Constructing Conformationally Constrained Macrobicyclic Musks

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Abstract: To investigate the structure–odor correlation of musks, (12*R*)-12-methyl-13-tridecanolide (**1**), a macrocyclic musk, and 13-tridecanolide, its nonmusky demethyl analogue, were conformationally constrained by introduction of methylene bridges between C-3 and C-8 or C-9. These [7.5.1]- and [8.4.1]-macrobicycles were synthesized starting from bicyclo[5.3.1]undec-8-en-9-one (**3**) and bicyclo[4.3.1]dec-7-en-8-one (**8**), respectively, by a sequence consisting of catalytic hydrogenation, α-alkylation with a TBS-protected (*tert*-butyldimethylsilyl) hydroxy halide, acid-catalyzed cyclization, oxidative cleavage of the formed enol ether double bond, and subsequent reduction of the carbonyl group via its tosylhydrazone. The compound (1*R*,6*R*,9*R*)-(+)-6-methyl-4-oxabicyclo[7.5.1]pentadecan-3-one (**22**) was found to possess the most pronounced musk odor, and this was rationalized by a superposition analysis with the polycyclic aromatic musk odorant (4*S*,7*R*)-Galaxolide (**2**). In its (1*S*,6*R*,9*S*)-(+)-stereoisomer **23** as well as in (1*S*,6*R*,10*R*)-(+)-6-methyl-4-oxabicyclo[8.4.1]-pentadecan-3-one (**18**) the (6*R*)-methyl group seems to hinder the interaction with the musk receptor, while the demethyl compounds **7** and **12** showed only very faint odors.

Keywords: conformation analysis · fragrances · macrocycles · molecular modeling · structure–activity relationships

Introduction

One of the most important problems in the design of macrocyclic musks is their conformational flexibility. It is certainly true that in this substance class an inexpensive synthesis is as important for commercial success as the odor characteristics,[1–4] yet for more intense compounds one can afford more complex synthetic approaches. Knowledge of the active conformations of these compounds would obviously facilitate the design of new potent macrocylic musk odorants. Furthermore, this knowledge could explain the odor similarities of macrocyclic and polycyclic musks,[5] and enable the creation of new classes of musk odorants, for example, linear aliphatic compounds,[1] which might turn out to be much cheaper to produce than the parent macrocyclic compounds. However, nothing is known about the active conformers of macrocyclic musk odorants.

To obtain some information about the active conformations of macrocycles their conformational freedom must be restricted, and this can be best achieved by introducing bridges, that is, by constructing macrobicycles. Methylene bridges seem to be ideally suited since they effectively confine the compounds to a few energetically different conformers and they do not increase the molecular weight too much. We chose (12*R*)-(+)-12-methyl-13-tridecanolide (**1**), a natural constituent of Angelica root oil,[6] *Angelica archangelica* L., as the target molecule for the introduction of methylene bridges. This compound (**1**) possesses a clean musk odor accompanied by strong sandalwood accents and a slight fruity undertone of pear,[7] while its enantiomer differs unambiguously with a more camphoraceous, animal-like musk note, and 13-tridecanolide is not musky at all.[8] The conformation of the 14-membered ring as well as the configuration of the methyl-bearing carbon atom are therefore crucial for its odor characteristics. This and its low molecular weight, which allows the introduction of bridges without exceeding the mass boundaries of macrocyclic musk odorants (ca. 286 u),[9] make (12*R*)-(+)-12-methyl-13-tridecanolide (**1**) especially suitable for conformation–odor correlation studies.

Conformational considerations: Compounds with 14-membered rings are the conformationally most restricted amongst the medium and large rings, and they exist largely in a [3434] rectangular diamond-lattice conformation.[10] X-ray crystallographic studies of cyclotetradecane,[11] cyclotetradecanone,[12] cyclotetradecane oxime,[13] 1,3,8,10-tetraoxacyclotetradecane,[14] and 13-tridecanolide[15] prove the preference for the [3434] conformation as lowest-energy conformer. A recent conformation analysis of methyl-substituted 14-membered macrocycles by DNMR (Dynamic Nuclear Magnetic Resonance) spectroscopy also confirmed the preference for [3434] conformations in solution.[16]

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Figure 1 shows the six lowest-energy conformations of (12*R*)-12-methyl-13-tridecanolide (**1**) as calculated by a *Low-Mode* molecular mechanics search with *MacroModel* 7.0 with the MM3* force field.[17] The conformations are designated according to the Dale system[10] with the extension of Clyne and Weiler,[16] which marks the oxa-position. The [3434]-1 conformation was found to be at the global energy minimum; however, the energy gap to the first [3344] conformer is just 0.43 kcal mol^{-1}. While the shape and relative position of the 12-methyl group of the [3434]-1 and the [3344]-1 conformer are quite similar, the other [3434] conformers are rather different, especially with regard to the odor-determining (12*R*)-methyl group.

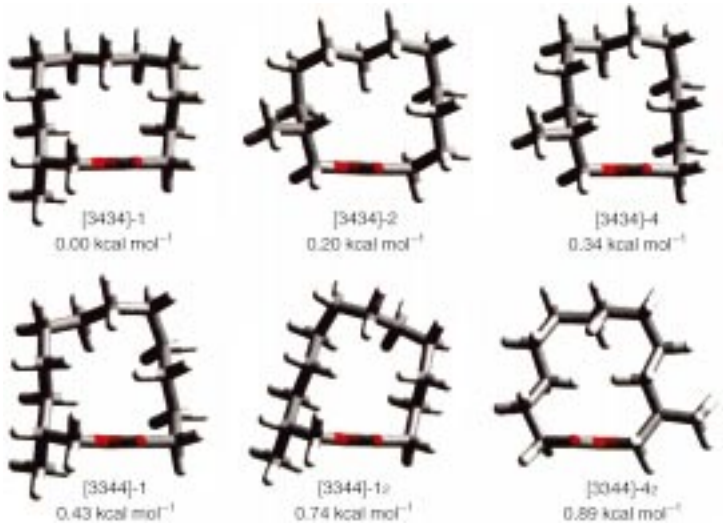
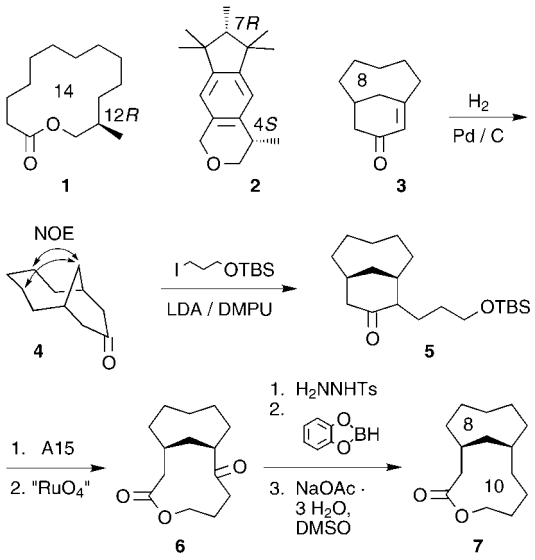


Figure 1. The six lowest-energy conformers of (12*R*)-(+)-12-methyl-13-tridecanolide (**1**).

The odor of the conformationally constrained polycyclic musk odorant Galaxolide (**2**, Scheme 1) is also strongly determined by the configuration of the methyl-bearing C-4 carbon atom. The (4*S*)-(−)-isomers of Galaxolide are about 400 times stronger than the (4*R*)-(+)-isomers that only possess very faint musk tonalities and were even considered odorless by some perfumers.[5] To mimic the shape of polycyclic musk odorants like **2**, and to restrict the conformational freedom of **1**, we planned to introduce a methylene bridge between C-3 and C-8 or C-9 of **1** to construct bicyclo[7.5.1]- and bicyclo[8.4.1]-macrolides. In addition, we wanted to study the influence of the (12*R*)-methyl group, so the 12-demethyl analogues **7** (Figure 2) and **12** were first on our agenda.



Scheme 1. The musk odorants (12*R*)-(+)-12-methyl-13-tridecanolide (**1**) and (4*S*,7*R*)-(−)-Galaxolide (**2**), and the synthesis of (1*R**,9*R**)-4-oxabicyclo[7.5.1]pentadecan-3-one (**7**).

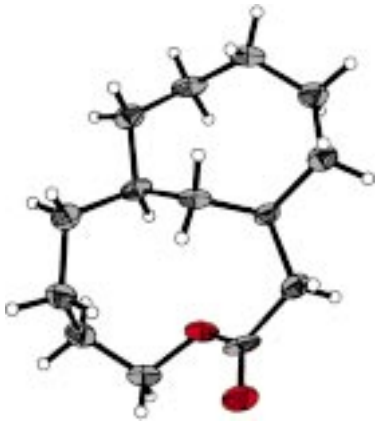


Figure 2. ORTEP view of the crystal structure of **7**, thermal ellipsoids at 30% probability level.

Abstract in German: *Um die Struktur-Geruchs-Zusammenhänge von Moschuskörpern zu untersuchen, wurden (12*R*)-12-Methyl-13-tridecanolid (**1**) – ein makrocyclischer Moschus-Riechstoff – und 13-Tridecanolid – sein nicht moschusartig riechendes Demethyl-Analogon – durch Einführen von Methylenbrücken zwischen C-3 und C-8 sowie C-9 in ihrer konformativen Beweglichkeit eingeschränkt. Diese [7.5.1]- und [8.4.1]-makrobicyclischen Systeme wurden ausgehend von Bicyclo[5.3.1]undec-8-en-9-on (**3**) bzw. Bicyclo[4.3.1]dec-7-en-8-on (**8**) über eine Sequenz aus katalytischer Hydrierung, α-Alkylierung mit einem TBS-geschützten Hydroxy-Halogenid, säurekatalysierter Cyclisierung, oxidativer Spaltung der entstandenen Enolether-Doppelbindung und anschließender Reduktion der Carbonylgruppe über ihr Tosylhydrazon synthetisiert. (1*R*,6*R*,9*R*)-(+)-6-Methyl-4-oxabicyclo[7.5.1]pentadecan-3-on (**22**) zeigte den ausgeprägtesten Moschus-Charakter und dies ließ sich durch Analyse der Überlagerungsstruktur mit dem polycyclischen aromatischen Moschus-Riechstoff (4*S*,7*R*)-Galaxolid (**2**) erklären. Bei seinem (1*S*,6*R*,9*S*)-(+)-Stereoisomer **23** sowie beim (1*S*,6*R*,10*R*)-(+)-6-Methyl-4-oxabicyclo[8.4.1]pentadecan-3-on (**18**) scheint die (6*R*)-Methylgruppe die Wechselwirkung mit dem Moschus-Rezeptor sterisch zu behindern, während die Demethyl-Verbindungen **7** und **12** überhaupt nur einen sehr schwachen Geruch besitzen.*

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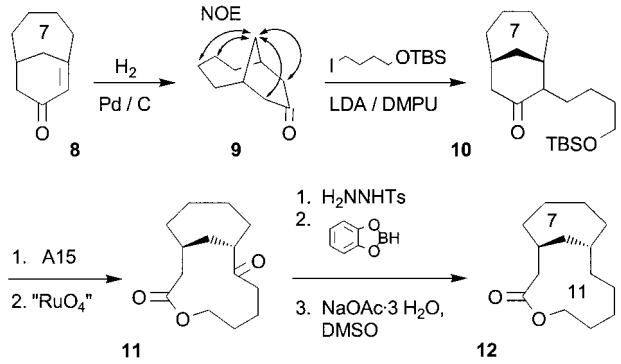
Syntheses, Results, and Discussion

Bicyclo[7.5.1]- and bicyclo[8.4.1]-macrolides should be accessible by ring enlargement of bicyclo[5.3.1]undecan-9-one (**4**) and bicyclo[4.3.1]decan-8-one (**9**) with bifunctional C_3- and C_4-building blocks,[7, 18] respectively. The starting materials, the bicyclic enones **3** and **8**, were prepared by Michael addition of ethyl acetoacetate to cycloalk-2-en-1-ones, intramolecular aldol condensation, and subsequent decarboxylation.[19, 20] In the case of **8** (Scheme 2), an additional demethoxylation step by treatment with boronic acid in refluxing xylene is necessary.[20, 21] The required cycloalk-2-en-1-ones were synthesized from the corresponding cycloalkanes by a bromination/debromination procedure.[22]



Scheme 2. Synthesis of (1*R**,10*S**)-4-oxabicyclo[8.4.1]-pentadecan-3-one (**12**).

The bridgehead α,β-unsaturated ketone **3** has often served as a model substrate for mechanistic studies,[23] and, as was proven by X-ray crystallography of a semicarbazone,[24] can be catalytically hydrogenated to provide the diaxially linked (1*R**,7*S**)-bicyclo[5.3.1]-undecan-9-one (**4**). We isolated **4** in 70% yield by heterogenous hydrogenation of **3** with a palladium on carbon catalyst, and independently proved its relative (1*R**,7*S**)-configuration by a NOESY experiment (crosspeaks from 11-H_a to 3- and 5-H_{ax}). Likewise we established the diaxially linked (1*R**,6*S**)-configuration of **9** (crosspeaks from 10-H_a to 7- and 9-H_{ax} as well as from 10-H_b to 3- and 4-H_{ax}), which we obtained in 88% yield by catalytic hydrogenation of **8**. Bicyclo[4.3.1]decan-8-one (**9**) was also prepared by Momose and Muraoka,[25] who started from the condensation product of *N*-cycloheptenylpyrrolidine and 2-benzoyl-1,3-dichloropropane; however, the reported melting point of 26–29 °C[25] deviates significantly from the one we found (136.0–137.5 °C).

The lithium enolates of the bicycloalkanones **4** and **9** were then alkylated with (*tert*-butyldimethyl)-(3-iodo-propoxy)-silane and (*tert*-butyldimethyl)-(4-iodobutoxy)silane, respectively, which were synthesized from the corresponding hydroxy esters by protection of the hydroxy group, reduction of the ester moiety with DIBAH (diisobutylaluminum hydride), and iodination of the resulting hydroxy group.[7, 18] The alkylation products **5** and **10** were both isolated by flash chromatography in 42% yield, and then cyclized to the intermediate tricyclic dihydropyran and tetrahydrooxepine systems, respectively, by refluxing in anhydrous tetrachloromethane in the presence of Amberlyst 15 and a molecular sieve (4 Å). These rather harsh conditions were necessary, because the TBSO-butylbicyclodecanone **10** did not cyclize to the corresponding tetrahydrooxepine under the standard reaction conditions, that is, stirring in a suspension of Amberlyst 15 in dichloromethane at room temperature.[7, 18] Without isolation, the enol ether double bonds of the intermediate tricycles were then cleaved by Sharpless catalytic ruthenium tetroxide oxidation[26] to provide as main products the oxolactones **6** and **11** in 31% and 41% overall yield, respectively. Astonishingly, as was revealed by the X-ray crystal structure of **11** (Figure 3), one bridgehead of the methylene bridge of **10** epimerized during the course of this reaction; and thus, the less-strained (1*R**,10*R**)-configured 4-oxabicyclo[8.4.1]pentadeca-3,9-dione (**11**) was isolated as the main product. This was not the case for the transformation of **5** into the oxolactone **6**; and by reduction of its tosylhydrazone with catecholborane[27] the (1*R**,9*R**)-configured crystalline 4-oxabicyclo[7.5.1]pentadecan-3-one (**7**) was obtained in 51% yield, an X-ray structure of which is shown in Figure 2. In an analogous manner, **11** was reduced to the (1*R**,10*S**)-configured 4-oxabicyclo[8.4.1]pentadecan-3-one (**12**), and the odor of both target molecules **7** and **12** was evaluated.

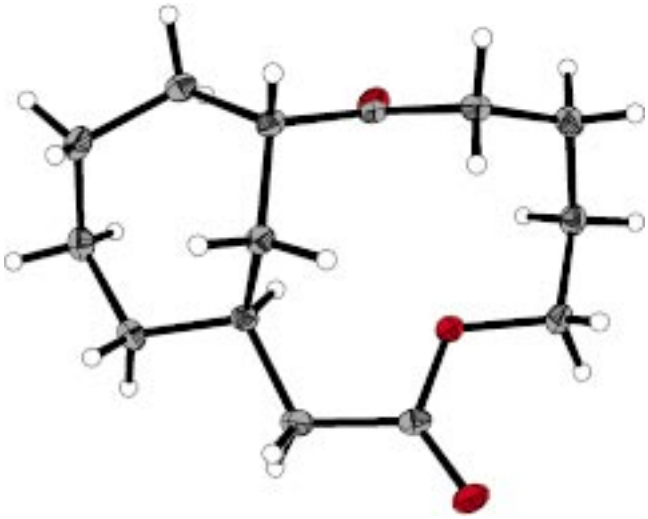


Figure 3. ORTEP view of the crystal structure of **11**, thermal ellipsoids at 30% probability level.

Next, we wanted to synthesize the (6*R*)-methyl derivatives of **6** and **12**, since this methyl group had such a crucial influence on the odor of (12*R*)-12-methyl-13-tridecanolide (**1**, vide infra). The required chiral building block **15** for the synthesis of the (6*R*)-methyl derivative **16** was prepared from (3*R*)-methyl-3-carboxybutanoate (**13**, Tokyo Kasei Kogyo, >98% *ee*) by reduction with the borane–dimethyl sulfide complex, protection of the resulting hydroxy group as a *tert*-butyldimethylsilyl (TBS) ether, reduction of the ester moiety with DIBAH, and subsequent iodination (Scheme 3).[28] The starting material, halfester **13** is produced from enantiomerically pure (*R*)-(+)-methylsuccinic acid, which can be obtained by microbial transformation of squalene.[29] The synthesis of

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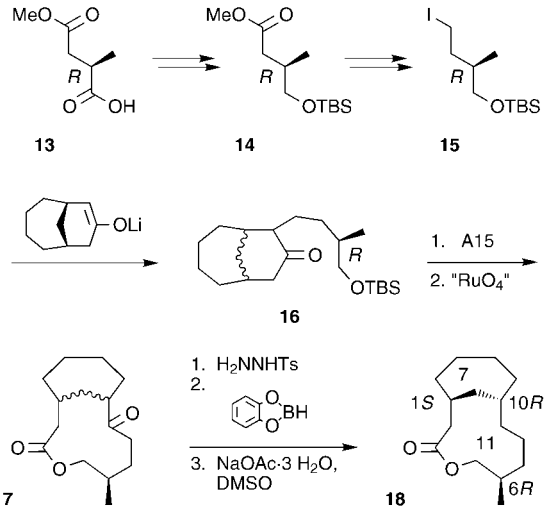
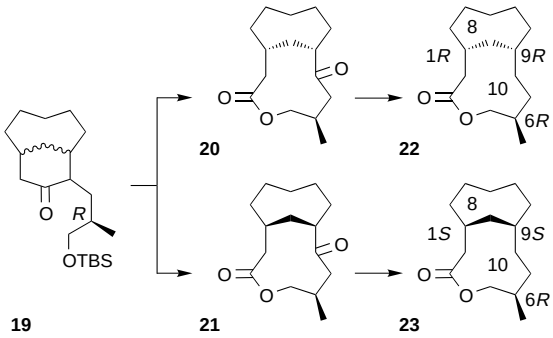


Scheme 3. Enantioselective synthesis of (1*S*,6*R*,10*R*)-(+)-6-methyl-4-oxabicyclo[8.4.1]pentadecan-3-one (**18**) by ring enlargement with the chiral building block **15**.

(2*S*)-(+)-(*tert*-butyldimethyl)-(3-iodo-2-methylpropoxy)silane (>98% *ee*), the building block for the synthesis of **22** and **23**, is described in ref. [7].

Alkylation of **4** and **9** with these chiral building blocks gave **16** and **19** in 38% and 42% yield, respectively, (Scheme 4), which were then subjected to the extended cyclization



Scheme 4. Syntheses of the enantiomerically pure 6-methyl-4-oxabicyclo[7.5.1]pentadecan-3-ones **22** and **23**.

sequence to provide, after isolation by flash chromatography, as main products the crystalline oxolactones **17** (54%) and **20** (30%) as well as **21** (33%). Reduction was again accomplished via the corresponding tosylhydrazones to furnish the target molecules **18**, **22**, and **23**.

As in the case of **12**, the bridgehead atom C-10 of **18** epimerized during the course of the cyclization, and a (1*S*,6*R*,10*R*)-configuration was assigned for **18** by X-ray crystallography (Figure 4). The configurations of **22** and **23** were determined from the X-ray crystal structures of the corresponding oxolactones **20** (Figure 5) and **21** (Figure 6), and as in the case of **7** the relative configuration of the methylene-bridge atoms of **4** was retained throughout the reaction sequence. So the bridgehead atoms of the oxabicyclo[7.5.1]pentadecan-3-ones **7**, **22**, and **23** have *like*-configuration, while the bridgeheads of the oxabicyclo[8.4.1]pentadecan-3-ones **12** and **18** have *unlike*-configuration. Though completely unintended, this makes the overall shapes of the target molecules resemble each other even more closely (Figure 7), and thus simplifies the structure – odor correlation.

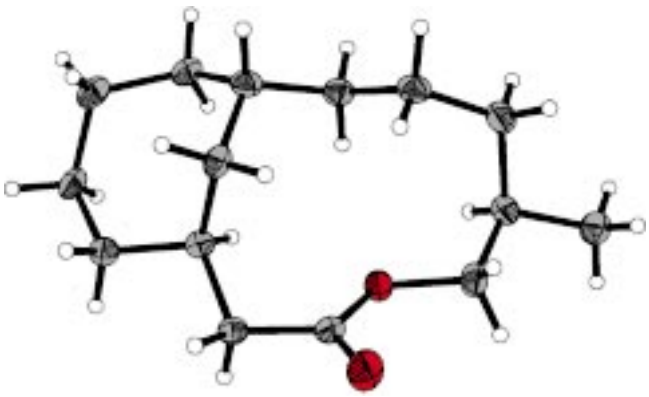


Figure 4. ORTEP view of the crystal structure of **18**, thermal ellipsoids at 30% probability level.

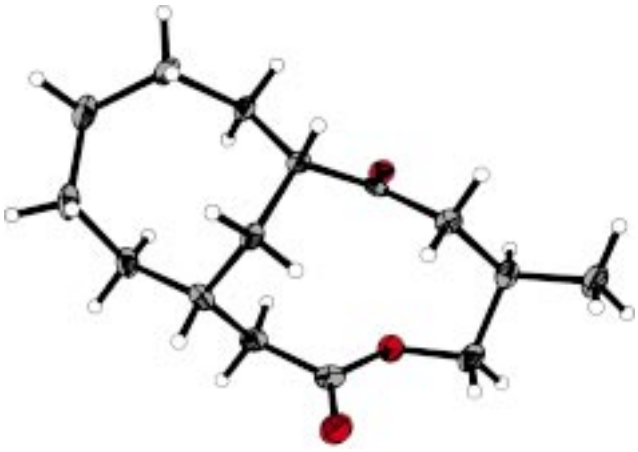


Figure 5. ORTEP view of the crystal structure of **20**, thermal ellipsoids at 30% probability level.

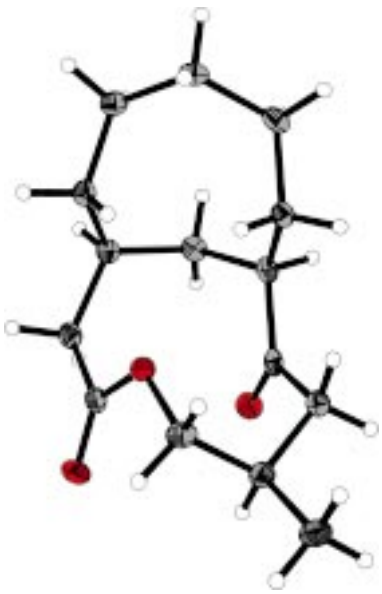


Figure 6. ORTEP view of the crystal structure of **21**, thermal ellipsoids at 30% probability level.

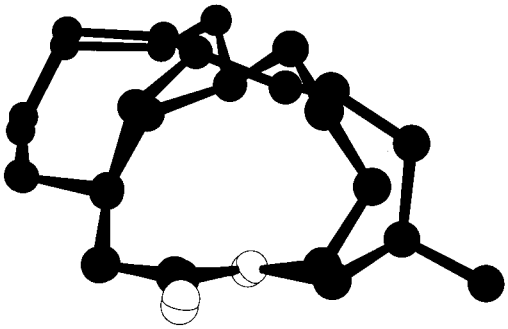


Figure 7. Superposition of the X-ray crystal structures of **7** with *like*-configured bridgeheads and **18** with *unlike*-configured bridgeheads.

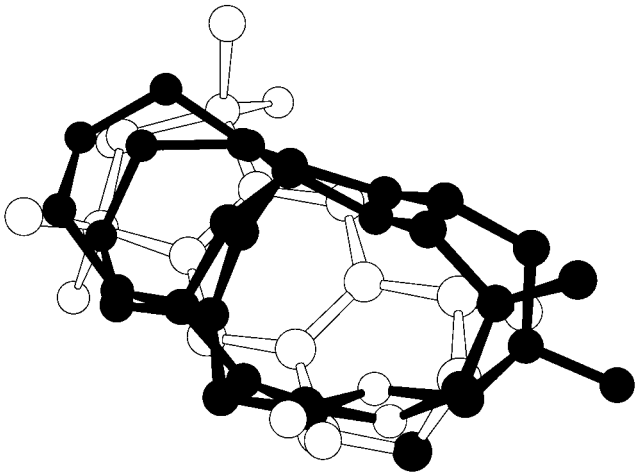


Figure 8. Superposition of **18** and **22** on the X-ray crystal structure of (4*S*,7*R*)-Galaxolide (**2**, ref. [5]).

Olfactory properties and Conclusion

Because the target molecules **7**, **12**, **18**, **22**, and **23** are conformationally constrained we did not expect them to be more musky than the parent compound (12*R*)-12-methyl-13-tridecanolide (**1**), which also shows a strong sandalwood inflection. In addition, the conformations of macrocycles can also alter by the interaction with the receptor and they thus can adapt much more during the receptor interaction than the rigid macrobicycles described in this paper. Therefore, we were looking rather for the beginning of a musk tonality than for a sheer musk note.

The compound (12*R*)-12-methyl-13-tridecanolide (**1**) was deliberately selected as the parent compound, since it is just at the beginning of the molecular dimensions of musk odorants and consequently depends critically on structural variations; this makes it especially suitable for structure–odor investigations. Like 13-tridecanolide, the demethyl compounds **7** and **12** were expected to be devoid of any musk character, and indeed both are extremely weak odorants; however, both possess a slight, very faint undertone of musk. Besides, **7** is mainly woody–ambery, and **12** is anisic–fruity–ambery.

The most powerful odorant of this series is **18**, but it does not possess any musky facets. Instead, it emanates a cedarwood-type, woody–ambery scent with animal-like nuances. The most typical musk note is present in **22** with its powerful fresh odor that, in addition to its musky aspects, is also anisic, fruity, and ambery. Its stereoisomer **23** is weaker than **22**, and mainly reminiscent of sawdust and hot iron; yet, to some perfumers it was also reminiscent of musk. So in summary, we found the following order of succession for the *muskiness* of the investigated macrobicycles: **22** > **23** ≫ **12** > **7** ≫ **18**. With regard to the odor intensity, the following order was observed: **18** > **22** > **23** ≫ **12** > **7**.

In the most musky compound **22** (Figures 5 and 8), the (6*R*)-methyl group is situated at a *gauche* corner in such a way that it elongates the edge of the ester moiety. Thereby, it imitates a larger ring system and also superimposes better with (4*S*,7*R*)-Galaxolide (**2**, Figure 8), while the (6*R*)-methyl group of the [8.4.1]-macrobicycle **18** (Figure 4 and 8) protrudes beyond the dimensions of (4*S*,7*R*)-Galaxolide (**2**, Figure 8). This could result in steric hindrance with the musk receptor, and could explain why the substance does not smell musky at all. Also in **23**, the (6*R*)-methyl group stands out from the ester edge, and furthermore the molecule is not as planar as **22**. Both features increase the steric hindrance, and could explain the odor differences in relation to **22**, particularly the severely diminished musk character.

The weak odor characteristics of **7** and **12**, finally, demonstrate the importance of the (6*R*)-methyl substituent. Their character, which is faintly reminiscent of musk odorants, may result from some shape similarity to (4*S*,7*R*)-Galaxolide (**2**), even without methyl substitution. However, their molecular dimensions seem too small to produce a typical musk odor.

In conclusion, we saw that we could rationalize the observed olfactory properties of the conformationally constrained compounds **7**, **12**, **18**, **22**, and **23** to some extent with the aid of the superposition analysis with (4*S*,7*R*)-Galaxolide (**2**). The macrobicycles **7**, **12**, **18**, **22**, and **23** provide some insight into the molecular dimensions of the binding site of the musk receptor, and this is likely to be the same receptor as that for the polycyclic aromatic musk **2**. However, it of course cannot be excluded that other conformers of **1** also play an important role; the role can even be a much more important one than that of **22**, which corresponds to a [12425]-conformation of **1**, or more roughly a [2435]-conformation that, according to Dale,[10] is energetically about 8 kcal mol^{-1} above the [3434]-conformation of 14-membered rings.

Experimental Section

1. General information: All reactions were performed under nitrogen using reagents and solvents (puriss. or purum) from Fluka without further purification. IR: Bruker VECTOR 22/Harrick SplitPea micro ATR, Si. NMR: Bruker AVANCE DPX-400, Bruker AVANCE DPX-700, TMS int., $CDCl_3$. MS: Finnigan MAT 95, HP Chemstation 6890 GC/5973 Mass Sensitive Detector. Polarimetry: Perkin-Elmer 241, $CHCl_3$. FC: Merck Kieselgel 60 (particle size 40–63 μm). TLC: Merck Kieselgel 60 F_{254} (particle size 5–20 μm, layer thickness 250 μm on glass, 5 cm × 10 cm), PMA spray soln. for TLC, Merck 1.00480.0100. Melting points: Büchi Melting Point B545 (uncorrected). Elemental analyses: F. Hoffmann-La Roche, Basel, PRPI-S. X-ray: F. Hoffmann-La Roche, Basel, PRBT; Siemens P4 diffractometer, SHELX-97.

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The bicycloalkenones **3** and **8** were prepared according to the procedures of Gioia et al.[19] and House et al.,[20] respectively. The hydroxy iodides were prepared from the corresponding hydroxy esters according to the method described in ref. [7, 18]. Compound (3*R*)-methyl-3-carboxybutanoate (**13**, >98% *ee*) was purchased from Tokyo Kasei Kogyo C1461, and methyl (2*S*)-(+)-methyl-3-hydroxy-2-propanoate (>98% *ee*) from Fluka 55412.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-148829 (**11**), CCDC-148828 (**20**), CCDC-148830 (**21**), CCDC-142427 (**7**), and CCDC-142428 (**18**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

2. Hydrogenations: general procedure: Pd/C (10%, 1 mol%) was added to a solution of the bicycloalkenone (166 mmol) in EtOAc (150 mL). After vigorous stirring for 7 h under a H_2 atmosphere at room temperature, the catalyst was removed by vacuum filtration through a pad of Celite. The solvent was evaporated under reduced pressure, and the residue purified by silica gel FC.

(*1R*,7S**)-*Bicyclo*[*5.3.1*]*undecan-9-one* (***4***): Scale 547 mmol (89.9 g of **3**), yield 70% (63.8 g of **4**), $R_f = 0.47$ (pentane/Et_2O, 4:1), colorless liquid; ^{1}H NMR (400 MHz): $\delta = 2.62$ (dd, $J = 12$, 6 Hz, 2H; 8-,10-H_a), 2.29 (m, 2H; 1-,7-H), 2.20 (dt, $J = 13$, 2 Hz, 1H; 11-H_a), 2.17 (d, $J = 12$ Hz, 2H; 8-,10-H_b), 1.89–1.72 (m, 6H; 2-H_a-6-H_a, 11-H_b), 1.31 (m, 2H; 3-,5-H_b), 1.16 (m, 1H; 4-H_b), 1.11 (m, 2H; 2-,6-H_b); NOESY (400 MHz, RT): $\delta \times \delta = 2.20 \times 1.31$ (dt × m, 11-H_a × 3-,5-H_{ax}, [1*R**,7*S**]); ^{13}C NMR (400 MHz): $\delta = 212.03$ (s, C-9), 48.35 (2t, C-8,-10), 35.58 (2d, C-1,-7), 32.39 (2t, C-2,-6), 30.88 (t, C-4), 26.51 (t, C-11), 24.95 (2t, C-3,-5); SELINQUATE (selective INADEQUATE) (35.58 MHz, RT, C-1,-7): $\delta = 48.35$ (C-8,-10), 32.39 (2t, C-2,-6), 26.51 (t, C-11); IR (ATR, attenuated total reflection): $\tilde{\nu} = 1706$ (ν C=O), 1474, 1476, 1421 cm^{-1} (δ CH_2); MS (70 eV): *m*/*z* (%): 166 (16) $[M]^+$, 151 (2), 137 (2), 123 (6), 109 (13), 95 (100), 81 (25), 67 (23) $[C_nH_{2n-5}O]^+$.

(*1R*,6S**)-*Bicyclo*[*4.3.1*]*decan-8-one* (***9***): Scale 166 mmol (30.4 g of **8**), yield 88% (22.2 g of **9**), $R_f = 0.33$ (pentane/Et_2O, 4:1), white crystals, M.p. 136.0–137.5 °C; ^{1}H NMR (400 MHz): $\delta = 2.66$ (m, 2H; 1-,6-H), 2.53 (dd, $J = 14$, 7 Hz, 2H; 7-,9-H_a), 2.19 (dt, $J = 14$, 1 Hz, 2H; 7-,9-H_b), 2.02 (dt, $J = 14$, 5 Hz, 1H; 10-H_a), 1.85 (dt, $J = 14$, 2 Hz, 1H; 10-H_b), 1.78–1.72 (m, 2H; 2-,5-H_a), 1.56–1.35 (m, 6H; 2-,5-H_b,3-,4-H_2); NOESY (400 MHz, RT): $\delta \times \delta = 2.53 \times 2.02$ (dd × dt, 7-,9-H_{ax} × 10-H_a, [1*R**,6*S**]), 1.85×1.51 (dt × m, 10-H_b × 3-,4-H_{ax}, [1*R**,6*S**]); ^{13}C NMR (400 MHz): $\delta = 213.14$ (s, C-8), 48.26 (2t, C-7,-9), 34.94 (2t, C-2,-5), 34.48 (2d, C-1,-6), 30.98 (t, C-10), 25.79 (2t, C-3,-4); IR (ATR): $\tilde{\nu} = 1712$ (ν C=O), 1457, 1416 cm^{-1} (δ CH_2); MS (70 eV): *m*/*z* (%): 152 (31) $[M]^+$, 137 (3), 123 (4) $[C_nH_{2n-5}O]^+$, 108 (54) $[C_8H_{12}]^+$, 95 (100), 81 (39), 67 (39) $[C_nH_{2n-5}O]^+$.

3. Alkylations: general procedure: Under N_2, a solution of LDA (lithium diisopropylamide) was prepared by addition of a BuLi solution (1.6 M) to *i*Pr_2NH (165 mmol) in anhydrous DMPU/THF (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone/THF, 2:1, 450 mL) at −78 °C and subsequent stirring at 0 °C for 30 min. At −78 °C, the bicycloalkanone (112 mmol) was added, after further stirring for 1 h at the same temperature by the dropwise addition of the protected hydroxy iodide (115 mmol) in anhydrous THF (100 mL). The cooling bath was then removed, and the reaction mixture stirred at room temperature for 40 h; then it was poured into Et_2O/water (1:1, 2 L). The aqueous layer was extracted twice with Et_2O (500 mL), and the combined organic solutions were concentrated by using a rotary evaporator. The resulting residue was purified by silica gel FC.

(*1R*,7S**)-*8*-[*3′*-(*tert-Butyldimethylsiloxy*)*propyl*]*bicyclo*[*5.3.1*]*undecan-9-one* (***5***): Scale 25 mmol (4.13 g of **4**), yield 42% (3.52 g of **5**), $R_f = 0.29$ (pentane/Et_2O, 10:1), colorless liquid; ^{1}H NMR (400 MHz): $\delta = 3.75$ (+, $J = 6$ Hz, 1H; 3′-H_a), 3.65 (+, $J = 6$ Hz, 1H; 3′-H_b), 2.63–1.09 (m, 21H; 1-H-11-H_2, 1′-,2′-H_2), 0.90 (s, 9H; CMe_3), 0.07 (s, 6H; $SiMe_2$); ^{13}C NMR (400 MHz): $\delta = 212.20$ (2s, C-9), 57.83 (d, C-8), 48.47 (t, C-10), 41.72 (d, C-7), 35.97 (d, C-1), 35.68 (t, C-2), 35.35 (t, C-2′), 32.49 (t, C-6), 30.98, 30.76 (t, C-4), 26.63 (t, C-11), 25.92 (q, C*Me*$_3$), 25.06, 24.77 (t, C-3,-5), 22.00 (t, C-1′), 18.23 (s, Si*C*Me_3), −5.38, −5.48 (2q, $SiMe_2$), main diastereomer; IR (neat): $\tilde{\nu} = 837$, 1103 (ν Si–OC), 1708 (ν C=O), 777 (ν O–Si–CH_3), 1256 (ν C–OSi), 1473 cm^{-1} (δ CH_3); MS (70 eV): *m*/*z* (%): 338 (1) $[M]^+$, 323 (2) $[M - CH_3]^+$, 281 (100) $[M - C_4H_9]^+$, 253 (4) $[M - C_4H_9 - CO]^+$, 189 (17) $[C_{13}H_{17}O]^+$, 145 (53) $[C_{11}H_{13}]^+$, 75 (88) $[SiMe_2OH]^+$.

(*1R*,6S**)-*7*-[*4′*-(*tert-Butyldimethylsiloxy*)*butyl*]*bicyclo*[*4.3.1*]*decan-8-one* (***10***): Scale 48 mmol (7.32 g of **9**), yield 42% (6.50 g of **10**), $R_f = 0.43$ (pentane/Et_2O, 9:1), colorless liquid; ^{1}H NMR (400 MHz): $\delta = 3.57$ (dd, $J = 7$, 2 Hz, 1H; 4′-H_a), 3.54 (br d, $J = 7$ Hz, 1H; 4′-H_b), 2.64–1.23 (m, 21H; 1-H-10-H_2, 1′-H_2-3′-H_2), 0.85, 0.84 (2s, 9H; CMe_3), 0.01, 0.00 (2s, 6H; $SiMe_2$); ^{13}C NMR (400 MHz): $\delta = 216.41$, 213.76 (2s, C-8), 62.88, 62.68 (2t, C-4′), 57.68, 54.73 (2d, C-7), 48.60, 45.21 (2t, C-9), 39.67, 38.79 (2d, C-6), 36.10, 34.52 (2d, C-1), 35.97, 35.37, 35.03 (3t, C-2,-5), 32.96, 32.87, 32.80, 32.42 (4t, C-3′,-10), 28.00, 27.11 (2t, C-1′), 26.11, 25.95, 25.59, 25.30 (4t, C-3,-4), 25.78 (q, C*Me*$_3$), 23.77, 23.39 (2t, C-2′), 18.14, 18.13 (2s, Si*C*Me_3), −5.44, −5.47 (2q, $SiMe_2$); IR (neat): $\tilde{\nu} = 1709$ (ν C=O), 836, 1101 (ν Si–OC), 776 (ν O–Si–CH_3), 1255 (ν C–OSi), 1460 cm^{-1} (δ CH_3); MS (70 eV): *m*/*z* (%): 338 (1) $[M]^+$, 323 (2) $[M - CH_3]^+$, 281 (100) $[M - C_4H_9]^+$, 239 (16) $[M - C_4H_9 - C_2H_2O]^+$, 159 (29) $[C_{12}H_{15}]^+$, 95 (41) $[C_7H_{11}]^+$, 75 (88) $[SiMe_2OH]^+$.

(*1RS,6SR,3′R*)-(−)-*7*-[*4′*-(*tert-Butyldimethylsiloxy*)-*3′-methylbutyl*]*bicyclo*-[*4.3.1*]*decan-8-one* (***16***): Scale 112 mmol (17.0 g of **9**), yield 38% (14.9 g of **16**), $R_f = 0.63$ (pentane/Et_2O, 9:1), colorless liquid; $[\alpha]_D^{22} = -9.4$, $[\alpha]_{546}^{22} = -11.7$ ($c = 1.95$ in $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 3.40$ (dd, $J = 9$, 6 Hz, 1H; 4′-H_a), 3.36 (dd, $J = 9$, 6 Hz, 1H; 4′-H_b), 2.56–1.29 (m, 20H; 1-H-10-H_2, 1′-H_2-3′-H), 0.86 (s, 9H; CMe_3), 0.86 (d, $J = 7$ Hz, 3H; 3′-Me), 0.00 (s, 6H; $SiMe_2$); ^{13}C NMR (400 MHz): $\delta = 213.98$ (s, C-8), 67.88 (t, C-4′), 55.20 (d, C-7), 48.64 (t, C-9), 38.80 (d, C-6), 36.10 (d, C-1), 35.92 (d, C-3′), 35.34, 33.00, 30.67 (3t, C-2,-5,-10), 27.99 (t, C-1′), 26.11, 25.30 (2t, C-3,-4), 25.79 (q, C*Me*$_3$), 23.26 (t, C-2′), 18.16 (s, Si*C*Me_3), 16.77 (q, 3′-Me), −5.51 (q, $SiMe_2$), main diastereoisomer; IR (ATR): $\tilde{\nu} = 835$, 1090 (ν Si–OC), 774 (ν O–Si–CH_3), 1708 (ν C=O), 1250 (ν C–OSi), 1461 cm^{-1} (δ CH_3); MS (70 eV): *m*/*z* (%): 352 (1) $[M]^+$, 337 (2) $[M - CH_3]^+$, 295 (88) $[M - C_4H_9]^+$, 239 (59) $[M - C_6H_{13}Si]^+$, 221 (3) $[M - C_6H_{13}Si - H_2O]^+$, 145 (25) $[C_{11}H_{13}]^+$, 95 (40) $[C_7H_{11}]^+$, 75 (100) $[SiMe_2OH]^+$.

(*1RS,7SR,2′R*)-(+)-*8*-[*3′*-(*tert-Butyldimethylsiloxy*)-*2′-methylpropyl*]*bicyclo*-[*5.3.1*]*undecan-9-one* (***19***): Scale 90 mmol (15.0 g of **4**), yield 42% (13.2 g of **19**), $R_f = 0.65$ (pentane/Et_2O, 4:1), colorless liquid; $[\alpha]_D^{22} = +10.1$, $[\alpha]_{546}^{22} = +12.2$ ($c = 2.00$ in $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 3.46–3.28$ (m, 2H; 3′-H_2), 2.78–1.10 (m, 20H; 1-H-11-H_2, 1′-H_2,2′-H), 0.86, 0.83, 0.81, 0.79 (4s, 9H; CMe_3), 0.86, 0.79, 0.77, 0.75 (4d, $J = 7$ Hz, 3H; 2′-Me), 0.00/0.00/−0.01 (3s, 6H; $SiMe_2$); ^{13}C NMR (400 MHz): $\delta = 215.90$, 215.60, 213.05, 212.79 (4s, C-9), 68.71, 68.49, 67.90, 67.04 (4t, C-3′), 55.43, 55.37, 52.97, 52.87 (4d, C-8), 48.79, 48.74, 44.76, 44.51 (4t, C-10), 41.42, 40.82, 39.58, 39.56 (4d, C-7), 36.77, 36.64, 36.09, 35.81 (4d, C-1), 33.93, 33.69, 32.69, 32.57 (4d, C-2′), 35.88, 35.11, 33.30, 33.09 (4t, C-6), 32.41, 32.37, 32.28, 32.22 (4t, C-2), 31.08, 31.02, 31.00, 31.00 (4t, C-4), 30.03, 28.96, 28.31, 28.27, 27.13, 26.96 (6t, C-11,-1′), 25.80, 25.78, 25.75, 25.74 (4q, CMe_3), 24.97, 24.85, 24.71, 24.66, 24.57, 24.53, 21.95, 21.70 (8t, C-3,-5), 18.17, 18.15, 18.11, 18.10 (4s, Si*C*Me_3), 17.42, 16.76, 16.66, 15.99 (4q, 2′-Me), −5.55 (q, $SiMe_2$); IR (ATR): $\tilde{\nu} = 835$, 1093 (ν Si–OC), 775 (ν O–Si–CH_3), 1705 (ν C=O), 1251 (ν C–OSi), 1472 cm^{-1} (δ CH_3); MS (70 eV): *m*/*z* (%): 352 (1) $[M]^+$, 337 (1) $[M - CH_3]^+$, 295 (31) $[M - C_4H_9]^+$, 277 (3) $[M - C_4H_9 - H_2O]^+$, 239 (4) $[M - C_6H_{13}Si]^+$, 221 (2) $[M - C_6H_{13}Si - H_2O]^+$, 159 (20) $[C_{12}H_{15}]^+$, 107 (26) $[C_8H_{11}]^+$, 95 (35) $[C_7H_{11}]^+$, 75 (100) $[SiMe_2OH]^+$.

4. Oxolactones: general procedure: Activated molecular sieve UOP (4 Å, 4.0 g) was added at room temperature under N_2 to a stirred solution of the *ω*-(*tert*-butyldimethylsiloxy)alkylbicycloalkanone (40 mmol) in dry CCl_4 (140 mL). After the addition of Amberlyst 15 (4.0 g), the reaction mixture was refluxed for 4 h. The solid reagents were then filtered off, and MeCN (50 mL), water (90 mL), and $NaIO_4$ (350 mmol) as well as $RuCl_3 \cdot 3H_2O$ (1.70 mmol) were added in turn to the filtrate. The resulting mixture was stirred at room temperature for 2 h, and then poured into CH_2Cl_2/water (1:1, 800 mL). The aqueous layer was extracted three times with CH_2Cl_2, and the organic solutions were combined and concentrated with a rotary evaporator. The crude product was purified by silica gel FC.

(*1R*,9S**)-*4-Oxabicyclo*[*7.5.1*]*pentadeca-3,8-dione* (***6***): Scale 10.2 mmol (3.46 g of **5**), yield 31% (0.76 g of **6**), $R_f = 0.23$ (pentane/Et_2O, 10:1), colorless crystals, M.p. 87.5–89.2 °C; ^{1}H NMR (400 MHz): $\delta = 4.66$ (td, $J = 10$, 4 Hz, 1H; 5-H_a), 3.88 (dd, $J = 10$, 4 Hz, 1H; 5-H_b), 2.67 (m, 2H; 2-H_2), 2.48–1.18 (m, 18H; 1-,9-H, 6-H_2-15-H_2); ^{13}C NMR (400 MHz): $\delta = 213.36$ (s, C-8), 173.01 (s, C-3), 64.22 (t, C-5), 52.91 (d, C-9), 40.32 (t, C-2), 36.99 (t, C-7), 35.85 (d, C-1), 34.11 (t, C-14), 31.53 (t, C-12), 25.59 (t, C-11), 25.43 (t, C-10), 25.05 (t, C-13), 24.24 (t, C-15), 23.82 (t, C-6); IR (KBr): $\tilde{\nu} = 1724$ (ν C=OO), 1150 (ν C–C(=O)–O, asym.), 1701 (ν C=O), 1474 cm^{-1} (δ CH_2); MS (70 eV): *m*/*z* (%): 238 (20) $[M]^+$, 220 (4) $[M - H_2O]^+$, 210 (6) $[M - CO]^+$, 179 (19) $[M - C_2H_3O]^+$, 152 (27) $[C_{10}H_{16}O]^+$, 137 (12), 123 (21), 109

(100), 81 (54), 67 (69) $[C_nH_{2n-3}]^+$, 96 (79) $[C_7H_{12}]^+$, 41 (57) $[C_3H_5]^+$; elemental analysis calcd (%) for $C_{14}H_{22}O_3$ (238.3): C 70.56, H 9.30; found C 70.42, H 9.24.

(1R,10R*)-4-Oxabicyclo[8.4.1]pentadeca-3,9-dione* (**11**): Scale 19 mmol (6.45 g of **10**), yield 41% (1.85 g of **11**), $R_f = 0.26$ (pentane/Et_2O, 4:1), colorless crystals, M.p. 41.7–42.8 °C; ^{1}H NMR (400 MHz): $\delta = 4.27$ (ddd, $J = 11$, 9, 2 Hz, 1H; 5-H_a), 3.95 (ddd, $J = 11$, 8, 2 Hz, 1H; 5-H_b), 2.94 (ddd, $J = 18$, 12, 3 Hz, 1H; 8-H_a), 2.73 (ddd, $J = 18$, 8, 3 Hz, 1H; 8-H_b), 2.26–1.06 (m, 18H; 1-,10-H, 2-,6-,7-H_2, 11-H_2-15-H_2); ^{13}C NMR (400 MHz): $\delta =$ 211.53 (s, C-9), 171.82 (s, C-3), 65.12 (t, C-5), 48.33 (d, C-10), 42.49 (t, C-2), 37.85 (t, C-8), 36.74 (t, C-14), 35.73 (t, C-15), 30.76 (d, C-1), 29.94 (t, C-13), 26.52, 25.65, 23.76 (3t, C-6,-11,-12), 20.93 (t, C-7); IR (ATR): $\tilde{\nu} =$ 1728 (ν C=OO), 1709 (ν C=O), 1246 (ν C–O–C, asym.), 1029 (ν C–O–C, sym.), 1468 cm^{-1} (δ CH_2); MS (70 eV): *m/z* (%): 238 (5) $[M]^+$, 220 (2) $[M - H_2O]^+$, 210 (4) $[M - CO]^+$, 192 (15) $[M - H_2O - CO]^+$, 151 (17) $[C_{10}H_{15}O]^+$, 138 (21) $[C_9H_{14}O]^+$, 111 (24) $[C_8H_{15}]^+$, 101 (33) $[C_7H_{17}]^+$, 94 (100) $[C_7H_{10}]^+$, 81 (32) $[C_6H_9]^+$, 67 (41) $[C_5H_7]^+$, 55 (52) $[C_4H_7]^+$, 41 (47) $[C_3H_5]^+$; crystal data and structure refinement: Empirical formula $C_{14}H_{22}O_3$, molecular mass 238.32, crystal dimensions $0.7 \times 0.7 \times 0.6$ mm, temperature 150 K, wavelength 0.71073 Å, monoclinic crystal system, space group $P2_1/c$, unit cell dimensions $a = 11.965(2)$ Å, $b = 9.926(2)$ Å, $c =$ 10.826(2) Å, $\alpha = 90°$, $\beta = 99.43(3)°$, $\gamma = 90°$, $V = 1268.2(4)$ Å^3, $Z = 4$, $\rho =$ 1.248 mg m^{-3}, $\mu(Mo_{K\alpha}) = 0.086$ mm^{-1}, $F(000)$ 520, θ range 2.68–25.84°, limiting indices $-14 \le h \le 13$, $-12 \le k \le 12$, $-13 \le l \le 10$, total reflections collected 6571, symmetry-independent reflections 2382, $R_{int} = 0.1124$, refinement full-matrix least squares on F^2, data 2382, parameters 154, goodness-of-fit on F^2 1.055, final R indices $[I > 2\sigma(I)]$ $R_1 = 0.0564$, $wR_2 =$ 0.1440, R indices (all data) $R_1 = 0.0642$, $wR_2 = 0.1496$, $\Delta\rho$ (max, min) = 0.358, -0.258 e Å^3; CCDC-148829 (see Section 1); elemental analysis calcd (%) for $C_{14}H_{22}O_3$ (238.3): C 70.56, H 9.30; found C 70.55, H 9.30.

(1RS,6R,10RS)-(+)-6-Methyl-4-oxabicyclo[8.4.1]pentadeca-3,9-dione (**17**): Scale 21 mmol (7.40 g of **16**), yield 54% (2.86 g of **17**), $R_f = 0.24$ (pentane/Et_2O, 9:1), colorless crystals, M.p. 34.8–36.0 °C; $[\alpha]_D^{22} = +7.7$, $[\alpha]_{546}^{22} = +9.4$ ($c = 1.94$ in $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 4.54$ (ddd, $J = 11$, 3, 2 Hz, 5-H_a), 3.91 (ddd, $J = 11$, 2, 1 Hz, 5-H_a), 3.84 (dd, $J = 11$, 10 Hz, 5-H_b), 3.34 (dd, $J = 11$, 11 Hz, 5-H_b), 3.11 (ddd, $J = 19$, 14, 4 Hz, 8-H_a), 2.75 (ddd, $J = 19$, 9, 1 Hz, 8-H_a), 2.72 (ddd, $J = 18$, 10, 2 Hz, 8-H_b), 2.71 (m, 10-H), 2.46 (ddd, $J = 18$, 10, 2 Hz, 2H; 8-H_b), 2.27–1.40 (m, 17H; 1-,6-,10-H,2-,7-,11-,12-,13-, 14-,15-H_2), 0.92, 0.93 (2d, $J = 7$ Hz, 3H; 6-Me); ^{13}C NMR (400 MHz): $\delta =$ 211.74, 211.52 (2s, C-9), 171.76, 171.71 (2s, C-3), 70.55, 69.76 (2t, C-5), 48.87, 47.95 (2d, C-10), 42.70, 42.43 (2t, C-2), 39.75, 37.39, 36.25, 36.11, 36.07, 35.57, 30.13, 29.69, 29.66, 29.17 (10t, C-7,-8,-11,-14,-15), 34.19, 30.82, 30.55, 28.69 (4d, C-1,-6), 26.66, 26.47, 24.06, 23.62 (4t, C-12,-13), 18.81, 18.50 (2q, 6-Me); IR (ATR): $\tilde{\nu} = 1728$, 1715 (ν C=OO), 1700 (ν C=O), 1245 (ν C–O–C, asym.), 1007 (ν C–O–C, sym.), 1458, 1468 cm^{-1} (δ CH_2); MS (70 eV): *m/z* (%): 252 (6) $[M]^+$, 234 (1) $[M - H_2O]^+$, 224 (2) $[M - CO]^+$, 206 (10) $[M - H_2O - CO]^+$, 183 (13) $[M - C_5H_9]^+$, 165 (20) $[M - C_5H_{11}O]^+$, 138 (34) $[M - C_6H_{10}O_2]^+$, 125 (30) $[C_9H_{17}]^+$, 115 (29) $[C_7H_{15}O]^+$, 94 (100) $[C_7H_{10}]^+$, 55 (60) $[C_4H_7]^+$, 41 (55) $[C_3H_5]^+$; elemental analysis calcd (%) for $C_{15}H_{24}O_3$ (252.4): C 71.39, H 9.59; found C 71.33, H 9.50.

(1R,6R,9S)-(+)-6-Methyl-4-oxabicyclo[7.5.1]pentadeca-3,8-dione (**20**): Scale 40 mmol (14.1 g of **19**), yield 30% (3.06 g of **20**), $R_f = 0.37$ (pentane/Et_2O, 4:1), colorless crystals, M.p. 122 °C; $[\alpha]_D^{22} = +69.3$, $[\alpha]_{546}^{22} =$ $+85.8$ ($c = 2.01$ in $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 4.29$ (dd, $J = 12$, 10 Hz, 1H; 5-H_a), 3.77 (dd, $J = 10$, 5 Hz, 1H; 5-H_b), 2.89 (m, 1H; 6-H), 2.61 (dd, $J = 17$, 3 Hz, 1H; 7-H_a), 2.38 (m, 1H; 9-H), 2.37–2.30 (m, 2H; 2-,15-H_a), 2.14 (m, 1H; 1-H), 2.06 (t, $J = 12$ Hz, 1H; 2-H_b), 2.03–1.77 (m, 8H; 10-,11-, 12-,13-,14-H_a, 7-,10-,15-H_b), 1.37–1.32 (m, 3H; 12-,13-,14-H_b), 1.21 (m, 1H; 11-H_b), 0.94 (d, $J = 7$ Hz, 3H; 6-Me); ^{13}C NMR (400 MHz): $\delta = 212.58$ (s, C-8), 172.63 (s, C-3), 69.21 (t, C-5), 52.95 (d, C-9), 45.76 (t, C-7), 40.25 (t, C-2), 35.94 (d, C-1), 34.19 (t, C-14), 31.39 (t, C-12), 29.81 (d, C-6), 25.58 (t, C-11), 25.24 (t, C-10), 24.92 (t, C-13), 24.10 (t, C-15), 15.91 (q, 6-Me), assignments by SELINQUATE experiments at $\delta = 31.4$, 34.2, 35.9, 53.0; IR (ATR): $\tilde{\nu} = 1151$, 1125 (ν C–O–C, asym.), 1704 (ν C=O), 1734, 1776 (ν C=OO), 1031, 1000 cm^{-1} (ν C–O–C, sym.); MS (70 eV): *m/z* (%): 252 (8) $[M]^+$, 234 (1) $[M - H_2O]^+$, 224 (2) $[M - CO]^+$, 193 (7) $[M - H_2O - 2CO]^+$, 152 (37) $[C_{10}H_{16}O]^+$, 123 (14) $[C_9H_{15}]^+$, 109 (100) $[C_8H_{13}]^+$, 95 (66) $[C_7H_{11}]^+$, 67 (65) $[C_5H_7]^+$, 55 (66) $[C_4H_7]^+$, 41 (78) $[C_3H_5]^+$; crystal data and structure refinement: Empirical formula $C_{15}H_{24}O_3$, molecular mass 252.34, crystal dimensions $0.9 \times 0.15 \times 0.01$ mm, temperature 150 K, wavelength 0.71073 Å, monoclinic crystal system, space group $P2_1$, unit cell dimensions $a = 10.484(2)$ Å, $b = 6.5030(13)$ Å, $c = 10.996(2)$ Å, $\alpha = 90°$, $\beta = 111.16(3)°$, $\gamma = 90°$, $V = 699.1(2)$ Å^3, $Z = 2$, $\rho = 1.199$ mg m^{-3}, $\mu(Mo_{K\alpha}) = 0.082$ mm^{-1}, $F(000)$ 276, θ range 1.99–22.22°, limiting indices $-9 \le h \le 11$, $-6 \le k \le 6$, $-11 \le l \le 11$, total reflections collected 2784, symmetry-independent reflections 1645, $R_{int} = 0.2094$, refinement full-matrix least squares on F^2, data 1645, parameters 163, goodness-of-fit on F^2 0.955, final R indices $[I > 2\sigma(I)]$ $R_1 = 0.0689$, $wR_2 = 0.1650$, R indices (all data) $R_1 = 0.0919$, $wR_2 =$ 0.1752, $\Delta\rho$ (max, min) = 0.308, -0.245 e Å^3; CCDC-148828 (see Section 1); elemental analysis calcd (%) for $C_{15}H_{24}O_3$ (252.4): C 71.39, H 9.59; found C 71.21, H 9.48.

(1S,6R,9R)-(−)-6-Methyl-4-oxabicyclo[7.5.1]pentadeca-3,8-dione (**21**): Scale 40 mmol (14.1 g of **19**), yield 33% (3.36 g of **21**), $R_f = 0.25$ (pentane/Et_2O, 4:1), colorless crystals, M.p. 55.2–57.6 °C; $[\alpha]_D^{22} = -18.8$, $[\alpha]_{546}^{22} = -25.0$ ($c = 2.07$ in $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 4.19$ (dd, $J =$ 10, 3 Hz, 1H; 5-H_a), 4.03 (dd, $J = 10$, 10 Hz, 1H; 5-H_b), 2.85–1.31 (m, 19H; 1-,6-,9-H, 2-,7-,10-,11-,12-,13-,14-,15-H_2), 1.01 (d, $J = 8$ Hz, 3H; 6-Me); ^{13}C NMR (400 MHz): $\delta = 214.68$ (s, C-8), 172.41 (s, C-3), 69.20 (t, C-5), 53.19 (d, C-9), 48.53, 44.61 (2t, C-7,-2), 40.16 (d, C-1), 38.02, 37.00 (2t, C-12,-14), 32.95, 31.85 (2t, C-11,-13), 30.70 (d, C-6), 28.46, 27.15 (2t, C-10,-15), 18.04 (q, 6-Me); IR (ATR): $\tilde{\nu} = 1729$ (ν C=OO), 1238, 1213, 1190 (ν C–O–C, asym.), 1676 (ν C=O), 997 cm^{-1} (ν C–O–C, sym.); MS (70 eV): *m/z* (%): 252 (4) $[M]^+$, 234 (1) $[M - H_2O]^+$, 224 (2) $[M - CO]^+$, 193 (2) $[M - H_2O - 2CO]^+$, 152 (37) $[C_{10}H_{16}O]^+$, 123 (12) $[C_9H_{15}]^+$, 109 (100) $[C_8H_{13}]^+$, 95 (62) $[C_7H_{11}]^+$, 67 (66) $[C_5H_7]^+$, 55 (68) $[C_4H_7]^+$, 41 (78) $[C_3H_5]^+$; crystal data and structure refinement: Empirical formula $C_{15}H_{24}O_3$, molecular mass 252.34, crystal dimensions $0.5 \times 0.4 \times 0.25$ mm, temperature 150 K, wavelength 0.71073 Å, orthorhombic crystal system, space group $P2_12_12_1$, unit cell dimensions $a = 17.706(4)$ Å, $b = 12.621(3)$ Å, $c = 6.1342(12)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 1370.8(5)$ Å^3, $Z = 4$, $\rho =$ 1.223 mg m^{-3}, $\mu(Mo_{K\alpha}) = 0.083$ mm^{-1}, $F(000)$ 552, θ range 1.98–25.84°, limiting indices $-20 \le h \le 21$, $-14 \le k \le 15$, $-7 \le l \le 7$, total reflections collected 15258, symmetry-independent reflections 2617, $R_{int} = 0.1805$, refinement full-matrix least squares on F^2, data 2617, parameters 164, goodness-of-fit on F^2 0.999, final R indices $[I > 2\sigma(I)]$ $R_1 = 0.0525$, $wR_2 =$ 0.1178, R indices (all data) $R_1 = 0.0590$, $wR_2 = 0.1203$, $\Delta\rho$ (max, min) = 0.327, -0.180 e Å^3; CCDC-148830 (see Section 1); elemental analysis calcd (%) for $C_{15}H_{24}O_3$ (252.4): C 71.39, H 9.59; found C 71.28, H 9.46.

5. Target molecules: general procedure: A solution of the bicyclic keto lactone (2.52 mmol) and 4-toluenesulfonohydrazide (2.77 mmol) in MeOH (15 mL) was refluxed under N_2 for 50 min. The solvent was removed by using a rotary evaporator, the crude product was dried on a high-vacuum line for 15 h, and then dissolved in anhydrous $CHCl_3$ (12 mL). At 0 °C under N_2, a catecholborane solution (1M) in MePh (5.52 mmol) was injected, and the reaction mixture was stirred for 2 h at this temperature prior to quenching by addition of anhydrous MeOH (0.7 mL). After a further 10 min. of stirring at 0 °C, $NaOAc \cdot 3H_2O$ (2.77 mmol) and DMSO (1.2 mL) were added, and the mixture was heated to reflux for 1 h. The reaction mixture was then poured into Et_2O/water (1:1, 120 mL), and the organic layer was separated, washed with water (2×50 mL), dried with Na_2SO_4, and concentrated under reduced pressure. Purification of the crude products by FC furnished the odoriferous target molecules.

(1R,9R*)-4-Oxabicyclo[7.5.1]pentadecan-3-one* (**7**): Scale 2.52 mmol (0.60 g of **6**), yield 51% (0.29 g of **7**), $R_f = 0.41$ (pentane/Et_2O, 19:1), colorless crystals, M.p. 47.6 °C; odor description: very weak, woody, ambery, with a slight, very faint undertone of musk; ^{1}H NMR (400 MHz): $\delta = 4.58$ (ddd, $J = 11$, 11, 3 Hz, 1H; 5-H_a), 3.92 (dd, $J = 11$, 4 Hz, 1H; 5-H_b), 2.42 (dd, $J = 15$, 4 Hz, 1H; 2-H_a), 2.18 (dd, $J = 15$, 13 Hz, 1H; 2-H_b), 2.07 (m, 1H; 11-H_a), 1.94 (m, 3H; 1-,12-,13-H_a), 1.73–1.59 (m, 5H; 7-,9-,10-H_a, 6-H_2), 1.50–1.02 (m, 11H; 7-,10-,11-,12-,13-H_b, 8-,14-,15-H_2); ^{13}C NMR (400 MHz): $\delta = 173.42$ (s, C-3), 64.55 (t, C-5), 45.34 (t, C-2), 41.19 (t, C-10), 40.59 (d, C-9), 38.31 (d, C-1), 37.75 (t, C-14), 36.86, 36.76 (2t, C-8,-15), 31.90 (t, C-13), 29.58 (t, C-11), 27.79 (t, C-12), 25.76 (t, C-6), 20.81 (t, C-7); IR (KBr): $\tilde{\nu} = 1730$, 1718 (ν C=OO), 1245, 1276 (ν C–O–C, asym.), 1182 (ν C–C(=O)–O), 1473, 1447 (δ CH_2), 996, 973 cm^{-1} (ν C–O–C, sym.); MS (70 eV): *m/z* (%): 224 (16) $[M]^+$, 206 (22) $[M - H_2O]^+$, 196 (7) $[M - CO]^+$, 182 (32) $[M - C_2H_2O]^+$, 180 (36) $[M - CO_2]^+$, 164 (19) $[M - C_2H_2O - H_2O]^+$, 136 (50) $[C_{10}H_{16}]^+$, 109 (62), 95 (67), 81 (94), 67 (100) $[C_nH_{2n-3}]^+$, 55 (89) $[C_4H_7]^+$, 41 (88) $[C_3H_5]^+$; crystal data and structure refinement: Empirical formula $C_{14}H_{24}O_2$, molecular mass 224.33, crystal dimensions $0.25 \times 0.25 \times 0.1$ mm, temperature 293(2) K, wavelength 0.71073 Å, monoclinic crystal system, space group $P2_1/c$, unit cell dimen-

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sions $a = 5.2340(10)$ Å, $b = 31.298(6)$ Å, $c = 8.2440(16)$ Å, $\alpha = 90°$, $\beta = 102.55(3)°$, $\gamma = 90°$, $V = 1318.2(4)$ Å^3, $Z = 4$, $\rho = 1.130$ mg m^{-3}, $\mu(Mo_{K\alpha}) = 0.073$ mm^{-1}, $F(000)$ 496, θ range 2.60–25.90°, limiting indices $-6 \le h \le 6$, $-38 \le k \le 38$, $-9 \le l \le 9$, total reflections collected 10086, symmetry-independent reflections 2517, $R_{int} = 0.0309$, refinement full-matrix least squares on F^2, data 2517, parameters 146, goodness-of-fit on F^2 1.021, final R indices $[I > 2\sigma(I)]$ $R_1 = 0.0439$, $wR_2 = 0.1074$, R indices (all data) $R_1 = 0.0610$, $wR_2 = 0.1172$, $\Delta\rho$ (max, min) = 0.182, −0.095 e Å^3; CCDC-142427 (see Section 1); elemental analysis calcd (%) for $C_{14}H_{24}O_2$ (224.3): C 74.95, H 10.78; found C 74.73, H 10.66.

(*1R*,10S**)-*4-Oxabicyclo[8.4.1]pentadecan-3-one* (***12***): Scale 5.17 mmol (1.23 g of **11**), yield 24% (0.28 g of **12**), $R_f = 0.43$ (pentane/Et_2O, 19:1), colorless liquid; odor description: very weak, slight and very faint musk tonality, anisic, fruity; quite close to **22** but much weaker; ^{1}H NMR (400 MHz): $\delta = 4.28$ (dd, $J = 11$, 11 Hz, 1H; 5-H$_a$), 4.02 (dd, $J = 11$, 6 Hz, 1H; 5-H$_b$), 2.33 (dd, $J = 15$, 4 Hz, 1H; 2-H$_a$), 2.17 (dd, $J = 15$, 12 Hz, 1H; 2-H$_b$), 2.00–1.80 (m, 4H; 1-,6-,11-,13-H$_a$), 1.71 (m, 1H; 6-H$_b$), 1.64–1.30 (m, 12H; 9-,10-,14-H$_a$, 13-H$_b$, 7-,8-,12-,15-H$_2$), 1.05–0.98 (m, 3H; 9-,11-,14-H$_b$); ^{13}C NMR (400 MHz): $\delta = 172.70$ (s, C-3), 64.74 (t, C-5), 43.14 (t, C-2), 36.99 (t, C-14), 36.05 (t, C-11), 34.27 (t, C-15), 34.22 (d, C-10), 31.12 (t, C-9), 30.59 (t, C-13), 29.87 (d, C-1), 26.41 (t, C-7), 24.79 (t, C-12), 23.99 (t, C-6), 23.12 (t, C-8), assignments by 2D-NMR experiments; IR (ATR): $\tilde{\nu} = 1730$ (ν C=OO), 1246 (ν C–O–C, asym.), 998 (ν C–O–C, sym.), 1471 cm^{-1} (δ CH_2); MS (70 eV): m/z (%): 224 (2) $[M]^+$, 206 (2) $[M - H_2O]^+$, 182 (14) $[M - C_2H_2O]^+$, 164 (29) $[M - C_2H_2O - H_2O]^+$, 138 (30) $[C_{10}H_{18}]^+$, 108 (35) $[C_8H_{12}]^+$, 95 (93), 81 (55), 67 (70) $[C_nH_{2n-3}]^+$, 55 (74) $[C_4H_7]^+$, 41 (100) $[C_3H_5]^+$; elemental analysis calcd (%) for $C_{14}H_{24}O_2$ (224.3): C 74.95, H 10.78; found C 74.93, H 10.86.

(*1S,6R,10R*)-(+)-*6-Methyl-4-oxabicyclo[8.4.1]pentadecan-3-one* (***18***): Scale 8.72 mmol (2.20 g of **17**), yield 32% (674 mg of **18**), $R_f = 0.45$ (pentane/Et_2O, 19:1), colorless crystals, M.p. 31.9 °C; odor description: very powerful, woody, cedarwood, ambery, slightly animal-like; $[\alpha]_D^{22} = +6.0$, $[\alpha]_{546}^{22} = +9.1$ ($c = 0.73$ in $CHCl_3$); ^{1}H NMR (700 MHz): $\delta = 4.05$ (dd, $J = 11$, 10 Hz, 1H; 5-H$_a$), 3.81 (br d, $J = 11$ Hz, 1H; 5-H$_b$), 2.33 (dd, $J = 16$, 4 Hz, 1H; 2-H$_a$), 2.18 (dd, $J = 16$, 12 Hz, 1H; 2-H$_b$), 2.17 (m, 1H; 6-H), 1.96 (m, 1H; 1-H), 1.87 (m, 1H; 11-H$_a$), 1.82 (m, 1H; 13-H$_a$), 1.62–1.56 (m, 2H; 12-,14-H$_a$), 1.55–1.48 (m, 4H; 7-,9-,15-H$_a$, 10-H), 1.45–1.35 (m, 3H; 8-H$_a$,12-,15-H$_b$), 1.30–1.23 (m, 3H; 7-,8-,13-H$_b$), 1.14 (dddd, $J = 13$, 12, 12, 5 Hz, 1H; 14-H$_b$), 1.08 (dddd, $J = 13$, 11, 8, 4 Hz, 1H; 9-H$_b$), 0.97 (m, 1H; 11-H$_b$), 0.91 (d, $J = 7$ Hz, 3H; 6-Me); ^{13}C NMR (700 MHz): $\delta = 172.49$ (s, C-3), 69.91 (t, C-5), 43.12 (t, C-2), 36.90 (t, C-14), 36.09 (t, C-11), 35.70 (t, C-7), 34.21 (t, C-15), 34.10 (d, C-10), 31.81 (t, C-9), 30.52 (t, C-13), 29.72 (d, C-1), 28.98 (d, C-6), 24.71 (t, C-12), 23.43 (t, C-8), 19.22 (q, 6-Me), assignments by 2D-NMR experiments; IR (ATR): $\tilde{\nu} = 1724$ (ν C=OO), 1263, 1281 (ν C–O–C, asym.), 993 (ν C–O–C, sym.), 1472, 1454 (δ CH_2), 1375 cm^{-1} (δ CH_3); MS (70 eV): m/z (%): 238 (2) $[M]^+$, 220 (3) $[M - H_2O]^+$, 196 (10) $[M - C_2H_2O]^+$, 178 (40) $[M - C_3H_8O]^+$, 138 (39) $[M - C_6H_{12}O]^+$, 122 (39) $[M - C_6H_{12}O_2]^+$, 108 (58) $[C_8H_{12}]^+$, 95 (100) $[C_7H_{11}]^+$, 81 (76) $[C_6H_9]^+$, 41 (77) $[C_3H_5]^+$; crystal data and structure refinement: Empirical formula $C_{15}H_{26}O_2$, molecular mass 238.36, crystal dimensions $0.2 \times 0.1 \times 0.04$ mm, temperature 150(2) K, wavelength 0.71073 Å, monoclinic crystal system, space group $P2_1$, unit cell dimensions $a = 10.664(2)$ Å, $b = 5.6180(11)$ Å, $c = 12.023(2)$ Å, $\alpha = 90°$, $\beta = 100.77(3)°$, $\gamma = 90°$, $V = 707.6(2)$ Å^3, $Z = 2$, $\rho = 1.119$ mg m^{-3}, $\mu(Mo_{K\alpha}) = 0.072$ mm^{-1}, $F(000)$ 264, θ range 1.72–22.24°, limiting indices $-11 \le h \le 11$, $-5 \le k \le 5$, $-10 \le l \le 12$, total reflections collected 2052, symmetry-independent reflections 1485, $R_{int} = 0.0632$, refinement full-matrix least squares on F^2, data 1485, parameters 154, goodness-of-fit on F^2 0.862, final R indices $[I > 2\sigma(I)]$ $R_1 = 0.0473$, $wR_2 = 0.1081$, R indices (all data) $R_1 = 0.0722$, $wR_2 = 0.1160$, $\Delta\rho$ (max, min) = 0.168, −0.158 e Å^3; CCDC-142428 (see Section 1); elemental analysis calcd (%) for $C_{15}H_{26}O_2$ (238.4): C 75.58, H 11.00; found C 75.50, H 11.01.

(*1R,6R,9R*)-(+)-*6-Methyl-4-oxabicyclo[7.5.1]pentadecan-3-one* (***22***): Scale 4.36 mmol (1.10 g of **20**), yield 9% (90 mg of **22**), $R_f = 0.45$ (pentane/Et_2O, 19:1), colorless liquid; odor description: powerful, fresh, musky, anisic, fruity, ambery; $[\alpha]_D^{22} = +16.2$, $[\alpha]_{546}^{22} = +19.2$ ($c = 1.99$ in $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 4.62$ (dd, $J = 10$, 4 Hz, 1H; 5-H$_a$), 3.37 (dd, $J = 10$, 10 Hz, 1H; 5-H$_b$), 2.42–1.21 (m, 21H; 1-H, 2-H$_2$, 6-H – 15-H$_2$), 0.92 (d, $J = 7$ Hz, 3H; 6-Me); ^{13}C NMR (400 MHz): $\delta = 173.65$ (s, C-3), 70.04 (t, C-5), 45.31 (d, C-9), 44.10 (t, C-2), 40.64 (t, C-10), 40.53 (d, C-1), 38.72, 37.98, 37.44 (3t, C-13–C-15), 34.71 (d, C-6), 32.89 (t, C-8), 30.25, 30.10 (2t, C-7,-11), 27.64 (t, C-12), 18.32 (q, 6-Me); IR (ATR): $\tilde{\nu} = 1734$ (ν C=OO), 1147, 1215 (ν C–O–C, asym.), 1014 (ν C–O–C, sym.), 1474 (δ CH_2), 1373 cm^{-1} (δ CH_3); MS (70 eV): m/z (%): 238 (2) $[M]^+$, 220 (7) $[M - H_2O]^+$, 194 (15) $[M - CO_2]^+$, 178 (14) $[M - C_3H_8O]^+$, 151 (31) $[C_{11}H_{19}]^+$, 122 (26) $[C_9H_{14}]^+$, 109 (57), 95 (73), 81 (86), 67 (83) $[C_nH_{2n-3}]^+$, 55 (95) $[C_4H_7]^+$, 41 (100) $[C_3H_5]^+$; elemental analysis calcd (%) for $C_{15}H_{26}O_2$ (238.4): C 75.58, H 10.99; found C 75.28, H 10.88.

(*1S,6R,9S*)-(+)-*6-Methyl-4-oxabicyclo[7.5.1]pentadecan-3-one* (***23***): Scale 7.62 mmol (1.92 g of **21**), yield 39% (0.71 g of **23**), $R_f = 0.37$ (pentane/Et_2O, 19:1); odor description: relatively weak, reminiscent of sawdust and hot iron, to some perfumers musky; $[\alpha]_D^{22} = +37.4$, $[\alpha]_{546}^{22} = +44.3$ ($c = 2.09$ in $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 4.20$ (dd, $J = 12$, 11 Hz, 1H; 5-H$_a$), 3.80 (dd, $J = 12$, 4 Hz, 1H; 5-H$_b$), 2.39 (dd, $J = 15$, 4 Hz, 1H; 2-H$_a$), 2.18 (dd, $J = 15$, 12 Hz, 1H; 2-H$_b$), 2.08 (m, 1H; 11-H$_a$), 1.95–1.91 (m, 4H; 1-,6-,12-,13-H$_a$), 1.62–1.26 (m, 9H; 7-,9-,10-,15-H$_a$, 11-,12-,13-H$_b$, 14-H$_2$), 1.25–1.05 (m, 5H; 7-,10-,15-H$_b$, 8-H$_2$), 0.91 (t, $J = 7$ Hz, 3H; 6-Me); ^{13}C NMR (400 MHz): $\delta = 173.14$ (s, C-3), 69.54 (t, C-5), 45.19 (t, C-2), 41.23 (t, C-10), 41.16 (d, C-9), 38.60 (d, C-1), 37.79 (t, C-14), 36.54 (t, C-15), 35.80 (t, C-8), 32.10 (t, C-13), 31.28 (d, C-6), 29.96 (t, C-7), 29.55 (t, C-11), 27.73 (t, C-12), 18.66 (q, 6-Me), assignments by an INADEQUATE (Incredible Natural Abundance Double-QUAntum Transfer Experiment) experiment; IR (ATR): $\tilde{\nu} = 1733$ (ν C=OO), 1240, 1285 (ν C–O–C, asym.), 1012 (ν C–O–C, sym.), 1449, 1474 (δ CH_2), 1371 cm^{-1} (δ CH_3); MS (70 eV): m/z (%): 238 (2) $[M]^+$, 220 (7) $[M - H_2O]^+$, 194 (15) $[M - CO_2]^+$, 178 (12) $[M - C_3H_8O]^+$, 152 (22) $[C_{11}H_{20}]^+$, 122 (21) $[C_9H_{14}]^+$, 109 (41), 95 (49), 81 (62), 67 (66) $[C_nH_{2n-3}]^+$, 55 (85) $[C_4H_7]^+$, 41 (100) $[C_3H_5]^+$; elemental analysis calcd (%) for $C_{15}H_{26}O_2$ (238.4): C 75.58, H 10.99; found C 75.81, H 10.89.

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