

Perfume and Flavor Synthetics

A model for research and academic-industrial cooperation

by Libor Cervený, Institute of Chemical Technology, Prague, Czech Republic

Cooperation between the Department of Organic Technology (DOT) at ICT Prague and Aroma Co. began in 1970 with research into problems with benzyl-acetate purity. The cooperative first consisted of an expert consultancy, which gradually grew into a systematic expert-research group focused on fields of basic research. The focus again moved to the field of the so-called creative-realization, before finally implicating new production processes of traditional and new perfumery substances. Original expert documents describing the obtained results were elaborated upon and today, together with about 50 authorizations, amount to approximately 80 papers.

The construction of the hydrogenation unit led to a breakthrough in the production assortment. This has occurred as a result of DOT's long scientific focus and because hydrogenation processes have particularly broad spectra of utilization in the synthesis of perfumery and flavor substances.¹ The so-called hydrocinnamic alcohol, 3-phenylpropane-1-ol was the first substance to be produced.²⁻⁶ Soon after this launch, the material found a broad utilization in perfumery compositions, becoming an advantageous export item. 3-Phenylpropane-1-ol was produced in two steps as shown by the two equations presented in F-1.

An analogous procedure was selected for the synthesis of 4-phenyl-4-methyl-1,3-dioxane, which was used for the production of 3-phenylbutane-1-ol by hydrogenolytic decomposition (F-2).^{2,3,5}

3-Cyclohexylpropane-1-ol and 3-cyclohexylbutane-1-ol were produced using hydrogenation of aromatic nuclei in both of the alcohols (F-3).⁷

All the four alcohols were used for the preparation of a number of esters; however, only esters of 3-phenylpropane-1-ol and 3-phenylbutane-1-ol with acetic acid have reached the industrial utilization.⁸⁻¹¹ Similarly, dehydrogenations of all the mentioned alcohols to relevant perfumic aldehydes have been elaborated and

consecutively used for the preparation of interesting acetals.¹² The fragrant properties of several of them, as well as fragrance properties of ethers, derived from 3-phenylpropane-1-ol have already been described.⁵

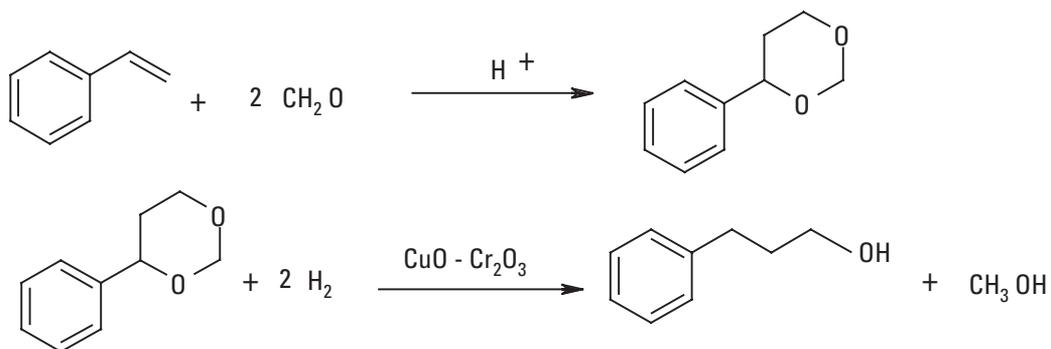
4-Phenyl-1,3-dioxane is a compound that is susceptible to a host of interesting transformations leading in some cases to compounds not yet described or substances with not yet described fragrance properties.⁵⁻¹⁴ Its acidolysis to 1-phenylpropane-1,3-diol-diacetate with the consequent re-esterification to 1-phenylpropane-1,3-diol, which is a very efficient repellent, has already been verified in a pilot system (F-4).

A number of new cyclic acetals with interesting fragrance properties, and naturally with excellent stability in alkaline environment, were prepared from 1-phenylpropane-1,3-diol.⁵ The transformations of 4-phenyl-1,3-dioxane on various catalysts are interesting. Besides the above-mentioned hydrogenolytic decomposition to 3-phenylpropane-1-ol, decomposition on palladium catalyst to 1-phenylpropane-1-one (propiophenone) and aluminosilicate catalyst to allylbenzene¹⁶ were discovered — both with high selectivity (F-5).^{3,15}

3-Phenylpropane-1-ol is a typical perfumery substance and an intermediate for other perfumery substances, whereas propiophenone and allylbenzene are semi-products with good opportunity for use in the synthesis of pharmaceuticals and herbicides. The decomposition of 4-phenyl-4-methyl-1,3-dioxane brings about more problems, and except the above-mentioned hydrogenolysis to 3-phenylbutane-1-ol, all

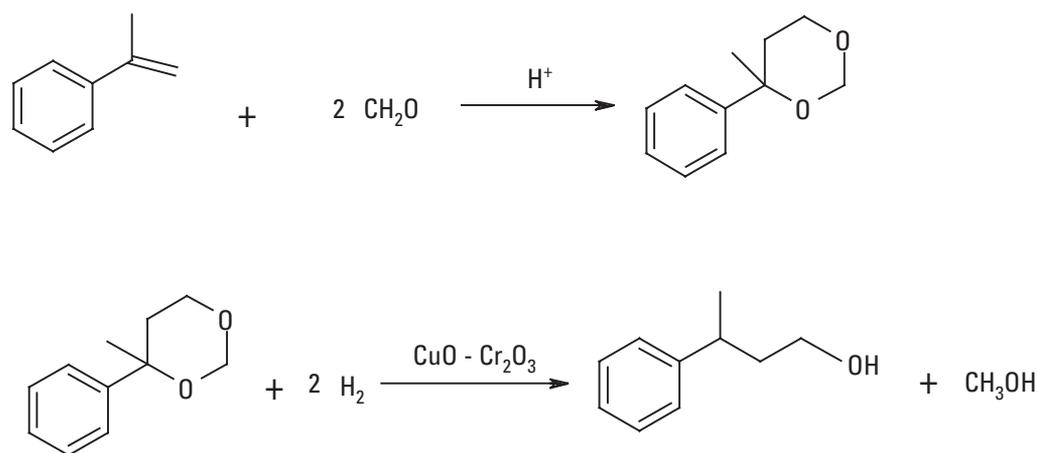
The two-step production of 3-phenylpropane-1-ol

F-1



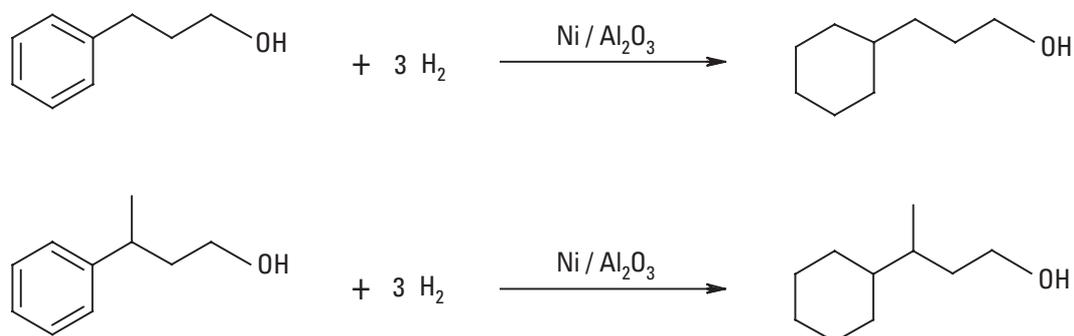
The synthesis of 4-phenyl-4-methyl-1,3-dioxane, which was used for the production of 3-phenylbutane-1-ol by hydrogenolytic decomposition

F-2



3-Cyclohexylpropane-1-ol and 3-cyclohexylbutane-1-ol were produced using hydrogenation of aromatic nuclei in both of the alcohols

F-3



attempts for analogous transformations were not successful.¹⁷

Following the above works, research on new substances based on 4-alkylstyrenes was initiated.¹⁸⁻²⁰ These materials were acquired using acylation of alkylbenzenes by acetic anhydride, followed by hydrogenation to relevant secondary alcohols and, finally, dehydration. Then, 4-alkylstyrenes were subjected to the Prins' reaction with formaldehyde; the resultant substituted 1,3-dioxanes were decomposed in the sense of transformations with 4-phenyl-1,3-dioxane. A number of new fragrance substances were acquired.^{18,19} New fragrance substances were also prepared from the above secondary alcohols.²⁰

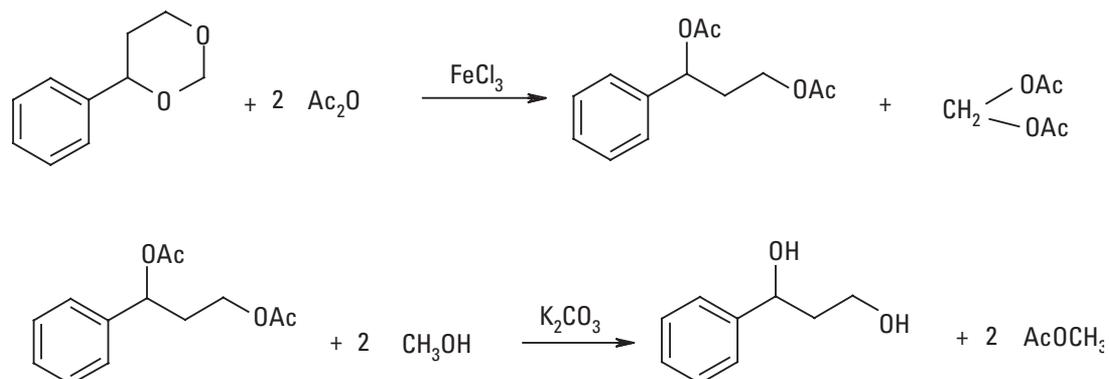
Production technology of 1-phenylethanol by acetophenone hydrogenation²¹ was elaborated by DOT and materialized in the Zidovice plant; selective hydrogenation of 2-ethylhex-2-enal to 2-ethylhexanal has gone through a shorter production period. To the contrary, selective hydrogenations of citral to citronellol and a mixture of citronellal, citronellol, geraniol and nerol have been solved on a laboratory scale but not yet materialized, especially for the reasons of price shifts on world markets. The resolved²² selective hydrogenations of dehydrolinalool and dehydrolinalyl-acetate to linalool and linalyl-acetate have so far experienced the same fate. Cyclization of citronellal to isopulegol and its subsequent hydrogenation to menthol is among the procedures verified in a large-scale plant.

Another scientific problem that has been solved is the chemoselective hydrogenation of C=C bonds located next to C=O bonds. It is the main benzyldiene double bond in the products of condensation of benzaldehyde with acetone and the double bond in the products of condensation of cyclopentanone with aliphatic aldehydes. Common perfumery and flavor substances generally result from this, including Jasmamol, Frambinone, Zingerone and alkylcyclopentanones, which are used as intermediates for production of fragrant lactones.

The research was also focused on the opposite problem, i.e. the chemoselective hydrogenation of the carbonylic function next to the double bond C=C. This hydrogenation is more complicated because it requires specific catalytic systems; in addition, the chemoselectivities are typically higher than in the previous case. Hydrogenation of cinnamic aldehyde to cinnamic alcohol was studied, and to a greater extent, the research on hydrogenation of methylester of sorbic acid (trans,trans-hexa-2,4-dienic) was initiated.²³⁻²⁵ This hydrogenation is very interesting in regards to the production of methylesters of cis-hex-3-enic and *trans*-hex-2-enic acids. These can be chemically reduced (LiAlH_4) to the relevant alcohols. These alcohols, the so-called leave alcohols, are very precious and difficult-to-synthesize substances. On the other hand, the reaction schema is rather complicated (kindly see its simplified form in F-6); the treatment of the reaction mixtures requires a very efficient rectification.

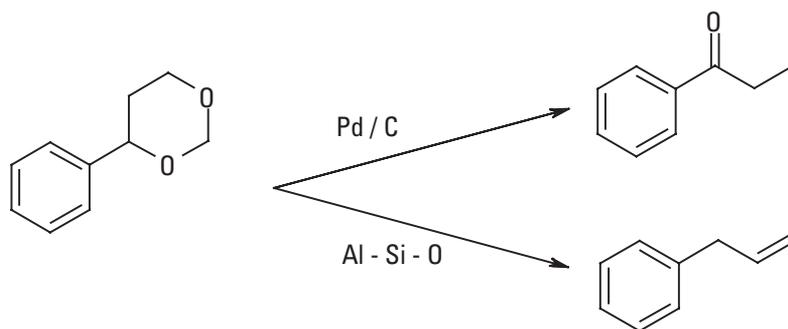
4-Phenyl-1,3-dioxane's acidolysis to 1-phenylpropane-1,3-diol-diacetate with the consequent re-esterification to 1-phenylpropane-1,3-diol (which is a very efficient repellent) has been verified in a pilot system

F-4



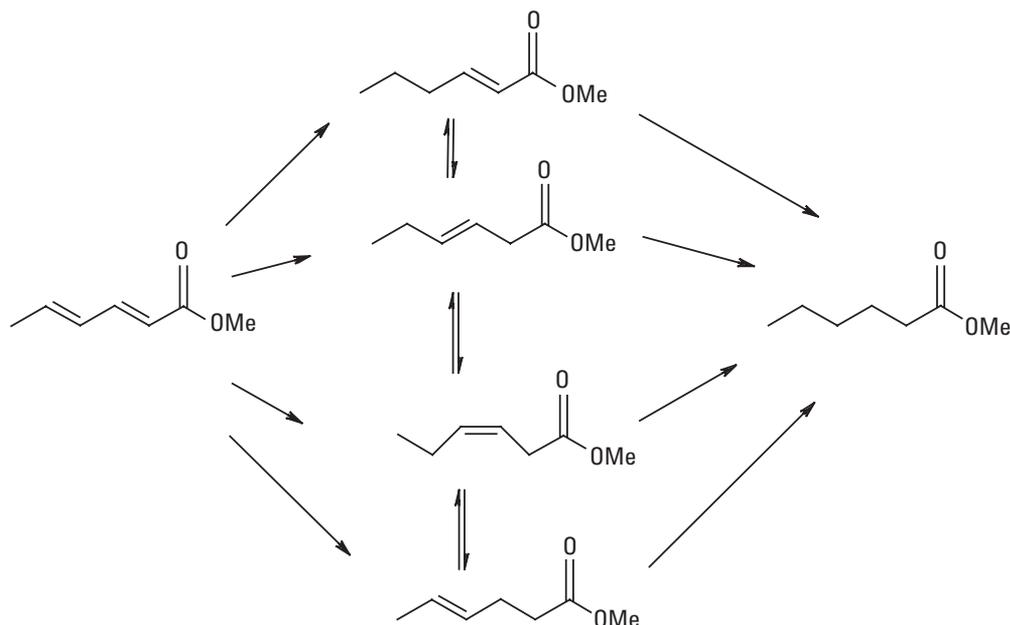
Decomposition of 4-phenyl-1,3-dioxane on palladium catalyst to 1-phenylpropane-1-on (propiophenone) and aluminosilicate catalyst to allylbenzene

F-5



The simplified reaction schema of the sorbic acid methylester hydrogenation leave alcohols

F-6



Alternatively, although it shows rather worse results, hydrogenation of trans,trans-hexa-2,4-diene-1-ol to relevant hexenols has been studied.²⁶ The starting dienol is again prepared by chemical reduction of methylester of sorbic acid using LiAlH_4 . The quantity of side products in this case is higher than during hydrogenation of methylester of sorbic acid, since isomerization of unsaturated alcohols to aldehydes occurs in addition to alcohol hydrogenolysis, or its dehydration followed by hydrogenation of the double bond.

Increased attention was in the past paid to modern ways of introducing aldehyde group to aromatic nucleus, especially in regards to the production of ethyl-vanillin, but also to heliotropine and 4-hydroxybenzaldehyde.^{27,28} In the 1980s, an original procedure for the production of 2-ethoxyphenol, the intermediate of ethyl-vanillin, was worked out by DOT.²⁹⁻³⁴ The first two steps have already been verified using pilot system testing (F-7).

In the laboratory scale, utilization of 2-ethoxyphenol for synthesis of fragrant allylether was studied (F-8).

In the period of systematic research on opportunities for utilization of domestic resources and waste products for perfumery substance production, three technological procedures have been elaborated by DOT:

A: methyl-benzoate, the waste product from the production of dimethyl-terephthalate, was re-esterificated by some alcohols to higher esters

B: 4-methylpent-3-en-2-one (mesityloxide), the waste product from the production of vitamin C, was treated by alkaline condensation to the mixture of isoxylithones, i.e. substances with fragrant properties (F-9)

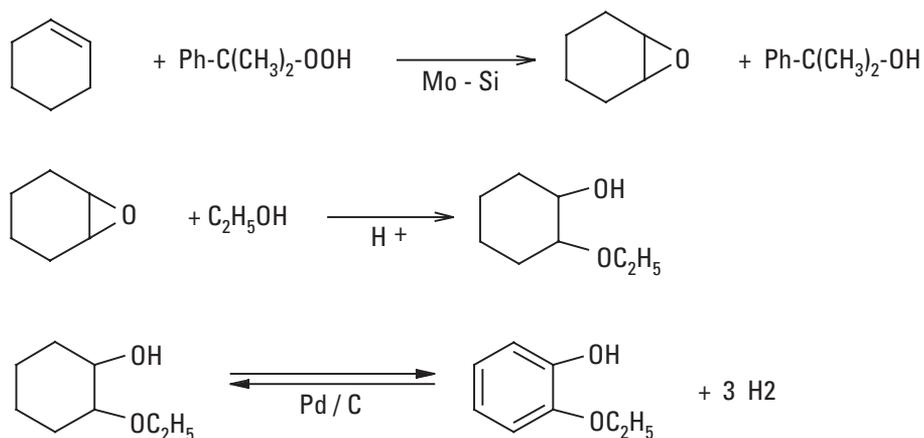
C: 2-phenylpropene, the waste product from the production of cumenic phenol, treated with formaldehyde in an environment of acetic anhydride and acetic acid, was transformed to a mixture³⁵ of fragrant phenylbutenyl-acetates (F-10)³⁵

At present, Aroma Co.'s key materials are Arol and Arocet, which are mixtures of the stereoisomers of 2-tert-butylcyclohexanol and its acetate, respectively (F-11). These are produced using catalytic hydrogenation of 2-tert-butylphenol, which was elaborated at DOT. From the commercial point of view, the ratio of *cis/trans* isomers has a fundamental significance, which, although it can be influenced by rectification, is more economically enacted by conducting the hydrogenation so that the required representation is achieved directly. The reason for this is the difference in fragrance characteristics of the two isomers, which illustrates that demands are derived from product contents. The discovery of a possibility for modest adjustment of the above-mentioned ratio is an important key to this technology. The resultant product is a fundamentally important export item for Aroma Co.; the production has continually increased. At present, several hundred tons is produced annually.

Although it is apparent that the dominant product

The three-step original procedure for the production of 2-ethoxyphenol, the intermediate of ethyl-vanillin

F-7



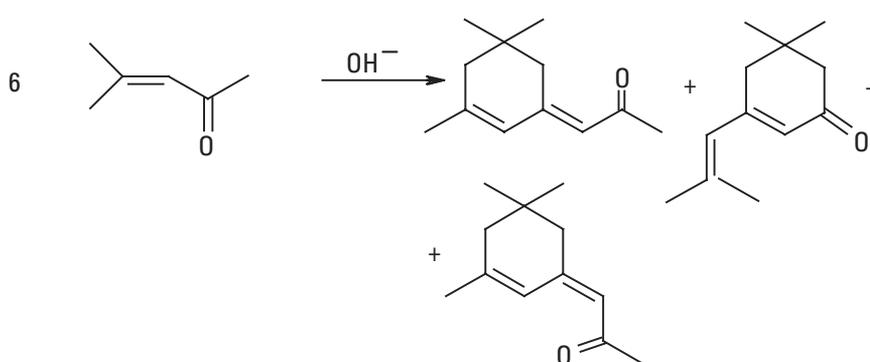
In the laboratory scale, utilization of 2-ethoxyphenol for synthesis of fragrant allylether was studied

F-8



4-Methylpent-3-en-2-one (mesityloxide), the waste product from the production of vitamin C, was treated by alkaline condensation to the mixture of isoxylithones, i.e. substances with fragrant properties

F-9



will continue to be the mixture of stereoisomers of 2-*tert*-butylcyclohexyl-acetate, other possibilities of utilization of 2-*tert*-butylcyclohexanol are being sought. For instance, its derived carbonates have compelling possibilities.

The hydrogenation of 2-*tert*-butylphenol can be carried out so that 2-*tert*-butylcyclohexanone (F-12), which can be separated using rectification, is pro-

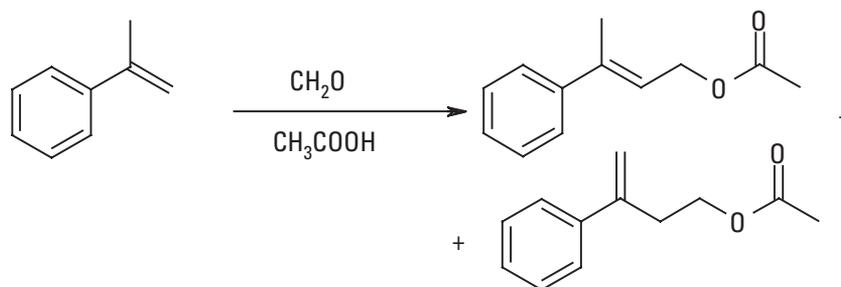
duced as well. Alternatively, this ketone can naturally be the main hydrogenation product. Its utilization in regards to preparation⁴⁶ of cyclic ketals is also interesting.

Several other alkylated phenols produced by Schenectady Co. were recently hydrogenated to alcohols or ketones (F-13).

Another scientifically resolved technology of production of allyl-3-cyclohexylpropanoate is prepared for testing in a large-scale plant. The pineapple scent of

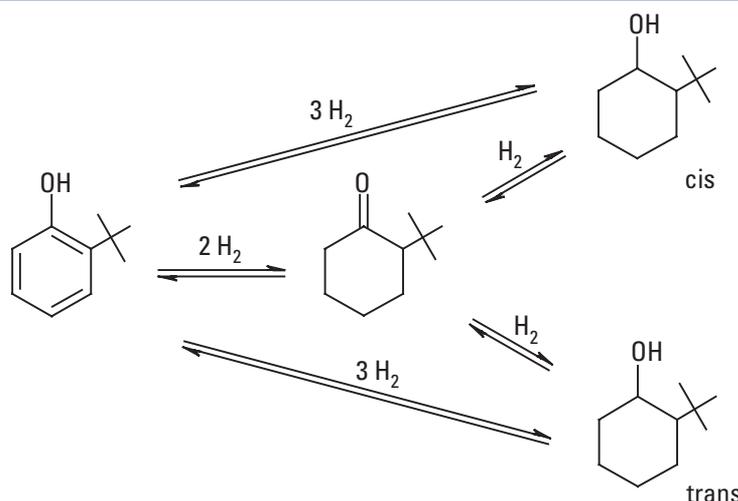
2-Phenylpropene, the waste product from the production of cumenic phenol, treated with formaldehyde in an environment of acetic anhydride and acetic acid, was transformed to a mixture of fragrant phenylbutenyl-acetates³⁵

F-10



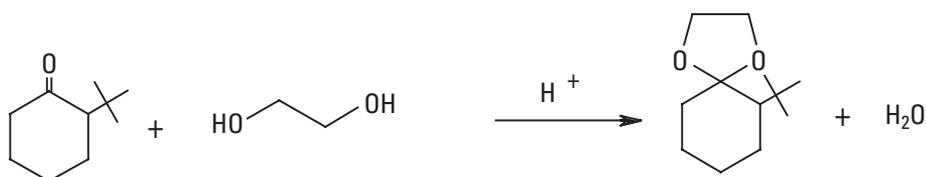
Reaction scheme of 2-*tert*-butylphenol hydrogenation; the main product is a mixture of *cis* and *trans* 2-*tert*-butylcyclohexanols, but 2-*tert*-butylcyclohexanone also should be produced by this way

F-11



2-*tert*-Butylcyclohexanon, separated using rectification from the mixture with 2-*tert*-butylcyclohexanols, can be transformed, for example, to cyclic ketals

F-12



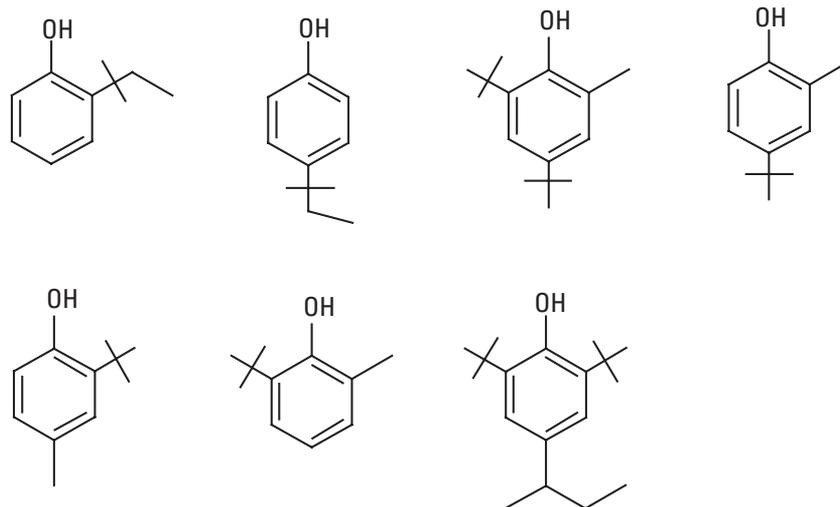
this substance makes it attractive. Its relatively simple production procedure elaborated in DOT was not found in the chemical literature. The starting compound is methylester of cinnamic acid; its C=C bond and aromatic ring are hydrogenated in the first step. In the next, allyl-3-

cyclohexylpropanoate is produced using re-esterification by allyl alcohol (F-14).

The cooperation of COT with Aroma Co. and Aroco Co. is an example of mutual, long-term and systematic advantageous cooperation of an academic workplace with industrial companies. Three years ago, cooperation with Miltitz Aromatics GmbH began. A

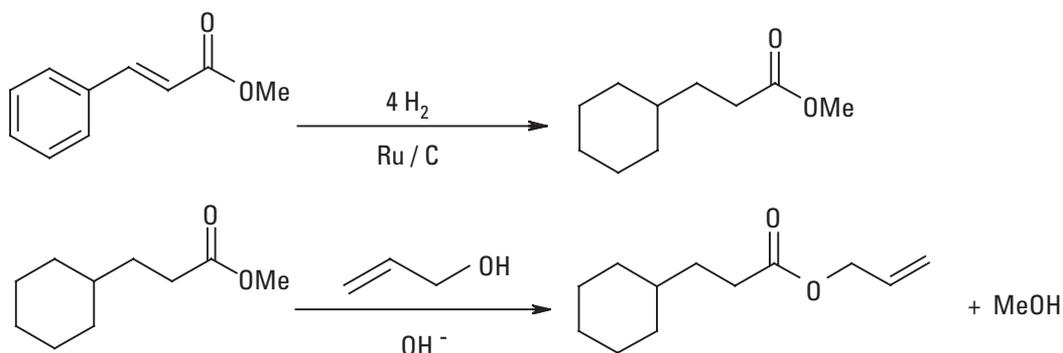
Several alkylated phenols produced by Schenectady Co. were recently hydrogenated to alcohols or ketones

F-13



The production of allyl-3-cyclohexylpropanoate: the starting compound is methyl ester of cinnamic acid; its C=C bond and aromatic ring are hydrogenated in the first step; in the next, allyl-3-cyclohexylpropanoate is produced using re-esterification by allyl alcohol

F-14



number of laboratory results have found use in industrial practice, especially due to targeted research. In addition, there has always been room for scholastic activities. Students of DOT have been broadly involved in the research; many of them not only remained loyal to the major they graduated from but also found use directly in the science, R&D or production of synthetic perfume and flavoring substances.

Address correspondence to Libor Cervený, Department of Organic Technology, Institute of Chemical Technology, 166-28 Prague 6, Czech Republic.

References

1. Červený L., Růžička V., *Fette, Seifen, Anstrichm.* 85, 362 (1983).
2. Červený L., Marhoul A., Růžička V., Dolník J., Sma V.: CS 189 945 (1978).
3. Červený L., Marhoul A., Růžička V.: *J. Prakt. Chem.* 319, 601 (1977).
4. Červený L., Wurzelová A., Marhoul A., Růžička V.: *J. Chem. Technol. Biotechnol.* 34 A, 311 (1984).
5. Červený L., Marhoul A., Růžička V.: *Perfum. Flav.* 11, 9 (1986/87).
6. Červený L., Marhoul A., Růžička V., Sma V.: CS 224 183 (1983).
7. Červený L., Marhoul A., Sma V.: CS 277 281 (1992).
8. Červený L., Marhoul A., Kovářová L., Havlíček V.: *Cosmet. Aerosols Toilet. Austral.* 5, 21 (1990).

9. Červený L., Marhoul A., Winklerová P.: *Perfum. Flav.* 16, 37 (1991).
 10. Červený L., Duben B., Marhoul A., Růžička V.: *Chem. Prům.* 28, 582 (1978).
 11. Červený L., Kačer P., Kalinová L., Valentová M., Pokorný J.: *Seifen, Ole, Fette, Wachse* 122, 612 (1996).
 12. Červený L., Marhoul A., Hrdličková L.: *Perfum. Flav.* 16, 41 (1991).
 13. Červený L., Marhoul A., Růžička V.: *Chem.- Ztg.* 105, 251 (1981).
 14. Červený L., Marhoul A., Růžička V.: *Chem. Prům.* 30, 127 (1980).
 15. Červený L., Marhoul A., Růžička V.: *CS 182 544* (1977).
 16. Červený L., Marhoul A., Růžička V.: *CS 239 665* (1985).
 17. Červený L., Marhoul A., Železný M., Růžička V.: *Chem. Prům.* 26, 519 (1976).
 18. Červený L., Křivská M., Hromas J.: *Seifen, Ole, Fette, Wachse* 119, 560 (1993).
 19. Červený L., Křivská M., Marhoul A.: *Chem. Listy* 87, 110 (1993).
 20. Červený L., Křivská M., Marhoul A., Pokorný J., Kalinová J.: *Perfum. Flav.* 18, 41 (1993).
 21. Červený L., Marhoul A., Zugárek M., Růžička V.: *Chem. Prům.* 30, 28 (1980).
 22. Červený L., Kuncová M., Růžička V.: *Collect. Czech. Chem. Commun.* 46, 1258 (1981).
 23. Kuzma M., Červený L.: *Res. Chem. Intermed.* 148, 245 (1999).
 24. Klusoň P., Kukula P., Kyslingerová E., Červený L.: *React. Kinet. Catal. Lett.* 59, 9 (1996).
 25. Kukula P., Červený L.: *Appl. Catal.* 177, 79 (1999).
 26. Kukula P., Červený L.: *J. Mol. Catal.* (in print).
 27. Červený L., Kozel J., Marhoul A.: *Perfum. Flav.* 14, 13 (1989).
 28. Červený L., Kovářová L., Marhoul A.: *Chimica Oggi-Chem. Today* 5, 37 (1996).
 29. Červený L., Marhoul A., Strohalm J., Růžička V.: *Chem. Prom.* 23, 117 (1973).
 30. Červený L., Marhoul A., Růžička V.: *Chem. Prům.* 23, 299, 357 (1973).
 31. Červený L., Marhoul A., Florián J., Růžička V.: *Chem. Prům.* 24, 296, 503 (1974).
 32. Červený L., Bartoň J., Růžička V.: *Collect. Czech. Chem. Commun.* 39, 2470 (1974).
 33. Červený L., Růžička V.: *Collect. Czech. Chem. Commun.* 40, 2622 (1975).
 34. Červený L., Marhoul A., Růžička V., Hora A.: *CS 165 744* (1976).
 35. Červený L., Marhoul A., Růžička V., Müller K., Sládková D.: *CS 212 915* (1981).
 36. Kačer P., Kuzma M., Liberková K., Červený L.: *Res. Chem. Intermed.* 24, 643 (1998). ■
-