Organic Process Research & Development

Highlights from the Patents

pubs.acs.org/OPRD

A Review of U.S. Patents in the Field of Organic Process Development Published During June and July 2012

SUMMARY

The current review contains 20 patents from an initial list of 238 that fitted the selection criteria. The range of subjects is quite wide with some patents having an extensive amount of chemistry. An example is the synthesis of aliskiren that is used to treat high blood pressure. The molecule has four chiral centres, and the new process gives the product with high stereoselectivity without the need to purify intermediates. Another comprehensive patent describes the synthesis of isoquinolines that are intermediates for a hepatitis C drug. Unusually the patent gives very detailed instructions for the preparation. Another detailed patent describes the synthesis of electronically tuned ligands for asymmetric hydrogenation of a specific molecule. The preparation of optically active quinuclidinols also involves asymmetric hydrogenation and chiral diphosphine amine Ru complexes are used to promote high selectivity. Another asymmetric hydrogenation process is described in the synthesis of hexahydroisoquinolines that are used as intermediates in the synthesis of a number of analgesics. A hydrogenation process is used to convert polyfunctional nitriles to polyamines, and a patent describes a method of significantly reducing the amount of catalyst required. This is done by changing the method of addition of the catalyst as well as performing the reaction under a pressure of H_2 and NH_3. Tetranolabdanes are used in perfumery, and two detailed patents cover the synthesis of some of these. The process involves a novel rearrangement of a propargylic alcohol and proceeds in high selectivity catalysed by vanadyl or molybdyl oxide compounds. One detailed patent lists over 150 novel compounds that were previously supposed to be impossible to prepare. The compounds are phenyl isocyanates or isothiocyanates that also contain an acyl sulfonamide group, and they can be useful in the synthesis of crop-protection agents. A very comprehensive patent describes a number of indole derivatives that cannot be prepared by the classical Fischer method. Two methods are described, and one proceeds via a novel indole boronic acid derivative while the other goes via a silylated acetylene. The treatment of aggressive brain tumours has been improved by the drug temozolomide, and a new synthesis is described. Unfortunately, half of a key intermediate is lost by side reaction. The process does avoid the use of the toxic and potentially explosive MeNCO that is used in alternative processes. Another anti-tumour drug is 2-fluoroadenosine, and this is often difficult to purify without using chromatographic methods. A new synthesis of this drug produces high-purity product without using such methods. A novel process is described for preparing phenyl-substituted propylamines that are used to treat urological disorders. The process also provides a wide range of derivatives. Two patents cover different synthetic routes for the antibacterial agent moxifloxacin. One describes a novel borate intermediate that can be obtained in a one-pot process. The patent also describes a novel polymorph of the HCl salt of the drug. The second patent on moxifloxacin uses a slight modification of an original process and utilises a magnesium salt to catalyse a condensation reaction that proceeds with high regioselectivity. It is proposed that a novel magnesium intermediate is formed that facilitates the reaction and inhibits a side reaction. Fluoroalkyl nitriles are used in agrochemical synthesis, and their syntheses may require processes operating at 400 °C. A new efficient process that takes place at rt is described that involves the reaction of acyl halides and fluorinated amides. DAST is a useful fluorinating reagent but is expensive and can be difficult to handle on a large scale. A process for preparing fluoroamino acids that are agrochemical intermediates avoids using DAST by using SOF_2. This reagent takes part in a reaction described as a dehydroxyfluorination accompanied by a 1,2-rearrangement, and the patent discusses in detail the proposed mechanism of this reaction. Acylamides are also agrochemical intermediates and used in the production of benoxacor by a three-step process. One of these is a hydrogenation step, and a patent introduces an improvement if an intermediate is recovered and crystallised before hydrogenation. A patent describes a range of quinoline derivatives that are said to be useful in the treatment of memory-related problems. Drugs to treat brain disorders such as Parkinsonism are of great interest, and a new method for preparing asenapine is disclosed that proceeds via a novel intermediate. Another drug in this area is rotigotine, and a new polymorph of this compound is described that is easily prepared and more stable than the only previously reported form. A number of the patents in this collection describe experiments carried out on a kilogram or multikilogram scale, thus suggesting an advanced stage of development or even commercial operation. However, there is no legal or commercial significance in the choice of patents in this review. The advantages mentioned in this review are those claimed in the patent, unless this reviewer has personal knowledge of the subject.

PATENT NO. U.S. 8,193,391

Assignee: Lek Pharmaceuticals D.D., Ljubljana, Slovenia

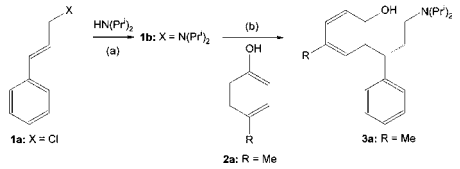
Title or Subject: Process for the Preparation of 3-(2-Hydroxy-5-substituted phenyl)-*N*-alkyl-3-phenylpropylamines

The patent describes a new method of preparing compounds such as **3a** that is marketed as the L-tartrate salt for the treatment of urological problems. The synthesis of this and related compounds requires a chiral route or a resolution step, and a more economical process is said to be required. The new process for preparing **3a** is shown in Scheme 1 and starts from cinnamyl chloride **1a**. This is aminated with $HN(Pr^i)_2$ in the presence of a base to give **1b** that is isolated in quantitative yield. This is then reacted with *p*-cresol **2a**, in the presence of MsOH to form **3a**. This is initially isolated as an oily mass, and the *R*-enantiomer is isolated from the mixture by extracting in PhMe followed by treatment with tartaric acid and HCO_2H. After crystallisation

Published: October 25, 2012

dx.doi.org/10.1021/op300287a | *Org. Process Res. Dev.* 2012, 16, 1684−1696

Scheme 1[a]

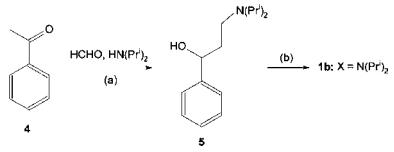


[a]Reagents and conditions: (a) (i) K_2CO_3, PhMe/MeOH, reflux, 24 h; (ii) add H_2O, separate, wash, evaporate. (b) (i) MsOH, 130 °C, 6 h; (ii) PhMe/H_2O, pH to 9.5; (iii) separate, H_2O wash, evaporate; (iii) dissolve in Pr^{i}OH, tartaric acid, HCO_2H, rt, 16 h; (iv) filter, dissolve in Pr^{i}OH, reflux, cool, filter, dry.

from hot Pr^{i}OH the tartrate salt of the *R*-isomer is isolated in 85% yield and 99.5% ee.

An alternative preparation of **1b** is said to involve the reaction of cinnamaldehyde with HN(Pr^i)$_2$ and $NaBH_4$. However, there is no example describing this precise reaction. There is a brief description of the preparation of **1b** by using the Mannich chemistry, outlined in Scheme 2, that starts with the reaction of **4**

Scheme 2[a]

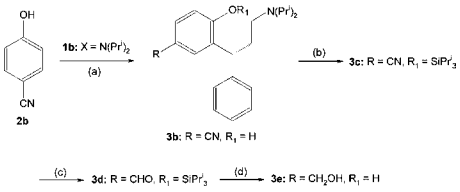


[a]Reagents and conditions: (a) (i) H_2O, HCl/MeOH, reflux, 2 h; (ii) evaporate, add EtOAc; (iii) separate, concentrate, add MeOH. (b) Strong alkali.

with HCHO and HN(Pr^i)$_2$ in acid solution to give **5** that, when treated with strong alkali, forms **1b**. There is no yield or purity information for either of these steps.

The patent also describes the preparation of analogues of **3a** (in which R = Cl, Br, or CN) using the same procedure. The nitrile is then used to synthesise the hydroxymethyl compound **3e** as shown in Scheme 3. The first step is preparation of the

Scheme 3[a]

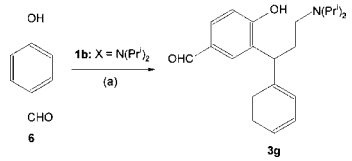


[a]Reagents and conditions: (a) similar to step b of Scheme 1. (b) (i) aq $NaHCO_3$, Et_2O, rt; (ii) separate, evaporate, dry; (iii) Pr$^i_3$SiCl, imidazole, EDC, reflux 0.5 h; (ii) rt, 16 h; (iii) add 0.5 M HCl; (iv) separate, extract into Et_2O, wash, dry evaporate. (c) (i) DIBAL-H, DCM, −5 °C, 3 h; (ii) add to ice; (iii) 6 M HCl, rt, 1 h; (iv) separate, extract in Et_2O, wash, dry, evaporate. (d) (i) $Et_3N{\cdot}3HF$, THF, rt, 16 h; (ii) cool to −5 °C, add aq K_2CO_3 (caution); (iii) extract in Et_2O, dry/evaporate.

tartrate salt of the *R*-enantiomer of the nitrile compound **3b** (R = CN) by reaction of **1b** with **2b**. This is isolated in 67% yield with 97% ee and is recrystallised twice from EtOH to achieve 99.9% ee. The purified salt is converted to the free base by treatment with aq $NaHCO_3$ and is isolated as an oil. The free base **3b** is then silylated to give **3c** that is isolated as a brown oil. This is then treated with DIBAL-H to form the aldehyde **3d** as an oily residue. Reaction of **3d** with $Et_3N{\cdot}3HF$ produces **3e** as a crude oil in 44% yield based on **3b**. After purification by column chromatography (ColC) the product is isolated as a solid, but no yield is reported. The patent claims actually cover a process for the preparation of **3e** by this route, although the use of **3e** is not described.

A similar preparation of **3e** is also described that starts from the bromo compound **3f** (R = Br). A method of preparing the compound **3g** is described and outlined in Scheme 4. This starts

Scheme 4[a]



[a]Reagents and conditions: (a) (i) MsOH, 130 °C, 8 h; (ii) cool add PhMe/H_2O to pH 9.5; (iii) separate, H_2O wash, dry, evaporate; (iv) ColC.

from **1b** and the benzaldehye **6** but gives only an 8% yield of the product as the racemic mixture after purification by ColC.

Advantages. The process provides a new route to the desired compounds that is claimed to be suitable for industrial use.

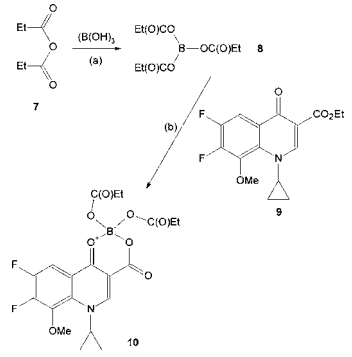
PATENT NO. U.S. 8,198,451

Assignee: CIPLA Limited, Mumbai, India

Title or Subject: Process for the Synthesis of Moxifloxacin

Moxifloxacin (**13**), as the HCl salt, is used as an antibacterial agent, and this is the first of two patents for its preparation. A number of processes for the preparation of **13** are summarised in this patent, and improved procedures are said to be needed. The patent describes the synthesis of **13** via a novel borate intermediate **10**. This is prepared by the method shown in Scheme 5,

Scheme 5[a]



[a]Reagents and conditions: (a) (i) add B(OH)$_3$ at 90 °C; (ii) reflux 2 h; (iii) cool to 70 °C. (b) (i) Add **9** at 70 °C; (ii) 100 °C, 4 h; (iii) cool to 0 °C, add H_2O, 1 h; (iv) filter, wash, dry.

and the first step is formation of the borate **8** from **7** and B(OH)$_3$. There is no need to isolate **8** that is reacted with **9** in a one-pot reaction, and **10** is obtained in 96% yield.

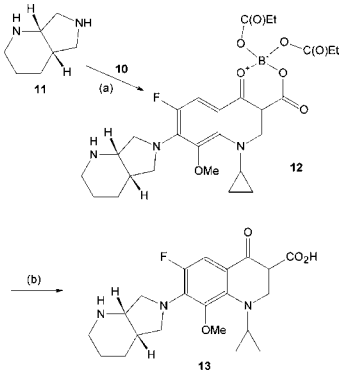
The borate **10** is then reacted with the amine **11** in a condensation reaction to form **12**. This is not isolated, and acid hydrolysis gives **13**. This is converted to its HCl salt that is

dx.doi.org/10.1021/op300287a | *Org. Process Res. Dev.* 2012, 16, 1684−1696

isolated in 75% yield. The borate **12** can be isolated in 90% yield by reaction of **10** with **11** in MeCN in the presence of Et_3N. The pure borate **12** can then be used to prepare the free base **13** by acid hydrolysis.

The patent describes a novel polymorph of **13**·HCl designated as Form C. The claims of the patent cover this form and the process used for its preparation. This is obtained by treating the salt formed by the process of Schemes 5 and 6 with Et_3N in MeOH.

Scheme 6[a]



[a]Reagents and conditions: (a) (i) BuOH, 10−15 °C; (ii) 100 °C, 3 h; (iii) add MeOH at 30 °C; (iv) HCl/MeOH to pH 1−2, 30 °C, 2 h; (v) evaporate, add H_2O, aq NH_4OH to pH 7.5−9; (vi) extract in DCM, dry, evaporate. (b) (i) Dissolve in MeOH, HCl/MeOH to pH 1−2, rt; (ii) cool <5 °C, 1 h; (iii) filter, MeOH wash, dry.

This is followed by acidification with HCl/MeOH. XRD, Raman, and FTIR spectra of the new form are provided.

Advantages. The patent provides a novel polymorph of the drug as well as a new process and novel intermediate.

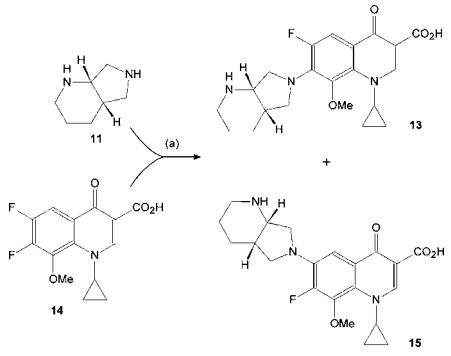
PATENT NO. U.S. 8,207,339

Assignee: Fabbrica Italiana Sintetici S.p.A., Vicenza, Italy

Title or Subject: Process for Preparing Moxafloxicin and Salts Thereof

This, the second patent for synthesising **13**, is carried out in a condensation reaction between **11** and **14**, and a European patent (EP 0550903) reports the preparation of **13** using a base catalyst (Scheme 7). However, the reaction has low regioselectivity,

Scheme 7[a]

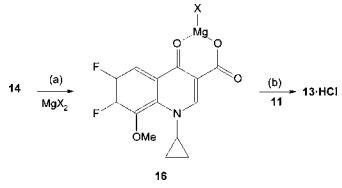


[a]Reagents and conditions: (a) base catalyst reported in EP 0550903.

and the isomer **15** is also formed that is difficult to remove from **13**.

The improved process disclosed in the current patent uses a magnesium salt and a base to catalyse the condensation reaction of **11** and **14**. It is found that this gives a higher regioselectivity, and it is suggested that the reaction proceeds via the magnesium complex **16** that facilitates nucleophilic substitution of the F group in position 7 in **14** rather than position 8 (Scheme 8). This

Scheme 8[a]



[a]Reagents and conditions: (a) (i) $Mg(OH)_2$, $Mg(OMe)_2$, DMF, 30 °C, 1 h; (ii) distill MeOH. (b) (i) Bu_4NCl, 45 °C, 16 h; (ii) concentrate, add H_2O, 12 M HCl to pH 3−4; (iii) 30 °C, 0.5 h; (iv) cool <10 °C, 0.5 h; (v) filter, H_2O wash; (vi) aq HCl, rt, 20 min; (vii) filter, concentrate, add EtOH; (viii) <5 °C, 1 h; (ix) filter, EtOAc wash, dry.

prevents formation of the isomer **15** and hence gives higher yields of **13**. The patent suggests that evidence for this comes from reports of magnesium complexes formed with structurally similar compounds such as ofloxacin and temafloxacin. The reaction is carried out by reacting **14** with $Mg(OH)_2$ and a base such as $Mg(OMe)_2$. After removal of the MeOH formed in the reaction, **11** and Bu_4NCl are added to the solution, and the reaction is monitored by HPLC. When reaction is complete, the solvent is removed and the mixture acidified with HCl to give the HCl salt of **13**. This is isolated in 89% yield and >99% purity after precipitation from cold EtOH. When the reaction is carried out without a base and using alternative magnesium salts such as hydroxide, sulphate, and carbonate, the conversion is >99%, and the mixture contains around 88% of **13**. The patent claims cover the use of bases such as DBU, DABCO, $EtNPr^i_2$, and Et_3N, but there are no examples describing their use.

Advantages. The process provides a selective method for preparing the drug molecule by a modification of the original process.

PATENT NO. U.S. 8,202,991

Assignee: Euticals S.p.A., Lodi, Italy

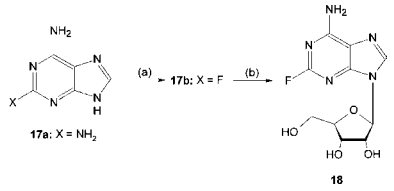
Title or Subject: Process for the Preparation of 2-Fluoroadenine

2-Fluoroadenine **17b**, is an intermediate in the synthesis of 2-fluoroadenosine **18**; an antitumour agent. The objective of the patent is to devise a process for the preparation of **17b** that has very high purity. Alternative methods are said to give the product with a purity of 98% and chromatographic methods are required to achieve the high purity material required for drug use. The process described is fluorination of a diazotised amine using HF/pyridine. The reaction is shown in Scheme 9 and is carried out by gradually adding the purine **17a** to HF/pyridine followed by continuous addition of Bu^tONO to the mixture over an extended period of time. After a workup procedure involving washing five times with H_2O, the product is isolated in 59% yield and purity of 99.2% (HPLC). An alternative procedure using $NaNO_2$ gave 56% yield of **17b** with 99.0% purity.

Two examples are described in the patent and they are both carried out on a kilo-scale indicating the advanced state of the development of the process.

dx.doi.org/10.1021/op300287a | Org. Process Res. Dev. 2012, 16, 1684−1696

Scheme 9[a]



[a]Reagents and conditions: (a) (i) HF/pyridine, 15 °C, 50 min; (ii) Bu^{t}ONO, −15 °C, 7 h; (iii) warm to 0 °C over 1.5 h; (iv) add to H_2O, 2 °C; (v) filter, H_2O wash (×5), dry. (b) No details.

Advantages. The process provides an efficient method of preparing high-purity product without the need to use chromatographic purification methods.

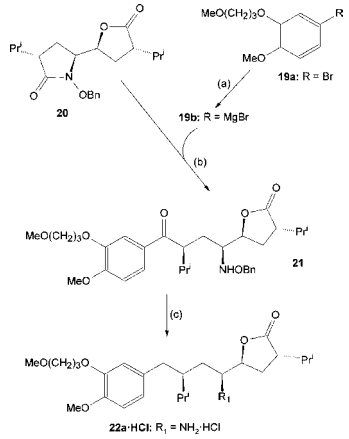
■ PATENT NO. U.S. 8,203,005

Assignee: Carbo Design LLC, Sarasota, Florida, United States

Title or Subject: Manufacturing Process for Enantiomerically Pure 8-Aryloctanoic acids as Aliskiren

Aliskiren **24**, is a renin inhibitor and used to treat high blood pressure. There are a number of reports of the synthesis of **23** and since the molecule contains four chiral centres they are all fairly complex. The current patent describes a novel process for the synthesis of enantiomerically pure **24** and this is outlined in Schemes 10 and 11. The first step is the preparation of the

Scheme 10[a]

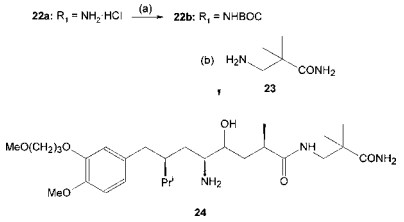


[a]Reagents and conditions: (a) (i) Mg, I_2, $BrCH_2CHBrC_2H_5$, THF rt, 3.5 h; (ii) THF, reflux 1 h. (b) (i) $CeCl_3$, THF, −78 °C, 2 h (ii) −35 °C, 4 h; (iii) HOAc, −35 °C; (iv) add to aq NH_4Cl, rt; (v) add H_2O, extract in EtOAc, wash, dry, evaporate. (c) (i) Pd/C, Concd HCl, HOAc, H_2 1 bar, rt, 3 h; (ii) filter, HCl to pH 1; (iii) evaporate.

Grignard **19b** that is then reacted with **20** in the presence of $CeCl_3$ to produce **21** as a single diastereoisomer that is isolated in crude form in 81% yield as a yellow oil. The reaction is also carried out by treatment of **19a** with BuLi and the final product **21** is again a yellow oil. Compound **21** is then reduced over Pd/C in HOAc to give **22a** that is recovered as the HCl salt as a brown oil and used without purification in the next stage outlined in Scheme 11.

The first part of the next stage is formation of the protected NH_2 group in **22a** using BOC or CBZ protection, and there are examples for both methods. The amine-protected compound **22b** is recovered in crude form and reacted with **23** in the presence of 2-hydroxypyridine (2-HOP). The BOC-protected

Scheme 11[a]

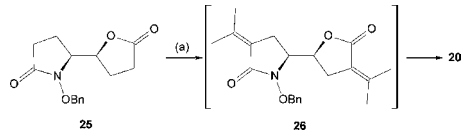


[a]Reagents and conditions: (a) (i) DMAP, Et_3N, $(BOC)_2O$, THF, rt, 24 h; (ii) add HOAc, extract in PhMe/H_2O; (iii) separate, evaporate. (b) (i) 2-HOP, Et_3N, MTBE, 80 °C, 18 h; (ii) add PhMe, rt; (iii) wash in aq $NaHSO_4$, (iv) separate, H_2O wash, dry, evaporate; (v) suspend in hexane, filter, evaporate; (vi) TFA, DCM, rt, 2 h; (vii) 37% aq NaOH to pH 10; (viii) extract in DCM, dry, evaporate.

derivative of **24** is isolated as a yellow oil, and after treatment with TFA the purified **24** is also recovered as a yellow oil in 48% yield based on crude **22a·HCl**. The analytical data are said to be identical to those reported in European patent EP 0678503.

Scheme 12 shows the method of preparing **20** that starts with the reaction of **25** with strong base to effect deprotonation

Scheme 12[a]

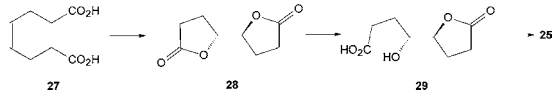


[a]Reagents and conditions: (a) (i) Bu^{n}Li, Pr$^i_2$NH,, THF, −40 °C; (ii) Pr^{i}I, - 40 °C, 1 h; (iii) - 10 °C, 2 h; (iv) add to H_2O, extract in EtOAc, dry, evaporate.

followed by in situ stereoselective alkylation with Pr^{i}I to give **26**. This is not isolated but converted to **20** as a single diastereoisomer that is recovered as a colourless oil in 86% yield. Both **20** and its precursor **25** are novel bicyclic compounds and the conversion of **25** through **26** to **20** with high stereoselectivity is said to be the key element of the process. It is suggested in the patent that the reason for the high stereoselectivity is that the −C(O)NOBn group in both **25** and **26** both protects and activates simultaneously. For more details of this argument the reader is encouraged to consult the patent. An alternative synthesis of **20** is said to involve deprotonation of **25** with strong base followed by condensation with Me_2CO, dehydration, and then reduction of the double bond. However, there are no examples describing this method of preparing **20**.

The preparation of **25** is not described in detail although a number of alternative methods are proposed. One route is outlined in Scheme 13 is based on literature reports referred to in the patent.

Scheme 13[a]



[a]No details are provided for the reaction conditions.

The patent contains a considerable amount of detail regarding the proposed mechanism of the reaction, and reasons for the high

dx.doi.org/10.1021/op300287a | Org. Process Res. Dev. 2012, 16, 1684−1696

stereoselectivity the patent should be consulted for more information.

Advantages. The process provides a highly stereoselective route to the desired drug molecule via a number of novel intermediates that do not need to be purified during the synthesis.

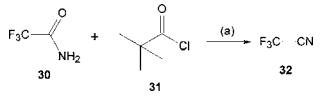
PATENT NO. U.S. 8,203,015

Assignee: Bayer Cropscience AG, Monheim, Germany

Title or Subject: Process for Preparing Fluoroalkyl Nitriles

The title compounds are intermediates for the synthesis of agrochemicals. A number of alternative processes for their manufacture require temperatures of 400 °C and higher, and others use expensive or hazardous reagents. The process described in this patent involves the reaction of a fluorinated carboxamide with an acyl halide, and Scheme 14 shows the reaction used to prepare **32** from **30** and **31**. The reaction is carried out by adding **31** dropwise to **30** and takes place in the presence of a fluorinated acid such as TFA or pyridine. The gaseous **32** is formed over the course of reaction and can be isolated in 92% yield by condensing at −100 °C. Alternatively, it may be introduced directly into a further reaction.

Scheme 14[a]



[a]Reagents and conditions: (a) TFA, pyridine, rt, 5 h.

The patent also includes examples for the preparation of **32** using BnCOCl in place of **31**, giving **32** in 86% yield. Also prepared is CF_2H−CN and CF_3CF_2−CN from the corresponding amides and **31** in yields of 88% and 82% respectively.

Advantages. The process is more efficient and takes place under milder conditions than alternatives.

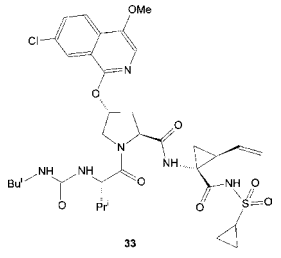
PATENT NO. U.S. 8,207,341

Assignee: Bristol-Myers-Squibb Company, Princeton, New Jersey, United States

Title or Subject: Process for Synthesising Substituted Isoquinolines

This patent describes a process for preparing the compound **39** that is an intermediate in the synthesis of **33**, a compound of interest for the treatment of hepatitis C.

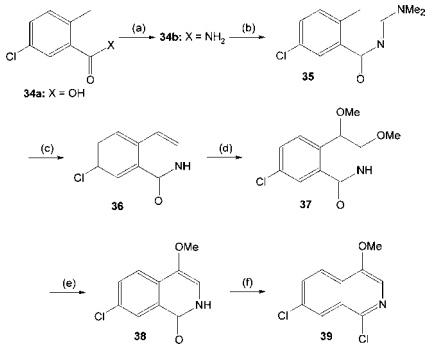
Compound **33**



33

Two methods of making **39** are provided, although only one is covered by the claims of the patent. This route is outlined in Scheme 15 and starts by converting the acid **34a** to the amide **34b** using $(COCl)_2$ with a catalytic amount of DMF, followed by NH_4OH. **34b** is recovered as a solution in Me-THF and after switching solvents the amide is treated with $Me_2NC(OMe)_2$ to give the amidine **35** that is not isolated and treated with a strong base to produce **36**. This is recovered in 89% yield and 98% purity and then oxidised with a hypervalent iodine compound. The example uses $PhI(OAc)_2$ in the presence of MsOH, although other reagents are mentioned and covered in the claims. The reaction initially gives the dimethoxy compound **37** that is not isolated and undergoes loss of MeOH to form **38**. This is isolated in yields of 75−85% and purity >97%. In the last step of the process **38** is chlorinated using $POCl_3$ to produce **39** that is recovered in yields of 77−87% with purity >98%.

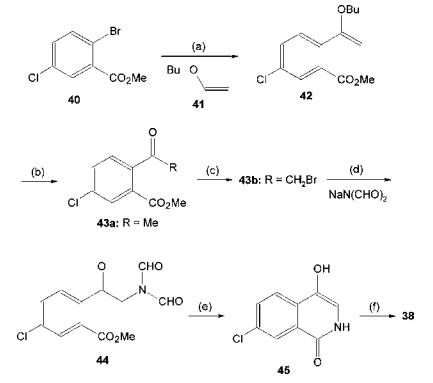
Scheme 15[a]



[a]Reagents and conditions (a) (i) $(COCl)_2$/DMF, Me-THF, rt, 1 h; (ii) add 5 M NH_4OH, Me-THF, rt, 7 min; (iii) rt, 10 min. (b) (i) distill Me-THF, add PhMe; (ii) $Me_2NC(OMe)_2$, PhMe, reflux, 3 h; (iii) distill MeOH. (c) (i) KOamyl^t, PhMe, 85 °C; (ii) add MeOH at 50 °C; (iii) concentrate, add heptane at rt; (iv) add *N*-methylpyrrolidone/H_2O, rt, 10 min; (v) separate, add HCl; (vi) filter, wash, dry. (d) (i) MsOH, MeOH, 0 °C; (ii) add $PhI(OAc)_2$/MeOH, 0 °C; (iii) rt, 1 h. (e) (i) reflux, 5 h; (ii) concentrate; (iii) rt, 16 h; (iv) add H_2O, rt, 1 h; (v) filter, wash, dry. (f) (i) $POCl_3$, MeCN, <30 °C; (ii) reflux; (iii) add K_3PO_4, H_2O, 10 °C, 0.5 h; (iv) add PhMe/THF, rt, 0.5 h; (v) separate, add active C, rt, 1 h; (vi) $MgSO_4$, rt, 1 h; (vii) filter, THF wash; (viii) distill THF, add heptane; (ix) 50 °C, 1 h; (x) cool −7 °C, filter, wash, dry.

An alternative route to **39** is also described and is shown in Scheme 16. The patent examples have very detailed steps, and only the main reagents are shown in the scheme. The procedure starts with the reaction of **40** and the vinyl ether **41** in the presence of a Pd/phosphine catalyst and $EtNPr^i_2$ to produce **42**.

Scheme 16[a]



[a]Reagents and conditions: (a) (*o*-tolyl)$_3$P, $Pd(OAc)_2$, Et_2NPr^i, MeCN, 82 °C, 1.25 h. (b) H_3PO_4, PhMe, 7 °C. (c) Br_2, PhMe, <0 °C. (d) Bu^n_4NBr, MeCN/THF, 0 °C, 0.25 h. (e) (i) MeOH, 25 °C, 8 h; (ii) HOAc. (f) (i) MsOH, MeOH, 3 °C, 25 min; (ii) 60 °C, 47 h.

dx.doi.org/10.1021/op300287a | *Org. Process Res. Dev.* 2012, 16, 1684−1696

This is not isolated and is hydrolysed under acid conditions to give the ketone **43a**. This is recovered as a solution in PhMe in 87.3% yield, and the patent stresses that the concentration of this solution should be between 95−108 mg/mL. If it is any higher, the patent states that the ketone **43a** decomposes to give what is described as a cyclised acetophenone that can be present at up to 12 area %. The solution of **43a** is treated with Br_2 to produce **43b** that is isolated in 60% yield as an orange solid. After recovering **43b** it is treated with $NaN(CHO)_2$ in a biphasic reaction to produce **44** that is not isolated but converted directly to **45** by treating with MeOH and then HOAc. Compound **45** is recovered as a brown solid in 78% yield and then methylated using MeOH/MsOH to obtain **38**. The reaction takes around 48 h, and after workup **38** is isolated in 90% yield. Chlorination of **38** to **39** uses $POCl_3$, and subsequent workup uses K_2HPO_4 rather than K_3PO_4 as described for reaction (f) in Scheme 15. The patent contains extensive details for all of the steps of this route and includes a large number of notes about the workup, pointing out how the various stages should be performed. Although the synthesis of **39** by this route is not covered in the patent claims, the examples are all carried out on a kilogram scale, whereas those for the route in Scheme 15 are on 10−20 g scale. The detailed description of the various steps suggest that this route may be of greater commercial significance than that of the first.

The examples in the patent are unusual in that they list the precise quantities of reagents and solvents that are used and give more experimental details than one would normally expect to find in many academic papers.

Advantages. The process provides an efficient process of preparing the desired compound without the need to isolate and purify many intermediates in the process.

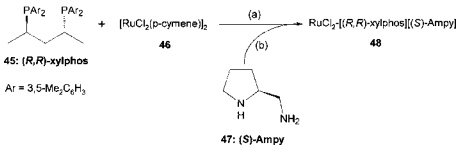
PATENT NO. U.S. 8,212,037

Assignee: Kanto Kagaku Kabushiki Kaisha, Tokyo, Japan and Nagoya Industrial Research Institute, Nagoya-Shi, Japan

Title or Subject: Process for Optically Active Quinuclidinols

The title compounds are synthetic intermediates in the preparation of pharmaceuticals, agrochemicals, and liquid crystal materials. This is the first of two patents covering asymmetric hydrogenation catalysis, and this patent discloses a range of chiral Ru diphosphine amine complexes that are effective asymmetric hydrogenation catalysts for the preparation of optically active 3-quinuclidinols. Scheme 17 outlines a method of making the

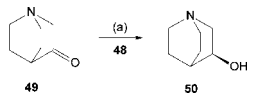
Scheme 17[a]



[a]Reagents and conditions: (a) DMF, 100 °C, 7 h. (b) (i) rt, 6 h; (ii) distill off DMF.

catalyst **48** from the chiral diphosphine **45**, the Ru complex **46**, and the chiral diamine **47**. The complex **48** is recovered in 90% yield, and brief ^{31}P NMR data are reported although the purity is not. Several other Ru complexes are prepared by similar methods using a range of diphosphines and chiral and nonchiral diamines. The patent states that the diphosphines such as **45** can easily be prepared from an optically active 2,4-pentanediol compound that can be obtained from

Scheme 18[a]



[a]Reagents and conditions: (a) Bu^tOK, EtOH, H_2, 10 atm, 0 °C, 19 h.

2,4-pentanedione. However, there are neither details nor references for this synthesis.

The Ru complex **48** is then used with Bu^tOK in the asymmetric hydrogenation of **49** to give **50**. Isolation of the product is not described and GC analysis indicated that **50** was formed in 89% yield with ee of 88%. The patent contains several examples of the asymmetric hydrogenation of **49** with a range of Ru complexes similar to **48** to give either enantiomer of **50** in high yields. Comparative examples are described using alternative chiral Ru diphosphine complexes that give much lower yields.

Advantages. The process provides a range of novel Ru compounds that are efficient catalysts for the asymmetric hydrogenation of quinuclidinone.

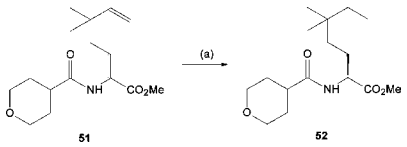
PATENT NO. U.S. 8,212,049

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

Title or Subject: Electronically Tuned Ligands for Asymmetric Hydrogenation

This intriguingly titled patent discloses a class of novel bidentate ligands that form transition metal complexes that are asymmetric hydrogenation catalysts. There are a number of ligands covered in the patent, and the claims cover chiral complexes with the metals Rh, Ir, Ru, Ni, Pd, and Pt. The specific asymmetric hydrogenation that is described in the patent is for the preparation of **52** from **51** as shown in Scheme 19. The

Scheme 19[a]

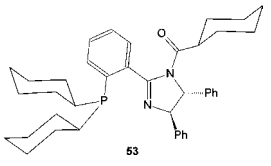


[a]Reagents and conditions: (a) Metal complex, rt H_2, 100−250 psi, 23 °C, 20 h.

patent does not mention what is the use or application of this compound.

A specific example of a novel ligand referred to in the patent is compound **53** that is prepared by the route outlined in Scheme 20.

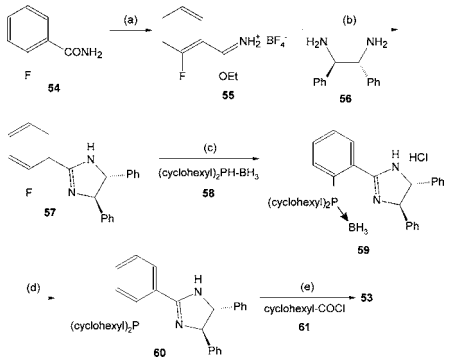
Ligand



The synthesis of **53** begins with the conversion of the amide **54** to the BF_4 salt **55** by treatment with Meerwein's reagent ($Et_3O^+BF_4^-$). The imidate salt, **55**, is isolated as a crystalline solid in 84% yield and then treated with **56**. After isolation, purification and crystallisation, the imidazoline **57** is isolated in 80% yield as a colourless solid. In the next step the phosphine−borane complex **58** is treated with NaH, and then

dx.doi.org/10.1021/op300287a | Org. Process Res. Dev. 2012, 16, 1684−1696

Scheme 20[a]

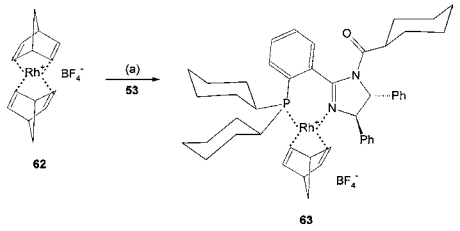


[a]Reagents and conditions: (a) $Et_3O^+BF_4^-$, DCM, 23 °C, 16 h. (b) (i) EtOH, 23 °C, 1 h; (ii) reflux, 16 h. (c) (i) NaH, Me_2NAc, <5 °C, 20 min; (ii) rise to 30 °C, 2 h; (iii) 23 °C, 14 h; (iv) NH_4Cl, HCl, MTBE, <5 °C. (d) (i) DABCO, PhMe, 60 °C, 2 h. (e) (i) DMAP, DCM, 23 °C, 1 h; (ii) $Me_2NCH_2CH_2NHMe$, 23 °C, 0.25 h; (iii) evaporate, add EtOAc/0.5 M HCl; (iv) separate, evaporate, ColC.

a solution of **57** is gradually added to this mixture to produce the phosphinoborane **59** as the HCl salt. After a complex workup this is obtained in 82% yield with HPLC purity of >99% and ee >99.5%. It can be recrystallised from boiling MeCN. Treatment of **59** with DABCO results in the formation of **60** that is isolated as a sticky oil in 99% yield. The final step is reaction of **60** with the acyl chloride **61** in the presence of DMAP to form **53**. Before the product is isolated, $Me_2NCH_2CH_2NHMe$ is added to remove traces of **61**. The crude **53** is isolated as a yellow oil, then purified by ColC, and recovered in 51% yield as a colourless foam. The reaction schemes only show the main reagents due to space limitations.

The ligand is then reacted with **62** to obtain the chiral Rh complex **63** as shown in Scheme 21, and **63** is isolated

Scheme 21[a].



[a]Reagents and conditions: (a) DCM, 23 °C, 1 h; (ii) evaporate, add Et_2O, filter; (iii) pulverise in Et_2O, filter, dry.

in 84% yield. The asymmetric hydrogenation of **51** to give **52** is carried out using Pd/C and the *S,S*- analogue of **63**. The product **52**, is isolated in 90% yield with 95% ee. The preparation of the *S,S*-analogue of **63** is not described nor is the use of **63** in the preparation of the *S,S*-enantiomer of **52**. However, an IrCOD complex of **53** is used in the asymmetric hydrogenation of **51**, giving the *S,S*-isomer of **52** in 90% yield with 62% ee.

The patent does provide detailed experimental details and ^1H and ^{13}C NMR spectra for most of the intermediates.

Advantages. The processes provides a novel asymmetric hydrogenation catalyst that is used in a specific application.

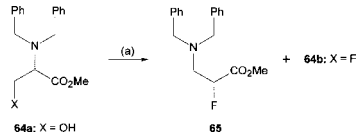
■ PATENT NO. U.S. 8,217,196

Assignee: Central Glass Company Limited, Ube-shi, Japan

Title or Subject: Process for Producing α-Fluoro-β-amino Acids

The title compounds are described as being important intermediates for the synthesis of pharmaceutical and agrochemical products. A particular example is compound **65** that is the main focus of this patent. An alternative synthesis of such compounds involves the use of DAST, and it is claimed that this means the method is not commercially viable because of cost and the danger of explosion. Another process is described as using commercially suitable reagents, but it requires complicated processing methods and post-treatment operations. The current patent describes a process for preparing compound **65** by the reaction of **64a** with SO_2F_2 in the presence of an organic base. It is carried out by passing gaseous SO_2F_2 through a solution of **64a** that contains $EtNPr^i_2$. The conversion is 100%, and the mixture contains **65** and **64b** in a total yield of 93% with GC purity of 91.8% and 1.4% respectively. There was found to be only a trace of a quaternary ammonium salt that is obtained in alternative processes.

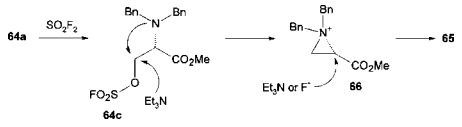
Scheme 22[a]



[a]Reagents and conditions: (a) (i) $EtNPr^i_2$, MeCN, −78 °C; (ii) rt, 16 h; (iii) add PhMe, wash in aq K_2CO_3, H_2O wash; (iv) dry, concentrate.

The reaction is described as being an example of a dehydroxyfluorination accompanied by a 1,2-rearrangement. The patent provides a detailed discussion on the proposed reaction pathway involving an intramolecular ring closure of **64c** giving the aziridinium intermediate **66** (Scheme 23). This

Scheme 23



intermediate undergoes ring-opening with inversion of the stereochemistry at the α-position to give the 1,2-rearranged product. The reaction takes place with high regioselectivity when the β-position of the substrate is unsubstituted and the preferred substrate is the dibenzyl derivatives of L-serine methyl ester **64a**. The patent also discusses the steric effect of the organic base used in the reaction, and a tertiary amine having 8−12 C atoms is preferred. Such a compound is effective in preventing the formation of quaternary ammonium salts. It is also stated that two of the alkyl groups should have three or more C atoms and $EtNPr^i_2$ is the preferred base.

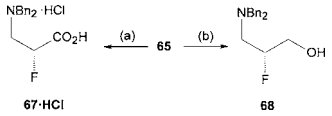
The patent also describes reactions of **65** such as hydrolysis to give the acid **67** that is recovered as its HCl salt in quantitative yield. The reduction of **65** using $LiAlH_4$ produces **68** that is isolated in quantitative yield with purity of 96.4%.

The patent contains ^1H and ^{19}F NMR data for all of the compounds. The experimental details include comparative examples based on alternative processes that are less selective.

Advantages. The process is highly selective and does not produce byproduct quaternary ammonium salts that are found in alternative methods.

dx.doi.org/10.1021/op300287a | *Org. Process Res. Dev.* 2012, 16, 1684−1696

Scheme 24[a]



[a]Reagents and conditions: (a) 35% HCl, H_2O, rt, 16 h. (b) $LiAlH_4$, THF, 0 °C, 2 h.

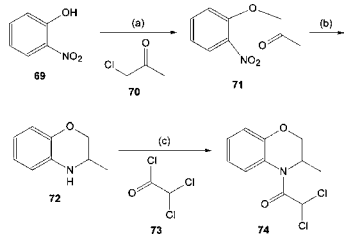
■ PATENT NO. U.S. 8,222,408

Assignee: Saltigo GmbH., Lagenfeld, Germany

Title or Subject: Process for Preparing Acylamide Compounds

Acylamides are used in dyestuffs and also in agrochemical products, and this patent describes a process to prepare **74** that is a pesticide known as benoxacor. An alternative preparation of **74** is described requiring three stages, one of which is hydrogenation. This stage is the rate-limiting and most expensive step, and the current patent describes an improved process for this step. The overall process for preparing **74** is shown in Scheme 25

Scheme 25[a]



[a]Reagents and conditions: (a) NaBr, $NaHCO_3$, Bu_3NMeCl, H_2O, PhMe, 65 °C, 6 h; (ii) add 35% HCl, H_2O to pH 7; (iii) separate, brine wash; (iv) add Pr^iOH, 30% aq NaOH to pH 8.5; (v) cool −10 °C, filter, wash, dry. (b) (i) Dissolve in MeOH/PhMe, 30% aq NaOH to pH 8−9; (ii) Ni/Mo, H_2 220 bar, 60 °C, 1.5 h; (iii) filter, evaporate; (iv) add PhMe. (c) (i) H_3PO_4, H_2O; (ii) add **73** in PhMe, 30% aq NaOH, 40−70 °C, 1.5 h, pH 2−3; (iii) 80 °C, 1 h; (iv) 30% NaOH to pH 7, 80 °C; (v) filter hot, evaporate; (vi) add H_2O, cool to rt, filter; (vii) wash in Pr^iOH/H_2O, H_2O wash, dry.

and starts with the condensation of the phenol **69** with **70** to give **71**. This is carried out in the presence of NaBr, $NaHCO_3$, and Bu_3NMeCl. The patent mentions that the reaction initially evolves a lot of CO_2. The workup and recovery of **71** are key aspects of the patent and involve adjustment of the pH of the reaction mixture followed by recrystallisation from Pr^iOH. The patent claims cover the crystallisation and removal of **71** from the reaction mixture before subsequent treatment, and when these steps are omitted, the purity of the product is too low to use in the subsequent hydrogenation. After workup, the **71** is isolated in 88% yield and then hydrogenated using a Ni/Mo sponge catalyst (Amperkat Ni−Mo 3706). This step results in ring closure and formation of **72** that is isolated as a solution in PhMe in a yield of >90%. The solution is used in the final stage of the process where it is mixed with H_2O containing H_3PO_4, and to this is added simultaneously a solution of **73** in PhMe and 30% aq NaOH. The product is isolated in 91% yield and >99.8% purity. All of the steps shown in Scheme 25 are carried out on a tonne scale, and hence the process is presumed to be in commercial operation.

The patent includes details of the extent of the hydrogenation reaction in both tabular and graphical form. Two claims of the patent appear to be inconsistent in that one refers to a structure of an acyl amide and a second refers to the structure as if it is an amine. One wonders where a chemist was in proof-reading the patent.

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

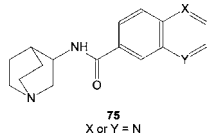
■ PATENT NO. U.S. 8,227,598

Assignee: Bayer Schering Pharma AG, Berlin, Germany

Title or Subject: Heteroaryl Carboxamides

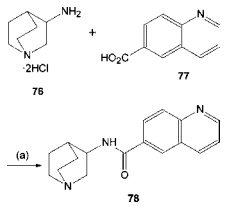
This patent covers a number of novel compounds that are said to be useful in the treatment of learning or memory-related problems. The compounds are all derivatives of compound **75** and have a variety of substituents on the quinoline ring.

Compound **75**



The simplest member of this group is **78** and this is prepared by the condensation reaction shown in Scheme 26. The reaction

Scheme 26[a]

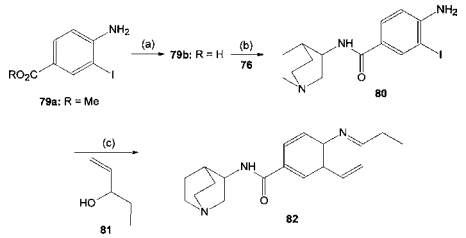


[a]Reagents and conditions: (a) HOBT, TBTU, $EtNPr^i_2$, DMF, rt, 4 h; (ii) concentrate, extract with $CHCl_3$/aq NaOH; (iii) separate, dry, concentrate; (iv) ColC; (v) HCl/Et_2O, THF; (vi) concentrate.

is carried out by adding the di-HCl salt of **76** to a solution of **77** containing HOBT, TBTU, and $EtNPr^i_2$ in DMF. After a workup that involves extraction into $CHCl_3$, the product is purified by ColC and isolated as the HCl salt in 47% yield.

A number of related compounds were prepared by this procedure from the acid. An alternative method is used to prepare compound **82** as shown in Scheme 27. The first step is hydrolysis

Scheme 27[a]



[a]Reagents and conditions: (a) (i) LiOH, dioxane/H_2O, rt, 6 h; (ii) distill dioxane, add 1 M HCl to pH 5; (iii) filter, wash, dry. (b) (i) HOBT, EDC, $EtNPr^i_2$, DMF, rt, 16 h; (ii) add H_2O, extract into EtOAc; (iii) dry, evaporate, flash ColC. (c) (i) $Pd(OAc)_2$, Bu_4NCl, K_2CO_3, DMF, 100 °C, 72 h; (ii) evaporate,add MeOH; (iii) thick-layer chromatography.

of the ester **79a** to form **79b** that is isolated in 98% yield and then condensed with **76** to form **80** that is recovered in 87% yield.

dx.doi.org/10.1021/op300287a | Org. Process Res. Dev. 2012, 16, 1684−1696

The 6-quinoline ring is formed by the coupling of **80** with **81** in the presence of $Pd(OAc)_2$, Bu_4NCl, and K_2CO_3. The product is isolated in 36% yield. The reaction of **80** with other unsaturated alcohols gives the analogous alkyl-substituted 6-quinolines. There are also examples describing the reaction of **76** with 3-amino-4-iodobenzoic acid in place of **79b**, and this produces the corresponding 7-quinoline derivatives.

There are several examples in the patent describing the preparation of almost 20 compounds. The examples are all micro scale, and purity details are not provided although ^1H NMR data are given as well as some MS information.

Advantages. The patent describes a range of novel compounds that are said to be useful for treating learning and memory problems.

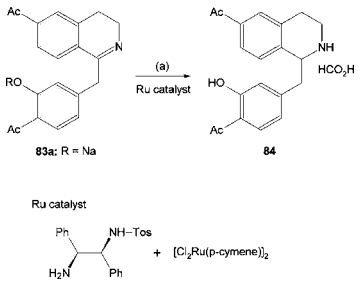
PATENT NO. U.S. 8,227,611

Assignee: Mallinckrodt LLC, Hazelwood, Missouri, United States

Title or Subject: Process for the Preparation of Hexahydroisoquinolines from 1,2,3,4-Tetrahydroisoquinolines

This patent is directed at the synthesis of morphinans that are intermediates in the production of several analgesics such as codeine, morphine, oxycodone, and oxymorphone. The reaction in Scheme 28 shows the first step in the preparation of the

Scheme 28[a]



[a]Reagents and conditions: (a) (i) Et_3N, HCO_2H, Ru catalyst, MeCN, rt, 16 h; (ii) filter, wash in MeCN, dry.

hexahydroisoquinoline **85** that is an asymmetric reduction of the imine moiety in **83a** using a chiral Ru catalyst. The reaction is carried out in the presence of HCO_2H as the source of hydrogen, and the product is the acid salt of **84** that is isolated in 97.9% yield with 97.3% purity and 99% ee (R). When starting from the phenol **83b** (R = H), the yield of **84** is 80–95% with 90% ee.

In the next stage of the process the acid salt **84** or the acid-free compound is subjected to a Birch reduction to produce the desired hexahydroisoquinoline **85**. Using the acid salt **84** the product is isolated in 96% yield and 98.6% ee (R). When starting from the acid-free compound the yield of **85** is around 90%. This reduction was also carried out using Li and $MeNH_2$ in place of Li and NH_3, allowing the reaction to take place between −10 and 10 °C, and **85** is isolated in 80% yield. Using Li and $EtNH_2$ the yield was between 50 and 70%. The octahydroisoquinioline **86** is also obtained when using Li and $(H_2NCH_2)_2$ for the reduction of **84**.

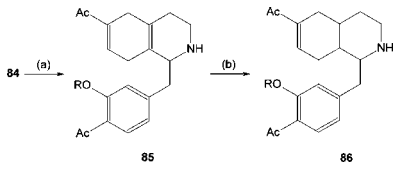
Advantages. The process is a highly stereoselective method of preparing the desired drug intermediates.

PATENT NO. U.S. 8,227,617

Assignee: MSD Oss B.V., Oss, The Netherlands

Title or Subject: Process for the Preparation of Asenapine and Intermediates Used in its Preparation

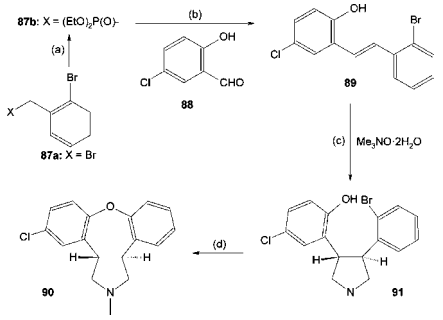
Scheme 29[a]



[a]Reagents and conditions: (a) (i) THF, Pr^iOH, −55 °C; (ii) liq NH_3, $NaOBu^t$, −55 °C, 0.25 h; (iii) Li, −55 °C, 50 min; (iv) add MeOH, warm to rt; (v) rt, 1 h; (vi) add degassed H_2O, rt, 0.5 h; (vii) add aq HOAc, NH_4OH to pH 8.8–9.2, rt, 1 h; (viii) filter, H_2O wash, dry. (b) $Li/(H_2NCH_2)_2$.

Asenapine **90**, is used to treat depression, schizophrenia, and acute mania associated with bipolar disorder, and an alternative synthesis has been reviewed (*Org. Process Res. Dev* **2011**, *15*, 491). The current patent discloses a method of preparing **90** that involves the synthesis of a novel intermediate **91**, and it is this compound that is covered by the claims of the patent. The synthetic route to **90** and **91** is outlined in Scheme 30 and starts

Scheme 30[a]



[a]Reagents and conditions: (a) (i) $(EtO)_3P$, xylene, 80 °C, 1 h; (ii) 110 °C, 16 h; (iii) evaporate. (b) (i) $KOBu^t$, THF, <33 °C; (ii) add H_2O/4 M HCl; (iii) separate, wash in Na_2CO_3; (iv) brine wash, evaporate. (c) (i) THF, rt; (ii) add LDA, 40 °C, 1 h; (iii) add H_2O, concentrate, add EtOAc; (iv) 18% HCl/EtOAc to pH 8; (v) separate, H_2O wash, dry, evaporate; (vi) crystallise from $EtOH/H_2O$. (d) (i) Cs_2CO_3, CuI, $Me_2NCH_2CO_2H$, dioxane, reflux; 68 h; (ii) filter, evaporate, add EtOH; (iii) add aq HBr, rt, 16 h; (iv) filter, dry; (v) add H_2O, 2 M NaOH to pH 8; (vi) extract in DCM, wash, dry, evaporate; (vii) maleic acid, $EtOH/H_2O$, rt, 16 h; (viii) add EtOH, rt, 1 h; (ix) filter, dry.

with the reaction of **87a** with $(EtO)_3P$ to give **87b**. This is isolated and used without purification in the reaction with the aldehyde **88** in the presence of $KOBu^t$ to form **89**. This is isolated in 92% yield and then treated with a solution of $Me_3NO{\cdot}2H_2O$ and LDA. After workup the crude product is obtained as an oil that is crystallised from $EtOH/H_2O$, and **91** is isolated in 79% with purity of 99% (HPLC). The preparation of **90** by ring closure of **91** is carried out by using Cs_2CO_3 and an equimolar mixture of CuI and $Me_2NCH_2CO_2H$. The compound is initially isolated as the HBr salt that is then converted to the maleate salt that is isolated in 39% yield and 99.8% purity.

The patent also describes alternative reagents for preparing **91** by the same route. For example, the chlorocompound **87c** (X = Cl) is used in place of **87a**, and in another example, the acetoxy derivative of **89** is an intermediate.

Advantages. The process provides an alternative route to a drug molecule via a novel intermediate.

dx.doi.org/10.1021/op300287a | *Org. Process Res. Dev.* 2012, 16, 1684–1696

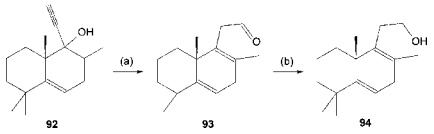
PATENT NOS. U.S. 8,227,629 AND 8,227,630

Assignee: Firmenich SA, Geneva, Switzerland

Title or Subject: Process for the Preparation of Tetranorlabdane Derivatives

Tetranorlabdanes such as **95a** are used as perfumery ingredients, and these two patents disclose different aspects of a novel process for their preparation. Alternative methods for the synthesis of these compounds are summarised and can be long and tedious and thus are not suitable for industrial production. The patents describe a novel rearrangement of a propargylic alcohol and a cyclisation step. The claims of the first patent focus on the rearrangement, and the second, on the cyclisation step. Scheme 31 outlines the first stage of a process to prepare **95a**

Scheme 31[a]



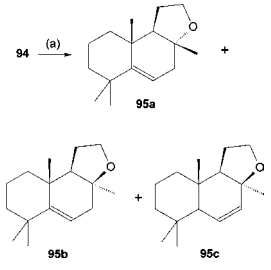
[a]Reagents and conditions: (a) (i) $[V_2O_6SiPh_2]_n$, *o*-xylene, reflux, 17 h; (ii) add 5% aq NaOH, extract in Et_2O, brine wash; (iii) dry, evaporate, distill. (b) (i) $LiAlH_4$, Et_2O, reflux, 0.5 h; (ii) cool to 0 °C, add H_2O, 5% aq NaOH, rt, 5 min; (iii) filter, concentrate, distill.

starting with the rearrangement of **92** catalysed by vanadyl- or molybdyl oxide compounds. This transformation is described as nontrivial since the reaction could have produced a number of other products. The reaction gives the aldehyde **93** that is isolated in 83% yield after distillation. Reduction of **93** using $LiAlH_4$ gives alcohol **94** in 90% yield. Both the aldehyde and alcohol are novel compounds and are covered by one of the patent claims; ^1H and ^{13}C NMR data are provided.

The next stage of the process is cyclisation of **94** to form **95a**, and this is carried out using $FeCl_3$. There are three options described for this reaction. The first uses 0.5 M amounts of $FeCl_3$ and SiO_2 and gives a 73% yield of **95a** after distillation together with **95b** (4% yield) and **95c** (2% yield) and 8% yield of **94**. When a stoichiometric amount of $FeCl_3$ is used, the yields are 63% **95a** and 3% **95b**. Using a catalytic amount of $FeCl_3$ gives yields of 39% of **95a**, 27% of **95b**, and 9% of **95c**.

The patent also describes the preparation of **99a**, the saturated analogue of **95a**, by the same route starting from **96** and using the same basic procedure described in Schemes 31 and 32. Full

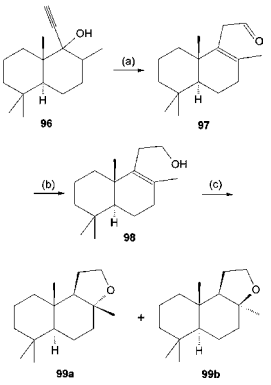
Scheme 32[a]



[a]Reagents and conditions: (a) (i) $FeCl_3$, SiO_2, DCE, DCM, 24 °C, 20 min; (ii) add 5% HCl, extract in Et_2O, wash, dry, evaporate, distill.

details are provided in the patent along with ^{13}C NMR data for compound **98**.

Scheme 33[a]



[a]Reagents and conditions: (a) and (b) see Scheme 31. (c) See Scheme 32.

Advantages. The process gives the desired products in high selectivity.

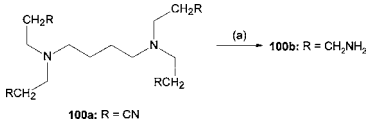
PATENT NO. 8,227,641

Assignee: Saltigo GmbH, Lagenfeld, Germany

Title or Subject: Process for the Preparation of Amino-alkylamines

This patent covers a process for preparing a compound such as **100b** that is used as a complexing agent, a monomer, or in the preparation of dendrimers. An alternative process describes the preparation of **100b** by hydrogenation of **100a** using a Raney catalyst. However, it is said that the process uses large quantities of the catalyst (>12.5 wt % based on **100a**) and hence is not very economical. This patent discloses that the hydrogenation of **100a** to give **100b** can be improved using significantly less catalyst. This is achieved by adding a solution of **100a** to the Raney catalyst and solvent that is under an atmosphere of NH_3 and H_2. Using 6.7 wt % Raney Co catalyst based on **100a**, the yield of **100b** is 97% yield with purity of 97% (GC).

Scheme 34[a]



[a]Reagents and conditions: (a) (i) Raney Co, H_2O, MeOH, NH_3; (ii) heat to 95 °C, add H_2 to 100 bar, 4 h; (iii) cool 25 °C,, filter, concentrate.

The patent also covers the application of the process to other polyfunctional nitriles although the only example is for hydrogenation of **100a**.

Advantages. The process gives high selectivity to the amine but does require very high pressure.

PATENT NO. U.S. 8,232,392

Assignee: Chemi S.p.A., Cinisello Balsamo, Milan, Italy

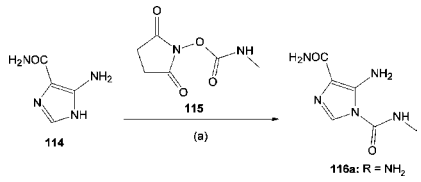
Title or Subject: Process for Preparing Temozolomide

Temozolomide **118** was first discovered over 30 years ago and in the past 10 years has been found to be useful in the treatment of aggressive brain tumours. A patent on an alternative synthesis of **118** has been reviewed (*Org. Process Res. Dev* **2010**, *14*, 311), and the current patent summarises several other processes. Some

dx.doi.org/10.1021/op300287a | *Org. Process Res. Dev.* 2012, 16, 1684−1696

of these processes use reagents such as MeNCO or $MeNHNH_2$ that are dangerous and/or toxic and not deemed to be desirable for commercial production of the drug. The method described in this patent is shown in Scheme 35 and starts from the amide **114**

Scheme 35[a]

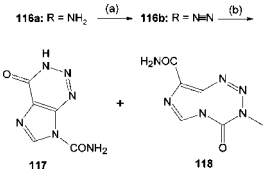


[a]Reagents and conditions: (a) $EtNPr^i_2$, MeCN, 25 °C, 16 h; (ii) <5 °C, 1 h; (iii) filter, H_2O wash, dry.

that is converted to the carbamoyl compound **116a** by reaction with the succinimidyl reagent **115** in the presence of a base. The product is isolated in 88% yield and 96.9% purity (HPLC). The reagent **115** is described as a nonexplosive, crystalline solid with comparatively low toxicity and is much safer to use in this reaction than MeNCO that is used in alternative methods.

The second stage of the process to prepare **118** converts the amine group in **116a** to the diazonium compound **116b** via a diazotisation reaction (Scheme 36). The precise details of this

Scheme 36[a]



[a]Reagents and conditions: (a) See *J. Org. Chem.* **1997**, *62*, 7293. (b) (i) 5% HCl to pH 2.2; (ii) pass over XAD 1600 IER; (iii) recrystallise.

reaction are not described, and reference is made to a literature method (*J. Org. Chem.* **1997**, *62*, 7293). Compound **116b** is not isolated and can cyclise by reaction of the diazonium group with either of the two amide groups, giving two products. If the primary amide group reacts, the product is **117**, and **118** is formed only by reaction of the secondary amide. The reaction produces a mixture of **117** and **118** in approximately equal amounts, and these can be separated. This is done by passing the acidified reaction mixture from the diazotisation reaction over a column of a polymeric adsorbent resin. The material used in the example is XAD 1600 from Rohm & Haas, although other resins are also covered in the claims. The first to elute from the column is **117**, and after it has eluted, **118** is eluted using acidified aq EtOH. After separation in this manner **118** is recrystallised from acidified Me_2CO and isolated in 30% yield with 99.9% purity.

Advantages. The process provides an alternative and safer route to temozolomide, but unfortunately half of the intermediate in the process is lost as waste.

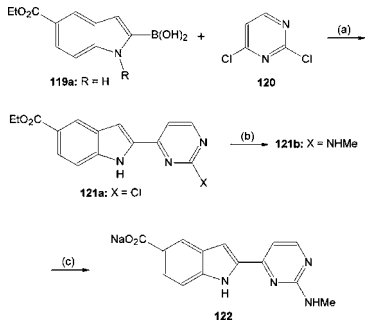
■ PATENT NO. U.S. 8,232,395

Assignee: Sanofi, Paris, France

Title or Subject: Method for Producing 2-(2-Aminopyrimidin-4-yl)-1*H*-indole-5-carboxylic Acid Derivatives

The compounds covered by this patent such as **121b** and **129** are described as intermediates for preparing 1kB kinase inhibitors. Although indoles can be prepared by classical Fischer synthesis, the patent states that this method is not satisfactory when applied to the desired compounds. Severe reaction conditions are needed, and oligomeric compounds are formed that are difficult to remove. Two routes for preparing the desired compounds are described in this patent, and Scheme 37 outlines the

Scheme 37[a]

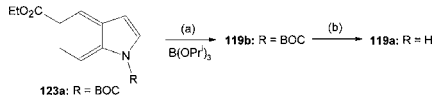


[a]Reagents and conditions: (a) (i) Na_2CO_3, EtOH, rt; (ii) $(Ph_3P)_4Pd$, 70 °C, 2 h; (iii) aq HCl, cool 0 °C; (iv) filter, dry. (b) (i) $MeNH_2$, EtOH, 80 °C, autoclave, 4 h; (ii) concentrate, EtOH wash. (c) (i) NaOH/EtOH, 70 °C, 4 h; (ii) cool, filter, wash in EtOH/H_2O, dry.

first of these. This begins with the reaction of the indole boronic acid **119a** and the chloropyrimidine **120** in the presence of $(Ph_3P)_4Pd$ to form **121a** that is isolated in 93% yield and 96% purity. This is then converted to the amino compound **121b** by treatment with $MeNH_2$, and the product is isolated in quantitative yield and 97.6% purity. The ester group in **121b** is then hydrolysed with NaOH to produce the Na salt **122** in 87.6% yield with purity of 98.1%. Further purification is not mentioned.

The indole boronic acid **119a** is obtained by the reaction of **123** with $B(OPr^i)_3$ in the presence of LDA (Scheme 38). The

Scheme 38[a]



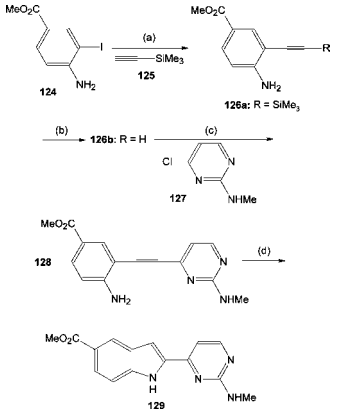
[a]Reagents and conditions: (a) LDA/THF, PhMe < 10 °C, 5 min; (ii) aq HCl, <10 °C, 0.5 h; (iii) filter; (iv) EtOH, 40 °C; (v) aq HCl/EtOH, 45 °C, 2.5 h; (vi) add H_2O, 15 °C, 0.5 h; (vii) filter, dry.

BOC-protected intermediate **119b** is subject to acid-promoted deprotection to give **119a** in 61% yield with purity of 92.7% (HPLC). The patent mentions that it is advantageous to use the unprotected indole **119a** in the reaction with **120** rather than the N-protected compound. The explanation for this is that, although some **123** is formed by loss of the boronic acid group from **119a** during the coupling reaction with **120**, **123** does not subsequently react with **120**. Hence, the yield of **121a** in the coupling step is not reduced.

The patent also describes a quite different method for preparing the desired compounds, and Scheme 39 outlines the process for preparing **129** and the methyl ester analogue **121b**. This route starts by preparing the silylated acetylene compound **126a** that is isolated in 90% yield with 99% purity after what is described as an aqueous workup. In the next step the silyl group is removed, and **126b** is isolated in quantitative yield. The acetylene **126b** is then reacted with the chloropyrimidine **127** in the presence of CuI and a Pd catalyst in DMF to give **128** that is

dx.doi.org/10.1021/op300287a | *Org. Process Res. Dev.* 2012, 16, 1684−1696

Scheme 39[a]

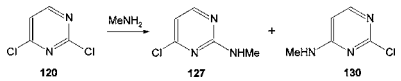


[a]Reagents and conditions: (a) (i) Et_3N, PhMe; (ii) CuI, PPh_3, 20 °C; (iii) aq workup. (b) (i) Bu^n_4NF, THF, <8 °C, 0.5 h; (ii) HOAc, 2 °C; (iii) add H_2O, extract in DCM; (iv) evaporate. (c) (i) Et_3N, DMF, rt; (ii) CuI, $(Ph_3P)_4Pd$, 71 °C, 3 h; (iii) aq workup. (d) (i) $KOBu^t$, *N*-methylpyrrolidone, rt, 24 h; (ii) aq workup.

isolated after aqueous workup in 85% yield and 99.7% purity. The cyclisation of **128** to form **129** is carried out using a strong base such as $KOBu^t$, and the product is isolated after an aqueous workup in 58% yield and 92.3% purity.

Although the patent does not provide details for the preparation of **127**, it is stated that it can be prepared by the route outlined in Scheme 40. The reaction produces **127** and

Scheme 40[a]

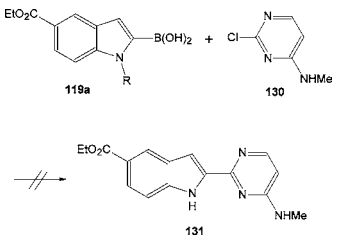


[a]Reagents and conditions: (a) no details provided.

130, and these can be separated by chromatographic methods or by steam distillation.

The patent discusses an alternative route to give **121b** by reacting **119a** with **127** in place of **120**. It is stated that **119a** will react with **127** that contains **130**, and this reaction produces **121b**. It may be expected that in this reaction **130** would react to give **131** as shown in Scheme 41. However, it is claimed that this

Scheme 41



reaction does not take place although there are no examples of the reaction of **119a** and **127** with or without **130**.

The examples in this patent mention aqueous workup a number of times, but the precise meaning of this term is not explained. Such nebulous terms are less than helpful when attempting to repeat the work.

Advantages. The process provides alternative routes to a drug intermediate that overcome problems of product isolation.

PATENT NO. U.S. 8,232,414

Assignee: UCB Pharma GmbH, Monheim, Germany

Title or Subject: Polymorphic Form of Rotigotine and Process for its Production

Compound **132** is used to treat Parkinsonism and other dopamine-related disorders, and a single crystalline form is known that is designated Form I. This patent describes a new polymorph designated Form II that appears to be thermodynamically more stable and is prepared from Form I. Two methods are described for the preparation of Form I, one of which is rather unusual and involves storing Form I in an aluminium foil bag for an extended period.

The precise details of the first method for preparing Form I are as follows:

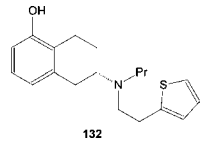
(1) Place Form I of **132** in a sealed Aluthene foil bag at 38−40 °C for 10 days.
(2) Dissolve the solid in EtOH to precipitate Form II crystals.

The above procedure is only carried out on small scale, whereas the second method uses over 5 kg of solid Form I. The details are as follows:

(1) An approximately equal mass of Form I of **132** and EtOH are slurried together and then transferred to a reactor with additional EtOH.
(2) Stir the mixture for 24 h at rt.
(3) Filter and wash crystals in EtOH.
(4) Dry at 40 °C for 43 h.

The two samples are characterised by XRD, DSC, and Raman spectroscopy and found to be identical, and these data are provided in the patent. It is also reported that the EtOH slurry of Form I can be converted to Form II when seeds of Form II are added to the slurry.

Rotigotine



Advantages. The process clearly shows that the new form of the drug is the most stable and can be produced quite easily.

PATENT NO. U.S. 8,232,421

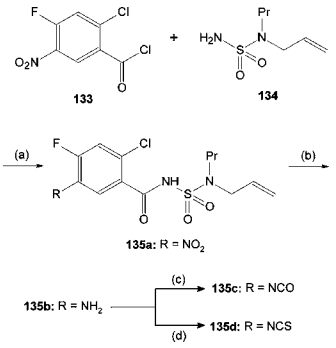
Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Bifunctional Phenyliso(thio)cyanates and Processes and Intermediates for Their Preparation

The compounds of interest in this patent are potential precursors for the preparation of crop protection agents. However, the patent states that phenyliso(thio)cyanate compounds that also contain an acylsulfonamide group were previously thought to be inaccessible. This is because it is known that sulfonamides react with iso(thio)cyanates to form sulfonylureas. Despite this, the patent describes a process for the preparation of a whole range of compounds that contain the two groups. There are over 150 of these compounds listed in the patent as having been prepared, and Scheme 42 outlines the preparation of the isocyanate **135c** and isothiocyanate **135d** by the new procedure. The process begins with the coupling of **133** with **134** that takes place in the presence of Et_3N and DMAP. The product **135a** is isolated in 91.9% yield and then reduced to **135b** using Fe powder in HOAc. The amine is isolated in 75.3% yield and can be converted to **135c** using $COCl_2$ or to **135d** using $CSCl_2$.

dx.doi.org/10.1021/op300287a | *Org. Process Res. Dev.* 2012, 16, 1684−1696

Scheme 42[a]

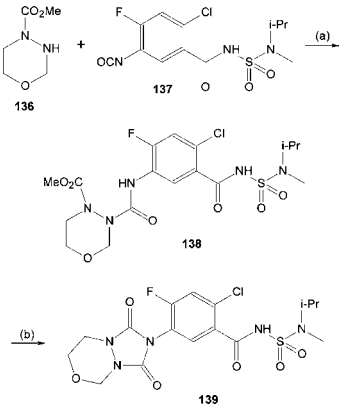


[a]Reagents and conditions: (a) (i) Et_3N, DMAP, DCM, <0 °C, 1.5 h; (ii) 22 °C, 2 h; (iii) add 1 M HCl, separate; (iv) wash in 1 M HCl, dry, concentrate; (v) Et_2O/pentane, filter, dry. (b) (i) Fe, THF, HOAc, 75 °C, 1.5 h; (ii) cool, concentrate, add EtOAc, filter; (iii) add active C, $MgSO_4$; (iv) filter, concentrate; (v) add EtOAc/pentane, filter, dry. (c) (i) Add 4 M HCl/dioxane, 22 °C, 1 h; (ii) $COCl_2$, 95 °C, 1 h; (iii) concentrate, add pentane, separate, concentrate. (d) (i) $CSCl_2$, EtOAc, 22 °C, 1 h; (ii) 75 °C, 1 h; (iii) concentrate, add pentane, filter, dry.

The yield of **135c** is 95.8% (purity 95% by ^{1}H NMR), and that of **135d** is 96.1% (purity 95% by ^{1}H NMR).

The patent describes the use of one of the bifunctional compounds in the preparation of compound **139** that is presumed to be a crop protection agent. The two-step reaction begins with the condensation of **137** with the oxadiazinane **136** to form the intermediate **138** that is isolated in 82.3% yield after purification by flash ColC. The second stage is a cyclisation that is carried out in the presence of $NaOBu^t$. The isolated yield of **139** is 76%, but the purity is not reported.

Scheme 43[a]



[a]Reagents and conditions: (a) (i) DCE, 22 °C, 18 h; (ii) flash ColC, evaporate. (b) (i) $NaOBu^t$, PhMe, reflux, 7 h; (ii) cool, add 1 M HCl/Et_2O; (iii) concentrate, add DCM, wash in 1 M HCl/H_2O; (iv) concentrate.

Advantages. The patent provides a wide range of novel compounds that are precursors for the preparation of crop-protection agents.

Keith Turner

Kappa Tau Consulting, Tinniswood, Rowlands Gill, Tyne and Wear NE39 1PN, United Kingdom.Telephone: +44 (0)1642 653484. E-mail: keith@kappa-tau.co.uk.

dx.doi.org/10.1021/op300287a | *Org. Process Res. Dev.* 2012, 16, 1684−1696