Organic Process Research & Development **2004**, *8,* 697–707

Highlights from the Patents

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

Summary

This review of patents contains 20 from a selection of 255, and they cover a variety of topics that, it is hoped, will be of interest. The heart and obesity problems that are common in western society means there are a great many drugs already available or under development to treat these conditions. Hence, the statins continue to stimulate great interest in the treatment of obesity and heart problems. An improved drying process for one type of crystalline atorvastatin is disclosed. Other patents on statins describe two new polymorphs of orlistat and a new synthesis of fluvastatin. Another drug used to treat heart diseases is plavix, and a method of racemising the unwanted enantiomer has been described. The synthesis of a range of novel diazo compounds is described that can be used in the preservation of old manuscripts by deacidification. Atropisomers exhibit chirality due to hindered rotation, and a range of such pyridine derivatives is described that are used as chiral catalysts in asymmetric acylation reactions. A new route to the piperidine intermediates that are useful in preparing the antihistamine drug fexofenadine is disclosed. The importance of mixing raises its head again in a process for oxidation of alcohols using TEMPO. The procedure is a continuous process in which the reagents are fed separately to a tube where they are mixed with a static mixer. This is said to require short residence times and gives improved selectivity and productivity. The use of drugs in areas far removed from the original use brings an unusual finding. The drug eflornithine was developed to treat African sleeping sickness and has been found to be useful in the treatment of unwanted facial hair. Two patents cover a novel method of producing meso-zeaxanthin which is used to treat age-related macular degeneration. The chemistry covered in these patents is extensive and not clearly explained. Hence, the review here has merely scratched the surface; anyone who has a particular interest in this subject is strongly advised to consult the patents. Factor Xa is involved in the coagulation of blood, and two patents from different companies disclose details of compounds that can inhibit this. As is often the case, experimental details in patents may be lacking in detail. In this collection there are two patents that claim improved methods for preparing compounds and yet provide no experimental details to back up the claim. On the other hand two other patents give details of making substantial quantities of chemicals and provide an indication that the processes are capable of being used commercially. As usual, the advantages are those claimed in the patent unless this reviewer has personal knowledge, and there is no legal or commercial significance in the choice of patents for review.

Patent No. U.S. 6,730,797

Assignee: Pfizer Science and Technology Ireland Limited, Dublin, Ireland

Title or Subject: Process for Producing Crystalline Calcium Atorvastatin

Statins are used to reduce cholesterol levels and are currently of great interest. Several patents on these compounds have been reviewed (*Org. Process Res. Dev.* **2004**, *8*, 311). Atorvastatin **2** is known to exist as four polymorphs; an amorphous form is also known and used in pharmaceutical formulations. This patent focuses on an improved method of drying the crystalline form of the trihydrate calcium salt **2**. The process, shown in Scheme 1, consists of converting the lactone **1** to **2** via a sodium salt in MTBE by the following steps: (1) reaction of **1** with aqueous NaOH in MeOH/MTBE to form the ring-opened Na salt, (2) removal of impurities by extraction with MTBE, (3) adding extra MTBE to aqueous mixture and heat to 57 °C, (4) slow addition of $Ca(OAc)_2 \cdot H_2O$ to mixture to form **2**, (5) isolation of product by filtration and drying in an agitated vacuum pan dryer.

The last step is the primary focus of this patent. It is stated that drying is particularly sensitive at about 6% w/v water content and the drying has to proceed slowly to prevent breakdown of particles by attrition. The continuous agitation of the mixture at around 1 rpm improves the product quality and also increases productivity. When medium-speed agitation is used for drying, the product formed clods or lumps, and a longer drying time is needed. The patent gives details of this procedure using 250 kg of **1**; hence, it can be assumed that this is capable of being used on a commercial scale.

Advantages

The process gives consistent high-quality product and at the same time allows increased production rates.

Patent No. U.S. 6,730,809

Assignee: Women First Healthcare Inc., San Diego, California, U.S.A.

Title or Subject: Processes for the Production of α-Difluoromethylornithine

The title compound **9**, also known as eflornithine, has been used to treat African sleeping sickness. However, it has recently been approved in the United States for treating unwanted facial hair by restricting its growth. It is stated in the patent that current processes for its manufacture are not suitable for large-scale production. The reasons given are that such processes use expensive reagents, involve poten-

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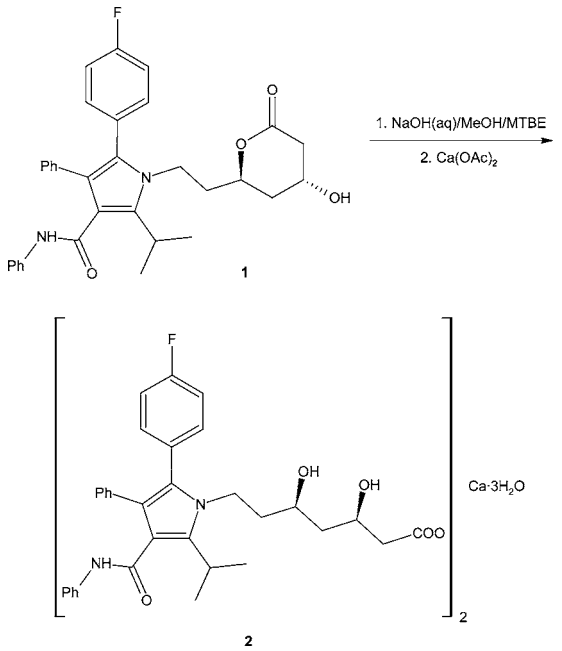
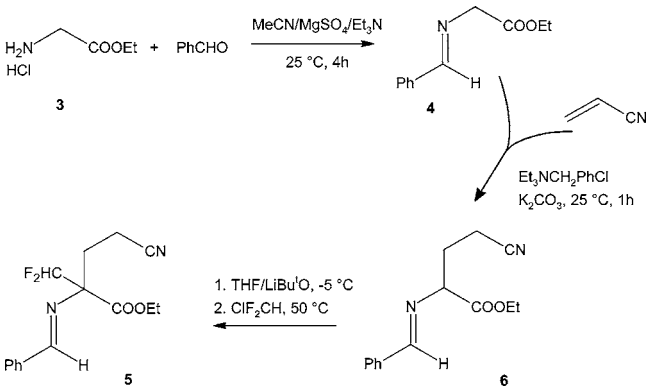
tially run-away reactions, or use halogenated solvents. The new process starts from a salt of a glycine ester such as **3**

Scheme 1



which is commercially available. The initial stage is the preparation of the cyano compound **5** by the route shown in Scheme 2.

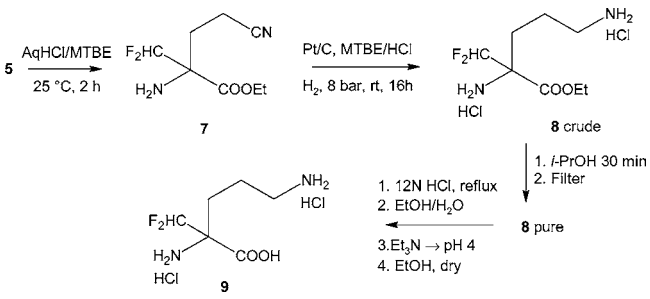
Scheme 2



There is no stereochemical information in the patent, and it is presumed that the reactions produce racemic mixtures.

In this route the various intermediates are not purified before being used in the subsequent reactions. The first step is the protection of the amino group as an imine **4** by condensation of **3** with PhCHO. This is carried out in the presence of $MgSO_4$ as dehydrating agent and Et_3N to neutralise the acid salt. Treatment of **4** with acrylonitrile in a Michael reaction, using a phase transfer catalyst, gives the cyanoester **6**. The formation of **5** is carried out by bubbling CF_2ClH into a solution of **6** in the presence of a strong base that can deprotonate the α-carboxylate C atom. The preparation of **9** from **5** can then be carried out by two possible routes. Both routes proceed via intermediate formation of **8** as shown in Scheme 3.

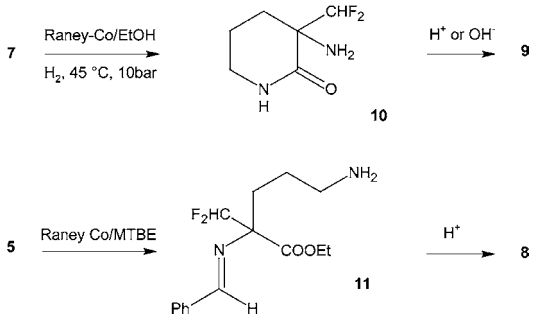
Scheme 3



In the first route, **5** is converted in two steps by initial hydrolysis with HCl to give **7** that is then hydrogenated to give crude **8** as a dihydrochloride salt. The alternative is direct hydrogenation of **5** to **8** over Pt/C in HCl/EtOH. In either case **8** is purified by washing with *i*-PrOH and can be recrystallised from $EtOH/H_2O$. The conversion of **8** to **9** as a dihydrochloride salt is carried out by hydrolysis of the ester with concentrated HCl.

The patent also describes the formation of the intermediates **10** from **7** and **11** from **5** as shown in Scheme 4.

Scheme 4



Each of these intermediates can be converted to the respective amine hydrochloride salts **9** and **8**.

Advantages

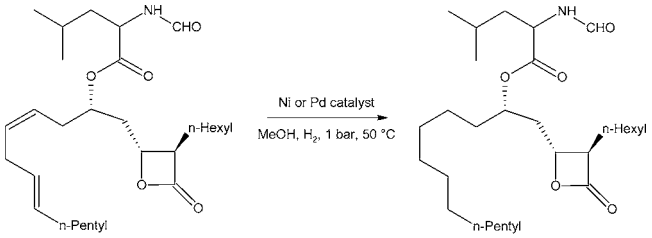
This process does use readily available starting materials; however, acrylonitrile cannot be said to be without hazard, being volatile, highly flammable, and carcinogenic.

Patent No. U.S. 6,734,314

Assignee: Biogal Gyogyszergyar Rt., Debrecen, Hungary Title or Subject: Preparation of Novel Crystalline Forms of Orlistat

Orlistat **13** is used in the treatment of obesity and is one of the many statin drugs that are of current interest. **13** can be prepared by fermentation processes, and although synthetic methods are available, they are said to be more expensive. The preparation described here is by the hydrogenation of lipastatin **12** (Scheme 5) that has been extracted from a fermentation broth. Exact details of the hydrogenation step are not given apart from the fact that a Ni or Pd catalyst is used.

Scheme 5



The major focus of the patent is the production and characterisation of two new polymorphs of **13** for which X-ray diffraction (XRD) data are provided. The exact experimental procedures are very unclear, and several examples report drying a solution without filtration to obtain crystals. It appears that the basic method is crystallisation from a solvent and anti-solvent mixture. The solvent mixture used to obtain Form I was methanol and hexane, whereas Form II was obtained from hexane. Other solvents are used, but they give mixtures of Forms I and II with Form I predominating. It is said that seeding can be used, but no examples are given that use this technique.

Advantages

The main advantage appears to be the production of two new polymorphs.

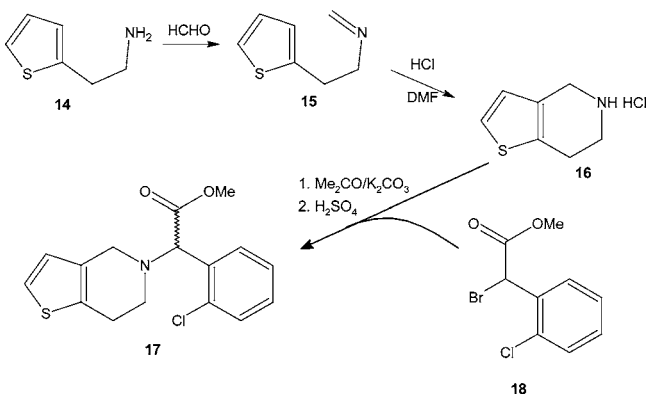
Patent No. U.S. 6,737,411

Assignee: Teva Pharmaceutical Industries Ltd., Petah Tiqva

Title or Subject: Racemisation and Enantiomer Separation of Clopidogrel

The *S*-form of clopidogrel **17** is used in the treatment of atherosclerosis and is administered in the form of its bisulphate salt known as plavix. The synthesis of **17** produces a racemic mixture; hence, separation of enantiomers, preferably with a racemisation step, is a commercially attractive process. This patent describes a method of separating the enantiomers and racemising the *R*-isomer by formation of a camphor sulphonate salt. The general route for the synthesis of a racemic mixture of **17** as the bisulphate salt is shown in Scheme 6 although there are no specific experimental conditions given in the patent.

Scheme 6



The separation of the *S*-isomer is accomplished by initial formation of the free base by treatment of **17** with NaOH in PhMe/H_2O and then proceeding as follows:

(1) A solution of **17** free base in PhMe is added to a solution of (−)-(*R*)-camphorsulphonic acid in DMF at 30 °C.

(2) To the above solution was added seeds of (+)-camphorsulphonate of **17**, and this is cooled to form the crystals that are collected by filtration.

(3) Add Bu^tOK at 0 °C, for 20 min, to the mother liquor from step 2.

(4) Neutralise with HOAc, wash with water, and then dissolve oily organic phase in Me_2CO.

(5) Add H_2SO_4 and collect crystals of racemic bisulphate of **17**.

The bisulphate salt of the pure *S*-isomer of **17** is obtained from the crystals formed in step 2 as follows:

(1) The crystals are added to EtOAc/H_2O and then treated with NaOH and $NaHCO_3$.

(2) The solution from step 1 is decolorised with charcoal and stripped to give an oil that is dissolved in acetone, acidified with H_2SO_4 to which seeds of polymorph Form I are added.

(3) Crystals were recovered, washed and dried at <25 °C.

The examples give only a very general description of the procedures, and no quantitative information is provided at all.

Advantages

The process gives improved overall yields of the product as a result of racemisation of the undesired isomer, making it available for recycle through the resolution−racemisation process.

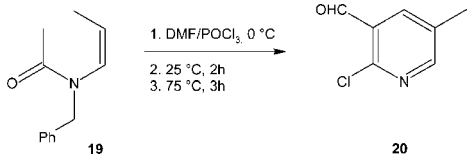
Patent No. U.S. 6,737,529

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

Title or Subject: Process for the Preparation of 2-Chloro-5-methylpyridine-3-carbaldehyde

The title compound **20** is a useful chemical intermediate, and it is claimed that there is only one literature method for its preparation. This patent describes an improved synthesis of **20** which is shown in Scheme 7.

Scheme 7



The product is obtained in 64% yield by reaction between the amide **19** and a Vilsmeier reagent formed from DMF and $POCl_3$. There is no indication as to how this reaction proceeds, but it is claimed to give the highest reported yield of **20**, and this is attributed to the controlled time and temperature of the reaction. The process also avoids the need

for additional solvent and this enables a simpler purification procedure.

Advantages

The process gives higher purity product in higher yields than previously reported.

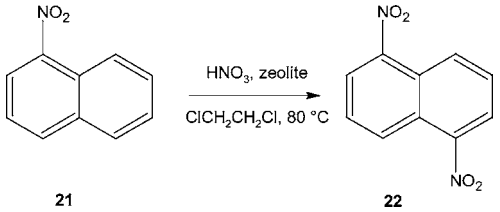
Patent No. U.S. 6,737,554

Assignee: Bayer AG, Leverkusen, Germany

Title or Subject: Production of Dinitronaphthalenes with a High Proportion of the 1,5 Isomer

The 1,5-dinitro isomer **22** is useful in the production of the corresponding diamine which is used for producing isocyanates among other things. As is commonly the case in aromatic nitration reactions, the selectivity is low. This patent discloses an improved method of making **22** by the use of a zeolite as a catalyst in the nitration of naphthalene or **21**. The use of the acidic zeolite means that there is no need to use H_2SO_4 which simplifies the recovery and purification of the product. The reaction is shown in Scheme 8

Scheme 8



and works using a selection of zeolites that are used in the acid form. All of the examples use H-Y zeolite, but claims cover H-β, H-mordenite, and H-ZSM-5. The selectivity for the 1,5- over the 1,8-isomer without using a zeolite is less than 40%, but this increases to over 55% when using zeolites.

Advantages

The process gives an improved yield of the desired isomer and simplified product recovery.

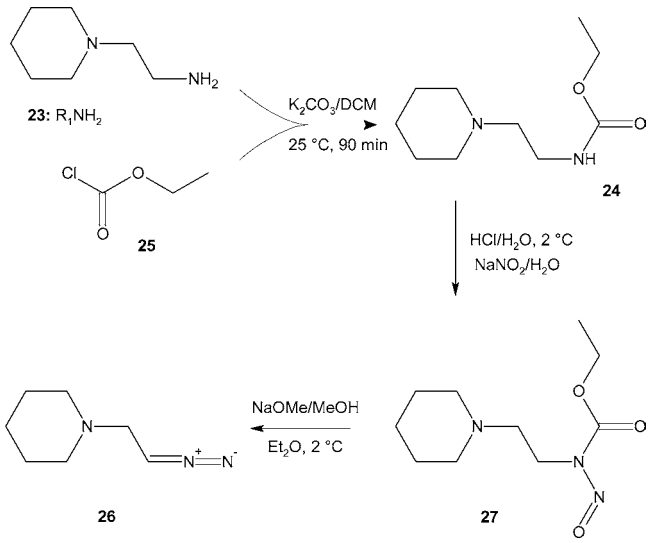
Patent No. U.S. 6,740,741

Assignee: Consiglio Nazionale delle Ricerche, Rome, and Universita'degli Studi di Udine, Udine, Italy

Title or Subject: Novel Diazo Derivatives and Process for Their Preparation

The patent is concerned with producing diazo compounds such as **26** that are used in the deacidification of old paper and manuscript materials and so protect them from deterioration. The preparation of **26** is shown in Scheme 9 and starts by forming the carbamate **24** in a reaction between the amine **23** and the chloroformate **25** in the presence of K_2CO_3. The patent claims that the ratio of **23** to K_2CO_3 to **25** must be 1:4:3, but no reason is given. The nitroso compound **27** is then prepared from **24** and converted to **26** by treatment with NaOMe in MeOH/Et_2O. **26** was obtained as a solution in Et_2O and used in this form to treat paper. The patent states that the most suitable diazo compounds for treating paper have a piperidine ring or a 4-morpholine ring, but no examples of the latter type are given.

Scheme 9



Advantages

These are novel compounds and are produced in a fairly simple manner.

Patent No. U.S. 6,743,922

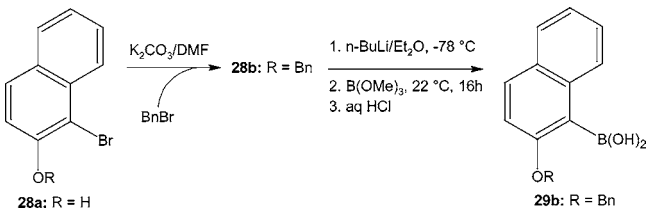
Assignee: University of Sheffield, Sheffield, United Kingdom

Title or Subject: Chiral Catalysts for Asymmetric Acylation and Related Transformations

The main subject of this patent is the preparation and use of disubstituted pyridines such as **33b** in which the 3-substituent on the pyridine is hindered from rotation about its bond to the pyridine nucleus. As a result of this restricted rotation, there exist atropisomers that have a chiral centre and are used as chiral catalysts in asymmetric acylation reactions.

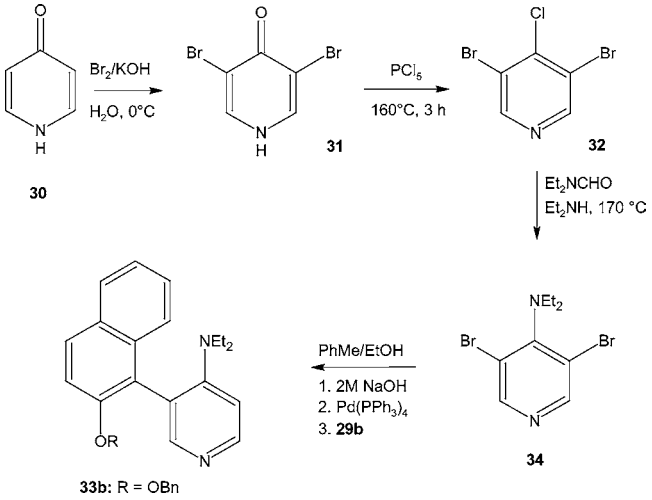
The synthesis of **33b** is by a Suzuki-type coupling reaction of the boronic compound **29b** and **34** as shown in Scheme 11. This reaction takes place with simultaneous removal of the second Br group. The preparation of **29b** is shown in Scheme 10 and starts from the bromonaphthol **28a.** This is converted to the benzyl ether **28b** which forms **29b** when treated with *n*-BuLi followed by $B(OMe)_3$ and a hydrolytic workup.

Scheme 10



The dibromo compound **34** is prepared by the route shown in Scheme 11 and begins with dibromination of 4-pyridone **30** to give **31**. The chlorodibromo compound **32** is formed from **31** by reaction with PCl_5, and heating **32** in a sealed tube with Et_2NCHO and Et_2NH gives **34**.

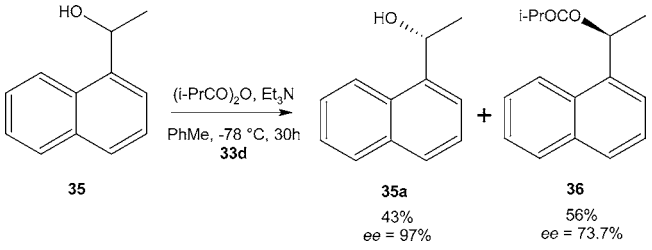
Scheme 11



The patent also describes the conversion of **33b** to **33c** (R = Tf) which in turn is used to prepare **33d** (R = Ph). The resolution of **33d** is described using semipreparative chiral HPLC and pure samples of both enantiomers were collected. A series of experiments is described in which resolution is carried out by formation of a wide range of acid salts using an automated robotic system.

The catalysts are used in asymmetric acylation reactions. An example is with the naphthylethanol **35** using the (+)-isomer of **33d**. In this reaction shown in Scheme 12

Scheme 12



the product is (*S*)-ester **36** and the (*R*)-alcohol **35a**. This reaction is a kinetic resolution which is common with enzymes but less common using chemical catalysts. The preparation of these catalysts by chemical means is perceived to be advantageous since both enantiomers can be obtained. A range of other acylations is also described.

Advantages

This process provides a means of making useful chiral catalysts that can be used in kinetic resolution reactions.

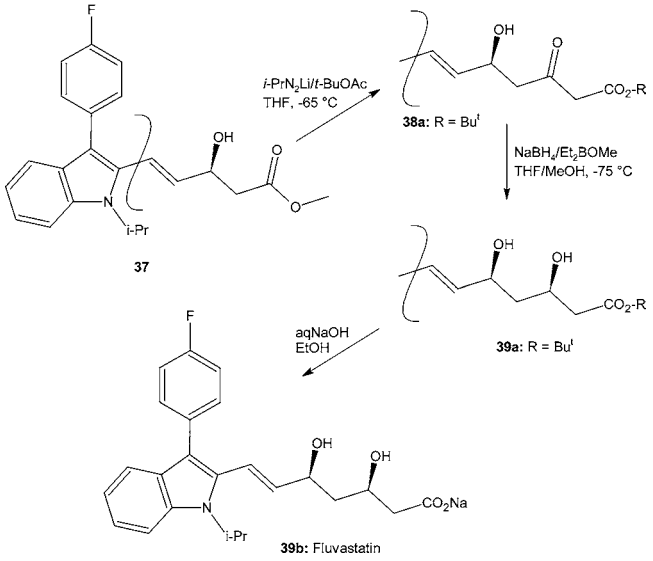
Patent No. U.S. 6,743,926

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

Title or Subject: Process for the Preparation of Indole Derivatives and Intermediates Useful in Preparing the Indole

The patent discloses preparative details for the indole compound **39b** which is known as fluvastatin, and like other statins, is used in treating arteriosclerosis. The process has several steps, and the final stages are shown in Scheme 13

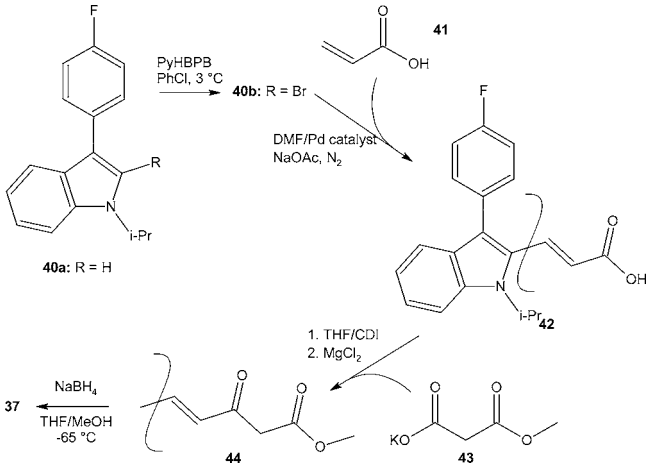
Scheme 13



in which the methyl ester **37** is converted to the *tert*-butyl ester **38a** by first reacting *i*-Pr_2NLi in THF with *t*-BuOAc and then adding **37** at −65°C. The enantiomeric mixture that is formed can be resolved by chiral HPLC but is used in the next step as a racemate. **38a** is reduced to **39a** by using $NaBH_4$ and Et_2BOMe in THF/MeOH at −75 °C. The *syn*/*anti* ratio of the product **39a** is >70:1, and the enantiomers can be resolved by chiral HPLC. The production of **39b** is carried out by treating a solution of **39a** in EtOH with aqueous NaOH.

The patent also describes the method of preparing the compound **37** by the route shown in Scheme 14.

Scheme 14



The first step bromination of **40a** with pyridine hydrobromide perbromide (PyHBPB) to give **40b** takes part in a Heck reaction with **41** to give the acrylic acid **42**. This is reacted with 1,1-carbonyldiimidazole (CDI) and $MgCl_2$ in THF followed by **43** to give the methyl ester **44**. Reduction of **44** with $NaBH_4$ gives a racemic mixture of **37** that can be resolved using HPLC.

Alternative syntheses of **42** and **44** are also given, and the compounds **39a**, **44**, **40b** are novel, but no data for them are provided.

Advantages

The patent provides a novel route to the statin which is said to be in as high a yield as possible.

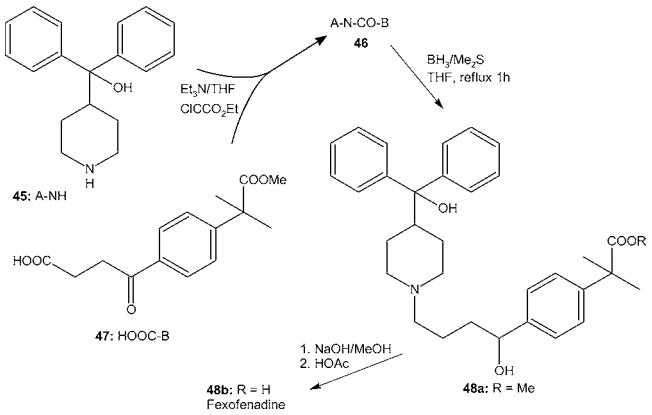
Patent No. U.S. 6,743,941

Assignee: Aventis Pharma Deutschland GmbH, Frankfurt am Main, Germany

Title or Subject: Process for Production of Piperidine Derivatives

The patent relates to processes for preparing the nonsedating antihistamine drug fexofenadine **48b** which in the United States is sold under the name of allegra. The final stages of the process are shown in Scheme 15

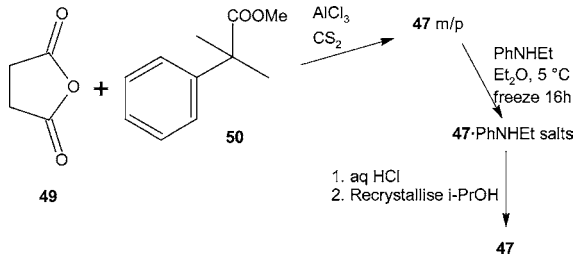
Scheme 15



and involve the production of the amide **46** by reaction of the piperidine **45** with the oxybutyric acid **47**. The amide is then selectively reduced to the methyl ester **48a** which is hydrolysed to give **48b** in 85% yield at 99.9% purity by HPLC.

The patent also describes how to prepare **47** by the acylation of **50** using succinic anhydride **49** under Friedel−Crafts conditions and is outlined in Scheme 16.

Scheme 16



In fact the claims of the patent only specify the novel compounds **47** and its ethyl ester analogue, and there are no claims relating to compound **48b**. Patent examples use either CS_2 or DCM/$PhNO_2$ as solvents for this reaction which gives a ratio of 60:40 para/meta isomers. These are separated by formation of the phenylethylamine salts. This is carried out by addition of PhNHEt to a solution of the isomers of **47** in Et_2O and by freezing overnight. The mixture of solid salts was recrystallised twice from hot *i*-PrOH to obtain the para isomer of the PhNHEt salt, and this was converted to the acid by treatment with concentrated HCl.

Advantages

The patent provides novel intermediates that are useful in the preparation of fexofenadine.

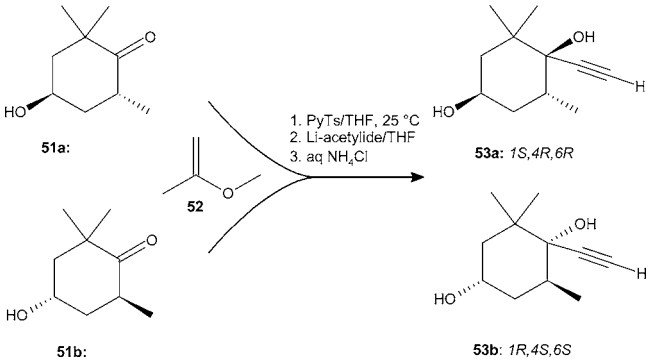
Patents No. U.S. 6,743,954 and No. U.S. 6,747,177

Assignee: BASF AG, Leverkusen, Germany

Title or Subject: Process for the Preparation of Meso-Zeaxanthin

These two patents describe the preparation of the compounds **53a** and **53b** that are used to prepare meso-zeaxanthin **59**, a drug for treating age-related macular degeneration. The claims of the second patent cover only compound **53b** itself, whereas the claims of the first cover the synthesis of **59**. Scheme 17 shows the formation of the racemic mixture of **53a** and **53b**.

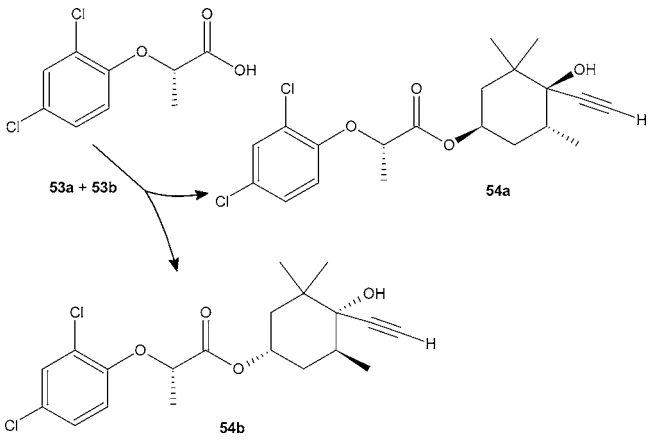
Scheme 17



This is carried out by reaction of the racemic *trans*-isomers **51a** and **51b** with **52** in the presence of pyridinium tosylate (PyTs) followed by treatment with Li acetylide. This presumably proceeds via a bulky mixed ketal of **51** that influences the stereochemistry of the subsequent reaction with the acetylide.

The separation of **53a** and **53b** is via the esters **54a** and **54b** by fractional crystallisation (Scheme 18).

Scheme 18

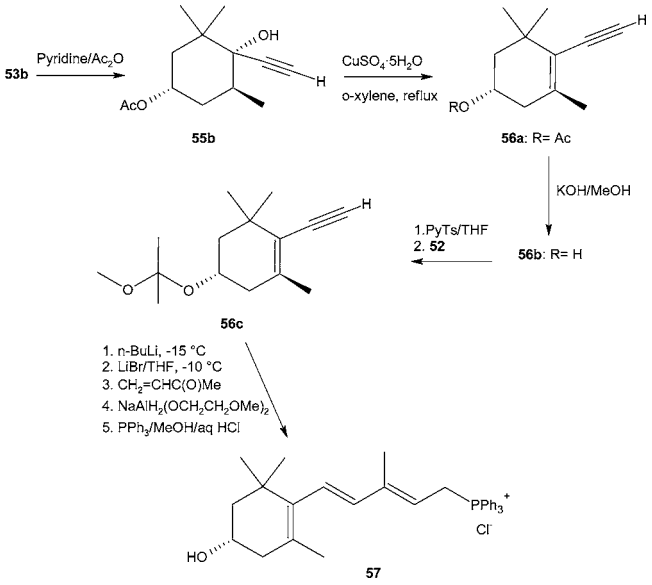


The procedure is to dissolve the mixture in *i*-Pr_2O and add

hexane to obtain crystals containing higher concentration of **54a**. This gave **54a** with a purity of >97% by GC and **53b** was recovered with a GC purity of 99.3%.

53b was then used to produce the acetylenic alcohol **55b** as shown in Scheme 19

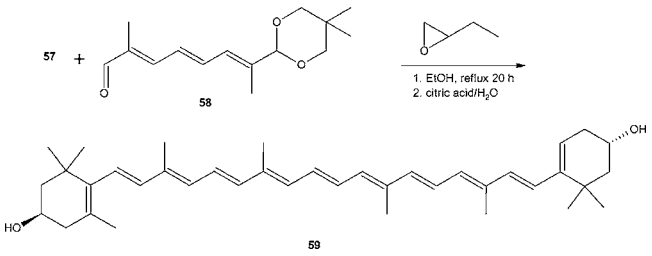
Scheme 19



and this was dehydroxylated in an unusual manner by refluxing with hydrated $CuSO_4$ in *o*-xylene to give the acetate **56a**. Hydrolysis of **56a** produced the alcohol **56b**, and in a series of several steps **56b** was then converted to the phosphonium salt **57**. The patent is not clear on the mechanism of the conversion of **56b** to **57** other than to indicate that the initial step involves the protection of the OH group by formation of the ether **56c**. The addition of the four C atoms to **56c** is accomplished by using the CH_2═CHC(O)Me.

The phosphonium salt **57** was then used in a Wittig reaction to prepare **59** as shown in Scheme 20.

Scheme 20



Again the patent is unclear on the reaction sequence but states that this is a key step and uses a C_{10} dialdehyde that is protected on one end as an acetal such as the neopentyl glycol **58**. It would appear that two moles of **57** are required for each mole of **58** to give **59**, and hence the role of the epoxybutane is not at all clear. **59** is obtained in high yield and high purity after the intermediate acetal is cleaved using citric acid.

Advantages

These patents provide a novel synthesis of the desired drug product in high yield and purity.

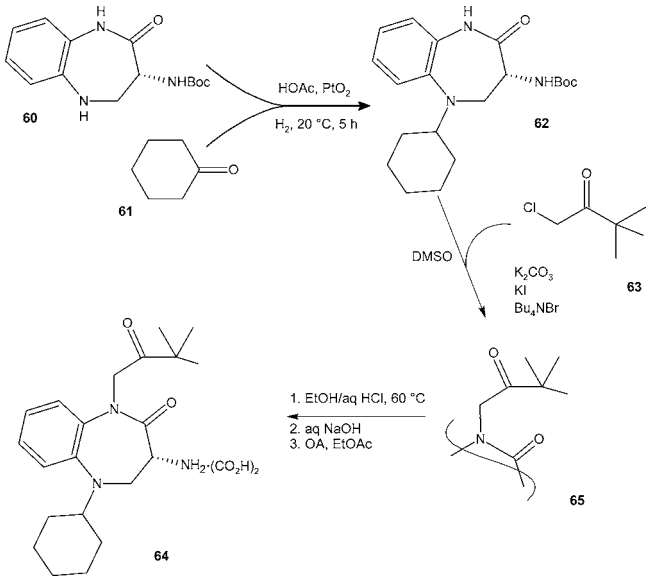
Patent No. U.S. 6,747,022

Assignee: Zeria Pharmaceutical Co., Ltd., Tokyo, Japan

Title or Subject: The Preparation of Calcium Salts of 1,5-Benzodiazepine Derivatives and Drugs Containing the Same

The calcium salts such as **69b** are useful in the inhibition of gastric secretions and hence are used in the treatment of gastric ulcers. The calcium salts are said to be better inhibitors than other benzodiazepine derivatives described elsewhere. There are several types of salt described and Scheme 21shows a typical route described in the patent.

Scheme 21



The first step is formation of the 5-substituted compound **62** from the Boc protected amine **60**. Reaction of **62** with the chloroketone **63** in the presence of a base and NBu_4Cl as phase transfer catalyst (PTC) gives the 1,5-disubstituted compound **65**. This is then converted to the oxalate by first removing the Boc group using HCl in EtOH and then adding oxalic acid dihydrate (OA) to give **64**.

The next stage in the overall process is the preparation of **69a** by reaction of **64** with **67**. The patent describes the synthesis of **67** from **66** and **68** in basic THF. The reaction of **64** with carbamate **67** (Scheme 22) takes place in the presence of Et_3N in DMSO followed by acidification.

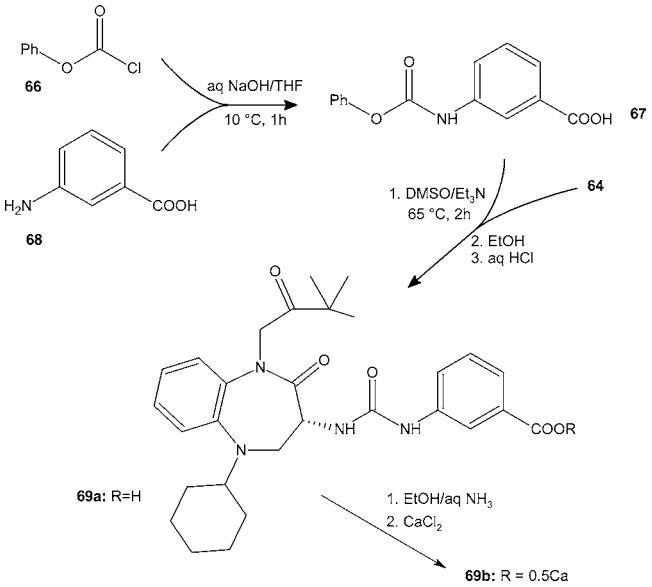
The final step to give **69b** is treatment of **69a** with aqueous NH_3 in EtOH followed by addition of $CaCl_2$ solution, and **69b** is obtained as the monohydrate salt.

The patent provides ^1H NMR assignments for all compounds, and some IR data are also given. Also described in the patent are details of how to administer the drug plus small-scale tests on toxicity in rats.

Advantages

The calcium form of the drug is said to be more effective, and the patent provides a novel synthetic route.

Scheme 22



Patent No. U.S. 6,747,153

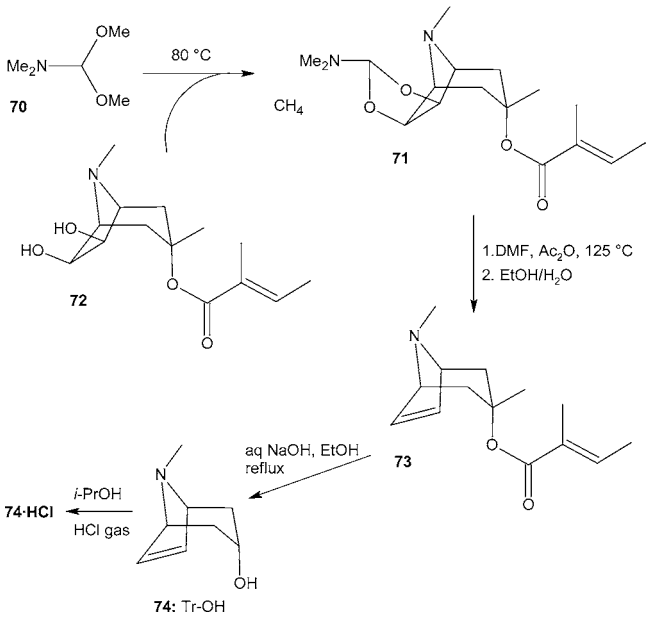
Assignee: Boehringer Ingelheim Pharma GmbH and Co. KG, Ingelheim, Germany

Title or Subject: Industrial Process for Preparing Tropenol

Tropenol **74** is used to prepare a range of pharmacologically active compounds that can contain impurities from **74** itself. Hence this patent discloses an improved synthesis of **74** and its HCl salt that is used to prepare **75**.

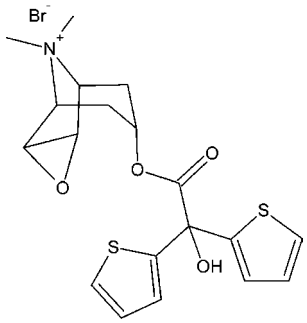
The process for preparing **74**·HCl is shown in Scheme 23 and starts by reacting the acetal **70** with **72** to give the cyclic acetal compound **71**.

Scheme 23



This is then deoxygenated using Ac_2O in DMF to produce **73** which is saponified with ethanolic NaOH to give **74** which on treatment with gaseous HCl in *i*-PrOH produces the salt **74**·HCl. The patent does mention that the 2-butenyl ester **72** is available as meteloidine, and it does state that this ester is preferred.

The salt **74**·HCl is used to prepare the tiotropium bromide **75**. The patent examples involve the use of over 20 kg of **72**, and it may be assumed that the process can be carried out on a commercial scale.



75

Advantages

The preparation of the salt **74**·HCl reduces the impurity levels and hence leads to higher-purity products when the salt is used as a starting material for the synthesis of **75**.

Patent No. U.S. 6,747,158

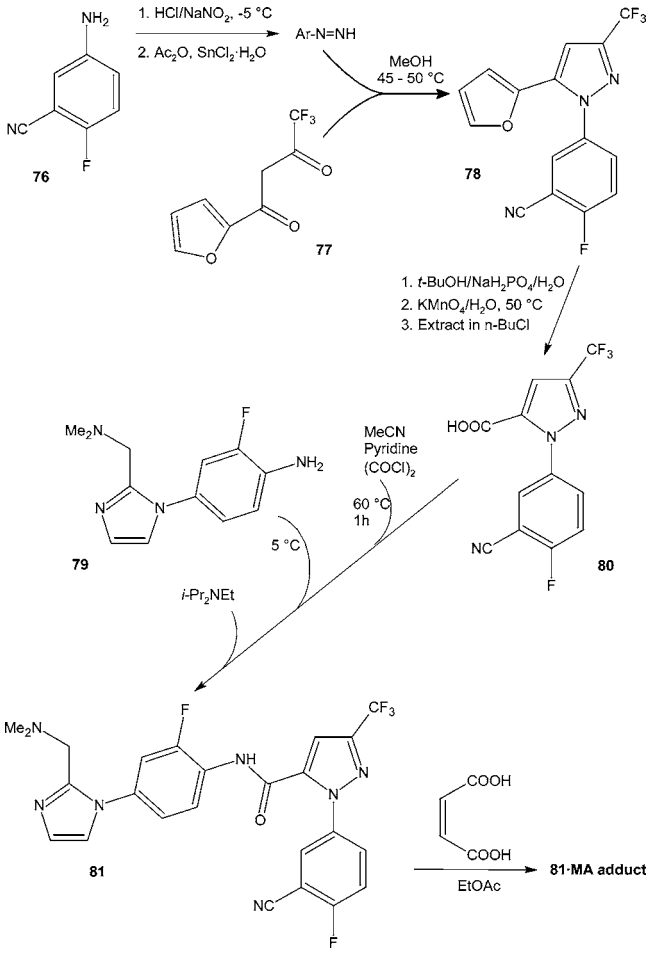
Assignee: Bristol-Meyers Squibb Pharma Company, Princeton, New Jersey, U.S.A.

Title or Subject: Efficient Process for the Preparation of a Factor Xa Inhibitor

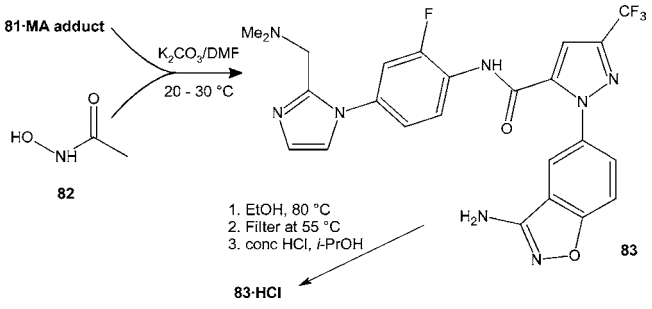
Factor Xa is a protease that is involved in the coagulation of blood, and there is general interest in finding compounds that inhibit this process. This and the next patent both disclose such inhibitors which are chemically quite different. The current patent describes the synthesis of one such compound, **83**·HCl. The first stage is shown in Scheme 24 and begins with the synthesis of the hydrazine Ar−N═NH from **76**. This hydrazine is not isolated but converted to **78** by an in situ trapping reaction with **77** in the presence of MeOH. The trapping reaction is claimed to be novel in that it is carried out in situ. **78** is then converted to the acid **80** by oxidation using $KMnO_4$ in the presence of NaH_2PO_4 as a buffer. **80** is then dissolved in MeCN and coupled with **79** to give **81** by using oxalyl chloride as an acid activator and a base. Compound **81** is an oil and hence is treated with maleic acid (MA) to form the crystalline adduct **81**·MA. The coupling of **79** and **80** has been used previously and is said to have problems because the product is difficult to purify. The procedure employed here is claimed to offer an improved process and a product of greater purity.

The final stage of the synthesis is shown in Scheme 25 and uses the adduct **81**·MA which reacts with **82** in the presence of K_2CO_3 in DMF to form the isoxazole ring in **83**. This is then converted to the hydrochloride salt **83**·HCl and isolated as such.

Scheme 24



Scheme 25



Advantages

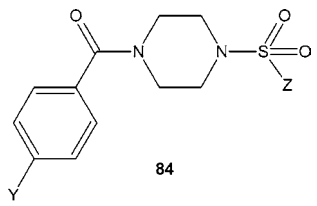
The patent provides a novel route to **83** that includes a new hydrazine trapping reaction and an improved method for the key coupling step.

Patent No. U.S. 6,753,331

Assignee: AstraZeneca AB, Sodertalje, Sweden

Title or Subject: Heterocyclic Derivatives Which Inhibit Factor Xa

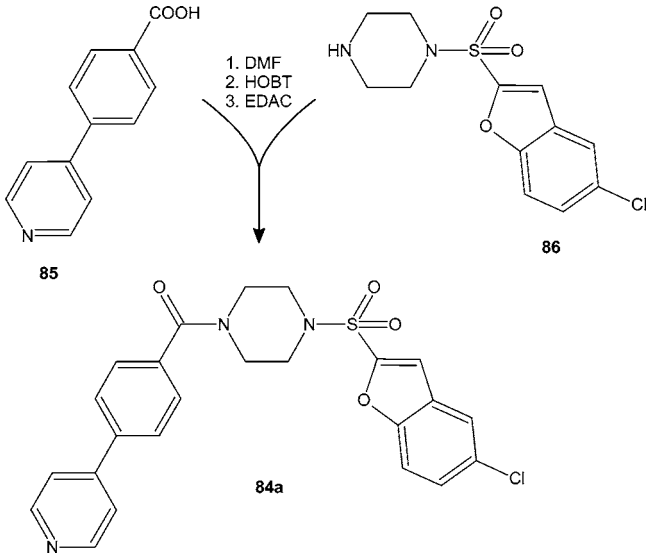
This patent has the same objective as the previous one and discloses compound with the general structure **84** that inhibits the formation of factor Xa. In **84** Y and Z are a range of heteroaromatics, and the patent states that compounds that contain halo substituents in either of the other two rings cannot be made by the route described.



84

A specific example of the type of compound that is included is **84a** which is prepared by the reaction shown in Scheme 26.

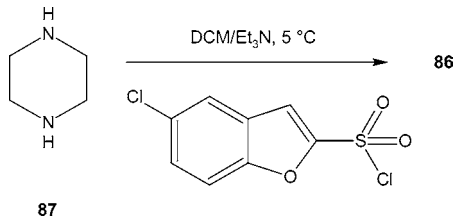
Scheme 26



This is carried out by suspending the acid **85** in DMF and then sequentially adding HOBT, EDAC, and **86**. This was left overnight, and **84a** was obtained by liquid chromatography. A range of over 20 analogous compounds was made by a similar procedure, and ^{1}H NMR data are given for each of them and for most other compounds.

The patent also describes a method for preparing the amine **85** which was not purified before use, and the reaction is shown in Scheme 27.

Scheme 27



Advantages

The compounds disclosed in this patent are all novel and said to be suitable as Factor Xa inhibitors.

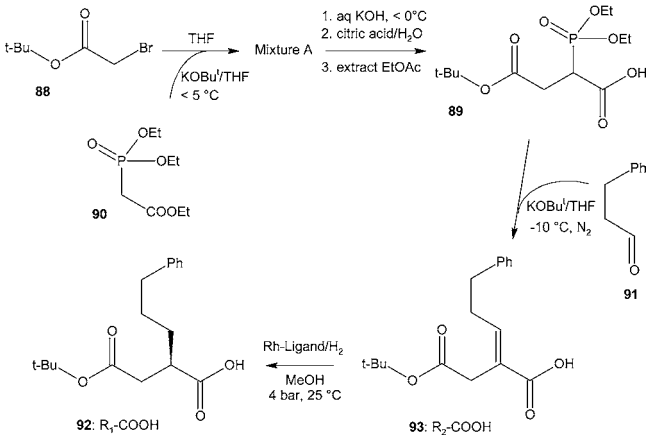
Patent No. U.S. 6,750,363

Assignee: Pfizer Inc., New York, New York, U.S.A.

Title or Subject: Olefination Process for Producing Itaconate and Succinate Derivatives

The objective of this patent is to produce compounds such as **93** which can be asymmetrically reduced to **92**. Typical olefination processes give a poor E/Z selectivity or mixtures of regio- and stereoisomers of **92**. This patent describes a novel olefination process which has good *trans*-selectivity to **91** and begins with the phosphoryl succinate **89** which is prepared by coupling of **88** and **90** in the presence of strong base as shown in Scheme 28.

Scheme 28

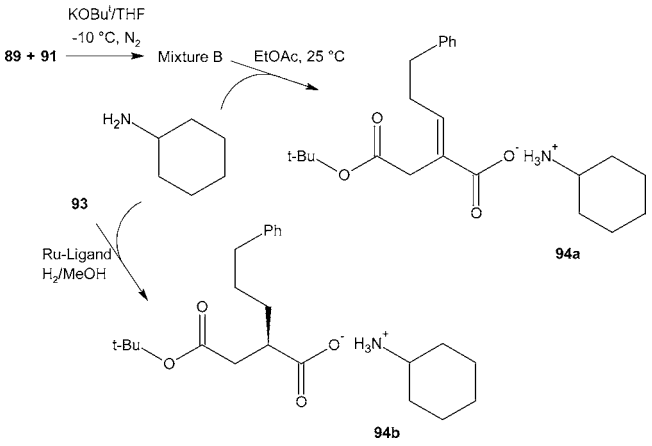


Reaction of **89** with the aldehyde **91** and a strong base produces **93**. ^{1}H NMR data are given for all compounds, and experiments describe the preparation of >10 kg of **89**.

The unsaturated acid **93** can be converted to the *R*-acid **92** by the use of asymmetric catalytic hydrogenation. The preferred catalysts used are those containing chiral ligands of biphosphinites and are Rh or Ru complexes. Rh-DUPHOS is a preferred catalyst. A 98% conversion of **93** to **92** is described with the product having an ee of 97% and a purity by NMR of 95%.

The patent also describes the production of various salts of **92** and **93**. As an example shown in Scheme 29 following the reaction of **89** with **91** the addition of cyclohexylamine to mixture B gives the salt **94a**.

Scheme 29



If the hydrogenation of **93** is carried out in the presence of cyclohexylamine and a Ru catalyst, the salt **94b** is formed.

Advantages

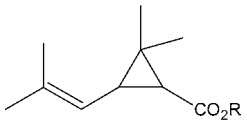
The process is claimed to be amenable to scale-up, and in fact a number of experiments described do use multikilogram amounts of reagent.

Patent No. U.S. 6,750,370

Assignee: Sumitomo Chemical Company Limited, Osaka, Japan

Title or Subject: Process for the Racemisation of Optically Active Vinylcyclopropanecarboxylic Acid Compounds

Vinylcyclopropane derivatives are useful in the synthesis of a number of chiral compounds including pyrethroid insecticides and pharmaceuticals. This patent describes a method of racemising compounds such as **95a** or **95b**. Alternative resolution methods are said to use Lewis acids that are corrosive, and this patent describes a process that is based on the use of metal nitrates. Examples are given using nitrates of Al, Ce, Fe, In, Zn or Zr, or even NO_2 in liquid or gaseous form. The procedure is to heat the compound in refluxing xylene containing the nitrate and nitric acid. A mixture of **95b** containing 93.2% (+)-*trans*, 2.8% (−)-*trans*, 2.7% (+)-*cis* and 1.2% (−)-*cis* gave the following isomer distribution: 48.3% (+)-*trans*, 41.6% (−)-*trans*, 5.0% (+)-*cis* and 5.2% (−)-*cis*.



95a: R = H
95b: R = Et

Advantages

The process is claimed to be more suitable than alternative procedures that use corrosive reagents.

Patent No. U.S. 6,750,371

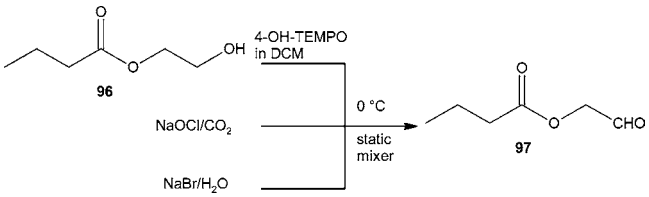
Assignee: Consortium für Elektrochemische Industrie GmbH, Munich, Germany

Title or Subject: Process for the Oxidation of Alcohols to Aldehydes and Ketones in the Presence of Nitroxyl Compounds as Catalysts

The use of TEMPO and its derivatives as oxidants is common practice, and the reactions are often conducted in batch reaction systems. However, in batch reactors it is difficult to remove the heat of the strongly exothermic reactions. Hence, to avoid excessive exotherms, long contact times are needed which can result in secondary reactions that produce undesirable by-products. This patent describes improvements using TEMPO as a catalyst in a continuous reaction system which has intensive mixing. This mode allows contact times of less than 15 min and a subsequent reduction in by-product formation. The preferred contact times are 1−30 s. The oxidation of **96** to **97** is carried out

by pumping the three separate solutions through a tube containing a static mixing element (Scheme 30).

Scheme 30



An 80% yield of **97** was obtained by fractional distillation after the reaction mixture was washed with HCl and $Na_2S_2O_7$.

Similar reactions were carried out for preparing pivaldehyde from neopentyl glycol and also *N*-(2-oxoethyl)phthalimide from *N*-(2-hydroxyethyl)phthalimide. When the oxidation of **96** was carried out in a batch system with high intensity mixing, the yield of **97** was only 37%.

Advantages

The process improves the selectivity and yield of aldehyde at a high productivity.

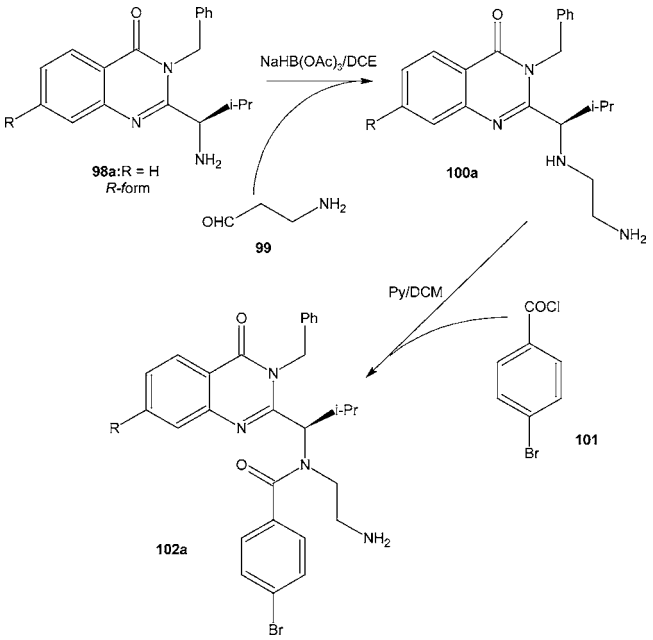
Patent No. U.S. 6,753,428

Assignee: Cytokinetics Inc., South San Franciso, California, U.S.A.

Title or Subject: Process for Racemisation of Chiral Quinazolinones

The title compounds such as **102a** have varied biological properties and have potential in treating cancers. The patent discloses a method of racemising the unwanted *S*-enantiomer of **98a** by refluxing with NaOEt in EtOH containing 5% PhMe for 36 h. After removal of the solvent by evaporation and acidification the mixture contained a 1:1.1 mixture of the *R*- and *S*-enantiomers. The pure *R*-enantiomer **98a** was then used to prepare **102a** by Scheme 31.

Scheme 31



No experimental details are given in the patent, but the route to **102a** proceeds via the intermediate amine **100a** that is formed by reductive amination of **99** with **98a**. Treatment of **100a** with the acyl chloride **101** produces **102a**. A similar route is used to prepare **102b** (R = Cl) from **98b** (R = Cl).

Advantages

The process improves the overall yield of the desired products by allowing the unwanted enantiomer to be racemised.

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