Organic Process Research & Development **2011,** *15,* 10–21

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published During August and September 2010

Summary

There are 20 patents in the current review from an original list of 372 that fitted the search criteria. Some of the patents contain a substantial amount of information and cover a great deal of chemistry; lack of space has meant that only very brief details have been included. A number of patents describe new processes for making drugs used in the treatment of heart-related diseases. A new method of making lercanidipine is described that uses a novel silyl compound, but the commercial viability of this is not known. A new method of making 4-hydroxypyran-2-one derivatives is described that is applied to the synthesis of statins, giving lower levels of byproducts. A novel method of resolving racemic verapamil is described that uses a fluorobenzoyloxy succinic acid derivative as resolving agent. An improved purification of clavulanic acid is described, and the patent also identifies impurities that were previously unknown. Another patent on an improved purification method covers the muscle relaxant and sleep-inducing drug, midazolam. The method gives a high-purity product but at the expense of using a large number of solvents. Two patents cover the antidepressant sertraline and describe methods for making two polymorphs. The key feature of the work is that precise temperature control is not needed during crystallisation. Two patents cover rizatriptan that is used to treat migraine. One describes two novel polymorphs, and the second covers a new process to make the benzoate salt and a range of novel intermediates. A new method of producing the insecticide fibronil replaces TFA as the reaction solvent with trichloroacetic acid by addition of dichloroacetic acid as a melting point depressant, thereby allowing the trichloro acid to be used at ambient temperature. A new process is described for preparing tetrahydroquinolines that are used to treat psychosis and obesity. Two alternative routes are disclosed that give high-purity products but require very extensive workup procedures. Two patents from two companies describe processes for the preparation of different types of thiazolopyrimidine derivatives. One focuses on preparing intermediates for the synthesis of immunomodulators, and the other describes an improved method for preparing compounds with unspecified therapeutic uses. A comprehensive patent covers the synthesis of a series of substituted indoles that are used to treat respiratory diseases. The patent also discloses several novel intermediates. Another comprehensive patent describes a process for preparing an intermediate in the synthesis of the antiviral drug entecavir. A multistep process for making 1,2-dialkoxy-3-fluorobenzenes is claimed to be efficient despite the many steps but does not provide any purity details of final product or intermediates. An improved hydrogenation process is described in the synthesis of bepromoline, an intermediate in producing the antifungal agent amorolfine, and multikilogram-scale examples suggest that the process has been commercialised. A process for preparing hydroxypyridines is described that is claimed to be the first microbiological one to be reported. A patent describes a method for the introduction of two F atoms in a single step into weakly activated aromatics. A number of the patents in this collection describe experiments carried out on a kilogram or multikilogram scale, thus suggesting an advanced stage of development or even commercial operation. However, there is no legal or commercial significance in the choice of patents in this review. The advantages mentioned in this review are those claimed in the patent, unless this reviewer has personal knowledge of the subject.

Patent No. U.S. 7,767,823

Assignee: SmithKline Beecham Ltd., Brentford, Middlesex, United Kingdom

Title or Subject: Process for the Purification of a Salt of Clavulanic Acid

Clavulanic acid **1a** is a hygroscopic oil, whereas its salts are stable and the K salt **1c** is used to enhance the effect of β-lactam antibiotics and prevent their deactivation. **1a** is normally prepared by fermentation processes using strains of microorganisms and is extracted from the culture medium in various ways. A number of impurities are also produced in the process, and many have not been identified. However, the patent reports that the inventors have identified **2** as being one impurity, and the focus of the patent is minimising the amount of **2** found in purified salts of **1a**. After fermentation the **1a** is extracted in a solvent and converted to an amine salt such as **1b** (R = Bu^t NH_3^+) that is converted to the K salt **1c** (R = K); the API. The patent describes a process for preparing **1c** that has low levels of **2**, and this is achieved by exposing the salts to a medium with a pH of around 4.5. The effect of pH is shown in an example wherein a sample of **1b** is dissolved in water and the pH adjusted to 4.5 using H_2SO_4 or HNO_3. Me_2CO is then added, and the mixture is then converted to the K salt **1c**. The impurity level of the resulting purified K salt was 0.03%; when the experiment was repeated without the acidification procedure, the pH was 7.5, and the resulting K salt contained 2.03% total impurities. The process involves taking the amine salt **1b** and washing it in a two-phase system comprising a ketone such as MIBK and an aqueous phase that is at pH of about 4.5. The conversion of **1b** to **1c** is carried out by treating the recovered **1b** with 2-ethylhexanoate K salt in Pr^iOH containing HOAc, and the product contains greatly reduced levels of **2**.

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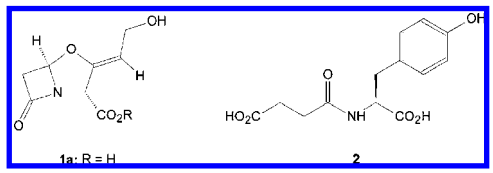
Clavulanic acid



Advantages

The relatively simple process provides a product with much higher purity.

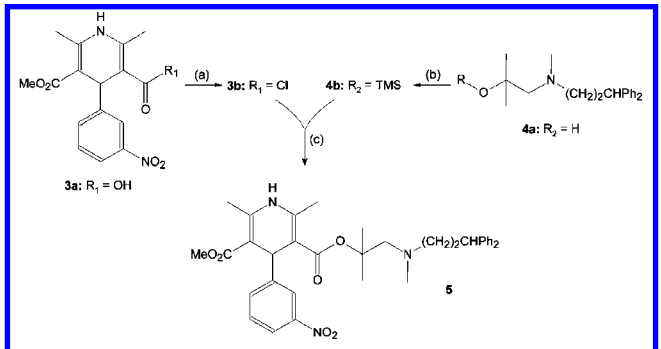
Patent No. U.S. 7,772,401

Assignee: Hetero Drugs Limited, Hyderabad, India

Title or Subject: Process for the Preparation of Lercanidipine

Lercanidipine **5** is an antihypertensive agent that is available as Zanidip for the treatment of angina and coronary disease. Two processes for preparing **5** are summarised and are unsatisfactory because one requires a long reaction time and the other uses chromatographic methods to purify the product. An improved method for preparing **5** is disclosed that is outlined in Reaction 1. A solution of the acyl chloride **3b** is prepared by treating a solution of **3a** in DCM with $SOCl_2$ and DMF. A second solution is prepared that contains **4b** by addition of Me_3SiCl to the alcohol **4a** in the presence of a base. The preferred base is Et_3N, and this is specified in the claims of the patent. The solution of **4b** is then slowly added to that of **3b** to form **5**. The pure HCl salt of **5** is isolated in 99.5% purity by seeding with **5·HCl** after crystallisation from a mixture of EtOH and EtOAc. The patent reports that the silyl compound **4b** is novel, and the commercial viability of the process presumably depends on the availability of **4a** and **3a**; surprisingly, no reference is made to this.

Reaction 1



Advantages

The process gives high-purity product, and its commercial viability is clearly dependent on the availability of the raw materials.

Patent No. U.S. 7,772,437 and U.S. 7,772,438

Assignee: Hetero Drugs Ltd., Hyderabad, India

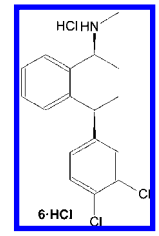
Title or Subject: Processes for Making Sertraline Forms I and II

Sertraline **6** is very widely available as the HCl salt for the treatment of depression. The first patent covers a method to prepare Form II of the drug, while the second covers a method to prepare Form I. Several crystal forms of **6** have been reported over the years, and these patents report that alternative methods of preparing Form II require careful control of the temperature during crystallisation. In the new method such control is not necessary, and it is claimed that this means that the process is commercially viable. The two patents contain exactly the same examples, and apart from the claims, the content appears to be identical. The preferred method for the preparation of Form II is as follows:

Dissolve the free base **6** in isoamyl alcohol at 25−30 °C.
Pass HCl gas into solution at around 2−4 °C to pH 2.0, or add concd HCl at 25−30 °C.
Stir mixture at around 30 °C for up to 7 h.
Filter and dry solid.

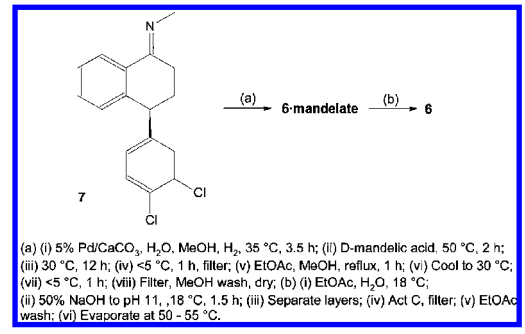
The product is isolated in yields up to 65%. The patent also claims that isoamyl alcohol and an ester can be used as solvents although the only example uses EtOAc, and there is also an example in which *tert*-amyl alcohol is used as solvent. The preparation of Form I is carried out by using *n*-amyl alcohol as the solvent, and the only example for making Form I uses concd HCl at 25 °C or below, although it is claimed that HCl gas can be used.

Sertraline



The patent describes the preparation of the free base by initial formation of the mandelate salt from the imine **7** as outlined in Reaction 2. The product of the hydrogenation step contains 99.8% *cis*- and 0.2% *trans*-isomers, and hence, it is assumed that **7** is a single enantiomer although the patent is not clear on this point.

Reaction 2



Advantages

The process is claimed to give good yield of either Form I or Form II of the desired salt without the necessity of strict temperature control.

Patent No. U.S. 7,776,852

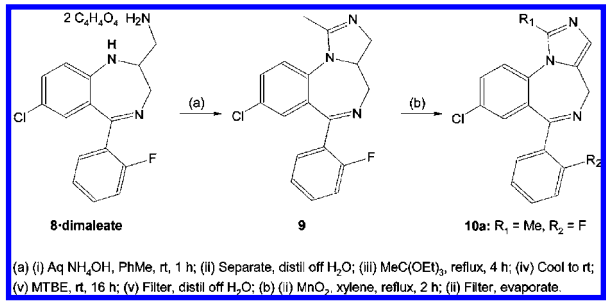
Assignee: Chemagis Ltd., Bnei Brak, Israel

Title or Subject: Process for Producing Highly Pure Midazolam and Salts Thereof

Midazolam **10a** is used for the short-term treatment of insomnia, as a muscle relaxant, and as an adjunct to local

anaesthetics. It is the only benzodiazepine available which is water soluble. The patent states that the preparation of **10a** by so-called conventional routes can give rise to a range of impurities such as **10b** (R_1 = Me, R_2 = H), **10c** (R_1 = Et, R_2 = F), and a dimeric compound formed from **10a**. The patent is particularly concerned with purifying **10a** by removing the compounds **10b** and **10c**. The process is based on the preparation of **10a** by a route described in the patent U.S. 4,280,957 and outlined in Reaction 3. This starts from the dimaleate salt of **8** that is mixed with aq NH_4OH in PhMe and then condensed with $MeC(OEt)_3$ to produce **9**. The water produced in this reaction is azeotropically removed, and then **9** is refluxed in xylene with MnO_2 to form **10a** that was isolated with 97.9% purity containing 0.44% **10b** and 1.14% **10c** (by HPLC).

Reaction 3



The purification of **10a** is carried out in two steps with **10b** being removed first, and **10c** is removed in the second. In the first step the free base **10a** is precipitated from a mixture of H_2O and either EtOAc or MeOAc. The base is isolated and then converted to the maleate salt by treatment with maleic acid in THF. The maleate salt is isolated and purified to remove **10c** by precipitation from a solvent mixture containing THF and another solvent. The solvents claimed include H_2O, MeOH, EtOH, Pr^nOH, Pr^iOH, Bu^nOH, Bu^sOH, or Me_2CO although there are only examples for EtOH and Pr^iOH. There are a number of examples in the patent, but they do not describe consecutive experiments, and so it is difficult to estimate the overall efficiency of the process. However, the purification of crude **10a** containing 0.32% **10b** and 1.02% **10c** gave a 67.6% yield of **10a** (99.4% pure) containing 0.06% **10b** and 0.34% **10c**. A separate series of examples covers the use of THF and EtOH or Pr^iOH in the second purification step. Starting from the **10a·maleate** containing 0.75% **10c** and an unknown amount of **10b** the **10a·maleate** was isolated in yields up to 89% containing <0.1% **10c** and purity >99.8%. The process includes a washing step after preparation of **10a·maleate** that uses a mixture of cyclohexane and MeOAc; thus, overall there are a considerable number of solvents involved.

Advantages

The process is capable of reducing the impurity levels to low levels but does involve the use of a large number of solvents.

Patent No. U.S. 7,777,049

Assignee: Ratiopharm GmbH, Ulm, Germany

Title or Subject: Crystalline Forms of Rizatriptan Benzoate

This is the first of two patents from the same company covering the tryptamine derivative **16** that is known as rizatriptan and marketed as the benzoate as an oral formulation for treating migraine. This patent covers two novel polymorphs, and the second describes the synthesis of **16·benzoate** and some novel intermediates. The original reports on the production of **16·benzoate** describe it as a white solid, and there is apparently no mention of polymorphism. Although the patent describes two polymorphs of **16·benzoate** designated A and B, the claims of the patent only cover Form B. XRD details are provided for both Forms, and A is the thermodynamically most stable form and is prepared by cooling a solution of **16·benzoate**. Examples describe the use of MTBE, EtOAc, and a range of alcohols. Form B is a metastable form obtained by fast crystallisation using antisolvents. The preparation of Form B is carried out by dissolving **16·benzoate** in MeOH or MeOH/EtOAc, and the antisolvent is hexane or heptane. It is also claimed that Form B can be obtained by evaporating to dryness a solution of **16·benzoate** in Pr^iOH or Bu^nOH.

Advantages

The patent describes novel polymorphs, but the commercial viability of isolating these is not known since all of the examples in the patent are only carried out on a milligram scale.

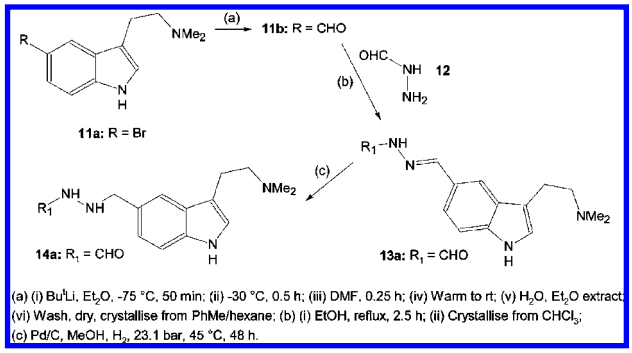
Patent No. U.S. 7,786,156

Assignee: Ratiopharm GmbH, Ulm, Germany

Title or Subject: Synthesis Methods and Intermediates for the Manufacture of Rizatriptan

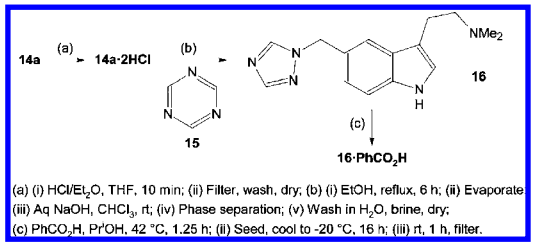
This patent covers a novel process for manufacturing rizatriptan, **16** and also covers some novel intermediates prepared and used in the process. Some of the routes for preparing **16** are outlined and their shortcomings described. Problems mentioned in alternative routes are the use of homogeneous Pd catalysts for coupling an acylsilane. The latter reagent is not readily available, and high quantities of the Pd catalyst are needed. The new route is designed without these materials and therefore avoids such problems. The preparation of **16** is shown in Reactions 4 and 5. The first stage is outlined in Reaction 4 and begins with the conversion of **11a** to the aldehyde **11b** by treatment with Bu^tLi at −75 °C followed by addition of DMF. The aldehyde **11b** is isolated in 81.8% yield and then purified by conversion to its oxalate salt before being used in the preparation of **13a**. The preparation of the oxalate is described but not its conversion to **11b**. The reaction of **12** with **11b** gives **13a** that is isolated in 87.2% yield, and this is hydrogenated using Pd/C catalysts to form **14a** that is recovered as a pale-yellow foam in 95% yield.

Reaction 4



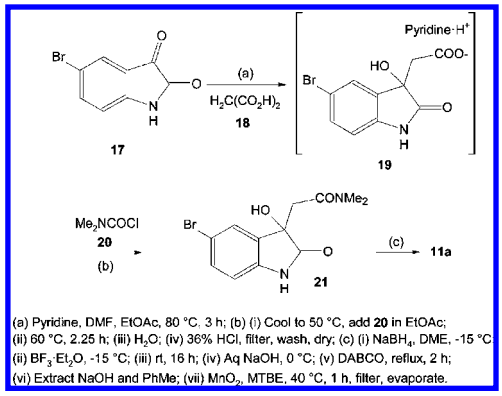
The next stage of the process is the formation of the triazole ring as shown in Reaction 5. The first step is the formation of the salt **14a·2HCl** from **14a** and HCl in Et_2O. The salt is isolated in 84% yield. Reaction of the salt with **15** produces **16** that is recovered as a brown oil that solidifies on standing. Treatment of **16** with $PhCO_2H$ in Pr^iOH gives the benzoate salt of **16** that is isolated 63.8% yield.

Reaction 5



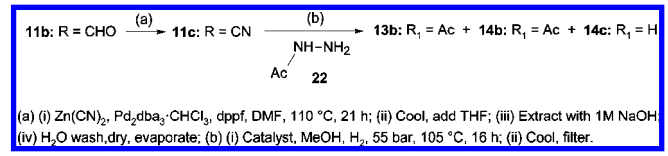
The patent contains details for the preparation of **11a** by the route outlined in Reaction 6. This starts from **17** that is reacted with **18** in the presence of pyridine and DMF to form the pyridinium salt **19** that precipitates from solution but is not isolated. Addition of Et_3N dissolves the salt that is then reacted with **20**, producing **21** that is isolated in 70.5% yield and used without further purification in the next step. The crude **21** is reduced using $NaBH_4$ in the presence of $BF_3·Et_2O$; the mixture is then treated with DABCO. After washing and extraction in aq NaOH and PhMe the mixture is taken to pH 14 with NaOH before treatment with MnO_2 in MTBE. The final product **11a** is recovered as a colourless viscous oil in 85% yield that crystallises on standing.

Reaction 6



The patent also reports on the synthesis of **16** and other tryptamines by reaction of the nitrile **11c** (R = CN) with a hydrazine under hydrogenation conditions. Reaction 7 outlines the synthesis of **11c** from **11b** and its reaction with the hydrazine **22** that gives a range of products with the distribution depending on the catalyst that is used. The synthesis of **11c** is by reaction of **11b** with $Zn(CN)_2$ in the presence of a homogeneous Pd catalyst and a ferrocenyl phosphine (dppf). The product **11c** is recovered in 84% yield and is then reacted with the hydrazine.

Reaction 7



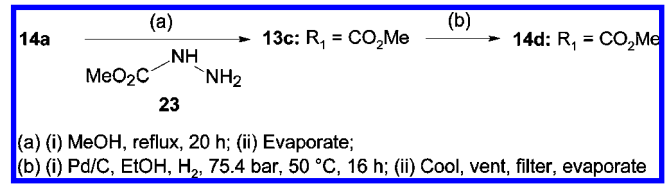
The example does not describe the isolation of the products, and the data in Table 1 are based on HPLC analysis of the filtrate.

Table 1

catalyst	% **13b**	% **14b**	% **14c**
Raney Ni	13	30	55
Ru/C (10%)	37	12	49
Rh/C (5%)	44	15	36

The patent also describes the synthesis of the ester derivative **13c** from **14a** and the hydrazine ester **23** as outlined in Reaction 8. The reaction takes place under reflux in MeOH; the crude product **13c** is isolated and then purified by column chromatography (Col C) in 55.4% yield. Hydrogenation of **13c** gives **14d** in 85% yield that is reported to be pure by ^1H NMR. Examples are also given for the preparation of a range of homologous esters to **13c** and **14d** using the same methods starting from hydrazine esters (Bu^i, Bu^t, and Bn).

Reaction 8



There are examples of the preparation of several other compounds, and the reader is encouraged to consult the patent for further details; for most compounds there are ^1H and ^{13}C NMR data.

Advantages

The process provides a novel route to the API and to a number of intermediates in the synthesis.

Patent No. U.S. 7,777,052

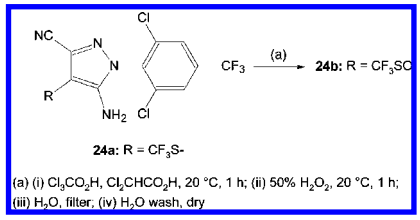
Assignee: Gharda Chemicals Ltd., Dombivli, Maharashtra, India

Title or Subject: Process for the Preparation of the Insecticide Fibronil and Related Pyrazoles

Fibronil **24b** is a highly effective, broad-spectrum insecticide, and the original process for its production uses TFA as solvent. This patent claims that the corrosive nature of TFA and its high cost mean that an improved method is needed to make the process economically attractive. The direct substitution of TFA by Cl_3CO_2H was not considered possible because at rt the chlorinated acid is a

solid. However, it has been found the melting point of Cl_3CO_2H can be depressed so that it can be used a solvent in the manufacture of **24b**. Compounds claimed to be suitable melting point depressants include $ClCH_2CH_2Cl$, PhCl, haloalkanes, $ClCH_2CO_2H$, Cl_2CHCO_2H, and DCM. The examples in the patent describe the use of the last two compounds in the oxidation of **24a** to give **24b** as shown in Reaction 9. The oxidation is carried out at 20 °C using 50% H_2O_2 using a 70/30 v/v mixture of Cl_3CCO_2H and Cl_2CHCO_2H as reaction solvent. The product precipitates from solution, and the reaction is monitored by HPLC until about 95% conversion is achieved. **24b** is isolated in 95% yield with 92% purity (HPLC). By using Cl_3CCO_2H containing 20% v/v DCM the yield was slightly less at 93.8%, and purity was 92%.

Reaction 9



Advantages

The procedure avoids the use of TFA, and by an innovative approach provides what is claimed to be a more economically viable and friendly process.

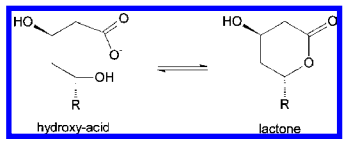
Patent No. U.S. 7,777,056

Assignee: Lupin Ltd., Mumbai, India

Title or Subject: Method for Manufacture of 4-Hydroxypyran-2-one Derivatives

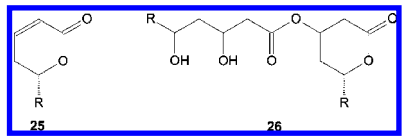
This patent describes an improved method of preparing statins that are used to reduce cholesterol levels in blood. The patent contains examples relating to both lovastatin **28a** and simvastatin **28b** that exist as cyclised lactones, whereas other statins exist as the open-chain hydroxy acid form. The patent reports that, in alternative methods for the preparation of **28a** and **28b**, the lactonisation reaction, shown below, is carried out by heating in an organic solvent with or without an acid. Alternatively, if a strong acid, such as MsOH, is used, then lower temperatures are possible.

Lactonisation



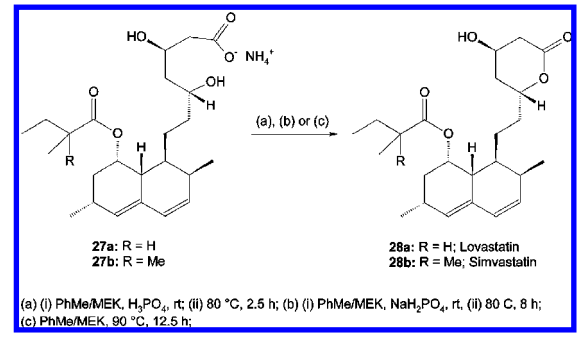
However, a problem encountered in the lactonisation reaction is the formation of byproducts such as **25** and **26**. The latter is obtained by reaction of the 3-hydroxy group of one molecule with the carboxy group of another. The objective of this patent is to provide a process for preparing **28a** and **28b** containing <0.1% of **25** and <0.15% of **26**.

Statin Impurities



It has been found that, by using a solvent mixture comprising an aromatic hydrocarbon and a ketone, the level of these byproducts can be reduced. The lactonisation can be carried out without an acid or with an acid or an acid salt. In addition, shorter times and higher concentration of the reagents are possible so that improved productivity is possible. The patent describes the new process as being carried out at a lower dilution than in alternative methods. For example the new process uses a ratio of solvent to hydroxyacid of between 13 to 17 (w/w) compared to a ratio of 40 to 50 for alternative methods. The basic reactions for the preparation of **28a** and **28b** are outlined in Reaction 10. Three methods are described for **28b** that use an acid, an acid salt, or no additional reagent. The preparation of **28b** takes less time with acid (2.5 h) than with the acid salt (8 h) and much less time than without any additional agent (12.5 h). The yield of **28b** using the acid is 67.3%, and purity is 99.7%; without acid the yield is 70.2%, and purity is 99.71%; with the use of NaH_2PO_4 the yield is 67.3%, and purity is 99.7%. For the preparation of **28a** there is a single example using H_3PO_4 that gives a 78.2% yield of **28a** with 99.7% purity.

Reaction 10



The scheme outlined in Reaction 10 excludes the detailed workup and purification procedure that is a key part of the overall process. This consists of a number of steps that are summarised below:

1. Isolate a product by cooling to rt and adding Et_3N.
2. Add a hydrophobic solvent such as cyclohexane and strip off PhMe/MEK.
3. Add more cyclohexane and filter off precipitated product.
4. A first purification is carried out by refluxing the wet filter cake from step 3 with cyclohexane for 15 min.
5. Cool to <15 °C to allow crystallisation and filter.
6. In a second purification the wet cake from step 5 is dissolved in a water-miscible solvent such as MeOH.
7. Antioxidants are added, and the mixture is treated with activated C and then filtered.
8. Water is added to the filtrate from step 7 at rt to complete crystallisation of the product.
9. Crystals are filtered and washed in 25% aq MeOH and then dried.

The yield of **28a** varies from 75 to 80% and for **28b** from 63 to 70%. The statins have purities of between 99.5% and 99.8% containing <0.15% of **25** and <0.1% of **26**. The patent also summarises investigations into the effect of temperature and of other proton donors for the lactonisation step. There are results for the use of KH_2PO_4, $NaHSO_4$, $KHSO_4$, and the mono K salt of pthalic acid, but none are as effective as H_3PO_4.

Advantages

The process produces high-purity final products, but the overall yields are low, and hence the economics of the process do not seem to be attractive.

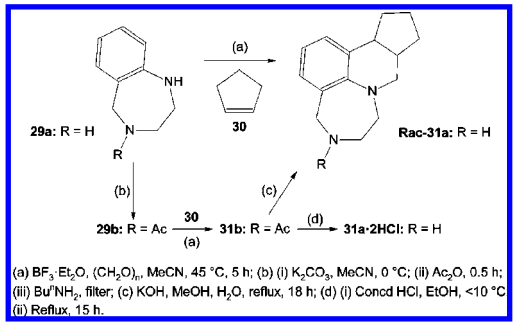
Patent No. U.S. 7,781,427

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

Title or Subject: Process for Preparing Quinoline Compounds and Products Obtained Therefrom

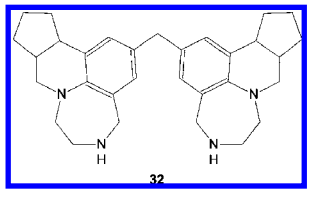
The patent discloses a process for preparing tetrahydroquinolines, such as **31a** and its salts, that are said to be useful in treating psychosis and obesity. The compounds are prepared as racemic mixtures by one of two routes outlined in Reaction 11. The extensive workup procedures are excluded from this scheme due to lack of space, and the patent should be consulted for full details. The first method begins with the reaction of benzodiazepine **29a** (R = H) with **30** and paraformaldehyde in the presence $BF_3 \cdot Et_2O$. The crude product was purified by flash chromatography (Flash C), and **Rac·31a** was obtained in 53% yield. The alternative route proceeds via initial protection of the NH group in **29a** by formation of the acetyl compound **29b** (R = Ac) that is isolated in 93% yield. This is then reacted with **30** and paraformaldehyde to form **31b** that is isolated in 93% yield and 94.5% purity (HPLC).

Reaction 11



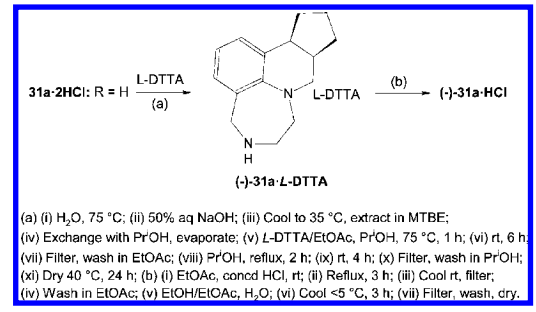
The product **31b** contains 3.15% of the dimeric compound **32**. This impurity is removed during the workup and purification, and the patent claims specifically cover the formation of compound **(−)-31a·HCl** containing **32** as the single largest impurity at a level of <0.6 area % by HPLC. The patent reports that the use of solid forms of formaldehyde in the reaction reduces the amount of **32** that is formed. The patent mentions that the use of $(MeO)_2CH_2$ or aqueous formaldehyde solution gives much higher levels of **32**. Unfortunately, no details are provided.

Quinoline Impurity



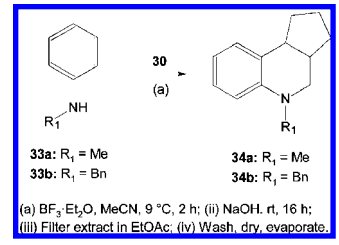
The resolution of **Rac-31a** involves the formation of the salt of di-*p*-toluoyltartaric acid (DTTA). The preparation is carried out from **31b** following either acid or alkaline hydrolysis. Reaction 12 shows the method where **31a·2HCl**, produced from **31b** as shown in Reaction 11, is isolated in 87% yield and then converted to the free base **31a**. Extraction of the base into MTBE followed by solvent exchange with Pr^iOH and addition of L-DTTA eventually produces the salt **(−)-31a·DTTA** in 32.3% yield (based on **31b**) with purity of 98.77% (HPLC) and ee of 90%. The DTTA salt can also be prepared from **31b** after alkaline hydrolysis with KOH, and the final yield is 24% (based on **31b**) with ee of 92%.

Reaction 12



The patent extends the process to the formation of **34a** (R = Me) and **34b** (R = Ph) by the reaction of the amines **33a** or **33b** with **30** and paraformaldehyde in the presence of $BF_3 \cdot Et_2O$. The reactions are complete in 2 h, and the products are isolated in yields of 57% (**34a**) and 91% (**34b**) after purification by Flash C. These compounds are also said to be useful in treating psychosis and obesity.

Reaction 13



Advantages

The process provides a novel route for these compounds.

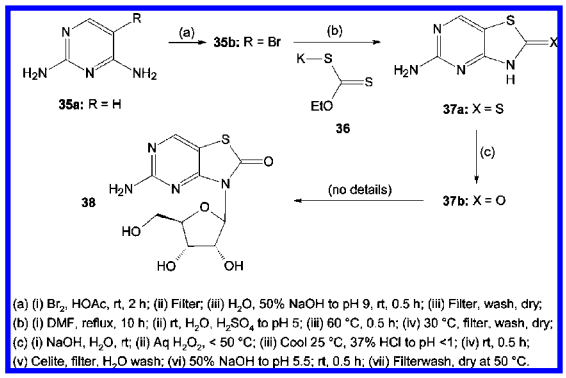
Patent No. U.S. 7,781,581

Assignee: Anadys Pharmaceuticals Inc., San Diego, California, U.S.A

Title or Subject: Process for the Preparation of 5-Amino-3H-thiazolo[4,5-d]pyrimidin-2-one

This is the first of two patents covering thiazolopyrimidines. The title compound **37b** is said to be an intermediate in the preparation of immunomodulators, and the patent specifically mentions compound **38** that is the subject of another patent from the assignee. Reaction 14 outlines the process for preparing **37b** that starts with bromination of the pyrimidine **35a** to give **35b** that is isolated in 87% yield. Cyclocondensation of **35b** is effected by refluxing with **36** in DMF, and this produces **37a** in 89% isolated yield. In the final step **37a** is oxidised using H_2O_2, urea, and H_2O_2 or NaOCl. The highest yield of 67% is obtained using urea and H_2O_2 although the preferred reagent is H_2O_2, and this gives a yield of 62%. The yield using NaOCl is only 27%.

Reaction 14



Advantages

The patent provides a novel process for a drug intermediate that is claimed to be inexpensive and is amenable to scale-up.

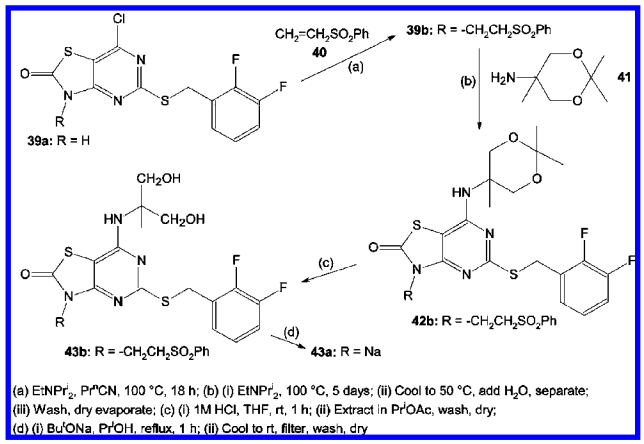
Patent No. U.S. 7,790,883

Assignee: AstraZeneca AB, Sodertalje

Title or Subject: Process for the Preparation of Thiazolopyrimidines

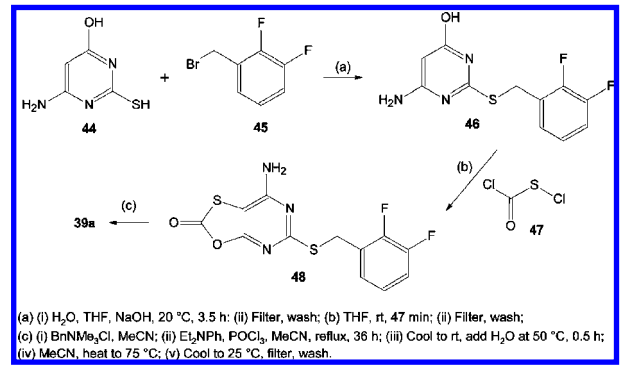
This, the second patent on thiazolopyrimidines, covers a different range of compounds and describes an improved synthesis of **43a** and related compounds that was previously reported by the assignee in patent WO/01/25242. The compounds are said to be used therapeutically, but no specific diseases or ailments are mentioned. The route used to prepare **43a** consists of several stages that have been separated for easier understanding. The final stage of the overall synthesis is shown in Reaction 15 and begins with the protection of the amine group in **39a** by formation of the sulfone **39b** through reaction of **39a** with **40** in the presence of $EtNPr^i_2$ in Pr^nCN at 100 °C for 18 h. The product is not isolated and is areacted with amine **41** for almost 5 days at 100 °C to give **42b** that is isolated as an orange oil and purified by Col C to give a white solid (no yield given). Acid hydrolysis of **42b** produces **43b** in 88% yield. Treatment of **43b** with the strong base Bu^tONa forms the Na salt **43a** in 81% yield, and this can be converted to the K salt using Bu^tOK. Alternatively, **43b** gives the K salt if treated with MeOK.

Reaction 15



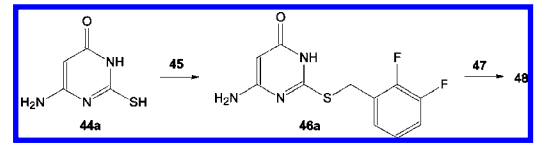
39a is a novel compound, and the patent examples describe a synthesis by the route outlined in Reaction 16. This begins with the condensation of **44** and **45** to give **46** that is isolated in 94.6% yield and then reacted with **47** to produce **48** that is obtained in 97% yield. This is then converted to **39a** by reaction with Et_2NPh and $POCl_3$ in MeCN in the presence of a phase transfer catalyst. The yield of **39a** is 66%.

Reaction 16



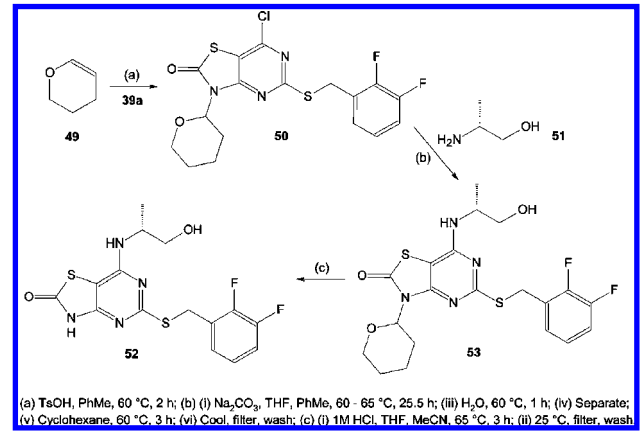
Although the patent examples describe the synthesis of **39a** by the route shown in Reaction 16, the discussion in the patent claims that the synthesis of **39a** involves the chemistry outlined in Reaction 17. This involves the reaction of compound **46a** and **47** to give **48**. **46a** is claimed to be novel and is obtained from the reaction of **44a** with **45** that is reported in another patent from the assignee, WO/03/24966. There is no mention in the current patent that this aspect centres around tautomerism between **46a** and **46** or between **44** and **44a**. One would have expected that some evidence would be supplied as to the existence of tautomerism if the patent is proposing that compound **46a** is involved.

Reaction 17



The patent also describes the synthesis of the thiazolopyrimidine **52** from **39a** by the route shown in Reaction 18. First the amine group in **39a** is protected by conversion to **50** by reaction with **49** in the presence of TsOH. **50** is not recovered pure but is isolated as a solution in PhMe and then reacted with **51** and Na_2CO_3 to form **53**. Yield and purity of this are not reported. In the last step the acid hydrolysis of **53** produces **52** that is isolated in 95% yield.

Reaction 18



The patent contains ^1H NMR data for all of the compounds shown in the schemes.

Advantages

The process is an improvement on an earlier one developed by the assignee.

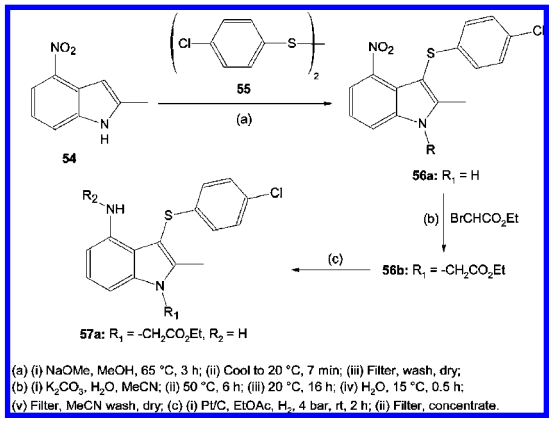
Patent No. U.S. 7,781,598

Assignee: AstraZeneca AB, Södertälje, Sweden

Title or Subject: Process for the Preparation of Substituted Indoles

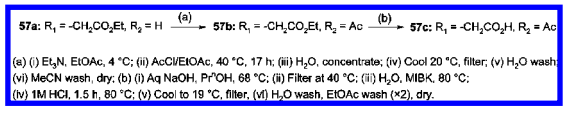
The compounds of interest are exemplified by **57c** and are said to be useful in treating respiratory diseases. The process for the preparation of **57c** is shown in two parts for clarity in Reactions 19 and 20. All of the steps in these reaction schemes are carried out on a kilogram scale. The first step is preparation of **56a** (R = H) by the base-catalysed reaction of the indole **54** with the disulfide **55**. The patent describes a kilogram-scale example using NaOMe that gives a 93% yield of **56a** and a small-scale experiment using trichlorocyanuric acid that gives **56a** in 81% yield. In the next step **56a** is treated with $BrCH_2CO_2Et$ in the presence of K_2CO_3 in MeCN to give **56b** in 91% isolated yield. The NO_2 group is then reduced using a Pt/C catalyst giving **57a**.

Reaction 19



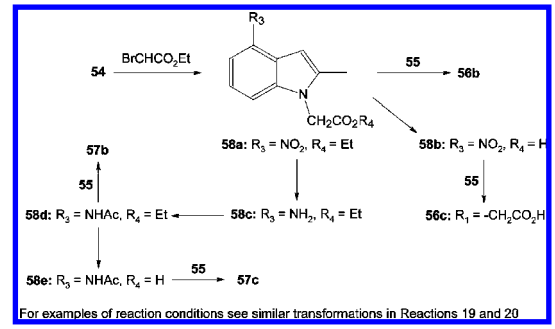
The amine **57a** is not isolated and is reacted with AcCl to form **57b** that is isolated in 82% yield as shown in Reaction 20. In the final step, base hydrolysis of the ester group gives **57c**, and this is obtained in 91% yield.

Reaction 20



The patent also describes several bench-scale experiments, providing alternative methods for the preparation of **57c** and some of the intermediates used in its preparation. These reactions and intermediates are outlined in Reaction 21. The reaction conditions used to prepare the compounds shown in this scheme are similar to those described above. The compounds **58a** and **58b** are novel, and these are covered by the patent claims. In addition the benzyl ester **58f** (R = NO_2, R_4 = Bn) is also claimed to be novel, but there are no details given for its preparation. The patent provides basic ^1H NMR data for most of the compounds shown in the reaction schemes.

Reaction 21



Advantages

The process gives very good yields of the desired product, and the process has been scaled up and demonstrated at kilogram scale.

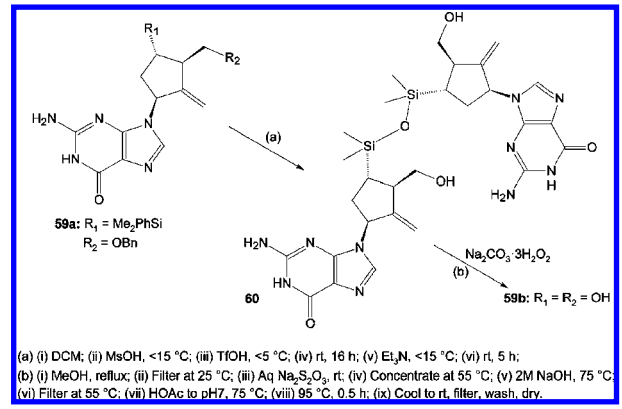
Patent No. U.S. 7,786,300

Assignee: Bristol-Myers Squibb Company, Princeton, New Jersey, U.S.A

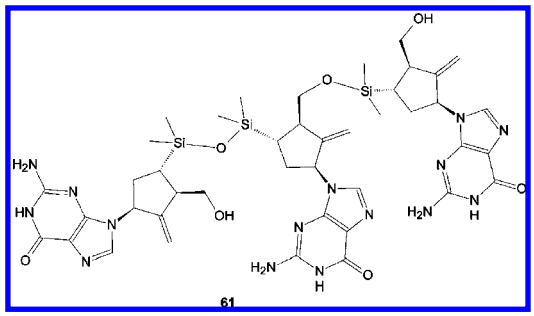
Title or Subject: Process for Preparation of Entecavir and Novel Intermediates Thereof via Carbon−Silicon Oxidation

Entecavir is the monohydrate of **59b** (R_1 = R_2 = OH) and is an antiviral agent used to treat hepatitis B infections. The claims of this patent actually cover a process for preparing **60** that is an intermediate used in the preparation of **59b**. The patent contains a substantial amount of experimental information; however, due to lack of space, only very limited details are included here. The patent contains an extensive review of published and patented methods for preparing **59b** and a number of intermediates. The preparation of **60** and its conversion to **59b** are shown in Reaction 22. The first stage involves a multistep procedure where **59a** is initially treated with MsOH followed by TfOH and finally Et_3N. The extensive workup is omitted from the reaction scheme due to space limitations and results in the isolation of **60** in 93.5% yield. The product can contain between 1 and 20% of **61**, but this does not need to be removed before the oxidation of **60** to **59b**. This reaction is carried out by using a peroxohydrate such as $Na_2CO_3 \cdot 1.5H_2O_2$ in refluxing MeOH. The progress is followed by HPLC, but no indication of the required reaction time is given. The peroxide is destroyed using $Na_2S_2O_3$, and then after workup the product is isolated in yields of 75−80%. The material may be purified by carbon treatment and crystallisation from MeOH and/or water, but the patent does not disclose the final purity.

Reaction 22

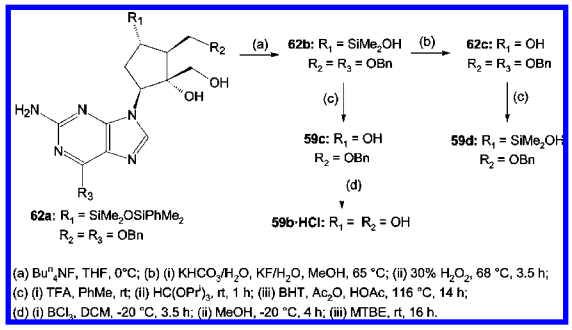


Oxidation Impurity

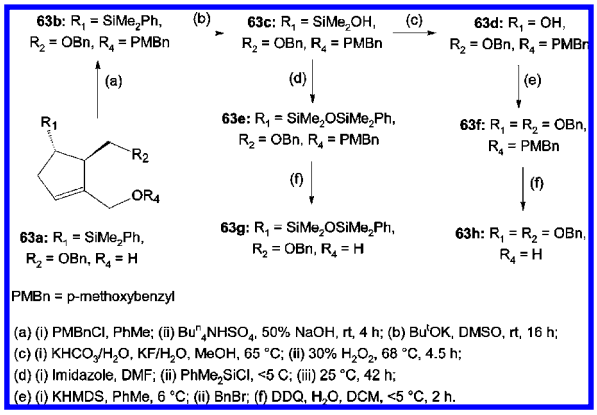


There are details in the patent for the preparation of the HCl salt of **59b** from **62a**, and Reaction 23 outlines this as well as various intermediates and derivatives. Reaction 24 outlines a number of transformations described in the patent including the preparation of **63g** that is used to prepare **62a**. Reaction 25 outlines the preparation of **64** from **63g**, and then **64** is reacted with **65** to give **62a**. The interested reader is encouraged to inspect the patent for full details of these reactions.

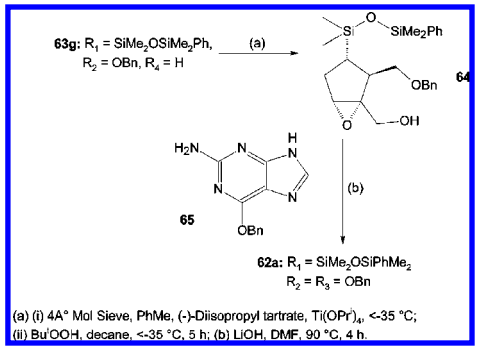
Reaction 23



Reaction 24



Reaction 25



Advantages

The patent describes a novel method for making the drug and includes several novel intermediates.

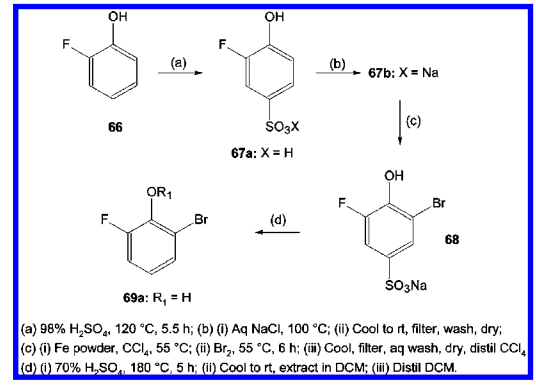
Patent No. U.S. 7,786,330

Assignee: Asahi Glass Co. Ltd., Tokyo, Japan, and Charna Chemicals Ltd., Beijing, China

Title or Subject: Process for Producing 1,2-Dialkoxy-3-fluorobenzene

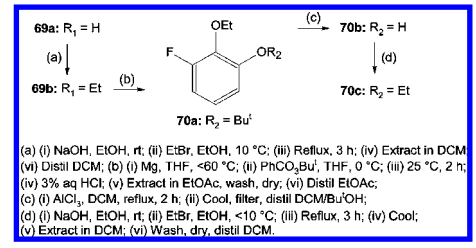
The title compounds are intermediates for the production of a range of unspecified medicaments. A process for preparing such compounds from an alkoxyphenol and an alkyl halides is said to be unsuitable for industrial production because of the high cost of starting materials, a low yield of product, and the need for large quantities of NaOH requiring troublesome postreaction treatment. The patent describes a new process for the production of **70c** from **66** with the first stage being the conversion of **66** to **69a** in four steps (Reaction 26). This begins with the protective sulfonation of the para position in **66** using 98% H_2SO_4 to give **67a** that is not isolated but converted to the Na salt **67b** by treatment with aq NaCl solution. The precipitated salt is recovered in 90% yield and then brominated to give **68**. Prior to this reaction all starting materials and equipment are subjected to an anhydrous treatment with the Br_2 being washed twice with concd H_2SO_4. The brominated product **68** is isolated in 85% yield, and in the final step the SO_3Na group in **68** is removed by treatment with 70% H_2SO_4 to give **69a** that is recovered as an oil in 80% yield.

Reaction 26



In the next stage of the process **69a** is first converted to the ethoxy derivative **69b** by reaction with EtBr in the presence of NaOH as shown in Reaction 27. **69b** is recovered as an oil in 70% yield and then converted to a Grignard reagent that is oxidised in situ by the perbenzoate $PhCO_3Bu^t$ followed by acid hydrolysis to form the *tert*-butoxy compound **70a**. This is isolated in 50% yield and then treated with $AlCl_3$ in refluxing DCM to form **70b** that is isolated as an oil in 95% yield. In the final step **70b** is etherified using EtBr in the presence of NaOH to produce the desired **70c** as an oil in 75% yield.

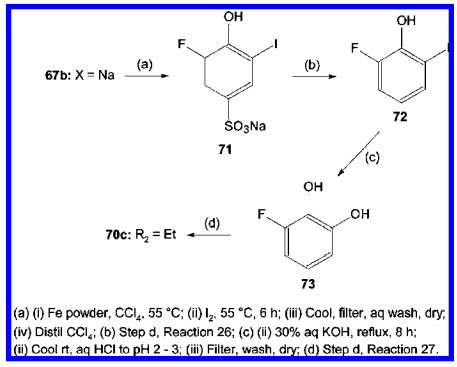
Reaction 27



An alternative route is shown in Reaction 28 for the preparation of **70c** via formation of the iodo-derivative **71**. This

is obtained from **67b** by a process similar to that used for preparing **68** using I_2 in place of Br_2. **71** is isolated in 79% yield and then converted to **72** that is obtained in 83% yield. Hydrolysis of **72** with KOH gives **73** in 78% yield, and this is etherified using EtBr to form **70c** that is isolated as an oil in 81% yield.

Reaction 28



The patent provides basic ^1H and ^{19}F NMR data for compounds **70b** and **70c** but does not provide purity details of any of the intermediates or final product.

Advantages

The overall process has many steps, as admitted in the patent, but it is claimed that they are easy to perform and do not require difficult reaction conditions.

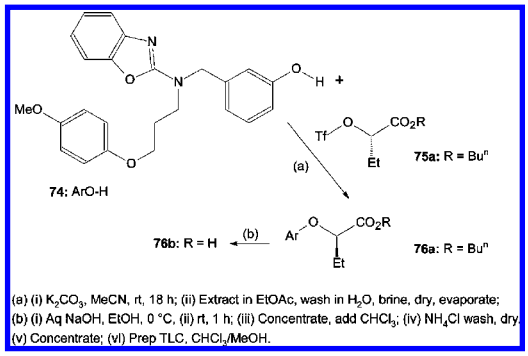
Patent No. U.S. 7,790,903

Assignee: Kowa Co. Ltd., Nagoya-shi, Japan

Title or Subject: Process for Production of Optically Active PPAR-Activating Compound and Its Intermediate

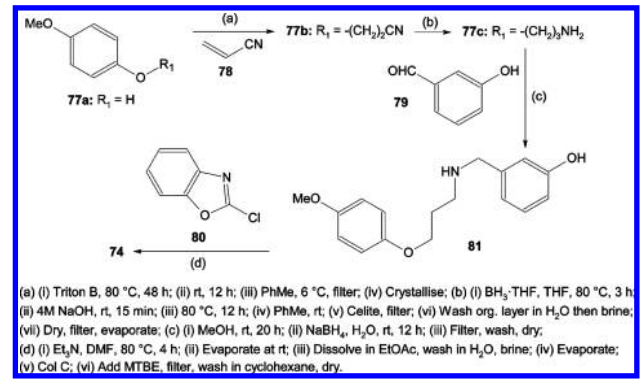
The compound of interest is the acid **76b**, and the patent describes a process for its preparation and also for reaction intermediates. The synthesis of **76b** is shown in Reaction 29 and begins with the etherification reaction between **74** and the chiral ester **75a** in the presence of K_2CO_3. This produces **76a** as a colourless oil in 98.3% yield that is then hydrolysed with NaOH to give **76b**. This is purified by preparative TLC and isolated in 100% yield as a colourless solid. There is a summary of several experiments for the preparation of **76a** in which the reaction temperature and time are varied. Also examined were the use of alternative bases such as Et_3N and Cs_2CO_3. The ee of the final product prepared is >99%.

Reaction 29



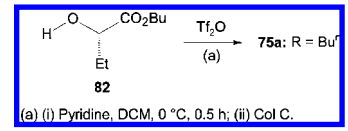
The patent gives details of the preparation of the starting material **74** by the route shown in Reaction 30. This begins with the formation of **77b** by reaction of **77a** and **78** in the presence of the base Triton B. The purification procedure involves several crystallisations giving four batches of crystals, and the total yield of pure product is 76.9% along with 5.8% of crude material. **77b** is then reduced with BH_3·THF to give **77c** that is isolated in 78% yield. Reaction of **77c** with **79** in MeOH followed by reduction with $NaBH_4$ gives **81** in 87.4% isolated yield. In the final step base-catalysed reaction of **81** with **80** forms **74** that is isolated in 92.2% yield.

Reaction 30



The synthesis of the chiral ester **75a** is by reaction of **82** with Tf_2O in the presence of pyridine (Reaction 31). The reaction mixture was subjected to Col C, and the product obtained is a colourless oil that is used without further treatment. The patent also gives details for the preparation of the benzyl ester **75b** (R = Bn). ^1H NMR data are provided for most of the compounds described.

Reaction 31



Advantages

The process gives high yields of product with high ee, but since the examples are all carried out on a semimicro scale, the commercial potential of the process is not clear.

Patent No. U.S. 7,795,425

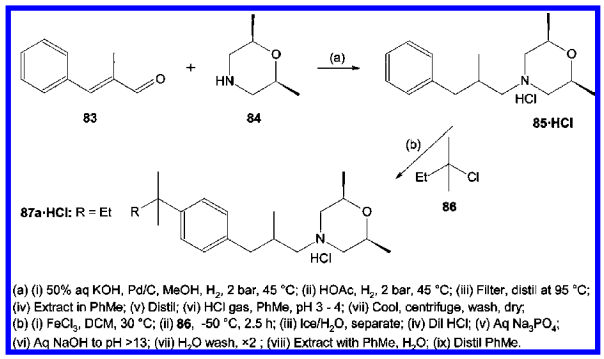
Assignee: Galderma S.A., Cham, Switzerland

Title or Subject: Production of Bepromoline

Bepromoline **85** is used as the HCl salt as an intermediate in producing amorolfine **87a** (R = Et) that is used as the HCl salt as an antifungal agent. The preparation of **85** is shown in Reaction 32 and involves the reaction of **83** and **84** under hydrogenation conditions. Alternative processes mention the use of a variety of catalysts including Pt, Pd, Pd/C, or Raney Ni but none mention the pH of the reaction process. The key aspect of the process in this patent is that it is carried out in the presence of a base. The catalyst used is Pd/C; once the reaction ceases to consume H_2 HOAc is added to the mixture and the reaction continued under H_2 pressure. The addition of HOAc is to promote the reduction of the C=N bond, and using KOH in

the first step avoids the reduction of the CHO group and improves the C=C bond reduction. *trans*-Isomers of **85** can be produced, but these are partially removed during crystallisation of the HCl salt that is recovered in 94% yield with purity >99.5%. The formation of **87a·HCl** is a Friedel−Crafts reaction between **86** and **85·HCl**. This is carried out by adding $FeCl_3$ to a solution of **85·HCl** in DCM at 20−30 °C. The mixture is then cooled to −50 °C, and **86** is added. At temperatures >−50 °C the amount of the byproduct **87b** (R = Me) increases. For example at −50 °C only around 0.2% is formed, but at −20 °C 2.7% is obtained, and it is difficult to remove. The examples in the patent describe production of both **85·HCl** and **87a·HCl** in batches >200 kg, and this is clearly on a commercialised scale. The crude **87a·HCl** is purified by a single crystallisation step from EtOH. The purified material contains <0.1% **85**, 0.25% **87b**, and <0.2% *trans*-isomers of **85**, and these values are within the desired specification.

Reaction 32



The patent describes the purification of the free base of **97a** by vacuum distillation, and there is an example in which 283 kg of crude **87a** is distilled to give190 kg of pure product.

Advantages

The process gives high-purity product and is clearly commercially viable.

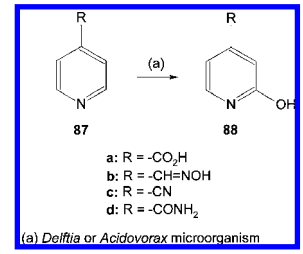
Patent No. U.S. 7,803,585

Assignee: Yuki Gosei Kogyo Co. Ltd., Tokyo, Japan

Title or Subject: Process for Preparing 2-Hydroxy-4-substituted Pyridines

The patent covers a microbiological process for preparing compounds such as **88** that are chemical intermediates. Several chemical syntheses are described and are claimed to be industrially unacceptable with one process that uses F_2 requiring special handling procedures and equipment. It is claimed that a microbiological route has not been reported previously, and hence, the new process is novel. The patent claims that the process is suitable for preparing a range of products using the microorganisms of the genus *Delftia* or *Acidovorax*, and several species are identified. The basic transformation for preparing the compounds **88** from **87** is shown in Reaction 33. The culture medium contains several reagents and buffers including Na_2HPO_4, KH_2PO_4, $FeSO_4$, Na_2MoO_4, $MgSO_4$, $NaO_2C(CH_2)_3$-CO_2H, and NaOH and is run at pH 7 at about 27 °C over a period of 1−3 days. The substrate **87** is added at a concentration of 0.3−2.0 w/v %. In one example 126.1 g of **87a** (R = CO_2H) gave 91.6 g of **88a** (R = CO_2H), and after purification and drying 81.5% of product was obtained that was 100% pure by HPLC. The patent also describes the preparation of the novel aldoxime compound **88b** (R = −CH NOH) in 87% yield from **87b** after 108 h.

Reaction 33



Advantages

The process does not require hazardous reagents or conditions, but whether the productivity is industrially acceptable is not known.

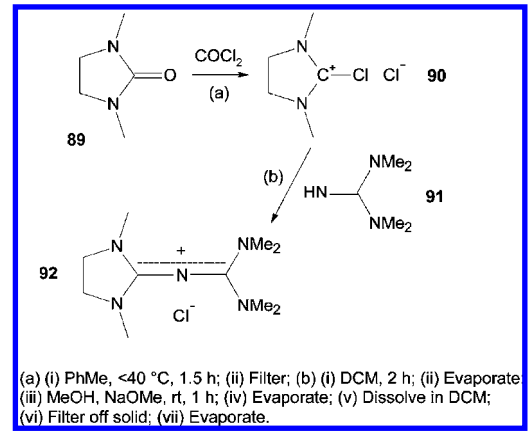
Patent No. U.S. 7,803,941

Assignee: Lanxess Deutschland GmbH, Leverkusen, Germany

Title or Subject: Process for Preparing Ring-Fluorinated Aromatics

This patent describes a fluorination method for introducing two or more F atoms in a single step. The patent states that processes for introducing two or more F atoms into weakly activated aromatics are costly and inconvenient. They usually require two or more steps with isolation of intermediates, and hence the yields of such processes are low. The new process involves a halogen exchange, using alkyl fluorides, carried out in the presence of an ionic compound such as **92** that acts as a catalyst. This is one of several ionic compounds claimed to be suitable in the process but is the only one for which examples are given. It is also the only one whose preparation is described, and this is outlined in Reaction 34. The first step is reaction of **89** with phosgene to form the salt **90** that is isolated as a solid in 85% yield. This salt is then dissolved in DCM and reacted with **91** over 2 h. After removal of the DCM, the residue is dissolved in MeOH and treated with NaOMe to form **92**. After workup this is isolated in 94% yield.

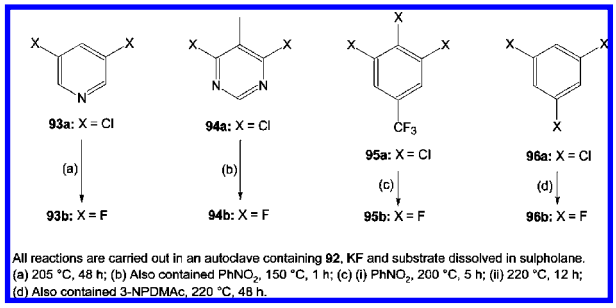
Reaction 34



The fluorination of a number of compounds is described and shown in Reaction 35. All reactions are carried out in an autoclave containing the substrate, KF, and **92** dissolved in sulfolane. Some reactions have additional compounds that are

added as free radical scavengers such as $PhNO_2$ or 3-nitrophenyldimethylamide (3-NPDMAc). The products are isolated by distillation, and the yields are reported as 60% (**93b**), 66% (**94b**), 75% (**95b**), and 74% (**96b**). In the reaction of **96a** a 6.7% yield of difluorochlorobenzene was also obtained, and this can be separated from **96b** by distillation.

Reaction 35



Advantages

The process provides a single-step, and efficient method of introducing two or more F atoms into weakly activated aromatic compounds.

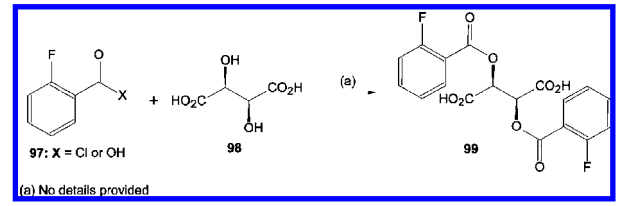
Patent No. U.S. 7,803,962

Assignee: Cosma S.p.A., Ciserano, Italy

Title or Subject: Process for the Resolution of Racemic Verapamil

Verapamil is used to treat hypertension, angina, and certain heart rhythm disorders. The resolution of the racemic mixture and recovery of the single enantiomers are claimed to be notoriously difficult. Methods are known that use tartrate salts, but they require three crystallisations of the mixture and a further crystallisation of the optical isomer to achieve high ee. This patent reports a new process that is said to be considerably different from alternatives. It uses the succinic acid derivative **99** as the resolving agent that is said to be made as shown in Reaction 36 by known esterification methods, although no details are given in the patent.

Reaction 36



The selectivity of the resolution of racemic verapamil using **99** was found to be influenced by the solvent used. Positive results were obtained using DMF, MeCN, or MeOH mixed with H_2O. The preferred volumetric ratios for the solvent mixture are H_2O/DMF 0.7:1 to 0.9:1; H_2O/MeCN 0.8:1 to 1.2:1; H_2O/MeOH 0.3:1 to 0.6:1. The patent claims that the resolution method can be applied to either the free base or the HCl salt of verapamil. The examples describe the resolution of the HCl salt, and the general procedure is to dissolve the salt in the solvent and add 30% NaOH solution and heat to 60−65 °C and then cool for about 12 h. The precipitated product is filtered off and dried and then crystallised from the same solvents used initially. Both *R*- and *S*-enantiomers of verapamil were prepared, and the optical purity of the products was as high as 99.7%. When the chloro-analogue of **99** was used, the reaction with racemic verapamil gave an oil that could not be solidified.

Advantages

The process gives product with very high optical purity by using a less common type of resolving agent.

Keith Turner

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