Organic Process Research & Development **2009,** *13,* 11–21

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published During August and September 2008

Summary

The current review covers 20 patents from an initial list containing 233 that fit the search criteria. The range of topics is diverse, and it is hoped there is something of interest to everyone. The extraction and identification of bioactive molecules from natural sources is an active area of R&D, and a number of patents cover various aspects of this topic. Taxanes are obtained from yew trees and used to treat tumours. Two crystalline forms of a known taxane intermediate are described that were previously unknown. Another range of naturally occurring compounds used to treat tumours is maytansinoids. These are obtained from shrubs in East Africa or by microbial processes, and the preparation of one such compound, maytansinol, is described. The alkaloid camptothecin is obtained from the bark of a tree and also has antitumour activity; a comprehensive patent covers the preparation of key intermediates used in a synthetic route to this compound. Vinblastine is used to treat lymphomas and was first obtained from the Madagascan periwinkle. A novel synthetic route to form vinblastine is described that is in the early stages of development. The preparation of pyrimidine-amine derivatives is disclosed that are also useful in treating tumours that are resistant to the taxanes. The compounds are obtained as stable salts that do not degrade on storage as do the parent amines. A patent describes a new process for the preparation of pyrimidine ethers that are used to treat diabetes and obesity. Diabetes is also treatable using nateglinide, and patents from two companies cover this compound. One extends an earlier patent describing 26 polymorphs and focuses on one form, while the other patent focuses on a different form. An interesting rearrangement of some novel ethers is described that is used in the synthesis of tolterodine,; a drug used to treat bladder problems. Four patents cover various aspects of statins and intermediates in their synthesis. One patent describes an additional 18 polymorphs of fluvastatin sodium, making a total of 105 polymorphs for this molecule. One patent describes novel intermediates used to prepare atorvastatin; in another patent on this statin there is an improved method of making known intermediates. The last patent on statins provides a range of novel compounds that can be used to prepare a statins by a convergent synthesis. There is continued interest in drugs to overcome decreased sexual desire in both men and women. One patent discloses a stable polymorph of flibenserin, a drug for women, and the other describes a method of making large-particle-size crystals of tadalafil, a drug for men. The antiepileptic drug topiramate when produced may not always be thermally stable, and an improved method is provided that claims to produce a good-quality, stable product. High-purity enamines can often be difficult to prepare, and a simple method of purifying certain types of enamines has been found that involves washing with aqueous acid. An improved process for preparing the antibiotic tazobactam in pure form is described that gives a high-purity intermediate, thereby improving the preparation of the final product. The production of a higher-purity intermediate is found in a patent covering the preparation of montelukast that is used to treat asthma and seasonal allergies. Away from specific chemical improvements there is one patent covering the production of liquid mixtures containing high concentrations of HCHO as polyoxymethylene glycols. The process works by using a film evaporator coated with ion-exchange resins to catalyse reactions that remove unwanted volatile materials. There are again a large number of errors in several patents in the current selection. Some are typographical and others structural with one molecule having a 5-valent C atom joined to a divalent Cl. In most cases the inclusion of a competent chemist in preparing the patent should have prevented such a thing appearing. A number of the patents describe kilo-scale processes, hence indicating the advanced stage of process development. At the other end of the development scale some patents disclose multistep syntheses that require chromatographic purification methods between steps. However, the inclusion of any patent does not have any legal or commercial significance, and advantages are those claimed in the patent unless this author has personal knowledge.

Patent No. U.S. 7,410,980

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

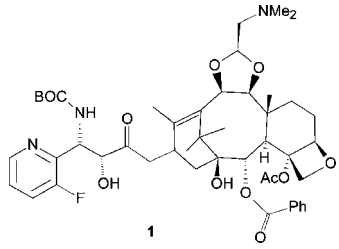
Title or Subject: Crystals of Taxane Derivative and Process for Their Production

Taxanes are compounds that exhibit antitumour activity and were originally extracted from the bark of yew trees. This patent describes a crystalline form of compound **1** (that was first reported in 2001). It is stated that the original report did not contain any evidence that the compound was crystalline, and all attempts at repeating the work by the current inventors were unsuccessful. The current patent concludes that it is absolutely impossible to obtain crystalline forms of **1** by the using EtOH and water as described in the original patent. This patent reports that crystalline **1** can be obtained and that at least two polymorphs exist. The method of obtaining crystals of **1** involves the use of Me_2CO or MeCN containing 40−50% of water. The crystallisation step is carried out at about 45 °C, and this is followed by a drying step under vacuum that appears critical and is done at 30−60 °C. The patent contains XRD,

10.1021/op800304a CCC: $40.75
Published on Web 01/16/2009

thermogravimetric (TG), and differential scanning analysis (DSC/DTA) data for the crystal form that is designated the β form.

Taxane



1

Advantages

The process provides a method of producing a crystalline form of a compound that has potential for treating tumours.

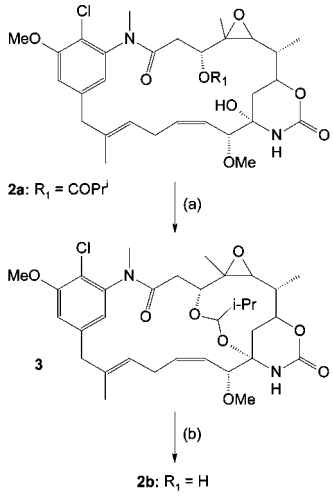
Patent No. U.S. 7,411,063

Assignee: Immunogen Inc., Waltham, Massachusetts, U.S.A

Title or Subject: Process for Preparation of Maytansinol

This patent covers the preparation of **2b** that is one of a range of maytansinoids that are highly cytotoxic compounds and are of interest in treating cancer. Some of these compounds occur in East African shrubs, and others are produced by microbial processes. The main focus of the patent is the preparation of **2b** from **2a** via **3**, and another aspect of the patent provides a method of isolating **3** that is described as a C3 to C9 bridged acetal. Reaction 1 shows the route used to prepare **2b** from **2a**, an ansamitocin that is the major product obtained from bacterial fermentation. **2a** is reduced to **2b** via **3** using $LiAl(OMe)_3H$ at −45 °C followed by a quenching. One problem identified is that the incomplete conversion of **3** to **2b** so that **2b** may contain **3**. In addition the Al byproduct can be gels if formed in basic conditions so that their removal is difficult. By introducing a holding period the incomplete conversion is substantially eliminated, and the Al products can be solubilised by quenching at a pH of about **2** using either HCO_2H or HCl. Treatment of **3** with $EtNPri_2$ produces a 50% conversion of **3** to **2b** in about 15 min. This step can also be carried out using TFA but takes 1 h to achieve the same conversion. **3** is isolated from the first-stage reaction mixture by chromatographic methods in about 15% yield.

Reaction 1



(a) (i) $Li(AlOMe)_3H$, THF, -35 °C, 2 h; (ii) Aq HCO_2H, EtOAc; (iii) Filter, rt, BuOAc; (b) $EtNPr^i_2$, THF/H_2O, pH 11, rt.

The patent gives ^1H NMR data for both **2b** and **3**.

Advantages

The process gives a higher purity of **2b** and also enables the isolation of **3** if required.

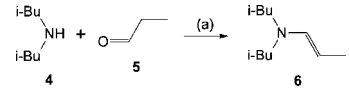
Patent No. U.S. 7,411,095

Assignee: Sankyo Company Limited, Tokyo, Japan

Title or Subject: Process for the Production of High-Purity Enamines

The usual method for the synthesis of enamines is the dehydrative condensation of an aldehyde or ketone with excess of a *sec*-amine. The use of excess amine means that the product contains some unreacted amine, and normally this is no problem. However, when the enamine is used in a reaction with a halogenated alkyl compound, the enamine requires purification because the amine inhibits the reaction. Distillation of enamines often results in their decomposition, and so the objective of the patent is to prepare highly pure enamines. Unexpectedly, it has been found that certain enamines are very stable to hydrolysis and so can be purified by treatment with an aqueous acid. Reaction 2 outlines the method used to prepare **6** that is specifically mentioned in the claims, and presumably the patent assignees have a specific application for it that is not disclosed. The condensation of **4** and **5** is carried out using $MgSO_4$ as the dehydrating agent. The enamine is purified by washing in dilute H_2SO_4 and then NaOH and is obtained in 76% yield at a purity of 96.7%. The analogous enamine of valeraldehyde was also similarly prepared in 80% yield and purity of 93.8%

Reaction 2



(a) (i) $MgSO_4$, 10 °C, 1.5 h; (ii) H_2O, 0 °C; (iii) Dil H_2SO_4, 5 °C, 10 min; (iv) Aq NaOH, 10 min

Advantages

The process gives high-purity enamines that are suitable for use in specific reactions.

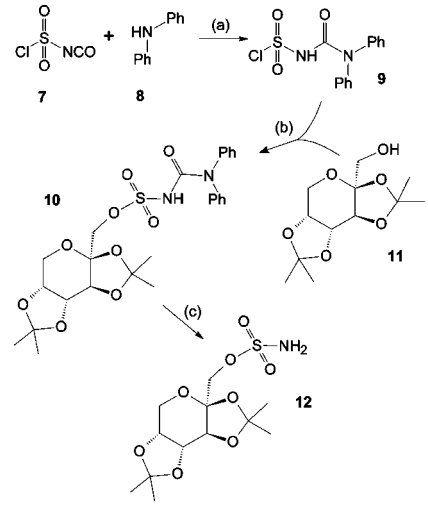
Patent No. U.S. 7,414,053

Assignee: Boehringer Ingelheim International GmbH, Ingelheim, Germany

Title or Subject: Process for the Preparation of Topiramate

Topiramate **10** is used to treat epilepsy, and a number of methods for its preparation are reviewed but said to have several disadvantages. One process uses $ClSO_2NH_2$, another uses metal azides, and both of these reagents are difficult and dangerous to handle. Other processes are said to be less hazardous, but the desired final product purity is not high enough, and the product is not always thermally stable. Hence, the various methods are said to be commercially unacceptable, and an alternative was sought. The new process involves the hydrolysis of the compound **10**, and Reaction 3 outlines the route used to prepare **12**. The procedure starts with the preparation of the urea **9** by reaction of the isocyanate **7** with the amine **8**. The urea **9** is used without purification in a reaction with the pyranose **11** in the presence of a base to give **10**. This is also used without purification in the next step in which **10** is hydrolysed in a buffered solution and produces **12** in a yield of 67%. The purity of the product is not given but can be improved by recrystallisation from aqueous Pr^iOH.

Reaction 3



(a) (i) DCM, argon, -20 °C; (ii) -10 °C, 0.5 h; (b) (i) Et_3N, DCM, -25 °C; (ii) 5 °C, (c) (i) Me_2CO, NaOH/HOAc, pH 3.5, reflux, 1.5 h; (ii) Cool, H_2O, NaOH, pH 13; (iii) Wash MTBE; (iv) 85% H_3PO_4, pH 5.5; (v) Filter, wash H_2O, dry 40 °C.

The patent also describes the preparation of ureas analogous to **8** using MePhNH or Et_2NH, and these are also used to prepare **12** by reaction with **11**. In addition the patent describes a one-pot process that begins with the reaction of **7** with Et_2NH and follows the whole scheme shown in Reaction 3. The final yield of **12** is reported as 55% after recrystallisation.

Advantages

The process produces pure topimarate that is thermally stable. However, it still requires the use of the isocyanate **7** that is a toxic and potentially hazardous reagent.

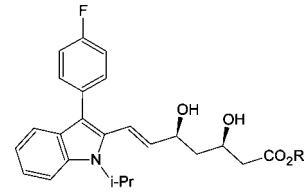
Patent No. U.S. 7,414,140

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

Title or Subject: Processes for Preparing Crystal Forms of Fluvastatin Sodium

Statins are used to reduce the levels of cholesterol and the risk of cardiovascular diseases, and they continue to attract considerable interest. A recent report of a major clinical trial showed that rosuvastatin could be beneficial to patients that may not have been thought to be at risk, and this is likely to stimulate further interest in the whole statin range. This is the first of four patents on statins or intermediates and extends work described in two previous patents from the same company that were recently reviewed (Org. Process Res. Dev. 2008, 12, 797.).The earlier patents reported 87 polymorphs of **13a** (R = Na), and the current patent describes even more, taking the total to 105 although the four claims of the patent only cover form XXXVI. The patent contains 189 examples and includes 134 sheets containing copies of DSC, DTA, TG, IR, and XRD details for a large number of the polymorphs. As is usually the case, the different forms are obtained by adjusting the crystallisation conditions. Interested readers are recommended to study the patent for themselves.

Fluvastatin



13a: R = Na

Advantages

The process provides additional polymorphs of an important drug that may bring new commercial opportunities.

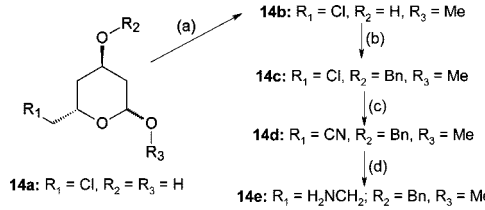
Patent No. U.S. 7,414,141

Assignee: Avecia Pharmaceuticals Ltd., Blackley, Manchester, U.K

Title or Subject: Process and Intermediates for Preparing Statins, Particularly Atorvastatin

This is another patent on statins and the first of two describing intermediates that are used for preparing the Ca salt of atorvastatin **18a** (X = 0.5 Ca). The claims in this patent specifically cover the novel compound **16c** and its preparation by the route outlined in Reactions 4 and 5. The first stage is the preparation of **14e** shown in Reaction 4. This starts from **14a**, described as crude chlorolactol, that is converted to **14e** via **14b**, **14c**, and **14d** by conventional methods. These intermediates are oils, and they are purified by column chromatography (CC) although their final purities are not given.

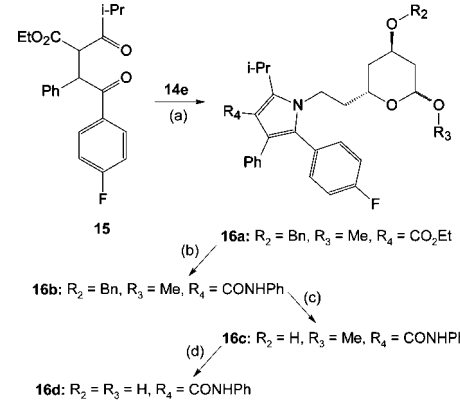
Reaction 4



(a) MeOH, H_2SO_4, 40 °C, 2 h; (b) NaH, BnBr, THF, 80 °C, 2 h; (c) KCN, DMSO, 80 °C, 4 days; (d) BH_3-THF, reflux 9 h

In the next stage of the process **14e** is coupled with the diketone ester **15** to produce **16a**. The anilide **16b** is then formed, and the OH protective groups are removed stepwise to finally give **16d**. Again these compounds are oils that are purified by CC.

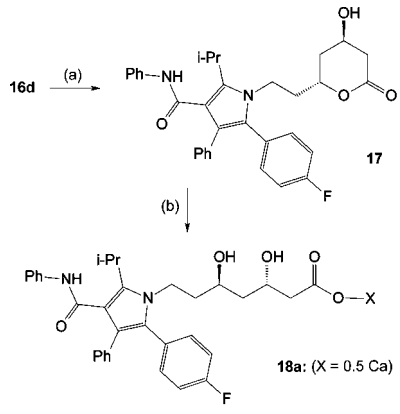
Reaction 5



(a) HOAc, THF, 80 °C, 2 days; (b) $PhNH_2$, DMF, 80 °C, 18 h; (c) MeOH, Pd/C, H_2, heat, 6 h; (d) Aq MeOH, 0.1 M HCl, rt, 2 h

The preparation of **18a** is shown in Reaction 6 and is carried out by initially oxidising **16d** to the lactone **17** using Dess–Martin periodinane (DMP). The product is another oil that does not appear to be purified before being converted to the desired Ca salt **18a**.

Reaction 6



(a) DCM, DMP, rt, 2.5 h (b) (i) EtOH,H_2O, $Ca(OH)_2$, 60 °C, 3 h; (ii) H_2O, cool slowly to rt, filter

^1H and some ^{13}C NMR data are given for all intermediates used in the overall process.

Advantages

The process provides a novel intermediate that can be used to prepare an important drug.

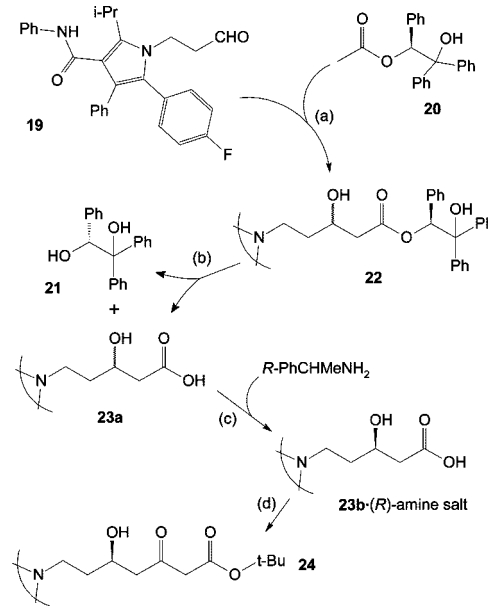
Patent No. U.S. 7,429,613

Assignee: Apotex Pharmachem Inc., Brantford, Ontario, Canada

Title or Subject: Process for the Preparation of Atorvastatin and Intermediates

This is the second patent on the statin **18a**, and it describes improvements in the stereoselectivity of a reaction used in the original synthesis of **18a**. The reaction in question is between the aldehyde **19** and the chiral ester **20** (Reaction 7). By carrying out the reaction in the presence of a chelating solvent, the product **21** is obtained having an increased amount of the *R,S* diastereomer compared to the *S,S*. Examples of such chelating reagents are TMEDA, $(EtOCH_2)_2$, DME, or dioxane. It is also stated that the original process required the presence of Mg ions; since the improvement removes this need, the process is thereby simplified. The aldol reaction of **19** and **20** is carried out in the presence of LDA in DME and produces **22** with an *R,S:S,S* ratio of 95:5 compared to 86:14 when using the original procedure. In the next step **22** is hydrolysed with MeOH/H_2O crude, and **21** is filtered off and recovered in 90% yield for recycling. The diastereoisomers of **22** are then resolved using *R*-$PhCHMeNH_2$ to obtain the *R*-amine salt of **23b** with an ee of 97.8%, and recrystallisation increased this to >99%.

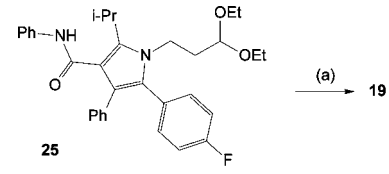
Reaction 7



(a) LDA, DMA, -78 °C, 0.5 h; (b) (i) MeOH, H_2O, warm to rt, reflux 3 h; (ii) H_2O, evaporate; (iii) MeOH, reflux 0.5 h; (iv) Cool to rt, filter off **21**, evaporate; (v) MeOH, MTBE, reflux 6 h; (vi) Cool to rt, filter, dry; (d) (i) CDI, THF, rt, 3 h; (ii) $(Bu^tO_2CCH_2CO_2)_2Mg$, rt, 20 h; (iii) Evaporate, extract in EtOAc, 1M HCl; (iv) Wash $NaHCO_3$, dry

In the last stage of the process the *R*-amine salt of **23b** is converted to the β-ketoester **24** by reaction with the Mg malonate salt in the presence of 1,1′-carbonyldiimidazole (CDI). **24** can then be used to prepare **18b**, but no details are given. Reaction 8 shows the preparation of the aldehyde **19** by acid hydrolysis of the acetal **25** that is obtained by a method reported in U.S. Patent 5,003,080.

Reaction 8



(a) 5% HCl, Me_2CO, 40 °C, 24 h; (ii) Filter, wash, dry.

Advantages

The process gives an improved stereoselective method for preparing a key intermediate in the synthesis of the drug.

Patent No. U.S. 7,420,078

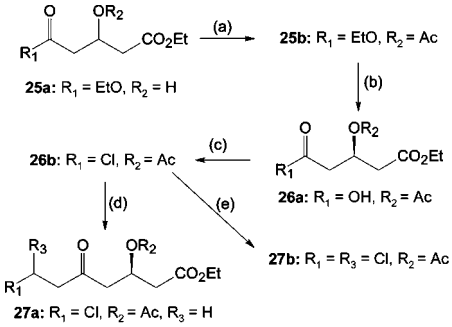
Assignee: Ciba Specialty Chemicals Corp., Tarrytown, New York, U.S.A

Title or Subject: Process for the Preparation of Atorvastatin and Intermediates

This, the last patent on statins, describes new methods of preparing statin intermediates and also some novel compounds. A key step in the synthesis of statins is a regioselective chain lengthening. The patent describes the use of a novel side-chain building block that allows a convergent synthesis as opposed to the many linear processes reported. Reaction 9 summarises

the synthesis of **27a** that is a key intermediate used to prepare several other compounds. The hydroxyl glutarate **25a** is acetylated to give **25b**, and this is then treated with α-chymotrypsin in a carefully controlled buffered system to produce the half ester **26a** that has an *R*/*S* ratio of 99/1. Chlorination of **26a** with $(COCl)_2$ in the presence of DMF gives coloured **26b** that is deemed pure by NMR but can be obtained colourless by molecular distallation. In the final step, alkylation of **26b** with C_2H_4 in the presence of $AlCl_3$ gives **27a** that is recovered as an oil. This reaction is also carried out using CH_2═CHCl and gives the dichloro compound **27b** that is also an oil.

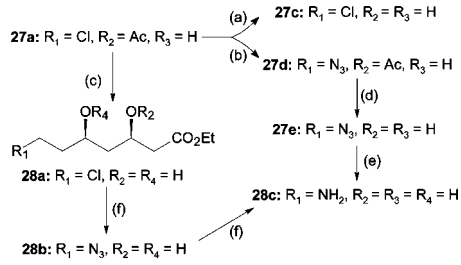
Reaction 9



(a) Pyridine, Ac_2O, rt, 12 h; (b) (i) H_2O, pH 7 buffer, α–CMT, aq NaOH; (ii) Wash in EtOAc, conc HCl to pH 1; (iii) Extract in EtOAc, filter, evaporate; (c) (i) DMF/$(COCl)_2$, DCM, 0 °C, 30 min; (ii) rt, 1.5 h; (iii) Evaporate; (d) (i) $AlCl_3$, EDC, C_2H_4, 40 °C; (ii) Aq NaCl, 0 °C; (iii) Et_2O, charcoal; (e) (i) $AlCl_3$, EDC, CH_2=CHCl, 0 °C, 1.5 h; (ii) Aq NaCl, 0 °C; (iii) Extract in DCM.

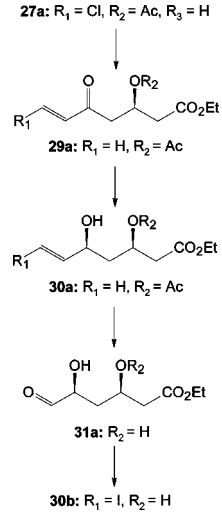
Compounds **27a** and **27b** are used in a number of reactions, and some of these are summarised in Reactions 10 and 11. The actual details of several of the conversions shown in the schemes are not described but are included in the reaction schemes in the patent. There are a considerable number of examples and schemes in this patent with other substituents such as MeOAc, $MeO(CH_2)_2OCH_2$− for R_2 in compounds **25**−**27** and also Br derivatives of **26b** and **27a** in which R_2 = Ac, MeOAc, or $MeO(CH_2)_2OCH_2$−. The comprehensive nature of this patent cannot be adequately covered here, and it is recommended that interested readers study it carefully.

Reaction 10



(a) (i) KH_2PO_4, pig liver esterase, aq NaOH, EtOH, rt; (ii) Extract in EtOAc, CC; (b) (i) NaN_3, DMF, 18-crown-6, rt; (c) (i) Et_3B, MeOH, THF, -65 °C, 30 min; (ii) $NaBH_4$, -65 °C, 1 h; (d) Chirazyne E1, buffer pH 7, aq NaOH, EtOH; (e) Pd/C, EtOH, H_2, 10 bar, 30 °C, 1 h, (f) No details provided.

Reaction 11



The patent mentions that aldehyde **31a** can be used to prepare **18a**, itavastatin, and cerivastatin but details are not provided.

There are a considerable number of spelling mistakes in this patent, such as naming an example of the R_1 group in **25b** as 2-methoxygethoxygrnvethvl. There are also examples of derivatives of the acids alutaric, valutaric, and plutaric. There can be no excuse for these errors unless both spell checkers and chemists are omitted from the patent preparation process.

Advantages

The process describes several intermediates that are suitable for the preparation of a range of statin drugs.

Patent No. U.S. 7,414,159

Assignee: BASF SE, Ludwigshafen, Germany

Title or Subject: Separation of Liquid Mixtures in a Film Evaporator

The liquid mixtures that this patent covers are polyoxymethylene glycols (POMGs) that are present in aqueous solutions of HCHO. Such solutions contain a number of such glycols of varying molecular weight as well as MeOH and acetals. The objective in this case is to produce a liquid mixture having a high concentration of HCHO that is present as POMGs. The solution can be used in subsequent reactions as a source of HCHO. The process is carried out in a film evaporator in which the heat exchange section is coated with an acidic ion exchange resin (IER) that catalyses two types of reaction. In the first MeOH forms the volatile methylal by reaction with HCHO, and in the second H_2O is produced when HCHO condenses to give POMGs. These compounds are nonvolatile, and so the volatile components (H_2O and methylal) are removed by evaporation. The solution that remains contains high concentrations of HCHO as POMGs. The reaction is carried out on a continuous basis at 100 °C and 200 mbar pressure. The process is similar to a technique known as reactive distillation.

Advantages

Although the process was developed for a specific need, it is an interesting application that could have uses elsewhere.

Patent No. U.S. 7,417,044

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

Title or Subject: Process for Preparing Tadalafil Having a Large Particle Size

Tadalafil is available under the name cialis and is used to treat erectile dysfunction. An improved synthesis of tadalafil has been reviewed (*Org. Process Res. Dev.* **2007**, *11*, 802), and this patent focuses on improving the physical aspects of the compound. The aim is to produce crystals in which 90% have a size in the range 200−600 μm.

This size range is achieved by a combined milling and crystallisation process that has the following steps:

(i) dissolve tadalafil in Me_2CO/H_2O under reflux to obtain a clear solution

(ii) filter through a series of filters (5, 1 and 0.2 μm)

(iii) gradually add H_2O to the solution at about 45 °C to obtain a suspension

(iv) the mixture is subjected to a series of heating and cooling steps between 50 and 20 °C

(v) when the temperature reaches 20 °C, filter off crystals, wash in H_2O, and dry

(vi) mill the crystals to achieve a size range from 40 to 100 μm

Advantages

The process produces crystals that have an improved size distribution for preparation of pharmaceutical formulations.

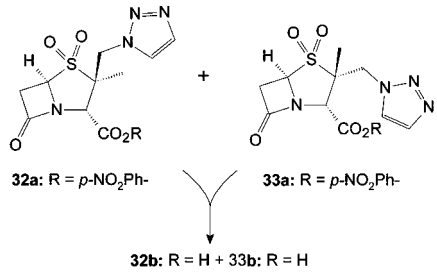
Patent No. U.S. 7,417,143

Assignee: Orchid Chemicals and Pharmaceuticals Limited, Chennai, India

Title or Subject: Process for the Preparation of Tazobactam in Pure Form

Tazobactam **32b** (R = H) is an orally effective penicillin antibiotic that has been known for many years and has broad spectrum activity. An isomer **33b** (R = H) can be present at levels of up to 22%, and this level needs to be reduced to <0.1%. This patent describes a method of purifying **32b** and removing **33b** at the last or penultimate stage of the synthesis or by a crystallisation method. The final stage in the synthesis of **32b** shown in Reaction 12 is the reduction of the ester **32a** to give **32b**, and at the same time **33a** forms **33b**. The patent describes a method for purifying a mixture of **32b** and **33b** as well as a method of carrying out the hydrogenation step and purifying the product in the workup. This process involves a two-stage acidification, and the final product **32b** is obtained with a purity of >99% containing <0.02% of **33b**.

Reaction 12



(a) (i) Pd/C, aq $NaHCO_3$, EtOAc, H_2, 20 kg/cm^2, 15 °C, 1 h; (ii) Aq layer to pH 5.5; (iii) Charcoal, 15 °C; (iv) MEK, aq HCl, to pH 2.5, 15 °C, 30 min; (v) Aq HCl, pH 1.3, 45 min; (vi) Filter, wash in H_2O, dry.

The crystallisation of **32b** containing up to 22% of **33b** is also described using MEK and HOAc as solvents. **32b** was obtained with >99.0% purity containing <0.06% **33b**. Also described is a crystallisation process for purifying **32a**. This involves the addition of L-tartaric acid (L-TA) to a solution of **32a** containing **33a**. Solvents used are MEK, HOAc, and DMSO, and **32a** is obtained with a purity >98%.

Advantages

The process enables a high-purity intermediate and final product to be obtained.

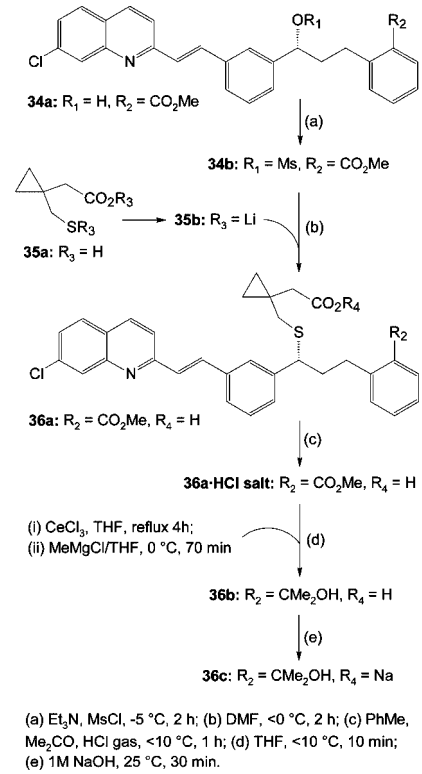
Patent No. U.S. 7,417,149

Assignee: Chemi SpA, Milan, Italy

Title or Subject: Process for the Preparation of Montelukast

The Na salt of montelukast acid **36c** is used to treat asthma and seasonal allergies. Alternative methods for the production of **36c** are described, and it is stated that purification of the final product is often difficult. Hence, the objective of this patent is to improve the synthesis and increase yields and purity of **36c**. Reaction 13 summarises the new route to synthesise **36c**. This begins with the protection of the OH group in **34a** to give the mesylate **34b** that is then treated with the Li salt **35b** to form **36a** in 80% yield. **35b** is prepared from LHMDS and **35a** (R_3 = H). The HCl salt of **36a** is then formed and isolated at 99.1% purity in a yield of 80%. Methylation of the salt is carried out with MeMgCl that is activated with Ce salt and gives **36b** that is isolated in 80% yield and 99.6% purity. In the final step the Na salt **36c** is obtained with 99.5% purity.

Reaction 13



(a) Et_3N, MsCl, -5 °C, 2 h; (b) DMF, <0 °C, 2 h; (c) PhMe, Me_2CO, HCl gas, <10 °C, 1 h; (d) THF, <10 °C, 10 min; (e) 1M NaOH, 25 °C, 30 min.

A surprising finding that is mentioned is the reaction of **34b** with **35b** to give the product **36a** in good yield. Formation of the HCl salt of **36a** gives a high-purity compound that can be used directly without the need to revert to the free base. The

advantage of forming **36a** and its salt is that it does not contain a *tert*-OH group that is subject to dehydration. Alternative processes for preparing **36c** introduce the *tert*-OH group earlier, and hence dehydration can occur in subsequent reactions forming impurities. The patent includes ^{1}H NMR data for compounds **34b**, **36a**, and **36b**.

Advantages

The process gives high-purity intermediates that are more easily and efficiently transformed into high-purity final product.

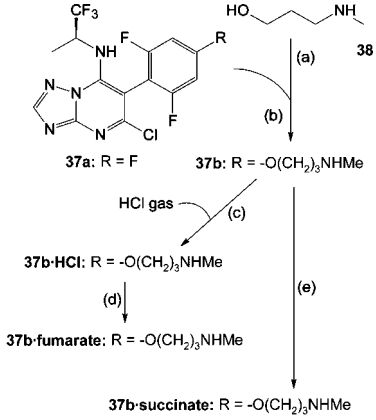
Patent No. U.S. 7,419,982

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

Title or Subject: Crystalline Forms of a [1,2,4]Triazolo[1,5-a]pyrimidin-7-amine Salt

The compounds of interest in this patent is **37b** and its salts that are said to have antitumour activity especially for tumours that are resistant to microtubule-active compounds such as taxanes or vincristine. The free amine **37b** is not stable at room temperature and undergoes a dimerisation reaction. Thus, on storage the compound decomposes. The HCl salt is known and has good aqueous solubility but is amorphous. Hence, the objective of this patent is to produce stable, crystalline, water-soluble salts of **37b** for use in drug formulations. The patent therefore describes fumarate, succinate, and mandelate salts of **37b** that fulfill these criteria. Reaction 14 shows the preparation of **37b** by reaction of **37a** with the aminoalcohol **38**. The HCl salt **37b·HCl** is easily produced and converted to the fumarate salt by treatment with fumaric acid. The product is the anhydrous salt, but this absorbs two moles of water to give the dihydrate form of the salt if the relative humidity is above 5%. The succinate salt can be prepared from **37b**, and this is also initially isolated as the anhydrous salt but easily forms the dihydrate. Drying the hydrates reforms the anhydrous salts. The patent also mentions the anhydrous mandelate salt of **37b** but not the dihydrate.

Reaction 14



(a) NaH, DMSO, rt, 1 h: (b) (i) **37a**, 60 °C, 3 h; (ii) EtOAc, rt; (iii) H_2O, aq NaCl; (iv) Evap., CC; (c) MeOH/DCM; (d) (i) Aq NaOH, fumaric acid, 75 °C; (ii) Cool to 5 °C, filter, wash, dry; (e) Succinic acid, H_2O, 75 °C; (ii) Cool 5 °C, filter, wash, dry.

The patent provides XRD, TGA, and DSC data for some of anhydrous and dihydrate salts.

Advantages

The process gives stable, crystalline salts that can be used to produce drug formulations.

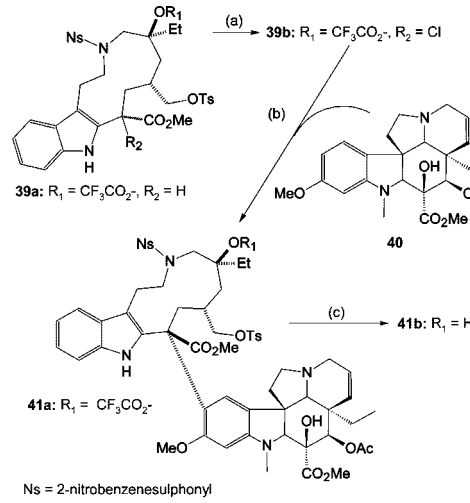
Patent No. U.S. 7,420,052

Assignee: Japan Science and Technology Agency, Saitama-ken, Japan

Title or Subject: Process for the Preparation of Vinblastine and Intermediates

Vinblastine **42** was first isolated from the Madagascan periwinkle plant and is effective against cancers of white blood cells such as lymphomas. The commercial synthesis of derivatives of **42** is said to require a totally synthetic route, and this patent describes the preparation of intermediates used in such a route. The patent describes the synthesis of **42** by a process in which the initial step is the chlorination of the ester **39a** to give **39b** using Bu^{t}OCl. This is not isolated and in the next step is coupled with vindoline **40** to give **41a** (Reaction 15). The mixture is purified using TLC and **41a** is obtained in 80.4% yield. In the next stage the protective TFA group is removed using Et_3N and **41b** is recovered in 90% yield.

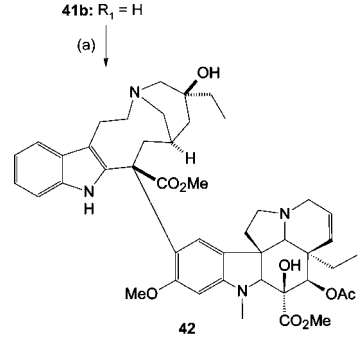
Reaction 15



(a) Bu^{t}OCl, DCM, 0 °C, 15 min, TLC; (b) (i)TFA, DCM, 0 °C, 10 min; (ii) rt, 20 min; (iii) Aq $NaHCO_3$, extract in DCM, evap., TLC; (c) Et_3N, MeOH, rt, 45 min, evap.

In the final stage of the process both the Ns and Ts groups in **41b** are removed to produce what is described as a cyclisation precursor. Treatment of this precursor with aqueous $NaHCO_3$ gives **42** that is isolated by TLC in 79% yield.

Reaction 16



(a) (i) DBU, $HSCH_2CH_2OH$, MeCN, 0 °C, 1 h; (ii) Extract in EtOAc, evap., TLC; (iii) $NaHCO_3$, Me_2CO/H_2O, rt, 16 h; (iv) Extract in EtOAc, evap., TLC.

The patent also contains extensive details for the preparation of the ester **39a** in a 21-step synthesis starting from 2-methylenebutan-1-ol. It is not proposed to cover this route here due to lack of space, and the interested reader is encouraged to consult the patent. Extensive ^{1}H and ^{13}C NMR data are provided for all intermediates, but the vast majority of the reactions are carried out on milligram scale and involve either TLC or CC.

Advantages

The patent does provide a stereoselective route to intermediates that can be used to prepare vinblastine, but the process appears to be a long way from commercialisation.

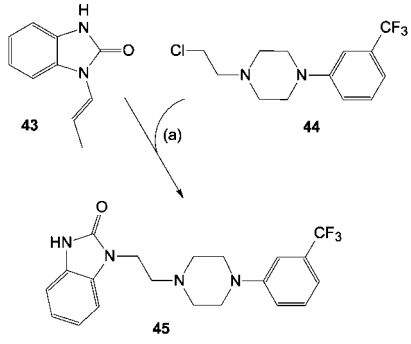
Patent No. U.S. 7,420,057

Assignee: Boehringer Ingelheim Pharma KG, Ingelheim, Germany

Title or Subject: Stable Polymorph of Flibanserin

Flibanserin **45** was initially developed as an antidepressant and used as the HCl salt. It is currently being investigated as a drug for women suffering from decreased sexual desire. Although the main claim of this patent is the production of a new stable polymorph of the free base **45**, the patent does describe a process for the manufacture of the polymorph. Reaction 17 shows the method of producing the stable polymorph of **45** by reaction of **43** with **44** in basic aqueous $Pr^{i}OH$. The patent specifically states that the 2-propenyl group is the preferred amine-protecting group in compound **43** and cleavage is by using conc HCl. There is an extensive and specific workup described, and the one example given is carried out to produce 280 kilo of **45**, thus indicating the commercial status of the process. The polymorph obtained is characterised by XRD.

Reaction 17



(a) (i) NaOH, H_2O, $Pr^{i}OH$, 85 °C; (ii) Conc HCl, H_2O, 85 °C, 45 min; (iii) Distil off $H_2O/Pr^{i}OH$; (iv) Aq NaOH, pH 7.5, 75 °C; (v) Cool to 50 °C, aq NaOH to pH 9; (vi) Cool to 35 °C, centrifuge, wash, dry; (vii) Me_2CO, reflux, filter, distil; (viii) Cool <5 °C, 1 h, filter, dry.

Advantages

The patent describes a commercially viable process for preparing a stable polymorph of the drug.

Patent No. U.S. 7,420,084

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

Title or Subject: Polymorphic Forms of Nateglinide

This is the first of two patents on polymorphs of the drug nateglinide **48b** that is available as Starlix for the treatment of type II diabetes. The patent extends the work of an earlier patent describing 26 new crystalline forms of nateglinide that has been reviewed (Org. Process Res. Dev. 2007, 11, 318.). The claims of the current patent focus on a specific polymorph designated form U, that is obtained from Form B by crystallisation from EtOAc or Me_2CO. XRD, DSC, and FTIR spectra are given for many of the polymorphs. The choice of solvent and crystallisation method are used to obtain the various polymorphs, many of which are thermally unstable and easily convert to other forms at room temperature. Form U is one of a number of thermally stable forms described and hence of interest in drug formulations.

Advantages

The process provides a stable polymorph of an established drug that can be used to produce marketable pharmaceutical formulations.

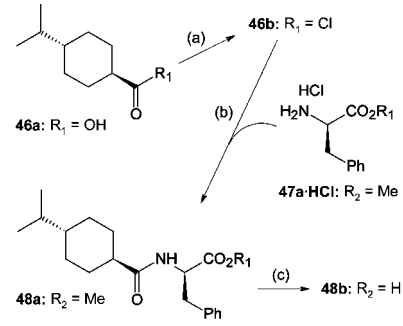
Patent No. U.S. 7,425,648

Assignee: A.M.S.A. Anonima Materie Sintetiche E. Affini S.p.A., Milan, Italy

Title or Subject: Process for the Preparation of Nateglinide, Preferably in B-Form

This is the second patent on **48b** and aims to produce the B-form free from contamination by the H-form. It is noted in this patent that recrystallisation of **48b** from $MeOH/H_2O$ is known to result in crystals of **48b** that are contaminated with the methyl ester **48a**. There are also problems of the formation of gels and of swelling of the crystals in some solvents. Hence, the objective of this patent is to remove the need to recrystallise the end-product. The preparation of **48b** is shown in Reaction 18 and takes place between the acyl chloride **46b** and the HCl salt of alanine ester **47a**. This gives the methyl ester **48a** that undergoes base hydrolysis to give the acid **48b**. This is precipitated using HCl; after the precipitate is washed, a yield of 97% of **48b** is obtained containing >99.9% of the polymorph form B.

Reaction 18



(a) (i) Et_3N, $Bu^{t}COCl$, Me_2CO, <5 °C, 30 min; (ii) 25 °C, 3 h; (b) (i) Et_3N, 25 °C, 18 h; (ii) H_2O; (iii) Cool <5 °C, 2 h; (iv) Filter, wash in H_2O; (c) (i) Aq KOH, PhMe, Aliquat 336, 50 °C, 5 h; (ii) Carbon, filter; (iii) Cool <20 °C, (iv) 10% HCl to pH 2.5, 20 °C; (v) Filter, wash in H_2O, dry.

The patent includes XRD and DSC spectra of the B-form and HPLC traces of **47a**, **48a**, and **48b** and mixtures of these compounds.

Advantages

The process gives a direct method of preparing the desired polymorph in high purity.

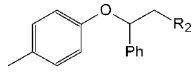
Patent No. U.S. 7,420,091

Assignee: Dipharma S.p.A., Mereto di Tomba, Italy

Title or Subject: Process for the Preparation of Tolterodine

Tolterodine **53** is used in treating urinary incontinence and other bladder problems and is available as the tartrate salt as Detrol. A patent on an alternative synthesis of **53** has been recently reviewed (*Org. Process Res. Dev.* **2008**, *12*, 1031). This patent describes a new method of preparing **53** by the acid-catalysed rearrangement of the novel ether **52a**. However, the key findings of this patent are the rearrangement reaction and the novel ethers **52a**, **52b**, and **52c**. In fact the two claims of the patent cover the three novel ethers rather than the preparation of **53**.

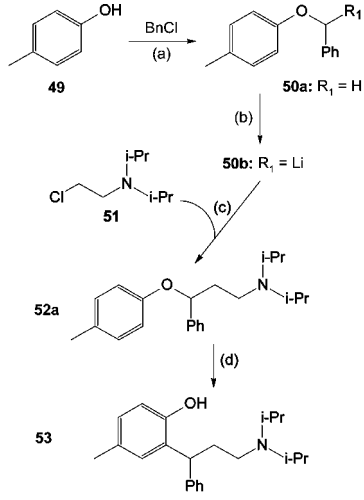
Ethers



52a: $R_2 = CH_2NPr^i_2$
52b: $R_2 = CONPr^i_2$
52c: $R_2 = CO_2Me$

Reaction 19 shows the method used to prepare **53** beginning with the formation of **50a** from **49** and BnCl. The Li compound **50b** is then produced and reacted with **51** to form **52a** that is isolated as a yellow oil in a 51% yield after purification by flash chromatography (FC). Heating **52a** with PPA results in the rearrangement to give **53** in 53% yield.

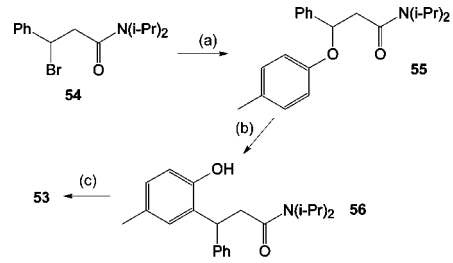
Reaction 19



(a) Bu^nLi, TMEDA, THF, <0 °C, 1 h; (b) (i) THF, 0 °C; (ii) warm to rt, 1 h; (iii) Aq NH_4Cl; (iv) Extract in PhMe, wash, evap., dry; (c) (i) PPA, rt, 3 h; (ii) Aq NaOH, to pH 10, 0 °C, 30 min; (iv) Extract in PhMe, evap.

The patent also describes a number of alternative methods of making **53** that incorporate the same type of rearrangement. An example is shown in Reaction 20 where **55** is prepared from **54** by reaction with **49** in the presence of NaOEt. After purification of **55** using FC it is obtained as a yellow oil, and on heating with PPA **56** is obtained. This is also an oil and is purified by FC and then reduced using $LiAlH_4$ to give **53**. A similar rearrangement occurs when **52c** is heated with PPA.

Reaction 20



(a) (i) NaOEt, EtOH, 0 °C; (ii) rt, 15 h; (iii) **49**, EtOH, <30 °C, 4 h; (iv) HOAc to pH 7; (v) Distil solvent, DCM, wash in H_2O, dry; (b) PPA, rt, 4 h; (c) (i) $LiAlH_4$, Et_2O, reflux, 4 days; (ii) H_2O, HOAc to pH 5; (iii) Evap. solvent, FC.

The patent gives ^1H NMR data for **50a** and **52a**.

Advantages

The patent provides some novel compounds that undergo an interesting rearrangement to give the desired drug molecule.

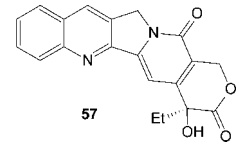
Patent No. U.S. 7,423,152

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

Title or Subject: Process for the Manufacture of Intermediates in Camptothecin Production

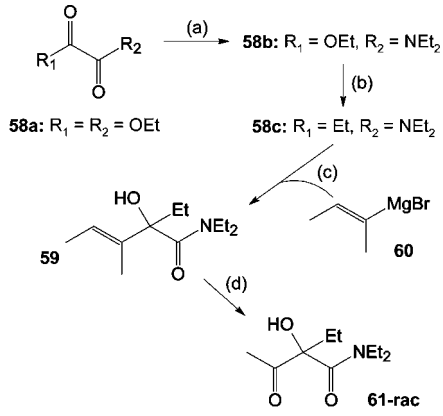
Camptothecin **57** is an alkaloid that has antitumour activity and can be obtained from the bark and wood of a Chinese tree, *Camptotheca acuminate*. A number of patents on this compound were reviewed some time ago (Org. Process Res. Dev. 2004, 8, 553.).

Camptothecin



The focus of the current patent is the synthesis of **71** that is a key intermediate in the synthesis of **57**. The patent contains a substantial amount of detail, and the reaction schemes presented here show only the main reagents; the workup methods are detailed in the patent. In the preparation of **71** an intermediate **61** is prepared that can be produced via a racemic approach giving racemic **61-rac** or an asymmetric approach that gives **61-S**. The patent does not describe how the desired enantiomer **61-S** is recovered if the racemic route is used. The racemic method is shown in Reaction 21 and begins with the conversion of **58a** to **58c** via **58b**. Reaction of the Grignard reagent **60** with **58c** produces **59** as a mixture of *E*/*Z* isomers in the ratio of 5.1:1. All of the products of these steps are liquids that are purified by vacuum distillation. The pure products are obtained in yields of 86% (**58b**), 68% (**58c**), and 46% (**59**). The crude racemate **61-rac** is obtained as a yellow oil by treating **59** with O_3.

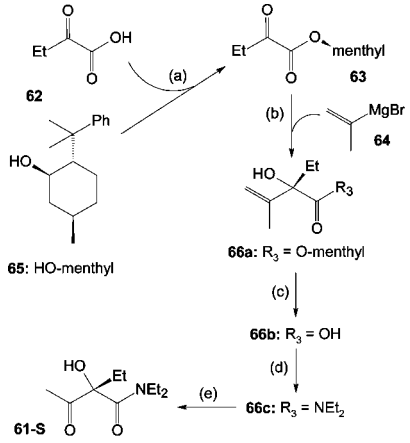
Reaction 21



(a) Et_2NH, reflux, 2.5 h; (b) EtMgBr, Et_2O, -15 °C, 75 min;
(c) Pr^i_2O, -78 °C, 1 h; (d) (i) O_3, DCM, -78 °C;
(ii) Me_2S, rt, 16 h.

The asymmetric approach to the preparation of **61-S** is shown in Reaction 22 and proceeds via quite a different route. The starting material is the oxo-acid **62** that is esterified with the chiral alcohol **66** to give **63** as a solid in 92% yield. Treatment of **63** with the Grignard **64** gives **66a** as an oil in a reported yield of 101%. Base hydrolysis of **66a** using LiOH produces **66b**, and then reaction with Et_2NH gives **66c** as another oil in 65% yield. Reaction of **66c** with O_3 produces **61-S** that is isolated in a yield of 98%.

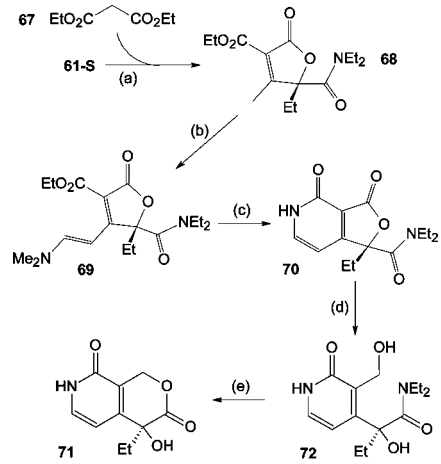
Reaction 22



(a) TsH, PhH, relux , 20 min; (b) THF, -78 °C, 50 min;
(c) Aq LiOH, THF/MeOH, 110 °C, 18.5 h;
(d) (i) $EtNPr^i_2$, DCM, -15 °C, 8 min; (ii) $SOCl_2$, -15 °C, 50 min;
(iii) Et_2NH, DCM, -15 °C, 1 h; (iv) rt, 16 h;
(e) (i) O_3, DCM, -78 °C; (ii) Me_2S, rt, 16 h.

The preparation of **71** takes place by the procedure summarised in Reaction 23 starting from **61-S** although there is also an example given using **61-rac** to give racemic **70**. In the first step **61-S** is condensed with **67** in the presence of Cs_2CO_3 to give crude **68** as a liquid in a yield reported as 141%. Treatment of **68** with $HC(NMe_2)_3$ gives crude **69** as an orange oil in 101% yield and this is cyclised with NH_4OAc **69** forming a red liquid that after purification affords crystals of **70** in 29% yield with an enantiomeric ratio (er) of 93.26:6.74. Using $CeCl_3$ followed by $NaBH_4$, the furan ring in **70** is opened, giving **72** that is recovered in 66% yield and treatment with conc HCl forms **71** that is recovered in 34% yield with an **9** of 95.0:5.0.

Reaction 23



(a) (i) Cs_2CO_3, EtOH, rt, 26 h; (ii) Cool 0 °C, aq HCl, 1 h;
(b) $HC(NMe_2)_3$, DMF, rt, 17 h; (c) NH_4OAc, DMF, 80 °C, 19 h;
(d) (i) $CeCl_3$, EtOH, rt, 10 min; (ii) $NaBH_4$, 15 °C, 5 h;
(e) Conc HCl, DME, 0 °C.

The patent describes the reactions used in the synthesis of **57** from **71** although no experimental examples are described. The patent claims that the various methods available for preparing **57** give low yields and use reagents that are toxic or give environmental problems. It is interesting to note that the route disclosed in the patent involves the use of DCM, benzene, O_3, and Me_2S all of which are less than desirable.

The patent contains ^1H and ^{13}C NMR data for many of the intermediates shown in the reaction schemes.

Advantages

The patent describes a new process for preparing a key intermediate but does involve the use of toxic and hazardous reagents.

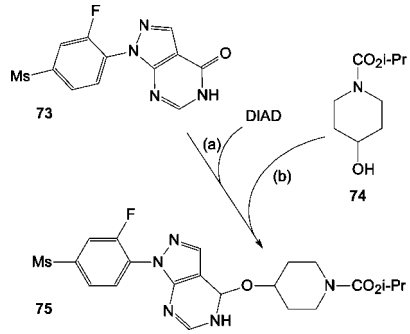
Patent No. U.S. 7,425,630

Assignee: Arena, Pharmaceuticals Inc., San Diego, California, U.S.A

Title or Subject: Processes for Preparing Pyrazolo[3,4-d]Pyrimidine Ethers

The title compounds are modulators of glucose metabolism and therefore useful in treating diabetes and obesity. The patent describes a process for preparing compounds such as **75** by a Mitsonobu reaction from **73** and **74** using DIAD and Ph_3P (Reaction 24). The reaction is carried out by multiple additions of Ph_3P, DIAD to the reaction mixture. The patent example gives details of a kilo-scale process using 4-methylmorpholine as the solvent and this gives a final yield of **75** of 57% after two recrystalliations. However, the patent then states that using THF as solvent and adding **74**, Ph_3P and DIAD in portions gives improved product yield and purity. In addition the mixture is stirred more easily, and only one crystallisation is needed. Unfortunately, the actual yield obtained using this method is not provided.

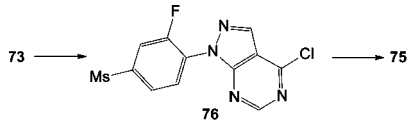
Reaction 24



(a) (i) Ph_3P, THF, <30 °C, 0.5 h; (ii) 55 °C, 2 h;
(b) (i) **74**, THF, 55 °C, 1.5 h; (ii) DIAD, Ph_3P, 55 °C, 9 h;
(iii) Cool 5 °C, 4 h, filter; (iv) Recrystallise from EtOH/H_2O.

Also described is the preparation of **76** by chlorination of **73** using $POCl_3$/DMF. The product is isolated in 90% yield with purity by HPLC of 99.26%. **76** is then converted to **75** by reaction with **74** in the presence of strong base as shown in Reaction 25.

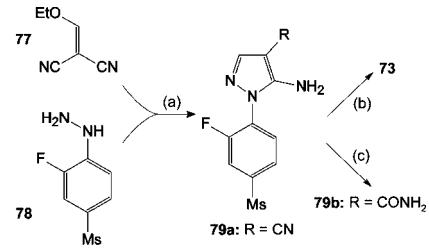
Reaction 25



(a) (i) DMF, $POCl_3$, reflux, 2 h; (ii) Cool to 55 °C, Me_2CO;
(iii) Cool to 23 °C, filter; (b) (i) **74**, PhMe, rt; (ii) Cool to 12 °C,
$NaOBu^t$; (iii) 25 °C, 2.5 h; (iii) Filter, wash in PhMe, H_2O, dry.

The patent also describes the methods used to prepare **73** and **74**. Reaction 26 shows the preparation of **73** by the reaction of the malonitrile **77** with the commercially available hydrazine **78** in the presence of a base to give **79** that is not isolated before the next step. In this reaction HCO_2H is added slowly to a concentrated solution of **79** while the solvent is distilled off. A key aspect of the preparation of **73** mentioned in the patent is the cooling step after reflux with HCO_2H. This is carried out rapidly, and in doing so hydrolysis of **79a** to give **79b** is inhibited. It is suggested that this hydrolysis reaction is favoured at temperatures of 70−80 °C. It appears that in some cases the amount of **79b** found in samples of **79a** may be as high as 5%, but by rapid cooling this can be reduced to <0.01%. Examples are given where the two steps shown in Reaction 26 are carried out on kilo scale, but the yields are not given. However, a smaller-scale experiment reports an overall yield of **73** of 89.2%. with purity by HPLC of 100%.

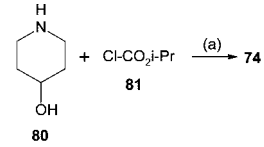
Reaction 26



(a) (i) MeOH, -10 °C, 1 h; (ii) Reflux, 5 h; (iii) Concentrate;
(b) (i) HCO_2H, H_2O, <35 °C; (ii) Distil off volatiles;
(iii) Reflux, 6 h; (iv) Cool to 0 °C, 70 min; (v) H_2O, filter,
wash in H_2O, dry; (c) H_2O, 75 °C.

The preparation of **74** is shown in Reaction 27 and involves the reaction of **80** with **81** in the presence of Et_3N. After workup, the crude product is obtained as an oil with purity by GC of 96.8% and a yield of 92%. Vacuum distillation provided 95.7% recovery of pure **74** as a colourless oil.

Reaction 27



(a) (i) Et_3N, EtOAc, <17 °C; (ii) 20 °C, 18 h;
(iii) H_2O, separate; (iv) Evaporate.

Some NMR data are given for compounds **75** and **76**, and several examples report kilo-scale experiments.

Advantages

The process gives good yields of products, and the fact that there are examples of large-scale reactions indicates the advanced stage of development of the process.

Keith Turner

Kappa Tau Consulting, 12 The Avenue, Fairfield, Stockton-on-Tees, TS19 7EY U.K.
E-mail: keith@kappa-tau.co.uk

OP800304A