Organic Process Research & Development **2010,** *14,* 1287–1298

*Highlights from the Patents*

# A Review of U.S. Patents in the Field of Organic Process Development Published During June and July 2010


## Summary

The current review contains 21 patents from an original list of 336 that fitted the search criteria. Separation and purification methods are as important as synthesis, if not more so, and there are a number of patents covering these aspects. The powerful opioid analgesic fentanyl contains up to 9% of the starting material before purification, and a purification method is described using reverse-phase chromatography with a solution of fentanyl HCl salt used as the mobile phase. The method reduces the impurity to <0.01%. Stiripentol is used to treat epilepsy in infants, and the drug form has a specific particle size distribution (PSD). An improved crystallisation method using PhMe in place of EtOH gives high-purity material with suitable PSD. Pregabalin has been developed as a follow-up compound to gabapentin for use in the treatment of epilepsy, and a new process for its production is described. Iodixanol is an X-ray contrast agent, and improvements in the recovery of an intermediate and iodixanol itself by crystallisation have significantly reduced solvent usage. Since the product is made on very large scale, even minor improvements are very cost-effective. A process using the same basic synthetic method as alternative processes has improved the recovery and crystallisation stage and gives a high-purity product. Avoiding the use of organic solvents is a goal in many processes, whereas the development of solvent-free processes is less common. The absence of solvents can create mixing difficulties and give mass- and heat-transfer problems. However, a process for the preparation of diketopyrrolopyrrole pigment dispersants without using solvents has overcome such problems by using a reactor that is used for dealing with viscous polymeric mixtures. A process for preparing tetralones is reported that avoids the oxidation of epoxides by such dangerous materials as $LiCl_2O_7$. The new, safer process isomerises the epoxides using $MgSO_4$ in PhMe. A method for producing a range of dihydroxy esters is disclosed that can proceed in two steps using different enzymes in each step. An enzyme is used in a bioreduction of the keto group in a dihydroxyketo-ester, and a lipase enzyme is used to catalyse the esterification of the primary OH group in previously formed trihydroxy-ester. Palonosetron is used to control nausea in various cancer chemotherapies, and an improved hydrogenation process is described to give high yields of the more active of the two isomers of the molecule. The HCl salt of bupropion is used as an antidepressant. and a new process for its production is described. Unusually the claims specify the use of $MgSO_4$ or $Na_2SO_4$ as drying agents in one part of the process. A detailed patent describes a new drug to treat erectile dysfunction that claims to be at least as effective as the current market leader. Solifenacin is used to treat urinary tract problems. and a new process is disclosed that gives high stereoselectivity of the desired isomer. A process for making *trans*-cinnamic esters is reported that claims to be green because it does not use cyanides as do other processes. The new method proposes to use microwave irradiation or ultrasound and ion-exchange resins as acid catalysts and does give high product yields. Reported is a process for preparing a range of triazolones that are useful in the treatment of new strains of AIDS and HIV. The patent contains extensive experimental details apart from the purity of the products. A new process for preparing pyranon-4-one and its tetrahydro analogue has an improved hydrogenation method, but a rather laborious workup procedure results in low yields of recovered products. The synthesis of the antipsychotic drug asenapine is reported in a comprehensive patent that proceeds via a novel *E*-stilbene intermediate. The process also uses a novel ether amine to produce an azomethine ylid intermediate more safely than using an amine oxide. Entacapone is used in the treatment of Parkinsonism, and its purification can be difficult because of a byproduct formed during the synthesis. By reducing the reaction temperature, the byproduct is not formed, and the process is improved. A novel free radical fluorination process is reported to make 3,3,3-trifluoropropionyl chloride from the aldehyde. The process uses AIBN as a radical initiator, but the use of this material can have safety issues because of the toxicity of its decomposition product. A substituted cyclohexane-1,3-diol used as an analgesic exists as two pairs of diastereoisomers with only one pair being active. A new process is disclosed that gives high yields of the desired pair without using protective group chemistry or chiral reducing agents. A number of the patents in this collection describe experiments carried out on a kilo or multikilo scale, thus suggesting an advanced stage of development or even commercial operation. However, there is no legal or commercial significance in the choice of patents in this review. The advantages mentioned in this review are those claimed in the patent, unless this reviewer has personal knowledge of the subject.


## Patent No. U.S. 7,728,139

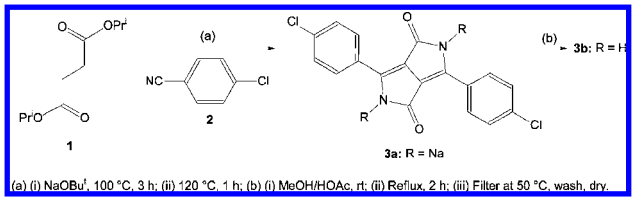
### *Assignee: MCA Technologies GmbH, Biel-Benken, Germany Title or Subject: Solvent-Free Process for the Preparation of Diketopyrrolopyrrole Derivatives*

The compounds of interest in this patent are alkali metal salts such as **3a** that are used as latent pigments in preparing pigment dispersions for colouring paints, printing inks, and wood stains. Alternative methods using organic solvents are said to yield unsatisfactory products, and hence the objective of the work is to develop a synthetic route avoiding solvents. Reaction 1 outlines the process for preparing **3a** that comprises

10.1021/op100263j 
Published on Web 10/15/2010

the condensation of the disuccinate **1** with 2 mol of the nitrile **2** in the presence of a strong base. The reaction is carried out by heating the two reactants together with the base in the absence of a solvent. The reaction is carried out in a reactor that was specially designed for mixing very viscous mixtures known as a Drais All-In-One-Reactor. A flow of $N_2$ is passed into the mixture to remove $Pr^iOH$ and $Bu^tOH$ formed during the process, and at about 80 °C the viscosity increases and the mixture forms a paste as the alcohol vapours are rapidly produced. Further heating removes the alcohols and leaves a crumbly, almost semi-powdery material. This is recovered from the reaction in about 95.5% yield. About 5% of the product remains in the reactor, and this is used in the next batch. The salt **3a** can be hydrolysed to give **3b** by addition to MeOH containing about 0.6 w/w % HOAc. The product is recovered in 95% yield.

Reaction 1




The patent contains over 50 examples that rely on the process outlined in Reaction 1. The preparation of **3a** is carried out on kilo scale as are several others described in the patent. Alternative disuccinates are used as well as a range of nitriles. Other strong bases are also used in the preparation. Some examples use two different nitriles to produce nonsymmetrical products. As may be expected, these give lower yields because of the possibility of three products being formed. The patent also describes the preparation of pigment dispersions using **3a**.

### Advantages

The process gives very high yields of product without using a solvent and is clearly capable of being scaled up.

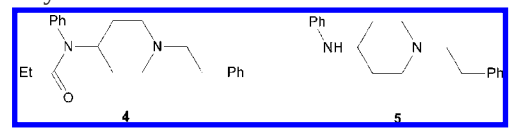
## Patent No. U.S. 7,728,145

### *Assignee: Mallinckrodt Inc., Hazelwood, Missouri, U.S.A*

### *Title or Subject: Industrial Method for Separation and Purification of Fentanyl by Reverse-Phase Preparative Chromatography*

Fentanyl **4** is a powerful opioid analgesic about 100 times more potent than morphine. It has been used as a tranquillizer in veterinary medicine and one product, called onsolis, has been approved by the FDA for the management of breakthrough pain in patients with cancer. The preparation of **4** starts from the aniline **5**, and this is the main impurity in the final product. The current purification method involves two crystallisations of the HCl salt and an alkaloid precipitation. Although the product is obtained in high purity, the recovery is low with about half the product lost to mother liquor streams. Several alternative methods have been proposed for the removal of **5** from **4**, but many are not appropriate for industrial use. The current patent discloses a procedure that involves reverse-phase preparative chromatography (RPPC). The method comprises recovery of the product from the preparation of **4**, and this is used to prepare the mobile phase. The reaction product containing **4** (91.2%) and **5** (8.6%) was dissolved in $H_2O$ to give a concentration of 19 g/L of **4**. This was acidified with HCl to pH 3.03 and forms the HCl salt of **4**. This solution is then passed over the stationary phase that is silica with C8 ligands and consists of 20 $\mu$m spherical particles with 120 Å pores. The mobile phase is passed over this in a vertical 5 cm diameter column at 3 mL/min. MeCN is also added to the mobile phase at around 2.5 vol %. The final level of **5** in the product is <0.01 wt %, and the recovery of **4** is about 87%. The patent discusses the importance of the loading ratio that is the ratio of stationary phase to fentanyl loaded. The preferred range is between 50 and 150, with low values giving higher levels of **5**.

Fentanyl




### Advantages

The process gives higher recovery rates of the product with very low levels of impurity.

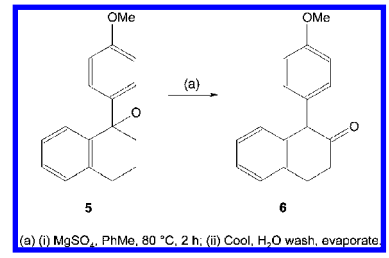
## Patent No. U.S. 7,728,154

### *Assignee: Tokuyama Corporation, Shunan-shi, Japan*

### *Title or Subject: Process for the Preparation of 1-Aryl-3,4-dihydro-1H-naphthalene-2-one*

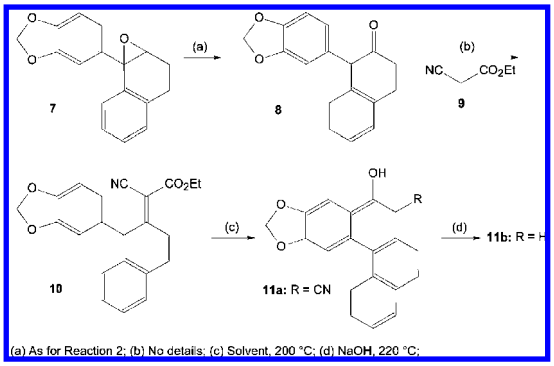
The title compounds are tetralones such as **6** and **8** that can be prepared by methods that proceed via oxidation of the epoxide. Three processes are mentioned using $LiCl_2O_7$, $H_2SO_4$, or $BF_3 \cdot Et_2O$ with $ZnI_2$. These methods are said to be complex, can be dangerous, and do not give high yields. The patent discloses a new process for preparing tetralones by isomerisation of epoxides, and Reaction 2 shows the route used to prepare **6** by isomerisation of **5** using $MgSO_4$ in PhMe at 80 °C. The product is isolated in quantitative yield, but the purity is not reported.

Reaction 2



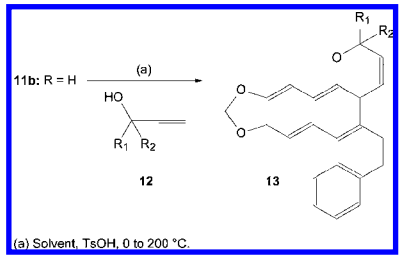

Examples are also described, using the same procedure, for the preparation of several other tetralones including **8** by isomerisation of **7** as shown in Reaction 3. **8** is recovered as an oil in quantitative yield, and the patent discusses its use in the preparation of the naphthol **11b**. The proposed method is shown in Reaction 3 although the patent does not include experimental details. The preparation of **11b** begins with the condensation of **8** with **9**, giving **10**, and this is heated at 200 °C to effect the cyclisation and produce **11a**. When **11a** is melted with NaOH, **11b** is said to be produced.

Reaction 3




The naphthol **11b** is then used in the preparation of the chromene compound **13**, and Reaction 4 outlines the proposed method although, again, no details are included. The method involves the reaction of the propargyl alcohol **12** with **11b** in the presence of an acid catalyst such as TsOH. The identity of $R_1$ and $R_2$ are not specified, and the patent claims that they may be the alkyl, aryl, or heteroaryl groups. Chromenes such as **13** are said to have photochromic properties and develop a neutral tint when irradiated with light and have excellent light resistance.

Reaction 4




## Advantages

The process is much safer than alternatives and gives very high yields of the desired tetralone compounds.

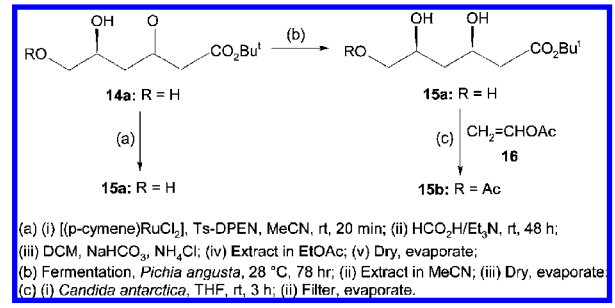
## Patent No. U.S. 7,732,171

### *Assignee: AstraZeneca UK Limited, London, United Kingdom*

### *Title or Subject: Process for the Preparation of Dihydroxy Esters and Derivatives Thereof*

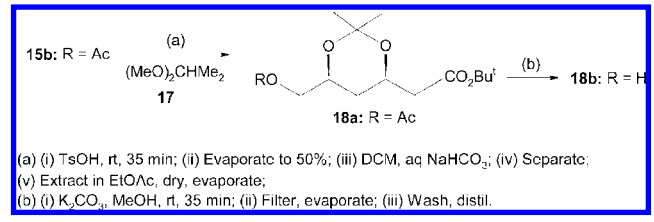
The compounds covered by this patent, such as **15b**, are said to be useful intermediates for the preparation of pharmaceutical compounds. The patent describes the invention as being a process to prepare **15b** by two alternative routes that both start from the dihydroxyketo-ester **14a**. One route proceeds via initial esterification of the primary OH group followed by reduction. The other route is shown in Reaction 5 where the two reactions are carried out in the reverse order. The reduction of the keto group in **14a** can be carried out by two methods with one being catalysed by a lipase and the other by a chiral Ru complex. From these various possibilities the patent's claims focus solely on the esterification of the trihydroxy-ester **15a** catalysed by a lipase enzyme to give **15b**. The first method for preparing **15a** involves a chiral transfer hydrogenation using a Ru catalyst, the chiral amine (1*S*,2*S*)-(+)-*N*-*p*-tosyl-1,2-diphenylethylenediamine (Ts-DPEN), and $HCO_2H/Et_3N$ as the hydrogen source. This reaction produces a 5.2:1 mixture of the diastereoisomers 3*R*,5*S* and 3*S*,5*S*. The second method for preparing **15a** involves a bioreduction process using *Pichia angusta* and gives the 3*R*,5*S*-isomer in >99.4% diastereomeric excess (de). The preparation of **15b** from **15a** and **16** is the focus of the claims and preferably uses the *Candida antarctica* lipase with the example in the patent using a commercially available supported type known as Chirazyme L2. After the reaction is complete, the mixture is filtered to remove the lipase, and then the solvent is evaporated to give crude **15b** as an oil in 93.7% yield.

Reaction 5




The second aspect of the patent is the preparation of the dioxane compound **18a** by reaction of crude **15b** with **17** that is used as reactant and solvent (Reaction 6). This is carried out in the presence of TsOH, and the crude **18a** is recovered by distillation and then purified by column chromatography (ColC) followed by three crystallisations. The isolated yield of pure **18a** is 24.4% with a 99.9% de as determined by chiral GC. Hydrolysis of **18a** with $K_2CO_3$ in MeOH gives **18b** that is isolated as a clear oil by distillation in 93% yield with de of >99%.

Reaction 6




## Advantages

The use of a lipase in the process gives a highly pure product.

## Patent No. U.S. 7,737,280

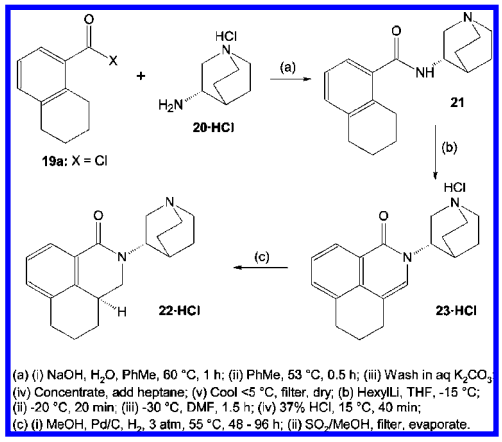
### *Assignee: Sicor Inc., Irvine, California, U.S.A*

### *Title or Subject: Processes for Preparing Palonosetron Salts*

The salts of **22** are available as Aloxi and are used for the prevention of nausea and vomiting associated with some cancer chemotherapies. Methods used to prepare **22** are summarised and involve the hydrogenation of a cyclic amide that can give rise to a mixture of isomers (3a-*S* and 3a-*R*). Only the 3a-*S* isomer is reported to be bioactive, and hence the main objective of the synthesis is to provide a better hydrogenation method that gives high yield of the desired isomer. Although the title and subject of this patent relate to the preparation of **22**, the main claim covers the preparation of the intermediate **21**. The route used to prepare **22·HCl** is shown in Reaction 7, and subsequent claims of the patent cover the use of **21** in the preparation of **23** and **22** and its HCl salt. The first stage of the synthesis is formation of **21** by reaction of **19** with the HCl

salt of **20**. The reaction is carried out in solvent that is not miscible with $H_2O$ such as PhMe and is catalysed by a strong base. NaOH is used as the base, and the mixture also contains $H_2O$. The reaction takes place at about 60 °C over about 1 h, and after workup the product **21** is isolated in 96% yield. In the next step **21** is treated with hexyl lithium followed by DMF and then HCl to obtain the HCl salt of **23**. After workup the salt is isolated in 85% yield with purity of 98% (HPLC). The last stage is the catalytic hydrogenation of **23** to give the HCl salt of **22**. This uses Pd/C catalyst, and following the reaction the mixture is treated with an oxidising agent, and $SO_2$/MeOH is preferred. Several experiments are described that use various amounts of catalyst. When using 1.25 wt % of catalyst, the reaction takes 96 h and gives the salt containing 95% of the 3a-*S* isomer. As the catalyst concentration is increased to 5 wt %, the reaction time is reduced to 24 h, but the isomeric purity falls to about 62%. Although lower catalyst quantities give higher-purity product, the patent describes one example using 10% catalyst that takes 21 h, and the product is crystallised twice from $Pr^iOH/H_2O$. The product obtained has 95.5% isomeric purity and is recovered in about 36% yield. The patent claims do cover the use of up to 10% catalyst and then purification using two crystallisations.

Reaction 7




(a) (i) NaOH, $H_2O$, PhMe, 60 °C, 1 h; (ii) PhMe, 53 °C, 0.5 h; (iii) Wash in aq $K_2CO_3$; (iv) Concentrate, add heptane; (v) Cool <5 °C, filter, dry; (b) HexylLi, THF, -15 °C; (ii) -20 °C, 20 min; (iii) -30 °C, DMF, 1.5 h; (iv) 37% HCl, 15 °C, 40 min; (c) (i) MeOH, Pd/C, $H_2$, 3 atm, 55 °C, 48 - 96 h; (ii) $SO_2$/MeOH, filter, evaporate.

The patent also includes details for the preparation of acyl chloride **19a** by chlorination of the acid **19b** (X = H) using either $SOCl_2$ or $(COCl)_2$ with a small amount of DMF in DCM as solvent. Examples are given for both reagents, and the crude product is recovered as an oil or in solution and used directly to prepare **21**.

### Advantages

The process provides a selective process for the synthesis of the desired bioactive isomer.

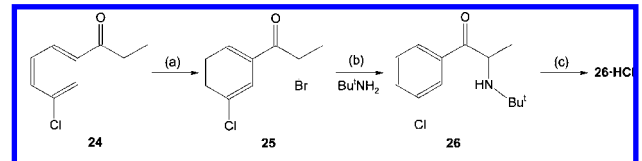
## Patent No. U.S. 7,737,302

***Assignee: Zhejiang Apeloa Medical Technology Co. Ltd., Zhejiang Province, China***

***Title or Subject: Process for Preparing Bupropion Hydrochloride***

The HCl salt of **26** is used to treat depression and can be prepared by a number of methods that are summarised but said to be unsuitable for industrial production. Problems such as low yield, waste disposal, long production cycle times, and safety concerns are mentioned. The process described in this patent is shown in Reaction 8 and consists of three steps starting from the ketone **24**. In the first step **24** is brominated using $Br_2$, and this can be carried out without a solvent although the use of $MeCHCl_2$ does give the highest yield. After evaporation of the solvent, the residual mixture is refluxed with $Bu^tNH_2$ to give **26** that is recovered by extraction into $HCO_2Et/H_2O$. The crude product is dried and then treated with HCl in $HCO_2Et$ to form the desired salt that is purified by treatment with activated C. The product is dried in vacuum and isolated in 80% yield, based on **24**, with purity of >99.9% (HPLC).

Reaction 8




(a) (i) $Br_2$, $MeCHCl_2$, 65 °C, 5 h; (ii) Evaporate at 60 °C; (b) (i) Reflux, 2.5 h; (ii) Evporate at 140 °C; (iii) Extract in $HCO_2Et/H_2O$, rt; (iv) Dry; (c) (i) HCl, $HCO_2Et$, rt; (ii) Filter; (iii) Act. C, $Pr^iOH/H_2O$, 90 °C, 40 min; (iv) Filter, dry in vacuum.

The patent claims cover the use of specified ranges of molar ratios of reagents, as may be expected, but it seems surprising that the claims also specify the use of anhydrous $MgSO_4$ or $Na_2SO_4$ as drying agents after the extraction with wet $HCO_2Et$. No reason is given, and perhaps other desiccants may give problems.

### Advantages

The process gives high yields of the product and is claimed to have low-cost and thus is suitable for commercial use.

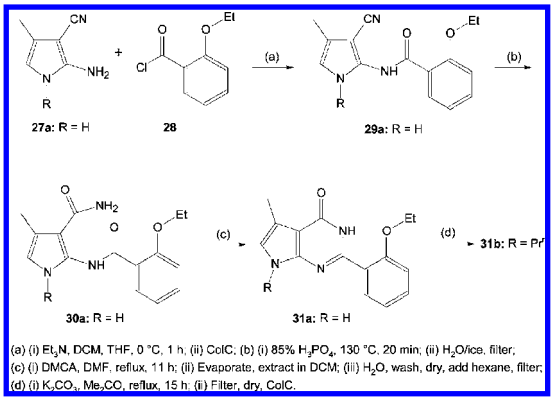
## Patent No. U.S. 7,741,483

***Assignee: Yangtze River Pharmaceutical (Group) Co., Ltd., Jiangsu, China, and Tianjin North Pharma Sci-Tech Co., Ltd., Tianjin, China***

***Title or Subject: Process for Making Substituted Pyrrolo-[2,3-d]pyrimidine Derivatives as Inhibitors of Phosphodiesterase 5***

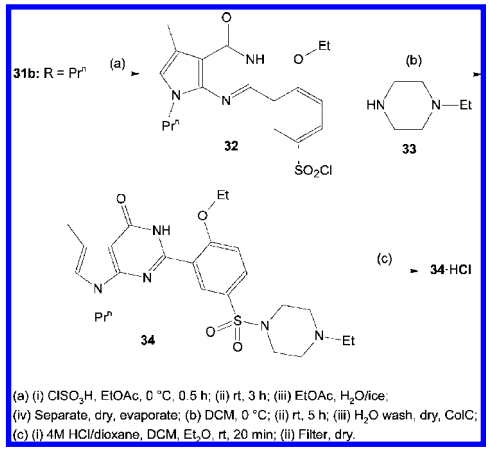
The patent discloses a process to produce compounds that are used to treat erectile dysfunction. A large range of compounds is described; the first stage is the preparation of **31b** by the route shown in Reaction 9. This starts with the condensation of **27a** with **28** in the presence of an organic base such as $Et_3N$ to give the benzamide **29a**. The ethoxybenzoyl chloride **28** used for this reaction is prepared from the ethoxybenzoic acid and $SOCl_2$ and the crude product is dissolved in DCM and used within 30 min. The crude product **29a** is recovered by mixing the reaction solution with silica gel and evaporation of the solvent. The residue is then subjected to column chromatography (ColC) using DCM as eluent, and the product is isolated in 48% yield. It can be purified by crystallisation from DCM/hexane. In the next step **29a** is refluxed with 85% $H_3PO_4$ to give the amide **30a** as a dark-red solid in 80% yield. This amide is used without purification to prepare **31a** by refluxing with dimethylcyclohexylamine (DMCA) in DMF. The product is isolated in 91% yield and then alkylated with $Pr^nBr$ and $K_2CO_3$ in refluxing $Me_2CO$. **31b** is obtained in 35% yield after purification by ColC. The patent also describes the preparation of **31b** starting from **27b** (R = $Pr^n$) but does not describe how **27b** is prepared.

Reaction 9




The next stage of the process, shown in Reaction 10, is the preparation of benzenesulphonyl chloride **32** by treating **31b** with $ClSO_3H$. The reaction takes place in EtOAc that the patent refers to as acetic ether. **32** is recovered as a yellow foam and used without further treatment in the preparation of **34** by adding **33** slowly to **32** in DCM at 0 °C. Crude **34** is isolated as a yellow foam and purified by ColC to give pure **34** in 75% yield. The free base is then converted to the HCl salt by treatment with dioxane solution of HCl in DCM and $Et_2O$. The salt is isolated in 94% yield.

Reaction 10




The patent includes details, using the same synthetic methods, for the preparation of several analogous compounds to **34** as well as the corresponding intermediates. $^1H$ NMR data are included for all intermediates and final products, and some IR and MS data are also provided. Clinical testing details on animals are also provided that compare Viagra with **34·HCl** and some analogous compounds.

### Advantages

The process is efficient for preparing drugs that claim to be as effective as the market leader.

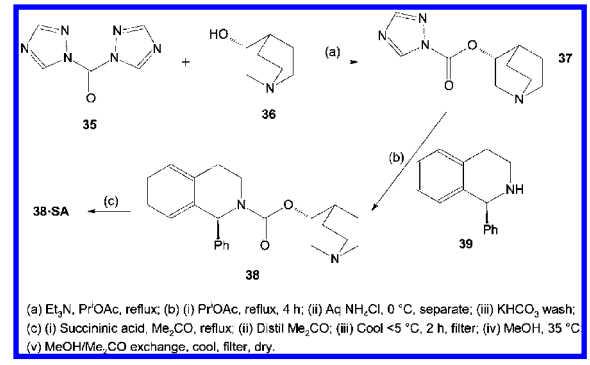
## Patent No. U.S. 7,741,489

### *Assignee: Medichem S.A., Saint Joan Despi, Barcelona, Spain*

### *Title or Subject: Process for the Synthesis of Solifenacin*

The succinate salt of title compound **38·SA** is used to treat bladder infections and urinary incontinence. The original process for the synthesis of **38** is claimed to involve laborious and costly workup procedures that are not suitable for commercial use. An additional problem that is mentioned is EtOH, produced during the process, reacting with **38** in the presence of a base used in the process. Hence, the EtOH must be removed during the process by azeotropic distillation using PhMe, and this can cause control problems. The patent therefore discloses an improved synthesis of **38** and its succinate salt that is outlined in Reaction 11. The process starts with the formation of the carbamate **37** by reaction of the bis-triazole **35** with the quinuclidinol **36** in an ester solvent containing $Et_3N$. **37** is not isolated, and a solution of **39** in $Pr^iOAc$ is added to the refluxing mixture containing **37**. After washing the resulting mixture with aq $NH_4Cl$ followed by $KHCO_3$, the crude base **38** is refluxed with succinic acid in $Me_2CO$ to form the salt **38·SA**. Workup involves heating in MeOH followed by exchange with $Me_2CO$, and the salt is isolated in 76.36% yield with purity of 99.96 area % (HPLC) and optical purity of 99.98 area % (*R*,*R*) containing 0.02% (*S*,*S*). This synthesis is carried out on a kilo-scale, indicating the advanced status of the process.

Reaction 11




The patent contains details of the HPLC methods that are used to analyse the product.

### Advantages

The process is efficient and gives high yields of the desired isomer.

## Patent No. U.S. 7,741,508

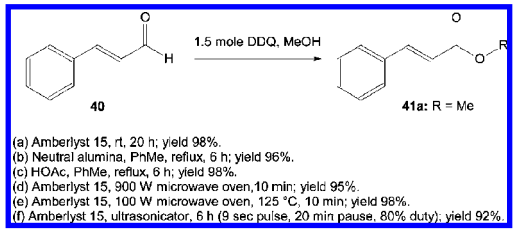
### *Assignee: Council of Scientific and Industrial Research, New Delhi, India*

### *Title or Subject: Single-Step, Green Process for the Preparation of Substituted Cinnamic Esters with Trans-Selectivity*

Cinnamic esters are used in a range of applications, and one specific application mentioned is in sunscreens as a UV filter. There are several alternative processes for preparing the desired esters, and the patent contains an extensive list of references to these. The problems associated with such processes include the use of expensive reagents and catalysts, harsh conditions, or toxic chemicals. The latter point is particularly significant because the main claim of the patent specifically excludes the use of hazardous cyanides as oxidising agents. The patent describes a process for preparing the esters that involves the direct oxidation of aldehydes or alcohols in a single step. The favored oxidant used in the process is DDQ although there are examples that use chloranil or $SeO_2$. The process is carried out in the presence of an acid catalyst and may be performed in the presence of microwave irradiation (MWI) or ultrasound (US). It is claimed to be an environmentally friendly and green process because it avoids the use of toxic reagents and solvents.

The acid catalysts used in the process are preferably ion-exchange resins (IERs), and these are recycled, thereby reducing the waste streams associated with liquid or soluble catalysts. Reaction 12 summarises the various methods of preparing the methyl ester **41a** by oxidation of **40** using DDQ. The reactions are carried out in an excess of MeOH and include the use the IER Amberlyst 15 with or without MWI or US. Also shown is the use of the acid catalysts HOAc and neutral alumina, and all experiments give a very high yield of the ester **41a**. The patent reports that the IER can be recovered by filtration and may be reused at least 15 times. The DDQ can also be recovered and regenerated by reported methods.

Reaction 12




The patent includes examples for the preparation of other cinnamate esters from **40** including R = Et, $Bu^n$, octyl, 2-$MeOCH_2CH_2$−, and $HOCH_2CH_2$−, and there are examples of preparing esters from substituted cinnamaldehydes. When chloranil is used as the oxidant and silica gel as catalyst with **40** and $Pr^iOH$ the $Pr^i$ ester is obtained in 49% yield. Using $SeO_2$ as oxidant and neutral alumina as catalysts with **40** and dodecanol, an 87% yield of the dodecyl ester is obtained after 6 h in refluxing PhMe. An example is included in which cinnamyl alcohol is used to prepare **41a** using 3 mol of DDQ and Amberlyst 15 in MeOH. After 20 h at rt an 86% yield of **41a** is obtained.

The use of microwave technology is certainly of great interest and undoubtedly has industrial potential for some applications. However, one of the patent's claims covers the use of a domestic microwave oven for this process, and realistically this cannot be viewed as a large-scale commercial operation. Other claims do cover the use of MWI in the range 900−3000 MHz and specifically 2450−2455 MHz.

### Advantages

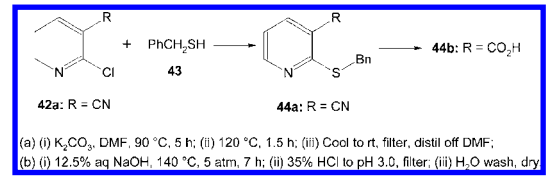
The process gives a highly selective yield of esters without the need to use toxic oxidation catalysts, but whether the process is commercially viable is debatable. The claim of it being green is stretching the definition too far especially as some of the reagents are toxic and used stoichiometrically.

## Patent No. U.S. 7,745,631

### *Assignee: Jubilant Organosys Limited, Uttar Pradesh, India*
### *Title or Subject: Process for Producing 2-Phenylmethylthio-3-pyridine Carboxylic Acid*

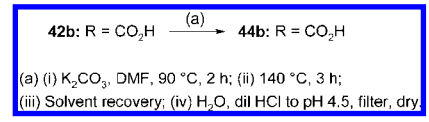
The compound of interest in this patent, **44b**, is an intermediate that is used to prepare agrochemical and pharmaceutical reagents. Some of processes for preparing **44b** are summarised and are claimed to be unsuitable for large-scale commercial operation because of unsatisfactory yields or purification problems. For example, processes that start with benzyl halides give rise to the formation of benzyl alcohol that is difficult to remove from **44b**. Hence, the process disclosed in this patent avoids using benzyl halides and expensive starting materials. The process is outlined in Reaction 13 and takes place in two stages. In the first stage **44a** is prepared by reaction of the nitrile **42a** with the thiol **43** in the presence of $K_2CO_3$. The product is recovered in 91.6% yield and used directly in the next stage where it is hydrolysed to give **44b** using aqueous NaOH in an autoclave. After neutralising with HCl the acid is isolated in 90.77% yield with purity 99.49% (HPLC).

Reaction 13




The patent also describes a comparative method for preparing **44b** shown in reaction 14. This involves the reaction of **42b** (R = $CO_2H$) with **43** in the presence of $K_2CO_3$ to form **44b** directly. The final yield is 71.49% with purity 99.23% (HPLC). Using DMSO as reaction solvent the yield of **44b** is 49.1%, and purity is 99.2%.

Reaction 14




### Advantages

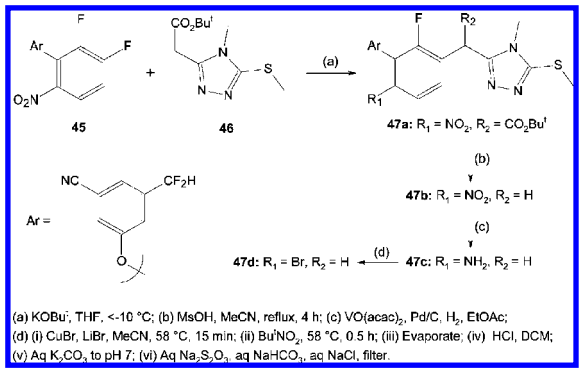
The process gives a high yield of the final product of a high purity, using low-cost starting materials and without the need to purify the intermediate.

## Patent No. U.S. 7,745,634

### *Assignee: Roche Palo Alto LLC, Palo Alto, California, U.S.A*
### *Title or Subject: Process for Preparing Triazolones*

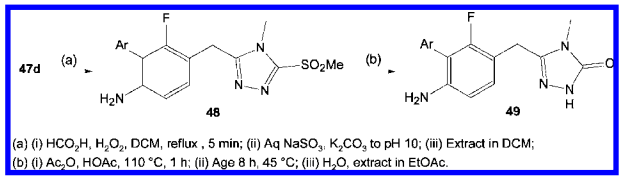
This patent relates to a process for preparing a range of triazolones such as **49** that are useful in the treatment of AIDS and HIV. The patent states that there is a need for safer drugs to treat strains of HIV that are resistant to many currently used drugs, and the compounds covered by this patent fulfill that need. The actual claims of the patent cover the preparation of the triazole **47d** that is used in the synthesis of **49**. The synthesis of **47d** is shown in Reaction 15 and begins with the base-catalysed condensation of **45** and **46** to give **47a**. This is isolated as a solution in MeCN that is refluxed with MsOH to hydrolyse the ester and at the same time cause decarboxylation of the acid to give **47b**. This is extracted into EtOAc, and the solution of **47b** is hydrogenated to give the amine **47c** using Pd/C and $VO(acac)_2$. The product is isolated in 71% yield after crystallisation from EtOAc and then converted to the bromo-derivative **47d** via a diazotisation reaction. The product is isolated as the Ts salt in 66.4% yield.

Reaction 15



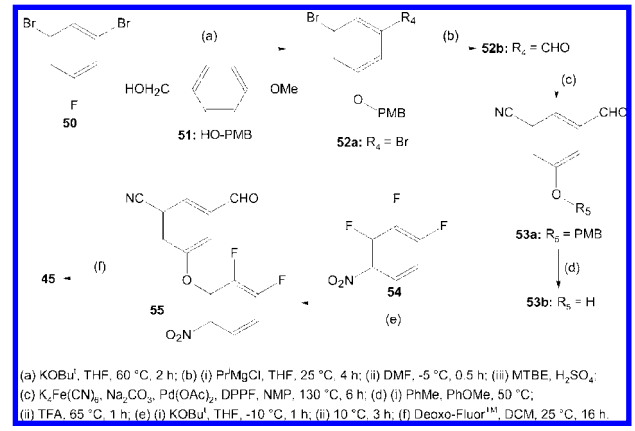

The next stage of the process is the conversion of **47d** to the triazolone **49** as shown in Reaction 16. The first step involves the oxidation of the thiol group using $HCO_2H$ and $H_2O_2$. After extraction into DCM and workup, the product **48** is crystallised from $Pr^iOH$ and hexane and isolated in 90% yield. **48** is then heated with $Ac_2O$ and HOAc at 110 °C for 1 h; then the mixture is cooled to 45 °C and aged for 8 h. The product **49** is recovered by extraction into EtOAc, purified by crystallisation from EtOAc/heptane, and obtained in 75% yield. This latter step is carried out at kilo scale, thus indicating the advanced stage of the process.

Reaction 16



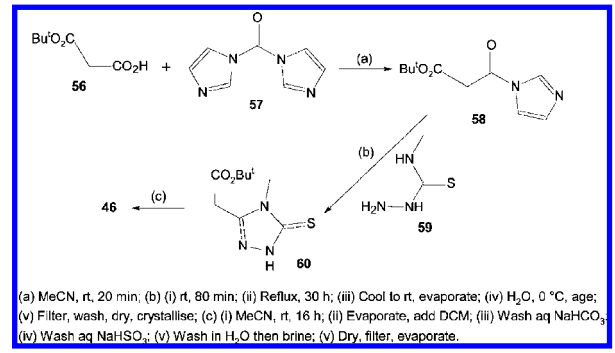

The patent also describes the preparation of the compounds **45** and **46**. **45** can be made by two routes, and examples are provided for both that start from **50**; since part of one route is carried out on a multikilo scale, this is the route shown in Reaction 17. The workup details for the whole scheme are quite detailed with a number of ageing periods mentioned during the workup procedures. Hence, only the main reagents are included because of space limitations. The first stage of the preparation of **45** is the introduction of the *p*-methoxybenzyl group into **50** using **51** in the presence of $KOBu^t$ to give **52a** that is isolated in 94% yield and then dissolved in THF and treated with $Pr^iMgCl$ at about 25 °C. After ageing for 4 h the solution it is cooled to −5 °C, and DMF is added and the temperature kept below 30 °C. After acidification with $H_2SO_4$ the crude aldehyde **52b** is recovered in 107% yield. In the next step the nitrile **53a** is produced by reaction of **52b** under anhydrous conditions with $K_4Fe(CN)_6$ and $Pd(OAc)_2$ in the presence of 1,1′-bis-(diphenylphosphine)-ferrocene (DPPF) and $Na_2CO_3$ in *N*-methylpyrrolidone (NMP). The product **53a** is recovered in 81% yield and is then treated with TFA in a mixture of PhMe and PhOMe, giving **53b** in 95.9% isolated yield. In the next step **53b** is treated with a mixture of **54** and $KOBu^t$ in THF to produce **55** that is isolated in 72% yield. The last step is reaction of **55** with Deoxo-Fluor that gives **45** in 77.4% isolated yield.

Reaction 17




The final section of the patent describes the preparation of the ester **46**, and this is shown in Reaction 18. This starts by treatment of the malonate half ester **56** with the diimidazole **57** in MeCN at rt to form **58**. This is not isolated but treated with the semicarbazide **59** at rt followed by refluxing for 30 h. Concentrating the solution and replacing MeCN with $H_2O$ followed by ageing for an unspecified time at 0 °C affords the product **60** that is filtered, washed and dried, and isolated in 73.7% yield, and then recrystallised from EtOAc. Methylation of **60** with MeI in MeCN produces a dark-brown oil that is dissolved in DCM, and the solution is washed in aq $NaHCO_3$, aq $NaHSO_3$, $H_2O$, then brine and filtered. After evaporation of the DCM **46** is recovered as an oil that solidifies on standing. The yield is 96.3%. Despite the large amount of experimental detail the patent does not report the purity of any of the products that are prepared in any of the reaction schemes.

Reaction 18




## Advantages

The process provides compounds that are of interest in the production of drugs to treat new strains of HIV.

## Patent No. U.S. 7,745,649

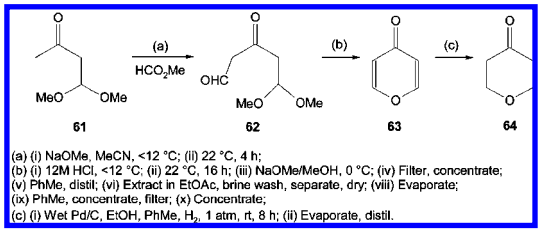
### *Assignee: Ube Industries Ltd., Ube-shi, Japan*

### *Title or Subject: Processes for Preparing Tetrahydropyran-4-one and Pyran-4-one*

The compounds **63** and **64** covered by this patent are used as intermediates in the synthesis of agrochemicals or medicines. **64** is usually prepared by hydrogenation of **63**, and one problem mentioned in preparing **63** is the need to handle HCl/MeOH solutions. It is also said that the reaction time for preparing **63** is too long, and overall the process is not industrially attractive. Most of the patent's 23 claims cover the hydrogenation of **63**

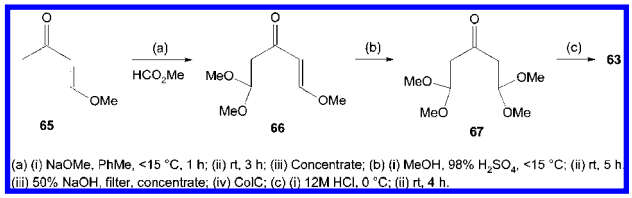
to give **64**, and five cover the preparation of **63**. There are two methods described for preparing **63**, and the first of these begins with the base-catalysed reaction of **61** and $HCO_2Me$ as shown in Reaction 19. The reaction actually produces the Na salt of **62** that is recovered as a solution although a separate experiment describes the isolation of this salt. The solution of the Na salt of **62** is then subjected to an extensive workup before the next step. First PhMe is added so that the mixture can be dehydrated by distillation off water as the PhMe/$H_2O$ azeotrope. This is repeated four times, and then the solution is extracted with EtOAc and washed with brine. The organic layer is dried over $MgSO_4$ and evaporated, and the residue is dissolved in PhMe and evaporated once more to give crude **63** as a brown liquid. This is then hydrogenated under 1 atm of $H_2$ at rt and the product recovered by vacuum distillation. The final isolated yield of **64** based on **61** is 14.9%.

Reaction 19




An alternative synthesis of **63** is shown in Reaction 20 and involves a two-step reaction in which the first step is the base-catalysed reaction of **65** with $HCO_2Me$. This is presumed to give **66** that is not isolated and gives **67** when treated with MeOH and $H_2SO_4$. After workup the tetramethoxy compound **67** is purified by ColC and isolated in 18% yield as an orange liquid.

Reaction 20




The patent also describes the preparation of the dihydropyran-4-one in 33% yield by hydrogenation of **63** using Pd/C catalysts in PhMe containing 10% EtOH. The patent gives basic $^1H$ NMR data for **62** and **67**.

## Advantages

The process is claimed to be simple and gives high yields, but the workup procedures seem rather laborious; as a result, the isolated yields of products are actually quite low.

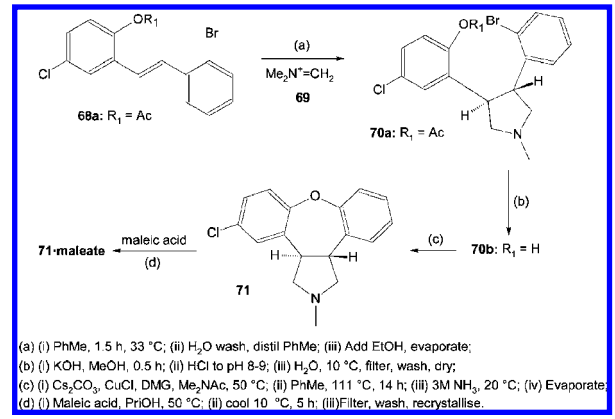
## U.S. 7,750,167

### *Assignee: N.V. Organon, Oss, Netherlands*

### *Title or Subject: Process for the Preparation of Asenapine and Intermediates Used in the Process*

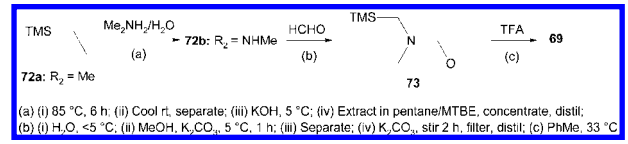
Asenapine **71** is an antipsychotic developed for treating schizophrenia and acute mania associated with bipolar disorder. **71** is available as the maleate salt under the name Saphris. A general method for making **71** is known, but the patent states that there is a need for a reliable industrial procedure. The patent contains a number of methods based on the route shown in Reaction 21. The route shown is the one covered by the patent claims and begins from a novel *E*-stilbene derivative such as **68a** that is reacted with an in situ generated azomethine ylid **69** to give the *trans*-pyrrolidine **70a**. This reaction is described as a [3 + 2] dipolar cycloaddition that conserves the stereochemistry and exclusively gives the *trans* form of **70a**. This is the key step in the process and enables high yields to be achieved. **70a** is not isolated and is hydrolysed to give **70b** in 96% yield and 98% purity (HPLC). **70b** then undergoes an Ullmann cyclisation to form **71** using the base $Cs_2CO_3$ with a catalyst comprising CuCl and dimethylglycine (DMG). The patent describes four options for this step with variations in workup procedure. In each case **71** is formed as an oil that is converted to the maleate salt by treatment with maleic acid in $Pr^iOH$. The salt is isolated in yield of 88% based on **70b** and purity 99% (HPLC).

Reaction 21




The ylid **69** is formed in situ from TFA and the novel ether amine **73**, with the latter being obtained by the route outlined in Reaction 22. The first step produces the amine **72b** by treatment of **72a** with aqueous $MeNH_2$ at 85 °C. **72b** is recovered by distillation in 50% yield containing 10 mol % MTBE. In the next step **72b** reacts with aqueous HCHO followed by MeOH in the presence of solid $K_2CO_3$. The novel ether amine **73** is recovered by distillation, but no yield is reported. The use of **73** in providing **69** is said to offer many advantages. For example, it is claimed that the process can be carried out with higher throughput because a smaller volume of solvent is required. The use of **73** is also said to be safer than using the amine oxide because a smaller exotherm is generated. Furthermore, **73** does not react to any extent with the *Z*-stilbene isomer, and hence more of this may be tolerated in the synthesis.

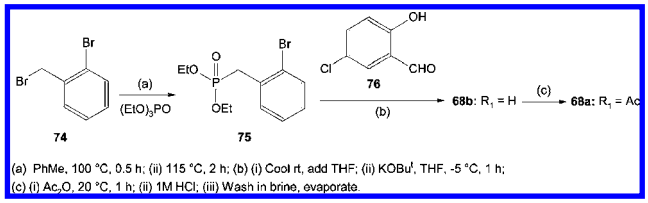
Reaction 22




The patent describes methods for the preparation of a number of intermediates related to **70a** and **70b** that can be cyclised by the Ullmann method to afford **71**. These compounds have different substituents in the two phenyl rings of the stilbene **68a**. The preparation of the novel stilbenes **68a** ($R_1$ = Ac) and **68b** ($R_1$ = H) are described as outlined in Reaction 23. This starts by heating **74** with $(EtO)_3PO$ in PhMe to form **75**. This

is not isolated and is treated with KOBu$^t$ in THF at −10 °C followed by the salicaldehyde **76** to form **68b**. This can be isolated in 92% yield, and acetylation with $Ac_2O$ forms **68a** that is isolated in 73% yield. The % of the *E*-isomer in **68a** is not reported, although for other stilbenes it varies between 88 and 99%.

Reaction 23




The patent contains $^1$H NMR details for all of the many compounds prepared. It also contains basic $^{31}$P NMR data for **75** and related compounds.

### Advantages

The process offers a stereospecific, high yield of the key intermediate that forms the basis of an overall efficient procedure.

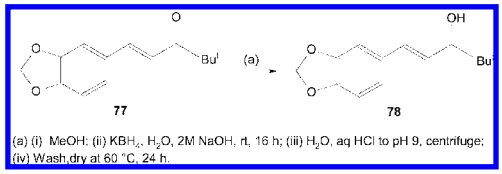
## Patent No. U.S. 7,750,169

### *Assignee: Biocodex, Gentilly, France*

### *Title or Subject: Process for the Preparation of Stiripentol Particles Having a Defined Particle Size Distribution*

Stiripentol **78** is an antiepileptic that is used to treat severe myoclonic epilepsy in infants. The drug is available as Diacomit that is given as gelatin capsules or as a drinkable suspension with a specific particle size distribution (PSD) that requires 50% of particles of **78** having a diameter <100 $\mu$m. The preferred range is from 50 to 85 $\mu$m, and furthermore at least 90% of particles should be <300 $\mu$m. The particles can be obtained by conventional grinding and screening methods although problems arise because **78** has a mp of only 75 °C. The grinding process causes melting due to friction resulting in particles sticking to one other and major product losses. **78** can be crystallised from EtOH, but its high solubility in EtOH at rt means the method is difficult to transfer to an industrial scale. The patent reports on a new crystallisation process that provides **78** with appropriate particle size and which is suitable for commercial operation. The process uses aromatic solvents and the patent claims cover the use of *m*- or *o*-xylene, dichlorobenzene, or PhMe with the latter being preferred. The preparation of **78** with defined PSD is carried out by reduction of the ketone **77** using $KBH_4$ as shown in Reaction 24.

Reaction 24




Following the recovery of the crude product from the reduction two crystallisations are carried out as follows:

1. Add **78** to PhMe at concentration of 1 kilo per litre of PhMe and heat to 90 °C to dissolve solid.
2. Add Clarcel and activated C and heat to reflux at 110 °C to remove water by azeotropic distillation.
3. Filter and cool to −5 °C, for 1 h.
4. Centrifuge to dry.
5. Redissolve dried product in 1 L of PhMe per kilo and heat to reflux at 110 °C to dissolve solid.
6. Filter off any solid impurities.
7. Cool rapidly to −5 °C and vigorously agitate at 75 to 125 rpm for 1 h.
8. Centrifuge to dry.
9. Wash in PhMe.

The isolated yield of **78** is 85% with 50% of particles having an average diameter of 50−85 $\mu$m and 90% with diameter <250 $\mu$m. The double crystallisation enables reproducible production of **78** that is homogeneous and colourless, and the product is claimed to contain <500 ppm PhMe, well within the specified limit of 890 ppm.

The patent has one example that does not mention the precise amount of **78** that is crystallised. However, the example clearly states that, in step 2, a kilo of Clarcel and 3 kilo of activated C is used and, in step 9, 50 L of PhMe is used. It is presumed that these quantities refer to the amount used per kilo of **78**, but this is not stated.

### Advantages

The process gives high-purity product with an appropriate PSD, and it appears to have been carried out on a kilo scale.

## Patent No. U.S. 7,750,177

### *Assignee: Dipharma Francis s.r.l., Baranzate, Italy*

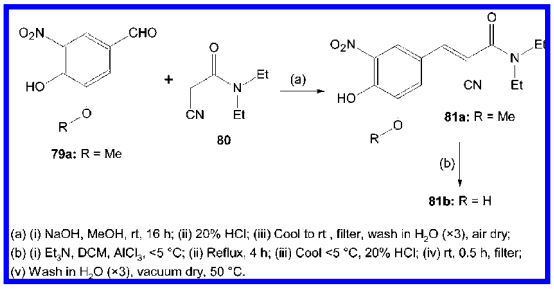
### *Title or Subject: Process for the Preparation of Entacapone*

Entacapone **81b** is used in combination with other drugs for the treatment of Parkinsonism. A number of methods for preparing **81b** are described along with their various shortcomings. The patent therefore claims that a process is needed that uses low-cost starting materials and provides high yields, and crystallisation should avoid using strong acids, high-boiling organic acids, and high temperatures. The first step of the process uses the same starting materials as an alternative method (**79a** and **80**) in a base-catalysed condensation reaction to form **81a**. In this case the reaction is carried out at rt (Reaction 25) as opposed to 110 °C in the alternative procedure. The use of a strong base allows the reaction to take place under mild conditions. This prevents formation of pitch-like byproducts that are produced when the nitrophenol **79a** is heated under reflux for prolonged periods. The patent claims that using a strong base for this condensation is surprising and contrary to what is previously known. The methoxy intermediate **81a** is recovered in 95% yield and then subjected to dealkylation using $AlCl_3$ in DCM and $Et_3N$ to give **81b**. The crude product is recovered in 98% yield and then purified by the following procedure.

1. Dissolve in MEK under reflux.
2. Cool to <40 °C to precipitate product then heat to 60 °C for 1 h.
3. Allow to cool to rt over 5 h.
4. Cool to <5 °C for 1 h then filter and wash in MEK.
5. Dry in static drier under vacuum at 50 °C.

The final yield is 90%, and analysis demonstrated that the physical characteristics of the product showed it to be the same as the original compound, designated polymorph A, with *E*-stereochemistry as reported in U.S. Patent 5,135,950.

Reaction 25




## Advantages

The process gives a high yield of the product under mild conditions and does so without the problem byproduct being formed.

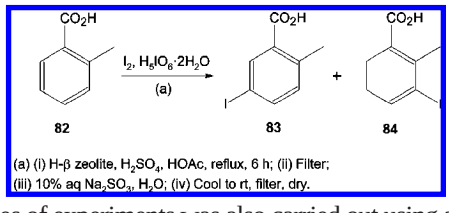
## Patent No. U.S. 7,750,182

### *Assignee: Mitsubishi Gas Chemical Co. Inc., Tokyo, Japan*

### *Title or Subject: Process for Production of Iodine Compounds and High-Purity 5-Iodo-2-methylbenzoic Acid*

Iodine compounds have a wide range of uses in many fields, and high-purity **83** is a raw material for performance chemicals as well as for medicines and agrochemicals. The patent discusses a number of methods for the introduction of an iodine atom into aromatic compounds. $I_2$, ICl, or periodides can be used as the iodination reagent, but it is claimed that these methods are not particularly effective and unsuitable for industrial use. Methods have been reported in which zeolites are used to enhance the processes, but it is claimed that the improvements are not to a satisfactory level. This patent describes a process for carrying out an iodination reaction in which a zeolite is used in an effective manner and is applied to the production of high-purity **83**. The process involves the use of an oxidising agent and mineral acid in conjunction with the iodination compound and the zeolite that has a pore size of 0.5−2 nm. The preparation of **83** by this process is outlined in Reaction 26 and involves the reaction of **82** with $I_2$ in the presence of $HIO_4$ and H-$\beta$ zeolite in HOAc containing about 0.24 wt % $H_2SO_4$. After the completion of the reaction, $Na_2SO_3$ is added to remove the remaining $I_2$. Analysis of the crystalline product showed that the conversion of **82** was 85% and that the yields of products were 70% of **83** and 7% of **84**. (regioisomer ratio 10). The crystals were then purified by dissolving in a 1:1 mixture of $H_2O$ and $Pr^iOH$ at 70 °C and then leaving overnight at rt. The precipitated crystals were recovered in 66% yield and analysed as 99% of **83** (HPLC) containing 5 ppm $I_2$. The purification can also be carried out using HOAc as solvent and gives similar results.

Reaction 26




A series of experiments was also carried out using alternative oxidants, no oxidant, and with and without the zeolite. These all showed that the combination of zeolite and oxidant with $I_2$ gave much better iodination products than when any of the two reagents was absent. The process was applied to a selection of other aromatic compounds such as PhF, Ph−Ph, PhMe, *o*-xylene, and 2- and 3- methylcyanobenzene, and all gave good results.

## Advantages

The process provides and efficient method of producing iodo-aromatic compounds.

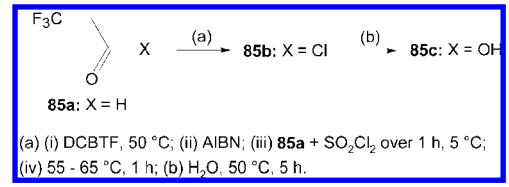
## Patent No. U.S. 7,754,927

### *Assignee: Central Glass Company, Limited, Ube-Shi, Japan*

### *Title or Subject: Method for Producing 3,3,3-Trifluoropropionyl Chloride*

The compound of interest **85b** (X = Cl) is a chemical intermediate used to make agrochemicals, pharmaceuticals, and fluorine-containing polymers. **85b** can be made by chlorination of the corresponding acid **85c** (X = OH), but since this is highly corrosive, a commercial process based on **85c** is said to be difficult and expensive. The process disclosed in this patent is based on the chlorination of the aldehyde **85a**. It is claimed that previously there has not been a technique for the chlorination of an aldehyde containing H atoms but no F atoms at the α-carbon position. The patent states that since **85a** contains a $CF_3$ group bound to the α-carbon, it was expected that its chlorination to give **85b** would be difficult because of the electron-withdrawing power of the $CF_3$ group. However, it has been found that the chlorination of **85a** to produce **85b** can be carried out using a radical initiator that may be an organic peroxide, an azo compound, halogen light, or UV light. The chlorinating agents that can be used are $Cl_2$, $SO_2Cl_2$, or organic *N*-chloro compounds. The reaction is carried out in a low-polarity solvent unless an *N*-chloro compound is used, in which case, other solvents are suitable such as MeCN. The patent claims do not specify which chlorinating agent is preferred although most of the examples use $Cl_2$ or $SO_2Cl_2$, and Reaction 27 outlines a method using $SO_2Cl_2$ that is carried out in 2,4-dichlorobenzotrifluoride (DCBTF) as solvent and uses AIBN as the initiator. The reaction is carried out by rapid addition of AIBN to the DCBTF at 50 °C followed by simultaneous addition of **85a** and $SO_2Cl_2$ over 1 h. After a further 1 h at 55−65 °C, the mixture is analysed by GC and contains 0.4% **85a**, 94.5% **85b**, 1.2% **85c**, and 0.2% of the 2-chloro derivatives of **85a** and **85b**. There is also 3.5% of other unspecified impurities. The solvent is recovered from the mixture by distilling off the products at atm pressure, and a fraction boiling between 40 and 70 °C contains 89.3% **85b** and 9.9% $SO_2Cl_2$. The reaction mixture can be hydrolysed with hot water to form acid **85c** that is recovered by distillation in 84.5% yield and 99.9% purity.

Reaction 27




The patent appears to prefer using AIBN as radical initiator at a level of about 2.5 to 3 wt % of **85**. The main decomposition

product of AIBN is tetramethylsuccinonitrile (TMSN) that easily sublimes and is an extremely toxic and hazardous substance with an OSHA-permitted exposure limit of 0.5 ppm. The patent makes no reference to this very dangerous material, and it is always produced when AIBN decomposes.

### Advantages

The process is claimed to provide an efficient route to the desired compound starting from low-cost starting materials, but could have safety concerns that must be addressed.

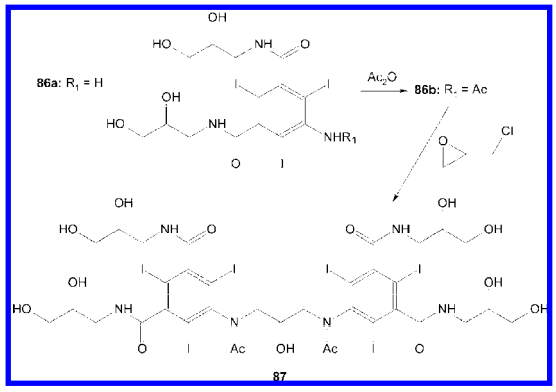
## Patent No. U.S. 7,754,918 and U.S. 7,754,920

### *Assignee: GE Healthcare AS, Oslo, Norway*

### *Title or Subject: Improvements in the Crystallisation of Iodixanol and Its Intermediate*

These two patents cover the minimisation of solvent usage and optimisation of a process to crystallise the X-ray contrast agent iodixanol **87** and the intermediate **86b** from which it is prepared. The first patent covers crystallisation of **87** from MeOH, $H_2O$, and $Pr^iOH$, and the second covers the crystallisation of **86b** from MeOH and $H_2O$. **87** is made on a large scale by the assignee, and therefore, small improvements in the manufacturing process can lead to significant savings, as stated in the patent. The last step in the process for producing **87** is the dimerization of **86b** that is obtained by acetylation of **91a**, and these steps are outlined in Reaction 28.

Reaction 28




After the formation of **86b** the product is recovered and usually crystallised from a mixture of MeOH and $H_2O$ by addition of dil HCl to reduce the pH from about 12 to 7. At this point, the compound crystallises because the anionic form of **86b** is protonated and the neutral form has poor solubility in the mixture. The solubility of **86b** is poor in the polar solvents and even moreso in $H_2O$ so that the yield is maximised by increasing the amount of $H_2O$. However, if the level is too high, the purity of the crystals is adversely affected. Normally the MeOH content is at least 25%, but it has been found the MeOH level is much less critical after the crystals have formed. Hence, by decreasing the MeOH content after the crystals form, the yield can be increased and the purity remains high. The second patent covers this aspect, and so the crystallisation process is carried out under reduced pressure to remove MeOH to about 20% or less by evaporation after the crystals form. A series of 10 experiments is described that use two parallel crystallisers where one had MeOH removed and the other did not. The results show the efficacy of the improvement.

The first patent covers the crystallisation of **87**, and it states that there have been several reports of attempts to improve the preparation and purification of **87**. These methods have included preparative liquid chromatography, alternative synthetic routes, or high pressure and high temperature crystallisation, but they have not been successful. Typically the crude **87** is only 83−84% pure, and the large production scale means that large quantities of product and solvents are handled. Hence, minimising volumes will reduce costs. It has been found that minimising the $H_2O$ content combined with gradual addition of $Pr^iOH$ during crystallisation gives an improved process. Small amounts of $H_2O$ increase the solubility of **87** significantly, and since the crude product from the preceding reaction is dissolved in $H_2O$ before crystallisation, the purification is made more difficult. The procedure begins by concentrating the aqueous **87** (purity 83−84%) on a falling film evaporator followed by distillation before the crystallisation stage. This produces a viscous solution containing about 0.17 L of $H_2O$/kilo crude **87** to which MeOH is added under reflux. Seeds of **87** are added followed by continuous addition of $Pr^iOH$ under reflux over a period of up to 10 h. After 30 h more $Pr^iOH$ is added at the same rate, and a third addition may also be made. After at least 65 h, and following seeding, the suspension is filtered at 60 °C on a pressure filter. The cake is washed in hot MeOH and dried. The yield of **87** is up to 90% and has a purity of 98.0−98.5% (HPLC). The example describes a process carried out starting from 700 kilo of crude **87**, and hence, it is probably safe to assume that this is in commercial operation.

### Advantages

The two processes reduce the volumes of solvents handled, and on the large scale of production this results in lower costs.

## Patent No. U.S. 7,763,749

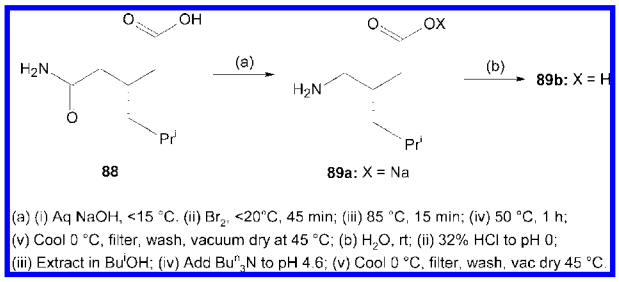
### *Assignee: Teva Pharmaceutical Industries Ltd., Petah Tiqva, Israel*

### *Title or Subject: Method for the Preparation of Pregabalin and Salts Thereof*

Pregabalin **89b** has been developed as a followup compound to gabapentin for use in the treatment of epilepsy. Two alternative, but similar, processes for the preparation of **89b** are outlined that both involve Hoffmann degradation of the amide **88** using $Br_2$/NaOH followed by precipitation using HCl and crystallisation from $Pr^iOH$ and $H_2O$. This patent claims that this preparation and purification method is in need of improvement. The new process, shown in Reaction 29, also consists of a Hoffmann degradation followed by precipitation and purification. The process is carried out by mixing the amide **88** with a NaOH solution at 10−15 °C, then $Br_2$ is added while maintaining the temperature <20 °C. After a period of heating the Na salt **89a** is produced, and this can be isolated or converted to **89b**. The isolation of **89a** is carried out by cooling the hot solution to 50 °C for 1 h then cooling to 0 °C to give a precipitate that is filtered off, and **89a** is isolated in 90% yield. The salt **89a** can then be converted to **89b** by dissolving in $H_2O$ followed by acidification with aq HCl to pH 0. The crude **89b** is extracted with an alcohol containing >4 C atoms, treated

with an amine, and cooled. The precipitated **89b** is filtered off and isolated in 54% yield and 98.6% purity.

Reaction 29




The amide **88** can be converted directly to **89b** in a one-pot process without isolation of **89a**. One example is described in which the isolated yield of **89b** is 80.4% with purity 99.7%. The conditions for this are as follows:

1. Dissolve **88** in 20% aq NaOH at 5 °C.
2. Add $Br_2$ at <10 °C then heat at 60 °C for 15 min.
3. Cool to rt and add $Bu^iOH$ followed by 66% $H_2SO_4$ and extract into $Bu^iOH$.
4. Add $Bu^n{}_3N$ and heat to dissolve.
5. Cool to 2 °C for 1.5 h.
6. Filter, wash in $H_2O$ and dry under vacuum at 55 °C.

This process bears striking similarities to the alternatives, and the major difference seems to be the use of an amine in step 4, and extraction using an alcohol with >4 C atoms.

## Advantages

The process is claimed to be an improvement on alternatives and starts from the same starting material.

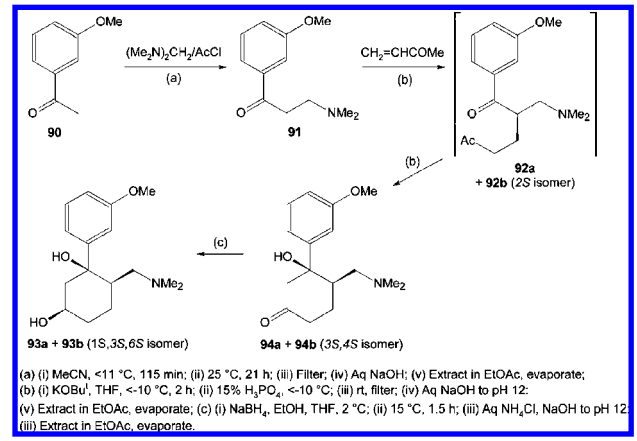
## Patent No. U.S. 7,763,754

### *Assignee: Gruenenthal GmbH, Aachen, Germany*

### *Title or Subject: Process for Producing (1RS,3RS,6RS)-Dimethylaminomethyl-1-(3-methoxyphenyl)cyclohexane-1,3-diol*

The title compound is a mixture of two stereoisomers **93a** and **93b** and is used as an analgesic. Of the various stereoisomers of this molecule that exist, it is the mixture of the (1*R*,3*R*,6*R*) and (1*S*,3*S*,6*S*) stereoisomers that are most active. Other isomers such as (1*R*,3*S*,6*R*) and (1*S*,2*R*,6*S*) are less active. Hence, the objective of the work in the patent is to develop a process to limit the formation of these less active isomers, and a major objective in the synthesis is to avoid the use of protective group chemistry. The process used to prepare a mixture of **93a** and **93b** is outlined in Reaction 30. This starts with the preparation of the Eschenmoser salt **91** by a Mannich reaction of the ketone **90** with $(Me_2N)_2CH_2$ and AcCl. The product is isolated as a colourless oil in 93% yield and with 96% purity (HPLC). The patent includes a detailed discussion of this reaction including the relative amounts of reagents and substrates that are needed. Alternative methods are also mentioned including the use of paraformaldehyde in place of AcCl, but no examples are given. The next stage is the reaction of **91** with $CH_2$═CHOMe to produce **92a** (and **92b**) followed by cyclisation to give **94a** (and **94b**). These two reactions take place consecutively without isolation of **92a**. The formation of the intermediate **92a** (and **92b**) is proven by LC/MS. The reaction results in an 85% yield of **94a** and **94b** with 83% purity (HPLC). The last step is significant in the overall process because it involves using an achiral reducing agent that leads to a diastereoselective reduction of the crude mixture of **94a** and **94b**. The procedure give a racemic mixture of **93a** and **93b**. The reaction gives a 100% yield of the crude mixture and the crude racemate. This can be converted to an acid addition salt by treatment with $H_3PO_4$ in 46% yield.

Reaction 30




## Advantages

The patent gives a high yield of the diastereomeric mixture and avoids the need to use protective group chemistry and chiral reducing agents.

Keith Turner

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