Leaf Alcohol Preparation

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cis-Hex-3-en-1-ol and *trans*-hex-3-en-1ol are called leaf alcohols, though their aromas resemble freshly cut grass. Perfumers define their aroma more precisely: *cis*-hex-3-en-1-ol has powerful and intensely green grassy odor.[1] Traces of *cis*-hex-3-en-1-ol are used in refreshing top notes in delicate floral fragrance types such as muguet and lilac; in addition, the alcohol is often used alongside geranium oil, galbanum, oakmoss, lavender and mint oils. *trans*-Hex-2-en-1-ol is powerful, fruity-green, slightly caramellic-fruity in its undertone, with an overall odor often compared to that of chrysanthemum foliage, or wine leaves. In flavors, traces are used in fruit complexes such as artificial strawberry.

The alcohols' specific fragrant properties are determined by the presence of a double bond and geometric isomery on the molecule. *cis*-Hex-3-en-1-ol has a very pleasant fragrance, though the *trans* isomer has an oily touch and is not used in fragrance compositions. *trans*-Hex-2-en-1-ol lacks typical "green" odor, but is more fruity.

Leaf Alcohol Preparation

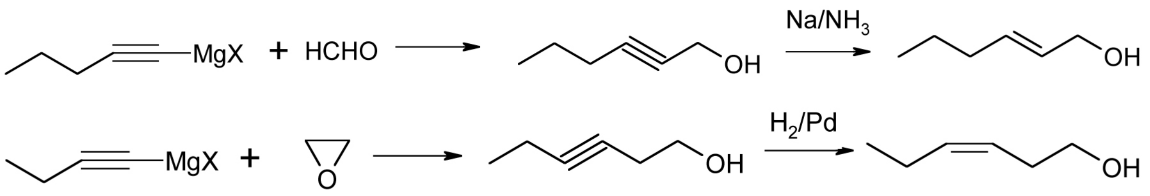
Leaf alcohol syntheses are difficult due to desired stereospecificity, the many steps involved in processing and low yields. The most common technological processes consist of a hexyn-1-ol preparation followed by selective catalytic hydrogenation or partial chemical reduction. Hydrogenations using poisoned palladium catalysts primarily produce *cis* isomers, while reductions using sodium in liquid ammonia yield *trans* isomers (**F-1**). Remains of hexynol can be banished using mercury salts.[2] Partial reduction of the triple bonds in acetylenic compounds can be stereoselectively realized using Zn powder activated by 1,2-dibromethan in absolute ethanol.[3,4] The short reaction times and simplicity of method are its primary advantages, contrary to catalytic hydrogenation. Another selective reduction of alkynes to *cis*-alkenes is based on a reduction system of hydrosilane functions immobilized on silicagel with acetic acid and a palladium catalyst, or on using an insoluble Pd(II) salicylidenethylendiamine (salen) complex.[5,6]

cis-Hex-3-en-1-ol Preparations

cis-Hex-3-en-1-ol was first synthesized via the reaction of 1-butyne with sodium in liquid ammonia, forming natriumcyanid. This was then reacted with oxiran; hex-3-yn-1-ol was then prepared by hydrolysis. Preparations of *cis*-hex-3-en-1-ol used up to now are based on the partial hydrogenation of hex-3-yn-1-ol.[7-9] Lindlar-type catalysts are used for partial hydrogenation of the triple bond to double bond. These supported catalysts have a Pd component partially deactivated by lead. $CaCO_3$ is used as a support (optionally, aluminum oxide). Partial hydrogenation of hex-3-yn-1-ol is carried out using high pressure (10 MPa) in the presence of water and hydroxide or a basic salt of alkali metal.[10] In a typical experiment, 98.2% of *cis*-hex-3-en-1-ol was obtained.

It is possible to prepare *cis*-hex-3-en-1-ol via a two-step synthesis using penta-1,3-diene and formaldehyde.[11,12] The first step is a Diels-Alder's reaction in which penta-1,3-diene and paraformaldehyde are warmed with hydroquinone in an autoclave (240°C), forming 2-methyl-5,6-dihydro-2H-pyran (yield 51.5%).[12] The second step is reductive splitting of obtained pyrane using metal lithium in ethylamine (-78°C) or reduction using dissolved metal (**F-2**).[13] Using this type of reduction

Leaf alcohol preparation from alkynes **F-1**

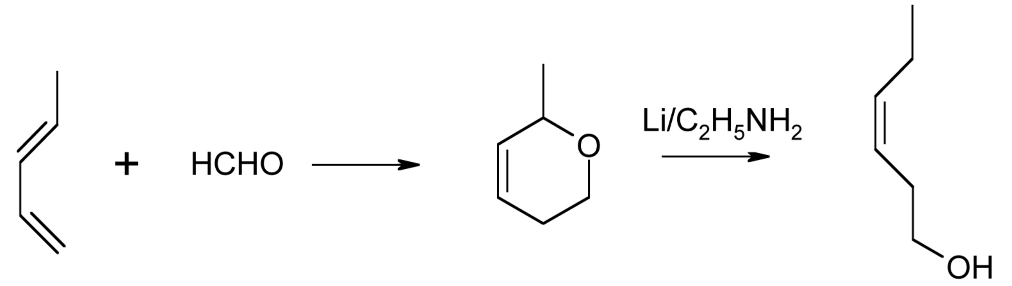


(calcium as a metal in ethylenediamine), the C-O bond can be selectively split to produce the desired *cis*-hex-3-en-1-ol with a yield of 60%. A mixture of *cis*- and *trans*-hex-3-en-1-ols can be prepared using hydrogenation and acetolysis of 4-(1-propenyl)-1,3-dioxane in an acidic medium.[14] 4-(1-Propenyl)-1,3-dioxane can be prepared by a Prins reaction using formaldehyde and 1,3-pentadiene and catex KU-2 in an acidic medium (H_2SO_4): temperature, 25°C; pressure, 2 MPa; yield, 49.8%.[15] Next, 4-propyl-1,3-dioxane was prepared by hydrogenation using Raney-nickel at 100°C. This, paired with acetic anhydride, produces 1,5-diacetoxy-3-propyl-2-oxopentane (66%). In the presence of sulfuric acid in vacuum, the acetates of *cis*- and *trans*-hex-3-en-1-ols are formed (64%). Performing hydrolysis using a water solution of KOH, the following product was obtained: 66.5% *trans*-hex-3-en-1-ol, 22.1% *cis*-hex-3-en-1-ol and 11.4% of a mixture of *cis*- and *trans*-hex-2-en-1-ols. Another possible way to prepare a mixture of *cis*- and *trans*-hex-3-en-1-ols is a vinyloxetans ring opening using organometallic compounds. By splitting 2-vinyloxetane by methylmagnesiumbromide with 5% of CuI in THF, the yield of the desired mixture (*trans:cis* = 73:27) was 72%. Alkylcopper and alkylbor form the *trans* isomer, while methylithium and phenyllithium prefer the *cis* isomer.[16] To produce *cis*-hex-3-en-1-ol, a preparation from acetylene and triethylaluminium can be used (**F-3**). Their mutual reaction in a nitrogen atmosphere (pressure 191 MPa, temperature 35°C) yielded diethyl-1-butenylaluminium. Subsequent reaction of diethyl-1-butenylaluminium with oxiran in different solvents (benzene, benzene-THF, 1,4-dioxane) obtained varying yields of *cis*-hex-3-en-1-ol (27%, 53%, 43%).[17,18] *cis*-Hex-3-en-1-ol preparation from anisol consists of a Birch reduction, oxidative ring opening and reduction using $NaBH_4$ (**F-4**).[19,20] The first step is the reduction of the anisol aromatic ring to 1-methoxy-1,4-cyklohexadien. Selective oxidative partitioning of the methoxy-substituted double bond forms an equimolar amount of ozone methyl-6-oxo-*cis*-hexenoate via the reduction of the aldehydic group, producing methyl-6-hydroxy-*cis*-hexenoate. This transforms to p-toluensuplhonic acid ester and, following selective reduction, $LiAlH_4$ yields *cis*-hex-3-en-1-ol.

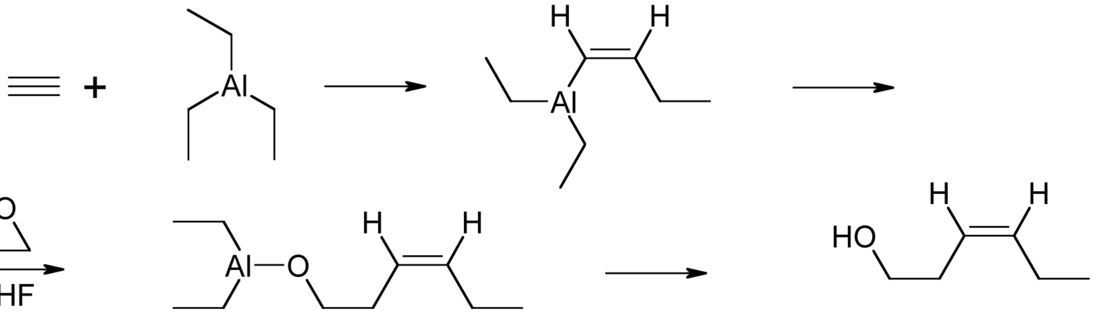
trans-Hex-2-en-1-ol Preparation

trans-Hex-2-en-1-ol can also be prepared by partial triple bond reduction of hex-2-yn-1-ol. *Cis*- or *trans*-hex-2-en-1ols can be prepared by the chemoselective reduction of hex-2-enal. Bis(cyclopentadienyl)zirconiumhydride or bis(cyklopentadienyl)-hafniumhydride can be used as catalysts. These materials possess catalytic activity for the Meerwein-Ponndorf-Verley method of reducing α-, β-unsaturated aldehydes to alcohols.[21] This selective reduction of aldehyde to alcohol can be also realized in the presence of propan-2-ol and ZrO_2.[22] Stereoselective preparation of *trans*-hex-2-en-1-ol can be realized by the addition of PhSLi to 1-nitropent-1-ene in THF and by adding the formed carbanion to methanal when the *anti*-izomer of 3-phenylthio-2-nitrohexan-1-ol is formed (**F-5**). The radical elimination of this isomer produces *trans*-hex-2-en-1-ol (99% purity).[23]

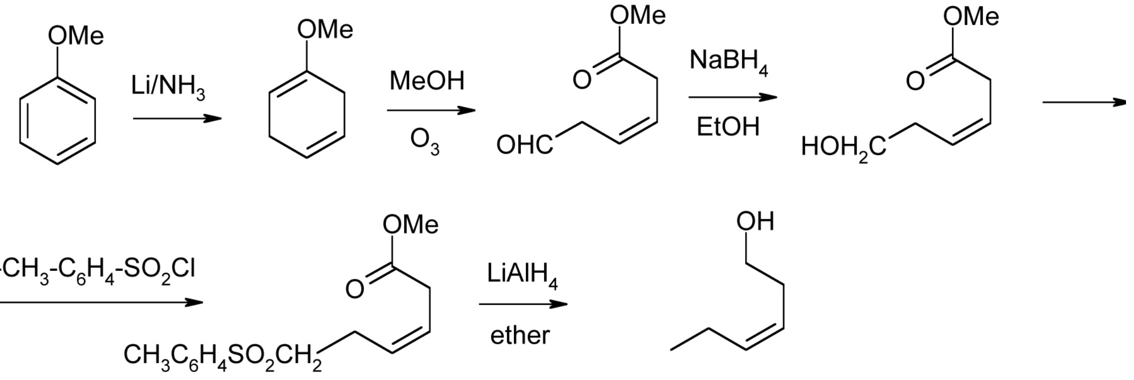
F-2 *cis*-Hex-3-en-1-ol preparation from pentadiene



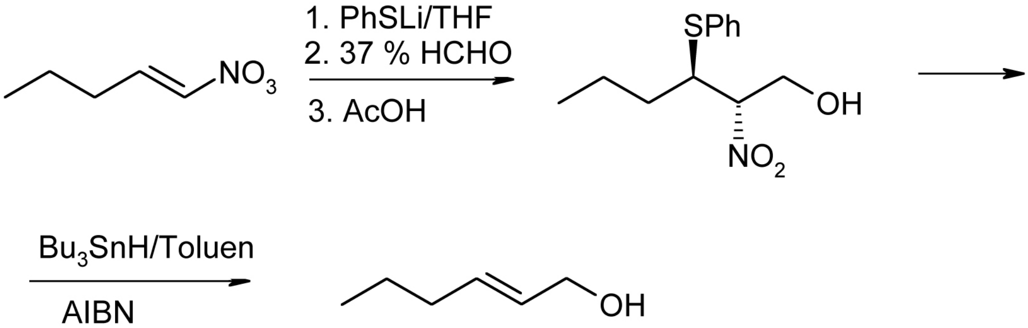
F-3 *cis*-Hex-3-en-1-ol preparation by trialkylaluminium



cis-Hex-3-en-1-ol preparation from phenylmethylether **F-4**



trans-Hex-2-en-1-ol preparation from nitrate **F-5**



Leaf Alcohol Preparations from Sorbic Acid and its Derivatives

The methods of leaf alcohol preparation starting from *trans,trans*-hex-2,4-dienoic acid appear advantageous due to the accessibility of the initial substance and small amount of reaction steps. There are two synthetic ways to obtain fragrant hexenols from methyl sorbate. [24] The first consists of a carboxylic group chemical reduction followed by catalytic hydrogenation of the dienic system. In the second case, the dienic system is hydrogenated at first, followed by the reduction of the carboxylic group of hexenoic acid (**F-6**).

Hydrogenations Catalyzed by Heterogeneous Catalysts

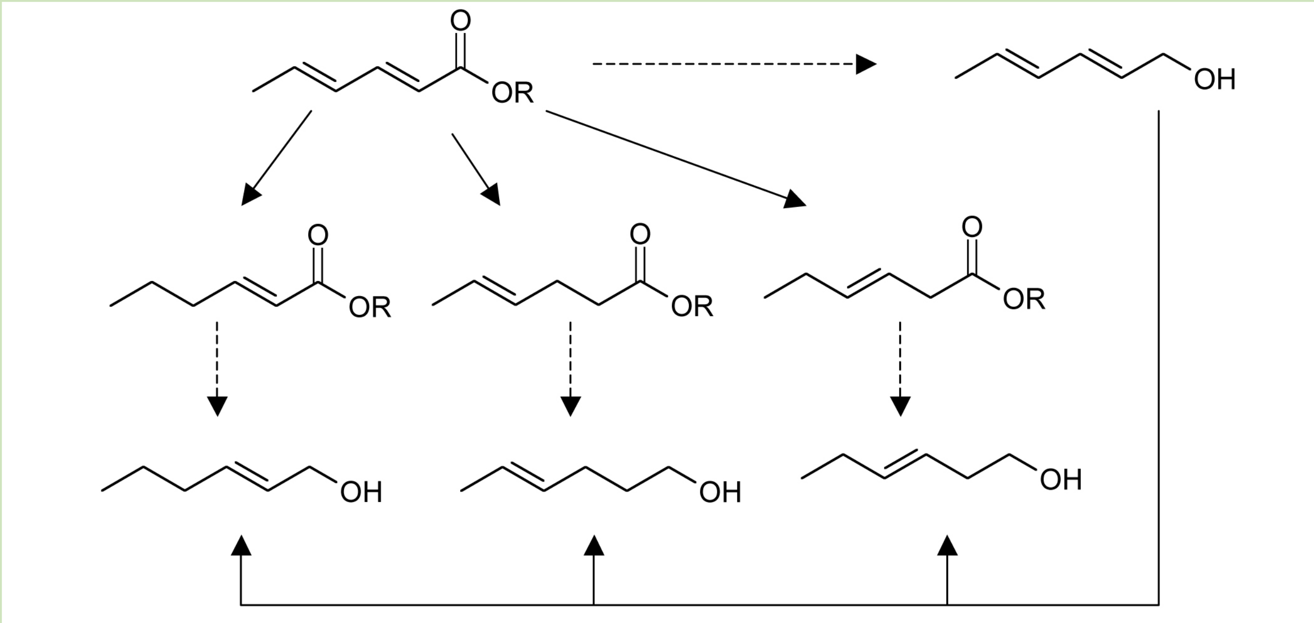
The first work dealing with sorbic acid hydrogenation using noble metal catalysts had only one product—saturated hexanoic acid.[25] Later work produced hydrogenated sorbic acid with relatively high selectivity to hex-2-enoic acid (Ra-Ni and palladium as catalysts).[26] The best catalyst was Pd/$BaSO_4$ (selectivity to hex-2-enoic acid 89.6%). Comparison of sorbic acid and its sodium salt showed a higher reaction rate of sorbic acid hydrogenation but higher selectivity using its sodium salt. Using Raney-nickel as a catalyst, the selectivity to hex-2-enoic acid was 83%. Using a platinum catalyst (Adams catalyst), only hexanoic acid was obtained. [27]

Other authors have realized methylsorbate hydrogenation using different commercial metal catalysts on active charcoal.[28-31] Using platinum, rhodium and ruthenium catalysts, only methyl-*trans*-hex-2-enoate (27–29%) and methyl-*trans*-hex-3-enoate (4–9%) were obtained. The palladium catalyst netted the best results—79% methyl-*trans*-hex-2-enoate and 16% methyl-*trans*-hex-4-enoate.

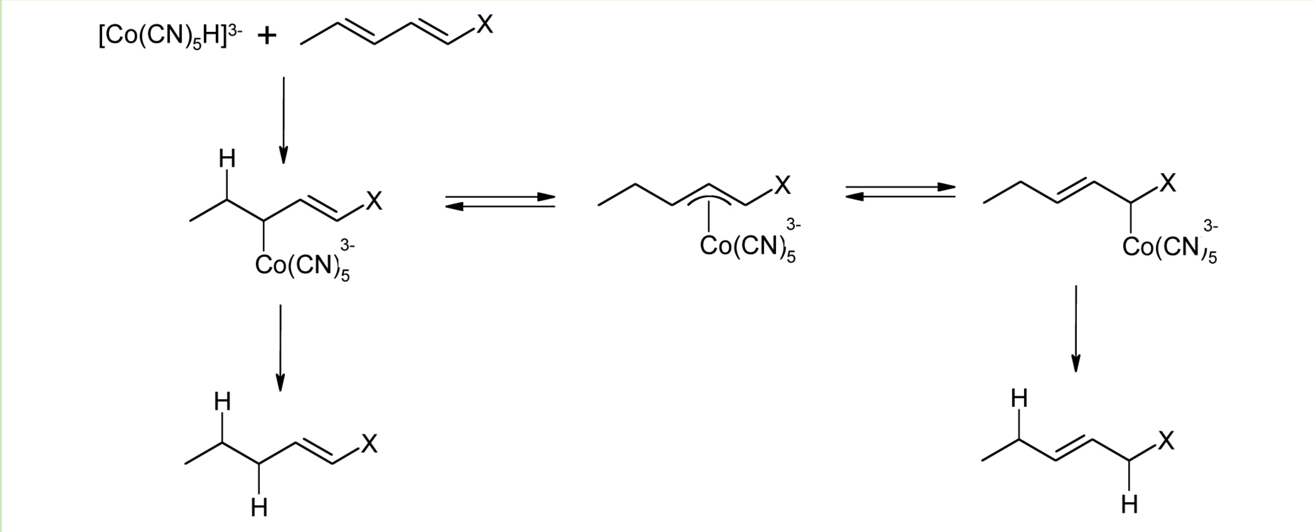
All papers mentioned above share the fact that, after total methyl sorbate conversion, the unsaturated products were consecutively hydrogenated to saturated hexanoic acid. It is possible to prepare only *trans*-hex-2-enoate, regioselectively. The double bond in position 2 is in conjugation with the carboxylic function, and its hydrogenation is less probable than hydrogenation of the double bond in position 4.

The hydrogen addition course to methyl sorbate was monitored using ruthenium and palladium black as catalysts.[32] These heterogeneous catalysts were compared with a homogeneous [$RhCl_2(PPh_3)_3$] complex. Using these catalysts, methyl hex-2-enoates and hex-3-enoates were formed. Palladium black displayed the highest selectivity. Ruthenium complex displayed the lowest selectivity; using ruthenium black, methyl-hexanoate was formed from the beginning of the reaction. The ruthenium complex catalyzed the addition of 4,5- and 2,5-hydrogen, forming a mixture of methyl-hex-2-enoate and hex-3-enoate. Using palladium black added the 4,5-hydrogen, forming

Sorbic acid reduction (or its derivatives) with following catalytic reduction (no izmoeration steps included); dash arrows = chemical reduction, full arrows = hydrogenation **F-6**



Hydrogenation of dienes using [CoIII(CN)5H]3- **F-7**



methyl-hex-2-enoate. With these catalysts present, the 2,3-hydrogen addition to double bond (which is in conjugation with carboxylic group) did not take place.

Hydrogenations Catalyzed by Homogeneous Catalysts

$K_3[Co(CN)_5]$ was the homogeneous catalyst used for sorbic acid hydrogenation.[33,34] Sorbic acid was selectively hydrogenated to *trans*-hex-3-enoic acid. Later work has selectivity defined more exactly by GC—(in water) 82% *trans*-hex-2-enoic acid, 17% *trans*-hex-3-enoic acid, and 1% *trans*-hex-4-enoic acid.[35] Using methanol as a solvent meant that the hydrogenation was more selective—95% *trans*-hex-2-enoic acid. The active catalyst particle was $[Co^{III}(CN)_5H]^{3-}$ (**F-7**). Formation both of hex-2-enoic and hex-3-enoic acid was attributed to the rearrangement of the intermediate.[36]

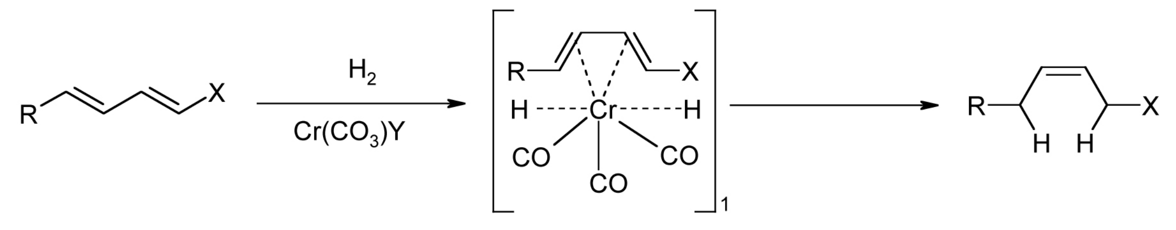
The influence of phase transfer catalysts was also studied.[37] Methyl sorbate hydrogenation in a two-phase system of water-dichloromethane yielded methyl-*trans*-hex-2-enoate and *trans*-hex-3-enoate in proportions of 65:35. The presence of benzyltriethylammonium chloride in the same two-phase system produced methyl-*trans*-hex-3-enoate at a level of 75%. The same result was obtained by Alper and Lee who used β-cyclodextrine as a phase transfer catalyst in a kalium-sorbate hydrogenation.[38]

The rhodium catalyst (room temperature, pressure 0.3. MPa, Wilkinson's catalyst) was used for sorbic acid hydrogenation using alkali conditions.[39] $[RhCl(PPh_3)_3]$ produced only hexanoic acid, even in low conversions. Complex $[RhCl(PPh_3)_2\ (Ph_2POOCH_2CH{=}CMe_{2)}]$ (evolved from Wilkinson catalyst by PPh_3 ligand exchange) produced, after total sorbic acid conversion, 52% *trans*-hex-4-enoic aid and 48% hexanoic acid. The later complex was even more active. The other of rhodium catalyst used was $[H_2Rh(Ph_2N_3(PPh_3)_2]$.[40] Using DMSO as a solvent, *trans*-hex-2-enoic acid was obtained with small amounts of *trans*-hex-3-enoic acid. The unsaturated acid was entirely hydrogenated to hexanoic acid using temperatures above 50°C.

Heinen prepared a water-soluble ruthenium complex $\{RuCl_2[P(CH_2CH_2OH)_3]_2\}$, which was able to catalyze in a two-phase system of water-ethylacetate sorbic acid hydrogenation to *trans*-hex-4-enoic acid with 82% selectivity.[41] Methyl-sorbate hydrogenation to methyl-*cis*-hex-3-enoate was realized using complexes $[Cr(CO)_3]$, $[Cr(CO)_6]$, $[W(CO)_3]$ and $[Cr(arene)(CO)_3]$ (**F-8**).[42] The activity of complexes differed due to the ligands, but selectivity was not dependent on ligand type. The best activity result produced a complex with methyl-3-methoxybenzoate as an arene ligand. Selectivities were in range of 91.8–98.8% of methyl-*cis*-hex-3-enoate. It was

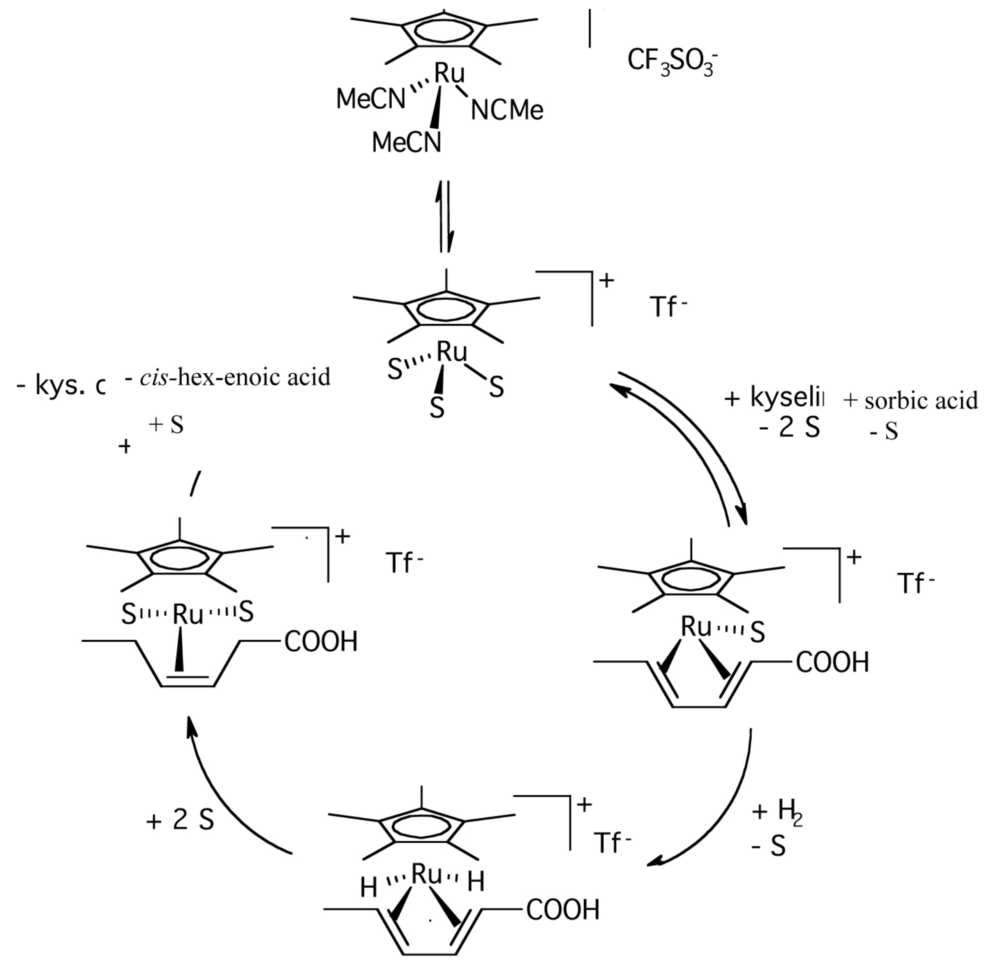
Hydrogenation of dienes using [(arenee)Cr(CO)3] complexes
S = molecule of solvent (THF, acetone), X = CO2Me, Y = arene

F-8



Mechanism of sorbic acid hydrogenation to *cis*-hex-3-enoic acid

F-9



found that an arene ligand is not necessary, because the complex [Cr(cycloheptatriene)$(CO)_3$] had higher activity than [Cr(arene)$(CO)_3$] complexes. It was proved that hydrogen was added to sorbate 2- and 5-carbon atoms.[43] 1,2- Addition and consecutive isomeration did not take place. Based on results mentioned above, the mechanism accepted up to now was formulated. It was found that electron-acceptor groups of arene accelerate the hydrogenation reaction and conversely electron-donor groups decrease catalysts' activity.[44] More distinct was the effect of using Cr complexes with polyaromatic compounds such as naphthalene, anthracene and phenanthrene. The most active complex up to now has been [Cr(naphthalene)$(CO)_3$], which can catalyze selective hydrogenation of methyl-sorbate at 30°C and 0.1 MPa.[45,46] In the most recent literature, the Cr complex with similar activity was synthesized $[\mathrm{Cr(C_6H_6)(CH_2{=}CHCOOCH_3}]$.[47] Utilization of chromium-carbonyl complexes has many disadvantages. The most serious problem is toxicity, low activity and no possible hydrogenation of the sorbic acid itself.

Heinen found the alternative water-soluble ruthenium complex $[\mathrm{RuCl(CO)Cp^*P(CH_2CH_2CH_2OH)_3}]$ (Cp* = pentamethylcyclopentadienyl).[48] This complex catalyzed sorbic acid hydrogenation to *cis*-hex-3-enoic acid in a two-phase system of water-heptane with selectivity of 66% (conversion 68%). The byproduct was hexanoic acid. Another complex described in this work was $[\mathrm{RuCp^*(MeCN)_3}]$Tf (Tf = trifluoromethanesulfonate). Following acetonitrile ligand dissociation, a transition state similar to those of chromium complexes is formed (**F-9**). This catalytic system produced *cis*-3-hexenoic acid with a selectivity of 67%. Due to the absence of ligands other than acetonitrile in the complex mentioned above, it was deduced that high reaction selectivity is caused only by cationic fragment RuCp*. The dienic system addition in *cis*-conformation was proved by Mashima and Fagan.[49,50] After a π-complex with sorbic acid forms, one molecule of hydrogen is added. Sorbic acid is in positions 2 and 5 in this hydride complex, directly adjusted to both hydride ligands. The transfer of hydrogen to these positions is very probable. In the last catalytic cycle step, formed *cis*-hex-3-enoic acid leaves the ruthenium center, and solvated complex RuCp* is formed. This can attach sorbic acid again.

Model complexes $[\mathrm{RuCp^*(\eta^4\text{-}MeCH{=}CHCH{=}CHCOOH)}]^+\mathrm{X}^-$ (X = Tf or $\{\mathrm{B[3,5\text{-}(CF_3)_2C_6H_3]_4}\}$) were synthesized.[51] These are very effective catalysts for sorbic acid hydrogenation to *cis*-hex-3-enoic acid and for sorbic alcohol (hexa-2,4-dien-1-ol) to *cis*-hex-3-en-1-ol (leaf alcohol) using mild conditions in a two-phase system. Obtained results showed that "naked" $[\mathrm{RuCp^*}]^+$ cation is more active than complexes used earlier.

Today, the sorbic acid and its derivatives' hydrogenation was studied using the homogeneous catalyst $[\mathrm{RuCp^*}$(dienic compound)$]^+$ in which the dienic compound is the hydrogenated substance. Using this catalyst in homogeneous arrangement, it was found that sorbic acid is hydrogenated to desired *cis*-hex-3-enoic acid; this is subsequently hydrogenated to more stable hexenoic isomers and hexanoic acid. Sorbic alcohol is hydrogenated to the desired leaf alcohol, *cis*-hex-3-en-1-ol, and isomered to unsaturated aldehyde. No subsequent isomeration was observed. Sorbic acid hydrogenation in a two-phase system was studied in more detail.[53] Sorbic alcohol hydrogenation in a two-phase system of ethyleneglycol-MTBE showed very high selectivity (up to 98%) to desired leaf alcohol because initial substance isomeration did not take place.[54] Hydrogenation of sorbic acid and sorbic alcohol was also carried out in heterogeneous arrangement. The catalyst was immobilized using two approaches: by means of hydrogen bonds on silica materials and by ionic exchange on anionic clays.[55,56] Using a catalyst immobilized by means of hydrogen bonds, sorbic acid and sorbic alcohol were hydrogenated with almost the same selectivity as in the case of homogeneous arrangement; moreover, the recycling of the catalyst was not able to be realized. On the opposite side, using a catalyst immobilized by ionic exchange on montmorillonite, the selectivity to desired *cis*-hex-3-enoic acid was very high (99% at 100% conversion). In addition, catalyst recycling was possible.

Conclusion

The classical leaf alcohol preparation beginning with acetylenic compounds is difficult, contains many operational steps and is plagued by low yields. The more promising processes start from sorbic acid and its derivatives, in which the desired alcohols are obtained by hydrogenation alternatively followed by chemical reduction. For *trans*-hex-2-en-1-ol preparation, the most simple and reasonable pathways are those from methyl sorbate hydrogenation. For *cis*-hex-3-en-1-ol preparation, the processes employing Ru complex were best. Leaf alcohol could be prepared from sorbic alcohol with a selectivity of 99%.

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