Organic Process Research & Development **2003**, *7*, 459–470

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during December 2002 through March 2003

Summary

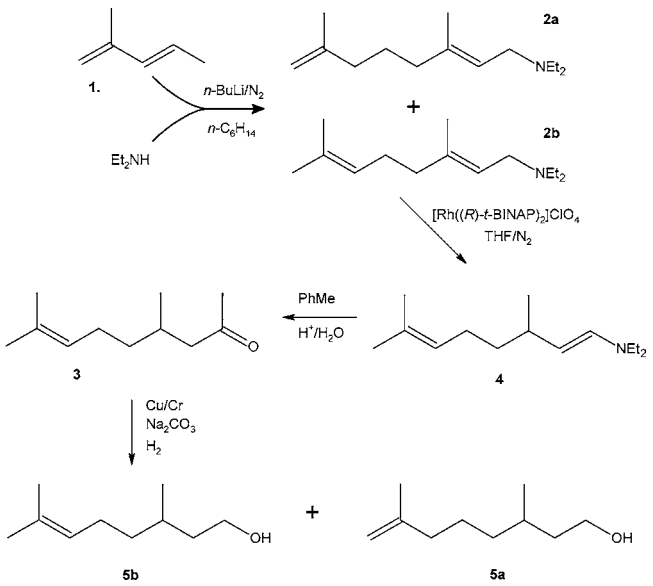
The initial search for this review produced 631 patents that fitted the search criteria, and of these 25 have been selected as being of interest to readers and have been summarised. There is no legal or commercial significance in the choice of patents, and it is hoped they cover a sufficiently broad range of topics to be of wide interest. Four patents from three companies are on the subject of the anticonvulsant drug gabapentin. One of these provides a new synthetic route involving a novel alkylation reaction of anions formed by Birch reduction. A novel synthetic route to the anti-cancer drug paclitaxel from taxanes is described. The route involves a selective reaction of hydrazine so that mixtures of taxanes can be used. Another patent on the synthesis of paclitaxel shows improvements over a previous route, allowing higher concentrations of substrates to be employed. Statin drugs continue to receive a great deal of attention, and three patents cover different aspects. All routes are hampered by the equilibrium between a hydroxyacid and lactone which makes purification difficult. One patent avoids the need for protecting a key OH group during a methylation step, thereby reducing the total number of steps. The other two patents cover improved purification methods. The use of a spinning disc reactor (SDR) for the preparation high-purity acid chlorides and amides is described. The products are used as bleach catalysts and often are difficult to purify because they are fairly reactive. The formation of a range of methyl esters using dimethyl carbonate is proposed as a way of avoiding handling more hazardous materials such as MeI or $(MeO)_2SO_2$. The reaction is catalysed by DBU or DABCO. A new route to arylsulphur hydroxamic acids is disclosed which has several novel intermediate sulphides. This patent gives many examples carried out in a 100-gal reactor, indicating that the process is more than a laboratory curiosity. The patent also describes a novel reduction/alkylation reaction of arylsulphonyl halides with trimethyl phosphite to give aryl methyl sulphides. A combination of ion-exchange resin catalysis and pervaporation, as a way of removing water, has been used to improve acetal formation. Acetals are also the subject of another patent in which the process is carried out in a distillation column with only partial conversion to limit byproduct formation. Experimental details in the patents vary from being quite detailed to not very informative. A number do give examples of using substantial quantities of reagents so that it can be inferred that they have scaled up successfully and in some cases gone to commercial production. The advantages claimed in patents are those made in the patent unless this author has prior knowledge. The advantages should be read with caution since the authors of the patent do not always compare their new process with the best alternative and are selective with their discussion of the prior art.

Patent No. U.S. 6,489,522

Assignee: Takasago International Corporation, Tokyo, Japan

Title or Subject: Process for Producing Optically Active 3,7-Dimethyl-6-Octenol and Its Intermediates

The title compound **5b** is commonly known as *S*-citronellol which is a constituent of perfumes. The process of producing **5b** is based on the formation of the intermediate amine compound **2b** from isoprene **1** and a *sec*-alkylamine such as Et_2NH in the presence of an alkyllithium compound such as *n*-BuLi. This route is shown below and is the basis of most of the previous methods used for synthesising **5b**, but it is claimed that long reaction times are often needed to achieve high yields. Reduced reaction times are possible but usually require large excess of **1** and recovery of unreacted **1** is difficult. Hence, these alternative routes are said to be unsuitable for the continuous large-scale production of **5b**.



The route to **5b** disclosed in the patent consists of the following steps that are claimed to be carefully selected to achieve a highly efficient route to **5b**: (1) reaction of the Et_2NH with **1** to give the amine **2b** with about 6% **2a**, (2) asymmetric isomerisation of **2b** to the *R*-enamine **4b** by

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reaction with the *R*-rhodium phosphine complex, (3) hydrolysis of the enamine **4b** to give the aldehyde **3b**, (4) reduction of **3b** to **5b** plus <10% **5a**.

The patent provides experimental details showing the effects of varying the ratio of **1** and Et_2NH as well as varying the reaction time and temperature. It is claimed that for a short reaction time the temperature should be >80 °C and the ratio of **1** to Et_2NH should be >4.

Advantages

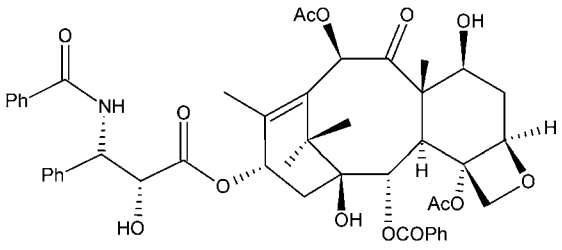
The main advantage is a reduced reaction time by optimising the temperature and reactant ratio in the first step of the process.

Patent No. U.S. 6,495,705

Assignee: NaPro BioTheraputics Inc., Boulder, Colorado, U.S.A.

Title or Subject: Efficient Process for the Production of 10-DAB-III by Selective Hydrazinolysis of Taxanes

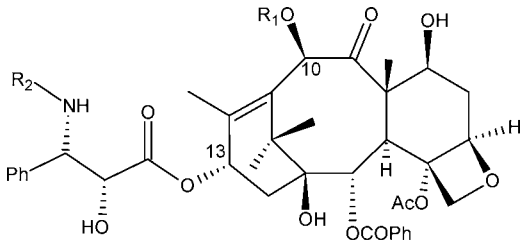
This patent is concerned with the production of 10-deacetyl baccatin-III **7e** which is a precursor to paclitaxel **6**. This is a naturally occurring compound found in the bark of yew trees and has been shown to be useful in treating various cancer tumours. A synthetic route to **6** is desirable because yew trees are very slow growing, and it requires 16 000 kg of bark for 1 kg of **6**. During the extraction of **6** from yew bark several structurally related taxanes are also obtained in higher yields. It is an objective to convert some of these to **7e** to increase the overall yield of **6** precursors from the extracts of the yew tree.



6: paclitaxel

Several of the taxanes found in the yew tree contain side chains connected to the C-13 via the sterically hindered hydroxy function. Some, such as **7a**, **7b**, and **7c** also contain an acetate group at C-10, and as a result, hydrolysis of the C−O bonds at C-13 and C-10 will produce the desired compound **7e**. However, the C-13 is sterically hindered because it is located within the concave hemispherical skeleton; thus its hydrolytic cleavage is difficult. The process described here and shown below, cleaves these bonds using hydrazine in a solvent which reacts with the hydrazine. The preferred solvent is isopropyl acetate.

The use of a solvent that reacts with the substrate is claimed to be surprising and, hence, the novel feature of this patent. Not surprisingly no explanation of this finding is offered. The preferred method is to extract the taxanes with an acetate ester and then adsorb the solution onto silica gel before treating with hydrazine hydrate.



7a: R_1 = Ac, R_3 = tigloyl; Cephalomannine
7b: R_1 = Ac, R_3 = phenylacetyl; Nitine
7c: R_1 = Ac, R_3 = hexanoyl; Taxol C
7d: R_1 = H, R_3 = benzoyl; 10-deacetyl taxol

$N_2H_4.H_2O$
i-PrOAc

7e: R_1 = R_2 = H; 10-DAB III

Advantages

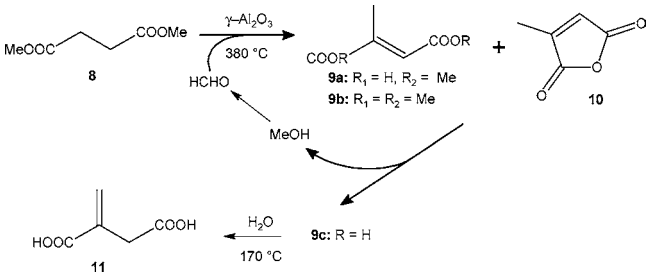
This procedure is more efficient than the alternatives which are not as effective when dealing with a mixture of taxanes.

Patent No. U.S. 6,504,055

Assignee: Board of Trustees of Michigan State University, East Lansing. Michigan, U.S.A.

Title or Subject: Catalytic Process for Conversion of Succinates to Citraconic acid and Itaconic acid

Itaconic acid **11** is used in the production of various polymers containing free carboxyl groups and is manufactured by fermentation of glucose using *Aspergillus terreus*. The existence of the carboxylic groups provides functionality and improvement of the properties of the resulting polymers. There are references to catalytic routes to **11** based on the condensation of succinic anhydride or the ester **8** with formaldehyde; however, there are no commercial processes based on these proposals. The current patent describes a process route shown below to produce **11** from **8** via **9c** using a porous γ-alumina catalyst for the condensation step. The patent also covers the complete process including a step to oxidise the MeOH to formaldehyde which is recycled to the first stage.



The condensation reaction produces three main products **9a, 9b**, and **9c** as shown, and these are hydrolysed to give the acid **9d**. A key feature of the process is the recovery of succinic acid from the hydrolysis mixture by crystallisation before isomerisation is carried out. The isomerisation of **9d** to **11** is a partial conversion process, and this prevents formation of byproducts and enables recovery of **11** by

recrystallisation to be improved. The production of the alumina catalyst is a key aspect of the patent as well as the process itself.

Advantages

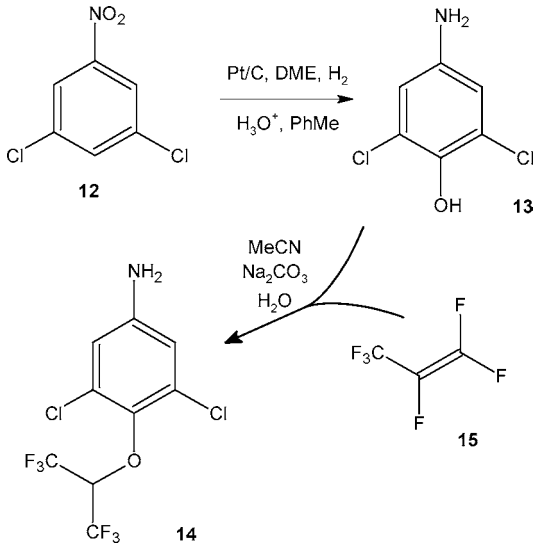
The process produces a high yield of **11** in a more efficient and economical manner than the fermentation route.

Patent No. U.S. 6,504059

Assignee: Bayer AG, Leverkusen, Germany

Title or Subject: Process for Converting Nitrobenzene to a Halo-4-aminophenol

The patent describes a method for producing aniline compounds such as **14** that are used to manufacture insecticidal ingredients. The normal methods for preparing such materials involve reaction of halogenated olefins with a variety of substrates such as nitrophenols or N-acylated nitrophenols. Such methods are said to involve several steps and hence the potential for high yield losses. The present process involves the reaction of a fluoroolefin such as **15** with the aminophenol **13**. The overall process is shown below and first involves a catalytic reductive hydroxylation of the nitro compound **12** in an acidic aqueous solution to give **13**. In the second stage **13** is treated with the olefin **15** in MeCN in the presence of a base such as Na_2CO_3 or Et_3N in aqueous solution.



It was found that a polar solvent such as MeCN was necessary in the second stage, and if it was not used the yield dropped from 90% to only 10%.

Advantages

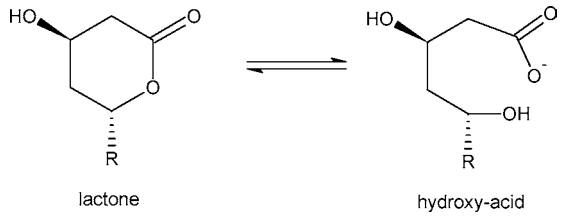
This process only requires two steps, starting from readily obtainable materials and is not as complex as alternative procedures.

Patent No. U.S. 6,506,929

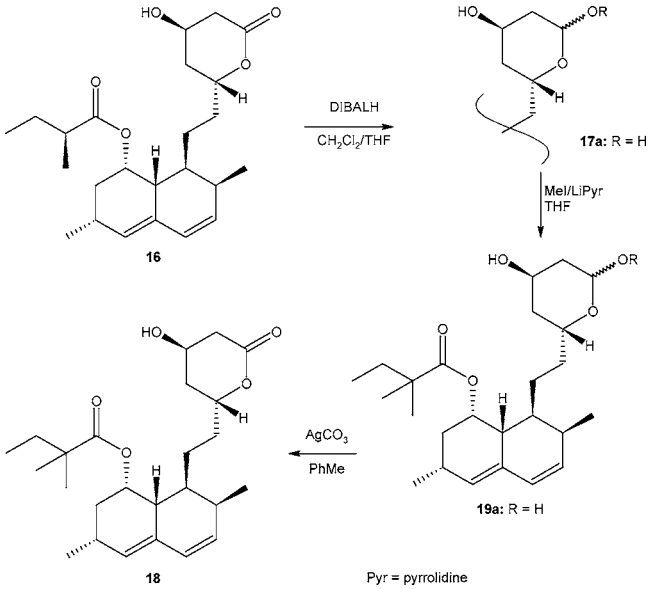
Assignee: Apotex Inc., Weston California, U.S.A.

Title or Subject: Process for the Manufacture of Simvastatin and Intermediates from Lovastatin

There is a great deal of interest in statins because they are capable of inhibiting cholesterol biosynthesis and are generally useful for treating cardiovascular diseases. Two further patents on these materials are summarised later in this review. Lovastatin **16** is sold by Merck under the name Mevacor, and there are reports that simvastatin **18** is twice as potent as **16**. The recovery and purification of statins is difficult because the compounds exist as open-ring hydroxy acids that are in equilibrium with the lactone form as shown below.

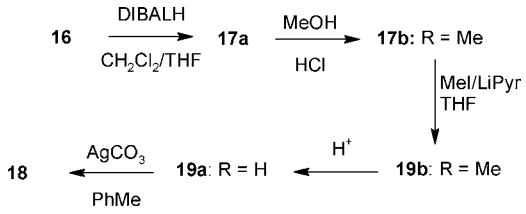


Hence, synthetic methods to give statins usually involve a strategy to protect the reactive group, and several methods are available but they all are said to have numerous steps and hence give low overall yields. This patent describes a procedure that has a reduced number of steps partly because it avoids the need to protect the 13-OH group. There are two routes from **16** to **18** described in the patent, and the first is shown below.



This is a three-step process in which the first step is selective reduction of the carbonyl group in **16** using DIBALH to give the hemiacetal **17a**. The key step is methylation of **17a** with MeI using a strong base such as Li pyrrolidine in THF gives **19a**. This step is highly regioselective without the need for protection of the 13-OH group in **16** that is necessary in alternative methylation procedures. The final step is oxidation of **19a** to **18** using $AgCO_3$ on Celite in toluene.

The alternative approach, which is shown below, is to convert the hemiacetal **17a** to the acetal **17b** using MeOH/HCl followed by methylation to give **19b**. This is then converted to the **19a** using mild acidic conditions, and subsequent oxidation of **19a** gives **18** as above. Although the second route has two extra steps, it is said to be simple, and each step proceeds in high yield.



The patent gives a summary of several other routes to statins, most of which involve manipulation of the lactone/hydroxy acid function and hence are claimed to be less efficient than the method described here.

Advantages

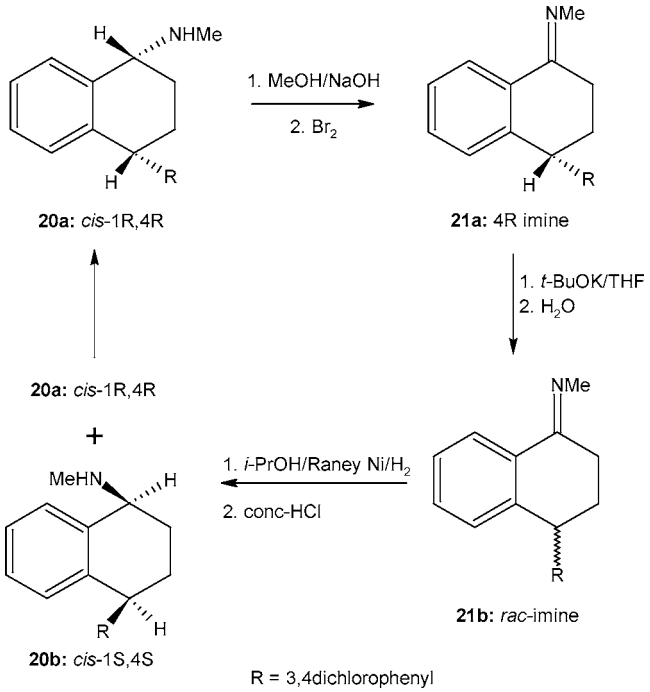
The avoidance of having to use a protective/deprotective strategy significantly reduces the complexity of the process and yet still gives a highly selective route to this important material.

Patent No. U.S. 6,506,940

Assignee: Sun Pharmaceutical Industries Ltd., Mumbai, India

Title or Subject: Process for Converting Stereoisomers of Sertraline into Sertraline

Sertraline **20b** is an antidepressant originally disclosed by Pfizer in 1985 and is now of great interest because of the expiration of the original patents. A number of patents on this subject have recently been reviewed (*Org. Process Res. Dev.* **2003**, *7*, 135), and this current patent describes a process for producing the desired *cis*-(1*S*,4*S*) isomer **20b** from the other three undesired stereoisomers via formation of an imine and a subsequent resolution. The scheme below shows the procedure for converting the cis(1*R*,4*R*) isomer **20a** to a mixture of the *cis*-isomers **20a** and **20b**.



The first step is production of the 4*R*-imine **21a** by oxidation using by Br_2 in the presence of NaOH which is then racemised to **21b** by treatment with a nonnucleophilic base such as *t*-BuOK. Catalytic hydrogenation of **21b** using Raney Ni gives the *cis*-isomers **20a** and **20b**. The desired isomer is recovered from the mixture by conventional resolution method such as fractional crystallisation, allowing the undesired isomer **20a** to be recycled. An example of applying the process to trans isomer pair going via the 4*S* imine is also given. The patent claims that the imine can be produced by oxidation of **20a** by using NBS or a hypohalide in place of Br_2, but no examples of this are given.

Advantages

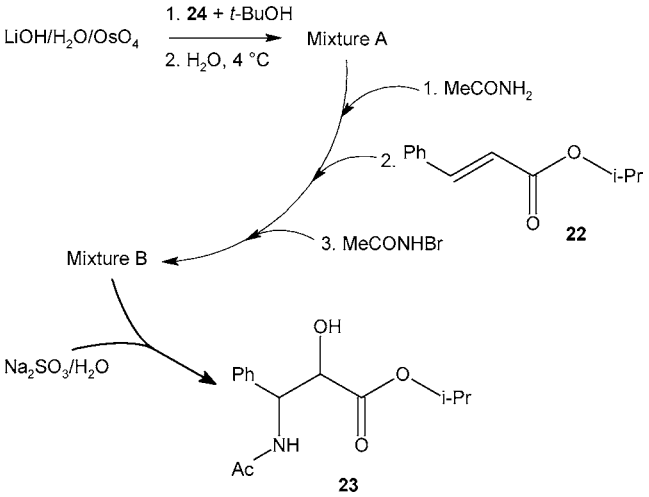
The process allows recycling of the undesired stereoisomers of **20b** to be used to enhance the yield of a non-sterospecific synthesis of **20b**.

Patent No. U.S. 6,509,491

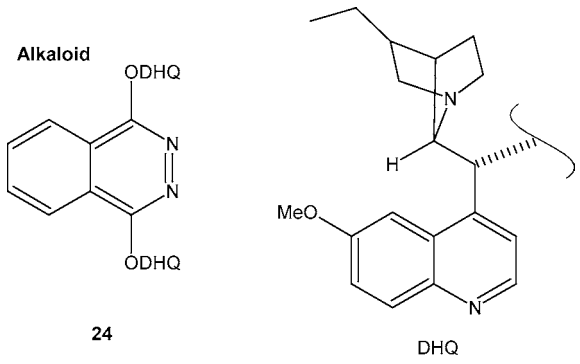
Assignee: Pharmacia & Upjohn Company, Kalamazoo, Missouri, U.S.A.

Title or Subject: Aminohydroxylation of Cinnamate to give Phenylisoserine Esters

The phenylisoserine esters such as **23** are intermediates in the synthesis of taxol (paclitaxel) **6** which is useful in treating various tumours. The process described here is similar to a previously known procedure involving the use of an osmium-catalysed aminohydroxylation of the cinnamate **22** in the presence of a cinchona alkaloid and *N*-bromoacetamide. This method is stereospecific, and by using the procedure of this patent much higher substrate levels can be employed. This is possible because the process is performed in the presence of acetamide, and the patent specifically has claims to this effect. It is said that the earlier method only permits the use of 1 g of substrate in 60 mL of solvent before byproduct formation increases. The current process claims that much higher, but unspecified concentrations, are possible without increased byproduct formation. The process route is shown below.



The first step is to make an aqueous mixture A from LiOH and OsO_4 with a cinchona alkaloid such as **24**. The mixture A is then treated at 4 °C with acetamide, **24** and an oxidising agent such as *N*-bromoacetamide which is present in stoichiometric amount. The reaction mixture B is then quenched with Na_2SO_3 and the product extracted with EtOAc.



Advantages

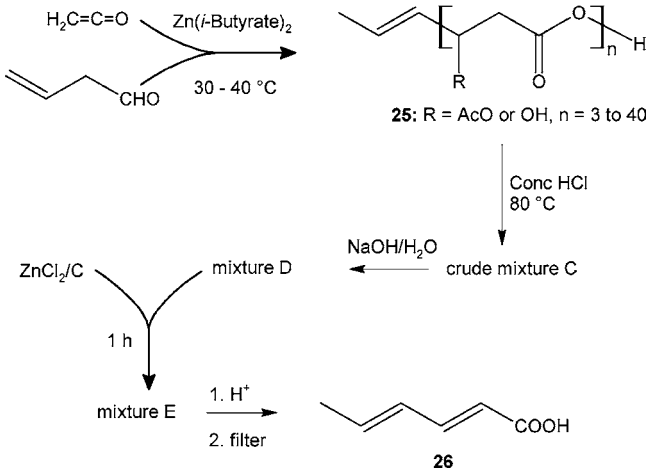
The ability to use higher concentrations of substrate in the reaction gives a more efficient method of recovery and purification of the product.

Patent No. U.S. 6,509,498

Assignee: Daicel Chemical Industries Ltd., Osaka, Japan

Title or Subject: Process for Preparing Sorbic Acid and Its Salts with Improved Color Transmittance

Sorbic acid **26** is a widely used as a food additive, and hence there are stringent limits on the levels and types of impurities that are allowed. It can be prepared by the decomposition of the polyester **25** that is produced from ketene and crotonaldehyde as shown below.



This method gives large quantities of tar-like materials, and traces of them impart a dark colour to solutions of **26**. There are procedures for reducing the impurities based on the use of activated carbon, but the efficiency is very dependent on the type and activation method of the carbon. It is claimed that the decolourisation method severely impacts on the crystallisation process that is used to further purify **26**. The process in this patent involves a chemical method of activating the carbon with $ZnCl_2$. The patent is specifically aimed at purifying **26** that has been made by the route shown above. The activation of the carbon appears to be carried out at the same time as the decolourising step since no separate stage is described in the patent. The method is applicable to both free **26** and its salts which are obviously present in mixture D.

Advantages

The process provides a more effective method of removing the impurities that cause discolouration of sorbic acid solutions.

Patent No. U.S. 6,515,132

Assignee: Torrent Pharmaceuticals Ltd., Abmedabad, India

Title or Subject: Process for Preparation of Rosiglitazone Maleate

The rosiglitazone **34a** is used in the form of the dimaleate **34b** as the preferred drug for the treatment of noninsulin-dependent diabetes mellitus. Processes for preparing **34b** generally involve a base-catalysed coupling reaction of 4-fluorobenzaldehyde **31** with the pyridyl compound **29**. NaH is a often used as the base, and it is claimed that the yield from these routes is at best 87% of crude material. Hence, there is potential for improvement, and the present process uses the same basic route but claims a yield of pure **34b** that is in excess of 90−95%.

The process route is shown below and initially involves production of **29** from the reaction of 2-chloropyridine **27** with amino alcohol **28**. No reaction conditions are indicated in the patent for this step. The next step is the key coupling reaction between **29** and **31** to give **30** which is carried out in an aprotic solvent such as DMF in the presence of *t*-BuOK at room temperature. A Knoevenagel condensation reaction between **30** and thiazolidine **32** in the presence of piperidine acetate in a Dean Stark apparatus gives **33**. Reduction of **33** using Mg in MeOH then gives **34a**, and treatment of **34a** with maleic acid in acetone gives the dimaleate **34b** in 90−95% yield. The low moisture content of **34b** means that it can be easily handled and used to prepare a pharmaceutical composition. It is claimed that the level of impurity in **34b** obtained by this process is so low (<0.1%) that under current USFDA and international regulations there is no need for further analysis.

Advantages

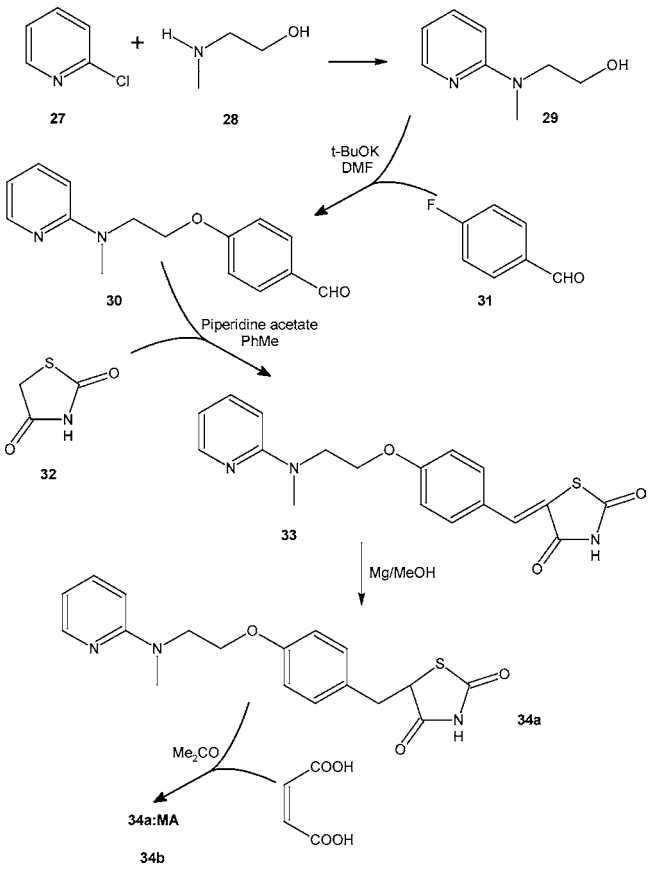
The new process is able to produce the desired product at a very high purity and in higher yield than was previously possible. This is made possible by carrying out the process at room temperature using a stronger base such as *t*-BuOH instead of NaH.

Patent No. U.S. 6,515,153

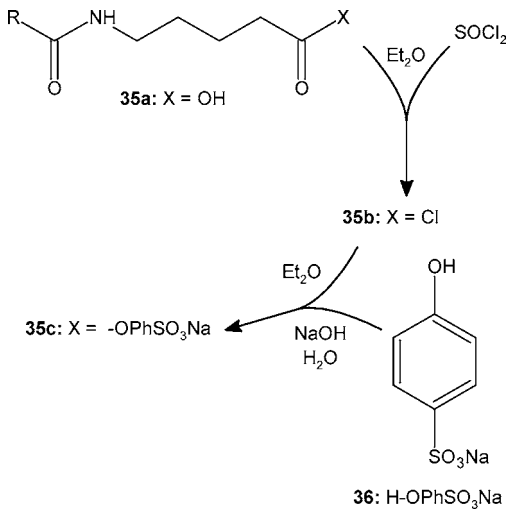
Assignee: The Proctor & Gamble Company, Cincinnati, Ohio, U.S.A.

Title or Subject: Use of a Spinning Disc Reactor for Preparation of Amide Esters and Acid Chlorides

The spinning disc reactor (SDR) is an example of process intensification in which the size of equipment is significantly reduced to minimise costs and improve performance. A common example which uses an applied accelerating force to enhance the settling of solids in liquids is the centrifuge. The use of gravity alone requires much larger equipment and long settling times. The SDR is a development of the spinning disc distillation unit known as Higee that was



developed in the United Kingdom in the 1980s. Both the SDR and the Higee unit provide very intensive mixing of fluids by the use of an applied centrifugal force. In this patent the actual type of SDR is not disclosed although a basic unit consists of a set of enclosed discs rotating at speeds up to 2000 rpm. Reactants are fed into the centre of the reactor via separate pipes and are intensely mixed as they are thrown outwards. The products are collected at the periphery of the unit and the residence time can be adjusted by the rotational speed and the diameter of the plates. Some plates may also have ridges to impede flow and enhance mixing. The patent uses a SDR to produce the amido ester **35c** by a conventional reaction from the amino acid **35a** by the route shown below.



The process involves two steps, and both are carried out using a SDR. The first step is the formation of the acid chloride **35b** from **35a** and $SOCl_2$. The second step is formation of the amido ester **35c** by reaction of **35b** with the sodium salt **36** at a pH of 9. In both steps the flow rates of reactants are carefully controlled to ensure a 1:1 molar ratio. The justification for using this method is that conventional procedures for forming **35c** give significant amounts of byproducts formed by transesterification and transamidation reactions. The amido ester **35c** is used as a bleach catalyst in detergents, and this process avoids the need for costly purification steps which are necessary due to the high levels of byproducts normally formed. The process is an attempt to overcome the problems of preparing and recovering reactive products before they can further react. If they are produced in a batch process where they are capable of undergoing further reaction, then the byproduct levels will be high. Hence, this is an example of using a continuous process to increase yield by removing products as they are formed.

Advantages

The use of the SDR gives the products in enhanced purity and higher yield than conventional processes.

Patent No. U.S. 6,515,167

Assignee: Novartis AG, Basel, Switzerland

Title or Subject: Preparation of Methyl Esters From Dimethyl Carbonate Using DABCO or DBU as Catalysts

This patent is an attempt to avoid the use of hazardous methylating agents such as MeI or $(MeO)_2SO_2$ in the preparation of methyl esters. It is claimed that it is environmentally safer to use dimethyl carbonate (DMC) as a methylating agent because it generates only MeOH and CO_2 as byproducts. Previous attempts at using DMC for preparing methyl esters are said to require the use high temperatures and pressures, thus limiting its use.

The process is used in preparing methyl esters such as **37b** and **38** and **39** from the corresponding acids as well as more simple esters such as methyl benzoate (MB) and methyl phenylacetate. The reactions are carried out by refluxing the acid in DMC which is the reaction solvent. The patent compares the new method of preparing MB using DMC with either DBU or *n*-Bu_3N as catalyst. The use of DBU gives a 98% yield in 2.5 h, whereas using *n*-Bu_3N gives 1% yield in 48 h. This is hardly a reasonable comparison given that *n*-Bu_3N is not usually regarded as a suitable catalyst for this type of reaction.

Advantages

The process is claimed to offer a low-temperature route to methyl esters using an environmentally safe methylating agent.

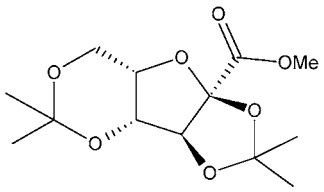
Patent No. U.S. 6,518,456

Assignee: Procos S.p.A., Cameri, Italy

Title or Subject: Process for the Production of Gabapentin

Gabapentin **41** is an anticonvulsant known as neurotonin that is used as the hydrochloride salt **41·HCl** to treat cerebral

Methyl Esters



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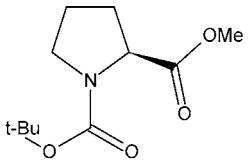

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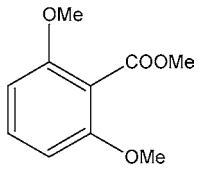
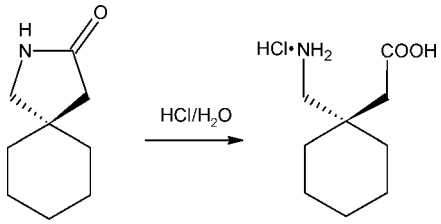


39

diseases such as epilepsy. This is an important drug, and this is the first of three patents in this review covering the recovery of this important material. The free salt **41** can be obtained from the hydrochloride by treatment with ion-exchange resins (IER), and such a method was recently reviewed (*Org. Process Res. Dev.* **2003**, *7*, 135). However, it is claimed that this procedure requires large volumes of solvents and massive amounts of IER. An alternative approach involves a membrane filtration process, but it is claimed such equipment is too complex for industrial use. The current process overcomes both of these problems and uses a crystallisation technique to obtain pure **41** free from inorganic salts or the lactam **40**. The scheme below shows the route to prepare pure **41** from **40** via formation of **41·HCl**.



40 41•HCl

There are a number of steps involved in the purification, and these are summarised in the following: (1) reflux **40** in aqueous HCl from which crystals of crude **41·HCl** are obtained, (2) digest crystals in acetone to remove HCl and dry to recover the hemihydrate HCl salt, (3) treat hot aqueous solution of crystals from **2** with NaOH to the amino acid isoelectric point, (4) cool and recover crystals and then wash with EtOH/H_2O to remove excess NaCl, (5) crystallise **41** from deionised water or wash with EtOH/*i*-Pr_2O to remove final traces of NaCl.

There are fairly detailed experimental procedures, and some begin with over 3 kg crude **41**, thus indicating the advanced nature of the process.

Advantages

This process requires shorter reaction times and is simpler than alternative procedures to produce high-purity **41**.

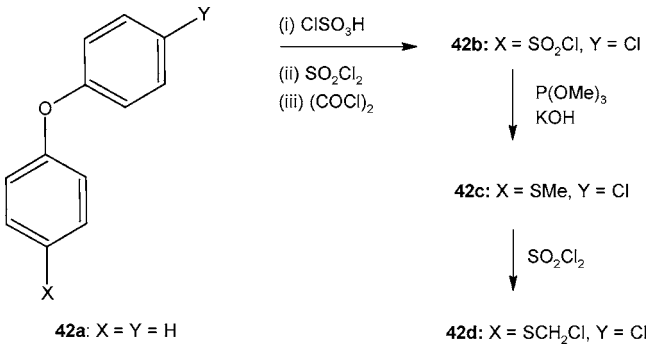
Patent No. U.S. 6, 518,460

Assignee: Syntex (U.S.A.) LLC, Palo Alto, California, U.S.A.

Title or Subject: Process for Preparing 3-Arlsulphur Hydroxamic Acids

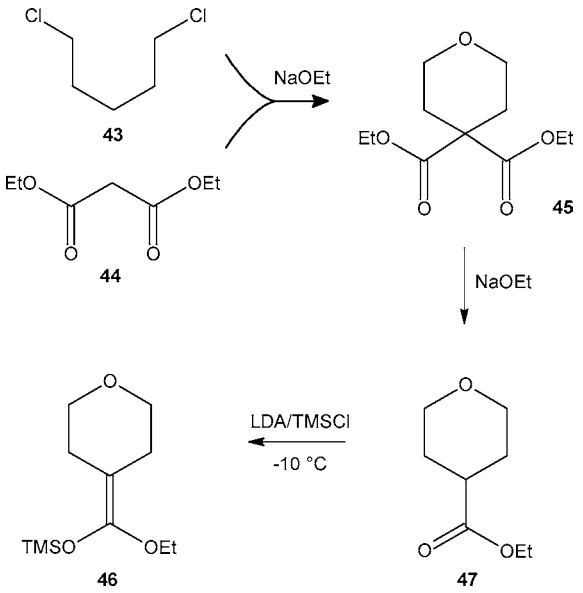
The title compounds such as **49** act as matrix metalloprotease (MMP) inhibitors and therefore are useful in treatment of diseases associated with degradation of connective tissues. This patent discloses a novel method of preparing **49** and also novel sulphide intermediates such as **48a**, **48b**, and **48c**.

The multistep route to **49** is in three stages with the first stage being the production of the aryl ether **42d** as shown below. This involves initial formation of the arylsulphonyl chloride **42b** which is converted in a novel reduction/alkylation reaction to the methyl sulphide **42c** by treatment with $P(OMe)_3$ in KOH. Chlorination of **42c** with SO_2Cl_2 then produces the key intermediate **42b**. The alkylation step is the subject of the first claim of the patent, thus indicating its significance.



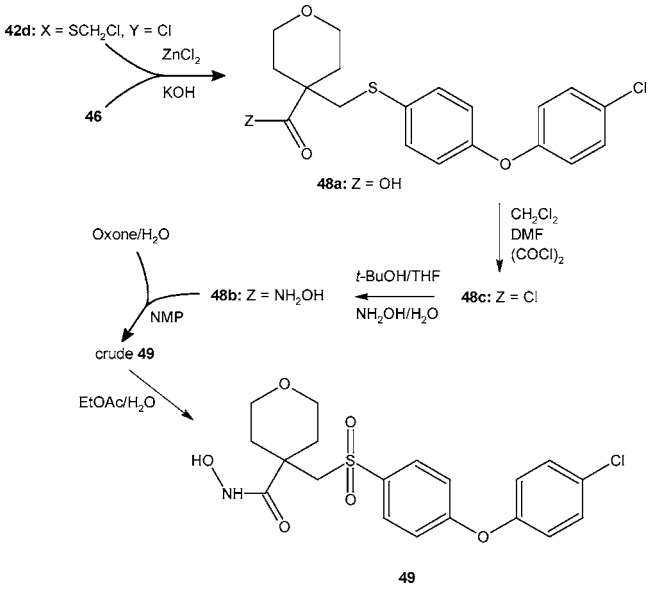
42a: X = Y = H **42b:** X = SO_2Cl, Y = Cl **42c:** X = SMe, Y = Cl **42d:** X = SCH_2Cl, Y = Cl

The second stage of the synthesis is the production of silylketene acetal **46**. This is shown below and begins with the formation of the ester **47** by base-catalysed alkylation of **44** with **43** which initially gives the diester **45**. No details are given for these reactions which are based on literature procedures given in other patents. The ester **47** is then converted to **46** by reaction with LDA and TMSCl.



43 44 45 46 47

The final stage of the process, shown below, begins with the Mukaiyama coupling reaction of **46** with **42d** to give the carboxylic acid sulphide **48a**. This is converted to the acid chloride **48c** using $(COCl)_2$, and then reaction of **48c** with hydroxylamine gives the hydroxamic acid compound **48b**. Oxidation of **48b** using oxone gives crude **49** which is purified by recrystallisation from EtOAc/H_2O.



Some of the examples in this patent describe reactions carried out in 100-gal reactors, indicating that the process is used in commercial production.

Advantages

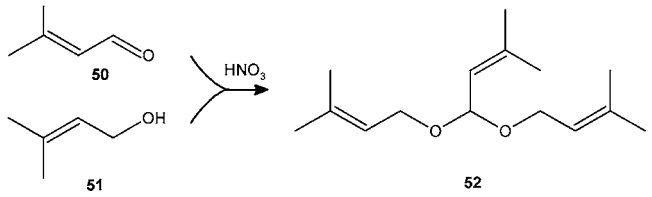
Alternative routes to **49** and related compounds are said to require reagents that are not readily available and which are needed in this process.

Patent No. U.S. 6,518,464

Assignee: BASF Ag, Ludwigshafen, Germany

Title or Subject: Continuous Process for Preparing Unsaturated Acetals

The patent focuses on the acetal **52** which is used in the preparation of the fragrance citral. The process is an acid-catalyzed condensation reaction between the unsaturated aldehyde **50** and allylic alcohol **51** shown below. The preferred acid for this process is nitric acid.



The process is carried out in a packed distillation column with continuous removal of water. With this type of condensation it is very difficult to ensure high conversion with high selectivity because of the reactive nature of the reactants and products. A common problem is the formation of large amounts of byproducts when impure starting materials are used. This is frequently the case because **50** and **51** are rarely available in high purity. The control of the correct amount of acid catalyst is a further problem, and this patent describes a method to overcome such problems. The basis of the method is to limit the conversion of the reaction and then to concentrate the acetal in two successive evaporation stages. Unreacted reagents are recovered and returned to the reaction column.

Advantages

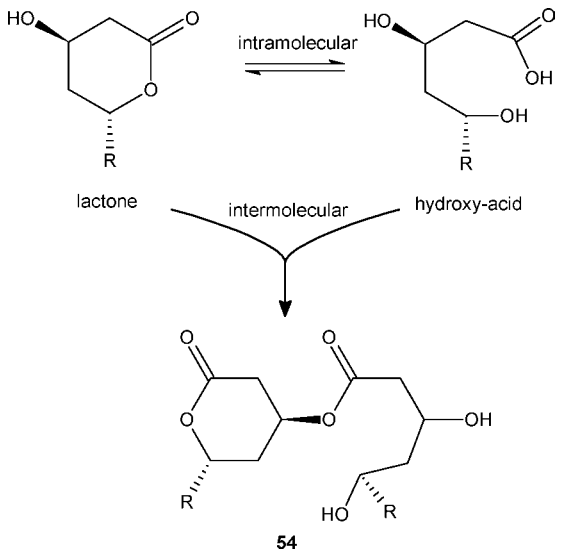
This process is easy to control and therefore gives a high selectivity to the product.

Patent No. U.S. 6,521,762

Assignee: Biogal Gyogyszergyar Rt., Debrecen, Hungary

Title or Subject: Purification of Lovastatin and Simvastatin with Reduced Level of Dimeric Impurities

Statins **53a** and **53b** are of great interest because they are very effective at treating cardiovascular diseases by reducing the levels of cholesterol in the blood stream. This patent is from a company active in the area, and a patent on this subject has previously been reviewed (*Org. Process Res. Dev.* **2002**, *6*, 749). The major problem with statins is the difficulty of purification because they exist as open-ring hydroxy acids in equilibrium with the lactone. The open-ring form is the biologically active material. The conversion is an intramolecular process, but intermolecular lactonisation gives rise to formation of dimeric species **54** as shown below.



These dimeric species may undergo further reactions, giving more byproducts. The statins are usually produced by fermentation, and hence considerable volumes of materials need to be handled in the work-up and purification stage. Thus, any route to the statins needs to limit the amounts of the dimeric species such as **54** or at least provide a simple method for their removal. The current patent uses a mild base such as ammonium hydroxide which selectively hydrolyses **54** without concomitant ring-opening of the lactone ring. The reaction is carried out by heating the statin in a 3:1 mixture of *i*-BuOAc/EtOH with NH_4OH and then

recovering crystals by cooling. The amount of **54** in the final product was <0.08%.

Advantages

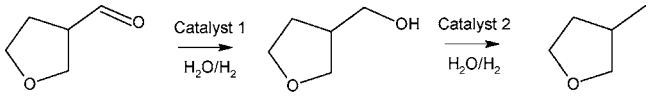
This process provides a simple method of removing byproducts from these important compounds.

Patent No. U.S. 6,521,765

Assignee: Eastman Kodak Company, Kingsport, Tennessee, U.S.A.

Title or Subject: Process for the Preparation of 3-Methyltetrahydrofuran

The title compound **57** is used as a monomer for the production of elastomers and can be prepared from citraconic anhydride. Another patent on the production of **57** from **55** by an alternative route involving a high-temperature pyrolysis step from this company was reviewed a short while ago (*Org. Process Res. Dev.* **2001**, *5*, 100). The current patent involves two hydrogenation steps with different catalysts and is shown below.



55 **56** **57**

The first step uses a supported nickel catalyst, which may be the same as the catalyst in step 2, and is carried out in the presence of water. The second step specifically states that an acidic catalysts is used. The catalysts used in the examples include a commercial catalyst from Criterion C-424. This catalyst contains Ni on alumina modified with P and Mo oxides. Other catalysts that are used contain Ni on Zr and Si oxides, and methods for their preparation are given. The second stage is carried out at about 280 °C and pressure up to 55 bar, using the products from the first step; hence, water is also present. The overall conversion of **56** for the process is nearly 100%, and selectivity is in excess of 80% in many cases.

Advantages

This process is simpler than the previous one from this company and is claimed to be more economical and efficient than alternative routes.

Patent Nos. U.S. 6,521,787 and 6,528,682

Assignee: Medichem S.A., Barcelona, Spain

Title or Subject: Processes for Producing Pharmaceutical Grade Gabapentin

These two patents describe different procedures for obtaining pure forms of gabapentin **41** either as the HCl salt or in the free form. The first patent describes a method to produce a new crystalline polymorphic form of nonhydrated **41** designated Form II. This is obtained by spray drying or turbo drying an aqueous solution of **41**. It has been found that when the new form is crystallised from solvents such as methanol then the original form of **41**, designated Form I, is obtained in high yield and high purity. X-ray and IR data for both forms of **41** are provided.

The second patent describes a method of obtaining pharmaceutical grade **41** from the HCl salt **41·HCl** by neutralisation with a basic IER. This is carried out by the following procedure: (1) dissolve **41·HCl** in MeOH, (2) treat solution with basic IER, (3) concentrate solution by distillation until a suspension of **41** is obtained, (4) add MeOH and water and heat to redissolve suspension, (5) precipitate anhydrous **41** by cooling and also add *i*-PrOH while cooling, (6) recover crystals and dry under vacuum <40 °C.

Advantages

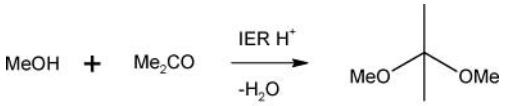
This procedure is claimed not to require the formation of any intermediates and hence is efficient, simple, and economic. The IER may be regenerated although whether this is acceptable under GMP is another matter.

Patent No. U.S. 6,528,025

Assignee: Roche Vitamins Inc., Parsippany, New Jersey, U.S.A.

Title or Subject: Manufacture of Acetals and Ketals Using Ion-Exchange Resins and Pervaporation To Remove Water

The production of acetals or ketals is reversible, and hence water needs to be removed to shift the reaction equilibrium in favour of the products. Removal of water would suffice, but the higher volatility of the starting products often makes this a difficult procedure for many reactions. Pervaporation is a technique that uses membranes to separate vapours, but it does not rely on differences in volatility for its success. The key is to choose a membrane that is hydrophilic and therefore prevents the passage of organic vapours. This patent specifically gives details for preparing **58** from MeOH and Me_2CO as shown below, but the method could be applied to other condensation reactions.



58

The process is shown in Figure 1 and involves the use of acidic IER to catalyse the condensation step. The products of the reaction from vessel A are then fed into a vessel containing a basic IER, and the mixture leaving vessel B is then fed to a pervaporation unit where water is removed.

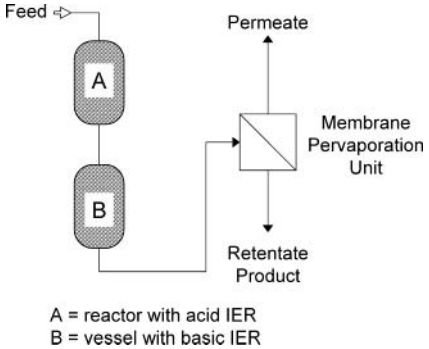


Figure 1. **Acetal production using ion-exchange resins and pervaporation unit.**

Although not shown on the diagram, the system also has heat exchangers to cool the stream temperature leaving A and B and adjust the equilibrium mixture. In Figure 1 the retentate stream is shown as product, but the patent shows this stream from the pervaporation unit being fed to two more IER/pervaporation units. The precise duty of the basic IER unit B is not discussed, but it presumably helps to adjust the equilibrium mixture from A. In the example in the patent the feed flow is 1 kg/h with an overall yield of **58** over three units of about 46%.

Advantages

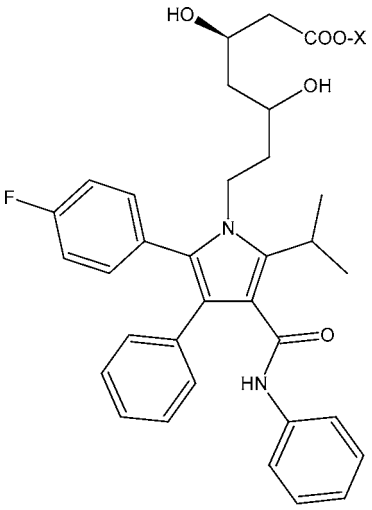
This process allows a more efficient method of producing the ketal **58** with simultaneous removal of water.

Patent No. U.S. 6,528,660

Assignee: Ranbaxy Laboratories Limited, New Delhi, India

Title or Subject: Production of Amorphous Atorvastatin Calcium

This is another patent on the subject of statins which are used in treating cardiovascular disorders. In this case the compound is calcium salt of atorvastatin **59b**. Several methods of producing **59a** give mixtures of crystalline and amorphous forms that are difficult to filter. Other methods give only crystalline forms; there are also procedures for converting one form to another, but these are claimed to be unsuitable for large-scale operation.



59a: X = H
59b: X = 0.5Ca

The process developed involves the following steps: (1) dissolve crystalline **59b** in a non-carboxylic solvent such as tetrahydrofuran, (2) add the solution to a nonpolar hydrocarbon anti-solvent such as cyclohexane to precipitate the **59b**, (3) recover crystals of amorphous **59b** by filtration.

The examples in the patent are carried out using 10 kg of material and include X-ray diffraction patterns for the crystalline and amorphous materials.

Advantages

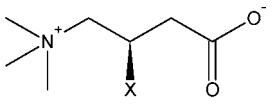
This process provides a simple fast method of making the amorphous form of the drug. It eliminates the need to remove solvent by drying and gives reproducible high-quality product.

Patent No. U.S. 6,528,684

Assignee: Sigma-Tau Industrie Farmaceutiche Riunite S.p.A., Rome, Italy

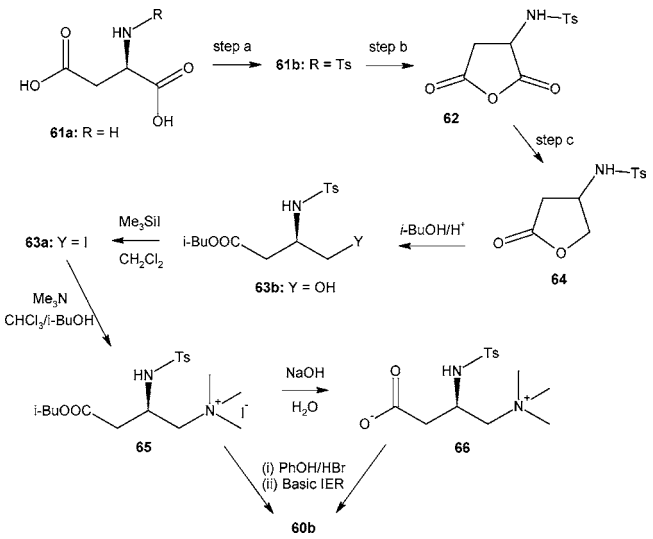
Title or Subject: Synthesis of (R)- and (S)-Amino-carnitine Derivatives Starting from D- and L-Aspartic Acid

Several of the carnitine derivatives have interesting pharmacological properties. The parent compound *R*-carnitine **60a** is present in living tissue and is used as a vitamin supplement in both animal and human use. The synthesis of **60a** is of interest to several companies, and some routes have been reviewed recently (*Org. Process Res. Dev.* **2002**, 6, 749; **2001**, 5, 350).



60a: X = OH, *R*-carnitine
60b: X = NH_2; *R*-aminocarnitine

The current process focuses on the amino-derivative **60b** which is a precursor to compounds which have potential for treating diabetes. The route to **60b** shown below starts from aspartic acid, a readily available reagent, that has the same configuration as the product and hence avoids the need for a resolution step.



The first three steps, a, b, and c, produce the lactone **64** and are based on literature methods, but no details are provided. The patent gives details of the conversion of **64** through to **60b** via **65** or **66**, and ^{1}H NMR data for each intermediate are provided. The conversion of **64** to the iodo compound **63a** can be carried out in one step or two as indicated. **63a** is then transformed to the salt **65** by reaction with Me_3N, and **65** can be converted to the internal salt **66.** Either **66** or **65** can be converted to **60b** by a two-step procedure via intermediate formation of a dibromohydrate derivative. This derivative is transformed to **60b** using basic IER to remove the amine protective group.

There are a number of alternatives within the synthetic route in which some of the intermediates are not isolated. For example, **64** is converted to **60b** in a one-pot reaction using the procedures shown. There are also examples of producing and using the methyl ester of **63b** instead of the *i*-butyl ester shown.

Advantages

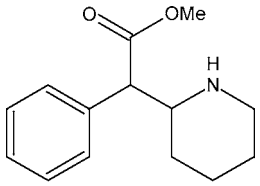
The process starts from a readily available reagent, and since it does not involve a resolution step it has an economic advantage over alternative routes.

Patent No. U.S. 6,531,489

Assignee: Chiroscience Ltd, Cambridge, United Kingdom

Title or Subject: Production of Single Isomer Methylphenidate by Resolution

Methylphenidate **67** is generally used as the hydrochloride salt under the name Ritalin to treat hyperactivity disorders and was first used as a racemic mixture. There have been concerns about the some of the side effects of the drug, and it is now known that the D-*threo* (or *R*,*R*) enantiomer is preferred; hence, efforts are directed at producing this isomer or devising resolution methods to obtain it pure.



67

This patent describes a resolution method using the popular resolving agent *O*,*O*′-di-toluyltartaric acid (DTTA). The process is carried out as follows; (1) dissolve **67** (*threo* mixture) in solution of 2% MeOH in Me_2CO, (2) add solution to suspension of *D*-DTTA in 2% MeOH in Me_2CO, (3) heat to reflux to dissolve reagents, (4) cool and leave to form crystals, (5) recover crystals of DTTA salt of D-*threo* **67** and dry under vacuum, (6) suspend crystals from 5 in 2% MeOH in Me_2CO and heat to 40 °C, (7) leave 24 h at room temperature, filter, and wash with Me_2CO to obtain 92% of **67** in 99% ee.

When compared with an alternative resolution process using (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate, the product contained 3.7% L-*threo*, and hence the new method gives a higher ee.

Advantages

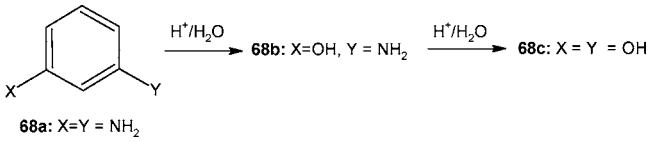
The method produces **67** with very high ee in a relatively simple procedure using a readily available resolving agent.

Patent No. U.S. 6,531,637

Assignee: Indspec Chemical Corporation, Pittsburgh, Pennsylvania, U.S.A.

Title or Subject: Production of Resorcinol by Hydrolysis of m-Phenylenediamine

Resorcinol **68c** can be made by a number of routes including acid hydrolysis of the diamine **68a** via **68b** as shown below. Since **68a** is readily available, this one-step process would be preferred if it were not for the fact that the process conditions require temperatures over 200 °C and specially corrosion-resistant reaction vessels. In addition **68b** and **68c** form high-molecular weight resinous materials under the reaction conditions, causing further operational problems and the need for frequent cleaning of the reaction vessel.



The patent describes a process for the acid hydrolysis of **68a** under a nitrogen atmosphere to give **68c** using H_2SO_4 in a reactor made from zirconium or a Zr alloy. The recovery of **68c** involves extraction with ether and the process gives yields in excess of 90%. This compares with alternative methods where the yield of **68c** may be as low as 10% in unfavourable conditions.

Advantages

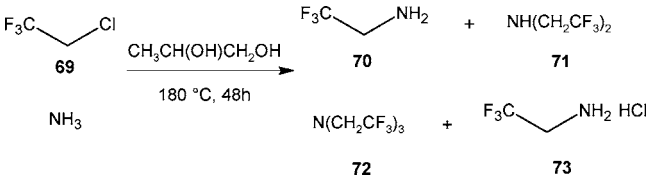
The process gives high yields of **68b** without formation of excessive quantities of resinous byproducts.

Patent No. U.S. 6,534,683

Assignee: Asahi Glass Company Limited, Tokyo, Japan

Title or Subject: Process for Producing Fluorinated Alkylamines

The patent specifically address the problems of producing **70** which is a useful chemical intermediate. Suitable methods for producing **70** usually involve the reaction of a halo compound such as **69** with anhydrous NH_3. Problems encountered include formation of the diamine **71**, triamine **72**, and the salt **73** as shown below.



The byproducts make purification and recovery of **70** more difficult; hence, their production needs to be minimised. A further problem is that of corrosion of the reactor. The process described in the patent uses the same basic route, but the reaction is carried out in a solvent such as propylene glycol. Alternative processes have used aqueous ammonia or no solvent at all. The solubility of NH_3 in **69** is limited; hence, this means that the reaction rate is low. The use of a solvent that dissolves both reactants increases the reaction rate, and the method of operation of the process reduces the problems of corrosion of the reactor.

Advantages

The process gives a higher yield and fewer operational problems than other processes using basically the same synthetic route.

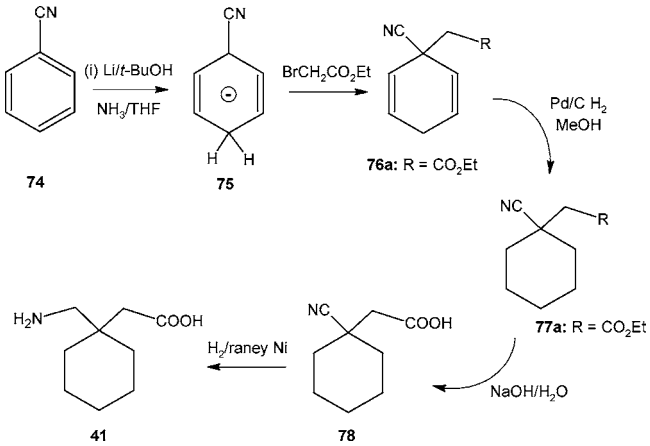
Patent No. U.S. 6,538,148

Assignee: Warner-Lambert Company, Morris Plains, New Jersey, U.S.A.

Title or Subject: Process for Preparing Gabapentin

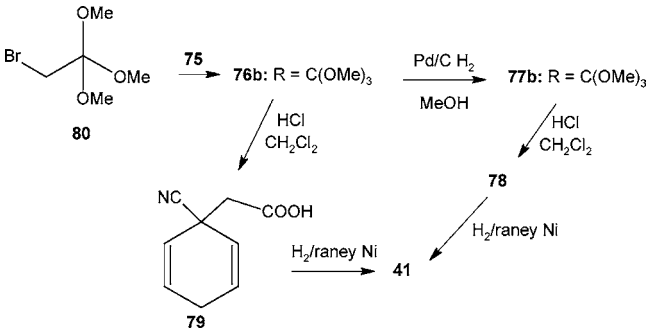
This is the fourth patent covering **41** which is useful in treating certain types of cerebral diseases. The previous patents provided improved recovery methods, whereas this patent discloses a new synthetic route to **41**. There are a number of novel intermediates described in this route which starts from benzonitrile **74**, a readily available material.

There are two processes, and the first which is shown below proceeds via the ethyl ester **76a**.



This ester **76a** is formed in a novel alkylation reaction between the ethyl bromoacetate and the anion **75** which is prepared by Birch reduction of **74**. The alkylation of **75** is the key step in this process. The ester **76a** is then hydrogenated to the cyclohexyl compound **77a**, and base hydrolysis gives the acid **79**. Reduction of the CN group in **79** to the amino group gives **41**, but the stereochemistry in this patent is not discussed. The reduction is carried out using a procedure covered by a 1992 Warner-Lambert patent (U.S. 5,132,451) which uses Raney Ni and is therefore not stereospecific. Hence, the product is a racemic mixture requiring a resolution step but no mention is made of this.

The alternative route shown below is via the trimethoxy compound **76b** which is formed from **75** and the bromo compound **80**. **76b** can be converted to **41** by acid hydrolysis to **79** followed by hydrogenation. Alternatively, hydrogenation of **76b** gives **77b** which on acid hydrolysis gives **78** which is hydrogenated to give **41** which again will be a racemic mixture.



Advantages

This route involves fewer steps than alternative schemes and results in higher yields. A particular feature of the process is the fact that **41** is not formed via a salt as is the case with most of the alternative methods. In addition the method starts from a cheap starting material.

Keith Turner

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