Organic Process Research & Development

HIGHLIGHTS FROM THE PATENTS

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A Review of U.S. Patents in the Field of Organic Process Development Published During April and May 2011

SUMMARY

The current review contains 19 patents from an original list of 250 that fitted the selection criteria. This is slightly fewer than usual, but some of those chosen contain a considerable amount of detailed chemistry and hopefully make up for the lower number reviewed. Some types of nonsteroidal anti-inflammatory drugs (NSAIDs) have serious side effects, but celecoxib is a drug with few problems. A new process for its preparation and purification is reported. However, the patent contains some serious errors that would embarrass first-year chemistry students. A range of NSAIDs that release nitric oxide are under investigation, and these can be made from 1,4-butanediol mononitrate. The synthesis and purification of this compound can be hazardous, and an improved method for its purification is reported that is safer and involves extraction with water and a water-immiscible solvent. The preparation of a range of aminothiophenes, that are herbicide intermediates, involves a chlorination step that is improved by using SO_2Cl_2 in place of Cl_2. In another step in the process it is found that an enamine is more efficiently produced when NH_3 gas is present, allowing only catalytic amounts of an NH_4^+ salt to be needed. A process that involves chlorination with $SOCl_2$ is the synthesis of levetiracetam, that is used to treat epilepsy. The *S*-enantiomer is reported to be 10 times more effective than the *R*-enantiomer, and the ratio of the *S*- to *R*-isomer is improved when NH_3 is used to neutralise the reaction mixture after chlorination with $SOCl_2$. A patent on the synthesis of insect pheromones improves the desired trans/cis ratio by ensuring that either the starting material or a Cu coupling catalyst contains a Br group. Another compound used to prepare agrochemicals is bromopicrin that is often prepared from the hazardous reagent picric acid. A new process involves direct bromination of nitromethane and gives a high-purity product. New methods for preparing drugs to treat various heart-related problems are regularly encountered, and an improved preparation of a compound used to produce ivabradine is reported that does not require the isolation of intermediates. Dialkoxy-3-fluorobenzenes are intermediates in the production of electroluminescent chemicals, and a new process uses readily available starting materials for their synthesis. A patent for the production of intermediates of an opioid receptor antagonist contains critical gas purging steps in a stereospecific catalytic hydrogenation step. Minimum times for purging with N_2 and H_2 are required for optimum efficiency, and this is covered by the claims of the patent. The final endo/exo ratio depends on H_2 pressure and reaction time. Statins continue to receive a great deal of attention, and a patent reports on an improved synthesis of pyrrole intermediates used to prepare atorvastatin. The process has fewer steps than alternatives but includes an oxidation reaction in which air is bubbled through a solution of DCM, and the patent ignores the VOC problems that would undoubtedly arise. Hypertension is treated with a variety of drugs, and two patents report improved methods of making some of these that avoid the use of chromatographic separation methods. Olmesartan medoxomil is one such drug, and a route is described that avoids the use of chromatography by using MeCN as reaction solvent in place of DMF. In the second patent the prodrug candesartan cilexetil is prepared from candesartan in a process that also avoids the use of chromatography. The antiviral drug valgancyclovir hydrochloride is synthesised by a stereoselective route that starts from L-valine adducts. The process has only two steps and gives low yields but does include a novel freeze-drying method for isolation of the salt. Another antiviral is emtrictabane that is used to treat HIV, and a patent reports that an earlier process for its synthesis is incorrect in claiming that an intermediate base is a solid. The newer patent reports that the material is a gel but can be isolated in solid form as a salt yet describes experiments in which the free base is used, and the claims cover the use of the oxalate salt. A hexahydrofurofuranol derivative is used to prepare an anti-AIDS drug, and a new process avoids the use of Sn or Se reagents and their attendant problems. A very comprehensive patent describes a process that is highly stereoselective and gives high yields of the products. Despite using a considerable number of solvents in the workup, it also gives high yields. Cabergoline is used to treat Parkinsonism, and a comprehensive patent reports a new process via an intermediate that has been previously prepared from lysergic acid. The use of a controlled substance was identified as a distinct disadvantage to commercialisation, and so an alternative route is described. Glaucoma is a disease affecting considerable numbers of people, and compounds known as latrunculins can be used to treat the disease. These compounds are found in marine sponges, and a stereoselective synthetic route is reported that starts from L-cysteine. The synthesis of a range of pyrrolo-pyrimidinols, that have biological interest, is described that avoids harsh conditions of alternative methods. The method also avoids the need to isolate intermediate products. Microscale experiments are valuable in data collection and in some cases are useful for preparation of reagents and products. Problems due to the presence of undissolved or precipitated solids can arise because of the small size of the reactors especially when low temperatures are needed. A patent reports that by using glycol ethers as solvents in continuous flow microreactors in Grignard reactions these problems are overcome. A number of the patents in this collection describe experiments carried out on a kilo- or multikilogram scale, thus suggesting an advanced stage of development or even commercial operation.

There is no legal or commercial significance in the choice of patents in this review and the advantages mentioned are those claimed in the patent, unless this reviewer has personal knowledge of the subject.

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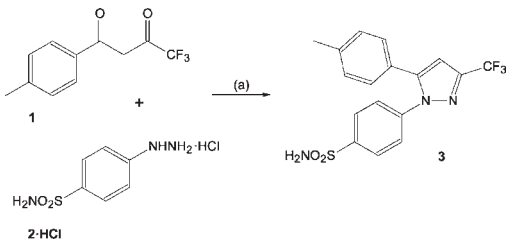
PATENT NO. U.S. 7,919,633

Assignee: Dr. Reddy's Laboratories, Hyderabad, India, and Bridgewater, New Jersey, U.S.A.

Title or Subject: Process for the Preparation of Celecoxib

Celecoxib **3** is a COX-2 inhibitor available as Celebrex and used as a nonsteroidal anti-inflammatory drug (NSAID). The patent describes a new preparation of **3** that also involves a method for its purification using aromatic solvents. The preparation of **3** is shown in Scheme 1 and involves the reaction of the ester **1** with the HCl salt of the phenylhydrazine **2** in a mixture of EtOAc and H_2O. The reaction produces **3** in very crude form. Although the patent does not mention its purity the example reports that, from 10.5 g each of **1** and **2**, 27 g of **3** is recovered, and this equates to 64.4% purity.

Scheme 1[a]



[a] Reagents and conditions: (a) (i) EtOAc/H_2O, 80 °C, 5 h; (ii) <5 °C, 1 h; (iii) filter, H_2O wash, dry.

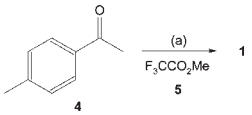
The crude **3** is then purified by the following procedure:

(1) Heat in PhMe at 80 °C for 15 min.
(2) Add active C, then heat for a further 0.5 h at 80 °C.
(3) Cool to <15 °C, and stir for 1 h.
(4) Filter, wash in PhMe, dry at 75 °C for 6 h.

The yield of pure **3** reported in the example does not correspond with the experimental details provided. The patent reports that 22.3 g of **3** with a purity of 99.97% (HPLC) is obtained from 25 g of crude **3** that is prepared by the method outlined in Scheme 1. However, 25 g of crude **3** with purity of 64.4% contains only 16.1 g of **3**, and yet the patent reports that 22.3 g of pure **3** is recovered. The patent also does not explain how the active C is separated from the purified **3** in step 4.

The patent also describes the preparation of **1** from the ketone **4** and **5** as shown in Scheme 2. The reported yield of **1** is 87%, but the purity is not reported.

Scheme 2[a]

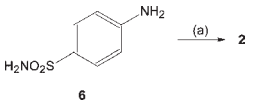


[a] Reagents and conditions: (a) (i) NaOMe, PhMe, 25 °C, 1 h; (ii) 110 °C, 24 h; (iii) cool 30 °C, add 3 M HCl, separate; (iv) extract in PhMe, H_2O wash, evaporate.

The preparation of the HCl salt of **2** is also described, and this is via formation of the diazonium compound followed by reduction using $Na_2S_2O_5$ as shown in Scheme 3. The yield of **2·HCl** is 52%, but the purity is not reported.

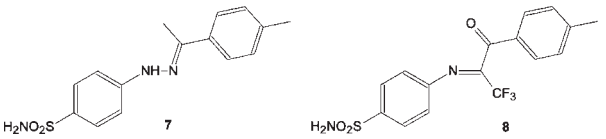
The patent mentions the use of the impurities, **7** and **8**, that may be used as reference standards in the analysis of **3**. The only

Scheme 3[a]



[a] Reagents and conditions: (a) (i) HCl, H_2O, −10 °C; (ii) aq $NaNO_2$, H_2O, −10 °C; (iii) aq NaOH, $Na_2S_2O_5$, 0 °C; (iv) 80 °C, 5 h; (v) HCl, 35 °C, 0.5 h; (vi) filter, wash in Pr^iOH, dry.

details of these two compounds is that they each are present in purified **3** at <0.1%.



Apart from the inconsistency in the yield described above, this patent also contains a serious error in the claims that contradicts the text in the patent. The main claims state that **3** is obtained by reacting a compound of formula **2**, or one of its salts, with a compound whose formula corresponds to the methyl equivalent of **1** and not with the trifluoro compound of formula **1**. This is clearly not possible, and one wonders whether a chemist actually looked at the patent application.

Advantages

The patent claims to provide a new process for the preparation of pure celecoxib.

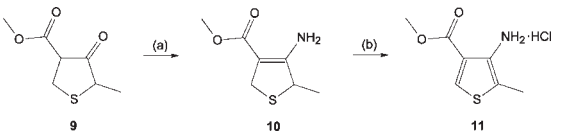
PATENT NO. U.S. 7,923,571

Assignee: Bayer Cropscience AG, Monheim, Germany

Title or Subject: Process for Preparing Substituted 2-Alkoxycarbonyl-3-aminothiophenes

The claims of this patent cover 4-alkoxycarbonyl-3-aminothiophenes and specifically mention compound **11**, whereas the title of the patent mentions the 2-alkoxy derivatives but this apparent discrepancy is ignored. The 4-alkoxy derivatives are intermediates in the manufacture of herbicides, and their preparation is said to involve the formation of undesired byproduct requiring complicated purification methods. The patent describes a process for preparing **11** by the method shown in Scheme 4. This begins with the reaction of **9** with HCO_2NH_4 to form **10**. This is recovered in 97% yield and 91% purity and then chlorinated using SO_2Cl_2 in PhCl to form **11** that is recovered as the HCl salt in 96% yield. It is reported that the product content is 58.7% determined as the free amine. The use of DCM as solvent gives a slightly lower yield (89%) and product content of 62.5%. When using Cl_2 in DCM in place of SO_2Cl_2 the yield of **11** is 59% with a product content of 42%. The efficiency of the reaction of SO_2Cl_2

Scheme 4[a]

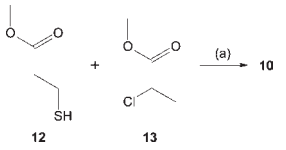


[a] Reagents and conditions: (a) (i) HCO_2NH_4, MeOH, reflux, 15 h; (ii) evaporate, dissolve in H_2O, extract with DCM; (iii) dry over Na_2SO_4, evaporate; (b) (i) SO_2Cl_2, PhCl, −10 °C, 2 h; (ii) evaporate at rt.

with **10** is claimed to be surprising since it is known that tetrahydrothiophenes do form Cl-complexes by S-chlorination.

The patent states that another surprising finding is that the intermediate enamine **10** can be produced in good yields using a catalytic amount of an ammonium salt if NH_3 is present. The claims include the option of carrying out the conversion of **9** to **10** in the presence of NH_3 gas. An example describes this procedure in which $MeCO_2NH_4$ and NH_3 are used and **10** is isolated in 96% yield with product content 73.6%. The patent also includes an example of an alternative method for preparing **10** by the route shown in Scheme 5. This starts from the thiol ester **12** and chloroester **13**. The reaction is carried out by adding **12** to a solution of NaOMe in MeOH followed by slow addition of **13** to the mixture. Xylene is then added, the MeOH is distilled off, and then more NaOMe/MeOH is added at 90 °C. HOAc is then added, and after workup of the intermediate, HCO_2NH_4 is added. **10** is isolated after an extended workup in 68% overall yield with a 72.5% content. There is no mention of this route in the patent or the claims, and it presumably proceeds via formation of **9**.

Scheme 5[a]



[a] Reagents and conditions: (a) (i) NaOMe, MeOH, 0−10 °C, 80 min; (ii) xylene, distill MeOH; (iii) NaOMe/MeOH, 90 °C, 75 min; (iv) HOAc, 80 °C; (v) H_2O, 70 °C; (vi) cool to rt, separate; (vii) extract in xylene, wash, dry, evaporate; (viii) HCO_2NH_4, MeOH, reflux, 12 h; (ix) concentrate, add H_2O; (x) extract in DCM, dry, evaporate.

Advantages

The novel process is claimed to give higher yields and fewer byproducts.

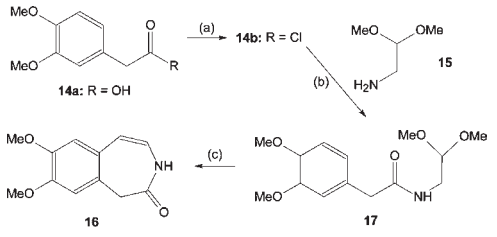
PATENT NO. U.S. 7,928,223

Assignee: Les Laboratoires Servier, Suresnes Cedex, France

Title or Subject: Process for the Synthesis of Ivabradine and Intermediates

This patent describes a process for the synthesis of **16** that is used to prepare **19**, an intermediate in the production of ivabradine **22**. This is available as Procoralan and is used to treat a number of heart-related problems. This patent is related to another from this company that describes the synthesis of **19** from **16** and has been reviewed previously (*Org. Process Res. Dev.* **2007**, *11*, 178). Scheme 6 outlines the process used to prepare **16**

Scheme 6[a]

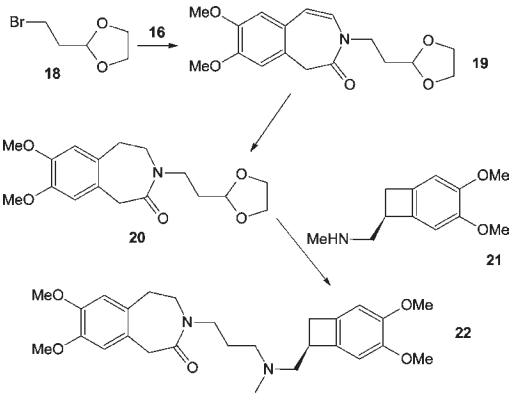


[a] Reagents and conditions: (a) (i) DCM, reflux; (ii) $SOCl_2$, reflux, 3 h; (b) (i) Et_3N, DCM, 10 °C; (ii) 15 °C, 2 h; (c) (i) 36 N H_2SO_4, <20 °C, 10 h; (ii) separate; (iii) NMP/H_2O

and this begins with the formation of the acyl chloride **14b** by reaction of **14a** with $SOCl_2$. This is not isolated, and the reaction solution is added to a mixture of **15** and Et_3N to produce **17**. This reaction solution is then treated with 36 N H_2SO_4 to effect ring-closure, giving **16**. The product is isolated by addition of 4/1 mixture of *N*-methylpyrrolidone (NMP) and H_2O to the acid phase. After filtration and drying **16** is obtained in 92.9% yield (based on **14a**) and having a purity >99.5%.

The claims of the patent cover the conversion of **16** to **22** by the route outlined in Scheme 7. The patent specifically mentions the reaction of **20** with **21** although there are no experimental details of any of the reaction steps.

Scheme 7[a]



[a] Reagents and condition: No details provided.

Advantages

The process gives an excellent yield of the desired product without the necessity of isolating intermediates between stages.

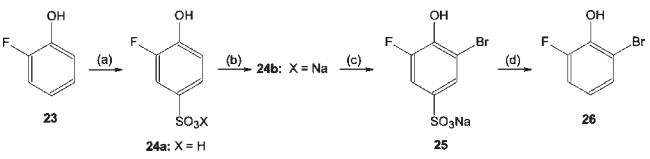
PATENT NO. U.S. 7,928,268

Assignee: Asahi Glass Company Limited, Tokyo, Japan, and Charna Chemicals Inc., Beijing, China

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

The title compounds are useful intermediates for the production of pharmaceuticals and electroluminescent displays. The patent describes a process for preparing compounds such as **28c** from **23**. Alternative processes start from 2-alkoxyphenols, and these are said to be expensive starting materials, producing large quantities of alkyl halides, therefore making them unsuitable for industrial production. The first stage in the process is the preparation of **26** by the route shown in Scheme 8. This starts with the sulphonation of **23** to form **24a** that is converted directly

Scheme 8[a]



[a] Reagents and conditions: (a) (i) 120 °C, add 98% H_2SO_4 over 0.5 h; (ii) 120 °C, 5 h; (b) (i) add brine at 100 °C, cool, filter, wash, dry; (c) (i) Fe, CCl_4, 55 °C; (ii) add Br_2 over 4 h, 50−60 °C; (iii) 55 °C, 2 h; (iv) cool, filter, wash, distill off solvent; (d) (i) 70% H_2SO_4, 180 °C, 5 h; (ii) cool to rt, extract into DCM; (iii) wash, dry, evaporate.

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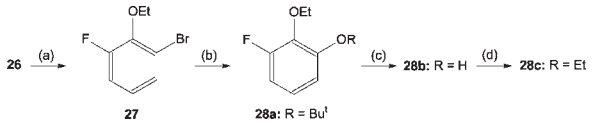
to **24b** without isolation. **24b** is isolated in 90% yield and then brominated using Br_2 and Fe powder to give **25**. All the reagents are dehydrated before use by washing twice with concd H_2SO_4, and **25** is recovered in 85% yield. In the last step the sulphonic acid group is removed using H_2SO_4, and **26** is recovered in 80% yield as an oily material.

In the next stage of the process **26** is converted to **28c** by the route outlined in Scheme 9. The first step is to form the ether **27** by reaction of **26** with EtBr, and the product is isolated as an oil in 70% yield. **27** is the converted to a Grignard reagent, and this is reacted with $PhCO_3Bu^t$ to give **28a** that is isolated in 50% yield. The formation of the Bu^tO group ensures that in the next step the EtO group is unaffected and so **28a** is then converted to **28b** by refluxing with $AlCl_3$ and the fluorophenol is isolated as an oil in 95% yield. In the last step alkylation of **28b** with EtBr forms **28c** that is isolated as an oily product in 75% yield.

Scheme 9[a]



[a] Reagents and conditions: (a) (i) NaOH, EtBr, EtOH, 10 °C; (ii) reflux, 3 h; (iii) extract in DCM, wash, dry, evaporate; (b) (i) Mg, THF, <60 °C; (ii) cool 0 °C, add $PhCO_3Bu^t$/THF; (iii) 25 °C, 2 h; (iv) add 3% HCl, extract in EtOAc; (v) wash, dry, evaporate; (c) (i) $AlCl_3$, DCM reflux, 2 h; (ii) cool, filter, evaporate; (d) follow step a.

The process was also used to prepare the methoxy compound **28d** (R = Me) in 82% yield by using Me_2SO_4 in step d of Scheme 9. **28c** can also be prepared from the iodo-analogues of **25** and **26**. Although the patent claims cover the synthesis of **28c**, there is one claim that specifically names the fluorophenol **28b**, thus suggesting that this is a novel compound.

Advantages

The process is claimed to suitable for the industrial production of the diethoxyfluorobenzene.

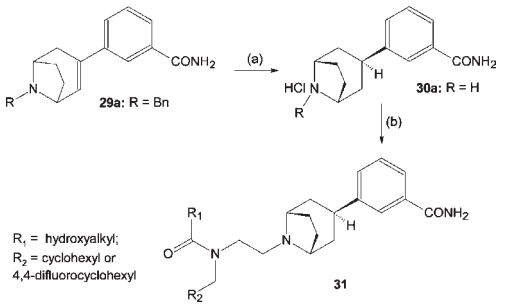
PATENT NO. U.S. 7,932,402

Assignee: Theravance Inc., San Francisco, California, U.S.A.

Title or Subject: Process for Preparing an Intermediate to Opioid Receptor Antagonists

The patent describes a process to prepare **30a** that is a key intermediate in the preparation of **31**, a mu opioid receptor antagonist used to treat gastrointestinal problems (Scheme 10). The objective of the work described is to minimise the number of steps in the synthesis of **30a** and maintain stereospecificity. The main focus of the patent is the stereospecific hydrogenation of **29a** to give **30a**. This is carried out by initially mixing **29a** with an acid such as HCl and then purging the mixture with N_2 gas. The catalyst is then added and the mixture purged with H_2 gas. The purging steps are a critical aspect of the process and are covered by the claims. The patent states that the time for H_2 purging on a kilo scale is of the order of 20−30 min and about 5 min on the laboratory scale. The hydrogenation catalyst is Pd/C used at about 10 wt %. The H_2 pressure and reaction time have a big impact on the reaction selectivity. For example at 1.36 atm above atmospheric pressure and a 40-h reaction time the ratio of endo/exo is 85/15, and the yield of the crude HCl salt of **30a** is around 95%. At 0.34 atm above

Scheme 10[a]

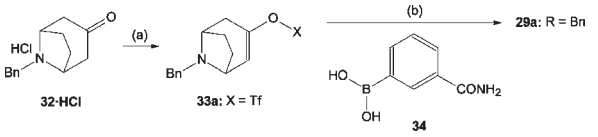


[a] Reagents and conditions: (a) (i) 6 M HCl, EtOH, N_2 purge, rt, 5 min; (ii) Pd/C, H_2 purge, rt, 5 min; (iii) H_2, 1.36 atm, 50 °C, 40 h; (iv) cool, filter, evaporate; (v) EtOH, 60 °C; (vi) cool to 30 °C, seed; (vii) stir at rt, 16 h; (viii) add MeTHF, rt, 4 h, filter; (b) see U.S. 7,522,508.

atmospheric pressure and over only 5 h of reaction time the ratio is 93/7 with a yield of 99%. The product is purified by crystallisation from EtOH/MTBE and isolated in 75% yield containing 0.4% exo isomer.

The patent also describes the route used to prepare **29a**, and this is outlined in Scheme 11. The comprehensive workup details have been omitted due to space limitations. The HCl salt of **32** is converted to the free base, and then this is converted to **33** by initial treatment with NaHMDS at −20 °C, followed by Tf_2NPh. **33** is isolated in 96% purity and then reacted with **34** catalysed by a $Pd(OAc)_2$/phosphine catalyst and KF. An example of the phosphine is 1,1′-bis(diphenylphosphino)ferrocene. After work-up the desired benzamide **29a** is isolated in 78% yield and 98.5% purity. There is also an example that proceeds via the Ts ester **33b** (X = Ts) that is prepared from **32** and LiHMDS followed by Ts_2O.

Scheme 11[a]



[a] Reagents and conditions: (a) (i) 4 M NaOH, EtOAc, 30 °C, 1 h; (ii) NaHMDS, THF, −20 °C, 75 min; (iii) $(Tf)_2NPh$, −20 °C, 1 h; (b) (i) $Pd(OAc)_2$/phosphine catalyst, KF, THF, reflux, 2 h.

The patent also describes the preparation of the **29b** (R = H) that proceeds via the BOC-protected amine **35** and is outlined in Scheme 12. Again, only the main reagents are shown. In the first step **32** is converted to **35** that is isolated in quantitative yield, and from this the triflate ester **36** is obtained in 82% yield. Reaction of **36** with **34** in the presence of Pd/phosphine catalyst gives **37** in 66% yield. In this step the catalyst system was formed from Pd_2dba_3 and $(cyclohexyl)_3P \cdot HBF_4$. Finally treatment of **37** with TFA produces **29b** (R = H) in 66% yield.

The patent provides ^1H NMR data for most intermediates shown in the reaction schemes and also summarises the HPLC methods used to analyse the products.

Advantages

The process gives good yields of the desired endo product with minimum levels of the exo compound.

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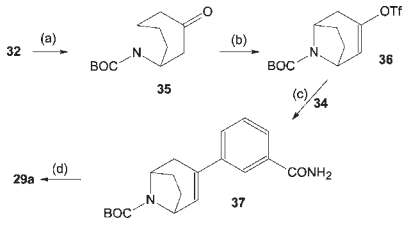
Scheme 12[a]



[a] Reagents and conditions: (a) (i) $(BOC)_2O$, Pd/C, EtOAc, 3.4 atm H_2, 20 °C, 28 h; (b) (i) NaHMDS, THF, −74 °C, (ii) $(Tf)_2NPh$, −20 °C, 1.5 h; (c) Pd/phosphine, KF, DMF/THF, 70 °C, 2 h; (d) TFA, rt, 0.5 h.

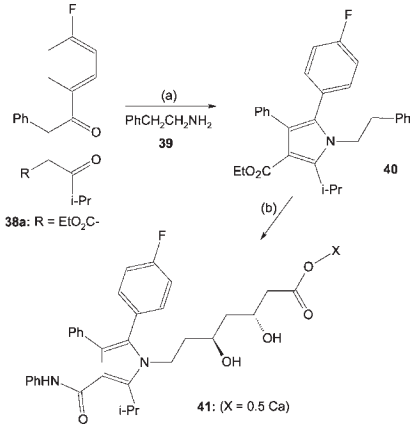
PATENT NO. U.S. 7,932,403

Assignee: Ratiopharm GmbH, Ulm, Germany

Title or Subject: Process for Preparing Pyrrole Derivatives and Intermediates

This patent covers a process to prepare pyrrole compounds such as **40** that are intermediates for the preparation of atorvastatin **41** that is used to treat high cholesterol levels. Several methods for preparing **41** are known and patents have been reviewed previously (*Org. Process Res. Dev.* **2009**, *13*, 11). Some of the alternative processes focus on the synthesis of the 3,5-hydroxyheptanoic acid side chain in **41** while others are concerned with formation of the pyrrole ring. This patent focuses on the pyrrole ring and states that alternative methods often use the Paal−Knorr reaction using a 1,4-diketone containing the PhNHCO− group that is in the desired position in **41**. However, the patent states that the desired intermediate is difficult to obtain, and so improved methods are needed. The approach taken in this process is to introduce the PhNHCO− group after forming the pyrrole ring. The synthesis of **40** is shown in Scheme 13 and involves the reaction of the 1,4-diketone compound **38a** with the amine **39** in the presence of pivalic acid (PA). In refluxing heptane/THF/PhMe with azeotropic removal of H_2O, and using a 1:1:1 ratio of **38a**/**39**/PA, the process gave a 72.4% yield of **40**. After refluxing for 24 h and a ratio of 1:1.5:1.5, the yield was 68.5%. Without a solvent and using a 1:1:2 ratio, the yield of **40** after 48 h at 125 °C was 65%. Details of the product recovery are not reported.

Scheme 13[a]

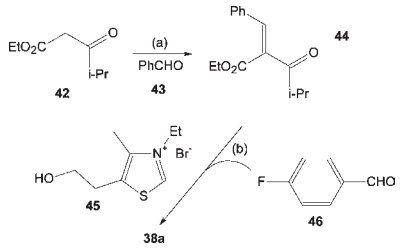


[a] Reagents and conditions: (a) (i) heptane/THF/PhMe, reflux, 96 h; (b) no details provided.

The patent examples report the use of **39** and also claim other amines may be used including NH_3. However, substituted amines containing a THP or 3,5-hydroxyheptanoate substituents are excluded presumably to avoid patent conflicts.

The patent also provides details for the synthesis of the starting compound **38a** in a two-step process that is outlined in Scheme 14. In the first step **42** is condensed with **43** in the presence of β-alanine while removing H_2O azeotropically. After workup, the product **44**, is isolated by distillation as a brown oil in 75% yield and then reacted with **46** in the presence of **45** and Et_3N. This produces the diketone **38** that is isolated by vacuum distillation as an oily product that slowly solidified. Part of the workup involves bubbling air through the solution for 24 h to oxidise the remaining **46**. The solvent at this stage is DCM, and since this is extremely volatile, it is necessary to add more to compensate for losses. This step is clearly going to have a large impact on control of VOCs at any industrial plant where this process is carried out. The patent ignores this major problem and yet emphasizes the environmental nature of the synthesis by pointing out that there is no solvent in step 2 and step 1 uses a nontoxic catalyst and does not require a recrystallisation stage.

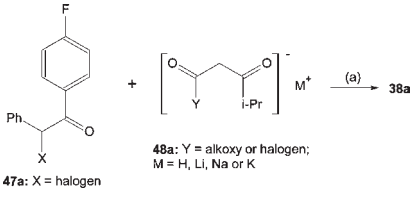
Scheme 14[a]



[a] Reagents and conditions: (a) (i) β-alanine, HOAc, PhMe, reflux, 24 h; (ii) cool, extract in EtOAc; (iii) wash in 1 M HCl, aq $NaHCO_3$, brine, dry, evaporate; (iv) distill; (b) (i) add Et_3N, rt; (ii) 70 °C; (iii) cool rt, add EtOAc/H_2O; (iv) step (a) (iii); (v) add DCM and silica gel, rt, 10 min, filter;(vi) bubble in air, rt, 24 h; (vii) wash in aq $NaHCO_3$, dry, evaporate.

The patent claims cover the above route for preparing **38a** and also cover an alternative method outlined in Scheme 15, but there are no experimental details. The route involves the reaction of **47a** with **47b**, and this is said to be carried out in an ether solvent such as THF.

Scheme 15[a]



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

The salt **48a** is preferably prepared in situ and **47b**; it is stated that it can be obtained by cleavage of **38b** (R = PhNH−) with H_2O_2 and **38b** that is apparently commercially available. A confusing series of claims in the patent include the statements that **47a** (R = halide) can be obtained by halogenation of **47b** (R = H) and **47b** is obtained by cleavage of **38a**. However, since the idea is to prepare **38a** this circular argument seems to be a prime example of a chicken and egg situation. What it means is not at all obvious.

dx.doi.org/10.1021/op200209d |*Org. Process Res. Dev.* 2011, 15, 957–969

Advantages

The process is claimed to have fewer steps than alternatives and is economically and environmentally advantageous but does have a potentially serious VOC problem.

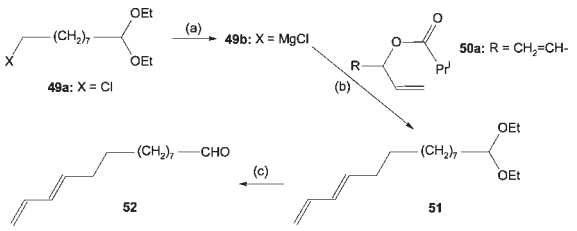
PATENT NO. U.S. 7,932,410

Assignee: Bedoukian Research Inc., Danbury, Connecticut, U.S.A.

Title or Subject: Production of Pheromones and Fragrances From Substituted and Unsubstituted 1-Alken-3-yl Alkylates

The patent discusses the damage caused by various insects on fruit trees, and the compounds covered by this patent are of interest in helping to deal with such problems. Some of the compounds are also useful as fragrances. An objective of the patent is to provide a method of producing the desired compounds with a high *trans*-isomer content since this is generally more effective as a pheromone. Other synthetic methods are said to be available but do not seem to give the desired improvements in the amount of the *trans*-isomer. The route used to prepare the compounds such as **52** is outlined in Scheme 16. The first step is conversion of **49a** to the Grignard reagent **49b** that is then reacted with isobutyrate ester **50a** in the presence of a copper catalyst such as $LiCuBr_2$. The product is the acetal **51** that is treated with HCO_2H to give **52** in 94% isolated yield with an *E*/*Z* ratio of 76:24. The key to achieving a high trans content in the product is to ensure that either the starting compound **49a** or the Cu catalyst contains a Br atom and preferably in the Cu catalyst. This is added at the rate of about 4 mol % and is preferably added to the ester **50a** before addition of the Grignard. The patent states that if **50a** is an ester of an acid containing at least 4 C atoms then the overall yield of product is higher than when using an acid with fewer C atoms.

Scheme 16[a]



[a] Reagents and conditions: (a) Mg, THF, reflux, 4 h; (b) (i) $LiCuBr_2$, THF, <30 °C, 0.25 h; (ii) aq citric acid, separate, H_2O wash; (iii) aq NaOH to pH >7, evaporate, distill; (c) HCO_2H, heptane, rt.

The patent claims cover the preparation of a number of specifically named compounds using the same procedure, and the examples cover five of these. In place of the acetal **49a** the starting material is an alcohol or THPO derivative, and the isobutyrate ester used has R = Et or Bu^n.

Advantages

The process gives high yields of the desired *trans*-isomer of these products.

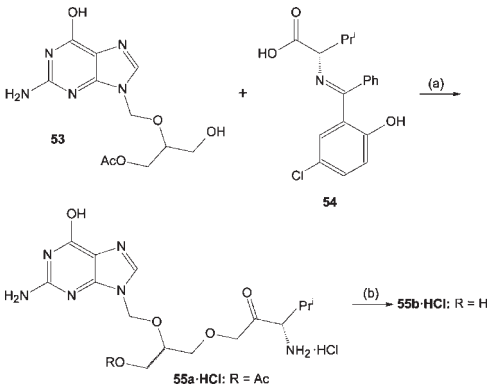
PATENT NO. U.S. 7,935,818

Assignee: Fidia Farmaceutici S.p.A., Abano, Italy

Title or Subject: Process for the Preparation and Purification of Valgancyclovir Hydrochloride

The title compound, **55b·HCl**, is an antiviral agent particularly effective against cytomegalovirus, a herpes virus. The known routes for preparing **55b·HCl** are said to be cumbersome and can involve protection and deprotection steps that reduce yields. The patent reports a surprising finding that the reaction of alcohols with L-valine adducts of certain ketones provides good stereochemical control and directly yields the desired compound. Scheme 17 shows the route used to prepare **55b·HCl** by the condensation reaction between the alcohol **53** and the valine adduct **54** that is carried out in DMF in the presence of HOBt, DMAP, and DCC or similar reagent. The reaction produces the HCl salt of the acetoxy compound **55a** that is isolated in a yield of around 44% and then hydrolysed to give **55b** as the HCl salt that is isolated in 75% yield but of unspecified purity.

Scheme 17[a]

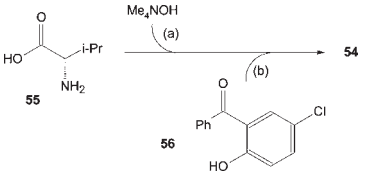


[a] Reagents and conditions: (a) (i) HOBT, DCC, DMAP, DMF, <5 °C, 1.5 h; (ii) filter, add MeOH/H_2O/2 M HCl; (iii) filter, wash, dry; (b) 2 M HCl, MeOH/H_2O, 35 °C, 24 h; (ii) cool to rt, Et_3N to pH 3−4; (iii) concentrate, add Pr^iOH, filter.

The purification of the crude **55b·HCl** is carried out by dissolving the salt in H_2O and acidifying at 5−10 °C using an unspecified acid. The precipitate is recovered and washed in EtOAc and then treated with two portions of Pr^iOH. After filtration and washing, the solid is dissolved in H_2O and charcoal added. The charcoal is filtered off, and then the solution is freeze-dried; the salt **55b·HCl** is isolated in 73% based on the crude product, but its purity is not reported. The isolation of the salt by freeze-drying is a novel aspect of the patent. The patent reports that the purification method used prevents its degradation that can occur in aqueous media.

The compound **53** can be prepared by a method described in U.S. 5,205,535, and the L-valine adduct **54** is prepared by the method outlined in Scheme 18. L-valine is treated with Me_4NOH, and after the solvent volume is reduced, **56** is added. The reaction takes place at room temperature over a few days, and the purified product is recovered as a yellow solid in 88% yield.

Scheme 18[a]



[a] Reagents and conditions: (a) (i) EtOH, rt; (ii) distill off 50% of EtOH; (b) (i) rt, few days; (ii) evaporate; (iii) dissolve in H_2O, wash in EtOAc; (iv) add EtOAc, 20% citric acid to pH 5.5, 10 °C; (v) extract in EtOAc, wash, dry, evaporate; (vi) slurry with cyclohexane, filter, dry.

dx.doi.org/10.1021/op200209d |*Org. Process Res. Dev.* 2011, 15, 957–969

The patent includes SEM pictures as well as DSC and XRD patterns of both crystalline and lyophilized **55b·HCl**.

Advantages

The process as described does have only two steps, but the yield is less than 50%, and the preparation of the starting materials may reduce the overall yield even more.

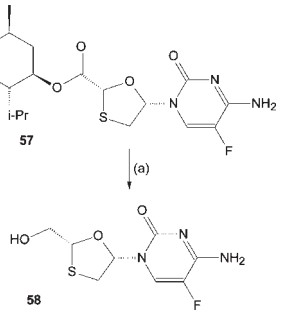
PATENT NO. U.S. 7,939,660

Assignee: Archimica S.r.l., Milan, Italy

Title or Subject: Process and Intermediates for Preparing Emtricitabane

Emtricitabane **58** is an antiviral drug for the treatment of HIV, available as Emtriva, and was formerly known as Coviracil. It can be synthesised by a number of methods that either give a racemic mixture or are stereoselective. A stereoselective synthesis of **58** is disclosed in U.S. 5,696,254 that proceeds via the production of the intermediate **57** (Scheme 19). The earlier patent reports that **57** is a filtrable solid, but the current patent has shown experimentally that this is not the case; the compound is a gel that cannot be isolated without recourse to chromatography. Hence, the entire process reported in that patent is claimed to be unsuitable for industrial production. The current patent describes a process based on the production of a salt of **57** that can be isolated, and so the new process is claimed to be industrially viable. The preparation of **58** from **57** is by reduction using $NaBH_4$ as shown in Scheme 19. There is some confusion in the patent on this reaction because the example describes the use of the free base **57** although the claims and text do specify that the oxalate salt is used. The yield of **58** is is 40%, but the purity is not reported.

Scheme 19[a]



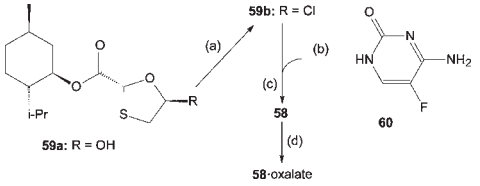
[a] Reagents and conditions: (a) (i) $KHCO_3$, K_2HPO_4, THF/MeOH/H_2O, rt; (ii) $NaBH_4$, 30% aq NaOH, <5 °C, 3 h; (iii) 25 °C, 1 h; (iv)37% HCl to pH4.0; (v) evaporate solvents, extract in PhMe; (vi) 30% aq NaOH to pH 7.4, (vii) evaporate H_2O, add Pr^iOH, evaporate, add Pr^iOH; (viii) filter, evaporate, crystallise from MeOH/Pr^iOAc.

The preparation of several salts of **57** is reported, and the preferred oxalate salt is obtained by the reaction shown in Scheme 20. The first step is formation of the chloro compound **59b** by treatment of **59a** with $SOCl_2$. This is not isolated and is reacted with the silylated form of **60** to produce **58** that is then converted to its oxalate salt in a yield of around 46%. The composition of the salt is not reported nor is the purity; thus, it is difficult to say what is the exact yield. Information regarding the purity of both intermediates and products is surely needed to justify the claims of process improvements.

Advantages

The process provides a method of isolating a key intermediate in the synthesis, and this enables the final product to be more easily purified.

Scheme 20[a]



[a] Reagents and conditions: (a) $SOCl_2$, DMF, MsOH, DCM, 15 °C, 4 h; (b) (i) HMDS, MsOH, PhMe, reflux 3 h; (ii) evaporate, add DCM; (iii) repeat step (ii); (c) (i) Et_3N, reflux, 18 h; (ii) cool to 25 °C, add H_2O, separate; (iii) wash in acidified H_2O (×5), evaporate; (d) (i) $(CO_2H)_2·2H_2O$, MeOH, 25 °C, 3 h; (ii) filter, wash, dry.

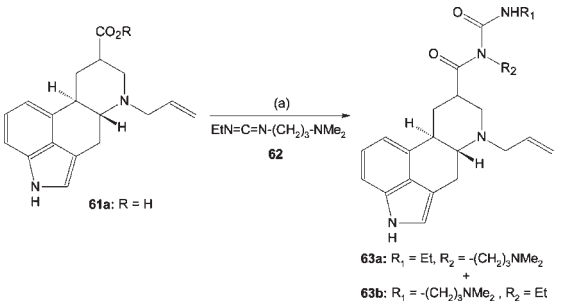
PATENT NO. U.S. 7,939,665

Assignee: Apotex Pharmachem Inc., Brantford, Canada

Title or Subject: Efficient Process for the Preparation of Cabergoline and its Intermediates

Cabergoline **63a** is used to treat Parkinsonism; there are a number of processes for its preparation, and one has been reviewed (*Org. Process Res. Dev.* **2007**, **11**, 802). The comprehensive patent reviews several processes and states that none allow for the preparation of **61a** (R = H) that is described as an advanced intermediate. There is a report that **61a** can be prepared starting from lysergic acid, and since this is a controlled substance any commercial process would have severe restrictions. Hence, the patent discloses a process for preparation of **63a** via the intermediate **61a** that does not start from a controlled substance. The preparation of **63a** from **61a** by reaction with the diimide **62** is shown in Scheme 21. The procedure is carried out by contacting the reagents with Et_3N in DCM. The reaction produces **63a** and around 20% of the byproduct **64b**. **63a** is isolated by column chromatography (ColC) in 54.7% yield and >99% purity.

Scheme 21[a]



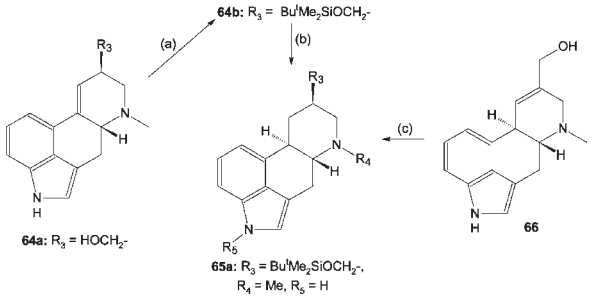
[a] Reagents and conditions: (a) (i) Et_3N, DCM, rt, 20 h; (ii) concentrate, extract in MTBE, wash, evaporate.

The patent also describes how the byproduct **63b** can be recovered and converted to **61a** or its methyl ester **61b** so that process losses are minimised. Hydrolysis of **63b** using NaOH/MeOH forms **61a** in 82% yield, and reaction with MeOH in the presence of Et_3N gives the methyl ester in 96.5% yield.

The preparation of **61a** is a substantial part of the work described in the patent, and it is only possible to cover limited details here. This has been divided into stages for clarity, and the first stage is the preparation of **65a** from either **64** or **66** (Scheme 22). Both routes are covered in the patent claims, but

dx.doi.org/10.1021/op200209d |*Org. Process Res. Dev.* 2011, 15, 957–969

Scheme 22[a]

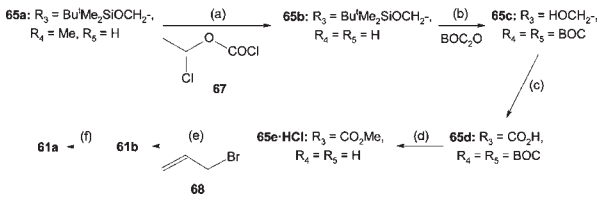


[a] Reagents and conditions: (a) TBDMS-Cl, Et_3N, DMF, rt, 3 h; (b) Pd/C, DMF, H2, 3.5 atm, 70 °C; (c) no details.

there is only experimental information for the conversion of **64a**. The first step is the protection of the OH group by silylation, and **64b** is recovered in 96.5% yield. This is then catalytically hydrogenated using Pd/C, and **65a** is isolated in 91% yield. In an alternative approach the hydrogenation is carried out first, followed by the protection step. **65a** can also be prepared from **66** by first protecting the OH followed by hydrogenation. There is no experimental information on this conversion in the patent.

65a is then used in the preparation of **61a**, and Scheme 23 outlines the next stage. The first step in this is the demethylation by reaction with **67** giving **65b** that is isolated in 78% yield after crystallisation from DCM. The two NH groups are then protected in a two-stage procedure followed by removal of the silyl group, producing **65c** in 80% yield after crystallisation from MeCN. In the next step oxidation of **65c** using TEMPO and $PhI(OAc)_2$ produces the acid **65d** in 88.5% yield. In the last step of this scheme **65d** is esterified, and the amines are deprotected using $SOCl_2$ and MeOH, giving **65e** that is recovered as the HCl salt in 94.5% yield. In the next stage of the synthesis of **61a** the allyl group is introduced into **65e** by reaction with **68** in the presence of Et_3N. The reaction initially forms the ester **61b** that is recovered in crude form and then hydrolysed with aq NaOH to give **61a** in 85% isolated yield.

Scheme 23[a]



[a] Reagents and conditions: (a) (i) DCM, <10 °C; (ii) rt, 15 h; (iii) MeOH, 60 °C, 4 h; (b) (i) Et_3N, DCM, <10 °C, 5 h; (ii) Et_3N, DMAP, $(BOC)_2O$, DCM, 25 °C, 5 h; (iii) Bu^t_4NF, THF, rt, 6 h; (c) TEMPO, $PhI(OAc)_2$, H_2O, DCM rt, 16 h; (d) $SOCl_2$, MeOH, 55 °C, 5 h; (e) (i) Et_3N, DMF, 30 °C, 5 h; (ii) H_2O, <5 °C, 3 h; (f) (i) aq NaOH, MeOH, 30 °C, 3 h; (ii) HCl to pH 6.5, <5 °C, 2 h; (iii) filter, wash, dry.

Advantages

The process provides a new route to making cabergoline and uses commercially available reagents. The multistep process has very good yields and also enables a major byproduct to be recovered and recycled.

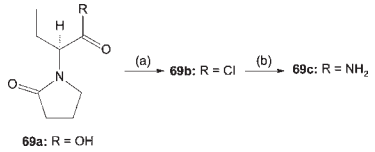
PATENT NO. U.S. 7,939,676

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

Title or Subject: Process for the Preparation of Levetiracetam

Levetiracetam **69c** is an anticonvulsant medication used to treat epilepsy, and it is the *S*-enantiomer that is used since it is reported to be 10 times more powerful than the *R*-enantiomer. Several processes are known for its preparation, and the patent claims to have discovered an improved process. All of the alternative processes are said to require the isolation of intermediate products before finally reacting with NH_3 to give the desired final product. The patent claims a surprising finding that the preparation of **69c** from **69a** can be carried out in a one-pot process if **69a** is first treated with a substoichiometric amount of a so-called activating agent before reaction with NH_3 (Scheme 24). The activating agent is preferably $SOCl_2$ although the claims also cover PCl_5, $POCl_3$, and $COCl_2$. The reaction presumably proceeds via the acyl chloride **69b** and is carried out by using about 0.5 mol of $SOCl_2$ per mol of **69a**. The process is carried out by adding $SOCl_2$ to **69a**, and after following the conversion of the acid by HPLC, the volatiles are removed. The mixture is then neutralised by bubbling NH_3 into the mixture at atm pressure, and solids are filtered off. The mixture is then pressurised with NH_3 to complete the reaction in about 0.5 h, and the crude product is recovered in 73.1% yield containing 1.171% *R*-enantiomer. After refluxing in Me_2CO the purified material is isolated in 60.0% yield containing 0.01% *R*-enantiomer. When the process is repeated without initial neutralisation, the yield of crude product is 73.1% and contains 2.21% *R*-enantiomer. The patent reports the effect of variable quantities of $SOCl_2$ on conversion of **69a** and yield of **69c**. By using twice the quantity, it was found that about 13% of **69a** had decomposed and substoichiometric amounts do not substantially reduce the conversion time or yield. Even catalytic quantities of $SOCl_2$ (0.05 mol) gave almost quantitative conversion of **69a** although the reaction time time increases to 24 h.

Scheme 24[a]



[a] Reagents and conditions: (a) (i) $SOCl_2$, MeOH, 45 °C, 1 h; (ii) evaporate, 40 °C; (iii) MeOH; (b) (i) 1 atm NH_3, to pH 5, 20 °C; (ii) 20 °C, 1 h, filter; (iii) NH_3, 3 bar, 20 °C; (iv) filter, evaporate, add Me_2CO, evaporate; (v) Me_2CO, reflux, 0.5 h; (vi) cool, 0 °C, filter; (vii) repeat steps (v) and (vi).

The patent states that the removal of volatiles after the activation step and then a two-stage neutralisation together improve the final product purity by reducing racemisation of **69a** that could be catalysed by high acidity. A higher level of $SOCl_2$ leads to both higher acidity and residual salt levels that would contaminate **69c** and hinder its purification.

Advantages

The process gives improved productivity and purity of the final product.

PATENT NO. U.S. 7,939,698

Assignee: Lonza AG, Basel, Switzerland

dx.doi.org/10.1021/op200209d |*Org. Process Res. Dev.* 2011, 15, 957–969

Title or Subject: Method for Grignard-Type Reactions in Microreactors

The use of microreactors is of increasing interest both for investigating reactions and for producing reagents and products. This patent describes a procedure for improving Grignard reactions that are carried out in continuous microreactors. The process is carried out in a continuous flowing microreactor into which the reagents are injected at multiple points along the reactor. One of the key findings disclosed in the patent is that the yield of the reaction increases with the number of injection points. The other key point is that the reactions are carried out using glycol ethers as reaction solvents especially for temperatures at 0 °C or less. Grignard reagents can flocculate, coagulate, or even crystallise and cause plugging and blocking in microreactors. The glycol ethers prevent these problems and also extend the storage time of pre-prepared Grignard solutions. The preferred solvents are DME or diglyme and can be used with other solvents but one of these should be present at up to 50%. The microreactor dimensions are covered in the patent claims. The cross-section of the reactor is 0.1 cm^2 or less, and the flow path is between 10 and 200 μm. The patent examples cover the two reactions listed below:

$$MeCHClCOCl + PhCH_2CH_2MgBr \rightarrow MeCHClC(O)CH_2CH_2Ph \quad (1)$$

$$(CO_2Me)_2 + EtMgCl \rightarrow EtC(O)CO_2Me \quad (2)$$

The examples are carried out in different types of microreactors using mixtures of diglyme and THF and a range of flow rates and temperatures. The systems had up to six injection points for either of the two solutions, and the reactions are carried out with and without cooling. The reactor effluent is quenched with HCl, collected, and then analysed. The results show that a higher yield, conversion, and selectivity are possible if there are between three and six injection points. The method allows better control over the exotherm of the reactions, and this in itself generally improves reaction selectivity and yield. The patent claims cover the use of the process in a large number of Grignard reactions, but there are no examples.

Advantages

The procedure improves the control of Grignard reactions, giving better overall yields and is especially useful in low-temperature reactions.

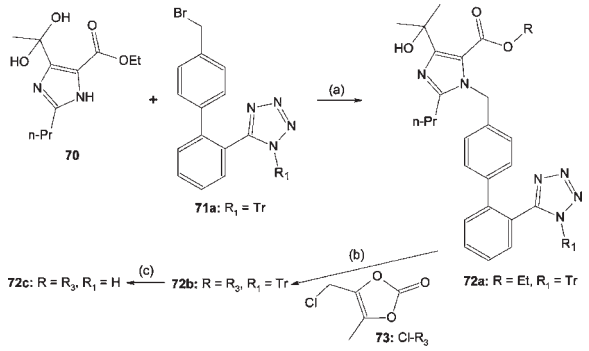
PATENT NO. U.S. 7,943,779

Assignee: KRKA, Novo Mesto, Slovenia

Title or Subject: Process for the Preparation of Olmesartan Medoxomil

The subject of this patent **72c** is used to treat hypertension and related diseases. Alternative processes for preparing **72c** are summarised, and many involve the use of ColC and additional crystallisation steps. The process disclosed in this patent avoids these requirements by using MeCN as reaction solvent in place of DMF that is used in alternative processes. The synthetic route developed is shown in Scheme 25, and the first stage is the alkylation of **70** with **71a** in MeCN to produce **72a**. The reaction is carried out in the presence of a base such as K_2CO_3, and the crude product is recovered in 89% yield. The next step is the base hydrolysis of the Et ester group in **72a**, giving the acid that is not isolated but converted to **72b** by reaction with **73**. The last stage is removal of the trityl group in **72b** to produce **72c**. This is carried out without isolation of **72b** by treatment with concd HCl, and the final yield of crude **72c** is 75%.

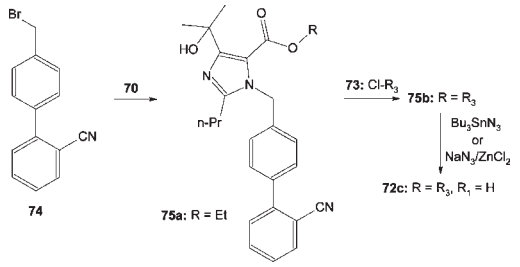
Scheme 25[a]



[a] Reagents and conditions: (a) (i) K_2CO_3, MeCN, reflux, 7 h; (ii) concentrate, (iii) 25 °C, 16 h; (iv) filter, wash; (v) H_2O, rt, 1.5 h, filter, dry; (b) (i) NaOH, Me_2NOAc, rt, 20 h; (ii) K_2CO_3, Me_2NOAc, 0 °C; (iii) 50 °C, 2 h; (iv) extract in EtOAc/10% brine, 10 °C, wash, dry, evaporate; (c) (i) concd HCl, EtOH, 25 °C, 3 h; (ii) H_2O, NaOH to pH 5; (iii) extract in EtOAc, dry, evaporate; (v) EtOAc, 20 °C, 1 h; (vi) filter, wash.

The purification of **72c** is by crystallisation, and several small-scale examples are described using *n*-heptane, Me_2CO, MEK, THF, EtOH, Pr^iOH, Bu^iOH, and DCM. Heptane gave a very poor yield of 22%, and the highest yield was from Pr^iOH giving a 98% recovery of crystalline **72c** that was the same as a sample reported in the literature. The actual analysis is not reported, although the patent claims that the process gives **72c** with HPLC purity as high as 99.9%. The patent also outlines an alternative route to preparing **72c** using **74** as an alternative alkylating agent to **71a** in the first step. Unfortunately, there are no experimental details for this route that is summarised in Scheme 26.

Scheme 26[a]



[a] Reagents and condition: No details provided.

Advantages

The process does not require the use of ColC and gives good yields of high-purity product.

PATENT NO. U.S. 7,943,780

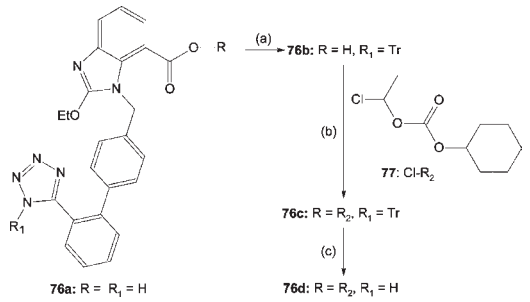
Assignee: Matrix Laboratories Ltd., Secunderabad, India

Title or Subject: Process for the Preparation of Candesartan Cilexetil

Candesartan **76a** is another drug used to treat hypertension, but it is poorly absorbed by the body; thus, the prodrug **76d** was developed. A patent covering an alternative synthesis of **76d** has been reviewed previously (*Org. Process Res. Dev.* **2007**, *11*, 178). Some processes for preparation require the use of ColC; thus, an

objective of the work described in this patent was to avoid this. The process is shown in Scheme 27 and starts with the protection of the tetrazole group by treatment with trityl chloride to give **76b** that is isolated in 83.8% yield. This is then converted to **76c** by reaction with **77** in the presence of K_2CO_3 and KI. **76c** can be isolated from the reaction as a solid containing EtOH and then treated with $B(OH)_3$, giving **76d** that is isolated in 78% yield. Alternatively **76c** is prepared in situ and directly converted to give **76d** that is recovered in 72.5% yield. Crystalline **76d**, identified as Type C, is obtained by refluxing the crude solid in Me_2CO, and then crystals are obtained in 90% yield by addition of H_2O and cooling.

Scheme 27[a]



[a] Reagents and conditions: (a) (i) TrCl, Et_3N, DCM, 25 °C; (ii) reflux, 2 h; (iii) cool <35 °C, add H_2O; (iv) separate, extract in DCM, wash, evaporate; (v) EtOAc, reflux, 2 h; (vi) cool, filter, wash, dry; (b) (i) K_2CO_3, KI, DMSO, 65 °C, 2.5 h; (ii) PhMe/H_2O, 65 °C; (iii) distill PhMe <60 °C; (iv) EtOH, 0.5 h; (v) distill <60 °C; (vi) EtOH, 30 °C, 2 h; (vii) filter, wash, dry; (c) (i) $B(OH)_3$, EtOH, 30 °C; (ii) reflux, 8 h; (ii) concentrate, cool <30 °C; (iii) *n*-hexane, 30 °C, 8 h; (iv) filter, wash, dry.

Advantages

The process gives high-purity product without the need to use ColC.

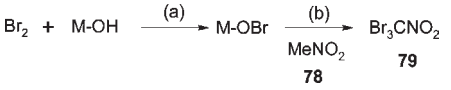
PATENT NO. U.S. 7,943,806

Assignee: Bromine Compounds Ltd., Beer-Sheva, Israel

Title or Subject: Process of Preparing Bromopicrin

Bromopicrin **79** is used to prepare a wide range of compounds such as antimicrobials, biocides, and antiseptic agents that are used in horticulture, agriculture, and general industry. Methods for preparing **79** and related compounds have been known for decades, and many have significant disadvantages. The patent mentions that picric acid can be used to prepare **79**, and since this is a potential explosive, there are serious safety issues in its use. This patent describes a method for preparing **79** that avoids using picric acid and involves the direct bromination of **78**. The reaction is carried out in the presence of water, and an aqueous solution base such as NaOH or KOH is slowly added to the mixture. A key aspect of the process is ensuring careful addition of the base such that an excess of base does not remain in the solution during addition. An organic solvent is not used in the process, and one reason for using water is that it acts as a heat sink for the exothermic reaction. It is postulated that, in the presence of water and base, the Br_2 produces the hypobromite M−OBr, and this reacts with **78** to form **79** as shown in Scheme 28. Effective mixing of the reaction medium is needed, and experiments in a 1-L laboratory reactor and a 16-L mini-pilot plant are described. The reaction can be monitored by the disappearance

Scheme 28[a]



[a] Reagents and conditions: (a) H_2O, 20−25 °C; (b) 22−45 °C, 4−6 h.

of the red-brown colour and formation of a yellow mixture. The crude product is recovered as the lower heavy layer that contains 98.3% of **79** that equates to a 94% yield. Unusually, the patent provides two detailed mass balances for the 1- and 16-L examples. These show the amounts of reactants, workup reagents, and waste products. The patent does not give details if the product is further purified although distillation and extraction are mentioned as recovery techniques. However, it later states that these methods are not required because the purity of **79** is so high (96−99%), and so this reduces the need for extra equipment and means lower production costs. The patent does provide details about the recovery of the aqueous wastes and its subsequent treatment.

Advantages

The process gives very good yields of high-purity product without the use of picric acid.

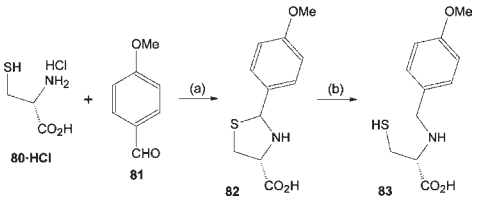
PATENT NO. U.S. 7,947,850

Assignee: Inspire Pharmaceuticals Inc., Durham, North Carolina, U.S.A.

Title or Subject: Process for the Preparation of 3,4-Disubstituted Thiazolidin-2-ones

This patent describes the synthesis of a range of compounds some of which are used as pharmaceutical intermediates in the synthesis of compounds known as latrunculins. These are naturally occurring compounds found in marine sponges and can be used to treat glaucoma. Current processes for the manufacture of synthetic materials are said to be lengthy and impractical. The current patent discloses a method of preparing the title compounds **85a**−**e**, although the claims of the patent actually cover the preparation of the intermediate **83** by the route outlined in Scheme 29. This synthesis starts by addition of a solution of the aldehyde **81** to the HCl salt of L-cysteine **80**. The reaction takes place in the presence of NaOAc to produce **82** that is recovered in 90% yield, and reduction of **82** produces **83**. The reduction is carried out by adding a solution of **82** in 0.62 M K_2CO_3 to a cooled mixture of $NaBH_4$ in aqueous basic solution; after workup **83** is obtained in 68% yield.

Scheme 29[a]



[a] Reagents and conditions: (a) (i) NaOAc, H_2O, EtOH, <30 °C, 0.5 h; (ii) EtOH, 30 °C, 1 h; (iii) filter, wash, dry; (b) (i) $NaBH_4$, 0.25 M NaOH, 0.62 M K_2CO_3, H_2O, 30 °C, 1 h; (ii) cool 0 °C, add HOAc to pH 5; (iii) filter, wash, dry.

The patent also describes the preparation of other analogues of **83** by the procedure outlined in Scheme 29. The products prepared are those in which the amino substituents are benzyl,

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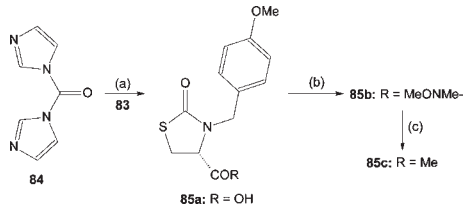
3,4-dimethoxybenzyl, and 4-fluorobenzyl. The preparative details are not given, but ^{1}H NMR data for the products are reported.

The next stage of the process to prepare the title compounds is the synthesis of **85a** from **83**. This is shown in Scheme 30 and involves carbonylation using **84** in the presence of K_2CO_3 to produce **85a**. This is isolated as a solution in Pr^{i}OAc that is dried by azeotropic distillation. The solution is then treated successively with *N*-methylmorpholine (N-MeM), pivaloyl chloride (PivCOCl), and MeONHMe to form **85b** that is isolated in 70% yield. This compound is then used to prepare other examples of the title compound. For example **85c** is isolated in 80% yield by reaction of **85b** with MeMgCl at <5 °C.

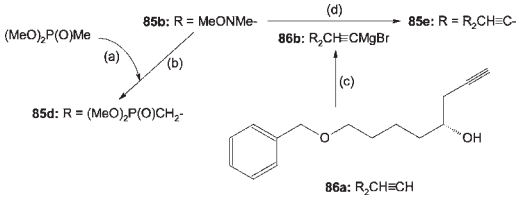
Scheme 30[a]



[a] Reagents and conditions: (a) (i) K_2CO_3, H_2O, 40 °C; (ii) add **84** in MeCN, 30 °C; (iii) distill off MeCN; (iv) add Pr^{i}OAc, 3 M H_2SO_4 to pH 2, separate; (v) distill off H_2O; (b) (i) N-MeM, <5 °C, (ii) PivCOCl, <5 °C, 0.75 h; (iii) MeONHMe, <5 °C, 0.5 h; (iv) 0.1 M HCl, aq $NaHCO_3$, separate, concentrate; (v) add *n*-heptane, agitate, filter, dry; (c) (i) MeMgCl, THF, 0 °C; (ii) 10% citric acid, 25 °C; (iii) add water, distill THF; (iv) Extract in EtOAc, concentrate; (v) add *n*-heptane, rt, 0.5 h; (vi) filter, wash, dry.

85b is also used to prepare **85d** and **85e** as shown in Scheme 31. **85d** is obtained by reacting **85b** with $(MeO)_2P(O)Me$ that has been treated with Bu^{n}Li. The reaction takes place at < −60 °C and is monitored by HPLC, but the time needed is not reported, and **85b** is isolated in 94% yield. The related product **85e** is obtained by reaction of **85b** with the Grignard formed from the alkyne **86a** and MeMgBr. **85e** is isolated as a yellow oil in 77% yield after workup and purification by ColC.

Scheme 31[a]



[a] Reagents and conditions: (a) Bu^{n}Li, THF, −60 °C; (b) (i) THF, < −60 °C; (ii) Add to aq citric acid, <5 °C; (iii) distill off THF; (iv) extract in EtOAc, separate, add *n*-heptane, stir, 0.5 h; (v) filter, dry; (c) (i) MeMgBr, THF, 0 °C; (ii) rt, 1 h; (d) (i) THF, 0 °C; (ii) rt, 2 h; (iii) aq citric acid, extract in EtOAc; (iv) brine wash, evaporate, ColC.

Some of the experiments are carried out on kilo scale, thus indicating the advanced stage of process development. The patent reports ^{1}H NMR data for all intermediates and products but does not give any details of their purity.

Advantages

The process gives high yields of intermediates and final products and could provide an industrial route to an important medicament.

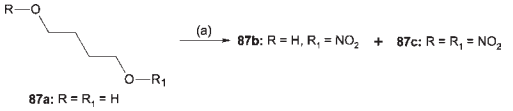
PATENT NO. U.S. 7,947,855

Assignee: Dipharma S.p.A., Mereto di Tomba, Italy

Title or Subject: Process for the Purification of 1,4-Butanediol Mononitrate

The title compound **87b** is a key intermediate in the synthesis of NSAIDs that release nitric oxide (NO). The NO-releasing NSAIDs markedly reduced gastrointestinal and cardiorenal toxicity, and this has been a problem for the conventional type of drug. The NO-releasing drugs are under investigation for prevention of stroke and heart attacks as well as for use as anti-inflammatory agents. **87b** can be produced by nitration of the diol **87a** or hydrolysis of the dinitrate **87c**, but both methods have separation problems because the mono- and dinitrates are potentially explosive materials. The nitration process for the synthesis of **87b** was the subject of an earlier patent from the same company and has been reviewed (*Org. Process Res. Dev.* **2008**, *12*, 556). The patent did not include any details of the purification process, and that is the subject of the current patent. The procedure is an extraction process that uses water and a water-immiscible solvent. The synthesis of **87b** is shown in Scheme 32 and uses HNO_3 stabilised with 0.75 wt % urea to nitrate **87a**. The reaction produces **87b** and **87c** in a 3:1 ratio with a small amount of unreacted **87a**. The purification process uses two Kuhni extraction columns that are operated counter-currently and under continuous operation. The example describes a process feeding a reaction mixture that is a DCM solution containing 11% **87b** and 4% **87c** at 6.5 kg/h. In the first column the mixture is extracted with water, and in the second DCM is used. There are a number of recycle streams, and the patent provides a process flow diagram. The final product is a solution around 15 wt % of **87b** in DCM that is 99.5% **87b** and 0.5% **87c**. This concentration is said to be safe to transport and use and does not pose a danger to plant personnel.

Scheme 32[a]



[a] Reagents and conditions: (a) (i) HNO_3, urea, DCM, 0 °C, 20 min; (ii) ice/water; (iii) 40% NaOH, <15 °C; (iv) separate, extract.

Advantages

The patent provides a safe process for the purification of a key reagent used to prepare improved drug types.

PATENT NO. U.S. 7,951,941

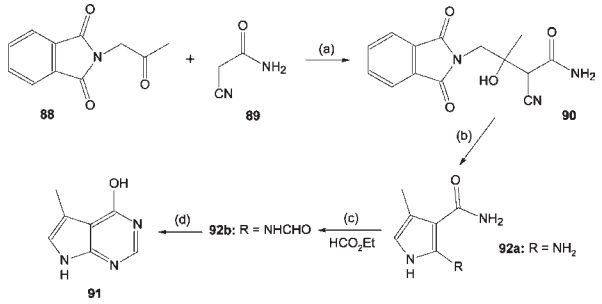
Assignee: Lexicon Pharmaceuticals Inc., The Woodlands, Texas, U.S.A.

Title or Subject: Process for Preparing 5-Alkyl-7*H*-pyrrolo-[2,3-*d*]pyrimidine-2-ols

The patent states that the title compounds are of interest because of their biological importance, and although it lists several references, there is no mention of a specific application or use. One method for preparing these compounds requires a desulphurisation step that produces large amounts of heavy metal wastes. An alternative procedure uses harsh conditions and gives low yields, and thus an improved synthesis is required. The method used to prepare **91** is outlined in Scheme 33 and starts with an aldol condensation of **88** and **89** that takes place in the presence of LiOH. The procedure is to add **88** in THF to a mixture of LiOH and **89** in MeOH. The product, **90**, is not

dx.doi.org/10.1021/op200209d |*Org. Process Res. Dev.* 2011, 15, 957–969

Scheme 33[a]



[a] Reagents and conditions: (a) LiOH, MeOH, rt, 1.5 h; (b) NaOMe, MeOH, 65 °C, 2 h; (c) NaOMe, MeOH, 55 °C, 7 h; (d) (i) H_2O, 60 °C, 0.5 h; (ii) concentrate, add H_2O; (iii) 6 M HCl to pH 7.6, 65 °C, 0.25 h; (iv) cool 5 °C, filter, wash, dry.

isolated and is treated with NaOMe to form **92a** that is also not isolated but reacted with HCO_2Et in the presence of NaOMe, giving the formyl compound **92b**. Hydrolysis of **92b** using hot water formed **91**, and an analysis of the solution indicated that the product is formed in 75% yield. After the pH was adjusted with 6 M HCl at 65 °C, the mixture was cooled, the solids were filtered off, and **91** was isolated in 61% yield as a light-brown solid with purity of 99% by HPLC.

The first step in the process is also carried out using cyanoacetamide in place of **88**, and the overall yield of **91** is 58% with a purity of 100% (HPLC). Bases other than LiOH can be used for the first step such as LiOMe, NaOMe, or NaOH. DMF can also be used as an alternative solvent in this step, and a table gives the results using different combinations of base and solvent. Isolated yields vary from 45 to 58% with 100% HPLC purity. Some ^1H and ^{13}C NMR data are reported for **92a** and **91**.

Advantages

The process gives good yields of the product without the need to isolate the intermediates and operates under moderate conditions.

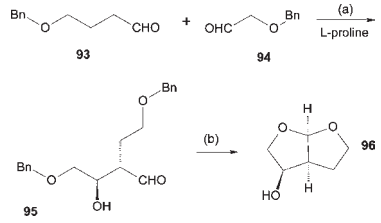
PATENT NO. U.S. 7,951,977

Assignee: Sumitomo Chemical Company Limited, Tokyo, Japan

Title or Subject: Process for Producing Hexahydrofurofuranol Derivative

The patent describes a process for preparing **96** that is used as an intermediate in the synthesis of an anti-AIDS drug. Alternative methods are reported that use toxic reagents such as Bu_3^nSnH or organoselenium compounds. Furthermore these methods produce the racemic mixture, and a resolution step is needed. The procedure described in this patent produces an optically active form and hence is claimed to be suitable for industrial use. The main claim of the patent covers the novel compound **95** and the process used for its preparation, although subsequent claims cover the preparation of **96** from **95**. Scheme 34 shows the route used to prepare **96** that starts with the reaction of **93** and **94** in the presence of a cyclic secondary amine such as L-proline to form **95**. The reaction is carried out by adding a solution of **93**, over a period of 22 h, to a cooled solution of **94** and L-proline in DMF. A further 24 h is required to complete the reaction, and after workup the crude **95** is isolated and then used in the next step. The patent provides ^1H NMR data for a pure sample of **95**. The formation of **96** is carried out by catalytic hydrogenolysis of

Scheme 34[a]

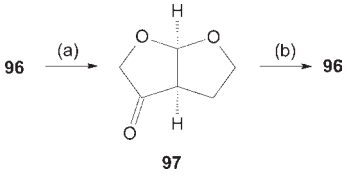


[a] Reagents and conditions: (a) (i) DMF, 4 °C, 46 h; (ii) add 5% saline, extract in EtOAc; (iii) dry over Na_2SO_4, filter, evaporate; (b) (i) Pd/C, Amberlyst 15E, THF, H_2, 1 atm, rt, 22 h; (ii) Filter, distill off solvent, ColC.

95 using Pd/C in the presence of the acid ion-exchange resin (IER) Amberlyst 15E. The product is obtained as a brown liquid in 53% yield (based on **93**) and is reported as containing the diastereoisomers (3*R*,3a*S*,6a*R*) and (3*S*,3a*S*,6a*R*) in the ratio 4:1. The material can be purified by ColC, and the product is obtained as a transparent liquid. The use of a cyclic secondary amine such as L-proline in step (a) is specifically covered by the claims in the patent, and clearly this is the key aspect of this patent and ensures that **95** is obtained with high stereoselectivity.

An example describes the hydrogenolysis and cyclisation step that is carried out in EtOH using 5% HCl in place of the IER. The product contains the diastereoisomers (3*R*,3a*S*,6a*R*) and (3*S*,3a*S*,6a*R*) in the ratio 3.8:1. Examples then describe using this mixture to obtain high purity **93**; however, the starting material used in the experiments is described as containing four isomers: 78.5% of (3*R*,3a*S*,6a*R*), 20.5% (3*S*,3a*S*,6a*R*), 0.5% (3*R*,3a*S*,6a*R*), and 0.5% (3*S*,3a*S*,6a*R*). Purification is carried out by first oxidising **96** to the ketone **97** using TEMPO as shown in Scheme 35. The ketone is isolated after recrystallisation from Pr^iOH as pale brown crystals in 73% yield and a purity of 98% with an ee of 100%. **97** is then reduced using $NaBH_4$ and the crude product is obtained after an extensive workup involving two extractions into EtOAc and evaporating. The residue is dissolved in MeOH, and **96** is isolated as a pale yellow oil in 96.6% yield as a mixture of the diastereoisomers (3*R*,3a*S*,6a*R*) and (3*S*,3a*S*,6a*R*) in the ratio of 98.2:1.8.

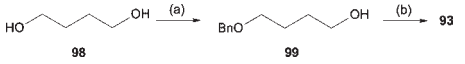
Scheme 35[a]



[a] Reagents and conditions: (a) (i) K_2HPO_4, KBr, TEMPO, EtOAc, 0 °C; (ii) Aq NaOCl, <15 °C, 1 h; (iii) add Pr^iOH, 0.5 h, separate; (iv) extract aqueous layer into EtOAc; (v) combine organics, dry, evaporate; (vi) recrystallise from Pr^iOH; (b) $NaBH_4$, EtOH, −15 °C, 2 h; (ii) 35% HCl, evaporate; (iii) add EtOAc, evaporate (×2); (iv) MeOH, evaporate.

The patent also describes the preparation of the two starting materials **93** and **94**. **93** is prepared by the route shown in Scheme 36 in which the first step is the reaction of **97** with BnCl to give **99**. This is isolated in 53.8% yield by vacuum distillation and then oxidised using TEMPO to give **93** that is isolated in 75.5% yield by vacuum distillation.

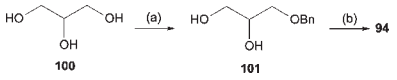
Scheme 36[a]



[a] Reagents and conditions: (a) (i) NaOH, PhMe, 95 °C, 0.5 h; (ii) BnCl, 95−105 °C, 4 h; (iii) H_2O, 35% HCl, extract in PhMe, saline wash, evaporate, distill; (b) (i) $NaHCO_3$, TEMPO, EtOAc; (ii) aq NaOCl, 15 °C over 2 h; (iii) wash in 5% NaH_2PO_2, 5% $NaHCO_3$, 5% saline; (iv) evaporate.

The preparation of **94** is outlined in Scheme 37 and starts by treating a solution of glycerol in Me_2CO with H_2SO_4 for 3 h. After addition of Et_3N and removal of solvent, the residue is added to a suspension of NaOH in PhMe followed by BnCl. There is then an extensive workup procedure that involves the use of three solvents and H_2O, and the product **101** is recovered, perhaps in a surprisingly high yield of 84%. **94** is then prepared by addition of **101** to a suspension of $NaIO_4$ in H_2O over 21 h. After leaving the mixture for a further 2 h, the product is isolated in 85.9% yield.

Scheme 37[a]



[a] Reagents and conditions: (a) (i) H_2SO_4, Me_2CO, 25 °C, 3 h; (ii) Et_3N, evaporate; (iii) NaOH, PhMe, 55−75 °C; (iv) BnCl, 95−105 °C, 5 h; (v) H_2O, separate; (vi) H_2SO_4/H_2O, 50 °C, 5 h; (vii) evaporate, add heptane/MeOH/H_2O, separate; (viii) distill off MeOH, add NaCl; (ix) extract in EtOAc, evaporate; (b) (i) $NaIO_4$, H_2O, 20 °C, 23 h; (ii) add EtOAc, filter, wash; (iii) wash in 10% $Na_2S_2O_3$; (iv) H_3PO_4 to pH 7; (v) saline wash, dry over $MgSO_4$, filter; (vi) add hydroquinone, distill off solvent.

Advantages

The process produces the desired compound in high purity and also provides a novel intermediate. One concern is that the workup procedures require the use of several solvents, and yet despite this, the yields are high.

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