

Tetrahydrofuran and Tetrahydropyran Derivatives as Odor Substances

By Jozef Kula and Jozef Gora, Technical University, Lodz, Poland

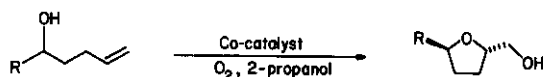
Organic compounds containing the cyclic ether skeletons tetrahydrofuran (THF) or tetrahydropyran (THP) are widely found in nature. In addition, they are also found as partial pyrolysis products of carbohydrates. Some THF and THP derivatives display characteristics of biological activity. The introduction of THF and THP structural elements into analgesics,¹ saluretics² and antibiotics³ may be considered as a curious discovery in this regard. Some THF-didesoxynucleosides are being studied recently as potential anti-HIV agents.⁴

During the last three decades, due to improved analytical methods, a number of tetrahydrofuranoids and tetrahydropyranoids have been isolated from plant extracts. It has been found that they are essential microcomponents of many plants (Table I) because of their high aroma value.

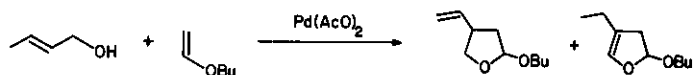
The importance of cyclic ethers as flavor and perfumery compounds is continually growing. This evolution originated with the two diastereoisomeric rose oxides which, after their discovery in rose and geranium oils, followed by their synthetic accessibility, are now among a group of most appreciated perfumery raw materials. Besides, at least three other cyclic ethers (nerol oxide, 2,2,6-trimethyl-6-vinyltetrahydropyran and dihydro rose oxide) have become commercially available.

The THF and THP nucleus is a very common structural feature of many naturally occurring compounds. There is currently an active interest in developing efficient ways of preparing these heterocyclic products.

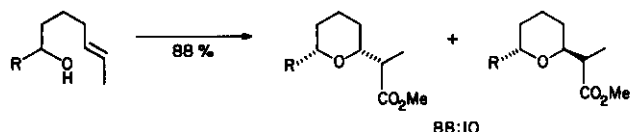
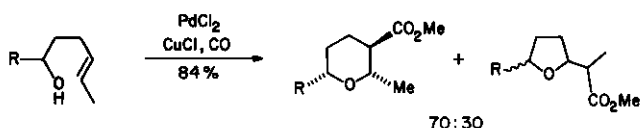
The heterocyclization of hydroxy-



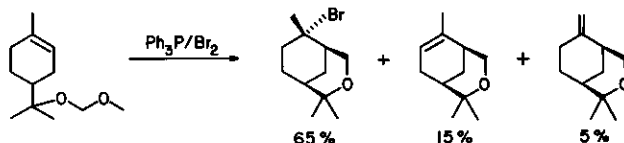
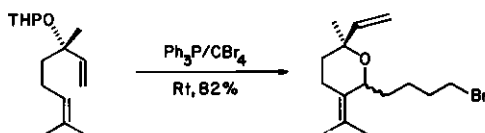
Scheme 1. Stereoselective synthesis of trans-hydroxy-methyl tetrahydrofuran according to Inoki and Mukiyama.⁵



Scheme 2. Reaction of allylic alcohols with vinylic ethers according to Fugami et al.⁶



Scheme 3. Palladium catalyzed intramolecular addition of the hydroxy group to the double bond.⁷



Scheme 4. Synthesis of THP derivatives from unsaturated acetals according to Wagner et al.¹⁰

alkenols is currently the most general method used to synthesize tetrahydrofuranoids and tetrahydropyranoids. Recently a few general (often stereoselective) methods for the THF and THP synthesis have been reported. These could have potential for the production of important oxacyclic odorous compounds.

New Methods for the Synthesis of THF/THP Derivatives

trans-2-Hydroxymethyltetrahydrofurans can stereoselectively be synthesized by the oxidative cyclization of 5-hydroxy-1-alkenes in the presence of a small amount of a cobalt catalyst (Scheme 1),⁵ the yield of which can be improved by hydroperoxide incorporation. Examples of the Schemes where stereoselectivity of the product is over 97% are given in Table II.

The reaction of allylic alcohols with vinylic ethers in the presence of 1 mol-eq. of palladium acetate is a simple way to get 2,4-substituted tetrahydrofuranoids and tetrahydropyranoids (Scheme 2).⁶ The palladium catalyst facilitates the addition of the hydroxy group to the double bond of a hydroxyalkene of appropriate length (Scheme 3).⁷ This route can be used for the synthesis of (6'-methyl-2'-tetrahydropyranyl) acetic acid, a glandular secretion of the civet cat.^{8,9} Other examples are shown in Table III.

For the synthesis of more complex THP derivatives, the unsaturated acetals can be utilized as substrate materials (Scheme 4).¹⁰ This reaction is carried out in the presence of triphenylphosphine and carbon tetrabromide or bromine. Under certain reaction conditions, a mixture of bromination and elimination products are sometimes formed.

On the other hand, the THF and THP derivatives can be synthesized from bicyclic acetals which are obtained by reacting

Table I. Occurrence and odor characteristics of some THF and THP monoterpene derivatives

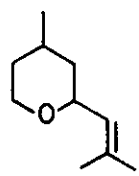
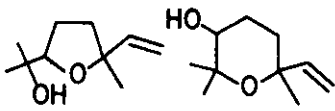
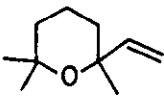
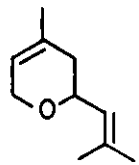
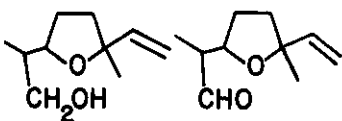
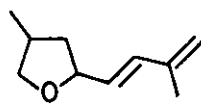
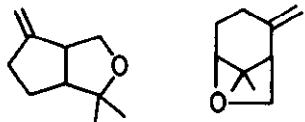
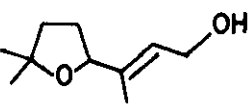
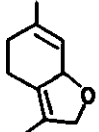
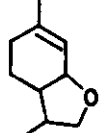
Compound	Occurrence	Odor	Ref.
 <p>Rose oxide [1]</p>	e.g. rose oil (<i>Rosa damascena</i>)	very characteristic, green, resembling rose and geranium	20,20a
 <p>Linalool oxide [10]</p>	"bois de rose oil"	floral, fluctuating between linalool and linalyl acetate	26-32
 <p>Linalyl oxide [11]</p>	geranium oil, lime oil (<i>Citrus medica</i>)	herbal, a little similar to cineol	34,35
 <p>Nerol oxide [12]</p>	rose oil, grapefruit oil, geranium oil (<i>Pelargonium graveolens</i>)	floral, intense, resembling a little geraniol	29,36
 <p>Lilac alcohols [13] Lilac aldehydes [14]</p>	extract of lilac blossoms (<i>Syringa vulgaris</i>)	[13] lilac odor, sweet [14] lilac odor with green tone	37-43
 <p>Marmelo oxide [15]</p>	fruit of quince (<i>Cydonia oblonga</i>)	strong, characteristic, fruit of quince odor	44,45
 <p>Hop ether [16] Karahana ether [17]</p>	Japanese hop oil	-	46,47 49,50

Table I (Continued).

Compound	Occurrence	Odor	Ref.
 [22]	peppermint oil (<i>Mentha piperita</i>)	dry grassy hay odor	53
 Linden ether [58]	linden blossoms (<i>Tilia cordata</i>)	flowery, mint-like	58,59
 Dill ether [59]	Dill herb (<i>Anethum graveolens</i> L.)	dill-like floral and herbaceous aroma	60-62

appropriate unsaturated ketones in an oxidation process using *m*-chloroperoxybenzoic acid (*m*CPBA) (Scheme 5).¹¹

The Lewis acid catalyzed condensation of alkylalkoxysilanes yields good amounts of *cis*-2,4,6-trisubstituted THP (Scheme 6).¹² This procedure can be applied to the enantioselective synthesis of the previously mentioned (6'-methyl-2'-tetrahydropyranyl) acetic acid.^{8,9}

The free radical cyclization of geraniol or citral epoxides can be used for the synthesis of mono- and bicyclic-tetrahydrofuranoids (Scheme 7).¹³

2(5)-Substituted THF derivatives are produced as a result of heterocyclization of terminally unsubstituted Δ^4 -alkenols by mercury acetate/sodium borohydride, NBS and *m*CPBA.¹⁴ Similarly, substituted THFs can also be produced from saturated secondary or tertiary alcohols under oxidative conditions (bromine, Ag-salts).¹⁵ Many other interesting routes to the THF and THP derivatives are discussed in another article.¹⁶

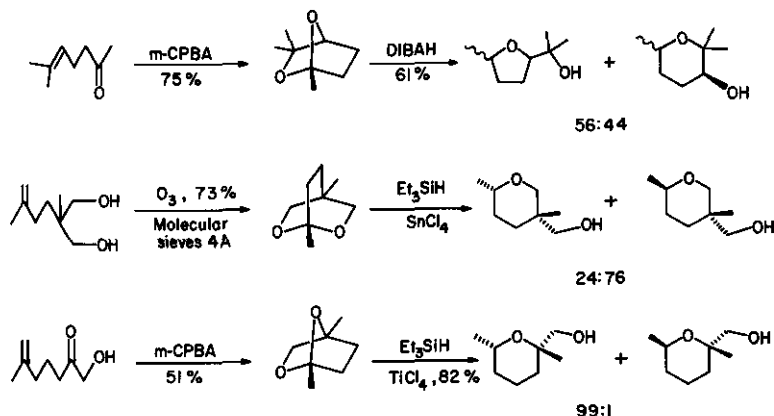
The monoterpene hydrocarbons α -pinene, δ -3-carene and limonene are potentially excellent raw materials for the synthesis of 3-substituted 2,2-dimethyltetrahydrofuranoids and tetrahydropyranoids.¹⁷⁻¹⁹ The method is simple and is of some interest by the fact that the products possess high chiral purity with a known absolute configuration of C-3 carbon atom (Scheme 8). Development of this synthetic procedure has facilitated the obtaining of a number of new oxacyclic odor compounds.

Review of THF and THP Odorant Synthesis

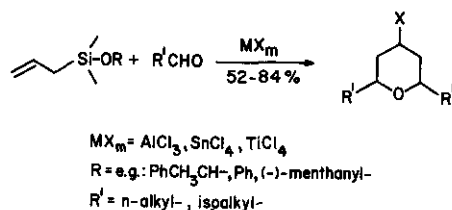
Rose oxide and its analogues—

Rose oxide [1] occurs in numerous essential oils and for many years has synthetically been manufactured. Olfactories of both diastereomers (*cis* and *trans*) are also well known.

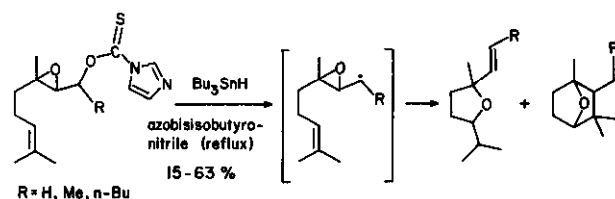
The synthesis of rose oxide [1] has been discussed in a number of publications,²⁰ and therefore here we will cite only two papers on the synthesis of *cis*-rose oxide [1] which



Scheme 5. Transformation of bicyclic acetals into tetrahydrofuran and tetrahydropyran derivatives.¹¹



Scheme 6. Synthesis of 2,4,6-trisubstituted THPs by the Lewis acid catalyzed condensation of alkylalkoxysilanes with aldehydes.¹²



Scheme 7. Transformation of geraniol-derived epoxides into tetrahydrofuranoids according to Johns and Murphy.¹³

appeared in 1989. The first paper deals with a multi-step synthesis of (-)-cis-rose oxide [1].^{20a} The key intermediate product in the second paper is a double unsaturated acetal resulting from protection of the hydroxyl in the Grignard reaction (Scheme 9) product.¹⁰ The racemic cis-isomer [1] formed this way is of over 95% purity.

Dihydro rose oxide [2] is commercially available as well. Its production is based on the reduction of rose oxide [1], or synthesis from lower molecular weight compounds.^{21,22} A brief description of the synthesis of cis-dihydro rose oxide [2] was published by Liu et al. (Scheme 10).²³ In this synthesis the substrate used was furanylketone which was isolated from the elsholtia oil. Using this method, the yield of the cyclic ether was 50%.

Recently a homologue [3] of the cis-rose oxide [1] has been known (Scheme 11).²⁴

A few interesting analogues [4-9] of rose oxide [1] have been found by Hoepfner and Weyerstahl (Scheme 12).²⁵ These compounds which possess one less carbon atom (nor-compounds) were characterized by being more or less rose oxide-like. The authors found that the 3-trans-tetrahydrofuranoid compound [9] possessed the most distinctive aroma of all compounds synthesized, while the 3-cis isomer possessed an indole-like-strong melon-like aroma. The mixture of 4-methyl-tetrahydrofuranoids [7] exhibited an intense rose oxide odor with apricot and carrot off-notes, while the (Z,E)-cis-THP derivatives [5] smelled green and herbal, and the (Z,E)-trans isomers [6] smelled herbal and minty.

Linalool, linaloyl and nerol oxides—In 1908 Prileschajew²⁶ isolated a sweet smelling "compound," C₁₀H₁₈O₂, from the Mexican "bois de rose," the structure of which was established at a later date.²⁷ The substance, which really was a mixture of THF and THP derivatives, was named "linalool oxide" [10] (also linalyl oxide or epoxylinalool). Linalool oxide [10] is formed during the distillation of linalool epoxidation products (cold

Table II. Some examples of preparation of 2-hydroxymethyltetrahydrofurans

Substrate	Product	Yield (%)
		73
		69
		69
		53
		55

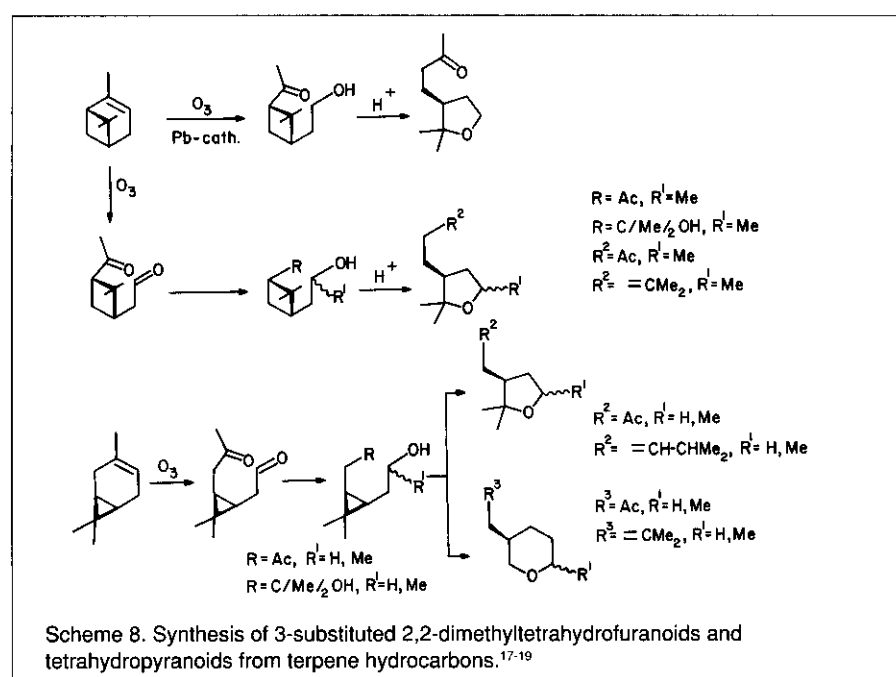
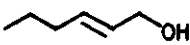
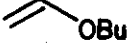
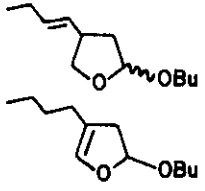
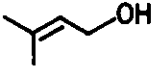
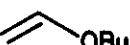
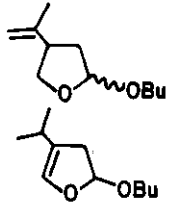
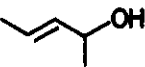
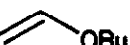
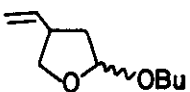
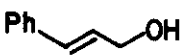
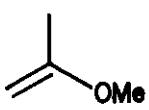
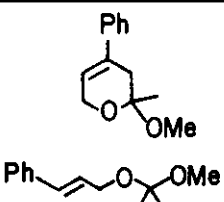
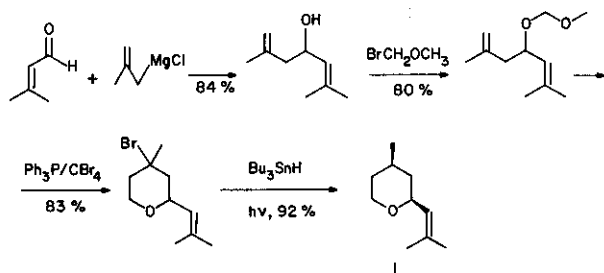
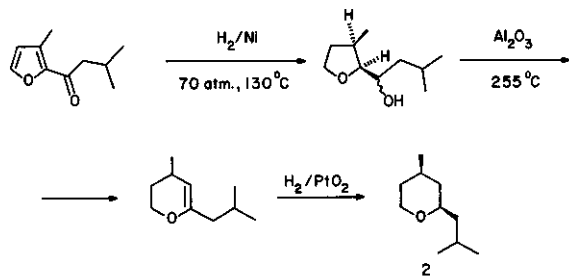


Table III. Tetrahydrofuranoids from allylic alcohols and vinylic ethers

Alcohol (mmole)	Ether (mmole)	Product	Yield (%)
 1.0	 10		82 12
 1.0	 6.5		58 23
 1.0	 16		75
 1.0	 		54 27

Scheme 9. Synthesis of cis-rose oxide [1] from 3-methyl-2-butenal.¹⁰Scheme 10. Synthesis of dihydro rose oxide [2] from furanylketone according to Liu et al.²³

reaction) (Scheme 13).²⁸

It has been shown that tetrahydrofuranoid derivatives are responsible for the odor of the mixture while the THP derivatives are odorless. Linalool oxide [10] can be synthesized from geraniol (Scheme 14).²⁹ It has also been used for the synthesis of the enantiomerically pure linalool oxide stereoisomers (Scheme 15).³⁰

Selective, microbiological oxidation of a double bond in geranyl phenylcarbamide³¹ gives a diol of high optical purity (>95%).

Myrcene hydrocobaltation can also result in the formation of a mixture of stereoisomeric linalool oxides [10] (Scheme 16).³² The hydrocobaltation process is carried out with cobalt dimethylglyoxime in the presence of hydrogen. It has also been found that linalool oxide esters are useful as raw materials for flavors and fragrances.³³

A dilute sulfuric acid catalyzed direct cyclization of linalool delivers a so-called "linalyl oxide" [11] or 2,2,6-trimethyl-6-vinyltetrahydropyran (Scheme 17).³⁴ The amount of the tetrahydrofuranoid by-products is dependent upon the temperature of the reaction. This "linalyl oxide" [11] has also been synthesized in a multi-steps method.³⁵

Like rose oxide [1], nerol oxide [12] has been found as a constituent of many plants. It can be produced synthetically from nerol or geraniol (Scheme 18).²⁹ The synthetic route is analogous to that used for the photochemical transformation of citronellol to rose oxide [1]; however, because of the presence of a double bond in the 2,3- position, both diols undergo cyclization to give a mixture which also contains about 36% of THF derivative.

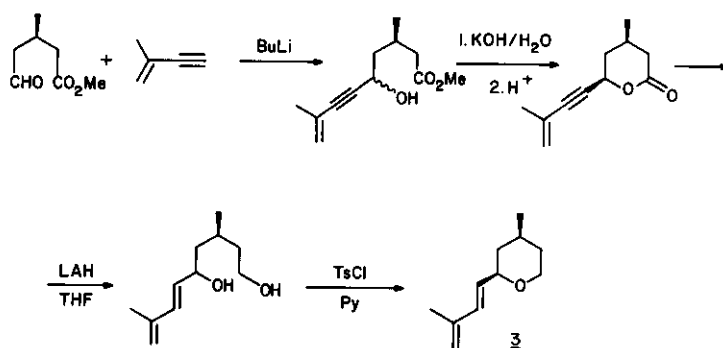
A synthesis of both pure enantiomers of nerol oxide [12] from (–)-(R)-linalool was achieved by Ohloff et al.³⁶ The olfactory properties of the enantiomeric oxides [12] are comparable to those of the diastereoisomeric rose oxides [1] with regard to their tonality and strength. It was determined that the aroma of the (S)-oxide [12] was dominated by a powerful greenish-spicy note of the geranium-type which was similar to that of (–)-cis rose oxide. The

odor profile of the (R)-oxide [12], which is striking greenish-floral in character, is less complex than that of the (S)-oxide [12] and is rather similar to the (+)-cis rose oxide. The racemic nerol oxide [12] mixture is dominated by the odor profile of (S)-enantiomer [12], the enantiomer of value to the perfumer.

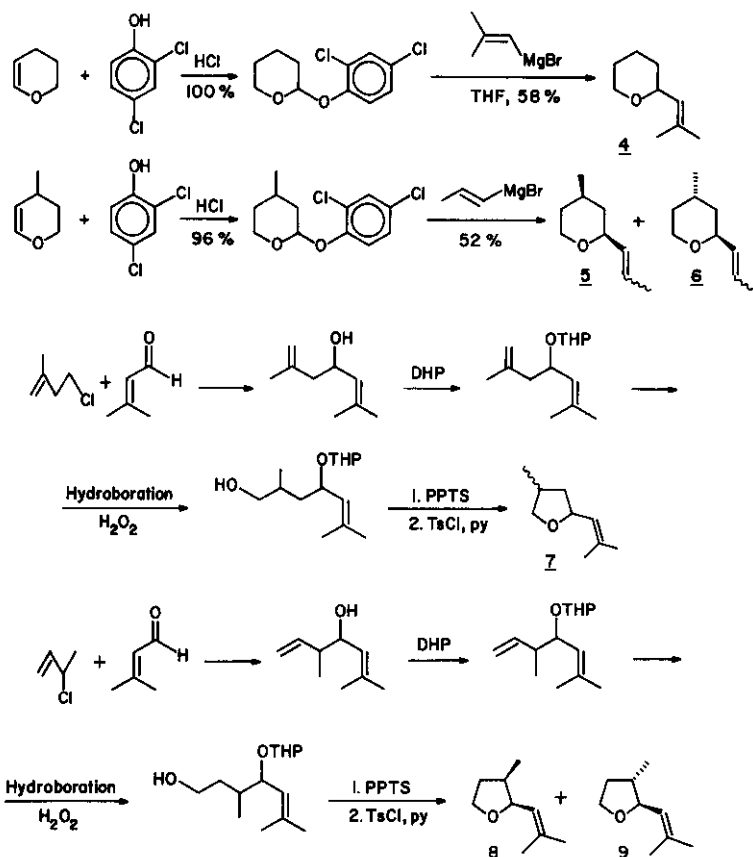
Lilac alcohols, marmelo oxides, hop ether and karahana ether—In the 1970s, Wakayama and Namba determined that the beautiful fragrance of lilac was caused by the presence of lilac alcohols [13] and lilac aldehydes [14] (Scheme 19).^{37,38} They amount to 70% of the steam-distilled oil from the lilac blossom extract. Investigations on the synthesis of the lilac alcohols and aldehydes are important because the materials used to formulate a modern lilac composition are probably still the same components that have been used for the past 60 years.³⁹ The first synthesis of these interesting compounds [13 and 14] was accomplished by Wakayama and Namba (Scheme 20),⁴⁰ using linalyl acetate as the starting compound. The lilac alcohols [13] were also synthesized by Vig et al. who used a combination of the Wittig and the Grignard reactions (Scheme 21).⁴¹ A key step in the total synthesis of the four lilac alcohols [13] was the formation of a mixture of (Z,E) isomers as products of UV irradiation of the α -methyl Dickmann ester (Scheme 22).⁴² The alcohols [13] can also be prepared from geraniol in a multi-step synthesis (Scheme 23).⁴³ In this reaction scheme, it was important that tert-butyl dimethylsilane (TBDMS) was used for blocking of the hydroxyl group, and selective deprotonation of the tetrahydropyranyl group was achieved using magnesium bromide etherate.

According to Tsuneya et al.⁴⁴ two diastereoisomers (A and B) of marmelo oxide [15] share the responsibility for the strong characteristic flavor of the fruit of quince. The synthesis of both isomers was based on D-glutamic acid (Scheme 24).⁴⁵

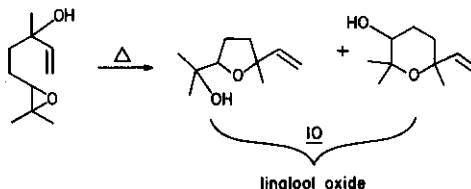
From the Japanese hop oil (fraction boiling at 50–53°C/15mm Hg) hop ether [16] and karahana ether [17] were isolated by silica gel column chroma-



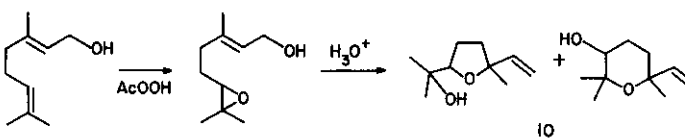
Scheme 11. Synthesis of cis-rose oxide homologue [3] according to Escher and Niclass.²⁴



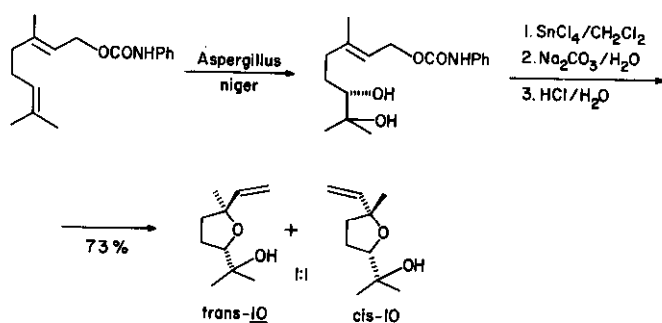
Scheme 12. Synthesis of rose oxide analogues [4–9] according to Weyerstahl.²⁵



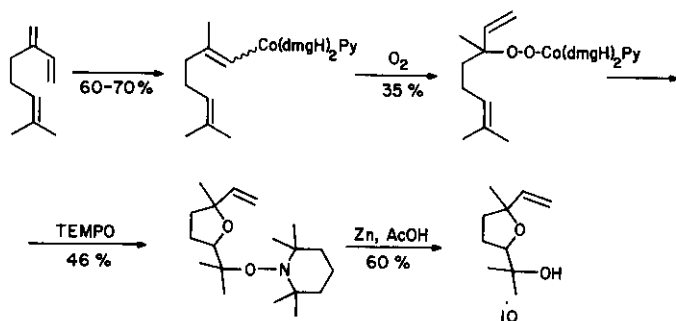
Scheme 13. Pyrolytic formation of linalool oxide [10] from epoxy linalool.²⁸



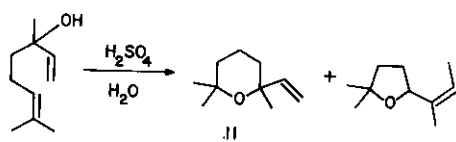
Scheme 14. Synthesis of linalool oxide [10] from geraniol.²⁹



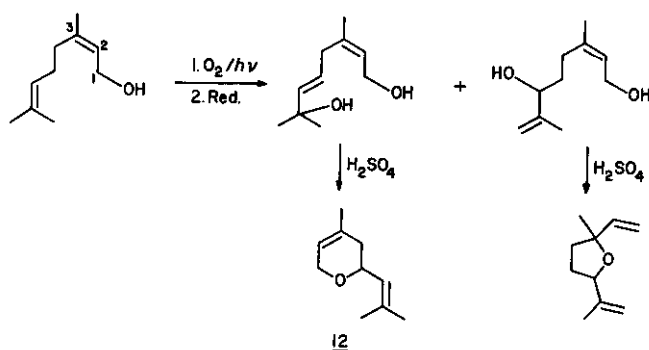
Scheme 15. Enantiosynthesis of the diastereoisomers of linalool oxide [10] according to Meou et al.³⁰



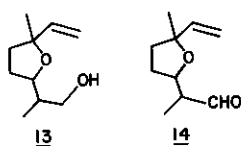
Scheme 16. Synthesis of linalool oxide [10] in the myrcene hydrocobaltation process.³²



Scheme 17. Cyclization of linalool to "linalyl oxide" [11] according to Strickler and Kovats.³⁴



Scheme 18. Photochemical synthesis of nerol oxide [12] according to Ohloff.²⁹



Scheme 19. Structures of lilac alcohols [13] and lilac aldehydes [14].^{37,38}

tography (Scheme 25).⁴⁶

The (+)- and (-)-hop ethers [16] have been synthesized by procedure which couples ketone methylenation with concomitant optical resolution (Scheme 26).⁴⁷ The substituted cyclopentanone was prepared according to Trost⁴⁸ and appears to be an attractive starting material. Dihydro-hop ether has also been synthesized from pulegone.⁴⁶

A brief total synthesis of karahana ether [17] has been reported from geraniol by Coates and Melvin (Scheme 27).⁴⁹ A more productive synthesis of karahana ether [17] was achieved by stereoselective cyclization of epoxy allylsilanes by Lewis acids (Scheme 28).⁵⁰

Spiro tetrahydrofuran derivatives—A few spiro tetrahydrofuranoids are known to occur in nature. Some of them are interesting as far as the odor is concerned and will be presented here.

From the low boiling fraction of the Reunion geranium oil, four spiro compounds of the bicyclic acetal structure [18 and 19] have been isolated (Scheme 29).⁵¹ Both [18] isomers, which possess a minty, fresh, herbaceous odor, represent ca. 0.005% of the total oil, while the corresponding dihydro derivatives [19] amount to 0.001% of the total oil. Both compounds [18 and 19] have been synthesized from α -methyl- γ -butyrolactone and rosefuran respectively (Scheme 30).

Starting from simple ketones, the synthesis of spiro ethers [20 and 21] which possess a pleasant flavor has been achieved (Scheme 31).⁵²

The spiro tetrahydrofurans [20 and 21] have similar olfactive properties. They possess flowery-fruity odors with turpentine-like undertones, which is dominant in [21] when R=H. The additional methyl group (R=Me) introduces a tonality of herbal-green accompanied by anise and eucalyptus.

2,2-Dimethyl-tetrahydrofuran and 2,2-dimethyl-tetrahydropyran derivatives—A new monoterpene alcohol [22] with a tetrahydrofuran structure was first isolated in 1982 from a higher boiling neutral fraction of peppermint oil.⁵³ The structure of this compound was confirmed by synthesis from ocimenol (yield 32.5%) (Scheme

Table IV. Odor characteristics of new THF and THP derivatives [27-57]

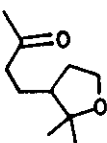
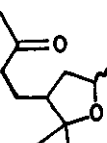
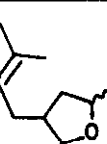
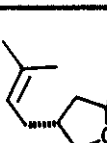
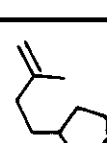
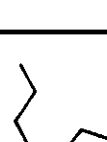
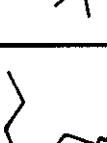
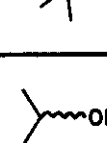
Compound	Odor characteristic
 [27]	almost odorless
 [28]	hardly perceptible
 [29]	sweet, interesting, similar to orange peel odor
 [30]	sweeter than [29], floral, orange peel odor-like
 [31]	similar to [29], less sweet, a little pungent
 [32]	light, ethereal, poppy odor-like
 [33]	light, intense, with a distinct woody note
 [34]	almost odorless

Table IV (Continued).

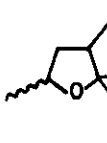
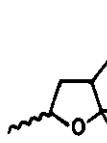
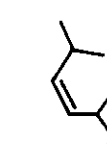
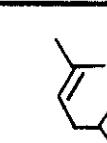
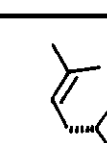
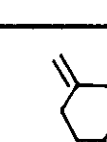
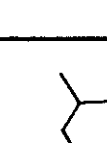
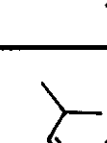
Compound	Odor characteristic
 [35]	weak, grassy and floral
 [36]	gentle, green, grassy
 [37]	sweet, floral, orange-citrus
 [38]	pleasant, lavender flower, sweet, intense
 [39]	very pleasant, distinct lavender, sweet
 [40]	similar to [38], but less interesting
 [41]	floral and woody, sweet
 [42]	similar to [37], with a woody note

Table IV (Continued).

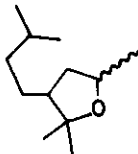
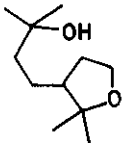
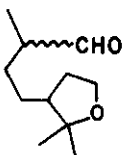
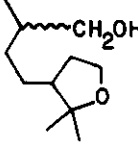
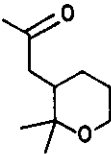
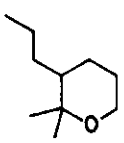
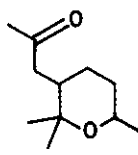
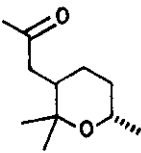
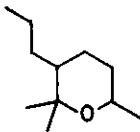
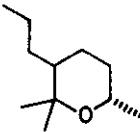
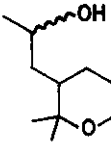
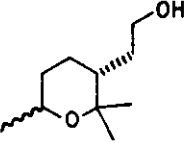
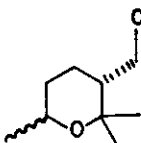
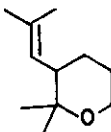
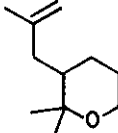
Compound	Odor characteristic
 [43]	floral with a distinct woody tone
 [44]	odorless
 [45]	attractive, flowery, cyclamen aldehyde odor-like
 [46]	almost odorless
 [47]	weak, a little similar to decaying litter of conifer needles
 [48]	intensive, ethereal with a weak cineol-camphor undertone
 [49]	almost odorless
 [50]	almost odorless

Table IV (Continued)

Compound	Odor characteristic
 [51]	light, intense with a little woody-cineol tone
 [52]	similar to cis-isomer [51]
 [53]	weak, woody-balsamic
 [54]	weak, woody and floral
 [55]	of medium intensity with a shade of greenery, not very interesting
 [56]	somewhat like litter of conifer needles with a wormwood shade
 [57]	similar to ground cover, not interesting

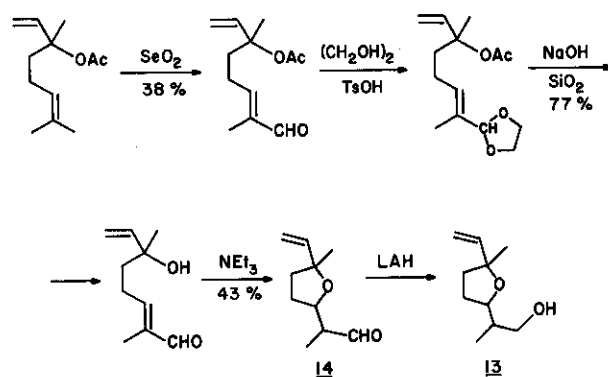
32). Both (Z)- and (E)-tetrahydrofuranoid [22] isomers were products of this synthesis. The (Z) isomer, which was found in the peppermint oil, was reported to possess a dry, grassy, hay-like odor with a floral rosy note reminiscent of geraniol. The (E)-isomer, which was suspected to be present in the oil, was found to smell similar to the (Z)-isomer.

A mixture of di-isopentylacetones that is a by-product of the manufacture of methyl heptenone, has been used for the synthesis of compounds of the THP structure [23-26] (Scheme 33).⁵⁴ The mixture of the cyclic ethers [23-26] has a floral odor with coniferous undertones.

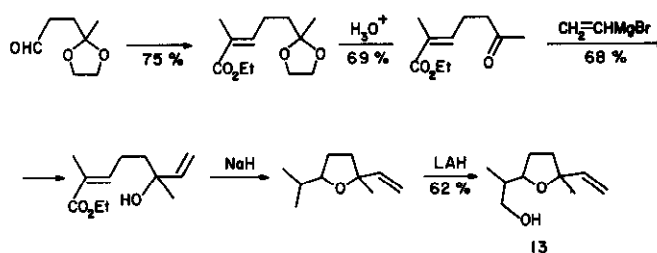
As mentioned earlier, α -pinene and δ -3-carene are excellent raw materials for the syntheses of many interesting 2,2-dimethyl-THF and 2,2-dimethyl-THP derivatives. Table IV shows the odor characteristics of a series of heterocyclic compounds [27-57] that have been synthesized from (+)- α -pinene, (+)- δ -3-carene and (+)-limonene.^{17-19, 55-57}

A review of the data presented in Table IV reveals that the tetrahydrofuranoids exhibit more agreeable, floral odors than their THP analogues. It is evident that the odors of the (3R)-enantiomers which were derived from (+)-limonene, are more attractive (sweeter) than those optical antipodes possessing (3S) configurations. Also, hydrogenation of a double bond in the side chain appears not to cause a change in the nature of the odor but introduces a distinguishing woody note. It is of interest to note that the THF alcohol [46],⁵⁶ whose structure is similar to brahmanol (a sandalwood-odored compound) is practically odorless (Scheme 34). The odor disappearance may possibly be due to an intramolecular bond formed between the hydroxyl group proton and the heterocyclic oxygen atom. Apparently the molecular shape of [46] is deformed enough not to match with any receptor responsible for odor creation.

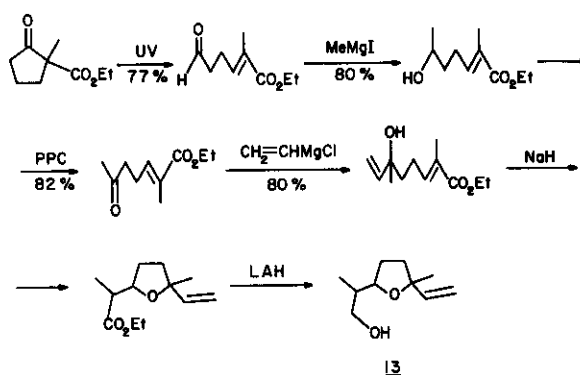
In summary, over the past few years many terpenoid THF and THP derivatives have been both synthesized and characterized in nature. Some of them have been shown to demonstrate unique



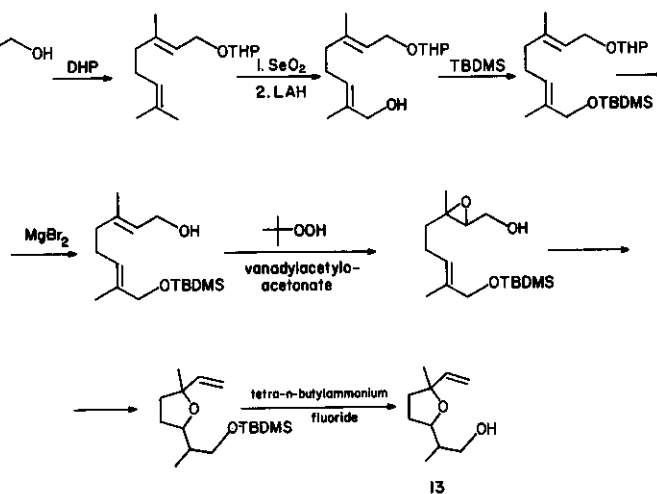
Scheme 20. Synthesis of lilac alcohols [13] and lilac aldehydes [14] from linalyl acetate.⁴⁰



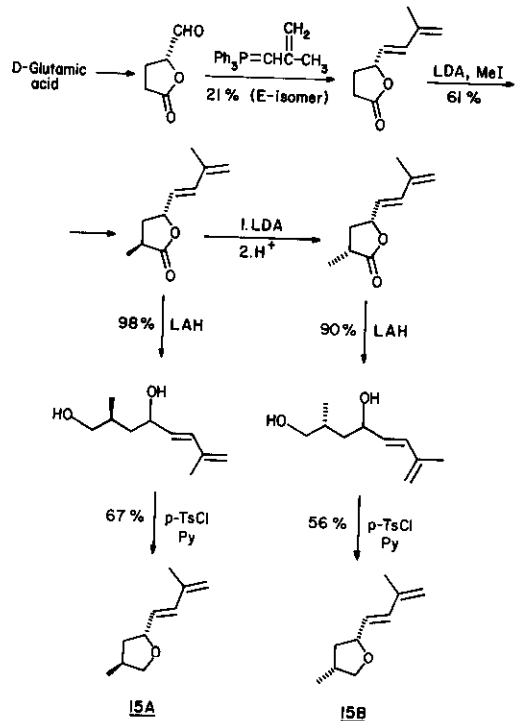
Scheme 21. Synthesis of lilac alcohols [13] according to Vig et al.⁴¹



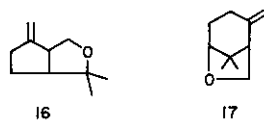
Scheme 22. Transformation of the α -methyl Dickmann ester to lilac alcohols [13].¹²



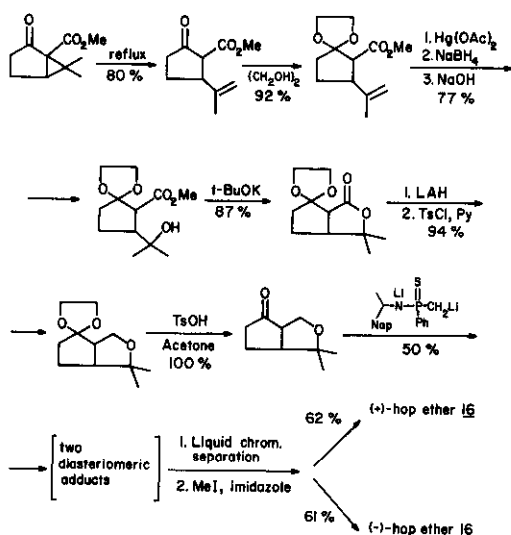
Scheme 23. Synthesis of lilac alcohols [13] from geraniol.⁴³



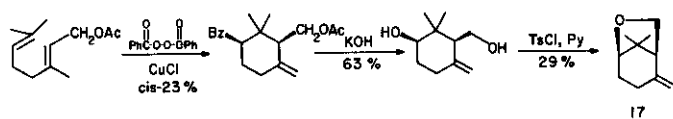
Scheme 24. A total synthesis of marmelo oxides [15] from D-glutamic acid according to Nishida et al.⁴⁵



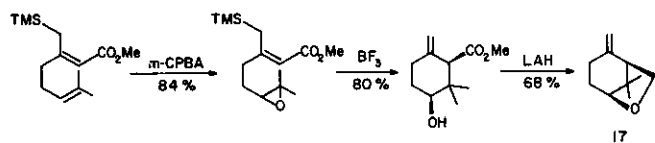
Scheme 25. Structures of hop ether [16] and karahana ether [17].⁴⁶



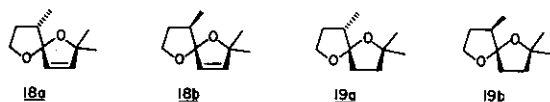
Scheme 26. Synthesis of optical isomers of hop ether [16] according to Johnson.⁴⁷



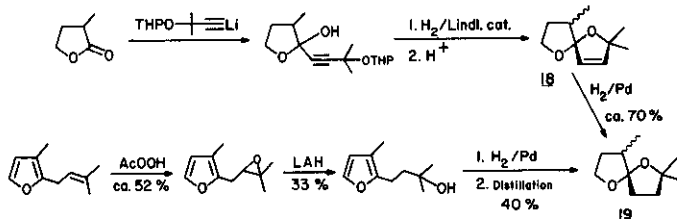
Scheme 27. A brief transformation of geraniol into karahana ether [17] according to Coates and Melvin.⁴⁸



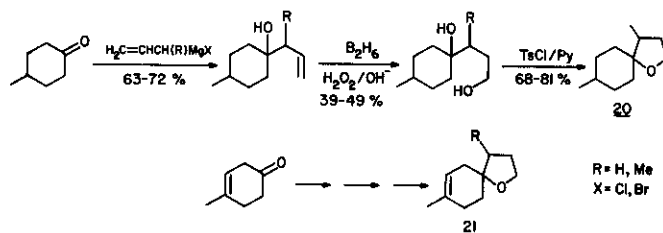
Scheme 28. Karahana ether [17] by stereoselective cyclization of epoxy allylsilanes.⁵⁰



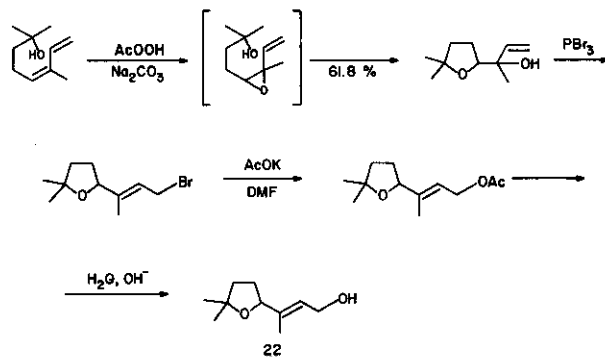
Scheme 29. Structures of the bicyclic acetals [18] and [19] isolated from the Reunion geranium oil.⁵¹



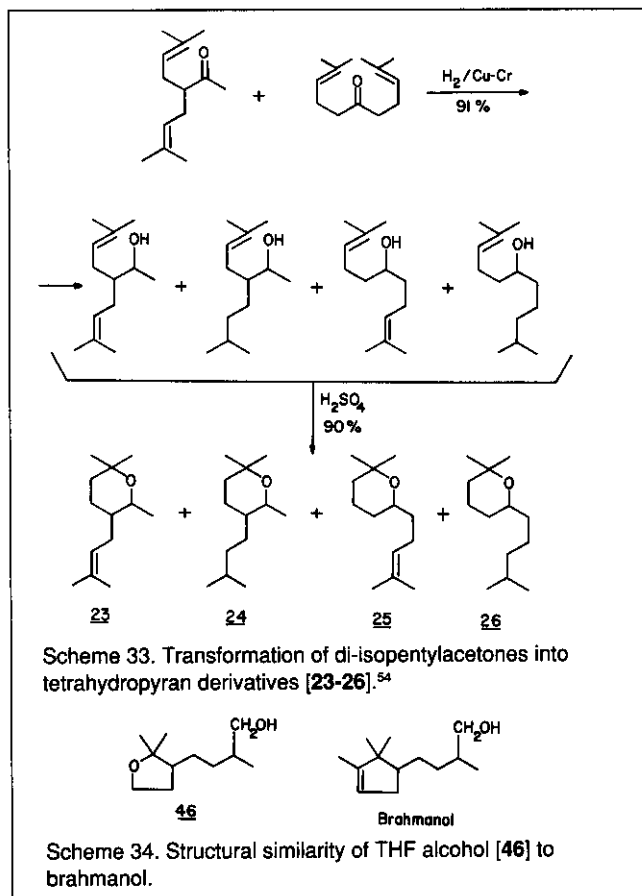
Scheme 30. Synthesis of the spiro bicyclic acetals [18] and [19] according to Kaiser.⁵¹



Scheme 31. Synthesis of the spiro ethers [20] and [21] from cyclohexanones.⁵²



Scheme 32. Tetrahydrofuranoid alcohol [22] from ocimenol according to Sakurai et al.⁵³



sensory properties, and together with their stability, they have attracted the attention of even the most fastidious of perfumers.

References

- H Merz and K Stockhaus, *J Med Chem* **22** 1475 (1979)
- PC Belauger and HWR Williams, *Can J Chem* **61** 1383 (1983)
- K Horito, Y Oikawa and O Yonemitsu, *Chem Pharm Bull* **37** 1698 (1989)
- MJ Bamford and DC Humber, *Tetrahedron Letters* **32** 271 (1991)
- S Inoki and T Mukiyama, *Chem Letters* **67** (1990)
- K Fugami, K Oshima and K Utimoto, *Bull Chem Soc Jpn* **62** 2050 (1989)
- MF Semmelhack and Ch Bodurow, *J Amer Chem Soc* **106** 1496 (1984)
- B Maurer A Grider and W Thommen, *Helv Chim Acta* **62** 44 (1979)
- B Maurer and W Thommen, *ibid* **62** 1096 (1979)
- A Wagner, MP Heitz and C Mioskowski, *Tetrahedron Letters* **30** 1971 (1989)
- K Ishiara, A Mori and H Yamamoto, *Tetrahedron* **46** 4595 (1990)
- ZY Wei, D Wang, JS Li and TH Chan, *J Org Chem* **54** 5768 (1989)
- A Johns and JA Murphy, *Tetrahedron Letters* **29** 837 (1988)
- D Marinkovic, *J Serb Chem Soc* **54** 633 (1989)
- NM Roscher and DK Schaffer, *Tetrahedron* **40** 2643 (1984)
- TLB Bovin, *ibid* **43** 3309 (1987)
- J Kula, *Liebigs Ann Chem* **890** (1983)
- J Podlejski and J Kula, *ibid* **477** (1989)
- J Kula, *Pol J Chem* **65** 333 (1991)
- For example: G Ohloff, E Klein and GO Schenck, *Angew Chem* **73** 578 (1961); T Shono, A Ikeda and Y Kimura, *Tetrahedron Letters* **3599** (1971); CF Garbers and F Scott, *ibid* **1625** (1976)
- K Homma and T Mukaiyama, *Chem Letters* **893** (1989)
- M Julia and B Jacquet, *Bull Soc Chim France* **1983** (1963)
- KC Brannock and HE Davis, *J Org Chem* **31** 980 (1966)
- Ch Liu, Ch Chang and T Chou, *J Heterocyclic Chem* **21** 129 (1984)
- S Escher and Y Niclass, *Helv Chim Acta* **74** 179 (1981)
- W Hoepfner and P Weyerstahl, *Liebigs Ann Chem* **99** (1986)
- N Prileschajew, *Chem Ber* **42** 4811 (1909)
- E Klein, H Farnow and W Rojahn, *Tetrahedron Letters* **1109** (1963)
- D Felix, A Melera, J Seibl and ES Kovats, *Helv Chim Acta* **46** 1513 (1963)
- For example: G Ohloff, KH Schulte-Elte and B Wilhalm, *ibid* **47** 602 (1964); R Kaiser, *Helv Chim Acta* **67** 1198 (1984)
- A Meou et al, *Synthesis* **752** (1990)
- JD Fourneron, A Archelas and R Furstoss, *J Org Chem* **54** 4686 (1989)
- AR Howell and G Pattenden, *J Chem Soc Chem Comm* **103** (1990)
- Pat JP 59,130,879 (1984); *Chem Abstr* **101** 211503 (1984)
- H Strickler and ES Kovats, *Helv Chim Acta* **49** 2055 (1966)
- M Uta, H Makimo, Y Oota, S Tsuboi and A Takeda, *Tetrahedron Letters* **24** 2567 (1983)
- G Ohloff, W Giersch, KH Schulte-Elte, P Enggist and E Demole, *Helv Chim Acta* **63** 1582 (1980)
- S Wakayama and S Namba, *Bull Chem Soc Jpn* **43** 3319 (1970)
- S Wakayama and S Namba, *ibid* **47** 1293 (1974)
- RJ Steltenkamp, *Perf & Flav* **4**(5) 1 (1979)
- S Wakayama, S Namba, K Hosoi and M Ohno, *Bull Chem Soc Jpn* **44** 875 (1971)
- OP Vig, RS Bhatt, J Kaur and JC Kapur, *J Indian Chem Soc* **50** 37 (1973)
- G Bidan, J Kossanyi, V Meyer and JP Morizur, *Tetrahedron* **33** 2193 (1977)
- A Johns, JA Murphy and MS Sherburn, *ibid* **45** 7835 (1989)
- T Tsuneya, M Ishihara, H Shiota and M Shiga, *Agric Biol Chem* **44** 957 (1980)
- Y Nishida, Y Fukushima, H Ohruai and H Meguro, *ibid* **48** 1217 (1984)
- Y Naya and M Kotake, *Tetrahedron Letters* **1645** (1968)
- CR Johnson, RC Elliot and NA Meanwell, *ibid* **23** 5005 (1982)
- BM Trost and WC Vladuchich, *J Org Chem* **44** 148 (1979)
- RM Coates and LS Melvin, *J Org Chem* **35** 865 (1970)
- RJ Armstrong and L Weiler, *Can J Chem* **61** 214 (1983)
- R Kaiser, *Helv Chim Acta* **67** 1198 (1984)
- B Buchmann, H Marschall-Weyerstahl and P Weyerstahl, *Tetrahedron* **40** 3393 (1984)
- K Sakurai, K Takahashi and T Yoshida, *Agric Biol Chem* **47** 1249 (1983)
- WM Andrew et al, *Maslo-Zhir Promyshl* **36** (1979)
- J Kula and J Gora, *Liebigs Ann Chem* **1860** (1984)
- J Gora and J Kula, *Pol J Chem* **60** 283 (1986)
- J Kula, Synthesis of new odoriferous compounds of 2,2-dimethyltetrahydrofuran and 2,2-dimethyltetrahydropyran derivatives, *Politechnika lodzka, Zeszyty Naukowe* No 570 (1990) (in Polish)
- I Blank, KH Fischer and W Grosch, *Z Lebensn-Unters Forsch* **189** 426 (1989)
- I Blank, W Grosch, W Eisenreich, A Bacher and J Firl, *Helv Chim Acta* **73** 1250 (1990)
- K Belafi-Rethy and E Kerenyi, *Acta Chim Acad Scient Hungaricae* **94** 1 (1977)
- R Huopalahti and RR Linko, *J Agric Food Chem* **31** 331 (1983)
- I Blank and W Grosch, *J Food Sci* **56** 63 (1991)

