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 2011

SUMMARY

The current review contains 20 patents from an original list of 338 that fitted the selection criteria. The imidazole molecule features in many pharmaceutical compounds, and a detailed patent describes a range of novel materials that are useful intermediates. Aripiprazole is used to treat schizophrenia, and two patents cover different aspects of this compound. One reports a novel and stable, low hygroscopic form that does not form a hydrate even after long periods. The second patent covers the preparation of novel acid addition salts that are used to prepare the drug without the formation of a dimeric impurity that is difficult to remove. Another drug used to treat schizophrenia is risperidone, and a method of making the 9-hydroxy derivative, known as paliperidone, is described. The patent claims that the new process is efficient but seems to lack the evidence to substantiate the claim. Patents covering drugs to treat a range of cancers are constantly being published, and a method of making anastrozole is described. This drug is used as a hormonal treatment for breast cancer, and the patent reports the preparation of multikilo batches using the new procedure. Perillyl alcohol is a natural terpene that has antimicrobial and anticancer properties, and a new method is disclosed for selectively producing the precursor *trans*-isocarveol. A new method for making a dialkoxypentanoic ester is described, and this material is an intermediate in the production of a 4-oxopentanoic ester; a caspase inhibitor of interest in the treatment of cancers. The new process does not require the purification of intermediates in a multistep process and avoids the need to use low temperatures. A naphthofurandione compound, that can be found in particular trees, is a potential anticancer compound, and a synthetic route to this compound is disclosed, whereas it has previously only been obtained by extraction methods in low yields. Delmopinol is used as the HCl salt for treating gum diseases, and three extensive patents from the same company cover two new routes and other aspects of its preparation. The patents describe two different routes, and within each there are alternatives to some of the steps. In addition there are several novel intermediates. The patents contain a great deal of NMR data but little information on product purity. A new method is described for making pyridine carboxamides that are intermediates in the synthesis of drugs for the treatment of iron-related disorders such as thalassaemia and anaemia. A feature of the process is that a key intermediate in the process can be produced in aqueous solutions. A highly stereoselective process is described for the production of arylaminopropanols that are intermediates in preparing antidepressant drugs. A new method is described for the resolution of the pair of threo enantiomers of Ritalin, the drug used to treat hyperactive children. The findings that the D-enantiomer is the active isomer and the L-enantiomer may give rise to side effects, including euphoria, are the driving force behind this work. The global market for coffee increases annually, and improved flavours and aromas are always of interest. A patent describes a process for producing a characteristic aroma component of coffee known as kahweofuran and also discloses a number of novel analogues. The process starts from a novel thiophene, and since high concentrations must be used, such compounds may not be to everyone's taste. The use of strong acids in chemistry has always been of interest. Some of the newer synthetic compounds are stronger and better than conventional mineral acids as well as being safer to use. A process is described that is suitable for the large-scale production of hydrofluoroalkanesulfonic acids and their potassium salts. Ubiquinones are naturally occurring antioxidants present in plants and animals. They are also made synthetically, and a patent describes a process for preparing isopolyprenols that form the backbone of the ubiquinone molecule. Dimethyl-1-naphthaldehydes are used to prepare various optical materials, and some of the isomers impart poor properties and thus need to be kept at as low a level as possible. A formylation process for preparing the desired isomers is described that uses HF and BF_3. The key to the process is to use a specified range of these reagents to maximise the selectivity. A process is described for the preparation of substituted anisidines that are intermediates in the preparation of drugs used to treat hepatitis C infections. The process involves a solvent-free method for making an oxime using hydroxylamine sulfate. Losartan as the potassium salt is used to treat hypertension, and a new process describes the use of commercially available starting materials, employs fewer steps than alternative methods. The process is claimed to be more efficient and economical but uses a toxic tin compound without indicating if and how the residues are removed. A number of the patents in this collection describe experiments carried out on a kilo or multikilo 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. 7,880,017

Assignee: Allergan Inc., Irvine, California, United States
Title or Subject: Process for the Synthesis of Imidazoles

The patent describes a process for synthesising imidazoles such as **3a**, and this compound is, in fact, the subject of the claims. This and related imidazole compounds are said to be useful as pharmaceutical intermediates. The patent lists several other patents in which imidazoles such as **3a** can be used to prepare pharmacologically active materials. The patent states that there are few methods that are suitable for the synthesis of highly functionalised imidazoles. Those that are known are said to require the use of intermediates that are difficult to prepare, and

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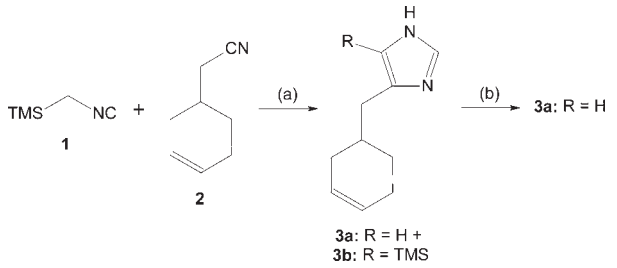
references to some of these are given. The general reaction used to prepare the desired compounds is that between a cyanide and a silylated isocyanide. Scheme 1 outlines the synthesis of **3a** by reaction of **1** with **2**, and after about 40 min the reaction mixture contains 71% **3a** and 26% **3b**. Treatment with KF and refluxing for a further 8 h gives a red-brown oil that is purified by column chromatography (ColC), and **3a** is isolated in 52% yield as a light-brown solid with 100% purity.

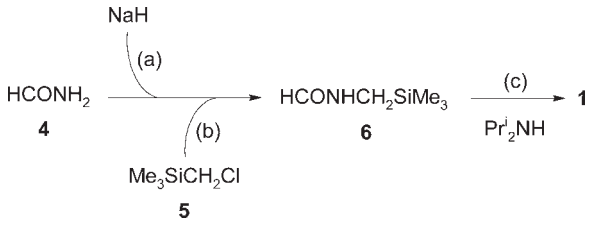
Scheme 1[a]



[a] Reagents and conditions: (a) KOBu^t, DME, rt, 70 min; (b) (i) KF, reflux, 8 h; (ii) cool, add brine, extract in EtOAc.

The patent describes the synthesis of a range of other imidazoles by reaction of **1** with other nitriles using the same procedure. Also described is the preparation of the starting compounds **1** as outlined in Scheme 2, and the reaction initially produces the formamide **6** from **4** and **5** in the presence of NaH in DMF. The product **6** is isolated by vacuum distillation in 78% yield and then is mixed with Pr$^i_2$NH in DCM followed by $POCl_3$ at −20 °C. The isocyanide **1** is obtained in 55% yield after vacuum distillation, but the purity is not reported.

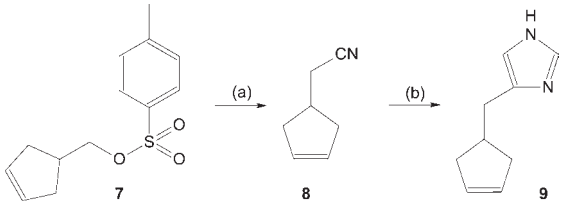
Scheme 2[a]



[a] Reagents and conditions: (a) (i) DMF, 0.5 h: (ii) 120 °C, 0.75 h; (b) (i) cool to 60 °C; (ii) 120 °C, 16 h; (iii) filter, distill; (c) (i) $POCl_3$, DCM, −20 °C, 75 min; (ii) 0 °C, 1 h; (iii) aq K_2CO_3, 0 °C; (iv) rt, 1 h; (v) separate, extract in DCM; (vi) wash, dry, evaporate, distill.

The patent contains examples for the preparation of the cyano compound **8** and also for the imidazole **9** (Scheme 3), but the experimental details for both compounds are poorly written. For example the patent reports that **8** is prepared by heating a mixture of NaCN in DMSO followed by addition of a solution of **1**. The reagent used to add the cyclopentyl ring is not initially mentioned until the example states that the reaction is monitored by NMR to follow the disappearance of the sulfonate **7**, but neither the point at which this reagent is added nor its amount is mentioned. The yield of **8** is reported to be 99% as a yellow oil with a purity of only around 90%. The patent then describes the preparation of **9** from **1** and **8**. The procedure is similar to that used to prepare **3a** and **3b**, although in this case the silyl group is removed using Bu$^n_4$F. The crude **9** is isolated as the oxalate salt in 53% yield. The preparation of **2** is not described, but it is presumed to be prepared in a manner similar to that used for **8**.

Scheme 3[a]



[a] Reagents and conditions: (a) (i) NaCN, DMSO, 80 °C, >2.75 h; (ii) cool, add H_2O, extract in hexane; (iii) wash, dry evaporate; (b) (i) KOBu^t, THF, −15 °C; (ii) rt, 2.5 h; (iii) wash, dry; (iv) Bu$^n_4$F, min.

Basic ^{1}H NMR data are given for **8** and the oxalate salt of **9**.

■ ADVANTAGES

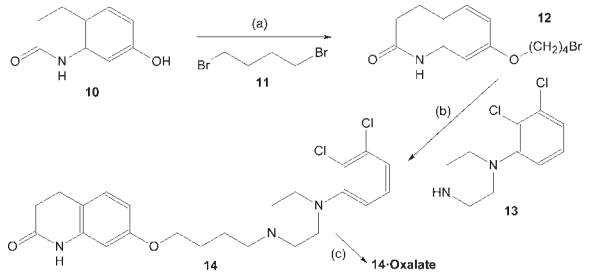
The patent provides a range of novel compounds that are useful intermediates.

■ PATENT NO. U.S. 7,884,205

Assignee: Sandoz AG, Basel, Switzerland
Title or Subject: Salts of Aripiprazole

This is the first of two patents covering the aripiprazole **14**, that is used to treat schizophrenia. Several forms of **14** and its salts are known, and a patent on novel forms has been reviewed recently (*Org. Process Res. Dev.* **2010**, *14*, 492). The current patent covers the preparation of novel acid addition salts, and the following patent describes salts of **14** that have low hygroscopicity. The patent summarises a method for the preparation of **14** that gives rise to the formation of a dimeric impurity **15**. This impurity is said to be difficult to remove without recourse to ColC, and hence, an improved process for preparing **14** is needed. The new method for preparing **14** described in this patent proceeds via novel acid addition salt such as the oxalate as outlined in Scheme 4. The reaction begins with the preparation of the carbostyril **12** by reaction of **10** with **11**. The details are not given, but the procedure used is from U.S. 5,006,528 apart from a step involving ColC. Crude **12** is then reacted with **13** in the presence of Pr$^i_2$NH to give **14** that is converted to the oxalate salt, and this is isolated in 78% yield (purity not reported). The

Scheme 4[a]



[a] Reagents and conditions: (a) From U.S. 5,006,528; (b) (i) Pr$^i_2$NH, 85 °C, 4 h; (ii) Cool to rt; (ii) Extract in DCM; (iv) H_2O wash; (v) H_2SO_4 to pH 6; (vi) wash in H_2O at pH 6; (vi) NaOH to pH 9, dry; (vii) $(CO_2H)_2$, DCM, 35 °C, 0.25 h; (viii) EtOH, 20 °C, 1 h; (ix) 0 °C, 1 h, filter, wash; (x) dry at 50 °C in vacuum.

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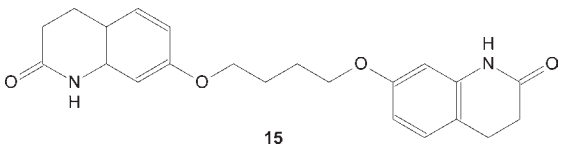
oxalate salt can be converted to a range of salts of **14**, and several examples are given.

Dimeric Impurity



15

The impurity **15** is formed in the reaction of **10** with **11** and is not removed before reaction of **12** with **13**. It can be removed when the crude oxalate salt of **14** is converted to **14**, and this is carried out as follows:

(1) Suspend salt in DCM/H_2O and add Na_2CO_3 to pH 9. forming a solution.
(2) Separate layers and wash in H_2O then dry over Na_2CO_3.
(3) Concentrate on rotary evaporator.
(4) Add EtOH and heat to 85 °C and add seed crystals of **14**.
(5) Cool to 4 °C, for 15 h then filter and dry in vacuo.

The final product contains <0.05% of **15** and an unidentified impurity at <0.05% (HPLC). The oxalate salt is also used to prepare Form X of **14** in 95% yield by treating the salt with a base such as tetramethylguanidine or DBU. The hydrate of **14** is prepared from the oxalate salt by treatment with Et_3N, and after recrystallisation from Pr^iOH is found to contain <0.05% **15**.

■ ADVANTAGES

The process provides the desired product in high purity without the need to use chromatographic techniques.

■ PATENT NO. U.S. 7,910,589

Assignee: Otsuka Pharmaceutical co. Ltd., Tokyo, Japan

Title or Subject: Low Hygroscopic Aripiprazole Drug Substance and Processes for Its Preparation

The second patent on the drug aripiprazole describes novel, low hygroscopic forms of **14** that will not convert to a hydrate nor lose their original solubility even when stored for long periods. Anhydrous crystals are known, and the hygroscopic nature of these varies. The methods of preparing them can sometimes involve heat treatment at temperatures up to 125 °C, and this can degrade the crystals. The patent describes a number of crystalline forms of **14**, and the claims specifically cover an anhydrous form designated as type C. The patent also describes anhydrous crystals designated as types A, B, D, E, F, and G. The starting material for preparing the crystal form A is a hydrate containing 3.82% H_2O that is prepared by a process disclosed in a Japanese Unexamined Patent JP 191256/1990. The term hygroscopicity of the crystals is defined in the patent as the H_2O content, as measured by Karl Fischer, after 24 h at 60 °C and 100% humidity. The type A crystals are prepared from the hydrate by milling and then used to prepare several of the other forms. Type C crystals are obtained from an anhydrous form of **14** that is prepared from the raw crystals via the method of the Japanese patent. The procedure is outlined as follows:

(1) Dissolve raw crystals by heating in EtOH containing 20% H_2O then cool to rt over 3 h.
(2) Cool mixture to 0 °C and filter off wet crystals and dry at 80 °C for 30 h.

These anhydrous crystals of **14** are designated type I that contain 0.03% H_2O and after 24 h have hygroscopicity of 1.78%. An example describes the use of these type 1 crystals in the preparation of type C anhydrous crystals claimed by the patent. The crystals are heated to 145 °C (±3 °C), whereupon the crystals melt and recrystallise and are recovered in 100% yield. The new crystals are colourless prisms with a mp of 150 °C, and their hygroscopicity is no higher than 0.4%.

The patent also describes details of the preparation, and interconversion of the other crystals and extensive physical property data are provided for all of the forms described. Some examples use multikilo batches of crystals, and details of formulations containing **14** are also reported.

■ ADVANTAGES

The process provides novel anhydrous forms of the API that are useful in preparing pharmaceutical formulations.

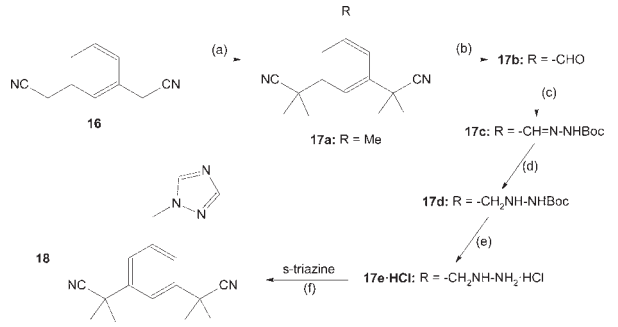
■ PATENT NO. U.S. 7,884,213

Assignee: Generics (UK) Limited, Hertfordshire, United Kingdom

Title or Subject: Process for the Preparation of Anastrozole

Anastrozole **18** is a nonsteroidal aromatase inhibitor used as a hormonal therapy in the treatment of advanced breast cancer in postmenopausal women. It is used in the free base form and available as Arimidex. A process focussing on the purification of **18** has been reviewed (*Org. Process Res. Dev.* **2010**, *14*, 759), and the current patent describes a process for its preparation involving a range of novel intermediates. The process route outlined in Scheme 5 only shows the main reagents and has omitted workup details for clarity. The process begins with the methylation of **16** to give **17a** by a process reported in EP 0296749. Details are not provided in the current patent apart from the yield that is reported as 79%. In the next step **17a** is oxidised to form the aldehyde **17b** using CrO_3 in Ac_2O containing H_2SO_4. The process proceeds via formation of a diacetate that is converted to the aldehyde by refluxing in aq EtOH and H_2SO_4. **17b** is isolated in a yield of 78.3% and then converted to the protected hydrazone **17c** by treatment with NH_2NHBoc. The hydrazone is isolated in 77.2% yield and then converted to the hydrazine **17d** in a transfer hydrogenation reaction with HCO_2NH_4 in the presence of Pd/C. The hydrazine **17d** is isolated as a yellow oil in 80% yield and then converted to **17e** by refluxing with HCl. The free base form is not isolated but converted to its HCl salt by treatment with HCl in Et_2O, and the salt **17e · HCl** is obtained in 52.8% yield. The final step is conversion of the HCl salt to **18** by refluxing with *s*-triazine in EtOH. The product is initially isolated as a light-yellow oil, and after mixing this product with EtOAc and hexane, **18** is isolated as a white solid in a yield of 72.5% with purity of >99.5% (HPLC). The patent contains a number of claims that mention specific batch sizes of **18** obtained using the new process. Claims cover the specific batches of 5.6 g, 0.5 kg, 5 kg, and 25 kg, and one claims that **18** can be obtained "on an industrial scale". The patent provides ^1H and ^{13}C NMR data for the novel intermediates along with some IR data.

Scheme 5[a]



[a] Reagents and conditions: (a) From EP 0296749; (b) (i) Ac_2O, H_2SO_4, −10 °C, 0.75 h; (ii) CrO_3/Ac_2O, −10 °C, 2 h; (iii) EtOH/H_2O, H_2SO_4, reflux, 1 h; (c) NH_2NHBoc, EtOH, reflux 5 h; (d) HCO_2NH_4, MeOH, Pd/C, reflux, 4 h; (e) (i) Concd HCl, DCM, reflux 3 h; (ii) Et_2O·HCl, THF, <5 °C, 0.5 h; (iii) filter, wash, dry; (f) (i) EtOH, reflux, 2 h; (ii) evaporate, add DCM; (iii) H_2O wash; (iv) EtOAc/hexane, rt, 0.5 h; (v) filter, wash, dry.

■ ADVANTAGES

The process provides a novel route to the API in high purity via a route that involves a number of novel intermediates.

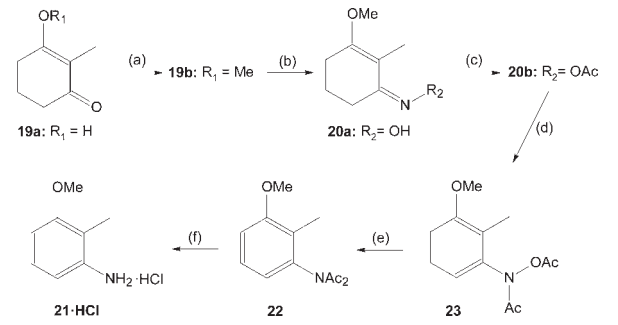
■ PATENT NO. U.S. 7,884,246

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

Title or Subject: Process for Preparing Substituted Anisidines

The compounds covered by this patent, such as **21**, are intermediates in the preparation of drugs used to treat hepatitis C infections. The patent states that a practical and economic process for preparing **21** is required and discloses a process that starts from cyclic hydroxy-ketones outlined in Scheme 6. The

Scheme 6[a]



[a] Reagents and conditions: (a) $(MeO)_3CH$, H_2SO_4, MeOH, rt, 2 h; (b) (i) $(NH_2OH)_2 \cdot H_2SO_4$, 40 °C; (ii) rt, 2.5 h; (c) (i) Ac_2O, pyridine, 30 °C; (ii), rt, 0.75 h; (iii) AcCl, Ac_2O; (iv) 100 °C, 1 h: (d) (i) HCl, EtOH, reflux, 6−8 h; (ii) Cool, 0 °C, 2 h, filter, wash in EtOAc and heptane, dry.

route begins with the methylation of **19a** to give **19b** using $(MeO)_3CH$ in the presence of H_2SO_4. The methylated product is not isolated but is converted to the oxime **20a** by treatment with $(NH_2OH)_2 \cdot H_2SO_4$. This reagent is claimed to have the advantage over standard procedures using other hydroxylamine salts in that no adjustment of pH is required and a solvent is not needed. The oxime **20a** is isolated in 92% yield, and in the next step **20a** is activated by an acetylation reaction. This is carried out by mixing **20a** with Ac_2O containing one equivalent of pyridine followed by the addition of one equivalent of AcCl in Ac_2O. The reaction is carried out using a mechanical stirrer and proceeds via the intermediates **20b** and **23** that are not isolated. The product is the protected aniline **22b**, and the crude material is treated with concd HCl to give the HCl salt **21** that is isolated in 82% yield (purity not reported).

The patent also describes the preparation of the 2-bromo analogue of **21** using a similar procedure. The main difference is that the acetylation step is carried out in Ac_2O, using 5.1 equiv of TFAA and 0.2 equiv of HBr. The resulting oxime is isolated in 55% yield, and the final aniline salt, in 65% yield.

■ ADVANTAGES

The process uses readily available reagents, avoids the use of cryogenic conditions and gives faster cycle times than alternative routes so that overall it is more economical.

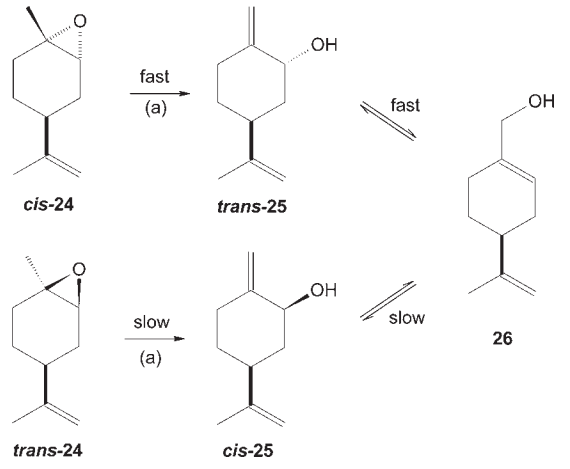
■ PATENT NO. U.S. 7,884,252

Assignee: LyondellBasell Flavors and Fragrances LLC, Houston, Texas, United States

Title or Subject: Process for Making *trans*-Isocarveol

trans-Isocarveol, ***trans*-25**, is an intermediate useful for the production of perillyl alcohol, **26**; a natural terpene that has antimicrobial and anticancer properties. Synthetic methods for preparing **26** use mixtures of *cis*- and *trans*-isomers of **25**, but they do not have high efficiencies, and using mixtures of isomers means that isolating the product can be difficult. This new process comprises a selective isomerisation of the *cis*- and *trans*-oxides of **24** to give ***trans*-25**, and it has also been found that this is the preferred isomer for preparing **26**. Scheme 7

Scheme 7[a]



[a] Reagents and conditions: (a) (i) Cr octoate, 2-AP, reflux (max 211 °C), 1.5 h; (ii) fractional distillation.

outlines the process that uses a Cr catalyst such as chromium octoate (Cr−O) and a phenolic modifier such as 2-aminophenol (2-AP). A mixture of ***cis*-/*trans*-24** (66/34) is refluxed with 0.066 wt % of Cr−O and 0.083 wt % of 2-AP with a Dean−Stark trap, and after 1.5 h GC showed that the mixture contains 3.6% ***cis*-24**, 29.7% ***trans*-24**, and 51.3% ***trans*-25**. Fractionation of this mixture gave 99% pure ***trans*-25** and pure ***trans*-24**. When the

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experiment was carried out using 1.7 wt % of Cr−O and 0.5 wt % 2-AP, as specified in U.S 6,835,686, the mixture contained essentially none of the oxides and 55% ***trans*-25** and 26% ***cis*-25**. Hence, the use of less catalyst gives improved selectivity.

■ ADVANTAGES

The process improves the selectivity of the preferred isomer.

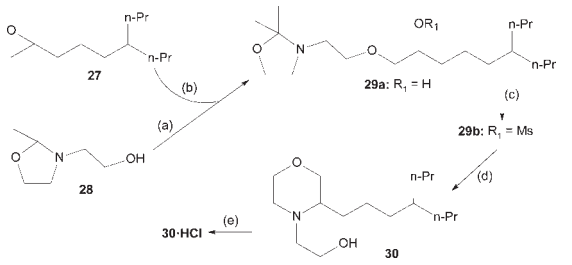
■ PATENT NO. U.S. 7,893,258

Assignee: Sinclair Pharmaceuticals Limited, Surrey, United Kingdom

Title or Subject: Preparation of Delmopinol and its Derivatives

The is the first of three extensive patents from the same company that relate to the preparation of delmopinol, **30**, that is available as the HCl salt for the treatment of the gum disease, gingivitis. Alternative processes for preparing **30** are said to use some very toxic and carcinogenic reagents such as bis(haloethyl) ethers, making the industrial processes difficult and expensive. Two processes for preparing **30** are described in the three patents, and the first, described in this patent, is outlined in Scheme 8. The process involves the reaction of **27** with **28** in the

Scheme 8[a]

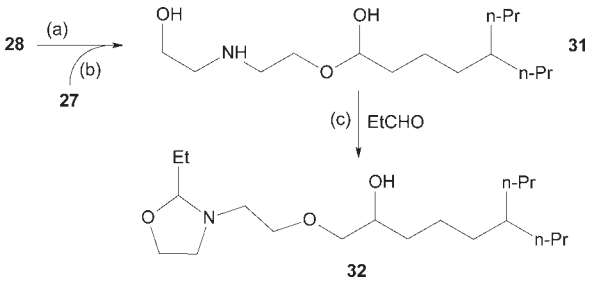


[a] Reagents and conditions: (a) (i) NaOMe, 50 °C, 20 min; (ii) vacuum, 1.5 h; (b) (i) 75 °C, 18 h; (ii) PhMe, rt; (iii) H_2O, 0 °C, 1 h; (iv) extract in PhMe, workup; (c) Et_3N, MsCl, PhMe, 0 °C, 1.5 h; (d) (i) H_2O, reflux, 17 h; (ii) cool to rt, extract in PhMe, evaporate; (iii) H_2SO_4 to pH 1; (iv) workup; (e) 37% HCl, PhMe, 60 °C.

presence of a base. The reaction is carried out by adding freshly distilled **28** to NaOMe under a vacuum to remove MeOH followed by addition of **27**. After workup and azeotropic drying using PhMe the crude product **29** is recovered as solution in PhMe and used directly in the next step. Dried Et_3N is added to the solution followed by MsCl and the reaction monitored by TLC. The mixture was used in the next step where it was refluxed with H_2O then extracted into PhMe, concentrated under vacuum, and then the solution was acidified to pH 1 with H_2SO_4. Further workup, involving washing in PhMe, xylene/Bu^n_2O, aq NaOH, and aq NH_4OH, followed by treatment with active C, gave crude **30** as a yellow oil in 89% yield. The solution of **30** in PhMe, xylene, or Bu^n_2O can be used for the preparation of its HCl salt that is isolated after crystallisation from heptane or Bu^n_2O in yields of up to 70% (purity not reported).

A modification of this route is also outlined in the patent and shown in Scheme 9. In this method the reaction of **27** with **28** is carried out in the presence of $KOBu^t$ followed by treating the reaction mixture with aq HCl. Addition of base yields **31**, and this can be isolated in neutral form in 90% yield. After removing the solvent from **31** it undergoes a protection reaction by reaction with an aldehyde such as EtCHO giving the oxazolidine **32**. This is obtained as two stereoisomers in 100% yield and can be converted to its mesylate that can be used to prepare **30** by the same procedure described above.

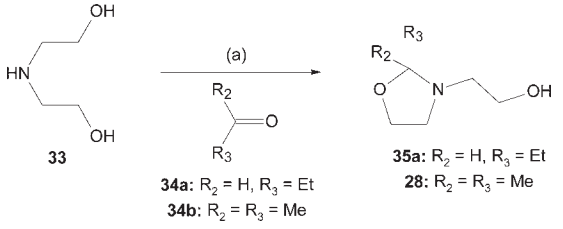
Scheme 9[a]



[a] Reagents and conditions: (a) $KOBu^t$, 75 °C; (b) (i) 75 °C, 7 h; (ii) cool to rt, Et_2O; (iii) Aq HCl; (iv) aq NaOH to pH 14; (v) extract in Et_2O, dry, evaporate; (c) (i) PhMe, rt; (ii) reflux 2 h; (iii) cool, evaporate.

The patent reports the preparation of the oxazolidine **28** from **33** and acetone by the method shown in Scheme 10. This procedure is also used to prepare the 2-ethyloxazolidine **35a** that is reported as being used to prepare **31** by reaction with **27**, but no details for this are given. **35a** and **28** are both prepared by condensation of **33** with a carbonyl compound in the presence of K_2CO_3. The products are isolated by distillation yield (72% for **28** and 87% for **35a**), but the purities are not reported. The patent also reports the preparation of similar products from **33** and paraformaldehyde and cyclohexanone.

Scheme 10[a]



[a] Reaction details: (a) K_2CO_3, DCM, 0 °C; (ii) rt, 3 h; (iii) filter, evaporate, distill.

The preparation of the other key starting material, **27**, is shown in Scheme 11. The scheme shows only the main reagents, and full details are provided in the patent. The route starts with the preparation of the diol **37** by treatment of **36** with PrMgCl followed by acid hydrolysis. The diol is recovered as a viscous oil in 96% yield and then dehydrated using TsOH produces a mixture of 3 isomeric ene-ols **39a**, **39b**, and **39c** as a pale-yellow oil in 98% yield. The mixture is catalytically hydrogenated to form **38a** as a colourless oil in 90% yield, and this is brominated using HBr and H_2SO_4 to form **38b**. This is a brown liquid and is recovered in 89% yield and then converted to **40** by treatment with $KOBu^t$. The alkene is then oxidised to **27** by either of two methods. Option 1 uses *m*-CPBA and gives **27** as a colourless oil in 88% yield after purification by ColC. Option 2 uses peroxyacetic acid and provides purified **27** in 81% yield after ColC.

The patent provides ^1H and ^{13} NMR data for all compounds, many of which are novel, but does not give information on their purity.

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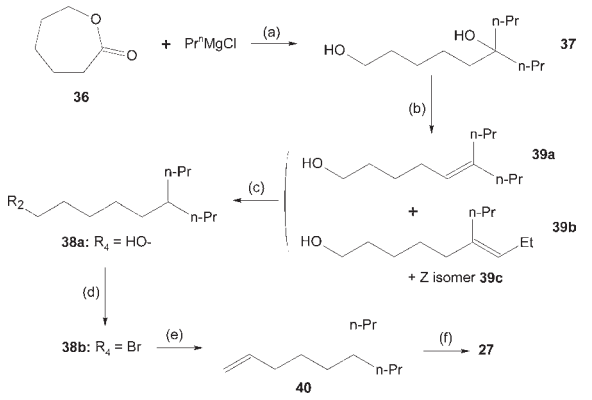
Scheme 11[a]



[a] Reaction details: (a) (i) THF, 0 °C; (ii) rt, 10 min; (iii) reflux, 2 h; (iv) aq NH_4Cl, 1 M HCl, rt; (b) TsOH, PhMe, reflux 2 h; (c) Pd/C, EtOH, H_2, 1 atm, rt, 24 h; (d) 48% HBr, H_2SO_4, reflux 14 h; (e) (i) $KOBu^t$, THF, 0 °C; (ii) rt, 2 h; (iii) 1 M HCl, rt; (f) option 1; *m*-CPBA, DCM, 0 °C, 20 min; option 2; (i) aq NaOAc, peroxyacetic acid, PhMe, 60 °C, 5 h; (ii) rt, 16 h.

■ ADVANTAGES

The process provides a new route to the desired compound via a route that includes several novel intermediates. The process avoids the use of harsh hydrogenation conditions and does not use toxic reagents.

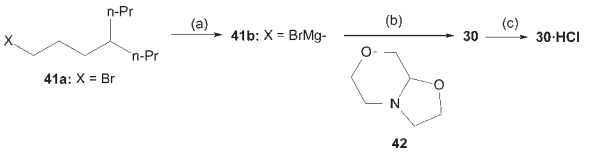
■ PATENT NO. U.S. 7,902,357 AND U.S. 7,910,730

Assignee: Sinclair Pharmaceuticals Limited, Surrey, United Kingdom

Title or Subject: Preparation of Delmopinol and its Derivatives

These two patents cover the preparation of derivatives of delmopinol **30** and are from the same company as the last patent on the subject. The experimental details of the two patents are identical and cover a substantial range of chemistry, but the claims cover different aspects of the invention. The second of these two patents has a single claim covering the novel morpholine compound **42**, while the first has claims covering the synthesis of **42** and **30** by an alternative method to the previously reviewed patent. The key aspect in the patents is that **30** can be prepared in a short and convergent synthesis by the reaction between a Grignard reagent and **42** as shown in Scheme 12. This process for preparing **30** is said to be a surprising finding, and the first stage is the formation of the Grignard **41b** from **41a** and Mg in the presence of I_2. This is followed by addition of **42** to the cooled mixture, and the product is isolated as an orange oil in 59.9% yield. This can be converted to the HCl salt by treatment with concd HCl in MIBK, and **30·HCl** is isolated as a white solid in 78.7% yield based on the free base.

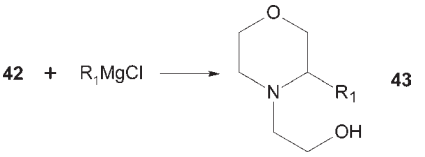
Scheme 12[a]



[a] Reagents and conditions: (a) Mg, I_2, THF, 64 °C, 2 h; (b) (i) PhMe, rt, 0.5 h; (ii) PhMe, aq NH_4Cl, 40 °C; (iii) separate at 40 °C, extract in PhMe at 40 °C; (iv) evaporate.

The patent also contains a number of examples, using the basic reaction for the preparation of **30**, to prepare of a range of morpholine derivatives, **43**, and a selection of these is shown in Scheme 13. The products are all oils.

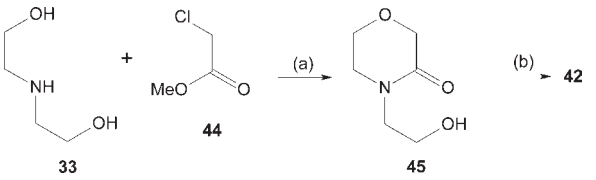
Scheme 13[a]



[a] R_1 = *n*-Pr, *n*-heptyl, Bn, 2-ethylyhexyl, 2-propylheptyl, *n*-octyl.

The patents describe the method for the preparation of the novel compound **42**, and this is outlined in Scheme 14. The process begins with the condensation of **33** and **44** in the presence of $KOBu^t$ to give **45** that is then reduced to give **42**. The process can be carried out with or without isolation of **45**, and both methods are described. In a one-pot process crude **42** is obtained in 80% yield as a brownish oil. In the two stage process **45** is isolated by distillation as a colourless oil in 80% yield and then converted to crude **42** that is isolated in 84% yield and after distillation pure **42** is obtained in 35% yield (based on **45**).

Scheme 14[a]



[a] Reaction details: (a) $KOBu^t$, PhMe, 75 °C, 2.5 h; (b) (i) vitride, PhMe, 30 °C, 0.5 h; (ii) 50% NaOH, extract in PhMe, evaporate.

The patents contains physical property details for all compounds including ^1H and ^{13}C NMR data plus brief MS information. On the face of it, this route to **30** seems simpler than the one described in the previous patent. Not surprisingly, the patents make no comment on this.

■ ADVANTAGES

The patents provide another route to delmopinol via a novel intermediate.

■ PATENT NO. U.S. 7,893,269

Assignee: Apotex Inc., Toronto, Canada

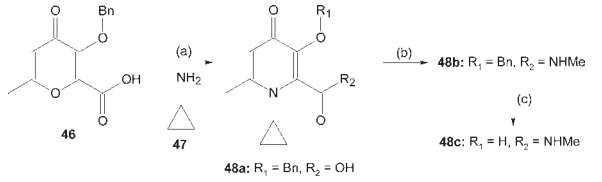
Title or Subject: Process for the Manufacture of 3-Hydroxy-*N*-alkyl-1-cycloalkyl-6-alkyl-4-oxo-1,4-dihydropyridine-2-carboxamide and Its Related Analogues

The compounds covered by this patent are useful in the synthesis of drugs for the treatment of iron-related disorders such as thalassaemia and anaemia. Three methods for synthesising the title compounds are mentioned, and they all proceed via a common amide intermediate derived from the pyran carboxylic acid **46**. It is stated that conversion of this amide to the desired pyridinone **48a** gives low yields, and so an alternative route to **48a** is required. A problem associated with one of the methods is the use of a 1,3-thiazolidine-2-thione compound that is a known

dx.doi.org/10.1021/op2001436 |*Org. Process Res. Dev.* 2011, 15, 736–747

skin irritant. The main compound of interest in the current patent appears to be **48c** that is identified as Apo6619, and the new synthesis is shown in Scheme 15. The route starts from the acid **46** that is refluxed for 19 h with **47** to produce **48a**. There are three different methods for the preparation of **48a** with examples of each. One method is carried out in MeOH and gives **48a** as an off-white solid in 88% yield. The second method uses H_2O containing NaOH; the third uses only H_2O, and both give **48a** in 93% yield. In the second step **48a** is reacted with the acid chloride formed from DMF and $(COCl)_2$. The amide **48b** is isolated as a brownish solid in 90% yield, and an alternative method using the Vilsmeier reagent gives **48b** in 73.7% yield. In the last step catalytic reduction of **48b** in the presence of HCl gives crude **48c** that is purified by stirring with aq EtOH at 0 °C and isolated as a light pinkish solid in 74% overall yield (based on **48b**).

Scheme 15[a]



[a] Reagents and conditions: (a) (i) MeOH, reflux 19 h; (ii) evaporate, filter, add concd HCl to pH 2; (b) (i) DMF, $(COCl)_2$, DCM, 10 °C, 1 h; (ii) $MeNH_2$/THF, Et_3N, DCM, 4 °C, 2.5 h; (c) (i) concd HCl, MeOH/H_2O, rt, 5 min; (ii) Pd/C, H_2, 3.4 bar, rt, 3 h.

The patent describes the preparation of several analogues of **48b** and **48c** using other amines in place of $MeNH_2$. Examples are given where R_2 = Me_2N, (cyclopropyl)NH, (cyclohexyl)NH, (cyclohexylmethyl)NH, 4-morpholinyl, (3-methylbutyl)NH, (n-hexyl)NH, and 4-methylpiperazinyl. This is another example of a patent that provides ^1H and ^{13} NMR data for all compounds but does not give information on their purity.

■ ADVANTAGES

The process gives the desired amides in higher yields than alternative methods, and it is claimed that it is amenable to industrial-scale production. The key intermediate **48a** can be made in aqueous solution and can be purified without recourse to using ColC methods.

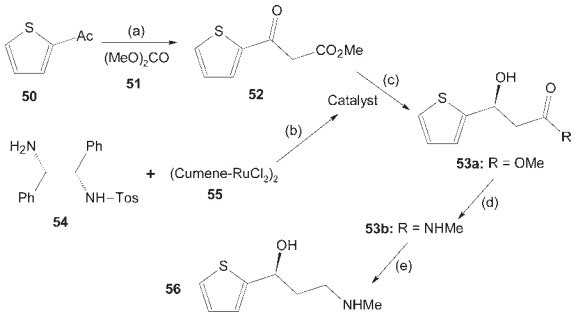
■ PATENT NO. U.S. 7,893,281

Assignee: Lanxess Deutschland, Leverkusen, Germany

Title or Subject: Process for Preparing Arylaminopropanols

The compounds covered by this patent are intermediates in the preparation of serotonin or noradrenalin take-up inhibitors that are used to treat depression and anxiety. The patent points out that usually only one enantiomer of the intermediate is desirable, and so new processes need to be stereoselective. The main claim of the patent covers novel amide compounds such as **53b**, and the remaining claims cover the preparation of **56** by the reduction of **53b**. Scheme 16 outlines the preparation of **56**, and this begins with the formation of the keto ester **52** by reaction of **50** with **51** in the presence of a strong base. MeOH formed in the reaction is removed by azeotropic distillation with PhMe. **52** is isolated as a light-yellow liquid in 74% yield and 98% purity after vacuum distillation. The next step of the process is the stereoselective conversion of **52** to give **53a** and does seem to be the key feature of the patent. This step is a hydrogen transfer reaction and uses a chiral Ru catalyst. This is obtained by dissolving **54** and **55** in DCM, and Et_3N is added in an equimolar amount to **54**. The catalyst mixture is ready to use after 0.25 h. The formation of **53a** takes place in a two-phase mixture of HCO_2H and Et_3N. After acidification the crude product **53a** is isolated and used in the next step without further purification. GC analysis showed that the conversion of **52** was 100%, and ee was 98.2%. Treatment of **53a** with $MeNH_2$ gives **53b** that is recovered in 88% yield and 86% purity. The crude product can be used directly in the next stage although crystallisation does provide a white crystalline solid. The patent also states that the product can be purified by distillation. In the final step **53b** is reduced to give **56** using $LiAlH_4$, and the crude product is isolated in 80% yield and 84% purity, but there are no details given for the purification of **56**. The patent claims cover the use of a boron hydride for this reduction although there are no examples.

Scheme 16[a]



[a] (a) (i) NaOMe, PhMe, 100 °C, 4 h; (ii) concd H_2SO_4, <40 °C, pH 1; (iii) separate, extract with aq Na_2SO_4, evaporate; (b) Et_3N, DCM, rt, 0.25 h; (c) (i) HCO_2H/Et_3N, 36 °C, 14 h; (ii) 1 M HCl, DCM; (iii) separate, extract in DCM, brine wash, dry evaporate; (d) (i) $MeNH_2$, MeOH, 60 °C, 4 h; (ii) evaporate; (e) (i) $LiAlH_4$, THF, reflux, 16 h; (ii) Cool to rt, add H_2O; (iii) 10% aq NaOH, filter; (iv) evaporate, 1 M NaOH; (v) extract in PhMe, evaporate.

The details of both the ^1H and ^{13}C NMR of **56** are given in the patent.

■ ADVANTAGES

The process is highly stereoselective and therefore is potentially of commercial importance.

■ PATENT NO. U.S. 7,897,777

Assignee: Archimica Inc., Springfield, Missouri, United States

Title or Subject: Process of Enantiomeric Resolution of D,L-(±)-*threo*-Methylphenidate

Methylphenidate **57** is used as the hydrochloride salt under the name Ritalin to treat hyperactive children. The commercial drug comprises the threo pair of D- and L-enantiomers and is used as a racemic mixture. It is considered that the D-threo enantiomer has the higher activity, and there are reports that the L-threo enantiomer can cause euphoria. As a result there is renewed interest in method for the preparation of the D-threo enantiomer directly or by resolution. The patent describes a procedure that gives high ee if a tailored stoichiometry is used in the resolution step. The process is outlined in Scheme 17 and starts with the

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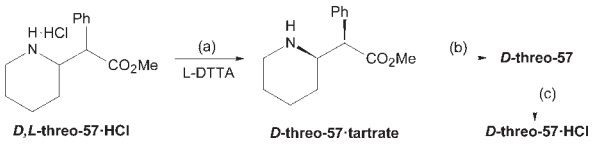
formation of a chiral acid salt of of D-**threo-57** using di-*O*,*O*′-*p*-toluoyl L-tartaric acid (L-DTTA) and a base. Pr^i_2EtN, Et_3N, NaOAc, and *N*-methylmorpholine (*N*-MM) were examined, and the latter is preferred. The ratio of base to L-DTTA is critical and should be in the range 0.5−1.0 with excess amine being detrimental to salt formation and crystallisation. The reaction is carried out by mixing the racemate HCl salt with L-DTTA in MeOH then adding *N*-MM and heating. H_2O is added until a cloud point is reached, and then the slurry is aged for 1 h. There is apparently no need to seed the mixture to obtain crystals with high ee, and after filtering and washing, the acid salt is isolated in 40.3% yield with HPLC purity 99.8% and ee of 99.7%. This is then converted to the free base by mixing with H_2O/Pr^iOAc and 25% NaOH, and after ageing 0.5 h, the organic layer is recovered and dried by azeotropic distillation, giving the free base as an oil. This is used directly to form the HCl salt by treatment with 37% HCl in Pr^iOH/MeOH. The D-threo HCl salt of **57** is isolated in 86% yield with 99.7% ee, containing 1% MeOH. (This would be unacceptable as a drug substance where the methanol limit is 0.3%.)

Scheme 17[a]



[a] Reagents and conditions: (a) (i) MeOH, *N*-MM, 45 °C; (ii) H_2O, 45 °C, 1 h; (iii) filter, wash, dry; (b) (i) H_2O/Pr^iOAc, 15 °C; (ii) 25% NaOH, <25 °C; (iv) 25 °C, 0.5 h; (v) separate, dry, evaporate; (c) (i) 37% HCl, Pr^iOH/MeOH, <10 °C, 2 h; (ii) filter, wash dry.

The key aspects of the patent are the use of less than stoichiometric amounts of base with the chiral acid and the lack of seeding to obtain high-quality crystals. There is no mention in the patent regarding racemisation or recovery of the L-threo enantiomer although the process can be used to recover pure L-threo enantiomer by using D-DTTA.

■ ADVANTAGES

The process gives the desired active enantiomer in high purity.

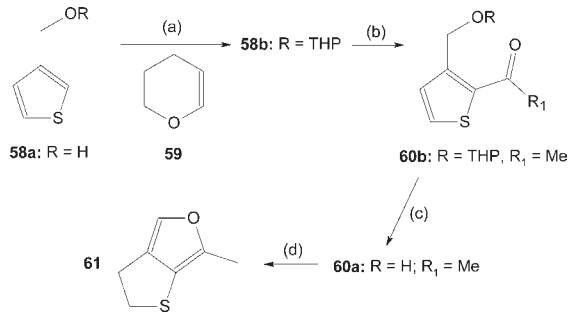
■ PATENT NO. U.S. 7,897,790

Assignee: San-Ei Gen FFI Inc., Osaka, Japan

Title or Subject: Process for Producing Caffenofuran or Analogue from a Novel Thiophene Compound

The compound of interest in this patent **61** is a characteristic aroma compound found in coffee and is more commonly known as kahweofuran. The compound can improve the flavour and aroma of coffee, and hence, its synthesis is of interest in the growing global market for coffee. The known methods for the synthesis of **61** are not particularly efficient and hence are not suitable for industrial production. The route developed for preparing **61** is shown in Scheme 18 and starts from the thiophene **58a**. The OH group in this compound is protected by reaction with **59** in the presence of PPTS to give the THP derivative **58b** that is isolated as an oil-like material in 100% yield after purification by ColC. **58b** is then acylated by metalation with Bu^nLi. followed by treatment with Ac_2O, giving **60b** that is isolated as an oily material in 68% after ColC. Deprotection of **60b** by treatment with camphor sulfonic acid (CSA) produces **60a** as an oil in 88% yield after ColC. This step can also be carried out using Me_2AlCl and gives **60a** in 82% yield after ColC. The final step is cyclisation and reduction of **60a** to give **61**, and this is carried out under 1 MPa (∼10 atm) of H_2 at 100 °C over 24 h using $(Ph_3P)_3RhCl$. **61** is purified by ColC and is isolated in 51% yield.

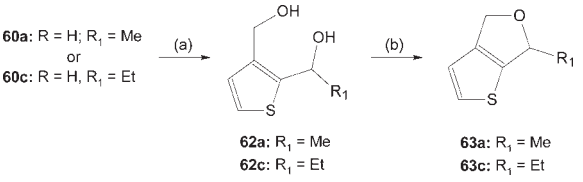
Scheme 18[a]



[a] Reagents and conditions: (a) (i) PPTS, DCM, rt, 0.5 h; (ii) evaporate, ColC; (b) (i) Bu^nLi, THF, −78 °C, 0.5 h; (ii) brine wash, dry, evaporate, ColC; (c) (i) CSA, MeOH, rt, 0.25 h; (ii) K_2CO_3, filter, evaporate, ColC; (d) (i) $(PPh_3)_3RhCl$, H_2, 1 MPa, 100 °C, 24 h; (ii) evaporate, ColC.

The patent also describes the preparation of the analogues of **61** by similar procedures including the 6-ethyl, 4,6-dimethyl, 4,6-diethyl, 4-ethyl-6-methyl, 4-methyl, and 4-ethyl derivatives. The patent also describes the preparation of thiophene compounds **63a** and **63b** by the route shown in Scheme 19. Using **60a** as an example the aldehyde group is first reduced using $LiAlH_4$ producing the alcohol **62a** that is isolated in 98% yield after ColC. The cyclisation of **62a** is performed using TsCl in the presence of Bu^nLi. The latter reagent is added in two portions, necessitating cooling to 0 °C then warming to rt to complete the reaction. After workup and ColC, **63a** is isolated in 32% yield. **63b** is obtained by the same procedure, although no experimental detail are provided.

Scheme 19[a]



[a] Reagents and conditions: (a) (i) $LiAlH_4$, THF, 0 °C, 10 min; (ii) add EtOAc, filter, wash, dry, evaporate, ColC; (b) (i) Bu^nLi, THF, 0 °C, 5 min; (ii) TsCl, rt, 1 h; (iii) Bu^nLi, THF, 0 °C; (iv) rt, 18 h; (v) wash, dry, evaporate, ColC.

The thiophenes **58b**, **60a**, **60b**, **63a**, and **63b** are claimed to be a novel compounds, and ^1H and ^{13}C NMR data are provided for them and other intermediates. A considerable amount of experimental data is provided in the patent, and the interested reader is encouraged to consult the patent for further details.

■ ADVANTAGES

The process gives good yields of the product and intermediates, but the possible need for chromatographic purification of all intermediates may inhibit the commercial potential of the process.

dx.doi.org/10.1021/op2001436 |*Org. Process Res. Dev.* 2011, 15, 736–747

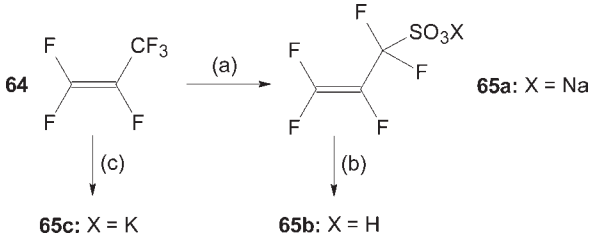
PATENT NO. U.S. 7,897,807

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

Title or Subject: Manufacture of Hydrofluoroalkanesulfonic Acids

The title compounds are strong acids that are used as catalysts and offer a safer alternative to mineral acids. The acids can be made by reaction of a metal sulfite with a fluoro-olefin; however, the patent claims that there are no detailed reports of an efficient process suitable for large-scale manufacturing. For example, a report from 1946 suggest the use of radical initiators. The patent discloses details of such a process for the manufacture of acids that have at least one H atom in the β position to the SO_3H group. The patent also describes the preparation of the potassium salts of the acids in high purity, and it is these potassium salts that are the subject of the claims of the patent. Scheme 20 outlines the method used to produce the acid **65b** and its potassium salt **65c** from the fluoro-olefin **64**. In one example the olefin (0.8 mol) was admitted to a pressurised vessel at 4 °C containing a solution of Na_2SO_3 (0.7 mol) and $NaHSO_3$ (0.2 mol) in H_2O at a pH of 5.7. The closed vessel is heated to 120 °C for 3 h whereupon the pressure increases to 1825 kPa (~18 atm) but quickly falls to 275 kPa. (~2.7 atm). After evaporation to remove the H_2O, the crude Na salt **65a** is recovered and dried at 140 °C under vacuum for 48 h. To the dry salt is added H_2SO_4 and oleum at 0 °C, the quantity of oleum being sufficient to remove the H_2O present in the H_2SO_4 and in the crude **65a**. H_2O and SO_3 are then removed under vacuum distillation, and the acid **65b** is recovered in 84% overall yield from **64**. The dried crude salt **65a** can be purified by extraction into Me_2CO followed by filtration and drying. The scheme also shows the preparation of the potassium salt **65c** that is formed by treating 64 with a mixture of $K_2SO_3 \cdot xH_2O$ and $K_2S_2O_5$ in H_2O. The olefin is admitted at −35 °C, and then the vessel is heated to 125 °C. The pressure rises quickly to 2.3 MPa (~23 atm) but quickly drops to 260 kPa. (~2.6 atm). The product crystallises from solution upon cooling and is isolated in 80% yield containing 0.15% H_2O. The preparation of **65c** takes less time than the Na salt **65a** and gives a higher-purity product that does not require further purification. Presumably the potassium salt can be used to prepare the acid, but no details are given.

Scheme 20[a]



[a] Reagents and conditions: (a) (i) Na_2SO_3, $NaHSO_3$, H_2O, 4 °C; (ii) 120 °C, 3 h; (iii) cool, evaporate, dry; (b) (i) H_2SO_4, oleum, 0 °C; (ii) Distill; (c) $K_2SO_3 \cdot xH_2O$, $K_2S_2O_5$, H_2O, −35 °C; (ii) 125 °C, 1.25 h; (iii) cool to 5 °C, vacuum filter, dry.

There are also details in the patent for the preparation of analogous acids from tetrafluorethylene (TFE). TFE is often shipped as a mixture with CO_2, and this does not have to be separated before preparing the sulfonic acid. In fact the patent claims that CO_2 acts as a buffer in solution since it is acting as CO_3^-, and this suppresses side reactions.

ADVANTAGES

The process gives high yields of product without using radical initiators that often give rise to poor selectivity.

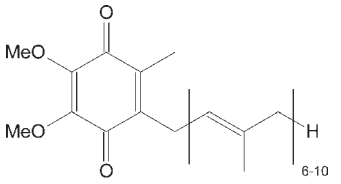
PATENT NO. U.S. 7,897,822

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

Title or Subject: Process for Ubiquinone Intermediates

Ubiquinones, **66**, are present in plants and animals including humans and are known as coenzymes Q_n (CoQ_n). They contain a benzoquinone molecule containing an isoprenyl side group where n is the number of isoprenyl subunits. Ubiquinones are naturally occurring antioxidants because of their capacity to exist in completely oxidised and reduced forms. The higher ones, especially CoQ_{10}, have been used in treating heart or neurological diseases or in cosmetics, food, and dietary supplements.

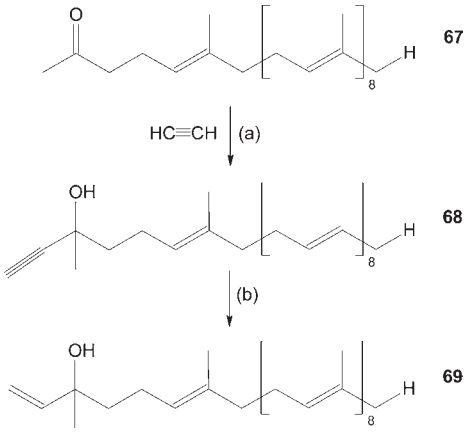
Ubiquinones



66

The patent covers the preparation of isopolyprenols such as **69** that are used in the production of ubiquinones, and several methods for their preparation are mentioned in the patent. The patent states that a surprising finding is that alkynyl compounds such as **68** can be formed from acetylene and the carbonyl compound **67** as shown in Scheme 21. The reaction is carried out by adding KOH, H_2O, and PhMe to the reactor, then pressurising with NH_3 and adding the acetylene. Further amounts of acetylene may be added during the process to maintain a constant ratio of ketone to acetylene. The reaction gives **68** in 95.5% yield, and then it is partially hydrogenated using a Lindlar catalyst in the presence of Tegochrome 22 (2,2-ethylenedithiodiethanol). The product is the isopolyprenol **69** that is recovered in 99.2% yield with 97% purity after distillation. Experiments using no solvent or n-hexane or MTBE are also carried out, and although not as effective as PhMe, they still give **68** in yields >90%. The patent reports that the process can be carried out continuously, but there are no examples provided.

Scheme 21[a]



[a] Reagents and conditions: (a) (i) 42.6% KOH/H_2O, PhMe, rt; (ii) evacuate, fill with NH_3, 20 °C; (iii) 15.9 bar, 20 °C, 5 h; (iv) evaporate, add 50% HOAc, H_2O wash, dry; (b) (i) Lindlar catalyst, Tegochrome 22, PhMe, H_2, 3 bar, 85 °C, 1 h; (ii) cool, filter, distill.

dx.doi.org/10.1021/op2001436 |Org. Process Res. Dev. 2011, 15, 736–747

■ ADVANTAGES

The process gives good yields of the desired product, but there is no indication as to the origin of the starting ketone.

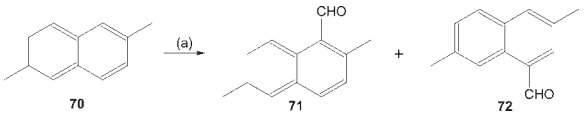
■ PATENT NO. U.S. 7,902,405

Assignee: Mitsubishi Gas Chemical Co., Inc., Tokyo, Japan

Title or Subject: Process for Production of 2,6-Dimethyl-1-naphthaldehyde

The title compound **71** is a useful intermediate for production of a range of products including optical functional materials. Methods for its preparation often produce equimolar amounts of the 3,7-dimethyl isomer **72** that is extremely difficult to separate from **71** because of their similar bp's. It is usual to keep the level of the 3,7-isomer <30 mol %, and the patent discloses a process for making **71** that achieves this objective by formylation of **70** using the route outlined in Scheme 22. The reaction takes place using anhydrous HF and BF_3, and at a temperature of 50 °C using 30 mol HF and 1.1 mol BF_3 per mole **70** it is possible to obtain a product containing as little as 12.7% of **72**. When the molar ratio of HF was reduced to 25, the amount of **72** increased to 28.3 mol %. At much lower levels of HF the amount of **72** increased substantially. For example, at HF/**70** ratio of 3.3 the product contained 67.6 mol % **72**, and even reducing the temperature to 25 °C gave 55 mol % **72**. It was also found that, if the amount of BF_3 is reduced, the level of **72** also increased, and if the mole ratio of BF_3 exceeded 3.5, the yield of **71** fell considerably. Hence, the key finding is that there is an optimum range of HF and BF_3 for the most efficient process.

Scheme 22[a]



[a] Reagents and conditions: (a) (i) HF, BF_3, *n*-heptane, 50 °C; (ii) CO, 2 MPa, 50 °C, 1 h; (iii) cool, H_2O, 0 °C, separate; (iv) distill.

■ ADVANTAGES

The process gives good selectivity using critical amounts of HF and BF_3.

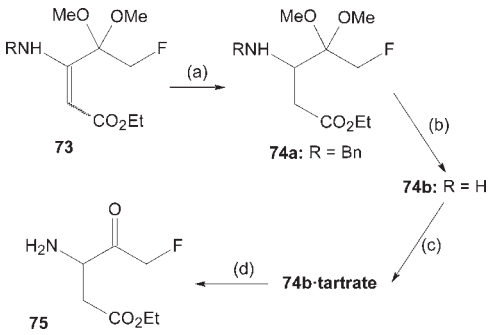
■ PATENT NO. U.S. 7,906,676

Assignee: LG Life Sciences Ltd., Seoul, Korea

Title or Subject: Process for Preparing 3-Amino-5-fluoro-4-dialkoxypentanoic Acid Ester

The title compound, **74b**, is a precursor to the 4-oxopentanoic acid ester **75** that has a role as a caspase inhibitor and is of interest in the treatment of cancers. Methods of preparing **74b** are said to require steps that use temperatures as low as −65 °C and have difficult purification methods. Hence, an objective of this patent is to avoid low-temperature reactions and improve the purification procedures. The actual claims of this patent cover the preparation of the ester **73** that is reduced to **74a** by using $NaBH_4$ as shown in Scheme 23. The Bn group is then removed using H_2 and Pd/C catalysts to give **74b** that is recovered as crude product in 94% yield and used in the next step to form the racemic tartrate salt. There are no details for converting this to **75**.

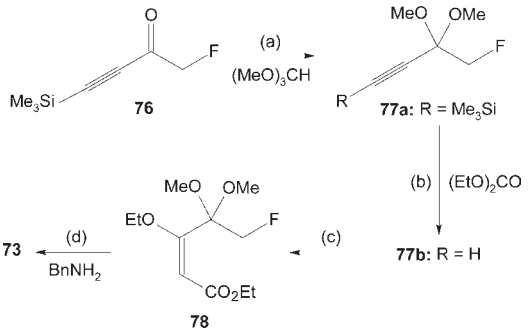
Scheme 23[a]



[a] Reagents and conditions: (a) (i) $NaBH_4$, HOAc, MTBE, <0 °C, 0.5 h; (ii) 3 M NaOH, 0 °C, 0.5 h; (iii) separate, brine wash, evaporate; (b) (i) Pd/C, H_2, 1 atm, 4 h, MeOH; (ii) filter, wash, evaporate; (c) (i) D, L-tartaric acid, H_2O, Pr^iOH, 50 °C; (ii) rt, 2 h; (iii) Add Pr^iOH/H_2O, rt, 2 h; (iv) filter, wash, dry; (d) No details.

The main focus of the patent, therefore, is the preparation of **73**. Scheme 24 shows the synthetic route used, starting with the formation of the dimethoxy-alkyne **77a** by reaction of **76** with $(MeO)_3CH$. Crude **77a** is recovered in 92% yield, and then the silyl protection is removed by treatment with Bu_4^nNBr, giving **77b** that is isolated in crude form in 107% yield and used directly in the next step. A mixture of **77b** and $(EtO)_2CO$ is treated with KOEt to produce crude **78** in 99.7% yield with a *Z*/*E* ratio of 6.5. The ester **78** is used in crude form and is heated with $BnNH_2$, producing **73** in 64% overall yield from **77b**. The patent states that **73** can be obtained in high purity by crystallisation, but experimental details are not provided apart from mentioning crystallisation is carried out by adding H_2O to solutions of **73** in MeOH, EtOH, Pr^iOH, or Me_2CO.

Scheme 24[a]



[a] Reagents and conditions: (a) (i) TsOH, MeOH, reflux, 6 h; (ii) concentrate, add 10% $NaHCO_3$, separate, evaporate; (b) (i) Bu^n_4NBr, 1 M NaOH, DCM, rt, 2 h; (ii) separate, brine wash, evaporate; (c) (i) KOEt, DMF, 0 °C, 4 h; (ii) Aq NH_4Cl; (iii) extract in MTBE, wash, dry evaporate; (d) (i) 100 °C, 20 h; (ii) EtOAc, 0 °C; (iii) 1 M HCl to pH 4, separate, wash in NH_4Cl, dry, evaporate; (iv) EtOH, H_2O, 80 °C; (v) rt, 4 h; (vi) 0 °C, 1 h; (vii) filter, wash, dry.

The patent describes the preparation of **76** by the route shown in Scheme 25. The fluoroketone **81** is obtained by treatment of **79** with **80** and the crude product is isolated in 74.6% yield. **81** is then reacted with **82** that has been treated with Bu^nLi. The reaction is quenched with $HOAc/H_2O$ and **76** is isolated in 64.8% yield by vacuum distillation after addition of PhMe to remove the residual HOAc by azeotropic distillation.

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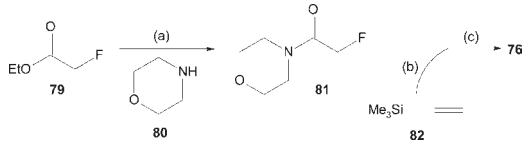
Scheme 25[a]



[a] Reagents and conditions: (a) (i) 70 °C, 20 h; (ii) 2 M HCl, DCM, rt, 20 min; (iii) separate, dry, evaporate; (b) Bu^{n}Li, THF, <10 °C, 50 min; (c) (i) THF, 0 °C, 1 h; (ii) HOAc/H_2O, <5 °C, 1 h; (iii) separate, wash, dry, evaporate; (iv) PhMe, distill.

A major aspect of the experimental work is that there does not seem to be any need to purify the various intermediates, and this is clearly an advantage over the alternatives. The patent does give ^{1}H and ^{13}C NMR data for the intermediates including the *Z*- and *E*-isomers of **78**.

■ ADVANTAGES

The process does not use low temperatures and avoids intermediate purification steps, giving high-purity product.

■ PATENT NO. U.S. 7,910,752

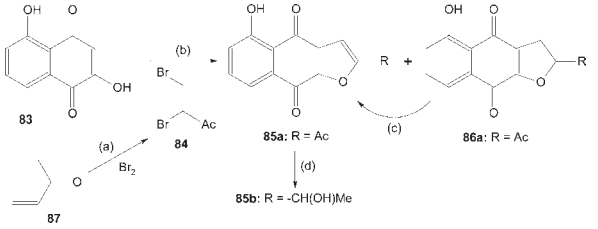
Assignee: Taheebo Japan Co., Ltd., Osaka, Japan

Title or Subject: Processes for Producing an Anticancer Compound and Intermediate Therefor

The patent describes a process for preparing the acetyl compound **85a** that can be converted to the alcohol **85b**; a naturally occurring compound that has anticancer properties. The alcohol **85b** is found in low concentrations in the tree species *Bignoniaceae*, and the patent states that there are no synthetic routes to **85b**; hence, the objective is to provide one. The main claims of the patent cover the preparation of **85a**, and subsequent claims cover its conversion to give **85b**. The process for preparing **85b** is shown in Scheme 26 and involves the condensation of **83** with the dibromo compound **84**. The reaction is carried out by formation of **84** in situ from **87** and Br_2. **84** is recovered as an oil and then added to a solution of **83** in the presence of DBU. The product is a mixture of **85a** (80%) and **86a** (20%) that is recovered in 95% yield. This mixture can be separated by ColC, and **86a** can be oxidised using MnO_2 to give **85a** in a yield of 51%. The MnO_2 was material used in the manufacture of battery cells containing 90% MnO_2. Lower-quality material containing only 80% MnO_2 gave only 33% yield of **85a**. The desired product **85b** is obtained by reduction of **85a** using $NaBH_4$, and this gives a racemic mixture of **85b** in 74% yield. The enantiomers can be separated by chiral ColC, and details are reported. The natural form of **85b** is designated the β-form, and the synthetic form is designated the α-form, but the patent does not indicate the configuration of these isomers.

The patent reports details of the cytotoxity of racemic **85b** as well as of the pure isomers. The patent also describes the preparation of the starting material **83**, and this is outlined in Scheme 27. The route starts from **88** that is known as juglone and is said to be comparatively inexpensive. This is treated with two batches of Me_2NH and gives a mixture of **89** and **90**. When using a solution of Me_2NH in THF the yields of products are quite low: 40% yield for **89** and 13% yield of **90**. Using H_2O instead of THF gave slightly better yields of 45% yield for **89** and 31% of **90**. This method is described as more environmentally friendly and safer. The two isomers can be separated by ColC, and ^{1}H NMR data

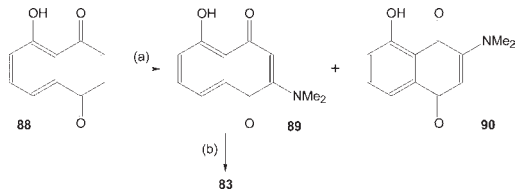
Scheme 26[a]



[a] Reagents and conditions: (a) (i) Pentane, −15 °C, 10 min; (ii) evaporate; (b) (ii) DBU, THF, 0 °C; (ii) rt, 16 h; (iii) 10% HCl, extract in $CHCl_3$, wash, dry, evaporate; (c) (i) active MnO_2, $CHCl_3$, reflux, 72 h; (ii) cool, filter, evaporate; (d) (i) $NaBH_4$, $CHCl_3$, EtOH, 0 °C, 0.5 h; (ii) 10% HCl, extract in $CHCl_3$, wash, dry, evaporate.

are provided for each one. The preparation of **83** from **89** is by acid hydrolysis and gives the product in 97% yield as a brown solid. It has a sharp mp of 220−221 °C, but its analytical purity is not reported although ^{1}H NMR data are given.

Scheme 27[a]



[a] Reagents and conditions: (a) (i) Me_2NH/H_2O, PhMe, −20 °C; (ii) −20 °C, 1 h; (iii) Me_2NH/H_2O, −20 °C, 0.5 h; (iv) evaporate; (b) (i) 10% HCl, dioxane, reflux, 0.5 h; (ii) cool, extract in $CHCl_3$, wash, dry, evaporate.

■ ADVANTAGES

The process provides a synthetic route to a potentially useful anticancer compound.

■ PATENT NO. U.S. 7,915,412

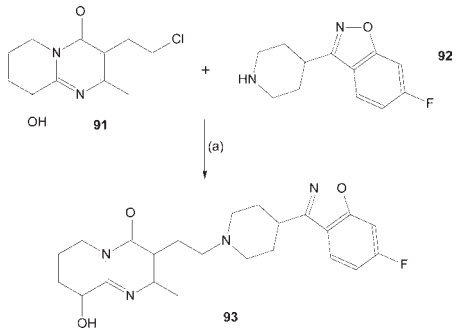
Assignee: Teva Pharmaceutical Industries Ltd., Petah Tiqva, Israel

Title or Subject: Process for the Synthesis of 9-Hydroxy Risperidone (Paliperidone)

Paliperidone **93** is a metabolite of risperidone that is used for the treatment of schizophrenia. One method for the preparation of **93** is described as being long and gives low yields. The patent describes a process, shown in Scheme 28, for preparing **93** by reaction of **92** with **91** in the presence of an inorganic base and optionally with a halide salt and/or phase transfer catalyst (PTC). The preferred base is Na_2CO_3, although K_2CO_3 is also claimed to be suitable. The halides used are KI and KBr, and the PTC may be Bu$^n{}_4$I or Bu$^n{}_4$Br. The reaction is carried out by heating the reagent as a suspension in MeCN, although Pr^{i}OH may also be used. After completion of the reaction the mixture is filtered, water is added and the product is isolated by filtration. One example using Na_2CO_3, but no halide, gives 82.5% yield of **93**, but the purity is not mentioned. An example that uses Na_2CO_3, KI, and DMF as solvent produces **93** in 58% yield and purity >90%. This is the only example in which the product purity is mentioned and DMF is not a preferred solvent.

dx.doi.org/10.1021/op2001436 |*Org. Process Res. Dev.* 2011, 15, 736–747

Scheme 28[a]



[a] Reagents and conditions: (a) (i) Na_2CO_3, MeCN, 65 °C, 26.5 h; (ii) Cool to −10 °C, filter, wash in MeCN (×3); (iii) slurry in H_2O, rt, filter; (iv) wash in H_2O (×3), wash in Me_2CO, dry.

The patent does not actually give details of the preferred method of obtaining and purifying **93**, although crystallisation from MeCN is mentioned as being suitable. The reactant **91** can be prepared by a method reported in U.S. 5,158,952, and **92** is said to be commercially available.

■ ADVANTAGES

The patent claims to describe an efficient method of making the desired product but does not provide much evidence to back up this claim.

■ PATENT NO. U.S. 7,915,425

Assignee: Suven Life Sciences, Hyderabad, India

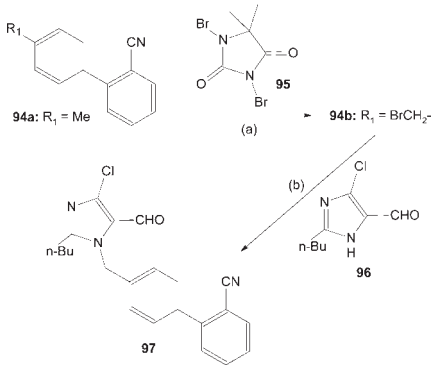
Title or Subject: Process for the Preparation of Losartan

Losartan is available as the potassium salt of **98b** for the treatment of hypertension. Several processes are reported for preparing **98b**, and the patent summarises a number of these. Some require six or more steps and give low overall yields, while one has only two steps but requires a reaction time of 13 days and only gives a 21% yield. Other patents on the synthesis of **98b** have been reviewed previously (*Org. Process Res. Dev.* **2006**, *10*, 866). The current patent claims to describe a simple, short process that starts from commercially available reagents and is an improvement over the alternatives. The process requires three steps, and the first stage is outlined in Scheme 29 in which bromination of **94a** is carried out using **95** in the presence of $(BnO)_2$. This gives **94b** that is isolated as the crude product and used directly in the next step. In this reaction **94b** is reacted with **96** in aq NaOH and PhMe in the presence of a base and a PTC to form the cyano aldehyde **97** that is isolated in 83% yield and 98% purity (HPLC).

In the next stage, outlined in Scheme 30, **97** is treated with Bu_3SnCl and NaN_3 at rt for up to 32 h. The reaction is followed by TLC, and the aldehyde **98a** is not isolated but reduced in situ to give **98b** using $NaBH_4$. The product is isolated in 75% yield and purity >97% (HPLC), and in the last stage of the process the potassium salt **98c** is prepared by treating **98b** with KOH/MeOH. This is isolated after crystallisation from Me_2CO in 87.15% yield with purity of 99.79% (HPLC).

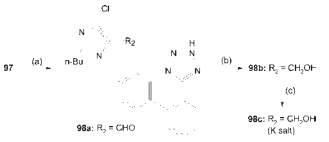
The patent provides IR, ^1H, and ^{13}C NMR data for compounds **97**, **98a**, and **98b**. The use of a highly toxic tin reagent near the end of the synthesis is surprising, The tin content of the drug is not mentioned, and tin is notoriously difficult to remove

Scheme 29[a]



[a] Reagents and conditions: (a) (i) $(BnO)_2$, CCl_4, reflux, 4 h; (ii) filter, wash, dry evaporate; (b) (i) Bu^n_4Br, NaOH, H_2O, PhMe, rt, 30 h; (ii) separate, extract in PhMe; (iii) wash in aq NaOH, wash in H_2O, evaporate.

Scheme 30



(a) (i) Bu^n_3SnCl, NaN_3, *o*-xylene, rt; (ii) reflux, 32 h; (iii) cool rt, add 1 M KOH, rt, 1 h; (iii) separate, collect aq layer, wash in PhMe; (b) (i) $NaBH_4$, rt; (ii) 45 °C, 1 h; (iii) cool <20 °C, dil HCl to pH 4; (iv) <20 °C, 6 h, filter, wash; (c) (i) KOH, MeOH, rt; (ii) reflux, 5 h; (iii) filter at <40 °C; (iv) evaporate, add MEK, distill; (v) crystallisation.

■ ADVANTAGES

The process uses commercially available starting materials, has fewer steps, and is more efficient than alternatives. However, there may be concerns regarding the tin levels in the final product.

Keith Turner

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