Organic Process Research & Development **2002**, *6*, 98–108

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during August to November, 2001

Summary

The current selection of 27 patents is taken from the 694 that fit the search criteria. There is a group of five patents that describe that the active ingredient in the well-known drug Prozac actually exists as five polymorphs. The patents provide four methods of producing a specific form including a simple compression method. This patent is interesting because the inventors do not appear to have any commercial affiliation. The use of supercritical water oxidation for treating wastes from nitration process is described, and there is an aromatic nitration process using liquid NO_2/O_2 with a zeolite catalyst in place of nitric and sulphuric acids. Two patents relate to omeprazole, and both provide new methods for the key final oxidation step. One of the patents uses urea/H_2O_2 and claims that this was supposedly first used in oxidations in 1941. A method of obtaining high selectivity in crossed aldol condensations is disclosed, and this involves forming an intermediate enamine from the ketone to prevent self-condensation of the ketone. Two patents from Schering describe an enantioselective alkylation method that achieves high selectivity by stabilisation of the intermediate anion with a chiral amino alcohol. The use of metallocenes or metal alkyls for preparing olefinic epothilones is described, and these compounds are of interest for treating various cancers. There are a number of patents in this selection that may be said to be less than helpful to chemists and could be given as examples of why many chemists ignore patents. Of course, patents are not meant to be helpful to chemists and are sometimes difficult to follow. However, there is certainly a great deal of interesting chemistry in patents, and hopefully this current selection provides readers with some useful ideas. As usual there is no commercial or legal significance in the choice, and no attempt has been made to use correct nomenclature. Several patents describe experiments on kilogram scale so that these are likely to be more commercially advanced.

Patent No. U.S. 6,288,119

Assignee: Ono Pharmaceutical Co. Ltd, Osaka, Japan

Title or Subject: Process for Producing 11,15-O-Dialkyl-prostaglandin E Derivatives

Prostaglandin E_2 (PGE_2) has activity in the treatment of various diseases, and it has been found that the PGE_2 receptors can be divided into four subtypes which have different roles. This patent attempts to find compounds such as **4** which bind only a single receptor. The patent claims a process for the production of **4** by oxidation of **3a** or **3b** using for example Jones reagent. The patent also describes routes (Scheme 1) to the hydroxy compounds **3a** from lactone **1a** and **3b** from **1c**.

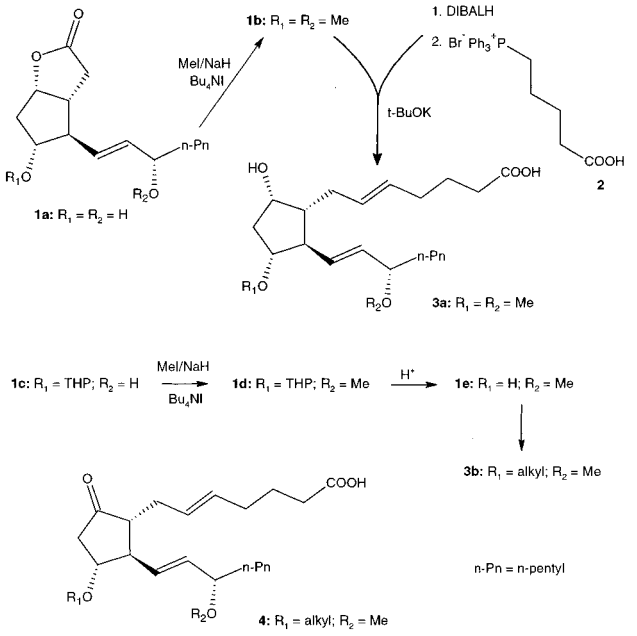
The dihydroxy compound **1a** is converted to the dimethoxy compound **1b** by conventional methods, and this is then treated with DIBALH followed by **2** to give the dimethoxy compound **3a**. Starting from **1c**, in which the ring hydroxy group in **1a** is protected using THP, then it would be possible to produce **1e.** When **1e** is treated with DIBALH and **2**, this would give **3b** in which there are two different alkoxy groups. However, no specific example is given for producing such a compound since all examples show $R_1 = R_2$ and either methoxy or ethoxy.

The patent describes several other compounds similar to **4** in which the *n*-pentyl group is replaced by a range of substituents and ^1H NMR data are provided for these compounds.

Advantages

The process claims that, although the compounds such as **4** were previously known, their use in specifically binding PGE_2 subtypes has not previously been reported.

Scheme 1



Published on Web 02/09/2002
10.1021/op025506b CCC: $22.00

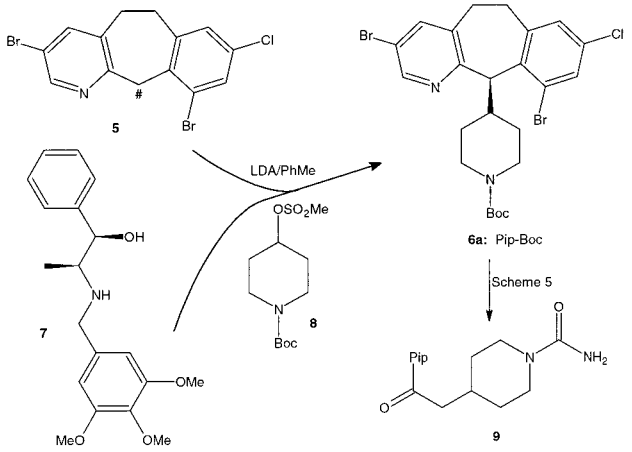
Patent Nos. U.S. 6,288,233 and 6,307,048

Assignee: Schering Corporation, Kenilworth, New Jersey, U.S.A.

Title or Subject: Enantioselective Alkylation of Tricyclic Compounds to Give Farnesyl Protein Transferase (FPT) Inhibitors

These patents describe a method of enantioselective alkylation using a chiral amino alcohol as a chiral ligand to allow the production of high ee of compounds such as **9** that are used to make FTP inhibitors. The patents describe a process for the manufacture of compounds such as **6a** via a route shown in Scheme 2 that starts from compound **5** and the mesylate **8** in the presence of a strong base and a chiral amino alcohol such as **7**. It is suggested that the reaction proceeds by formation of an anion of **5** at the # methylene group which forms a complex with **7** and the base. This complex reacts with **8** by displacing the mesyl group to form **6a**. The route shown introduces Boc as a protecting group which when removed allows compound **9** to be prepared (Scheme 5). The tricyclic compound **5** is the subject of the single claim in the first patent, whereas the second patent covers the route to **6**. One of the variations on the route in Scheme 2 involves the use of quinine as the chiral amino alcohol in place of **7**.

Scheme 2

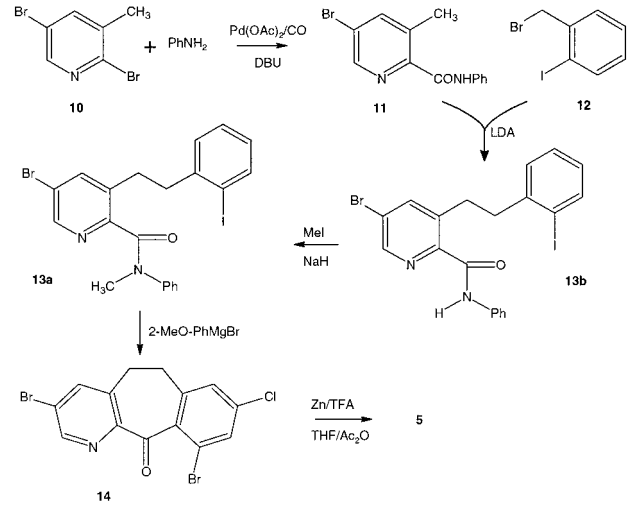


The patents also disclose details for the synthesis of **5** and of **7**. Scheme 3 shows one route to **5** that involves reaction of aniline with the pyridine compound **10** to give the amide **11**. Treatment of **11** with **12** in the presence of LDA gives amide **13b** which is methylated to give **13a**. Cyclisation using a Grignard converts **13a** to ketone **14**, and this is reduced to give **5**.

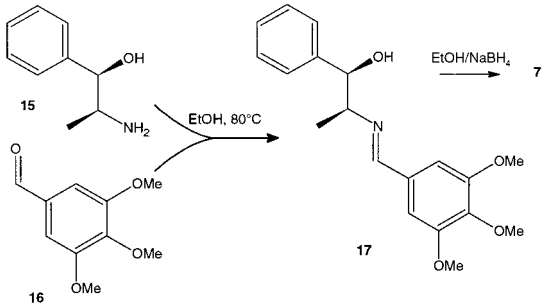
Scheme 4 shows a one-pot two-step route to give **7** by refluxing (1*R*,2*S*)-(−) norephedrine **15** and aldehyde **16** to give **17** which on reduction produces **7**.

The conversion of **6a** to **9** is shown in Scheme 5 and proceeds by hydrolysis to remove the Boc protecting group and give the free base **6b**. In this step the chiral amino alcohol is released and can be recovered. The base **6b** is then treated with *N*-acetyl-L-phenylalanine to give the salt **18**. This is then treated with piperidinyl acid **20** in the presence of HOBT

Scheme 3



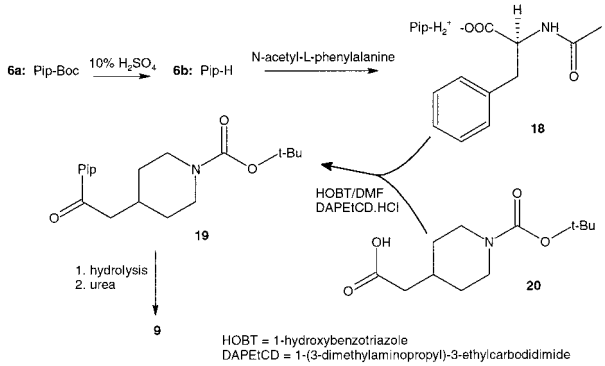
Scheme 4



and DAPEtCD.HCl to give the piperidine derivative **19** which after hydrolysis and reaction with urea gives **9**.

The experimental details for both patents are identical and describe the production of kilogram quantities of materials for several of the steps. There are a considerable number of ^{1}H and ^{13}C NMR spectral details included in these patents, giving the peak assignments.

Scheme 5



Advantages

The key step is the stabilisation of the anion from **5** and enabling enantioselective alkylation without resorting to resolution methods and thus lowering the overall yields. The procedure also allows recovery and reuse of the chiral amino alcohols, thus further improving the process efficiency.

Patent No. U.S. 6,288,241

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

Title or Subject: New Crystalline Polymorphic Form of 1-Methyl-5-p-toluoylpyrrole-2-acetamidoacetic Acid Guaiacyl Ester

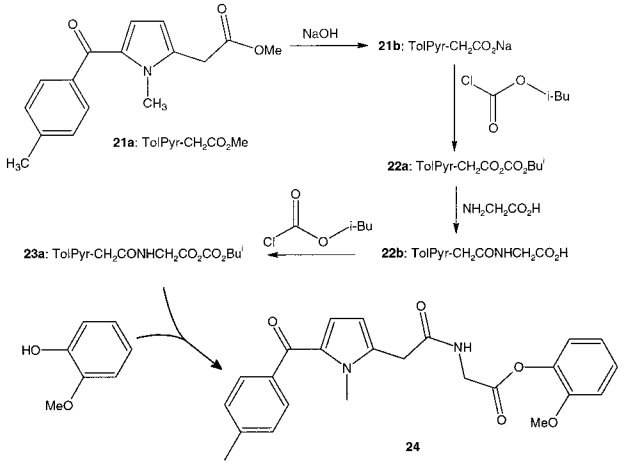
The patent describes the synthesis of a new polymorph (Form 2) of the title compound **24** which has antiinflammatory, analgesic, and antipyretic activity. One form of **24** designated here as Form 1 was disclosed by the same company in a 1986 patent (U.S. 4,578,481), but the current patent claims the earlier synthesis of Form 1 is not suitable for industrial production.

The new route is shown in Scheme 6 and starts by hydrolysis of the methyl ester **21a** to give the sodium form **21b** which when treated with isobutylchloroformate gives the mixed anhydride **22a**. Reaction of **22a** with glycine gives the acetamidoacetic acid **22b** which reacts with isobutylchloroformate to give the anhydride **23a**. The desired compound **24** (Form 2) is produced when **23a** is reacted with guaiacol.

Advantages

The wording in the patent leads one to suspect that the original form of **24** was not stable when it was milled to produce pharmaceutical formulations. This new crystalline form is claimed not to suffer from these drawbacks, and hence the drugs produced are stable.

Scheme 6



Patent No. U.S. 6,288,272

Assignee: Samsung Fine Chemicals Co. Ltd. Daejeon, Korea

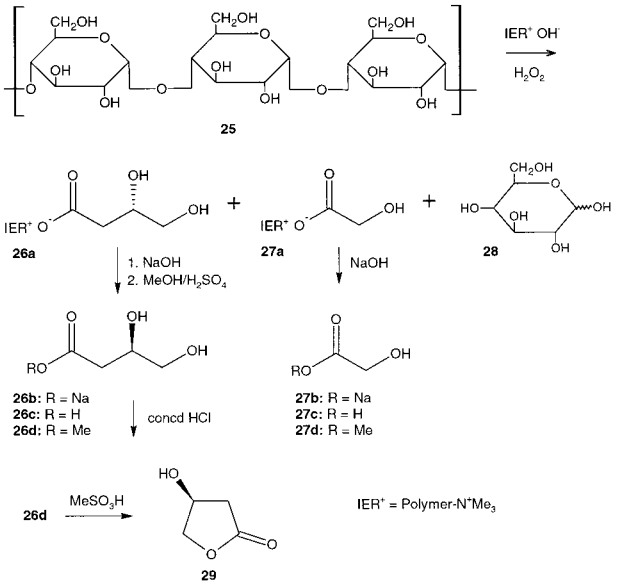
Title or Subject: Continuous Process for Preparation of Optically Pure (S)-3,4-Dihydroxybutyric Acid Derivatives

This patent continues work discussed previously (*Org. Process Res. Dev.* **2001**, *5*, 557) and describes how the process can be carried out continuously. Experimental details describe kilogram quantities of **29** being produced in very high ee (99.9%).

The steps in the process shown in Scheme 7 are (1) preparation of α-(1,4)-linked oligosaccharide **25** from amylopectin using enzymes, (2) oxidation of **25** using H_2O_2 and an anionic ion-exchange resin (IER) to give acid **26c** (R = H), and (3) esterification of **26c** to afford ester **26d** (R = Me).

The enzymes used in step 1 are first α-amylase and then pullulanase. It was found that this combination proved more effective than either enzyme alone. The oxidation reaction is shown in Scheme 7, and this produces the IER-absorbed acids **26a** and **27a** and the glucose **28**. By washing the IER with alkali the Na salts are released, and these can be converted to the acids **26c** and **27c**. The IER is also released and can be reused. Esterification of the acids **26c** and **27c** with methanol gives the esters **26d** and **27d**, and the lactone **29** can be formed by cyclisation of **26d** using $MeSO_3H$. An alternative oxidant to using H_2O_2 is *tert*-butylhydroperoxide.

Scheme 7



Advantages

The normal low reactivity of amylopectin to oxidation is overcome by transforming it to the oligosaccharide. The use of the two enzymes improves the selectivity and rate, and the process can run continuously by regenerating and reusing the IER. In practice this would probably be done by using two columns in which one was regenerating while the other was reacting.

Patent No. U.S. 6,288,289

Assignee: Noram Engineering and Contracting Ltd, Vancouver, Canada

Title or Subject: Integrated Effluent Treatment Process for Nitroaromatic Manufacture

The treatment of waste streams from aromatic nitration processes is a key issue in many chemical plants. This patent describes an integrated process that includes a supercritical water oxidation as the final step in effluent treatment. The integrated process consists of the following steps: (1) Acid washing of crude nitration product to remove sulphuric and nitric acids. (2) Alkaline washing of organic phase from step 1 to remove nitrophenols. (3) Concentration of aqueous phase from step 2. (4) Recovery of water and volatiles from step

3. (5) Oxidation of concentrated phase from step 3 with oxygen in supercritical water.

The alkaline washing in step 2 can be carried out using either NaOH or ammonia. There are significant differences between the two methods that are discussed in some detail in the patent. Ammonia is a weaker base, and thus the extraction of nitrophenols is less effective and requires more alkali to be used. However, the greater vapour pressure of ammonia permits recovery of excess ammonia, and the volatility of ammonia and ammonium salts reduces the fouling of equipment used in the oxidation step. Overall it seems that the use of ammonia is preferred.

The patent provides detailed flow-stream analysis at flows of up to 50 000 kg/h for a nitrobenzene plant containing nitrophenols at 0.2 wt % which presumably is from an actual plant. The data for the supercritical oxidation plant is from a pilot plant using a synthetic effluent containing 1.1−1.4 wt % 2,4-dinitrophenol at flow rates of up to 1.3 L/min. The conditions for the oxidation step are given as 25 Mpa pressure and a temperature of 500−600 °C with residence times from 10 to 70 s. Analysis showed that there was no CO or NOx in the gaseous effluent and no oxygenated organics in the liquid. Hence, the oxidation process appears to have been effective.

Advantages

The patent claims that this process is suitable for plants that do not have biological treatment facilities available. A key feature of the process is that it is integrated with the nitration process so that there are benefits in recycle of water, product, and chemicals; as a result their overall consumption is reduced. A further benefit for large-scale plants is the reduced energy consumption and much lower NOx emissions.

Patent No. U.S. 6,291,726

Assignee: Inha University Foundation, Inchon, Korea

Title or Subject: Nitration of Aromatics Using Nitrogen Dioxide and Oxygen

This patent is also concerned with effluents from nitration processes and addresses the problem by not using the acids that cause the effluent. The process uses liquid nitrogen dioxide and oxygen in the presence of an insoluble inorganic oxide catalyst such as zeolite X or Y. This is somewhat similar to a patent reviewed previously (*Org. Process Res. Dev.* **2000**, *4*, 246) in which nitric acid and a zeolite were used in place of sulphuric acid.

The patent indicates that the oxygen activates the nitrogen dioxide although no experimental evidence is given to support this. The patent refers to other work by the inventors where nitrogen dioxide has been used in the presence of oxidising agents such as ozone or to work elsewhere in which N_2O_5 has been used directly as a nitrating agent.

The process here uses inorganic oxides which have a surface area >100 m^2/g and pore size >0.5 nm, and examples give the operating pressure of 3−8 bar. The procedure is to add liquid nitrogen oxide to the reactor containing the aromatic and examples are given for producing nitrobenzene in yields in excess of 99% (by GC) at a scale of 0.1 mol. The recovery of the product is claimed to be straightforward, involving filtration to recover the catalyst followed by addition of water to remove the nitric acid that is formed. The examples only give analytical yields, and actual details of product recovery are not described.

Advantages

The use of acids does create problems in purification, and effluent treatment is a major problem. This process claims to reduces both of these problems and give high yields of product.

Patent No. U.S. 6,291,731

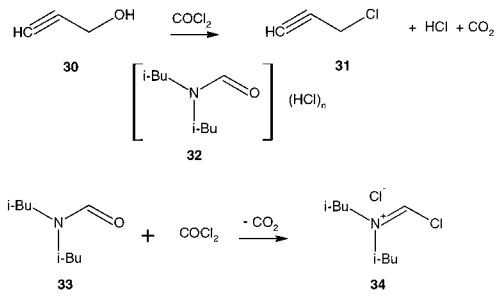
Assignee: BASF Ag, Ludwigshafen, Germany

Title or Subject: Continuous Catalytic Method for Producing Propargyl Chloride

Propargyl chloride **31** is used in the synthesis of pharmaceuticals and crop protection chemicals, and in these applications there is a need for low levels of dichloropropenes which this patent claims to be able to achieve. Alternative methods employing the chlorination of propargyl alcohol **30** with phosgene are said to give high levels of these by-products that are difficult to remove. The process described here also uses phosgene to chlorinate **30**, but the reaction is carried out in the presence of a catalyst. The catalyst is claimed to be the diisobutylformamide HCl adduct **32** (Scheme 8) which is said to be formed during the reaction. There is no evidence given for the presence of **32**, and the use of amides and $COCl_2$ is normally accepted as proceeding via the standard Vilsmeier-type chlorination agent **34** that is easily formed from the amide **33** and $COCl_2$. Similar reactions occur with $POCl_3$ or $SOCl_2$.

This use of the catalyst is claimed to reduce the amounts of dichloropropenes that are formed and hence improve the purification of **31**. The process is continuous with a two-stage reactor system. The first is the main reactor where the excess phosgene that leaves is condensed and returned to the second reactor. Any phosgene leaving the second reactor is removed in a stripper and returned to the inlet of the second reactor.

Scheme 8



Advantages

The reduction in the levels of dichloropropenes that are formed allows the desired product to be obtained in higher purity so that it can be used without further workup.

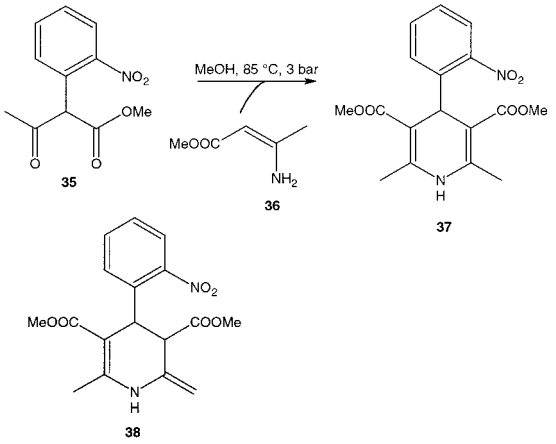
Patent No. U.S. 6,294,673

Assignee: Bayer Ag, Leverkusen, Germany

Title or Subject: Process for Preparing Nifedipine

Nifedipine **37** is used to lower hypertension and also to treat angina. A previously patented method for its synthesis (Scheme 9) involves the condensation of the esters **35** and **36**. The process is carried out by simply refluxing the two materials together in methanol at atmospheric pressure using a carboxylic acid catalyst. After purification a yield of 70−75% of **37** was obtained. The current patent claims that by carrying out this reaction above atmospheric pressure the temperature is increased and there is no need for any catalyst. The increased temperature reduces the time needed for the production of the by-product **38**, and the yield is improved to over 85%. A temperature of 85 °C is used in the example, and the pressure needed to achieve this will be about 3 bar. The alternative methods of improving the yield in the same reaction using carboxylic acids as catalysts are claimed to increase production of **38** and give insufficiently pure **37**. No experimental information is provided as to how **35** is obtained except in a reference to another patent.

Scheme 9



Advantages

The improved yield and purity by simply increasing pressure is a significant improvement. The patent claims that methanol is required as a solvent, and consequently, it would seem that simply changing to a higher-boiling solvent is not all that is needed. Using higher alcohols would probably give transesterification by-products.

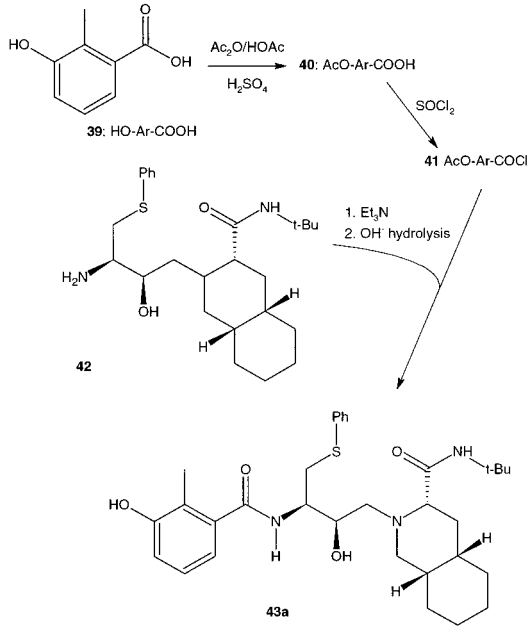
Patent No. U.S. 6,303,786

Assignee: Agouron Pharmaceuticals Inc., La Jolla, California, U.S.A. and Japan Tobacco Inc., Tokyo, Japan

Title or Subject: Processes for Making Nelfinavir Mesylate, A HIV-Protease Inhibitor

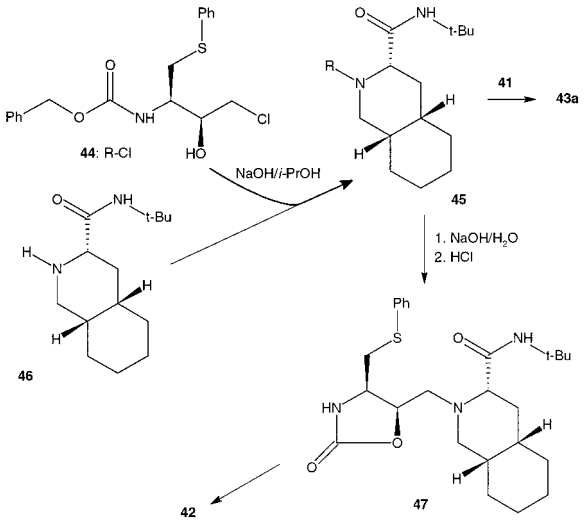
HIV-protease inhibitors block a key enzyme pathway in the action of the virus, and the title compound has been found to be effective for this. The patent describes a process to make the free base nelfinavir **43a** and its mesylate salt **43b.** The route shown in Scheme 9 provides a method for the free base **43a** by coupling the benzoyl chloride **41** with the amine **42** in the presence of Et_3N in THF. The mesylate **43b** can be produced from the base by treatment with $MeSO_3H$ in ethanol to give a slurry of the salt. The slurry is then spray-dried using an atomiser spray drier to produce up to 92% of the salt **43b**. The patent gives details of converting the acid **39** to **41** via the acetyl compound **40** (Scheme 10).

Scheme 10



The patent also gives details for the synthesis of the amine **42**, and this is shown in Scheme 11. This is carried out by reaction between the chloro alcohol **44** and the carboxamide **46** which gives **45** by elimination of HCl. The base hydrolysis of **45** then gives **42** via the oxazolidinone **47** which is not isolated.

Scheme 11



The patent also describes how compound **45** can be converted to free base **43a** by reaction with the benzoyl chloride **41**. The examples give details of producing multi-kilogram quantities, indicating the advanced status of the work.

Advantages

This patent builds on earlier work and provides syntheses of several intermediates and product in high yields.

Patent No. U.S. 6,303,787

Assignee: Natco Pharma Limited, Banjara Hills, India

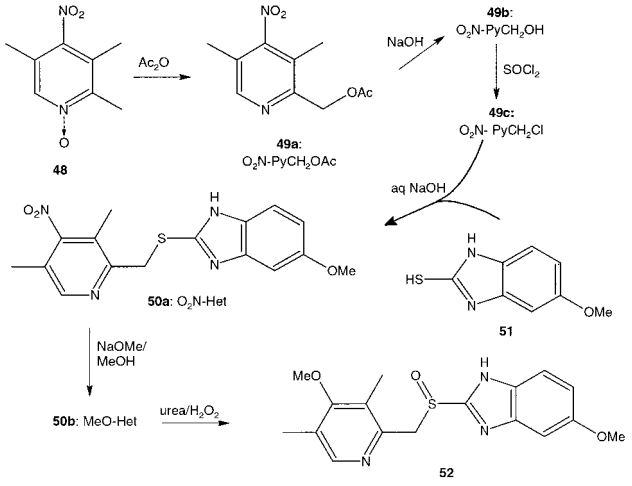
Title or Subject: Process for Preparing Omeprazole via Novel Intermediates

Omeprazole **52** is available as the anti-ulcer drug Losec or Prilosec, and there is continuing interest in this material because of the impending expiry of key patents. See also the next patent.

The route shown in Scheme 12 starts from the nitropyridine *N*-oxide **48** that is converted to the acetate **49a** with Ac_2O. This is hydrolyzed to give **49b** and then chlorinated with $SOCl_2$ to give **49c**. Both **49b** and **49c** are novel compounds. The coupling of **49c** with the benzimidazole **51** gives the nitro compound **50a** which is converted to the methoxy derivative **50b.** Oxidation of **50b** gives omeprazole **52**. Several types of oxidising agents have been used for this key step, and in this process the reagent that is used is a urea/H_2O_2 complex. This has not previously been used although apparently it dates from 1941 (*J. Am. Chem. Soc.* **1941**, *63*, 1507).

Other routes for synthesising **52** involve coupling of **51** with the hydrochloride salt of **49c** (O_2N-$PyCH_2Cl$.HCl). One such route has been reviewed (*Org. Process Res. Dev.* **2001**, *5*, 557), and it is claimed that the use of the salt gives rise to high levels of chlorine-containing impurities such as **49d** Cl−$PyCH_2Cl$.

Scheme 12



Advantages

The new process involves novel intermediates and reaction steps, especially the final step of oxidation using urea/H_2O_2. The avoidance of hydrochloride salts reduces the level of impurities and hence improves overall yield.

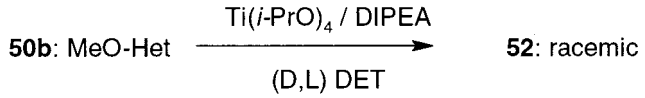
Patent No. U.S. 6,303,788

Assignee: AstraZeneca AB, Sodertalje, Sweden

Title or Subject: Process for Preparing Omeprazole

This patent is from the original developer of the drug and focuses on the key oxidation step to convert **50b** to **52**. The method disclosed here is to use a peroxide such as cumene hydroperoxide in the presence of a titanium alkoxy catalyst and a base such as diisopropylethylamine (DIPEA). The catalyst can be produced from $Ti(OiPr)_4$ and a racemic mixture of diethyl(D,L)tartrate, and using this gives **52** as the racemic mixture. The product is precipitated from the reaction while the catalyst remains in solution, and this is in contrast to the fact that the single enantiomers of **52** are both soluble in the reaction mixture. This enables the omeprazole to be purified without recourse to an extraction step (Scheme 13).

Scheme 13



Advantages

The oxidation step is a key reaction, and much effort has been directed towards improving this reaction. The current process provides a method of obtaining **52** by precipitation which avoids potential over-oxidation that often occurs using other procedures.

Patent No. U.S. 6,303,820

Assignee: Bayer Ag, Leverkusen, Germany

Title or Subject: Preparation of Nitrosobenzenes by Oxidation of Amines

Nitrosobenzenes are useful intermediates frequently prepared by oxidation of amines. By using the alternative approach of stepwise reduction of nitrobenzenes it is difficult to stop the reaction at the intermediate nitrosobenzene since it easily proceeds to give the hydroxylamine. Alternative routes via amine oxidation use toxic reagents such as HMPA and are expensive on a large scale because of safety considerations. This patent describes a catalytic oxidation process using H_2O_2 and sodium molybdate. This is a less problematical reagent and is used in water-immiscible solvents such as toluene or cyclohexane <25 °C. The only example given is for the production of 1 mmol of nitrosobenzene from aniline so that its commercial applicability cannot be inferred.

Advantages

The process is simpler and less expensive than alternatives.

Patent No. U.S. 6,303,823

Assignee: BASF Ag, Ludwigshafen, Germany

Title or Subject: Production of 6-Methylheptan-2-one via a Crossed Aldol Condensation

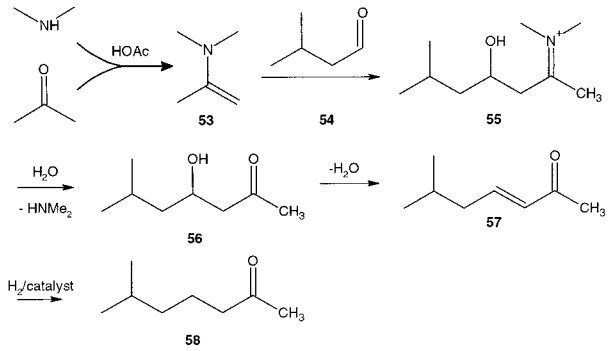
The title compound **58** is an important precursor in the synthesis of vitamin E. The production of **58** described here uses a cross aldol condensation between isovaleraldehyde **54** and acetone that is catalysed by a mixture of dimethylamine and acetic acid. Normally cross aldol reactions are unselective because of self-condensation reactions of the

aldehyde or ketone. These problems are overcome by reacting acetone with dimethylamine to give the enamine **53** and then slowly reacting this with **54** to give the hydroxy enamine salt **55** (Scheme 14). This salt loses dimethylamine on hydrolysis to give the hydroxyketone **56** which loses water to give the enol **57**. This is converted to **58** by conventional catalytic hydrogenation using Pd/C.

This process is similar to the Mannich reaction in which formaldehyde is reacted with amines before reaction with ketones. The current process protects the ketone group from self-condensation and adds the aldehyde to the enamine salt.

Alternative amines are suitable, including pyrrolidine, but acids other than acetic did not seem to be so effective.

Scheme 14



Advantages

This is an effective way of improving the low selectivity normally obtained in cross aldol reactions. It would be interesting to try it with other systems.

Patent No. U.S. 6,307,050

Assignee: R. T. Alamo Venture I LLC, Beverly Hills, California, U.S.A.

Title or Subject: Synthesis of Flosequinan from 4-Fluoroanthranilic Acid

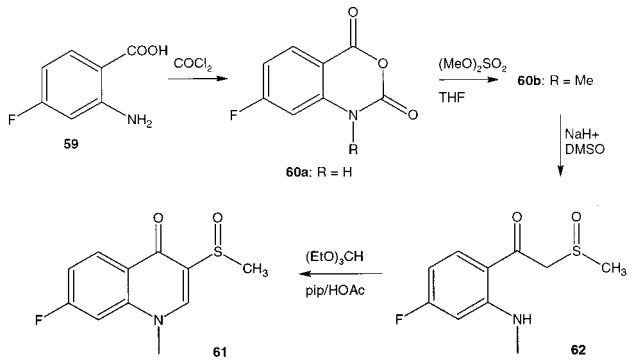
Flosequinan **61** was originally used to treat heart failure, and its synthesis is covered in patents from 1991 (U.S. 5,011,931 and 5,079,264). In 2000 it has been claimed to be potentially useful in treating male erectile dysfunction (U.S. 6,110,489), and hence it could compete with Viagra which, interestingly, also was originally used to treat heart problems.

The process shown in Scheme 15 starts from the fluoroanthranilic acid **59** which with phosgene forms the anhydride **60a**. This is methylated with dimethyl sulphate to give **60b** which with dimsylsodium (NaH + DMSO) gives the intermediate **62**. When treated with $(EtO)_3CH$ in piperidine and acetic acid, **62** cyclises to give flosequinan **61**. Experimental details are given for preparing 500 g of **62**, indicating the advanced stage of development of this process.

Advantages

No details of the previous synthesis are given, but the current route is claimed to be novel. An unusual feature of this patent is that the claims specifically state minimum yields for each of the reaction steps.

Scheme 15



Patent No. U.S. 6,307,066

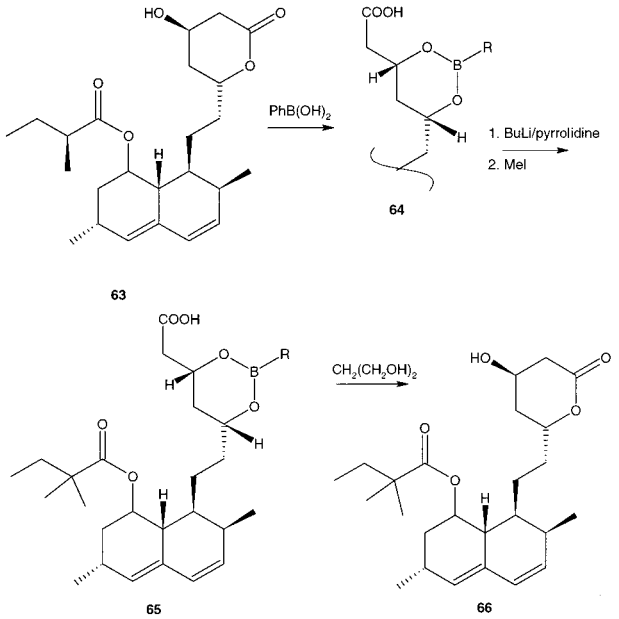
Assignee: Brantford Chemicals Inc., Brantford, Canada

Title or Subject: Process for Producing Simvastatin from Lovastatin

Lovastin **63** is a naturally occurring HMG-CoA reductase inhibitor and can be used to control human serum cholesterol levels. If the C-8 2-methylbutyryloxy group in **63** is replaced by a 2,2-dimethylbutyryloixy group, then simvastatin **66** is obtained, and this is a more potent inhibitor than **63**. Hence, the conversion of **63** to **66** is very desirable. Previous methods of undertaking this conversion are discussed in detail in the patent and are said to require several steps, which involve opening of the lactone ring in **63** or require a synthetic route involving adding and removing protecting groups. The present route achieves the conversion in fewer steps via the introduction of a boronate group in **64** that allows highly selective deprotonation at the α-position in the 2-methylbutyrate side chain.

Scheme 16 outlines the route from **63** to **66**, and the first stage is to produce the boronate ring compound **64**. This is done by treatment of **63** with phenylboronic acid in refluxing toluene. The selective alkylation of the side chain is then carried out using lithium pyrrolidide at −50 °C. Removal of the boronate group is simply done by using a diol such as 1,3-propanediol, and **66** is obtained.

Scheme 16



Advantages

The key boronation step reduces the number of stages previously needed for this reaction and hence improves the reaction efficiency.

Patent No. U.S. 6,307,105

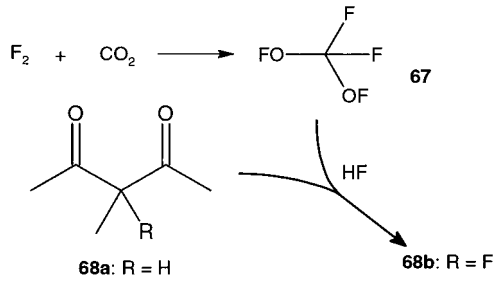
Assignee: Air Products and Chemicals Inc., Allentown, Pennsylvania, U.S.A.

Title or Subject: Preparation of High Purity Fluorinated 1,3-Dicarbonyls Using Bis-fluoroxydifluoromethane

Fluorinated compounds are especially useful chemical intermediates, and there are many methods for their synthesis. This patent is especially aimed at the production of the fluorodiketone **68b**. The novel method of fluorination is the fluoroxymethane **67** which is used in the presence of HF as shown in Scheme 17. **67** is produced in a flow system from F_2 and CO_2 and in the presence of up to 99.5% of an inert gas such as N_2. It is desirable that the F_2 is completely converted to **67**, otherwise fluorination yields are decreased.

Alternative methods for producing **68b** involve direct fluorination with fluorine, but radical reactions are common; hence, yields of by-products are high. It is claimed that impurities formed by radical reactions in this process can be limited to <4% in some cases.

Scheme 17



Advantages

It is claimed that the process provides a significantly higher yield of **68b** for a cost that is comparable to direct fluorination.

Patent Nos. U.S. 6,258,853, 6,310,250, 6,310,251, 6,310,350, and 6,316,672

Inventors: G. W. Stowell and R. R Whittle, Wilmington, North Carolina, U.S.A.

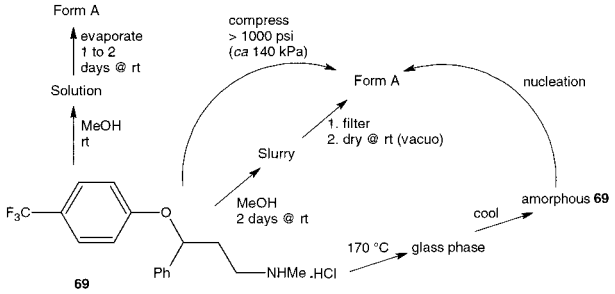
Title or Subject: Form of Fluoxetine Hydrochloride

The active pharmaceutical ingredient (API) of fluoxetine hydrochloride **69** is available as the widely used antidepressant Prozac, and although **69** has a chiral centre, the drug is used as the racemate. **69** has not previously been known to exhibit polymorphism; the API that is sold must be a mixture of amorphous and polymorphic forms. These five patents describe details of the existence, characterisation, and production of a single polymorph, Form A, of the title compound **69**. The patent claims that **69** has not been fully or completely characterised, and an examination, by the inventors, of the X-ray diffraction (XRD) data at the International Center for Diffraction Data (ICDD) revealed that there are inconsistencies in the data for **69**. By using XRD and differential scanning calorimetry (DSC) the existence of three polymorphs (Forms A, B, and C) of **69** was established. The patent provides a method of preparing pure Form A in a robust controllable process.

Four methods are disclosed for preparing Form A from the API, and these are by recrystallisation, a slurry method, compression, and a melting method. Scheme 18 outlines the procedures used to make Form A of **69**. The recrystallisation method is least favoured because it can give rise to two further polymorphs (D and E), while the most preferred method is compression. An amorphous form of **69** was also produced by heating above the melting point. This amorphous form could be converted to Form A by what is described as nucleation. No details are given of this process except that it means disturbing the sample either physically or by air currents, vibration, or with dust particles.

The patents contain XRD patterns and DSC thermograms as well as extensive crystallographic parameters.

Scheme 18



Advantages

The significance of these patents is unclear because the patents covering fluoxetine are almost expired, and the drug has been approved for use in the current form. It is interesting that the inventors have no affiliation shown on the patents although they were recently listed as research students at University of North Carolina at Wilmington.

Patent No. U.S. 6,313,341

Assignee: Fuji Yakuhin Kogyo Kabushiki Kaisha, Toyama, Japan

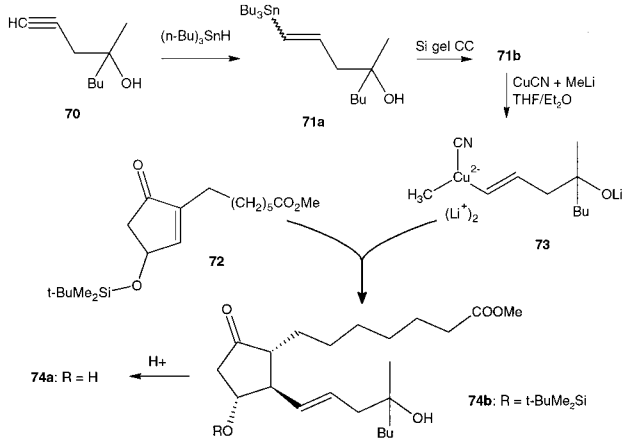
Title or Subject: Process for the Preparation of Prostaglandins

Many natural prostaglandins have broad physiological activity, and their synthesis is a goal of organic chemists. Such compounds have an (*E*) configuration of the double bond at the 13,14 position, and an (*E*)-vinylstannane is often used to introduce this group. However, the pure (*E*)-vinylstannane is not always available, and separation of the resulting (*E*) and (*Z*) isomers of the prostaglandin is not easy. This patent describes a method of synthesising such compounds by using the pure (*E*) isomer of the vinylstannane **71b** that is obtained by separation of the (*E*) and (*Z*) isomers **71a** using silica gel column chromatography (Si gel CC). This separation is achieved because the vinylstannane has a free hydroxy group that allows a simple chromatographic method to be used.

Scheme 19 shows the route from the hydroxy-1-alkyne **70** that is converted to the stannane **71a** with *n*-Bu_3SnH. The

pure (*E*) isomer **71b** was then treated with a 1:2 Cu:Li complex made from CuCN and MeLi to give the vinylcopper **73** complex. The cyclopentenone ester **72** was then reacted with **73** in a 1,4 conjugate addition, and the protected prostaglandin **74b** was obtained which on hydrolysis gave the desired **74a** in 84% yield. Although the patent does not discuss the synthesis of the protected ester **72**, this is presumably by standard procedures.

Scheme 19



Advantages

The key point of this patent is that there is no need to protect the OH group in **70** when forming the vinylstannane **71a**. The presence of the hydroxy group enables the (*E*) and (*Z*) isomers to be easily separated. High yields of the desired (*E*) isomer are obtained and used in the synthesis of the prostaglandins.

Patent No. U.S. 6,316,632

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

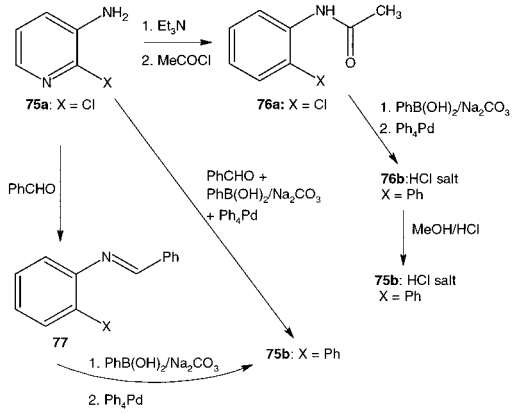
Title or Subject: Process for Preparing 2-Phenyl-3-aminopyridines

The title compound **75b** is useful in preparing compounds that are substance P antagonists. Substance P is a tachykinin that is involved in pain transmission and central nervous system disorders. Hence, there is interest in preparing **75b** and its derivatives.

Three routes to **75b** or its hydrochloride salt are described in the patent and start from the chloropyridine **75a** (Scheme 20). The route to the hydrochloride of **75b** proceeds via the chloroacetamide **76a**. This is obtained by acetylation of **75a**, and **76a** is converted to the hydrochloride salt of **76b** by a Suziki coupling reaction with phenylboronic acid using Ph_4Pd as catalyst. The amine salt of **75b** is then obtained by acid hydrolysis.

The free amine can be obtained by two routes also shown in Scheme 20. They also involve the Suziki coupling reaction which can be carried out stepwise or in one stage. The first method proceeds via the benzylidene compound **77** that is formed from **75a** and benzaldehyde. **77** then undergoes the Suziki coupling reaction and produces the free amine **75b**. The main finding of the patent is that if the chloropyridine **75a** is treated with both benzaldehyde and the Suzuki reagents, then the amine **75b** is formed directly. An example is given in which the Pd catalyst is prepared in situ and other reagents are simply added consecutively without isolation of any intermediates.

Scheme 20



Advantages

The key feature is the direct conversion of the chloropyridine to the phenyl derivative. This makes the process more suitable for industrial production, whereas previous routes to **75b** are said to require the use of very air-sensitive compounds and to give low yields.

Patent No. U.S. 6,320,045

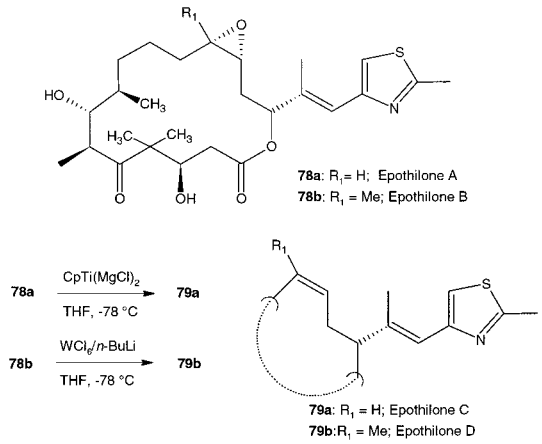
Assignee: Bristol-Myers Squibb Company, Princeton, New Jersey, U.S.A.

Title or Subject: Process for Reduction of Oxiranyl Epothilones to Olefinic Epothilones

Epothilones A **78a** and epothilone B **78b** are naturally occurring macrolides that are produced by the myxobacterium *Sorangium cellulosum*. They both have antitumor activity and are being examined for their use in treating several forms of cancer. This patent describes a method to convert **78a** and **78b** to other epothilones that may also have antitumor activity.

Both **78a** and **78b** contain an epoxide ring, and this is reduced to an olefinic group by using metal alkyls or metallocene reagents. Scheme 21 shows the different routes that are used to produce epothilone C **79a** from **78a** using $CpTi(MgCl)_2$ and epothilone D **79b** from **78b** using WCl_6/*n*-BuLi.

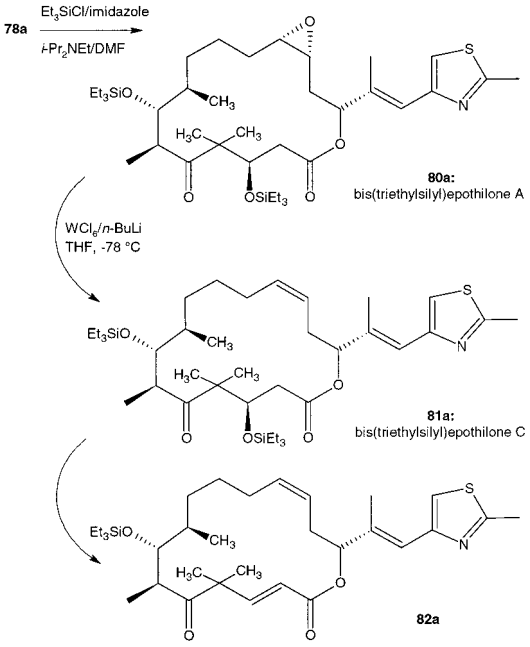
Scheme 21



The patent also describes how **78a** can be converted to the diene **82a** by protecting the hydroxy groups with Et_3Si groups (Scheme 22). The first step is to produce the triethylsily epothilone A **80a**, and this is reduced to the olefinic compound **81a** using WCl_6/*n*-BuLi. Details of the next two stages to convert **81a** to **82a** are not given, but the procedure used is based on work from an earlier patent (WO 97/19086).

The patent also describes compounds in which the O atom in the 16-membered ring is replaced by NH and contains over 40 references to other work epothilones.

Scheme 22



Advantages

There are no specific advantages claimed for this patent over other work although it does claim that the compounds can be used to treat a whole range of diseases from various cancers to Alzheimer's disease.

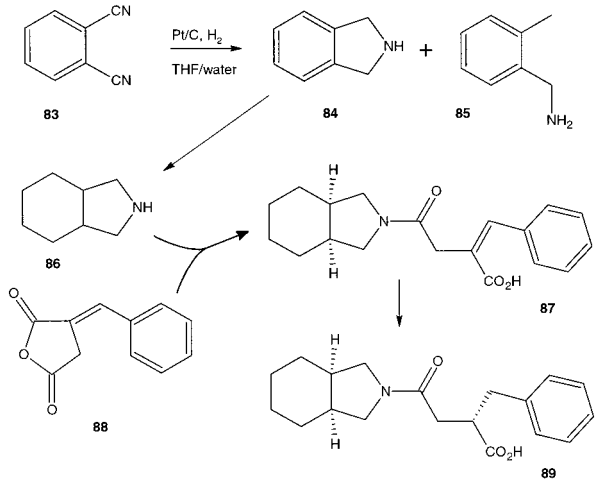
Patent No. U.S. 6,320,058

Assignee: Adir at Compagnie, Couirbevoie, France

Title or Subject: Process for Preparation of Isoindoline

Isoindoline **84** is widely used in the synthesis of pharmaceuticals, and this patent specifically mentions the acid **89**. It is claimed that previous routes to **84** give yields of below 50% and are not attractive on an industrial scale. A particular aim stated in the patent is to avoid using ammonia. The route shown in Scheme 23 involves catalytic hydrogenation of phthalonitrile **83**. The key aspect of the patent is that the only catalyst that gave high conversion and selectivity in a reasonable time was Pt/C. It was also found that this was only suitable in the solvents THF/water or dimethoxymethane. In the former solvent mixture the water content was below 5%, and in the example no water was added. Using this catalyst system a 75% yield of 89% pure **84** was obtained. The main by-product was **85**, and the patent claims to limit the amount in **84** to below 0.2%. A drawback of this process is that a pressure of 150−180 bar is required, and very high catalyst levels are needed. The example indicates that 20% of the weight of **83** is needed. There is no information as to how many times the catalyst can be used, and hence the catalyst cost could be very high.

Scheme 23



Although there are no experimental details for preparing **89** from **84**, the route is said to involve the enantioselective reduction of **84** to give *cis*-perhydroisoindole **86** which is then reacted with the anhydride **87** to give the unsaturated acid **88**. Asymmetric hydrogenation of **88** gives **89**, but again no details of this step are provided.

Advantages

The process is a single-step method and gives a much higher yield than previously. In addition the amount of the benzylamine by-product is limited to low levels.

Patent No. U.S. 6,320,083

Assignee: ExxonMobil Chemical Co., Houston, Texas, U.S.A

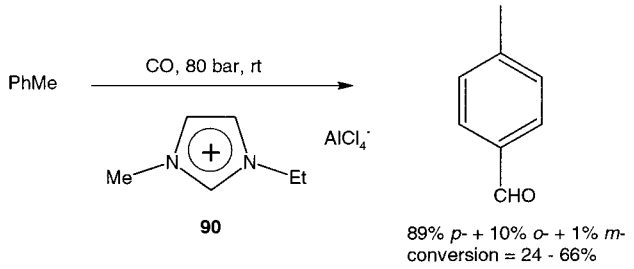
Title or Subject: Process for Making Aromatic Aldehydes Using Ionic Liquids

The use of ionic liquids as catalysts has been receiving a great deal of attention over the past few years. In particular such materials have been used as catalysts in Friedel−Crafts reactions, and they have high activity and give less waste disposal problems.

This patent describes a method of producing aromatic aldehydes by carbonylation of alkyl aromatics in an ionic liquid consisting of alkylimidazolium ions **90** and $AlCl_4^-$ ions. Scheme 24 shows the route from toluene to tolualdehydes which gives mainly the *p*-tolualdehyde at various toluene conversions.

The acid strength of the ionic liquids employed here is determined by its concentration of $AlCl_4^-$ ions. As this increases, so then does the acid strength. At the higher levels the anions are likely to be polynuclear species such as $Al_2Cl_7^-$ and $Al_3Cl_{10}^-$.

Scheme 24



The ionic species **90** can be obtained by boiling methylimidazole with chloroethane. After completion of the reaction the aldehyde can be recovered by volatilisation using a wiped film evaporator leaving the ionic liquid behind.

The patent goes on to discuss the use of the aldehydes to prepare acids or anhydrides by oxidation. Specific claims mention terephthalic acid from *p*-tolualdehyde and pyromellitic dianhydride from 2,4,5-trimethylbenzene. Both of these oxidation products are widely used in producing polyesters.

Advantages

The process provides good conversion and high selectivity while at the same time allowing relatively easy separation of products from the catalysts which do not cause disposal difficulties. Conventional methods use HCl and $AlCl_3$ or CuCl which both give handling and effluent disposal problems.

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