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 December 2011 and January 2012

SUMMARY

The current review contains 21 patents from an original list of 321 that fitted the selection criteria. It is not often that water improves a process, but that is what happens when it is present during the synthesis of a diaminodinitrobenzene. The water hydrolyses a byproduct formed in a reaction between the solvent and the reactant. On the other hand a new process for the preparation of abacavir, a drug used to treat HIV, requires anhydrous conditions to achieve high yield in a cyclisation step. Improving the physical characteristics of crystals can be important in preparing drug formulations. A comprehensive patent describes a process for the synthesis of the anti-insomnia drug, ramelteon. The method provides crystals that have much lower charge density when crystallised from PhMe compared with crystals of EtOAc, and the lower electrostatic charge improves flow properties of the crystals. In a process for purifying the ant-ulcer drug, rabeprazole sodium, the use of a mixture of solvents provides an amorphous form suitable for preparing formulations. A herbicide intermediate is produced in an asymmetric hydrogenation reaction using cheaper Ru catalysts in place of Rh catalysts. A different range of herbicides is produced by one-step fluorination of lactate esters using a fluorinated amine. The reaction proceeds via inversion with high stereoselectivity. The preparation of the anti-inflammatory drug, meloxicam, can contain byproducts at up to 20% levels, and their removal is difficult. A new process gives high-purity material via formation of the K salt of the drug. A process for the synthesis of sitagliptin, used to treat diabetes, describes a novel route that is claimed to give high yield and high-purity product; the patent contains a lot of experimental information yet no yield and purity details. Another drug used to treat diabetes is repaglinide, and by using $B(OH)_3$ as dehydrating agent in a condensation reaction, the process is simplified, and yield and product purity are improved. Diabetes can also be treated with corosolic acid that is found in plant extracts. A method is reported for extracting this acid in high purity along with the related compound ursolic acid, used to treat wrinkles and help muscle growth. The anticoagulant drug rivaroxaban is produced by a new route involving several novel intermediates, but again purity details are not provided for many compounds. An extensive patent describes a new route to an indole compound that is used to treat bipolar disorders. The patent includes a number of alternative methods and intermediates that can be used. Resveratrol and piceatannol are *E*-stilbene derivatives that are antioxidants, and a patent describes how they can be obtained in high purity without the *Z*-isomers. Alprazolam and triazolam are benzodiazepines used to treat depression, and a method of making these drugs is described that improves a cyclisation step. An improved process is reported for producing 14-hydroxymorphinane derivatives that are used as sedatives. The process starts from oripavine, a little-used extract from the poppy plant, in place of thebaine that necessitates protection and deprotection steps in the process. Plant extracts are also a source of tocotrienols that are used as dietary supplements and claimed to overcome hair loss. The molecules exist as four isomers with the α-molecule being in demand. The process converts the undesired isomers to intermediates that can be decomposed to the α-isomer but the workup is complicated. An ester salt of 3-phenylisoserine is used to prepare anticancer drugs known as taxanes. These molecules have several chiral centres and a patent provides the desired isomers in an efficient process. Cancer drugs often cause nausea and aprepitant is a drug used to overcome this problem. A detailed patent describes a method for the synthesis of a specific polymorph of the drug. The use of microreactors for the production of hazardous intermediates is described, and these are then used to prepare stable organic molecules, at least on a small scale. Thiobutyrate compounds are intermediates in the synthesis of penem antibiotics, and a new process for their preparation is described that gives such poor yields that it does not seem useful. A biphenyl-cyclopropanecarboxylic acid is used to treat Alzheimer's disease, and an improved synthetic method gives higher yields and lower levels of byproducts that are formed in a free radical bromination step. A number of the patents in this collection describe experiments carried out on a kilo or multikilo scale. This may suggest 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. 8,071,781

Assignee: Syn-Tech Chem and Pharm Co. Ltd., Sinying, Taiwan

Title or Subject: Process for Preparing Rabeprazole Sodium

Rabeprazole sodium **1** is used to treat gastric ulcers and a method for its preparation was reported recently (*Org. Process Res. Dev.* **2009**, *14*, 492). The conventional processes for making **1** are said to produce an amorphous form, and one method used for the purification of **1** uses Me_2CO to form a complex of **1** and Me_2CO. This is not suitable for preparing a medicinal formulation, and so this patent discloses a process that is claimed to give material that is acceptable. The procedure is summarised as follows:

(1) Dissolve **1** in a mixture of two organic solvents and heat to 40 −45 °C.
(2) Filter off any insoluble impurities then cool to 25 °C.
(3) Maintain at 25 °C for >3 h.
(4) Recover precipitated solid by filtration and wash with the solvent mixture.
(5) Dry the solid to obtain amorphous **1**.

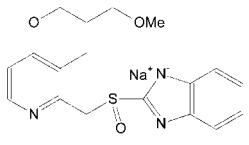
The solvents are chosen from different classes such as ketones, ethers, and hydrocarbons. Specific examples are described using

Published: March 29, 2012

   dx.doi.org/10.1021/op300071h | *Org. Process Res. Dev.* 2012, 16, 727−740

MEK/PhMe, MEK/cyclohexane, PhMe/THF, THF/cyclohexane, THF/xylene, and MEK/Et_2O. An example also describes the use of a mixture of three solvents, MEK/Me_2CO/PhMe, giving **1** in 79% yield and purity of 99.2%. This is somewhat of a surprise because the patent criticises alternative processes that use Me_2CO. Depending on the solvent system, there are specific ratios that are used. All of the examples gave a product that has purity >99.3% (HPLC), and the recovered yield is >85%. One example using MEK/PhMe gave **1** in a recovered yield of 85% and purity of 99.5%, and the XRD pattern is provided.

Rabeprazole



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Advantages. The process gives a high-purity product that is suitable for use in pharmaceutical formulations.

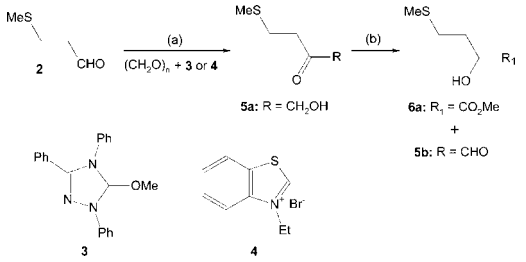
PATENT NO. U.S. 8,071,805

Assignee: Sumitomo Chemical Company Limited, Tokyo, Japan

Title or Subject: Process for Producing 2-Hydroxy-4-(methylthio)butyrate Compounds and Intermediates Thereof

The compounds of interest in this patent are exemplified by **6a** and are used in the synthesis of penem antibiotics or analogues of the essential amino acid methionine. The synthesis is outlined in Scheme 1 and starts with the condensation of

Scheme 1[a].



[a]Reagents and conditions: (a) Et_3N, Bu^tOH, 80 °C, 24 h; (ii) extract in EtOAc, H_2O wash, evaporate; (iii) vac distill; (b) (i) $Cu(OAc)_2$, in air, MeOH, rt, 74 h; (ii) 5% aq H_2SO_4, extract in EtOAc; (iii) evaporate.

paraformaldehyde with **2** in the presence of a base plus either **3** or **4** to produce the oxo-butanol **5a**. The crude product is isolated by vacuum distillation, but the reaction gives a very poor yield. For example, from 23.7 g of **2** 15 g of a fraction is obtained that contains 40% of **5a**. This fraction is purified by column chromatography (Col C) to give a total of 3.4 g of fractions containing <90% **5a**. The oxo-alcohol **5a** is converted to **6a** by reaction with O_2 (air) and MeOH in the presence of a Cu catalyst. The product is obtained as a residue containing 34% of **5a** plus **6a** and oxo-1-butanal **5b**. The analysis showed that the yield of **6a** is 12% and that of **5b** is 23% yield. The patent postulates that the reaction proceeds via formation of the intermediate **5b**, and if the oxidation is carried out using H_2O and KOH in place of MeOH, the acid **6b** ($R_1 = CO_2H$) is obtained.

Advantages. The yields in this process are so poor that it is hard to perceive any advantages.

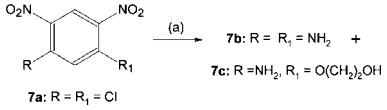
PATENT NO. U.S. 8,071,812

Assignee: E.I. du Pont de Nemours & Company, Wilmington, Delaware

Title or Subject: Process for the Synthesis of 1,3-Diamino-4,6-dinitrobenzene

The title compound, **7b**, is used in the synthesis of dyes, pharmaceuticals, and monomers for preparing polybenzimidazole polymers. It is apparently difficult and costly to purify **7b** by recrystallisation because of its low solubility in common solvents. A further problem is that the crude material contains the glycol ether **7c** ($R = NH_2$, $R_1 = O(CH_2)_2OH$) formed by reaction with the reaction solvent $(CH_2OH)_2$. The objective of the patent is to provide a method of making **7b** in high purity, and the route is outlined in Scheme 2. A key finding is that the

Scheme 2[a].



[a]Reagents and conditions: (a) (i) NH_3, H_2O, $(CH_2OH)_2$, 140 °C, 7 h; (ii) filter at 60 °C; (iii) wash at 60 °C with $(CH_2OH)_2$, H_2O wash, MeOH wash, dry.

presence of even small amounts of H_2O actually provides a higher-purity product by reducing the amount of **7c** that is formed. Since the reaction solvent is hygroscopic, this is quite fortuitous. The reaction is carried out by passing NH_3 gas or adding NH_4OH solution to a suspension of **7a** in a mixture of $(CH_2OH)_2$ containing H_2O, and the mixture is heated under pressure. The amount of water is claimed to be in the range 2−25%, and when NH_3 gas is used, the example shows the mixture contains about 2.2 vol %. When aq NH_4OH solution is used, the mixture contains considerably more (56 g of 28 wt % NH_4OH and 225 mL $(CH_2OH)_2$). In each case it is reported that no **7c** is produced and **7b** is recovered in yields >93% with purity >99%. When carried out under anhydrous conditions, the reaction gave around 4 wt % of **7c**.

The preparation of **7a** is not described in any examples although the claims cover its preparation from 1,3-dichlorobenzene using fuming nitric or sulphuric acid.

Advantages. The procedure gives improved quality product and can probably be applied easily to a plant that is currently in operation making the material.

PATENT NO. U.S. 8,076,503

Assignee: Meiji Seika Pharma Co. Ltd., and Takasago International Corporation, Tokyo, Japan

Title or Subject: Process for Production of Optically Active Aminophosphinylbutanoic Acids

The patent describes a process for preparing the **9a** that is an intermediate in the synthesis of a broad spectrum herbicide, **9b**. The preparation involves an asymmetric hydrogenation reaction, and although these are very common, it is stated that there are few methods that can be applied to compounds such as **8** that contain highly polar groups in a side chain. There are Rh catalysts that could be used, but Rh is expensive; thus, the hydrogenation is carried out using cheaper Ru catalysts containing chiral diphosphine ligands. A large number of ligands is claimed, although the examples primarily use *S*- or *R*-binap. By choosing the chirality of the ligand, the desired *R*- or *S*-enantiomer of **9a** is produced (Scheme 3). The product

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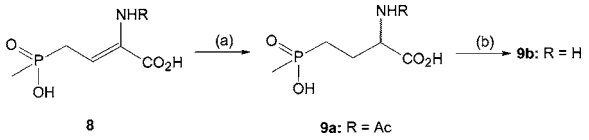
Scheme 3[a].



[a]Reagents and conditions: (a) (i) RuCl(*p*-cymene)(*S*-binap)Cl, MeOH, H_2, 1 MPa, 70 °C, 5 h; (ii) cool to rt, evaporate; (iii) add H_2O, extract in PhMe, evaporate; (b) no details provided.

is recovered as an oil with ee 90−94.1%, and the conversion of **8** is reported as 100%.

Advantages. The process is claimed to be highly efficient with high enantioselectivity.

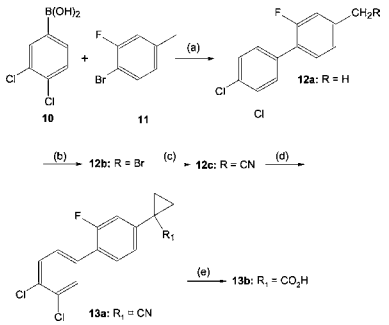
PATENT NO. U.S. 8,076,505

Assignee: Chiesi Farmaceutici S.p.A., Parma, Italy

Title or Subject: Process for Preparing Derivatives of 1-(2-Halobiphenyl-4-yl)-cyclopropanecarboxylic Acid

An example of the title compound is **13b** that is of interest in the treatment of Alzheimer's disease. Such compounds can be prepared by methods involving a Suzuki coupling reaction between a phenylboronic acid and a dihalocyclopropanecarboxylic acid. However, the process has several problems such as a low overall yield of 12−14% and includes a free radical bromination step that has low selectivity and uses CCl_4. Thus, it is unsuitable for commercial production, and the patent discloses a process that is claimed to be better. The route to **13b** is outlined in Scheme 4 and begins with a Suzuki coupling

Scheme 4[a].



[a]Reagents and conditions: (a) (i) Na_2CO_3, Pd/C, EtOH, reflux, 4 h; (ii) cool, filter evaporate; (iii) 1 M NaOH, Pr^iOAc, separate; (iv) 3 M HCl, brine wash, concentrate; (v) MeCN/H_2O, 40 °C; (vi) <5 °C, 0.5 h, filter; (b) (i) NBS, $(PhCO)_2O_2$, MeCN, reflux, 3 h; (ii) cool, aq Na_2SO_3, 0.5 h; (iii) separate, extract in DCM; (iv) H_2O wash, evaporate; (c) (i) NaCN, H_2O/EtOH, 50 °C, 3 h; (ii) evaporate, add H_2O/EtOH, <5 °C, 0.5 h; (iii) filter, dry; (iv) EtOH, 25 °C, (v) filter, dry; (d) (i) Bu_4^nNCl, $(BrCH_2)_2$, H_2O, PhMe; (ii) add 30% aq NaOH, 25 °C, 0.5 h; (iii) 25 °C, 6 h; (iv) separate, H_2O wash, 3 M HCl; (v) evaporate, add heptane 80 °C; (vi) <5 °C, 0.5 h, filter, wash, dry; (e) (i) KOH, H_2O, MeOH, reflux, 48 h; (ii) 36% aq HCl, 25 °C, filter, wash, dry; (iii) active C, Pr^iOH, reflux; (iv) filter, concentrate, add heptane; (v) cool, filter, wash, dry.

of **10** and **11** to produce **12a** that is isolated in 86% yield with purity of 95% measured by HPLC-UV. The biphenyl **12a** is then brominated using NBS and $(PhCO)_2O_2$ to form **12b** that is isolated in 94% yield and 77.1% purity. To avoid formation of a dibrominated compound in this reaction step NBS is used in only slight excess, around 1.05 mol per mol of **12a**. Treatment of **12b** with NaCN forms **12c** that is obtained in 57% yield and 92.3% purity. Reaction of **12c** with $(BrCH_2)_2$ in the presence of NaOH and a phase transfer catalyst (PTC) produces **13a** that is recovered in 65% yield and 98.2% purity. In the final step the nitrile group is hydrolysed using KOH, and **13b** is obtained after crystallisation from Pr^iOH/heptane in 68% yield and 99.8% purity.

Advantages. The process is suitable for use on a large scale, and compounds **10** and **11** are either commercially available or can be made by known methods, although the yields are only moderate.

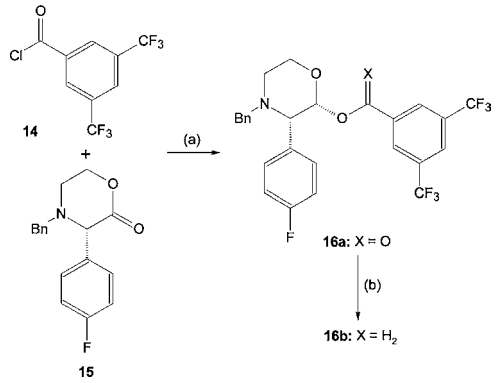
PATENT NO. U.S. 8,080,656

Assignee: Ranbaxy Laboratories Limited, New Delhi, India

Title or Subject: Process for the Preparation of Aprepitant

Aprepitant, **20**, is used to treat nausea and vomiting in patients undergoing chemotherapy treatment for cancer. A key intermediate in the preparation of **20** is **16a**, and this can be made by a number of processes that are summarised. The patent discloses a method of making **16a**, shown in Scheme 5, that is

Scheme 5[a].



[a]Reagents and conditions: (a) (i) $LiBHBu^s_3$, THF, −75 °C, 1 h; (ii) add HOAc, warm to rt; (iii) evaporate, add H_2O/hexane; (iv) separate, wash in aq Na_2CO_3; (v) evaporate, crystallise Pr^iOH; (b) (i0 Cp_2TiMe_2 PhMe, 80 °C, 6 h, in dark; (ii) concentrate, add heptane, filter; (iii) evaporate, add Na_2CO_3, H_2O, MeOH, 40 °C, 12 h; (iv) filter at 25 °C, PhMe wash, evaporate; (v) crystallise from MeOH/H_2O.

claimed to give **20** with superior yield and purity compared to alternatives. The process starts with the HCl salt of **15** that is converted to the free base by treatment with Na_2CO_3. **15** is then treated with L-selectride ($LiBHBu^s_3$) followed by addition of **14** to give **16a**. After workup and crystallisation from Pr^iOH the product is isolated in 62.6% yield with 99.94% purity (HPLC). The patent provides DSC and XRD spectra of **16a**, and these are described as being polymorphic Form A of the compound although there is no further mention of this or any other polymorphs. Treatment of **16a** with Cp_2TiMe_2 gives **16b** that is recovered in 92.4% yield with 99.9% purity after crystallisation from MeOH/H_2O.

The intermediate **16b** is then used in the preparation of **20** as shown in Scheme 6. The first step is removal of the Bn protection by hydrogenation using Pd/C catalyst forming the free base **17**. This is not isolated and converted to the tosylate salt **17·TsOH** that is recovered in 62.3% yield (purity not reported). The tosylate salt can be purified by treatment with aq Na_2CO_3, followed by TsOH and then crystallised from MTBE/hexane.

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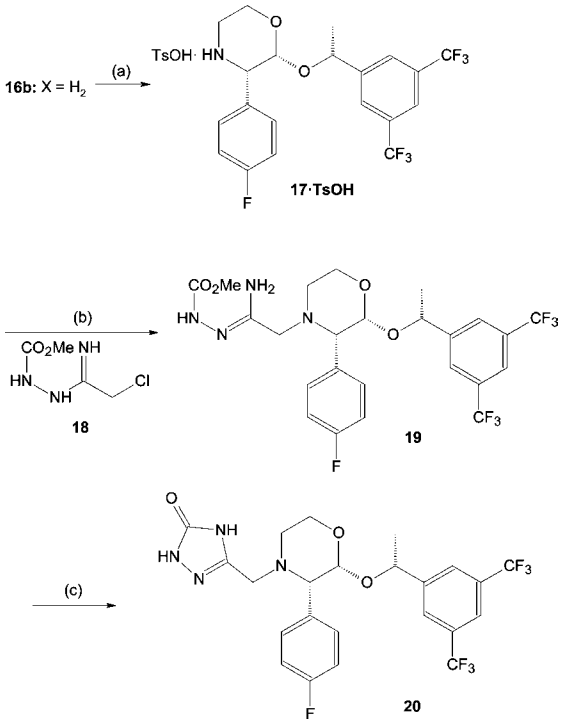
Scheme 6[a].



[a]Reagents and conditions: (a) (i) Pd/C, EtOAc/EtOH, H_2, 3 bar, rt, 8 h; (ii) filter, evaporate; (iii) active C, MTBE, rt, filter; (iv) evaporate, TsOH, MTBE, rt, 0.25 h; (v) add hexane, rt, 2 h; (vi) filter, wash, dry; (b) (i) K_2CO_3, DMSO, 23 °C, 1.5 h; (ii) add H_2O, extract in PhMe, evaporate; (c) (i) 135−137 °C, 2 h; (ii) add PhMe, filter at rt, PhMe wash;(iii) add MeOH, active C, 62 °C, 1 h; (iv) filter, cool 25 °C, add H_2O over 1 h, filter; (v) wash in MeOH/H_2O, dry.

The product is recovered in 90% yield and 99.9% purity. Reaction of **17·TsOH** with **18** in the presence of K_2CO_3 produces the intermediate **19** that is used in a number of alternative routes to **20**. **19** is obtained as a viscous oil after removal of the solvent and used without any further treatment to prepare **20**. The cyclisation of **19** to give **20** is by heating the oil to obtain a solid that after workup and crystallisation from MeOH/H_2O gives **20** in 63.6% yield and 99.8% purity. The practicalities of scaling up this last step are debatable.

Advantages. The process gives a specific polymorph of the molecule in high purity that is presumably the desired Form.

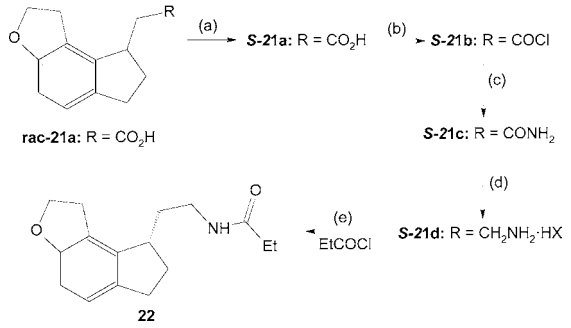
PATENT NO. U.S. 8,084,630

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

Title or Subject: Process for the Synthesis of Ramelteon and its Intermediates

Ramelteon, **22** is available as Rozerem and used to treat insomnia. A number of different processes for its preparation are described, and they all have several steps. No comments are made on the relative merits of these but the patent states there is a need for a new industrial scale process. The main patent claim covers the novel acid **21a** as a racemic mixture, and this is converted to **22** by the route shown in Scheme 7. The mixture is resolved by diastereomeric crystallisation by formation of an amine salt of *S*-PhCHMeNH$_2$. The amine salt of the *R*-isomer is first recovered, and the salt of ***S*-21a** is isolated from the solution and acidified to give the free acid ***S*-21a**. Each enantiomer is isolated with purity and ee both >99.0%. The acid is then

Scheme 7[a].



[a]Reagents and conditions: (a) (i) *S*-PhCHMeNH$_2$, Pr^{i}OH/H_2O, 65 °C, 0.75 h; (ii) cool <10 °C, filter; (iii) evaporate, add Me_2CO, recrystallise; (iv) H_2O, concd HCl to pH 2, filter, dry; (v) *R*-PhCHMeNH$_2$, Me_2CO, 65 °C, 0.75 h; (vi) cool <10 °C, filter, dry, recrystallise; (b) $SOCl_2$, rt, 3 h; (ii) evaporate, add DCM; (iii) NH_3 gas to pH >7, rt; (iv) filter, wash, dry; (c) (i) $NaBH_4$, BF_3·Et_2O, THF, 0 °C, 24 h; (ii) evaporate; (d) (i) add EtOAc, 1 M HCl; (ii) evaporate EtOAc, (iii) 50 °C, 40 min; (iv) add Pr$^i_2$O, filter, wash; (e) (i) 30% aq NaOH, THF/H_2O, rt, 3 h; (ii) evaporate, add EtOAc, brine wash; (iii) evaporate, recrystallise from EtOH.

converted to the amide **21c** via the acyl chloride **21b** by reaction with $SOCl_2$. The chloride is not isolated and treated with NH_3 gas to give **21c** that is recovered in 85−90% yield with purity 95−98%. Using aq NH_4OH the purity of **21c** is slightly less at 93−96%. An alternative method of preparing **21c** is treatment of **21a** with Et_3N and $ClCO_2Et$ followed by NH_3, and this gives **21c** with yields of 80−95% and purity 97−99%. In the next step reduction of **21c** is carried out using $NaBH_4$ and BF_3·Et_2O, and the amine **21d** is purified by formation of a salt (X = Cl or oxalate). Examples are given for both salts with yields of up to 85% and purity 96−98%. These salts are then used to prepare **22** in the last step by reaction with EtCOCl in the presence of base; using NaOH with the Cl salt and Na_2CO_3 with the oxalate. The yields of **22** are again >92%, and the purity is up to 99.9% after recrystallisation from EtOH. The patent also discusses the recrystallisation of **22** from PhMe in an effort to produce what is described as a nonelectrostatic crystalline form. This is designated Form A, and the measurement of the electrostatic charge of the crystals is described. The results show that the average charge density of this material is about 15 times less than that obtained from EtOAc. This improves the flow characteristics of the solid, and this is important in preparing drug formulations. Details of flowability tests are reported in the patent.

The patent also give details for the preparation of **rac-21a** by a multistep procedure that is shown in Schemes 8 and 9. In most of the reaction steps the product is isolated in crude form, and the patent does not indicate if the compound is purified before being used in the next stage. The synthesis of **rac-21a** starts by conversion of **23a** to the aldehyde **23b** by reaction with $POCl_3$ followed by hydrolysis. The crude product is isolated as a liquid in 85−90% yield with purity 90−92%. In the next step **23b** is condensed with **24** in the presence of piperidine and HOAc to form **25** that is isolated in 92−95% and 95% purity. Catalytic hydrogenation of **25** is carried out to produce **26a** that is obtained in 95% yield and 94−96% purity. The hydrogenation can also be carried out in the presence of NaOH and HCO_2NH_4 giving a similar yield and purity of **26a**, but the reaction takes 6 h instead of 2. Bromination of **26a** is then carried out to produce the acid **26b** that is isolated in 50−60% yield and 92−95% purity.

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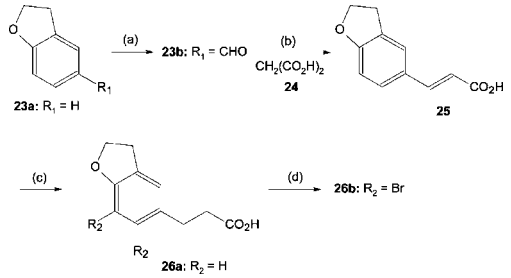
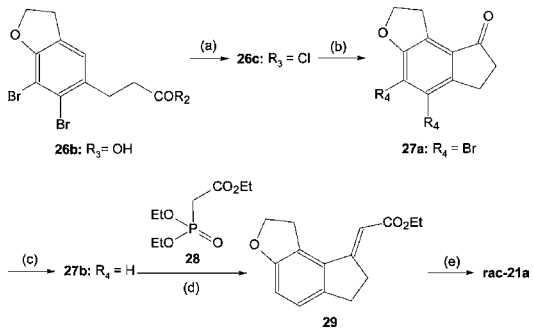
Scheme 8[a].



[a]Reagents and conditions: (a) (i) $POCl_3$, DMF, 85 °C, 5 h; (ii) ice/H_2O, extract in PhMe, wash, evaporate; (b) (i) HOAc, piperidine, pyridine, 100 °C, 5 h; (ii) cool to rt, add dil HCl, 3 h; (iii) filter, dry; (c) (i) MeOH/H_2O, Pd/C, H_2, rt, 2 h; (ii) filter, evaporate; (iii) add H_2O, filter, dry; (d) (i) NaOAc, HOAc, Br_2, <5 °C; (ii) 45 °C, 3 h; (iii) 15% aq $NaHSO_3$, 45 °C; (iv) filter, dry.

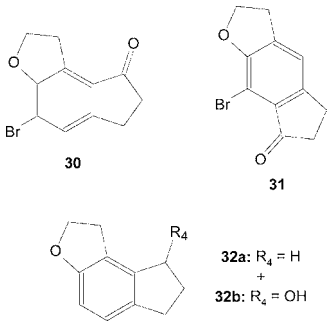
Scheme 9[a].



[a]Reagents and conditions: (a) $SOCl_2$, *o*-$PhCl_2$, rt, 2 h; (b) (i) $AlCl_3$, <5 °C, 2 h; (ii) add MeOH, filter, wash, dry; (c) (i) NaOAc, HOAc, Pd/C, 2−3 kg/cm^3 H_2, rt; (ii) filter, evaporate at 60 °C; (d) (i) NaH, PhMe, 100 °C, 18 h; (ii) cool, add H_2O, separate; (iii) brine wash, evaporate at 60 °C; (e) (i) H_2O/MeOH, Pd/C, 2−3 kg/cm^3 H_2, rt, 3 h; (ii) filter, add NaOH, rt, 3 h; (iii) evaporate, add H_2O and then HCl, cool, filter, dry.

The next stage of the synthesis (Scheme 9) begins with the activation of the carboxylic group in **26b** by reaction with $SOCl_2$ to form the acyl chloride **26c** (R_3 = Cl). This is not isolated but cyclised under Friedel−Crafts conditions to give **27a** that is isolated in yields of 85−92% and purity 90−95%. Two impurities, **30** and **31**, are produced in this reaction although the amounts are not reported. The patent states that removal of these gives **27a** in good yield, but it does not describe how to do this. The impurities can be isolated, and ^{1}H and ^{13}C NMR data are provided for each, but the method used to isolate them is not reported. In the next step the Br atoms are removed from **27a** by treatment with H_2 in the presence of Pd/C catalyst to give **27b** in 85−90% yield and 96−97% purity. The impurities obtained in this reaction are **32a** and **32b**, and again the levels present are not reported, but there are ^{1}H and ^{13}C NMR data. After refluxing in MeOH and active C, **27b** is isolated in 80−85% yield with 99.3−99.8% purity. It is then converted to **29** by reaction with a solution of **28** that had been treated with NaH. The crude product, **29**, is isolated in 80−85% yield and 92−95% purity as a mixture of *E*- and *Z*-isomers. These are not separated and are hydrogenated using Pd/C catalyst followed by base hydrolysis to give the racemate **rac-21a** that is isolated in 90−95% yield and 95−98% purity.

Impurities



Advantages. The patent claims to be suitable for production of **22** on an industrial scale, and a form of the crystals is described that has improved flow characteristics.

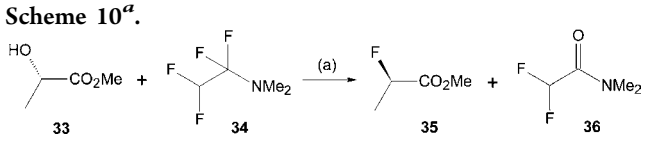
PATENT NO. U.S. 8,093,421

Assignee: Bayer Cropscience AG, Monheim, Germany

Title or Subject: Stereoselective One-Step Fluorination Process for the Preparation of Alkyl 2-Fluoropropionates

The compounds of interest in this patent are intermediates in the production of herbicides. The specific compounds covered are the chiral ethyl and methyl esters although the actual title of this patent simply mentions "The Preparation of 2-Flouropropionate". Not only is this name on its own quite meaningless, it is also misspelt. Alternative methods of making the compounds are summarised, and many are said to give products with low ee or use reagents that are too expensive for industrial production. The new process disclosed in this patent uses **34** as the fluorinating agent with alkyl lactates to give the 2-fluoropropionates with inverted configuration at the chiral centre and very high ee. The compound **34** has been used previously in fluorination of chiral compounds but is reported to have given products with low ee. Hence, it is surprising that the patent claims that this reagent gives the desired products with such high ee. Scheme 10 shows the preparation of **35** from

Scheme 10[a].



[a]Reagents and conditions: (a) (i) rt, 12 h; (ii) add to ice, extract in DCM, distill.

33 using a slight excess of **34** that is converted to **36** as the coproduct of the reaction. The patent claims a solvent can be used, but the single example does not do so. The products are recovered by vacuum distillation, and the first fraction contains 98% of **35** with 96% ee. The product contained unreacted **33** and the yield of **35** corresponded to 83%. The patent reports that that the *S*-enantiomer of **35** can be prepared from the *R*-lactate, but details are not provided.

Advantages. The process gives high yields of the required fluoroester in a single step and is claimed to be commercially viable.

PATENT NO. U.S. 8,097,616

Assignee: Egis Gyogyszergyar Nyilvanosan Mukodo Reszvenytarsasag, Budapest, Hungary

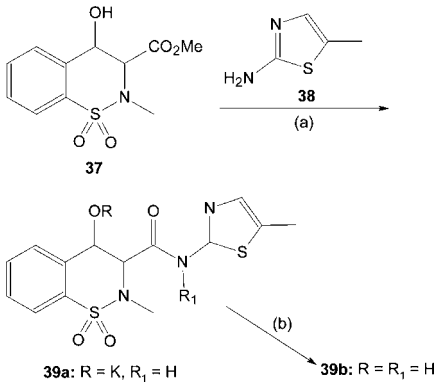
Title or Subject: Process for Preparation of High-Purity Meloxicam and Its Potassium Salt

Meloxicam **39b** (R = R_1 = H) is a nonsteroidal anti-inflammatory drug (NSAID) that is approved for use on

dx.doi.org/10.1021/op300071h | *Org. Process Res. Dev.* 2012, 16, 727−740

humans and dogs. The drug has fewer gastrointestinal side effects than some other NSAIDs, some of which have been withdrawn. The methods for preparing **39b** by the reaction of **37** and **38** are said to produce impurities such as **39c** (R = H, R_1 = Me) that are present at levels of up to 20%. Even after crystallisation from DCM the level of **39c** can be >0.1%, and this exceeds the allowable concentration. Several recrystallisations from DCM are said to be needed to achieve the maximum allowed level of **39c** in **39b**. Using the Et or Pr^i esters of **37** in the preparation of **39b** the corresponding impurity is present at lower levels, and the Pr^i ester gives the lowest level of impurity. The patent describes a method of making **39b** with low levels of **39c**, and this is achieved by initially forming the K salt **39a** (R = K, R_1 = H) that can be recrystallised from H_2O and then converted to **39b** as shown in Scheme 11. The patent claims

Scheme 11[a].



[a]Reagents and conditions: (a) (i) active C, argon purge, xylene, 180 °C, 24 h; (ii) filter at 25 °C; (iii) 0.5% aq KOH, 50 °C, 1 h; (iv) filter at 25 °C; (v) add 30 wt % aq KOH; (vi) 10 °C, 2 h, filter, wash; (b) (i) 0.5% aq KOH, EtOH, 45 °C, 0.5 h; (ii) Active C, 45 °C, 10 min, filter; (iii) aq HCl, 10 °C, 2 h, filter.

that there are no reports of the preparation and properties of the solid form of the K salt **39a** although it is known. The patent states that crystalline **39a** can be obtained by crystallisation from H_2O in 81% yield as the monohydrate with purity 99.5%. Despite the presence of an aromatic OH group in **39c** it does not form a K salt and so is easily removed, and the K salt **39a** can then be acidified to give **39b** that is isolated in 97.1% yield with purity 99.8%. The patent reports that a pharmaceutically acceptable form of **39b**, polymorph Form I, can be obtained by neutralising **39a** using HOAc instead of HCl in a yield of 98.5% and purity 99.8%.

Advantages. The process gives the drug molecule in high purity as well as the pure form of the K salt.

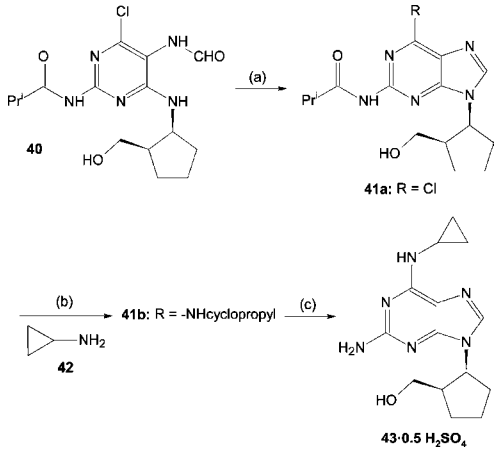
PATENT NO. U.S. 8,097,723

Assignee: Esteve Quimica S.A., Barcelona, Spain

Title or Subject: Process for the Preparation of Abacavir

The hemisulphate salt of abacavir **43** is used in the treatment of HIV, and this patent describes a process for its preparation that is based on the formation of the purine ring using specific conditions. Alternative preparations of **43** are summarised, and an improved method is said to be desirable. The process is outlined in Scheme 12 and begins with the pyrimidine compound **40** that is reacted with $(EtO)_3CH$ to effect

Scheme 12[a].



[a]Reagents and conditions: (a) (i) HCl/Pr^iOH, 42 °C, 2 h; (ii) $(EtO)_3CH$, 10 °C, 2 h; (iii) $NaHCO_3$, 0.5 h, filter; (b) (i) $NaHCO_3$, reflux, 1 h; (ii) filter, evaporate; (iii) hot Pr^iOH, (iv) cool 2 °C, filter, dry; (c) (i) NaOH, Pr^iOH, reflux, 1 h; (ii) cool <25 °C, add MTBE, separate; (iii) 96% H_2SO_4; (iv) cool <5 °C, filter, dry.

cyclisation and formation of the purine **41a** (R = Cl). The reaction is best carried out using anhydrous HCl in Pr^iOH, and **41a** is not isolated but reacted with **42** in the presence of $NaHCO_3$ to form the cyclopropylamine derivative **41b**. This is initially obtained as a syrup that is solidified after treatment with hot Pr^iOH and is isolated in 73% yield and 95% purity. It can be converted to the free amine, **43**, by treatment with NaOH and is isolated in 77% yield, but the purity is not reported. The hemisulphate salt of **43** can be obtained from **41b** in 97% yield by treatment with NaOH in Pr^iOH followed by H_2SO_4 in MTBE. When PhMe is used in place of MTBE, the yield falls to 88%, but purity details are not provided in either case.

It is important that the cyclisation reaction is carried out in the absence of H_2O, and when aq HCl is used for this reaction, the yield is only 21%. The use of anhydrous conditions for this cyclisation is said to be contrary to reports for similar reactions referred to in the patent, and the use of an alcohol enables a high yield and high-purity purine intermediate to be obtained.

Advantages. The process gives high yield of intermediate that can then be efficiently converted to the desired product.

PATENT NO. U.S. 8,097,724

Assignee: Dipharma Francis S.r.l., Baranzate, Milan, Italy

Title or Subject: Process for the Preparation of Sitagliptin

Sitagliptin, **45d**, is used in the treatment of Type II diabetes, and processes for its preparation are said to use reagents that are either toxic, dangerous, difficult to prepare, or involve complex catalyst systems. Hence, the objective of the patent is to provide a process that uses low-cost starting materials and that gives safe and reproducible results. The first stage of the process, to produce the *R*-enantiomer of the acid **44b**, is outlined in Scheme 13. This starts from the novel diethyl malonate derivative **44a** that is hydrolysed with KOH to produce the racemic acid **44b**. The acid can be recrystallised from an 80/20 mixture of H_2O/MeOH, but there are no yield or purity details provided. Resolution of **44b** can be carried out using *L*-cinchonidine, and the product is isolated as a 82:18 mixture of the *S*:*R* enantiomers in a reported quantitative yield. The process to make **R-44d** proceeds by esterification of **rac-44b** to give the racemic ester **rac-44c** in 95% isolated yield.

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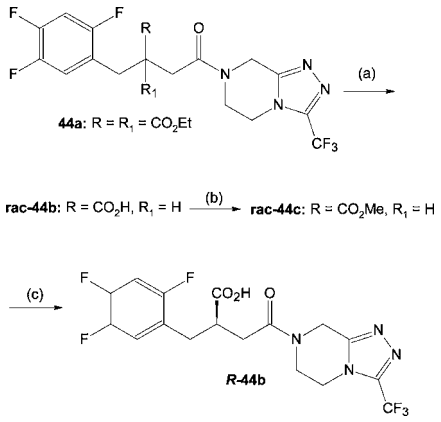
Scheme 13[a].

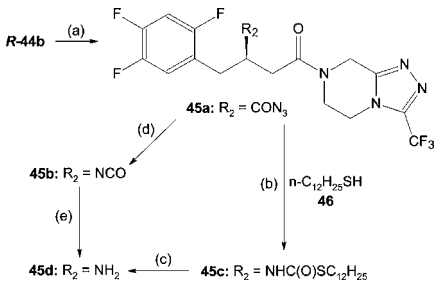


[a]Reagents and conditions: (a) (i) Aq KOH, EtOH, 80 °C, 10 h; (ii) concentrate, extract in EtOAc, wash, dry, evaporate; (b) (i) H_2SO_4, MeOH, 25 °C, 16 h; (ii) aq $NaHCO_3$, extract in EtOAc, dry, evaporate; (c) (i) enzyme, buffer pH 8.1, PhMe, 50 °C, 6 h; (ii) filter, PhMe wash; (iii) 37% HCl to pH 1; (iv) filter, extract in EtOAc, dry, evaporate.

The racemic ester then undergoes enzymatic hydrolysis with the protease enzyme *Bacillus licheniformis* to give the *R*-acid while the *S*-ester is unaffected. The ester can be recovered, racemised, and recycled, but unfortunately there are no details for these steps. The *R*-acid is recovered as a brown oil in 32.2% yield and has ee of 99.9% (HPLC).

The next stage is shown in Scheme 14 and starts by conversion of **R-44b** to the azide **45a** by reaction with $(PhO)_2PON_3$.

Scheme 14[a].

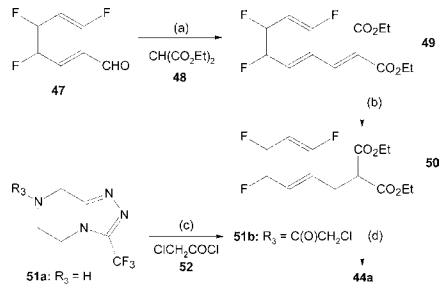


[a]Reagents and conditions: (a) $(PhO)_2P(O)N_3$, Et_3N, THF, 25 °C, 1 h; (b) (i) THF, 65 °C, 1.5 h; (ii) evaporate, add EtOAc, H_2O wash; (iii) concentrate, add hexane, filter, wash, dry; (d) and (e) no details provided.

The azide is not isolated and can be converted to **45b** and subsequently to **45d** via a Curtius rearrangement. These steps are included in the claims of the patent, although no details are provided. The examples describe the reaction of **45a** with the thiol **46** to form **45c** that is isolated in 78% yield. Base hydrolysis of **45c** then gives **45d** that is isolated as a yellow solid, but no yield or purity details are provided.

The patent claims cover the conversion of **rac-44b**, or a pure enantiomer of **44b**, to the amide **44d** (R = $CONH_2$), and this is followed by a Hofmann degradation to give **45d**. The claims also cover the conversion of **44b** to the isocyanate **45b** via a Lossen or Schmidt procedure and the subsequent preparation of **45d**. However, there are no examples covering any of these reactions The patent does describe the preparation of the novel malonate derivative **44a** by condensation of **50** with **51b** as shown in Scheme 15. The malonate **50** is obtained by

Scheme 15[a].



[a]Reagents and conditions: (a) (i) $PhCO_2H$, piperidine, Na_2SO_4, PhMe, 110 °C, 10 h; (ii) cool, filter, wash in H_2O; (iii) 1 M HCl, aq $NaHCO_3$, H_2O; (iv) evaporate, Flash C; (b) (i) Pd/C, HCO_2Na, H_2O, 80 °C, 0.5 h; (ii) cool, filter, MeOH wash, evaporate, extract in EtOAc; (iii) separate, dry, evaporate; (c) (i) Et_3N, PhMe, −5 °C, 0.5 h; (ii) add H_2O, separate; (iii) extract in DCM, evaporate; (iv) add EtOAc, H_2O wash, extract in PhMe, evaporate; (d) (i) NaH, THF, 25 °C, 22 h; (ii) add H_2O, separate, evaporate; (iii) extract in EtOAc, dry, evaporate.

condensation of aldehyde **47** with **48** to give **49** that is isolated in 57% yield as a yellow oil after purification by flash chromatography (Flash C). Catalytic transfer hydrogenation of **49** with HCO_2Na gives **50** that is also obtained as a yellow oil in 70% yield. The free amine **51a** is obtained from its HCl salt and then reacted with **52** to form **51b** that is isolated in 98% yield as a yellow oil that can be crystallised from THF/MTBE, but no yield or purity details are given. Reaction of **51b** with **50** in the presence of NaH forms **44a** that is isolated as a pale-yellow solid in 58% yield after purification by Flash C.

The patent provides some basic ^1H NMR data for **44a**, **44c**, **49**, **50**, and **51b**.

Advantages. The process is claimed to give the API in high yield and with high ee but does not provide sufficient evidence to substantiate these claims.

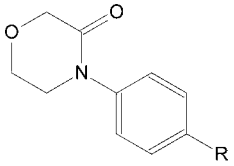
PATENT NO. U.S. 8,101,609

Assignee: Apotex Pharmachem Inc., Brantford, Canada

Title or Subject: Process for the Preparation of Rivaroxaban and Intermediates Thereof

Rivaroxaban, **56**, is an anticoagulant drug used to treat various thromboembolic diseases. The claims of the patent cover a number of novel compounds that are intermediates in the synthesis of **56**. These intermediate compounds are based on the morpholinone derivative **53** where R is an amino group or heterocyclic compound.

Intermediates



53: Morph-R

One method for the synthesis of **56** is by the condensation of **55** with **54a** as shown in Scheme 16. The reaction is carried out in the presence of strong base such as LHMDS that gave a

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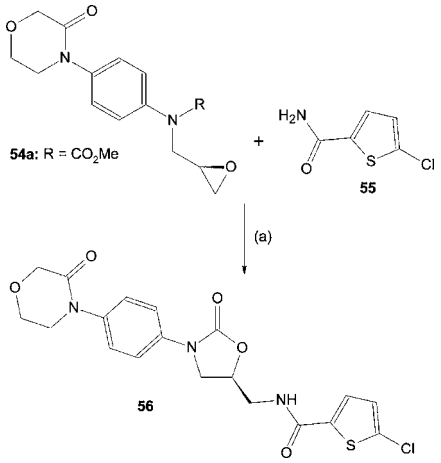
Scheme 16[a].

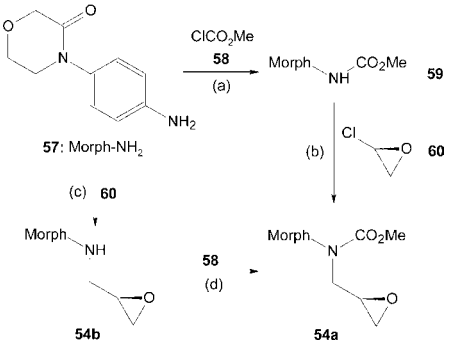


[a]Reagents and conditions: (a) (i) LHMDS, THF, reflux, 3 h; (ii) evaporate, add aq NH_4Cl, 5 °C; (iii) filter, H_2O wash, 5 °C; (iv) dissolve in MeOH/DCM, concentrate; (v) filter, wash, dry.

yield of **56** of 64%, Bu^nLi (yield 62%) or Bu^tOK (yield 31%). The patent also proposes the reaction between **55** and other morpholinone derivatives that can be formed from **54a** or can be converted to **54a**. However, there are no examples using other derivatives, and the preparation and reactions of these are discussed below.

The derivative **54a** can be obtained from the amine **57** by one of two routes that are both outlined in Scheme 17. The first

Scheme 17[a].

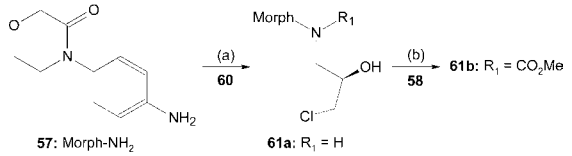


[a]Reagents and conditions: (a) (i) DCM, rt, 1 h; (ii) filter, wash, dry; (b) (i) NaH, DMF, 60 °C, 3 h; (ii) aq NH_4Cl, rt; (iii) extract in EtOAc/DCM, dry, evaporate; (iv) flash C; (c) (i) Pr^iOH, reflux, 2 h; (ii) add aq $NaHCO_3$, reflux 1.5 h; (iii) evaporate, add H_2O; (iv) extract in EtOAc, dry, evaporate; (v) flash C; (d) (i) $EtNPr^i_2$, MeCN, 0 °C, 5 min; (ii) rt, 0.5 h; (iii) add H_2O, extract in EtOAc, dry, evaporate; (iv) flash C.

begins with the formation of the carbamate **59** by reaction of **57** with **58**. The product is isolated in 95% yield as a crystalline solid and is then reacted with **60** in the presence of NaH to produce **54a**. The crude product is purified by Flash C and recovered in 42% yield as a crystalline solid. In the second route to **54a** the first step is reaction of **57** with **60** in the presence of $NaHCO_3$ to produce **54b**. This is isolated in 46% yield after purification by Flash C and then reacted with a slight excess of a 1:1 mixture of **58** and $EtNPr^i_2$ to give **54a**. After purification by Flash C the product is isolated in 87% yield as white crystalline solid. There is no information on the purity of any of the compounds produced in this scheme although ^1H NMR data are provided.

The patent also describes the preparation of the derivatives **61a** and **61b** from **57** as shown in Scheme 18. The reaction of

Scheme 18[a].



[a]Reagents and conditions: (a) (i) Pr^iOH, reflux, 24 h; (ii) evaporate, flash C; (b) (i) $EtNPr^i_2$, MeCN, rt, 1 h; (ii) evaporate, 35 °C; (iii) extract in DCM, H_2O wash, dry, evaporate.

57 with **60** over an extended period produces **61a**, and this presumably proceeds via the formation of **54b**. The product is isolated in 83% yield after Flash C and then reacted with **58** to form **61b** that is recovered in quantitative yield. Purity details for **61a** and **61b** are not reported although ^1H NMR data are provided.

The patent also discusses the formation of the *S*-enantiomer of **56** via the appropriate intermediates although there are no examples provided. The claims of the patent cover both *R*- and *S*- enantiomers of all of the intermediates shown in the schemes.

Advantages. The patent describes the preparation of a number of novel intermediates that are used in the synthesis of the API.

PATENT NO. U.S. 8,101,750

Assignee: AstraZeneca AB, Sodertalje, Sweden

Title or Subject: Process for the Manufacture of 2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1*H*-indole-5-carbonitrile

Salts of the title compound **63a**, are said to be useful pharmaceutical agents with the citrate salt being specifically mentioned and treatment of bipolar disorder being of particular interest. An alternative process for the manufacture of **63a** uses pyridine *N*-oxides, and handling these compounds on a large scale is said to be a concern. The purification of the final product is also said to require the use of Col C, and so this patent describes processes that are claimed to overcome these problems and are suitable for the large-scale manufacture of **63a**. There are three methods covered by the patent that all involve reduction of the intermediate nitro compound **62a**. The first process is shown in Scheme 19 and proceeds by reduction of **62a** using a catalyst of Pt/V on active C. The reaction actually starts from the HCl salt of **62a** that is treated with aq $NaHCO_3$ to give the free amine that is not isolated before the reduction. The reaction produces the intermediate amine **62b** that is obtained as a solution in PhMe/DMF. Heating this solution with a solution of citric acid forms the citrate salt of **63a** as an orange solid in 83% yield and 96.3% purity.

The second method for preparing **63a** from **62a** proceeds via the intermediate dihydroxy compound **63b** and is shown in Scheme 20. The free amine **62a** is prepared from the HCl salt and then treated with $(NH_4)_2S$ to give **63b** that is isolated in 76% yield and 94% purity. Treatment of **63b** with Fe powder in HOAc forms **63a** that is purified by Col C, reslurried with Pr^iOH, and isolated in 81% yield; the purity is not reported.

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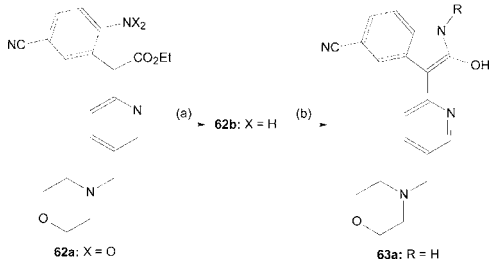
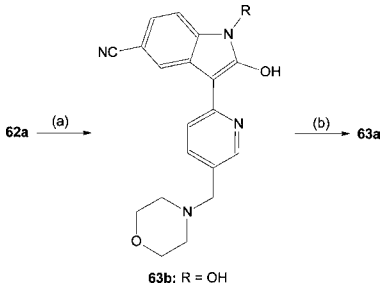
Scheme 19[a].



[a]Reagents and conditions: (a) (i) Pt/V on C, H_2, 4 bar, PhMe/DMF, 40 °C, 0.5 h; (ii) 70 °C, 6 h; (iii) cool rt, filter, concentrate; (b) (i) PhMe/DMF, 60 °C; (ii) citric acid, Pr^iOH, 50 °C; (iii) 90 °C, add seed; (iv) add citric acid in Pr^iOH at 50 °C, 2 h; (v) cool 5 °C, over 6 h; (vi) 5 °C, 20 h; (vii) filter, wash in PhMe/DMF, Pr^iOH, dry.

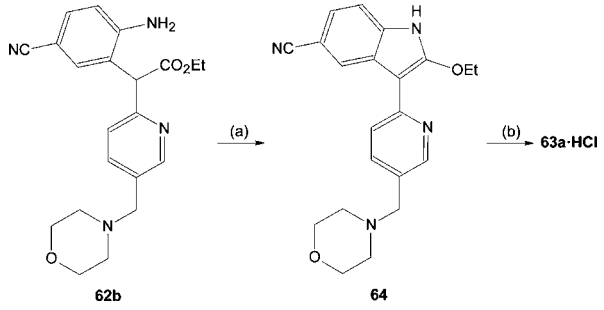
Scheme 20[a].



[a]Reagents and conditions: (a) (i) aq $(NH_4)_2S$, EtOH, 50 °C, 80 min; (ii) cool 0 °C, filter; (iii) wash in H_2O, Pr^iOH; (iv) dry, 50 °C; (b) (i) Fe, HOAc, 60 °C, 3 h; (ii) cool, add Celite, evaporate; (iii) Col C; (iv) reslurry in Pr^iOH, filter, wash, dry.

The third method for the preparation of **63a** is shown in Scheme 21 and starts from the amine **62b**. This is treated with

Scheme 21[a].

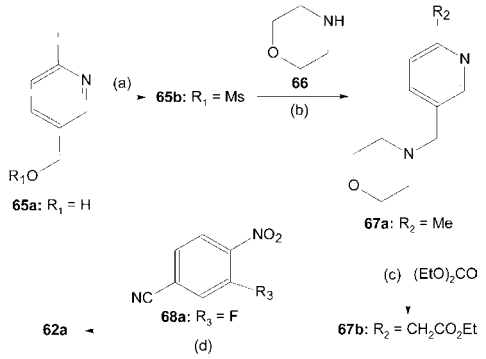


[a]Reagents and conditions: (a) HCl/Pr^iOH, PhMe, DMF, rt, 1 h; (b) (i) 90 °C, 16 h; (ii) filter at rt; (iii) Pr^iOH wash × 2, dry at 50 °C.

HCl, giving the ethoxy compound **64** that is not isolated, and the reaction mixture is heated to give **63a** that is recovered in 62% yield as the HCl salt.

The patent also describes the preparation of the intermediate **62a** by the route outlined in Scheme 22. The first stage is to convert the OH in **65a** to a facile leaving group by treatment with MsCl giving **65b**. The reaction is carried out in the presence of sufficient Et_3N to remove HCl, and the product is recovered, but yield and purity are not reported. The example describes using 24 kilo of **65a**, and the next stage is also carried

Scheme 22[a].



[a]Reagents and conditions: (a) (i) MsCl, Et_3N, THF, −3 °C, 4 h; (ii) filter, wash in THF × 4; (b) (i) THF, 21 h; (ii) filter, wash in THF × 5; (iii) concentrate, add heptane, filter at 40 °C; (iv) heptane wash × 2; (v) cool 20 °C, 3 h; (vi) cool −12 °C, 5 h; (vii) −12 °C, 12 h; (viii) filter, heptane wash, 0 °C, dry; (c) (i) LDA, THF, −13 °C, 2.75 h; (ii) aq NH_4Cl, 0 °C; (iii) separate at 30 °C; (iv) extract in PhMe, concentrate; (d) (i) Bu^tOLi, THF, PhMe, −20 °C, 2.3 h; (ii) aq NH_4Cl, 0 °C; (iii) add Celite, filter at 30 °C; (iv) separate, H_2O wash; (v) concentrate.

out on a large scale where the mesyl derivative is reacted with **66**, and 25 kilo of **67a** is recovered, after an extensive workup procedure, in 67% yield. **67a** is then reacted with $(EtO)_2CO$ in the presence of LDA to produce **67b** that is recovered as a 74.5 wt % solution in PhMe equating to 92% yield. An alternative method is to recover the product as a 80.7 wt % solution in THF corresponding to a yield of 80%. A sample of the PhMe solution was evaporated, yielding **67b** as a yellow oil. The solution of the ester in THF or THF/PhMe is reacted with **68a** to produce **62a**, and this can be obtained as the HCl salt or as a solution of the free base in a solvent. The reaction is carried out in the presence of Bu^tOLi and the product isolated in solutions that can be used to prepare red crystals of HCl salt of **62a** or the free base itself as a beige crystalline solid. The preparation of **62a** from **67b** is also carried out by using **68b** (R_3 = H) in place of **68a**, and the crude **62a** is isolated in 51% yield.

An alternative synthesis of **67a** is described from the chloro compound **67c** (R_2 = Cl) using $Fe(acac)_3$ and MeMgCl, and this gives **67a** as a solid in 68% yield. The origin of **67c** is not disclosed. Although the purity of many of the intermediate compounds is not reported, the ^1H and ^{13}C NMR data are provided for all compounds shown in the reaction schemes.

Advantages. The process provides a number of alternative intermediates and methods for producing the desired compound, and some steps have been demonstrated on a large scale.

■ PATENT NO. U.S. 8,101,769

Assignee: Actavis Group PTC EHF, Ireland

Title or Subject: Process for Preparing Ethyl (*S*)-2-Ethoxy-4-[*N*-[1-(2-piperidinophenyl)-3-methyl-1-butyl]aminocarbonyl methyl]benzoate and Its Use in the Preparation of Repaglinide

Repaglinide **71b** (R = H) is used in the treatment of type 2 diabetes and is a key intermediate in the preparation is **71a**. An alternative method for preparing this compound is by the condensation of **69** and **70** as shown in Scheme 23.

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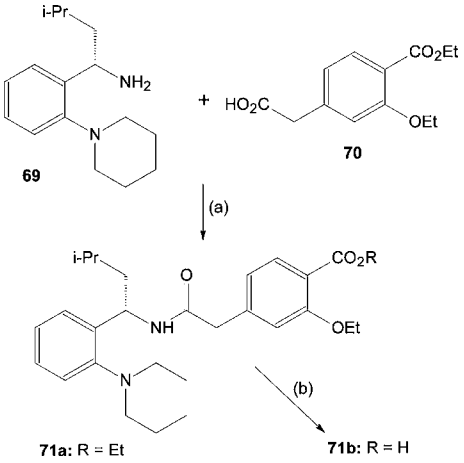
Scheme 23[a].



[a]Reagents and conditions: (a) (i) $PhOB(OH)_2$, PhMe, reflux, 18 h; (ii) filter at 25−30 °C; (iii) wash in H_2O, aq $NaHCO_3$, evaporate; (iv) add hexane, filter, 25−30 °C; (v) wash, dry at 55 °C; (b) (i) aq NaOH, MeOH, 65 °C, 3−4 h; (ii) evaporate; (iii) add H_2O, 1 M HCl to pH 6.5−7.0; (iv) stir 4 h, filter, H_2O wash, dry.

The reaction is carried out in the presence of a dehydrating agent and a base, and a number of dehydrating agents have been used. These include $SOCl_2$, $POCl_3$, P_2O_5, DCC, Ph_3P/CCl_4, Bu^tCOCl, and a number of diimidazoles. This patent claims that the purity of the **71b** that is obtained via such processes is not satisfactory, and hence an alternative method of making **71a** is required. The patent reports a surprising finding that $B(OH)_3$ or its derivatives are effective dehydrating agents in this reaction, and a base is not required. Reacting **69** and **70** and using $B(OH)_3$ gives **71a** in 73.3% yield and 99.5% purity. When $PhOB(OH)_2$ is used, the yield of **71a** is 89.6% with purity 99.7%. Subsequently, base hydrolysis gives **71b** in 83.2% yield and 99.9% purity.

The patent claims that a number of solvents can be used apart from PhMe such as DCM, DMF, and MeCN, but there are no examples of their use. It is also claimed that other esters of **70**, in addition to ethyl, are suitable, but again no examples are described.

Advantages. The process gives improved yield and purity product from the same starting materials as alternative processes.

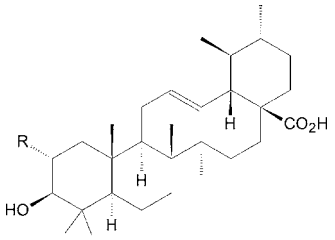
PATENT NO. U.S. 8,101,795

Assignee: Kenko Corporation, Tokyo-To and Tokiwa Phytochemical Co. Ltd., Chiba-Ken, Japan

Title or Subject: Process for Preparing High-Purity Corosolic Acid and Ursolic Acid

Corosolic acid, **72b**, can suppress the elevation of blood glucose levels and is of interest in treating diabetes. Ursolic acid, **72a**, can prevent wrinkles and help muscle growth and is used in many cosmetic preparations. Both compounds can be found in a number of plant materials; **72a** is found in basil, blueberries, cranberries, rosemary, oregano, thyme, plums, and apple peel, while **72b** is found in the leaves of the banaba tree in southern Asia. They are also both found in the leaves of the Japanese loquat or Japanese medlar, a low, evergreen fruit tree that is widely distributed in China and Japan. This patent describes a method of extracting both compounds in high purity from the leaves of this tree.

Acids



72a: R = H; ursolic acid
72b: R = OH; corosolic acid

The procedure for isolating these acids is as follows

(1) Dry and crush the leaves, then reflux in MeOH (1 kilo per 10 L).
(2) Collect liquor and add active C to remove chlorophylls.
(3) Concentrate liquid to 20% of original volume.
(4) Add H_2O and leave to form a precipitate.
(5) Filter off solid and dry.

The solid containing 12−13 wt % each of **72a** and **72b** is treated with NaOH/MeOH, and insoluble solids are removed. The filtrate is collected, and the acids are separated by Col C using a nonpolar adsorption resin such as styrene/divinylbenzene or acrylic/divinylbenzene. The claims specify HP20 (from Mitsubishi Chemical Corp.) or XAD4 (from Rohm and Haas) although only HP20 is used in the example. A mixture of TFA and MeCN is used as the mobile phase, and after the fractions are collected, they are acidified with HCl. Crystals of both acids are obtained that are said to be high purity, but analytical details are not provided. The process is claimed to be applicable to obtaining **72a** from rosemary leaves and **72b** from banaba leaves.

Advantages. The process allows for the first time the isolation of both acids from the same plant source.

PATENT NO. U.S. 8,101,804

Assignee: Clariant Specialty Fine Chemicals (France), Trosly Breuil, France

Title or Subject: Process for the Synthesis of *E*-Stilbene Derivatives as Intermediates for Resveratrol and Piceatannol

Resveratrol, **77b** (R = R_2 = H), and piceatannol, **77c** (R = OH, R_2 = H), are polyhydroxystilbenes and are of interest as antioxidants. A number of alternative syntheses of these compounds are summarised and said to be unsatisfactory for industrial use. Most of the problems are said to be because of the need for protection and deprotection steps or the necessity to separate the *E*- and *Z*-isomers. This patent discloses a novel process for producing *E*-stilbene derivatives that can be easily converted to the desired compounds without the need to separate *E*- and *Z*-isomers. The first stage of the synthesis of **77b** is outlined in Scheme 24 and begins with a Claisen condensation between the ether esters **73a** and **74**. The reaction takes place by adding a solution of **73a** to a refluxing THF solution of **74** and NaH and gives **75a**. This is recovered in crude form as a yellow oil in 89% yield and is used in the next step. A purified sample of **75a** is obtained by treating the oil with MeOH, producing a white solid that is further purified by heating in MTBE and then MeOH. The final yield of purified **75a** is about 26%. The crude oil is converted to **75b** by decarboxylation by heating with $B(OH)_3$ while distilling off volatiles. The product is recovered as an oily material that is purified by treatment in MTBE to give a cream-white solid in 54.4% yield based on **75a**.

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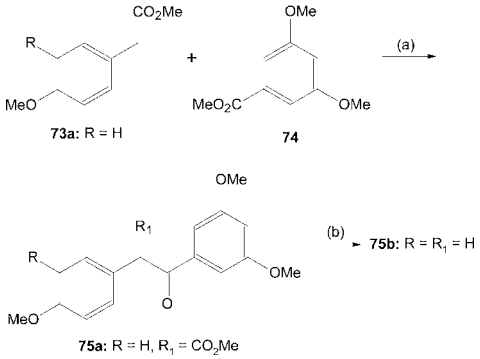
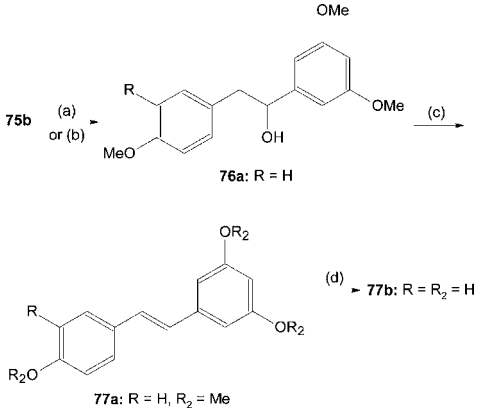
Scheme 24[a].



[a]Reagents and conditions: (a) (i) NaH, THF, reflux, 15 h; (ii) cool <5 °C, add HOAc/THF, 0.5 h; (iii) add THF at rt; (iv) distill THF; (v) extract in MTBE, wash in aq $NaHCO_3$, H_2O wash, evaporate; (b) (i) $B(OH)_3$, 100 °C, 1 h: (ii) 120 °C, 1 h; (iii) 140 °C, 1 h; (iv) 160 °C, 4 h; (v) cool to 80 °C, add H_2O + PhMe; (vi) 60 °C, 1 h; (vii) separate, wash in aq $NaHCO_3$; (viii) concentrate, add MTBE, filter, dry.

Scheme 25[a].

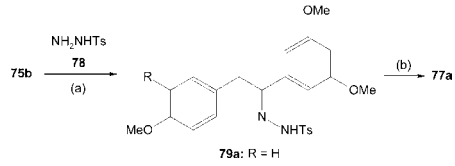


[a]Reagents and conditions: (a) (i) Pd/C, MeOH, H_2, 6 bar, rt, 10 h; (ii) filter at 40 °C; (iii) cool to rt, filter, dry; (b) (i) $NaBH_4$, MeOH/THF, rt, 2 h; (ii) evaporate, add H_2O/MeOH, (iii) filter, wash, dry; (c) (i) TsOH, PhMe, reflux, 2.5 h; (ii) cool to rt, add aq $NaHCO_3$; (iii) H_2O wash, evaporate; (iv) reflux in MeOH; (v) filter at rt, wash, dry; (d) (i) BBr_3, DCM, −20 °C, 1.5 h; (ii) rt, 4 h; (iii) add to ice/H_2O, extract in MTBE; (iv) wash in aq $NaHCO_3$ and H_2O; (v) evaporate, add DCM, filter, dry.

The conversion of **75b** to **77b** can be carried out by two routes. In the first of these, shown in Scheme 25, catalytic hydrogenation of **75b** gives the alcohol **76a** that is isolated in 88.4% yield. Reduction using $NaBH_4$ produces **76a** in virtually quantitative yield, but the product purity is not reported using either method. In the next step the alcohol is dehydrated with catalytic amount of TsOH to form **77a**. The reaction is carried out in PhMe so that the H_2O is removed azeotropically and the product is in 70% yield. In the final step **77a** is treated with BBr_3 to produce **77b**, and the crude product is isolated in 88% yield. It can be purified by crystallisation from EtOH/H_2O, but the final yield and purity are not provided.

The second method of converting **75b** to **77b** proceeds via the formation of the novel tosylhydrazone **79a** as shown in Scheme 26. First **75b** is treated with **78**, and this produces a 65.4% yield of purified **79a** although the purity is not reported. Reaction of **79a** with Bu^tOK, in the presence of a PTC such as Triton X100, results in the production of **77a** that is isolated in 58% yield after recrystallisation from MeOH. **77a** can then be converted to **77b** as in Scheme 26.

Scheme 26[a].



[a]Reagents and conditions: (a) (i) EtOH, reflux, 3 h; (ii) rt, 2 h; (iii) filter, wash in EtOH; (iv) MTBE, reflux, 2 h; (v) filter at rt, wash in MTBE; (b) (i) Bu^tOK, Triton X100, PhMe, reflux, 3 h; (ii) add H_2O at rt, separate, evaporate; (iii) add EtOH, rt, 16 h; (iv) filter, recrystallise.

The preparation of **77b** is also carried out starting from the benzyloxy analogues of **73a** and **74**, and examples describe the preparation and use of the equivalent intermediates shown in the above schemes. The preparation of piceatannol **77c** (R = OH, R_2 = H) starts from **74** and the dimethoxy ester **73b** (R = OMe) and is carried out using the procedures described above. Examples are also given for the preparation of **77c** via the benzyloxy derivatives. Although the patent does not report the purity of intermediates or final product, it does provide ^1H and ^{13}C NMR data and a sharp mp for each compound.

Advantages. The process provides a novel route to the desired compounds via a series of novel intermediates.

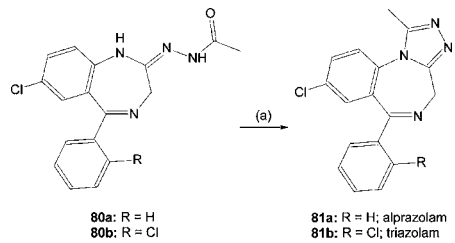
PATENT NO. U.S. 8,106,189

Assignee: Centaur Chemicals Pvt. Ltd., Mumbai, India

Title or Subject: Process for Preparation of Triazolbenzodiazepine Derivatives

The compounds covered by this patent are used in the treatment of anxiety and depression; examples are alprazolam **81a** and triazolam **81b**. There is a common step in the synthesis of these and similar compounds that involves cyclisation and formation of a triazole ring from acetyl hydrazones. An alternative method for this is described and said to give a low yield of crude product that is difficult to purify. A second method uses an expensive catalyst and $MeC(OEt)_3$ that is said to be difficult to handle on an industrial scale because it is flammable. This patent claims to provide a convenient process for the cyclisation step, and it is shown in Scheme 27. The reaction is carried out by refluxing

Scheme 27[a].

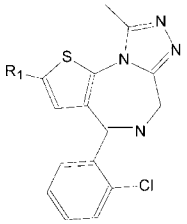


[a]Reagents and conditions: (a) (i) TsOH, PhMe, reflux, 10−12 h; (ii) 10−15 °C, 4−5 h; (iii) filter, wash in cold PhMe.

80a or **80b** in PhMe in the presence of TsOH while removing H_2O. The products are isolated in crude form and then crystallised from Pr^iOH to give **81a** in 80% yield and **81b** in 77% yield.

The patent also covers the application of the process to the preparation of the related compounds brotizolam **82a** and etizolam **82b** (see graphic next page) although there are no examples provided.

dx.doi.org/10.1021/op300071h | Org. Process Res. Dev. 2012, 16, 727−740



82a: R_1 = Br; brotizolam
82b: R_1 = Et; etizolam

Advantages. The patent claims to provide a facile cyclisation of the hydrazone using readily available and nonhazardous reagents. However, PhMe is also flammable as $MeC(OEt)_3$ and so the safety issue has not been removed, although the solvent is much less expensive.

PATENT NO. U.S. 8,106,201

Assignee: Johnson Matthey PLC, London, United Kingdom, and GlaxoSmithKline Australia Pty. Ltd., Port Fairy, Australia

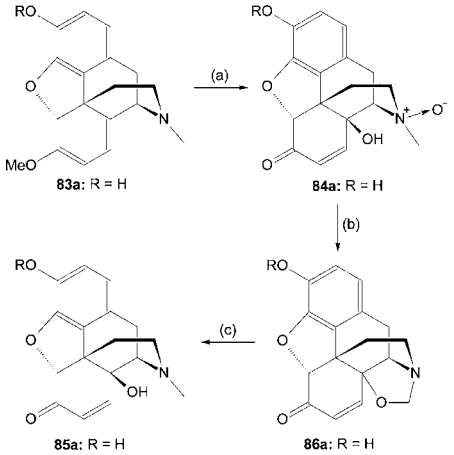
Title or Subject: Process for the Synthesis of 14-Hydroxymorphinane Compounds and Intermediates Thereof

Morphine derivatives are used as sedatives and for the treatment of severe pain. Some of the naturally occurring compounds can cause unpleasant side-effects, and so there is a great deal of interest in semi- synthetic derivatives, and a patent on this subject from another company was recently reviewed (*Org. Process Res. Dev.* **2012**, *16*, 11). A common, naturally occurring, starting material for preparing 14-hydroxymorphinanes is thebaine **83b** (R = Me). This compound contains a protected 3-hydroxy group; hence, an additional step is required to remove the protection when preparing commercially valuable materials such as naloxane and naltrexone. Hence, it is suggested that an alternative starting material is oripavine **83a** (R = H) that is also extracted from the poppy plant. Although **83a** is only recovered in low yield, it has not been commercially used, and so it is suggested that there is no shortage of this compound. Hence, it is an ideal starting material for commercial production of morphinanes. The claims of the current patent actually cover the novel compounds such as **84a** and **86a** and their synthesis, and their synthesis from **83a** is shown in Scheme 28. The first stage is formation of the *N*-oxide **84a** using H_2O_2, and the product is isolated in 80% yield. The isolation procedure is carried out by neutralisation with a base such as NaOH, ensuring that the reaction temperature reaches 55 °C. This is carried out over 2 h before recovery of the product. The next step is described as a surprising finding and involves the reduction and cyclisation of the *N*-oxide **84a** to form the novel oxazolidine **86a**. The reaction is carried out using Fe(II) salts such as $FeSO_4$ in the presence of HCO_2H. The separation of the product from the Fe salts is made easier because of the insolubility of **86a** in the acidic mixture. The product is isolated in 55%% yield, and the structure is confirmed by 2D NMR methods. Hydrolysis of **86a** using HCl gives **85a**, and this is isolated in 85% yield. The examples in the patent describes these steps being performed on a kilo scale, and hence it is clearly at an advanced stage of development.

The process is also applied to producing other oxazolidine compounds, but these are on a small scale and do not give high yields of products.

Advantages. The process provides an alternative method of making important API molecules from potentially less expensive starting materials and is clearly suitable for large-scale production.

Scheme 28[a].



83a: R = H **84a:** R = H **85a:** R = H **86a:** R = H

[a]Reagents and conditions: (a) (i) HCO_2H, EtOH; (ii) 50% H_2O_2, 20 °C, 2 h; (iii) 23% NaOH, 55 °C, over 2 h; (iv) 55 °C, 2 h; (v) filter at 15 °C, wash in H_2O, EtOH wash; (b) (i) MeOH, slurry, 5 min; (ii) $FeSO_4 \cdot 7H_2O$, stir 5 min; (iii) 85% HCO_2H; (iv) filter, MeOH wash; (c) (i) 25% NH_4OH; (ii) 30% HCl, 50 °C, (iii) add active C, 0.5 h; (iv) filter; (v) 25% NH_4OH, to pH 9.0; (vi) 50 °C, 15 h; (vii) filter <20 °C, H_2O wash.

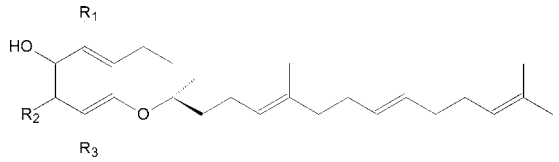
PATENT NO. U.S. 8,106,223

Assignee: Edison Pharmaceuticals Inc., Mountain View, California, U.S.A.

Title or Subject: Process for the Production of α-Tocotrienol and Derivatives

Tocotrienols (**87a–d**) are found in plant extracts such as palm oil, and there are a number of commercial extracts available that are used as dietary supplements and also are claimed to overcome hair loss. There are four naturally occurring tocotrienols designated α-, β-, γ-, and δ-, and methods used to extract these materials also extract the four related compounds known as tocopherols that contain a fully saturated side chain. In order to isolate individual compounds, it is often necessary to resort to chromatographic methods or molecular distillation processes.

Tocotrienols



87a: $R_1 = R_2 = R_3$ = Me; α-tocotrienol
87b: $R_1 = R_3$ = Me, R_2 = H; β-tocotrienol
87c: R_1 = H, $R_2 = R_3$ = Me; γ-tocotrienol
87d: $R_1 = R_2$ = H, R_3 = Me; δ-tocotrienol

This patent provides a method that minimises the use of chromatographic techniques and is said to be suitable for large-scale production of α-tocotrienol **87a**. The process begins with a sample of palm oil extract, and the patent uses a commercially available mixture known as Tocomin 50. This contains a mixture of **87a–d** plus α-tocopherol. The first stage is an aminomethylation reaction in which the aromatic H atoms in the three tocotrienols are replaced. Since both α-tocoprienol and α-tocopherol do not contain aromatic H atoms, these are unaffected. Scheme 29 outlines the reaction that occurs when **87d** is treated with paraformaldehyde and **88** to give **89d**. The reaction mixture obviously contains similar products from **87b**

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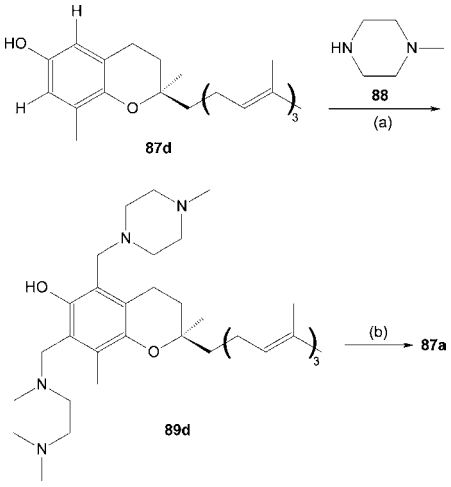
Scheme 29[a].

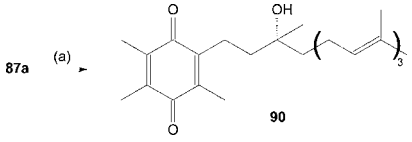


[a]Reagents and conditions: (a) (i) HCHO, rt, 0.5 h; (ii) 75 °C, 3 h; (iii) 125 °C; (iv) cool 40 °C, add MeCN/heptane; (v) cool <5 °C, add HCO_2H; (vi) recover MeCN solution, heptane wash; (vii) further extractions; (b) (i) add PhMe, exchange with 3-MeBuOH; (ii) $NaBH_3CN$, rt, 0.5 h; (iii) 125 °C, °C, 1.5 h; (iv) cool <50 °C, add heptane; (v) cool to 0 °C, add aq K_3PO_4; (vi) rt, 2 h; (vii) separate, wash in aq K_3PO_4, evaporate; (viii) add PhMe and silica gel, rt 1 h; (ix) filter, evaporate.

and **87c** and any α-tocopherol analogues that are present. This mixture of amines may be separated from the unreacted **87a** and α-tocopherol either by extraction into an acidified polar solvent ($MeCN/HCO_2H$) or by conversion to their acid salts. The patent covers the cases where **87a** and α-tocopherol are recovered at this point as well as where they are not. The first step in the workup is addition of MeCN and heptane to the reaction mixture followed by HCO_2H. The MeCN layer is then treated to a series of extractions, evaporations, and distillations using the solvents heptane, MTBE, PhMe plus a number of aqueous solutions in order to recover the amines. Space limitations preclude the inclusion of these steps, and the interested reader is encouraged to consult the patent for details. It is presumed that **87a** and α-tocopherol are extracted into the heptane solution during workup of the reduction mixture. Unless this is treated, there is obviously a significant loss of product, but the patent does not mention this. The amines in PhMe or their salts are then reduced using $NaBH_3CN$ when they all form **87a**. This step initially involves a solvent exchange of PhMe for 3-MeBuOH, and the final product is recovered by distillation. The patent provides basic ^{1}H NMR data but does not report the yield or purity of the product.

The patent also describes the preparation of the quinone **90** by oxidation of **87a** using a Ce(IV) salt as shown in Scheme 30; because the oxidation produces HNO_3, the mixture is buffered

Scheme 30[a].



[a]Reagents and conditions: (a) (i) H_2O, Pr^iOAc, 0 °C; (ii) add aq $Ce(NH_4)_2(NO_3)_6$, aq Na_2CO_3, 0 °C; (iii) add solid $NaHCO_3$ and Na_2SO_4 in Pr^iOAc, rt, 2 h; (iv) filter, wash in aq $NaHCO_3$, evaporate; (v) add heptane, Col C.

with Na_2CO_3. As before, the workup procedure is complex, and the patent should be consulted for full details. The ^{1}H NMR of the quinone is provided, but there are no purity or yield details, nor is there mention of the use of the quinone.

Advantages. This process uses an innovative procedure for removal of the unwanted tocotrienols, although whether the complexity of the workup is cost-effective for use on on industrial scale is not clear.

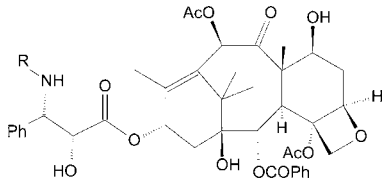
PATENT NO. U.S. 8,106,231

Assignee: Indena S.p.A., Milan, Italy

Title or Subject: Process for the Preparation of (2*R*,3*S*)-3-Phenylisoserine Methyl Ester Acetate Salt

The title compound **96b·HOAc** (R = OMe), is useful in the synthesis of taxane derivatives such as Paclitaxel **91a** and Docitaxel **91b** that are used to treat breast, ovarian, and prostate cancers. Taxanes occur naturally in the slow-growing yew tree but only in very low concentrations (<0.01 wt %); thus, their extraction is expensive. The complex structure of the taxane molecule means that synthetic routes have many steps, and industrial production is a challenge.

Taxanes



91a: paclitaxel, R = PhCO-
91b: docetaxel, R = Bu^t-OCO-

Although there are literature reports for the synthesis of **96b·HOAc**, these are said to be unsuitable for industrial-scale production. The focus of this patent is the synthesis of **96b·HOAc** by the route outlined in Scheme 31 although the patent claims only cover the last step of this route, its preparation from the amide **96a**. The amide is prepared by a literature method and begins with base-catalysed condensation of **92** and **93** followed by treatment with HBr to form **94** as the racemate. After an extensive workup this is isolated in 45% yield and then converted to the *cis*-glycidic ester **95** by treatment with Na_2CO_3. The ester is recovered as an oil in 88% yield and converted to the amide **96a** by reaction with NH_3. The product is the racemic threo compound that is then resolved via formation of the L(−)-dibenzoyltartrate salt **96a·LDBTA**. This salt is converted to the HCl salt **96a·HCl** that is isolated in 82% yield and then reacted with MeOH to give the ester **96b**. The ester is treated with HOAc and isolated as the salt **96b·HOAc** in 87% yield. The fate of the unwanted isomer during the resolution step is not disclosed.

The patent provides basic ^{1}H NMR data for the intermediates shown in the scheme although purity details are not reported.

Advantages. The process provides an efficient method of producing the desired isomer.

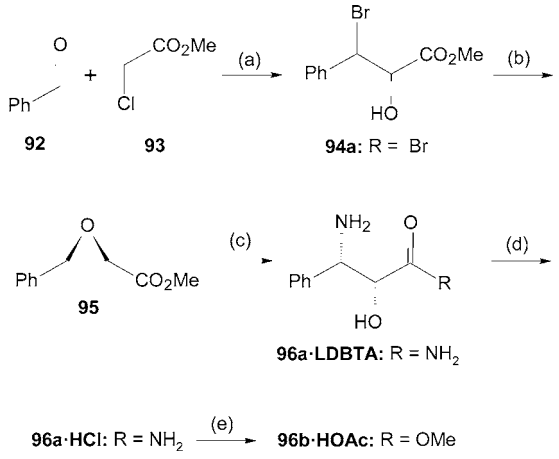
PATENT NO. U.S. 8,106, 242

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

Title or Subject: Process for Production of Compounds via Hazardous Intermediates in a Series of Microreactors

The use of microreactors is now commonplace for the rapid screening of reactions and catalysts. It is also under

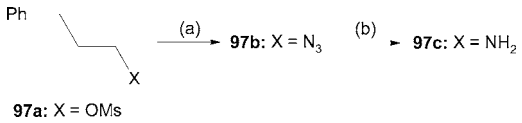
Scheme 31[a].



[a]Reagents and conditions: (a) (i) NaOMe, MeOH, 0 °C, 3 h; (ii) 22 °C, 2 h; (iii) add HOAc, PhMe, H_2O; (iv) separate, distill H_2O/MeOH; (v) add HBr, 25 °C, 4 h: (vi) aq $NaHCO_3$, 25 °C; (vii) separate, add PhMe; (viii) distill PhMe/H_2O; (ix) cool 20 °C, add PhMe, heptane; (x) seed, cool 0 °C, 3 h; (xi) filter, heptane wash, dry; (b) (i) aq Na_2CO_3, 50 °C, 2 h; (ii) add PhMe, separate at rt; (iii) H_2O wash, evaporate; (c) (i) NH_3, MeOH, 25 °C; (ii) 60 °C, 18 h; (iii) 10 °C, 1 h; (iv) filter, MeOH wash, dry, 55 °C; (v) LDBTA, EtOH, reflux, 2 h; (vi) rt, 1 h; (vii) filter EtOH wash, dry 50 °C; (d) (i) concd HCl, EtOH, 45 °C; (ii) cool 0 °C, 2 h; (iii) filter, EtOH wash, dry 80 °C; (e) (i) HCl gas, MeOH, 25 °C; (ii) reflux 3 h; (iii) distill MeOH; (iv) add EtOAc at rt; (v) Et_3N, 25 °C; (vi) distill, add EtOAc; (vii) filter at 50 °C, EtOAc wash; (viii) add HOAc at 40 °C; (ix) 0 °C, 2 h; (x) filter, EtOAc wash, dry 50 °C.

investigation for commercial production of small and medium quantities of high-value products. The major advantage of such methods is that they minimise the inventory of the hazardous reagent, maximise heat transfer, and hence reduce potential safety issues. This patent describes the use of continuous flow microreactors for producing compounds via a number of hazardous intermediates such as azides or peroxo compounds. Scheme 32 shows the preparation of the amine **97c** via the

Scheme 32[a].

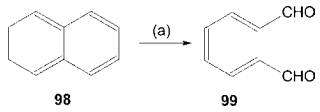


[a]Reagents and conditions: (a) NaN_3, NMP, rt; (b) NMP, Pd/Al_2O_3, H_2, 1 bar, 26 °C.

azide **97b** that is obtained by reaction the mesyl ester **97a** with NaN_3. The reaction is carried out by pumping a 3.45 wt % aq solution of NaN_3 into a T-piece where it mixes with a 6.33 wt % solution of **97a** in NMP. The mixture then passes through a 21.6-m-long tubular microreactor of diameter 0.35 mm with residence time of 2.5 min. A sample collected between 0.5 and 1 h contained 2.2 wt % of **97b** and 0.22 mol % **97a**, corresponding to a 95% conversion of **97a** with 76% selectivity to **97b**. This mixture was diluted with NMP to 0.93 wt % **97b** and hydrogenated in a 0.5 m tubular microreactor of 0.53 mm diameter coated with a layer of Pd/Al_2O_3 as catalyst. The effluent from the reactor contained 0.48 wt % **97b** and 0.42 wt % of **97c**, corresponding to 48% conversion of **97b** and 100% selectivity to **97c**.

The patent also describes the ozonolysis of naphthalene **98** to give **99** as shown in Scheme 33. The reaction is carried out

Scheme 33[a].

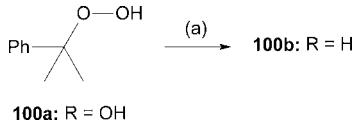


[a]Reagents and conditions: (a) O_2/O_3, 5% MeOH in BuOAc,

in what is described as a falling film microreactor that is 75 mm long and has a holdup of 13.6 mL. With a flow of 2 g/min of 2 wt % of **96** in the solvent, a conversion of 52.1% was achieved, and the selectivity to **99** was 95.8% at 49.9% yield.

A third example in the patent is the hydrogenation of the hydroperoxide **100a** to give the alcohol **100b** as shown in Scheme 34. A 1.035 wt % solution of **100a** in EtOH is passed

Scheme 34[a].



[a]Reagents and conditions: (a) EtOH, Pd/Al_2O_3, H_2, 1 bar, 22 °C.

through the hydrogenation reactor used in Scheme 33 at a rate of 0.25 mL/min. The liquid flows through the reactor as slugs of liquid, and the effluent showed 73% conversion of **100a** with >99% selectivity to **100b**. The hydroperoxide **100a** is an intermediate in the production of PhOH and Me_2CO, and this process is carried out on a huge scale so that **100b** could be produced from a readily available chemical.

The patent discusses the application of this method to reactions of organic compounds such as alkenes or dienes with peroxides, hydroperoxides, or singlet oxygen to give an intermediate that is then hydrogenated to give an aldehyde, alcohol, or ketone.

Advantages. The process allows the production of hazardous intermediates that can be safely converted to stable organic compounds, at least on a small scale.

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