Organic Process Research & Development **2008,** *12,* 797–806

Highlights from the Patents

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

Summary

There are 19 patents in the current selection from an original list of 321. Several of these contain experimental details involving many stages, and because of space limitations only very brief details are given here. By a strange coincidence there are several patents in the current selection that are assigned to the same company (Teva), and some explanation may be appropriate. When selecting patents the initial list contains only the title and patent number, and the final selection is made purely on the title of the patent so there is no significance in the presence of so many from one company. Having said that, there is one patent that stands out by virtue of the fact that it describes some novel crystalline polymorphs of the drug fluvastatin sodium. The striking point is that the patent claims to have identified 87 polymorphs, and this must be rather difficult to deal with. Another patent on statins covers a new synthesis of pitavastatin. Polymorphs appear in a patent on the anti-insomnia drug indiplon. In this case amorphous forms are described that have improved solubility. Avoiding chromatographic separation methods is common, and an improved method of crystallising calcipotriene gives good particle size distribution and 99.9% pure product. An improved separation method is also reported for recovering levulinic acid by reactive extraction from esterification reactions. This must be deemed to be in commercial use since the patent reports multiton/h production rates. The identification and isolation of impurities and their use as reference standards is reported for the anti-hyperactivity drug atomoxetine and the immunosuppressant mycophenolate mofetil. An improved process is described for tolterodine that is used to treat bladder problems. A safer method for the production of the intermediate glyceraldehyde acetonide is reported that removes the need for close control of pH. The patent reports large-scale production, thus indicating that it is, indeed, safe. A safer process for the production of LAF-237, a diabetes drug in phase 2 trials, is reported that removes the need for isolation of irritant intermediates. On the subject of safety, a new method of producing aromatic carboxylic acids by oxidation of alkyl groups is reported. It uses catalytic ozonolysis and reports yields of 98%. Multiple fluorination of aryl groups is reported that uses KF and is catalysed by an iminium chloride compound. A very large number of novel pteridinones is reported that have potential in treating tumours, but one step in the process is a reduction that takes nine days. A process for preparing a sterically hindered *N*-alkoxyamine involves the reaction of TEMPO and an alkyl borane in the presence of a catalyst and O_2. It is no surprise that the reaction was speeded up by bubbling the gas through the solution. In a static atmosphere the reaction takes 48 h but only one hour when bubbling the gas. The patent coverage suggests that over 180 compounds have been produced. Another very comprehensive patent covers the synthesis of benzazepines that are useful in treating inflammatory diseases, and multikilo batches are reported. Patents describing large-scale experiments can indicate commercialisation or, at the very least, advanced development. A process for preparing CCR-2 antagonists is very comprehensive and reports using multikilo quantities of reagents. The titles of patents can be misleading, and one describing the synthesis of alkynols actually turns out to be a method of removing protective silyl groups to give the alkynol. The inclusion of a patent does not imply any commercial or legal significance, and the advantages listed are those claimed in the patent unless this reviewer has personal knowledge of the subject.

Patent No. U.S. 7,351,710

Assignee: Mai De Ltd., Northborough, Massachusetts, U.S.A

Title or Subject: Preparation of Amorphous Form of Indiplon

Indiplon is used to treat insomnia, and this patent describes two methods of preparing a novel amorphous form of the drug that has improved solubility over the crystalline forms. There are three crystalline forms of indiplon, and these are said to have very low solubility in water (20−30 μg/mL). Although no solubility data are provided for the amorphous form, it is implied that it has a higher solubility. The first method used to prepare the amorphous form is to dissolve any of the crystalline forms in a solvent, heat for a short time, then distill off the solvent under vacuum, and finally dry the solid. Solvents used are dichloromethane (DCM), Me_2CO, MeCN, or low alcohols. The second method is to dissolve the crystalline form in a solvent and remove the solvent by spray drying. In this case the same solvents are used apart from MeCN. The amorphous form contains <0.5% of the crystalline material, and it can be prevented from converting to the crystalline forms by mixing with a carrier such as polyethylene glycol, starches, alkylcelluloses, cyclodextrins, etc.

Advantages

This novel form of the drug has potential application in the production of pharmaceutical compositions.

Patent No. U.S. 7,351,869

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

Title or Subject: Crystallization Method for the Purification of Calcipotriene

Calcipotriene is a synthetic derivative of vitamin D used in the treatment of psoriasis that is available under the name

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Dovonex or Daivonex. The synthesis involves many stages, and purification by chromatographic methods is frequently used. Particle size distribution (PSD) is also important, and purification by crystallisation is desirable if acceptable solvents can be found. The patent describes a method of purifying calcipotriene by dissolution in a polar solvent such as THF or Me_2CO and using HCO_2Me as antisolvent. The ratio of THF to HCO_2Me is about 1:30, and the mixture is cooled to about −18 °C for up to 24 h. The procedure gives crystals that have purity of 99.9% and a nominal particle size of between 15 and 40 micron.

Advantages

The process gives higher-purity product without the need to use chromatography and by using lower volumes of solvents than alternative crystallisation processes.

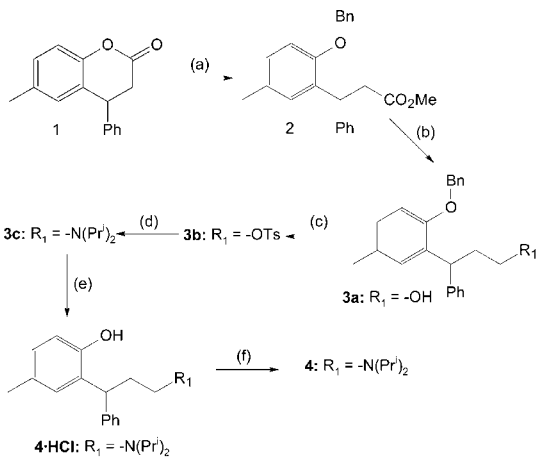
Patent No. U.S. 7,355,077

Assignee: Dr. Reddy's Laboratories, Hyderabad, India and Bridgewater, New Jersey, U.S.A

Title or Subject: Process for Preparing Tolterodine

Tolterodine **4** is used in treating urinary incontinence and other bladder problems and is available as the tartrate salt known as Detrol. The processes available for producing **4** are summarised and are said to require the use of hazardous regents such as MeI, BBr_3, or DIBAL or involve several stages and give poor yields. The current process is said to overcome these problems, and a summary of the reaction steps is shown in Reaction 1. The initial reaction is preparation of **2** by treating **1** with BnBr. Compound **2** is specifically named in one of the claims and by implication is novel. The ester group in **2** is then reduced to give **3a**, the OH is protected by conversion to **3b**, and its reaction with $HN(Pr^i)_2$ forms **3c**. The Bn group is removed from **3c** using Raney Ni, and the product **4·HCl** is recovered. The intermediate products are all solids that can be isolated. However, the patent claims cover the situation where they are not isolated in the process. The desired L-(+)-tartrate salt of **4** can be prepared from the HCl salt.

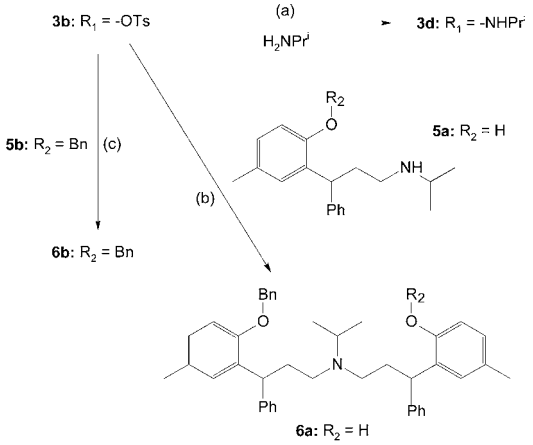
Reaction 1



(a) BnBr, K_2CO_3, MeOH/Me_2CO, reflux 3 h; (b) Vitride, PhMe, <40 °C, 25 min
(c) (1) Et_3N, DCM, 35 °C, 20 min; (2) TsCl, DCM, 35 °C, 10 min;
(d) MeCN, $HN(Pr^i)_2$, autoclave, 115 °C, 14 h;
(e) (1) MeOH, Raney Ni, H_2O, H_2, 5.5 kg/cm^2, 35 °C, 6 h; (2) MeOH, 36% HCl
(f) Aq NaOH, DCM, 35 °C, 10 min.

The patent also describes the preparation of the compounds **3d**, **6a**, and **6b**. These are said to be impurities and the tartrate salt of **4** contains <0.05% (by HPLC) of them. These three compounds are themselves the subject of three claims of the patent, and by implication they are novel compounds. All three compounds are prepared from **3b** by the methods summarised in Reaction 2. **3d** is obtained as a solid by reacting **3b** with H_2NPr^i, whereas **6a** and **6b** are obtained as syrups after reaction with **5a** and **5b**, respectively. ^{1}H NMR data are given for all three compounds plus the other intermediates indicated in Reaction 1.

Reaction 2



(a) (1) MeCN, 40 °C, 12 h; (2) Distil MeCN; (3) Recrystallise from EtOAc
(b) (1) MeCN, 115 °C, 18 h, autoclave; (2) Distil MeCN at 65 °C;
(3) Extract in EtOAc; (4) Wash with H_2O; (5) Column chromatography
(c) (1) DMSO, 70 °C, 20 h; (2) Cool to 30 °C, H_2O, extract in PhMe;
(3) Aq HCl; (4) Wash with H_2O; (5) distil PhMe

Advantages

The process does not require expensive reagents to obtain high yields of the desired product.

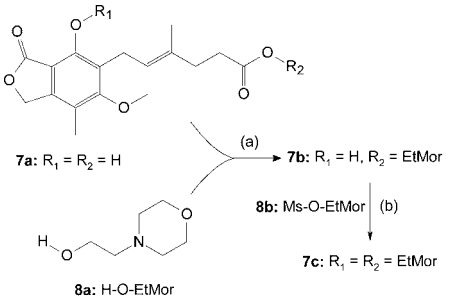
Patent No. U.S. 7,358,247

Assignee: TEVA Gyógyszergyár Zrt., Debrecen, Hungary

Title or Subject: Mycophenolate Mofetil Impurity

Mycophenolate mofetil **7b** is an immunosuppressant used in combination with other medications to prevent rejection of transplanted kidneys or other organs. This patent describes the preparation of **7c** that is identified as an impurity in **7b** and can be used as a reference marker. **7b** is prepared by esterification of the acid **7a** using a 6 M excess of **8a** in the presence of a catalyst (Reaction 3). The main example in the patent uses $SnCl_2$, but alternative catalysts may be used. Data show that these give variable amounts of the impurity **7c**, with levels up to 6.8% being found. The impurity **7c** may be obtained and isolated by treating **7b** with a base such as NaH in DMF followed by addition of the mesylate **8b**. The crude product of the reaction is then purified by column chromatography. A method for the preparation of **8b** is described in the patent by reaction of **8a** with MsCl in the presence of Et_3N. ^{1}H and ^{13}C NMR and basic MS data are given for **7c**.

Reaction 3



(a) (1) $SnCl_2$, 155 °C, 4 h; (2) Cool to rt, extract in Bu^iOAc;
(3) Wash in aq $NaHCO_3$, H_2O; (4) Recrystallise from Me_2CO/Pr^iOH
(b) (1) DMF, NaH, rt, 25 min; (2) **8b**, DMF, 50 °C, 14 h;
(3) Cool rt, H_2O; (3) Extract in EtOAc; (4) Evaporate

Advantages

The process provides for the preparation of a material that can be used as a reference standard for the analysis of the drug.

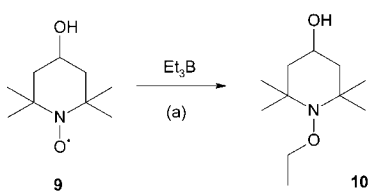
Patent No. U.S. 7,361,755

Assignee: Ciba Specialty Chemicals Corp., Tarrytown, New York

Title or Subject: Transition-Metal-Catalysed Process for the Conversion of Alkenes to Sterically Hindered Substituted N-Alkoxyamines

The compounds produced by the process described in this patent have a wide range of uses in the manufacture of printing inks, polymer stabilisers, and candles. Alternative methods for their preparation can involve the reaction of hindered amines with hydroperoxides in the presence of metal ions. However, using this type of process does not allow the presence of functional groups on amine, nor does it enable the preparation of primary alkoxyamines. The process in this patent involves the catalysed reaction of an alkyl borane with a stabilised nitroxyl radical such as hydroxyl-TEMPO. Reaction 4 shows the method of preparing **10** by the reaction of **9** with Et_3B in the presence of catalytic amounts of Ag and Cu salts under an O_2 atmosphere. If the O_2 is a static atmosphere, then the reaction can take up to 48 h; however, if the gas is bubbled through the mixture, the reaction is complete in one hour. A number of other products are also reported in which alternative boranes are used. Examples are given in which the ethyl group is replaced by cyclohexyl, *n*-butyl, and *n*-octyl, and there are indications that at least 180 compounds of this type have been produced in yields up to 98%. In fact the patent makes the point that the alkyl boranes used are those that can be prepared by hydroboration of BH_3 with an alkene. Examples are also described where other nitroxyl radicals are used, and the claims cover a vast range of these.

Reaction 4



(a) (1) Aq NaOH, $AgNO_3$,CuOAc, O_2, rt;
(2) Et_3B/THF; (3) Extract in EtOAc, evaporate;
(4) Purify by flash chromatography

Basic ^1H and NMR data are given for some of the compounds described.

Advantages

The process enables a very large range of the alkoxyamines to be prepared under mild conditions and in very high yields.

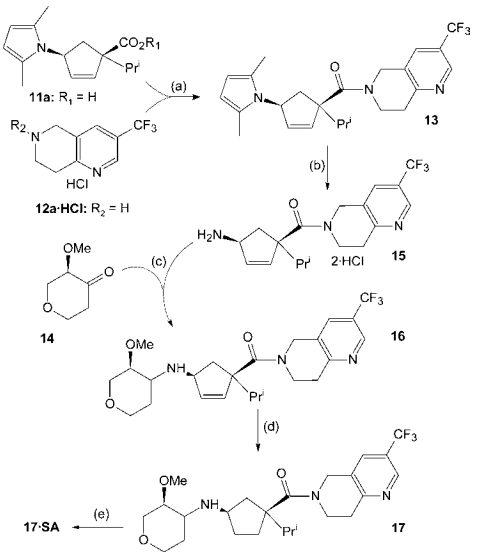
Patent No. U.S. 7,361,765

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

Title or Subject: Process for the Preparation of CCR-2 Antagonists

This patent discloses a synthetic route to make compounds such as **17** that are used to treat inflammatory diseases. Alternative methods for synthesising **17** are said to be time-consuming and not suitable for large-scale use. The patent describes the synthesis of an extensive series of compounds including starting materials and intermediates in the multistep synthesis of **17**, summarised in Reaction 5. The first step is an amidation between **11a** and the HCl salt of **12** using MsCl to give **13** in quantitative yield. The pyrrole ring is then removed using H_2NOH giving the di-HCl salt of **15** in 91% yield. In the next stage the salt of **15** is coupled with **14** in a reductive amination reaction using $NaBH(OAc)_3$ using an amine buffer to form **16** as an oil. Reduction of the C═C bond in the cyclopentene ring produces the free base **17** as an oil in 98.5% yield that is converted to the succinate salt **17·SA** by heating with succinic acid in EtOH.

Reaction 5

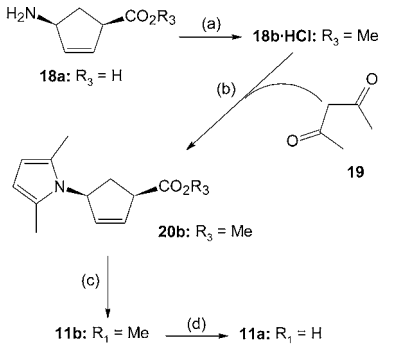


(a) (1) MsCl, $EtN(Pr^i)_2$, THF, 0 °C; (2) **12**, rt, 4 h; (b) $H_2NOH·HCl$, H_2NOH, MeOH, H_2O, reflux, 6 h; (c) (1) Bu^n_3N, Pr^iOAc, PriOH, $NaBH(OAc)_3$, 5 °C, 1 h; (2) **14**, Pr^iOAc, 1 °C, 6 h; (d) H_2, 40 psi, Pd/C, MeOH, 25 °C, 18 h
(e) (1) EtOH, succininc acid, 65 °C; (2) n-heptane, seed, cool to rt

The syntheses of the compounds **11a**, **12**, and **14** are also described in the patent. Reaction 6 shows the method used to prepare **11a** starting with the esterification of **18a** using MeOH/$SOCl_2$ to form the HCl salt of **18b** in 77% yield. Reaction of **18b·HCl** with **19** in the presence of $EtNPr^i_2$ forms **20b** that is isolated as an air-sensitive oil in 92% yield with 99% ee. The oil is stored under N_2 at 5−7 °C before being used in the next step where it is treated with LHMDS and then alkylated with IPr^i to give **11b** that is also an air-sensitive oil. In the final stage **11b** undergoes acid hydrolysis to form **11a** in 95% yield. The

patent suggests that the cyclopentene ring present in **20b** and **11b** may be hydrogenated so that an alternative range of compounds can be produced, but examples are not provided.

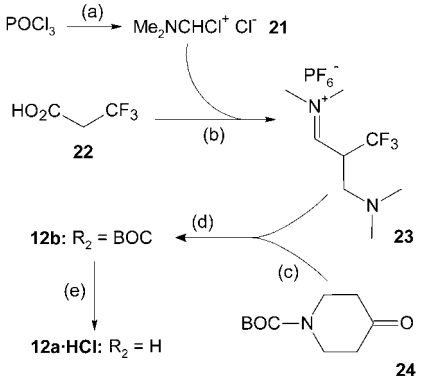
Reaction 6



(a) $SOCl_2$, MeOH, 0 - 20 °C, 2 h; (b) $EtN(Pr^i)_2$, MeOH, 25 °C, 16 h;
(c) (1) LHMDS, THF, -20 °C, 70 min; (2) IPr^i, 20 °C, 6 h;
(d) (1) 10N NaOH, MeOH, 65 °C, 16 h; (2) 10 °C, aq HCl, pH 4.5, 19 h; (3) Filter, aq MeOH, dry

The synthesis of compound **12** is shown in Reaction 7 in which the iminium salt **21** is first formed from $POCl_3$ and DMF. This is reacted with **22** followed by aqueous HPF_6 and NaOH to give the PF_6 salt **23** in 87% yield. The salt **23** is then treated with the protected piperidone **24** and LHDMS to produce the protected naphthyridine **12b** in a 64% yield after workup. Removal of the BOC group gives a 75% yield of the free base **12a**.

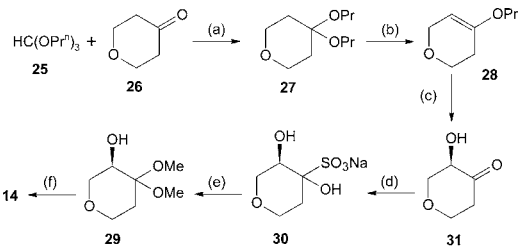
Reaction 7



(a) DMF, 4 °C, 1 h; (b) (1) 50 °C, 4 h; (2) rt;
(3) Aq HPF_6, NaOH, 5 °C, 2 h; (4) Filter;
(c) (1) LHDMS, THF, -12 °C, 45 min; (2) rt;
(d) (1) THF, -24 °C, 2 h; (2) HOAc, rt, 75 min;
(3) NH_4OAc, 64 °C, 2 h; (4) extract in methylcyclohexane

Finally the patent gives details of the synthesis of **14**, and this is summarised in Reaction 8. Initially the ketal **27** is formed by reaction of **25** with **26**, but it is not isolated; on heating, PrOH is eliminated, producing **28** that is recovered as a solution in PhCl in 73% yield. The enol ether **28** is then oxidised under modified Sharpless dihydroxylation conditions to form **31**. *N*-Methylmorpholine (NMO) is used as the stoichiometric oxidant. **31** is not isolated but treated with fresh $Na_2S_2O_5$ to form **30** that is isolated in a yield of 57% and 97.2% ee. In the next step **30** is treated with $HC(OMe)_3$ in the presence of HCl/MeOH, giving the dimethylketal **29** that is recovered in 88% yield and 97.5% ee as a solution in PhMe after a solvent switch. The final stage is the methylation of **29** using Me_2SO_4 and $NaOBu^t$ to give **14** that is isolated in 93% yield and 97.2% ee.

Reaction 8



(a) PhCl, A-15, rt, 16 h; (b) Heat to 125 °C, 16 h;
(c) $(DHQD)_2PHAL$, K_2OsO_4, NMO, Me_2CO, H_2O, 0 °C, 7 h;
(d) (1) Aq $Na_2S_2O_5$; (2) HOAc, rt, 16 h; (3) Evaporate Me_2CO;
(4) Wash in Pr^iOH, filter, dry;
(e) (1) $(MeO)_3CH$, MeOH, 50 °C; (2) HCl/MeOH; (3) 50% NaOH, 7 °C;
(4) Distil off MeOH, PhMe; (5) Concentrate solution;
(f) (1) $NaOBu^t$, THF; (2) Me_2SO_4, <36 °C, 4 h; (3) H_2O, 2N HCl, rt, 20 h;
(4) Extract in Pr^iOAc; (5) Concentrate solution

Many of the examples in the patent involve the use of multikilo quantities of reagents; hence, it is clear that this process is at an advanced stage of development. There is a considerable amount of experimental detail in this patent, and because of space constraints the reaction schemes shown here give only brief details.

Advantages

The process provides a high-yield synthesis of the drug molecule and also allows the production of a suitable salt form.

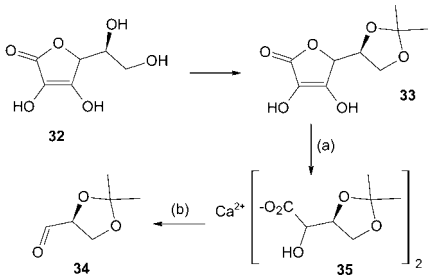
Patent No. U.S. 7,361,775

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

Title or Subject: Process for the Preparation of (S)-Glyceraldehyde Acetonide

The compound **34** is an intermediate in the synthesis of antiviral drugs, insecticides, and agrochemicals. The patent specifically mentions the use of **34** in the synthesis of a range of HIV protease inhibitors. Methods for the preparation of **34** are claimed to be difficult to control on a large scale because they involve the simultaneous addition of alkaline hypochlorite solutions and acids. Rapid evolution of Cl_2 gas is the major problem, and hence the objective of the patent is to provide a safe method of preparing **34** by working at a pH >7.5 and not using simultaneous addition of acids. The overall route to produce **34** is shown in Reaction 9, and schemes in the patent indicate that the synthesis can start from **32** although the patent examples begin with reaction of **33** with H_2O_2 in the presence of a base such as $CaCO_3$. This is followed by addition of catalase to remove the excess H_2O_2, and the product is recovered as a solution of the Ca salt **35** in 89.4% yield. An alternative to this procedure is to use Pd/C and activated carbon in place of the catalase to destroy the remaining H_2O_2, but this gives a lower yield of 77%. The solution of **35** is then treated with NaOCl, and the product **34** is obtained in a yield of 67.2% as a 4.7 wt % aqueous solution. The acetonide can be recovered by extraction using THF, but few details are given for this step. The patent gives an example in which the whole process is carried out consecutively in a large-scale batch starting with 48 kg of **33**, thus indicating the advanced nature of the process. There are also examples of using simultaneous addition of HCl and NaOCl that gives lower yields.

Reaction 9



(a) (1) $CaCO_3$, H_2O, 0 °C, 1 h; (2) Anti-foam agent, H_2O_2, <10 °C, 20 h; (3) Catalase, rt, 2 h; (4) 50 °C, filter aid, filter; (5) Concentrate filtrate
(b) (1) Aq NaOCl, 50 °C, 1 h; (2) Cool to 20 °C

Advantages

The new process gives higher yield, and careful control of pH is not required when compared with methods using simultaneous addition of acid and NaOCl.

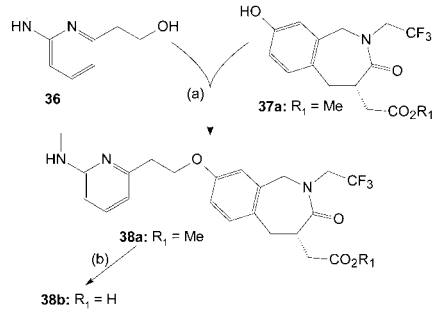
Patent No. U.S. 7,368,566

Assignee: SmithKline Beecham Corporation, Philadelphia, Pennsylvania, U.S.A

Title or Subject: Process and Intermediates for Preparing Benzazepines

The compounds of interest in this patent, such as **38b** and **41**, are fibrinogen or vitronectin antagonists, and such compounds are useful in the treatment of several disorders including inflammation, cardiovascular problems, and osteoporosis. Known methods for preparing the desired compounds are described as using expensive reagents and require many stages. This patent contains a substantial amount of detail in many of the examples, and the reaction schemes shown here are very basic. The interested reader is advised to consult the patent for detailed information. The basic process disclosed in this patent is exemplified by the production of **38a** by the condensation of **36** and **37a** using PPh_3 and diispropylazodicarboxylate (DIAD) as shown in Reaction 10. The ester **38a** is not isolated but hydrolysed using LiOH to give **38b** that is isolated in 56% yield and has purity of 98.3% by HPLC.

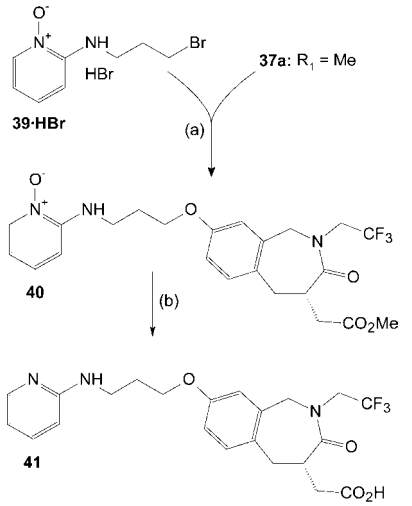
Reaction 10



(a) (1) MTBE, PPh_3, <5 °C; (2) DIAD, MTBE, 15 min; (3) rt, 3 h; (4) Evaporate, cool 2 °C, filter; (5) Extract filtrate with aq NaOH, NaCl;
(b) Aq LiOH, 55 °C, 1 h; (2) Cool , rt, H_2O/MeOH; (2) Concd HCl; (3) Cool 2 °C, filter, MeOH, wash, dry; (4) Recrystallise hot MeOH.

A second example of the process is provided in Reaction 11 in which **37a** is condensed with the HBr salt of **39** to give **40** in which the N−O group is subsequently reduced, and **41** is produced upon hydrolysis. Although the production of **40** and **41** is included in the claims, the patent does not provide a detailed experimental example for their preparation.

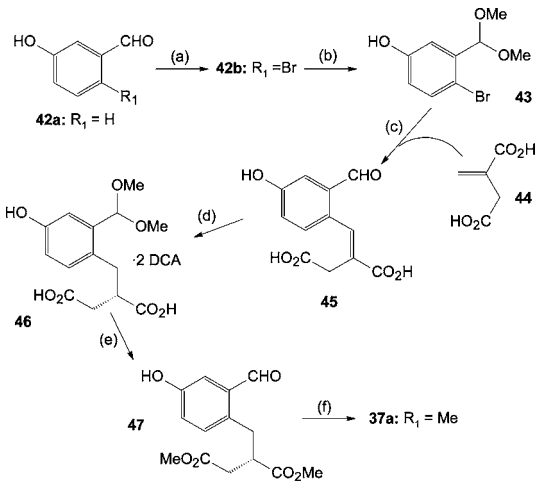
Reaction 11



(a) NaOH, MeCN; (b) (1) Zn dust, 3M HCl, MeOH; (2) Aq NaOH, MeCN, MeOH

The patent does give details for the preparation of the key intermediate **37a**, and this is briefly summarised in Reaction 12. This begins with bromination of **42a** to give **42b** in 63% isolated yield. The next step is formation of the acetal **43** that is not isolated but reacted with **44** under Heck conditions and then deprotected to form **45** in 79% isolated yield. The acetal of **45** is then produced in situ and undergoes stereoselective hydrogenation in the presence of dicyclohexylamine (DCA) to give the bis-DCA salt **46** in 84% yield. The salt **46** is then esterified, and at the same time the acetal protection is removed to give the diester **47**. This is recovered as a solution in MeCN and then treated with the HCl salt of $CF_3CH_2NH_2$, $ZnCl_2$ and $NaBH(OAc)_2$ followed by TFA to produce **37a** in 72% yield.

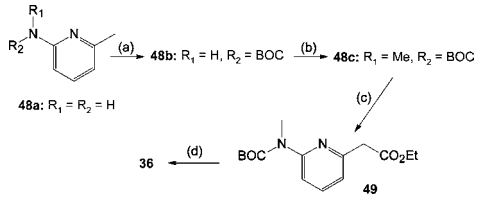
Reaction 12



(a) DCM, Br_2, 40°C, 16 h; (b) MeOH, 2h, rt; (c) (1) Et_3N, MeCN, $Pd(OAc)_2$, $P(o\text{-tolyl})_3$, Bu^n_4NBr, reflux, 10 h; (2) Aq KOH, rt; (d) (1) MeOH, reflux, 4 h; (2) rt, DCA, $[RuCl_2(R\text{-BINAP})]_2$-TEA, H_2, 60 psi, 60 °C, 36 h;
(e) MeOH, H_2SO_4, relux, 19 h; (f) (1) MeCN, $CF_3CH_2NH_2$·HCl, $ZnCl_2$, reflux 2 h; (2) $NaBH(OAc)_2$, DMF, rt, 15 min; (3) PhMe, TFA, reflux, 24 h.

Details are also given for the preparation of **36**, and the route is briefly outlined in Reaction 13. In the first stage almost 9 kilo of **48b** is recovered in 66% yield as a crude product thus indicating the advanced nature of this stage of the process. The examples given for subsequent stages are carried out on smaller scales that produce up to 125 g of product.

Reaction 13



(a) $(BOC)_2O$, PhMe, 106.5 °C, 14 h; (b) (1) NaH, THF, rt, 1 h; (2) MeI, rt, 4 h; (c) (1) $(EtO)_2CO$, THF; (2) LDA, -15 °C, 1 h; (d) $LiBH_4$, THF, reflux, 5h

Advantages

The patent claims to provide a new process that is more efficient and cost-effective than alternatives.

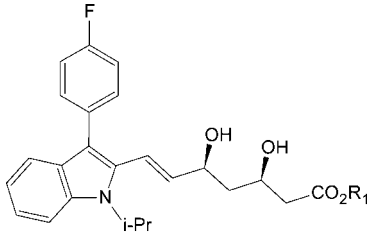
Patent No. U.S. 7,368,468 and 7,368,581

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

Title or Subject: Processes for Preparing Crystal Forms XIV, LXXIII, LXXIX, LXXX, and LXXXVII of Fluvastatin Sodium

These related patents cover several new and hydrolytically stable, polymorphic, crystalline forms of the statin compound **50a** (R_1 = Na). Statins are now widely used to reduce high blood cholesterol levels and can prevent coronary diseases. The patent states that a known crystalline polymorph of **50a**, designated as Form B, is not as hydrolytically stable as the amorphous form. Hence, the objective of the work was to produce a crystalline form that had improved hydrolytic stability. The fact that one of these polymorphs is given the number 87 shows that a considerable amount of work has been carried out. The existence of such enormous numbers of new polymorphs of known drug molecules is highly advantageous from a legal and commercial viewpoint. However, it does nothing to assist the poor chemist who has to try to recover and identify them and develop processes for their production. The first patent describes six new crystalline forms, and the second patent focuses on one of these. As is often the case, new forms result by varying the solvent and conditions under which the crystals are obtained. The preparation of the various polymorphic forms can start from an alkyl ester such as **50b** (R_1 = Me) or **50c** (R_1 = Bu^t). These esters are then hydrolysed with NaOH in aqueous alcohols. The various polymorphs are obtained by crystallisation. This method is used to obtain the six forms specified in the patent. Alternativel, Form B of the salt can be heated in various solvent mixtures, and Form XIV is recovered. This can then be used to prepare some of the other forms. For full details of the many examples the patent should be consulted. XRD and IR data are given for the polymorphs.

Fluvastatin



50a: R_1 = Na

Advantages

Several new polymorphs of a widely used drug are described that can give enhanced marketing opportunities.

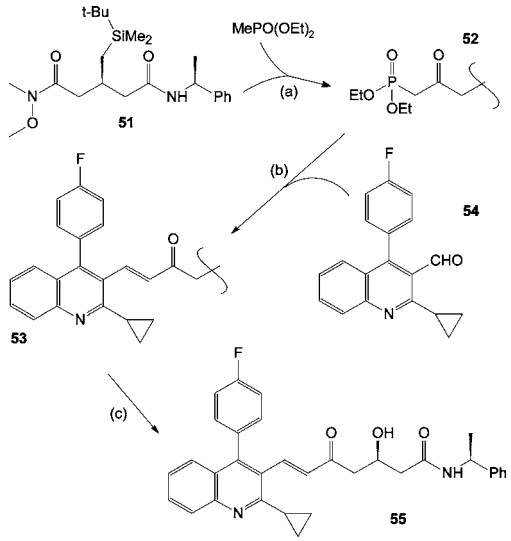
Patent No. U.S. 7,371,865

Assignee: Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, U.S.A

Title or Subject: Process for the Manufacture of HMG-COA Reductase Inhibitors

This is another patent covering statins that describes a process to manufacture enantiomerically pure or racemic forms of some of these compounds. The patent is mainly directed towards the manufacture of pitavastatin **57a** and its Ca salt **57b**, but examples are also given for the preparation of fluvastatin **47a**. This patent is another that contains a considerable amount of experimental work, and so the reaction schemes show only very briefly the steps involved. Reaction 14 summarises the production of the amide **55** that is an intermediate in the process. This begins with the preparation of the phosphonic acid ester **52** by treatment of **51** with $MePO(OEt)_2$ and Bu^nLi. The product is isolated as a viscous oil and then reacts with **54** in the presence of $CsCO_3$ to produce **53** that can be isolated or used directly in the next step where the silyl protecting group is removed. This is done using H_3PO_4, and **55** is obtained.

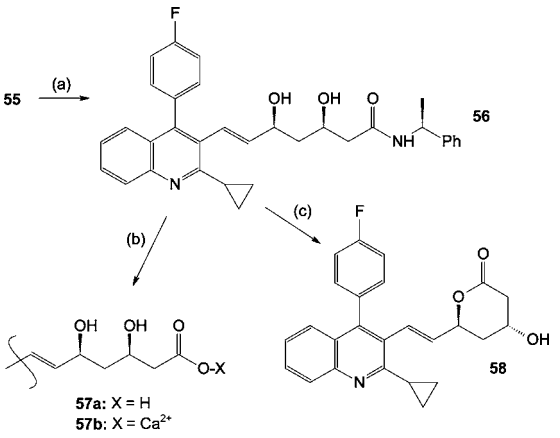
Reaction 14



(a) Bu^nLi, THF, -78 °C, 2h; (b) Cs_2CO_3, Pr^iOH, rt, 16 h; (c) H_3PO_4, MeCN, 45 °C, 29 h

In the next stage of the process, summarised in Reaction 15, the ketone **55** is reduced to give **56** using $NaBH_4$ in the presence of Et_2BOMe, and this is followed by oxidation of the intermediate boronic ester using H_2O_2. The product **56** is purified by column chromatography before crystallisation and can be converted to the Ca salt **57b** by treatment with NaOH followed by $CaCl_2$. Alternatively, the hydrolysis using H_3PO_4 produces the lactone **58**.

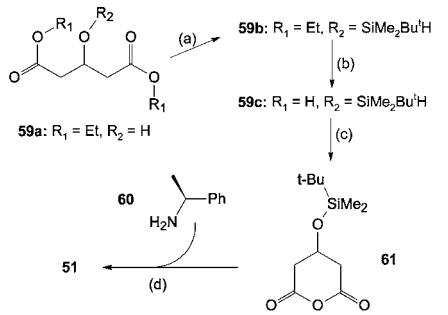
Reaction 15



(a) (1) $NaBH_4$, Et_2BOMe, THF, -78 °C, 1.5 h (2) H_2O_2, PriOAc, 50 °C, 2 h; (b) (1) Aq NaOH, EtOH, 80 °C, 18 h; (2) $CaCl_2$, H_2O, 35 °C, 4.5 h, filter (c) H_3PO_4, MeCN, 70 °C, 18 h

The patent also describes the preparation of **51**, the starting material for the whole process, and this is shown in Reaction 16. The first stage of this is the preparation of **61** although it is pointed out that this is a commercially available material. Preparation of **61** begins with protection of the OH group and then hydrolysis of the ester groups to form **59c**. Neither **59b** nor **59c** are isolated, and the preparation of **61** is a one-pot process. The formation of **51** is by reaction of **61** with the amine **60** in what is described as an improved method reported in the literature. The improvement is the use of the hindered chiral amine **60** in place of Et_3N, and this results in better yields and a higher ratio (>98%) of the desired diastereomer.

Reaction 16



(a) $ClSiMe_2Bu^t$, imidazole, xylene, 80 °C, 6 h; (b) (1) Aq KOH, EtOH, 25 °C, 20 h; (2) Aq H_2SO_4, EtOAc,15 °C; (c) (1) Tetrahydronaphthalene, H_2O; (2) Ac_2O, 65 °C, 40 min; (3) Heptane, cool, crystallise; (d) (1) MTBE, heptane, -78 °C, 3.5 h; (2) Aq H_3PO_4, 25 °C; (3) Reflux, 30 min, cool, filter

Advantages

The patent does claim that the process gives enantiomerically pure product and has fewer steps than alternatives. However, there are no yields reported in the examples, and so the efficiency of this process cannot be assessed.

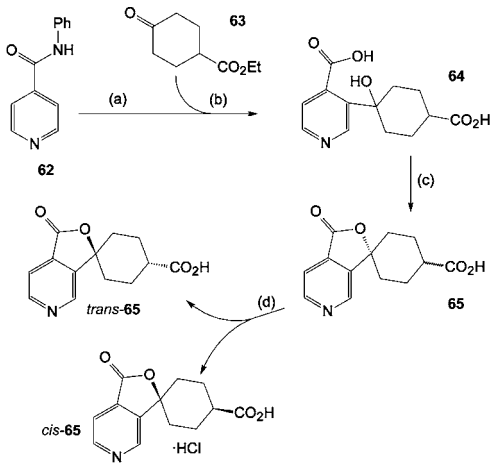
Patent No. U.S. 7,368,569

Assignee: Merck & Co. Inc., Rahway, New Jersey, U.S.A. and Banyu Pharmaceutical Co. Ltd., Tokyo, Japan

Title or Subject: Process for Making Spirolactone Compounds

The particular compounds covered by this patent are intermediates in the production of NPY5 antagonists that can be used to treat bulimia, obesity, or diabetes. Alternative processes for preparing the desired spirolactones are said to require many steps and can give overall yields of only 15−20%. This patent has a considerable amount of information about a process that has fewer steps and is summarised in Reaction 17. The first step is formation of the anion of the amide **62** by treatment with Bu^nLi, and this is followed by addition of **63** to produce **64** that is recovered as an aqueous solution. Acidification of the solution and extraction gives a suspension of the *cis/trans* mixture of **65** in THF. These isomers are separated by formation of the HCl salt of the *cis* isomer that is filtered off. In the various stages an aging step is mentioned, and the times mentioned cover a wide range. The time shown in the reaction scheme is the longest said to be required.

Reaction 17



(a) LiBr/THF, Bu^nLi, -55 °C, 7 h; (b) (1) THF, -55 °C, 1 h; (2) H_2O, 40 °C, 4 h; (3) Cool rt, wash in THF; (c) (1) H_2O, H_2SO_4, 30 °C, 4 h; (2) Extract in THF, evaporate; (d) (1) 3M HCl/EtOAc, rt; (2) Age at 60 °C, 48 h; (3) Filter, extract in THF, evaporate; (4) DMF/H_2O, vac distil; (6) H_2O, rt, 5 h; (7) Filter, wash, dry

The patent also mentions the production of amides from the *cis*- or *trans*-acids of **65**, but no experimental details are given. However, there are details given for the preparation of the ethyl ester of **64** that can be carried out adding EtOH/HOAc to the reaction mixture of **62** and **63**. This ester can then be converted to the *cis-/trans*-ethyl esters of **65** that can be separated by conversion to the camphor sulfonic acid salt of the ester that upon hydrolysis gives the acid **65**.

Advantages

The patent provides a process that requires fewer steps than alternatives and gives an overall higher yield of the spirolactones.

Patent No. U.S. 7,371,753

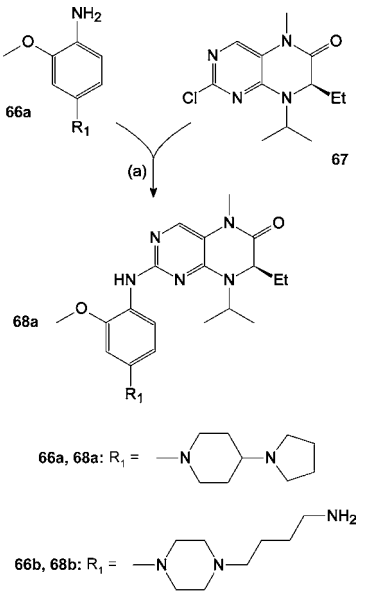
Assignee: Boehringer Ingelheim International GmbH, Ingelheim, Germany

Title or Subject: Processes for Preparing Dihydropteridinones and Their Use as Pharmaceutical Compositions

This patent discloses a large range of novel compounds such as **68a** or **68b**. Pteridinone derivatives are known to have antiproliferative activity by acting as inhibitors of polo-like kinases and hence are useful in treating tumours. The patent states that it is surprising that compounds like **68a** or **68b** act as cell cycle kinases and specifically polo-like kinases so that they may also have potential use in treating tumours. The basic method of preparing compounds **68a** or **68b** is the condensation

of **67** with an aniline derivative **66** as shown in Reaction 18. Two examples of the group R_1 in **66** and **68a** or **68b** are shown, and there are over 35 examples of related compounds are described. The patent gives ^{1}H NMR data plus *m*/*z* and UV max data for all examples of **68**. The only yield reported is 32% for **68a**.

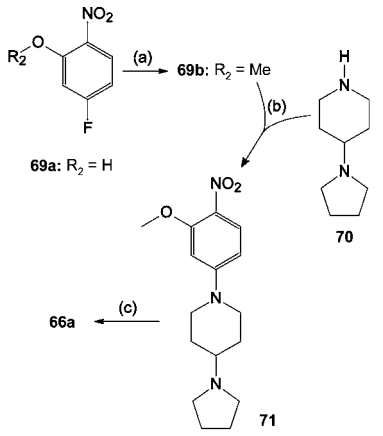
Reaction 18



(a) (1) EtOH/H_2O, aq HCl, 100 °C, 3 h;
(2) Evaporate, column chromatography

The patent does give details for the preparation of the anilines, and the route used to prepare **66a** is shown in Reaction 19. In the first stage the nitrophenol **69a** is methylated, giving **69b** in 98% yield. Base-catalysed condensation of **69b** with **70** in *N*-methylpyrrolidone (NMP) forms **71**, and this is recovered in 90% yield. Reduction of **71** using Raney Ni catalyst gives a 93% yield of **66a** but the reaction is very slow taking nine days, and it would seem likely that other catalysts could improve on this. The patent lists the anilines used to prepare the whole range of pteridinones and states that they are all prepared by the same method.

Reaction 19



(a) (1) K_2CO_3, Me_2CO, 20 °C, 30 min; (2) MeI, Me_2CO, 20 °C, 18 h; (3) 65 °C, 12 h; (b) (1) NMP, $EtNPr^i_2$, 80 °C, 17 h; (2) Column chromatography; (c) Raney Ni, THF, 4 bar H_2, 20 °C, 9 days

The patent also describes some experiments assessing the cytotoxicity of the compounds on human tumour cells.

Advantages

The patent describes a new range of compounds that are of potential use in treating tumours.

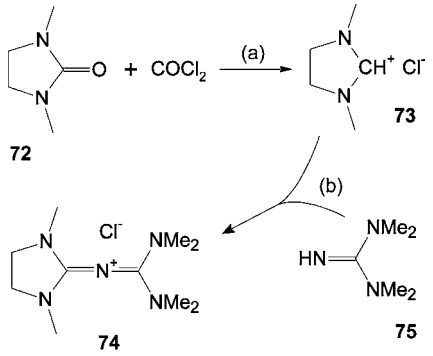
Patent No. U.S. 7,371,861

Assignee: Lanxess Deutschland GmbH, Leverkusen, Germany

Title or Subject: Process for Preparing Ring Fluorinated Aromatics

Aromatic fluorinated compounds are important intermediates for preparing agrochemicals and pharmaceuticals. Such compounds are prepared by halogen exchange reactions that are said to present difficulties when attempting to introduce two or more F atoms. Problems occur because high temperatures and long reaction times are needed, and these reduce product yield. This patent describes a process to prepare di- and trifluoro benzenes, pyridines, and pyrimidines. The process involves the use of a compound **74** as the catalyst for the reaction, and Reaction 20 shows how this is prepared. The first stage is reaction of **72** with $COCl_2$ to give the iminium salt **73** in 85% yield. Reaction of **73** with **75** gives **74** that is isolated in 94% yield.

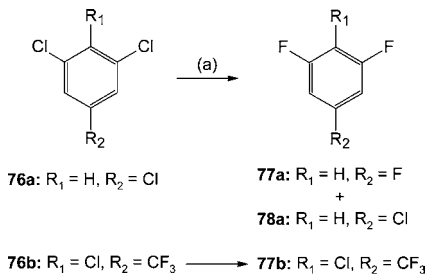
Reaction 20



(a) PhMe, ,40 °C, 5 h, filter; (b) (1) DCM, 2 h;
(2) Evaporate DCM; (3) NaOMe, MeOH, rt, 1 h;
(4) Evaporate MeOH; (5) DCM, filter, dry

The salt **74** is then used to catalyse various fluorination reactions, and Reaction 21 shows examples of using the chlorobenzenes that are described in the patent. The fluorination reaction takes place in sulfolane under pressure at about 200 °C and can take up to 48 h. Yields vary from 60 to 75%. The conversion of **76a** gives a mixture of **77a** (87%) and **78a** (6.7%) that are separated by distillation.

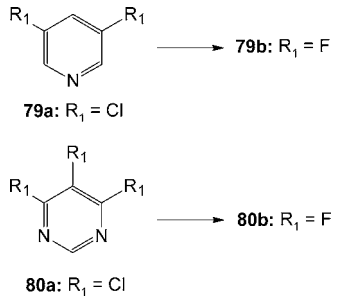
Reaction 21



(a) **74**, KF, sulpholane, 200 °C, up to 48 h

The fluorination of the pyridine **79** and the pyrimidine **80** is carried out in identical manner and shown in Reaction 22.

Reaction 22



The patent claims a number of other iminium salts that are suitable catalysts but there are no examples given for any of them.

Advantages

The conditions employed in this process appear to suffer from the same drawbacks as alternative processes in using high temperatures and long reaction times. However, the patent does claim to be able to produce multiply fluorinated products in high yields.

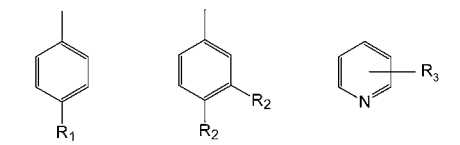
Patent No. U.S. 7,371,866

Assignee: DSM Fine Chemicals Austria Nfg GmbH & Co KG, Linz, Austria

Title or Subject: Preparation of Aromatic and Heteroaromatic Carboxylic Acids by Catalytic Ozonolysis

Oxidation reactions can be very unselective unless very specific reagents are used, and this increases the process costs. The patent describes a method of preparing acids by oxidation of an alkyl group in alkyl aromatics and alkyl pyridines. Oxidation of alkyl aromatics using O_2 in HOAc using Mn or Co salts is well-known but the yields are said to be unsatisfactory. The oxidation described in this patent is carried out in a solution of HOAc using O_3 and is catalysed by transition metal salts although only $Mn(OAc)_2$ is used in the examples. Also present in the reaction mixture is H_2SO_4. Reaction 23 shows examples of the starting compounds that are oxidised. The yields are reported to be as high as 98% by GC or HPLC although the examples do not describe the isolation of the products.

Reaction 23



Reaction conditions: HOAc, O_3, $Mn(OAc)_2$, 16 °C, 60 - 75 min

Advantages

The yields reported for this process are high and claimed to give low quantities of byproduct although the difficulties of using O_3 need to be overcome.

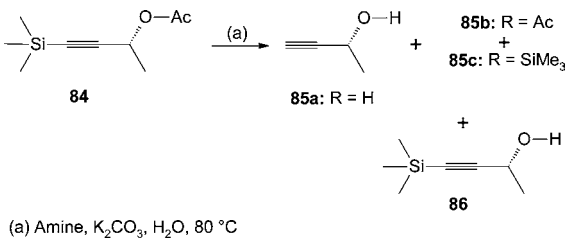
Patent No. U.S. 7,371,901

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

Title or Subject: Process for the Preparation of Alkynols

The aim of this patent is the development of an efficient method for the deprotection of a silylated alkynol. The patent states that methods for removing an alkylsilane protecting group that use MeOH and a base require a large excess of MeOH. The separation of the product from the reaction mixture is difficult because of the small difference in boiling point between the product and the reaction mixture. The silylated alkynol specifically mentioned in the patent is **84**, and this may be prepared by enzymatic resolution although there are no experimental details given. The final desired product is **85a**, and Reaction 24 shows the products formed in the reaction. The deprotection is carried out using an amine in the presence of a base and water, and only a slight excess of amine is required. The amines used in the examples are Bu^nNH_2, $(EtO)_2NH_2$, and $H_2NCH_2CH_2NH_2$ with K_2CO_3 as base. The byproducts are removed by distillation, and in one experiment a 92% yield of pure **85a** is obtained when using $(EtO)_2NH_2$.

Reaction 24



(a) Amine, K_2CO_3, H_2O, 80 °C

Advantages

The process allows easier separation of the desired product by distillation and does not require large excess of reagents.

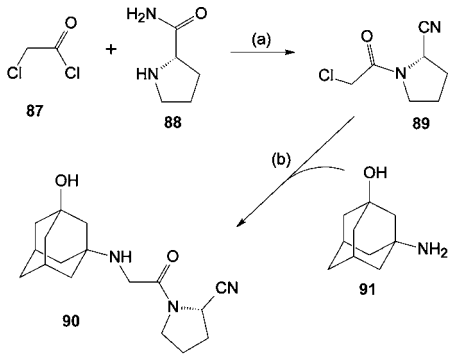
Patent No. U.S. 7,375,238

Assignee: Novartis AG, Basel, Switzerland

Title or Subject: Process for the Preparation of N-Substituted 2-Cyanopyrrolidines

This patent is specifically aimed at the preparation of compound **90** that is known as LAF-237. This is under phase 2 trials for the treatment of type-2 diabetes, and it acts as an inhibitor of the enzyme dipeptidyl peptidase (DPP)-IV. Drawbacks in methods for synthesising **90** are said to be the need to isolate the highly irritant material **89** that is a key intermediate. There is also the need for several aqueous work up steps that give waste disposal problems and lower yields. Reaction 25 summarises the new route that does not require the isolation of **89**. The preparation of **89** is carried out by the reaction of **87** and **88** in the presence of DMF followed by dehydration using the Vilsmeier reagent, and this produces a solution of **89**. This solution is used directly in the next step in which **86** reacts with **91** in the presence of K_2CO_3 and KI. The recovery of **90** involves filtration of the reaction mixture in the presence of DBU. The final yield is difficult to estimate because the various experiments are carried out on different scales. However, some of the steps are on a kilo scale thus indicating the advanced stage of development.

Reaction 25



(a) (1) DMF, Pr^iOAc, 15 °C, 1 h; (2) 35 °C, 1.5 h; (3) Me_2NCH_2Cl, 5 °C, 1 h; (4) H_2O; (b) (1) K_2CO_3, KI, MEK, 35 °C, 2.5 h; (2) 70 °C, 0.5 h; (3) Filter, evaporate; (4) DBU, Pr^iOH, 60 °C, 30 min; (5) 20 °C, MTBE, 2 h; (6) Cool to -10 °C, filter, wash, dry

Advantages

The process does not require isolation of intermediates, thus improving the safety aspects and the overall yield of product.

Patent No. U.S. 7,378,549

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

Title or Subject: Process for the Reactive Extractive Extraction of Levulinic Acid

Esters of levulinic acid are used as plasticizers and the acid can be obtained by acid hydrolysis of a variety of biomass sources including sugars. The esters are obtained by esterification, but one problem is that the unreacted acid is present as an aqueous solution, and its recovery can be very energy intensive because of the large volumes of water that need to be removed. This patent discloses a process for the recovery of the acid from esterification reactions that involves simultaneous extraction and reaction. This is possible by using the esterifying alcohol as both reactant and extractant for the ester. The alcohol must be water-immiscible and hence has at least four C atoms and in fact n-pentanol is specifically covered in the claims. The esterification is catalysed by mineral acids with H_2SO_4 being preferred and the whole process of hydrolysis of the biomass and esterification is carried out virtually simultaneously. The claims specifically mention that formic acid and furfural are present in the mixture. This appears to be because these compounds are formed in the acid hydrolysis of the biomass. One example describes a process that feeds hardwood sawdust at a rate of 83.3 tons/h that undergoes acid hydrolysis at about 220 °C followed by esterification with *n*-pentanol. The conversion of the acid is in excess of 70%, and 88% of the pentyl levulinate recovered is in the organic phase.

Advantages

This process obviously has a very specific application and is clearly commercially viable, but the principle may be applied elsewhere.

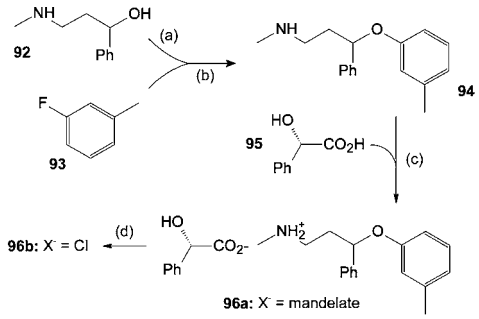
Patent No. U.S. 7,378,553

Assignee: Teva Pharmaceutical Fine Chemicals S.r.l., Bulciago, Italy

Title or Subject: Processes for the Preparation and Isolation of Atomoxetine Impurities and Their Use as Reference Standards

The first claim in this patent covers the compound **96b** that is an impurity produced during the preparation of atomoxetine **97**. This is also known as tomoxetine and is available as the HCl salt under the name Strattera for treating attention-deficit hyperactivity disorder. Interestingly, this is another patent in this review that focuses on identifying impurities and using them as reference standards. This patent describes the preparation of **96b** by the method summarised in Reaction 26. In the first stage **92** is dissolved in hot basic DMSO, and then **93** is added to give **94**. This is not isolated pure but is extracted into PhMe and then reacted with mandelic acid **95** to produce the mandelate salt **96a**. The filtration of this salt and its washing with PhMe are both described as being very difficult and very slow. The HCl **96b** salt is produced from **95a** by treatment with HCl and is recovered in a yield of 28% based on **92**.

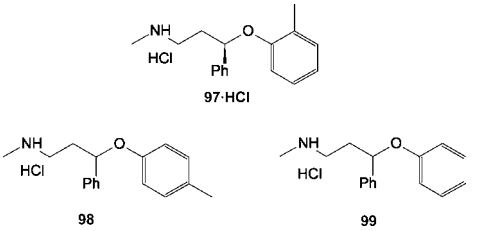
Reaction 26



(a) KOH, DMSO, 100 °C, 3 h; (b) (1) **93**, 83 °C, 6 h; (2) Extract in PhMe; (c) (1) PhMe, MeOH, 70 °C; (2) Cool <10 °C, filter, dry; (d) (1) Aq NaOH, Bu^nOAc, rt,; (2) 36% HCl, <25 °C, 1 h; (3) filter, dry

The patent also describes two other impurities **98** and **99** that are similar to **96b** and are prepared in an identical manner. ^1H NMR data for the three impurities are provided in the patent.

Atomoxetine and Impurities



Advantages

The patent covers compounds that are impurities in a well-known drug that can be used as references in the analysis of the drug.

Keith Turner

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Telephone/fax: +44 (0)1642 653484.
E-mail: keith@kappa-tau.co.uk

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