Organic Process Research & Development **2005**, *9,* 9–17

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during September and October 2004

Summary

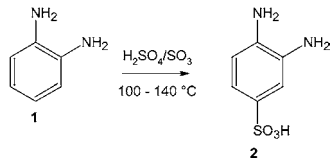
The current selection of 21 patents was taken from an original list of 213, and it is hoped that readers will find something interesting and useful. Two patents in this crop are concerned with avoiding the problems caused by using HCl. One solves the problem of handling corrosive solutions in making sulphonic acids by using an alternative synthetic route. The second is concerned with imidoester synthesis and removes the need for handling gaseous HCl by using dioxane solutions of HCl. There is a report of a new crystalline form of neotame, the improved derivative of the well-known sweetener aspartame. An improved synthesis of vitamin E claims that removing the water formed in the process by azeotropic distillation actually reduces yield. By not removing water the yield increases by 4% and allows recycling of the catalyst. The synthesis of a range of sulphonate surfactants normally requires the use of anhydrous Na salts of phenylsulphonic acids, and methods used to dry the starting materials affect product quality. One patent shows how these problems can be overcome by using a special reaction solvent system. A process for the production of selenoamino acids is described as much safer because it avoids handling small pieces of Na metal. Since handling any selenium compound is hazardous, this seems an overstatement. A highly selective method of preparing chiral trifluorophenylethylamines is described that includes a new hydrogenolysis step of a *sec*-amine to remove the amine protective group. Cabergoline is used to treat Parkinsonism, and one patent reports the discovery of a second polymorph that can be obtained from the reaction mixture of the standard synthesis. Two patents from the same company describe structurally similar antibiotics. One of these is ceftiofur for animal use, while the other cefixime is for use in humans. The Na salt of ceftiofur is normally administered to animals, and a method of making this without going via the HCl salt is described which gives improved yields and higher purity. The synthesis of cefixime involves a hydrolysis of an amino ester, and it has been possible to perform this without protection of the amino group. Another patent on antibiotics describes an improved method of making quinolones without the need to remove byproducts from an early stage of the synthesis. Chiral β-amino alcohols are valuable reagents, and a new method of making them from α-amino acids is described. A new method for the synthesis of a range of pyrazines is described with experiments involving the preparation of 12 kg of product, suggesting an advanced stage of development. An improvement in the Pauson−Khand reaction for synthesis of cyclopentenones has been disclosed that involves the use of immobilised catalysts. This reduces the problems caused by using the volatile cobalt carbonyl catalysts. As usual there is no commercial or legal significance attached to any of the patents reviewed. It may be surmised that patents that include kilogram-scale experiments are at a more commercial stage than some of the others. The advantages stated are those claimed in the patent unless the author has personal knowledge. From the original short list of patents for inclusion in this review there were a few that had no chemical equations or formulae. This does not often present too much of a problem, given the easy access to the Internet. However, the names used for some of the reagents defied any logical naming method known to this reviewer and the usual search engines; hence, they were not included.

Patent No. U.S. 6,787,666

Assignee: Bayer Chemicals AG, Leverkusen, Germany
Title or Subject: Process for the Preparation of Isolated 3,4-Diaminobenzenesulphonic Acid

The patent describes a method of preparing the sulphonic acid **2** that is a useful intermediate particularly for UV absorbents in light-protection agents. The route to **2** is shown in Scheme 1 and is carried out by reacting **1** with anhydrous H_2SO_4 containing SO_3. One alternative method of preparing **2** involves the sulphonation of the HCl salt of **1**, and a second method involves the reduction of 2-nitroaniline sulphonic acid with Sn/HCl. Both methods are claimed to be expensive because of the corrosive nature of HCl. The major hurdle to overcome in the present route is to limit the formation of the disulphonic acid. This is done by using SO_3 in stoichiometric amounts and by quenching the reaction with water or ice. The product is precipitated from the reaction mixture and is of high purity.

Scheme 1



1 2

Advantages

This process gives high-purity product without the use of expensive corrosion-resistant equipment.

10.1021/op049773o CCC: $30.25
Published on Web 01/04/2005

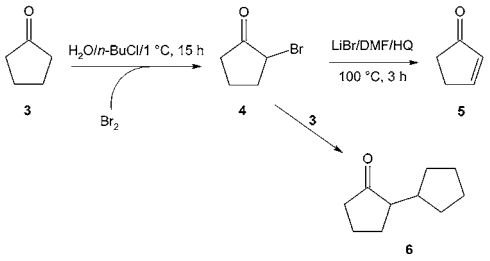
Patent No. U.S. 6,787,673

Assignee: Sumitomo Chemical Company Limited, Osaka, Japan

Title or Subject: Process for Producing 2-Bromocyclopentanone

4 is a useful intermediate and can be prepared by bromination of **3** using $Br_2/CHCl_3$ or NBS. Such processes are said to be unsuitable for industrial scale production; hence, this patent provides an improvement involving a biphasic system of water and *n*-BuCl. The reaction is carried out at by adding Br_2 to a mixture of **3** in water and *n*-BuCl at around 1 °C (Scheme 2). After 15 h more of the water and *n*-BuCl solution is added and the product recovered as an oily phase in *n*-BuCl. The patent specifically mentions that the new process does not produce the byproduct **6**. In fact, the patent contains examples showing that **6** is formed as a byproduct when the reaction is carried out with excess **3** which is the normal procedure in the alternative processes. The patent also describes how to prepare **5** by treatment of the oily phase from the reaction mixture with LiBr in DMF in the presence of hydroquinone (HQ).

Scheme 2



Advantages

The process gives a higher quality product than alternative methods.

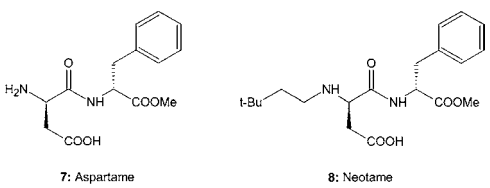
Patent No. U.S. 6,790,470

Assignee: Ajinomoto Co. Inc., Tokyo, Japan

Title or Subject: Process for Producing a New Aspartame Derivative Crystal

This patent describes a procedure for the production of a new crystalline form of neotame, **8**, the improved derivative of the well-known sweetener aspartame, **7**. Since the original patents on **7** have expired, there has been much interest in alternative and more effective sweeteners, and **8** is one of these. The original form of **8**, designated the A form, is claimed to have poor dissolution properties; this patent provides a new form of **8** with improved solubility that is designated form C. The normal A form has a water content of about 5%, and the C form is obtained by drying the A form at 50 °C in a vacuum until the water content is <0.8%. The new form was identified by X-ray diffraction (XRD) and was shown to dissolve more rapidly than the A form.

Aspartames



7: Aspartame **8:** Neotame

Advantages

The procedure gives an improved, new, crystalline form of this sweetener with improved dissolution characteristics.

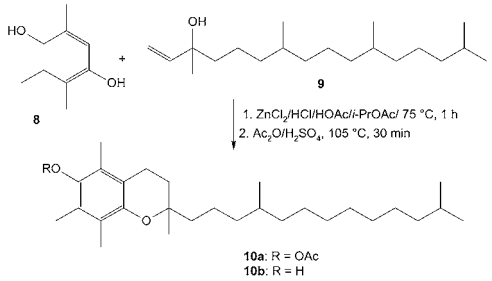
Patent No. U.S. 6,790,967

Assignee: Adisseo France S.A.S., Antony, France

Title or Subject: Process for the Preparation of Vitamin E

Vitamin E, **10b**, is produced on a substantial scale by condensation of trimethylhydroquinone **8** with isophytol **9** using Lewis acids (Scheme 3). The reaction is normally carried by using excess **8** and simultaneously removing the water by azeotropic distillation using a hydrocarbon solvent. However, this patent claims that the presence of water actually improves the efficiency of the reaction. The reaction is carried out in a polar solvent such as *i*-PrOAc containing HOAc, an acid such as HCl, and a Lewis acid such as $ZnCl_2$. The water is said to increase selectivity by 4%, allows recycling of the $ZnCl_2$, reduces consumption of **8** by using only stoichiometric quanities, and prevents esterification of **8** by the solvent mixture. The HOAc is used to prevent the separation of two phases in the system. The patent primarily covers the preparation of the acetate **10a**, and this is then hydrolysed to obtain **10b**. Experiments are described showing the effect of optimising the amount of $ZnCl_2$ and also of using recycled $ZnCl_2$. This is a key feature of the process since the use of Lewis acids usually gives rise to waste disposal problems.

Scheme 3



Advantages

This process gives higher yields of the product, and since the catalyst can be recycled, this reduces waste products.

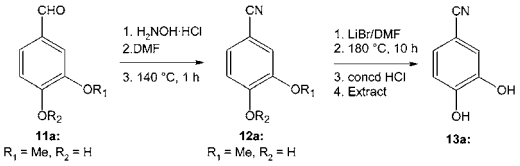
Patent No. U.S. 6,790,977

Assignee: Sinon Corporation, Taichung, Taiwan

Title or Subject: Process for Preparing 3,4-Dihydroxybenzonitrile

This patent discloses an improved process for making **13** that is a useful chemical starting material for preparing oxazolines, tetraazoles, benzamidines, and other intermediates. There are several routes for preparing **13**; however, it is stated that these use expensive starting materials, give low yields, or are not generally suitable for commercial production. A route described in this patent starts from the aldehyde **11a** that is converted to the nitrile **12a** by reaction with $H_2NOH{\cdot}HCl$. The next stage (which is outlined in Scheme 4) is treatment of **12a** with LiBr in DMF. The work up of the reaction mixture involves acidification, extraction with EtOAc, and cooling to obtain crystals of **13** in 67% yield and >99% purity.

Scheme 4



The dihydroxy compounds similar to **11a** in which R_1 and R_2 are both H are not covered under the patent claims, and this point is specifically mentioned in the patent. Thus, the novel aspect of this patent is not clear, and the fact that similar processes have been known for many years tends to contradict the claimed advantages. Other examples in the patent start from the aldehydes **11b** ($R_1 = R_2 =$ Me) or **11c** ($R_1 = R_2 =$ Et) that give the nitriles **12b** and **12c**, and these are also converted to **13** by treatment with LiBr in DMF.

Advantages

This process claims to give a better yield than alternative methods and is suitable for large-scale commercial production.

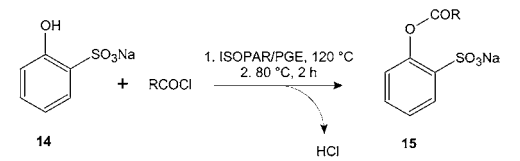
Patent No. U.S. 6,790,981

Assignee: Clariant Finance (BVI) Ltd., Tortola, Virgin Islands

Title or Subject: Process for the Preparation of Acyloxybenzenesulfonates

Compounds such as **15** are used as surfactants or bleach activators, depending on the chain length of the acyl group. These compounds are usually prepared from phenylsulphonic acid derivatives such as the Na salt **14**. All processes are said to require the use of anhydrous **14**, whereas it is normally available commercially as the dihydrate that contains 15% water. Hence, before use in this reaction **14** must be dried; otherwise there is a significant loss in yield of **15**. The method of drying **14** can have a detrimental effect on the process efficiency, and both under- or over-dried **14** causes problems. The objective of the process described in this patent is to use any grade of dried **14** that has water content <0.2%. The reaction shown in Scheme 5 is carried out by suspending the dried **14** in a hydrocarbon solvent containing a polyglycol ether (PGE). The solvent used in the examples is mixture of isoparaffins known as ISOPAR. An example of the PGE is diethyleneglycol dimethyl ether, and the acyl chlorides used are nonanoyl or lauroyl. The process is carried out continuously, and the water remaining in the **14** forms unspecified impurities that can be easily removed.

Scheme 5



Advantages

The process allows the use of lower quality and hence cheaper raw materials while at the same time producing a higher quality product.

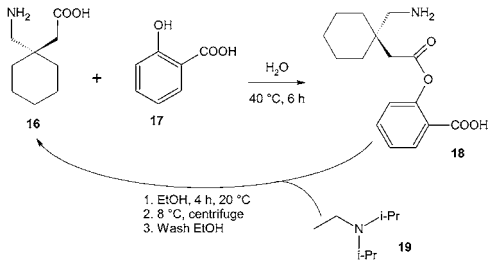
Patent No. U.S. 6,790,986

Assignee: Farchemia S.r.l., Treviglio, Italy

Title or Subject: Process for the Preparation of Gabapentin Free from Inorganic Acid Anions

Gabapentin **16** is used as the HCl salt in the treatment of cerebral diseases such as epilepsy, and patents on this compound have previously been reviewed (*Org. Process Res. Dev.* **2003**, *7*, 784). Many of the difficulties in the synthesis and purification of this compound relate to the removal of salts formed, and membranes and ion-exchange techniques have both been used. The process described in this patent is shown in Scheme 6 and starts by heating an aqueous solution of **16** with **17** to form a solution of the salicylate **18**. Cooling of this solution and centrifuging gives **18** that is treated with **19**; purified **16** is obtained after further work up in aqueous EtOH. One experiment describes the use of 20 kg of **16**, indicating the advanced stage of development of the process.

Scheme 6



Advantages

The process affords a convenient method of purification of this important drug.

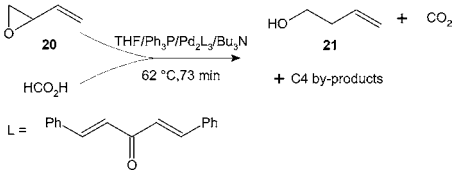
Patent No. U.S. 6,790,999

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

Title or Subject: Process for the Production of 3-Buten-1-ol

21 is a useful chemical intermediate that may be made from propylene and formaldehyde or from various C4 precursors. This patent describes a route to **21** from **20** that is a frequently used starting material. Some of the previous routes from **20** to **21** are said to be inefficient or use dangerous or expensive chemicals. It is also noted that loss of yield of product is common by isomerisation to the 2-butene-1ol. The new route is shown in Scheme 7 is a catalytic transfer hydrogenation using formic acid and a Pd catalyst. The catalyst is used for several cycles, and one example equates to a catalyst turnover ratio of 37,500 mol. The process can be operated in batch, semi-continuous, or continuous modes. The reaction produces CO_2, and the products are collected as vapours from the reactor outlet, condensed, and purified by fractional distillation.

Scheme 7



Although THF is used in a batch experiment as a solvent, the patent does claim that the reaction byproducts are used as solvents when the reaction is operated in continuous mode. In this case the turnover ratio increased to 40,900.

Advantages

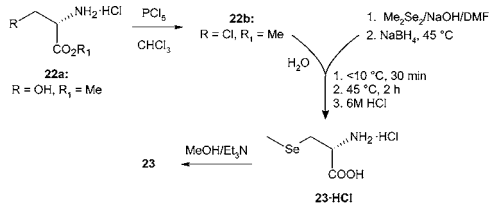
The process efficiently uses the expensive catalyst, and the distillation of the product prevents its isomerisation and subsequent yield losses.

Patent No. U.S. 6,794,537

Assignee: Sami Labs Limited, Bangalore, India
Title or Subject: Manufacturing Process for Se-Methyl-L-selenocysteine

Selenium is an essential element for human nutrition and is available from a variety of food sources. This patent describes a method of preparing the selenoamino acid **23** that is found in garlic and broccoli. Alternative methods of preparing **23** are known, and these usually start from amino acids and selenium derivatives. Scheme 8 shows the basic route to the preparation of **23** which starts from the ester salt **22a** that is chlorinated using PCl_5 in $CHCl_3$ to give **22b**. Treatment of **22b** with MeSeNa that is formed from $NaBH_4$ and Me_2Se_2 gives the HCl salt of **23** by precipitation with concd HCl. The salt is then decomposed using Et_3N and **23** recovered in 99% purity.

Scheme 8



The patent also describes the use of hypophosphorous acid (H_3PO_2) to cleave the Se−Se bond in Me_2Se_2 and form MeSeNa. The conversion of the L-isomer of **23** to a racemic mixture can be carried out by heating **23** in HOAc and PhCHO.

Advantages

The process claims to be safer than alternatives because it does not involve handling dangerous materials. One of the alternative processes is said to be hazardous because it uses small pieces of sodium. This seems to be a trivial problem when compared to the difficulties of handling most selenium compounds.

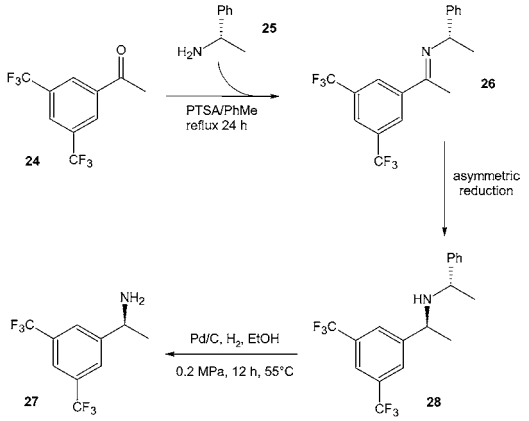
Patent No. U.S. 6,797,842

Assignee: Central Glass Company Limited, Ube, Japan
Title or Subject: Process for Producing Pure Optically Active Trifluoromethylphenylethylamines

This is an extensive patent covering the production and purification of ethylamines such as **27**. Such compounds are intermediates in the production of agrochemicals and pharmaceuticals. A variety of procedures is available for the synthesis of the compounds, but they are said to be incapable of producing optically active compounds efficiently and in high yield.

Scheme 9 shows a route to **27** described in the patent that begins with the dehydration and condensation of the ketone **24** with the chiral amine **25** to give the imine **26**. In the next step asymmetric reduction of **26** using $NaBH_4$ or $LiAlH_4$ in MeOH, EtOH, *i*-PrOH, or THF gives the amine **28**. The ratio of *S*,*S* to *R*,*S* isomers was as high as 7.8 using $NaBH_4$ or as low as 2.1 when using $LiAlH_4$ in THF. The final step is hydrogenolysis of **28** to give **27** in 75% yield and ee of 76%. The stages leading up to the last one are said to allow the hydrogenolysis reaction to take place with reduced catalyst usage and at significantly reduced pressure. It is claimed that this step has not been reported previously and the high selectivity at the cleavage position is the key aspect of the patent.

Scheme 9



The patent describes a large number of experiments, and there are examples for the synthesis of monotrifluoro derivatives using the same procedure.The second aspect of the patent is the purification of the amine **28** by formation of salts of PTSA, mandelic or tartaric acids.

Advantages

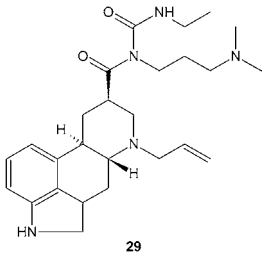
The development of the hydrogenolysis of the *sec*-amine provides an efficient route to these amines that is an improvement over alternative processes.

Patent No. U.S. 6,800,635

Assignee: Pharmacia Italia S.p.A., Milan, Italy
Title or Subject: Crystalline Form II of Cabergoline

The subject of this patent **29** is a dopamine receptor agonist that was originally disclosed in 1985 and is available as Dostinex for the treatment of Parkinsonism. In some brief background research on **29** there were claims that it can be used in enhancing sexual activity. This aspect was not discussed in the current patent. Until now the drug has so far only been known as a single polymorph, and this patent describes a second form that is said to be the thermodynamically most stable form between −70 °C and +30 °C.

Cabergoline



29

The procedure is to take the crude oil from the conventional synthesis and dissolve it in a solvent such as MTBE, Et_2O, or MeOAc. An unspecified form of carbon and Na_2SO_4 are then added, and the mixture is stirred at room temperature. After filtration the solution is concentrated and cooled to −5 °C for up to 4 days. The crystals of Form II that are collected are characterised by XRD, DSC, IR, and NMR, and copies of the spectra are given in the patent. The patent also discloses that Form I can be converted to Form II if the two materials are suspended in hexane at 25 °C or Et_2O at −5 °C for about 12 h.

Advantages

The discovery of the new form of this drug can extend patent coverage.

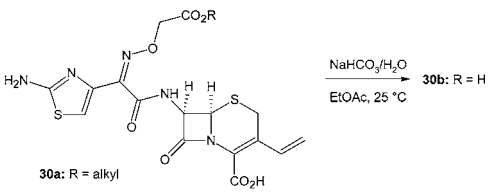
Patent No. U.S. 6,800,755

Assignee: Orchid Chemical and Pharmaceuticals Limited, Chennai, India

Title or Subject: Process for the Preparation of Cefixime

30b is a cephalosporin antibiotic that is more potent against Gram-negative bacteria and available as Suprax. The synthetic routes to give **30b** initially produce the ester **30a**, and this is hydrolysed to give the acid **30b**; it is this difficult step that is the focus of this patent. In some processes the amino group is protected, in others it is not, but it is said that the final product from the alternative processes is obtained in low yield and is of poor quality containing coloured impurities. The conversion of **30a** to **30b** is carried out at 25 °C using $NaHCO_3$ in a biphasic mixture of EtOAc and aqueous $NaHCO_3$ (Scheme 10). After addition of NaOH and then neutralisation with HCl the product is extracted with Me_2CO and cooled to give crystals of the trihydrate form of **30b**. The key aspect of the process is the use of a weak base to hydrolyse the ester and then the use of NaOH to improve the colour of the final product. The patent also specifically claims that Me_2CO should be used for the extraction step. It is also claimed that the product obtained by this process has enhanced solubility although no details are provided.

Scheme 10



Advantages

The process gives a higher quality product without the need to use protective group methods.

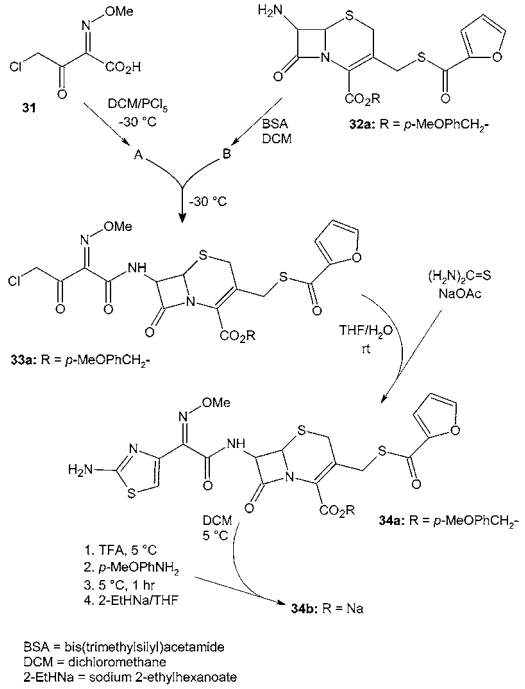
Patent No. U.S. 6,800,756

Assignee: Orchid Chemicals and Pharmaceuticals Limited, Tamilnadu, India

Title or Subject: Method of the Preparation of Ceftiofur Sodium Salts and Its Intermediates

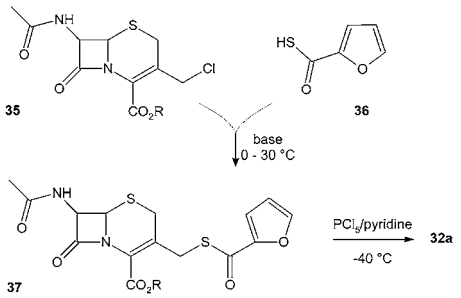
The title compound **34c** (R = H) has the same basic central molecular structure as the subject of the previous patent and is also an antibiotic. However, in this case it is used in the treatment of animals. Most of the synthetic routes to **34c** give the HCl salt that is then converted to the Na salt **34b** for veterinary use, but this patent discloses a direct route to **34b** (Scheme 11). The procedure begins with the reaction of **31** with PCl_5 in DCM to give mixture A that is kept for an hour before being mixed with mixture B at −30 ° C. This mixture contains the silylated form of the cephalosporin ester **32a** formed from *N*,*O*-bis(trimethylsilyl)acetamide (BSA). The condensation reaction gives the novel compound **33a** that is cyclised to give the novel thiazole **34a** using thiourea and NaOAc in a water-miscible solvent. The Na salt is then obtained by treatment with TFA followed by anisole and sodium 2-ethylhexanoate in THF. Spectroscopic data are given for the new compounds.

Scheme 11



The patent also describes how to prepare the ester **32a** from **32c** (R = H) and *p*-$MeOPhCH_2Cl$. An alternative route to **32a** is shown in Scheme 12 although there are no experimental details given in the patent. The first step is a base-catalyzed condensation of **35** with the thiol **36**. In the second step the *N*-acetyl in **37** is removed by using, for example, PCl_5/pyridine at temperatures down to −40 °C.

Scheme 12



Advantages

The process provides a method of making the required Na salt without the need to produce and isolate the HCl salt. This enables a better yield of higher purity product to be obtained on a commercial scale.

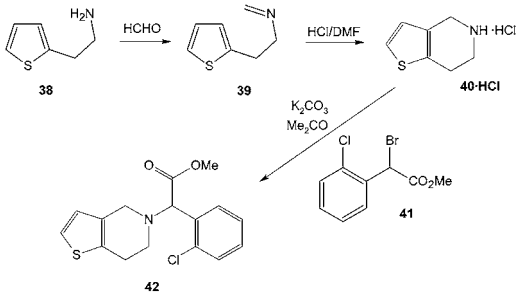
Patent No. U.S. 6,800,759

Assignee: Teva Pharmaceutical Industries Ltd., Petah Tiqva, Israel

Title or Subject: Racemisation and Enantiomer Separation of Clopidogrel

Clopidogrel **42** is used to treat atherosclerosis, and patents on the compound have previously been reviewed (*Org. Process Res. Dev.* **2004**, *8*, 823). The synthesis of **42** gives both enantiomers, and since only the *S*-form is active, it is desirable to remove and preferably recycle the inactive *R*-isomer. The basis of the current process is to prepare **42** by the route shown in Scheme 13.

Scheme 13



The route to **42** begins with the reaction of HCHO and the amine **38** to give the imine **39**, but no experimental details are given. The imine is then cyclised to give the hydrochloride of **40** that, on reaction with **41**, gives racemic **42**. The product is recovered as the bisulphate salt by addition of H_2SO_4, and the free base is obtained by neutralisation with NaOH solution. Resolution was by formation of the *S*-enantiomer as the camphor sulphonate salt from DMF/PhMe. The *R*-enantiomer is then racemised using KOBu^t, and from the racemic mixture more *S*-isomer can be obtained. It is stated that the procedure can be carried out continuously.

Advantages

The process provides a simple procedure that may be used for obtaining an overall higher yield of this important drug.

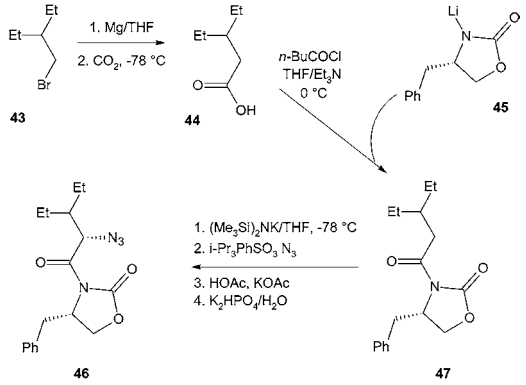
Patent No. U.S. 6,800,764

Assignee: Wyeth, Madison, New Jersey, U.S.A

Title or Subject: Process for the Synthesis of Chirally Pure *β-Amino Alcohols*

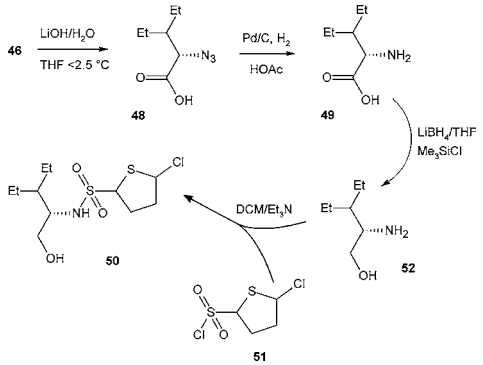
This patent provides a novel process for preparing chirally pure *S*-enantiomers of amino alcohols such as **52.** Also described are α-amino acids that are intermediates in the synthesis of **52**. The first part of the synthesis is shown in Scheme 14 and involves the preparation of the azide **46**. The reaction starts with the preparation of the acid **44** by reaction of solid CO_2 with the Grignard reagent from **43**. The acid is reacted with *n*-BuCOCl and Et_3N and converted to a mixed anhydride that is not isolated but converted to oxazolidinone **47** using **45**. Treatment of **47** with the strong base $(Me_3Si)_2NK$ forms the enolate anion of **47** that reacts with triisopropylbenzenesulphonyl azide to give **46**.

Scheme 14



The second stage of the synthesis is shown in Scheme 15 and begins with the conversion of the azide **46** to the azido acid **48** by conventional treatment using LiOH. The azide group in **48** is then reduced to give the amino acid **49** using Pd/C catalyst in glacial HOAc. The amino acid **49** can be isolated or converted to the desired amino alcohol **52** by using $LiBH_4/Me_3SiCl$ in 90% yield, but this can take up to 3 days for completion. The patent also describes that **50** gives **52** by reaction with the sulphonyl chloride **51** in the presence of a base such as Et_3N. A variety of pharmaceutical uses is indicated for **52**.

Scheme 15



Advantages

This process gives a high yield of chirally pure amino acids and alcohols and these are valuable synthetic intermediates.

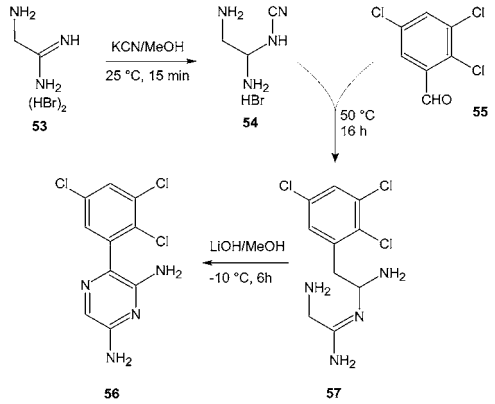
Patent No. U.S. 6,803,464

Assignee: SmithKline Beecham Corporation, Philadelphia, Pennsylvania, U.S.A.

Title or Subject: Process for the Preparation of Pyrazine Compounds

Pyrazine compounds such as **56** are useful in the treatment of central nervous system disorders, and this patent describes an improvement in a previously known synthesis of **57**. A major problem with the earlier method is said to be that it gives poor yields because **53** is unstable in the basic conditions that exist towards the end of the reaction. The process disclosed in this patent overcomes this problem by changing the order of addition and reaction conditions while still using the same basic route shown in Scheme 16.

Scheme 16



The procedure is to add the acid salt **53** to a solution of KCN in MeOH and form the intermediate cyano salt **54**. This is reacted immediately with the benzaldehyde **55** to form the intermediate **57** that is cyclised using LiOH in MeOH giving **56** in 91% yield. The single experiment in the patent describes the preparation of 12 kg of product, thus indicating the advanced stage of development of the work.

The improvement is believed to be due to the reduction in the acidity of the reaction mixture that prevents formation of acetals and hemiacetals of **55**. The lower acidity is thought to be because of the reaction of the KCN with the acid salt **53** to give **54** that is less acidic.

Advantages

This procedure gives an improvement in yield of about 35% compared with the alternative method without changing the process costs.

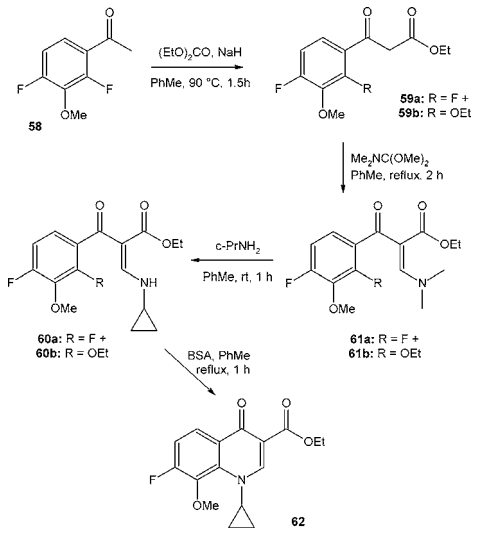
Patent No. U.S. 6,803,469

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

Title or Subject: Process for Preparing Quinolone Antibiotic Intermediates

The title compounds such as **62** are used to prepare broad-spectrum antimicrobials that are effective against Gram-positive pathogens. The patent discloses what is said to be the surprising discovery that the ester byproducts **59b**, **60b**, and **61b** formed during the synthesis can be allowed to remain in the reaction mixture and used to prepare **62** themselves. Although no figures are given, it is said that **59b** is formed in substantial amounts in the first stage of this process. The route shown in Scheme 17 starts from the acetophenone **58** that reacts with $(EtO)_2CO$ to give a mixture of ketoesters, **59a** and **59b**. Normally, the ethoxy compound **59b** would be removed, but it not necessary in this case. Hence, the mixture from the first step takes part in a Knoevenagel reaction with $Me_2NC(OMe)_2$ to give the enamines **61a** and **61b**. Again the two compounds are not separated but reacted with cyclopropylamine (*c*-$PrNH_2$) to give the cyclopropyl derivatives **60a** and **60b**. In the final step these two compounds are treated with BSA to give the desired quinolone **62**. The patent states that the reaction can be extended to other derivatives of **58** in which the OMe group is replaced by other substituents, but no examples are given.

Scheme 17



Advantages

This process converts byproducts into the desired product thereby substantially increasing the efficiency and overall yield of the reaction.

Patent No. U.S. 6,806,380

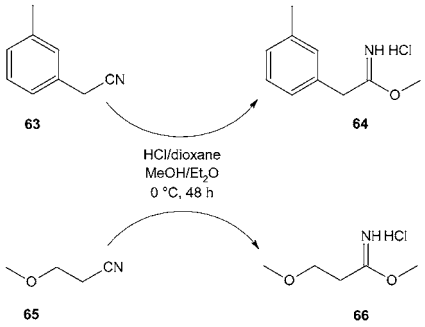
Assignee: Lexicon Pharmaceuticals Inc., New Brunswick, New Jersey, U.S.A.

Title or Subject: Modified Safe and Efficient Process for the Environmentally Friendly Synthesis of Imidoesters

Imidoesters are versatile intermediates and are typically prepared by a Pinner reaction using excess HCl gas. Hence, the patent describes a less hazardous process that uses solutions rather than gaseous HCl. The basic reaction is shown in Scheme 18 and involves treating an anhydrous mixture of a nitrile such as **63** or **65** with MeOH and a prepared solution of 4 M HCl in dioxane at 0 °C for up to 48 h. The excess HCl is then removed by bubbling N_2 gas through the solution at 40 °C. The products **64** or **66** are

obtained by concentrating the solution, adding Et_2O to precipitate the solid, and then filtering. A range of other substrates is described, and HMR data are given for the products. Other alcohols are claimed in the patent, but no data are provided.

Scheme 18



Advantages

The process avoids the difficulties of handling gaseous HCl; by using a solution of known concentration the process is less wasteful and hence can claim to be environmentally friendly.

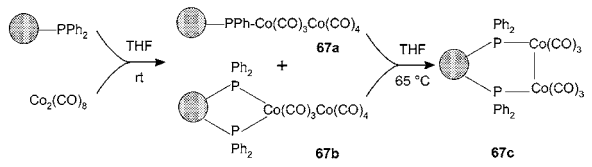
Patent No. U.S. 6,806,389

Assignee: AstraZeneca AB, Sodertalje, Sweden

Title or Subject: Immobilised Catalyst for Use in the Pauson−Khand Reaction

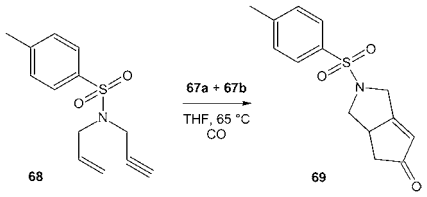
The production of cyclpentenones from an olefin and CO using a π-alkynylcobaltcarbonyl catalyst is generally referred to as a Pauson−Khand reaction. A problem with the reaction is the volatility and toxicity of $Co_2(CO)_8$ from which the catalysts are usually made. The catalyst precursor is required in high purity, and commercial reagents are usually not of sufficiently high purity. Hence, the objective of this patent is to produce a nontoxic catalyst that can be easily prepared and recovered from the reaction mixture. Scheme 19 indicates the preparation of the supported catalyst **67c** by treatment of $Co_2(CO)_8$ with a polystyrene-linked resin containing PPh_2 ligands. It is believed that the initial reaction gives the precursors **67a** and **67b,** and these form **67c**. The structures of the precursors and final catalyst are merely suggestive, and the actual catalyst in the Pauson−Khand reaction is formed from **67c** and the alkyne or alkene substrate.

Scheme 19



The catalyst **67c** is not isolated and the mixture of the precursors is used to catalyse the conversion of **68** to **69** under CO in THF as shown in Scheme 20. It is suggested that by using a chiral ligand the product can be prepared with the desired that may be resolved or partially resolved. While this is likely there are no examples. The only example in the patent uses a ratio of **68** to precursors of 20:1 and no information on the reuse of the catalyst is given.

Scheme 20



Advantages

The use of immobilised catalysts does help product recovery in many catalytic reactions, but it is not clear in this patent how high the activity of the catalyst is.

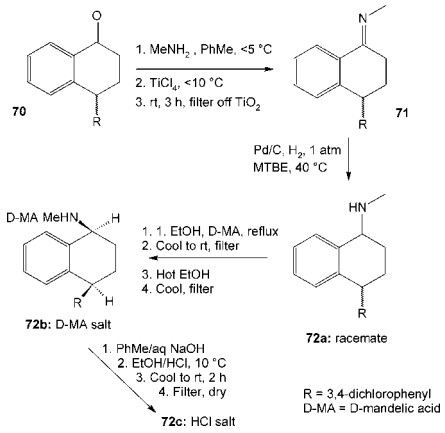
Patent No. U.S. 6,809,221

Assignee: Teva Pharmaceutical Industries Ltd., Petah Tiqva, Israel

Title or Subject: Process for Making cis-Sertraline

Sertraline hydrochloride, **72c**, is a widely used antidepressant available as Zoloft or Lustral. It was disclosed by Pfizer in 1985 and is currently of great interest because of the expiration of the original patents and the new routes to **72c** that have previously been reviewed (*Org. Process Res. Dev.* **2004**, *8*, 553). The route to **72c** in this patent starts with the formation of the Schiff base **71** from sertralone **70** by reaction with gaseous $MeNH_2$ in the presence of $TiCl_4$. The racemic sertaline free base **72a** is then formed by hydrogenation of **71** using Pd/C at 1 atm pressure of H_2 and 40 °C. The recovery of the hydrochloride **72c** is carried out via formation of the D-mandelic acid (D-MA) derivative **72b** that is purified and then converted to **72c**. The final product obtained was polymorphic Form V and contained 99% of the *SS*-enantiomer.

Scheme 21



The patent also describes the resolution of a racemic mixture of the hydrochloride **72c** by formation of the D-MA

salt. A range of solvents was used with either 20% aqueous NaOH or 85% KOH powder being used to neutralise the HCl salt of **72c**.

Advantages

The process provides an alternative method of making a generic form of a commonly used drug product.

Keith Turner

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