Organic Process Research & Development

HIGHLIGHTS FROM THE PATENTS

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

## SUMMARY

The current review covers 20 patents from an original list of 282 that fitted the search criteria. The widely used Mitsunobu reaction normally uses the reagent DEAD or DIAD, but an alternative proposal is to use a bis(alkoxyethyl) azodicarboxylate, a thermally stable solid that is easier and safer to use. The preparation of novel polymorphs of established drugs is reported in two patents. In one of these, novel solvates of the HIV drug Reyataz are described, and the second covers novel hydrates and an amorphous form of the antibiotic gemifloxacin. Patents specifically covering the purification of final products are frequently published. The compound hydrazaline is used to treat hypertension and is frequently yellow when isolated. A patent describes a method for removal of the yellow impurity as well as residual hydrazine from the preparation. A reaction, originating in 1915, for preparing 1,2-diphenylethanones has been improved by changing the reaction solvent, and in so doing high-purity products are obtained. A process to prepare high-purity morphinans is described that uses anhydrous conditions. This is achieved by adding an anhydride to the mixture that at the same time prevents formation of polymeric materials, thereby improving product purity and atom efficiency. Avoiding the use of hazardous reagents such as azides is an important objective. A new process for preparing irbesartan avoids using $Bu^nSnN_3$ that causes safety issues and requires reaction times of several days. Tartaric acid derivatives are widely used as resolving agents, and the acid is often discarded after use, causing disposal issues and increasing process costs. A method of recovering (+)-di-*O*,*O*′-toluoyl-(D)-tartaric acid after resolution of the drug paroxetine is described, and the acid can be reused for subsequent resolutions. Another patent covering tartrates describes a method of preparing pure tartrate salts that are used as platelet aggregation inhibitors that are alternatives to the well-known drug Plavix. A patent for preparing pure optical isomers of aminopentanes without resolution is described. The compounds have potential as psychotropic agents and are obtained from pure chiral precursors. A patent describes a series of hydroxymethylpyrazoles that are used as intermediates for making agrochemicals. A novel process is disclosed for preparing these in a novel single-step reaction from 5-hydroxypyrazoles. Introducing F-containing groups into molecules is an important step in the synthesis of materials such as agrochemicals and liquid crystals. The methods used often require hazardous reagents, and a patent describes the synthesis of aromatics containing $SF_5$ groups that can be used to introduce groups containing the F atom. A process patent describes an engineering solution to a method of preparing and purifying the solvent *N*-methylpyrrolidone. The problem relates to condensing volatile components from a vapour stream without the use of costly refrigeration. A method of making bicyclohexanols is described that uses catalytic amounts of a Li reagent amine so that the process costs are significantly reduced. The catalytic, air-oxidation of cycloalkanes to form cyclic ketones is widely practised in the production of intermediates for various grades of nylon. The major problem is low selectivity due to overoxidation. A new process for preparing cyclododecanone involves oxidation of cyclododecene with $N_2O$ and is more selectively efficient although it operates at high pressures and temperatures. A very comprehensive patent describes a process for making azaspiroheptanes that are used in preparing quinolone antibacterial agents. The preparation of cyanoacrylates and their use as herbicides are described, which is interesting since such materials are normally encountered as superglues. A new, less costly process for preparing the perfumery compound timberone is described that starts from citral that is commercially available. A noticeable feature of many patents in this selection is the large number of intermediates and sometimes final products that are obtained as oils after evaporation to dryness. Such procedures can lead to poor-quality product, especially on larger scale. 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. 7,807,830

**Assignee: Navinta LLC, Ewing, New Jersey, U.S.A.**
**Title or Subject: Manufacture of Pure Hydralazine Salts.**

Hydrazaline **2b** is available as the HCl salt, under the name Apresoline, for the treatment of hypertension and other heart-related diseases. A number of processes for preparing **2b** are summarised, and these can give a product that is generally pale-yellow in colour and requires recrystallisation to remove the yellow impurity and residual hydrazine. The maximum allowed level of hydrazine is 0.001%, and the objective of this patent is to provide a process that gives high-purity salts of **2b**. The preparation of **2b** is shown in Reaction 1 and starts with the chlorination of **1** using $POCl_3$ to form **2a** that is converted to a mixed Cl and $SO_4$ salt that is isolated in 85% yield with 99% purity. The mixed salt of **2a** is then reacted with hydrazine hydrate in the absence of a solvent to form the free base **2b**. The base is recovered in 99% yield and then converted to the HCl salt after treatment with active C in MeOH.

The HCl salt of **2b** is then purified by a procedure that is the basis of the patent claims and is summarised as follows:

1 Dissolve the salt in $H_2O$ or aqueous mixture at up to 80 °C.
2 Treat the hot solution with activated C and EDTA.
3 Filter off the solids, and adjust pH to between 2 and 5 using NaOH or another base.
4 Cool to −20 °C to precipitate the salt, filter, wash in cold MeOH, and dry under vacuum.

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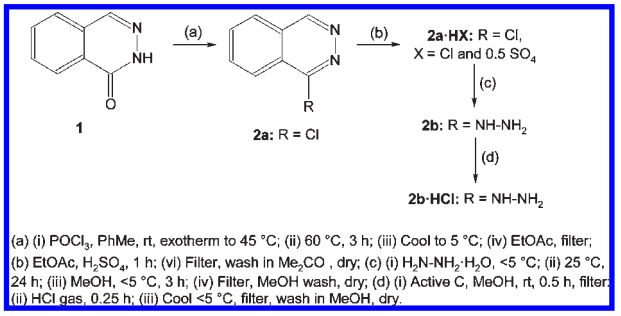
Reaction 1




The purified salt is isolated as a white solid in about 95% yield containing 0.00004% hydrazine. The patent is not forthcoming on how such a low level of hydrazine is measured. In one example HPLC is mentioned, in a second, RPLC; in another, the method used is stated as 1-1 PLC, whatever that may be.

**Advantages.** The process gives very good yield of highly pure product.

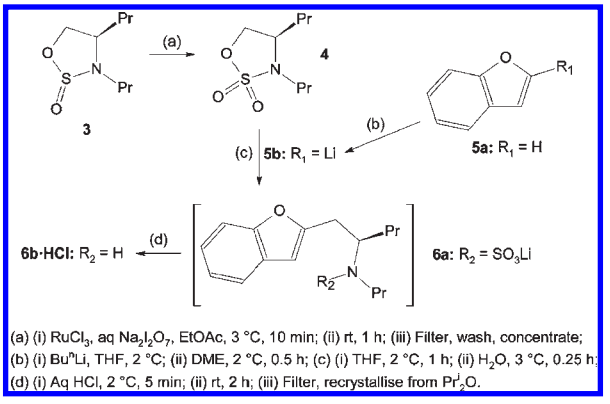
## PATENT NO. U.S. 7,807,840

**Assignee: Fujimoto Co., Ltd., Osaka, Japan.**

**Title or Subject: Process for Preparing Optically Active Aminopentane Derivative and Its Intermediate.**

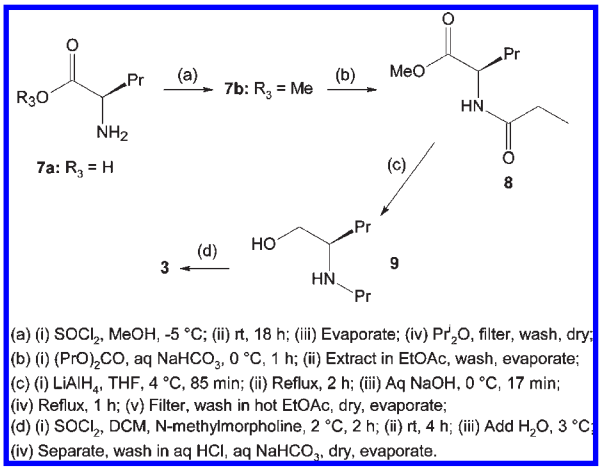
The main compound covered by this patent is **6b** that is of interest as a psychotropic agent. Other analogues of **6b** are also described, and alternative processes for preparing such compounds are said to give efficient methods of producing both optical isomers but they are not suitable for industrial production. Hence the objective of the work in the patent is to develop a commercially viable process for preparing the desired compounds and their intermediates. The *R*-form of the HCl salt of **6b** is prepared from **3** by the method outlined in Reaction 2. The examples in the patent describe the preparation of both *R*- and *S*- forms of **6b** from the appropriate pure chiral isomer of **3**. The first stage of the process is the oxidation of **3** to the novel oxathiazolidine **4** by the use of periodate in the presence of a Ru catalyst. The product **4** is isolated as a brown oil in 93−94% yield and then reacted with the lithiated benzofuran **5b** to give the intermediate **6a** that is not isolated but hydrolysed with HCl to form **6b**. The salt is purified by several crystallisations from $Pr^i_2O$ and isolated as white needles in 47−52% yield.

Reaction 2




The patent describes the preparation of both the *R*- and *S*-forms of **3** by the route shown in Reaction 3. This starts from the appropriate chiral isomer of the acid **7a** that is esterified using $MeOH/SOCl_2$ to form **7b**. This is isolated in 95% yield and then reacted with $(PrO)_2O$ to give the amide **8** in 99% yield as a pale-yellow oil. Reduction of the carboxyl amide groups in **8** with $LiAlH_4$ produces **9** that is isolated a yellow oil in 97% yield. In the last step **9** is treated with $SOCl_2$ in the presence of a base, and **3** is obtained as a red oil in 81% yield. The *R*-form of **3** is a mixture of *cis* and *trans*-isomers that is estimated by $^1H$ NMR to be 45% *cis*, whereas the *S*-form contains 38% *cis*. The patent also describes the preparation of other analogues of **6b** formed by the reaction of **4** with lithiated benzothiophene, or indoles. IR, $^1H$ NMR, and some basic MS data are given for many compounds.

Reaction 3




**Advantages.** The patent claims to provide an efficient and commercially suitable process for preparing the pure chiral compounds without the need for resolution. However, the synthesis of the starting amterials is rather laborious.

## PATENT NO. U.S. 7,812,175

**Assignee: Ihara Chemical Industry Co., Ltd., Tokyo, Japan.**

**Title or Subject: Process for Production of 5-Alkoxy-4-Hydroxymethylpyrazole Compound.**

The compounds of interest, such as **11a** and **11b**, are intermediates used to prepare agrochemicals and medicines. The patent states that there are no known processes for preparing the desired compounds from 5-hydroxypyrazoles in a single step, and the present work describes how this can be done. Reaction 4 shows the methods used to make **11a** and **11b** from **10**. The first stage is treatment of **10** with *para*-HCHO at rt in the presence of aq KOH. **11a** is obtained by passing $ClCF_2H$ through the mixture after adding more base, and the crude product is recovered as a solution in MeCN in 88% yield and 82% purity. This was purified by vacuum distillation, giving a colourless liquid, but the final yield and purity were not given. **11b** was obtained by carrying out the reaction in DMF with the use of $K_2CO_3$, followed by alkylation with $Me_2SO_4$. The crude product was isolated in 84% yield and 75.4% purity. Vacuum distillation gave **11b** as a light-yellow liquid. Examples are also given in which **11a** is prepared using MeI as alkylating agent, and the yield of crude product is 79% at 67.5% purity. A range of analogous alkoxy derivatives of **11a** were prepared including examples where R = Et, $Pr^i$, Bn, cyclopentyl, or propargyl, and these are all obtained by alkylation using the bromides. Other derivatives are prepared, and tables include 50 examples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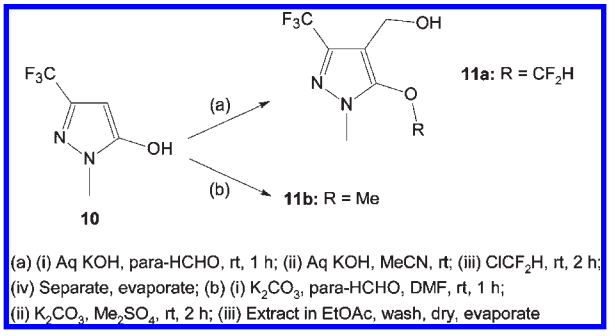
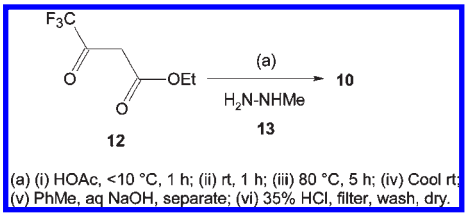
although no details are given for the preparation of most of them.

Reaction 4




The patent describes the preparation of the starting material **10** by the method shown in Reaction 5. An aqueous solution of **13** is added to **12** in HOAc. The addition is <10 °C, and after gradually warming to rt and then heating to 80 °C the mixture is extracted and acidified and the product isolated as yellow crystals in 86.5% yield. An analogous Ph derivative was prepared from PhNH−$NH_2$.

Reaction 5




Basic $^1$H NMR data are given for some of the compounds.

**Advantages.** The process enables the production of the desired alkoxy pyrazoles in one step from the hydroxy compounds.

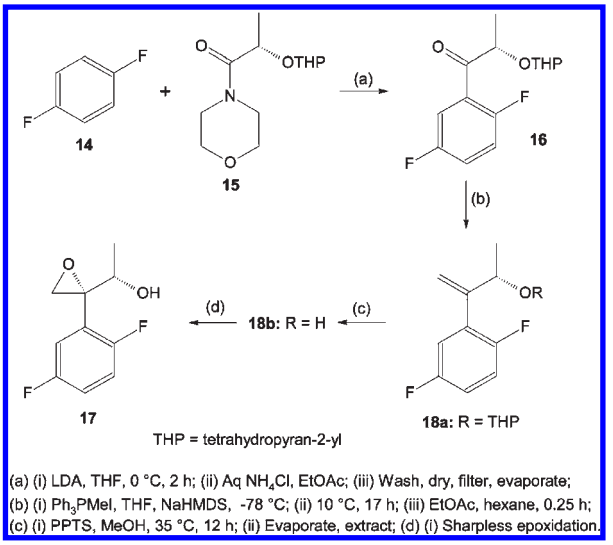
## ■ PATENT NO. U.S. 7,816,537

**Assignee: Basilea Pharmaceutica AG, Basel, Switzerland.**

**Title or Subject: Process for the Manufacture of Epoxybutanol Intermediates.**

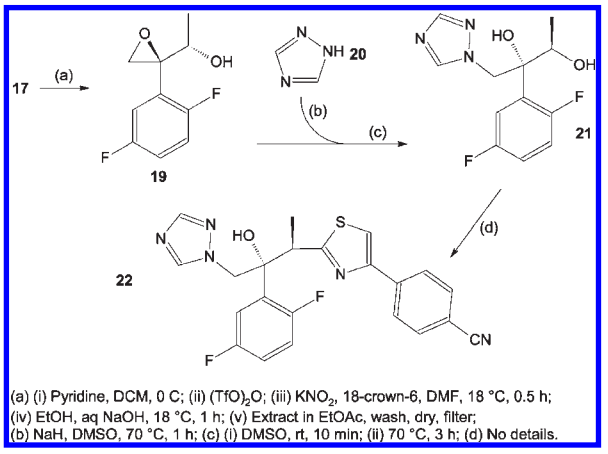
The title compounds such as **17** are used in the synthesis of azole antifungal agents such as isavuconazole **22**. This compound is under advanced clinical studies for the treatment of invasive yeasts and molds. Alternative processes for preparing **17** and analogues are summarised, and it is stated that problems encountered on large-scale production include the unacceptable levels of waste that are formed. It is reported that using the new process the disadvantages can be overcome making the process commercially viable. The preparation of **17**, outlined in Reaction 6, starts with the reaction of **14** and **15** in the presence of LDA to give **16** that is recovered after column chromatography (Col C) in 44.8% yield and 96.2% purity (HPLC). In the next stage **16** is treated with $Ph_3PMeI$ and NaHMDS to produce **18a** that is isolated as a colourless oil in 69% yield and 99.9% purity and ee of 99.2% after purification by Col C. The protective group is then removed using PPTS to form **18b** as a yellow oil in 81.4% isolated yield with 99.9% purity and 99.2% ee. In the last step a Sharpless epoxidation reaction is carried out to form **17** that after Col C is isolated as a light yellow oil in 82% yield and 82% purity.

Reaction 6




The patent then describes the conversion of **17** to **21** by the route outlined in Reaction 7. The first step is transformation of **17** to **19** via the triflate that is recovered as an oil then treated with $KNO_2$ and 18-crown-6 to produce **19** in 65% yield as a yellow oil after Col C. **19** is then treated with the Na salt of triazole **20** to give **21** that is isolated in 66.7% yield with optical purity reported as >95% (No other isomer is reported as being visible by NMR). **21** is converted to **22** by a method covered in another patent (WO 99/45008) but details are not described in this patent.

Reaction 7




**Advantages.** The process gives high optical purity of the products and is more efficient than alternative procedures so is suitable for commercial production.

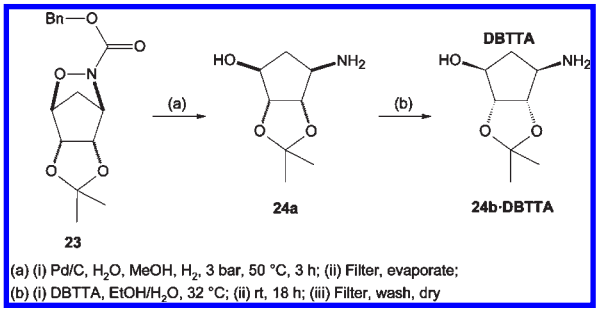
## ■ PATENT NO. U.S. 7,816,545

**Assignee: AstraZeneca AB, Sodertalje, Sweden.**

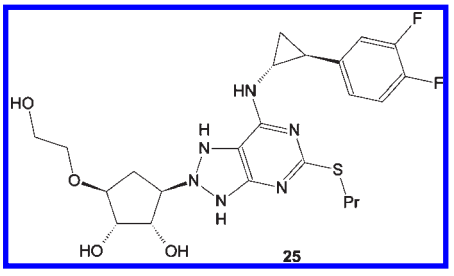
**Title or Subject: Process for the Preparation of a Pure Dibenzoyl Tartrate Salt.**

The actual title of this patent is 'Process 054' and it is difficult to believe that this less than descriptive title was accepted by the U.S. Patent Office. The subject of the patent is a resolution process for the preparation of the diastereomerically pure salt of **24b·DBTTA**. This salt is used in the preparation of ticagrelor **25** that is available as Brilinta. This is a platelet aggregation inhibitor used in the prevention of cardiovascular disease and an alternative to clopidogrel (Plavix). The process starts from the racemic benzyl ester **23** that is hydrogenated to give racemic **24a** using a Pd/C catalyst. The crude product with 95% purity is isolated in 97% yield and then used directly in the second step where it is treated with the dibenzoyl L-tartaric acid (DBTTA). Crystals of the salt are recovered in 39% yield with 99% purity. An example also describes the formation of **24b·DBTTA** without isolation of **24a**. In this case the hydrogenation is carried out in EtOH/$H_2O$, and the final yield of **24b·DBTTA** is 37%. The fate of the undesired isomer of **24b** is not reported. $^1H$ and $^{13}C$ NMR data are reported for **24b·DBTTA**.

Reaction 8




Ticagrelor




**Advantages.** The process gives the desired isomer in high purity.

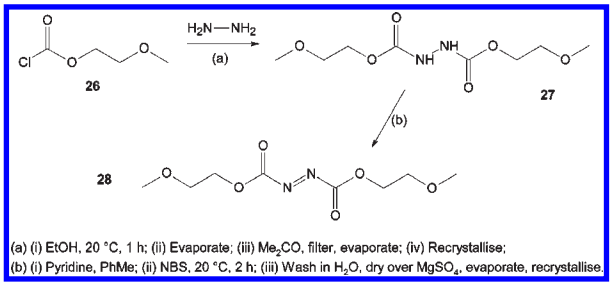
## PATENT NO. U.S. 7,820,802

**Assignee: Kazutake Hagiya and Takashi Sugimura, Hyogo, Japan.**

**Title or Subject: Production of an Azodicarboxylic Acid Bis(2-Alkoxyethyl)Ester Compound and Intermediate in its Production.**

The patent describes the preparation of **28** that is claimed to be suitable for use in the Mitsunobu reaction. Lower alkyl esters of azodicarboxylic acids, such as DEAD or diisopropyl azodicarboxylate (DIAD), that are used in this reaction are liquids, and the patent states that they are difficult to purify by distillation because they are thermally unstable. The alkoxylalkyl esters such as **28** are crystalline and are more thermally stable than the alkyl esters, and **28** is prepared by the route shown in Reaction 9. This starts with the reaction of hydrazine with the chloroformate **26** to form **27** that is isolated in 71.9% yield after recrystallisation from $Me_2CO$/PhMe. Treatment of an equimolar mixture of pyridine and **27** with NBS forms **28** that is recovered in 88% yield after recrystallisation from PhMe/hexane. The material is a pale-yellow crystalline solid melting at 40 °C.

Reaction 9




The patent contains examples of using **28** in a number of Mitsunobu reactions and compares their use with DIAD. The yields of products using these two reagents are very similar. A distinct advantage of using **28** in the Mitsunobu reaction is that the byproduct of **28** is **27**, and this is easily removed from the reaction mixture by washing in $H_2O$ wherein its solubility at 22 °C is 0.55 g/mL. $^1H$ and $^{13}C$ NMR and IR data are reported for **27** and **28**. These reagents are said to be more thermally stable than DEAD or DIAD and do not require purification via distillation. However no DSC or similar data are presented to back up this claim

**Advantages.** The compounds can be readily prepared, purified, and handled safely, and they are suitable for use in the Mitsunobu reaction.

## PATENT NO. U.S. 7,820,836

**Assignee: DSM IP Assets B.V., Heerlen, The Netherlands.**

**Title or Subject: Process for the Manufacture of Hydroxylated Isoflavones.**

The compounds covered by this patent are naturally occurring antioxidants and are reported to provide a number of health benefits. One method of preparing the compounds involves a step known as the Hoesch reaction to form 1,2-diphenylethanones. This reaction originates from 1915, and the patent states that it has been reported that the reaction only gives products of acceptable purity when using $Et_2O$ as solvent. The patent discloses that this is not the case and alkyl esters can be used as solvents and provide a better process. Reaction 10 shows the route used to make **32** also known as genistein. The first stage is the reaction of the nitrile **30** with phloroglucinol **29** in the presence of gaseous HCl. This reaction must be carried out under anhydrous conditions and produces the HCl salt of the imine **31a** (R = NH). This salt is not isolated and is hydrolysed with NaOH to give the ketone **31b**. One example describes the isolation of >50 kilo of **31b** in 78.6% yield. The conversion of **31b** to **32** is achieved by treatment of **31b** with a mixed formic acid anhydride that is formed by using $HCO_2Na$ and an acyl chloride **33** where R = Me, Et, and $Pr^i$. After the initial mixing of **31b** and **33**, $Et_3N$ is added to the mixture followed later by $H_2SO_4$ to promote hydrolysis. The examples indicate that $Pr^iCOCl$ is the most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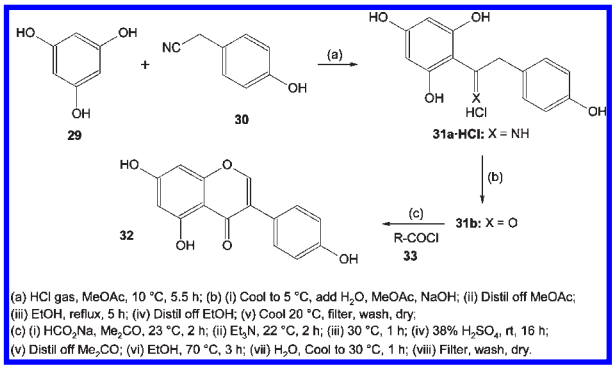
effective acyl chloride and gave **32** in 90.2% yield and purity of 99.7%.

Reaction 10




**Advantages.** The process significantly improves an old procedure and gives high yield and purity of the desired isoflavone.

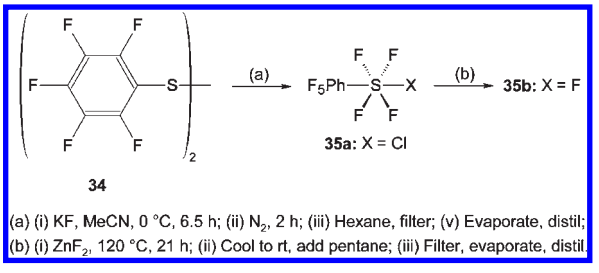
## PATENT NO. U.S. 7,820,864

**Assignee: IM& T Research Inc., Denver, Colorado, U.S.A.**

**Title or Subject: Process for Producing Arylsulfur Pentafluorides.**

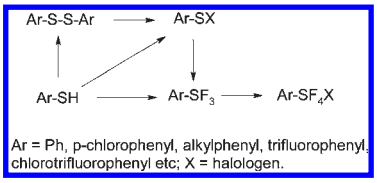
The compounds covered by this patent are used to introduce one or more $SF_5$ groups into organic molecules. The resulting compounds are of use in the development of materials such as liquid crystals and agrochemicals. The introduction of groups containing F atoms can frequently involve the use of hazardous reagents or give low yields of products. One method involves the use of $XeF_2$, and this is not a commercially viable process, and so the patent work focuses on a viable alternative. The single claim in the patent covers compound **35b** although the focus of the work in the patent is the reaction of tetrafluoroaryl compounds such as **35a** with a fluoride source to produce the pentafluoroaryl compounds such as **35b**. The production of **35a** is carried out by three methods, and the first is shown in Reaction 11. $Cl_2$ gas is passed through a solution of disulfide **34** and KF in MeCN. The product **35a** is isolated by vacuum distillation in 88% yield and $^{19}F$ NMR showed it to be the *trans*-isomer. Treatment of **35a** with $ZnF_2$ provides **35b** that is isolated in 75% yield.

Reaction 11




The second process for preparing **35a** starts from PhSH that is dissolved in MeCN with KF at <10 °C, and $Cl_2$ gas is passed through. The product is isolated in 83% yield and shown to be identical to that obtained by the first method. A third method of preparing **35a** is by reaction of $PhSF_3$ with KF and $Cl_2$ in MeCN. The yield of product is 84% and NMR showed it again to be the *trans*-isomer. The patent does not provide details for the preparation of $PhSF_3$, but it does include a generalized reaction scheme that includes its formation, and this is shown in Reaction 12. This scheme also summarises some of the other compounds analogous to **35a** and **35b** that can be made using the process in the patent.

Reaction 12




An alternative method of preparing **35b** is to treat **35a** with a solution of 70% HF in pyridine at rt and then at 50 °C. Isolation of **35b** was not described although analysis showed the yield of **35b** was 93%. A number of the compounds described are novel, and the patent contains $^1H$ and $^{19}F$ NMR data for many of them.

**Advantages.** The patent provides a method of producing a number of organic compounds $SF_5$ that may be commercially viable as well as a means of making some novel compounds.

## PATENT NO. U.S. 7,829,720 AND U.S. 7,838,678

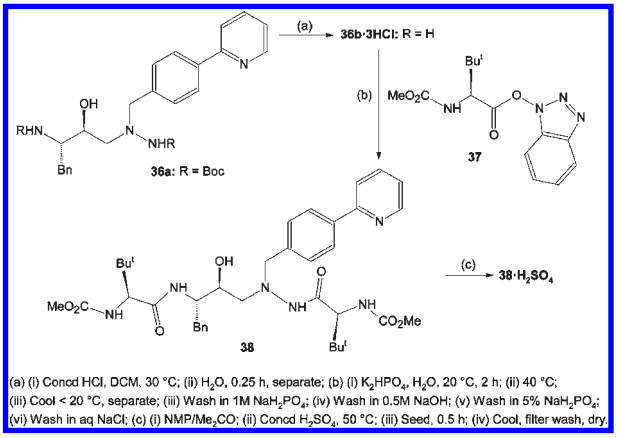
**Assignee: Bristol-Myers Squibb Company, Princeton, New Jersey, U.S.A.**

**Title or Subject: Process for Preparing Atazanavir Bisulfate and Novel Forms.**

The bisulfate salt **38**·$H_2SO_4$ is available as Reyataz and is used in the treatment of HIV. These patents describes a process to prepare novel crystalline forms of **38**·$H_2SO_4$ including a novel, highly crystalline triethanolate solvate of the bisulfate salt designated Form E3. The first patent claims cover the preparation of Form A crystals, and the second covers Pattern C material of Form A crystals that is the preferred form. A detailed report on the synthesis of **38** and various intermediates has been published (*Org. Process Res. Dev.* **2002**, *6*, 323). The patent describes the synthesis of **38** and the bisulfate plus the methods used to prepare the polymorphs and the solvate. Reaction 13 shows the route used to prepare **8** from the BOC protected diamine **36a**. In the first step the BOC groups are removed, and the salt **36b**·**3HCl** is recovered as an aqueous solution. This is then treated with 2 mol of the active ester **37** in the presence of $K_2HPO_4$ to form **38**. This is recovered as a solution in DCM, and then a solvent-exchange step produces a solution of **38** in *N*-methylpyrrolidone (NMP) and $Me_2CO$. Treatment of this solution with concd $H_2SO_4$ produces the bisulfate salt. This procedure is carried out by adding the acid at an increasing rate in five stages over 5 h. The amounts added and time between additions is defined by a cubic equation that is part of the claims of the patent. The crystals obtained are designated as Form A bisulfate, and these can be converted to what is termed Pattern C material. This is carried out by suspending the Form A crystals in $H_2O$ and stirring to produce a gel. This gel is dried and then ground to give Pattern C that is characterised by XRD, TGA, and DSC. The solvate of Form E3 is obtained from the free base **38** by slurrying in EtOH followed by addition of

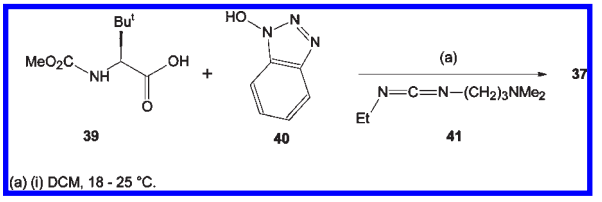
$H_2SO_4$ and crystallisation. The yield of Form E3 is 74.3%, but other yields are not reported.

Reaction 13




The patents describe the preparation of **37** from **39** and **40** in the presence of an approximately equimolar amount of **41** (Reaction 14). The reaction takes place at rt in DCM and is followed by HPLC, but the reaction time is not reported nor is the yield of **37** that is recovered as a solution and used in the preparation of **38**.

Reaction 14




The patent includes XRD, TGA, DSC, and $^1$H NMR data and details of formulations made using Pattern C crystals.

**Advantages.** The patents describe stable crystalline forms of the API that are suitable for preparing formulations.

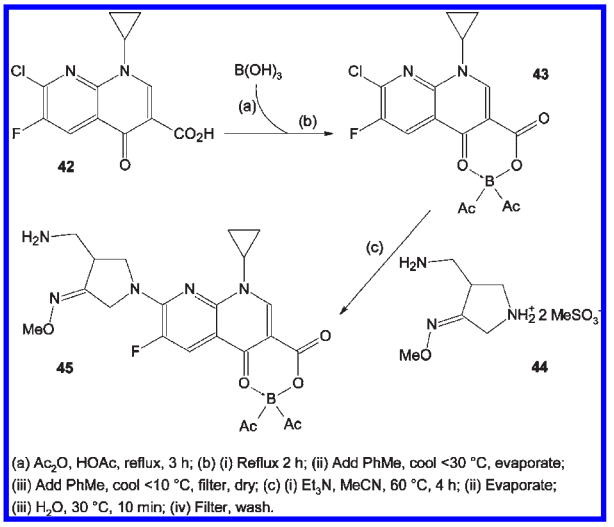
## PATENT NO. U.S. 7,834,027

**Assignee: Hetero Drugs Limited, Hyderabad, India.**

**Title or Subject: Process for Preparing Gemifloxacin and Polymorphs.**

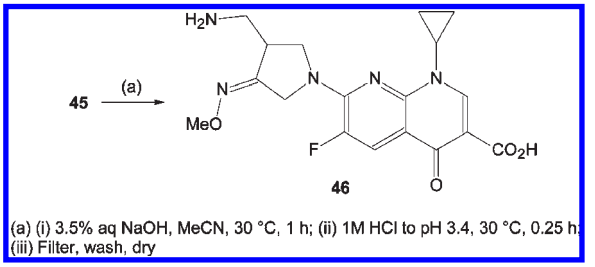
Gemifloxacin **46** is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria. A patent describing an improvement in the production of **46** by intensive mixing has been reviewed previously (*Org. Process Res. Dev.* **2007**, *11*, 802.). The current patent discloses a new synthesis of amorphous **46** plus novel hydrates and crystalline lactate and formate salts. The preparation of **46** proceeds via the formation of two novel borates **43** and **45** that are obtained by the route shown in Reaction 15. The synthesis starts from the acid **42** that is added to a hot solution of $B(OH)_3$ in $Ac_2O$ and HOAc, forming borate **43**. This is isolated in 90% purity and then added to **44** in MeCN containing $Et_3N$ producing **45**. After evaporation of the solvent, the crude product is recovered for use in the next step.

Reaction 15




Crude **45** is simply washed in $H_2O$ and then treated with aq NaOH in MeCN followed by acidification to produce the free base **46** (Reaction 16). This is recovered as a wet solid then dried and isolated in 99.7% purity and 84.9% yield based on **42**. The amorphous form of **46** is obtained by heating the free base in DMF and is isolated in 52% yield with 99.92% purity. Alternatively, dissolution in DCM at 30 °C followed by dilution with $Pr^i_2O$ and cooling gives the amorphous form in 66% yield and 99.8% purity. The lactate and formate salts are formed by dissolution of the free base in EtOH followed by addition of the acid and cooling. Yields are >77% for both salts. The patent also describes the formation of a hemihydrate, monohydrate, and sesquihydrate forms. The four claims in the patent only cover the hemihydrate, and this is obtained in 99.92% purity when the wet product from Reaction 16 is dried under vacuum at 50−55 °C until the $H_2O$ content is 2%. The patent contains XRD spectra for amorphous **46** and the lactate salt.

Reaction 16




**Advantages.** The process gives a novel hemihydrate form of the compound that is used in preparing formulations and also provides acid salts that may be useful.

## PATENT NO. U.S. 7,834,196

**Assignee: Davy Process Technology Limited, London, United Kingdom.**

**Title or Subject: Process for the Preparation of *N*-Alkylpyrrolidones.**


dx.doi.org/10.1021/op200025t |*Org. Process Res. Dev.* 2011, 15, 314–324

This is a chemical engineering patent containing a process flowsheet and operational details for the continuous production and purification of alkylpyrrolidones from $\gamma$-butyrolactone and alkylamines. It specifically covers the use of $MeNH_2$ to produce NMP that is used as an intermediate and solvent especially in the replacement of chlorinated solvents. Alternative processes for preparing and purifying NMP recommend that the reaction should be carried out with a minimum of water present and to use a small excess of amine. The NMP is purified by distillation, and a major drawback is that it is not possible to condense the overhead stream containing excess amine at low pressure, without refrigeration, when only small amounts of water are present. Refrigeration costs are expensive, and an alternative solution to the problem has been developed. It has been found that, by adding water to the distillation system and thereby increasing the dew point of the stream, it can be condensed with regular cooling water. The preparation of NMP is carried out in a column reactor containing about 1% water. The reactor effluent is then sent to a distillation system containing three columns to recover pure NMP, unreacted $MeNH_2$, water, and any byproducts. Additional water is injected into the first distillation column, and this improves the overall recovery and purification process. The NMP produced is claimed to have low colour because of the low level of impurities but no analyses are given as evidence. An interesting aspect of the patent is the discussion of the effect of the seasonal variation of cooling water temperature on the process efficiency. Obviously during the summer months the cooling water is much hotter worldwide than it is in winter. This not only impacts the efficiency of the condensation of hot overhead streams but also affects the amount of water that needs to be added to the distillation columns. Readers who are engineers are encouraged to consult the patent for details, and chemists may be interested in an engineer' s approach to problem solving.

**Advantages.** The process improves the efficiency of the purification of NMP and is claimed to be more energy efficient.

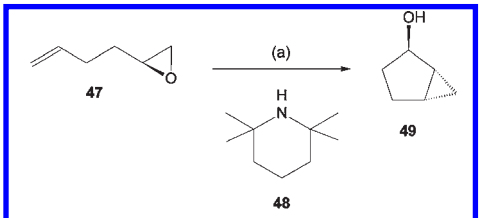
## PATENT NO. U.S. 7,834,222

**Assignee: Merck Sharp & Dohme Ltd., Hoddesdon, United Kingdom.**

**Title or Subject: Process for the Preparation of Bicyclo-[3.1.0]Hexanols.**

The patent describes a process to make bicyclic alcohols containing a cyclopropyl ring but does not indicate what use these compounds may have. The desired compounds can be prepared from unsaturated epoxides using 2 equiv of the Li salt of **48** or 2.5 equiv of **48** and excess BuLi. However, **48** is said to be expensive, and so commercial production is probably not viable. The patent discloses that it is possible to use **48** in catalytic amounts and reduce the quantities of alkyl Li reagents that are needed. The only example in the patent describes the preparation of **49** by the process shown in Reaction 17. This involves the intramolecular cyclopropanation of the epoxide **47** in the presence of 0.5 equivalent of **48** and just over 1 equivalent of n-hexyl Li. After quenching the reaction with HCl the product is recovered as a solution in MTBE (about 25% w/w), and the yield is reported to be 86%. The isolation of **49** from this solution is not reported, and hence the isolated yield may be much lower.

Reaction 17




(a) (i) n-hexyl Li, MTBE, <0 °C, 4 h; (ii) 3M HCl, <0 °C; (iii) Separate; (iv) Extract in 3M HCl; Extract in MTBE; (v) Evaporate.

**Advantages.** The process uses significantly less of the expensive reagent than alternative methods.

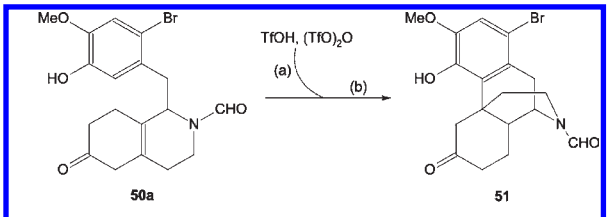
## PATENT NO. U.S. 7,838,677

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

**Title or Subject: Process for Preparing Morphinans and Intermediates Thereof.**

The patent is specifically directed towards the preparation of nordihydrothebainone **51**; an important intermediate in the synthesis of a range of drugs used to relieve pain. Processes for preparing **51** and its analogues generally employ a procedure known as a Grewe cyclisation reaction that uses strong acids as catalysts. However, the presence of water in the acids and starting materials can give rise to low yields and impurity formation. The process to prepare **51** by the Grewe cyclisation of **50a** is shown in Reaction 18 and is catalysed by a mixture of TfOH and $(TfO)_2O$. It is suggested in the patent that the addition of the anhydride reduces the water content of the mixture and may associate in some way with the functional groups in **50a** to assist the cyclisation. It is stated that the anhydride does reduce the level of polymeric side products and improves the overall efficiency of the reaction. The reaction is carried out by initially heating the mixture of TfOH and $(TfO)_2O$ until the vapour temperature reaches 130 °C, and this procedure undoubtedly removes water. The cyclisation of **50a** then takes place at around rt in $CHCl_3$. The workup involves addition of the mixture to ice/water followed by washing in 3% $Na_3PO_4$ adjusted to pH 12 with NaOH. This is followed by washing in $HCO_2H$ and then filtration through $K_2SO_4$. The solids are washed in $CHCl_3$, and then evaporation of the combined organic solution produces **51** in 96% yield that analysed 95 area % by HPLC.

Reaction 18

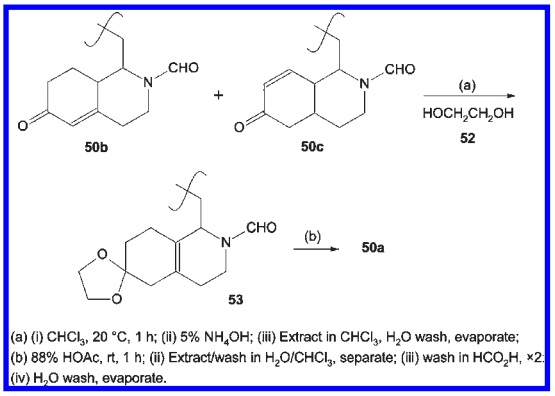



(a) (i) 130 °C; (ii) Cool < 10 °C; (b) (i) $CHCl_3$, <15 °C, 0.5 h; (ii) rt, 12 h; (iii) $H_2O$/ice, separate; (iv) Wash 3 times in 3% $Na_3PO_4$;(v) 1M NaOH to pH 12; (v) Wash in 3% $HCO_2H$; (vi) Filter through $K_2SO_4$ powder; (vii) Wash solids in $CHCl_3$; (viii) Evaporate, 60 °C.

An important aspect of the patent is that it starts from the $\beta,\gamma$-eneone **50a** and not the $\alpha,\beta$-isomers **50b** or **50c**. It is stated that these isomers do not readily participate in the Grewe reaction, and so the patent describes the preparation of **50a** by a two-stage isomerisation process outlined in Reaction 19. The $\alpha,\beta$-eneone isomers are often formed as byproducts in Grewe reactions, and so this isomerisation allows recycling of the

normally discarded byproducts. The isomerisation of the mixed isomers **50b** and **50c** begins by reacting them with **52** to protect the ketone group and form the dioxolane **53**. This is recovered as a solid in 70% purity (HPLC) and is then dissolved in HOAc and hydrolysed to produce **50a**. After an extensive workup procedure involving washing and extraction in $CHCl_3$, $HCO_2H$, and $H_2O$, **50a** is isolated as a yellow solid in 88% yield and 94% purity (HPLC).

Reaction 19




**Advantages.** The process improves the selectivity of the reaction and recycles a normally unwanted byproduct, thus increasing the overall efficiency.

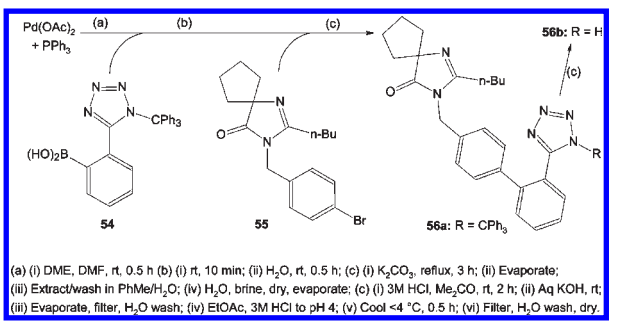
## PATENT NO. U.S. 7,838,683

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

**Title or Subject: Synthesis of Irbesartan.**

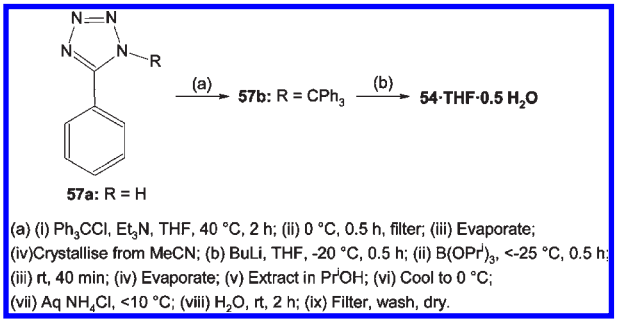
Irbesartan **56b** is available as Avapro for lowering blood pressure in patients with kidney disease. It is also used to treat diabetes mellitus. In an alternative syntheses of **56b** the penultimate step involves the reaction of a cyano group with tribuyltin azide which is a hazardous procedure that can require reaction times of up to 210 h. An additional problem is that dipolar aprotic solvents such as NMP are used, and the high boiling point means it is difficult to remove. Hence, the patent describes a new process that avoids these problems. The final steps in the new process are shown in Reaction 20 and involve the reaction of **54** with **55** to form **56a**. This reaction takes place in a two-phase system; initially, a catalyst solution is prepared from $Pd(OAc)_2$ and $PPh_3$ in a mixture of DME and DMF. **54** is added to this mixture, followed after a short time by **55** along with solid $K_2CO_3$. After refluxing for 3 h the solvent is evaporated and the mixture extracted and washed with PhMe and $H_2O$. The crude product is crystallised from $Pr^iOH$ and isolated in 90% yield with purity of 98%. Hydrolysis of **56a** using HCl gives **56b** that is recovered in 58% yield (purity not reported).

Reaction 20



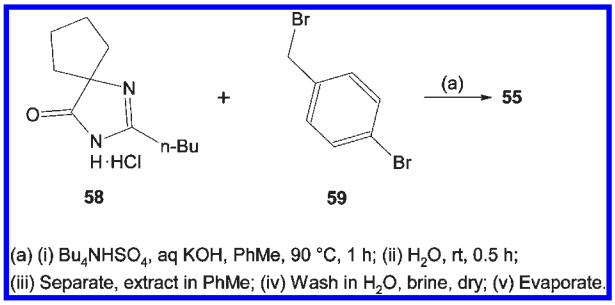

The patent describes the preparation of both starting materials; that of **54** is outlined in Reaction 21. This begins with the alkylation of **57a** using TrCl in the presence of $Et_3N$ to form **57b** that is isolated in 94% yield and 94% purity. A solution of **57b** in THF is then treated with $Bu^nLi$ followed by $B(OPr^i)_3$. The reaction is extracted with $Pr^iOH$ and hydrolysed using aq $NH_4Cl$. The product is isolated as a 1:0.5 $THF/H_2O$ solvate in 92% yield and 94.5% purity.

Reaction 21




The preparation of **55** is by the reaction of the HCl salt of **58** with **59** as shown in Reaction 22. The reaction takes place in a two-phase mixture of PhMe and $H_2O$ in the presence of KOH and $NH_4HSO_4$ as a phase transfer catalyst (PTC). The product is isolated as a colourless oil in 94% yield and 94% purity. The patent does not indicate if the two starting materials are purified before being used to prepare **56b**.

Reaction 22




**Advantages.** The patent provides a novel process of preparing the drug compound without the necessity to use a hazardous azide reagent.

## PATENT NO. U.S. 7,838,700

**Assignee: Aesica Pharmaceuticals, Cramlington, United Kingdom.**

**Title or Subject: Recovery and Recycling of Chiral Tartaric Resolving Agents**

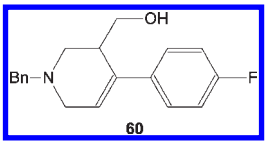
The recovery and reuse of resolving agents can be economically attractive, and tartaric acid (TA) derivatives are widely used for chiral resolutions. Alternative methods for recovery of TA resolving agents are said to give products of low purity and in poor yield. One of the problems is from solvent exchange operations resulting from extractions into water-immiscible solvents. The patent addresses this problem by employing a process that uses water-soluble solvents. The process is particularly useful for the recovery of TA resolving agents in the manufacture of **60**; an intermediate in the synthesis of the antidepressant paroxetine. The compound is used to resolve **60** and is recovered as (+)-di-*O*,*O*′-toluoyl-(D)-tartaric acid

(DTTA). After formation and recovery of the DTTA salt of the (+)-isomer of **60**, the solid is subjected to the following treatment to recover the DTTA.

1 Suspend the salt in PhMe at 35 °C.
2 Slowly add a 1 M solution of $NaHCO_3$ and keep at 35 °C for 2 h.
3 Recover the lower aqueous phase and wash the organic phase with $H_2O$.
4 Combine aqueous phases and add 2-BuOH.
5 Heat to 40 °C and slowly add HCl.
6 Cool to 10 °C for 0.5 h and filter off DTTA.
7 Wash solid with $H_2O$ (×2) and dry at 50 °C under vacuum.

The product is recovered as its 2-BuOH solvate in 98% yield containing 24% 2-BuOH, and this can be used as a resolving agent without further purification.

Intermediate




**Advantages.** The process allows recovery of a resolving agent that can be reused for further resolutions.

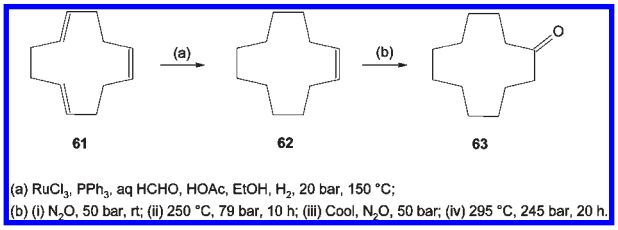
## PATENT NO. U.S. 7,838,705

**Assignee: BASF AG, Ludwigshafen, Germany.**

**Title or Subject: Process for the Preparation of Cyclododecanone.**

Cyclododecanone **63** is an intermediate used to produce a range of speciality chemicals and polyamides such as nylon-12 and nylon-6,12. It is usually prepared by catalytic oxidation of the cyclodecane using air in the presence of $H_3BO_3$ giving a borate that is hydrolysed to produce **63** and cyclododecanol. The alcohol and ketone are then separated by distillation. Such oxidation processes inevitably produce large numbers of byproducts and can be inefficient. This new process is outlined in Reaction 23 and starts from the triene **61** that is hydrogenated to give **62** that is oxidised by $N_2O$ to give **63**. The hydrogenation of **61** to **62** is carried out using a homogeneous $Ru/PPh_3$ catalyst. The reaction can be carried out batchwise or continuously, and kilo scale examples are given for each mode. The reaction mixture contains aq HCHO and an acid with HOAc being used in the batch example and adipic acid in the continuous one. The yield of **62** determined by GC analysis of the reaction mixture was 98.1% from the batch test and 97% when run continuously. The hydrogenation reaction produces a mixture of *cis*- and *trans*-**62**; the continuous test gave a 64/33 mixture of *trans* and *cis*, but there are no data for the batch example. The patent does not describe the method for recovery of **62** although examples are given in which the mixture from the hydrogenation step, still containing catalyst, is used in the second step. If the catalyst is removed, there is only 1% conversion of the *cis*-isomer to **63** compared to 21% when catalyst remains. This is ascribed to isomerisation promoted by the Ru catalyst. The oxidation of **62** to **63** is carried out by admitting $N_2O$ at rt to the system to 50 bar and then heating at 250 °C. The pressure increases as the reactor is heated and more $N_2O$ is added after cooling. After adding more $N_2O$ the temperature is increased to 295 °C, and the pressure rises to 245 bar. The conversion of *trans*-**62** in this procedure is 99%, and that of the *cis*-isomer is 32% with total selectivity of 95%.

Reaction 23




The patent includes a flow diagram for a continuous process for preparing **63** from **61**.

**Advantages.** The process avoids the use of air as the oxidant and appears to give much higher selectivity, although whether the process is applicable to other cyclic olefins at more moderate conditions is not known.

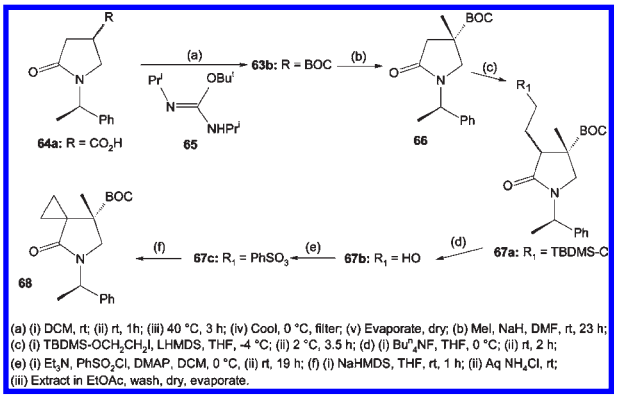
## PATENT NO. U.S. 7,842,818

**Assignee: Daiichi Sankyo Company Limited, Tokyo, Japan.**

**Title or Subject: Process for Preparation of Tetrasubstituted 5-Azaspiro[2,4]heptane Derivatives and Optically Active Derivatives Thereof.**

The particular compound of interest is **68**, an intermediate in the production of **74**, an antibacterial agent. The optical isomers of the this quinolone compound have different activity, and hence the methods for the synthesis of **74** are aimed at maximising the desired isomer. However, the patent states that it had not previously been known which isomer was the more active. This is a very comprehensive patent with the claims and main focus being the synthesis of **68**, via the preferred route summarised in Reaction 24. The first step is reaction of **64a** with **65** to produce **64b** that is a mixture of 3-position diastereoisomers. These are not separated, but purification of the isomer mixture by Col C gives the isomers as a yellow syrup isolated in 64% yield in an example describing a kilo-scale experiment. The $^1H$ NMR data are provided for the pure isomers although no details are given for their separation. The two isomers of **64b** are then methylated with MeI, producing a mixture containing the 3*S*-isomer **66** described as the high-polar isomer in 33.7% yield and the 3*R*-low-polar isomer in 47.3% yield. These are separated by Col C, and the OH group of the 3*S*-isomer **66** is silylated to give **67a**; hydrolysis gives **67b**. The hydroxyethyl compound **67b** is isolated in 85% yield as a transparent syrup after Col C and converted to the sulphonyl derivative **67c**. In the final stage **67c** is used without purification and treated with NaHMDS to produce **68**. The crude product is purified by Col C and isolated in 89% as a white solid. $^1H$ NMR, IR data, and elemental analysis are given in addition to XRD data to confirm the configuration of 7-Me position.

Reaction 24

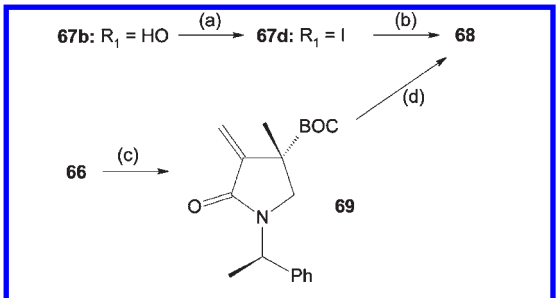




dx.doi.org/10.1021/op200025t |*Org. Process Res. Dev.* 2011, 15, 314–324

The patent also describes two further methods for the synthesis of **68** shown in Reaction 25. The first of these converts **67b** to the iodo derivative **67d** ($R_1$ = I) by treatment with MsCl and $Et_3N$ followed by NaI. The product is recovered as a pale-yellow oil in 96% yield; although the purity is not reported, $^1H$ NMR data are given. The cyclopropyl group in **68** is formed by treating **67b** with KHMDS followed by addition of aq $NH_4Cl$. The product is purified by Col C and recovered in 100% yield although the example refers only to a milligram-scale experiment. The second route also shown in Reaction 25 starts from **66** that is converted to the methylene compound **69** by reaction with LHMDS followed by $HCO_2Et$ and paraformaldehyde. After workup and purification by medium pressure LC, **69** is isolated in 61% yield and treated with NaH followed by $Me_3SI$ in DMSO. Upon completion of the reaction aq citric acid is added, and after workup the product is purified by Col C, giving **68** in 60.3% yield but again only on a milligram scale.

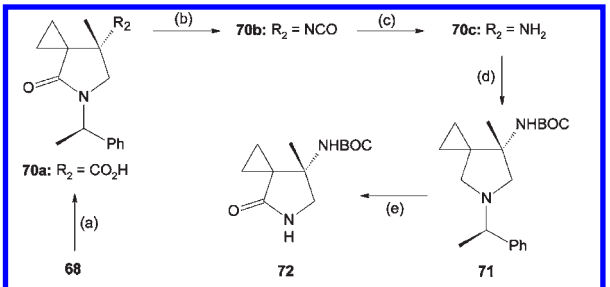
Reaction 25




(a) (i) MsCl, $Et_3N$, DCM, rt, 2.5 h; (ii) NaI, $Me_2CO$, 80 °C, 17.5 h; (b) KHMDS, THF, 0 °C, 10 min; (c) (i) LHMDS, THF, 0 °C, 0.5 h; (ii) $HCO_2Et$, 0 °C, 80 min; (iii) $(HCHO)_n$, DMF, rt, 17 h; (iv) 1 M HCl (d) (i) NaH, DMSO; (ii) $Me_3SI$, 90 °C, 0.5 h; (iii) Aq citric acid; (iv) C

The patent also describes the preparation of some derivatives of **68** as shown in Reaction 26. The acid **70a** is obtained by treatment of **68** with TFA. The workup involves a number of evaporations to dryness and the use of PhMe, $CHCl_3$, and hexane as well as aq NaOH and HCl. The product **70a** is obtained in quantitative yield and used without purification in a reaction with the azide $(PhO)_2PON_3$. This forms an acid azide that is not isolated and rearranges to the isocyanate **71b** that is isolated as an oil. Acid hydrolysis of **70b** forms the amine **70c** that is recovered in 87% yield (based on **70a**) and used without further purification in the next step. The conversion of **70a** to **70c** is described as an example of a Curtius rearrangement. The carbonyl group in **70c** is then reduced with $(MeOCH_2CH_2O)_2AlH$ and the amine group protected to form **71**. This is isolated as a colourless oil in 73% yield and then converted quantitatively to **72** by hydrogenolysis with Pd/C catalyst.

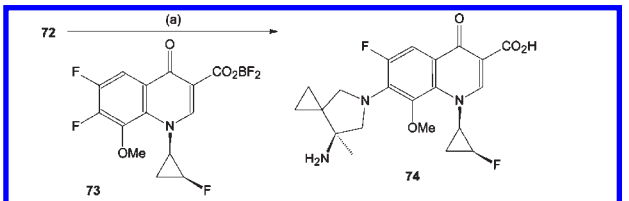
Reaction 26




(a) (i) TFA, DCM, 0 °C, 2 h; (ii) Evaporate; (b) (i) $(PhO)_2PON_3$, $Et_3N$, PhMe, 125 °C, 1 h; (c) (i) HCl, dioxane, 50 °C, 1 h; (ii) Aq NaOH to pH 9.5; (d) (i) $(MeOCH_2CH_2O)_2AlH$, PhMe, <70 °C, 0.25 h; (ii) $(BOC)_2$, PhMe, rt, 3 h; (e) (i) Pd/C, MeOH, $H_2$, rt, 18 h; (ii) 40 °C, 5.5 h;

The antibacterial agent **74** is obtained from **72** by reaction with **73** in DMSO in the presence of $Et_3N$, and this is shown in Reaction 27. The isolation procedure of **74** is extremely complicated; despite this, the yield is reported to be 79%.

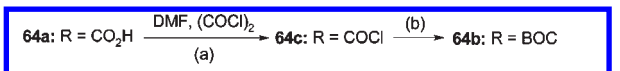
Reaction 27




(a) (i) $Et_3N$, DMSO, 40 °C, 17 h; (ii) $H_2O$, filter; (iii) $Et_3N$, EtOH/$H_2O$, reflux, 1.5 h; (iv) Evaporate; (v) Add EtOAc; (vi) Wash in citric acid, $H_2O$, brine, dry; (vii) Evaporate; (viii) $CHCl_3$/MeOH, silica gel, rt, 1 h (ix) Filter, evaporate; (x) Concd HCl, 0 °C; (xi) rt, 0.5 h; (xii) Wash in $CHCl_3$; (xiii) Aq NaOH to pH 11.8; (xiv) HCl to pH 7.4; (xv) Extract in $CHCl_3$, dry, evaporate; (xvi) Recrystallise from EtOH.

The patent describes an alternative route to **64b** from **64a** via the acyl chloride **64c** (Reaction 28). The example describes a milligram experiment and gives the two isomers of **64b** in 85% yield, and the isomer ratio is reported as 2.2:1.0.

Reaction 28




(a) (i) DCM, 0 °C, 0.25 h; (ii) rt, 0.25 h; (b) (i) $Bu^tOH$, DCM, 0 °C; (ii) $Et_3N$, rt, 0.5 h;

This is a very detailed patent, and interested readers are encouraged to consult the patent for more information.

**Advantages.** The process provides a route to the precursor to the desired active isomer of the antibacterial agent. Indications are that at least part of the process is at an advanced stage of development and has been scaled up to kilo scale.

## PATENT NO. U.S. 7,842,832

**Assignee: BASF SE, Ludwigshafen, Germany.**

**Title or Subject: β-Amino-α-cyanoacrylates and Their Use as Herbicides.**

Cyanoacrylates are normally encountered as so-called superglues, but this patent describes a range of compounds that have herbicidal activity. Cyanoacrylates suppress the growth of weeds by inhibiting electron excitation which consequently inhibits a route in photosynthesis. The compounds have not previously been used as herbicides because large doses were needed to achieve the desired effect, and presumably the costs were too high. A table in the patent includes 74 specific methyl esters that are covered by the invention. Equal numbers of analogous esters are also mentioned as being covered, and these include Et, $Pr^n$, $Bu^n$, allyl, crotyl, ispropenyl, and alkoxyalkyl esters. In total 1100 compounds are covered by the invention, and the patent outlines five processes for their preparation. Despite the claimed extensive coverage of the patent, there are detailed examples for only three compounds by two methods. Reaction 29 describes the route used to make **77c**, and this begins with the reaction of the butyroyl chloride **75** with **76** to produce the Na salt of the enol **77a**. The patent example states that mixture is hydrolysed but does not mention the conditions. There are further ambiguities in this procedure where the example states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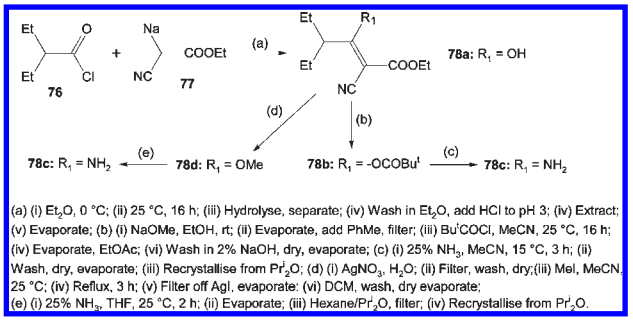
that the enol is extracted but does not indicate the solvent used. The product **77a** is recovered as a colourless liquid in 70% yield by something described as customary purification. This term features throughout the examples without any explanation. The enol **77a** can be converted to the desired product **77c** by two methods. The most efficient is to convert **77a** to **77b** by reaction with $Bu^tCOCl$ in the presence of NaOMe. The product is a liquid recovered in 83% yield by customary purification. The amine **77c** is obtained from **77b** by treatment with $NH_3$ and the product recovered by crystallisation in 68% yield. The alternative route to **77c** proceeds via the enol ether **77d** that is formed in 39% yield, and this is converted to **77c** in only 8% yield.

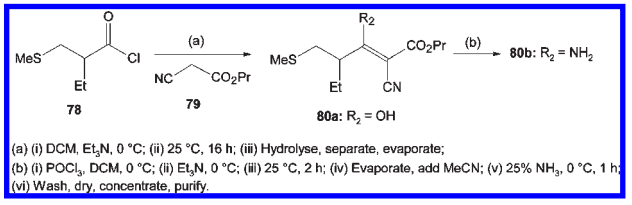
Reaction 29




(a) (i) $Et_2O$, 0 °C; (ii) 25 °C, 16 h; (iii) Hydrolyse, separate; (iv) Wash in $Et_2O$, add HCl to pH 3; (iv) Extract; (v) Evaporate; (b) (i) NaOMe, EtOH, rt; (ii) Evaporate, add PhMe, filter; (iii) $Bu^tCOCl$, MeCN, 25 °C, 16 h; (iv) Evaporate, EtOAc; (vi) Wash in 2% NaOH, dry, evaporate; (c) (i) 25% $NH_3$, MeCN, 15 °C, 3 h; (ii) Wash, dry, evaporate; (iii) Recrystallise from $Pr^i_2O$; (d) (i) $AgNO_3$, $H_2O$; (ii) Filter, wash, dry;(iii) MeI, MeCN, 25 °C; (iv) Reflux, 3 h; (v) Filter off AgI, evaporate: (vi) DCM, wash, dry evaporate; (e) (i) 25% $NH_3$, THF, 25 °C, 2 h; (ii) Evaporate; (iii) Hexane/$Pr^i_2O$, filter; (iv) Recrystallise from $Pr^i_2O$.

The patent also describes the preparation of the *n*-propyl ester analogue of **77c** by a similar route, and the third compound for which a detailed example is given is the *n*-propyl ester **80b**. This is obtained by the method outlined in Reaction 30. Initially the enol **80a** is obtained from **78** and **79** in the presence of $Et_3N$. The product is obtained as a liquid in 58% yield by customary purification. The enol is then treated with $POCl_3$ followed by $NH_3$, and the customary purification method affords the amine 81b as a brown liquid in 52% yield.

Reaction 30




(a) (i) DCM, $Et_3N$, 0 °C; (ii) 25 °C, 16 h; (iii) Hydrolyse, separate, evaporate; (b) (i) $POCl_3$, DCM, 0 °C; (ii) $Et_3N$, 0 °C; (iii) 25 °C, 2 h; (iv) Evaporate, add MeCN; (v) 25% $NH_3$, 0 °C, 1 h; (vi) Wash, dry, concentrate, purify.

The patent contains a table of 30 compounds that are mostly solids for which the mp is given. Some compounds are described as oils; thus, from the 1100 possible compounds covered, a number have been prepared. The patent claims that imido esters or amidines can react with cyanoacetates to give the amino-cycanoacrylates in the presence of a base, but there are no details provided. Some of the enol ethers formed such as **77d** are novel. It is claimed that these can be obtained containing from 5% *E*-isomer to 5% *Z*-isomer but usually contain 50% of each although no details are given. The patent describes formulations containing the amino-cycanoacrylates and their use to suppress various weeds. The effective dosage rates are up to 1 kilo per hectare, but whether this is cost-effective is not known.

**Advantages.** The patent describes an effective process for preparing some novel enol ethers and a range of amino-cyanoacrylates that are effective herbicides.

## PATENT NO. U.S. 7,842,841

**Assignee: DSM IP Assets B.V., Heerlen, The Netherlands.**

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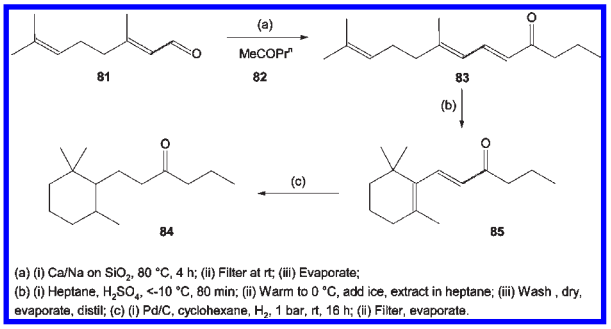
**Title or Subject: Process for Preparing Timberone.**

Timberone **84** is used in perfumery and cosmetic manufacture and has a woody/amber-like odor. The patent states that methods for the preparation of **84** require raw materials that are not readily available and hence an alternative synthesis is required. The new method is shown in Reaction 31 and starts from citral **81** that is a commercially available material. This undergoes an aldol condensation with **82** that is carried out using a supported base as catalyst. Ca/Na on $SiO_2$ is preferred and the catalyst contains 20−30 wt % Ca and 24−32 wt % Na on $SiO_2$ having a surface area of <200 $m^2/g$. The preparation of the catalyst is not described and is based on the patent WO01/87812. The reaction gives a E/Z mixture of **83** that is isolated in 87.5% yield (63.3% by GC) and used in the cyclisation step to give **85**. This is carried out in heptane and catalysed by acids. The preferred acid contains S and MsOH gives the highest yield (87% by GC) but full details are not given. Using $H_2SO_4$ the yield is 52% and TFA gives 65%. When using $H_3PO_4$ a 56% yield was obtained but no solvent was used. The reaction scheme shows **85** as the cyclohex-1-ene isomer ($\beta$) although the cyclohex-2-ene isomer ($\alpha$) was also formed. The isomer ratio was dependent on the acid used with S-acids giving more $\beta$. For example $H_2SO_4$ gave 99% $\beta$, and $H_3PO_4$ gave 85.4% $\alpha$. The mixture was not separated, and in the final step hydrogenation of **85** using Pd/C catalyst at rt and 1 bar gives **84** in 91.2% isolated yield as a mixture of diastereoisomers.

Reaction 31




(a) (i) Ca/Na on $SiO_2$, 80 °C, 4 h; (ii) Filter at rt; (iii) Evaporate; (b) (i) Heptane, $H_2SO_4$, <-10 °C, 80 min; (ii) Warm to 0 °C, add ice, extract in heptane; (iii) Wash , dry, evaporate, distil; (c) (i) Pd/C, cyclohexane, $H_2$, 1 bar, rt, 16 h; (ii) Filter, evaporate.

The patent provides $^1H$ and $^{13}C$ NMR data for all compounds.

**Advantages.** The process uses a readily available raw material and hence is economically more attractive than alternatives.

**Keith Turner**

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