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 June and July 2011

SUMMARY

The current review contains 19 patents from an original list containing 267 that fitted the selection criteria. This is slightly fewer than usual although several of the patents reviewed cover a considerable volume of process chemistry. A notable feature in several of the current collection is the lack of analytical detail or reaction yield information. It is quite unacceptable that many patents omit vital process information such as the yield of a reaction and even details regarding its purity or method of analysis. If this information was omitted from papers submitted for publication in the open literature, it is expected that they would be rejected. At the very least, these details would be submitted as Supporting Information. It is a fact of life that patents claims can be excessive, but at the least, some evidence for them should be presented. As an example, an extensive patent reports on the synthesis of an intermediate used to make a drug for treating diabetes. The patent does not contain physical property data apart from the bp of those compounds recovered by distillation. Treatments for inflammatory diseases have a large market and are of great value; a process to prepare individual stereoisomers of arylcyclopentane carboxylates is described. The patent contains a large amount of detailed chemistry, but process yields are low.

Chemical reactions can often produce sticky solids, syrups, or gels that are difficult to handle on a large scale, and a number of patents report such findings. A patent describes an improved preparation of a range of aniline derivatives, useful in the treatment of thyroid disorders. The original process gave unpredictable yields because of light-sensitive intermediates that were intractable solids. A new process is reported for preparing the active enantiomer of clopidogrel, the drug used to treat blood clots and heart disease. This involves handing four intermediates that are described as syrupy or viscous masses, and the reported yields are generally high. Nebivolol is a beta blocker used to treat hypertension and has four chiral centres. Oily compounds are produced in a new stereoselective synthesis of a key epoxide intermediate. Another drug used to treat blood pressure is trandolapril, and a new process synthesises the molecule in high stereoselectivity. The patent claims that the preferred solvent for the product isolation is MeCN but only describes examples using EtOAc. A new method for making a key epoxide intermediate is described, and this also involves oily intermediates. A new process reports improved yields and efficiency for the preparation of erlotinib, a drug used to treat lung cancer and pancreatic cancer. The new process has a number of improvements including a reduction of the molar excess of HBr used in one step by using 48% concentration in place of 38%. In another step in the process the amount of Ac_2O used for an acylation is reduced by a factor of 18 by adding catalytic amounts of pyridine. Another drug used in chemotherapy for the treatment of ovarian cancer and lung cancer is topotecan. This is a semi-synthetic derivative of camptothecin that is extracted from the bark of certain trees, and an improved process for its preparation is described. A process for carbonylation of amines to give amides uses Pd catalysts as a cheaper alternative to Rh catalysts. Unfortunately, the conditions are rather extreme, and any benefit of a cheaper catalyst may be outweighed. Armodafinil is the (*R*)-enantiomer of the drug modafinil that is used to treat sleep disorders, and a method for its purification is described. Impurities usually present are a disulfide and an acid, and the new method involving passing a solution of the drug molecule over Al_2O_3 gives very high-purity product. In the usual synthesis of the reagent *N*,*N*′-carbonyldiimidazole the atom yield of the starting material is poor since half acts as a HCl sink. A new process recovers and reuses the HCl salt and thereby gives improved process efficiency. An enzyme catalyst is used in an esterification reaction to stereoselectively produce theaspirane that is a naturally occurring compound used in flavours and fragrances. The process enables both enantiomers to be obtained pure, starting from a commercially available material. Formoterol is used to treat chronic pulmonary diseases, and a new polymorph is reported of the more potent (*R*),(*R*)-enantionmer that can be converted to the thermodynamically stable polymorph. A comprehensive patent describes a large-scale synthesis of molecules that are of interest as male contraceptives and the treatment of prostate-related problems. An efficient method of producing a stable crystalline salt of an aralkyloxypyrrolidine derivative is described, and since the salt is easily handled, this is beneficial because the compound is said to be a pharmaceutical intermediate. Some nitroguanidines have insecticidal activity, and a new synthesis of the compounds is described that uses a stable nitroisourea in place of an expensive isourea. The starting compounds are less likely to decompose and give higher reaction selectivity. Olanzapine is used to treat schizophrenia and bipolar disorders in adults and an improvement on an original process avoids the formation of *N*-oxides by replacing DMSO as solvent since this appears to oxidise the product. The new solvent is a mixture of 1,3-dimethylimidazolidin-2-one and PhMe. 2-Cyanocinnamic esters are used as UV stabilisers, and an improved synthesis gives high yields and minimises byproducts. The patent involves variable-pressure refluxing to remove water in a condensation reaction without increasing the temperature, and this avoids byproduct formation. Galanthamine can be extracted from the bulbs of snowdrops or daffodils and is approved for treating Alzheimer's disease. A patent describes the synthesis of a compound that can be used to make galanthamine although the patent does not say how this is carried out. A number of the patents in this collection describe experiments carried out on a kilo or multikilo scale, and this may suggest that the process is at 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

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this review are those claimed in the patent, unless this reviewer has personal knowledge of the subject.

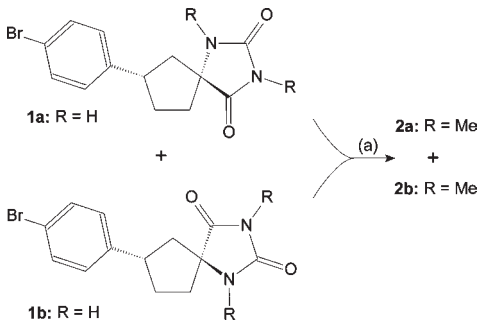
PATENT NO. U.S. 7,956,195

Assignee: Abbott Laboratories, Abbott Park, Illinois, U.S.A.

Title or Subject: Process for the Preparation and Isolation of Individual Stereoisomers of 1-Amino, 3-Substituted Phenylcyclopentane Carboxylates

The compounds covered by this patent are intermediates in the preparation of drugs used to treat inflammatory diseases. Alternative processes for preparing the desired compounds are known, but it is claimed that they do not address the isolation of individual stereoisomers. The patent reports methods for isolation of these, and the main claim of the patent covers the preparation of a mixture of **2a** and **2b** by alkylation of **1a** and **1b** (Scheme 1). The reaction is carried out by treatment of **1a** and **1b** with MeI in the presence of K_2CO_3. The mixture of crude diastereoisomers is isolated in quantitative yield and then dissolved in MeCN at 70 °C and filtered hot. Upon cooling, the isomer **2a** crystallises from solution and is recovered in 12% yield. The fate of the other isomer is not reported.

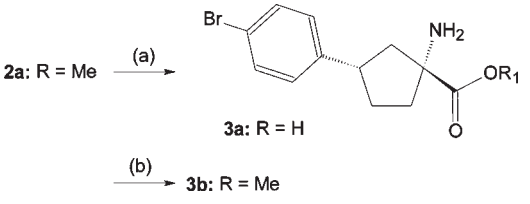
Scheme 1[a]



[a] Reagents and conditions: (a) (i) MeI, K_2CO_3, DMF, rt, 48 h; (ii) concentrate, 25 °C; (iii) H_2O, 0 °C, 1 h, filter, wash, dry.

The isomers **2a** and **2b** can be hydrolysed as a mixture or separately, in the presence of NaOH, to give the corresponding amino acid. An example describes the base hydrolysis of **2a** to give **3a** that is isolated in 95% yield (Scheme 2), and then esterification of **3a** using $SOCl_2$/MeOH produces **3b** in 96% isolated yield. The patent also describes the esterification of the mixture of acids **2a** and **2b** to give a mixture of the methyl ester **3a** and its enantiomer the (1*S*,3*S*)-isomer.

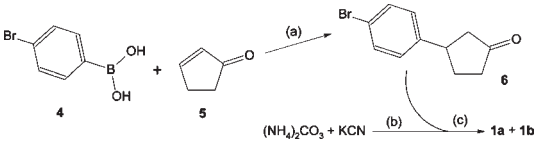
Scheme 2[a]



[a] Reagents and conditions: (a) (i) 2 M NaOH, dioxane/H_2O, reflux, 24 h; (ii) cool, add concd HCl; (iii) add HOAc, filter, wash; (iv) add PhMe, 45 °C, filter, dry.

The patent describes the preparation of **1a** and **1b** by the route shown in Scheme 3. The first step is a Michael addition of the boronic acid **4** with **5** in the presence of a chiral Rh catalyst to form **6**. The crude product is purified by column chromatography (ColC) and **6** is isolated in 89% yield with 95% ee. In the second stage, **6** is added to a hot aqueous solution of KCN and $(NH_4)_2CO_3$, and this produces a 1:1 mixture of **1a** and **1b** that is isolated in 95% yield.

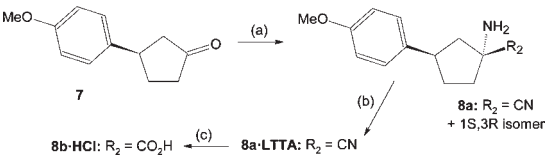
Scheme 3[a]



[a] Reagents and conditions: (a) (i) ([(*S*)-BINAP]RhOH)$_2$, dioxane/H_2O, 35 °C, 16 h; (ii) cool rt, concentrate; (iii) add EtOAc, filter, wash, dry, ColC; (b) add H_2O, 80 °C; (c) (i) EtOH, reflux 16 h; (ii) filter, add Et_2O; (iii) filter, wash, dry.

The patent also describes the preparation of analogues of **3a**, **3b**, and **6** in which the Br group is replaced by MeO. Scheme 4 shows the route used to prepare the nitrile **8a** from **7** by reaction with NaCN and NH_4Cl in MeOH/NH_3 solution. After workup the product is a mixture of **8a** and the (1*S*,3*R*)-enantiomer. This mixture is isolated as an oil in 98% yield and can be resolved without further purification by treatment with L-tartaric acid (LTTA) giving **8a·LTTA** in 28% yield. This compound can be hydrolysed with HCl to give the salt **8b·HCl** (R_2 = CO_2H) in 74% yield.

Scheme 4[a]



[a] Reagents and conditions: (a) (i) NaCN, NH_4Cl, 7 M MeOH/NH_3, rt, 48 h; (ii) concentrate, add aq $NaHCO_3$, (iii) extract in DCM, wash, concentrate dry; (b) (i) LTTA, MeOH, rt; (ii) filter, wash in MeOH, dry; (c) (i) 6 M HCl, dioxane, 100 °C, 16 h; (ii) cool to 0 °C, filter, wash, dry.

The preparation of the bromine analogues of **8a**, **8a·LTTA**, and **8b·HCl** by similar procedures are also described, and basic ^{1}H NMR data are reported for many of the compounds.

Advantages. The process does provide methods for preparing single enantiomers, but the yields appear to be quite low.

PATENT NO. U.S. 7,956,201

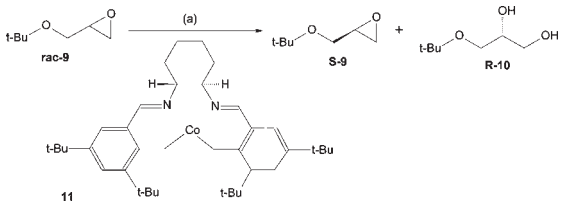
Assignee: Hoffman-La Roche Inc., Nutley New Jersey, U.S.A.

Title or Subject: Process for the Preparation of (*S*)-4-Fluoromethyldihydrofuran-2-one

The title compound **14** is an intermediate in the preparation of **18b**; a DPP-IV inhibitor that is used to treat diabetes. It is unusual that the patent does not refer to any alternative methods for preparing **14**, and the main focus seems to be its use in preparing **18b**. The first part of the synthesis of **14** is outlined in Scheme 5 and begins with the preparation of the (*S*)-glycidyl ether **S-9** from

the racemic compound **rac-9** by treatment with the chiral Co complex **11** and HOAc, followed by addition of H_2O. The product is isolated by vacuum distillation (vac distn) in 43.5% yield. The reaction also produces **R-10**, but the patent does not report what can be done with this.

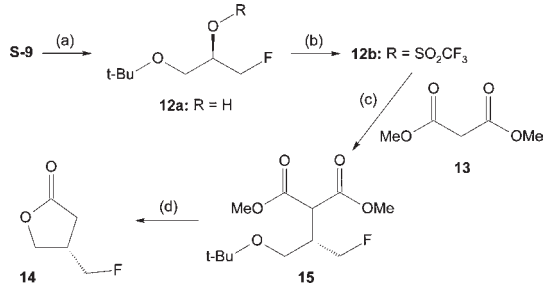
Scheme 5[a]



[a] Reagents and conditions: (a) (i) HOAc, THF, 0 °C; (ii) add H_2O, 0 °C, 0.5 h; (iii) rt, 23 h; (iv) vac distn.

In the next stage, shown in Scheme 6, **S-9** is converted to the fluoro compound **12a** by treatment with KHF_2 in the presence of a phase transfer catalyst (PTC) in triethylene glycol (TEG). The product is recovered by vac distn in 63.3% yield. **12a** is then sulphonated using Tf_2O forming **12b** that is isolated as a yellow oil, and the crude form is reacted with **13** in the presence of $NaOBu^t$ to produce **15**. This is not isolated and is refluxed with 2 M H_2SO_4 to undergo cyclisation, hydrolysis and decarboxylation giving **14** that is isolated as a colourless oil by vac distn in 84% yield. An alternative example describes the use of NaH in place of $NaOBu^t$, but this procedure gave a lower yield (82%) of crude **14** as a light-yellow oil.

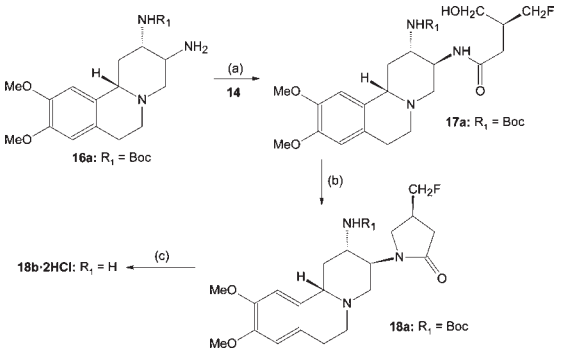
Scheme 6[a]



[a] Reagents and conditions: (a) (i) KHF_2, Bu_4NHSO_4, TEG, 130 °C, 20 h; (ii) cool, add DCM, wash, evaporate, vac distn; (b) (i) Tf_2O, pyridine, DCM, −10 °C, 1 h; (ii) wash in Na_2CO_3, extract in DCM, evaporate; (c) (i) $NaOBu^t$, DME, 0 °C, 7 h; (d) (i) 2 M H_2SO_4, reflux, 48 h; (ii) cool, extract in DCM, wash in Na_2CO_3, evaporate, vac distn.

The use of **14** in the preparation of **18b** is outlined in Scheme 7, and this begins with the reaction of **14** with **16a** in the presence of 2-hydroxypyridine (2-HP). This reaction forms the amide **17a** that is isolated in 94% yield as a solid with 100% purity. In the next step cyclisation of **17a** is carried out by addition of MsCl and Et_3N followed by treatment with the base LiHMDS. After workup and crystallisation from MTBE, **18a** is isolated in 77% yield with 99.5% purity. In the final step the Boc protective group is removed using AcCl/Pr^iOH to form **18b** that is obtained as the bis-HCl salt in 100% yield and 99% purity after crystallisation.

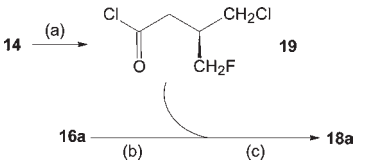
Scheme 7[a]



[a] Reagents and conditions: (a) (i) 2-HP, PhMe, rt; (ii) reflux, 23 h; (iii) cool to rt, add DCM, 0.5 h; (iv) filter, PhMe wash, DCM wash, dry.

The patent also describes an alternative route to **18a** from **16a** and **14** that is shown in Scheme 8. In this route **14** is initially converted to the chloride **19** by treatment with $SOCl_2$ in the presence of $ZnCl_2$. This is then added in two portions over 3.5 h to a solution of **16a** in THF containing Et_3N. A solution of $KOBu^t$ in THF is then added to the mixture, and after an extensive workup involving extraction, ColC, refluxing in MeOH, and cooling to −20 °C the product **18a** is obtained in 64% yield and 100% purity.

Scheme 8[a]



[a] Reagents and conditions: (a) (i) $SOCl_2$, $ZnCl_2$, reflux, 66 h; (ii) cool to rt, filter, wash in $SOCl_2$, vac distn; (b) (i) Et_3N, THF, <5 °C; (c) (i) THF, <5 °C, 3.5 h; (ii) $KOBu^t$, THF, 35 min, <6 °C; (iii) 16 h, 0 °C; (iv) add brine, extract in EtOAc, dry, evaporate; (v) ColC; (vi) MeOH, reflux, 0.25 h; (vii) rt, 4 h; (viii) 16 h, 0 °C; (ix) −20 °C, 2 h; (x) filter, MTBE wash, dry.

The patent does not contain any physical property data apart from the bp of those compounds recovered by vac distn, nor does it explain how the analysis is carried out.

Advantages. The patent claims a new process for preparing an intermediate and also its use in the preparation of the drug molecule.

PATENT NO. U.S. 7,956,214

Assignee: Karo Bio AB, Huddings, Sweden, and Bristol-Myers-Squibb Company, Princeton, New Jersey, U.S.A.

Title or Subject: Process for the Preparation of Aniline-Derived Thyroid Receptor Ligands

The main focus of the patent is the synthesis of a range of compounds exemplified by **27** that are useful in the treatment of thyroid disorders. However, the two claims of the patent cover the novel compound **22** that can be used to prepare **27**. An alternative method for the synthesis of **27** is summarised and said to give variable yields because of the formation of an intermediate that is an intractable solid. In addition an intermediate light-sensitive iodonium salt and its yields are also unpredictable. Hence,

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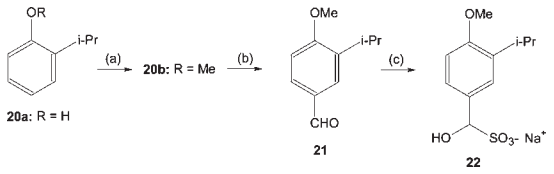
an improved route to **27** is required, and it is claimed that this is offered by the process described in the patent. The synthesis of **22** is shown in Scheme 9 and begins with the formation of the methyl ether **20b** by reaction of **20a** with MeI in the presence of a base and a PTC. The product is isolated as a yellow oil in 94% yield and then dissolved in DMF followed by $POCl_3$, whereupon the mixture darkens. After workup the aldehyde **21** is recovered in 86.5% yield. The Na salt **22** is formed by treatment of **21** with $NaHSO_3$ and is isolated in 93.4% yield.

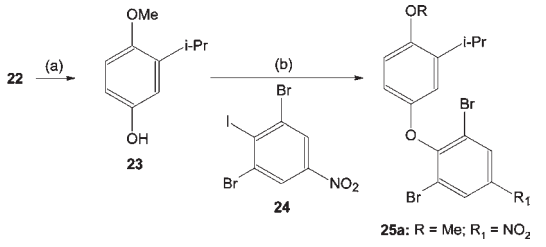
Scheme 9[a]



[a] Reagents and conditions: (a) (i) Bu_4NHSO_4, KOH, H_2O, <25 °C; (ii) DCM, Pr^iOH, <25 °C, 0.5 h; (iii) MeI, rt, 5 h, separate; (iv) Et_3N, 0.25 h; (b) (i) DMF, 80 °C; (ii) add $POCl_3$, 80 °C, 19 h; (c) cyclohexane, THF, aq $NaHSO_3$, rt, 16 h; (ii) filter, wash, dry.

The synthesis of **27** from **22** is outlined in Schemes 10 and 11. In the first step **22** is oxidised using H_2O_2 in the presence of TsOH giving **23** that is isolated in 66.7% yield. **23** is then converted to **25a** by condensation with **24** in the presence of NaOH. After workup the anisole ether **25a** is recovered in 92.6% yield. An alternative method for the conversion of **23** to **25a** is described using KHMDS, but this gives a lower yield of 76% and involves a more complicated workup procedure.

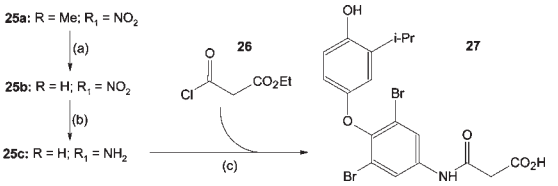
Scheme 10[a]



[a] Reagents and conditions: (a) (i) H_2O_2, TsOH, MeOH, 0 °C, 2 h; (ii) rt, 16 h; (iii) aq $(NaO_2S)_2$, 0 °C, 0.5 h; (iv) filter off solids, wash in EtOAc; (v) combine organic and aq phases, separate; (vi) wash in aq $NaHCO_3$, brine, evaporate; (b) (i) 11 M NaOH, DMF, <35 °C; (ii) add **24** in DMF over 0.75 h, <35 °C; (iii) rt, 24 h; (iv) add H_2O, cool to 5 °C, filter, dry.

In the next stage, shown in Scheme 11, **25a** is reacted with BBr_3 and converted to phenol ether **25b** that is recovered in crude form in a yield reported as 110%. In the next step the aniline compound **25c** is produced by treating **25b** with $(NaO_2S)_2$ and is recovered in crude form in 96.9% yield. Recrystallisation from Pr^iOH gave the purified material in 90% yield. In the last step **25c** is reacted with the malonyl chloride **26** in the presence of NaOH in a biphasic reaction to obtain **27**. The reaction is carried out by adding **26** to a slurry of **25c** and NaOH in MTBE. This is then followed by additional NaOH after HPLC analysis showed that no starting material remained. The crude product was recovered after workup and then recrystallised from MeOH. A 90% recovery was achieved, but the purity was not reported.

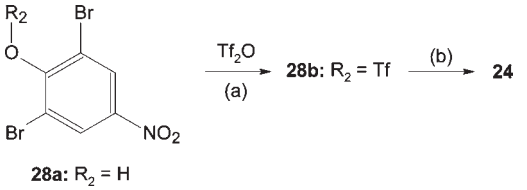
Scheme 11[a]



[a] Reagents and conditions: (a) (i) BBr_3, DCM, 8.7 °C, 10 min; (ii) rt, unspecified time; (iii) quench with MeOH, <18 °C; (iv) wash in $NaHCO_3$, separate, evaporate; (b) (i) aq $(NaO_2S)_2$, THF, 50 °C, unspecified time; (ii) 6 M HCl, to pH3, 50 °C, 0.75 h; (iii) cool rt, aq $NaHCO_3$ to pH6.6; (iv) extract in EtOAc, wash, evaporate, dry; (c) (i) aq NaOH, MTBE, 2 °C, 0.5 h; (ii) rt, 40 min; (iii) aq NaOH, 2 °C, 2 h; (iv) separate organic layer, extract in H_2O, evaporate solvents; (v) cool to 1 °C, filter, wash, dry.

The patent also describes the preparation of **24** by the method shown in Scheme 12. The first step is conversion of the phenolic group to the TfO group using Tf_2O and pyridine giving **28b** that is isolated in 99% yield. This is then reacted with NaI in DMF to produce **24** that is isolated in 82.9% yield and is then recrystallised from EtOH but the final purity and yield are not reported.

Scheme 12[a]



[a] Reagents and conditions: (a) (i) DCM, 0 °C; (ii) add pyridine, <8 °C; (iii) Tf_2O/DCM, <10 °C; (iv) rt, 0.5 h; (v) 1 M HCl, <35 °C; (vi) separate organic layer, wash, evaporate, dry.

The patent reports a comparative example for preparing **25b** by a process involving an intermediate iodonium salt that is light-sensitive. The method produces a gummy solid that is difficult to purify and the overall procedure is described as inefficient and gives unpredictable yields of intermediates. This patent is yet another that does not contain any physical property data nor does it provide any analytical information and purity of intermediates or final product. However, the majority of examples describe kilo or semikilo scale preparations thus showing that the process has been scaled up beyond the laboratory.

Advantages. The process provides an improved method of preparing the desired molecule without the need to handle light-sensitive materials.

PATENT NO. U.S. 7,960,545

Assignee: Natco Pharma Limited, Andhara Pradesh, India
Title or Subject: Process for the Preparation of Erlotinib

Erlotinib, **32c**, is available as the HCl salt under the name Tarceva and is used to treat lung cancer, pancreatic cancer and several other types of cancer. Alternative methods of making

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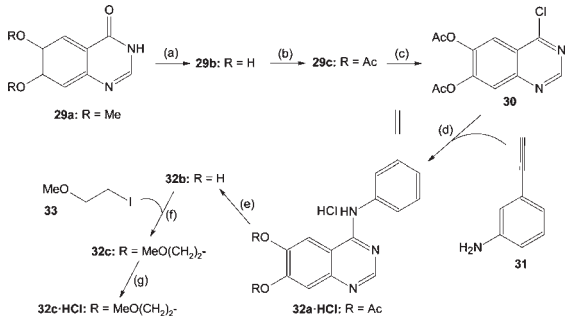
32c are summarised and are said to be uneconomic. Reasons given include the use of expensive PtO_2 catalyst, poor yield at larger scale, and the use of flash chromatography. The current patent describes a process that starts from a commercially available material **29a** and this process is outlined in Scheme 13. Workup details are omitted from the scheme for clarity. The first stage is conversion of the two OMe groups to OH by reaction with 48% HBr followed by neutralisation. Alternative processes use 38% HBr, and by using a higher concentration the amount of HBr used is reduced from 46 to 26 mol equiv, giving higher yield (98.6%) and purity (99.25%) of **29b**. The acylation of **29b** to give **29c** uses Ac_2O plus pyridine that enables a significantly reduced amount of Ac_2O to be used; 15 equiv compared with 275 in the alternative process reported in WO 96/09294. The product **29c** is recovered in 92.5% yield and 99.0% purity. In the next step the keto group is converted to a leaving group such as Cl, although OMs, OTs, and OBs are also mentioned. This conversion is carried out by using $(COCl)_2$ in the presence of DMF, and **30** is isolated and used in the next step without purification. The use of $SOCl_2$/DMF for this reaction is also described and gives an equally good yield. Reaction of **30** with the aniline **31** produces the novel compound **32a** that is recovered as the HCl salt in 79% yield and 96.76% purity. Treatment of **32a** with a solution of NH_3 in MeOH removes the acyl groups, giving **32b** in 97.6% isolated yield and 99.0% purity. Erlotinib base **32c** is then prepared by reaction of **32b** with the iodo ether **33** in the presence of anhydrous K_2CO_3. The use of alternative bases in this reaction is covered by the claims, but there are no examples. The compound is isolated in 59.1% yield and 99% purity and then recrystallised from hot EtOAc and converted to the HCl salt. There are several examples describing the preparation of **32c·HCl**, and these use a solution of HCl in MeOH, Pr^iOH, or concd acid. Yields of the salt are around 93% with purity of around 99.8%.

Scheme 13[a]



[a] Reagents and conditions: (a) (i) 48% HBr, 110 °C, 1 h; (ii) reflux, 12 h; (iii) NH_4OH to pH7.5, 30 °C; (b) Ac_2O, pyridine, 120 °C, 2 h; (c) $(COCl)_2$, DMF, reflux, 6 h; (d) reflux, 14 h; (e) NH_3/MeOH, 30 °C, 4 h; (f) K_2CO_3, DMF, 45 °C, 12 h; (g) HCl/Pr^iOH, 65 °C, 1 h.

The patent provides IR, ^1H, and ^{13}C NMR data for the majority of compounds, and the purity reported is measured by HPLC.

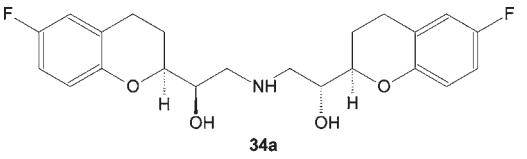
Advantages. The use of catalysts in the first step and in the acylation reaction reduces the amounts of HBr and Ac_2O substantially, and this increases the efficiency of the whole process that has some very good yields.

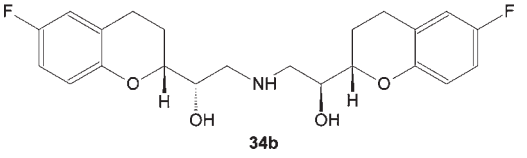
PATENT NO. U.S. 7,960,572

Assignee: Zach System S.p.A., Bresso, Italy

Title or Subject: Process for Preparing Nebivolol

Nebivolol is a racemic mixture of **34a** and **34b** and is a beta blocker used to treat hypertension.

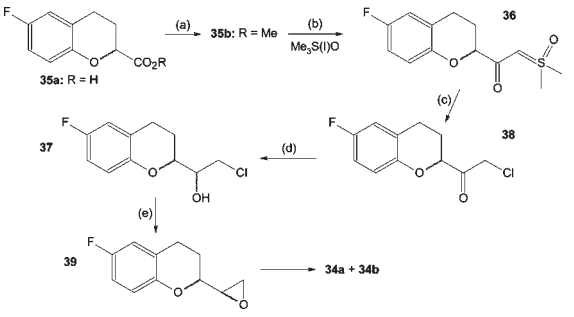




Nebivolol

This patent describes an improved method for the synthesis of the racemic epoxide **39**; a key intermediate used in the preparation of Nebivolol. Alternative methods for preparing **39** are summarised, and these give low yields, produce oils, or give racemic mixtures and so are not commercially attractive. The new method for preparing **39** that is disclosed in this patent is outlined in Scheme 14, and workup details are omitted because of space limitations.

Scheme 14[a]



[a] Reagents and conditions: (a) 96% H_2SO_4, MeOH, 60 °C, 3.25 h; (b) (i) $KOBu^t$/$Me_3S(I)O$, THF, 70 °C, 2 h; (ii) add to **35b** in THF, 20 °C, 3.5 h; (iii) add H_2O, 20 °C, 16 h; (c) LiCl, MsOH, THF, 0 °C, 10 min; (ii) 20 °C, 10 min; (iii) 70 °C, 2.5 h; (iv) 20 °C, 16 h; (d) $NaBH_4$, EtOH, 0 °C, 2 h; (e) (i) THF, Pr^iOH, $KOBu^t$, 16 °C, 3 h; (ii) HOAc to pH 7.

The process starts with the esterification of the racemic acid **35a**, and examples are given for preparing the methyl ester **35b** using MeOH and H_2SO_4 catalyst. The racemic ester **35b** is isolated as a pale-yellow oil in 87.9% yield and purity reported as 96.8 area (A)%. Also described is the preparation of the 4-nitrophenyl ester from 4-nitrophenol and $(COCl)_2$. This is isolated in 40.5% yield and purity 85.0 A%. In the next step **35b** is reacted with $Me_3S(I)O$ to form the ylide **36**. The reaction is carried out in the dark in the presence of $KOBu^t$, and **36** is isolated as a pale-yellow solid in 96% yield with 97.9 A% purity. **36** is also obtained by a similar reaction using the 4-nitrophenyl ester, but the yield is only around 50%. **36** is then transformed into **38** by reaction with anhydrous HCl that is generated in situ using LiCl and MsOH in the presence of THF, and this in situ generation of anhydrous HCl is one of the claims of the patent. Crude **38** is isolated as a brown oil in 78% yield and 88.4 A% purity and this is reduced with $NaBH_4$ to give **37** that is a mixture of diastereoisomers in

70% yield and 67.9 A% purity. The crude **37** is then treated with $KOBu^t$ to effect ring closure and formation of **39** as a mixture of diastereoisomers (ratio 54:46) in 100% yield and 77.3 A% purity. The epoxide can also be produced by treating **37** with NaOH in Pr^iOH, giving a yield of 96% and purity 86.1 A%.

The patent states that using specific enantiomers of **35a** would enable stereoselective reactions to be performed. The patent reports ^1H NMR data for all intermediates. It is interesting to note that the patent comments on alternative procedures giving oily products, and yet oils are obtained in the route described here.

Advantages. The process is claimed to be more stereoselective than alternatives.

PATENT NO. U.S. 7,960,585

Assignee: Tamino, Ghent, Belgium

Title or Subject: Process for Preparing Secondary Amides by Carbonylation of a Corresponding Tertiary Amine

The patent states there are several reports for producing amides by carbonylation of amines using Co catalysts but few reports using other metals, with only one report using a Rh catalyst. The objective of the patent is to provide a carbonylation process using a less expensive metal than Rh for producing *sec*-amides from *tert*-amines. The process uses $PdCl_2$ as catalyst and Me_4NI as promoter, although other Pd compounds are said to be suitable. The process is carried out by mixing the catalysts with the amine and promoter in a solvent and then pressurising the system to 65 bar of CO at rt. The mixture is then heated to about 240 °C for up to 130 min. The solvent that may be the amide or *N*-methylpyrrolidinone (NMP) is said to give excellent results. The process is applied to several amines, and results are compared to those using other metal catalysts. For example, Me_3N is converted to $Me_2NC(O)Me$ with 96% selectivity, $PhNMe_2$ gives 92% $PhNMeC(O)Me$, and Et_3N gives 43% $Et_2NC(O)Me$, 37% $Et_2NC(O)Et$, and 12% $MeN(Et)C(O)Me$. The conversion of the amines is usually 100%, but the process can be rather unselective, and in view of the rather harsh reaction conditions it does not look to be commercially attractive.

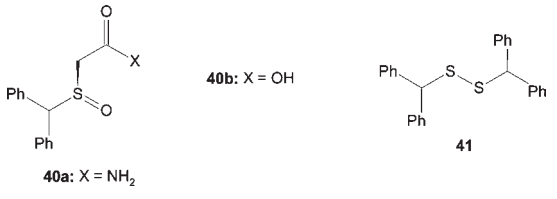
Advantages. The process does use cheaper catalysts but does not look to be commercially viable.

PATENT NO. U.S. 7,960,586

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

Title or Subject: Purification of Armodafinil

Armodafinil **40a** is the *R*-enantiomer of the drug modafinil that is used to treat sleep disorders. Although both enantiomers of modafinil are pharmacologically effective the *S*-enantiomer is eliminated from the body 3 times faster than the *R*-enantiomer. Hence, it is advantageous to produce only the *R*-form. During the production of **40a** the disulfide **41** is produced, and it is necessary to reduce this to level to <0.2 area % by HPLC. In addition, there are usually residues of the acid **40b**, and this patent provides a method of achieving the desired purity.



Armodafinil and Impurities

The patent describes the purification of 28.8 kg of **40a** that contains 0.05% of the *S*-enantiomer, 1.23% of **41**, and an unspecified amount of **40b**. The procedure used was as follows:

(1) Dissolve crude **40a** in 597.7 kg of absolute EtOH at 55.5 °C.
(2) Circulate the solution through a bed of activated Al_2O_3 and Hyflo for 8 h until no **40b** remains.
(3) Wash bed with EtOH, and combine with filtrate.
(4) Cool solution to 9.8 °C while stirring.
(5) Reduce pressure, and reflux at 44.1 °C.
(6) Arrange equipment to distill off EtOH, and concentrate solution to 10.7 kg/L.
(7) Increase pressure to atmospheric, and heat to 53.2 °C.
(8) Add 9 volumes of MTBE, and heat at 57 °C for 2 h.
(9) Cool slurry to −6.2 °C over 6 h, and maintain for 2 h.
(10) Recover in pressure filter, wash in EtOH, and dewater by squeezing.
(11) Dry under vacuum at 60 °C.

The dried product was isolated in 74.3% yield and contained 0.03% of the *S*-enantiomer and no trace of **40b** or **41**. The analysis was carried out by HPLC, and details of the method are described in the patent.

Advantages. The process gives very high-purity product and is clearly suitable for commercial-scale operation.

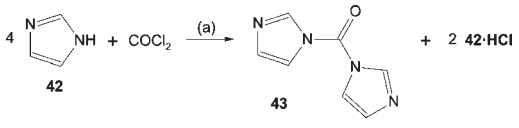
PATENT NO. U.S. 7,964,626

Assignee: Hodogaya Chemical Co. Ltd., Kawasaki-shi, Japan

Title or Subject: Process for Producing *N,N′*-Carbonyldiimidazole

N,N′-Carbonyldiimidazole, **43**, is a useful synthetic reagent that is usually prepared by reaction of **42** with $COCl_2$ as shown in Scheme 15. Unfortunately, only half of the **42** is utilised since the other half removes the HCl formed in the production of **43** and forms the salt **42·HCl**. Unless this can be recovered and reused, it is discarded and is a waste product. The current patent describes how this salt can be recovered and used to prepare **43**. The example in the patent for preparing **43** actually uses diphosgene, and the claims cover the use of this as well as $COCl_2$ and triphosgene. After the reaction is complete, the salt is recovered by filtration, the filtrate concentrated, and **43** isolated by crystallisation from PhMe.

Scheme 15[a]



[a] Reagents and conditions: (a) (i) THF, rt, 3 h; (ii) 55 °C, 1 h; (iii) filter off **42·HCl** and dry at 40 °C; (iv) concentrate filtrate, crystallise from PhMe.

The recovery of **42** from the salt is carried out as follows:

(1) Suspend salt in THF and introduce NH_3 gas at 30−40 °C for 4 h.
(2) Stir at 35 °C for 1 h.
(3) Cool to rt, filter off NH_4Cl.
(4) Concentrate filtrate, and collect solution of **42** in THF (90% recovery).

dx.doi.org/10.1021/op200266b |*Org. Process Res. Dev.* 2011, 15, 1222–1234

The THF solution of **42** can be used to prepare further batches of **43**.

Advantages. The procedure significantly improves the efficiency of the process using a fairly straightforward and economical method.

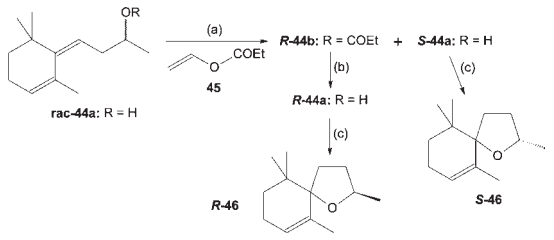
PATENT NO. U.S. 7,964,637

Assignee: Takasago International Corporation, Tokyo, Japan

Title or Subject: Process for Producing Optically Active Theaspirane

Theaspirane **46** is used in flavours and fragrances and is found in raspberry oil and passion fruit oil. The molecule has two chiral centres, and the ratio of diastereoisomers depends on the source of the oil. A synthetic route to the material is an objective, but developing stereoselective reactions can be difficult. This has been achieved in a route shown in Scheme 16 that uses an enzyme to stereoselectively catalyse the esterification of one enantiomer of racemic **44a**, giving the ester ***R*-46** and leaving the alcohol ***S*-44a**. GC analysis showed that the conversion was 43.7% and the ee of the ester was >99%. After the solution was separated from the enzyme, a second reaction was carried out using the recovered enzyme, and conversion was 45.3% with the ee of the ester >99%. This was repeated four times in total, and the results are reported as being the same each time. The method for the separation of the ester and alcohol is not described although the patent states that this may be achieved by ordinary methods such as distillation, extraction, crystallisation, or ColC. The ester is then hydrolysed using NaOMe to give the crude alcohol ***R*-44a** that is used without purification and converted to ***R*-46** by a ring-closing reaction using TsOH. The product is purified by distillation and isolated in 76.8% yield; in an identical manner the ***S*-alcohol** is converted to ***S*-46**. The examples in the patent describe the method of recovering the products as being "in the conventional manner". This is a totally meaningless phrase because what is conventional in one laboratory may be anathema to chemists in another.

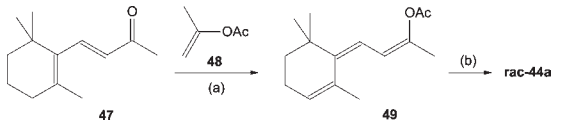
Scheme 16[a]



[a] Reagents and conditions: (a) (i) Novozyme 435, PhMe, 35 °C, 4 h; (i) decant, evaporate; (b) (i) NaOMe, MeOH, rt, 2 h; (ii) add H_2O, extract in PhMe; (c) (i) TsOH, PhMe, 80 °C, 3 h; (ii) cool to rt, wash, evaporate, distill.

The patent describes the preparation of starting material **rac-44a** from β-ionone **47** as shown in Scheme 17. In the first step **47** reacts with the enol ester **48** in the presence of TsOH to give **49** that is obtained as the crude material and then reduced with $NaBH_4$ to produce **rac-44a**. The crude product is purified by distillation and recovered in 68.8% yield.

Scheme 17[a]



[a] Reagents and conditions: (a) (i) TsOH, Pr^iOH, reflux, 5 h; cool to rt, evaporate, add PhMe; (ii) wash in aq Na_2CO_3, evaporate; (b) (i) $NaBH_4$, EtOH, 25 min, rt; (ii) rt, 3 h; (iii) aq NH_4Cl, 0 °C.

The patent also describes the synthesis of the racemic ester **44b** by reaction of **44a** with EtCOCl and Me_2NPh. The resolution and hydrolysis of the racemic ester is then carried out using Novozyme 435 that gives **R-44a** that is purified by distillation and recovered in 33.7% yield. The patent has a number of examples describing the preparation of a range of flavours using the single enantiomers of **46**.

Advantages. The process gives high yields of the pure enantiomers from readily available starting materials.

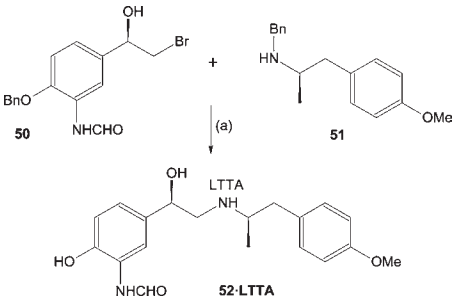
PATENT NO. U.S. 7,964,753

Assignee: Sunovion Pharmaceuticals Inc., Marlborough, Massachusetts, U.S.A.

Title or Subject: Process for Preparation of Polymorph of Formoterol Tartrate

Formoterol **52** is used used in the management of asthma and other chronic pulmonary diseases. It is supplied for drug use as the dihydrate of the fumarate salt as a 1:1 racemic mixture of the *R,R*- and *S,S*-isomers, The *R,R*-form is the most potent being over 1000 times more effective than the *S,S*-isomer, and an objective is to develop a selective method for the synthesis of only this isomer. A report in U.S. Patent 6,268,533 discloses two polymorphs of the LTTA salt of the *R,R*-isomer, and the current patent discloses a third polymorph that can be converted to the thermodynamically most stable form of the salt that is designated Form A. It is stated in this patent that there are two reports of the synthesis of all four isomers of **52**, but they are long processes giving a low overall yield of the optically pure *R,R*- or *S,S*-isomers. It is stated that there is only one practical synthesis of the pure *R,R*-isomer of **52** that is described in U.S. Patent 6,268,533 and shown in Scheme 18.

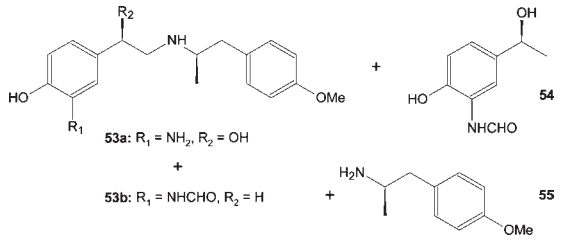
Scheme 18[a]



[a] Reagents and conditions: (a) (i) K_2CO_3, MeOH, THF; (ii) 120 °C; (iii) Pd/C, H_2, Pr^iOH, PhMe; (iv) LTTA, H_2O, Pr^iOH.

The crystallisation of the final product initially gives the kinetically stable polymorph designated Form B that can be converted to Form A. However, the resulting Form A material

always contains four impurities no matter how many times it is recrystallised. The impurities are shown below, and it is claimed that it is not possible to produce Form A containing <0.5% of these impurities. It is postulated that the amine **53a** is formed by partial hydrolysis of the formamide group in **52** during crystallisation. The hypothesis in the patent for the formation of **53b** is that it arises by dehydroxylation of **52** and that compounds **54** and **55** are proposed to arise by hydrogenation of **50** and **51**, respectively.



Impurities

The patent reports that it was unexpectedly found that, when a slurry of the crude **52** is heated in a mixture of Pr^iOH/H_2O containing >13% PhMe to 45−50 °C for 1−5 h, the levels of all impurities are reduced. The crude **52·LTTA** contained 0.11% **53a**, 0.64% **53b**, 0.12% **54**, and 0.04% **55**; after the heating stage the levels were 0.04% **53a**, 0.11% **53b**, with **54** and **55** not being detectable. After recrystallisation, the product still had no detectable levels of **54** and **55**, and the amount of **53a** had increased slightly to 0.12%, while the amount of **53b** was 0.05%. When heating the slurry to 45−50 °C, the mixture thickens, and it is suggested that a polymorph interconversion occurs. Investigations showed that a new polymorph is formed during heating, and this is designated Form C. Upon crystallisation, this is converted to the thermodynamically stable polymorph, Form A.

A detailed experimental procedure for in situ polymorph conversion/purification and crystallisation process is described in the patent and is summarised below. The patent claims stipulate that the amount of PhMe in the initial solution is >13%.

(1) Dissolve crude free base **52** in a Pr^iOH/PhMe mixture containing 21.6 wt % PhMe.
(2) Add aq LTTA to above mixture at rt for 2 h forming a slurry.
(3) Heat to 45−50 °C until level of **53a** <0.15% (this takes 2−3 h during which time the slurry thickens).
(4) Cool mixture to 22 °C and filter off crude product.
(5) Add $PriOH/H_2O$ and heat to 50 −55 °C to dissolve solid.
(6) Seed with polymorph A followed by Pr^iOH.
(7) Cool to 40−45 °C for 0.5 h then to 0 °C for 2 h.
(8) Filter off solid (85% yield).

The patent includes IR, XRD, and DSC scans for each of the polymorphs.

Advantages. The process provides an improved method for purification of the API and also describes a new polymorph that is converted to the thermodynamically most stable form of the crystal.

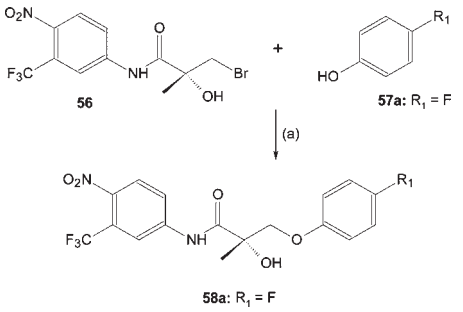
PATENT NO. U.S. 7,968,721

Assignee: University of Tennessee Research Foundation, Knoxville, Tennessee, U.S.A.

Title or Subject: Large-Scale Synthesis of Selective Androgen Receptor Modulators

The compounds covered by this patent are exemplified by **58a** (R_1 = F) and **58b** (R_1 = NHAc) and are said to have a wide variety of pharmaceutical applications related to male sex hormones. Mention is made of their use as male contraceptives and in the treatment of prostate-related problems. The patent describes two kilo-scale experiments for the production of **58a** and **58b** by the condensation of **56** with **57a** or **57b** as shown in Scheme 19. The reaction is carried out in the presence of a substantial excess of Cs_2CO_3 in THF. For the preparation of **58b** 5.4 mol of Cs_2CO_3 is used with 2.7 mol of **56**, and for **58a** 6.17 mol is used for 3.37 mol of **56**. (The patent mistakenly shows the formula of the base as $CsCO_3$ although the calculation of the molar amount is correct.) The reaction is monitored by HPLC, and the preparation of **58a** takes 3 h at 50 °C, whereas **58b** takes 8 h in refluxing THF, monitored by TLC. The workup of **58a** involves three precipitations by adding deionised H_2O to an EtOH solution at rt. The final yield of **58a** is 83%. The purification of the product using alcohol and water is a key aspect of the patent and is covered by the claims, and despite claims in the patent that the process gives highly pure products, there are no analytical data to support this. Workup of **58b** also involves the use of EtOH and H_2O; in addition the solvents EtOAc and MTBE are also used, and the product is isolated in 52% yield.

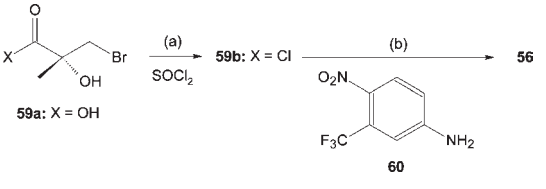
Scheme 19[a]



[a] Reagents and conditions (a) (i) Cs_2CO_3, THF, argon, 50 °C, 3 h; (ii) filter, wash in THF, evaporate; (iii) add EtOH, evaporate; (iv) EtOH, H_2O, rt, 16 h; (v) filter, wash in H_2O; (v) repeat steps iv and v (2×); (vi) filter, dry at 25 °C.

The patent also describes the synthesis of compound **56** by the route outlined in Scheme 20 that is carried out at kilo scale. Initially the acyl chloride **59b** is prepared by reaction of acid **59a** with $SOCl_2$. This is not isolated, and a solution of **60** and Et_3N in THF is added to **59b** over 3 h. After the mixture is warmed to rt, the mixture is then heated to 50 °C for 15 h. The reaction is monitored by TLC; 3.7 kg of **56** is isolated by crystallisation from warm PhMe in 70.3% yield.

Scheme 20[a]

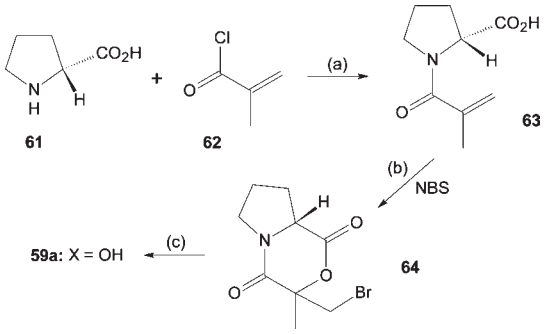


[a] Reagents and conditions (a) THF, 5−10 °C, 4 h; (b) (i) Et_3N, THF, <10 °C, 3 h; (ii) rt, 0.5 h; (iii) 50 °C, 15 h; (iv) cool 30 °C, wash in H_2O × 2; (v) wash in 10% $NaHCO_3$, evaporate; (vi) add PhMe, evaporate; (vii) PhMe, 65 °C; (viii) cool, filter, wash, dry.

dx.doi.org/10.1021/op200266b |Org. Process Res. Dev. 2011, 15, 1222–1234

The preparation of **59a** is also described, and again this is a multikilo-scale synthesis. The route is shown in Scheme 21 and starts with the preparation of **63** by simultaneous addition of 4 M NaOH and a solution of **62** in Me_2CO to a mixture of **61** and 4 M NaOH in Me_2CO. The pH of the reaction mixture is kept above 10 by adding more 4 M NaOH as required. **63** is isolated by crystallisation from MTBE in 55.6% yield and then treated with NBS in DMF to effect the cyclisation and form **64**. This is isolated in 87.7% yield by addition of H_2O to the reaction mixture. The final step is refluxing **64** with 24% HBr to produce **59a** that is isolated as a crystalline solid from hot PhMe in 81.3% yield.

Scheme 21[a]



[a] Reagents and conditions (a) (i) 4 M NaOH, Me_2CO, pH >10, 5−10 °C, 160 min; (ii) rt, 16 h; (iii) evaporate, extract in MTBE; (iv) concd HCl to pH <2; (v) extract in DCM; (vi) concentrate, add MTBE; (vii) add ice, filter, dry; (b) (i) DMF, rt, 10 h; (ii) H_2O, rt, 4 h; (iii) filter, dry; (c) (i) 24% HBr, H_2O, reflux, 6 h; (ii) cool 30 °C, add brine, extract in MTBE; (iii) evaporate, add PhMe, distill off PhMe/H_2O; (iv) evaporate, add PhMe, 100 °C; (v) cool, filter, wash, dry.

The patent claims also cover compounds related to **58a** and **58b** in which the NO_2 group is replaced by CN. Unfortunately, there are no examples describing the synthesis of these compounds.

Advantages. The patent describes an efficient process for the synthesis of these compounds that has been shown to be suitable for larger-scale production.

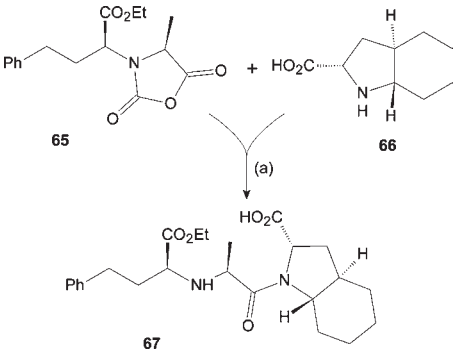
PATENT NO. U.S. 7,973,173

Assignee: Cipia Limited, Mumbai, India

Title or Subject: Process for the Synthesis of an ACE Inhibitor

The patent covers the synthesis of **67** that is known as trandolapril, a drug used to lower blood pressure. A number of processes for preparing **67** are summarised and their shortcomings mentioned. Some of these are said to be nonstereoselective, and hence a resolution step is necessary. The objective of this patent is to provide a stereoselective synthesis of **67**. The route used is shown in Scheme 22 and involves the condensation of the anhydride **65** with the acid **66** and in a solvent that is not miscible with water. The product is then isolated using a second solvent in yields of up to 39% and HPLC purity of 99.3−99.5%. The preferred solvent for the product isolation is MeCN although there are no examples that describe its use, and the four examples in the patent all use EtOAc. The reaction in Scheme 22 shows the use of the pure isomer of **66**, and there are also examples using the racemic mixture.

Scheme 22[a]

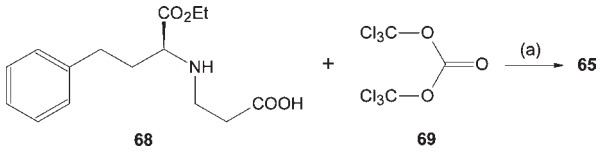


[a] Reagents and conditions: (a) (i) Et_3N, DCM, rt, 3 h; (ii) add H_2O, cool to 15 °C, 2 M HCl to pH 4.2; (iii) separate, dry, evaporate; (iv) add, EtOAc, reflux; (v) cool to rt, filter, dry.

This route is similar to alternatives with the main difference being that the other methods tend to use esters of **66**. It is stated that there is no attempt in the alternative processes to resolve the esters of **66** and convert the resolved ester to the desired isomer **66**. This patent describes the resolution of the *trans* mixture of **66** to the desired isomer using *R*-(+)-PhNHEt, and it is recovered in 97.6% yield.

The preparation of the anhydride **65** from the alanine derivative **68** and triphosgene **69** is described in the patent and shown in Scheme 23. The procedure is to add a solution **68** in DCM to an aqueous solution of Na_2HPO_4 followed by a solution of **69** over 40 min. After a further 30 min a catalytic amount of pyridine is added to complete the reaction, and the crude product is recovered in 94% yield and used directly in the preparation of **67**.

Scheme 23[a]



[a] Reagents and conditions: (a) (i) Aq Na_2HPO_4, DCM, 15−20 °C, 40 min; (ii) pyridine, 15−20 °C, 1 h; (iii) neutralise with 2 M HCl, H_2O wash, dry, evaporate.

A key aspect of the process is the use of less than the stoichiometric amount of **65** in preparing **67**, and the patent claims specify that the preferred ratio of **65**:**66** is 0.5−0.8 to 1. If an equimolar amount of **65** is used with the racemic *trans*-**66**, then a significant amount of **65** does not react and is recovered as **68**.

Advantages. The process provides a stereoselective method of preparing trandolapril.

PATENT NO. U.S. 7,973,176

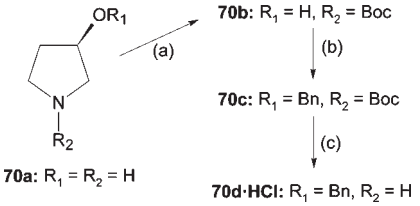
Assignee: Kaneka Corporation, Osaka, Japan

Title or Subject: Process for Production of Aralkyloxypyrrolidine Derivative

The compound of interest in this patent is the HCl salt of novel compound **70d** that is said to be useful as a pharmaceutical

intermediate. Alternative methods for the preparation of **70d** are summarised, and the use of ColC, difficulty in crystallisation, and reagent handling problems mean that an industrially viable process is needed. Scheme 24 outlines the method used to prepare **70d** that is recovered as the HCl salt. The first step is protection of the amine group by conversion to the Boc derivative **70b**. This is recovered as the crude product in 96% yield and used without purifying in the next step in which the benzyloxy compound **70c** is formed. This is a biphasic reaction in PhMe containing Bu^n_4NBr as PTC and KI. The crude product is recovered in 92% yield and then dissolved in Pr^iOH and treated with a solution of HCl in Pr^iOH to form **70d·HCl**. After crystallisation from EtOAc/hexane the product is isolated in 82% yield and 99.8% purity. The level of the HCl salt of **70a** was reduced from 0.92 to 0.42 wt % and that of BnOH from 1.9 to 0.01 wt %.

Scheme 24[a]



[a] Reagents and conditions: (a) (i) Aq K_2CO_3; (ii) $(Boc)_2CO$, THF, rt; (ii) extract in PhMe, concentrate; (b) Bu^n_4NBr, KI, PhMe; (ii) 10% aq NaOH, 50 °C; (iii) BnCl, 50 °C; (iv) cool to 25 °C, H_2O wash, concentrate; (c) (i) Pr^iOH, 40 °C; (ii) add HCl/Pr^iOH over 6 h, 40 °C; (iii) cool to 23 °C, concentrate; (iv) add EtOAc, concentrate; (v) heat to 40 °C, add Pr^iOH; (vi) cool, seed, add hexane, filter; (vii) EtOAc wash, dry.

The patent describes the preparation of the free base **70d** and also a wide range of salts of **70d** including HBr, TsOH, sulphate, LTTA, DTTA, and L- and D-aspartate. The ^1H NMR spectra of all of these salts are provided. The patent states that handling of the novel salt **70d·HCl** is easy; thus, it is useful as a pharmaceutical intermediate.

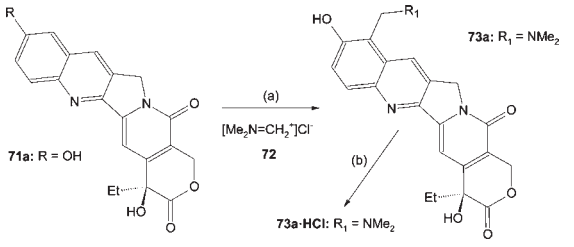
Advantages. The process provides a stable and easily handled crystalline material that can be used in industrial applications.

PATENT NO. U.S. 7,977,483

Assignee: Scinopharm Taiwan Ltd., Tainan County, Taiwan
Title or Subject: Process for Making Topotecan

Topotecan **73a** (R = NMe_2) is available as the HCl salt under the name Hycamine and is used in chemotherapy for the treatment of ovarian cancer and lung cancer, as well as other cancer types. **73a** is a semisynthetic derivative of camptothecin **71b** (R = H), that is extracted from the bark of the Asian tree *Camptotheca acuminate*. A patent describing an alternative synthesis of **73a** has been reviewed recently (*Org. Process Res. Dev.* **2009**, *13*, 1046). The current patent describes a process for preparing **73a** from hydroxycamptothecin **71a** (R = OH) that is reacted with the iminium salt **72** in the presence of a base such as Et_3N in a mixed solvent of DCM and an alcohol (Scheme 25). The reaction is carried out under anhydrous conditions so as to avoid the formation of a hydroxymethyl impurity **73b** (R_1 = OH) that is often found in the conventional synthesis of **73a**. The initial product of the reaction of **71a** with **72** is the free base that is converted to the HCl salt that is isolated in the crude form. The example describes the production of 1.5 kg of crude **73a·HCl**, but its purification is not described. The patent does claim that the process gives **73a** that contains **73b** at levels <0.10%, but analytical details or results are not reported.

Scheme 25[a]



[a] Reagents and conditions: (a) Et_3N, Pr^iOH, DCM, 20−35 °C, 12 h; (b) 32% HCl, Pr^iOH, filter, wash, dry.

The patent proposes a mechanism for the reaction, and it is suggested that the function of Et_3N is to catch the proton of the C10 OH group and also combine with the HCl formed from **72**.

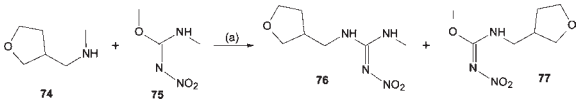
Advantages. The process is a straightforward method of producing the desired salt in high yields and has been scaled up.

PATENT NO. U.S. 7,977,496

Assignee: Mitsui Chemicals Inc., Minato-Ku, Japan
Title or Subject: Process for Producing Nitroguanidine Derivatives

The compounds covered in this patent such as **76** have insecticidal activity. Methods for their production that are based on the reaction of an isothiourea and an amine can give rise to the production of mercaptans that cause environmental problems. Alternative methods use an isourea that is expensive or nitroisoureas that may be unstable or give large amounts of byproduct; thus, these are also commercially unattractive. The process for preparing **76** in this patent is based on the reaction of nitroisourea **75** and amine **74** that is carried out at 0 to −10 °C in an aqueous solution of NaCl at >50% of the saturation level (Scheme 26). The solution also contains a base that is is added to suppress the formation of byproduct from **75** such as **77**. The product is isolated in yield of around 81% and 99% purity by crystallisation from a hot solution, although the actual details are not reported. The ^1H NMR data of **76** are provided.

Scheme 26[a]



[a] Reagents and conditions: (a) (i) NaCl, NaOH, H_2O, −10 °C, 4 h; (ii) 0 °C, 18 h; (iii) 35% HCl to pH 4; (iv) Heat to dissolve, crystallise, filter, H_2O wash, dry.

The parent compound of **76** is nitroguanadine, $(H_2N)_2C{=}N{-}NO_2$, that is a detonator; for safety reasons alone it would be useful to know if **76** has explosive properties.

Advantages. The process reduces decomposition of starting material and hence byproduct formation and gives high selectivity to the desired product.

dx.doi.org/10.1021/op200266b |*Org. Process Res. Dev.* 2011, 15, 1222–1234

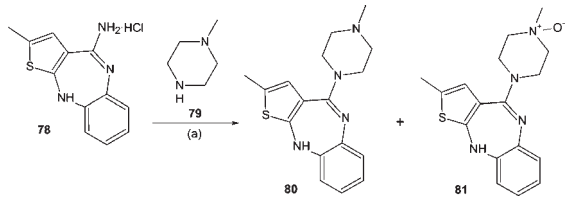
PATENT NO. U.S. 7,981,884

Assignee: Egis Gyogyszergyar Nyilvanosan Mukodo Reszvenytarsasag, Budapest, Hungary

Title or Subject: Process for the Preparation of Olanzapine

Olanzapine, **80**, is an antipsychotic drug that is used to treat schizophrenia and bipolar disorders in adults. Other patents covering the preparation of **80** have been reviewed (*Org. Process Res. Dev.* **2009**, *13*, 669). The last step of the original route for the synthesis of **80** involves the reaction of **78·HCl** with **79** (Scheme 27). The current patent reports that, when following this procedure, an undesirable amount of the *N*-oxide **81** is formed. The original reports specify that the reaction is carried out in DMSO and it has been found that even if it is performed under an inert gas **81** is still formed. This patent states that this is surprising because there are no reports in the literature that DMSO oxidises **80**. In view of this problem an improved method of carrying out the last step of the synthesis has been developed that does not use DMSO and reduces the amount of **81** that is formed. The reaction is carried out in a dipolar aprotic solvent that is a mixture of 1,3-dimethylimidazolidin-2-one (DMI) and PhMe, and the patent claims cover the use of mixtures of PhMe and DMI in volumetric ratios 1:1, 2:1, and 3:1. The reaction is carried out under argon and gives 89.6% yield of crude free base **80** that is recrystallised from MeCN, giving pure product (99.87%) in 76% yield.

Scheme 27[a]



[a] Reagents and conditions: (a) (i) DMI, PhMe, reflux, 9 h; (ii) evaporate at <55 °C; (iii) cool <5 °C, add H_2O, 1 h; (iv) filter, wash, dry under IR lamp; (v) recrystallise MeCN.

The trihydrate bis-HCl salt of **80** is formed by treating the free base with 37% HCl in EtOH/H_2O, and the salt is isolated in 83.5% yield (purity not reported). Also described in the patent is a method for preparing the *N*-oxide **81** by reaction of **80** with *m*-CPBA. The product is isolated in 99.6% purity and 79.1% yield. ^{1}H NMR data are reported for both **80** and **81** and IR and ^{13}C NMR data for **81**.

Advantages. The process gives high-purity product in good yields using an established synthetic route.

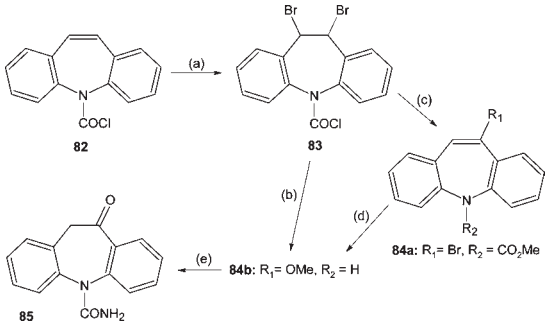
PATENT NO. U.S. 7,982,032

Assignee: Sun Pharmaceutical Industries Ltd., Andheri, Mumbai, India

Title or Subject: Process for the Preparation of Oxcarbazepine

Oxcarbazepine, **85**, is a drug used primarily in the treatment of epilepsy but also used to treat anxiety and mood disorders. This patent describes a novel route for the preparation of **85** that is outlined in Scheme 28. Alternative routes used to make **85** also involve the intermediate **84b**, and this is obtained by a number of different methods. The current patent discloses a route to **85** in which **84b** is prepared by a method that is claimed to have shorter reaction times than alternatives. The first stage of the process is the bromination of **82** to give **83** that can be converted to intermediate **84b** directly or via **84a**. Both methods involve treatment of **83** with NaOMe to effect both dehydrobromination and esterification, The isolation of **84a** is achieved by limiting the amount of NaOMe, and when excess base is used, the product is **84b**. Although all of the examples describes kilo-scale experiments, none report the yield or purity of the intermediate products. It is likely that, on a large-scale production of **85**, the intermediate **84a** is not isolated. However, to claim the isolation and existence of **84a** without providing any analytical evidence cannot be deemed acceptable. This is particularly important since the patent claims do cover the formation of **84a** from **83**. The preparation of **85** from **84b** is carried out by reaction with NaOCN in HOAc. The crude product is partially purified by adding PhMe/MeOH and then is crystallised from hot DMF/PhMe; the purity of the recovered **85** is 99.87%, but the yield is not reported.

Scheme 28[a]



[a] Reagents and conditions: (a) (i) HOAc, add Br_2, 35 °C, over 2 h; (ii) 35 °C, 2 h; (iii) cool <20 °C, NaS_2O_3; (iv) cool, filter, wash, dry; (b) (i) NaOMe, MeOH, 50−55 °C, 1 h; (ii) cool 35 °C, add NaOMe/MeOH; (iii) 90 °C, 16 h; (iv) cool, filter, H_2O wash, Pr^{i}OH wash; (c) (i) NaOMe, MeOH, 50−55 °C, 1 h; (ii) cool, filter, wash, dry; (iii) NaOMe/MeOH, rt; (iii) 90 °C, 16 h; (iv) cool, filter, H_2O wash, dry; (e) (i) NaOCN, rt; (ii) add HOAc over 0.5 h, 33−35 °C; (iii) 35 °C, 1 h; (iv) add concd H_2SO_4, 35 °C, 2 h; (v) Me_2CO, charcoal, filter; (vi) add H_2O, cool, filter; (vii) PhMe/MeOH; (viii) DMF, 100 °C, 1 h; (ix) add PhMe at 100 °C; (x) cool <6 °C, 1 h; (xi) filter, PhMe wash.

Advantages. The process claims to provide a novel method of making the drug molecule, and although it has clearly been scaled up, there are no details of the reaction yields to establish the commercial viability of the method.

PATENT NO. U.S. 7,985,859

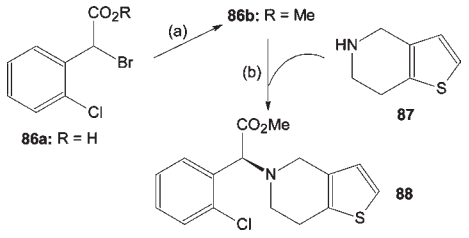
Assignee: Wockhardt Ltd., Bandra-Kurla Complex, Bandra East, Mumbai, India

Title or Subject: Process for the Preparation of Clopidogrel

The bisulphate salt of clopidogrel **88** is available as Plavix and is used to prevent blood clots that may lead to heart problems. Alternative syntheses of **88** have been reviewed previously (*Org. Process Res. Dev.* **2010**, *14*, 292). The active form of the drug is *S*-(+)-enantiomer whereas the *R*-(−)-isomer is inactive; thus, either the resolution of a racemic mixture or a stereoselective synthesis is needed. The current patent describes a process to prepare racemic **88**, recovery of the *R*-(−)-isomer, and its

racemisation. Scheme 29 shows the preparation of the *S*-(−)-isomer of **88** and its isolation as the *L*-(−)-camphor 10-sulphonic acid (LCSA) salt that starts with the esterification of bromo-acid **86a** to give crude **86b** that is recovered as a syrupy mass in 95% yield and 95.85% purity. The ester is then reacted with **87** in the presence of solid $NaHCO_3$ that is recovered as a viscous mass after removal of MeOH. After addition of H_2O and extraction in $CHCl_3$ followed by removal of solvent, another viscous material was obtained that is treated with LCSA. The LCSA salt of **88** is isolated as a solid in 38% yield, while the mother liquor is converted to racemic **88**. The **88**·LCSA salt is treated with aq $NaHCO_3$, forming the free base **88** that is isolated as a syrupy mass and used directly in the preparation of salts. The HCl salt is obtained by treating a solution of **88** in EtOAc with HCl/Pr^iOH and produces the salt in 66.9% yield and 99.9% purity (HPLC). The HSO_4 salt is obtained by adding H_2SO_4 to **88** in EtOAc, and the salt is isolated in 68.6% yield and 99.96% purity (HPLC).

Scheme 29[a]



[a] Reagents and conditions: (a) (i) H_2SO_4, MeOH, reflux 4 h; (ii) evaporate, add H_2O; (iii) extract in $CHCl_3$, wash aq $NaHCO_3$, H_2O wash, evaporate; (b) (i) $NaHCO_3$, MeOH, reflux 4 h; (ii) evaporate, add H_2O, extract in $CHCl_3$, evaporate; (iii) LCSA, Me_2CO, 18−20 °C; (iv) 10−12 °C, 1 h; (v) reflux, 4 h; (vi) cool, filter; (vii) 10% aq $NaHCO_3$, $CHCl_3$, rt, 2 h; (viii) evaporate.

The mother liquor from formation of the salt **LCSA**·**88** is treated with 10% $NaHCO_3$ in $CHCl_3$ to obtain the free base of *R*(−)-isomer of **88**. This is then treated with anhydrous K_2CO_3 that is used in powder form, having a particle size of <400 μm. The reaction is carried out in MeOH over 24 h at 15−20 °C. The racemate is recovered with 96.3% assay after removal of solvent, but the yield is not reported.

Advantages. The process gives the desired enantiomer in high purity and also allows recovery and racemisation of the inactive enantiomer, thereby improving the process efficiency. However, a concern is that the process uses chloroform as solvent, and this is not generally acceptable in North America and Europe.

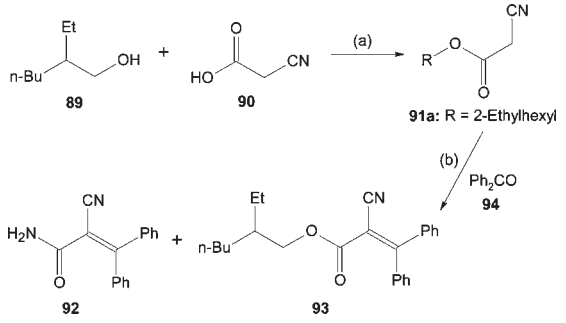
PATENT NO. U.S. 7,985,870

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

Title or Subject: Process for the Manufacture of Substituted 2-Cyanocinnamic Esters

Esters such as **93** are effective UV absorbers and are used as light stabilisers in plastic products or as sunscreens in cosmetics. Processes are known in which the esters can be prepared by a Knoevenagel condensation between cyanoacetic esters and carbonyl compounds. However, depending on the catalyst used, the processes require long reaction times and produce unwanted byproducts, or they give low conversions. The process disclosed in this patent achieves better results by the same route by using a specific molar ratio (MR) of reagents in the presence of NH_4^+ ions and a carboxylic acid. Scheme 30 outlines the route used to prepare **93** from **91a** and **94**. This also produces the amide **92** as the byproduct, and since this has a bp similar to that of **93**, it cannot be removed by distillation; thus, its formation is minimised by controlling the reaction temperature. The first step of the process is the esterification of **89** with aqueous **90** to give **91a**, that is carried out using TsOH with the H_2O being removed azeotropically under increasing vacuum. The preparation of around 400 g of **91a** takes around 8 h, and the product is isolated by vac distn in 92% yield. The condensation of **91a** and **94** is catalysed by NH_4OAc and $EtCO_2H$, and this has been investigated to determine the optimum MR of **91a**:**94** and also the amount of NH_4OAc. Results from a series of experiments indicate that the optimum MR of **91a**:**94** is 0.7:1. Another series of experiments is reported to determine the optimum amount of the catalyst. These experiments investigate the Knoevenagel reaction of the methyl ester **91b** (R = Me) and **94** catalysed by NH_4OAc. The results show that an increase in the amount of catalyst increases the yield of the product but a decrease in the conversion of **94**. Using a MR of 0.4 of catalyst:**94** the conversion of **94** is 28.05%, and yield of product is 80.07%. Increasing the MR to 0.6 gives 92.42% product yield with a 73.15% conversion of 15. At a MR of 0.85 the product yield is 92.4%, and the conversion of **94** is 77.24%. The patent example for the preparation of **93** from **91a** and **94** uses a MR ratio of catalyst to **94** of 0.41, and it is advantageous to add the NH_4OAc in portions to the reaction mixture. The amount of the byproduct amide, **92**, is reduced by keeping the temperature of reaction mixture below 100 °C. The H_2O formed in the condensation reaction is removed by azeotropic distillation with $EtCO_2H$ and the reaction solvent *n*-heptane. As the reaction proceeds, the temperature is kept at around 95 °C by reducing the pressure, and this maintains the reaction at reflux. The control and maintenance of reaction reflux by this procedure is covered by the claims of the patent. The crude product contains 0.04% of the amide, and after distillation the yield of **93** is 68% with an amide content of 0.38%.

Scheme 30[a]



[a] Reagents and conditions: (a) (i) MsOH, H_2O, reflux, 8 h; (ii) cool to 90 °C, add H_2O; (iii) separate, vac distin; (b) (i) NH_4OAc, $EtCO_2H$, *n*-heptane, 95 °C, 6 h; (ii) distill.

There are some interesting aspects to this patent, such as varying the pressure to maintain reflux and enable the removal of water without increasing temperature. These may be termed engineering solutions to problems that R&D chemists may not always consider.

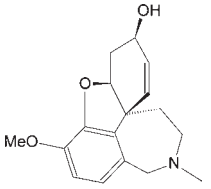
Advantages. The process improves a known method and gives high yield of the product with minimum byproduct formation.

dx.doi.org/10.1021/op200266b |*Org. Process Res. Dev.* 2011, 15, 1222–1234

PATENT NO. U.S. 7,985,879

Assignee: Scinopharm Taiwan Ltd., Tainan County, Taiwan
Title or Subject: Process for Making Galanthamine

Galanthamine (or galantamine), **95**, is a drug approved for the treatment of Alzheimer's disease, and it can be isolated from the plants, snowdrops and daffodils. Its synthesis is difficult because the molecule has three chiral centres. Despite the title, the patent does not actually describe how to make **95** apart from stating that it can be made from **98a**. The patent actually covers a process to prepare **98a** that can be converted to **98b**, a key intermediate in the synthesis of **95**.

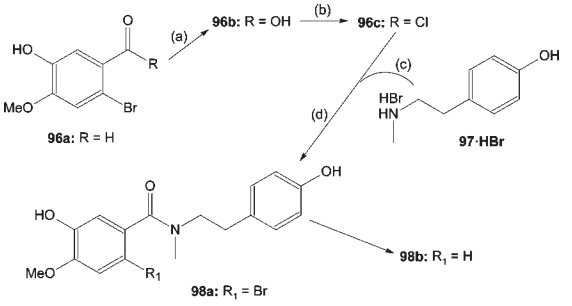


95

Galanthamine

Alternative methods for synthesising **98a** are summarised; one has nine steps resulting in a low overall yield and a difficult purification procedure. The process reported in this patent is said to be shorter and relatively inexpensive. The preparation of **98a** is shown in Scheme 31, and a key aspect is the use of the Br atom as a blocking group to prevent attack at the 2-position.

Scheme 31[a]

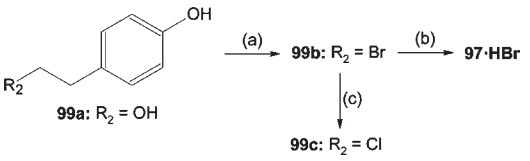


[a] Reagents and conditions (a) (i) H_2NSO_3H, EtOAc, H_2O, −10 °C; (ii) NaOCl, H_2O, 0 °C, 1 h; (iii) extract in EtOAc, rt; (iv) vac distill, 40 °C; (v) add PhMe, 35 °C; (vi) cool <0 °C, filter; (b) $SOCl_2$, DMF, EtOAc, 50 °C, 1 h; (ii) concentrate, add DCM; (c) (i) NaOH, MeOH, (ii) concentrate; (d) (i) DCM, 5 °C, 0.5 h, concentrate; (ii) 15% NaOH/MeOH, 30 °C, 8 h; (iii) 32% HCl to pH <5, concentrate; (iv) add DCM, H_2O, 5 °C, 2 h; (v) filter, wash; (vi) active C, MeOH, reflux, 1 h; (vii) DCM, H_2O <10 °C.

The process begins with the oxidation of the aldehyde **96a** to the acid **96b** with NaOCl in the presence of sulphamic acid. The acid is recovered in 89% yield and then converted to the benzoyl chloride **96c** by reaction with $SOCl_2$ in the presence of DMF. This step is described as the activation of the R group in **96b** by the use of a $SOCl_2$ that is described as a coupling agent. The patent claims cover the use of alternative coupling agents for this step such as *N*-hydroxyamides, but no examples are provided. The benzoyl chloride **96c** is recovered as a solution in DCM and then reacted with the amine **97** in the presence of NaOH. The amine is obtained by treating the HBr salt with NaOH prior to addition of the DCM solution of **96c**. The reaction produces **98a** that is purified by refluxing with activated C in MeOH followed by concentrating and dissolving in DCM. Addition of H_2O precipitates **98a** that is recovered and can be used to prepare **98b**, the intermediate used to prepare **95**. There are no details for the conversion of **98a** to **98b** nor for the preparation of **95** although the formation of **95** from **98a** is covered in the patent claims. The purity and yield of **98a** are not reported, although all of the reactions shown in Scheme 31 are carried out on a kilo scale, thus suggesting the advanced scale of development. Two alternative, and slightly modified, methods are also described for preparing **98a**, but these are both smaller-scale experiments with yields of 56−63%. It is stated in the patent that **98a** can be converted to **98b** but no details are provided.

The patent also describes the preparation of **97·HBr** by the route outlined in Scheme 32. This starts by treatment of the alcohol **99a** with HBr. After the mixture is heated at 75 °C for 2.5 h, seed crystals of **99b** are added, and the mixture is kept at this temperature for 24 h. Upon cooling, the bromide **99b** is isolated in 96% yield. It is then aminated by addition to a solution of $MeNH_2$ in Pr^iOH. After the reaction is completed, the excess $MeNH_2$ is removed, and the amine **97** is isolated as its HBr salt in 90% yield. The preparation of the chloro compound **99c** is also described, and this involves treating **99a** with 12 M HCl. The product is obtained in 70% yield.

Scheme 32[a]



[a] Reagents and conditions (a) (i) 48% HBr, 75 °C, 2.5 h; (ii) add seeds of **20b**; (iii) 75 °C, 24 h; (iv) cool to 20 °C, filter, wash in aq $NaHCO_3$; (b) (i) $MeNH_2$, Pr^iOH, 0 °C; (ii) rt, 12 h; (iii) distill $MeNH_2$, 50 °C; (iv) distill Pr^iOH, 100 °C; (v) cool rt, filter, wash; (c) 12 M HCl.

The ^1H NMR data are reported for all of the compounds prepared.

Advantages. The process has fewer steps than alternatives, and since it has been scaled up to kilo scale, this is an indication of the advanced stage of development.

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