Organic Process Research & Development **2005**, *9,* 386–396

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during March and April 2005

Summary

This review covers 20 patents from an original list of 239 that, it is hoped, will be of interest. One thing that struck me in this selection is that there are a number of patents in which mixing or changing the order of reagent addition appears to be central to the work. This could imply that chemists are becoming more aware of mixing or that engineers are becoming more involved in R&D. Whatever is the reason, it is refreshing to note that the chemistry and process engineering aspects are being viewed in parallel. The first patent on mixing is an aromatic nitration that uses static mixers to improve conventional nitration reactions, and changing the order of addition also reduces wastes. An improved method of making the disinfectant bronopol is based on changing the method of adding the reactants. This allows better control of the heat released in the highly exothermic process, and temperature control is key to obtaining high yields. An improvement in making the macrocyclic ketone civetone, without recourse to high dilution methods, also relies on mixing and changing the method of adding reagents. The addition of a corrosion inhibitor to a reaction mixture is probably not something normally considered, but this is what is done in an improved method of making a pesticide. The key reagent is trifluoroperacetic acid, and this is highly corrosive to glass-lined reactors. However, it has been found that by adding boric acid to the reaction the rate of corrosion was reduced by a factor of 60. Clearly it is much cheaper and quicker to do this than to buy a new corrosion-resistant reactor. Naturally occurring or renewable materials continue to be of interest as sources of intermediates for drugs and other products. In one patent sugars are used to produce monomers used in polyester manufacturer. In a second patent the subject is taxols that are anti-cancer drugs that can be obtained from yew tree bark. The taxols are present in very low concentrations, and a simplified process of purifying them is described that does not require chromatographic equipment. Vitamin E and tocopherols are the subjects of two patents with one describing a method of isolating one isomer, with potential in treating prostate cancer, from vegetable oils. The second patent describes a process to prepare a range of intermediates suitable for vitamin E production. The use of highly active organometallic catalysts is of increasing importance in synthetic organic chemistry as well as in larger-scale production. One problem often overlooked is that high activity usually means high susceptibility to poisons and inhibitors. An interesting patent describes the preparation of sulphonated phosphines that are used as catalysts in two-phase hydroformylation of olefins. The production of the phosphines leaves sulphur residues that actually poison the catalyst, and a simple method to remove these residues is described. A method for preparing polyfluorinated alkyllithium compounds is described that discloses a novel deprotonation step using a lithium base. The process also claims to be environmentally friendly by avoiding the use of chlorofluoro compounds. Another patent describes methods of producing fluorinated derivatives by transferring a fluorinated group. This is done by reacting an electrophilic carbenium salt containing a CF_3 group with a suitable nucleophilic reagent. A novel process for producing substituted propanols involving a highly stereoselective coupling reaction is described. However, it also involves an extremely high-pressure hydrogenation process (1000 bar) that would probably deter most people from using it. There is no legal or commercial significance in the choice of patents reviewed. However, the fact that some patents describe examples using substantial quantities of materials does suggest the advanced commercial status of the respective process. Many patents claim advantages over alternative processes based on selective referencing. The advantages described are those claimed in the patent unless this reviewer has personal knowledge of the subject.

Patent No. U.S. 6,861,527

Assignee: Merck Patents GmbH, Darmstadt, Germany
Title or Subject: Nitration of Aromatic and Heteroaromatic Compounds in a Static Micromixer

Nitration reactions are highly exothermic and require extremely intensive mixing to give high yields and avoid runaway reactions. This patent describes a process, using conventional or novel nitration mixtures, that provides the desired mixing in a miniaturised reactor. The examples in the patent are carried out on a small scale using two disposable plastic syringes to separately store the nitration reagents and the substrate. These syringes are connected to a static silicon mixer, and the two liquids are pumped to the mixer where the reaction occurs. Specific details about the tubing diameter and flow rates are described in the patent. The isoquinoline compound **4** is an intermediate used in the synthesis of medicaments and can be prepared by the nitration to give **2**, followed by acylation. The reaction, when carried out on a small scale, gives problems in the narrow

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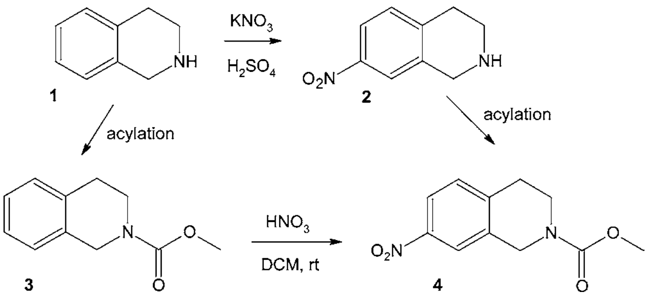
tubing and micromixer due to the high viscosity of 100% H_2SO_4, causing an increase in pressure. The reaction is efficient but does require neutralisation before separation of products and hence can give rise to environmental disposal problems. It was found that these problems are circumvented if the reaction sequence is altered so that the carbamate group is formed before nitration. In doing this, an alternative nitration mixture can be used as shown in Scheme 1.

Scheme 1



Thus, **1** is acylated to give **3**, and nitration of **3** with 65% HNO_3 in dichloromethane (DCM) at ambient temperature gives high yields of **4**. This procedure allows direct extraction of **4** from the acidic reaction mixture thereby removing the neutralisation step and eliminating disposal problems. When operated this way, the process was run continuously for 6 days on a bench-scale unit. The process can also be applied to nitration of simple aromatics such as PhMe using 65% HNO_3 in DCM at room temperature. It is claimed that many nitration reactions can be carried out in the micromixer provided that the mixture does not produce precipitates.

Advantages

The use of small inventories of material improves mass- and heat transfer that also improves safety with highly exothermic reactions. The change in order of the reaction also gives improvements in environmental aspects of the reaction.

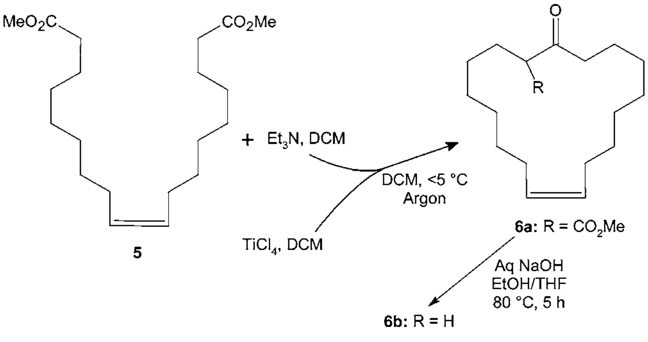
Patent No. 6,861,551

Assignee: Japan Energy Corporation, Tokyo, Japan

Title or Subject: Processes for the Preparation of Macrocyclic Ketones

Macrocyclic ketones such as civetone **6b** are used in fragrances, and many are obtained from natural sources. Synthetic methods frequently employ cyclisation reactions of α,ω-diesters in high-dilution reactions. This patent describes a process for converting an α,ω-diester to **6b** without recourse to high-dilution methods. Scheme 2 shows the process that involves separately adding a DCM solution of $TiCl_4$ and a DCM solution of the diester **5** plus an amine such as Et_3N to DCM under argon. The product **6a** is recovered by silica gel chromatography in 54% yield. Also produced is a 34-membered ring compound in 14% yield. The ketone **6b** is produced in 95% yield by refluxing **6a** in a mixture of aqueous NaOH/EtOH/THF. The reactions are carried out in 5 mL of solvent using 0.5 mmol of **5**, and hence this is far from being described as high dilution.

Scheme 2



Advantages

The process improves the general method of making macrocyclic ketones without the need to use large volumes of dilute solutions.

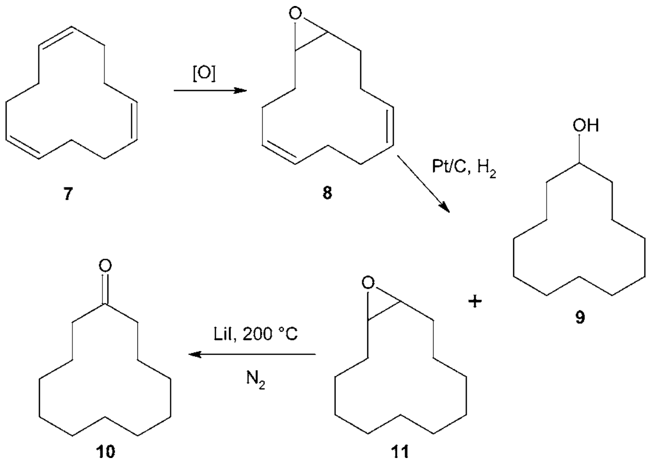
Patent No. U.S. 6,861,563

Assignee: Ube Industries, Japan and EMS-Chemie AG, Switzerland

Title or Subject: Process for Preparation of Cyclododecanone

The title compound **10** is an intermediate used in the manufacture of Nylon-11. The processes for preparing **10** involve isomerisation of the epoxy derivative **11** using lithium halides (Scheme 3). In some cases a solvent is used, and in others none is required. **11** is normally produced from **7** by oxidation to **8** followed by hydrogenation. The production of **11** in the hydrogenation step also forms **9**, and the presence of this in **11** reduces the rate of the isomerisation of **11** to **10**. Hence, excess **9** must be removed before the isomerisation reaction. A common problem for all processes is that **9** and **11** are very difficult to separate by distillation, crystallisation, or extraction techniques. Hence, this patent is aimed at developing a method of forming **11** that contains a reduced amount of **9**. The process thus enables an almost 100% conversion of **11** to **10** and eliminates the separation of **9** from **11**. The key aspect of the patent is that the hydrogenation of **8** to **11** is carried out using Pt catalysts. Alternative processes using Ni or Pd catalysts give higher levels of **9**. The Pt catalyst gives 100% conversion of **8** to **11** containing only 0.2 mol % of **9**. The subsequent isomerisation of **11** proceeded to give **10** in 99% selectivity.

Scheme 3



Advantages

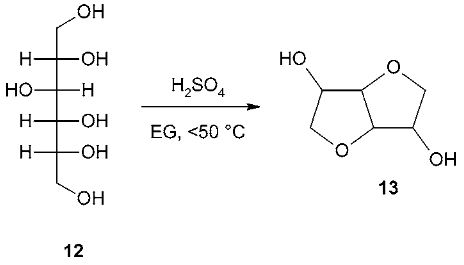
The process increases the overall yields of **10** without changing the overall process, thus making it simple to use in an existing production plant.

Patent No. U.S. 6,864,378

Assignee: E.I. Du Pont De Nemours and Company, Wilmington, Delaware, U.S.A.
Title or Subject: Integrated Continuous Process for Manufacture of Anhydro Sugar Alcohol

Sugars are finding increasing use as raw materials for a variety of nonfood products, and this patent is aimed at **13** that is used as a monomer for preparing polyesters. The patent describes a process for the production of isosorbide **13** from sorbitol that can be compared to an alternative process that was reviewed recently (*Org. Process Res. Dev.* **2005**, *9*, 244). The major obstacle to overcome in such processes is the removal of water. In the current process this is achieved by combining the dehydration reaction with separation in a multistage vessel. The process is run continuously by feeding a solution of sorbitol **12** into a reactor containing a dehydration catalyst. The preferred catalyst is H_2SO_4. The solvent can be water, although it is stated in the patent that, if the product is to be used in polyester production, then ethylene glycol (EG) is preferable. If water is used, the reaction temperature is around 130 °C. When using EG, the temperature is between 25 and 50 °C, and the process is operated under vacuum. Purification of the product is achieved by removing the product stream as a vapour, and this leaves behind the high-boiling byproduct monoanhydro sugar alcohols and polymeric materials. The vapour is condensed, the water evaporated, and the product may be purified by a crystallisation step. The high-boiling residue is diluted with water and acidified to precipitate any polymeric species that are removed and the solution returned to the reactor. The process is fully integrated, and the patent describes a process that produces around 9000 tonnes per year of **13**.

Scheme 4



Advantages

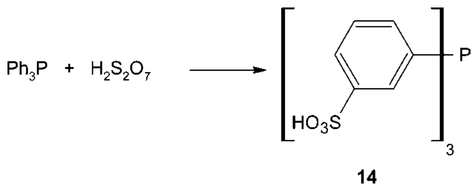
The scale of operation described in the example indicates that the process is obviously commercially viable.

Patent No. U.S. 6,864,387

Assignee: Celanese Chemicals Europe GmbH, Germany
Title or Subject: Process for Preparing Sulphonated Arylphosphines

The title compounds are used as ligands that impart water solubility in rhodium catalysts used in two-phase hydroformylation of olefins to produce aldehydes. (See *Aqueous-Phase Organometallic Catalysis: Concepts and Applications* by B. Cornils and W. Herrmann, Wiley-VCH, 1998). The sulphonated phosphines such as **14** are made by sulphonation of an arylphosphine using oleum. The reaction leaves sulphur-containing compounds (SCC) in the products, and their presence poisons the Rh hydroformylation catalysts. This can occur by formation of phosphine sulphides. The SCC also poison the hydrogenation catalysts that are used to convert the aldehyde formed in the hydroformylation reaction. Hence, there are two reasons for removing SCC. This patent describes a method of reducing the amount of SO_2 or sulphites in aqueous solutions of **14**. The phosphine **14** is the main subject of the patent, and Scheme 5 shows the general method used for its preparation.

Scheme 5



The process used to remove SCC is to dilute the reaction mixture with water and then adjust the pH to 3 with H_2SO_4. This step is then followed by degassing by passage of N_2 through the solution in a packed column. Addition of aqueous NaOH to the degassed solution results in the formation of salts that are soluble in the water phase. The salts are extracted using trioctylamine/PhMe mixtures by a process covered by EP0632047. The surprising finding mentioned in this patent is that this simple degassing process is effective in removing the SCC. This is apparently due to the fact that the sulphites and SO_2 do not react very rapidly with the Rh catalysts in the absence of CO and H_2. Thus, no poisoning of the catalyst occurs until the hydroformylation reaction begins. It is concluded that the most pernicious sulphur compounds are only formed in the presence of CO, H_2, and Rh. Therefore, by removing the sulphites and SO_2 from the sulphonation mixture the problems of downstream catalyst poisoning are removed.

Advantages

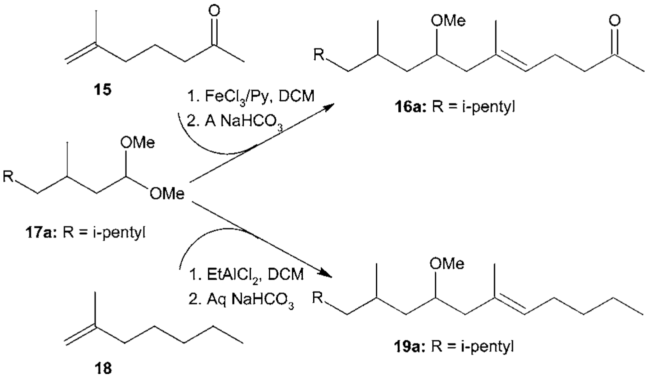
This is a simple method to avoid catalyst-poisoning which is a major problem with highly active Rh catalyst in hydroformylation reactions.

Patent No. U.S. 6,867,307

Assignee: Adisseo France S.A.S., Antony, France
Title or Subject: Intermediates for Use in the Preparation of Vitamin E

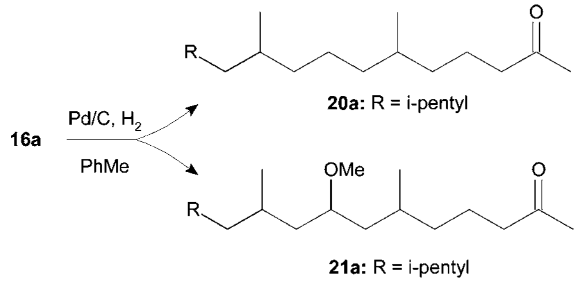
Vitamin E, **25b** (R = H), is also known as tocopherol, and patents covering its synthesis have been reviewed previously (*Org. Process Res. Dev.* **2005**, *9*, 9). This is the first of two patents on **25b** in this review, and it covers a range of novel intermediates plus a synthesis of the acetate form of vitamin E, **25a**. Scheme 6 shows an example of the synthetic route described that is used to make the ketone intermediate **16a** and the methyl ether **19a**. The ketone **16a** is prepared by condensation of the acetal **17a** with **15** in DCM in the presence of a Lewis acid and base such as aqueous $NaHCO_3$. In this case $FeCl_3$/pyridine at −30 °C is the preferred catalyst, but to prepare **19a** the reaction of **17a** with **18** gives better yield using the catalyst $EtAlCl_2$. The condensation reaction can also be carried out using the corresponding aldehyde instead of **17a**. Examples are also summarised in which a range of Lewis acids is used, and yields of products vary quite widely.

Scheme 6



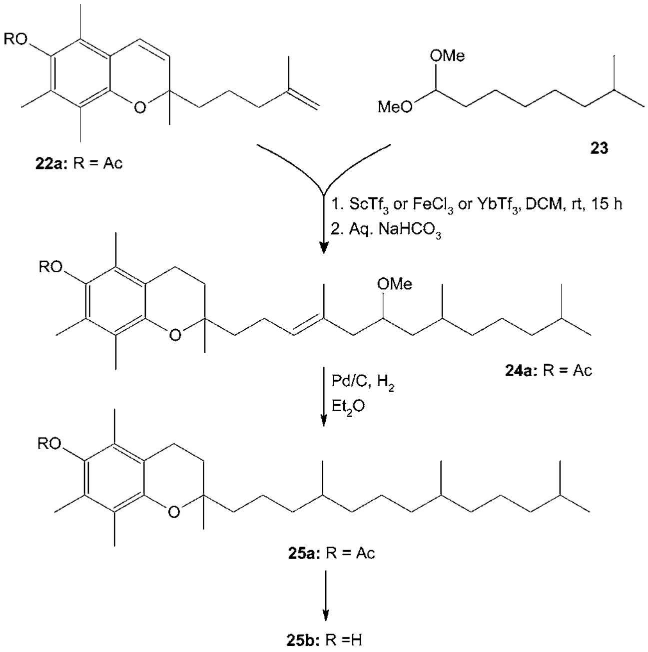
The second part of the patent is concerned with the preparation of phytone **21a** and is shown in Scheme 7. **21a** can be converted to **25b** and is prepared by hydrogenation of **16a** to give a mixture of 80% **21a** and 20% **20a** using Pd/C in PhMe. When HOAc was used in place of PhMe the selectivity to **21a** fell to 30%.

Scheme 7



The patent also describes a synthetic route to **25a** using the above condensation reaction as a key step in the synthesis. This is shown in Scheme 8 where the condensation between the acetal **23** and the chromene **22** to give **25a** is catalysed by triflates of Sc or Yb or $FeCl_3$. There is no mention in the patent about whether any of the reactions are stereoselective.

Scheme 8



Advantages

The process provides a range of beta olefinic compounds including novel intermediates and procedure that can be used to prepare vitamin E.

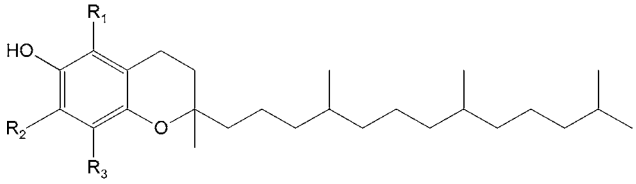
Patent No. U.S. 6,867,308

Assignee: Archer-Daniels-Midland Company, Decatur, Illinois, U.S.A.
Title or Subject: Process for Separation of Tocopherols

This is the second patent related to vitamin E, and in this case it focuses on the separation of **25d** from vegetable oils that also contain other isomers such as **25b,c** and **e**. The γ-isomer **25d** has been reported as having some potential in the treatment of prostate cancer. It is also an effective free radical trap and an inhibitor of oxidative damage of cells.

The γ-isomer is not produced synthetically, and hence there is claimed to be a need for improved methods of extraction from natural sources. This patent describes a method for obtaining **25d** from various vegetable oil fractions. The oils are dissolved in a solvent and then passed over a resin. The desired isomer is bound to the resin and then later eluted. A number of options are described in carrying out the process. The first option involves dissolution of the oil in a nonpolar solvent such as *n*-heptane and passing the solution over a nonionic absorbent resins such as silica gel. The product is eluted using a mixture of a nonpolar solvent (heptane) and a polar solvent (Me_2CO) or a mixture of two polar solvents. No example is given for this latter procedure. The second option is to dissolve the oil in a polar solvent such as MeOH or Me_2CO and then to pass the mixture over a strong basic ion-exchange resin (IER) in the OH form. The product is eluted with a mixture of the two polar solvents, and the examples focus on this method. It was possible to obtain fractions containing >95% of **25d** in the eluate.

Tocopherols



25b: $R_1 = R_2 = R_3 = Me$
25c: $R_1 = R_3 = Me, R_2 = H$
25d: $R_1 = H, R_2 = R_3 = Me$
25e: $R_1 = R_2 = H, R_3 = Me$

Advantages

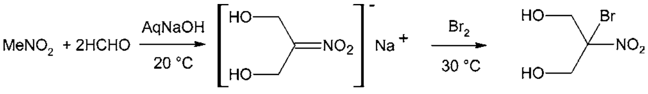
The process provides and effective method of obtaining the desired active tocopherol from natural sources in a simple procedure.

Patent No. U.S. 6,867,336

Assignee: BASF AG, Ludwigshafen, Germany
Title or Subject: Method for the Continuous Production of 2-Bromo-2-nitro-1,3-propanediol

The title compound **27** is known as bronopol and is an important biocide that is used as a disinfectant in a range of consumer products. It is often made from $MeNO_2$ by hydroxymethylation using HCHO in the presence of a base followed by bromination (Scheme 9). Both reactions are very exothermic, and hence the process is usually carried out in dilute solution. An additional problem is that **27** decomposes in alkaline solution. The patent states that the highly exothermic nature of the reactions has prevented the process being run continuously, and that is why most processes are run in batch reactors. This statement is contrary to my own experience in that exothermic reactions are actually easier to control when designed properly to run continuously. The patent describes a method of operating the process continuously so that the heat of reaction can be removed. This is done by feeding stoichiometric amounts of $MeNO_2$, aqueous HCHO, and NaOH solutions to a reaction zone to form **26**. The whole mixture is then passed into a second reaction zone with Br_2 to give **27**. The example given in the patent uses two coiled, tubular Teflon reactors that are cooled in a bath to maintain the temperature of <20 °C in reactor 1 and < 30 °C in reactor 2. The product crystallised in a receiver at −5 °C placed at the exit of reactor 2 and was collected by filtration. The yield of **27** based on $MeNO_2$ was about 90% with a $MeNO_2$ feed rate of 0.54 mL/min. To achieve high yields it is stated that the residence time in reactor 1 should be very low, and times of 10 to 30 s are mentioned. Residence time in reactor 2 should be from 15 to 60 s.

Scheme 9



26

27

Advantages

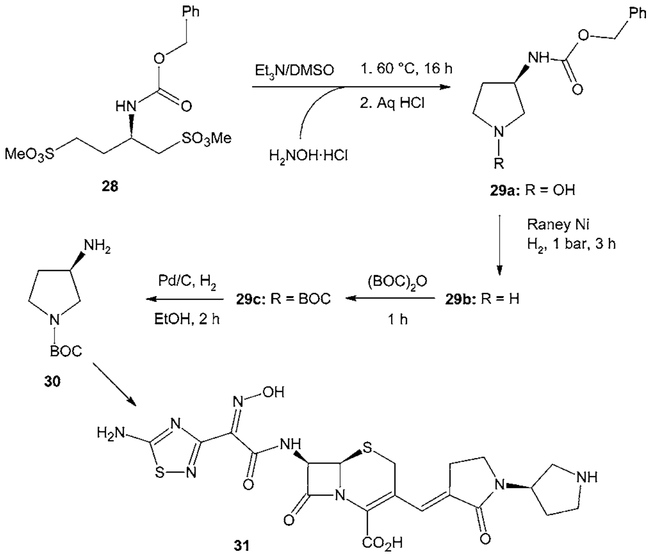
The process allows more concentrated solutions to be used, and hence an improved productivity is obtained. The method also produces product of higher purity, and recovery is much simpler.

Patent No. U.S. 6,872,836

Assignee: Basilea Pharmaceutica AG, Basel, Switzerland
Title or Subject: Process for the Manufacture of 3-Protected-Aminopyrrolidine Derivatives

The title compounds and especially optically active compounds such as **30** are intermediates used in the preparation of vinylpyrrolidinone−cephalosporin derivatives. Alternative methods for preparing **30** are summarised and said to be time-consuming and often involving resolution steps. Other processes involve using hazardous materials, and allylamine (AA) is mentioned. This material is very toxic and highly flammable and, hence, difficult to handle on a commercial plant. The present patent describes a process that is claimed to be safer and more cost-effective than the alternatives. This has been done by using NH_2OH or its acid salt in place of AA. Scheme 10 shows the route to give **30** that starts with the reaction of **28** with $NH_2OH{\cdot}HCl$ to give the *N*-hydroxyl derivative **29a**. This is reduced using Raney Ni to give the pyrrrolidine **29b** that is reacted with $(BOC)_2O$ to protect the pyrrolidine N by forming **29c**. In the final step **30** is prepared by hydrogenolysis of **29c** using Pd/C. ^{1}H NMR data are given for several of the intermediates. The product **30** can be used to prepare the cephalosporin **31** by a modification of a method described in EP-A-0849269. The experimental details are not given except to say that **30** may be used in place of an *N*-allyloxycarbonyl derivative.

Scheme 10



Advantages

The process avoids the use of hazardous AA and improves the safety aspects, giving higher yields of the desired product.

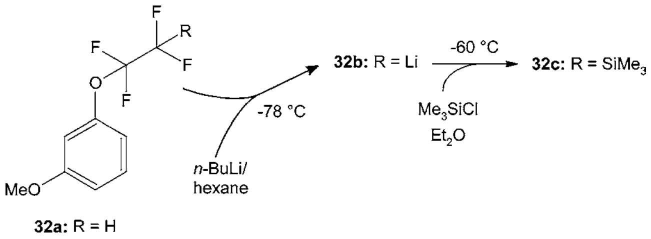
Patent No. U.S. 6,872,861

Assignee: Bayer AG, Leverkusen, Germany

Title or Subject: Process for Preparing Polyfluoroalkyllithium Compounds

Fluorinated compounds are important in the preparation of many drugs and agrochemicals. This patent describes a method of preparing lithium derivatives that are then used as reagents for introducing a fluorinated group into a molecule. The key aspect of the method is production of a lithium compound by deprotonation using a lithium base. Scheme 11 shows the preparation of **32c** from **32a** via the lithium derivative **32b**. The product was purified by distillation and obtained in 75% yield. The reaction of **32b** with Me_3SiCl is a standard procedure; the difference here is that **32b** is usually made from a chlorofluoro compound (CFC) such as **32d** (R = Cl).

Scheme 11



The patent also gives examples of using the technique for the following transformations:

93% yield of $F_3CCF_2SiMe_3$ from F_3CCF_2H and Me_3SiCl

70% yield of $F_3CCF_2CF_2CH(OH)Ph$ from $F_3CCF_2CF_2H$ and PhCHO

Advantages

The deprotonation procedure avoids the use of environmentally unacceptable CFCs without sacrificing product yields.

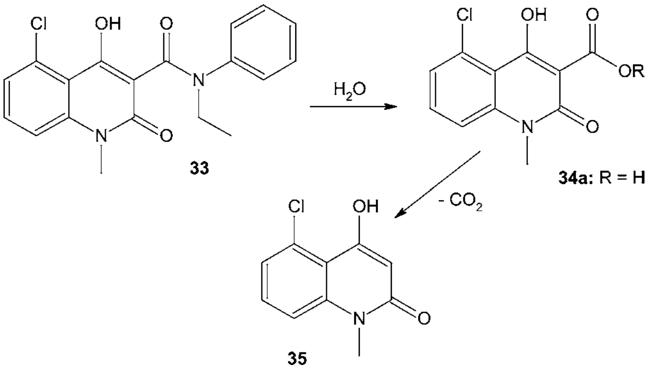
Patent No. U.S. 6,875,869

Assignee: Active Biotech AB, Lund, Sweden

Title or Subject: Process for the Manufacture of Quinoline Derivatives

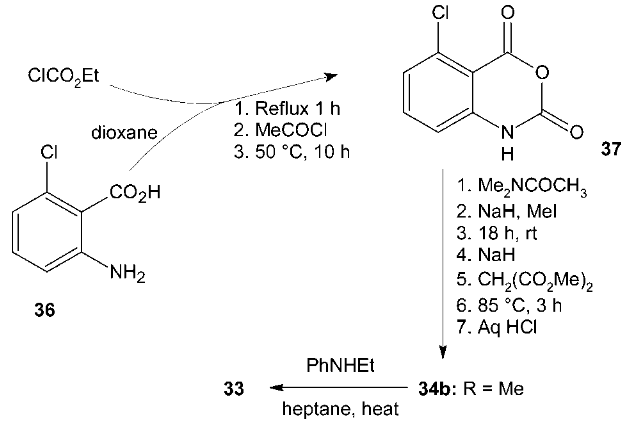
The title compounds are of value in the treatment of pathological inflammation and also malignant tumours. This patent focuses on the preparation of **33** that can easily decompose by hydrolysis to the acid **34a** that then gives **35** by decarboxylation (Scheme 12). This decomposition can occur during the normal preparation of **33**, and hence the patent attempts to improve the route to **33** and at the same time avoid its degradation.

Scheme 12



The process to prepare **33** begins with the preparation of the anhydride **37** by treatment of **36** with $ClCO_2Et$ followed by reaction with MeCOCl. The next stage is to prepare the ester **34b** (R = Me) by a multistep sequence indicated in Scheme 13. The final step is a condensation reaction of **34b** with PhNHEt in heptane to produce **33** in 98% yield. The use of heptane in this step is the key to the process improvement. When the condensation reaction is carried out in PhMe a 90% yield is obtained and the increase in yield when using heptane is said to be due to a number of factors. The insolubility of the product in the solvent increases the rate of reaction and prevents the product from reacting with any water present in the solution.

Scheme 13



Advantages

The change of solvent in the last stage of the synthesis produces a significant improvement in the overall yield and purity of the product.

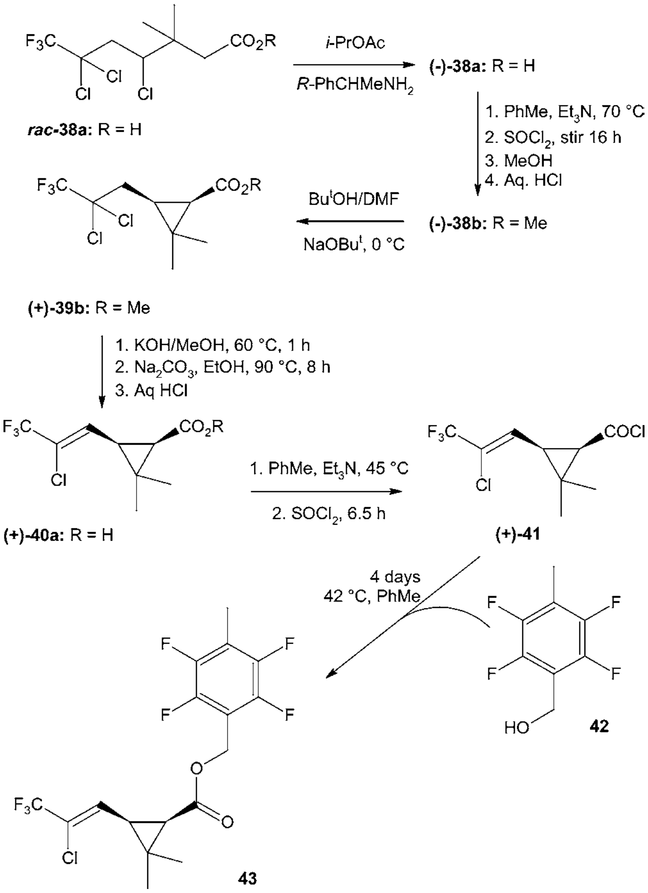
Patent No. U.S. 6,875,885

Assignee: Syngenta Limited, Huddersfield, United Kingdom

Title or Subject: Process for the Preparation of Enantiomerically Pure Pyrethroid Insecticides

The compounds of interest in this patent are the esters of cyclopropanecarboxylic acid such as **43** that is known as tefluthrin. The patent discloses a stereoselective method used to prepare either enantiomer of **43** although the most active and hence desired isomer is the *cis*-1*R*(+). The general route to give **43** is shown in Scheme 14 and begins with the racemic acid **38a** that is resolved using *R*-PhCHMeNH$_2$. The (−) acid **38a** is then esterified to give methyl ester **38b**, and this is cyclised to give **39b** by using NaOBu^t. The production of **40a** from **39b** is carried out using standard methods of dehydrochlorination and hydrolysis as is the next step to give the acid chloride **41**. The last stage to give the ester **43** is conventional, but it does take over 4 days. The patent includes the X-ray crystal structure of **38a** as well as ^{1}H NMR data for several of the novel intermediates shown in Scheme 14. Unfortunately, there is no information in the patent as to how **38a** is prepared.

Scheme 14



The patent states that the enantiomerically pure forms of the compounds from **38a** through to **41** are not commercially available. It is claimed that techniques for resolving **38a** are unknown or at least unusual because the resolving agent is acting on a group quite remote from the chiral centre. Resolving compounds such as **38a** can result in lactonisation of the carboxylate salt giving enantiomeric lactones. The method employed in the patent prevents this happening.

Advantages

This process provides an accessible method of preparing either enantiomer of starting compound **38a** and maintains the stereochemistry throughout the chemical processing steps.

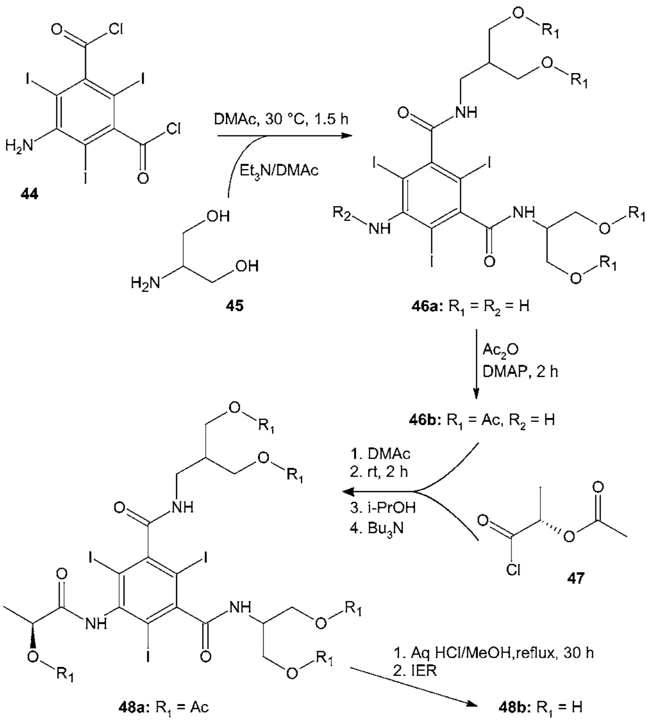
Patent No. U.S. 6,875,887

Assignee: Bracco Imaging S.p.A., Milan, Italy

Title or Subject: Process for the Preparation of Iopamidol

The main subject of this patent **48b** is an X-ray contrast agent. Several types of contrast agents are known, and many are ionic that are usually prepared by precipitation from aqueous solutions. However, neutral agents such as **48b** have very high water solubility, and hence this method is unsuitable. The problems associated with preparing **48b**, therefore, are usually in their recovery and purification. The patent describes a method to prepare **48b** that is shown in Scheme 15. The reaction starts from **44** that is also used in alternative routes to **48b**. The first stage of the process is the reaction of **44** with **45** to give tetrahydroxy compound **46a** that is acetylated with Ac$_2$O to give **46b**. The two-stage reaction is carried out in a single-reaction vessel without isolation of **46a**. In the next stage **46b** is treated with serinol **47** to form the pentaacetyl compound **48a** in 90% yield. The final step is acid hydrolysis of **48a** to give **48b**, and an IER is used to neutralise the residual acid in the mixture. The product **48b** is purified further by passage through a bed of a nonionic adsorbent resin (Amberlite XAD-16) and then recrystallised from MeCN/EtOH and obtained in 74% yield.

Scheme 15



The use of acid hydrolysis in the final step does not cause racemisation of the product in contrast to alternative processes that use bases and do give racemic mixtures.

Advantages

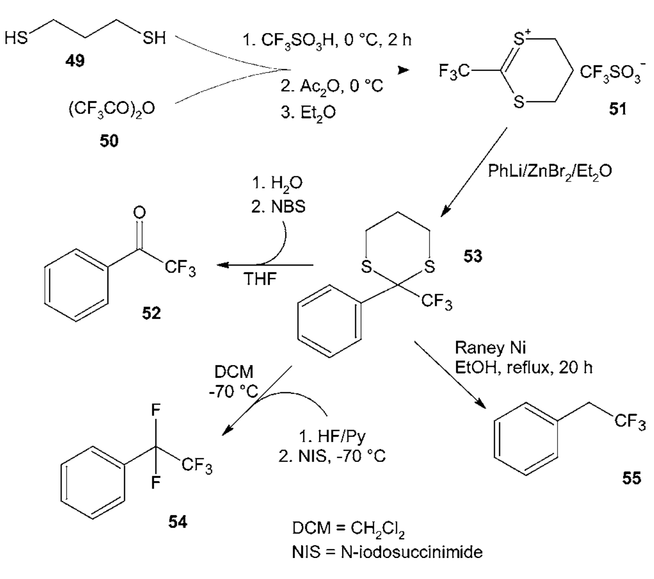
The process gives a high yield of product that is of sufficiently high optical purity that it can be used directly as a contrast agent

Patent No. U.S. 6,875,894

Assignee: Merck Patent GmbH, Darmstadt, Germany
Title or Subject: Bis(alkylthio)carbenium Salts

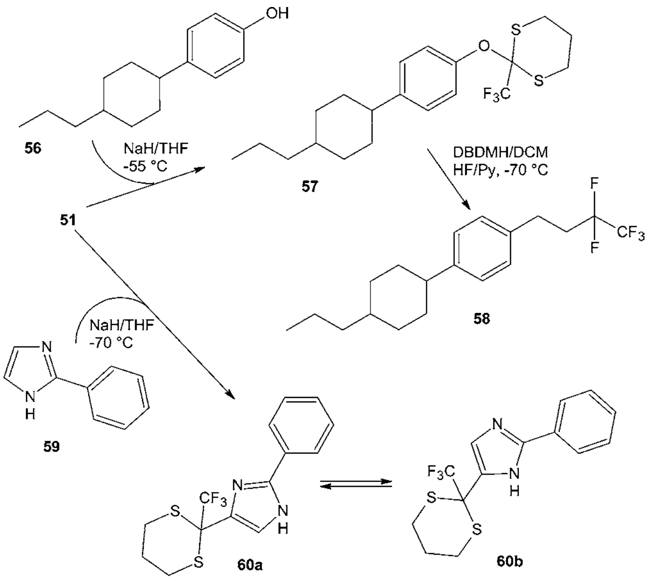
The salts such as **51** are electrophilic reagents that are used to transfer fluorinated groups onto nucleophilic compounds. Such reactions are used in the preparation of liquid crystalline compounds and drug intermediates. An aim of the patent is to introduce a CF_2 group that is in the α-position to the electrophilic C atom such as in $-CF_2-CH_2-$, $-CF_2-CF_2-$ or $-CF_2-CO-$ bridges. The alternative methods to introduce these groups are said to be commercially unattractive for a variety of reasons. The salts covered in this patent are low molecular weight with respect to the group to be transferred. This means that less mass of reagent is needed when compared with alternative processes. Scheme 16 summarises the preparation of **51** from the dithiol **49** and the anhydride **50** in CF_3CO_2H. **51** was then converted to **53** by reaction with PhLi in the presence of $ZnBr_2$. **53** was then used in a number of reactions to introduce the $PhCCF_3$ group as shown in Scheme 16.

Scheme 16



The patent also describes reactions between **51** and nucleophiles as shown in Scheme 17. The phenol **56** reacts to give **57**, and this undergoes a fluorodesulphuration reaction using dibromodimethylhydantoin (DBDMH) to give **58**. The reaction of **51** with the imidazole **59** gives the dithiortho ester **60**. The ^{13}C NMR spectra of **60** suggest that it is an equilibrium mixture of **60a** and **60b**. The patent contains a large amount of IR and NMR data for all of the compounds prepared in both of the above schemes.

Scheme 17



Advantages

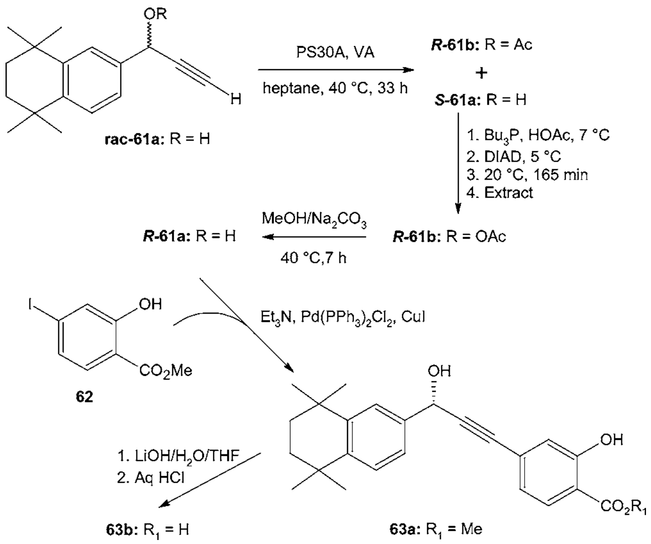
The process provides a facile method of introducing the CF_2-containing bridging group into a range of compounds.

Patent No. U.S. 6,878,842

Assignee: Galderma R & D, S.N.C., Valbonne, France
Title or Subject: Process for the Enantioselective Synthesis of (R)-Propargyl Alcohol Derivatives from Racemic Mixtures

The products of interest in this patent are compounds such as **63b** obtained by the process shown in Scheme 18. The procedure involves the use of the Mitsunobu reaction to invert the configuration of an ***S***-enantiomer and improve the overall yield of the reaction. In the first step the racemic alcohol **rac-61a** is treated with vinyl acetate (VA) in the presence of lipase PS30 Amano (PS30A). This catalyses a stereoselective acylation reaction of the *R*-alcohol to give the acetate ***R*-61b**. The whole mixture then undergoes a Mitsunobu reaction so that the *S*-alcohol is converted to ***R*-61b**. Transesterification of the acetate using Na_2CO_3/MeOH then produces the alcohol ***R*-61a**, and this is purified by crystallisation. The patent claims that previous work on the stereoselective acylation stage necessitates the isolation of the acetate and alcohol before the Mitsunobu reaction is carried out. The removal of this need to separate the acetate and alcohol is a key feature of the patent. In the final step of the process the coupling reaction of ***R*-61a** with **62** gives the methyl ester **63a**, and this is hydrolyzed to the acid **63b** using LiOH in THF. The final yield and ee of the product is not reported although 18.5 kilograms of ***R*-61a** is obtained with a chiral purity of 99%. The scale reported in the patent indicates the advanced commercial status of the process.

Scheme 18



Advantages

The process gives an improved overall yield primarily because of the finding that the Mitsunobu reaction can be carried out on the mixture of acetate and alcohol.

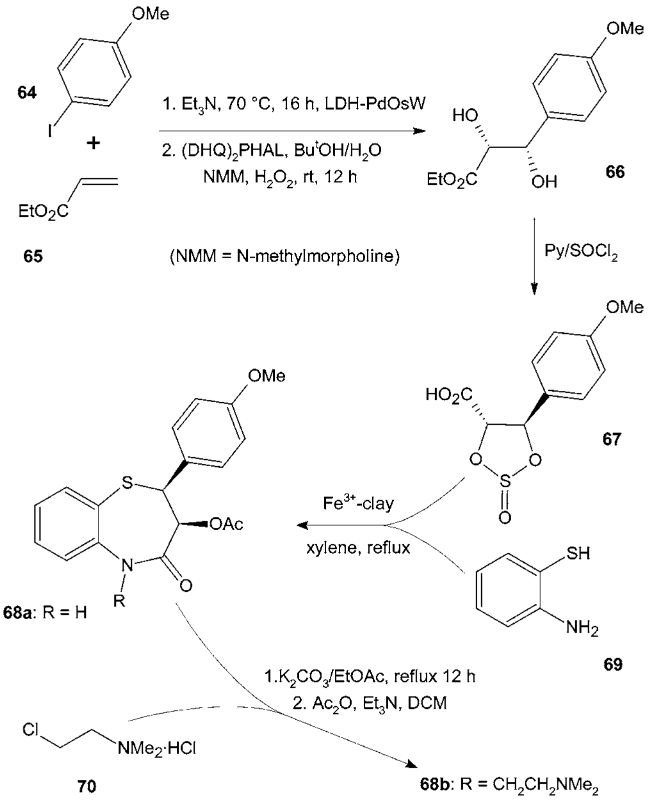
Patent No. U.S. 6,881,839

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

Title or Subject: Process for Preparing Diltiazem Using a Heterogeneous Trifunctional Catalyst

Diltiazem **68a** is a calcium antagonist that is used for treating angina and hypertension. Several processes for synthesising **68a** are known, and all have to overcome the problem of producing one stereoisomer from the four that are possible. The patent describes a method for the preparation and use of a trifunctional catalyst in the production of **68a**. Alternative routes to **68a** involve the production of a chiral 1,2-diol using OsO_4 catalysts, and because OsO_4 is highly toxic, there are difficulties in the recovery of the product and catalyst. The process described in this patent uses a heterogeneous catalyst that can be easily recovered and recycled. Scheme 19 shows the route to **68a** in which the chiral diol **66** is produced in a two-stage reaction. The first stage is a Heck coupling reaction between **64** and **65**, and this is carried out in the presence of a trifunctional catalyst designated LDH−PdOsW. The catalyst is prepared from layered double hydroxide (LDH), Na_2PdCl_4, $K_2OsO_4{\cdot}2H_2O$, and $Na_2WO_4{\cdot}2H_2O$. This coupling reaction is followed by oxidation in the presence of a chiral alkaloid such as $(DHQ)_2PHAL$ to give **66**. In the next stage the crude **66** is treated with pyridine (Py) and $SOCl_2$ to give the cyclic sulphite **67**. The reaction of **67** with **69** in the presence of an Fe^{3+}-exchanged clay produces the cyclic lactam **68a** and N-alkylation with **70** gives the desired product **68b** as the HCl salt.

Scheme 19



The key step in this process is probably the Fe^{3+} clay-catalysed ring opening and insertion reaction to give **68a**.

Advantages

The patent provides a simplified synthesis of **68b**, and by using a heterogeneous Os-based catalyst it removes some of the problems of alternative synthetic methods in preparing chiral diols.

Patent No. U.S. 6,881,848

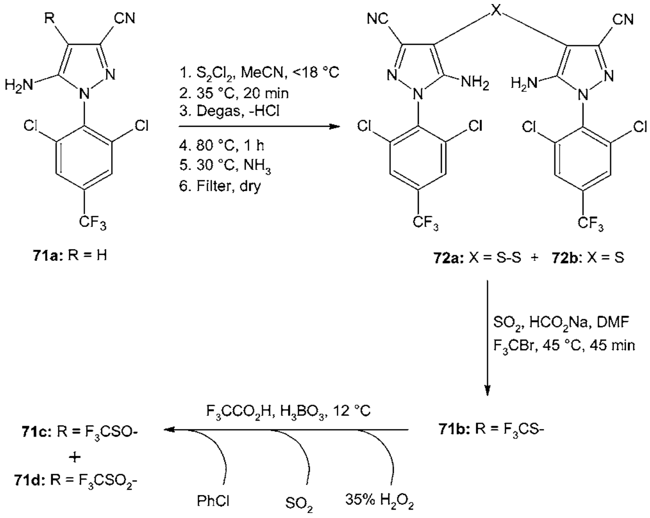
Assignee: BASF Agro B.V. Arnhem (NL), Wädenswil-Branch, Switzerland

Title or Subject: Process for Preparing 4-Trifluoromethylsulfinylpyrazole Derivative

The patent covers a method for producing the pesticides **71b** and **71c** from **71a**. The compound **71c** can be made by oxidation of **71b**, and alternative processes are known that use chloroperbenzoic acid. However, one problem that is said to occur is formation of the Sulphone **71d** ($R = F_3CSO_2-$), and it is difficult to separate this from **71c**. The use of trifluoroperacetic acid is also known to be suitable in oxidising sulphides, but it is a corrosive mixture that corrodes glass-lined vessels. The problem is solved in this patent by the addition of a corrosion inhibitor and H_3BO_3 is added to the reaction mixture. This reduces the corrosion of the vessels from over 300 μm/year at ambient temperature to less than 5 μm/year. Scheme 20 shows the route used to prepare **71c** from **71a** and proceeds via the formation of the disulphide **72**. The first stage is to prepare **72a** by treatment of **71** with

S_2Cl_2 followed by a multistep workup procedure. A byproduct in this step is the formation of the monosulphide **72b**, but this is avoided by using MeCN as solvent. When the reaction is carried out in PhMe, the amount of **72b** increases substantially, and it is difficult to remove. The method and order of addition is important in this step, and the S_2Cl_2 must be added rapidly to the solution of **71**. In the next step the disulphide **72a** is converted to **71b** by addition of SO_2 to a mixture containing **72a**, HCO_2Na, and F_3CBr in DMF. Again the method of addition is important to obtain high yields and enable the exothermic reaction to be more easily and safely controlled. The final stage is oxidation of **72b** as discussed above.

Scheme 20



Advantages

This process includes a number of process improvements that cover both chemical and engineering aspects to allow high yields of the desired product to be achieved.

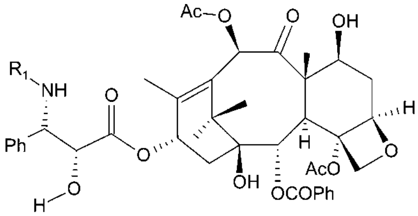
Patent No. U.S. 6,881,852

Assignee: Dabur India Limited, Nadia, India

Title or Subject: Purification of Paclitaxel and Docetaxel

The title compounds are both useful in the treatment of various cancers. Paclitaxel **73a** is available as Taxol and docetaxel **73b** as Taxotere. **73a** occurs naturally in the yew tree although the concentration is very low (<0.01% w/w); hence, its extraction is quite difficult because vast amounts of biomass are required. **73b** is a synthetic material that is made from a naturally occurring precursor; thus, its availability is also limited. **73a** can also be synthesised and this has been previously reviewed (*Org. Process Res. Dev.* **2004**, *8,* 823). The patent describes a method of purifying both compounds using an extraction technique based on a solvent mixture of hexane and DCM that does not involve sophisticated equipment. Alternative purification methods are known that involve the use of chromatographic methods involving sophisticated equipment.

Taxels



73a: paclitaxel, R = PhCO-
73b: docetaxel, R = But-OCO-

The method has four basic steps that are summarised below. The same procedure is used to purify for either compound.

(i) The crude taxel (50% purity) is added to a 1:9 DCM: hexane mixture and mixed for 4 h at 20−25°C. The mixture is filtered and the procedure repeated nine times. After this the product purity is increased to about 65−75%

(ii) Crude product is dissolved in Me_2CO at 30 °C and hexane added to give a precipitate. After 4 h the solid is removed by filtration and dried. Purity is about 91%

(iii) Crude product from step (ii) is dissolved in MeOH at 30 °C. Water is added to give a precipitate and the mixture stirred for 4 h. The solid is filtered off, dissolved in DCM and the solvent removed by evaporation. Purity at this point is 98%.

(iv) In the final stage the purified product is dissolved in Me_2CO and filtered though a 10 μm filter, and hexane is added. The suspension is stirred 4 h and filtered; after drying, the solid is 99.5% pure.

Although the process is undoubtedly simple, it does involve the use of DCM and this is clearly not acceptable in many production facilities.

Advantages

The process is very simple, requiring only basic equipment.

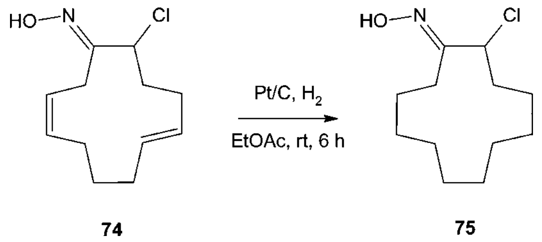
Patent No. U.S. 6,881,863

Assignee: Ube Industries Ltd., Ube, Japan

Title or Subject: Process for Producing 2-Chlorocyclododecanone Oxime

The title compound **75** is a precursor to 1,12-diaminododecane that is used to produce Nylon 12. The method is based on a selective reduction reaction using a supported Pt catalyst. The reduction of 2-chlorocycloalkenone oximes to 2-chlorocycloalkanone oximes using Pd catalysts is known, but it also gives products in which the chlorine atom is removed. PtO_2 catalysts are not particularly effective, giving only 10% yields. The patent describes a method of effecting the desired reduction without removing the 2-chloro group. This is done by using a Pt catalyst supported on activated charcoal and in a range of solvent. Using EtOAc solvent gave a 100% conversion of **74** in 86% yield. When the reaction is carried out using PtO_2 and EtOAc, there is a 12% conversion of **74**, but no **75** is obtained. Using Pd/C in EtOAc the conversion of **74** was 5%, and again no **75** was obtained. Using HOAc as solvent also gave 97% yield with the Pt/C catalyst, but when PhMe was used, the yield of **75** was only 47%.

Scheme 21



The patent does claim that the process is applicable to other cyclic oximes, but no examples are given.

Advantages

The process gives an improved method of making the chlorinated oxime without a major process change. The catalyst is insoluble, and hence it can be recovered and reused.

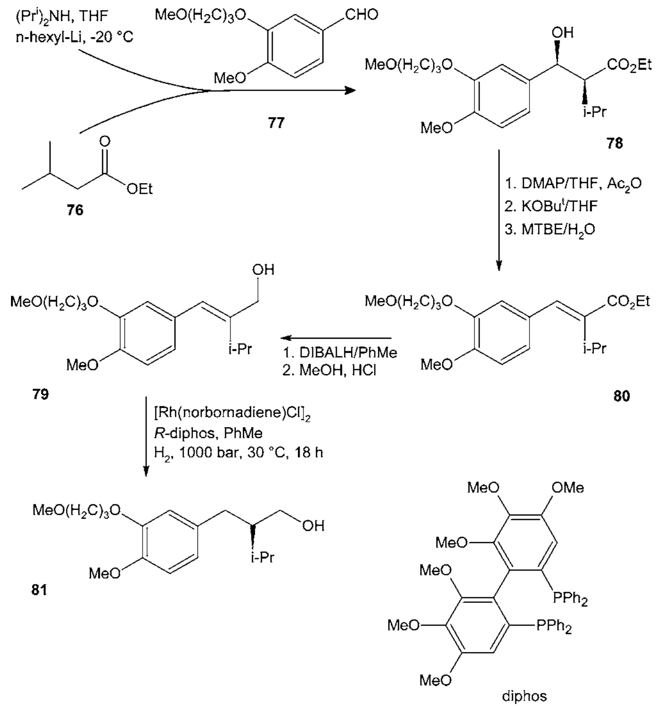
Patent No. U.S. 6,881,868

Assignee: Speedel Pharma AG, Basel, Switzerland

Title or Subject: Process for the Preparation of (R)-2-Alkyl-3-phenyl-1-propanols

The subject of this patent is the production of **81** that is used to prepare amides having antihypertensive properties. The syntheses of **81** and the amides involve several steps, and it is claimed that poor yields of pure diastereoisomers are obtained. Scheme 22 shows the route used to prepare **81** beginning with the condensation of **76** with the benzaldehyde **77** to form **78** stereoselectively. The desired diastereoisomer is surprisingly formed at up to 75%, and no explanation is given for this key aspect of the process. **78** is crystalline and can be readily isolated without significant losses. In the next step the OH group is converted to a leaving group. This uses a standard procedure with Ac_2O and treatment with $KOBu^t$ and gives **80** with high regioselectivity. In the next step the ester is treated with DIBALH in a hydrogenolysis reaction giving the allylic alcohol **79**. The final step is asymmetric hydrogenation using a Rh chiral phosphine catalyst to give **81**. This reaction takes place over 18 h at 30 °C, but the pressure used is 1000 bar, and even on a small scale this is an excessively high pressure, and I would be surprised that this is viable on a commercial scale.

Scheme 22



Advantages

The process does provide an interesting new route to the desired alcohols and includes some surprising new reactions, but the hydrogenation step seems to be at too high a pressure for commercialisation.

Keith Turner

Kappa Tau Consulting, 12 The Avenue,
Fairfield, Stockton-on-Tees, TS19 7EY,
Telephone/fax: +44 (0)1642 653484.
E-mail: keith@kappa-tau.co.uk

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