Organic Process Research & Development **2008,** *12,* 369–380

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published During December 2007 and January 2008

Summary

The current selection of patents comprises 22 from an initial collection of 217 that fitted the search criteria. A wide range of subjects is covered that includes compounds for the restoration of hair to aroma chemicals and fungicides. It is hoped that readers find something of interest. The improvements claimed in some patents often are prone to more than a little exaggeration. There are a number of examples of such claims in the current selection especially in the increasing use of chlorinated solvents that is contrary to the move towards green chemical processes. One patent includes a new process for preparing arylalkynes that uses the extremely carcinogenic gas vinyl chloride. The new process supposedly avoids drastic conditions necessary in alternatives. Of course if such reagents are already handled, then presumably, the necessary safety features are in place and new entrants to the field will be scared off using such processes. Phosgene is an extremely useful reagent but very difficult to handle and cannot be transported in many countries. A new process for preparing the antibiotic linezolid is described that avoids the use of phosgene and is claimed to give good yields. Interest in producing drugs to treat coronary diseases remains high, and a new process to prepare a range of pyrazolo-pyridones from phenyl hydrazines is described. Drugs to treat respiratory diseases are also of interest, and a new method for preparing tropenol is described that is used to make Spiriva, an anticholinergic bronchodilator. One patent describes the preparation of alkylsulphonyl halides that are intermediates in preparing cPLA2 inhibitors that are useful in treating asthma. Antiviral drugs are under continuing research, and a stereoselective method for preparing azabicyclohexanes is described. These compounds are intermediates in the synthesis of hepatitis C virus antagonists. Dronabinol is present in marijuana and an approved antiemetic. A new synthetic route for its preparation is described that is claimed to give high yields, but it has several stages with low yields in many of them. A simple new route to imiquimod is described, the active ingredient of the cream Aldara that is used to treat skin problem. A new method of making a range of naphthylindoles is described. These compounds are used to treat fibrinolytic disorders, and although the process gives good yields, it does involve two solvent-exchange steps. Although many reactions require the use of metallic catalysts, there can be problems of metallic residues in the product or of waste disposal. One patent reports a novel method that avoids using heavy metals for making a precursor to the aroma chemical furaneol. The process involves an aldol condensation that is catalysed by Zn or Mg compounds. Another patent reports a metal-free oxidation process for forming a spirolactone group in a steroid molecule. The process uses hypochlorites and TEMPO as catalyst. Processes for the preparation of herbicides and fungicides feature in this selection of patents. One patent describes a novel compound that is claimed to be an intermediate for an herbicide and has explosive properties that make it potentially useful in vehicle airbags. The compound is 5-azidolaevulininic acid. A large range of pyridazines is produced by a process that takes place at ambient temperature, and this seems to prevent side reactions taking place. The products are used to prepare sulfonylurea herbicides. Another patent that describes a process being carried out at lower temperatures than previously used is for the preparation of dihalogenopurines. The new route takes place at 80 °C lower than an earlier method and avoids corrosive reagents, thereby improving efficiency and avoiding expensive equipment. Aminomethylpyridines are intermediates for fungicides and are prepared by the hydrogenation of cyanopyridines. A new catalytic process is described that can be applied to cyanopyridines containing halogen groups without causing dehalogenation reactions. Aldol condensations involving lower aldehydes and ketones are notoriously unselective. A patent describes the production of tetrahydropyran-4-ol by condensation of HCHO in the form of trioxane. The reaction is carried out using HCO_2H as catalyst rather than H_2SO_4 and gives high selectivity and allows easier product purification. The preparation of several novel intermediates is reported and a new process for a piperazinyl compound that has antipsychotic activity with few side effects. A range of cyclohexane amides (that have potential as antiobesity drugs) is prepared from intermediates that have a *trans* configuration, and these can be obtained by isomerisation of *cis*-isomers. A patent on this subject describes a large amount of work but has some serious errors that detract from the content. The use of renewable raw materials for making chemicals has come under the spotlight recently and may not be so environmentally acceptable as it once

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was. A process to prepare furfuraldehyde derivatives that are made from high fructose corn syrup is reported using ion-exchange resin catalysts. A novel stereoselective oxidation of a sulfide is described for the synthesis of modafinil. The compound is used to treat narcolepsy, and the oxidation step uses a chiral Ti alkoxide and cumene hydroperoxide. Recycling undesired enantiomers by racemisation is always desirable, and a method is described for recycling the less active enantiomer of tomoxetine that is used to treat hyperactivity. Several patents describe experiments on kilo scale and greater, and this may suggest that the process is at an advanced stage of development. However, the selection of patents does not imply that there is any legal or commercial significance in the patents reviewed, and the advantages are those claimed in the patent unless this reviewer has personal knowledge of the subject.

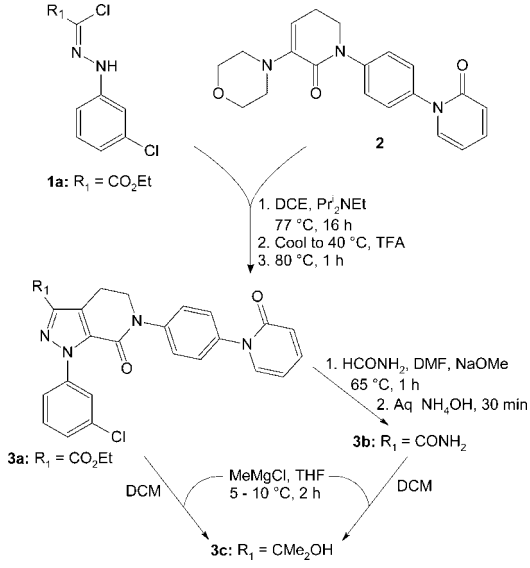
Patent No. U.S. 7,304,157

Assignee: Bristol-Myers Squibb Company, Princeton, New Jersey, U.S.A

Title or Subject: Efficient Synthesis of 4,5-Dihydropyrazolo[3,4-*c*]pyrid-2-ones

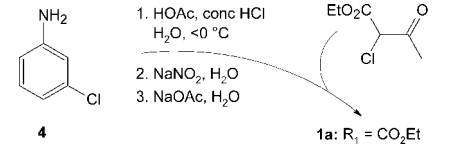
The title compounds are under clinical trials as factor Xa inhibitors for the prevention of the coagulation of blood that can lead to thrombosis. There is wide interest in such compounds, and patents on these have been reviewed previously (*Org. Process Res. Dev.* **2006**, *10*, 703). This patent describes a novel process for preparing a number of compounds such as **3a**, **3b**, and **3c** and Reaction 1 shows their synthesis. This is carried out by an initial 1,3-dipolar addition reaction of **1a** and **2** in 1,2-dichlorethane (DCE) in the presence of a base such as Pr^i_2NEt to give **3a**. The conversion of **3a** to **3d** is carried out by two possible routes. In the first method the reaction of **3a** with $HCONH_2$ using another base, NaOMe, forms **3b** that is recovered in 96% yield. **3b** is then treated with MeMgCl in dichloromethane (DCM) followed by hydrolysis to produce **3c**. The second method of converting **3a** to **3c** is by direct reaction with MeMgCl and then hydrolysis.

Reaction 1



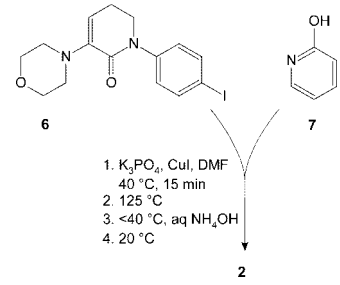
The patent also describes the production of **1** by the straightforward route shown in Reaction 2.

Reaction 2



Compound **2** can be prepared by an Ullmann coupling reaction, between **6** and **7**, shown in Reaction 3. The reaction mixture is heated at 125 °C until it is over 90% completed although the patent fails to state how this is measured or how long it takes.

Reaction 3



The patent provides several examples giving a range of compounds similar to **3a**, **3b** and **3c**, and basic ^1H and ^{13}C NMR data are given for **3c**. Some examples describe kilo scale reactions indicating the advanced status of the development.

Advantages

The process provides a potentially commercial route to these compounds, but it does use two undesirable, chlorinated solvents.

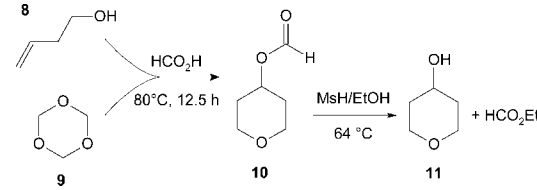
Patent No. U.S. 7,304,169

Assignee: Ube Industries Ltd., Ube-shi, Yamaguchi, Japan

Title or Subject: Process for Producing Tetrahydropyran-4-ol from Its Formate Intermediate

The compound **11** is a useful synthetic intermediate and can be made by a condensation reaction involving HCHO and **8** catalysed by H_2SO_4. However, this produces several byproduct and requires a complicated post-treatment procedure. The objective of this patent is to produce **11** without the need for such complicated purification methods, and by using HCO_2H in the condensation the patent claims to have succeeded. Reaction 4 shows that the route to **11** proceeds via production of the formate **10** from trioxane **9** and **8** in 98% HCO_2H. A transesterification reaction of the formate **10** with EtOH in the presence of MsH produces **11** and HCO_2Et. Removal of the volatile formate drives the reaction and **11** is obtained in 81.6% yield with a purity of 99.2% by GC. Examples are also described in which MeOH is used in place of EtOH. **10** is a novel compound, and examples are given in which it is isolated; basic ^1H NMR data are given.

Reaction 4



Advantages

The process gives high yields of the alcohol and also provides a novel intermediate formate compound.

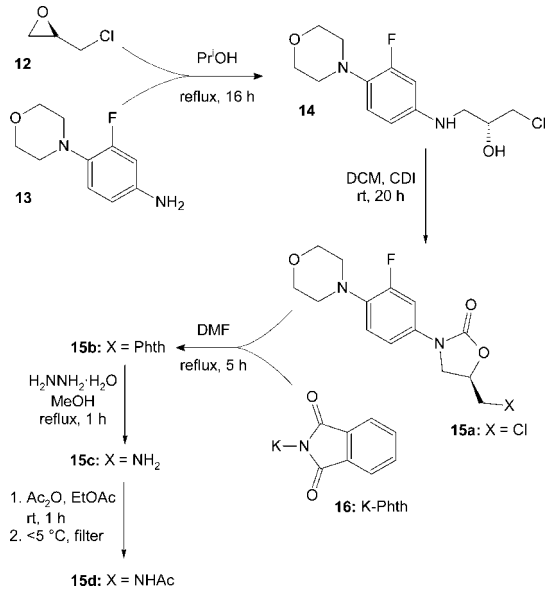
Patent No. U.S. 7,307,163

Assignee: Symed Laboratories Limited, Erragadda, Hyderabad, Andhrapradesh, India

Title or Subject: Process for the Preparation of Linezolid and Related Compounds

Linezolid **15d** is an oxazolidinone antibiotic that is effective against multiresistant bacteria and is available as Zyvox or Zyvoxid. An alternative process for preparing **15d** uses phosgene, and this can be hazardous to handle. Other processes require the use of Bu^nLi at low temperatures, and it is claimed this is also difficult to handle, whereas the novel process is claimed not to suffer from such drawbacks. The new process for preparing **15d** is based on the initial formation of the intermediate **15c** by the route shown in Reaction 5.

Reaction 5



In the first stage **12** and **13** are condensed in refluxing Pr^{i}OH to form **14** in very high yield. **14** is then carbonylated using *N*,*N*′-carbonyldiimidazole (CDI) to produce **15a** (X = Cl), and this is converted to the phthalimide **15b** using **16**. The treatment of **15b** with $H_2NNH_2 \cdot H_2O$ produces **15c** and acetylation with Ac_2O gives **15d**.

The patent also states that **15a** can be converted to the azide **15e** (X = N_3) by reaction with NaN_3 and this can be hydrogenated to give **15c**, but no experimental details are given for these two procedures. The intermediates **14** and **15a** are novel, but no physical or spectroscopic data are provided for them.

Advantages

The process avoids the hazards associated with the use of phosgene and appears to give good yields for the various steps.

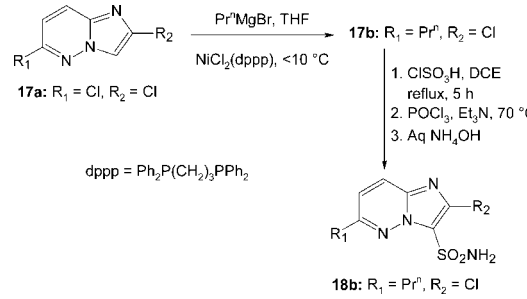
Patent No. U.S. 7,307,165

Assignee: Sumitomo Chemical Takeda Agrop Co. Limited., Tokyo, Japan

Title or Subject: Process for Producing an Imidazo[1,2-*b*]Pyridazine Derivative

This patent describes the production of an intermediate such as **18b** that is used to prepare sulfonylurea herbicides. A particular problem mentioned in the patent is that of easily producing the title compounds containing a substituent in the 6-position when a halogen is in position 2. Alternative methods require the use of polar solvents such as HMPA or Me_2NCOMe that create handling problems. In addition, the process can be carried out at or below ambient temperature compared to other methods that require heating. Reaction 6 shows the method used to prepare the sulfonamide **18b** via **17b**. The first step to prepare **17b**, with a yield of 88.5%, is key to the process, and alternative transition metal compounds such as Pt or Fe can be used in place of Ni. The sulfonamide **18b** is obtained in 43.5% yield by reaction of **17b** with $ClSO_3H$.

Reaction 6



The patent also describes the preparation of a number of other compounds analogous to **17b** and **18b** in which R_2 is Cl and R_1 is Cl, Et, Bu^i, Bu^n, 1-propenyl, or cyclopropyl.

Advantages

The process does not utilise boiling or hot solvents and is suitable for preparing derivatives that would otherwise be difficult to prepare.

Patent No. U.S. 7,309,717

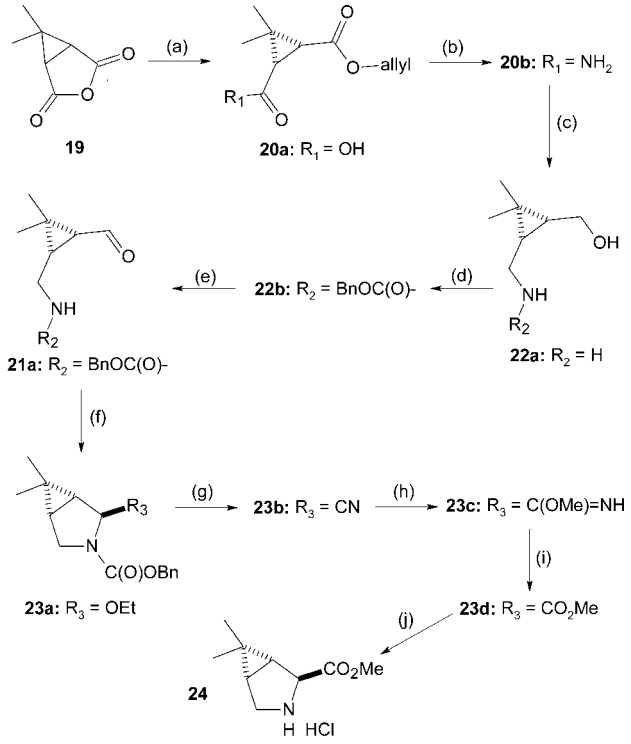
Assignee: Schering Corporation, Kenilworth, New Jersey, U.S.A

Title or Subject: Process for Preparing Azabicyclohexane Carboxylates

This patent describes a process for preparing compounds that are key intermediates in the synthesis of hepatitis C virus antagonists. An example of such a compound is **24**, and the route to produce the HCl salt is a complex multistep synthesis that is summarised in Reaction 7. The patent describes these steps in some detail and provides ^{13}C and ^1H NMR data for all of the intermediates shown. The chiral reagent used in step 1 is quinidine or *R*-(+)-α-methylbenzylamine although others are also covered in the claims. There are also alternative reactions described for some of the other reactions. One important point to note is that if EtOH is omitted from step f, then **21a** is converted to the alcohol **23e** (R_3 = OH), and this produces an ether by elimination of H_2O and thus is a yield loss. Yield data

are not given for all steps although the patent does state that it is a high-yielding process.

Reaction 7



(a) allyl alcohol, chiral reagent; (b) NH_4HCO_3, BOC_2O; (c) $LiAlH_4$/THF, $PhCO_2H$
(d) BnOC(O)Cl, K_2CO_3; (e) NaOCl, TEMPO; (f) EtOH, HOAc
(g) TMSCN, $BF_3{\cdot}Et_2O$; (h) NaOMe, MeOH; (i) Aq HCl; (j) Pd/C, H_2, HCl

Advantages

The patent claims that the process allows control of the stereochemistry and gives a high overall yield of product without the need for chromatographic purification.

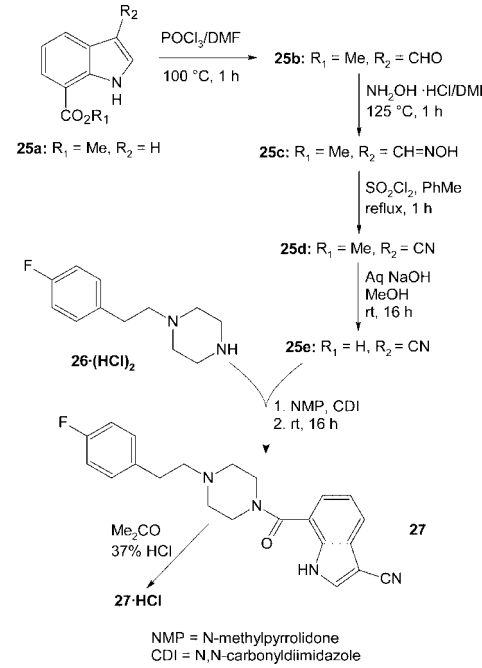
Patent No. U.S. 7,312,342

Assignee: Merck Patent Gesellschaft Mit Beschrankter Haftung, Darmstadt, Germany

Title or Subject: Process for the Preparation of (3-Cyano-1H-indol-7-yl)[4,4-(fluorophenethyl)piperazin-1-yl]methanone and Its Salts

The title compound **27** is a selective 5-HT_{2A} antagonist and has antipsychotic activity with few side effects so is useful in treating a range of neurological disorders. The patent claims cover several intermediates in the synthesis of **27** and also the preparation of **27** and its HCl salt by the route shown in Reaction 8. The method begins with the formylation of **25a** by a Vilsmeier reaction to give **25b** that is then converted to the oxime **25c**. Treatment of the oxime with SO_2Cl_2 produces the cyano compound **25d** and upon base hydrolysis **25e** is obtained. Condensation of **25e** with the HCl salt of **26** in the presence of CDI produces the free base **27** that can be converted to the HCl salt.

Reaction 8



The patent also describes the synthesis of the intermediate **25 g** (R_1 = Et, R_2 = Br) by reaction of the ethyl ester **25f** (R_1 = Et, R_2 = H) with pyridine hydrobromide perbromide. **25 g** can be used to prepare **25e** by treatment with CuCN in *N*-methylpyrrolidone (NMP), or it can be used to introduce other functional groups into the molecule.

Advantages

The patent gives a route to the important drug and provides a number of novel intermediates.

Patent No. U.S. 7,312,350

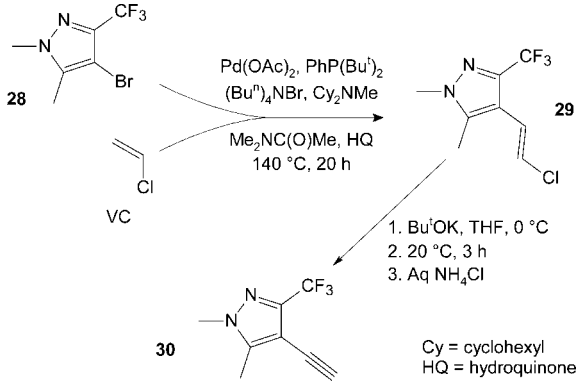
Assignee: Lanxess Deutschland GmbH, Leverkusen, Germany

Title or Subject: Process for Preparing Arylalkynes

Arylalkynes are industrially important intermediates for preparing polymers and fine chemicals. The patent states that the available processes require drastic conditions for their preparation. As a result, product yields are often low to moderate. The method described in this patent produces an arylvinyl halide or sulfonate that can then be converted to the arylalkyne. The examples in the patent and one of the claims specifically refer to the preparation of **29** and its conversion to **30** as shown in Reaction 9. The first stage involves a Pd-catalysed coupling reaction between vinyl chloride (VC) and the bromopyrazole **28** to form **29** that is isolated in 83% yield. This reaction is carried out in

the presence of hydroquinone (HQ) to prevent the free radical polymerisation of the VC. The second stage of the process is the treatment of **29** with strong base to give **30** that is isolated in a yield of 79%.

Reaction 9



Advantages

It is claimed that the first reaction step produces the arylvinyl halides in high yield in a simple and efficient manner. However, the process uses VC that is highly carcinogenic, easily polymerised, and a gas. Although the process may not require drastic conditions, it imposes very stringent safety requirements on companies that have not previously handled the reagent.

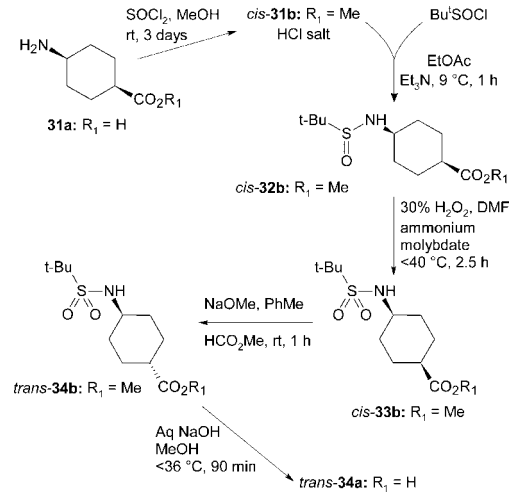
Patent No. U.S. 7,314,950

Assignee: Shionogi & Co. Ltd., Osaka-shi, Japan

Title or Subject: Process for Producing *trans*-4-Amino-1-cyclohexanecarboxylic Acid Derivatives

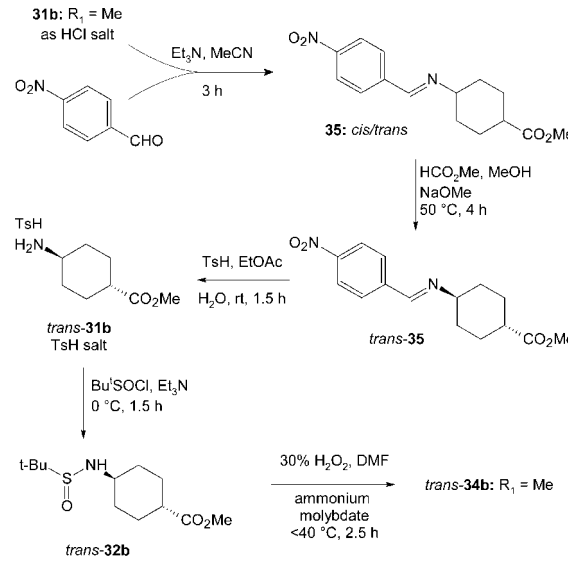
The compounds covered by this patent are the ester and acids such as **34a** and **34b** that are intermediates for the preparation of amides such as **38**. These amides are NPYY5 receptor antagonists and of interest as antiobesity drugs. The desired compounds have the *trans* geometry and are obtained by isomerisation of the *cis* materials. Alternative reports of the preparation of the *trans* compounds by isomerisation methods give yields of only 40%; hence, improved methods are desirable. The patent describes two methods of making the *cis* compounds such as **34a** (Reaction 10). The process starts by preparation of the HCl salt of the ester **31b** in 81% yield from **31a** in a process that takes three days. The salt is then reacted with Bu^{t}SOCl to give **32b** as an oil in a yield reported as 109% although the purity of the product is not mentioned. Oxidation of **32b** using H_2O_2 and ammonium molybdate gives **33b** in a yield of 79% based on **31b**. The *trans*-isomer of the ester **34b** is obtained in a yield of 70% by isomerisation of **33b** using NaOMe/HCO_2Me in PhMe. Base hydrolysis of **34b** produces the acid **34a** that is obtained in 87% yield.

Reaction 10



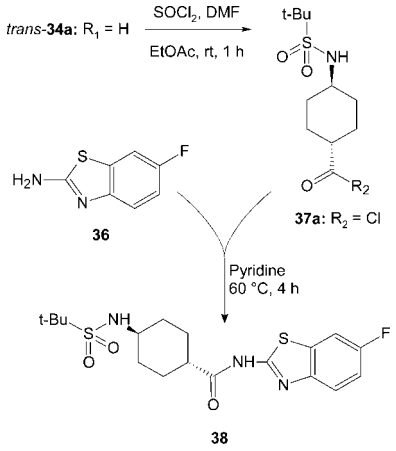
An alternative method of preparing *trans*-**34b** is also described (Reaction 11) and begins with the conversion of the salt **31b** to a *cis/trans* mixture of **35**.Treating this mixture with NaOMe produces an 82.7% yield of the *trans*-isomer of **35** that is converted to the Ts salt of *trans*-**31b** in 94% yield. This salt is then converted to *trans*-**32b** and subsequently to *trans*-**34b** in 100% yield by the same procedures shown in Reaction 10.

Reaction 11



The conversion of the acid **34a** to a number of amides such as **38** is also covered in the patent. Details are given for the preparation of **38** by reaction of the acid chloride **37a** with **36** as shown in Reaction 12. A large number of other amides are listed as being prepared using a variety of amines by this reaction, but actual details are not provided.

Reaction 12



This patent contains a number of errors including formulae showing the wrong geometrical isomer and an ester in place of an acid. There are also typographical errors including the misspelling of carboxylic in the title of the patent. The report of a yield of 109% in one example does not inspire confidence in the other reported experimental details. Several of the examples report that multikilo quantities of reagents are used, and so the advanced stage of development is suggested. ^{1}H NMR data are provided for most of the intermediates and products.

Advantages

The patent provides an improved process for the desired *trans*-isomers, and the several large-scale experiments indicate the possibility of commercial success of the process.

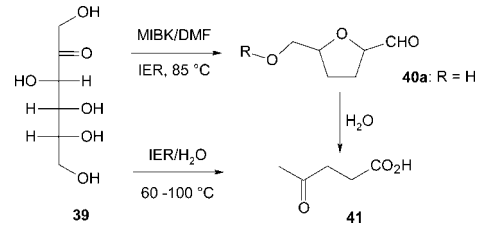
Patent No. U.S. 7,317,116

Assignee: Archer-Daniels-Midland Company, Decatur, Illinois, U.S.A

Title or Subject: Process for the Preparation and Purification of Hydroxymethylfurfuraldehyde and Derivatives

Using naturally occurring and renewable plants as a source of raw materials for chemicals is often perceived as an attractive proposition. This patent describes using carbohydrate sources as raw materials to produce **40a** that is useful in the preparation of polymers, solvents, surfactants, and pharmaceuticals. **40a** is produced by dehydration of carbohydrates, but the previously reported processes are complicated by a rehydration reaction that gives **41** and formic acid as a byproduct or that results in polymerisation of **40a**. This patent describes a process that reduces or avoids these complications while still using the same basic dehydration procedure. The preferred source of the carbohydrate used in this patent is high fructose corn syrup (HFCS). Key aspects of the patent are the use of reusable acid catalysts such as ion-exchange resins (IERs) and specific solvents or two-phase solvent mixtures. In the case of a two-phase solvent system there are specific limitations on the Log *P* values of the two solvents. One solvent must have a Log *P* value <0, and the other solvent must have a *P* value of up to 3.4. A specific example of a suitable solvent mixture is DMF (−1.04) and MIBK (+1.32). Examples are also given in which a single solvent is used with NMP seemingly preferred. Reaction 13 shows the production of **40a** from fructose (**39**) present in HFCS. This reaction can be carried out in MIBK/DMF containing strong acid IERs as catalysts. The reaction can take up to 7 hours for completion, and if a single solvent is used, the product is obtained by extraction. In the two-phase system the product is recovered from the MIBK layer.

Reaction 13



The patent also describes methods for specifically preparing **41** by acid-catalysed hydration of **40a** or by reaction of HCFS with water in the presence of acid IERs. The preparation of the ethoxy derivative **40b** (R = Et) is also described. This can be carried out by heating EtOH with **39** and an acid IER. There are examples of this being done is a batch or continuously in a column.

Advantages

The process gives improved yields of the aldehyde **40a** and a method for preparing derivatives from renewable raw materials.

Patent No. U.S. 7,317,126

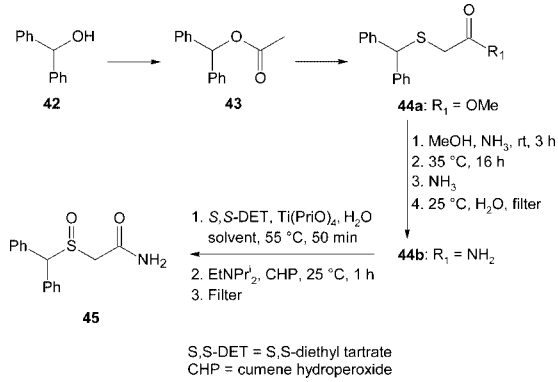
Assignee: Cephalon France, Maisons-Alfort, Cedex, France

Title or Subject: Process for Enantioselective Synthesis of Modafinil by Asymmetric Oxidation

The patent describes a novel process for preparing single enantiomers of modafinil **45**. This compound is used to treat narcolepsy, and a patent on the synthesis of intermediates in its synthesis has been reviewed recently (Org. Process Res. Dev. 2007, 11, 940). **45** has a stereogenic centre at the S atom and exists as a pair of enantiomers. It is approved for use as the racemic mixture, although only the L-isomer is active. The patent states that methods for the resolution of the racemic mixture are inefficient. A key step in the synthesis of **45** is a sulfide oxidation, and a stereoselective method would be beneficial. A number of asymmetric oxidation methods are reviewed in the patent and are said to have various shortcomings. The patent describes a novel method that gives an improved process providing high yields of the desired enantiomer with high ee. Reaction 14 shows the key step of oxidation of **44b** to **45** using

a chiral Ti complex in the presence of a base and cumene hydroperoxide (CHP). The Ti complex is formed from a Ti alkoxide and (*S*,*S*)-(−)-diethyl tartrate (*S*,*S*-DET) and H_2O prior to adding to the solution of **44b**. The patent provides details of a large number of experiments for oxidising **44b**, one for the preparation of **44b** but none for the production of **44a**. The patent claims cover the conversion of **42** to **44a**, and there are also references to other methods of preparing **43a**. The experiments described show the effects on ee and purity of changing solvent, order of addition, changing base, and the amount of Ti complex. The most suitable solvents used were PhMe, EtOAc, or MeCN with DCM, THF, and Me_2CO giving lower product yields. It was possible to obtain purity and ee >99% with a yield of 88% using PhMe.

Reaction 14



Advantages

The process provides a method of obtaining high yield of the desired single enantiomer without recourse to resolution.

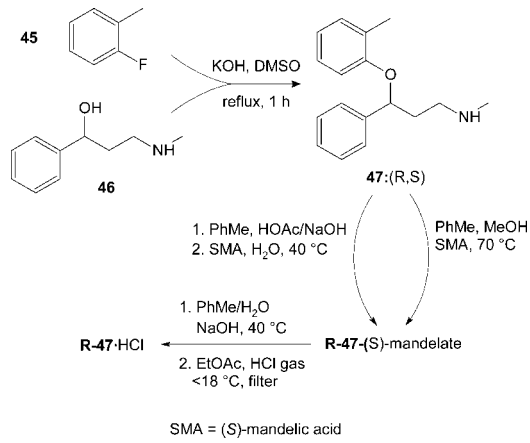
Patent No. U.S. 7,317,127

Assignee: Teva Pharmaceutical Fine Chemicals S.r.l., Petah Tiqva, Israel

Title or Subject: Process for Optical Resolution and Recycling of Tomoxetine

Tomoxetine **47**, also known as atomoxetine and available as the HCl salt as Strattera, is used to treat attention-deficit hyperactivity disorder. The active molecule is the (*R*)-(−)-enantiomer that is about 9 times more effective than the (+)-enantiomer. Resolution processes are used to separate the isomers, and epimerisation methods are known but said to be inefficient. The patent claims to offer an efficient process for resolving the racemic mixture and also for epimerisation of the unwanted (+)-enantiomer. Reaction 15 outlines the process used to prepare the racemic mixture **47** by condensation of **45** and **46** using KOH in DMSO. The racemic product is obtained in 92.7% yield by extraction with PhMe and the solution is used in the resolution procedure. This involves formation of the (*R*)-**47**-(*S*)-(+)-mandelate salt that can be carried out by two methods. In one of these MeOH is added to the PhMe solution of the racemic **47** and (*S*)-mandelic acid (SMA). The (*S*)-mandelate salt of (*R*)-**47** is recovered as crystals. In the other procedure the acetate salt of **47** is initially produced by addition of HOAc and aqueous NaOH to the racemate. The acetate is then treated with SMA and the mandelate salt recovered. The yield of the mandelate salts in each case is about 40%. Recrystallisation of the salt increased the *R/S* ratio to >99/1. Racemisation of the unwanted (*S*)-**47** is carried out by concentrating the PhMe mother liquor from the crystals then treating it with KOH in DMSO. The HCl salt of (*R*)-**47** is obtained by treating the mandelate salt with gaseous HCl.

Reaction 15



Advantages

The process allows recovery and recycling of the unwanted enantiomer, thereby increasing the atom yield of the product.

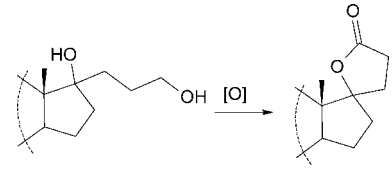
Patent No. U.S. 7,319,154

Assignee: Bayer Schering Pharma AG, Berlin, Germany

Title or Subject: Production of 3-Oxo-pregn-4-ene-21,17-carbolactones by Metal-Free Oxidation Process

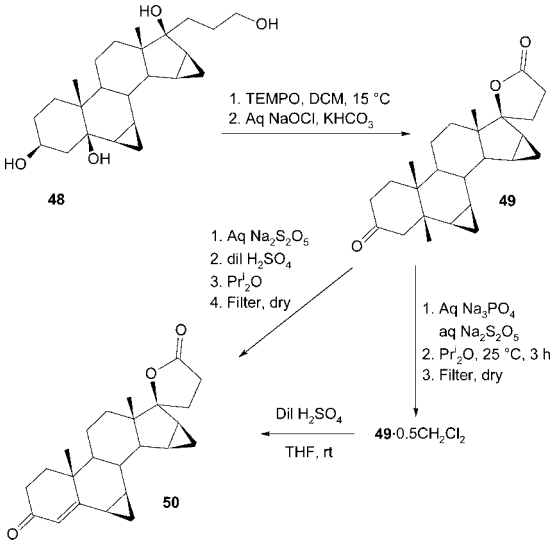
This patent is concerned with the conversion of the hydroxypropyl group to the spirolactone as represented by Reaction 16. A variety of reagents can be used for this oxidation including salts of Cr and Ru, but such processes can give poor yields and produce wastes that have high disposal costs or leave undesirable traces of metals in the product. The objective of the patent is to provide a method of carrying out this oxidation without the use of metal-containing oxidants.

Reaction 16



The process involves the use of hypochlorites as oxidants in the presence of catalytic amounts of TEMPO. The reaction is specifically applied to the production of **49** by oxidation of **48** as shown in Reaction 17. By maintaining the pH >5 in the subsequent workup, the DCM hemisolvate of **49** is formed. If the pH is lowered to <5 using H_2SO_4, then the dehydration of **49** produces **50** that can also be obtained from the hemisolvate by acidification.

Reaction 17



Advantages

The process is efficient, avoids the problem of traces of metals in the product, and also avoids waste disposal problems.

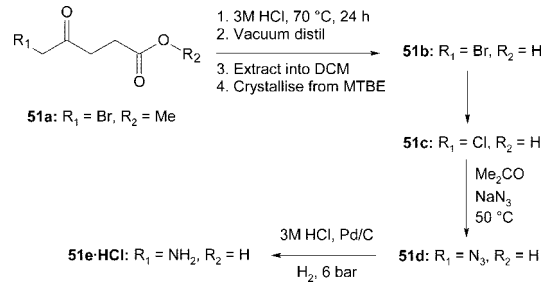
Patent No. U.S. 7,319,164

Assignee: Sven Aldenkortt, Würzburg, Germany

Title or Subject: The Production and Use of 5-Azidolaevulininc Acid

This patent is not assigned to an organisation although the inventor is associated with Innochemie GmbH, a company that supplies specialty chemicals. The title compound **51d** is novel and can be used to prepare **51e** that is an herbicide, a drug for treating actinic keratosis, and a possible hair-restorer. There are apparently a great number of reported methods of preparing **51e**, and some start from **51a**, a compound obtained by bromination of readily available laevulininc acid. A problem mentioned with the use of **51a** to make **51e** is that it is lachrymatory, difficult to handle, and can decompose when traces of acids are present. Reaction 18 shows how **51a** is converted to the acid **51b** that can be isolated but further reacts to give **51c**. The transformation from **51a** to **51c** is claimed to be previously unknown and takes place quantitatively. **51c** is said to be storable and nonlachrymatory. Reaction of **51c** with NaN_3 gives **51d** in a 95% yield, and hydrogenation of **51d** in HCl gives the HCl salt of **51e**. The overall yield of the four-step process is said to be 31−35%. The patent also describes preparation of **51d** from NaN_3 and **51b** or a mixture of **51b** and **51c**. IR, ^1H NMR, and ^{13}C NMR data are provided for all compounds.

Reaction 18



The compounds **51b** and **51c** are said to be nonlachrymatory and therefore do not create handling problems. However, since they are made from **51a**, there is still a potential handling problem in the overall process. The patent reports that **51d** is a crystalline, storable compound that does not decompose if prepared according to the process described. However, it is also reported that, surprisingly, **51d** possesses explosive properties and detonates with an impact energy of 40 J. It is not reported how this explosive property was discovered, and it is not known whether this important piece of information has been reported in the open literature. The patent suggests that this property of **51d** means it could be used as a priming fuse and explosive for airbags in the motor industry. Such an application may be the subject of other patents.

Advantages

The process gives excellent yield of the amino laevulinic acid via a novel intermediate that may have some interesting uses.

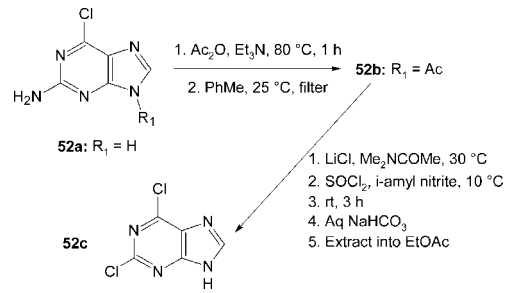
Patent No. U.S. 7,321,035

Assignee: Sumitomo Chemcial Company Limited, Osaka, Japan

Title or Subject: Process for Producing 2,6-Dihalogenopurine

The compounds of interest in this patent are raw materials for the synthesis of nucleoside analogues that are pharmaceutical precursors. The examples cover the preparation of **52c** and alternative methods used to prepare this compound are said to require the use of corrosion-resistant reactors due to the high temperatures (165 °C) and corrosive nature of reagents used. The procedure described in the patent is to treat **52a** that contains a protective group at the 7- or 9-position on the purine ring. The protection is afforded by the Ac group that is introduced by reaction of **52a** with Ac_2O to give **52b** in 100% yield. Simultaneous diazotisation and chlorination of **52b** give the desired dichloropurine **52c** in 70.5% yield. Alternative chlorination agents used include SO_2Cl_2 (yield 73.7%) and $POCl_3$ (yield 65.2%). The two steps can be combined so that the reaction is carried out without isolation of **52b**, and the yield is 76.6%.

Reaction 19



Advantages

The process avoids the use of high temperatures and uses less corrosive reagents so that the process is more efficient and commercially attractive.

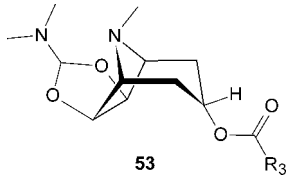
Patent No. U.S. 7,321,039

Assignee: Boehringer Ingelheim Pharma GmbH & Co. KG., Ingelheim, Germany

Title or Subject: Industrial Process for Preparing Tropenol

Tropenol **54a** is used to prepare a range of pharmacological compounds, and this is a continuation of an earlier patent that has been reviewed (Org. Process Res. Dev. 2005, 9, 537). One drug prepared from **54a** is **56·MeBr** that is known as Spiriva or tiotropium bromide. This is an anticholinergic bronchodilator used in the management of chronic obstructive pulmonary disease. The major problem associated with preparing **54a** is its purification because it is difficult to remove structurally similar impurities. The earlier patent disclosed that the acid salt of **54a** is more useful since it can be more easily purified and this patent extends that work and gives details for the preparation of **56** from the HCl salt of **54a**. The single claim in the patent covers the preparation of compounds represented by **53**, the details of which are not included in this patent but are described in the earlier one.

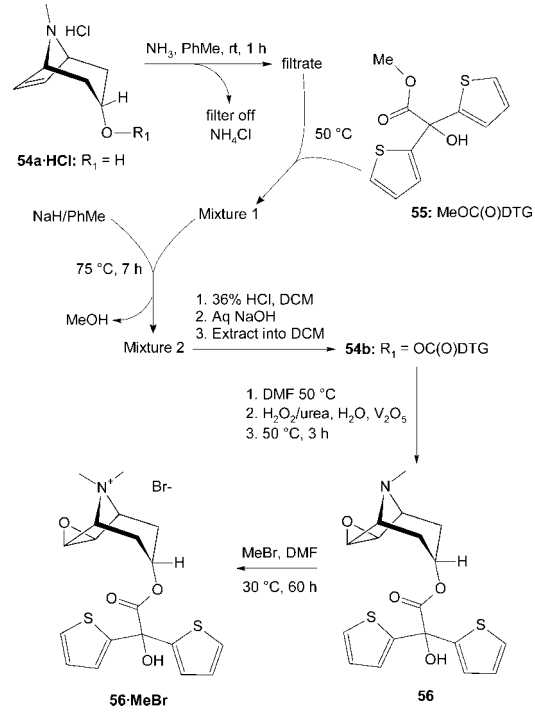
Compound 53



53

The route used to make **56** is shown in Reaction 20 and begins with the conversion of the HCl salt of **54a** to the free base using NH_3 that precipitates NH_4Cl that is removed by filtration. The filtrate is heated with the ester **55** to form Mixture 1 that is treated with NaH/PhMe at 75 °C, releasing MeOH that is distilled off leaving Mixture 2. Acidification of Mixture 2 followed by neutralisation and extraction into DCM gives the tropenol ester **54b** in 83% yield. At this point in the patent example there is considerable confusion or a serious mistake regarding the preparation of **56**. The patent example refers to the tropenol ester **53** as the molecule that is converted to **56** by an epoxidation reaction. However, **53** is not a tropenol ester, and in the body of the patent it is **54b** that is epoxidised, giving **56** as shown in Reaction 20. Such an error would suggest that nobody has read the patent including the examiner. The desired form of the drug is **56·MeBr** and is produced by reaction of **56** with MeBr in DMF over 60 h. After workup the product is obtained in 88% yield, and this step is carried out on a multikilo scale.

Reaction 20



The examples in the patent are carried out using multikilo quantities of reagent, thus indicating the advanced commercial status of the process.

Advantages

The process appears to be at an advanced stage of development and may even be in commercial operation.

Patent No. U.S. 7,321,043

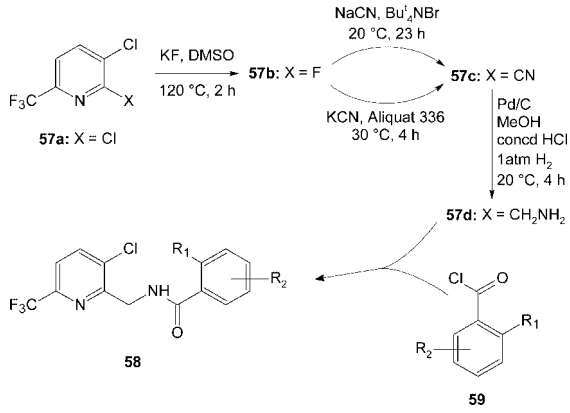
Assignee: Bayer Cropscience S.A., France

Title or Subject: Processes for the Preparation of 2-Aminomethylpyridines and 2-Cyanopyridines

The patent covers the preparation of the cyano compound **57c** and its use in preparing **57d** that is an intermediate in manufacturing fungicidally active compounds exemplified by **58**. The hydrogenation of cyanopyridines to aminomethylpyridines is acknowledged as a known process, but if the molecule contains halogen groups, the reaction is complicated by competing dehalogenation reactions. The patent states that the literature indicates that Pd catalysts promote such dehalogenation reactions and Pt or Rh catalysts are better if this is to be avoided. The patent reports that it has been found that catalysts made from finely divided Pd on charcoal are effective in reducing **57c** and can be used to prepare **57d**. The reaction requires a catalyst inhibitor that prevents dehalogenation, and metal or hydrogen halides are used. The patent also reports on the synthesis of the cyano compound **57c**, and the two processes can be combined to give a commercially useful process for preparing **57d**. Reaction 21 shows the route used to prepare **57c** by treatment of **57b** with either KCN or NaCN in the presence of a quaternary ammonium salt. In the examples using KCN and Aliquat 336, 98% pure **57c** was recovered in 90% yield, whereas the yield by HPLC was 82% with the use of NaCN . The patent also describes the preparation of **57b** in 98% purity and 92% yield from **57a**. Although the details of

the preparation of the pesticide **58** are not described, the groups R_1 and R_2 are the same or different halogen groups. However, it is mentioned that if the preparation of **57d** is carried out in the presence of HCl then the product is the HCl salt and this can be used directly in the preparation of **58**.

Reaction 21



Advantages

The process provides an efficient means of reducing cyanopyridines and gives high yields of the product that can be used directly to make fungicides.

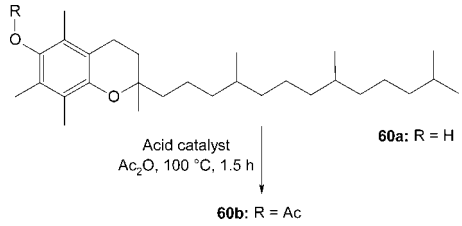
Patent No. U.S. 7,321,053

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

Title or Subject: Process for the Manufacture of Tocyl and Tocopheryl Acylates

This patent is primarily concerned with the production of vitamin E and its derivatives, and previous patents on this topic have been reviewed (Org. Process Res. Dev. 2007, 11, 318). The main commercial form of vitamin E is α-tocopheryl acetate **60b**. This can be prepared by refluxing α-tocopherol **60a** and Ac_2O for up to 5 h or by using pyridine as catalyst. The reaction takes place at rt and takes 3 days but does give a 96% yield. The process described in this patent uses a supported solid Brønsted acid catalyst at up to 100 °C and takes about 1.5 h. The acids used are H_2SO_4 or H_3PO_4, and the preferred support covered by the claims are mixtures of SiO_2 and TiO_2. However, the patent does mention the use of polysiloxanes containing sulfo groups, and one commercially available material, Deloxan ASP 1/9, is mentioned. The patent also specifies that the catalysts should have a BET area between 10 and 800 m^2/g and a pore volume within the range 0.1 to 2.0 mL/g. The basic method used to prepare **60b** is shown in Reaction 22. The reaction is carried out under argon in either batch mode or continuously, and one example reports a test using Deloxan ASP 1/9 that is run for a period of 12 days with a continuous feed rate of 0.4 mL/min that produced a yield of 97% with a purity of 97.5%.

Reaction 22



Advantages

The process is highly efficient, gives high-purity product and has commercial potential for an important product.

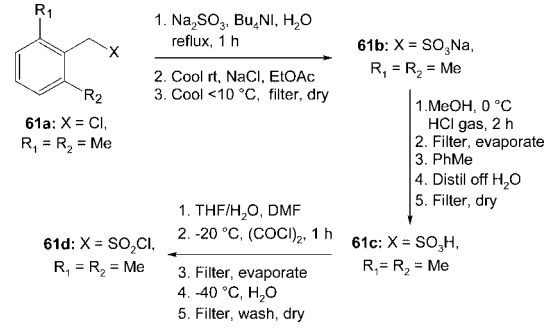
Patent No. U.S. 7,321,061

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

Title or Subject: Process for the Preparation of Aryl- and Heteroaryl-Alkylsulfonyl Halides

The title compounds are widely used as intermediates to make a variety of chemical and pharmaceutical products. A particular compound covered is **61d** that is used to prepare cPLA2 inhibitors. The enzyme cPLA2 plays a pivotal role in adult respiratory distress syndrome, asthmatic or rheumatic disorders; hence, inhibitors are of interest in treating these conditions. Typical methods for preparing sulfonyl chlorides are said to involve heating Na salts of sulfonic acids and PCl_5 sometimes in combination with $POCl_3$ or $SOCl_2$. Such harsh conditions are often unsuitable for preparing sterically hindered sulfonyl chlorides as a result of SO_2 elimination. Hence, the aims of the patent are to provide a suitable process for preparing the desired sterically hindered compounds. Reaction 23 shows how **61d** is prepared by a series of reactions beginning with **61a**. The yields of the three reactions shown are 88%, 89%, and 96%, respectively.

Reaction 23



The patent also gives details of a range of analogous compounds in which R_1 and R_2 are H and Me, both F, F and CF_3, both CF_3, H and CF_3, H and CHO, or H and BnO. In addition the 2,3-dichlorophenyl and 3,4-dichlorophenyl compounds are also prepared. The yields of intermediates and products for each these compounds is generally >80% although some do give a poor yield in one step or other.

Advantages

The process gives very good yields of the desired sulfonyl halides without the need to use harsh conditions and hence byproduct are minimised.

Patent No. U.S. 7,321,067

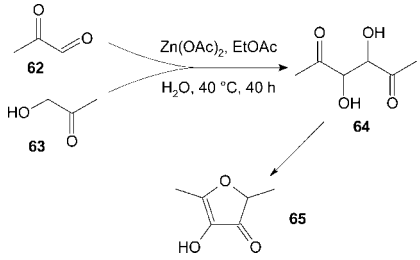
Assignee: Firmenich SA., Geneva, Switzerland

Title or Subject: Process for the Preparation of 1,4-Dialkyl-2,3-diol-1,4-butanedione

The compounds covered by this patent such as **64** are useful in preparing aroma chemicals such as furaneol **65** that has a sweet strawberry aroma and is partly responsible for the smell of fresh pineapple. Alternative methods for the synthesis of **64** are said to involve long procedures using expensive heavy metal reagents that are difficult to remove and give waste disposal

problems. The method used in this patent involves an aldol condensation that is claimed to be a novel way of making **64**. The aldol reaction is between a glyoxal **62** and **63** using a catalyst such as $Zn(OAc)_2$, $Zn(acac)_2$, $Mg(OAc)_2$, or $Mg(acac)_2$. The reaction is carried out in the presence of H_2O, and for high yields the pH of the solution should be between 4 and 6.5. Reaction 24 shows the procedure used to prepare **64** that is obtained in 32% yield as a mixture of two isomers and purified by distillation. The highest yield of 42% was obtained by using the same catalyst at 20 °C over a period of 168 h.

Reaction 24



Advantages

The process involves only a single step but requires very long reaction times and gives low yields. Whether it is more commercially viable than alternatives is not known.

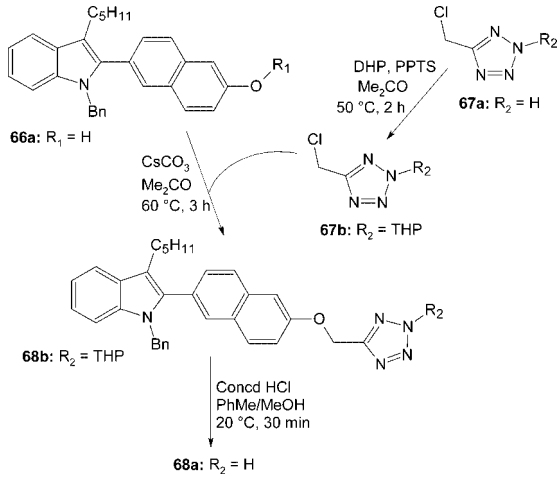
Patent No. U.S. 7,323,483

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

Title or Subject: Intermediates and Processes for Preparing Naphthylindole Derivatives

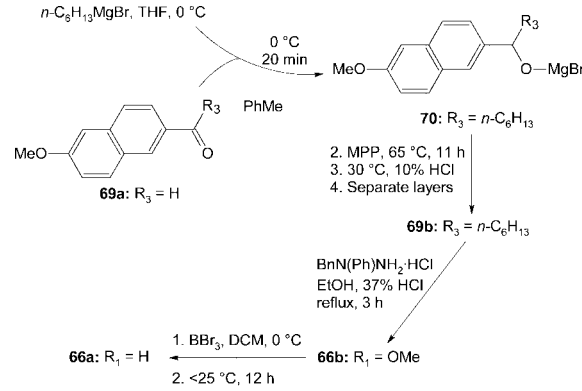
The compounds described in this patent are used for the treatment of deep vein thrombosis, pulmonary fibrosis and other conditions resulting from fibrinolytic disorders. The main claim of the patent covers the synthesis of **68a** by the condensation of the indole-naphthol **66a** with the THP-protected tetrazole **67b** as shown in Reaction 25. The reaction is carried out using Cs_2CO_3 and gives 100% conversion to **68b** that is treated with concd HCl to give **68a** that is recovered after workup in 76.4% yield and 99.26% purity. This reaction is carried out using kilo quantities indicating its advanced stage of development.

Reaction 25



The patent also gives details for the preparation of **66a** and this is summarised in reaction 26. The first step is formation of the ketone **69b** that involves the reaction of **69a** and *n*-hexylMgBr to form the Mg alkoxide **70** that is not isolated and undergoes an Oppenhauer oxidation reaction using 1-methyl-4-piperidone (MPP) as hydride acceptor. An alternative route to **69b** is also given involving the reaction of n-hexyl lithium with **69a**. This reaction gives a yield of 77.5% of a crystalline material with purity of 97.9% after vacuum distillation. Using the Grignard route the product was obtained in 98% yield and purity of 97.8% without distilling. The ketone **69b** is reacted with a hydrazine in refluxing EtOH and HCl in a Fischer indole synthesis to give **66b** that was recovered in 78% yield by crystallisation from n-heptane. In the last step the ether was demethylated using BBr_3 giving **66a** in 81.7% yield. The workup in this latter step involves two solvent exchange steps. In the first DCM is replaced by PhMe and then the PhMe is replaced by n-heptane. The product is obtained by crystallisation from heptane at 0 − 5 °C.

Reaction 26



Advantages

The process gives high yields of the desired materials and the examples indicate it is scalable and at an advanced stage of development.

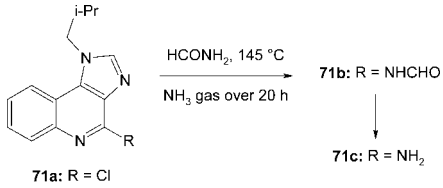
Patent No. U.S. 7,323,568

Assignee: Chemagis Ltd., Bnei-Brak, Israel

Title or Subject: Process for Preparing Imiquimod

Imiquimod **71c** is an immunomodulator that is used to treat genital warts, small superficial skin cancers, and actinic keratoses and is available as a cream under the name Aldara. A patent on the synthesis of this compound from another company was recently reviewed (Org. Process Res. Dev. 2008, 12, 146) and the expiry of the original patents has probably stimulated interest in new routes. A number of methods used to prepare **71b** are reviewed, and these are described as having various problems including the hazard associated with the formation of HCN gas when BnNCO is used as starting material. The method used in this patent is the reaction of **71a** with $HCONH_2$ while bubbling gaseous NH_3 into the reaction mixture (Reaction 27). The patent suggests that the reaction proceeds via the formation of the *N*-formyl compound **71b** (R = NHCHO). The yield of crude **71c** product is 80.2%, and after treatment in a boiling mixture of MeOH and aqueous NaOH the yield of pure product was 78%. Without using NH_3 in the synthesis the product yield falls to 47.6%. The product can be recrystallised from DMSO and has a purity of 99.91% by HPLC. The patent does not divulge how **71a** is prepared, and this may be a key aspect of a process to prepare **71c**.

Reaction 27



Advantages

The process gives high yields of the product using this very easy transformation.

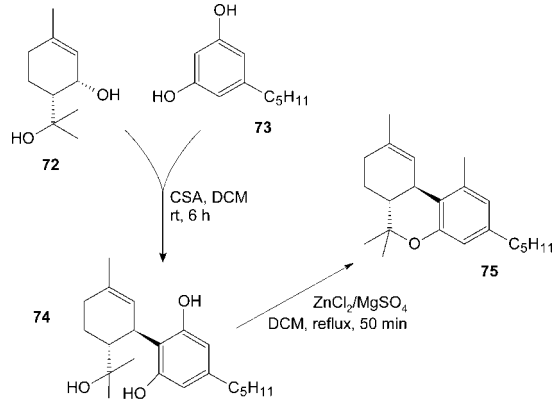
Patent No. U.S. 7,323,576

Assignee: Alphora Research Inc., Mississauga, Ontario, Canada

Title or Subject: Synthetic Route to Dronabinol

Dronabinol **75** is the active constituent in marijuana and has been approved as an antiemetic for patients undergoing chemotherapy, suffering from AIDS or for those with anorexia. The compound occurs naturally but is said to be difficult to extract, and synthetic routes have to be stereoselective and hence can be inefficient. A high-yield synthesis of **75** is claimed in this patent using the route shown in Reaction 28. The first stage of this is reaction of the *cis*-diol **72** with olivetol **73** to form the *trans*-compound **74** in 39% yield. This is carried out in DCM in the presence of camphor sulfonic acid (CSA). The cyclisation of **74** to **75** is carried out in refluxing DCM containing $ZnCl_2$ and $MgSO_4$. The product **75** was purified by column chromatography and recovered in 49% yield.

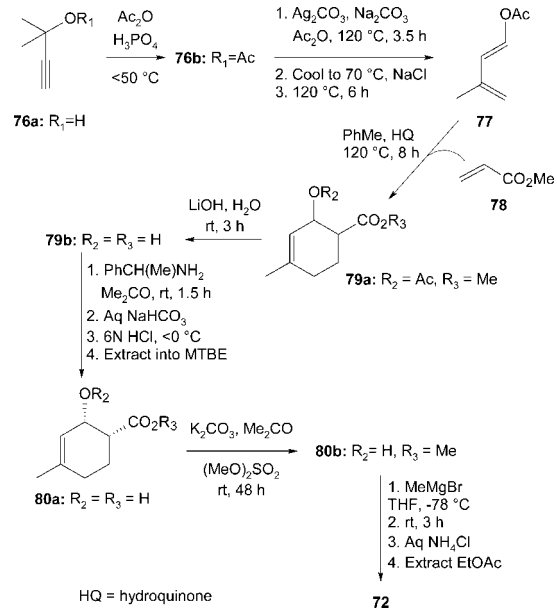
Reaction 28



CSA = camphor sulphonic acid

The patent also gives details of the preparation of the **72** that is used to prepare **75**. Reaction 29 shows the route used to prepare **72** that starts by acylation of the commercially available alkynol **76a** to give **76b**. This is not isolated and undergoes a rearrangement using $AgCO_3$ to form **77** that is recovered by distillation in 32% yield. A Diels−Alder reaction of **77** with **78** produces **79a** in 47% yield, and this is a novel compound. The reaction initially produces a mixture of *cis*- and *trans*-isomers that is isolated by hexane extraction, and upon cooling to −20 °C the racemic *cis*-isomer crystallises from solution essentially pure. Base hydrolysis of the *cis*-isomer of **79a** then gives the novel racemate **79b** in 72% yield. Resolution is used to obtain the (1*R*, 2*S*) enantiomer **80a** that is another novel compound. The resolution is carried out in two stages with the salt being isolated in 31% yield. The pure **80a** is obtained in 79% yield, and esterification of **80a** using $(MeO)_2SO_2$ produces **80b** as an oil in 92% yield. Alkylation of **80b** using MeMgBr gives **72** in 95% yield.

Reaction 29



Advantages

The process is claimed to give a high yield of **75**, but the preparation of starting material **72** has a number of steps that have low yields; thus, the overall yield of **75** must be very poor. However, whether it is still commercially viable is not known.

Keith Turner

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