Organic Process Research & Development **2006**, *10,* 703–711

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during March and April 2006

Summary

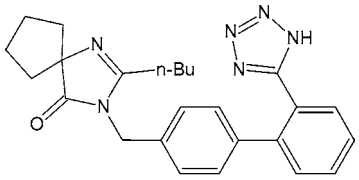
The current review summarises 21 patents from an initial list of 253 that fitted the search criteria. A variety of subjects is included, and it is hoped there are some of interest to readers. Novel polymorphs of existing drugs continue to be discovered, and there are several examples of these. For example a novel crystalline form of the antihypertensive drug irbesartan is described. Another patent describes a novel synthesis of this drug using a novel intermediate. A new crystalline form of a carbapenem antibiotic is reported as are two new forms of the trometamol salt of (*R*)-thioctic acid; a cytoprotective reagent. A second patent on carbapenems describes a novel synthetic route. There are two patents on the subject of factor Xa inhibitors, and one discloses new crystalline forms. The importance of mixing is shown in a method for the nitration of aniline derivatives. Di- and tri-nitro products are frequently found in these reactions, and by changing the method of mixing the process selectivity was improved. Process development chemists often ignore simple process changes that can give greater improvements than many realise. While continuously operating processes are not compatible with pharmaceutical syntheses they are compatible where reactive intermediates are used. As an example a method for producing peracetic acid is described that gives high concentrations of the acid free from byproducts. This is achieved by preparing the material in a small continuous reactor and using it as it is formed. In another continuous process the methylation of N-heterocycles using dimethyl carbonate is described in place of Me_2SO_4 and hence is less of a safety hazard. The development of environmentally friendly processes remains a major goal, and the elimination of organic solvents is desirable. Hence any process that can do this is welcome. One patent discloses a process using water as solvent for the production of cilostazol an alternative drug to Viagra. A novel process for preparing the anticonvulsant carbamazepine is described using a method that the prior art would appear to predict would not work. This sort of finding is extremely valuable in claiming novelty in patents. A multistep high yield process for preparing substituted phenylureas is described, and unusually, details of experiments are given which gave poor results. A patent covering the production of quinazolines for treating benign prostatic hyperplasia is reviewed, and this has extensive details of several intermediate steps. There is no legal or commercial significance for choosing any of the patents in this review, and readers should be aware that the advantages of each patent listed in the review are those claimed in the patent unless this reviewer has personal knowledge of the subject. The reader should also be aware that comparison with other patents or work is sometimes selective so as to enhance the claimed improvements made in a patent. A small number of patents report experimental details on multi-kilogram quantities, and while this does not mean the process is commercial, it does mean that the work has been scaled-up from the laboratory.

Patent No. U.S. 7,008,959

Assignee: Sanofi-Aventis, Paris, France

Title or Subject: Processes for the Preparation of a Novel Form of Irbesartan and Pharmaceutical Compositions Containing It

Irbesartan **1** is an antihypertensive that is used in treating a variety of cardiovascular diseases. This is the first of two patents on this compound and covers a novel crystalline form of **1**. There are two crystalline forms of **1** known, and this patent describes an additional crystal habit of the A form. Form A is needlelike and difficult to filter, whereas the new form is described as bricklike with an aspect ratio of width to length of between 1:1 and 1:5. The process for producing this new habit involves subjecting a suspension of the A form of **1** to ultrasound, a heating and cooling procedure, and high shear mixing. The X-ray diffraction (XRD) and solubility data are given for the new form.



1

Advantages

The new crystal habit is easier to filter and has better flow characteristics, so formulations of **1** can be more easily prepared.

Patent No. U.S. 7,019,148

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

Title or Subject: Synthesis of Irbesartan

The second patent covering **1** describes a new synthetic route using a novel intermediate in a Suzuki reaction. The original route used to prepare **1** is said to involve the use of hazardous reagents such as Bu_3SnN_3 and requires long reaction times. The patent discloses the route shown in Scheme 1, and this starts by forming **4** in a Suzuki reaction from **2** and **3** in the presence of $Pd(OAc)_2$. The reaction is carried out in a mixed solvent system with DME and THF being preferred. The trityl group in **4** is then removed by

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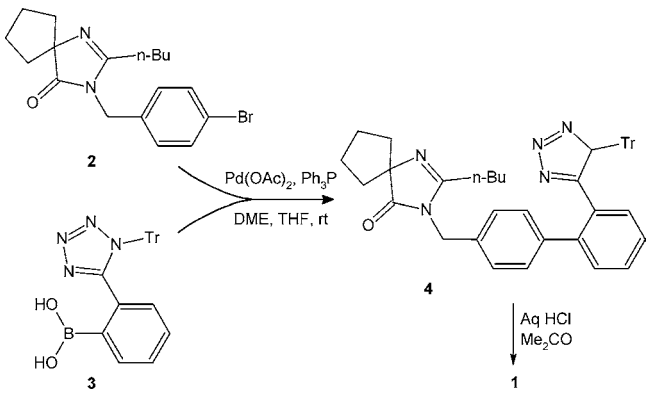
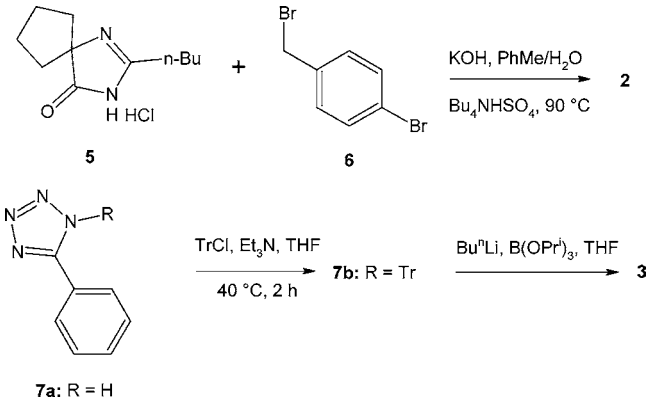
treatment with acidified Me_2CO followed by neutralisation and cooling to obtain crystals of **1**.

Scheme 1



The patent also describes the methods used to prepare the compounds **2** and **3**, and these are summarised in Scheme 2. Compound **2** is obtained in 94% yield from the reaction of the salt **5** with **6** in the presence of a phase transfer catalyst. Compound **3** is formed in a two-step procedure that gives a 94% yield of **7b** from **7a** and TrCl. The phenylboronic acid **3** is then prepared in 92% yield from **7b** and $B(OPr^i)_3$.

Scheme 2



Advantages

The process provides a novel route to **1** and avoids using hazardous azides.

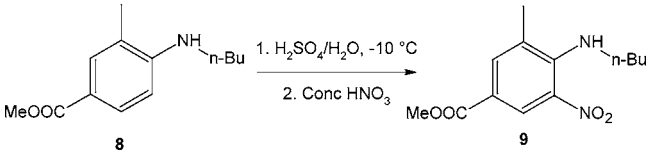
Patent No. U.S. 7,012,151

Assignee: Boehringer Ingelheim Pharma KG, Ingelheim, Germany

Title or Subject: Method for Nitrating Aniline Derivatives

This patent describes a process for producing **9**, an intermediate in the preparation of pharmaceutically active benzimidazole derivatives. Nitration reactions can frequently produce di- and tri-nitro derivatives that can give rise to safety problems on a commercial scale. The production of **9** is by a regioselective nitration of **8**, and the procedure is to dissolve **8** in a mixture of HNO_3, H_2SO_4, and water and then add HNO_3 (Scheme 3). It is essential that the temperature is kept below −5 °C, and during the subsequent workup the temperature is maintained below 40 °C. These appear to be the key aspects of the process.

Scheme 3



The patent includes comparative experiments in using alternative mixing methods and temperatures. These gave lower yields of the desired isomers, and one experiment was carried out producing over 150 kg of **9**.

Advantages

The process provides high selectivity to the desired mononitro product.

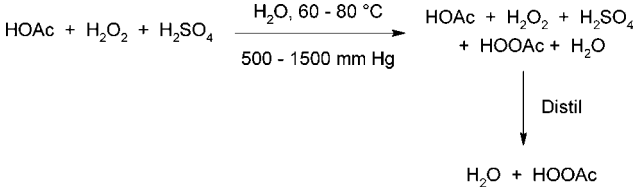
Patent No. U.S. 7,012,154

Assignee: Peragen Systens LLC, Eagan, Minnesota, U.S.A.

Title or Subject: Continuous Process for On-Site and On-Demand Production of Aqueous Peracetic Acid

HOOAc is a versatile reagent that is used in chemical oxidation reactions as well as in bleaching, sterilising, and disinfection processes. It can be produced by oxidation of HOAc using H_2O_2, and the material is available as an aqueous solution containing an equilibrium mixture of reactants and product. However, since the solutions do contain unreacted raw materials, this does limit its use. There are methods available for on-site production of HOOAc, but these are claimed to have significant limitations for small and medium scale use. A further problem is that transport by road of large quantities of solutions of HOOAc is restricted. This process allows the production of HOOAc at the required downstream demand rate in a tubular reactor coupled to a distillation column. The process chemistry of producing HOOAc is shown in Scheme 4 and is based on the usual procedure of oxidation of HOAc using H_2O_2. The reaction is carried out in water, and the mixture is distilled to recover an overhead stream of water and HOOAc. This may be used as a vapour or can be condensed and used as a liquid in downstream operations.

Scheme 4



Process flow diagrams are shown, and the patent also describes a method of forming HOOAc in a continuous pot system. This is said to be suitable for smaller production rates. Several end-use applications are described including chemical reactions such as epoxidations and hydroxylatons plus operations such as sterilisation, waste treatment, deinking, and bleaching of pulp, paper, and textiles.

Advantages

This process potentially enables the wider use of a versatile reagent in large and small-scale applications.

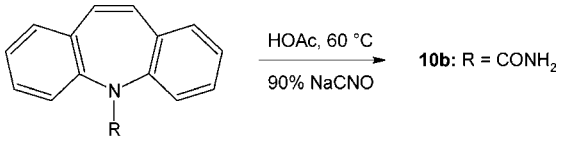
Patent No. U.S. 7,015,322

Assignee: Degussa AG, Hanau-Wolfgang, Germany

Title or Subject: Process for Producing Carbamazepine

Carbamazepine **10b** is used as an anticonvulsant and an analgesic. Several processes for its production are known, but some involve using toxic reagents such as $COCl_2$ or HCN. The patent reports the unexpected finding that iminostilbene **10a** reacts with alkali cyanates and acetic acid to give **10b** in high yield. The reaction is shown in Scheme 5 and is carried out by adding portions of NaCNO to a suspension of **10a** in HOAc over a period of up to 3 h. During the reaction the **10a** almost completely dissolves in the mixture before the product **10b** crystallises out. After the addition the excess HOAc is removed by distillation, and the residue is washed with water to remove the NaOAc. After recrystallisation from PhMe the overall yield of **10b** can be almost 99%. The reaction mixture may also contain EtOH or water, and KNCO is also suitable.

Scheme 5



The patent claims that the reaction is surprising because it is known that primary aromatic amines can be converted to ureas using alkali cyanates in aqueous HOAc but secondary amines such as **10a** do not react. **10a** is much less basic than aromatic primary amines, and it is also less soluble in HOAc. The solubility of **10a** is even less when water or alcohols are in the reaction mixture. Hence it is suggested in the patent that this would lead to the conclusion that traces of water would detrimentally affect the reaction of **10a** with cyanates. Thus on the basis of previous work the new finding could not have been predicted.

Advantages

The simple finding provides a simple method of producing the desired product in high yield.

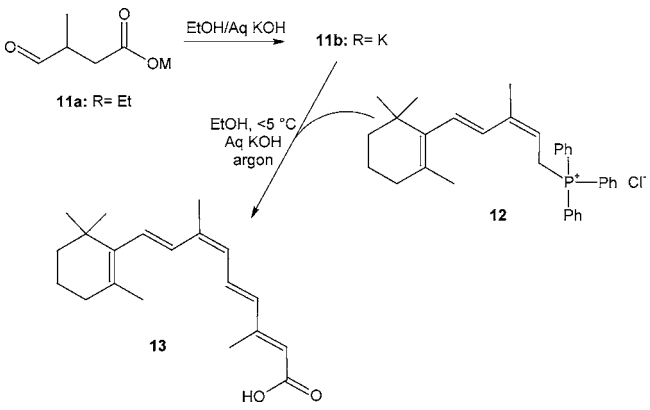
Patent No. U.S. 7,015,353

Assignee: Hoffmann-La Roche Inc., Nutley, New Jersey, U.S.A.

Title or Subject: Process for the Production of 9-(Z)-Retinoic Acid

The title compound **13** is useful in treating a range of dermatological diseases. One method of preparing **13** from **12** is said to produce significant amounts of isomers and hence gives low yields. This patent discloses an efficient method of preparing **12** by the reaction of the salt **11b** with **13**. The process is summarised in Scheme 6 and in fact starts from a mixture of the *E*- and *Z*-isomers of **12** that is obtained from β-carotene. The *Z*-isomer of **13** is obtained in 93.6% purity from the mixture by extraction into CH_2Cl_2, solvent exchange with EtOAc or *n*-BuOH, and then crystallisation. Although the production of **13** gives high yields of the *Z*-isomer, the yield of the *Z* form from the isomeric mixture **12** is only 31%.

Scheme 6



It is stated in the patent that it is crucial that the reaction is carried out under argon and in the absence of light and oxygen. A critical feature in achieving high selectivity to **13** in this process is the use of the purified *Z*-isomer.

Advantages

Although the process gives high yield of the desired isomer by use of the purified Z-isomer, the overall yield from β-carotene may be low.

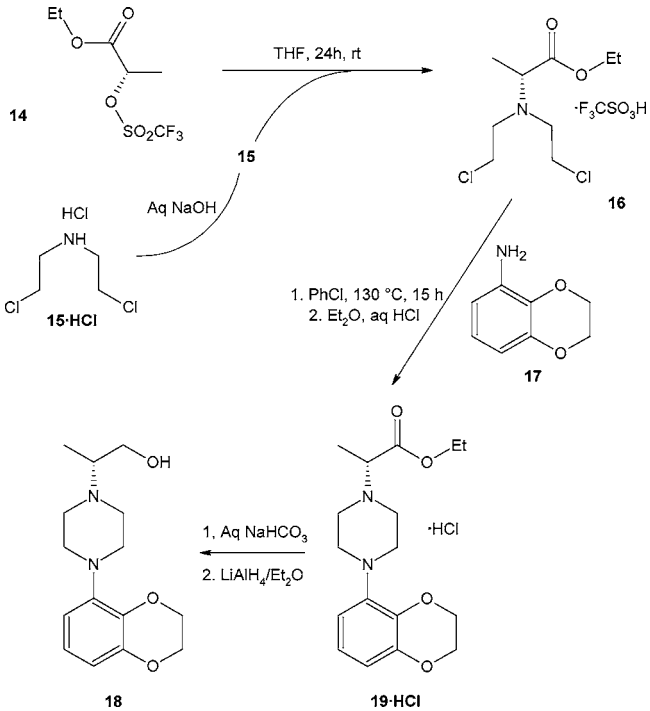
Patent No. U.S. 7,019,137

Assignee: Wyeth, Madison, New Jersey, U.S.A.

Title or Subject: Process for Making Chiral 1,4-Disubstituted Piperazines

Piperazines such as **18** are used in the treatment of a variety of central nervous system disorders. Some of the methods used to prepare these compounds are summarised. One shortcoming in many of these is that specific replacement of the OH group in **18** typically results in racemisation. This patent claims to provide a method for preparing specific enantiomers as intermediates in the formation of the piperazines. Scheme 7 shows a route to the salt **18** via the HCl

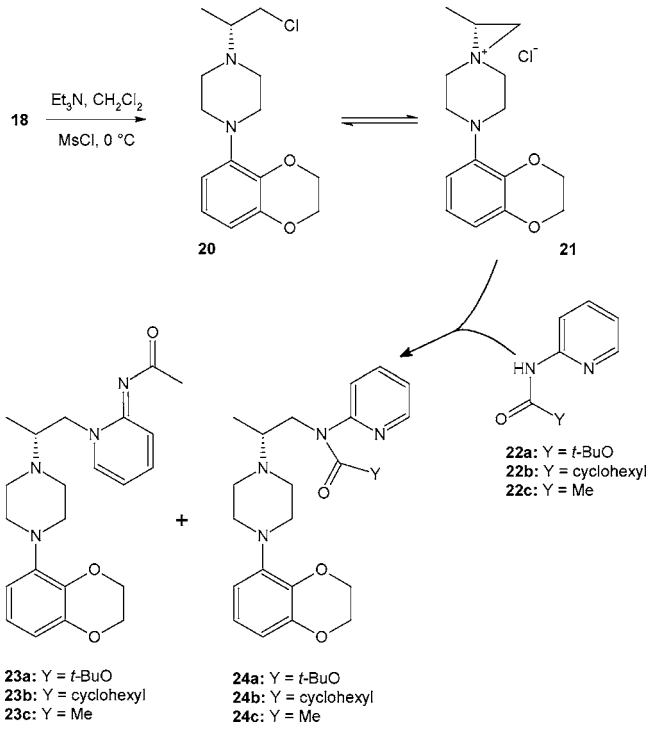
Scheme 7



salt **19**·HCl, and this starts from the commercially available compound **14**. This is treated with the free base **15** to give the salt **16**. In the next stage the piperazine ring is formed and **19**·HCl is produced by alkylation of **17** with **16** in PhCl. This reaction can be carried out without isolation of **16**. The alcohol **18** is then produced by reduction using $LiAlH_4$.

18 can be converted to a range of derivatives, and when it is treated with Et_3N and MsCl the resulting piperazine **20** may exist in equilibrium with the salt **21** as shown in Scheme 8. This salt can be reacted with the aminopyridines **22** to give **24**, but **23** is formed as an undesired byproduct. The amount of **23** is significantly reduced if Y in **22** is *t*-BuO. It is claimed that the BOC group in **24a** can be easily removed and replaced, so **24a** can be used to prepare other derivatives in higher yield. However, there are no experimental details of these reactions to substantiate this, and they may in fact be the subject of other patents.

Scheme 8



Advantages

The process results in a more simple sequence of reactions to obtain the chiral piperazines.

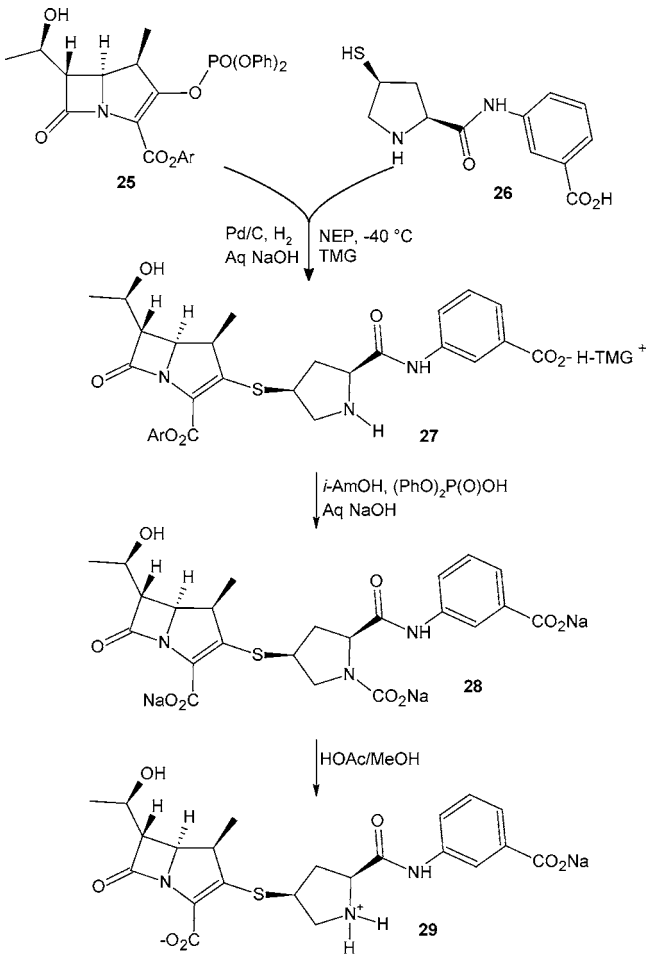
Patent No. U.S. 7,022,841

Assignee: Merck & Co. Inc., Rahway, New Jersey, U.S.A.

Title or Subject: Process for Making Carbapenem Compounds

Carbapenems are a class of antibiotics with activity against a wide range of bacteria. This is the first of two patents that describe new methods for producing such compounds. This patent mentions that there are significant problems in reaching the low levels of residual organic solvents in such compounds because they are thermally unstable. The patent therefore focuses on this aspect of the manufacture of **29** by the route shown in Scheme 9. This begins with the reaction of the phosphate **25** and the thiol **26** in the presence of Pd/C. The reaction initially takes place under H_2, but since it does not seem to be a reduction the reason is not clear. The product is converted to the tetramethylguanidine salt **27** and then via a series of pH adjustments to **29** via **28**. There is a complex workup procedure in which three crystalline forms of **29** are recovered by using different solvents for recrystallisation. These forms are termed A, B, and C with the latter being a novel form. The process for removing residual solvents involves washing with MeOAc containing water and then using a vacuum or an inert gas below 7 °C. XRD data are given for all three forms of **29**.

Scheme 9



Ar = p-nitrobenzyl; NEP = N-ethylpyrrolidinone;
TMG = 1,1,3,3-tetramethylguanidine

Advantages

The process provides a novel form of the carbapenem and enables the residual solvent content to be minimised without thermally degrading the product.

Patent No. U.S. 7,034,150

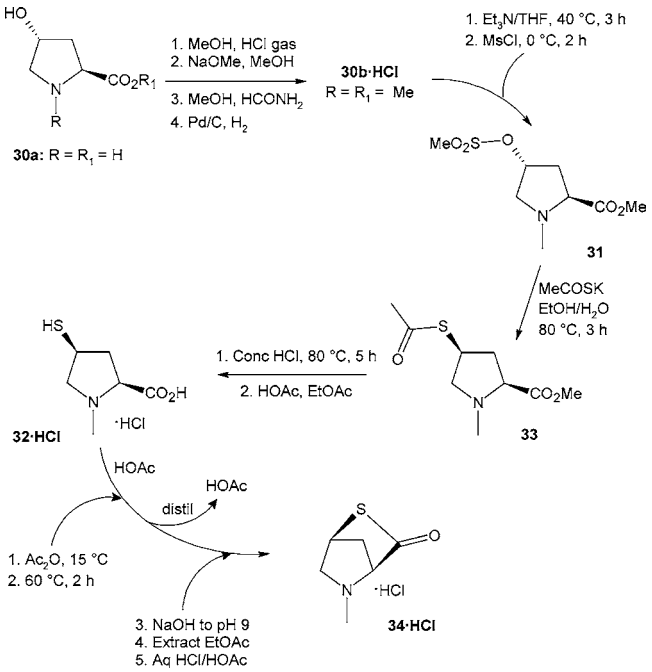
Assignee: Sankyo Company, Limited, Tokyo, Japan

Title or Subject: Processes for the Preparation of Carbapenem-Type Antibacterial Agents

The second patent on this topic starts from the acid **30a**, and the HCl salt of **34** is prepared by the route shown in

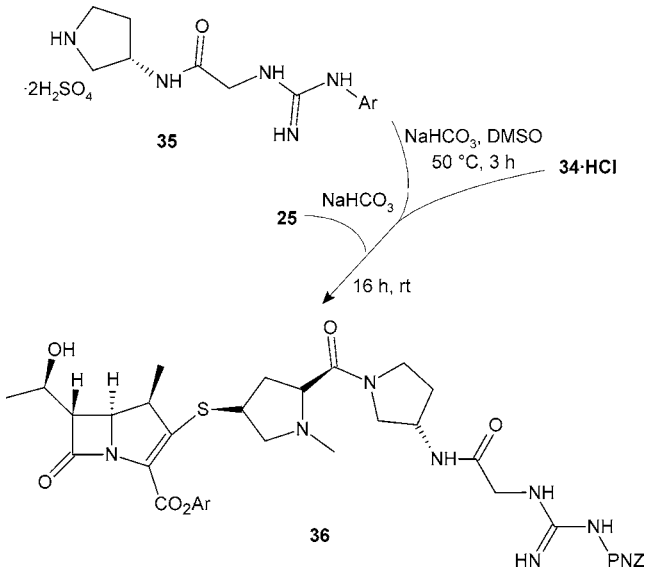
Scheme 10. The process begins with the esterification of **30a** followed by an unusual alkylation using $HCONH_2$ and catalytic reduction to give **30b** as the HCl salt. Sulphonylation of the OH in **30b** produces **31**, and this is converted to **33** using MeCOSK which when hydrolyzed in HCl forms the salt **32**·HCl. The final stage is the formation of the salt **34**·HCl via an intramolecular cyclisation using Ac_2O in HOAc.

Scheme 10



The salt **34**·HCl is then used to prepare the carbapenem **36** by the method shown in Scheme 11. This begins with a mixture of **34**·HCl and **35** in a basic solution to which are added **25** and $NaHCO_3$. The product **36** is collected as a precipitate after adding water in a yield of 85%.

Scheme 11



Advantages

The process is claimed to be suitable for large-scale production because it is cheap and gives high purity products. The production of **34** is also claimed to be economical and safe on a large-scale process.

Patent No. U.S. 7,022,845

Assignee: Group SNPE, France

Title or Subject: Monomethylation of Nitrogenous Heterocycles

This patent describes a method of methylating a range of N-heterocyclic compounds using dimethyl carbonate (DMC). A common methylating agent for these N-heterocycles is Me_2SO_4, but this is highly toxic and hence an alternative reagent has been sought. DMC has been used for some methylation reactions but these are said to be limited to reactants that boil at around 250 °C. The patent is aimed at those heterocyclic compounds that contain an NH group. The process is applied to the synthesis of the following compounds with the yield of product shown: 1-methylimidazole (98%), *N*-methylmorpholine (43%), *N*-methylpiperazine (29%), *N*-methylpyrazole (70%), 1,3,5-dimethylpyrazole (57%) from 3,5dimethylpyrazole. The key to the process is the continuous addition of DMC and simultaneous removal of MeOH as it is formed. In one example where it was not removed, the yield of *N*-methylpyrazole was only 14%. The procedure is carried out at temperatures of at least 100 °C and as high as 200 °C depending upon the boiling point of the feedstock.

Advantages

The process avoids the use of toxic Me_2SO_4 but does need to be run continuously to gain the advantage claimed.

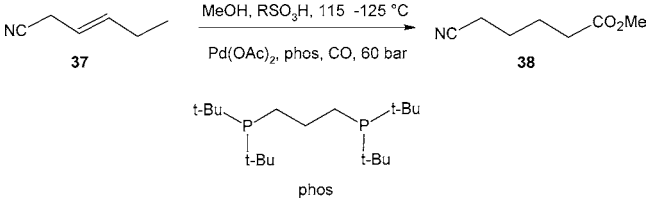
Patent No. U.S. 7,026,473

Assignee: Shell Oil Company, Houston, Texas, U.S.A.

Title or Subject: Process for the Carbonylation of Pentenenitrile

The patent is concerned with the production of the ester **38** by the carbonylation of **37**. **38** or its acid can be used to prepare adipic acid or ϵ-caprolactam, and these are feedstocks for polyamides as well as being synthetically useful materials. The process described in the patent is a homogeneous Pd catalysed reaction shown in Scheme 12. A variety of diphosphines is used, but preferably it should be one with at least three C atoms between the two P atoms. The reaction is carried out in MeOH containing MsOH or *t*-$BuSO_3H$. The highest conversion of **37** to **38** is 98% with 98% selectivity and 93% linearity when *t*-$BuSO_3H$ is used. The acid used is preferably one having a pK_a of <3 in aqueous solution at 18 °C.

Scheme 12



Other work on carbonylation of **37** using diphosphines is said to give very poor results in the production of **38**. It is therefore claimed that the current work is unexpected, and if this is the case then this strengthens the inventive aspect of the patent.

Advantages

The process gives high yields of the desired product under relatively low temperatures.

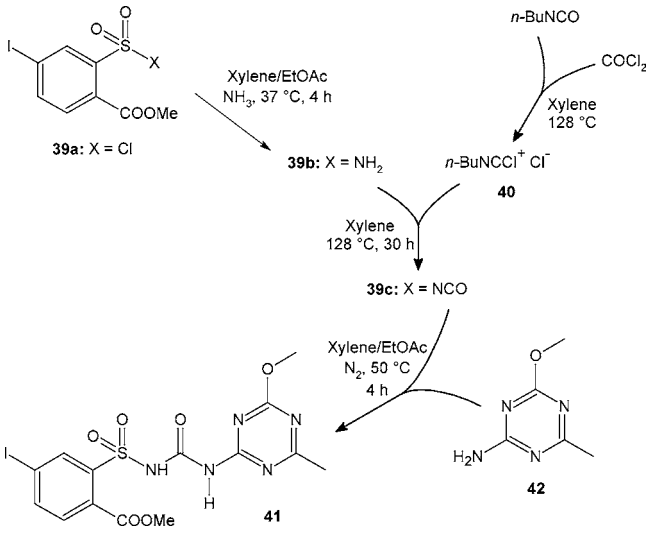
Patent No. U.S. 7,026,477

Assignee: Aventis CropScience GmbH, Frankfurt, Germany

Title or Subject: Process for Preparing Substituted Phenylsulfonylureas from Sulfonyl Halides

The title compounds are used as herbicides and plant growth regulators. It is said that the synthesis of this type of compound containing a carboxylic group on the Ph ring is particularly challenging. Some routes that have been used are summarised and are all claimed to have disadvantages of one type or another. Scheme 13 summarises the route used to prepare **41**, and this starts with the production of the aminosulphonate **39b** by ammonolysis of **39a** with NH_3. The next step is the formation of the isocyanto-derivative **39c** by reaction of **39b**, and the iminium salt **40** is produced in situ by treating *n*-BuNCO with phosgene and **39b**. This step is carried out by adding **39b** to the solution of **40**. Coupling of **39c** with the triazine **42** by heating at 50 °C gives the desired urea **41** in 99% yield. The yield of all steps in the synthesis appears to be >90%.

Scheme 13



A number of variations on the procedure are described including some that give poorer yields of the intermediates, and it is unusual to include these details in patents. For example, if the last step of the synthesis is carried out using pure PhMe as solvent, then the yield of **41** is only 81% even after 24 h. The use of a mixture of xylene and EtOAc is preferred, since this gives shorter reaction times and also allows the use of stoichiometric amounts of **41** and **42**.

Advantages

The process appears to give high overall yields to the desired products, and the purification is simplified by not having to use an excess of reagents in the final step.

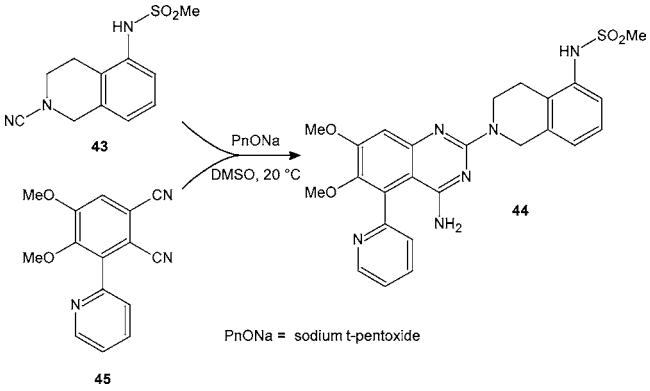
Patent No. U.S. 7,026,479

Assignee: Pfizer Global R&D, Sandwich, Kent, United Kingdom

Title or Subject: Process for the Production of Quinazolines

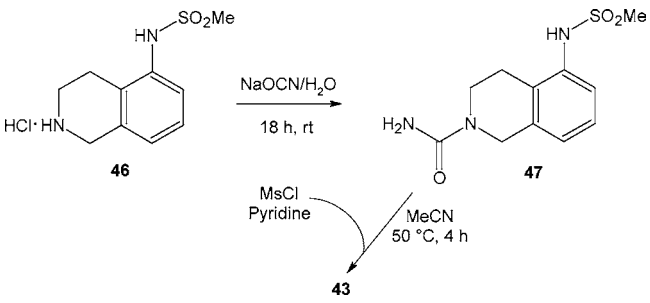
The compounds covered by this patent are used in the treatment of benign prostatic hyperplasia. A selection of alternative routes to such compounds is described but these give low yields. Other problems found in these processes are the production of pebblelike aggregates that are claimed could erode the inner surface of the reactor. The patent focuses on the production of **44**, and the final step in the synthesis is the coupling of **43** and **45** shown in Scheme 14. This is catalysed by a strong base with sodium *tert*-pentoxide being preferred.

Scheme 14



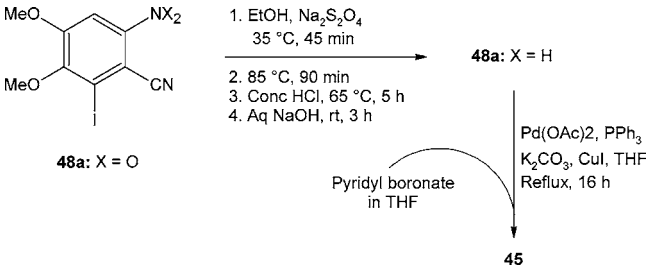
The patent also describes the syntheses of the intermediates **43** and **45**. The synthesis of **43** is from the HCl salt **46** that is treated with NaOCN to give **47** shown in Scheme 15. Reaction of a suspension of **47** in MeCN with MsCl in pyridine produces **43** in 79% yield. The preparation of **46** is by a method from another patent (WO98/30560), but the experimental details are not given.

Scheme 15



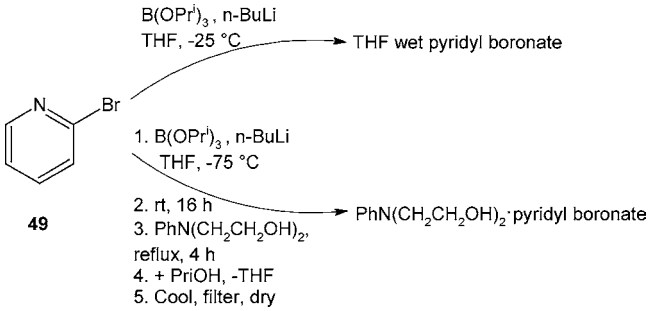
The intermediate **45** is obtained by the reduction of **48a** to give **48b** followed by treatment with so-called pyridyl boronates.

Scheme 16



The structures of these boronates are unknown, and they are prepared by the methods shown in Scheme 17. The simple boronate is prepared by reaction of **49** with the $B(OPr^i)_3$ in the presence of a base such as *n*-BuLi at −25 °C. ^{1}H NMR showed that the solution contained the boronate with a pyridine to *i*-Pr methine CH ratio of 1:3.75. A second boronate is prepared by treating $B(OPri)_3$ with *n*-BuLi at −75 °C, and this mixture is reacted with $PhN(CH_2CH_2OH)_2$ at room temperature. After solvent exchange the product is obtained as a solid. ^{1}H NMR showed that this boronate contained a pyridine/$PhN(CH_2CH_2OH)_2$/*i*-Pr ratio of 1:1.25:1.55.

Scheme 17



Advantages

The process provides an improved process for synthesis of the product and avoids many of the problems encountered in alternative routes.

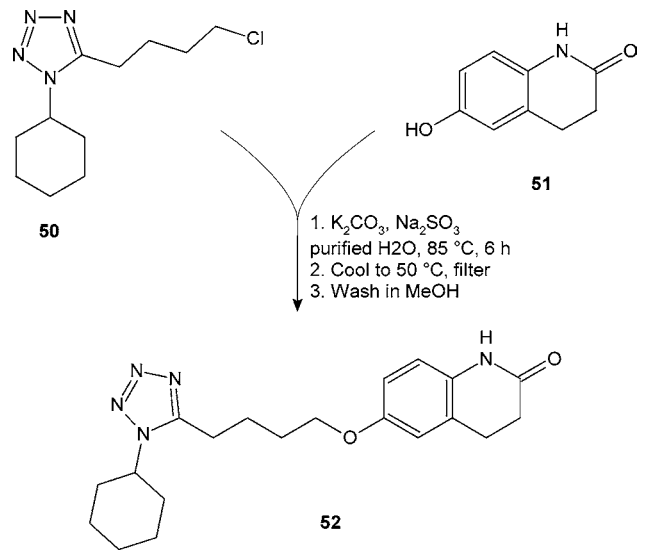
Patent No. U. S. 7,026,486

Assignee: Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan

Title or Subject: Process for Producing Cilostazol

The drug cilostazol **52** is used to treat erectile dysfunction although this is not mentioned in the current patent. Patents on alternative syntheses of **52** have been reviewed previously (*Org. Process Res. Dev.* **2004**, *8*, 146). The current patent discloses a more environmentally friendly process for the production of **52** using water as solvent, whereas other methods use organic solvents. The route is shown in Scheme 18 and involves a simple condensation between **50** and **51** in the presence of weak bases K_2CO_3 and Na_2SO_3. The reaction is carried out in purified water using 3 to 7 times by weight more water than **51**. The bases are used at 1 to 6 times the molar amount of **51**. The highest yield of **52** is reported as 92.44% with a purity of 99.61%. Other variations on the reaction also give high yields of high purity product. The equipment used is described as a continuous disperser or pipeline homogeniser, and the use of this appears to be important. The mixture is continuously removed from the reaction vessel, homogenised, and recirculated back to the reactor. It is said that this prevents the agglomeration of crystals.

Scheme 18



Advantages

The use of water as solvent significantly improves the environmental credentials of this process, and it also appears to give a very efficient and high yielding procedure.

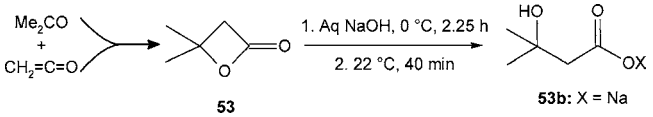
Patent No. U.S. 7,026,507

Assignee: Lonza AG, Basel, Switzerland

Title or Subject: Method for the Production of Solid Formulations of Sodium 3-Hydroxy-3-methylbutyrate

The acid **54a** (X = H) is a food additive that can lower blood cholesterol and decrease nitrogen excretion especially in elderly patients. It is usually more useful to use salts, but apparently there is no method for the industrial production of **54b** in the solid form. This is ascribed to the fact that the salt is not stable to storage and is hygroscopic. It has been found a solution of **54b** can be obtained from the base hydrolysis of **53**, and this solution is suitable for producing solid **54b**. The process used initially forms a solution as shown in Scheme 19. **53** is formed from Me_2CO and ketene, but no details are provided as to how this is carried out.

Scheme 19



The solution obtained in the reaction is concentrated under a vacuum, and then it is added to an intensive mixer containing a synthetic silica known as sipernat from Degussa. The solid free-flowing mixture of **54a** and silica is obtained after about 1 h.

Advantages

The process gives a free-flowing solid mixture of the desired product and silica.

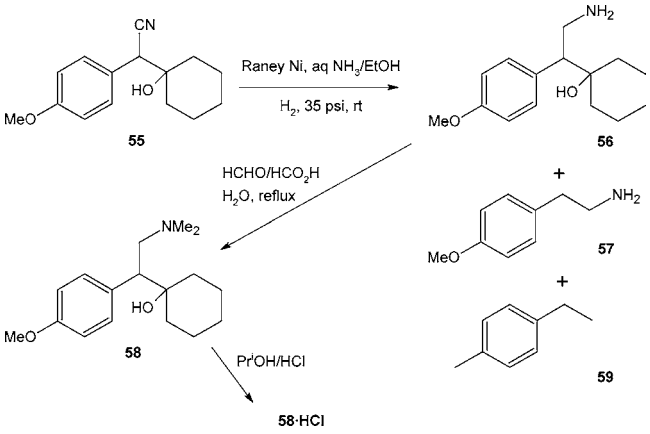
Patent No. U.S. 7,026,513

Assignee: Nicholas Piramal India Limited, Maharashtra, India

Title or Subject: Manufacture of Phenylethylamine Compounds Particularly Venlafaxine

Venlafaxine **58** is an antidepressant, and this patent describes a method for the preparation of intermediates for making **58** and other similar compounds such as **56**. Several methods are available for producing intermediates and compounds similar to **58**. These involve reduction steps, and $NaBH_4$ is used but is a potential fire hazard. The process described in this patent provides a reduction method that is safe and also selective. The route to give **58** is shown in Scheme 20 and involves the selective reduction of **55** to **56**. This is the major problem step in the scheme and can easily produce byproducts such as **57** and sometimes **59**. The use of a variety of catalysts is described in the patent, and the selectivity to **56** varies widely. The best catalyst was one named as Raney nickel CORMIII. The precise identity is not given, and yet it is stated as the catalyst of choice in the main claim in the patent. The use of this catalyst gave >90% yield of **56** in 89% selectivity with 11% of **57**. It is mentioned in the patent that catalysts that had been aged for 3 weeks gave better results. The amine group in **56** is then methylated to give **58** that is isolated as the HCl salt **58**·HCl.

Scheme 20



Advantages

The reduction step is more selective than many other catalysts. It is also claimed to be safer than using $NaBH_4$, and yet the use of hydrogen is surely more dangerous.

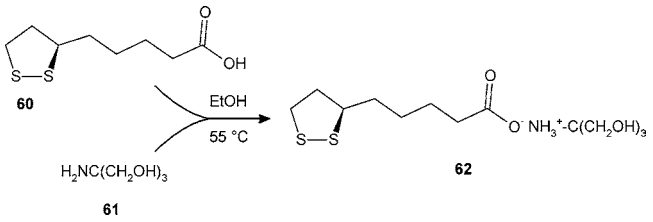
Patent No. U.S. 7,030,251

Assignee: Viatris GmbH & Co. KG, Frankfurt, Germany

Title or Subject: Modifications of the Trometamol Salt of (R)-Thioctic Acid and a Process for Their Production

The subject of this patent, **62**, is an antiinflammatory agent and cytoprotective reagent. It is used to treat diabetes mellitus and insulin resistance plus metabolic disorders of the central nervous system. Previously there were no known modifications of this compound, and the patent describes two new forms, A and B, which are characterised by XRD. Form A is described as existing as small platelets, and form B, as aggregates. The A form has higher solubility in water and organic solvents such as alcohols and Me_2CO. The salt is generally formed from the free acid **60** and **61**. The two forms A and B can be produced by heating the two compounds together in anhydrous EtOH and then cooling to form crystals after adding a filter aid. The rate of cooling and final temperature dictate the form obtained.

Scheme 21



Advantages

The process gives new forms of the drug that may extend its use in pharmaceutical formulations.

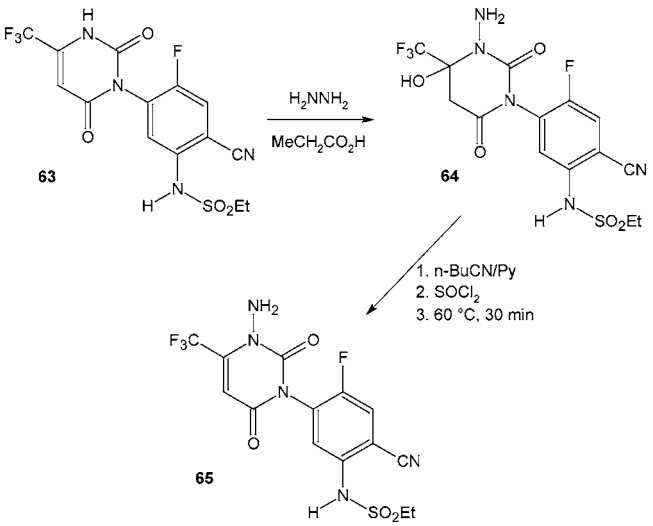
Patent No. U.S. 7,034,156

Assignee: Bayer CropScience AG, Monheim, Germany

Title or Subject: Method for the Production of 1-Amino-3-phenyluracil Derivatives

The phenyluracils such as **65** are used as herbicides for controlling weeds. Several methods are known for the synthesis of these compounds, but it is said that these give low yields. The new process for preparing **65** is shown in Scheme 22 and is based on the dehydration of **64** using $SOCl_2$ in the presence of what are termed reaction assistants. Pyridine is preferred and *n*-BuCN is used as solvent, and **65** is obtained in 89% yield. The patent also describes the preparation of the novel compound **64** by reaction of **63** with hydrazine hydrate using propionic acid as the reaction assistant and diluent.

Scheme 22



Advantages

The process is claimed to have several advantages such as the ready production of starting materials and the ease of isolation of the products.

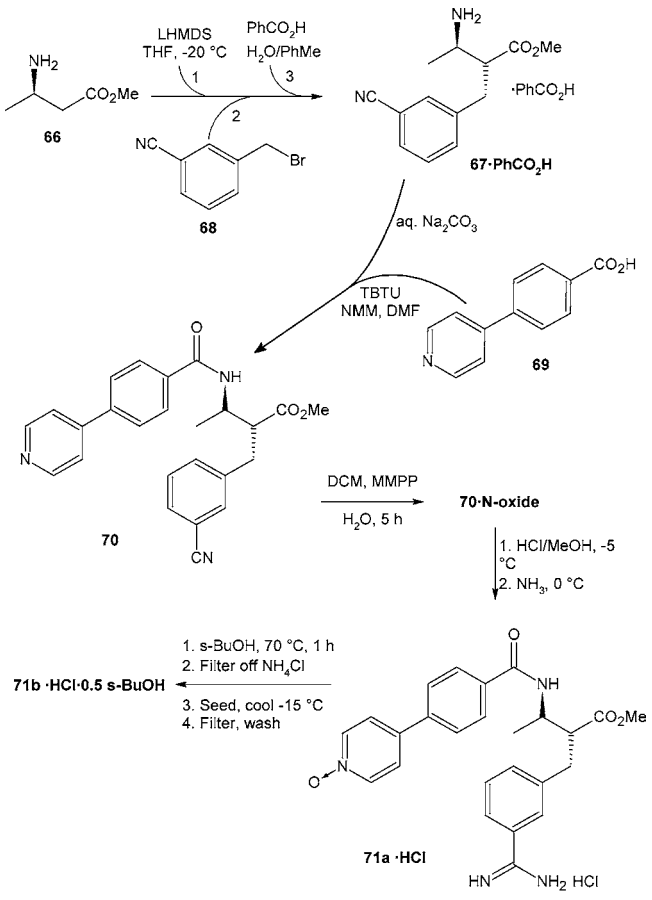
Patent No. U.S. 7,034,160

Assignee: Aventis Pharmaceuticals Inc., Bridgewater, New Jersey, U.S.A.

Title or Subject: Crystalline Forms of a Factor Xa Inhibitor

Factor Xa is a protease that is involved in the coagulation of blood that can lead to thrombosis, so there is wide interest in such compounds (*Org. Process Res. Dev.* **2004**, *8*, 823). This patent describes the production of **71** as a hydrochloride salt and also a solvated HCl salt. These compounds are Factor Xa inhibitors, and such crystalline forms of **71** have not been previously reported. The synthesis of the salts is summarised in Scheme 23. The first stage is formation of the benzoic salt of **67** by stereoselective coupling of **66** and **68**. The salt is then decomposed using Na_2CO_3 and treated with **69** in the presence of TBTU and NMM in DMF to form the amide **70**. Oxidation of **70** using MMPP produces the *N*-oxide of **70**, and this is converted to the HCl salt **71a**; when treated with *s*-BuOH, the solvated salt **71b** is formed. If either (*R*)- or (*S*)-*s*-BuOH is used, then the enantiomerically pure solvated salts are obtained. XRD and NMR data for the salts are provided.

Scheme 23



TBTU = O-(1H-benzotriazol-1-yl)N,N,N',N'-tetramethyluronium tetrafluoroborate
NMM = N-methylmorpholine
MMPP = magnesium monoperoxyphthalate

The patent gives details of the preparation of a range of formulations containing the API.

Advantages

The process gives crystalline forms of the compound that had not previously been known.

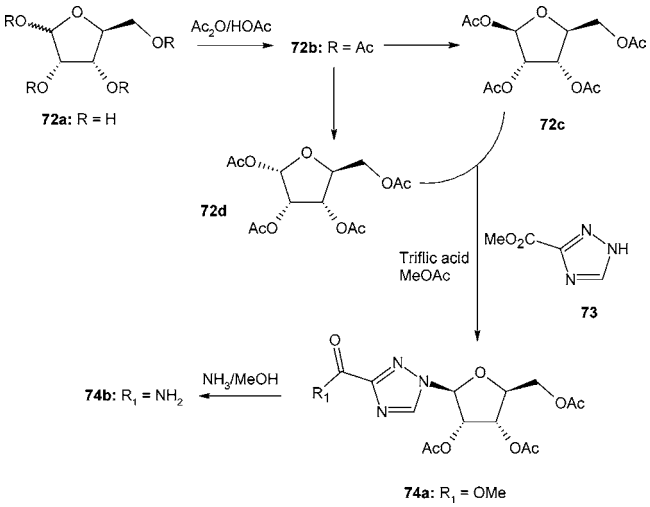
Patent No. U.S. 7,034,161

Assignee: Hoffmann-La Roche Inc., Nutley, New Jersey, U.S.A.

Title or Subject: Process for a Ribofuranose

The use of sugars as sources of useful intermediates is of wide interest. This patent describes a method of preparing **74a** from L-ribose **72a** via **72b**. **74a** is used in the production of the antiviral agent levovirin **74b**, and although there are methods known for preparing **74b** from **72c**, these are said to be unsuitable for large-scale operation. It was believed that these methods could only use the β-anomer **72c** and the α-anomer was not suitable and thus the overall cost of the process is increased. It has been found that it is possible to convert the α-anomer to **74b**, and hence this significantly improves the overall economics of the process. Scheme 24 summarises the procedure to make **72c** from L-ribose **72a**. The conversion of **72a** to **72b** is done in several conventional acetylation steps using Ac_2O and HOAc as solvent. The pure β-anomer is obtained from the mixture **72b** by concentrating, adding water, and cooling. The α-anomer is obtained by extraction from the mother liquor after crystallisation of **72c** using EtOAc/MTBE and flash chromatography.

Scheme 24



The conversion of **72c** and **72b** to **74a** is carried out by reaction with **73** in the presence of triflic acid in MeOAc. A mixture of the two is used, and the patent claims that there should be at least 10 mol %. The conversion of **74a** to **74b** is not described but is via conventional ammonolysis.

Advantages

This process can utilise the previously unused α-anomer in producing the desired product, and hence the overall costs of production are much reduced.

Keith Turner

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