Organic Process Research & Development **2001**, *5*, 100–109

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during August to December, 2000

Patent No. U.S. 6,103,904

Assignee: BASF Corporation, New Jersey, U.S.A.

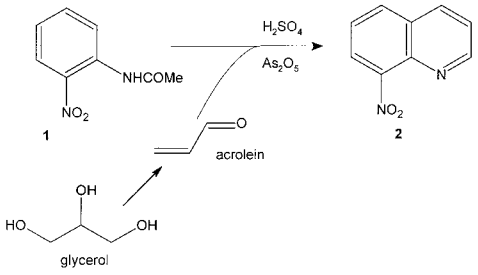
Title or Subject: Synthesis of Quinolines by an Improved Skraup Reaction

The Skraup reaction is a well-known and versatile method for the synthesis of quinolines from anilines and an α,β unsaturated aldehyde in sulphuric acid in the presence of an oxidising reagent Scheme 1 shows the production of the quinoline **2** by reacting the aniline **1** with the aldehyde acrolein (propenal) which may be added directly or produced via a dehydration reaction from glycerol. The aldehyde can also be formed in situ from an aldol condensation. The Skraup reaction normally requires a large excess of sulphuric acid at temperatures of up to 180 °C, and such conditions can result in poor yields and waste disposal problems. The improvement here involves carrying out the process under a pressure of only about 0.5 barg. This reduces the amount of sulphuric acid that is needed and also reduces the operating temperature to below 153 °C. The patent has only one claim covering the operating conditions for each stage to be used in the general Skraup synthesis. No specific examples are given, but there is reference to the use of a 1000-gallon reactor.

Advantages

The patent claims that the use of a slight pressure gives improved yields by virtue of using a smaller excess of sulphuric acid and lower temperature.

Scheme 1



Patent No. U.S. 6,107,490

Assignee: Brantford Chemicals Inc., Brantford, Canada

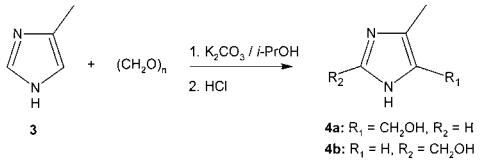
Title or Subject: Process for the Manufacture of 4-Methyl-5-Hydroxymethylimidazole

The title compound **4a** is used to make cimetidine which is an antihistamine used to treat ulcers. The normal method for making **4a** is by treatment of 4-methylimidazole **3** with formaldehyde in water in the presence of a strong base. An earlier patent in 1980 (U.S. 4,189,591) claimed that using water was essential and using methanol gave a very poor yield of **4a**. This work unexpectedly found that lower alcohols, except methanol, are good solvents and allow the use of mild bases such as K_2CO_3 (Scheme 2). The preferred solvent is 2-propanol, and the base is used as a solid so that it can be filtered off after the reaction. Since the conditions are anhydrous, a suitable source of formaldehyde is paraformaldehyde. The product was isolated as the hydrochloride salt by adding concentrated HCl or bubbling HCl gas through the mixture after the initial reaction.

There is no mention in the patent of the undesired isomer **4b**. This is usually produced when this reaction is carried out in water and can be a problem in aqueous systems because of the solubility of the products in water.

This patent demonstrates that previous work in a field may not have fully evaluated a subject and may have missed something important. The original work had used water and claimed alcohols and other solvents were unsuitable, and this statement created an opportunity for later workers to obtain a valid patent as appears to have happened here.

Scheme 2



Advantages

The use of anhydrous conditions allows milder bases to be used at lower temperatures and gives a cleaner reaction.

Patent No. U.S. 6,107,527

Assignee: Rutgers Kureha Solvents GmbH, Duisberg, Germany

Title or Subject: Process for the Production of β-Naphthol

Phenol is produced on a vast scale by decomposition of cumyl hydroperoxide which is formed by oxidation of cumene (isopropylbenzene). The corresponding oxidation of 2-isopropylnaphthalene **5** is not effective, and attempts to carry out this reaction on an industrial scale failed because of low conversion to give the intermediate hydroperoxide **6**. An additional problem is that **5** is often contaminated with the 1-isomer, which oxidises more easily than **5**, thus requiring subsequent separation of **7** from α-naphthol. This patent describes a process for producing β-naphthol **7** by catalytic oxidation (Scheme 3) using technical grade **5** without problems. The reaction is carried out in two steps,

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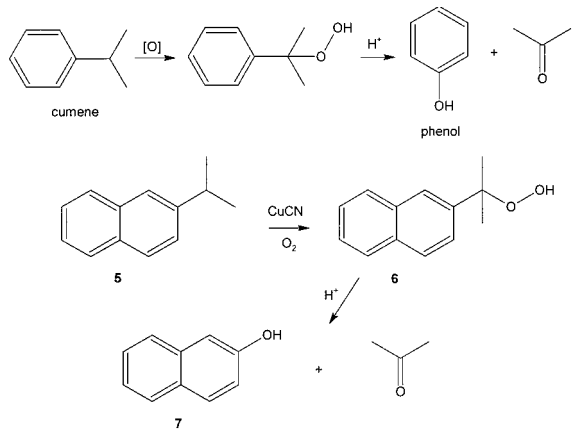
and in the first step the hydroperoxide **6** is produced by oxidation of **5** in an aqueous emulsion containing copper cyanide as a catalyst in the presence of oxygen. The mixture is emulsified by addition of 1% NaOH and palmitic acid. In the second step **6** is decomposed using mineral acids to give **7** and acetone. The overall conversion of **5** can be as high as 70% compared with <30% previously.

The patent suggests that the oxidation reaction is applicable to isoalkylaromatics in general but claims only hydroxynaphthalene compounds.

Scheme 3



Advantages

Since previously it was not possible to produce **7** from **5** on an industrial scale by catalytic oxidation, this is a significant improvement.

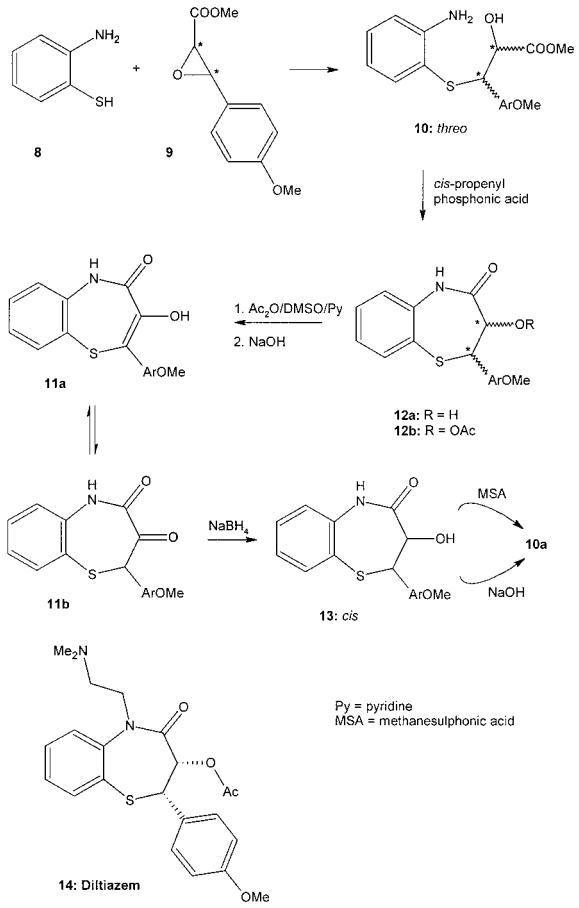
Patent No. U.S. 6,114,523

Assignee: Zambon Group S.p.A., Vicenza, Italy

Title or Subject: Process for Recycle and Reuse of Waste Products in Diltiazem Synthesis

Diltiazem **14** is a known calcium antagonist, and during its synthesis two enantiomers of the *threo* form of **10** are obtained (Scheme 4). The (*2S,3S*)-enantiomer **10a** is required to produce **14,** but the (*2R,3R*)-form **10b** cannot be reused and hence is a loss to the process. The mixture of **10a** and **10b** is produced by reaction of the epoxide **9** with the aminothiol **8**, and this work describes how **10b** can be racemised to a mixture of **10a** and **10b** such that **10b** is not lost. The racemisation is carried out in a number of stages via cyclisation of **10b** using *cis*-propenylphosphonic acid to give the (*2R,3R*)-form of the hydroxy compound **12a** which is then converted to the acetoxy compound **12b**. This is then converted to **11a** via oxidation and hydrolysis. The enol **11a** is in equilibrium with its tautomer **11b**, and reduction gives the *cis* form of **13** which, after ring-opening in methanol using either MSA or strong base gives the desired enantiomer **10a**. The ring-opening reaction to produce **10a** is claimed to be totally new and a major feature of this process.

Scheme 4



Advantages

The racemisation of **10** enables the overall yield in the diltiazem synthesis to be significantly improved. Hence, this is a major advantage over previous processes. An earlier patent (U.S. 5,102,999) covering racemisation of **12**, also assigned to Zambon, is said to be the only other example of the recycle of an intermediate with (2*R*,3*R*)-configuration.

Patent No. U.S. 6,114,543 and 6,143,554

Assignee: Sumitomo Chemical Company, Osaka, Japan

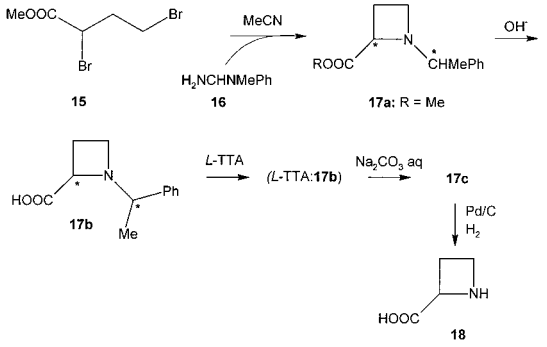
Title or Subject: Production of Optically Active Azetidine-2-Carboxylic Acid and Its Compounds

The title compounds such as **18** are intermediates in the production of antithrombotic agents. Previous synthetic routes to either enantiomer of **18** included a resolution step involving the use of L-tyrosine hydrazide, an expensive material not readily available on a large scale.

The patent U.S. 6,114,543 describes a method of resolving **18** that involves the preparation of a salt with a readily available dicarboxylic acid such as L-tartaric acid (L-TTA). The process proceeds via the route in Scheme 5 that involves the production of an *N*-alkylbenzylamine **17a** from the racemic dibromo acid **15** and a chiral amine **16**. The stereochemistry of the resulting **18** is determined by the use of the appropriate form of **15** and **16.** Thus from *S*-**16** and *R,S*-**15** the *S*-methylbenzylamine-*R,S*-carboxylate ester **17a** is obtained which on hydrolysis gives the acid **17b**. When treated with L-TTA one diastereomer of **17b** then forms a

salt which precipitates from solution. This is recovered and decomposed to give the pure diastereomer **17c** by treatment with aqueous Na_2CO_3, and the L-TTA is recovered for reuse. Hydrogenolysis of **17c** using a Pd/C catalyst produces **18** with retention of configuration and examples are given for producing the *R*,*S*-, *R*-, and *S*-forms of **18**.

Scheme 5



A second approach in U.S. 6,143,554 only covers the hydrolysis of the azetidine ester **17a** and uses an enzyme to effect asymmetric hydrolysis, and hence from a racemic mixture of **17a** only one diastereomer of the **17b** is obtained. The patent examples cover enzymes that are obtained from various Arthrobacter or Chromobacter strains, and details of DNA recombinant methods are provided in the patent.

Advantages

Both patents improve the previous resolution methods by the use of more readily available agents, and additionally the second patent achieves this in a single step. However, compare these patents with two from Astra in Sweden and another from Kaneka Corporation in Japan (see later).

Patent No. U.S. 6,114,578, 6,118,024, 6,124,468, 6,147,219

Assignee: AstraZeneca UK Ltd, London, UK

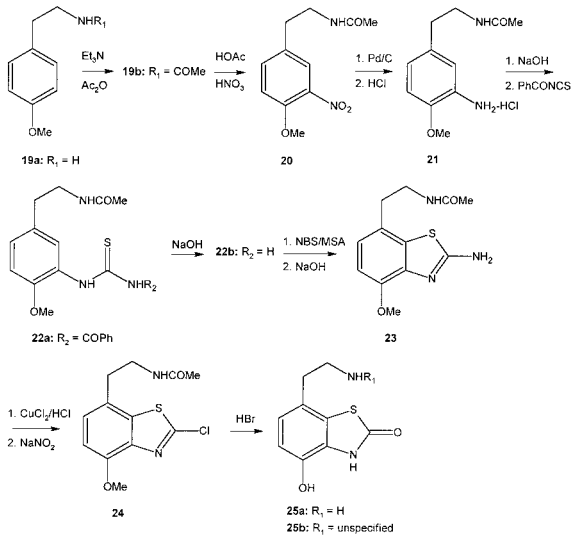
Title or Subject: Process for Preparation of Benzothiazolones

The compound **25a** is a known compound that is a D-1 and D-2 dopamine receptor antagonist. These four patents all relate to a novel synthetic route to **25a**, and each patent covers a different novel intermediate produced during the route (Scheme 6). The patents claim the novel compounds **22b** (patent 6,114,578), **20** (patent 6,118,024), **23** (patent 6,124,468), and **24** (patent 6,147,219). The intermediates **21** and **22a** are also novel and may be the subject of other patents. The four patents are what are known as composition of matter patents which means that each patent has a single claim, and this is the novel compound. The patents describe the synthesis of **25a** via the route shown in Scheme 6, and the experimental details in all four patents are identical. The patents refer to other routes to **25a** (Weinstock et al. *J. Med. Chem.* **1987,** *30*, 1166) that involve the use of undesirable starting materials.

The first stage in the route to **25a** is the conversion of the amine **19a** to the amide **19b** which is nitrated to give the nitroamide **20**. Hydrogenation and treatment with HCl converts **20** to the hydrochloride **21**, and then **21** with benzoylisothiocyanate produces the benzoylthiourea **22a**. This is converted to the thiourea **22b** by base hydrolysis which on oxidation with NBS in MSA produces the aminobenzothiazole **23**. Chlorination of **23** with $CuCl/CuCl_2$ followed by treatment with sodium nitrite gives **24**, and on treatment with HBr the desired **25a** is obtained.

The compounds **25b** have various substituents R_1 and are produced by alkylation of **25a**. No details of actual identities of R_1 are given, but there are references to other work on this subject.

Scheme 6



Advantages

The patents claim that the route to **25a** does not involve the use of undesirable starting materials and gives good yields.

Patent No. U.S. 6,121,026

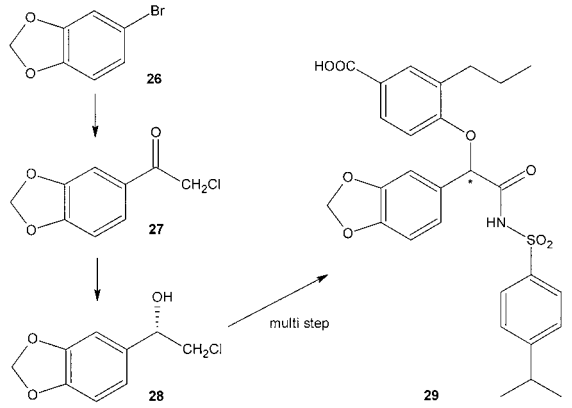
Assignee: Merck & Co. Inc., New Jersey, U.S.A.

Title or Subject: Preparation of Enantiomerically Pure Benzodioxole Compounds via Bioreduction Using Yeast

The title compounds such **28** are useful in the synthesis of endothelin antagonists such as **29** which have potential use in the treatment of many conditions causing muscle deterioration. The benzodioxole **28** is produced from the ketone **27** by enantioselective reduction using a yeast, and this is the subject of this patent. The ketone **27** is prepared by known means from the bromo compound **26** which is a commercially available material.

The patent outlines the route to **29** from **28** and also that to **27** from **26** (Scheme 7) but contains only experimental details for the preparation of the culture used to reduce **27** to **28** and the reduction step itself. The reduction is carried out using a culture obtained from *Rhodotorula piliminae*. As with other yeast reductions the process is run under dilute conditions with the concentration of **28** being only 1 g/L.

Scheme 7



Advantages

This process does not require a resolution step in the synthesis of enantiomerically pure **29**.

Patent No. U.S. 6,121,493

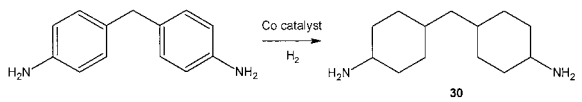
Assignee: Air Products and Chemicals Inc., Pennsylvania, U.S.A.

Title or Subject: Isomerization of Cyclohexylamines to Produce Thermodynamic Isomeric Form

Hydrogenation of bridged aromatic amines is widely used to produce bridged bis-cyclohexylamines such as **30**. The amino groups in **30** can be oriented *cis*−*cis*, *trans*−*trans*, or *cis*−*trans*, and it is difficult to control the relative amounts of each. These amines are used as monomers in the production of various polyamides, and the physical properties of the polymer are determined by the orientation of the amino groups in the monomer. For example, low *trans*−*trans* content gives liquid products, and with a high *trans*−*trans* content a solid product is obtained which is the most desirable form of **30**. The equilibrium mixture contains about 50% of this form. Most commercial hydrogenation processes do not approach the equilibrium mixture and hence there is a need to be able to direct the hydrogenation or to adjust the isomer ratio in a later step.

The work in this patent focuses on the isomerisation of the hydrogenated mixture of **30** using bimetallic catalysts of Co with Ru or Rh on alumina (Scheme 8). The isomerisation is carried out in THF at 180 °C under hydrogen and at an elevated pressure of up to 40 bar. It is possible to obtain **30** with a more favourable and higher *trans*−*trans* content.

Scheme 8



Advantages

Other catalytic methods of isomerisation or hydrogenation that give the required high *trans*−*trans* ratio require temperatures up to 400 °C to maintain the Co in the active form. This high temperature can easily degrade the products. The bimetallic catalyst appears to allow the catalyst to remain active at much lower temperatures.

Patent No. U.S. 6,124,122

Assignee: Samsung Fine Chemicals Co. Ltd, Republic of Korea

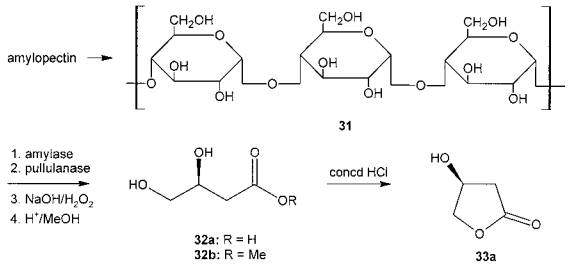
Title or Subject: Preparation of Optically Pure (S)-3-Hydroxy-γ-butyrolactone from Polysaccharide

The title compound **33a** is an intermediate in preparing various chiral drug compounds. It is also converted to the dihydroxyacid **32a** that is also a useful intermediate. There are several methods that have been used to prepare **32a** and **33a** from naturally occurring materials by enzymatic, chemical, or catalytic oxidation methods. The patent claims that there are no methods for the mass production of **33a** from high-molecular weight polysaccharides using enzymes. This process comprises the following steps:

1. preparation of α-(1,4)-linked oligosaccharide **31** from amylopectin
2. oxidation of **31** and then esterification to afford the ester **32b**
3. cyclisation of ester **32b** to give desired lactone **33a**

Scheme 9 shows the synthetic route, and the inventive step claimed in the patent is the selective degradation of α-(1,4)- and α-(1,6)-linkages in the amylopectin using specific enzymes. This produces a linked oligosaccharide **31** which has the optimal sugar distribution for preparation of **33a**. The degradation of amylopectin is carried out using sequentially α-amylase which splits the α-(1,4)-link and pullulanase that splits the α-(1,6)-link selectively. The oxidation of **31** produces the acid **32a** which is converted to the methyl ester **32b**, and this is cyclised to give **33a**. The experimental details describe production of kilogram amounts of **33a** which indicates its advanced commercial status.

Scheme 9



Advantages

This method is highly selective in comparison to chemical oxidation methods and starts with readily available, cheap raw materials. The key aspect is using different enzymes to degrade 1,4- and 1,6-linkages rather than try to do both in one step.

Patent No. U.S. 6,127,552

Assignee: Sigma-Tau Industrie Farmaceutiche Riunite S.p.A., Rome, Italy

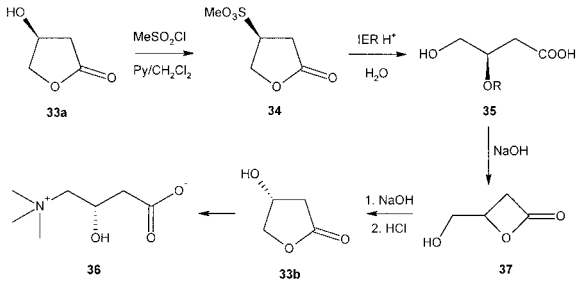
Title or Subject: Preparation of (R)-3-Hydroxy-γ-butyrolactone from its S Enantiomer and Its Use in the Preparation of (R)-Carnitine

This and the previous patent are unusual in that they are from different companies and each is aimed at one of a pair of enantiomers which has a specific use. This patent provides

a method for converting the *S*-enantiomer **33a** to the *R*-form **33b** which is then used for producing *R*-carnitine **36** that is a vitamin-like nutritional supplement for both animal and human use. The *S*-form of **36** is apparently toxic; hence, any method of producing **36** must ensure that the *S*-form is not produced.

Other methods available for synthesising **36** are claimed not to be practical on an industrial scale. However, since Lonza do sell **36** which is manufactured by biological hydroxylation of $Me_3N^+CH_2CH_2CH_2CO_2^-$, this is a rather spurious claim. Other methods start from *S*-carnitine, which is a waste product from the production of **36**, or they are based on resolution of racemic mixtures. The process described here is shown in Scheme 10 and involves the acylation of **33b** with mesyl chloride to give **34**. Hydrolysis of **34** in the presence of an acid ion-exchange resin (IER) gives the acid **35**, which in basic media gives the novel lactone **37**; further base hydrolysis of **37** and then acidification gives the *R*-lactone **33b.** The conversion of **34** to **37** can be carried out without isolation of the acid **35**.

Scheme 10



Advantages

This method has a reduced number of steps compared to others, and since it does not involve a resolution step, it also gives increased yields of **33b**. Another aspect of this patent is that it can be used to prepare *R*-carnitine from the unwanted *S*-carnitine. It is interesting to speculate on combining the process described here with that in the previous patent which would in fact be a novel patentable process in itself.

Patent No. U.S. 6,127,553, 6,147,228

Assignee: Department of Science & Technology, Government of India, India

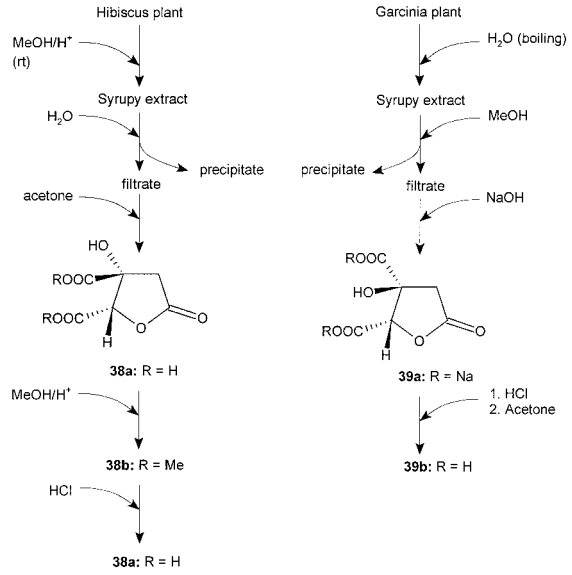
Title or Subject: Large-Scale Synthesis of Crystalline, Optically Pure Hibiscus Acid and Garcinia Acid

The title compounds are a pair of enantiomers of a functionalised lactone and these patents describe how they are isolated from hibiscus or garcinia plants. Scheme 11 shows the routes used to extract and purify the two compounds which differ slightly. Hibiscus acid **38a** is purified by extraction into cold acidic methanol, conversion to its dimethyl ester **38b** and then hydrolysis back to the acid, whereas garcinia acid **39a** is extracted with boiling water, converted to the Na salt, and recrystallised in the acid form.

Other methods for producing these acids on a large scale are not available. In fact the two acids are unavailable commercially in the crystalline, optically pure forms. Extraction from natural sources require large amounts of ethers, and synthetic methods start from materials that are not readily available.

The patents contain ^{1}H-, ^{13}C NMR, and mass spectral data with some corrections for previously published data. A large number of literature references to the use of the acids for synthesis of chiral intermediates is given in these patents.

Scheme 11



Advantages

These patents provide the first methods for the synthesis of the crystalline, optically pure acids. Since functionalised lactones have great synthetic use, this could have some potential in organic chemistry.

Patent No. U.S. 6,127,556

Assignee: G. D. Searle & Co., Illinois, U.S.A.

Title or Subject: Continuous in Situ Preparation of Chiral Aminoepoxides

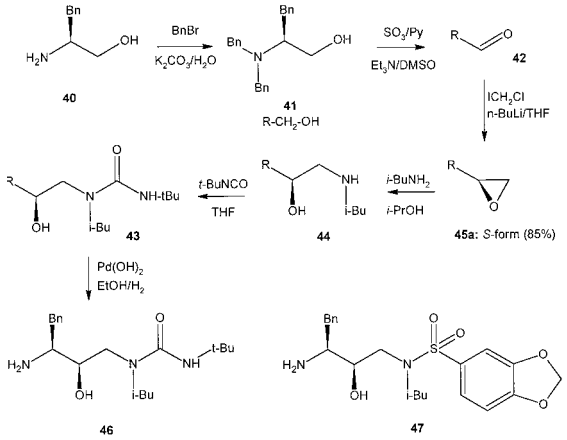
The epoxide **45a** is used in the synthesis of the substituted urea **46** that is an intermediate for the synthesis of HIV protease inhibitors. The route to **46** in Scheme 12 starts from the amino alcohol **40** that is converted to the dibenzylamino alcohol **41** derivative to protect the amine group during the synthesis. The aminoaldehyde **42** is made by oxidation of **41**, and the preferred method is to use the SO_3/pyridine complex in the presence of Et_3N and DMSO. This reaction occurs at room temperature and gives excellent yields of **42** which can be used in the next step without further purification. The patent describes a method for the continuous synthesis of aminoepoxides such as **45a** from the protected aminoaldehyde **42** using *n*-BuLi and ICH_2Cl. This step gives fairly high selectivity (85%) to the *S*-form and is the key part of the process. This reaction is very exothermic, and batch addition on a multikilogram scale can take up to 24 h because of the need to cool the system and maintain a constant temperature. In this process *n*-BuLi/ICH_2Cl is added continuously to a solution of **42** in an agitated reactor with cooling applied to keep the temperature below 25 °C. At

the same time the reaction products are withdrawn, and on warming the epoxide **45a** is formed. A number of variations on the mixing and addition methods for this step are described. The epoxide **45a** is then converted to the amino alcohol **44** by reaction with a primary amine, and the urea **43** is obtained by reaction of *tert*-butyl isocyanate with **44**. The protecting group is removed from **44** by hydrogenation using Pd catalysts to afford the desired compound **46**.

There are a number of alternative routes to **46** which involve different protecting groups, but each uses the same step for synthesising the intermediate epoxide. There are over 30 examples in the patent with several on multikilogram scale, and ^{1}H NMR data are generally provided.

The final Experimental Section of the patent describes the preparation of the 1,3-benzodioxole derivative **47**, but no reference to this compound is given in the patent itself.

Scheme 12



Advantages

Epoxides are often prepared by multistep methods requiring very low temperatures and giving low yields, and on a large scale such methods are expensive. Other routes to **46** necessitate the use of diazomethane which requires special handling procedures. The route described here does not use diazomethane and gives high yields of intermediates and final product with high optical purity. The route is claimed to be versatile, controllable, and more efficient than other methods.

Patent No. U.S. 6,127,583

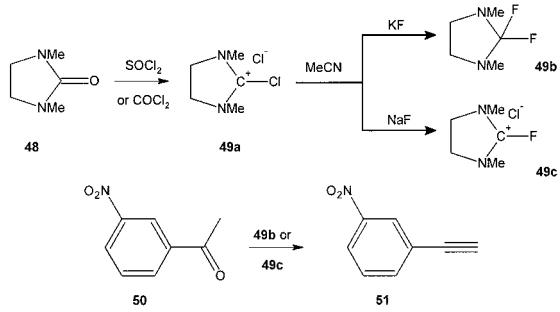
Assignee: Mitsui Chemicals Inc., Japan

Title or Subject: Preparation of Phenylacetylene Derivatives from Ketones

Acetylene derivatives are useful synthetic intermediates, and this patent describes the preparation of various phenylacetylenes from aryl ketones that must contain two α H atoms; hence, acetophenone derivatives are ideal. Several methods exist for the synthesis of acetylenes, and these are claimed to give low yield, use severe conditions, or start from expensive raw materials. Scheme 13 shows the route to 3-nitroacetylene **51** from the ketone **50** by reaction with the fluoroformamidinium halides **49b** or **49c** in refluxing acetonitrile which gave selectivities of **51** of 94 and 100%, respectively. The patent provides details of the preparation of **49b** and **49c** from the imidazolinium chloride **49a** which can be made by chlorination of the urea **48**.

Other acetylenes that were prepared include diphenylacetylene (from benzylphenyl ketone), 4-hydroxyphenylacetylene (from 4-hydroxyacetophenone), and phenylacetylene (from acetophenone). A key feature of this reaction is that the active halide compounds **49a**−**c** can be recovered and used again.

Scheme 13



Advantages

The process is simple and takes place under mild conditions and thus compares very favourably with other methods for synthesising these acetylenes. The fact that the active halides can be reused is especially beneficial since their preparation involves the use of hazardous materials.

Patent No. U.S. 6,130,218, 6,133,269, 6,140,334

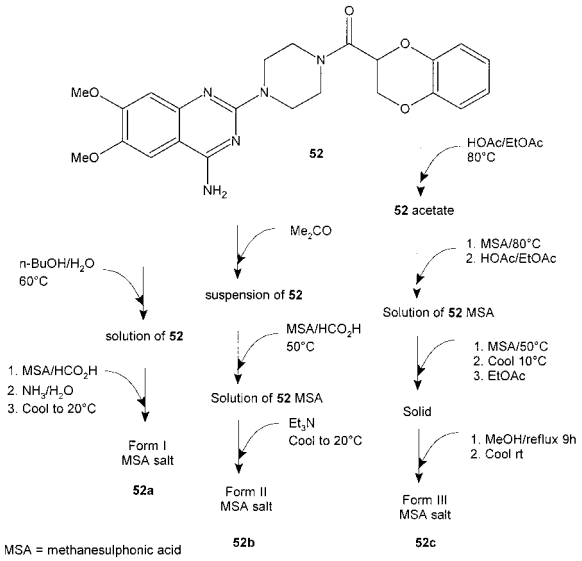
Assignee: Heumann Pharma GmbH, Nuremburg, Germany

Title or Subject: Polymorphic Forms I, II and III of Doxazosin Mesylate

The title compound **52** is an α_1-receptor that is used to treat high blood pressure and also benign prostatic hyperplasia. It is normally used as the mesylate salt because the hydrochloride is very sparingly soluble in water. The mesylate is difficult to prepare by conventional means, and the purpose of these patents is to overcome these problems. These three patents each cover a single polymorph (PM) of the mesylate form of **52**, and their preparation is shown in Scheme 14. The patents give full physical data of each PM including copies of X-ray Diffraction (XRD) patterns and differential thermal analysis (DTA) spectra.

Form I **52a** is simply made by dissolving the base **52** in *n*-BuOH followed by addition of MSA/HCO_2H, and then neutralisation with NH_3 solution produces crystals of **52a**. The preparation of the other two forms is slightly more complicated. Form II **52b** is obtained by suspending the base **52** in acetone, and the MSA salt is formed by adding MSA/HCO_2H and then neutralising with Et_3N to produce crystals of **52b**. Form III **52c** requires two additions of MSA to a hot solution of **52** in glacial HOAc and EtOAc. A second addition of MSA is then made after slight cooling and more EtOAc is added to precipitate a solid which is then subjected to a long reflux in MeOH before cooling to afford crystals of **52c**. Not surprisingly, the reasons for each method are not explained.

Scheme 14



Advantages

It is claimed in the patents that, although medicaments containing the MSA salt of **52** are on the market, no methods to prepare the salt are described. This seems odd since the original patent assigned to Pfizer (U.S. 4,188,390) was published in 1980. However, if indeed this is so, then the original patent is likely to have expired in 2000. Hence, these new patents provide an improved process for producing the different PM of **52** and possible new business opportunities.

Patent No. U.S. 6,136,591, 6,143,903

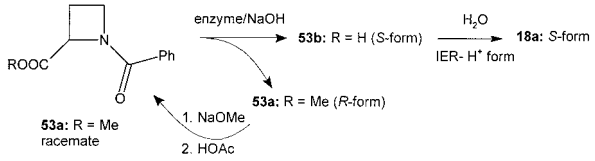
Assignee: Astra AB, Sodertalje, Sweden

Title or Subject: Production of Enantiomerically Pure Azetidine-2-carboxylic Acids

These two patents describe two further methods to obtain the pure *S*-form of the acid **18** from racemic mixtures (compare route in Scheme 5). The first patent involves the use of an enzyme to resolve racemic *N*-amyl derivative **53a**, and the second describes the use of tartrate salts to directly resolve the acid **18**. The patents state that the *S*-enantiomer of **18** is useful in the synthesis of an analogue of the amino acid proline but **18** is not readily available from natural sources. Previous methods of producing resolved **18** involve several steps, thereby reducing overall yields. The first patent claims to be the first reported bioresolution method for obtaining **18** (Scheme 15), and in fact the patent was actually published two weeks before U.S. 6,143,554 which is discussed earlier in this review.

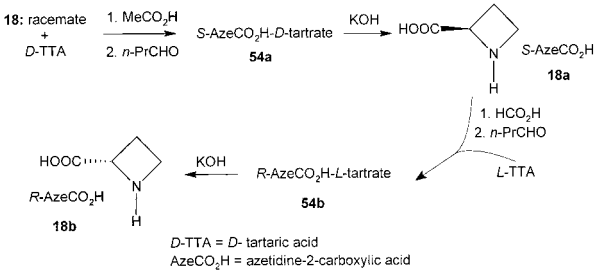
The enzyme catalyses the hydrolysis of the *S*-ester of **53a** to give the *S*-acid **53b** leaving the *R*-form of the ester **53a**. The acid **53b** is then extracted in ethyl acetate, and the benzoyl group in **53b** is removed by hydrolysis in the presence of acid IER, giving the *S*-form of **18** which is then recrystallised. The *R*-form of the ester **53a** is recovered and then racemised using NaOMe. The two enzymes that were used in the patent were *Candida antarctica* and *Aspergillus tamarii*.

Scheme 15



The second patent provides a method of obtaining one enantiomer of **18** by conversion of the other enantiomer or by resolution via formation of a crystalline tartrate salt with D- or L-TTA. Scheme 16 shows the resolution of racemic **18** which comprises dissolving the racemic mixture in acetic acid then treating with butyraldehyde. A solid residue was obtained, and this was dissolved in aqueous ethanol and treated with D-TTA to give the salt **54a** which was recrystallised. **54a** was decomposed to give the free *S*-form **18a** by treatment with aqueous KOH. The *S*-form **18a** could then be converted to the *R*-form **18b** via formation and decomposition of the L-tartrate salt **54b**. Although no example is given, it is claimed to be able to convert **18b** to **18a** via a similar process. The tartaric acid is recoverable, thus improving the process efficiency. The process in this patent can be described as being an example of adductive crystallisation since the acetic acid/butyraldehyde seems to allow one enantiomer to form the tartrate salt while preventing the other from so doing.

Scheme 16



Advantages

The first patent uses enzymes which invariably gives highly selective resolution, whereas the second patent allows the selective conversion of one enantiomer to the other using cheap and readily available reagents. These patents certainly improve on work referred to in the patent, but compare this with the other patents in this review from Sumitomo Chemical and Kaneka Corporation from Japan.

Patent No. U.S. 6,136,977

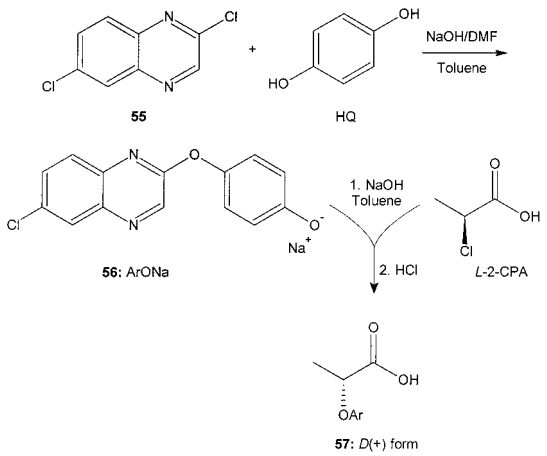
Assignee: Nissan Chemical Industries Ltd., Tokyo, Japan

Title or Subject: Processes for Production of Quinoxalyloxyphenoxy Propionic Acid Derivatives

The title compounds are used to prepare selective herbicides that control grass-type weeds in broad leaf crops. Other similar methods of producing the title compounds are available that use barium salts but are said not to be suitable on an industrial scale and do not give products of high optical purity.

The process in Scheme 17 involves reaction of the chloroquinoxaline **55** with hydroquinone (HQ) in DMF and the presence of NaOH giving the Na salt **56**. This is then treated with the Na salt of L-2-chloropropionic acid (L-2-CPA) to form the sodium salt of chloroquinoxalyloxy compound **57** which on acidification gives the acid form of **57** with inversion of configuration and at 96% ee. **56** can then be esterified with a range of alcohols including ethanol, tetrahydrofurfuryl alcohol, and isopropylidene aminoxyethanol.

Scheme 17



Advantages

The process achieves a high conversion and efficient synthesis of **57** with high optical purity. The use of Na salts as opposed to Ba salts reduces the costs and improves the effluent disposal problems.

Patent No. U.S. 6,140,321

Assignee: Eisai Co. Ltd, Tokyo, Japan

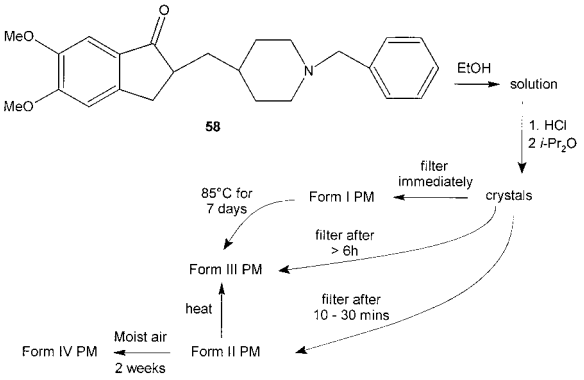
Title or Subject: Process for Production of Polymorphs of Donepezil Hydrochloride

The title compound **58** is used in the treatment of senile dementia and as with most drugs needs to be stable to storage under a range of conditions. **58** is normally supplied as the hydrochloride **58**·HCl. Previously, it was not known that PM of **58** existed and a stable form had not been found. This patent describes four PM of **58** that have excellent stability, and methods are given for the preparation of all four types.

The patent gives detailed XRD and IR absorption data for all four PM with copies of spectra as well as peak assignments. Thermogravimetric (TG) and DTA traces are also supplied. Also supplied is accelerated decomposition and PM interconversion data at storage temperatures of up to 80 °C and comparison with the amorphous form of **58** that is not very stable.

Scheme 18 indicates the methods used to obtain each of the four PM, and for each PM there are several methods given; those in Scheme 18 are claimed as the preferred methods. The Type IV PM is made from Type II, although it is claimed that it can also be made from Type I in the same way.

Scheme 18



Advantages

Since it was not previously known that PM of **58** existed, this patent has provided valuable new important data on a potential drug candidate.

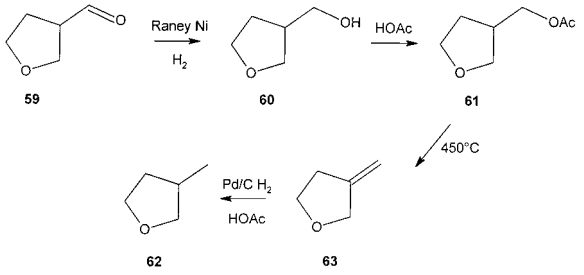
Patent No. U.S. 6,147,233

Assignee: Eastman Chemical Company, Tennessee, U.S.A.

Title or Subject: Preparation of 3-Methyltetrahydrofuran

The title compound **62** (3-MeTHF) is an industrial solvent but more importantly is a monomer used in the production of elastomers. It is often produced by high-pressure hydrogenation of citraconic anhydride and is relatively expensive. Other methods including hydroformylation of 2-butenediol and HCN addition to methyl methacrylate have been attempted but are not economical at the scale required. This process is based on the conversion of the 3-hydroxymethyl-THF **60** via a multistep route shown in Scheme 19. **60** may be obtained by hydrogenation of **59** which is generally available as a byproduct from furfural production. Acylation of **60** gives **61** which is then pyrolysed under rather extreme conditions to produce the 3-methylene-THF **63**. Simple olefin hydrogenation affords the desired methyl compound **62**. Despite the harsh conditions needed for making **63** the overall yield of **62** from **60** is almost 95%.

Scheme 19



Advantages

The route gives very high yields and starts from much less expensive raw materials; hence, appears to have the economic advantage over other processes.

Patent No. U.S. 6,147,238, 6,153,780

Assignee: Bayer AG, Leverkusen, Germany

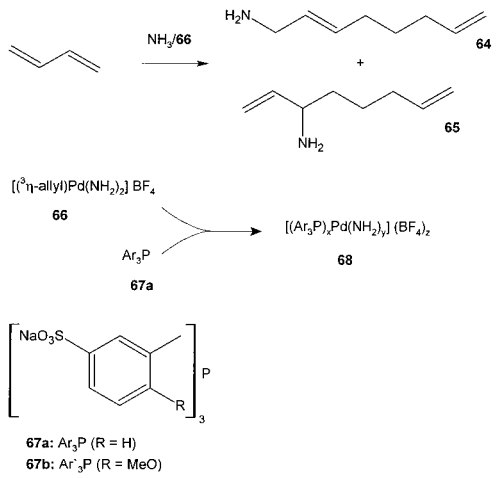
Title or Subject: Process for Preparation of Octa-2,7-dienyl-1-amine from Butadiene and Ammonia using a Pd Complex Catalyst

The amine **64** is used to prepare 1-octylamines that are required for the production of fabric softeners, corrosion inhibitors, and other surface-active reagents. The claims in these patents actually cover the novel Pd complexes **66** and **68** themselves rather than a process for the preparation of the amine **64**. The second patent covers only the Pd complex **66** which can be used to prepare **68**, and the first covers the Pd complexes **68** which are used as catalysts to prepare **64** (Scheme 20).

The detailed formulae of specific examples of complexes **68** are not specified so that exact values of *x*, *y*, and *z* are not known. There are no physical or spectroscopic data provided for them since their isolation is not mentioned. However, ^{1}H- and ^{13}C NMR data are given for several of the phosphine ligands **67** and also for the allyl complex **66.** The patents do give details of the use of a number of types of the complexes **68** in the syntheses of amine **64** from butadiene and ammonia.

The synthesis of **64** also produces the 3-amine **65** which is not desirable but is often produced at higher selectivity than **64**. Hence, there is a need to reduce its production or isomerise **65** to give **64**, and the Pd complexes **68** allows both of these possibilities.

Scheme 20



Advantages

The use of the Pd complexes **68** allows high selectivity to amine **64** by isomerisation of the 3-amine **65** to the 1-amine **64**.

Patent No. U.S. 6,150,535

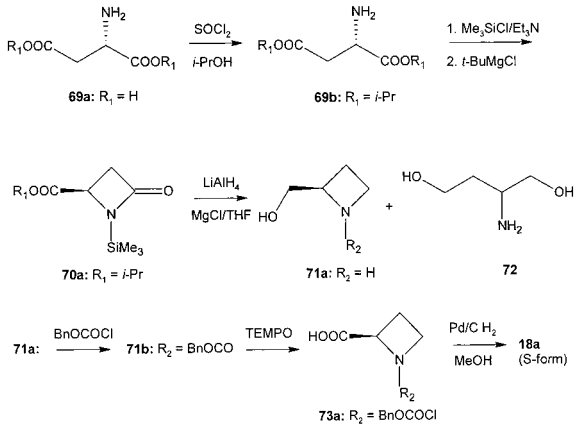
Assignee: Kaneka Corporation, Osaka, Japan

Title or Subject: Processes for Production of Azetidine-2-carboxylic Acid and Intermediates

This is another patent on the subject of the synthesis of acid **18** via the route shown in Scheme 21. In this case the synthesis starts from the oxo compound **70a** which is reduced to the amino alcohol **71a**. The patent claims that other routes to **18** can give rise to the diol **72** during this reduction, and hence the step may be carried out by first treating **70a** with $MgCl_2$. The patent includes examples and claims to this effect since it increases the yield by reducing formation of **72**. It is assumed that adding the $MgCl_2$ leads to the formation of a lactam *N*-magnesium salt, resulting in more efficient hydride reduction. The next step is protection of the amino group using benzoyloxy chloride (BnOCOCl), giving **71b** which is oxidised with TEMPO to the acid **73a.** Final removal of the protecting group by hydrogenation affords **18** (S-form). The patent also gives details of the synthesis of **70a** from L-aspartic acid **69a**.

The patent includes copies of the ^{1}H NMR spectra of several of the intermediates in Scheme 21.

Scheme 21



Advantages

As is usual it is claimed that the route can start from cheap and readily available starting materials. This appears to be the case because there is no resolution step, and it does start from the readily available chiral precursor aspartic acid **69a**, and all steps maintain the configuration.

Patent No. U.S. 6,153,414

Assignee: Bayer AG, Leverkusen, Germany

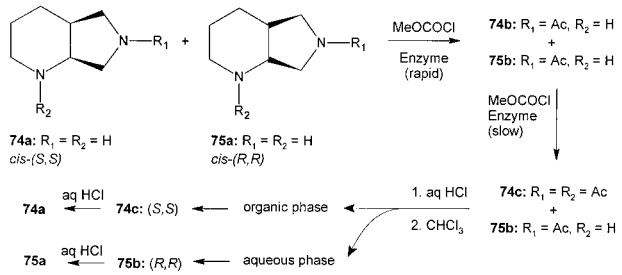
Title or Subject: Biochemical Racemic Resolution of cis- and trans-Pyrrolopiperidine

The enantiomerically pure forms of the pyrrolopiperidnes **74a** and **75a** are used to prepare quinolones and naphthyridines that have antibacterial properties. The process described here uses enzymatically catalysed acylation of **74a** and **75a** which is a 2-step reaction to give mono and diacylates (Scheme 22). The monoacylation step is quite rapid, and a mixture of the two monoacylates **74b** and **75b** is obtained from **74a** and **75a**. The subsequent diacyaltion step is faster for the (*S*,*S*)-isomer, and hence one obtains a mixture of the diacylate **74c** and monoacylate **75b**. Overall, the two steps in the example took 14 days, and they were carried out without intermediate isolation of the mixture of **74b** and **75b**. The final mixture contains **74c** and **75b** which are separated by extraction into chloroform when the (*S*,*S*)-diacylate **74c** is recovered from the organic phase while the (*R*,*R*)-monoacylate **75b** is recovered from the aqueous phase. Acid hydrolysis of these acylates then produces the corresponding pyrrolopiperidnes **74a** and **75a**.

Similarly from a mixture of the (*S,R*)- and (*R,S*)-pyrrolopiperidnes one can obtain the (*S,R*)-diacylate and (*R,S*)-monoacylate, and again the free bases are obtained without racemisation.

The enzymes used are hydrolases such as *Candida antartica*, and the particular example in the patent uses Novocym 435.

Scheme 22



Advantages

The key aspect is the different rates in the diacylation step so that it is possible to selectively produce only one diacylate. This allows selective solvent extraction and separation of the di- and mono-acylates.

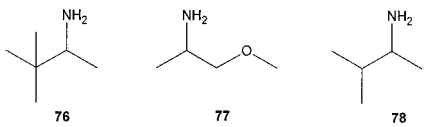
Patent No. U.S. 6,153,797

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Racemisation of Optically Active Amines

This patent describes a liquid-phase catalytic process and is analogous to an earlier one from BASF which was a vapour-phase process and has previously been reviewed (*Org. Process Res. Dev.* **2000**, *4*, 450). The racemisation is again carried out by reaction of the amine in the presence of hydrogen and a hydrogenation/dehydrogenation catalyst primarily containing oxides of Cu and Ni on alumina but which may also contain oxides of Zr, Mo, or Co.

Examples of amines that were racemised are **76**, **77**, and **78**. The racemisation takes place at up to about 200 °C and 150 bar pressure of H_2, and although methods using Raney Co catalysts are effective at lower temperature and pressure, they give lower yields. This process is more useful than the previously described vapour-phase method having a greater potential for less volatile amines. However, the range of amines was small, and only laboratory-scale experiments are described.



76 77 78

Advantages

The process gives good yields of racemate with improved yields over other methods and is potentially more practical than the vapour-phase method.

Summary

This review of U.S. patents in the field of organic process development covers the period from 1 August to 1 December, 2000, and there were 771 patents that fitted the original selection criteria. This is 200 more than the last review, and this review covers 31 patents which, hopefully, will be of interest to readers. There are no legal or commercial significances in the choices, although there are several patents reviewed (from three different companies) that dealt with the subject of azetidine-2-carboxylic acids, and hence this appears to be a subject of great interest to these companies at least. As usual the advantages given here are based on those claimed by the inventors of the patent unless this author has prior knowledge. The subject of polymorphism is an important one for chemists involved in drug development work, and three separate patents from Heumann Pharma in Germany each cover one polymorph of doxazosin, while a single patent from Eisai in Japan describes four polymorphs of donepexil. Patents describing polymorphs invariably have actual copies of X-ray diffraction spectra and also differential thermal analysis data. AstraZeneca has four patents on benzothiazolone compounds, and there is an interesting patent on formation of aminoepoxides on a continuous basis from G.D. Searle that gives better yields by improved temperature control. A feature that has been noticed in the current selection is the very large number of spelling mistakes in many of the published patents. The patents are available in electronic format, and full-text searching is available, but some of the errors would make electronic searching extremely difficult if not impossible. An example of this is fosforic acid which is claimed in one patent as an acid for use in a ring-opening reaction. The patent is from Zambon Company in Italy, and since they use U.S.-based patent agents, there really is no excuse. On the same patent the name of the company is also misspelled. There are also some examples of what appear to be deliberately misleading nomenclature in many patents, and it has already been stated in previous reviews that no attempt has been made in these reviews to give IUPAC names to any compounds mentioned here. However, it would be anticipated that for simple molecules the correct name could be given. For instance the amine **78** is referred to as 2,2-dimethyl-3-aminobutane in the patent instead of 3,3-dimethyl-2-aminobutane. The correct identity of this simple molecule is not difficult to determine, but for more complex molecules the problems are much greater. Since a patent is a legal document, it should not be too much to expect correct terminology to be used.

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Keith Turner*

Kappa Tau Consulting, 12 The Avenue, Fairfield, Stockton-on-Tees, TS19 7EY, UK

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