Organic Process Research & Development **2004**, *8*, 10–17

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published between August and October 2003

Summary

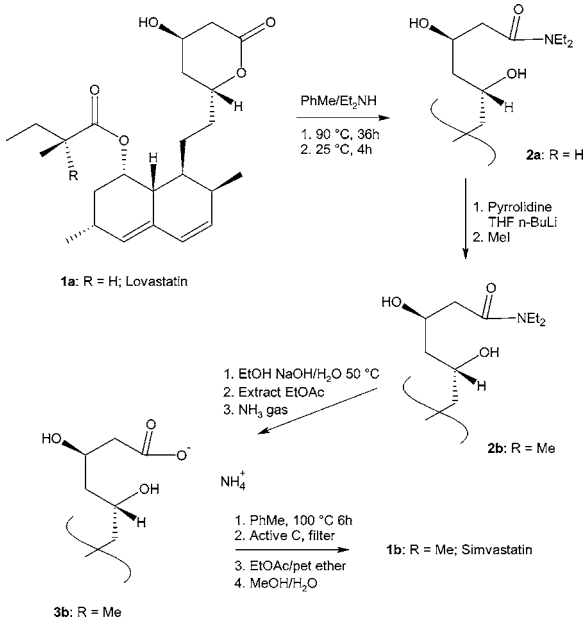
Beginning with the current issue of the journal there will be a review of U.S. patents in each issue, but in view of the reduced time available this review is shorter than normal. There are only 14 patents that were selected from an initial list of 401 that fitted the search criteria, and it is hoped that these are of interest to readers. It seems that each review contains patents that disclose new polymorphs of existing drugs, and this selection is no exception. The anti-allergy drug norastemizole has been thought to exist as a single crystalline form, but it has been found that the commercial material actually only contains 20% of the thermodynamic polymorph and 80% of the kinetic form. A method of producing the thermodynamic form is disclosed. Polymorphs are obviously a problem in drugs, but another patent describes the discovery of four new polymorphs of a pigment. The new forms have different colours, and hence there are new potential applications for the pigment in its new forms. Statins continue to attract interest, and another new route to simvastatin is disclosed. One patent describes how a simple washing procedure can purify the anti-ulcer drug prilosec by removing an isomer that can affect the stability of the drug. The importance of mixing cannot be overlooked in process development, and one patent describes how a reduction process, to produce an azetidinone intermediate, was improved by the method and order of mixing reagents. The discovery that charcoal can be used to catalyse a bromination is interesting since one normally uses this material in the work up and purification of reaction mixtures. However, the bromination process uses CS_2 as a reaction solvent which is rarely used because of its extremely high flammability so that the advantages of the improvement may be outweighed by the use of this solvent. Crown ethers have been used to catalyse the formation of cefpodoxime proxetil in an improved method over the use of alternative phase transfer catalysts. In a number of the patents, experiments using kilogram quantities of reagents are described, indicating the advanced state of the work. However, there is no commercial or legal significance in the choice of patents that have been reviewed. The advantages described are usually those claimed in the patent unless this reviewer has prior knowledge.

Patent No. U.S. 6,603,022

Assignee: Biocon India Limited, Hebagodi, India

Title or Subject: Process for Manufacturing Simvastatin and Novel Intermediates Thereof

Statins continue to be of interest because of their use as inhibitors of cholesterol biosynthesis and for treatment of cardiovascular diseases, and patents on these compounds have been.reviewed (*Org. Process Res. Dev.* **2003**, 7, 459). Many of the routes to these compounds involve a step to protect the reactive lactone ring, whereas this patent describes a process for preparing simvastatin **1b** from lovastatin **1a** that does not require this protection procedure. The direct conversion of **1a** to **1b** is not possible because of the presence of the reactive lactone. The process described here involves the formation of the amide **2a** which is then methylated to give **2b** and then subsequently converted to **1a**. The scheme below shows one example in which **1a** is first treated with Et_2NH to form the amide **2a**. Reaction of **2a** with Li pyrrolidide followed by MeI gives the amide **2b**. After acidification the partially purified **2b** was then hydrolysed and converted to the NH_4 salt **3b** which was then decomposed by heating under N_2 and purified to give pharmaceutical grade **1b**. There are a number of alternatives disclosed in the patent that revolve around the strategy of producing an amide. There is an example using piperidine as the secondary amine in place of Et_2NH, and the claims refer to several other amines.



Advantages

The process has only four stages and proceeds via the secondary amides that are chemically stable under the reaction conditions. This contrasts with the use of alternative procedures that use primary amides that contain a reactive H atom and give rise to undesired side reactions.

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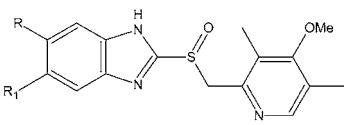
Patent No. 6,608,091

Assignee: L. B. Whittall, G. W. Walker, and R. R. Whittle, Wilmington, North Carolina, U.S.A.

Title or Subject: Process for Purifying 6-Methoxyomeprazole

The drug prilosec is used for treating gastric ulcers and was originally believed to be the 5-methoxyomeprazole compound **4a**. It was originally sold as this compound but was later shown to be a mixture of two positional isomers that cocrystallised in a single-crystal lattice. The second isomer is the 6-methoxyomeprazole **4b**. The stability of the drug is affected by the ratio of the 5- and 6-isomers with the 6-isomer being preferred. Hence, processes that can increase the amount of the 6-isomer or reduce or convert the 5-isomer are commercially attractive. This patent discloses a method of fulfilling this objective using a very simple procedure of rinsing the mixture and removing the 5-isomer by washing with a low alcohol such as MeOH or THF. The procedure is carried out at ambient temperatures and removes the 5-isomer since this is more soluble in the rinsing solvent. The remaining solid is then dried under vacuum at ambient temperature. Examples show that it was possible to increase the amount of **4b** from 67 to 91% using MeOH compared to 76% of **4b** using EtOH or 69% with *i*-PrOH. THF increased the amount of **4b** from 67 to 73%.

Omeprazole



4a: R = H, R_1 = MeO
4b: R = MeO, R_1 = H

Advantages

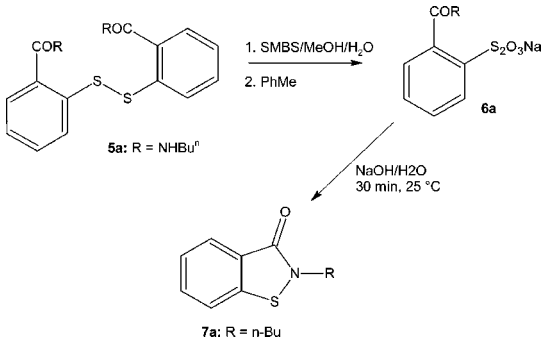
This is such a simple procedure that it is surprising that it has been overlooked in earlier work.

Patent No. U.S. 6,608,208

Assignee: Zeneca Limited, London, United Kingdom

Title or Subject: Process for Preparation of 1,2-Benzisothiazolin-3-ones

The title compounds are used as industrial biocides and can be made by cleaving disulphides using sulphuryl chloride, but this can involve production of undesirable by-products. This patent describes an environmentally acceptable process for producing **7a** by cleavage of a bisamide such as **5a** to give a Bunte salt **6a** which can then be converted to the product **7a**. The cleavage of **5a** is carried out using a bisulphite or a precursor to a bisulphite such as sodium metabisulphite (SMBS). The cleavage of disulphides is said to have been reported only for amino-substituted bisamides, and poor results are described for other bisamides. This patent discloses that the reaction can be carried out using bisamides that are contaminated with polysulphide compounds. Such compounds would normally be expected to produce byproducts that would be difficult to remove and would adversely affect the performance of the biocide. It is an unexpected finding that these polysulphides can also be cleaved in the same reaction and produce the same Bunte salt, thus giving higher overall yield of the final product. The scheme below shows the process which is carried out in a single reaction vessel.



The cleavage is carried out under reflux and then the majority of MeOH/H_2O removed azeotropically after addition of PhMe to the cooled filtered mixture. The suspension of the salt **6a** in PhMe was then treated with NaOH, and this caused cyclisation to give **7a** in 95% yield. When using sodium bisulphite the overall yield was 70%, and with oxygen this fell to 49.5%.

Advantages

The process does not require the use of chloro compounds, and hence does not produce hazardous byproducts; in addition it gives higher yields than the alternative processes.

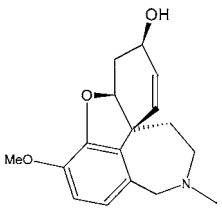
Patent No. U.S. 6,617,452

Assignee: LTS Lohmann Therapie-Systeme AG, Neuwied, Germany

Title or Subject: Process for the Isolation of Galanthamine

This is the second patent from this company on this subject that has been reviewed previously(*Org. Process Res. Dev.* **2003**, *6*, 784) and involves the extraction of **8** which is of interest in the treatment of Alzheimer's disease. Synthesis of **8** is difficult since it has three chiral centres and it can be extracted from the plants, snowdrops and daffodils. This patent and the earlier one describe how **8** may be extracted from plants that normally are said to be weeds, and although chlorinated solvents can be used to extract **8**, residues of such solvents are not acceptable in drug formulations. The process developed by this company by extraction uses petroleum ether as extracting solvent. The two patents cover the detail and the overall process for extracting **8** from *Narcissus pseudonarcissus* which is basically a weed but is capable of being cultivated.

Galanthamine



8: (-)-galanthamine

The basic extraction method is summarised as follows:

1. Mix the comminuted bulbs with Na_2CO_3 at about 4 wt %.

2. Add petroleum ether (80/110) and leave 24 h.

3. Renew solvent twice, collect, and evaporate to dryness under vacuum.

4. Mix extracts with 2% H_2SO_4 and adjust pH to 4 using aqueous ammonia.

5. Extract five times with Et_2O and evaporate extract to give yellow oil.

6. Recrystallise from hot *i*-PrOH to give pure **8**.

Advantages

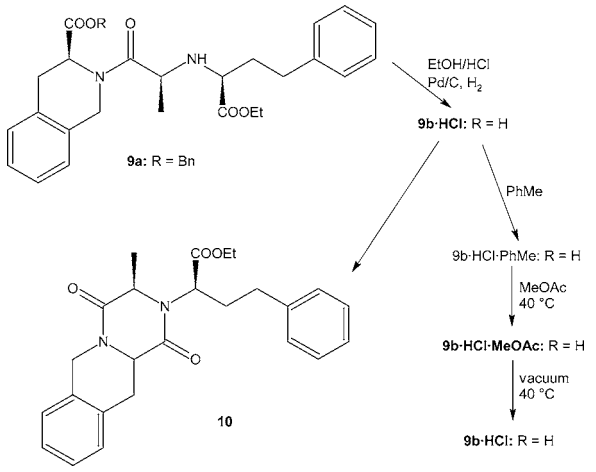
The process is applicable to using common weedlike plants as a source of this valuable drug rather than using less common species. It allows the selective extraction of small amounts of **8** from the source without the use of chlorinated solvents which leave undesirable residues.

Patent No. U.S. 6,617,457

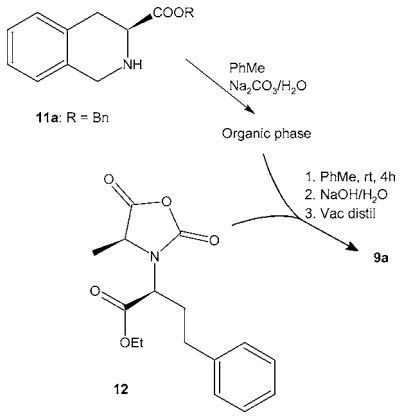
Assignee: Esteve Quimica S.A., Barcelona, Spain

Title or Subject: Isolation and Purification of Quinapril Hydrochloride and Its Solvates

Quinapril **9b** and its salts are used as antihypertensive agents, and this patent describes a process to obtain it from the benzyl ester **9a**. Alternative methods of preparing **9b** have been known for several years but are said to give low yields; isolation of **9b** is hindered by virtue of the fact that it degrades easily to give the diketopiperazine **10**. Solvates tend to be more stable, but it is stated that the only known solvate of **9b** that can be dried without degradation is the acetonitrile solvate. The carcinogenic nature of MeCN means that using this solvate as a drug substance is not attractive. Hence, this patent discloses a procedure for forming solvates of **9b** that are stable to drying using class 3 solvents such as HCO_2Et and MeOAc. The scheme below shows the formation of **9b** and its and its degradation product **10**. The formation of the hydrochloride **9b**·HCl is carried out by hydrogenation of **9a** in an alcoholic solvent in the presence of HCl. The toluene solvate is then formed in 88% yield by removing the EtOH from the mixture and replacing it with PhMe. Treatment of the toluene solvated salt **9b**·HCl·PhMe with HCO_2Et or MeOAc at 40 °C replaces the PhMe by the ester. The ester-solvated salt can be dried in a vacuum oven without degrading the product, and the residual of solvents is below the maximum allowable.



The patent also describes the preparation of **9a** by condensation of the *N*-carboxyanhydride **12** with the benzyl ester **11a**. This is carried out at room temperature in aqueous $NaHCO_3$/toluene and gives a 98% yield of **9a**. Comprehensive ^1H and ^{13}C NMR spectroscopy and X-ray diffraction details are given for each compound and intermediate.



Advantages

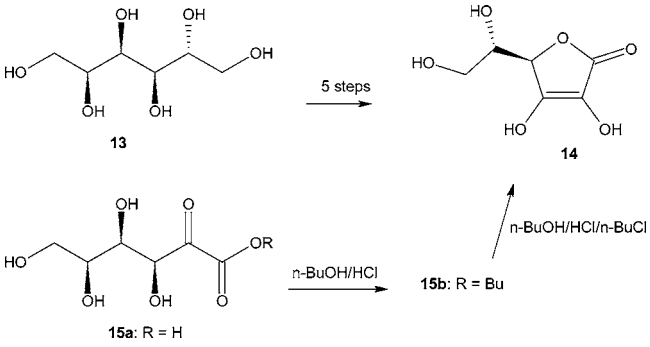
This process gives high yields of thermally stable solvate salts of **9b** that can be freed from solvents and are thus suitable as drug substances.

Patent No. U.S. 6,617,463

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Production of L-Ascorbic Acid by Lactonisation of 2-Keto-L-Gulonic Acid or its Esters

Ascorbic acid (vitamin-C) **14** is produced commercially on a substantial scale by two main processes. One is from sorbitol **13** and is a multistep process; the newer method is a two-stage process that produces 2-keto-L-gulonic acid **15a** as an intermediate. This is then converted to **15**, and it is this process that is operated by BASF. The route from **15a** to **14** described in this patent is the acid-catalysed lactonisation of **15a** and is presumed to be part of the commercial process operated by BASF.



There are said to be alternative methods for this rearrangement of **15a** to **14** but these involve long reaction times or use solvents that cause problems during workup. The patent specifically mentions using solvents that are immiscible with water such as hydrocarbons or chlorinated solvents. Since **15a** is generally not very soluble when using such solvents, the long reaction times are not surprising. Hence, an objective of this patent is to improve the overall process, and this is achieved by using solvents that are

partially miscible with water and in which **14** is not very soluble. Alcohols are preferred, and *n*-BuOH is used in the examples. In fact, what happens is that the acid **15a** is esterified with *n*-BuOH, and it is the butyl ester **15b** which is converted to **14**. The rearrangement reaction is carried out by treating a mixture of **15b** in *n*-BuOH with concentrated HCl and then adding *n*-BuCl. The presence of *n*-BuCl is said to improve the lactonisation process as well as improving the removal and recovery of the *n*-BuOH. The desired **14** is precipitated from the mixture and can be obtained in 86% yield at 99% purity. Recrystallisation then produces vitamin-grade material. The process can be operated continuously or batchwise, and examples are described for both techniques.

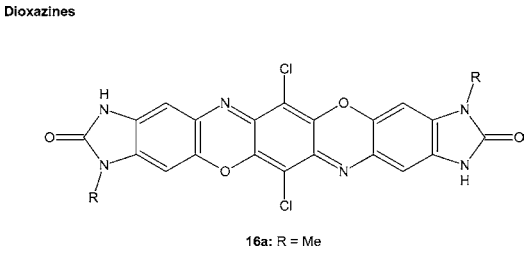
Advantages

The process appears to be in commercial operation and hence must be assumed to be an improvement over the alternatives.

Patent No. U.S. 6,620,931

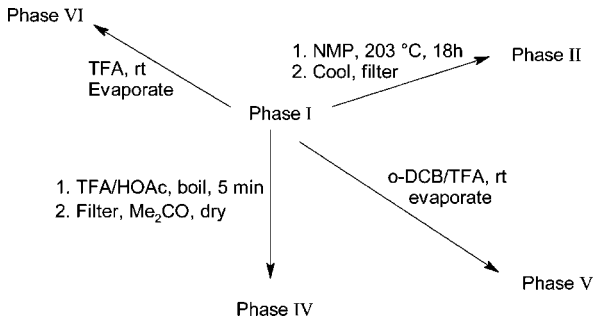
Assignee: Clariant GmbH, Frankfurt, Germany
Title or Subject: Preparation of New Crystal Polymorphs of a Methylbenzimidazolone−Dioxazine Pigment

The title compound **16** was previously thought to exist in only two crystalline polymorphic forms which are referred to in this patent as Phases I and III. This patent discloses that there are in fact six polymorphs; these are distinguished by X-ray diffraction data which are provided, and they all exhibit different colour properties. The new forms are obtained by treating the original forms with different solvents. This is said to be a surprising finding because the equivalent *N*-ethyl compound **16b** (R = Et) does not exhibit such conversions.



16a: R = Me

The scheme below shows the various methods that are used to obtain the new polymorphic forms of **16a**. The patent contains examples of the use of the new forms in various dyeing tests.



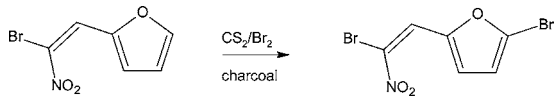
Advantages

The new polymorphs are essentially new pigments with different properties and hence could have alternative applications to the original forms.

Patent No. U.S. 6,624,316

Assignee: Centro de Bioactivos Quimicos, Villa Clara, Columbia
Title or Subject: Method for Obtaining 2-Bromo-5-(2-bromo-2-nitrovinyl)furan

This patent discloses a new procedure for producing **18** which is a microbiocide and suitable for both human and animal use. The novel aspect claimed in the patent is the use of a large excess of charcoal in the bromination of **17** which is carried out in CS_2. It is recommended that the amount of charcoal used is at least 20 wt % of the amount of **17**. The reaction mixture is then treated with pyridine in CS_2 in a neutralisation and dehydrobromination step, and after a preliminary crystallisation crude **18** is obtained in purity of 95%. This compares to only 80% using the previous synthesis. Recrystallisation of **18** from EtOH gives a final purity >99%. It is noted that the use of charcoal has the effect of eliminating the exotherm in the reaction so that a constant temperature is maintained. In addition there is no emission of Br_2 from the reactor. It is also stated that by adding charcoal it is possible to significantly reduce the amount of CS_2 that is needed. This then reduces the need for a distillation step to separate CS_2 from Br_2.



17 **18**

Regarding the novelty aspect, not surprisingly there is no comment in the patent as to why the charcoal has such an impact on the process. Charcoal is very widely used to remove or reduce impurities, and it is interesting to speculate whether it has had other effects in other reactions where it has been used. In practice it is not common to add charcoal at the start of a reaction but rather to use it as part of the workup procedure.

Advantages

The patent claims that the procedure reduces the total reaction time and also the amounts of solvent needed. However, the process uses a solvent that is so highly flammable that it is usually avoided at almost any cost. There is also the claim that the control of the reaction is improved since it is no longer exothermic and a reduction in the emission of Br_2 has a positive environmental impact. The use of CS_2 at any level hardly seems to be an improvement over prior art and cannot claim to have a positive environmental impact.

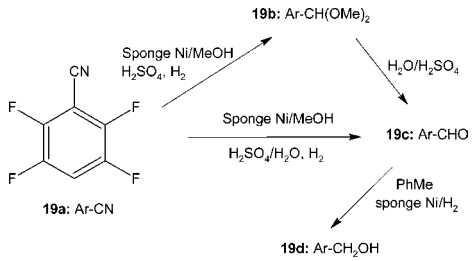
Patent No. U.S. 6,624,336

Assignee: Showa Denka K.K., Tokyo, Japan

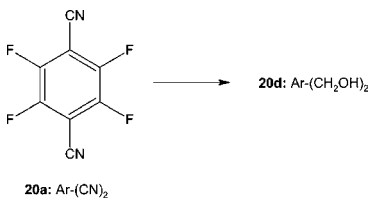
Title or Subject: Process for Producing Tetrafluorobenzyl Alcohols

The title compounds such as **19d** and related aldehydes **19c** are intermediates for producing various cyclopropanecarboxylates that are used as insecticides. Alternative methods for the production of the alcohols involve reduction of the acids with alkali borohydrides or electrolysis or by reduction of a cyanomethyl compound. If the aldehyde **19c** is required, the presence of residual **19d** causes purification problems because **19d** is difficult to remove in view of its higher boiling point. It is said to be difficult to stop the formation **19d** if **19c** is required, and thus an improved process for **19c** is necessary. The alternative processes are not industrially attractive for the various intermediates, and hence the patent therefore discloses improved procedures for these useful intermediates.

The process begins with the cyano compound **19a** which can be converted to the aldehyde **19c** via the acetal **19b** or by direct hydrogenation of **19a**. The formation of **19b** occurs if the reaction is carried out at 20 °C or above or if water is added and the reaction carried out at 10 °C. The acetal is converted to the aldehyde by acid hydrolysis, and hydrogenation of the aldehyde **19c** gives **19d**. The scheme below shows the overall route for the production of **19d** from **19a**. The catalyst used is mainly sponge Ni, but the patent also describes catalysts that also contain copper sulphate.



The procedure is also applied to formation of the alcohol **20d** from the dicyano compound **20a** as shown below. In a manner similar to that described above, the reaction can also be conducted to allow isolation of the diacetal **20b** and the dialdehyde **20c**.



Advantages

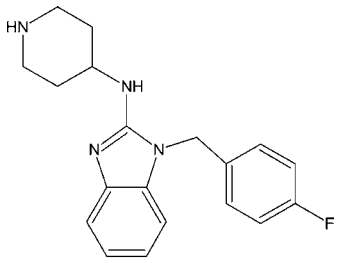
The process allows the isolation of several intermediates and the final alcohol product in high purity and at higher yields than alternative methods.

Patent No. U.S. 6,627,646

Assignee: Sepracor Inc., Marlborough, Massachusetts, U.S.A.

Title or Subject: New Polymorphic Forms of Norastemizole

The compound **21** is used in the treatment of allergic disorders, and it has only been thought to exist as a single polymorph. This patent discloses that the material produced by literature methods actually contains 80% of the kinetically controlled product (Form B) and only 20% of the preferred thermodynamic polymorph (Form A).



21

The patent describes how to produce the thermodynamic form by a procedure involving dissolution, addition of antisolvents, and various heating and cooling stages.

The process for producing high yields of Form A comprises the following steps:

1. Dissolve **21** in a minimum amount of refluxing EtOH.
2. Add sufficient water as antisolvent to initiate crystallisation of **21** at reflux.
3. Stir under reflux for 1 h to allow equilibration of polymorphs and formation of 95% of A.
4. Add a further portion of water at reflux over a period of 2 h to allow crystallisation of >85% of **21**.
5. Stir and cool to 70 °C over at least 3 h and then cool to 30 °C over further 3 hours.

The last two steps are critical, and in these it is essential that the solubility of Form B is not exceeded so that it remains in solution.

As is usual, the patent contains detailed X-ray diffraction spectra plus solubility details of the two polymorphs. There is also a detailed description of the crystalline structure and differences between the two forms. The main differences are the sequence H bonds linking the N atoms in the molecule. There are also some details of the rate of interconversion of the two polymorphs which is important in developing the method summarised above. The rates are affected by temperature, rate of cooling, degree of agitation, and relative amounts of EtOH and water. The findings show that both the rate of cooling and the rate of water addition are critical. Comparison of the literature methods showed they all used techniques favouring Form B.

Advantages

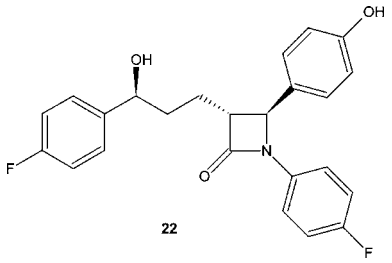
The patent has shown that the thermodynamically favoured polymorph can be produced in a controlled manner, although whether this form is more pharmaceutically active is not mentioned.

Patent No. U.S. 6,627,757

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

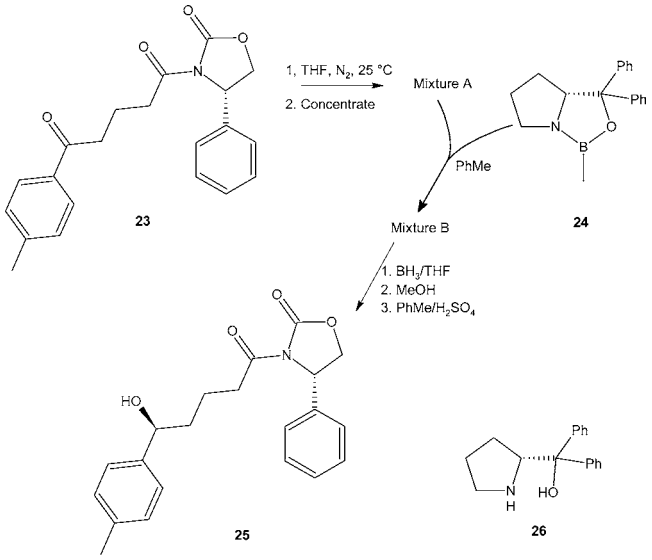
Title or Subject: Enantioselective Synthesis of Azetidinone Intermediate Compounds

The alcohol **25** is used in the production of azetidinones such as **22** which are hypocholesterolemic agents and used to treat and prevent atherochlerosis.



22

One of the methods described is shown below, and this initially involves making a solution of **23** in THF under N_2 at 25 °C. This is then concentrated under vacuum to produce mixture A to which is added the oxazaborolidine **24**. This acts as an enantioselective catalyst in the reduction of the keto group with BH_3·THF to give **25**. The reaction is then quenched with MeOH, and the final yield is said to be in excess of 97%. The ee was also high with the result reported as the difference between % *SS* and % *SR* being in excess of 93%. An important aspect of the synthesis is the mode of mixing of **24**, **23**, and BH_3·THF. It was found that by adding the catalyst **24** to the mixture and then adding the BH_3·THF a better yield was obtained since reduction of the amide bond in **23** was prevented. An earlier method of reducing **23** to **24** used BH_3·Me_2S complex in the second stage, but this gives rise to environmental problems when disposing of the waste products. Simple replacement of this complex with BH_3·THF was only improved when the mode of mixing and addition in the second stage was investigated.



23 24 25 26

It is possible to use an acid such as TsOH in the first stage, and another alternative is to use the pyrrolidine compound **26** in place of **24** in the second stage. However, it is claimed that if **26** is used then $(MeO)_3B$ must also be present although no experimental details are provided for this option. Some of the examples for preparing **25** use 15 kg of **23**, and hence the process appears to have been developed to a substantial scale.

Advantages

This process reduces the environmental problems of the alternative process by replacing the BH_3·Me_2S compound and also provides improved yields.

Patent No. U.S. 6,630,593

Assignee: LG Chem Investment Ltd., Seoul, Korea

Title or Subject: Process for Preparing Substituted 5-Hydroxymethylimidazole

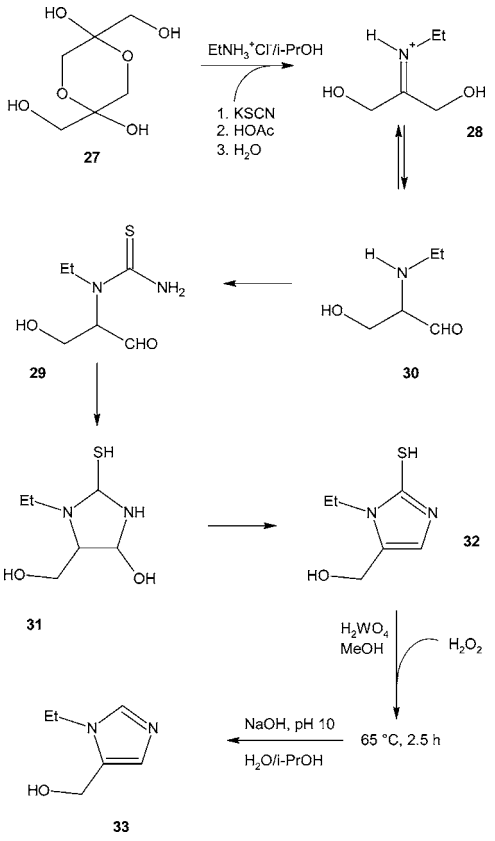
The title compounds **32** and **33** and related imidazoles are key intermediates in the preparation of a number of potential anticancer agents such as farnesyl transferase inhibitors. A number of processes are known for the preparation of **32** which start from the 1,3-dihydroxyacetone dimer **27**. In these processes **27** is reacted with amines in the presence of KSCN. However, it is claimed that isolation of the product is complicated because of the formation of a black tar. The imidazole **33** is frequently prepared from **32** by an oxidative desulphurisation using concentrated HNO_3. However, this reaction produces NO_2, is difficult to control, and can also give nitration of aromatic rings that may be present as substituents on the N of the imidazole ring.

The process described in this patent uses the same basic routes to produce **32** and **33**, but by using different reagents the problems of the alternative processes are reduced or even eliminated. The scheme below shows the overall steps for conversion of **27** to **32** and then **33**. Also shown is the suggested mechanism of the reaction which is believed to proceed via the iminium ion **28** that tautomerises to the aldehyde **30**. Reaction of **30** with the thiocyanate gives the thiourea intermediate **29** which on cyclisation produces **31**, and subsequent dehydration gives **32**. The conversion of **32** to **33** is carried out by using H_2O_2 as oxidising agent in the presence of tungstic acid as catalyst. This removes the environmental problems that exist when using HNO_3 and allows better control over the process.

It is believed that in the alternative process for converting **27** to **32** using free amine the presence of excess amine results in the formation of the black tar. Hence, by controlling the amount of free amine the byproduct can be reduced, and this is achieved by using the acid salt such as $EtNH_3Cl$.

Advantages

The process gives a safer and cleaner route to the important imidazoles, and the yields are higher than the alternative process since byproduct formation is significantly reduced.

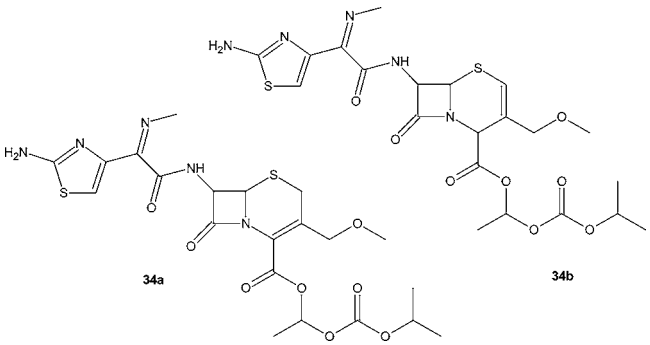


Patent No. U.S. 6,639,068

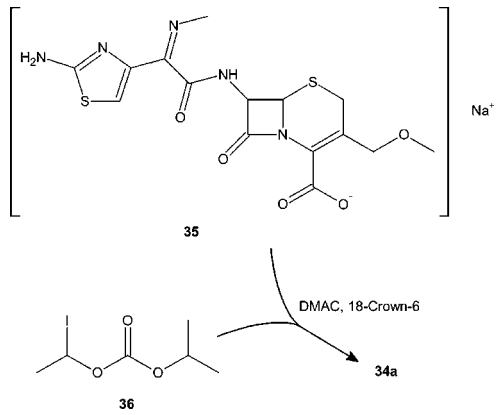
Assignee: Hanmi Pharm. Co., Ltd., Seoul, Korea

Title or Subject: Method of Preparing Highly Pure Cefpodoxime Proxetil

The title compound is a cephalosporin ester prodrug that is used as an antibacterial agent for treating intestinal Gram positive and negative bacteria.



The desired compound is **34a**, but this is usually contaminated with the isomer **34b** from which it is very difficult to separate. It is also difficult to convert **34b** to **34a**, and hence efforts are directed at minimising the formation of **34b**. The synthesis of **34a** from the salt **35** has been described previously, and although the methods do limit the amount of **34b**, they do not give good yields of **34a** and require long reaction times. One process uses dicyclohexylamine as catalyst, and the other uses $Bu_4N{\cdot}HSO_4$ as a phase-transfer catalyst. This salt is said to be used in large quantities, and because of the expense it is desirable to use alternative reagents. This patent discloses an improved procedure for preparing **34a** from the salt **35** which is shown in the scheme below.



The procedure involves treating the salt **35** suspended in dimethylacetamide with the iodo compound **36** in the presence of a crown ether. The crown ethers used are 18-crown-6, 15-crown-5, and 12-crown-4. It was found that the addition of **36** must be done rapidly to reduce the amount of **34b** that is formed because when **36** was added slowly the amount of **34b** increased. It is also important to use at least 0.5 wt % of the crown ether otherwise the level of the impurity **34b** increases. When no crown ether was used, there was between 6 and 8% of **34b** formed. By using the new procedure, the amount of **34b** could be controlled at <0.5%.

Advantages

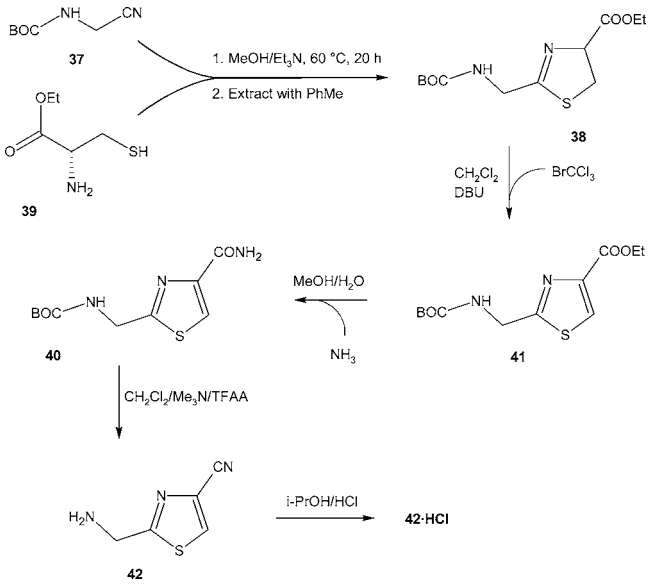
The new procedure significantly improves the purity of the product without resorting to a new synthetic route.

Patent No. U.S. 6,639,081

Assignee: Abbott GmbH & Ci, KG, Munich, Germany

Title or Subject: Method for Producing 4-Cyano-2-aminomethylthiazole

The thiazole **42** is described as having potential as an intermediate for preparing thrombin inhibitors. However, the known synthetic route to **42** is said not to be commercially



viable on an industrial scale. The reasons are due to the use of expensive reagents and poor yields when the processes are scaled up. The key step in the synthesis of **42** is the construction of the thiazole ring, and the customary procedure is to react a thioamide with a bromopyruvic acid derivative. A particular problem with this method is claimed to be the difficulty of synthesising the thioamide. The current patent provides a novel way of constructing the thiazole ring which is said to make the industrial synthesis of **42** commercially viable.

The scheme above summarises the route to **42** which begins with the reaction of the protected aminonitrile **37** with the ethyl ester of L-cysteine **39** to form the basic ring structure in **38**. This is oxidised to the thiazole **41** using DBU in $CH_2Cl_2/BrCCl_3$, and the amide **40** is then produced from **41** by reaction with NH_3. **42** can then be produced by treatment with Me_3N and TFAA, and the salt of **42**·HCl can be readily obtained.

Advantages

This new process provides an efficient method of forming the basic ring structure in the desired compound which is amenable to commercial production.

Keith Turner

Kappa Tau Consulting, 12 The Avenue, Fairfield, Stockton-on-Tees TS19 7EY, UK
E-mail: keith@kappa-tau.co.uk

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