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Reviews

Organic Processes to Pharmaceutical Chemicals Based on Fine Chemicals from Lignosulfonates

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Abstract:

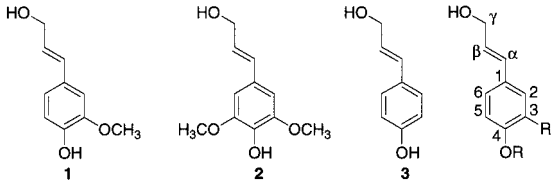
This is a general overview of some *first-*, *second-* and *third-generation* fine chemicals with origins from the lignin oxidation process. The synthetic organic processes of these substances are presented as well as several applications for the synthesis of a variety of pharmaceutical chemicals.

1. Introduction

The side stream from chemical pulping by means of the sulfite pulping process creates a side stream known as sulfite-spent liquor. The major component of the sulfite-spent liquor is water-soluble lignosulfonates. During the past decades, lignosulfonates, have been shown to be a highly valuable raw material for fine chemicals. A hydrolytic and oxidative depolymerization is the crucial step in the process of making fine chemicals from the lignosulfonates. This process, also referred to as lignin oxidation, produces the compounds that in the following will be referred to as *first-generation* fine chemicals. Due to the composition of the functional groups of these compounds, a range of valuable derivatives that can be used as substrates or reagents within a wide field of synthetic processes can be obtained. By performing one or some few simple functional group transformations on these, a great variety of *second-generation* fine chemicals can be obtained. *Third-generation* fine chemicals are obtained when more extensive molecular transformations or changes in the molecular framework are performed. *First-*, *second-*, and *third-generation* compounds may all be utilized for the production of a pharmaceutical chemical that is an active ingredient of a pharmaceutical product. In the following, organic processes leading to several of the fine chemicals that can be obtained from lignosulfonates will be discussed. Moreover, organic processes yielding a variety of pharmaceutical chemicals will be discussed, both phased out pharmaceuticals as well as substances that at the moment are in the early-development phase.

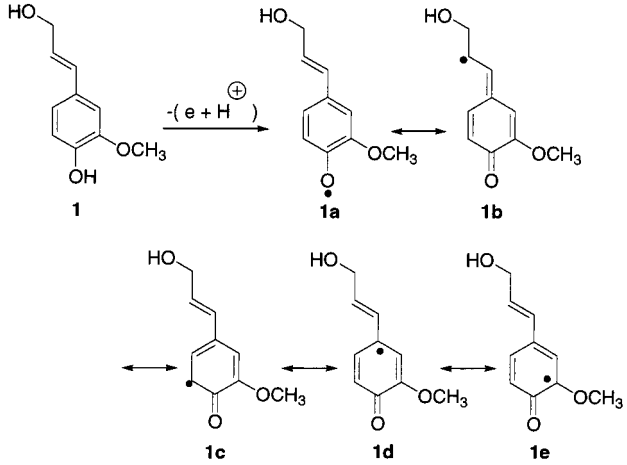
2. The Origin of the Raw Material

All kinds of lignins are composed by some few phenylpropene derivatives, namely, coniferyl alcohol [4-(3-hydroxypropenyl)-2-methoxyphenol] **1**, sinapyl alcohol [4-(3- hydroxypropenyl)-2,6-dimethoxyphenol] **2**, and *p*-hydroxycoumaryl alcohol [4-(3-hydroxypropenyl)phenol] **3**. The relative quantities of the original phenylpropene units **1**−**3** are dependent on the source of the lignin. Typically, hardwood lignin is composed mostly of sinapyl alcohol **2**, while softwood lignin, for example the lignin orginating from Norwegian spruce, is principally composed of coniferyl alcohol **1**, with minor quantities of both sinapyl alcohol **2** and *p*-hydroxycoumaryl alcohol **3** present.



The biosynthesis of lignin proceeds through radical polymerization processes with the phenylpropenol derivatives **1**−**3** as the monomers. The first step of the process is an enzymatic dehydrogenation of one of the phenylpropenol derivatives, for example in softwood, the coniferyl alcohol **1** gives the phenoxy radical **1a**, Scheme 1. Several resonance forms (**1a**−**1e**) stabilize the phenoxy radical but provide also the origin of the complex lignin biopolymer structure due to random coupling of the radicals **1a**−**1e**. These coupling reactions leads to the formation of linkages such as β-*O*-4, α-*O*-4, β-5, 5−5, 4-*O*-5, β-1, and $\beta-\beta$ between the original monomers.

Scheme 1



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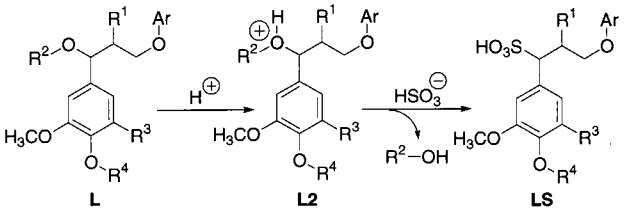
3. The Lignin Biopolymer Dissolving Process: Sulfite Pulping

Lignosulfonates (**LS**), also known as *black liquor* or *sulfite-spent liquor*, is a mixture of lignin fragments that contain a certain number of sulfonic groups introduced during the sulfite pulping of wood. The sulfite-pulping process may be performed under several conditions, depending on the desired quality of the cellulose to be produced. Such processes are digestion for 6−7 h within temperature intervals such as 126−129 °C and 140−145 °C. Moreover, variation of the amounts of Ca^{2+}/SO_2 is also an important process variable, which gives rise to a variation in the number of sulfonic groups found in the lignosulfonates.

The practical benefits of the sulfonating are that the lignin fragments are released from the cellulose fibers and that the lignins becomes water-soluble.

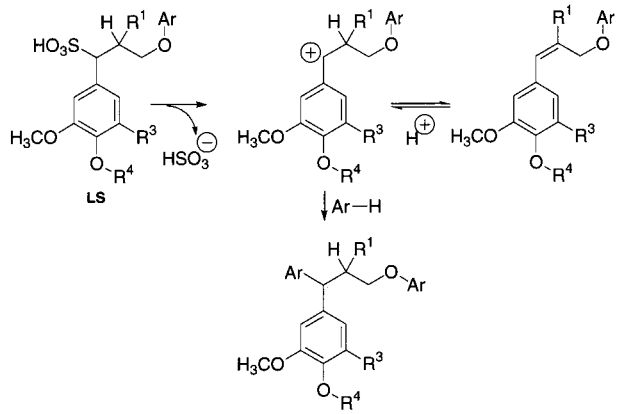
The key chemical reactions that occur in the acidic sulphite pulping process can schematically be described as the following; the benzyl ether bond of the lignin fragment **L** is protonated, giving **L2** which is subsequently attacked by the nucleophile HSO_3^- performing a substitution reaction resulting in formation of the fragment R^2-OH and the sulfonated lignin **LS**. An outline of this lignin-dissolving process is given in Scheme 2.

Scheme 2



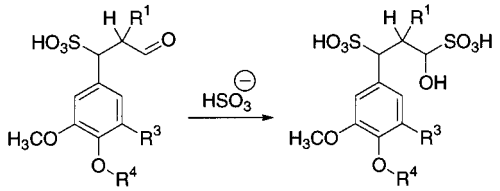
During the chemical-pulping process, some of the various feasible process conditions may, however, also induce consecutive reactions where a lignosulfonate fragment first loses a HSO_3^- group, giving a carbocation that may undergo a Friedel−Craft alkylation reaction on an aromatic nucleus in another lignin unit or a lignosulfonate fragment yielding "*condensation products*" as outlined in Scheme 3. Moreover,

Scheme 3



substitution of α-carbonyl groups and sulfonation of aldehyde groups yields α-hydroxysulfonic acid. The reaction is outlined in Scheme 4.

Scheme 4



It is obvious that, when materials without exactly defined molecular structures such as lignosulfonates with various molecular weights and a large variety of alkyl−aryl and aryl−aryl linkages are subjected to hydrolytic and oxidative depolymerization, a range of different products may be formed. The conditions used during the pulping process may also influence the product profile obtained during the oxidation process. Due to these variations one may also anticipate a different product profile with respect to the quantities of the principal products as well as to which products formed during the depolymerization process. Despite all the possible variations of the raw material, the only significant variation observed is in the mutual quantities of the different depolymerization products.

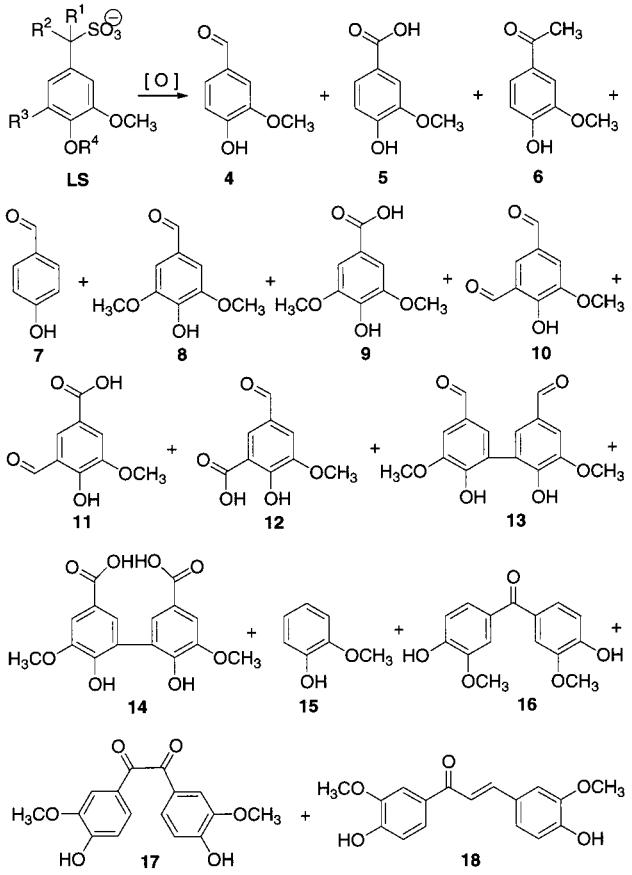
4. Producing First-Generation Fine Chemicals from Lignosulfonate by Means of the Lignin Oxidation Process

Several hydrolysis and oxidation processes yielding low-molecular weight well-defined molecular entities may be implemented for depolymerization of lignosulfonate (**LS**). Such methods are basic hydrolysis and oxidation, alkaline nitrobenzene oxidation, and metal salt-catalyzed air oxidation in alkaline media. Common for all of the processes are that they are performed under elevated reaction pressure and temperature. The method that has found the widest application in industry involves basic hydrolysis and oxidation using sodium hydroxide and copper(II)-catalyzed air oxidation, a process originally developed by Monsanto Chemical Company.[1,2]

Several studies of lignin oxidation have been performed with the objective of determining the product profile and thus giving insight into lignin structure. A variety of products are determined after such oxidation experiments. Scheme 5 outlines products determined after oxidation experiments on Norwegian spruce lignin. Leopold[3] determined the following compounds as reaction products after alkaline nitrobenzene hydrolysis and oxidation experiments: vanillin **4**, vanillic acid **5**, acetovanillone **6**, *p*-hydroxy benzaldehyde **7**, syringealdehyde **8**, syringic acid **9**, 5-formylvanillin **10**, 5-formylvanillic acid **11**, 5-carboxyvanillin **12**, dehydrodivanillin **13**, and dehydrodivanillic acid **14**. In experiments carried out using copper(II)-catalyzed air oxidation in alkaline media, four additional products were reported by Pearl,[4,5] guaiacol **15**, bis-(4-hydroxy-3-methoxyphenyl)methanone **16**,

(1) Hocking, M. B. *J. Chem. Educ.* **1997**, *74(9)*, 1055.
(2) Final Report on Vanillin from Sulfite Waste Liquor. Monsanto Chemical Company, Organic Chemical Division. St. Louis Research Department, U.S.A. *Research Report No. 1343*.
(3) Leopold, B. *Acta Chem. Scand.* **1952** , *6*, 38.
(4) Pearl, I. A. *J. Am. Chem. Soc.* **1942**, *64*, 1429.
(5) Pearl, I. A. *J. Am. Chem. Soc.* **1950**, *72*, 2309.

Scheme 5



1,2-bis-(4-hydroxy-3-methoxyphenyl)ethane-1,2-dione **17**, and 1,3-bis-(4-hydroxy-3-methoxyphenyl)propenone **18**.

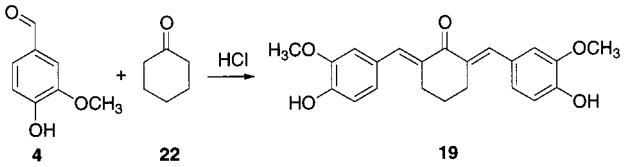
Vanillin **4**, vanillic acid **5**, and acetovanillone **6**, are however the three principal compounds found in the reaction mixture. In a process that recently was further developed and optimized by Bjørsvik and Minisci,[6] using lignosulfonates from Norwegian spruce as raw material, yields of 2−8% of the three major compounds **4**, **5**, and **6** were obtained. However, substantial amounts of several inorganic compounds including sodium sulphate, sodium carbonate, calcium carbonate, calcium oxalate, and copper oxides (the catalyst) are also found in the reaction mixture. Substantial quantities of other higher-molecular weight carboxylic and phenolic compounds as well as volatile organic acids such as acetic acid are found.

5. First- and Second-Generation Fine Chemicals From Lignosulfonate and Pharmaceutical Chemicals

Vanillin **4** is the most important *first-generation* fine chemical directly obtained from the hydrolysis-oxidation of lignosulfonates. In addition to being employed as a flavoring and fragrance ingredient, vanillin **4** may be used as a reagent or substrate in the synthesis of several *second-generation* fine chemicals, such as veratraldehyde, veratric acid, protocatechualdehyde, and protocatechuic acid. Moreover, vanillin **4** can also be used in synthetic processes leading to several

(6) Bjørsvik, H.-R.; Minisci, F. *Org. Process Res. Dev.* **1999**, *3*, 330.

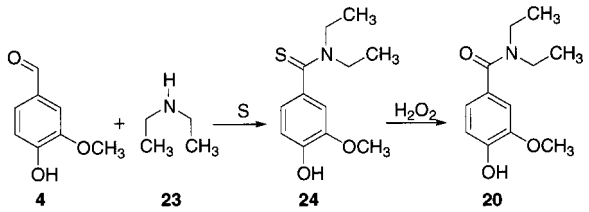
Scheme 6



pharmaceutical chemicals, namely, cyclovalone[7] **19**, etamivan[8] (ethamivan) **20** and levodopa[9] **21**. These compounds cover a variety of areas of pharmaceutical applications: cyclovalone **19** is a digestant or choleretic, etamivan **20** is an analeptic and a central nervous system and respiratory system stimulant, and levodopa **21** is an antiparkinson agent. Reaction of vanillin **4** with cyclohexanone **22** in the presence of hydrochloric acid yields cyclovalone **19** in one synthetic step, as shown in Scheme 6.

Etamivan **20** can be obtained via two synthetic routes, one starting from vanillin **4** and the other from vanillic acid **5**. The process involving vanillin **4** as starting material is carried out by reacting vanillin **4** and diethylamine **23** in the presence of sulphur and gives thiovandid [*N*,*N*-diethyl-4-hydroxy-3-methoxythiobenzamide] **24** as an intermediate. Etamivan **20** is obtained when thiovanidid is oxidized with hydrogen peroxide. The process is outlined in Scheme 7.

Scheme 7



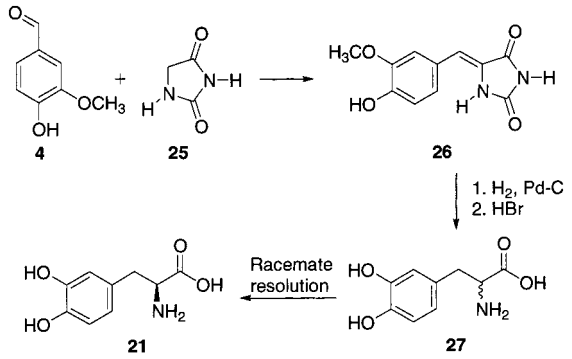
The other process for the synthesis of etamivan **20** starting from vanillic acid **5** is described in the section concerning vanillic acid **5**.

Levodopa **21** can be synthesized following several different synthetic pathways. Two of them are based on vanillin **4** as substrate. Vanillin **4** is reacted with hydantonin **25** to give the intermediate 5-(4-hydroxy-3-methoxybenzylidene)-imidazolidine-2,4-dione **26**, which is hydrogenated over palladium on charcoal and treated with hydrobromic acid to give DL-dopa **27**. Levodopa **21** is separated from the racemic mixture by a racemate-resolution process.[10−12] The process is outlined in Scheme 8.

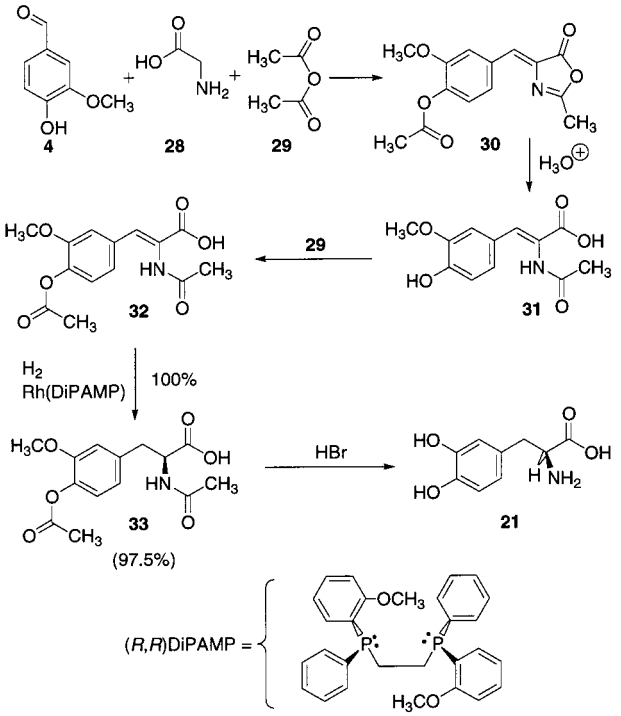
Dr. William S. Knowles (Nobel laureate, 2001) developed the first asymmetric synthesis for the production of levodopa (L-DOPA) **21**, today called the Monsanto process.[13−19] An

(7) Rumpel, W. (A. V. Waldheim Chemisch-Pharmazeutische Fabrik). AT 180 258, 1954.
(8) Kratzl, K.; Kvasnicka, E. (Österreichische Stickstoffwerke AG). U.S. Patent 2,641,612, 1953.
(9) Britton, E. C.; White, H. C. (Dow Chemical Company). U.S. Patent 2,605,282, 1952.
(10) Kaiser, A.; Scheer, M.; Häusermann, W.; Marti, L. (F. Hoffmann-La Roche & Co AG). DE 1 964 420, 1970.
(11) Berenyi Poldermann, E.; Budai, Z.; Pallos, L.; Benko, P.; Magdanyi, L. (E.GY.T Gyogyszervegyeszeti Gyar). DE 2 052 953. 1971.
(12) Berenyi Poldermann, E.; Budai, Z.; Pallos, L.; Magdanyi, L.; Benko, P. (E.GY.T Gyogyszervegyeszeti Gyar). DE 2 052 995, 1971.
(13) Losse, G.; Barth, A.; Jasche, K. *J. Prakt. Chem.* **1963** *21(1−2)*, 32.

Scheme 8



Scheme 9



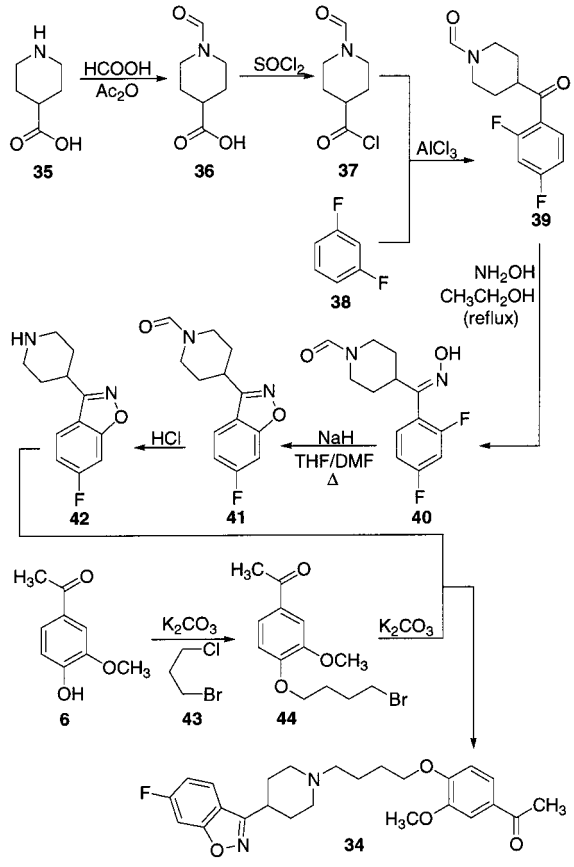
outline of the process is given in Scheme 9. The crucial reaction of this process is the asymmetric hydrogenation of 3-(4-acetoxy-3-methoxyphenyl)-2-acetylaminoacrylic acid **32**. In this step Knowles and co-workers used a stereoselective catalyst known as Rh(DiPAMP). The intermediate *N*-acetyl-3-(4-acetoxy-3-methoxyphenyl)-L-alanine **33** obtained from this asymmetric hydrogenation reaction, is deacetylated using hydrobromic acid to give levodopa **21**.

The synthetic process to the key intermediate **32** involves the reaction of vanillin **4**, glycine **28**, and acetic acid anhydride **29** to give acetic acid 4-(2,5-dioxoimidazolidin-4-ylidenemethyl)-2-methoxyphenyl ester **30**. Upon treatment with acid in water this last gives 2-acetylamino-3-(4-hydroxy-3-methoxyphenyl)acrylic acid **31**, the free hydroxy group of which is acetylated using acetic acid anhydride **29** to afford **32**.

Acetovanillon (4-hydroxy-3-methoxyacetophenone) **6** is also a *first-generation* fine chemical obtained as a reaction product from the oxidation−hydrolysis of lignosulfonate **LS**. The compound serves as substrate in synthetic processes leading to several *second-generation* fine chemicals, such as acetoveratron, veratric acid, and veratric acid chloride. Moreover, recently, a new compound iloperidone[20,21] **34** [1-(3-(4-acetyl-2-methoxyphenoxy)propyl)-4-(6-fluorobenzisoxazol-3-yl)piperidine] that includes an acetovanillon **6** moiety was reported to be under development for use as an antipsychotic dopamine D_2 antagonist and a 5-HT_{2A} antagonist.

The synthesis of iloperidone **34** is performed by means of an eight-step synthetic process. The acetovanillon **6**, which constitutes an integral part of this substance, is condensed with 3-chloropropylbromide **43** in DMF in the presence of potassium carbonate or sodium hydride as base to obtain the key intermediate **44**. In the last step of the process **44** is reacted with **42** to afford iloperidone **34**. The intermediate **42** is synthesised by reacting piperidine-4-carboxylic acid **35** with formic acid and acetic acid anhydride to obtain 1-formylpiperidine-4-carboxylic acid **36** that upon treatment with thionyl chloride in acetic acid anhydide gives the corresponding acyl chloride **37** (1-formylpiperidine-4-carbonyl chloride). Under Friedel−Craft conditions, the acyl chloride **37** is condensed with 1,3-difluorobenzene **38** to afford 4-(2,4-difluorobenzoyl)piperidine-1-carbaldehyde **39**. Treatment of this intermediate with hydroxylamine in re-

Scheme 10

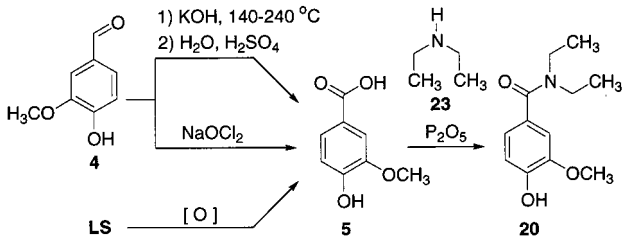


(14) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D. (Monsanto Company). U.S. Patent 4,005,127, 1977.
(15) Knowles, W. S.; Sabaky, M. J. (Monsanto Company). DE 2 123 063, 1971.
(16) Knowles, W. S.; Sabaky, M. J.; Vineyard, B. D. (Monsanto Company). DE 2 210 938, 1972.
(17) Knowles, W. S.; Sabacky, M. J. (Monsanto Company). U.S. Patent 4,-124,533, 1978.
(18) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 2567.
(19) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946.

fluxing ethanol yields the oxime **40** (4-[(2,4-difluorophenyl)-hydroxyiminomethyl]piperidine-1-carbaldehyde). When the oxime **40** is exposed to basic conditions by means of sodium hydride in hot DMF and THF in the following step, a cyclisation proceeds to afford benzo[*d*]isoxazol **41** (4-(6-fluorobenzo[*d*]isoxazol-3-yl)piperidine-1-carbaldehyde), which upon treatment with HCl in refluxing ethanol affords the key intermediate **42**.

Even though vanillic acid (4-hydroxy-3-methoxybenzoic acid) **5** is found in the reaction mixture after the hydrolysis-oxidation of **LS**, vanillic acid **5** is usually obtained from vanillin **4** by oxidation with, for example, sodium chlorite $NaOCl_2$.[22] Moreover, vanillic acid **5** may also be obtained via a process reported by Pearl.[23] That process involves treatment of vanillin **4** with fused potassium hydroxide at a temperature in the range 140−240 °C followed by quenching the reaction mixture with water and acidifying with a mineral acid such as hydrochloric acid or sulphuric acid to give vanillic acid **5**. Vanillic acid **5** may be used in the synthesis of etamivan **20** as outlined in Scheme 11. Etamivan **20** can

Scheme 11



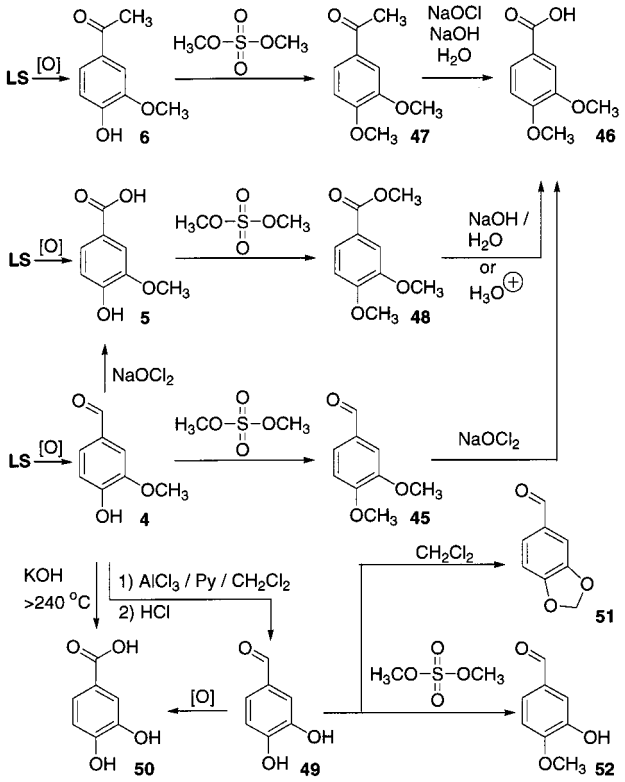
also be obtained from vanillin **4** via the process as earlier described in Scheme 7.

Veratraldehyde (3,4-dimethoxybenzaldehyde) **45**, Scheme 12, is a *second-generation* fine chemical, obtained by methylation of vanillin **4**. Veratraldehyde **45** is a versatile reagent usable as substrate or reagent in several processes leading to valuable active ingredients for pharmaceuticals. Examples of such ingredients are verabutine,[24] also known as profenveramine, and revatrine that is used as a uterus relaxant. Rimiterol,[25] bronchodilator, and moxaverine,[26] antispasmodic agent, are two other active ingredients synthesized from veratraldehyde **45**.

Veratric acid (3,4-dimethoxybenzoic acid) **46**, Scheme 12, is a *second-generation* fine chemical that can be obtained either by oxidation of veratraldehyde **45**, methylation of vanillic acid **5** to veratric acid methyl ester **48** followed by a smooth ester hydrolysis to give the compound **46**, or by methylation of acetovanillone **6** to obtain acetoveratrone **47** which is oxidized using the haloform reaction to give veratric acid **46**. Such a process was recently improved and optimized

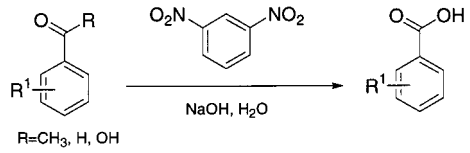
(20) Mucke, H. A. M.; Castañer, J. *Drugs Future* **2000**, *25(1)*, 29.
(21) Steiner, G.; Bach, A.; Bialojan, S.; Greger, G.; Hege, H.-G.;.Höger, T.; Jochims, K.; Munschauer, R.; Neumann, B.; Teschendorf, H.-J.; Traut, M.; Unger, L.; Gross, G. *Drugs Future* **1998** *23(2)*, 191.
(22) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888.
(23) Pearl, I. A. *J. Am. Chem Soc*. **1946**, *68*, 2180.
(24) Seeger, E.; Kottler, A. (Dr. T. Thomae Gesellschaft). DE 963 424, 1957.
(25) Sankey, G.. H.; Whiting, K. D. E. (Minnesota 3M Lab Ltd.). DE 2 024 049, 1970.
(26) (Orgamol SA, Evionnnaz, Sc.). GB 1 030 022 1966.

Scheme 12



by Bjørsvik and Norman.[27] Furthermore, veratric acid **46** and other benzoic acid derivatives may also be obtained by using a modified nitrobenzene oxidation process lately reported by Bjørsvik et al.[28] This method is based on oxidizing the corresponding acetophenone, benzyl alcohol, benzaldehyde, or mandelic acid derivative using 1,3-dinitrobenzene in alkaline aqueous media at a moderate temperature (100 °C), Scheme 13.

Scheme 13

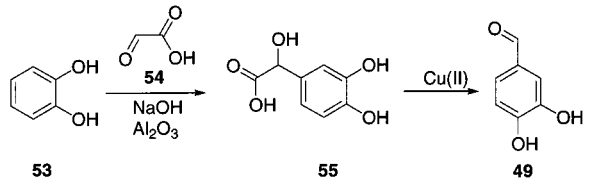


Protocatechualdehyde (3,4-dihydroxybenzaldehyde) **49** and protocatechuic acid (3,4-dihydroxybenzoic acid) **50** are two other important intermediates that can be obtained by using vanillin **4** as starting material. Lange[29] has reported a synthetic procedure to protocatechualdehyde **49** starting from vanillin **4**. In this process vanillin **4** is treated with anhydrous aluminium chloride and pyridine in CH_2Cl_2 under reflux for 24 h, followed by treatment with dilute hydrochloric acid (15−20%) at a temperature around 25−30 °C. In this process, the organic phase contains the unreacted vanillin **4**, whereas the aqueous phase is extracted with ethyl ether to give 3,4-dihydroxybenzaldehyde **49** in high yields, Scheme 12.

(27) Bjørsvik, H.-R.; Norman, K. *Org. Process Res. Dev.* **1999**, *3*, 341.
(28) Bjørsvik, H.-R.; Liguori, L.; Minisci, F. *Org. Process Res. Dev.* **2001**, *5*, 136.
(29) Lange, R. G. *J. Org. Chem.* **1962**, *27*, 2037.

Bjørsvik et al.[30] have recently reported another process (Scheme 14) to protocatechualdehyde **49**, although with cate-

Scheme 14

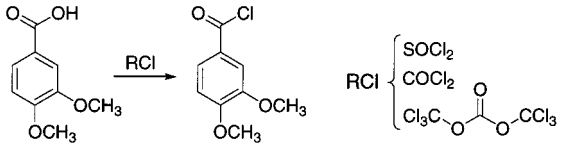


chol **53** as starting material. Catechol **53** is reacted with glyoxylic acid **54** in basic medium in the presence of aluminium oxide to obtain the corresponding mandelic acid derivative **55**. When the mandelic acid derivative **55** is subjected to copper(II) oxidation, protocatechualdehyde **49** is obtained in good yield. Protocatechualdehyde **49** can be used for the synthesis of two very useful *second-generation* fine chemicals, namely, heliotropin (benzo[1,3]dioxole-5-carbaldehyde) **51** and *iso*-vanillin (3-hydroxy-4-methoxybenzaldehyde) **52** (Scheme 12), both serving as flavouring and fragrance agents as well as intermediates for the synthesis of several pharmaceutical chemicals. Much attention has been focused on *iso*-vanillin **52** as a synthetic building block for the synthesis of several PDE4 inhibitors, that are used in the treatment of chronic obstructive pulmonary disease and asthma.[31]

The pathway to protocatechuic acid **50** reported by Pearl[23] is a composite process comprising a concurrent demethylation and oxidation by treating vanillin **4** in fused KOH at a temperature in the range 245°−255 °C for 30 min, diluting with water, and concluding the process with acidification with hydrochloric acid. Moreover, oxidation of the corresponding aldehyde **49** may also be a synthetic path to follow, although protection of the free hydroxylic groups may be necessary.

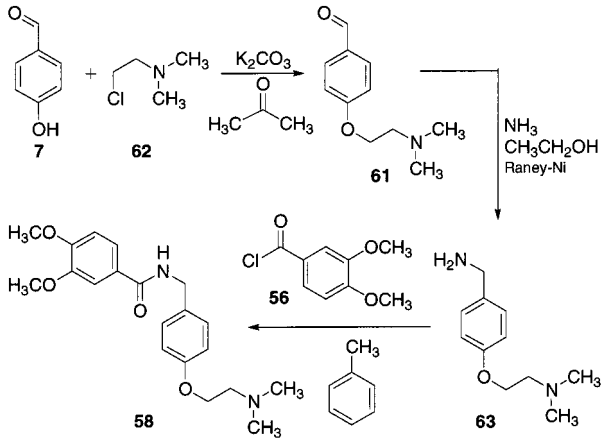
Veratric acid chloride **56** (3,4-dimethoxybenzoic acid chloride) is obtained from veratric acid **46** by treating the carboxylic acid with thionyl chloride, phosgene, or with triphosgene **57**, Scheme 15.

Scheme 15



Veratric acid chloride **56** is used as a building block in the synthesis of a variety of pharmaceutical chemicals: itopride[32,33] [*N*-[4-(2-dimethylaminoethoxy)benzyl]-3,4-dimethoxybenzamide] **58**, a gastric prokinetic agent (peristaltic stimulant), mebeverine[34,35] **59**, an antispasmodic, and vesnarinone[36−38] **60**, a cardiotonic.

Scheme 16



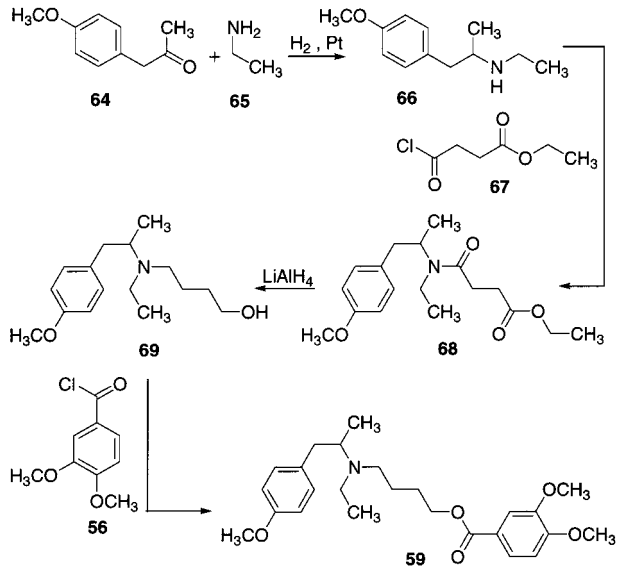
The process to itopride **58** is composed of the three synthetic steps outlined in Scheme 16. The intermediate 4-(2-dimethylaminoethoxy)benzaldehyde **61** is obtained by reacting *p*-hydroxybenzaldehyde **7** (which also is a *first-generation* fine chemical produced from the lignin oxidation, although in small amounts) with *N*-(2-chloroethyl)dimethylamine **62** in potassium carbonate dissolved in acetone. The aldehyde **61** is then reacted with ammonia in ethanol over Raney nickel, to obtain [2-(4-aminomethylphenoxy)ethyl]-dimethylamine **63** that in the last step is reacted with veratric acid chloride **56** in toluene to obtain itopride **58**. The product is stabilized as a hydrochloride salt made by treatment with hydrochloric acid when the amidation step is finished.

In the synthesis of mebeverine **59** [3,4-dimethoxybenzoic acid 4-{ethyl-[2-(4-methoxyphenyl)-1-methylethyl]amino}-butyl ester], veratric acid chloride **56** is also used as a building block. In the first step 4-methoxyphenylacetone **64** is reacted with ethylamine **65** and hydrogenated over platinum, yielding ethyl-[2-(4-methoxyphenyl)-1-methylethyl]-amine **66** that is in turn reacted with the acid chloride ethyl 3-chloro formylpropionate **67** to give the amide *N*-ethyl-*N*-[2-(4-methoxyphenyl)-1-methylethyl]succinamic acid ethyl ester **68**. The ester group of this intermediate is reduced using lithium aluminium hydride to give the corresponding alcohol 4-{ethyl-[2-(4-methoxyphenyl)-1-methylethyl]amino}butan-1-ol **69**. The alcohol **69** in the last step is reacted with veratric acid chloride **56** to form the ester linkage of the final product, mebeverine **59**. The complete process is outlined in Scheme 17.

Vesnarinone **60** is also obtained from a linear multistep synthetic process. In this process, all of the steps, except the last one, build an intermediate, 6-piperazin-1-yl-3,4-dihydro-1*H*-quinolin-2-one **76**, that is reacted with veratric acid chloride **56** in the ultimate step. *p*-Nitroaniline **70** is monoacetylated using acetic acid anhydride **29** and reduced by hydrogenation over platinium on charcoal to give *p*-aminoacetanilide **71**. Reacting this intermediate with β-ethoxyacryloyl chloride **72** gives *N*-(4-acetylaminophenyl)-3-eth-

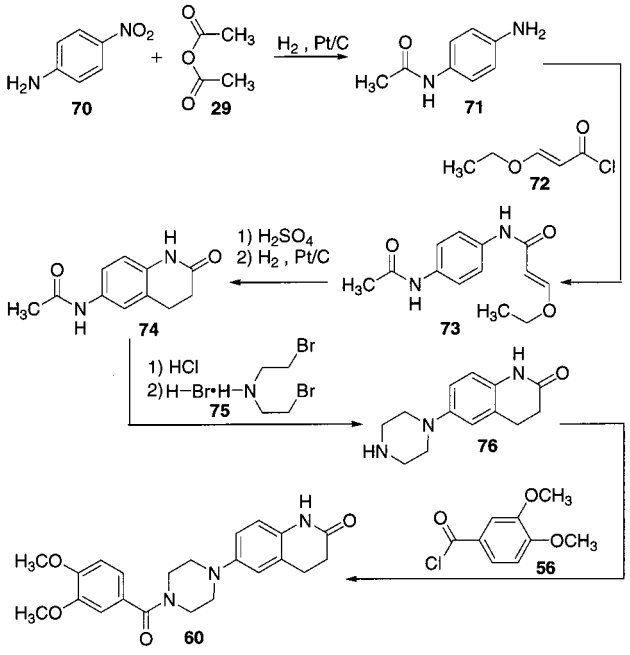
(30) Bjørsvik, H.-R., Liguori, L.; Minisci, F. *Org. Process Res. Dev.* **2000**, *4*, 534.
(31) Sorbera, L. A.; Leeson, P. A.; Castañer, J. *Drugs Future* **2000**, *25(12)*, 1261.
(32) Yasuo, I.; Hideo, K.; Eiichi, K.; Nobuo, O.; Hiroyuki, N.; Jun, S. (Hokuriku Pharmaceutical). EP 0 306 827, 1989.
(33) Goldberg, M. W.; Teitel, S. (Hoffmann-La Roche Inc.). U.S. Patent 2,-879,293, 1959.
(34) Kralt, T.; Moed, H. D.; Lindner, A.; Asma, W. J. (N.V. Philips). DE 1 126 889, 1958.
(35) (N.V. Philips). GB1 009 082, 1965.
(36) Kazuyuki, N.; Michiaki, T.; Yang Yung H.; Hidenori, O. (Otsuka Pharmaceutical Co., Ltd.). DE 31 42 982, 1983.
(37) Kazuyuki, N.; Michiaki, T.; Yang Yung, H,; Hidenori, O. (Otsuka Pharmaceutical Co., Ltd.). U.S. Patent 4,415,572, 1982.
(38) Tominaga, M.; Yo, E.; Ogawa, H.; Yamashita, S.; Yabuuchi, Y.; Nakagawa, K. *Chem. Pharm. Bull* **1984**, *32(6)*, 2100.

Scheme 17



oxyacrylamide **73** that is treated with sulfuric acid followed by hydrogenation on platinum on charcoal. The intermediate **74** [*N*-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)acetamide] is then treated with hydrochloric acid and reacted with bis(2-bromoethyl)amine hydrobromide **75** to give 6-piperazin-1-yl-3,4-dihydro-1*H*-quinolin-2-one **76** that in the final step is reacted with veratric acid chloride **56** to give vesnarinone **60**. The complete process is given in Scheme 18.

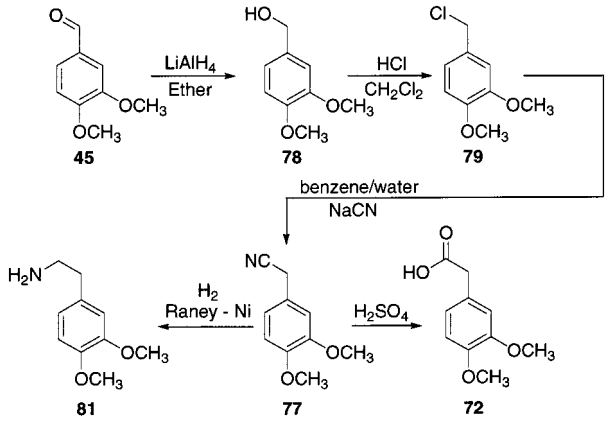
Scheme 18



6. Second- and Third-Generation Fine Chemicals From Lignosulfonate and Pharmaceutical Chemicals

6.1. Synthesis and Application of Homoveratronitrile, Homoveratrylamine, and 3,4-Dimethoxyphenylacetic Acid. Homoveratronitrile **77** [(3,4-dimethoxyphenyl)acetonitrile] is a versatile compound for synthesis of several pharmaceutical chemicals. It can be synthesized following a four-step

Scheme 19



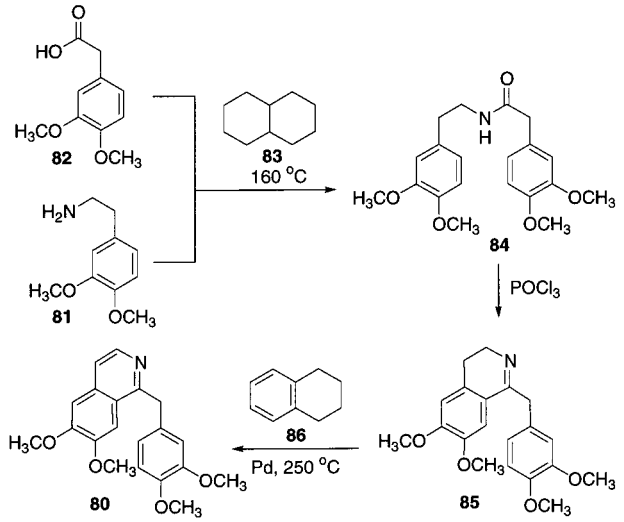
synthetic path[39−42] starting from veratraldehyde **45**. The first step is a reduction of the carbonyl group to the corresponding alcohol carried out by dissolving veratraldehyde **45** in ethyl ether, after which the reducing agent $LiAlH_4$ is added. The thus obtained 3,4-dimethoxybenzyl alcohol **78** is in the following step converted to 3,4-dimethoxybenzyl chloride **79** [4-(2-chloroethyl)-1,2-dimethoxybenzene], a step that may be performed following several different procedures. For example, 3,4-dimethoxybenzyl alcohol **78** is dissolved in dichloromethane and reacted with concentrated HCl. The final step of the synthesis of homoveratronitrile **77** is the introduction of the cyano group. This is carried out by refluxing 3,4-dimethoxybenzyl chloride **79** and NaCN in benzene and water. The process to homoveratronitrile **77** from veratraldehyde **45** is shown in Scheme 19.

Homoveratronitrile **77** can, as mentioned above, be used as a building block in the synthesis of several pharmaceutical chemicals. Papaverine **80**, an antispasmodic and vasodilator, is one such substance. The synthetic path to papaverine **80** includes two different compounds derived from lignosulfonate. In addition to homoveratronitrile **77**, 2-(3,4-dimethoxyphenyl)ethylamine **81** is also used. The compound **81** is obtained by reduction of homoveratronitrile **77**. The reduction (hydrogenation) can be performed over Raney nickel as shown in Scheme 19. (3,4-Dimethoxyphenyl)acetic acid **82** is obtained from homoveratronitrile **77** by hydrolysis in strong mineral acid (e.g., example sulfuric acid).

The synthetic path to papaverine[43,44] **80** is shown in Scheme 20. The two substances **81** and **82** are reacted at elevated temperature (160 °C) in decahydronaphthalene **83** to obtain 2-(3,4-dimethoxyphenyl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]acetamide **84**. The intermediate **84** [2-(3,4-dimethoxyphenyl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]acetamide] is treated with $POCl_3$ in the following step to give the 3,4-dihydroisoquinoline derivative **85**, that in the last step is treated with Pd in 1,2,3,4-tetrahydronaphthalene **86** at ele-

(39) Anand, R. C.; Ranjan, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 791.
(40) Jung, M. E.;. Long-Mei, Z. *Tetrahedron Lett.* **1983**, *24(42)*, 4533.
(41) Ogura, F.; Nakao, A.; Nakagawa, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1165.
(42) Mueller, J.; Wiersdorff, W.-W.; Burst, W.; Dralle, H.; Schaeffner, E.; Steinkamp, R. (BASF AG). DE 3 527 338, 1987.
(43) Budesinsky Z.; Protiva, M. *Synthesizche Arzneimittel*; Akademie-Verlag: Berlin 1961; p 87.
(44) Mauvernay, R. Y. (Centre Europeen de Recherches). U.S. Patent 3,823,-234, 1974.

Scheme 20



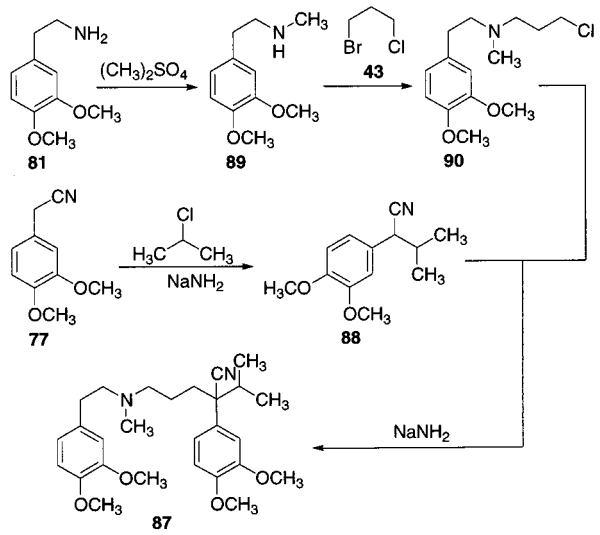
vated temperature to give papaverine **80** [1-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinoline].

Verapamil[45−47] **87**, also known as iproveratril, is a coronary vasodilator and another pharmaceutical chemical that is produced from homoveratronitrile and 2-(3,4-dimethoxyphenyl)ethylamine.

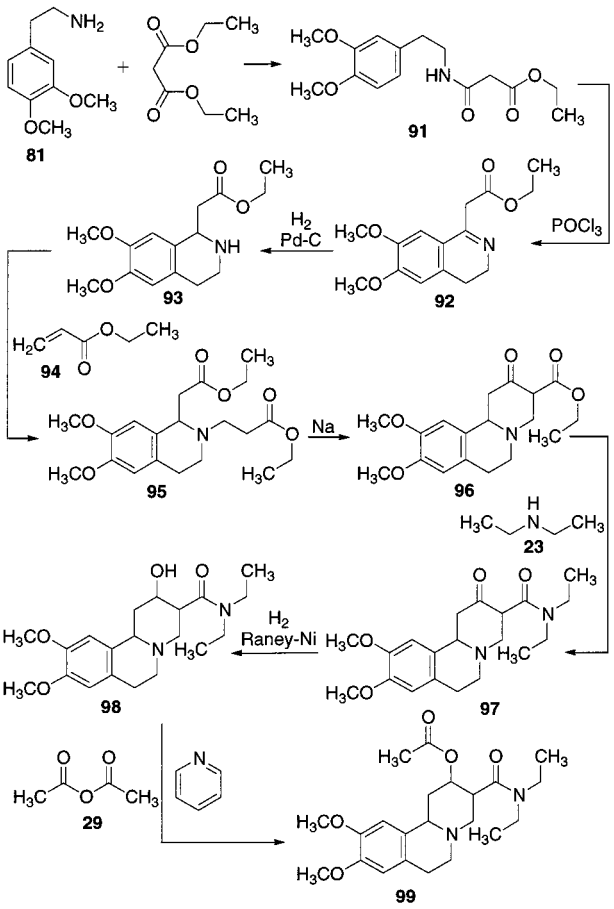
Verapamil **87** is synthesized by reacting homoveratronitrile **77** with isopropyl chloride in the presence of sodamide to give 2-(3,4-dimethoxyphenyl)-3-methylbutyronitrile **88** that is one of two intermediates in the short convergent synthesis of verapamil **87**. The other intermediate is synthesized from 2-(3,4-dimethoxyphenyl)ethylamine **81** that is monomethylated using dimethylsulphate to give [2-(3,4-dimethoxyphenyl)ethyl]methylamine **89**, which is further reacted with 1-bromo-3-chloropropane **43** to yield the second building block (3-chloropropyl)-[2-(3,4-dimethoxyphenyl)-ethyl]methylamine **90**. The two intermediates **88** and **90** are in the last step coupled in the presence of sodamide to give **87**. The process is outlined in Scheme 21.

Homoveratrylamine **81** is a very versatile fine chemical, which can be used in several synthetic processes, thus providing a range of different pharmaceutical chemicals. In the following, a series of synthetic processes for a wide range of pharmaceutical substances is presented. Common to all of these is that homoveratrylamine **81** is a key building block. The antiemetic and tranquilizer, benzquinamide[48−51] **99**, can be obtained via an eight-step linear synthesis (Scheme 22). Homoveratrylamine **81** is reacted with malonic acid diethyl ester to give *N*-[2-(3,4-dimethoxyphenyl)ethyl]malonamic acid ethyl ester **91**. Treatment of this product with $POCl_3$ gives a dehydroisoquinolin derivative **92** which upon hydrogenation over Pd/C gives (6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)acetic acid ethyl ester **93**.

Scheme 21



Scheme 22

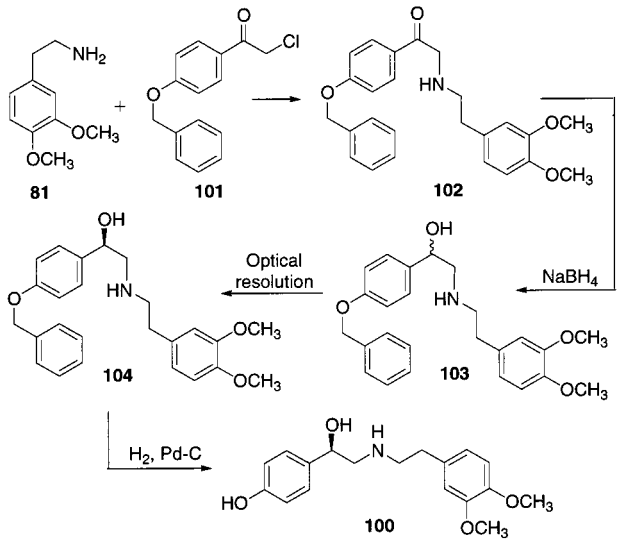


Reacting this intermediate with ethyl acrylate **94** followed by treatment with sodium, gives the hexahydro-2*H*-pyrido-[2,1-a]isoquinoline derivative **96** that on treatment with diethylamine gives the hexahydro-2*H*-pyrido[2,1-a]isoquinoline carboxamide derivative **97**. The keto function is reduced by hydrogenation over Raney nickel, and the synthesis is completed by acetylation using acetic anhydride (Scheme 22).

Denopamine **100**, which is a β_1-receptor agonist and orally active cardiostimulant, is also synthesized using **81** as a building block in a two-step synthetic process. 1-(4-Benzyl-

(45) Dengel, F. (Knoll AG Chemische Fabriken). DE 1 154 810, 1963.
(46) Dengel, F. (Knoll AG Chemische Fabriken). DE 1 158 083, 1963.
(47) Dengel, F. (Knoll AG Chemische Fabriken). U.S. Patent 3,261,859, 1966.
(48) Tretter, J. R. (Pfizer & Co., Inc.). U.S. Patent 3,053,845, New York, 1962.
(49) Lombardino, J. G.; McLamore, W. M. (Pfizer & Co, Inc.). U.S. Patent 3,055,894, 1962.
(50) Tretter, R. (Pfizer & Co, Inc.). BE 621 895, 1963.
(51) Brossi, A.; Lindlar, H.; Walter, M.; Schnider, O. *Helv. Chim. Acta* **1958**, *41*, 119.

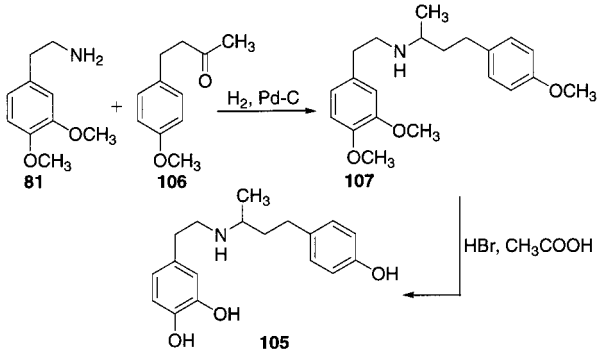
Scheme 23



oxyphenyl)-2-chloroethanone **101** is reacted with **81** to form 1-(4-benzyloxyphenyl)-2-[2-(3,4-dimethoxyphenyl)ethylamino]ethanone **102**. The benzylic ketone is reduced by $NaBH_4$ to obtain a racemic mixture of the alcohol **103**, that is then separated by racemic resolution using D(−)-acetylphenylalanine. The last step of this process is hydrogenation over Pd−C to remove the benzyl moiety used to protect the phenolic group. The outline of the process is given in Scheme 23.

The cardiotonic substance dobutamine[52,53] **105** is synthesized in a two-step process starting with the reaction of **81** and 4-(4-methoxyphenyl)butan-2-one **106** and hydrogenation over Pd−C. The following step is treatment with hydrogen bromide in acetic acid, which gives the free phenolic groups on the aromatics. The process is outlined in Scheme 24.

Scheme 24

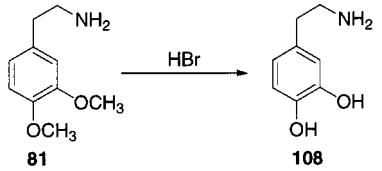


Dopamine **108**, a sympathomimetic, is obtained from homoveratrylamine **81** in one step, namely treatment with hydrogen bromide, to demethylate the phenolic hydroxy groups (Scheme 25).

6.2. Synthesis and Application of (3,4-Dimethoxyphenyl)acetone. (3,4-Dimethoxyphenyl)acetone [1-(3,4-dimethoxyphenyl)propan-2-one] **109** is another very versatile fine chemical that can be derived from the oxidation products of

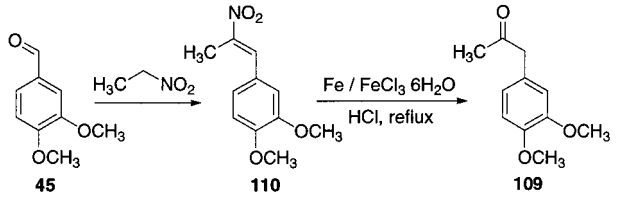
(52) Tuttle, R. R.; Mills, J. (Eli Lilly & Co.). DE 2 317 710, 1973.
(53) Tuttle, R. R.; Mills, J. (Eli Lilly and Co.). U.S. Patent 3 987 200, 1976.

Scheme 25



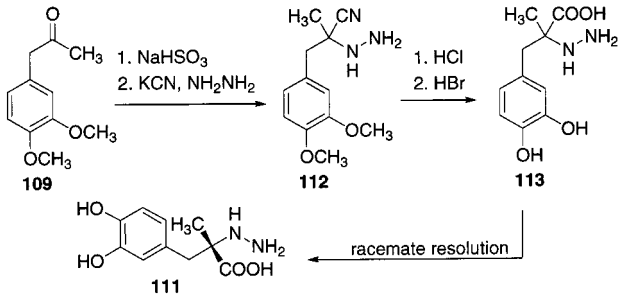
lignosulfonates. The compound can be applied in a wide range of pharmaceutical chemicals used in some different therapeutic areas. (3,4-Dimethoxyphenyl)acetone **109** is synthesized from veratraldehyde **45** by treatment with nitroethane to obtain the intermediate 1-(3,4-dimethoxyphenyl)-2-nitro-1-propene **110** which is then reduced by refluxing for several hours in the presence of $Fe/FeCl_3\ 6H_2O$ and concentrated hydrochloric acid.[54−56] The process is given in Scheme 26.

Scheme 26



Carbidopa **111**, a decarboxylase inhibitor used in levodopa therapy, is synthesized from **109**. The derivative **109** is, in the first step of the synthetic process, treated with sodium hydrogen sulfite and reacted with potassium cyanide and hydrazine to obtain 3-(3,4-dimethoxyphenyl)-2-hydrazino-2-methylpropionitrile **112**. In the following steps, the nitrile group is hydrolyzed to the carboxylic acid, and the phenolic hydroxyl groups are demethylated by treatment with the strong mineral acids, hydrochloric and hydrobromic acids. The last step is constituted by racemate resolution to obtain carbidopa **111**. The process is shown in Scheme 27.

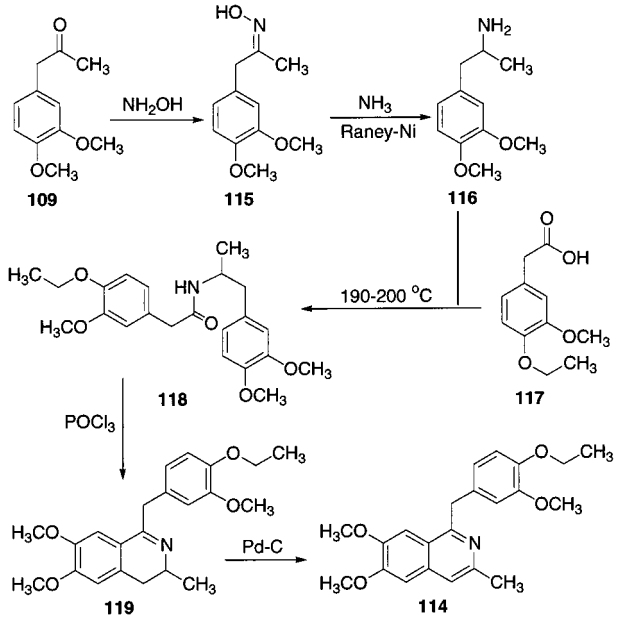
Scheme 27



The antispasmodic and vasodilator dimoxyline[57] **114** is also synthesized using **109**. The first step of the process is the reaction of **109** with hydroxylamine to obtain 1-(3,4-dimethoxyphenyl)propan-2-one oxime **115**, which is then treated with NH_3 over Raney nickel to yield 2-(3,4-

(54) Pearl, I. A.; Beyer, D. L. *J. Org. Chem.* **1951**, *16*, 221.
(55) Shepard, E. R.; Noth, J. F.; Porter, H. D.; Simmans, C. K. *J. Am. Chem. Soc.* **1952**, *74*, 4611.
(56) Chuksanova, A. A.; Sergeeva, L. L.; Shorygina, N. N. *Otdel. Khim. Nauk* **1959**, 2219.
(57) Shepard, E. E. (Eli Lilly & Co.). U.S. Patent 2,728,769, 1955.

Scheme 28

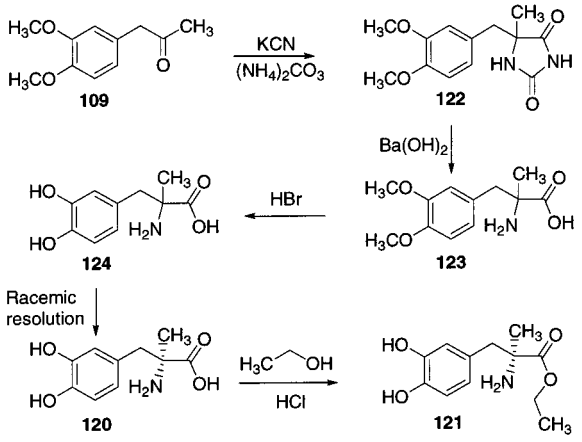


dimethoxyphenyl)-1-methylethylamine **116**. In the subsequent step, this substance is reacted with (4-ethoxy-3-methoxyphenyl)acetic acid **117** at elevated temperature, giving the amide *N*-[2-(3,4-dimethoxyphenyl)-1-methylethyl]-2-(4-ethoxy-3-methoxyphenyl)acetamide **118**, which is treated with phosphorus oxychloride and then with Pd−C to give dimoxyline **114**. The process is outlined in Scheme 28.

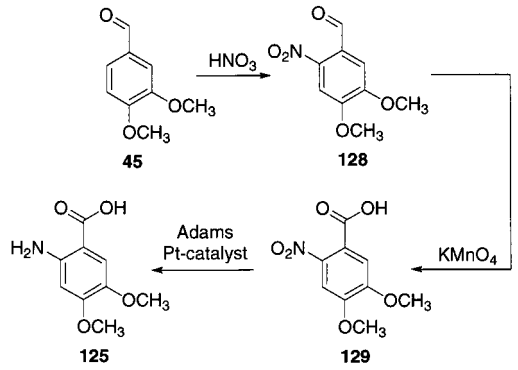
Methyldopa **120** and methyldopate **121** are both antihypertensive agents. The synthesis of these compounds starts by the reaction of **109** with potassium cyanide and ammonium carbonate to obtain 5-(3,4-dimethoxybenzyl)-5-methylimidazolidine-2,4-dione **122**. Treatment of **122** with barium hydroxide yields 2-amino-3-(3,4-dimethoxyphenyl)-2-methylpropionic acid **123**. Some different synthetic pathways may be followed from this point of the process.

An example given in the Scheme 29 shows how the intermediate **123** is treated with HBr to liberate (demethylate) the phenolic groups, and this is followed by a racemate resolution step based on selective crystallization. The synthetic process to methyldopate **121** consists of only one more synthetic step, namely, building the methyldopa ethyl

Scheme 29



Scheme 30



ester. This is carried out by means of ethanol and hydrochloric acid. The processes to methyldopa **120** and methyldopate **121** are shown in Scheme 29.

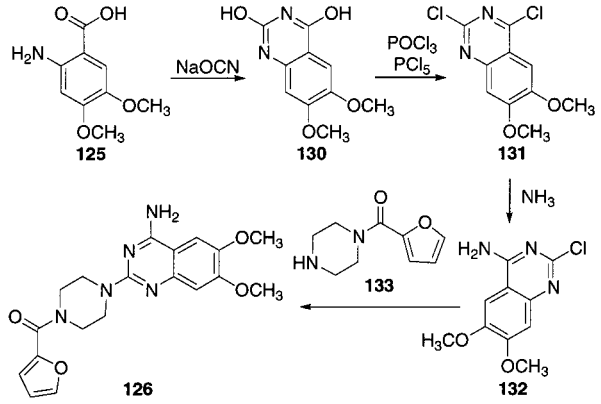
6.3. Synthesis and Application of 4,5-Dimethoxyanthranilic Acid. 4,5-Dimethoxyanthranilic acid [2-amino-4,5-dimethoxybenzoic acid] **125** has been used in the synthesis of the two antihypertensive compounds: prazosin[58−61] **126** and terazosin[62−65] **127** (α-blocker). The preparation[66,67] of 4,5-dimethoxyanthranilic acid **125** can be performed via a three-step synthetic process.[67] The first step is to prepare 6-nitroveratraldehyde **128** by nitration of veratraldehyde **45** with a subsequent oxidation of the formyl group in **128** with potassium permanganate to give the corresponding benzoic acid **129**. The product **129** is dissolved in ethanol, and catalytic reduction using Adams platinum catalyst provides the pure amino acid **125** in high yield. The process is given in Scheme 30.

Prazosin[58] **126** can be synthesized by reaction of **125** with sodium cyanate, to give 6,7-dimethoxyquinazoline-2,4-diol **130** which is then dichlorinated in the subsequent step, using $POCl_3$ and PCl_5. Treatment with NH_3 gives 2-chloro-6,7-dimethoxyquinazolin-4-ylamine **132** that is reacted with furan-2-yl-piperazin-1-ylmethanone **133** to yield the target molecule prazosin **126**, see Scheme 31.

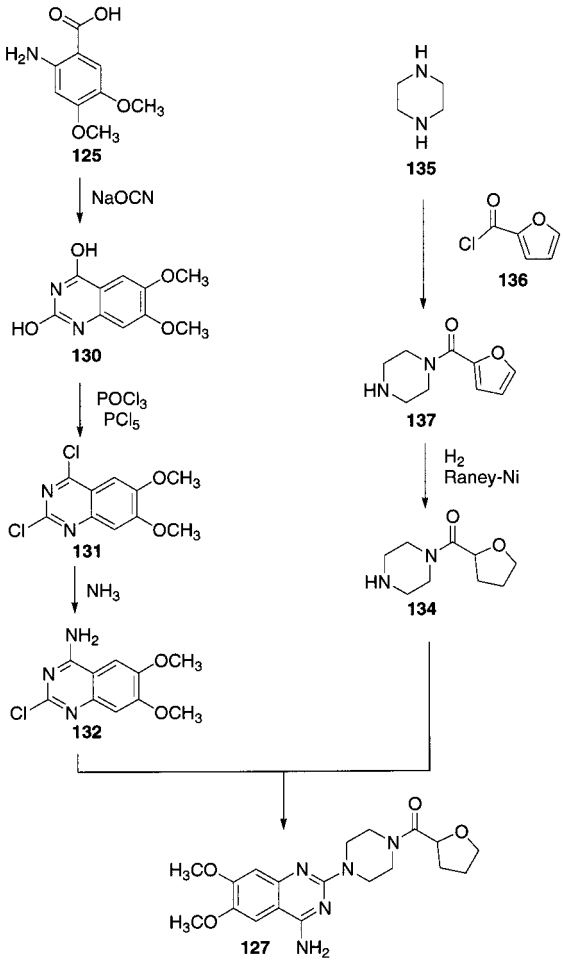
Terazosin **127** is also prepared following a short convergent synthetic process starting from 4,5-dimethoxyanthranilic acid **125** to obtain 2-chloro-6,7-dimethoxyquinazolin-4-ylamine **132**, following a synthetic path similar to that of the process to prazosin **126**. This compound serves as one of two key intermediates. The other key intermediate piperazin-1-yl-(tetrahydro-furan-2-yl)methanone **134** is obtained by reacting piperazine **135** with furan-2-carbonyl chloride **136**, giving furan-2-yl-piperazin-1-ylmethanone **137** which is then hydrogenated over Raney nickel to give the compound **134**, Scheme 32.

(58) Hess, H.-J. E. (Pfizer & Co. Inc.). U.S. Patent 3,511,836, 1970.
(59) Hess, H.-J. E. (Pfizer & Co. Inc.). U.S. Patent 3,635,979, 1972.
(60) Hess, H.-J. E. (Pfizer & Co. Inc.). U.S. Patent 3,663,706, 1972.
(61) Hess, H.-J. E. (Pfizer & Co. Inc.). DE 1 620 138, 1970.
(62) Winn, M.; Kyncl, J.; Dunnigan, S. A.; Jones, P. H. (Abbott Laboratories). DE 2 646 186, 1977.
(63) Winn, M.; Kyncl, J.; Dunnigan, S. A.; Jones, P. H. (Abbott Laboratories). U.S. Patent 4,026,894, 1977.
(64) Roteman, R. (Abbott Laboratories). DE 2 831 112, 1981.
(65) Roteman, R. (Abbott Laboratories). U.S. Patent 4,251,532, 1979.
(66) Heidelberger, N.; Jacobs, W. A. *J. Am. Chem. Soc.* **1919**, *41*, 2131.
(67) Fetscher, C. A.; Bogert, M. T. *J. Org. Chem.* **1939**, *4*, 71.

Scheme 31



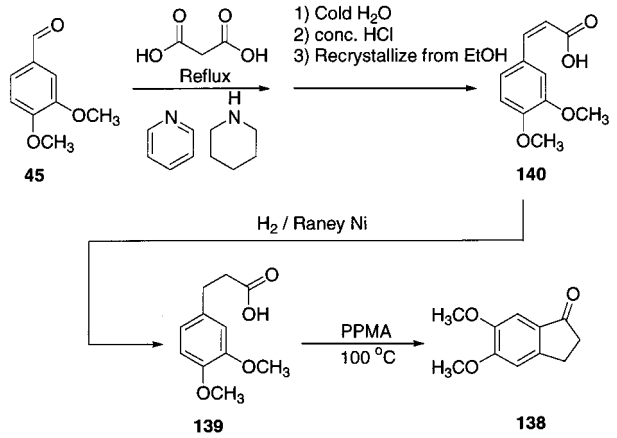
Scheme 32



6.4. Synthesis and Application of 3-(3,4-Dimethoxyphenyl)acrylic Acid, 3-(3,4-Dimethoxyphenyl)propionic Acid, and 5,6-Dimethoxyindan-1-one. 5,6-Dimethoxyindan-1-one **138** belongs to another class of *third-generation* fine chemicals that may be obtained from lignosulfonate. The synthetic process[68] to 5,6-dimethoxyindan-1-one **138** is performed by treating 3-(3,4-dimethoxyphenyl)propionic acid **139** with PPMA (*p*hosphorus *p*entoxide *m*ethanesulphonic *a*cid) at a temperature of 100 °C. After only few minutes, the reaction mixture can be worked up, affording the pure

(68) Cho, H.; Matsuki, S. *Heterocycles* **1996** *43*, 127.

Scheme 33



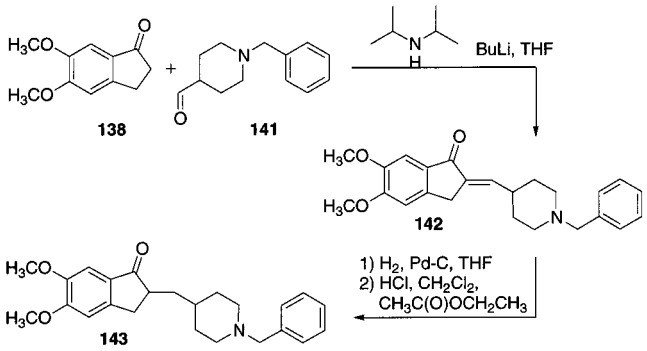
product **138** in 95% yield, Scheme 33. The reaction can also be performed using PPA (*p*oly*p*hosphoric *a*cid), albeit PPMA is superior since PPA is very troublesome to handle due to the viscosity. Several other methods for construction of the indanone framework have also been reported in the chemical literature.[69−71]

The synthesis[72,73] of 3-(3,4-dimethoxyphenyl)propionic acid **139** can be performed by reacting veratraldehyde **45** and malonic acid in the presence of pyridine and piperidine first at 80 °C than at reflux. The reaction is quenched by pouring the reaction mixture into cold water followed by acidifying with concentrated hydrochloric acid. The obtained product, 3,4-dimethoxycinnamic acid [3-(3,4-dimethoxyphenyl)acrylic acid] **140**, is isolated by filtration and purified by recrystallization from aqueous ethanol (90%). The 3-(3,4-dimethoxyphenyl)propionic acid **139**, is obtained by reduction of **140** (e.g., by hydrogenation over Raney nickel),[74] Scheme 33.

Similar to many of the other derivatives from lignosulfonate, 5,6-dimethoxyindan-1-one **138** is also very versatile. It is used in the preparation of truxenes as mesogens for discotic liquid crystal,[75] and it is a key intermediate in an organic process[76] to donepezil hydrochloride **143** that is used for the treatment of cognitive disorder and as an acetylcholinesterase inhibitor. It is used as the active ingredient in the anti-Alzheimer drug Aricept. The pharmaceutical chemical **143** is synthesized by reacting 5,6-dimethoxyindan-1-one **138** with 1-benzylpiperidine-4-carbaldehyde **141** in the presence of BuLi, diisopropylamine, and tetrahydrofuran. The intermediate 2-(1-benzyl-piperidin-4-ylmethylene)-5,6-dimethoxyindan-1-one **142** is hydrogenated over Pd−C and treated with HCl in methylene chloride and ethyl acetate to obtain donepezil hydrochloride **143**. The process is outlined in Scheme 34.

(69) Kusama, H.; Narasaka, K. *Bull. Soc. Chem. Jpn.* **1995**, *68*, 2379.
(70) Taniguchi, K.; Yoshimura, T. Tokuno; Kosugi, T. (Fukuju Pharmaceutical Co., Ltd.). JP 11302216, 1999.
(71) Laurain N.; Saint Jalmes, L. (Rhone Poulenc Chimie). FR 278 8764, 2000.
(72) De Silva, S. O.; Ahmad, I.; Snieckus, V. *Can. J. Chem.* **1979**, *57*, 1598.
(73) Koo, J.; Fish, M. S.; Walker, G. N.; Blake, J. *J. Org. Synth. Coll.* **1963**, *IV*, 327.
(74) Tuttle, R. E.; Mills, J. (Lilly, Eli, and Co.) DE 2,317,710, 1973.
(75) Sato, Y.; Takimoto, J. (Nippon Oil Co., Ltd.). JP 11092427, 1999.
(76) Kunizou, H.; Yoshiharu, Y.; Hiroo, O.; Yuoichi, I.; Norio, K.; Takashi, K.; Michiko, K.; Atsuhiki, K.; Atsushi, S.; Yutaka, T.; Kiyomi, Y.; Shin, A.; Mansion, K.; Hachiro, S. (Eisai Co Ltd.). EP 296 560, 1988.

Scheme 34



7. Conclusions

When browsing the chemical literature it is interesting to see how simple "old" molecules such as vanillin **4**, vanillic acid **5**, and acetovanillone **6** are still used as substrates for new drugs and other fine chemicals.

Degradation of the complex materials, lignosulfonates, affords a large variety of compounds **4**−**18** (Scheme 5) that may be potential building blocks for more complex molecular entities. Due to the low achieved yields of most of these substances, only a very few of the *first-generation* fine chemicals have been isolated for further synthetic applications. Even though only a very few of the *first-generation* fine chemicals from oxidation of lignosulfonates have been isolated, a huge variety of organic processes to pharmaceutical chemicals are based on them. Future discovery and optimization of more selective depolymerization processes of lignosulfonates may extend the employment of such fine chemicals as building blocks.

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