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# Unexpected Tethering in the Synthesis of Methyl-Substituted Acetyl-1-oxaspiro[4.5]decanes: Novel Woody–Ambery Odorants with Improved Bioavailability

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*Dedicated to Professor Elias J. Corey on the occasion of his 80th birthday*

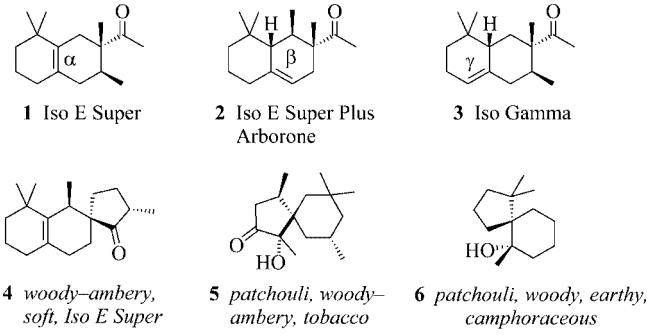
**Keywords:** Biodegradation / Diels–Alder reactions / Fragrances / Structure–activity relationships / Tethering effects

To study the olfactory properties of spirocyclic analogs of Iso Gamma (**3**) with improved water solubility and bioavailability, it was envisaged to spiroannulate 1-acetyl-1,2-dimethylcyclohexanone at the 4-position with a 3,3-dimethyltetrahydrofuran-2-yl moiety that would mimic the polarity of the double bond by its ether function. 3,3-Dimethyl-4-methylenehex-5-en-1-ol (**9**) was prepared by copper(I)-mediated 1,4-conjugate addition of the Grignard reagent of chloroprene (**7**) to 3-methylbut-2-enal with subsequent LAH reduction. However, the Diels–Alder reaction of diene **9** with (*E*)-3-methylpent-3-en-2-one in the presence of $Me_2AlCl$ unexpectedly provided exclusively the undesired *meta* adduct **10**, as was discovered after cyclization to **11** with $MeSO_3H$. The wrong selectivity was due to a tethering effect of the Lewis acid, and this could be evaded by changing the carbonyl function of the dienophile to a hydroxy group. Thereby the (5′*R**,7′*S**,8′*S**)-configured 1-(4′,4′,7′,8′-tetramethyl-1′-oxaspiro[4.5]decan-7′/8′-yl)ethan-1-ones **11** and **14**, as well as the *like*-configured 1-(4′,4′,7′-trimethyl-1′-oxaspiro[4.5]-decan-7′/8′-yl)ethan-1-ones **16** and **19**, were prepared selectively and studied for their odor characters, threshold values, and octanol/water partition coefficients.


## Introduction

Due to its transparent woody–ambery character, Iso E Super remains one of the most important odorants both in terms of production volume and number of perfumes in which it is used. While its main component, the α-isomer **1**, bearing the double bond between the bridgehead carbon atoms, is very weak in smell, with an odor threshold of 500 ng/L,[1,2] the β-isomer **2**, which has been termed Iso E Super Plus[3] or Arborone,[4] determines the odor of this perfumery raw material with an odor threshold that is 100,000 times lower. The β-isomer **2** constitutes only 3–4% of commercial grade Iso E Super, but recently a higher-quality material, in which the β-isomer is enriched by a factor of two, has been manufactured by a different process. This quality is known as Iso Gamma Super,[2] since it contains in addition 18% of the γ-isomer **3**, which also possesses a very pleasant woody–ambery odor note (Figure 1).

Recently, we reported on the synthesis of potent spirocyclic ketones,[3] including the spirocyclic Georgywood analog **4**, which emanated the soft, woody–ambery odor of the β-isomer **2** accompanied by additional aspects of orris. These rigidified spirocyclic analogs had been designed to probe the α-helical leu-gly-gly-leu motif that Hong and Corey[4] had proposed for the binding of **2**, and to elucidate the active conformation(s) of these woody–ambery odorants on the olfactory receptor(s). Despite its limited conformational flexibility, the spirocyclic analog **4** proved to be a very powerful odorant with an odor threshold of 0.094 ng/L air.[3] Moreover, the spirocyclic ketol **5** was discovered to be one of the most powerful patchouli odorants,[5] possessing an odor threshold of 0.027 ng/L, in addition to woody–am-




**1** Iso E Super | **2** Iso E Super Plus Arborone | **3** Iso Gamma

**4** *woody–ambery, soft, Iso E Super* | **5** *patchouli, woody–ambery, tobacco* | **6** *patchouli, woody, earthy, camphoraceous*

Figure 1. The woody–ambery benchmark odorants **1**–**3**, the powerful soft, woody–ambery spirocyclic ketone **4**, and two intense patchouli-like, woody spirocycles **5** and **6**.

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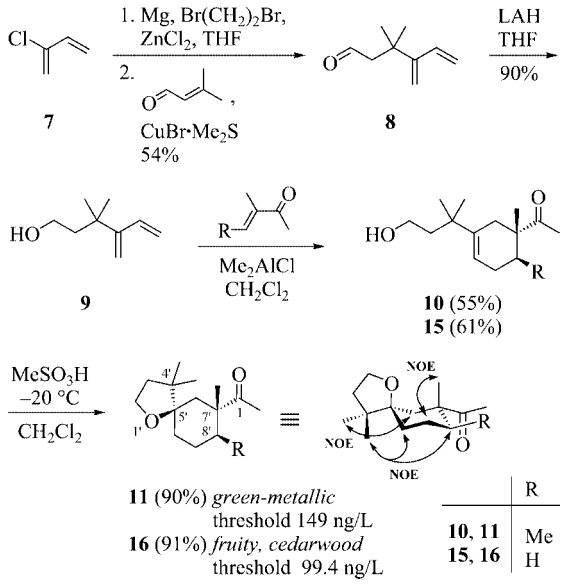
bery, tobacco-like facets, and the dimethylcyclopentyl-spiroannulated cyclohexanol **6** also displayed very interesting olfactory properties,[6] again in the patchouli direction, but with additional woody, earthy, and camphoraceous undertones.

It thus seemed interesting to study spirocyclic analogs of Iso Gamma (**3**), but these should exhibit an improved water solubility and bioavailability, since all Iso E Super isomers **1**–**3** have a calculated octanol/water partition coefficient of $\log(P_{ow})_{calcd.} = 5.01$ and are prone to bioaccumulation. The $\log(P_{ow})$ value corresponds to the bioavailability of the substances in aquatic systems, and a high $\log(P_{ow})$ value indicates bad biodegradability or even persistency in the environment. According to the European REACH regulations now in place, all substances with $\log(P_{ow}) > 4.5$ are suspected of being persistent in the environment. To mimic and even augment the polarity of the γ-double bond of **3**, it was therefore planned to spiroannulate 1-acetyl-1,2-dimethylcyclohexanone at the 4-position with a 3,3-dimethyltetrahydrofuran-2-yl moiety. Thereby, the calculated octanol/water partition coefficient $\log(P_{ow})_{calcd.}$ improves from $\log(P_{ow})_{calcd.} = 5.01$ for **1**–**3** to $\log(P_{ow})_{calcd.} = 3.48$ for the first target structure **14** (Scheme 2), which makes **14** an attractive target compound also from an environmental point of view.

## Results and Discussions

At first glance, synthetic access to target structure **14** by the Diels–Alder reaction and a subsequent acid-catalyzed cyclization seemed rather straightforward. The appropriate starting material, chloroprene (**7**), is an inexpensive bulk chemical prepared by gas-phase chlorination of butadiene with subsequent dehydrohalogenation. The preparation of the corresponding Grignard reagent of chloroprene (**7**) is not possible by direct reaction with magnesium in ether, THF, or xylene, as reported by Aufdermarsh,[7] but it can be achieved in the presence of anhydrous zinc(II) chloride, as Nunomoto and Yamashita found 15 years later.[8] We, however, decided to employ the entrainment method of Pearson et al.,[9] which uses, in addition to zinc(II) chloride, 1,2-dibromoethane as entrainer to activate the magnesium surface. The 1,2-dibromoethane reacts with magnesium, and the intermediate magnesium species immediately decomposes to $MgBr_2$ and ethene, thereby generating a highly activated, nascent metal surface.[10] In this manner, the Grignard reagent of the 2-chlorobuta-1,3-diene (**7**) was conveniently prepared, and its copper(I)-mediated 1,4-conjugate addition to 3-methylbut-2-enal furnished dienal **8** in 54% yield after chromatographic purification (Scheme 1). The corresponding dihomoallylic dienol **9** was isolated in 90% yield by standard lithium aluminum hydride (LAH) reduction in THF.

As the hydroxy function of **9** was too far away from the diene double bonds to have any decisive influence on the frontier orbitals, it was expected that **9** would behave like a normal 2-alkyl-substituted buta-1,3-diene. Buta-1,3-dienes




Scheme 1. Synthesis of undesired *meta*-configured 7-acetyl-4,4-dimethyl-1-oxaspiro[4.5]decanes **11** and **16** by an aluminum-tethered Diels–Alder reaction.

bearing an alkyl substituent at the 2-position react with acceptor-substituted olefins to give predominantly the *para*-configured Diels–Alder adduct, especially in the presence of Lewis acids that by complexation with the acceptor group extend the allylic cation character of the dienophile and polarize the LUMO even more. By lowering the LUMO energy of the olefin, Lewis acids also increase the reactivity of Diels–Alder reactions. Without the addition of an aluminum Lewis acid, no reaction was observed between diene **9** and (*E*)-3-methylpent-3-en-2-one. However, in the presence of 10 mol-% of dimethylaluminum chloride, the reaction went smoothly, and only one regioisomer was formed with complete selectivity. Yet, as was discovered by 2D NMR spectroscopy of the subsequent cyclization product **11**, the formed Diels–Alder adduct **10** did not have the desired and expected *para*-orientation, but was indeed *meta*-configured.

As detailed HOMO/LUMO investigations offered no explanation, it was concluded that the aluminum Lewis acid must have tethered the Diels–Alder reaction to complete *meta*-selectivity. Such a tethering of [4+2] cycloadditions by magnesium and aluminum salts was first described by Stork and Chan in connection with allylic dienols,[11] and Batey et al.[12] also reported a case of a homoallylic dienol in a boron-tethered Diels–Alder reaction with (*E*)-dicyclohexylbuta-1,3-dienyl boronate. Bertozzi et al.[13] enabled otherwise "noncompatible" combinations of dienes and dienophiles by temporary tethering allylic dienols with allylic alkenols by using $AlMe_3$ or $ZnMe_2$, and more recently Barriault et al.[14] examined Diels–Alder reactions of dienes with an allylic alcohol function at the α- or β-position in the presence of PhMgBr or $MgBr_2{\cdot}OEt_2$ and triethylamine. Covalent tethering of Diels–Alder reactions is also possible, and type 2 intramolecular Diels–Alder reactions have been extensively reviewed.[15,16] Already in the 1980s, Tamao, Ko-

bayashi, and Ito demonstrated covalent tethering on the example of silicon,[17] while Shea and co-workers reported on uncatalyzed[18a] and $Et_2AlCl$-catalyzed[18b] intramolecular cycloadditions with high *meta*-selectivity.

To the best of our knowledge, a tethering with a dihomoallylic dienol such as **9** has never been observed. The proposed transition state **A** (Figure 2) involves an unusual 4-alumina-3,5-dioxabicyclo[7.3.1]tridec-1(12),2,9(13),10(11)-tetraene ring system, in which transannular strain in the 10-membered ring favors an *endo*-orientation of the dienophile. Even if (8*Z*)-4,4,7,8,10,10-hexamethyl-5-methylene-3,4,5,10-tetrahydro-2*H*-oxecine is taken as a completely flexible model of this partial ring, the global minimum (PM3) of the (6*Z*)-isomer representing the *endo*-conformation is favored by 20 kJ/mol (4.8 kcal/mol) over the (6*E*)-isomer representing an *exo*-orientation. A better model to account for the complete regio- and stereoselectivity of the reaction, which furnished **10** in a good yield of 55%, could not be devised, and further studies concerning the *endo*-/*exo*-selectivity of the reaction were beyond the scope of this work.

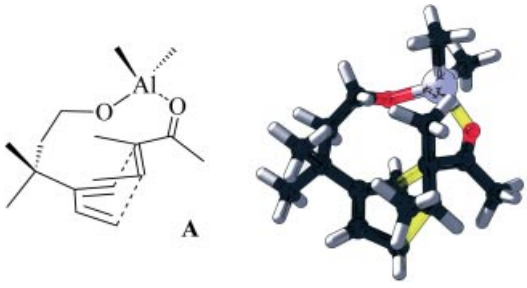


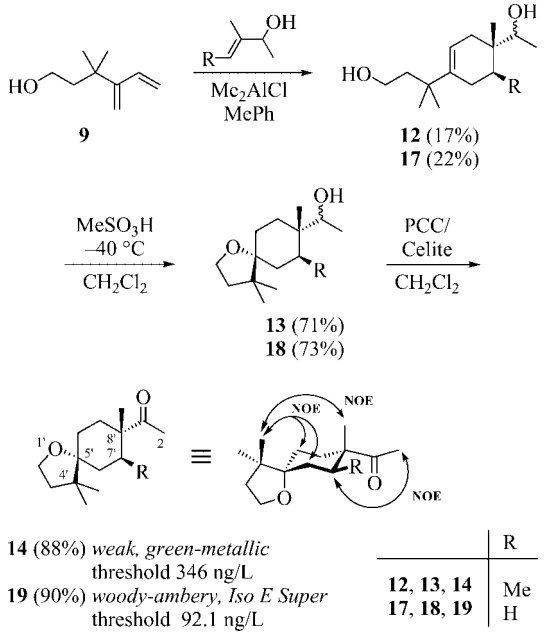

Figure 2. Proposed 10-membered transition state **A** for the Diels–Alder reaction of the dihomoallylic dienol **9** and (*E*)-3-methylpent-3-en-2-one, tethered by dimethylaluminum chloride.

The undesired course of the Diels–Alder reaction was discovered in the cyclization product **11**. Treatment of the hydroxy cyclohexenone **10** with methanesulfonic acid in $CH_2Cl_2$ at –20 °C furnished exclusively the (5′*R**,7′*S**,8′*S**)-configured 1-(4′,4′,7′,8′-tetramethyl-1′-oxaspiro[4.5]decan-7′-yl)ethan-1-one (**11**). This high diastereoselectivity, for which low temperatures were indispensable, is explicable by the bis(equatorial) orientation of the 1′-acetyl and 6′-methyl substituent with the axial 1′-methyl group, forcing the hydroxy function to attack the cationic center from the same side in order to avoid 1,3-diaxial interaction of 1′-$Me_{ax}$ with $Me_2C$-2′′. The side chain can thus swing in the direction of the carbenium ion only from the side of the axial methyl group on the carbon atom that also bears the acetyl moiety. This stereochemistry of **11** was proven by distinct NOE effects between 7′-$Me_{ax}$ and 9′-$H_{ax}$, 4′-$Me_{ax}$ and 10′-$H_{ax}$, as well as 4′-$Me_{eq}$ and 6′-$H_{ax}$, with assignments of the atoms by INADEQUATE and HSQC experiments. The *meta*-configured 7-acetyl-1-oxaspiro[4.5]decane **11** was thus isolated in 90% yield as a single diastereoisomer. Yet, not only was it spiroannulated at the wrong position, but also the odor character was not that which was desired. Though **11** smelled sweet, with a distinct woody–earthy character as well as root-like nuances, its main note was green-metallic, and with an odor threshold of 149 ng/L air it was rather weak.

The problem was therefore to avoid the undesired tethering effect, so that the Diels–Alder reaction would take the desired course. Though this could have been done by protection of the hydroxy function of **9**, we wanted to employ the same diene **9** without protecting groups and wondered if the increased acidity of the corresponding allyl alcohol dienophile would not prevent the reaction of the catalytic amounts of $Me_2AlCl$ with the dihomoallylic dienol, so that complexes with multiple allyl alcohol ligands would rather result. First, an intermediate allyloxy(methyl)aluminum chloride species should be formed, and frontier-orbital calculations indicated this also to exhibit a lower LUMO energy and therefore an enhanced reactivity. Most importantly, however, the tethering effect should thereby be "switched off" and could thus indirectly be proven. Indeed, as the 2D NMR experiments of the final product revealed, the Diels–Alder reaction of **9** with (3*E*)-3-methylpent-3-en-2-ol in refluxing toluene in the presence of 20 mol-% of $Me_2AlCl$ provided exclusively the desired *para* product **12**, albeit in a mere 17% yield, which is due to the thermal instability of diene **9** (Scheme 2). Matsubara et al.[19] had also reported a 17.2% yield for the thermal Diels–Alder reaction of alloocimene with allyl alcohol to afford the slightly woody-smelling diastereomeric mixture of the corresponding Diels–Alder adducts, again due to thermal instability. Thus, one could have also suspected a purely thermal course of the Diels–Alder reaction in our case, but we can exclude a purely thermal course, since only decomposition products, but no adduct **12**, were formed in the absence of $Me_2AlCl$. An alternative explanation for the non-tethering in the case of the allyl alcohol could be an excessively high activation energy of the formed complex, as the dienophile is less reactive, and type 2 cycloadditions typically show high activation energies.[16]

Diol **12** was then treated, in analogy to the synthesis of **11**, with methanesulfonic acid at –40 °C, and the resulting cyclization product **13** was isolated in 71% by flash chromatography (FC). After oxidation of the remaining hydroxy function of **13** with pyridinium chlorochromate (PCC) on Celite in $CH_2Cl_2$, the target compound **14** was obtained in 88% yield as a single diastereomer. The relative (5′*R*,7′*S*,8′*S*)-stereochemistry was unambiguously derived from distinct crosspeaks of 7′-$H_{ax}$ with 2-$Me_{eq}$, 6′- and 10′-$H_{ax}$ with 4′-$Me_2$ as well as 8′-$Me_{ax}$ with 4′-$Me_2$ in the NOESY spectrum after assignment of all atoms by HSQC and INADEQUATE experiments. As the equatorially situated side chain of **12** is now displaced by one position, the steric interaction of the hydroxy group with the axial methyl group on the acetyl carbon atom predominates, and the side chain swings in the opposite direction as in the cyclization of **10**; yet, consequently lower temperatures are necessary to ensure a clean course of the cyclization. So, by changing the dienophile, we could avoid tethering and arrive at our target molecule **14**. However, in terms of olfactory properties, the 8-acetyl-substituted 4,4,7,8-tetramethyl-1-oxaspiro[4.5]decane was also disappointing: with an odor




Scheme 2. Synthesis of the *para*-configured 8-acetyl-substituted target compounds **14** and **19** by Diels–Alder reaction with (3*E*)-3-methylpent-3-en-2-ol and 3-methylbut-3-en-2-ol.

threshold of 346 ng/L air, it was even weaker than **11**, and despite earthy-woody accents, its main odor character was green-metallic just as was **11** – so the position of the spiro-annulated dimethyltetrahydrofuran ring was not of the expected importance.

To study the structure–odor relationship and the selectivity of the Diels–Alder reaction in more detail, it was planned to investigate the reactions of diene **9** with 3-methylbut-3-en-2-one and its corresponding alcohol. As was the case for (*E*)-3-methylpent-3-ene-2-one, the $Me_2AlCl$-catalyzed Diels–Alder reaction of 3-methylbut-3-en-2-one with **9** provided also the *meta*-configured adduct **15**, in a slightly increased yield of 61%. Cyclization of **15** at –20 °C in the presence of methanesulfonic acid afforded the corresponding *like*-configured 7-acetyl-1-oxaspiro[4.5]decane **16** in 91% yield as a single diastereoisomer, the stereochemistry of which was again assigned by NOESY and HSQC experiments. The woody aspects now came to the fore, and **16** emanated a fruity, cedarwood note with slightly agrestic and spicy facets. The odor threshold also improved to 99.4 ng/L air, though this is still not very potent.

Again the presumed tethering of the aluminum Lewis acid could be evaded by changing over to the corresponding allylic alcohol. Diels–Alder reaction of 3-methylbut-3-en-2-ol with dienol **9** in the presence of 20 mol-% $Me_2AlCl$ in refluxing toluene furnished the *para*-configured adduct **17** in a slightly improved yield of 22%. Subsequent acid-catalyzed cyclization employing methanesulfonic acid in $CH_2Cl_2$ at –40 °C provided the spirocyclic alcohol **18** in 73% yield. This was oxidized by PCC on Celite in $CH_2Cl_2$ to afford the final target compound **19** in 90% yield after purification by flash chromatography (FC). The *like*-stereochemistry of the 8-acetyl trimethyloxaspiro[4.5]decane **19** was assigned first by 2D NMR spectroscopy. As the target structure **19** was crystalline, the *trans*-orientation of the tetrahydrofuran oxygen atom with respect to the methyl substituent could be confirmed independently by a single-crystal X-ray structure analysis (Figure 3).

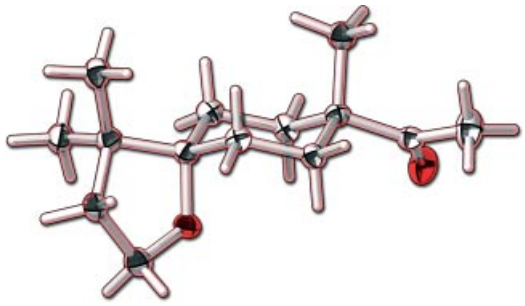


Figure 3. Molecular structure of (±)-(5′*R**,8′*R**)-1-(4′,4′,8′-trimethyl-1′-oxaspiro[4.5]decan-8′-yl)ethan-1-one (**19**) in the crystal, with thermal ellipsoids at the 50% probability level.

### Olfactory Properties and Water Solubility

Of all acetyl-1-oxaspiro[4.5]decanes investigated, the *like*-8-acetyl trimethyloxaspiro[4.5]decane **19** possesses the lowest odor threshold (92.1 ng/L air), and it is also the one that resembles the lead structure Iso E Super (**1**) most closely in character. Its odor was described as woody–ambery, reminiscent of **1**, with some agrestic, conifer-type facets, and a slightly medicinal touch. The *meta*-configured analog, the *like*-7-acetyl trimethyloxaspiro[4.5]decane **16** was quite similar in odor intensity (99.4 ng/L air). Its woody character was, however, purely cedarwood-like, without ambery facets, but instead with a strong fruity inclination, and additional agrestic as well as spicy facets. The introduction of an 8-methyl group into **16** diminished the odor intensity significantly, and a threshold value of 149 ng/L air was measured for the respective 7-acetyl tetramethyloxaspiro[4.5]decane **11**. The odor also shifted towards sweet, green, and metallic attributes, while a woody tonality accompanied by earthy and root-like nuances was perceptible only in the background. The first target structure **14** was the weakest of the series investigated, and, with an odor threshold of 346 ng/L air, not far from the very weak α-isomer **1** of Iso E Super with an odor threshold of 500 ng/L air. Its weak green-metallic odor with earthy-woody accents was indeed quite close in character to its 7-acetyl analog **11**.

While for Iso E Super (**1**) the octanol/water partition coefficient according to the OECD guideline No. 117[20] is $\log(P_{ow}) = 5.7$, $\log(P_{ow}) < 4.5$ was measured for all target compounds. The most water-soluble odorants investigated were the crystalline 8-acetyl trimethyloxaspiro[4.5]decane **19** and its *meta*-configured 7-acetyl analog **16**, for which a $\log(P_{ow}) = 3.2$ was measured in both cases. As expected, the tetramethyloxaspiro[4.5]decanes **11** and **14** were less water-soluble, the *meta*-configured 7-acetyl analog **11** being the least water-soluble with $\log(P_{ow}) = 4.0$. For the *para*-configured 8-acetyl **14**, an intermediate value of $\log(P_{ow}) = 3.7$ was determined according to the OECD guideline No. 117.[20]

## Conclusions

All target compounds display an improved bioavailability, but only (5′*R**,8′*R**)-1-(4′,4′,8′-trimethyl-1′-oxaspiro[4.5]decan-8′-yl)ethan-1-one (**19**) resembles the commercial Iso E Super closely in olfactory character. With an odor threshold of 92.1 ng/L, this is, however, much weaker than the commercial Iso E Super quality with 3–4% of the high-impact β-isomer **2**. Even though the woody–ambery odorant **19** is thus economically not competitive; it represents a forward-looking idea for the design of novel odorants with improved bioavailability. The $Me_2AlCl$-mediated tethering concept of dihomoallylic dienols such as **9**, which can simply be controlled by the functional group of the dienophile, leading to complete *meta*-selectivity of the Diels–Alder reaction in case of an α,β-unsaturated carbonyl compound, and complete *para*-selectivity in case of an allylic hydroxy dienophile, will certainly be useful for directing the selectivity of related Diels–Alder reactions. As Diels–Alder reactions constitute one of the most important C–C-bond-forming reactions, the extension of the tethering concept to dihomoallylic dienol systems should have a broader applicability to organic synthesis, and possibly could even be extended much further still.

## Experimental Section

IR: Bruker VECTOR 22/Harrick SplitPea micro ATR, Si. NMR: Bruker AVANCE DPX-400, Bruker AVANCE 500 (TCI), TMS int. (= 0 ppm). MS: Finnigan MAT 95 (EI: 70 eV), HP Chemstation 6890 GC / 5973 Mass-Sensitive Detector. FC (flash chromatography): Brunschwig Silica 100726 (32–63 μm, 60 Å). TLC: Merck Kieselgel 60 $F_{254}$ (particle size 5–20 μm, layer thickness 250 μm on glass, 10 cm × 10 cm); visualization reagent: phosphomolybdic acid spray (Merck 1.00480.0100). Melting points: Büchi Melting Point B545 (uncorr.). Elemental analyses: Mikroanalytisches Laboratorium Ilse Beetz, 96301 Kronach, Germany. X-ray: Hoffmann-La Roche, CH-4070 Basel, Switzerland; Stoe IPDS I diffractometer (Image Plate Diffraction Systems); SHELX-97.[21] Unless otherwise stated, all reactions were performed under a $N_2$ atmosphere. Starting materials, reagents, and solvents were used without further purification: SAFC or Acros, except 2-chlorobuta-1,3-diene (**7**, 50% in xylene) from ABCR, 76151 Karlsruhe, Germany.

Odor thresholds were determined by GC–olfactometry: Different dilutions of the sample substance were injected into a gas chromatograph in descending order of concentration until the panelist failed to detect the respective substance at the sniffing port. The panelist smelled in blind and pressed a button on perceiving an odor. If the recorded time matched the retention time, the concentration was halved. The last concentration detected at the correct retention time is the individual odor threshold. The reported threshold values are the geometrical means of the individual odor thresholds of different panelists.

**3,3-Dimethyl-4-methylenehex-5-enal (8):** At room temp., a solution of 1,2-dibromoethane (9.58 g, 51.0 mmol) in THF (50 mL) was added to a stirred suspension of Mg turnings (22.0 g, 905 mmol) in THF (50 mL), the reaction being initiated by occasional heating with a heat gun. A solution of $ZnCl_2$ in $Et_2O$ (1 M, 5.60 mL, 5.60 mmol) was added by syringe, which caused vigorous reflux. Under reflux, a solution of 2-chlorobuta-1,3-diene (**7**, 50% in xylene, 100g, 565 mmol) and 1,2-dibromoethane (22.2 g, 119 mmol) in THF (800 mL) was then added within 1 h. After being kept at reflux for an additional 2 h, the reaction mixture was cooled to –60 °C, and $CuBr{\cdot}Me_2S$ (18.6 g, 90.5 mmol) was added portionwise within 45 min. After further stirring for 20 min at this temp., a solution of 3-methylbut-2-enal (76.1 g, 905 mmol) in THF (200 mL) was added over a period of 30 min. The reaction mixture was then quenched at –10 °C by addition of satd. aq. $NH_4Cl$ solution (700 mL), and the product was extracted with $Et_2O$ (3 × 500 mL). The combined organic extracts were washed with brine (2 × 200 mL), dried ($Na_2SO_4$), and concentrated under reduced pressure. The resulting residue was purified by silica gel FC (pentane/$Et_2O$, 98:2, $R_f$ = 0.20) to furnish **8** (42.2 g, 54%). IR (neat): $\tilde{\nu}$ = 1719 (s, $\nu_{C=O}$), 1466 [w, $\delta_{as}(CH_3)$], 1366 [w, $\delta_s(CH_3)$], 902 (m, $\delta_{C=C-H}$) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ = 1.26 (s, 6 H, 3-$Me_2$), 2.40 (d, $J$ = 3.0 Hz, 2 H, 2-$H_2$), 4.88 (dd, $J$ = 1.0, 1.0 Hz, 1 H, 6-$H_E$), 5.11 (dd, $J$ = 11.0, 2.0 Hz, 1 H, 6-$H_Z$), 5.21 (dd, $J$ = 1.0, 1.0 Hz, 1 H, 1′-$H_Z$), 5.44 (dd, $J$ = 17.0, 2.0 Hz, 1 H, 1′-$H_E$), 6.42 (dddd, $J$ = 17.0, 11.0, 1.0, 1.0 Hz, 1 H, 5-H), 9.62 (d, $J$ = 3.0 Hz, 1 H, 1-H) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 27.6 (q, 3-$Me_2$), 37.1 (s, C-3), 53.4 (t, C-2), 109.9 (t, C-1′), 116.4 (t, C-6), 135.9 (d, C-5), 153.4 (s, C-4), 203.0 (d, C-1) ppm. MS (EI): *m*/*z* (%) = 138 (2) $[M]^+$, 120 (3) $[M - CH_3]^+$, 96 (100) $[M - C_2H_2O]^+$, 95 (26) $[M - C_2H_3O]^+$, 81 (95) $[C_6H_9]^+$.

**3,3-Dimethyl-4-methylenehex-5-en-1-ol (9):** At 0–2 °C, a solution of **8** (40.3 g, 292 mmol) in THF (500 mL) was added dropwise with stirring over a period of 1.5 h to a suspension of $LiAlH_4$ (11.1 g, 292 mmol) in THF (300 mL), and the reaction mixture was stirred for additional 4 h at room temp., prior to cautious quenching at 0 °C with water (11.1 mL), followed by aq. NaOH solution (15%, 11.1 mL), and again water (33.3 mL). The resulting precipitate was stirred for 30 min at room temp., filtered off with suction, and washed with $Et_2O$ (200 mL). The filtrate was concentrated, and the resulting residue was purified by silica gel FC (pentane/$Et_2O$, 8:2, $R_f$ = 0.18) to afford **9** (36.8 g, 90%) as a colorless liquid. IR (neat): $\tilde{\nu}$ = 3320 (m, $\nu_{O-H}$), 1461 [w, $\delta_{as}(CH_3)$], 1363 [w, $\delta_s(CH_3)$], 1021 (m, $\nu_{C-O}$), 897 (s, $\delta_{C=C-H}$) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ = 1.11 (s, 6 H, 3-$Me_2$), 1.62 (br. s, 1 H, OH), 1.70 (dt, $J$ = 7.5, 7.5 Hz, 2 H, 1-$H_2$), 3.56 (t, $J$ = 7.5 Hz, 2 H, 2-$H_2$), 4.80 (dd, $J$ = 1.0, 1.0 Hz, 1 H, 6-$H_E$), 5.05 (dd, $J$ = 11.0, 2.0 Hz, 1 H, 6-$H_Z$), 5.15 (dd, $J$ = 1.0, 1.0 Hz, 1 H, 1′-$H_Z$), 5.42 (dd, $J$ = 17.0, 2.0 Hz, 1 H, 1′-$H_E$), 6.41 (dddd, $J$ = 17.0, 11.0, 1.0, 1.0 Hz, 1 H, 5-H) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 27.6 (q, 3-$Me_2$), 37.0 (s, C-3), 43.5 (t, C-2), 59.9 (t, C-1), 109.1 (t, C-1′), 115.3 (t, C-6), 136.5 (d, C-5), 154.7 (s, C-4) ppm. MS (EI): *m*/*z* (%) = 125 (3) $[M - CH_3]^+$, 96 (100) $[M - C_2H_4O]^+$, 81 (71) $[M - C_2H_4O]^+$.

**(±)-(1′*R**,6′*R**)-1-[3′-(4′′-Hydroxy-2′′-methylbutan-2′′-yl)-1′,6′-dimethylcyclohex-3′-enyl]ethan-1-one (10):** At 0 °C, a $Me_2AlCl$ solution (1 M in hexanes, 3.30 mL, 3.30 mmol) was added within 5 min to a solution of **9** (4.63 g, 33.0 mmol) and (*E*)-3-methylpent-3-en-2-one (3.88 g, 39.6 mmol) in $CH_2Cl_2$ (10 mL). The reaction mixture was stirred overnight at room temp., poured into water (100 mL), and extracted with $Et_2O$ (3 × 200 mL). The combined organic extracts were dried ($Na_2SO_4$), and the solvents were evaporated. The resulting residue was purified by silica gel FC (pentane/$Et_2O$, 1:1, $R_f$ = 0.18) to furnish **10** (4.32 g, 55%). IR (neat): $\tilde{\nu}$ = 3377 (m, $\nu_{O-H}$), 1698 (s, $\nu_{C=O}$), 1454 [m, $\delta_{as}(CH_3)$], 1353 [m, $\delta_s(CH_3)$], 1020 (m, $\nu_{C-O}$) $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ = 0.80 (d, $J$ = 7.0 Hz, 3 H, 6′-Me), 1.00 (s, 6 H, 2′′-$Me_2$), 1.04 (d, $J$ = 7.0 Hz, 3 H, 1-Me), 1.65 (t, $J$ = 8.0 Hz, 2 H, 3′′-$H_2$), 1.69–1.80 (m, 1 H, 5′-$H_b$), 1.90 (br. s, 1 H, OH), 2.05–2.08 (m, 1 H, 5′-$H_a$), 2.06 (qd, $J$ = 7.0, 1.0 Hz, 1 H, 2′-$H_{ax}$), 2.11–2.12 (m, 1 H, 6′-H), 2.16 (s, 3 H, 2-$H_3$), 2.34 (qd, $J$ = 7.0, 1.0 Hz, 1 H, 2′-$H_{eq}$), 3.55 (td, $J$ = 8.0, 5.5 Hz, 2

H, 4′′-$H_2$), 3.57–3.59 (m, 1 H, 4′-H) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 15.9 (q, 6′-Me), 16.2 (q, 1′-Me), 25.2 (q, C-2), 27.4/27.5 (2q, 2′′-$Me_2$), 31.4 (t, C-5′), 32.2 (d, C-6′), 33.2 (t, C-2′), 37.2 (s, C-2′′), 42.9 (t, C-3′′), 50.7 (s, C-1′), 60.0 (t, C-4′′), 117.8 (d, C-4′), 140.8 (s, C-3′), 214.3 (s, C-1) ppm. MS (EI): *m/z* (%) = 238 (2) $[M]^+$, 223 (3) $[M - CH_3]^+$, 195 (74) $[M - C_2H_3O]^+$, 151 (58) $[C_{11}H_{19}]^+$, 43 (100) $[C_2H_3O]^+$.

**(±)-(5′*R**,7′*S**,8′*S**)-1-(4′,4′,7′,8′-Tetramethyl-1′-oxaspiro[4.5]decan-7′-yl)ethan-1-one (11):** At –20 °C, $MeSO_3H$ (1.87 g, 19.5 mmol) was added within 15 min to a stirred solution of **10** (3.82 g, 16.2 mmol) in $CH_2Cl_2$ (80 mL). The resulting dark brown solution was warmed slowly to 0 °C, stirred for 1 h at this temp. and then for 4 h at room temp., prior to being poured into water (200 mL) and extracted with $Et_2O$ (3 × 300 mL). The combined organic extracts were washed with brine (2 × 100 mL), dried ($Na_2SO_4$), and the solvents were evaporated. The resulting residue was purified by silica gel FC (pentane/$Et_2O$, 95:5, $R_f$ = 0.17) to provide the odoriferous title compound **11** (3.44 g, 90%). IR (neat): $\tilde{\nu}$ = 1698 (s, $\nu_{C=O}$), 1469 [m, $\delta_{as}(CH_3)$], 1365 [m, $\delta_s(CH_3)$], 1026 (m, $\nu_{C-O}$) $cm^{-1}$. $^1$H NMR ($CDCl_3$): $\delta$ = 0.71/0.73 (2s, 4′-$Me_2$), 0.76 (d, *J* = 7.0 Hz, 3 H, 8′-Me), 1.02 (td, *J* = 17.0, 4.0 Hz, 1 H, 10′-$H_{ax}$), 1.25 ($m_c$, 1 H, 6′-$H_{ax}$), 1.28 ($m_c$, 1 H, 9′-$H_{ax}$), 1.33 (s, 3 H, 7′-Me), 1.34 ($m_c$, 1 H, 6′-$H_{eq}$) 1.35 ($m_c$, 1 H, 3′-$H_{ax}$), 1.36 ($m_c$, 1 H, 10′-$H_{eq}$), 1.39 (td, *J* = 6.5, 3.0 Hz, 1 H, 3′-$H_{eq}$), 1.62 (qd, *J* = 17.0, 3.5 Hz, 1 H, 10′-$H_{eq}$), 1.86 (s, 3 H, 2-$H_3$), 1.93 (tq, *J* = 17.0, 7.0 Hz, 1 H, 8′-H), 3.59 (td, *J* = 6.5, 3.0 Hz, 2 H, 2′-$H_2$) ppm. $^1$H,$^1$H NOESY ($CDCl_3$): 7′-$Me_{ax}$ × 9′-$H_{ax}$, 4′-$Me_{ax}$ × 10′-$H_{ax}$, 4′-$Me_{eq}$ × 6′-$H_{ax}$, 8′-$H_{ax}$ × 10′-$H_{ax}$, 8′-$H_{ax}$ × 6′-$H_{ax}$. $^{13}$C NMR ($CDCl_3$): $\delta$ = 16.0 (q, 7′-Me), 17.5 (q, 8′-Me), 23.7/23.9 (2q, 4′-$Me_2$), 25.4, (q, C-2), 27.1 (t, C-9′), 31.0 (t, C-10′), 35.6 (d, C-8′), 38.9 (t, C-6′), 39.7 (t, C-3′), 43.6 (s, C-4′), 52.3 (s, C-7′), 63.1 (t, C-2′), 84.0 (t, C-5′), 213.3 (s, C-1) ppm. MS (EI): *m/z* (%) = 238 (5) $[M]^+$, 223 (2) $[M - CH_3]^+$, 195 (22) $[M - C_2H_3O]^+$, 169 (58) $[C_{10}H_{17}O_2]^+$, 125 (100) $[C_8H_{13}O]^+$, 43 (36) $[C_2H_3O]^+$. $C_{15}H_{26}O_2$ (238.4): calcd. C 75.58, H 10.99; found C 75.62, H 10.97. Odor (10% DPG, blotter): Sweet, green-metallic odor with a woody tonality and earthy, root-like nuances. Odor threshold: 149 ng/L air. Partition coefficient (HPLC): log($P_{ow}$) = 4.0.

**(±)-(4′*R**,5′*R**,1′′*R**)-3-[4′-(1′′-Hydroxyethyl)-4′,5′-dimethylcyclohex-1′-enyl]-3-methylbutan-1-ol (12):** A mixture of **9** (6.32 g, 45.1 mmol), (3*E*)-3-methylpent-3-en-2-ol (9.02 g, 90.0 mmol), and $Me_2AlCl$ (1 M in hexanes, 9.0 mL, 9.0 mmol) in toluene (100 mL) was heated at reflux for 3 d. After the heating source was removed, the reaction mixture was poured into water (100 mL) and extracted with $Et_2O$ (3 × 400 mL). The combined organic extracts were dried ($Na_2SO_4$), and the solvents were evaporated. The resulting residue was purified by silica gel FC (pentane/$Et_2O$, 3:7, $R_f$ = 0.17) to provide **12** (1.84 g, 17%). IR (neat): $\tilde{\nu}$ = 3358 (m, $\nu_{O-H}$), 1454 [m, $\delta_{as}(CH_3)$], 1376 [m, $\delta_s(CH_3)$], 1052 (s, $\nu_{C-O}$), 905 (m, $\delta_{C=C-H}$) $cm^{-1}$. $^1$H NMR ($CDCl_3$): $\delta$ = 0.68/0.69 (2s, 3 H, 4′-Me), 0.81/0.84 (2d, *J* = 6.5 Hz, 3 H, 5′-Me), 1.02/1.03 (2s, 6 H, 3-$Me_2$), 1.14/1.16 (2d, *J* = 6.5 Hz, 3 H, 2′′-$H_3$), 1.62–1.66 (m, 2 H, 2-$H_2$), 1.70–1.73 (m, 1 H, 3′-$H_{ax}$), 1.75–1.77 (m, 1 H, 6′-$H_{ax}$), 1.84–1.87 (m, 1 H, 5′-H), 2.08–2.10 (m, 1 H, 3′-$H_{eq}$), 2.11–2.15 (m, 1 H, 6′-$H_{eq}$), 3.53/3.54 (2t, *J* = 7.5 Hz, 2 H, 1-$H_2$), 3.73–3.76 (m, 1 H, 1′′-H), 5.33–5.36 (m, 1 H, 2′-H) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 15.1/15.2 (2q, 5′-Me), 15.3/15.6 (2q, 4′-Me), 17.0/17.2 (2q, C-2′′), 25.6 (t, C-6′), 27.2/27.5/27.7/28.0 (4q, 3-$Me_2$), 31.1/31.9 (2d, C-5′), 37.3/37.4 (2s, C-3), 38.6/38.8 (2s, C-4′), 42.9/43.2 (2t, C-3′), 60.1/60.2 (2t, C-2), 67.9 (t, C-1), 70.5/72.7 (2d, C-1′′), 117.7/118.0 (2d, C-2′), 141.7/141.8 (2s, C-1′) ppm. MS (EI): *m/z* (%) = 240 (2) $[M]^+$, 222 (3) $[M - H_2O]^+$, 195 (12) $[M - C_2H_5O]^+$, 109 (80) $[C_8H_{13}]^+$, 45 (35) $[C_2H_5O]^+$.

**(±)-(1*RS*,5′*R**,7′*S**,8′*S**)-1-(4′,4′,7′,8′-Tetramethyl-1′-oxaspiro[4.5]decan-8′-yl)ethan-1-ol (13):** At –40 °C, $MeSO_3H$ (740 mg, 7.70 mmol) was added within 10 min to a stirred solution of **12** (1.54 g, 6.41 mmol) in $CH_2Cl_2$ (50 mL). The resulting dark-brown solution was allowed to slowly warm to 0 °C, and it was stirred for 3 h at this temp., then 3 h at room temp. The reaction mixture was poured into water (100 mL) and extracted with $Et_2O$ (3 × 300 mL). The combined organic layers were washed with brine (2 × 100 mL), dried ($Na_2SO_4$), and the solvents were evaporated. The resulting residue was purified by silica gel FC (pentane/$Et_2O$, 6:4, $R_f$ = 0.15) to furnish **13** (1.10 g, 71%). IR (neat): $\tilde{\nu}$ = 3430 (m, $\nu_{O-H}$), 1457 [m, $\delta_{as}(CH_3)$], 1366 [m, $\delta_s(CH_3)$], 1033 (s, $\nu_{C-O}$) $cm^{-1}$. $^1$H NMR ($CDCl_3$): $\delta$ = 0.69 (s, 3 H, 8′-Me), 0.75/0.80 (2d, *J* = 7.0 Hz, 3 H, 7′-Me), 0.95/0.96 (2s, 6 H, 4-$Me_2$), 1.12/1.15 (2d, *J* = 6.5 Hz, 3 H, 2-$H_3$), 1.19–1.26 (m, 2 H, 6′-, 9′-$H_{ax}$), 1.32–1.38 (m, 2 H, 9′-$H_{eq}$, 10′-$H_{ax}$), 1.46/1.50 (2q, *J* = 7.0 Hz, 1 H, 7′-H), 1.69–1.73 (m, 2 H, 6′-$H_{eq}$, 3′-$H_{ax}$), 1.78–1.83 (m, 2 H, 3′-, 10′-$H_{eq}$), 3.72–3.78 (m, 2 H, 2′-$H_2$), 3.79–3.80 (m, 1 H, 1-H), 5.08 (br. s, 1 H, OH) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 14.5/14.8 (2q, 7′-Me), 15.6/15.7 (2q, 8′-Me), 17.0/17.2 (2q, C-2), 23.6/23.9 (2q, 4′-$Me_2$), 25.6/26.0 (2t, C-9′), 25.8/26.2 (2t, C-10′), 29.8/32.0 (2d, C-7′), 35.4/35.6 (2t, C-6′), 39.0/39.4 (2s, C-4′), 39.9/40.1 (2t, C-3′), 42.5/42.6 (2s, C-8′), 67.9 (t, C-2′), 71.9/74.4 (2d, C-1), 84.0/84.2 (2s, C-5′) ppm. MS (EI): *m/z* (%) = 240 (15) $[M]^+$, 222 (2) $[M - H_2O]^+$, 195 (5) $[M - C_2H_5O]^+$, 125 (100) $[C_8H_{13}O]^+$, 45 (26) $[C_2H_5O]^+$.

**(±)-(5*R*′*,7′*S**,8′*S**)-1-(4′,4′,7′,8′-Tetramethyl-1′-oxaspiro[4.5]decan-8′-yl)ethan-1-one (14):** At room temp., PCC (1.17 g, 5.43 mmol) was added portionwise to a suspension of **13** (870 mg, 3.62 mmol) and Celite (3.00 g) in $CH_2Cl_2$ (15 mL). The reaction mixture was stirred for 5 h at room temp., filtered through a pad of Celite, and washed with $Et_2O$ (10 mL). The filtrate was concentrated, and the resulting residue was purified by silica gel FC (pentane/$Et_2O$, 95:5, $R_f$ = 0.14) to furnish the odoriferous title compound **14** (760 mg, 88%) as a colorless liquid. IR (neat): $\tilde{\nu}$ = 1700 (s, $\nu_{C=O}$), 1457 [m, $\delta_{as}(CH_3)$], 1364 [m, $\delta_s(CH_3)$], 1029 (m, $\nu_{C-O}$) $cm^{-1}$. $^1$H NMR ($C_6D_6$): $\delta$ = 0.64 (d, *J* = 7.0 Hz, 3 H, 7′-Me), 0.77/0.79 (2s, 6 H, 4′-$Me_2$), 0.93 ($m_c$, 1 H, 6′-$H_{ax}$), 0.95 (s, 3 H, 8′-Me), 1.07 ($m_c$, 1 H, 10′-$H_{ax}$), 1.12 ($m_c$, 1 H, 9′-$H_{ax}$), 1.24 ($m_c$, 1 H, 10′-$H_{eq}$), 1.28 ($m_c$, 1 H, 6′-$H_{eq}$), 1.50 (t, *J* = 7.5 Hz, 2 H, 2′-$H_2$), 1.93 (s, 3 H, 2-$H_3$), 2.08 (td, *J* = 12.5, 4.0 Hz, 1 H, 9′-$H_{eq}$), 2.49 ($m_c$, 1 H, 7′-$H_{ax}$), 3.61 (t, *J* = 7.5 Hz, 2 H, 3′-$H_2$) ppm. $^1$H,$^1$H NOESY ($C_6D_6$): 8′-$Me_{ax}$ × 10′-$H_{ax}$, 7′-$H_{ax}$ × 2-$Me_{eq}$, 6′-$H_{ax}$ × 4′-$Me_2$, 8′-$Me_{ax}$ × 4′-$Me_2$, 10′-$H_{ax}$ × 4′-$Me_2$. $^{13}$C NMR ($C_6D_6$): $\delta$ = 12.5 (q, 8′-Me), 17.6 (q, 7′-Me), 23.6/23.7 (2q, 4′-$Me_2$), 24.3 (q, C-2), 26.0 (t, C-10′), 31.5 (d, C-7′), 32.0 (t, C-9′), 35.1 (t, C-6′), 40.3 (t, C-3′), 42.4 (s, C-4′), 51.5 (s, C-8′), 63.1 (t, C-2′), 83.8 (s, C-5′), 214.6 (s, C-1) ppm. MS (EI): *m/z* (%) = 238 (22) $[M]^+$, 223 (5) $[M - CH_3]^+$, 195 (10) $[M - C_2H_3O]^+$, 169 (68) $[C_{10}H_{17}O_2]^+$, 125 (100) $[C_8H_{13}O]^+$, 43 (100) $[C_2H_3O]^+$. $C_{15}H_{26}O_2$ (238.4): calcd. C 75.58, H 10.99; found C 75.51, H 10.95. Odor (10% DPG, blotter): Weak, green-metallic odor, with slightly earthy-woody accents. Odor threshold: 346 ng/L air. Partition coefficient (HPLC): log($P_{ow}$) = 3.7.

**1-[3′-(4′′-Hydroxy-2′′-methylbutan-2′′-yl)-1′-methylcyclohex-3′-enyl]ethan-1-one (15):** In analogy to the preparation of **10**, compound **15** was obtained from **9** (4.21 g, 30.0 mmol), 3-methyl-3-buten-2-one (3.03 g, 36.0 mmol), and a solution of $Me_2AlCl$ (1 M in hexanes, 3.0 mL, 3. 0 mmol) in $CH_2Cl_2$ (10 mL) after standard workup and silica gel FC (pentane/$Et_2O$, 1:1; $R_f$ = 0.17). Yield 61% (4.11 g); colorless oil. IR (neat): $\tilde{\nu}$ = 3391 (m, $\nu_{O-H}$), 1700 (s, $\nu_{C=O}$), 1458 [m, $\delta_{as}(CH_3)$], 1355 [m, $\delta_s(CH_3)$], 1024 (m, $\nu_{C-O}$) $cm^{-1}$. $^1$H NMR ($CDCl_3$): $\delta$ = 1.02/1.03 (2s, 6 H, 2′′-$Me_2$), 1.11 (s, 3 H, 1′-Me), 1.54–1.60 (m, 2 H, 5′-, 6′-$H_{ax}$), 1.63 (td, *J* = 7.5, 3.0 Hz, 2 H,

3′′-$H_2$), 1.85–1.90 (m, 2 H, 2′-$H_{ax}$, 6′-$H_{eq}$), 2.01–2.07 (m, 2 H, 2′-, 5′-$H_{eq}$), 2.14 (s, 3 H, 2-$H_3$), 3.48 (t, $J$ = 7.5 Hz, 2 H, 4′′-$H_2$), 5.43–5.45 (m, 1 H, 4′-H) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 21.7 (t, C-5′), 23.1 (q, 1′-Me), 24.6 (q, C-2), 27.5/27.7 (2q, 2′′-$Me_2$), 31.3 (t, C-2′), 33.9 (t, C-6′), 37.2 (s, C-2′′), 43.2 (t, C-3′′), 46.0 (s, C-1′), 59.9 (t, C-4′′), 117.7 (d, C-4′), 142.6 (s, C-3′), 213.8 (s, C-1) ppm. MS (EI): $m/z$ (%) = 224 (2) $[M]^+$, 211 (2) $[M - CH_3]^+$, 206 (5) $[M - H_2O]^+$, 180 (36) $[C_{12}H_{20}O]^+$, 43 (100) $[C_2H_3O]^+$.

**(±)-(5′*R**,7′*R**)-1-(4′,4′,7′-Trimethyl-1′-oxaspiro[4.5]decan-7′-yl)-ethan-1-one (16):** In analogy to the preparation of **11**, the odoriferous title compound **16** was obtained from **15** (3.37 g, 15.0 mmol) and $MeSO_3H$ (1.73 g, 18.0 mmol) in $CH_2Cl_2$ (80 mL) after standard workup and silica gel FC (pentane/$Et_2O$, 95:5; $R_f$ = 0.16). Yield 91% (3.07 g); colorless liquid. IR (neat): $\tilde{\nu}$ = 1701 (s, $\nu_{C=O}$), 1470 [m, $\delta_{as}(CH_3)$], 1365 [m, $\delta_s(CH_3)$], 1028 (m, $\nu_{C-O}$) $cm^{-1}$. $^1$H NMR ($C_6D_6$): $\delta$ = 0.74/0.78 (2s, 6 H, 4′-$Me_2$), 0.86 (td, $J$ = 7.5, 3.0 Hz, 1 H, 10′-$H_{ax}$), 1.16 (td, $J$ = 7.0, 3.5 Hz, 1 H, 8′-$H_{ax}$), 1.37 (s, 3 H, 7′-Me), 1.41 ($m_c$, 1 H, 10′-$H_{eq}$), 1.43 ($m_c$, 1 H, 9′-$H_{eq}$), 1.45 ($m_c$, 1 H, 3′-$H_{ax}$), 1.47 ($m_c$, 1 H, 6′-$H_{ax}$), 1.49 ($m_c$, 1 H, 3′-$H_{eq}$), 1.50 ($m_c$, 1 H, 8′-$H_{eq}$), 1.56 ($m_c$, 1 H, 6′-$H_{eq}$), 1.82 (s, 3 H, 2-$H_3$), 1.86 (2t, $J$ = 7.5 Hz, 9′-$H_{ax}$), 3.57 ($m_c$, 2 H, 2′-$H_2$) ppm. $^1$H,$^1$H NOESY ($C_6D_6$): 7′-$Me_{ax}$ × 2′-$H_{ax}$, 1-$Me_{eq}$ × 4′-$Me_{eq}$, 4′-$Me_{ax}$ × 8′-$H_{ax}$. $^{13}$C NMR ($C_6D_6$): $\delta$ = 18.4 (t, C-9′), 21.8 (q, 7′-Me), 23.6/23.8 (2q, 4′-$Me_2$), 23.9 (q, C-2), 30.5 (t, C-10′), 33.5 (t, C-8′), 35.7 (t, C-6′), 39.7 (t, C-3′), 43.8 (s, C-4′), 48.1 (s, C-7′), 63.1 (t, C-2′), 84.3 (s, C-5′), 212.1 (s, C-1) ppm. MS (EI): $m/z$ (%) = 224 (2) $[M]^+$, 209 (2) $[M - CH_3]^+$, 181 (30) $[M - C_2H_3O]^+$, 155 (100) $[C_9H_{15}O_2]^+$, 43 (100) $[C_2H_3O]^+$. $C_{14}H_{24}O_2$ (224.3): calcd. C 74.95, H 10.78; found C 74.98, H 10.70. Odor (10% DPG, blotter): Fruity, cedarwood note with slightly agrestic and spicy facets. Odor threshold: 99.4 ng/L air. Partition coefficient (HPLC): log($P_{ow}$) = 3.2.

**(±)-3-[4′-(1′′-Hydroxyethyl)-4′-methylcyclohex-1′-enyl]-3-methylbutan-1-ol (17):** In analogy to the preparation of **12**, compound **17** was obtained from **9** (7.01 g, 50.0 mmol), 3-methylbut-3-en-2-ol (8.61 g, 100 mmol), and $Me_2AlCl$ (1 M in hexanes, 10.0 mL, 10.0 mmol) in toluene (100 mL) after standard workup and silica gel FC (pentane/$Et_2O$, 3:7, $R_f$ = 0.16). Yield 22% (2.49 g); colorless oil. IR (neat): $\tilde{\nu}$ = 3332 (m, $\nu_{O-H}$), 1458 [m, $\delta_{as}(CH_3)$], 1374 [m, $\delta_s(CH_3)$], 1058 (s, $\nu_{C-O}$), 912 (m, $\delta_{C=C-H}$) $cm^{-1}$. $^1$H NMR ($CDCl_3$): $\delta$ = 0.81/0.82 (2s, 3 H, 4′-Me), 1.04/1.05 (2s, 6 H, 3-$Me_2$), 1.12/1.14 (2d, $J$ = 6.5 Hz, 3 H, 2′′-$H_3$), 1.35–1.42 (m, 2 H, 2-$H_2$), 1.54–1.60 (m, 1 H, 5′-$H_{ax}$), 1.61–1.69 (m, 2 H, 5′-$H_{eq}$, 3′-$H_{ax}$), 1.84–1.87 (m, 1 H, 6′-$H_{ax}$), 1.97–2.09 (m, 2 H, 3′-$H_{eq}$, 6′-$H_{eq}$), 3.51 (td, $J$ = 7.0, 4.0 Hz, 2 H, 1-$H_2$), 3.73–3.76 (m, 1 H, 1′′-H), 5.38–5.42 (m, 1 H, 2′-H) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 17.3/17.4 (2q, 4′-Me), 18.0/18.2 (2q, C-2′′), 21.2/25.5 (2t, C-6′), 27.4/27.5/27.6/27.7 (4q, 3-$Me_2$), 30.4/31.1 (2t, C-5′), 34.0/34.6 (2t, C-3′), 35.3/35.4 (2s, C-3), 37.1/37.2 (2s, C-4′), 42.8/43.2 (2t, C-2), 60.1/67.8 (2t, C-1), 72.7/74.3 (2d, C-1′′) 118.0/118.2 (2d, C-2′), 142.1/142.5 (2s, C-1′) ppm. MS (EI): $m/z$ (%) = 226 (2) $[M]^+$, 208 (13) $[M - H_2O]^+$, 163 (52) $[C_{12}H_{19}]^+$, 121 (100) $[C_9H_{13}]^+$, 45 (39) $[C_2H_5O]^+$.

**(±)-(1*R**,5′*S**,8′*S**)-1-(4′,4′,8′-Trimethyl-1′-oxaspiro[4.5]decan-8′-yl)ethan-1-ol (18):** In analogy to the preparation of **13**, compound **18** was obtained from **17** (2.15 g, 9.50 mmol) and $MeSO_3H$ (1.10 g, 11.5 mmol) in $CH_2Cl_2$ (70 mL) after standard workup and silica gel FC (pentane/$Et_2O$, 6:4, $R_f$ = 0.13). Yield 73% (1.57 g); colorless oil. IR (neat): $\tilde{\nu}$ = 3449 (s, $\nu_{O-H}$), 1456 [m, $\delta_{as}(CH_3)$], 1365 [m, $\delta_s(CH_3)$], 1019 (s, $\nu_{C-O}$) $cm^{-1}$. $^1$H NMR ($CDCl_3$): $\delta$ = 0.85 (s, 3 H, 8′-Me), 0.96 (s, 6 H, 4′-$Me_2$), 1.11 (d, $J$ = 6.5 Hz, 3 H, 2-$H_3$), 1.35–1.39 (m, 2 H, 7′-, 9′-$H_{ax}$), 1.41–1.46 (m, 2 H, 6′-, 10′-$H_{ax}$), 1.49–1.50 (m, 2 H, 7′-, 9′-$H_{eq}$), 1.52–1.55 (m, 2 H, 6′-, 10′-$H_{eq}$), 1.81 (t, $J$ = 7.5 Hz, 2 H, 3′-$H_2$), 2.18 (br. s, 1 H, OH), 3.42 (q, $J$ = 6.5 Hz, 1 H, 1-H), 3.77 (t, $J$ = 7.5 Hz, 2 H, 2′-$H_2$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 15.6 (q, 8′-Me), 17.1 (q, C-2), 23.8 (q, 4′-$Me_2$), 26.0 (t, C-7′, -9′), 29.7 (t, C-6′, -10′), 36.5 (s, C-4′), 40.1 (t, C-3′), 42.5 (s, C-8′), 62.9 (t, C-2′), 77.1 (d, C-1), 83.6 (s, C-5′) ppm. MS (EI): $m/z$ (%) = 226 (5) $[M]^+$, 208 (2) $[M - H_2O]^+$, 125 (100) $[C_8H_{13}O]^+$, 45 (9) $[C_2H_5O]^+$.

**(±)-(5′*R**,8′*R**)-1-(4′,4′,8′-Trimethyl-1′-oxaspiro[4.5]decan-8′-yl)-ethan-1-one (19):** In analogy to preparation of **14**, the odoriferous title compound **19** was obtained from **18** (1.24 g, 5.48 mmol) and PCC (1.77 g, 8.22 mmol) in $CH_2Cl_2$ (20 mL) after standard workup and silica gel FC (pentane/$Et_2O$, 95:5, $R_f$ = 0.13). Yield 90% (1.10 g); colorless crystals, m.p. 49.3–50.5 °C. IR (neat): $\tilde{\nu}$ = 1697 (s, $\nu_{C=O}$), 1467 [m, $\delta_{as}(CH_3)$], 1367 [m, $\delta_s(CH_3)$], 1030 (s, $\nu_{C-O}$) $cm^{-1}$. $^1$H NMR ($C_6D_6$): $\delta$ = 0.76 (s, 6 H, 4′-$Me_2$), 0.93 (s, 3 H, 8′-Me), 1.10 (td, $J$ = 13.0, 4.0 Hz, 2 H, 6′-, 10′-$H_{ax}$), 1.28 ($m_c$, 2 H, 7′-, 9′-$H_{ax}$), 1.31 ($m_c$, 2 H, 6′-, 10′-$H_{eq}$), 1.47 (t, $J$ = 7.5 Hz, 2 H, 3′-$H_2$), 1.84 (s, 3 H, 2-$H_3$), 2.11 (td, $J$ = 13.0, 4.0, Hz, 2 H, 7′-, 9′-$H_{eq}$), 3.58 (t, $J$ = 7.5 Hz, 2 H, 2′-$H_2$) ppm. $^1$H,$^1$H NOESY ($C_6D_6$): 4′-$Me_{ax}$ × 6′-$H_{ax}$, 6′-$H_{ax}$ × 8′-$Me_{ax}$, 9′-$H_{ax}$ × 1-$Me_{eq}$. $^{13}$C NMR ($C_6D_6$): $\delta$ = 18.5 (q, 8′-Me), 23.7 (2q, 4′-$Me_2$), 24.3 (q, C-2), 26.2 (2t, C-6′, -10′), 29.5 (2t, C-7′, -9′), 40.2 (t, C-3′), 42.4 (s, C-4′), 46.6 (s, C-8′), 69.9 (t, C-2′), 82.8 (s, C-5′), 212.0 (s, C-1) ppm. MS (EI): $m/z$ (%) = 224 (6) $[M]^+$, 209 (2) $[M - CH_3]^+$, 155 (27) $[C_9H_{15}O_2]^+$, 125 (100) $[C_8H_{13}O]^+$, 43 (45) $[C_2H_3O]^+$. Crystal structure data and refinement: empirical formula $C_{14}H_{24}O_2$, molecular mass 224.33, crystal dimensions 0.38 × 0.2 × 0.02 mm, temperature 110 K, wavelength 0.71073 Å, monoclinic crystal system, space group $P2_1/c$, unit cell dimensions $a$ = 10.714(2) Å, $b$ = 10.263(2) Å, $c$ = 11.781(2) Å, $\alpha$ = 90°, $\beta$ = 101.60(3)°, $\gamma$ = 90°, $V$ = 1268.9(4) Å$^3$, $Z$ = 4, $\rho$ = 1.174 Mg/m$^3$, $\mu$(Mo-$K_\alpha$) = 0.076 mm$^{-1}$, $F$(000) 496, $\theta$ range 1.94–23.26°, limiting indices $-11 \le h \le 11$, $-11 \le k \le 11$, $-13 \le l \le 13$, total reflections collected 10287, symmetry-independent reflections 1770, $R_{int}$ = 0.1127, refinement full-matrix least-squares on $F^2$, data 1770, parameters 149, goodness-of-fit on $F^2$ 0.747, final $R$ indices [$I > 2\sigma(I)$], $R_1$ = 0.0372, $wR_2$ = 0.0644, $R$ indices (all data) $R_1$ = 0.0928, $wR_2$ = 0.0737, $\Delta\rho$(max, min) = 0.220, –0.153 e/Å$^3$. CCDC-646998 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. $C_{14}H_{24}O_2$ (224.3): calcd. C 74.95, H 10.78; found C 74.97, H 10.72. Odor (10% DPG, blotter): Woody–ambery odor, reminiscent of Iso E Super (**1**), with some agrestic, conifer-type facets also present in Cashmeran (1,1,2,3,3-pentamethyl-6,7-dihydro-5*H*-indan-4-one) accompanied by a slightly medicinal touch. Odor threshold: 92.1 ng/L air. Partition coefficient (HPLC): log($P_{ow}$) = 3.2.

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