Organic Process Research & Development **2006**, *10,* 381–390

# *Highlights from the Patents*

## A Review of U.S. Patents in the Field of Organic Process Development Published during January and February 2006

A landmark was reached in the U.S. Patent Office on February 14th when patent number 7,000,000 was published. It has not been reviewed but is about cotton-like polysaccharide fibres if anyone is interested. There are 22 patents in this selection from an original list of 214, and it is hoped that they are of interest to readers. The production of a racemic mixture can involve waste if the unwanted isomer cannot be recovered and reused. Hence, any process that makes a specific enantiomer is desirable. On this point, a new synthesis of the desired enantiomer of atenolol, a drug used to treat heart diseases, is disclosed. Also on the subject of waste reduction is a patent that addresses the recovery of compounds used to prepare the anaesthetic sevoflurane. The process improves overall yields and reduces wastes by a hydrolysis method that allows reuse of waste products. A group of four patents describe the synthesis of an extensive range of compounds used as topoisomerase target agents, and hence they are of interest in cancer treatments. A novel compound is described that can be used to prepare phytone, an intermediate in the production of the nutritional supplement vitamin E. A particular problem with reactive intermediates can be their reactivity and instability. Some 2-bromobenzoic acid derivatives require cold storage, and any degradation can form mutagenic alkyl bromides. A method of synthesising alternative reagents is reviewed, and the compounds are used in preparing a PPAR agonist for diabetes treatment. Many patents report interesting chemistry that is unlikely to result in a commercial process. There are examples of this including one using microwaves and another using excessively high pressures. The statin drugs continue to be of interest, and an improved process for preparing simvastatin with reduced by-product dimer is described. The process adds a well-known antioxidant and free radical trap to the reaction mixture and also to the solvents used during the workup. The surprising point is that the reaction is not known to involve free-radical oxidation processes. A novel method is described of producing eflornithine, a drug that is used for treating African sleeping sickness and for removing facial hair. A new process is described for preparing the drug ritalin the drug that is used to calm down hyperactive children. Novel methods of preparing polymorphs continue to be described, and examples are given for torsemide and mannitol. The former is used to treat hypertension, and the latter is used as an excipient in many tablet forms of drugs. The metathesis of functionalised olefins catalysed by carbene complexes is used to prepare a range of alkenediols. The reaction is stereoselective so that chiral materials can be used. A number of patents describe processes using multikilogram amounts of materials, and these may be at an advanced stage of development. There is no legal or commercial significance in the patents selected, and any advantages mentioned are those claimed in the patent unless this reviewer has personal knowledge of the subject.

### Patent No. U.S. 6,982,349

***Assignee: Emcure Pharmaceuticals Limited, Pune, India***

***Title or Subject: Process for Producing Atenolol of High Optical Purity***

Atentolol **5**, in the form of the racemic mixture, is used as a $\beta$-adrenegic blocker for the treatment of a range of heart diseases. It is known that the *S*-isomer is more active, and although methods of resolution are known, this patent provides an improved process for its direct preparation. The process used to prepare the *S*-form **5** is shown in Scheme 1 and starts with the condensation of **1** with **2** to give a mixture of the glycidyl ether **3** and the chlorohydrin **4** in a ratio of 3:2. This reaction is carried out using a phase transfer catalyst with NaOH or KOH. The patent states that the temperature of this reaction should be $<5$ °C to obtain the highest optical purity of **3** and results of experiments showed that temperatures $<-4$ °C were preferred. It is suggested in the patent that improved optical purity is due to the relative reaction rates of the phenoxide ion from **1** with the C1 and C3 atoms in **2**. Attack at the chloro-substituted carbon (C1) gives lower yields of **5**, and this is favoured at the higher temperatures. The final step of the process is carried out by reaction of the mixture of **3** and **4** with *i*-$Pr_2NH$ to give **5** in 91% yield with an ee of 99.1%. The patent does not mention how **4** is made, nor does it mention the optical purity since this would have an impact on the yield. However, it is assumed that the **4** used was of high optical purity since it is referred to as *R*-epichlorohydrin.

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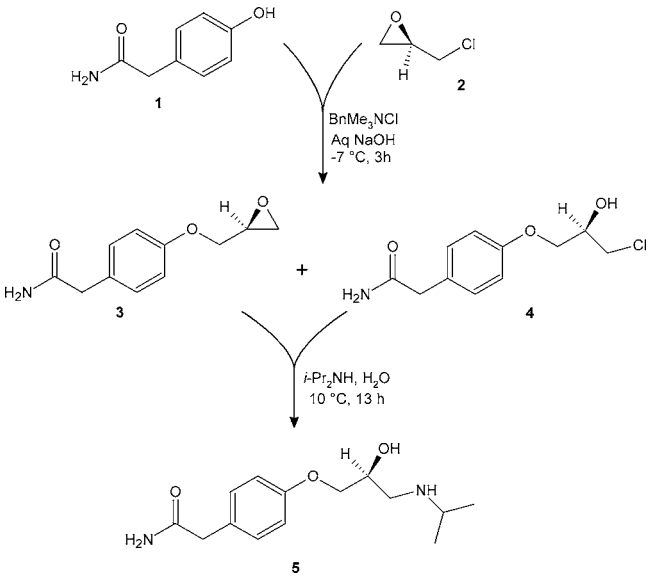
***Scheme 1***




The patent provides $^1$H NMR and IR data for the product.

## Advantages

The reaction scheme used removes the need for resolving a racemic mixture and therefore greatly improves the efficiency of the process.

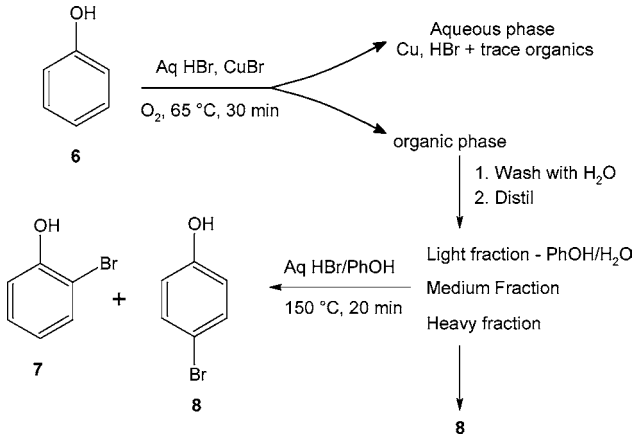
## Patent No. U.S. 6,982,356

***Assignee: General Electric Company, Niskayuna, New York, U.S.A.***

***Title or Subject: Method for the Preparation of p-Bromophenol***

The main subject of this patent, **8**, is used to prepare 4,4′ dihydroxybiphenyl, a particularly useful material for the manufacture of high-value polymers such as polycarbonates, polysulfones, or polyetherimides. The first claim of the patent actually covers a recovery method for the catalyst that is used in the oxybromination of hydroxyaromatic compounds. The focus of the patent is on selectively producing **8** from PhOH by isomeric equilibration and separation procedures. The process is summarised in Scheme 2. The reaction is carried out in a single-phase mixture with a volatile solvent or as an aqueous and organic two-phase mixture. Experimental details describe using MeCN as solvent although EtOAc, $CHCl_3$, or HOAc are claimed to be suitable. The catalyst comprises $CuBr_2$ and 48% HBr, and the reaction is conducted at 65 °C and 34 atm of air to supply $O_2$ needed for the reoxidation of the catalyst. The organic phase from the two-phase reaction is distilled to obtain three fractions. The product is contained within the middle and heavy fractions. The middle phase contains >90% of **7**, and this is isomerised by heating with HBr and PhOH to give a 1:1 mixture of **7** and **8** that is separated by distillation.

***Scheme 2***




When the reaction is carried out in MeCN, 2,4-dibromophenol is also formed. This is heated in the isomerisation reaction with the mixture of **7** and **8** and presumably reacts with PhOH to form the monobromo compounds.

## Advantages

The reaction improves the overall selectivity of the process without having to improve the selectivity of the bromination reaction.

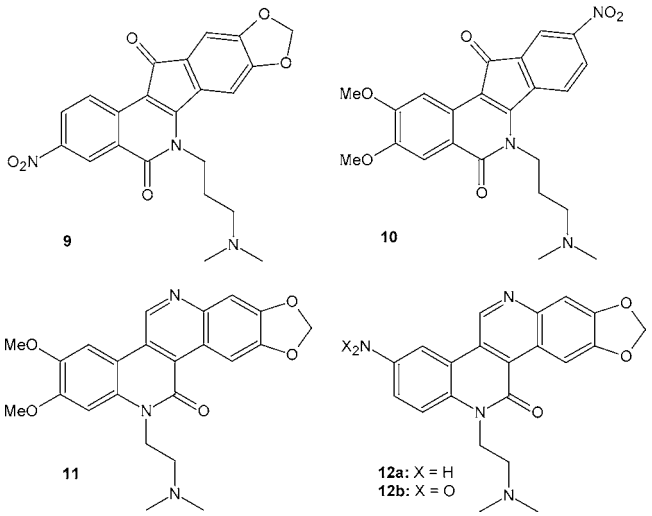
## Patent No.s U.S. 6,987,109, 6,989,387, 6,992,088, and 6,992,089

***Assignee: Rutgers, The State University of New Jersey, New Brunswick, New Jersey, U.S.A.***

***Title or Subject: Substituted Heterocyclic Compounds as Topoisomerase I Targeting Agents***

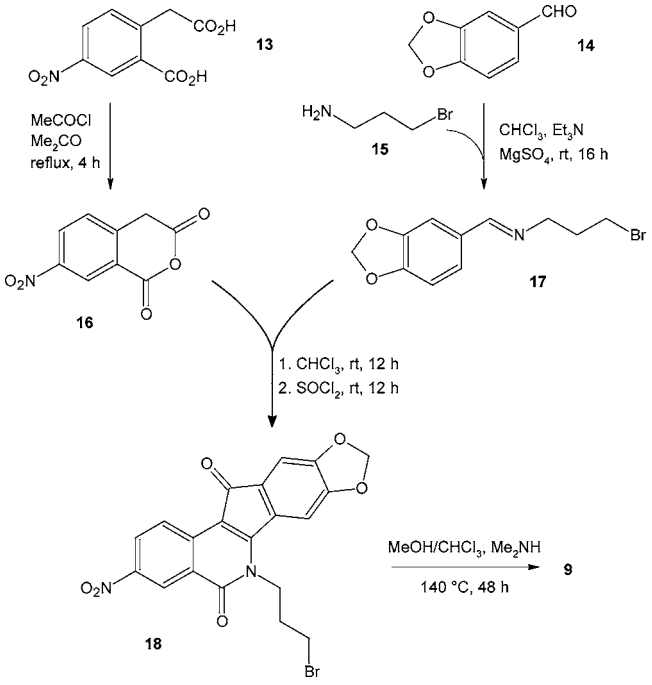
These four patents cover different aspects of the production of compounds that can inhibit the activity of topoisomerase enzymes. The enzymes control the breaking and rejoining of DNA strands and are thus responsible for the production of malformed cells and the formation of tumours. The patents cover a considerable number of compounds, such as **9**−**12** and analogues, that are of interest in the treatment of cancers. Each patent focuses on the different compounds that are covered.

Compounds **9**−**12**



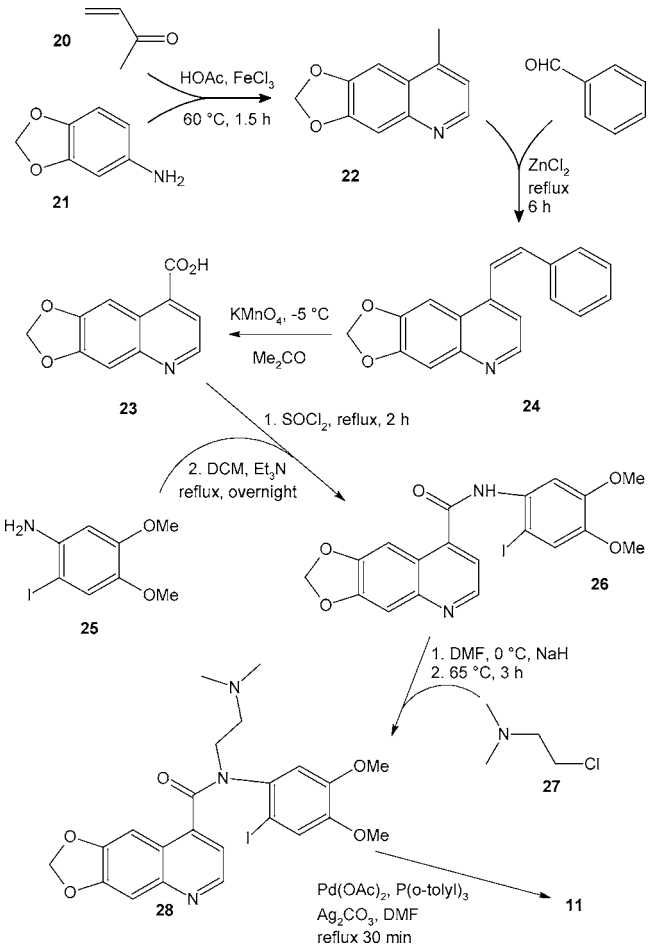

The preparation of one of these compounds, **9**, is shown in Scheme 3. The overall efficiency does not seem to be very good because in the final step in this synthesis, the amination of **18**, the reported yield of **9** is only 21%, and the reaction takes 48 h. In addition the intermediate **18** is produced in a very poor yield of 8% from **16** and **17**.

***Scheme 3***




Scheme 4 shows the multistep route used to prepare compound **11**. Several of the steps give yields of around 50%, and so the overall yield of **11** may also be low. The final reaction also gives an unspecified by-product, and no details are given as to how to remove it.

***Scheme 4***




The patents give $^{1}H$ and $^{13}C$ NMR data for most of the intermediates and also information on cytotoxicity tests of some of the products.

## Advantages

The patent provides synthetic methods for making a range of novel compounds that have potential use in the treatment of cancers.

## Patent Nos. U.S. 6,987,192 and 6,992,195

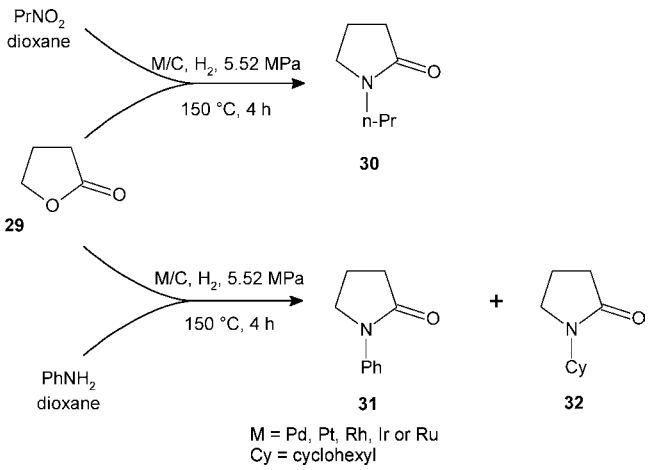
***Assignee: E.I. Du Pont de Nemours and Company***

***Title or Subject: Production of N-Substituted-2-Lactams by Reductive Amination of Lactones***

These two patents are similar to a range of others from the same company that have been reviewed previously (*Org. Process Res. Dev.* **2005**, *9*, 537). The first patent covers alkyl- and aryl-substituted lactams made from nitro compounds, while the second covers aryl and cycloalkyl lactams made from arylamines. The lactam products are used in a range of applications from inks for inkjet printers to cleaning agents, refrigerants, and pharmaceuticals. Like the earlier patents the reaction condi-

tions are rather severe, and very high pressures are required. Scheme 5 shows the reaction used to prepare the compounds **30**−**32**. One example in the first patent actually claims that the reaction of **29** with $PrNO_2$ gives the 5-methyl derivative of **30**. This seems to be highly unlikely, and the presence of such basic errors is inexcusable and all too common in many patents.

***Scheme 5***




## Advantages

Whatever advantages this reaction may have must be outweighed by the extreme reaction conditions used.

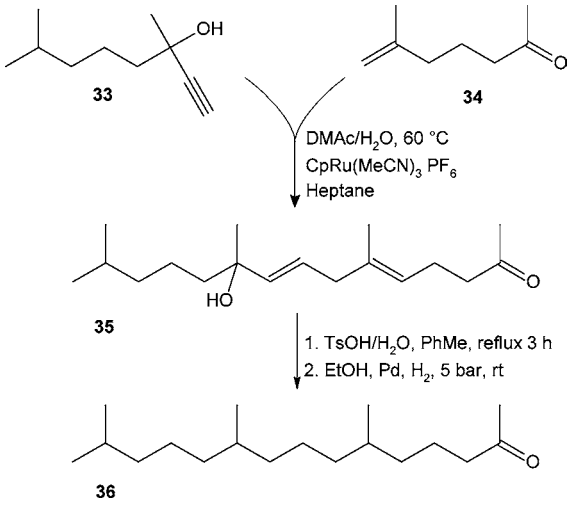
## Patent No. U.S. 6,987,203

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

***Title or Subject: Process for the Preparation of Phytone***

Phytone **36** is used in the manufacture of vitamin E, and this patent describes the synthesis of the novel compound **35** that can be converted to **36** by the procedure shown in Scheme 6. The synthesis of **35** is carried by the coupling of **33** with **34** catalysed by a Ru catalyst. It is preferred to add a solution of the reactants to the catalyst solution. It is stated that this inhibits the degradation of the reactants. A two-phase solvent system is used, and the product is recovered from the nonpolar solvent. The second stage of the process is the hydrolysis of **35** using TsOH as catalyst followed by hydrogenation using a Pd catalyst. The product **36** is obtained in a yield of 89%.

***Scheme 6***




## Advantages

The process provides a novel intermediate for the synthesis of vitamin E, an important nutritional supplement.

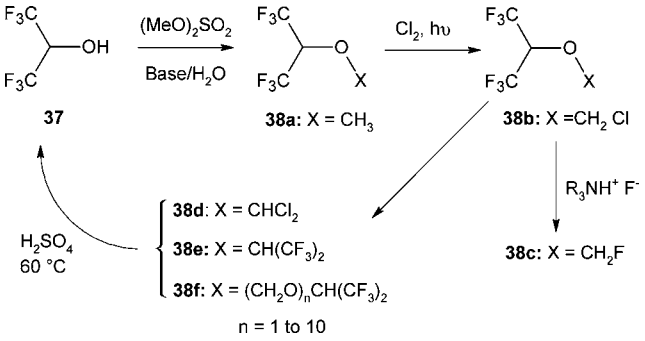
## Patent No. U.S. 6,987,204

***Assignee: Baxter International Inc., Deerfield, Illinois, U.S.A.***

***Title or Subject: Process for the Recovery of 1,1,1,3,3,3-Hexafluoroisopropanol from the Waste Streams of Sevoflurane Synthesis***

Sevoflurane **38c** is probably the most widely used an inhalation anaesthetic because it allows rapid onset of anaesthesia and rapid recovery after use. Many processes for the manufacture of **38c** use **37** as a starting material that can be lost in significant quantities. Hence, methods of recovering **37** from the wastes can improve the overall economics of the process. The principle of the process is to hydrolyse the waste products that contain a $(F_3C)_2CHO$-group to give **37** that is then recovered. The hydrolysis is carried out using strong protic acids such as $H_2SO_4$. Scheme 7 shows the reaction scheme and some of the compounds that are present in the waste streams that can be hydrolysed to give **37**.

***Scheme 7***



The patent gives details of how a single charge of $H_2SO_4$ can be reused five times without significant loss of performance.

### Advantages

The process improves the process efficiency and reduces the volume of wastes produced.

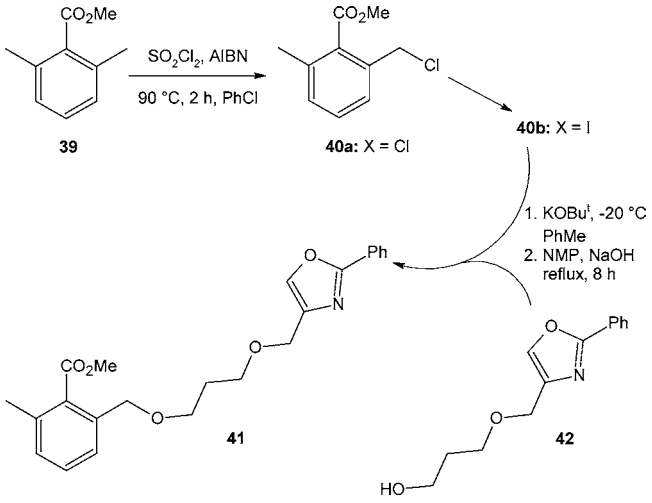
### Patent No. U.S. 6,989,462

***Assignee: Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany***

***Title or Subject: Synthesis of 2-Chloromethyl-6-methylbenzoic Esters***

2-Bromobenzoic acid derivatives such as **40c** (X = Br) are useful starting materials but are said to be thermally labile and require cold storage. The main problem with these compounds is a cyclisation reaction that can produce alkyl bromides that are mutagenic. Thus bromo-derivatives such as **40c** can be potentially difficult to use in the preparation of pharmaceutical ingredients. The object of this patent is to prepare reagents that are not thermally labile, and the patent describes the synthesis of **40a**. This is used to prepare **41**, a PPAR agonist that is useful in the treatment of Type 2 diabetes. Alternative methods for the synthesis of **40a** involve a ring-opening chlorination of lactones. Although the chloro-compounds such as **40a** are stable, they are not so useful in the production of **41**. Scheme 8 shows the route used to produce **40b** from **39** by a free radical chlorination reaction. The iodo-derivative **40b** is then obtained by reaction of **40a** with NaI, and then treatment with **42** in the presence of base gives **41** in 50% yield. This reaction is carried out without isolation of **40b**.

*Scheme 8*




### Advantages

The process provides a method of forming and using a labile intermediate without the necessity of isolation and possible degradation on storage.

### Patent No. U.S. 6,989,467

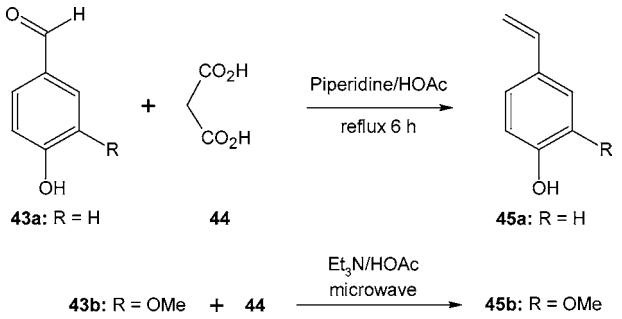
***Assignee: Council of Scientific and Industrial Research, New Delhi, India***

***Title or Subject: Microwave Induced Process for the Preparation of Substituted 4-Vinylphenols***

The compounds of interest in this patent are used as flavours and fragrances. There are natural sources available for some of these, but they cannot fill the demand and hence the need for synthetic materials. The patent claims to provide the first example of using microwave irradiation for the preparation of vinylphenols from 4-hydroxybenzaldehydes. The only alternative method for preparing vinylphenols is said to involve the decarboxylation of cinnamic acid. Several references are given for this process and all are claimed to have significant disadvantages such as low yield or the use of expensive reagents.

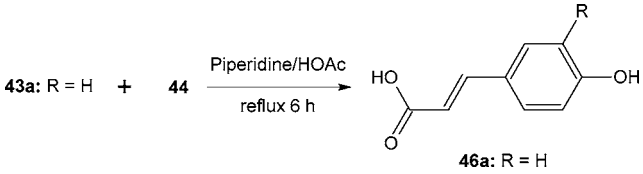
Scheme 9 shows the method used to prepare the compounds **45a** and **45b** by condensation of malonic acid **44** with the aldehydes **43a** or **43b** in HOAc in the presence of a base. The mixtures are irradiated for up to 8 min using a standard 1200-W microwave oven operating at 2450 MHz.

*Scheme 9*




When the reaction between **43a** and **44** was carried out by refluxing without irradiation, the product was **46** (Scheme 10.). This indicates that the reaction probably proceeds via **46**, and presumably irradiation of **46** would give **45a**, but this was not reported.

*Scheme 10*



The patent also reports examples of preparing other vinylphenols by condensation of **44** with other hydroxyaldehydes.

### Advantages

The process does give a rapid method of producing the vinylphenols although whether the use of microwave irradiation is commercially viable is not known.

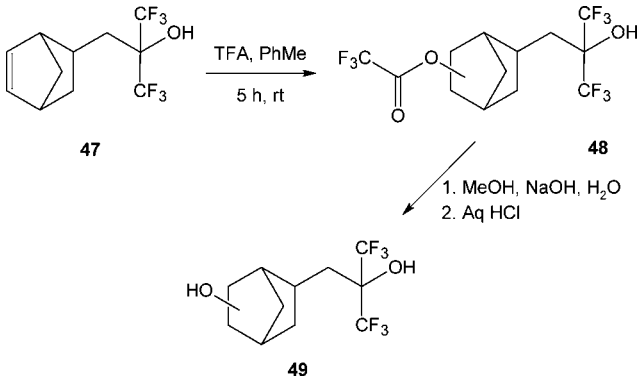
## Patent No. U.S. 6,992,210

***Assignee: Central Glass Company Limited, Ube, Japan***

***Title or Subject: Production of Fluorine-Containing Cyclic Esters and Alcohols***

Fluorine compounds are useful intermediates for a variety of agrochemicals, pharmaceuticals, and special monomers. This patent describes a process for producing novel compounds such as the ester **48** and alcohol **49**. The ester **48** is formed by the addition reaction of TFA with the norbornene **47** (Scheme 11). The patent does not specify which isomer is obtained, and presumably this is a mixture. The alcohol **49** is formed by hydrolysis of the ester, and again no specific isomer is mentioned.

*Scheme 11*




### Advantages

The reaction is very facile, and as long as the norbornene is readily available it provides a route to some novel compounds.

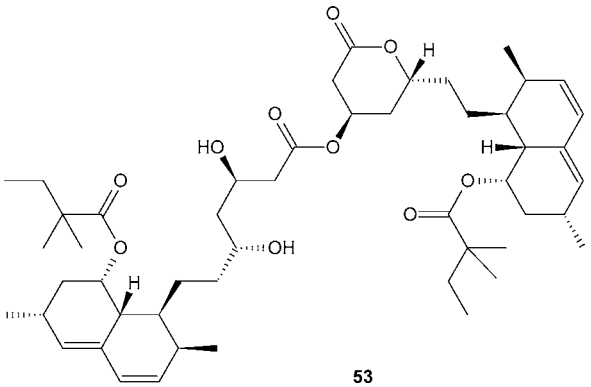
## Patent No. U.S. 6,995,277

***Assignee: Plus Chemicals, B.V., Mijdrecht, The Netherlands***

***Title or Subject: Process for Preparing Simvastatin with Controlled Dimer Content***

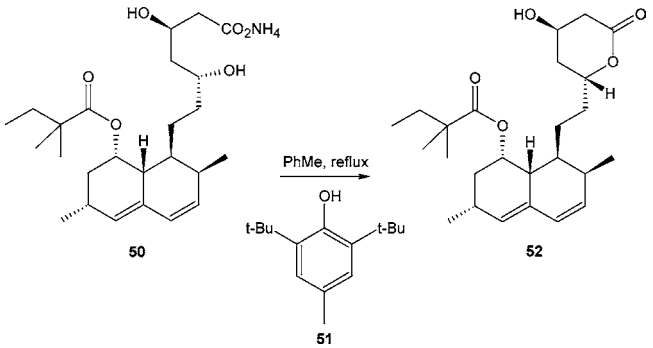
The statins are powerful drugs that are used to treat a variety of diseases, and patents on some of these have been reviewed (*Org. Process Res. Dev.* **2005**, *9*, 537). This patent describes a method of producing simvastatin **52**, a drug used to lower cholesterol. The production of **52** is often via a salt such as **50**, and this gives a dimer **53** that is an ester produced as a result of reaction of the lactone ring in **52**. It is postulated in the patent that the dimer is formed by an intermolecular reaction that can be accelerated by increasing the concentration of **52**.

Dimer




The maximum allowable content of **53** in the drug is 0.4 wt %, and its production must be minimised or it must be removed. The method described in this patent is to invoke the lactonisation of **50** by refluxing in PhMe followed by a crystallisation step. The lactonisation is carried out in the presence of **51**, but the reason for this is not disclosed (Scheme 12). Following this lactonisation step the product is crystallised from MeOH/$H_2O$ or PhMe/hexane, and **51** is added to the solvent mixtures used for crystallisation. The fact that **51** is used throughout the process may imply that free radical processes are involved. This proposal by this reviewer is based on the fact that **51** is an antioxidant that is very widely used in polymerisation processes and is also used in foods. The patent does not mention the reason for using **51**.

*Scheme 12*




The patent describes a range of experiments in which the impurity profile and dimer content of **52** is investigated as the source of the salt **50** is changed. Laboratory or production plant **50** was used, and no change in dimer content was found. However, it was determined that the impurity profile in **52** depended on the purity of **50**.

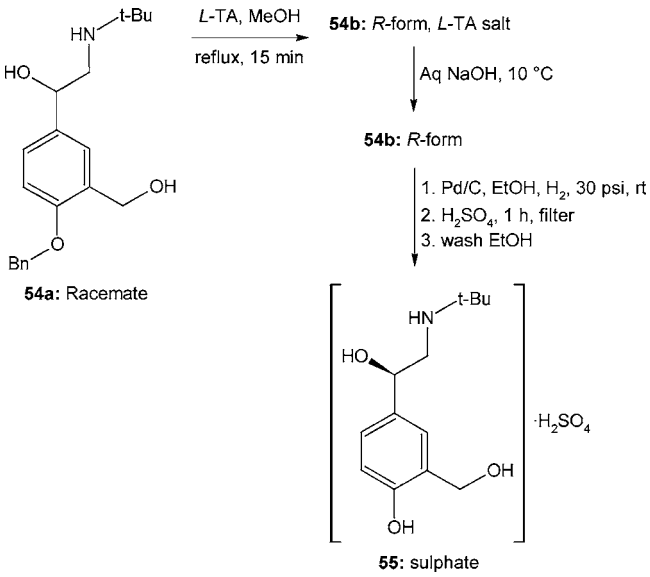
## Advantages

The process reduces the dimer content of this important drug by a straightforward and interesting procedure.

### Patent No. U.S. 6,995,286
***Assignee: Cipla Limited, Mumbai, India***
***Title or Subject: Process for Preparing Salbutamol***

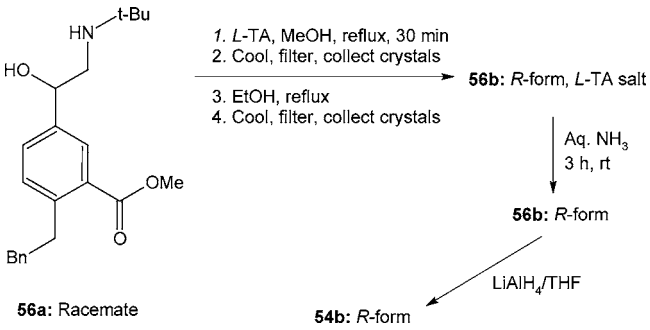
Salbutamol **55** is one of the most widely used drugs for the treatment of asthma, and generic forms of this drug are available now that the original patents have expired. As is usually the case, one enantiomer is more active than the other, and in this case it is the *R*- or *l* form that is preferred. Several methods are available for the resolution of the racemic mixture that is obtained, and derivatives of tartaric acid (TA) are commonly employed. It is claimed that these can be expensive, and hence this patent describes a resolution method for obtaining either form of **55** by the use of optically pure (TA) itself. Scheme 13 outlines the procedure to make the sulphate salt of **55**.

*Scheme 13*




As an alternative to using **54a** it is also possible to start with **56a** that is the precursor to **54a** and perform the resolution with *L*-TA to obtain **54b** (Scheme 14). The patent does not mention whether the unneeded enantiomer can be recovered and racemised.

*Scheme 14*




## Advantages

The process provides an alternative route to a widely used drug using a cheap resolving agent.

### Patent No. U.S. 6,998,481, 6,998,482
***Assignee: Merck Patent GmbH, Darmstadt, Germany***
***Title or Subject: Processes for the Preparation of Directly Compressible α- and β-Mannitol***

D-Mannitol (D-M) is used as an excipient in the formulation of tablets. D-M exists in three polymorphic forms α, $\beta$, and $\delta$, and each has its own particular uses. The $\beta$ form is the most stable although the other forms have applications. These two patents describe a method of producing either the α or $\beta$ forms that are compressible and hence useful in the preparation of tablets. The procedure involves spray drying an aqueous solution of the appropriate polymorph followed by fluidised bed drying of the solid. The procedure uses the same equipment in each patent.

## Advantages

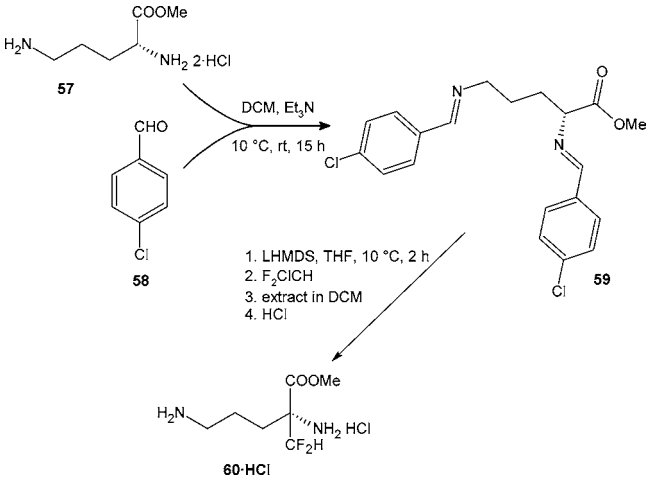
The processes give material that is suitable for use in tablet production.

### Patent No. U.S. 6,998,502
***Assignee: Sabinsa Corporation, Piscataway, New Jersey, U.S.A.***
***Title or Subject: Convenient Process for the Manufacture of Difluoromethylornithine and Related Compounds***

The title compound **60**, also known as eflornithine, is an active inhibitor of ornithine decarboxylase. It is used in the treatment of parasitic diseases such as African sleeping sickness and has recently been approved in the U.S.A. for treating unwanted facial hair by restricting its growth. An earlier patent on the production of **60** has been reviewed (*Org. Process Res. Dev.* **2005**, *8*, 697). It is stated that alternative processes for preparing the salt of **60** use gaseous

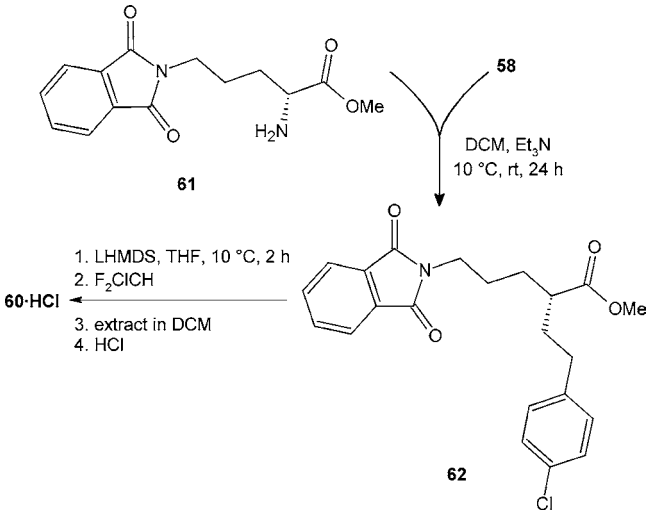
HCl or $SOCl_2$ and are cumbersome and hazardous. They also involve handling oily materials that can be difficult to purify. The process described in this patent is shown in Scheme 15. This starts by reacting the dihydrochloride salt **57** with the aldehyde **58** in the presence of a base to give the bis Schiff base **59**. The treatment of **59** with LHMDS followed by passing $F_2ClCH$ gas through the mixture and subsequent acid hydrolysis gives the desired product as a hydrated salt, **60**·HCl. By using alternative aldehydes to **58** a range of compounds analogous to **59** can be prepared, and these may also be converted to **60**.

*Scheme 15*




A second procedure to prepare **60** is shown in Scheme 16 via the compound **62**. This is converted to **60** by the same alkylation procedure used with **59**, and **62** itself is made from the ester **61** and **58** in a base-catalysed condensation. It is this process that is the subject of the single claim in the patent.

*Scheme 16*




## Advantages

The process involves the production of solid crystalline materials that are easy to handle and purify, thus making the overall process easier and more efficient than alternatives.

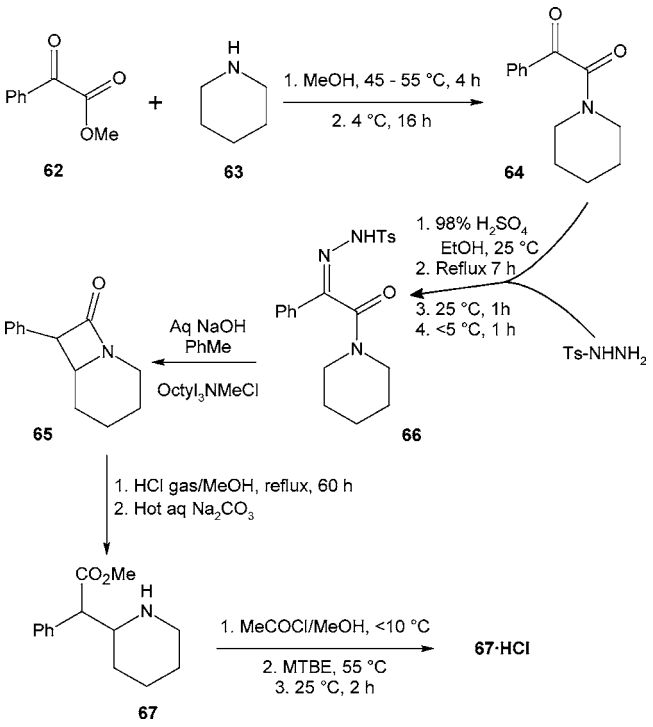
## Patent No. U.S. 7,002,016

***Assignee: ISP Investments Inc., Wilmington, Delaware, U.S.A.***

***Title or Subject: Process for the Preparation of Threo-methylphenidate Hydrochloride***

Methylphenidate **67** is available as the hydrochloride salt under the name ritalin and is used to treat hyperactive children. The commercial drug comprises the threo pair of *d*- and *l*- enantiomers and is used as a racemic mixture. The synthetic routes to **67** are summarised in the patent and are said to involve the use of expensive reagents and give yields of only 60%. The process described in this patent is shown in Scheme 17 and the last stage of this gives a **67** via the acid-catalysed ring opening and esterification of **65**. The route starts with the formation of the glyoxylyl compound **64** from **62** and **63**. This is then treated with Tshydrazide to give the hydrazone **66** that is converted to **65** in a two-phase system using a quaternary ammonium salt as a phase transfer catalyst. The threo-enriched diastereomer of **67** is formed in high yield without epimerisation by treating **65** with gaseous HCl in MeOH. In the formation of the HCl salt of **67** a mixture of MeCOCl in MeOH is used to provide the source of HCl.

*Scheme 17*



The patent includes examples in which several kilos of intermediates are used, thus indicating the advanced stage of development of the process.

### Advantages

The process is said to give high yields and uses readily available and cheap starting materials.

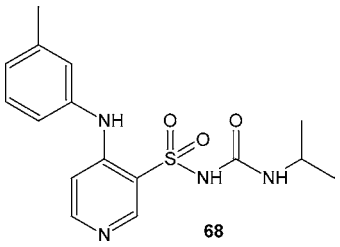
### Patent No. U.S. 7,002,018

***Assignee: Ranbaxy Laboratories Limited, New Delhi, India***

***Title or Subject: Process for the Preparation of Amorphous Forms of Torsemide***

Torsemide **68** is a diuretic that is effective in the treatment of hypertension and edema associated with chronic renal failure. **68** is reported to exist in different polymorphic forms, and these have different activities. An amorphous form is also known, but it is said that the method of its production is not commercially viable because it requires temperatures as low as −80 °C and takes 80 h. This patent discloses a method of making the amorphous form of **68** that does not require drastic process conditions. The method is to dissolve crystalline **68** in $Me_2CO$ and then subject the solution to spray drying using an inlet temperature of 75−77 °C and an outlet temperature of between 30 and 35 °C. The fine powder obtained was shown to be amorphous by X-ray diffraction.

Torsemide




**68**

### Advantages

This process provides a simple procedure for preparing the amorphous form of this drug that may have new commercial opportunities.

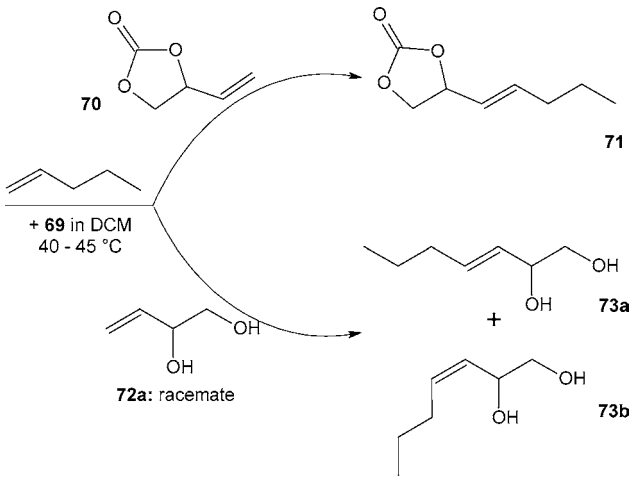
### Patent No. U.S. 7,002,049

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

***Title or Subject: Process for α,β-Dihydroxyalkenes and Derivatives***

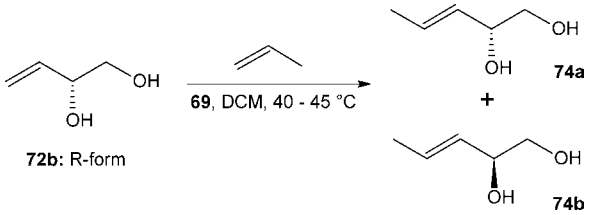
The title compounds are intermediates in the production of a variety of chemical and polymeric materials. Existing methods for preparing dihydroxyalkenes typically involve dihydroxylation of dienes. There are also methods involving the epoxidation of dienes with $H_2O_2$ followed by hydrolysis. Both of these methods are said to require multiple process steps, and the starting dienes are not easily obtained. Hence, this patent avoids the use of dienes by making use of olefin metathesis to produce the desired products. The development of olefin metathesis processes to include functionalised olefins has been a significant step in recent years. Metal carbene complexes have been found to catalyse these reactions, and the Ru complex $Cl_2Ru{=}CHPh[P(cyclohexyl)_3]_2$ **69** is used in the metathesis reactions in the patent. As with all metathesis reaction there are two olefinic products. If terminal olefins are used, then one product is ethylene; the reactions shown in Scheme 18 produce equimolar amounts of ethylene as well as the products shown. Being a gas, ethylene is easily separated from the other products. However, if internal olefins are used, then the by-product will not be so volatile, and separation problems may result. In addition the atom efficiency of a metathesis reaction can be poor if the by-product is not recyclable.

***Scheme 18***




If chiral olefins are used, the products maintain their chiral centre. Scheme 19 shows that in the reaction of **72b** with propylene, the product is ethylene and a mixture of the trans enantiomers containing 97.2% of the *R*-isomer **74a**.

***Scheme 19***




An additional aspect of the patent is the hydrogenation of the metathesis products to give the corresponding saturated

diols. A range of hydrogenation catalysts can be used. Also mentioned in the patent is the decarboxylation of olefins such as **71** to give epoxides. There are no experimental details for this reaction, but the patent does mention a very wide range of decarboxylation catalysts that can be used, including salts that are ionic liquids.

## Advantages

The process provides a route to the desired products that avoids the use of dienes. However, the desired olefin starting materials may not always be readily available.

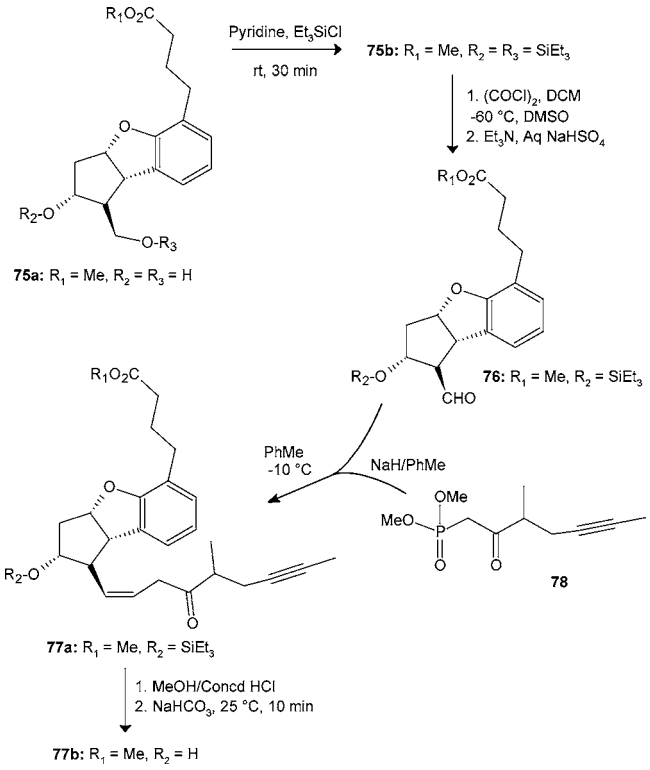
## Patent No. U.S. 7,002,527

***Assignee: Chinoin Gyogyszer Es Vegyeszeti Termekek Gyara Rt., Budapest, Hungary***

***Title or Subject: Process for the Production of Beraprost and Its Salts***

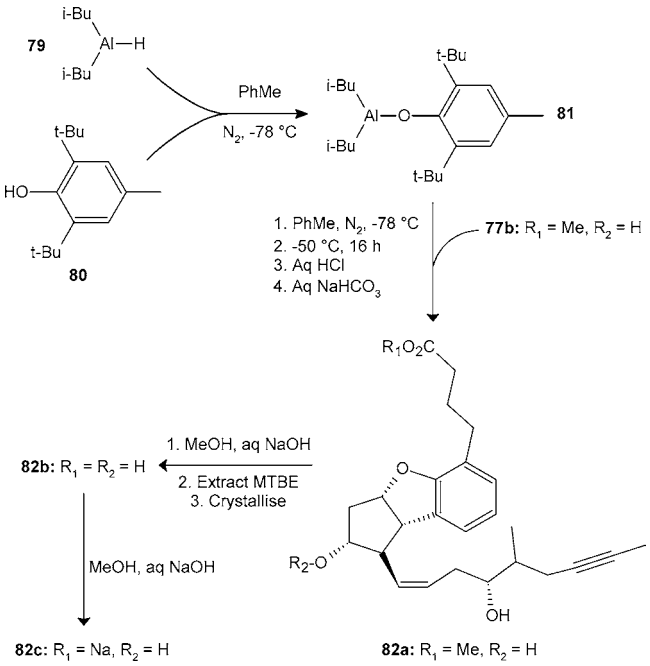
The salts of the compound of interest in this patent such as **82c** are orally applicable prostacycline derivatives. They are used in the treatment of arterial thrombosis, peripheral vascular disease, and pulmonary hypertension. The alternative syntheses of **82c** are said to be long and give low overall yield. The first part of the synthesis of **82c** is shown in Scheme 20 and produces **77b** by a series of reactions that begin with protecting the OH groups in **75a**. The starting compound **75a** and the phosphonate **78** are prepared by a method reported in the literature (*Tetrahedron* **1999**, *55*, 2449).

*Scheme 20*




The next stage of the synthesis is shown in Scheme 21 and starts with the stereoselective reduction of the carbonyl group in **77b**. It is in this step that the key aspect in this work is found. This relates to the method used for protecting the two OH groups. The use of both base-sensitive and acid-sensitive groups has been avoided by using the same silyl group to protect both OH groups. This protection method coupled with the use of the reducing agent **81** is said to improve the stereoselectivity of the reduction of the C═O group in **77b**. This significantly improves the overall efficiency of the whole process. In the final steps the free acid **82b** is formed, and this is easily converted to the salt **82c**.

*Scheme 21*




There are several novel compounds prepared in this synthesis, and extensive NMR data are supplied for these compounds.

## Advantages

The process claims to provide a more efficient route to the product and also produces a number of novel intermediates.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