Organic Process Research & Development **2009,** *13,* 829–841

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published During April and May 2009

Summary

The current review covers 20 patents from an original list of 264 that fitted the search criteria. Two patents are very timely in that they cover methods for the synthesis of Tamiflu, the drug recommended for treating swine flu. Two other patents describe improvements in the synthesis of the antidepressant Cymbalta. One focuses on the final purification stage, while the other describes a new synthesis of the active pharmaceutical ingredient (API). The detection of traces of blood using the chemiluminescence of the hydrazide luminol is the subject of one patent. As well as providing a new synthesis of luminol it also describes an improved technique for detecting blood without the use of UV light. An examination into the synthesis of the pain relief drug cilostazol has identified impurities not previously reported, and a patent describes how they are removed. Another patent focusing on impurities describes a better method of producing Apresoline that is used to treat high blood pressure. The synthesis of the antiviral drug emtricitabine has been improved by forming crystalline intermediates that are more easily isolated in high purity. Another patent uses crystallisable intermediates as a means of improving the preparation of the β-blocker carvedilol. Letrozole is used to treat advanced breast cancer, and a new synthetic route that avoids the production of an intermediate byproduct improves the purity of the final product. Singulair is used to treat asthma, and a new method for the production of its active ingredient is described that avoids the use of Bu^nLi. Another antiasthmatic drug is a quinolinone maleate salt, and a patent describes improvements in the preparation. The free base form of the molecule is unstable, and the new method avoids the need to isolate the base, thereby improving the overall process efficiency. Another patent avoids using toxic SbF_3 or highly sensitive organolithium reagent in the preparation of difluorobenzodioxoles. However, the new process still has safety concerns since it uses liquid HF. An improved method of producing tetrahydropyran compounds is described that involves hydrogenation of dihydropyrans under milder conditions than normally employed. A patent describes the preparation of a series of anthranilic acids that promote the activity of doxorubicin, a drug used to treat leukaemia and Hodgkin's lymphoma. A very comprehensive patent describes a process for preparing acyclic diol intermediates by hydride reduction. These compounds are used to prepare quinolones that are antimicrobial agents. Continuous processes are becoming more common in fine chemicals production, and a patent describes such a process for the cyanation of a hydroxyester that can be used to prepare statins. The sulphone, dapsone, has been known for over 70 years and has a wide variety of medical and nonmedical uses. A novel method for its preparation is disclosed that gives high yields and uses procedures that are said to be industrially acceptable. The search continues for low-calorie, safer sweeteners to replace sucrose, and monatin is such a compound that is found in the bark of a South African plant. A method for its purification is described that racemises the pair of optical isomers that are less sweet into the pair that have the very sweet taste. An example of a misleading patent title relates to the essential amino acid methionine. Although the patent discusses the chemical process, it actually focuses on the composition of the grade of stainless steel that is used in the reactor. There is no legal or commercial significance in the choice of patents in this review although a number of patents describe experiments on kilo scale and above. In one in particular all examples are on kilo scale experiments, and hence this may indicate an advanced stage of development or even commercial operation. The advantages mentioned in this review are those claimed in the patent, unless this reviewer has personal knowledge of the subject.

Patent No. U.S. 7,514,580

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

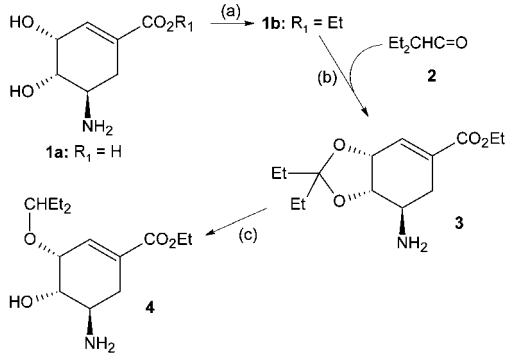
Title or Subject: Process for the Preparation of 4,5-Diaminoshikimic Acid Derivatives

This is the first of two patents to describe processes to prepare oseltamivir **7c** that is used as the H_3PO_4 salt and more commonly known as Tamiflu, the primary drug for the treatment of H1N1 virus or swine flu. These patents are timely since, while this review was written, the WHO has declared the outbreak of swine flu as a pandemic. The patent states that the problem at the root of the invention is to prepare **7c** from the acid **1a** that is a readily available starting material obtainable from biotech processes. The patent claims that the new synthesis is achieved in fewer steps than in the original method, and the route is outlined in Reactions 1 and 2. The route is split into two schemes

10.1021/op900200t CCC: $40.75
Published on Web 08/18/2009

purely for clarity. The first stage (Reaction 1) is to prepare **4** starting from **1a**, and the initial step is esterification of **1a** to give **1b** using MsOH as catalyst. The example describes the isolation of the ester as the crude mesyl salt. Also described is the formation of the HCl salt by using HCl in the esterification. However, the examples do not use these salts in the following steps. The ester **1b** is treated with the ketone **2** in the presence of MsOH to form crude **3** that is isolated in 87% yield. The next stage is described as a reductive ketal-opening reaction using Et_3SiH and $TiCl_4$. This reaction is started at −70 °C, and then further silane is added at −25 °C. After workup and purification using column chromatography (ColC) **4** is obtained as a yellow oil in 47% yield.

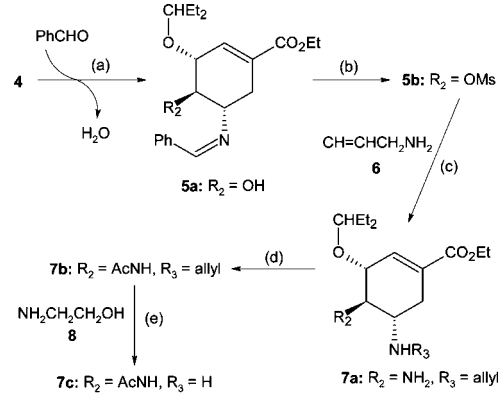
Reaction 1



(a) MsOH, EtOH, reflux, 1 h; (b) MsOH, reflux, 2 h; (c) (i) Et_3SiH, $TiCl_4$, DCM, -70 C; (ii) -25 °C, 18 h; (iii) Et_3SiH, -25 °C, 6 h.

The next stage is the preparation of **7a** and consists of a very long sequence of steps in a one-pot reaction via the intermediates **5a** and **5b** that are not isolated. In the first step **4** is refluxed with PhCHO to form the Schiff base **5a**. The formation of the Schiff base is the preferred method for the conversion of the free amine group in **4** to the substituted amine in **7a**. After the formation of **5a** it is then treated with Et_3N and portions of MsCl over an extended period. The reaction is followed by monitoring the amount of **5a** and **5b** using HPLC. When there is <1% of **5a** remaining, **6** is added to the mixture and heated under pressure. After this stage and workup the crude diamine **7a** is obtained as a red-brown oil in 89% yield. In the next step **7a** is acetylated to produce **7b**, and again there are several stages in the reaction sequence including an initial stage where the MTBE solvent is added, 50% is distilled off, and then more is added before cooling and performing the acetylation. The workup in this stage is quite lengthy, and the patent should be consulted for full details. The product **7b** is isolated in 83% yield and then undergoes an isomerisation/hydrolysis step to form **7c**. Pd/C catalyses the reaction in the presence of an amine, and **8** is the preferred option. The patent states that **7c** can be isolated in this final step in 70% yield by evaporation and crystallisation, but it is preferred to keep it in solution and then convert it to the 1:1 salt with H_3PO_4. There are no details given for this step.

Reaction 2



(a) MTBE, reflux, 2 h; (b) (i) Et_3N, 0 °C; (ii) MsCl, <5 °C, 85 min; (iii) rt, 45 min; (iv) MsCl, rt; (c) (i) MTBE, argon, 4.5 bar, 110 °C, 15 h; (ii) Evaporate; (iii) 2M HCl, EtOAc, rt; (iv) Aq KOH to pH 10.1, < 20 °C; (d) (i) MTBE, HOAc, <5 °C; (ii) MsOH, Ac_2O, <5 °C; (iii) rt, 14 h; (e) (i) Pd/C, EtOH, reflux, 3 h, cool, filter; (ii) Evaporate.

Advantages

The process seems to be complicated in places but does give high yields and perhaps has been developed at an opportune time.

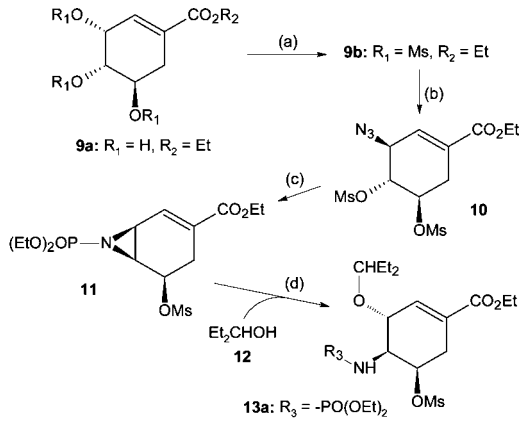
Patent No. U.S. 7,531,687

Assignee: Roche Palo Alto LLC, Palo Alto, California, U.S.A

Title or Subject: Preparation of Oseltamivir Phosphate

This is the second patent that describes a process to prepare this now very important drug. As with the previous patent the process consists of a number of steps, and only the main reagents are shown in the following reaction schemes. The first stage of the process is the preparation of the phosphoramide **13a** by the route outlined in Reaction 3. The process starts with formation of the trimesylate ester **9b** that is recovered in the crude form as a brown resin in 97% yield. The azide **10** is then produced as a light-yellow oil in a regioselective reaction of **9b** with NaN_3 in DMSO. The crude product is purified by ColC and obtained as a colourless oil in 67% yield. The azide **10** then undergoes a Staudinger reduction with $P(OEt)_3$ to form the crude iminophosphorane **11** as an oil in 67% yield. This is also purified by ColC to give an oil in only 18% yield. The last step of this stage is the opening of the aziridine ring using BF_3 in **12** to give **13a** that is isolated as an oil in 91% yield that gives a solid when purified using ColC.

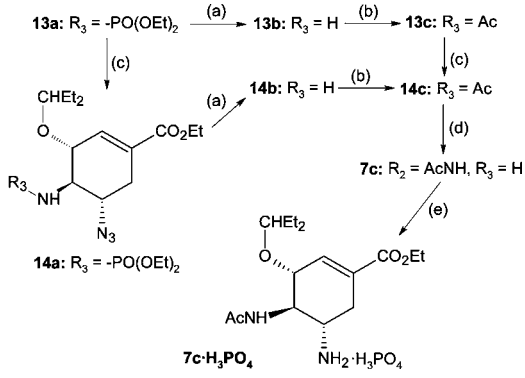
Reaction 3



(a) MsCl, Et_3N, EtOAc, <5°C, 76 min; (b) NaN_3, DMSO, rt, 19 h; (c) $(EtO)_3P$, PhMe, reflux 7 h; (d) $BF_3{\cdot}Et_2O$, rt, 16 h;

The next stage of the process has two possible routes, and these are shown in Reaction 4. Both options proceed via azide and only differ in the order of the steps. The first option converts **13a** to the amine **13b** by acid-catalysed hydrolysis, and this is then converted to the acylamine **13c** that reacts with NaN_3 to form **14c**. The alternative route to **14c** initially produces the azide **14a** that is hydrolysed to **14b**, and this is converted to **14c**. In the final step the free base **7c** is obtained from **14c** in a Staudinger reduction using PBu^n_3. It is reported that, if this reduction is carried out in the presence of an acid, then the hydrolysis of the ester group in **14c** is suppressed, and HOAc is a suitable acid. The preparation of the phosphate salt of **7c** is described and is obtained in 91% yield with an assay of >99%, containing <0.5% total impurities and no individual impurity >0.1%.

Reaction 4



(a) (i) H_2SO_4, EtOH, reflux, 16 h; (ii) Cool, 28% NaOH; (b) 1M $NaHCO_3$, EtOAc, Ac_2O, rt 1 h; (c) NaN_3, EtOH, DMSO, 90 °C, 21 h; (d) (i) HOAc, H_2O, EtOH, rt; (ii) PBu^n_3, EtOH, 5 °C, 3 h; (iii) 25 °C, 4 h; (iv) HOAc, evaporate; (v) EtOH; (e) H_3PO_4, EtOH, 55 °C, seed.

Advantages

The process does provide an alternative synthesis of this very important drug, and it is claimed that it is not necessary to isolate and purify the intermediates so that the overall process efficiency is enhanced.

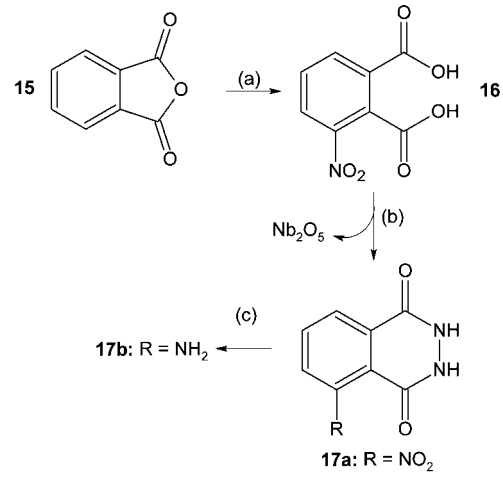
Patent No. U.S. 7,517,983

Assignee: Universidade Federal Do Rio De Janeiro-UFRG, Rio de Janeiro, Brazil

Title or Subject: Process for the Production of Hydrazides and Derivatives from Hydrazines and Dicarboxylic Acid

This patent is aimed at providing a simple and safe method of producing a hydrazide compound that can be made to undergo chemiluminescence under oxidising conditions. Specific mention is made of the new process for the synthesis of luminol **17b** and its use in a blood-testing kit that does not require the use of UV light. Many readers who watch TV programmes such as *Crime Scene Investigation* (*CSI*) will be familiar with the method used to detect traces of blood at crime scenes. The synthesis of **17b** is by the route shown in Reaction 5 and starts with the nitration of **15** using HNO_3/H_2SO_4 to form **16**; however, no specific details are given for this step. The next step is the formation of the hydrazide **17a** by reaction of **16** with H_2NNH_2 in the presence of $NbCl_5$. It known that this reagent is a mild Lewis acid, and its use in this reaction is the key aspect of the patent. The patent suggests that the reaction is likely to proceed via the acid chloride since Nb_2O_5 is formed in this step. The final stage to make **17b** is the reduction of the NO_2 group in **17a**, but full details are not given. The use of $Na_2S_2O_4$ for this reduction is mentioned, and by using catalytic hydrogenation over a Pd/C catalyst the final product **17b** is obtained in quantitative yield.

Reaction 5



(a) HNO_3/H_2SO_4; (b) (i) $NbCl_5$, dioxane, rt; (ii) 40% aq H_2NNH_2, 50 °C, 4 h; (iii) Cool, filter off solids; (iv) Extract with EtOAc, wash, dry; (c) Pd/C, H_2, dioxane.

The blood-test kits are composed of two solutions that, when mixed with trace materials containing Fe, cause chemiluminescence and a strong blue colour. The Fe catalyses the reaction, and only traces are needed; hence, the use of the technique in the detection of blood. The first solution contains an alkaline solution of **17b**, and the second is an alkaline solution of H_2O_2. In each case the preferred alkali is an alkali metal hydroxide. By using an alkaline solution of H_2O_2 the chemiluminescence reaction can be seen for a longer time and without the need for UV light. The patent states that the alkali stabilises the H_2O_2 solution and slows its degradation. Alternative kits are said to

contain weaker alkalis such as Na_2CO_3 or Na_3BO_4 that require the use of UV light and do not maintain the chemiluminescence reaction as long as that in the present invention.

Advantages

The process uses a gives an improved method of producing luminol and also provides an improved, stable blood-test kit that could see widespread use in forensic investigations.

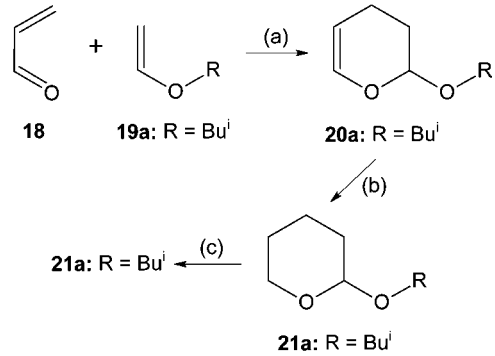
Patent No. U.S. 7,518,003

Assignee: Showa Denko K.K., Tokyo, Japan

Title or Subject: Process for the Production of Tetrahydropyran Compounds

The main compounds mentioned in the patent are the alkoxy derivatives such as **21a**, whereas the process described in the patent is directed towards the production of **21b** as a solvent for Grignard reactions, in polymerisations, and also as a reaction intermediate. Catalytic hydrogenation of a dihydropyran is the usual method used to prepare the tetrahydropyran, and it is claimed that such processes have low selectivity, require very high pressure, or give low yields. The patent discloses that by using acidic conditions it is possible to perform the hydrogenation under milder conditions. The overall process in the patent to produce **21b** is shown in Reaction 6. The initial step for the preparation of **20a** is based on a 1950 report and gives a 94% yield of crude **20a** that is purified by distillation. One example in the patent describes the production of 17.1 kg of **20a**, and another produces the *n*-butoxy analogue on a similar scale. The hydrogenation of **20a** is carried out in two steps with the first being carried out at rt to give a quantitative yield of **21b**. Addition of an acidic component such as $NaHSO_4$ and an increase in temperature to 80 °C gives **21a**. A 92% yield of **21b** was obtained from a batch of almost 47 kg of **20a**, and Bu^iOH was recovered in 93% yield. Smaller-scale examples that were carried out at higher temperatures with $NaHSO_4$ added at the start were less efficient. The yield of **21b** was down to 50%, and a lower yield of alcohol was obtained.

Reaction 6



(a) BHT, 135 °C, 16 h; (b) Pd/C, 0.8 MPa H_2, rt, 2.5 h;
(c) (i) $NaHSO_4$, 0.8 MPa H_2, 80 °C, 12 h;
(ii) 1.2 MPa H_2, 80 °C, 4 h.

Advantages

The process is clearly at an advanced scale of development and gives high yields of product and good recovery of alcohol. It does provide a route to the desired product under milder conditions than alternatives.

Patent No. U.S. 7,524,861

Inventors: D.F. Hayman and M. Wright, Slough, Berkshire SL1 4NL, United Kingdom

Title or Subject: Process for the Preparation of a Hydrate of an Anthranilic Acid Derivative

This patent is not assigned to a company although the address of the inventors on the patent is that of the biopharmaceutical company, Xenova Ltd. The compounds mentioned in the patent are used to enhance the efficacy of anticancer drugs, and one drug specifically mentioned is doxorubicin that is commonly used to treat some types of leukaemia and Hodgkin's lymphoma. The patent lists 45 separate compounds with that of main interest being the hexahydrate of the bismesylate salt of **22**. The patent describes that this is prepared by the following sequence of steps:

(i) combine **22** with EtOH, excess H_2O, and MsOH then heat to 55 °C

(ii) filter at 55 °C, then wash in EtOH/H_2O (four times) at 55 °C

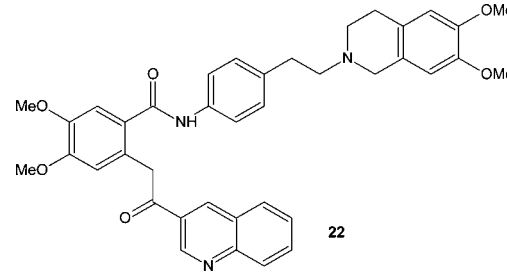
(iii) add filtrate and washes to refluxing Me_2CO and heat for 1 h

(iv) cool for 2 h at −5 °C, filter, wash in Me_2CO, then dry in vacuum for 30 min

(v) dry in an open dish in a gentle air stream at ambient temperature and humidity overnight.

The hexahydrate salt was obtained in 91.5% yield, and the purity by HPLC was 99.7% and has a better shelf life than several indeterminate hydrates obtained by alternative processes. However, the salt loses water in a vacuum but can be rehydrated in a moist atmosphere, and the last stage of the process seems to do this. The relative humidity level is preferably between 50 to 80%.

Compound 22



22

The patent gives details of the effectiveness of the hydrate salt **22** and of several related compounds in promoting the activity of doxorubicin and a selection of other cytotoxic agents.

Advantages

The process provides an effective method of making a stable hydrate salt that has good stability and can be used in pharmaceutical formulations.

Patent No. U.S. 7,524,960

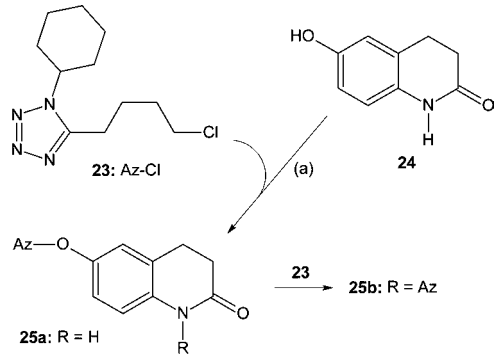
Assignee: Chemagis Ltd., Bnei-Brak, Israel

Title or Subject: Highly Pure Cilostazol and an Improved Process for Obtaining the Same

Cilostazol **25a** inhibits platelet aggregation and is used to relieve pain in the limbs by dilating the arteries and increasing blood flow. Alternative processes for the preparation of **25a**

have been reviewed (*Org. Process Res. Dev.* **2008**, *12*, 1031) and the usual method is the reaction of the chloro compound **23** with **24** in the presence of a base such as DBU or inorganic bases (Reaction 7). In some processes a phase transfer catalyst (PTC) may be used, and all are said to use an excess of one of the starting materials. This or the use of a PTC creates problems in the purification of **25a** and an additional, previously unreported problem in the synthesis of **25a** is mentioned. It is stated that a substantial amount of the compound **25b** is produced in the synthesis of **25a** using any of the alternative processes. Several examples are described in the patent for preparing **25a** that follow the procedures described in other methods, and up to 1.64% of **25b** is found. The amount of **25b** seems to be higher when inorganic bases are used. The patent suggests that **25b** may not have been observed previously because, when the analysis is carried out by HPLC, it has longer retention time (>30 min) compared to <10 min for **25a**. The improved process involves a more efficient reaction stage and an improved recrystallisation step. The level of **25b** is reduced by carrying out the reaction in an alcohol containing water in the ratio of about 18:1 and using **24** and **23** in the ratio of 1.3:1. The isolation and purification of **25a** is carried out by recrystallising from Pr^nOH in the presence of aqueous NaOH. The yield of crude **25a** reported is 70−80%, and after recrystallisation the purity of **25a** is up to 99.9% with <0.06% of **25b**.

Reaction 7



(a) (i) KOH, Pr^iOH, reflux, 7 h; (ii) Cool <15 °C, 6 h, filter; (iii) Wash in Pr^iOH, H_2O, dry 50 °C, 16 h;

Advantages

The process is more efficient than alternatives while using the same reagents, and in addition, it provides higher-purity product.

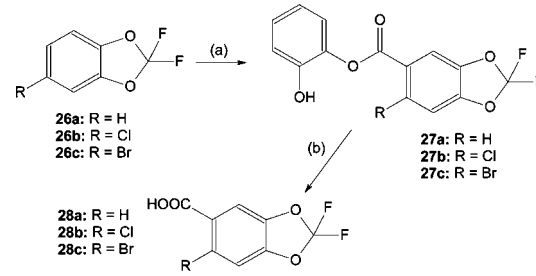
Patent No. U.S. 7,524,976

Assignee: Lanxess Deutschland GmbH, Leverkusen, Germany

Title or Subject: Process for Preparing Difluorobenzo-1,3-dioxole-5-carboxylic Acid Derivatives

The patent describes a process to produce a range of esters **27a**, **b**, and **c** and the corresponding acids **28a**, **b**, and **c** that are intermediates for agrochemicals and pharmaceuticals. The patent states that there are two processes for preparing the acids, but one involves the use of SbF_3 that is expensive and highly toxic. The other involves using highly sensitive organolithium reagents, and so neither is practical for industrial use. The patent discloses a process for preparing the esters that can then be hydrolysed to give the acids. The esters are novel compounds with the halo-esters **27b** and **27c** being specifically claimed as such in the patent. Details for the preparation of **27a** are shown in Reaction 8, carried out by initially preparing a solution of HBF_4 by injecting BF_3 into liquid HF at 0 °C. To this is then added **26a**, and after the reaction the product is precipitated by addition of ice-cold water. It is then redissolved by addition of DCM, and after further workup **27a** is obtained in a yield 43.3% or 86.6% based on **26a**. The acid **28a** is obtained by base hydrolysis of **27a**, and the example in the patent describes the preparation without isolation of the ester.

Reaction 8



(a) (i) HBF_4, 15 °C, 10 h; (ii) H_2O, 0 °C; (iii) DCM, 0 °C, filter; (iv) Aq $NaHCO_3$, dry, evaporate; (b) (i) Aq KOH, pH 11, 50 °C, 6 h; (ii) Cool, filter; (iii) H_2SO_4, pH 5, filter, dry

Basic ^1H NMR data are given for the esters **27a**, **b**, and **c** and the acid **28a**.

Advantages

The process enables a novel range of esters to be obtained that can be hydrolysed to the acids. It avoids the use of SbF_3 but does require the use of liquid HF and hence still has significant safety and handling issues.

Patent No. U.S. 7,528,254

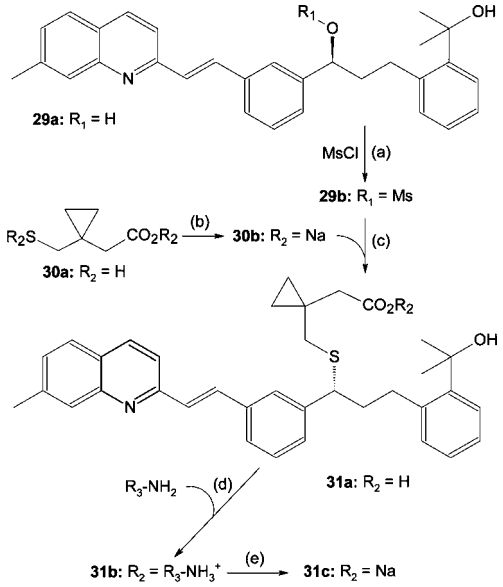
Assignee: Chemagis Ltd., Bnei-Brak, Israel

Title or Subject: Process for Preparing Montelukast and Salts Thereof

The Na salt **31c** is used to treat asthma and allergic rhinitis and is available under the name Singulair. Several of the processes for its preparation are summarised, and a major problem mentioned in the patent is the use of Bu^nLi because it is expensive and dangerous. The new process does not use this reagent and is summarised in Reaction 9. The preparation of **31c** begins with the conversion of the alcohol **29a** to the mesylate **29b** using MsCl in the presence of a Pr^i_2NEt. The reaction is monitored by HPLC, and, when <1% of **29a** remains, the crude material is recovered as a solution in THF and used in the next stage. In this step **30a** is converted to the disodium salt **30b** using solid NaOH and then dissolved in DMF or NMP followed by portions of the THF solution of **29b**. The mixture is then acidified using tartaric acid (TTA), and the crude thioether acid **31a** is obtained as an oil. In the next step **31a** is treated with a cyclic amine to form the ammonium salt **31b**. The patent uses either cyclohexyl- or cyclooctylamines, and the salts are recovered in 70% yield and up to 99% purity by HPLC. The salt is then converted to the Na salt

31c by dissolving in DCM containing citric acid then treated with aqueous NaOH. After freeze-drying the Na salt is obtained in 99% yield and 99.8% purity by HPLC.

Reaction 9



(a) (i) Pr^{i}_2EtN, THF, -15 °C, 2 h; (ii) Filter, -15 °C; (b) (i) DMF, rt; (ii) NaOH, rt, 1 h; (c) (i) THF, 25 °C, 5 h; (ii) EtOAc, aq NaCl, TTA, 25 °C, 15 min; (iii) Evaporate; (d) (i) EtOAc, 25 °C; (ii) Seed, filter, wash, dry; (e) (i) DCM, citric acid, rt, 30 min; (ii) 1M NaOH to pH 10.5, spray dry.

In the reaction of **30b** with **29a** it is essential that water is present, and it is postulated that this dissolves the dianion **30b** more efficiently, thus allowing improved reactivity with **29a**. The final purification of **31c** includes crystallisation and then spray- or freeze-drying with the latter being specifically mentioned in one of the claims.

Advantages

The patent provides an improved method of preparing the desired salt without the need to use $Bu^{n}Li$ as required in alternative processes.

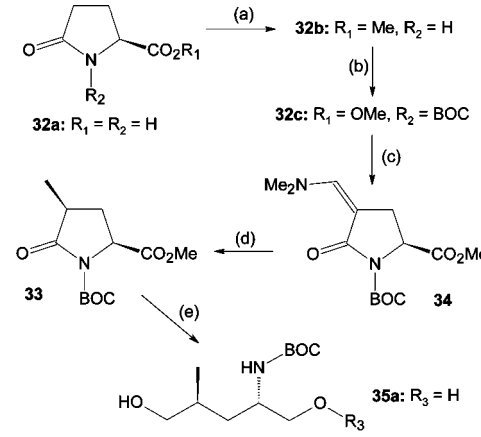
Patent No. U.S. 7,528,264

Assignee: The Proctor & Gamble Company, Cincinnati, Ohio, U.S.A

Title or Subject: Hydride Reduction Process for Preparing Quinolone Intermediates

The intermediates of interest in this patent are acyclic diols such as **35a** that are useful in the preparation of antimicrobial compounds. The patent briefly mentions alternative methods for preparing related quinolone compounds and states that improvements are required. The patent contains a substantial amount of experimental details with the preparation of **35a** actually only a relatively small part. Reaction 10 summarises the method used to prepare **35a** and for brevity only the main reagents are shown. The first stage is the conversion of the amino acid **32a** to the ester **32b** using $SOCl_2$ and MeOH, and this is recovered as a thick oil. Et_3N is added, and after removal of the Et_3NHCl, DMAP and $(BOC)_2CO$ are added to form the protected amine **32c** in 52.4% isolated yield. Reaction of **32c** with Bredereck's reagent gives **34** that is isolated in 77.9% yield, and hydrogenolysis produces **33**. This reaction is carried out using the supported Pd catalyst ESCAT-142 with **33** being isolated in quantitative yield. The diol **35a** is obtained from **33** using $NaBH_4$ followed by $CaCl_2 \cdot 2H_2O$. After phase separation and workup **33** is isolated in 66% yield.

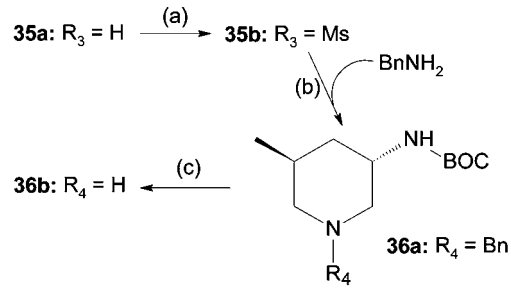
Reaction 10



(a) (i) $SOCl_2$, MeOH, <30 °C, 2 h; (ii) Et_3N, EtOAc, 30 °C, 0.5 h; (iii) $(BOC)_2CO$, DMAP, < 30 °C, 1.5 h; (c) (i) $(Me_2N)_2OBu^{t}$, DME, 75 °C, 3 h; (ii) Cool to 5 °C, filter, dry; (d) Pd/C, $Pr^{i}OH$, H_2, 3 atm, 45 °C, 18 h; (e) (i) $NaBH_4$, EtOH, MTBE, <5 °C; (ii) $CaCl_2 \cdot 2H_2O$, 1 h; (iii) 20 °C, 12 h.

The diol **35a** is then used to prepare the protected amine **36b** as shown in Reaction 11. The first step is formation of the mesylate **35b** using MsCl and Et_3N. The patent reports that the reaction is monitored by HPLC or TLC, but no time is specified other than a few hours. The product **35b** is obtained as a slurry, but neither yield nor purity is mentioned. The slurry is used directly in the next step where it is reacted with $BnNH_2$. Again, an unspecified time is mentioned for the reaction that produces a triphasic system after addition of EtOAc, hexane, and an aqueous K_2CO_3 solution to the reaction mixture. Separate workup of the middle and upper layers gives a solution that after evaporation and large-scale preparative chromatography provides **36a** as an oil in unspecified yield. Removal of the Bn group by hydrogenolysis using Pd/C catalyst (E101) gives an unreported yield of **36b** as a waxy solid.

Reaction 11

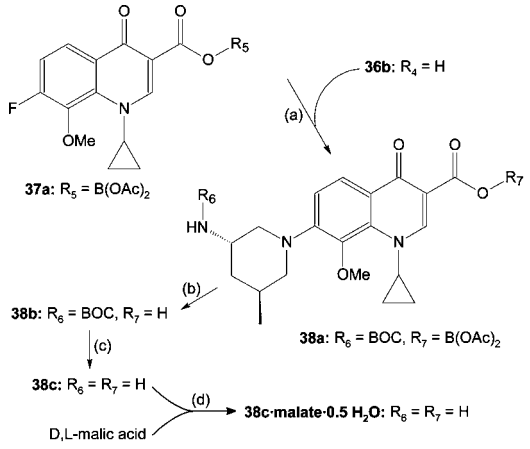


(a) (i) Et_3N, PriOAc, 15 °C; (ii) MsCl, 0 °C; (b) (i) DME, 55 °C; (ii) Evaporate, EtOAc, hexane, aq K_2CO_3, rt, separate; (c) Pd/C, H_2, 3 atm, EtOH, 45 °C; (ii) Cool, filter, wash.

The amine **36b** is then used in the synthesis of the malate salt of the quinolone **38c** by the route shown in Reaction 12. This starts with the reaction of **36b** with **37** to give the intermediate **38a** that

is not isolated. This reaction is monitored by HPLC or TLC and takes 72 h for completion. **38a** is then hydrolysed to give the acid **38b**, but again this is not isolated. Several extractions with DCM are needed in the workup of this step, and HOAc is used to adjust the pH. The DCM solution of **38b** is then treated with HCl to remove the BOC group, and several more extractions and further pH adjustment with NaOH are needed. The product **38c** is isolated as a solid in 79% yield and then converted to the hemihydrate malate salt in 70% yield.

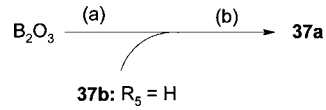
Reaction 12



(a) Et_3N, MeCN, 50 °C, 72 h; (b) (i) Aq NaOH, 35 °C, 4 h; (ii) HOAc to pH 6-8, extract in DCM; (c) (i) 6M HCl, 35 °C, 12 h; (ii) Wash in DCM, aq NaOH to pH 6-8; <65 °C, filter; (d) (i) EtOH, H_2O, reflux; (ii) Charcoal, filter, cool 45 °C, 2 h.

The patent also provides details for the preparation of the borate **37** as outlined in Reaction 13. Initial acetylation of B_2O_3 with Ac_2O/HOAc is followed by cooling and addition of **39**. The product is isolated in 86.4% yield by precipitation using MTBE.

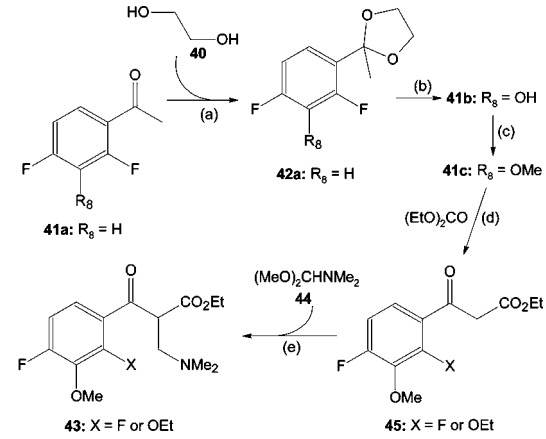
Reaction 13



(a) (i) HOAc, Ac_2O, reflux, 2 h; (ii) Cool 40 C; (b) (i) Reflux, 6 h; (ii) Cool to 90 °C, PhMe; (iii) Cool 50 °C, MTBE; (iv) Cool to 20 °C, filter, wash in MTBE, dry.

The patent also provides full details for the preparation of the fluoroquinolinic acid **39**, and this is shown in Reactions 14 and 15. The first step is preparation of the cyclic acetal **42a** by the reaction of **41a** with **40** in the presence of TsOH. The product **42a** is obtained as an oil in 86% and used without purification in the formation of the phenol **41b**. This comprises a series of four steps in which **42a** is treated with Bu^nLi followed by $B(OMe)_3$, HOAc, and H_2O_2. After workup **41b** is obtained as a solid in 79% yield and then converted to the ether **41c** using $(MeO)_2SO_2$. The **41c** is obtained in 90% yield and used without further purification in the next stage where it reacts with $(EtO)_2CO$ in the presence of NaH to produce **45**. This is a mixture of the fluoro and EtO derivatives that is used directly in the next step where the mixture is reacted with **44**, and the mixture **43** is obtained. The next step in the synthesis is shown in Reaction 14 that, in the patent, is carried out without isolation of **43** and is shown separately for clarity.

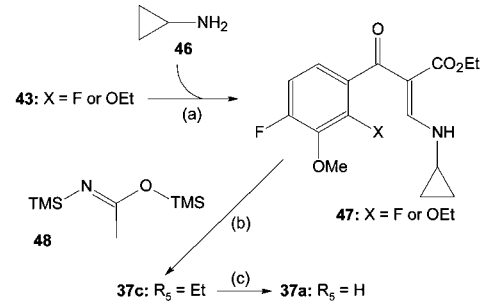
Reaction 14



(a) TsOH, PhMe, reflux; (b) (i) Bu^nLi, THF, -40 °C, 1 h; (ii) $B(OMe)_3$, -40 °C, 1 h; (iii) HOAc, -30 °C; (iv) H_2O, rt, 16 h; (v) H_2O_2, rt, 1 h; (c) $(MeO)_2SO_2$, K_2CO_3, PhMe, reflux, 1 h; (d) NaH, PhMe, 90 °C, 1 h; (e) PhMe, reflux,1 h;

After the formation of **43** the mixture is cooled and then reacted with **46** at rt. The product **47** is a mixture of fluoro and EtO derivatives (Reaction 15) that is recovered as a solution in PhMe. After the mixture is concentrated, it is treated with **48** in two portions, and the ethyl ester **37c** (R_5 = Et) is obtained in 82% yield. In the final step hydrolysis of **37c** with HCl in EtOH produces **37a** (R_5 = H) that is isolated in 95% yield.

Reaction 15



(b) PhMe, rt, 0.5 h; (b) PhMe, reflux, >0.5 h; (c) 32% HCl, EtOH, reflux 5 h.

All of the experimental work described in the patent and summarised here is carried out at kilo scale, suggesting that the process is at an advanced stage of development. The patent includes some ^1H and ^{19}F NMR data as well as brief Raman and IR spectral data for some of the intermediates.

Advantages

The process is clearly suitable for large-scale use and gives very good yields in the many steps that are involved in the process.

Patent No. U.S. 7,531,653

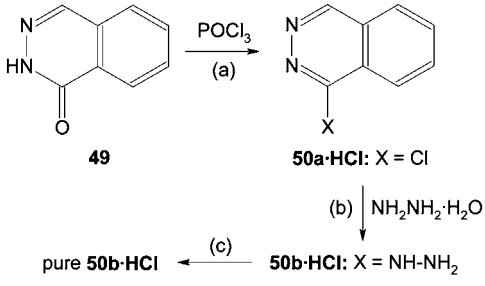
Assignee: Navinta LLC, Ewing, New Jersey, U.S.A

Title or Subject: Manufacture of Pure Hydralazine Salts

Hydralazine **50b** as the HCl salt is available as Apresoline and used to treat high blood pressure and a number of coronary problems. The patent summarises a number of reports related to the instability of the drug during storage and the formation of insoluble yellow materials. It is stated that there are no known

methods for reducing the level of these <0.001%, and the objective of the patent is to provide a process for making pure **50b** containing <0.05% of any individual impurity. The preparation of **50b** is shown in Reaction 16, and this uses the same basic chemistry as for alternative methods. The first step is the chlorination of **49** using $POCl_3$ to produce **50a** that is recovered as a salt. This is either the HCl salt or a mixture of the HCl and HSO_4 salts. The alternative processes use four or more equivalents of $POCl_3$, and this does lead to a larger reaction exotherm, increased safety issues, and a waste disposal and product purification problem. Hence, the patent recommends the use of much less $POCl_3$, and the highest yield (85%) of **50a** is obtained when using only 1.5 equiv of $POCl_3$. Examples do describe the use of more $POCl_3$, but the yield of **50a** drops to 65%. The reaction is carried out by adding **49** to $POCl_3$ in PhMe at rt, and this causes the temperature to rise to 45 °C. The mixture is then heated to about 65 °C, and excess $POCl_3$ removed by distillation before addition of HCl or HCl/H_2SO_4 precipitates the salt of **50a**. The formation of **50b** is carried out by addition of hydrazine hydrate to **50a** at <5 °C. This is preferably carried out in a water-miscible solvent such as an alcohol or THF, although there is an example where no solvent is used, and a yield of 99% of the free base **50b** is obtained. The free base is then converted to the HCl salt, and this is purified by treatment with Et_3N followed by activated C and EDTA. The yield of the HCl salt **50b** is 95%, containing 0.00004% hydrazine.

Reaction 16



(a) (i) $POCl_3$, PhMe, rt; (ii) 65 °C, 3 h; (iii) Aq HCl, EtOAc, rt; (b) (i) EtOH, <5 °C, 24 h; (ii) MeOH, C, rt. 0.5 h, filter; (iii) HCl gas, 0.25 h, filter; (c) (i) MeOH, Et_3N, 65 °C, filter; (ii) HCl gas, <5 °C, 1 h, filter; (iii) H_2O, C, EDTA, 80 °C, 0.5 h, filter hot; (iv) MeOH, <5 °C; (v) -20 °C, filter, wash, dry.

The patent contains comparative examples carried out using procedures from an alternative process. These gave yields of **50a·HCl** at up to 80% and **50b·HCl** at 65% containing 0.0004% hydrazine. There are no details in the patent regarding the stability of the product made by this improved method.

Advantages

The process does give higher-purity product, but it is not known if the stability is improved.

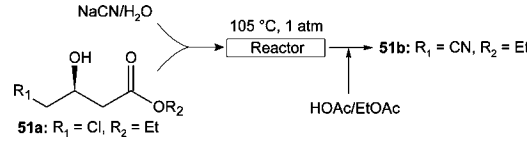
Patent No. U.S. 7,531,683

Assignee: Phoenix Chemicals Limited, Bromborough, United Kingdom

Title or Subject: Continuous Process for the Cyanation of Hydrogenated β-Ketoesters

The patent describes a process to produce the ester **51b** (R_1 = CN, R_2 = Et)) that is used in the preparation of hypolipidemic agents such as statins for reducing high blood cholesterol levels. Although the patent title mentions hydrogenated β-ketoesters, there are no experimental details reported for the hydrogenation step. The focus of the patent is the use of the ester **51a** for the preparation of **51b**, and **51a** itself is preferably obtained by a continuous enantioselective hydrogenation of a β-ketoester. A range of chiral Ru phosphine catalysts is mentioned as being suitable for this step. Several processes for preparing **51b** are summarised, and they are said to suffer from a number of disadvantages. These include being laboratory-scale methods, giving low yield or conversion, using expensive or unnecessary reagents, or providing poor stereoselectivity. The assignee of this patent specialises in developing continuous processes, and the patent discloses such a method for making **51b** by the cyanation of the hydroxyester **51a**. The patent describes a method for preparing the cyanoester **51b** and also one for the cyanoacid **51c** (R_1 = CN, R_2 = H). The ester process is shown in Reaction 17, and in this procedure two streams are separately pumped into a reactor maintained at 105 °C. The streams are **51a** and an aqueous solution of NaCN. The residence time (RT) is 48 s, and at the reactor exit a mixture of HOAc and EtOAc is injected to quench the reaction. The product was isolated in a 67.4% yield by recovery of the EtOAc and evaporation. The flow rates were 0.14 mL/min of a 14.7% NaCN solution and 0.8 mL/min of pure **51a**.

Reaction 17



The method used to prepare the cyanoacid **51c** (R_1 = CN, R_2 = H) involves mixing a NaCN solution with an 80% aqueous solution of HOAc and feeding this to a plug flow reactor (PFR), with a RT of 1.4 s, at ambient temperature. This mixture is then fed to a two-stage PFR at 105 °C where it is premixed in the first stage with **51a**. The RT in this case is 4.5 s, and the mixed reactants pass to the second stage of the PFR at the same temperature and with a residence time of 72 s. The mixture that leaves the reactor is quenched with aq HOAc at ambient temperature in a PFR having a RT of 4.0 s. The product **51c** is recovered by steam distillation and purified by extraction in DCM, followed by vacuum distillation. The acid is obtained in 80% yield. Flow rates for this procedure were not given.

Advantages

The process gives high yields of the desired product and seems to have been specially developed in conjunction with a continuous process for preparing the chiral starting material.

Patent No. U.S. 7,531,694

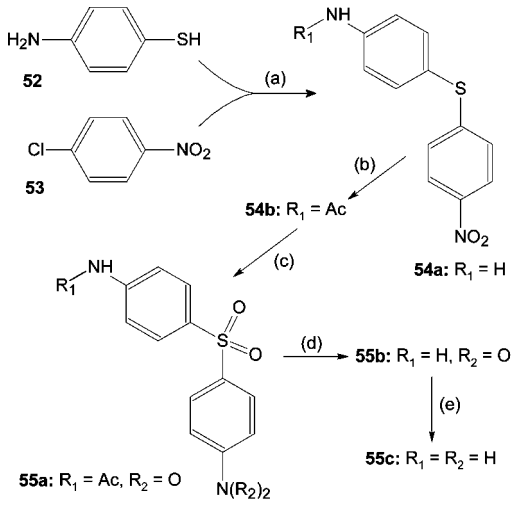
Assignee: Lundbeck Pharmaceuticals Italy S.p.A., Padova, Italy

Title or Subject: Process for Synthesis of 4,4′-Diaminodiphenyl Sulfone

The title compound is known as dapsone **55c** that has a diverse range of uses including as a hardening agent in epoxy resins and as an antibiotic for treating leprosy or dermatitis

herpetiformis. It has also been investigated for treating certain types of pneumonia associated with HIV. **55c** was first reported in 1938 and there have been several methods describing its synthesis. These generally involve a condensation of para-substituted phenyl compounds or oxidation of para-substituted diphenylsulphides, and byproduct formation is often high. Hence, the new process is aimed at overcoming this problem, and the route is outlined in Reaction 18. The first step is the base-catalysed condensation of **52** with **53** to form the thioether **54a**. This is carried out in the presence of a PTC, and after workup the product is isolated in 95% yield at 99% purity. The next step is the oxidation of the thioether group in **54a**, and the patent states that in order to obtain a good yield and purity it is necessary to protect the amine group prior to oxidation. Hence the NH_2 group in **54a** is acetylated with Ac_2O to give amide **54b**. The amide is not isolated but is oxidised directly to the sulphone **55b** using Na_2WO_4 followed by H_2O_2 in the presence of an acid. When oxalic acid is used, the yield of **55a** is 83%, and when MsOH is used, the yield is 90% with the purity being 90% in both cases. From this point on the patent is not clear on the procedures involved for the last stage. The examples in the patent describe the reduction of the amine **55b** to **55c** but do not indicate how **55a** is converted to **55b**. The reduction of **55b** is carried out using Pd/C catalyst in the presence of TsOH, and crude **55c** is isolated in a yield 82% yield and 99.5% purity. An alternative procedure uses MsOH instead of TsOH. The final workup stage is a neutralisation with NH_4OH, and the crude product is obtained in 94% yield. After crystallisation the yield of pure product is 80%, but the purity is reported as only 90% and this may be a typographical error.

Reaction 18



(a) (i) 30% NaOH, $Bu^t_4NHSO_4$, PhMe, 85 °C, 2 h; (ii) H_2SO_4, evaporate, cool, filter; (b) Ac_2O, 55 °C, 1 h; (c) (i) HOAc, Na_2WO_4, H_2O, 85 °C; (ii) 35% H_2O_2, 85 °C, 2 h; (iii) 21% HCl, reflux, 1 h; (iv) Distil solvent, H_2O, filter; (d) No details; (e) (i) Pd/C, TsOH, H_2O, MeOH, H_2, 4 bar, 50 °C, 4 h; (ii) Filter, wash MeOH/H_2O; (iii) Aq HCl, filter wash, dry.

Advantages

The patent claims that the process gives very high yields in all steps and the purification steps are suitable for use in an industrial plant.

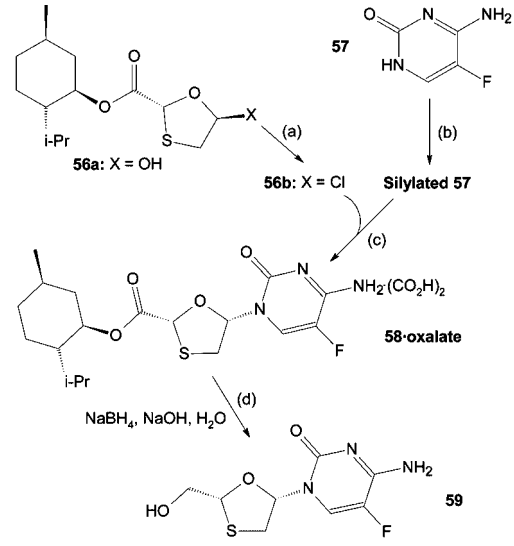
Patent No. U.S. 7,534,885

Assignee: Archimica S.r.l., Milan, Italy

Title or Subject: Process and Intermediates for Preparing Emtricitabine

Emtricitabine **59** is an antiviral drug that is used with other retrovirals to treat HIV infection. Several routes have been reported for its synthesis, and these are summarised. A major problem is said to be the difficulty of isolating the key intermediate **58**, and so a novel process has been developed that is claimed to give a good yield of the intermediate and then the final product. The improvement is the formation of the intermediate **58** as a crystallisable salt that is easily isolated. Reaction 19 shows the route used to prepare **59** where the first stage is the conversion of −OH group in **56a** to a good leaving group in **56b**. The patent does mention that the choice of leaving group will dictate the stereochemistry at this carbon with Cl or AcO being preferred. Thus, **56b** is condensed with an activated form of the cytosine **57** to form **58**. **57** is activated by treatment with HMDS prior to reaction with **56b**, and after the reaction has been carried out oxalic acid is added so that **58** is isolated as the oxalate salt **58·oxalate** in around 35% yield. A range of salts other than the oxalate was prepared including maleate, succinate, HCl, Ms, and *p*-chlorobenzene sulphonate. The next step is carried out using the free base **58** although it does not describe how this is obtained from the salt. Treatment of **58** with $NaBH_4$/NaOH in the presence of $KHCO_3$ and K_2HPO_4 gives **59** in about 25% isolated yield.

Reaction 19



(a) (i) MsOH, DMF, DCM, 8 °C; (ii) 15 °C, 4 h; (iii) Evaporate; (b) (i) HMDS, MsOH, PhMe, reflux, 3 h; (ii) Evaporate; (iii) Et_3N, DCM, 25 °C; (c) (i) Reflux, 21 h; (ii) Cool, 25 °C, H_2O; (iii) $(CO_2H)_2$, MeOH, 25 °C, 3 h, filter; (d) (i) $KHCO_3$, K_2HPO_4, THF, MeOH, H_2O, <5 °C, 3 h; (ii) 25 °C, 1 h; (iii) 37% HCl to pH 4; (iv) Evaporate.

An alternative method for preparing **58·oxalate** is described in which **57** is silylated with HMDS and then **56a** is added followed by Me_3SiI at rt. After workup including washing in a solution of $Na_2S_2O_5$ the oxalate is prepared as above and obtained in about 21% yield.

Advantages

The formation of a crystalline intermediate improves the isolation of the intermediate, although whether the final product yield is commercially acceptable is not known

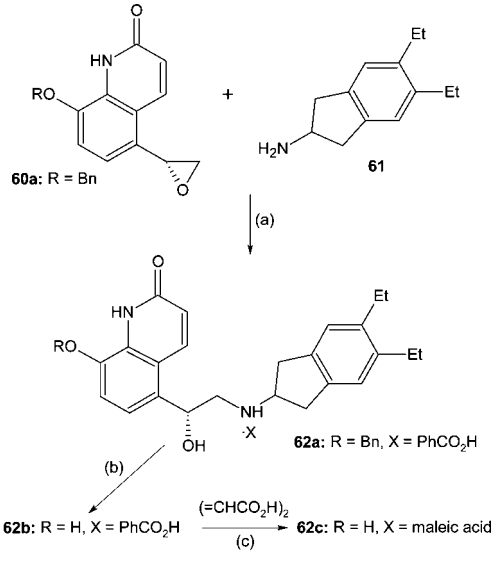
Patent No. U.S. 7,534,890

Assignee: Novartis AG, Basel, Switzerland

Title or Subject: Process for Preparing a Quinolin-2-one Salt as an Adrenoceptor Agonist

The compound of interest in this patent is the maleate salt **62c** that is used to treat asthma and other pulmonary diseases. The objective of the patent is to provide a process for making this salt without needing to isolate the free base since it is unstable in organic solvents. Alternative methods are said not to be regioselective and give the unwanted regioisomer **64** as well as the compound **63** as a byproduct. The desired compound may be present at levels of only 60 to 80%. These two compounds are difficult to remove without resorting to chromatography, and hence the other processes are claimed to be commercially unattractive. Reaction 20 shows the method used to prepare the maleate salt of **62b**. Reaction 20 comprises the heating a solution of **60** and **61** in diglyme. The reaction actually produces a mixture of the free base of **62a** (68.7%), its regioisomer **64** (7.8%) plus the byproduct **63** (12.4%). This mixture is not separated, and a solution of $PhCO_2H$ is added to produce the benzoate salt **62b** that is recrystallised and isolated in 63.6% yield. This salt is hydrogenated in the presence of Pd/C to remove the Bn group and give **62b** that is converted to the maleate salt **62c**. The crude salt **62c** is recrystallised, and the pure material is obtained in 60% yield.

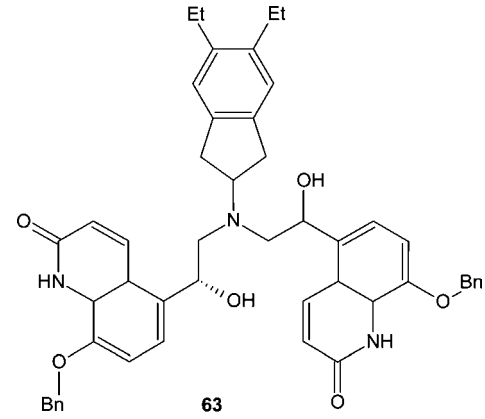
Reaction 20

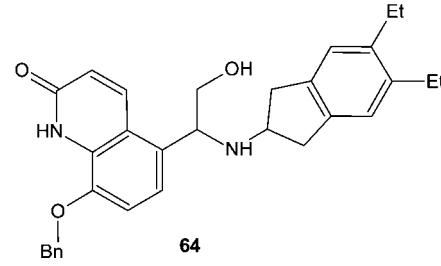


(a) (i) Diglyme, 110 °C, 15 h; (ii) Cool to 70 °C, $PhCO_2H$, EtOH; (iii) Cool <50 °C, seed; (iv) Cool <5 °C, filter, wash; (b) (i) H_2, Pd/C, HOAc, rt, 2 - 8 h; (ii) Evaporate; (c) EtOH, 50 °C, seed; (ii) Cool <5 °C, filter.

The patent describes the use of alternative acids to benzoic after the first reaction and compares the purity and yield of the salts obtained to those of **62a**. The acids include maleic, fumaric, succinic, tartaric, and HCl. The latter gives a salt with only 87% purity compared to >96% for the organic acids. The yield varies from 25 to 48%, indicating that the benzoate salt is the preferred option.

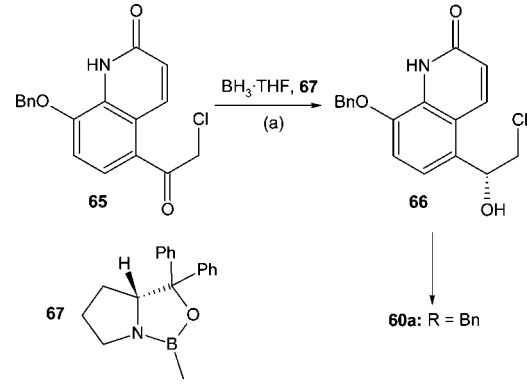
Byproducts





The patent also describes the preparation of the key starting material **60a**, and this is outlined in Reaction 21. This begins with the stereoselective reduction of **65** to **66** using BH_3·THF complex in the presence of **67** as the chiral auxiliary. The chiral alcohol **66** is obtained in 94.8% yield and then treated with solid K_2CO_3 in Me_2CO containing a 1% water to give crude **60a** in 78.8% isolated yield.

Reaction 21



(a) (i) THF, <2 °C, 2 h; (ii) MeOH; (iii) 25 °C, evaporate; (iv) H_2O, 37% HCl, 25 °C, 0.5 h, filter, wash, dry; (b) (i) K_2CO_3, H_2O, Me_2CO, reflux, 10 h; (ii) Filter hot, concentrate; (iii) Heptane, cool <2 °C, 3 h; (iv) Filter, wash.

Advantages

The process enables the desired salt to be obtained in high purity without the need to isolate the free base of an intermediate.

Patent No. U.S. 7,534,895

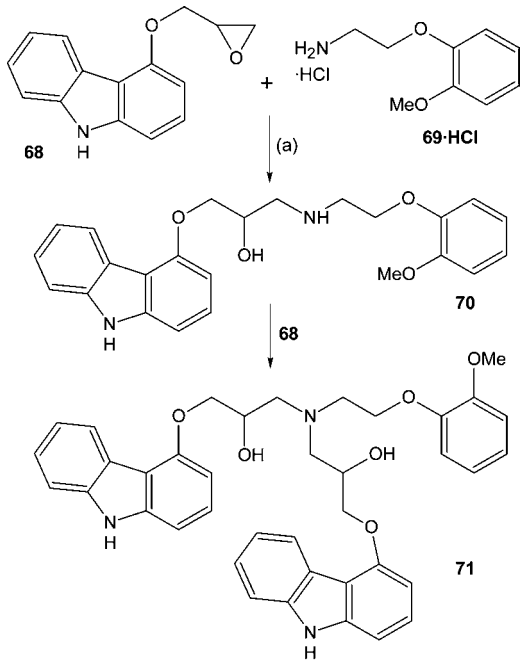
Assignee: Zentiva A.S., Hlohovec, Slovakia

Title or Subject: Process for the Preparation of Carvedilol

Carvedilol **70** is a nonselective β-blocker used for the treatment of mild to moderate congestive heart failure and

hypertension. A patent describing another new process has been reviewed recently (*Org. Process Res. Dev.* **2008**, *13*, 381). The objective in processes for preparing **70** is to minimise the amount of the byproduct **71** that is formed from **70** and the oxirane **68**. This new patent uses the same basic reaction scheme as the recently described process, and the improvement claimed is the use of the amine salt **69·HCl** in place of the free amine **69** as shown in Reaction 22. The reaction takes place in Pr^iOH using anhydrous K_2CO_3 with intensive mixing. The crude **70** that is obtained contains <1.5% of **71** and after treatment with activated C and recrystallisation from EtOAc the yield of **70** is 45%. It is described as being of pharmacopoeia-grade quality. The example in the patent is carried out on a kilo scale, thus indicating the commercial viability of the process. The patent also describes alternatives to using alternative bases and amine salts. Examples are described using the HSO_4 salt with K_2CO_3 or the HCl salt with $CaCO_3$.

Reaction 22



(a) (i) K_2CO_3, Pr^iOH, 83 °C, 5 h; (ii) Filter, distil Pr^iOH; (iii) EtOAc, 35 °C, seed; (iv) Centrifuge.

Advantages

The process gives the desired free base directly and minimises the amount of byproduct formation.

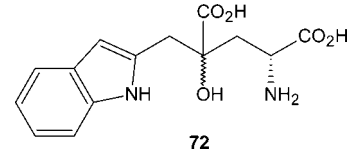
Patent No. U.S. 7,534,898

Assignee: Ajinomoto Co. Inc., Tokyo, Japan

Title or Subject: Process for Producing Monatin or Salt Thereof

Monatin **72** is a sweetener that occurs naturally in the bark of the plant *Sclerochiton ilicifolius* in the Northern Transvaal region of South Africa. **72** is several hundred times sweeter than sucrose and (not being a carbohydrate) is nonfattening. In addition it does not have the bitter aftertaste of some artificial sweeteners. The molecule has two chiral centres and hence four optical isomers, but readers who consult this patent should note that IUPAC nomenclature is not used in naming the molecule. This means that the 2 and 4 positions in the molecule are reversed, and the patent states that the preferred isomer is that in which the amino group is at position 2 with *R* configuration, whereas using the IUPAC name this would be 4*R*. To avoid confusion the following discussion uses the naming method used in the patent. Apparently both the (2*R*,4*R*) and (2*R*,4*S*) isomers are equally desirable in having increased sweetness compared to the 2*S* pair of isomers. Hence, the patent describes a method racemising the 2*S* isomers of salts of **72** to the pair of 2*R* isomers. The patent does not describe a synthetic method for producing **72** although reference is made to one in a patent from the applicants (WO 03/059,865).

Monatin



72

The racemisation process takes place by heating the mixture with 0.2 equiv of salicaldehyde and 1 equiv of HOAc in 25% aq MeOH. In one example a 26:74 mixture of the Na salts of the (2*R*,4*R*) and (2*S*,4*R*) isomers after 6 h at 85 °C was converted to a solution containing a 63:27 mixture of isomers. Crystallisation provided a solid that contained the (2*R*,4*R*) and (2*S*,4*R*) isomers in the ratio of 15:85. The crystals were converted to the NH_4 salts and the ratio of (2*R*,4*R*) and (2*S*,4*R*) isomers increased to 4:96. The mother liquor from the crystallisation was treated with NaOH, and after workup and crystallisation the ratio of (2*R*,4*R*) to (2*S*,4*R*) isomers was 88:12. ^1H NMR data are provided for the isomers. A second example produces a mixture containing 92% of the desired pair of 2*R* isomers.

The economic justification of the process is not entirely clear to this reviewer. If monatin is indeed several hundred times sweeter than sucrose, then clearly very little is needed. If the two less-sweet isomers were safe, then it would seem economically more attractive to spend the time and money to obtain a purified mixture of four isomers and use that. The process as described gives a mixture containing all four isomers, including at least 8% of the less-sweet isomers. Hence, if these isomers are not safe, then this level of them is too high.

Advantages

The process improves the content of the more active isomers.

Patent No. U.S. 7,534,900

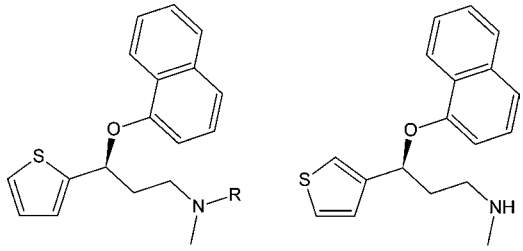
Assignee: Teva Pharmaceutical Industries Ltd., Petah Tiqva, Israel

Title or Subject: Process for the Purification of Duloxetine Hydrochloride

This is the first of two patents on duloxetine **73a** that is available as the HCl salt under the name Cymbalta for the treatment of major bouts of depression. This patent focuses entirely on purifying the compound by crystallisation and does not mention its synthesis that is the subject of the second patent. The process described in this patent is aimed at purifying the HCl salt of **73a** by removing the impurity **74a** and the *R*-enantiomer of **73a**. The preferred solvents for the crystalli-

sation are Pr^iOH or mixtures of Me_2CO and H_2O. The latter seems to be particularly suitable with the H_2O content being in the very narrow range of 1.75−3 vol %. The process involves refluxing a solution of **73a·HCl** in the solvent with the ratio of 1:10 by volume of **73a·HCl** to solvent. This solution is then cooled <30 °C and stirred for up to 24 h to precipitate the crystals. The examples report a number of experiments in which the product is free from the *R*-enantiomer and contains as little as 0.03% of **74a**.

Duloxetine



Advantages

The process gives high-purity product.

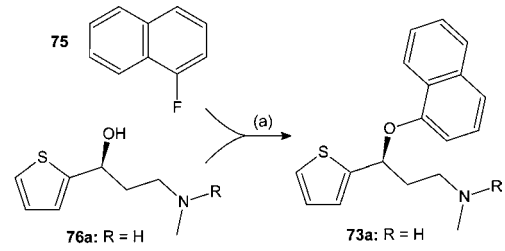
Patent No. U.S. 7,538,232

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

Title or Subject: Process for the Asymmetric Synthesis of Duloxetine

The second patent on **74a** focuses on a new synthesis of the molecule and states that most processes for the synthesis of **74a** involve an arylation step using NaH and DMSO. These two reagents produce the dimsyl anion $MeS(O)CH_2^-$ that can cause racemisation during the synthesis when it is only the *S*-enantiomer that is desired. It is also stated that NaH can be used in DMSO if a phase transfer catalyst such as 18-crown-6 is used. However, the crown ether is toxic. It is also reported that using the base KOH in DMSO can also cause racemisation and give products with up to 50% of the *R*-enantiomer. Hence, the objective of the patent is to provide a process that avoids racemisation by not using NaH and by reducing the amount of DMSO that is used. The patent discloses that the use of NaH can be completely avoided and that KOH can be used in DMSO if PhMe is also present. Alternatively, diglyme can be used as the solvent with KOH as the base. The production of **73a** is by the reaction of **75** with **76a** in PhMe containing up to 25% DMSO at 85 °C (Reaction 23). The ee of the crude amine **73a** is not actually reported, and the purity of the product is given in terms of % Δ*R*. This is defined as the difference in the amount of the *R*-enantiomer between the **76a** and **73a**. The value of % Δ*R* is reported as 1.0, but this is not very meaningful without knowing the actual purity of either **76a** or **73a** although indications are that the pure enantiomer **76a** is used in the reaction, and so the reaction does seem to be stereoselective.

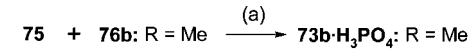
Reaction 23



(a) (i) KOH, PhMe, DMSO, 85 °C, 12 h; (ii) Cool to rt, wash in H_2O; (iii) Evaporate.

The patent also describes the production of the H_3PO_4 adduct of the dimethylamine derivative **73b** as shown in Reaction 24. The product was isolated and has a % Δ*R* value of 0.2.

Reaction 24



(a) (i) KOH, diglyme, 120 °C, 6 h; (ii) Extract in EtOAc; (iii) H_3PO_4, rt, 15 min, seed.

Advantages

The process gives very high stereoselective reactions with only a relatively small change in the process.

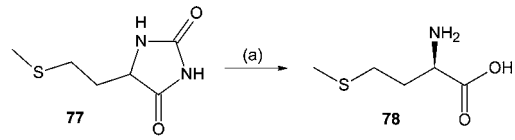
Patent No. U.S. 7,534,916

Assignee: Sumitomo Chemical Company Limited, Tokyo, Japan

Title or Subject: Process for Producing Methionine

Methionine **78** is an essential amino acid found in several foods and is also commercially produced and available as a food supplement. Despite the title of this patent its main focus is actually on the composition of the stainless steel (SS) used in the reactors in which **78** is produced. While laboratory-based chemists are often blissfully unaware of such things, those who move to process development need to know the limitations of any equipment that they may use when scaling up laboratory processes to the pilot plant and commercial production. There are many well-known examples of an industrial plant failing because simple corrosion testing was not undertaken during scale-up studies. It is interesting to speculate whether this patent is the result of problems encountered in a plant that uses the process. The details for the preparation of **78** are shown in Reaction 25b and involve basic hydrolysis of the hydantoin **77**. The conditions are quite severe, and there is the likelihood of corrosion of commonly used grades of SS such as 304 L or high-grade austenitic. (Most pharmaceutical equipment is 316 grade SS.) The patent points out that while Zr reactors could be used they are expensive. It should also be mentioned that Ti- or Ta-lined or Hastelloy reactors are even more expensive. The patent contains results of corrosion tests, and the preferred grade of SS contains Cr, Ni, W and Cu as well as N.

Reaction 25



(a) K_2CO_3, H_2O, 150 - 200 °C, 0.5 to 1.5 MPa.

Advantages

The patent describes a suitable material that can be used to manufacture reactors for carrying out the production of this important material.

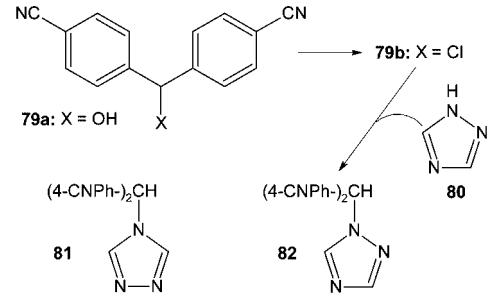
Patent No. U.S. 7,538,230

Assignee: Chemagis Ltd., Bnei Brak, Israel

Title or Subject: Letrozole Production Process

Letrozole **82** is a nonsteroidal aromatase inhibitor and used to treat advanced breast cancer in postmenopausal women. Processes for preparing **82** are summarised, and it is claimed that they have a problem in that during the synthesis an intermediate byproduct is produced that subsequently forms isoletrazole **81**. The byproduct can be removed at an intermediate stage in the synthesis, but this requires an extra purification step. Alternatively, **81** can be removed at the end by ColC. The objective of this patent is to reduce the amount of **81** and avoid using ColC. The patent achieves this by using the route outlined in Reaction 26 in which **79b** is reacted with the triazole **80** in the presence of base to produce **82**. The first step is formation of the chloro compound **79b** by reaction of **79a** with HCl in the presence of $ZnCl_2$. The crude product is isolated in 85% yield with purity of 98% (HPLC). The reaction of **79b** with **80** takes place in a multiphase system containing a water-miscible solvent (DMF), PhMe, and solid K_2CO_3. The reaction is followed by HPLC, and when complete HOAc is added followed by further DMF and H_2O. The precipitated crude product is washed in hot H_2O and obtained in 74.4% yield. It is then crystallised from MeOH to give an 87% yield of **82** containing 0.5% of **81**, and recrystallisation from MeOH provides **82** with purity of 99.8% and 0.1% of **81**. Recrystallisation from alternative solvents such as alcohols, esters, and MIBK is described, but they give product of lower purity. The production of **82** can also be carried out by reacting **80** with the bromo compound **79c** (X = Br), but this gives **82** in lower yield (70.5%) and purity (96%).

Reaction 26



(a) (i) 37% HCl, $ZnCl_2$, PhMe, 65 °C, 4 h; (ii) Aq Na_2CO_3, distil PhMe; (iii) Hexane, 40°C; (iv) Cool 5 °C, filter; (b) (i) DMF, PhMe, 60 °C; (ii) K_2CO_3, 80 °C, 4 h; (iii) Cool rt, HOAc; (iv) DMF, H_2O, 30 °C; (v) Cool rt, filter; (vi) H_2O, 70 °C, filter, dry.

Advantages

The process minimises the production of isoletrazole and gives a higher-purity product than alternative methods.

Keith Turner

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