A Green and Sustainable Approach: Celebrating the 30th Anniversary of the Asymmetric *l*-Menthol Process

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Dedicated to the memory of Professor *Mugio Nishizawa*

Takasago has been devoted to producing *l*-menthol since 1954, and our long history of manufacturing this important aroma chemical is reviewed here. The current asymmetric catalytic process had its 30th anniversary in 2013. Our *l*-menthol process is considered carbon-neutral, and, therefore, 'green' and sustainable. It uses renewable myrcene obtained from gum rosin as a starting material. In addition, the Rh-BINAP (=2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) catalytic system is highly efficient. This pathway not only leads *l*-menthol, but a variety of 100% biobased aroma chemical products as well. By measuring the ^{14}C levels in a material, one can determine the percentage of carbon that is biobased. This biobased assay, described as the ratio plant-derived C/fossil-derived C, can clarify how renewable a product really is. This will be highlighted for several of *Takasago*'s key aroma chemicals.

Introduction. – *l*-Menthol ((−)-**1**) is one of the most abundant chiral chemicals in the world. Before World War II, it was prepared mainly in Japan and China by crystallization of the extracted oil of *Mentha arvensis*. It is reported that, by 1938, 886 t of natural *l*-menthol were produced, and 375 t were exported from Japan to the world. Japan was the world leader in menthol production. *Takasago* submitted the first patent for the synthesis of *l*-menthol in 1928 [1] and began the synthetic manufacturing of *l*-menthol in 1954. At that time, the starting material was *d*-citronellal ((+)-**2**) isolated from citronella oil, and the total production volume was *ca.* 300 t. By 1972, with the advance of the petroleum industry, thymol (**3**) replaced *d*-citronellal as the starting material. However, this only lasted *ca.* five years due to the oil crisis of the late 1970s, which suddenly increased the price of petroleum. Thus, we began to prioritize sustainable or renewable materials over petroleum-based materials when developing aroma chemicals. Other natural products such as *d*-limonene ((+)-**4**) and *d*-Δ^3-carene (**5**) have also been utilized as starting materials for *l*-menthol synthesis. In 1983, *Takasago* completed the asymmetric synthesis of *l*-menthol which is still the basis of our process today (*Fig. 1*). The current asymmetric catalytic process uses renewable myrcene (**6**) as the starting material, and, through the years, the process has continuously been modified and improved. From this process, a variety of aroma chemicals are produced. Our three key commitments are *i*) to use renewable or sustainable raw materials when available, *ii*) to apply catalytic processes when possible, and *iii*) to target optically pure chemicals.

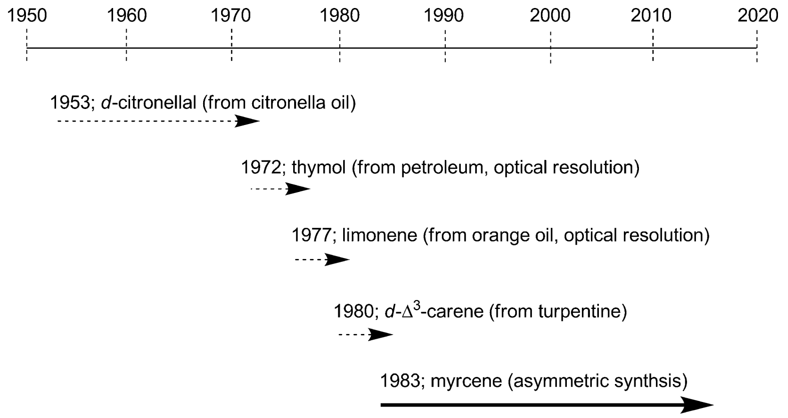
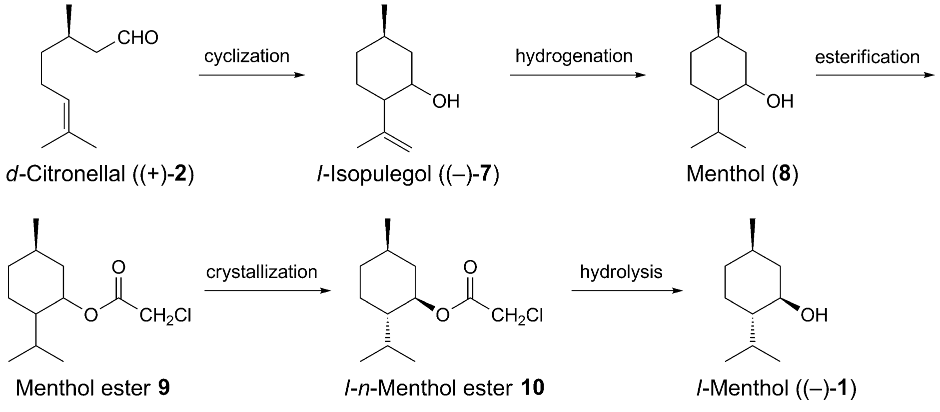


Fig. 1. *History of the production of* l-*menthol*

Chronological Review. – *From 1954 to 1972.* The 60-year history of synthetic *l*-menthol ((−)-**1**) began when *d*-citronellal ((+)-**2**) was isolated in 35% yield from citronella oil. At that time, citronellal (**2**) was a lesser-used aroma chemical, while other components of citronella oil, such as geraniol and its esters, were much more highly valued. Because the optical purity of (+)-**2** was 80% ee, it was considered as a useful chiral starting material. The first industrial *l*-menthol synthesis from (+)-**2** was performed in Japan [2] (*Scheme 1*). Purification *via* the 2-chloroacetate **9** of the menthol isomers was a key step, from which ultimately 300 t of *l*-menthol were produced.

From 1972 to 1977. To manufacture 300 t of *l*-menthol, 1,300 t of citronella oil were required to obtain the necessary (+)-**2**. This comprised nearly half of the worldwide natural citronella oil consumption at the time. As a result, thymol (**3**), which is derived from the petroleum-based compound *m*-cresol, was developed as an alternative starting material for the *l*-menthol synthesis. Since **3** is achiral, optical resolution was

Scheme 1. d-*Citronellal Process from 1954 to 1972*

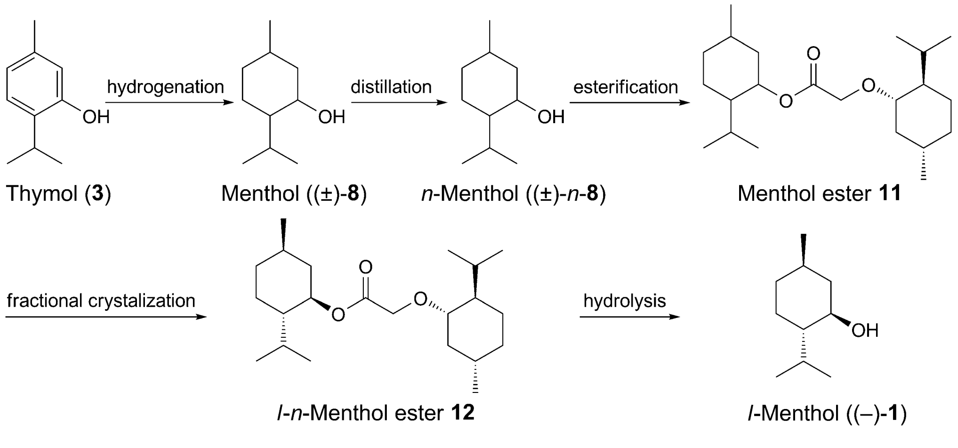


necessary, which was accomplished by preferential crystallization of the corresponding diastereoisomer, *l*-menthyl *d*-menthoxyacetate (**12**), obtained from the reaction with *d*-menthoxyacetic acid, and was subsequently converted to pure *l*-menthol by hydrolysis [3] (*Scheme 2*). The antipodal *d*-menthyl *d*-menthoxyacetate remaining in the mother liquor was converted to *dl*-menthol by Ni-catalyzed isomerization under high pressure and subsequently recycled back into the process. A fine distillation system, equipped with a successively feeding 80 theoretical plate setup, was installed to enable separation of the desired *dl*-*n*-menthol from iso-, neo-, and neoisomenthol.

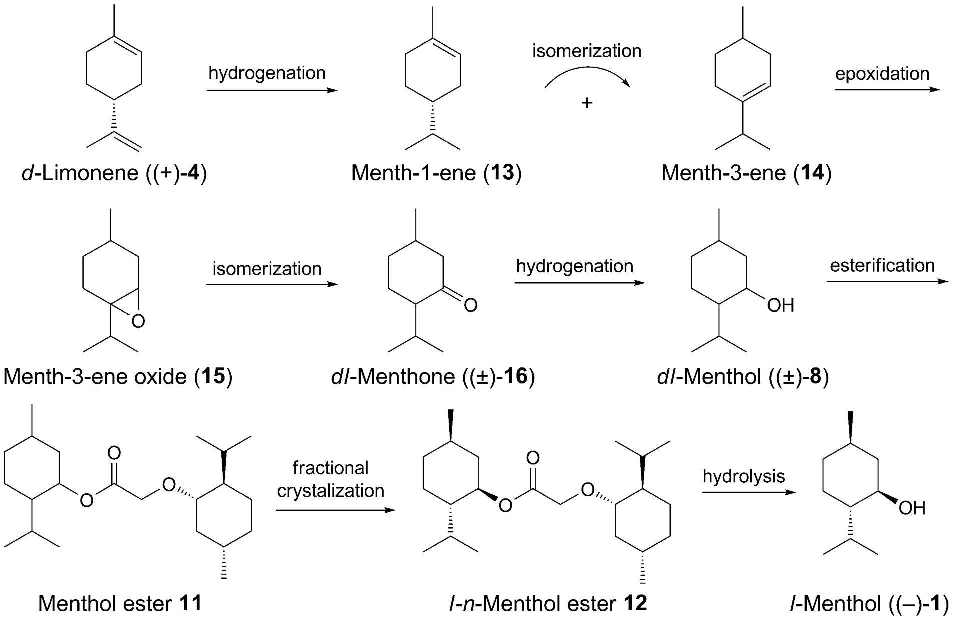
From 1977 to 1980. The oil crisis of 1973 caused a drastic price increase in petroleum feedstocks and led to a shortage of thymol, hence, the thymol-based process needed to be replaced. The search thus began for a new natural feedstock to support a novel *l*-menthol synthesis. *d*-Limonene ((+)-**4**), which occurs in very high concentrations in orange oil, was selected as an inexpensive raw material [4] (*Scheme 3*). Although the optical purity of (+)-**4** is very high, the manufacturing process was too costly to take advantage of this chirality, and it afforded only *dl*-menthol. As a consequence, *dl*-menthol still needed to be subjected to the same optical resolution techniques as in the aforementioned thymol process.

From 1980 to 1983. Both the thymol and *d*-limonene processes mentioned above required an optical resolution step to produce *l*-menthol. The equivalent amount of undesired *d*-menthol produced from the resolution process was subjected to further racemization and recycling steps. This in turn yielded higher fuel costs, which became a serious issue during the second oil crisis of 1979. *Takasago* decided to adopt a technology from *PFW* that used optically active *d*-Δ^3-carene (**5**) as the feedstock for the *l*-menthol synthesis. This process was improved through isomerization of **18** to a mixture of **19** and **20** by *Takasago* in 1982 [5] (*Scheme 4*). Consequently, (1*R*)-menth-3-ene (**21**) was obtained from **19** and **20** by selective reduction, respectively, without formation of (1*R*)-menth-2-ene. This avoided the production of the undesired *p*-menthan-2-ol in the reaction mixture, which could not easily be separated from *l*-menthol by distillation and could not be recycled.

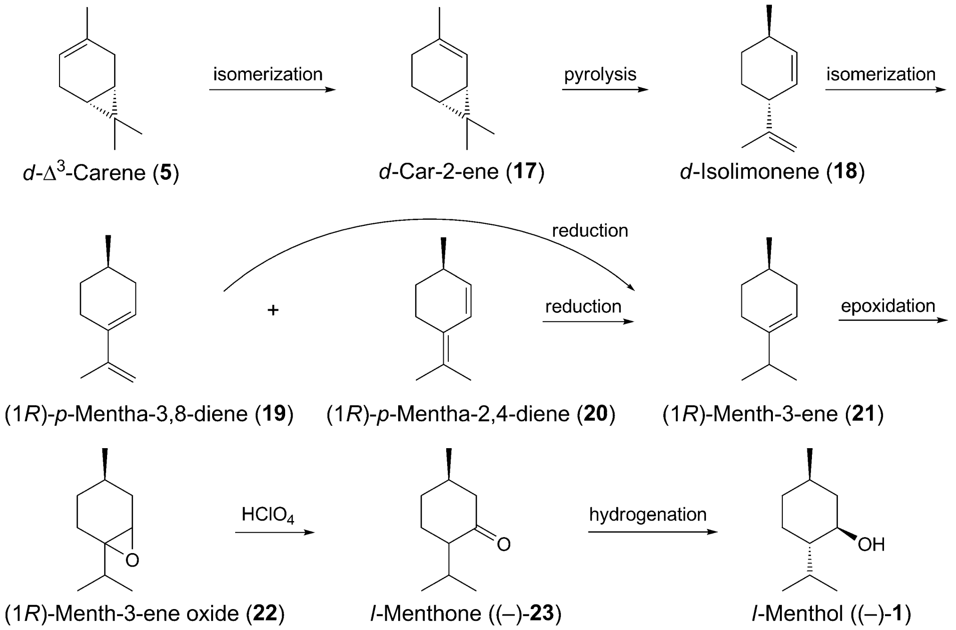
Scheme 2. *Thymol Process from 1972 to 1977*



Scheme 3. *Limonene Process from 1977 to 1980*



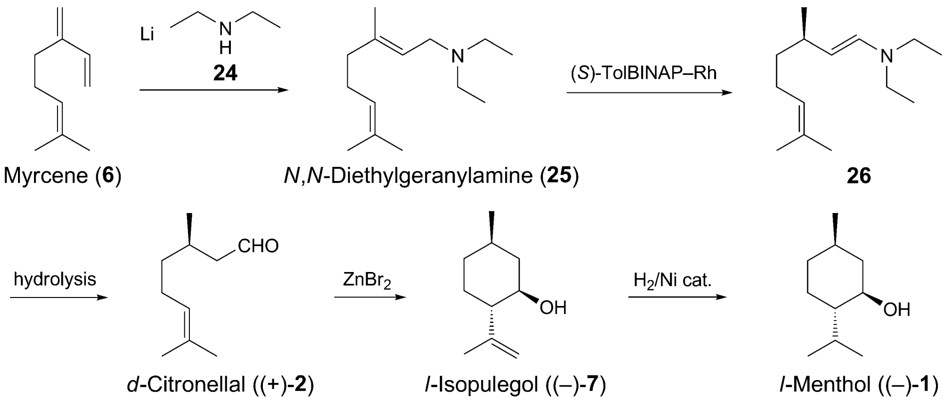
Scheme 4. d-*Δ³-Carene Process from 1980 to 1983*



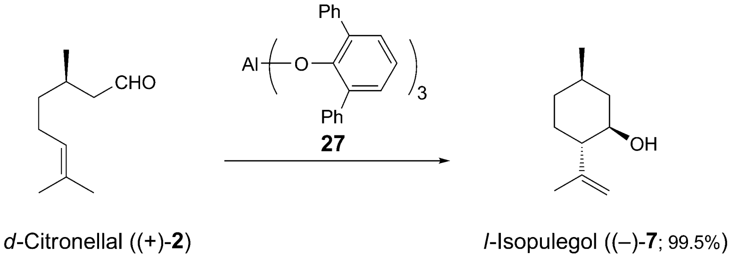
From 1983 to Present. In 1983, *Takasago* established one of the largest industrial asymmetric catalytic manufacturing plants in the world with the collaboration of professors, Dr. *R. Noyori*, Dr. *H. Takaya*. Dr. *K. Tani*, and Dr. *S. Otsuka* [6–9]. This process (*Scheme 5*), which just celebrated its 30th anniversary in 2013, has not changed much in more than three decades since its inception, notwithstanding the fluctuations of the world economy. The current process contains many aspects of past technologies. For instance, the fine distillation that separates *n*-menthol from iso-, neo-, and neoisomenthol, and the industrial use of metal/amine-catalyzed reaction was introduced in the *d*-citronellal and *d*-Δ^3-carene processes, respectively. One advantage of this method is its efficiency. By simply switching the configuration of the homogeneous organometallic catalyst, the Rh-BINAP (=2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), one can change the chirality of the product. Both optically active isomers can be produced in the same manufacturing plant, as the chemical purity and enantiomeric ratios of these products are completely identical. In contrast, a biocatalyst does not have such flexibility.

Although there has been little change in this process over the last 30 years, we have implemented a 'KAIZEN' (continuous improvement) approach. Instead of using a petroleum-based Et_2NH, a bio-ethanol-derived Et_2NH is now used to reduce our reliance on petroleum-based chemicals. Another improvement has been implemented in the cyclization of (+)-**2** to give (−)-**7**, which originally gave 92% selectivity. Here, the

Scheme 5. *Myrcene Process from 1983 to Present*



Scheme 6. *ATPH-Catalyzed Cyclization*



original $ZnBr_2$ catalyst was replaced with aluminum tris(2,6-diphenylphenoxide) (ATPH; **27**), which now provides (−)-**7** with 99.5% selectivity [10] (*Scheme 6*).

Results and Discussion. – *A Green and Sustainable Process.* The current process uses renewable myrcene (**6**), which can be isolated from gum rosin, wood rosin, toll rosin, tree sap, wood chips, or the waste fluid of wood pulp. Currently, gum rosin is being used as our feedstock in the asymmetric *l*-menthol synthesis. The entire process involves four different catalytic reactions in an effort to maintain a focus on green chemistry. The Rh-BINAP catalyst works highly efficiently, as one molecule of Rh-BINAP can produce more than 200,000 molecules of *l*-menthol.

In terms of molecular carbon, there is no increase in atmospheric CO_2 from the use of natural *l*-menthol due to the equilibrium between the CO_2 released by biodegradation and the CO_2 adsorbed by photosynthesis. In a similar manner, **6** produced from gum rosin can be considered carbon-neutral. It is well-known that the use of petroleum feedstock for chemical synthesis poses problems for future sustainability. In addition, products obtained from these sources can release CO_2 stored in fossil fuels and increase the CO_2 levels in the environment which may exacerbate climate change. In this study, the biobased index was investigated for a variety of products derived from our sustainable myrcene source.

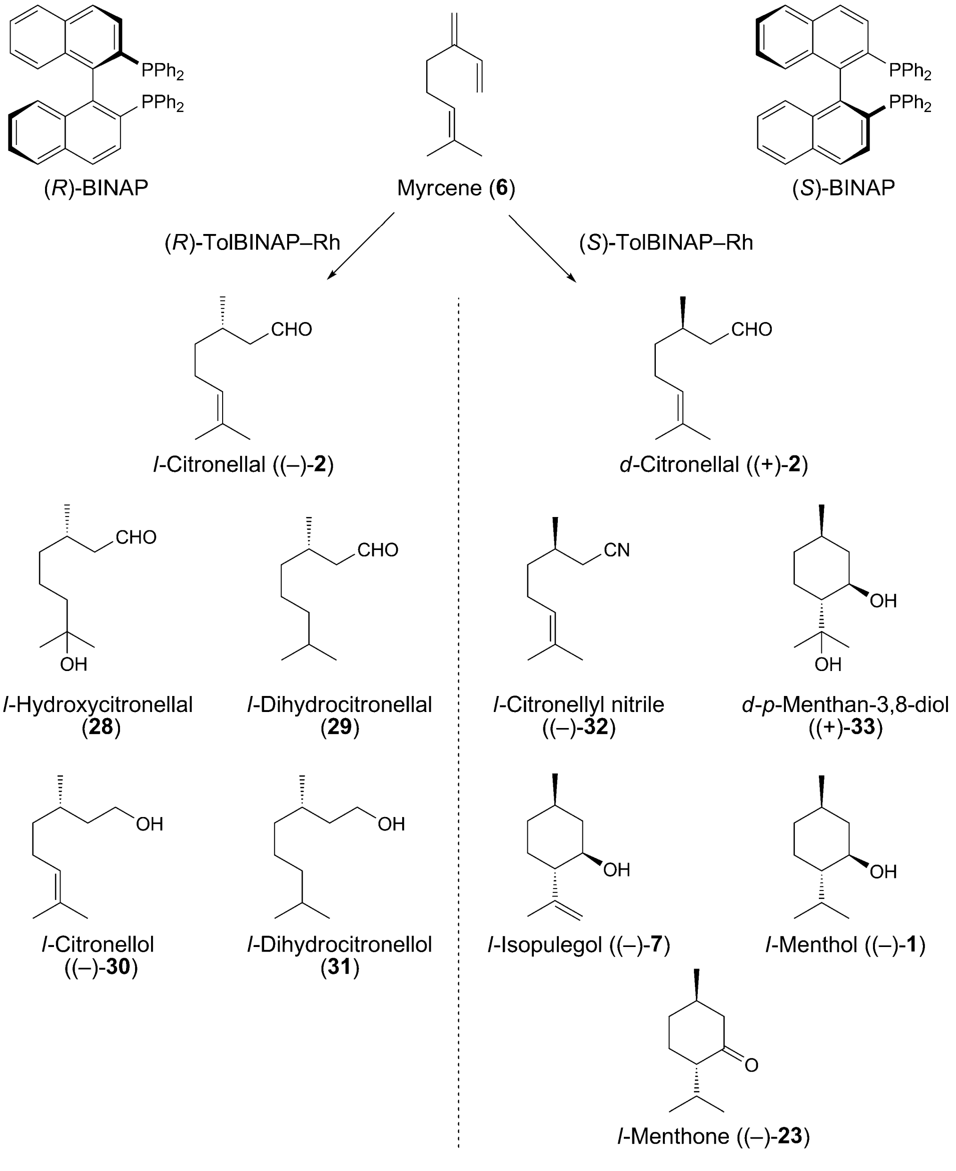
Biobased Index. When a plant or animal dies, the amount of ^{14}C in its composition begins to slowly decrease over time at a known rate. The half-life of radioactive ^{14}C is 5,730 years. For fossil material, the quantities of ^{14}C are much lower, since life activity ceased in the distant past. Using this principle [11], by measuring the radioactive ^{14}C in a material, one can tell not only what is the age of the material but also the ratio of petroleum-derived material to plant-derived material within a product. In this biobased analysis, the ^{14}C from fossil sources is essentially zero. From this, the balance of fossil-

Table. *Biobased Analytical Result of Aroma* Chemicals

Compounds	Biobased [%]
l-Citronellol ((−)-**30**)	100
Petroleum-derived citronellol ((±)-**30**)	0
Natural *l*-menthol ((−)-**1**)	100
Myrcene-process *l*-menthol ((−)-**1**)	100
Petroleum-derived *l*-menthol ((−)-**1**)	0
Myrcene-process *l*-citronellyl nitrile ((−)-**32**)	100
Petroleum-derived citronelly nitrile ((±)-**32**)	0
d-*p*-Menthane-3,8-diol ((+)-**33**)	100
N,*N*-Diethyl-3-methylbenzamide (**35**)	34
(1*R*)-8-sulfanylmenthone ((+)-**37**)	100
(1*S*)-8-sulfanylmenthone ((−)-**37**)	100
8-Sulfanylmenthone as a natural flavor substance ((+)-**37**)	100
l-*cis*-Rose oxide ((−)-*cis*-**40**)	100
Petroleum-derived rose oxide ((±)-**40**)	0
Thesaron® ((+)-*trans*-**43**)	100
β-Damascone (**45**)	0
γ-Decalactone from Castor oil (**48**)	100
Synthetic *γ*-decalactone ((±)-**48**)	70

and plant-derived carbon in the molecule can be calculated. Samples of *l*-menthol synthesized from our myrcene process, isolated from a natural mint oil, and synthesized from a fossil feedstock were analyzed by this assay. Both the *l*-menthol from the myrcene process and the one isolated from natural mint showed a 100% biobased index, whereas *l*-menthol from the fossil material showed a 0% biobased index (*Table*).

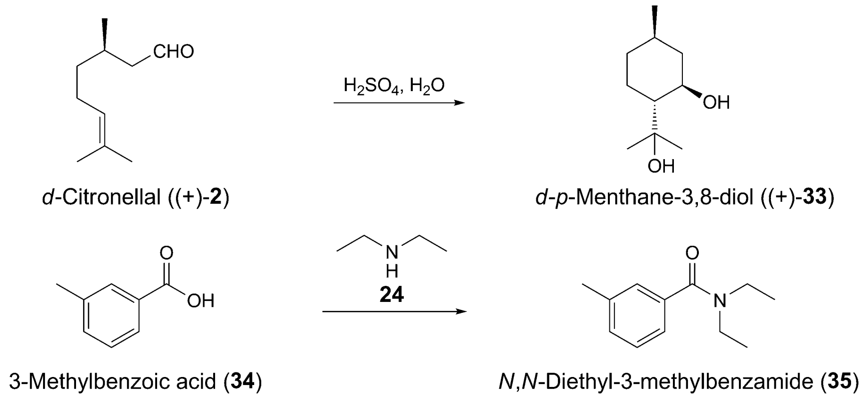
Scheme 7. *Myrcene Process-Derived Aroma Chemicals*



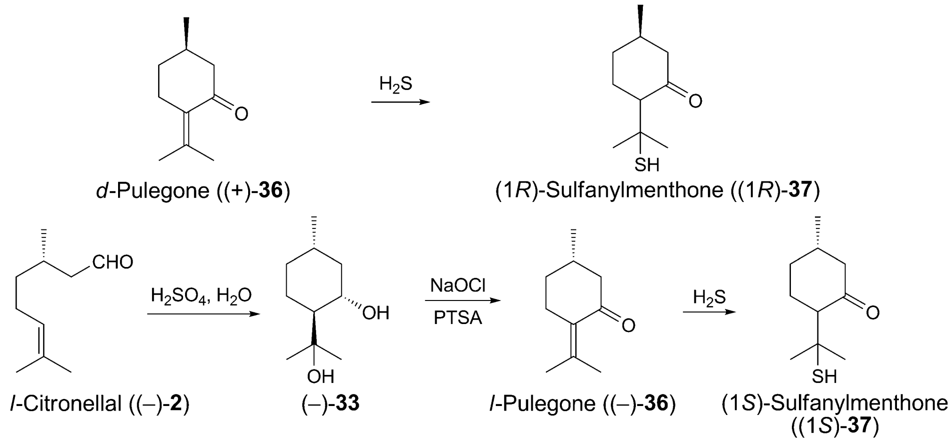
Myrcene-Derived Aroma Chemicals. From the aforementioned myrcene process, *l*-citronellal ((−)-**2**), *l*-citronellol (**30**), and their analogs are synthesized using the (*R*)-TolBINAP–Rh catalyst. Alternatively, *d*-citronellal ((+)-**2**), *l*-citronellyl nitrile ((−)-**32**), *l*-isopulegol ((−)-**7**), and their analogs are prepared by the (*S*)-TolBINAP–Rh catalyst (*Scheme 7*). They are all found to have a 100% biobased index. In addition, the following specialty chemicals have been investigated.

*(1*R*)-*p*-Menthane-3,8-diol* ((+)-**33**). Naturally identical (1*R*)-*p*-menthane-3,8-diol ((+)-**33**) was synthesized from (+)-**2**, derived from myrcene, and has been developed as a commercial cooling material [12] (*Scheme 8*). It also acts as a mosquito repellant. It was found that the (+)-**33** from mycrene has a 100% biobased index, while the popular artificial insect repellant *N*,*N*-diethyl-3-methylbenzamide (DEET; **35**) contains only 34% biobased carbon. This result suggest that the 34% biobased carbon in **35** is from

Scheme 8. *Synthesis of* d-p-*Menthane-3.8-diol and the Structure of* N,*N-Diethyl-3-methylbenzamide* (DEET)



Scheme 9. *Synthesis of 8-Sulfanylmenthone*



Et_2NH (**24**), derived from bioethanol, while the residual 66% carbon is contributed by the petroleum-based 3-methylbenzoic acid (**34**). Interestingly, this observed biobased index for **35** is almost identical to that calculated if we assume the four biobased carbons (33% of total) are derived from bioethanol precursor of **24**, and the eight fossil-based carbons (67% of total) are from **34**.

(1S)-8-Sulfanylmenthone ((1*S*)-**37**). Enantioselective GC analysis gave a clear separation of the isomers of 8-sulfanylmenthone. It is known that there is a significant olfactory difference for the optical isomers of 8-sulfanylmenthone [13][14], and while the (*S*)-isomer is strong, the (*R*)-isomer is dirty and oily. The conventional production of 8-sulfanylmenthone (**37**) starts from commercially available *d*-pulegone ((+)-**36**), which has a configuration opposite to that of the desired natural (1*S*)-**37**. Its odor is not preferable, therefore. Enantioselective GC analysis revealed that **37** from *l*-pulegone, derived from the myrcene process (*Scheme 9*), has the same configuration as (1*S*)-**37** found in natural Buchu oil [15] (*Fig. 2*). In addition, it was found to possess an intense odor reminiscent of natural Buchu. Interestingly, 8-sulfanylmenthone, labeled as natural flavoring substance in accordance with the EU Flavor Regulation 1334/2008/

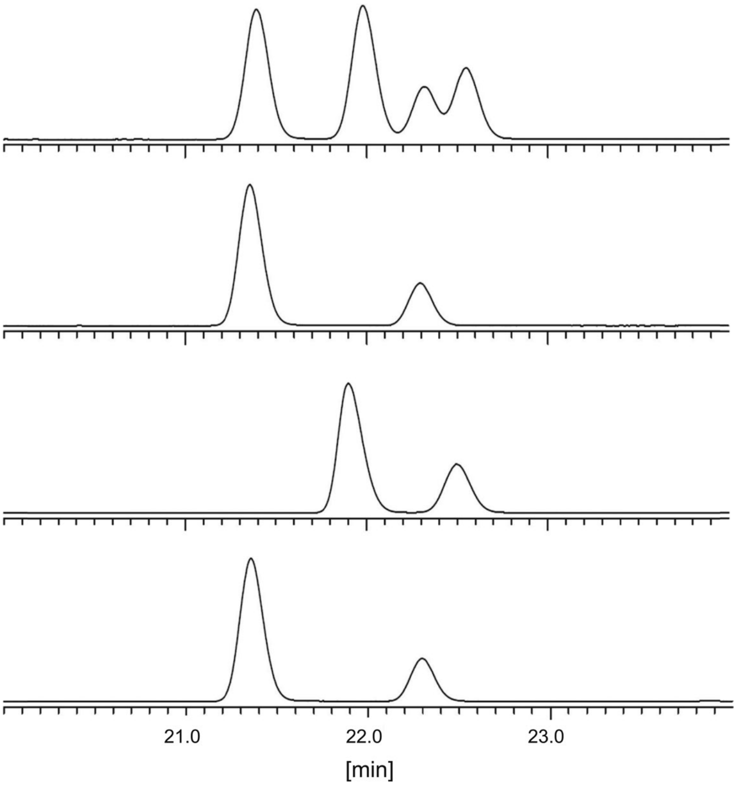


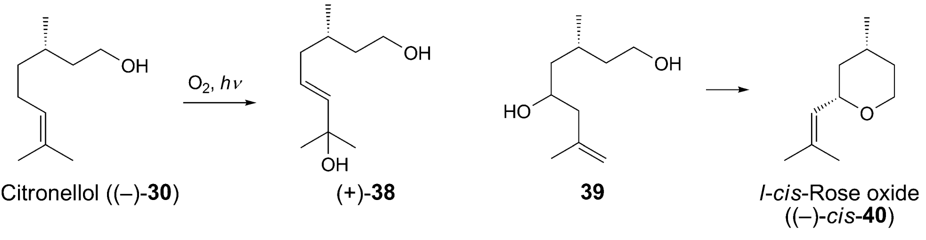
Fig. 2. *GC Analysis of the four isomers of 8-sulfanylmenthone.* Upper to lower: mixture of four isomers; (1*R*,4*R*)-8-sulfanylmenthone and (1*R*,4*S*)-8-sulfanylmenthone; (1*S*,4*S*)-8-sulfanylmenthone and (1*S*,4*R*)-8-sulfanylmenthone; and 8-sulfanylmenthone labeled as a natural flavoring substance.

EC, is identical to (1*R*)-**37**, and is the antipode of (1*S*)-**37**, which is identified in natural Buchu (*Table*). Both of these **37** have a 100% biobased index, since they are prepared from natural starting materials.

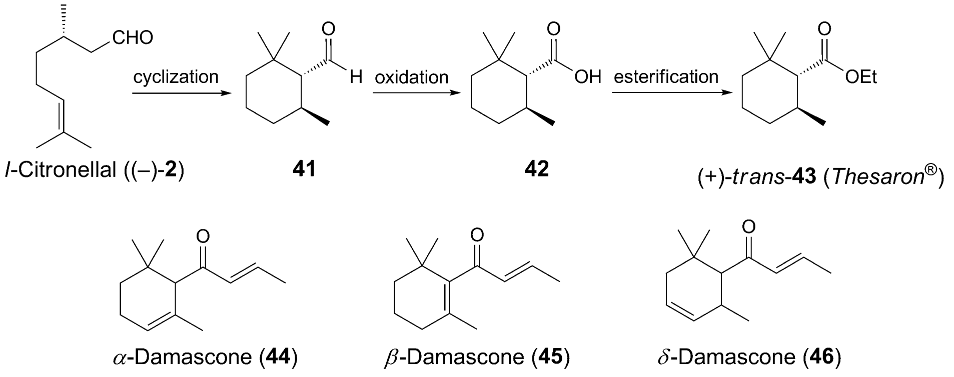
l-cis-*Rose Oxide* ((−)-*cis*-**40**). Rose oxide (**40**) has four optical isomers, and it is well-known that *l*-*cis*-rose oxide ((−)-*cis*-**40**) is the preferred enantiomer in terms of both odor threshold and olfactory character [16]. The odor thresholds of *l*-*cis*-rose oxide, *l*-*trans*-rose oxide, *d*-*cis*-rose oxide, and *d*-*trans*-rose oxide are 0.005, 0.160, 0.05, and 0.08 ppm, respectively. Using our myrcene process, (−)-*cis*-**40** was synthesized selectively (*Scheme 10*) from (−)-**30** and was found to have a 100% biobased index. Whereas, the conventional synthetic rose oxide ((±)-**40**) comprises a mixure of those four isomers and has a 0% biobased index.

Thesaron® ((+)-*trans*-**43**). An important family of chemicals derived from natural rose oil are the rose ketones, represented by *α*-damascone (**44**), *β*-damascone (**45**), and *δ*-damascone (**46**). It is known that use of rose ketones is restricted in some cases, because they cause skin sensitization. *Takasago* developed the aroma chemical *Thesaron®* ((+)-*trans*-**43**; *Scheme 11*), and specifically designed it to reduce this skin sensitization problem by eliminating the conjugated C=C bond of **44**–**46** and replacing it with an O-atom to form an ester [17]. Another advantage of (+)-*trans*-**43** is that the sterically hindered ester function is rather stable and difficult to hydrolyze in a variety of consumer product applications, thus enhancing its odor stability.

Scheme 10. *Synthesis of* l-cis-*Rose Oxide*



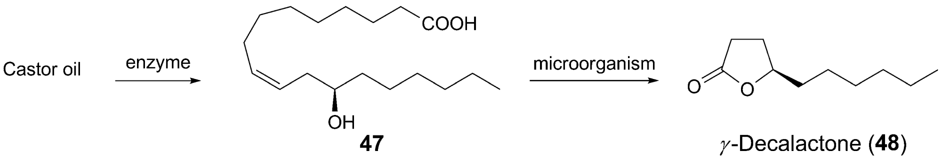
Scheme 11. *Synthesis of* Thesaron® *and Structures of Damascones*



Although there are four possible stereoisomers, (+)-*trans*-**43** was selectively developed (*Scheme 11*) for its unique odor intensity and character. *Thesaron*® ((+)-*trans*-**43**) has an intense sweet flowery character with an odor threshold of 0.02 ppm, while (−)-*trans*-**43** possesses an oily character with an odor threshold of 0.10 ppm. It was initially found that the biobased index of *Thesaron*® ((+)-*trans*-**43**) was 80%, since the cyclic terpene portion is derived from myrcene, with the remaining 20% being derived from synthetic EtOH, which was replaced with bioethanol to improve the biobased index to 100%. In contrast, it was found that commercially available *β*-damascone (**45**), which is synthesized from a petroleum feedstock, has a 0% biobased index.

*(*R*)-γ-Decalactone* (**48**). Other green and sustainable approaches include chemical biotransformations utilizing microorganisms or enzymes from a natural feedstock, as they require less organic solvent and generate less chemical waste. In addition, products derived by these methods can be labeled as natural flavors, in accordance with CFR21 Sec. 101.22 and EU Flavor Regulation 1334/2008/EC. (*R*)-*γ*-Decalactone (**48**) was developed from the renewable castor oil *via* **47** by screening a variety of natural microorganisms [18] (*Scheme 12*). Compound **48** was identified to have a (*R*)-configuration by enantioselective GC analysis and was preferred olfactively. Interestingly, some natural *γ*-decalactone products on the market were found to be racemic, although all products have 100% biobased indices. In contrast, synthetic **48** was found to be 70% biobased.

Scheme 12. *Biotransformation of γ-Decalactone*



Conclusions. – Public interest in environmental concerns has been continuously increasing, and environmentally friendly products have become an important area for both chemical producers and consumers. Finding natural and sustainable sources of key aroma chemicals has been a focus of the flavor and fragrance industry even before the environmental concerns became main stream. As discussed in this review, the biobased index can play a major role in identifying the use of plant-derived feedstock, as well as in helping to identify the synthetic pathway to prepare a chemical. Throughout the history of the *l*-menthol process, we have shared our successes with the world. Today, we continue to retain our core commitments to use renewable or sustainable raw materials, to apply catalytic processes, and to target optically pure chemicals.

Experimental Part

General. (±)-Citronellol ((±)-**30**), *(±)-rose oxide* ((±)-**40**), *8-sulfanylmenthone* ((+)-**37**) as natural flavoring substances, and *β-damascone* (**45**) were purchased from *Sigma–Aldrich Corporation* (St. Louis, Missouri, USA). DEET (**35**) and synthetic *γ-decalactone* (**48**) were purchased from *Tokyo*

Chemical Industry Co., Ltd. (Tokyo, Japan). Other materials, unless otherwise noted, are produced or obtained from *Takasago International Corporation*. Enantioselective gas charomatography (GC): a GC system (*Agilent Technologies Inc.*, Santa Clara, CA) combined with a flame ionization detector (FID) equipped with a 25 m × 0.25 mm i.d. β-DEX325 fused cap. column coated with 0.25-μm film; carrier gas, He; 100 kPa; oven temp., started at 130° up to 135° at an rate of 0.1°/min, detector, FID; in *m*/*z*.

*Synthesis of (1*S*)-Sulfanylmenthone* ((−)-**37**) *from* l-*Pulegone* ((−)-**36**). A reactor equipped with a thermometer and a gas-introducing tube was charged with (−)-**36** (3 g, 23 mmol) CH_2Cl_2 (30 ml) and anh. $AlCl_3$ (612 mg, 0.2 equiv.) were added, and then H_2S gas was blown through the gas-introducing tube at 60° for 3 h. After completion of the reaction, a portion of the mixture was taken out, and the conversion ratio (100%) was determined by GC.

After releasing the remaining H_2S from the mixture by N_2, a crude product was obtained in the usual way by dil. HCl treatment, washing with H_2O, and concentration. By distilling the obtained crude product under a reduced pressure (95°/600 Pa), 2.8 g (65%) of (−)-**37** was obtained with a purity of 96%.

The ratio (4*S*)/(4*R*) of this compound was 60 : 40. A 1.0-g portion of the obtained (1*S*)-8-sulfanylmenthone ((−)-**37**) with a (4*S*)/(4*R*) ratio of 60 : 40 was purified by a recycling method using GC.

*(1*S*,4*R*)-8-Sulfanylmenthone* (*cis*-form). $[\alpha]_D^{20} = -43.5$ ($c = 1.3$, MeOH). IR (neat): 1709, 2583. ^{1}H-NMR ($CDCl_3$): 1.02 (*d*, $J = 6.35$, 3 H); 1.40 (*s*, 6 H); 2.30 (*s*, 1 H). MS (*m*/*z*): 153 ($[M - SH]^+$).

*(1*S*,4*S*)-8-Sulfanylmenthone* (*trans*-form). $[\alpha]_D^{20} = +29.6$ ($c = 1.5$, MeOH). IR (neat): 1709, 2583. ^{1}H-NMR ($CDCl_3$): 0.96 (*d*, $J = 7.15$, 3 H); 1.40 (*s*, 3 H); 1.45 (*s*, 3 H); 2.35 (*s*, 1 H). MS: 153 ($[M - SH]^+$).

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