Organic Process Research & Development **2010,** *14,* 492–503

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published During December 2009 and January 2010

Received for review March 29, 2010.

Summary

The current review contains 23 from an original list of 262 patents that fitted the search criteria. Hazard reduction is a major aspect of process development, and several patents focus on this as a reason for the work described. A process for the production of the antifungal compound butoconazole reduces the amount of $SOCl_2$ used in a key chlorination step by not using the reagent as solvent and reactant and uses $MeCHCl_2$ as reaction solvent. A new, safer method for preparing the anticoagulent clopidogrel avoids the isolation of an unstable formimine intermediate that is necessary in alternative processes. The introduction of a nitro group into any compound can be hazardous, and a safer method of making nitro esters of monohydric alcohols is described that is carried out on a continuous basis. Handling acetylene requires special equipment and expertise, and an improvement on a 1962 patent for preparing unsaturated alcohols also involves a continuous process to minimise the inventory of acetylene in the reactor. The preparation of *N*-alkylnaltrexone halides involves using the toxic compounds BnBr and Me_2SO_4, but hazards of handling these materials are minimised by avoiding the purification of intermediate mixtures where these reagents are used. Handling DCC on a large scale is the impetus for developing a new process for preparing the antihypertensive drug irbesartan. In addition to avoiding the use of DCC the process does not require the isolation of pure intermediates. A safer process for preparing an intermediate for the antiepileptic drug gabapentin avoids the use of NaCN and may have commercial potential having been scaled up to kilo scale. Two other patents from the same company related to gabapentin are also reviewed. One of these describes the preparation of pure stereoisomers containing Bu^t groups that can be used to investigate the relationship between activity and structure. The other patent on gabapentin describes a method of preparing a HCl salt free from acetone. A new, environmentally friendly process is disclosed for preparing the antiulcer drug rabeprazole sodium. A key step is oxidation of a thioether to a sulphinyl compound, and the new process avoids expensive or hazardous oxidising agents by using NaOCl. Some of the patents reviewed describe the use of reagents that may increase hazards or at least have an adverse environmental impact. For example, a process for the preparation of the sterol paricalcitol uses ozone, Me_2S, and SeO_2 as well as OsO_4, and a favored solvent in the workup appears to be DCM. This and other chlorinated solvents are reported as being used in other patents with one using both CCl_4 and $CHCl_3$ in the workup. A very comprehensive patent describes novel lactones that are intermediates, and their use for synthesising the prostaglandins, latanoprost and dinoprost, is described. A new process for producing a range of aromatic hydroxyacids is described that uses Cu complexes in a redox system to increase the rate of hydrolysis of halogenated aromatic acids. The complexes contain diimine ligands, and one of these that takes 8 days to make is recovered in an extremely poor yield of 6.5%. Impurities in drugs or other products are often used as reference standards, and this technique is applied to the antiviral compound acyclovir. An *N*-formyl derivative is prepared and is isolated in pure form and then used as a standard. The hydrolysis of esters must be one of the oldest known reactions for preparing acids, and a patent describes a continuous process for preparing cyclopropane carboxylic acids that uses this procedure. A preferred technique involves passing the ester and water over a fixed bed of ion-exchange resin as catalyst in the hydrolysis. A patent describes the preparation of benzyl epoxides, and these are used to prepare drugs to treat Alzheimer's disease. This also uses ion-exchange resins as catalysts and in this case for the removal of the BOC protection of an amine group. A patent listing several hundred compounds describes the preparation of cyclopropylphenols from readily available raw materials, and these are used for producing agrochemicals. Patents are also included that cover novel methods of producing new or known polymorphs of established drugs. A number of the patents describe experiments carried out on a kilo or multikilo scale, thus suggesting an advanced stage of development or even commercial operation. However, there is no legal or commercial significance in the choice of patents in this review. 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. 7,625,935

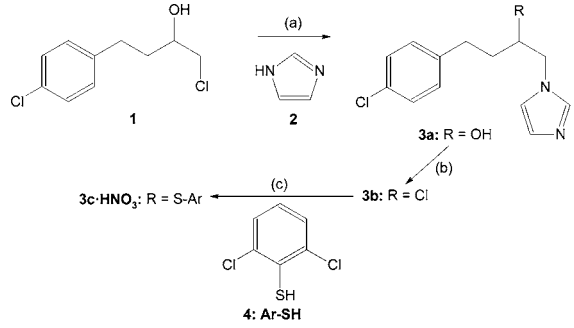
Assignee: Richter Gedeon Vegyeszeti Rt., Budapest, Hungary
Title or Subject: Process for the Preparation of High-Purity Butoconazole Nitrate With Specified Particle Size

The subject of this patent **3c**, has antifungal properties and is used as the nitrate to treat vaginal infections. Alternative processes for preparing **3c** are described, and their various problems are listed. These include the use of solvents that are highly flammable (ether), toxic (DMF), or corrosive ($SOCl_2$). In addition the use of the reagent NaH is said to be undesirable. The patent claims that a surprising finding is that the key intermediate **3a** can be obtained in excellent yield and with a short reaction time. This is done by the reaction of **1** with **2** in

10.1021/op100085j
Published on Web 04/09/2010

a biphasic mixture of PhMe and H_2O in the presence of a base and a phase transfer catalyst (PTC) as shown in Reaction 1. The crude product **3a** is obtained in 95% yield, and after recrystallisation is recovered in 85% yield. The next stage is production of the chloro compound **3b** and alternative procedures describe the use of $SOCl_2$ as both solvent and reagent. This patent also uses $SOCl_2$ as chlorinating agent but avoids the need to remove large amounts of $SOCl_2$ by using only 1−1.2 mol $SOCl_2$ per mol **3a** and $(CH_2Cl)_2$ as solvent. DMF is added to facilitate the reaction by forming the Vilsmeier reagent $Me_2NCHCl^+Cl^-$ with $SOCl_2$. The chloro compound **3b** is not isolated, and after the excess $SOCl_2$ is hydrolyzed, the mixture is extracted into MIBK. After basification and removal of water and excess solvent, the last stage of the process is carried out in which **4** reacts with **3b** in the presence of dry K_2CO_3 to give **3c** that is treated with HNO_3 to form the desired final product as the nitrate salt in 90% isolated yield.

Reaction 1



(a) (i) Aq NaOH, $BnEt_3NCl$, PhMe, 95 °C, 1 h; (ii) Cool 60 °C, phase separation, H_2O;
(b) (i) DMF/$SOCl_2$, $(CH_2Cl)_2$, 38 °C, 1.5 h; (ii) H_2O, 18 °C; (iii) Extract in MIBK; (iv) Na_2CO_3 to pH 9;
(v) Concentrate; (c) (i) K_2CO_3, MIBK, 108 °C, 4 h; (ii) Cool <25 °C, filter, wash, activated C;
(iii) 65% HNO_3, 25 °C, 1 h; (iv) Cool 8 °C, filter, wash, dry.

The patent also describes a method for producing the nitrate salt with a specific particle size. The desired range is > 95% < 75 μm and 99% < 250 μm. This is achieved by dissolving the wet salt in a mixture of MeOH and MIBK at 70 °C followed by addition of the solution to MIBK at −5 °C. The product is removed by filtration after stirring for 1 h, and after vacuum drying at 50 °C the yield of specificly sized particles is 95% with 0.05% impurities.

Advantages

The process avoids the use of large amounts of $SOCl_2$ thereby reducing the hazards of alternative methods. At the same time the process gives high yield of the products with high purity. A drawback of the process is the necessity to use $(CH_2Cl)_2$ as solvent.

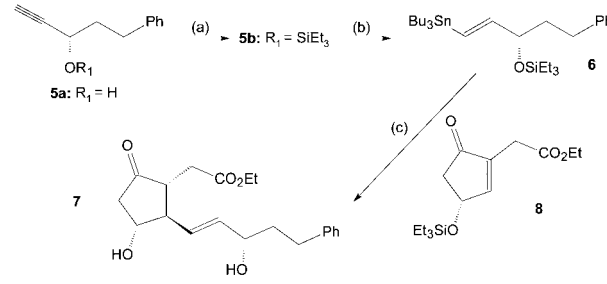
Patent No. U.S. 7,626,024

Assignee: Irogate International Inc., Taipei, Taiwan

Title or Subject: Processes and Intermediates for the Preparation of Prostaglandins

The claims of this patent cover novel cyclopentanone compounds such as **7** and the patent, also describes lactones such as **9**, **10a**, and **10b**. These compounds are of interest as intermediates in producing prostaglandins and in particular latanoprost **13c**. This compound is used as a topical medication for controlling the progression of glaucoma or ocular hypertension. The patent covers a large amount of material with alternative routes described for preparing the key intermediates. This review therefore covers only a limited selection of the work, and the interested reader is encouraged to consult the patent. The desired lactones are reported to be produced in low yield by a process developed by Corey that involves 12 reaction steps. The Corey route is also said to give excessive amounts of an undesirable isomer that necessitates the use of chromatographic methods for its removal. The objective of the patent is to provide a simpler cost-effective process for producing the desired lactones and other intermediates in high yield and without high levels of impurities. Reaction 2 summarises one method used to prepare the cyclopentanone **7** that begins with protection of the OH group in **5a** by silylation to form **5b**. This is then converted to the vinyl stannane **6** by reaction with $Bu^n{}_3SnH$ in the presence of AIBN, and the product is obtained as an oil in 82% yield. The next step proceeds via the initial formation of a Li cuprate complex from **6** and CuCN and MeLi. The complex is allowed to stand for 3 h before addition of the cyclopentenone **8** at −70 °C. After workup involving hydrolysis with TsOH catalyst, the product **7** is purified using column chromatography (ColC) and isolated in 89% yield containing a trace of an unspecified epimer that can be removed by crystallisation.

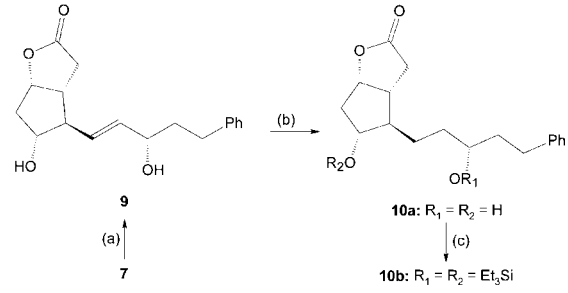
Reaction 2



(a) Et_3SiCl, imidazole, EtOAc, 5 °C, 0.5 h; (b) Bu_3SnH, AIBN, 130 °C, 2 h;
(c) (i) CuCN, MeLi, THF, -10 °C; (ii) rt, 3 h; (iii) **7a**, THF, -70 °C, 0.5 h; (iv) H_2O, TsOH, rt, 1 h.

The next stage of the process is the preparation of the lactones, and this is shown in Reaction 3. The first step is treatment of **7** with $LiBHBu^s{}_3$ at −70 °C to give **9** that is isolated in crystalline form in 75% yield. In the next step the double bond is reduced using a Pd/C catalyst to give **10a** that is purified using ColC and isolated in yields up to 78%. The OH groups are then protected by silylation to give **10b** and this is used to prepare **13** as shown in Reaction 4.

Reaction 3

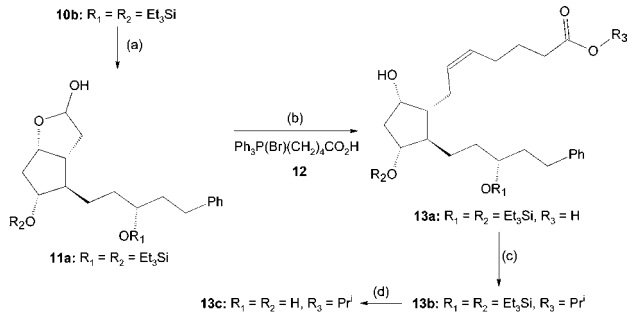


(a) $LiBHBu^s{}_3$, THF, -70 °C, 2 h; (b) Pd/C, NaOH, EtOAc, H_2, rt, 16 h;
(c) Et_3SiCl, imidazole, EtOAc, rt, 0.5 h;

The preparation of **13c** starts with the reduction of the lactone **10b** using DIBALH to give the lactol **11** that is extracted from the reaction mixture with PhMe and obtained as a colourless

oil. The crude material is used in the next step where it is reacted with **12** at −10 °C over 18 h to form the acid **13a**. This is recovered by extraction with EtOAc and then esterified using Pr^iI in DMF and K_2CO_3 to produce the protected lantanoprost **13b** that is purified by ColC. Deprotection using HCl provides **13c** that is purified by flash ColC and isolated in a 35% yield based on **10b**.

Reaction 4



(a) DIBALH, PhMe, -78 °C, 2 h; (b) (i) KOBu^t, THF, -10 °C, 18 h;
(c) Pr^iI, K_2CO_3, DMF, rt, 12 h; (d) Concd HCl, THF, rt, 0.5 h.

The patent includes details for the preparation of other cyclopentanones and lactones and their use in the preparation of the prostaglandin dinoprost. Brief ^1H NMR data are provided for the majority of the compounds prepared.

Advantages

The patent describes the preparation of a range of novel compounds without the high levels of impurities obtained in alternative procedures. The compounds are then used in the preparation of important prostaglandins.

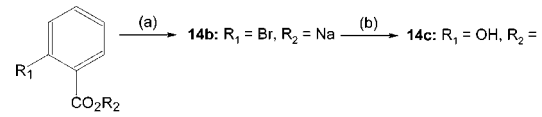
Patent No. U.S. 7,626,053 and 7,626,489

Assignee: E.I. Du Pont de Nemours and Company, Wilmington, Delaware, U.S.A

Title or Subject: Process for the Synthesis of Hydroxy Aromatic Acids

Aromatic hydroxyacids have a wide range of uses as synthetic intermediates and as monomers for the production of polymers. These patents state that processes for making the hydroxyacids have long reaction times and give poor productivity or require high pressures to attain an acceptable reaction rate. The improvement claimed in the patents is the hydrolysis of a halogenated aromatic acid in the presence of a Cu complex. In the first patent the Cu complex is formed from a Cu source and an amino acid, whereas the second patent claims a Schiff base or a diimine as the ligand. The reaction proceeds via the initial formation of the salt of the acid followed by treatment with the Cu complex, and Reaction 5 outlines the process covered by the first patent. The examples in this patent only cover the preparation of the hydroxyacid **14a** although several other acids are listed as being prepared by this method. The hydroxyacid is initially converted to the salt **14b** by reaction with Na_2CO_3 at under N_2. This is then followed by addition of a Cu salt such as $CuSO_4$ and the amino acid that acts as a ligand with valine or proline being preferred. This reaction uses up to 5 mol % of Cu per mol of substrate, and since it takes place in air it presumably involves a redox system of Cu and O_2. After cooling the mixture, it is acidified with 35% HCl, and the product **14c** is collected by filtration. The reaction selectivity is >98% with conversion as high as 99%.

Reaction 5

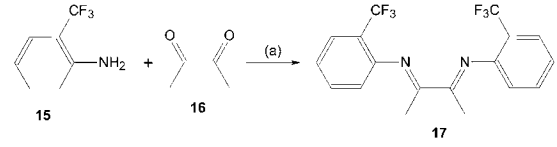


(a) Na_2CO_3, H_2O, N_2, 50 - 75 °C; (b) (i) $CuSO_4$, valine, H_2O, air, 80 °C, 9 h;
(ii) Cool to rt, 35% HCl, filter, wash, dry.

The amino and acid groups in the ligand are separated by no more than two C atoms. The use of *N*-methyl anthranilic acid is covered in the claims although the experimental details indicate that it is much less effective than valine or proline.

The second patent covers the use of the ligand **17** for the preparation of **14c** from **14a** in a yield of 90% with 94% conversion and selectivity of 96%. The preparation of **17** is shown in Reaction 6 and involves the condensation of the amine **15** and diketone **16** in the presence of HCO_2H. It takes 8 days and gives a very poor yield of 6.5% of **17**. ^1H NMR data are given for ligand **17**.

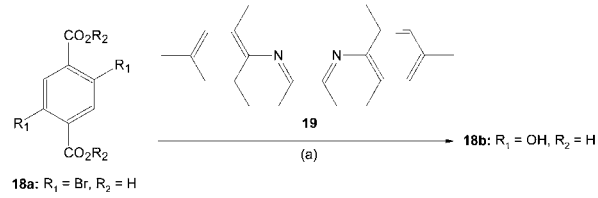
Reaction 6



(a) (i) HCO_2H, MeOH, 35 °C, 8 days; (ii) Evaporate, wash in CCl_4; (iii) Dissolve in $CHCl_3$;
(iv) Pass over Al_2O_3; (v) Evaporate.

The second patent also describes the preparation of the acid **18b** from **18a** using a Cu complex formed from CuBr and the ligand **19** (Reaction 7). The reaction gives crude **18b** in a yield of 72% that is 81% pure by ^1H NMR. **19** is also used in the preparation of **14c** from **14a** in 94% yield with 97% conversion and selectivity. There are no details for the preparation of **19**.

Reaction 7



(a) (i) Na_2CO_3, H_2O, N_2, reflux, 0.5 h; (ii) CuBr, air, 80 °C, 9 h; (iii) 35% HCl, 25 °C, filter, wash, dry.

Advantages

The process gives high yield of the products and is claimed to be suitable for large-scale operation.

Patent No. U.S. 7,629,461

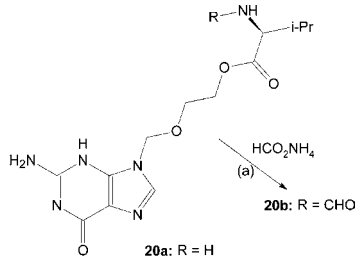
Assignee: Teva Pharmaceutical Industries Ltd., Petah Tiqva, Israel

Title or Subject: Process for the Preparation of Valacyclovir Impurity and Use as a Reference Standard

Valacyclovir **20a** is marketed as Valtrex as the hydrochloride salt of the L-valyl ester of the antiviral drug

acyclovir. *N*-formyl valacyclovir **20b** is an impurity that can be formed if **20a** is stored with residual process solvents. The patent reports on the preparation and isolation of **20b** and its use as a reference marker or standard and claims that this is the first report of the structure of **20b** and of its isolation free from **20a**. The examples describe the quantitative analysis of **20b** in **20a** by HPLC and also the preparation of **20b** by reaction of **20a** with HCO_2NH_4 in the melt (Reaction 8). This releases NH_3 gas and H_2O vapour from the mixture, and crystallisation from hot water gives **20b** with purity of 95.85%.

Reaction 8



(a) (i) 125 °C, 2.5 h; (ii) Hot H_2O, filter, cool.

The ^1H and ^{13}C NMR confirmed that the CHO group is attached to the valine NH_2 moiety in the molecule.

Advantages

The impurity can be used as a reference standard for analysis of the drug.

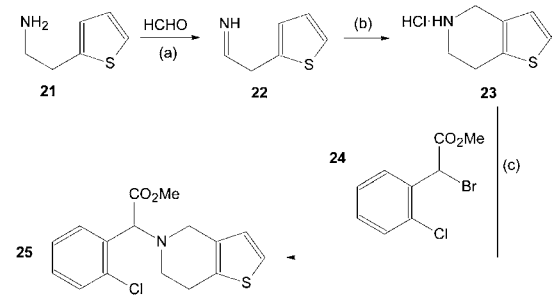
Patent No. U.S. 7,629,465

Assignee: IPCA Laboratories Ltd., Mumbai, India

Title or Subject: Industrial Process for Preparation of Clopidogrel Hydrogen Sulphate

The title compound is the HSO_4 salt of **25** that is used to prevent blood clots that may lead to heart problems. New processes for preparing **25** have been developed and some have been reviewed (*Org. Process Res. Dev.* **2008**, *12*, 556). There are several polymorphs of **25**, and the patent states that there is a need for an improved industrial method of making Forms I and II without contamination of other forms. Some alternative processes for the synthesis of **25** proceed via the preparation and isolation of a formimine intermediate **22** that is not very stable and forms a trimer, so that handling it on an industrial plant is difficult. The new process also proceeds via the formation of this intermediate, but its isolation and purification is not necessary. Reaction 9 shows the route used to prepare **25** that begins with the reaction of **21** with HCHO in refluxing dichloroethane (DCE) to form the formimine **22**. This compound is not isolated, and the water formed in the reaction is azeotropically removed. At the completion of the reaction the next step is cyclisation of **22** to give the HCl salt **23**. This is carried out at 70 °C using a solution of dry HCl in DMF, and **23** is isolated in 90% yield. The salt is then reacted with **24** to give the product as the free base **25** that is isolated as an oil and then converted to the HSO_4 salt by treatment with H_2SO_4 in Me_2CO. The final yield of the salt is 88%. The whole process can be carried out in a single pot and gives a final yield of the salt of 85%.

Reaction 9



(a) DCE, reflux, 4 h; (b) (i) Cool to 30 °C, dry HCl/DMF; (ii) 70 °C, 4 h; (iii) Cool 15 °C, filter, wash, dry; (c) (i) Et_3N, DCE, 25 °C, 1h; (ii) reflux 4 h;

The process as described gives the racemic mixture, and this is resolved using l-camphor-10-sulphonic acid to provide the *S*-(+) enantiomer. The patent also describes kilo-scale experiments in which the free base is used to prepare Forms I and II of the HSO_4 salt of **25**. The patent claims cover the preparation of these polymorphs as the *S*-(+) enantiomer salts although the examples do not, in fact, specify that pure enantiomers are used.

Advantages

The process gives an improved synthesis of pure polymorphs that does not require the isolation of an unstable intermediate. However, the possibility of residual DCE in the final product is a concern.

Patent No. U.S. 7,629,490

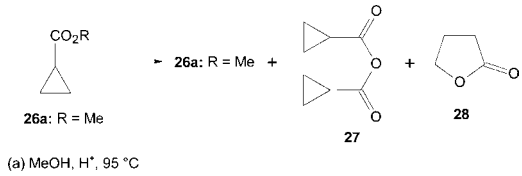
Assignee: Lanxess Deutschland GmbH, Leverkusen, Germany

Title or Subject: Process for Hydrolyzing Cyclopropanecarboxylic Esters to the Free Acid

This patent describes a continuous process for preparing **26b** by hydrolysis of its Me or Et ester **26a**. The acid is an intermediate for a range of chemicals, pharmaceuticals, and crop protection agents. Although ester hydrolysis is an obvious method for producing an acid the patent states that a simple industrial process for its formation, by hydrolysis of the esters with water, is unknown. The process disclosed in the patent is carried out by feeding a mixture of the ester **26a**, alcohol, water, and acid to a reactor at about 95 °C. The acid can be HCl or a solid acidic ion-exchange resin (IER). The mixture leaving the reactor is then separated in a series of distillation columns with the desired product being removed as a bottoms product from the last column. The patent includes a number of process flow diagrams showing options for various operating methods. If an IER is used to catalyse the reaction, the solid is retained in the reactor by screens or suitable packing, or the liquid is pumped through a stationary bed of the IER. Such methods are essential to prevent physical degradation of the IER. The examples describe a process that hydrolyses 550 g/h of **26a** with 10% HCl as catalyst, and this produces 480 g/h of **26b** containing 2.1% of **27**. When the HCl strength is increased, the product is also found to contain **28**. With 37% HCl the level is 0.08%, and with 50% HCl the amount of **28** increases to 0.14%. The amount of **27** found at higher acid strength is not reported. The formation of **28** from this process is intriguing, but no comment on this is made in the patent. Using Lewatit K2431 IER the hydrolysis of 280 g/h of **26a** produced 240 g/h of **26b** containing

3.5% of **27**. There is no report of the presence of **28** using IER. The IER is reported to suffer no loss in activity after 1000 h operation.

Reaction 10



Advantages

The process provides a continuous and efficient method for the preparation of the desired acid by hydrolysis of the ester.

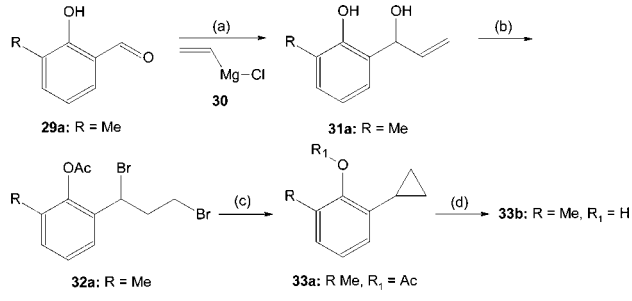
Patent No. U.S. 7,629,494

Assignee: Mitsui Chemicals Agro, Inc., Tokyo, Japan

Title or Subject: Process for Producing Cyclopropylphenol Derivatives

This very comprehensive patent describes a process for producing compounds that are intermediates in the production of agrochemicals and pharmaceuticals. The patent lists several hundred compounds that are either intermediates used in the process or examples of the cyclopropylphenols themselves, and the actual claims of the patent specify compound **33b**. Alternative methods for preparing the desired compounds are reviewed and rejected because they use methods or reagents that are expensive or not readily available. The process for the production of **33b** is shown in Reaction 11 and starts with the reaction of the aldehyde **29a** with **30** in THF to form **31a** that is obtained as a brown gum in a yield of 95%. In the next step **31a** undergoes bromination and acetylation using HBr and Ac_2O in HOAc. The crude product is **32a** that is obtained as a brown gum in 87% yield. The cyclisation of **32a** to **33a** is then carried out by treatment of **32a** using Mg with a trace of I_2 in THF. The crude product is isolated as a brown gum in 113% yield and then treated with K_2CO_3 in MeOH to give **33b** as a brown oil. This is purified by vacuum distillation to give **33b** as a light-purple oil in a 67.8% yield.

Reaction 11



(a) (i) THF, <15 °C, 0.75 h; (ii) Aq NH_4Cl, 0 °C; (b) (i) HBr/HOAc, Ac_2O, 4 min, <43 °C; (ii) rt, 2 h; (iii) 50 °C, 4 h; (c) (i) Mg, I_2, THF, 80 °C, 0.75 h; (ii) rt, 1.5 h; (iii) 1M HCl, <40 °C; (d) (i) K_2CO_3, MeOH, rt, 1.25 h; (ii) H_2O, evaporate; (iii) 4M HCl, 0 °C.

The examples in the patent also describe the preparation of the chloro and fluoro compounds **33c** (R = Cl, R_1 = H) or **33d** (R = F, R_1 = H).

Advantages

The process starts from a readily available raw material and does not use expensive reagents.

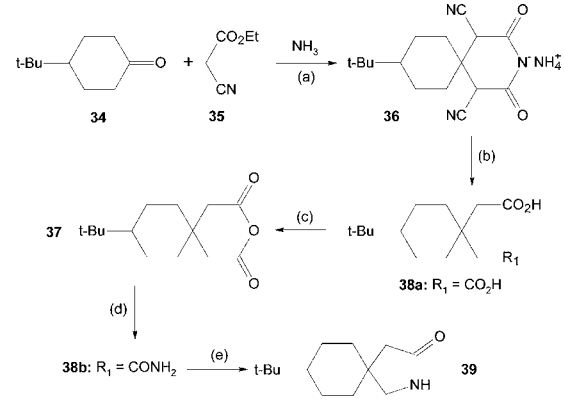
Patent No. U.S. 7,632,864

Assignee: Hikal Ltd. and Indian Institute of Science, Bangalore, India

Title or Subject: Gabapentin Analogues and Process for Their Production

This is the first of three patents, from the same company, that are concerned with the production of the antiepileptic drug gabapentin **42**. This patent describes the *E*- and *Z*-isomers of the Bu^t derivative of gabapentin **38c** (Reaction 13). These compounds are of interest because the Bu^t group exclusively occupies the equatorial conformation of the ring. Hence, the synthesis of compounds containing the Bu^t group that is *cis* or *trans* to the NH_2CH_2 group would be useful in determining the optimum conformation for maximum activity of the drug molecule. The route used to prepare a mixture of the two isomers is shown in Reaction 12. The first step is the condensation of the ketone **34** with 2 mol of the cyanoester **35** in the presence of NH_3 over 96 h to give the ammonium salt **36**. No yield is reported, and the salt is then heated with H_2SO_4 to give the crude diacid **38a**. This is purified by warming with NH_4OH followed by acidification using HCl. The pure solid diacid **38a** was then converted to the anhydride **37** by refluxing with MeCOCl followed by distilling off the volatiles. The anhydride was then quenched with NH_4OH, washed in PhMe to remove impurities, and then acidified to give the monoamide **38b**. Treatment of the amide with NaOH and Br_2 followed by extraction in DCE produced **39** as a mixture of the stereoisomers.

Reaction 12

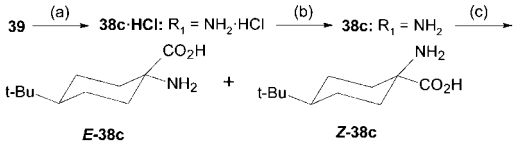


(a) MeOH, -5 °C, 1.5 h; (b) (i) 60% H_2SO_4,130 °C, 18 h; (ii) Cool 30 °C, filter; (iii) NH_4OH, filter; (iv) Aq HCl, filter, dry; (c) MeCOCl, reflux, 3 h; (d) (i) NH_4OH, 30 °C, 0.5 h; (ii) HCl to pH 2, filter; (e) (i) Aq NaOH, Br_2, -5 °C; (ii) 85 °C, 6 h; (iii) Extract in EDC, evaporate.

The next stage of the process is the preparation of the individual *E*- and *Z*-isomers of the aminoacid ***E*-38c** and ***Z*-38c** (Reaction 13). The lactam **39** is converted to the HCl salt **38c·HCl** by treatment with hot concd HCl, and after workup a mixture of the *cis*- and *trans*-isomers of the salt is obtained. The salt is converted to the free base **38c** by treatment with charcoal in hot water followed by neutralisation with NaOH. The product is a mixture of isomers from which the individual isomers ***E*-38c** and ***Z*-38c** are obtained by crystallisation. None of the experimental details in the patent include information on yield or product purity. The only reference to yield is in the formation of **38c** that is reported to be produced in surprisingly good yield. However, the patent does contain copies of NMR

and IR spectra as well as crystallographic details for both isomers of **38c**.

Reaction 13



(a) Concd HCl, 100 °C, 16 h; (b) H_2O, charcoal, 50 °C, filter; (ii) Aq NaOH, filter; (iii) Warm MeOH, filter, dry; (c) Crystallise from MeOH/EtOH/H_2O

Advantages

The process enables the production of pure isomers of gabapentin intermediates to study their activity.

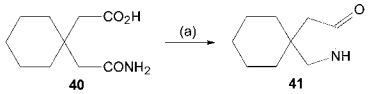
Patent No. U.S. 7,632,953

Assignee: Hikal Ltd., Bangalore, India

Title or Subject: Process for the Preparation of Gabalactam

This patent focusses on the preparation of gabalactam **41** that is an intermediate in the preparation of gabapentin **42**. Alternative methods for preparing **41** are described and are not considered as commercially acceptable because of various problems including the use of hazardous reagents such as $MeNO_2$ or NaCN. The procedure described in this patent is based on that used for the preparation of the Bu^t derivative **39** described in the previous patent and is shown in Reaction 14. Thus, the amide **40** is treated with a preprepared mixture of NaOH and Br_2 at −5 °C followed by heating to 85 °C for 10 h. After this the product is extracted and crystalline **41** obtained in yields up to 80.7%. Various solvents were used for the extractions including DCE, DCM, and PhMe with the latter giving the highest yield. The purity of the product by HPLC was up to 99%. The examples describe kilo-scale experiments, thus indicating that the process can be scaled up.

Reaction 14



(a) (i) Aq NaOH, Br_2, -5 °C, 3 h; (ii) 85 °C, 10 h; (iii) Cool 40 °C; (iv) Extract in PhMe, add charcaol, filter, wash in water, evaporate.

Advantages

The process gives good yields of the lactam without the need to use expensive or hazardous reagents.

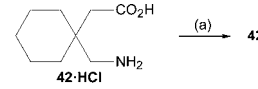
Patent No. U.S. 7,635,717

Assignee: Hikal Ltd., Bangalore, India

Title or Subject: Process for the Preparation of Aminomethyl Cycloalkane Acetic Acids

In this final patent on the subject of gabapentin **42**, the first claim of the patent mentions an acetone-free process for the preparation of **42** from the HCl salt **42·HCl** (Reaction 15). The patent discusses several alternative methods for carrying out this procedure most of which make use of a basic IER. Such methods produce aqueous solutions of **42**, and to recover the dry free base necessitates the use of low temperatures and high vacuum evaporation because of the low vapour pressure of water. The patent states that the liberation of the free base **42** from the HCl salt by neutralisation using an alkali has surprisingly not been reported earlier. The preferred reagent used to neutralise the acid salt is KOH or NaOH, and this is done at 15 °C or less before heating to 75 °C. The solution is cooled to precipitate the solid, and an ageing period is required of up to 8 h before filtration. The wet solid is recovered and dissolved in wet MeOH and treated with charcoal. Addition of Pr^iOH followed by cooling <5 °C produces crystals of **42** that are recovered by centrifuge. The product contains total impurities of 0.032%. From the mother liquor gabalactam **41** can be recovered, and this can be converted to the HCl salt and so increase the overall process efficiency. The patent reports that the process can be scaled up to use 400 kilo of the salt, thus indicating its commercial viability.

Reaction 15



(a) (i) <15 °C; (ii) 75 °C, 3 h; (iii) 10 °C, 5 h; filter.

Advantages

The process gives an effective method for recovery of high-purity free base without the need to use IER methods.

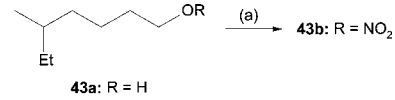
Patent No. U.S. 7,632,960

Assignee: J. Pöhlmann et al., Germany

Title or Subject: Process for the Preparation of Nitric Esters of Monohydric Alcohols

This patent is from a group of individuals and specifically covers the nitration of **43a** to give **43b** that is used to increase the cetane number of diesel fuel. Although the product **43b** is not itself explosive, its preparation can be hazardous as is often the case with nitration reactions, and the combination of low reaction temperature and short residence time are usually used to minimise the hazards. Alternative processes for preparing alkyl nitrates are said to employ isothermal conditions, whereas the new process is carried out under adiabatic conditions. The reaction is carried out on a continuous basis in a tubular reactor at a temperature of 20 to 60 °C with a residence time of between 0.01 and 30 s and an adiabatic temperature rise of between 25 and 40 °C. The patent also specifies that a minimum energy input is needed to fully mix the reaction mixture. The nitration of **43a** is carried out using a mixture containing 69.2% H_2SO_4, 18.2% HNO_3, and 12.6% H_2O and is shown in Reaction 16. The inlet temperature is 20 °C, and the outlet is 51.5 °C with a residence time of 4 s and energy input of 64 J/L. The example in the patent feeds 1.563 kg/h of **43a** to the reactor and produces **43b** with purity of 99.6% containing 0.31% impurities that is mostly **43a**. A second example includes recirculating the recovered acid mixture with temperature increasing from 20 to 45.2 °C and with a residence time of 8 s with fed rate of 0.63 kg/h of **43a**. The energy input in this case is 36 J/L and the process produces 99.54% pure ester with 0.4% impurities. After the reaction the mixture is cooled <20 °C, and the two phases are separated. The crude ester is washed and neutralised, and a part of the acid phase is recirculated.

Reaction 16



(a) HNO_3, H_2SO_4, H_2O, 20 - 51.5 °C, 4 s.

The patent states that the process is not restricted to monohydric alcohols and it may be applied to other nitrates that are immiscible with the nitrating mixture.

Advantages

The process allows the desired reaction to be carried out safely and with good productivity.

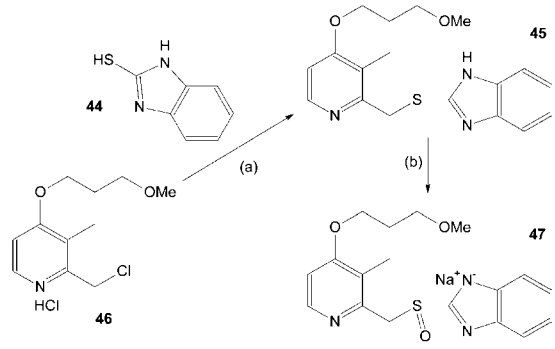
Patent No. U.S. 7,638,633

Assignee: Cipla Limited, Maharashtra, India

Title or Subject: Process for the Synthesis of Proton Pump Inhibitors

The compound covered by this patent, rabeprazole sodium **47**, is one of a group of similar compounds that are used to treat gastric ulcers. A common problem encountered in the synthesis of these compounds is the oxidation of a thioether to a sulphinyl compound, and patents on this subject have been reviewed previously (*Org. Process Res. Dev.* **2006**, *11*, 318). Alternative processes are said to use hazardous or expensive oxidants that are not suitable for industrial scale. This patent claims to provide an efficient, safe, and environmentally friendly method of producing **47**. The synthetic route is shown in Reaction 17 and begins by condensation of **44** with **46** in purified water containing NaOH to give the thioether **45**. This is recovered as a wet solid and is used directly in the second step where it is suspended in water containing NaOH. The oxidation of **45** to **47** is carried out using NaOCl with pyridine present as a catalyst. The reaction is quenched with $Na_2S_2O_3$, and after the solution is saturated with NaCl, the product is extracted into DCM. Following evaporation of the solvent, the residue is dissolved in EtOAc, and the Na salt **47** is precipitated by addition of heptane and isolated in a yield of 78% based on **46**. The purity was not reported.

Reaction 17



(a) (i) NaOH, H_2O, 30 °C, 2 h; (ii) Filter; (b) (i) NaOH, pyridine, H_2O, rt; (ii) NaOCl, 8 °C, 4 h; (iii) 5% $Na_2S_2O_3/H_2O$; (iv) NaCl, extract in DCM, evaporate; (v) EtOAc, 50 °C, 0.5 h; (vi) Heptane, rt, filter, wash, dry.

The claims of the patent cover the oxidation step being carried out using water or water and a solvent that is miscible with water. Solvents mentioned are alcohols, ketones, or nitriles although there are no examples of where these are used.

Advantages

The process does provide an efficient method of producing the desired compound in good yield without resorting to the use of hazardous oxidising reagents.

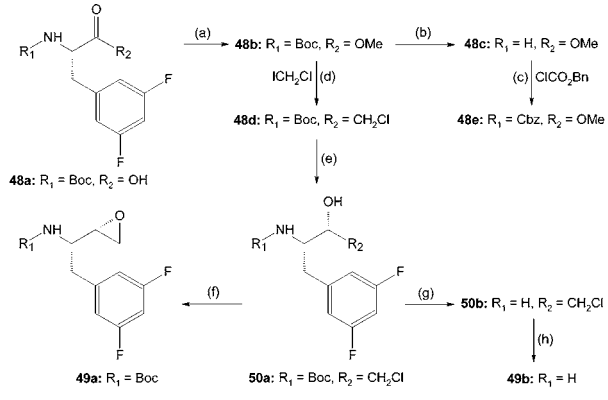
Patent No. U.S. 7,638,646

Assignee: Elan Pharmaceuticals Inc., San Francisco, California, U.S.A

Title or Subject: Processes and Intermediates for Preparing Benzyl Epoxides

The claims of this patent actually cover the novel esters **48a**−**e** with one claim specifically listing the methyl ester **48c**. These esters are intermediates in the preparation of benzyl epoxides such as **49a** and **49b** that are used to prepare compounds such as **53**. This is one of a number of similar compounds that are of interest in the preparation of biologically active molecules for treating Alzheimer's disease. The patent contains a substantial amount of information, but space limits the amount that can be covered here. Reaction 18 summarises the synthesis of the esters **48a**−**e** and their use in the preparation of the benzyl epoxides **49a** and **49b**. Although extensive experimental details are provided, there is no information reported for the yield or purity of the compounds that are obtained in any of the reaction schemes. The first stage of the process in the preparation of the epoxide **49a** is the esterification of **48a**. This is carried out using Me_2SO_4 and LiOH to give **48b** that is isolated as a crystalline solid after recrystallisation from hexane. Hydrolysis of **48b** with HCl in MeOH produces the amine ester **48c** that can be converted to alternative protected amine esters such as **48e** (R_1 = BnOCO−, R_2 = OMe). The synthesis of **49a** proceeds with the alkylation of **48b** by reaction with ICH_2Cl and LDA at −78 °C to give **48d** that is reduced at −78 °C using $NaBH_4$ to give **50a**. The product is recrystallised from hexane with a *syn/anti* ratio reported to be between 4 and 9:1. The final stage of the synthesis of **49a** is formation of the epoxide ring by treatment of **50a** with KOH in EtOH. The unprotected epoxide **49b** is prepared from **50a** by removal of the Boc protection using an IER to produce **50b** that is treated with KOH to form the epoxide ring.

Reaction 18

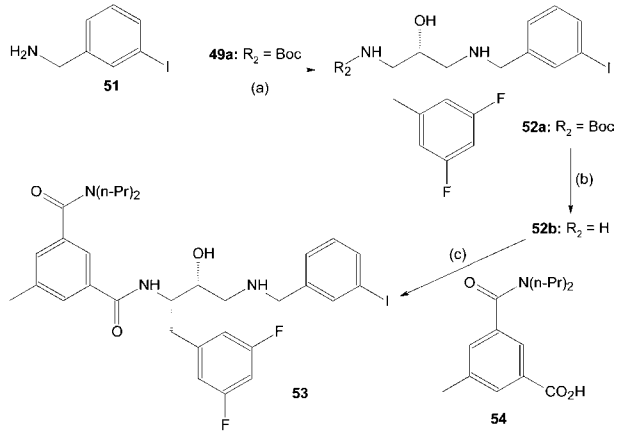


(a) (i) LiOH, THF, 0 °C, 0.5 h; (ii) Me_2SO_4, 0 °C, 0.5 h; (iii) 50 °C; (b) HCl, MeOH, 50 °C; (ii) Cool, aq $NaHCO_3$; (iii)Evaporate; (c) (i) Na_2CO_3, H_2O, 25 °C; (ii) EtOAc, concentrate; (d) (i) LDA, THF, -78 °C, 0.25 h; (ii) HOAc, -65 °C, 0.25 h; (e) (i) $NaBH_4$, THF, EtOH, -78 °C, 2 h; (ii) 0 °C, 1 h; (f) KOH, EtOH, 0 °C, 2 h; (ii) 20 °C, 1 h; (g) Dowex50WX2-400, MeOH, 50 °C, 2 h; (h) KOH, EtOH, 25 °C, 0.5 h.

The epoxide **49a** is then used in the preparation of compounds such as **53** by the route shown in Reaction 19. The experimental details for this scheme actually describe the reaction of **49a** with 3-methoxybenzylamine to give the methoxy analogues of **52a**, **52b**, and **53**. However, the patent states that the preferred

product of this reaction sequence is the compound **53**, and hence the reaction scheme shows the synthesis of this compound. The first stage is condensation of **49a** with benzylamine **51** in refluxing Pr^iOH to form **52a** that is isolated in the crude form and used in the next step. Here the Boc protection is removed using TFA to give **52b**, and the final compound **53** is obtained by reaction of **52b** with the acid **54** in the presence of Et_3N, 1-hydroxybenzotriazole (HOBT), and the HCl salt of the carbodiimide $EtN{=}C{=}N(CH_2)_3NMe_2$. The product is purified by flash chromatography.

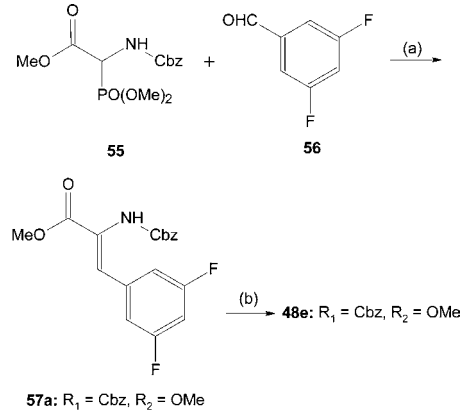
Reaction 19



(a) (i) Pr^iOH, reflux, 2 h; (ii) Evaporate; (b) (i) TFA, DCM, 25 °C, 1 h; (ii) Evaporate; (c) (i) Et_3N, DMF, 0 °C; (ii) HOBT, $EtN{=}C{=}N(CH_2)_3NMe_2{\cdot}HCl$, 0 °C; (iii) 25 °C, 15 h; (iv) Citric acid quench, basic wash, evaporate; (v) Flash chromatography.

The patent also contains details of alternative methods for the preparation of the esters **48**, and Reaction 20 shows this method for **48e**. The two-stage process starts with the reaction of the phosphorus compound **55** with the aldehyde **56** in the presence of tetramethylguanidine (TMG) to form the olefin **57a**. No yield or purity are reported, and the example states that additional material is recovered that is a mixture of *E*- and *Z*-olefin isomers. The olefin **59a** is then hydrogenated to give **48e** using a chiral Rh phosphine catalyst.

Reaction 20



(a) (i) TMG, THF, 0 °C, 5 min; (ii) 25 °C, 2 h;
(b) Rh(phosphine), MeOH, H_2, 20 psig, 25 °C, 16 h;

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

Advantages

The patent describes novel compounds that are used in the synthesis of useful pharmaceutical intermediates. The lack of information on the yield and purity of products means that it is not possible to assess the industrial potential of the process.

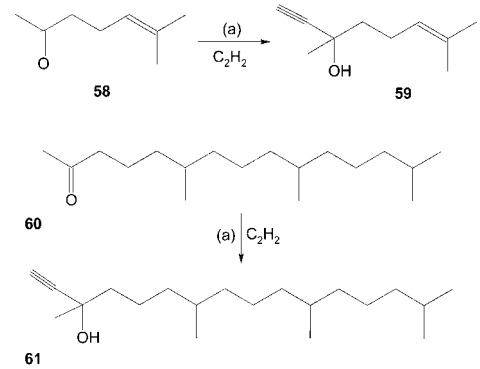
Patent No. U.S. 7,638,658

Assignee: DSM IP Assets B.V., Te Heerlen, Netherlands

Title or Subject: Ethynylation Process

This patent describes a process for the manufacture of unsaturated alcohols such as **59** and **61** that are useful in the synthesis of vitamins A and E. The process involves the reaction of acetylene and a ketone in the presence of NH_3 and an alkali metal hydroxide (Reaction 21). This reaction was reported in a 1962 patent (DE1232573) and used a molar ratio (MR) of metal hydroxide to ketone of between 1:10 and 1:200. As this ratio increases, the yield of product falls and that of a diol byproduct increases. The current patent reports that it has been surprisingly found that the yield of desired product can be obtained using a MR that is higher than that previously claimed to be required. Reaction 21 shows the preparation of **59** from **58** and **61** from **60** by using a molar ratio of KOH to ketone of 1:250. The process takes place at 30 °C under a pressure of acetylene of 16.1 to 16.8 bar, and this pressure maintains the NH_3 as a liquid. The MR of NH_3 to ketone is between 10:1 and 30:1. The mixture for producing **59** was analysed by GC and showed 94.1% of product containing 2.3% of **58**. The mixture also contained 1.7% of a diol byproduct. The lower levels of akali metal hydroxide and lower temperatures not only give a better product yield but also mean that there is a lower level of salts for disposal. For product **61** the mixture contained 94.5% **61** with 2.6% **60** and 0.8% of a diol. The process was also successfully applied to the reaction of MEK, C9, and C14 ketones. The experiments in the patent are carried out in batch systems although it is stated that a continuous process is preferable, and the patent claims specifically cover a continuous process. Despite this claim there are no examples given of a continuous process. It would certainly seem to be safer to use something as reactive as acetylene in a continuous process where the inventory in the reactor can be minimised.

Reaction 21



(a) Liq NH_3, 45% aq KOH, 16.1 - 16.8 bar, 30 °C, 5 h.

The use of acetylene as a raw material for making organic chemicals on a large scale is generally limited to existing users that have the expertise and equipment; thus, if this is a viable process, it is unlikely to be widely used.

Advantages

The process gives greatly improved yield of product with a small change to a previously known procedure.

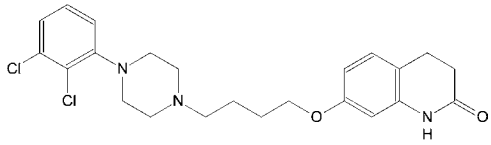
Patent No. U.S. 7,642,353

Assignee: Synthon BV, Nijmegen, Netherlands

Title or Subject: Process of Making Crystalline Aripiprazole

The compound of interest in this patent, **62**, is used to treat schizophrenia. Several forms of **62** are known, and the hygroscopic nature of these varies. The methods of preparing these forms can sometimes involve heat treatment at temperatures up to 125 °C that can degrade the crystals. An objective of the patent is to produce an anhydrous form that is not hygroscopic and that does not require the use of high temperatures. The process described in the patent produces the desired crystals of Form B by crystallising the compound preferably from either Pr^iOH or EtOAc. The solvents should contain <1% water. The procedure is to dissolve the crystals in the solvent and heat to reflux. The crystallisation is carried out by cooling the solution followed by addition of seed crystals or addition of heptane. The patent contains XRD, IR, and NMR data for crystals of Form B produced by a method that involves addition of ice-cold heptane to a hot solution of **62** in Pr^iOH followed by cooling to 0 °C. The patent claims also cover the production of crystals with 95% <200 μm and 20% <10 μm.

Aripiprazole



62

Advantages

The process produces nonhygroscopic crystals that are suitable for use in preparing pharmaceutical compositions.

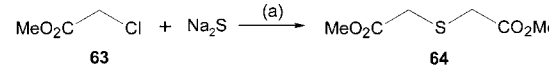
Patent No. U.S. 7,642,371

Assignee: Saltigo GmbH, Langenfeld, Germany

Title or Subject: Process for Preparing Dialkyl Thiodiglycolates

The title compounds such as **64** are precursors for chemicals used in the preparation of electronically conductive polymers. Synthesis of such compounds is said to be carried out either by esterification of thiodiglycolic acid or by reaction of chloroacetic esters with Na_2S. These methods are said not to give high yields. The patent discloses an improved method of preparing **64** that is described as an astonishing finding and is the reaction of **63** with a Na_2S or NaHS that under suitable conditions gives the desired product in high yields. The key to the process is that the Na_2S is quickly depleted and the pH is maintained between 5 and 8 and this is done by using a buffered aqueous solution containing a PTC. Reaction 22 outlines the process that is carried out by preparing a solution of NaH_2PO_4 and adjusting to pH 6.0 with NaOH. The solution is warmed to 33 °C and Bu_3NMeCl added followed by **63**. Additional **63** and an aqueous solution and Na_2S are simultaneously metered into the reactor over 2 h with a further solution of Na_2S being added over 1 h. After extraction into PhMe and distillation, the product **64** is obtained in 93% yield containing 6% PhMe. The patent also describes the preparation of the Et ester by the same procedure in a yield of 95% containing 9% PhMe. The products can be used without further purification. An important environmental point is that since the Na_2S is totally converted there is no significant amount of H_2S in the wastewater nor in the air extracted from the process.

Reaction 22



63 **64**

(a) (i) NaH_2PO_4, NaOH, H_2O, pH 6.0, Bu_3NMeCl, 33 °C, 3 h; (ii) PhMe, phase separation; (iii) Distillation.

Advantages

The process gives very good yields of the products without significant waste disposal problems.

Patent No. U.S. 7,645,876

Assignee: Teva GZMR, Debrecen, Hungary

Title or Subject: Processes for Crystalline Macrolides

Macrolides are large ring compounds having a lactone group and one or more deoxy sugar substituents. A number of mycins are macrolides that have bacteriological activity such as erythromycin. This patent describes a process for the preparation of crystalline forms of the macrolides tacrolimus and pimecrolimus. The former is an antibiotic and immunosuppressive agent while the latter is an anti-inflammatory compound. A patent covering the synthesis of tacrolimus has been reviewed (*Org. Process Res. Dev.* **2009**, *13*, 371). The process described in this patent comprises the preparation of a solution of the macrolide in a polar solvent A followed by addition of a second polar solvent B and an antisolvent C and then allowing crystallisation to occur. The preferred solvent A is EtOAc, B is preferably DMF but could be water, and C is cyclohexane. The initial solution in A is prepared at about 50 °C, and the crystallisation takes place at between 0 and 8 °C; the process is applied to both tacrolimus and pimecrolimus. The patent claims that the preferred ratios of solvents are (A+C):B = 300 to 350:1 and C:A = 6:1, and the concentration of macrolide in A is 0.5 to 1.0 kg/L. The patent lists peaks in the XRD pattern for tacrolimus obtained by this process but does not have similar details for pimecrolimus.

Advantages

The process provides crystals of macrolides that can be used in preparing pharmaceutical formulations.

Patent No. U.S. 7,645,880

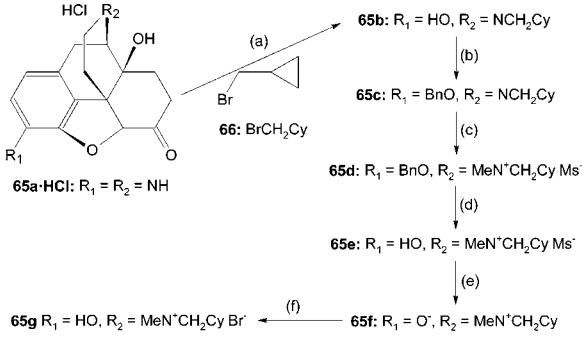
Assignee: Sanofi-Aventis, Paris, France

Title or Subject: Process for Preparing N-Alkylnaltrexone Halides

The specific compound of interest is the *N*-methylbromide compound **65g**, the *R*-isomer of which is used to alleviate the side effects of patients receiving morphine. The *S*-isomer actually has activity that is opposite to the desired effect, and hence its concentration in the medication must be minimised. An alternative method for the preparation of **65g** is described as being incompatible with industrial operation because it uses super atmospheric pressure and an IER method. Another process that takes place at lower pressures uses the solvent *N*-methylpyrrolidone that is said to be unsuitable because of impurities. Hence, the patent discloses an improved method that is suitable for commercial production. The process, outlined in

Reaction 23, starts from the HCl salt of **65a** that is alkylated with **66** to form **65b**. The process is monitored by HPLC and stopped when <0.5% of **65a** remains. The crude product is isolated in a 88.6% yield and then used in the next step as the free base or as the HCl salt. Treatment of **65b** with BnBr protects the OH, and **65c** is formed. The crude product is isolated by extraction in basic DCM, and this makes it possible to totally remove residual **65b** and also avoid formation of *O*-methyl derivative. The DCM solution is concentrated, and the crude intermediate **65c** is isolated as an oil and used directly in the next stage. It is explained that this is done to avoid manipulating a mixture containing BnBr that is toxic and a lachrymator. Quaternisation of **65c** is then carried out by treatment with Me_2SO_4, and the product **65d** is recovered as a crude solid and dissolved in basic solution ($NaHCO_3$ or NaOH) to destroy the toxic Me_2SO_4. The filtered solution is concentrated to remove Me_2CO, and water is added before catalytic hydrogenation of **65d** using Pd/C to remove the Bn group and produce **65e** that is recovered in aqueous solution. The aqueous solution of **65e** is treated with base, and the zwitterion **65f** is produced that is treated with HBr to give the desired bromide salt **65g** in an isolated yield of 70% relative to the starting material **65a**.

Reaction 23



(a) (i) $NaHCO_3$, $AcNMe_2$, 69 °C, 10 min; (ii) **66**, 69 °C, 6.5 h;
(b) K_2CO_3, Me_2CO, BnBr, reflux, 2 h; (c) (i) Me_2CO, $NaHCO_3$, 20 °C; (ii) Me_2SO_4, reflux, 72 h;
(iii) Cool 20 °C, filter, wash in Me_2CO; (iv) Aq $NaHCO_3$; (v) Concentrate;
(d) Pd/C, H_2O, H_2, 2.5 bar, 40 °C, 2 h; (e) (i) Na_2CO_3, H_2O, pH 9.8, 20 °C, 1 h; (ii) Filter;
(f) (i) HBr, MeOH/H_2O, 60 °C; (ii) Filter, cool filtrate to 0 °C, crystallise.

The patent gives detailed ^1H and ^{13}C NMR data for all intermediates including assignments of peaks and coupling data.

Advantages

The process gives the desired product in high yield despite requiring several steps, and this is possible because there is no need to purify intermediates.

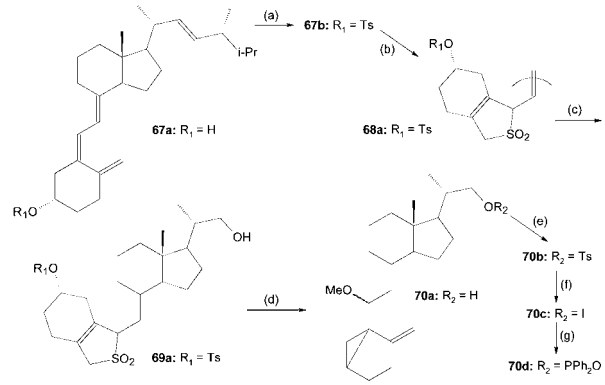
Patent No. U.S. 7,645,911

Assignee: Formosa Laboratories Inc., Taoyuan, Taiwan

Title or Subject: Process for Preparation of Paricalcitol and Intermediates Thereof

Paricalcitol **76b** is a vitamin D2-derived sterol, available as Zemplar, and used for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure. This patent contains a very large amount of information and describes a multistep process for the preparation of **76b** from vitamin D2. The complexity of the process and lack of space mean that only the main reaction details are included in the schemes. For ease of following the overall process the synthetic route has been divided into three sections. The first of these, shown in Reaction 24, is the conversion of vitamin D2 **67a** (R_1 = H) to the diphenylphosphine derivative **70d** (R_2 = PPh_2O). The first stage is conversion of **67a** to its tosylate **67b** followed by treatment with SO_2 to give **68a** that is isolated as an orange foam. The crude residue is reacted with O_3 followed by $NaBH_4$ to rupture the side-chain C=C bond and form the hydroxy compound **69a**. This is isolated as a mixture of isomers and used without purification in the next step where it is treated with $NaHCO_3$ in MeOH to produce the bicyclic ring compound **70a**. This is converted in stages to **70d** (R_2 = PPh_2O). The intermediates **70b** and **70c** are not purified and isolated as yellow to orange foams or oils.

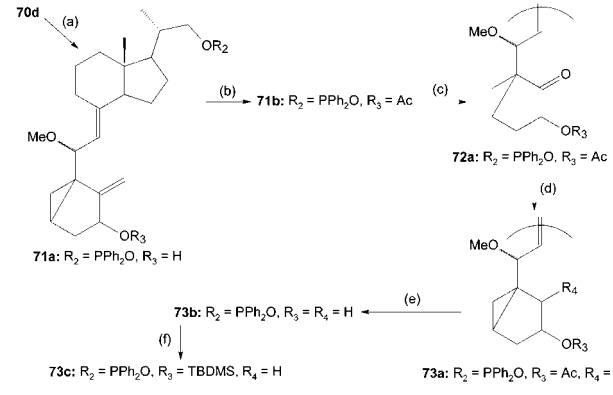
Reaction 24



(a) TsCl, pyridine, DMAP. 10 °C, 24 h; (b) SO_2, H_2O, DCM, 10 °C, 1 h; (c) (i) O_3, MeOH,DCM, aq $NaHCO_3$, 2 h;
(ii) $NaBH_4$, 2 h; (d) $NaHCO_3$, MeOH, reflux, 2.5 h; (e) TsCl, DCM, pyridine, 30 °C, 2 h; (f) NaI, Me_2CO, reflux, 2.5 h:
(g) (i) Ph_2PH, BuLi, THF, -78 °C, 0.75 h; (ii) rt, 3 h; (iii) Extract in MTBE, 10% H_2O_2.

The next stage of the process is shown in Reaction 25 and is the hydroxylation of **70d** with SeO_2 and Bu^tOOH to give **71a** that is acetylated to form **71b**. Treatment of **71b** with O_3 followed by Me_2S forms the ketone **72a** that is isolated as a yellow oil, and this is reduced to the alcohol **73a** using $NaBH_4$ and $CeCl_3$. An alternative method for the conversion of **71b** to **73a** involves reaction of **71b** with OsO_4 to form a diol that is treated with $NaIO_4$ to produce **73a**. Reaction of **73a** with MsCl followed by reduction with LiAlH4 gives the alcohol **73b** that is then protected by formation of the TBDMS ether **73c**.

Reaction 25

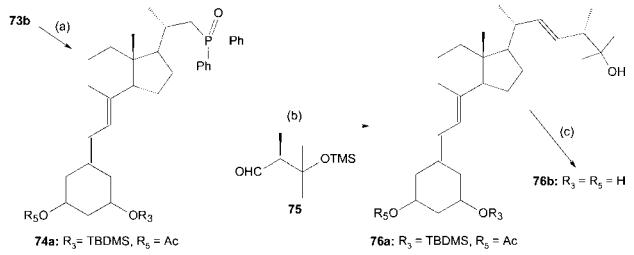


(a) SeO_2, Bu^tOOH, pyridine, DCM, 15 °C, 5 h; (b) Ac_2O, pyridine, rt, 1 h;
(c) (i) O_3, MeOH, aq $NaHCO_3$, -10 °C, 1 h; (ii) Me_2S, rt, 1 h; (d) $CeCl_3·7H_2O$, $NaBH_4$, MeOH;
(e) (i) MsCl, Et_3N, PhMe, 0 °C, 2 h; (ii) LiAlH4, THF, 0 °C, 2 h; (f) Imidazole, DCM, TBDMSCl, 20 °C, 1.5 h;

The last stage of the process is summarised in Reaction 26 in which heating **73c** in HOAc causes removal of the MeO group with formation of a C=C bond and breaking of the bicyclic

ring to form **74a**. Treatment of **74a** with Bu^nLi followed by addition of the aldehyde **75** and then Bu^tOK adds the hydroxy side chain to **74**, forming **76a**. Treatment of **76a** with NaOH in MeOH followed by evaporation gives a residue that is dissolved in THF to which imidazole and Bu_4NF are added. Refluxing for 1 h ensures the completion of the reaction that is followed by TLC analysis. Extraction of the residue in EtOAc followed by addition of $PhB(OH)_2$ gives a mixture of crude **76b** and its cyclic 1,3-boronate derivative. The composition of this mixture is not reported, nor is the separation mentioned, but crystallisation of crude **76b** from MeOH/DCM./HCO_2Me or Me_2CO/DCM gives the product with a purity of 99.8%.

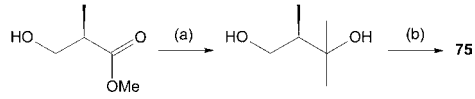
Reaction 26



(a) HOAc, 55 °C, 1 h; (b) (i) Bu^nLi, THF, 0.75 h; (ii) **75**, THF, -78 °C, 1 h; (iii) Bu^tOK, THF, -12 °C, 3 h;
(c) (i) Aq NaOH, MeOH, rt, 2h; (ii) Evaporate, wash; (iii) Bu_4NF, imidazole. THF, reflux, 1 h;

The patent gives details for the preparation of the aldehyde **75** that is used in the formation of the side chain in **76a**. This is shown in Reaction 27 and starts from the ester **77** that is reacted with MeMgCl followed by acidification to form crude **78** as an oil that is purified by flash ColC. Oxidation of **78** with TEMPO followed by silylation gives **75** that is obtained pure after flash ColC.

Reaction 27



(a) (i) MeMgCl, Et_2O, 0 °C; (ii) THF, rt, 2 h; (iii) 5M HCl, 0°C;
(b) (i) TEMPO, NaBr, H_2O, PhMe, rt, 0.5 h; (ii) 12% NaOCl, 1.5 h;
(iv) Imidazole, Et_3N, 10 °C; (v) TMSCl, 10 °C.

It is not possible to determine the final yield of the product since many intermediates are used without purification, and the yields of individual steps are not always given. The scale-up and commercialisation potential of this process are not known, but some of the steps involve the use of some hazardous or environmentally nonfriendly reagents such as O_3, Me_2S, and DCM. The patent contains ^1H NMR data for many of the intermediates.

Advantages

The patent describes a novel process for the preparation of the desired compound, and the nature of the process is such that is not possible to assess its commercial potential.

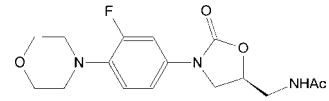
Patent No. U.S. 7,649,096

Assignee: Glenmark Pharmaceuticals Limited, Mumbai, India

Title or Subject: Process for the Preparation of a Crystalline Form of Linezolid

Linezolid **79** is an oxazolidinone antibiotic that is effective against multiresistant bacteria and is available as Zyvox or Zyvoxid. A new process for its synthesis has been reviewed (*Org. Process Res. Dev.* **2008**, *12*, 369), whereas the current patent reports a method of preparing a specific polmorph.

Linezolid



79

The claims of the patent cover the crystallisation by addition of an antisolvent to a solution of **79** in a number of solvents including chlorinated solvents, alcohols, or ethers such as THF or monoglyme. However, the two examples in the patent only describe the use of DCM or a mixture of THF/DCM as solvent and *o*-xylene as the antisolvent. After addition of the *o*-xylene the solvent is evaporated at 60−70 °C to achieve supersaturation and crystallisation. The crystals are filtered off and characterised by XRD and IR data, and these are shown in the patent. Earlier patents report that the crystals of **79** are obtained as Form II. The main claim of the current patent covers a process for preparing crystals of **79** with specific XRD and IR spectra shown in the patent. It is not claimed if the process provides a new form of **79** or whether this is a new method of obtaining Form II. Although the patent includes copies of the XRD and IR spectra of the crystals obtained by this process, it is not clear whether these are the same as those reported for Form II. The data provided for Form II in the original patent lists only peak positions and copies of the spectra are not available for comparison.

Advantages

The patent provides a method of obtaining crystals of linezolid, but it uses chlorinated solvents, and it is not clear what advantages there are of the process or the crystals obtained.

Patent No. U.S. 7,652,052

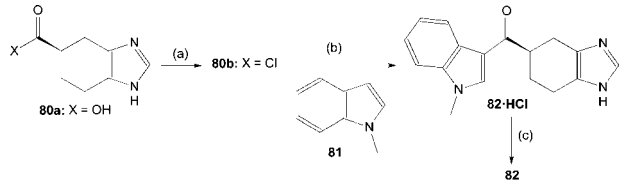
Assignee: Astellas Pharma Inc., Tokyo, Japan

Title or Subject: Process for Producing Ramosetron or its Salt

Ramosetron **82** is used to treat nausea and digestive problems caused by antitumour drugs and is also under trial for treating irritable bowel syndrome. A number of methods for producing **82** and its salt are summarised, and maintaining the stereochemistry is said to be a problem. The new patent describes a process for producing **82** that retains stereochemistry in the synthesis and is shown in Reaction 28. The synthesis starts by formation of the acyl chloride **80b** from the acid **80a** and $SOCl_2$. The yield is not reported, and the crude material is used in the next step where it is undergoes a Friedel−Crafts reaction with **81** at −40 °C in the presence of $Et_3Al_2Cl_3$. The workup procedure involves a long sequence of washing and extraction steps with THF, water, PhMe, MEK, aq NaOH, brine, EtOH, and EtOAc to isolate the free base **82** that is then converted to the HCl salt by treatment with HCl in EtOAc. The final yield of the salt is 78.8% with ee of 99.5%. A second procedure is also

described using Et_2AlCl, and this takes place at −25 °C and gives a 86.3% yield of **82·HCl** with 99.2% ee.

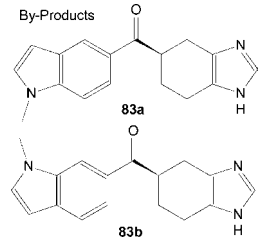
Reaction 28



(a) (i) $SOCl_2$, DME, 70 °C, 2 h; (ii) Evaporate; (b) (i) PhMe, $Et_3Al_2Cl_3$, -40 °C, 3 h; (ii) Add THF; (iii) Water, 0 °C; (iv) Extraction/washing, evaporate; (c) (i) EtOH/EtOAc, 70 °C, 1 h; (ii) HCl/EtOAc; (iii) 0 °C, filter, wash, dry.

The patent reports that the route shown produces the two byproducts, **83a** and **83b**. By using $Et_3Al_2Cl_3$ in the first procedure, **83a** is present at 0.04% and **83b** at 0.02%. When Et_2AlCl is used, the levels increase to 0.63% and 0.35%, respectively. The patent reports the analytical method used to determine the amounts of **83a** and **83b**, and ^1H NMR data are given for both compounds as well as for **82·HCl**.

Byproducts



Advantages

The process does not require a resolution stage and retains the stereochemistry of the starting material, giving high product yield.

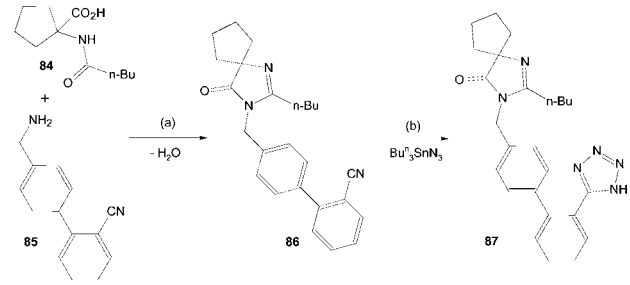
Patent No. U.S. 7,652,147

Assignee: Alembic Limited, Vadodara, Gujarat, India

Title or Subject:Process for Preparation of Irbesartan

Irbesartan **87** is available as Avapro for lowering blood pressure in patients with kidney disease. It is also used to treat diabetes mellitus. Several methods for synthesising **87** are reviewed, and the disadvantages claimed for these include the use of chromatography for purification, the use of hazardous or corrosive reagents, low yield, and the need for a multistep procedure. A specific problem mentioned in one method is the use of DCC that is said to be difficult to handle on a large scale. The new patent claims to overcome these problems, and the route used to prepare **87** is shown in Reaction 29. The first step is the condensation of amido acid **84** with the amino group in the biphenyl **85** in the presence of MsOH or TsOH to give the diazo spiro compound **86**. This is carried out in an aromatic solvent and the water azeotropically removed. The product is obtained in a yield of 80% using MsOH or 88% with TsOH. The tetrazole group is formed in the second step by reaction of **86** with the azide Bu_3SnN_3 in refluxing in *o*-xylene for 80 h. After neutralisation with NaOH and workup that includes treatment with charcoal, the desired product **87** is recrystallised from 95% EtOH and isolated in up to 86% yield, but the purity is not reported. The final step involves the use of the Sn azide, and there is no information regarding analysis of any Sn residues in the product. This important aspect is not addressed in the patent.

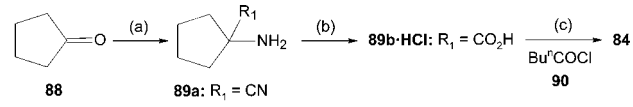
Reaction 29



(a) (i) TsOH, PhMe, reflux, 48 h; (ii) Cool, evaporate; (iii) Aq NaOH, 0.5 h; (iv) Separate, brine wash; (v) Charcoal, filter; (vi) MTBE wash, dry; (b) (i) o-xylene, reflux, 80 h; (ii) 1M NaOH, separate; (iii) Wash in o-xylene + Pr^i_2O; (iv) Charcoal, filter; (v) 3M HCl, filter wash H_2O, dry 60 °C.

The patent gives details of the preparation of the amido acid **84** by the method summarised in Reaction 30. Cyclopentanone **88** is converted to the aminonitrile **89a** by reaction with NaCN in the presence of NH_4Cl. The yield is not reported, and the crude product is hydrolysed using aq HCl to form the acid **89b** that is isolated as its HCl salt. Reaction of this salt with **90** is carried out in the presence Bu^n_4NBr as a PTC to produce the amido acid **84** that is isolated in 68% yield.

Reaction 30



(a) NaCN, aq NH_4Cl, MeOH, 60 °C, 1.5 h; (b) Aq HCl, 100 °C, 24 h; (c) (i) Bu^n_4NBr, aq NaOH, 5 °C, 1 h; (ii) PhMe/H_2O, separate; (iii) HCl, filter.

Advantages

The process does not require purification of intermediates, has less steps than alternatives, and avoids the use of hazardous reagents such as DCC. However, the amount of Sn in the final product needs to be determined.

Keith Turner

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