Organic Process Research & Development **2009,** *13,* 381–390

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published During December 2008 and January 2009

Summary

The current review contains 20 from a list of 242 that fitted the search criteria. A few of the patents contain extensive experimental details, and space limitations prevent these being reproduced here. Hence, in some reaction schemes the workup details are omitted. Drugs for the treatment of insomnia and other sleeping disorders are the focus of a number of patents in the current selection. Three patents cover different aspects of the synthesis of an intermediate for preparing agomelatine, and one details the synthesis of the active isomer in zopiclone. Two patents provide details for the preparation of several cephalosporin antibiotics. In one the process gives improved Z/E ratios in the production of cefditoren that includes an enzymatic hydrolysis. The second patent reports on more efficient preparation of Maxipime that proceeds via a silylester that protects an acid group during the reaction. A very detailed patent describes improvements for increasing the *trans/cis* ratio in an amino cyclohexane acid. The compound is used to prepare antiobesity drugs and includes a *cis* to *trans* isomerisation step. There are patents covering improvements in the purification of L-menthol and the breast-cancer drug letrozole. The latter relies on more rapid oxidation of an isomeric impurity that can be easily removed, whereas the former changes a solvent in the crystallization. An improved process is described for making methyl phenidate, the active ingredient in Ritalin. The new process uses less expensive catalysts, and a change of solvent improves the product recovery method and hence its purity. A novel diester of ranelic acid is reported that is then used to prepare the Sr salt of ranelic acid, a drug for the treatment of osteoporosis. A novel dehydroxyfluorination reaction with triflyl fluoride is reported in the preparation of some chiral fluoroalcohols and esters. The process involves intermediate triflate formation in conjunction with a hydrogen fluoride salt of an amine that enables fluorination. The first one-step process for the preparation of the antidepressant venlafaxine is described that removes the need to isolate an amine intermediate, thereby increasing the process yield. A new process to prepare the drug pioglitazone is described that involves the production of several new intermediates. The patent contains 101 examples and includes several variations for producing the final product. Carvedilol is a nonselective β-blocker, and an improved method for its production using fundamentally the same reaction involves using oxalic acid in place of mineral acids in the workup. This gives an oxalate salt that improves product recovery. An improved method for making the insecticide γ-cyhalothrin does not require a resolution stage and so a higher atom yield is obtained. Roflumilast is under development as an anti-inflammatory for treating lung diseases, and a new method for its preparation is described that gives reduced quantities of a byproduct. The patent is lacking in quantitative experimental detail but does have 162 claims. Another patent describes a method for preparing a cyanonaphthyl ester that is also used as an anti-inflammatory agent. The key aspect of the patent is the method of isolation of the product. The use of a supported lipase enzyme is described for preparing the flavour compound *cis*-pellitorin, and this avoids the use of toxic SeO_2. The use of supercritical fluids has increased dramatically, and a patent describes their use in ring-closing metathesis of functionalized olefins. The process also involves the use of ionic liquids, and although commercialisation may not be imminent, it draws together two interesting technologies. There are several patents in the current selection that include examples carried out on kilo and multikilo scale. This does suggest that the processes are at an advanced stage of development and perhaps in some cases even in commercial operation. However, there is no legal or commercial significance in the patents that are included and the advantages are those mentioned in the patent unless this reviewer has personal knowledge of the subject.

Patent No. U.S. 7,459,467

Assignee: IPCA Laboratories Ltd., Mumbai, India

Title or Subject: Manufacturing Process for Methyl Phenidate and Intermediates

Methyl phenidate **2a** is used as the hydrochloride salt under the name Ritalin to treat hyperactive children. The commercial drug comprises the threo pair of D- and L-enantiomers and is used as a racemic mixture. This patent makes no reference to stereochemistry although it is considered that the D-threo enantiomer has the higher activity. **2a** is usually prepared by selectiveof the pyridyl ring of a biaryl derivative such as **1a** as shown in Reaction 1. The patent summarises a number of methods used for this process and concludes that they are expensive because they use Pt catalysts with high Pt loading. In alternative processes HOAc is used as reaction solvent and to protonate the N atom in the pyridine ring. The use of this solvent is claimed to make it difficult to isolate high-purity product from the process. Having said that, the new process still uses HOAc but uses cheaper Pd catalysts and an alcohol solvent that improves the isolation of **2a**. The protonation of the N atom in **1a** is achieved by using $HClO_4$ and HOAc. The

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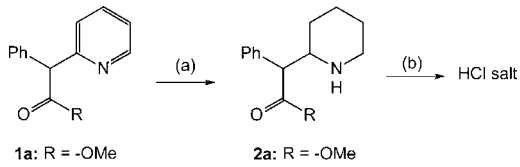
free base **2a** is obtained from theof **1a** in 90% yield, and this is then converted to the HCl salt that is obtained in 78% yield. Theprocess is also applicable to the amide **1b** (R = NH_2) that gives **2b** (R = NH_2) in 93% yield.

Reaction 1



1a: R = -OMe **2a:** R = -OMe

(a) 0.1 N $HClO_4$ in HOAc, Pd/C, MeOH, H_2, 15 kg/cm^2, 50 °C, 18 h;
(b) (i) HCl, Pr^iOH, 15°C; (ii) 30 °C, 5 h.

Advantages

The process gives improved yields of product that is easier to isolate in pure form.

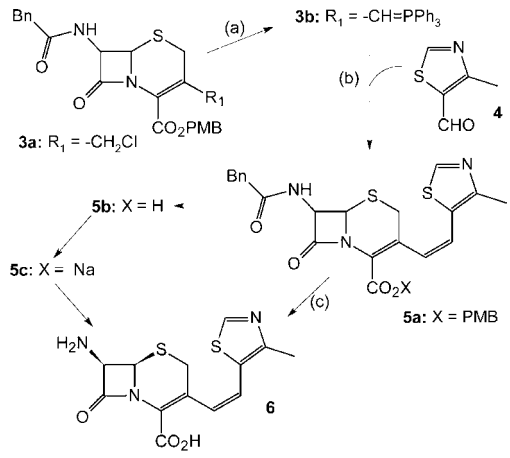
Patent No. U.S. 7,459,550

Assignee: Orchid Chemicals & Pharmaceuticals Ltd., Chennai, India

Title or Subject: Process for the Preparation of Cefditoren

This is the first of two patents in this review on cephalosporins and focuses on cefditoren **8a**.This is described as a third-generation broad-spectrum, cephalosporin antibiotic that has low mammalian toxicity. A high Z/E isomer-ratio is desirable, and the objective of most syntheses is to reduce the amount of E-isomer formed. The synthetic route described in this patent is shown in Reactions 2 and 3. In the first stage the protected ester **3a** (PMB = *p*-methoxybenzyl) is converted to the ylide **3b** by reaction with PPh_3 and NaI (Reaction 2). **3b** is not isolated from this reaction but treated with **4** in basic solution to give **5a** (X =PMB). **5a** is then converted to **6** by PMB removal with TFA followed by enzymatic hydrolysis using penicillin G amidase (PGA). The patent also mentions that the acid **5b** and Na salt **5c** can be produced from **5a** and **6** is obtained from **5c** using PGA although precise details of these steps are not given.

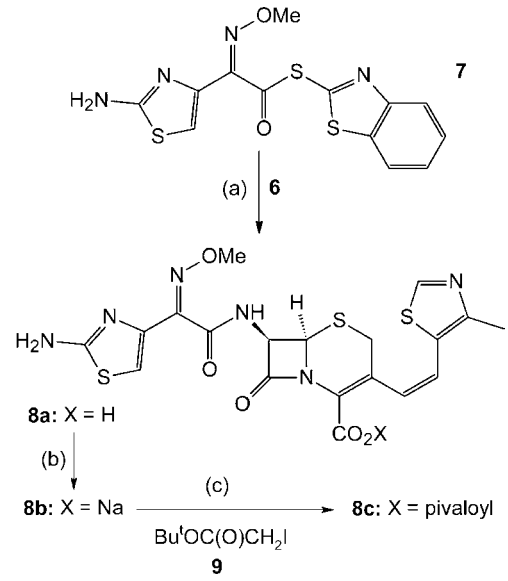
Reaction 2



(a) PPh_3, NaI, H_2O, THF, 30 °C; (b) (i) $NaHCO_3$, 25 °C;
(c) (i) PhOH, TFA, 45 °C; (ii) PGA, NH_4OH, pH 8.5, 30°C.

In the second stage of the process **6** is reacted with the thioester **7** at pH 7.5 to give the desired product **8a** (Reaction 3). The acid **8a** can then be converted to the Na salt **8b** by treatment with Na ethyl hexanoate. **8b** is converted to the pivaloyl ester **8c**, known as cefditoren pivoxil, by reaction with the iodomethyl ester **9** that is obtained from the corresponding chloromethyl ester.

Reaction 3



(a) THF/H_2O, Et_3N pH 7.5, 20 °C;
(b) Me_2CO/H_2O, Na-2-Ethylhexanoate, 30 °C;
(c) $NaHCO_3$, Bu_4NHSO_4, DMF, -20 °C, 1 h.

The key step in the process seems to be the enzymatic hydrolysis, and the patent does mention that the stereochemistry of **8a** is the 6*R*,7*R* isomer, but the stereochemistry of the starting material **3a** is not discussed. There are no analytical details showing the Z/E isomer ratio although it is stated that the ratio is higher when THF and water are used in steps (a) and (b) of Reaction 2. The scheme shown in Reaction 2 indicates that **3a** is a PMB ester, and this is mentioned in the examples although the patent does mention the *p*-methoxyphenyl ester. It is not clear if both are used or if one is a mistake.

The yields of the products of most reactions are not stated although **6** is reported as being obtained at 90−95% purity, and **8c** is isolated with purity of up to 99%. The patent does not mention any reaction times and merely states that the reactions are carried out until complete. How this is determined is not discussed.

Advantages

The process is claimed to be commercially viable and gives a high Z/E isomer ratio.

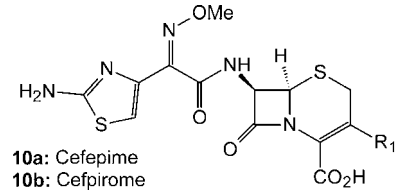
Patent No. U.S. 7,479,556

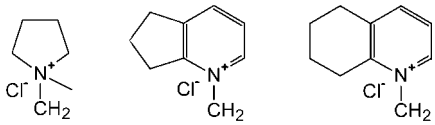
Assignee: ACS Dobfar S.p.A., Tribiano, Italy

Title or Subject: Process for Producing Cefepime and Cephalosporin Analogues

The second patent on cephalosporins in this review primarily covers cefepime **10a**, commonly known as Maxipime, that is used to treat severe infections caused by multidrug-resistant microorganisms. The patent claims also cover the production of the related compounds **10b** (cefpirome) and **10c** (cefquinome).

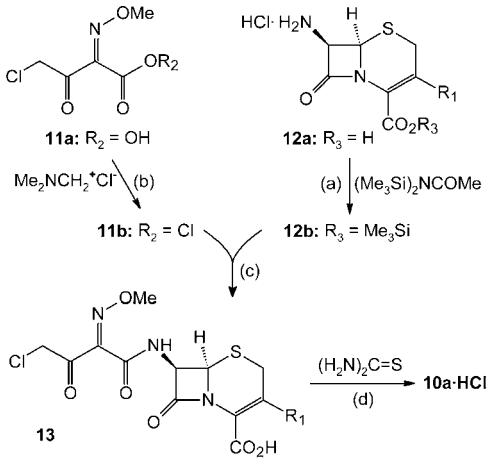
Cephalosporins





An alternative method for preparing cephalosporins involves the reaction of the iminium salt **11b** with a benzathine salt of the acid **12a**. This is claimed to be inapplicable if R_1 is strongly basic and hence not suitable for preparing **10a**, **10b**, or **10c**. This is attributed to the formation of an internal salt. The process reported in the patent for the production of **10a** is outlined in Reaction 4 and the use of the silylated ester **12b** is described as a surprising discovery. In the process the iminium salt **11b** and silyl ester **12b** are produced separately in MeCN solutions and then mixed together at −40 °C to give **13** in 98% isolated yield. Treatment of **13** with thiourea and NaOAc followed by HCl gives the monohydrate HCl salt of **10a** in 93% yield. The SO_4^{2-} salt of **10a** is similarly produced and isolated in 72% yield. By applying similar methods the SO_4^{2-} salts of **10b** and **10c** are produced, but no details are provided.

Reaction 4



(a) (i) MsH, MeCN, 10 °C; (ii) 35 °C, 1.5 h; (b) MeCN, 0 °C, 1 h; (c) MeCN, -40 °C, 20 min; (d) (i) NaOAc, H_2O, 25 °C, 3 h; (ii) Me_2CO, 35% HCl, pH 1.5, 25 °C, 1.5 h.

Advantages

The process gives very good yields of the desired compounds from the same starting materials.

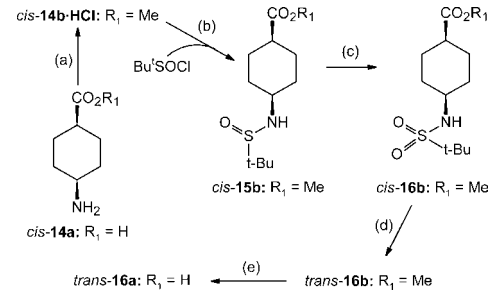
Patent No. U.S. 7,459,580

Assignee: Shiongi & Co. Ltd., Osaka, Japan

Title or Subject: Process for trans-4-Amino-1-cyclohexane Carboxylic Acid Derivatives

This patent covers the preparation of derivatives such as *trans*-**16a** that are used to produce pharmaceutical compounds having activity as NPY Y5 receptor antagonists and are suitable as antiobesity drugs. Alternative processes are said to give too much of the *cis*-isomer, and this cannot easily be isomerised to the desired *trans*-isomer. The objective of this patent is to improve the *trans*/*cis* ratio and develop a method to easily isomerise the *cis*-isomer thereby improving the yield. The patent describes a substantial amount of work and only a small amount is covered here. Reaction 5 summarises the route used to prepare the *trans*-acid **16a**. This starts from the *cis*-amino acid **14a** that is first converted to the HCl salt of the ester **14b** using $SOCl_2$/MeOH. **14b** is recovered in 88% yield and then converted to compound **15b** by reaction with Bu^tSOCl. **15b** is recovered as an impure oil (reported yield 109%) and then oxidised using H_2O_2 and ammonium molybdate to give sulfonamide **16b** that is isolated in 79% yield. In the next step *cis*-**16b** is isomerised to give *trans*-**16b** by heating with a base in a nonpolar solvent. The initial product obtained contains 82% *trans*-isomer, and after recrystallization a yield of 56% of pure *trans*-**16b** is obtained. Acid hydrolysis of the product gives the *trans* acid **16a** in a yield of 87%. The conversion of *cis*-**16b** to *trans*-**16a** can be carried out in a one-pot procedure, and the yield of *trans*-**16a** is 92.5%.

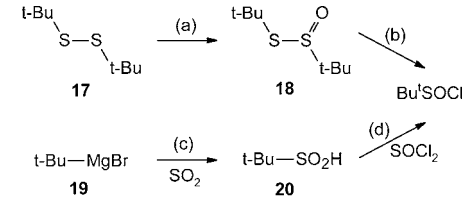
Reaction 5



(a) (i) $SOCl_2$, MeOH, 6 h, rt; (ii) 72 h; (b) (i) Et_3N, EtOAc, <9 °C, 1 h; (c) (i) NH_4Molybdate/H_2O, DMF, 30% H_2O_2, 43 °C, 2.5 h; (d) NaOMe/PhMe, HCO_2Me, reflux 145 min, cool; (e) (i) Aq NaOH, MeOH, 30 min, <12 °C; (ii) 1 h, 12 - 36 °C.

The patent also gives details for the preparation of Bu^tSOCl by two routes shown in Reaction 6. The first route begins with the disulfide **17** that is oxidised using H_2O_2 to give **18** in 98% yield, and this is chlorinated with Cl_2 to give Bu^tSOCl that is recovered in 94% yield. In the second route **19** is treated with gaseous SO_2 to give **20** that is obtained in 79% yield and then chlorinated with $SOCl_2$, giving Bu^tSOCl in a yield claimed to be 112%.

Reaction 6

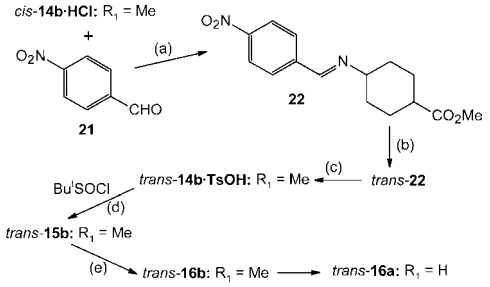


(a) (i) 30% H_2O_2, HOAc, 3.5 h, 38 °C; (ii) Aq Na_2SO_3, 19 min, 6 - 13 °C; (b) (i) Cl_2, DCM, <20 °C; (c) THF, 2 - 20 °C; (d) THF, 0 °C, 30 min.

The patent also provides details for the preparation of a number of other intermediates that can be converted to *trans*-

16a or its analogues. Reaction 7 shows the route used to prepare a *cis*/*trans* mixture of **22** that is isomerised to *trans*-**22** using NaOMe and this is converted to the *trans*-tosic acid salt of **14b** and further converted to *trans*-**16a** by methods similar to those shown in Reaction 7.

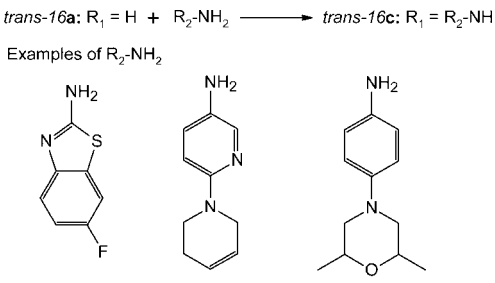
Reaction 7



(a) Et_3N, MeCN, 3 h; (b) (i) NaOMe/MeOH, HCO_2Me, 50 °C, 4 h; (c) TsOH, H_2O, EtOAc, rt, 1.5 h; (d) Et_3N, THF, rt, 1.5 h; (e) Step (c) in Reaction 4.

The patent also provides details for the preparation of a wide range of amides, *trans*-**16c**, by reaction of **16a** and an amine. Reaction 8 shows the general method used and three of the many amines described in the patent. The reactions are carried out in the presence of a catalytic amount of DMF and used either $COCl_2$, $SOCl_2$, or $(COCl)_2$ thereby producing a Vilsmeier reagent that would improve the reaction rate. Yields of amines were up to 80%.

Reaction 8



A number of experiments in the patent used multikilo amounts of reagents, thereby indicating that the process is at an advanced stage of development. ^1H NMR data are given for many of the compounds.

Advantages

The process enables the conversion of the unwanted *cis*-isomers to the *trans*-form and is clearly capable of being carried out on a large scale.

Patent No. U.S. 7,459,587

Assignee: Takasago International Corp., Tokyo, Japan

Title or Subject: Process for Purifying Menthol

L-Menthol is widely used in flavours and fragrances, and it is stated that its purification is difficult and made more so by its low mp (42 °C) that necessitates the use of low temperatures for crystallization. The patent describes an improved method of purifying L-menthol by crystallization from nitrile solvents with MeCN being preferred. The process is carried out by dissolving L-menthol in MeCN <42 °C and then gradually cooling the solution to a temperature of <10 °C. Examples show that a sample of L-menthol with purity of 95% and ee of 97.3% can be purified by crystallization at 5 °C to give a product having ee of 99.6% and chemical purity of 99%. Comparative experiments using Me_2CO, Pr^i_2O, or EtOH did not give increased purity or did not give any crystals.

Advantages

The simple method claims gives improved purity of an important product.

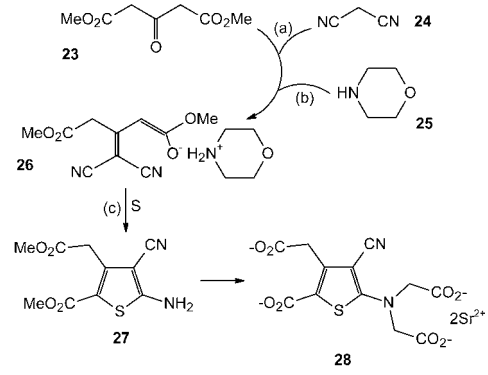
Patent No. U.S. 7,462,714

Assignee: Les Laboratoires Servier, Courbevoie Cedex, France

Title or Subject: Process with Application to the Synthesis of Bivalent Salts of Ranelic Acid and their Hydrates

The patent covers the industrial synthesis of the novel diester **27** that is useful for the synthesis of the Sr salt of ranelic acid **28**, a drug used to treat osteoporosis. The patent actually only has one claim, and this is for the novel compound **26**. The process is outlined in Reaction 9, and the first stage is the preparation of **26** by treatment of **23** in MeOH with **24** followed salt by formation with **25**. The compound **26** is isolated and then refluxed with sulfur, giving **27** that is isolated in 77% yield with 98% purity. The patent gives two examples for making **26** using 400 kilos of **23**, thus indicating the commercial status of the process. Details for the conversion of the diester **27** to **28** are not described in the patent. However, mention is made of reacting **27** with a bromoacetate ester to give a tetraester that is hydrolysed and then converted to **28**.

Reaction 9



(a) MeOH, 40 °C; (b) <40 °C; (c) Reflux, 2 h.

Advantages

The process is clearly viable on a large scale and gives high yields of novel intermediates and final product.

Patent No. U.S. 7,462,734

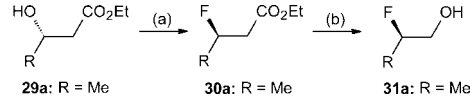
Assignee: Central Glass Company Limited, Ube-shi, Japan

Title or Subject: Process for Producing Optically Active α-Fluorocarboxylic Ester Derivatives

The process covered by this patent describes a method of producing compounds such as **30a** and **31a** that are intermediates in the production of medicinal chemicals and optical materials. Alternative processes are described as being unable to produce products with high optical purity or use DAST that

is expensive and dangerous to handle on a large scale. Reaction 10 shows the route used initially to prepare **30a** by the reaction of optically active α-hydroxycarboxylate **29a** with TfF in the presence of an organic base. The reaction proceeds with inversion of the stereochemistry and the yield of **30a** is 72%. The ee for **30a** is not reported although the patent describes the preparation of **30b** (R = $PhCH_2CH_2$-) where the ee is reported as 99.2%. The ester **30a** is reduced with $LiAlH_4$ to give the alcohol **31a** that is recovered in 75% after distillation with ee of 98.0%. The key feature of this process is claimed to be the previously unreported dehydroxyfluorination of **29a** using TfF. The reaction is postulated to proceed via initial activation of the OH by formation of the triflate. The subsequent fluorination takes place only because of the formation of a HF salt of Et_3N that is formed in the same reaction system. As evidence of this comparative experiments carried out to prepare **30b** (R = $PhCH_2CH_2$-), using an alternative base such as DBU gave a yield of only 32% as compared to 75% when using Et_3N. ^1H and ^{19}F NMR data are given for the reaction products.

Reaction 10



29a: R = Me **30a:** R = Me **31a:** R = Me

(a) (i) TfF, Et_3N, mesitylene, -40 °C; (ii) rt, 19 h;
(b) (i) $LiAlH_4$, THF, <10 °C, 20 min; (ii) rt, 130 min.

Advantages

The process gives the desired products in good yield with high optical purity.

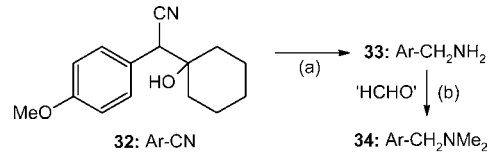
Patent No. U.S. 7,462,742

Assignee: Zach System, Arville, France

Title or Subject: In Situ or One-Pot Hydrogenation and Reductive Amination Process for Production of Venlafaxine

Venlafaxine **34** is an antidepressant, and processes for its preparation have been reviewed previously (*Org. Process Res. Dev.* **2006**, *10*, 703). The reported methods for preparing **34** are two-step processes involving the hydrogenation of the nitrile **32** to the amine **33** that is usually isolated and then subjected to reductive amination to give **34** (Reaction 11). Several different hydrogenation catalysts are used, and the presence of HCHO is usually required. The patent claims to report, for the first time, a one-step process for producing **34** by this method. The process described in this patent uses a Pd/C catalyst that is carried out in aqueous HOAc containing HCHO. Paraformaldehyde, trioxane, or tetraoxane are used as the source of the methylating agent HCHO. Reaction 11 summarises the reaction conditions for the two steps. At the end of the nitrile hydrogenation step the temperature is raised to generate the methylating agent and enable the reductive amination to take place. The time for the second step is between 15 min and 5 h and is determined by noting when the consumption of H_2 ceases. After a workup involving two-stage washing with NaOH and HOAc solutions the product is isolated in 93.8% yield.

Reaction 11



32: Ar-CN

(a) HOAc/H_2O, Pd/C, H_2, 12 bar, < 15 °C, 3.5 h;
(b) 60 °C, H_2, 12 bar

Advantages

The process takes place in a single step, enabling an improvement in process efficiency.

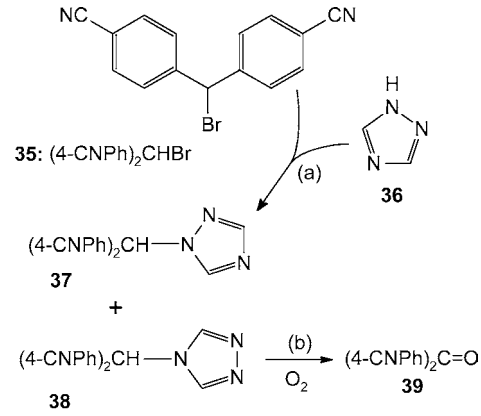
Patent No. U.S. 7,465,749

Assignee: Chemagis Ltd., Bnei Brak, Israel

Title or Subject: Letrozole Purification Process

Letrozole **37** is a nonsteroidal, aromatase inhibitor that is used to treat advanced breast cancer and is available as Femara. The preparation of **37** is from **35** and **36** as shown in Reaction 12, and it produces the impurity, isoletrazole **38**. This impurity can be present at levels up to 15%, and the patent discloses a new method for its removal from **37**. It has been found that **38** is more rapidly oxidised than **37** and the oxidation product **39** is easily separated from **37** by crystallization. After the first part of the process is complete, in which **36** reacts with **35** in the presence of K_2CO_3, air is bubbled into the mixture to oxidise **38** to **39**; under the reaction conditions oxidation of **37** is very slow. Oxidation of **37** would also give **39**, and so no additional byproducts are produced. Examples are described in which the content of **38** is reduced from around 15% to 2% or less, and then crystallization gives **37** with purity >99.4%. The average crystallization yield from three experiments is 88.5%, and the patent reports that the overall yield of **37** using the oxidation procedure and one crystallization is 56% compared with 51.5% for two crystallizations. Thus, the new process is more economical. The patent also reports on the effect of the impeller on the oxidation step. Using a pump-up impeller a lower yield of **37** was obtained, a result that is ascribed to overoxidation. A pump-down impeller took longer but did not cause yield loss by oxidation of **37**.

Reaction 12



(a) DMF, PhMe, K_2CO_3, 80 °C, 1.5 h;
(b) Air 3.5 litre/min, 80 °C

Advantages

The process enables the undesired impurity to be removed without significant loss of yield of the desired product.

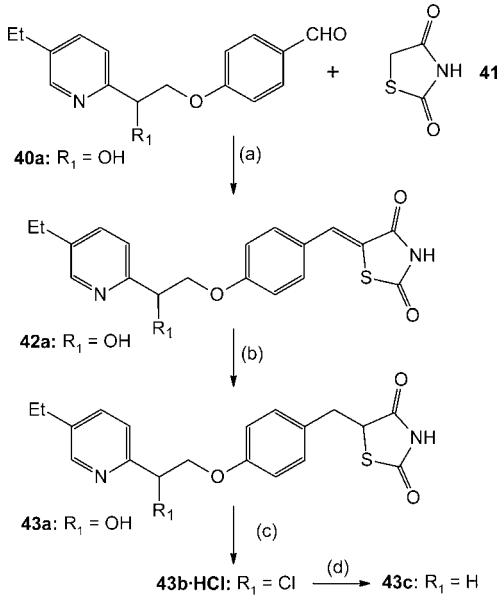
Patent No. U.S. 7,465,801

Assignee: Cadila Healthcare Limited, Gujarat, India

Title or Subject: Process to Prepare Pioglitazone via Several Novel Intermediates

Pioglitazone **43c** (R_1 = H) is used as the HCl salt to treat type 2 diabetes and is known as Actos. There are a number of methods for preparing **43c** that are mentioned in the patent and said to be technically difficult, involving low temperature diazotisation with evolution of large volumes of gas. The patent describes several novel compounds that are intermediates in the preparation of **43c**. The patent contains a huge amount of information with 101 examples, and a number of these involve the use of about 10 kg of reagents. This implies an advanced stage of development of the process, and so these examples have been used as the basis for this review. Reaction 13 shows the conversion of the key intermediate **40a** (R_1 = OH) to **43c**. The first step is the condensation of **40a** with **41** to give **42a** in the presence of an organic base and an acid. The procedure uses about 1.1 mole each of **40a** and pyrrolidine per mole of **41** with 1 mole of HOAC per mole of **41**. The product of the reaction, **42a** (R_1 = OH) is obtained as a solid in 91% isolated yield. In the next stage selectiveof **42a** gives **43a**, and several catalytic and noncatalytic methods are reported. The kilo-scale example describes the use of $NaBH_4$ with $CoCl_2$ and dimethylglyoxime in DMF/H_2O to give **43a** as a solid that is isolated in 95% yield. Chlorination of **43a** with $SOCl_2$ then gives the HCl salt of **43b**. In the final step **43b** is treated with Zn/HOAc to obtain **43c** in 91% isolated yield, and this can be converted to its HCl salt.

Reaction 13

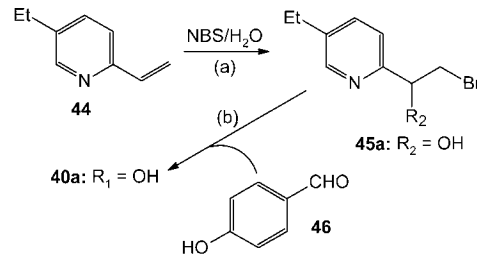


(a) (i) Pyrrolidine, MeOH, 55 °C, 2 h; (ii) HOAc, 30 °C, 1 h; (b) (i) Dimethylglyoxime, H_2O, $CoCl_2 \cdot 6H_2O$, DMF, 70 °C; (ii) $NaBH_4$, H_2O, 70 °C, 4 h; (c) $SOCl_2$, $CHCl_3$, reflux, 3 h; (d) Zn, MeOH, HOAc, rt.

The patent also provides details for the preparation of the key intermediate **40a**. There are several routes from **44** to **40a** that are outlined in the patent. The route shown in Reaction 14 is based on a one-pot, kilo-scale example and involves the formation of the bromohydrin **45a** by reaction of **44** with NBS and H_2O using NaOH in aqueous polyethylene glycol. The second step is the condensation of **45a** with **46** in the presence of a NaOH to give **40a** in 83% yield.

The formation of **45a** is also described using NaOH as base in the solvents THF, dioxane, or Bu^tOH. Alternatively, by using DMSO as solvent with bases such as NaH, K_2CO_3, or NaOH **45a** is isolated in yields up to 95%. The conversion of the isolated **45a** to **40a** can be carried out in THF, DMF, MeOH, Bu^tOH, or Pr^iOH using the bases NaH or K_2CO_3.

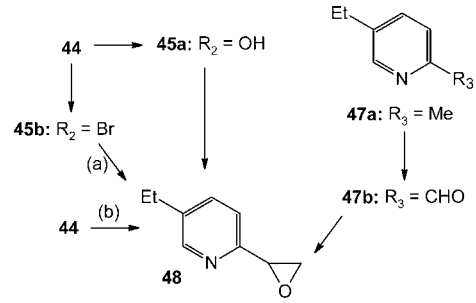
Reaction 14



(a) (i) Bu^tOH/H_2O, 25 °C, 1.5 h; (ii) 2M NaOH, 25 °C, 45 min; (b) NaOH, H_2O, PhMe, PEG 4000, 78 °C, 17 h.

The patent also discusses the formation of **48** via a number of other intermediates related to **45a**, and these are summarised in Reaction 15. Apparently **45b** or **48** react with **46** to produce **40a**. Of those reactions shown experimental details are given only for the conversion of **44** or **45b** to **48**.

Reaction 15



(a) K_2CO_3, H_2O, Bu^tOH, 30 °C, 1 h; (b) (i) NBS, H_2O, Bu^tOH, 30 °C, 1.5 h; (ii) Aq NaOH, 30 °C, 45 min.

Also described in the patent are derivatives of **40a** and **43a** in which R_1 = Br, OSO_3H, OMs, or OTs. The claims of this patent focus on theof **42a** to **43a** and the formation of **43b** and **43c**, and these steps have clearly been successfully scaled up. The preferred route to make **40a** is not stated, and there are many options mentioned if not described in detail, and so the interested reader is encouraged to read the patent. There are ^1H NMR data for many of the novel compounds.

Advantages

The overall process has fewer steps than alternatives, and since many of these have been operated on kilo-scale to provide high yields of products, it seems to be commercially attractive.

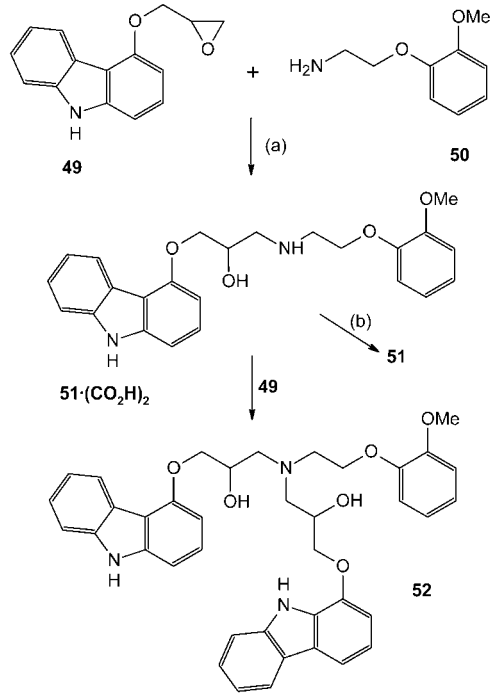
Patent No. U.S. 7,468,442

Assignee: Matrix Laboratories Ltd., Andhra Pradesh, India

Title or Subject: Process for the Preparation of Carvedilol Form II

Carvedilol **51** is a nonselective β-blocker used for the treatment of mild to moderate congestive heart failure and hypertension. A patent describing new polymorphs of **51** has been reviewed previously (*Org. Process Res. Dev.* **2004**, *8*, 553). Both the racemic form and pure stereoisomers are produced, and some of these are discussed. Reaction 16 shows the common route to produce **51** by addition of the epoxide **49** to the amine **50**. A particular problem with this route is the formation of the compound **52** formed by further reaction of **51** and the starting epoxide **49**. This can be avoided by using protective group methods, but extra reaction steps are needed. Alternatively, up to a 6-fold excess of **50** is employed, but this makes the process uneconomical. The new process starts with the same reagents using a lower excess of **50** so that molar ratio of **49** to **50** is in the range 1:2.0 to 1:2.5. In addition during the workup the pH is adjusted using an organic acid such as $(CO_2H)_2$ instead of mineral acids. This results in the formation of the oxalate salt **51·(CO$_2$H)$_2$** that is recovered in 77% yield and then the base liberated with NH_4OH to give Form II of **51** in 76% yield after crystallization from EtOAc. The patent does not mention how much if any of **52** is produced, and a drawback is the use of chlorinated solvents although the use of monoglyme is covered in the claims.

Reaction 16



(a) (i) PhCl, reflux, 3 h; (ii) 90 °C, H_2O; (iii) 70 °C, $(CO_2H)_2$, pH 2.8, 1 h; (iv) rt, 2 h; (b) H_2O, DCM, NH_4OH, pH 9.3, 1 h, rt.

Advantages

The process gives improvements in the isolation of the desired product while using the same reagents as other methods.

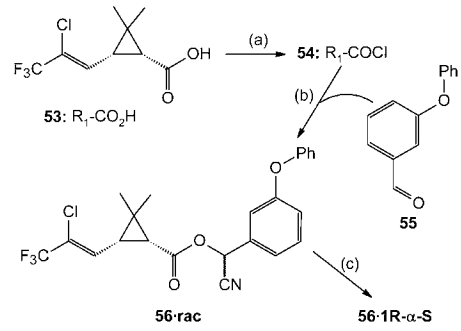
Patent No. U.S. 7,468,453

Assignee: Syngenta Limited, Huddersfield, United Kingdom

Title or Subject: Production Process of γ-Cyhalothrin

γ-Cyhalothrin **56·1*R*-α-*S*** is a single-isomer pyrethroid insecticide that is often regarded as the most active pyrethroid in the world. Its enhanced activity is due to the fact that the less active isomers have been removed or were not produced during synthesis. The compound provides broad-spectrum control of insect pests in a wide range of agricultural crops and is sold under the names Nexide and Fentrol. The synthesis of **56·1*R*-α-*S*** can be carried out using a chiral cyanohydrin, but this is very expensive for use on an industrial scale. To avoid doing this the patent discloses a process for preparing **56·1*R*-α-*S*** that produces a diastereoisomeric mixture from which the desired isomer crystallizes and the solution is epimerised to improve yield. The method is shown in Reaction 17 and starts with the chlorination of the 1*R*,3*R* enantiomer of the acid **53** that is a known compound. This produces **54** that is recovered as a 54% solution in PhMe in 97% yield. In the next stage both **54** and **55** are added simultaneously to an aqueous solution of NaCN containing hexane with additional **54** being added after 17 h to complete the reaction. The product is an oil that contains 45.5% of the 1*R-cis-Z*-α-*S* diastereoisomer and 45.9% of the 1*R cis-Z*-α-*R* isomer. In the final stage the mixture is slurried with seed crystals of **56·1*R*-α-*S*** for 65 h, and then after recovering the solid it is acidified; after washing, the desired isomer **56·1*R*-α-*S*** is obtained as a dark, viscous oil that produced a solid upon standing. The yield is 97% with diastereomer ratio of 95:5, and basic ^{1}H NMR and MS data are given.

Reaction 17



(a) (i) $SOCl_2$, Et_3N, PhMe, 45 °C, 6.75 h; (ii) Cool to rt, add $SOCl_2$; (iii) rt, 16 h; (b) (i) NaCN/H_2O, hexane, 10 °C, 20 h; (ii) Add **54**, 10 °C, 2 h; (c) (i) Seed crystals, Pr^iOH, H_2O, Pr^i_2NH, -5 °C, 65 h; (ii) Recover solid, hexane, H_2SO_4, 0 °C, 0.5 h; (iii) Hexane, 55 °C, 0.5 h, separate, evaporate.

Advantages

The process gives higher atom yields of the desired isomer than alternatives without the need for a resolution stage.

Patent No. U.S. 7,470,791

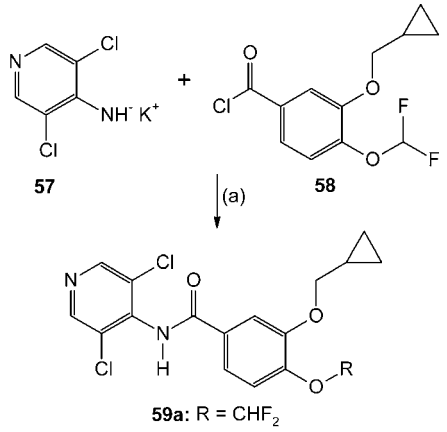
Assignee: Nycomed GmbH, Konstanz, Germany

Title or Subject: Process for the Preparation of Roflumilast

Roflumilast **59a** (R = CHF_2) is an anti-inflammatory that is under development as an orally administered drug for the treatment of inflammatory conditions of the lungs such as asthma, chronic obstructive pulmonary disease and emphysema.

Methods for preparing **59a** are summarised, and they are said to be unsuitable for its industrial production in high purity. A particular difficulty relates to the compound **59b** (R = H) that cannot be removed even with multiple recrystallizations. The patent therefore describes a process for producing **59a** that minimises the formation of **59b**. The process involves the coupling of the K salt **57** with the acyl chloride **58** as shown in Reaction 18. The reaction is described as a surprising finding and takes place in DMF at 20−30 °C. **59a** is recrystallized from Pr^iOH/H_2O, and the patent claims that the purity of the product is >99% that can be increased to >99.8% with further crystallization with <0.1% of **59b**. The patent does not report the quantities used in the examples and mentions only the relative equivalents of reagents. Neither does the patent mention the reaction time for the coupling, and no yield data are given although it does claim to be suitable for use on batches up to 500 kg.

Reaction 18



(a) (i) DMF, 20 - 30 °C; (ii) Aq HCl, pH 2 - 3, 15 - 25 °
(iii) Aq NaOH, pH 9 - 10,

The patent also describes methods for the preparation of both **57** and **58**. The K salt **57** is obtained by treatment of the amine with $KOBu^t$ in DMF or *N*-methylpyrrolidone. The preparation of **58** is by chlorination of the acid using $SOCl_2$ in the presence of DMF. Both compounds are used in the preparation of **59a** without purification.

The patent contains 162 claims and includes the use of the acyl bromide or alkyl ester instead of the chloride **58**. A number of claims also cover variations in the recrystallization of **59a**.

Advantages

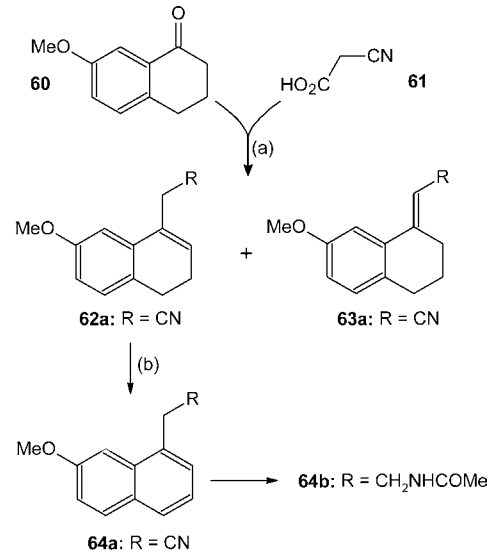
The process gives very low levels of the unwanted impurity in a straightforward reaction, but its commercial suitability cannot be determined due to a lack of information.

Patent No. U.S. 7,470,806, U.S. 7,476,751 and U.S. 7,479,569

Assignee: Les Laboratoires Servier, Courbevoie Cedex, France
Title or Subject: Process for the Synthesis of (7-Methoxy-1-naphthyl)acetonitrile and Its Application in the Synthesis of Agomelatine

Agomelatine **64b** (R = $CH_2NHCOMe$) is used in the treatment of a range of disorders such as depression, insomnia, and jetlag. These three patents cover different aspects of the synthesis of **64a** (R = CN) that is an intermediate used to prepare **64b**. The preparation of **64a** is summarised in Reaction 19, and the first stage is the formation of **62a** from the condensation of **60** with **61**. The patents discuss reports of the synthesis of **64b** in which the condensation of **60** with MeCN or MeCN derivatives is involved. Such processes usually produce only minor amounts of **62a** with the *exo* compound, **63a** being the major product formed. Since **63a** cannot easily be converted to **64a**, these processes are said to be unsuitable for commercial production of **64a** because the overall yield of **64b** is only 30%. The patents state that formation of the desired *endo* compound, **62a**, is surprising in view of the prior art. In the new process the reaction of **60** and **61** is carried out in the presence of heptanoic acid (HA) and an amine. In the reaction the amine and HA form a quaternary ammonium salt (QAS) that acts as the catalyst for the condensation reaction. Alternative methods report that NH_4OAc catalyses the condensation and gives *exo* products, and it is the use of the QAS that gives rise to the preferred formation of *endo* product. Thus, the reaction produces **62a** free from **63a**, and two examples are described on a multikilo scale in which the amine is either $PhNH_2$ or $BnNH_2$. The former gives a yield of 87% and the latter 90% with the purity in both cases >99%. In the second stage of the process **63a** is dehydrogenated to give **64a**. This reaction is carried out using Pd/C catalyst in the presence of an allyl compound as hydrogen acceptor. Allyl methacrylate is used, and the one example is again on a multikilo scale that gives **64a** isolated in yield with purity >99% after recrystallization. **64b** can be obtained from **64a**, although details are not provided.

Reaction 19



(a) $BnNH_2$, n-$C_6H_{13}CO_2H$, PhMe, reflux;
(b) Pd/C, allyl methacrylate, PhMe, reflux.

Advantages

The patent describes a process giving high yields, and from the scale of the examples it is clearly at an advanced stage of development.

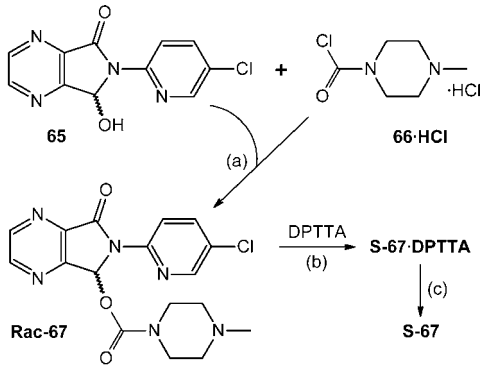
Patent No. U.S. 7,476,737

Assignee: Dr. Reddy's Laboratories, Hyderbad, India and Bridgewater, New Jersey, U.S.A

Title or Subject: Eszoplicone Process

Zopiclone (**Rac-67**) is used to treat insomnia, and eszopiclone (**S-67**) is the more active isomer that is commercially available as Lunesta. The other-isomer is inactive and may be the cause of some of the drug's side effects. A process for the synthesis of **Rac-67** has been reviewed previously (*Org. Process Res. Dev.* **2006**, *10*, 184) although it is not referred to in the discussion of the prior art in this patent. One alternative process is claimed to be unsuitable for commercial operation because it uses the free base form of compound **66** that is unstable and not commercially available. However, the new process uses the HCl salt **66·HCl** that is probably stable, but it is not clear whether it is a commercially available product. Reaction 20 shows the method used to prepare the racemic product **Rac-67** by reaction of **65** with the salt **66·HCl** in the presence of K_2CO_3 and Bu^t_4NBr. The crude product is treated with charcoal before use and is isolated in a yield of around 72% before being used in the next stage of the process where it is treated with di-*p*-toluoyl-D-tartaric acid monohydrate (DPTTA) to form the salt of the *S*-isomer **S-67-DPTTA**. This is isolated and then decomposed to give **S-67** with purity >99.9%, but unfortunately there does not seem to be any mention of the recovery and racemisation of the *R*-isomer.

Reation 20



DPTTA = Di-p-toluoyl-D-tartaric acid monohydrate

(a) K_2CO_3, Bu^t_4NBr, H_2O, MIBK, 30 °C, 3 h;
(b) (i) DPTTA, MeCN, 75 °C, 10 min; (ii) Cool 30 °C, 30 min;
(c) Aq Na_2CO_3 to pH 8.5, DCM, 45 min, 5 °C.

Advantages

The process is claimed to be ecofriendly, simple and efficient but there are aspects regarding the handling of a reagent precursor that would require a full safety assessment.

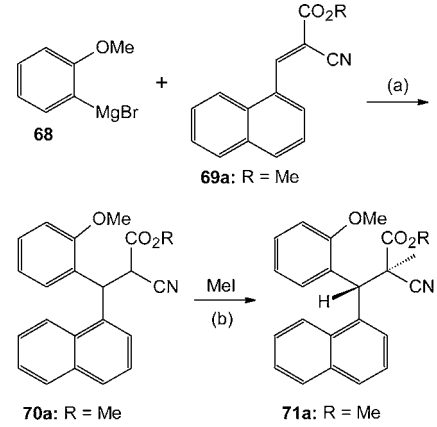
Patent No. U.S. 7,476,752

Assignee: Wyeth, Madison, New Jersey, U.S.A

Title or Subject: Process for the Preparation of 2-Cyano-3-naphthalene-1-yl-3-phenylpropionic Acid Esters

The particular esters of interest in this patent are alkyl or benzyl esters such as **71a**. These esters are used to prepare corresponding amides that have potential use as anti-inflammatory agents. The patent contains a single example on a kilo scale for the preparation of the methyl ester **71a** (R = Me), and Reaction 21 shows the method used. The reaction takes place in a nonprotic solvent, and the first step is the reaction of the Grignard reagent **68** with **69** in THF at <5 °C to produce **70a**. This is not isolated but treated with MeI to form **71a**. The method of isolating **71a** is a critical aspect of this patent and specifically covered in one of the claims. The isolation procedure involves reducing the volume of the reaction mixture and then adding a protic solvent such as MeOH, acidifying, and filtration. The final product is a racemic mixture of the single diastereomer **71a** and was isolated in a yield of 81% with diastereomeric excess of 100%.

Reaction 21



(a) THF, 5 °C, 30 min; (b) (i) 40 °C, 28 h; (iii) 0.5 N HCl, 25 °C

Advantages

The process gives high yields of the pure diastereoisomeric product.

Patent No. U.S. 7,482,479

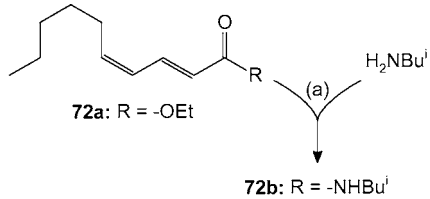
Assignee: Symrise GmbH & Co. KG, Holzminden, Germany

Title or Subject: Production of cis-Pellitorin and Use as Flavouring

cis-Pellitorin **72b** is found in the tarragon plant and is used as a pungent flavouring giving a hot taste to foods and oral hygiene products. Previously reported methods of making **72b** have involved the use of toxic SeO_2 and require chromatographic separation techniques. This patent describes a method of preparing synthetic **72b** by the reaction between the ester **72a** and NH_2Bu^i in the presence of an enzyme catalyst as shown in Reaction 22. The crude product is purified by silica gel chromatography and isolated in a yield of about 80% with a GC purity of 99.4%. The patent claims do not mention a specific enzyme catalyst other than to say it has to have lipase activity and is on a support. The enzyme used in the examples is Chirazyme L-2 from Roche. Examples indicate that the reaction can be carried out without solvent or in PhMe with the concentration of the enzyme used being about 40 wt % of the amount of ester **72a**. Much of the discussion in the patent relates to plants or molecules with similar pungent taste properties. There are also details on the preparation and the testing of flavours for chewing gum, mouthwash, and toothpaste using **72b**, and ^1H and ^{13}C NMR data are given. The patent does not

provide a preferred method of isolating and purifying **72b** on a commercial scale although one example mentions molecular distillation.

Reaction 22



(a) (i) Enzyme, 55 °C, 4 days; (ii) Et_2O, filter, Evaporate; (iii) 10% KOH/MeOH, rt, 45 min; (iv) Extract in Et_2O, dry, filter, evaporate

Advantages

The preparation of the desired product is straightforward and does not use toxic reagents although the method of isolating the product is not clear.

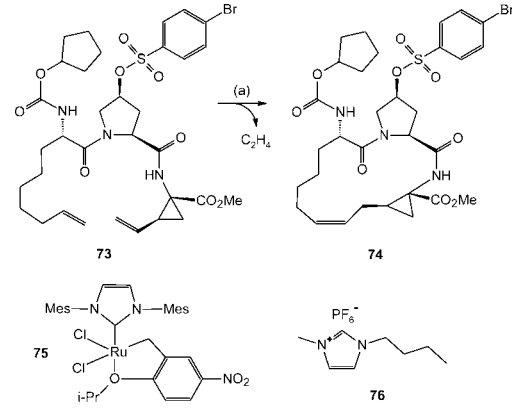
Patent No. U.S. 7,482,501

Assignee: Boehringer Ingelheim International GmbH, Ingelheim, and Studiengesellschaft Kohle mbH, Muelheim an der Ruhr, Germany

Title or Subject: Process for Continuous Ring-Closing Metathesis in Compressed Carbon Dioxide

This patent describes a metathesis process that is carried out in liquid CO_2 and specifically covers the production of the multifunctional compound **74** from **73**. Interestingly, the patent makes no mention of the use of **74** or of the origin of **73**. Metathesis reactions of functional olefins have been used for many years, and the production of cyclic molecules by this reaction usually uses homogeneous catalysts that are predominantly Ru complexes. The use of supercritical fluids (SCF) as solvents in many reactions is increasing, and combining CO_2 with conventional solvents enhances the solvent properties of the mixture under SCF conditions. This patent describes a process that combines CO_2 as a SCF and an ionic liquid to allow the solubilisation of the Ru catalyst in the ionic liquid while the reactant and product dissolve in the SCF. The process has been developed for continuous operation and examples are described for both batch and continuous systems. The preferred catalysts are 5-fold coordinated Ru carbene complexes such as **75** and an example of the ionic liquid used is **76**. Reaction 23 outlines the process for producing **74** from **73**, and like all metathesis reactions a second olefin is formed that in this case is ethene. The reaction is carried out in a continuously flowing system that is described in detail in the patent. The isolation of the product is not described for the continuous reactor, and it is followed by HPLC. In the batch example the reaction mixture is extracted with PhMe and an oil obtained that showed a ratio of **74**:**73** of 59:1. The ratio in the continuous experiments varies from 0.02 to 5.4, thus indicating that the batch process is more efficient.

Reaction 23



(a) **75**, **76**, CO_2, 400 bar, 70 °C

Advantages

The patent indicates that the process can be carried out, but it is difficult to see any particular advantages.

Keith Turner

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