Organic Process Research & Development **2000**, *4*, 246–253

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during December, 1999, to March, 2000

This is the second review covering a selection of U.S. patents that are in the field of organic process development chemistry. During the period from 1 December, 1999, to 31 March, 2000, there were 660 patents that fit the criteria, and of these, 22 have been selected and are summarised here. As before, there is no legal or commercial significance attached to the inclusion of any particular patent, and those chosen were perceived to have interest to readers of this journal. The novelty, usefulness, or legal validity of these patents has not been assessed, and the advantages given here are those claimed in the patent unless the reviewer has prior knowledge. The selection this time ranges from the use of microwave radiation to promote a ring-closure reaction to a process for a one-step synthesis of vitamin C. Readers are again warned that systematic nomenclature is often not a feature of patents, and no attempt is made here to give correct IUPAC names to any compounds mentioned. It is not unusual for a chemical patent to have no chemical structures or even formulae to assist the reader in understanding the subject matter of the patent.

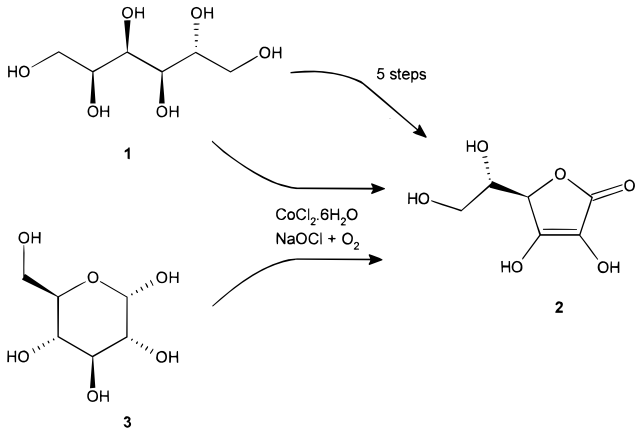
Patent No. U.S. 5,998,634

Assignee: U.S. Secretary of the Interior

Title or Subject: One Step Synthesis of Vitamin C

Vitamin C (ascorbic acid) **2** is usually produced commercially on a substantial scale from sorbitol **1** in a multistep process (Scheme 1). This patent claims a single-step process

Scheme 1



employing the catalytic oxidation of **1**, sorbose, glucose **3**, or 2-keto-L-gulonic acid. The catalyst is hydrated cobalt oxide formed by adding NaOCl to aqueous cobalt chloride, and the reaction is carried out in air to supply oxygen for the oxidation. Although NaOCl is often used as an oxidising agent, in this case it is the oxygen that is the oxidant, and hence the amount of NaOCl needed is significantly reduced. Limited reuse of the catalyst was shown to be possible.

Advantages

Clearly a single-stage process is cheaper than a multistage one, and this process claims to be able to use alternative starting materials to sorbitol. The key finding is that oxygen from the air is the real oxidising agent, and clearly this is much cheaper than NaOCl. The experimental work was limited to producing gram quantities; therefore, the real potential of the process is not indicated.

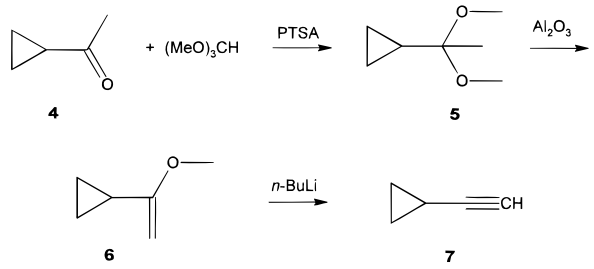
Patent No. U.S. 6,002,062

Assignee: Lonza AG, Gampel/Valais, Switzerland

Title or Subject: Process for the Preparation of Ethynylcyclopropane

Interest continues in the synthesis of cyclopropylacetylene **7** compounds for producing the anti-AIDS drug efavirenz. The previous review (*Org. Process Res. Dev.* **2000**, *4*, 68) summarised two different methods, and this patent describes yet another. In this case the method is based on a two-stage elimination of methanol from the cyclopropane acetal **5** that proceeds via the enol ether **6** as shown in Scheme 2. The

Scheme 2



acetal **5** is produced from the commercially available ketone **4** by treatment with trimethyl orthoformate in the presence of *p*-toluene sulphonic acid (PTSA). The first stage of the elimination is catalysed by alumina, and the second stage uses a strong base such as *n*-BuLi.

Advantages

Previous methods cited describe low-temperature cyclization with *n*-BuLi or require the synthesis of a *gem* dichloride using PCl_5. Both of those processes produce halide wastes, whereas this method does not require such extreme

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Published on Web 06/16/2000

conditions, produces no such wastes, and starts from the ketone **4** which is commercially available.

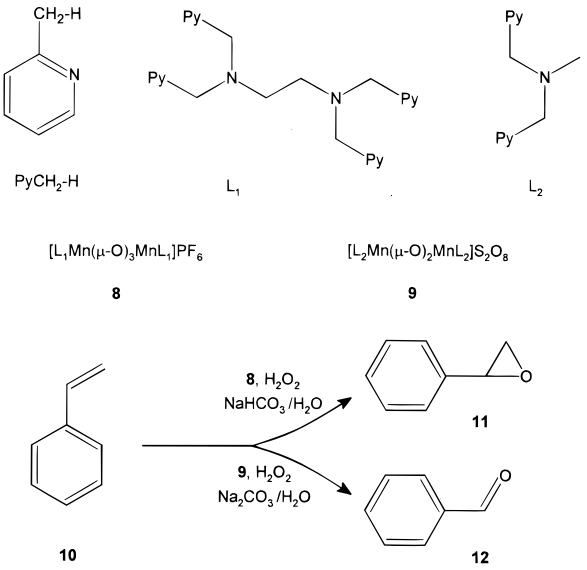
Patent No. U.S. 6,008,387

Assignee: Hoechst AG, Frankfurt, Germany

Title or Subject: Oxidation of Organic Compounds Using Dimanganese μ-oxo Complex Salts

This patent describes the use of oxo-bridged manganese salts such as **8** and **9** to catalyse the oxidation of vinyl compounds using H_2O_2 or NaOCl. Scheme 3 shows that with

Scheme 3



different catalysts in a weakly basic solution styrene gives the oxide **11** or benzaldehyde **12**. The manganese salts are similar to those developed by Unilever in the mid 1990s as bleach activators and were used in a new type of washing powder that had to be withdrawn from sale, apparently because it damaged the clothes. This reviewer has long considered that such compounds could be useful chemical oxidising agents, and this patent demonstrates an example. Although this patent mentions oxidation of organic compounds, it claims vinyl compounds and only gives examples for styrene.

Advantages

The original Unilever complexes contained triazacyclononane ligands that were difficult to make and hence costly, whereas the current complexes are prepared from less costly ligands (Scheme 3).

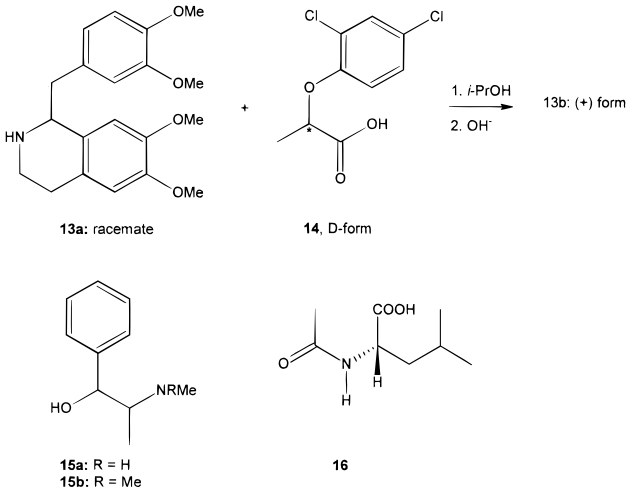
Patent No. U.S. 6,015,903

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Resolution of Tetrahydropapavarine

The patent describes a method of resolving tetrahydropapavarine **13** by formation of a crystalline salt using the (+) or (−) forms of the acid **14** (Scheme 4). Since **14** is available in both (+) and (−) forms it is possible to directly obtain both forms of **13**. The method is also applied to resolution of ephedrine **15a**.

Scheme 4



Advantages

The feature of this patent is the stable nature and availability of the resolving agent **14** compared to those of *N*-acetylleucine **16** which was previously used to resolve **13**. Since **16** is a naturally occurring material, an extra step is needed if it is used to resolve both forms of **13**.

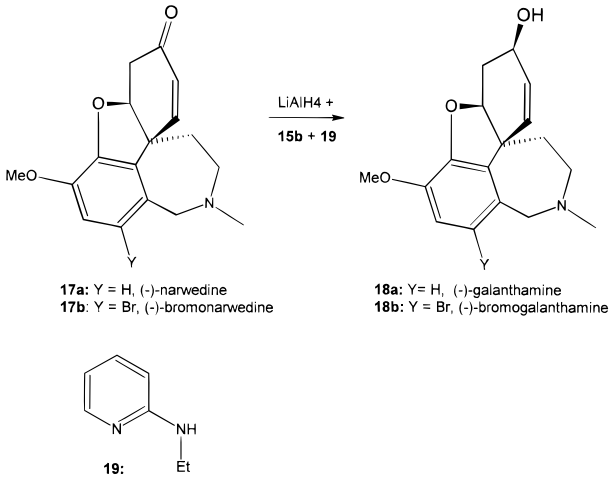
Patent No. U.S. 6,018,043

Assignee: Janssen Pharmaceutica N. V., Belgium

Title or Subject: Process for Preparing Galanthamine Derivatives by Asymmetric Reduction

(−)-Galanthamine **18a** and its derivatives can be used in the treatment of Alzheimer's disease and may be obtained by extraction from daffodils or snowdrops. A synthetic route to **18a** begins with narwedine **17a** which is reduced to the alcohol **18a** (Scheme 5). A resolution step is needed since

Scheme 5



17a is produced as a racemic mixture. This patent describes the preparation of **18a** from **17a** by asymmetric reduction using $LiAlH_4$ and a chiral modifier. The modifier is a mixture of (−)-*N*-methylephedrine **15b** and *N*-ethyl-2-aminopyridine **19**. It is possible to use racemic **17a** because the (+) form is not reduced under the conditions and may be racemised and recycled. Alternatively if a pure enantiomer of **17a** is

available, then asymmetric reduction can be performed directly. The patent also describes the preparation and resolution of bromogalanthamine **18b** from **17b**.

Advantages

The key step is the asymmetric reduction of a racemic mixture of **17a** to give **18a**. This allows racemic **17a** to be used directly since resolution of the enantiomers of **17a** is difficult due to its facile racemization.

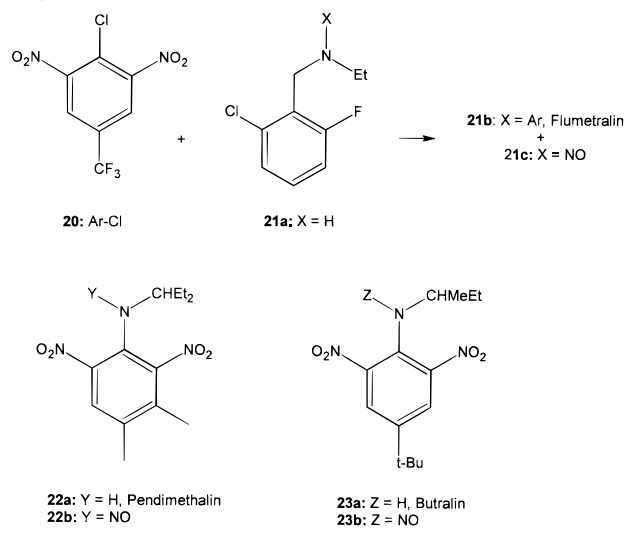
Patent No. U.S. 6,018,079

Assignee: SRM Chemical Ltd Co., Texas, U.S.A.

Title or Subject: Removal of N−Nitroso Compounds from Dinitroaniline Herbicides

Dinitroaniline herbicides such as **21b**, **22a**, and **23a** often contain *N*-nitroso impurities at levels >10% that must be removed to well below 100 ppm before use (Scheme 6). The

Scheme 6



process here involves heating the herbicide and its *N*-nitroso impurity until the impurity decomposes by NO elimination. A vacuum may be applied to assist the NO removal. The method is only suitable where the *N*-nitroso compound decomposes before the herbicide and accelerated rate calorimetry is used to determine if this is the case. The process is applicable to flumetralin **21b** and its *N*-nitroso derivative **21c** which are produced from the dinitrobenzene **20** and the secondary amine **21a**. The process is also applied to pendimethalin **22a** and butralin **23a** which are contaminated with their respective *N*-nitroso compounds **22b** and **23b**. If the original level of *N*-nitroso compound is higher than about 10% it is recommended that a pretreatment method is used before thermolysis. This is because excessive heating will degrade the herbicide and the exothermic nature of the NO elimination may be difficult to control on a commercial scale when large quantities of impurity are present.

Advantages

Other methods used to remove *N*-nitroso impurities are based on the addition of chemicals that react with the *N*-nitroso compound. This results in excessive usage of reagents and production of waste. With some herbicides it is possible to remove the *N*-nitroso compound by fractional or steam distillation, but this can take several hours and the *N*-nitroso compounds still need to be destroyed. This process is often effective in minutes and does not use extra reagents.

Patent No. U.S. 6,020,530

Assignee: Elf Atochem S. A., France

Title or Subject: Process for the Purification of DMSO

High purity DMSO (>99.7%) can contain traces of metals such as Na and Fe that are not allowable in many uses in the electronics and pharmaceutical industries. This process uses conventional ion-exchange resins in the SO_3NH_4 form under anhydrous conditions to remove these metals to <1 ppb. Other metals are also claimed to be removed but no examples are given. It was possible to reduce the Na to <2 ppb and Fe to <1 ppb from about 1000 ppb in 2 h.

Advantages

Conventional ion exchange takes place in aqueous media, and the method allows treatment of dry DMSO and thus avoids having to add water then to distill.

Patent No. U.S. 6,025,177

Assignee: Sepracor Inc., Mississippi, U.S.A.

Title or Subject: Asymmetric Synthesis of α-Hydroxycarboxylic Acids

Cyclohexylphenylglycolic acid **28** is one example of the title acids that is a useful drug intermediate. It is produced in a four-stage synthesis employing a 1,2-aminoindanol **25** as a chiral auxiliary. The process is summarized as follows and shown in Scheme 7:

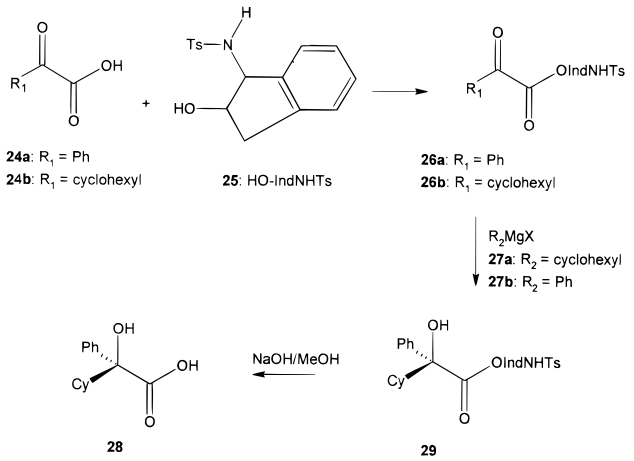
(a) Reaction of the α-ketocarboxylic acid **24** with a single enantiomer of **25** in the presence of DCC gives the aminoindanyl ester **26**.

(b) Treatment of the ester **26** with excess Grignard reagent **27** gives a mixture containing α-cyclohexylphenylglycolate ester **29**.

(c) Separation of a single diastereomer of the ester **29**

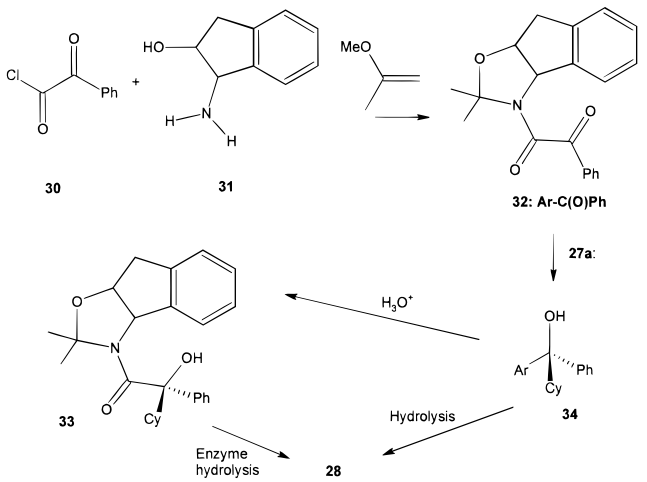
(d) Hydrolysis of the ester **29** to give the acid **28**.

Scheme 7



An alternatives route is shown in Scheme 8 and starts with the acid chloride **30** and the amine **31** in place of the

Scheme 8



tosylate **25**. In this case methoxypropene is used to protect the amino alcohol which produces a glyoxylyloxazolidine **32**. Treatment of **32** with Grignard **27a** produces the hydroxy derivative **34** and two-stage hydrolysis of **34** gives first the amide **33** and then **28** by enzymatic hydrolysis. Alternatively, **34** can be hydrolyzed directly to **28**.

Advantages

Other routes to **28** give poorer stereoselectivity or use more expensive chiral auxiliary reagents than those employed here.

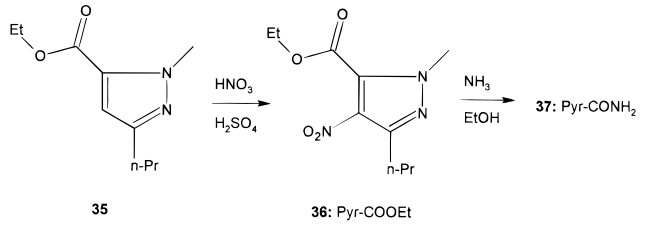
Patent No. U.S. 6,025,499

Assignee: Bayer AG, Leverkusen, Germany

Title or Subject: Process for Preparation of a Nitropyrazole Amide

A new nitropyrazole ester **36** is prepared by nitration of the pyrazole ester **35** and then used to prepare the amide **37** (Scheme 9). **37** is a known intermediate in the synthesis of

Scheme 9



sildenafil which is more commonly known as Viagra, the male anti-impotence treatment. The reactions in Scheme 9 can be carried out sequentially without isolation of **36**, thereby giving **37** in one stage. It is interesting to compare this process to the work recently described by Pfizer (*Org. Process Res. Dev.* **2000**, *4*, 17) on the development of its own commercial route to sildenafil. The Pfizer work specifically mentions the hazardous and highly exothermic nitration to produce **37** from the acid form of **36** (Pyr-COOH) and describes in some detail the effort that was expended in the safe scale-up of this step. Although this patent does not mention safety problems with nitration, it may be significant that both this and the Pfizer work was carried out by initially dissolving the substrate Pyr-COOH in concentrated sulphuric acid before addition of premixed HNO_3 and H_2SO_4. Pfizer reported that these precautions prevented an exotherm during the reaction that could have raised the reaction temperature by between 50 and 127 °C.

Advantages

The route to the amide **37** described by Pfizer is from the acid Pyr-COOH via a three-step method involving nitration, acid chloride formation, and then treatment with ammonia. Isolation of intermediates at each step is required, and this complicates the process whereas the route here is effectively a single stage without requiring intermediate isolation. In the potentially lucrative market for Viagra this could prove a significant development if it really is a commercially viable process.

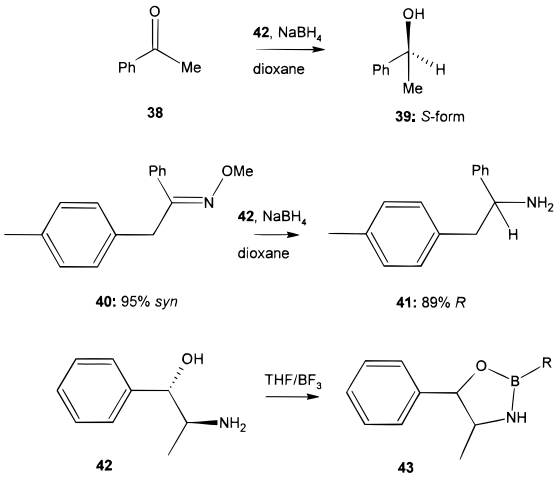
Patent No. U.S. 6,025,531

Assignee: Sumitomo Chemical Company, Osaka, Japan

Title or Subject: Processes for Preparing Optically Active Alcohols and Amines

This patent describes the asymmetric reduction of ketones to alcohols or oximes to amines. The reduction is carried out using a mixture of sodium borohydride and an optically active boron compound as a chiral auxiliary (Scheme 10). The boron compound is effectively an oxazaborolidine such as **43** which can be added in its pure form or produced in situ from an amino alcohol **42** by reaction with boronic acid or THF/BH_3 complex.

Scheme 10



Scheme 10 shows the process for producing *S*-1-phenylethanol **39** from acetophenone **38** using (1*S*,2*R*)-(+)-norephedrine **42** and sodium borohydride in dioxane. The reaction produced about 90% *S* and 10% *R* of **38** with 100% conversion. Also shown in Scheme 10 is the reduction of the oxime **40** to amine **41** using the same procedure. Other examples of amino alcohols were also used, and the process was applied to a number of ketones most of which contained at least one aryl substituent.

Advantages

This method uses less borane compounds than others while at the same time it gives higher optical yields.

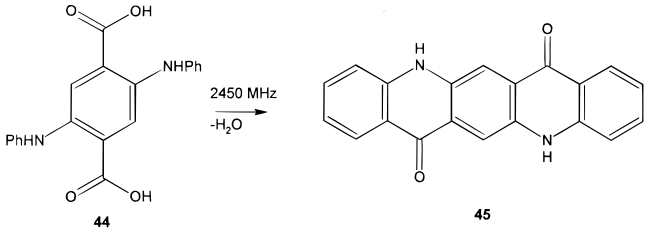
Patent No. U.S. 6,031,100

Assignee: Bayer Corp., Pennsylvania, U.S.A.

Title or Subject: Synthesis of Quinacridones using Microwave Radiation

The use of microwave radiation is not as unusual as it may be assumed and there is in fact a considerable amount of work underway on its use as an energy source in chemical reactions. This patent describes a process that uses microwave radiation to produce quinacridone **45** by ring closure of the anilinoterephthalic acid **44** (Scheme 11). **45** is a violet

Scheme 11



44 **45**

pigment that is very widely used in paints and inks and is generally produced by using thermal means to effect the ring closure. In this process the ring closure is promoted by irradiation of **44** with microwaves in the presence of polyphosphoric acid as a dehydrating agent. This is followed by precipitation of **45** by adding the reaction melt to water. It is claimed that the properties of the pigment can be improved by including various pigment additives during the synthesis. Examples of other quinacridone derivatives are described in the patent.

Advantages

Thermally induced ring closure can result in degradation of the product because of the temperatures that are needed, but this process is operated at lower temperatures and gives a purer product. The opportunity to include various additives during synthesis of **45** means that the final pigment has better colour properties especially for automotive uses.

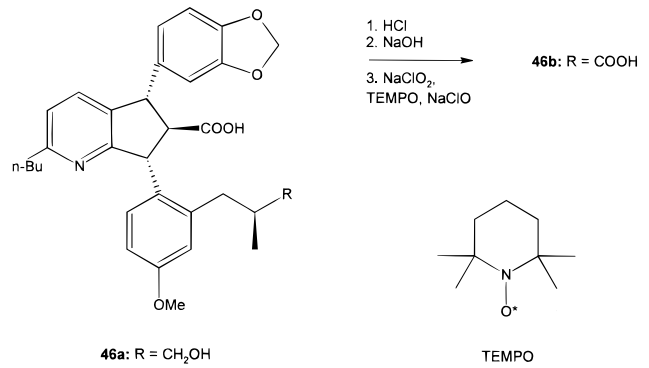
Patent No. U.S. 6,031,101

Assignee: Merck & Co. Inc, New Jersey, U.S.A., and Banyu Pharmaceuticals Co., Ltd, Tokyo, Japan

Title or Subject: Preparation of an Endothelin Antagonist by Oxidation of Primary Alcohol to Acid using TEMPO as Catalyst

This patent describes a process for preparing a compound such as **46b** by oxidation of the alcohol group in **46a**

Scheme 12



46a: R = CH_2OH TEMPO

(Scheme 12). The reaction takes place by using the benzylamine salt of **46a** in a buffered biphasic mixture and uses sodium chlorite, a catalytic amount of TEMPO and sodium hypochlorite. The patent also describes the multistep synthetic route to produce **46a**.

Advantages

This oxidation method does not produce wastes that are obtained when a Jones oxidation is employed. In addition the method also reduces epimerisation of chiral centres in the molecule and is a one-step process.

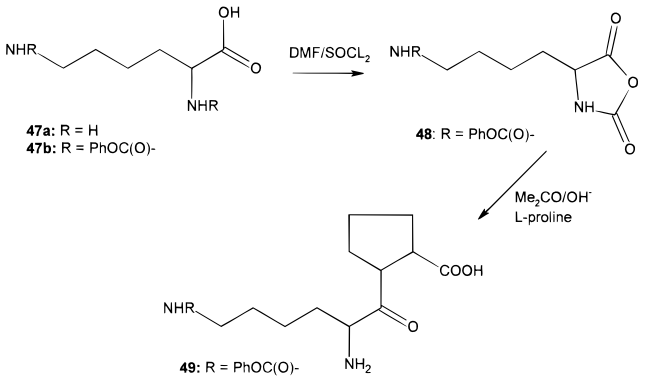
Patent No. U.S. 6,031,112

Assignee: P. F. C. Italiana S.r.l., Italy

Title or Subject: Production of Alkoxycarbonyldipeptides Intermediates in the Synthesis of Lisinopril

Lisinopril is a hypertensive drug that is produced from alkoxycarbonyldipeptides such as **49** (Scheme 13). These are

Scheme 13



47a: R = H
47b: R = PhOC(O)-

48: R = PhOC(O)-

49: R = PhOC(O)-

produced in a process described here that starts from the hydrochloride of L-lysine **47a** which is first converted to the bis-alkoxycarbonyl derivative **47b** using benzyl chloroformate. Cyclization of **47b** using DMF/$SOCl_2$ then follows, giving the anhydride **48** which is reacted with L-proline in alkaline hydroxyacetonic solution to give the desired dipeptide derivative **49**.

Advantages

This process for **49** uses readily available and cheaper reagents than other methods and is simple to carry out, giving good yields.

Patent No. U.S. 6,034,287

Assignee: Council of Scientific and Industrial Research, New Delhi, India

Title or Subject: Highly Selective Process for Producing p-Nitroarenes Using Aluminosilicate Catalysts

The process here uses zeolites as catalysts in place of sulphuric acid for the nitration of monosubstituted aromatics. The selectivity is achieved by the shape- and size-selective nature of the zeolite that allows the preferential production of para-substituted products. The process is carried out with

continuous water removal, and the zeolite catalyst is said to facilitate this along with simultaneous generation of electrophilic nitronium ions to enhance the para selectivity. The examples are only on gram scale but are given for the production of mononitro derivatives of toluene, chlorobenzene, ethylbenzene, cumene, and anisole.

Advantages

The zeolites enable nitration to proceed without using sulphuric acid and give improved separation of catalyst from the reaction mixture. Thus, reduced effluent volumes would result, and a less corrosive system is used.

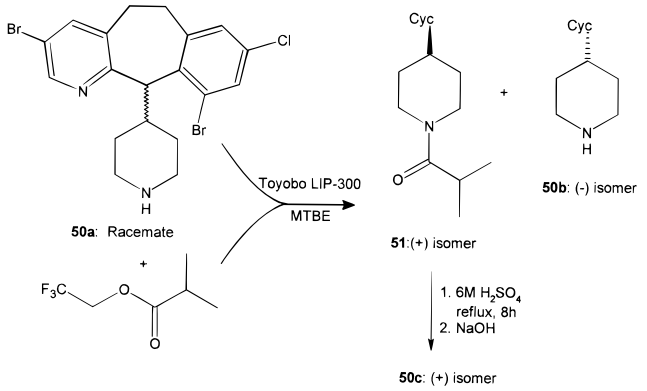
Patent No. U.S. 6,037,166

Assignee: Schering Corporation, New Jersey, U.S.A.

Title or Subject: Enzymatic Kinetic Resolution of an Intermediate Useful for Preparing Substituted Tricyclics

The tricyclic piperidine derivative **50c** is useful as an intermediate for preparing antihistamines and also as an inhibitor for farnesyl protein transferase (FPT). Scheme 14

Scheme 14



shows how **50c** is prepared by enzymatically catalysing the acylation of racemic **50a** to give (−)-**50b** and **51** which is subsequently hydrolyzed to give (+)-**50c**. The unreacted (−) isomer **50b** can be racemised by heating to 250−320 °C in glycol ethers and further acylated to improve the yield of **50c**. Various enzymes are used with trifluoroethyl esters as the acylating agents, and the reaction is carried out under anhydrous conditions in methyl tertiary butyl ether (MTBE).

Advantages

This is a highly selective process using readily available enzymes and a racemic precursor. The yield is enhanced by racemization of the unreacted isomer of **50a**, whereas other methods to prepare **50c** do not give such efficient resolution or high yields.

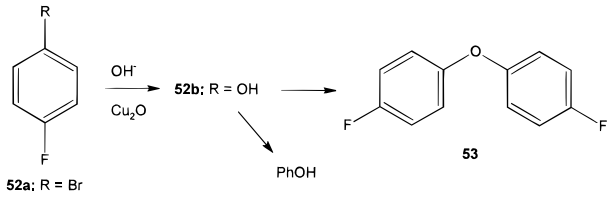
Patent No. U.S. 6,037,503

Assignee: Bromine Compounds Ltd., Israel

Title or Subject: Process for Preparation of p-Fluorophenol

The method described is hydrolysis of *p*-bromofluorophenol **52a** using a strong base and in the presence of cuprous oxide catalyst (Scheme 15). Although it is well-known that base hydrolysis of **52a** gives *p*-fluorophenol **52b** there are yield losses due to production of the ether **53** and also of phenol from hydrolysis of the product itself. Phenol is very

Scheme 15



difficult to remove from **52b**, and hence the amount produced must be minimized. The prior art is claimed to favour hydrolysis using copper catalysts with $Ca(OH)_2$ rather than with stronger bases such as NaOH. It is claimed that hydrolyzing **52a** using a mixture of $NaOH/Na_2CO_3$ with Cu_2O gives **52b** containing <0.1% phenol in >85% yield and almost 100% conversion. The ether **53** was obtained in only about 6−8% concentration, and these results compare with other methods which reportedly give 0.7% phenol and around 10−20% of **53.** Kilo scale examples are given, suggesting the advanced commercial status of the process.

Advantages

The preparation of **52b** containing low levels of phenol and low losses of the ether **53** are important aspects. The use of the more readily available NaOH in preference to $Ca(OH)_2$ is an important finding.

Patents Nos. U.S. 6,040,319 and 6,040,450

Assignee: Merck & Co., Inc., New Jersey, U.S.A.

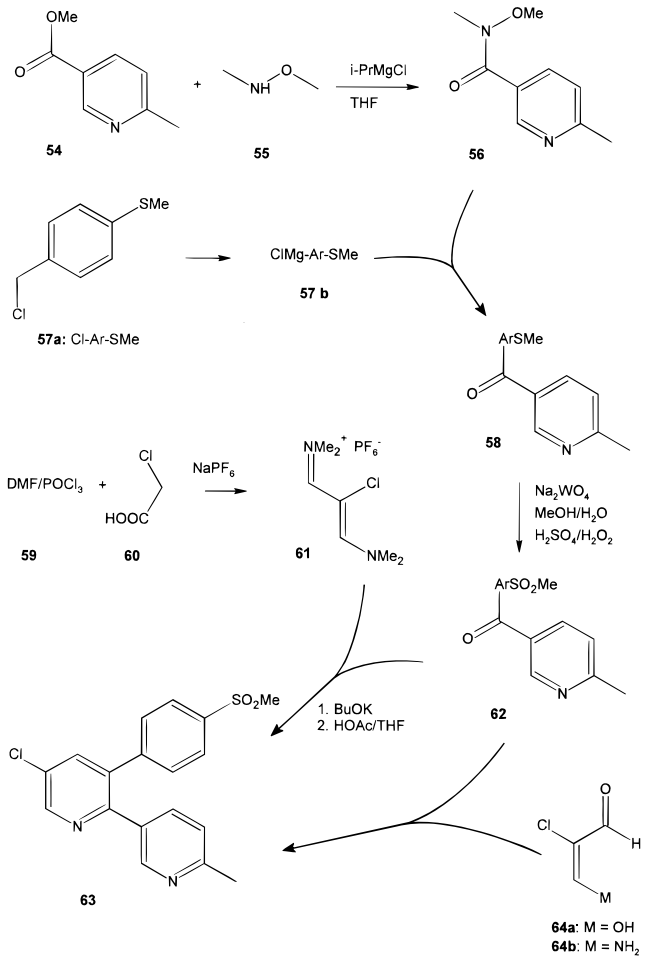
Title or Subject: Process for Synthesising Cyclooxygenase-2 Inhibitors

Cyclooxygenase-2 (COX-2) is an enzyme that appears to be connected with pain and inflammation and perhaps cancerous growths. Hence, production of COX-2 inhibitors is of interest, and these patents disclose two routes to a potential inhibitor the aryl pyridine **63** (Scheme 16). Both patents involve the synthesis of the ketosulphone **62** as the key intermediate. In the first patent **62** is treated with the iminium salt **61** in the presence of BuOK, and in the second patent **62** is condensed with **64** under acidic conditions. Both patents describe the same basic method to produce **62**. The route to **63** starts by reacting methyl nicotinate **54** with the hydroxylamine **55** and *i*-PrMgCl to give the amide **56**. This is then treated with the Grignard **57b**, made from the benzyl chloride **57a**, to give the ketone **58** that is then oxidised by sodium tungstate and H_2O_2 to **62**. The hexafluorophosphate form of the iminium salt **61** is made via the chloride from chloroacetic acid **60** and the Vilsmeier reagent $DMF/POCl_3$ **59**. Compounds **64a** and **64b** are derivatives of 2-chloroacrolein, and the second patent gives references and some details for their synthesis.

Advantages

The patents claim that the process is simple to perform and expensive palladium reagents, needed in the protection and deprotection steps in other processes for the production of **63**, are not required.

Scheme 16



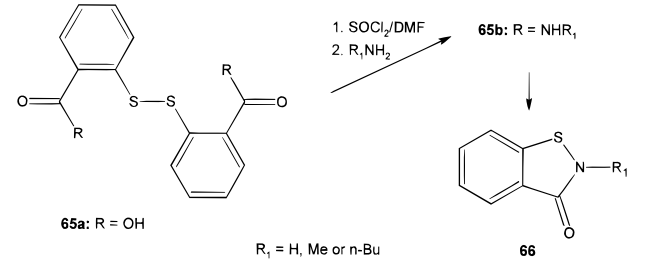
Patent No. U.S. 6,040,452

Assignee: Zeneca Limited, Huddersfield, UK

Title or Subject: Process for Making 1,2-Benzisothiazolin-3-ones

The title compounds are biologically active and used as bactericides and fungicides. The synthesis of the compound **66** is shown in Scheme 17 and carried out by cyclization of the bisamide **65b** in aqueous NaOH solution containing chlorobenzene and in the presence of oxygen. This basic reaction is known from previous work, but the method described in this patent also uses a catalyst. The catalyst is a nucleophilic N-containing compound, and NH_3, thiourea, or DMAP were found to be suitable, giving >99% conversion while Et_3N or DMF were used but were less effective. The bisamide **65b** was produced from the bis-acid **65a** by chlorination using $SOCl_2$/DMF followed by amine treatment.

Scheme 17



Advantages

The rate of cyclization can be speeded up significantly by using a catalyst, and this can also increase the yield, thus improving the economic viability of the process.

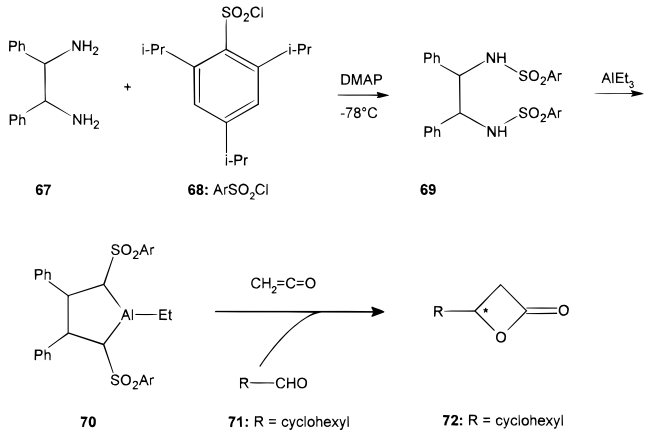
Patent No. U.S. 6,040,465

Assignee: Takasago International Corporation, Tokyo, Japan

Title or Subject: Process for Producing Optically Active β-Lactones

The lactone **72** is used to produce liquid crystals and pharmaceutical compositions, and similar lactones have been produced by [2 + 2] addition reactions of trichloroaldehydes with ketene. Lonza developed a process some years ago to produce **72** (R = Cl_3C−) with high ee by reaction of chloral and ketene using quinine as catalyst. The process described here claims to be able to use a wide variety of aldehydes that give lactone products with high ee. The production of **72** is shown in Scheme 18 and involves the use of a specific

Scheme 18



diastereomeric form of the complex **70** as an symmetric catalyst for the addition of ketene to aldehyde **71**. The complex **70** is produced from $AlEt_3$ and the appropriate enantiomer of diphenylethylenediamine **67** via the sulphonylamino compound **69**. Thus, using (1*R*,2*R*)-**67** gave (1*R*)-**72**, and (1*S*)-**72** was obtained from (1*S*,2*S*)-**67**.

Advantages

By using a specific optically active catalyst the [2 + 2] addition reaction of the aldehyde and ketene is directed to produce the required enantiomer of the lactone **72** at high ee. This process is more widely applicable than for example the Lonza process which is limited to specific aldehydes such as chloral, and hence this process is potentially more commercially useful.

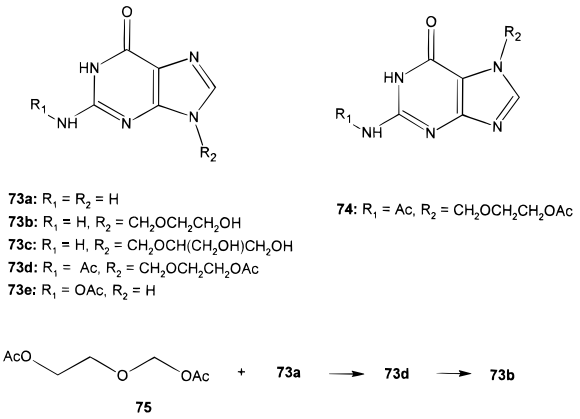
Patent No. U.S. 6,043,364

Assignee: Lupin Laboratories Limited, Bombay, India

Title or Subject: Regiospecific Process for Synthesis of Acyclic Nucleosides

Acyclic nucleosides such as acyclovir **73b** and ganciclovir **73c** are used in the treatment of the herpes virus and are normally made from alkylated 2-aminopurines such as **73d** (Scheme 19). The alkylation of the 2-aminopurine **73a** is

Scheme 19



thermodynamically controlled, and all methods of preparing **73d** (N-9 isomer) also produce **74** (N-7 isomer). Thus, there is a difficult separation either of **73d** from **74** or of **73b** from its N-7 isomer. Since it is the N-9 isomer that is required, an objective of previous processes was to limit the production of the N-7 isomer **74** which in some methods can be almost 35% of the product. Rather than focus on doing this, the process described here has devised a method of converting the N-7 to the N-9 isomer which can then be applied to any other synthetic route. This is carried out by heating a suspension of **73d** and **74** in the diacetate **75** but importantly without a catalyst or solvent. This is done at about 100 °C for between 18 and 20 h, and the resulting mixture can contain up to 97% of **73d**. The diacetate **75** is actually used to produce **73d** by acid-catalyzed alkylation of **73a** or **73e**, giving a mixture of **73d** and **74**. This can be done by using PTSA, but this patent discloses that the use of such catalysts is not required in the isomerization, and its use is in fact less efficient. The implication may be that not using acids in the alkylation may be beneficial.

Advantages

This patent improves the prior art by recycling the undesired N-7 isomer **74** to the N-9 isomer **73d** and hence has the potential to improve the efficiency of processes used to make acyclovir **73b** or ganciclovir **73c** without the need for a complex separation step.

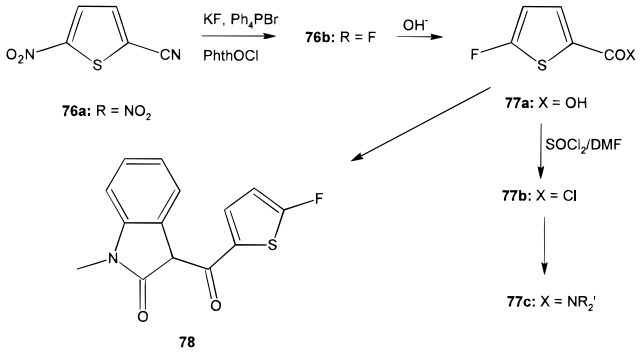
Patent No. U.S. 6,043,379

Assignee: Pfizer Inc., New York, U.S.A.

Title or Subject: Processes and Intermediates for Preparing 2-Fluorothiophene Derivatives

This patent focuses on the preparation of the acid **77a** which is used in the production of 2-oxindole compounds such as **78**, an antiinflammatory agent and interleukin-1 biosynthesis inhibitor. The route to **77a** is shown in Scheme 20 and starts with fluorination of the cyano compound **76a**.

Scheme 20



This step is carried out in sulpholane using the phosphonium salt Ph_4PBr and in the presence of phthaloyl chloride (PhthOCl). Conventional base hydrolysis of **76b** gives the acid **77a**. The patent also describes the conversion of **77a** to the acetyl chloride **77b** and the amide **77c**.

Advantages

The patent builds on an earlier one from Pfizer (U.S. 5,290,802) which describes the synthesis of compound **78** and its various medicinal uses. This patent therefore appears to complement the earlier patent, and no other background is provided apart from one reference to a preparation of **77a** by lithiation; however, this is not discussed.

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Keith Turner

Kappa Tau Consulting, 12 The Avenue, Fairfield, Stockton-on-Tees, TS19 7EY, UK

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