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 August and September 2011

SUMMARY

The current selection of patents contains 21 from an initial list of 316. During the period covering the publication of these patents there were two significant events relating to U.S. Patents. One was the publication of patent number 8,000,000, and the second, and more important, was the change in the law covering priority in U.S. Patents. From March 2013 changes in the U.S. law mean that priority is given to the inventor who is first to file a patent rather than the person who is first to invent. These changes mean that the U.S. Patent system is more in line with the rest of the world. Definitions relating to prior disclosure are also changing, and those readers who are active in both publishing papers and filing patents should seek legal advice on how these changes will affect them. The current crop of patents covers a wide range of topics and includes several that provide little evidence for the claims made. An example is a process for preparing pemetrexel, a chemotherapy drug that is usually given to treat non-small-cell lung cancers. The patent describes a new process for an intermediate, but the yield is very poor, and there are no details of the purity and yield of the final product made using the intermediate. Another patent describes a new method of preparing ezetimibe, a drug used to reduce blood cholesterol levels. This patent is also lacking in purity and yield details of intermediates and final product. Yet another patent with no details discloses a process for the preparation of a molecule for treating hepatitis C virus. There is no experimental information, and yet the patent claims cover a number of novel intermediates. A process for preparing hydroxytyrosol, a constituent of olive oil, claims to give high yields of product but contains no details of how to recover the product. In addition, the yields of some of the intermediate steps seem to be too low for the process to be commercially viable. Derivatives of the antihistamine terfenadine are of interest since the parent drug was withdrawn in the 1990s because of serious side effects. A method for preparing the derivative compounds is described without giving crucial purity or yield information. A process for preparing vinylene carbonate involves the formation of an intermediate formed by a chlorination step carried out under UV irradiation. The procedure gives fewer byproducts, and the final product is claimed to be recoverable in pure form without crystallisation although no evidence is supplied. Patents often claim that a new process is environmentally friendly or avoids using a particular toxic reagent. An example is a process for the synthesis of cloretazine; an alkylating agent that is under investigation for the treatment of high-grade brain tumours. An older method uses methyl isocyanate that is as well-known as highly toxic material. The new process avoids using this reagent, but the synthesis uses phosgene and hydroxyhydrazine, both of which are highly toxic. Rivastigmine is used to treat dementia caused by Alzheimer's or Parkinson diseases, and a new process is described that claims to be environmentally friendly yet uses a considerable number of solvents in the product workup. A process for preparing the powerful semisynthetic opioid analgesic oxymorphone includes the use of dichloroethane that would not be acceptable in many establishments. Liquid thiophenes, used in the production of conductive organic polymers, are required with very high purity. Most impurities are coloured, and a simple method for the purification of these compounds is described. Cefixime is a cephalosporin antibiotic, and its purification can be difficult because of coloured impurities. An improved synthesis gives high purity product by control of temperature in an acidification step during workup. A novel polymorph of a pyrazolopyrimidine compound, used to treat sleep disorders, is described that is more stable than the originally reported form. Another patent covers novel polymorphs of eltrombopag, a compound used to treat conditions that lead to abnormally low platelet counts. Sixteen novel polymorphs are described including one that is stable and suitable for use in drug formulations. Modifying the habit of crystals may be desirable to improve their recovery, but it is often a difficult procedure. A process is described for changing the habit of acicular crystals of mycophenolic acid or its Na salt. The method involves changing the temperature of a solution by oscillating up and down about a mean. In so doing the bulk density of the crystals is increased. Ionic liquids are being used in a wide range of applications, and alkali tricyanomethanides are such materials that are used in rechargeable batteries. The materials have a low limit on halide content, and the new process provides very pure products. A highly regioselective process for preparing trifluoro-5-(iodo or bromo)-benzoic acids is described, and the patent points out some key factors for carrying out the process. The acids are used to prepare an unspecified anticancer agent. Protection of ω-amine groups in α-ω-amino acids is often required, and a patent describes a method to indirectly introduce the protective BOC group by using a benzotriazole. The patent also describes subsequent protection of the second amine group. Coelenteramide is an intermediate for the synthesis of green fluorescent protein that is partly responsible for bioluminescence in marine animals. A patent describes how this intermediate can be made, but there are significant losses on purification. A very comprehensive patent covers a process for the preparation of a tetrahydropyran carboxylic acid. The process does not require purification or isolation of intermediates, and the compound is used to produce an alkaloid used in chemotherapy treatment. The opiate (−)-bupreonorphine is used to treat heroin addiction and has different bioactivity from that of the (+)-enantiomer. A patent reports on a high-yield synthesis of the (+)-enantiomer in high purity so that its bioactivity can be explored. The *R*-enantiomer of tamsulosin is available as Flomax for the treatment of an enlarged prostate, and a selective method for the synthesis of the isomer is described that gives a high yield. A number of the

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patents in this collection describe experiments carried out on a kilo or multikilo scale, therefore suggesting an advanced stage of development or even commercial operation. However, there is no legal or commercial significance in the choice of patents in this review. The advantages mentioned in this review are those claimed in the patent, unless this reviewer has personal knowledge of the subject.

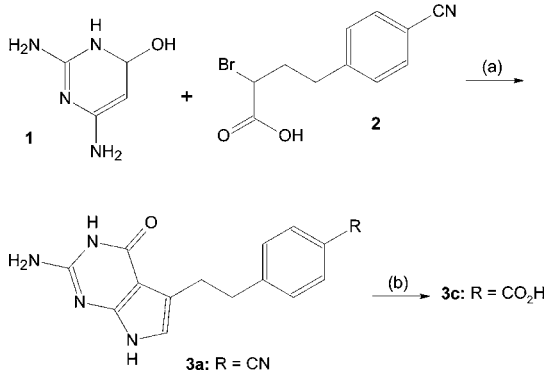
PATENT NO. U.S. 7,994,180

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

Title or Subject: Processes for Preparing Intermediates of Pemetrexed

The disodium heptahydrate salt of pemetrexed **8c** is available as Altima, a chemotherapy drug that is usually given to treat non-small-cell lung cancers and pleural mesothelioma. Various methods for the synthesis of **8c** are reviewed, and a key intermediate in these routes is **3c** (R = CO_2H). The patent states that there is a need for a concise process for the synthesis of **3c**, and this is the subject of the patent. The claims of this patent actually cover the novel compound **3a** that can be prepared by the route shown in Scheme 1 and then converted

Scheme 1. [a]

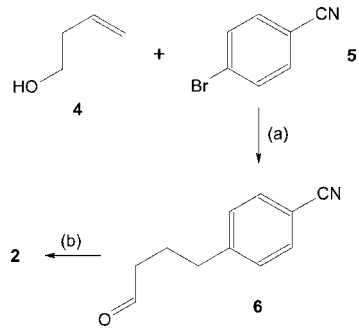


[a]Reagents and conditions: (a) (i) NaOAc, H_2O, DCM, 40 °C, 2 h; (ii) stir, 24 °C, 42 h; (iii) stand, 24 °C, 2 h; (iv) filter, wash, dry; (b) (i) 2 M NaOH, 90 °C, 3 h; (ii) 24 °C, 1.5 h; (iii) dil HCl to pH 9, 24 °C, 1 h; (iv) filter, dry.

to **3c**. Condensation of **1** with **2** in the presence of NaOAc produces **3a** that is isolated in a very poor yield of around 15% based on **1** at 95.8% purity (HPLC). The nitrile is then treated with NaOH to give the Na salt **3b** that is isolated in 80.8% yield and 99.6% purity. The Na salt is then converted to the free acid **3c** that is isolated in 99.6% purity, but no yield is reported. The patent mentions that the nitrile **3a** can be obtained in crystalline form and hence is more useful in the preparation of **3c** compared to other routes that do not produce crystalline intermediates.

The preparation of the starting material **2** is described in the patent and outlined in Scheme 2. The bromonitrile **5** is reacted with **4** in a Heck-coupling reaction to give the aldehyde **6**. The reaction is monitored by HPLC and **6** is isolated as a concentrated solution in EtOAc. The solution is evaporated to remove the solvent, and this is replaced by MeCN. The solution of **6** in MeCN is treated with Br_2, the reaction quenched with $NaHSO_3$, and the product recovered as a solution in DCM that is used without further purification in the production of **3a**.

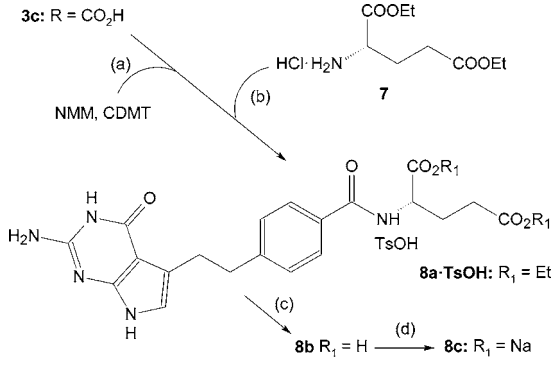
Scheme 2. [a]



[a]Reagents and conditions: (a) (i) LiOAc, LiCl, Bu^n_4NCl, DMF, degas, rt; (ii) $Pd(OAc)_2$, 65 °C, 17 h; (iii) cool 25 °C, add H_2O, EtOAc; (iv) separate, wash, concentrate, 37 °C; (b) (i) evaporate, add MeCN; (ii) Br_2, 5 °C; (iii) rt, 2 h; (iv) add $NaHSO_3/H_2O$, rt, 1 h; (v) extract in DCM, wash, concentrate.

The preparation of **8c** from the acid **3c** or its Na salt **3b** (R = Na) is described and based on details from U.S. 6,262,262. The route is shown in Scheme 3 and begins with the preparation

Scheme 3. [a]



[a]Reagents and conditions: (a) (i) DMF, rt, 20 min; (ii) NMM; (iii) CDMT, 5 °C, 1 h; (b) (i) 5 °C; (ii) rt, 1 h; (iii) H_2O, DCM, 0.25 h; (iv) separate, concentrate; (v) TsOH, EtOH, reflux, 1 h; (vi) cool to rt, filter, dry, wash, dry; (c) (i) aq NaOH; (ii) H_2O, dil HCl to pH 3, rt; (iii) 70 °C, 1 h; (iv) filter; (d) (i) H_2O, aq NaOH; (ii) 1 M HCl to pH 8; (iii) EtOH, 70 °C; (iv) cool to rt, filter, wash, dry at 50 °C, 18 h.

of TsOH salt of the diethyl L-glutamate derivative, **8a·TsOH**. This is produced by reaction of **3c** and **7** in the presence of *N*-methylmorpholine (NMM) and chlorodimethoxytriazine (CDMT). The reaction is carried out by adding CDMT to a DMF solution of **3c** and NMM, and after 1 h **7** is added. The salt **8a·TsOH** is obtained by refluxing a EtOH solution of **8a** with TsOH, and the product is recovered in % yield, but the purity is not reported. The free acid **8b** is then prepared by treatment with aq NaOH and dil HCl, and this is isolated in 99.6% purity, but the yield is not reported. The disodium salt **8c** is produced by treating **8b** with aq NaOH followed by dil HCl; the product is isolated as a white solid, but neither the yield nor purity is reported.

Advantages. The patent claims an improved process for a key intermediate, but the reported yield is very poor. In the subsequent steps using this intermediate the patent fails to report yield and purity details so that the process efficiency cannot be assessed.

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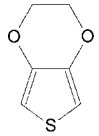
PATENT NO. U.S. 7,994,345

Assignee: H. C. Starck GmbH, Leverkusen, Germany

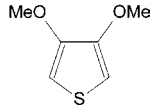
Title or Subject: Process for Purification of Thiophenes

The patent reports a method for purifying liquid thiophenes that are used in the production of conductive organic polymers. The polymers are used in printed circuit boards and other electronic devices, and the presence of impurities cause yellow to brown colour and give problems in the polymerisation process. In addition, the polymers obtained may have reduced conductivity or be coloured. For some applications high transparency is required, hence the need to have high-purity monomers. The desired thiophene compounds are generally liquids at rt, and purification by distillation, melt crystallisation, or chromatographic methods are said to be unsuitable for the production of products with the required high purity. The method disclosed in this patent is applied to materials that have an initial purity of 70% or more. The examples in the patent describe the purification of **9** that contains 0.3% of **10** as an undesired impurity. The procedure is to dissolve the impure thiophene in EtOH that is then cooled to a temperature of at least 20 °C below the melting point of the thiophene. In the case of **9** the solution is cooled to −15 °C for 3 h, and the mixture is filtered to recover the precipitated thiophene **9**. This solid is then warmed to rt and then distilled under reduced pressure of 12−16 hPa (9−12 mmHg). The product is a colourless liquid that contains no detectable amount of **10**. One example described the purification of **9** with 98.4% purity containing 0.3% **10**, and the product is recovered in 76% yield with 100% purity. A second example starts from **9** with 70% purity containing 0.3% **10** ,and 99.2% pure **9** is recovered in 55% yield containing no **10**.

Thiophenes



9



10

Several other compounds structurally similar to **10** are mentioned in the patent, but the only examples relate to **9** containing **10**.

Advantages. The process gives very high purity product using a simple procedure.

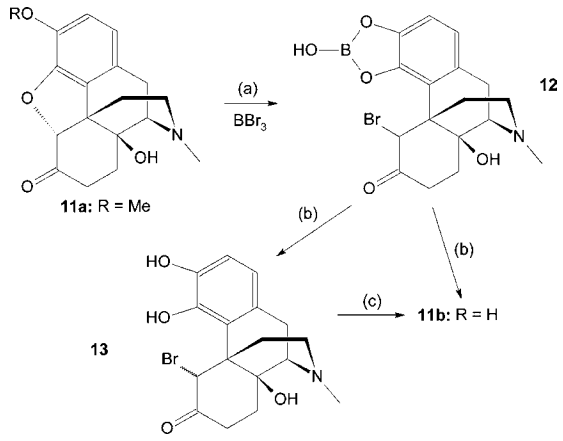
PATENT NO. U.S. 7,999,105

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

Title or Subject: Process for the Preparation of 3-Hydroxymorphinan Derivatives

The subject of the patent is **11b** (R = H, oxymorphone), a powerful semisynthetic opioid analgesic that is used to relieve moderate to severe pain and also as a preoperative medication. **11b** was first developed ca. 1914 and is usually prepared by O-demethylation of oxycodone **11a** (R = Me). Patents on the purification of **11b** were reviewed recently (*Org. Process Res. Dev.* **2011**, *15*, 491), whereas the current patent reports on improving the synthesis of **11b** by converting reaction byproducts to **11b**. Scheme 4 outlines the synthesis of **11b** that starts with the demethylation of **11a** by treatment with BBr_3. The reaction proceeds via boron compounds such as **12** that are the subject of some of the patent claims. The acid hydrolysis of **12** using dil H_3PO_4 gives **11b** and also produces the dihydroxy compound **13**, of which there are a number of

Scheme 4. [a]



[a]Reagents and conditions: (a) (i) PhCl, <25 °C, 14 h; (ii) H_2O, 55 °C; (b) (i) 5 wt % H_3PO_4 in H_2O, 65 °C; (ii) extract/wash with DCE; (c) (i) 50% aq NaOH to pH 2.6, 80 °C, 2 h; (ii) cool rt.

isomers. The hydrolysis of **12** is said to decrease the pH of the reaction mixture to <0, and if this mixture is heated, decomposition of **11b** and **13** takes place, thus reducing yield. This can be avoided by adding base to increase the pH >5 and then heating when it has been found that **13** can be hydrolysed to **11b**, thus improving the reaction yield. However, raising the pH to >7 also causes decomposition, and hence the control of the pH of the hydrolysis is critical. After reacting **11a** and BBr_3 the procedure involves a number of extracting and washing steps with material being transferred back and forth between two reactors for extractions and washings. Space limitations preclude the inclusion of the details, and the interested reader should consult the patent. It should be noted that the extractions include the use of dichloroethane (DCE) which would not be acceptable in many locations. The crude **11b** contains around 2% of **13**.

A series of experiments is described that study the effect of pH on **11b** yield. The experiments are only carried out on semimicro scale and use NaH_2PO_4/NaOH to adjust the pH. The data are presented as area % of the **11b** peak vs pH and show that, as pH increases from 0 to 2.6, the area % of **11b** rises and then falls as the pH increases to 5.2 and the area % of peaks from decomposed materials rises. At pH 9 the area % falls, but there are no data between pH 5.2 and 9.

Advantages. The process does have the potential for improved product yield but control of pH on a large scale can be a problem; thus, the scale-up of this process may present some difficulties.

PATENT NO. U.S. 8,008,478

Assignee: Lupin Limited, Mumbai, India

Title or Subject: Process for the Preparation of Cefixime

Cefixime **16** is a cephalosporin antibiotic, and this patent describes a method of preparing **16** that has improved colour and solubility. Several alternative processes for preparing **16** are mentioned, and these are said to suffer from low yield and give poor quality material or require the use of chromatographic methods to purify the product. The method is shown in Scheme 5 and involves the condensation of **14** with **15** in water under slightly acidic conditions (pH 5.7) that are achieved by adding $NaHCO_3$. After completion of the reaction the mixture is treated with active C and $(NaO_2S)_2$. After filtering, the

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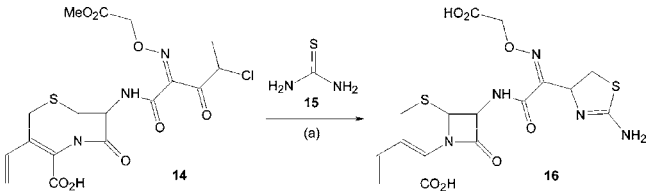
Scheme 5. [a]



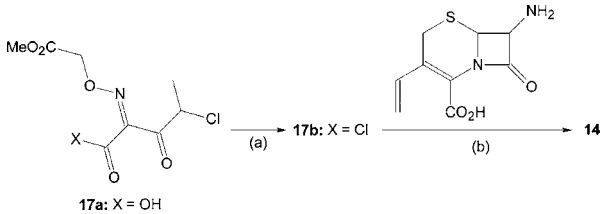
[a]Reagents and conditions (a) (i) H_2O, 10 °C; (ii) 10% aq $NaHCO_3$ to pH 5.7, <15 °C; (iii) add **15**, 32 °C, 2 h; (iv) active C, $(NaO_2S)_2$, 10 min, filter; (v) heat to 65 °C, add 17% HCl to pH 2.2, 0.5 h; (vi) filter, hot water wash; (vii) NaOH, H_2O, 2 °C, 5 min; (viii) 17% HCl to pH 5.1; (ix) active C, EDTA, 5 °C, 0.5 h, filter; (x) Me_2CO, 17% HCl to pH 2.3, 35 °C; (xi) seed, 30 °C, 16 h; (xii) Cool, 5 °C, 3 h, filter, wash dry.

solution is acidified, and the methyl ester of **16** is isolated and then hydrolysed with NaOH to give crude **16**. This is purified by treatment with active C and EDTA, and after filtration the product is precipitated by adding Me_2CO to give **16** in 28.4% % yield with purity of 99.76%.

The patent provides evidence that the final purity and colour of the isolated product is dependent upon the temperature of the initial acidification in step (v) of the workup. When this is carried out at 25−30 °C, the purity of **16** is 98.81%; a solution of 3% of **16** in MeOH is described as hazy, and the transmittance at 650 nm is not reported. As the acidification temperature is increased, the product quality improves, and at 65−67 °C the purity of **16** is 99.78% with the MeOH solution being described as clear with transmittance at 650 nm of 97.5−98.5%.

The patent outlines the method of preparing **14**, and this is shown in Scheme 6, but there are no experimental details.

Scheme 6. [a]



[a]Reagents and conditions (a) PCl_5, DCM; (b) NMM, DCM.

Advantages. The process gives high purity product, but the yield seems to be quite poor.

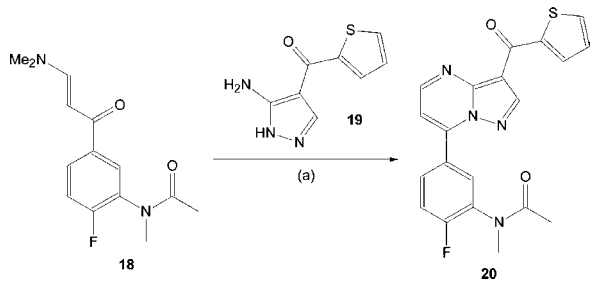
PATENT NO. U.S. 8,008,486

Assignee: Ferrer International S.A., Barcelona, Spain

Title or Subject: Process for the Manufacture of a Crystalline Pyrazolo[1,5-*a*]Pyrimidine Compound

The patent reports a method for the industrial manufacture of polymorph B of **20** that is used to treat sleep disorders, anxiety, or epilepsy. The original preparation of **20** is reported in a 2006 patent, EP 1,899,343, by the same assignee and produces polymorph A. The patent example describes the production of >12 kg of **20** by reaction of **18** and **19** in HOAc (Scheme 7). After reaction the product is precipitated by addition of Pr^iOH, and the product is isolated in 85% yield and 95% purity. It is not reported that this material is further

Scheme 7. [a]



[a]Reagents and conditions: (a) (i) HOAc, 120 °C, 4 h; (ii) cool <70 °C, add Pr^iOH; (iii) cool <45 °C, age 1 h; (iv) cool to <5 °C, over 2.5 h; (v) age 2 h at <5 °C; (vi) filter, wash (× 2) in cold Pr^iOH; (vii) dry in vacuo, 50 °C.

purified, and it is not known if the XRD, FT-Raman, and DSC spectra that are provided are of the crude or purified material.

The patent states that polymorph B is more stable than polymorph A, but no data are provided. It is claimed that B can therefore be handled more conveniently and formulated drugs have greater stability over time.

Advantages. The process gives a new polymorph in high yield and claims to give constant purity product; since it has been scaled up, it seems to be commercially viable.

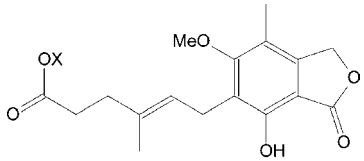
PATENT NO. U.S. 8,008,511

Assignee: Novartis AG, Basel, Switzerland

Title or Subject: Process for Modifying Drug Crystal Formation

This patent is actually only concerned with modifying the crystal habit of acicular crystals of mycophenolic acid **21a** or its Na salt **21b** despite the wide ranging title. The acid and Na salts are immunosuppresants that are said to be useful to treat a variety of problems. It is well known that acicular or needle-shaped crystals are very difficult to handle and are generally not preferred when preparing formulated drug products. Changing the crystal habit is therefore desirable but not always possible. The procedure employed in this patent is to suspend the crystals of **21b** that have been obtained from Pr^iOH in a 95:5 $MeOH/H_2O$ mixture and that vary the temperature repeatedly. The temperature is varied about a mean of 44 °C with an amplitude of ±6 °C. The time for one complete cycle or temperature oscillation is 110 min. Thus, the temperature is controlled such that it varies with time in a zigzag manner. The product is recovered by adding EtOH, cooling the suspension to 0 °C, filtering, and drying. By increasing the number of oscillations the crystal habit is changed, and the bulk density increases with time. The initial bulk density was 180−200 kg/m^3, and after five oscillations the bulk density increased to 280 kg/m^3; after 10 this had increased to 380 kg/m^3; after a total of 16 oscillations the density increased to 490 kg/m^3 kg.

Mycophenolic Acid



21a: X = H
21b: X = Na

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The patent also reports on changing the crystal habit of the Na salt **21b** by using the same technique. Using oscillations of 160 min and the same temperature variations a final bulk density of 350 kg/m^3 was achieved after eight oscillations. The patent includes several XRD patterns for various crystals including anhydrous and hydrated forms of the Na salt.

Advantages. The procedure changes the crystal habit and increases the handling properties of the compounds.

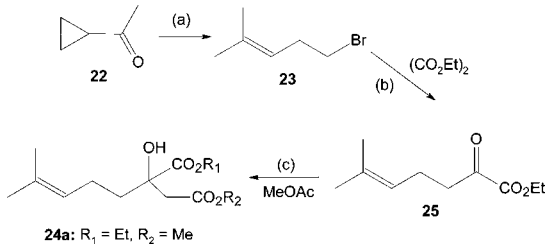
PATENT NO. U.S. 8,008,514

Assignee: Erregierre S.p.A., S. Paolo D'Aragon, Italy

Title or Subject: Process for Preparing 2-Methoxycarbonylmethyl-6,6-dimethyl-2-tetrahydropyran Carboxylic Acid

The title compound **25b** is a key intermediate in the synthesis of an alkaloid used in chemotherapy treatment. An alternative process for preparing **25b** produces significant byproducts, and in the final reaction step there are large quantities of an unreacted acid intermediate. This results in a need for extensive purification by chromatography; because of this it is claimed that the process is not industrially viable. The current patent reports a finding that is said to overcome these drawbacks and provides a commercially attractive process. The multistep process has been divided into two parts; for clarity most of the workup details are omitted. The first part of the process, shown in Scheme 8, begins with the preparation of the

Scheme 8. [a]

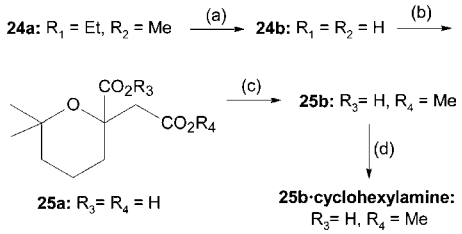


[a]Reagents and conditions: (a) (i) MeMgBr, THF, 35 °C, 1 h; (ii) 35% H_2SO_4, <10 °C, (b) (i) Mg, THF, reflux, 1.75 h; (ii) cool to −70 °C, add $(CO_2Et)_2$, 1 h; (iii) 32% HCl, H_2O, <10 °C; (c) (i) LDA, THF, −80 °C, 0.5 h; (ii) 32% HCl, H_2O, <10 °C.

bromopentene **23** by a Grignard reaction of the ketone **22**. The product is recovered as an oily residue in 77% yield and then dissolved in THF solution for use directly in the next step. In this step **23** is converted to the Grignard and then reacted with $(CO_2Et)_2$ to form **25**. This is also recovered as an oil that is dissolved in THF, and the solution used for the next step where it is added to a mixture of LDA and MeOAc in THF at −80 °C. The product **24a** is recovered as an oily residue that is dissolved in MeOH and used in the next stage.

Scheme 9 outlines the next stage, and in the first step the diester **24a** is hydrolysed under basic conditions to give the diacid **24b**. This is not initially recovered but is first converted to the cyclohexylamine salt as a means of purification. The salt recovered by centrifuge and treated with NaOH to release the diacid that is isolated as a solution in EtOAc with an overall yield of 37.7% from **23**. The solution of **24b** is then treated with HCO_2H to effect the cyclisation and formation of **25a**. This is recovered as an oily residue and purified by dissolution in EtOAc and then washed in water. After phase separation and removal of solvent, the purified **25a** is recovered as another oil that is dissolved in MeOH, and the solution is used for the next

Scheme 9. [a]



[a]Reagents and conditions: (a) (i) KOH, H_2O, 30 °C; (ii) reflux, 0.5 h; (iii) cool to <30 °C, add DCM, separate, discard organic phase; (iv) add 32% HCl, THF, <30 °C, (v) discard aq phase; (vi) add Bu^{s}OH, heat to 60 °C; (vii) add cyclohexylamine, centrifuge; (viii) 30% NaOH, DCM, H_2O, 25 °C; (ix) 32% HCl, EtOAc, 25 °C; (x) separate, discard aq phase; (b) (i) 99% HCO_2H, <30 °C; (ii) 75 °C, 4 h; (iii) cool 55 °C, evaporate; (iv) add EtOAc, H_2O wash, separate, evaporate, add MeOH; (c) (i) 96% H_2SO_4, 30 °C, 6 h; (ii) $KHCO_3$, H_2O, <10 °C; (iii) distill solvent, add DCM, 30 °C; (iv) separate, discard organic phase; (v) add DCM, 85% H_3PO_4, <35 °C; (vi) separate, discard aq phase; (vii) evaporate; (d) (i) add MeOAc, cyclohexylamine, 30 °C; (ii) stand 0.5 h; (iii) centrifuge, wash in MeOAc, dry.

stage. To this solution is added 96% H_2SO_4 to catalyse the esterification of **25a**, forming **25b**. The product is initially obtained as an oil that is converted to the cyclohexylamine salt and isolated as a solid with purity of >95% and a yield of 46% based on **24b**.

A key aspect of the process is that there is no need to isolate most of the intermediates apart from **24b**. Although the route uses the same reaction steps as the alternative method, one major change is the use of LDA in the conversion of **25** to **24b**. The alternative process uses LHMDS, and by using LDA it is not necessary to purify the intermediate. There are some quite specific claims in the patent relating to the solvents used in different steps, and the interested reader is encouraged to consult the patent.

Advantages. The process does not require isolation of most intermediates, and all of the steps describe experiments that are carried out on a multikilo scale, thus indicating the advanced commercial status of the process.

PATENT NO. U.S. 8,013,150

Assignee: MSN Laboratories Ltd., Andhra Pradesh, India

Title or Subject: Process for the Preparation of Ezetimibe

Ezetimibe, **34b**, is used to reduce high cholesterol levels in the blood. The current patent discusses a 1998 patent covering an alternative synthesis of **34b** that is claimed to be uneconomical but does not refer to a more recent one that has been reviewed previously in this journal (*Org. Process Res. Dev.* **2009**, *13*, 1046). The 1998 patent is said to have poor reproducibility and gives byproducts and wastes such as Ph_3PO, and it is claimed that the process is not suitable for commercial production. The current patent offers a process to produce **34b** that is said to be eco-friendly and commercially viable. The multistep process has been divided into sections for clarity, and the first part, outlined in Scheme 10, starts by by reaction of **26** with MeOH in the presence of NaOMe, forming the monoester **27** that is isolated in 97% yield and then used directly in a reaction with **28** to form the ketone **29**. The reaction is carried out in the presence of Bu^{t}COCl and Et_3N, and **29** is obtained in 55% yield after crystallisation from pet-ether. The ketone is then condensed with the imine **31** in the presence of a Lewis

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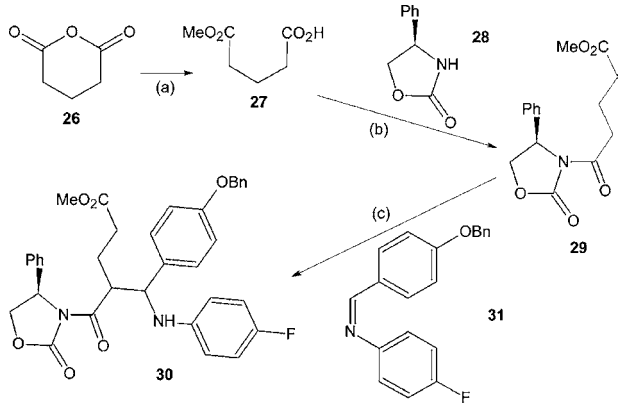
Scheme 10. [a]

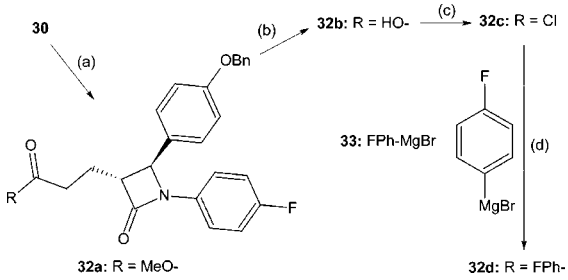


[a]Reagents and conditions: (a) NaOMe, MeOH, 35 °C, 6 h; (b) (i) Et_3N, DCM, rt, 10 min; (ii) Bu^tCOCl, 35 °C, 2.75 h; (iii) add **28**, DMAP, DMF, reflux 7 h; (c) (i) $TiCl_4$, $Ti(OPr^i)_4$, DCM, <5 °C, 0.25 h; (ii) DIPEA, −15 °C, 0.75 h; (iii) add **31**, −15 °C, 4 h.

acid to form the amide **30** that is isolated in 65% yield after recrystallisation from MeOH.

In the next stage of the process **30** undergoes a cyclisation reaction by treatment with a silylating agent and a F^- ion catalyst to form the lactam **32a** that is isolated in 71.5% yield (purity not reported). Treatment of **32a** with NaOH produces **32b** that is recovered in a yield of 91% and used without purification in the next step. The crude **32b** is converted to the acid chloride **32c** by reaction with $(COCl)_2$ in the presence of DMF. In the next step crude **32c** is condensed with the Grignard **33** to produce **32d** (Scheme 11). The reaction is

Scheme 11. [a]

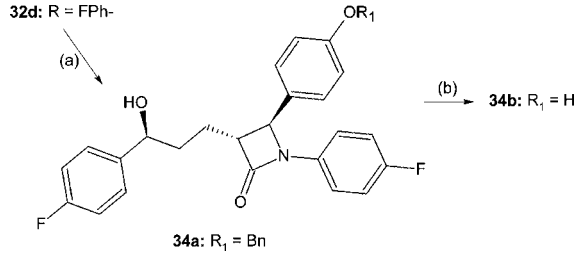


[a]Reagents and conditions: (a) (i) PhMe, 45 °C; (ii) add BSA, $Bu^n_4F{\cdot}3H_2O$, 45 °C, 2 h; (b) NaOH, Me_2CO, rt, 3 h; (c) $(COCl)_2$/DMF, rt, 3 h, evaporate; (d) (i) $Pd(OAc)_2$, PhMe, 10 °C, 0.25 h; (ii) $ZnCl_2$, rt, 0.75 h.

carried out in the presence of $Pd(OAc)_2$ and $ZnCl_2$, and the product is isolated after treatment with silica gel in cyclohexane. The yield of **32d** is around 61% based on **32b**, but the purity is not reported.

In the last stage of the process, shown in Scheme 12, the first step is the stereoselective reduction of the ketone group to give **34a**. The reduction is carried out using DIP chloride or the borane−DMS complex with the chiral catalyst *R*-phenyl oxazaborolidine. There are examples for both methods, and although there is no yield information using the former reagent, the yield using the latter method is 59.7%. There is no purity reported for either although in the last step crude **34a** is used where the Bn group is removed to give **34b** using catalytic

Scheme 12. [a]



[a]Reagents and conditions: (a) borane−DMS, *R*-phenyl oxazaborolidine, PhMe, <5 °C, 3 h; (b) Pd/C, Pr^iOH, H_2, 50 °C, 3 h.

reduction under an unspecified pressure of H_2. The yield of **34b** is 73% after recrystallisation from DCM, but the purity is not reported.

Advantages. The process is claimed to be eco-friendly even though it uses DCM as solvent in several stages. It is also claimed to be commercially viable, and yet declines to report the purity of several intermediates and the final product.

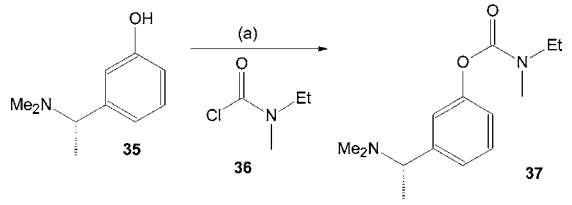
PATENT NO. U.S. 8,013,181

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

Title or Subject: Preparation of Rivastigmine and its Salts

The tartrate salt of rivastigmine, **37**, is available as Exelon and used to treat dementia caused by Alzheimer's or Parkinson diseases. Alternative methods covering its synthesis are mentioned, and it is stated that an environmentally friendly process is required that is suitable for commercial manufacture. The basis of the patent claims is the synthesis of **37** in which the dimethylamine **35** is condensed with the carbamoyl chloride **36** in the presence of a base and Bu_4^nNBr as phase transfer catalyst (PTC) (Scheme 13). After completion of the

Scheme 13. [a]



[a]Reagents and conditions: (a) (i) pyridine, Bu^n_4Br, MIBK, 30 °C, 15 h; (ii) add H_2O, 36% HCl to pH 1.5, 25 °C, 0.5 h; (iii) extraction with MIBK and EtOAc.

reaction the mixture is acidified with HCl, and the workup and product recovery involve extraction alternately into MIBK and EtOAc. The full details are omitted here, but the example in the patent starts from 6 kg of **35** and produces **37** with HPLC purity of 99.3% yet does not report the yield. The tartrate salt of **37** is obtained by heating **37** with L-(+) tartaric acid (LTTA) in Me_2CO at 60 °C. After filtration and concentration crystals of the salt are obtained by seeding in a yield of 85.4% with HPLC purity of 97.3%. The patent claims that the salt can be prepared containing residual solvent levels of <700 ppm for Me_2CO, <200 ppm for EtOAc, <100 ppm PhMe, and <20 ppm each of Pr^iOH, *n*-heptane, DCM, MIBK, and pyridine, all of which are used in the synthesis.

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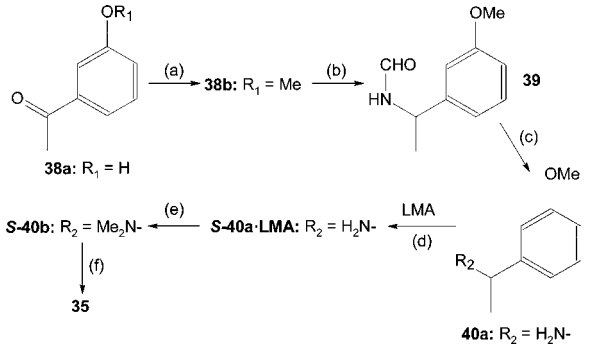
Scheme 14. [a]



[a]Reagents and conditions: (a) (i) K_2CO_3, Me_2SO_4, Me_2CO, 45 °C, 2 h; (ii) H_2O, separate; (b) (i) HCO_2NH_4, 180 °C, 2 h; (ii) cool, add H_2O, extract in EtOAc; (c) (i) HCl/Pr^iOH, 75 °C, 3 h; (ii) evaporate, add EtOAc, evaporate; (d) (i) Pr^iOH, 0.25 h; (ii) 75 °C, 0.75 h; (iii) cool to 37 °C for 10 min; (iv) filter, wash, dry; (v) Pr^iOH, reflux, 0.75 h; (vi) cool, filter, dry; (e) (i) 40% HCHO, HCO_2H, H_2O, 100 °C, 5 h; (ii) cool to 30 °C, add PhMe, separate; (iii) 40% NaOH to pH 10.5, extract in EtOAc; (iv) evaporate; (f) (i) 48% HBr, 110 °C, 6 h; (ii) cool 30 °C, add NaOH to pH 10.5; (iii) extract in EtOAc, wash, charcoal, filter, evaporate; (iv) *n*-heptane, 25 °C, 1.5 h; (v) filter, dry.

The patent also describes the preparation of **35** by the route outlined in Scheme 14. The first stage is conversion of **38a** to **38b** using Me_2SO_4 and K_2CO_3. The product is not isolated but aminated by treatment with HCO_2NH_4, giving **39** that is not isolated but decomposed to give **40a** by treatment with HCl. After workup **40a** is isolated in 57.6% yield and 99.1% purity (HPLC), and in the next step **40a** is resolved using L-(+)-mandelic acid (LMA). The salt of the *S*-enantiomer **S-40a·LMA** is isolated in 68.7% yield and 99.9% purity. The amine group is then methylated using HCHO and HCO_2H, giving **S-40b** in 91% yield and 98.15% purity (HPLC). In the final step the methoxy group is removed using HBr to give **35** in 90% yield with 99.1% purity (HLPC).

Two alternative procedures are also described for the preparing **40a** in which the amination of **38a** is carried out using different reagents. Using NH_3 in MeOH in the presence of Raney Ni the yield of **40a** is 53.9%, but the purity is not reported. When using $HONH_2$·HCl and K_2CO_3 a yield of 37.8% of **40a** is is obtained that has purity of 99.1% (HPLC). The patent also describes the racemisation of the *R*-enantiomer, *R*-**40a**·LMA by heating in NaOH, thus improving the overall process yield.

Advantages. The process provides an improved method of producing the API in high yield, but it does use a large number of solvents in the extensive workup procedures.

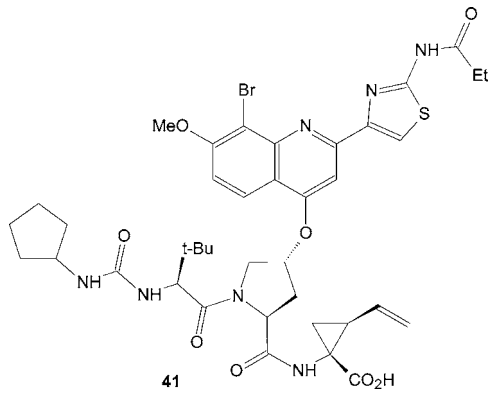
■ PATENT NO. U.S. 8,017,771

Assignee: Boehringer Ingelheim International GmbH., Ingelheim am Rhein, Germany

Title or Subject: Process for Preparing Acyclic HCV Protease Inhibitors

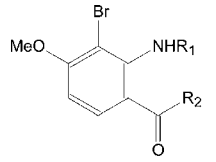
This patent states that it provides what are termed highly convergent processes for preparing compounds such as **41**. This is an active agent for the treatment of hepatitis C virus. Alternative processes for preparing **41** are described as extremely linear with groups being added sequentially.

HCV Inhibitor



However, the patent does not actually include any specific experimental examples for the synthesis of **41** which is covered by U.S. 6,323,180 published in 2001. The current patent has a single claim that covers the general compounds **42a** and **42b** that are intermediates in the synthesis of **41**.

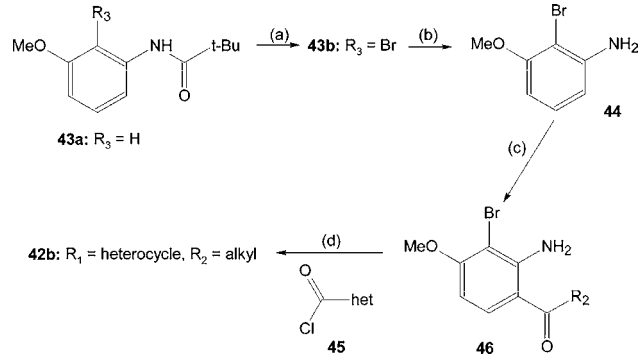
Intermediates



42a: R_1 = H, R_2 = alkyl
42b: R_1 = heterocycle, R_2 = alkyl

Unfortunately, the patent does not even provide specific examples of how these novel compounds are made and merely provides several schemes with suggested reaction conditions listing reagents and conditions that could be used. Scheme 15

Scheme 15. [a]



[a]Reagents and conditions: (a) Br_2, base; (b) acid, H_2O; (c) alkylnitrile, $BCl_3/AlCl_3$; (d) Et_3N.

outlines a suggested route for preparing **42b** that begins with bromination of **43a** in the presence of a base to form **43b** that undergoes acid hydrolysis to give **44**. Treatment of **44** with an alkylated nitrile and a Lewis acid gives **46** and acylation using **45** and a base forms **42b**. The patent lists over 50 possible variations of **41** that could be prepared by the proposed process, although without experimental evidence, this is difficult to accept.

Advantages. It is difficult to assess any process advantages since there is no experimental data although the patent claims cover a number of novel intermediates.

dx.doi.org/10.1021/op200353t | *Org. ProcessRes. Dev.* 2012, 16, 11−24

PATENT NO. U.S. 8,017,777

Assignee: Mallinckrodt LLC, Hazelwood, Missouri, U.S.A.

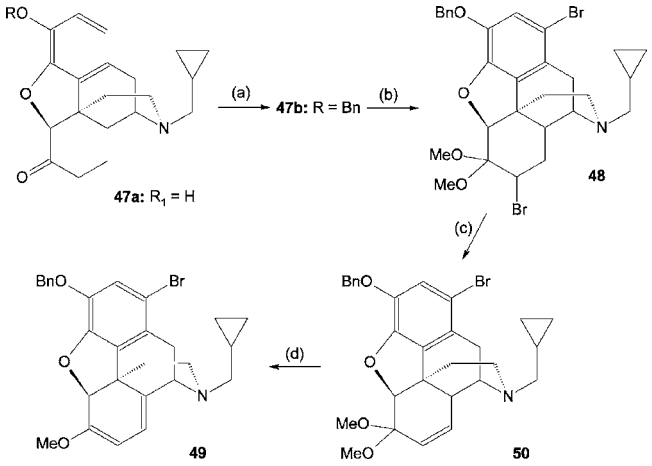
Title or Subject: Process for the Preparation of Buprenorphine and Its Derivatives

The patent reports that there is a difference in the bioactivity of the (−)- and (+)-enantiomers of a number of opiate derivatives and the (−)-enantiomers of several of these compounds have been used to treat various addictions. For example (−)-buprenorphine is used to treat heroin addiction, and in order to explore the bioactivity of (+)-buprenorphine, **54**, a viable process for its preparation is required that is disclosed in the patent. For clarity the process is divided into two parts that are shown in Schemes 16 and 17, and only the reaction conditions are included. The preparation of **54** starts from the (+)-norhydromorphone derivative **47a** with the protection of the OH group giving **47b** (R_1 = Bn). This is recovered as a sticky oil with 86% purity in 100% yield. In the next step **47b** is reacted with $(MeO)_3CH$ in the presence of MsOH as proton donor, followed by bromination to form **48**. The molar ratio of **47b** to orthoformate and MsOH is a key aspect of the process, and the range covered by the claims is from 1:1:1.5 to 1:2:3. **48** is recovered as a sticky solid and then treated with a proton acceptor such as KOH to remove HBr, giving **50** as a light-yellow oil. Reaction of **50** with Me_3SiCl as a MeOH scavenger produces **49** that is obtained as a sticky oil.

In the second stage of the process, shown in Scheme 17, **49** is reacted with **51**; the reaction takes between 20 and 30 h to give **52**. This is catalytically reduced to form **53**, and subsequent alkylation forms **54**. The intermediates in Scheme 17 are sticky oils or solids, and the patent claims state that the overall yield of **54** from **47a** is from 8 to 20% and the purity is >98% as determined by chromatography. The yield and purity details for intermediates produced in each of the steps are not always reported.

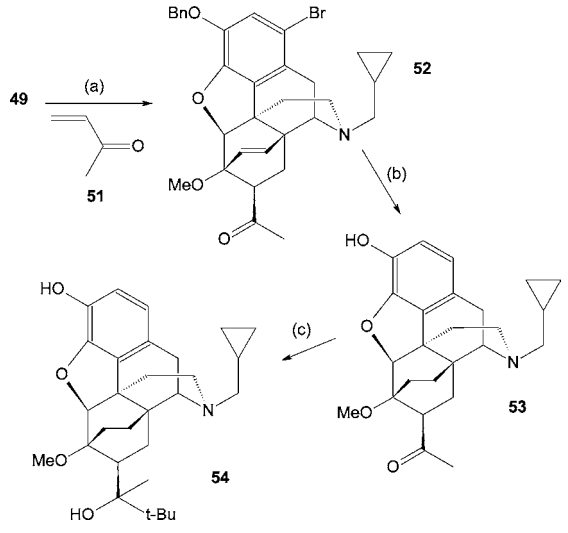
Advantages. The process is claimed to be a cost-effective method of providing the desired product in high yield and with high purity.

Scheme 16. [a]



[a]Reagents and conditions: (a) BnBr, K_2CO_3, H_2O, DMF, rt, 3 h;(b) (i) $(MeO)_3CH$, MsOH, $CHCl_3$, MeOH, 50 °C, 1 h; (ii) Br_2, $CHCl_3$, 50 °C, 0.75 h; (c) KOH, DMSO, 30 °C, 3 h; (d) (i) Me_3SiCl, $CHCl_3$, 0 °C; (ii) add MsOH, rt, 0.5 h; (iii) 35 °C, 0.75 h; (iv) add MsOH, 35 °C, 2 h.

Scheme 17. [a]



[a]Reagents and conditions: (a) PhMe, 60 −75 °C, 20−30 h; (b) Pd/C, MeOH, H_2, 3−4 bar, 60 °C, 2 h; (c) Bu^tLi, PhMe, rt, 2 h.

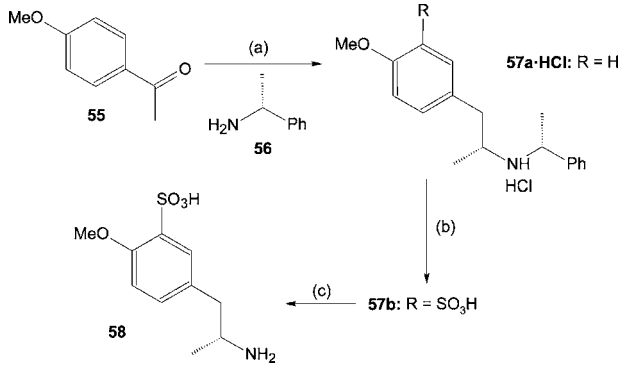
PATENT NO. U.S. 8,017,803

Assignee: Hovione Inter Ltd., Lucerne, Switzerland

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

Tamsulosin **60c** causes blood vessels to relax, and the HCl salt of the *R*-enantiomer is available as Flomax for the treatment of an enlarged prostate. A patent on an alternative synthesis of **60c** has been reviewed previously (*Org. Process Res. Dev.* **2008** *12*, 556). This patent summarises a number of methods for producing **60c** including one that starts from an amine that is hallucinogenic and others that produce a racemic material. The new method starts with the preparation of the HCl salt of the chiral amine **57a** by reaction of **55** and **56** in the presence of PtO_2 under H_2 followed by addition of HCl in EtOH. The amine salt is isolated in 48%% yield and purity 96.2% (HPLC) after crystallisation. Sulphonation of **57a·HCl** with $ClSO_3H$ forms **57b** that is isolated in 96% yield and 95% purity. Then hydrogenolysis of **57b** by using HCO_2NH_4 and Pd/C produces **58** (Scheme 18). This is isolated in 94% yield and 97% purity after crystallisation and then used in the next phase of the process.

Scheme 18. [a]

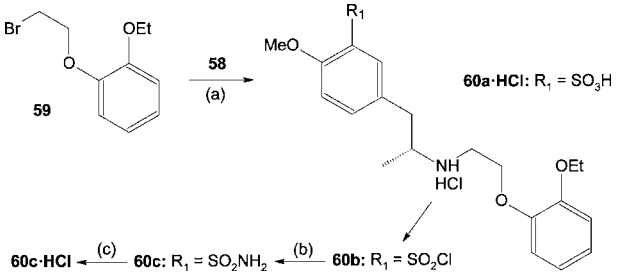


[a]Reagents and conditions: (a) (i) PtO_2, MeOH; (ii) H_2, 2 bar, 50 °C, 12 h; (iii) filter, evaporate; (iv) add HCl/EtOH, rt, 3 h; (v) evaporate, add MTBE/Me_2CO, filter, wash, dry; (b) (i) $ClSO_3H$, DCM, 5 °C, 2 h; (ii) add EtOH, evaporate; (iii) add to H_2O, filter, wash, dry; (c) (i) Pd/C, HCO_2NH_4, MeOH, 55 °C; (ii) add H_2O, rt, 1 h; (iii) filter, evaporate.

dx.doi.org/10.1021/op200353t | *Org. ProcessRes. Dev.* 2012, 16, 11−24

In the next stage **58** is condensed with **59** in the presence of K_2CO_3 to give **60a** that is isolated as the HCl salt in 75% yield and 97.9% purity. The salt is then reacted with $SOCl_2$ to give **60b** that is not isolated but treated with NH_3, giving **60c** (Scheme 19). The amine is not isolated, and addition of HCl in EtOH precipitates the HCl salt that is isolated in 98.8% purity

Scheme 19. [a]



[a]Reagents and conditions: (a) (i) K_2CO_3, H_2O, DMF, 95 °C; (ii) filter, add HCl/EtOH, rt, 1 h; (iii) add MTBE, filter, wash, dry; (b) (i) $SOCl_2$, DMF, DCM, <0 °C; (ii) add to ice/H_2O, separate; (iii) evaporate; (c) (i) NH_3, THF; (ii) add H_2O, DCM, evaporate; (d) (i) HCl/EtOH, rt, 1 h; (ii) filter, dry, recrystallise from EtOH.

by HPLC; the yield is not reported although the chiral purity is said to be within specification.

Advantages. The process gives the pure enantiomer of the desired salt in high yield.

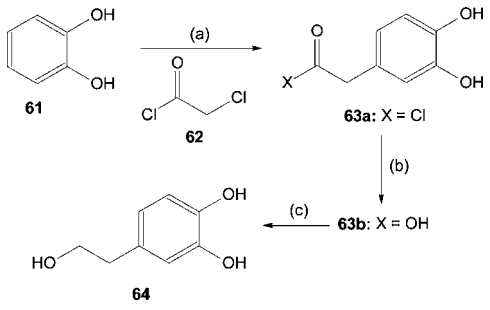
PATENT NO. U.S. 8,017,815

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

Title or Subject: Process for the Preparation of Hydroxytyrosol

Hydroxytyrosol **64**, is a constituent of olive oil and is of interest in nutrition because of its antioxidant properties. However, there is also interest in its pharmacological effects; thus, an objective of the patent is to provide a synthetic route to **64**. Although synthetic routes for preparing **64** are known, it is claimed that they are not commercially viable. The current patent describes a process for preparing **64** by catalytic hydrogenation of **63b** and the overall route, is shown in Scheme 20. There is reference to a report on the preparation of **64** from **63a** that proceeds via the triacetate, takes 40 h, and

Scheme 20. [a]



[a]Reagents and conditions: (a) (i) $POCl_3$, 125 °C, 4.5 h; (ii) evaporate, add H_2O at 80 °C; (iii) add H_2O at 0 °C; (iv) reflux, 2 h; (v) rt, 16 h; (b) (i) HCO_2H, HCO_2Na, H_2O, EtOH, reflux, 24 h; (ii) concentrate, 37% HCl to pH 0.5; (iii) add H_2O, reflux, 10 min; (iv) rt, 16 h; (v) filter, wash, dry; (c) Pd/C, H_2 5 bar; MTBE, 40 °C, 7.5 h.

gives a yield of only 65%. The current process actually begins with the formation of **63a** by reaction of **61** and **62** in the presence of $POCl_3$. The crude **63a** is isolated in 65% yield and 90% purity and is then converted to **63b** that is isolated by crystallisation or extraction. In one example crude **63a** with 90% purity is refluxed with HCO_2H and HCO_2Na in aq EtOH. After addition of concd HCl, crystalline **63b** product is isolated in 82.6% yield but is only 89.2% pure. In the other example, **63a** that is 99% pure, is also treated with refluxing HCO_2H and HCO_2Na, and after adding HCl the product is extracted with EtOAc. **63b** is recovered in 98.9% yield and 97.4% purity. The origin of the 99% pure **63a** is not revealed. The hydrogenation of **63b** is carried out in MTBE or EtOAc using Pd/C or Ru/C catalyst containing H_2O. Examples indicate that an equimolar amount of H_2O to **63b** is needed to achieve maximum yield of **64** of around 88% with purity of 75%. This information is from the analysis, and there are no experimental details of how to isolate and purify the product.

Advantages. The patent states that hydrogenation gives high yields without indicating how the product is actually isolated. However, the yield and purity in each step are poor; thus, the process does not seem to have any obvious advantages.

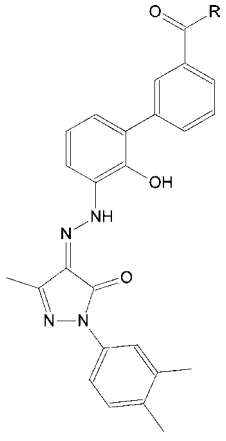
PATENT NO. U.S. 8,022,093

Assignee: Pliva Hrvatska D.O.O., Zagreb, Croatia

Title or Subject: Polymorphs Eltrombopag and Eltrombopag Salts and Processes for Their Preparation

The bisethanolamine (BEA) salt of eltrombopag **65a**, is available as Promacta for treating conditions that lead to abnormally low platelet counts. This patent describes 16 novel polymorphs of **65a**, and the claims specifically cover a polymorph of the BEA salt of **65a** designated as Form II. This is said to have advantageous physical properties including being stable to dehydration, polymorphic conversion, and decomposition in storage.

Eltrombopag

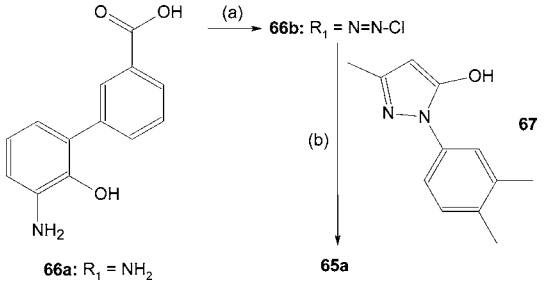


65a: R = OH
65b: R = NH_2
65c: R = OMe

The synthesis of **65a** is shown in Scheme 21, the first stage of which is diazotisation of polymorph Form I of the amine **66a**. The solution containing the diazo compound **66b** is then treated with NH_2SO_3H and then reacted with Form I polymorph of the pyrazole **67** in the presence of Et_3N to give **65a**. This is isolated as Form III in 95.4% yield with <10% Form I and 98.5% purity with the main impurities being **65b** and **65c**.

dx.doi.org/10.1021/op200353t | Org. ProcessRes. Dev. 2012, 16, 11−24

Scheme 21. [a]



[a]Reagents and conditions: (a) (i) 4 M HCl, MeOH, rt, 0.5 h; (ii) aq $NaNO_2$, <10 °C, 1.33 h; (iii) NH_2SO_3H, H_2O, 5 °C, 1 h; (b) (i) Et_3N, to pH 7−8, rt; (ii) add **67**, rt, 2 h; (iii) add HCl to pH 1.8, rt, 20 min; (iv) filter, wash, dry.

The crude **65a** is then purified and converted to Form I by refluxing in glacial HOAc for 5 h. After cooling to 40 °C the crystals are filtered off, washed in a 1:1 mixture of MeOH and H_2O, and then dried. The final yield is 88%, and HPLC purity is 99.8% of Form I. The patent also describes the production of the other polymorphs from heating in various solvents. XRD spectra are provided for all polymorphs of **65a**, as well as for Forms I and II of both **66a** and **67**, plus ^{13}C NMR spectra for some polymorphs of **65a**. The patent also includes several examples describing the preparation of a number of polymorphs of the BEA salt of **65a**. In addition, the preparation of the impurities **65b** and **65c** plus Form I polymorphs of both **66a** and **67** are described. The patent examples mention the particular polymorphs that are used in the experiments, and one would assume that this is irrelevant, so the reason for naming them is not clear.

Advantages. The novel polymorph is stable and suitable for preparing drug formulations.

PATENT NO. U.S. 8,022,220

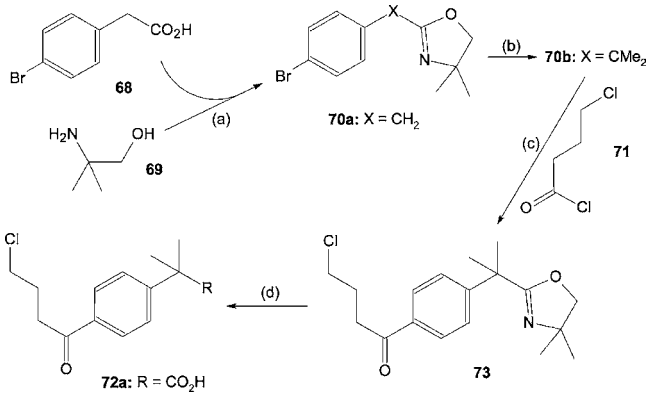
Assignee: Albany Molecular Research Inc., Albany, New York, U.S.A.

Title or Subject: Process for Production of Piperidine Derivatives

This patent covers a process for producing analogues of the antihistamine terfenadine **76c** (R = Me). **76c** was withdrawn from use in the 1990s because of serious side effects, such as cardiac arrhythmia; hence, there have been attempts to develop analogous forms of the drug. The patent refers to reports that accumulation of the terfenadine carboxylic acid **76b** is not the cause of these problems; thus, the objective of the patent is to develop a process to produce the acid metabolite and also analogues of **76b**. The synthesis of **76b** is outlined in Schemes 22 and 23 with workup details omitted. The method begins with the condensation of **68** with **69** forming the oxazole ring in **70a** that is isolated in 75% yield and then methylated using MeI in the presence of KHMDS. The reaction is carried out in two stages to ensure that there is no residual monomethylated compound (X = CHMe), and analysis proved this to be the case. **70b** is isolated as an oil that crystallises after treatment with Pr^iOH, and the resulting solid is isolated in 84% yield and described as pure. In the next step **70b** is treated with BuLi followed by **71** to give **73** that on acid hydrolysis gives the acid **72a**. This is purified by column chromatography (ColC) and recrystallised from DCM, but the patent does not provide any details of the yield or purity of either **72a** or **73**.

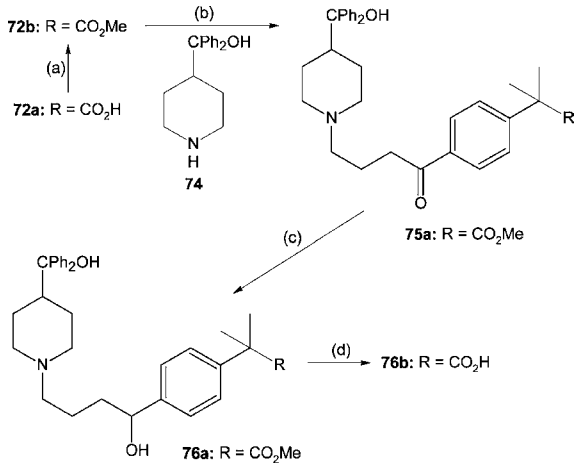
The next stage of the process is shown in scheme 23 and begins with esterification of the acid **72a** to form **72b**. This is

Scheme 22. [a]



[a]Reagents and conditions: (a) xylene, reflux, 24 h; (b) MeI, KHMDS, THF, 27−46 °C; (c) (i) Bu^nLi, THF, −78 °C, 0.5 h; (ii) **71**, THF, −78 °C, 0.5 h; (d) (i) concd HCl, dioxane, reflux, 18 h.

Scheme 23. [a]



[a]Reagents and conditions: (a) HCl/MeH, reflux, 1 h; (b) K_2CO_3, PhMe, reflux, 7 h; (c) $NaBH_4$, MeOH, 0 °C, 1 h; (d) (i) NaOH, H_2O, MeOH, reflux, 1 h; (ii) evaporate, add $H_2O/CHCl_3$; (iii) acid to pH to 5.5, separate, extract in $CHCl_3$, dry, evaporate.

recovered as an oil, purified by ColC, and then reacted with the piperidine derivative **74** in the presence of K_2CO_3 to form **75a**. Reduction of the ketone group using $NaBH_4$ produces **76a** that is isolated as a foam and then subjected to base hydrolysis to produce **76b**. The crude material is purified by ColC, but there are no details of the yield or purity of this, nor of any of the other compounds shown in Scheme 23.

The patent also describes the preparation of a number of analogues of **76b**, but again yield and purity details are not reported.

Advantages. The process provides a route to derivatives of terefenadine but omits crucial product purity and reaction yield information.

PATENT NO. U.S. 8,022,231

Assignee: Evonik Degussa GmbH, Essen, Germany

Title or Subject: Process for Preparing Monochloroethylene Carbonate and Subsequent Conversion to Vinylene Carbonate

Vinylene carbonate **79**, is an intermediate used in the synthesis of pharmaceuticals, agrochemicals, and polymers. One

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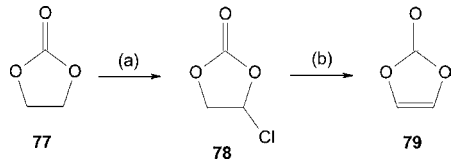
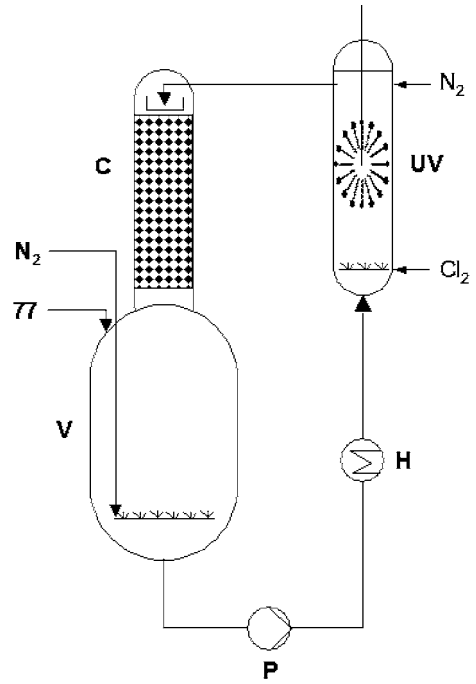
important use is as an additive in solutions for lithium ion batteries. **79** is generally prepared by HCl elimination from **78** that is obtained by free radical chlorination of **77**. Alternative processes using this route are said to include recrystallisation from MTBE/hexane, but this is expensive and gives a product that is not sufficiently pure for certain applications. The patent claims to provide highly pure **79** using an improved version of the same route as that shown in Scheme 24. The process is

Scheme 24. [a]



[a]Reagents and conditions: (a) Cl_2, 45 °C; (b) (i) Et_3N, DE, MTBE, reflux, 18 h; (ii) cool to rt, filter, wash, dry.

carried out in equipment shown in Figure 1 in which molten **77** is circulated through the irradiation reactor while injecting Cl_2



[a] Key: C = packed column, V = receiving vessel, P = pump, H = heat exchanger, UV = UV source.

Figure 1.

gas into the unit. N_2 is also injected into the liquid phase in vessel V, and this apparently reduces the amount of unwanted chlorinated byproducts and removes HCl from the liquid phase. After a known quantity of Cl_2 had been introduced, the reaction mixture was found to contain 80.7 area % of **78**, 15.7 area % **77**, and 3.5 area % of dichlorinated material. The presence of the dichloro material is said not to interfere with the production of **79**. The patent claims cover the exclusive use of thermal separation methods for the recovery and isolation of **78** although there are no examples. Following the irradiation step the mixture is refluxed in MTBE containing a diatomaceous earth (DE) and Et_3N to form **79**. After filtration to remove Et_3NHCl, GC analysis of the solution showed it contained 15% of **79**. Details of the recovery were not described although the patent states that the expensive recrystallisation step is not needed and distillation or evaporation methods are suitable.

The patent claims cover the possibility that step a of the process may be carried out in the presence of a chlorinated solvent. The single example in the patent uses 6.42 kg of **77**, and so the process is clearly amenable to scale-up, but the methods used for the product recovery, yield, and purity are not described.

Advantages. The patent claims that the process gives fewer byproducts than alternatives but does not provide evidence for the improved purity of the final product.

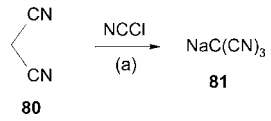
PATENT NO. U.S. 8,022,242

Assignee: Lonza AG, Basel, Switzerland

Title or Subject: Process for Preparing Alkali Metal or Alkaline Earth Metal Tricyanomethanides

The title compounds are components of ionic liquids that are important raw materials in the production of rechargeable batteries and other electrical and electronic devices. Processes for preparing these compounds are summarised and date back to 1896. However, the methods require extensive purification steps and do not remove halogens that give corrosion problems or unwanted secondary reactions. The current patent describes a method for making the desired products that contain <20 ppm of halides. The method is shown in Scheme 25 and starts

Scheme 25. [a]



[a]Reagents and conditions: (a) (i) H_3PO_4, H_2O, MeOH; (ii) 50% aq NaOH to pH, 7.5; (iii) NCCl, 30 °C, 4.5 h; (iv) 50% aq NaOH to pH, 8.5; (v) 70 °C; (vi) cool to 10 at 6 °C/h; (vii) centrifuge.

by adding NCCl to a solution of **80** that is kept at pH 7.3−7.5 by addition of NaOH. After addition of NCCl the pH is increased to 8.5, and the mixture is heated. After cooling to 10 °C the moist suspension is recovered by centrifugation and contains 72 wt % of **81**. This equates to a 49% yield and a further 47 wt % of **81** can be obtained from the mother liquor.

The next stage is purification of the moist product that contains 2.7 wt % NaCl. This is carried out as follows:

(i) dry under vacuum at 55 °C and dissolve in Me_2CO
(ii) treat solution with activated C then filter
(iii) add MTBE and cool to 10 °C
(iv) filter and dry at 40 °C

The product is isolated in 94% yield with purity of 99.9% and Cl^- content <5 ppm.

Advantages. The process gives very high purity product.

PATENT NO. U.S. 8,022,247

Assignee: Chugai Seiyaku Kabushiki Kaisha, Tokyo, Japan

Title or Subject: Process for Production of 2,3,4-Trifluoro-5-(iodo or bromo)-benzoic Acid

The title compounds (**82b:** X = I and **82c:** X = Br) are intermediates in the production of pharmaceuticals or agrochemicals.

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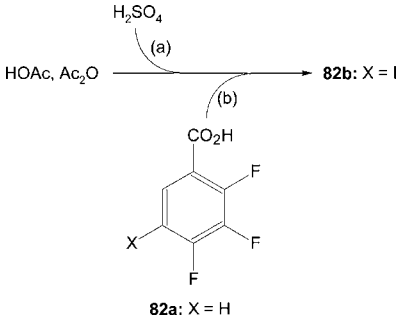
Processes for their preparation are listed and said to give yields that are too low for economic production. The method for their preparation is by direct halogenation of the acid **82a** with the halogen in the presence of an oxidising agent, such as activated MnO_2, and an acid anhydride (Scheme 26). The anhydride is

Scheme 26. [a]



[a]Reagents and conditions: (a) <40 °C; (b) (i) I_2, MnO_2, rt; (ii) 50 °C, 3 h; (iii) add I_2 and MnO_2, 50 °C, 6 h; (iv) add I_2 and MnO_2, 50 °C, 24 h; (v) add ice/water, extract in DCM (×3); (vi) wash in $Na_2S_2O_3$, (vii) H_2O wash (×4), dry, evaporate.

described as an activator for the halogenation and also acts as a water scavenger. The recovery of the product is by extraction into DCM, and the **82b** is isolated in 94% yield with purity of 99 area% (by HPLC). The patent includes a HPLC trace that shows that there are three impurities that are <0.1 area %, thus demonstrating the process gives high purity product. The preparation of **82c** using Br_2 gave a product in 63% yield and with purity of 98.2 area % (by HPLC). The patent also describes an example for the preparation of **82c** using $NaBrO_3$ as brominating agent in the presence of K_2SO_4 and H_2SO_4. The product yield was 53%, the purity, 98%, and the amounts of 6-halo-isomers of **82b** or **82c** that are formed in the process are very low.

The patent points out a number of factors that should be taken into account when carrying out the procedure described, and these are listed as follows:

(i) dealing with the exotherm when H_2SO_4 is added to the solution
(ii) controlling the temperature during and after the addition of the Br_2 or I_2
(iii) when isolating the product, the reaction mixture should be cooled in an ice bath, and extraction should be followed by washing with a reducing agent
(iv) the crude product can be purified by distillation or recrystallisation

The patent mentions that the products **82b** or **82c** can be used for the preparation of **84b** by the route outlined in Scheme 27. The compound is said to be useful as an intermediate in the preparation of anticancer agents. There are no details for any of the steps in the scheme although literature references are given for some of the reactions.

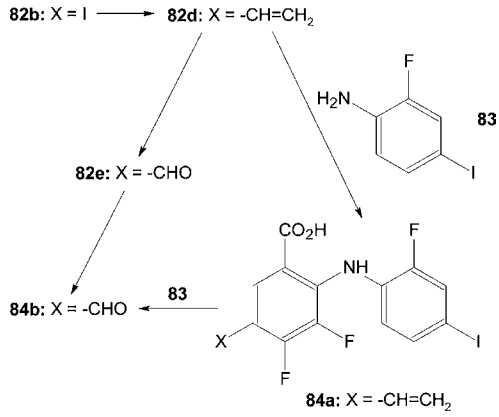
The patent provides HPLC traces for **82b** and **82c** and some basic ^1H NMR data for these compounds.

Advantages. The process gives high yield and high regioselectivity to the desired product.

■ PATENT NO. U.S. 8,026,372

Assignee: FIS Fabbrica Italiana Sintetici S.p.A., Vincenza, Italy

Scheme 27. [a]

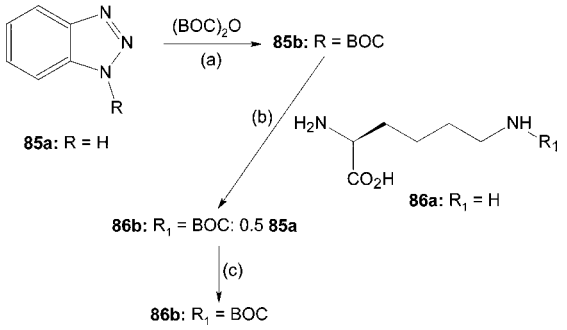


[a]Reagents and conditions: not provided

Title or Subject: Process for the Preparation of ε-Alkoxycarbonyllysines and Their Analogues

The patent describes a process for the selective protection of ω-amino group of α,ω-aminoacids, and in particular the method is applied to lysine **86a**. The protection of the ω-amino group in aminoacids is an important reaction, and the patent states that the classical method, of forming a Cu(II) complex, is widely used. This method is long and tedious and can result in excessive residual levels of Cu, and thus is not acceptable. Alternatives methods using the BOC group are claimed not to be viable on a commercial scale. The patent claims that, although certain benzotriazoles have been used to protect aminoacids, they have not been used to protect α,ω-aminoacids. The basis of the invention is the use of compounds such as **85b** to introduce protecting groups into α,ω-aminoacids. Scheme 28 shows one

Scheme 28. [a]



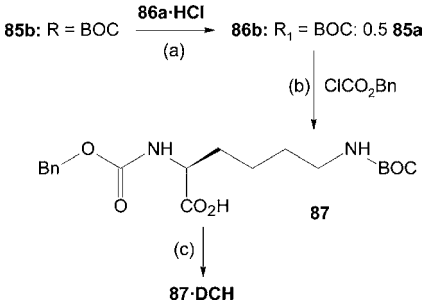
[a]Reagents and conditions: (a) DMAP, THF, rt, 3 h; (b) (i) NaOH, H_2O, pH 12, 0 °C, 2 h; (ii) evaporate THF; (iii) extract in EtOAc, add HCl to pH 5.6; (iv) rt, 16 h, filter; (c) sublimation, 140 °C, 0.3 mbar, 3 h.

method of protecting the ω-amino group of **86a** by reaction with **85b** as a means of introducing the BOC protecting group and forming **86b**. Initially **85b** is prepared by reaction of **85a** with $(BOC)_2O$ in the presence of DMAP, and the resulting mixture is added to a solution of **86a** maintained at pH 12 with NaOH. The reaction produces the intermediate complex **86b**−**0.5**·**85a** that can be isolated in 93% yield. The benzotriazole can be removed by sublimation of the complex, giving crude **86b** that can be purified by ion-exchange ColC. The pure **86b** is isolated in 81% yield and is shown to be essentially free from impurities by ^1H and ^{13}C NMR and LC−MS.

dx.doi.org/10.1021/op200353t | Org. ProcessRes. Dev. 2012, 16, 11−24

When the procedure was carried out without **85a** and using only $(BOC)_2O$ and **86a**, the product contained only 43.5% of **86a**. The patent also describes the preparation of the benzyloxy derivative **85c** (R = BnOCO) from **85a** and $ClCO_2Bn$ that is then used to produce **86c** (R_1 = BnOCO). An additional aspect of the patent is the preparation of diprotected diaminoacids and their purification by formation of a salt of dicyclohexylamine (DCH). Scheme 29 shows the procedure applied to the HCl

Scheme 29. [a]



[a]Reagents and conditions: (a) aq NaOH, THF, pH 11.5, 0 °C, 16 h; (b) (i) 0 °C, 2 h; (ii) evaporate off THF, add Pr^iOAc/H_2O; (iii) add concd HCl to pH 2, 0 °C; (iv) H_2O wash, dry; (c) (i) DCH, Pr^iOAc, rt, 16 h; (ii) filter, wash in Pr^iOAc, dry.

salt of **86a** that is initially converted to the complex **86b**–**0.5·85a**. This is not isolated but treated with $ClCO_2Bn$ to form **87** that is then converted to the DCH salt **87**·DCH that is isolated by crystallisation from MEK. A first crop of crystals is obtained in 60% yield with 94.5% purity, but there are no details of the isolation of additional crystals or of improving their purity.

Advantages. The process enables the selective protection of the ω-amino group of α,ω-aminoacids that is claimed to be environmentally friendly since it does not use toxic Cu reagents.

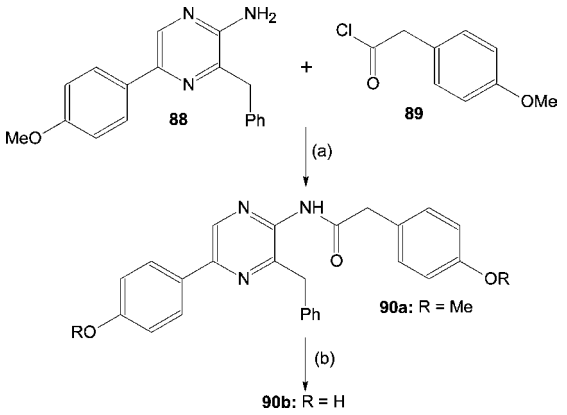
PATENT NO. U.S. 8,026,363

Assignee: JNC Corporation, Tokyo, Japan

Title or Subject: Process for Producing Coelenteramide or an Analogue Thereof

Coelenteramide **90b** can be used in the preparation of green fluorescent protein (GFP) that is partly responsible for bioluminescence in marine animals. GFP was first isolated in the early 1960s from the jellyfish *Aequorea victoria* and has been engineered to produce colour-shifted genetic derivatives that have been used to study live-cell imaging experiments without damage to the cell. The technique is reported to have heralded a new era in cell biology, and the discovery and development of GFP was awarded the 2008 Nobel Prize in Chemistry. Some interesting and bizarre applications of introducing GFP into living organisms have also been reported. Examples are green fluorescent zebrafish that were initially developed to detect pollution in waterways and green fluorescent mice as pets. Also reported is a green fluoresent cat for potential use as a model organism for diseases, particularly HIV. An alternative process for preparing **90b** is reported to give a yield of only 50%, and hence an improved synthesis was devised that is shown in Scheme 30. The condensation reaction of the amine **88** with acetyl chloride **89** produces the amide crude **90a** in 81.5% yield that is purified and isolated in 61.5% yield after two crystallisations from EtOAc. Treatment of **90a** with BBr_3

Scheme 30. [a]



[a]Reagents and conditions (a) (i) pyridine, DMAP, rt to 50 °C, 22.5 h; (ii) aq $NaHCO_3$, extract in DCM, dry, evaporate; (iii) add PhMe, distill; (b) (i) BBr_3, DCM, 0 °C, 25 min; (ii) rt, 21 h; (iii) aq $NaHCO_3$, evaporate DCM, filter, dry.

followed by $NaHCO_3$ removes the ether groups, giving crude **90b** in 92.3% yield that is recrystallised from EtOH to obtain the analytically pure solid in 16.7% yield.

The patent claims cover the preparation of a large number of analogues of **90a** and **90b**, containing different substituents in place of the OMe and Ph groups. However, there are no examples describing the preparation of these compounds.

Advantages. The process gives high initial yields of the desired compound, but there are significant losses on purification.

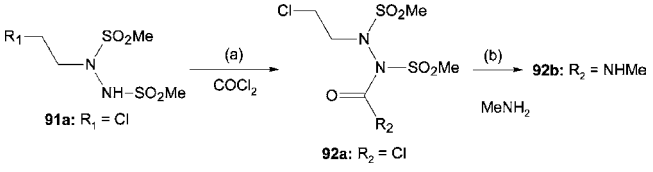
PATENT NO. U.S. 8,026,395

Assignee: Nanotherapies Inc., Alachua, Florida, U.S.A.

Title or Subject: Process for the Synthesis of Anti-neoplasia Agent VNP40101M

The compound of interest in this patent is known as cloretazine **92b**, an alkylating agent that is under investigation for the treatment of high-grade brain tumours. An alternative process for the preparation of **92b** is known but gives an overall poor yield of 10%. Not only does it give poor yield, but it also uses methyl isocyanate that is most certainly not an acceptable reagent for industrial use. The current patent provides two syntheses of **92b**, and the first of these is shown in Scheme 31.

Scheme 31. [a]



[a]Reagents and conditions: (a) (i) Pr^i_2NEt, MeCN, 0 °C, 0.5 h; (b) Pr^i_2NEt, THF, 0 °C, 1 h; (ii) rt, 1.5 h; (iii) evaporate, brine wash, extract in DCM; (iv) dry, filter, concentrate, crystallise EtOH.

This route proceeds via the intermediate **92a** that can be obtained from **91a** by treatment with $COCl_2$ in the presence of Pr^i_2NEt. **92a** is not isolated, and the mixture is treated with $MeNH_2$ and additional Pr^i_2NEt. The reaction is monitored by TLC and HPLC/UV, and after workup and crystallisation **92b** is isolated in 94% yield with purity of 97%.

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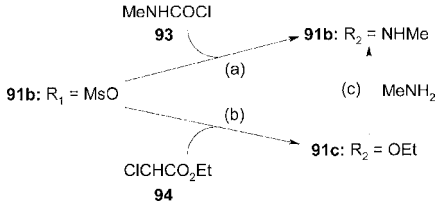
Scheme 32. [a]

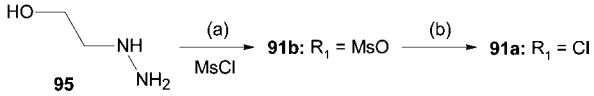


[a]Reagents and conditions: (a) (i) Et_3N, MeCN, rt, 20 min; (ii) reflux, 36 h; (iii) cool, evaporate, brine wash, extract in DCM; (iv) dry, filter, concentrate, crystallise EtOH; (b) (i) MeCN, rt, 10 min; (ii) 90 °C, 16 h; (iii) cool, evaporate, add EtOAc; (iv) wash in 5% HCl, brine, dry; (v) filter, evaporate, dry; (c) (i) $AlCl_3$, THF, DCM, rt, 16 h; (ii) add ice/H_2O, 1 h; (iii) filter, dry, concentrate, crystallise EtOH.

The second route to **92b** is shown in Scheme 32 and starts from the mesylate **91b** that can be converted directly to **92b** by reaction with **93** in the presence of Et_3N. After workup and crystallisation **92b** is isolated in 67% yield and 97% purity. The alternative route from **91a** is via the ester intermediate **92c** that is formed by reaction with **94** and can be isolated in 63% yield. It is then reacted with $MeNH_2$ in the presence of $AlCl_3$ giving **92b** that is isolated in 68% yield and 97% purity after crystallisation.

The preparation of **91b** and its conversion to **91a** are described in the patent, and the methods are outlined in Scheme 33. **91b** is obtained by reaction of the hydroxyhydrazine **95** with MsCl, and the product is isolated in 58% yield. The purity is not reported, although the ^1H NMR is said to be clean. The chloro compound **91a** is then prepared from **91b** in a reaction with LiCl that takes 24 h. The product is isolated in 88% yield, and again the ^1H NMR is reported as being clean and identical to an earlier reported spectra.

Scheme 33. [a]



[a]Reagents and conditions: (a) (i) pyridine, DCM, ←10 °C, 20 min; (ii) rt, 72 h; (iii) add 1 M HCl, 0 °C; (iv) filter, add EtOH, rt, 2 h; (v) filter, dry; (b) (i) LiCl, DMF, 60 °C, 24 h; (ii) add H_2O, 0 °C, filter; (iii) hexane, rt, 2 h, filter, dry.

Some of the experiments are carried out on half-kilo scale suggesting the advanced stage of development of the process. Although the process avoids the dangers of using MeNCO, it does use $COCl_2$ that is an extremely hazardous material and is only safe to use when generated on site.

Advantages. The process gives higher yields than the alternative but still uses very hazardous reagents.

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