Organic Process Research & Development **2004**, *8,* 553–563

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during March and April 2004

Summary

The current selection of 22 patents was taken from an initial list of 313 that fitted the criteria, and it is hoped that there will be something useful and interesting. There are five patents from four companies on the subject of camptothecin, the anticancer drugs. The parent compound is quite toxic, but by changing substituents the antitumour activity can be maintained and the toxicity reduced. Four new polymorphs of the antihypertensive drug carvedilol have been described and also an improved method for its synthesis. The new method does not give such high levels of an impurity that was formed from previous procedures. Removing a product as it is formed is always an effective method of reducing by-products and the use of a semi-continuous process to make bisphenol-S has reduced the quantity of by-products that are found in batch reactions. A continuous method of making vitamin B_6 precursor is described in which an azeotrope is separated by distilling twice at different pressures. Many azeotropes will have different compositions at different pressures, and hence, distilling twice will allow the recovery of both components. Unfortunately this is not easy with batch columns. The use of naturally occurring materials as sources of chemicals is a popular area of R&D work. Three patents are reviewed on this subject with two of them both on the subject of (*S*)-3-hydroxy-γ-butyrolactone. The third covers the formation of 2,5-diformylfuran. A novel reaction of diazonium pyridine salts is described in which alkoxy compounds are formed from fluorinated alcohols and the salt. Salen catalysts are the subject of two patents. One uses Co catalysts to prepare chiral epoxides and diols, and the second uses Mn catalysts in an enantioselective amination reaction. An improved hydrogenation process using Cu in place of Pd or Ni catalysts gives high *cis*-selectivity in the synthesis of the antidepressant sertraline. Another antidepressant mirtazapine is not easy to purify, and one patent discloses hydrated and anhydrous forms that can be produced and purified more easily. The procedure must be effective since one of the experiments starts with 84 kg of material. Other patents also indicate medium- to large-scale processes are being carried out possibly on a commercial scale. There is no legal or commercial significance for the patents selected, and advantages are those usually claimed in the patent unless this author has prior knowledge. It has to be noted that since the change to faster publication of patents there has been an increase in the number of errors. One patent in particular reports an *m*/*e* value in a mass spectra as being evidence of the formula of the compound. Unfortunately both the numerical value and molecular formula are totally wrong. In addition there are structural formulae that show a NO_2 group as an NC_2 group in one and as a CN group in the other. This is not at all acceptable in a legal document, and again shows that whatever input a chemist might have had in the work they cannot have had much in preparing the patent. If one's name is going on the patent then one should make sure to read it as one presumably does with papers.

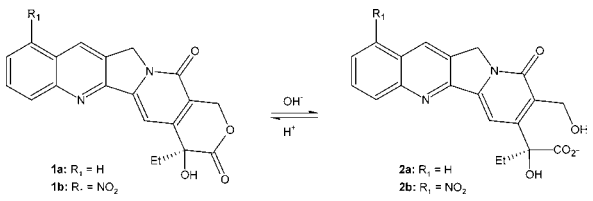
Patents No. U.S. 6,699,875 and U.S. 6,703,399

Assignee: The Stehlin Foundation for Cancer Research, Houston, Texas, U.S.A.

Title or Subject: Camptothecin Esters and Their Use in Treatment of Cancer

These are two of five patents in this review on the subject of camptothecin **1a** (R_1 = H). This is an alkaloid that can be obtained from the bark and wood of a Chinese tree, *Camptotheca acuminata* and has been shown to have antitumour activity. It is effective against mouse leukaemia but is very toxic to humans, and there has only been limited testing. In addition it has poor water solubility and has limited availability; hence, most studies are aimed at efficient methods of producing its derivatives. The 9-nitro derivative **1b** has been found to be much less toxic than the parent compound and is currently undergoing phase III trials. The potency of the camptothecins is attributed to those compounds that maintain the integrity of the lactone ring, have an intact (*S*)-OH group at C20, and have a 5-ring system. However, it is known that the lactone ring is opened above pH 7 and the biologically inactive form **2a** is obtained as shown in Scheme 1.

Scheme 1



In human blood the hydrolysis problem is exacerbated because the carboxylate form is bound by the blood serum

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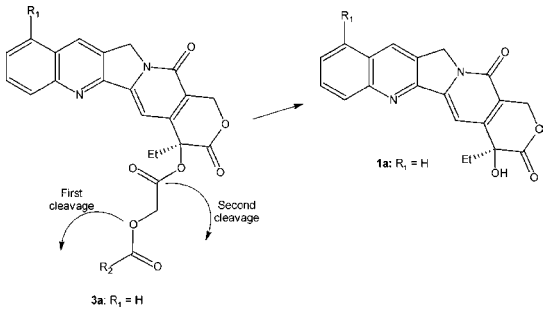
albumin, thereby shifting the equilibrium toward the inactive form. Hence, the ideal situation is to introduce a stable precursor that then forms the active form in the blood stream of the patient. These patents describe procedures for making such compounds.

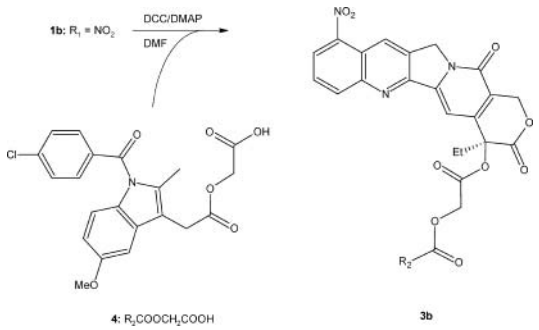
The first patent describes what are termed cascade esters such as **3a** which are so named because they are believed to cleave in a sequential manner to give the parent compound as shown in Scheme 2. It is suggested that the first bond is broken while the drug is in the circulating blood, whereas the second bond cleaves in the tumour tissue to give the potent parent compound at the actual cancerous site.

Scheme 2



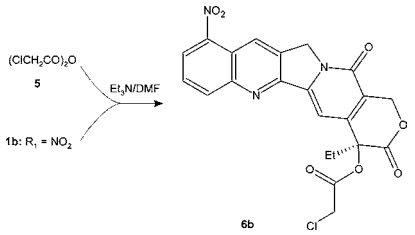
The ester **3b** is one of the active precursors and is prepared in 32% yield by the esterification route shown in Scheme 3. This involves the treatment of the nitro compound **1b** ($R_1 = NO_2$) with acemetacin **4** in the presence of DCC and DMAP in DMF. NMR and MS data are given for compound **3b**, although it has to be said that the molecular formula and *m*/*e* value of the parent ion of **3b** are both incorrect in the patent. In addition the structural formula for **4** and **3b** are both incorrect with the NO_2 group in **1b** shown as a NC_2 group and as a CN group in **3b**.

Scheme 3



The second patent describes an alternative range of precursors that are haloalkyl esters exemplified by **6b** which is prepared from **1b** and **5** in the presence of Et_3N as shown in Scheme 4. The analogous chloro-propyl and -butyl esters were also prepared by using the acyl chloride in the presence of H_2SO_4.

Scheme 4



Advantages

The processes produce compounds that are less toxic than the actual tumour-killing compound but will remain active in the human body and produce the potent compound at the site of the tumour.

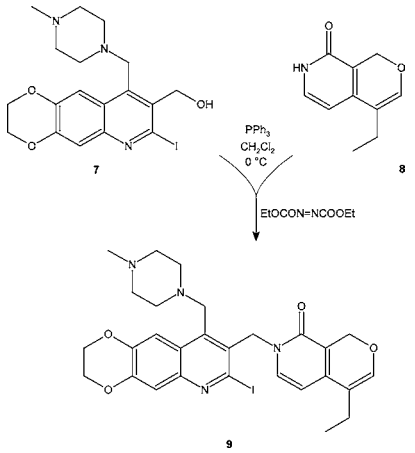
Patent No. 6,716,982

Assignee: OSI Pharmaceuticals Inc., Melville, New York, U.S.A.

Title or Subject: Method for Preparing Camptothecin Derivatives

This patent describes a multistep synthetic route to the camptothecin derivative **12** that delays introduction of the chiral centre at C-20 until the penultimate step. This is said to have the advantage of reducing the accidental contamination of the toxic intermediates to production workers. The process begins with the condensation of **7** with **8** to give **9** as shown in Scheme 5. Alternative substrates to **7** can be used in which the OH group is replaced by groups such as Tf, Ts, or Ms. When using these compounds it is said to be necessary to use solvents such as DMF or Bu^tOH, and Bu^t-OK as catalyst. No examples are provided, but there is a reference to patented work.

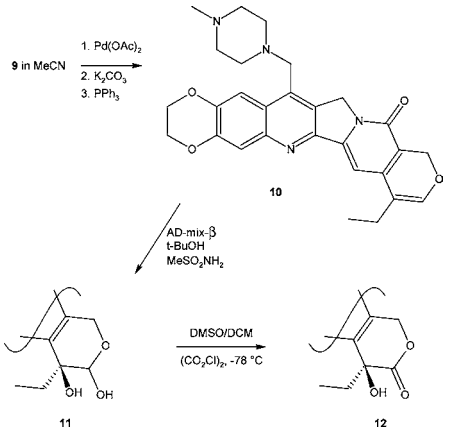
Scheme 5



The conversion of **9** to **12** proceeds via several steps shown in Scheme 6. The first step is the conversion of **9** to **10** by cyclisation using an intermolecular Heck reaction. This is carried out by treating a solution of **9** in MeCN with a

mixture of $Pd(OAc)_2$, PPh_3, and powdered K_2CO_3. Compound **9** is then converted to the dihydroxy compound **11** by using the asymmetric reagent AD-mix-β containing hydroquinidine 1,4-phthalazinediyl ether. This reaction is carried out in Bu^{t}OH containing methanesulphonamide and produces a mixture of two distereoisomers in the ratio 83:17 that are presumed to be epimeric at the hemiacetal carbon. Conversion of the major product to (*R*)- and (*S*)-*O*-methylmandelates is used to assess the enantioselectivity of the above reaction. The dihydroxy compound **11** is then oxidised to **12** by using DMSO at −78 °C in dichloromethane (DCM) containing oxalyl chloride. ^{1}H NMR data are provided for all compounds.

Scheme 6



Advantages

The procedure is claimed to be a safer method of manufacturing the desired camptothecin and does not require a resolution step.

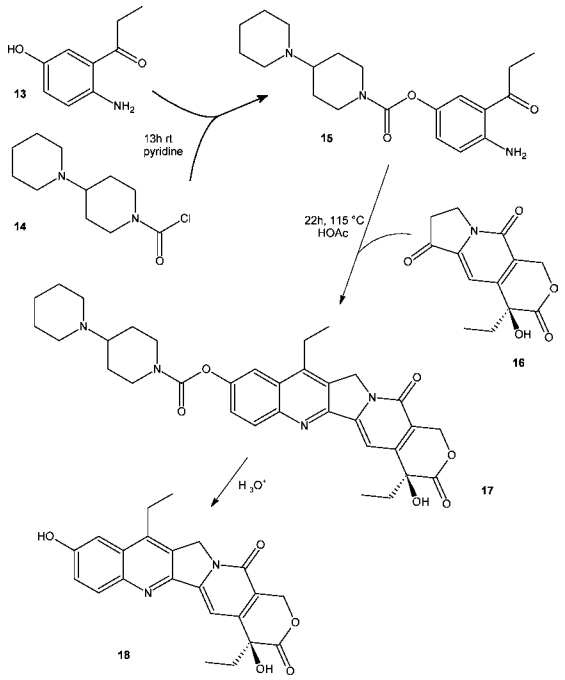
Patent No. U.S. 6,723,729

Assignee: Pharmacia and Upjohn Company, Kalamazoo, Michigan, U.S.A.

Title or Subject: Novel Compounds Useful in Preparing the Camptothecin Derivative Irinotecan

This is another patent on the subject of camptothecins, and it discloses details for preparing irinotecan **17** which is an antineoplastic drug used to treat cancers of the colon and rectum. A process for the preparation of **17** from **16** was disclosed in U.S. Patent 6,121,451 in 2000. The route disclosed in this patent is shown in Scheme 7 and begins with the reaction of **13** and the hydrochloride form of the acyl chloride **14** at room temperature to give the ester **15**. This is then heated with **16** in pyridine to give **17** which was obtained as the free base, and subsequent recrystallisation from 1 M HCl gave the hydrochloride salt of **17**. One of the patent claims covers **18** which is formed by the acid hydrolysis of **17**, but no experimental details are provided.

Scheme 7



An interesting statement made in the patent is that when using **15** to produce **17** there will be a detectable amount of **15** in the final product. It is also said that **15** will also be detectable when any process to make **17** involves the use of reagents that produce **15** such as **13** and **14**. Thus, the presence of **16** can be used as an analytical marker, and clearly this can be used to determine if anybody other than the assignees of this patent are carrying out this process to produce **17**.

Advantages

This patent provides a process for the production of novel intermediates useful in preparing camptothecins. The presence of these intermediates in the final product could be used to the identify the route that was used to make the drug and help in protecting the patented process.

Patent No. U.S. 6,723,849

Assignee: BioNumerik Pharmaceuticals Inc., San Antonio, Texas, U.S.A.

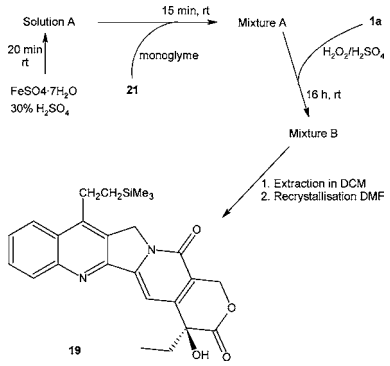
Title or Subject: Process for Making Highly Lipophilic Camptothecin Derivatives

This is the last patent on this subject in this review and covers the highly lipophilic alkylsilyl-substituted compounds such as **19** which is known as karenitecin and is undergoing clinical trials. The current preferred method for producing **19** is by a Minisci-type alkylation involving the reaction of **1a** with **21** and H_2O_2 in the presence of a metal sulphate as described in U.S. Patent 6,194,579. However, that and other processes are said to be unsuitable for the large-scale

production of **19**. The process described in this patent is a modification of the preferred method, including a different mode of adding the reagents.

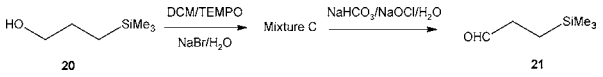
The process starts by recrystallisation of **1a** from the naturally occurring material using DMF. The process shown in Scheme 8 involves initial production of Solution A that is acidified $FeSO_4$. To this solution is then added a solution of **21** in monoglyme to give Mixture A. To this mixture is added a solution of purified **1a** in 30% H_2SO_4 and 30% H_2O_2 to give Mixture B. Extraction of Mixture B with DCM followed by recrystallisation from DMF gave **19** for which ^{1}H NMR data are provided.

Scheme 8



The patent also describes a method for preparing **21** by oxidation of **20** as shown in Scheme 9. An initial solution of **20** in DCM is prepared to which is added an aqueous solution of TEMPO and NaBr to give Mixture C. An aqueous solution of $NaHCO_3$/NaOCl is then added to the mixture, and work up gives **21** as an oil.

Scheme 9



Advantages

This process is more suitable for large-scale production of the lipophilic camptothecins than were previous procedures.

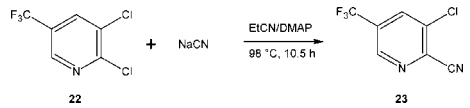
Patent No. U.S. 6,699,993

Assignee: Bayer CropScience UK, Cambridge, United Kingdom

Title or Subject: Process for Preparation of 2-Cyanopyridines

The title compounds such as **23** are used in the production of pesticides and pharmaceuticals. They are prepared by a number of methods that typically start by displacing Br of F groups to introduce the 2-cyano group into the pyridine moiety. Many such processes are said to use heavy metal reagents containing Cu or Ni. However, such processes produce toxic effluents and give low yields; hence, there is a need for an improved manufacturing process. The process disclosed here starts from 2-Cl substituents such as **22** and uses NaCN or KCN as sources of the CN group. The process uses DMAP as an activating agent, and the reaction is carried out in EtCN as shown in Scheme 10.

Scheme 10



It is necessary to use equimolar amounts of DMAP when a 2-Cl group is displaced, but it is possible to use 2-F or 2-Br substrates, and with a 2-F group only about 20% as much DMAP is needed. However, it is pointed out that the DMAP can be recycled so that the reagent in this respect behaves as a catalyst.

Advantages

The process uses cheaper starting materials than alternative routes and gives an improved yield of products with less effluent disposal problems.

Patent No. U.S. 6,699,997 and U.S. 6,710,184

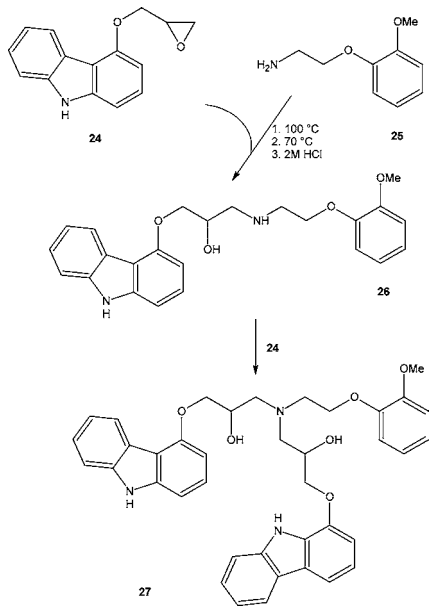
Assignee: Teva Pharmaceutical Industries Ltd., Petah Tiqva, Israel

Title or Subject: Processes for the Preparation of Crystalline Forms of Carvedilol

Carvedilol **26** is used as a racemic mixture in the treatment of congestive heart failure and hypertension. **26** was initially isolated as two polymorphs (I and II) and these patents disclose four new polymorphs (III, IV, V, and VI) and a new method of preparation as well as novel hydrated and solvated forms of the drug.

The process uses the same substrates as the original preparation and is shown in Scheme 11. The original route is said to give low yields because of the formation of **27** by reaction of **26** with more **24**. There have been suggestions to reduce the formation of **27** by using protecting groups in **25**; however, the strategy used in this patent is to use up to a 6-fold excess of **25** over **24**. The reaction is carried out without solvent by adding **24** to **25** that is at 100 °C. After cooling to 70 °C and adding H_2O and EtOAc, 2 M HCl is added to give the hydrated HCl salt of **26**. This salt is isolated and converted to **26** by treatment with Na_2CO_3 and the free **26** can be recrystallised from MeOH or *i*-PrOH. The crystalline **26** formed from this procedure can then be used to prepare the existing and new polymorphs. The patent does not mention if the excess **25** is recovered and reused or simply lost in the workup.

Scheme 11



The first patent describes three new polymorphs designated Forms III, IV, and V that are obtained by controlled crystallisation of **26** by using different solvents and cosolvents and by changing the temperature. The second patent discloses Form VI which is obtained from Form II by cooling a EtOAc solution of **26** with vigorous agitation. Form VI can be partially converted to Form II by heating at 55 °C in a vacuum tray oven; after storing this mixture at room temperature for four weeks, Form I was also found. The new hydrated form of **26** contains about 2% water, and the solvated form of **26** contains about 14% of MEK. Form II can be crystallised from a wide range of solvents or solvent mixtures. Examples of such mixtures are Me_2CO, DCM, or THF with hexane or cyclohexane. Form III is obtained by precipitation from an alcohol, pyridine, or dioxane using water, and Form IV is precipitated from MEK by cyclohexane. Form V can be obtained by precipitation from MEK with hexane or by cooling a MEK solution. X-ray diffraction and thermogravimetric data are given for the new polymorphs.

Advantages

The new process for **26** gives improved yields without producing the undesirable impurity that alternative methods gave. The patents also show that there are new polymorphs and provide procedures for their formation.

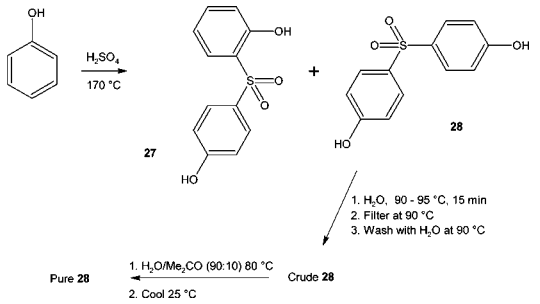
Patent No. U.S. 6,700,020

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Semi-Continuous Method For Producing 4,4′-Dihydroxydiphenyl Sulphone

The title compound is also known as bisphenol-S **28**, and has a variety of uses such as in electroplating, resin manufacture, and as a leather tanning agent. It is especially useful in production of polymers for fibres and plastics. The preparation of **28** can give significant effluents from the phenol that is used in the manufacturing process and the production of high purity **28** can be difficult. The route to **28** is shown in Scheme 12, and a particular problem is the removal of the 2,4′-isomer **27**. Problems may also occur by formation of trisubstituted materials.

Scheme 12



This new process overcomes such difficulties by using a semi-continuous process that removes the product and prevents further substitution reactions from taking place. The reaction is carried out by metering concentrated H_2SO_4 into the reactor containing PhOH at around 170 °C, and the water formed in the reaction is removed azeotropically with PhOH. The reaction mixture is further heated to ensure isomerisation of **27** to **28**, and then the solid is suspended in hot water that has been recovered from the initial step. The crude material is then recrystallised from a water/Me_2CO mixture at 80 °C. The liquors are recycled to the preparative step, and it is claimed that after 10 cycles the final product obtained has a purity of 99.7% with an overall yield of 92% based on PhOH.

Advantages

The process gives high-purity product without excessive effluent disposal problems.

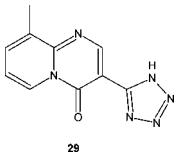
Patent No. U.S. 6,703,505

Assignee: Dinamite Dipharma S.p.A., Basiliano, Italy

Title or Subject: Process for the Preparation of High Purity Pemirolast

The K salt of the title compound **29** is an antiallergenic pharmaceutical product that is not particularly soluble so that it is difficult to purify. This patent describes a procedure for purifying **29** via formation of an amine salt that can be recovered in high purity and then decomposed to give **29**. The procedure is to suspend crude **29** in a 2:1 mixture of MeOH and water and heat at 50 °C. An aqueous solution of an amine such as $MeNH_2$ is then added; after heating to 70 °C, HCO_2H is added. The crystalline **29** is obtained in 92% yield after cooling to 20 °C and found to have a purity > 99.8% by HPLC. The K salt of **29** can be formed by adding an aqueous KOH solution to a suspension of **29** in MeOH followed by cooling to 20 °C.

Compound 29



29

Advantages

The process provides a simple method of obtaining the product in high purity.

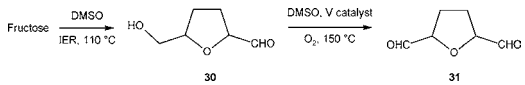
Patent No. U.S. 6,706,900

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

Title or Subject: One Pot Process for Preparing 2,5-Diformylfuran from Carbohydrates

The title compound **31** can be used to make polypinacols and is also a useful intermediate for antifungal agents, drugs, and ligands. It is said that the only industrial process for producing **31** is by selective oxidation of **30**. No details of this process are given, but mention is made of using CrO_3, $K_2Cr_2O_7$, H_2O_2, or N_2O_4 as well as O_2 with a Pt/C catalyst. The process disclosed here is the direct oxidation of fructose using an oxidised V catalyst. The process is shown in Scheme 13 and proceeds via the initial formation of **30**. The fructose is dissolved in DMSO containing a cationic ion-exchange resin (C-IER), and the mixture is heated to 110 °C for 5 h. After this time the catalyst (e.g., $VOPO_4 \cdot 0.5H_2O$) is added to the solution, and oxidation to **31** takes place when air is bubbled through the mixture at 150 °C for 13.5 h.

Scheme 13



The mixture is extracted with DCM, and a 41% yield of crude **31** is obtained. A similar yield of **31** was obtained using V_2O_5 as catalyst, and the direct oxidation of **30** was also carried out using various V catalysts. The oxidation of fructose using $Me_2NCONMe_2$ as solvent is reported, but this gave a yield of **31** of only 32%.

Advantages

The use of fructose provides potentially a much cheaper route to this useful intermediate because fructose is more readily available than **30**.

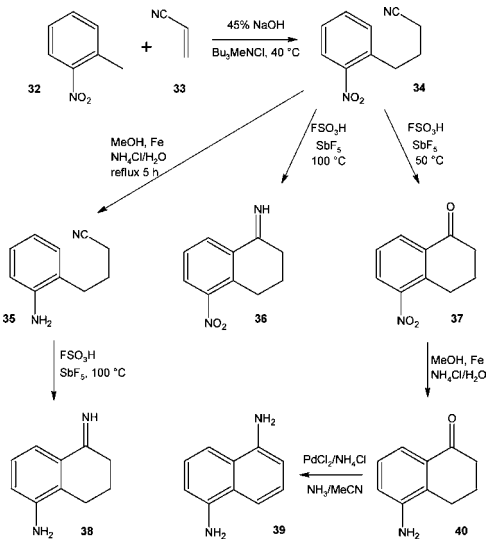
Patent No. U.S. 6,706,924

Assignee: Bayer AG, Leverkusen, Germany

Title or Subject: Process for the Production of 1,5-Diaminonaphthalene

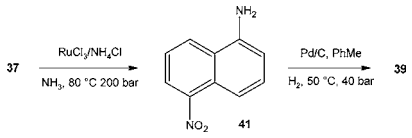
This patent describes a process for making the title compound **39** and also a range of compounds that are intermediates in the formation of **39**. There are various processes for the preparation of **39**, and many start from a substituted naphthalene; these invariably produce a range of isomers that are difficult to separate. The route in this patent is shown in Scheme 14 and starts from **32** which, in the presence of a base, reacts with acrylonitrile **33** to give **34**. This compound can be converted to a range of intermediates and eventually to **39** as shown in Scheme 14. The scheme is a very much simplified version of the possible reactions that are described in the patent. Several more conversions of intermediates are discussed, and these are not shown since experimental details are not provided.

Scheme 14



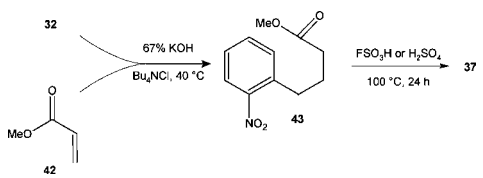
The patent also describes the preparation of **39** by hydrogenation of **41** which is produced by amination of the ketone **37** as shown in Scheme 15.

Scheme 15



A further useful intermediate is the butyrate ester **43** which can be prepared in a manner similar to **34** by reaction of **32** with methyl acrylate **41**. **43** can then be used to prepare **37** by using either FSO_3H or 98% H_2SO_4 as shown in Scheme 16.

Scheme 16



Advantages

This patent provides a relatively simple procedure for preparing a wide range of useful intermediates.

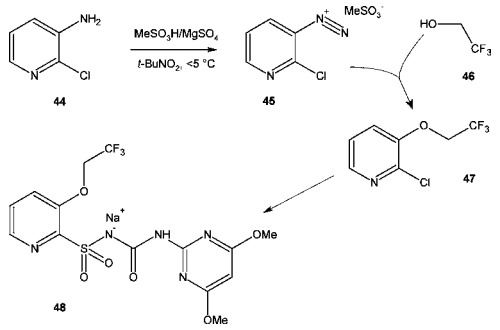
Patent No. U.S. 6,710,180

Assignee: Syngenta Participations AG, Basel, Switzerland

Title or Subject: Diazonium Salts as Intermediates in the Preparation of 3-Trifluoroethoxypyridines

The patent describes the preparation of the pyridine derivative **47** which is useful in the synthesis of pyridylsulphonylurea herbicides such as **48**. The route to **47** is via the diazotisation of 3-aminopyridines such as **44** under anhydrous conditions to give a salt such as **45**, and it is these salts that are the subject of the claims of the patent. The reaction of the salt **45** with **46** takes place in a strong acid solvent such as $MeSO_3H$ or TFA containing $MgSO_4$, and this gives **47** in >70% yield (Scheme 17). The $MgSO_4$ is described as an addition salt that presumably acts as a dehydrating agent to maintain the anhydrous conditions.

Scheme 17



The patent claims that the reaction of halogenated alcohols such as **46** is novel since aryl diazonium salts such as ArN_2^+ usually react with alcohols to form the ArH species, whereas in this process the alcohol reacts to give the alkoxy derivative. The reaction was also successfully applied to 2-bromo and 2-isopropyl analogues of **44** to produce the corresponding alkoxy compounds.

Advantages

The process provides a novel route for the production of diazonium pyridine salts in high yields from readily available reagents.

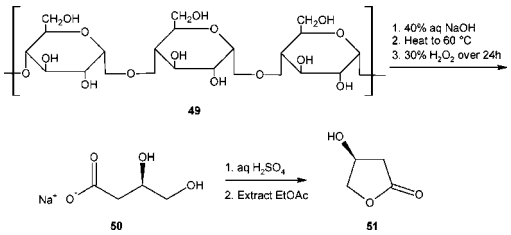
Patent No. U.S. 6,713,290

Assignee: Samsung Fine Chemicals Co. Ltd., Daejeon, Korea

Title or Subject: Process for Preparing Optically Active Pure (S)-3-Hydroxy-γ-butyrolactone

This and the next patent disclose similar processes for preparing **51** from a carbohydrate source. **51** is used as an intermediate to produce chiral pharmaceutical compounds and agrochemicals. The process described in this patent is related to an earlier one from the same company (U.S. Patent 6,251,642) which has been reviewed (*Org. Process Res. Dev.* **2001**, *5*, 557). The current route to **51** is shown in Scheme 18 and starts from starch which is converted enzymatically to α-1,4-linked oligosaccharide **49**. This is then oxidised in basic H_2O_2 to give the Na salt **50** that upon acidification gives **51**. The oxidation of **49** to **50** uses a method similar to that in the earlier patent, and the major difference between the two patents is the feedstock used for the formation of **49**. The conversion of the starch to **49** avoids the oxidation of starch.

Scheme 18



The formation of **49** is from starch and is carried out in a series of steps that are summarised as follows:

1. Dried starch is heated in water at 55 °C and α-amylase added.

2. Heat to 85 °C for 2 h with stirring.

3. Adjust pH to 3.5 using dilute HCl and heat for 1 h to deactivate α-amylase.

4. Cool to 30 °C and adjust to pH 5 with HOAc.

5. Heat to 60 °C, add pullulanase, and stir 22 h.

The pullulanase used in step 5 was Promozyme, EC 3.2.1.4 from *Bacillus acidopullulyticus* supplied by Novo Nordisk. At this stage a solution containing **49** is obtained, and this is then oxidised to **50**. The patent claims cover the use of oxidants other than H_2O_2 such as Bu^tOOH and metal peroxides, but no experimental details are given. The patent describes experiments carried out producing kilogram quantities of **51**, indicating the advanced stage of development.

Advantages

This patent claims overall yields for production of **51** via **49** of 57% based on the amount of starch used. This compares very favourably (22−27%) with experiments that attempted to convert starch directly to **51**, and the low yield is due to facile oxidation of the starch which is prevented by its conversion to the intermediate **49**.

Patent No. U.S. 6,713,639

Assignee: Council of Scientific and Industrial Research, New Delhi, India

Title or Subject: Process for Preparing Enantiomerically Pure (S)-3-Hydroxy-γ-butyrolactone

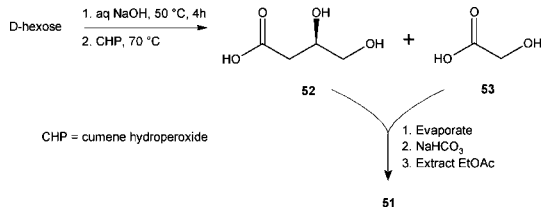
This patent uses the same approach to preparing **51** from carbohydrate sources by first forming an intermediate α- or β-1,4-linked oligosaccharide **49**. The carbohydrates used are D-hexose sources such as maltose or maltodextrin. The process described here consists of the following two steps that give a solution containing a mixture of **52** and **53** as shown in Scheme 19:

1. Dissolve D-hexose in aqueous NaOH and heat to 50 ° for up to 4 h.

2. Add an oxidising agent such as cumene hydroperoxide or Bu^{t}OOH and heat to 70 °C.

After this, the solution is cooled and acidified to pH 1 with HCl. Evaporation of the solution under vacuum at 60 °C removes the water and **53**, leaving an oil. **51** is obtained from this oil by extraction with EtOAc after neutralisation with solid $NaHCO_3$ in yields of up to 56%, depending on the source of D-hexose.

Scheme 19



Advantages

The patent starts from a cheap source of feedstock, and it is claimed that the process is a practical method of making **51**. However, the details only describe the production of about 100 mg compared to the kilogram amounts in the previous patent.

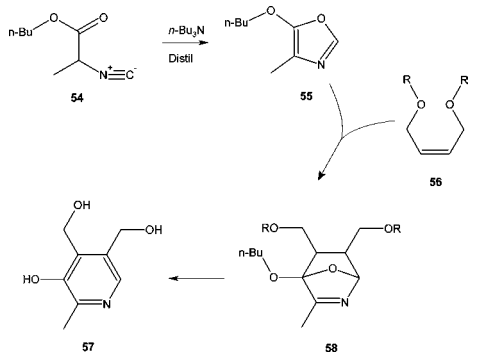
Patent No. U.S. 6,713,630

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Continuous Preparation of 5-Alkoxy-Substituted Oxazoles

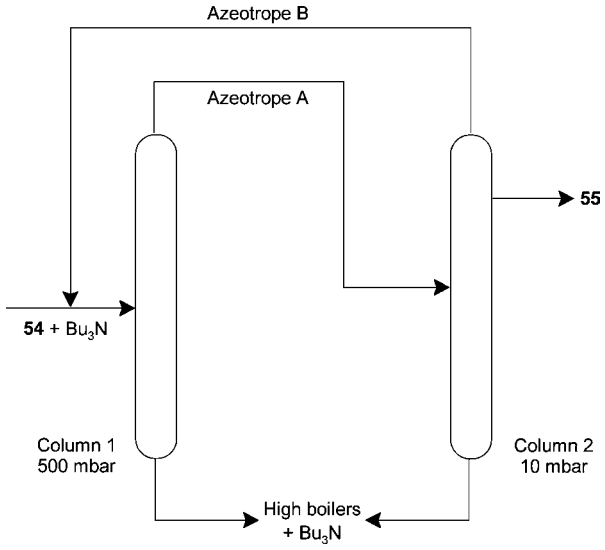
The patent is specifically aimed at the preparation of **55** which is used in the industrial manufacture of pyridoxine (vitamin B_6) **57**. The production of **55** is by the base-catalyzed cyclisation of **54** (Scheme 20). Bu_3N is the preferred base although examples using other amines such as tris(2-ethylhexyl)amine are provided.

Scheme 20



The process is carried out in a distillation column or in a tubular reactor connected to a distillation column. The patent specifically mentions in the claims that the process must be carried out in a tubular reactor that has a Bodenstein Number > 50. This is essentially a measure of the residence time and is related to the reactor diameter and fluid velocity. The use of Bu_3N gives a minimum boiling azeotrope of **55** and Bu_3N whose composition varies with the operating pressure in the distillation column. Figure 1 shows the arrangement for distilling a reaction mixture that is fed first to column 1. The pressure at the top of column 1 is 500 mbar, and azeotrope A, containing 90 wt % of **55**, is taken off overhead at 158 °C. This azeotrope is then passed to column 2 operating at a top pressure of 10 mbar so that azeotrope B, containing 70 wt % of **55**, is distilled overhead at 98 °C. **55** with a purity of 99.8% is obtained from a side stream, and azeotrope B is recycled to column 1 for high overall conversion to be achieved. The use of two columns at different pressures is a fairly common procedure that is used commercially for splitting azeotropes. One example is obtaining pure THF and water from the THF/water azeotrope.

Figure 1. Separation of azeotropes by variable pressure distillation.



This patent also proposes that the production of **57** can be made by the route shown in Scheme 20. There are no experimental details for any of the steps, but the reaction of **55** with the protected diol **56** gives the Diels−Alder adduct **58**. It is suggested that **58** can be converted to **57** by acid treatment and deprotection.

Advantages

The novelty of the process lies in the continuous operating procedure that improves the overall yield and purity of the product.

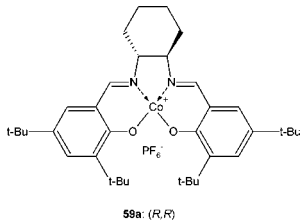
Patent No. U.S. 6,720,434

Assignee: RSTECH Co., Ltd., Daejeon, Korea

Title or Subject: Process for Preparing Chiral Epoxides and 1,2-Diols Using Salen Cobalt Catalysts

This and the next patent cover the use of salen catalysts for preparing chiral products. The current patent describes the preparation and use of Co catalysts such as **59a** for the preparation of a chiral epoxides from a chlorohydrin or for the preparation of a chiral 1,2-diol by hydrolysis of an epoxide.

Compound 59

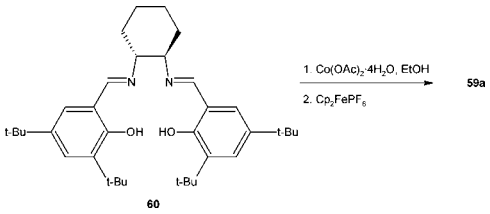


59a: (*R*,*R*)

The main feature of **59a** is that the counterion is nonnucleophilic and PF_6^- or BF_4^- are preferred. It is claimed that using nucleophilic ions such as OAc^- or Cl^- leads to deactivation of the catalyst, and hence an activation procedure is needed when using such catalysts. In contrast catalysts containing PF_6^- or BF_4^- remain active, and no reactivation is required.

The preparation of **59a** is shown in Scheme 21 and carried out by reaction between the salen compound **60a** and Co-$(OAc)_2$ followed by treatment with Cp_2FePF_6. ^{31}P NMR and IR data are given for **59a** and for the analogous compounds that are also prepared. By choosing the salen compound with the appropriate configuration, it is possible to make a range of catalysts with the same configuration.

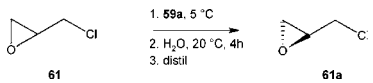
Scheme 21



60

The chiral salen catalysts are used to prepare chiral compounds as shown in Scheme 22. For example (*S*)-epichlorohydrin **61a** is obtained by treating the racemic **61** with **59a** at 5 °C. After adding water and stirring at 20 °C for 4 h, **61a** is obtained with over 99% ee by fractional distillation. The residue is extracted to recover **59a** that is used for another experiment, and no deactivation is noted. The enantiomers of styrene oxide and 1,2-epoxyhexane are similarly obtained. The catalysts are also used in the stereospecific hydrolysis of racemic epoxides such as 1,2-epoxybutane to give the corresponding 1,2-diol.

Scheme 22



61 **61a**

Advantages

The catalysts are produced in a fairly simple manner and retain their activity so that no activation process is needed before the catalysts can be reused.

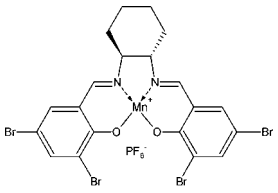
Patent No. U.S. 6,723,879

Assignee: Japan Science and Technology Corporation, Saitama-Ken, Japan

Title or Subject: Process for the Enantioselective Preparation of Amines Using Salen Manganese Catalysts

This patent uses Mn salen compounds such as **62** as catalysts in the asymmetric amination of allylic or benzylic C−H bonds to give the amine. This is claimed to be the first attempt at using Mn salen complexes in this reaction. The amination agent used is the iminoaryliodinane **63**, and the main feature of the catalysts is that they should have electron-withdrawing groups such as a bromine atom.

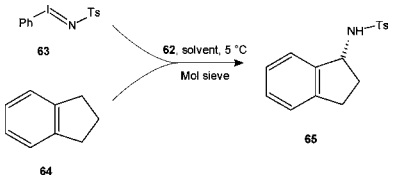
Compound 62



62

Scheme 23 shows that indane **64** is converted to **65** in 74% yield with 54% ee by carrying out the reaction with **63** in $(CHCl_2)_2$ in the presence of molecular sieves as the dehydrating agent. Other solvents were used, but unfortunately it seems that halogenated solvents are preferred. The ee is improved by reducing the temperature, but obviously the reaction time increases. The time increases from 3 h at 5 °C to 12 h at −24 °C, the yield falls to 72%, and the ee rises to 61%. A range of other substrates is also examined including cyclohexene, cycloheptene, and tetralins, but the preparation of the catalysts is not described, and this may be the subject of another patent.

Scheme 23



Advantages

The patent provides a novel asymmetric amination process for converting allylic or benzylic C−H bonds.

Patent No. U.S. 6,720,454

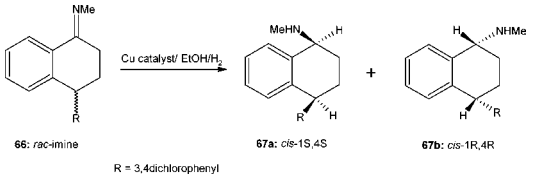
Assignee: Ciba Specialty Chemicals Corporation, Tarrytown, New York, U.S.A.

Title or Subject: Process for Cis-Selective Catalytic Hydrogenation of Cyclohexylidenamines

The specific subject of this patent is sertraline **67** which is used in the hydrochloride form and known as the antidepressant Zoloft or Lustral. **67** was originally disclosed by Pfizer in 1985 and is currently of great interest because

of the expiration of the original patents. The process described in this patent is the catalytic hydrogenation of the imine **66**, and this has been examined in several patents, one of which has been reviewed previously (*Org. Process Res. Dev.* **2003**, *7*, 459). The catalysts previously used include Pd/C and Raney Ni, and since this hydrogenation step usually starts from the racemic imine, a mixture of four products is obtained. The cis isomers are the most desirable, and hence the objective is to increase the cis/trans ratio in this step. It is disclosed in this patent that copper-containing catalysts in the presence of a protic solvent such as EtOH give >95% of the cis isomers as shown in Scheme 24.

Scheme 24



The catalyst used in the examples is a Ba-promoted copper chromite although other types are claimed to be suitable. The reaction can also be carried out using the ketones and MeNHOH to introduce a N → O group which forms the imine as an intermediate when hydrogenated, but no experimental details are given.

Advantages

The process gives very high yields of the cis isomer, and it is claimed that under favourable conditions there is very little trans so that it does not have to be removed.

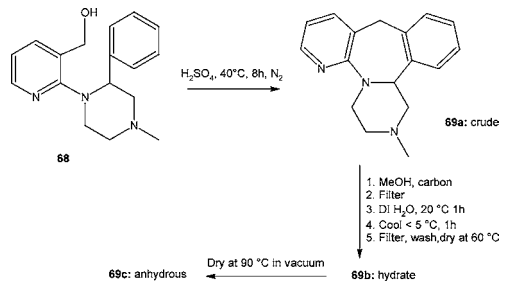
Patent No. U.S. 6,723,845

Assignee: Sumika Fine Chemicals Co., Ltd., Osaka, Japan

Title or Subject: Process for Preparing Anhydrous Mirtazapine Crystals

Mitrazapine **69** is used as an antidepressant, and it is said that it is difficult to purify by crystallisation because the crystals are often obtained in an oily state. Additionally the crystals have hygroscopic properties and need to be stored under dry conditions. This patent describes a process for producing high-purity **69** from the crude form and also a method for obtaining the anhydrous form that has low hygroscopic properties. The main focus and claims of the patent relate to the purification of **69** and to the production of an anhydrous form. However, there are examples of preparing the crude material **69a** by the dehydration and cyclisation of **68** using concentrated H_2SO_4. One example uses almost 1.5 kg of **68**, and the method is based on that described in U.S. Patent 4,062,848 (Scheme 25). After workup an 85% yield of **69a** with a purity of 99% is obtained by crystallisation from toluene/heptane.

Scheme 25



The crude **69a** is used to prepare hydrated and anhydrous forms by the procedures outlined in Scheme 25. For example, the hydrate **69b** is obtained in 97.1% yield by crystallisation from MeOH. The purified **69b** is then converted to the anhydrous form **69c** after first drying by heating and then pulverising **69b** to achieve an average particle diameter of20−60 μm. After 500 h the **69c** produced by this method is found to have a relatively low hygroscopic degree when compared with material produced by a method described in U.S. Patent 4,062,848. An example of preparing both **69b** and **69c** starts with 84 kg of **69a**, and hence the process is presumably being carried out on commercial basis. The patent gives X-ray crystal data for the various forms of **69** including bond angles and lengths.

Advantages

The patent provides a commercially useful method of manufacturing pure crystalline forms of the drug substance.

Patent No. U.S. 6,723,856

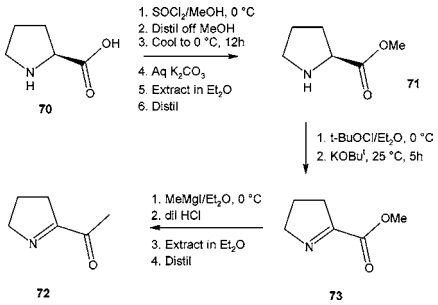
Assignee: Council of Scientific and Industrial Research, New Delhi, India

Title or Subject: Process of the Preparation of 2-Acetyl-1-pyrrolline, the Basmati Rice Flavourant

Scented or flavoured varieties of rice are highly valued, and this patent describes a synthetic route to **72** which is the principle aroma component of basmati rice and can be used as a flavour agent in food products. There are several other methods available for the preparation of **72**, but it is claimed that they suffer from a number of drawbacks such as the use of expensive catalysts (Rh) and toxic reagents (KCN), being very slow,and having several stages. This patent claims to overcome these problems and to produce high-quality product.

The route is shown in Scheme 26 and starts from L-proline **70** which is converted to **71** by reaction with MeOH and $SOCl_2$. Reaction of **71** is with Bu^tOCl followed by $KOBu^t$ to give **73**. This is the method described in the examples, and the claims cover the use of KOAc for this reaction although no experimental evidence is provided. The final stage is reaction of **73** with the Grignard reagent MeMgI to give **72** which is purified by distillation.

Scheme 26



Advantages

The new route starts from a readily available reagent and gives fewer problems than alternative routes.

Patent No. U.S. 6,727,367

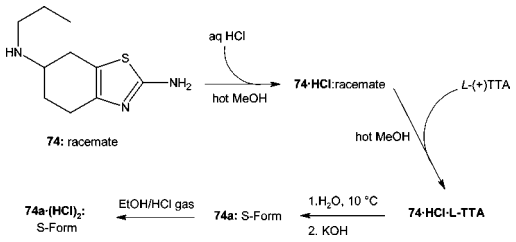
Assignee: Synthon BV, Nijmegen, thr Netherlands

Title or Subject: Process and Compounds for Resolution of 2-Amino-6-propylamino-4,5,6,7-tetrahydrobenzthiazole

The title compound **74** and other tetrahydrobenzthiazoles are thought to be useful in treating schizophrenia, Parkinsonism, and hypertension. The drug is supplied and used as the dihydrochloride salt of the *S*-form **74a** and is commonly known as pramipexole. The usual preparation of **74** gives a racemic mixture, and hence a resolution step is necessary. Such methods are said to be uneconomic, and there is a reference to an enantioselective synthesis. However, it is claimed that this does not give high enough ee, and so there is still a need for an improved resolution procedure.

The method developed is based on the formation of a mixed salt with tartaric acid derivatives followed by fractional crystallisation. The patent gives examples of forming both the D- and L-tartrate salts using tartaric acid and dibenzoyl or ditoluyl tartaric acids. The procedure is summarised in Scheme 27. The first step is formation of the racemic mixture of the monohydrochloride salt **74**·HCl. This is then reacted with L-tartaric acid (L-TTA) in hot MeOH to give the mixed salt **74**·HCl·**L-TTA**. The free *S*-form is then liberated as the free base by adding KOH, and in the final stage reaction with gaseous HCl in EtOH forms **74a**. Optical purity in terms of ee of the product is not given, but instead the value of [α] in MeOH is provided. Examples are also described in which a mesyl/tartrate mixed salt is formed in place of the chloride. The patent gives no experimental details as to whether the undesired enantiomer can be recycled.

Scheme 27



Advantages

The procedure described is fairly straightforward, but it does not indicate if the *R*-isomer can be recovered and recycled to improve the overall atom yield.

Keith Turner

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