Organic Process Research & Development **2004**, *8,* 311–319

Highlights from the Patents

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

Summary

This review contains 21 patents from an initial list of 264 in which it is hoped readers will find some interest. Statins continue to attract attention, and there are four patents on these drugs. Three relate to fermentation processes, two of which cover a new culture for producing pravastatin. Recovery of statins is a major area of research, and the other two patents focus on this. The use of ion-exchange resins in the recovery and purification of many chemicals is a growing area, and several patents describe using such a technique. The ease of separation of the resin after use greatly assists in broadening their applicability. The increasing demand for CDs and DVDs requires very high-purity colour-free raw materials which are produced by condensation reactions involving Me_2CO. Thus, there are usually highly coloured impurities, and a process is described in which carrying out the reaction in the slurry phase appears to reduce impurities. This is interesting because many chemists try to avoid nonsolution reactions which can create handling and mixing problems. In another example of using slurry-reaction mixtures the antidepressant paroxetine can be made more conveniently by changing to a mixed-solvent system. A new route to the vitamin supplement *R*-carnitine provides a range of novel chiral chlorosuccinates that could have other useful synthetic applications. One patent is unusual in that it actually describes the strategy used to purify an aldehyde, and this focuses on choosing a solvent. The method involves conversion to an imine that can be crystallised and purified more easily than the aldehyde. There is a new prostaglandin intermediate that can be used to make latanoprost, and this involves a rare example of reducing an α,β unsaturated enone with a chiral chloroborane reagent. Unusually, there are no examples of large-scale experiments in this selection. There is no commercial or legal significance in the choice of patents that are reviewed, and the advantages are those claimed in the patent unless this reviewer has prior knowledge.

Patent No. U.S. 6,673,942

Assignee: Degussa AG, Dusseldorf, Germany, and Yeda Research & Development Co. Ltd, Rehovot, Israel

Title or Subject: Resolution of DL-Racemic Mixtures

The title of this patent is rather wide ranging, but the subject matter and claims cover resolution of compounds that crystallise in the form of a conglomerate. The process allows recovery of both enantiomers, and specific examples are given for amino acids such as the hydrochlorides of methionine, glutamic acid, histidine, cysteine and others.

The basis of the process is to inhibit the crystallisation of one enantiomer by addition of a chiral enantioselective polymer to a solution of the racemic mixture. Thus, one enantiomer is obtained as crystals, and the other remains in solution. The second form is obtained from the solution by adding the solid racemic mixture to the solution and cooling to obtain crystals of the second enantiomer. The mother liquor from this step has roughly the same composition as that of the original solution and hence can be recycled. This procedure allows continuous production of both enantiomers.

An example of the chiral polymer used is poly(*N*-methacryloyl-D-lysine) (D-PMAL), and the current patent follows similar work carried out by the assignees described in a 1989 patent (U.S. 4,864,031).

Thus, using D-PMAL, DL-methionine hydrochloride (DL-M-HCl)was resolved from an aqueous solution. After adding the polymer to the solution, it was seeded with L-M-HCl, and cooling the solution produced crystals of L-M-HCl. The D-M-HCl enantiomer was recovered from the mother liquor.

Advantages

The process improves on the original method since both enantiomers can be recovered without removing the polymeric additive. The process is said to be particularly useful in separating mixtures where crystal twinning is common. It is also claimed to be suitable for separating polymorphs although no examples are given.

Patent No. U.S. 6,673,945

Assignee: Archer-Daniels Midland Company, Decatur, Illinois, U.S.A.

Title or Subject: Process for Production of High Purity Tocopherols

There are four principal tocopherols (α, β, γ, and δ) that are different forms of vitamin E and are powerful antioxidants with the α form having the highest activity. They are isolated from vegetable oils using distillation, liquid chromatography, or supercritical extraction processes. Such processes are said to have several drawbacks and give low-purity product. The process described here uses weakly basic ion-exchange resins (IER) which selectively bind to the tocopherols and give a solution having an increased α content while allowing impurities to be separated. The examples use Reillex polyvinyl pyridine IER in columns through which a solution of the tocopherol mixture in hexane or heptane is passed. The purified products are subsequently eluted from the column with a low alcohol such as MeOH or *i*-PrOH. The process enabled the tocopherol content to be increased from about 89% in the feed to over 96% and higher in the

10.1021/op0499270 CCC: $27.50
Published on Web 04/23/2004

eluted fractions. One example uses a feed from one of the assignee's commercial plant; hence, it may be assumed that the commercialisation of the process is at an advanced stage.

Advantages

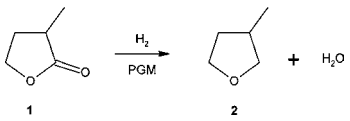
The process does not require specialised equipment and produces tocopherols of enhanced purity.

Patent No. U.S. 6,673,946

Assignee: E. I. Du Pont de Nemours and Company, Wilmington, Delaware, U.S.A.

Title or Subject: Manufacture of 3-Methyltetrahydrofuran from 2-Methyl-γ-butyrolactone

3-Methyltetrahydrofuran **2** is a solvent with properties similar to those of THF but is less volatile and boils at 86 °C. Perhaps it may also be an alternative solvent to dichloromethane (DCM) as has been reported for the 2-isomer (*Org. Process Res. Dev.* **2004**, *8*, 138). **2** is used in the production of elastomers and is prepared by hydrogenation of a range of esters such as itaconates, 3-formyl-2-methylpropionates, or methylsuccinates. A problem with these processes is that the alcohol formed from the ester forms an azeotrope with **2**, and subsequent separation and purification of **2** can be difficult and expensive. The process disclosed here removes this problem by producing **2** by an alternative route that does not produce an alcohol. The route is shown below and involves hydrogenation of **1** that gives **2** and water, using supported platinum group metal (PGM) catalysts that may contain an acidic promoter such as $Zn(BF_4)_2$, Nafion(R), various zeolites, or methane sulphonic acid. The claims cover all platinum group metals except certain types of Re catalysts that are specifically excluded, presumably because they are the subject of competitive patents. The reaction is carried out at about 225 °C and a pressure of up to 100 bar. The distillation and recovery of **2** from **1** and the water is fairly easy since **1** is much higher boiling than **2** and there are no azeotropes in the system.



Advantages

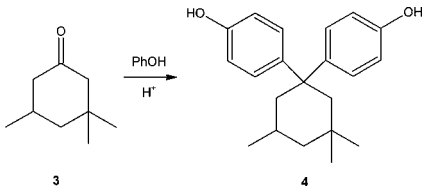
The process simplifies the recovery of the product by avoiding the production of alcohols that form azeotropes with the desired products.

Patent Nos. U.S. 6,673,973, 6,673,974, and 6,673,975

Assignee: Honshu Chemical Industry Co., Ltd., Tokyo, Japan

Title or Subject: Method of Producing 1,1-Bis-(4-hydroxyphenyl)-3,3,5-trimethylcyclohexane

These three patents disclose details of a process for preparing **4** which is a raw material for the preparation of optical products such as polycarbonate CDs and DVDs. Such uses demand raw materials free of phenols that give rise to coloured by-products or sodium which affects final product performance. Several processes for producing **4** are known that are based on the reaction shown below, and it is said that they require use of large quantities of PhOH. Hence, traces of PhOH often remain in the final product, and they are difficult to remove. The basic synthetic route is shown below and is an acid-catalyzed condensation of the ketone **3** with PhOH.



The actual process described in these patents is not so straightforward, and the three patents describe various parts of the process that is carried out in a slurry mixture. This is said to enhance the selectivity and reduce by-products, apparently because the formation of the adduct prevents further undesired reactions.

1. The first stage is to prepare a phenol adduct of **4** by the reaction of aqueous PhOH with **3** in the presence of aqueous phosphoric acid,

2. The next step involves recovery of the phenol adduct from step 1 by neutralisation using NaOH and removal of water followed by cooling to obtain crystals of the adduct.

3. In the next stage an aqueous slurry of the crystals of the adduct is prepared under N_2 gas, and then a further reaction between PhOH and **3** takes place in the slurry mixture in the presence of gaseous HCl. This reaction takes place at 20−30 °C, and a thiol is also added at this stage as a promoter with NaMeS being preferred.

The recovery of the final product is carried out by a number of steps in which the slurry is heated, cooled, reheated, and cooled with crystals of **4** being obtained after each cooling step.

Advantages

The procedure is said to produce very high-purity **4** that contains only 100 ppm PhOH and 0.3 ppm Na; hence, it seems to be effective even though it does seem to involve a great deal of materials handling.

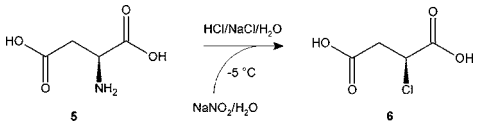
Patent No. U.S. 6,677,476

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

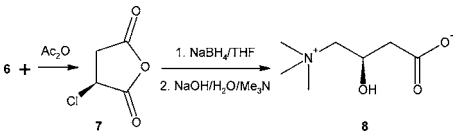
Title or Subject: Process for the Preparation of R-(−)-Carnitine from S-(−)-Chlorosuccinic Acid or its Derivatives

Carnitines have interesting pharmacological properties. The parent compound *R*-carnitine **8** is present in living tissue and is used as a vitamin supplement for both animal and human use. A number of routes to carnitines have been reviewed recently (*Org. Process Res. Dev.* **2003**, *7*, 459). It is stated that there are three basic routes to **8**; however, only two are in commercial use, and they both start from nonchiral starting materials. This patent discloses a third route that starts from a chiral product and involves highly stereo- and regiospecific steps leading to high-purity **8**.

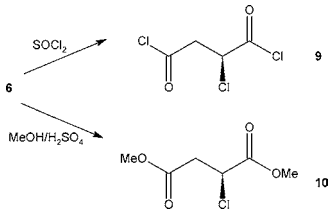
The route to **8** described here starts from *S*-(−)-chlorosuccinic acid **6** and proceeds via the novel anhydride **7**. The patent also describes an efficient synthesis of **6** from *S*-(−)-aspartic acid **5**. This is shown below and involves adding aqueous $NaNO_2$ to a suspension of **5** in aqueous HCl containing NaCl. The recovery of **6** is achieved by cooling to about −15 °C to precipitate the crude solid which is collected and dried. The mother liquors from this precipitation step are reused in subsequent syntheses of more **6**, and this is a crucial aspect of the invention.



The conversion of **6** to **8** is shown below and proceeds via the anhydride **7** which is obtained by dehydration of **6** using Ac_2O or MeCOCl/HOAc. This reaction can be carried out using crude **6** that contains up to 25% NaCl from the synthesis of **6** because the NaCl is removed in this step since it does not dissolve in the reaction mixture. The reduction of **7** to **8** is carried out in THF using $NaBH_4$ followed by treatment with aqueous NaOH and Me_3N. After recrystallisation from *i*-BuOH a 60% yield of **8** was obtained with an ee of >99.6%. A range of other reducing agents is also claimed including $LiBH_4$ and diborane.



The patent also describes the synthesis of novel derivatives of **6** including the dichloride **9** and the dimethyl ester **10** by the procedures shown below. ^1H NMR details are given for all new compounds. These derivatives can also be converted to **8** by reduction by using the procedure and reagents that were used for reducing **7** to **8**.



Advantages

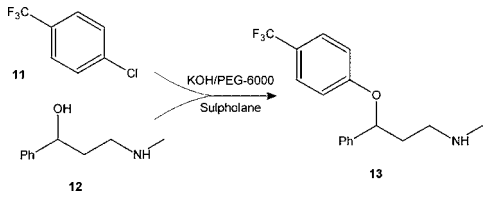
This patent provides an economical alternative to the current methods of forming **8** and also provides a route to some potentially useful novel chiral starting materials.

Patent No. U.S. 6,677,485

Assignee: Ranbaxy Laboratories Limited, New Delhi, India

Title or Subject: Process for Preparation of Fluoxetine Hydrochloride

The subject of this patent is a new process for the production **13** which is the well-known antidepressant Prozac, and although **13** has a chiral centre, it is used as the racemate. The expiry of the original patents for producing **13** has prompted new routes such as the current proposal which is a modification of the known etherification reaction between **11** with **12** in the presence of a strong base. Bases that have been used include $NaNH_2$, NaH and $KOBu^t$, and KOH in a range of solvents. The base chosen here is KOH that is used in a mixture of high-molecular weight poly(ethylene glycol) (PEG-6000) and sulpholane. Crown ethers are also claimed to be suitable, but no examples are given for these. The reaction is shown below and gave, after recrystallisation from EtOAc, a 95% yield of **13** that was >99% pure.



Advantages

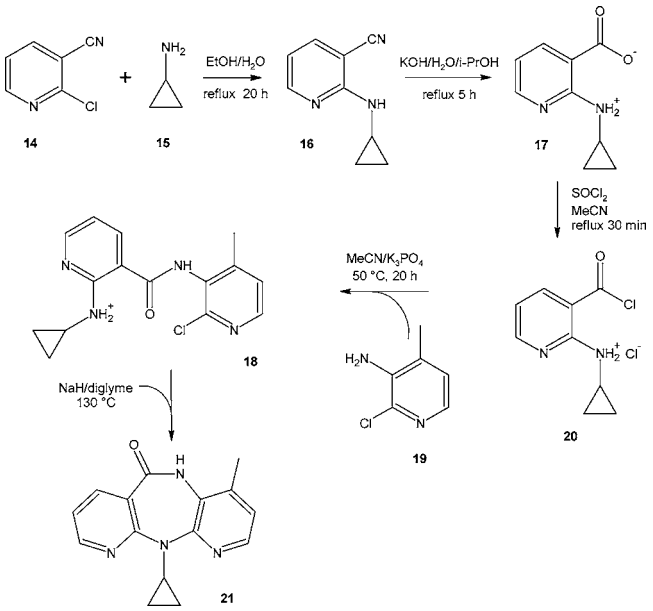
This process is claimed to give high-purity product in better yields, is economical, and is completed in under 1 h compared to 20 h for some of the alternatives.

Patent No. U.S. 6,680,383

Assignee: Boehringer Ingelheim Chemicals Inc., Petersburg, Virginia, U.S.A.

Title or Subject: Method for Making Nevirapine

Nevirapine **21** is used in the treatment of HIV and is commonly known as viramune. The first synthesis was described in 1994 in U.S. 5,366,972 and requires high pressures because it uses the volatile cyclopropylamine **15** and the reaction is carried out at up to 145 °C. A further problem is the thermal instability of one of the intermediates and the exothermic nature of the reaction. This patent describes a new route that removes some of these problems and is shown in the scheme below.



The first stage is formation of the nitrile **16** by heating **15** with **14** in EtOH/H_2O followed by removal of excess **15** and cooling to give the crude **16**. The next stage is preparation of the zwitterion **17** by treating **16** with KOH in aqueous *i*-PrOH, and these two reactions may be carried out without isolation of **16**. Adjusting the pH to about 6 precipitates **17** which is treated with $SOCl_2$ in MeCN to produce the hydrochloride **20**. The next reaction to form **18** from **19** and **20** is carried out under anhydrous conditions, and it is essential to remove all of the chlorinating agent used in the previous step. The K_3PO_4 is added as acid scavenger. This final step is cyclisation of **18** to give **21** with the use of a strong base. Experiments using either NaH in diglyme or sodium hexamethyldisilazane in THF are described.

The patent states that the steps may be carried out with isolation of intermediates, and there are experiments describing this. There are also experiments describing that **14** may be converted to **17** in one pot, and then **17** can be isolated and converted to **18** in another one-pot reaction.

Advantages

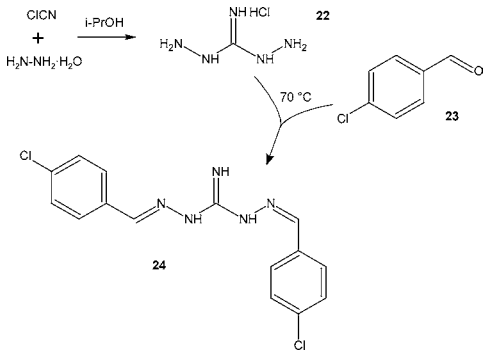
All of the reactions take place at atmospheric pressure or slightly below and hence do not require the expensive high-pressure equipment used in the earlier synthesis.

Patent No. U.S. 6,680,409

Assignee: Lonza AG, Basel, Switzerland

Title or Subject: Process for the Preparation of Robenidine and Salts Thereof

Robenidine **24** is used to treat poultry against coccidiosis which is an intestinal disease found in many birds and animals. **24** is produced in a multistep process starting from hydrazine hydrate and ClCN, and the objective of this patent is to develop a one-pot process using the same basic route. The problem with the current method is that it requires the separation and isolation of the diaminoguanidine salt **22**. The scheme below shows the route that begins with formation of **22** by treatment of ClCN and hydrazine hydrate in *i*-PrOH initially below 12 °C. Addition of concentrated HCl to pH 1.0 was followed by heating to 70 °C. The next reaction step was then carried out by adding the molten aldehyde **23** to the hot mixture. Further heating followed by cooling and washing with water gave moist solid **24** which was dried at 90 °C for 48 h. Product purity of up to 99.3% was obtained in a series of experiments with alternative alcohol solvents.



Advantages

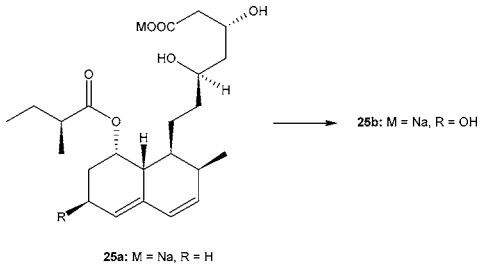
This process removes the need to isolate the intermediate salt and results in an overall higher yield of the product than that from the original process.

Patent Nos. U.S. 6,682,913 and 6,696,599

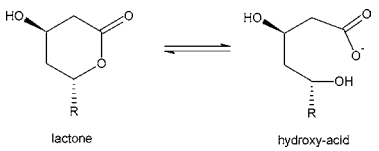
Assignee: Institute for Drug Research Ltd., Budapest, Hungary

Title or Subject: Microbial Process for Preparing Pravastatin

These two patents are the first of four on statins that are examined in this review. They describe a method for making pravastatin **25b** which, like other statins, is used to lower cholesterol levels and thus prevent various cardiac diseases. The claims and subject of the first patent cover the fermentation process, whereas the second patent covers the actual cultures used in the aerobic fermentation. The culture used is a *Mortierella maculata* filamentous mould species and was selected from a screening programme covering about 5500 strains. The objective was to identify a strain that was stable in the fermentation broth and could introduce a hydroxyl group into the Decalin ring of **25a** at the 6-position.



The patents focus on the microbiological aspects of the process, and to this one-time chemist the detail is somewhat intimidating. Hence, no attempt has been made to explain the microbiology involved. As is usually the case with fermentation processes, the concentration of products is low. This is no exception, and after fermentation the concentration of **25b** in the broth was between 660 and 3360 mg/L. There are a number of methods described for isolating **25b**, including extraction with EtOAc or absorption onto an IER. The actual method depends on whether the acid or Na form of the product was required, and since statins can exist as an equilibrium between the lactone and hydroxy-acid forms as shown below, their isolation can be difficult:



The patent describes the isolation of the Na form **25b** from the fermentation broth by the following steps:

1. filtration of culture broth
2. loading filtered culture broth onto an anionic IER
3. elution of pravastatin free acid from resin
4. lactonisation of pravastatin free acid
5. isolation of pravastatin lactone
6. hydrolysing lactone with NaOH to form **25b**

7. purification of **25b** by chromatography on a nonionic absorption resin.

The patent also describes the conversion of the free acid form to a secondary amine salt and of this salt to **25b**.

Advantages

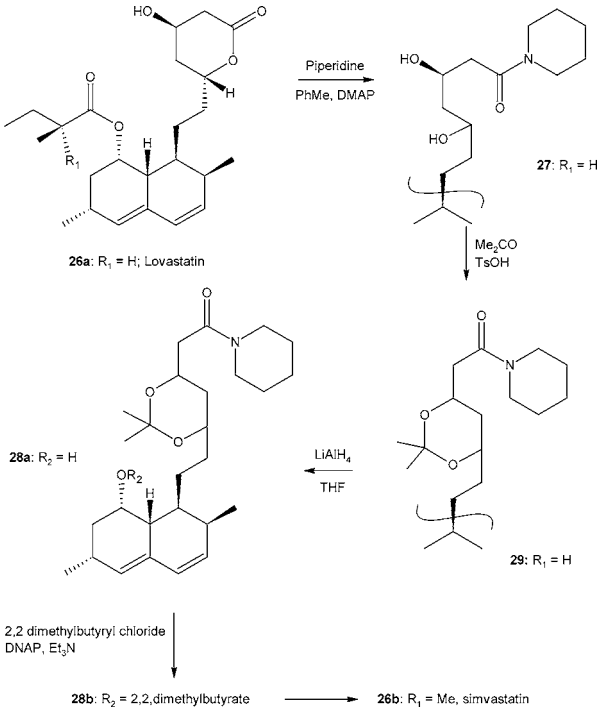
The patent claims that this process is suitable for commercial production of **25b** and is much better than alternative procedures.

Patent No. U.S. 6,686,481

Assignee: Plus Chemicals B.V., Mijdrecht, Netherlands
Title or Subject: Highly Purified Simvastatin Compositions

This is the third patent on the subject of the important statin drugs, and it relates to a process for making and purifying simvastatin **26b**. Of the two most common statins **26b** is more potent than lovastatin **26a**, and this patent describes a process to convert **26a** to **26b**.

The conversion of **26a** to **26b** is carried out according to the following steps which are depicted in the scheme below.



1. The lactone ring is opened by reaction of **26a** with an amine such as piperidine to give the amide **27**.

2. The 1,3-diol grouping in **27** is then protected by conventional means such as by formation of the acetal **28** with Me_2CO.

3. The 2-methylbutyrate ester group is removed in **29** to give **28a** by reduction using $LiAlH_4$.

4. Attachment of the 2,2-dimethylbutyrate group by acylation to give **28b**.

5. The final stages involve the removal of the protecting group. This can be done by formation of an ammonium salt of the hydroxy form of the statin which can then be converted to the lactone **26b** on acidification.

There are a great many variations on this basic scheme, which involve using a range of amines in step 1, alternative protecting groups in step 2, and reducing agents in step 3.

The patent specifically mentions a variety of impurities that can be removed to levels <0.1%. The patent claims that **26b** can be obtained by the above procedure from a mixture containing **26a** that can initially contain up to 30% of the impurities.

Advantages

The process can convert impure **26a** to high-purity **26b** and hence has the potential to use cheap sources of **26a**.

Patent No. U.S. 6,689,590

Assignee: Biogal Gyogyszergyar Rt., Debrecen, Hungary
Title or Subject: Process for Recovering Statin Compounds from a Fermentation Broth

This patent is aimed at the recovery of **25a** that is free from the lactone form of the compound. The method used to produce **25a** is a fermentation process similar to that described in the patents above which are also from a Hungarian group. One of the objectives of this patent was to avoid the use of a chromatographic purification technique such as HPLC which is said to be not feasible on a large scale. The process involves the extraction of the statin into an organic solvent, and *i*-BuOAc is used in an example. The solution of **25a** was then treated with NH_3 gas and then NH_4Cl to give the ammonium salt **25c** ($M = NH_4$). After further crystallisations from water **25c** was converted to **25b**, and this was treated with a cationic IER to remove excess Na^+ ions. Recrystallisation from water/Me_2CO/MeCN gave 99.3% pure **25a** in about 65% yield.

Advantages

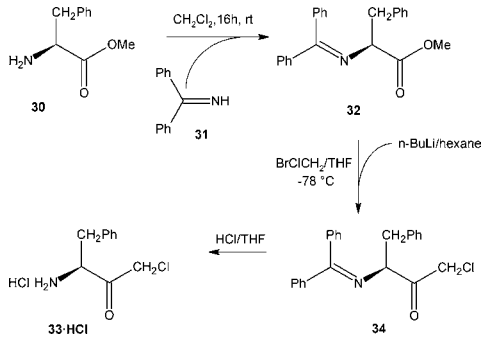
The process enables extraction of high-purity statin from the fermentation broth without resorting to chromatographic methods that are not feasible on a large scale.

Patent No. U.S. 6,683,214

Assignee: Ajinomoto Co., Inc., Tokyo, Japan
Title or Subject: Process for Producing α-Amino-halomethyl Ketones

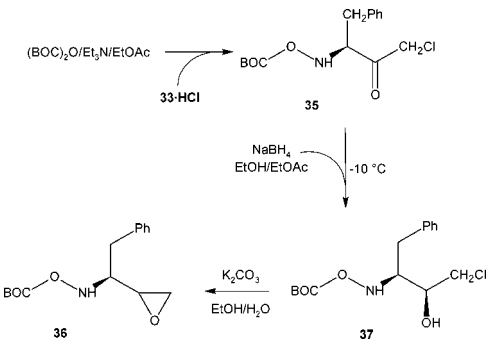
Compounds such as **33** and **36** are reported to be useful as intermediates for the synthesis of HIV protease inhibitors. This patent describes a process to produce these compounds plus a range of novel N-protected intermediates. It is stated that the production of α-aminohalomethyl ketones from amino acid esters is difficult because suitable amino protecting groups are not available when a haloketone group is present in the molecule. This patent describes that the amino group in an amino acid ester can be protected as a Schiff base that then reacts with a halomethyllithium compound to give the desired compound. The scheme below shows the route for converting the ester **30** to **33**.

The first step is protection of the amino group by formation of the imine **32** by reaction of **31** with the amino acid ester **30** at room temperature. Low-temperature reaction



of **32** with $LiCH_2Cl$ gives α-chloromethyl ketone **34**, which on acidification removes the protective group giving the salt **33**·HCl.

The salt can then be used to prepare a range of other compounds as shown in the following scheme. The reactions require protection of the amino group in **33**·HCl by the BOC group by a novel process in which $(BOC)_2O$ is mixed with base such as Et_3N in EtOAc, and a solution of the salt is added to the mixture to give **35**. The ketone group is then stereoselectively reduced to the hydroxy compound **37** using $NaBH_4$, and conversion to the epoxide **36** is then carried out by reaction with K_2CO_3 in $EtOH/H_2O$. There are a number of alternative reagents for several of the reaction steps, and the patent contains details for over 25 experiments covering various reactions in the two schemes.



Advantages

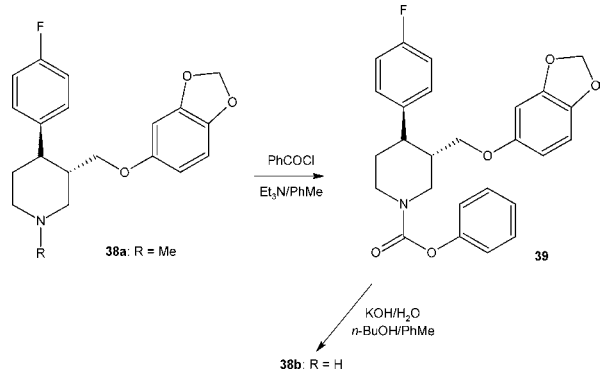
The patent discloses some novel intermediates and procedures and claims that the process for their production is amenable to commercial production. The optical activity is maintained throughout the process; hence, the optically active amino acids can be used as starting materials.

Patent No. U.S. 6,686,473

Assignee: Synthon BCT Technologies LLC, Chapel Hill, North Carolina, U.S.A.

Title or Subject: Process for the Production of Paroxetine

One method for the synthesis of the antidepressant paroxetine **38b** involves base hydrolysis of the phenylcarbamate **39**, but it is said that this is a difficult procedure. The hydrolysis in a liquid−solid suspension has been used, and as already mentioned in this review above, such processes are generally not favoured. This patent describes an improved hydrolysis procedure using a solvent mixture that allows dissolution of reactants. The scheme below shows the route from **39** which is produced from **38a** by reaction with PhCOCl in PhMe. It is not necessary to isolate **39** before the hydrolysis step to give **38b** which is carried out using KOH in refluxing aqueous EtOH. The experiments report the synthesis of almost 15 kg of **38b**.



Advantages

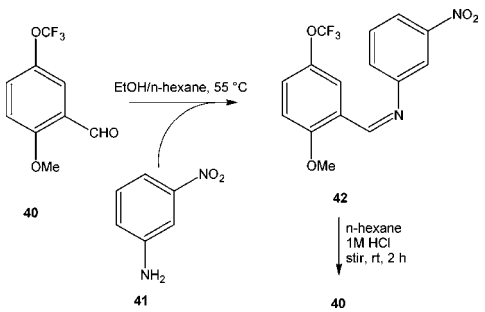
The procedure simplifies a key step in the production of this important drug, and the scale reported indicates that it is at an advanced stage of development.

Patent No. U.S. 6,686,507

Assignee: Pfizer Inc., New York, New York, U.S.A.

Title or Subject: Purification of 2-Methoxy-5-trifluoromethoxybenzaldehyde

The title compound **40** is used in the manufacture of nonsteroidal antiinflammatory agents. **40** is described as an oil, and such materials are often difficult to purify. Attempts to purify **40** by protection of the aldehyde group were carried out by making the acetal, but this was said to be unsuccessful although no details are given. The formation of an imine, however, did provide a solid compound that could be purified and then converted back to **40**. This is the basis of the method shown below and described in the patent. The imine **42** was formed by reaction of **40** with a nitroaniline such as **41** by adding **40** to a vigorously stirred heterogeneous mixture of EtOH and hexane and then adding **41**. Cooling gave **42** as a solid which was recrystallised as a single isomer from hexane and then was decomposed in hexane/HCl to give **40**. An important feature of the process is that the formation of **42** and the corresponding imine from 4-methyl-2-nitrophenylaniline gave only a single isomer. A range of other nitroanilines was used, and the different conditions required for producing the imines are provided.



Unusually, this patent does give some reasoning behind the development of the process. It is suggested that the

formation of the imine implies an equilibrium reaction and that its formation is driven by the conjugated structure. In addition, the difference in solubility between the nitroaniline and corresponding imine helps to drive the reaction to completion. Hence, part of the development of the process was to identify a suitable solvent that ensured precipitation of the imine, and temperature control was also important to adjust solubility.

Advantages

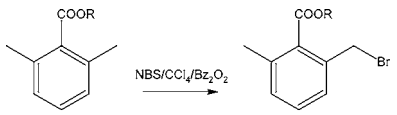
This is an efficient method of purifying the intermediate which drastically reduces the impurities normally present from its synthesis.

Patent No. U.S. 6,689,891

Assignee: Prime Euticals Therapeuticals S.p.A., San Grato-Lodi, Italy

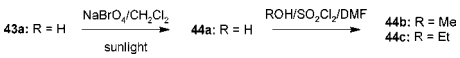
Title or Subject: Process for the Preparation of 2-Bromomethyl-6-methylbenzoic Acid and Its Esters

44a (R = H) and its esters are used as intermediates in the synthesis of peroxisome proliferator-activated receptors (PPARs) that play an important role in many cellular functions. PPARs have been found to interact with a number of endogenous lipids and drugs for the treatment of human metabolic diseases. It is claimed that **44b** is usually made by bromination of **43b** in the presence of Bz_2O_2 as shown below, but the purity of the product is only about 85% with the remainder being unreacted **43b**.



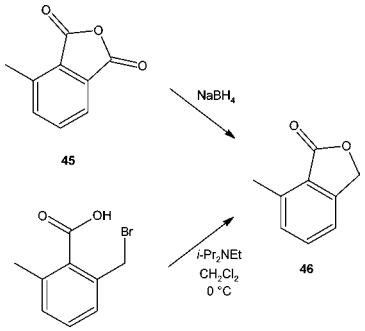
43b: R = Me **44b:** R = Me

This patent discloses a process for production of the acid **44a** by photolytic bromination of **43a** (R = H) using $NaBrO_4$/HBr in water. The reaction shown below is carried out by dissolving **43a** in a chlorinated solvent such as DCM and keeping the solution at about 5 °C while exposing to sunlight and slowly adding the brominating mixture. The product is crystallises from solution during the reaction, thus making its isolation easier.



The preferred wavelength of light is claimed to be 200−750 nm The single experiment states that the reaction was exposed to sunlight and experiments in the dark failed. On this basis it is clearly not possible for this to be scaled up without an artificial source of light, and there was no mention of this in the patent. The patent claims that by carrying out the reaction at low temperature there is never an excess of bromine; hence, polybrominated compounds are not formed. The patent also describes the formation of the esters **44b** (R = Me) and **44c** (R = Et) by using $SOCl_2$/DMF.

The final aspect of the patent is the synthesis of the compound **46** from **44a**. **46** has biological interest and can be made by reduction of **45** using $NaBH_4$, but a more convenient route would be ring closure of **44a**. This method is carried out by treating a base such as a tertiary amine as shown below. Alternatively, the reaction can be carried out using $NaHCO_3$.



It is stated in the patent that although **44a** does not contain any free **43a** it may contain small amounts of **46**. Since **44a** is often used to prepare **46** or other compounds that are made via **46**, this is not a drawback.

Advantages

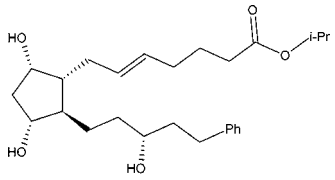
The patent claims to disclose an efficient route to the monobromo derivative, but the use of sunlight does not seem to provide a commercially viable process.

Patent No. U.S. 6,689,901

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

Title or Subject: Novel Intermediates for the Preparation of Latanoprost

Latanoprost **47** is used to treat a range of ophthalmic conditions, and this patent describes a route to **53** which is a novel intermediate used in the synthesis of **47**.

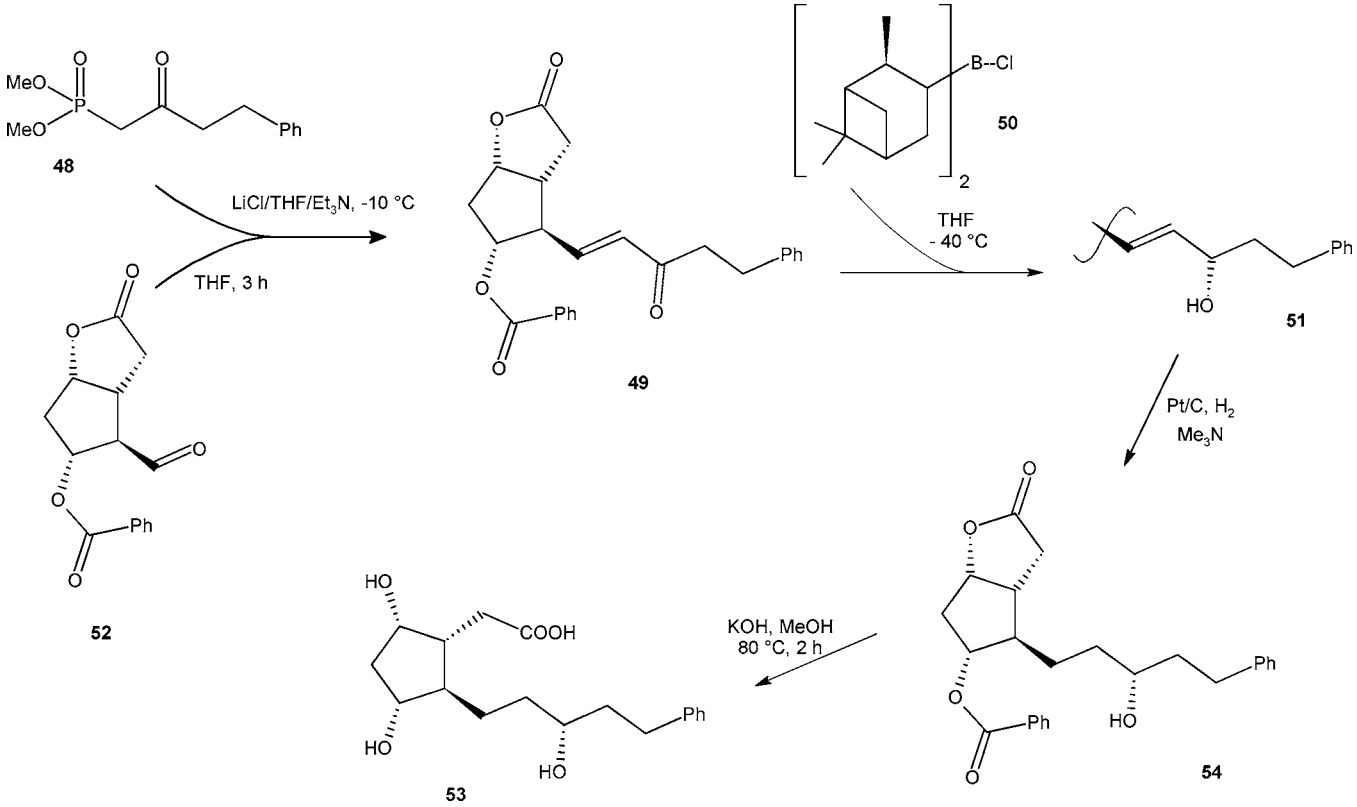


47: Latanoprost

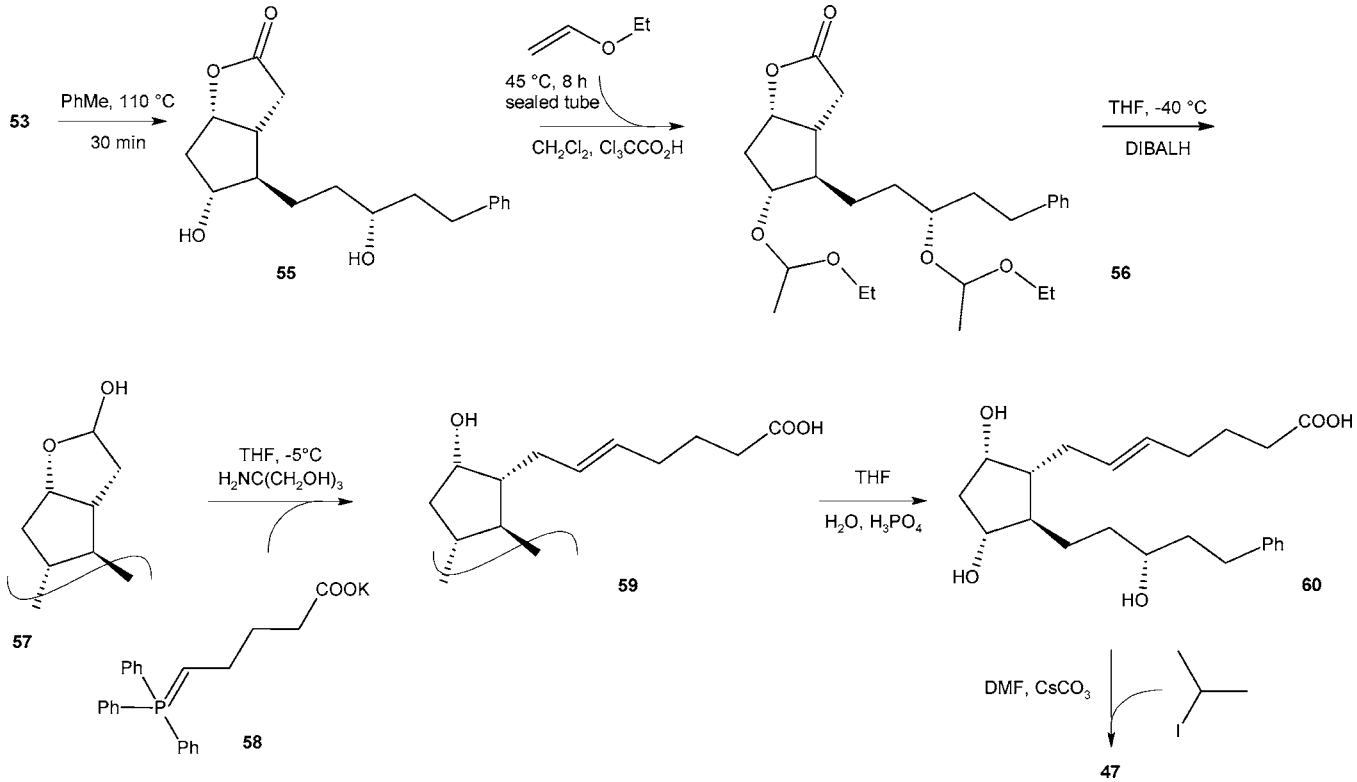
The synthesis of **53** is shown below and starts from the Corey aldehyde benzoate **52** which reacts with **48** to give the enone **49**. This is then reduced to the enol **51** by using the chiral chloroborane **50**. This is said to be a rare example of reducing an α,β unsaturated enone with this reagent. Reduction of the C=C bond in **51** then produces **54** which is subjected to base hydrolysis to give the novel compound **53**. ^{1}H NMR data are given for all intermediates shown in Scheme 1.

The novel compound **53** is converted to **47** in a series of reactions shown below. In the first step **53** is converted to the lactone **55** by refluxing in PhMe. The hydroxy groups on **55** are then protected by reaction with ethylvinyl ether to give **56**, and the C=O group in **56** is then reduced using

Scheme 1



Scheme 2



DIBALH to give **57**. Treatment of **57** with the ylid **58** produces **59** which when treated with H_3PO_4 gives latonoprost acid **60**, and reaction of **60** with *i*-PrI in the presence of $CsCO_3$ gives **47** (see Scheme 2).

Advantages

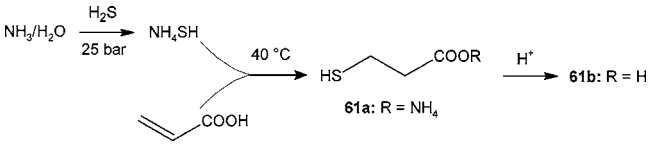
The process provides a novel route to prostaglandin intermediates that is stereoselective.

Patent No. U.S. 6,689,907

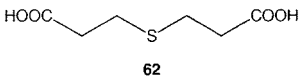
Assignee: Atofina, Puteaux, France

Title or Subject: Process for the Manufacture of Mercaptocarboxylic Acids from Unsaturated Carboxylic Acids

Mercapto acids such as **61b** are useful intermediates for producing modifying agents for epoxide resins and acrylic polymers used in paints and for treating papers. Alternative methods for synthesising these acids use CS_2 or frequently produce sulphides and hence have significant effluent disposal problems. The objective of this work is to eliminate these problems and start from a cheap raw material such as acrylic acid (AA). The process is based on the reaction shown below in which a hydrosulphide such as NH_4SH reacts with AA to form **61a** which on acidification gives the acid **61b**.



The reaction is apparently possible because H_2S is quite soluble in the reaction medium, and this promotes the formation of the desired mercaptan. A side reaction to give the sulphide **62** is not observed, and this is attributed to the increased rate of formation of **61a** by virtue of the solubility of H_2S in the reaction mixture and the slow reaction of **61a** with AA in the presence of H_2S.



62

An important parameter in the process is the H_2S/AA ratio which should be as high as possible. By working under high pressure this ratio is increased. An alternative mode of carrying out the process is to add 3-chloropropionic acid which reacts directly with NH_4SH and produces more H_2S in the reaction mixture itself.

Advantages

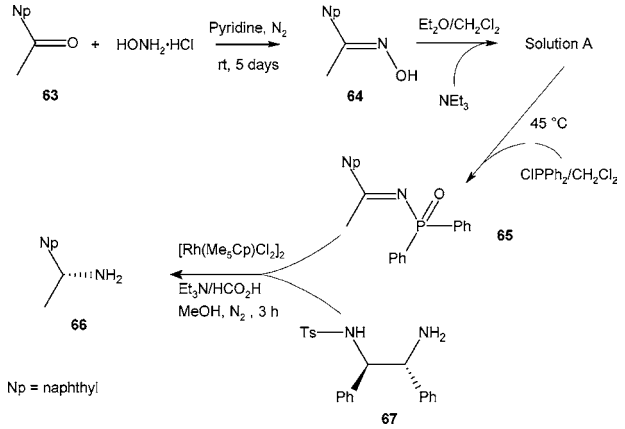
Although this process gives an improved yield and fewer by-products than the alternative methods, it does involve the use of H_2S under pressure which can be hazardous.

Patent No. U.S. 6,696,608

Assignee: Avecia Limited, Manchester, United Kingdom

Title or Subject: Process for Producing Amines by a Catalytic Transfer Hydrogenation Process

The patent describes a process for the formation of primary or secondary amines from imines or iminium salts. An example is shown below that summarises the enantioselective conversion of the ketone **63** to the amine **66**. This is carried out by first forming the oxime **64**. The reaction mixture contains a mixture of E and Z isomers, but crystallisation gave only the *E*-oxime, and this was dissolved in Et_2O/DCM along with NEt_3 to give solution A. This solution is then treated with $ClPPh_2$ to produce the phosphoryl imine **65**. The reduction of the imine to give **66** takes place in the presence of HCO_2H/NEt_3 as the H transfer reagent using a catalyst system of $[Rh(Me_5Cp)Cl_2]_2$ and the chiral diamine **67**. It is suggested that this catalyst system produces a Rh compound which is coordinated to the bidentate diamine, and this seems reasonable.



63 64 65 66 67

There are a number of variations in the patent of the catalyst with examples for Ir, Ru, and Rh complexes with **67** and a selection of chiral monotosyldiamines. The H-transfer reagent is preferably a mixture of NEt_3 and HCO_2H although alcohols are also mentioned. It has to be pointed out that there are a number of errors in the experimental description such as the apparent use of acetophenone oxime instead of octan-2-one that was supposedly used to produce a methylhexyl imine.

Advantages

The patent claims cover a very large number of possibilities, and it provides a ready route to a variety of amines.

Keith Turner

Kappa Tau Consulting, 12 The Avenue, Fairfield, Stockton-on-Tees, TS19 7EY, UK
E-mail: keith@kappa-tau.co.uk

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