DOI: 10.1002/ejoc.200600815

Ring Reversal of a Spirocyclic Patchouli Odorant: Molecular Modeling, Synthesis, and Odor of 6-Hydroxy-1,1,6-trimethylspiro[4.5]decan-7-one

Philip Kraft*[a] and Audrey Bruneau[a][‡]

Dedicated with best wishes to Dr. Dieter Merkel[‡‡]

Keywords: Ketohydroxylation / Olfactory properties / Patchouli / Spiro compounds / Structure–activity relationships

Molecular modeling calculations on the recently discovered high-impact patchouli odorant (+)-(1*S*,4*R*,5*R*,9*S*)-1-hydroxy-1,4,7,7,9-pentamethylspiro[4.5]decan-2-one (**1**) indicated that ring reversal of the spirocyclic system should lead to molecules in which two of the five methyl substituents could be spared without significantly affecting the overall shape or conformational equilibrium. Intramolecular ene reactions promised simple access to the desired target compound, (5*R**,6*R**)-6-hydroxy-1,1,6-trimethylspiro[4.5]decan-7-one (**2**), but all attempts failed utterly. The elaborated alternative six-step synthesis of target structure **2** commenced with the addition of HCl gas to 5-bromo-2-methyl-2-pentene (**16**), giving 1-bromo-4-chloro-4-methylpentane (**15**). Spiroannulation of cyclohexanone with this building block by $TiCl_4$-mediated alkylation of the TMS enolate **14** and subsequent cyclization by means of *t*BuOK afforded 1,1-dimethylspiro[4.5]decan-6-one (**12**). The reaction of this spirocyclic ketone with MeLi furnished the corresponding tertiary alcohol **17**, which was dehydrated by Appel–Lee bromination with concomitant dehydrohalogenation. The resulting alkene mixture containing 1,1,6-trimethylspiro[4.5]dec-6-ene (**4**) as the major component was subjected to the ketohydroxylation method developed by Plietker to provide, after repeated chromatography, target compound **2** in 33 % yield. To study the influence of the *gem*-dimethyl position on the olfactory properties, the analogous spirocyclic 2,2,6-trimethylketone **22** was also synthesized. Spiroannulation of cyclohexanone with 1,4-dibromo-2,2-dimethylbutane (**18**), with the use of 2.2 equiv. *t*BuOK as base, furnished 2,2-dimethylspiro[4.5]decan-6-one (**19**). The reaction of **19** with MeLi and subsequent Appel–Lee bromination/dehydrohalogenation led to an isomeric mixture containing 2,2,6-trimethylspiro[4.5]dec-6-ene (**21**) as the main component. The ketohydroxylation method according to the protocol of Plietker concluded the synthesis of the second target structure **22**. In contrast to methyl carbinol **17**, which has a typical woody-earthy patchouli odor, the odor of target molecule **2** was displaced towards the camphoraceous and minty side. The 2,2,6-trimethylalcohol **20** emanated a camphoraceous and vetiver-type note, while the second target molecule, **22**, was only weakly woody, cedar-like, and powdery in smell.

(© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2007)

Introduction

"*E una delle commesse, Martine, già mi titillava sotto l'orecchio col polpastrello bagnato di patchoulì (e intanto spingeva sotto la mia ascella il pungolo del suo seno), e Charlotte [...] mi prendeva di mira stringendo la peretta del polverizzatore come invitandomi a una schermaglia amorosa.*"

Italo Calvino, "*Il nome, il naso*"[1a]

"*And one of her shopgirls, Martine, was already tickling the tip of my ear with her finger wet with patchouli (pressing the sting of her breast, at the same time, beneath my armpit), and Charlotte [...] aimed an atomizer at me, pressing its bulb, as if inviting me to an amorous skirmish.*"

Italo Calvino, "*The Name, the Nose*"[1b]

Although patchouli leaves had been used since antiquity as insect repellants,[2] and although "*camphoraceous*" is considered a prime anti-erogenous attribute in perfumery, the typical camphoraceous, woody, and earthy scent of patchouli oil has always had a sensual and seductive connotation. Indian girls ritually used to perfume their hands with jasmine, their feet with saffron, and their backs with patchouli oil to bewitch a lover, and even in modern perfumery, about one third of all fine fragrances launched contain patchouli as a main base-note ingredient. Despite intense work in this domain, no synthetic substitute has so

[a] Givaudan Schweiz AG, Fragrance Research,
Überlandstrasse 138, 8600 Dübendorf, Switzerland
Fax: +41-44-824-29-26
E-mail: philip.kraft@givaudan.com

[‡] Master's thesis of Audrey Bruneau, Université de Nantes, France, carried out during her six-month stay at the Givaudan Fragrance Research Center, Switzerland.

[‡‡] Dr. Dieter Merkel has made many outstanding contributions to the chemistry of odorants, terpenoids, and essential oils.

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim InterScience

far been able to replace this, in the truest sense of the word, "*essential*" oil. At $40–50/kg, patchouli oil is on the one hand rather cheap and difficult to compete with, and on the other hand, it is very difficult to find odorants in which the three prime olfactory attributes, "*camphoraceous*", "*woody*", and "*earthy*", are as perfectly balanced. Recently, however, we discovered a very powerful spirocyclic odorant of structure **1** that exhibits a very natural and typical patchouli odor.[3] With an odor threshold of 0.027 ng/L air,[3] it is even 30 times more intense than (–)-patchoulol, the principal odorant of patchouli oil.[2] The importance of the methyl substituents of compound **1** in pushing the cyclohexyl ring in the direction of the carbinol function was shown by X-ray crystallography in comparison with a 7,7,9-demethyl analog, and this steric proximity seemed essential for the olfactory properties of the spirocyclic patchouli odorant **1**. Unfortunately, its synthesis is rather cumbersome and costly; and thus, more easily accessible alternative structures are much in demand. To minimize torsional (Pitzer) strain, a spiro atom in a cyclopentyl ring should be situated at the flap of a C_2-symmetric, envelope-shaped conformer, and inversion or puckering of the ring should energetically be significantly more restricted than that in an analogously substituted cyclohexyl chair. These conformational considerations keyed the idea of reversing the spirocyclic rings of lead structure **1**. This ring reversal could simplify the structure in that: (a) a 2-hydroxy-2-methylcyclohexanone substructure could mimic the *like*-configured 2-hydroxy-2,4-dimethylcyclopentanone ring, thus omitting one stereogenic methyl group, and (b) only one *gem*-dimethyl group in the cyclopentyl ring of the inverted spirocyclic system should be necessary to mimic the steric bulk of the trimethylcyclohexyl unit, as it is less prone to inversion and puckering. To mimic the short interatomic distance between 7-Me_{ax} (Figure 1) and 1-Me in lead structure **1**, the *gem*-dimethyl moiety should best be situated in α-position to the spiro atom. As shown in Figure 1, the resulting target structure **2** (black model) can indeed be superimposed very well on lead compound **1** (depicted in gold) in this biflexible alignment with the MOE software package. Although the cyclohexyl ring in lead molecule **1** became twisted upon superposition, it did not invert; a barrier of only 0.1 kcal mol^{-1} had been estimated for this ring inversion.[3] So the two structures, **1** and **2**, are indeed quite similar with regard to their geometry and steric demand, and even if a potentially simpler synthetic access to a patchouli odorant is not possible, the olfactory properties of the derived target molecule **2** make it interesting in its own right for structure–odor correlation.

At first sight, the spirocyclic ring system seems easily accessible by a thermal Alder ene reaction[4] of 2-methyl-3-(4′-methylpent-4′-enyl)cyclohex-2-en-1-one (**3**, Figure 2). Yet, both double bonds of dienone **3** bear allylic hydrogen atoms, and consequently both can act as ene components. Transition state **A**, with the ring double bond as the ene component, would lead to the desired spiro[4.5]decane system, while **B**, with the chain double bond as the ene component, provides 1-methyl-8-methylenespiro[5.5]undecan-2-one (Figure 2). Ene reactions proceed by the interaction of the LUMO of the alkene (enophile) with the HOMO of the allylic partner (ene), and an electron-withdrawing group such as the conjugated carbonyl function in dienone **3** polarizes the LUMO much more than the HOMO, with the result that the LUMO coefficients of the chain double bond

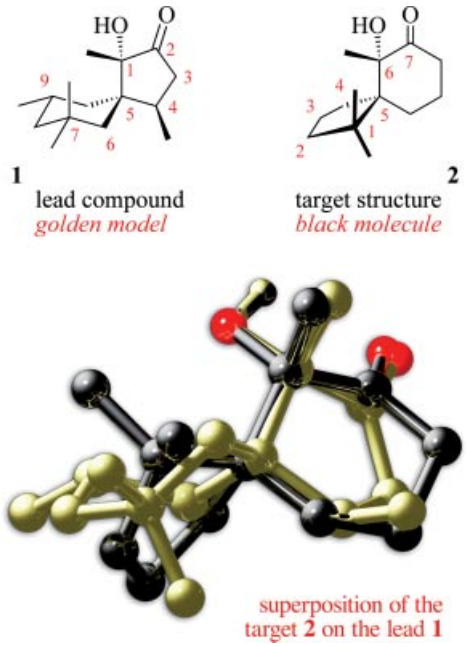


Figure 1. Biflexible alignment of target molecule **2** and the lead structure, 1-hydroxy-1,4,7,7,9-pentamethylspiro[4.5]decan-2-one (**1**), with the MOE software package.

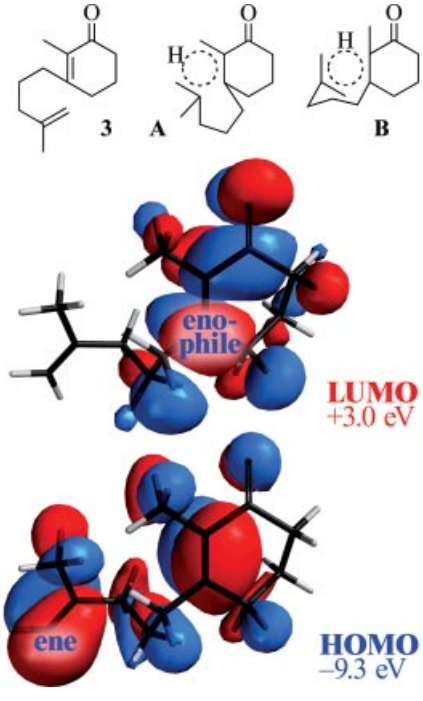
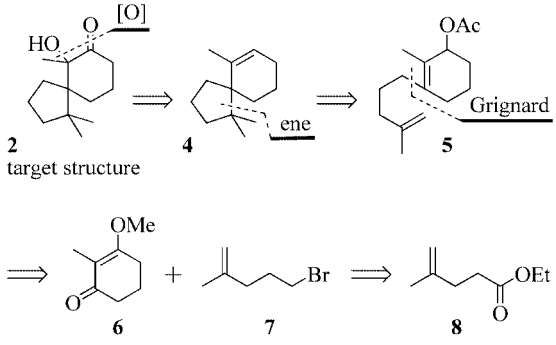


Figure 2. HOMO and LUMO frontier orbitals as calculated for 2-methyl-3-(4′-methylpent-4′-enyl)cyclohex-2-en-1-one (**3**) on the Hartree–Fock 6-31G* level to determine the course of a thermal Alder ene reaction.

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

in this case actually vanish, as was confirmed by the frontier orbital calculations on the Hartree–Fock 6-31G* level, which are delineated in Figure 2. Accordingly, only the conjugated double bond of **3** can act as the enophile, forcing the side chain to become the ene component, and **B** the only transition state electronically possible. The transition state **B**, however, leads to the wrong spirocyclic ring system, and thus this idea was abandoned.

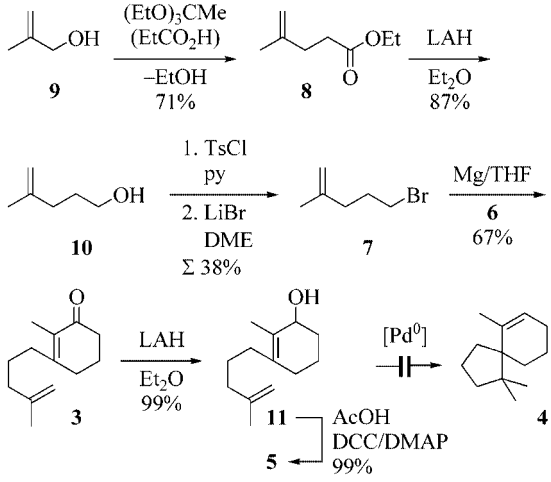
Nevertheless, an intramolecular ene reaction seemed an appealing strategy for the construction of the spirocycle, and the course of the cycloaddition could be directed by a metallo ene reaction. This transform-guided strategy keyed the retrosynthetic analysis presented in Scheme 1. Target compound **2** could be devised by oxidative cleavage of an epoxide,[5] itself accessible by oxidation of the ene retron **4**. A palladium ene reaction,[6] for instance, would reveal the dienol acetate **5** as the precursor of the spiro[4.5]dec-6-ene **4**. After reduction of the corresponding ketone, dienol acetate **5** is available by Grignard reaction of 3-methoxy-2-methylcyclohex-2-enone (**6**) with 5-bromo-2-methylpent-1-ene (**7**), by applying the Stork–Danheiser trick.[7] Bromide **7** leads retrosynthetically to the corresponding γ-unsaturated ester **8**, a product of a Johnson–Claisen rearrangement, after condensation of an allyl alcohol with an ortho ester.



Scheme 1. Retrosynthetic analysis of the modeled target molecule **2**.

Results and Discussion

Following the retrosynthetic analysis sketched out above, commercially available 2-methylprop-2-en-1-ol (**9**) was treated with triethyl orthoacetate in the presence of propionic acid with distillative removal of the formed EtOH in accordance with the procedure of Avery et al.,[8] and the [3,3]-sigmatropic rearrangement of the intermediate allyl vinyl ether provided the γ-unsaturated ester **8** in 71% yield after purification by fractional distillation. $LiAlH_4$ reduction of the ethyl ester **8** in Et_2O furnished 4-methylpent-4-en-1-ol (**10**) in 87% yield. However, pentenol **10** could not be converted directly into its bromide, and even the mild conditions of the Appel–Lee bromination[9] only led to a complex product mixture with 2,2-dimethyltetrahydrofuran as the main product and 2,5-dibromo-2-methylpentane as the most important side product. Thus, the detour was taken by bromide displacement of the tosylate, just as Avery et al. had done.[8] Alcohol **10** was first converted into its toluenesulfonate and then treated with LiBr in 1,2-dimethoxyethane to provide 5-bromo-2-methylpent-1-ene (**7**) in 38% yield after chromatography. This was then transformed into the corresponding Grignard reagent, and according to the procedure of Pirrung[10] added to 3-methoxy-2-methylcyclohex-2-enone (**6**),[11] which had been prepared in 77% yield by etherification of methyl dihydroresorcinol with trimethyl orthoformate in the presence of TsOH (Scheme 2).



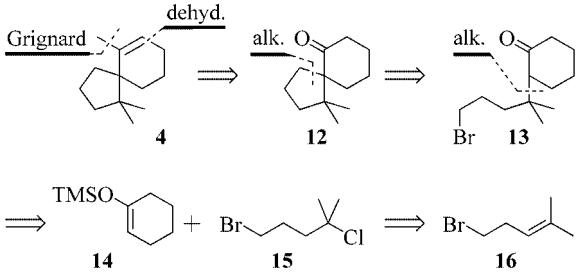
Scheme 2. Synthetic attempts by metallo ene reactions.

The Grignard reaction of the vinylogous ester **6** with (4-methylpent-4-enyl)magnesium bromide provided dienone **3**, by means of the Stork–Danheiser trick,[7] in 67% yield after acidic hydrolysis and chromatography. Having the ene retron **3** in hand, it was obviously interesting to check if the thermal ene reaction would indeed proceed, and if it would lead, as anticipated, to the undesired 1-methyl-8-methylenespiro[5.5]undecan-2-one via transition state **B**. With a slow flow of argon, a 0.5-M solution of dienone **3** in toluene was therefore passed at atmospheric pressure through a vertical 35-cm tube packed with glass rings and placed in a pyrolysis oven. The experiment was conducted at different temperatures, and GC monitoring indicated no reaction up to 450 °C, at which point decomposition to a complex product mixture without ene reaction products was observed. Heating dienone **3** in tetraethylene glycol dimethyl ether to 270 °C for two days also provided only a mixture of isomeric dienones and products of solvent degradation. Nevertheless, our strategy remained the application of a metallo ene reaction, mediated either by magnesium[12] or by palladium/zinc.[13] For this purpose, dienone **3** was reduced to alcohol **11**; however, all attempts to convert this into the corresponding chloride by the Appel reaction[14] with CCl_4 or *N*-chlorosuccinimide (NCS), with TMSCl in the presence of $BiCl_3$,[15] with AcCl and EtOH,[16] or by making use of the Corey–Kim reagent prepared in situ from NCS and Me_2S[17] failed utterly because of elimination and successive reactions. As a result, the magnesium ene approach was abandoned in favor of a palladium-mediated ene reaction, which allowed for an acetate leaving group in the formation of the allyl palladium complex. Steglich esterification[18] of

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

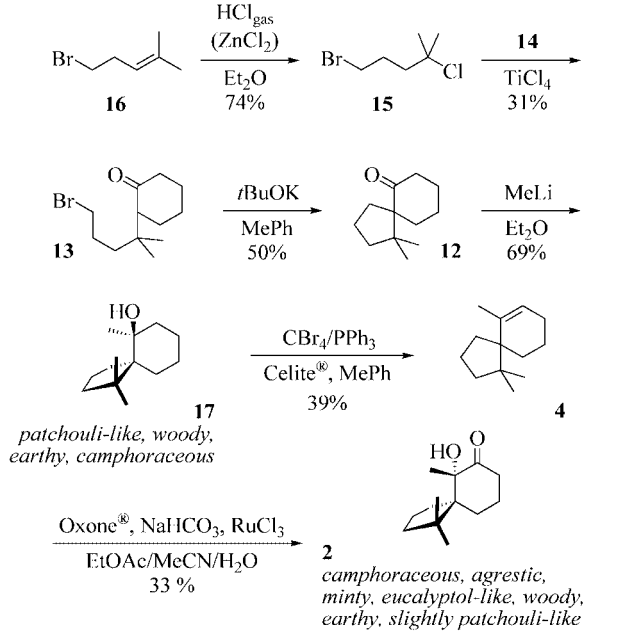
the allyl alcohol **11** went smoothly, and acetate **5** was isolated quantitatively. However, because of the severely sterically shielded tetrasubstituted allylic double bond of acetate **5**, it turned out to be impossible to substitute the acetate group by an electron-rich Pd^0 nucleophile such as $Pd[PPh_3]_4$, $Pd[OAc]_2/PPh_3$ or $Pd[OAc]_2/nBu_3P$ (10 mol-%) in acetic acid, THF, or ether. Upon heating, only the elimination products were obtained, particularly in acetic acid. Moreover, heating acetate **5** in acetic acid without any catalyst resulted in the same product mixture. So finally, the metallo ene approach to 1,1,6-trimethylspiro[4.5]dec-6-ene (**4**) failed completely, and a new route to this central intermediate had to be sought. In view of the intrinsic problem of the tetrasubstituted double bond in π-allyl palladium chemistry, it also did not seem very promising to attempt the synthesis of the key intermediate **4** by palladium-catalyzed spirocyclization[19] of a precursor with a malonate-substituted nucleophilic side chain.

As delineated in the alternative retrosynthesis in Scheme 3, instead of the ene disconnection to precursor **5** or a replacement of the geminal methyl substituents by ester groups, an auxiliary carbonyl function in α-position to the spiro atom can strategically be easily placed by retrosynthetic hydration of the double bond, which reveals a simple Grignard methyl carbinol retron. The resulting spirocyclic ketone **12** can thus easily be constructed by a simple enolate alkylation. For this disconnection, the fully substituted single bond is out of question, as the steric constraints would only cause elimination of the *tert*-halide precursor but probably no ring closure. This shifts the construction of the quaternary dimethyl-substituted carbon atom to the stage of the halo ketone **13**, but for the regio- and position-specific α-*tert*-alkylation of ketones, Reetz et al.[20] had worked out a reliable Lewis acid mediated methodology. Disconnecting the bond between the two highest substituted carbon atoms provides the silyl enol ether of cyclohexanone **14** and 1-bromo-4-chloro-4-methylpentane (**15**) as building blocks, the latter of which should be accessible by addition of HCl gas to 1a-homoisoprenyl bromide (**16**).



Scheme 3. Alternative retrosynthetic analysis of the central intermediate **4**.

As summarized in Scheme 4, the addition[21] of HCl gas to 5-bromo-2-methylpent-2-ene (**16**) in the presence of $ZnCl_2$ in Et_2O went smoothly and provided the 1-bromo-ω-chloro building block **15** in 74% yield. Following the procedure of Reetz et al.,[20] cyclohexenyloxy trimethylsilane (**14**) was then selectively α-alkylated with the *tert*-substituted chloro side of the bifunctional building block **15** in CH_2Cl_2 in the presence of titanium tetrachloride as stoichiometric Lewis acid. The resulting 2-(5′-bromo-2′-methylpentan-2′-yl)cyclohexanone (**13**) was isolated by flash chromatography in 31% yield and cyclized in the next step in the presence of potassium *tert*-butoxide in toluene. The desired spirocyclic ketone **12** was isolated in 50% yield, together with the cyclic enol ether, 5,5-dimethyl-2,3,4,5,6,7,8-octahydro-1-benzoxepine, as the main byproduct (14%). The C-6 methyl group was then introduced by treatment of ketone **12** with methyllithium at room temp., which, after mild hydrolysis and chromatographic purification, provided the tertiary alcohol **17** in 69% yield. The *gem*-dimethyl group, which is situated right in the Bürgi–Dunitz trajectory of the carbonyl function of **12**, blocks that side of the carbonyl plane and forces the incoming nucleophile to approach from the opposite direction. The resulting *unlike*-configuration of methyl carbinol **17** was proven by 2D NMR experiments of the corresponding methoxymethyl (MOM) ether, prepared by protection of the tertiary hydroxy group with chloromethyl methyl ether, in the presence of excess sodium iodide and diisopropyl ethylamine in DME according to the procedure of Narasaka.[22] The observed NOE cross peak between 1-Me_{ax} and 10-H_{ax} indicated a relative (5*R**,6*S**)-configuration of MOM **17**. Distinct cross peaks of the OCH_2O methylene group with both the equatorial and the axial methyl substituents at C-1 proved this conformation, in which the axial MOM group is freely rotary, parallel to the plane of the cyclohexyl ring.



Scheme 4. Synthesis of target structure **2** from 5-bromo-2-methylpent-2-ene (**16**).

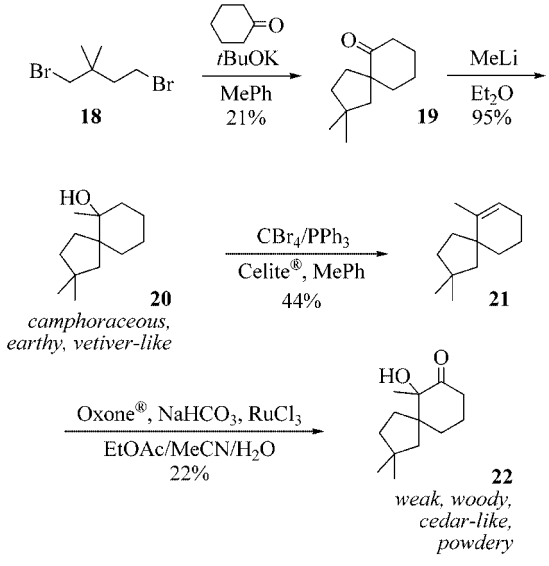
In the next step of our synthesis of α-hydroxy ketone **2**, methyl carbinol **17** was selectively dehydrated to the pivotal intermediate **4** by Appel–Lee bromination[23] and concomi-

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

tant dehydrohalogenation.[23b] In the presence of Celite®, the reaction of alcohol **17** with triphenylphosphane and CBr_4 in toluene provided alkene **4** as the main component (53%, GC) of a mixture of isomers. As it proved impossible to isolate the desired isomer **4** by flash chromatography, the isomeric mixture containing **4** was employed without further purification. Initially, it was envisaged that target structure **2** would be achieved by oxidative cleavage of the corresponding epoxide.[5] This was obtained by epoxidation with MCPBA in CH_2Cl_2 in moderate 21% yield as the major compound (79%, GC) of an inseparable isomeric mixture. However, subsequent oxidation with DMSO under acidic conditions according to Tsuji and Cohen[24a] or Santosusso and Swern[24b] provided almost exclusively dehydration products. Jones oxidation[25] furnished a mixture composed of rearrangement and elimination products, such as 1,1-dimethyl-6-methylenespiro[4.5]decan-7-one. Employing PCC under similar reaction conditions[26] provided a complex mixture, which, apart from elimination products, also contained some minor components with the expected molecular ion of m/z = 210. Yet, as it turned out to be impossible to separate and isolate these, it was attempted to open the epoxide to the corresponding *vic*-diol with perchloric acid in aqueous THF[27] and to oxidize the latter to α-hydroxy ketone **2**. However, this reaction was not clean either, and it led to a complex inseparable mixture.

Instead of subjecting the alkene mixture containing **4** now to an Upjohn dihydroxylation protocol[28] by employing *N*-methylmorpholine *N*-oxide as stoichiometric oxidant in the presence of catalytic amounts of OsO_4, the direct ketohydroxylation method developed by Plietker[29] appeared to us to be a very elegant one-step alternative. Just like the Katsuki–Sharpless oxidation,[30] the Plietker ketohydroxylation reaction uses catalytic amounts of RuO_4, generated in situ from $RuCl_3$ with Oxone® ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) as stoichiometric oxidant, but in contrast to the Katsuki–Sharpless conditions, the Plietker protocol does not lead to cleavage of the double bond, although the cyclic ruthenate formed by [3+2] cycloaddition and subsequent oxidation was proposed to be identical.[29c] Yet, instead of an electrocyclic fragmentation as in the case of the Katsuki–Sharpless reaction, in the presence of Oxone® the nucleophilic addition of the peroxomonosulfate anion (SO_5^{2-}) leads to the formation of an α-hydroxy ketone. In addition, the reaction is diastereoselective and an attack from the least hindered face should furnish target compound **2** with the desired *like*-stereochemistry. Subjecting the alkene mixture containing 1,1,6-trimethylspiro[4.5]dec-6-ene (**4**) to the Plietker ketohydroxylation reaction indeed provided, after purification by repeated chromatography, the (5*R**,6*R**)-configured 6-hydroxy-1,1,6-trimethylspiro[4.5]decan-7-one **2** in 33% yield as a colorless, semicrystalline solid. The *like*-configuration of our first target compound **2** was unambiguously assigned by the prominent cross peaks between the hydroxy function and 4-H_a in the NOESY spectrum, which proved that the hydroxy function at C-6 and the C-4 methylene unit were in *cis*-1,2 relation to one another.

Despite some slight resemblance to patchouli, the odor tonality of our first target structure **2** was displaced towards the camphoraceous and minty side of the patchouli odor attributes. So the question was raised as to whether this was due to the position of the *gem*-dimethyl moiety and what the analogous 2,2,6-trimethylketone (**22**) would smell like. Transposition of this bulky hydrophobic unit from C-1 to C-2 could even improve the superposition on lead structure **1** as depicted in Figure 1. At least it would not compare much worse than the first target molecule **2**. The synthesis of this new target structure, 6-hydroxy-2,2,6-trimethylspiro[4.5]decan-7-one (**22**), commenced with the spiroannulation of cyclohexanone with 1,4-dibromo-2,2-dimethylbutane (**18**). This bifunctional building block **18** was prepared from diethyl 2,2-dimethylsuccinate by reduction with $LiAlH_4$ and bromination of the resulting 2,2-dimethylbutane-1,4-diol with phosphorus tribromide in the presence of pyridine according to the procedure of Brown and van Gulick.[31] The spiroannulation of cyclohexanone with the 1,4-dibromide **18** was effected by 2.2 equiv. potassium *tert*-butoxide in refluxing toluene, and this furnished 2,2-dimethylspiro[4.5]decan-6-one (**19**) in a moderate 21% yield, after purification by flash chromatography with subsequent Kugelrohr distillation. Following the route elaborated for the synthesis of the first target compound **2**, the 2,2-dimethyl ketone **19** was treated with methyllithium in Et_2O at room temp. The corresponding methyl carbinol **20** was isolated in 95% yield and subsequently dehydrated by Appel–Lee bromination with in situ dehydrohalogenation to provide 2,2,6-trimethylspiro[4.5]dec-6-ene (**21**) as the main component of an inseparable mixture of alkene isomers. Subjecting this isomeric mixture containing **21** to the Plietker ketohydroxylation reaction afforded the second target structure **22** in 22% yield as a colorless liquid (Scheme 5).



Scheme 5. Synthesis and olfactory properties of the isomeric 6-hydroxy-2,2,6-trimethylspiro[4.5]decan-7-one (**22**).

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Olfactory Properties and Conclusions

The key odor descriptors for "*patchouli*" are "*camphoraceous*", "*woody*" and "*earthy*",[32] and in the odor profile of the intense patchouli lead compound **1**, these are perfectly balanced, accompanied only by slightly woody-ambery and tobacco-like facets. Our spirocyclic ketol target **2** displayed a camphoraceous, minty, eucalyptol-like odor with slightly woody and earthy facets, and only a slight resemblance to patchouli. Thus, the camphoraceous side of the racemic spirocyclic target structure **2** outweighed the woody and earthy character, and with an odor threshold of 17.2 ng/L air, it was about 250 times weaker than the racemic lead compound **1**, for which an odor threshold of 0.067 ng/L air was measured.[3] The low odor intensity and the pronounced camphoraceous character of ketol **2** could be an indication that the spirocyclic cyclopentyl ring sterically hinders the interaction of the receptor with the hydroxy function, which is the osmophore of (–)-patchoulol as indicated by the weaker intensity of a ketol analog prepared in a recent publication.[2] Indeed, the odor of ketol **2** is not far from that of 2-(1,1-dimethylethyl)-4-methylcyclohexanol (Rootanol®), which emanates a camphoraceous, minty odor with earthy and root-like nuances.[33] So the bulky *tert*-butyl substituent could to some extent mimic the fused *gem*-dimethyl cyclopentyl ring. In the alcohol precursor **17** to the first target compound **2**, the configuration of the hydroxy group is inverted, and thus sterically even less accessible for a receptor, as it is situated on the same side of the cyclohexyl plane as the *gem*-dimethyl substituent. However, with an odor threshold of 5 ng/L air, methyl carbinol **17** is stronger in odor than target compound **2**, and it displays a far more typical patchouli odor with well-balanced woody, earthy, and camphoraceous elements and only a weakly borneol-like undercurrent.

The second target structure **22** was, with an odor threshold of 233 ng/L air, the weakest odorant of the series, and only characterized by woody, cedar-type facets and a somewhat powdery connotation. As ketol **22** was obtained and evaluated as the racemic mixture of both diastereoisomeric forms, apparently no stereoisomer possesses a distinct olfactory profile, let alone typical patchouli characteristics. The intermediate methyl carbinol **20**, also a racemic mixture of diastereoisomers, in fact the decarbonyl analog of **22**, is, with a threshold of 68 ng/L air, significantly stronger than the second target compound **22**, but clearly weaker than the first target molecule **2**. Moreover, like the first target compound **2**, the odor profile of methyl carbinol **20** is also dominated by camphoraceous aspects. Some earthy and woody facets are present as well, yet the woody note is more similar to vetiver than patchouli oil, with some resemblance to grapefruit peel.

In conclusion, the carbonyl function of ketols **2** and **22** seems to be responsible for the shift of the odor character towards the camphoraceous side. Odor intensity and patchouli character are, however, influenced more distinctly by the position of the *gem*-dimethyl group, and the 1,1-dimethyl substitution favors the typical patchouli odor characteristics. Methyl carbinol **17** is the only typical patchouli odorant of this series, and although weaker than our lead compound **1**, it indicates that the study of further substitution patterns is promising. The synthetic sequence reported in this paper opens up a new, short, and easy-to-perform procedure for access to related target structures.

Experimental Section

IR: Bruker VECTOR 22/Harrick SplitPea micro ATR, Si; frequencies in order of decreasing intensity. NMR: Bruker AVANCE DPX-400, Bruker AVANCE 500 (TCI), Bruker AVANCE 600, TMS as internal standard taken as $\delta = 0$ ppm. MS: Finnigan MAT 95 (EI: 70 eV), HP Chemstation 6890 GC/5973 Mass Sensitive Detector. FC: Merck Kieselgel 60 (40–63 μm). TLC: Merck Kieselgel 60 F_{254} (particle size 5–20 μm, layer thickness 250 μm on glass, 5 cm × 10 cm); visualization reagent: phosphomolybdic acid spray and plunge soln. (Fluka 02553). Melting points: Büchi Melting Point B545 (uncorrected). Elemental analyses: Mikroanalytisches Laboratorium Ilse Beetz, 96301 Kronach, Germany. Unless otherwise stated, all reactions were performed under N_2 with reagents and solvents (*puriss.* or *purum*) from SAFC that were used without further purification. 1,4-Dibromo-2,2-dimethylbutane (**18**) was prepared from diethyl 2,2-dimethylsuccinate by reduction with $LiAlH_4$ and subsequent bromination with phosphorus tribromide according to the procedure of Brown and van Gulick.[31]

The 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 corresponding substance at the sniffing port. The panelist smelled in blind and pressed a button upon perceiving an odor. If the recorded time matched the retention time, the sample was further diluted. The last concentration detected at the correct retention time was recorded as the individual odor threshold. The reported threshold values are the geometrical means of the individual odor thresholds of the different panelists.

Ethyl 4-Methylpent-4-enoate (8): A mixture of 2-methylprop-2-en-1-ol (**9**, 50.0 g, 693 mmol) and triethyl orthoacetate (283 g, 1.74 mol) was heated at 125 °C for 4 h in the presence of propionic acid (3.08 g, 41.6 mmol) with continuous removal of the distilled EtOH (82 mL). The reaction mixture was cooled to room temp., diluted with Et_2O (200 mL), washed with aq. HCl solution (1 M, 2 × 100 mL), saturated aq. $NaHCO_3$ solution (2 × 200 mL), and brine (2 × 200 mL). After being dried (Na_2SO_4) and filtered, the organic solution was concentrated in a rotary evaporator under reduced pressure. The resulting residue was purified by fractional distillation in a Vigreux assembly to furnish, at 31.5–33.0 °C/2 mbar, compound **8** (69.9 g, 71%) as a colorless liquid. IR (ATR): $\tilde{\nu}$ = 1734 (νC=O), 1153 (νC–O–C), 888 (γ=C–H, 1,1-disubst.), 1030 (νC–O–C), 1371 (δCH_3), 1445 (δC–H), 1651 (νC=C), 3079 (ν=C–H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.26 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.75 (br. s, 3 H, 4-Me), 2.33 (m_c, 2 H, 3-H_2), 2.45 (m_c, 2 H, 2-H_2), 4.13 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 4.69 (m_c, 1 H, 5-H_E), 4.74 (m_c, 1 H, 5-H_Z) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2 (q, CH_2CH_3), 22.4 (q, 4-Me), 32.6 (2t, C-2,-3), 60.2 (t, CH_2CH_3), 110.3 (t, C-5), 144.1 (s, C-4), 173.2 (s, C-1) ppm. MS (EI): m/z (%) = 142 (10) [M^+], 114 (1) [$M^+ - C_2H_4$], 97 (20) [$M^+ - C_2H_5O$], 96 (18) [$M^+ - C_2H_6O$], 69 (100) [$C_5H_9^+$], 55 (20) [$C_4H_7^+$], 41 (42) [$C_3H_5^+$]. Odor: Fruity, reminiscent of strawberries, pineapple, and ethyl 2-methylpentanoate (Manzanate®).

4-Methylpent-4-en-1-ol (10): $LiAlH_4$ (13.1 g, 344 mmol) was added in portions with vigorous stirring over 120 min to a solution of

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

ethyl 4-methylpent-4-enoate (**8**, 69.9 g, 499 mmol) in dry Et_2O (500 mL), while the temp. was maintained between –10 and –5 °C (dry ice/EtOH bath). The resulting suspension was heated under reflux for an additional 2 h, and the reaction was quenched between 0 and 5 °C by careful addition of water (13 mL), aq. NaOH solution (15%, 13 mL), and water (39 mL) with vigorous stirring over a period of 60 min. After the mixture was stirred for further 30 min at room temp., the resulting precipitate was filtered off and washed with Et_2O (300 mL). The filtrate was dried (Na_2SO_4) and concentrated in a rotary evaporator under reduced pressure. The resulting residue (57.5 g) was used for tosylation and bromination without further purification, a sample purified by fractional distillation in a Vigreux assembly furnished, at 40–45 °C/2 mbar, compound **10** (43.5 g, 87%) in pure form as a colorless liquid. IR (ATR): $\tilde{\nu}$ = 3318 (νO–H), 884 (γ=C–H, 1,1-disubst.), 1444 (δC–H), 1650 (νC=C), 1375 (δCH_3), 3075 (ν=C–H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.69 (tt, J = 8.0, 6.5 Hz, 2 H, 2-H_2), 1.73 (br. s, 3 H, 4-Me), 2.09 (t, J = 8.0 Hz, 2 H, 3-H_2), 2.40 (s, 1 H, OH), 3.63 (t, J = 6.5 Hz, 2 H, 1-H_2), 4.71 (m, 2 H, 5-H_2) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.3 (q, 4-Me), 30.5 (t, C-2), 34.0 (t, C-3), 62.5 (t, C-1), 110.1 (t, C-5), 145.4 (s, C-4) ppm. MS (EI): *m*/*z* (%) = 100 (1) [M^+], 82 (5) [$M^+ – H_2O$], 81 (9) [$C_6H_9^+$], 72 (17) [$C_4H_8O^+$], 69 (20) [$C_5H_9^+$], 67 (84) [$C_5H_7^+$], 56 (100) [$C_4H_8^+$], 41 (91) [$C_3H_5^+$], 31 (13) [CH_3O^+]. Odor: Fatty, green, ethereal, with a slightly powdery character.

1-Bromo-4-methylpent-4-ene (7): A mixture of 4-methylpent-4-en-1-ol (**10**, 48.0 g, 479 mmol) and TsCl (137 g, 719 mmol) in pyridine (192 mL) was stirred at 0 °C for 3 h prior to being poured into toluene (350 mL) and careful addition of aq. HCl (6 M, 1 L) with stirring below 10 °C (ice/water bath). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 300 mL). The combined organic layers were washed with water (2 × 300 mL), saturated aq. Na_2CO_3 solution (2 × 300 mL), and brine (2 × 300 mL). After being dried (Na_2SO_4) and filtered, the organic solution was concentrated in a rotary evaporator under reduced pressure, and the resulting crude 4-methyl-4-pentenyl 4′-methylbenzenesulfonate (70.2 g, 276 mmol, 58% yield) was heated with anhydrous LiBr (50.4 g, 580 mmol) in 1,2-dimethoxyethane (600 mL) under reflux for 35 min. The reaction mixture was cooled to room temp. and poured into saturated aq. Na_2CO_3 solution. The layers were separated, and the aqueous one was extracted with Et_2O (2 × 200 mL). The combined organic extracts were washed with saturated aq. Na_2CO_3 solution (3 × 200 mL) and brine (2 × 200 mL). After being dried (Na_2SO_4) and filtered, the organic solution was concentrated in a rotary evaporator under reduced pressure, and the resulting residue was purified by silica gel FC (pentane/Et_2O, 9:1, R_f = 0.92) to provide compound **7** (29.6 g, 38% overall yield) as a slightly yellowish liquid. IR (ATR): $\tilde{\nu}$ = 888 (γ=C–H, 1,1-disubst.), 1439 (δC–H), 641 (νC–Br), 1650 (νC=C), 1375 (δCH_3) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.72 (br. s, 3 H, 4-Me), 2.00 (quint, J = 7.0 Hz, 2 H, 2-H_2), 2.16 (t, J = 7.0 Hz, 2 H, 3-H_2), 3.40 (t, J = 7.0 Hz, 2 H, 1-H_2), 4.72 (m_c, 1 H, 5-H_E), 4.76 (m_c, 1 H, 5-H_Z) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.3 (q, 4-Me), 30.6 (t, C-2), 33.2 (t, C-1), 36.0 (t, C-3), 111.0 (t, C-5), 143.9 (s, C-4) ppm. MS (EI): *m*/*z* (%) = 162 (3) [M^+], 134 (1) [$M^+ – C_2H_4$], 83 (9) [M^+ – Br], 67 (12) [$C_5H_7^+$], 56 (100) [$C_4H_8^+$], 55 (42) [$C_4H_7^+$], 41 (26) [$C_3H_5^+$].

3-Methoxy-2-methylcyclohex-2-en-1-one (6): A mixture of 2-methylcyclohexane-1,3-dione (50.0 g, 396 mmol), trimethyl orthoformate (63.1 g, 595 mmol) and TsOH (754 mg, 4.38 mmol, 1 mol-%) in methanol (400 mL) was stirred at room temp. for 2 d. The resulting yellow solution was concentrated in a rotary evaporator under reduced pressure, and the residue was purified by silica gel FC (pentane/Et_2O, 8:2 → Et_2O pure, R_f = 0.16) to provide compound **6** (42.7 g, 77%) as a slightly yellowish amorphous solid. IR (ATR): $\tilde{\nu}$ = 1600 (νC=C), 1629 (νC=O), 1091 (ν_{as}C–O–C), 1243 (ν_sC–O–C), 1376 (δCH_3), 1351 (ν_{as}C–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.68 (t, J = 1.5 Hz, 3 H, 2-Me), 1.99 (quint, J = 6.5 Hz, 2 H, 5-H_2), 2.33 (t, J = 6.5 Hz, 2 H, 4-H_2), 2.58 (tq, J = 6.5, 1.5 Hz, 2 H, 6-H_2), 3.83 (s, 3 H, O*CH₃*) ppm. ^{13}C NMR ($CDCl_3$): δ = 7.2 (q, 2-Me), 20.8 (t, C-5), 24.7 (t, C-4), 36.2 (t, C-6), 55.1 (q, O*CH₃*), 114.6 (s, C-2), 171.9 (s, C-3), 198.7 (C-1) ppm. MS (EI): *m*/*z* (%) = 140 (100) [M^+], 125 (22) [$M^+ – CH_3$], 112 (40) [M^+ – CO], 95 (18) [$M^+ – C_2H_5O$], 83 (54) [$C_5H_7O^+$], 69 (18) [$C_4H_5O^+$], 54 (88) [$C_4H_6^+$], 43 (73) [$C_3H_7^+$].

(±)-2-Methyl-3-(4′-methylpent-4′-enyl)cyclohex-2-en-1-one (3): A suspension of Mg turnings (2.08 g, 86.0 mmol) and 1-bromo-4-methyl-4-pentene (**7**, 3 drops) in THF (4 mL) was heated with a heating gun until an exothermic reaction set in. Thereupon, the reaction mixture was diluted with THF (40 mL) and heated under reflux for 5 min. The hot plate was switched off, 1-bromo-4-methylpent-4-ene (**7**, 7.35 g, 45.1 mmol) was added dropwise with stirring over 20 min, and the reaction mixture was heated under reflux for 10 min. The freshly prepared Grignard solution was cooled to room temp. and added dropwise with stirring to a solution of 3-methoxy-2-methylcyclohex-2-en-1-one (**6**, 4.07 g, 29.0 mmol) in THF (10 mL). The reaction mixture was then heated under reflux for 20 min, cooled to room temp., and poured into ice (20 g)/aq. HCl (10%, 25 mL). After being stirred at room temp. for 2 h, the resulting mixture was saturated with NaCl, and the layers were separated. The aqueous one was extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed in turn with saturated aq. $NaHCO_3$ solution (3 × 50 mL), water (3 × 50 mL), and brine (2 × 50 mL). After being dried (Na_2SO_4) and filtered, the organic solution was concentrated in a rotary evaporator under reduced pressure. The resulting residue was purified by silica gel FC (pentane/Et_2O, 8:2, R_f = 0.33) to provide compound **3** (3.72 g, 67%) as a slightly yellowish oil. IR (ATR): $\tilde{\nu}$ = 1661 (νC=O), 884 (γ=C–H, 1,1-disubst.), 1356 (ν_{as}C–C), 1376 ($\delta_s$$CH_3$), 1326/1303 (rβ=CH), 1454 ($\delta_{as}$$CH_3$), 1430 ($\delta_s$=$CH_2$ ip) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.57–1.65 (m, 2 H, 2′-H_2), 1.73 (br. s, 3 H, 2-Me), 1.77 (t, J = 1.5 Hz, 3 H, 4′-Me), 1.93 (tdd, J = 7.5, 7.0, 6.0 Hz, 2 H, 5-H_2), 2.06 (t, J = 7.5 Hz, 2 H, 4-H_2), 2.24 (t, J = 8.0 Hz, 2 H, 1′-H_2), 2.34 (td, J = 6.0, 1.5 Hz, 2 H, 3′-H_2), 2.39 (dd, J = 7.0, 6.0 Hz, 2 H, 6-H_2), 4.69 (m_c, 1 H, 5′-H_E), 4.74 (m_c, 1 H, 5′-H_Z) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.5 (q, 2-Me), 22.3 (q, 4′-Me), 22.5 (t, C-5), 25.2 (t, C-2′), 30.8 (t, C-4), 34.8 (t, C-6), 37.6/37.7 (2t, C-1′,-3′), 110.4 (t, C-5′), 130.9 (s, C-2), 145.0 (s, C-4′), 158.8 (s, C-3), 199.4 (s, C-1) ppm. MS (EI): *m*/*z* (%) = 192 (18) [M^+], 177 (12) [$M^+ – CH_3$], 164 (9) [M^+ – CO], 149 (38) [M^+ – CO – CH_3], 136 (78) [$M^+ – C_4H_8$], 124 (100) [$M^+ – C_5H_8$], 108 (93) [$C_8H_{12}^+$], 96 (83) [$C_7H_{12}^+$], 79 (75) [$C_6H_7^+$], 69 (75) [$C_5H_9^+$], 55 (74) [$C_4H_7^+$], 41 (98) [$C_3H_5^+$].

(±)-2-Methyl-3-(4′-methylpent-4′-enyl)cyclohex-2-en-1-ol (11): At 0 °C, 2-methyl-3-(4′-methylpent-4′-enyl)cyclohex-2-en-1-one (**3**, 3.88 g, 20.2 mmol) was added dropwise to a stirred suspension of $LiAlH_4$ (383 mg, 10.1 mmol) in dry Et_2O (50 mL). The cooling bath was removed, and stirring was continued at room temp. for 15 min, prior to pouring the reaction mixture into ice/water (100 mL). The product was extracted with Et_2O (3 × 25 mL), and the combined extracts were washed with brine (2 × 50 mL), dried (Na_2SO_4), filtered, and concentrated in a rotary evaporator under reduced pressure to furnish compound **11** (3.87 g, 99%) as a colorless oil. IR (ATR): $\tilde{\nu}$ = 3319 (νO–H), 885 (γ=C–H), 965 (γ=C–O–H), 1649 (νC=C), 1439 (δC–H), 1373 (δCH_3), 1271 (νC–O), 3073 (ν=C–H) cm^{-1}. ^1H NMR (C_6D_6): δ = 1.42 (m_c, 1 H, 5-H_b), 1.48 (ddddd, J = 14.0, 7.0, 7.0, 0.5, 0.5 Hz, 1 H, 2′-H_b), 1.58 (m_c, 1 H,

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

6-H_b), 1.63 (m_c, 1 H, 5-H_a), 1.66 (s, 3 H, 4′-Me), 1.68 (m_c, 1 H, 6-H_a), 1.69 (br. s, 1 H, O–H), 1.76 (br. s, 3 H, 2-Me), 1.77–1.83 (m, 2 H, 4-H_2), 1.93 (t, J = 7.0 Hz, 2 H, 1′-H_2), 1.94 (m_c, 1 H, 2′-H_a), 1.95 (t, J = 7.0 Hz, 2 H, 3′-H_2), 3.85 (t, J = 4.0 Hz, 1 H, 1-H), 4.79 (s, 1 H, 5′-H_E), 4.81 (s, 1 H, 5′-H_Z) ppm. ^{13}C NMR (C_6D_6): δ = 16.0 (q, 2-Me), 18.8 (t, C-5), 22.2 (q, 4′-Me), 26.0 (t, C-2′), 29.9 (t, C-4), 32.6 (t, C-6), 33.3 (t, C-1′), 37.9 (t, C-3′), 69.2 (d, C-1), 110.1 (t, C-5′), 128.7 (s, C-2), 134.0 (s, C-3), 145.4 (s, C-4′) ppm. MS (EI): m/z (%) = 194 (2) [M^+], 179 (1) [$M^+ - CH_3$], 176 (20) [$M^+ - H_2O$], 138 (18) [$M^+ - C_4H_8$], 123 (29) [$M^+ - C_4H_8 - CH_3$], 111 (100) [$C_8H_{15}^+$], 105 (49) [$C_8H_9^+$], 93 (65) [$C_7H_9^+$], 79 (42) [$C_6H_7^+$], 67 (23) [$C_5H_7^+$], 55 (45) [$C_4H_7^+$], 41 (44) [$C_3H_5^+$]. $C_{13}H_{22}O$ (194.31): calcd. C 80.35, H 11.41; found C 80.36, H 11.38. Odor: green-earthy, linalool-like, with citrusy and slightly pyrazine-like facets.

(±)-2-Methyl-3-(4′-methylpent-4′-enyl)cyclohex-2-en-1-yl Acetate (5): *N*,*N*′-Dicyclohexylcarbodiimide (2.27 g, 11.0 mmol) was added at 0 °C to a stirred solution of 2-methyl-3-(4′-methylpent-4′-enyl)-cyclohex-2-en-1-ol (**11**, 1.94 g, 10.0 mmol), AcOH (600 mg, 9.99 mmol) and 4-(dimethylamino)pyridine (120 mg, 0.982 mmol) in CH_2Cl_2 (30 mL). Stirring was continued at room temp. for 16 h prior to filtration of the insoluble materials. The filter cake was washed with CH_2Cl_2 (10 mL), and the combined extracts were concentrated in a rotary evaporator under reduced pressure. The resulting residue was purified by silica gel FC (pentane/Et_2O, 19:1, R_f = 0.47) to provide compound **5** (2.33 g, 99%) as a colorless oil. IR (ATR): $\tilde{\nu}$ = 1233 (νC–O), 1731 (νC=O), 885 (γ=C–H, 1,1-disubst.), 960 (δ=C–H), 1010 (νC–O–C), 1369 (δCH_3), 2934 (ν=C–H), 1164 (νC–O–C), 1441 (δC–H) cm^{-1}. ^{1}H NMR (C_6D_6): δ = 1.37 (m_c, 1 H, 5-H_b), 1.38–1.46 (m, 2 H, 2′-H_2), 1.59 (m_c, 1 H, 6-H_b), 1.60 (m_c, 1 H, 5-H_a), 1.62 (s, 3 H, 4′-Me), 1.63 (s, 3 H, 2-Me), 1.73 (m_c, 1 H, 4-H_b), 1.75 (s, 3 H, OCO*CH*$_3$), 1.79 (m_c, 1 H, 6-H_a), 1.84 (m_c, 1 H, 4-H_a), 1.89 (t, J = 8.0 Hz, 2 H, 1′-H_2), 1.90 (t, J = 7.0 Hz, 2 H, 3′-H_2), 4.76 (s, 1 H, 5′-H_E), 4.79 (s, 1 H, 5′-H_Z), 5.40 (br. s, 1 H, 1-H) ppm. ^{13}C NMR (C_6D_6): δ = 15.6 (q, 2-Me), 18.8 (t, C-5), 20.6 (q, OCO*CH*$_3$), 22.0 (q, 4′-Me), 25.7 (t, C-2′), 29.2 (t, C-6), 29.4 (t, C-4), 33.1 (t, C-1′), 37.6 (t, C-3′), 71.6 (d, C-1), 110.0 (t, C-5′), 124.7 (s, C-2), 136.9 (s, C-3), 145.1 (s, C-4′), 169.8 (s, O*C*-*O*CH$_3$) ppm. MS (EI): m/z (%) = 236 (1) [M^+], 194 (1) [$M^+ - C_2H_2O$], 180 (2) [$M^+ - C_4H_8$], 176 (37) [$M^+ - C_2H_4O_2$], 161 (11) [$M^+ - C_2H_4O_2 - CH_3$], 147 (5) [$M^+ - C_4H_9O_2$], 133 (19) [$M^+ - C_5H_{11}O_2$], 121 (54) [$M^+ - C_6H_{11}O_2$], 120 (42) [$M^+ - C_2H_4O_2 - C_4H_8$], 108 (51) [$C_8H_{12}^+$], 105 (80) [$C_8H_9^+$], 93 (100) [$C_7H_9^+$], 91 (72) [$C_7H_7^+$], 79 (54) [$C_6H_7^+$], 60 (12) [$C_2H_4O_2^+$], 55 (27) [$C_4H_7^+$], 43 (39) [$C_2H_3O^+$]. $C_{15}H_{24}O_2$ (236.35): calcd. C 76.23, H 10.24; found C 76.19, H 10.20.

1-Bromo-4-chloro-4-methylpentane (15): Gaseous hydrogen chloride was slowly bubbled through a solution of 5-bromo-2-methyl-2-pentene (**16**, 110 g, 675 mmol) and zinc chloride (4.60 g, 33.8 mmol, 5 mol-%) in Et_2O (675 mL) at room temp. over a period of 27 h. The mixture was then stirred at room temp. overnight, washed with saturated aq. $NaHCO_3$ solution (2 × 200 mL), and dried (Na_2SO_4). After evaporation of the solvent in a rotary evaporator under reduced pressure, the residue was purified by fractional distillation in a Vigreux assembly to furnish, at 45–46 °C/2 mbar, compound **15** (100 g, 74%) as a colorless liquid. IR (ATR): $\tilde{\nu}$ = 1260 (ωCH$_2$BrCH$_2$), 1369 (δCH$_3$), 1100 (rβCH$_2$CH$_2$), 1452 (δC–H), 761 (ν_{as}C–Cl), 1150 (*t*CH$_2$BrCH$_2$CH$_2$), 647 (ν_sC–Br), 1386 (δ_sCH$_3$), 1296 (νCH$_3$ClC–CH$_3$) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.59 (s, 6 H, 4-Me_2), 1.88 (m_c, 2 H, 3-H_2), 2.07 (m_c, 2 H, 2-H_2), 3.44 (t, J = 6.5 Hz, 2 H, 1-H_2) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.6 (t, C-2), 32.5 (2q, 4-Me_2), 33.6 (t, C-1), 44.5 (t, C-3), 69.9 (s, C-4) ppm. MS (EI): m/z (%) = 183 (1) [$M^+ - CH_3$], 165/163 (24)/(25) [M^+ – Cl], 121 (2) [$M^+ - C_3H_6Cl$], 107 (4) [M^+ – Cl – C_4H_8], 83 (100) [M^+ – Cl – HBr], 77 (42) [$C_3H_6Cl^+$], 67 (116) [$C_5H_7^+$], 56 (52) [$C_4H_8^+$], 55 (55) [$C_4H_7^+$], 41 (58) [$C_3H_5^+$].

(±)-2-(4′-Bromo-1′,1′-dimethylbutyl)cyclohexan-1-one (13): A cold (–40 °C) solution of titanium tetrachloride (49.0 mL, 450 mmol) in CH_2Cl_2 (200 mL) was added over 4 min, at –40 °C and with vigorous stirring, to a mixture of 1-trimethylsiloxycyclohexene (**14**, 76.7 g, 450 mmol) and 1-bromo-4-chloro-4-methylpentane (**15**, 99.8 g, 500 mmol) in CH_2Cl_2 (900 mL). Following complete addition, the dark red mixture was stirred at –40 °C overnight, prior to pouring the cold mixture into ice/water (1:1, 3 L) with vigorous stirring. The layers were separated, and the organic layer was washed with saturated aq. $NaHCO_3$ solution (3 × 600 mL) and water (3 × 600 mL). The combined aqueous layers were extracted with CH_2Cl_2 (in portions, 100 mL CH_2Cl_2 per L). The organic extracts were combined, dried (Na_2SO_4), and concentrated in a rotary evaporator under reduced pressure. The resulting residue was purified by silica gel FC (pentane/Et_2O, 19:1, R_f = 0.30) to afford compound **13** (36.4 g, 31%) as a yellow liquid. IR (ATR): $\tilde{\nu}$ = 1705 (νC=O), 1125 (ν_{as}C–C), 1448 (δC–H), 1386 (δ_sCH$_3$), 835/647 (νC–Br) cm^{-1}. ^{1}H NMR (C_6D_6): δ = 0.87 (s, 3 H, 1′-Me), 0.96 (s, 3 H, 1′-Me), 1.14 (m_c, 1 H, 4-H_b), 1.15 (m_c, 1 H, 3-H_b), 1.24 (m_c, 1 H, 2′-H_b), 1.29 (m_c, 1 H, 5-H_b), 1.46 (m_c, 1 H, 4-H_a), 1.43–1.52 (m, 2 H, 3′-H_2), 1.50 (m_c, 1 H, 2′-H_a), 1.59 (m_c, 1 H, 5-H_a), 1.72 (m_c, 1 H, 3-H_a), 1.80 (ddd, J = 12.5, 4.5, 1.0 Hz, 1 H, 2-H), 1.84 (tdd, J = 12.5, 6.0, 1.0 Hz, 1 H, 6-H_b), 2.13 (dddd, J = 12.5, 4.5, 3.0, 2.0 Hz, 1 H, 6-H_a), 2.97 (m_c, 2 H, 4′-H_2) ppm. ^{13}C NMR (C_6D_6): δ = 24.4 (q, 1′-Me), 24.7 (q, 1′-Me), 25.9 (t, C-4), 27.8 (t, C-3′), 28.3 (t, C-5), 29.1 (t, C-3), 33.9 (s, C-1′), 34.2 (t, C-4′), 38.6 (t, C-2′), 43.9 (t, C-6), 57.9 (d, C-2), 210.1 (s, C-1) ppm. MS (EI): m/z (%) = 260 (1) [M^+], 245 (1) [$M^+ - CH_3$], 180 (1) [M^+ – HBr], 163 (1) [$C_6H_{12}Br^+$], 139 (2) [$M^+ - C_3H_6Br$], 98 (100) [$C_6H_{10}O^+$], 83 (19) [$C_6H_{11}^+$], 70 (9) [$C_5H_{10}^+$], 69 (11) [$C_5H_9^+$], 55 (20) [$C_4H_7^+$], 41 (15) [$C_3H_5^+$].

(±)-1,1-Dimethylspiro[4.5]decan-6-one (12): A solution of 2-(4′-bromo-1′,1′-dimethylbutyl)cyclohexan-1-one (**13**, 32.7 g, 125 mmol) in toluene (150 mL) was added slowly, at room temp. and with mechanic stirring, to a suspension of potassium *tert*-butoxide (15.4 g, 138 mmol) in toluene (250 mL) over a period of 60 min. In the course of the addition, which was exothermic but was adjusted to a reaction temperature below 35 °C, the mixture thickened and liquefied again. The mixture was then heated at 70 °C for 60 min. After being cooled, the resulting solution was diluted in Et_2O (250 mL) and washed with saturated aq. NH_4Cl solution (3 × 100 mL) and brine (3 × 100 mL). After being dried (Na_2SO_4), the organic phase was concentrated in a rotary evaporator under reduced pressure. The resulting residue was purified by silica gel FC (pentane/Et_2O, 39:1, R_f = 0.30) to furnish compound **12** (11.2 g, 50%) as a colorless liquid. IR (ATR): $\tilde{\nu}$ = 1697 (νC=O), 1450 (δC–H), 1128 (ν_{as}C–C), 1384 (δ_sCH$_3$) cm^{-1}. ^{1}H NMR (C_6D_6): δ = 0.82/1.03 (2s, 6 H, 1-Me_2), 1.23 (m_c, 1 H, 9-H_b), 1.27 (m_c, 1 H, 10-H_b), 1.33 (m_c, 1 H, 4-H_b), 1.38 (m_c, 1 H, 2-H_b), 1.39 (m_c, 1 H, 9-H_a), 1.39–1.46 (m, 2 H, 8-H_2), 1.50 (m_c, 1 H, 3-H_b), 1.58 (m_c, 1 H, 10-H_a), 1.67 (dtdd, J = 13.0, 10.0, 6.0, 4.5 Hz, 1 H, 3-H_a), 1.95 (ddd, J = 12.0, 10.0, 7.0 Hz, 1 H, 2-H_a), 2.10 (m_c, 1 H, 7-H_b), 2.11 (m_c, 1 H, 4-H_a), 2.22 (m_c, 1 H, 7-H_a) ppm. ^{13}C NMR (C_6D_6): δ = 20.4 (t, C-3), 22.0 (t, C-9), 24.6/25.5 (2q, 1-Me_2), 25.7 (t, C-8), 33.8 (t, C-10), 35.5 (t, C-4), 40.4 (t, C-2), 40.8 (t, C-7), 44.1 (s, C-1), 60.4 (s, C-5), 212.8 (s, C-6) ppm. MS (EI): m/z (%) = 180 (11) [M^+], 124 (9) [$M^+ - C_4H_8$], 111 (100) [$C_7H_{11}O^+$], 95 (16) [$C_7H_{11}^+$], 81 (15) [$C_6H_9^+$], 70 (11) [$C_5H_{10}^+$], 67 (18) [$C_5H_7^+$], 55 (24) [$C_4H_7^+$], 41 (16) [$C_3H_5^+$]. $C_{12}H_{20}O$ (180.29): calcd. C 79.94, H 11.18; found C

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

79.80, H 11.26. Odor: camphoraceous, eucalyptol-like, and herbaceous, reminiscent of rosemary with a slight woody inflection.

(±)-(5*R,6*S**)-1,1,6-Trimethylspiro[4.5]decan-6-ol (17):** At room temp., 1,1-dimethylspiro[4.5]decan-6-one (**12**, 3.61 g, 20.0 mmol) was injected by syringe over 2 min to a stirred solution of methyllithium (1.6 M in Et_2O, 40.0 mL, 64.0 mmol). Stirring was continued for 30 min at room temp., prior to quenching with cold saturated aq. NH_4Cl solution (50 mL). After separation of the layers, the aqueous one was extracted with Et_2O (2 × 30 mL). The organic extracts were combined and washed in turn with saturated aq. $NaHCO_3$ solution (3 × 30 mL) and brine (3 × 30 mL). After being dried (Na_2SO_4), the resulting solution was concentrated in a rotary evaporator under reduced pressure. The resulting residue was purified by silica gel FC (pentane/Et_2O, 37:3, R_f = 0.27) to furnish compound **17** (2.71 g, 69%) as a colorless liquid. IR (ATR): $\tilde{\nu}$ = 1172 (νC–O, *tert*-OH), 1044/929 (νC–O, *trans-gauche*), 1375 ($\delta_s CH_3$), 1448 (δC–H), 1474 (δC–O–H), 3499 (νO–H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.99/1.20 (2s, 6 H, 1-Me_2), 1.28 (m_c, 1 H, 9-H_b), 1.29 (m_c, 1 H, 10-H_b), 1.30 (m_c, 1 H, 7-H_b), 1.30 (s, 3 H, 6-Me), 1.39–1.46 (m, 2 H, 3-H_2), 1.46–1.64 (m, 2 H, 2-H_2), 1.52–1.63 (m, 2 H, 8-H_2), 1.54 (m_c, 1 H, 9-H_a), 1.60–1.73 (m, 2 H, 4-H_2), 1.63 (m_c, 1 H, 7-H_a), 1.67 (m_c, 1 H, 10-H_a), 1.72 (m_c, 1 H, OH). ^{13}C NMR ($CDCl_3$): δ = 20.5 (t, C-8), 21.8 (t, C-3), 22.8 (t, C-9), 28.2/28.3 (2q, 1-Me_2), 28.8 (q, 6-Me), 29.9 (t, C-10), 32.5 (t, C-4), 41.1 (t, C-7), 42.7 (t, C-2), 46.6 (s, C-1), 52.8 (s, C-5), 76.5 (s, C-6) ppm. MS (EI): *m*/*z* (%) = 196 (7) [M^+], 178 (9) [$M^+ - H_2O$], 163 (75) [$M^+ - CH_3 - H_2O$], 136 (60) [$M^+ - C_3H_8O$], 122 (50) [$M^+ - C_4H_{10}O$], 109 (64) [$C_8H_{13}^+$], 95 (54) [$C_7H_{11}^+$], 82 (91) [$C_6H_{10}^+$], 71 (86) [$C_5H_{11}^+$], 67 (51) [$C_5H_7^+$], 55 (63) [$C_4H_7^+$], 43 (100) [$C_3H_7^+$]. Odor: patchouli, woody, earthy, and camphoraceous with some borneol-like undercurrent. Odor threshold: 5 ng/L air.

(±)-(5*R,6*S**)-6-(Methoxymethoxy)-1,1,6-trimethylspiro[4.5]-decane:** A mixture of NaI (300 mg, 2.00 mmol) and chloromethyl methyl ether (224 mg, 2.50 mmol) in DME (1 mL) was stirred at room temp. for 10 min, prior to addition of a solution of 1,1,6-trimethylspiro[4.5]decan-6-ol (**17**, 98.2 mg, 0.500 mmol) and diisopropyl ethylamine (355 mg, 2.75 mmol) in DME (3 mL). After being stirred at room temp. for an additional 1 h and at reflux for 5.5 h, the reaction mixture was cooled to room temp., and the reaction was quenched by addition of saturated aq. Na_2CO_3 solution (4 mL) and water (3 mL). The crude product was extracted with CH_2Cl_2 (4 × 5 mL), and the combined organic extracts were washed with brine (5 mL). After the extracts were dried (Na_2SO_4) and filtered, the solvent was removed in a rotary evaporator under reduced pressure. The resulting residue was purified by silica gel FC (pentane/Et_2O, 9:1, R_f = 0.75) to furnish the title compound (64.0 mg, 53%) as a colorless liquid. IR (ATR): $\tilde{\nu}$ = 1028 ($\nu_s CH_3$–O–CH_2), 1003/919 ($\nu_s CH_2$–O–C), 1087/1153 ($\nu_{as} CH_3$–O–CH_2), 2874 (νH–CHO_2), 1135/1113/1178 ($\nu_{as} CH_2$–O–C), 1450 (δC–H), 1376 ($\delta_s CH_3$) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.06 (s, 3 H, 1-Me_{ax}), 1.15 (s, 3 H, 1-Me_{eq}), 1.22 (dddd, *J* = 13.0, 3.5, 3.5, 1.5 Hz, 1 H, 10-H_{eq}), 1.31 (s, 3 H, 6-Me_{eq}), 1.33 (m_c, 1 H, 9-H_b), 1.35 (m_c, 1 H, 3-H_b), 1.37 (m_c, 1 H, 7-H_b), 1.43 (m_c, 1 H, 2-H_b), 1.45 (m_c, 1 H, 3-H_a), 1.52 (m_c, 1 H, 9-H_a), 1.53–1.59 (m, 2 H, 8-H_2), 1.56 (m_c, 1 H, 2-H_a), 1.61–1.71 (m, 2 H, 4-H_2), 1.63 (m_c, 1 H, 7-H_a), 1.91 (dddd, *J* = 13.0, 13.0, 3.5, 1.0 Hz, 1 H, 10-H_{ax}), 3.42 (s, 3 H, OCH_3), 4.68/4.70 (2d, *J* = 17.0 Hz, 2 H, OCH_2O) ppm. ^1H, ^1H NOESY ($CDCl_3$): 1-Me_{ax} × 10-H_{ax}, 1-Me_{ax} × 10-H_{eq}, 1-Me_{eq} × OCH_2O, 1-Me_{ax} × OCH_2O, 6-Me_{eq} × OCH_2O. ^{13}C NMR ($CDCl_3$): δ = 20.4 (t, C-8), 22.0 (t, C-3), 22.6 (t, C-9), 24.4 (q, 6-Me_{eq}), 27.6 (q, 1-Me_{ax}), 29.4 (q, 1-Me_{eq}), 29.7 (t, C-10), 31.4 (t, C-4), 36.5 (t, C-7), 42.7 (t, C-2), 46.8 (s, C-1), 53.3 (s, C-5), 56.3 (q, OCH_3), 81.9 (s, C-6), 90.7 (t, OCH_2O) ppm. MS (EI): *m*/*z* (%) = 240 (1) [M^+], 225 (1) [$M^+ - CH_3$], 208 (2) [$M^+ - CH_3OH$], 193 (3) [$M^+ - CH_3OH - CH_3$], 177 (80) [$C_{13}H_{21}^+$], 163 (13) [$C_{12}H_{19}^+$], 136 (29) [$C_{10}H_{16}^+$], 121 (24) [$C_9H_{13}^+$], 109 (53) [$C_8H_{13}^+$], 95 (72) [$C_7H_{11}^+$], 81 (47) [$C_6H_9^+$], 69 (32) [$C_5H_9^+$], 55 (42) [$C_4H_7^+$], 45 (100) [$C_3H_9^+$].

(±)-1,1,6-Trimethylspiro[4.5]dec-6-ene (4): At room temp., triphenylphosphane (2.83 g, 10.8 mmol) was added in portions to a stirred suspension of 1,1,6-trimethylspiro[4.5]decan-6-ol (**17**, 1.77 g, 9.00 mmol), tetrabromomethane (3.58 g, 10.8 mmol) and Celite® (750 mg) in toluene (20 mL). The reaction mixture was stirred at room temp. for 1 h prior to filtering off the insoluble materials. This filter cake was macerated with hexane (15 mL), and the washings were again filtered. The combined filtrates were washed with saturated aq. $NaHCO_3$ solution (15 mL) and brine (15 mL), and, after being dried (Na_2SO_4), they were concentrated in a rotary evaporator under reduced pressure. The resulting residue was purified by filtration (pentane) over a pad of silica gel to furnish a slightly cloudy mixture of isomers containing compound **4** (1.69 g of mixture, GC: 37% in **4**, 39% yield). IR (ATR): $\tilde{\nu}$ = 2922/2863 (νC–H), 1442 (δC–H), 1373 ($\delta_s CH_3$), 803 (νC=C–H, out-of-plane, trisubst.), 1703 (νC=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.94/0.96 (2s, 6 H, 1-Me_2), 1.40–1.85 (m, 10 H, 2-, 3-, 4-, 9-, 10-H_2), 1.74 (td, *J* = 2.0, 1.5 Hz, 3 H, 6-Me), 1.92–1.97 (m, 2 H, 8-H_2), 5.38 (m_c, 1 H, 7-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.9 (t, C-9), 21.7 (t, C-3), 23.3 (q, 6-Me), 25.7 (t, C-8), 26.5/27.0 (2q, 1-Me_2), 34.5 (t, C-10), 38.7 (t, C-4), 43.8 (t, C-2), 44.6 (s, C-1), 49.9 (s, C-5), 124.1 (d, C-7), 139.7 (s, C-6) ppm. MS (EI): *m*/*z* (%) = 178 (19) [M^+], 163 (2) [$M^+ - CH_3$], 135 (8) [$M^+ - C_3H_7$], 121 (17) [$M^+ - C_4H_9$], 108 (100) [$M^+ - C_5H_{10}$], 93 (92) [$M^+ - C_5H_{10} - CH_3$], 82 (51) [$C_6H_{10}^+$], 79 (31) [$C_6H_7^+$], 67 (15) [$C_5H_7^+$], 55 (19) [$C_4H_7^+$], 41 (22) [$C_3H_5^+$].

(±)-(5*R,6*R**)-6-Hydroxy-1,1,6-trimethylspiro[4.5]decan-7-one (2):** At room temp., Oxone® (29.2 g, 47.5 mmol) was added in one dash to a stirred suspension of $NaHCO_3$ (2.00 g, 23.8 mmol) and $RuCl_3 \cdot 2H_2O$ (39.4 mg, 0.162 mmol) in EtOAc/CH_3CN/H_2O (6:6:1, 130 mL). After being stirred for 5 min at room temp., the resulting suspension was cooled down to 0 °C (ice/water bath), prior to addition of the crude 1,1,6-trimethylspiro[4.5]dec-6-ene mixture (1.69 g, 37% in **4**, 3.49 mmol). The reaction mixture was stirred at 0 °C for 40 min, diluted with EtOAc (100 mL), and filtered by suction through a sintered funnel. The filter cake was washed with saturated aq. Na_2SO_3 solution (2 × 25 mL), dried (Na_2SO_4), and concentrated in a rotary evaporator under reduced pressure. The resulting residue was purified by repeated silica gel FC (pentane/EtOAc, 19:1, R_f = 0.35; pentane/Et_2O, 9:1, R_f = 0.45) and subsequent recrystallization (MeO*t*Bu) to furnish target compound **2** (244 mg, 33%) in the form of a colorless semicrystalline solid. M.p. 50–51 °C. IR (ATR): $\tilde{\nu}$ = 1705 (νC=O), 1149/1123 (νC–O), 1370 ($\delta_s CH_3$), 1466 (δCH_2), 3447 (νO–H) cm^{-1}. ^1H NMR (C_6D_6): δ = 1.10 (s, 3 H, 1-Me_{ax}), 1.11 (m_c, 1 H, 10-H_b), 1.12 (m_c, 1 H, 4-H_{ax}), 1.27 (s, 3 H, 6-Me), 1.33–1.41 (m, 2 H, 9-H_2), 1.36 (m_c, 1 H, 3-H_b), 1.41 (s, 3 H, 1-Me_{eq}), 1.42 (m_c, 1 H, 2-H_b), 1.50 (m_c, 1 H, 10-H_a), 1.54 (m_c, 1 H, 2-H_a), 1.66 (m_c, 1 H, 3-H_a), 2.05 (m_c, 1 H, 8-H_b), 2.14 (m_c, 1 H, 4-H_{eq}), 2.20 (m_c, 1 H, 8-H_a), 4.59 (s, 1 H, O–H) ppm. ^1H, ^1H NOESY (C_6D_6): 1-Me_{ax} × 6-Me, 1-Me_{eq} × 6-Me_{ax}, 1-Me_{eq} × 6-OH, 4-H_{eq} × 6-OH. ^{13}C NMR (C_6D_6): δ = 19.3 (t, C-3), 21.5 (t, C-9), 23.0 (q, 6-Me), 25.5 (q, 1-Me), 26.6 (t, C-4), 28.2 (q, 1-Me), 28.5 (t, C-10), 36.0 (t, C-8), 42.5 (t, C-2), 45.8 (s, C-1), 56.7 (s, C-5), 80.4 (s, C-6), 213.5 (s, C-7) ppm. MS (EI): *m*/*z* (%) = 210 (14) [M^+], 195 (3) [$M^+ - CH_3$], 192 (1) [$M^+ - H_2O$], 182 (8) [$M^+ - C_2H_4$], 167 (8) [$M^+ - C_3H_7$], 149 (49) [$M^+ - C_3H_7 - H_2O$], 139 (12) [$M^+ - C_5H_{11}$], 122 (21) [$C_9H_{14}^+$], 109 (42) [$C_8H_{13}^+$], 95 (46) [$C_7H_{11}^+$], 82 (41) [$C_6H_{10}^+$], 71 (44) [$C_5H_{11}^+$], 55 (50) [$C_4H_7^+$], 43 (100) [$C_3H_7^+$]. $C_{13}H_{22}O_2$ (210.31): calcd. C 74.24, H 10.54;

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

found C 74.20, H 10.47. Odor: camphoraceous, agrestic, minty, reminiscent of eucalyptol, with woody and earthy facets, slightly reminiscent of patchouli. Odor threshold: 17.2 ng/L air.

(±)-2,2-Dimethylspiro[4.5]decan-6-one (19): At room temp., a solution of 1,4-dibromo-2,2-dimethylbutane (**18**, 20.0 g, 82 mmol) prepared according to ref.[31] and cyclohexanone (8.05 g, 82 mmol) in toluene (200 mL) was added slowly with mechanical stirring to a suspension of potassium *tert*-butoxide (20.2 g, 180 mmol) in toluene (300 mL) over a period of 80 min. The resulting reaction mixture was heated to 95 °C overnight and then cooled. At room temp., the resulting solution was diluted with Et_2O (300 mL) and washed in turn with saturated aq. NH_4Cl solution (4 × 100 mL) and brine (4 × 100 mL). After being dried (Na_2SO_4), the combined organic extracts were concentrated in a rotary evaporator under reduced pressure, and the resulting residue was purified by silica gel FC (pentane/Et_2O, 29:1, R_f = 0.36) and subsequent Kugelrohr distillation (82 °C/0.2 mbar) to furnish compound **19** (3.07 g, 21%) as a colorless oil. IR (ATR): $\tilde{\nu}$ = 1703 (νC=O), 1127 (ν_{as}C–C), 1449 (δC–H), 1384 ($\delta_s CH_3$) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.95/1.03 (2s, 6 H, 2-Me_2), 1.29 (d, J = 13.5 Hz, 1 H, 1-H_b), 1.42 (dd, J = 10.0, 7.0 Hz, 2 H, 3-H_b), 1.44 (dd, J = 10.0, 7.0 Hz, 2 H, 3-H_a), 1.53 (dt, J = 12.5, 7.0 Hz, 1 H, 4-H_b), 1.66–1.73 (m, 2 H, 9-H_2), 1.72–1.78 (m, 2 H, 10-H_2), 1.77–1.84 (m, 2 H, 8-H_2), 1.99 (d, J = 13.5 Hz, 1 H, 1-H_a), 2.23 (dt, J = 12.5, 7.0 Hz, 1 H, 4-H_a), 2.40 (t, J = 6.5 Hz, 2 H, 7-H_2) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.8 (t, C-9), 27.4 (t, C-8), 28.9/30.0 (2q, 2-Me_2), 34.3 (t, C-4), 39.3 (t, C-7), 39.4 (s, C-2), 40.2 (t, C-3), 41.6 (t, C-10), 49.5 (t, C-1), 57.4 (s, C-5), 214.1 (s, C-6) ppm. MS (EI): *m*/*z* (%) = 180 (29) [M^+], 165 (39) [$M^+ - CH_3$], 147 (18) [$M^+ - CH_3 - H_2O$], 136 (16) [$M^+ - C_3H_8$], 121 (18) [$M^+ - C_3H_8 - CH_3$], 111 (100) [$C_7H_{11}O^+$], 95 (45) [$C_7H_{11}^+$], 81 (47) [$C_6H_9^+$], 67 (30) [$C_5H_7^+$], 55 (34) [$C_4H_7^+$], 41 (27) [$C_3H_5^+$]. $C_{12}H_{20}O$ (180.29): calcd. C 79.94, H 11.18; found C 79.98, H 11.10. Odor: very weak with slightly earthy and minty aspects.

(±)-2,2,6-Trimethylspiro[4.5]decan-6-ol (20): At room temp., 2,2-dimethylspiro[4.5]decan-6-one (**19**, 3.00 g, 16.6 mmol) was injected by syringe over 2 min to a stirred solution of methyllithium (1.6 M in Et_2O, 33.3 mL, 53.2 mmol). Stirring was continued for 30 min at room temp., prior to quenching with cold saturated aq. NH_4Cl solution (50 mL). After separation of the layers, the aqueous one was extracted with Et_2O (3 × 25 mL). The organic extracts were combined and washed in turn with saturated aq. $NaHCO_3$ solution (3 × 25 mL) and brine (3 × 25 mL). After being dried (Na_2SO_4), the resulting solution was concentrated in a rotary evaporator under reduced pressure. The resulting residue was purified by silica gel FC (pentane/Et_2O, 37:3, R_f = 0.21) to furnish the diastereomeric mixture of compound **20** (3.11 g, 95%) as a colorless liquid. IR (ATR): $\tilde{\nu}$ = 1464 (δO–H, ip), 1364 ($\delta_s CH_3$), 1115/1174 (νC–O, *tert*-OH), 3473 (νO–H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.01/1.01/1.03/1.05 (4s, 6 H, 2-Me_2), 1.16/1.17 (2s, 3 H, 6-Me), 1.15/1.19 (2d, J = 18.0/14.0 Hz, 1 H, 1-H_b), 1.31 (br. s, 1 H, OH), 1.34/1.36 (2m_c, 1 H, 10-H_b), 1.36/1.42 (2m_c, 1 H, 4-H_b), 1.28–1.45 (m, 4 H, 8-,9-H_2), 1.36–1.47 (m, 2 H, 3-H_2), 1.40–1.48 (m, 2 H, 7-H_2), 1.50/1.69 (2m_c, 1 H, 1-H_a), 1.59/1.61 (2m_c, 1 H, 10-H_a), 1.76/1.93 (2m_c, 1 H, 4-H_a) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.3/22.4 (2t, C-8), 22.8/22.9 (2t, C-9), 24.5/24.7 (2q, 6-Me), 30.0/30.5/30.6/31.1 (4q, 2-Me_2), 32.5/34.0 (2t, C-4), 36.7/37.1 (2t, C-10), 37.9/38.3 (2t, C-7), 39.0/39.1 (2s, C-2), 40.9/41.2 (2t, C-3), 47.6/48.8 (2t, C-1), 51.4/51.5 (2s, C-5), 74.0/74.3 (2s, C-6) ppm. MS (EI): *m*/*z* (%) = 196 (9) [M^+], 181 (24) [$M^+ - CH_3$], 178 (12) [$M^+ - H_2O$], 163 (100) [$M^+ - CH_3 - H_2O$], 149 (13) [$M^+ - C_2H_7O$], 136 (64) [$M^+ - C_3H_8O$], 121 (44) [$M^+ - C_4H_{11}O$], 107 (35) [$C_8H_{11}^+$], 95 (41) [$C_7H_{11}^+$], 81 (52) [$C_6H_9^+$], 71 (78) [$C_4H_7O^+$], 55 (41) [$C_4H_7^+$], 43 (63) [$C_3H_7^+$]. Odor: camphoraceous, earthy, somewhat reminiscent of vetiver and grapefruit peel. Odor threshold: 68 ng/L air.

(±)-2,2,6-Trimethylspiro[4.5]dec-6-ene (21): At room temp., triphenylphosphane (4.71 g, 18.0 mmol) was added in portions to a stirred suspension of 2,2,6-trimethylspiro[4.5]decan-6-ol (**20**, 2.94 g, 15.0 mmol), tetrabromomethane (5.96 g, 18.0 mmol) and Celite® (1.25 g) in toluene (30 mL). The reaction mixture was stirred at 40 °C for 1 d, prior to filtering off the insoluble materials. The filter cake was extracted with hexane (15 mL), and the combined extracts were filtered again. The combined filtrates were concentrated in a rotary evaporator under reduced pressure, and the resulting residue was purified by filtration (pentane) over a pad of silica gel to furnish a slightly cloudy mixture containing compound **21** as the main product (2.73 g of mixture, GC: 43% in **21**, 44% yield). MS (EI): *m*/*z* (%) = 178 (45) [M^+], 163 (87) [$M^+ - CH_3$], 149 (11) [$M^+ - C_2H_5$], 135 (18) [$M^+ - C_3H_7$], 122 (38) [$M^+ - C_4H_8$], 107 (67) [$M^+ - C_5H_{11}$], 93 (100) [$M^+ - C_6H_{13}$], 81 (48) [$C_6H_9^+$], 67 (26) [$C_5H_7^+$], 55 (30) [$C_4H_7^+$], 41 (35) [$C_3H_5^+$].

(±)-6-Hydroxy-2,2,6-trimethylspiro[4.5]decan-7-one (22): At room temp., Oxone® (46.1 g, 75.0 mmol) was added in one dash to a stirred suspension of $NaHCO_3$ (3.15 g, 37.5 mmol) and $RuCl_3 \cdot 2H_2O$ (62.2 mg, 0.255 mmol) in EtOAc/CH_3CN/H_2O (6:6:1, 195 mL). After 5 min of stirring at room temp., the resulting suspension was cooled down to 0 °C (ice/water bath), prior to addition of the crude 2,2,6-trimethylspiro[4.5]dec-6-ene mixture (43% in **21**, 2.68 g, 6.46 mmol). The reaction mixture was stirred at 0 °C for 40 min, diluted with EtOAc (150 mL), and filtered by suction through a sintered funnel. The filter cake was washed with saturated aq. Na_2SO_3 solution (2 × 35 mL), dried (Na_2SO_4), and concentrated in a rotary evaporator under reduced pressure. The resulting residue was purified by repeated silica gel FC (pentane/Et_2O, 19:1, R_f = 0.21; pentane/Et_2O, 9:1, R_f = 0.43) to furnish the second target compound **22** (272 mg, 22%) as a ca. 1:1 mixture of diastereoisomers in the form of a colorless oil. IR (ATR): $\tilde{\nu}$ = 1706 (νC=O), 1142 (νC–O), 1364 ($\delta_s CH_3$), 1462 (δCH_2), 3478 (νO–H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.84/1.02 (2d, J = 13.0 Hz, 1 H, 1-H_b), 0.93/0.99/1.08/1.09 (4s, 6 H, 2-Me_2), 1.08/1.10 (2s, 3 H, 6-Me), 1.12/1.22 (2m_c, 1 H, 4-H_b), 1.24/2.07 (2m_c, 2 H, 10-H_2), 1.27–1.35 (m, 2 H, 9-H_2), 1.30/1.33 (2m_c, 1 H, 3-H_b), 1.34/1.99 (2m_c, 1 H, 8-H_b), 1.42/1.97 (2d, J = 13.0 Hz, 1 H, 1-H_a), 1.43/1.60 (2m_c, 1 H, 3-H_a), 1.60/2.14 (2m_c, 1 H, 4-H_a), 2.01/2.09 (2m_c, 1 H, 8-H_a), 4.14/4.19 (2s, 1 H, OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.3/22.6 (2q, 6-Me), 22.5/22.6 (2t, C-9), 28.9/29.4/30.3/31.6 (4q, 2-Me_2), 31.2/34.6 (2t, C-4), 35.3/36.2 (2t, C-10), 36.3/36.3 (2t, C-8), 38.7/39.7 (2s, C-2), 40.3/41.8 (2t, C-3), 44.5/49.1 (2t, C-1), 55.4/56.2 (2s, C-5), 79.4/80.6 (2s, C-6), 213.7/213.8 (2s, C-7) ppm. MS (EI): *m*/*z* (%) = 210 (40) [M^+], 195 (3) [$M^+ - CH_3$], 192 (2) [$M^+ - H_2O$], 182 (4) [$M^+ - CO$], 177 (11) [$M^+ - CH_3 - H_2O$], 167 (25) [$M^+ - CH_3 - CO$], 149 (97) [$M^+ - CH_3 - H_2O - CO$], 122 (41) [$C_9H_{14}^+$], 109 (49) [$C_8H_{13}^+$], 95 (59) [$C_7H_{11}^+$], 87 (64) [$C_5H_{11}O^+$], 71 (52) [$C_5H_{11}^+$], 55 (61) [$C_4H_7^+$], 43 (100) [$C_3H_7^+$]. $C_{13}H_{22}O_2$ (210.31): calcd. C 74.24, H 10.54; found C 74.20, H 10.50. Odor: weak, woody, cedar-like, with a powdery connotation. Odor threshold: 233 ng/L air.

Acknowledgments

We are indebted to Professor Dr. Jean-Paul Quintard, Université de Nantes, for making this external master's thesis of Audrey Bruneau possible. We thank Professor Manfred T. Reetz, Max-Planck-Institut für Kohlenforschung Mülheim an der Ruhr, for the procedure for the preparation of 1-bromo-4-chloro-4-methylpentane (**15**) from the diploma thesis of Athanassios Giannis[21]. Thanks are also due

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

to Dr. Gerhard Brunner for the NMR experiments, to Katarina Grman for GC-threshold determinations, and to Alain E. Alchenberger for the olfactory evaluations. Careful proofreading of the manuscript by Dr. Markus Gautschi, Dr. Samuel Derrer, and Tony McStea is also acknowledged with gratitude.

[1] a) I. Calvino, "Il nome, il naso" in *Sotto il sole giaguaro*, Opere di Italo Calvino, Oscar Mondadori, Milano, **2002**, p. 7; b) English ed: I. Calvino, "The Name, the Nose" in *Under the Jaguar Sun*, A Harvest Book, Harcourt Brace & Company, San Diego, CA, **1988**, p. 69; c) German ed.: I. Calvino, "Der Name, die Nase" in *Unter der Jaguar-Sonne – Drei Erzählungen*, Carl Hanser Verlag, München, **1987**, pp. 9–10.

[2] P. Kraft, C. Weymuth, C. Nussbaumer, *Eur. J. Org. Chem.* **2006**, 1403–1412.

[3] P. Kraft, W. Eichenberger, D. Frech, *Eur. J. Org. Chem.* **2005**, 3233–3245.

[4] a) W. Oppolzer, V. Snieckus, *Angew. Chem.* **1978**, *90*, 506–516; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 476–504; b) D. F. Taber, *Intramolecular Diels–Alder and Alder Ene Reactions*, Reactivity and Structure Concepts in Organic Chemistry Vol. 18, Springer-Verlag, Berlin, **1984**, pp. 61–93.

[5] S. Antoniotti, E. Duñach, *Synthesis* **2003**, 2753–2762.

[6] a) W. Oppolzer, *Angew. Chem.* **1989**, *101*, 39–53; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 38–60; b) W. Oppolzer, *Pure Appl. Chem.* **1990**, *62*, 1941–1948; c) W. Oppolzer in *Comprehensive Organic Synthesis* (Ed.: B. M. Trost), Pergamon Press, Oxford **1991**, Vol. 5, pp. 29–61.

[7] G. Stork, R. L. Danheiser, *J. Org. Chem.* **1973**, *38*, 1775–1776.

[8] J.-C. Jung, R. Kache, K. K. Vines, Y.-S. Zheng, P. Bijoy, M. Valluri, M. A. Avery, *J. Org. Chem.* **2004**, *69*, 9269–9284.

[9] P. J. Kocienski, G. Cernigliaro, G. Feldstein, *J. Org. Chem.* **1977**, *42*, 353–355.

[10] M. C. Pirrung, *J. Am. Chem. Soc.* **1981**, *103*, 82–87.

[11] a) G. Dauphin, J.-C. Gourcy, H. Veschambre, *Tetrahedron: Asymmetry* **1992**, *3*, 595–598; b) B. Delpech, D. Calvo, R. Lett, *Tetrahedron Lett.* **1996**, *37*, 1015–1018.

[12] a) H. Lehmkuhl, *Bull. Soc. Chim. Fr.* **1981**, 87–95; b) W. Oppolzer, P. Schneider, *Helv. Chim. Acta* **1986**, *69*, 1817–1820.

[13] a) W. Oppolzer, F. Schröder, S. Kahl, *Helv. Chim. Acta* **1997**, *80*, 2047–2057; b) W. Oppolzer, F. Flachsmann, *Helv. Chim. Acta* **2001**, *84*, 416–430.

[14] a) R. Appel, *Angew. Chem.* **1975**, *87*, 863–874; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801–821; b) A. K. Bose, B. Lal, *Tetrahedron Lett.* **1973**, *14*, 3937–3940.

[15] M. Labrouillère, C. Le Roux, H. Gaspard-Iloughmane, J. Dubac, *Synlett* **1994**, 723–724.

[16] V. K. Yadav, K. G. Babu, *Tetrahedron* **2003**, *59*, 9111–9116.

[17] E. J. Corey, C. U. Kim, M. Takeda, *Tetrahedron Lett.* **1972**, *13*, 4339–4342.

[18] B. Neiss, W. Steglich, *Angew. Chem.* **1978**, *90*, 556–557; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 522–523.

[19] a) S. A. Godleski, R. S. Valpey, *J. Org. Chem.* **1982**, *47*, 383–384; b) J.-E. Bäckvall, J.-O. Vågberg, K. L. Granberg, *Tetrahedron Lett.* **1989**, *30*, 617–620.

[20] M. T. Reetz, W. F. Maier, I. Chatziiosifidis, A. Giannis, H. Heimbach, U. Löwe, *Chem. Ber.* **1980**, *113*, 3741–3757.

[21] A. Giannis, Diplomarbeit, Rheinische Friedrich-Wilhelms-Universität Bonn, **1980**, p. 49.

[22] K. Narasaka, T. Sakakura, T. Uchimaru, D. Guédin-Vuong, *J. Am. Chem. Soc.* **1984**, *106*, 2954–2961.

[23] a) I. M. Downie, J. B. Holmes, J. B. Lee, *Chem. Ind.* **1966**, 900–901; b) P. Kraft, K. Popaj, *Eur. J. Org. Chem.* **2004**, 4995–5002.

[24] a) T. Cohen, T. Tsuji, *J. Org. Chem.* **1961**, *26*, 1681; b) T. M. Santosusso, D. Swern, *J. Org. Chem.* **1975**, *40*, 2764–2769.

[25] J. A. Ramírez, E. G. Gros, L. R. Galagovsky, *Tetrahedron* **2000**, *56*, 6171–6180.

[26] Y. Q. Tu, S. K. Ren, Y. X. Jia, B. M. Wang, A. S. C. Chan, M. C. K. Choi, *Tetrahedron Lett.* **2001**, *42*, 2141–2144.

[27] H. Hioki, H. Ooi, M. Hamano, Y. Mimura, S. Yoshio, M. Kodama, S. Ohta, M. Yanai, S. Ikegami, *Tetrahedron* **2001**, *57*, 1235–1246.

[28] V. VanRheenen, R. C. Kelly, D. J. Cha, *Tetrahedron Lett.* **1976**, *17*, 1973–1976.

[29] a) B. Plietker, *J. Org. Chem.* **2003**, *68*, 7123–7125; b) B. Plietker, *Org. Lett.* **2004**, *6*, 289–291; c) B. Plietker, *J. Org. Chem.* **2004**, *69*, 8287–8296; d) B. Plietker, *Tetrahedron: Asymmetry* **2005**, *16*, 3453–3459; e) B. Plietker, *Eur. J. Org. Chem.* **2005**, 1919–1929.

[30] P. H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936–3938.

[31] R. F. Brown, N. M. van Gulick, *J. Am. Chem. Soc.* **1955**, *77*, 1089–1092.

[32] a) P. Weyerstahl, *J. Prakt. Chem.* **1994**, *336*, 95–109; b) B. D. Mookherjee, K. K. Light, I. D. Hill in *178th ACS National Meeting*, *Washington D. C., Sept. 9–14, 1979, Abstracts of papers, I, AGFD 55*; B. D. Mookherjee, K. K. Light, I. D. Hill in *Essential Oils* (Eds.: B. D. Mookherjee, C. J. Mussinan), Allured Publishing Corp., Wheaton, IL, **1981**, pp. 246–272.

[33] R. Becker, K. Jansen, F. G. M. Vogel, *Perfum. Flavor.* **1990**, *15 (Nov./Dec.)*, 29–33.

Received: September 18, 2006
Published Online: January 3, 2007

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim