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 April and May 2012

SUMMARY

The current review contains 21 patents from an original list of 277 that fitted the selection criteria. One patent in particular evoked memories of the stories of horrific birth defects that appeared in the 1950s and 60s due to the drug thalidomide. Derivatives of this compound are under investigation for treating cancers, and a patent describes the synthesis of some of these molecules. There is a wide range of subjects in this selection. Some of the patents contain extensive amounts of experimental information, while others have very little. A feature of several patents is that changing solvents gives marked improvement in selectivity and productivity as well as reducing environmental impact. High cholesterol levels lead to coronary problems and are treated by a number of drugs including a range of statins. A comprehensive patent covers the synthesis of the side chain of several statins and contains a number of novel intermediates. Another drug used to treat the same problem is ezetimibe, and a detailed patent describes its synthesis that includes a previously unpublished finding that a side product, from a Ti(IV)-catalysed Mannich reaction, can be converted into a useful intermediate. A detailed patent describes the synthesis of azobicyclohexane esters that are used to prepare drugs for the treatment of hepatitis C. The route proceeds via novel bisulfite compounds that do not need to be isolated. Carbamoyl leucine derivatives are alternative antiviral drugs for treating hepatitis C, and a patent describes how they can be made with minimum byproducts by careful control of pH. A third patent covers a range of aminohydroxycarboxamides that are intermediates for another class of hepatitis C drugs. The process produces crystals that are easy to filter and avoids the use of solvents such as DMF and dioxane that give solid masses. Another antiviral drug is etravirine that is used in treating HIV, and a new process for its synthesis proceeds via a novel ether compound. The ether is formed along with an isomer that can also be converted to the final product, thus increasing overall yield. A process is described for producing sterile batches of the β-lactam antibiotic meropenem trihydrate. The process is claimed to be commercially viable, but in a catalytic hydrogenation step an almost stoichiometric amount of a Pd catalyst is required. A patent covering the preparation of pyrroles involves the synthesis of γ-nitrodicarbonyl and subsequent oxidation to an γ-dicarbonyl with H_2O_2. Reducing the amount of H_2O in the process gives improved selectivity. Two patents describe methods for preparing aminobenzene compounds by processes that reduce the need for solids handling and, thereby, exposure to compounds that are toxic and skin sensitizers. Another patent on amine compounds covers an aminopyridine that is used to produce the fungicide fluazinam. The process uses the same reagents as an original procedure and gives improved selectivity, yield, and productivity by using MIBK instead of DMF as reaction solvent. Imatinib is used for the treatment of leukaemia and is available as the mesylate, under the name Gleevec. An improved synthetic route for a key intermediate is described that avoids some of the complex workup methods of alternative routes. An aldehyde that is used as perfume in soaps, shampoos, and cosmetics can contain unacceptably high levels HOAc that is unsuitable in these applications. An improved synthesis of the compound is reported that does require isolation of intermediates and gives a product with very low HOAc levels. The synthesis of the antidepressant mirtazapine involves the use of concd H_2SO_4 in a cyclisation step. The subsequent product extraction is improved by using Pr^nOH or Pr^iOH in place of DCM that can leave unacceptable residues. Ziprasidone is an antipsychotic drug used to treat schizophrenia, and it can contain impurities causing discolouration in the final product. Despite a multistep purification procedure using several solvents and filtration steps the yield and the final purity are both very high. A one-pot process is described for the synthesis of rufinamide, an anticonvulsant used with other drugs for the treatment of seizure disorders. The process is carried out in aqueous solution and avoids the need to isolate or purify intermediates. A detailed patent covers the synthesis of novel cyclopropyl carboxylic acid derivatives that are pharmaceutical intermediates. Dihydropteridione derivatives are useful in treating tumours, and a very detailed patent describes the preparation of crystalline salts but uses a large number of solvents. The cis isomer of a azabicycloalkanol derivative is an intermediate in agrochemical synthesis, but the trans isomer is unsuitable. A new process gives improved yield of the cis isomer and provides an isomerisation step to increase the cis/trans ratio. 2,2-Difluoroethylamine is a useful intermediate, and a patent describes an improved synthesis by amination with NH_3 that gives high yields when the amount of H_2O in the system is minimised. Several of the patents in this collection describe experiments carried out on a kilo or multikilo scale, and 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. 8,148,520

Assignee: Orchid Chemicals and Pharmaceuticals Limited, Chennai, India

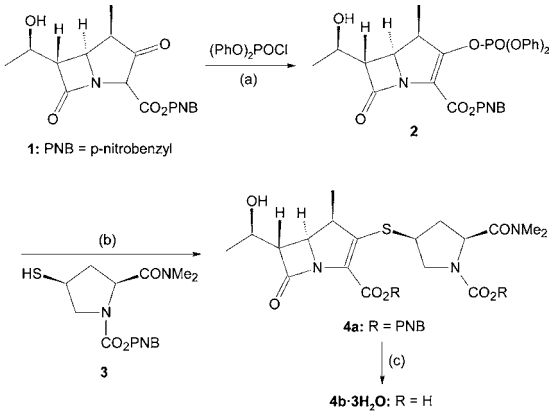
Title or Subject: Process for the Preparation of β-Lactam Antibiotic Meropenem Trihydrate

Meropenem **4b**, is used to treat a number of infections and is available as the trihydrate as Merrem in the United States. A number of synthetic routes to **4b** are mentioned, some of which use chromatographic methods or multiple solvent systems for the preparation of the sterile product. This patent describes a method for the preparation of sterile **4b** by crystallisation, and this is the subject of the patent claims. The patent also describes a method for the synthesis of **4b** by the route outlined in Scheme 1. This is claimed to be commercially viable and does not require

Published: August 24, 2012

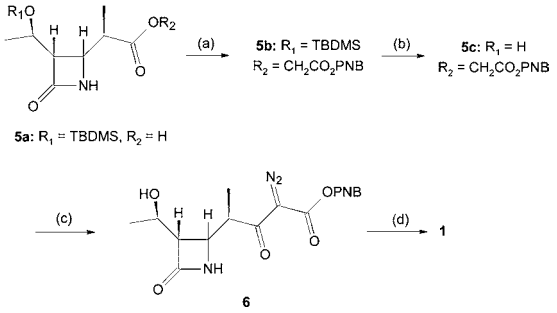
dx.doi.org/10.1021/op3002118 | *Org. Process Res. Dev.* 2012, 16, 1468−1481

Scheme 1[a]



[a]Reagents and conditions: (a) (i) $EtNPr^i_2$, MeCN, −10 °C; (ii) K_2HPO_4, EtOAc, rt, 0.25 h; (iii) Pr^i_2O, rt, 1 h; (iv) filter, dry; (b) step a at 15 °C. (c) (i) Pd/C, rt, H_2, EtOAc/THF/H_2O; (ii) filter, H_2O wash, separate, active C; (iv) filter, add THF, filter, dry.

Scheme 2[a]



[a]Reagents and conditions: (a) $Mg(CO_2CH_2PNB)_2$, carbonyldiimidazole, 30 °C. (b) HCl, EtOAc. (c) Et_3N, 4-dodecylbenzenesulphonylazide, MeCN. (d) Rh octanoate, ZnCl.

multiple solvent systems or chromatographic techniques. The synthesis starts from **1** that is activated by treatment with $(PhO)_2POCl$ in the presence of an amine base to give **2** that is isolated in 45% yield and 98% purity. **2** is then reacted with the thiol **3** at a slightly lower temperature than the first step to form **4a** that is recovered in 65% yield and 98% purity. In the final step **4a** is hydrogenated using a 10% Pd/C catalyst to give **4b** that is recovered as the trihydrate with purity up to 99.5%. The hydrogenation requires a considerable amount of catalyst, and examples describe the use of equal weight of catalyst and substrate. Whether the recovered catalyst can be reused is not mentioned. To recover the sterile product the solid is dissolved in H_2O and NH_4OH added until the solution is clear. After carbon treatment and microfiltration, the pH of the filtrate is adjusted to 5−6 with HCO_2H, and addition of THF precipitates the product. After washing in aq THF the crystals are dried and isolated with purity of 99.0−99.9%.

The starting material for the process is prepared by the route outlined in Scheme 2 and is based on a method reported in the literature (*Heterocycles* **1984**, *21*, 29). Unfortunately, this patent does not give any experimental details for the route.

Advantages. The process does provide a route to high-purity product but uses considerable quantities of Pd catalyst.

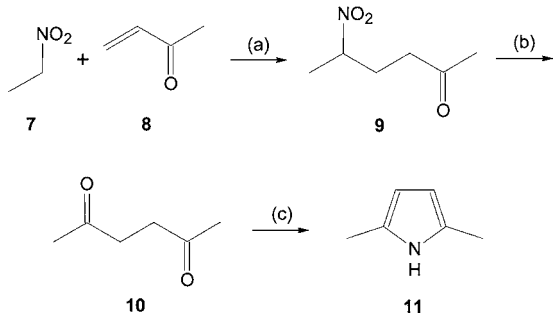
PATENT NO. U.S. 8,148,545

Assignee: Chevron Phillips Chemical Company LP, The Woodlands, Texas, United States

Title or Subject: Process for the Synthesis of γ-Nitrodicarbonyl and γ-Dicarbonyl Compounds and Their Pyrrole Derivatives

The patent covers methods for synthesising the γ-nitrodicarbonyl **9** that is used to prepare the pyrrole **11**. This is a component of a catalyst system used in the polymerisation of olefins. The process for preparing **11** is outlined in Scheme 3 and

Scheme 3[a]



[a]Reagents and conditions: (a) K_2CO_3, H_2O, rt, 1 h. (b) (i) 30% H_2O_2, <65 °C, 1 h; (ii) extract in DCM (×3), dry, evaporate; (iii) vac distill. (c) (i) $(NH_4)_2CO_3$, 95 °C, 1.5 h; (ii) 115 °C, 1 h; (iii) extract in DCM, dry, evaporate, distill.

proceeds via the initial formation of **9** and **10**. This method for preparing **10** is an improvement on a literature report (*J. Org. Chem.* **2003**, *68*, 9173) and involves condensation of **7** with **8** in the presence of a base such as K_2CO_3. The patent reports that the yield of **9** falls unexpectedly as the reaction time is increased because of the formation of three byproducts. These byproducts are not identified although the patent shows GC plots of samples taken at intervals during the reaction and up to 2 h when total impurity levels are as high as 47 area%. The optimum reaction time is around 1 h and the yield of **9** is claimed to be 75 to 90 mol % based on **8**. These yields are based on GC analysis of the reaction mixture. The second step in the process is carried out without isolation of **9** from the mixture in step 1. This oxidation is carried out by adding portions of H_2O_2 and produces **10** that can be isolated by solvent extraction using DCM, and **10** is isolated in 71% overall yield based on **8** with purity of 97% (by GC). DCM is reported to be better than either EtOAc or PhMe and when EtOAc is used for the extraction multiple components were found in the organic phase. The final step in the process of making **11** is based on a literature method (*Org. Synth. Collect.* **1943**, *2*, 219) and involves reaction of **10** with ammonia or an ammonium salt. Using $(NH_4)_2CO_3$ the crude pyrrole **11** is extracted into DCM and then purified by distillation and isolated in 78% yield with purity of 99.4% (by GC).

The patent describes experiments investigating the effect of using reduced quantities of H_2O and H_2O_2 in steps 1 and 2. and this results in a higher yield of **10**. The patent provides GC plots of reaction mixtures for the various reactions steps in the process.

Advantages. The process gives a more selective reaction than alternatives.

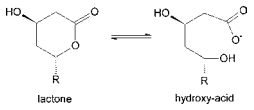
PATENT NO. U.S. 8,148,550

Assignee: Ratiopharm GmbH, Ulm, Germany

Title or Subject: Method for the Production of Statins

dx.doi.org/10.1021/op3002118 | *Org. Process Res. Dev.* 2012, 16, 1468−1481

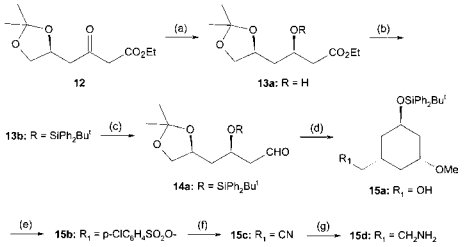
Statins are used to treat high blood cholesterol levels and some statin molecules contain a side chain that can exist as an open-chain hydroxyacid in equilibrium with a lactone as shown below.



The existence of this equilibrium can make isolation of statins more difficult and patents covering methods for producing statins have been reviewed (*Org. Process Res. Dev* **2011**, *15*, 10).

The current patent describes methods of making statins and the claims cover the steps for the formation of the side chain. The claims also cover a number of novel compounds that are intermediates in the synthesis of statins. One such novel compound is the amine **15d**, and Scheme 4 outlines its preparation

Scheme 4[a]



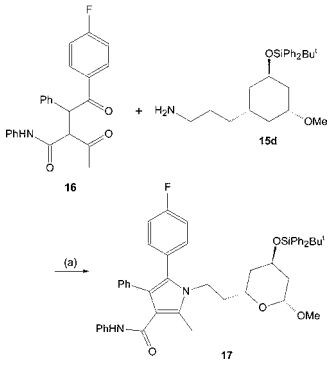
[a]Reagents and conditions: (a) *R*-Ru(tol-BINAP)Cl_2, AcONa, EtOH, H_2, 100 bar, 50 °C, 4 h. (b) imidazole, DMF, Bu^tPh_2SiCl, rt, 16 h. (c) DIBAH/PhMe, Et_2O, −78 °C, 0.25 h. (d) $(MeO)_3CH$, TsOH, MeOH, reflux, 1 h. (e) *p*-$ClC_6H_4SO_2Cl$, pyridine, 0 °C, 1 h; (ii) rt, 16 h; (f) NaCN, DMSO, rt 4 h. (g) Raney-Ni, NH_3, MeOH, H_2, 50 bar, rt, 5 h.

that proceeds via the novel compounds **13b**, **14a**, **15b**, and **15c**. Workup details are omitted because of space limitations and the route starts from the keto-ester **12** that is reduced to the alcohol **13a** using a chiral Ru catalyst. The crude alcohol **13a** is isolated in quantitative yield and then silylated with Bu^tPh_2SiCl to form **13b**. This is purified by column chromatography (ColC) and isolated as a colourless oil in 94.1% yield. The ester is then reduced using DIBALH to give aldehyde **14a** that is isolated as a viscous oil and used without purification in the next step. This reduction is covered by the main claim of the patent. Reaction of **14a** with $(MeO)_3CH$ in the presence of TsOH forms **15a** that is recovered as a solid in 53.5% yield. The lactol is then converted to **15b** using *p*-$ClC_6H_4SO_2Cl$, and the product is isolated as a viscous oil and treated with NaCN, forming **15c** that is isolated as a crystalline solid in 74% yield. Reduction of **15c** using a Raney Ni catalyst in the presence of NH_3 gives the amine **15d** as a viscous oil in quantitative yield.

The amine **15d** is used for the preparation of **17** by reaction with the diketone **16** as shown in Scheme 5. The reaction takes 30 h in a refluxing mixture of heptane/THF/PhMe in the presence of Me_3CCO_2H. The pyrrole **17** is recovered in 71.6% yield and can be used to prepare atorvastatin, although no details are provided.

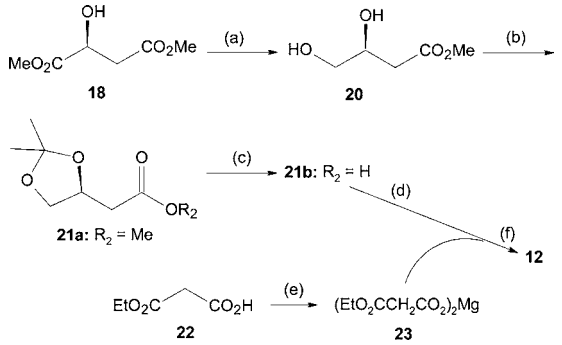
The preparation of the starting material **12** is described and proceeds by the method outlined in Scheme 6. The starting point is the ester **18** in which one of the ester groups is selectively reduced using $NaBH_4$ and $BH_3{\cdot}Me_2S$. This gives **20** that is isolated in crude form as a viscous residue then treated with $Me_2C(OMe)_2$ in the presence of TsOH to form ester **21a** that is

Scheme 5[a]



[a]Reagents and conditions: (a) Me_3CCO_2H, heptane/THF/PhMe, reflux, 30 h.

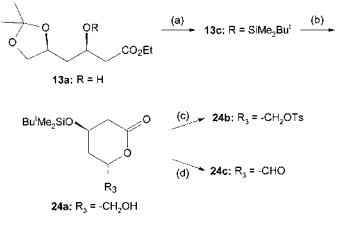
Scheme 6[a]



[a]Reagents and conditions: (a) (i) $NaBH_4$, THF, rt; (ii) $BH_3{\cdot}Me_2S$, rt, 3 h; (iii) MeOH, rt, 16 h; (iv) evaporate. (b) (i) $Me_2C(OMe)_2$, TsOH, Me_2CO, rt, 16 h; (ii) Na_2CO_3, rt, 1 h; (iii) filter, evaporate. (c) (i) 2 M NaOH, 0 °C; (ii) rt, 2 h; extract with DCM; (iii) add Et_2O to aq layer, 0 °C; (iv) 2 M $NaHSO_4$, 0 °C, 0.25 h; (v) separate, extract in EtOAc; (vi) dry, evaporate. (d) (i) CDI, THF, rt, 10 min; (ii) rt, 2 h. (e) Mg, THF, reflux, 4 h. (f) (i) rt, 16 h; (ii) evaporate, dissolve in EtOAc; (iii) 2 M aq $NaHSO_4$, separate; (v) wash in aq $NaHSO_4$, wash in aq $NaHCO_3$, dry, vac distill.

isolated in 74.4% yield after vacuum distillation. The ester is hydrolysed to give **21b** that, after a workup using three different solvents, is recovered as a liquid in 78.3% yield and 95% purity and is used directly in the next step. **21b** is initially treated with *N,N′*-carbonyldiimidazole (CDI) then the Grignard **23** that is prepared from **22**. The crude **12** is purified by vacuum distillation giving a final yield of 72.4% that was shown by NMR to contain 10% of the enol form.

Scheme 7[a]



[a]Reagents and conditions: (a) use Bu^tMe_2SiCl as in Scheme 4, step (b); no details provided for steps b, c, or d.

dx.doi.org/10.1021/op3002118 | *Org. Process Res. Dev.* 2012, 16, 1468−1481

The patent also mentions that the silylated compound **13c** can be made from **13a** by the same procedure used to prepare **13b**. The yield is 88% although no details are provided. **13b** is then used to in the preparation of a number of lactones as shown in Scheme 7. There are no experimental details provided for these reactions and they use methods reported in the literature. However, yield data are given for **24a** (60%) and **24b** (91%). The tosylate **24b** is then mentioned as being used to prepare several other derivatives although no details are provided and the examples listed are for R_3 = Cl, Br, I, $-CH_2P(O)(Oalkyl)_2$, and $-CH_2PPh_3^+ \cdot OTs^-$.

The patent contains both ^1H and ^{13}C NMR data for many compounds.

Advantages. The patent provides a new process for making statins via a range of novel intermediates.

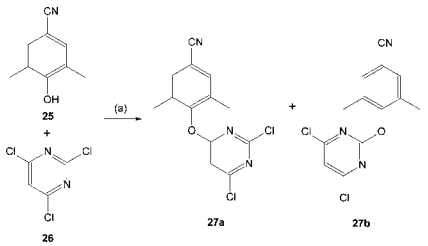
PATENT NO. U.S. 8,153,790

Assignee: Irena Krizmmanić et al., Sisak, Croatia

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

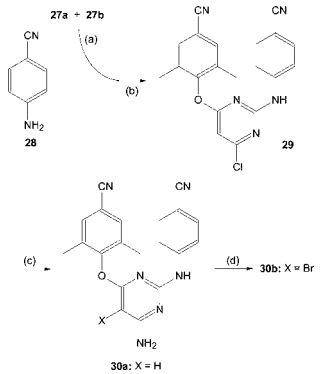
Etravirine **30b**, is used in the treatment of HIV and is available as Intelence. A number of processes for the preparation of **30b** are summarised and said to give very poor yields of <10%. The patent describes a new process for making **30b** that includes the preparation of the novel ether **27a** that is an intermediate and is the subject of the main claims of the patent. The synthesis of **27a** is shown in Scheme 8 and is by the condensation of **25** with **26**

Scheme 8[a]



[a]Reagents and conditions: (a) (i) aq NaOH, Me_2CO, <5 °C, 1 h; (ii) 30 °C, 4 h; (iii) add H_2O at rt, filter, wash, dry.

Scheme 9[a]



[a]Reagents and conditions: (a) NaH, Me_2NAc, 10 °C, 10 min. (b) (i) Me_2NAc, 10 °C, 2 h; (ii) add EtOAc, <5 °C; (iii) aq NaCl; (iv) separate, extract with EtOAc; (v) wash in aq NaCl, concentrate, filter, wash, dry. (c) (i) aq NH_3, *N*-methylpyrrolidone, rt; (ii) 120 °C, autoclave, 20 h; (iii) cool to rt, add H_2O; (iv) <5 °C, 2 h; (iv) filter, dry. (d) (i) Br_2, Pr^nOH, 5 °C, 0.5 h; (ii) Br_2, 10 °C, 0.5 h; (iii) rt, 2 h; (iv) aq NaOH, rt, 1 h; (v) <5 °C, 1 h; (vi) filter, Pr^nOH wash, dry.

that also produces the isomer **27b**. The total yield of the **27a** and **27b** is 97% containing 87.4% of **27a**.

The mixture of **27a** and **27b** is then used in the synthesis of **30b** as outlined in Scheme 9. In the first step the mixture of ethers is treated with NaH followed by the amine **28** to give **29** that is isolated in 53.7% yield with purity of 95%. After recrystallisation from THF and aq EtOH the product is recovered in 92% yield with purity 98.7%. Reaction of **29** with NH_3 gives **30a** that is isolated in 90% yield and 95.1% purity. This is purified by treating with TsOH in Pr^iOH to form the tosylate salt that is treated with NaOH to give **30a** with purity 97.9% in 83.5% yield. The purified material is then used to prepare **30b** by reaction with Br_2, and **30b** is obtained in yield of 92.8% with purity of 99.4%.

The patent describes how **30b** can be purified via formation of salts of acids such as TsOH, HNO_3, H_3PO_4, $PhSO_3H$, and $EtSO_3H$. For example, the TsOH salt is obtained in 88.2% yield with a purity of 99.8% as follows

(1) suspend **30b** in Me_2CO at rt,
(2) add a solution of TsOH in Me_2CO then keep at rt for 1 h,
(3) filter off and suspend solid in Me_2CO and add 10% aq NaOH
(4) stir at rt for 0.5 h,
(5) add H_2O, stir at rt for 1 h,
(6) filter, dry.

The patent provides XRD patterns for the acid salts and for the novel ethers **27a** and **27b**. The ^1H and ^{13}C NMR data for these two compounds are also provided.

Advantages. The process provides an alternative route to the drug compound as well as novel intermediates.

PATENT NO. U.S. 8,153,806

Assignee: The Children's Medical Center Corporation, Boston Massachusetts, United States

Title or Subject: Synthesis of 4-Amino-Thalidomide Enantiomers

The word thalidomide evokes memories of horrific birth defects in children born in the late 1950s and early 1960s. Despite the emotive issues involved in research on the compound, in the past decade it has found that derivatives of the drug molecule are effective in the treatment of various cancers. The current patent describes methods for preparing both enantiomers of **35b** and discusses their use in inhibiting the growth of new blood vessels (angiogenesis) and hence are of interest in treating a number of diseases. Scheme 10 shows the route used to prepare the *S*-enantiomer **35b** that starts with the formation of the imide **32**. This can be carried out by by heating **31** with CDI or by treating **31** with DMF/$SOCl_2$ at −70 to 0 °C. Both methods give **32** in 90% yield, and the imide is converted to the HBr salt of **33** by treatment with HBr in HOAc. The salt is isolated in 80% yield and then reacted with **34** to form **35a** for which no yield or purity data are provided. Catalytic hydrogenation of **35a** using Pd/C catalyst produces **35b** that is isolated in 85% purity, but no yield is reported. The product can be purified by crystallisation from H_2O followed by EtOAc/dioxane, but details are not provided.

The patent provides ^1H NMR data for **32**, **35a**, and **35b** and also mentions that the *R*-enantiomer of **35b** is prepared by an analogous route starting from the commercially available enantiomer of **31**.

Advantages. The process provides a route to compounds that are of interest for treating cancers and other diseases.

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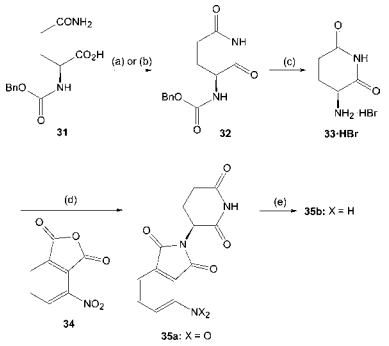
Scheme 10[a]



[a]Reagents and conditions: (a) (i) CDI, THF, reflux, 18 h; (ii) evaporated, add $CHCl_3$; (iii) wash in H_2O, brine wash, dry, evaporate, crystallise from Et_2O. (b) (i) $SOCl_2$, DMF, −70 to 0 °C, 1 h; (ii) add $CHCl_3$; (iii) wash in aq Na_2CO_3, dry evaporate. (c) (i) HBr, HOAc, 20 °C; (ii) rt 1 h; (iii) filter, HOAc wash, Et_2O wash. (d) (i) DMF, HOAc, 80 °C, 24 h; (ii) evaporate, add EtOH; (iii) filter, EtOH wash, dry. (e) (i) Pd/C, MeOH/dioxane, H_2, 3 bar, rt, 4 h; (ii) filter, evaporate, crystallise.

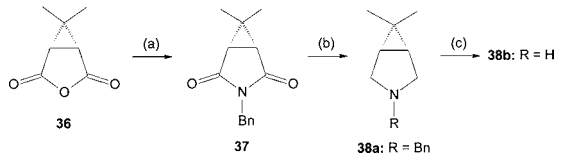
■ PATENT NO. U.S. 8,158,807

Assignee: Schering Corporation, Kenilworth, New Jersey, United States

Title or Subject: Process for the Preparation of 6, 6-Dimethyl-3-azabicyclo-[3.1.0]-hexane Compounds Utilizing Bisulfite Intermediate

This patent describes a method for preparing compounds such as **40a** that can be used to prepare an intermediate in the synthesis of a drug used to treat the hepatitis C virus. The patent summarises several methods for making azabicyclohexane ester compounds, and the high stereoselectivity is a key objective. Some of the known processes require the use of chiral ColC to isolate the desired isomer and are unsuitable for commercial production. The current patent is claimed to provide a viable industrial procedure for making a racemic mixture of the **40a** enantiomers, and Schemes 11 and 12 outline the method. The

Scheme 11[a]

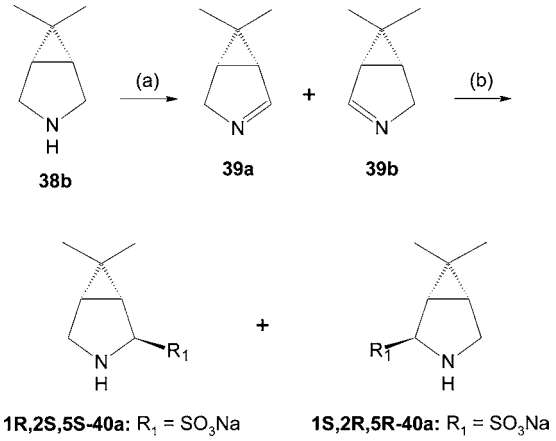


[a]Reagents and conditions: (a) (i) $BnNH_2$, MTBE, <10 °C, 0.5 h; (ii) distill off MTBE; (iii) 170 −180 °C, 5 h; (iv) cool <70 °C, add aq Pr^iOH; (v) cool to <10 °C, filter, wash, dry. (b) (i) $LiAlH_4$, THF, 50 °C; (ii) reflux, 2 h; (iii) cool to rt; (iv) add KNa tartrate, H_2O, NaOH, 20 °C, 1.5 h; (v) 45 °C, 0.25 h; (vi) separate, extract in MTBE, evaporate. (c) (i) charcoal, MeOH, filter; (ii) Pd/C, HOAc, MeOH, H_2, 3 bar, 25 °C, 6 h; (iii) filter, wash, concentrate at 40 °C; (iv) add H_2O, 20 °C; (v) 10 M NaOH, MTBE agitate, 10 min; (vi) separate; (vii) heat 90 °C, concentrate, distill.

first stage is shown in Scheme 11 in which caronic anhydride, **36** is aminated with $BnNH_2$ to give the imide **37** that is isolated in 85% yield. Reduction of **37** using $LiAlH_4$ produces **38a** that is obtained as an orange oil in 95% yield. Debenzylation is carried out using Pd/C catalyst, and **38b** is obtained as a colourless liquid in 97.8% yield after distillation. The patent reports that **36** can be prepared by literature methods and refers to U.S. application 2005/0059648.

In the next stage of the process, shown in Scheme 12, **38b** is oxidised to give a mixture of the imines **39a** and **39b** using $K_2S_2O_8$ and a catalytic amount of $AgNO_3$. The product is recovered by fractional distillation as an oil that solidifies on cooling. The solid is isolated in 65−75% yield, but the purity is not reported although ^1H NMR data are given. The isomer mixture is then converted to the racemic mixture of sulfonate adducts **40a** by treatment with $NaHSO_3$ that is obtained by dissolving $Na_2S_2O_5$ in H_2O.

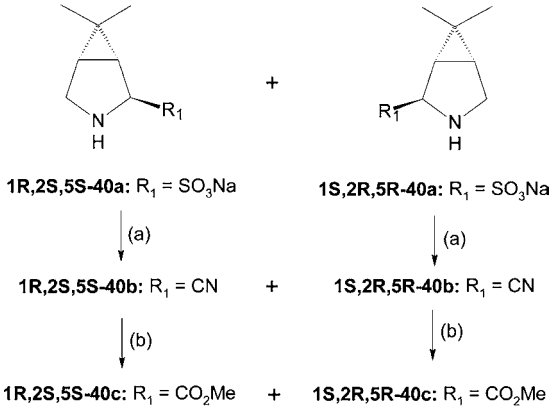
Scheme 12[a]



[a]Reagents and conditions: (a) (i) $K_2S_2O_8$, NaOH, MeCN, H_2O, −5 °C; (ii) add aq $AgNO_3$, −5 °C, 2 h; (iii) 2 °C; (iv) extract in MTBE, rt, separate; (v) dry, evaporate, distill; (b) (i) $Na_2S_2O_5/H_2O$, MTBE, rt, 2 h; (ii) separate, MTBE wash.

The mixture of sulfonates is isolated as an aqueous solution that is used in the next stage as shown in Scheme 13. These two compounds are novel and are covered by the patent claims.

Scheme 13[a]



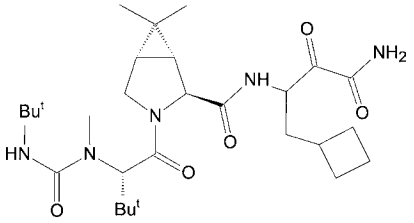
[a]Reagents and conditions: (a) (i) NaCN, H_2O, <25 °C, 1 h; (ii) add MTBE, rt, 5 min; (iii) separate, brine wash; (b) (i) 28% HCl in MeOH, <30 °C, 0.75 h; (ii) reflux, 5 h; (iii) evaporate <50 °C; (iv) cool <5 °C, add H_2O; (v) add aq K_3PO_4, <5 °C, 10 min; (vi) add aq NaOH to pH 9.3, < 5 °C, 0.25 h; (vii) extract in MTBE, brine wash.

The aqueous solution of the racemic sulfonate mixture **40a** is then converted to the nitriles **40b** by treatment with NaCN. The mixture is isolated as a solution in MTBE that is used to prepare the racemic esters **40c** by treatment with a solution of HCl in MeOH. The racemic ester mixture is recovered as a solution in

dx.doi.org/10.1021/op3002118 | Org. Process Res. Dev. 2012, 16, 1468−1481

MTBE in 75% yield based on **40b**. This solution is treated with di-*O*,*O*′-*p*-toluyl-D-tartaric acid (DTTA) to recover the desired **1*R*,2*S*,5*S*-40c** enantiomer in 50% yield as the DTTA salt with ee of 97.5%. The undesired enantiomer can be isolated using LTTA, although no examples are provided for this reaction.

The DTTA salt of the **1*R*,2*S*,5*S*-40c** enantiomer can be converted to the HCl salt, and this is used in the synthesis of **41** that is used to treat hepatitis C.



41

Advantages. The process provides a novel method for making the desired enantiomer that is used to prepare an important a drug molecule.

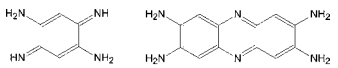
PATENT NO. U.S. 8,158,830

Assignee: E.I. du Pont de Nemours and Company, Wilmington, Delaware, United States

Title or Subject: Integrated Process for the Preparation of 1,2,3,4-Tetraaminobenzene

This is the first of two patents on the subject of aromatic amino compounds from the same company. The title compound **44d** is used in the production of polybenzimidazole-based high-performance fibres. Alternative processes for making **44d** are mentioned that involve reduction of nitro compounds, and these have waste disposal issues. An additional problem is that oxidation of **44d** and its impurities give rise to byproducts that are unacceptable in subsequent polymerisation processes. The patent discusses that problems, such as oxidation, occur when reaction intermediates and products are isolated in dry solid form in the presence of oxygen. The main products are shown below.

Impurities



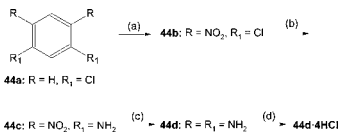
42 **43**

Hence, the process disclosed in this patent avoids handling solids by transferring slurries and carries out the reactions in the absence of O_2. In fact the exclusion of O_2 is specifically covered by one of the claims of the patent. The overall route to producing **44d** is shown in Scheme 14. The first step is nitration of **44a** by using fuming HNO_3, oleum, and H_2SO_4. The dinitro compound **44b** was recovered as a wet cake in 80% yield containing around 12% H_2O. This is then used in the second stage to produce **44c** by passing NH_3 gas into a glycol solution of **44b** that had been purged of O_2 using N_2 gas. The final stage is reduction of the nitrogroups in **44c** by catalytic hydrogenation with a Pt/C catalyst. Again N_2 purging was used to remove residual O_2 before starting the reaction. The amine product is isolated as the tetra-HCl salt by treatment with deaerated 38% aq HCl in the presence of Sn powder. The final yield of solid is 93% with a further 5% remaining in the mother liquor. Product purity is not reported. The reduction step is carried out on a kilo-scale, thus indicating the advanced stage of development of the procedure.

The patent provides a diagrammatic process operating scheme along with a detailed description of the various process steps.

Advantages. The process avoids the need to handle solid materials that are toxic and have skin-sensitizing properties. The use of an O_2-free system also avoids the formation of byproducts that give rise to problems in the use of the product.

Scheme 14[a]



[a]Reagents and conditions: (a) (i) HNO_3, H_2SO_4, $H_2S_2O_7$, <5 °C, 1.5 h; (ii) 100 °C, 1 h; (iii) cool to 5 °C, 2 h; (iv) filter, H_2O wash, wash in NH_4OH. (b) (i) NH_3, $(CH_2OH)_2$, 140 °C; (ii) cool to 60 °C, filter; (iii) glycol wash (×2), H_2O wash (×2). (c) (i) Pt/C, H_2O, H_2, 2.07 MPa, 81 °C, 3 h; (ii) cool to 40 °C, N_2 purge; (iii) aq HCl, heat to 80 °C; (iv) filter over active C, 65 °C. (d) (i) Sn, 38% HCl, 70 °C, 0.25 h; (ii) cool <10 °C, filter; (iii) H_2O wash, EtOH wash, dry.

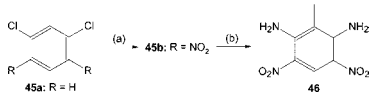
PATENT NO. U.S. 8,163,955

Assignee: E.I. du Pont de Nemours and Company, Wilmington, Delaware, United States

Title or Subject: Process for the Synthesis of 2,6-Diamino-3,5-dinitrotoluene

This is the second patent on aromatic amino compounds from the same company, and it describes a process for preparing **46** that is used in the production of dyes or pharmaceuticals. The process is reported to be enhanced by the presence of H_2O, and this results in highly pure products. As reported in the previous patent the process is also improved by excluding O_2 from the reaction. The patent claims cover the preparation of **46** from **45b**, and the latter compound is obtained by nitration of **45a**. Scheme 15

Scheme 15[a]



45a: R = H **46**

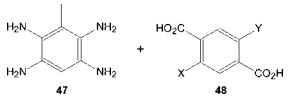
[a]Reagents and conditions: (a) see Scheme 14, step a; (b) (i) N_2 purge, $(CH_2OH)_2$, rt; (ii) NH_3, 150 °C, 9.5 h (iii) filter at 65 °C; (iv) glycol wash (×2), H_2O wash (×2), MeOH wash (×3); (iv) dry.

shows the overall route, although experimental details for the preparation of **45b** are not included. The patent merely outlines the method used which appears to be similar to the nitration process used for the preparation of **44b** from **44a** shown in Scheme 14. The amination of **45b** to give **46** is carried out using NH_3 gas in the absence of O_2, and this is covered by the claims of the patent. The reaction is improved by the presence of H_2O with the claims covering a range of 2−25%. However, the single example in the patent does not indicate that any additional H_2O is actually added. It is stated that the initial amount is around 2% and this increases over the course of the process to around 17%. The presence of H_2O is said to inhibit the formation of glycol ethers that can form at high conversions although the identity of these ethers is not disclosed. It is pointed out that the beneficial effect of H_2O means that aq NH_3 can be used although the patent does not describe an example of this. After the reaction is completed, the product is isolated as a bronze solid in 96% yield and purity of 96.4% (GC).

dx.doi.org/10.1021/op3002118 | *Org. Process Res. Dev.* 2012, 16, 1468−1481

The product **46** can be hydrogenated to tetraaminotoluene **47** using a similar procedure to that described in the previous patent but no details are provided. **47** can be used to prepare polybenzimidazole-based high-performance fibres. The patent discusses the formation of the complex formed from **47** and the acid **48** where X and Y may be halides, alkyl groups, OH, or SH. However, no details are provided, and the use of these complexes is not mentioned.

Complex



47 **48**

Advantages. The process enables the preparation of toxic and potentially hazardous materials without the need to handle the solids.

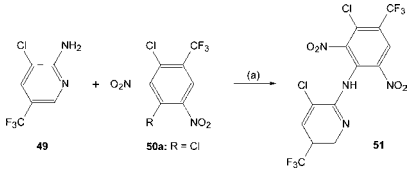
PATENT NO. U.S. 8,163,930

Assignee: Makhteshim Chemical Works Ltd., Beer Sheva, Israel

Title or Subject: Process for Preparing Pyridineamines and Novel Polymorphs Thereof

This patent covers the synthesis and purification of fluazinam, **51**, that is a broad-spectrum contact fungicide. The synthetic route used to prepare **51** is shown in Scheme 16 and involves the base-catalysed reaction of **49** with **50a** that was originally reported in U.S. 4,331,670. The original process used either THF or DMF as solvent at a concentration of <8.2% w/v of reactants. The reactants were not completely converted, and product yield was 75% for THF and 22% for DMF. A competing side reaction is the hydrolysis of **50a** to form the phenol **50b** (R = OH), and it is stated that, since THF and DMF are water-miscible and also form azeotropes with water, then any recycle of the solvent increases the amount of **50b** formed by hydrolysis. An additional problem with the original process is that workup involved extraction with EtOAc and purification using silica gel. These methods are claimed to be unsuitable for commercial operation. The improvement described in this process is the use of MIBK as reaction solvent, and this allows the reactant concentration of around 40% w/v and gives a product yield as high as 98%. The patent provides a table of data showing the effect of a selection of pure and wet solvents on reactant conversion and selectivity. The data show that both wet and pure MIBK are superior to other solvents. Using the MIBK/H_2O azeotrope, containing 1.6% H_2O, 1.8% of hydrolysis byproduct was produced, and pure MIBK gave only 1.2%. This compares with 8.5% for pure DMF and 14.1% for pure DMSO. The preparation of **51** is carried out according to Scheme 16 by adding seven portions of KOH every 20 min to the solution of **49** and **50a** and maintaining the temperature at <30 °C. The crude **51** is obtained with 95% purity and in 98% yield. This is then purified by crystallisation from hot EtOH and isolated in 90% yield with purity of 98%. The patent reports that the reaction is very sensitive to temperature, and above 40 °C there is significant formation of tars. By using MIBK this temperature sensitivity is reduced, and hence, the yield is improved. The low miscibility of MIBK and H_2O is suggested as being responsible for the improvements observed.

Scheme 16[a]



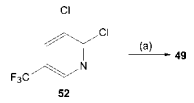
49 **50a**: R = Cl **51**

[a]Reagents and conditions: (a) (i) KOH, MIBK, <30 °C, 165 min; (ii) 5% HCl; (iii) wash in 5% NaCl, separate; (iv) evaporate, crystallise from hot EtOH.

The patent also describes two novel polymorphs of **51** and claims that crystalline polymorphs were previosuly unknown. The patent claims cover these polymorphic forms. Form I polymorph is obtained by crystallisation from EtOH, DCM, MeCN, and from Et_2O by slow evaporation. Form II is obtained by rapid evaporation from Et_2O or by allowing a solution in EtOH to evaporate in air. A mixture of Forms I and II was obtained from Pr^iOH or PhMe. The patent includes XRD, DSC/TG, and electron microscopy of both polymorphs.

The preparation of the reactants **49** and **50** is also outlined in the patent although full details are not provided. Scheme 17 shows the amine **49** is obtained from **52** and aq NH_3 by a process reported in the patent EP 0031218.

Scheme 17[a]

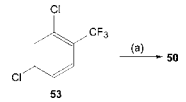


52

[a]Reagents and conditions: (a) Aq NH_3, 2−30 atm, 3−12 h.

Scheme 18 outlines the preparation of **50** by what seems to be standard nitration reaction of **53**, but no precise details are provided.

Scheme 18[a]



53

[a]Reagents and conditions: (a) HNO_3/H_2SO_4.

Advantages. The process gives improved yields of the product while using the same starting reagents as alternative methods and also provides novel polymorphs.

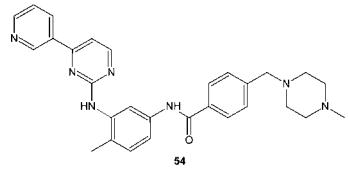
PATENT NO. U.S. 8,168,787

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

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

Imatinib, **54**, is available as Gleevec as the mesylate for the treatment of leukaemia, and a process for its production has been reviewed previously (*Org. Process Res. Dev* **2009**, *13*, 1046). The current patent states that the original synthetic route has many steps, gives an overall yield of <15%, and so an improved procedure is desirable.

Imatinib

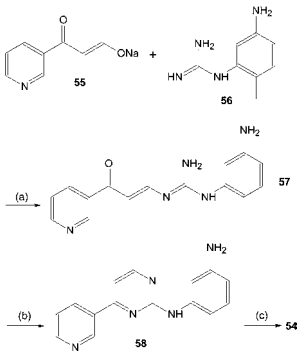


54

dx.doi.org/10.1021/op3002118 | *Org. Process Res. Dev.* 2012, 16, 1468−1481

A particular problem in the preparation of **54** is said to be in the synthesis of the intermediate **58**, and it is this that is focus of the current patent. Scheme 19 outlines the route for preparation

Scheme 19[a]

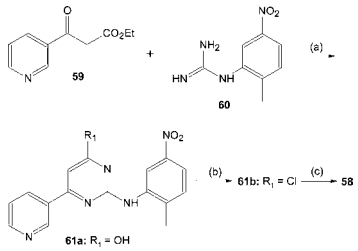


[a]Reagents and conditions: (a) HOAc, Bu^{n}OH, rt, 1 h. (b) (i) KOH, reflux 18 h; (ii) cool to rt, H_2O wash, concentrate; (iii) add PhMe, filter, dry. (c) No details provided.

of **58** via the intermediate **57** by reacting the Na salt **55** with the guanidine **56** in the presence of HOAc. The preparation is carried out in a one-pot reaction by adding KOH, with continuous removal of H_2O, to promote cyclisation. Compound **58** is recovered with 99.2% purity (HPLC) in 78% yield. The intermediate **57** can be isolated by omitting the KOH, although details are not provided.

An alternative method of preparing **58** is shown in Scheme 20 that starts with the reaction of oxyester, **59**, with guanidine, **60**, to

Scheme 20[a]

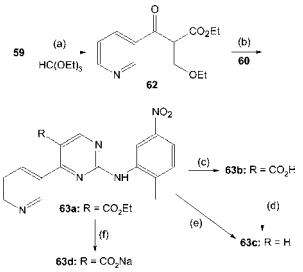


[a]Reagents and conditions: (a) (i) *N*-methylpyrrolidone, 150 °C, 5 h; (ii) cool, add EtOH, filter, dry. (b) (i) K_2CO_3, $POCl_3$, 50 °C, 6 h; (ii) evaporate, add H_2O, cool, filter, dry. (c) (i) Pd/C, Et_3N, EtOH/H_2O, H_2, 5 bar, rt, 40 h; (ii) filter, evaporate, add Pr^{i}OH; (iii) wash in aq Na_2CO_3, separate; (iv) evaporate, dry.

give the hydroxy compound **61a**. The product is isolated in 69.7% yield and 99% purity (HPLC area %), and this is converted to the chloro-derivative **61b** by treatment with $POCl_3$ in the presence of base. The product is isolated in crude form with 80% purity containing an unspecified impurity that is not removed; the mixture is used directly in the next step. The reduction of **61b** and the impurity is carried out with Pd/C catalyst in the presence of Et_3N in aq EtOH, and the product, **58**, is recovered in 85% purity.

The patent also describes the synthesis of a number of analogues of **58**, and these are shown in Scheme 21. The first step is condensation of **59** with $HC(OEt)_3$ in the presence of PPTS to give **62**. This is isolated in crude form as a dark oil with 80% purity that is then reacted with **60** to produce **63a**. This is

Scheme 21[a]



[a]Reagents and conditions: (a) (i) PPTS, reflux, 3 h; (ii) cool, evaporate, add PhMe; (iii) active C, filter, evaporate. (b) (i) PhMe, reflux; (ii) active C, 110 °C; (iii) filter at 0 °C. (c) (i) Na_2CO_3, EtOH/H_2O, reflux, 3 h; (ii) cool to 50 °C, add HOAc to pH 6; (iii) filter, dry. (d) CuO, 180 °C, 2 h; (ii) add aq NH_3 at 60 °C; (iii) cool to 25 °C, filter, dry. (e) (i) K_2CO_3, EtOH/H_2O, reflux, 1 h; (ii) distill 50% solvent; (iii) add HOAc at 80 °C to pH 7; (iv) CuO, *N*-methylpyrrolidone, distill H_2O; (v) 180 °C, 2 h; (vi) cool <90 °C, add EDTA/H_2O; (vii) filter at rt, H_2O wash, dry. (f) (i) Na_2CO_3, H_2O, EtOH, reflux 4 h; (ii) cool to rt, filter.

obtained in 88.2% with 97% purity and can be used to prepare **63b**, **63c**, and **63d**. Base hydrolysis produces the acid **63b** that is isolated with 95% purity, and decarboxylation with CuO gives **63c** that is obtained in quantitative yield and 97% purity. **63c** can also be obtained in 80% yield and 98% purity after crystallisation, by treatment of **63a** with K_2CO_3 followed by CuO. The Na salt **63d** is obtained in 85.7% yield from **63a** by treatment with Na_2CO_3 but the purity is not reported. The claims of the patent cover several other analogues of **58** in which the NH_2 group is replaced by a variety of amides, amines, or halogens, but there are no examples provided.

The patent gives basic ^{1}H NMR data and some GC−MS data for several of the intermediates prepared.

Advantages. The process provides an alternative synthesis of a key intermediate that gives good yields and avoids complex workup procedures.

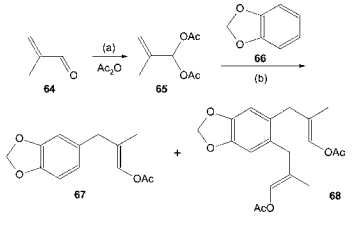
PATENT NO. U.S. 8,168,809

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

Title or Subject: Method for the Production of 2-Methyl-3-(3,4-methylenedioxyphenyl)propanal

The title compound, **69**, is used as a perfumery ingredient in soaps, shampoos, and cosmetics. The patent reports that synthesis of **69** by the method described in the Japanese patent, JP-A-57-45124, gives a product that contains HOAc, and is thus not suitable for use as a perfume. The current patent describes a process for preparing **69** containing <40 ppm of HOAc and is suitable for use as a perfume. The first stage of the synthesis is shown in Scheme 22 and begins with the preparation of **65** by

Scheme 22[a]



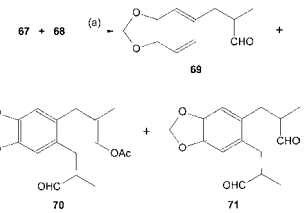
[a]Reagents and conditions: (a) (i) BF_3·Et_2O, Ac_2O, 0−20 °C; (ii) 10 °C, 2 h; (b) (i) BF_3·Et_2O, 40 °C, 4 h; (ii) H_2O wash, separate.

dx.doi.org/10.1021/op3002118 | *Org. Process Res. Dev.* 2012, 16, 1468−1481

acetylation of **64** with Ac_2O in the presence of BF_3. The product is not isolated, and **66** is reacted with the reaction mixture in the presence of BF_3 to form **67** as the major product (90.6%) and **68** (9.4%) in a yield of around 91%. Again the product is not purified, and the reaction mixture used in the next step. The patent also describes a method of preparing **67** and **68** in which **64**, Ac_2O, and **66** are mixed together, and then $FeCl_3$ is added. This method gives a 78.1% yield of **67** and 7.1% yield of **68**, both based on **64**, and the mixture was used to prepare **69**.

The mixture of **67** and **68** is used in a transesterification reaction with MeOH to form MeOAc. The reaction residue contains 78% of **69** with 20% of the high boiling compounds **70** and **71** (Scheme 23) and this equates to a 88.8% yield of **69** based

Scheme 23[a]



[a]Reagents and conditions: (a) (i) K_2CO_3, MeOH, 30−50 °C, 4 h; (ii) add 75% H_3PO_4; (iii) distill MeOH/MeOAc; (iv) H_2O wash, vac distill.

on **67** and 75.9% based on **64**. The mixture of **69**, **70** and **71** is separated by two distillations at temperatures <210 °C to avoid product decomposition and HOAc formation. After the second distillation **69** is isolated in 69.1% yield with 99.4% purity and HOAc content of 19 ppm. Examples describe distillations in which the temperature exceeded 220 °C, and higher levels of HOAc were found in the product. It is also shown that removal of the high-boiling compounds **70** and **71** before final distillation gives lower levels of HOAc. The patent points out that, when using batch distillation, it is very important to keep the temperature low because extended residence times in batch distillations will cause increased product decomposition. The patent also covers an option that can be carried out after the final distillation step. This may include washing with H_2O and then neutralisation with a base or neutralisation followed by adsorption onto a basic ion-exchange resin (IER).

The patent contains several examples that describe kilo-scale experiments and small-scale experiments that use metallic catalysts such as $Ti(OPr^i)_4$ for the transesterification step.

Advantages. The process gives a high-purity final product and does not require the purification or isolation of of intermediates.

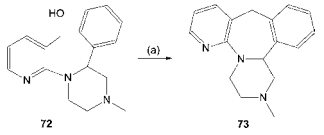
PATENT NO. U.S. 8,173,804

Assignee: Sumitomo Chemical Company Limited, Tokyo, Japan

Title or Subject: Process for Production of Mirtazapine

Mirtazapine, **73**, is an antidepressant that is prepared by cyclisation of **72** using concd H_2SO_4 (Scheme 24). The extraction

Scheme 24[a]



[a]Reagents and conditions: (a) 98% H_2SO_4, 40 °C, 9 h.

and purification of **73** from the reaction mixture presents the biggest difficulty, and a patent addressing this has been reviewed previously (*Org. Process Res. Dev.* **2004**, *8*, 553). The current patent states that DCM or PhMe have been used in the isolation of **73**, but there are strict limits on the residues of both of these solvents. The objective of the patent is to provide an improved extraction process, and it has been found that propanol is suitable for extracting **73** from aqueous mixtures under alkaline conditions, and the patent examples use both Pr^nOH and Pr^iOH. The cyclisation is carried out by adding **72** to H_2SO_4, and when the reaction is complete, the mixture is diluted by adding to an equal volume or more of H_2O. The pH of this mixture is adjusted to 1.5 with aq NaOH and decolourising charcoal added. After filtration the liquid is extracted with Pr^iOH and 25% aq NaOH added to a pH of 11. There then follows a sequence of steps including phase separation at 76 °C, addition of Pr^iOH and alumina, a second decolourising step, filtration, and evaporation of the solvent. The residue is dissolved in heptane and the mixture seeded at 53 °C, kept at 50 °C for 1 h, then cooled to 1 °C over 6 h to produce crystals of **73** that are recovered in 80% yield with purity of 99.98%. Using Pr^nOH the yield is slightly lower at 73%, and the purity is 99.97%.

Advantages. The process gives a high-purity product without using a problematic solvent such as DCM.

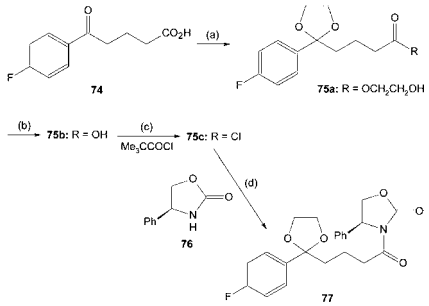
PATENT NO. U.S. 8,178,665

Assignee: Richter Gedeon Nyrt, Budapest, Hungary

Title or Subject: Process for the Production of Ezetimibe and Intermediates Used in This Process

Ezetimibe, **83b**, is used to reduce high levels of cholesterol in the blood, and the expiry of the original patent has spurred interest in new methods for its synthesis with one having been reviewed recently (*Org. Process Res. Dev.* **2012**, *16*, 11). The current patent summarises several approaches to the synthesis of **83b** and concludes that an improved method is required. This patent describes a procedure that includes a previously unpublished finding that a side product, from a Ti(IV)-catalysed Mannich reaction, can be converted into a useful intermediate. The overall process involves seven steps, and these are outlined in Schemes 25−28. The process begins with the preparation of the acid **75b**

Scheme 25[a]



[a]Reagents and conditions: (a) (i) $(CH_2OH)_2$, $HC(OEt)_3$, H_2SO_4, DCM, 25 °C, 6 h; (ii) $NaHCO_3$, 5 min; (iii) evaporate, add MeOH. (b) (i) 10% aq NaOH, <25 °C, 1 h; (ii) evaporate; (iii) aq citric acid, to pH 3, 0 °C; (iv) extract in EtOAc, H_2O wash (×5), dry, evaporate. (c) (i) Et_3N, THF, −20 °C, 0.5 h; (ii) −10 °C, 2 h. (d) (i) LiCl, 20 °C, 4 h; (ii) aq NH_4Cl, PhMe, separate; (iii) wash in aq citric acid (×2), aq NaOH (×2), H_2O (×3); (iv) dry, evaporate.

by reaction of the acid **74** with $(CH_2OH)_2$ and $HC(OEt)_3$ in the presence of H_2SO_4. The reaction proceeds via the ester **75a**

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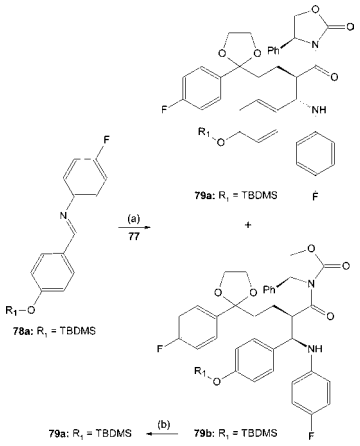
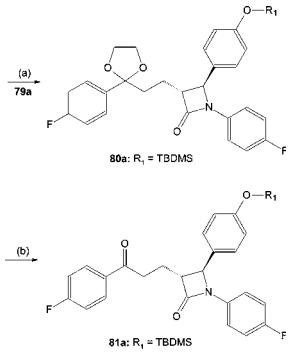
Scheme 26[a]



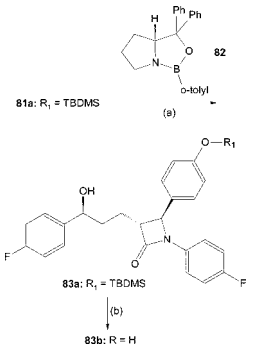
[a]Reagents and conditions: (a) (i) $Ti(OPr^i)_4$, $TiCl_4$, $EtNPr^i_2$, DCM, −40 °C, 1.5 h; (ii) Pr^iOH/DCM, −30 °C, 0.5 h; (iii) tartrate buffer pH 7, 0.25 h; (iv) separate, extract in DCM, dry, evaporate; (v) MeOH, 25 °C, 10 min, filter, dry. (b) (i) evaporate, add PhMe; (ii) silica gel, 25 °C, 0.25 h; (iii) filter, PhMe wash, evaporate; (iv) follow step (a).

Scheme 27[a]



[a]Reagents and conditions: (a) (i) BTSA, MeCN, 25 °C, 2 h; (ii) add $Bu^n_4NF{\cdot}3H_2O$, 1 h; (iii) add hexane/H_2O, separate; (iv) dry, evaporate. (b) (i) K10 clay, DCM, 25 °C, 4 h; (ii) filter, evaporate; (iii) crystallise from aq EtOH.

Scheme 28[a]



[a]Reagents and conditions: (a) (i) DCM, <0 °C; (ii) $BH_3{\cdot}Me_2S$, <0 °C, 6 h; (iii) 5% H_2O_2/MeOH, H_2SO_4, 0.5 h; (iv) separate, wash in 2 M H_2SO_4, aq Na_2SO_3, dry, evaporate. (b) (i) 2 M H_2SO_4, Pr^iOH, 70 °C, 2 h; (ii) cool, add H_2O, filter, wash, dry.

which is not isolated, and **75b** is recovered in 90% yield after recrystallisation and then treated with Me_3CCOCl to form **75c**. This is also not isolated but treated with **76** in the presence of anhydrous LiCl to form **77** that is isolated in 93% yield after crystallisation from Pr^iOH.

The next stage is outlined in Scheme 26 and begins with the Ti-catalysed Mannich reaction of **77** with the protected imine **78a** to give **79a**. This is recovered in 76% yield. Also produced is the isomer **79b** that is present in the MeOH mother liquor after **79a** is filtered off. The conversion of **79b** to **79a** is carried out under the conditions of the Mannich reaction, thus giving a final yield of **79a** of 89%. An alternative method for preparing **79a** is to start from the hydroxy compound **79b** (R_1 = H) that is silylated, but **79a** is not isolated before reaction with **77**.

In the next stage of the process, shown in Scheme 27, the isomer **79a** is silylated with *N*,*O*-bis(trimethylsilyl)acetamide (BTSA) then cyclised with Bu^n_4NF to give the azetidinone **80a** that is recovered as an oil with 92.9% purity. This is used without further treatment in the next step where the ketal is hydrolysed in the presence of an acid clay to form **81a**. The overall yield of **81a** from **79a** is 80%.

In the final stages of the process **81a** is enantioselectively reduced with $BH_3{\cdot}Me_2S$ in the presence of the chiral borane reagent **82** to produce **83a** that is isolated as an oil with 98% ee and converted to **83b** and treated with Pr^iOH and H_2SO_4 (Scheme 28). The product is crystallised from deionised H_2O and recovered in 81% yield (from **81a**). The patent does not report the analytical purity of the intermediates or final product but provides ^1H NMR data.

The patent claims that the compounds **75b**, **77**, **79a**, **79b**, **80a**, **81a**, and **83a** are all novel. It is also stated that the starting material, **74**, is a novel compound, but there are no details of its preparation.

Advantages. The process is claimed to be an economic, industrially viable method for producing ezetimibe.

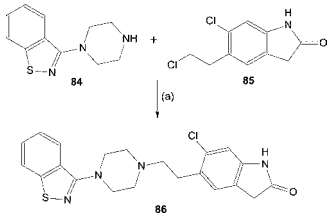
PATENT NO. U.S. 8,178,674

Assignee: Ranbaxy Laboratories Limited, New Delhi, India

Title or Subject: Process for the Preparation of Ziprasidone

Ziprasidone, **86**, is antipsychotic drug used as the HCl salt to treat schizophrenia. Methods for its preparation are summarised and said to give impurities that darken the product and complicate its purification. The patent describes a method of preparing **86** that is colour stable and of high purity. The synthesis involves the reaction between **84** and **85** by heating them together in an aqueous solution in the absence of a base (Scheme 29). After this

Scheme 29[a]



[a]Reagents and conditions: (a) (i) H_2O, reflux, 6 h; (ii) filter at 98 °C; (iii) H_2O, 95 °C, 0.5 h; (iv) filter at 95 °C; (v) Pr^iOH, reflux, 1 h; (vi) 35 °C, 2 h; (vii) filter, wash, dry at 55 °C; (viii) THF, reflux, 0.25 h; (ix) add H_2O, reflux, 0.25 h; (x) active C, reflux, 1 h; (xi) filter at 65 °C; (xii) concentrate at 55 °C; (xiii) 35 °C, 0.5 h; (xiv) 3 °C, 2 h; (xv) filter, wash in PriOH, dry at 55 °C, 8 h.

step the solid is filtered off from the hot mixture, then refluxed in H_2O, and filtered. The wet solid is refluxed in an organic solvent, such as Pr^iOH, filtered off, and dried. The crude solid has a purity of around 97% and is then refluxed in THF before H_2O is added,

dx.doi.org/10.1021/op3002118 | Org. Process Res. Dev. 2012, 16, 1468−1481

followed by active C. After a further period of refluxing, the C is removed from the hot solution, and most of the THF is removed by evaporation. The concentrated solution is cooled and the product isolated in 71% yield with 99.75% purity (HPLC). Compound **86** can be converted to its HCl salt by treatment with HCl/Et_2O in a chlorinated solvent. The salt is isolated in 94% yield with purity of 99.9%.

The patent also reports on the synthesis of **86** using the 2-bromethyl analogue of **85** and claims that derivatives with other leaving groups can be used, but there are no examples.

Advantages. The process gives high purity of the desired product and high yields despite the use of several solvents and filtration steps in the purification stage.

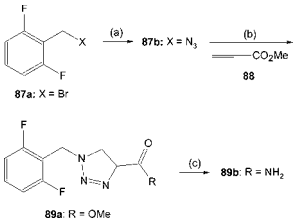
PATENT NO. U.S. 8,183,269

Assignee: CIPLA Ltd., Mumbai, India

Title or Subject: Process for the Preparation of Rufinamide

Rufinamide, **89b**, is an anticonvulsant used with other medications in the treatment of seizure disorders. The original synthesis of **89b** is said to require isolation of intermediates in each of the four steps of the synthesis. In addition, the process uses nonenvironmentally friendly reagents and solvents, and so an alternative route is described. The synthetic route described in this patent is outlined in Scheme 30 and is carried out in aq

Scheme 30[a]



[a]Reagents and conditions: (a) NaN_3, H_2O, 75 °C, 30 h. (b) (i) rt; (ii) 65 °C, 5 h. (c) (i) aq NH_3, rt; (ii) 75 °C, 5 h; (iii) filter, H_2O wash, dry.

solution as a one-pot process beginning with the preparation of the azide **87b** from **87a**. The examples use NaN_3, and the claims also cover the use of KN_3 and Me_3SiN_3. The azide is then reacted with the acetylenic ester **88** to form the triazole **89a** that is treated with aq NH_3 to give **89b** in an overall yield of 52%. The reaction is also carried out with isolation of the intermediates **87b** and **89a**, and the overall yield is 29.5%. The product purity is not reported for either method. This new route is similar to the original route that uses the acid in the second step instead of the methyl ester. The product of this reaction is then esterified to give **89a**.

Advantages. The use of the ester **88** and the development of a one-pot process improves the overall yield and process efficiency of the original method.

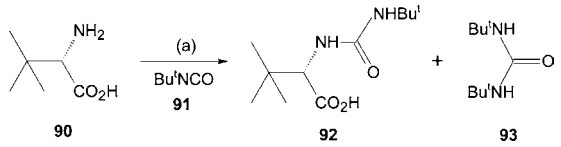
PATENT NO. U.S. 8,183,408

Assignee: Kaneka Corporation, Osaka, Japan

Title or Subject: Process for Production of *N*-Carbamoyl-*tert*-leucine

The title compound **92** is used as an intermediate in the synthesis of pharmaceuticals and agrochemicals. **92** is referred to as a useful compound in the synthesis of a drug for treating hepatitis C. The patent mentions that *N*-carbamoyl amino acids can be prepared from an amino acid and isocyanic acid. However, investigations showed that **92** cannot be made by this method because of the formation a dipeptide and a urea as byproducts. The problem has been overcome by carrying out the reaction under conditions where the pH is carefully controlled. Scheme 31

Scheme 31[a]



[a]Reagents and conditions: (a) (i) 48% aq NaOH to pH 12.4, <5 °C; (ii) **91**, <5 °C, 6 h; (iii) 35% HCl to pH 3, extract in EtOAc; (iv) H_2O wash, concentrate; (v) add PhMe, filter, dry.

shows the reaction used to prepare **92** that limits the amount of the urea **93** and the unidentified dipeptide. The reaction is carried out by adding 48% aq NaOH to **90** to give a pH of 12.4 followed by addition of **91**. Analysis of the reaction mixture showed that the yield of **92** is 99% and contained 0.3% dipeptide and 0.2% **93**. After extraction and purification **92** was isolated in 96% yield with purity 99.9%.

When the reaction is carried out at an initial pH of 10.2, the amount of **93** is 5.6% with 0.3% dipeptide, and the yield of **92** is 91%.

Advantages. The process provides a route to the desired compound without producing high levels of byproducts.

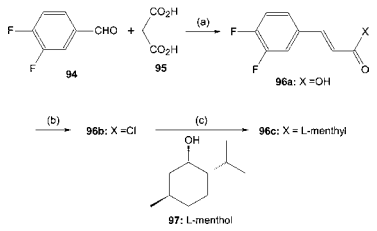
PATENT NO. U.S. 8,183,412

Assignee: AstraZeneca AB., Sodertalje, Sweden

Title or Subject: Process for Preparation of Cyclopropyl Carboxylic Acid Esters and Derivatives

This patent describes the synthesis of a range of novel cyclopropyl derivatives that are intermediates in the production of pharmaceuticals. The single claim in the patent covers the novel acyl chloride compound **99b**, and the route for its preparation is shown in Schemes 32 and 33. The first stage of the

Scheme 32[a]



[a]Reagents and conditions: (a) (i) piperidine, pyridine, 90 °C, 5.5 h; (ii) add H_2O, vac distill; (iii) 37% HCl to pH 1; (v) cool 25 °C, filter, wash, dry. (b) (i) pyridine, PhMe, 65 °C, ; (ii) add $SOCl_2$ over 0.5 h; (iii) 65 °C, 2.25 h; (iv) add PhMe, vac distill. (c) (i) PhMe, 65 °C, 5 h; (ii) 25 °C, 14 h; (iii) add PhMe, brine wash, aq $NaHCO_3$ wash, H_2O wash; (iv) azeotropic distill; (v) add DMSO, distill PhMe.

process is the synthesis of the *L*-menthyl ester **96c** by the method outlined in Scheme 32 . This starts with the condensation of the aldehyde **94** with **95** in the presence of piperidine to form the acid **96a** that is isolated in 88% yield. The acid is then converted to the acyl chloride **96b** by treatment with $SOCl_2$, and the product is recovered as a solution in PhMe in almost quantitative yield. Esterification of **96b** with **97** in the presence of pyridine produces the *L*-menthyl ester **96c** that is recovered as a solution in DMSO.

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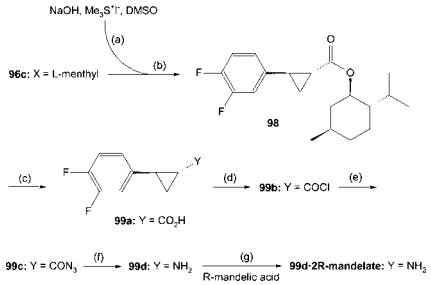
Scheme 33[a].



[a]Reagents and conditions: (a) 25 °C, 1.5 h. (b) (i) 25 °C, 20 min; (ii) 25 °C, 3 h; (iii) recrystallise from heptane. (c) (i) EtOH, 46 °C; (ii) 45% aq NaOH, 46 °C, 3 h; (iii) distill EtOH/H_2O; (iv) cool 24 °C, add H_2O; (v) PhMe wash, 37% aq HCl to pH 2; (vi) extract in PhMe, wash in 1% HCl; (vii) add PhMe, azeotropic drying; (viii) add PhMe, concentrate. (d) (i) $SOCl_2$, pyridine, PhMe, 65 °C, 1 h; (ii) 70 °C, 6 h; (iii) cool 40 °C, add PhMe, distill. (e) (i) NaN_3, PhMe, Bu^n_4NBr, Na_2CO_3, H_2O 1.5 °C, 1.25 h; (ii) 0 °C, 2 h; (iii) add H_2O, separate, brine wash, 0 °C. (f) (i) PhMe, 100 °C, 1.5 h; (ii) cool 20 °C; (iii) add to 3 M HCl, 80 °C, 2.25 h; (iv) add H_2O, cool 25 °C, separate; (v) 45% aq NaOH to pH 12; (vi) extract in EtOAc, H_2O wash. (g) (i) EtOAc, 17 °C; (ii) 25 °C, 3.1 h; (iii) filter, wash in EtOAc (×2), dry.

Scheme 33 outlines the next stage which is quite lengthy, and the workup details are very briefly described. In the first step the DMSO solution of **96c** is added to a solution of the ylid prepared from Me_3SI and finely powdered NaOH. This produces the menthyl ester **98** that is initially isolated as a solution in DMSO. Crystallisation is used to isolate the trans (1*R*,2*R*) enantiomer, and examples report the preparation of **98** containing from 82 to 96% of this enantiomer. Base hydrolysis of **98** (91.8% ee) gives the acid **99a** that is isolated in 61% and then treated with three portions of $SOCl_2$ in the presence of pyridine to obtain the acyl chloride **99b**. This is recovered as a solution in PhMe in quantitative yield that is used to produce the azide **99c** by reaction with NaN_3 in a two-phase mixture containing Bu^n_4NBr as phase transfer catalyst (PTC). The azide **99c** is isolated as a solution in PhMe that is used to prepare the amine **99d**. This is carried out by heating to 100 °C, then treating with HCl and neutralising with aq NaOH. The amine is recovered as a solution in EtOAc and then converted to the mandelate salt by treatment with *R*-mandelic acid.

All of the examples describe preparations on a multikilo scale, thus indicating the advanced commercial status of the process.

Advantages. The process provides a novel method of preparing the desired compounds via novel intermediates.

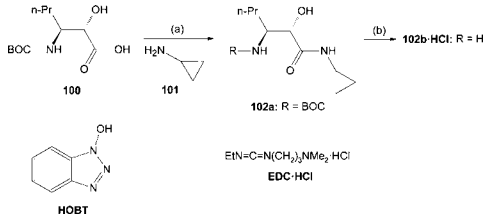
PATENT NO. U.S. 8,183,413

Assignee: Kaneka Corporation, Osaka, Japan

Title or Subject: Process for Production of *β*-Amino-*α*-hydroxycarboxamide Derivative

This patent describes a process for producing the amine salt, **102b·HCl**, that is used in the preparation of antiviral agents for treating HIV and hepatitis C. Alternative processes for preparing this compound are mentioned as having problems such as the use of undesirable solvents such as DMF, $CHCl_3$, and dioxane. In addition the patent reports that following one method resulted in crystals that could not be filtered, and hence the method is not commercially suitable. The new method avoids the use of the problem solvents and uses esters, THF, or other ethers. The process is outlined in Scheme 34 and begins with the amidation of **100** in a condensation reaction with **101** in the presence of

Scheme 34[a]



[a]Reagents and conditions: (a) (i) EDC·HCl/HOBt, EtOAc, H_2O, 0 °C, 22 h; (ii) 5% aq $NaHCO_3$, 40 °C; (iii) separate at 40 °C. (b) (i) evaporate; (ii) add Pr^iOH, 60 °C; (iii) add HCl/Pr^iOH, 1 h; (iv) 60 °C, 8 h; (v) cool to 0 °C over 6 h; (vi) filter, wash, dry.

HOBT and EDC·HCl. The crude amide **102a** is isolated as a solution in EtOAc in 90% yield with purity 96.1% and 99.3% ee. The amide can be crystallised and the purified material is recovered in 78% yield and 100 area % purity and 100% ee. The formation of **102b** can be carried out without isolation of the pure amide. This is done by evaporation of the EtOAc from the solution and dissolving in Pr^iOH followed by treatment with HCl. This removes the BOC protection and forms the amine that is isolated as the HCl salt in yields up to 90% with 100% purity and 100% ee. ^1H NMR data are provided for **102a** and **102b**.

The patent reports comparative experiments using DMF or dioxane as solvent in the first step. The reaction mixture solidified, and recovery of products proved very difficult.

Advantages. The process gives crystals than can be easily recovered and is more suitable for commercial production.

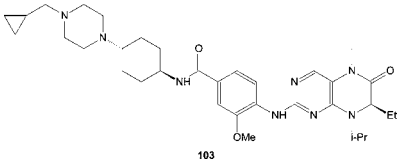
PATENT NO. U.S. 8,188,086

Assignee: Boehringer Ingelheim International GmbH., Ingelheim, Germany

Title or Subject: Specific Salt Anhydrous and Crystalline Form of a Dihydropteridione Derivative

A number of dihydropteridione derivatives are known to be effective in preventing cell proliferation and are therefore useful in treating tumours. This comprehensive patent provides a method of preparing suitable crystalline and anhydrous forms of the compound **103** that are pharmacologically active and also suitable for use in preparing drug formulations.

Dihydropteridione



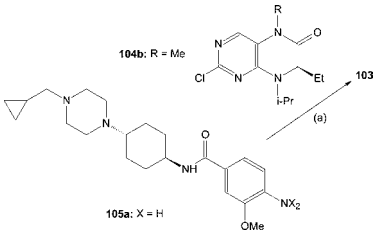
103

The patent reports what is described as a surprising finding that the tri-HCl salt of **103** is a suitable material. The free base **103** is prepared by the condensation of **104b** with **105a** in the presence of TsOH, as shown in Scheme 35. After completion of the reaction the crude free base **103** is recovered as a viscous oil and then treated with HCl in an organic solvent to form the tri-HCl salt that is isolated in 91% yield. Alternatively, the free base is not isolated, and the workup involves adding concd HCl to the reaction mixture followed by Me_2CO, and the crude tri-HCl salt is recovered in 92% yield. Purification is by crystallisation from refluxing EtOH, addition of H_2O, and cooling to precipitate the crystals, but the purity is not reported.

A hydrated form of the tri-HCl salt is obtained by dissolving the free base in EtOH at rt followed by addition of concd HCl

dx.doi.org/10.1021/op3002118 | *Org. Process Res. Dev.* 2012, 16, 1468−1481

Scheme 35[a]

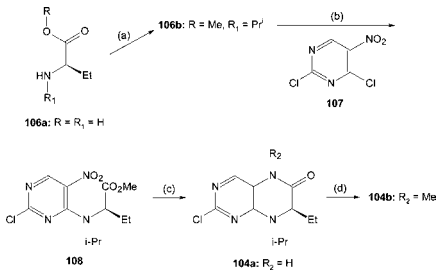


[a]Reagents and conditions: (a) (i) TsOH, 4-methylpentan-2-ol, reflux, 24 h; (ii) add concd HCl at 100 °C; (iii) add Me_2CO at 60 °C; (iv) rt, 16 h; (v) filter, wash, dry.

then cooling to 2 °C. An anhydrous form of the tri-HCl salt can be obtained by drying the salt at 130 °C. The patent does not provide details of the purity of the free base or any of the salts. However, solubilities of the hydrated salt in aqueous and organic media are reported, and the XRD data for the hydrated form are provided. It is also reported that the hydrated salt has very good solid state stability.

The patent also describes the synthesis of the two reactants, **104b** and **105a**. Scheme 36 shows the method used to prepare

Scheme 36[a]

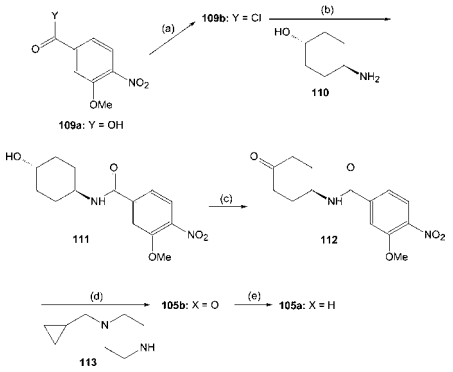


[a]Reagents and conditions: (a) (i) $HC(OMe)_3$, MeOH, 50 °C; (ii) $SOCl_2$, 60 °C, 0.5 h; (iii) reflux, 3 h; (iv) distill off MeOH, add PhMe; (v) $NaBH(OAc)_3$, PhMe, 60 °C; (vi) add Me_2CO, 40 °C; (vii) rt, 16 h; (viii) add NH_4OH (exotherm); (ix) add H_2O, 50 °C; (x) separate, H_2O wash; (xi) HCl/EtOH; (xii) distill off EtOH, add THF, cool <2 °C; (xiii) filter, wash, dry. (b) (i) 50% aq NaOH, cyclohexane/H_2O; (ii) separate; (iii) $NaHCO_3$, cyclohexane, reflux, 5 h; (iv) distill off solvent; (v) filter off salts at 75 °C; (vi) evaporate, add Pr^iOH; (vii) concentrate, cool to 2 °C; (viii) filter, wash, dry. (c) (i) Pt/C, $V(acac)_3$, THF, H_2, 3 bar, 35 °C; (ii) filter, evaporate; (iii) Pr^iOH, reflux; (iv) add H_2O, cool to 2 °C; (v) filter, wash, dry. (d) (i) $(MeO)_2CO$, K_2CO_3, 130 °C, autoclave, 5 h; (ii) cool, add H_2O/EtOAc; (iii) separate, evaporate; (iv) add EtOH/H_2O, 60 °C; (v) cool rt, filter, wash, dry.

104b. This starts from the readily available amino acid **106a** that is esterified and alkylated to form **106b**. This is carried out in a multistep, one-pot procedure by first reacting **106a** with $HC(OMe)_3$ and $SOCl_2$. This is followed by treatment with $NaBH(OAc)_3$, Me_2CO, NH_4OH, and finally **106b** is recovered as the HCl salt in 90% yield. The salt is treated with aq NaOH to form the free base that is reacted with **107** in the presence of $NaHCO_3$. This forms **108** that is isolated in 79% yield and then hydrogenated using Pt/C catalyst and $V(acac)_3$. **104a** is recovered in 90% yield and then methylated with $(MeO)_2CO$ and K_2CO_3 to form **104b** that is isolated in 82% yield. Again no purity details are provided for any reaction products.

The preparation of **105a** is shown in Scheme 37 and begins with the formation of the amide **111**. The acid **109a** is first treated with $SOCl_2$/DMF to form **109b**, and the crude product is

Scheme 37[a]

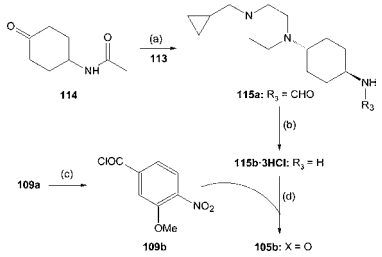


[a]Reagents and conditions: (a) (i) $SOCl_2$/DMF, PhMe, reflux, 2 h; (ii) evaporate. (b) (i) 30% K_2CO_3, THF, <13 °C; (ii) 20 °C, 1 h; (iii) add H_2O, filter, wash, dry. (c) (i) $RuCl_3$, NMMO, MeCN, reflux, 1 h; (ii) evaporate, add H_2O; (iii) cool 5 °C, filter, wash, dry. (d) (i) PhMe, MsOH, reflux, 3 h; (ii) evaporate; (iii) add EtOH, $NaBH_4$, 20 °C, 3 h; (iv) $NaBH_4$, 20 °C, 16 h; (v) evaporate, add H_2O/cyclohexane; (vi) cool 5 °C, filter; (vii) 1 M HCl, active C, filter; (viii) add MTBE, NH_4OH to > pH 7; (ix) cool 4 °C, filter, H_2O wash; (x) MTBE, reflux, cool, filter, wash, dry. (e) (i) Raney Ni, DMF, MeOH, H_2, 3 bar, 20 °C; (ii) filter, evaporate, add H_2O; (iii) cool 5 °C, filter, wash, dry.

added to a suspension of **110** in THF and aq K_2CO_3. This produces **111**, and the crude product is recovered in 98% yield and then oxidised to **112** by treatment with $RuCl_3$ and *N*-methylmorpholine *N*-oxide (NMMO). Compound **112** is obtained in 91% yield and then reacted with the piperazine **113** in the presence of MsOH. The solvent is evaporated off, and the reaction mixture is then treated with $NaBH_4$; after further workup involving the use of two further solvents, H_2O and dil HCl, the product **105b** is isolated in 46% yield. The nitro group is then reduced using Raney Ni to give **105a** that is obtained in 90% yield.

An alternative method of preparing **105b** is also described, and this is outlined in Scheme 38. The method starts with the

Scheme 38[a]



[a]Reagents and conditions: (a) (i) MsOH, PhMe, reflux; (ii) add EtOH at 50 °C; (iii) add $NaBH_4$, 20 °C, 16 h; (iv) add 4 M HCl, 20 °C; (v) evaporate, add aq K_2CO_3, MIBK; (vi) active C, filter hot; (vii) cool, filter, dry. (b) (i) 24% HCl, reflux, 6 h; (ii) evaporate, crystallise from Pr^iOH; (iii) MTBE wash, dry. (c) (i) $SOCl_2$/DMF, PhMe, reflux 1 h; (ii) evaporate, add THF. (d) (i) Pr^i_2NEt, THF, 0 °C; (ii) aq NaOH to pH 10; (iii) separate, brine wash; (iv) evaporate; (vi) MTBE, reflux; (vii) cool 20 °C, filter, dry.

condensation reaction of the amide **114** with **113** in the presence of MsOH followed by reduction with $NaBH_4$ to form the trans compound, **115a**. This is isolated in 41% yield and then treated with HCl to give **115b** that is isolated in quantitative yield as the tri-HCl salt containing 5% H_2O. For the final step **109a** is

dx.doi.org/10.1021/op3002118 | *Org. Process Res. Dev.* 2012, 16, 1468−1481

converted to the acid chloride **109b** by reaction with $SOCl_2$/DMF. The product is not isolated, and the solution is added to a mixture of the tri-HCl salt of **115b** and $EtNPr^i_2$. The reaction is monitored by TLC; when complete, the mixture is treated with aq NaOH. The crude product is recovered and crystallised from MTBE. The yield of **105b** is 83%, but the purity is not reported.

Advantages. The patent does provide a route for making a crystalline salt that is suitable for preparing pharmaceutical formulations. However, the multiple steps of the synthesis use a considerable number of solvents and frequent steps that involve evaporation to dryness.

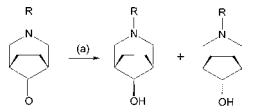
PATENT NO. U.S. 8,188,286

Assignee: Nippon Soda Co. Ltd., Tokyo, Japan

Title or Subject: Process for Production of Azabicycloalkanol Derivative

The particular compound covered by this patent is **117a** (R = Bn) that is an intermediate in the synthesis of agrochemicals or pharmaceuticals, while the trans isomer **117b** is not as desirable. The preparation of similar alkyl-substituted compounds usually involve the reduction of the corresponding ketone **116**. The production of the cis alcohol with high selectivity is not always efficient or commercially viable. The patent refers to a process for reducing the methyl compound using metallic Na and benzophenone that gives the cis alcohol, but the process requires heating for 230 h. In a second process the trans isomer is prepared then converted to the triflate followed by inversion. Another process is known using a transitional metal catalyst that involves a racemisation step, but this gives only 50% yield, and the other isomer is lost. These procedures are said to be unsuitable for industrial production. The process disclosed in this patent involves the formation of an asymmetric *tert*-OH group by a hydrogen-transfer reaction, and this is isomerised with a transition metal complex to form the thermodynamically more stable diastereomer. Scheme 39 outlines the method for the

Scheme 39[a]



116 117a 117b

[a]Reagents and conditions: (a) (i) $RuCl_2(PPh_3)_3$, Bu^tOK, Pr^iOH, PhMe, reflux, 0.5 h; (ii) distill Pr^iOH; (iii) reflux, 6 h; (iv) add PhMe, cool, filter; (v) wash in cold PhMe.

preparation of **117a** from **118** using Pr^iOH as the source of H atoms and $RuCl_2(PPh_3)_3$ in the presence of Bu^tOK. One example gave a 98/2 mixture of **117a** and **117b** in 49% yield.

An isomerisation reaction was carried out starting with a 49/51 mixture of **117a** and **117b**. With the use of $RuCl_2(PPh_3)_3$ in the presence of Bu^tOK, the product was recovered in 69% yield and contained 98% **117a**.

Advantages. The procedure gives high selectivity to the desired cis isomer and the isomerisation step can be applied to cis/trans mixtures to increase the level of cis isomer.

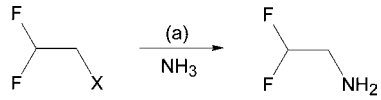
PATENT NO. U.S. 8,188,319

Assignee: Bayer CropScience AG, Monheim, Germany

Title or Subject: Process for Preparing 2,2-Difluoroethylamine

The title compound, **119**, is a useful chemical intermediate, and there are a number of methods reported for its preparation that are referred to in this patent. Some processes use excessively long reaction times or use what are described as hazardous reagents. These are all said to be uneconomic and unsuitable for commercial production of **119**. The process is shown in Scheme 40 and involves

Scheme 40[a]



118a: X = Cl
118b: X = Br

119

[a]Reagents and conditions: (a) (i) KI, *N*-methylpyrrolidine, autoclave, 145 °C, 5.5 h; (ii) cool <50 °C, remove NH_3; (iii) filter, wash in *N*-methylpyrrolidine, distill.

the reaction of **118a** with excess NH_3 in a solvent containing a minimum amount of H_2O containing KI or other halides as catalyst. A wide range of solvents is claimed to be suitable, and the examples in the patent use *N*-methylpyrrolidine, Bu^nOH, or DMSO. With the use of **118a** and DMSO as solvent the yield of **119** is 87%, and when the bromo derivative **118b** (X = Br) is used, the yield is 82%. Using **118a** in NMP the yield is 88%. The product is isolated by vac distillation after removal of NH_3 and filtration to remove the ammonium salt that is formed. The claims state that the water content of the reaction mixture is <15%, but the examples all have 250 ppm or less.

A comparative experiment is described in which the bromo compound **118b** is reacted with an excess of 25% aq NH_3 in the presence of KI. After 1.2 h at 100 °C, the reaction produced only a 13% yield of **119** after workup and distillation. This indicates that the presence of H_2O is detrimental to the reaction.

Advantages. The process gives high yields of product and is said to be suitable for industrial production.

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dx.doi.org/10.1021/op3002118 | *Org. Process Res. Dev.* 2012, 16, 1468–1481