Organic Process Research & Development **2002**, *6*, 749–758

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during April to July 2002

Summary

During the period that this review covers there were 836 patents that met the original selection criteria. This is at least 100 more than previous searches over a comparable period and may be related to the faster-track system that the U.S. Patent Office is now using. The review covers 21 patents with several describing new polymorphs of known drugs. Polymorphs are a major headache in the pharmaceutical industry and may be produced knowingly or unknowingly. One patent describes how a new polymorph was formed during wet granulation to produce the formulated product. It is interesting to speculate whether this was a deliberate discovery. The use of simulated moving bed chromatography (SMBC) for resolution of enantiomers is a topic of increasing importance in the manufacture of pharmaceutical intermediates and products. SMBC is the subject of one patent where it is used for separating chiral precursors to an antidepressant and is known that SMBC is used commercially in the production of another similar product. The SMBC is coupled with a racemisation step so that overall atom yield is enhanced. A phase-transfer catalyst is used in one patent to increase the yield and selectivity of a two-phase oxidation reaction to produce quinones. The bulk density of a disuccinic acid derivative used in detergent manufacture was increased by changing the method of mixing reactants. This is a good example of making a change in the procedure to produce a different physical material. Again this is something that can be accidental or deliberate and needs to be taken into consideration when both bench- and larger-scale experiments are carried out. As usual, the advantages are usually those claimed in the patent unless the reviewer has prior knowledge. There is no legal or commercial significance attached to the selection, although one patent has an example involving the production of 1600 kg of an insecticide; therefore, the process is probably in commercial production.

Patent No. U.S. 6,365,747

Assignee: H. Lundbeck A/S, Valby-Copenhagen, Denmark

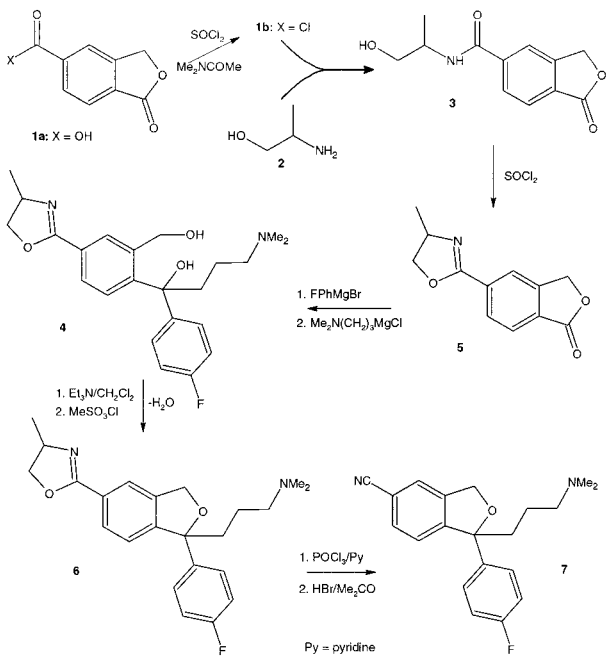
Title or Subject: Method for the Preparation of Citalopram

Citalopram **7** is an antidepressant, and a number of methods are known for its synthesis. A key step in most routes appears to be the ring-closure reaction shown below:

This patent discloses a route to **7** that involves a new ring-closure method which does not give rise to side reactions. The route to **7** starts from the carboxyphthalide **1a** which is first converted to the acid chloride **1b**. This is then reacted with the hydroxyamine **2** to give the amide **3** that is treated with $SOCl_2$, resulting in dehydration and ring formation giving the oxazoline **5**. **5** is then subjected to two consecutive Grignard reactions to give the dihydroxy compound **4**. The key ring closure of **4** to **6** is carried out by formation of the methane sulphonyl ester of **4** and dehydration in the presence of a base such as Et_3N. **7** is then formed as a salt such as a hydrobromide by conversion of the oxazoline ring in **6** to a CN group by reacting **6** with a Vilsmeier reagent. The route shown gives the two enantiomers of **7** although only the *S*-isomer is desired. The patent states that the enantiomers may be separated by resolution using tartaric or other acids, but no details are given, and no mention is made of any stereospecific steps in the synthesis of **7**. However, it is known that Lundbeck has recently completed installation of a SMBC plant at its UK site specifically for separation of the enantiomers of **7**. Hence, the new route and use of SMBC is most likely to be the method used by Lundbeck for commercial production of **7**.

Advantages

The route is claimed to be high-yield, and the steps from **1a** to **5** can be conducted in one-pot process.



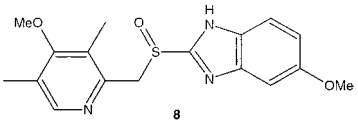
10.1021/op025591n CCC: $22.00 © 2002 American Chemical Society
Published on Web 10/23/2002

Patent No. 6,369,085

Assignee: AstraZeneca AB, Sodertalje, Sweden

Title or Subject: Form of S-Omeprazole

The title compound **8** is commonly known as Losec or Prilosec and is very widely used to treat gastric ulcers. Some of the original patents are due to expire soon or have already expired; hence, there is considerable activity in identifying new routes or new forms of **8**.



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It has been found that the Mg salt of **8** is an effective form of the drug. The Mg salt occurs in a number of polymorphic forms, and the patent describes how to obtain a stable form of the trihydrate salt from any other polymorphs of the salt. The potassium salt of **8** can be converted to the stable Mg salt trihydrate as follows:

1. treat K salt of **8** in methanol with $MgSO_4 \cdot 7H_2O$
2. precipitate Mg salt by adding acetone and leave 4 h
3. collect wet crystals from step 2, add water, and then heat at 38 °C for 3 h
4. isolate crystals from step 3 and dry under vacuum

The trihydrate salt is characterised by X-ray diffraction, and full details are given including copies of the X-ray powder diffraction patterns. One example describes the synthesis of over 30 kg of the Mg salt, indicating that this is a serious commercial method.

Advantages

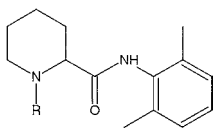
The patent claims that the Mg trihydrate salt is an active drug and that it can be obtained as a well-defined compound in a highly pure form. As a result it can be more easily characterised and handled in a full-scale production.

Patent No. U.S. 6,384,227

Assignee: Darwin Discovery Ltd, Cambridge, United Kingdom

Title or Subject: Racemisation Process Used in the Manufacture of Levobupivacaine

The title compound **9a** is one of a class of anaesthetic agents known as piperidine-2-carboxanilides. The desired enantiomer is the *S*-form, and routes to **9a** produce both *R* and *S* forms; hence, there is a need to improve atom yield by racemisation of the *R* form. The patent describes a method of racemisation by heating either enantiomer at concentrations >100 mg/mL in aqueous solution containing ethylene glycol at pH above 6. Previous studies had shown that racemisation was inhibited if the concentration of **9a** was <30 mg/mL. The patent also claims that compounds related to **9a** where R = Me or *n*-Pr can be racemised similarly.



9a: R = n-Bu

Advantages

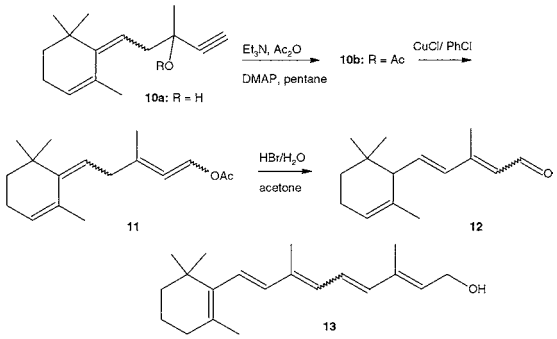
The current process thus provides a method of improving atom yield in a relatively concentrated solution.

Patent No. U.S. 6,384,270

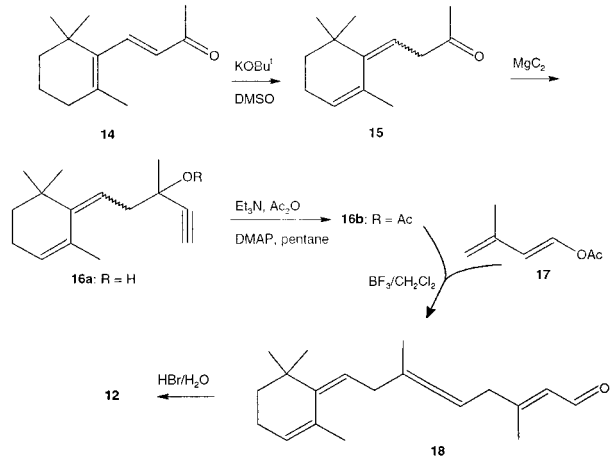
Assignee: Aventis Animal Nutrition, S. A., Antony, France

Title or Subject: Method of Preparing an Aldehyde Intermediate for Vitamin A

This is the first of two patents in this review covering synthesis of intermediates for vitamin A, **13.** One route to **13** is from the aldehyde **12**, and this patent describes a synthesis of the aldehyde **12** and also a route to vitamin A starting from β-ionone **14**. The route to **12**, which is shown below, involves production of a novel intermediate allene ester **11** by isomerisation of the propargyl acetate **10** using cuprous chloride. This isomerisation did not occur when using Ni or Pd catalysts that have been used for formation **13** via rearrangement of other allenes. The acetate **10** is obtained by treating the alcohol **9** with Ac_2O in the presence of a tertiary amine such as Et_3N and DMAP as an activating agent.



The second aspect of the patent is a route to **13** starting from β-ionone **14**, and this is shown below. The first step is isomerisation of **14** to the retro-α-ionone **15** by a previously known process using $KOBu^t$ in DMSO. The second stage is the ethynylation of **15** with Mg acetylide which is produced by the reaction between acetylene and *i*-PrMgCl. This gives the alcohol **16a** which is acetylated to give **16b** using the same technique as in the synthesis of **10**. The next stage is condensation of **16b** with the butadiene acetate **17** in the



presence of BF_3 in CH_2Cl_2 to give the allene **18**. This is relatively unstable and isomerises to **12** when treated with hydrobromic acid.

Advantages

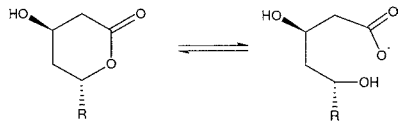
The patent gives a new route to **13** from a known material **14** and also provides a route for the synthesis of novel intermediate **12** via an improved allene rearrangement reaction.

Patent No. U.S. 6,387,258

Assignee: Biogal Gyogyszergyar Rt. Debrecen, Hungary

Title or Subject: Purification of Statins from Fermentation Broths

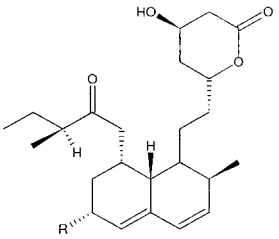
Statin drugs are extremely effective for treating cardiovascular diseases by reducing the levels of low-density lipoprotein in the bloodstream. The statins exist as open-ring hydroxy-acids which are in equilibrium with the lactone form as shown below:



lactone hydroxy-acid

The existence of this equilibrium means that purification of statins can be difficult. The two forms have quite different polarities, yet chromatographic techniques are claimed to be too expensive on an industrial scale, and other methods give low yields because they remove one form so that the overall yield is reduced.

The process described here is exemplified by purification of compactin **19a** and lovastatin **19b**. Lovastatin is the generic version of Merck's anti-hyperchlesterolemic drug, Mevacor.



19a: R = H
19b: R = Me

The process involves extraction and crystallisation steps as follows:

1 add hydrophobic solvent such as isobutyl acetate to broth and then treat with NaOH at 60 °C to convert statin to acid salts
2 separate two layers and remove nonpolar impurities in organic layer
3 acidify aqueous layer from 2 and extract with isobutyl acetate
4 separate and collect hydrophobic solvent solution
5 concentrate organic solution by evaporation
6 wash concentrated solution from 5 with aqueous base such as sodium bicarbonate
7 concentrate washed solution from 6 and allow statin to crystallise

The examples are carried out on a substantial scale with one starting with 70 m^3 of broth. The key aspect of the method is to carry out the initial extraction under alkaline conditions which causes the lactone to be converted to the hydroxy acid salt, thus allowing the oily and fatty impurities to be removed in the aqueous phase.

Advantages

As with the vast majority of fermentation processes the workup involves handling dilute solutions and hence large volumes. Alternative methods of isolation of statins are low-yield because of losses. This patent provides an efficient isolation method with minimal losses.

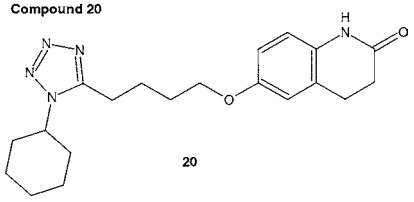
Patent No. U.S. 6,388,080

Assignee: G. R. Stowell and R. R. Whittle, Wilmington, North Carolina, U.S.A.

Title or Subject: Polymorphic Forms of 6-[4-(1-Cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2-(1H)-quinoline

The title compound is commonly known as cilostazol **20**, and its synthesis was first disclosed in 1983 (U.S. Pat No. 4,277,479). **20** is a vasodilator and is claimed to be useful in the treatment of erectile dysfunction. The current patent describes two new polymorphic forms of **20** referred to as B and C with the original form being named Form A and the only one mentioned in the early patent. The patent also mentions an amorphous form of **20**. The original material, Form A, is claimed to have limited aqueous solubility and low bioavailability; thus, it's use is limited. The patent describes how to produce Forms B or C from A, and the new forms are both stable, have improved solubility, and are more useful in preparing an active pharmaceutical ingredient (API). The claims of the patent all relate to Form C although the examples cover the preparation of both B and C.

Compound 20



20

The method of producing Forms B or C from A is a heating and cooling technique, and this appears to have been developed from a detailed study of the differential scanning calorimetry (DSC) thermogram. An example of the method for converting Form A to C is summarised as follows:

1 heat A under nitrogen from 30 past its melting point of about 160−200 °C at 10 °C per min
2 cool the molten material to 0 °C at 10 °C per min
3 reheat material to 100° C at 10 °C per min and hold for 5 min
4 cool the molten material to 0 °C at 10 °C per min
5 reheat material to 145 °C at 10 °C per min and hold for 5 min
6 cool the molten material to 0 °C at 10 °C per min

Form C melts at about 145 °C, and to prepare Form B the sequence is identical except that in step 5 the heating is

to 170 °C which is the melting point of Form B. There is no discussion in the patent as to how practical this method may be.

The patent has copies of DSC thermograms, FTIR and FT-Raman spectra, and X-ray diffraction (XRD) patterns for all of the polymorphs.

Advantages

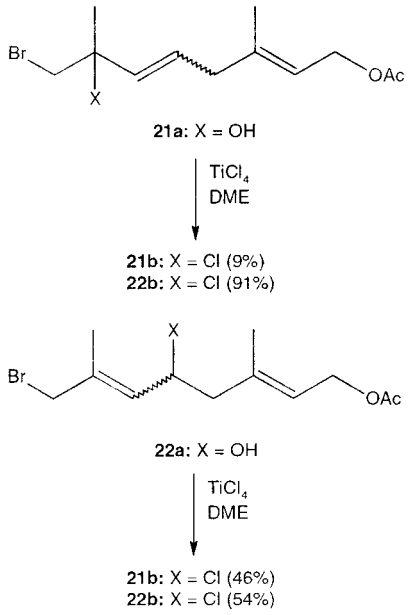
The fact that the original patent has probably expired means that patent protection of **20** can be extended by the new forms disclosed in this patent. It is interesting to note that the authors of the patent have been granted several patents in the past covering polymorphic forms of the drug fluoxetine, and some of these have been reviewed (*Org. Process Res. Dev.* **2002**, 6 (2), 98).

Patent No. U.S. 6,388,124

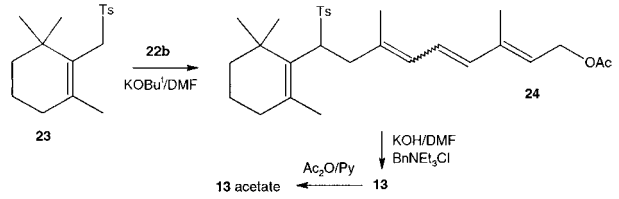
Assignee: Sumitomo Chemical Company Limited, Osaka, Japan

Title or Subject: Process for Producing a Dihalo Compound as a Vitamin A Intermediate

This is the second patent in this review describing intermediates for the synthesis of vitamin A, **13**. In this case the intermediate is a novel dihalo compound such as **22b** which is the subject of the claims of the patent. The synthesis of **22b** also produces the isomer **21b** and starts from the alcohol **21a** or **22a** which are chlorinated using $TiCl_4$ in DME. The route to **21b** and **22b** is shown below. The isomer **21b** is not useful in the synthesis of **13**, but no details of how to separate **21b** from **22b** are given.



The route to **13** is via **24** which is formed by reaction of **22b** with the tosylate **23** in the presence of a base such as $KOBu^t$ in DMF. The tosyl group is removed from **24** with KOH in DMF and a phase-transfer catalyst (PTC), producing **13**. An example of a PTC is benzyltriethylammonium chloride. The crude **13** was not isolated but converted to the acetate with Ac_2O using pyridine as catalyst as shown below.



The patent claims that either the *E*- or *Z*-isomers of **21a** or **22a** may be used or even mixtures, but no details of precise stereochemistry are given in the examples. The alcohols **21a** and **22a** and the tosylate **23** are synthesised by published methods, and references are given.

Advantages

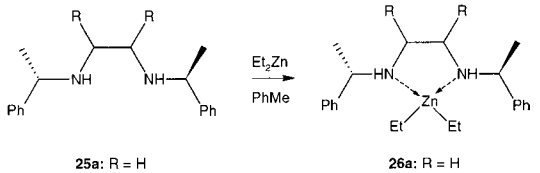
This patent claims that routes to **13** from β-ionone **14** are not attractive because of the high cost of **14**. Contrast this claim with the earlier patent that uses this route to **13**. Alternative routes that start from the tosylate **23** involve coupling with an aldehyde that is expensive to produce, whereas this patent provides an improved route to **13** from **23**.

Patent No. U.S. 6,392,103

Assignee: Firmenich SA. Geneva, Switzerland

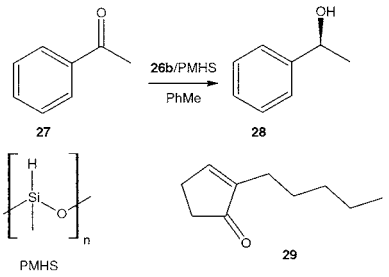
Title or Subject: Catalyst System for the Enantioselective Reduction of Ketones

The patent describes a catalyst system for reducing prochiral ketones to chiral alcohols. There are a variety of methods that have been used for this reaction, and one employs silanes with Ti compounds in the presence of chiral amines. Such methods are said to give ee < 40% and are not very active. Another method uses polymethylhydrosiloxane (PMHS) and chiral titanocenes activated by BuLi. This process is said to require large quantities of catalyst and hence is too expensive to be commercially useful. The catalyst system in the present patent is a combination of PMHS with a zinc compound such as **26a**. This is formed by reaction of a chiral diamine such as **25a** and diethylzinc in toluene as shown below.



The patent provides several examples of using compounds similar to **26a** that are formed from a range of chiral diamines. The reduction of acetophenone **27** to (*S*)-2-phenylethanol, with an ee of 88%, is carried out using **26b** as shown below. The procedure is to first form the Zn compound **26b** and then to add the ketone followed by PMHS at 20 °C.

Most of the examples are for reducing acetophenone or its derivatives, but there is an example of reducing the cyclopentenone **29**. However, this is done using different diamines to **25**, and the ee is less than 30%.



Advantages

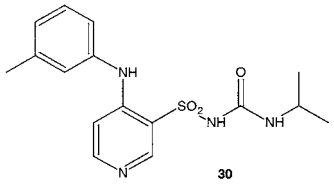
The process gives high yields of alcohol in high ee by using easily handled catalysts that are not overly expensive.

Patent No. U.S. 6,399,637

Assignee: PLIVA, Zagreb, Hungary

Title or Subject: Crystal Modification of Torasemide

Torasemide **30** is a diuretic and is claimed to be useful in the treatment of a very wide variety of ailments from epilepsy to thrombosis. It has been known since 1978 that **30** exists in two forms with Form I being more stable than Form II, but there is disagreement about the actual melting points of the two forms and which form melts at the higher temperature. Hence, it would seem that there is much confusion over what has been synthesised. To complicate matters further this patent describes another form of **30** designated as Form III. This new form can be obtained from an alkaline extract obtained during work up of the product from the synthesis of **30** by the original route described in DE 2,516,025. The new form is stable under normal storage conditions and can be used as the API in the various drug treatments. Full XRD data are given for the new form



The procedure for obtaining Form III of **30** is as follows:

1. acidify the alkaline extract from the synthesis mixture with 10% HOAc
2. stir suspension for 90 min at room temperature then filter off and collect crystals
3. wash crystals with demineralised water and dry in vacuo at 50 °C to obtain Form III crystals in 99% purity
4. the crystals from step 3 are dissolved in 5% aqueous KOH and acidified with 5% HCl
5. the solution was seeded with pure Form III crystals and after collecting, washing, and drying as above the purity increased to >99.5%

The other forms of **30** can be converted to Form III by a similar procedure.

Advantages

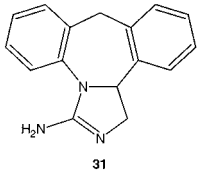
The new form is more stable than either of the previously known forms and can be produced easily and fully characterised.

Patent No. U.S. 6,403,790

Assignee: Boehringer Ingelheim Pharma KG., Ingelheim, Germany

Title or Subject: Production of the High-Melting Crystal Modification of Epinastine Hydrochloride

Epinastine **31** is active as an antiallergenic and antihistaminergic agent and is often used as the hydrochloride **31**·HCl. Unfortunately the synthesis of **31**·HCl cannot always be controlled to produce the same crystal modification. There are two forms of **31**·HCl, and it is the higher-melting one that is required. The synthetic route involves the use of DMF, and since this is classified as damaging to the foetus, it is essential to remove all traces or not to use it at all.



The process for obtaining the desired form is as follows:

1. dissolve **31** in water by addition of aqueous HCl to a pH of 8 at 60 °C
2. extract aqueous solution twice with BuOAc
3. separate and collect aqueous phase and remove remaining BuOAc by azeotropic distillation
4. treat solution with activated charcoal at 90 °C and clear solution collected.
5. acidify solution with HCl at 30−40 °C until pH is about 4
6. cool to 20 °C, seed with **31**·HCl and cool to below 5 °C to obtain the pure high melting from required

Advantages

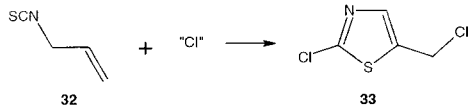
The procedure removes completely the need to use DMF and hence also the problems associated with the removal of the solvent.

Patent No. U.S. 6,407,251

Assignee: Takeda Chemical Industries Ltd., Osaka, Japan

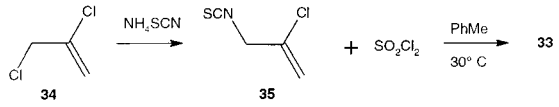
Title or Subject: Process for Preparing 2-Chloro-5-chloromethylthiazole

The title compound **33** is an intermediate in the synthesis of various insecticides and can be prepared by chlorination of allyl isothiocyanate **32** at high temperatures as shown below. It is said that this is an unselective reaction requiring large amounts of the unspecified chlorinating agent "Cl".



The process disclosed in this patent uses chloroallyl isothiocyanate **35** and sulphuryl chloride as chlorinating agent at 30−40 °C as shown below. The reaction is carried out in a monosubstituted aromatic hydrocarbon with either chlorobenzene or toluene being used in the examples. One example describes the production of >1600 kg of **33**. The patent states

that **35** can be produced by known methods such as from **34** and NH_4SCN but no details are given.



Advantages

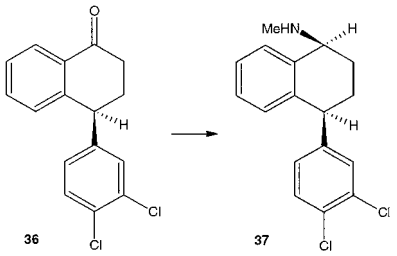
The process operates at low temperatures ,and hence higher selectivity is to be expected. The fact that large-scale production is described indicates that the process is a commercial reality.

Patent No. U.S. 6,410,794

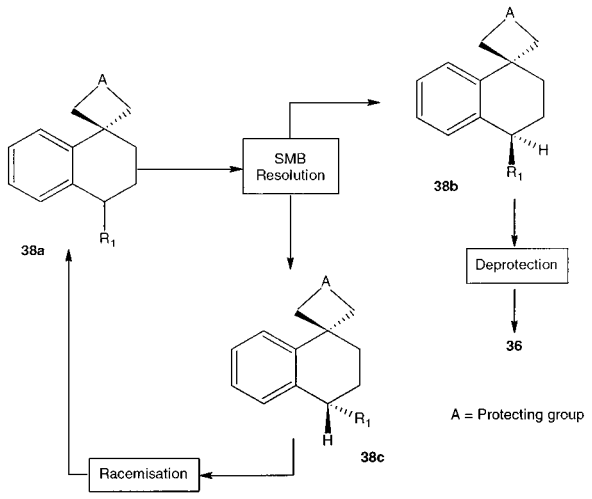
Assignee: UOP LLC, Des Plaines, Illinois, U.S.A.

Title or Subject: the Use of Simulated Moving Bed Chromatography for Separation of Chiral Tetralone from Tetralones

The use of SMBC in chiral separations has made great progress in the past 5 years, and it is regularly used in commercial production. Equipment is available which meets GMP guidelines, and hence its use is only likely to increase. This patent is from one of the leading companies in the area and describes how a pure enantiomer of the tetralone **36** is obtained by using SMBC which can then be used in the synthesis of the antidepressant drug sertraline **37**.



There are two aspects to the process. One involves the separation of an enantiomer of **36** in which the ketone group is protected. The other aspect separates the desired enantiomer of the corresponding racemic alcohol that is then oxidised to **36**. The resolution in each case uses SMBC, and then the unwanted enantiomer is racemised and recycled to the SMBC unit to recover more of the desired enantiomer.



The scheme below shows the process for separating the protected ketone **38a** into the two enantiomers, **38b** and **38c**. The desired enantiomer **38b** is converted to **36** by removing the protecting group, while the undesired enantiomer **38c** is racemised. The actual protecting group A is not specified although ketals from 1,2-glycols or 1,3-glycols and thioketals from dithiols are claimed, and the group clearly must contain a chiral centre.

Identical schemes are given in the patent for the other aspect of the patent although there are no actual experimental details given for any of the steps.

Advantages

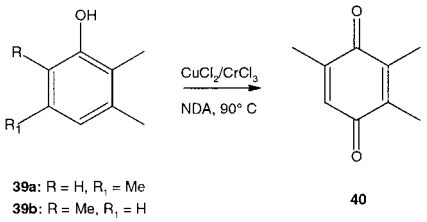
The use of SMBC coupled with a racemisation step is a very efficient method of resolving enantiomers. The technique allows the use of less expensive racemic mixtures if a suitable racemisation method can be developed for the appropriate molecule of interest.

Patent No. U.S. 6,410,798

Assignee: Degussa-Huls Ag, Frankfurt Am Main, Germany

Title or Subject: Process for the Preparation of 2,3,5-Trimethyl-p-benzoquinone

The title compound **40** is used in the synthesis of vitamin E and is prepared by catalytic liquid-phase oxidation of the trimethylphenols, **39a** and **39b**. A number of processes are known, but all of these are said to be unsafe because they operate close to or above the flash point of the reaction solvent which is usually a long-chain alcohol or a hydrocarbon. The process here overcomes this problem by carrying out the reaction in a aqueous system containing neodecanoic acid (NDA). The catalyst is $CuCl_2$ with chlorides of Mg, Ca, or Cr, and the yield of **40** is >85%. The reaction temperature is less than 100 °C which is well below the flash point of NDA. The NDA is actually a mixture of C8, C9, and C10 acids which are commercially available. This mixture boils at >240 °C and melts at −39 °C so that it does not solidify in pipelines as do the long-chain alcohols used in other processes. The process is shown below.



The process is efficient despite the fact that the NDA is insoluble in water so that it may have been anticipated that there would be poor mass transfer of aqueous catalyst to organic substrate. No explanation of the effect is provided, but it is likely that PTC is involved with the NDA enabling the transfer of catalyst between the phases.

Advantages

A distinct advantage of this process is the ease of separation of the aqueous catalyst from the reaction mixture.

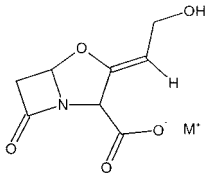
It is also relatively easy to separate the **40** from the NDA product by distillation because the bp of **40** is 50 °C lower than that of NDA.

Patent No. U.S. 6,414,142

Assignee: SmithKline Beecham Corporation, Philadelphia, Pennsylvania

Title or Subject: Process for Preparing a New Form of Potassium Clavulanate

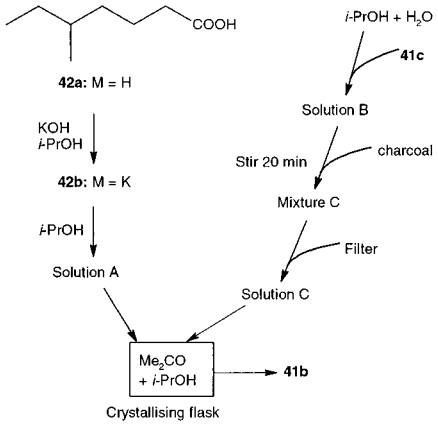
This is the first of two patents on the subject of clavulanic acid **41a** and its salts such as **41b** or **41c.** The acid is a hygroscopic oil, whereas salts are stable and **41b** is particularly used to enhance the effect of β-lactam antibiotics and prevent their deactivation. **41a** is normally prepared by fermentation processes using various strains of microorganisms. This patent discloses a new crystalline form of the potassium salt **41b** and a method of preparing it from the *tert*-butylamine salt **41c** which is an intermediate in the synthesis of **41a**.



41a: M = H
41b: M = K
41c: M = Bu^tNH_2

The normal crystals of **41b** are rodlike or needles and hence are difficult to recover and to handle. A form of **41b** has also been reported that is rosette-like and is formed by agglomeration of needles; this form is much easier to handle. The new form of crystalline **41b** disclosed here is described as rosette-like starburst, but it differs from the previously reported type. The patent includes photomicrographs of the different types of crystal, and these show the differences. The crystals of the new form are less tightly packed and therefore less likely to trap contaminants during crystallisation and are more stable than the other rosette type.

An example of the preparation of the new form of **41b** is shown below



The acid **42a** is converted to its potassium salt **42b**, and a solution in *i*-PrOH is prepared (solution A). A second solution C is prepared containing the *tert*-butylamine salt **41c**, and the two solutions A and C are concurrently added at a constant rate to a mixture of acetone and *i*-PrOH at 15−17 °C. This is carried out in a crystallising flask, and crystals of the new form of **41b** are precipitated from the solution. A comparison of the crystals with other forms shows that they have a higher density and better flow characteristics.

Advantages

The patent claims that the new form of crystals is more easily handled and more suitable for producing pharmaceutical formulations.

Patent No. U.S. 6,417,352

Assignee: CIPAN S.A, Castanheira Do Ribatejo, Portugal

Title or Subject: Process for the Isolation of a Salt of Clavalunic Acid

This is the second patent on this subject and focuses on the isolation from the fermentation broth. It is claimed that the isolation of the potassium salt **41b** by the usual precipitation methods using amine salts gives impure crystals of **41b** that require further recrystallisation. The toxicity of the amines is mentioned as a particular problem.

An example of the process includes the following steps:

A1 Filter aid and water were added to the fermentation broth, and a commercial quaternary ammonium salt flocculating agent was also added. The mixture was filtered to remove suspended solids.
A2 The filtrate from A1 was adsorbed onto an anionic ion-exchange resin (IER) in columns.
A3 The adsorbed **41a** was eluted from the column using NaCl solution.
A4 Acidified EtOAc (pH 1.4) was added to the eluate from A3 to extract the acid **41a**.
A5 The extract from A5 was treated with anhydrous Na_2SO_4 and activated C and filtered.
A6 A solution of the sodium salt 2-ethylhexanoic acid **42a** was added to the filtrate from A6 to form **41d**, the sodium salt of **41a**.
A7 Crystals of **41d** were obtained after washing and drying in 58% yield from the original broth.

The potassium salt **41b** was then obtained as follows:

B1 Crystals of **41d** were suspended in *n*-BuOAc containing 3% water.
B2 Dilute HCl was added to give pH of 1.3 at <5 °C to produce the acid **41a**.
B3 The organic phase from B2 was collected and treated with anhydrous Na_2SO_4 and activated C and filtered.
B4 The filtrate from B3 was diluted with *i*-PrOH, and a solution of the salt **42b** in *i*-PrOH was added.
B5 Crystals of **41b** were obtained and after washing and drying the yield was 78%.

A surprising feature of this process seems to be the first step in A1 in which the broth is diluted because fermentation broths are generally quite dilute. However, this dilution and the addition of a flocculating agent and filter aid improves the filtration step so that a purer filtrate is obtained which in turn improves the downstream steps. Another feature of the process is the use of an IER which removes the acid

from impurities in the solution. The purified acid is then obtained after elution from the column.

Advantages

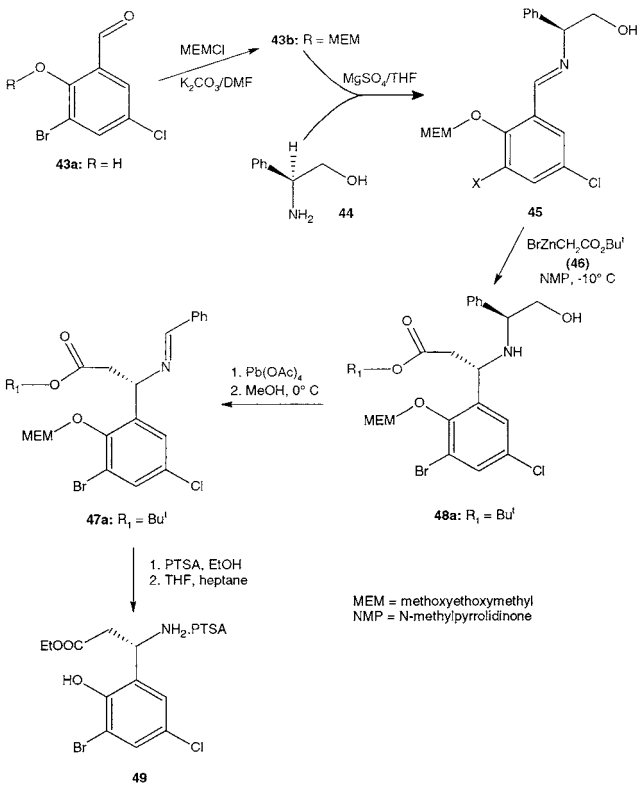
There a number of improvements in this process that significantly improve the purity and yield of the product.

Patent No. U.S. 6,414,180

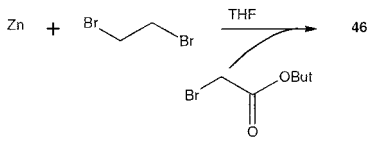
Assignee: G. D. Searle, Chicago, Illinois, U.S.A.

Title or Subject: Synthesis of Chiral β-Amino Acids

The particular chiral β-amino acids described here such as **49** are used to prepare $\alpha_v\beta_3$ integrin antagonists which are used to treat and prevent tumours. The route to **48** begins with protection of the carbonyl in the aldehyde **43a** by conversion to the MEM derivative **43b** as shown in the scheme below or as a benzyl derivative. Reaction of **43b** with *S*-phenylglycinol **44** produces the chiral imine **45**. This is then subjected to a Reformatsky reaction to give **48a** stereoselectively. The amino acid residue in **48a** is then oxidatively cleaved with $Pb(OAc)_4$ in MeOH to give the imine **47a**. This step can also be carried out using periodic acid in EtOH in the presence of $MeNH_2$. The β-amino ester **49** is then obtained by refluxing **47a** in EtOH in the presence of excess *p*-toluenesulphonic acid (PTSA). The crystals are obtained by precipitating with THF an heptane. In the process the intermediates **45**, **48a**, and **47a** are not isolated and used without purification.



The patent gives details of the preparation of the Reformatsky reagent **46** that is used to convert **45** to **48a**. The reagent **46** can be prepared from 1,2-dibromoethane and *tert*-butylbromoacetate as shown below, and **46** can be recovered as a solid and is stable for at least 6 months.



Advantages

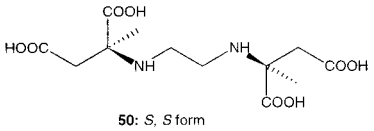
This is claimed to be a safe, convenient, and cost-effective process that can be scaled up. It uses readily available raw materials and does not need complicated or expensive resolution methods.

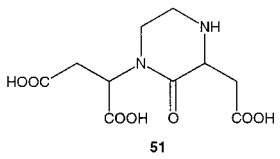
Patent No. U.S. 6,414,189

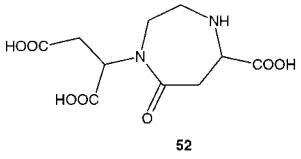
Assignee: Mitsubishi Rayon Co. Ltd., Tokyo, Japan

Title or Subject: Method of Obtaining Crystals of [S,S]-Ethylenediamine-N,N′-disuccinic Acid with High Bulk Density

The title compound **50** is said to be potentially useful as a biodegradable chelating agent in detergents. However, previous methods of preparing **50** by acid precipitation methods produced bulky crystals of low density that had poor detergent efficiency and were difficult to dry. An additional problem is that these other methods can also give rise to the production of the cyclised compounds **51** and **52** resulting in yield losses. Hence, the patent describes a method that attempts to solve both the byproduct and the density problems by an improved method of precipitation to obtain the crystals.







50 has been previously prepared chemically from L-aspartic acid and dibromoethane in a basic medium. There is an enzymatic reaction which starts from fumaric acid (FA) and ethylenediamine (EDA) and also a fermentation technique using actinomyces. The recovery of **50** involves acid precipitation, and it is this that gives low-density crystals.

The method in this patent is based on the production of **50** from FA and EDA by an enzymatic method that uses *Brevundimonas sp*. TN-3 strain. The procedure involves the following steps:

1. FA and EDA are treated with the TN-3 strain in a $Mg(OH)_2$ solution containing NaOH to maintain pH at 8.5. The procedure takes 3 days at 40 °C.
2. Centrifuge the reaction mixture to remove cells and collect supernatant liquid containing a solution of 98.8% of isomers as **50**.
3. The solution of 50 was treated with H_2SO_4 at 80 °C with pH at 3 to 3.75.
4. Cool solution to 60 °C and hold for 1 h.
5. Cool solution to 21.5 °C over 1 h and add H_2SO_4 to maintain pH at 3.2.
6. Filter off the crystals of **50**, wash and dry at 80 °C overnight.

The yield of column-like crystals obtained was up to 99.5%, and the cyclised products remained in the mother liquor. The bulk density varied between 0.45 and 1.2 g/L which compares with that of the needles crystals of about 0.2 g/L.

Advantages

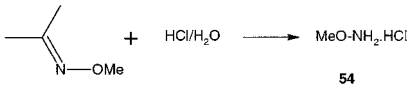
This procedure gives much better yield than had been previously possible and is another example of how changing the method of precipitation of a material can give dramatic changes in the physical properties of the crystals that are obtained.

Patent No. U.S. 6,414,191

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Method for the Continuous Production of Methoxyamine Hydrochloride

The title compound **54** is an important intermediate in the preparation of crop protection chemicals and also a number of drugs. It is usually prepared by of acid cleavage of acetone oxime methyl ether **53** as shown below.



53 **54**

It is usually produced in a batch process but has been reported as being produced continuously from **53**. Although continuous processes can give consistently better product quality than batch processes, there are particular problems when attempting to produce **54** continuously. The main problem is that the reaction is carried out in a distillation column and requires in excess of 20 theoretical plates. In addition a high reflux ratio is needed, and this means that the production rate is low and energy consumption is high.

The patent describes a process engineering solution to column operation and chooses the optimum combination of feed position, reflux ratio, and column temperature profile. The examples describe using a column containing 25 actual bubble cap trays with the feed mixture 500 g/h of aqueous HCl and **53** entering the column at the 11th tray from the bottom. The reflux ratio was 3, and the heat input to the bottom of the column was adjusted so that the temperature at tray 22 was >84 °C with the column top pressure of 450 mbar and a bottom temperature of 98 °C of **54** in the bottom product. The product was removed from the bottom at a rate of 350 g/h containing 37.5% of **54** at 99.5% yield.

Advantages

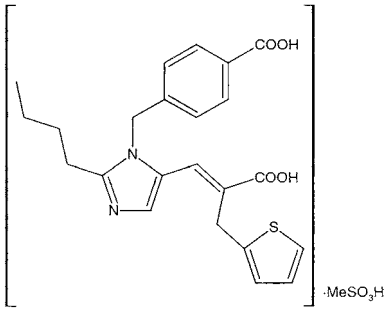
The process claims to produce **54** continuously in less expensive columns than was previously possible.

Patent No. U.S. 6,420,412

Assignee: SmithKline Beecham Corporation, Philadelphia, Pennsylvania, U.S.A.

Title or Subject: Process for the Production and Formulation of Eprosartan Dihydrate

The anhydrous form of eprosartan **55** is used in treating hypertension, congestive heart failure, and renal failure. It has been found that a dihydrate form is produced in situ during preparation of the solid dosage forms of **55** by wet granulation or by recrystallisation from aqueous acid solution.



55

The production of **55**·$2H_2O$ by wet granulation is carried out in two stages. In the first stage the anhydrous form of **55** is mixed with conventional pharmaceutical fillers and binders, and then this mixture is granulated with water and dried. The API in this granulated product is found to be the dihydrate **55**·$2H_2O$.

The recrystallisation method is carried out by suspending **55** in aqueous $MeSO_3H$ and heating to 70 °C. After filtration the filtrate is cooled, and the crystals of the dihydrate form of **55** are obtained after drying in air. The new form is characterised by DSC, thermogravimetric analysis (TGA), and XRD, and the patent includes copies of these spectra.

Advantages

The dihydrate form of **55** is claimed to be just as effective as the anhydrous form but is more easily compacted into tablets.

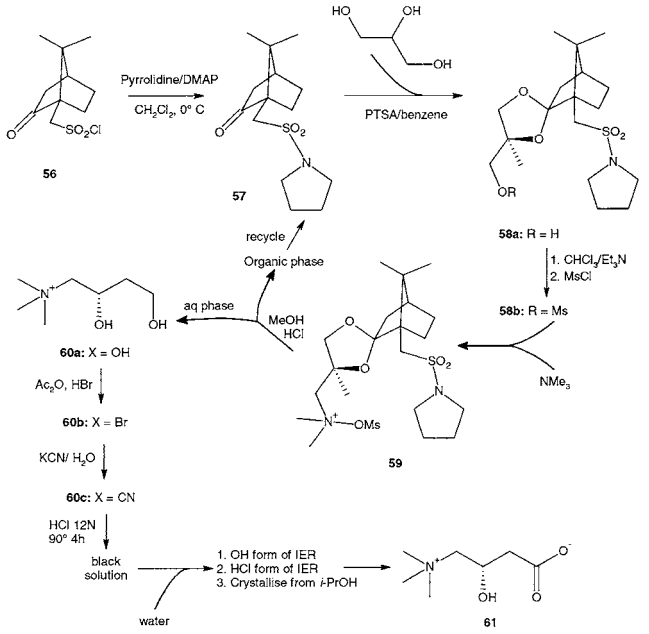
Patent No. U.S. 6,420,599

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

Title or Subject: Chemical Process for Stereoselective Synthesis of (R)-(−)-Carnitine

(*R*)-carnitine **61** is present in living tissue and acts as a carrier for fatty acids across mitochondrial membranes. It used as a vitamin supplement in both animal and human use, and since the *S*-form is reported to be toxic or causes depletion of (*R*)-carnitine in cardiac tissues, the *S*-form cannot be present and has to be removed. Other methods of producing the *R*-form have previously been reviewed (*Org. Process Res. Dev.* **2001**, *5*, 350). This patent claims that even newer processes for **61** start from a precursor with opposite configuration and require a resolution step and there is a potential for overall yield loss. The route to **61** described in this patent comprises seven steps and is shown below.

The process starts from the (−)-camphorsulphonic acid chloride **56** which is converted to the (*1R*)-sulphonamide **57** with pyrrolidine in the presence of DMAP. Treatment of **57** with anhydrous glycerol in the presence of PTSA gives the (*1R*)-spiro compound **58a**. This is converted to the (*1R*)-mesyl derivative **58b** and then to the (*1R*)-trimethylammonium salt **59** by simply dissolving **59** in a solution of Me_3N. The camphor group is liberated in the next step by treating



59 with HCl in methanol. The aqueous phase contains the (*R*)-carnitine precursor **60a**, and the camphor residue is obtained as the sulphonamide **57** which is recycled. The OH group in **60a** is then transformed to the nitrile **60c** via the bromide **60b**. Acidification of **60c** with 12 N HCl gives a black solution which is diluted with water and then passed over an anionic IER and then an acidic IER. The eluted solution was concentrated, and recrystallisation from *i*-PrOH gave an 80% yield of **61**. Alternative routes proceeded via the dibenzylamine or dimethylamine analogues of **57**.

This process uses an elegant method of maintaining the stereochemistry and again demonstrates the use of IER to purify a salt-like material.

Advantages

The process does not require a resolution step and starts from a fairly readily available starting material which already contains the required stereochemistry.

Patent No. U.S. 6,423,853

Assignee: E. I Du Pont De Nemours & Comp., Wilmington, Delaware, U.S.A.

Title or Subject: Production of Ozonides of Cycloalkenes by Continuous Ozonolysis

Cycloalkene ozonides are used to produce α,ω-dicarboxylic acids or the aldehyde acids which are useful intermediates for cyclic lactams and lactones. This patent covers ozonides of C6 to C12 cycloalkenes and describes a continuous ozonolysis process that can be carried out in a multitray glass Oldershaw column. The single example in the patent relates to cyclododecene dissolved in propionic acid. The reaction takes place at 20 °C, and hence efficient cooling is required and is carried out by pumping the feed of cycloalkene and solvent to the top of the column so that it flows down the column. An ozone generator supplies ozone which is fed to the bottom of the column and flows upwards where it meets the cycloalkene and solvent solution countercurrently on the trays in the column. The feed and ozone ratio are adjusted to allow complete conversion of the cycloalkene. The off-gases containing unreacted ozone are removed at the top, and the product is removed from the bottom of the column, containing 27.5% of the ozonide. The equipment allows recycling of part of the bottom product and can run continuously.

Advantages

This procedure allows a higher concentration of ozonide to be produced so that subsequent process steps are carried out more efficiently.

Keith Turner

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