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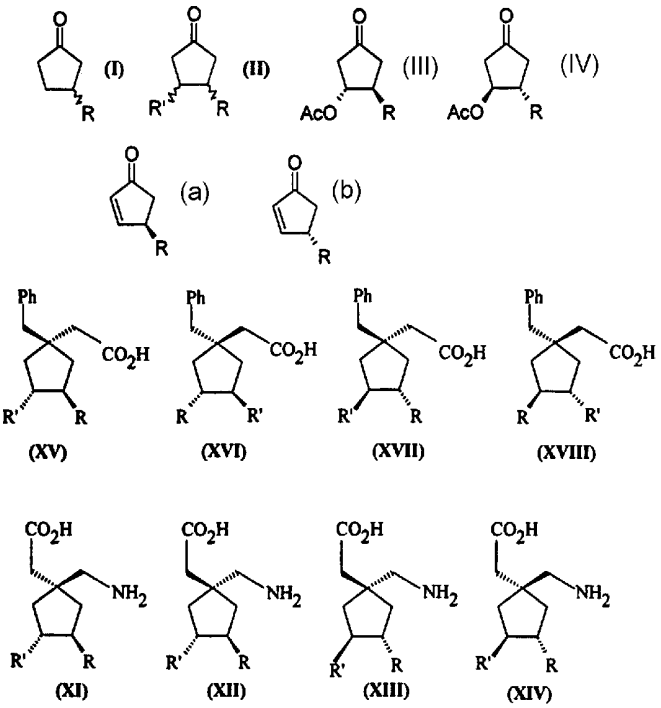
(54) **Title:** CYCLIC KETONES, THEIR PREPARATION AND THEIR USE IN THE SYNTHESIS OF AMINO ACIDS



(57) Abstract: A method is provided for making an enantiomerically pure compound of the formula: in which R and R' represent C1?C10 alkyl, C2?C10 alkenyl or C3?C10 cycloalkyl and the wedges signify (S)- or (R)- stereochemistry, the substituents in compound (II) being trans. Conjugate addition is carried out between an organometallic nucleophile that provides a group R as defined above and (R)-4-acetoxycyclopent-2-en-1-one, (S)- 4-acetoxycyclopent-2-en-1-one or a similar compound in which acetoxy is replaced by another leaving group to give, e.g. in the case of the acetoxy compound, a trans 3,4-disubstituted addition product of formula III or IV; The acetyl group is eliminated from the addition product to give an (R)- or (S)- 4-alkyl or 4-alkenyl cyclopent-2-en-1-one the compound of formula is then to be hydrogenated to give a cyclopentanone of formula (I) or conjugate addition of a second organometallic nucleophile that provides a group R' as defined above to the compound of the above formula may be carried out to give a trans 3,4-disubstituted addition product of formula (II). One of the above compounds may be converted e.g. via an intermediate (XV)-(XVIII) (in which the substituents R and R' and the wedges have the meanings indicated above) to a gabapentin analogue of one of the formulae shown below: in which the substituents R and R' and the wedges also have the meanings indicated above.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

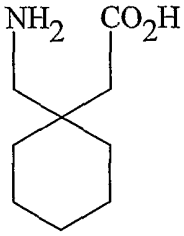
CYCLIC KETONES, THEIR PREPARATION AND THEIR USE IN THE SYNTHESIS OF AMINO ACIDS

FIELD OF THE INVENTION

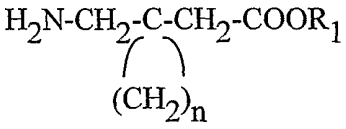
The present invention relates to methods for the synthesis of alkyl- and alkenyl- and cycloalkyl-substituted cyclopentanones that are useful *inter alia* as intermediates for the synthesis of analogues of gabapentin (Neurontin®). It also relates to methods for the synthesis of gabapentin analogues using these intermediates, and also to certain novel intermediates *per se*.

BACKGROUND TO THE INVENTION

Gabapentin (Neurontin®) is an anti-convulsant agent that is useful in the treatment of epilepsy and that has recently been shown to be a potential treatment for neurogenic pain. It is 1-(aminomethyl)-cyclohexaneacetic acid of structural formula:



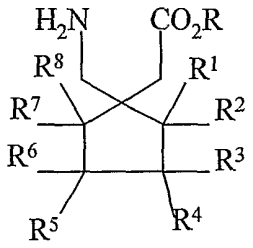
Gabapentin is one of a series of compounds of formula



in which R_1 is hydrogen or a lower alkyl radical and n is 4, 5, or 6. These compounds are described US-A-4,024,175 and its divisional US-A-4,087,544. Their disclosed uses are: protective effect against cramp induced by thiosemicarbazide; protective action against cardiazole cramp; the cerebral

diseases, epilepsy, faintness attacks, hypokinesia, and cranial traumas; and improvement in cerebral functions. The compounds are useful in geriatric patients. The disclosures of the above two patents are hereby incorporated by reference.

WO 99/21824, whose disclosure is also incorporated by reference, discloses further cyclic amino acids that are useful in the treatment of epilepsy, faintness attacks, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders, gastrointestinal disorders such as irritable bowel syndrome (IBS) and inflammation, especially arthritis. The compounds disclosed include those of the formula:



and salts thereof, in which:

R is hydrogen or a lower alkyl;

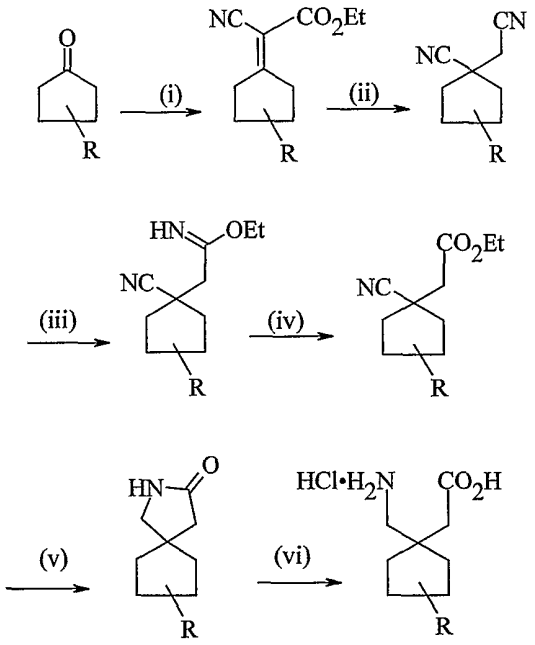
R^1 to R^8 are each independently selected from hydrogen, straight or branched alkyl of from 1 to 6 carbons, phenyl, benzyl, fluorine, chlorine, bromine, hydroxy, hydroxymethyl, amino, aminomethyl, trifluoromethyl, $-CO_2H$, $-CO_2R^{15}$, $-CH_2CO_2H$, $-CH_2CO_2R^{15}$, $-OR^{15}$ wherein R^{15} is a straight or branched alkyl of from 1 to 6 carbons, phenyl, or benzyl, and R^1 to R^8 are not simultaneously hydrogen.

The compounds of WO 99/21824 may be synthesized:

- using a general strategy (General Scheme 1) outlined by G. Griffiths et al., *Helv. Chim. Acta*, 1991;74:309;

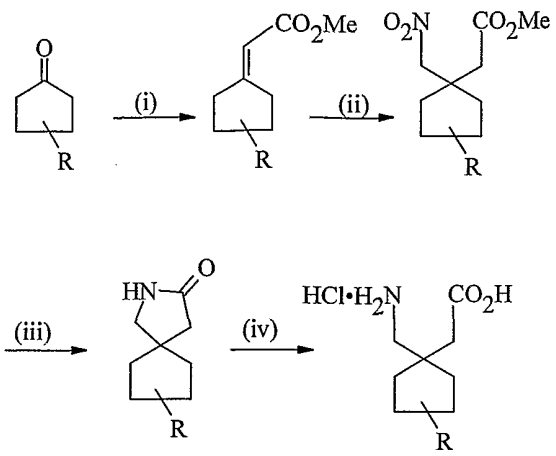
- analogously to the published procedure for the synthesis of 3-oxo-2,8-diazaspiro[4,5]decane-8-carboxylic acid tert-butyl ester, see P. W. Smith et al., *J. Med. Chem.*, 1995;38:3772 (General Scheme 2);
- by the methods outlined by G. Satzinger et al., (Ger Offen 2,460,891; US 4,024,175, and Ger Offen 2,611,690; US 4,152,326) (General Schemes 3 and 4);
- by a route outlined by G. Griffiths et al., *Helv. Chim. Acta*, 1991;74:309 (General Scheme 5).

General Scheme 1



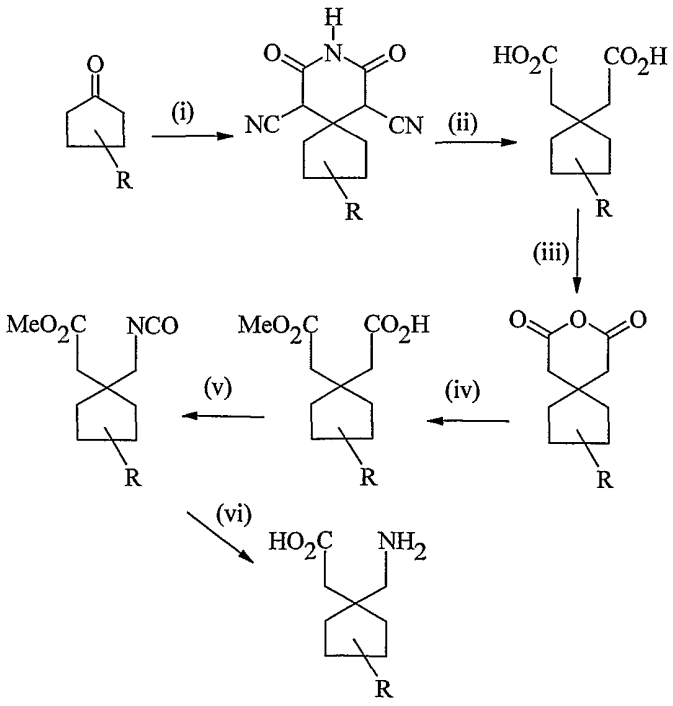
(i) Ethyl cyanoacetate, piperidine (Cope et al., *J. Am. Chem. Soc.*,1941;63:3452); (ii) NaCN, $EtOH/H_2O$; (iii) EtOH, HCl; (iv) H_2O/H^+; (v) H_2, Rh/C, MeOH; (vi) HCl.

General Scheme 2



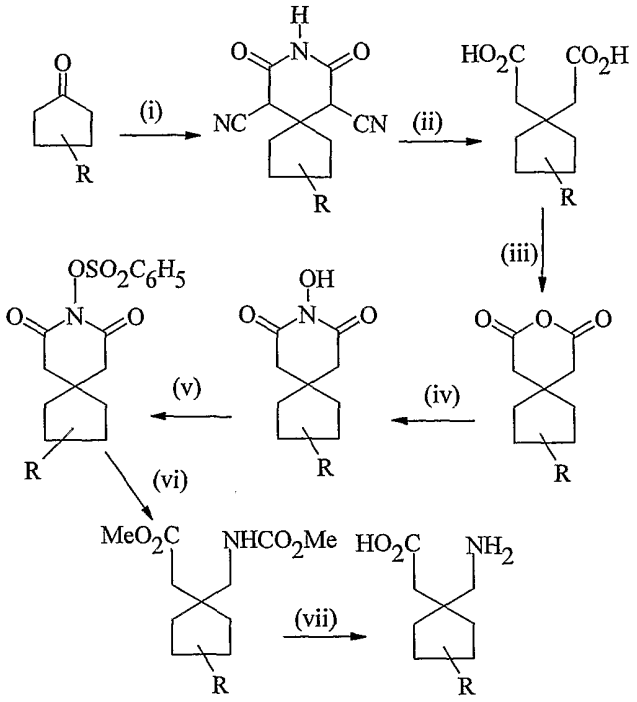
(i) $Ph_3P{=}CHCO_2Me$; (ii) $MeNO_2$, 1,1,3,3-tetramethylguanidine; (iii) Raney nickel, $EtOH/H_2O$; (iv) HCl.

General Scheme 3



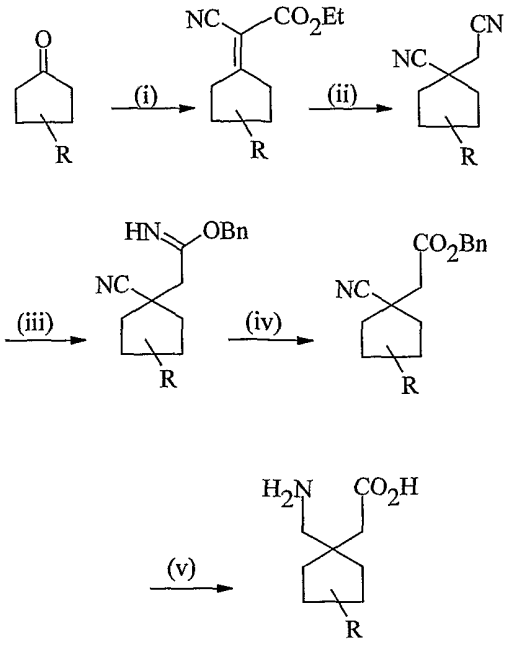
(i) Ethylcyanoacetate, ammonia then H_3O^+; (ii) H_2SO_4; (iii) Ac_2O; (iv) MeOH;(v) Curtius Reaction; (vi) HCl, H_2O then anion exchange.

General Scheme 4



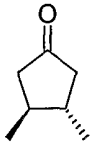
(i) Ethylcyanoacetate, ammonia then H_3O^+; (ii) H_2SO_4; (iii) Ac_2O; (iv) H_2NOH; (v) $PhSO_2Cl$; (vi) Et_3N, MeOH; (vii) HCl, H_2O then anion exchange.

General Scheme 5

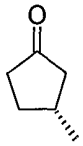


(i) Ethyl cyanoacetate, piperidine (Cope et al., *J. Am. Chem. Soc.*, 1941;63:3452); (ii) NaCN, $EtOH/H_2O$; (iii) BnOH, HCl; (iv) H_2O/H^+; (v) H_2, Rh/C, MeOH.

Intermediates disclosed in WO 99/21824 include the following:

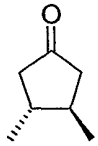


(3S,4S)-3,4-Dimethyl-cyclopentanone



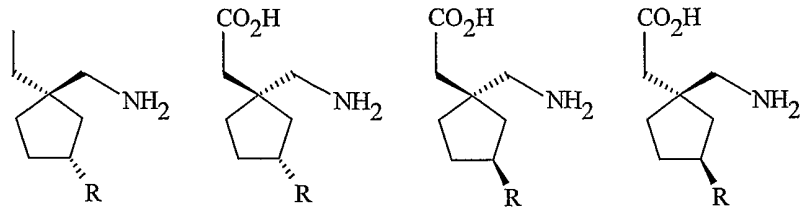
(R)-3-Methyl-cyclopentanone

and



(3R,4R)-3,4-Dimethyl-cyclopentanone

Our US Patent Application 60/169602, the disclosure of which is also incorporated herein by reference, describes and claims methods for the stereocontrolled synthesis of five-member ring Gabapentin analogues that are pure stereoisomers of compounds of formulae shown below and to salts thereof.



wherein R represents C_1-C_{10} alkyl and C_3-C_{10} cycloalkyl. The synthesis starts with the Knoevenagel condensation of a 3-substituted cyclopentanone of the kind described above with ethyl cyanoacetate and proceeds via the key intermediates

A method for preparing a compound of formula *(I)* in the following reaction scheme and pharmaceutically acceptable salts thereof comprises:

a) adding ethyl cyanoacetate to a mixture of a chiral cyclopentanone of formula (1) in a solvent to which a C_1-C_6 carboxylic acid and an amphoteric catalyst were added, and stirring the mixture to produce the alkene of formula (2);

b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in a dry solvent to produce the addition product of formula (3);

c) adding the product of Step b) above to a mixture of a base in a solvent and stirring the mixture to produce the carboxylic acid of formula (4);

d) contacting the product of Step c) above with (S)-α-methyl-benzylamine in a solvent, and recrystallizing the salt so formed to produce the enriched diastereomer of formula (5) as the (S)-α-methyl-benzylamine salt;

e) adding the product of Step d) to an inorganic acid dissolved in a solvent and stirring to produce the carboxylic acid of formula (6);

f) adding the product of Step e) to a mixture of iodomethane in a solvent to which 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added, and stirring to produce the ester of formula (7);

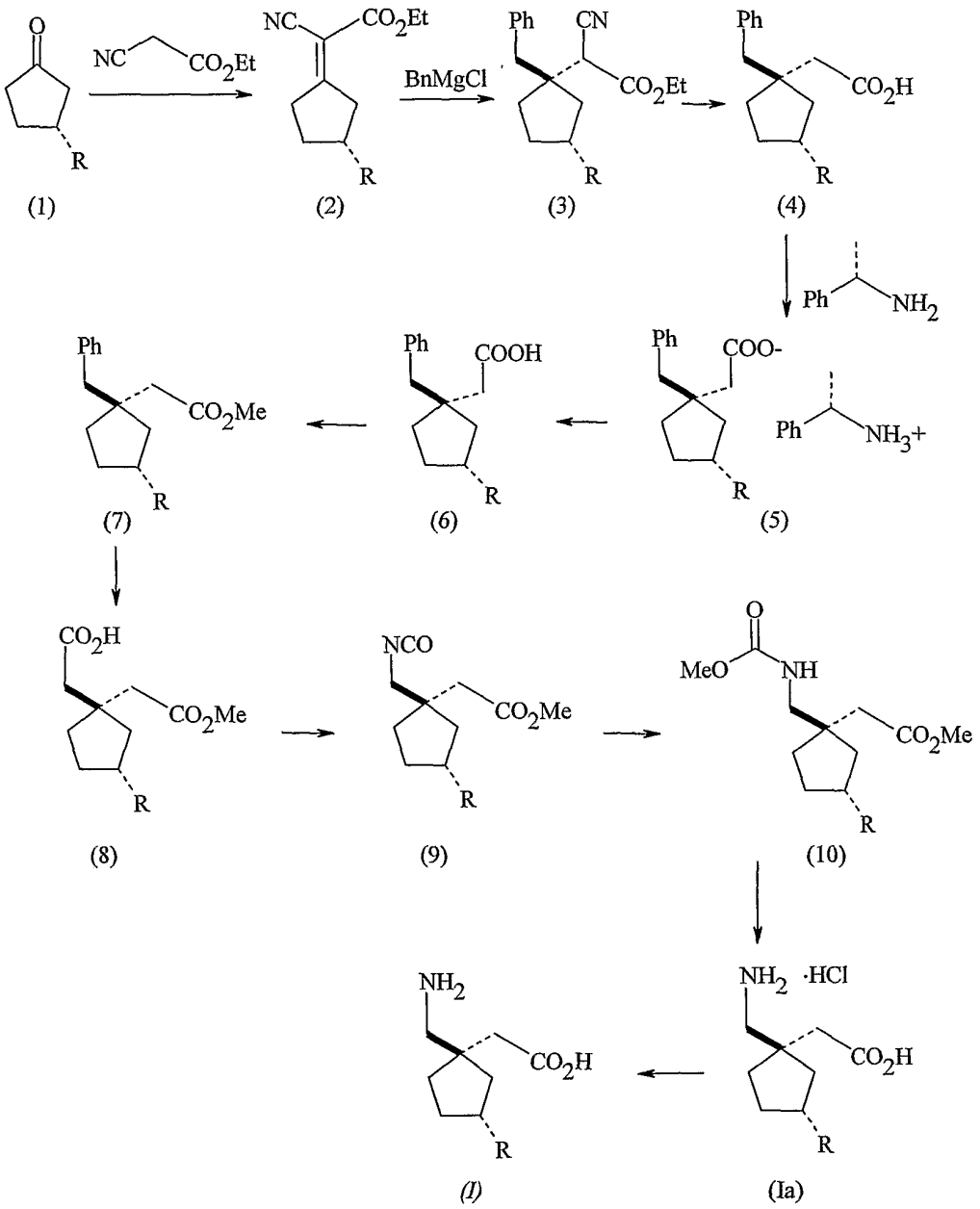
g) adding the product of Step f) to a mixture of carbon tetrachloride and acetonitrile to which water, sodium periodate, and ruthenium(III) chloride were added, and stirring to produce the carboxylic acid of formula (8);

h) adding the product of Step g) to a mixture of an amine base and a solvent to which diphenylphosphoryl azide (DPPA) was added, and stirring to produce the isocyanate of formula (9);

i) adding the product of Step h) to a solvent to which methanol was added, and stirring to produce the carbamate of formula (10);

j) adding the product of Step i) to a solvent to which aqueous hydrochloric acid was added, and stirring to produce a compound of Formula Ia;

k) converting the product of Step j) to a compound of Formula I, and further converting, if desired, to a pharmaceutically acceptable salt by known means:



Preparation of a compound of formula *II* can proceed by a method which involves following the above-described sequence of steps (a) to (e) to produce the intermediate of step (6), and thereafter following the further steps indicated below:

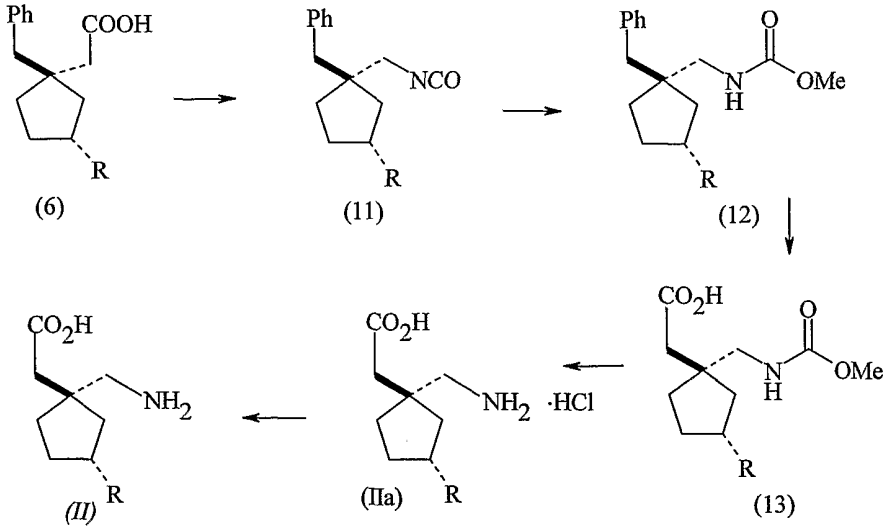
f) adding the product of Step e) to a mixture of an amine base and a solvent to which diphenylphosphoryl azide (DPPA) was added, and stirring to produce the isocyanate of formula (11);

g) adding the product of Step f) to a solvent to which methanol was added and stirring to produce the carbamate of formula (12);

h) adding the product of Step g) to a mixture of carbon tetrachloride and acetonitrile to which water, sodium periodate, and ruthenium(III) chloride were added, and stirring to produce the carboxylic acid of formula (13);

i) adding the product of Step h) to a solvent to which aqueous hydrochloric acid was added, and stirring to produce a compound of Formula IIa;

k) converting the product of Step i) to a compound of Formula II, and further converting, if desired, to a pharmaceutically acceptable salt by known means:



An alternative route to the compounds of formula *(II)*, also proceeding from compound (6) above involves the further steps of:

f) adding oxalyl chloride to a mixture of the product of Step e) and a solvent to which N,N-dimethylformamide (DMF) was added, and stirring to produce the acid chloride of formula (14);

g) adding the product of Step f) to a mixture of *tert*-butyl alcohol in a solvent to which an amine base was added, and stirring to produce the ester of formula (15);

h) adding the product of Step g) to a mixture of carbon tetrachloride and acetonitrile to which water, sodium periodate, and ruthenium(III) chloride were added, and stirring to produce the carboxylic acid of formula (16);

i) adding the product of Step h) to a solvent to which methanol and (trimethylsilyl)diazomethane were added, and stirring to produce the bis ester of formula (17);

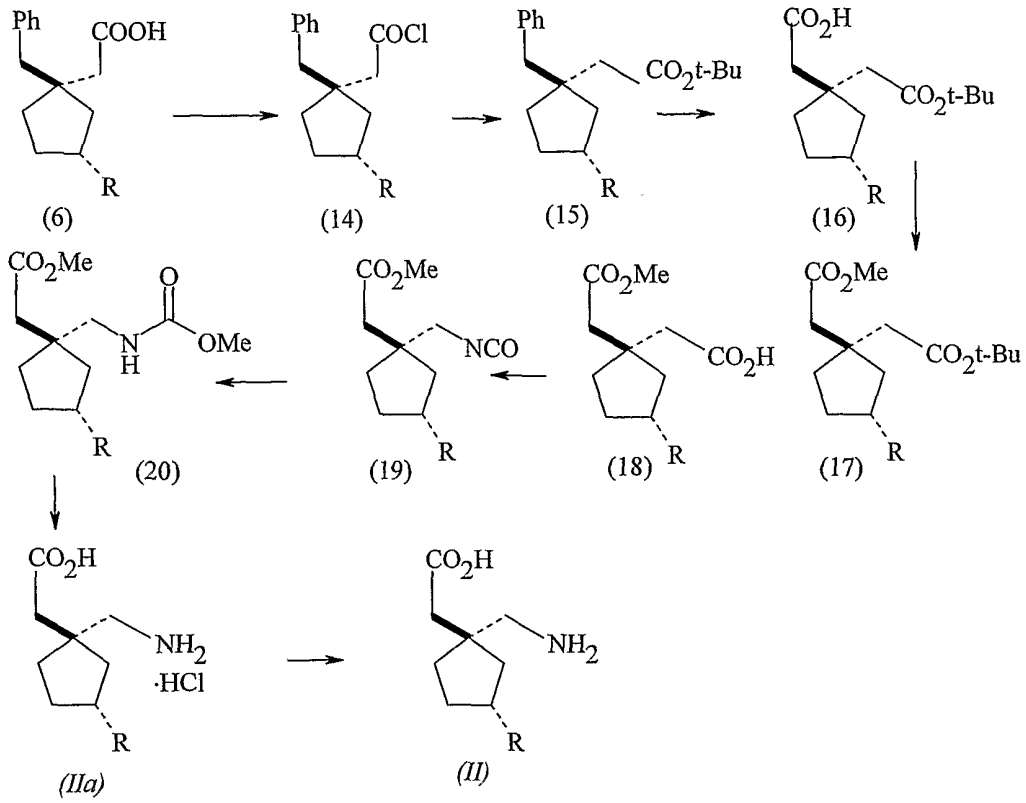
j) adding an acid to a mixture of the product from Step i) and a solvent and stirring to produce the carboxylic acid of formula (18);

k) adding the product of Step j) to a mixture of an amine base and a solvent to which diphenylphosphoryl azide (DPPA) was added, and stirring to produce the isocyanate of formula (19);

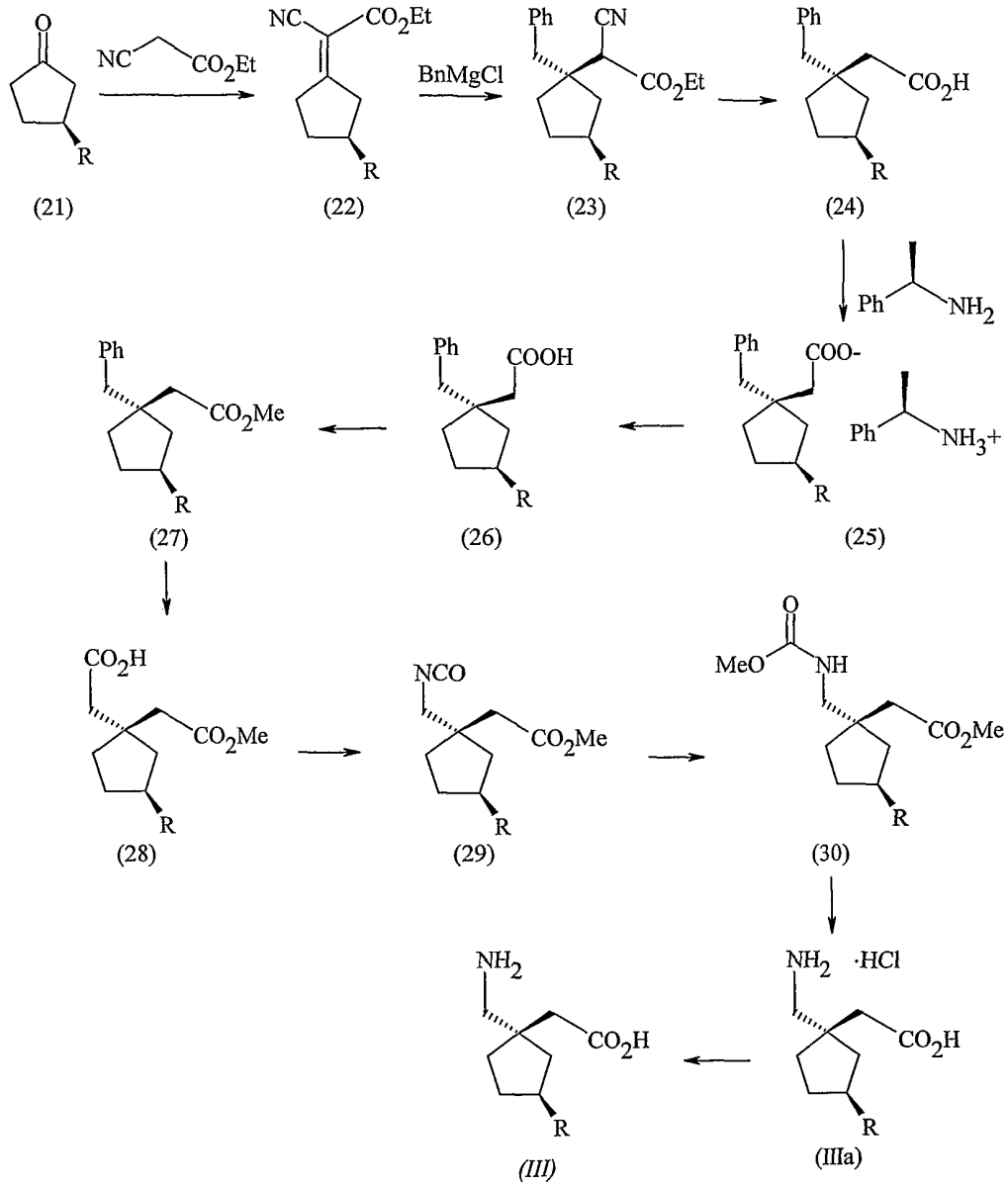
l) adding the product of Step k) to a solvent to which methanol was added and stirring to produce the carbamate of formula (20);

m) adding the product of Step l) to a solvent to which aqueous hydrochloric acid was added, and stirring to produce a compound of Formula *IIa;*

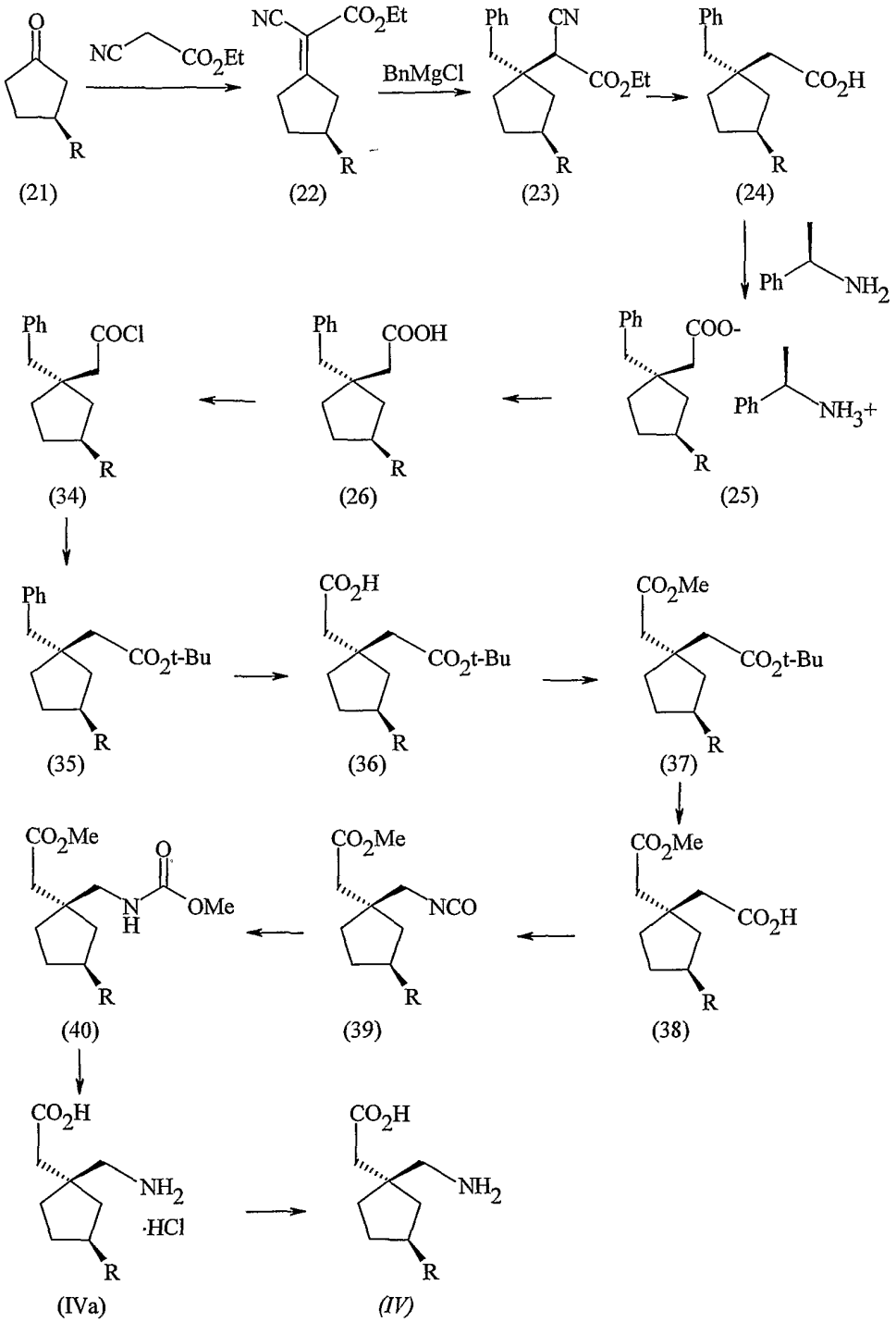
n) converting the product of Step m) to a compound of Formula *II*, and further converting, if desired, to a pharmaceutically acceptable salt by known means:



Compounds of formula *(III)* can be prepared by processes that involve the same steps as those for the compounds of formula (I), for example by following the sequence of reactions set out below:



Similarly, compounds of formula *(IV)* may be made by a sequence of reactions analogous to those described above:

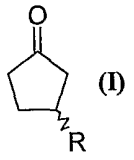


It will be noted that the synthetic methods disclosed in both WO 99/21824 and USSN 60/169602 rely on 3- or 3,4-substituted cyclopentanones.

SUMMARY OF THE INVENTION

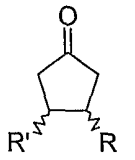
This invention is concerned with the problem that the cyclopentanones available up to now have been limited in their range of stereoisomers and substituents because they have been derived from natural sources, or have been complex. For example, (R)-3-methyl-cyclopentanone is a compound that is readily available commercially from natural sources, whereas (S)-3-methyl-cyclopentanone is not. It is an object of the invention to provide a simple stereospecific synthetic route to 3-substituted or 3,4-disubstituted cyclopentanones that permits a range of desired substituents to be introduced and a range of desired stereoisomers to be made.

That problem is solved, according to the invention, by a process method of making an enantiomerically pure compound of the formula **(I)** or **(II)**:



(I)

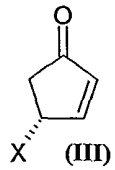
or



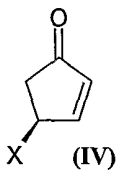
(II)

wherein R and R' represent C_1-C_{10} alkyl, C_2-C_{10} alkenyl or C_3-C_{10} cycloalkyl and the wedges signify (S)- or (R)- stereochemistry, the substituents in compound (II) being *trans*, which method comprises:

conjugate addition of an organometallic nucleophile that provides a group R as defined above to a compound of the formula **(III)** or **(IV)**:

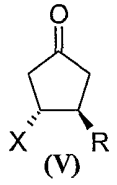


(III)



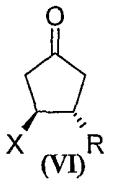
(IV)

wherein X represents a leaving group (e.g. an acetoxy group as in (R)-4-acetoxycyclopent-2-en-1-one or (S)- 4-acetoxycyclopent-2-en-1-one) to give a trans 3,4-disubstituted addition product of formula **(V)** or **(VI)** in which R and X are as previously defined;



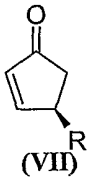
(V)

or



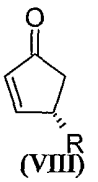
(VI)

eliminating the leaving-group from the addition product of formula **(V)** or **(VI)** to give an (R)- or (S)- 4-alkyl or 4-alkenyl cyclopent-2-en-1-one of formula **(VII)** or **(VIII)**



(VII)

or



(VIII)

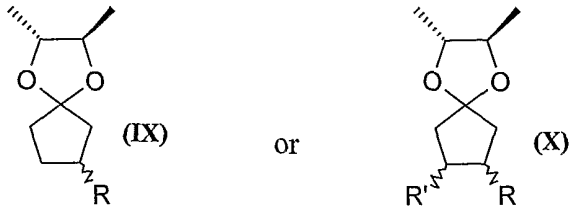
; and either

(i) hydrogenation of the compound of formula **(VII)** or **(VIII)** to give a cyclopentanone of formula **(I)** or

(ii) conjugate addition of a second organometallic nucleophile that provides a group R' as defined above to the compound of formula **(VII)** or **(VIII)** to give a trans 3,4-disubstituted addition product of formula **(II)**.

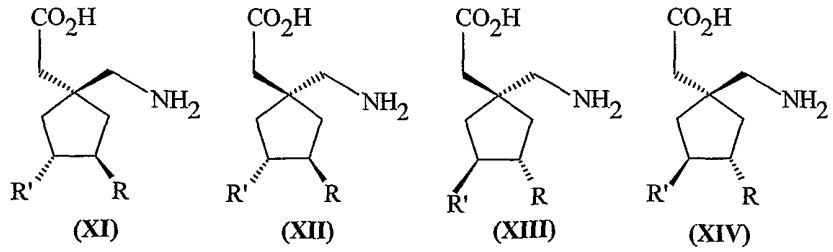
While conjugate addition to conjugated cyclopentenones is known for soft nucleophiles such as enolates, sulfides and bromides, such reactions have not been carried out with carbon-based nucleophiles with a view to producing chirally pure ketones. The group AcO- in the starting material brings about stereospecific addition of the group R during the first Michael addition, and where a second Michael addition is carried out, the group R that is already present in the compound of formula **(VII) or (VIII)** brings about stereospecific addition of the group R'. The enantiomeric purity of the resulting compounds of formula **(I)** and

(II) can be tested by reacting them with an asymmetric diol such as (2R,3R)-2,3-butanediol to give an acetal having an additional asymmetric centre in the molecule, e.g



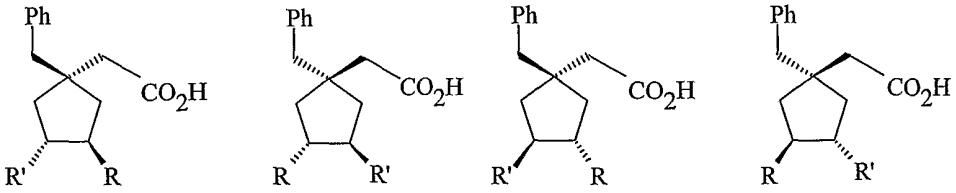
and obtaining the NMR spectrum of the resulting chiral acetal. If the starting material is an enantiomeric mixture, then the two resulting cyclic acetals will be diastereomeric and give distinguishable peaks in the NMR spectrum provided that the enantiomeric impurity is present in an amount of 2% or above. No such peaks have been observed in the materials that we have made, and we therefore believe that the method of the invention gives desired enantiomers with a purity of at least 98%.

According to a further aspect of the invention, a compound of formula **(I)** and **(II)** may be converted in manner known *per se* to a gabapentin analogue of one of the formulae shown below:



in which the substituents R and R' and the wedges have the meanings indicated above, and may be further converted into a pharmaceutically acceptable salt thereof.

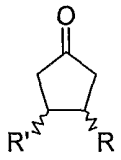
Conversion to a compound of formula **(XI)** – **(XIV)** may, for example, follow one of the general schemes disclosed in WO 99/21824, or it may follow the Knoevenagel addition route disclosed in USSN 60/169602. In the latter case, there may be produced the key intermediates **(XV)** - **(XVIII)** shown below:



(XV) **(XVI)** **(XVII)** **(XVIII)**

in which the substituents R and R' and the wedges have the meanings indicated above. Thereafter, the intermediate of formula **(XV)** - **(XVIII)** may be converted to a compound of formula **(I)** or **(II)** by one of the three principal strategies disclosed in USSN 60/169602, i.e. (i) transforming the phenyl ring to a carboxylic acid and then to an amine; (ii) transforming the carboxylic acid group into an amine and oxidizing the phenyl group to an acid, or (iii) protecting the carboxylic acid group, oxidizing the phenyl ring to a second carboxylic acid group, protecting the second carboxylic acid group, selectively de-protecting the first carboxylic acid group, transforming the first carboxylic acid group to an amine, and de-protecting the second carboxylic acid group.

Certain of the present intermediates are believed to be new. In a further aspect, therefore, the invention provides enantiomerically pure compounds of the formula:

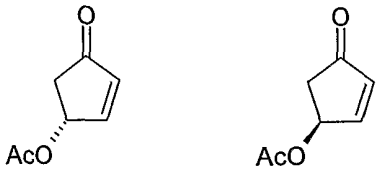


(II)

wherein R and R' represent C_1-C_{10} alkyl, C_2-C_{10} alkenyl or C_3-C_{10} cycloalkyl and the wedges signify (S)- or (R)- stereochemistry, the substituents being *trans*, and at least one of R and R' not being methyl.

DESCRIPTION OF PREFERRED FEATURES

As previously stated, the compounds of the invention can be prepared in chirally pure form from (R)-4-acetoxycyclopent-2-en-1-one (1) or (S)- 4-acetoxycyclopent-2-en-1-one (2).



(1) (2)

The reactions of 4-Oxo-2-cyclopentenyl Acetate (4-Acetoxy-2-cyclopenten-1-one) have been reviewed by M. Harre, P. Raddatz, R. Walenta and E. Winterfeldt, *Angew. Chem. Int. Ed. Engl.*, 1982, **21**, 480. It has been synthesised in enantiomerically pure form using two main approaches:

- Acetylation of chirally pure 4-hydroxy-2-cyclopenten-1-one, see K. Ogura, M. Yamashita and G. Tsuchihashi, *Tetrahedron Letters*, 1976, 759. For examples of approaches to chiral 4-hydroxy-2-cyclopenten-1-one see the following and references therein: S.R. Ghorpade, K.B. Bastawade, D.V. Gokhale, P.D. Shinde, V.A. Mahajan, U.R. Kalkote and T. Ravindranathan, *Tetrahedron Asymmetry*, 1999, **10**, 4115; S.P. Khanapure, N. Najafi, S. Manna, J-J. Yang and J. Rokach, *J. Org. Chem.*, 1995, **60**, 7548; E. Mezzina, D. Savoia, E. Tagliavini, C. Trombini and A. Umani-Ronchi, *J. Chem. Soc. Perkin Trans. 1*, 1989, 845; M. Kitamura, K. Manabe and R. Noyori, *Tetrahedron Letters*, 1987, **28**, 4719; R. Noyori, I. Tomino, M. Yamada and M. Nishizawa, *J. Am. Chem. Soc.*, 1984, **106**, 6717; M. Suzuki, T. Kawagishi, T. Suzuki and R. Noyori, *Tetrahedron letters*, 1982, **23**, 4057; R. Noyori, *Pure & Appl. Chem.*,

1981, **53**, 2315; T.J.N. Watson, T.T. Curran, D.A. Hay, R.S. Shah, D.L. Wenstrup and M.E. Webster, *Organic Process Research & Development*, 1998, **2**, 357; S.R. Ghorpade, K.B. Bastawade, D.V. Gokhale, P.D. Shinde, V.A. Mahajan, U.R. Kalkote and T. Ravindranathan, *Tetrahedron: Asymmetry*, 1999, **10**, 4115-4122).

- Oxidation of 3-acetoxy-5-hydroxycyclopent-1-enes, for example see: M. Korach, D.R. Nielsen and W.H. Rideout, *Org. Synth., Collect. Vol. 5*, 1973, 414; D.R. Deardoff and D.C. Myles, *Org. Synth.*, 1989, **67**, 114; D.R. Deardorff, C.Q. Windham and C.L. Craney, *Org. Synth.*, 1995, **73**, 25; C.R. Johnson and S.J. Bis, *Tetrahedron Letters*, 1992, **33**, 7287.

The following reactions may be used to make compounds according to the invention:

A) Conjugate addition to a cyclopent-2-en-1-one (1) or (2) can be carried out using an organo-Grignard reagent in the presence of dimethylzinc giving a trans 3,4-disubstituted intermediate e.g. an addition product of formula (3) or (4). In particular, the chiral cyclopentenone of formula (1) or (2) may be added to the organo-Grignard reagent or to an organo-lithium reagent in the presence of a dialkylzinc or zinc chloride or a copper (I) salt or a trialkylaluminium in a solvent, for example, tetrahydrofuran, 1,4-dioxane, *n*-heptane, toluene, diethyl ether or *tert*-butyl methyl ether at a temperature from –100 °C to 0 °C to produce said addition product.

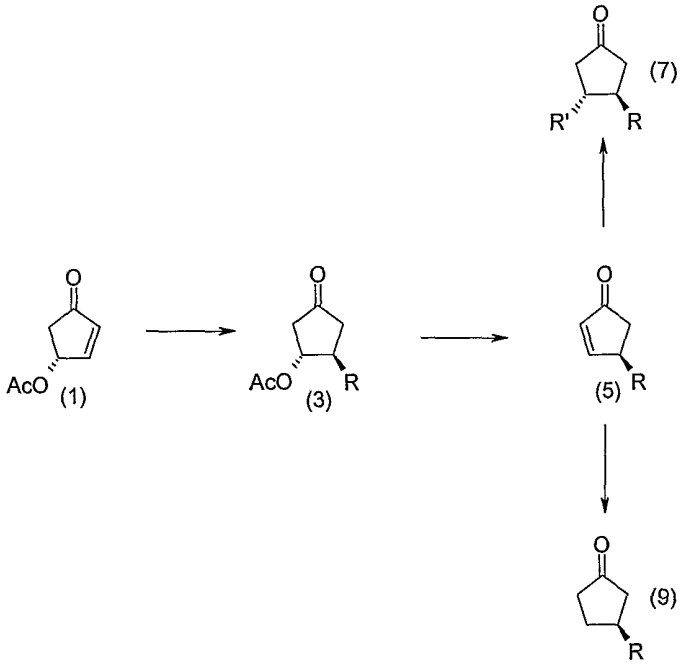
B) Adding the product of step A) above to a mixture of base, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,1,3,3-tetramethyl guanidine (TMG), lithium hydride or sodium hydride in a solvent, for example, dichloromethane, diethyl ether, tetrahydrofuran, *tert*-butyl methyl ether or 1,4-dioxane to produce an elimination product of formula (5) or (6).

C) Adding the product of step B) above to a mixture of organo-Grignard reagent or organo-lithium reagent in the presence of a dialkylzinc or zinc chloride or a copper (I) salt or a trialkylaluminium salt in a solvent, for example, tetrahydrofuran, 1,4-dioxane, *n*-heptane, toluene, diethyl ether or *tert*-butyl methyl ether at a temperature from –100 °C to 0 °C can be used to produce an addition product of formula (7) or (8).

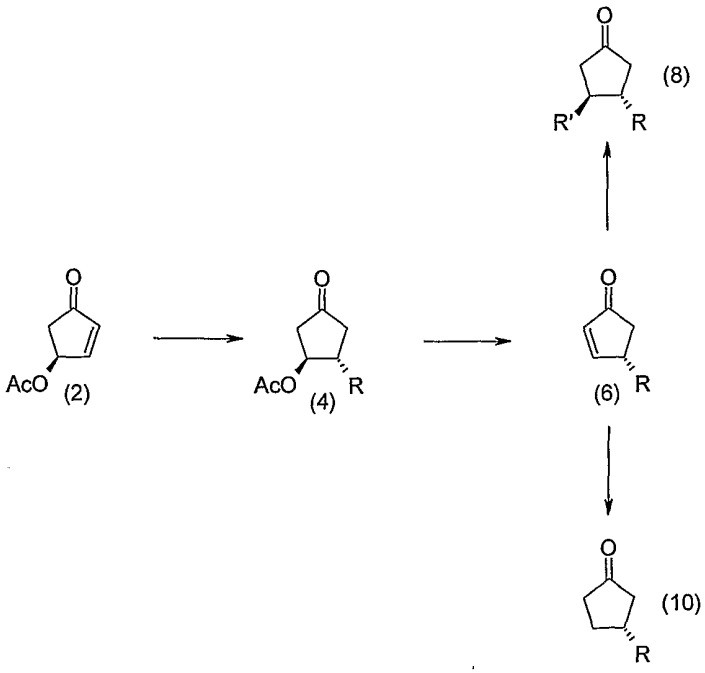
D) Adding the product of step B) above to a hydrogenation catalyst, for example, palladium on charcoal, platinum oxide, Raney nickel, Rhodium on alumina in a solvent, for example, ethyl acetate or methanol under a hydrogen atmosphere at 1 to 30 atmospheres pressure and at a temperature in the range 0-60°C, can be used to make a product of formula (9) or (10).

The above described reactions are illustrated in the following schemes:

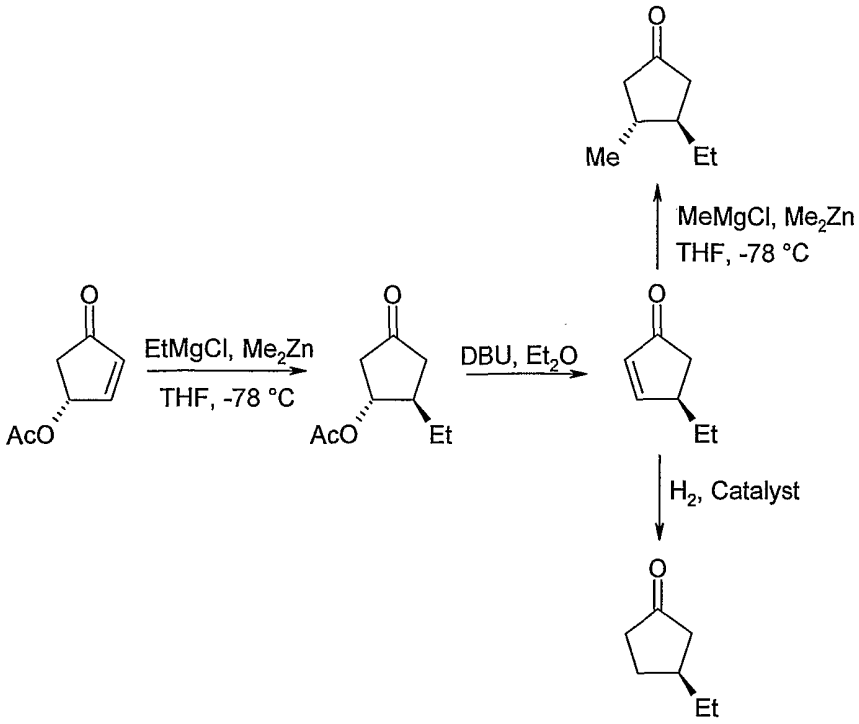
Scheme 1



Scheme 2



An example of the utility of the above reaction scheme is shown below:



Compounds that can be made by the present process are shown below, and the following are believed to be new:

(3S,4S)-3,4-diethyl-cyclopentanone;

(3R,4R)-3,4-diethyl-cyclopentanone;

(3S,4S)-3-ethyl-4-methyl-cyclopentanone;

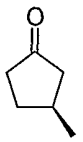
(3R,4R)-3-ethyl-4-methyl-cyclopentanone;

(3S,4S)-3-methyl-4-propyl-cyclopentanone;

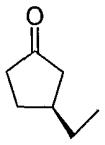
(3R,4R)-3-methyl-4-propyl-cyclopentanone;

(3S,4S)-3-ethyl-4-propyl-cyclopentanone; and

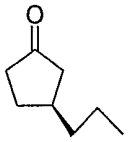
(3R,4R)-3-ethyl-4-propyl-cyclopentanone.



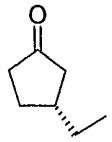
(S)-3-Methyl-cyclopentanone



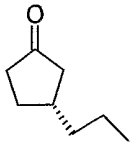
(S)-3-Ethyl-cyclopentanone



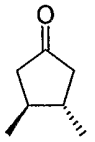
(S)-3-Propyl-cyclopentanone



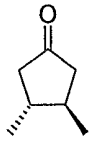
(R)-3-Ethyl-cyclopentanone



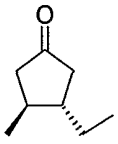
(R)-3-Propyl-cyclopentanone



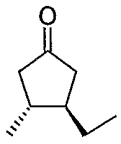
(3S,4S)-3,4-Dimethyl-cyclopentanone



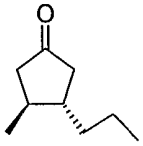
(3R,4R)-3,4-Dimethyl-cyclopentanone



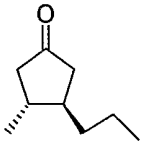
(3S,4S)-3-Ethyl-4-methyl-cyclopentanone



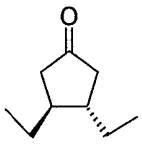
(3R,4R)-3-Ethyl-4-methyl-cyclopentanone



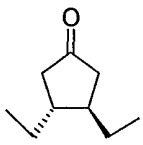
(3S,4S)-3-Methyl-4-propyl-cyclopentanone



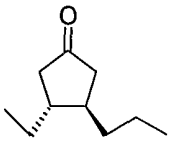
(3R,4R)-3-Methyl-4-propyl-cyclopentanone



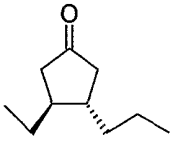
(3S,4S)-3,4-Diethyl-cyclopentanone



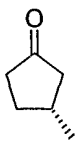
(3R,4R)-3,4-Diethyl-cyclopentanone



(3R,4R)-3-n-Pr-4-Et-cyclopentanone

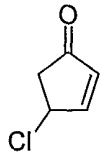


(3S,4S)-3-n-Pr-4-Et-cyclopentanone

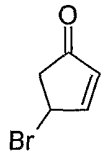


(R)-3-Methyl-cyclopentanone

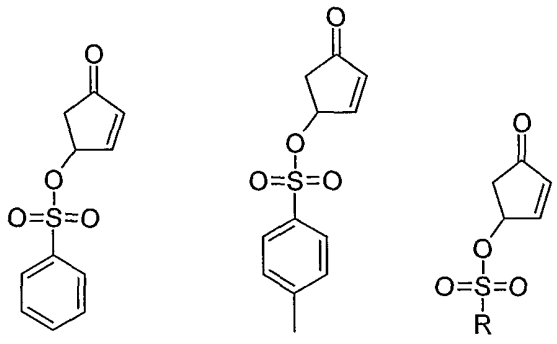
Other leaving groups may be present in the starting materials employed in the above process in place of the acetoxy compounds, and in general any compound that is available in optically pure form and that has a 4-substituent that permits stereospecific addition to the en-one conjugated system and can then undergo elimination can be used. Examples of such leaving groups are halides and sulfonic acid ester groups. Examples of alternative starting materials include:



For preparation see T. Hirao, S. Mikami, M. Mori, Y. Ohshiro, *Tet. lett.*, **1991**, *32(14),* 1741-4. For stereospecific preparation of R and S enantiomers see R. Gerdil, H. Liu, G. Bernardinelli, *Helv. Chim. Acta.*, **1999**, *82(3),* 418-34.



For preparation see: F. Gavina, A. Costero, A. Gonzalez, S. Luis, *J. Org. Chem.*, **1987**, *52(14),* 2997-9; C. H. DePuy, M. Isaks, K. L. Eilers, G. F. Morris, *J. Org. Chem.*, **1964**, *29*, 3503-10; J.A. Bloodworth, H. J. Eggelte, *J. Chem. Soc. Perkin Trans. I*, **1981**, *12*, 3272-8.

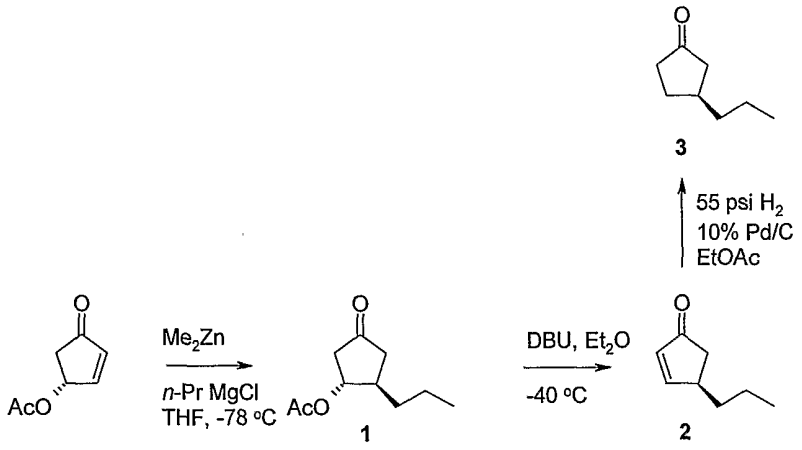


For preparation of the above two compounds or the class of compounds of the third formula, in which R = straight or branched alkyl of C_1-C_6, see M. Minamii, Y. Ueda, JP 62116537 (JP 85-262204), JP 85-167970 and M. Minamii, Y. Ueda, EP-A-0170506.

The invention will now be further described in the following Examples.

EXAMPLE 1

Enantiomerically pure (S)-3-*n*-propyl-cyclopentanone (3).



(3R,4R)-3-acetoxy-4-*n*-propyl-cyclopentanone (1).

n-Propylmagnesium chloride (15.7 ml of a 2M solution in ether, 31.4 mmol) was added slowly to a stirred solution of dimethylzinc (15.7 ml of a 2M solution in toluene, 31.4 mmol) in THF (80 ml) under argon at 0 °C. After 30 minutes, the mixture was cooled to –78 °C and (R)-4-acetoxycyclopent-2-enone (4.0 g, 28.5 mmol) in THF (45 ml) was added dropwise over 1 hour. The reaction mixture was stirred for a further 20 minutes and then quenched by the addition of saturated ammonium chloride solution (20 ml). The reaction mixture was allowed to warm to room temperature, diluted with 1N hydrochloric acid (100 ml) and extracted with ether (3 x 200 ml). The organic layer was washed with brine (200 ml), dried ($MgSO_4$) and the solvent was removed under reduced pressure to yield the *acetoxy cyclopentanone* **1** as a solution in toluene which was used without further purification in the next step.

ν_{max}(film)/cm^{-1} 1740 (C=O).

δ_H(400 MHz; $CDCl_3$) 5.08 (1H, m, C*H*OAc), 2.70 (1H, dd, *J* 19.2, 5.9), 2.59 (1H, dd, *J* 8.1, 1.2), 2.34 (1H, m), 2.23 (1H, dd, *J* 19.1, 4.6), 2.07 (3H, s, OCO*Me*), 1.98 (1H, dd, *J* 18.4, 6.4), 1.54 (1H, m), 1.46-1.21 (3H, m), 0.94 (3H, t, *J* 7.1, Me).

(R)-4-*n*-propyl-cyclopent-2-enone (2).

The acetoxy cyclopentanone **1** (approx. 28.5 mmol) in ether (40 ml) was added dropwise over 1 hr to a stirred solution of DBU (4.27 ml, 28.5 mmol) in ether (50 ml) at –40 °C under argon. The mixture was allowed to warm to –30 °C and stirred for 30 minutes before being quenched with dilute hydrochloric acid (20 ml). The reaction mixture was partitioned between ether (100 ml) and 1N HCl (150 ml). The organic layer was separated and the aqueous layer was further extracted with ether (2 x 100 ml). The combined ether layers were washed with brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was chromatographed (SiO_2, pentane-ether, 1:0 to 8:2) to give the *propylcyclopentenone* **2** (2.4 g, 68% from (R)-4-acetoxycyclopent-2-enone).

ν_{max}(film)/cm^{-1} 1708 (C=O).

δ_H(400 MHz; $CDCl_3$) 7.64 (1H, dd, *J* 5.6, 2.4, C*H*=CHC=O), 6.14 (1H, dd, *J* 5.6, 2.0, CH=C*H*C=O), 2.75 (1H, m), 2.53 (1H, dd, *J* 18.8, 6.4, CH_AH_BC=O), 2.00 (1H, dd, *J* 18.8, 2.0, CH_AH_BC=O) 1.60-1.20 (4H, m), 0.96 (3H, t, *J* 6.8, Me).

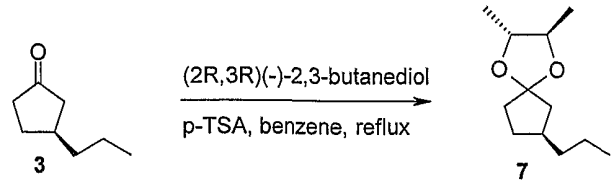
(S)-3-*n*-propylcyclopentanone (3)

A mixture of **2** (1.2 g, 9.7 mmol) and 10 % palladium on charcoal (catalytic quantity) in ethyl acetate (30 ml) was shaken in hydrogen at 55 psi and at 30 °C for 6 hours. The reaction mixture was filtered and the solvent was evaporated under reduced pressure. The residue was chromatographed (SiO_2, pentane-ether, 1:0 to 9:1) to give the *3-propylcyclopentanone* **3** (1.07 g, 88%).

ν_{max}(film)/cm^{-1} 1744 (C=O).

δ_H(400 MHz; $CDCl_3$) 2.29 (1H, dd, *J* 16.0, 8.4), 2.38 (1H, dd, *J* 18.8, 7.6), 2.21-2.09 (2H, m), 1.79 (1H, dd, *J* 18.0, 9.6), 1.56-1.34 (6H, m), 0.93 (3H, t, *J* 7.2, Me).

Enantiomeric purity by conversion to acetal (7)



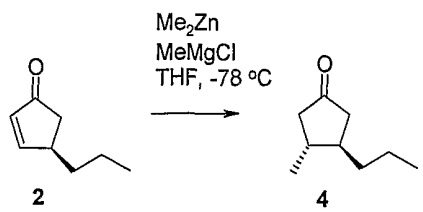
3 7

The ketone **3** (0.12 g, 0.95 mmol), (2R,3R)-(-)-2,3-butanediol (0.087 ml, 0.96 mmol) and *p*-toluenesulphonic acid (0.018 g, 0.095 mmol) were refluxed together in benzene (10 ml) for 3 hours using a Dean-Stark trap. The reaction mixture was allowed to cool, taken up in ethyl acetate (100 ml) and washed with saturated sodium bicarbonate solution, brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a single diastereoisomeric *acetal* **7** (0.12 g, 65%).

δ_H(400 MHz; $CDCl_3$) 3.61-3.57 (2H, m), 2.1-1.76 (5H, m), 1.47-1.40 (2H, m), 1.35-1.20 (10H, m), 0.88 (3H, t, *J* 6.8, Me); δ_C($CDCl_3$) 117.2, 78.3, 78.1, 44.6, 38.4, 37.6, 37.2, 30.1, 21.3, 17.2, 17.1, 14.2.

EXAMPLE 2

(3R,4R)-3-methyl-4-*n*-propyl-cyclopentanone (4)



2 4

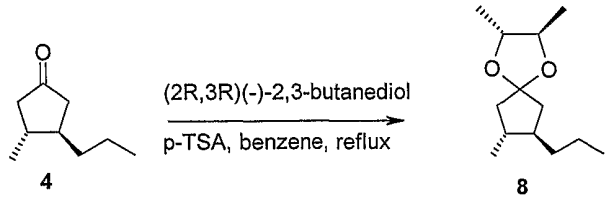
Methylmagnesium chloride (7.1 ml of a 3M solution in ether, 21.3 mmol) was added slowly to a stirred solution of dimethylzinc (5.3 ml of a 2M solution in

toluene, 10.6 mmol) in THF (80ml) under argon at 0 °C. After 30 minutes the mixture was cooled to –78 °C and **2** (1.2 g, 9.7 mmol) in THF (45 ml) was added dropwise over 1 hour. The reaction mixture was stirred for 20 minutes and then quenched by the addition of saturated ammonium chloride solution (20 ml). The reaction mixture was allowed to warm to room temperature, diluted with 1N hydrochloric acid (100ml) and extracted with ether (3 x 200 ml). The organic layer was washed with brine (200 ml), dried ($MgSO_4$) and the solvent was removed under reduced pressure to yield **4** as a solution in toluene which was purified by column chromatography (SiO_2, pentane-ether, 1:0 to 9:1 to give the *cyclopentanone* **4** (0.86 g, 63%).

$\nu_{max}(CDCl_3)/cm^{-1}$ 1733 (C=O).

δ_H(400 MHz; $CDCl_3$) 2.49-2.42 (2H, m), 1.87-1.80 (3H, m), 1.79-1.61 (2H, m), 1.80-1.43 (3H, m), 1.12 (3H, d, *J* 6.1, Me), 0.93 (3H, t, *J* 7.3, Me); $\delta_C(CDCl_3)$ 220.0, 48.1, 46.2, 45.5, 38.4, 37.0, 232.1, 19.6, 15.8.

Enantiomeric purity by conversion to acetal 8



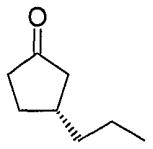
The ketone **4** (0.12 g, 0.86 mmol), (2R,3R)-(-)-2,3-butanediol (0.086 ml, 0.94 mmol) and *p*-toluenesulphonic acid (0.0163 g, 0.086 mmol) were refluxed together in benzene (10 ml) for 3 hours using a Dean-Stark trap. The reaction mixture was allowed to cool, taken up in ethyl acetate (100 ml), washed with saturated sodium bicarbonate solution, brine, dried ($MgSO_4$) and concentrated *in vacuo* to give **8** (0.08 g, 44%).

δ_H(400 MHz; $CDCl_3$) 3.61-3.58 (2H, m), 2.51-2.39, 2.27, 2.19-2.06, 1.90-1.60 (6H, m), 1.60-1.04 (10H, m), 0.98 (3H, d, *J* 6.6, Me), 0.89 (3H, t, *J* 7.3, Me);

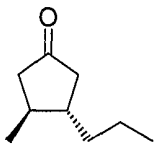
δ_C(400 MHz; $CDCl_3$) 115.8, 78.2, 78.1, 47.2, 45.1, 45.0, 38.4, 36.5, 21.4, 18.8, 17.3 (x2), 14.4.

EXAMPLES 3 & 4

(R)-3-*n*-propyl-cyclopentanone (5) and (3S,4S)-3-methyl-4-*n*-propyl-cyclopentanone (6).



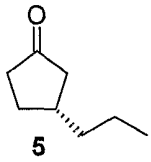
5



6

Ketones **5** and **6** were made using the same procedures as in the preceding examples, but starting from (S)-4-acetoxycyclopent-2-enone.

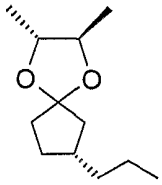
Enantiomeric purity by conversion to chiral acetals 9, 10.



5

(2R,3R)(-)-2,3-butanediol

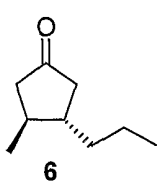
p-TSA, benzene, reflux



9

The enantiomeric purity of ketone **5** was confirmed by making acetal **9** using the procedure of the foregoing examples.

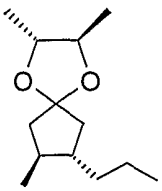
δ_H(400 MHz; $CDCl_3$) 3.60-3.48 (2H, m), 2.45-1.76 (5H, m), 1.44-1.41 (2H, m), 1.38-1.14 (10H, m), 0.88 (3H, t, *J* 7.1, mE); δ_C($CDCl_3$) 117.2, 78.2, 78.1, 44.9, 38.2, 38.0, 37.7, 30.5, 21.3, 17.0, 16.9, 14.2.



6

(2R,3R)(-)-2,3-butanediol

p-TSA, benzene, reflux



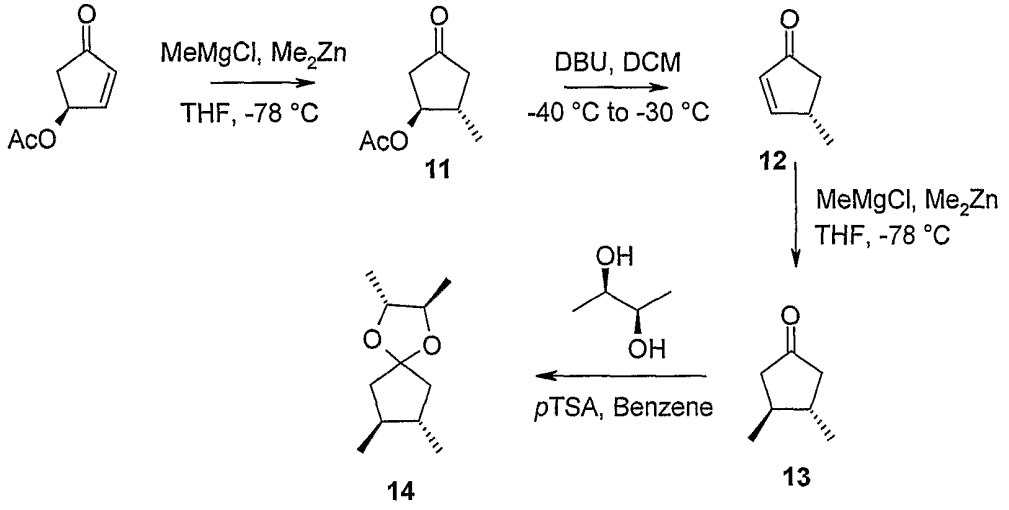
10

The enantiomeric purity of ketone **6** was confirmed by making acetal **10** using the procedure of the above examples.

δ_H(400 MHz; $CDCl_3$) 3.56-3.49 (2H, m), 2.49-2.22, 2.13-2.04, 1.90-1.62 (6H, m), 1.60-1.02 (10H, m), 0.97 (3H, d, *J* 6.1, Me), 0.89 (3H, t, *J* 7.3, Me); δ_C($CDCl_3$) 115.7, 78.1, 47.6, 45.5, 45.2, 38.6, 36.0, 21.4, 18.2, 16.9 (x2), 14.4.

EXAMPLE 5

Enantiomerically pure (3S,4S)-3,4-dimethylcyclopentanone (13)



The acetoxy cyclopentanone 11

Methylmagnesium chloride (11.3 ml of a 3M solution in THF, 33.9 mmol) was added slowly to a stirred solution of dimethylzinc (17.0 ml of a 2M solution in toluene, 34.0 mmol) in THF (80 ml) at 0 °C under argon. After 20 minutes, the mixture was cooled to –78 °C and (S)-4-acetoxycyclopent-2-enone (4.33 g, 30.9 mmol) in THF (45 ml) was added dropwise over 1 hour. The reaction mixture was stirred for a further 20 minutes and then quenched by the addition of saturated ammonium chloride solution (20 ml). The reaction mixture was allowed to warm to room temperature, diluted with 1N hydrochloric acid (100ml) and extracted with ether (3 x 200 ml). The organic layer was washed with brine (200 ml), dried ($MgSO_4$) and the solvent was removed under reduced pressure to yield the *acetoxy*

cyclopentanone **11** as a solution in toluene which was used without further purification in the next step.

ν_{max}(film)/cm^{-1} 1737 (C=O).

δ_H(400 MHz; $CDCl_3$) 5.01 (1H, m, C*H*OAc), 2.72 (1H, dd, *J* 19.0, 6.6), 2.59 (1H, m), 2.46 (1H, m), 2.24 (1H, dd, *J* 19.0, 4.6), 2.07 (3H, s, OCO*Me*), 1.95 (1H, dd, *J* 18.6, 5.7), 1.13 (3H, d, *J* 7.1, CH*Me*).

The methylcyclopentanone 12

Acetoxy cyclopentanone **11** (approx. 30.9 mmol) in dichloromethane (40 ml) was added dropwise over 1 hour to a stirring solution of DBU (4.6 ml, 30.9 mmol) in dichloromethane (50 ml) at –40 °C under argon. The mixture was allowed to warm to –30 °C and stirred for 30 minutes before being quenched with dilute hydrochloric acid (20 ml). The reaction mixture was partitioned between ether (100 ml) and 1N HCl (150 ml). The organic layer was separated and the aqueous layer was further extracted with ether (2 x 100 ml). The combined ether layers were washed with brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was chromatographed (SiO_2, pentane-ether, 7:3) to give *methylcyclopentenone* **12** (1.51 g, 51% from (S)-4-acetoxycyclopent-2-enone).

ν_{max}(film)/cm^{-1} 1715 (C=O).

δ_H(400 MHz; $CDCl_3$) 7.59 (1H, dd, *J* 5.6, 2.4, C*H*=CHC=O), 6.14 (1H, dd, *J* 5.6, 2.0, CH=C*H*C=O), 3.02 (1H, m), 2.60 (1H, dd, *J* 18.8, 6.3, CH_AH_BC=O), 1.95 (1H, dd, *J* 18.8, 2.2, CH_AH_BC=O) 1.21 (3H, d, *J* 7.1, CH*Me*).

The dimethylcyclopentanone 13

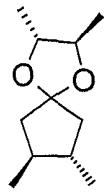
Methylmagnesium chloride (5.2 ml of a 3M solution in ether, 15.6 mmol) was added slowly to a stirred solution of dimethylzinc (3.9 ml of a 2M solution in toluene, 7.8 mmol) in THF (20 ml) under argon at 0°C. After 30 minutes the mixture was cooled to –78 °C and **12** (0.67 g, 7.0 mmol) in THF (10 ml) was

added dropwise over 1 hour. The reaction mixture was stirred for 20 minutes and then quenched by the addition of saturated ammonium chloride solution (10 ml). The reaction mixture was allowed to warm to room temperature, diluted with 1N hydrochloric acid (40 ml) and extracted with ether (3 x 50 ml). The organic layer was washed with brine (50 ml), dried ($MgSO_4$) and the solvent was removed under reduced pressure to yield **13** as a solution in toluene which was purified by column chromatography (SiO_2, pentane-ether, 95:5) to give the *dimethylcyclopentanone* **13** (0.45g, 52%).

ν_{max}(film)/cm^{-1} 1732 (C=O).

δ_H(400 MHz; $CDCl_3$) 2.50-2.39 (2H, m), 1.89-1.72 (4H, m), 1.12 (6H, d, *J* 5.6, 2 x Me).

Enantiomeric purity of 13 was established by conversion to acetal 14.



14

The ketone **13** (0.25 g, 2.23 mmol), (2R,3R)-(-)-2,3-butanediol (0.23 ml, 2.45 mmol) and *p*-toluenesulphonic acid (0.042 g, 0.22 mmol) were refluxed together in benzene (10 ml) for 3 hours using a Dean-Stark trap. The reaction mixture was allowed to cool, taken up in ethyl acetate (100 ml), washed with saturated sodium bicarbonate solution, brine, dried ($MgSO_4$) and concentrated *in vacuo* to give **14** (0.21 g, 51%).

δ_C($CDCl_3$) 115.5, 78.0, 47.8, 40.1, 17.7, 16.9.

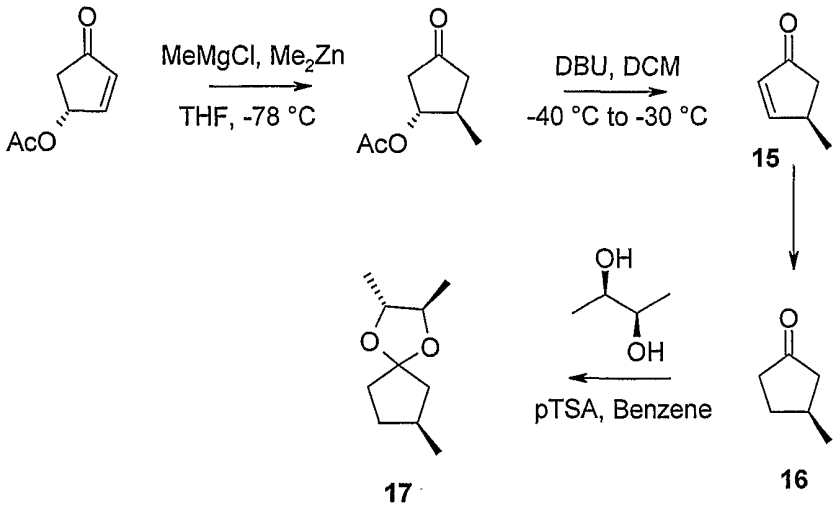
m/z (CI^+) 185 (M+H, 70%)

The acetal made from racemic (3RS,4RS)-3,4-dimethylketone has signals as shown below:

$\delta_C(CDCl_3)$ 115.6, 115.5, 78.2, 78.1, 47.8, 47.5, 40.2, 40.0, 18.1, 17.7, 17.3, 16.9

EXAMPLE 6

Enantiomerically pure (S)-3-methylcyclopentanone (16).



The methylcyclopentenone 15.

Compound **15** was prepared using the same method as **12.**

The methylcyclopentanone 16

A mixture of **15** (1.17 g, 12.2 mmol) and 10 % palladium on charcoal (catalytic quantity) in ethyl acetate (30 ml) was shaken at 55 psi Hydrogen at 30 °C for 6 hours. The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was chromatographed (SiO_2, pentane-ether, 9:1) to give the *3-methylcyclopentanone* **16** (1.09 g, 91%).

ν_{max}(film)/cm^{-1} (C=O) 1731.

δ_H(400 MHz; $CDCl_3$) 2.42-2.08 (5H, m), 1.78 (1H, ddd, *J* 16.8, 9.3, 0.7), 1.51 (1H, m), 1.13 (3H, d, *J* 6.8).

The acetal 17

The ketone **16** (0.25 g, 2.55 mmol), (2R,3R)-(-)-2,3-butanediol (0.26 ml, 2.80 mmol) and *p*-toluenesulphonic acid (0.05 g, 0.255 mmol) were refluxed together in benzene (10 ml) for 3 hours using a Dean-Stark trap. The reaction mixture was allowed to cool, taken up in ethyl acetate (100 ml), washed with saturated sodium bicarbonate solution, brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the *acetal* **17** (0.20 g, 47%).

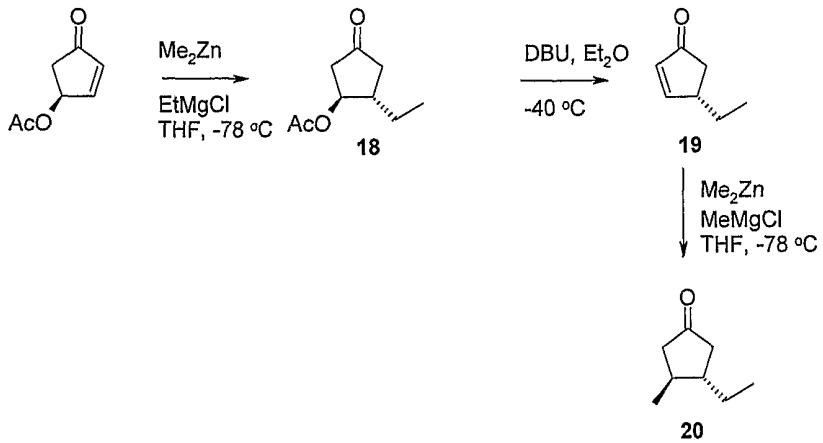
δ_H(400 MHz; $CDCl_3$) 3.59 (2H, m), 2.08-1.17 (13H, m), 1.01 (3H, d, *J* 6.8, Me); δ_C($CDCl_3$) 117.4, 78.3, 78.0, 46.4, 38.0, 32.1, 20.6, 17.2, 17.1

The acetal of the racemic 3-methylcyclopentanone has signals as shown below:

δ_C($CDCl_3$) 117.4, 78.3, 78.1 (x2), 78.0, 46.7, 46.4, 38.5, 38.0, 32.5, 32.1, 20.6, 20.2, 17.2, 17.1, 16.9 (x2).

EXAMPLE 7

Enantiomerically pure (3S,4S)-3-ethyl-4-methyl-cyclopentanone (20)



The acetoxy cyclopentanone 18

Ethylmagnesium chloride (19.6 ml of a 2M solution in THF, 39.2 mmol) was added slowly to a stirred solution of dimethylzinc (19.6 ml of a 2M solution in toluene, 39.2 mmol) in THF (80 ml) at 0 °C under argon. After 20 minutes, the

mixture was cooled to –78 °C and (S)-4-acetoxycyclopent-2-enone (5.0 g, 35.7 mmol) in THF (45 ml) was added dropwise over 1 hour. The reaction mixture was stirred for a further 20 minutes and then quenched by the addition of saturated ammonium chloride solution (20 ml). The reaction mixture was allowed to warm to room temperature, diluted with 1N hydrochloric acid (100ml) and extracted with ether (3 x 200 ml). The organic layer was washed with brine (200 ml), dried ($MgSO_4$) and the solvent was removed under reduced pressure to yield the *acetoxy cyclopentanone* **18** as a solution in toluene which was used without further purification in the next step.

ν_{max}(film)/cm^{-1} 1741 (C=O).

δ_H(400 MHz; $CDCl_3$) 5.10 (1H, m, C*H*OAc), 2.70 (1H, dd, *J* 19.3, 6.7), 2.57 (1H, ddd, *J* 18.5, 8.3, 1.2), 2.32-2.20 (2H, m), 2.07 (3H, s, OCO*Me*), 2.00 (1H, m), 1.62 (2H, m), 0.98 (3H, t, *J* 7.2, Me).

The ethylcyclopentenone 19

Acetoxy cyclopentanone **18** (approx. 35.7 mmol) in dichloromethane (45 ml) was added dropwise over 1 hr to a stirring solution of DBU (5.34 ml, 35.7 mmol) in dichloromethane (100 ml) at –40 °C under argon. The mixture was allowed to warm to –30 °C and stirred for 30 minutes before being quenched with dilute hydrochloric acid (30 ml). The reaction mixture was partitioned between ether (100 ml) and 1N HCl (150 ml). The organic layer was separated and the aqueous layer was further extracted with ether (2 x 100 ml). The combined ether layers were washed with brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was chromatographed (SiO_2, pentane-ether, 8:2) to give *ethylcyclopentenone* **19** (3.4 g, 86% from (S)-4-acetoxycyclopent-2-enone).

ν_{max}(film)/cm^{-1} 1713 (C=O).

δ_H(400 MHz; $CDCl_3$) 7.65 (1H, dd, *J* 5.6, 2.4, C*H*=CHC=O), 6.16 (1H, dd, *J* 5.6, 2.0, CH=C*H*C=O), 2.88 (1H, m), 2.54 (1H, dd, *J* 19.0, 6.3, CH_AH_BC=O),

2.02 (1H, dd, *J* 18.8, 2.2, CH_AH_BC=O) 1.63 (1H, m), 1.47 (1H, m), 0.99 (3H, t, *J* 7.6, Me).

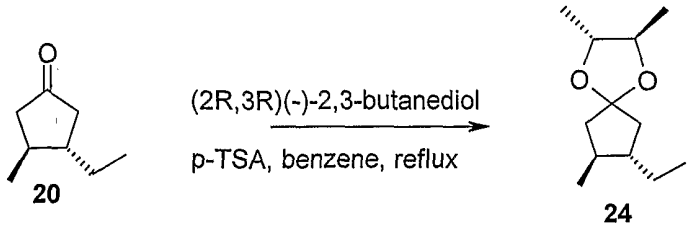
The cyclopentanone 20

Methylmagnesium chloride (22.5 ml of a 3M solution in ether, 67.5 mmol) was added slowly to a stirred solution of dimethylzinc (16.9 ml of a 2M solution in toluene, 33.8 mmol) in THF (100 ml) under argon at 0°C. After 30 minutes the mixture was cooled to –78 °C and **19** (3.37 g, 30.6 mmol) in THF (45 ml) was added dropwise over 1 hour. The reaction mixture was stirred for 20 minutes and then quenched by the addition of saturated ammonium chloride solution (25 ml). The reaction mixture was allowed to warm to room temperature, diluted with 1N hydrochloric acid (100 ml) and extracted with ether (3 x 100 ml). The organic layer was washed with brine (50 ml), dried ($MgSO_4$) and the solvent was removed under reduced pressure to yield **20** as a solution in toluene which was purified by column chromatography (SiO_2, pentane-ether, 95:5) to give the *cyclopentanone* **20** (2.4 g, 62%).

ν_{max}(film)/cm^{-1} 1738 (C=O).

δ_H(400 MHz; $CDCl_3$) 2.50-2.40 (2H, m), 1.92-1.60 (6H, m), 1.12 (3H, d, *J* 6.1, Me), 0.93 (3H, t, *J* 6.5, Me).

Conversion to an acetal



20 **24**

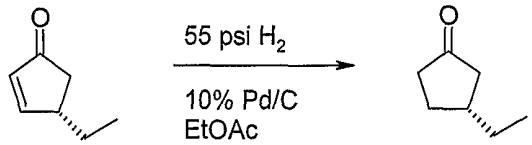
The ketone **20** (0.22 g, 1.74 mmol), (2R,3R)-(-)-2,3-butanediol (0.18 ml, 1.91 mmol) and *p*-toluenesulphonic acid (0.033 g, 0.174 mmol) were refluxed together in benzene (10 ml) for 3 hours using a Dean-Stark trap. The reaction mixture was allowed to cool, taken up in ethyl acetate (100 ml), washed with

saturated sodium bicarbonate solution, brine, dried ($MgSO_4$) and concentrated *in vacuo* to give **24** (0.19g, 55%).

$\delta_C(CDCl_3)$ 115.6, 78.1 (x2), 47.6, 47.1, 44.9, 38.2, 26.2, 19.3, 18.2, 16.9, 14.2; *m/z* (CI^+) 199 (M+H, 82%).

EXAMPLE 8

Enantiomerically pure (R)-3-ethylcyclopentanone (21)



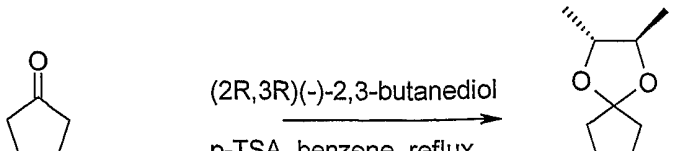
19 **21**

A mixture of **19** (3.4 g, 30.9 mmol) and 10 % palladium on charcoal (catalytic quantity) in ethyl acetate (50 ml) was shaken at 55 psi in hydrogen at 30 °C for 6 hours. The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was chromatographed (SiO_2, pentane-ether, 9:1) to give the *3-ethylcyclopentanone* **21** (3.4 g, 98%).

ν_{max}(film)/cm^{-1} 1737 (C=O).

δ_H(400 MHz; $CDCl_3$) 2.38 (1H, dd, *J* 18.1, 7.3), 2.29 (1H, dd, *J* 16.1, 8.8), 2.21-2.04 (4H, m), 1.79 (1H, ddd, *J* 18.1, 9.8, 1.1), 1.47 (2H, m), 0.95 (3H, t, *J* 7.6, Me).

Conversion to acetal 25



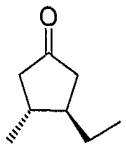
21 **25**

The ketone **21** (0.098 g, 0.874 mmol), (2R,3R)-(-)-2,3-butanediol (0.088 ml, 0.96 mmol) and *p*-toluenesulphonic acid (0.017 g, 0.087 mmol) were refluxed together in benzene (10 ml) for 3 hours using a Dean-Stark trap. The reaction mixture was allowed to cool, taken up in ethyl acetate (100 ml), washed with saturated sodium bicarbonate solution, brine, dried ($MgSO_4$) and concentrated *in vacuo* to give **25** (0.12 g, 73%).

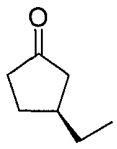
$\delta_C(CDCl_3)$ 117.2, 78.2, 78.1, 44.5, 39.8, 38.0, 30.1, 28.6, 17.0, 16.9, 12.5; *m/z* (CI^+) 185 (M+H, 75%)

EXAMPLES 10 & 11

(3R,4R)-3 ethyl-4-methyl-cyclopentanone (22) and (S)-3-ethyl-cyclopentanone (23)



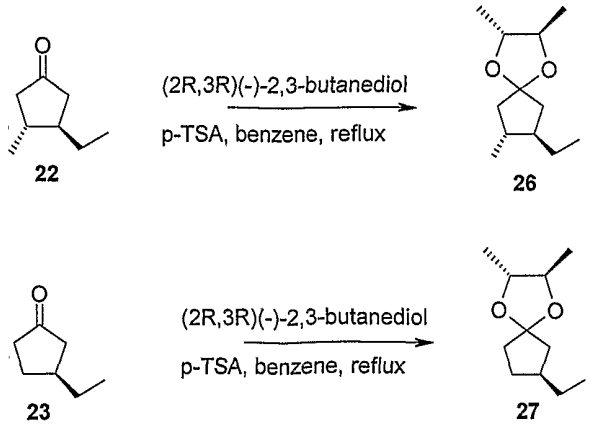
22



23

Compounds **22** and **23** were made using the procedure of the previous examples.

Conversion to acetals 26, 27



The enantiomeric purity of ketone **22** was confirmed by making acetal **26** using the previously described procedure.

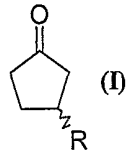
$\delta_C(CDCl_3)$ 115.7, 78.2, 78.1, 47.3, 46.9, 44.6, 38.0, 26.6, 19.3, 18.8, 17.3, 17.2, 14.2; *m/z* (CI^+) 199 (M+H, 80%)

The enantiomeric purity of ketone **23** was also confirmed by making acetal **26** using the previously described procedure.

$\delta_C(CDCl_3)$ 117.2, 78.3, 78.1, 44.2, 39.3, 37.6, 29.7, 28.8, 17.2, 12.5; *m/z* (CI^+) 185 (M+H, 78%).

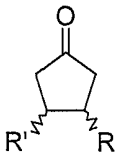
CLAIMS

1. A method of making an enantiomerically pure compound of the formula **(I)** or **(II)**:



(I)

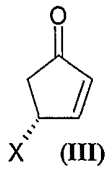
or



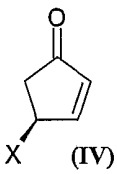
(II)

wherein R and R' represent C_1-C_{10} alkyl, C_2-C_{10} alkenyl or C_3-C_{10} cycloalkyl and the wedges signify (S)- or (R)- stereochemistry, the substituents in compound (II) being *trans*, which method comprises:

conjugate addition of an organometallic nucleophile that provides a group R as defined above to a compound of the formula **(III)** or **(IV)**:

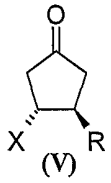


(III)



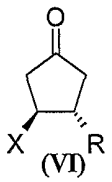
(IV)

wherein X represents a leaving group to give a trans 3,4-disubstituted addition product of formula **(V)** or **(VI)** in which R and X are as previously defined;



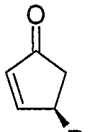
(V)

or



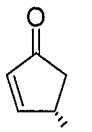
(VI)

eliminating the leaving-group X from the addition product of formula **(V)** or **(VI)** to give an (R)- or (S)- 4-alkyl or 4-alkenyl cyclopent-2-en-1-one of formula **(VII)** or **(VIII)**



(VII)

or



(VIII)

; and either

(i) hydrogenation of the compound of formula **(VII)** or **(VIII)** to give a cyclopentanone of formula **(I)** or

(ii) conjugate addition of a second organometallic nucleophile that provides a group R' as defined above to the compound of formula **(VII)** or **(VIII)** to give a trans 3,4-disubstituted addition product of formula **(II)**.

2. The method of claim 1, when used to make an (S)- compound of formula **(I)**.

3. The method of claim 1, when used to make an (R)- compound of formula **(I)**.

4. The method of claim 1, when used to make a (3S,4S)- compound of formula **(II)**.

5. The method of claim 1, when used to make a (3R,4R)- compound of formula **(II)**.

6. The method of any preceding claim , when used to make a compound in which R and R' (if present) represent methyl, ethyl or *n*-propyl.

7. The method of claim 1, when used to make any of the following compounds:

(S)-3-methylcyclopentanone;

(R)-3-methylcyclopentanone;

(S)-3-ethylcyclopentanone;

(R)-3-ethylcyclopentanone;

(S)-3-n-propylcyclopentanone;

(R)-3-n-propylcyclopentanone;

(3S,4S)-3,4-dimethyl-cyclopentanone;

(3R,4R)-3,4-dimethyl-cyclopentanone;

(3S,4S)-3,4-diethyl-cyclopentanone;

(3R,4R)-3,4-diethyl-cyclopentanone;

(3S,4S)-3-ethyl-4-methyl-cyclopentanone;

(3R,4R)-3-ethyl-4-methyl-cyclopentanone;

(3S,4S)-3-methyl-4-propyl-cyclopentanone;

(3R,4R)-3-methyl-4-propyl-cyclopentanone;

(3S,4S)-3-ethyl-4-propyl-cyclopentanone;

(3R,4R)-3-ethyl-4-propyl-cyclopentanone.

8. The method of any preceding claim, wherein the conjugate addition is carried out by adding the chiral cyclopentenone of formula **(III)** or **(IV)** to an organo-Grignard reagent or to an organo-lithium reagent in the presence of a dialkylzinc or zinc chloride or a copper (I) salt or a trialkylaluminium in a solvent at a temperature from –100 °C to 0 °C.

9. The method of claim 8, wherein the solvent is selected from tetrahydrofuran, 1,4-dioxane, *n*-heptane, toluene, diethyl ether and *t*-butyl methyl ether.

10. The method of any preceding claim, wherein the elimination product of formula **(VII)** or **(VIII)** is produced by treating the trans 3,4-disubstituted addition product of formula **(V)** or **(VI)** with a strong organic base or with a metal hydride in a solvent.

11. The method of claim 10, wherein the base or hydride is selected from 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,1,3,3-tetramethyl guanidine (TMG), lithium hydride and sodium hydride.

12. The method of claim 10 or 11, wherein the solvent is selected from dichloromethane, diethyl ether, tetrahydrofuran, *t*-butyl methyl ether and 1,4-dioxane.

13. The method of any preceding claim, wherein the elimination product of formula **(VII)** or **(VIII)** is treated with hydrogen at a pressure of 1-30 atmospheres at a temperature in the range 0-60°C in a solvent and in the presence of a hydrogenation catalyst to give a compound of formula **(I)**.

14. The method of claim 13, wherein the hydrogenation catalyst is selected from palladium on charcoal, platinum oxide, Raney nickel, and rhodium on alumina.

15. The method of claim 13 or 14, wherein in the solvent is ethyl acetate or methanol.

16. The method of any of claims 1-12, wherein the conjugate addition is carried out by treating the elimination product of formula **(VII)** or **(VIII)** with a second organo-Grignard reagent or with a second an organo-lithium reagent in the presence of a dialkylzinc or zinc chloride or a copper (I) salt or a trialkylaluminium in a solvent at a temperature from –100 °C to 0 °C to produce a compound of formula **(II)**.

17. The method of claim 16, wherein the solvent is selected from tetrahydrofuran, 1,4-dioxane, *n*-heptane, toluene, diethyl ether and *t*-butyl methyl ether.

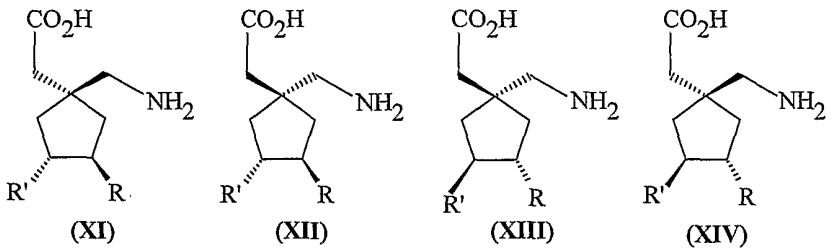
18. The method of any preceding claim, wherein the leaving group X in the compound of formula **(III)** or **(IV)** is acetoxy.

19. The method of any of claims 1-17, wherein the leaving group X in the compound of formula **(III)** or **(IV)** is halogen or sulfonic acid ester group.

20. An enantiomerically pure compound made by the method of any of claims 1-19.

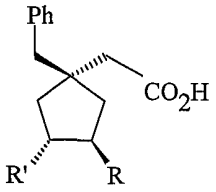
21. The compound of claim 20, whose enantiomeric purity is 98% or above.

22. A method of producing a compound of one of the formulae shown below:

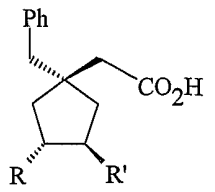


in which the substituents R and R' and the wedges have the meanings indicated in claim 1, which comprises providing a compound of formula **(I)** or **(II)** produced by the method of any of claims 1 – 17 or according to claim 18 or 19, converting said compound to a compound of formula **(XI)**, **(XII)**, **(XIII)** or **(XIV)**, and optionally further converting said compound into a pharmaceutically acceptable salt.

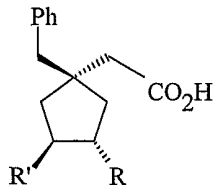
23. The method of claim 22, wherein said conversion is via an intermediate **(XV) - (XVIII)** shown below:



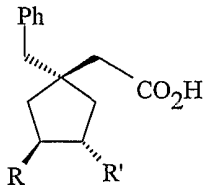
(XV)



(XVI)



(XVII)



(XVIII)

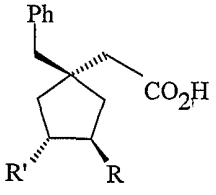
in which the substituents R and R' and the wedges have the meanings indicated above.

24. The method of claim 23, wherein the intermediate of formula **(XV) - (XVIII)** is converted to a compound of formula **(I)** or **(II)** by transforming the phenyl ring to a carboxylic acid and then to an amine.

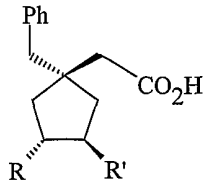
25. The method of claim 23, wherein the intermediate of formula **(XV) - (XVIII)** is converted to a compound of formula **(I)** or **(II)** by transforming the carboxylic acid group into an amine and oxidizing the phenyl group to an acid.

26. The method of claim 23, wherein the intermediate of formula **(XV) - (XVIII)** is converted to a compound of formula **(I)** or **(II)** by protecting the carboxylic acid group, oxidizing the phenyl ring to a second carboxylic acid group, protecting the second carboxylic acid group, selectively de-protecting the first carboxylic acid group, transforming the first carboxylic acid group to an amine, and de-protecting the second carboxylic acid group.

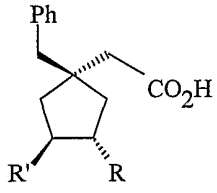
27. A method of producing a compound of the formula **(XV) - (XVIII)** shown below:



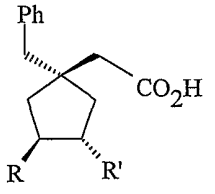
(XV)



(XVI)



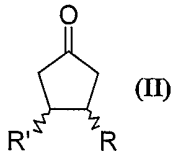
(XVII)



(XVIII)

in which the substituents R and R' and the wedges have the meanings indicated in claim 1, which comprises providing a compound of formula **(I)** or **(II)** produced by the method of any of claims 1 – 19 or according to claim 20 or 21, and converting said compound to a compound of formula **(XV) - (XVIII)**.

28. An enantiomerically pure compound of the formula:



(II)

wherein R and R' represent C_1-C_{10} alkyl, C_2-C_{10} alkenyl or C_3-C_{10} cycloalkyl and the wedges signify (S)- or (R)- stereochemistry, the substituents being *trans*, and at least one of R and R' not being methyl.

29. Any of the following compounds

(3S,4S)-3,4-dimethyl-cyclopentanone;

(3R,4R)-3,4-dimethyl-cyclopentanone;

(3S,4S)-3,4-diethyl-cyclopentanone;

(3R,4R)-3,4-diethyl-cyclopentanone;

(3S,4S)-3-ethyl-4-methyl-cyclopentanone;

(3R,4R)-3-ethyl-4-methyl-cyclopentanone;

(3S,4S)-3-methyl-4-propyl-cyclopentanone;

(3R,4R)-3-methyl-4-propyl-cyclopentanone;

(3S,4S)-3-ethyl-4-propyl-cyclopentanone;

(3R,4R)-3-ethyl-4-propyl-cyclopentanone.

INTERNATIONAL SEARCH REPORT

In pplication No
PCT/GB 01/02900

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C45/69 C07C49/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MASE, N. ET AL.: "Diastereomer-Differenciating Radical beta-Addition to 4- or 5-methyl-2-'(2,4,6-triisopropylphenyl)-sulfinyl!-2-cyclopentenones" JOURNAL OF ORGANIC CHEMISTRY, vol. 63, no. 12, 1998, pages 3899-3904, XP001029082 examples 7A,7B; table 2 ---	20,21, 28,29
X	SWANSON D.R. ET AL.: "Regioselective and Diastereoselective Alkyl-Alkene and Alkene-Alkene Coupling Promoted by Zirconene and Hafnocene" JOURNAL OF ORGANIC CHEMISTRY, vol. 54, no. 13, 1989, pages 3521-3523, XP001028975 example 8A --- -/--	20,21, 28,29

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 October 2001	30/10/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Janus, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte Application No
PCT/GB 01/02900

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	SMITH, A.B. III ET AL.: "Cuprate Additions to 5-Methoxycyclopentenones : a Novel Stereoelectronic Effect" TETRAHEDRON LETTERS, vol. 29, no. 4, 1988, pages 439-442, XP001029088 example 12; table 1	20,21, 28,29
A		1-19, 22-27
X	KOKKE, W.C.M.C. & VARKEVISSER, F.A.: "Two Syntheses of Optically Pure (1R,2R)-1,2-Dimethylcyclopentane" JOURNAL OF ORGANIC CHEMISTRY, vol. 39, no. 11, 1974, pages 1535-1539, XP001029096 example 19	20,21, 28,29
X	BATTERSBY, A.R. ET AL.: "Ipecacuanha Alkaloids. Part VIII. Chemical Correlation of the Indole and Ipecacuanha Alkaloids" JOURNAL OF THE CHEMICAL SOCIETY C, no. 19, 1968, pages 2467-2471, XP001029737 example 21	20,21, 28,29
A	WO 99 21824 A (BRYANS JUSTIN STEPHEN ;HORWELL DAVID CHRISTOPHER (GB); WARNER LAMB) 6 May 1999 (1999-05-06) cited in the application the whole document	1-19, 22-27
A	US 5 134 238 A (ROSSITER BRYANT E ET AL) 28 July 1992 (1992-07-28) example 5	1-19

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 20, 21 and 28 (all in part)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty for claims 20, 21 and 28. So many documents were retrieved that it is impossible to determine which parts of said claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of claims 20, 21 and 28 is impossible. Consequently, and in the light of claim 29, the search has been restricted to the compounds of formula (II) wherein R and R' represent methyl, ethyl, propyl or butyl, whereby all isomers of propyl and butyl groups have been included in the scope of the search. The compounds of formula (I) were not searched per se, but only in relation to their process of preparation (see claim 1).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

›rmation on patent family members

Inte — Application No
PCT/GB 01/02900

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9921824	A	06-05-1999	AU	9663898 A	17-05-1999
			BR	9813284 A	22-08-2000
			CN	1276784 T	13-12-2000
			EP	1032555 A1	06-09-2000
			HU	0004310 A2	28-04-2001
			NO	20002118 A	26-04-2000
			PL	340285 A1	29-01-2001
			TR	200001170 T2	23-10-2000
			WO	9921824 A1	06-05-1999
			ZA	9809740 A	25-04-1999
US 5134238	A	28-07-1992	NONE		