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 February and March 2012

SUMMARY

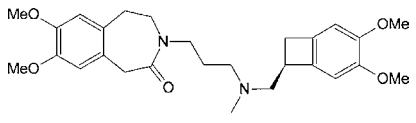
The current review contains 20 patents from an original list containing 313 patents that fitted the selection criteria. Several of the patents describe new methods for making agrochemicals, and two covering difluoromethylpyrazoles from different companies may provide interesting discussions for patent lawyers. A detailed patent describes a process for making the fungicide azoxystrobin using DABCO as a catalyst in a coupling reaction. It is found that the order of adding the reagents has an impact on the yield with the best results when DABCO is added last. Another fungicide is mandipropamid, and a comprehensive patent describes a new synthesis of this and related compounds that does not require isolation of intermediates. A series of novel alkylthiopyridines is described that may have potential in the synthesis of agrochemicals. A patent describes new methods for the preparation of pyrimidines that are intermediates in the synthesis of sulphonamide herbicides. The new process avoids the use of toxic reagents such as hydrazine and cyanogen halides. β-Santalol is a sesquiterpene found in sandalwood and used in perfumery, and a very detailed patent describes a number of novel dieneols used in the synthesis of the compound. Furanones are used in flavours and fragrances, and a process is described for preparing a dihydroxybutanedione intermediate used in the synthesis. Unfortunately the reaction involves a mixed aldol condensation and is rather unselective. Oxymorphone is used for treating moderate to severe pain, and a process for its synthesis is described that starts from a oripavine, a less commonly used and cheaper starting material. The patent is very similar to a recently reviewed patent on the same subject, and patent lawyers may again find their services required. The compound cilastatin is often used in conjunction with antibiotics to prevent degradation of the antibiotic, and a new method for its preparation starts from the readily available amino acid L-cysteine and avoids chromatographic separation methods. Ivabradine is used to treat heart-related diseases, and two patents from the same organisation cover intermediates and a novel synthesis of the drug itself that improves an earlier, very low-yield route from the same organisation. The anti-allergy drug montelukast sodium can contain a range of impurities when synthesised, and crystals are often needle-shaped that are not desirable in drug formulated products. A detailed patent describes several of these and provides an improved synthetic route by preparing a high-purity diol that is used in the synthesis. A further aspect is that the process gives non-needle-shaped crystals. Another product with impurity problems is adapalene that is used to treat acne and other skin conditions. The compound is normally white but can discolour, becoming yellow because of impurities. A patent describes both a method of determining the impurity level, a process for its removal, and the synthesis of adapalene itself. A new method for the preparation of an intermediate in the synthesis of the anticancer drug erlotinib is described. Although the process gives good overall yield, it involves the use of a toxic chloroether compound. TEMPO is widely used in synthesis by organic chemists and also in polymerisation reactions as an inhibitor. A new process for its preparation is described that does not require close pH control that is needed by alternative methods to avoid potential explosions. A new synthesis of the antifungal agent voriconazole is reported as well as new polymorphs of the free base and its camphorsulphonate salt. The process also avoids using chlorinated solvents. Asoxime chloride is used to treat the effects of poisoning by organophosphate nerve agents. A new method for preparing the salt avoids the use of highly toxic and extremely carcinogenic bis-chloromethyl ether. Tin compounds are useful, but toxic reagents and a process for producing monotosylates of diols is described that uses low concentrations of Sn oxides. A patent describes a new process for the preparation of agomelatine that is used to treat jet-lag among other things. The new method uses a cheaper starting material. A number of the patents in this collection describe experiments carried out on a kilo or multikilo scale that 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. 8,110,701

Assignees: Les Laboratoires Servier, Suresnes Cedex; Centre National de la Recherche Scientifique, Paris Cedex; Universite Claude Bernard Lyon, Villeurbanne Cedex, France

Title or Subject: Process for the Preparation of Functionalised Benzocyclobutenes and Application in the Synthesis of Ivabradine and its Pharmaceutically Acceptable Salts

This is the first of two patents covering ivabradine **1** that is used as the HCl salt to treat heart-related diseases. An earlier patent from one of the assignees, covering the synthesis of an intermediate, has been reviewed (*Org. Process Res. Dev.* **2011**, *15*, 957).



1

Ivabradine

The current patent describes the synthesis of the amine **5** that is also used in the preparation of **1**, and its synthesis is outlined in Scheme 1. The route starts from the malonate derivative **2**, but the patent does not describe how this is

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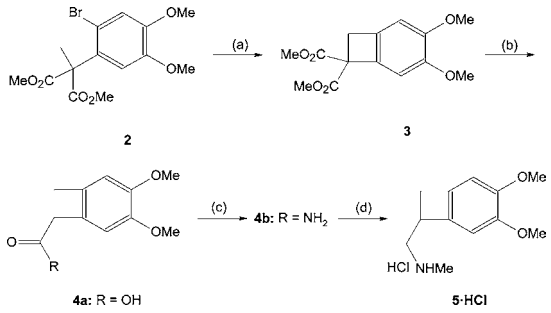
Scheme 1[a]



[a]Reagents and conditions: (a) (i) $Pd(OAc)_2$, $P(Bu^t)_3$, K_2CO_3, DMF, 140 °C; (ii) cool to rt, add Et_2O, filter; (iii) brine wash, dry evaporate; (b) (i) KCN, DMSO, 130 °C, 12 h; (ii) cool to rt, add 1 M HCl+ Et_2O, 1 h; (iii) wash in aq NaOH, add 6 M HCl, rt; (iv) extract in Et_2O, dry, evaporate; (c) (i) H_2SO_4, MeOH, reflux, 2 h; (ii) cool to 10 °C, add aq $MeNH_2$, 2 h; (iii) evaporate, extract in DCM; (iv) wash, dry, evaporate; (d) (i) BH_3/THF, rt, 16 h; (ii) add EtOH, rt, 1 h; (iii) HCl/EtOH, rt, 4 h; (iv) filter, dry.

obtained. In the first step **2** undergoes a cyclisation reaction by using a base and a Pd phosphine catalyst to effect C−H bond activation and formation of **3**. The mixture is heated in a sealed tube for an unspecified amount of time, although the reaction is apparently monitored by GC/MS. The crude product **3** is purified by flash chromatography (FC), but the yield and purity details are not provided. In the next step **3** is treated with KCN followed by HCl, and the patent does warn of the production of HCN at this stage. After workup, the crude acid **4a** is isolated and purified by FC, and again no yield or purity data are given. The acid is then converted to the amide **4b** by reaction with $MeNH_2$ and isolated in crude form in 83% yield. The purity is not provided but its mp is given as 142−147 °C. Reduction of **4b** using BH_3 gives **5** that is isolated as the HCl salt in 77% yield with mp 174−177 °C. The patent mentions that **5** can be resolved and the 7*S*-isomer isolated using camphorsulphonic acid although no details are given.

The patent also outlines the preparation of a number of cyclobutene analogues of **3**, **4**, and **5** by similar procedures, but yield and purity details are lacking.

Advantages. The patent provides a route to the synthesis of an important intermediate for the preparation of ivabradine, although the industrial potential is not known since all of the examples relate to small-scale experiments.

PATENT NO. U.S. 8,119,794

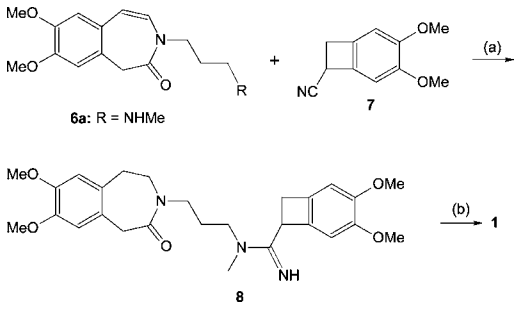
Assignee: Les Laboratoires Servier, Suresnes Cedex, France

Title or Subject: Process for the Synthesis of Ivabradine and its Pharmaceutically Acceptable Salts

This is the second patent covering **1** that describes a novel method for its synthesis. The new route is shown in Scheme 2, and the first step is a coupling reaction of the amine **6a** and the nitrile **7** in the presence of a CuCl to give **8**. This is isolated as a brown oil in 35% yield containing 21% of **6**. This mixture is used in the second stage where reduction of **8** is carried out using $NaBH_4$. The product is racemic **1** that is isolated as an oil then purified by FC to give a crystalline solid in 33% yield after two steps. The racemic mixture is separated by chiral column chromatography (ColC), and the two enantiomers are each isolated in 81% yield.

The current method is a significant improvement over an earlier route to **1** covered by a 1993 patent from the same

Scheme 2[a]



[a]Reagents and conditions: (a) (i) CuCl, MeOH, reflux, 24 h; (ii) cool 0 °C, add concd HCl to pH 2; (iii) 20% aq NaOH to pH 8; (iv) extract in DCM, dry, evaporate; (b) (i) $NaBH_4$, MeOH, 25 °C, 16 h; (ii) 20% aq NaOH; (iii) add DCM, vigorously stir. 0.25 h; (iv) separate, H_2O wash, dry, evaporate; (v) FC; (vi) chiral ColC.

company (EP 0534859). The earlier method starts from **7**, but this is converted to the chiral amine **5** before being coupled with the iodo derivative **6b** (R = I), and in the current patent it is admitted that the original route gives an overall yield of only 0.5%.

Advantages. The process greatly improves the earlier route, but the yield is still quite low and requires two chromatographic separation steps.

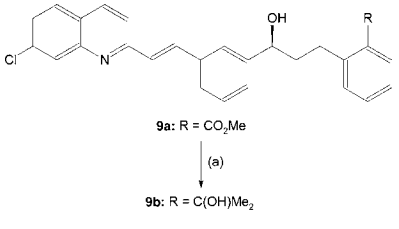
PATENT NO. U.S. 8,115,004

Assignee: MSN Laboratories Limited, Hyderabad, Andhra Pradesh, India

Title or Subject: Process for Pure Montelukast Sodium and Amine Salts Using Pure Intermediates

Montelukast sodium **12b** is used in the treatment of asthma and allergic rhinitis, and a patent covering its synthesis has been reviewed (*Org. Process Res. Dev.* **2009**, *13*, 829). A number of methods for preparing **12b** are discussed in the current patent, and one problem with these is that the final product can contain one or more of a range of impurities that are difficult to remove. Many of these impurities are found in the starting materials **9b** and **11b**, and these can give derivatives that contaminate the final product. A further problem with the alternative processes is that they are said to produce needle-shaped crystals, and these are difficult to use in formulations. The major aspect of the current patent is the preparation of the high-purity diol **9b** and thiol **11b** and their subsequent use in the synthesis of **12b**. The preparation and purification of almost 20 kg of the diol **9b** is outlined in Scheme 3. The ester **9a** is treated with MeMgCl in DCM, and the product is purified by heating in PhMe to remove the impurities. The procedure is quite lengthy and the patent should be consulted for full details. The alkylation reaction is carried out using two portions of

Scheme 3[a]



[a]Reagents and conditions: (a) MeMgCl/THF, DCM, −5 °C.

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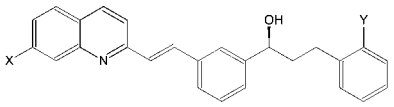
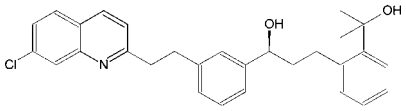
Grignard with workup using aq HOAc and PhMe, between each Grignard addition. The recovery of the crude material involves distilling off the DCM solvent and heating the residue in two batches of PhMe. The crude product is isolated in 65% yield with HPLC purity of 98.1% by cooling the PhMe solution and adding hexane. The precipitated **9b** is recovered and then purified by further heating in PhMe and crystallised by addition of hexane. The purified solid is isolated in 91.3% yield with purity of 99.84% (HPLC). This is then used in the preparation of **12b**.

Of the many impurities that can be found in **9b** the patent claims specifically mention **10a**–**10d**.



10a: X = Cl, Y = -CO_2Me
10b: X = Cl, Y = -Ac
10c: X = H, Y = -C(OH)Me_2

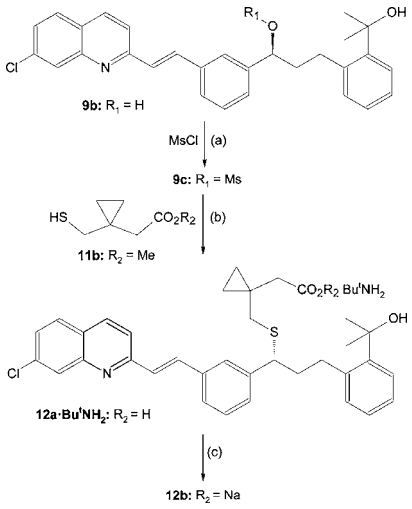


10d

Diol Impurities

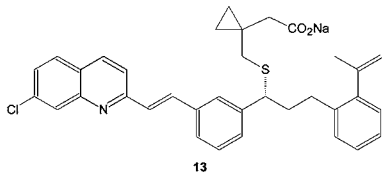
The claims of the patent cover the preparation of **12b** from purified **9b** that is specified to be free from the impurities **10a**–**10d**. The preparation of **12b** is shown in Scheme 4. Again the procedure is lengthy, and full details are given in the patent. The first step is conversion of **9b** to the mesylate **9c** by treatment with MsCl in the presence of $EtNPr^i_2$. The product is isolated as a wet solid and treated with **11b** and NaOMe in DMSO. The reaction mixture is then subjected to an extensive workup procedure involving treatment with H_2O, PhMe, aq NaOH, HOAc and extraction into EtOAc. After further washing and drying, the EtOAc is replaced by PhMe, and this is finally replaced by EtOAc. Addition of Bu^tNH_2 to the solution produces the amine salt **12a·Bu^{t}NH$_2$** that is isolated and then purified by heating in PhMe. The patent example describes a kilo-scale reaction that produces 5.7 kg of the amine salt of 99.67% purity (HPLC). This contains 0.1% of the impurity formed from **10d** and **11b**, and the level of other impurities is not reported. The amine salt is then used to prepare **12b** by treatment with NaOH/MeOH; amine and solvent are distilled off. PhMe is added in two portions to help remove MeOH. The solution is treated with active C, the filtrate is concentrated, heptane is added to precipitate the product, and 4.4 kg of **12b** is isolated in 86.7% yield with purity 99.72%. The product is obtained as non-needle-shaped crystals, and microscope images of these are included in the patent.

Scheme 4[a]



[a]Reagents and conditions: (a) (i) PhMe/MeCN (1:4.5), 50 °C, 0.5 h; (ii) cool −20 °C, add $EtNPr^i_2$, 0.75 h; (iii) add MsCl, −20 °C, 10 h; (iv) filter, wash; (b) (i) DMSO, NaOMe. −5 °C, 10 h; (ii) workup with H_2O, PhMe, aq NaOH, HOAc, extract into EtOAc; (c) (i) Bu^tNH_2, EtOAc, 30 °C, 8 h; (ii) filter, wash, dry; (iii) PhMe, 80 °C, 0.5 h ; (iv) 30 °C, 10 h; (v) filter, repeat (iii) and (iv); (vi) filter, dry at 55 °C.

The final product contains impurities from the reaction of **11b** with **10d** and **10a** (0.1% and 0.01%, respectively). Three other impurities are also identified, the styrene **13** (0.1%), formed by dehydration of the *tert*-alcohol group; the sulfoxide **14** (0.04%) formed by air oxidation of **12b**; and the cis isomer of montelukast sodium, ***cis*-12b** (0.08%).



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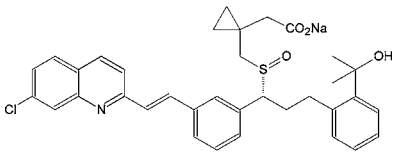

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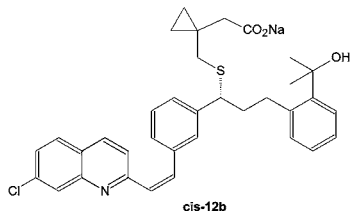
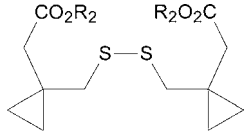


cis-12b

Additional Impurities

Impurities in the mercapto ester **11b** are also discussed in the patent. This material can contain the diacid **15a** and diester **15b** that can be found in the final sample of **12b**. An example describes the purification of a 10 kg batch of the mercapto acid **11a** (R_2 = H). Purification of **11** containing 13% of **15a** is carried out by recrystallisation from PhMe. The product contains 4.93% **11a** which is used to prepare the ester **11b**, but the details of this are not described.



15a: R_2 = H
15b: R_2 = Me

Thiol Impurities

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The patent also describes the gram-scale preparation of the amine salts using Bu^nNH_2, Bu^sNH_2, and Bu^iNH_2. DSC, XRD, and IR data are provided for the Bu^nNH_2 salt.

Advantages. The process provides a very high-purity product and has been carried out at a large scale. However, there are a considerable number of solvents used.

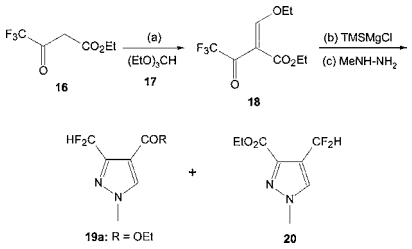
PATENT NO. U.S. 8,115,012

Assignee: BASF SE, Ludwigshafen, Germany

Title or Subject: Process for Preparing Difluoromethyl-pyrazolyl Carboxylates

This is the first of two patents covering the synthesis of difluoromethylpyrazoles that are used in the synthesis of crop protection chemicals. In this patent, compounds such as **19a** are used in the preparation of fungicides such as **22**. Alternative methods for preparing the fungicides are described as using difluoroacetoacetates that are expensive. The current patent attempts to provide a cheaper route to the fungicides and reports a surprising finding that the more readily available trifluoroacetoacetates, such as **16**, can be used to make the desired pyrazole compounds. This has been achieved by the reaction shown in Scheme 5 for the preparation of **19a**. The

Scheme 5[a]

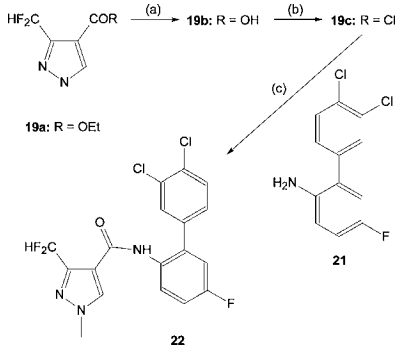


[a]Reagents and conditions: (a) (i) Ac_2O, 120 °C, 6 h; (ii) distill; (b) (i) TMSCl, Mg, DMF, ultrasound, <10 °C, 1.5 h; (ii) distill TMSCl; (c) (i) EtOH, −50 °C, 3 h; (ii) rt, 10 h; (iii) evaporate, extract in EtOAc; (iv) wash in aq NaCl/HCl (×3); (v) evaporate, recrystallise from hexane.

reaction starts with the preparation of **18** by condensation of **16** with **17** in the presence of Ac_2O. The product is a colourless liquid that is recovered by distillation in 90% yield and purity of >98%. The next step is a key aspect of the process and provides the means for converting the CF_3 group in **18** to the CF_2H group in **19a**. In this step **18** is treated with a chlorosilane in the presence of a metal. The patent claims cover the use of a metal that has a redox potential of −0.7 V and the example uses Mg to form a Grignard reagent with Me_3SiCl and ultrasound is used to activate the Mg metal. After reaction with the Grignard a solution of $MeNHNH_2$ is added to this mixture to produce **19a**, and GC analysis of the reaction mixture showed that it contained 82% **19a** and 18% of the regioisomer **20**. After workup and recrystallisation, **19a** was recovered in 70% overall yield and 95% purity, containing 6% of isomer **20**. An alternative preparation gave a mixture containing 84% of **19a** and 16% of **20**. The patent reports on the use of different solvents for the reaction of **18** with $MeNHNH_2$. The results showed that the ratio of **19a** to **20** varied slightly as the solvent changed: MeOH (86:14), MeCN (84:16), PhMe (80:20), THF (80:20). Also prepared are the Me and Pr^i ester analogues of **19a**.

The ester **19a** can be hydrolysed with aq NaOH to produce the acid **19b** that is isolated as a light-brown solid. The isomer purity of **19b**, and yield details are not given. The acid is then converted to the acyl chloride **19c** by reaction with $SOCl_2$, and the product is obtained in 92% yield with purity of 99% after vacuum distillation as outlined in Scheme 6. The acyl chloride

Scheme 6[a]

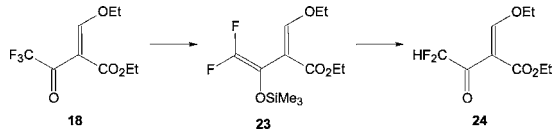


[a]Reagents and conditions: (a) (i) 50% aq NaOH, EtOH, reflux, 4 h; (ii) evaporate, add 10% HCl to pH 1; (iii) filter; (b) (i) $SOCl_2$, PhMe, 90 °C, 3.5 h; (ii) cool, concentrate, add PhMe; (iii) concentrate, vac dist; (c) (i) pyridine, PhMe, 45 °C, 0.5 h: (ii) 75 °C, 1 h; (iii) wash hot solution with 5% aq HCl, then 10% aq $NaHCO_3$, then H_2O; (iv) cool to rt, filter, dry.

is then condensed with the biphenylamine **21** in the presence of pyridine to obtain the **22** that is an example of one of the desired fungicides. After washing with aq HCl, aq $NaHCO_3$, and then H_2O the final product is isolated in 81% yield and purity of >99%. The patent reports on the preparation of a range of compound analogous to **22** that are prepared by reacting **21** with different phenylamines and biphenylamines.

The patent discusses the possible mechanism by which the CF_3 group in **18** is converted to the CF_2H group during preparation of **19a**. It is suggested that the reaction of the Grignard reagent affords a silylated enol such as **23** that is hydrolysed during workup to the intermediate **24** as shown in Scheme 7. It is stated that **23** can be identified in the reaction

Scheme 7[a]



[a]No reaction details provided.

solutions, and in some cases the analogue of **23** can be isolated, but details are not provided. The suggested formation of the compound **24** is of interest in view of the second patent, reviewed next, covering the preparation of **19b**.

Advantages. The process enables the use of cheaper and more readily available reagents than alternatives.

PATENT NO. U.S. 8,124,787

Assignee: Syngenta Crop Protection Inc., Greensboro, North Carolina, United States

Title or Subject: Process for Production of Pyrazoles

This is the second patent covering difluoromethylpyrazoles that also describes a process for the preparation of the compound **19b**. In this case the route starts from the difluoromethyl compound **24** directly, and this is reacted

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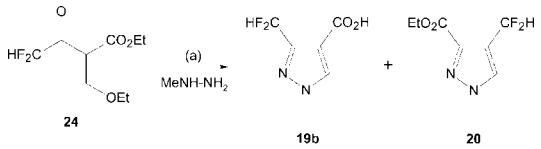
with aq methylhydrazine in the presence of NaOH in H_2O and a solvent that is immiscible with H_2O. As is the case with the previous patent the reaction also formed the regioisomer **20**, and similarly the amount formed varies with different solvent. Xylene is the preferred solvent and gives a 94% yield with 3% of **20**. Other solvents used are PhMe, PhCl, MIBK, and cyclohexane that give yields of **19b** >86% with <5% of **20** (Scheme 8). When dioxane was used, the yield of **19b** was 78% with 9% **20**, and using EtOH the yield of **19b** was 74% with 20% of **20**.

Scheme 8[a]



[a]Reagents and conditions: (a) (i) NaOH, H_2O, xylene, 15 °C, 0.5 h; (ii) 25 °C, 10 min; (iii) 30% aq NaOH, 65 °C, 0.75 h: (iv) phase separation at 65 °C; (v) add 32% aq HCl, 95 °C; (vi) cool 25 °C in 3 h; (vii) filter, H_2O wash (×2) at 0 °C; (viii) dry at 60 °C.

The claims of this patent cover very specific steps in the reaction such as the order of addition of reagents and their relative amounts. Although there are certainly differences between the process in this patent and that of the previous one, the similarities may be sufficient to engage the minds of patent attorneys.

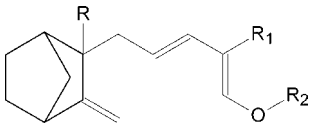
Advantages. The process provides a regioselective method of making the desired pyrazole.

PATENT NO. U.S. 8,115,020

Assignee: Firmenich S.A., Geneva, Switzerland

Title or Subject: Process for the Preparation of *β*-Santalol and Derivatives Thereof

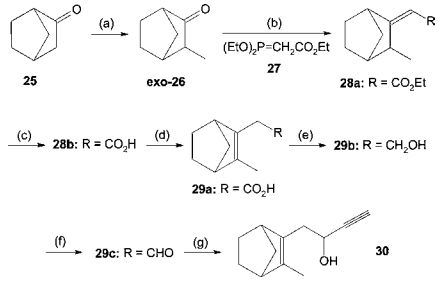
This patent describes a process to prepare *β*-santalol, **37**; a sesquiterpene found in sandalwood and used in perfumery. The claims of the patent do not cover the synthesis of **37** but actually cover a range of novel dieneol compounds, and these may be used to prepare **37** or its intermediates. The general formula of these compounds is shown below where R = Me or Et; R_1 = H, Me, or Et; and R_2 = alkyl, alkenyl, acyl with up to three C atoms, or a silyl group with three to eight C atoms.



Dieneols

The patent describes a considerable number of experiments but does not report the stereochemistry of most of the intermediates that are prepared. It is stated in the patent that the reactions can be carried out using pure or mixed isomers, but in very few cases are specific isomers mentioned. Hence, the schemes only show nonspecific isomers except in the few cases where these are mentioned in the patent. Alternative synthetic routes to **37** are described as being unsuitable for industrial manufacture because they are very long or require expensive starting materials or reagents. The use of two Wittig reactions in one of the alternative methods is specifically mentioned as being undesirable. The synthesis of **37** described in this patent involves the preparation of the alkynol **30**, a key compound that is prepared from (±)-norcamphor **25**. There are two routes from **25** to **30** that are described in the patent, the first of which is shown in Scheme 9. The workup details of

Scheme 9[a]

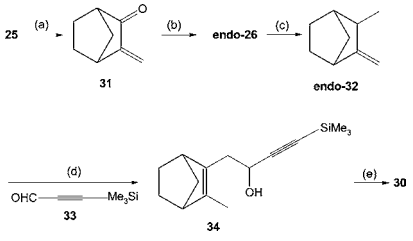


[a]Reagents and conditions: (a) (i) BuLi, Pr^i_2NH, THF, −78 °C; (ii) MeI, −78 °C, 0.5 h; (iii) aq NH_4Cl, rt; (b) (i) THF, 50 °C, 25 min; (ii) reflux, 2 h; (c) aq KOH, EtOH, reflux, 3.5 h; (d) BuLi, Pr^i_2NH, THF, −78 °C; (ii) aq HCl, rt; (e) (i) $LiAlH_4$, Et_2O, rt, 1 h; (ii) reflux, 1.5 h; (f) (i) DMP, DCM, rt, 140 min; (ii) aq NaOH, 0 °C; (g) (i) EtMgBr, THF, rt, 0.5 h; (ii) aq HCl.

the reactions are omitted from all of the reaction schemes due to lack of space, and interested readers are encouraged to consult the patent. The first stage of this is the preparation of **exo-26** by alkylation of **25** with MeI and BuLi. The product is isolated in quantitative yield after vacuum distillation (vac dist). In the next step **exo-26** is treated with **27** that is formed from NaH and $(EtO)_2P(O)CH_2CO_2Et$. The crude product is the ester **28a** that is isolated by vac dist in 85.5% purity. The ester is then hydrolysed using KOH to form the acid **28b** that is recovered by vac dist in 75% yield (from **exo-26**). **28b** is then converted to **29a** by treatment with BuLi/Pri_2NH, and the acid is recovered by vac dist in 86% yield and 95% purity. Reduction of **29a** using $LiAlH_4$ gives the alcohol **29b** in 76% yield and 89% purity after vac dist. Oxidation of the alcohol using Dess–Martin periodinane (DMP) produces the aldehyde **29c** that is isolated by vac dist in 83% yield and 88% purity. In the final step, the aldehyde is treated with EtMgBr to form **30** that is purified by FC and isolated in 79% yield. The product contains two isomers whose NMR spectra are provided, but their structures and relative amounts are not.

The second method of preparing **30** from **25** is outlined in Scheme 10, and this begins with the preparation of **31** by reacting **25** with $HCHO/MeOH/H_2O$ in the presence of

Scheme 10[a]



[a]Reagents and conditions: (a) (i) Et_2NH, $HCHO/MeOH/H_2O$, 0 °C; (ii) add HOAc; (iii) warm rt, add **25**, BHT; (iv) reflux 5 h; (vi) aq HCl; (b) Pd/C, H_2, 1 atm, rt, 2 h; (c) Bu^tOK, $MePPh_3Br$, THF, rt, 23 min; (d) (i) Me_2AlCl, DCM, −78 °C, 0.25 h; (ii) aq HCl; (e) K_2CO_3, MeOH, rt, 1 h.

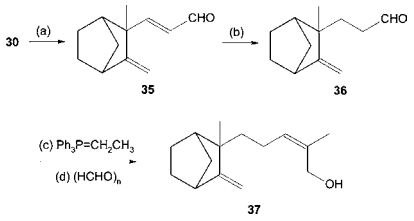
dx.doi.org/10.1021/op3001367 | Org. Process Res. Dev. 2012, 16, 1198–1211

Et_2NH and **31** is isolated by vac dist in 48% yield. Catalytic hydrogenation of **31** over Pd/C gave the **endo-26** that is recovered by vac dist in quantitative yield, and methylation using Bu^tOK and $MePPh_3Br$ produces **endo-32**. This is isolated in 76% yield by vac dist and then treated with the alkynal **33** in the presence of Me_2AlCl. **33** is obtained from EtMgBr and Me_3Si-CH≡CH in 49% yield after vac dist. The product of the reaction of **33** and **endo-32** is **34** that is recovered in 59% yield after purification by FC. The patent reports that this reaction can also be carried out by using $BF_3{\cdot}Et_2O$ and gives complete conversion in 5 min. In the last step of the process, treatment of **34** with an excess of K_2CO_3 in MeOH give **30** that is recovered in quantitative yield. The purity of intermediates is not reported although their ^1H and ^{13}C NMR data are provided.

The patent indicates that the preferred route to **30** is from **31** and follows Scheme 10. An alternative method of preparing **31** is described in the patent that does not start with **25** but involves a Diels–Alder reaction between cyclopentadiene and crotonaldehyde. Two examples are described that both involve a pyrolysis step at very high temperatures; one at 415 °C, and the other at 610 °C. These reactions are based on literature reports and although they are described in the patent they are not reviewed here.

The patent also describes two routes for the preparation of **37** that both proceed via the aldehyde **36**. The first route is outlined in Scheme 11, and **36** is obtained by conversion of **30**

Scheme 11[a]

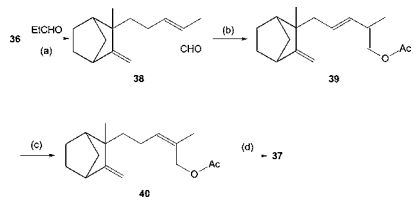


[a]Reagents and conditions: (a) (i) $CuBF_4(MeCN)_4$, DCE, rt; (ii) 50 °C, 140 min; (b) $Pd/CaCO_3$, MeOH, H_2, 1 atm, rt, 4.5 h; (c) (i) THF, −78 °C, 20 min; (ii) BuLi, −78 °C, 20 min; (iii) warm to 0 °C, add $(HCHO)_n$, 0.5 h; (iv) rt, 1 h, add NH_4Cl.

to **35** using $CuBF_4(MeCN)_4$ and is recovered by vac dist in 96% yield. The preparation of **35** is also carried out using $AgBF_4$ or $AgNO_3/KNO_3$ in place of the Cu salt, but the yields are lower. Hydrogenation of **35** using $Pd/CaCO_3$ produces **36** that is isolated in 87% yield after purification by FC. In the final stage of this route to **37** the Wittig reagent, formed from Ph_3PEtI and BuLi, is reacted with **36**, and then hydroxymethylation using HCHO (from paraformaldehyde) in the presence of BuLi produces **37**. The final product **37** is recovered by vac dist in 50% yield and consists of the Z/E isomers in the ratio of 95:5.

The second method for the conversion of **36** to **37** is shown in Scheme 12 and starts with aldol condensation of **36** with EtCHO catalysed by hexamethyleneimine (HMI) and $PhCO_2H$. This gives **38** that is isolated in 80% yield after FC. The aldehyde **38** is then converted to the diene acetate **39** by reaction with Ac_2O in the presence of DMAP. The ester is recovered after FC in 82% yield with 93% purity and has a E/Z ratio of 79:21. Partial hydrogenation using $[CpRu(COD)]BF_4$ and maleic acid gives **40** that is isolated after vac dist in 92% purity containing 81% Z isomer and 5% E. A simple treatment

Scheme 12[a].

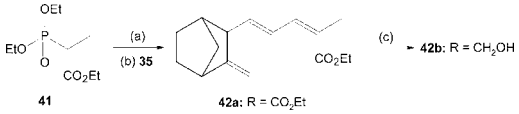


[a]Reagents and conditions: (a) HMI, $PhCO_2H$, PhMe, reflux, 6 h; (b) Ac_2O, DMAP, Et_3N, reflux, 22 h; (c) $[CpRu(COD)]BF_4$, $CH_2(CO_2H)_2$, Me_2CO, 60 °C, H_2, 4 bar, 24 h; (d) K_2CO_3, MeOH, rt, 1 h.

of **40** with excess K_2CO_3 in MeOH is said to give **37** in quantitative yield.

The patent also describes the use of the acraldehyde **35** in the preparation of compounds **42a** and **42b** as shown in Scheme 13. The ester **42a** is obtained by reaction of **35** with

Scheme 13[a]



[a]Reagents and conditions: (a) NaH, THF, 50 °C, 0.75 h; (b) (i) add **35**, 50 °C; (ii) reflux, 1 h; (iii) aq HCl, rt; (c) (i) DIBALH, DCM, −78 °C, 70 min; (ii) aq HCl, 0 °C.

the phosphoryl ester **41**, followed by acid hydrolysis. The ester is isolated in 78% yield after vac dist and is then reduced using DIBALH to give **42b** that is obtained in 83% yield after FC. These compounds and their possible use are not mentioned further.

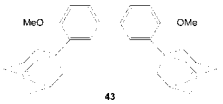
Advantages. The process provides a new route to the desired compound and provides some novel compounds. However, the patent criticises alternative routes for using Wittig reactions; yet this reaction is used twice in this new process. The process also has a large number of steps in common with alternative routes.

■ PATENT NO. U.S. 8,119,834

Assignee: Medichem S.A., Barcelona, Spain

Title or Subject: Process for the Preparation of Adapalene and Related Compounds

Adapalene **46c** is used to treat skin conditions such as acne and is available as Differine in the United States. The compound is described as white but can become yellow, and this is attributed to the quality of starting materials. Another problem is the presence of the dimeric impurity **43** that has very low solubility in many solvents and requires removal by chromatographic methods. This patent seeks to overcome these difficulties and claims to produce high-purity material. Despite the title of the patent the claims actually cover a method for assessing the purity of **46c** by determining the amount of **43** in the final product. The method, based on colorimetry, is described in the patent.



Dimer Impurity

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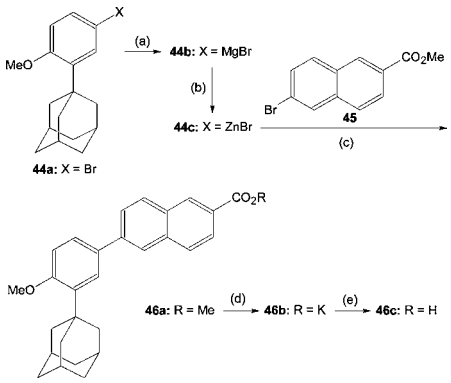
The synthetic route used to prepare **46c** is shown in Scheme 14, and it starts with the preparation of the zinc compound **44c**

Scheme 14[a]

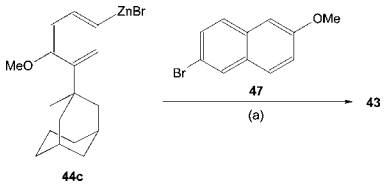


[a]Reagents and conditions: (a) (i) Mg, THF, 45 °C; (ii) add $Br(CH_2)_2Br$, 55 °C, 1.5 h; (b) cool <25 °C, add $ZnCl_2$, 1 h; (c) (i) (diphos)$NiCl_2$, rt, 2 h; (ii) H_2O, 1 M HCl, rt, 16 h; (iii) filter, wash in MEK; (iv) 1 M HCl, MEK, rt, 1 h.

via the Grignard **44b**. The reagent is not isolated, and in the next step it is reacted with the naphthoate ester **45** in the presence of the catalyst (diphos)$NiCl_2$ to produce **46a**. After a workup that involves heating in MEK and HCl and then heating in THF, the ester **46a** is isolated in 88.8% yield and contains 2.05% of the impurity **43** that is removed during the next step in the process. The crude ester **46a** is treated with Bu_4NBr and KOH to form the K salt **46b** that after workup is recovered in 99.2% yield and 99.86% purity and contains no detectable level of **43**. In the last step the K salt is acidified to form **46c** that is isolated in 89.3% yield (from **46b**) and 99.99% purity with the overall yield from **44a** being 78.7%. The patent includes XRD data for **46c**.

The patent describes a method for preparing pure **43** that is shown in Scheme 15. The Zn compound **44c** is treated with **47**

Scheme 15[a]



[a]Reagents and conditions: (a) (i) $Pd(OAc)_2$, THF, reflux, 24 h; (ii) evaporate, add 0.015 M HCl; (iii) add DCM/H_2O; (iv) filter, separate organic layer; (v) H_2O wash (×2); (vi) evaporate, MeOH wash, dry.

in the presence of $Pd(OAc)_2$, and after workup the product is isolated in 39.9% yield. Although the analytical purity is not given, the patent provides IR, ^1H, and ^{13}C NMR data, and the compound has a very sharp mp.

Advantages. The process provides an improved process for preparing adapalene and also a method to determine the product purity.

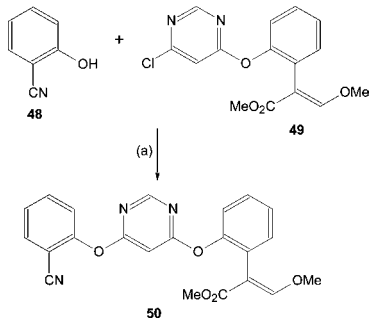
PATENT NO. U.S. 8,124,761

Assignee: Syngenta Limited, Guildford, Surrey, United Kingdom

Title or Subject: Process for the Preparation of Azoxystrobin Using DABCO as a Catalyst and Novel Intermediates Used in the Process

Azoxystrobin, **50**, is one of a group of fungicides known as strobilurins that can be extracted from the wood-rotting mushroom fungus *Strobilurus tenacellus*. A synthetic method of preparing **50** is known that uses DABCO as catalyst at levels of up to 20%. It is noted in the patent that this reagent is expensive, and hence an improved process is said to be desirable. The patent describes a process for preparing **50** by the coupling of **48** and **49** using DABCO as catalyst at levels of up to 2% (Scheme 16). Also present in the reaction mixture is

Scheme 16[a]



[a]Reagents and conditions: (a) (i) K_2CO_3, DMF, 60 °C; (ii) add DABCO; (iii) 80 °C, 1 h; (iv) vac distillation; (v) add PhMe/H_2O, 80 °C, 40 min; (vi) separate.

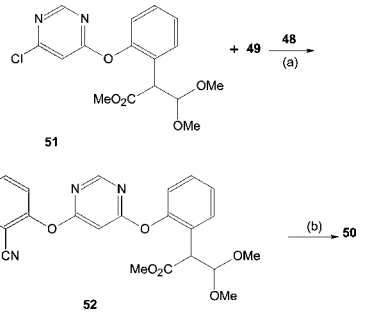
K_2CO_3 that forms the K salt of **48**. The preferred solvent is DMF although other solvents can be used, and there are examples for MIBK, cyclohexanone, Pr^iOAc, and $EtNPr^i_2$. The product is recovered as a 43.6% w/w solution in PhMe in 98.7% yield, but further details of recovery of the pure material are not discussed. The pyrimidine **49** is obtained by a process described in WO/92/08703, but there are no details in the current patent.

The patent gives examples showing the effect of the amount of DABCO on the reaction time and the recovered yield of **50**. When no DABCO is used, the yield is 86.6%, and this rises to 98.7% when 1% DABCO is used and falls slightly to 97.5% using 2% DABCO. The reaction time is 8 h without using DABCO, and this falls to 1 h when 1 or 2% DABCO is used. The patent also describes experiments to assess the effect of the order of addition of the reagents, and the yield is improved if the DABCO is the last component added. The patent claims also cover the case where **50** can also be prepared by reaction of **48** with the acetal **51** as shown in Scheme 17. This patent example actually describes a reaction between **48** and a mixture of **49** and **50** that produces a mixture of **50** and **52**. The proportion of **50** in the product is found to be higher than may be expected from the relative amounts of **49** and **51** because MeOH is eliminated from **52** forming **50**. From a mixture of **49** and **51** containing 12.4% of **51** the product was recovered as a solution in cyclohexanone and contained 27% of **50** and 73% of **52**. It is stated that MeOH can be eliminated from **52** to give **50** by treatment with MsOH and Ac_2O, but experimental details are not provided.

Another option for preparing **50**, that is covered by the claims, is the reaction of **53** and **54a**, shown in Scheme 18. Unfortunately there are no examples in the patent that describe this procedure.

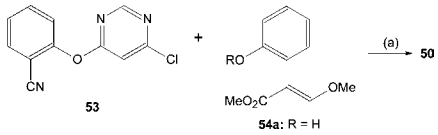
dx.doi.org/10.1021/op3001367 | Org. Process Res. Dev. 2012, 16, 1198−1211

Scheme 17[a]



[a]Reagents and conditions: (a) (i) K_2CO_3, DABCO, cyclohexanone 90 °C, 4 h; (ii) H_2O, 90 °C, 10 min; (iii) separate; (iv) add 1% aq HCl, NaCl; (v) separate; (b) MsOH, Ac_2O, 40 °C;

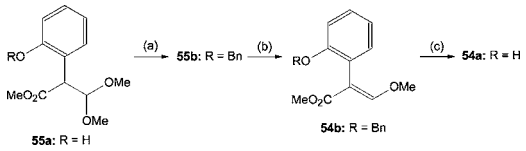
Scheme 18[a]



[a]Reagents and conditions: (a) no details provided.

The preparation of **54a** is from **55a** that is prepared by a method reported in GB 2,291,874, but there are no details included in the current patent. **54a** is prepared by the method outlined in Scheme 19, and the first step is protection of the

Scheme 19[a]



[a]Reagents and conditions: (a) (i) K_2CO_3, DMF, rt, add BnBr over 0.25 h, stir 6 h; (ii) add BnBr, rt, 16 h; (iii) H_2O, rt; (iv) filter, wash, dry; (b) (i) Ac_2O, MsOH, 40 °C, 1.5 h; (ii) cool to rt, add PhMe; (iii) H_2O wash (×3), separate, evaporate; (c) (i) Pd/C, EtOAc, H_2, 1 atm, rt, 40 h; (ii) filter; (iii) add Pd/C, H_2 1 atm, rt, 2 h; (iv) filter, evaporate.

OH group in **55a** using BnBr to give the novel compound **55b** that is recovered in 57% yield. Elimination of MeOH from **55b** is carried out by treatment with Ac_2O in the presence of MsOH, and this produces **54b**. The product is isolated in PhMe, and then, after evaporation of solvent, crystals are isolated in 44% yield. In the final step the protective Bn group is removed by catalytic hydrogenation using Pd/C. The product is initially recovered as an oil that crystallises on standing, but the yield is not reported.

The patent provides ^{1}H NMR data for compounds **52**, **54a**, **54b**, and **55b**.

Advantages. The process provides an improved route to the preparation of azoxystrobin using much less catalyst than alternative methods.

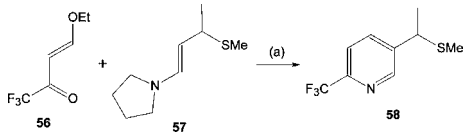
PATENT NO. U.S. 8,129,539

Assignee: Dow Agro Sciences LLC, Indianapolis, Indiana, United States

Title or Subject: Process for the Preparation of 2-Substituted-5-(1-Alkylthio)-Alkylpyridines

This patent discloses a series of novel compounds such as **58** that are prepared by a cyclisation reaction, and the claims of the patent only cover these compounds. It is presumed that these are agrochemicals or intermediates although the patent does not refer to the use of these novel compounds. The synthesis of **58** is shown in Scheme 20 and involves a cyclisation of the

Scheme 20[a]

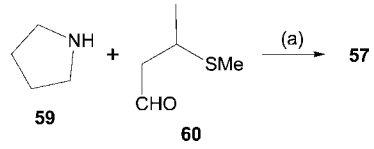


[a]Reagents and conditions: (a) (i) MeCN, <10 °C′ (ii) rt, 1.5 h; (iii) NH_4OAc, 80 °C, 1.5 h; (iv) cool, evaporate, add Et_2O; (v) H_2O wash (×3), dry, evaporate, distill.

unsaturated ketone **56** with the enamine **57**. The reaction is carried out in the presence of an excess of NH_3 or a reagent that generates NH_3 such as NH_4OAc. The crude product is purified by short-path vac dist and then isolated in 59% yield as a yellow oil. The purity is not reported, but basic ^{1}H NMR data are provided. An alternative method uses the Me_2N analogue of **57** instead of the pyrrolidine and gives a 44% yield of **58**.

The preparation of the enamine **57** is described in the patent and outlined in Scheme 21. This is done by reacting an excess

Scheme 21[a]



[a]Reagents and conditions: (a) (i) K_2CO_3, <10 °C; (ii) warm to rt, filter; (iii) wash solids in Et_2O; (iv) combine liquids, evaporate.

of **59** with **60** under anhydrous conditions in the presence of solid K_2CO_3 for an unspecified time. The product is recovered as a red liquid in almost quantitative yield, and similarly, the preparation of the Me_2N analogue of **57** from Me_2NH and **60** is described. Although the purity of these enamines is not reported, basic ^{1}H NMR data are provided.

Advantages. The process provides novel compounds that may have use in the synthesis of agrochemicals.

PATENT NO. U.S. 8,129,560

Assignee: Syngenta Crop Protection Inc., Greensboro, North Carolina, United States

Title or Subject: Process for the Synthesis of Mandipropamid and its Derivatives

Mandipropamid, **63b**, is one of a range of fungicidally active phenylpropargylether derivatives that were first reported in WO/01/87822. The current comprehensive patent describes an alternative route to making these compounds, and the final stages of the synthesis of **63b** are outlined in Scheme 22. The first step is reaction of the glycol ester **61** with the amine **62** in the presence of $Me_2NCH_2CH_2OH$ to form the amide **63a**. The reaction is performed under vacuum while distilling off the PhCl. When the reaction is complete, excess **62** and the

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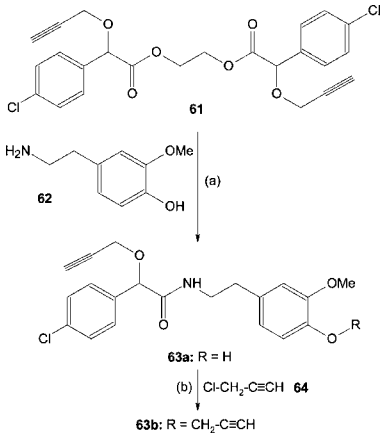
Scheme 22[a]

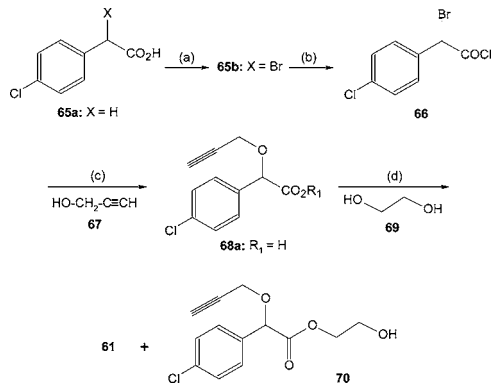


[a]Reagents and conditions: (a) (i) $Me_2NCH_2CH_2OH$, PhCl, 100 °C, 4 h, vacuum; (ii) add PhMe/H_2O; (iii) 70 °C, 5 min; (iv) separate, aq HCl to pH 1; (b) (i) K_2CO_3, Bu^n_4Br, PhMe, 90 °C, 3.5 h; (ii) add H_2O, separate; (iii) evaporate, add MeOH; (iv) cool to 0 °C, filter, wash, dry.

aminoethanol are removed using aq HCl; the amide **63a** is recovered as a solution in PhMe in 92% yield (HPLC), and this is used directly in the next step, although the product can be crystallised by cooling and isolated in 60% yield. Treatment of the solution of **63a** with **64**, in the presence of K_2CO_3 and Bu^n_4Br, gives **63b** that is isolated after crystallising from MeOH in 76.5% yield and purity of 98%.

The glycol ester **61** that is used in the reaction contains the monoester **70**, and it is the mixture that is used in Scheme 22, although the relative amounts are not reported. The mixture of esters is obtained via a route outlined in Scheme 23. This starts

Scheme 23[a]

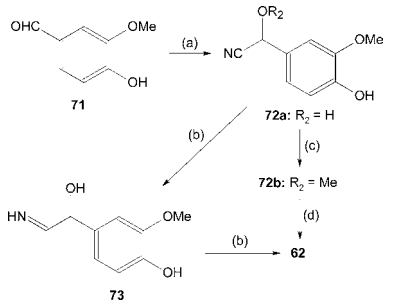


[a]Reagents and conditions: (a) (i) PhCl, 105 °C, 0.5 h; (ii) add $SOCl_2$; (iii) add Br_2, 108 °C, 3 h; (iv) evaporate; (b) (i) KOH, PhCl, 20 °C, 4 h; (ii) add H_2O, HCl to pH 0.5, 40 °C; (iii) separate, concentrate; (c) (i) TsOH, PhCl, reflux, vacuum, 1 h; (ii) concentrate.

from the acid **65a** that is brominated using $SOCl_2$ and Br_2 and produces a mixture of **65b** and **66** that is recovered as a solution in PhCl after distilling off the excess Br_2. This solution is then used in the reaction with **67** in the presence of KOH to produce **68a** that is recovered as a solution in PhCl in a yield reported as 97% by HPLC based on **65b**. The compound can be isolated in crystalline form if desired. The solution of **68a** is reacted with **69** to produce the mixture of **61** and **70** as a solution in PhCl, and this is used in the reaction with **62** in Scheme 22.

The patent also reports an improved process for the preparation of amine **62**, one of the key starting materials. Alternative methods for preparing **62** are said to use expensive reagents or generate considerable amounts of aqueous waste that contain CN residues. The synthesis of **62** described in this patent starts from vanillin, **71**, that is converted to the cyanohydrin and subsequently to **62** by two possible routes, shown in Scheme 24. Preparation of the cyanohydrin **72a** is

Scheme 24[a]

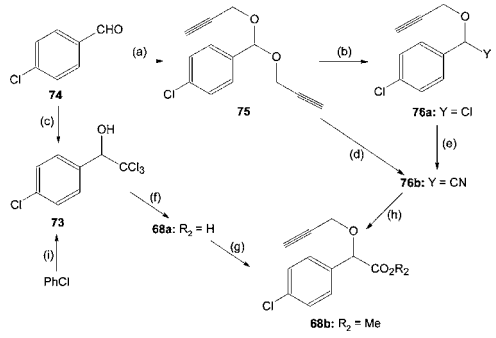


[a]Reagents and conditions: (a) (i) H_2O, 15 °C, 0.5 h; (ii) NaCN/H_2SO_4, 15 °C, pH 6, 6 h; (iii) stir, 15 °C, 2 h; (iv) H_2SO_4 to pH 0.5; (v) extract into MTBE, separate, add $ClSO_3H$; (vi) distill MTBE; (b) (i) Pd/C, MeOH/H_2SO_4, H_2, 5 bar, 25 °C, 4 h; (ii) depressurise, add H_2O, 45 °C; (iii) filter; (c) MeOH/H_2SO_4; (d) Pd/C, H_2.

carried out using NaCN/HCl, NaCN/H_2SO_4, aq HCN or HCN/THF, and there are examples for all of these procedures. **72a** is obtained as a yellow oil or crystalline solid in yields of 83–96%. The highest yield of 96% was achieved using NaCN and H_2SO_4, fed in parallel to an aqueous solution of **71**. Also reported is the use of acetone cyanohydrin and NaCN, but a low yield of only 36% was achieved. The reduction of **72a** to **62** can proceed by two routes. If the reaction is carried out by adding the Pd/C catalyst at the same time as MeOH/H_2SO_4, then the imine **73** is formed. Using this procedure the product is recovered as a 10% solution in MeOH in 86% yield.

If the MeOH/H_2SO_4 is added first and then the reduction is performed, the patent states that intermediate **72b** is formed, and this is reduced after addition of the Pd/C catalyst to **62**. Unfortunately there is no example of using this method. Both

Scheme 25[a]



[a]Reagents: (a) (i) **67**, HCl; (ii) $(EtO)_3CH$; (b) $SOCl_2$; (c) Cl_3CCO_2H/Cl_3CCO_2Na; (d) Me_3SiCN, $BiBr_3$; (e) NaCN; (f) **67**, aq NaOH; (g) TsOH, $(MeO)_3CH$, MeOH; (h) MeOH, 37% HCl; (i) $Cl_3CCHO/AlCl_3$.

dx.doi.org/10.1021/op3001367 | Org. Process Res. Dev. 2012, 16, 1198–1211

72b and **73** are claimed to be novel compounds although the patent does not provide any physical properties or spectral data for them.

The patent also provides examples for the preparation of a number of the acid **68a**, its methyl ester **68b**, and a number of other derivatives shown in Scheme 25. Only the reagents used are shown, and the patent should be consulted for details, although there is very little data for some of these novel compounds.

Advantages. The patent provides an alternative route to the fungicides in a series of reactions that do not often require the isolation and purification of intermediates. This aspect enhances the commercial viability of the process.

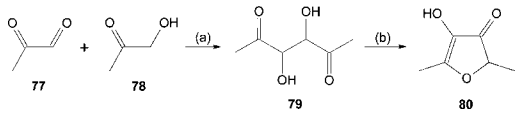
PATENT NO. U.S. 8,129,570

Assignee: Firmenich S.A., Geneva, Switzerland

Title or Subject: Process for the Preparation of 1,4-Dialkyl-2,3-diol-1,4-butanedione

The title compounds are starting materials for the preparation of furanones that are used in flavours and fragrances. The only example in the patent describes the preparation of **80** that has a strawberry flavour and odor and is available as Furaneol. Alternative methods for the preparation of such furanones are mentioned that use expensive reagents or have purification and waste disposal problems. For example, one method uses OsO_4 that is both toxic and expensive. The patent describes a process involving the aldol condensation of an alkyl glyoxal such as **77** with a hydroxyketone such as **78** that are used to produce **79** (Scheme 26). The reaction takes place

Scheme 26[a]



[a]Reagents and conditions: (a) (i) HOAc, H_2O, 70 °C, 16 h; (ii) concentrate, distill; (b) no details provided.

in an aqueous solution in the presence of HOAc at a pH of around 2. GC analysis showed that the crude reaction mixture contained 56% of **79** and after distillation this was isolated as a pale-yellow solid in 66% yield and 74% purity. The furanone **80** is said to be obtained from **79** by a cyclisation step reported in the literature (*J. Org. Chem.* **1973**, *38*, 123), but no details are provided. A series of experiments is reported for the reaction of **77** and **78** using a range of acids and/or buffers that all gave lower yields.

Aldol condensation reactions between two carbonyl compounds are notoriously unselective, and the moderate yield is not too surprising.

Advantages. The process avoids the use of metal catalysts.

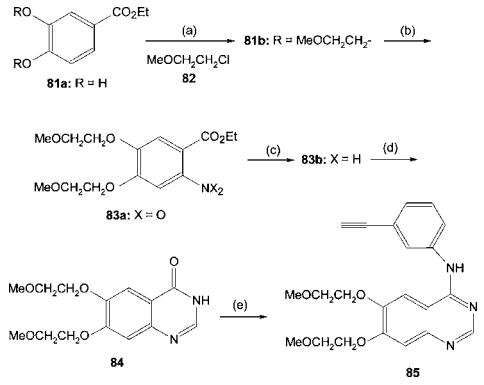
PATENT NO. U.S. 8,133,999

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

Title or Subject: Process for Preparation of 6,7-Bis(2-methoxyethoxy)quinazolin-4-one

The title compound, **84**, is said to be useful in the synthesis of **85** that is known as as erlotinib and used as one salt to treat lung and pancreatic cancers. The patent describes a new method of preparing the **84** starting from **81a** as shown in Scheme 27. The first step is formation of **81b** by reaction of **81a** with the ether **82** in the presence of K_2CO_3. The product is

Scheme 27[a]



[a]Reagents and conditions: (a) (i) K_2CO_3, DMF, 100 °C, 9 h; (ii) filter at rt, wash in Me_2CO, evaporate; (iii) add EtOAc and aq Na_2CO_3; (iv) separate, brine wash, add HOAc; (v) distill EtOAc; (b) (i) H_2SO_4, rt; (ii) 69% HNO_3, 70 °C, 2 h; (iii) cool to rt, add 20% brine and PhMe; (iv) separate, wash in aq NaOH, brine wash (×2); (v) evaporate; (c) (i) Pt/C, MeOH, H_2, 60 °C, 6 h; (ii) filter at rt, evaporate; (d) (i) $(MeO)_3CH$, $MeCO_2NH_4$, MeOH, reflux, 7 h; (ii) cool to 60 °C, add MeOH, 0.5 h; (iii) cool <5 °C, 1 h; (iv) filter; (e) no details provided.

recovered as solution in EtOAc, and HPLC showed that the yield was 95%. After addition of HOAc the EtOAc is removed and the acid solution used in the next step when nitration of **81b** using H_2SO_4/HNO_3 produces **83a**. This is isolated in 100% yield as an orange liquid, but the purity is not reported. In the next step reduction using Pt/C catalysts give **83b** that is isolated as an orange liquid in 92% yield. In the final step **83b** is refluxed with $(MeO)_3CH$ in the presence of $MeCO_2NH_4$ to form **84** that is isolated as white crystals in 91% yield. The examples all describe kilo-scale experiments, and the overall yield of **84** from **81a** is reported to be 80%.

Advantages. The process gives a very good overall yield without the need to isolate all of the intermediates. However, the chloroether **82** is a toxic reagent with a very low flash point of 10 °C; thus, handling this material on a commercial scale is hazardous.

PATENT NO. U.S. 8,134,002

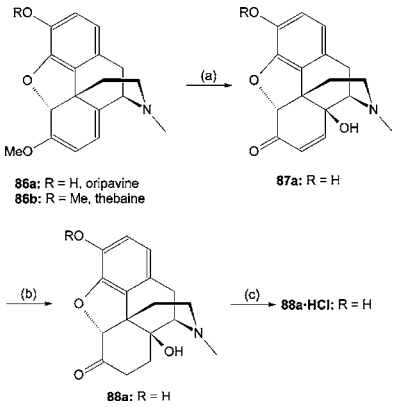
Assignee: Penick Corporation, Pennsville, New Jersey, United States

Title or Subject: Process for Preparing Oxymorphone

Oxymorphone **88a** (R = H) is semisynthetic opioid analgesic that is used in preoperative medication and also to relieve moderate-to-severe pain. The preparation of semisynthetic opiates is a subject of current interest, and this patent discloses a method for the synthesis of **88a** from oripavine **86a** (R = H). This is a less expensive raw material, and a recent patent that uses **86a** for the synthesis of **88a** has been reviewed (*Org. Process Res. Dev.* **2012**, *16*, 727). An earlier patent on the synthesis of **88a** from oxycodone **88b** (R = Me) has also been reviewed (*Org. Process Res. Dev.* **2012**, *16*, 11). This latter method involves a demethylation step, and other processes involve the need for protection of the OH group. These steps reduce the overall yield, and so the current patent avoids such procedures by using the route outlined in Scheme 28. This starts with the oxidation of **88a** to produce **87a** (R = H) that is not isolated but is reduced in situ using a Pd/C catalyst to give **88a** that is isolated in crude form. When H_2O_2 and HCO_2H are used in the oxidation step, the yield of crude **88a** is 95.2%.

dx.doi.org/10.1021/op3001367 | *Org. Process Res. Dev.* 2012, 16, 1198−1211

Scheme 28[a]



[a]Reagents and conditions: (a) (i) 90% HCO_2H, H_2O, 40 °C; (ii) 35% H_2O_2, < 40 °C; (iii) 40 −50 °C, 4 h; (b) (i) Pd/C, Pr^{i}OH, H_2, 3 bar, rt, 18 h; (ii) filter, add 50% NaOH to pH 9.16, <30 °C; (iii) rt, 1 h; (iv) filter, dry, 90 °C, 18 h; (v) H_2O, 55 °C, add TA to pH 4.35; (vi) active C, cellulose, 55 °C, 1 h; (vii) filter, add active C, cellulose, $NaHSO_3$, 55 °C, 1 h; (viii) filter, add Bu^{n}OH, 55 °C; (ix) add 50% NaOH to pH 8.56, 50.5 °C; (x) cool to rt, filter, vac dry, 65 °C; (c) (i) aq EtOH, 60 °C, concd HCl to pH 2.58; (ii) cool to <10 °C, stir 2 h; (iii) filter, wash in EtOH, vac dry, 75 °C.

Another oxidation was carried out using *m*-CPBA, and this gave a similar yield. The product is purified by treating with tartaric acid (TA), activated C, and powdered cellulose. After addition of $NaHSO_3$ and aq NaOH the purified solid is recovered in 91% yield and then converted to the HCl salt using HCl/EtOH. This is recovered in 86.7% yield, but the purity is not reported.

The first stage of this process, involving the oxidation of **86a**, uses the same reagents as those described in the earlier patent. This may be expected to provide the basis of interesting discussions between legal representatives of the companies involved.

Advantages. The process provides a route to an important analgesic without the need to isolate some of the intermediates.

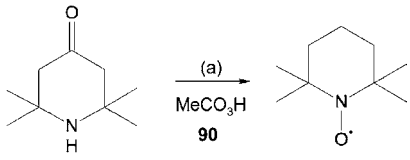
PATENT NO. U.S. 8,134,009

Assignee: BASF SE, Ludwigshafen, Germany

Title or Subject: Process for Oxidation of Secondary Amines to Corresponding Nitroxides

This patent describes a process for the preparation of nitroxides such as TEMPO, **91**. Apart from its use in organic chemistry, this and related compounds are also used as polymerisation inhibitors. Methods for preparing these nitroxides often involve oxidation of sec-amines with peracids, and the patent states that this has a number of problems. One is that close control of pH is needed, and this is difficult on a large scale. At low pH the reaction may proceed too slowly, and if too high the reaction can form an explosive mixture. The process disclosed in this patent is said to overcome such problems, and the preparation of TEMPO from **89** is shown in Scheme 29. The oxidation is carried out using a slight excess of **90** in a solution of HOAc, and this is added in one portion to **89** in a two-phase mixture of EtOAc and H_2O containing 6 mol excess of a weak base such as $NaHCO_3$. After workup, the product is recovered as an oil, crystallised from hexane, isolated in 94.7% yield, and is said to be identical to a commercial sample of **91**.

Scheme 29[a]



[a]Reagents and conditions: (a) (i) $NaHCO_3$, EtOAc/H_2O, add 90 over 50 min, <30 °C; (ii) <30 °C, 0.5 h; (ii) add H_2O, separate, extract into EtOAc, dry, evaporate, crystallise.

The patent describes the preparation of other analogous nitroxides by the same procedure. There are a number of key aspects of this process that overcome problems of earlier methods. The use of a solvent immiscible with H_2O and the use of the minimum amount of H_2O that dissolves the weak base are important. This means that the overall volume of the reaction mixture is less than that from alternative methods, and hence, productivity can be increased. The use of a weak base means that it does not cause decomposition of the peracid.

Advantages. The process gives improved yields, is more efficient than alternatives, and does not require pH control.

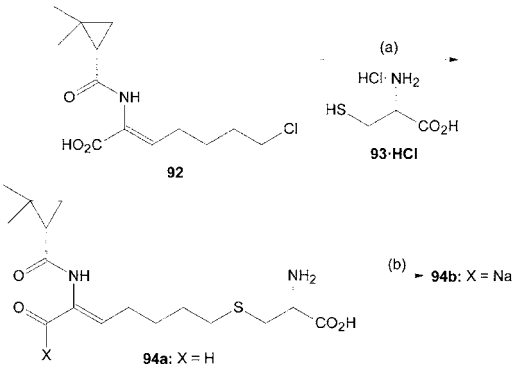
PATENT NO. U.S. 8,134,026

Assignee: Orchid Chemicals and Pharmaceuticals Limited, Chennai, India

Title or Subject: Process for the Preparation of Cilastatin and its Sodium Salt

Cilastatin **94a** is used in conjunction with the antibiotic imipenem to prevent degradation although **94a** does not have antibiotic activity itself. Alternative preparations of **94a** are said to use ColC and so are not commercially attractive. The preparation of **94a**, disclosed in the current patent, is carried out by condensation of **92** with the HCl salt of *L*-cysteine **93** (Scheme 30). The reaction can be carried out in H_2O or aq MeOH in the presence of NaOH. The product is isolated with purity of >99.5%, but the yield is only around 30%. For the preparation of the Na salt **94b** the acid is treated with active C and Et_3N in EtOH or Bu^{n}OH. This is then filtered twice, and a solution of sodium 2-ethylhexanoate (Na-2EH) is added to the

Scheme 30[a]



[a]Reagents and conditions: (a) (i) NaOH, MeOH, 65 °C; (ii) add concd HCl to pH 7, filter, evaporate; (iii) add H_2O, wash in DCM; (iv) adjust pH from 5.5 to 3−4, add Bu^{n}OH; (v) wash in H_2O; (vi) concentrate at 25 °C; (vii) filter, wash in Bu^{n}OH, wash in Me_2CO; (b) (i) active C, Bu^{n}OH, Et_3N, 30 °C,; (ii) filter; (iii) Na-2EH, Bu^{n}OH, 30 °C, 3 h: (iv) filter, wash in Bu^{n}OH, wash in Me_2CO, dry.

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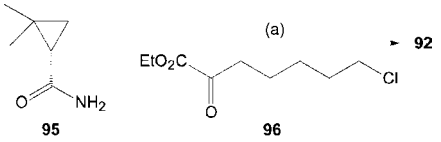
filtrate. The Na salt is isolated as an amorphous solid in 75.4% yield and 99.8% purity.

The preparation of the starting material **92** is described in the patent and outlined in Scheme 31. It involves the condensation

Scheme 31[a]



[a]Reagents and conditions: (a) (i) TsOH, PhMe, reflux 20 h; (ii) cool <10 °C, add aq NaOH; (iii) 30 °C, 8 h; (iv) separate, wash in PhMe, adjust pH to 4.5; (v) extract into PhMe; (vi) add HCl, 30 °C, 4 h; (vii) separate, H_2O wash, brine wash; (viii) concentrate, add hexane/Pr^i_2O, cool <5 °C; (ix) filter, hexane wash, dry.

reaction of the amide **95** with oxo-ester **96** in the presence of TsOH. The H_2O produced is removed azeotropically with PhMe, and the product is a recovered as a PhMe solution of the Z/E isomers of **92** in a 90/10 ratio. The solution is treated with HCl to isomerise the E isomer, and the pure Z isomer is isolated in 62% yield (based on **95**) and 99% purity.

Advantages. The process produces pure cilastatin without the need to use chromatographic methods.

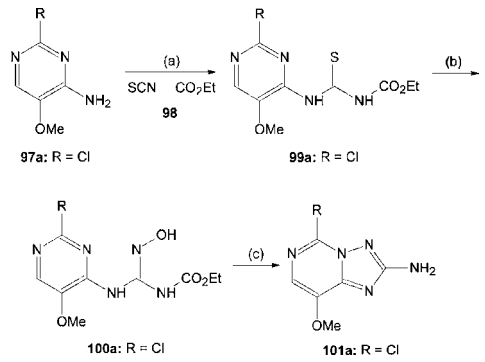
PATENT NO. U.S. 8,143,395

Assignee: Dow AgroSciences LLC, Indianapolis, Indiana, United States

Title or Subject: Process for the Preparation of 5-Substituted-8-Alkoxy[1,2,4]-triazol[1,5-C]pyrimidine-2-amines

The compounds of interest in this patent are intermediates in the preparation of sulfonamide herbicides. Alternative processes for preparing the compounds use hazardous reagents such as hydrazine and cyanogen halides. The objective of the work in this patent is to avoid the use of these materials, and the route used to prepare an example of one compound, **101a**, is shown in Scheme 32. The process starts by reaction of the aminopyrimidine **97a** with **98** to form **99a**. The product is isolated in 67% yield and then reacted with $H_2NOH{\cdot}HCl$ in the form of a salt formed with $NaHCO_3$. The reaction produces **100a** that can be isolated in 59% yield. However, it is preferred

Scheme 32[a]



[a]Reagents and conditions: (a) (i) EtOAc, reflux, 10 h; (ii) cool <15 °C, filter, wash in EtOAc, dry; (b) (i) $H_2NOH{\cdot}HCl/NaHCO_3$, H_2O, rt, 1 h; (ii) filter; (c) (i) Na_2CO_3, Bu^tOH, rt, 5 h; (ii) filter, H_2O wash, dry.

to avoid isolation of **100a**, and this is done by the addition of Na_2CO_3 to the mixture of reactants in solution. The product **101a** is isolated in 83% yield if Bu^tOH is used as solvent and 68% when MeCN is used. The ^1H and ^{13}C NMR data of **99a**, **100a**, and **101a** are provided.

The patent also describes the preparation of **101b** (R = MeO) by an identical route. The starting material **97b** (R = MeO) is obtained by treatment of **97a** with NaOMe and the product is isolated in 88% yield. ^1H and ^{13}C NMR data for the intermediates and products obtained in this route are provided. The claims of the patent actually cover the novel compounds **99a**, **99b**, **100a** and **100b** rather than the process for producing **101a**.

Advantages. The process provides a potentially safer method of producing the desired compounds and also provides some novel intermediates.

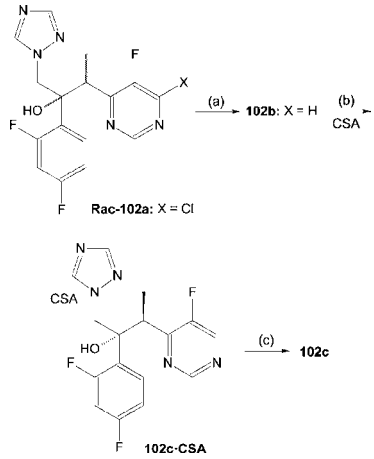
PATENT NO. U.S. 8,143,397

Assignee: Medichem S.A., Barcelona, Spain

Title or Subject: Process for Preparing Voriconazole, A New Polymorphic Form of an Intermediate

Voriconazole **102c** is useful for treating fungal infections and can be prepared by various routes that are summarised in this patent. The synthesis produces four stereoisomers as two pairs of enantiomers that are separable by chromatography, and from one of the pairs pure **102c** is isolated. Some methods use chlorinated solvents, and the patent seeks to avoid the use of these. The patent describes new polymorphs of both **102c** and its salt with 1*R*-camphor-10-sulphonic acid (CSA), and these have not previously been reported. The polymorphs of **102c** are covered in the claims along with the method for their preparation. Form I of **102c** and forms A and B of the CSA salt are prepared by the method outlined in Scheme 33. The procedure for preparing form I of **102c** begins with the dechlorination of the (2*R*,3*S*) and (2*S*,3*R*) racemic mixture **102a** that is 94.2% pure by HPLC. The reaction is a catalytic transfer hydrogenation that gives the racemic mixture **102b**. This is treated with CSA in MeOH, forming the CSA salt of

Scheme 33[a]



[a]Reagents and conditions: (a) (i) HCO_2NH_4, Pd/C, EtOAc, 65 °C, 2.5 h; (ii) filter at 35 °C; (iii) distill off 50% EtOAc; (iv) cool 25 °C; (b) (i) CSA, MeOH, reflux; (ii) distill off solvent, cool 21 °C; (iii) stir 2 h, filter; (c) (i) aq $NaHCO_3$, EtOAc, rt, 10 min; (ii) separate, H_2O wash, evaporate; (iii) Pr^iOH, 65 °C; (iv) <2 °C, 1 h; (v) filter, wash, dry.

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enantiomer **102c** that is isolated as the form B polymorph as a wet filter cake in 59% yield. A portion, when dried, had ee of 97.15% and 99.96% purity although it is the wet solid that is used to prepare the free base **102c**. This is carried out by suspending the salt in EtOAc and treating it with aq $NaHCO_3$. The crude product is crystallised from Pr^iOH, and form I of **102c** is isolated in 81.4% yield with 99.92% ee and 99.3% purity. If the salt is treated with an aq basic solution, it is possible to prepare **102c** that has a small particle size distribution (PSD) and mean particle size of 20 μm or less.

The patent provides XRD and DSC data for the polymorphs and also PSD details, and perhaps unusually in a patent, the methods of analysis are also described.

Advantages. The process provides an improved preparation and novel polymorphs of the desired active pharmaceutical ingredient (API) while avoiding the use of chlorinated solvents.

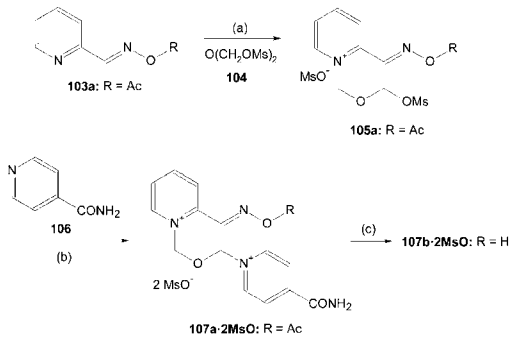
PATENT NO. U.S. 8,143,406

Assignee: Phoenix Chemicals Limited, Bromborough, Wirral, United Kingdom

Title or Subject: Process for the Manufacture of HI-6 Dimethanesulfonate

Salts of HI-6, **107b**, are used to treat the effects of poisoning by organophosphate nerve agents. The dichloride salt is known as asoxime chloride, and methods for its preparation have involved the use of the ether $(ClCH_2)_2O$ that is highly toxic and extremely carcinogenic. Other salts of **107b** are also known to be effective, and some routes for preparing MsOH salts also use $(ClCH_2)_2O$. This patent discloses a route to the bis MsOH salt of **107b** that does not require the use of $(ClCH_2)_2O$ and which is outlined in Scheme 34. The process starts with the

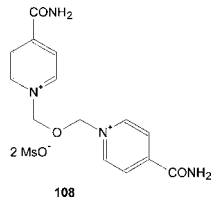
Scheme 34[a]



[a]Reagents and conditions: (a) MeCN, DCM, rt, 6 h; (b) DMF, rt, 17 h; (c) (i) EtOH, rt, 6 h; (ii) filter, recrystallise.

reaction of the O-protected aldoxime **103a** with the ether **104** to give the mesylate salt **105a**. This is not isolated but treated with amide **106** in the presence of excess **104** to form the bis-mesylate salt **107a·2MsO**. This is again not isolated but treated with EtOH to effect deprotection, giving the oxime salt **107b·2MsO** that is recovered in 53% yield based on **103a** and found to be 95% pure by HPLC. Recrystallisation from aq EtOH gives the desired product in 78% yield and HPLC purity >99 area %. An important aspect of the process is choosing an ether such as **104** that will provide the anion of the pyridine salts, **105a** and **107a**. A downside of this reaction scheme is that the final mixture contains four solvents.

The process proceeds via the quaternisation of the O-protected pyridine aldoxime **103a**, and the patent discusses alternative means for protecting the O-group prior to quaternisation. By using more readily removable groups such as benzoyl there are reports that quaternisation leads to destruction of the oxime function by a β-elimination reaction. By protecting the O-group using the Ac group the β-elimination does not occur to any appreciable extent. An additional advantage of using the Ac protective group is that impurities that are formed in the reaction can be easily removed. The compound **108** can be formed when starting from the free aldoxime **103b**, by reaction of **106** if used in excess. The impurity is difficult to remove because its solubility is similar to that of **107b·2MeO**. When proceeding via the protected aldoxime **103a** the solubility difference between **108** and **107a** allows for the facile removal of **108**.



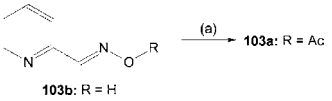
108

Impurity

A 1992 patent, U.S. 5,130,438, describes a route in which the first step in Scheme 34 reacts **104** with the unprotected oxime **103b** (R = H). This gives low yields and high levels of impurity **108**, and at one point in the workup of this method, a tar-like paste is produced that would be difficult to handle on a manufacturing scale. Hence, it is advantageous to use the protected oxime **103a** in this reaction.

The protected oxime **103a** is prepared from **103b** by reaction with Ac_2O in the presence of Et_3N and DMAP, and the product is isolated in 91% yield as a pale-yellow oil that solidifies on standing (Scheme 35).

Scheme 35[a]



[a]Reagents and conditions: (a) (i) Ac_2O, Et_3N, DMAP, DCM, rt, 14 h; (ii) H_2O, 0 °C; (iii) separate, H_2O wash, dry, evaporate.

The preparation of other protected aldoximes is also described, including **103c** (R = Et) and **103d** (R = $Si(OEt)_3$). Basic ^1H and ^{13}C NMR data are given for **107b** and also for the protected aldoximes **103b**–**103d**.

Advantages. The process gives good yields of the salt without the need to use a highly toxic reagent.

PATENT NO. U.S. 8,143,432

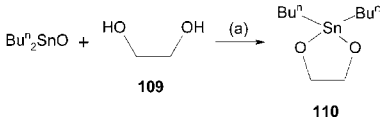
Assignee: Janssen Pharmaceutica N.V., Belgium

Title or Subject: Process for Regioselective Monotosylation of Diols

This patent describes the use of low concentrations of Bu^n_2SnO in the monotosylation of diols. The patent mentions that it is often necessary to use stoichiometric amounts of Bu^n_2SnO in such reactions and this leads to expensive methods to remove excess Sn compounds, especially in the production of APIs. The process claimed in the patent involves the use of the acetal compound of Sn **110** that is prepared from Bu^n_2SnO and **109** in refluxing PhMe (Scheme 36). The H_2O formed in

dx.doi.org/10.1021/op3001367 | Org. Process Res. Dev. 2012, 16, 1198–1211

Scheme 36[a]

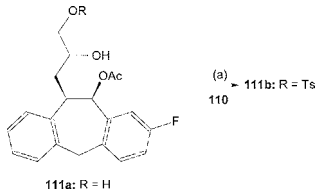


[a]Reagents and conditions: (a) (i) PhMe, 114 °C, 5 h; (ii) cool to 20 °C over 12 h; (iii) filter, dry, 40 °C.

the reaction is removed as an azeotrope with the solvent. The crude product is isolated in 93% yield and can be purified by recrystallisation from PhMe. The ^{1}H NMR data for **110** are reported.

The regioselective monotosylation of a number of diols is carried out using catalytic amounts of **110**. Scheme 37 shows

Scheme 37[a]



[a]Reagents and conditions: (a) (i) TsCl, EtNPr$^i_2$, rt, 16 h; (ii) 1 M HCl, stir, rt; (iii) filter over Na_2SO_4.

the formation of **111b** from **111a** that is specifically described in the patent, but there is no mention of the end-use of **111b**. The results of the reaction are reported using from 0.005 to 0.1 mol % of **110** in this reaction. The conversion of **111a** to **111b** is 97% when 0.05−0.1 mol % **110** is used, and a selectivity of >99.1% is achieved using 0.05 mol % **110**. When using 0.1 mol % of Bu$^n_2$SnO and EtNPr$^i_2$ the conversion of **110** is 97% with selectivity of 96.4%. The patent reports that product **111b** is recovered in solution and used in the next step although it does not mention what the next step entails. The isolation of pure **111b** is not discussed. An example of the preparation of **111b** on a pilot-plant scale is provided using 0.1 mol % Bu$^n_2$SnO and EtNPr$^i_2$, and this gives a yield of **111b** of 80%, thus indicating that the improved process gives high yields at much lower levels of the Sn compound.

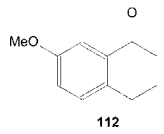
Advantages. The process allows for the use of much lower levels of Sn catalyst, and this will result in less expensive methods being required to remove excess Sn from the final product.

■ PATENT NO. U.S. 8,143,449

Assignee: Les Laboratoires Servier, Suresnes Cedex, France

Title or Subject: Process for the Synthesis of Agomelatine

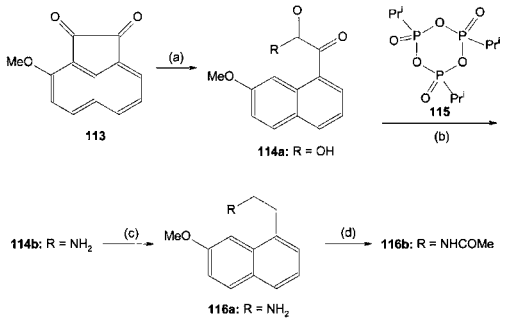
Agomelatine **116b**, is used to treat depression, insomnia, and jet-lag, and patents from this company, covering intermediates for its preparation, have been reviewed (*Org. Process Res. Dev.* **20109**, *13*, 381). The earlier patents start from the tetralone **112** that is said to be expensive; hence, alternatives are desirable. The current patent describes a process for preparing **116b** that starts from **113**. This compound is said to be more readily available than **112** and hence more suitable for commercial production of **116b**.



Tetralone

The process is outlined in Scheme 38, and this starts by formation of the oxoacid **114a** by treatment of **113** with

Scheme 38[a]



[a]Reagents and conditions: (a) (i) 18-C-6, $NaNH_2$, DMSO, rt, 0.5 h; (ii) add H_2O and 2 M HCl; (iii) extract in EtOAc, dry, evaporate; (b) (i) NH_4Cl, MeCN; (ii) Pr$^i_2$NH, rt, 4 h; (iii) evaporate, dissolve in add aq NaCl; (iv) extract in EtOAc, dry, evaporate; (c) (i) $AlCl_3$, THF; (ii) BH_3·THF, rt, 2.5 h; (iii) add H_2O, 1 M NaOH, NaOH; (iv) extract into MTBE, dry, evaporate; (d) (i) NaOAc, EtOH; (ii) Ac_2O, reflux; (iii) add H_2O, cool to rt, filter; (iv) wash in EtOH/H_2O, dry.

$NaNH_2$ in the presence of 18-crown-6 ether (18-C-6). The product is isolated in 88% yield with purity >94%, and this is used in the next step where it is reacted with the phosphonic anhydride **115** in the presence of NH_4Cl and Pr$^i_2$NH to form the novel hydroxyamide **114b**. This is isolated as an orange solid in 80% yield and purity of 90% and then reduced to **116a** using $AlCl_3$ and BH_3·THF. The amine is isolated in 80% yield and purity of 95% and then reacted with Ac_2O in the presence of NaOAc to produce **116b**. This is recovered in 80% yield and purity 99%. The patent briefly describes the determination of the crystal structure of the final product and provides basic XRD data. The patent claims cover the hydroxyamide **114b** and its use as an intermediate in the preparation of **116b**.

The examples are all carried out on a milligram scale, and hence, the large-scale production viability is not known.

Advantages. The process provides an alternative route to the API using a potentially cheaper starting material.

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