Organic Process Research & Development **2007,** *11,* 802–812

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published During April and May 2007

Summary

This latest review of U.S. patents contains 21 from an initial set of 264 that fitted the search criteria. Previously the majority of the patents chosen have been selected by the editor, but as an experiment all of the current patents were selected by the reviewer. Hence even though readers may notice a difference in the focus of the subjects of the patents that have been chosen, it is hoped there are still some of interest. A new process is reported for the insecticide gemifloxacin using an intensive mixing method that has the capability of dramatically improving productivity. Another patent on insecticides describes some novel malonic ester intermediates that are used to prepare indanecarboxylates, intermediates used to prepare insecticides. Treatments for coronary diseases feature; one patent reports a range of novel diphenylazetidinones for treating high levels of cholesterol, while another reports on a new process for preparing the angina drug amlodipine. A third reports on two new processes for making perindopril, an inhibitor of angiotensin-converting enzymes used in cardiovascular treatments. Novel indazole compounds are reported for treating neurological diseases and the production of cabergoline for the treatment of Parkinsonism is reported, while another describes a range of isoquinolinyl indoles for treating dementia. Diabetes is the subject of two patents, with one providing very extensive details for preparing some novel phenoxazines. The other patent reports on benzotriazoles that are useful in treating non-insulin-dependent diabetes. Cancer treatments are understandably widely studied, and a range of tetrahydropyrimidines has been found to assist apoptosis by crossing cell membranes in a manner similar to ceramides. Another patent describes over 150 compounds that are intermediates or potential topisomerase-targeting agents and hence of use in cancer treatments. Novel pyrrolidines have been found that are said to be useful for treating asthma without the side effects associated with other drugs. An improvement in the bioavailability of the COX-2 inhibitor celecoxib by the manufacturers is described. This is made possible by producing an amorphous form of the drug in a simple procedure, but whether it is in use is not known. A novel method of producing tadalafil, for treating erectile dysfunction, is described. The new method reduces significantly the processing time and avoids the use of corrosive reagents. Moving away from pharmaceuticals, there is a process for producing fluorinated diols used in making advanced photoresist materials. Light-emitting diodes are important in many electronic devices, and a new process of preparing benzothiadiazoles is described that uses reagents less hazardous than alternative methods. The Kumada coupling reaction is a very widely used reaction, and it has been applied to an improved synthesis of 3-alkylthiophenes by simply changing the solvent. Also on the subject of 3-substituted thiophenes is a patent that describes how 3-halothiophenes can be produced by isomerisation of the readily available and cheaper 2-isomer. There is no legal or commercial significance in the choice of patents, although some do describe experiments on moderate to large scale. This may suggest advanced development or commercial activity. In fact the newly described process for gemifloxacin is suggested as being capable of being used to produce 1500 kg per week of the product. The advantages described in this review are those claimed in the patent unless this reviewer has personal knowledge of the subject.

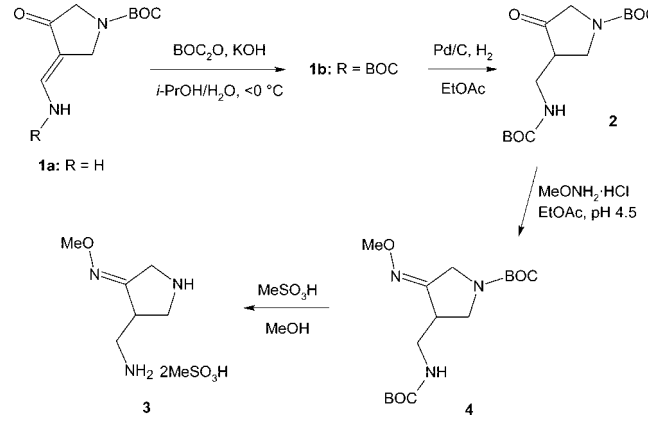
Patent No. U.S. 7,199,242

Assignee: LG Life Sciences Limited, Seoul, South Korea

Title or Subject: Processes for the Production of Gemifloxacin and Intermediates for its Production

Gemifloxacin **6** is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria. A key compound in the synthesis of **6** is **1b** that is produced from the protected amine **1a** in a very rapid and also extremely exothermic reaction (Scheme 1). In order to ensure an efficient

Scheme 1



process, the control of this reaction is very important but quite difficult in batch operation. This patent describes a continuous process for producing **1b** by using mixing devices that promote efficient mass and heat transfer, allowing the reaction to be more easily controlled. The production of **1b** is carried out by separately pumping an aqueous solution of KOH and a solution of **1a** in aqueous *i*-PrOH to a mixing device. The mixer is maintained at −20 °C, and after the reaction takes place the mixture is quenched in a separate step using HOAc. The conversion of **1a** was as high as 98%, and several experiments are described that show the effects of KOH strength and flow rate on the conversion of **1a** and the level of impurities in **1b**. The impurities that are normally found are dimers formed by condensation and isomers of **1a**. The levels of these impurities are found to be an order of magnitude lower than those found in batch processes. A range of different mixing devices was

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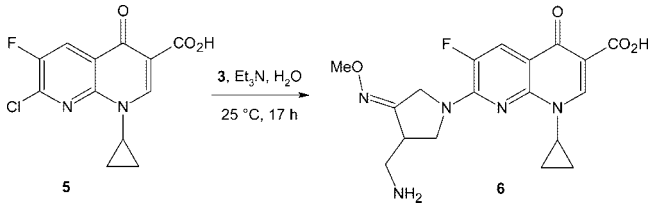
used such as Sulzer, Kenics, vortex, static and Intensified Plug Flow Reactors, and examples are given for each. Some of the mixers are described in detail that may be of interest to chemical engineers. In a series of initial pilot scale experiments it is stated that the tests indicated that production targets of over 500 kg per week would be possible. It is also stated that with minor modifications this figure could be increased to 1500 kg per week. Whether this has been done is not known.

Scheme 1 also summarises the route used to convert **1b** to **3** in a yield of 70%. The salt **3** is then used to produce **6** by reaction with **5** in the presence of Et_3N as shown in Scheme 2.

Scheme 2



The patent also describes the preparation of the anhydrous and sesquihydrate mesyl salts of **6**. The production of **6** was scaled up to a batch of around 100 kg.

Advantages

The modified process gives a better degree of control over the key reaction and enables high productivity of the important intermediate.

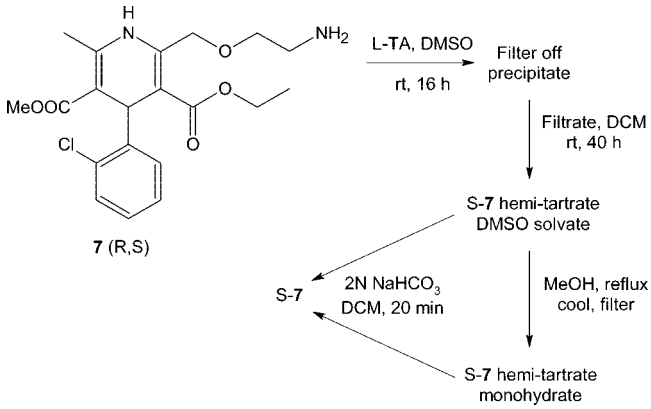
Patent No. U.S. 7,202,365

Assignee: Hamlim Pharmaceutical Co. Ltd., Seoul, South Korea

Title or Subject: Processes for the Preparation of S-(−)-Amlodipine

Amlodipine **7** is an antihypertensive reagent used in controlling angina. The industrial production of **7** gives the enantiomeric mixture that is resolved to give the desired *S*-enantiomer using cinchonidine salts or D-tartaric acid. This patent describes a method of obtaining the *S*-enantiomer using L-tartaric acid (L-TA) that is much cheaper than using D-TA. The process is outlined in Scheme 3, and forms the L-TA salt as DMSO

Scheme 3



solvates that can contain 0.25–1 mol of DMSO. These solvates can be converted to the pure *S*-enantiomer either via the hydrate or directly using $NaHCO_3$ in dichloromethane (DCM). The hydrate salt is prepared by crystallisation from MeOH that presumably must have been wet since no water is added during this step. There is no mention in the patent of racemising the *R*-enantiomer that is precipitated during the formation of the L-TA salt.

Advantages

The process uses a cheaper resolving agent but does not indicate whether the unwanted enantiomers are recovered and reused.

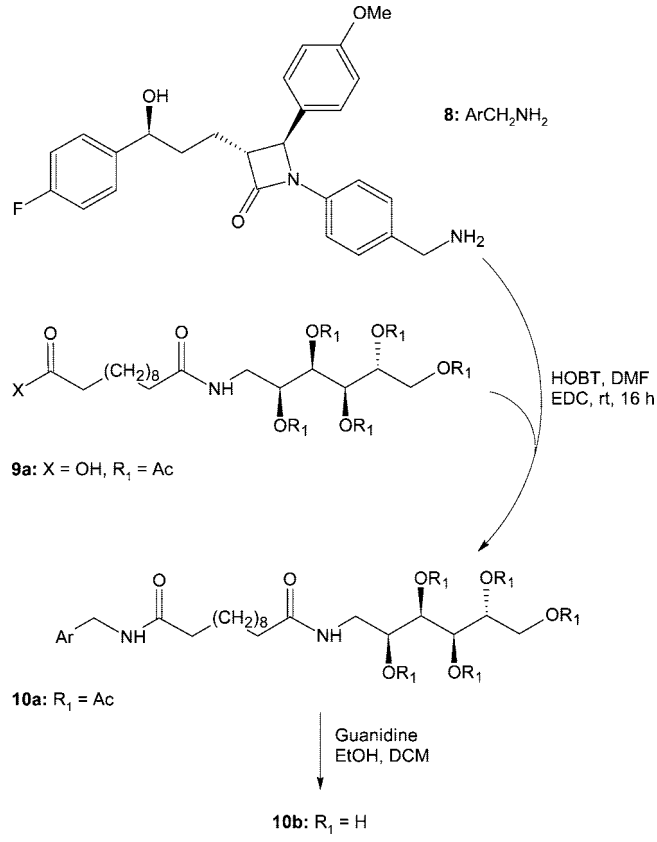
Patent No. U.S. 7,205,290

Assignee: Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany

Title or Subject: Process for Preparing Diphenylazetidinones with Improved Physiological Properties

The novel compound **10b** is claimed to be useful in treating high levels of cholesterol and hence in preventing heart diseases. The patent claims cover the novel compounds **10b** and the intermediate **10a** as well as medicinal uses of **10b**. There are three synthetic routes to **10b** that are disclosed in the patent, and Scheme 4 shows one that involves the use of the

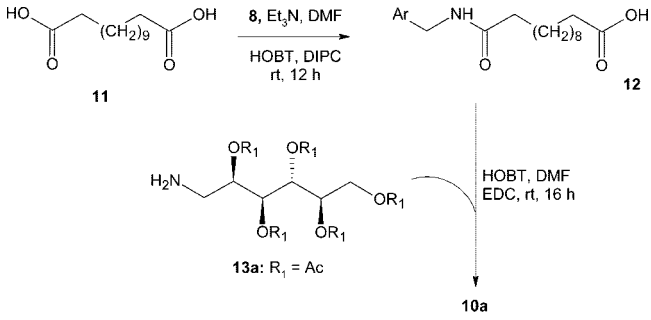
Scheme 4



intermediate **10a**. The procedure begins with a straightforward peptide coupling reaction between the amine **8** and the protected monoglucamide **9a** to form the acetoxy intermediate **10a**. The reaction takes place at room temperature in DMF in the presence of the hydroxybenzotriazole (HOBT) and *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDC). The removal of the acetoxy groups from **10a** using guanidine in DCM and EtOH gives **10b**.

The patent also provides details for the preparation of **10a** from **8** and the acyl chloride **9b** (X = Cl). The third route to **10b**, shown in Scheme 5, starts by reacting **8** with the diacid

Scheme 5



11 in a peptide coupling reaction to give **12**. In the next step **12** reacts with **13a** in HOBT/EDC in another coupling reaction to form **10a**. If this latter reaction is carried out using glucamine **13b** (R = H) then the reaction produces **10b** directly.

The patent also provides details of tests using formulations that include **10b**, and these are said to demonstrate the effectiveness of **10b** in treating a number of coronary diseases as well as insulin resistance.

Advantages

The patent describes a novel molecule for treatment of coronary problems.

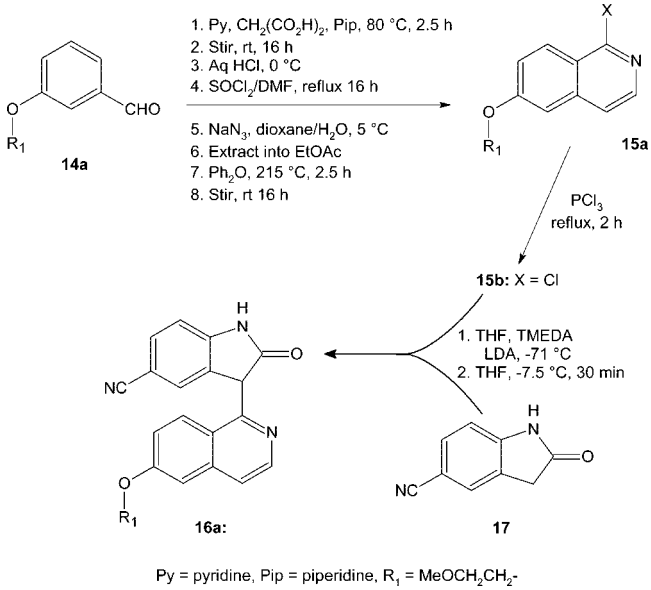
Patent No. U.S. 7,205,314

Assignee: AstraZeneca AB, Sodertalje, Sweden

Title or Subject: Compounds for the Treatment of Dementia

This patent describes a range of novel compounds that are claimed to have potential for the inhibition of glycogen synthase kinase 3 (GSK3). GSK3 is said to be involved in many diseases from hair loss to schizophrenia and dementia, and hence its inhibition is important. The patent claims cover the novel compound **16a** and several intermediates used in the process. Scheme 6 summarises the route used to prepare **16a** starting from the aldehyde **14a**. The first step involves producing **15a**

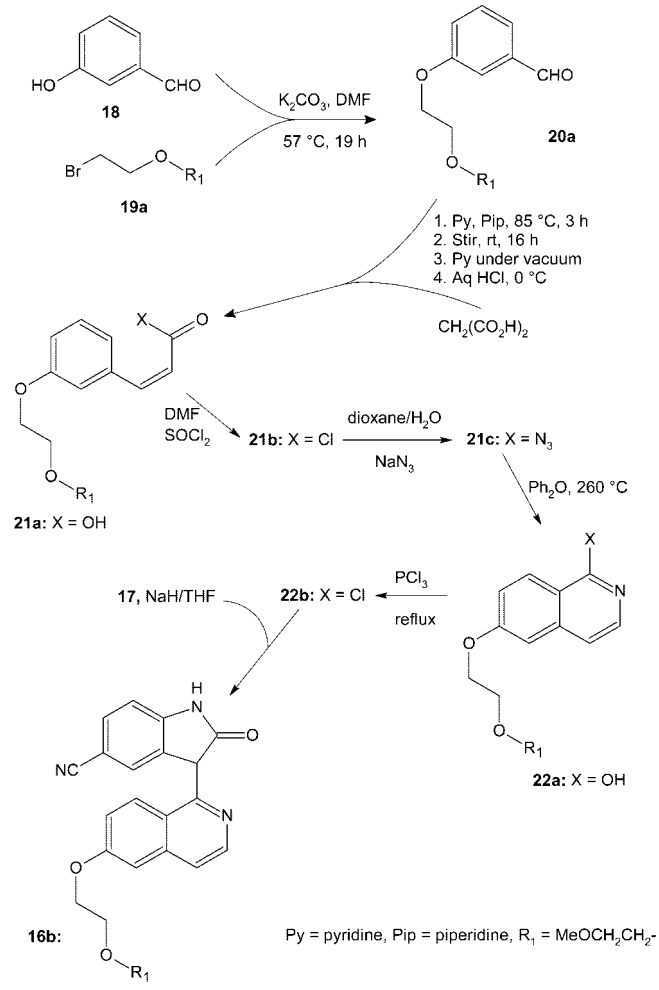
Scheme 6



in a method that requires several stages and a change of solvent from EtOAc to Ph_2O to allow the final high temperature step to be carried out. This series of reactions is carried out in one pot without isolating any of intermediates produced. The final recovered yield of **15a** is 37%. However, it does involve some rather unsavoury materials and may be difficult to scale up for commercial production. The chloro-compound **15b** is then prepared from **15a** and PCl_3 and recovered in 80% yield. In the final step **15b** is reacted with the indole **17** to produce **16a** in a yield of 51%.

Although the various intermediates in the preparation of **16a** are not isolated, there are details of isolating intermediates in the synthesis of compound **16b**. Scheme 7 shows intermediates

Scheme 7



in the synthesis of **21a** and some are isolated in high yields. The alkylation of **18** with the bromo-ether **19** gives **20** that is isolated in 99% yield, and reaction of **20** with malonic acid forms the acrylic acid derivative **21a**, again in 99% yield. The acyl chloride **21b** (X = Cl) produced from **21a** and $SOCl_2$ is not isolated but converted to the acyl azide **21c** ($X = N_3$) that again is not isolated. Cyclisation of **21c** forms **22a** in 37% yield, and this reaction requires a temperature of 260 °C achieved by refluxing Ph_2O. Chlorination of **22a** using PCl_3 gives a 30% yield of **22b**, and this reacts with **17** to give **16b** that is isolated as a TFA salt in 27% yield. ^1H NMR data are given for some

of the compounds. The patent provides some details of pharmaceutical tests using the novel compounds.

The overall yield of the products is quite low and this may be because of the high temperatures needed for the cyclisation reaction. This is unfortunate because the early reaction stages provide excellent product yields.

Advantages

The process gives novel products with wide ranging potential applications.

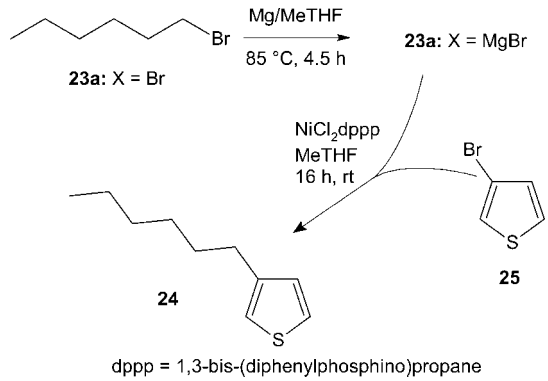
Patent No. U.S. 7,205,414

Assignee: Honeywell International Inc., Morristown, New Jersey, U.S.A

Title or Subject: Process for the Kumada Coupling Reaction

The Kumada coupling reaction is a well-established method for forming carbon-carbon bonds and this patent describes its use in preparing 3-alkylthiophenes. The patent states that if 3-halothiophenes are used in the traditional Kumada reaction in the solvents THF, Et_2O or MTBE, then there are significant quantities of dithienyl side-products that interfere in the main reaction. The problems have been overcome by using 2-methyltetrahydrofuran (MeTHF) as solvent, and this is claimed to be an unexpected finding. In addition the solvent is less prone to peroxide formation than the solvents normally used. Scheme 8 shows the route used to prepare **24** from **25** and the Grignard

Scheme 8



reagent **23a** in MeTHF. In five experiments the conversion of **25** was 100%, and the reaction product was found to contains <1% of the side-products. Experiments with C_{10} *n*-alkyl bromide gave similar performance, and the product contained <2% side-products. The patent also provides details of several comparative experiments using Ni or Pd catalysts and solvents other than MeTHF. These all gave much higher levels of side-products (up to 16%), and in many cases the conversion of **25** was not complete. Apart from the use of MeTHF as solvent, the patent also claims that the concentration of the Grignard reagent must be >0.5 mol/L and the preferred range is 3–3.5 mol/L.

The synthesis of the 3-halothiophenes is not mentioned in this patent, and this topic is covered in a patent later in this review.

Advantages

The process enables the production of high purity products by changing to a better and safer solvent.

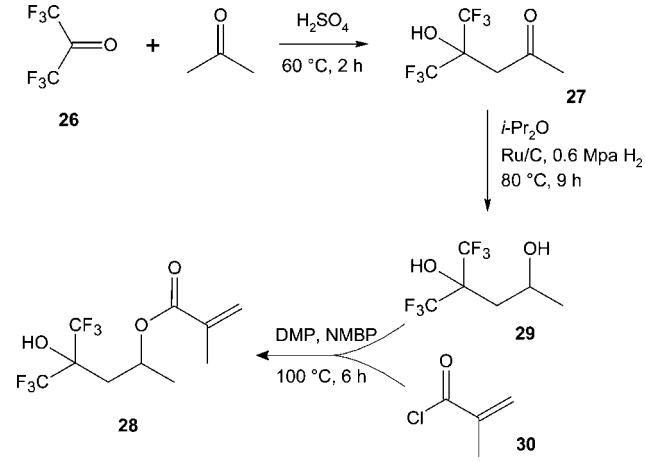
Patent No. U.S. 7,205,443

Assignee: Central Glass Company Limited, Ube-shi, Japan

Title or Subject: Processes for Producing Fluorine-Containing 2,4-Diols and Their Derivatives

The title compounds exemplified by **29** are raw materials used in making an acrylic ester such as **28**, a monomer used in producing advanced polymeric photoresist materials. The production of **29** proceeds via an aldol condensation between **26** and a ketone such as Me_2CO to give the hydroxyketone **27** that is then reduced to the diol **29** (Scheme 9). Previous reports

Scheme 9



from 1972 claim that the condensation reaction can be carried out by heating the two reactants to 160 °C in a sealed reactor and for the reduction step *i*-PrO_3Al is used. The current patent states that such a process requires pressure-proof equipment and is inefficient and unsuitable for industrial production. Additionally a substantial quantity of Al-containing waste would be produced. The improvements claimed are the use of a so-called additive for the condensation step and a catalyst for the reduction reaction.

The preferred additive used in the condensation is H_2SO_4, although BF_3, TFA, TsH and Lewis acids are also used. Fluoroalcohols such as $(CF_3)_2CHOH$ are also used, although the reaction proceeds at a lower rate. The concentration of additive used is <0.2 mol %. For the reduction stage a Ru catalyst is needed, and there are experiments that show that Pt or Pd catalysts are not effective. The production of the acrylate ester **28** is carried out by reaction of the diol **29** with an acrylic derivative such as **30** or an anhydride. The reaction takes place without solvent in the presence of a base and 2,6-dimethylpyridine (DMP) is preferred. A polymerisation inhibitor is also needed and in the experiments NONFLEX MBP (NMBP) is used. The mixture from the condensation step contains about 87% of **27**, and the final recovered yield of **27** is 63%. It is often difficult to achieve high yields in acid-catalysed aldol condensation reactions with Me_2CO, and these yields are very good. In the reduction reaction **29** was recovered in 88% yield, and a 57% yield of **28** was obtained. The reactions were also carried out using ketones other than Me_2CO. Examples are given using cyclohexanone and indanone. Brief ^1H NMR data are given for many products.

Advantages

The process gives a good yield of desired product in the aldol condensation step and this helps in improving the overall process efficiency.

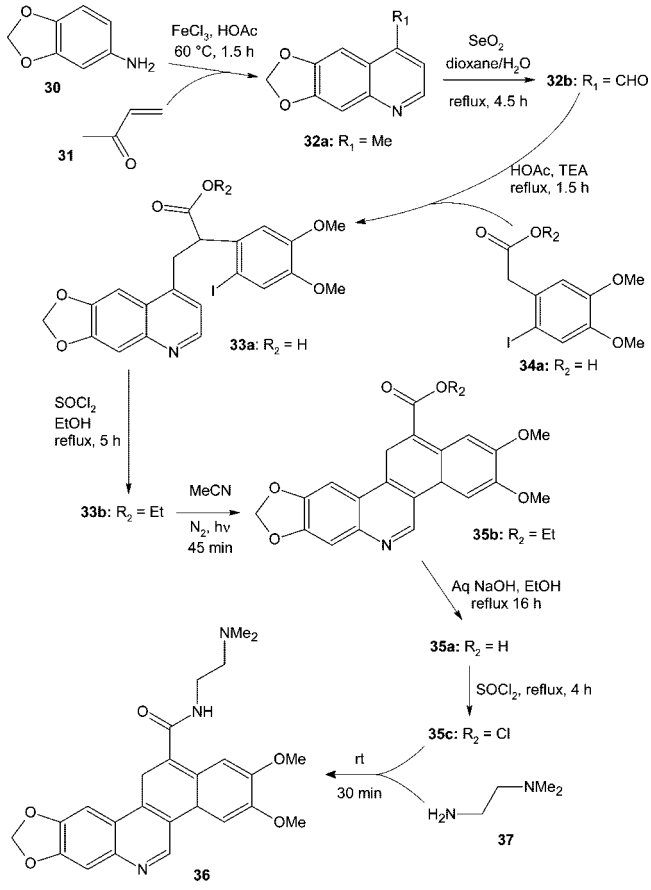
Patent No. U.S. 7,208,492

Assignee: Rutgers, The State University of New Jersey, New Brunswick, New Jersey, U.S.A

Title or Subject: Topoisomerase-Targeting Agent

Topoisomerases (TI) are enzymes that cause modification of DNA strands, and this can result in tumours and other problems in cells. The range of novel compounds described in this patent is of interest in inhibiting TI and therefore in the treatment of cancer. There are two series of molecules described in the patent that are isomers, and representative examples are **36** and **41**. In all there are probably over 150 compounds mentioned in this patent that are novel intermediates or potential drug molecules covered by the patent claims. Hence it is possible to give only a very brief summary of the patent. Scheme 10 summarises the route used to prepare **36**. This begins

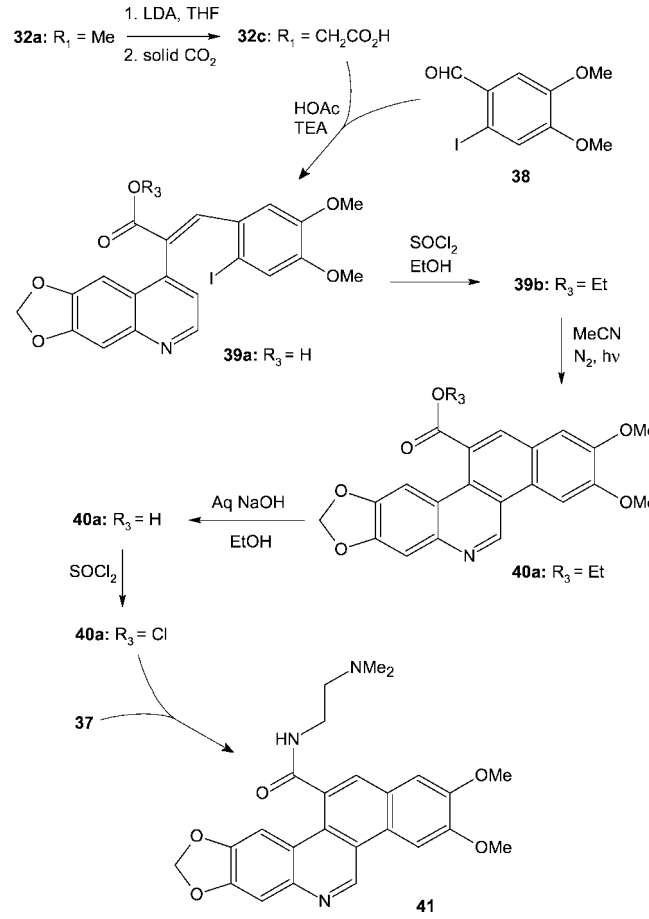
Scheme 10



with the formation of the quinoline **32a** in 44% yield from **30** in a cyclisation reaction with **31** using $FeCl_3$ in HOAc. This is then oxidised to **32b** using SeO_2 in 65% yield. In the next step **32b** reacts with **34a** in HOAc in the presence of TEA to give the acid **33a** in 73% yield. The acid group in **33a** is esterified using $SOCl_2$ and EtOH to give **33b** that is then cyclised to form **35b** in a 51% yield by photolysis in MeCN. The ester group in **35b** is then hydrolysed using NaOH to give **35a** (R_2 = H) that is converted to the acyl chloride **35c** (R_2 = Cl), and finally reaction with **37** gives **36**. This last step is carried out to introduce a group that solubilises the molecule.

The patent also describes a second type of compound, and an example is **41** that is an isomer of **36**. This is synthesised by the series of reactions shown in Scheme 11. As with the synthesis of **36** the starting point is **32a**, but in this case a C

Scheme 11



atom is added and converted to the acid **32c** that reacts with the aldehyde **38** to give **39a**. The cyclisation of **39a** to **40a** and the production of **41** is by the same series of reactions as described for **36**. However, the actual experimental details are not described in detail. ^1H and ^{13}C NMR data are summarised for many of the compounds.

This is a very comprehensive patent and the interested reader should certainly read the patent. However, there are a considerable number of errors that are not merely typographical. As an example the abbreviation Ac_2O is used on schemes, whereas in the examples acetic acid is mentioned. Presumably the R&D chemists will know which reagent was used.

Advantages

The patent provides a large number of intermediates and drug molecules with potential for treating tumours.

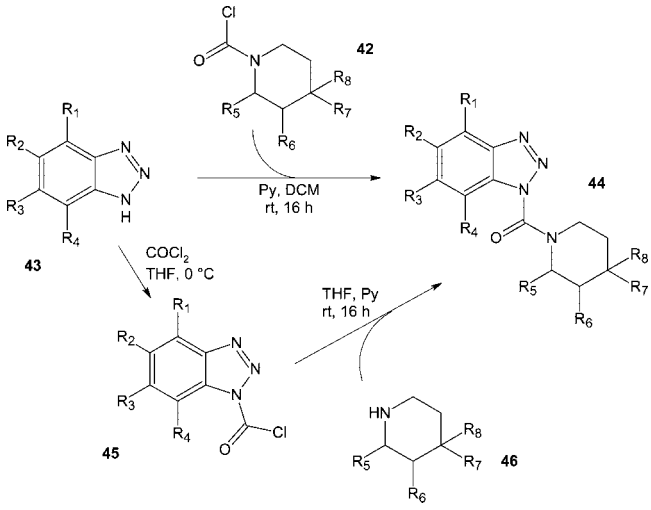
Patent No. U.S. 7,208,504

Assignee: Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany

Title or Subject: Bicyclic Inhibitors of Hormone Sensitive Lipase

The compounds covered by this patent are benzotriazoles, and it is said that surprisingly they have been found to inhibit hormone sensitive lipase. Hence they are of interest in the treatment of non-insulin-dependent (NID) diabetes. This patent lists over 50 specific molecules in the claims, and they are prepared by one of two reactions shown in Scheme 12. The reaction methods used are known, and so the patent claims cover

Scheme 12



the novel molecules and their use to treat NID diabetes. Unfortunately the patent does not state which route is used for making specific products. In the first method the benzotriazole **43** reacts with the carbamoyl chloride **42** in THF in the presence of pyridine (Py). In the second method **43** is converted to the acyl chloride **45**, and this is treated with an amine **46** to give **44**. Both reactions methods take place at room temperature over a 16 h period, but no yields are given. Simple examples of specific compounds with the identities of the substituents R_1 to R_8 are as follows (R groups not specifically mentioned are H):

R_8 = Me, Et, Pr^i, Bu^t, CF_3, Br, Cl or CO_2Me

R_3 = CO_2Me, R_8 = Me

R_2 = PhO or PhS, R_8 = Me

There are other more complex groups, and the interested reader should refer to the patent for details.

Advantages

The patent lists a great many novel and potentially useful compounds and provides two possible methods for making them.

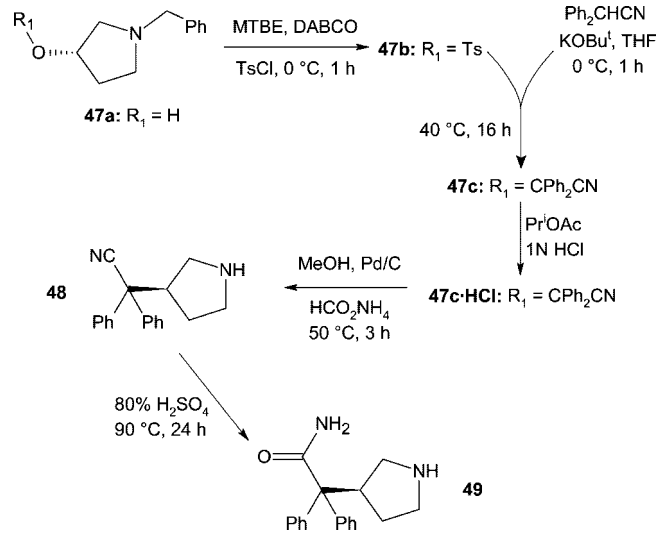
Patent No. U.S. 7,208,515

Assignee: Theravance Inc., South San Francisco, California, U.S.A

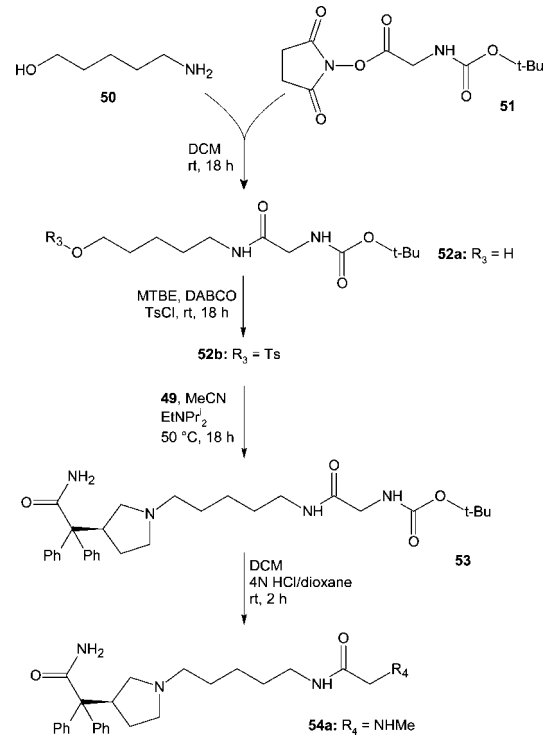
Title or Subject: Diphenylmethyl Compounds Useful as Muscarinic Receptor Antagonists

The compounds described in this patent such as **54a** are used in formulations that are taken by inhalation for treating asthma and other respiratory diseases. It is stated that there is a need for new compounds that produce fewer side effects than current drugs used for the same purpose. The compounds are derivatives of diphenylacetamide containing 3-pyrrolidinyl substituents. Scheme 13 shows the procedure used to prepare the key pyrrolidinyl acetamide **49**. The process begins with the formation of the Ts reagent **47b** that is reacted with the K salt of Ph_2CHCN to form **47c**. These stages each give a yield of >94%. The HCl salt of **47c** is then prepared, although it can be made during the workup of the previous step. Removal of the benzyl group from **47c**·HCl in a H-transfer reaction then produces **48** in >99% yield. In the final stage the amide **49** is produced in 58% yield after acid hydrolysis. **49** is then used to prepare **54a** by the route shown in Scheme 14.

Scheme 13



Scheme 14



The first stage is the reaction of **50** and **51** to give the carbamate ester **52a** (R_3 = H). There is no indication as to how **51** is prepared. The tosylate **52b** is then formed from **52a** and reacted with **49** to give **53** that upon acid hydrolysis produces **54a**. The patent also gives details of several analogues of **54a** that differ in the substituent R_4. Example are given for R_4 = NH_2, NHEt, NHPr^n, NMe_2, $NH(CH_2)_2OMe$, NHBz, cyclopropylNH, cyclobutylNH or cyclopentylNH. The products are often isolated as the Tf_2 salts. Details are also provided on preparing various drug formulations and on testing the efficacy of the compounds.

Advantages

The patent provides a range of novel compounds that have improved performance and few side effects.

Patent No. U.S. 7,208,610

Assignee: Honeywell International Inc., Morristown, New Jersey, U.S.A

Title or Subject: Process for Isomerization of 2-Halothiophene to 3-Halothiophene

This patent may be of interest to users of the earlier one on the Kumada reaction of 3-alkylthiophenes. The patent states that 2-halothiophenes can be synthesised by direct halogenation reactions of thiophene but the 3-derivatives cannot be made this way. Thus they are more expensive, and since they are actually more useful as starting materials, improved synthetic methods are desirable. Isomerization reactions using zeolites are known, and these are said to offer poor yields, reduced catalyst lifetime and high cost. It is suggested that the poor yields are due to the acidic nature of the zeolite that degrades the thiophene ring. The patent reports that by using a zeolite with a base the process can be much improved and commercially viable. The procedure is applied to bromo- and chloro-compounds and is carried out using H-ZSM 5 zeolites with MgO. The reactions tend to be carried out by heating the 2-halothiophene containing about 3–4% of the catalysts at around 150 °C for 30 h or more at 1 bar. The reaction is an equilibrium process with the maximum amount of 3-isomer being almost 90%. This is recovered by distillation, and the 2-isomer is recycled for further processing. The catalysts can be regenerated by heating in air at 300–650 °C, although no indication of their lifetime is given.

Advantages

The process provides a more straightforward and cheaper route to the desirable reagents.

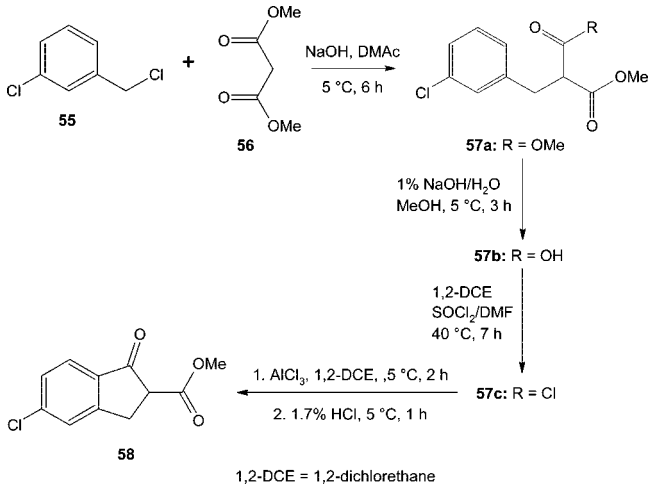
Patent No. U.S. 7,208,621

Assignee: Daicel Chemical Industries Ltd., Osaka, Japan

Title or Subject: Processes for the Production of Malonic Acid Monomethyl Derivatives

The novel compound specifically covered by the two claims of this patent, **57b**, is a precursor to indanecarboxylic esters such as **58** that is used to prepare insecticides. Alternative methods of making compounds such as **58** can involve diazonium salts that are difficult to handle. This patent describes a method using a novel malonic acid derivative, and Scheme 15 shows the overall route to prepare **58** from the chloroformyl compound **57c** (R = Cl). Initially **57a** (R = Me) is prepared in 95% yield by a base-catalysed reaction between **55** and **56** and then hydrolysis to produce **57b** in 92% yield. Chlorination of **57b** with $SOCl_2$/DMF forms **57c** and this is cyclised to give **58** using $AlCl_3$. The product is purified by chromatography, and a 70% yield obtained. Very basic ^1H NMR data are given for **57b** and **57c**.

Scheme 15



Advantages

The patent describes some novel compounds that are relatively easy to make and provide a new route to manufacturing insecticide precursors.

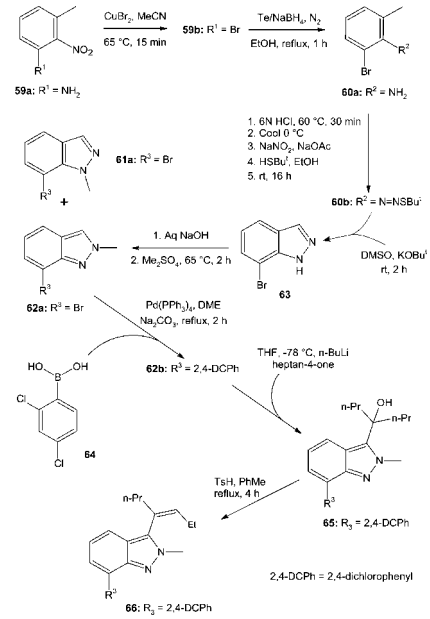
Patent No. U.S. 7,214,699

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

Title or Subject: Indazole Derivatives as CRF Antagonists

The novel compounds described in this patent have potential for the treatment of psychiatric disorders and neurological diseases. The new compounds are described as corticotrophin release factors (CRF), and a representative example is **66** that is prepared by the route shown in Scheme 16. A key intermediate is **63** that is prepared by cyclisation of the thioazo compound **60b** using KOBu^t in DMSO. Deprotonation of **63** followed by N-alkylation of the tautomeric anion with Me_2SO_4 produces the two isomers **61a** and **62a**. These are separable by flash chromatography on SiO_2. **62a** is then used to prepare **66**, while **61a** can be used to produce the 1-methyl isomer by a similar set of reactions. **66** can be isolated as the HCl salt as well as in the free base form as shown.

Scheme 16



The patent also describes other compounds in which the 2,4-DCPh group is replaced by 2,4,6-Me_3Ph or other aryl or heteroaryl groups. The patent also includes details of formulations made using some of the new compounds and tests carried out to determine their activity.

Advantages

There are a wide range of novel compounds described in the patent, and they have potential as CRF antagonists.

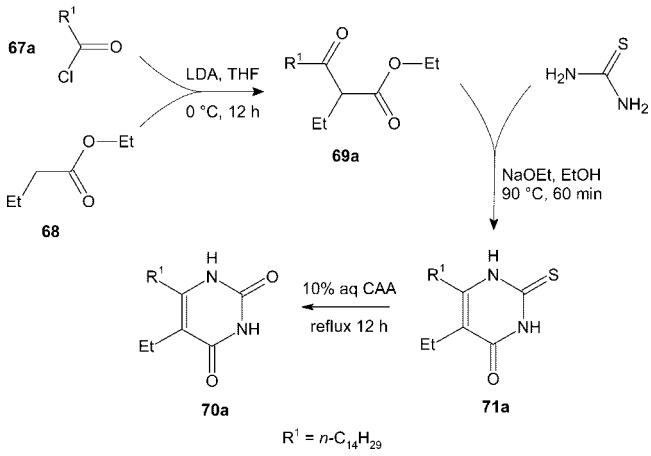
Patent No. U.S. 7,214,794

Assignee: Bracco S.p.A., Milan, Italy

Title or Subject: Process for the Preparation of Ceramide Analogs, and Their Use as Antitumor Agents

Ceramides in cell membranes have been found to assist apoptosis or cell death and therefore inhibit tumour growth. Hence such compounds are of great interest, and this patent describes a range of novel compounds of which **70a** and **71a** are simple examples of compounds are described as ceramide analogues. As such they have the potential for treating tumours and Scheme 17 shows the method used to prepare them. The

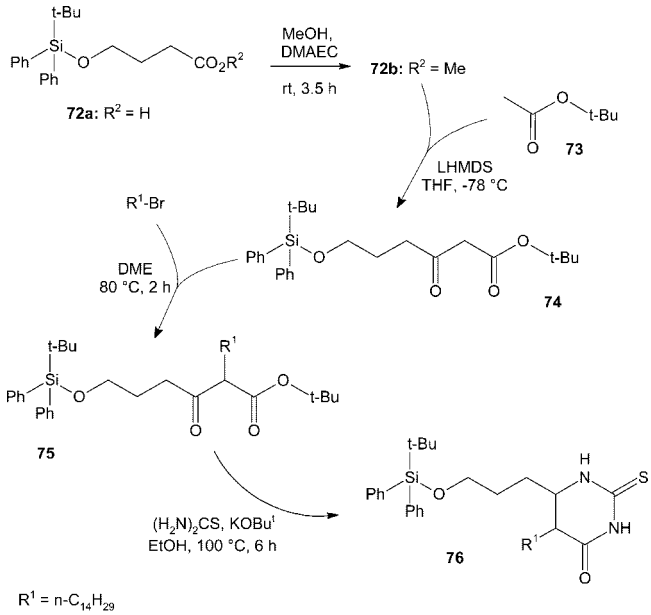
Scheme 17



method begins with a condensation of **67a** with **68** using LDA to give the β-ketoester **69a**. This is used in the crude form in a reaction with thiourea in the presence of NaOEt to form **71a** in 26% after purification using chromatography on silica gel. The O analogue **70a** is produced in 32% yield by refluxing **71a** in chloroacetic acid (CAA) for 12 h.

The patent also describes a wide range of other derivatives, and Scheme 18 summarises the route to prepare **76**. This is

Scheme 18



then used as a precursor to further derivatives that are prepared from the hydroxylpropyl compound after removal of the silyl protecting group. Details are provided in the patent to which the interested reader is referred.

Advantages

This patent contains a considerable number of novel compounds that may have potential uses in treating tumours.

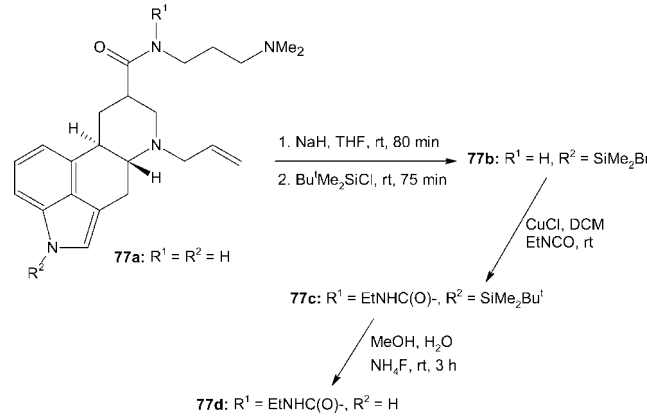
Patent No. U.S. 7,217,822

Assignee: Synthon IP Inc., Gainesville, Virginia, U.S.A

Title or Subject: Process for Making Cabergoline

Cabergoline **77d** is a dopamine receptor agonist with possible uses in the treatment of Parkinson's disease. Alternative methods for making **77d** are reviewed and said not to provide high conversion processes and high purity products. The key finding reported here is the protection of an indole N atom by silylation that allows a novel synthesis of **77d**. The use of this protective procedure is claimed not to be indicated in the alternative routes to **77d**. Scheme 19 shows the reaction sequence in which the

Scheme 19



protective measure is used with the amide **77a** to give **77b** in 87% yield. The reaction of **77b** with EtNCO in the presence of CuCl produces **77c**, and the crude material can be converted to **77d** by treatment with NH_4F in aqueous MeOH. An example is described in which the process was scaled up to produce >0.5 kg of **77d** with a purity of 99.9%.

Advantages

The process provides a novel route to the drug that can be recovered in high purity.

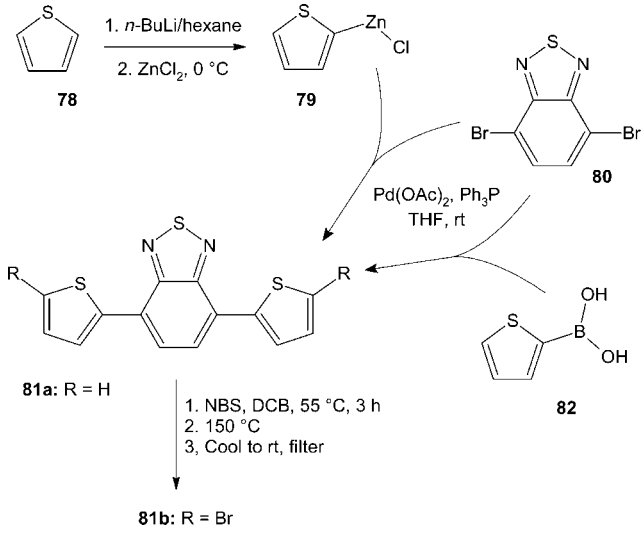
Patent No. U.S. 7,217,824

Assignee: Sumitomo Chemical Company Limited, Tokyo, Japan

Title or Subject: Process for Preparing a 4,7-Bis(5-halothien-2-yl)-2,1,3-benzothiadiazole and One of Its Precursors

The subject of this patent, **81b**, is used as a co-monomer in preparing polymers having optical and electronic properties making them suitable as light emitting diodes (LED). The patent says that other routes to **81b** can involve hazardous Sn reagents, and hence improved methods are desired. The patent describes two cross-coupling methods used to prepare the precursor **81a** as shown in Scheme 20. The first is described as a modified Negishi coupling reaction between the **79** and **80**. An alternative route is the reaction of the boronic acid reagent **82** with **80** in a Suzuki cross-coupling reaction. Both coupling reactions take place in THF at room temperature in the presence of $Pd(OAc)_2$

Scheme 20



and PPh_3. The conversion of **81a** to **81b** is carried out using NBS in *o*-dichlorobenzene (DCB), and the product was obtained in 84.8% yield at 99.7% purity (by GC) after crystallisation.

Advantages

The process uses less hazardous reagents than alternative procedures and gives high purity products in high yield.

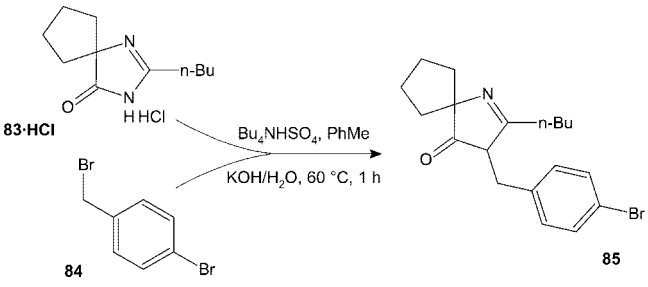
Patent No. U.S. 7,217,825

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

Title or Subject: Synthesis of Irbesartan

Irbesartan **88a** is used in treating high blood pressure, and the usual synthesis involves a step that involves an azide and is described as having safety risks. In addition the reaction time for this step can be as long as 210 h, and the patent states that therefore there is a need for an improved process. The first stage of the process is the preparation of **85** by the reaction of the acid salt **83**·HCl with **84** as shown in Scheme 21. The reaction

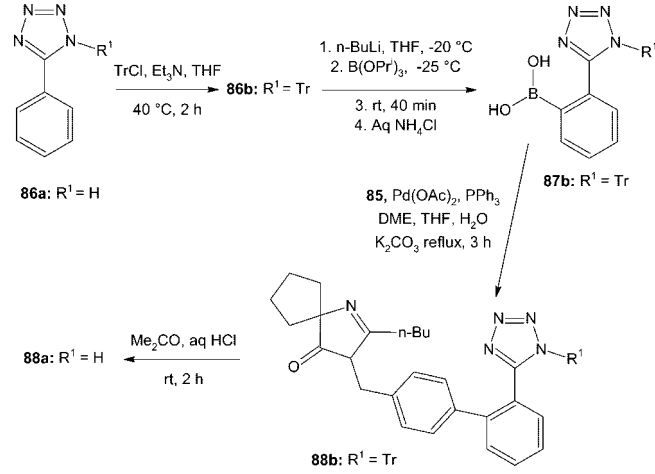
Scheme 21



is carried out using Bu_4NHSO_4 as a phase transfer catalyst (PTC).

The second stage of the process is the preparation of **87b** as shown in Scheme 22. This is done by initially protecting the NH group in the tetrazole **86a** by conversion to the trityl compound **86b**. The subsequent reaction of **86b** with $B(OPr^i)_3$ followed by hydrolysis produces **87b**. The Suzuki coupling using **87b** and **85** is the novel aspect of this route and requires a mixture of organic solvents such as DME and THF plus H_2O. The mixture after cooling produces two layers, and the aqueous

Scheme 22



layer is extracted to recover additional product. The reaction produces **88b** that on acidification gives the desired product **88a**.

In each step of the process there are very particular sequences and procedures to be followed that although necessary may give rise to operational problems.

Advantages

The process uses a novel intermediate in a Suzuki reaction to give high quality product. However, there does seem to be a considerable amount of materials handling that may make give rise to a less robust process.

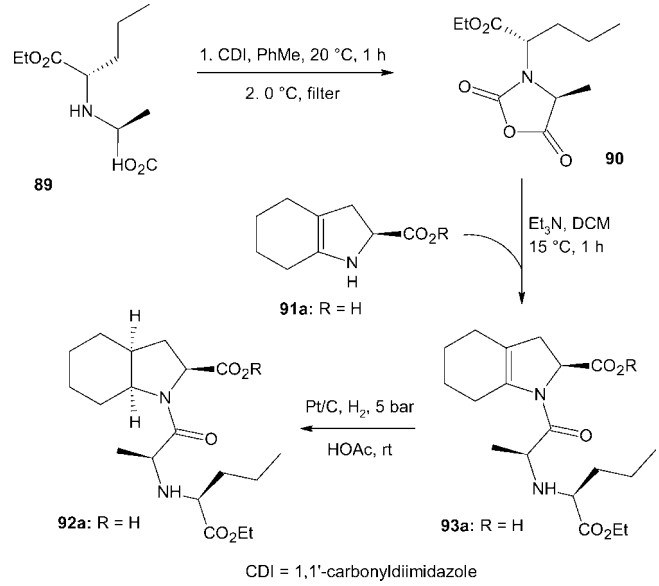
Patent No. U.S. 7,220,776 and 7,223,872

Assignee: LES Laboratoires Servier, Courbevoie Cedex, France

Title or Subject: Process for the Synthesis of Perindopril and its Pharmaceutically Acceptable Compositions

Perindopril **92a** is used as the *tert*-butylamine salt to treat cardiovascular diseases. The commonly used procedure for preparing **92a** involves a coupling step using DCC, and the patent states that this produces impurities from the coupling reaction as well as dicyclohexylurea

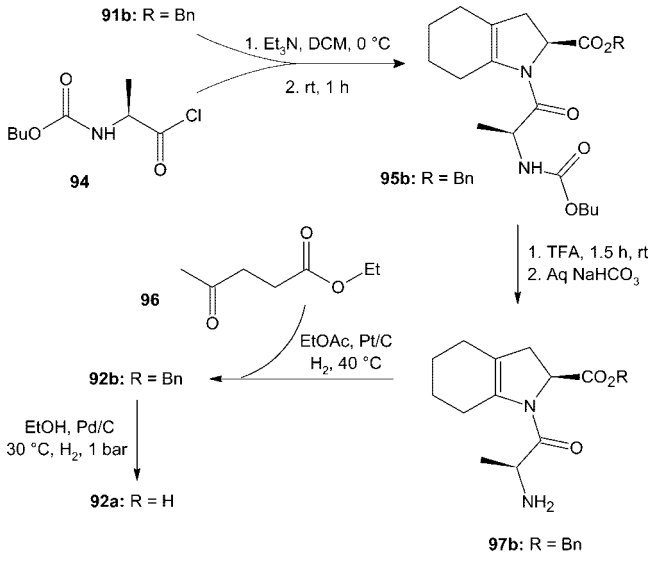
Scheme 23



that is difficult to remove. Hence the objective of these two patents is to provide improved processes for producing **92a** that avoids these problems. Each patent has slightly different processes that use similar intermediates **91a** or **91b**, and Scheme 23 outlines the process described in the first patent. This begins with the alanine ester **89** that is converted to the oxazolidine **90** in 90% yield using 1,1′-carbonyldiimidazole (CDI). In the next step **90** is reacted with **91a** to form **93a** and hydrogenation gives **92a** in unknown yield. The compound is finally isolated as the *tert*-butylamine salt in 95% yield. The patent claims cover the use of alternatives to CDI in the production of **90**, although there are no examples.

The second patent has a different approach, and this is shown in Scheme 24. In this the benzyl ester **91b** is reacted

Scheme 24



with **94** in the presence of Et_3N to give **95b**. The amino protective group is removed using TFA to give **97b**, and this reacts with **96** in a reducing environment with Pt/C catalyst giving **92b** in 85% yield. A further reduction using Pd/C catalyst then converts **92b** to **92a** in 85% yield. As in the first patent the product is converted to the *tert*-butylamine salt.

Advantages

The patents give two alternative processes that are claimed to be an improvement on other methods. However, there is insufficient data on the yields of each step to assess this statement.

Patent No. U.S. 7,220,867

Assignee: Pharmacia Corporation (of Pfizer Inc.), St. Louis, Missouri, U.S.A

Title or Subject: Solid-State Form of Celecoxib Having Enhanced Bioavailability

Celecoxib is a COX-2 inhibitor available as Celebrex and used as a nonsteroidal anti-inflammatory agent. This patent describes an amorphous form of the drug that has increased activity in orally administered forms of the drug. As is often the case with preparing different polymorphs of a compound, a combination of thermal treatments and solvents is needed to obtain novel forms. In this case the process comprises the following steps:

1. Melt the crystalline form of celecoxib at 180 °C in an oven
2. Cool the melt rapidly in liquid N_2
3. Grind the solid to obtained desired material

The patent also mentions the formation of a crystallisation inhibitor composite containing a range of polymeric materials as well as the novel amorphous form. These composites are prepared by dissolving the amorphous solid and polymer and then spray drying the solution.

Advantages

This new form of the widely used drug has improved activity for use in oral formulations.

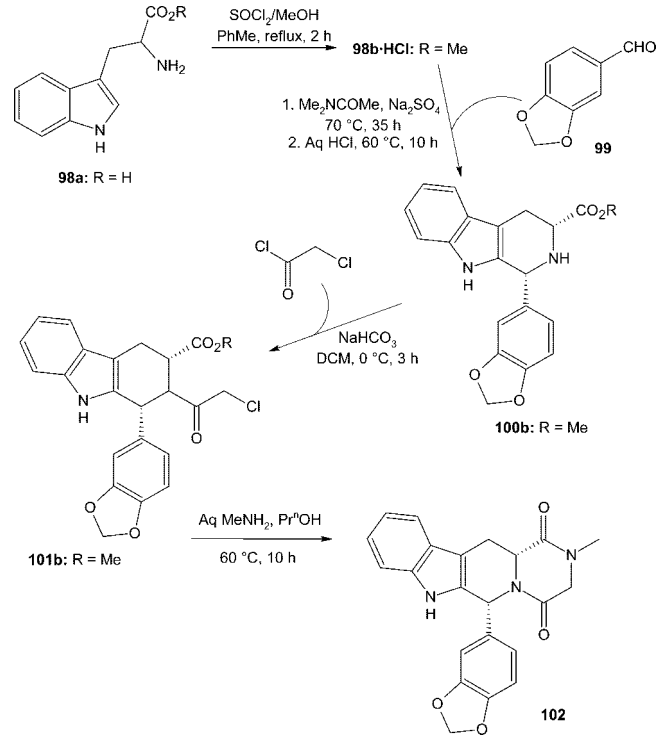
Patent No. U.S. 7,223,863

Assignee: Alembic Limited, Gujarat, India

Title or Subject: Process for Preparing Tadalafil and Its Intermediates

Tadalafil **102** is available under the name Cialis and is used to treat erectile dysfunction. The patent states that there are several drawbacks to the known processes for preparing **102** including requiring long processing time, giving low yield and using highly corrosive reagents such as TFA. The objectives of the process described in this patent include improvement in yield by recovering and converting an undesired *trans* isomer formed during the process as well as eliminating the use of TFA. Scheme 25 outlines the method used to prepare **102** and

Scheme 25



starts with the formation of the HCl salt of the tryptophan methyl ester **98b** from D-tryptophan **98a**. The salt is then reacted with **99** in a high boiling solvent (Me_2NCOMe) and a dehydrating agent (Na_2SO_4) to produce **100b**. Both *cis* and *trans* isomers are formed, and the preferred *cis* isomer is recovered by forming the HCl salt. The indications are that the *trans* isomer is

epimerised in this stage, and the reaction is driven by precipitation of the *cis*-HCl salt. The *cis*-HCl salt of **100b** is converted to the free base before the next step in which *cis*-**100b** is reacted with $ClCH_2COCl$ at <5 °C to produce **101b**. Treatment of **101b** with aqueous $MeNH_2$ in Pr^nOH gives the product **102** that is recrystallised from Pr^iOH.

Advantages

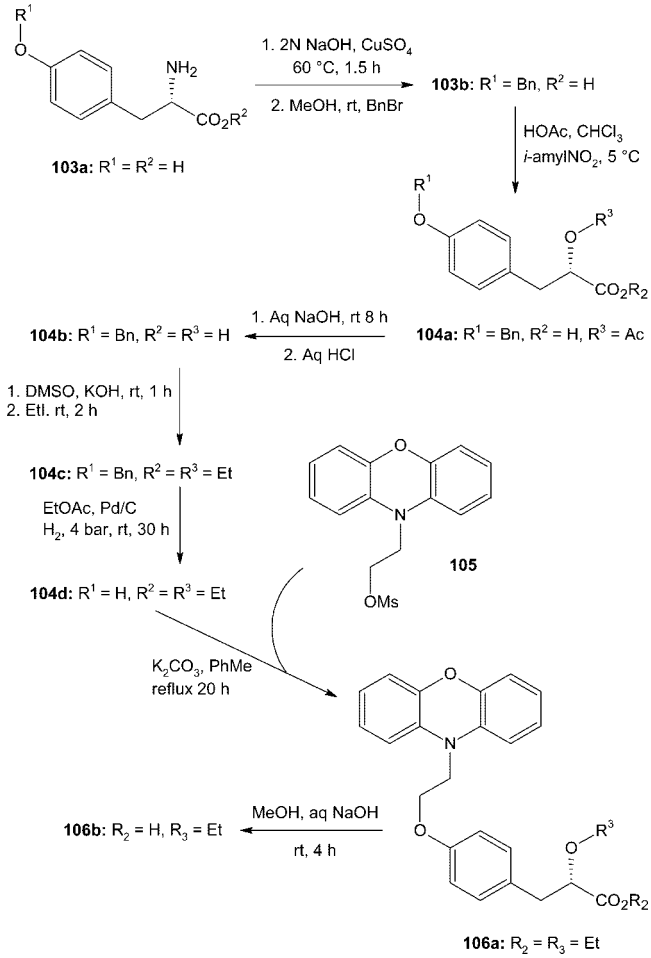
The process improves the overall process yield by epimerisation of the unwanted *trans*-isomer, avoids the use of TFA and also reduces the reaction times. If this is indeed the case, then presumably the applicants are using this improved process to manufacture the drug.

Patent No. U.S. 7,223,881

Assignee: Dr Reddy's Laboratories Limited, Hyderabad, India
Title or Subject: Process for the Preparation of New Antidiabetic Agents

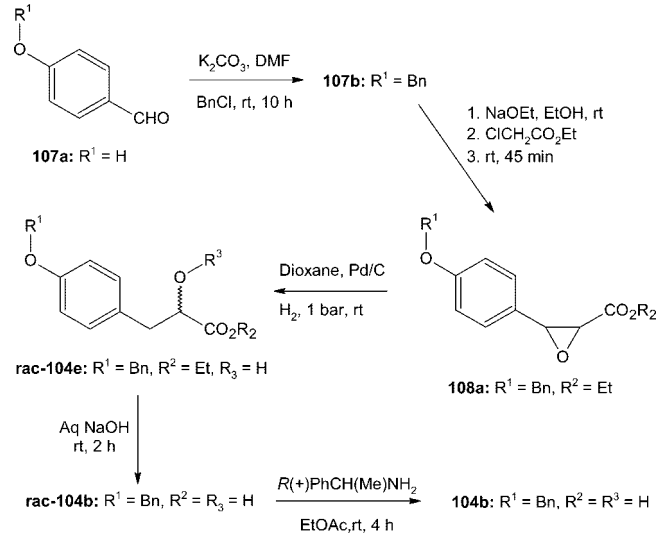
The patent provides a very large amount of information on different aspects of preparing **106b**, although the three claims in the patent only cover the compound itself. A key intermediate appears to be **104d**, and one method for its preparation is shown in Scheme 26 starting from L-tyrosine **103a**. In the first stage this is converted to the benzyl derivative **103b** in 66.8% yield using BnBr and $CuSO_4$. The amine group in **103b** is then converted to the acetoxy acid **104a** in 78% yield via diazotisation in HOAc. In the next phase **104a** is converted to **104d** via the intermediates **104b** and **104c**. The yields reported for each of the compounds are 85.4% (**104b**), 87% (**104c**) and 95% (**104d**). In the last stages of the overall process for the preparation of **106b**, the reaction of **104d** with the mesylate **105** gives **106a** in 99% yield, and finally hydrolysis produces **106b** in 92% yield.

Scheme 26



Another alternative method for preparing **104b** begins with **107a**, and this is shown in Scheme 27. In the first step the OH group is protected by formation of **107b**, and then **108a** is formed in a Darzen's condensation reaction. Upon hydrogenation over Pd/C catalyst the racemic **104e** is produced. Hydrolysis with NaOH forms racemic **104b**. This is resolved using *R*-(+)-α-methylbenzylamine, and the *S*-**104b** is recovered in a yield of 47%. The solution containing the *R*-**104b** is racemised and mixed with other batches for additional resolution steps.

Scheme 27



This patent does contain an extensive amount of detail, and the interested reader is advised to read it carefully.

Advantages

The patent provides a novel compound for treating diabetes and several methods for its preparation.

Keith Turner

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