Organic Process Research & Development **2004**, *8,* 823–833

Highlights from the Patents

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

Summary

The current selection of 20 patents was chosen from an initial list of 225, and it is hoped readers will find something of interest. Polymorphs of known drugs continue to be discovered, and new forms of clopidogrel have been described. There are three patents covering paclitaxels that are found in yew trees and can be used to treat various cancers. Improved methods of extracting the materials as well as new synthetic routes are described. The high stereoselectivity of enzyme-catalysed reactions is described in three different patents. One describes a dehydrogenation step to prepare azaandrostane, another covers an ester hydrolysis, and the third is a cyanide addition reaction to C═O bonds. Although the reaction selectivity can be high, the reactions are often carried out in dilute solution making product recovery difficult. Two patents from the same company describe the use of citronellal in the manufacture of various aroma chemicals. In one of these, sterically hindered aluminate complexes are used as novel cyclisation catalysts to prepare isopulegol. New routes to statin drugs continue to appear, and a new method of making the Ca salts of statins is described. This involves the direct use of $Ca(OH)_2$ rather than the conventional route that goes via formation of Na salts. A novel method of forming a hydroxylamine during the synthesis of aminopyrrolidinones has been reported. The reaction involves the use of a chloronitrosocyclopentane as an aminating reagent. The production of fluorosubstituents is described in two patents. One is specifically for trifluorocarbinols in which CF_3^- anions can be generated from CF_3I in the presence of an electron-rich olefin known to be a strong reducing agent. The other patent covers the replacement of H atoms by F in a very extensive range of compounds using IF_5. The production of Boc-protected hydantoins and dihydrouracils on solid Merrifield resins is described, and a large number of such compounds is presented. Several patents provide IR and NMR data for the identity of compounds produced, and another patent provides only C, H, and N analysis plus an *m*/*e* value as proof of the identity of several compounds. There are examples of multikilogram quantities of materials being made, and so an advanced stage of development is indicated. There is no legal or commercial significance in the selection, and the advantages listed are those claimed by the assignees unless this author has personal knowledge of the subject.

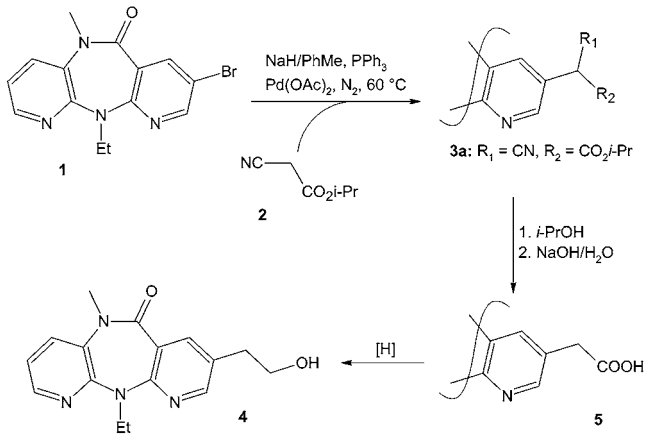
Patent No. U.S. 6,759,533

Assignee: Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut, U.S.A.

Title or Subject: Process and Intermediates for Making Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitors

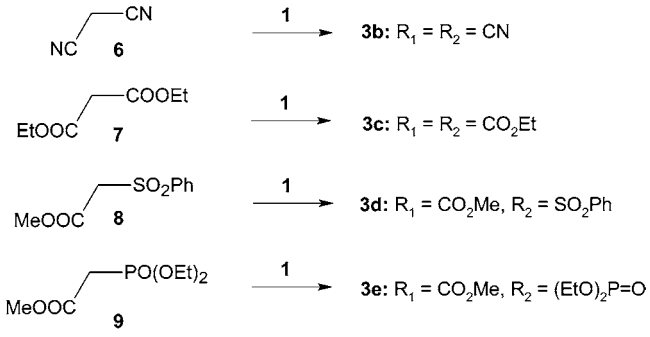
This patent provides a new route for making intermediates such as **4** that can be used to make reverse transcriptase inhibitors for mutant strains of HIV-1. The route shown in Scheme 1 begins with a Pd-catalysed coupling of the bromo compound **1** with a malonate derivative such as **2** to give the novel compound **3**. This is then hydrolysed with aqueous base to give the novel acid **5**. Experimental details are given for these two steps, and NMR data for **3** and **5** are provided. However, experimental details for the conversion of **5** to **4** are not given, although a borane is suggested as being suitable.

Scheme 1



The patent also describes a number of compounds similar to **3** that are produced from substituted malonates or so-called malonate surrogates. Examples are shown in Scheme 2 in which **2** is replaced by **6**, **7**, **8**, or **9** in the reaction with **1**, giving the corresponding analogues **3b** to **3e** respectively. The reaction conditions are broadly similar, although alternative Pd compounds can be used. In the conversion of compounds **3d** or **3e** to **5** the sulphonyl or phosphonyl groups must first be removed by reductive cleavage. No details of this are given, although Raney Ni is suggested as being suitable.

Scheme 2



Advantages

The process provides an alternative route and novel intermediates that can be used to produce important HIV-1 drugs.

10.1021/op049814g CCC: $27.50
Published on Web 10/27/2004

Patent No. U.S. 6,759,539

Assignee: Chaichem Pharmaceuticals International, Laval, Canada

Title or Subject: Process for Isolation and Purification of Paclitaxel from Natural Sources

This is the first of three patents covering paclitaxel **10a** that is a naturally occurring compound found in the bark of yew trees and has been shown to be useful in treating various cancer tumours. The amount of **10a** obtained from the bark is low, and hence, large amounts of biomass and solvents are needed to obtain reasonable quantities. Synthetic procedures are under investigation and have been reviewed (*Org. Process Res. Dev.* **2003**, *7*, 459). This patent, covering **10a** and its derivatives, describes an improved process to extract **10a** from twigs and needles of coniferous trees of the genus *Taxus*. An earlier process from the same company to extract **10a** involves several chromatography stages and recrystallisations, and it is not particularly amenable to large-scale production. The new procedure involves an initial aqueous extraction step to remove soluble impurities from the biomass. This is then followed by extraction of **10a** with methanol, followed by its isolation by chromatography and crystallisation.

The various stages of the process are summarised below:

A porous bag containing twigs and needles of the tree is immersed in distilled water for 3 h at room temperature,

the water is drained from the bag of biomass, and MeOH is added to the biomass in the tank at room temperature,

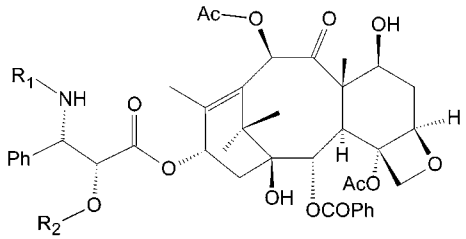
the extract is collected and the solution concentrated by distilling off the MeOH,

the crude solid is precipitated by addition of aqueous NaCl solution, collected by filtration, and then dried,

the solid is dissolved in Me_2CO, leaving resins and pigments,

hexane is added to the solution to produce an oil that is collected and purified by low-pressure column chromatography at least once,

the purified oil is dissolved in acetone and cooled to give crystals of **10a**, and these may be recrystallised to improve the purity.



10a: paclitaxel
R_1 = PhCO-, R_2 = H

Advantages

The process is claimed to be an improvement on the earlier procedure and involves handling smaller quantities of biomass and solvents to achieve the same yield. Although it still involves a chromatographic step, the volumes of solvents used are less than those used in previous methods since many impurities are removed early in the procedure.

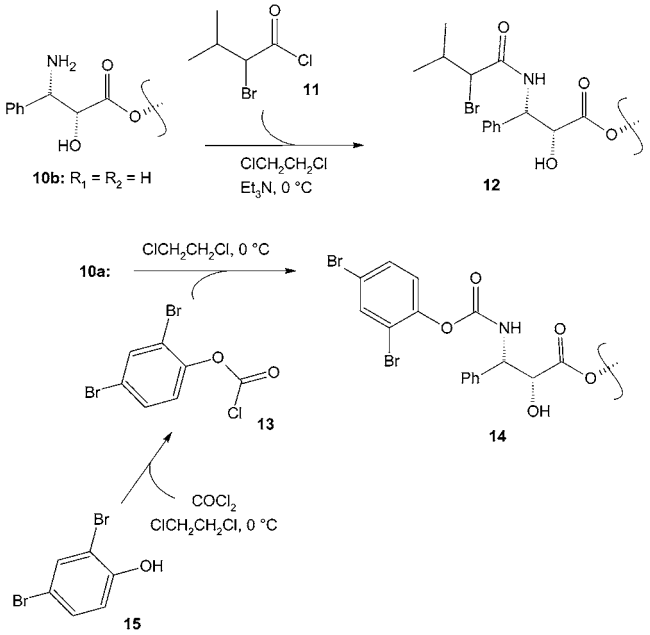
Patent No. U.S. 6,765,015

Assignee: Xechem International Inc., New Brunswick, New Jersey, U.S.A.

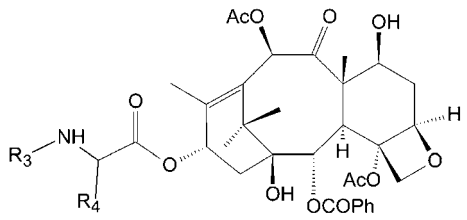
Title or Subject: Halogenated Paclitaxel Derivatives

The second patent on derivatives and analogues of paclitaxels such as **10a** is a comprehensive piece of work that describes an extremely wide range of compounds. The patent describes a range of derivatives in which there are 95 different types of the halogenated R_1 substituents in **10a** in which R_2 is H or Ac. Not surprisingly, experimental details are not described for many types. In view of the large number of compounds involved, this review only covers two examples that are shown in Scheme 3. The chemistry is quite straightforward and involves condensation reactions of amines and bromine containing acyl or aroyl chlorides. For example, the bromo-acyl derivative **12** is formed by reaction of **10b** with **11** in the presence of Et_3N, and the dibromophenyl carbamate **14** is produced by reaction of **10a** with **13**. The substrate **13** is made from **15** using triphosgene as the source of $COCl_2$.

Scheme 3



The patent also covers the formation of compounds called cephalomannines **16** by similar methods to those used for the paclitaxels. The patent again claims a very large number of derivatives in which R_3 and R_4 are halogenated groups.



16: Cephalomannines
R_3 = halogenated acyl, R_4 = H or Me

Advantages

The process allows the production of these synthetic paclitaxels using naturally occurring material as the source of starting materials.

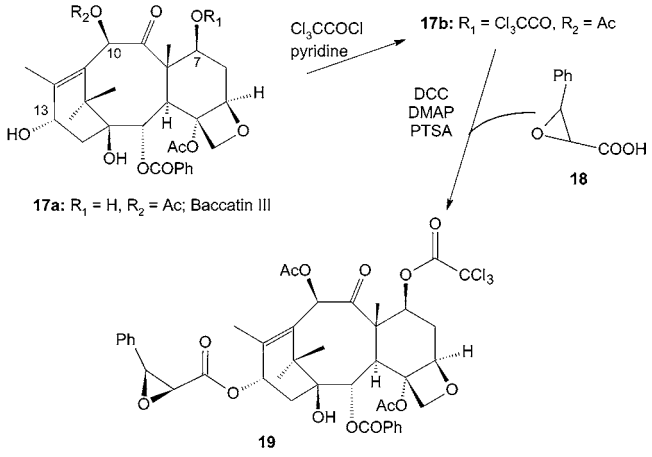
Patent No. 6,768,012

Assignee: Indena S.p.A., Milan, Italy

Title or Subject: Process for the Preparation of Paclitaxel

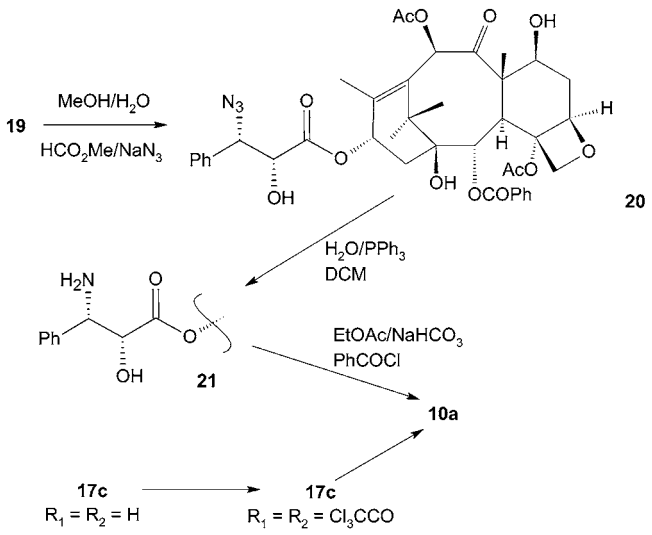
This third patent on the subject of paclitaxels describes a synthetic route to **10a** from baccatin III, **17a** (R_1 = H, R_2 = Ac). This conversion has been examined previously and hinges on being able to protect the hydroxyl groups on the diterpene moiety. The focus of this work is to protect either the 7- or both the 7- and 10-hydroxy groups in **17a** by formation of esters. Scheme 4 shows the formation of the ester **17b** ($R_1 = Cl_3CCO$, R_2 = Ac) from **17a** and Cl_3CCOCl. The ester **17b** is then converted to the **19** using the epoxyacid **18**.

Scheme 4



The final stages to **10a** are shown in Scheme 5 and begin with the opening of the epoxide in **19** using NaN_3. At the same time the protecting group at C-7 is removed, and the azide **20** is produced. The subsequent reduction of the azide group in **20** using PPh_3/H_2O in CH_2Cl_2 (DCM) gives the amine **21.** Finally, **10a** is formed in a Schotten−Bauman by reaction between **21** and PhCOCl in the presence of a biphasic mixture of EtOAc and aqueous $NaHCO_3$.

Scheme 5



The patent also describes experiments to prepare **10a** starting from deacetylbaccatin III **17c** ($R_1 = R_2$ = H). This proceeds via a similar route with initial formation of the bis-trichloroacetyl ester **17d** ($R_1 = R_2 = Cl_3CCO$).

The epoxy acids formed in these reactions are novel compounds, and ^1H and ^{13}C NMR data are given for these and other compounds.

Advantages

This process uses a good method of protection of the hydroxyl groups and provides higher overall yields than alternative methods.

Patent No. U.S. 6,762,302

Assignee: Gedeon Richter Ltd., Budapest, Hungary

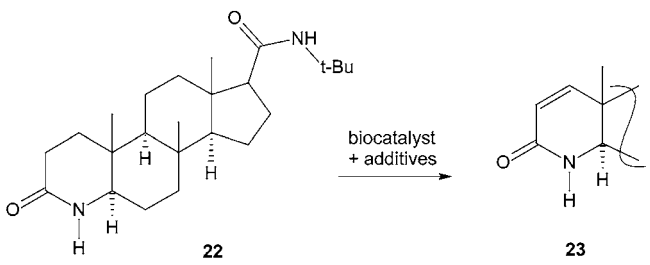
Title or Subject: Process for Dehydrogenation of Azaandrostane Compounds

This patent covers an enzymatic process for producing 4-azasteroids that are known to be specific inhibitors of the testosterone 5α-reductase enzyme. Inhibition of this enzyme has become a pharmacological strategy for the design and synthesis of new antiandrogenic drugs. Suitable compounds are used for the treatment of androgen dependent diseases such as hirsutism, androgenic alopecia, benign prostatic hyperplasia, and prostate cancer.

It has been found that the activity of 4-azasteroids such as **22** can be increased by introducing a double bond at the C-1,2 position of the molecule to give **23** (Scheme 6). There are both chemical and biochemical methods for performing this reaction, but it is claimed that the chemical procedure requires aggressive conditions. The biochemical processes give low yields and are not suitable for operation on a commercial scale.

The patent describes a process using a biocatalyst having steroid -Δ_1-dehydrogenase activity, and this activity is produced by adding an inducer, such as hydrocortisone. In addition to the inducer, other additives are required such as an electron carrier, a stabiliser, and a complexing agent. The latter compound is required to promote continuous dissolution of the substrate, and examples are cyclodextrins. Stabilisers are exemplified by a 13-ethyl-10,11α-dihydroxy-gon-4-ene-3,17-dione, and suitable electron carriers are naphthoquinones. The reaction is carried out by preparing a culture of the biocatalyst and then adding the various additives and substrate. The biocatalyst used is a bacterium such as *Arthrobacter simplex*, and the incubation takes at least 24 h. One experiment gave a 94.4% conversion (by HPLC), and from a mixture with a total volume of about 5 L, 755 mg of **23** was obtained.

Scheme 6



Advantages

The process is said to be suitable for commercial operation. Although it gives good yields of the desired product, it does not look to be an attractive process.

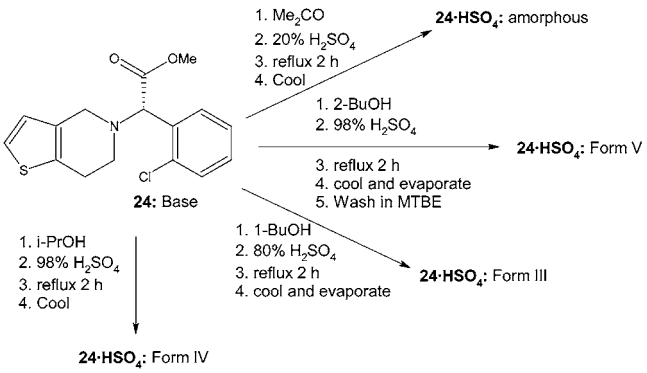
Patent No. U.S. 6,767,913

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

Title or Subject: Preparation of New Polymorphic Forms of Clopidogrel Hydrogensulphate

The hydrogensulphate salt of the base clopidogrel **24** is known as plavix, and it is used in the treatment of atherosclerosis. This patent describes the preparation of three new crystalline forms designated III, IV, and V plus an amorphous form and also discloses a method of preparing form I. A summary of the methods used to obtain the various forms is shown in Scheme 7. These simply involve the production of acid solutions in different solvents followed by crystallisation. The patent contains X-ray and FTIR spectroscopic details as well as thermogravimetric data for the various forms. A new method for the production of the known polymorph form I is also described. This involves dissolving the amorphous form in MeOH and precipitation of form I using Et_2O. The patent also describes drug compositions using the new forms.

Scheme 7



Advantages

The patent provides simple procedures for the preparation of new forms of a widely used drug.

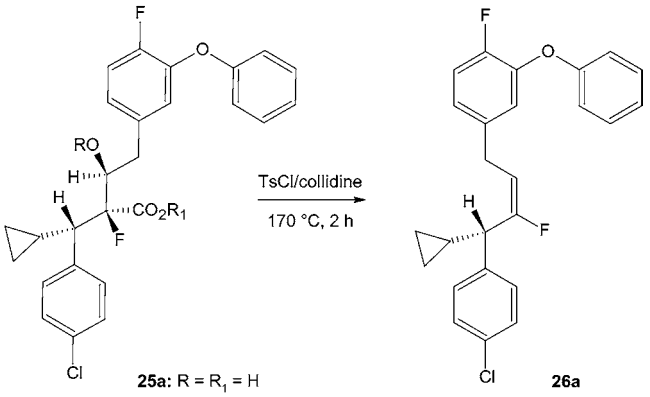
Patent No. U.S. 6,770,463

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Process for the Preparation of Chiral Diarylfluorobut-2-enes

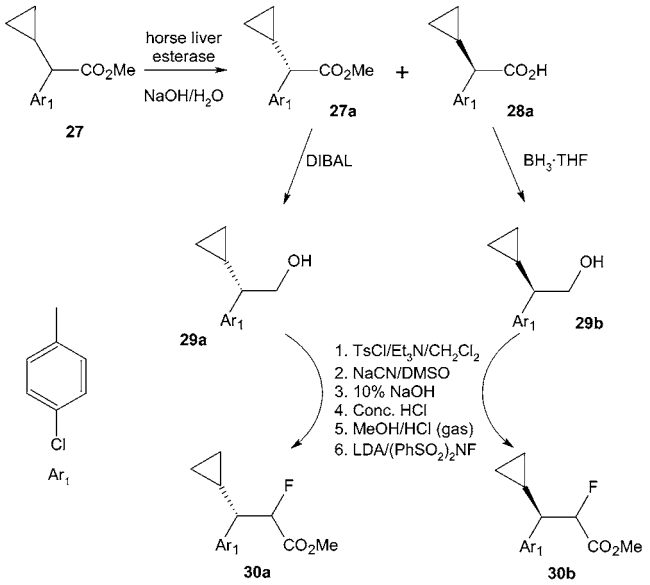
This patent discloses a process for preparing compounds that are used as insecticides in plant protection. The compounds are exemplified by **26a** that is made by heating **25a** with TsCl in collidine. The reaction shown in Scheme 8 refers to a single diastereoisomer, and examples are given, starting from the different diastereomers of **25a** or mixtures that form the *E* or *Z* isomers of **26a**. No specific details of separating the diasteroisomeric mixtures are given except to mention the use of chromatographic methods.

Scheme 8



The patent describes a multistep synthesis for the preparation of **25a** from the racemic ester **27** beginning with the enzymatic hydroysis with horse liver esterase. This is shown in Scheme 9, and **27** gives the nonhydrolysed *S*-ester **27a** and the *R*-acid **28a**. These compounds are recovered and separately converted to the *S*- and *R*-alcohols **29a** and **29b** by reduction. The alcohols are then converted by conventional chain extension reactions to give a methyl ester so that **30a** is obtained from **29a**; **29b** reacts similarly to give **30b**.

Scheme 9

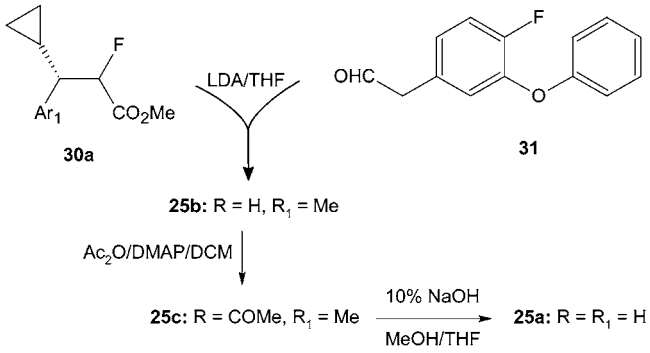


The base-catalyzed coupling of **30a** with **31** gives a mixture of four diastereoisomers of the hydroxyl-ester **25b** (Scheme 10). This mixture may be separated by chromatographic methods, and the diastereoisomers then undergo acylation. The acylation step appears to be used to allow separation of pure chiral diastereomeric esters. Thus, **25b** gives the diester **25c,** and this is converted to pure **25a**. There are also examples for other diastereoisomers and mixtures and although the patent is not exactly clear on the stereochemistry. It appears that, if pure isomers are used, then the reactions proceed stereospecifically.

Advantages

The process is said to be a useful method of making the desired chiral intermediates.

Scheme 10

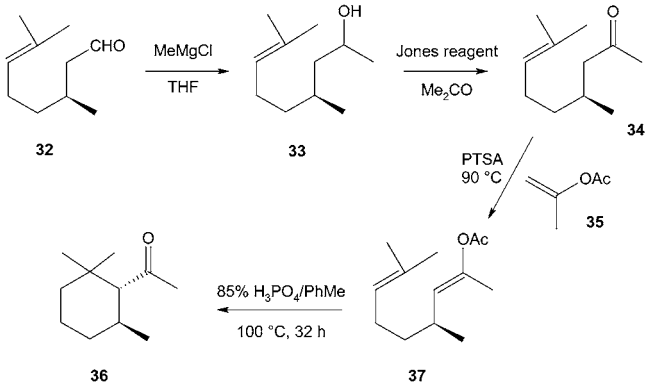


Patent No. U.S. 6,770,618

Assignee: Takasago International Corp., Tokyo, Japan
Title or Subject: Process for Making 2,2,6-Trimethylcyclohexylmethyl Ketones

The title compounds have been found to have potential for use in perfumes and they possess eucalyptus and mint-like odour. The patent discloses a method of producing the two *trans*-isomers in 98% *ee*. The pure isomers are said to be expensive and although there are alternative syntheses they are said to be unsuitable for commercial use. The route developed is shown in Scheme 11 and starts from *S*-citronellal **32** that is treated with MeMgCl to give the alcohol **33**. This is oxidised using Jones reagent to give the ketone **34** that on reaction with **35** produces **37** as a mixture of enol acetates. These are not separated but cyclised using H_3PO_4 to produce the *1R, 6S* isomer **36**. The opposite enantiomer was similarly prepared from *R*-citronellal.

Scheme 11



The key aspect of this synthesis is the production of the novel enol acetate **37** that is a mixture of three isomers but there is no need to separate them to produce **36**.

Advantages

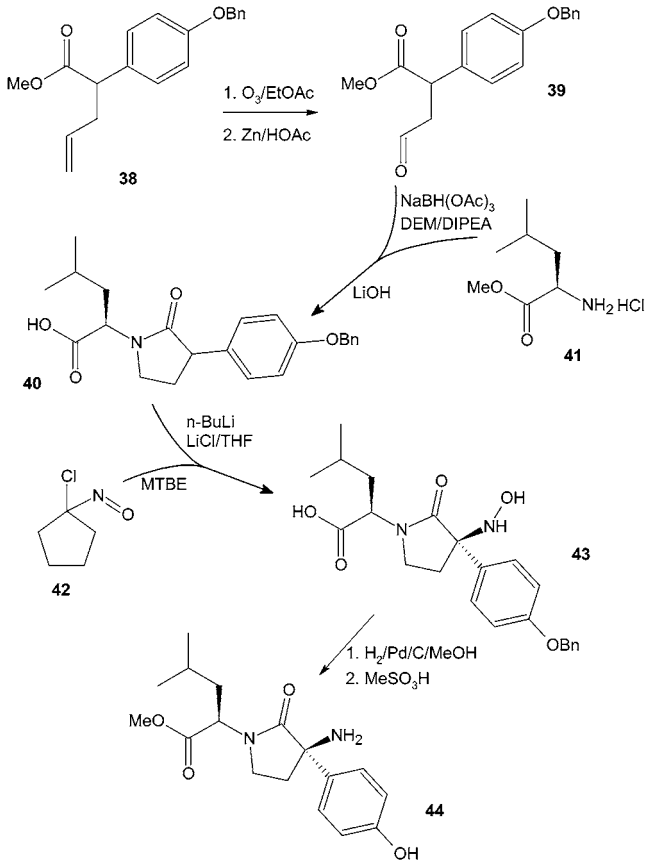
These compounds have not previously been used for perfume manufacture, and the synthesis opens up this new opportunity.

Patent No. U.S. 6,770,763

Assignee: Bristol-Myers Squibb Company, Princeton, New Jersey, U.S.A.
Title or Subject: Asymmetric Synthesis of Aminopyrrolidinones

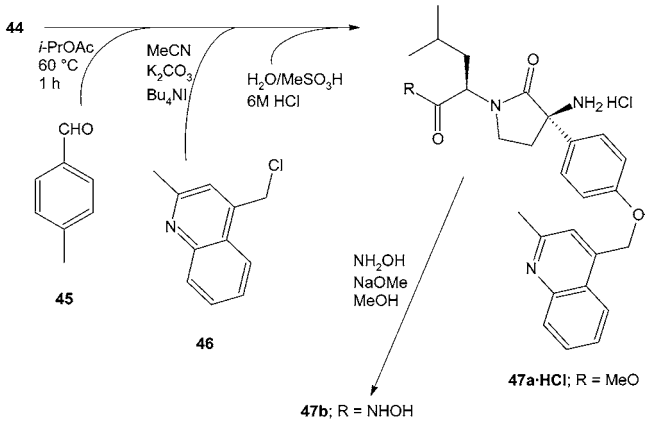
The aminopyrrolidinones such as **47a** and **47b** are of interest as MMP and TACE inhibitors for use in treating rheumatoid arthritis. The claims of the patent cover the novel intermediate **44** and its production by the route shown in Scheme 12. The preparation of **44** starts with the ozonolysis of **38** to give aldehyde **39**, and this is converted to the lactam **40**. This conversion is achieved in two stages by reaction of **39** with the enaminoester **41** under reductive amination conditions followed by hydrolysis of the methyl ester group with the use of LiOH. The conversion of **40** to **44** involves initial deprotonation of **40** using *n*-BuLi followed by treatment with the nitroso compound **42** to give the hydroxylamine **43** and then reduction. The reaction of **44** is described as a novel use of this reagent, but this is arguable.

Scheme 12



The production of the salt **47a**·HCl from **44** is shown in Scheme 13 and proceeds via formation of the intermediate imine from **45** and **44**. This is not isolated but treated with **46** in MeCN followed by HCl to give the **47** as a hydrochloride salt; this is converted to **47b** by reaction with NH_2OH/MeOH/NaOMe. An example is described to produce >20 kg of **47b**, indicating the advanced development status of this process.

Scheme 13



Advantages

This is a novel process that is potentially capable of being carried out on a commercial scale.

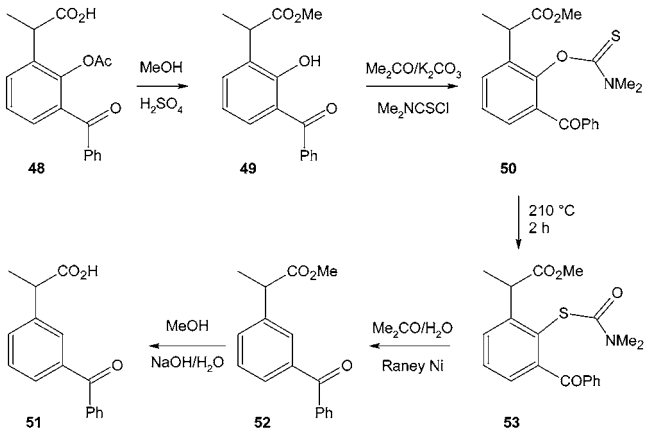
Patent No. U.S. 6,770,781

Assignee: Dompe S.p.A., L'Aquila, Italy

Title or Subject: Process for the Preparation of a-Arylalkanoic Acids

This patent is specifically aimed at producing the meta acid **51**, and it also claims that the corresponding para acid can be made by using the same procedure, although no example is given. The route is shown in Scheme 14 and begins by forming the *o*-hydroxy ester **49** by simultaneous esterification and hydrolysis of **48**. The use of **49** as a starting material for preparing acids such as **51** is common, but such routes are said to have many difficulties because they require expensive reagents and have a low selectivity. **49** is converted to the thiocarbamyl compound **50** by reaction with Me_2NCSCl in the presence of a base at room temperature. An alternative reagent for this conversion is said to be $CSCl_2$ although no examples are given. This patent does not describe how Me_2NCSCl is prepared, but it is likely to involve $CSCl_2$. Thermal rearrangement of **50** gives **53**, and the carbamyl group is removed by hydrogenation using Raney Ni to give **52** that, on base hydrolysis, affords the acid **51**.

Scheme 14



Advantages

The process is said to give higher selectivities and use cheaper reagents than alternative processes. However, if it does involve the use of thiophosgene to prepare a key intermediate. This is going to be a potentially problematic procedure.

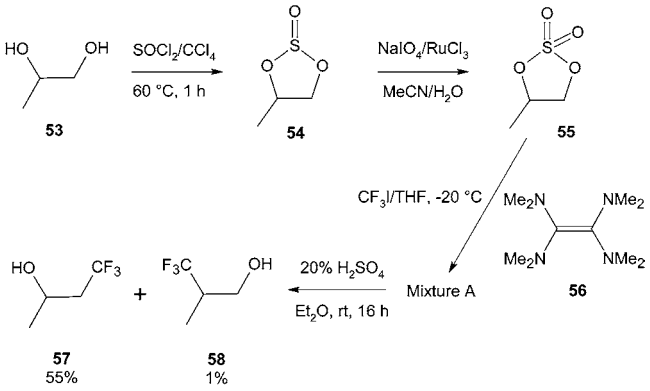
Patent No. U.S. 6,770,789

Assignee: University of Florida Research Foundation, Gainesville, Florida, U.S.A.

Title or Subject: Process for Trifluoromethylation of Sulphates

The introduction of CF_3 groups into pharmaceutical and agrochemical compounds is of great interest, and improved methods are continually being sought. This patent discloses a method of preparing trifluoromethyl carbinols such as **58** from sulphates. It is claimed that cyclic or acyclic sulphates can be used although no experimental examples are given for any acyclic compounds. The process to make **58** is shown in Scheme 15 and is based on the finding that CF_3^- anions can be generated from CF_3I in the presence of **57**, an electron-rich olefin, that is known as a strong reductant. The 1,2-diol **54** is initially heated with $SOCl_2$ in CCl_4 to form the intermediate **55.** It would seem that **55** is not isolated but directly oxidised to **56** in 97% yield using $NaIO_4$ in the presence of $RuCl_3$. The sulphate **56** is then reacted with CF_3I at −20 °C in the presence of **57**; the mixture A that is obtained is acidified and left overnight. The product is a mixture of **58** and **59** with a high selectivity for the former.

Scheme 15



The patent claims also cover the use of the alternative reagent consisting of HCF_3/DMF and $(Me_3Si)_3N/Me_4NF$, but no examples are provided.

Advantages

The process gives a good selectivity to a specific type of trifluorocarbinol if the precursor 1,2-diol is available.

Patent No. U.S. 6,774,231

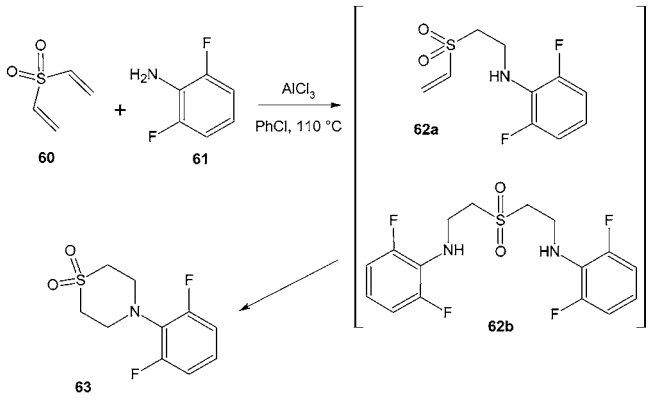
Assignee: Pharmacia & Upjohn Company, Kalamazoo, Missouri, U.S.A.

Title or Subject: Method for the Preparation of Oxazolidinones

The main claim of this patent covers the preparation of **63** by the reaction of the bis-vinyl sulphone **60** with **61** as shown in Scheme 16. However, the patent also describes the use of **63** in the preparation of the oxazolidinone **68** that is an antibacterial agent with wide-ranging activity. The preparation of **63** is a double-Michael addition that is carried

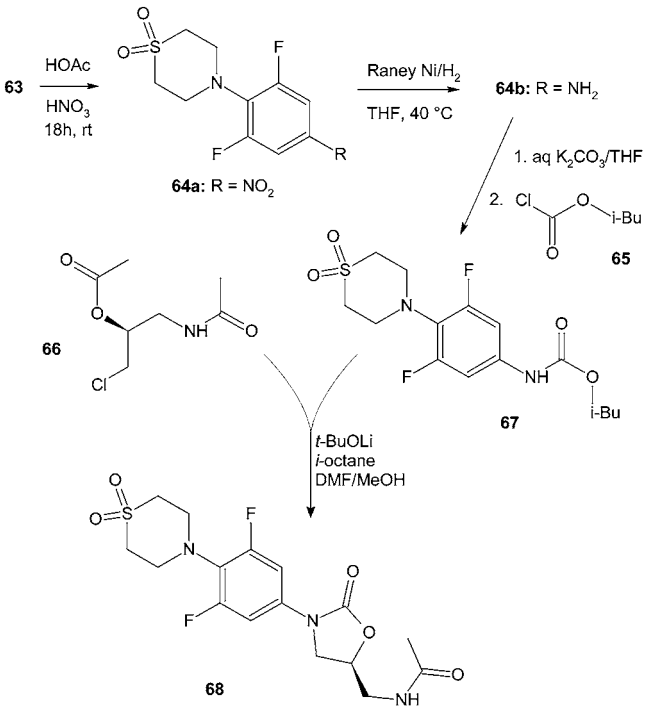
out by heating the reactants in PhCl with $AlCl_3$. This produces the intermediates **62a** and **62b**. Samples of these intermediates were isolated and purified, and ^1H NMR data are given for **62a**, **62b**, and **63.** This double-Michael addition proceeds at a much faster rate than similar reported reactions, and this is attributed to the use of the $AlCl_3$ catalyst. Without the catalyst, previous reports of similar reactions are said to be very sluggish and require an excess of the amine reactant.

Scheme 16



The next stage of the process is the conversion of **63** to the amine **64b** via **64a** (Scheme 17). The nitration of **63** is carried out using $HOAc/HNO_3$ at room temperature over 18 h, and the reduction of **64a** uses Raney Ni catalyst. The amine **64b** is converted to the carbamate **65** by reaction with chloroformate **65** in the presence of K_2CO_3 in THF. The final reaction step to make **66** is between **67** and the *S*-acetamide **66** in the presence of a strong base such as *t*-BuOLi. Extraction of the mixture into gives a 79% yield of **68**. Experiments are described in which >9 kg of **68** is prepared, indicating the advanced nature of the process.

Scheme 17



Advantages

This patent provides an efficient process for preparing the desired product by using an improved double-Michael addition reaction.

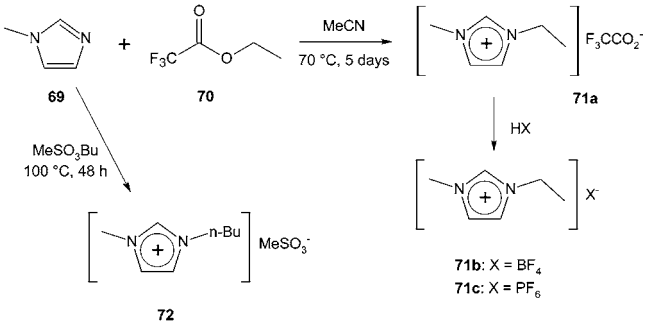
Patent No. U.S. 6,774,240

Assignee: The Queen's University of Belfast, Belfast, United Kingdom

Title or Subject: Process for Preparing Ambient Temperature Ionic Liquids

Ionic liquids have received much interest in recent years as solvents for a range of reactions and also as catalytic materials. Some types are very sensitive to moisture and air, and others can contain halides or metal salts. These systems are extremely corrosive and require expensive corrosion-resistant equipment. Other systems are only liquid at elevated temperatures and hence not as useful for low- and moderate-temperature reactions. This patent describes ionic liquids based on fluorinated counterions such as **71** that are stable liquids at room temperature and are not corrosive. Scheme 18 shows the method for preparing **70a** by an alkylation reaction carried out by heating **69** and **70** in a sealed tube for 5 days. The production of the *n*-Bu salt **72** is carried out similarly but does not take as long. Treatment of **71a** with HBF_4 or HPF_6 produced the respective salts **71b** and **71c** via a metathesis reaction. This step is efficient and relies on using a less volatile acid than CF_3CO_2H that is released and hence easily removed.

Scheme 18



The patent admits that although using fluorinated compounds is expensive it is desirable. The fluorinated ester activates the molecule for the alkylation step and produces a more volatile product than would be obtained from nonfluorinated esters. In addition the patent claims that the CF_3CO_2H that is released can be recycled and used to make the ester **70**. However, there are no examples showing that this has been demonstrated. The melting points of the products are not given although **72** is described as a low-melting solid.

Advantages

The method is simple and avoids the use of corrosive halides, although the reaction times are extended. By recycling the CF_3CO_2H the process efficiency is significantly improved.

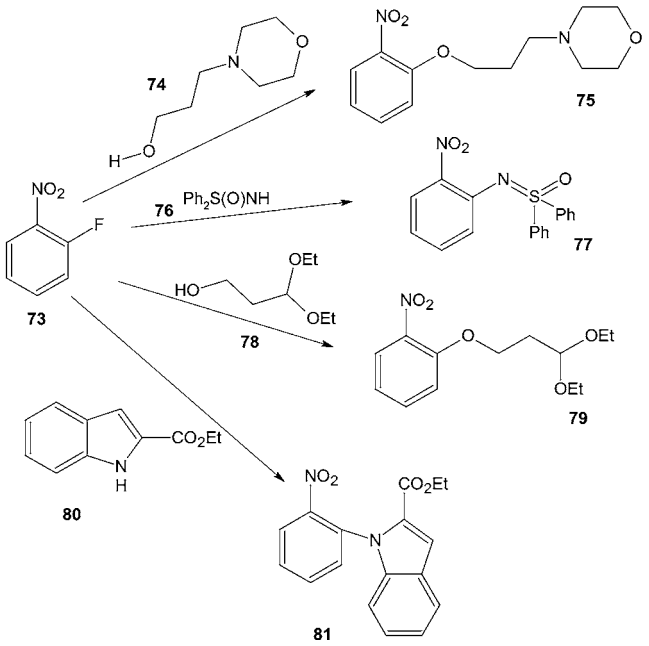
Patent No. U.S. 6,774,242

Assignee: Goedecke GmbH, Freiburg, Germany

Title or Subject: Arylation of Azaheterocycles with Activated Aromatics Using Cesium Carbonate

The patent describes a process for the nucleophilic substitution of activated aromatics such as **73** at room temperature in the presence of $CsCO_3$. A very wide range of nucleophiles is used, and 49 examples of the reaction are included in the patent. Scheme 19 shows a selection of the reactions of some of these with **73**. The reactions are carried out by stirring the reactants at room temperature with $CsCO_3$ in DMF, and they take between 24 and 64 h to complete. This is followed by addition of water and extraction of the product with EtOAc. Yields of 98% were found in some cases. The use of $CsCO_3$ as a coupling catalyst alone is claimed to be novel. Although the reagent has been used in similar reactions, these require additional catalysts such as Pd and are carried out at higher temperatures. There are also examples in the patent of using 4-fluoronitrobenzene and 2- or 4-fluorobenzonitrile derivatives.

Scheme 19



Advantages

The process gives high yields at moderate conditions, but the long reaction times may be acceptable at modest production volumes.

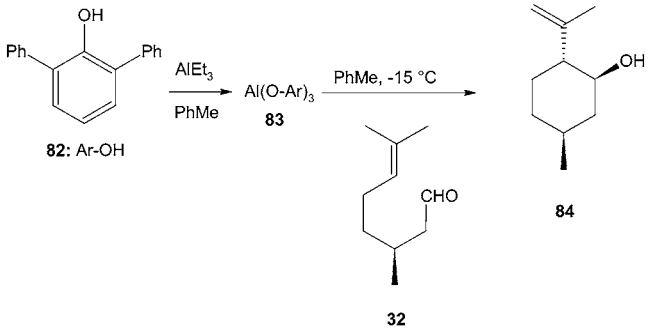
Patent No. U.S. 6,774,269

Assignee: Takasago International Corporation, Tokyo, Japan

Title or Subject: Process for Producing Isopulegol

This patent is the second from this company on the use of **32** as a feedstock and the product in this case, isopulegol **84**, is used to make a range of aroma chemicals. The cyclisation reaction to convert **32** to **84** is well-known and catalysed by a range of acidic compounds. The patent discloses an improved process that uses the aluminate catalyst **83** that is prepared from the phenol **82** and $AlEt_3$. This patent also uses a number of similar Al compounds that are prepared from 2,6-diarylphenols. The process is highly selective, and **84** is obtained in >99.3% selectivity and in a yield of >82%. Other phenols were not nearly as effective. Phenol and 2-phenylphenol gave low yields and the highly sterically hindered compound 2,6-di-tibutylphenol, did not give any formation of **84**. The method is an improvement over a process that uses $ZnBr_2$ as catalyst (which was previously developed at Takasago) and gave yields of <20% with selectivity of 93%.

Scheme 20



Advantages

The catalysts give the desired product in a reaction that is more highly selective than alternative processes.

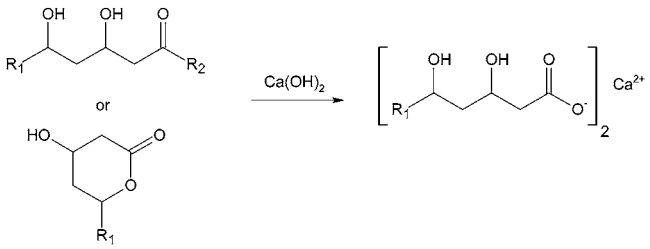
Patent No. U.S. 6,777,552

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

Title or Subject: Processes for Preparing Calcium Salt Forms of Statins

The statin drugs are widely used to treat cardiovascular disease by reducing low-density lipoproteins, and patents on these compounds have previously been reviewed (*Org. Process Res. Dev.* **2004**, *8*, 311). Some of the statins are administered in the lactone form, others as the Na salt and some as the Ca salt. This patent describes how to prepare Ca salts from $Ca(OH)_2$ and an ester or protected ester such as a lactone. The general reaction is shown in Scheme 21 and the patent covers the Ca salts of the statins atorvastatin **87**, simvastatin, lovastatin, rosuvastatin, and pitavastatin. The patent examples only describe the production of **87** and the latter two statins that are relatively new and described as superstatins in the patent.

Scheme 21

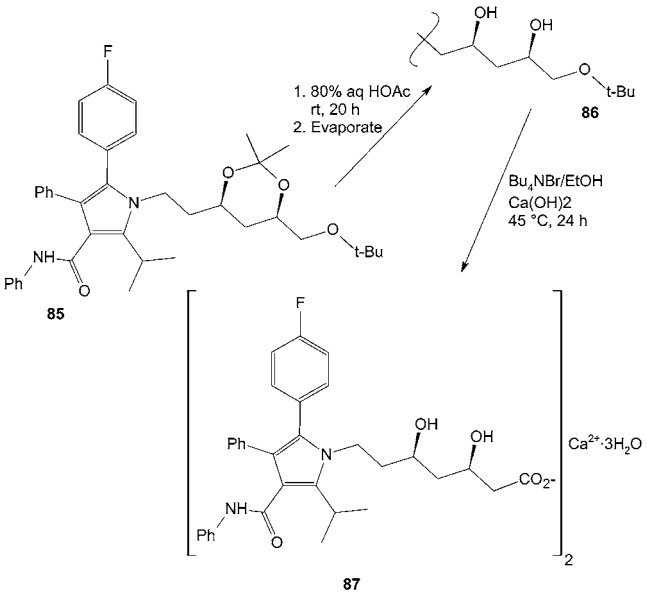


The standard method of producing Ca salts of acids is via the Na salt; not needing to prepare the Na salt means that the final product can be obtained in higher purity. It is also claimed that the amount of $Ca(OH)_2$ that is used does

not have to be so carefully controlled; this should mean that the process is more robust.

Scheme 22 summarises the method for the preparation of the Ca salt **87** from the dioxane ester **85**. The first stage of the reaction is hydrolysis of the dioxane ester group to give the diol ester **86**; this is followed by formation of the Ca salt without purification of **86**. The second step to form the salt is carried out using BuN_4Br as phase transfer reagent.

Scheme 22



The claim that the use of $Ca(OH)_2$ to hydrolyse esters is novel may be surprising to many readers who may consider it obvious. However, the patent does cite several literature sources that claim that $Ca(OH)_2$ cannot be used to hydrolyse esters; any readers interested in this subject are encouraged to read the patent and the references therein.

Advantages

The process provides a commercially suitable method of making high-purity Ca salts of a number of statins without the need to proceed via Na salts.

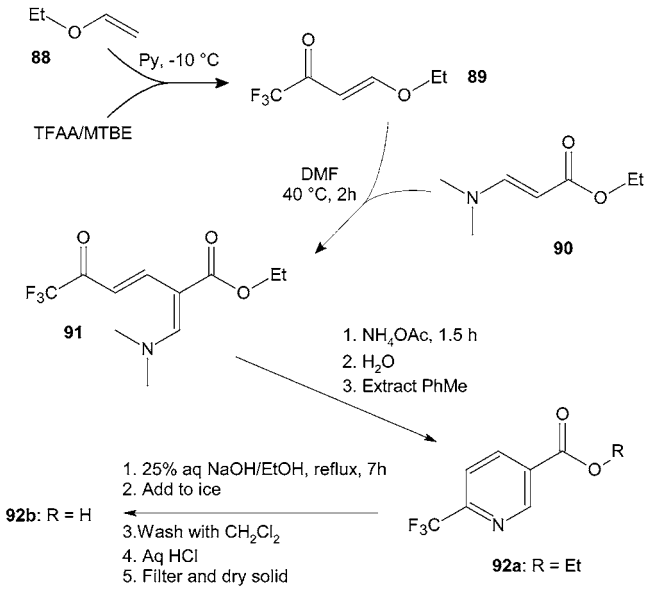
Patent No. U.S. 6,777,556

Assignee: Bayer Chemicals AG, Leverkusen, Germany

Title or Subject: Process for Preparing 2-Trifluoromethyl Nicotinic Acids

The main subject of this patent, **92b**, is useful in the production of APIs or agrochemicals. Processes are known for preparing this and similar compounds, but they are claimed to involve the use of more expensive reagents such as enaminonitriles or β-acetylvinylamines. Hence, the processes are uneconomic; as a result, this patent describes a new process using more readily available reagents. The procedure shown in Scheme 23 is a two-stage process that begins with coupling of the enaminoester **90** with the enol ether **89** by heating in DMF. The patent describes how to prepare **89** from **88** and TFAA. The final cyclisation step to give **92a** is carried out by reacting **91** with NH_4OAc that is not a commonly used reagent for this step. The acid **92b** is then obtained by basic hydrolysis of **92a**.

Scheme 23



The yields of the two main steps are in excess of 94% and the final purity by GC was >99%. The examples involve the production of > 2kg of **92b**, indicating the stage of the development of this process.

Advantages

The high yield of the process and the use of readily available materials are improvements over alternative routes.

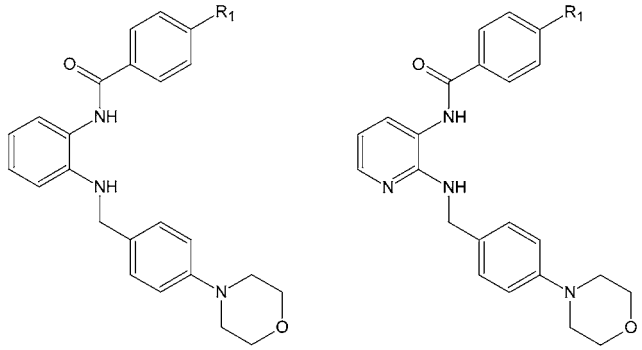
Patent No. U.S. 6,780,878

Assignee: Eli Lilly and Company, Indianapolis, Indiana, U.S.A.

Title or Subject: Antithrombotic Amides as Factor Xa Inhibitors

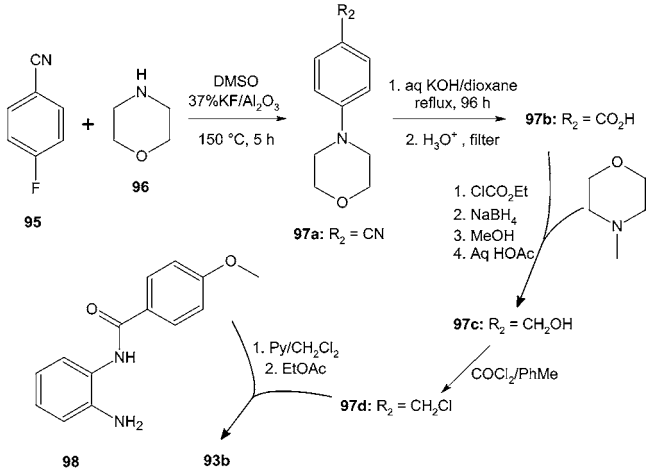
Factor Xa is a protease that is involved in the coagulation of blood that can lead to thrombosis; consequently, there is wide interest in compounds that inhibit this process (*Org. Process Res. Dev.* **2004**, *8*, 697). The amides **93a**, **93b**, **94a**, and **94b** are such inhibitors and are typical of the compounds covered by this patent, although there are also several others for which experimental details are given.

Amides



The synthesis of **93b** is shown in Scheme 24 and involves the preparation of the benzonitrile **97a** in 60% yield by reaction of **95** with **96** in the presence of KF on alumina. **97a** is then hydrolyzed to give a 99% yield of the acid **97b**; this is then reduced to the benzyl alcohol **97c** in 18% yield. Treatment of **97c** with $COCl_2$ gives the chloride **97d** that is used to alkylate the amine group in **98** to give **93b**. The yield in the last step was reported as 14%. The other amides are made by similar procedures and several of the intermediates are novel compounds. The only analytical data that are given are elemental analyses and *m*/*e* values from FD-MS. The patent also describes the preparation of the HCl salts of **94a** and **94b** and mentions clinical tests to indicate the anticoagulant activity without mentioning any specific compound in the tests.

Scheme 24



Advantages

The patent discloses details of a range of novel compounds that are claimed to be effective Factor Xa inhibitors.

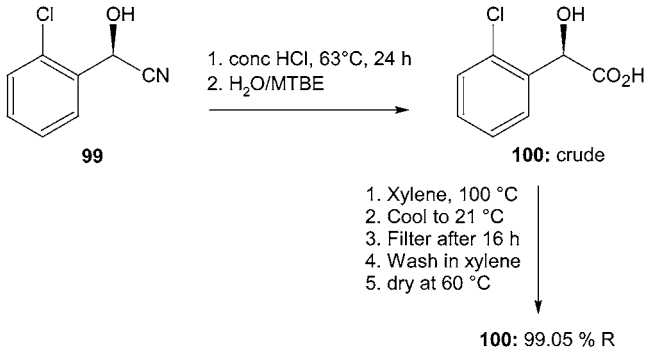
Patent No. U.S. 6,781,012

Assignee: DSM Fine Chemicals Austria NFG GmbH & Co KG, Linz, Austria

Title or Subject: Process for Preparation of Optically and Chemically Pure (R)- or (S)-α-Hydroxycarboxylic Acids

The patent specifically relates to the production of hydroxy acids that are prepared from cyanohydrins by enzyme-catalysed cyanide addition to aldehydes or ketones. Specifically the examples in the patent all relate to the production of **100** from **99**. The procedure shown in Scheme 25 is to heat the nitrile **99** with concentrated HCl and then recrystallise the crude product from an aromatic hydrocarbon such as xylene. The pure product is then obtained by cooling and crystallisation. It was also shown that by using different solvents during the purification of the crude product the ee could be increased. Thus, when using xylene/THF the ee increased to 99.9%. There were no examples of preparing the (*S*)-isomer although the patent claims do cover this.

Scheme 25



The **99** that is used is made by adding HCN to 2-chlorbenzaldehyde in the presence of *R*-oxynitrilase. The hydrolysis reaction is known not to cause racemisation; thus, optically pure nitriles can be assured of producing optically pure acids.

Advantages

This patent improves the recovery and purity of the product in a specific application.

Patent No. U.S. 6,784,293

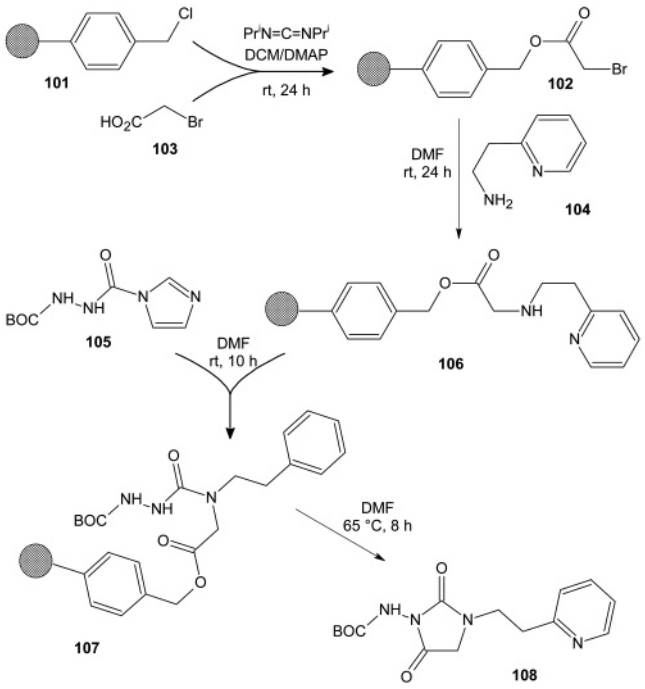
Assignee: the Procter & Gamble Company, Cincinnatti, Ohio, U.S.A.

Title or Subject: Process for Making Boc-Protected Hydantoins and Dihydrouracils

The title compounds are useful chemical intermediates for pharmaceuticals and agrochemicals. The 3-amino derivatives are said to be useful anticonvulsants, antibacterials, diuretics, and pesticides. Alternative routes to these compounds are said to require multiple steps, use harsh conditions, and give low yields. A large number of references is given to such procedures. The patent describes a one-pot solution-phase process and a so-called solid-phase process using supported Merrifield resins. Scheme 26 shows the route to making **106** by a process that is described as a solid-phase reaction that is carried out on the functionalised Merrifield resin **102** suspended in DMF. The preparation of **102** is by reaction of the chloromethylated resin **101** with **103** in the presence of disiopropylcarbodiimide and DMAP in DCM. Reaction of **101** with the aminopyridine **103** in DMF affords the supported resin compound **106**, and this is reacted with the hydrazine compound **105** in DMF to produce **107**. Upon heating **107** in DMF, **108** is formed which is recovered in 63% yield.

An alternative route to some of the desired products is shown in Scheme 27. This summarises a solution-phase process to prepare **112** from Boc-carbazate **109** and **110**. The reaction is carried out by stirring the two compounds in dioxane solution and then heating with **111**. An 80% yield of **112** was obtained. The claims of the patent only cover the solution-phase process although there are several experiments describing both approaches. The patent lists 44 specific compounds that can be made using these processes.

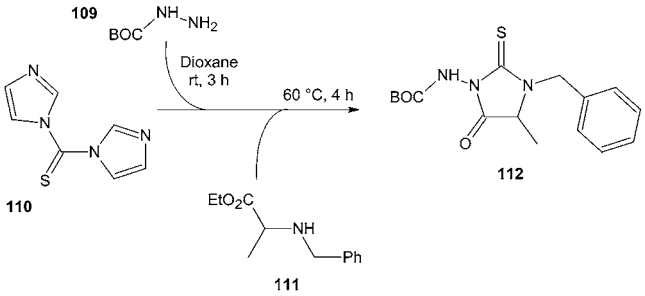
Scheme 26



Advantages

These processes are said to be suitable for preparing a wide range of compounds having a variety of N-1 substituents in high yields from readily available starting materials.

Scheme 27



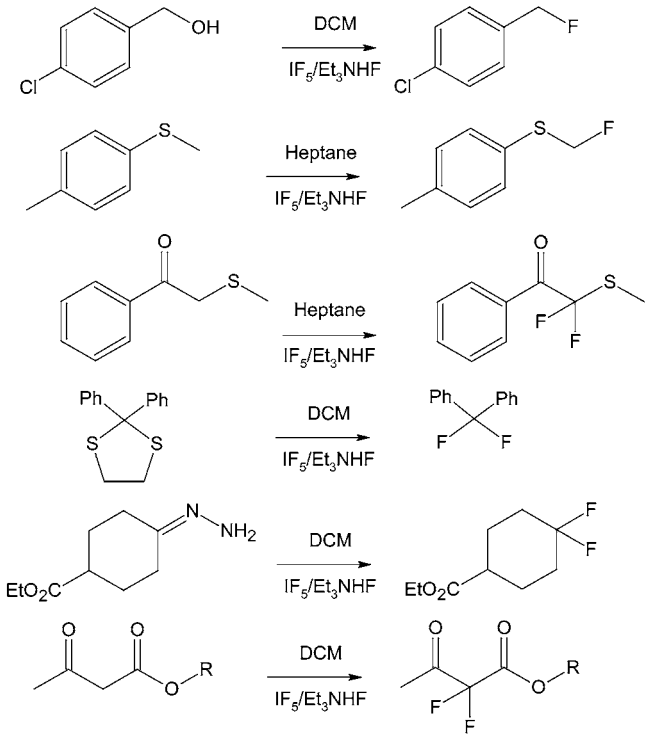
Patent No. U.S. 6,784,327

Assignee: Daikin Industries Ltd., Osaka, Japan

Title or Subject: Process for Fluorinated Organic Compounds Using IF5 as Fluorinating Agent

Fluorinated organic compounds are very widely used in pharmaceuticals and agrochemicals, and so there is considerable interest in improved methods of fluorination. Many fluorinating agents are difficult to handle or have low reactivity, thus limiting their uses. IF_5 is nonexplosive, melts at 9.4 °C, and boils at 100.5 °C thereby demonstrating that it has a widely usable temperature range. A drawback in its use is said to be its high oxidising power. The current patent describes how IF_5 can be used to fluorinate compounds that contain a wide range of functional groups. The basis of the process is to react the compound with IF_5 in the presence of a salt that is molten at room temperature; an example of such a salt is Et_3NHF. The process is carried out in a solvent, and Scheme 27 shows some of the compounds that may be prepared using this technique.

Scheme 28



The reactions shown are carried out at room temperature by adding the substrate to a solution of IF_5/Et_3N-3HF in the appropriate solvent. After completion of the reaction, the mixture is neutralised with Na_2CO_3 and reduced with $Na_2S_2O_7$ solution. The reducing agent is added to reduce those organic compounds that were overoxidised and to reduce the IF_5. The product is extracted with Et_2O and purified by column chromatography. ^1H and ^{19}F NMR and IR data are given for many compounds.

Advantages

The procedure is applicable to a very wide range of compounds and takes place under mild conditions using a reagent that is easy to handle.

Keith Turner

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