thus, the olfactory properties of both potent musks **6** and **7** confirmed the design principles conceived in the beginning. Most importantly, however, ring-closing alkyne metathesis proved chemoselective in the presence of double bonds, even if those were not deactivated by conjugation with a carbonyl function. The presented methodology should thus be applicable for the *E*/*Z*-selective synthesis of many other double- or possibly even triple-unsaturated macrocycles with interesting properties and not only in the domain of fragrance chemistry.

All reactions involving chemicals sensitive to H_2O or O_2 were carried out in flame-dried glassware with magnetic stirring under argon or N_2 atmosphere. Unless otherwise stated, reagents and solvents (*puriss.* or *purum*) were purchased from SAFC or Acros, and used without further purification. *rac*-Citronellol (**19**) was used as supplied by Givaudan (Vernier, Switzerland) in perfumery-grade quality. Schrock's alkylidyne catalyst and other metathesis catalysts were purchased from Strem Chemicals, Newburyport. Flash chromatography was carried out on Brunschwig silica gel (particle size 0.032–0.063 mm). TLC analyses were performed on precoated Polygram Sil G/UV 254 foils (Macherey & Nagel, Düren) with UV detection (254 nm) under a UV lamp, and subsequent treatment with aq $KMnO_4$ (0.5%). Melting points were determined on a Büchi melting point apparatus B-545 and are uncorrected. Attenuated-total-reflection (ATR) IR spectroscopic data were recorded on a Bruker VECTOR 22 instrument with a Harrick SplitPea unit (Si). NMR experiments, of samples in $CDCl_3$ or benzene-d_6, as indicated, were performed on Bruker Avance DPX-400 or Bruker Avance DPX-500 (TCI) spectrometers. ^{1}H NMR chemical shifts are given relative to TMS (δ = 0), and ^{13}C NMR chemical shifts are given relative to $CDCl_3$ (δ = 77) or benzene-d_6 (δ = 128 ppm). The multiplicities were assigned by DEPT experiments. MS data were collected on Finnigan MAT 95 or HP Chemstation 6890 GC-5973 Mass Sensitive Detector equipment. Elemental analyses were performed by the Mikroanalytisches Laboratorium Ilse Beetz, 96301 Kronach, Germany. Olfactory evaluations of samples in 10% soln in EtOH and 10% soln in dipropylene glycol (DPG) on smelling blotters were performed by expert perfumers. The odor thresholds were determined by GC–olfactometry. Different dilutions of the sample substances were injected into a gas chromatograph in descending order until the panelist failed to detect an odor at the correct retention time. The reported values are geometrical means of the individual odor thresholds of different panelists.

1-Methyl-7-oxabicyclo[4.1.0]heptan-2-one (10)

At r.t., 2 N aq NaOH (7.00 mL, 14.0 mmol), followed by 30% aq H_2O_2 (11.0 mL, 112 mmol) were added to a stirred soln of commercially available 2-methylcyclohex-2-enone (**8**; 2.20 g, 20.0 mmol) in MeOH (250 mL), upon which the resulting red color of the soln faded within 10 min. After stirring at r.t. for 24 h, the reaction mixture was diluted with H_2O (200 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were washed with H_2O (200 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the resulting residue was purified by chromatography (silica gel, 40 g, pentane–Et_2O, 9:1); this furnished **10**.

Yield: 1.18 g (47%); colorless liquid; R_f = 0.29 (pentane–Et_2O, 9:1).

IR (neat): 1703 (C=O), 1439, 1378 (CH_3), 1276, 891, 811 (C–O–C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 3 H, 2-Me), 1.68 (m, 1 H, 5-H$_{ax}$), 1.97–2.12 (m, 3 H, 4-H$_2$, 5-H$_{eq}$), 2.22 (m, 1 H, 6-H$_{eq}$), 2.56 (m, 1 H, 6-H$_{ax}$), 3.41 (dd, *J* = 3.5, 3.5 Hz, 1 H, 3-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4 (q, 2-Me), 18.3 (t, C-5), 23.3 (t, C-4), 36.4 (t, C-6), 59.4 (s, C-2), 62.7 (d, C-3), 206.6 (s, C-1).

MS (EI, 70 eV): *m*/*z* (%) = 43 (100) [$C_2H_3O^+$], 55 (50) [$C_3H_3O^+$], 71 (58) [$C_4H_7O^+$], 82 (26) [$M^+ - C_2H_4O$], 98 (3) [$M^+ - CO$], 108 (1) [$M^+ - H_2O$], 111 (3) [$M^+ - CH_3$], 126 (27) [M^+].

Hept-5-ynal (12)

At –10 °C, H_2NNHTs (6.14 g, 33.0 mmol) was added portionwise to a stirred soln of the 2,3-epoxy ketone **10** (3.78 g, 30.0 mmol) in AcOH–CH_2Cl_2 (1:1, 80 mL). The reaction mixture was allowed to warm up slowly. At 10 °C, GC monitoring indicated complete conversion, whereupon crushed ice (20 g) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic solns were neutralized with ice-cold sat. aq $NaHCO_3$. After drying (Na_2SO_4) and removal of the solvent under reduced pressure, chromatography of the resulting residue (silica gel, 50 g, pentane–Et_2O–Et_3N, 3:1:0.01) afforded **12**.

Yield: 1.74 g (53%); colorless liquid; R_f = 0.48 (pentane–Et_2O, 5:1).

IR (neat): 1723 (HC=O), 1437 (CH_3), 1352 (CH_3) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.77 (t, *J* = 2.5 Hz, 3 H, 7-H_3), 1.80 (quin, *J* = 7.0 Hz, 2 H, 3-H_2), 2.20 (qt, *J* = 2.5, 7.0 Hz, 2 H, 4-H_2), 2.57 (dt, *J* = 1.5, 7.0 Hz, 2 H, 2-H_2), 9.80 (t, *J* = 1.5 Hz, 1 H, 1-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.4 (q, C-7), 18.5 (t, C-4), 21.4 (t, C-3), 42.8 (t, C-2), 75.9 (s, C-6), 78.6 (s, C-5), 202.1 (s, C-1).

MS (EI, 70 eV): *m*/*z* (%) = 44 (5) [$C_2H_4O^+$], 53 (62) [$C_4H_5^+$], 66 (63) [$C_5H_6^+$], 68 (100) [$M^+ – C_2H_2O$], 82 (27) [$M^+ – CO$], 95 (10) [$M^+ – CH_3$], 109 (2) [$M^+ – H$], 110 (1) [M^+].

Oct-6-ynal (13)

Alkynal **13** was synthesized as follows, according to a synthetic scheme of Herndon and co-workers,[27] with additional THP protection during the methylation step. PTSA·H_2O (300 mg, 1.58 mmol) was added to a stirred soln of commercially available hex-5-yn-1-ol (**16**, 15.2 g, 155 mmol) and DHP (29.8 mL, 232 mmol) in CH_2Cl_2 (150 mL) at 0 °C. The cooling bath was removed and stirring continued for 5 h, prior to addition of H_2O (100 mL) and separation of the layers. The organic layer was washed with H_2O (50 mL) and brine (50 mL), and the combined aqueous solns were re-extracted with CH_2Cl_2 (100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude brownish product (40.2 g) was taken up in THF (500 mL), and 1.6 M BuLi in THF (136 mL, 218 mmol) was added dropwise at –78 °C. After the mixture had stirred for 2 h at –40 °C, it was cooled to –78 °C, and MeI (15.4 mL, 248 mmol) was added. The cooling bath was removed, and stirring continued overnight at r.t. After quenching of the mixture with H_2O (500 mL), the product was extracted with Et_2O (2 × 500 mL). The combined organic extracts were washed with sat. aq NH_4Cl (500 mL), dried (Na_2SO_4), and concentrated under reduced pressure, and the resulting brownish residue was dissolved in MeOH (250 mL). PPTS (370 mg, 1.47 mmol) was added, and the reaction mixture was stirred at r.t. overnight; then sat. aq NH_4Cl (150 mL) was added, and the mixture was extracted with Et_2O (4 × 400 mL). The combined organic extracts were washed with sat. aq NH_4Cl (400 mL) and dried (Na_2SO_4). After removal of the solvent under reduced pressure, chromatography of the resulting residue (silica gel, 400 g, pentane–Et_2O, 4:1) afforded hept-5-yn-1-ol (**17**).

Yield: 10.6 g (61%); colorless liquid; R_f = 0.06 (pentane–Et_2O, 4:1).

MsCl (9.50 mL, 123 mmol) was added dropwise to a stirred soln of alkynol **17** (10.6 g, 94.5 mmol) and Et_3N (19.8 mL, 142 mmol) in Et_2O (150 mL) at 0 °C. The cooling bath was removed, and the reaction mixture was stirred overnight. H_2O (150 mL) was added, and the organic layer was separated and washed with H_2O (2 × 100 mL) and sat. aq NH_4Cl (50 mL). The combined aqueous solns were re-extracted with Et_2O (100 mL), and the organic extracts were combined, dried (Na_2SO_4), and concentrated under reduced pressure. KCN (9.23 g, 142 mmol) was added to the soln of the crude mesylation product (19.0 g) in DMF (250 mL), and the resulting suspension was refluxed for 3.5 h. After the mixture had cooled, the precipitate was dissolved by the addition of H_2O; then brine (20 mL) was added, and the mixture was extracted with Et_2O (5 × 200 mL). The combined organic extracts were washed with brine (200 mL) and sat. aq $FeSO_4$ (200 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography of the resulting residue (silica gel, 150 g, pentane–Et_2O, 5:1) provided oct-6-ynenitrile (**18**).

Yield: 7.90 g (69%); colorless liquid; R_f = 0.35 (pentane–Et_2O, 4:1).

A 1 M soln of DIBAL-H in hexane (97.8 mL, 97.8 mmol) was added dropwise to a stirred soln of nitrile **18** (7.90 g, 65.2 mmol) in THF (150 mL) at 0 °C. The cooling bath was removed and the mixture was stirred overnight at r.t., prior to being poured into ice-cold sat. aq tartaric acid (50 mL). Further tartaric acid was added with stirring until the precipitate dissolved completely, and the product was extracted with Et_2O (3 × 200 mL). After drying of the mixture (Na_2SO_4), the solvent was removed under reduced pressure; this provided alkynal **13** without further purification being necessary (GC).

Yield: 6.70 g (83%); colorless liquid.

IR (neat): 1723 (HC=O), 1439 (CH_3), 1356 (CH_3) cm^{-1}.

^1H NMR (400 MHz, benzene-d_6): δ = 1.21 (quin, *J* = 7.0 Hz, 2 H, 4-H_2), 1.38 (quin, *J* = 7.0 Hz, 2 H, 3-H_2), 1.55 (t, *J* = 2.5 Hz, 3 H, 8-H_3), 1.73 (dt, *J* = 1.5, 7.0 Hz, 2 H, 2-H_2), 1.94 (qt, *J* = 2.5, 7.0 Hz, 2 H, 5-H_2), 9.25 (t, *J* = 1.5 Hz, 1 H, 1-H).

^{13}C NMR (100 MHz, benzene-d_6): δ = 3.1 (q, C-8), 18.5 (t, C-5), 21.1 (t, C-3), 28.4 (t, C-4), 43.0 (t, C-2), 75.7 (s, C-7), 78.6 (s, C-6), 200.2 (s, C-1).

MS (EI, 70 eV): *m*/*z* (%) = 44 (5) [$C_2H_4O^+$], 53 (100) [$C_4H_5^+$], 79 (84) [$M^+ – C_2H_5O$], 91 (33) [$M^+ – H_2O – CH_3$], 106 (7) [$M^+ – H_2O$], 109 (32) [$M^+ – CH_3$], 123 (7) [$M^+ – H$], 124 (2) [M^+].

(3*E*)-Non-3-en-7-ynoic Acid (14)

A piperidinium acetate soln, freshly prepared by mixing of piperidine (35.0 μL, 0.354 mmol) and AcOH (19.0 μL, 0.332 mmol) in DMSO (1.00 mL), was injected into a stirred soln of aldehyde **12** (1.50 g, 13.6 mmol) and malonic acid (2.83 g, 27.2 mmol) in DMSO (50 mL) at r.t. After the reaction mixture had refluxed for 4 h, H_2O (10 mL) and Et_2O (20 mL) were added at r.t., and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 25 mL), and the combined organic extracts were washed with H_2O (25 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Kugelrohr distillation (149 °C/14 mbar) furnished acid **14**.

Yield: 902 mg (44%); Δ^3/Δ^2 = 98:2 (GC); colorless crystals; mp 43–45 °C.

IR (neat): 2916 (O–H), 1691 (C=O), 1335 (CH_3), 969 (C=C, *trans*) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.77 (t, *J* = 2.5 Hz, 3 H, 9-H_3), 2.18–2.24 (m, 4 H, 5-, 6-H_2), 3.10 (dd, *J* = 1.0, 6.0 Hz, 2 H, 2-H_2), 5.54–5.70 (m, 2 H, 3-, 4-H), 11.36 (br s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.4 (q, C-9), 18.8 (t, C-6), 32.0 (t, C-5), 37.7 (t, C-2), 76.1 (s, C-8), 78.3 (s, C-7), 122.0 (d, C-3), 133.6 (d, C-4), 178.5 (s, C-1).

MS (EI, 70 eV): *m*/*z* (%) = 45 (20) [CO_2H^+], 53 (100) [$C_4H_5^+$], 57 (89) [$C_4H_9^+$], 60 (7) [$CH_3CO_2H^+$], 79 (33) [$C_6H_7^+$], 92 (42) [$M^+ – CH_3CO_2H$], 93 (97) [$M^+ – CH_3CO_2$], 99 (3) [$M^+ – C_4H_5$], 107 (68) [$M^+ – CO_2H$], 124 (2) [$M^+ – CO$], 137 (3) [$M^+ – CH_3$], 151 (7) [$M^+ – H$], 152 (1) [M^+].

(3*E*)-Dec-3-en-8-ynoic Acid (15)

In analogy to the synthesis of **14** from **12**, acid **15** was prepared from **13** (6.70 g, 54.0 mmol), malonic acid (11.2 g, 108 mmol), DMSO (200 mL), and freshly prepared piperidinium acetate (160 mg, 1.10 mmol) in DMSO (5.00 mL). The crude material [Δ^3/Δ^2 = 70:30 (GC)] was purified by chromatography (silica gel, 200 g, pentane–Et_2O, 4:1) and subsequent Kugelrohr distillation (160 °C/13 mbar) to afford **15**.

Yield: 3.79 g (42%); colorless crystalline solid; mp 40–43 °C; R_f = 0.24 (pentane–Et_2O, 5:1).

IR (neat): 2937, 2860 (O–H), 1689 (C=O), 1347 (CH_3), 964 (C=C, *trans*) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.56 (quin, *J* = 7.0 Hz, 2 H, 6-H_2), 1.78 (t, *J* = 2.5 Hz, 3 H, 10-H_3), 1.99–2.18 (m, 4 H, 5-, 7-H_2), 3.08 (ddd, *J* = 1.0, 1.0, 6.0 Hz, 2 H, 2-H_2), 5.50–5.63 (m, 2 H, 3-, 4-H), 11.34 (br s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.4 (q, C-10), 18.1 (t, C-7), 28.3 (t, C-6), 31.5 (t, C-5), 37.8 (t, C-2), 75.7 (s, C-9), 78.8 (s, C-8), 121.5 (d, C-3), 134.4 (d, C-4), 178.8 (s, C-1).

MS (EI, 70 eV): *m*/*z* (%) = 41 (100) [$C_3H_5^+$], 45 (24) [CO_2H^+], 53 (68) [$C_4H_5^+$], 60 (7) [$CH_3CO_2H^+$], 66 (39) [$C_5H_6^+$], 70 (40) [$C_5H_{10}^+$], 93 (68) [$C_7H_9^+$], 106 (59) [$M^+ - CH_3CO_2H$], 112 (9) [$C_6H_8O_2^+$], 121 (28) [$M^+ - CO_2H$], 133 (3) [$M^+ - H_2O - CH_3$], 138 (2) [$M^+ - C_2H_4$], 147 (1) [$M^+ - H - H_2O$], 151 (5) [$M^+ - CH_3$], 165 (2) [$M^+ - H$], 166 (1) [M^+].

3-Methyloct-6-yn-1-ol (20)

Alkynol **20** was synthesized as follows, according to ref. 30a. $NaNO_2$ (93.2 g, 135 mmol) was added portionwise, within 90 min, to a vigorously stirred soln of *rac*-citronellol (**19**; 7.81 g, 50.0 mmol) in AcOH–H_2O (5:2, 210 mL) at 0–6 °C; this resulted in a large amount of gas (NO_x) and lather being produced. The reaction mixture was stirred for 1 h at 0 °C, then the cooling bath was removed, and stirring continued at r.t. for 1 d. The reaction mixture was then heated to 54 °C for 1 d, and again stirred for 1 d at r.t., after which it was poured into H_2O (500 mL), and extracted with EtOAc (2 × 200 mL). The combined organic extracts were washed with H_2O (200 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (silica gel, 250 g, pentane–Et_2O, 2:1) provided alkynol **20**.

Yield: 1.80 g (26%); colorless liquid; R_f = 0.25 (pentane–Et_2O, 2:1).

IR (neat): 3337 (O–H), 1378 (CH_3) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.5 Hz, 3 H, 3-Me), 1.29–1.47 (m, 2 H, 2-, 4-H_b), 1.48–1.63 (m, 2 H, 2-, 4-H_a), 1.70 (m, 1 H, 3-H), 1.77 (t, *J* = 2.5 Hz, 3 H, 8-H_3), 2.11–2.25 (m, 2 H, 5-H_2), 3.70 (m, 2 H, 1-H_2), 6.51 (br s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.4 (q, C-8), 16.3 (t, C-5), 19.1 (q, 3-Me), 20.7 (d, C-3), 36.2 (t, C-2), 39.3 (t, C-4), 60.9 (t, C-1), 75.4 (s, C-7), 79.1 (s, C-6).

MS (EI, 70 eV): *m*/*z* (%) = 31 (23) [CH_3O^+], 41 (100) [$C_3H_5^+$], 67 (75) [$C_5H_7^+$], 68 (67) [$C_5H_8^+$], 95 (54) [$C_7H_{11}^+$], 107 (67) [$M^+ - H_2O$], 125 (6), [$M^+ - CH_3$], 140 (1) [M^+].

(3*E*)-3′-Methyloct-6′-ynyl Non-3-en-7-ynoate (21)

DMAP (68.4 mg, 0.559 mmol) was added to a stirred soln of acid **14** (850 mg, 5.59 mmol) and alcohol **20** (790 mg, 5.59 mmol) in Et_2O (20 mL) at r.t. At 0 °C, DCC (1.27 g, 6.14 mmol) was added, and the reaction mixture was stirred for 5 min at this temperature, upon which a colorless precipitate formed. This insoluble material was removed by suction filtration on a sintered-glass funnel, and the filtrate was concentrated under reduced pressure. Chromatography of the residue from the filtrate (silica gel, 50 g, pentane–Et_2O, 20:1) afforded **21**.

Yield: 470 mg (31%); colorless liquid; R_f = 0.65 (pentane–Et_2O, 5:1).

IR (neat): 1734 (OC=O), 967 (C=C, *trans*) cm^{-1}.

^1H NMR (400 MHz, benzene-d_6): δ = 0.70 (d, *J* = 6.5 Hz, 3 H, 3′-Me), 1.14–1.26 (m, 2 H, 2′-, 4′-H_b), 1.36–1.52 (m, 2 H, 2′-, 4′-H_a), 1.55 (m, 1 H, 3′-H), 1.56 (t, *J* = 2.5 Hz, 3 H, 8′-H_3), 1.59 (t, *J* = 2.5 Hz, 3 H, 9-H_3), 1.97–2.14 (m, 6 H, 5-, 5′-, 6-H_2), 2.88 (dd, *J* = 1.0, 6.0 Hz, 2 H, 2-H_2), 4.01 (m, 2 H, 1′-H_2), 5.47 (ttd, *J* = 1.0, 6.5, 15.5 Hz, 1 H, 4-H), 5.64 (ttd, *J* = 1.0, 6.0, 15.5 Hz, 1 H, 3-H).

^{13}C NMR (100 MHz, benzene-d_6): δ = 3.1 (2q, C-9, -8′), 16.5 (t, C-6), 18.7 (q, 3′-Me), 19.0 (t, C-5′), 29.1 (d, C-3′), 32.2 (t, C-5), 35.2 (t, C-2′), 36.1 (t, C-4′), 38.0 (t, C-2), 62.5 (t, C-1′), 75.4 (s, C-7′), 75.8 (s, C-8), 78.5 (s, C-7), 79.0 (s, C-6′), 123.3 (d, C-3), 132.6 (d, C-4), 170.8 (s, C-1).

MS (EI, 70 eV): *m*/*z* (%) = 41 (55) [$C_3H_5^+$], 53 (76) [$C_4H_5^+$], 60 (2) [$CH_3CO_2H^+$], 67 (50) [$C_5H_7^+$], 81 (100) [$C_6H_9^+$], 93 (60) [$C_7H_9^+$], 107 [$C_{10}H_{16}O_2^+ - CO_2H$], 121 (44) [$C_9H_{13}^+$], 124 (34) [$C_{10}H_{14}O_2^+ - C_3H_6$], 147 (7) [$C_9H_{11}O^+$], 207 (1) [$M^+ - C_5H_7$], 259 (1) [$M^+ - CH_3$], 274 (1) [$M^+$].

Anal. Calcd for $C_{18}H_{26}O_2$ (274.40): C, 78.79; H, 9.55. Found: C, 78.82; H, 9.48.

(3*E*)-3′-Methyloct-6′-ynyl Dec-3-en-8-ynoate (22)

In analogy to the synthesis of **21** from **14** and **20**, ester **22** was prepared from **15** (1.66 g, 9.99 mmol), **20** (1.40 g, 9.99 mmol), DMAP (122 mg, 1.00 mmol), and DCC (2.27 g, 11.0 mmol) in Et_2O (30 mL). Chromatography (silica gel, 50 g, pentane–Et_2O, 20:1) afforded **22**.

Yield: 1.34 g (47%); colorless liquid; R_f = 0.50 (pentane–Et_2O, 10:1).

IR (neat): 1735 (OC=O), 968 (C=C, *trans*) cm^{-1}.

^1H NMR (500 MHz, benzene-d_6): δ = 0.49 (d, *J* = 7.0 Hz, 3 H, 3′-Me), 1.17 (m, 1 H, 4′-H_b), 1.20 (m, 1 H, 2′-H_b), 1.40 (m, 1 H, 4′-H_a), 1.44 (m, 1 H, 2′-H_a), 1.46 (quin, *J* = 7.0 Hz, 2 H, 6-H_2), 1.55 (t, *J* = 2.5 Hz, 3 H, 8′-H_3), 1.56 (m, 1 H, 3′-H), 1.57 (t, *J* = 2.5 Hz, 3 H, 10-H_3), 1.99 (m, 2 H, 5-H_2), 2.02 (m, 2 H, 5′-H_2), 2.04 (m, 2 H, 7-H_2), 2.86 (dd, *J* = 1.0, 7.0 Hz, 2 H, 2-H_2), 4.01 (m, 2 H, 1′-H_2), 5.31 (ttd, *J* = 1.0, 7.0, 15.5 Hz, 1 H, 4-H), 5.61 (ttd, *J* = 1.0, 7.0, 15.5 Hz, 1 H, 3-H).

^{13}C NMR (125 MHz, benzene-d_6): δ = 3.3 (q, C-10), 3.4 (q, C-8′), 16.7 (t, C-7), 18.4 (t, C-5′), 18.9 (q, 3′-Me), 28.8 (t, C-6), 29.3 (d, C-3′), 31.8 (t, C-5), 35.4 (t, C-2′), 36.3 (t, C-4′), 38.3 (t, C-2), 62.8 (t, C-1′), 75.6 (s, C-7′), 75.8 (s, C-9), 79.1 (s, C-8), 79.2 (s, C-6′), 123.2 (d, C-3), 133.5 (d, C-4), 171.2 (s, C-1).

MS (EI, 70 eV): *m*/*z* (%) = 41 (80) [$C_3H_5^+$], 55 (80) [$C_4H_7^+$], 60 (1) [$CH_3CO_2H^+$], 67 (69) [$C_5H_7^+$], 81 (100) [$C_6H_9^+$], 93 (59) [$C_7H_9^+$], 121 (44) [$C_9H_{13}^+$], 124 (34) [$C_{10}H_{14}O_2^+ - C_3H_6$], 149 (7) [$C_{10}H_{13}O^+$], 166 (7) [$C_{10}H_{14}O_2^+$], 273 (1) [$M^+ - CH_3$].

Anal. Calcd for $C_{19}H_{28}O_2$ (288.43): C, 79.12; H, 9.78. Found: C, 79.13; H, 9.77.

(4*E*)-12-Methyloxacyclotetradec-4-en-8-yn-2-one (23)

A soln of **21** (350 mg, 1.28 mmol) in absolute PhCl (120 mL) was degassed with argon for 15 min, prior to the addition of Schrock's alkylidyne catalyst [*t*-BuC≡W(O*t*-Bu)$_3$][34] (60.5 mg, 0.128 mmol). With a slow flow of argon bubbling through, the resulting mixture was refluxed for 24 h and then allowed to cool to r.t. The solvent was removed under reduced pressure, and the resulting residue was purified by chromatography (silica gel, 50 g, pentane–Et_2O, 1:1); this provided **23**.

Yield: 220 mg (78%); colorless liquid; R_f = 0.55 (pentane–Et_2O, 5:1).

IR (neat): 1731 (OC=O), 966 (C=C, *trans*) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.5 Hz, 3 H, 12-Me), 1.19 (m, 1 H, 13-H_b), 1.29–1.47 (m, 2 H, 11-H_b, 13-H_a), 1.68 (m, 1 H, 11-H_a), 2.02 (m, 1 H, 12-H), 2.13–2.33 (m, 6 H, 6-, 7-, 10-H_2), 3.00 (ddd, *J* = 1.5, 7.0, 14.0 Hz, 1 H, 3-H_b), 3.05 (ddd, *J* = 1.5, 7.0, 14.0 Hz, 1 H, 3-H_a), 4.21–4.24 (m, 2 H, 14-H_2), 5.56 (ttd, *J* = 1.5, 7.0, 15.0 Hz, 1 H, 5-H), 5.64 (ttd, *J* = 1.5, 7.0, 15.0 Hz, 1 H, 4-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0 (t, C-7), 18.1 (t, C-10), 18.5 (q, 12-Me), 25.3 (d, C-12), 31.4 (t, C-6), 34.6 (t, C-13), 35.2 (t, C-11), 39.4 (t, C-3), 61.2 (t, C-14), 79.8 (s, C-9), 80.0 (s, C-8), 123.7 (d, C-4), 132.5 (d, C-5), 171.6 (s, C-2).

MS (EI, 70 eV): *m*/*z* (%) = 41 (39) [$C_3H_5^+$], 60 (1) [$CH_3CO_2H^+$], 99 (2) [$C_7H_{15}^+$], 160 (2) [$M^+ - C_2H_4O_2$], 178 (100) [$M^+ - C_2H_2O$], 205 (1) [$M^+ - CH_3$], 220 (1) [M^+].

(4*E*)-13-Methyloxacyclopentadec-4-en-9-yn-2-one (24)

In analogy to the synthesis of **23** from **21**, macrocycle **24** was prepared from **22** (435 mg, 1.51 mmol) and Schrock's alkylidyne catalyst [*t*-BuC≡W(O*t*-Bu)$_3$][34] (71.3 mg, 0.151 mmol) in absolute PhCl (80 mL). Purification by chromatography (silica gel, 50 g, pentane–Et_2O, 50:1) provided **24**.

Yield: 150 mg (42%); colorless liquid; R_f = 0.44 (pentane–Et_2O, 5:1).

IR (neat): 1733 (OC=O), 968 (C=C, *trans*) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.5 Hz, 3 H, 13-Me), 1.24 (m, 1 H, 12-H_b), 1.35 (m, 1 H, 14-H_b), 1.41–1.61 (m, 3 H, 7-H_2, 12-H_a), 1.72 (ttd, *J* = 3.5, 10.5, 14.5 Hz, 1 H, 14-H_a), 1.93 (m, 1 H, 13-H), 2.09–2.31 (m, 6 H, 6-, 8-, 11-H_2), 3.03 (ddd, *J* = 1.5, 2.5, 6.5 Hz, 2 H, 3-H_2), 4.19 (dd, *J* = 3.5, 10.5 Hz, 1 H, 15-H_b), 4.23 (dd, *J* = 3.5, 10.5 Hz, 1 H, 15-H_a), 5.50 (ttd, *J* = 1.5, 7.0, 15.0 Hz, 1 H, 5-H), 5.67 (ttd, *J* = 1.5, 7.0, 15.0 Hz, 1 H, 4-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.4 (t, C-11), 17.0 (t, C-8), 18.5 (q, 13-Me), 25.5 (t, C-7), 26.7 (d, C-13), 30.3 (t, C-6), 35.7 (t, C-14), 35.9 (t, C-12), 39.0 (t, C-3), 62.0 (t, C-15), 79.7 (s, C-10), 80.2 (s, C-9), 123.8 (d, C-4), 132.5 (d, C-5), 171.7 (s, C-2).

MS (EI, 70 eV): *m*/*z* (%) = 41 (91) [$C_3H_5^+$], 60 (1) [$CH_3CO_2H^+$], 91 (100) [$C_7H_7^+$], 99 (6) [$C_7H_{15}^+$], 178 (11) [$C_{13}H_{22}^+$], 192 (66) [$M^+ - C_2H_2O$], 206 (16) [M^+ – CO], 219 (2) [$M^+ - CH_3$], 234 (1) [M^+].

(4*E*,8*Z*)-12-Methyloxacyclotetradeca-4,8-dien-2-one (6)

Quinoline (27.5 μL, 0.232 mmol) and 10% Pd/$BaSO_4$ (4.90 mg, 0.0461 mmol) were added to a stirred soln of **23** (256 mg, 1.16 mmol) in EtOH (20 mL). The reaction flask was flushed with argon followed by H_2, and the reaction mixture was stirred under an H_2 atmosphere at r.t. and ambient pressure. After 5 h, GC monitoring indicated complete conversion, upon which the catalyst was removed by filtration of the mixture through a pad of Celite®, which was washed with EtOH. The solvent was removed from the filtrate under reduced pressure, and the resulting residue was purified by chromatography (silica gel, 30 g, pentane–Et_2O, 20:1) to furnish **6**.

Yield: 223 mg (86%); colorless, odoriferous liquid; R_f = 0.60 (pentane–Et_2O, 5:1).

Odor description: powerful, warm-metallic, powdery musk odor with herbaceous and floral facets as well as a strong hot-iron inclination; odor threshold: 2.4 ng/L air.

IR (neat): 1732 (OC=O), 967 (C=C, *trans*), 714 (C=C, *cis*) cm^{-1}.

^1H NMR (500 MHz, benzene-d_6): δ = 0.77 (d, *J* = 6.5 Hz, 3 H, 12-Me), 1.07 (dddd, *J* = 3.0, 5.5, 6.5, 10.5 Hz, 1 H, 13-H_b), 1.09 (dt, *J* = 6.5, 7.0 Hz, 1 H, 11-H_b), 1.28 (dt, *J* = 6.5, 7.0 Hz, 1 H, 11-H_a), 1.40 (dddd, *J* = 3.0, 6.5, 9.5, 10.5 Hz, 1 H, 13-H_a), 1.48 (ttq, *J* = 6.5, 6.5, 6.5 Hz, 1 H, 12-H), 1.90 (td, *J* = 7.0, 7.0, 2 H, 6-H_2), 1.94 (td, *J* = 7.0, 7.5 Hz, 2 H, 10-H_2), 1.99 (td, *J* = 7.0, 7.5, 2 H, 7-H_2), 2.74 (d, *J* = 6.5 Hz, 2 H, 3-H_2), 4.01 (ddd, *J* = 3.0, 9.5, 11.5 Hz, 1 H, 14-H_b), 4.10 (ddd, *J* = 3.0, 5.5, 11.5 Hz, 1 H, 14-H_a), 5.21 (ttd, *J* = 1.0, 7.5, 11.0 Hz, 1 H, 8-H), 5.31 (ttd, *J* = 1.0, 6.5, 15.5 Hz, 1 H, 4-H), 5.37 (ttd, *J* = 1.0, 7.5, 11.0 Hz, 1 H, 9-H), 5.48 (ttd, *J* = 1.0, 7.0, 15.5 Hz, 1 H, 5-H).

^{13}C NMR (125 MHz, benzene-d_6): δ = 19.9 (q, 12-Me), 24.9 (t, C-10), 27.9 (t, C-7), 29.1 (d, C-12), 31.8 (t, C-6), 35.3 (t, C-13), 36.7 (t, C-11), 38.6 (t, C-3), 62.2 (t, C-14), 122.9 (d, C-4), 129.6 (d, C-8), 131.0 (d, C-9), 134.1 (d, C-5), 170.8 (s, C-2).

MS (EI, 70 eV): *m*/*z* (%) = 41 (41) [$C_3H_5^+$], 54 (62) [$C_4H_6^+$], 60 (2) [$CH_3CO_2H^+$], 67 (58) [$C_5H_7^+$], 81 (100) [$C_6H_9^+$], 95 (17) [$C_7H_{11}^+$], 107 (16) [$C_8H_{11}^+$], 123 (15) [$C_9H_{15}^+$], 149 (6) [$C_{11}H_{17}^+$], 162 (7) [$M^+ - CH_3COOH$], 194 (1) [M^+ – CO], 204 (1) [$M^+ - H_2O$], 222 (2) [M^+].

Anal. Calcd for $C_{14}H_{22}O_2$ (222.33): C, 75.63; H, 9.97. Found: C, 75.67; H, 9.96.

(4*E*,9*Z*)-13-Methyloxacyclopentadeca-4,9-dien-2-one (7)

In analogy to the synthesis of **6** from **23**, macrocyclic diene lactone **7** was prepared from **24** (48.2 mg, 206 μmol), quinoline (4.86 μL, 41.1 μmol), and 10% Pd/$BaSO_4$ (0.88 mg, 8.24 μmol) in EtOH (2.0 mL). After 3.5 h, GC monitoring indicated complete conversion. Purification by chromatography (silica gel, 20 g, pentane–Et_2O, 10:1) furnished **7**.

Yield: 44.8 mg (92%); colorless, odoriferous liquid; R_f = 0.78 (pentane–Et_2O, 5:1).

Odor description: intense, pleasant, sweet, aromatic-powdery musk odor with floral facets in the direction of jasmine and slightly green aspects; odor threshold: 0.42 ng/L air.

IR (neat): 1733 (OC=O), 968 (C=C, *trans*), 696 (C=C, *cis*) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.5 Hz, 3 H, 13-Me), 1.20–1.44 (m, 2 H, 12-, 14-H_b), 1.46–1.63 (m, 3 H, 7-H_2, 12-H_a), 1.72 (m, 1 H, 14-H_a), 1.95–2.12 (m, 7 H, 6-, 8-, 11-H_2, 13-H), 3.03 (ddd, *J* = 1.0, 1.0, 6.5 Hz, 2 H, 3-H_2), 4.12 (ddd, *J* = 3.0, 9.5, 11.5 Hz, 1 H, 15-H_b), 4.21 (ddd, *J* = 3.0, 6.0, 11.5 Hz, 1 H, 15-H_a), 5.28 (ttd, *J* = 1.0, 6.5, 11.0 Hz, 1 H, 5-H), 5.38 (ttd, *J* = 1.0, 6.5, 11.0 Hz, 1 H, 4-H), 5.41–5.53 (m, 2 H, 9-, 10-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7 (q, 13-Me), 24.2 (t, C-11), 25.6 (t, C-7), 27.4 (t, C-8), 29.9 (d, C-13), 30.1 (t, C-6), 34.8 (t, C-14), 36.5 (t, C-12), 39.2 (t, C-3), 62.9 (t, C-15), 123.1 (d, C-4), 129.7 (d, C-9), 130.8 (d, C-5), 133.9 (d, C-10), 172.0 (s, C-2).

MS (EI, 70 eV): *m*/*z* (%) = 41 (72) [$C_3H_5^+$], 60 (2) [$CH_3CO_2H^+$], 67 (89) [$C_5H_7^+$], 81 (100) [$C_6H_9^+$], 176 (5) [$M^+ - CH_3COOH$], 203 (1) [$M^+ - H_2O - CH_3$], 208 (1) [M^+ – CO], 218 (1) [$M^+ - H_2O$], 236 (2) [M^+].

Anal. Calcd for $C_{15}H_{24}O_2$ (236.35): C, 76.23; H, 10.23. Found: C, 76.30; H, 10.30.

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