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Laure Gilles, Sylvain Antoniotti. Spirocyclic Compounds in Fragrance Chemistry: Synthesis and Olfactory Properties. *ChemPlusChem*, 2022, 87 (11), pp.e202200227. 10.1002/cplu.202200227. hal-04256933

HAL Id: hal-04256933

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Submitted on 24 Oct 2023

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Spirocyclic Compounds in Fragrance Chemistry: Synthesis and Olfactory Properties

Laure Gilles^[a, b] and Sylvain Antoniotti^{*[a]}*In memory of Prof. David A. Evans.*

In this Review, both the scientific literature and patents have been analysed to gather, examine and classify synthetic strategies developed to access spirocyclic molecules having olfactory properties of interest for the perfume industry. New structures have been reported at a steady state since 1961 with a particularly intense activity in the 80's. In the diversity of

olfactory properties observed, spirocyclic molecules were found to be quite frequently woody, as well as fruity and ambery, among other tonalities. More recent data reflect the evolution of modern synthetic organic chemistry towards bioinspiration, enantioselective reactions, green and sustainable chemistry and biotechnology.

1. Introduction

Spirocyclic molecules in organic chemistry are bicyclic molecules for which the two constitutive cycles have one atom in common. If more than two cycles are connected only by single atoms, we talk of polyspirocyclic compounds. In spirocyclic molecules, the atom common to both cycles is called the spiro-atom. It is more frequently a carbon atom but can be any tetravalent atom. A spirocyclic motif can also be part of a more complex polycyclic system where fused rings, sharing two adjacent atoms, or bridged bicycles, sharing more than two atoms are present.

Spirocyclic molecules are named following the standard bicyclic naming system considering the total number of atoms of the spirocycle skeleton and using brackets to notify the number of atoms of each ring separated by a point, besides the spiro-atom, and numbered starting with the atom adjacent to the spiro-atom on the smaller ring (Scheme 1).

Numbering then proceeds along the smaller ring, then the spiroatom, then the larger ring. Standard priority rules apply to decide in which direction proceed on both rings, depending on the presence of substituents or heteroelements.

For heterocyclic spiro compounds, the nucleophilicity of heteroatoms is definitely an advantage for synthetic purposes, and even more if two heteroatoms are involved. Conventional procedures for the condensation of 1,2-difunctional compounds (e.g. α -diols, α -aminoalcohols, α -sulfanylalcohols, ...) with ketones under acid-catalysis are thus plethora.

For all-carbon spirocyclic compounds however it is a different story since the intrinsic difficulty of building a quaternary carbon atom adds to the fact that it should be the unique bridgehead of two cycles.

Fragrance chemists have a general interest for cyclic molecules which are numerous in the odorants catalogue, and also because many examples of odoriferous natural complex substances are containing cyclic molecules. Spirocyclic mole-

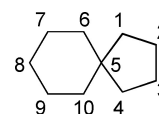
cules are scarce, but they can be found in Nature, as actual spirane derivatives or embedded in a more complex polycycles like for khusimone or related zizaene structures.^[1] Synthetic spiranes designed by chemists have thus been studied for their olfactory properties and some candidates have even reached the market.

In this review, we cover the scientific literature and patents dealing with spirocyclic molecules in fragrance chemistry, focusing on the synthetic methods developed to construct their spiro structure and the determination of their olfactory properties. Prior reviews exist for spirocyclic molecules synthesis but to our knowledge never specifically addressed olfactory properties associated to these structures.^[2] Spirocyclic molecules have also been used as antagonists of butyric acid (synthesis not described) aimed at malodor modulation, butyric acid having a strong cheesy odor unpleasant at high concentration but these approaches will not be considered in this review.^[3]

2. Classification of Synthetic Strategies

The analysis of articles and patents to prepare this review revealed that in a large majority, mostly ionic approaches were developed for spirocyclic molecules synthesis. From a retrosynthetic viewpoint, the disconnections could be either considered at the spiroatom or at a remote position along one of the rings. In the former case, the spiro atom is formed during the process like for example through hydroalkoxylation, cycloaddition, bis-alkylation, α -ketone alkylation, ene-reaction, Nazarov cyclisation, carbene insertion, cyclopropanation, radical coupling, carbonyl condensation, or rearrangement. In the latter case, the all-carbon quaternary atom is already present, and functional groups on substituting side chains react intramolecularly to ensure the desired ring closure. Several methods can thus be envisaged such as aldolization, lactonization, cyclo-dehydration, acetalization, or ring-closing metathesis (Scheme 2). Examples of functional groups interconversions on already existing spirocyclic structure will not be covered in this review neither.

In terms of ring size, in most cases, spiro[4.5]decane and spiro[5.5]undecane were described (Scheme 3), and rarely 1-



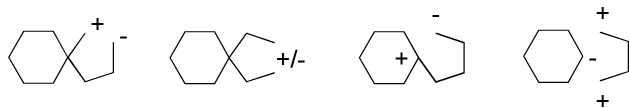
Scheme 1. Numbering system for spirocyclic compounds, case of spiro[4.5]decane.

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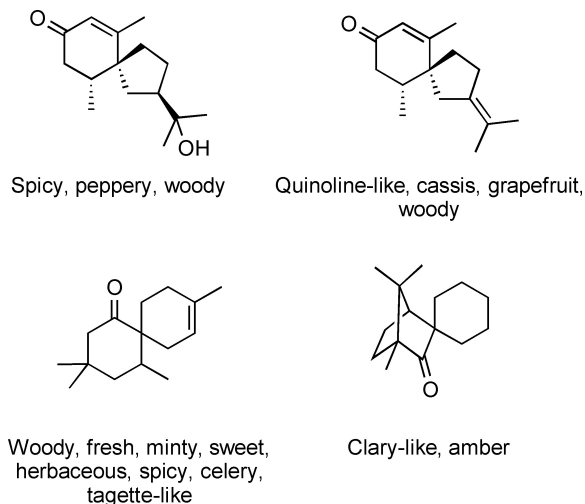
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Scheme 2. Frequent disconnections observed in synthetic strategies developed to form spirocyclic compounds.



Scheme 3. Examples of spirocyclic compounds reported along with their olfactory properties.

oxaspiro[5.2]octane and 1-oxaspiro[9.2]dodecane where the smaller ring is actually an oxirane.

3. Synthesis of Spirocyclic Compounds

In this part, syntheses are classified depending on the key step for spirocyclisation. Olfactory descriptors are provided and gathered in Table 1, which summarizes the structures in order of appearance, the references and olfactory families they can be related to. Although chirality can have an influence on olfactory properties,^[4] it is frequent that stereoisomers differ mostly on their perception threshold, even if striking examples are found in textbooks (e.g. carvone or limonene). Unless otherwise indicated, spirocyclic compounds presented herein are racemates, and their odors are provided for mixtures, as described in the primary sources used.



Sylvain Antoniotti is Director of Research at CNRS and group leader at the Institut de Chimie de Nice of Université Côte d'Azur. His research interests are in synthetic methods development in organic chemistry, catalysis, biocatalysis, and analysis of natural complex substances in the context of sustainable chemistry and with applications in the Flavour and Fragrance sector.



Laure Gilles obtained her engineering and master's degrees from Ecole Européenne d'ingénieurs de Chimie, Polymères et Matériaux, Université de Strasbourg in 2018. She is currently pursuing doctoral studies under the supervision of Dr. Sylvain Antoniotti, in the synthesis of natural odorant spirocyclic molecules, at Institut de Chimie de Nice, Université Côte d'Azur, in partnership with the company Alysophil based in Strasbourg.

3.1. Aldolization

A Michael addition involving cyclohexane carbaldehydes and acrolein has been used to generate δ -ketoaldehydes subjected to an aldolization reaction furnishing upon crotonisation the desired spiro[5.5]undec-1-en-3-one structures **1a–d** (Scheme 4).^[5]

Alternatively, similar outcome could be observed by preparing the corresponding enamine with either pyrrolidine or morpholine and reacting it with acrolein. Eventually, the carbon-carbon double bond of **1a–d** could be reduced by catalytic hydrogenation to products **2a–d**. Fruity, spicy and iris olfactory notes were found for spirocycles **1a** and **2a–d**.

A Michael addition followed in a domino process by an intramolecular aldolisation/crotonisation (Robinson annulation) was also used to access tricyclic spiroketones **3** and **4** starting from 3-formylpiperane and 4-formylcarane, respectively (Scheme 5).^[6] They respectively presented balsamic/vanilla notes, and woody notes, reminiscent of vetiver, as well as balsamic and floral notes, respectively. Also involving a reaction with methylvinylketone but with cyclooctane carbaldehyde, either used directly or after been transformed into its piperidine-enamine, the corresponding spiro[5.7]dec-1-en-3-one **5** could be formed and presented costus, animalic and leather notes.^[7]

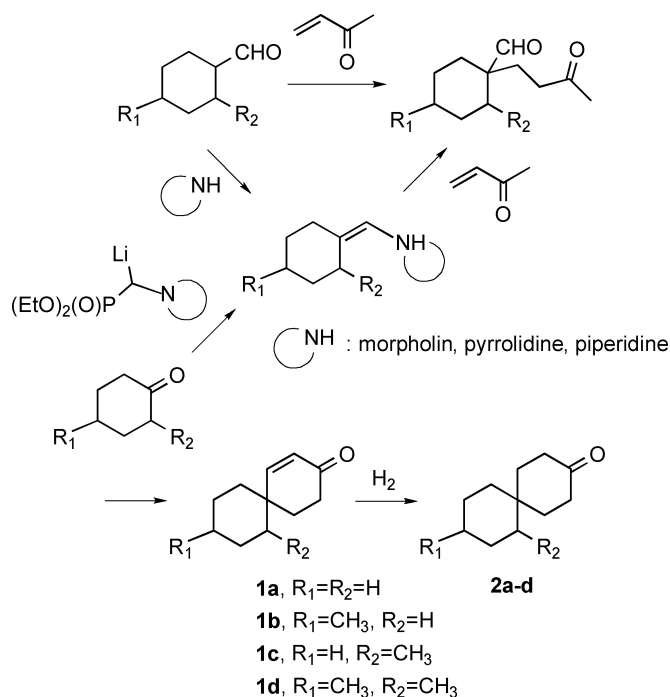
Acorenone B **6**, a spiro sesquiterpenoid isolated from *Euphorbia macrorrhiza*, *Angelica lucida*, *Niphogeton dissecta*, and *Aquilaria sp.*, and described as a minor contributor to the odor of agarwood essential oils,^[8] can be stereoselectively synthesized using an intramolecular aldolisation to create the spiro structure (Scheme 6).^[9]

Stereospecific synthesis of (–)-agarospirol **7** and (–)- β -vetivone **8** could also be envisaged by intramolecular aldolisation of a suitable 7-oxaheptan-2-one derivative as the key step generating the final spiro structure (Scheme 7).^[10]

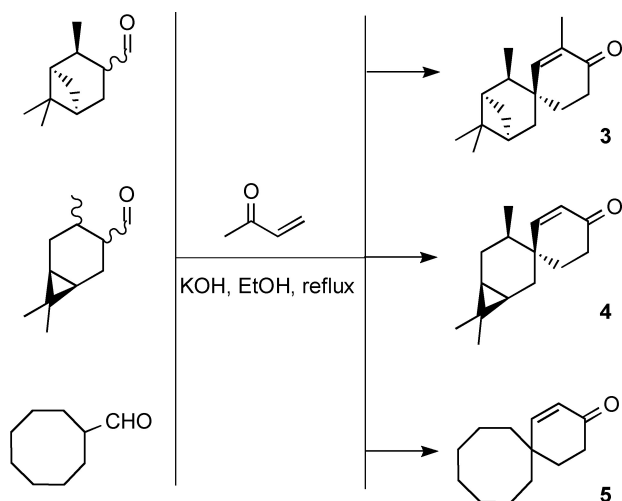
Similar approach was used to achieve (–)- α -acoradiene synthesis, a spiro compound found in essential oils such as vetiver essential oil, but not really used per se as odorant.^[11]

3.2. Lactonisation

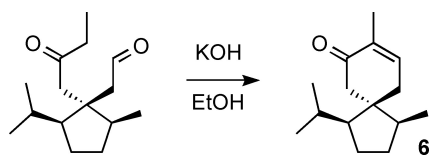
By the formation of the appropriate δ -hydroxycarboxylic acid in two steps from terpineol by addition to ethylene oxide and oxidation, spontaneous lactonization occurs and leads to 9-



Scheme 4. Michael addition/aldolization sequence.



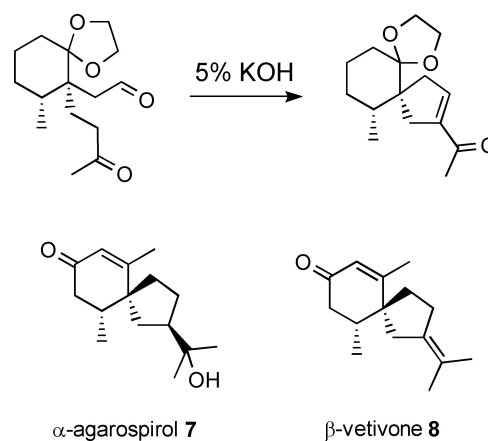
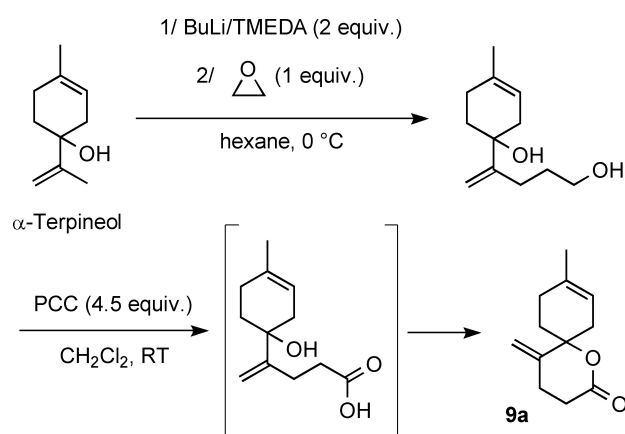
Scheme 5. Michael addition-intramolecular aldolization/crotonisation of cycloalkane carbaldehydes with vinyl ketones.



Scheme 6. Acronone B 6 stereocontrolled synthesis by aldolisation as the key step.

methyl-5-methylidene-1-oxaspiro[5.5]undec-8-en-2-one **9a** (Scheme 8).^[12]

This spiro lactone **9a** was presented as having spicy coumarine-like odor. If the isoprenyl substituent is hydro-

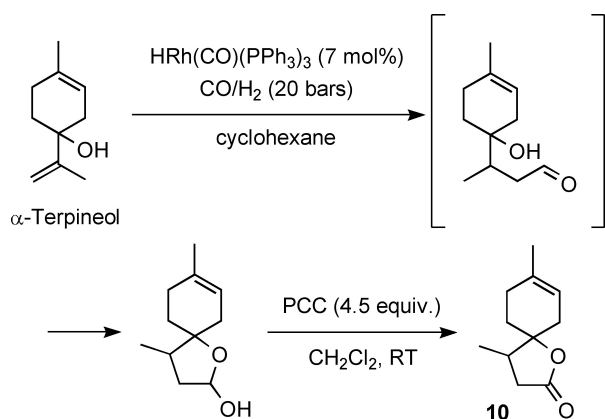
Scheme 7. Intramolecular aldolisation to achieve the 5-membered ring-closing reaction to the 10-methylspiro[4.5]dec-2-ene structure en route to (-)-agarospiro **7** and (-)- β -vetivone **8** syntheses.Scheme 8. A 3-steps sequence from α -terpineol to 9-methyl-5-methylidene-1-oxaspiro[5.5]undec-8-en-2-one **9a** by lactonisation.

generated prior to the sequence, the corresponding lactone **9b** is similarly obtained but possesses a woody odor reminiscent of cedarwood. In a related approach but involving a hydroformylation of α -terpineol followed by the attack of the alcohol function on the newly installed aldehydic function, a spirohemiacetal can be formed and be further oxidized to get spiro- γ -lactone **10** also presenting a woody character (Scheme 9).

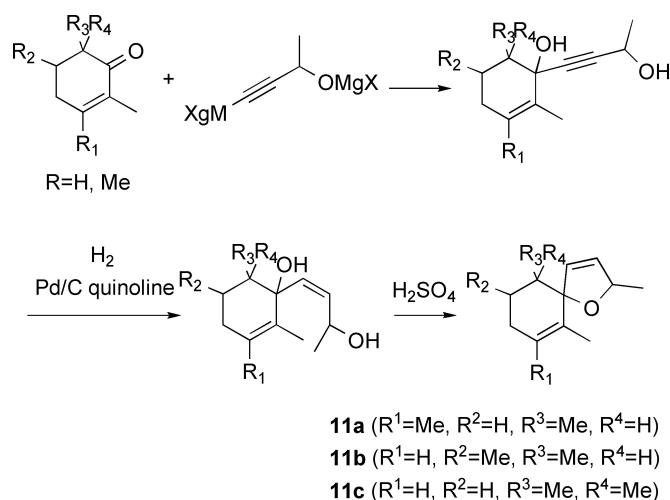
3.3. Cyclodehydration

1-Oxaspiro[4.5]decane structures **11a–b** could be formed by cyclodehydration of the corresponding 1,4-diol. The desired diol could be obtained by treatment of a substituted cyclohexanone by the Grignard reagent derived from but-3-yn-2-ol followed by partial *cis*-hydrogenation and Brønsted acid-catalysed cyclodehydration (Scheme 10).^[13,14]

Compounds **11a** (R¹=Me, R²=H) and **11b** (R¹=H, R²=Me) were submitted to sensory evaluation and were shown to enhance fresh and flowery notes of perfume compositions as



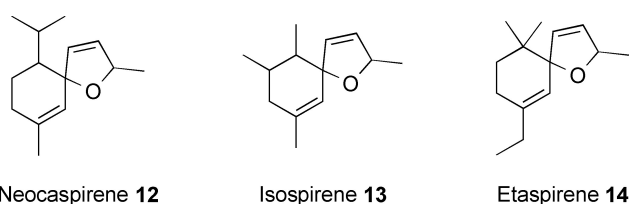
Scheme 9. Alternate access to 4,8-dimethyl-1-oxaspiro[4.5]dec-7-en-2-one **10**.



Scheme 10. Formation of 1-oxaspiro[4.5]dec-3,6-diene derivatives **11 a–c** by cyclodehydration as the key step.

well as fresh, herbal and fruity notes of raspberry and black-currant syrups.

By a slight modification in the acetylenic partner, the cassis-odorant neocaspirene (7-isopropyl-2,10-dimethyloxaspiro[4.5]deca-3,6-diene) **12** could be obtained.^[15] 2,6,9,10-Tetramethyl-1-oxa-spiro[4.5]deca-3,6-diene **13** (isospirene),^[16] and 6-ethyl-2,10,10-trimethyl-1-oxa-spiro[4.5]deca-3,6-diene **14** (etaspirene),^[17] other cassis odorants found on the market, could be obtained by the same approach (Scheme 11). Theaspirene (see below) could also be



Scheme 11. Neocaspirene **12**, isospirene **13**, and etaspirene **14**.

formed by cyclodehydration,^[18] or an equivalent assisted by forming a tosylate derivative^[19] but most approaches involving hydroalkoxylation of the C=C double bond, it will be presented in the corresponding section.

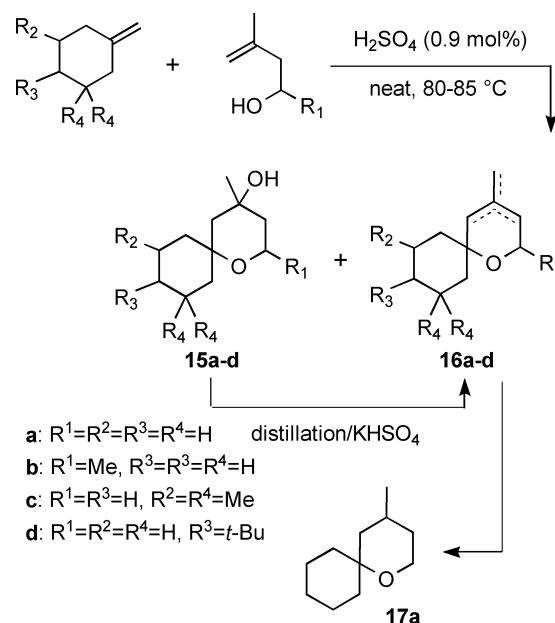
The key tertiary alcohol could also be prepared by an intermolecular carbonyl-ene reaction between a cyclohexanone derivative and a substituted homomethyl alcohol, followed by cyclodehydration, both steps being Brønsted acid-catalysed. The intermediate carbenium ion could be intercepted by hydration and yield 4-hydroxy-4-methyl-1-oxaspiro[5.5]undecane derivatives **15 a–d** eventually leading to olefinic isomers **16 a–d** by dehydration upon treatment by $KHSO_4$ and distillation as exemplified in a patent (Scheme 12).^[20] Standard hydrogenation of **16 a** led to **17 a**.

Notes described as green, herbal, floral, eucalyptol, minty, basil were found for compounds **16 a–d** and compound **17 a** obtained by hydrogenation of the mixture of isomers exhibited basil, herbaceous and eucalyptol notes.

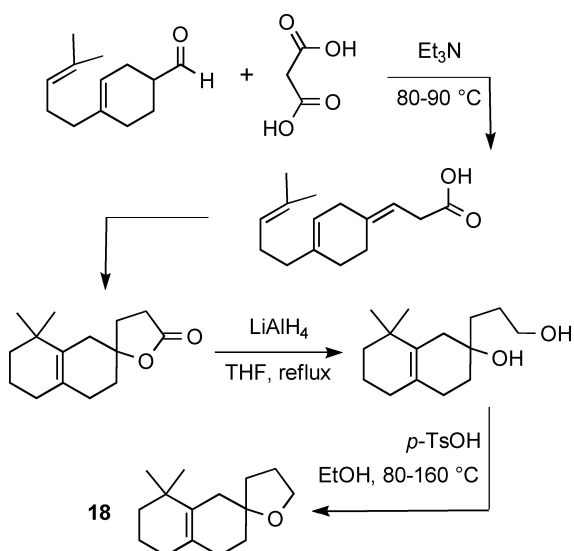
Cyclodehydration was also used after reducing a parent lactone by $LiAlH_4$ leading to the corresponding 1,4-diol further cyclized in the presence of a Brønsted acid such as *p*-TSA, leading to octahydrodimethylnaphthalene spirofuran **18** (Scheme 13).^[21]

3.4. Acetalisation and hemiacetalisation

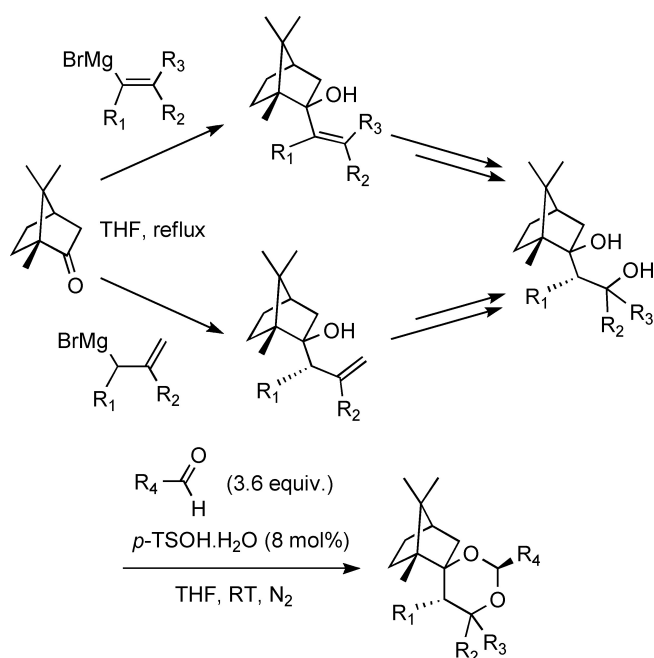
Using camphor as starting material and upon the formation of either vinylisborneol or allylisborneol further transformed into the corresponding 1,3-diols, spiro[bornyl-2,4'-(1,3-dioxanes)] **19 a–f** can be formed by condensation with low-molecular weight carbonyl partners (Scheme 14).^[22]



Scheme 12. Carbonyl-ene reaction followed by cyclodehydration en route to 4-methyl-1-oxaspiro[5.5]undecane derivatives.



Scheme 13. Multistep synthesis of 3',4,4',5,5',6',7',8'-octahydro-8',8'-dimethylspiro[furan-2(3H),2'(1'H)-naphthalene] **18**.



- 19a** ($R^1=Me, R^2=R^3=H, R^4=Me$)
19b ($R^1=Me, R^2=R^3=H, R^4=Et$)
19c ($R^1=Me, R^2=R^3=H, R^4=iPr$)
19d ($R^1=Me, R^2=R^3=H, R^4=Me_2$)
19e ($R^1=Me, R^2=R^3=Me, R^4=Me_2$)
19f ($R^1=Me, R^2=R^3=Et, R^4=Me$)

Scheme 14. Camphor-derived spiroketals **19a-f**.

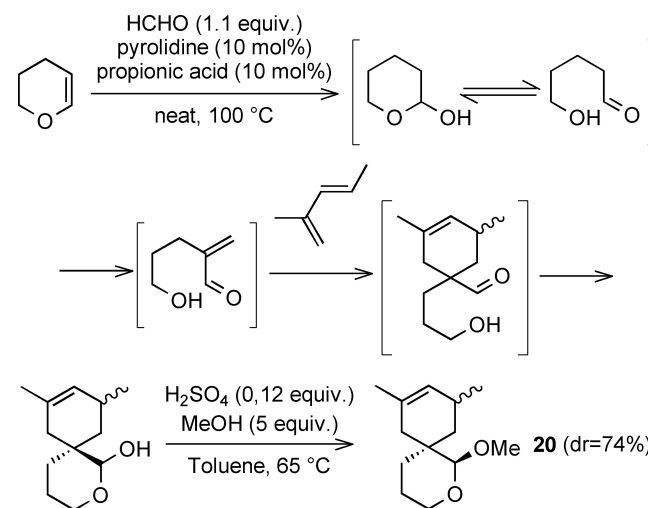
Olfactory properties of these camphor-derived spiroketals were described as follows: **19a**: generally woody, ambery, fruity, rich, sweet varying depending on diastereomers with earthy/mossy, balsamic, green, cedarwood, powdery undertones; **19b**: woody, green; **19c**: woody, ambery + sweet, dry, cedarwood,

creamy, green, floral, fruity, animalic, ambrette seed, carrot, sweet, green; **19d**: woody, ambery, earthy/mossy + camphoraceous, agrestic, dry, cedarwood, vetiver, fruity; **19e**: woody, earthy/mossy, cedarwood; **19f**: woody, cedarwood + fruity, green, pine, eucalyptus, floral, sweet, ambery, carrot-like. The substitution at carbon atom 5 was found to lower perception thresholds as evaluated by GC–O.

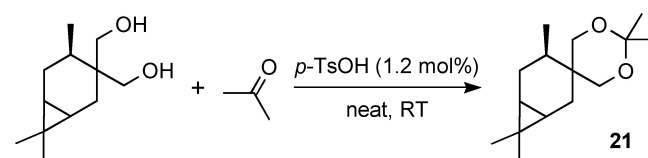
By generating by cycloaddition a cyclohexene featuring a quaternary carbon atom bearing both a carbaldehyde function and a 3-hydroxypropyl side chain, ring-closure by hemiacetalisation could occur giving rise to 2-oxaspiro[5.5]undec-8-en-1-ol stereoisomers further converted into the corresponding methyl ether **20** with fruity, cassis, grapefruit and juicy olfactory notes (Scheme 15).^[18]

Acetalisation was also used to form spirodioxanes starting from bis(hydroxymethyl)carane derivatives and ketones to obtain spirobicyclic products such as **21** with green, herbaceous, balsamous and resinous olfactory notes (Scheme 16).^[24]

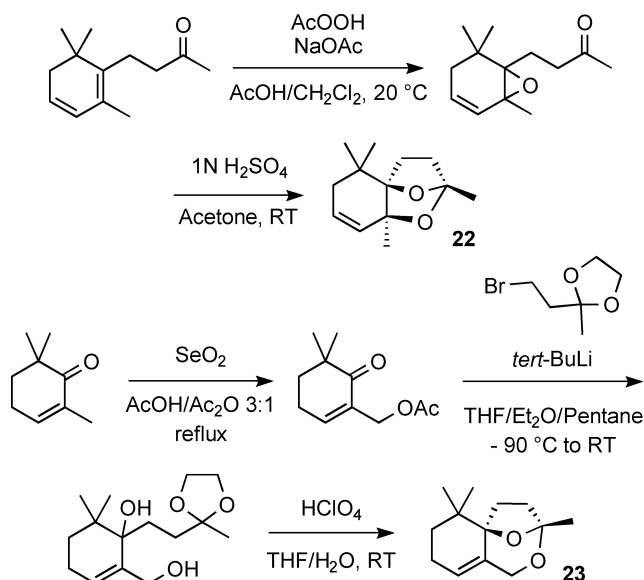
Acetalisation using an epoxyketone or a dihydroxyketone could be used to form tricyclic spiro compounds **22** and **23** respectively featuring an acetal motif (Scheme 17).^[25] These compounds were found in quince brandy (*Cydonia oblonga* Mil.) and are presenting woody, camphoraceous and camphoraceous, herbal, slightly floral notes, respectively.



Scheme 15. Multistep synthesis of 8,10-dimethyl-2-oxaspiro[5.5]undec-8-en-1-ol methyl ether **20** via hemiacetalisation featuring in its early steps an organocatalytic domino α -methylenation/Diels-Alder reaction.



Scheme 16. Acid-catalysed cyclohexanone in the carane series.

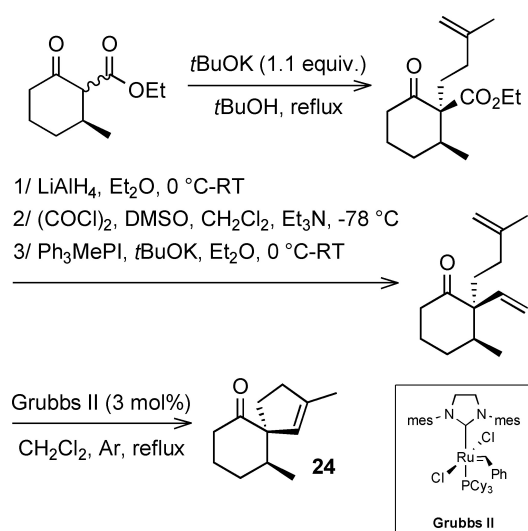
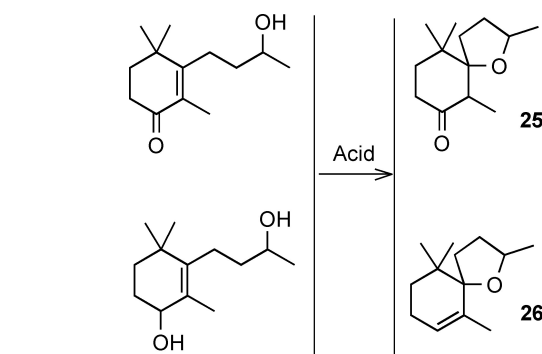
Scheme 17. Formation of spiro compounds **22** and **23**.

3.5. Olefination by ring-closing metathesis

The strength of ring-closing metathesis has been exploited to access various naturally-occurring spiro compounds including for the most fragrant ones (+/-)-agarospirol **7**, β -vetivone **8**, and related spiro derivatives, all accessible by securing the synthesis of 2,10-dimethylspiro[4.5]dec-1-en-6-one **24** (Scheme 18).^[26]

3.6. Hydroalkoxylation and related reactions

Somehow related to cyclodehydration, 1-oxaspiro[4.5]decane structure can be envisaged by mean of hydroalkoxylation of C=C double bonds. In a patent, for 2,6,10,10-tetramethyl-1-

Scheme 18. Synthesis of 2,10-dimethylspiro[4.5]dec-1-en-6-one **24**.Scheme 19. Hydroalkoxylation in acidic conditions as the key step towards 2,6,10,10-tetramethyl-1-oxaspiro[4.5]decan-7-one **25**^[27] and theaspirane **26**.^[28]

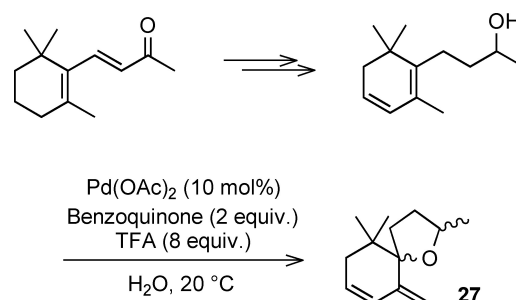
oxaspiro[4.5]decan-7-one **25** synthesis, this was the strategy chosen using a cyclohexanone derivative bearing a 3-hydroxybutyl side chain at position 3 (Scheme 19).^[27,28] Various Brønsted and Lewis acids could be used to achieve this transformation (e.g. *p*TsOH, H₂SO₄, HCl, BF₃, LiClO₄, ...) which proceeds via an intramolecular oxa-Michael addition.

Starting with the corresponding diol, theaspirane **26** was obtained after a final acid-catalysed alcohol elimination. Compound **25** was described as presenting woody, tobacco, cedarwood, patchouli and armoise olfactory notes.

Similarly, hydrocarboxylation of a double bond could be used to attain 1-oxaspiro[4.5]decan-2-one structures.^[21]

The well-known odorant theaspirane **26** has received a large attention and various synthetic routes were devised. Several syntheses involved indeed an intramolecular hydroalkoxylation for which the regioselectivity can be controlled. Acidic activation can be brought by Amberlyst,^[29] KHSO₄,^[30] TsCl/Py,^[14] APTS.^[31] Using β -ionol as starting material, a first lipase-catalysed resolution by acylation followed by saponification and intramolecular hydroalkoxylation led to optically active theaspirane **26** derivatives.^[32]

The spiro compound 2,10-trimethyl-6-methylidene-1-oxaspiro[4.5]dec-7-ene **27** (vitispirane) present in grape juice and therefore in wine,^[33] was synthesized by palladium(II)-catalysed oxaspirocyclisation of suitably substituted dienic alcohol obtained from β -ionone through Π -allyl palladium complex formation (Scheme 20).^[34]

Scheme 20. Synthesis of vetispirane **27** by Pd-catalysed oxaspirocyclisation.

This compound was described as a contributor to the odor of vanilla aroma and could be also hemisynthesized from theaspirane **26**.^[35]

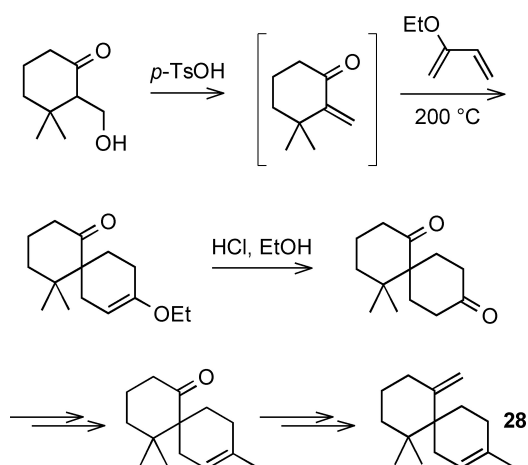
3.7. Cycloaddition

Diels-Alder type [4 + 2] cycloaddition could be used to generate spiro[5.5]undecane derivatives using pulegone as dienophile and penta-1,3-diene^[36] or α -methylidene 3,3-dimethylcyclohexanone and 2-ethoxybuta-1,3-diene dienic partners en route to spiro sesquiterpene (\pm)-chamigrene **28** (Scheme 21).^[37]

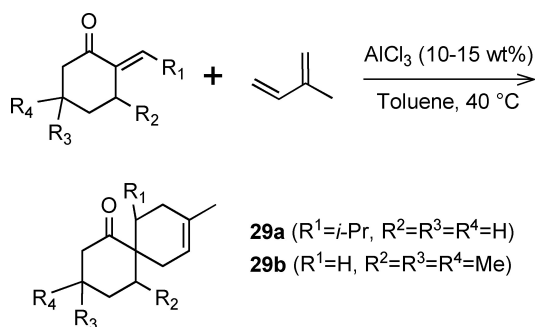
This strategy was applied using α -alkylidene cyclohexanone and a Lewis acid such as AlCl₃ in toluene (Scheme 22).^[38]

Spirocyclic compound **29a** exhibited woody, fruity, minty and floral aromas with pepper and geranium topnotes and **29b** exhibited woody, fresh minty, sweet, herbaceous, spicy and celery aroma with tagette-like undertones.

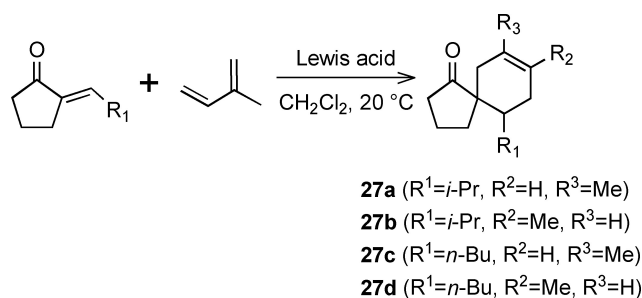
Similarly, spiro[4.5]decane derivatives could be obtained by reacting α -alkylidene cyclopentanone with dienes in the presence of AlCl₃, ZnCl₂, SnCl₂, Et₂AlCl, EtAlCl₂, either in CH₂Cl₂, CH₃CHCl₂, or toluene (Scheme 23).^[39] The reaction was not described as being regioselective and mixture of isomers were obtained and separated by distillation. Floral, rose-like, jasmine,



Scheme 21. (\pm)-Chamigrene **28** synthesis with a [4 + 2] cycloaddition as the key step generating the spirostructure.



Scheme 22. [4 + 2] cycloaddition of α -alkylidene cyclohexanones with 2-methylbuta-1,3-diene to spirocyclic products **29a–b**.



Scheme 23. [4 + 2] cycloaddition of α -alkylidene cyclopentanones and 2-methylbuta-1,3-diene.

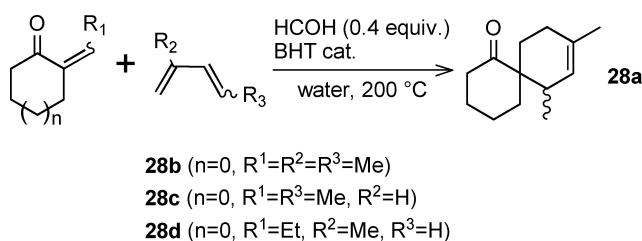
minty and woody descriptors were claimed with cardamom, fig-like, date-like, vetiver-like, sweet, natural balsam, lemon, spicy, woody and camphoraceous undertones for spiro[5.5]decanones **30a–d**.

By generating an α -methylidenecyclopentanone in situ from 2-(dimethylaminomethyl)cyclopentanone and reacting it with homomyrcene, spirocyclic compounds could be obtained, exhibiting a woody-ambery character and excellent perception thresholds.^[40] Using protoanemonine (5-methylidenefuran-2-one) and various dienes (2-methylpenta-1,3-diene, β -myrcene, *para*-mentha-1,3-diene, phellandrene, myrcenol, 2-methoxybuta-1,3-diene), Diels-Alder cycloaddition under thermal activation (150 °C) led to the formation of various spiroketones presenting various warm, fruity, coconut, and coumarine-like notes.^[41]

An α -methylidene cycloalkanone could be generated in situ and engaged into a [4 + 2] cycloaddition with 2-methylpenta-1,3-diene to yield and spiro[4.5]decane spiro[5.5]undecane structures (Scheme 24).^[42] Compounds were described as presenting woody, floral, herbaceous (**31a**), sage, fruity, damascenone (**31b**), aromatic, thujonic, floral (**31c**), fruity, eucalyptus and sage (**31d**) olfactory notes, for example.

The spiroketones obtained under various conditions (Lewis acid or not, temperature, solvents) could either be reduced by the action of alkali metals or hydrides such as LiAlH₄ or submitted to the action of organometallics such as MeLi to access the corresponding alcohols. Further functionalization of these alcohols could be envisaged through acetylation or alkylation reactions.

By submitting 3-methylidene succinic anhydride to thermal [4 + 2] cycloaddition with substituted 1,3-dienes, the corre-



Scheme 24. [4 + 2] cycloaddition of α -alkylidene cycloalkanones with various dienes to spiroketones **31a–d**.

spending 2-oxaspiro[4.5]dec-7-ene-1,3-dione derivatives can be obtained and further transformed in three steps into 2-oxaspiro[4.5]dec-7-ene derivatives **32a–c** exhibiting fruity, green and woody notes (Scheme 25).^[43]

Rather than using alkylidene cycloalkanones, the dienophile could also be presented by alkyl carboxylate methyldiene cycloalkanes and reacted with 1,3-dienes.^[44]

3.8. α -dialkylation of carbonyl compounds

Although some kind of obvious, the strategy of α -dialkylation of carbonyl compounds to access spirocyclic structures has been very moderately exploited. By the double alkylation of substituted cyclohexanones such as isophorone or camphor in basic medium with 1,4- and 1,5-dihaloalkanes, spiro[4.5]decane **33a** and spiro[5.5]undecane **34a** derivatives, respectively were formed (Scheme 26).^[45]

Compounds **33a** and **34a** were described as having woody, ambery, earthy, and sassy clary-like amber tone. Reduction of **33a** to the corresponding alcohol **33b** modified the olfactory note towards cedarwood. By hydrogenation of bornane-3-spiro-

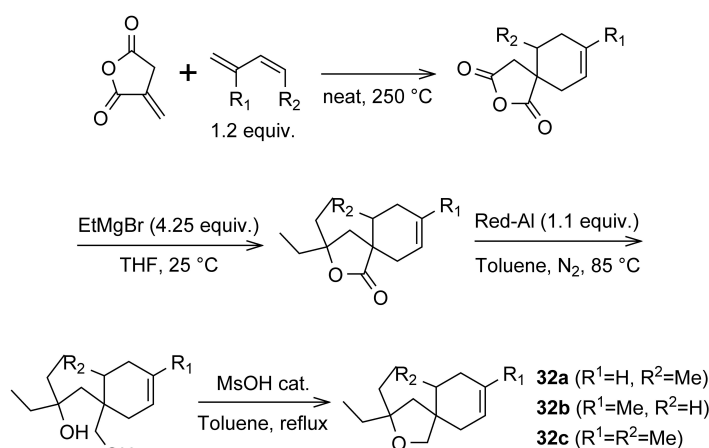
1'-cyclopentan-2-one in the presence of a carbon-supported Ru catalyst, the corresponding alcohol was obtained and featured woody aroma.^[46]

3.9. Nucleophilic substitution

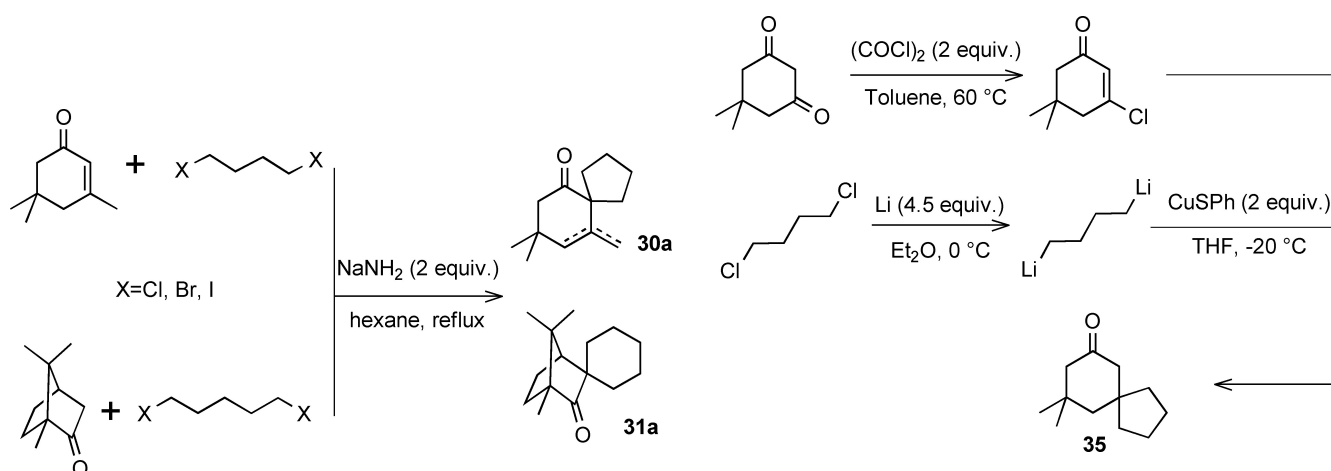
Using a substituted 3-chlorocyclohex-2-en-1-one derivative, an elegant access to a spiro[4.5]decanone **35** was proposed through conjugated addition of 1,5-dilithiopentane and subsequent nucleophilic substitution with a ring-closure to form the spiranic motif (Scheme 27).^[47]

The strategy was also used to prepare spiroketones further used as starting material to get substituted spirocyclic compounds with particular olfactory notes described as fresh, metallic, green-galbanum and fruity-pineapple.^[48] An alternate route to these spiroketones was also proposed relying on a Saucy-Marbet reaction, acetylide addition, allylation and 1,5-diene cyclisation.

In 1988, an asymmetric synthesis of the know vetiver constituent (–)- β -vetivone **8** was proposed based on a carbonyl-ene reaction mediated by SnCl₄ as the key step of

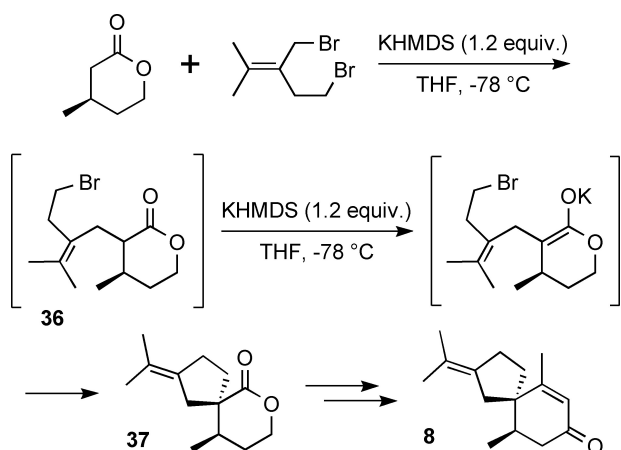


Scheme 25. 4-step synthesis of 2-oxaspiro[4.5]dec-7-ene derivatives **32a–c**.

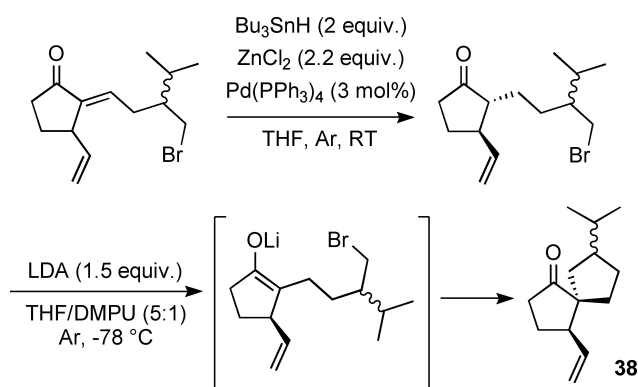


Scheme 26. Spirocyclisation by double alkylation of carbanions.

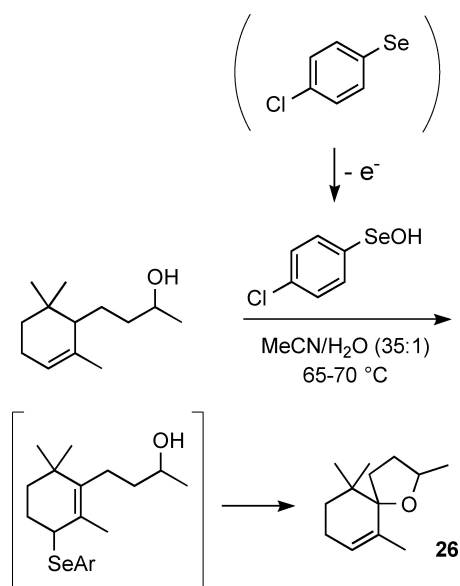
Scheme 27. Spirocyclisation by tandem conjugated addition/nucleophilic substitution.



Scheme 28. Synthesis of (–)-β-vetivone **8** featuring two spirocyclisation as important steps.



Scheme 29. Synthesis of seco-khusimone **36** featuring a nucleophilic attack of a lithium enolate as the key step.



Scheme 30. Oxidative cyclisation of dihydroionol to theaspirane **26** mediated by electrochemically generated arylselenenol.

spirocyclisation.^[49] Interestingly, the quaternary carbon atom, further becoming the spiro atom, was actually generated by a first spirocyclisation proceeding by intramolecular alkylation of an enolate generated from intermediate **36** (Scheme 28). Spirolactone **37** was formed and then opened by the action of MeLi further leading to the δ,ε-unsaturated aldehyde itself substrate of an intramolecular carbonyl-ene reaction, the resulting alcohol being oxidized by the Collins reagent.

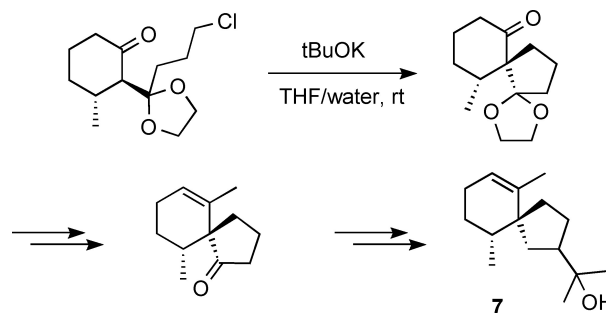
By analysis of the structure of khusimone, one of the main constituent of vetiver essential oil and an important contributor to its odor, seco-derivative **38** was designed and its synthesis realized, based on an intramolecular nucleophilic substitution of a bromine atom by a lithium enolate as the key step of spirocyclisation (Scheme 29).^[50] With a perception threshold 10 times higher and with floral, rosy, green, and geranium-type odor instead of vetiver, the seco-khusimone did not meet the expectations thereby showing the limit of superposition analyses of structures for rational odorant design.

Exploiting a conjugated nucleophilic substitution, a selenium-mediated electrochemical oxidation of α-dihydroionol leading to theaspirane **26** was described (Scheme 30). An electrophilic ene-type addition of selenium followed by displacement of the seleno group by intramolecular addition of the alcohol function at ψ-position was key to produce the spiro structure.^[51] Similar outcomes could be observed with 2,6-lutidine in acetonitrile.^[52]

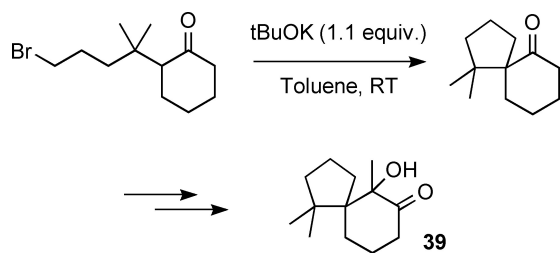
The spirocyclisation en route to the core structure of (+/–)-agarospirol **7** could also be achieved by intramolecular enolate alkylation (Scheme 31).^[53]

The spicy, peppery-woody-odorant agarospirol **7**, found in agarwood essential oils as well as in tansy or zingiber oils, has been the subject of many syntheses and could deserve a review article in itself.

Similarly, tBuOK-mediated cyclisation of a 2-(4-bromo-1,1-dimethylbutyl)cyclohexane allowed a ring-closure to access a spiro[4.5]decane structure en route to the synthesis of spiroketol **39** having a slight patchouli-like odor (Scheme 32).^[54]



Scheme 31. Enolate alkylation in the presence of tBuOK for a spirocyclisation en route to (+/–)-agarospirol **7**.

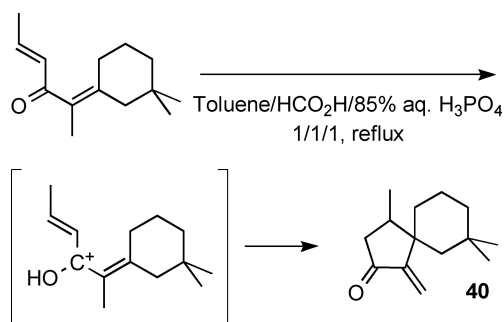


Scheme 32. Intramolecular alkylation of a cyclohexanone derivative mediated by tBuOK.

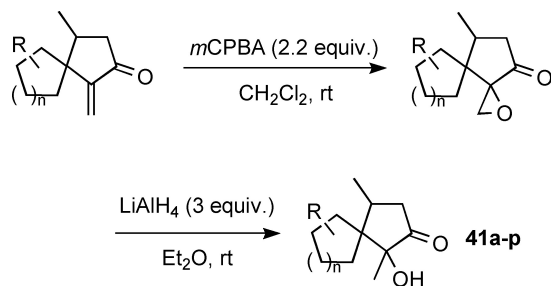
3.10. Ene-reaction and Nazarov cyclisation

In a 2002 paper, the formation of an unexpected 1-methylidenespiro[4.5]decan-2-one found to exhibit a woody-vetiver odor was reported as a secondary product during a Rupe rearrangement of the corresponding butyne-1,4-diol by a Brønsted acid-catalysed Nazarov cyclisation of the dienone product (Scheme 33).^[55] Optimisation of the Nazarov reaction allowed to obtain 4,7,7-trimethyl-1-methylidenespiro[4.5]decan-2-one **40** in good yield by using excess HCO₂H/85% H₃PO₄ (1:1 v/v) in refluxing toluene.

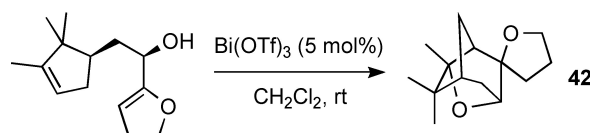
A large set of compounds related to **40** was synthesized by this method with various methyl-substitution patterns and ring size and structure-odor correlation were proposed. The olfactory family was generally found to be woody in the series, from cedar to cedarwood to vetiver and patchouli, with spicy, nutty, or fruity undertones.^[56]



Scheme 33. Nazarov cyclisation to 1-methylidenespiro[4.5]decan-2-ones.



Scheme 34. Access to various spiroketols via epoxidation/reduction of methylidenespiroketones.



Scheme 35. Bi(OTf)₃-catalysed cyclisation of a campholenic enol ether derivative to spiro diether **42**.

Some 1-methylidenespiro[4.5]decan-2-ones were also found to be useful starting material to access the related α -ketols **41a–p** by epoxidation with *m*-CPBA followed by hydride reduction (Scheme 34).^[57] These ketols presented variations of patchouli odor, and interestingly, although evaluated as diastereomerically pure racemates, compounds with C1–C4 substituents in a *cis*-relationship were found more powerful, i.e. having lower perception thresholds.

Dienes cyclisation triggered by acid-catalysis could also be used to generate the starting material.^[44]

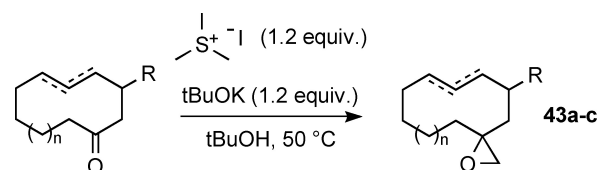
Initially identified in the course of the study of Bi(OTf)₃-catalysed rearrangement of 2-alkoxydiallyl alcohols,^[58] a stereocontrolled cascade cyclisation of campholenic enol ether derivatives was described to lead to spiro diethers as exemplified with **42** with woody olfactory notes reminiscent of vetiver essential oil (Scheme 35).^[59]

3.11. Epoxide formation

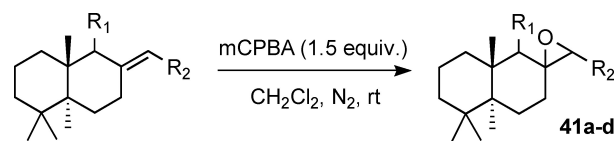
By treating macrocyclic ketones with trimethylsulfoxonium iodide in the presence of tBuOK, oxiranes are formed by formal carbene insertion into the carbonyl yielding 1-oxaspiro[2,*n*] compounds **43a–c** with a musky odor reminiscent of nitro-musks (Scheme 36).^[60]

In the perhydronaphthalene series, spiroepoxy compounds **44a–d** inspired by ambrox structure could also be obtained by epoxidation of alkylidene carbocycles (Scheme 37).^[61]

44a (R¹ = H, R² = Me) was found to exhibit woody, ambery, gourmand, slightly buttery and vetiver odor. **44b** (R¹ = Me, R² =



Scheme 36. Spiroepoxy derivatives **43a–c** by formal carbene insertion into carbonyls.

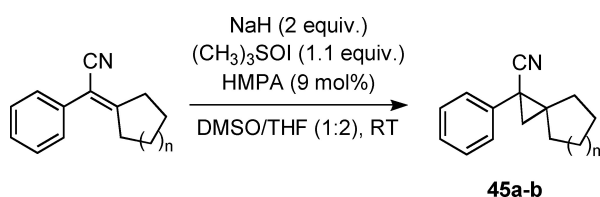


Scheme 37. Spiroepoxy compounds by epoxidation of alkylidene carbocycles.

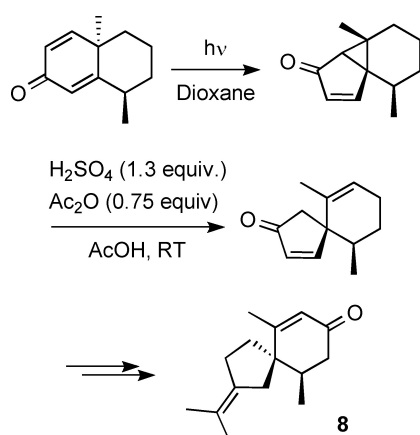
H) was found to be woody, ambery as well, with a slight Iso E super facet. **44c** ($R^1 = \text{Me}$, $R^2 = \text{Me}$) was found to be woody, ambery as well, more powdery, sawdust, and **44d** ($R^1 = \text{H}$, $R^2 = \text{Et}$) was found to be woody, ambery.

3.12. Cyclopropanation

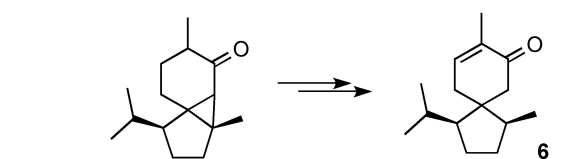
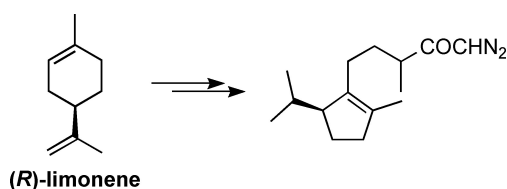
Johnson-Corey-Chaykovsky cyclopropanation protocol^[62] with sulphur ylides such as trimethylsulfoxonium iodide was used to access odorant spiro[2,4]heptane derivatives **45a–b** (Scheme 38).^[63] Compounds including non-spirocyclic tetrasubstituted cyclopropanes were described as having fresh, floral, ionone, soft, substantive, citrus and green notes but individual evaluations were not available.



Scheme 38. Access to 2-cyanospiro[2.4]heptane derivatives **45a** ($n = 1$) and **45b** ($n = 2$).



Scheme 39. Photochemical rearrangement of cyclohexadienone further opened by Brønsted acid treatment to the corresponding spiro[4.5]decadienone.



Scheme 40. Acorenone B **6** synthesis featuring a cyclopropanation.

En route to β -vetivone **8**, a photochemical rearrangement generating a cyclopropane fused with to 6-membered rings was proposed, followed by ring-opening to the desired spiro[4.5]decane structure (Scheme 39).^[64]

Similarly, acorenone B **6** could be produced in 11 steps from (*R*)-(+)-limonene via the formation of a fused cyclopropane via a diazo intermediates followed by acid-promoted chemoselective ring-opening (Scheme 40).^[65]

Cyclopropanation/ring-opening of phenolic diazoketones by CuCl ^[66] followed by Birch reduction^[67] was an approach used to get various naturally occurring spirocompounds including agarospirol **7** via intermediate **46** (Scheme 41).^[68] Also through cyclopropanation followed acid-promoted ring-opening, agarospirol and other related spiro compounds could be obtained.^[69]

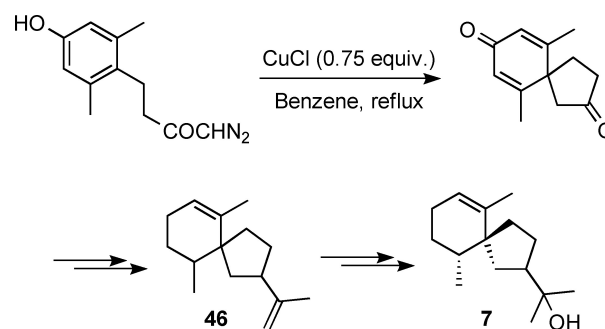
3.13. Radical coupling

The radical addition of an acrylic ester to cyclohexanols has been used to generate 1-oxaspiro[4.5]decan-2-one derivatives **47a–e** in the presence of di-tert-butyl peroxide (DTBP) (Scheme 42).^[70]

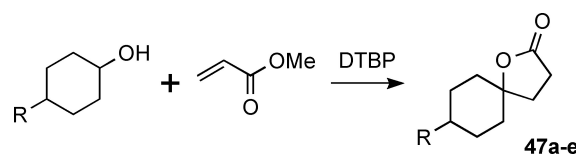
Variation at position 8 (R group) was studied in the alkyl series and the olfactory descriptors were described as woody, creamy, powdery, lactonic, fruity and ambery (see Table 1 for details).^[71]

3.14. Biotechnology

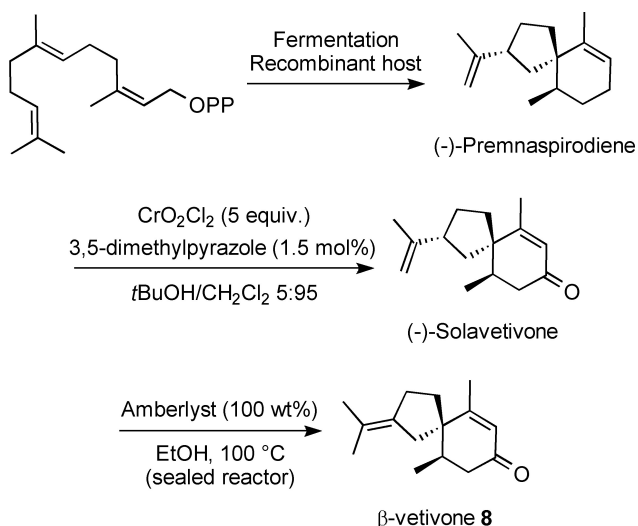
Combining biotechnology and organic synthesis, an original access to β -vetivone **8** and isomers was proposed, relying on the biotechnological production of premnaspirodiene from terpenes (Scheme 43).^[72]



Scheme 41. Spirocyclisation by cyclopropanation through diazoketone addition to phenols.



Scheme 42. Radical addition of an acrylic ester to cyclohexanol derivatives.



Scheme 43. Synthesis of β -vetivone **8** and isomers from premnaspirodiene obtained by biotechnology.

The target sesquiterpene was produced by heterologous expression of premnaspirodiene synthase from *Hyoscyamus muticus* in a recombinant host supplied with farnesyl diphosphate in a continuous fermentation process.

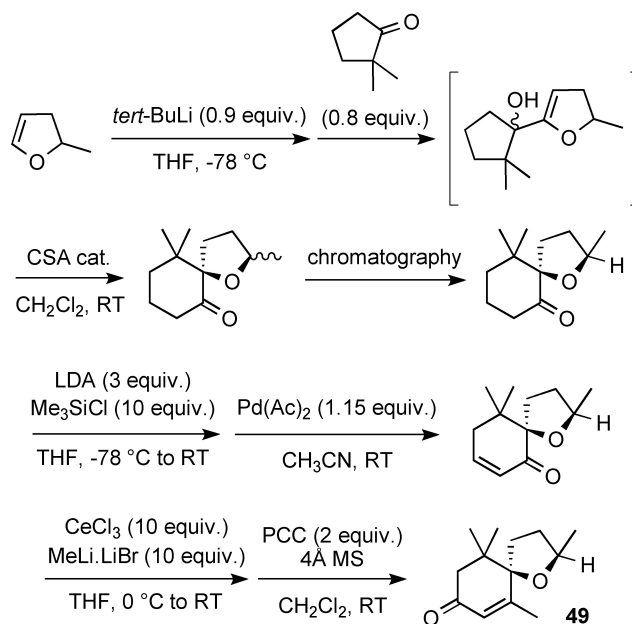
3.15. Carbonyl condensation

As mentioned in the introduction, the access to spiroheterocycles featuring a 1,3-dihetero motif can be relatively easy using carbonyl condensation with 1,2-difunctional partners. To attain heterocyclic spiro structures featuring for example a thiazolidine motif, a Brønsted acid-catalysed condensation of 1,2-aminothioethylene with carbonyl compounds has been used.^[73] Similar approach was used to condense cyclohexanone derivatives with 2-thiolacetic and 2-thiopropanoic acid in the presence of *para*-toluene sulphonic acid (1–5 mol%) to yield spirooxathiolanones **48** featuring fruity, peach, exotic fruits notes.^[74] We will not focus any further on these approaches.

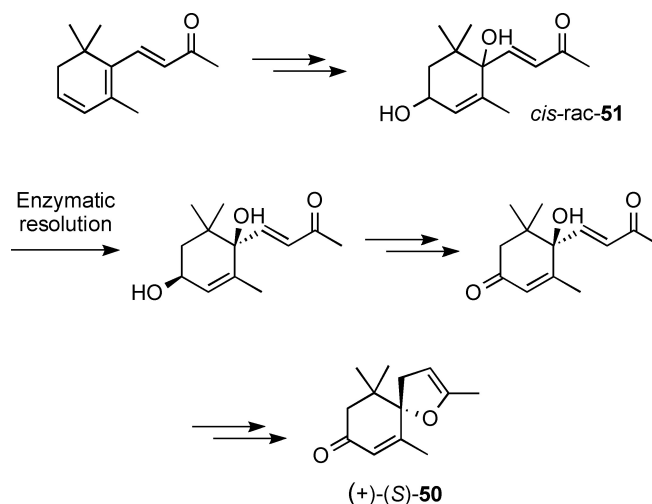
3.16. Rearrangement

Theaspirone **49**, the odoriferous principle of black tea described as having a sweet tea-like odor has been synthesis taking advantage of an oxonium ion initiated pinacol-type rearrangement (Scheme 44).^[75]

Starting from 3,4-dehydro- β -ionone and including a lipase-catalysed resolution step, enantiomeric forms of 8,9-dehydrotheaspirone **50** could be obtained in excellent yields (Scheme 45).^[76] They presented woody notes with (–)-(*R*)-**50** being more dry, cedarwood with green, earthy, tobacco and olibanum facets and floral-fruity nuances while (+)-(*S*)-**50** was more floral, woody-ambery, powdery with natural fruity, orris-like facets.



Scheme 44. Access to theaspirone **49** by ring expansion.



Scheme 45. Access to (–)-(*R*) and (+)-(*S*)-**50** by including a lipase-catalysed resolution step of diol intermediate **51**.

4. Conclusion and Outlook

Spirocyclic molecules occupy a small niche in perfumery. Some **50** structures were presented in this review along with the synthetic strategies allowing an access to them. Olfactory properties were generally in the woody family, but a significant diversity of aromas have been described. In the future, there will be a possible area for bioinspiration, with structures identified in complex natural substances for instance by GC coupled with olfactometry taking advantage of the latest technological development with GC–O–MS and multidimensional GC coupled with olfactometry (MDGC–O). As it is observed in all fields of application of organic synthesis, securing an access to all enantiomers of a target should be

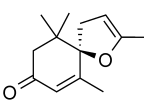
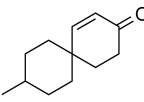
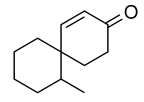
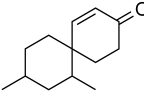
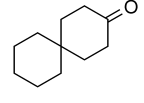
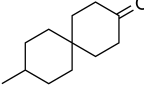
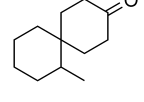
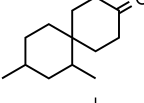
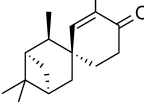
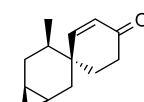
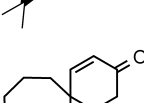
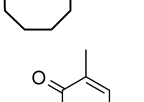
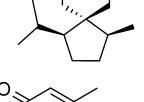
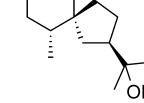
Table 1. Summary of the olfactory properties of spiro compounds presented in this review, in order of appearance in the text.				
Number in manuscript	Structure	Reference(s)	Olfactory family	Main olfactory descriptors
1a		5	Multiple	Fruity, spicy, iris
1b		5	Multiple	Fruity, spicy, iris
1c		5	Multiple	Fruity, spicy, iris
1d		5	Multiple	Fruity, spicy, iris
2a		5	Multiple	Fruity, spicy, iris
2b		5	Multiple	Fruity, spicy, iris
2c		5	Multiple	Fruity, spicy, iris
2d		5	Multiple	Fruity, spicy, iris
3		6	Multiple	Balsamic, vanilla, woody, vetiver
4		6	Multiple	Balsamic, floral
5		7	Multiple	Costus, animalic, leather
6		9, 65	Woody	Agarwood
7		10, 53, 67, 68	Woody	Spicy, peppery, woody
8		10, 49, 64, 72	Multiple	Quinoline-like, cassis, grapefruit, woody

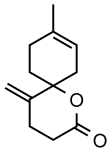
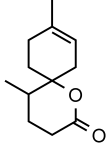
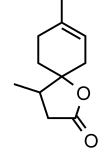
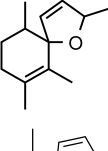
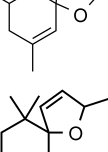
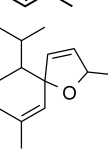
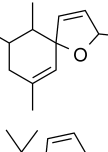
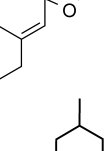
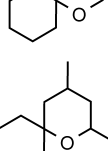
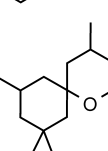
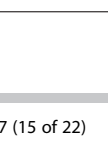

Table 1. continued				
Number in manuscript	Structure	Reference(s)	Olfactory family	Main olfactory descriptors
9a		12	Multiple	Spicy, coumarine-like
9b		12	Woody	Cedarwood
10		12	Woody	Woody
11a		13	Multiple	Fresh, flowery, herbal, fruity
11b		13	Multiple	Fresh, flowery, herbal, fruity
11c		14	Multiple	Fruity, woody
12		15	Fruity	Cassis
13		16	Fruity	Cassis
14		17	Fruity	Cassis
16a		20	Multiple	Green, herbal, floral, eucalyptol, minty, basil
16b		20	Multiple	Green, herbal, floral, eucalyptol, minty, basil
16c		20	Multiple	Green, herbal, floral, eucalyptol, minty, basil

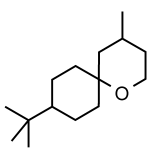
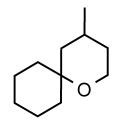
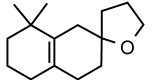
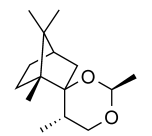
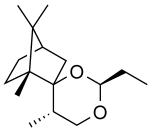
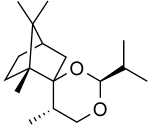
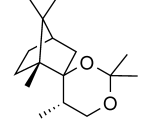
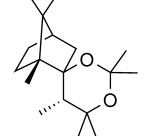
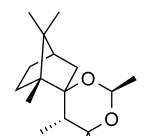
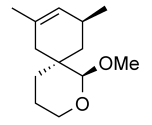
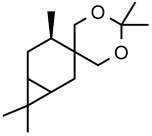
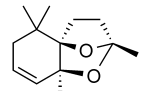
Table 1. continued				
Number in manuscript	Structure	Reference(s)	Olfactory family	Main olfactory descriptors
16d		20	Multiple	Green, herbal, floral, eucalyptol, minty, basil
17a		20	Multiple	Basil, herbaceous, eucalyptol
18		21	Multiple	Basil, herbaceous, eucalyptol
19a		22	Woody	Woody, ambery, fruity, sweet, earthy/mossy, balsamic, green, cedarwood, powdery
19b		22	Woody	Woody, green
19c		22	Woody	Woody, ambery, sweet, dry, cedarwood, creamy, green, floral, fruity, animalic, ambrette seeds, carrot, sweet, green
19d		22	Woody	Woody, ambery, earthy/mossy, camphoraceous, agrestic, dry, cedarwood, vetiver, fruity
19e		22	Woody	Woody, earthy/mossy, cedarwood
19f		22	Woody	Woody, cedarwood, fruity, green, pine, eucalyptus, floral, sweet, ambery, carrot-like
20		23	Fruity	Fruity, cassis, grapefruit, juicy
21		24	Multiple	Green, herbaceous, balsamous, resinous
22		25	Woody	Woody, camphoraceous

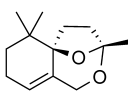
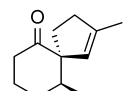
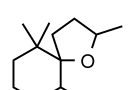
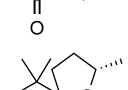
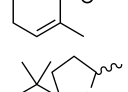
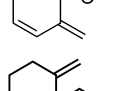
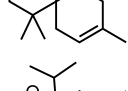
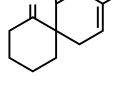
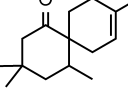
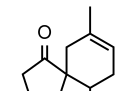
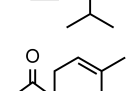
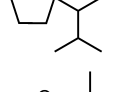
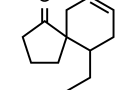
Table 1. continued				
Number in manuscript	Structure	Reference(s)	Olfactory family	Main olfactory descriptors
23		25	Multiple	Camphoraceous, herbal, slightly floral
24		26	N.D.	N.D.
25		27	Woody	Woody, tobacco, cedarwood, patchouli, armoise
26		14, 28–32, 51, 52	Herbal	Tea, herbal, green, wet tobacco, leaf, woody, spicy, cooling, minty, camphoreous, fresh
27		34	Spicy	Vanilla
28		36, 37	N.D.	N.D.
29a		38	Multiple	Woody, fruity, minty, floral, pepper, geranium
29b		38	Multiple	Woody, fresh, minty, sweet, herbaceous, spicy, celery, tagette-like
30a		39	Multiple	Floral, rose-like, jasmine, minty, woody, cardamom, fig-like, date-like, vetiver-like, sweet, natural balsam, lemon, spicy, camphoraceous
30b		39	Multiple	Floral, rose-like, jasmine, minty, woody, cardamom, fig-like, date-like, vetiver-like, sweet, natural balsam, lemon, spicy, camphoraceous
30c		39	Multiple	Floral, rose-like, jasmine, minty, woody, cardamom, fig-like, date-like, vetiver-like, sweet, natural balsam, lemon, spicy, camphoraceous
30d		39	Multiple	Floral, rose-like, jasmine, minty, woody, cardamom, fig-like, date-like, vetiver-like, sweet, natural balsam, lemon, spicy, camphoraceous
31a		42	Multiple	Woody, floral, herbaceous

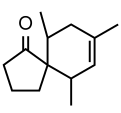
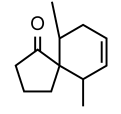
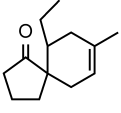
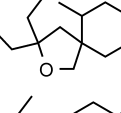
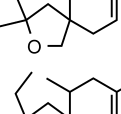
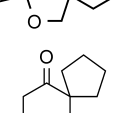
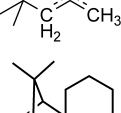
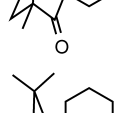
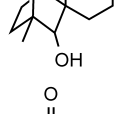
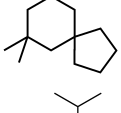
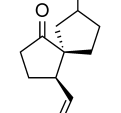
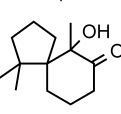
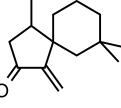
Table 1. continued				
Number in manuscript	Structure	Reference(s)	Olfactory family	Main olfactory descriptors
31b		42	Multiple	Sage, fruity, damascenone
31c		42	Multiple	Aromatic, thujonic, floral
31d		42	Multiple	Fruity, eucalyptus, sage
32a		43	Multiple	Fruity, green, woody
32b		43	Multiple	Fruity, green, woody
32c		43	Multiple	Fruity, green, woody
33a		45	Multiple	Woody, ambery, earthy
34a		45	Multiple	Clary-like, amber
34b		46	Woody	Cedarwood
35		47	Multiple	Fresh, metallic, green-galbanum, fruity-pineapple
38		50	Floral	Floral, rosy, green, geranium-type
39		54	Woody	Camphoraceous, agrestic, minty, eucalyptol-like, woody, earthy, slightly patchouli-like
40		55, 56	Woody	Woody, vetiver

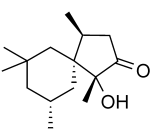
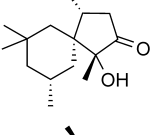
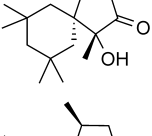
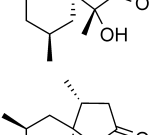
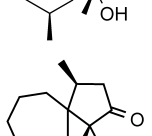
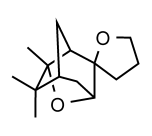
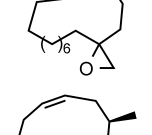
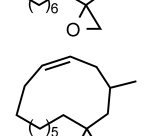
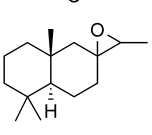
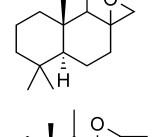
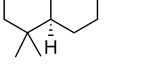
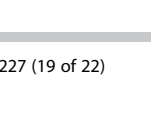

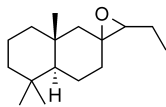
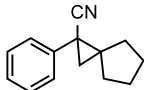
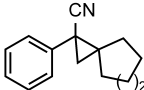
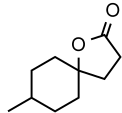
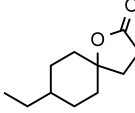
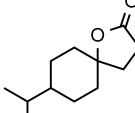
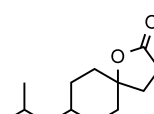
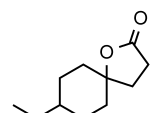
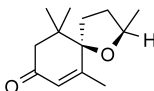
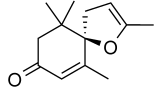
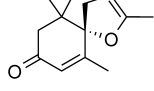
Table 1. continued				
Number in manuscript	Structure	Reference(s)	Olfactory family	Main olfactory descriptors
rac-41a		57	Woody	Patchouli, woody-ambery, tobacco-like
rac-41b		57	Woody	Patchouli
rac-41c		57	Woody	Patchouli
rac-41d		57	Woody	Patchouli
rac-41e		57	Woody	Patchouli
rac-41f		57	Woody	Woody, herbaceous, camphor
42		59	Woody	Vetiver-like
43a		60	Musk	Nitromusk, floral, weak animalic
43b		60	Musk	Nitromusk, waxy-fatty, aldehydic, floral
43c		60	Musk	Nitromusk, waxy-fatty, aldehydic, floral
44a		61	Woody	Woody, ambery, gourmand, buttery, vetiver
44b		61	Woody	Woody, ambery
44c		61	Woody	Woody, ambery, powdery, sawdust

Table 1. continued

Number in manuscript	Structure	Reference(s)	Olfactory family	Main olfactory descriptors
44d		61	Woody	Woody, ambery
45a		63	Multiple	Fresh, floral, ionone, soft, substantive, citrus, green
45b		63	Multiple	Fresh, floral, ionone, soft, substantive, citrus, green
47a		70, 71	Multiple	Creamy, lactonic, coumarine-like, cresylic
47b		70, 71	Multiple	Creamy, lactonic, slightly woody
47c		70, 71	Multiple	Woody, milky-lactonic, powdery
47d		70, 71	Multiple	Peach, apricot, lactonic
47e		70, 71	Multiple	Woody, ambery, weak
49		75	Herbal	Sweet, tea-like
(R)-50		76	Woody	Cedarwood, green, earthy, tobacco
(S)-50		76	Multiple	Floral, woody, ambery, powdery, natural fruity, orris-like

envisaged, in order to test separately their olfactory properties, as the most performant compound in terms of odor and perception thresholds does not have to be the naturally occurring one. As targets could gain in complexity, future challenges will also reside in the synthesis of spirocyclic motifs embedded into polycyclic molecules. Last but not least, a reassessment of chemical processes to access existing molecules but taking into account the principles of green and sustainable chemistry could also gain in importance, with a

focus on biobased resources and clean technologies, notably with the impact of biotechnology in perfumery.^[77]

Acknowledgements

This research was supported by Université Côte d'Azur and CNRS. L.G. doctoral thesis is funded by Alysophil. We are grateful to our

three reviewers for their very interesting comments and suggestions.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: odorants · perfumery · ring-closure · spirocyclisation · synthetic methods

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Manuscript received: July 8, 2022

Revised manuscript received: September 27, 2022